

General Method for the Synthesis of 2'-Azido-2',3'-dideoxynucleosides by the Use of [1,2]-Hydride Shift and β -Elimination Reactions¹

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The title nucleosides (**16U**, **C**, **G** and **H**) were synthesized from pyrimidine and purine ribonucleosides in about 30% overall yield in 6 steps *via* key intermediates, protected 3'-deoxy-'*arabino*'-nucleosides, which were obtained by deoxygenative [1,2]-hydride shift and β -elimination reactions of sulfonylated *ribo*-counterparts. Xanthine analogues (**9X** and **16X**) were prepared from the corresponding guanine nucleosides. The unprotected 3'-deoxy-'*arabino*'-nucleosides (**9U**, **C**, **A**, **G**, **H**, **X**) and their azido nucleosides **16** did not show any significant activity against HIV *in vitro* or P388 leukaemia in mice.

Deoxygenative [1,2]-hydride shift² and β -elimination³ reactions of vicinal *cis*-diol sulfonates have been in numerous instances found to be powerful methods⁴⁻¹⁰ for the synthesis of deoxygenated nucleosides from the corresponding ribonucleosides involving a 2',3'-diol system. The discovery¹¹ that 2',3'-dideoxynucleosides and their 3'-azido derivatives possess significant anti-HIV (human immunodeficiency virus) activity has generated considerable interest in the chemistry and biochemistry of deoxygenated nucleosides.¹² In going programmes to develop potential antiviral and/or antitumour agents, we succeeded in the general synthesis of biologically interesting 2'-azido-2',3'-dideoxy pyrimidine and purine nucleosides (**16U**, **C**, **A**, **G**, **H**, **X**) by the application of [1,2]-hydride shift and β -elimination reactions^{6,7} at the key steps (Scheme 1). Our method involves two synthetic approaches to common intermediates for the synthesis of the desired azido nucleosides starting from readily available ribonucleosides, uridine, cytidine, adenosine, guanosine, and inosine (**1U**, **C**, **A**, **G**, and **H**). *Route A* is for both pyrimidine and purine nucleosides and *route B* for the latter.

Results and Discussion

In the first route, the simultaneous protection of both 5'-hydroxy and amino functions in substrates **1C**, **A**, and **G** was carried out by the use of chlorobis(4-methoxyphenyl)phenylmethane (4,4'-dimethoxytrityl chloride, DMTrCl),¹³ while substrates **1U** and **H** were protected at their 5'-hydroxy groups. However, since 5'-DMTr-protected inosine was found to be rather unstable under conditions used for the work-up procedures in further reactions, we utilized a 4-methoxytrityl (MMTr) group¹⁴ for the protection of compound **1H**. The MMTr protecting group was also effective for the protection of the other nucleosides (data not shown).

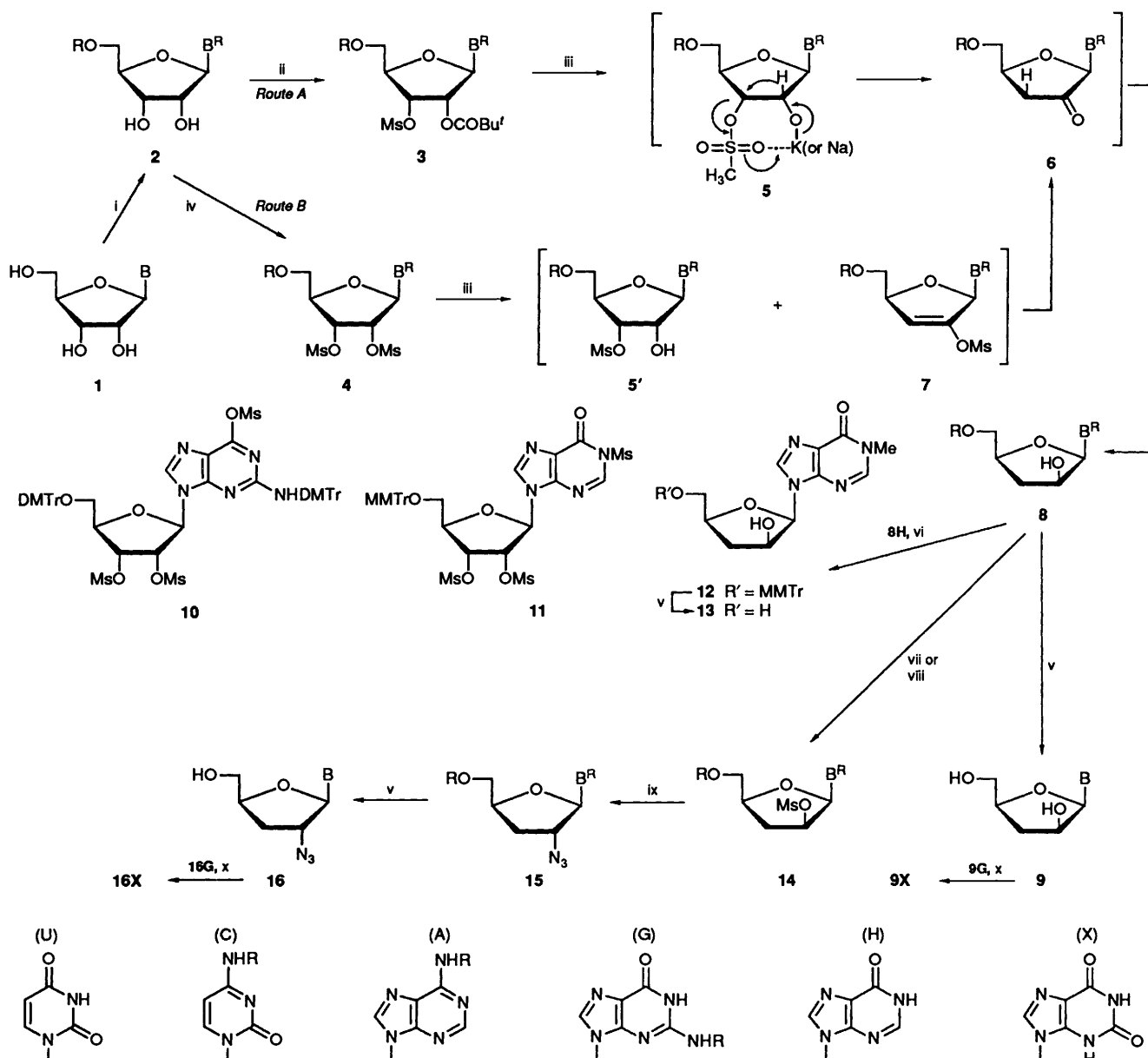
For *route A*, the DMTr- or MMTr-protected pyrimidine and purine nucleosides **2U**,¹⁵ **2C**, **2A**,^{6b} **2G** and **2H**¹⁶ were regioselectively pivaloylated¹⁷ at their 2'-hydroxy groups with trimethylacetyl chloride (pivaloyl chloride, PivCl) followed by methanesulfonylation with methanesulfonyl chloride (MsCl) in a one-pot reaction⁷ to furnish 3'-*O*-methylsulfonyl-2'-*O*-pivaloyl nucleosides (**3U**, **C**, **A**, **G**, **H**) as the main products. In this step compound **2A** gave an inseparable mixture (86:14, determined by ¹H NMR spectroscopy, Table 3) of compound **3A** and its 2'-methylsulfonyl-3'-pivaloyl isomer. Furthermore, the *N*¹- or *O*⁶-position of compounds **2G** and **2H** were also methanesulfonylated (or pivaloylated) to some extent.¹⁸ However, the main products (**3A**, **G**, and **H**) contaminated with these by-products could be used for the next reaction without puri-

fication, because under the alkaline conditions employed for the next hydride-shift rearrangement the *N*¹- and *O*⁶-substituted groups in acylated substrate **3G** or **3H** were found to be easily cleaved to reproduce the parent compound (**3G** or **3H**), judging from TLC analyses; in the case of compound **3A**, products derived from the 2'-methylsulfonyl-3'-pivaloyl isomer could be removed by chromatography.

