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An efficient and highly stereoselective synthesis of nucleoside derivatives from furanoid 1,2-diols

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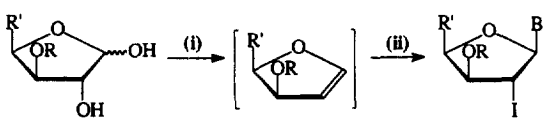
Abstract: Reaction between suitably protected furanoid glycals **1b-4b**, readily obtained from furanoid 1,2-diols (**1a–4a**), and different silylated pyrimidine bases, gave the corresponding 3′,5′- and 3′,5′,6′-*O*-protected 2′-deoxy-2′-iodo-β-D-*xylo*-pentofuranosyl **5–10** and β-D-*gluco*-hexofuranosyl **11** nucleosides, respectively. Compound **5** has been transformed into its 2′-deoxy **12** and 2′,3′-*anhydro* **14** derivatives. The high stereoselectivity of the reaction is discussed. © 1997 Elsevier Science Ltd

The synthesis of nucleoside analogues in which the sugar and/or the heterocyclic moiety have been modified have received much attention in the last recent years as a consequence of their general biological activity[1] and the potential use of such molecules as antiviral[2] and antineoplasic[3] therapeutic agents.

Among the different synthetic methods used in the chemistry of nucleosides, the most important are those that used a reaction between peracylated furanosyl halides[4], peracylated furanoid sugars[5], and *O*-protected glycofuranosyl trichloroacetimidates[6] with silylated pyrimidinic bases assisted by Lewis acid catalysts such as tin(IV) chloride, trimethylsilyl triflate, boron trifluoride etherate, etc. More recently, furanoid glycals have been also used in the synthesis of nucleosides through 1,2-*anhydro*-furanose[7] and *S*-aryl 1,2-episulfonium[8] or selenium analogues[9]. These latter methods take advantage over those previously mentioned of proceeding with higher stereoselectivities.

Recently, our group has reported[10] a new and short method for the synthesis of furanoid glycals from furanoid 1,2-diols. A general procedure for the synthesis of modified nucleosides by using such glycals by application of the Kim and Misco's methodology[11] is outlined below (see Scheme 1).



1a-4a **1b-4b**

1 R = Bz; R′ = CH_2OBz
2 R = Ac; R′ = CH_2OAc
3 R = Bn; R′ = CH_2OBn
4 R = Bz; R′ = BzO, BzO

5 R = Bz; R′ = CH_2OBz; B = Thymine
6 R = Bz; R′ = CH_2OBz; B = Uracil
7 R = Bz; R′ = CH_2OBz; B = 5-F-Uracil
8 R = Bz; R′ = CH_2OBz; B = Cytosine
9 R = Ac; R′ = CH_2OAc; B = Thymine
10 R = Bn; R′ = CH_2OBn; B = Thymine
11 R = Bz; R′ = BzO, BzO; B = Thymine

(i) I_2/Ph_3P/Imidazole; (ii) Silylated Base/ NIS/CH_2Cl_2

Scheme 1.

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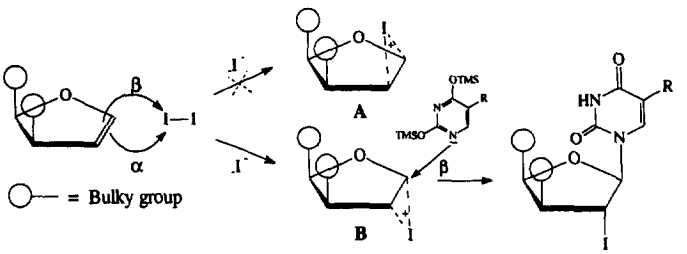
Different *O*-protected furanoid 1,2-diols with D-*xylo* **1a–3a** and D-*gluco* **4a** configurations were used as starting materials and transformed into the corresponding glycals **1b–4**. On the basis of previous results[10] and due to the general instability and lowering of yield during purification by column chromatography of **1b–4b**, they were partially purified (see experimental) and used in the next *N*-glycosidation step.

Reaction of the appropriated silylated pyrimidine bases with glycals **1b–4b** is promoted by *N*-iodosuccinimide (NIS) according to the mechanism proposed by Kim and Misco, where they postulated a cyclic iodonium intermediate that is regio and stereospecifically opened by the lone electron pair at N-1 of the base to produce the corresponding nucleosides **5–11** (see Scheme 1).

