3.86–3.30 (4 H, m, H5′, H3″), 2.40 (1 H, m, H3′); MS m/z 261 $(M + H)^+$, 283 $(M + Na)^+$. Anal. ($C_{10}H_{13}FN_2O_5$) C, H, N.

Antiviral Assay Procedures. Determination of antiviral activity and cytotoxicity was carried out as previously described.[16]

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Synthesis and Antiviral Activity of 3′-Deoxy-3′-*C*-hydroxymethyl Nucleosides

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A series of 3′-branched-chain sugar nucleosides, in particular 3′-deoxy-3′-*C*-hydroxymethyl nucleosides, have been synthesized and evaluated as antiviral agents. Reaction of 1-(2,3-epoxy-5-*O*-trityl-β-D-*lyxo*-pentofuranosyl) derivatives **12** and **13**, of uracil and thymine, respectively, with 5,6-dihydro-2-lithio-5-methyl-1,3,5-dithiazine **14** afforded the corresponding 3′-functionalized nucleosides **15** and **16**, respectively. Replacement of the trityl group with *tert*-butyldiphenylsilyl allowed high yielding hydrolysis of the 3′-function to give the 3′-deoxy-3′-*C*-formyl-β-D-*arabino*-pentofuranosyl nucleosides **21** and **22**. Desilylation afforded the 1-(3-deoxy-3-*C*-formyl-β-D-*lyxo*-pentofuranosyl) 3′,5′-*O*-hemiacetal nucleosides **33** and **34**, respectively. Reduction of the formyl group of **21** and **22**, followed by desilylation, yielded the 3′-deoxy-3′-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl) analogues **7** and **8**, respectively. The uracil base moiety of **7** was converted to 5-iodouracil and then to (*E*)-5-(2-bromovinyl)uracil to furnish an analogue **10** of BV*ara*U. The 1-(3-deoxy-3-*C*-(hydroxymethyl)-β-D-*lyxo*-pentofuranosyl) and 1-(2,3-dideoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl) derivatives of uracil (**31** and **6**, respectively) and 5-iodouracil (**32** and **9**, respectively) were also obtained. All novel, fully deprotected nucleoside analogues were evaluated for antiviral activity against human immunodeficiency virus type-1, herpes simplex virus types-1 and -2, varicella zoster virus, human cytomegalovirus and influenza A. Of the compounds tested only (*E*)-5-(2-bromovinyl)-1-[3-deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]uracil (**10**) inhibited VZV (alone), but did so at concentrations well below the cytotoxicity threshold.

Introduction

Nucleosides and nucleoside analogues have achieved considerable success in the fight against viral infection.[1] The first nucleoside antiviral, and the first antiviral chemotherapeutic agent to be licensed for use in humans, was 5-iodo-2′-deoxyuridine (**1**, IDU). This was successful in the topical treatment of herpes simplex keratitis in rabbits and man.[2] However, its selectivity was poor. The search for improved activity led to compounds such as (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (**2**, BVDU) which has been shown to be active against a number of viruses. In particular, it is one of the most potent and selective agents known against herpes simplex virus type-1 (HSV-1) (MIC = 0.007–0.01 $\mu g/mL^{-1}$)[3] and varicella zoster virus (VZV) (MIC = 0.0002–0.003 $\mu g\ mL^{-1}$).[4] Its selectivity stems from its 5′-phosphorylation by virus-induced thymidine kinase[5] initially to the monophosphate and then probably also to the diphosphate.[6] The 5′-triphosphate (BVDUTP), obtained through further phosphorylation by cellular kinases, then inhibits viral polymerase (selectively[7]) and can also be incorporated by this polymerase into viral DNA.[8]

For a number of years now it has been recognized that branched-chain sugar nucleosides show biological activity.[9] For example, 2′,3′-dideoxy-3′-*C*-(hydroxymethyl)thioguanosine (**3**), a simple 3′-homologue of 2′-deoxythioguanosine, was found[10] to be inhibitory to the growth of WI-L2 cells. It was proposed[10] that acceptance by kinase and polymerase enzymes was improved if two primary hydroxyls were provided. More recently, the naturally occurring purine nucleosides analogue oxetanocin **4** and its derivatives were shown to be effective anti-human immunodeficiency virus type-1 (HIV-1)[11] and antiherpes virus[12] agents. Such reports prompted us to investigate the effect on biological activity of an hydroxymethyl substituent at the 3′-position of pyrimidine nucleoside analogues, with a view to maintaining or improving acceptance by viral enzymes and improving selectivity. It is known that modifications at the 3′-position of, for example, BVDU can be tolerated by processing enzymes; 3′-amino-(*E*)-5-(2-bromovinyl)-2′,3′-dideoxyuridine (**5**,

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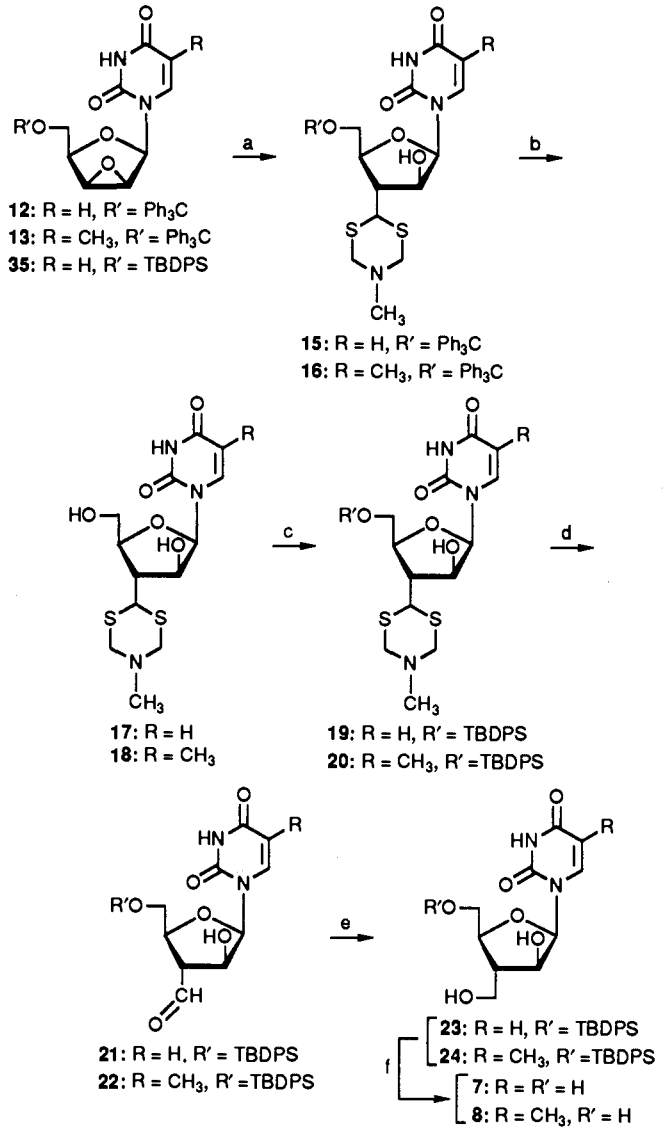
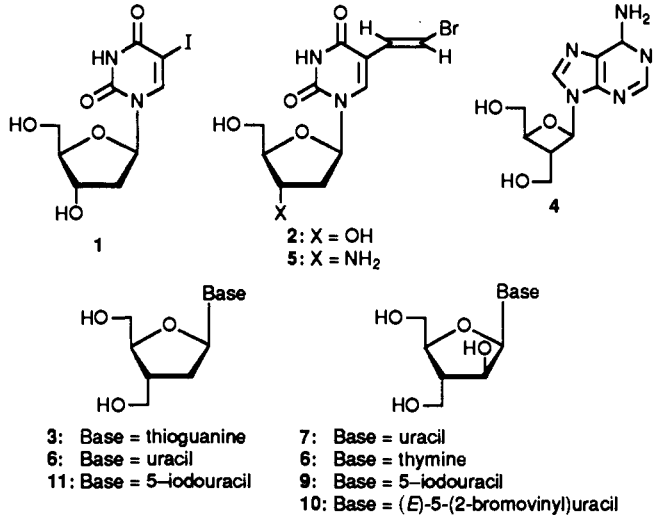
Scheme I[a]



[a] (a) 14, THF/HMPA; (b) TFA/*n*BuOH or DCA/CH_2Cl_2; (c) TBDPS-Cl, Et_3N, DMAP, DMF; (d) HgO/$HgCl_2$, aqueous THF; (e) $NaBH_4$, aqueous EtOH; (f) TBAF, THF.

3'-NH_2-BVDDU)[13] has substantial activity against HSV-1, and especially against VZV.



