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# 2′ AND 3′-KETONUCLEOSIDES AND THEIR *ARABINO* AND *XYLO* REDUCTION PRODUCTS

## CONVENIENT ACCESS *VIA* SELECTIVE PROTECTION AND OXIDATION OF RIBONUCLEOSIDES†

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**Abstract**—A number of 2′,5′- or 3′,5′-diprotected ribonucleosides and 5′-protected 2′- or 3′-deoxy-β-D-*erythro*-pentofuranosyl nucleosides have been oxidized to the corresponding 3′ or 2′-ketonucleoside derivatives using chromium trioxide/pyridine/acetic anhydride or dimethyl sulfoxide/ acetic anhydride. Reduction of the carbonyl functions with sodium borohydride gave the inverted *arabino*, *xylo*, or deoxy-*threo* isomers as predominant products by attack at the less hindered α-face of the sugar ring. Parallel reductions using sodium borodeuteride corroborated the epimeric ratios by demonstrating that complete oxidation of the original hydroxyl groups had occurred. The deuterium labeling also aided in making NMR spectral assignments.

Ketosugar nucleosides are potentially very useful synthetic intermediates for the preparation of a variety of sugar-modified products since the organic chemistry of the CO group has been developed so extensively. However, these pentofuranulosyl nucleosides have been considered to be rather inaccessible and of limited applicability owing to their reported instability, especially under basic conditions, and the difficulty in obtaining appropriately protected precursors.[2] Early attempts to prepare the 3′-ketonucleoside from 5′-O-tritylthymidine using chromium trioxide/pyridine as oxidant resulted in loss of the thymine base.[3] Oxidation of 5′-O-acetylthymidine under the mild Pfitzner–Moffatt conditions (dimethyl sulfoxide/dicyclohexylcarbodiimide/pyridinium trifluoroacetate) resulted in spontaneous β-elimination of thymine.[4]

Moffatt *et al.* separated 3′,5′- and 2′,5′-di-O-trityluridine[5] and cytidine[6] derivatives from tritylation mixtures and subjected them to their DMSO/DCC oxidation to obtain the first reported furanosyl 2′- and 3′-ketonucleosides. Treatment of these compounds with sodium borohydride gave epimers of the starting ribonucleosides. Rosenthal *et al.* treated 9-(3,5-O-isopropylidene-β-D-xylofuranosyl)adenine with ruthenium tetroxide to give a furanosyl purine 2′-ketonucleoside.[7] Antonakis *et al.*[8,9] have oxidized several hexopyranosyl theophylline and related nucleoside derivatives to give 2′ and 4′-keto pyranosyl products using Pfitzner–Moffatt and chromium reagents. Sasaki *et al.* have reported the formation of 2′-keto furanosyl pyrimidine nucleosides from elimination sequences.[10,11]

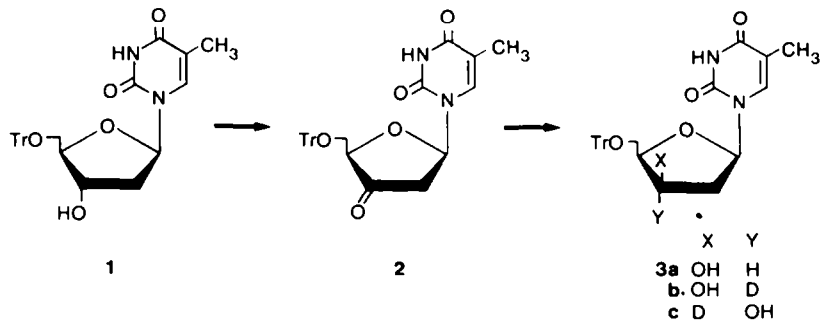
The first isolation of a 3′-keto-2′-deoxynucleoside was reported by Binkley *et al.* in 1977.[12,13] The 3′-pyruvate ester of 5′-O-tritylthymidine was subjected to photolysis in dry benzene to give the 3′-keto-5′-O-tritylthymidine product in 61% yield.

A recently described $CrO_3$/pyridine/$Ac_2O$ complex (1:2:1 molar ratio) was reported by Garegg *et al.* to oxidize selectively protected carbohydrate derivatives smoothly.[14,15] We have examined oxidations of a number of protected nucleosides with this reagent[1] and with DMSO/$Ac_2O$. High yields of the conveniently accessible 2′ and 3′-ketonucleosides have been obtained in most cases. The first *chemical* oxidation of 5′-O-tritylthymidine to give its 3′-keto product has been effected in 87% recrystallized yield and the first example of a 3′-keto furanosyl purine nucleoside has been obtained. A 4-stage sequence has been developed for the conversion of ribo to arabino nucleosides by selective 3′,5′-protection of the ribonucleoside, oxidation of the 2′-OH group, stereoselective reduction of the derived 2′-CO function, and deprotection of the resulting arabinonucleoside. Although attack of borohydride at the less hindered α-face of the sugar ring is predominant in all cases, different ratios of epimeric alcohols are produced. The 2′- or 3′-location of the CO group, OH protecting groups, and heterocyclic base at C1′ appear to exert effects on the reduction stereoselectivity. Corroborative measurement of the ratios of deuterionucleosides produced by treatment of the carbonyl intermediates with sodium borodeuteride has been employed to exclude the possibility of having carried incompletely oxidized starting material through the sequence.

### RESULTS AND DISCUSSION

Treatment of 1 mmol of 5′-O-tritylthymidine (**1**) with 3 molar equivs of the preformed complex of $CrO_3$(1)/pyridine(2)/$Ac_2O$(1) in 7 mL of $CH_2Cl_2$ for 45 min at room temperature was followed by addition of the mixture to 50 mL of ethyl acetate and filtration of the resulting suspension using a 1 cm layer of silica gel. Evaporation of the filtrate gave a colorless crystalline solid that was recrystallized to provide an 87% yield of 1-(5-O-trityl-β-D-*glycero*-pentofuran-3-ulosyl) thymine (**2**). This product has an identical

†This paper constitutes Nucleic Acid Related Compounds. 44. For the previous paper in this series, see Ref. 1. Dedicated to Prof. Dr. Friedrich Cramer on the occasion of his 60th birthday.




melting point with that reported and was obtained in some 25% higher yield than by the noted photochemical procedure.[12,13]

Reduction of **2** with sodium borohydride had been reported to give 1-(2-deoxy-5-O-trityl-β-D-*threo*-pentofuranosyl)thymine (**3a**).[13] However, preparative TLC of the mixture resulting from treatment of our unpurified **2** with sodium borohydride gave **3a** (77%) plus a minor quantity (8.7%) of 5′-O-tritylthymidine (**1**). In order to evaluate the possibility that some unchanged **1** had been carried through the sequence, a parallel reduction of unpurified **2** was repeated using sodium borodeuteride. Preparative TLC resolved a 79% yield of 1-(2-deoxy-3-deuterio-5-O-trityl-β-D-*threo*-pentofuranosyl)thymine (**3b**) and 9% of 3′-deuterio-5′-O-tritylthymidine (**3c**). The reduction stereoselectivity for the *threo/erythro* epimers at C3′ is pronounced (~9:1) but not exclusive.

Ogilvie *et al.* have reported the preparation and facile chromatographic separation of the 2′,5′ and 3′,5′-bis-O-(t-butyldimethylsilyl)† derivatives of uridine and adenosine.[16] Subsequent to completion of this phase of our work, specific catalysts were reported to enhance the 2′,5′- vs 3′,5′-protection selectivities for the TBDMS group.[17]

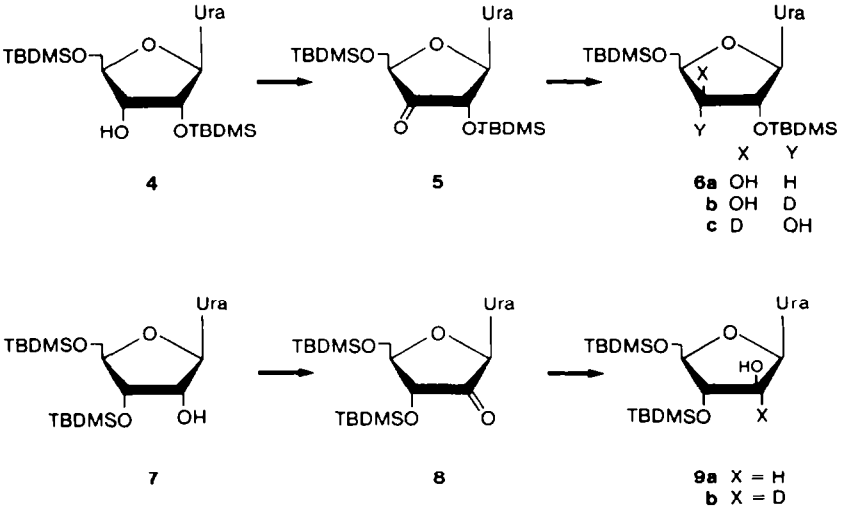
Oxidation of 2′,5′-bis-O-TBDMS-uridine (**4**) by the general procedure used for the conversion of **1**→**2** gave 1-(2,5-bis-O-TBDMS-β-D-*erythro*-pentofuran-3-ulosyl)uracil (**5**) in 89% purified yield. Reduction of **5** with sodium borohydride gave 98% of an analytically pure amorphous glass with a ratio (¹H NMR) of the *xylo* (**6a**) to *ribo* (**4**) epimers of 82:18. Repetition of this reduction using sodium borodeuteride gave 1-(2,5-bis-O-TBDMS-3-deuterio-β-D-xylofuranosyl)uracil (**6b**) and 2′,5′-bis-O-TBDMS-3′-deuteriouridine (**6c**) with the identical 82:18 ratio.

