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# Nucleosides and Nucleotides

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Synthesis and <sup>1</sup>H and <sup>13</sup>C NMR Spectral Characteristics of 8-Bromo-2',3'-Dideoxyguanosine and 8-Bromo-2',3'-Dideoxyinosine

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## SYNTHESIS AND <sup>1</sup>H AND <sup>13</sup>C NMR SPECTRAL CHARACTERISTICS OF 8-BROMO-2',3'-DIDEOXYGUANOSINE AND 8-BROMO-2',3'-DIDEOXYINOSINE<sup>1</sup>

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ABSTRACT: Reaction of 2',3'-dideoxyguanosine 1a as 5'-O-tert-butyldimethylsilyl derivative 1b and 2',3'-dideoxyinosine 2a with bromine in acetate buffer conducted in heterogeneous medium afforded 8-bromo-2',3'-dideoxyguanosine 3a (44% after deprotection) and 8-bromo-2',3'-dideoxyinosine 4a (12%) respectively. The change of conformational preferences anti  $\rightarrow$  syn on 8-bromo substitution of 2',3'-dideoxynucleosides is reflected in the <sup>1</sup>H and <sup>13</sup>C NMR spectra by characteristic shifts of H-2', H-3', C-2' and C-3' signals.

#### INTRODUCTION

2',3'-Dideoxynucleosides: 3'-azido-3'-deoxythymidine (AZT, zidovudine), 2',3'dideoxyinosine (ddI, didanosine) and 2',3'-dideoxycytidine (ddC, zalcitabine), inhibitors of human immunodeficiency virus (HIV) reverse transcriptase are the first antiretroviral agents approved for the treatment of HIV infection.<sup>2</sup> There is therefore a considerable interest in the synthesis of their analogues aimed at establishing structure-activity relationships for the members of 2',3'-dideoxynucleoside family and improving their chemotherapeutic properties.

We present here the synthesis of new analogues of anti-HIV agents: 2',3'dideoxyguanosine (1a, ddG) and 2',3'-dideoxyinosine (2a) namely 8-bromo-2',3'dideoxyguanosine (3a, Br<sup>8</sup>ddG) and 8-bromo-2',3'-dideoxyinosine (4a, Br<sup>8</sup>ddI).

Presumed dominance of the syn conformation<sup>3,4</sup> in the structure of these analogues may be expected to alleviate one of the shortcomings of the parent

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dideoxynucleosides - their strong susceptibility to catabolic phosphorolysis caused by the action of purine nucleoside phosphorylase (PNP).<sup>5,6</sup> Earlier studies on the structure-activity relationship for substrate and inhibitor properties towards PNP revealed that the substrate should occur in the anti conformation.<sup>7</sup> In addition, bromo substituents may also improve lipophilic properties of the parent compounds 1a and 2a and enhance their penetration potential into the central nervous system.<sup>8</sup>

### **RESULTS AND DISCUSSION**

#### Synthesis

For preparing ddG and ddI to be used as starting materials for 8-bromo derivatives we introduced some modifications which significantly improved known procedures<sup>9-11</sup> in terms of simplicity and yield.

Thus our route towards 1a employed silulation for 5'-OH protection of starting 2'-deoxyguanosine (5a); on application of literature procedure<sup>12</sup> 5'-O-(*tert*-butyldimethylsilyl-2'-deoxyguanosine (5b) was obtained in 82% yield. The protected compound 5b was subsequently converted into corresponding 3'-O-(imidazol-1-yl)thiocarbonyl derivative (5c) in 75% yield, deoxygenated with tri-*n*-butyltin hydride/AIBN to 1b in 91%. In all the stages, pure compounds were obtained without recourse to chromatography. The product 1b was then deprotected with tetra-*n*-butylammonium fluoride to give 1a in 77% yield.

Aiming towards 2a, we successfully challenged the known acid instability of the glycosidic bond of 2',3'-dideoxynucleosides<sup>13,14</sup> by using acid-labile protecting group (dimethoxytrityl) for 5'-OH protection of starting 2'-deoxyinosine (5d). 5'-O-(4,4'-Dimethoxytrityl)-2'-deoxyinosine (5e)<sup>15</sup> was converted into thioimidazolide (5f) and then deoxygenated with tri-*n*-butyltin hydride/AIBN to yield 5'-O-dimethoxytrityl-2',3'-dideoxyinosine 2b in 84%. 5'-O-Detritylation of 2b with 80% acetic acid at 0°C for 1.5 h was followed by careful adjustment to pH 9.5 with aqueous ammonia. Chromatographic purification and crystallization afforded 2a in 65% yield. It is noteworthy that under the above conditions the glycosidic bond underwent hydrolysis to a very small extent.

We applied a commonly used bromination method of 2'-deoxyguanosine  $5a^{16}$  to its 2',3'-dideoxy congener 1a. Bearing in mind the enhanced instability of the

ROJOJ NH2

1a; R = H b; R = TBDMS



2a; R = H b; R = DMTr c; R = TBDMS d; R = Ac



**3a**; R = H b; R = TBDMS



**5a**;  $R^1 = NH_2$ ,  $R^2 = R^3 = H$ ; **b**;  $R^1 = NH_2$ ,  $R^2 = TBDMS$ ,  $R^3 = H$ ; **c**;  $R^1 = NH_2$ ,  $R^2 = TBDMS$ ,  $R^3 = IThC$ ; **d**;  $R^1 = R^2 = R^3 = H$ ; **e**;  $R^1 = R^3 = H$ ,  $R^2 = DMTr$ ; **f**;  $R^1 = H$ ,  $R^2 = DMTr$ ,  $R^3 = IThC$ ;



4a; R = Hb; R = Ac



6a; R = H, X = H; b; R = H, X = Br; c; R = Ac; X = Br;

