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SYNTHESIS 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 using an aldol condensation followed by in situ cross Canizzaro reduction in order to introduce the 4'-hydroxymethyl group. Glycosylation using silylated pyrimidine bases furnished the 2',3'-dideoxy -3',4'-dihydroxymethyl nucleoside analogues.

Introduction

Nucleoside analogues occupy a prominent position among inhibitors of HIV activity *in vitro*. Some of the most promising modifications of nucleosides has involved 2',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 highly potent inhibitors of HIV replication *in vitro*.[1] Introducing substituents in the 4'-position of nucleosides has also emerged as an attractive route to active substances and 4'-azidothymidine[2] demonstrates a similar inhibitory profile to that of AZT. Anti-HIV activity has also been reported for 4'-cyanothymidine.[3] 4'-Hydroxymethyl substituted nucleoside analogues have been synthesised but no biological results were reported.[3]

In this paper we describe the synthesis and biological activity of 2',3'-dideoxy-3',4'-dihydroxymethyl substituted pyrimidine nucleosides.

Result and Discussion

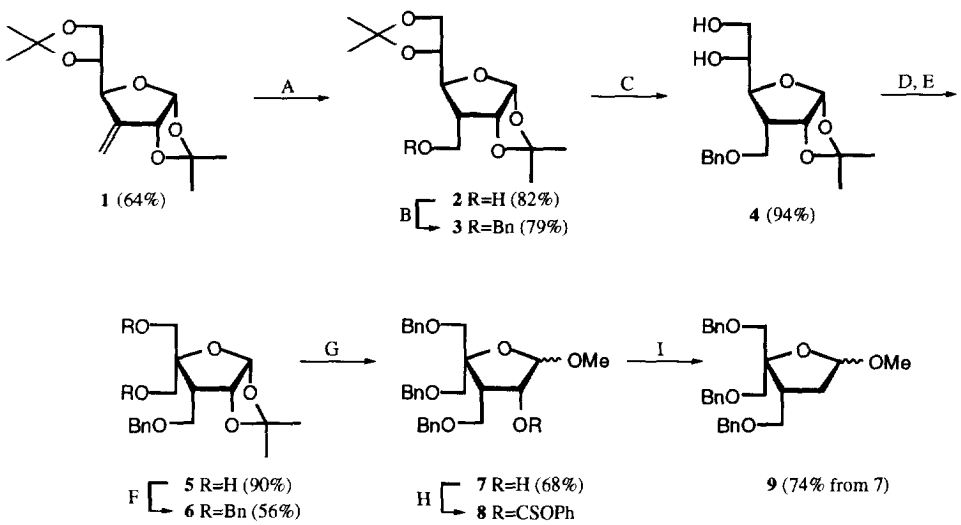
The starting material, 3-deoxy-3-methylene-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose[4] (**1**), was readily obtained from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose in two steps. The olefin **1** was converted regio and stereo selectively to the 3-hydroxymethyl compound **2** (82% yield) via hydroboration

using borane-dimethylsulphide followed by oxidation with aqueous hydrogen peroxide in tetrahydrofuran-water.[4] Benzylation of **2** with benzylbromide and sodium hydride in dimethylformamide gave **3** in 79% yield. Compound **3** was hydrolysed selectively using 70% acidic acid to the 5,6-diol **4** in 94% yield. 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 to give the reduced alkylated product **5** in 90% yield from the diol **4**.[5,6] Benzylation of **5** 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 aqueous acetic acid followed by acetylation with acetic anhydride in pyridine. Attempts to glycosylate this product with bis-(trimethylsilyl)thymine[9], in various solvents failed and as a consequence, we chose to activate the glycosyl donor by deoxygenating the 2-position prior to glycosylation.

