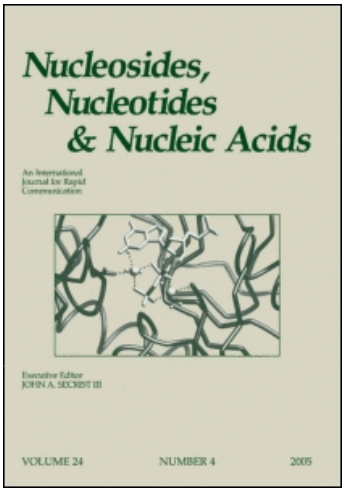

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Synthesis of the β-2',3'-Unsaturated Pentopyranosyl Nucleosides and Their 3'-Hydroxymethyl Congeners

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SYNTHESIS OF THE β-2',3'-UNSATURATED PENTOPYRANOSYL NUCLEOSIDES AND THEIR 3'-HYDROXYMETHYL CONGENERS

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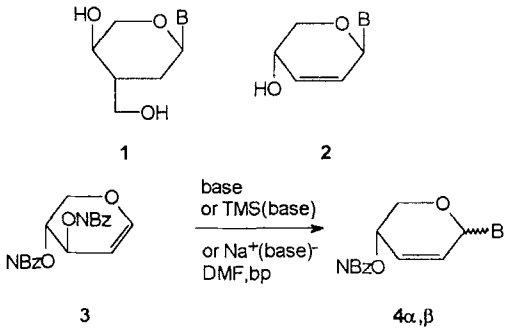
ABSTRACT : Fusion of the glycal **3** and purines/pyrimidines without acid catalyst provides anomeric mixtures of the 2',3'-unsaturated pentopyranosyl nucleosides **4**, which have been worked out to furnish the 3'-hydroxymethyl analogues, e.g. **5**.

Recently we became interested in the synthesis of pentopyranosyl nucleosides as building blocks for oligonucleotides synthesis[1].

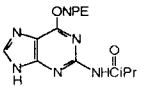
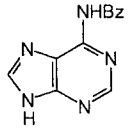
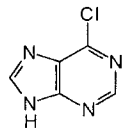
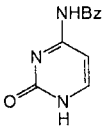
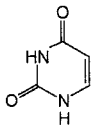
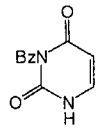
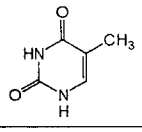
Compounds **1** which have a 3'-hydroxymethyl appendix represent one of the target molecules. These nucleoside analogues have not been reported before[1,2]. These compounds (B=T,U) have been prepared from 2',3'-unsaturated derivatives **2**, which in turn have been prepared from the β-D-xylopyranosyl nucleosides via a stepwise procedure[2]. Here we report a simple synthesis of **2** by a "no acid added" Ferrier rearrangement of 3,4-di-O-p-nitro-benzoyl-D-xylal **3** and purine/pyrimidine bases, which furnishes compounds **4α,β**.

Fusion of **3** with the heterocyclic bases, their sodium salts or trimethylsilylated bases in boiling DMF without adding acid catalyst furnished compounds **4α,β** (SCHEME 1), from which the β anomers

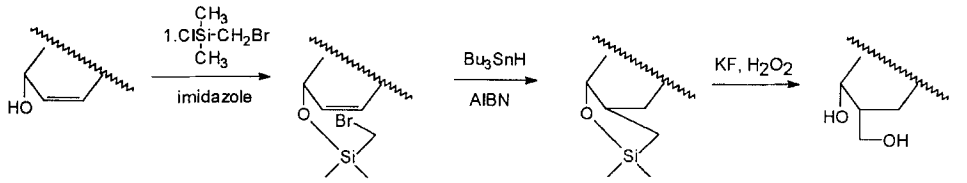


SCHEME 1

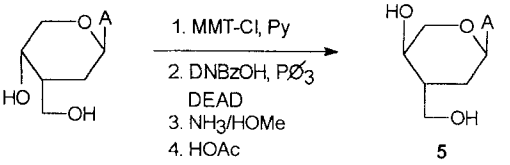
TABLE 1

Base	Reactive form (action time)	4, total yield, %	β : α	δ C5' (DMSO-d_6)	
				2 β	2 α
	TMS derivative 40 min	52 %	47:26[a]	67,17	65,02
	1. used as such 10 min	60 %	25:20[a]	67,16	65,02
	2. TMS derivative 10 min	28-44 %	ca 2:1		
	1. used as such 10 min	57 %	1:1[b]	66,94[c]	64,75[c]
	2. Na salt 15 min	39 %	1:2		
	TMS derivative 15 min	73 %	1:1[b]	68,00	67,05
	Na salt 1 h	23 %	3:5[b]	68,03	67,36
	used as such 1,5 h	30 %	1:1[b]		
	TMS derivative 7 h	48 %	1:1[a]	68,17	67,72

a separable after 4'-O-deprotection (cat. NaOMe in dioxane-methanol)
b separable as 4'-p-nitrobenzoates
c recorded for 6-methoxypurine derivative and further confirmed after conversion to adenine derivative