The methanesulfonates, **3U**, **C**, **A**, **G**, and **H**, were then individually subjected to the deoxygenative [1,2]-hydride-shift rearrangement with combined reagents, potassium hydroxide-sodium borohydride^{6,7} in methanolic solution, where the following three-step reaction proceeded very nicely in one pot. First, the 2'-pivaloyl group in substrates **3** was cleaved to form an intermediate (**5**) under the alkaline conditions. Secondly, the hydride shift and the removal of the 3'-methylsulfonyloxy group occurred in a concerted manner to afford a 3'-deoxy-2'-keto nucleoside (**6**). Finally, ketonucleosides **6** was reduced with the hydride to provide a 3'-deoxy-'*arabino*'-nucleoside derivative (**8U**,¹⁹ **8C**,^{7a} **8A**,^{6b} **8G**, or **8H**) in good yield (Table 1). The reduction of substrates **6** proceeded with high stereoselectivity (>95%, judging from TLC analyses) except for compound **6G**. In this case, 2'-'down'-hydroxy anomers of compound **8G** were formed in ~20% combined yield, but these have not yet been fully characterized.

The spectral data of compounds **8U**,¹⁹ **8C**,^{7a} **8A**,^{6b} **8G**, and **8H** were compatible with their assigned structures (Tables 2 and 3). Furthermore, deprotection of these nucleosides with an acid gave the corresponding free 3'-deoxy-'*arabino*'-nucleosides (**9U**, **C**, **A**, **G**, and **H**) in high yields. The ¹H NMR spectra of the products **9U**, **9C**, **9A**, and **9G** were identical with those of the respective authentic samples.^{7b,20} The structure of the new compound **8H** was determined on the basis of its elemental analysis and spectral data (UV and ¹H NMR). In addition, the structure of the sugar moiety of compound **9H** was also confirmed by its methanolysis: the obtained mixture of methyl glycosides was identical with those prepared from the known compound **9A**.^{6b,7b} Recently the synthetic utilities of modified nucleosides related to **8U**⁸ and **8A**^{9,21} have been reported.

An alternative method (*route B*) for the synthesis of the intermediates **8** was performed by the application of our reaction⁶ of *N*⁶,*O*⁵-bis(dimethoxytrityl)-2',3'-bis-*O*-(methylsulfonyl)adenosine **4A** with KOH-NaBH₄, giving compound **8A** in 96% yield. The method was more practical than that *via route A*, although its application was limited to nucleosides such as **1G** and **1H**, the base moiety of which had no group participating with the C-2' bearing the methanesulfonyloxy group. We have demonstrated earlier that a 3'-*O*-methylsulfonyl-2'-*O*-(tolylsulfonyl)adenosine derivative was susceptible



B = R = H, B^R = DMTr (4,4'-dimethoxytrityl) or MMTr [(4-methoxytrityl), (H) series], and Ms = MeSO₂-

Scheme 1 Reagents and conditions: i, DMTrCl (MMTrCl for 1H), pyridine–DMSO; ii, Bu^tCOCl, pyridine then MeSO₂Cl; iii, NaBH₄, KOH, MeOH–(PhH); iv, MeSO₂Cl, CH₂Cl₂–Et₃N (for 2G), pyridine (for 2H); v, 80% AcOH; vi, MeI–DBU, DMF or MeSO₃Me–KOH, MeOH–PhH; vii, MeSO₂Cl, pyridine (for 8U,C); viii, MeSO₂Cl then KOH (for 8G,H); ix, NaN₃, DMF; x, NaNO₂, HCO₂H, water.

to selective methanolysis at the 2'-position under alkaline conditions, producing a 2'-hydroxy-free compound (5').⁶ Therefore we propose that, in a similar way, the conversion of a protected 2',3'-bismethanesulfonate (4G or 4H) into the corresponding 3'-deoxy-2'-hydroxy compound 8 would take place via a 2'-hydroxy-free nucleoside (5') as well as an enol methanesulfonate (7) formed by the β-elimination¹⁰ of the 2',3'-bis(methanesulfonate).

Direct methanesulfonylation of compounds 2G and 2H with MsCl produced disulfonates 4G and 4H, respectively, in good yield along with O^{6,2',3'}- and N¹,O^{2',3'}-trismethanesulfonylated guanosine and inosine derivatives [10 (22%) and 11 (11%), respectively]. These trismethanesulfonates were isolated and fully characterized by means of spectroscopy as well as elemental analysis. Here again, the reaction of compounds 10 and 11 with methanolic KOH provided the parent 2',3'-bismethanesulfonates, 4G and 4H, respectively, so that the crude products 4G and 4H, contaminated by the trisulfonate

were used for the next deoxygenation without purification. Upon treatment of compound 4G under conditions similar to those for the deoxygenative [1,2]-hydride shift, compound 8G was obtained in 75% yield together with its isomer (19%), results analogous to those in route A. In contrast to this, the yield (78%) of compound 8H produced from disulfonate 4H (route B) was 10% lower than that through route A. We found that the reaction of disulfonate 4H with KOH–NaBH₄ gave an unexpected N¹-methylated derivative (12) as a by-product in 9% isolated yield. This side reaction caused a decrease in the yield of compound 8H via route B. No formation of compound 12 from 3H was detectable.

The structure of compound 12 and of its deprotected nucleoside 13 were determined on the basis of their elemental analyses as well as physical properties, in which the IR spectra of both compounds showed strong absorption at 1660–1680 cm⁻¹ characteristic of the carbonyl group in the hypoxanthine base moiety,^{16,22} thus indicating the presence of N¹- rather

Table 1 The nucleoside derivatives 2–16 prepared

Compound	Reaction time (h) ^a [temp. (°C)]	Yield (%)	Column chromatography		M.p. (°C) ^d (Recryst. solvent)
			Adsorbent ^b (g)	Eluent ^c (ratio)	
2U	22 (rt)	73	A (140)	a (95:5)	117 (sintered), 120–124 (from CH ₂ Cl ₂ -Et ₂ O)
2C	18 (rt)	70	A (90)	d (7:3:0 → 9:1:0.1)	amorph.
2A	20 (rt)	89	A (70)	c (7:3)	amorph.
2G	3.5 (rt)	88	B (120)	b (99:1:1 → 9:1:0.1)	amorph.
2H	19	98			197–199 (from EtOH)
3U	P: 1 (0–5) M: 1 (0–5) → 2 (rt)	73	A (40)	a (95.5:0.5 → 99:1)	amorph.
3C	P: 0.8 (0–5) M: 0.5 (0–5) → 1.7 (rt)	93	A (100)	a (99:1)	amorph.
3A	P: 0.8 (0–5) M: 0.5 (0–5) → 4 (rt)	95 ^e	A (130)	a (99:1)	amorph.
3G	P: 0.25 (0–5) M: 0.17 (0–5)	not isolated			
3H	P: 1.17 (rt) M: 4 (rt)	not isolated			
4A ^f	[2.5 (0–5) → rt]	94	B	e (99.5:0.5 → 95:5) ^f	
4G	0.3 (0–5)	77	A (44)	a (99.5:0.5 → 95:5)	amorph.
4H	0.17 (0–5) → 3.5 (rt)	70	B (400)	a (97:3 → 95:5)	amorph.
8U	23 (rt)	84	A (20)	a (99:1 → 97:3)	amorph.
8C	25 (rt)	86	A (40)	a (99:1)	amorph.
8A	(from 3A) 22 (rt) (from 4A) [24 (rt)]	74 96	A (50) B	a (99.5:0.5) f (9:1:0.1:0 → 9:1:0.1:0.1) ^f	amorph.
8G	(from 3G) 28 (rt) (from 4G) 24 (rt)	72 ^g 75 ^g	A (25) A (20)	a (98:2) a (99:1 → 98:2 → 97:3)	amorph.
8H	(from 3H) 27.5 (rt) (from 4H) 20 (rt)	89 78	A (35) A (40)	a (99.5:0.5 → 98:2) a (97:3 → 95:5 → 9:1)	amorph.
9U	5 min (65)	91			144–145 (from Pr ⁱ OH)
9C	35 min (65)	100			amorph.
9A	15 min (65)	98			193–194 (from MeOH)
9G	30 min (65)	83			> 240 (decomp.) (from EtOH–water, 6:1)
9H	15 min (65)	100			193.5–194.5 (sintered), > 250 (decomp.) (from EtOH–water, 20:3)
9X	1.5 (rt)	56	C (120 cm ³)	h	> 240 (decomp.) (from EtOH–water, 3:1)
10	0.3 (0–5)	22	A (44)	a (99.5:0.5 → 95:5)	amorph.
11	0.17 (0–5) → 3.5 (rt)	11	B (400)	a (97:3 → 95:5)	amorph.
12	(From 8H with MeI) 10 min (rt)	75	B (50)	a (98:2)	amorph.
13	0.5 (65)	75	B (150)	a (95:5 → 9:1 → 7.3)	185–186 (decomp.) ^h
14U	2.75 (rt)	92	A (15)	a (99:1 → 97:3)	amorph.
14C	4.5 (rt)	79	B (22)	f (50:50:1:2)	amorph.
14A ^f	[5 (rt)]	93	B	b (99:1:1) ^f	
14G	0.25 (rt) ⁱ	89	A (44)	a (9:1)	amorph.
14H	5 min (0–5) → 2.7 (rt) ^j	73	B (15)	a (95:5)	amorph.
15U	3 (110–115)	89	A (15)	a (99.5:0.5)	amorph.
15C	4 (110–115)	93	B (48)	f (50:50:1:0.2)	amorph.
15A ^f	[5 (105–110)]	78	B	g (97:3:1) ^f	
15G	7 (110–115)	71	A (50)	a (99:1)	amorph.
15H	6.3 (110–115)	80	A (20)	a (99:1 → 96:4)	amorph.
16U	3 (rt)	80			167–168 (decomp.) (from Pr ⁱ OH)
16C	1.25 (50–55)	84			171–172 (decomp.) (from Pr ⁱ OH)
16A ^f	[4 (rt)]	75	B	a (19:1) ^f	
16G	0.25 (rt) → 0.5 (65)	90			217–218 (sintered), > 219 (decomp.) (EtOH–water, 1:1)
16H	0.5 (65)	90			193.5.5–194.5 (melted, then solidified), > 250 (decomp.) (from EtOH–water, 87:13)
16X	1 (rt)	65	C (50 cm ³) then B (25)	i (9:1 → 1:1) j (75:20:5)	amorph.