DMTr = 4,4<sup>-</sup>- dimethoxytrityl; IThC = (imidazol-1-yl)thiocarbonyl; TBDMS = *tert*-butyldimethylsilyl; glycosidic bond of the latter in the acidic pH range we carried out the experiments in concentrated acetate or phosphate buffers. Compound 1a, soluble in buffer underwent solvolysis and provided only traces of the desired product 3a. On the contrary, poor solubility of 5'-O-*tert*-butyldimethylsilyl-2',3'-dideoxyguanosine 1b and extremely poor solubility of its 8-bromo derivative (3b) allowed us to slow down the solvolytic cleavage and obtain 3b in 55% yield. The optimal conditions for this transformation were the following: 1 M acetate buffer pH 4.5, 2.18 molar excess of bromine as saturated bromine water, 1.5 h at 20°C. When the reaction was performed in water for 0.5 h, it furnished a 36% yield of 3b. Desilylation with tetran-butylammonium fluoride in pyridine resulted in pure 3a in 81% yield.

A series of 8-substituted 2',3'-dideoxyinosine derivatives e.g. 8-amino-, 8hydroxy<sup>17</sup> and 8-mercapto<sup>18</sup> have been conveniently prepared from their adenosine counterparts by hydrolytic deamination with adenosine deaminase. This approach could not be applied for preparation of 8-bromo-2',3'-dideoxyinosine 4a from already described 8-bromo-2',3'-dideoxyadenosine (6b)<sup>19</sup> because 8-bromoadenosine has been found highly resistant to this enzyme.<sup>19</sup>

Encouraged by the successful bromination of 1a in the form of poorly soluble 1b in the heterogeneous medium, we attempted the same approach in the case of 2a. We first used 5'-O-tert-butyldimethylsilyl-2',3'-dideoxyinosine (2c) suspended in acetate buffer at pH 5. Unlike 1b, hypoxanthine - bearing substrate 2c did not react with the excess of bromine even when warmed up to 60°C. Unprotected 2a was also poorly soluble in acetate buffer. Direct bromination of that starting material in suspension occurred, but proceeded very slowly. Prolongation of the reaction time resulted in almost complete decomposition of the already preformed product 4a to 8-bromo-hypoxanthine while most of 2a remained unreacted. By careful investigations the following optimal conditions were settled: 1.5 M acetate buffer pH 4.65, 1.3 molar excess of bromine, 7 h at 20°C. Yield of the product 4a initially estimated by TLC was approximately 20%. After tedious work-up procedure which was necessary to remove 2,3-dideoxyribose, the yield of pure 8-bromo derivative 4a was 12%; 2,3-dideoxyribose and 4a showed similar chromatographic mobility.

An attempt to accomplish the bromination of **2a** in solution in acetate buffer/methanol medium following the conditions described for bromination of 2',3'-

dideoxyadenosine  $(6a)^{19}$  was unsuccessful. In this case we observed fast acid catalysed hydrolysis of preformed 4a while unreacted 2a predominated in the reaction mixture.

We also applied a method patterned after bromination of 2',3',5'-tri-Oacetylinosine with N-bromoacetamide in chloroform.<sup>20</sup> 5'-O-Acetyl-2',3'-dideoxyinosine<sup>21</sup> (2d) underwent partial substitution with bromine when refluxed in chloroform with excess of N-bromosuccinimide. 5'-O-Acetyl-8-bromo-2',3'-dideoxyinosine (4b) was isolated in 9% yield together with degradation products 8-bromohypoxanthine and hypoxanthine. Numerous further experiments in which various reaction conditions were used (ethylene chloride as another solvent, various reaction times, factors favouring either ionic or radical course of reaction) did not improve the original result.

In view of the recent report on satisfactory chemical deamination of adenosine 5'-thioether derivatives to the corresponding inosine and nebularine derivatives<sup>22</sup> it seemed of interest to use this method for the preparation of the desired **4a**. For this purpose, 8-bromo-2',3'-dideoxyadenosine<sup>19</sup> **6b** was acetylated with acetic anhydride in pyridine to give 5'-O-acetyl-8-bromo-2',3'-dideoxyadenosine (**6c**). Compound **6c** reacted readily with n-pentyl nitrite in refluxing tetrahydrofuran. According to TLC the starting material was transformed into two products, which after the work-up gave two other non-nucleosidic compounds as shown by <sup>1</sup>H and <sup>13</sup>C NMR analysis.

Studies on the biological properties of 8-bromo derivatives 3a, 3b and 4a will be published elsewhere.

## <sup>1</sup>H and <sup>13</sup>C NMR characteristics

It has been shown for a number of purine 9-( $\beta$ -D-ribofuranosides), 9-( $\beta$ -D-2'deoxyribofuranosides) and their 5'-monophosphates that substitution of their 8position with various bulky substituents causes characteristic chemical shift changes in the carbohydrate portion of their NMR spectra. The signal of H-2' is shifted to higher frequencies and that of C-2' to lower frequencies.<sup>3,4,23,24</sup> These shifts have been assumed to be due to the syn conformation of 8-substituted purine nucleosides placing the lone pair of electrons of the base N-3 close to the sugar C-2'-H-2' bond.<sup>25</sup> Along this line Nair and Young established an empirical rule correlating syn-anti conformation of purine ribofuranosides in solution with <sup>13</sup>C NMR chemical shift difference between C-2' and C-3'. According to it the unprotected compounds in the anti conformation exhibit  $\Delta(C-2'-C-3')$  greater than 2.8 ppm and those in syn conformation  $\Delta(C-2'-C-3')$  smaller than 0.5 ppm.<sup>26</sup>

In Table 1 and Table 2 we summarized the <sup>1</sup>H and <sup>13</sup>C NMR data of parent purine 2',3'-dideoxynucleosides 1a, 1b, 2a, 2d and 6a and their corresponding 8bromo derivatives 3a, 3b, 4a, 4b and 6b in DMSO-d<sub>6</sub>.

