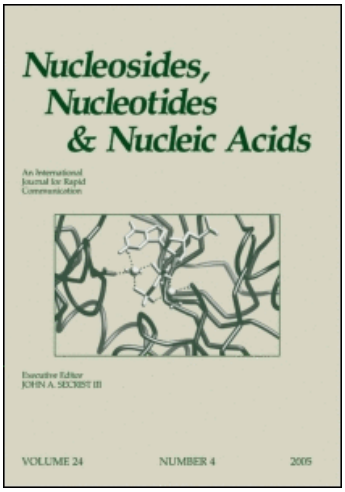

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4'-THIO-L-XYLOFURANOSYL NUCLEOSIDES

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4′-THIO-L-XYLOFURANOSYL NUCLEOSIDES

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ABSTRACT

A series of 4′-thio-L-xylofuranosyl nucleosides were prepared and evaluated as potential anticancer and antiviral agents. The details of a convenient and high-yielding synthesis of the carbohydrate precursor 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-4- thio-L-xylofuranose (**6**) are presented. Proof of structure and configuration at all chiral centers of the nucleosides was obtained by proton and carbon NMR. All target compounds were evaluated in a series of human cancer cell lines in culture and as antiviral agents.

As a part of research in our laboratories to develop novel anticancer and antiviral agents we have been pursuing the synthesis of 4′-thionucleosides for the past several years (1–8). Based upon the significant activity in animals from certain arabino and 2′-deoxy thionucleosides (1,7,8), we have prepared a series of new purine and pyrimidine 4′-thio-L-xylonucleosides. All the sugar intermediates and the corresponding nucleosides have been characterized and the anomeric configuration was determined by PMR.

Our goal in this L-xylofuranose series, as with other 4′-thionucleoside analogs, was to prepare a series of compounds that included natural and modified purines and pyrimidines, chosen on the basis of biological evaluations within the series and biological information from our laboratories and others suggesting compounds with

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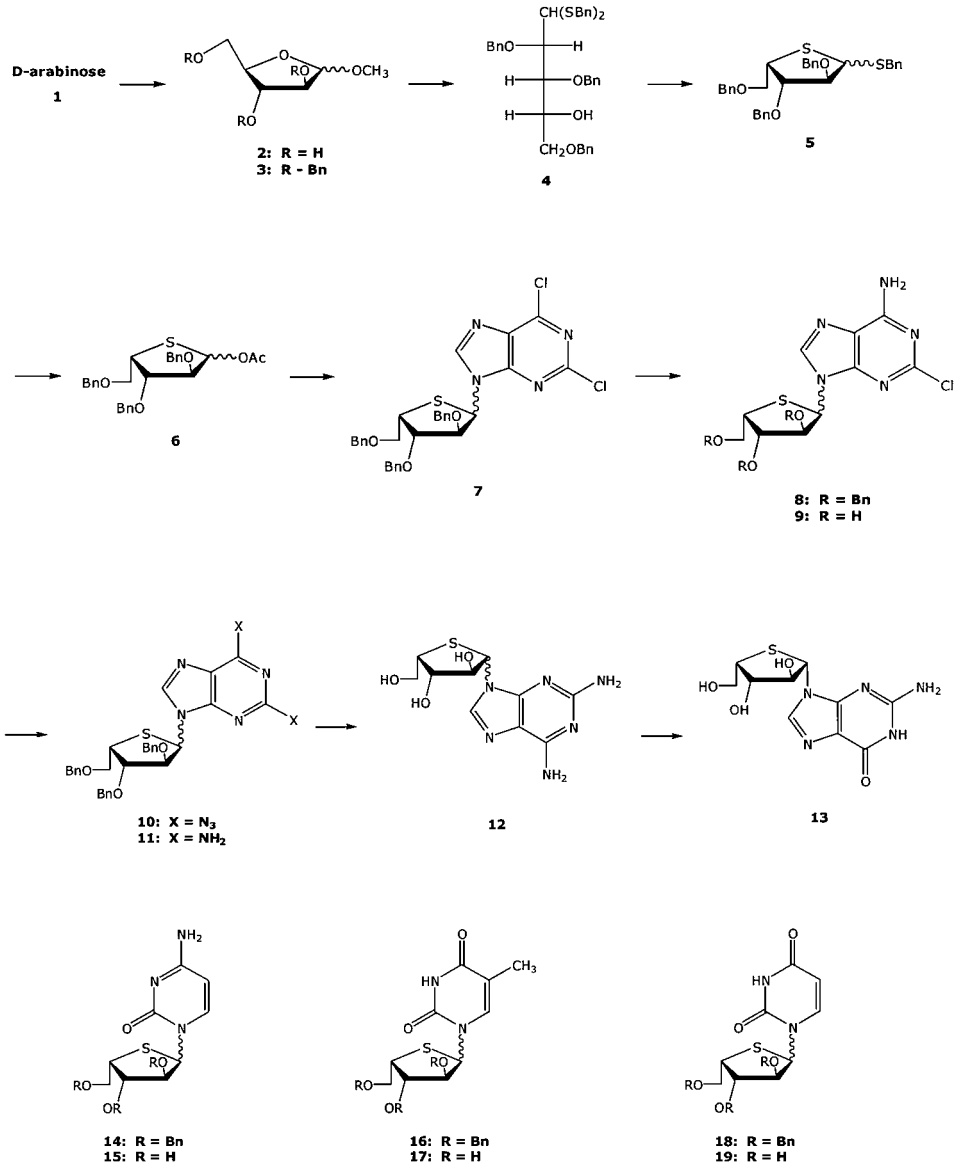