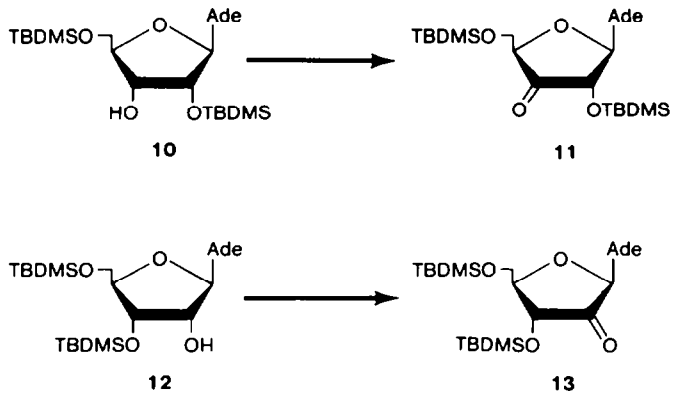
Analogous oxidation of 3′,5′-O-TBDMS-uridine (**7**) gave 1-(3,5-bis-O-TBDMS-β-D-*erythro*-pentofuran-2-ulosyl)uracil (**8**) in 89% purified yield. Reduction of **8** with sodium borohydride or borodeuteride gave the unlabeled **9a** or 1-(3,5-bis-O-TBDMS-2-deuterio-β-D-arabinofuranosyl)-uracil (**9b**) in 97 or 98% yields, respectively, as analytically pure amorphous glasses after preparative TLC. The high-field ¹H and ¹³C NMR spectra of **9a** and **9b** did not have peaks corresponding to the *ribo* epimer (**7**). Therefore, the reduction stereoselectivity at C-2′ of **8** was >95% for the *arabino* epimer (**9**), using TBDMS protecting groups, in contrast with an 82:18 *arabino/ribo* ratio reported by Cook and Moffatt for an analogous reduction of the corresponding 3′,5′-di-O-trityl-2′-ketouridine derivative.[5]

Oxidation of 2′,5′-O-TBDMS-adenosine (**10**) gave 9-(2,5-O-TBDMS-β-D-*erythro*-pentofuran-3-ulosyl) adenine (**11**) in 88% purified yield. This represents the first noted example of a 3′-keto derivative of a naturally occurring purine nucleoside. Crystalline **11** melts with decomposition at 177–178° and is stable at room temperature.

Treatment of 3′,5′-bis-O-TBDMS-adenosine (**12**) under the usual oxidation conditions gave 9-(3,5-bis-O-TBDMS-β-D-*erythro*-pentofuran-2-ulosyl)-adenine (**13**) in 84% yield as an off-colored crystalline product with no defined mp. The presence of

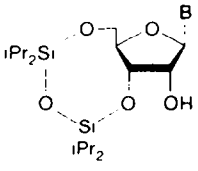
†Hereafter abbreviated TBDMS for t-butyldimethylsilyl.



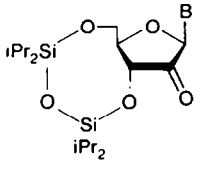



Cr was suggested by line broadening and doubling of some peaks in the $^1$H NMR spectrum, and poor agreement with theory was observed with the microanalytical results. Rechromatography on silica gel produced a colorless product which, however, retained some doubling of the base and anomeric proton signals. This presumed complexing with Cr proved to be troublesome with other purine-type nucleosides. Therefore, the Pfitzner–Moffatt type oxidation using DMSO/$Ac_2O$[18] was used routinely for the conversion of ribo to arabinonucleosides for biological evaluation (*vide infra*).

Oxidation of 3′,5′-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)inosine† (**14**) with $CrO_3$/pyridine/$Ac_2O$ gave the corresponding 9-(3,5-O-TPDS-β-D-*erythro*-pentofuran-2-ulosyl)hypoxanthine (**15**) in 80% yield as an off-white glassy solid. This product also experienced $^1$H NMR line broadening, had no defined mp, and gave poor microanalytical agreement with theory. Further chromatography resulted in significant purification from presumed metal contaminants.




**14** B = Hyp
**16** B = Ura
**18** B = Cyt




**15** B = Hyp
**17** B = Ura
**19** B = Cyt

Analogous oxidation of 3′,5′-O-TPDS-uridine (**16**) proceeded smoothly to give 1-(3,5-O-TPDS-β-D-*erythro*-pentofuran-2-ulosyl)uracil (**17**) in 93% yield as an analytically pure and colorless amorphous glass. Similarly, oxidation of 3′,5′-O-TPDS-cytidine (**18**) proceeded without incident to give the colorless crystalline 1-(3,5-O-TPDS-β-D-*erythro*-pentofuran-2-ulosyl)cytosine (**19**) in 78% yield.

From the limited results available, it would appear that complexing may occur with ring N atoms having "exposed" lone-pair electrons. No apparent complexing difficulties have been observed with any of our thymine or uracil compounds, which have the pyrimidin-2,4-dione system with "covered" (NH) ring N's. The one cytosine example (**18**) with an "exposed" N3 was converted to its 2′-ketosugar product (**19**) smoothly. It should be noted that the adenine nucleoside derivatives **10** and **20** also were oxidized at C3′ and C2′, respectively, without complications and both have "exposed" basic ring N's. Therefore, it cannot be concluded that a basic pyrimidine ring will escape complexing or that a given purine compound will be susceptible with the evidence presently at hand.

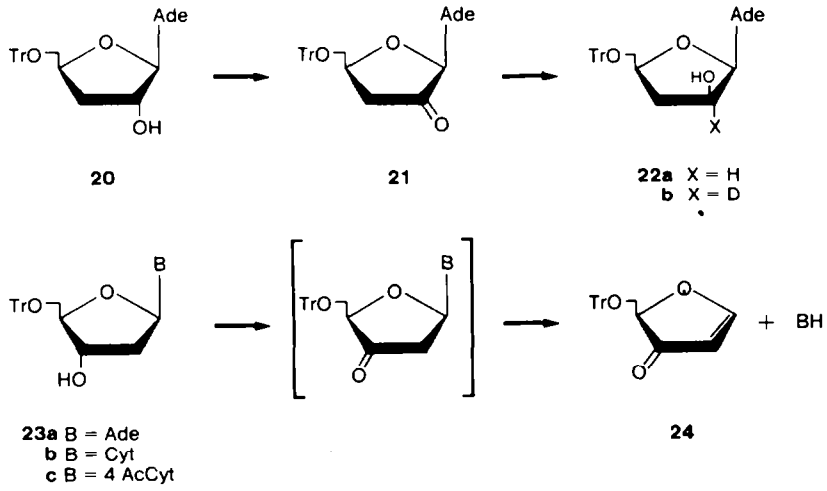
Tritylation of 3′-deoxyadenosine in the usual manner gave 3′-deoxy-5′-O-trityladenosine (**20**). Oxidation of **20** with $CrO_3$/pyridine/$Ac_2O$ gave 9-(3-deoxy-5-O-trityl-β-D-*glycero*-pentofuran-2-ulosyl) adenine (**21**) in 67% crystalline yield. Reduction of crude **21** with sodium borohydride or borodeuteride followed by preparative TLC and recrystallization of the product gave unlabeled **22a** (50%) or 9-(3-deoxy-2-deuterio-5-O-trityl-β-D-*threo*-pentofuranosyl)adenine (**22b**; 52%) with overall yields calculated from starting **20**. None of the corresponding *erythro* epimer of **22** was detected in either of the purified reduction products.

Subjection of 2′-deoxy-5′-O-trityladenosine (**23a**), 2′-deoxy-5′-O-tritylcytidine (**23b**), and 4-N-acetyl-2′-deoxy-5′-O-tritylcytidine (**23c**) to the usual $CrO_3$/pyridine/$Ac_2O$ oxidizing conditions resulted in loss of the base from the presumed 2′-deoxy-3′-ketonucleoside intermediates. The resulting 4,5-dihydro-5-trityloxymethylfuran-4-one[13] (**24**) was characterized by $^1$H and $^{13}$C NMR and mass spectral data as a pale yellow oil. A solution of the 3′-ketothymidine derivative (**2**) in DMSO-$d_6$ at ambient operating temperature in the NMR spectrometer was found to undergo β-elimination to give **24** plus thymine. This decomposition also occurred when **2** was allowed to remain in contact with silica gel.