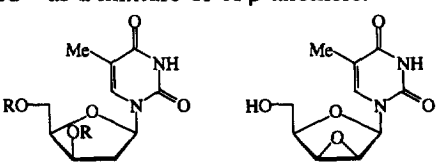
The stereochemistry of the *N*-glycosidation process seemed to be controlled by that of the formation of cyclic iodonium intermediate **A** or **B**. In our case the presence of two bulky groups at C-3′,4′ favoured the preferential attack of iodine by the α-face of the carbon–carbon double bond and hence the exclusive formation of intermediate **B**, which is also regio and stereospecifically opened at C-1 by the base to give the 2′-deoxy-2′-iodo β-nucleosides **5–11** (Scheme 2). Table 1 summarizes the results obtained from the different reactions.



Scheme 2.

The structures and configurations of compounds **5–11** were established on the basis of their analytical and spectroscopic data. Thus, the $J_{1',2'}$ and $J_{2',3'}$ values for all compounds (see Table 2) indicate a *trans*-relationship between the H-1′-2′-3′ protons (β-D-*xylo* for **5–10** and β-D-*gluco* for **11**, respectively). In addition, the transformation of **5** into the 2′,3′-*anhydro*-β-D-*lyxo* compound **14** also confirmed the assigned stereochemistry.

Finally, the diversity of the functional groups present in the nucleosides increases their synthetic potential since that will permit their transformations into other modified nucleosides. Thus, the transformation **5**→**14**, as well as the radical reductive dehalogenation of the compound **5** with tri-*n*-butyltin hydride gave the corresponding 2′-deoxy nucleoside **12** are clear examples of this. Compound **12** has been previously reported[12] as a mixture of α/β anomers.



12 R = Bz
13 R = H

14

Experimental

General

Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300 and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin–Elmer 782 instrument. Optical rotations were

Table 1.

Compound	M.p. (°C)	$[\alpha]_D$ $[\alpha]_{405}$	Yield %	IR ν_{max}^{KBr} (cm^{-1})	Elemental Analysis					
					Calcd.			Found		
					C	H	N	C	H	N
5	114-116	+89.5 (c 1)	80	1707, 1689	50.01	3.67	4.86	50.45	3.97	4.75
6	152-153	+107 (c 1.2)	87	1723,1690	49.12	3.41	4.98	49.33	3.57	5.25
7	181-182	+124 (c 1.5)	88	1724, 1709	47.60	3.13	4.83	48.10	3.25	4.92
8	209-211d	+83.5 (c 1.5)	80	1729, 1646	49.21	3.59	7.49	49.41	3.77	7.89
9	67-68	+5.5 (c 1) +30 (c 1)	60	1723, 1695	37.18	3.79	6.20	36.91	3.85	6.62
10	145-146	+5 (c 2) -10 (c 2)	75	1694, 1662	52.56	4.60	5.11	52.32	4.21	4.83
11	95-96	+3 (c 0.8) +32 (c 0.8)	quant.	1730, 1695	54.09	3.83	3.94	54.39	3.42	4.08

Table 2. ^{1}H-NMR data for compounds **5–14**

Compound	*^{1}H-Chemical shifts (δ), with multiplicities*											
	H-1'	H-2'	H-3'	H-4'	H-5'*a*	H-5'*b*	H-6'*a*	H-6'*b*	H-3	H-5	H-6	Me
5	6.44d	4.42t	5.79dd	5.16m	4.88dd	4.68dd	--	--	9.10bs	--	7.55s	1.84s
6	6.37d	4.48s	5.80d	5.22m	4.87dd	4.69dd	--	--	9.14bs	5.69dd	7.81d	--
7	6.39s	4.43s	5.78d	5.21m	4.93dd	4.69dd	--	--	9.15d	--	7.95d	--
8	6.32s	4.58s	5.79d	5.28m	4.89dd	4.65dd	--	--	--	5.96d	7.89d	--
9	6.31d	4.21t	5.38dd	4.83ddd	4.44dd	4.28dd	--	--	9.95bs	--	7.36s	1.88s
10	6.40d	4.27bs	4.30bd	4.73m	3.86dd	3.83dd	--	--	8.55bs	--	7.34s	1.66s
11	6.53d	4.39bs	5.73dd	5.14dd	~6.06m~		5.06dd	4.57dd	9.49s	--	7.51s	1.84s
12	6.33dd	2.93ddd(e) 2.32dd(β)	5.78t	4.53m	4.78dd	4.72dd	--	--	9.11s	--	7.58s	1.81s
13	6.05dd	2.54ddd(e) 1.87dd(β)	4.22t	3.78m	3.70dt	3.72dt	--	--	11.23s	--	7.79s	1.75s
14	6.13s	~3.90-3.86m~		4.12t	~3.90-3.86m~		--	--	10.00bs	--	7.45s	1.86s