^a rt: room temperature; P: PivCl; M: MsCl. ^bA: neutral silica gel (SilicAR 100–200 mesh, Mallinckrodt); B: Silica gel 60 (70–230 mesh, Merck); C: Diaion HP 20 (highly porous resin, Mitsubishi Chemical Co.). ^ca: CHCl₃–MeOH; b: CHCl₃–MeOH–Et₃N; c: PhH–AcOEt; d: PhH–AcOEt–MeOH; e: PhH–AcOEt–Et₃N; f: PhH–AcOEt–Et₃N–MeOH; g: CHCl₃–AcOEt–Et₃N; h: water; i: water–MeOH; j: AcOEt–water–PrⁱOH. ^dUncorrected; measured on a Yamato micro melting-point apparatus. ^eA combined yield of a mixture (86:14) of 3A and its isomer. ^fRef. 6b. ^gIn addition, 9-(3-deoxy- α - and - β -D-erythro-pentofuranosyl)guanines were formed in ~20% yield. ^hCrystallized by trituration with EtOH. ⁱFollowed by treatment with KOH at r.t. for 5 min. ^jFollowed by treatment with KOH at 0–5 °C for 8 min.

than O⁶-methylation. The following chemical conversion also supported the assigned structures. The reaction of compound 8H with methyl iodide in the presence of 1,8-diazabicyclo-

[5.4.0]undec-7-ene (DBU) provided a sole product (75% yield) that was identical with compound 12 obtained from 4H. We considered that N¹-methylation of the hypoxanthine moiety

Table 2 Analytical and spectral data of the nucleosides 2–16

Compound	Formula (FW) [or Lit. m.p. (°C)]	Found ^{a,b} (%) (Required) [Calc.]				$[\alpha]_D^{20}$ (c, CHCl ₃) ^c	Temp. (°C)	UV ^d $\lambda_{\text{max}}^{\text{MeOH}}$ / $\epsilon/\text{dm}^2 \text{ mol}^{-1}$ cm ⁻¹	IR ^{e,v} $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹
		C	H	N	S				
2U	[111–112 (Et ₂ O)] ^f	65.1 [65.3]	5.6 5.7	5.0 5.0		+7.2 (0.91)	25	235 (23 600) 265 (11 900)	
2C	C ₅₁ H ₄₉ N ₃ O ₉ ·0.3H ₂ O (853.4)	71.8 (71.8)	5.9 (5.9)	5.0 (4.9)		+17.9 (1.11)	22	231 (45 000) 281 (19 400)	
2A	[amorph.] ^h					[–4.5 (0.75)]	24	274 (31 000) 232sh] ^h	
2G	C ₅₂ H ₄₉ N ₅ O ₉ ·0.5H ₂ O (897.0)	69.3 (69.6)	5.7 (5.6)	7.7 (7.8)		+29.0 (0.78)	20	234 (43 600) 275 (19 800)	
2H	[175–176 (from CHCl ₃ –Et ₂ O)] ⁱ	66.4 [66.7]	5.2 5.2	10.2 10.4]		–14.8 (1.06, DMF)	25	235 (21 400) [235 (21 400)] ⁱ	
3U	C ₃₆ H ₄₀ N ₂ O ₁₁ S·1.6C ₅ H ₁₂ (824.2)	64.2 (64.1)	7.5 (7.2)	3.2 (3.0)	3.9 (3.9)	+19.4 (1.47)	22	235 (23 000) 262sh	
3C	C ₅₇ H ₅₉ N ₃ O ₁₂ S (1010)	67.5 (67.8)	5.9 (5.9)	4.25 (4.2)	3.0 (3.2)	+34.9 (1.29)	22	232 (44 400) 276 (19 700)	
3A	C ₅₈ H ₆₀ N ₅ O ₁₁ S·0.5C ₅ H ₁₂ ^h (1071)	67.8 (67.8)	6.1 (6.2)	6.6 (6.5)	2.9 (3.0)				
3G	(not isolated)								
3H	(not isolated)								
4G	C ₅₄ H ₅₃ N ₅ O ₁₃ S ₂ (1044)	62.3 (62.1)	5.3 (5.1)	6.55 (6.7)	6.1 (6.1)	–50.4 (0.87)	20	234 (45 000) 263 (22 000), 275 (21 900)	1 700 (C=O)
4H	C ₃₂ H ₃₂ N ₄ O ₁₀ S ₂ ·0.3C ₅ H ₁₂ (718.4)	55.9 (56.0)	5.1 (5.0)	7.5 (7.8)	8.7 (8.9)	–19.3 (0.79)	20	235 (22 100)	1 690 (C=O)
8U	C ₃₀ H ₃₀ N ₂ O ₇ ·1.0C ₅ H ₁₂ (602.7)	69.7 (69.8)	7.3 (7.0)	4.4 (4.65)		+12.9 (1.47)	22	234 (24 200) 265 (12 900)	
8C	C ₅₁ H ₅₁ N ₃ O ₈ (834.0)	73.2 (73.45)	6.5 (6.2)	4.8 (5.0)		+17.1 (1.1)	25	281 (17 400)	
8A	[amorph.] ^h					[+9.2 (0.9)]	22	274 (30 000)] ^h	
8G	C ₅₂ H ₄₉ N ₅ O ₈ ·0.5H ₂ O (881.0)	70.9 (70.9)	5.7 (5.7)	7.9 (7.95)		+30.4 (0.89)	20	234 (45 000) 275 (19 400)	
8H	C ₃₀ H ₂₈ N ₄ O ₅ ·0.5H ₂ O (533.6)	67.5 (67.5)	5.3 (5.5)	10.5 (10.5)		–66.0 (0.95)	20	235 (21 600)	
9U	[146–147 (from Pr ⁱ OH)] ⁱ	[144– 145]	(from EtOH)] ^m			[+146 (0.8, water)]	27	263 (10 300)] ⁱ	
9C	[hygroscopic amorph.] ⁱ								
9A	[195–196 (MeOH)] ⁱ					[–24.3 (1.1, DMF)]	20	259 (14 200)] ⁱ	
9G	[>235 (from EtOH)] ⁱ	43.8 [43.8]	4.8 5.1	25.6 25.5]		[+8.7 (1.1, DMF)]	20	253 (14 800) 271sh] ⁱ	
9H	C ₁₀ H ₁₂ N ₄ O ₄ (252.2)	47.4 (47.6)	4.8 (4.8)	21.9 (22.2)		–18.7 (0.83, DMSO) +28.3 (0.57)	21 21	249 (11 800)	1 710 (C=O)
9X	C ₁₀ H ₁₂ N ₄ O ₅ (268.2)	44.5 (44.8)	4.5 (4.5)	20.9 (20.9)		–8.3 (0.90, water, DMF)	25	235 (10 000) 261 (10 200)	
10	C ₅₅ H ₅₅ N ₅ O ₁₅ S ₃ ·1.5C ₅ H ₁₂ (1230)	61.0 (61.0)	6.2 (6.0)	5.5 (5.7)	7.6 (7.8)	–28.8 (1.65)	20	283 (10 400) 307 (10 400)	1 620 (C=N, C=C)
11	C ₃₃ H ₃₄ N ₄ O ₁₂ S ₃ ·0.9C ₅ H ₁₂ (839.8)	53.6 (53.6)	5.45 (5.4)	6.6 (6.7)	11.4 (11.45)	–14.7 (0.96)	21	234 (18 900)	1 720 (C=O)
12	C ₃₁ H ₃₀ N ₄ O ₅ ·0.3C ₅ H ₁₂ (560.2)	69.4 (69.7)	6.0 (6.1)	9.8 (10.0)		–3.9 (0.77)	21	234 (20 700)	1 680 (C=O)
13	C ₁₁ H ₁₄ N ₄ O ₄ ·0.1H ₂ O (268.1)	49.4 (49.3)	5.3 (5.3)	20.7 (20.9)		–12.2 (1.36, DMF)	20	250 (9 800)	1 660 (C=O)
14U	C ₃₁ H ₃₂ N ₂ O ₉ S·0.9C ₅ H ₁₂ ^o (673.6)	63.1 (63.3)	6.65 (6.4)	3.9 (4.2)	4.8 (4.8)	+41.7 (1.59)	20	235 (34 200) 262sh	
14C	C ₅₂ H ₅₃ N ₃ O ₁₀ S·1.0C ₅ H ₁₂ (984.2)	69.4 (69.6)	6.7 (6.7)	4.1 (4.3)	3.3 (3.3)	+27.6 (1.0)	25	276 (20 900)	
14G	C ₅₂ H ₅₁ N ₅ O ₁₀ S (938.1)	66.7 (66.6)	5.5 (5.5)	7.25 (7.5)	3.4 (3.4)	+11.1 (0.8)	20	234 (45 800) 260 (21 300), 275 (20 300)	(19 800)
14H	C ₃₁ H ₃₀ N ₄ O ₇ S·1.4C ₅ H ₁₂ (703.7)	64.6 (64.9)	6.7 (6.7)	7.7 (8.0)	4.6 (4.6)	+11.2 (0.9) –4.6 (1.43, DMF)	21 21	235 (22 700) 235 (22 400)	
15U	C ₃₀ H ₂₉ N ₅ O ₆ ·0.6C ₅ H ₁₂ ·0.5H ₂ O (607.9)	65.5 (65.2)	5.9 (6.2)	11.3 (11.5)		–42.2 (0.8)	22	264 (11 100)	2 120 (N ₃)
15C	C ₅₁ H ₅₀ N ₆ O ₇ (859.0)	71.1 (71.3)	5.9 (5.9)	9.5 (9.8)		–31.0 (0.9)	25	281 (19 900)	2 110 (N ₃)
15G	C ₅₂ H ₄₈ N ₈ O ₇ ·0.5H ₂ O (906.0)	68.95 (68.9)	5.4 (5.45)	12.3 (12.4)		–5.6 (1.04)	22	234 (43 600) 263 (20 000), 276 (19 800)	2 110 (N ₃)
15H	C ₃₀ H ₂₇ N ₇ O ₄ ·0.9C ₅ H ₁₂ (614.5)	67.3 (67.4)	6.2 (6.2)	16.0 (16.0)		–49.7 (0.77)	20	235 (21 700)	2 100 (N ₃)
16U	[167–169 (from EtOH)] ^p	42.7 [42.4]	4.4 4.4	27.3 27.5]		–17.5 (0.87, DMF)	20	262 (10 300) [263 (EtOH)]	2 110 (N ₃) (10 000) 2 140] ^p
16C	C ₉ H ₁₂ N ₆ O ₃ ·0.1H ₂ O (254.0)	42.4 (42.55)	4.8 (4.8)	33.1 (33.1)		–42.6 (0.3, DMF)	25	271 (9 000)	2 130 (N ₃)