Treatment of 5′-O-trityluridine or its *arabino* epimer under the usual oxidizing conditions resulted in decomposition of the nucleosides. Rapid liberation of uracil and triphenylmethanol was observed.

Since the discovery of tumor inhibitory effects[19] and antiviral activity[20] of 9-β-D-arabinofuranosyladenine (araA), a substantial number of publications has appeared describing biological results.[21] The original synthesis of araA employed coupling of a derivative of D-xylose,[22,23] and subsequent coupling procedures with D-arabinose were noted.[24–26] Cyclonucleoside transformations,[27–30] 2′-triflate replacement,[31] 3′,5′-di-O-benzoyladenosine oxidation-reduction,[32] and combined chemical and enzymatic

†Hereafter abbreviated TPDS for 1,1,3,3-tetraisopropyldisilox-1,3-diyl.




(transglycosylation) procedures[33,34] have been devised. An organism that presumably[35] effects oxidation-reduction at C-2′ of adenosine is utilized for the fermentation synthesis of araA.[36] Syntheses of 2-amino-araA (2,6-diamino-9-β-D-arabinofuranosylpurine) have been effected by coupling[37] and chemical-enzymatic[34] procedures. Coupling,[38] cyclonucleoside interconversion,[39,40] and chemical-enzymatic[37,41] methods have been used to prepare 9-β-D-arabinofuranosylguanine. Ikehara's purine-O-8→C-2′-cyclonucleoside approach[27] also has been employed to convert adenosine and guanosine cyclic 3′,5′-monophosphates to the corresponding arabinosyl cyclic nucleotides.[42] We have reported an extended sequence for conversion of the pyrrolo[2,3-*d*]pyrimidine nucleoside antibiotic tubercidin into its much less cytotoxic arabinosyl epimer.[43] Seela *et al.* have reported novel phase transfer catalyzed couplings of arabinose derivatives with suitable hetrocyclic precursors to give the arabino epimer of tubercidin plus its α-anomer.[44,45]

We now have developed a general four-stage biomimetic sequence for the oxidation-reduction conversion of ribo to arabinonucleosides. Selective bis-protection of ribonucleosides using 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[46] in pyridine was followed by oxidation of the resulting partially purified 3′,5′-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl) derivatives with DMSO/$Ac_2O$. Reduction of the crude 2′-keto-3′,5′-O-TPDS intermediates *in situ* with sodium borohydride followed by deprotection using tetra-n-butylammonium fluoride gave the desired arabinonucleosides as major products. Minor quantities of the 2′-O-methylthiomethyl ether derivatives of the starting ribonucleosides were isolated as expected[18] by-products of the oxidation step. Variable minor quantities of the ribonucleosides were observed depending on the oxidation conditions. Reduction of the 2′-ketoadenosine derivative *in situ* with sodium borodeuteride resulted in a ratio of 2′-deuterio/2′-protio adenosine of ~1:1 after deprotection and purification (as estimated by $^1H$ NMR and mass spectral analysis). Therefore, some starting ribonucleoside remains unchanged during the oxidation process. Thin layer electrophoresis on cellulose strips using 0.1 M sodium borate at pH 10.0 provides a convenient evaluation of the deprotected product mixture. Anodic migration of the borate complexes of ribonucleosides is observed whereas the arabinonucleosides undergo cathodic drift at about half the mobility of the ribonucleoside 2′-O-methylthiomethyl ethers.

Adenosine (**25a**) was converted to 9-β-D-arabinofuranosyladenine (**27a**) in 63% overall yield via the 4-stage *in situ* sequence using DMSO/$Ac_2O$ as oxidant. A 67% overall yield of **27a** was realized using $CrO_3$/pyridine/$Ac_2O$, but the noted problem of presumed complexing of chromium with basic nucleosides (*vide supra*) dictated general use of the DMSO/$Ac_2O$ procedure. Overall yields of 48% of 2,6-diamino-9-β-D-arabinofuranosylpurine (**27b**), 41% of 9-β-D-arabinofuranosylguanine (**27c**), 62% of 4-amino-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine (**27d**), 36% of 4-amino-5-cyano-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine (**27e**), and 35% of 4-amino-5-carboxamido-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine (**27f**) were obtained from the parent ribonucleosides (**25b–e**), respectively. This represents the first syntheses of the arabino epimers **27e** and **27f** of the nucleoside antibiotics toyocamycin (**25e**) and sangivamycin (**25f**).

Electronegative substituent and anisotropic effects of the CO group exert major influences on the $^1H$ NMR spectra of ketonucleosides. Variable magnetic effects (usually deshielding) of the CO unit on α, β, γ and base protons can be seen in the chemical shift data of Table 1. For instance the H1′ and H4′ resonance peaks of the 3′-ketothymidine derivative (**2**) in $CDCl_3$ are shifted downfield by ~0.2 ppm relative to those of **1**. The H2′,2″ peaks are downfield shifted by ~0.5 and 0.8 ppm, and one H5′(5″) peak by ~0.3 ppm. This latter shift results in first order resolution of the ~ −11 Hz geminal coupling of the 5′-methylene protons. Decomposition of **2** in DMSO-$d_6$ solution seriously complicated measurement of its $^1H$ NMR spectrum, but its $^{13}C$ NMR peaks could be identified in this solvent (*vide infra*). The H1′ peaks for the pyrimidine 2′-ketonucleosides **8** and **19** in DMSO-$d_6$ are shifted ~0.3 ppm upfield relative to their precursor ribonucleosides **7** and **18**.[47]

Introduction of a ring CO function markedly enhanced the geminal coupling of an α-methylene unit in the deoxynucleosides, as has been noted in steroids[48] and furanose sugars.[49] Compound **2** has

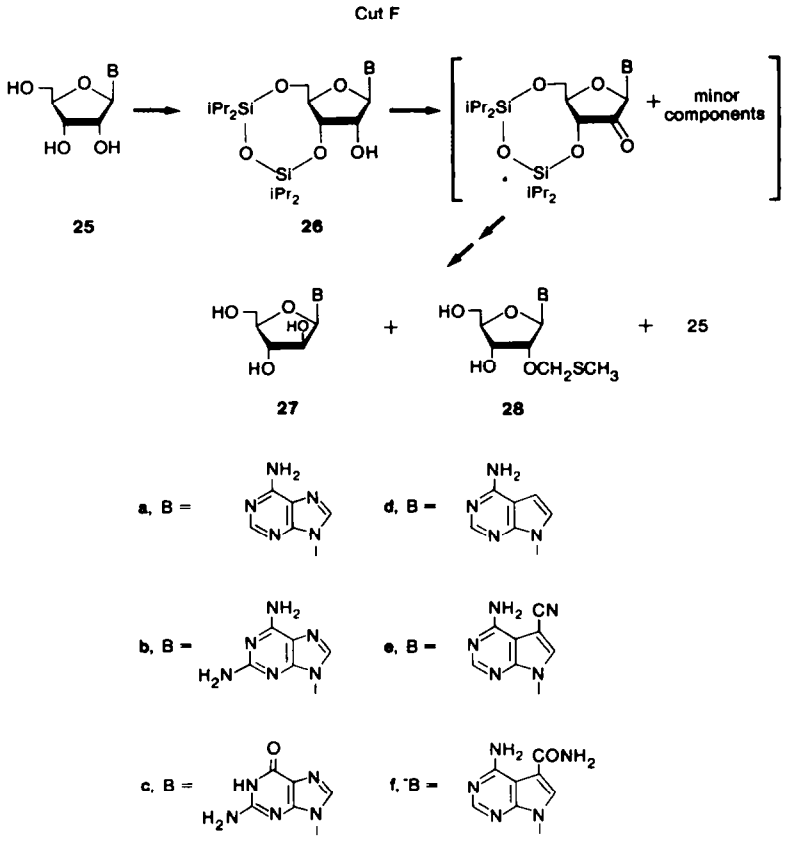



Table 1. $^1$H NMR chemical shift data[a]

| Compound | H1′[b] | H2′(2″)[c] | H3′(3″)[c] | H4′[c] | H5′(5″)[d] | H5[d] or H2[e] | H6[b] or H8[e] |
|---|---|---|---|---|---|---|---|
| 1 | 6.38[d] | 2.32 | 4.55 | 4.03[d] | 3.41[f] | | 7.53 |
| 2 | 6.58[f] | 3.11[d]<br>2.80[d] | | 4.20[g] | 3.70<br>3.45 | | 7.65[e] |
| 3a | 6.13[d] | 2.60<br>1.85[d] | 4.15 | 4.15 | 3.40[c]<br>3.18[c] | | 7.60 |
| 3b | 6.40[d] | 2.55<br>1.87[d] | | 4.15[d] | 3.42<br>3.18 | | 7.60 |
| 3c | 6.22[f] | 2.20 | | 3.89[f] | 3.36[c]<br>3.20[c] | | 7.50 |
| 4 | 5.81 | 4.10[f] | 3.93 | 3.93 | 3.86<br>3.75 | 5.40 | 7.81 |
| 5 | 6.12 | 4.27[b] | | 4.42[f] | 3.84[h] | 5.85 | 7.78 |
| 6a[i] | 5.62 | 4.09 | 3.92 | 4.12 | 3.96<br>3.85 | 5.62 | 7.72 |
| 7 | 5.77 | 4.09 | 4.09 | 3.90 | 3.83<br>3.68 | 5.60 | 7.74 |
| 8 | 5.45[e] | | 4.86[b] | 3.88 | 3.95<br>3.80 | 5.70 | 7.73 |
| 9a[j] | 6.01 | 4.04 | 4.11[f] | 3.75 | 3.82<br>3.72 | 5.54 | 7.51 |
| 10 | 5.95 | 4.63[f] | 4.15 | 4.02 | 3.95<br>3.79 | 8.14 | 8.29 |
| 11 | 6.18 | 5.28[b] | | 4.47[f] | 3.90<br>3.84 | 8.14 | 8.34 |
| 12 | 5.89 | 4.77[d] | 4.35[d] | 3.94 | 3.89<br>3.68 | 8.13 | 8.31 |