Compound	Coupling constants (Hz)											
	$J_{1',2'}$	$J_{2',3'}$	$J_{2'a,2'b}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,6'b}$	$J_{5,6}$
5	2.1	1.2	--	3.5	7.0	4.2	12.2	--	--	--	--
6	0.0[a]	0.0	--	3.4	6.8	4.2	12.3	--	--	--	8.2
7[b]	0.0	0.0	--	3.3	6.7	4.2	12.3	--	--	--	--
8	0.0	0.0	--	3.3	7.2	4.3	12.1	--	--	--	7.5
9	2.4	1.5	--	3.5	6.8	4.4	12.1	--	--	--	--
10	2.3	0.0	--	3.7	5.4	5.9	10.6	--	--	--	--
11	2.0	0.0	--	3.3	- 9.3 -		--	2.5	6.1	12.3	--
12	7.9(α) 2.7(β)	5.8(α) 0.0(β)	15.7	4.5	6.8	4.4	12.0	--	--	--	--
13[c]	8.3(α) 2.3(β)	5.5(α) 0.0(β)	14.6	5.6	5.5	6.0	11.5	--	--	--	--
14	0.0	--	--	0.0	5.8	5.8	--	--	--	--	--

[a] $^4J_{1',3'}$ 1.6 Hz; [b] $J_{3,F}$ 4.5, $J_{6,F}$ 6.0 Hz; [c] $J_{5'A,OH}$ 5.1, $J_{5'B,OH}$ 6.0 Hz.

measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated silica gel 60 F_{254} aluminium sheets and detection by charring with 0.1% ninhydrin, 5% conc. H_2SO_4 in ethanol. Column chromatography was performed on silica gel (Merck, 7734).

Preparation of the silylated pyrimidine bases

To a well stirred suspension of the pyrimidine base (1.2 mmol) in anhydrous Cl_2CH_2 (10 mL), *N,O*-bis(trimethylsilyl)acetamide (3.5 mmol) was added. Stirring was continued until a clear solution was obtained. The solvent and the excess of silylating agent was removed under vacuum to yield a colourless thick liquid, that was redissolved in Cl_2CH_2 (20 mL) and used in the next step.

General protocol for N-*glycosidation reaction for 1 mmol scale*

a) To a well stirred solution of iodine (508 mg, 2 mmol) in anhydrous Cl_2CH_2 (20 mL), triphenylphosphine (524 mg, 2 mmol) was added and the original deep purple solution changed to brown. Imidazole (300 mg, 4.4 mmol) was added and the solution turned into a yellow suspension of a crystalline product. To this suspension, furanoid 1,2-diol (1 mmol) was added and immediately a deep brown colour developed. TLC, then showed the absence of the starting 1,2-diol **1a–4a** and the

presence of the related furanoid glycal **1b–4b**[10] as a faster-running product. The mixture was diluted to a final volume of 100 ml with Cl_2CH_2 and then washed with 10% aqueous sodium thiosulfate solution untill discolouration, water, aqueous 5% potasium hydrogensulfate, water until neutral, then concentrated to a white crystalline residue. The solution of the above silylated base was then added to the latter residue and the mixture left at room temperature for 2 h. TLC (ether) then revealed the absence of the starting glycal and the presence of a new compound of lower mobility. The mixture was supported on silica gel and chromatographed[13] (3:1 ether–hexane→ ether) to yield the corresponding 2′-deoxy-2′-iodo- nucleoside derivative **5–11**.