Table 2 (continued)

Compound	Formula (FW) [or Lit. m.p. (°C)]	Found ^{a,b} (%) (Required) [Calc.]				[α] _D ^o (c, CHCl ₃) ^c	Temp. (°C)	UV ^d $\lambda_{\text{max}}^{\text{MeOH}}$ /nm ($\epsilon/\text{dm}^3 \text{ mol}^{-1}$ cm^{-1})	IR ^{e,f} $\nu_{\text{max}}^{\text{KBr}}$ / cm^{-1}
		C	H	N	S				
16G	C ₁₀ H ₁₂ N ₈ O ₃ ·0.5H ₂ O (301.3)	39.8 (39.9)	4.3 (4.35)	36.9 (37.2)		-13.0 (1.02, DMF)	22	255 (15 200)	2 110 (N ₃)
16H	C ₁₀ H ₁₁ N ₇ O ₃ (277.2)	43.2 (43.3)	4.0 (4.0)	35.15 (35.4)		-60.6 (0.78, DMF)	20	245 (11 600) 249 (11 700)	2 140 (N ₃)
16X	C ₁₀ H ₁₁ N ₇ O ₄ ·0.8H ₂ O (307.7)	39.2 (39.0)	3.8 (4.1)	31.6 (31.9)		-57.4 (0.13, DMF)	25	241 (9 400) 258 (10 200)	2 100 (N ₃)

^a Performed by the Microanalytical Laboratory of this Institute. ^b Amorphous analytical samples were obtained by precipitation from CH₂Cl₂-pentane; all samples were dried at 60 °C for 4 h *in vacuo* over phosphorus pentoxide. ^c Measured with a Perkin-Elmer Model 241MC polarimeter. ^d Recorded using a Varian Cary 2200 instrument. ^e Obtained on a Shimadzu IR-27 spectrophotometer. ^f Ref. 15. ^g Calc. for C₃₀H₃₀N₂O₈·0.1Et₂O·0.3H₂O (559.4). ^h Ref. 6b. ⁱ Ref. 16. ^j Calc. for C₃₀H₂₈N₄O₆ (540.6). ^k A mixture (86:14) of 3A and its isomer. ^l Ref. 7b. ^m Ref. 20. ⁿ Calc. for C₁₀H₁₃N₅O₄·0.4H₂O (274.4). ^o Dried at rt for 4 h over phosphorus pentoxide. ^p Ref. 25. ^q Calc. for C₉H₁₁N₅O₄·0.1H₂O (255.0).

would take place by the attack of an anion on the N¹-position of species 4–8 to the methyl carbon of methyl methanesulfonate²³ that was generated *in situ* by the methanolysis of disulfonates 4 to sulfonates 5' as well as enol sulfonates 7 to ketones 6. We found that when compound 8H was treated with 1 mol equiv. of methyl methanesulfonate under conditions similar to those for the deoxygenation (4H → 8H), we could isolate compound 12 in 15% yield with a 51% recovery of the starting material. On the other hand, the N¹- or O⁶-methylated derivative of compound 8G was not isolated in route B or in the reaction of this compound with methyl methanesulfonate, presumably because of electronic and/or steric reasons attributable to the N²-protected guanine moiety of substrate 8G.

The final azido nucleosides (16U, C, G, and H) were synthesized from substrates 8 through a conventional 3-step sequence, according to the method reported for compound 16A.^{6b} A preliminary report on the synthesis of azide 16C from 8C has been published.^{7a} Treatment of substrates 8 (U, C, G or H) with MsCl, followed by S_N² substitution of the resulting methanesulfonate (14) by an azido anion, afforded the corresponding protected 2'-down'-azido-2',3'-dideoxy nucleoside (15) in good overall yield. The ¹H NMR spectra of these azido derivatives showed small values (0–2.2 Hz)²⁴ of the coupling constants between 1'-H and 2'-H, thus assigning the R-configuration of the azido group at C-2'. Lastly, deprotection of azides 15 (U, C, G and H) was effected with 80% acetic acid to give the corresponding 5'-hydroxy azides 16 in 80–90% yields. The physical properties of compound 16U²⁵ were identical with those reported earlier. The structures of azides 16C, 16G and 16H were also confirmed on the basis of their elemental analyses and spectral data (IR, UV, and ¹H NMR).

For the purposes of biological testing, the preparation of xanthine congeners of species 9 and 16 was carried out according to the method reported in the literature.²⁶ Individual treatment of compounds 9G and 16G with sodium nitrite in acidic media provided 3'-deoxy-'arabino'- and 2'-azido-2',3'-dideoxy-xanthosines (9X and 16X) in 56 and 65% yield, respectively.