Table 1 (*Contd*)

| Compound | H1'[b] | H2'(2")[c] | H3'(3")[c] | H4'[c] | H5'(5")[d] | H5[d] or H2[e] | H6[b] or H8[e] |
|---|---|---|---|---|---|---|---|
| 13 | 6.14[e] | | 5.32[b] | 4.12[k] | 3.99<br>3.85 | 8.04 | 8.32 |
| 15 | 6.18[e] | | 5.26[b] | 4.23 | 4.08[c] | 7.82 | 8.32 |
| 17 | 5.47[e] | | 4.98[b] | 4.04 | 4.00[c] | 5.70[b] | 7.77 |
| 19 | 5.26[e] | | 5.02[b] | 4.00 | 4.00[c] | 5.76[b] | 7.65 |
| 20 | 5.96 | 4.75 | 2.40<br>1.98 | 4.52 | 3.20[h] | 8.14 | 8.20 |
| 21 | 6.14[e] | | 2.99[d]<br>2.83[d] | 4.73 | 3.40<br>3.24 | 8.01 | 8.31 |
| 22a[l] | 6.21 | 4.49 | 2.37<br>1.98 | 4.27 | 3.37<br>3.09 | 8.11 | 8.14 |
| 24 | 8.85 | 5.90[b] | | 4.79 | 3.40<br>3.30 | | |
| 27a | 6.26 | 4.13 | 4.13 | 3.78 | 3.65[c] | 8.13 | 8.18 |
| 27b | 6.09 | 4.08 | 4.08 | 3.76 | 3.65[c] | | 7.80 |
| 27c | 6.04 | 4.08 | 4.08 | 3.77 | 3.65[c] | | 7.80 |
| 27d[m] | 6.41 | 4.05 | 4.05 | 3.70 | 3.62[c] | 8.05 | 7.30 |
| 27e | 6.44 | 4.14 | 4.08 | 3.78 | 3.67[c] | 8.23 | 8.26[e] |
| 27f | 6.48 | 4.12 | 4.08 | 3.80 | 3.72[c] | 8.06 | 8.08[e] |
| 28a[n] | 6.04 | 4.81 | 4.34 | 4.01 | 3.62[c] | 8.16 | 8.40 |
| 28b[n] | 5.91 | 4.73[d] | 4.32 | 4.00 | 3.63[c] | | 8.00 |
| 28c[n] | 5.80 | 4.61[d] | 4.28 | 3.94 | 3.59[c] | | 7.95 |
| 28d[n,o] | 6.16 | 4.65[d] | 4.28 | 3.95 | 3.60[c] | 8.06 | 7.40 |
| 28e[n] | 6.24 | 4.60[d] | 4.31 | 4.01 | 3.66[c] | 8.26 | 8.50[e] |
| 28f[n] | 6.20 | 4.56[d] | 4.29 | 3.98 | 3.64 | 8.12 | 8.18[e] |

[a]Shifts in δ ppm downfield from internal $Me_4Si$ in $Me_2SO$-$d_6$ solutions (except in $CDCl_3$ for compounds 1 and 2). [b]Doublet unless noted. [c]Multiplet unless noted. [d]Doublet of doublets unless noted. [e]Singlet unless noted. [f]Apparent "triplet". [g]Broad unresolved singlet. [h]Apparent "doublet". [i]Identical spectrum for 6b except no multiplet at δ3.92 and simplification of splitting at δ4.09[b] and 4.12[f]. [j]Identical spectrum for 9b except no multiplet at δ4.04 and simplification of splitting at δ6.01[e] and 4.11[b]. [k]Doublet of doublets of doublets. [l]Identical spectrum for 22b except no multiplet at δ4.49 and simplification of splitting at δ6.21,[e] 2.37,[d] and 1.96[d]. [m]δ6.53 (d, $J_{5-6}$ = 4.0 Hz, H5). [n]Spectra of these compounds had δ~4.75 & 4.64 (d & d, $J_{gem}$ = 11.5 Hz, $OCH_2S$), ~2.82 (s, $SCH_3$). [o]δ6.61 (d, $J_{5-6}$ = 3.8 Hz, H5).

$J_{H2'-2'} = -18.5$ Hz and **21** has $J_{H3'-3'} = -18.8$ Hz. Large *trans* vicinal couplings were observed for H3'-H4' of 2'-ketonucleosides ($J_{H3'-H4'} = 8.3$, 9.5, 9.8, 9.0, 8.0, and 8.3 Hz for compounds **8**, **13**, **15**, **17**, **19**, and **21**, respectively) and H1'-H2' of 3'-ketonucleosides ($J_{H1'-H2'} = 8.0$, 8.0, and 8.3 Hz for compounds **2**, **5**, and **11**). These values suggest pronounced 3'-*endo*, 4'-*exo* and 1'-*exo*, 2'-*endo* orientations in the conformer populations of the 2' and 3'-ketonucleosides, respectively. Small *meta* coupling ($J_{NH-CH} = 1.5$–2.0 Hz) of the 3 and 5 protons of uracil nucleosides **4**–**9** was observed in DMSO-$d_6$ as has been noted previously with related compounds.[5]

Conversion of the ribo (**25a–f**) to arabino (**27a–f**) nucleosides resulted in relative deshielding of the anomeric protons ($\Delta\delta = 0.3$–0.7 ppm for H1') as is well established upon removal of the diamagnetic effect of a *cis* 2'-OH.[50] An expected decrease of the anomeric proton coupling from $J_{H1'-H2'} \sim 6$ Hz (**25**) to 4.1–4.8 Hz (**27**) also was observed. The anomeric proton peaks of the 2'-O-methylthiomethyl by-products (**28a–f**) were shifted downfield

($\Delta\delta = 0.13$–$0.22$ ppm) relative to those of their precursors (**25a–f**), but had similar coupling values ($J_{H1'-H2'} = 6.0$–$6.5$ Hz). The magnetically non-equivalent –$OCH_2S$–methylene protons gave pairs of doublets with $J_{gem} \sim -11.5$ Hz.

Oxidation of the secondary carbinol $sp^3$ carbon to an $sp^2$ carbonyl group results in a downfield shift of 130–140 ppm for its $^{13}C$ NMR signal to the $\delta$ 205–210 range. Much smaller shifts for the other ring carbon peaks occur as seen in Table 2. Observed relative (to starting material) shifts for the 2′-ketonucleosides (**8, 13, 15, 17, 19, 21**) were 4–9 ppm upfield for C1′, 131–136 ppm downfield for C2′, 3.3 ppm downfield to 1.3 ppm upfield for C3′, and 1.5–6.3 ppm upfield for C4′. The shifts for the 3′-ketonucleosides (**2, 5, 11**) were 3–3.5 ppm upfield for C1′, 0.5–1 ppm downfield for C2′, 138–139 ppm downfield for C3′, and 2.6–3.2 ppm upfield for C4′. This limited data suggests that a greater relative downfield shift for the C3′ CO resonance can be anticipated when a pair of 2′,5′- and 3′,5′-protected ribonucleosides are oxidized.