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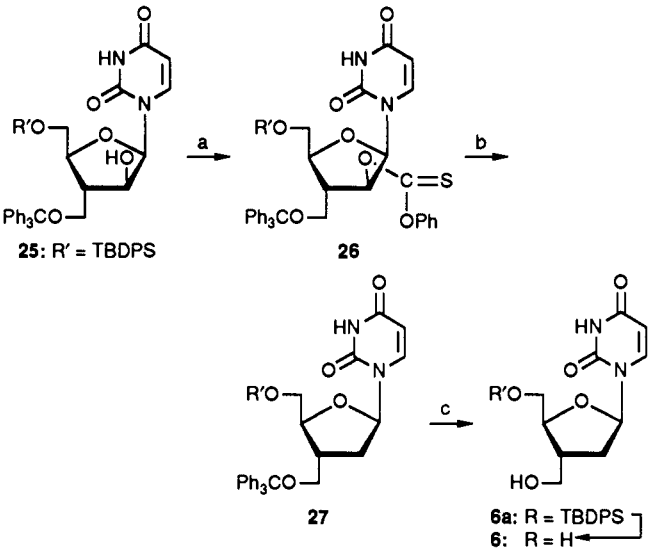
Scheme II[a]



[a] (a) PhOC(S)Cl, DMPA, CH_3CN; (b) Bu_3SnH, AIBN, $PhCH_3$; (c) (i) DCA, CH_2Cl_2; (d) TBAF, THF.

Although Ueda and co-workers[14] have reported a novel ring contraction of a 3'-amino-hexopyranosyl nucleoside to give a 3'-*C*-formyl nucleoside and its subsequent reduction to a 3'-*C*-hydroxymethyl nucleoside **6**; the synthesis of 3'-*C*-derivatized nucleosides has been achieved generally by elaboration of 3'-keto nucleosides or of 3-keto sugars followed by condensation with a suitably protected nucleobase.[9] However, such approaches suffer from elaborate and low yielding procedures and a lack of complete stereospecificity. Work carried out in this laboratory[15,21] has demonstrated the ability of the formyl synthon, 1,3-dithian-2-yl anion, to open a 2',3'-anhydro nucleoside in a regio- and stereospecific manner to give 3'-*C*-derivatized *arabino*-pentofuranosyl nucleosides. Nucleosides with an *arabino*-pentofuranosyl sugar moiety such as 9-(β-D-*arabino*-pentofuranosyl)adenine (*ara*A)[16] and 1-(β-D-*arabino*-pentofuranosyl)thymine (*ara*T)[17] were among the first antiviral agents, and while the *arabino*-pentofuranosyl analogues of IDU (I*ara*U)[18] and BVDU (BV*ara*U)[19] are less active than their parents against HSV-1, BV*ara*U is one of the most potent anti-VZV agents known.[4]

This paper describes a new and efficient stereo- and regiospecific synthesis of 3'-*C*-formyl nucleosides, based on the hydrolysis of analogues derivatized at C3' with a formyl synthon. Thus, the 3'-*C*-hydroxymethyl nucleosides **7** and **8** are obtained. The subsequent conversion of compound **7** to the 5-iodo and (*E*)-5-(2-bromovinyl) analogues **9** and **10**, respectively, is also described. 2'-Deoxygenation to afford uracil and 5-iodouracil analogues **6** and **11**, respectively, is reported as well as antiviral test results.

Chemistry

The key epoxide intermediates **12** and **13** were syn-

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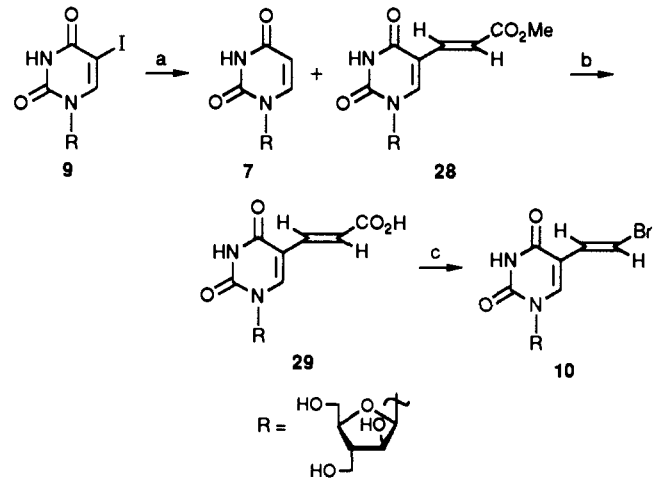
thesized by a modification[15] of the procedure of Fox and co-workers.[20] Reaction with 4,5-dihydro-2-lithio-5-methyl-1,3,5-dithiazine (14, lithium methylthioformaldine, LiMTF)[25] allowed preparation of compounds 7 and 8 according to Scheme I. Thus, treatment of epoxides 12 and 13 with 4 equiv of LiMTF in THF/HMPA at −60 °C gave the desired 3′-derivatized nucleosides 15 (65%) and 16 (75%), respectively. Reaction of 15 and 16 with HgO/$HgCl_2$ in wet THF[25] resulted in little isolated nucleoside product. However, prior replacement of the Lewis acid sensitive[22] triphenylmethyl group allowed successful subsequent hydrolysis of the formyl synthon. Thus, while attempted removal of the 5′-*O*-trityl protecting group from 15 and 16 with acetic acid–water[15] gave only poor yields of the desired deprotected derivatives 17 and 18, respectively, reaction of 15 with trifluoroacetic acid (TFA) in *n*-butyl alcohol (*n*-BuOH)[26] gave 17 (90%), and reaction of 16 with dichloroacetic acid (DCA) in dichloromethane[27] gave 18 (69%). Reprotection of 17 and 18 with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) gave 19 and 20 in 62% and 67% yields, respectively.

Reaction of compounds 19 and 20 with HgO/$HgCl_2$ in wet THF[25] at 0 °C for 5 min furnished the required 3′-*C*-formyl nucleosides 21 (85%) and 22 (90%), respectively. Reduction of 21 and 22 with sodium borohydride in aqueous ethanol, followed by desilylation in each case with tetrabutylammonium fluoride (TBAF) in THF,[23] afforded 7 (62%) and 8 (73%), respectively.

The 2′-deoxy nucleoside analogue 6 was achieved according to Scheme II by deoxygenation[30] of the 3′,5′-di-O-protected *arabino*-pentofuranosyl derivative 25, which was obtained from the 5′-O-protected derivative 23 by reaction with triphenylmethyl chloride in pyridine (81%). Reaction of 25 with (phenyloxy)thiocarbonyl chloride and 4-(dimethylamino)pyridine afforded the fully derivatized 26. This was reacted with tributyltin hydride in the presence of α,α′-azobis(isobutyronitrile) (AIBN) to afford some remaining starting material 26 (15%), together with the required deoxygenated 27 (27%), and also compound 25 (6.2%) due to reversion to starting alcohol, presumably by hydrolysis of unreacted 26. Complications in 2′-deoxygenation of nucleosides have previously been attributed[31] to an interaction of the nucleobase with tin species; the close proximity of the arabino-2′-functionality in compound 26 to the nucleobase enhances the possibility of such interference with tin-mediated reaction at the 2′-position. Treatment of compound 27 with DCA and

Scheme III[a]



[a] (a) Pd(0), CH_2=$CHCO_2Me$; (b) (i) NaOH, (ii) H^+; (c) NBS, K_2CO_3, DMF.

then TBAF furnished 6 (55%), data for which agreed with that published.[14]

Iodination at C5 of compounds 6 and 7 by reaction with iodine and nitric acid in boiling aqueous 1,4-dioxane[32] afforded 11 (46%) and 9 (85%), respectively. Conversion of 5-iodo nucleoside 9 to the (*E*)-5-(2-bromovinyl) analogue 10 was effected by the method of Herdewijn and co-workers[33] (Scheme III). Reaction of 9 with methyl acrylate under Heck conditions[34] resulted in isolation of the ester 28 (31%), together with deiodinated product 7 (38%).[35] While the yields of this coupling reaction are generally not excellent, the reaction of 1-(β-D-*arabino*-pentofuranosyl)-5-iodouracil by this method gave[36] a 55% yield of the desired vinyl ester, and no deiodinated product was detected. The 3′-C-substituent thus appears to have significant effects, probably on steric hindrance in intermediary palladium(0) complexes. Alkaline hydrolysis of 28 to the acid 29 (55%) and treatment of this with *N*-bromosuccinimide gave the BV*ara*U analogue 10 (51%).