Upon substitution of the 8 position we observed characteristic chemical shift changes not only for H-2' and C-2' but also for H-3' and C-3' signals. The changes concerning H-2' and H-3' have not been described so far. In the previously published <sup>1</sup>H NMR spectra of a series of other 8-substituted purine 2',3'-dideoxynucleosides (e.g. 8-methylthio- and 8-amino-2',3'-dideoxyadenosine) in DMSO-d<sub>6</sub><sup>17</sup> or in the spectrum of 8-bromo-2',3'-dideoxyadenosine **6b** in CDCl<sub>3</sub>,<sup>19</sup> the signals of H-2' and H-3' have been reported to appear as a four proton multiplet.<sup>17,19</sup>

In the case of 8-bromoguanine- and 8-bromoadenine-2',3'-dideoxynucleosides (3a, 3b and 6b respectively), 2' and 3' protons appeared as a conspicuous pattern of three multiplets integrating for 1H, 2H and 1H, which on the basis of 2D experiment were ascribed, in order of lowering frequency, to H-2', H-2"+H-3' and H-3". For the corresponding 8-bromohypoxanthine derivatives 4a and 4b, the signals of the four studied protons were completely separated. Chemical shift changes towards higher frequencies of the H-2' signals in compounds 3a, 3b, 4a, 4b and 6b, being in the range 0.33-0.5 ppm, were similar to those described earlier for the corresponding 9-( $\beta$ -D-ribofuranosyl) and 9-( $\beta$ -D-2'-deoxyribofuranosyl) derivatives<sup>3,23,24</sup> as diagnostic for anti  $\rightarrow$  syn conformational changes. New diagnostic features emerged, specific for 2',3'-dideoxynucleosides namely the shifts to higher frequencies of H-3' (0.22-0.35 ppm) and of C-3' (1.18-1.56 ppm) signals. These effects had been reported as very weak in the corresponding 8-bromo derivatives of the 9-( $\beta$ -D-ribofuranosyl) series (not greater than 0.1<sup>23</sup> and 0.25<sup>4</sup> ppm, respectively).

Chemical shift changes to lower frequencies of C-2' signal were in the range 2.88-3.49 ppm, analogous to those reported for the ribo series.<sup>4</sup>

Compd	H-2	H-8	H-1' (J <sub>1',2'</sub> ;J <sub>1'2</sub> .)	H-2'	H-2" H-	3,	H-3"
1a*	-	7.96 s,1	6.00 dd,1 (6.6;3.6)	°2.30 m,2		2.01 m,2	
3a⁵	-	•	6.03 dd,1 (7.8;4.7)	2.70 m,1	2.30 m,2		2.02 m,1
1b	-	7.86 s,1	5.97 dd,1 (6.7;3.2)	°2.30 m,2		1.99 m,2	
3b	-		6.03 dd,1 (7.5;3.9)	2.80 m,1	2.34 m,2		2.01 m,1
2a*	8.34 s,1	8.06 s,1	6.20 dd,1 (6.7;3.3)	<sup>c,d</sup> 2.40 m,2		2.03 m,2	
4a <sup>b</sup>	8.09 s,1		6.16 dd,1 (7.8;4.7)	2.78 <sup>d</sup> 2 m,1	2.45 2.2 m,	25 1	2.06 m,1
2d	8.23 s,1	8.06 s,1	6.22 dd,1 (6.5;4.1)	<sup>d</sup> 2.47		2.11 m,2	
4b	8.09 s,1	-	6.21 dd,1 (7.6;4.0)	2.80 m,1	<sup>c,d</sup> 2.43		2.12 m,1
6a*	8.36 s,1	8.15 s,1	6.23 ¶pt,1	2.41 m,2		2.04 m,2	
6 <b>b</b> <sup>a,b</sup>	8.13 s,1	-	6.17 m,1	2.88 m,1	2.35 m,2		2.09 m,1

TABLE 1. <sup>1</sup>H NMR Data of Purine 2',3'-Dideoxynucleosides and their 8-Bromoderivatives. Chemical shifts  $\delta_{\rm H}$  (ppm) in DMSO-d<sub>6</sub>-TMS and Coupling Constants (Hz).

<sup>4</sup> <sup>1</sup>H NMR data already published: **1a**, **6a**<sup>9</sup>; **2a**<sup>11</sup>; **6b**(CDCl<sub>3</sub>)<sup>18</sup>. <sup>b</sup> 2D Spectrum measured. <sup>c</sup> Center of two partially overlapping multiplets. <sup>d</sup> Partially overlapping DMSO-d<sub>5</sub>. <sup>e</sup> pt: pseudotriplet.

(continued)

H-4'	H-5' H-5" [J <sub>gem</sub> ;J <sub>5′(5'),4</sub> ,]	5'-OH	N-1-H	NH2	5'-OR
4.06 m,1	°3.55 m,2	4.96 t,1,ex [6.0]	10.64 brs,1 ex	6.48 brs,2 ex	•
4.03 m,1	3.52 t,2 [5.6]	4.79 t,1,ex [5.9]	10.80 brs,1 ex	6.50 brs,2 ex	-
4.06 m,1	3.76 3.65 dd,1 dd,1 [11.2;3.6] [11.2;4.5	- ]	10.59 brs,1 ex	6.47 brs,2 ex	0.84 s,9,(CH <sub>3</sub> ) <sub>3</sub> C 0.01 s,6,(CH <sub>3</sub> ) <sub>2</sub> Si
4.04 m,1	3.68 m,2	-	10.77 brs,1 ex	6.50 brs,2 ex	0.80 s,9,(CH <sub>3</sub> ) <sub>3</sub> C 0.08,s,3 0.05,s,3 (CH <sub>3</sub> ) <sub>2</sub> Si
4.11 m,1	3.63 3.51 dd,1 dd,1 [11.8;3.5] [11.8;4.3	4.98 brs,1 ] ex	12.35 brs,1 ex	-	-
4.07 m,1	3.49 m,2	4.79 m,1 ex	12.53 brs,1 ex	-	-
4.30 m,1	4.20 4.13 dd,1 dd,1 [12.0;3.4] [12.0;6.2	-	12.41 brs,1 ex	-	1.98 s,3 COCH <sub>3</sub>
4.28 m,1	4.09 m,2	-	12.56 brs,1 ex	-	1.91 s,3 COCH₃
4.12 m,1	3.62 3.53 m,1 m,1	5.08 t,1,ex [5.6]	-	7.28 brs,2 ex	
4.10 m,1	3.55 3.44 dd,1 dd,1 [11.5;4.1] [11.5;5.4	5.06 brs,1 ex	•	7.46 brs,2 ex	-

