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Synthesis of β Configured 2',3'-unsaturated Pentopyranosyl Nucleosides

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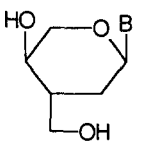
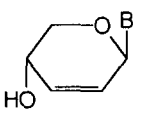
Abstract *: Coupling of 3,4-di-O-p-nitrobenzoyl-D-xylal with heterocyclic bases in boiling DMF in the absence of externally added acid catalyst constitutes a convenient way to β configured 2',3'-unsaturated pentopyranosyl nucleosides. Formation of the 3'-substituted products (without migration of a double bond) has been practically avoided.*

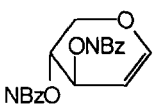
Recent synthetic efforts in our laboratory are concentrated on the synthesis of pentopyranosyl nucleosides of the general formula **1**[1,2]. Compounds of this type can be obtained from 2',3'-unsaturated nucleosides (**2**) via a known three step process[3,4] [(i) $(BrCH_2)Cl(CH_3)_2Si$, (ii) Bu_3SnH, (iii) KF,H_2O_2] to introduce the 3'-hydroxymethyl group, followed by inversion of configuration at the 4' position[2]. The successful execution of this process is highly dependent on the availability of the starting compound **2**.



(1)



(2)

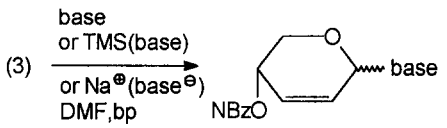


(3)

The olefins **2** (B=T,U) have been previously obtained from 2',3',4'-tri-O-acetyl-β-D-xylopyranosyl nucleosides[2,5] using a three step reaction sequence. Alternatively, the acid mediated Ferrier rearrangements of 3,4-di-O-acetyl-D-xylal using trimethylsilylated thymine[6] or N-benzoyladenine[7] have furnished only α-nucleoside or 3'-substituted product respectively. Although N-benzoylcytosine[7], 6-chloropurine[8] and some benzotriazoles[9] have furnished preparatively acceptable yields of the β/α nucleosides (**2**) together with 3'-substituted derivatives the above mentioned results with thymine and N-benzoyladenine originally discouraged us to follow this approach. Spurred by the finding that glycals can react with alcohols without added acid catalyst[10] we have investigated the reaction of 3,4-di-O-p-nitrobenzoyl-D-xylal (**3**) with heterocyclic bases in the absence of added acid. The compound (**3**) was prepared from 3,4-di-O-acetyl-D-xylal[11] [(i) NaOMe/HOMe; (ii) NBz-Cl(2.1 eq), Py; 76 %; mp. 123-124°, cryst. from EtOAc-hexane]. Reaction of equimolar amounts of the heterocyclic bases (adenine, cytosine, thymine, guanine, 6-chloropurine) and (**3**) in

DMF at b.p. during 10-40 min. (reaction with TMS(T) at ca 110° required 7 h) has furnished separable β/α mixtures of N^9 (purines) or N^1 (pyrimidines) 2',3'-unsaturated pentopyranosyl nucleosides (**4**) (Scheme 1). The same results were obtained when the sodium salt of the heterocyclic bases or when the trimethylsilylated bases were used. Some relevant data is listed in Table 1.

Scheme 1



(4)

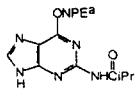
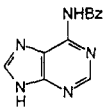
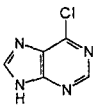
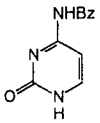
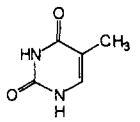
The assignment of the anomeric configurations in the 4'-O-deprotected nucleosides (**2**) is based on the ^{13}C spectra. The C-5' carbon atoms in the β anomers resonate downfield from the C-5' carbon atoms in the α anomers due to smaller steric compression in vicinity of the respected nuclei. This identification is confirmed by the further transformations of the unsaturated nucleosides to their branched chain analogues (**1**)[2] and by X-ray analysis of (**2**)[12].

From a preparative standpoint it is advantageous that the (**2α**) anomers are chromatographically less polar then the corresponding (**2β**) anomers.

The experimental procedure for this conversion is exemplified for a guanine derivative. N^2-isobutyryl-O^6-[2-(p-nitrophenyl)ethyl] guanine 12.0 g (32.4 mmol) was silylated with 250 ml of HMDS and cat. $(NH_4)_2SO_4$ overnight. The solution was evaporated and co-evaporated with dry DMF. To a DMF solution (250 ml) of this compound was added 12.8 g (31 mmol) of the glycal (**3**) at b.p. [all these operations have been performed under dry nitrogen]. After 40 min. the solvent was evaporated and co-evaporated with xylenes. During extractive workup ($CHCl_3$-sat. aq. $NaHCO_3$) the unreacted protected guanine (3.7 g) crystallized from the chloroform layer and removed. Chromatographic purification (CH_2Cl_2-MeOH 20:0.3) furnished 10.49 g of the mixture of **4α** and **4β** (52 % counted on a total guanine or 76 % counted on resorted guanine). This mixture was dissolved in 200 ml of dioxane and 300 ml of MeOH and treated with cat. NaOMe to furnish 2.58 g of (**2α**) and 4.67 g of (**2β**) (as N,O-protected compounds) after chromatography in CH_2Cl_2-MeOH 20:1).

The reactions described in this communication, proved that 2',3'-unsaturated pentapyranosyl nucleosides with a β configuration are easily available using a fusion process between di-nitrobenzoyl protected D-xylal and the heterocycle base. Because formation of the 3'-substituted side compounds can be avoided, the present procedure is currently the most straightforward for the synthesis of these anomalous nucleosides.

Table 1

Base	Reactive form	β:α	4α+β, yield,%	δ C5' (in ppm)[h]		$J_{H1'-H2'}$ (in Hz)[h]	
				2α	2β	2α	2β
	TMS derivative	47:26[d]	76[b] (52[c])	65.02	67.07	2.4	not determined
	used as such	25:20[d]	60	65.02	67.16	2.6	2.9
	1. used as such 2. Na salt	1:1[e,f] 1:2	57 39	64.75[f]	66.94[f]	1.7[f]	2.9[f]
	TMS derivative	52:46[e,g]	73	67.05	68.00	not determined	2.0
	TMS derivative	1:1[d]	48	67.7	68.2	2.0	1.9

(a) NPE, p-nitrophenylethyl;

(b) counted on a base which effectively reacted;

(c) counted on a total base used;

(d) separable after 4'-O-deprotection (cat. NaOMe in dioxane-HOMe);

(e) separable as 4'-O-nitrobenzoates;

(f) identified as 6-methoxypurine derivatives (excess NaOMe/HOMe);

(g) 4'-O-deprotected as in (d);

(h) recorded on a Varian Gemini 200 spectrometer in DMSO-d_6 solutions.

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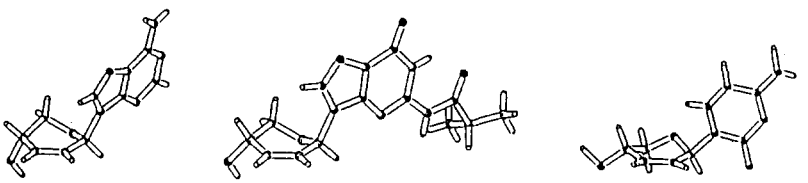
12. X-Ray structures of (**2**) B = A,G^{iBu} and C are shown below.



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