The nucleosides 9 (U, C, A, G, H and X) and the corresponding 2'-azido congeners 16 (U–X) were tested against both HIV-1 *in vitro* and P388 leukaemia in mice (for 16X, *in vitro*), but no significant activity was detected.^{27,28}

In summary, we have developed a general method for the deoxygenation of the 3'-hydroxy group with the configurational inversion of the 2'-hydroxy function in the pyrimidine and purine ribonucleosides. The resulting 3'-deoxy-'arabino'-nucleosides were converted into the corresponding 2'-azido-2',3'-dideoxynucleosides. From the biological evaluation of the prepared nucleosides, it was concluded that the 2'-down' azido groups of the 2',3'-dideoxynucleosides played no essential role in anti-HIV activity, and that the lack of 3'-down' hydroxy groups

in 1-β-D-arabinofuranosylcytosine (*ara-C*)²⁹ and its adenine analogue (*ara-A*)³⁰ caused their lack of anti-tumour activity.

Experimental

All ribonucleosides, DMTrCl, and MMTrCl were purchased from Dojin Chemical Co. (Japan), and used without purification. Reagent-quality solvents were dried over molecular sieves 4Å and used without further purification. Analytical HPTLC plates (Silica Gel 60, F₂₅₄) were purchased from Merck. Detection of spots on TLC was done by UV (254 nm) or by spraying the plates with a solution of MeOH-sulphuric acid-*p*-anisaldehyde (85:15:5, v/v/v), followed by heating them on an electric plate. Reaction times and temperatures, yields, and the conditions for column chromatography are summarized in Table 1, unless otherwise specified. The physical and spectral data of the prepared nucleosides are listed in Tables 1–3.

5'-O-(4,4'-Dimethoxytrityl)uridine 2U,¹⁵ 4-N,5'-O-Bis(4,4'-dimethoxytrityl)cytidine 2C, 6-N⁵-O-Bis(4,4'-dimethoxytrityl)-adenosine 2A,^{6b} 2-N,5'-O-Bis(4,4'-dimethoxytrityl)guanosine 2G, and 5'-O-(4-Methoxytrityl)inosine 2H.—Substrate 1C, 1A, 1G or 1H (10 mmol) was dissolved in dry dimethyl sulfoxide (DMSO) (30–50 cm³) at room temperature (r.t.), after which dry pyridine (20 cm³) was added, while compound 1U (10 mmol) was dissolved in dry pyridine (40 cm³). To this solution was added DMTrCl (for 1U, 10.5 mmol; 1C, 1A, 21 mmol; 1G, 30 mmol) or MMTrCl (for 1H, 11 mmol) at r.t. and the mixture was stirred at this temperature for 3.5–22 h. After the mixture had cooled, it was quenched with 50% aq. pyridine (2 cm³), and the mixture was extracted with CHCl₃ (250 cm³). The extract was washed successively with water (80 cm³), aq. NaHCO₃ (50 cm³), and water (2 × 80 cm³), dried (MgSO₄), and evaporated. The pyridine was removed by co-evaporation with toluene. In the case of 1U, 1G or 1H, the residue was triturated with Et₂O (100 cm³), and the undissolved material was collected by filtration. The amorphous crude product (2U, C, A, G or H), was dried at 60 °C *in vacuo* for 4 h, and was used for the next reaction. An analytically pure sample was obtained by column chromatography or recrystallization under conditions given in Table 1.

DMTr- or MMTr-Protected 3'-O-Methylsulfonyl-2'-O-pivaloyl Nucleosides 3U, C, A and H.—The protected nucleoside (2U, C, A or H) (5 mmol), which had been dried by co-evaporation with benzene or dry pyridine, was dissolved in dry pyridine (30–40 cm³). To this solution cooled to 0–5 °C was added PivCl (for 2U, 7 mmol; for 2C, A and H, 10 mmol), after which the mixture was stirred at this temperature (for 2U, C and A) for 0.8–1 h or at r.t. (for 2H) for 70 min. MsCl (20 mmol) was

Table 3 ¹H NMR^{a,b} spectral data (δ_H) for the nucleosides 2–16 prepared

Compound	1'-H (J _{1,2'})	2'-H (m)	3',3''-H (ddd)	(ddd)	4'-H (m)	5.5''-H (J _{A(B),X})	J _{A,B}	2-or 5-H (J _{5,6})	6-or 8-H (J _{5,6})
2U	A: 5.85 (2.5)	4.32 (dd, 2.8, 5.1)	4.40 (t, 5.4)		4.20	3.47 (2.8, 11.3)	3.53 (2.5, 11.1)	5.39 (8.2)	7.96 (8.3)
2C	A: 5.72 (4.6)	4.50 (t, 4.7)	4.31 (m)		4.31	4.31 (m)		4.92 (7.6)	7.41 (7.6)
2G	B: 5.20 (3.8)	3.87	3.87 (m)		3.67–3.76	3.09 (m)			7.71
2H	B: 5.92 (5.0)	4.58 (t, 4.8)	4.24 (t, 5.1)		4.08 (dd, 4.8, 9.3)	3.23 (m)		7.98	8.12
3U ^c	A: 6.16 (6.1)	5.47 (t, 5.8)	5.30 (dd, 3.7, 5.5)		4.37	3.58 (dd, 2.8, 11.3)		5.38 (dd, 1.8, 8.2)	7.64 (7.9)
3C	A: 6.09 (3.4)	5.46 (dd, 3.4, 5.2)	5.35 (t, 5.8)		4.20	3.49 (2.6, 11.5)	3.53 (2.3, 11.5)	4.72 (7.6)	7.53 (7.6)
3A ^c	A: 6.14 (5.7)	6.00 (t, 5.5)	5.64 (t, 4.9)		4.39 (dd, 3.8, 7.8)	3.41 (3.7, 11.0)	3.61 (3.8, 11.0)	7.85	8.00
Isomer of 3A ^c	A: 6.23 (4.0)	5.89 (dd, 4.3, 5.2)	5.64 (t, 4.9)		4.35	3.39 (3.7, 11.0)	3.52 (2.7, 11.0)	7.97	7.98
3G	Others 1.19 (9 H, s, Bu'), 2.97 (3 H, s, SMe), 3.76 and 3.77 (12 H, each s, 4 × OMe), 6.7–8.4 (27 H, m, ArH and NH)								
3H	not isolated								
4G	B: 5.29 (7.4)	5.57 (br t, 6)	5.25 (br s)		4.24	3.24–3.36 (m)			7.71
4H	A: 6.21 (5.3)	6.06 (t, 5.3)	5.61 (dd, 4.1, 4.9)		4.48	3.44 (3.3, 11.0)	3.62 (3.3, 11.0)	7.93	7.98
8U	A: 5.95 (4.3)	4.57	2.05 (5.8, 7.3, 13.4)	2.33 (6.4, 7.2, 13.4)	4.24	3.34 (3.8, 10.8)	3.55 (2.6, 10.8)	5.45 (8.0)	7.90 (8.0)
8C	A: 5.98 (5.1)	4.68	2.04 (9.3, 9.5, 12.7)	2.20 (6.1, 6.3, 12.7)	4.15	3.28 (3.4, 11.0)	3.41 (2.3, 11.0)	4.82 (7.6)	7.90
8G	B: 5.14 (4.2)	4.12	1.67 (4.5, 5.7, 13.3)	2.23 (5.7, 6.3, 13.3)	3.79	2.94 (3.0, 9.7)	3.24 (7.5, 9.7)		7.49
8H	B: 6.17 (5.0)	4.52	1.95 (7.9, 7.9, 12.9)	2.43 (6.6, 6.6, 12.9)	4.25	3.11 (2.7, 10.2)	3.35 (6.9, 10.2)	8.02	8.04
9C	B: 5.88 (4.3)	4.25	1.72 (4.1, 6.0, 13.4)	2.27 (6.1, 7.6, 13.4)	4.00	3.56		5.66 (7.3)	7.66 (7.6)
9H	B: 6.11 (5.7)	4.52	2.00 (8.3, 8.3, 12.7)	2.26 (6.4, 6.4, 12.7)	4.10	3.57 (4.1, 12.0)	3.66 (2.9, 12.0)	8.02	8.27
9X	B: 5.91 (5.8)	4.50	1.93 (8.7, 9.1, 12.5)	2.15 (6.2, 6.6, 12.5)	4.08	3.57 (3.3, 12.0)	3.73 (2.9, 12.0)		7.91
10	C: 6.28 (6.1)	5.96 (t, 5.8)	5.63 (dd, 3.1, 5.2)		4.51	3.86 (2.4, 12.5)	3.95 (2.5, 12.5)		8.26
11	A: 6.19 (5.5)	5.94 (t, 5.5)	5.60 (dd, 4.3, 5.5)		4.48	3.45 (3.2, 11.2)	3.62 (3.2, 11.2)	7.94	8.43
12	B: 6.15 (5.5)	4.53	1.95 (7.9, 8.2, 12.5)	2.33 (6.6, 6.7, 12.8)	4.26	3.10 (3.1, 10.4)	3.36 (7.2, 10.4)	8.05	8.36
13	B: 6.09 (5.5)	4.53	2.00 (8.2, 8.2, 12.8)	2.26 (6.4, 6.7, 12.8)	4.09	3.57 (br m)	3.67 (br m)	8.28	8.36

