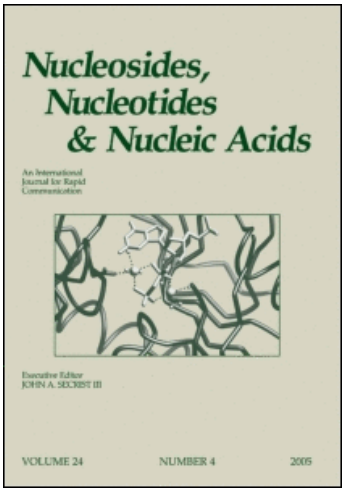

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Jean-François Griffon[a]; John A. Montgomery[a]; John A. Secrist III[a]
[a] Southern Research Institute, Birmingham, Alabama, U.S.A.

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SYNTHESIS AND ANTIPROLIFERATIVE ACTIVITY OF SOME 4′-C-HYDROXYMETHYL-α- AND -β-D-*ARABINO*-PENTOFURANOSYL PYRIMIDINE NUCLEOSIDES

Jean-François Griffon, John A. Montgomery, and John A. Secrist III*

Southern Research Institute, P.O. Box 55305, Birmingham, Alabama 35255-5305

ABSTRACT

A suitably protected 4-C-hydroxymethyl-*arabino*-pentofuranose was prepared and condensed with the following nucleobases: uracil, 5-fluorouracil and thymine. The corresponding cytosine and 5-fluorocytosine derivatives have also been obtained respectively from the uracil and 5-fluorouracil nucleosides. Separation of the anomeric mixtures followed by deprotection afforded the target compounds that were found to be non-cytotoxic to CCRF-CEM leukemia cells.

In the search for new antineoplastic or antiviral agents, recent interest has been focused on 4′α-C-branched-chain sugar nucleosides: various 4′α-C-branched-chain 2′-deoxynucleosides, such as 4′α-C-methyl- (1–5), -fluoromethyl- (6), -cyano- (1,7) -ethynyl- (1,3,8) and -ethenyl (1) -2′-deoxycytidine have been reported to have potent antileukemic activity in vitro. Two 4′α-C-branched *arabino*-pentofuranonucleosides, 1-(4α-C-methyl- (4,5) and -fluoromethyl (1) -β-D-*arabino*-pentofuranosyl)cytosine have also exhibited a significant cytotoxic effect on leukemia cells. Nevertheless, very few 4′-C-hydroxymethyl have been reported in the literature and the authors have limited their work to the synthesis of β-D-xylo-, ribo- and -2′-deoxyribo nucleosides (9,10). 4′-C-hydroxymethyl analogues of AZT, d4T, and

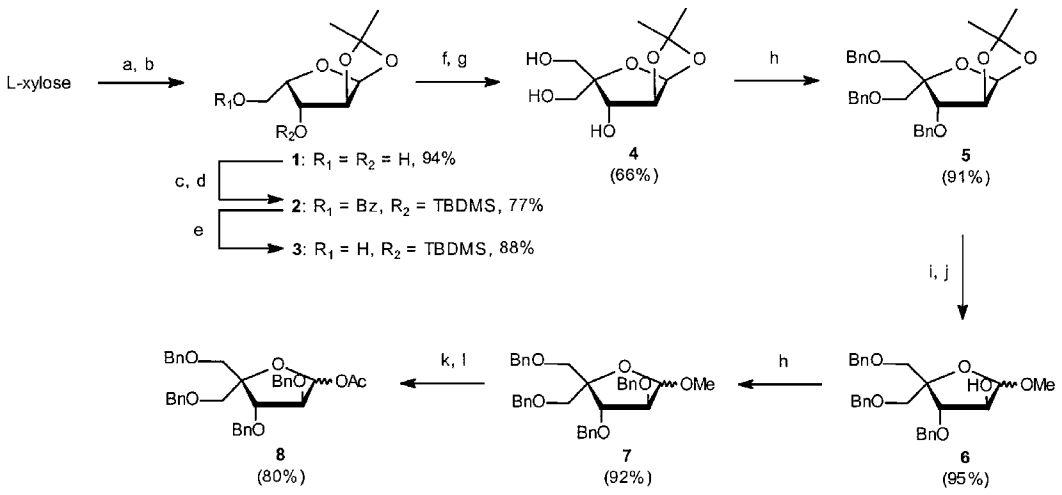
*Corresponding author.

ddT have also been reported (7,12). Based on these considerations, a series of 4′-C-hydroxymethyl-α- and -β-D-*arabino*-pentofuranosyl pyrimidine nucleosides has been prepared and evaluated as potential anticancer agents.

