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EFFICIENT SYNTHESIS OF 1,2-*seco* AND 1,2-*seco* 2-*nor* PYRIMIDINE AND PURINE NUCLEOSIDES.

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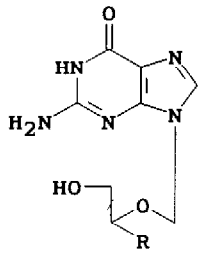
Unprotected silylated purines and pyrimidines (adenine, guanine, cytosine, thymine) reacted with acetoxymethyl ether (acyclic sugar analogues) under solid PTC conditions, using KI and dibenzo-18-crown-6 in benzene-acetonitrile (1:1, v/v) to give regiospecifically the corresponding N-9 purine and N-1 pyrimidine acyclic nucleosides in fairly good yields.

Since the discovery of Acyclovir **1** [9-(2-hydroxyethoxy)-methyl]guanine as a selective antiherpes agent[1], attention has focused to the synthesis and antiviral evaluation of an increasing number of acyclic nucleoside analogues[2,3]; one of the most potent compounds synthesized to date is DHPG **2** ([9-(1,3-dihydroxy-2-propoxy)methyl] guanine[4].

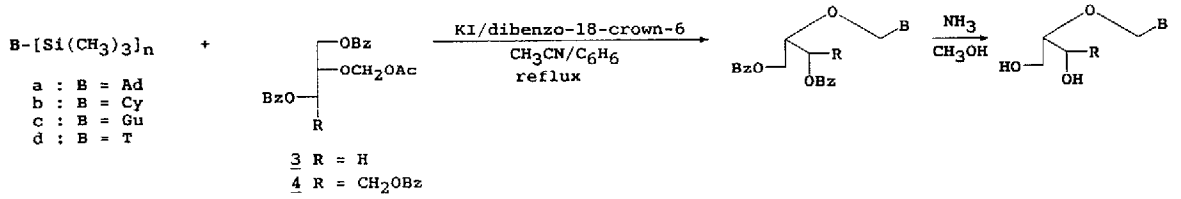


1 R = H
2 R = CH_2OH

Altered nucleosides bearing acyclic variations in the sugar moiety were synthesized either from natural nucleosides[5] (*i.e.* 2,3-*seco* nucleosides) or by reaction between the appropriate pseudo-sugar moiety and the purine or pyrimidine ring. To date, these latter procedures applied to the synthesis of acyclic nucleosides of the general formula R-O-CH_2-B (B=N-9 purinyl or N-1 pyrimidinyl) started from halomethyl ethers R-O-CH_2X (X = Br, Cl) which were reacted with silylated nucleobases with or without[6,7] catalyst (Friedel-Crafts[8], p.toluene sulfonic acid[4], triethylamine[9,10], mercuric cyanide[11,12], nBu_4NI[12-16], ZnI_2[17], CsI[18], $(CH_3)_3SiI$[19,20], TDA[21]). Whenever it

was possible, condensation occurred between the sodium salt of the base and halomethyl ether[22]. Finally, transpurination reaction had been applied to the synthesis of acyclonucleosides[23].

Most of these reactions described in the literature exhibit low regioselectivity and their yields are generally unsatisfactory. As we are interested in the synthesis of chiral acyclic nucleosides, we devised a simple and general method which affords high yields of the natural N-9 purine and N-1 pyrimidine derivatives as exemplified in scheme 1. In this way the readily available protected acetoxymethyl ether of glycerol **3**[10] and homochiral (2S,3S) L-threitol **4**[24] were reacted with silylated nucleobases (**a**,**b**,**c**,**d**) (1 mmol) in refluxing acetonitrile-benzene mixture (1:1, v/v, 10 ml) under phase transfer conditions using dibenzo-18-crown-6 (0.2 mmol) and potassium iodide (0.8 mmol). After filtration, the solution was evaporated under reduced pressure. The residue was subjected to a short column chromatography in order to eliminate the coronand from the desired compounds **5** and **6**. As reported in scheme 1, N-9 purinyl and N-1 pyrimidinyl acyclic nucleosides were obtained as the sole products in fairly good yields. Removal of the benzoyl groups by methanolic ammonia gave the compounds **7** and **8** in quantitative yields.