The stability of 21 and 22 to elimination and, especially, epimerization on silica gel is noteworthy, as is the fact that little hydration of aldehyde was observed by NMR (δ 9.70, s, CHO). This is in contrast to 4′-*C*-formyl nucleosides,[24,28] where the adjacent sugar ring oxygen presumably results in a more acidic α-hydrogen and a more electropositive carbonyl carbon. However, treatment of 19 with HgO/$HgCl_2$ at room temperature for 90 min resulted in isolation in poor yield of a mixture of two nucleosides which were inseparable by silica column chromatography, but the ^1H NMR spectrum indicated an aldehyde proton resonance. Reduction of this crude mixture with sodium borohydride furnished two more polar products; the first was identical with 1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]uracil (23) (4.6%) and the other, due to acid- or base-catalyzed epimerization at C3′ via the enol form of the aldehyde, was characterized as its 3′-*lyxo* epimer 30 (5%). Desilylation

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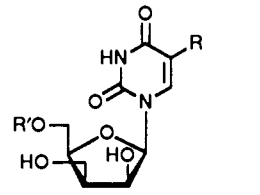
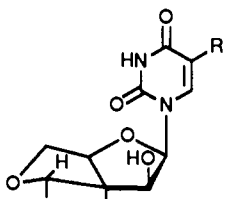
of the latter gave the previously unknown 3'-C-branched sugar nucleoside **31** (77%), which was iodinated at C5 as before to give **32** (66%). Further examples of the epimerization of the 3'-*C*-formyl group[14] were provided in the desilylation of **21** and **22** to yield 1-(3-deoxy-3-*C*-formyl-β-D-*lyxo*-pentofuranosyl)uracil 3',5'-*O*-hemiacetal (**33**) (58%) and -thymine (**34**) (59%), respectively. Epimerization at C3' induced by the basic fluoride ion has been noted with 3'-*C*-cyano nucleosides.[29]



30: R' = TBDPS, R = H
31: R = R' = H
32: R' = H, R = I



33: R = H
34: R = CH_3

An attempt was made to obviate the need for the detritylation/reprotection sequence by synthesis of 1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-epoxy-β-D-*lyxo*-pentofuranosyl]uracil (**35**), which was achieved with an overall yield of 49% in a manner analogous to that of the synthesis of **12** and **13**. However, the yield of **19**, from the reaction of **35** with LiMTF as before, was much reduced, possibly due to increased steric hindrance at C3', and so the more circuitous route was preferred.

The assignment of nucleoside structures was based on UV and mass spectra and largely on ^{1}H NMR data. The NMR coupling pattern (doublet) and the coupling constant ($J_{1'-2'}$ = 5 Hz) for H-1', and the coupling pattern for H-2' (quartet which appears as a triplet on addition of D_2O) was that expected[37,38] for the *arabino*-pentofuranosyl nucleosides. That nucleophilic attack on epoxides **12** and **13** had occurred at C3' rather than C2' was further confirmed by the coupling pattern (unresolved "multiplet"—the possibility that this multiplet indicates anomerization under the acidic deprotection conditions is not supported by the lack of signals attributable to resonances of other protons in an α-anomer) for H-1' in deoxygenated compounds **6** and **11**. The *arabino*-pentofuranosyl product is that expected on mechanistic considerations[39] and while formation of some of the corresponding 2'-deoxy-2'-substituted-*xylo*-pentofuranosyl nucleosides cannot be precluded, TLC showed only one product in the reaction of the epoxides.

The stereochemistry at C3' of *lyxo*-pentofuranosyl nucleosides **31** and **32** was confirmed by the downfield shift of NMR signals relative to their arabinofuranosyl analogues **7** and **9**, for H-5, OH-2', and particularly H-6 for **31** and of H-6 and OH-2' for **32**, due to the closer proximity of OH-3''. The H-1' signal was shifted upfield. Also, the coupling constants and patterns characteristic of the arabinofuranosyl moiety were no longer observed for **31** and **32**. The 5'-protected **30** exhibited a singlet for H-1', as for epoxides **12**, **13**, and **35**; its H-2' signal was a triplet rather than a quartet.

The ^{1}H NMR data for hemiacetals **33** and **34** compared favorably with that previously reported[14] for such compounds. The configuration at C3'' was further established by the coupling pattern (singlet) for the H-3'' resonance, indicating a torsion angle between bonds H3''–C3'' and H3'–C3' approaching 90°.

The procedure discussed above constitutes a new and efficient route to 3'-C-branched-sugar nucleosides. It also serves to demonstrate further[25] the relative ease of hydrolysis of the MTF group and is the first example of the use of LiMTF in the nucleophilic opening of nonterminal epoxides. The key 3'-*C*-formyl nucleoside intermediate provides the possibility of further elaboration at the 3'-position, and work based on this is ongoing. The synthesis of the 2'-deoxy analogue of **10** and of 2',3'-dideoxy-3'-*C*-hydroxymethyl purine nucleosides as analogues of oxetanocin is also being persued.

Antiviral Testing

Antiviral and cytotoxicity assays of compounds **6–11**, **17**, **18**, **28**, **29**, and **31–34** against HIV-1 in MT-4 cells, HSV-1 and -2 in Vero cells, human cytomegalovirus (CMV) in MRC-5 cells, VZV in MRC-5 and/or CV-1 cells, and influenza A in MDCK cells were carried out at concentrations up to 100 μM. BVDU and acyclovir (ACV) were assayed as references.

Perhaps not surprisingly none of the compounds showed marked activity against HIV-1. The results indicated that the substitution of 3'-hydroxyl with 3'-*C*-hydroxymethyl severely reduces the general antiviral activity. In particular, 5-iodouracil nucleoside analogues **9** and **11** showed no activity at the concentrations studied. Of the compounds tested only (*E*)-5-(2-bromovinyl)uracil nucleoside **10** exhibited significant antiviral activity; inhibition of VZV was observed at IC_{50} 4.4 μg mL^{-1} in CV-1 cells and 15.3 μg mL^{-1} in MRC-5 cells. No activity against the other viruses was detected. The anti-VZV activity of **10** is much reduced compared to that of BVDU (IC_{50} = 0.0024 μg mL^{-1}). However, in addition none of the compounds exhibited toxic effects in uninfected Vero cells up to 100 μM, and compounds **10** and **29** were nontoxic at 500 μM. It is interesting to note that replacement of 3'-OH in BVDU with NH_2 (to give 3'-NH_2-BVDDU) also reduced the anti-VZV activity by less than the anti-HSV-1 activity,[13] as did introduction of 2'-OH to give BV*ara*U.[4] The activity spectrum of compound **10** supports the suggestion that this may be a general effect of such sugar modifications, and may lead to more selective antiviral agents.

Although no activity was observed for compound **10** against HSV-1, it should be recognized that the anti-VZV activity may be due, at least in part, to its degradation by phosphorylases and subsequent direct pentosyl transfer by the same enzymes to the (*E*)-5-(2-bromovinyl)uracil thus formed to produce BVDU. The mode of action of **10** has not been determined, however.

The findings obtained here warrant further investigation of the effect of such 3'-modification on antiviral activity.

Experimental Section

General Procedures. Melting points were obtained with use of a Gallenkamp apparatus. ^{1}H NMR spectra were recorded with a Jeol FX90Q (90 MHz) or a Jeol GX270 (270 MHz) spectrometer in DMSO solution relative to an internal tetramethylsilane reference. FAB mass spectra were obtained on a Kratos MS80 spectrometer from samples dissolved in DMSO with 3-nitrobenzyl alcohol as matrix; sodium ion doping to give enhanced peaks was used as necessary. Samples for UV spectrophotometry were dissolved in spectroscopic grade ethanol and spectra were recorded on a Perkin-Elmer 552 spectrophotometer. Precoated, aluminum-backed, silica gel TLC plates (silica gel 60 F_{254}, 0.2-mm thickness) were supplied by E. Merck, A.G. Detection was achieved under UV light (254 nm) or by spraying with 30% H_2SO_4 in ethanol and heating. Column chromatography was performed on silica gel 60, 230–400 mesh (Merck). Semi-preparative HPLC

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(39) Perlman, M. E.; Watanabe, K. A. *Nucleosides Nucleotides* **1987**, *6*, 621.

was carried out on a Kontron 25 cm × 4.6 mm column (o.d. 1/4 in.) packed with Partisil (5 μm); detection was by optical density measurement (290 nm).

1-[3-Deoxy-3-*C*-(4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yl)-5-*O*-trityl-β-D-*arabino*-pentofuranosyl]uracil (15). 4,5-Dihydro-5-methyl-1,3,5-dithiazine (1.28 g, 9.45 mmol) was dissolved in dry THF (10.4 mL) and HMPA (1.7 mL) was added. The solution was cooled to −78 °C under dry nitrogen. *n*-Butyllithium (1.55 M in hexanes, 6.1 mL) was then added over 2 min to produce a white precipitate. Metallation was allowed to proceed for 1 h. While the low temperature was maintained, a solution of 1-(2,3-epoxy-5-*O*-trityl-β-D-*lyxo*-pentofuranosyl]uracil[20] (1.0 g, 2.15 mmol) in dry THF (4.2 mL) and HMPA (5.8 mL) was added dropwise with vigorous stirring. An initially orange coloration was produced which darkened with time to a deep red/brown. After 90 min TLC indicated no remaining starting material and a single more polar product. The mixture was poured into water (250 mL), neutralized with 1 M HCl and extracted with ethyl acetate (×2). The organic phase was dried ($MgSO_4$), filtered, and evaporated and the residue chromatographed on a silica column with toluene–acetate 7:4 to give **15** as an off-white foam (0.84 g, 65%). A sample was reprecipitated from aqueous ethanol to give an off-white solid: UV λ_{max} 261 nm (ε 10390); ^{1}H NMR δ 11.35 (1 H, s, NH), 7.55 (1 H, d, H6), 7.50–7.25 (15 H, m, trityl), 5.95 (1 H, d, J = 4.70 Hz, H1′), 5.65 (1 H, d, OH-2′), 5.45 (1 H, d, H5), 4.70 (3 H, m, SCHS, SCH_2N), 4.40 (1 H, q (t on D_2O-shake), H2′), 4.20 (3 H, m, H4′, SCH_2N), 3.30 (2 H, m, H5′), 2.45 (3 H, s, CH_3), 2.30 (1 H, m, H3′); MS m/z 604 $(M + H)^+$, 626 $(M + Na)^+$, 648 $(M + 2Na)^+$, 243 $(Ph_3C)^+$. Anal. ($C_{32}H_{33}N_3O_5S_2$) C, H, N.