Table 3 (continued)

Compound	1'-H ($J_{1',2'}$)	2'-H (m)	3',3"-H (ddd)	(ddd)	4'-H (m)	5,5"-H ($J_{A(B),X}$)	$J_{A,B}$	2-or 5-H ($J_{5,6}$)	6-or 8-H ($J_{5,6}$)
14U	A: 6.12 (4.9)	5.30	2.35 (5.7, 7.6, 14.0)	2.53 (7.0, 7.0, 14.0)	4.26	3.36 (4.9, 10.7, (3.4, 10.7)	3.47	5.50 (dd, 1.7, 8.2)	7.75 (8.2)
14C	Others 2.92 (3 H, s, SMe), 3.80 (6 H, s, 2 × OMe), 6.8–7.4 (13 H, m, ArH), 8.45 (1 H, br s, NH) A: 6.11 (4.6)	5.31	2.28 (5.5, 8.6, 14.2)	2.49 (7.1, 7.1, 14.2)	4.17	3.30 (m)		4.94 (7.6)	7.56 (7.8)
14G	Others 2.88 (3 H, s, SMe), 3.74, 3.75, 3.76 and 3.77 (12 H, each s, 4 × OMe), 6.7–7.4 (27 H, m, ArH and NH) B: 5.37 (4.6)	4.74	2.13 (4.6, 6.7, 14.0)	2.50 (m)	4.21	3.11 (3.5, 10.3)	3.16 (6.4, 10.3)		7.48
14H	Others 2.57 (3 H, s, SMe), 3.70 and 3.73 (12 H, each s, 4 × OMe), 6.80–7.61 (27 H, m, ArH and 2-NH), 10.6 [1 H, s, N(1)-H] A: 6.37 (4.6)	5.39	2.48 (5.3, 7.6, 14.3)	2.63 (6.7, 7.2, 14.3)	4.39	3.41 (4.0, 10.1)	3.47 (5.9, 10.1)	8.02	8.17
15U	Others 2.66 (3 H, s, SMe), 3.79 (3 H, s, OMe), 6.8–7.5 (14 H, m, ArH), 12.8 (1 H, br s, NH) A: 5.87 (s)	4.28 (br d, 5.8)	1.92 (1.2, 5.0, 13.6)	2.28 (5.8, 10.8, 13.6)	4.44	3.36 (3.1, 11.3)	3.65 (2.3, 11.3)	5.32 (dd, 1.8, 8.2)	8.03 (8.2)
15C	Others 3.80 (6 H, s, 2 × OMe), 6.8–7.4 (13 H, m, ArH), 8.49 (1 H, br s, NH) A: 5.89 (s)	4.27 (d, 5.1)	1.77 (dd, 4.9, 13.7)	2.04 (m)	4.35	3.30 (3.1, 11.3)	3.54 (br, 2, 11.3)	4.72 (7.8)	7.84 (7.8)
15G	Others 3.73 and 3.74 (12 H, each s, 4 × OMe), 6.7–7.3 (27 H, m, ArH and NH) B: 5.39 (1.4)	4.19	1.63 (m)	1.73 (m)	4.19	3.01 (br d, 4)			7.66
15H	Others 3.67 and 3.73 (12 H, each s, 4 × OMe), 6.77–7.59 (27 H, m, ArH and 2-NH), 10.7 [1 H, s, N(1)-H] A: 6.03 (2.2)	4.67	2.14 (2.6, 5.6, 13.4)	2.37 (6.5, 10.0, 13.9)	4.57	3.39 (3.7, 10.4)	3.44 (5.0, 10.4)	8.00	8.12
16U	Others 3.79 (3 H, s, OMe), 6.8–7.5 (14 H, m, ArH), 12.9 (1 H, br s, NH) B: 5.74 (2.0)	4.47	1.89 (2.4, 5.9, 13.7)	2.11 (6.3, 9.8, 13.7)	4.22	3.54 (2.7, 12.5)	3.76 (2.2, 12.5)	5.59 (8.2)	7.99 (7.8)
16C	Others 5.17 (1 H, br s, OH), 11.4 (1 H, br s, NH) B: 5.72 (1.2)	4.32 (br d, 5.9)	1.81 (1.7, 5.3, 13.7)	2.00 (6.1, 10.4, 13.7)	4.20	3.56 (ddd, 3.3, 5.1, 12.2)	3.78 (ddd, 2.9, 5.6, 12.2)	5.69 (7.3)	7.96 (7.6)
16G	Others 5.14 (1 H, very br t, OH), 7.14 (2 H, br d, J 7.5, NH ₂) B: 5.76 (2.7)	4.72	2.11 (3.5, 6.2, 13.5)	2.41 (6.5, 8.5, 13.5)	4.26	3.54 (m)	3.67 (m)		7.97
16H	Others 5.07 (1 H, br t, OH), 6.48 (2 H, br s, NH ₂) B: 6.01 (2.5)	4.77	2.11 (3.3, 6.1, 13.5)	2.41 (6.5, 9.0, 13.5)	4.32	3.55 (3.5, 11.9)	3.72 (2.5, 11.9)	8.09	8.36
16X	Others 5.12 (1 H, br s, OH), 12.4 (1 H, br s, NH) B: 5.88 (3.5)	4.68	2.13 (5.0, 7.1, 13.5)	2.41 (7.1, 7.1, 13.5)	4.31	3.52 (2.8, 12.0)	3.71 (2.8, 12.0)		7.93

^a Obtained with a JEOL JNM-GX 500 spectrometer. ^b Determined in CDCl₃ (A), (CD₃)₂SO (B), or (CD₃)₂CO (C) with Me₄Si as internal standard; coupling constants in Hz. ^c The sugar protons were assigned by spin-spin decoupling experiments.

added to the mixture cooled to 0–5 °C and the mixture was then stirred at this temperature for 0.5–1 h and then at r.t. for 1.7–4 h. After the mixture had cooled, 50% aq. pyridine (2 cm³) was added to quench the reaction, and the mixture was extracted with CHCl₃ (250 cm³). The extract was washed successively with water (80 cm³), aq. NaHCO₃ (50 cm³), and water (80 cm³), dried (MgSO₄), and evaporated. The resulting crude product, **3**, was used for further reactions without purification. An analytically pure sample was obtained by chromatography.

2-N,5'-O-Bis(4,4'-dimethoxytrityl)-3'-O-methylsulfonyl-2'-O-pivaloylguanosine 3G.—Compound **2G** (4.44 g, 5 mmol) was evaporated with benzene to remove traces of water, and dissolved in a mixture of dry CH₂Cl₂ (50 cm³) and pyridine (7.5 cm³). To this solution at 0–5 °C was added PivCl (1.85 cm³, 15 mmol), then the mixture was stirred at this temperature for 15 min. MsCl (1.17 cm³, 15 mmol) was added, followed by addition of triethylamine (4 cm³), after which the mixture was stirred at 0–5 °C for 10 min. The reaction was then quenched with 50% aq. pyridine (2 cm³) and the mixture was extracted with CHCl₃ (250 cm³). The extract was washed successively with water (80 cm³), aq. NaHCO₃ (50 cm³), and water (80 cm³), dried (MgSO₄), and evaporated to give crude title compound **3G**

(6.69 g). This product was used for further reactions without purification.

