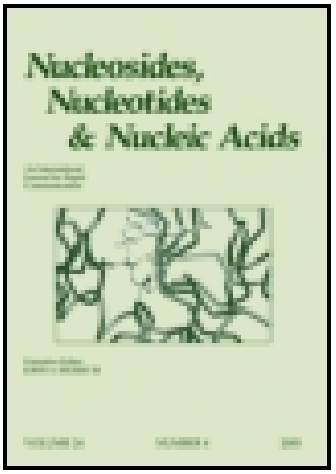

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Synthesis and Properties of Some 2′-O-d-Ribofuranosyl-nucleosides

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SYNTHESIS AND PROPERTIES OF SOME 2'-*O*-D-RIBOFURANOSYL-NUCLEOSIDES

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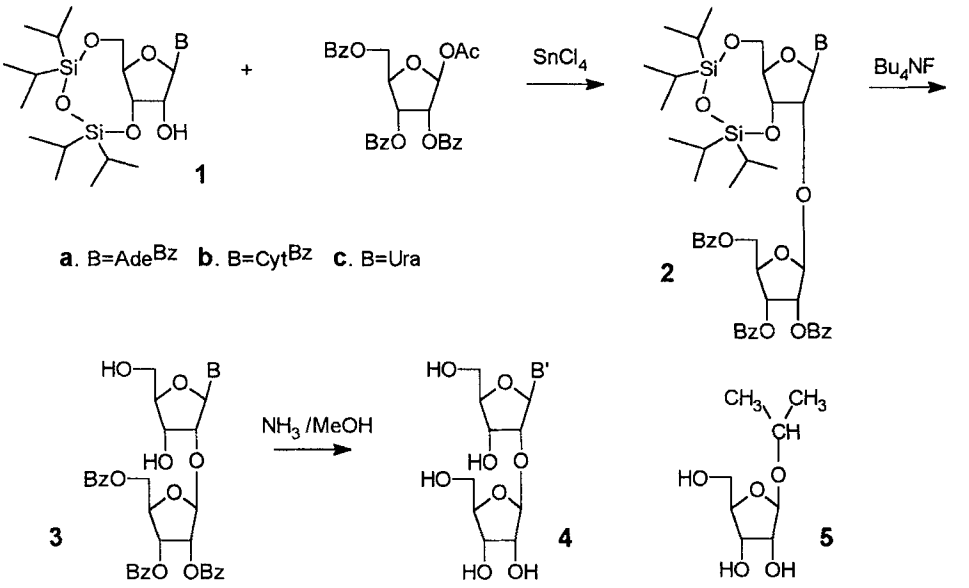
ABSTRACT : A high yield preparation of 9-(2-*O*-β-D-ribofuranosyl-β-D-ribofuranosyl)-adenine and its pyrimidine analogues has been achieved and their physico-chemical properties were investigated.

Disaccharide nucleosides are important structural elements of several antibiotics such as amicetin, hikizimycin, thuringiensin, tunicamycin and others. Recently some new derivatives of disaccharide nucleosides have been isolated from natural products and shown to possess interesting biological activities[1]. Disaccharide nucleosides have been prepared either by coupling of suitably blocked disaccharides with nucleic acid bases or by condensation of protected nucleosides with monosaccharide. Most of complex nucleoside antibiotics have been prepared using the first route. This route is rather lengthy and it may be shortened in some cases starting from natural nucleosides. Several attempts are discribed to use classical methods of glycosidic bond formation with blocked nucleosides as a alcohol component. The yields of these reactions were usually very low (20-30%) due to a formation of several by-products[1]. Till now no general high yielding synthetic procedure to disaccharide nucleosides from natural nucleosides has been developed and their physico-chemical and biological properties have not been studied systematically.

Here we present our results on the preparation of *O*-D-ribofuranosyl-nucleosides starting from readily available partially blocked N-acylribonucleosides[2] **1a-c** and a slight excess of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of tin tetrachloride. The glycosylation reaction proceeded stereospecifically with the formation of the β-glycosidic bond. The yields of **2a-c** were in the range of 70% to 80%, which is higher than reported for similar condensation reactions between blocked nucleosides and monosaccharides[1]. The reaction conditions are near the same as earlier used for the preparation of alkyl ribofuranosides[3]. The silyl group was selectively deblocked to yield partially protected **3a-c**, which may be used for further modification.

Deblocking with ammonia in methanol gave free disaccharide nucleosides **4a-c** in high overall yield. It should be mentioned that adenine disaccharide **4a** have been isolated from yeast methionine initiator tRNA[4,5] and prepared previously[6] utilizing nearly the same approach.



The chemical shifts of **4a-b** were identified from a COSY 90 (absolute value mode) experiment. For the nucleoside moiety we followed the connectivities starting from H-1'. The glycosidic protons were assigned by comparison of their chemical shifts with reference compounds. Thus the resonance of the proton at the highest frequency is assigned to that of the nucleoside. For the assignment of the resonances of the β-D-ribofuranosyl moiety we could not start by H-1', since the coupling constant J1',2' is smaller than the resolution. Therefore we started the following up of the connectivities from the resonances of H-5'a and H-5'b. The NMR data including NOE proved the introduction of the ribose moiety into the 2'-position.

According to ^{1}H NMR data the incorporation of a ribose moiety in 2'-position of nucleoside resulted in a small shift of the S ↔ N equilibrium towards the S-conformer. The chemical shifts and coupling constants of the pyrimidine disaccharide nucleosides **4b,c** have near the same values as in the case of Urd, Cyd (data are not shown) and isopropyl β-D-ribofuranoside (**5**). The

Table : ^{1}H NMR Chemical Shifts and coupling constants

compound →	**4a**		**4b**		**4c**		**5**
moiety →	Ado	Rib	Cyd	Rib	Urd	Rib	Rib
chemical shifts							
H-8 (H-6)	8.32		7.85		7.87		
H-2 (H-5)	8.19		6.12		5.92		
H-1'	6.12	5.07	6.09	5.15	6.04	5.15	5.10
H-2'	4.80	4.13	4.42	4.19	4.44	4.16	3.98
H-3'	4.55	3.99	4.38	4.20	4.36	4.19	4.16
H-4'	4.29	3.82	4.15	4.00	4.11	3.99	3.98
H-5'a	3.92	3.32	3.91	3.73	3.88	3.75	3.79
H-5'b	3.83	2.75	3.82	3.40	3.79	3.48	3.62
coupling constants							
5,6			7.6		8.1		
1',2'	6.4	<0.5	5.2	<0.5	5.0	<0.5	1.5
2',3'	5.0	4.5	5.4	4.6	5.4	4.8	4.8
3',4'	3.3	7.4	4.7	6.8*	5.1	6.9	6.5
4',5'a	2.6	3.7	3.1	3.5	2.9	3.4	3.5
4',5'b	3.6	6.8	4.5	6.7	4.5	6.6	6.6
5'a,5'b	-13.0	-12.0	-12.7	-12.2	-12.7	-12.1	-12.2

^{1}H NMR spectra were recorded on a Bruker AM 360 apparatus operating at 360.031 MHz at 20°C with a pulse angle of 19° and a resolution of 0.33 Hz/point for 10 mg samples in 0.5 ml of D_2O.

* Coupling constant was measured from the pattern for H-4' (ribose moiety).

anisotropical influence of purine ring in **4a** is much more pronounced not only for sugar protons of the nucleoside moiety but also for the ribose residue, especially for 5'a and 5'b protons. Also NOE constraints were observed between base protons and H-5'a and H-5'b of ribose residue. A detailed study on the conformational aspects of these disaccharide nucleosides is in preparation.

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