As expected,[51] the $^{13}C$ NMR signal for a secondary

Table 2. $^{13}C$ NMR chemical shift data[a]

| Compound | C2 | C4 | C5 | C6 | 5-R or C8 | C1′ | C2′ | C3′ | C4′ | C5′ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1[b] | 150.31 | 163.56 | 109.54 | 135.56 | 11.67 | 83.83 | 39.50 | 70.49 | 85.43 | 63.94 |
| 2 | 150.45 | 163.53 | 109.75 | 136.93 | 11.44 | 80.59 | 40.32 | 209.79 | 82.48 | 63.54 |
| 3a[c] | 150.38 | 163.64 | 108.25 | 136.65 | 12.25 | 83.10 | 40.66 | 68.87 | 84.01 | 62.90 |
| 4[d] | 150.62 | 163.05 | 101.69 | 139.82 | | 87.83 | 75.98 | 69.59 | 84.56 | 62.58 |
| 5 | 150.71 | 162.78 | 103.37 | 139.29 | | 84.33 | 76.54 | 208.57 | 81.90 | 62.85 |
| 6a[e] | 150.38 | 163.12 | 100.59 | 140.63 | | 90.77 | 81.30 | 74.21 | 83.43 | 60.88 |
| 7 | 150.78 | 163.13 | 101.75 | 140.35 | | 87.89 | 72.87 | 71.59 | 84.58 | 62.34 |
| 8 | 149.80 | 163.08 | 102.27 | 144.74 | | 83.83 | 206.89 | 70.28 | 79.05 | 61.26 |
| 9a[f] | 150.32 | 163.06 | 100.02 | 141.79 | | 84.53 | 75.31 | 76.35 | 83.49 | 61.59 |
| 10 | 152.79 | 149.53 | 119.14 | 156.21 | 138.79 | 87.49 | 76.06 | 70.05 | 84.89 | 62.90 |
| 11 | 153.02 | 149.97 | 119.36 | 156.40 | 139.43 | 84.35 | 76.54 | 209.27 | 82.19 | 62.85 |
| 12 | 152.66 | 149.66 | 119.33 | 156.23 | 139.70 | 87.19 | 72.53 | 72.22 | 85.03 | 62.53 |
| 13 | 152.75 | 148.91 | 118.82 | 156.29 | 140.92 | 79.41 | 208.46 | 71.95 | 78.70 | 60.96 |
| 14 | 145.62 | 147.39 | 124.76 | 156.43 | 138.09 | 89.23 | 73.88 | 69.71 | 81.03 | 60.75 |
| 15 | 145.70 | 147.40 | 124.58 | 156.18 | 140.50 | 79.74 | 205.90 | 72.38 | 77.59 | 61.15 |
| 16 | 150.12 | 163.11 | 100.92 | 139.71 | | 90.51 | 73.61 | 68.86 | 80.90 | 60.28 |
| 17 | 149.99 | 163.03 | 102.40 | 144.85 | | 84.38 | 205.43 | 71.33 | 78.01 | 62.03 |
| 18 | 154.78 | 165.67 | 93.26 | 139.80 | | 90.69 | 74.09 | 68.46 | 80.45 | 60.01 |
| 19 | 154.47 | 166.69 | 94.93 | 145.69 | | 85.38 | 205.24 | 71.73 | 78.89 | 63.21 |
| 20 | 152.52 | 149.01 | 119.00 | 156.04 | 138.82 | 90.87 | 74.20 | 34.95 | 78.90 | 65.23 |
| 21 | 152.56 | 148.77 | 118.63 | 156.00 | 140.48 | 81.19 | 208.05 | 37.37 | 74.43 | 65.19 |
| 22a[g] | 152.32 | 149.50 | 118.78 | 155.82 | 139.89 | 84.20 | 69.59 | 34.80 | 75.83 | 65.99 |
| 23a | 152.50 | 149.12 | 119.35 | 156.07 | 139.50 | 85.71 | 38.60 | 70.70 | 83.44 | 64.21 |
| 23b | 155.35 | 165.84 | 94.23 | 140.82 | | 85.39 | 40.60 | 70.30 | 84.98 | 63.90 |
| 23c | 154.35 | 162.28 | 95.26 | 144.41 | | 85.96 | 40.74 | 69.39 | 85.63 | 63.15 |
| 24 | | | | | | 180.42 | 107.07 | 202.33 | 83.17 | 62.11 |
| 25a | 152.29 | 149.00 | 119.33 | 156.09 | 139.87 | 87.93 | 73.44 | 70.61 | 85.86 | 61.62 |
| 27a[h] | 152.33 | 149.35 | 118.22 | 155.80 | 140.25 | 83.58 | 75.65 | 75.13 | 84.10 | 60.84 |
| 28a[i] | 152.44 | 148.99 | 119.25 | 156.11 | 139.66 | 86.72 | 77.75 | 68.85 | 85.94 | 61.56 |
| 25b | 156.41 | 151.50 | 113.70 | 160.14 | 136.64 | 87.34 | 73.34 | 70.84 | 85.70 | 61.84 |
| 27b | 155.93 | 151.54 | 112.39 | 160.09 | 136.94 | 83.15 | 75.46 | 75.46 | 84.02 | 61.03 |
| 28b[i] | 156.20 | 151.42 | 113.41 | 160.07 | 135.95 | 86.46 | 77.65 | 68.92 | 84.97 | 61.67 |
| 25c | 153.67 | 151.34 | 116.70 | 156.81 | 135.63 | 86.41 | 73.72 | 70.41 | 85.23 | 61.45 |
| 27c | 153.56 | 150.93 | 113.63 | 156.72 | 136.77 | 83.34 | 75.43 | 75.36 | 84.25 | 60.95 |

Table 2. (*Contd.*)

| Compound | C2 | C4 | C5 | C6 | 5-R or C8 | C1' | C2' | C3' | C4' | C5' |
|---|---|---|---|---|---|---|---|---|---|---|
| 28c[i] | 153.63 | 151.15 | 115.94 | 156.59 | 135.22 | 86.10 | 78.10 | 68.68 | 84.31 | 61.30 |
| 25d[j] | 151.09 | 157.72 | 99.42 | 123.19 | | 87.71 | 73.93 | 71.00 | 85.33 | 62.10 |
| 27d[k] | 151.29 | 157.24 | 98.43 | 123.70 | | 83.07 | 75.95 | 75.56 | 83.45 | 61.20 |
| 28d[i,l] | 151.50 | 157.41 | 99.65 | 121.79 | | 85.74 | 77.68 | 68.82 | 85.42 | 61.58 |
| 25e[m] | 152.98 | 157.12 | 83.11 | 133.22 | 115.41 | 87.84 | 74.46 | 70.36 | 85.63 | 61.39 |
| 27e[n] | 153.27 | 156.80 | 81.83 | 133.66 | 115.53 | 84.15 | 75.64 | 74.76 | 84.22 | 62.16 |
| 28e[i,o] | 153.57 | 157.05 | 83.20 | 132.05 | 115.20 | 86.31 | 78.74 | 68.71 | 86.02 | 61.11 |
| 25f[p] | 152.28 | 158.19 | 111.06 | 126.35 | 166.46 | 87.16 | 73.97 | 70.65 | 85.41 | 61.94 |
| 27f[q] | 152.50 | 157.90 | 109.86 | 127.53 | 166.57 | 83.48 | 75.95 | 75.63 | 84.21 | 61.82 |
| 28f[i,r] | 152.82 | 158.05 | 111.12 | 125.35 | 166.25 | 85.97 | 78.01 | 68.88 | 85.45 | 61.70 |

[a]Shifts in δ ppm downfield from internal $Me_4Si$ in $Me_2SO$-$d_6$ solutions. [b]Spectrum of 3c had no peak at δ70.49. [c]Spectrum of 3b had no peak at δ68.87. [d]Spectrum of 6c had no peak at δ69.59. [e]Spectrum of 6b had no peak at δ74.21. [f]Spectrum of 9b had no peak at δ75.31. [g]Spectrum of 22b had no peak at δ69.59. [h]Spectrum of 2'-deuterio 27a had no peak at δ75.65. [i]Spectra of these compounds had δ~73.57 ($OCH_2S$) & 12.66 ($SCH_3$). [j]δ103.37 (C4a), 150.05 (C7a). [k]δ102.24 (C4a), 149.89 (C7a). [l]δ102.97 (C4a), 149.83 (C7a). [m]δ101.43 (C4a), 150.19 (C7a). [n]100.75 (C4a), 149.84 (C7a). [o]δ101.25 (C4a), 150.09 (C7a). [p]δ101.25 (C4a), 150.92 (C7a). [q]δ100.55 (C4a), 150.57 (C7a). [r]δ101.04 (C4a), 150.67 (C7a).

carbinol C bonded to deuterium is very weak or absent in a spectrum obtained with broad band proton decoupling. This allowed unequivocal assignment of $^{13}C$ signals for several specifically deuterated compounds (Table 2). It was found that the peak for C2′ is at lower field than the C3′ resonance for 9-β-D-arabinofuranosyladenine (**27a**) and the arabino epimer (**27d**) of tubercidin. Selective decoupling at the anomeric proton frequency for **27a** and **27d** allowed assignment of the C1′ peak at higher field than C4′. These reversals in the assignments of C1′, C4′ and C2′, C3′ resonances from earlier determinations [44,52] provide a low to high field peak order of C4′, C1′, C2′, C3′, C5′ for the arabino compounds **27a** and **27d**. Parallel assignment of the sugar carbon peaks for all of the arabino compounds (**27a–f**) with the order noted provides a compatible set. Only the reversal of C4′ and C1′ differs from the ordering of their ribonucleoside counterparts.