TABLE 1. continued.

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TABLE 2.  $^{13}\text{C}$  NMR Data of 2',3'-Dideoxynucleosides and their 8-Bromoderivatives. Chemical shifts  $\delta_c$  (ppm) in DMSO-d\_s-TMS.

									-		
Compd	C-2	C - 4	C-5	C-6	C-8	c-1,	C-2 '	C-3'	۵ (C-2' -C-3' )	C-4'	C-5'
<b>1</b> a	153.47 S	150.47 S,m	116.63 Sd	156.69 S	135.05 Dd	83.54 Dm	31.80 Тш	25.53 Tm	6.27	81.53 Dm	62.73 Td
3a	153.32 S	151.81 Sd	117.37 S	155.49 S	120.43 Sd	85.80 Dm	28.55 Tm	27.09 Tm	1.46	81.42 D	63.74 Tm
1b <sup>ª</sup>	153.56 S	150.54 Sd	116.68 S	156.72 S	134.76 Dd	83.47 Dm	31.79 T	25.35 T	6.44	81.12 Dm	64.44 T
3b°	153.23 S	151.74 Sd	117.25 S	155.45 S	120.58 Sd	85.82 Dm	28.30 Tm	26.81 Tm	1.49	81.16 Dm	65.16 Tm
2a	145.68 D	147.66 Sdd	124.38 Sd	156.68 Sd	138.25 Dd	84.52 D	32.21 T	25.52 T	6.69	82.11 D	62.71 T
4a	145.79 D	148.86 Sdd	125.03 S	155.17 Sd	125.24 Sd	86.70 D	28.90 T	26.87 T	2.03	81.67 D	63.43 T
6a	152.29 D	148.71 Sddd	119.00 Sdt	155.90 Sd	138.92 Dd	84.32 D	31.63 T	25.60 T	6.03	81.57 D	62.85 T
6b	152.31 D	149.80 Sdd	119.46 St	154.85 Sd	126.46 Sd	86.82 D	28.75 T	26.78 T	1.97	81.38 D	63.64 T
30	δ <sub>c</sub> (ppm) ( β (mqq) β	of TBDMS of TBDMS	carbon a carbon a	atoms: 25 atoms: 25	5.81, 18 5.67, 17	02, -5 90, -5	47.	53.			

8-BROMO-2',3'-DIDEOXYGUANOSINE AND INOSINE

We analyzed the <sup>13</sup>C NMR data shown in Table 2 also from the viewpoint of the possible extension of the above mentioned  $\Delta$ (C-2'-C-3') rule to the dideoxy series. For parent dideoxynucleosides **1a**, **1b**, **2a** and **6a** we found chemical shift differences between C-2' and C-3' in the range of 6.03-6.69 ppm. It seems that  $\Delta$ (C-2'-C-3') value of approx. 6 ppm may be safely considered indicative of the preferred anti conformation around the glycosidic bond of the 2',3'-dideoxynucleoside. It has been found previously by a semiquantitative 1D <sup>1</sup>H NOE differential method that 2',3'-dideoxyguanosine **1a**, 2',3'-dideoxyadenosine **6a** and a derivative of 7-deazapurine, 4-chloro-7-(2,3-dideoxy- $\beta$ -D-glyceropentofuranosyl)-7*H*-pyrrolo[2,3-d]-pyrimidine, exhibit preferentially anti conformation.<sup>27</sup> The  $\Delta$ (C-2'-C-3') value for the last compound calculated from literature data<sup>28</sup> is also 6.1 ppm. Furthermore, **6a** is known from X-ray crystallographic data to exist in the anti conformation in the solid state.<sup>11</sup>

On the other hand, for 8-bromo counterparts **3a**, **3b**, **4a** and **6b** the chemical shift differences between C-2' and C-3' are found in the range of 1.46-2.03 ppm and reflect dominating syn conformation.  $\Delta$ (C-2'-C-3') in the similar range, 1.9-2.2 ppm, can be calculated from <sup>13</sup>C NMR data reported<sup>17</sup> for 8-methylthio-, 8-methoxy-and 8-benzyloxy-2',3'-dideoxyadenosine; for the less bulky 8-amino- substituent that value is 3 ppm.

From the above it may be concluded that similarly to ribo series, the glycosidic bond conformation of purine 2',3'-dideoxynucleosides in solution expressed in terms of preferred anti or syn conformation can be conveniently qualitatively determined by the magnitude of the <sup>13</sup>C NMR chemical shift difference between C-2' and C-3'.