1-[3-Deoxy-3-*C*-(4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yl)-β-D-*arabino*-pentofuranosyl]uracil (17). **15** (3.46 g, 5.73 mmol) was dissolved in a mixture of *n*-butyl alcohol (143 mL) and trifluoroacetic acid (48 mL) (to give a 0.03 M solution) and stirred at room temperature for 10 min. TLC then indicated reaction to a more polar nucleoside to be complete. The reaction mixture was quenched with *n*-butyl alcohol (290 mL) and evaporated under high vacuum at, or below, 40 °C to give a yellow foam. This was partitioned between diethyl ether and water, and the aqueous layer was evaporated to an off-white foam. Elution from a silica column with chloroform–ethanol 9:1 gave **17** as a white foam (1.86 g, 90%). A sample was recrystallized from ethyl acetate to give short needles: UV λ_{max} 262 nm (ε 9380); ^{1}H NMR δ 11.25 (1 H, s, NH), 7.80 (1 H, d, H6), 5.85 (1 H, d, J = 4.45 Hz, H1′), 5.55 (2 H, 2d, H5, OH-2′), 5.05 (1 H, t, OH-5′), 4.85–4.70 (3 H, m, SCHS, SCH_2N), 4.40 (1 H, q (t on D_2O-shake), H2′), 4.20 (2 H, d, SCH_2N), 4.05 (1 H, m, H4′), 3.65 (2 H, m, H5′), 2.45 (3 H, s, CH_3), 2.30 (1 H, m, H3′); MS m/z 362 $(M + H)^+$, 384 $(M + Na)^+$. Anal. ($C_{13}H_{19}N_3O_5S_2$) C, H, N.

1-[3-Deoxy-3-*C*-(4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yl)-β-D-*arabino*-pentofuranosyl]thymine (18). 1-(2,3-Epoxy-5-*O*-trityl-β-D-*lyxo*-pentofuranosyl)thymine[20] (4.81 g, 9.97 mmol) was reacted as in the synthesis of compound **15** above. Purification was effected by flash silica column chromatography with chloroform–ethanol 17:1, to give **16** as an off-white foam (4.62 g, 75%). A sample was reprecipitated from aqueous ethanol to give a white powder: UV λ_{max} 267 nm (ε 9860); λ_{min} 242 nm (ε 4070); ^{1}H NMR δ 11.32 (1 H, s, NH), 7.46–7.27 (16 H, m, H6, trityl), 5.95 (1 H, d, J = 4.45 Hz, H1′), 5.62 (1 H, d, OH-2′), 4.68 (3 H, m, SCHS, SCH_2N), 4.38 (1 H, q (t on D_2O-shake), H2′), 4.19–4.11 (3 H, m, H4′, SCH_2N), 3.30 (2 H, m, H5′), 2.50 (1 H, m, H3′), 2.43 (3 H, s, CH_3); MS m/z 618 $(M + H)^+$, 640 $(M + Na)^+$, 374 $(M - Ph_3C)^+$, 243 $(Ph_3C)^+$. **16** (1.29 g, 2.10 mmol) was dissolved in a mixture of dichloromethane (70 mL) and dichloroacetic acid (7.7 mL). TLC showed reaction to a more polar product to be complete within 10 min. The solution was neutralized with sodium methoxide (ca. 5 g) and partitioned between chloroform and water. The aqueous layer was then repeatedly extracted with ethyl acetate until no further nucleoside was taken up. The combined ethyl acetate washings were dried ($MgSO_4$), filtered, and evaporated to an off-white solid. This was chromatographed on a silica column with chloroform–ethanol 15:1 to give **18** as a white foam (0.54 g, 69%). A sample was recrystallized from ethyl acetate–petroleum ether: UV λ_{max} 268 nm (ε 9990); λ_{min} 234 nm (ε 2240); λ_{max} 210 nm (ε 8400); ^{1}H NMR δ 11.26 (1 H, s, NH), 7.59 (1 H, s, H6), 5.85 (1 H, d, J = 4.70 Hz, H1′), 5.57 (1 H, d, OH-2′), 5.10 (1 H, m, OH-5′), 4.81–4.73 (3 H, m, SCHS, SCH_2N), 4.40 (1 H, q (t on D_2O-shake), H2′), 4.10 (2 H, d, SCH_2N), 4.02 (1 H, m, H4′), 3.67 (2 H, m, H5′), 2.48 (3 H, s, NCH_3), 2.31 (1 H, m, H3′), 1.76 (3 H, s, CH_3); MS m/z 376 $(M + H)^+$, 398 $(M + Na)^+$, 751 $(2M + H)^+$, 773 $(2M + Na)^+$. Anal. ($C_{14}H_{21}N_3O_5S_2$) C, H, N.

General Procedure for the Synthesis of *O*-(*tert*-Butyldiphenylsilyl) Nucleosides. Nucleoside (1 mmol) was dissolved in dry DMF (4.4 mL) and dry triethylamine (0.17 mL, 1.22 mmol) and DMAP (30 mg, 0.247 mmol) were added, followed by dropwise addition of *tert*-butylchlorodiphenylsilane (0.283 mL, 1.09 mmol). This was stirred at room temperature with exclusion of moisture overnight, producing copious white crystalline deposit. Water (0.5 mL) was added and the clear solution stirred for 30 min. Solvent was removed under high vacuum, and the orange gum triturated with water. The water was decanted off and the process repeated to give a white gum. This was taken up in acetone and evaporated, repeating the process to obtain a white foam. This was purified by silica column chromatography.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-3-*C*-(4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yl)-β-D-*arabino*-pentofuranosyl]uracil (19). **17** (200 mg, 0.553 mmol) was reacted with *tert*-butylchlorodiphenylsilane by the general procedure and the crude product was chromatographed on a silica column with chloroform–ethanol 9:1 to give **19** as a white foam (196 mg, 62%): UV λ_{max} 263 nm (ε 10860); λ_{min} 236 nm (ε 4510); ^{1}H NMR δ 11.30 (1 H, s, NH), 7.70–7.30 (11 H, m, H6, Ph_2), 5.95 (1 H, d, J = 4.7 Hz, H1′), 5.60 (1 H, d, OH-2′), 5.10 (1 H, d, H5), 4.80 (3 H, m, SCHS, SCH_2N), 4.40 (1 H, q (t on D_2O-shake), H2′), 4.20 (3 H, m, H4′, SCH_2N), 3.95 (2 H, m, H5′), 2.50 (3 H, s, NCH_3), 2.00 (1 H, m, H3′), 1.00 (9 H, s, *t*Bu); MS m/z 600 $(M + H)^+$, 488 $(M - base)^+$. Anal. ($C_{29}H_{37}N_3O_5S_2Si$) C, H, N.

1-5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-3-*C*-(4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yl)-β-D-*arabino*-pentofuranosyl]thymine (20). **18** (0.412 g, 1.098 mmol) was silylated by the general procedure and the crude product was purified by elution from a silica column by flash chromatography with chloroform–ethanol 20:1 to give **20** as a white powder (0.45 g, 67%). A sample was reprecipitated from ethanol with hexane: UV λ_{max} 268 nm (ε 9840); λ_{min} (ε 870); ^{1}H NMR δ 11.31 (1 H, s, NH), 7.73–7.38 (11 H, m, H6, trityl), 5.91 (1 H, d, J = 4.70 Hz, H 1′), 5.87 (1 H, d, OH-2′), 4.80–4.71 (3 H, m, SCHS, SCH_2N), 4.44 (1 H, q (t on D_2O-shake), H2′), 4.23–4.13 (3 H, m, H4′, SCH_2N), 4.03–3.89 (2 H, m, H5′), 2.55 (1 H, m, H3′), 2.45 (3 H, s, NCH_3), 1.50 (3 H, s, CH_3), 1.05 (9 H, s, *t*Bu); MS m/z 614 $(M + H)^+$, 636 $(M + Na)^+$. Anal. ($C_{30}H_{39}N_3O_5S_2Si$) C, H, N.