Minor upfield shifts of the peaks for C1′ (0.9–2 ppm for **28a,b,d–f** and 0.3 ppm for **28c**) and C3′ (1.6–2.2 ppm) and more pronounced downfield shifts (3.7–4.4 ppm) for C2′ of the 2′-O-methylthiomethyl by-products relative to those of **25a–f** were observed. These shifts parallel those recently noted for 2′-O-methyl ribonucleosides, but the present C2′ peak shifts are about half the magnitude found in that series.[53]

## EXPERIMENTAL

Mps were determined on a Reichert microstage block and are uncorrected. UV spectra were recorded on a Cary 15 spectrophotometer. $^1H$ NMR spectra were determined by the High-Field NMR Laboratory of this department using Bruker WH-200 or WH-400 spectrometers. Chemical shift data are compiled in Table 1. $^{13}C$ NMR spectra were determined by the same Laboratory using Bruker HFX-90, WH-200 and WH-400 instruments at 22.6, 50.1 and 100.6 MHz. Data are compiled in Table 2. High resolution electron impact mass spectra (MS) were determined by the Mass Spectrometry Laboratory of this department using an AEI MS-50 instrument at 70 eV with computer processing. Direct probe sample introduction was employed. Chemical ionization mass spectra ($NH_3$ reagent gas) of all isolated ketonucleosides were obtained using an AEI MS-12 instrument, and an $M^+ + 1$ ion at the correct nominal mass was observed in every case. Elemental analyses were determined by the Microanalytical Laboratory of this department. Evaporations were effected using a Büchi rotary evaporator equipped with a Dewar Dry-Ice condenser under mechanical oil pump vacuum at <40° (or cooler as indicated).

All solvents were distilled before use and all chemicals were of reagent grade. Pyridine was dried by refluxing over and distillation from KOH. DMSO was refluxed over and distilled from $CaH_2$.

*General oxidation procedure using chromium trioxide/pyridine/acetic anhydride*

*Method A.* A 1 mmol sample of the protected nucleoside (solid or a concentrated soln in $CH_2Cl_2$) was added to a soln of 3 molar equiv of the pre-mixed complex of $CrO_3$(1)/pyridine(2)/$Ac_2O$(1) (300 mg/0.5 mL/0.3 mL) in 7 mL of $CH_2Cl_2$ and the mixture was stirred at ambient temp for 45–60 min. The resulting dark brown soln was carefully transferred by pipet into 50 mL of supernatent EtOAc over a ~1 cm layer of Woelm neutral silica gel (0.2–0.5 mm) contained in a 4 cm diam chromatography column. The supernatent soln was filtered through the support, and the flask, ppt, and silica gel were washed with EtOAc. The combined filtrate was evaporated (<25°) and 25 mL portions of toluene, $CHCl_3$, and sometimes $Et_2O$ were sequentially added and evaporated to leave a crystalline solid or

crisp amorphous glass. Crystallization or reprecipitation from $CHCl_3/CCl_4$, $CHCl_3$/hexane, $Et_2O$/hexane, or EtOAc/hexane usually gave the chromatographically (TLC), spectroscopically, and analytically pure ketonucleosides.

*Method B.* The oxidation was performed as in Method A except only 5 mL of $CH_2Cl_2$ was used and the reaction was allowed to proceed for 45–75 min. The dark brown mixture was carefully added to 100 mL stirred EtOAc and the resulting ppt was filtered using a Whatman glass microfibre "filter paper" GF/A. The filtrate was concentrated to ~3 mL (< 25°) and subjected to fast chromatography on a 4 cm (2 cm diameter) column of Merck silica gel 60 (70–230 mesh) using EtOAc. The eluates were processed as in Method A. This procedure afforded colorless products in all cases examined.

1-(5-O-*Trityl*-β-D-*glycero*-*pentofuran*-3-*ulosyl*)*thymine* (**2**) was prepared from 1 mmol of **1**[54] by Method A and recrystallized from $CHCl_3/CCl_4$ to give 419 mg (87%) of **2**, m.p. 171–174° (lit.[13] m.p. 171–174°) UV (MeOH) max 266 nm (ε 9000). (Found: C 72.05, H 5.45, N 5.75. Calc for $C_{29}H_{26}N_2O_5$ (482.5): C 72.18, H 5.43, N 5.81%).

1-(2-*Deoxy*-5-*O*-*trityl*-β-D-*threo*-*pentofuranosyl*)*thymine* (**3a**). A 0.5 mmol sample of **1** was oxidized to give **2** and the total unpurified product was dissolved in 8 mL of abs EtOH. The soln was cooled to 0° and 76 mg of $NaBH_4$ was added. The mixture was stirred at 0° for 2.5 hr and then 5 mL MeOH was added. The mixture was evaporated and the residue partitioned between EtOAc and 3 M NaCl/$H_2O$ containing 2% AcOH. The organic phase was washed 3 times with the NaCl aq HOAc solution, dried over $Na_2SO_4$, and evaporated. Toluene and then $CHCl_3$ were added and evaporated to give a colorless solid foam. This material was subjected to preparative TLC ($CHCl_3$/MeOH, 95:5, silica gel) to give a faster zone of 186 mg (77%) of recrystallized (abs EtOH) **3a**, mp 239–240° (lit.[55] mp 240–241°), UV (MeOH) max 266 nm (ε 9200). (Found: C 71.69, H 5.86, N 5.68. Calc. for $C_{29}H_{28}N_2O_5$ (484.5): C 71.88, H 5.82, N 5.78%). The slower zone contained 21 mg (8.7%) of **1**, m.p 128–129° (lit.[54] m.p. 128–130°).

1-(2-*Deoxy*-3-*deuterio*-5-*O*-*trityl*-β-D-*threo*-*pentofurano*-*syl*)*thymine* (**3b**) *and* 1-(2-*deoxy*-3-*deuterio*-5-*O*-*trityl*-β-D-*erythro*-*pentofuranosyl*)*thymine* (**3c**). An identical sequence to that described above for **1**→**2**→**3a** + **1** was effected using 78 mg of $NaBD_4$ to give 191 mg (79%) of **3b**, m.p. 238–240°, and 22 mg (9%) of **3c**, m.p. 128–130°.

1-(2,5-*Bis*-*O*-*TBDMS*-β-D-*erythro*-*pentofuran*-3-*ulosyl*)*uracil* (**5**). Oxidation of 0.25 mmol of **4**[16] by Method A and reprecipitation using EtOAc/hexane gave 105 mg (89%) of **5**, m.p. 177°, UV (MeOH) max 261 nm (ε 9900). (Found: C 53.67, H 8.10, N 5.86. Calc for $C_{21}H_{38}N_2O_6Si_2$ (470.7): C 53.58, H 8.14, N 5.95%).

1-(2,5-*Bis*-*O*-*TBDMS*-β-D-*xylofuranosyl*)*uracil* (**6a**). Reduction of 0.25 mmol of crude **5** as described above for **2**→**3a** + **1** and preparative TLC (EtOAc/hexane, 2:1, silica gel) gave 116 mg (98%) of an analytically pure solid foam with UV (MeOH) max 261 nm (ε 9700). $^1H$ NMR integration showed **6a**/**4** = 82:18. (Found: C 53.43, H 8.46, N 5.83. Calc for $C_{21}H_{40}N_2O_6Si_2$ (472.7): C 53.25, H 8.53, N 5.93%).

1-(2,5-*Bis*-*O*-*TBDMS*-3-*deuterio*-β-D-*xylofuranosyl*)*uracil* (**6b**) *and* 1-(2,5-*bis*-*O*-*TBDMS*-3-*deuterio*-β-D-*ribofuranosyl*)*uracil* (**6c**). The identical procedure used for **6a** above with substitution of $NaBD_4$ gave 116 mg (98%) of **6b**/**6c** (82:18 by $^1H$ NMR).

1-(3,5-*Bis*-*O*-*TBDMS*-β-D-*erythro*-*pentofuran*-2-*ulosyl*)*uracil* (**8**). Oxidation of 0.25 mmol of **7**[16] by Method A and reprecipitation using EtOAc/hexane gave 105 mg (89%) of pure **8**, m.p. 179–181°, UV (MeOH) max 261 nm (ε 9800). (Found: C 53.65, H 8.09, N 5.82. Calc for $C_{21}H_{38}N_2O_6Si_2$ (470.7): C 53.58, H 8.14, N 5.95%).

1-(3,5-*Bis*-*O*-*TBDMS*-β-D-*arabinofuranosyl*)*uracil* (**9a**). Oxidation of 0.25 mmol of **7** followed by reduction of the isolated crude **8** as described above for **2**→**3a** + **1** and preparative TLC (EtOAc/hexane, 1:2, silica gel) gave 115 mg (97%) of **9a** as a colorless solid foam with m.p. 68–71°, UV (MeOH) max 261 nm (ε 9600). (Found: C 53.45, H 8.49, N 5.85. Calc for $C_{21}H_{40}N_2O_6Si_2$ (472.7): C53.35, H 8.53, N 5.93%). High field $^1H$ and $^{13}C$ NMR spectra of **9a** had no observed signals for **7**. The presence of **7** could be detected in a prepared mixture of **9a**/**7** with a ratio of 95:5.