#### EXPERIMENTAL SECTION

Melting points were determined in open capillaries on Laboratory Devices MEL-TEMP II capillary micromelting point apparatus and are uncorrected. UV spectra were measured in water or methanol on Beckman DU-65 Spectrophotometer. High resolution mass spectrum of 4a, measured in Mass Spectrometry Laboratory of the Institute of Organic Chemistry of the Polish Academy of Sciences in Warsaw, was obtained by LSIMS method on AMD-604 mass spectrometer - the sample in mnitrobenzyl alcohol matrix (NBA) was bombarded with cesium ions of energy 10 kV. Elemental analyses were performed by Microanalytical Laboratories of the aforementioned Institute in Warsaw.

Analytical thin-layer (TLC) and preparative-layer chromatography (PLC) were conducted on Merck precoated silica gel  $F^{254}$  type 60 plates of layer thickness 0.25 and 0.5 mm respectively. For preparative short-column chromatography Merck TLC silica gel type 60 H and silanized silica gel type 60 H were used. All solvents used were of the reagent grade. Dried dioxane and tetrahydrofuran purified from peroxides, were refluxed over calcium hydride and distilled prior to use. n-Pentyl nitrite<sup>29</sup> was dried over sodium sulphate, distilled and stored at 10°C over 4- Å molecular sieves. <sup>1</sup>H and <sup>13</sup>C spectral measurements - <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in DMSO-d<sub>6</sub> on Unity 300 Varian spectrometer operating at 299.95 MHz and 75.43 MHz respectively. 2D <sup>1</sup>H NMR COSY spectra were measured in DMSO-d<sub>6</sub> using mode Absolute Value with a resolution of 6 Hz in both directions (Me<sub>4</sub>Si as internal reference, chemical shifts expressed as  $\delta$  values).

<u>5'-O-(*tert*-Butyldimethylsilyl)-2',3'-dideoxyguanosine (1b)</u> To a stirred at 5°C suspension of dried 2'-deoxyguanosine (0.81 g, 3 mmol) and imidazole (0.82 g, 12 mmol) in DMF (24 ml) was added *tert*-butyldimethylsilyl chloride (0.90 g, 6 mmol). The reaction mixture was stirred at 5°C for 15 min and then quenched with methanol (0.5 ml). The solvent was removed under vacuum and the residue was stirred with cold water (45 ml). The white precipitate was collected, washed with water and dried, redissolved in methylene chloride (45 ml) and stirred for 1 h to wash out traces of disubstituted product. 5'-O-(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (5b) was filtered off and dried to yield 0.93 g of white solid (82%, m.p. >221°C dec.; lit.<sup>12</sup> m.p. >230°C dec.). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$ : 0.03 (6H, s, Me<sub>2</sub>Si), 0.86 (9H, s, Me<sub>3</sub>CSi), 2.36-2.52 (m, overlaps with DMSO-d<sub>5</sub>, H-2'), 3.73-3.81 (3H, m, H-4', H-5'), 4.36 (1H, m, H-3'), 5.09 (1H, br s, exchangeable, 3'-OH), 6.12 (1H, t, H-1'), 6.57 (2H, br s, exchangeable, NH<sub>2</sub>), 7.83 (1H, s, H-8), 10.90 (1H, br s, exchangeable, NH).

To a solution of 5'-O-(*tert*-butyldimethylsilyl)-2'-deoxyguanosine 5b (0.54 g, 1.42 mmol) in DMF (2 ml), 1,1'-thiocarbonyldiimidazole (0.50 g, 2.84 mmol) was added. It was set aside for 20 h, then the volatiles were removed. The residue treated with

ethyl acetate (3 ml) yielded crystalline 5'-O-(*tert*-butyldimethylsilyl)-3'-O-(imidazol-1yl)thiocarbonyl-2'-deoxyguanosine (5c) 0.53 g (75%, m.p. 208-210°C dec.).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$ : 0.06 (6H, s, Me<sub>2</sub>Si), 0.86 (9H, s, Me<sub>3</sub>CSi), 2.82-3.90 (4H, complex, H-2', H-5'), 4.44 (1H, m, H-4'), 5.99 (1H, m, H-3') 6.28 (1H, dd, J: 6.5, 3.7 Hz, H-1'), 6.51 (2H, br s, exchangeable, NH<sub>2</sub>), 7.12 (1H, m, imidazole), 7.88-7.90 (2H, m, imidazole and H-8), 8.57 (1H, s, imidazole), 10.67 (1H, br s, exchangeable, NH).

To a suspension of 5'-O-(*tert*-butyldimethylsilyl)-3'-O-(imidazol-1-yl)thiocarbonyl-2'-deoxyguanosine (0.49 g, 1 mmol) in anhydrous dioxane (20 ml) at reflux a solution of tri-n-butyltin hydride (0.627 g, 2.15 mmol) and azobisisobutyronitrile (0.053 g, 0.32 mmol) in dioxane (7 ml) was added dropwise over 20 min. The mixture was refluxed for 1 h, cooled to 10°C. 1b precipitated, it was carefully washed with dioxane, then with n-hexane, dried to yield 0.33 g (91%) of material homogeneous by TLC: m.p. >188°C dec. did not raise after recrystallization from butan-2-one. NMR data of 1b given in Tables 1, 2.

<u>2'.3'-Dideoxyguanosine (1a)</u>. To a solution of 1b (0.236 g, 0.65 mmol) in anhydrous pyridine (8 ml) a 1 M solution of tetra-n-butylammonium fluoride in THF (1.3 ml, 1.3 mmol) was added. The mixture was set aside overnight. The volatiles were removed under vacuum and the residue treated with water (4 ml) and filtered through Celite pad. The filtrate was applied to a column packed with silanized silica gel (60 x 50 mm) which was eluted first with water then with aqueous 10% acetone. Fractions containing 1a were pooled and evaporated to dryness. Crystallization of 1a from hot methanol afforded 0.125 g of white solid (77%, m.p. >250°C, the same as reported<sup>11</sup>).