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

Scheme 1

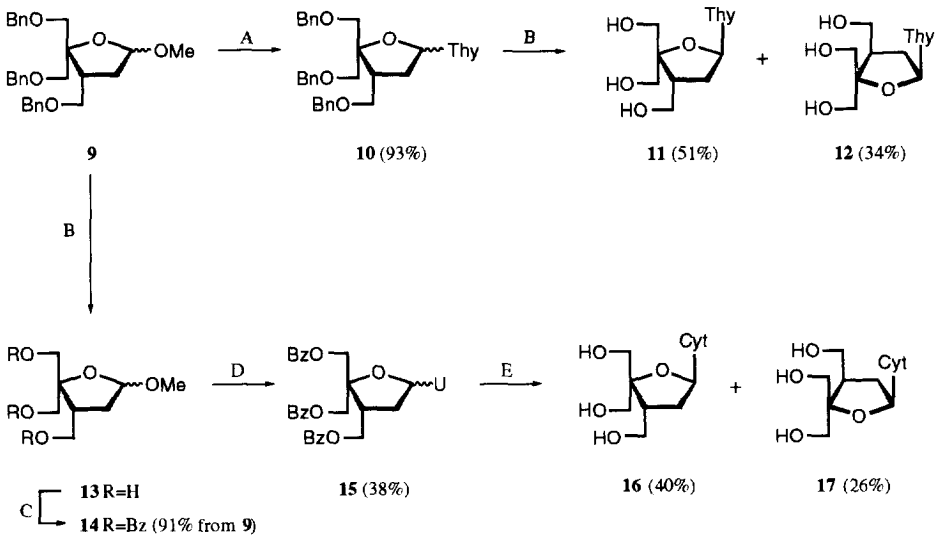


A; 1. BH_3:Me_2S, THF 2. H_2O_2 (aq.), 2M NaOH, THF/H_2O B; NaH, BnBr, DMF C; 70% HOAc D; $NaIO_4$, THF/H_2O E; HCHO (aq), 1M NaOH F; NaH, BnBr, DMF G; 1% I_2 in MeOH H; Phenoxythiocarbonyl chloride, 1,2-dichloroethane-pyridine I; Bu_3SnH, AIBN, toluene.

Furanoside **9** was condensed with bis(trimethylsilyl)thymine[9] in the presence of *tert*-butyldimethylsilyl triflate in dichloromethane-acetonitrile (4:1) to give an anomeric mixture of nucleoside **10** in 93% yield. Catalytic hydrogenation in ethylacetate followed by separation of the anomers by silica gel column chromatography gave 1-[2,3-dideoxy-3,4-*C*-dihydroxymethyl-β-D-*erythro*-pentofuranosyl]thymine (**11**) and 1-[2,3-dideoxy-3,4-*C*-dihydroxymethyl-α-D-*erythro*-pentofuranosyl]thymine (**12**) in 51% and 34% yield, respectively. To obtain the corresponding cytosine derivative, compound **9** was debenzylated by catalytic 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. 1-[2,3-Dideoxy-3,4-*C*-di-hydroxymethyl-α- and -β-D-*erythro*-pentofuranosyl]cytosine (**16** and **17**) were prepared in 66% yield (α:β ratio 1:1.5), by reacting the anomeric mixture of **15** with triazole, phosphorus oxychloride and triethyl amine in acetonitrile followed by methanolic ammonia at 40°C.[10] Attempts to separate the anomeric mixture using either silica gel column chromatography or HPLC was unsuccessful.

Scheme 2



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.*

Biological Results

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

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References and Notes

(1) Johnston, M. I.; Hoth, D. F. *Science* **1993**, *260*, 1286-1293.

(2) Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440-1451.

(3) O-Yang, C.; Wu, H. Y.; Fraser-Smith, E. B.; Walker, K. *Tetrahedron Letters* **1992**, *33*, 37-40.

(4) Mazur, A.; Tropp, B. E.; Engel, R. *Tetrahedron* **1984**, *40*, 3949-3956.

(5) Youssefyeh, R. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1979**, *44*, 1301-1309.

(6) Attempts to introduce the hydroxymethyl group with the hydroxyl group protected as the corresponding *t*-butyldimethylsilyl ether resulted in a dramatically lower yield.

(7) Szarek, W. A.; Zamojski, A.; Tiwari, K. N.; Ison, E. R. *Tetrahedron Letters* **1986**, *27*, 3827-3830.

(8) Compound **9**: ^{1}H NMR spectra (recorded on a JEOL GSX-270 instrument, shifts are given in ppm downfield from tetramethylsilane in $CDCl_3$ at 25°C). δ 1.99 (m, 2H, H2'), 2.58 (m, 1H, H3'), 3.34 (s, 3H, OMe), 3.48-3.73 (m, 6H, CH_2O), 4.37-4.66 (m, 6H, CH_2Ph), 5.12 (d, 1H, H1'), 7.20-7.37 (m, 15H, arom.)

(9) Vorbrüggen, H.; Bennua, B. *Chem. Berichte* **1981**, *114*, 1279-1285.

(10) Divakar, K. J.; Reese, C. B. *J. Chem. Soc. Perkin I* **1982**, 1171.

(11) Vrang, L.; Bazin, H.; Remand, G.; Chattopadhyaya, J.; Öberg, B. *Antiviral Res.* **1987**, *7*, 139.

(12) Weislow, O. S.; Kiser, R.; Fine, D. L.; Bader, J.; Shoemaker, R. H.; Boyd, M. R. *J. Nat. Cancer Inst.* **1989**, *81*, 577-586.

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