General Procedure for the Hydrolysis of 3′-*C*-(4,5-Dihydro-5-methyl-1,3,5-dithiazin-2-yl) Nucleosides. 3′-*C*-(4,5-Dihydro-5-methyl-1,3,5-dithiazin-2-yl) nucleoside (0.52 mmol) was dissolved in 15% (v/v) aqueous THF and the reaction vessel purged with nitrogen. To this, with rapid stirring, was added red mercuric oxide (0.247 g, 1.145 mmol) followed by mercuric chloride (0.310 g, 1.145 mmol), causing deposition of a white precipitate. Stirring was continued, and reaction was followed by TLC (TLC samples were prepared by dilution with THF, treatment with sodium sulphide (1 M), and spotting of the supernatant solution). After the desired reaction time the mixture was diluted with THF (20 mL) and treated with aqueous sodium sulfide (1 M, 2.30 mL). The black precipitate was filtered off, and the filtrate was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$), filtered, and evaporated.

General Procedure for the Reduction of 3′-*C*-Formyl Nucleosides with Sodium Borohydride. 3′-*C*-Formyl nucleoside (0.364 mmol) was dissolved in a mixture of ethanol and water (75:25 v/v; 3.15 mL). A solution of sodium borohydride (48 mg, 2.54 mmol) in ethanol (7.5 mL) was then added in a dropwise manner at room temperature with stirring. After 30 min TLC showed no remaining starting material and formation of more polar product. The whole mixture was then taken up in ethyl acetate (35 mL) and washed with water. The organic layer was dried, filtered, and evaporated to a white foam.

General Procedure for the Deprotection of (*tert*-Butyldiphenylsilyl) Nucleosides with Tetrabutylammonium Fluoride. (*tert*-Butyldiphenylsilyl) nucleoside (0.40 mmol) was dissolved in dry THF (20 mL) and tetrabutylammonium fluoride (dried under high vacuum) (0.140 g, 0.535 mmol) was added. Stirring was continued with exclusion of moisture until TLC

indicated complete reaction. Solvent was then removed in vacuo.

1-[3-Deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]uracil (7). **19** (0.606 g, 1.011 mmol) was hydrolyzed according to the general procedure at 0 °C for 5 min. The crude residue was chromatographed on a silica column with chloroform–ethanol 15:1. Evaporation of solvent gave **21** as a white foam (0.43 g, 85%): UV λ_{max} 263 nm (ε 9045); ^{1}H NMR δ 11.35 (1 H, s, NH), 9.70 (1 H, d, CHO), 7.70–7.35 (11 H, m, H6, Ph_2), 6.05 (1 H, d, J = 5.44 Hz, H1'), 5.95 (1 H, d, OH-2'), 5.30 (1 H, d, H5), 4.80 (1 H, q (t on D_2O-shake), H2'), 4.30 (1 H, m, H4'), 4.00–3.80 (2 H, m, H5'), 3.15 (1 H, t, H3'), 1.00 (9 H, s, *t*Bu); MS m/z 495 $(M + H)^+$. Reduction of **21** (0.18 g, 0.36 mmol) with sodium borohydride according to the general procedure followed by silica column chromatography with chloroform–ethanol 9:1 as solvent gave **1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]uracil (23)** as a white foam (0.13 g, 70%); ^{1}H NMR δ 11.25 (1 H, s, NH), 7.70–7.40 (11 H, m, H6, Ph_2), 5.95 (1 H, d, J = 5.44 Hz, H1'), 5.50 (1 H, d, OH-2'), 5.20 (1 H, d, H5), 4.85 (1 H, t, OH-3''), 4.20 (1 H, q (t on D_2O-shake), H2'), 4.00–3.80 (3 H, m, H4', H5'), 3.55 (2 H, m, H3''), 2.20 (1 H, m, H3'), 1.05 (9 H, s, *t*Bu); MS m/z 497 $(M + H)^+$, 519 $(M + Na)^+$. **23** (0.15 g, 0.30 mmol) was desilylated according to the general proceudre, all reactant being consumed in 2 min. Purification of the crude product was achieved by silica column chromatography with chloroform–ethanol 2:1 as eluent. Reduction of the solvent volume in vacuo resulted in crystallization of **7** as a white solid. Evaporation of the mother liquor gave a white foam (total yield, 69 mg, 89%): UV λ_{max} 263 nm (ε 9730); λ_{min} 230 nm (ε 830); ^{1}H NMR δ 11.21 (1 H, bd, NH), 7.79 (1 H, d, H6), 5.89 (1 H, J = 5.19 Hz, H1'), 5.55 (1 H, d, H5), 5.39 (1 H, d, OH-2'), 5.03 (1 H, t, OH-5'), 4.83 (1 H, t, OH-3''), 4.18 (1 H, q (t on D_2O-shake), H2'), 3.78 (1 H, m, H4'), 3.61 (2 H, m, H-5'), 3.52 (2 H, m, H-3''), 2.30 (1 H, m, H3'); MS m/z 259 $(M + H)^+$. Anal. ($C_{10}H_{14}N_2O_6$) C, H, N.