1-(3,5-*Bis*-*O*-*TBDMS*-2-*deuterio*-β-D-*arabinofuranosyl*)*uracil* (**9b**). The procedure for the preparation of **9a** was followed using $NaBD_4$ to give 116 mg (98%) of **9b**, m.p. 68–71°. Again, no 3′,5′-bis-O-TBDMS-2′-deuteriouridine was detected.

9-(2,5-*Bis*-*O*-*TBDMS*-β-D-*erythro*-*pentofuran*-3-*ulosyl*)*adenine* (**11**). Oxidation of 0.25 mmol of **10**[16] by Method A or B and recrystallization from $Et_2O$ gave 109 mg (88%) of colorless **11**, m.p. 177–178° (dec), UV (MeOH) max 259 nm (ε 15 400). (Found: C 53.67, H 7.87, N 14.10. Calc for $C_{22}H_{39}N_5O_4Si_2$ (493.8): C 53.51, H 7.96, N 14.19%).

9-(3,5-*Bis*-*O*-*TBDMS*-β-D-*erythro*-*pentofuran*-2-*ulosyl*)*adenine* (**13**). Oxidation of a 0.25 mmol sample of **12**[16] by Method A gave a slightly colored product that required further chromatographic purification. Use of Method B followed by crystallization from $Et_2O$/hexane gave 104 mg (84%) of colorless **13** with no defined m.p., UV (MeOH) max 259 nm (ε 14 800). (Found: C 53.28, H 8.02, N 13.90. Calc for $C_{22}H_{39}N_5O_4Si_2$ (493.8): C 53.51, H 7.96, N 14.19%).

9-(3,5-*O*-*TPDS*-β-D-*erythro*-*pentofuran*-2-*ulosyl*)*hypoxanthine* (**15**). Oxidation of **14**[47] by Method A resulted in isolation of a grayish solid with poor $^1H$ NMR and analytical data. A 0.25 mmol sample of **14** was oxidized by Method B to give 102 mg (80%) of **15** with no defined m.p., UV (MeOH) max 249 nm (ε 12 800). (Found: C 51.64, H 7.24, N 10.89. Calc for $C_{22}H_{36}N_4O_6Si_2$ (508.7): C 51.94, H 7.13, N 11.01%).

1-(3,5-*O*-*TPDS*-β-D-*erythro*-*pentofuran*-2-*ulosyl*)*uracil* (**17**). Oxidation of 0.25 mmol of **16**[56] by Method A and reprecipitation using EtOAc/hexane gave 112 mg (93%) of colorless **17** as an amorphous solid glass with no defined m.p., UV (MeOH) max 261 nm (ε 9800). (Found: C 52.13, H 7.41, N 5.69. Calc for $C_{21}H_{36}N_2O_7Si_2$ (484.7): C 52.03, H 7.49, N 5.78%).

1-(3,5-*O*-*TPDS*-β-D-*erythro*-*pentofuran*-2-*ulosyl*)*cytosine* (**19**). Oxidation of 0.25 mmol of **18**[47] by Method B and recrystallization from EtOAc/$Et_2O$ gave 95 mg (78%) of pure **19**, m.p. 148–151° (dec.), UV (MeOH) max 271 nm (ε 8900). (Found: C 51.95, H 7.54, N 5.71. Calc for $C_{21}H_{36}N_2O_7Si_2$ (484.7): C 52.03, H 7.49, N 5.78%).

3′-*Deoxy*-5′-*O*-*trityladenosine* (**20**). A mixture of 502 mg (2 mmol) of 3′-deoxyadenosine, 1.08 g (3.88 mmol) trityl chloride and 10 mL pyridine was stirred at ambient temp for 5 days. The solvent was evaporated and the residue partitioned between EtOAc and 3 M NaCl/$H_2O$. The organic phase was washed with 3 M NaCl/$H_2O$, dried over $Na_2SO_4$, and evaporated. Toluene was added and evaporated to give a slightly colored solid foam that was dissolved in a small volume of hot toluene and precipitated with hexane. Recrystallization of this product from toluene gave 647 mg (66%) of **20**, m.p. 202–204°, UV (MeOH) max 259 nm (ε 15 200). (Found: C 70.62, H 5.49, N 14.03. Calc for $C_{29}H_{27}N_5O_3$ (493.6): C 70.57, H 5.52, N 14.19%).

9-(3-*Deoxy*-5-*O*-*trityl*-β-D-*glycero*-*pentofuran*-2-*ulosyl*)*adenine* (**21**). A 0.25 mmol sample of **20** was oxidized by Method A. During the evaporation of added toluene, crystallization of **21** occurred. The product was collected by filtration and washed with toluene/hexane to give 83 mg (67%) of pure **21**, m.p. 219°, UV (MeOH) max 259 nm (ε 15 100). (Found: C 70.93, H 5.08, N 14.14. Calc for $C_{29}H_{25}N_5O_3$ (491.5): C 70.86, H 5.13, N 14.25%).

9-(3-*Deoxy*-5-*O*-*trityl*-β-D-*threo*-*pentofuranosyl*)*adenine* (**22a**). Oxidation of a 0.25 mmol sample of **20** followed by reduction of the crude **21** with $NaBH_4$ as described above for **2**→**3a** + **1**, preparative TLC of the mixture ($CHCl_3$/MeOH, 9:1, silica gel), and crystallization of the eluted product zone from abs EtOH gave 63 mg (51%) of **22a**, m.p. 120–125° (melting and resolidification) and 216°, UV (MeOH) max

259 nm (ε 15 400), no $^1H$ or $^{13}C$ NMR peaks observed for the *erythro* isomer (**20**). (Found: C 70.68, H 5.40, N 14.10. Calc for $C_{29}H_{27}N_5O_3$ (493.6): C 70.57, H 5.52, N 14.19%).

9-(3-*Deoxy*-2-*deuterio*-5-*O*-*trityl*-β-D-*threo*-*pentofuranosyl*)*adenine* (**22b**). An identical procedure as described above for the preparation of **22a** was effected using $NaBD_4$ in the reduction step. Preparative TLC gave 64 mg (52%) of **22b**, m.p. 120–125° (melting and resolidification) and 216°. Again, no *erythro* isomer peaks were present in the NMR spectra.

*Formation of* 4,5-*dihydro*-5-*trityloxymethylfuran*-4-*one*[13] (**24**). Treatment of **23a**, **23b**, or **23c** by oxidation Method A resulted in elimination of the heterocyclic base. Compound **24** was isolated as a slightly yellow oil that had $^1H$ (Table 1) and $^{13}C$ (Table 2) NMR data in harmony with the assigned structure. Measurement of NMR spectra of compound **2** in $Me_2SO$-$d_6$ solution gave rapid appearance of peaks corresponding to formation of **24**. The mass spectrum of **24** had *m/z* 356.1416 corresponding to $M^+(C_{24}H_{20}O_3) = 356.1412$.

*Syntheses of* 3′,5′-*O*-*TPDS*-*nucleosides* (**26a,c–e**) were as reported previously.[47,56] Compound **26b**[47] was prepared by the procedure reported for **26c**.[56]

9-β-D-*Arabinofuranosyladenine* (**27a**) *and* 2′-*O*-*methylthiomethyladenosine* (**28a**)

*Method A*. A soln of 2 mmol **26a** in 8 mL DMSO was treated with 1 mL $Ac_2O$ (distilled from Mg turnings) and the mixture was stirred at ambient temp (~22°) for 22 hr. Tetrahydrofuran (40 mL) was added and the mixture was cooled to −12°. A soln of 1 g $NaBH_4$ in 32 mL 50% $H_2O$/n-PrOH was added dropwise over a period of 20 min. Stirring was continued for an additional 30 min and 30 mL sat NaCl/$H_2O$ was added. The mixture was extracted with EtOAc and the combined organic phase was washed with sat NaCl/$H_2O$, dried over $Na_2SO_4$, and evaporated to dryness. The residue was dissolved in THF and stirred with 4 mL of 1 M n-$Bu_4N^+F^-$/THF at ambient temp for 15 hr. The soln was evaporated and the oily residue was partitioned between $Et_2O$ and $H_2O$. The aqueous phase was concentrated and applied to a column (2 × 20 cm) of Dowex 1 × 2($OH^-$) resin packed in $H_2O$. The column was developed with $H_2O$ to elute 26 mg (4%) of **28a**, m.p. 144–145°, MS *m/z* 327.0995 (Calc for $M^+$ 327.1001). (Found: C 44.02, H 5.25, N 21.32. Calc for $C_{12}H_{17}N_5O_4S$ (327.4): C 44.02, H 5.24, N 21.40%).

Further elution with 50% MeOH/$H_2O$ eluted 20 mg (4%) of **25a**, and 70% MeOH/$H_2O$ eluted 336 mg (63%) of **27a**, m.p. 257–258° (lit.[22] m.p. 257°), UV ($H_2O$, pH 7) max 260 nm (ε 14 500), MS *m/z* 267.0964 (Calc for $M^+$ 267.0968). (Found: C 45.19, H 4.95, N 26.01. Calc for $C_{10}H_{13}N_5O_4$ (267.2): C 44.94, H 4.90, N 26.20%).

