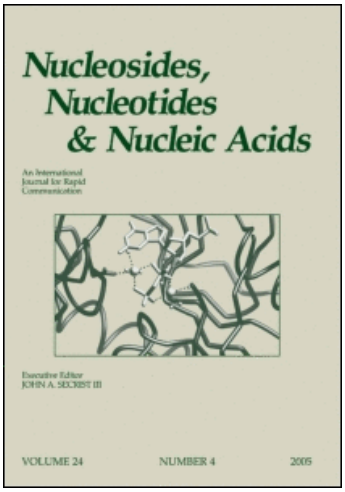

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SYNTHESIS OF SOME 2′-FLUORO-2′-DEOXY-3′-C-ETHYNYL AND 3′-C-VINYL-β-D-LYXOFURANOSYL NUCLEOSIDES

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▫ *1-(2-Fluoro-2-deoxy-β-D-arabinofuranosyl)uracil (**5**) and 1-(2-fluoro-2-deoxy-β-D-arabinofuranosyl)cytosine (**6**) were synthesized as reported earlier. Both of these compounds were converted into 2′-fluoro-2′-deoxy-3′-C-ethynyl and 3′-C-vinyl-β-D-lyxofuranosyl nucleosides (**16—19**) by a multistep sequence. All these new nucleosides were evaluated against seven human tumor cell lines in vitro.*

INTRODUCTION

The search for nucleoside analogues which function as selective inhibitors of polymerases, and other enzymes for the control of viral diseases and cancer has been the subject of intense research.[1] However, as some of these nucleosides also undergo enzymatic degradations, a number of modifications has been carried out on both the sugar portion and the heterocycle to circumvent these deactivating processes. Nucleoside analogues that are good substrates for cellular kinases, but are resistant to other host enzymes such as phosphorylases and deaminases are potentially important for the development of therapeutic agents.

One important discovery in this area is that the replacement of the hydroxyl in the sugar portion of the nucleosides with a fluorine results in nucleoside analogues which have been found to have interesting biological activities. Clofarabine (2-chloro-2′-fluoro-ara-A) (**1**) (Figure 1), for example, which has been synthesized in our laboratory,[2] was found to have potent anti-leukemic activity and currently is in human clinical trials.

In addition, the 3′-alkyl or alkynyl branched nucleoside analogues have been reported to exhibit a potent antiviral and anti-cancer activity. Several years ago,

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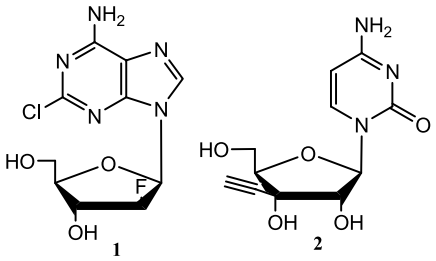
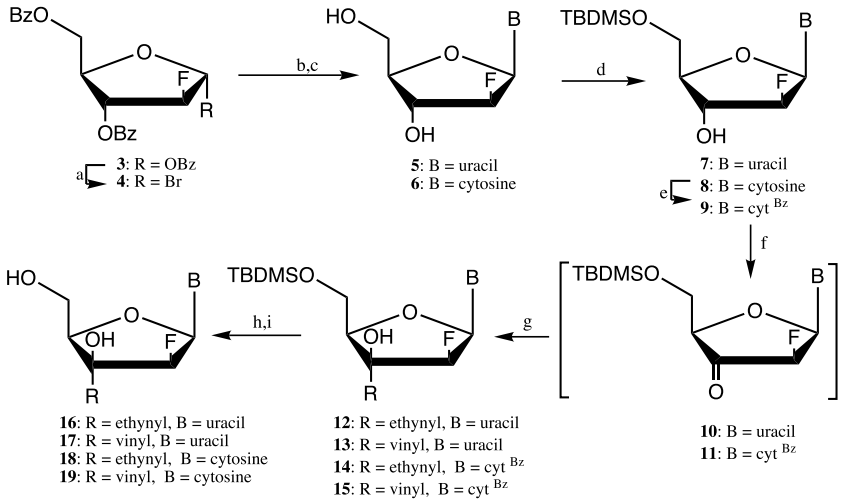


FIGURE 1

1-(3-C-ethynyl-β-D-*ribo*-pentofuranosyl)cytosine (**2**) (Figure 1) was synthesized by Matsuda et al.[3] and showed good activity against various human solid tumors. This compound is undergoing human clinical trials. On the basis of these considerations, we have prepared some 2′-fluoro-2′-deoxy-3′-C-ethynyl and 3′-C-vinyl-β-D-lyxofuranosyl nucleosides. The synthesis and biological data on these compounds are presented.

RESULTS AND DISCUSSION

Our route (Scheme 1) to this series was accomplished by preparing the 2′-fluoro-2′-deoxy-β-D-arabinofuranosyl nucleosides (**5**) and (**6**) following the synthetic pathway previously described.[4] Protection of the primary alcohol of these nucleosides was carried out using *tert*-butyldimethylsilyl chloride in pyridine at room temperature for 3 h to lead to compounds (**7**) and (**8**) in 94 and 92% yields,



SCHEME 1 Conditions: (a) HBr/HOAc; (b) bis-silylated uracil or cytosine/CCl_4/reflux; (c) NH_3/MeOH, r. t.; (d) TBDMSCl/pyridine, r.t; (e) BzCl/DMF, r.t; (f) Dess-Martin periodinane/CH_2Cl_2; (g) HCCMgBr or $H_2CCHMgBr$, THF, − 78°C; (h) TBAF/THF, r.t.; (i) NH_3/MeOH, r.t.

respectively. Benzoylation of amino group in cytosine nucleoside (**8**) with benzoic anhydride in DMF provided compound (**9**) in 91% yield.

We next investigated the oxidation of the secondary alcohol at C-2′ position of (**8**) and (**9**) using CrO_3-pyridine-Ac_2O or Ac_2O-DMSO mixtures. Attempts to prepare the desired ketonucleosides (**10**) and (**11**), however, failed because of their instability under these conditions. Only the α,β-unsaturated ketone resulting from the elimination of the base was observed.

As an alternative, we decided to use Dess-Martin periodinane. Thus, treatment of (**10**) and (**11**) with Dess-Martin periodinane (4.5 eq) in methylene chloride at 0°C during 10 h followed by addition, in situ, of ethynyl magnesium bromide or vinyl magnesium bromide in tetrahydrofuran at −78°C gave lyxo-adducts (**12**–**15**), respectively, with high stereoselectivity.

For the deblocking of these nucleosides, compounds (**12**) and (**13**) were treated with tertrabutylammonium fluoride in tetrahydrofuran to obtain compounds (**16**) and (**17**), respectively. On the other hand, compounds (**14**) and (**15**) were deblocked as in the case of nucleosides (**12**) and (**13**) and further treated with NH_3/MeOH to furnish quantitatively the desired nucleosides (**18**) and (**19**).

The structures of these compounds were confirmed by ^1H and ^{13}C-NMR and mass spectrometry along with elemental analysis. Nucleosides (**16–19**) were examined in vitro against a panel of human tumor cell lines. No marked cytotoxicity was noted. The antiviral tests of these nucleosides are still in progress.

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