1-[3-Deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]thymine (8). **20** (1.01 g, 1.65 mmol) was treated with mercuric oxide and mercuric chloride according to the general procedure for 5 min at 0 °C and worked up in the usual way to give a white foam. This was flash column chromatographed on silica with chloroform–ethanol 15:1 as solvent. Evaporation of fractions in vacuo afforded **1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-*C*-formyl-β-D-*arabino*-pentofuranosyl]thymine (22)** as a white solid (0.75 g, 90%): ^{1}H NMR δ 11.33 (1 H, s, NH), 9.71 (1 H, d, CHO), 7.67–7.33 (11 H, m, H6, Ph_2), 6.02 (1 H, d, J = 5.69 Hz, H1'), 5.86 (1 H, d, OH-2'), 4.74 (1 H, q (t on D_2O-shake), H2'), 4.28 (1 H, m, H4'), 3.98–3.83 (2 H, m, H5'), 3.18 (1 H, m, H3'), 1.57 (3 H, s, CH_3), 1.01 (9 H, s, *t*Bu); MS m/z 509 $(M + H)^+$, 1017 $(2M + H)^+$. **22** (0.13 g, 0.256 mmol) was reduced with sodium borohydride following the general procedure. The crude **1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]thymine (24)** (100 mg, 78%) was of sufficient purity to be used directly: UV λ_{max} 269 nm (ε 11930); λ_{min} 235 nm; ^{1}H NMR δ 11.28 (1 H, s, NH), 7.68–7.35 (11 H, m, H6, Ph_2), 5.92 (1 H, d, J = 5.19 Hz, H1'), 5.38 (1 H, d, OH-2'), 4.86 (1 H, t, OH-3''), 4.18 (1 H, q (t on D_2O-shake), H2'), 3.87 (3 H, m, H4', H5'), 3.53 (2 H, m, H3''), 2.18 (1 H, m, H3'), 1.53 (3 H, s, CH_3), 1.02 (9 H, s, *t*Bu); MS m/z 511 $(M + H)^+$, 533 $(M + Na)^+$, 1021 $(2M + H)^+$, 1043 $(2M + Na)^+$. Desilylation of **24** (100 mg, 0.196 mmol) was effected according to the general procedure. The crude residue was flash chromatographed on a silica column with chloroform–ethanol 4:1 to give **8** as a white foam (50 mg, 94%). This was recrystallized from ethyl acetate: UV λ_{max} 268 nm (ε 10140); λ_{min} 235 nm (ε 2260); λ_{max} 210 nm (ε 9030); ^{1}H NMR δ 11.20 (1 H, s, NH), 7.70 (1 H, s, H6), 5.85 (1 H, d, J = 5.4 Hz, H1'), 5.35 (1 H, d, OH-2'), 5.05 (1 H, t, OH-5'), 4.80 (1 H, t, H-3''), 4.20 (1 H, q (t on D_2O-shake), H2'), 3.80–3.50 (5 H, m, H4', H5', H3''), 2.10 (1 H, m, H3'), 1.75 (3 H, s, CH_3); MS m/z 273 $(M + H)^+$, 295 $(M + Na)^+$. Anal. ($C_{11}H_{16}N_2O_6$) C, H, N.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-2-*O*-[(phenyloxy)thiocarbonyl]-3-*C*-[[(triphenylmethyl)oxy]methyl]-β-D-*arabino*-pentofuranosyl]uracil (26). To a solution of **23** (0.37 g, 0.79 mmol) in dry pyridine (2 mL) was added triphenylmethyl chloride (0.24 g, 0.85 mmol), previously dried under high vacuum at 40 °C for 3 h. This was then heated with exclusion of moisture at 103 °C for 3.5 h. The dark brown solution was cooled, poured with vigorous stirring into iced water (20 mL) and filtered. The gummy residues were combined and dissolved in ethyl acetate. This solution was washed several times with water, and the organic phase dried over magnesium sulfate, filtered, and evaporated to an off-white foam. This was further purified by elution from a silica column with diethyl ether–hexane 4:1 to give **1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-*C*-[[(triphenylmethyl)oxy]methyl]-β-D-*arabino*-pentofuranosyl]uracil (25)** as a white solid (0.47 g, 81%): ^{1}H NMR δ 11.26 (1 H, s, NH), 7.61–7.26 (26 H, m, H6, trityl, Ph_2), 6.00 (1 H, d, J = 5.69 Hz, H1'), 5.59 (1 H, d, OH-2'), 5.14 (1 H, d, H5), 4.25 (1 H, q (t on D_2O-shake), H2'), 4.00–3.81 (3 H, m, H4', H5'), 3.16 (2 H, m, H3''), 2.40 (1 H, m, H3'), 0.99 (9 H, s, *t*Bu); MS m/z 761 $(M + Na)^+$, 783 $(M + 2Na)^+$. Anal. ($C_{45}H_{46}N_2O_6$) C, H, N. **25** (0.46 g, 0.623 mmol) was dissolved in dry acetonitrile (9 mL), and DMAP (0.154 g, 1.25 mmol) was added. To this with stirring was then added phenyl chlorothionocarbonate (0.129 mL, 0.65 mmol) in a dropwise manner. Stirring was continued at room temperature with exclusion of moisture overnight. Solvent was then removed in vacuo to give an orange foam which was dissolved in chloroform (30 mL). This was washed with successive portions (30 mL) of water, cold HCl (1 M, ×2), water, saturated sodium bicarbonate, and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated to a pale orange foam, which was chromatographed on a silica column by flash chromatography with diethyl ether–hexane 4:1. Evaporation of solvent in vacuo gave **26** (0.52 g, 98.5%) which was of sufficient purity (as indicated by TLC) for direct use. A sample was purified by further column chromatography and recrystallized from aqueous ethanol: UV λ_{max} 258 nm (ε 12300); λ_{min} 246 nm (ε 11700); ^{1}H NMR δ 11.45 (1 H, s, NH), 7.65–7.25 (30 H, m, PhO, Ph_2, Ph_3), 6.35 (1 H, d, J = 5.40 Hz, H1'), 5.95 (1 H, t, H2'), 5.45 (1 H, d, H5), 4.05–3.70 (3 H, m, H4', H5'), 3.35–3.20 (2 H, m, H3''), 2.90 (1 H, m, H3'), 1.00 (9 H, s, *t*Bu); MS m/z 875 $(M + H)^+$. Anal. ($C_{52}H_{50}N_2O_7SSi$) C, H, N.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-3-*C*-[(triphenylmethyl)oxy]methyl]-β-D-*erythro*-pentofuranosyl]uracil (27). Compound **26** (3.82 g, 4.37 mmol) was dissolved in dry toluene (90 mL), and α,α'-azobis(isobutyronitrile) (AIBN) (140 mg, 1.02 mmol) and tributyltin hydride (1.75 mL, 6.45 mmol) were added. The solution was degassed by evacuation at the water pump and then a stream of dry nitrogen was bubbled through it for 20 min. It was then heated at 75–80 °C with exclusion of moisture for 3 h. After cooling, solvent was removed in vacuo and the gum partitioned between ethyl acetate and water. The organic layer was washed with a further portion of water and then dried ($MgSO_4$), filtered, and evaporated to a gum. Elution from a silica column by flash chromatography with diethyl ether–hexane 4:1 as solvent allowed the separation of **26** (first eluted compound) (0.59 g, 15%) from **27** (0.84 g, 27%) and **25** (0.20 g, 6.2%). Samples of compounds **25** and **27** were recrystallized from aqueous ethanol. Second eluted nucleoside **27**: ^{1}H NMR δ 11.30 (1 H, s, NH), 7.75 (1 H, d, H6), 7.65–7.20 (25 H, m, Ph_2, Ph_3), 6.00 (1 H, t, H1'), 5.25 (1 H, d, H5), 4.00 3.70 (3 H, m, H4', H5'), 3.10 (2 H, m, H3''), 2.55 (1 H, m, H3'), 2.20 (2 H, m, H2'), 1.00 (9 H, s, *t*Bu); MS m/z 723 $(M + H)^+$, 745 $(M + Na)^+$. Anal. ($C_{45}H_{46}N_2O_5Si$) C, H, N. Third eluted nucleoside **25**: UV λ_{max} 263 nm (ε 9920); λ_{min} 243 nm (ε 5140); ^{1}H NMR δ 11.25 (1 H, s, NH), 7.70–7.20 (26 H, m, H6, Ph_2, Ph_3), 6.00 (1 H, d, J = 5.69 Hz, H1'), 5.60 (1 H, d, OH-2'), 5.15 (1 H, d, H5), 4.25 (1 H, q (t on D_2O-shake), H2'), 4.00–3.60 (3 H, m, H4', H5'), 3.20 (2 H, m, H3''), 2.40 (1 H, m, H3'), 1.00 (9 H, s, *t*Bu); MS m/z 761 $(M + Na)^+$, 783 $(M + 2Na)^+$. Anal. ($C_{45}H_{46}N_2O_6Si$) C, H, N.

1-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]uracil (6). Compound **27** (0.84 g, 1.162 mmol) was dissolved in a mixture of dichloroacetic acid (4.4 mL) and dichloromethane (39.6 mL). This was stirred at room temperature with exclusion of moisture for 30 min and then neutralized with sodium methoxide. The solution was diluted with dichloromethane (250 mL), washed with water, and dried over magnesium sulfate. This was then filtered and evaporated to a gum which was purified by column chromatography with chloroform–ethanol 9:1. Evaporation of solvent gave **1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]uracil (6a)** as a white foam (0.34 g, 61%): UV λ_{max} 263 nm (ε 7560); λ_{min}, 237 nm (ε 2250); ^{1}H NMR (δ 11.30 (1 H, s, NH), 7.80 (1 H, d, H6), 7.65–7.30 (10 H, m, Ph_2), 6.00 (1 H, m,

H1′), 5.20 (1 H, d, H5), 4.80 (1 H, m, OH-3″), 4.00–3.70 (3 H, m, H4′, H5′), 3.40 (2 H, m, H3″), 2.30–2.00 (3 H, m, H3′, H2′), 1.00 (9 H, s, *t*Bu); MS *m/z* 503 (M + Na)$^+$. Removal of the protecting group was effected by the general procedure. The crude gummy product was chromatographed on a silica column with chloroform–ethanol 3:1 to furnish **6** as a white foam (0.15 g, 90%). This was recrystallized from ethyl acetate: UV λ_{max} 263 nm (ϵ 7310); λ_{min} 230 nm; ^{1}H NMR δ 11.25 (1 H, s, NH), 8.00 (1 H, d, H6), 5.95 (1 H, m, H1′), 5.60 (1 H, d, H5), 5.05 (1H, t, OH-5′), 4.80 (1 H, t, OH-3″), 3.80 (1 H, m, H4′), 3.75–3.55 (2 H, m, H5′), 3.45 (2 H, d, H3″), 2.40–2.00 (3 H, m, H2′, H3′); MS *m/z* 243 (M + H)$^+$, 265 (M + Na)$^+$, 485 (2M + H)$^+$. Anal. ($C_{10}H_{14}N_2O_5 \cdot 0.2H_2O$) C, H, N.

General Procedure for the Preparation of 5-Iodouracil Analogues. Uracil derivative (0.387 mmol) was dissolved in a mixture of 1,4-dioxane (3.12 mL) and M/2 nitric acid (0.78 mL). Iodine (0.198 g, 0.775 mmol) was added and the dark red-brown solution refluxed for 3 h. The mixture was then allowed to cool and was evaporated in vacuo to a brown solid. This was repeatedly coevaporated with ethanol to give a light orange-pink solid, which was washed with diethyl ether (3 × 1 mL) and dried in vacuo.

1-[3-Deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]-5-iodouracil (9). Compound **7** (100 mg, 0.387 mmol) was iodinated by the general procedure to give **9** (0.144 g, 97%) which was chromatographed on a silica column with chloroform–ethanol 4:1 to give an analytically pure sample as a white powder: UV λ_{max} 285 nm (ϵ 8600); λ_{min} 244 nm (ϵ 840); λ_{max} 217 nm (ϵ 6990); ^{1}H NMR δ 11.62 (1 H, s, NH), 8.35 (1 H, s, H6), 5.87 (1 H, d, *J* = 5.44 Hz, H1′), 5.44 (1 H, d, OH-2′), 5.18 (1 H, t, OH-5′), 4.80 (1 H, t, H3″), 4.19 (1 H, q (t on D_2-shake), H2′), 3.80–3.40 (5 H, m, H4′, H5′, H3″), 2.07 (1 H, m, H3′); MS *m/z* 385 (M + Na)$^+$. Anal. ($C_{10}H_{13}N_2O_6I$) C, H, N.