<u>5'-O-(4,4'-Dimethoxytrityl)-2'-deoxyinosine (5e</u>). 2'-Deoxyinosine (5d) (0.40 g, 1.59 mmol) in anhydrous pyridine (40 ml) was treated with 4,4'-dimethoxytrityl chloride (0.66 g, 2.0 mmol) according to the described procedure.<sup>15</sup> Product 5e was purified by column chromatography on silica gel with 5-20% methanol in chloroform (with 0.2% Et<sub>3</sub>N). It afforded 0.71 g (81%) of white foam. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$ : 2.35 (1H, m, H-2"), 2.77 (1H, m, H-2'), 3.15 (2H, m, H-5'), 3.72 (6H, s, methoxy groups), 3.97 (1H, m, H-4'), 4.42 (1H, m, H-3'), 5.38 (1H, d, exchangeable, 3'-OH),

6.34 (1H, t, H-1'), 6.68 (4H, m, dimethoxytrityl), 7.18-7.31 (9H, m, dimethoxytrityl), 7.99 (1H, s, H-8), 8.18 (1H, m, H-2) 10.36 (1H, s, exchangeable, NH).

5'-O-(4,4'-Dimethoxytrityl)-2',3'-dideoxyinosine (2b).

a) A solution of 5e (0.60 g, 1.1 mmol) in DMF (6 ml) was reacted with 1,1'thiocarbonyldiimidazole (0.39 g, 2.2 mmol) to form 5'-O-(4,4'-dimethoxytrityl)-3'-O-(imidazol-1-yl)thiocarbonyl-2'-deoxyinosine 5f in 20 h. The volatiles were removed under vacuum and the residue was directly used in step b).

A portion of **5f** was purified by PLC with 5% MeOH in CHCl<sub>3</sub> (with 0.2%  $Et_3N$ ) and characterized by <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$ : 2.90 (1H, m, H-2"), 3.35 (3H, m, H-2', H-5'), 3.72 (6H, s, methoxy groups), 4.58 (1H, m, H-4'), 6.07 (1H, m, H-3'), 6.53 (1H, dd, J: 7.3, 6.2 Hz, H-1'), 6.82 (4H, m, dimethoxytrityl), 7.13-7.38 (10H, m, 9H dimethoxytrityl, 1H imidazole), 7.91-7.96 (2H, m, imidazole), 8.25 (1H, s, H-8), 8.61 (1H, s, H-2), 12.45 (1H, br s, exchangeable, NH).

b) To a solution of crude 5f (ca 1.1 mmol) in anhydrous dioxane (50 ml) at reflux, a solution of tri-n-butyltin hydride (1.716 g, 5.85 mmol) and azobisisobutyronitrile (0.143 g, 0.087 mmol) in dioxane (10 ml) was added dropwise for 30 min. After the reaction was completed (1 h) the volatiles were removed under reduced pressure. The residue was partitioned between n-hexane and acetronitrile. The acetonitrile layer was washed with n-hexane, concentrated under vacuum and purified by chromatography over silica gel eluting with 1-7% MeOH in chloroform (with 0.2% Et<sub>3</sub>N) to yield 0.496 g (84%) of 2b as off-white foam.

Chromatography over silica gel eluting first with 0.2% Et<sub>3</sub>N in n-hexane (v/v) then with MeOH:Et<sub>3</sub>N:methylene chloride 2.8:0.2:97 (v/v/v) yielded an analytical sample of 2b as white foam: UV [MeOH]  $\lambda_{max}$  236 {25500} sh 273 {6670} 282 {4530}. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$ : 2.07 (2H, m, H-3'), 2.50 (m, overlaps with DMSO-d<sub>5</sub>, H-2'), 3.09 (2H, m, H-5'), 3.72 (6H, s, methoxy groups), 4.26 (1H, m, H-4'), 6.26 (1H, dd, J: 5.7, 4.0 Hz, H-1'), 6.81 (4H, m, dimethoxytrityl), 7.16-7.32 (9H, m, dimethoxytrityl), 8.06 (1H, s, H-8), 8.19 (1H, s, H-2), 12.38 (1H, br s, exchangeable, NH).

Anal. Calcd for  $C_{31}H_{30}N_4O_5 + 1/2 H_2O$ : C, 67.99; H, 5.71; N, 10.23; Found C, 67.98; H, 5.64; N, 10.17.

<u>2'.3'-Dideoxyinosine (2a)</u>. 2b (0.810 g, 1.5 mmol) cooled in an ice bath was treated with 80% aqueous acetic acid (20 ml) at 0°C. The mixture was stirred at 0°C until TLC revealed the absence of starting material (1.5 h). It was then carefully neutralized dropwise with conc. aqueous ammonia at 0°C, finally pH was adjusted to 9.5 and 60 ml of cold ethanol was added. The volatiles were removed under vacuum and the residue was partitioned between methylene chloride (30 ml) and water (30 ml). The aqueous layer was concentrated to ca 5 ml and applied on a column packed with silanized silica gel (60 x 50 mm). The column was washed first with water (200 ml) to remove salts, then with 10-25% aqueous acetone. Fractions containing pure 2a were pooled and evaporated to yield a white solid, later crystallized from methanol to form 0.227 g (65%) of 2a as white crystals: m.p. soft. 180-185°C, dec. 197°C (lit<sup>11</sup> [EtOH-H<sub>2</sub>O] soft. 184-186°C, does not melt up to 300°C). <sup>1</sup>H and <sup>13</sup>C NMR data presented in Tables 1, 2.

