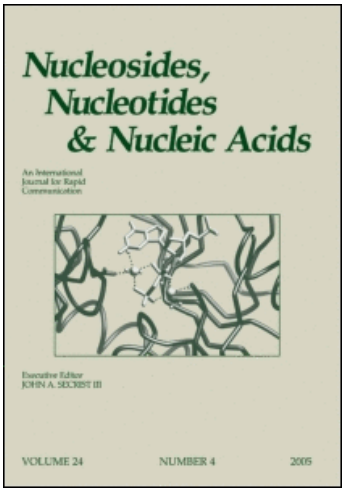

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SYNTHESIS AND ANTI-VIRAL PROPERTIES OF 2',3'-DIDEOXY-3',4'-DIHYDROXYMETHYL SUBSTITUTED PYRIMIDINE NUCLEOSIDE ANALOGUES

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Abstract *Some 2',3'-dideoxy-3', 4'-dihydroxymethyl nucleoside analogues have been synthesised starting from diacetone-D-glucose. The 3-C-hydroxymethyl group was introduced by selective hydroboration-oxidation of the 3-C-methylene derivative. The 4-C-hydroxymethyl group was obtained by an aldol condensation followed by* in situ *cross Canizzaro reduction. Glycosylation using silylated pyrimidine bases furnished the 2',3'-dideoxy -3',4'-dihydroxymethyl nucleoside analogues.*

Introduction

Nucleoside analogues are today used in therapy to combat HIV. Some of the most useful modifications of nucleosides has involved 3'-deoxygenation of the ribose moiety combined with 3'-hydroxy substitution. This has resulted in compounds such as AZT, FLT, ddI, ddC, and 2',3'-dideoxy-3'-hydroxymethylcytidine which are higly potent inhibitors of HIV replication *in vitro.*[1] Introducing substituents in the 4'-position of nucleosides, eg. 4'-azidothymidine[2] and 4'-cyanothymidine,[3] have also resulted in active

compounds. 4'-Hydroxymethyl substituted nucleoside analogues have also been synthesised altough no biological results were reported.[3]

We were interested in investigating the anti-viral properties of compounds having hydroxymethyls both in the 3'- and 4'-position of 2',3'-dideoxynucleosides. This paper describes the synthesis and biological activity of 2',3'-dideoxy-3',4'-dihydroxymethyl substituted nucleosides.

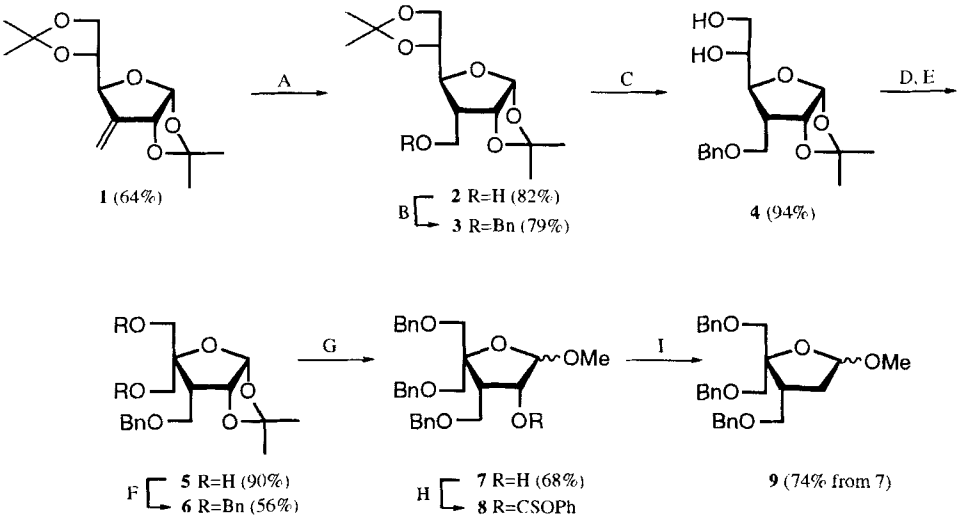
Result and Discussion

The starting material, 3-deoxy-3-methylene-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**1**), was readily obtained from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose in two steps. The olefin **1** was converted regio- and stereo-selectively to the 3-hydroxymethyl compound **2** (82% yield) via hydroboration using borane-dimethyl sulfide followed by oxidation with aqueous hydrogen peroxide in tetrahydrofuran-water.[4] Benzylation of **2** with benzylbromide and sodium hydride in dimethyl formamide gave **3** in 79% yield. The 3-deoxy-3-benzyloxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**) was hydrolysed selectively using 70% acidic acid to the 5,6-diol **4** almost quantitatively. The resulting diol was cleaved with sodium meta-periodate in tetrahydrofuran-water (3:1) to give the corresponding aldehyde which was immediately alkylated using 37% aqueous formaldehyde followed by *in situ* Canizarro reduction[5] to give the reduced alkylated product **5** in 90% yield from the diol **4.** Benzylation of the hydroxy groups gave **6** in 56% yield.