1-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]-5-iodouracil (11). The general procedure was employed to effect iodination of the uracil moiety of compound **6** (129 mg, 0.533 mmol). The crude product was column chromatographed on silica with chloroform–ethanol 5:1 to give **11** as a white foam (90 mg, 46%): ^{1}H NMR δ 11.60 (1 H, s, NH), 8.60 (1 H, s, H6), 5.90 (1 H, m, H1′), 5.20 (1 H, t, OH-5′), 4.75 (1 H, t, OH-3″), 3.80 (1 H, d, H4′), 3.75–3.50 (2 H, m, H5′), 3.40 (2 H, m, H3″), 2.35 (1 H, m, H3′), 2.10 (2 H, m, H2′); MS *m/z* 369 (M + H)$^+$, 391 (M + Na)$^+$. Anal. ($C_{10}H_{13}N_2O_5I$) C, H, N.

(*E*)-5-[2-(Carbomethoxy)vinyl]-1-[3-deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]uracil (28). Triphenylphosphine (33 mg, 0.124 mmol), palladium(II) acetate (13.6 mg, 0.061 mmol), and triethylamine (0.23 mL) were combined in dry 1,4-dioxane 1.81 mL) and heated at 70 °C with stirring and exclusion of moisture until a deep red developed (ca. 4 min). Compound **9** (0.469 g, 1.221 mmol) was then added as a solution in dry 1,4-dioxane (3.5 mL). Methyl acrylate (0.220 mL, 2.44 mmol) was also added, and the temperature was increased to reflux for 1 h. While still hot, the solution was decanted from the brown-black residue and the supernatant cooled. Solvent was removed in vacuo to give a brown gum. This was chromatographed on a silica column by flash chromatography with chloroform–ethanol 2:1 as solvent to give the more polar **7** (0.12 g, 38%) and the less polar **28** (0.13 g, 31%). Further column chromatography gave the title compound in analytical purity: ^{1}H NMR δ 11.65 (1 H, bd, NH), 8.50 (1 H, s, H6), 7.40 (1 H, d, *J* = 17.1 Hz, C*H*=CHCO$_2$Me), 6.85 (1 H, d, *J* = 17.1 Hz, CHCO$_2$Me), 5.95 (1 H, d, *J* = 4.5 Hz, H1′), 5.45 (1 H, d, OH-2′), 5.30 (1 H, t, OH-5′), 4.80 (1 H, t, OH-3″), 4.25 (1 H, q (t on D_2O-shake), H2′), 3.85 (1 H, m, H4′), 3.70 (5 H, m, H5′, CO$_2$Me), 3.55 (2 H, m, H3″), 2.10 (1 H, m, H3′); MS *m/z* 343 (M + H)$^+$. Anal. ($C_{14}H_{18}N_2O_8$) C, H, N.

(*E*)-5-(2-Carboxyvinyl)-1-[3-deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]uracil (29). Compound **28** (0.105 g, 0.307 mmol) was dissolved in aqueous sodium hydroxide (1 M, 3.8 mL) and stirred at room temperature. After 2.5 TLC showed no remaining starting material and only base-line product. The solution was cooled in an ice bath and acidified to pH 2 with HCl (4 M). Precipitation occurred on standing. The solid was filtered, and the mother liquor reduced in volume and cooled again. Further precipitate was filtered. Combined solid **29** was dried under high vacuum (55 mg, 55%): UV λ_{max} 303 nm (ϵ 14 960); λ_{shldr} 269 nm (ϵ 8750); ^{1}H NMR δ 11.55 (1 H, bd, NH), 8.44 (1 H, s, H6), 7.28 and 6.75 (2 H, 2d, *J* = 15.8 Hz, vinyl), 5.94 (1 H, d, *J* = 5.19 Hz, H1′), 5.46 (1 H, d, OH-2′), 5.28 (1 H, m, OH-5′), 4.82 (1 H, m, OH-3″), 4.22 (1 H, q (t on D_2-shake), 3.82–3.50 (5 H, m, H4′, H5′, H3″), 2.12 (1 H, m, H3′); MS *m/z* 329 (M + H)$^+$, 351 (M + Na)$^+$. Anal. ($C_{13}H_{16}N_2O_8 \cdot 1.8H_2O$) C, H, N.

(*E*)-5-(2-Bromovinyl)-1-[3-deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]uracil (10). Compound **29** (75 mg, 0.228 mmol) was dissolved in dry DMF (0.7 mL), and potassium carbonate (68 mg, 0.53 mmol) was added. The mixture was stirred at room temperature with exclusion of moisture for 15 min. *N*-Bromosuccinimide (41 mg, 0.228 mmol) in dry DMF (0.7 mL) was then added dropwise over 10 min. After a further 30 min TLC showed a less polar product to have been formed. Solid deposits were filtered and washed well with DMF. Combined DMF solutions were evaporated under high vacuum and the gummy residue flash chromatographed on a silica column with chloroform–ethanol 4:1. Evaporation of solvent afforded **10** as an off-white foam (42 mg, 51%). A sample was further purified by semipreparative HPLC with chloroform–ethanol 4:1 as eluent: UV λ_{max} 290 nm (ϵ 10 000) λ_{min} 272 nm; λ_{max} 252 nm; ^{1}H NMR δ 11.30 (1 H, bd, NH), 8.15 (1 H, s, H6), 7.20 and 6.85 (2 H, 2d, *J* = 13.6 Hz, vinylic), 5.90 (1 H, d, *J* = 4.95 Hz, H1′), 5.45 (1 H, d, OH-2′), 5.20 (1 H, t, OH-5′), 4.85 (1 H, m, OH-3″), 4.25 (1 H, q (t on D_2O-shake), H2′), 3.85–3.35 (5 H, m, H4′, H5′, H3″), 2.15 (1 H, m, H3′). Anal. ($C_{12}H_{15}N_2O_6Br \cdot 0.6H_2O$) C, H, N.

1-[3-Deoxy-3-*C*-(hydroxymethyl)-β-D-*lyxo*-pentofuranosyl]uracil (31). **19** (300 mg, 0.52 mmol) was treated under the hydrolytic conditions of the general procedure at room temperature for 90 min. The crude white foam was chromatographed on a silica column with chloroform–ethanol 9:1 to give a mixture of two very closely running, inseparable compounds. This mixture was reduced with sodium borohydride according to the general procedure. The crude product was chromatographed on a silica column with chloroform–ethanol 9:1 allowing separation of **23** and **30**. First eluted nucleoside **30** (13 mg, 5%): UV λ_{max} 264 nm (ϵ 8750); ^{1}H NMR δ 11.35 (1 H, s, NH), 7.85 (1 H, d, H6), 7.70–7.35 (10 H, m, Ph$_2$), 5.70 (1 H, s, H1′), 5.65 (1 H, d, OH-2′), 5.05 (1 H, d, H5), 4.60 (1 H, t, OH-3″), 4.20 (1 H, t, H2′), 4.05 (2 H, m, H5′), 3.80 (1 H, m, H4′), 3.65–3.45 (2 H, m, H3″), 2.35 (1 H, m, H3′), 1.00 (9 H, s, *t*Bu); MS *m/z* 497 (M + H)$^+$, 519 (M + Na)$^+$. Second eluted nucleoside **23** (12 mg, 4.6%): ^{1}H NMR δ 11.25 (1 H, s, NH), 7.40–7.70 (11 H, m, H6, Ph$_2$), 5.95 (1 H, d, *J* = 5.44 Hz, H1′), 5.50 (1 H, d, OH-2′), 5.20 (1 H, d, H5), 4.85 (1 H, t, OH-3″), 4.20 (1 H, q (t on D_2O-shake), H2′), 4.00–3.80 (3 H, m, H4′, H5′), 3.55 (2 H, m, H3″), 2.20 (1 H, t, H3′), 1.05 (9 H, s, *t*Bu); MS *m/z* 497 (M + H)$^+$, 519 (M + Na)$^+$.

30 (0.45 g, 0.906 mmol) was treated for 10 min under the desilylation conditions of the general procedure. The crude product was flash chromatographed on a silica column. Removal of solvent in vacuo gave **31** as a white solid (0.18 g, 77%). A sample was recrystallized from ethyl acetate–ethanol: mp 194–196 °C; UV λ_{max} 263 nm (ϵ 10 390); λ_{min} 231 nm (ϵ 2010); λ_{max} 208 nm (ϵ 8300); ^{1}H NMR δ 11.35 (1 H, s, NH), 8.15 (1 H, d, H6), 5.70–5.55 (3 H, m, H5, H1′, OH-2′), 5.15 (1 H, t, OH-5′), 4.55 (1 H, t, OH-3″), 4.20 (1 H, t, H2′), 4.00 (1 H, d, H4′), 3.85–3.40 (4 H, m, H5′, H3″), 2.20 (1 H, m, H3′); MS *m/z* 259 (M + H)$^+$, 281 (M + Na)$^+$, 517 (2M + H)$^+$. Anal. ($C_{10}H_{14}N_2O_6$) C, H, N.