<u>5'-O-(*tert*-Butyldimethylsilyl)-2',3'-dideoxyinosine (2c)</u>. 2a (0.047 g, 0.2 mmol) was coevaporated with anhydrous pyridine, then suspended in pyridine (2 ml). *tert*-Butyldimethylsilyl chloride (0.054 g, 0.36 mmol) was added and the resulting mixture was stirred overnight. It was treated with sodium bicarbonate sat. solution (10 ml) and extracted with chloroform (3 x 5 ml). Organic layers were combined, dried with sodium sulphate and evaporated under vacuum. The residue was triturated with anhydrous n-hexane (10 ml), 2c was filtered off, washed with n-hexane and dried over  $P_2O_5$  to yield 0.066 g (89%): m.p. 168-170°C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$ : 0.01 (6H, s, Me<sub>2</sub>Si), 0.85 (9H, s, Me<sub>3</sub>CSi), 2.04 (2H, m, H-3'), 2.44 (H-2', overlaps with DMSO-d<sub>5</sub>), 3.68 (1H, dd, J: 11.4, 3.8 Hz, H-5"), 3.82 (1H, dd, J: 11.4, 3.8 Hz, H-5'), 4.15 (1H, m, H-4'), 6.21 (1H, dd, J: 6.8, 3.1 Hz, H-1'), 8.04 (1H, s, H-8), 8.26 (1H, s, H-2), 12.33 (1H, br s, exchangeable, N-1 H).

<u>5'-O-Acetyl-2',3'-dideoxyinosine</u> (2d).<sup>21</sup> 2a (0.121 g, 0.51 mmol) was coevaporated with anhydrous pyridine suspended in 2 ml of pyridine and treated with acetic anhydride (0.068 g, 0.66 mmol). The mixture was stirred overnight then coevaporated with toluene (3 x 10 ml) under vacuum. The sole product 2d was recrystallized from hot methanol (10 ml) to give 0.121 g (85%) of white crystals: m.p. 165-167°C, UV[H<sub>2</sub>O]  $\lambda_{max}$  249 {7900}. <sup>1</sup>H NMR data given in Table 1. <u>8-Bromo-5'-O-(*tert*-butyldimethylsilyl)-2',3'-dideoxyguanosine (3b)</u>. To a stirred at 20°C suspension of 1b (0.200 g, 0.55 mmol) in acetate buffer (6 ml, 1 M, pH 4.5) bromine water [0.060 ml Br<sub>2</sub> (0.19 g, 1.2 mmol) in 5.3 ml H<sub>2</sub>O] was added dropwise in 2 portions: 2.5 ml within 30 min, pause of 20 min, the other portion in 30 min. The reaction was continued for 15 min more, then refrigerated for 30 min. Precipitated product 3b was filtered off, carefully washed with acetate buffer (20 ml, 1 M, pH 5) then with cold water. It afforded 0.196 g of crude material. 3b was purified by column chromatography (40 x 60 mm) on silica gel with chloroform/ /ethanol/triethylamine (90:9:1 v/v/v) as the eluent. Fractions containing pure 3b were combined and concentrated under vacuum to ca 4 ml volume. Upon cooling, it slowly crystallized to give analytically pure 3b as white, shiny flakes (0.058 g, 24%, m.p. 197°C, UV [MeOH]  $\lambda_{max}$  262 {14260}). The filtrate afforded 0.075 g (31%) of 3b. <sup>1</sup>H and <sup>13</sup>C NMR data presented in Tables 1, 2.

Anal. Calcd for C<sub>16</sub>H<sub>26</sub>BrN<sub>5</sub>O<sub>3</sub>Si: C, 43.24; H, 5.90; N, 15.76; Br, 17.98. Found C, 43.19; H, 6.27; N, 15.84; Br, 17.70.

<u>8-Bromo-2',3'-dideoxyguanosine (3a)</u>. A solution of **3b** (0.127 g, 0.28 mmol) in anhydrous pyridine (5 ml) was treated with 1 M solution of tetra-n-butylammonium fluoride in THF (0.9 ml) and set aside overnight. It was coevaporated with toluene under vacuum below 20°C to an oily residue. The product **3a** was isolated by chromatography on silica gel column (40 x 60 mm) with 5-10% methanol in chloroform (with 0.2% Et<sub>3</sub>N). Fractions containing pure **3a** were combined and evaporated below 20°C to the oily residue. It was dissolved in water (5 ml) and filtered. The filtrate was concentrated to ca 1.5 ml and refrigerated overnight. Resulting white crystals were filtered off, washed with icy water and dried to yield 0.056 g of analytically pure **3a** (56%, m.p. 195°C dec., UV [MeOH]  $\lambda_{max}$  261 {15300}). The filtrate yielded additional 0.023 g (25%) of **3a** as off-white solid. <sup>1</sup>H and <sup>13</sup>C NMR data given in Tables 1, 2.

Anal. Calcd for C<sub>10</sub>H<sub>12</sub>BrN<sub>5</sub>O<sub>3</sub> + 1/2 H<sub>2</sub>O: C, 35.41; H, 3.86; N, 20.65; Br, 23.56. Found C, 35.67; H, 3.90; N, 20.45; Br, 23.27.

<u>8-Bromo-2',3'-dideoxyinosine (4a)</u>. To a stirred solution of 2a (0.047 g, 0.2 mmol) in 1.5 M acetate buffer pH 4.65 (1 ml), bromine (0.041 g, 0.26 mmol) was added at 20°C. The solution turned heterogeneous and cleared again after 6 h of intensive stirring. The reaction was continued for 1 more hour then it was stopped by cooling to 0°C and pH of the solution was carefully adjusted to 7 with cold 1 M phosphate buffer (pH 7.2, 15 ml). Unreacted bromine was removed under vacuum below 10°C. The residual mixture was applied to a column packed with silanized silica gel (40 x 50 mm). The column was first washed with water (200 ml) to remove the salts, then with a gradient of acetone in water (1-15%). Fractions ca 10 ml were collected: #7-11 contained **2a** (recovered 0.031 g), #14-15 contained **4a** (0.015 g contaminated with UV not-absorbing material). Finally, **4a** was purified by TLC: it was applied on 2 plates (0.25 mm each). The separation was conducted with chloroform/ ethanol/ water 40:10:1 (v/v/v) as a solvent system (it contained 0.2% Et<sub>3</sub>N) at 4°C. The bands were cut off and the product **4a** was eluted with the same solvent system, filtered through silica gel 10 mm pad. The filtrate was evaporated under vacuum below 15°C to yield 0.007 g (12%) of **4a** as white solid: m.p. soft. 126°C, dec. 177°C. UV [H<sub>2</sub>O]  $\lambda_{max}$  254 {15200}.