Compound **6** was converted to the corresponding 1,2-diacetate by hydrolysis of the 1,2-*O*-isopropylidene group using acidic acid followed by acetylation with acetic anhydride in pyridine. Attempts to glycosylate this product with bis-(trimethylsilyl)thymine, in various solvents, failed in our hands. We therefore chose to activate the glycosyl donor by deoxygenating the 2-position prior to glycosylation.

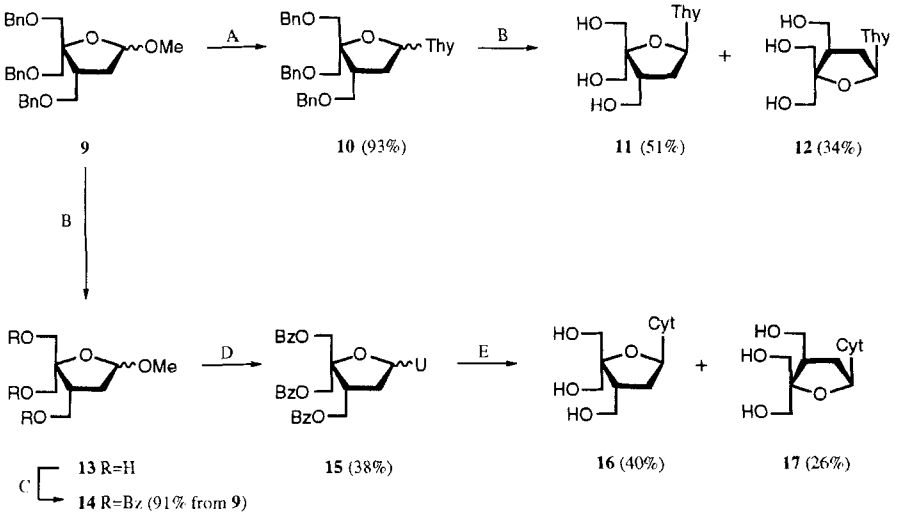
Treatment of **6** with 1% iodine in methanol[6] gave the methyl glycoside **7** (68% yield), as an anomeric mixture which was treated with 1.3 equivalents of phenoxythiocarbonyl chloride in 1,2-dichloroethane/pyridine yielding methyl 3,4-*C*-debenzyloxymethyl-5-*O*-benzyl-2-*O*-phenoxythiocarbonyl-α,β-D-*erythro*-pentofuranoside (**8**). Treatment of **8** with an excess of tri-*n*-butyltin hydride in refluxing toluene furnished, after column chromatography, the key intermediate methyl 3,4-*C*-debenzyloxymethyl-5-*O*-benzyl-2-deoxy-α,β-D-*erythro*-pentofuranoside (**9**) in 74% yield from **7**.

The furanoside **9** was condensed with bis(trimethylsilyl)thymine in the presence of *tert*-butyldimethylsilyl triflate in dichloromethane and acetonitrile (4:1) to give an anomeric mixture of nucleoside **10** in 93% yield.[7] Catalytic hydrogenation in ethylacetate and



A; 1. BH_3:Me_2S, THF 2. H_2O_2 (aq.), 2M NaOH, THF/H_2O B; NaH, BnBr, DMF C; 70% HOAc D; $NaIO_4$, THF/H_2O E; HCHO (aq), 1M NaOH F; NaH, BnBr, DMF G; 1% I_2 in MeOH H; Phenoxythiocarbonyl chloride, 1,2-dichloroethane/pyridine I; Bu_3SnH, AIBN, toluene

Scheme 1



A; Bis(trimethylsilyl)thymine, TBDMSiOTf, CH_2Cl_2/MeCN B; H_2, Pd/C, EtOAc C; BzCl, pyr. D; Bis-(trimethylsilyl)uridine, TBDMSiOTf, CH_2Cl_2/MeCN E; Triazole, $POCl_3$, MeOH/NH_3

Scheme 2

separation of the anomers by column chromatography gave **11** and **12** in 51% and 34% yield respectively. To obtain the corresponding cytosine derivative, compound **9** was debenzylated using hydrogenation *cf. vide supra*, and subsequently protected as its benzoylesters using benzoyl chloride in pyridine to give **14** in 91% yield from **9**. Condensation of **14** with bis(trimethylsilyl)uracil cf. *vide supra,* gave **15** as an anomeric mixture in 38% yield. Compound **16** and **17** was prepared, in 40% and 26% yield, respectively, by reacting the anomeric mixture of **15** with triazole, phosphorus oxychloride and triethyl amine in acetonitrile followed by methanolic ammonia at 40°C.[8] Attempts to separate the anomeric mixture using either column chromatography or HPLC was unsuccessful.

Compounds **11**, **12**, **16** and **17** were tested in an *in vitro* assay for HIV-1 RT inhibition[9] and in a XTT assay for anti-HIV-1 cytopathic effects.[10] All compounds were found to be inactive in the assays.

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