*1-(3′,5′-di-*O*-benzoyl-2′-deoxy-β-*D*-*threo*-pentofuranosyl)thymine (12)*

A well stirred and refluxed solution of 1-(3′,5′-di-*O*-benzoyl-2′-deoxy-2′-iodo-β-D-*xylo*-pentofuranosyl)thymine (**5**, 0.67 g, 1.16 mmol) in anhydrous toluene (25 mL) was treated with tributyltin hydride (0.4 mL, 1.5 mmol) and azobis(isobutyronitrile) (100 mg) in the same solvent (15 mL) for 1 h. TLC (ether) then revealed the absence of **5** and the presence of a slower-running compound. The reaction mixture was concentrated and the residue was treated with ether to yield crystalline **12** (506 mg, 95%), m.p.: 152–154°C (from ether); $[\alpha]_D^{27}$:+70.5 (c 1.2); ν_{max}^{KBr} 1730, 1715, 1705, 1683 cm^{-1} (C=O). NMR data, see Tables 2 and 3. Anal. Calcd. for $C_{24}H_{22}N_2O_7$: C, 63.99; H, 4.92; N, 6.22. Found: C, 64.35; H, 4.73; N, 6.37.

Conventional debenzoylation of **12** (250 mg, 0.55 mmol) in anhydrous methanol (15 mL) with a catalytic amount of sodium methoxide gave crystalline 1-(2′-deoxy-β-D-*threo*-pentofuranosyl)thymine (**13**) (125 mg, quantitative) m.p.: 175–177°C (from methanol), $[\alpha]_D^{29}$:+11 (c 1, water) [lit.[14] m.p.: 174–175°C]; ν_{max}^{KBr} 3522, 3466, and 3381 (OH), 1724, 1711 and 1705 cm^{-1} (C=O). NMR data (DMSO-d_6), see Tables 2 and 3. Anal. Calcd. for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83. N, 11.57. Found: C, 49.62. H 6.03; N, 11.80.

Treatment of 5 with sodium methoxide

A suspension of **5** (350 mg, 0.6 mmol) in anhydrous methanol (10 mL) was sonicated until a clear solution was obtained, then 2 *N* sodium methoxide solution (1.5 mL) was slowly added and the mixture maintained at room temperature for 24 h. TLC (ether) then revealed the presence of a non mobile product. The reaction was neutralized with acetic acid, concentrated and the residue chromatographed (10:1 ether–methanol) to afford crystalline 1-(2′,3′-*anhydro*-β-D-*lyxo*-pentofuranosyl)thymine (**14**, 60 mg, 41%) m.p.: 68–70°C (from ether–chloroform), $[\alpha]_D^{25}$:+13 (c 1.5, methanol); ν_{max}^{KBr} 3388 and 3203 (OH), 1730, 1675 and 1661 cm^{-1} (C=O). NMR data, see Tables 2 and 3, were in accordance with those found in the literature.[15]

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Table 3. ^{13}C-NMR data for compounds **5–14** (for sugar and nucleoside base only)

Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	C-2	C-4	C-5	C-6	Me
5	94.3	24.2	79.6*	79.3*	61.8	--	150.1	164.7	110.8	134.4	12.6
6	94.9	24.3	79.8*	79.5*	61.8	--	150.1	162.9	102.0	138.7	--
7	94.7	24.0	79.9*	79.3*	61.7	--	148.5	156.5[a]	140.3[b]	123.3[c]	--
8	94.7	25.4	80.0*	79.3*	62.1	--	155.3	165.5	95.8	140.0	--
9	93.6	23.8	78.4*	78.5*	61.3	--	150.4	164.2	110.4	134.4	12.6
10	93.4	21.4	85.0*	80.9*	67.8	--	150.2	163.6	110.2	137.6	12.4
11	94.4	24.0	78.8*	78.6*	68.3	64.1	150.2	163.8	111.2	134.1	12.5
12	84.5	39.8	72.7	80.6	62.1	--	150.4	163.7	111.0	135.2	12.6
13	84.8	40.7	68.7	83.5	59.6	--	150.6	163.8	108.6	137.2	12.5
14	81.3	55.8*	55.5*	77.8	61.1	--	150.9	164.3	111.1	136.8	12.5

*Interchangeable assignments; [a]J 27.2 Hz; [b]J 238.5 Hz; [c]J 35.2 Hz.

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