2-N,5'-O-Bis(4,4'-dimethoxytrityl)-2',3'-bis-O-methylsulfonylguanosine 4G and its 6-O-Methanesulfonate 10.—MsCl (0.58 cm³, 7.5 mmol) was added to a stirred solution of compound **2G** (2.22 g, 2.5 mmol) in a mixture of dry Et₃N (2.5 cm³) and CH₂Cl₂ (20 cm³) at 0–5 °C, and the mixture was stirred at this temperature for 18 min. The reaction mixture was then quenched with ice-water and extracted with CHCl₃ (200 cm³). The extracts were washed successively with water (60 cm³), aq. NaHCO₃ (2 × 40 cm³), and water (60 cm³), dried (MgSO₄), and evaporated. The residual Et₃N was removed by co-evaporation with benzene (30 cm³) to give a crude mixture of the title products **4G** and **10** (3.38 g; 7:3, by ¹H NMR). The mixture was used without purification. An analytically pure sample was obtained by chromatography.

De-6-O-methanesulfonylation of the Trismethanesulfonate 10.—To a stirred solution of compound **10** (572 mg, 0.51 mmol) in CH₂Cl₂ (5 cm³) at 0–5 °C was added a solution of KOH (140 mg, 2.5 mmol) in a mixture of MeOH and water (7:3; 1 cm³). The mixture was stirred at this temperature for 10 min, diluted

with CH_2Cl_2 (70 cm^3), and then washed with water (3 \times 20 cm^3). The organic layer was dried (MgSO_4), and evaporated. The residue was chromatographed on a neutral silica gel column with CHCl_3 -MeOH (99:1) to give disulfonate **4G** (456 mg, 86%). The ^1H NMR spectrum of this product was identical with that of a sample prepared from diol **2G**.

5'-O-(4-Methoxytrityl)-2',3'-bis-O-methylsulfonylinosine 4H and its 1-N-Methanesulfonyl Derivative 11.—Compound **2H** (9.74 g, 18 mmol) was evaporated with dry pyridine to remove traces of water, and was then dissolved in dry pyridine (185 cm^3). To this stirred solution at 0–5 °C, was added MsCl (4.2 cm^3 , 54 mmol), and the mixture was then stirred first at this temperature for 10 min, and then at r.t. for 3.5 h. After cooling of the mixture (0–5 °C), 50% aq. pyridine (20 cm^3) was added, and then the mixture was diluted with CHCl_3 (900 cm^3). The mixture was washed successively with water (300 cm^3), aq. NaHCO_3 (200 cm^3), and water (2 \times 300 cm^3), dried (MgSO_4), and evaporated. The residual pyridine was removed by repeated co-evaporation with toluene. The residue was chromatographed on a silica gel column to give compounds **4H** (8.97 g, 70%) and **11** (1.54 g, 11%).

De-N¹-methanesulfonylation of the Trismethanesulfonate 11.—A solution of KOH (140 mg, 2.4 mmol) in MeOH (3 cm^3) was added to a stirred solution of compound **11** (233 mg, 0.3 mmol) in tetrahydrofuran (THF) (1.5 cm^3) at 0.5 °C, and the mixture was stirred first at this temperature for 20 min, and then at r.t. for 1.5 h. The progress of the reaction was monitored by TLC with CHCl_3 -MeOH (85:15). After the mixture had been cooled, it was neutralized to pH 6–7 (by a pH test paper) with a mixture of MeOH and conc. HCl (20:3, v/v; \sim 1.3 cm^3), then diluted with CHCl_3 (40 cm^3). The mixture was washed with water (3 \times 20 cm^3), dried (MgSO_4), and evaporated. The residue was chromatographed on a silica gel column with CHCl_3 -MeOH (99:1 \rightarrow 97:3) to give disulfonate **4H** (166 mg, 79%). The ^1H NMR spectrum of this product was identical with that of a sample prepared from diol **2H**.

DMTr-Protected 1-(3-Deoxy- β -D-threo-pentofuranosyl)-uracil and -cytosine 8U and 8C, 9-(3-Deoxy- β -D-threo-pentofuranosyl)-adenine, -guanine, and MMTr-Protected Hypoxanthine Derivative 8A, 8G and 8H; General Procedure.—From esters **3**. Substrate **3U** or **3H** (1 mmol) was dissolved in MeOH (4 cm^3), while substrate **3C**, **3A** or **3G** (1 mmol) was dissolved in a mixture of benzene (5 cm^3) and MeOH (10 cm^3). To this stirred solution at 0–5 °C was added a solution of KOH (for **3U**, 3 mmol; for **3C**, **3A** and **3H**, 5 mmol; for **3G**, 10 mmol) in MeOH (3 cm^3), immediately after which NaBH_4 (for **3U**, **C**, **A** and **H**, 2 mmol; for **3G**, 3 mmol) was added. The mixture was stirred at r.t. for 22–28 h. The progress of the reaction was monitored with TLC with CHCl_3 -MeOH (for **3U**, **A** and **G**, 95:5; **3C** and **3H**, 9:1). After the mixture had been cooled to 0–5 °C, it was quenched with acetone (2 cm^3) for substrates **3C**, **A** and **G**; in the other cases, the reaction mixture was neutralized to pH 7–8 (by a pH test paper) at this temperature with a mixture (9:1, v/v) of MeOH and conc. HCl . The mixture was partitioned between CHCl_3 (250 cm^3) and water (80 cm^3). The organic layer was washed with water (2 \times 80 cm^3), dried (MgSO_4), and evaporated. The residue was chromatographed on a neutral silica gel with CHCl_3 -MeOH to give products **8**.

From disulfonates 4. To a stirred solution of substrate **4A**, **G** or **H** (1 mmol) in a mixture of benzene (5 cm^3) and MeOH (12 cm^3) at 0–5 °C was added a solution of KOH (for **4A**, **G**, 10 mmol; for **4H**, 8 mmol) in MeOH (4 cm^3), immediately after which NaBH_4 (3 mmol) was added. The mixture was treated in a manner similar to that described for the synthesis of

compounds **8** from the esters **3** to give the product, after chromatography.

1-(3-Deoxy- β -D-threo-pentofuranosyl)-uracil and -cytosine 9U and 9C, and 9-(3-Deoxy- β -D-threo-pentofuranosyl)-adenine, -guanine and -hypoxanthine 9A, 9G and 9H; General Procedure.—A stirred suspension of substrate **8U**, **C**, **A**, **G** or **H** (1 mmol) in acetic acid (8 cm^3) was heated at 65–70 °C (bath temp.) for 2–5 min until dissolution had occurred. To this solution was added water (2 cm^3), and the mixture was stirred at this temperature for 5–35 min. The progress of the reaction was monitored by TLC with CHCl_3 -MeOH (8:2). After the reaction (for **8U**, **C**, **A** or **H**) was complete, the cold mixture was diluted with Et_2O (70 cm^3), and extracted with water (3 \times 10 cm^3). The combined extracts were concentrated, and the residual acetic acid was removed by co-evaporation first with EtOH -water (1:1; 8 cm^3), then with EtOH (4 cm^3), to provide the product, **9U**, **C**, **A** or **H**, in 91–100 yield. In the case of substrate **8G**, the reaction mixture was evaporated and the residue was co-evaporated with EtOH -toluene-water (1:1:1; 3 \times 12 cm^3) to give compound **9G** in 83% yield. An analytically pure sample of compound **9H** was obtained by recrystallization of the product from aq. EtOH .

9-(3-Deoxy- β -D-threo-pentofuranosyl)-xanthine 9X.—The method of Sato *et al.*²⁶ was slightly modified. To a stirred suspension of compound **9G** (534 mg, 2 mmol) in water (20 cm^3) was added 88% formic acid (0.6 cm^3). Sodium nitrite (0.69 g, 10 mmol) was then added at r.t. over a period of 30 min and the mixture was stirred for a further 1.2 h, immediately after which the resulting solution was chromatographed on a HP 20 column to give the title compound, **9X** (300 mg, 56%) as crystals.

9-[3-Deoxy-5-O-(4-methoxytrityl)- β -D-threo-pentofuranosyl]-N¹-methylhypoxanthine 12.—From disulfonate **4H**. The crude product **8H**, prepared from compound **4H** (1 mmol) according to the general procedure, was chromatographed on neutral silica gel (40 g) with CHCl_3 -MeOH (97:3 \rightarrow 95:5 \rightarrow 9:1) to provide the title compound **12** (47 mg, 9%) and recovered substrate **8H** (408 mg, 78%).

From compound 8H with methyl iodide. A mixture of compound **8H** (1.10 g, 2.1 mmol), methyl iodide (0.3 cm^3 , 4.8 mmol), and DBU (0.95 cm^3 , 8.6 mmol) in dry DMF (8 cm^3) was stirred at r.t. for 10 min, after which the mixture was diluted with Et_2O - CHCl_3 (8:2; 300 cm^3), washed with water (5 \times 50 cm^3), dried (MgSO_4), and evaporated. The residue was chromatographed to give the title product **12** (843 mg, 75%), whose spectral data (IR and ^1H NMR) were identical with those of a sample prepared from disulfonate **4H**.