	R	Yield (%)	time (days)		R
5a	H	76	5	**7a**	H
5b	H	81	2	**7b**	H
5c	H	80	1	**7c**	H
5d	H	80	2	**7d**	H
6a	CH_2OBz	78	4	**8a**	CH_2OH
6b	CH_2OBz	87	5	**8b**	CH_2OH
6c	CH_2OBz	88	4	**8c**	CH_2OH
6d	CH_2OBz	87	3	**8d**	CH_2OH

Scheme 1

The unprotected acyclic nucleosides **7** derived from glycerol were fully characterised[25,31] and their analytical data were in accordance with the literature.

Among the 1,3S,4-trihydroxy-2S-butoxymethyl nucleosides **8a**-**8d**, two (*i.e.* **8a** and **8c**) were prepared[14,28,29] in an overall yield not exceeding 30%. It is worth mentioning that in the case of the guanine derivative **8c**, an equal amount of N-9 and N-7 isomers were obtained[29,14] and had to be separated. Analytical data[30,31] for all compounds **6a**-**6d** and **8a**-**8d** reported

in this communication were consistent with the structures given.

This process constitutes a simple and highly useful methodology for the regiospecific synthesis of acyclic nucleosides. Moreover, it has three advantages: - The exocyclic amino groups of nucleobases (Ad, Cy, Gu) need no further protection. - An acetoxymethyl ether can be used directly avoiding the preparation of the corresponding halomethyl ether. - High coupling yields are obtained. This approach opens the way to an easy regiospecific synthesis of various other series of acyclonucleosides.

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24. This compound and its enantiomer were easily synthesized in five steps from L and D-tartaric acid dimethyl esters respectively. Their synthesis will be published in the forthcoming full paper.
25. **7a**: mp 182-183° (lit[9] mp 184-186°) λ_{max} (EtOH) 260; **7b**: mp 141-142° (lit[25] mp 141-142°) λ_{max} (EtOH) 269; **7c**: mp > 300°dec. (lit[4,27] mp > 285°dec.) λ_{max}(EtOH)255; **7d**: mp 155-156° (lit[9] mp 155-156°) λ_{max} (EtOH) 264.
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30. ^{1}H-NMR (300 MHz, $CDCl_3$) ppm from TMS: **6a**: 8.2 (s,H_8), 7.36-7.93 (m,H_2, aromatics), 6.72 (br s, NH_2), 5.80 (ABq,NCH_2O), 5.64 (q,$H_{3'}$), 4.46-4.69 (m, $H_{4'4"}$,$H_{1'1"}$, $H_{2'}$). **6b**: 7.19-7.96 (m,NH_2,H_6,aromatics), 5.74 (d,H_5,J= 7.35Hz), 5.67 (m,$H_{3'}$), 5.41 (d,NCHO,J=10.58Hz), 5.19 (d,NCHO), 4.41-4.65 (m,$H_{4'4"}$,$H_{1'1"}$,$H_{2'}$). **6c**: (DMSO-d_6): 10.84 (s,NH), 8.17 (s,H_8), 7.45-7.88 (m,aromatics), 6.22 (s,NH_2), 5.80 (s,NCH_2O), 5.64 (m,$H_{3'}$), 4.39-4.67 (m, $H_{4'4"}$, $H_{1'1"}$,$H_{2'}$). **6d**: 7.39-8.13 (m,NH,aromatics), 7.03 (d,H_6,J=1.28Hz), 5.72 (q, $H_{3'}$), 5.43 (d,NCHO,J=10.91Hz), 5.20 (d,NCHO), 4.53-4.76 (m, $H_{4'4"}$,$H_{1'1"}$,$H_{2'}$), 1.67 (d,CH_3,J=1.28Hz).
31. **8a**: mp 200° (lit[14] mp 205°) λ_{max}(EtOH) 260; **8b**: foam, λ_{max}(EtOH) 269; **8c**: mp 295°dec. (lit[29] no data) λ_{max}(EtOH) 253; **8d**: mp 112-113° λ_{max} (EtOH) 264.

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