4a: HR MS sample mass 315.0089, calcd for  $C_{10}H_{12}BrN_4O_3$  (M+H)<sup>+</sup>: 315.0093. <sup>1</sup>H and <sup>13</sup>C NMR data presented in Tables 1, 2.

<u>5'-O-Acetyl-8-bromo-2',3'-dideoxyinosine (4b)</u>. To a protected from moisture solution of 2d (0.042 g, 0.15 mmol; dried in vacuo: 0.01 Torr, 30°C, 3 h) in anhydrous chloroform (3 ml) at reflux N-bromosuccinimide was added (0.134 g, 0.75 mmol). The resulting suspension was heated at reflux for 8 h. After that time, the reaction mixture was cooled to remove the excess of NBS. The solution was decanted and applied on 2 PLC plates. The separation was conducted in darkness at 4°C with chloroform/methanol 95:5 (v/v) as a solvent system. Bands corresponding to 4b were cut off and the product was eluted from silica gel with the same solvent system. It yielded 0.005 g of 4b (9%): UV pH  $\lambda_{max}$  235 {13090}, pH 11  $\lambda_{max}$  258 {12200}. <sup>1</sup>H NMR data presented in Table 1.

Other experimental conditions were investigated. When a mixture of 2d and NBS (5 eq) in chloroform was refluxed with benzoyl peroxide in argon atmosphere for 6 h, only minute amounts of 4b were observed by TLC. When 2d and NBS were heated in ethylene chloride up to  $60^{\circ}$ C in the presence of ZnCl<sub>2</sub> for 4-8 h traces of 4b were observed followed by depurination of the starting material.

<u>8-Bromo-2',3'-dideoxyadenosine<sup>19</sup> (6b</u>). A solution of 2',3'-dideoxyadenosine (0.120 g, 0.5 mmol) in methanol (5 ml) - 1 M acetate buffer pH 4.65 (3 ml) was treated with bromine (0.175 g, 1.1 mmol) and kept for 3 h at 20°C. Bromine and methanol were removed in vacuo. The residual solution was treated with 1 M phosphate buffer pH 7 (6 ml) and extracted with pyridine/methylene chloride (1:3, 4 x 7 ml). Organic layers were combined and evaporated, the residue was purified by chromatography on silica gel with 5% methanol in methylene chloride. It yielded 0.135 g (86%) of 6a: m.p. soft. 159°C (lit.<sup>19</sup> m.p. soft. 164°C). <sup>1</sup>H and <sup>13</sup>C NMR data presented in Tables 1, 2.

<u>5'-O-Acetyl-8-bromo-2',3'-dideoxyadenosine (6c)</u>. 6b (0.133 g, 0.42 mmol) was dried by coevaporation with 2 successive volumes of anhydrous pyridine (5 ml) and dissolved in pyridine (2 ml). Acetic acid anhydride (0.086 g, 0.084 mmol) was added at 0°C. After the reaction was completed (12 h), it was cooled to 0°C and MeOH (0.5 ml) was added. The volatiles were removed under vacuum. The product 6c was purified by chromatography on a silica gel column with 1-3% methanol in methylene chloride. It yielded 0.130 g (86%) of pure crystalline 6c: m.p. 127-129°C, <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$ : 1.85 (3H, s, CH<sub>3</sub>), 2.09 (2H, m, H-3"), 2.45 (m, overlaps with DMSO-d<sub>5</sub>, H-2", H-3'), 2.97 (1H, m, H-2'), 4.06 (1H, dd, J: 11.5, 6.4 Hz, H-5"), 4.21 (1H, dd, J: 11.5, 3.4 Hz, H-5'), 4.27 (1H, m, H-4'), 6.21 (1H, dd, J: 7.4, 3.8 Hz, H-1'), 7.42 (2H, br s, exchangeable, NH<sub>2</sub>), 8.14 (1H, s, H-2).

Attempted conversion of 6c to 4b and 5'-O-acetyl-8-bromo-2',3'-dideoxynebularine with n-pentyl nitrite. To a stirred at reflux solution of 6c (0.050 g, 0.14 mmol) in anhydrous tetrahydrofuran (4 ml), a solution of n-pentyl nitrite (0.40 ml, 2.8 mmol) in THF (4 ml) was added dropwise within 15 min. Gas evolution began and the reaction mixture turned yellow. Reflux was continued for 5 h until TLC revealed that the reaction was stopped. About 85% of 6c underwent transformation - two UV absorbing products A and B were observed (Rfs: A 0.39, B 0.11 with 5% methanol in chloroform as TLC solvent system). The volatiles were removed under vacuum, below 20°C. An oily residue, cooled to 0°C was treated with ethanol (10 ml). The solvent was removed under vacuum. Neither product A nor B were found in the residue. It contained two other unidentified UV absorbing products C and D (Rfs: C 0.25, D 0.00 with 5% methanol in chloroform). C (UV [MeOH]  $\lambda_{max}$  257, sh 262) and D (UV [MeOH]  $\lambda_{max}$  260) were isolated by PLC with 10% methanol in chloroform containing traces of Et<sub>3</sub>N.

<sup>1</sup>H and <sup>13</sup>C NMR spectra of C and D measured in DMSO-d<sub>6</sub> confirmed that neither C nor D were nucleosides.

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