From compound 8H with methyl methanesulfonate. To a stirred solution of compound **8H** (105 mg, 0.2 mmol) in a mixture of benzene (0.4 cm^3) and MeOH (0.8 cm^3) at 0–5 °C was added a solution of KOH (67 mg, 1.2 mmol) in MeOH (0.3 cm^3). A solution of methyl methanesulfonate (22 mg, 0.2 mmol) in MeOH (0.3 cm^3) was added, and the mixture was treated in the manner described for the synthesis of compound **8H** from disulfonate **4H** to give, after chromatography, the title compound **12** (15 mg, 14%) and recovered substrate **8H** (54 mg, 51% recovery). The ^1H NMR spectrum of the product was identical with that of a sample prepared from compound **8H** with methyl iodide.

9-(3-Deoxy- β -D-threo-pentofuranosyl)-N¹-methylhypoxanthine 13.—To a stirred solution of the ether **12** (4.04 g, 7.5 mmol) in acetic acid (80 cm^3) at 65 °C (bath temp.) was added dropwise water (20 cm^3), and the mixture was stirred at this temperature for 30 min. After the mixture had been cooled to r.t., EtOH (20 cm^3) was added, and then the mixture was

concentrated. The residual acetic acid was co-evaporated, first with EtOH–toluene–water (1:1:1; 2 × 60 cm³) and then with EtOH–water (1:1; 60 cm³). The residue was chromatographed to give the product **13** (1.50 g, 75%) as an amorphous solid, which was crystallized by trituration with EtOH.

DMTr-Protected 1-(3-Deoxy-2-O-methylsulfonyl-β-D-threo-pentofuranosyl)-uracil and -cytosine 14U and 14C.—The nucleoside **8U** or **8C** (1 mmol) was evaporated twice with benzene to remove traces of water, and was then dissolved in dry pyridine (for **8U**, 3 cm³; for **8C**, 6 cm³). To this solution was added MsCl (3 mmol) at r.t. and the mixture was stirred at this temperature for 3–5 h. After the mixture had been cooled to 0–5 °C, it was quenched with 50% aq. pyridine (1 cm³). The mixture was extracted with CHCl₃ (75 cm³), and the extract was washed successively with water (30 cm³), aq. NaHCO₃ (30 cm³), and water (30 cm³), dried (MgSO₄), and evaporated. The pyridine was removed by repeated co-evaporation with toluene. The residue was purified by chromatography to give the product **14U** (560 mg, 92%) or **14C** (725 mg, 79%).

2-N,5'-O-Bis(4,4'-dimethoxytrityl)-9-[3-deoxy-2-O-methylsulfonyl-β-D-threo-pentofuranosyl]guanine 14G.—Compound **8G** (2.00 g, 2.3 mmol) was evaporated with benzene to remove traces of water, and dissolved in a mixture of dry CH₂Cl₂ (25 cm³) and Et₃N (2 cm³). To this stirred solution at 0–5 °C was added MsCl (0.44 cm³, 5.7 mmol, 2.5 mol equiv.), and the mixture was stirred at r.t. for 15 min. A small amount of ice was added, immediately after which a solution of KOH (1.12 g) in MeOH (10 cm³) was added to cleave the 6-O-methanesulfonyl group. The progress of the reaction was monitored by TLC with CHCl₃–MeOH (95:5). After the mixture had been stirred at r.t. for 5 min, it was diluted with CH₂Cl₂ (70 cm³). The solution was washed with brine (3 × 40 cm³), dried (MgSO₄), and evaporated. After chromatography, the title compound **14G** (2.01 g, 89%) was obtained.

9-[3-Deoxy-5-O-(4-methoxytrityl)-2-O-methylsulfonyl-β-D-threo-pentofuranosyl]hypoxanthine 14H.—Compound **8H** (262 mg, 0.5 mmol) was evaporated twice with dry pyridine to remove traces of water, and dissolved in dry pyridine (5 cm³). To this stirred solution at 0–5 °C was added MsCl (0.12 cm³, 1.5 mmol), and the mixture was stirred first at this temperature for 5 min and then at r.t. for 2.7 h. The progress of the reaction was monitored by TLC with CHCl₃–MeOH (85:15). After the mixture had been cooled to 0–5 °C, it was quenched with 50% aq. pyridine (1 cm³) and extracted with CHCl₃ (250 cm³). The extract was washed with water (25 cm³) and then cooled to 0–5 °C. To this solution was added a solution of KOH (140 mg, 2.5 mmol) in MeOH (4 cm³), and the mixture was stirred at 0–5 °C for 8 min to cleave the N¹-methanesulfonyl group of the trismethanesulfonate. The progress of the reaction was monitored by TLC with the same solvent system as described above. The CHCl₃ solution was washed with cold brine (3 × 70 cm³), dried (MgSO₄), and evaporated. The pyridine was removed by repeated co-evaporation with toluene. The residue was purified by chromatography to give the title compound **14H** (220 mg, 73%).

DMTr-Protected 1-(2-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-uracil and -cytosine 15U and 15C, 9-(2-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)guanine, and MMTTr-Protected Hypoxanthine Derivative 15G and 15H; General Procedure.—Substrate **14U**, **C**, **G**, or **H** (1 mmol) was evaporated twice with benzene to remove traces of water, and was then dissolved in dry DMF (10 cm³). To this stirred solution was added sodium azide (for **14U** and **H**, 3 mmol; for **14C**, 5 mmol;

for **14G**, 7 mmol), and the mixture was stirred at 110–115 °C (bath temp.) for 3–7 h. After cooling, the mixture was diluted with Et₂O–CHCl₃ (8:2; 100 cm³) and washed with water (4 × 30 cm³), dried (MgSO₄), and evaporated. The residue was purified by chromatography to give the corresponding compound **15**.

1-(2-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-uracil and -cytosine 16U and 16C, and 9-(2-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-guanine and -hypoxanthine 16G and 16H.—A mixture of substrate **15U** (3.0 g, 5.4 mmol), **15C** (1.71 g, 2.0 mmol), **15G** (850 mg, 0.95 mmol), or **15H** (3.3 g, 6.0 mmol) and 80% acetic acid (for **15U**, 19 cm³; for **15C**, 30 cm³; for **15G**, 13 cm³; for **15H**, 60 cm³) was stirred at r.t. or at 50–65 °C (bath temp.) for 0.5–3 h. In the case of compound **15U**, **G** or **H**, the mixture was then partitioned between Et₂O (for **15U** and **H**, 100 cm³; for **15G**, 50 cm³) and water (20 cm³), and the organic layer was extracted several times with water (20 cm³) until the product in the water layer could not be detected by TLC; the combined water layers were evaporated, and the acetic acid was removed by repeated co-evaporation with aq. EtOH to give the corresponding product **16U** (1.10 g, 80%), **16G** (248 mg, 90%), or **16H** (1.40 g, 90%). In the case of substrate **15C**, the reaction mixture was concentrated, and the acetic acid was removed by repeated co-evaporation with EtOH–toluene. The residue was triturated with CH₂Cl₂ to give compound **16C** (42 mg, 84%).

9-(2-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)xanthine 16X.—To a stirred suspension of the guanine **16G** (230 mg, 0.79 mmol) in water (15 cm³) at r.t. was gradually added 88% formic acid (4 cm³) and the mixture was stirred until solids completely disappeared. Sodium nitrite (545 mg, 7.9 mmol) was added portionwise to the solution over a period of 20 min, and the mixture was treated in a manner similar to that described for the synthesis of compound **9X**. An amorphous product (189 mg) was rechromatographed on a silica gel column to afford the title compound **16X** (150 mg, 65%).

Methanolysis of 9-(3-Deoxy-β-D-threo-pentofuranosyl)hypoxanthine 9H.—A mixture of compound **9H** (20 mg, 0.08 mmol) and Dowex 50W-X8 (80 mg; H⁺ form, 100–200 mesh) ion-exchange resin in MeOH (5 cm³) was refluxed for 10 min. After the mixture had been cooled, the resin was removed by filtration and washed with MeOH (5 cm³). The combined filtrate and washings were evaporated to afford a mixture of methyl pentosides. The characteristic peaks of the ¹H NMR spectrum of the mixture were identical with those of a sample prepared from the known compound **9A**.^{6b,7b}

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