1-[3-Deoxy-3-*C*-(hydroxymethyl)-β-D-*lyxo*-pentofuranosyl]-5-iodouracil (32). Compound **31** (70 mg, 0.271 mmol) was iodinated according to the general procedure. The crude product was reprecipitated from aqueous ethanol to give **32** as a white solid (69 mg, 66%): mp 199–200 °C; UV λ_{max} 288 nm (ϵ 8240); ^{1}H NMR 11.64 (1 H, s, NH), 8.75 (1 H, s, H6), 5.61 (2 H, m, H1′, OH-2′), 5.31 (1 H, t, OH-5′), 4.49 (1 H, t, OH-3″), 4.18 (1 H, q (t on D_2O-shake), H2′), 3.98 (1 H, d, H4′), 3.70–3.40 (4 H, m, H5′, H3″), 2.25 (1 H, m, H3′); MS *m/z* 385 (M + H)$^+$, 770 (2M + H)$^+$. Anal. ($C_{10}H_{13}N_2O_6I$) C, H, N.

1-(3-Deoxy-3-*C*-formyl-β-D-*lyxo*-pentofuranosyl)uracil 3′,5′-*O*-Hemiacetal (33). **21** (200 mg, 0.404 mmol) was treated with tetrabutylammonium fluoride by the general procedure; complete reaction was observed to have occurred in 5 min. Elution of the crude product from a silica column with chloroform–ethanol 3:1 by flash chromatography gave **33** as a white foam (60 mg, 58%). A sample was recrystallized from methanol: UV λ_{max} 262 nm (ϵ 9140); λ_{min} 229 nm (ϵ 620); ^{1}H NMR δ 11.30 (1 H, bd, NH), 7.45

(1 H, d, H6), 6.10 (1 H, m, OH-3″), 5.85 (1 H, d, H1′), 5.60 (3 H, m, H5, H3″, OH-2′), 4.60 (1 H, d, H4′), 4.45 (1 H, m, H2′), 3.95 (2 H, s, H5′), 2.85 (1 H, t, H3′); MS m/z 257 $(M + H)^+$, 279 $(M + Na)^+$. Anal. ($C_{10}H_{12}N_2O_6$) C, H, N.

1-(3-Deoxy-3-*C*-formyl-β-D-*lyxo*-pentofuranosyl)thymine 3′,5′-*O*-Hemiacetal (34). **22** (0.16 g, 0.315 mmol) was deprotected following the general procedure with a reaction time of 7 min. The crude product was flash column chromatographed with chloroform–ethanol 6:1 on silica, to give **34** as a white solid (50 mg, 59%). A sample was recrystallized from methanol: UV λ_{max} 267 nm (ε 9395); λ_{min} 233 nm (ε 1140); ^{1}H NMR δ 11.29 (1 H, s, NH), 7.34 (1 H, s, H6), 6.13 (1 H, d, OH-3″), 5.80 (1 H, d, H1′), 5.53 (2 H, m, H3″, OH-2′), 4.59 (1 H, m, H4′), 4.44 (1 H, m, H2′), 3.96 (2 H, m, H5′), 2.83 (1 H, t, H3′), 1.74 (3 H, s, CH_3); MS m/z 271 $(M + H)^+$. Anal. ($C_{11}H_{14}N_2O_6$) C, H, N.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-epoxy-β-D-*lyxo*-pentofuranosyl]uracil (35). Dry 5′-*O*-(*tert*-butyldiphenylsilyl)uridine[23] (6.46 g, 13.39 mmol) was dissolved in dry pyridine (81 mL) and cooled to 0 °C. Methanesulfonyl chloride (2.28 mL, 29.4 mmol) in dry pyridine (26 mL) was then added with stirring over a period of 1 h, with exclusion of moisture. The orange solution was stored at 4 °C for 48 h and then poured into ice water (400 mL). The solid was filtered, washed well with water, and taken up in ethyl acetate. After washing several times with water, the mixture was dried ($MgSO_4$), filtered, and evaporated to an off-white foam (7.75 g, 91%): UV λ_{max} 258 nm (ε 9500); ^{1}H NMR δ 11.50 (1 H, s, NH), 7.75–7.40 (11 H, m, H6, Ph_2), 6.00 (1 H, d, H1′), 5.80–5.30 (3 H, m, H5, H2′, H4′), 4.30 (1 H, m, H3′), 3.95 (2 H, m, H5′), 3.35 (6 H, 2 s, SO_2CH_3), 1.00 (9 H, s, *t*Bu). This was dissolved in the minimum amount of acetone, and sodium hydroxide (1 M, 43 mL) was slowly added with stirring, while the solution was maintained by prudent additions of acetone. Stirring was continued at room temperature overnight, giving rise to a slightly less polar nucleoside as indicated by TLC. The orange solution was neutralized with hydrochloric acid (1 M), causing some precipitation. The whole was then partitioned between ethyl acetate and water and the organic layer dried ($MgSO_4$) and evaporated to an off-white foam. A sample was chromatographed on a silica column with diethyl ether–hexane 4:1 to give 35 as a white solid (4.06 g, 72%): UV λ_{max} 259 nm (ε 10 590); λ_{min} 236 nm (ε 5180); ^{1}H NMR δ 11.40 (1 H, bd, NH), 7.75–7.35 (11 H, m, H6, Ph_2), 6.10 (1 H, s, H1′), 5.60 (1 H, d, H5), 4.30–3.70 (5 H, m, H2′, H3′, H4′, H5′), 1.00 (9 H, s, *t*Bu); MS m/z: 465 $(M + H)^+$, 487 $(M + Na)^+$. Anal. ($C_{25}H_{28}N_2O_5Si$) C, H, N.

Antiviral Assay Procedures. The human immunodeficiency virus (HIV) assay was based on the ability of compound to reverse HIV-mediated growth inhibition in MT-4 cells infected with the HTLV-III_B strain grown in T-cell line H9. The test involved infection of cells (1 h at 37 °C with 10 $TCID_{50}$ HIV) followed by immediate exposure to the candidate drug at concentrations of 100, 10, 1, and 0.1 μM. Mock infected cells were used as controls for all drug concentrations on the same 96-well dish, allowing a simultaneous assessment of toxicity (by growth inhibition). Triplicate wells were used for infected or uninfected cells at each drug concentration. After 5 days cell number was assessed by the uptake of a tetrazolium dye MTT into viable cells, extraction with acidified propan-2-ol, and spectrophotometric determination.

For the cytomegalovirus assay, monolayers of MRC-5 cells were formed in 24-well tissue culture panels. After 24 h the wells were infected and overlaid with 0.5% indubiose A37 medium. The candidate drug was dissolved in a suitable solvent and incorporated into the overlay medium at 10 and 100 μM. After 5 days giant cells (plaques) were visualized by methylene blue stain and examined by microscope.

The other antiviral assays were based on plaque reduction. Confluent monolayers of the appropriate cells in 50-mm diameter plastic petri dishes were infected with a suspension of the virus and overlaid with nutrient agarose in which the candidate drug was dissolved in doubling dilutions. After 5 days plaques were counted and estimated as a percentage of the control and plotted against the logarithm of the compound concentration. From this the IC_{50} was determined.

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S-[2-[(2′-Carbamoylethyl)amino]ethyl] Phosphorothioate and Related Compounds as Potential Antiradiation Agents

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A reinvestigation of the radiation protection activity of *S*-[2-[(2′-carbamylethyl)amino]ethyl] lithium hydrogen phosphorothioate (**4a**) revealed that this compound possessed good (70% protection at a dose of 600 mg/kg) activity. The thione and imino bioisosteres of **4**, *S*-[2-(2′-thiocarbamylethylamino)ethyl] lithium hydrogen phosphorothioate (**13a**) and *S*-[2-(2′-amidinoethylamino)ethyl] phosphorothioic acid (**18b**) showed 100% protection at doses of 300 and 150 mg/kg, respectively. The *N*-methyl (**4b**) and *tert*-butyl (**4c**) analogues of amide **4a**, the *N*-methyl (**13b**) analogue of the thioamide **13a**, the *N*-methyl (**18a**) analogue of amidine (**18b**), and the cyclic amidine *S*-[2-[[2′-(4,5-dihydroimidozoyl)ethyl]amino]ethyl] lithium hydrogen phosphorothioate (**21**) all showed 80% protection at the highest dose tested.

In 1959 the U.S. Army Medical Research and Development Command initiated a program of drug development for chemoprophylactic agents that would protect personnel against ionizing radiation. The most effective radioprotective agent developed in the 1959–1972 U.S. Army Program was *S*-[2-[3-aminopropylamino]ethyl] dihydrogen phosphorothioate (**1**, WR2721).[1-3] This compound is the phosphorothioate derivative of 2-[(3-aminopropyl)-amino]ethanethiol (**2**, WR1065). Compound **2** has been shown to be active in radioprotection,[2] and it is believed that **1** serves as a prodrug which releases **2** in tissue

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