Scheme.

desirable properties. We have developed a five step sequence to the key intermediate **6**. Conversion of D-arabinose to methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranoside (**3**) was accomplished in two steps by the usual method. Conversion to dibenzyl dithioacetal **4** employing benzyl mercaptan and stannic chloride proceeded in 63% yield after chromatographic purification. Cyclization at C-4 involving a single inversion, thus converting the D-*arabino* to the L-*xylo* configuration, was

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accomplished employing triphenylphosphine, iodine, and imidazole in 72% yield. The final step, replacement of the benzylthio group at C-1 by an acetoxy group, involved treatment of **5** with mercuric acetate in acetic acid at room temperature. The overall yield of **6** from **1**, including four column purifications, was 32%, and afforded a *ca*. 1:1 mixture of α,β anomers.

A series of purine nucleoside analogs was prepared through the coupling of **6** and 2,6-dichloropurine. A Lewis acid catalyzed reaction utilizing stannic chloride (6) in acetonitrile was found to be an efficient method to achieve this coupling, and 30 and 25% yields of α and β anomers of **7** were obtained after chromatographic purification/separation. After treatment with ethanolic ammonia to produce the respective blocked 2-chloroadenine nucleosides **8**α and **8**β, removal of the *O*-benzyl groups was accomplished with boron trichloride in dichloromethane at -50°C to yield the final nucleoside targets **9**α (55%) and **9**β (45%). Treatment of **7**α and **7**β with sodium azide in 95% aqueous ethanol at reflux produced the corresponding 2,6-diazido intermediates **10**α and **10**β, which were subjected to reduction with stannous chloride in dichloromethane to afford the blocked diaminopurine nucleosides **11**α (80%) and **11**β (82%). Deblocking of **11**α and **11**β with boron trichloride in dichloromethane produced the target diamino nucleoside **12**α (71%) and **12**β (75%). The conversion of **12**β to the corresponding guanine nucleoside **13** (45%) was accomplished by treatment with adenosine deaminase under standard conditions. Though the deamination was slow, it went to completion at room temperature in 72 hours. Cytosine, Thymine and Uracil were coupled (8) with thiosugar **5** to afford **14**α (31%), **14**β (30%), **16**$\alpha\beta$ (60%) and **18**$\alpha\beta$ (70%) respectively which were deblocked by boron trichloride to give the desired nucleosides **15**α (70%), **15**β (70%), **17**$\alpha\beta$ (65%) and **19**$\alpha\beta$ (65%) respectively.

In order to provide confirmatory evidence that the carbohydrate configuration and the anomeric configurations of our target compounds had been properly assigned, the NMR spectra of several compounds were examined by NOE difference spectroscopy.

BIOLOGICAL DATA

All the compounds were screened for cell culture cytotoxicity against several different human cancer cell lines and a variety of viruses HBV, RSV (Respiratory Syncytial), influenza, influenza A/PR/8, HHV8, and CMV for antiviral activity. None of the compounds have significant cytotoxicity and activity against any of the viruses tested except for compounds **12**α, **15**α, and **15**β, which showed very good activity against CMV.

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