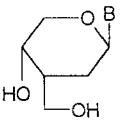
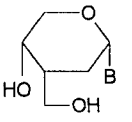


SCHEME 2



SCHEME 3

TABLE 2

		
B[a] = A	76 %	57 %
C	6 %[b]	64 %[b]
G	13 %[b]	20 %[b]

a N-deacylation has taken place in all cases during the KF-H_2O_2 reaction.
b Isolated after O,N-acetylation

could be isolated in synthetically satisfactory amounts. By using this methodology formation of the 3'-substituted products could be avoided. Lewis acid promoted reactions of di-O-acetyl-D-xylal with N-benzoyl adenine or thymine have been published to furnish exclusively 3'-substituted[3] or α-configured[4] nucleosides, respectively.

The anomeric configurations of the olefins **2α,β** have been assigned on the basis of the ^{13}C spectra : in all β anomers the carbon atoms C5' resonate downfield when compared to the α anomers as a consequence of smaller steric compression around the C5' nuclei. This assignment has been confirmed by X-ray analysis of **2β** (B=A,C,G^{iBu}) and by comparison with **2β** (B=T,U) prepared independently from the β-D-xylopyranosyl nucleosides[2].

Using a free radical procedure (SCHEME 2) a 3'-hydroxymethyl appendix has been introduced in **2α,β**, ($B=A^{Bz},C^{Bz},G^{iBu}$) to furnish the compounds listed in TABLE 2.

Transformations as shown in SCHEME 3 provided the target compound **5**.

This scheme has been used only for the synthesis of the adenosine analogue due to very low yields of the branching reactions for the b anomers of B=C,G (TABLE 2). Therefore, an alternative synthesis of the cytidine and guanosine analogues based on L-arabinose has been devised which circumvents a free-radical branching. This research is in progress now.

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Technical assistance of Yves Van Roosbroeck and editorial help of Mieke Vandekinderen are highly appreciated.

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2. D. Doboszewski, P. Herdewijn, in preparation.
3. N.B. Khripatsh, J.A. Mikhalopulo, A.A. Akhryem, *Khim. Hetero. Soedin.* **1982**, 111-117.
4. M. Bessodes, M.-J. Egnon, J. Filippi, K. Antonakis, *J. Chem. Soc. Perkin I* **1990**, 3035-3039.
5. Selected data of the compound **5** : cryst. MeOH, no mp. up to 300°;
   λ_{max} 260.0 nm (ε = 12850 (MeOH)).
   The symbols H6',6" and C6' refer to the 3'-hydroxymethyl appendix.
   ^1H (200 MHz, CH_3OD) : 8.45, 8.29 (s, H2,8); 6.10 (dd, 1H, $J_{1'2'eq}$ = 3.7 Hz; $J_{1'2'ax}$ = 8.0 Hz, H1'); 4.05 (dd, 1H, $J_{5'eq4'}$ = 2.5 Hz; $J_{5'eq5'ax}$ = -11.9 Hz, $H_{5'eq}$); 3.98-3.77 (unresolved, 3H, H4',6',6"); 3.70 (dd, 1H, $J_{5'ax4'}$ = 4.4 Hz; $J_{5'ax5'eq}$ = -11.8 Hz, $H_{5'ax}$); 2.81 (ddd, 1H, $J_{2'ax3'}$ = 5.0 Hz; $J_{2'ax1'}$ = 7.7 Hz; $J_{2'ax2'eq}$ = -13.5 Hz, $H_{2'ax}$); 2.31-2.20 (unresolved, 1H, H3'); 2.12 (ddd, 1H, $J_{2'eq1'}$ = 3.5 Hz; $J_{2'eq3'}$ = 5.9 Hz; $J_{2'eq2'ax}$ = -13.6 Hz; $H_{2'eq}$).
   ^{13}C NMR (50 MHz, CD_3OD) : 156.48, 152.92, 149.33, 139.81, 119.16 (C adenine); 79.05, C1'; 67.77, 62.02, C5',6'; 65.22, C4'; 41.76, C3'; 28.33, C2'.