*Method B*. A stirred suspension of 3 g $CrO_3$ in 60 mL $CH_2Cl_2$ was cooled to 0° and 3 mL $Ac_2O$ and 5 mL pyridine were added. After a clear soln was formed, a soln of 10 mmol of **26a** in 20 mL $CH_2Cl_2$ was added slowly. The mixture was stirred at 0° for 5 min and then allowed to warm to 5–10° over a period of 2 hr. Volatile materials were evaporated and the residue was cooled to 0° and dissolved in 25 mL 95% EtOH. The stirred soln was treated by dropwise addition of a soln of 570 mg $NaBH_4$ in 6 mL $H_2O$. After 30 min a second 570 mg $NaBH_4$ in 6 mL $H_2O$ was added and a 200 mg portion in 2.5 mL $H_2O$ was added at 1 hr. The mixture was processed as in Method A to give 1.8 g (67%) of **27a**, m.p. 257–258°.

2,6-*Diamino*-9-β-D-*arabinofuranosylpurine* (**27b**) *and* 2-*amino*-2′-*O*-*methylthiomethyladenosine* (**28b**). A 2 mmol sample of **26b** was oxidized for 24 hr according to Method A for the synthesis of **27a**. EtOH (25 mL) and 250 mg boric acid were added to the mixture which was cooled to 0° and treated carefully with 3 × 230 mg portions of solid $NaBH_4$. Processing and chromatography were effected as in Method A. Elution with 30% MeOH/$H_2O$ gave 28 mg (4%) of **28b**, m.p. 157–157.5°, MS *m/z* 342.1107 (Calc for $M^+$ 342.1110). (Found: C 42.13, H 5.35, N 24.37. Calc for $C_{12}H_{18}N_6O_4S$ (342.4): C 42.09, H 5.30, N 24.56%).

Elution with 40–50% MeOH/$H_2O$ gave 176 mg (32%) of **25b**, and 70% MeOH/$H_2O$ gave 268 mg (48%) of **27b**, m.p. 260–261° (lit.[34] m.p. > 250°), UV ($H_2O$, pH 7) max 280 & 256 nm (ε 11,000 & 10,500), MS *m/z* 282.1075 (calc for $M^+$ 282.1077). (Found: C 42.42, H 4.98, N 29.45. Calc for $C_{10}H_{14}N_6O_4$ (282.3): C 42.54, H 4.99, N 29.77%).

9-β-D-*Arabinofuranosylguanine* (**27c**) and 2′-*O*-*methylthiomethylguanosine* (**28c**). A 2 mmol sample of **26c** was oxidized for 30 hr according to Method A for the synthesis of **27a**. EtOH (10 mL) was added and the mixture was cooled to 0° and treated with 3 × 100 mg portions of solid $NaBH_4$. After reduction was complete, the mixture was evaporated and subjected to deprotection directly. The deblocked nucleoside fraction was applied to a column (2 × 10 cm) of Dowex 1 × 2($OH^-$) resin and the column was washed with $H_2O$ for 18 hr. Elution of **27c** was effected using 0.03 M aqueous triethylammonium bicarbonate. Evaporation of appropriate fractions, repetitive addition of $H_2O$ and coevaporation of $Et_3NH_2CO_3$, crystallization of the residue from MeOH, and recrystallization from $H_2O$ gave 234 mg (41%) of pure **27c**, m.p. > 340° (lit.[38] m.p. > 300°), UV ($H_2O$, pH 7) max 252 nm (ε 13 600), MS *m/z* 266.0645 (Calc for $M^+$–$NH_3$ 266.0652). (Found: C 42.17, H 4.61, N 24.53. Calc for $C_{10}H_{12}N_5O_5$ (283.3): C 42.39, H 4.62, N 24.72%).

Deamination of a sample of **28b** (to be published separately) and recrystallization of the sample from $H_2O$ gave **28c**, m.p. > 286° (dec), MS *m/z* 343.0931 (Calc for $M^+$ 343.0951). (Found: C 41.97, H 5.05, N 20.58. Calc for $C_{12}H_{16}N_5O_5S$ (342.4): C 42.10, H 4.71, N 20.46%). This compound had identical migration on TLE with the deprotected minor component (**28c**) produced during the oxidation of **26c**.

4-*Amino*-7-β-D-*arabinofuranosylpyrrolo*[2,3-*d*]*pyrimidine* (**27d**) and 2′-O-*methylthiomethyltubercidin* (**28d**). A 2 mmol sample of **26d** was oxidized for 27 hr according to Method A for the synthesis of **27a**. EtOH (25 mL) was added and the mixture was cooled to 0° and treated with 2 × 230 mg portions $NaBH_4$. After stirring for 1 hr, the standard Method A processing was followed. The column (2 × 25 cm) of Dowex 1 × 2($OH^-$) resin was washed with $H_2O$ to elute 48 mg (7%) of **28d**, m.p. 89–90°, MS *m/z* 326.1049 (Calc for $M^+$ 326.1049). (Found: C 47.76, H 5.53, N 16.73. Calc for $C_{13}H_{18}N_4O_4S$ (326.4): C 47.84, H 5.56, N 17.18%).

Elution with 35% MeOH/$H_2O$ gave 63 mg (12%) of **25d**, and 50% MeOH/$H_2O$ gave 332 mg (62%) of **27d**, m.p. 125–126° (lit.[43] m.p. 125–126°), UV ($H_2O$, pH 7) max 271 nm (ε 12 000), MS *m/z* 266.1008 (Calc for $M^+$ 266.1015), (Found: C 49.57, H 5.42, N 20.94. Calc for $C_{11}H_{14}N_4O_4$ (266.3): C 49.57, H 5.25, N 21.03%).

An identical sequence was effected with a 45 hr oxidation period. The recovered product yields were 7.5% (**28d**), 7.9% (**25d**), and 54% (**27d**).

4-*Amino*-5-*cyano*-7-β-D-*arabinofuranosylpyrrolo*[2,3-*d*]*pyrimidine* (**27e**) *and* 2′-*O*-*methylthiomethyltoyocamycin* (**28e**). A 2 mmol sample of **26e** was oxidized for 30 hr according to Method A for the synthesis of **27a**. EtOH (40 mL) was added and the mixture was cooled to 0° and carefully treated with 3 × 430 mg portions $NaBH_4$. The standard Method A processing, deprotection, and partitioning between $Et_2O$ and $H_2O$ was effected. The aqueous phase was applied to a column (2 × 25 cm) of washed and activated C.[56,57] The column was washed exhaustively with $H_2O$ and then the nucleosides were eluted with MeOH. The appropriately pooled fractions were evaporated and the residue was subjected to medium pressure column chromatography on Merck silica gel H 60 using MeOH/$CHCl_3$ 2:8. A small quantity (8 mg) of **28e** was isolated with MS *m/z* 351.1000 (Calc for $M^+$ 351.1001). The arabinonucleoside was crystallized from MeOH with diffusion of $Et_2O$[57] to give 210 mg (36%) of **27e**, m.p. 259–260, UV ($H_2O$, pH 1) max 272 nm (ε 12 200), MS *m/z* 291.0959 (Calc

for $M^+$ 291.0967). (Found: C49.25, H 4.50, N 23.99. Calc for $C_{12}H_{13}N_5O_4$ (291.3): C 49.48, H 4.50, N 24.05%).

*4-Amino-5-carboxamido-7-β-D-arabinofuranosylpyrrolo [2,3-d]pyrimidine* (**27f**) *and 2'-O-methylthiomethyl-sangivamycin* (28f). A 2 mmol sample of **26e** was oxidized, reduced and processed identically to the above synthesis of **27e** up to the partitioning of the deprotection mixture between $Et_2O$ and $H_2O$. The aqueous phase was concentrated and applied to a column (2 × 40 cm) of Dowex 1 × 2($OH^-$) resin. The column was washed with 2 L of 10% MeOH/$H_2O$ to allow complete hydrolysis of the toyocamycin to sangivamycin (5–CN→5–$CONH_2$) analogues. Elution with 35% MeOH/$H_2O$ gave 38 mg (5%) of **28f**, m.p. 114–116°, MS *m/z* 369.1108 (Calc for $M^+$ 369.1108). (Found: C 43.21, H 5.28, N 18.77. Calc for $C_{14}H_{19}N_5O_5S$ (369.4): C 43.35, H 5.19, N 18.97%).

Elution with 65–70% MeOH/$H_2O$ gave 72 mg (12%) of **25f**, and 90–95% MeOH/$H_2O$ gave 219 mg (36%) of **27f**, m.p. 258–260°, UV ($H_2O$, pH 1) max 273 nm (ε 12 800), MS *m/z* 309.1067 (Calc for $M^+$ 309.1073). (Found: C 46.48, H 4.90, N 22.59. Calcd. for $C_{12}H_{15}N_5O_5$ (309.3): C 46.60, H 4.89, N 22.65%).

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