CHEMISTRY

The suitably protected 4-C-hydroxymethyl-*arabino*-pentofuranose **8** was prepared in 13 steps from L-xylose (Scheme 1). Selective benzoylation of the primary hydroxyl group of the 1,2-*O*-isopropylidene intermediate **1**, followed by silylation of the 3-hydroxyl group, and debenzoylation gave **3**. Oxidation of the 5 position of **3** under Pfitzner-Moffatt conditions afforded a 5-aldehydo pentofuranose intermediate which was subsequently subjected to an aldol condensation-crossed Cannizzaro reaction sequence in the presence of formaldehyde in aqueous sodium hydroxyde (10,12). The introduction of the C-4 linked hydroxymethyl in basic conditions also resulted in the deprotection of the 3-*O*-*t*-butyldimethylsilyl group (1), but without any epimerisation at the C-3 (13). The 3,5 and 6-hydroxyl groups of **4** were then benzylated to afford **5**. Cleavage of the 1,2-*O*-isopropylidene group followed by methylation of the anomeric hydroxyl led to the methyl glycoside **6**. The 2-hydroxyl group of **6** was benzylated to give the tetrabenzylated derivative **7**. Compound **8** was finally obtained after hydrolysis of the methyl glycoside **7** and acetylation of the anomeric hydroxyl.

Condensation of **8** respectively with silylated uracil, thymine or 5-fluorouracil afforded the fully corresponding benzylated nucleosides as α:β mixtures, separable by silica gel chromatography. Conversion of **9**α, β and **11**α, β into the corresponding cytosine and 5-fluorocytosine nucleosides **15**α, β and **16**α, β was carried



Conditions: (a) Me_2CO, H_2SO_4, $CuSO_4$; (b) 0.2% HCl; (c) C_6H_5COCl, pyridine, 0°C; (d) TBDMSCl, imidazole, pyridine, r. t; (e) MeONa, MeOH/toluene; (f) DMSO, DCC, Cl_2CHCO_2H, benzene/pyridine, r. t.; (g) CH_2O, NaOH, H_2O/dioxane, r. t.; (h) BnBr, NaH, $Bu_4N^+I^-$, THF, r. t.; (i) 85% CH_3CO_2H, H_2SO_4, r. t.; (j) MeOH, H_2SO_4, r. t.; (k) 90% CF_3CO_2H, 5-15°C; (l) Ac_2O, pyridine, r. t.

Scheme 1.

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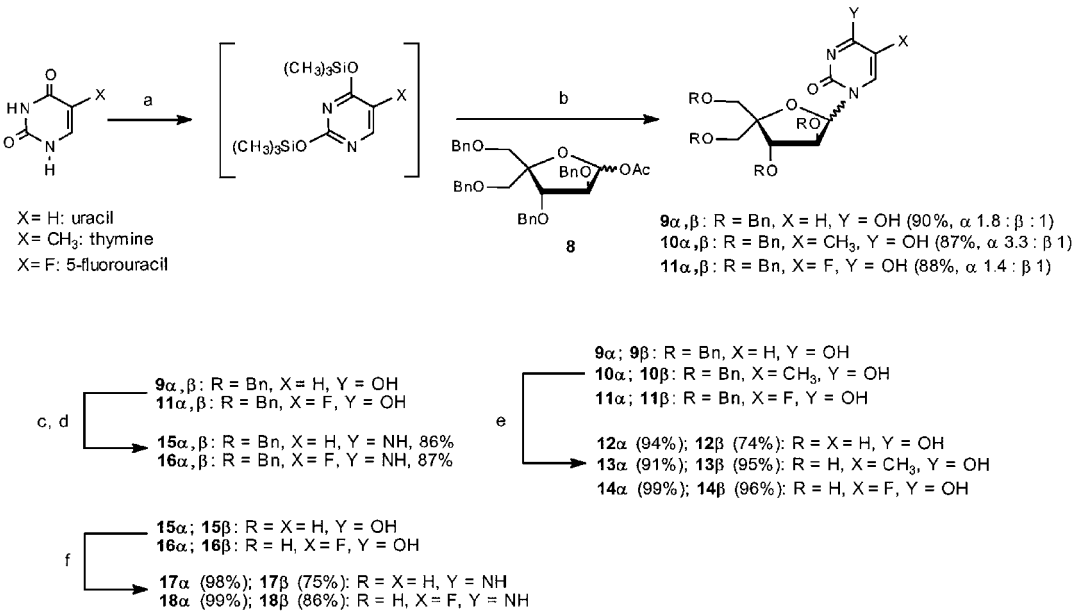

Conditions: (a) HMDS, $(NH_4)_2SO_4$, reflux; (b) trimethylsilyltrifluoromethanesulfonate, 1,2-dichloroethane, r. t.; (c) Lawesson's reagent, 1,2-dichloroethane, reflux; (d) methanolic ammonia, steel bomb, 100°C; (e) atm. pres. H_2, Pd/C, methanol/AcOH, r. t.; BCl_3, dichloromethane, -70°C

Scheme 2.

out *via* a treatment with Lawesson's reagent, which led to the **4**-thioamide derivatives, followed by a treatment with methanolic ammonia at 100°C. Finally, benzyl ether protective goups were cleaved by catalytic hydrogenation or treatment with a boron trichloride solution to afford the target compounds **12–14**α, **12**β**–14**β and **17–18**α, **17–18**β (Scheme 2).

BIOLOGICAL EVALUATIONS

All the 4′-C-hydroxymethyl-*arabino*-pentofuranosyl pyrimidine nucleosides **12**α, **13**α, **14**α, **17**α, **18**α and **12**β, **13**β, **14**β, **17**β, **18**β were found to be non-cytotoxic to CCRF-CEM leukemia cell at the highest level tested (40 μg/ml).

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