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

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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 either HIV *in vitro* or P388 leukaemia in mice.

Deoxygenative [1,2]-hydride shift[2] and β-elimination[3] reactions of vicinal *cis*-diol sulfonates have been in numerous instances found to be powerful methods[4–10] for the synthesis of deoxygenated nucleosides from the corresponding ribonucleosides involving a 2',3'-diol system. The discovery[11] 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

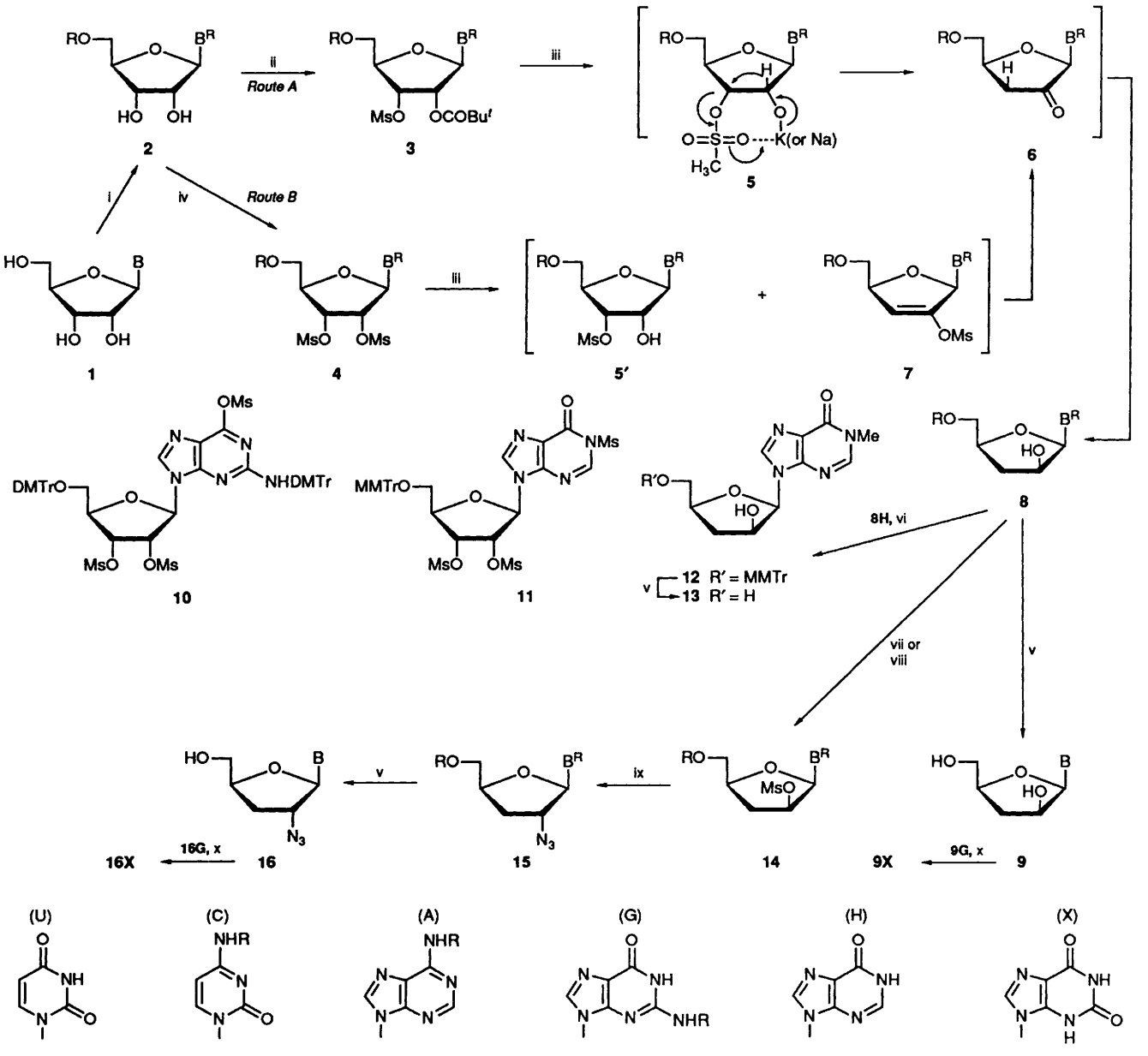
In the first route, the simultaneous protection of both 5'-hydroxy and amino functions in substrates **1C, A,** and **G** was carried out by the use of chlorobis(4-methoxyphenyl)phenylmethane (4,4'-dimethoxytrityl chloride, DMTrCl),[13] while substrates **1U** and **H** were protected at their 5'-hydroxy 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) group[14] 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 pivaloylated[17] at their 2'-hydroxy groups with trimethylacetyl chloride (pivaloyl chloride, PivCl) followed by methanesulfonylation with methanesulfonyl chloride (MsCl) in a one-pot reaction[7] 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 ^{1}H 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 purification, 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 ^{1}H 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 ^{1}H 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 reaction[6] of N^6,$O^{5'}$-bis(dimethoxytrityl)-2',3'-bis-*O*-(methylsulfonyl)adenosine **4A** with KOH–$NaBH_4$, 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



Scheme 1 *Reagents and conditions:* i, DMTrCl (MMTrCl for **1H**), pyridine–DMSO; ii, Bu^{t}COCl, pyridine then $MeSO_2Cl$; iii, $NaBH_4$, KOH, MeOH–(PhH); iv, $MeSO_2Cl$, CH_2Cl_2–Et_3N (for **2G**), pyridine (for **2H**); v, 80% AcOH; vi, MeI–DBU, DMF or $MeSO_3Me$–KOH, MeOH–PhH; vii, $MeSO_2Cl$, pyridine (for **8U,C**); viii, $MeSO_2Cl$ then KOH (for **8G,H**); ix, NaN_3, DMF; x, $NaNO_2$, HCO_2H, 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-elimination[10] 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 $N^1,O^{2',3'}$-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–$NaBH_4$ gave an unexpected N^1-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 N^1- rather

Table 1 The nucleoside derivatives **2–16** prepared

Compound	Reaction time (h)[a] [temp. (°C)]	Yield (%)	Column chromatography Adsorbent[b] (g)	Eluent[c] (ratio)	M.p. (°C)[d] (Recryst. solvent)
2U	22 (rt)	73	A (140)	**a** (95:5)	117 (sintered), 120–124 (from CH_2Cl_2–Et_2O)
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)	74	A (50)	**a** (99.5 : 0.5)	amorph.
	(from **4A**) [24 (rt)	96	B	**f** (9:1:0.1:0 → 9:1:0.1:0.1)][f]	
8G	(from **3G**) 28 (rt)	72[g]	A (25)	**a** (98:2)	amorph.
	(from **4G**) 24 (rt)	75[g]	A (20)	**a** (99:1 → 98:2 → 97:3)	amorph.
8H	(from **3H**) 27.5 (rt)	89	A (35)	**a** (99.5:0.5 → 98:2)	amorph.
	(from **4H**) 20 (rt)	78	A (40)	**a** (97:3 → 95:5 → 9:1)	amorph.
9U	5 min (65)	91			144–145 (from Pr^iOH)
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^iOH)
16C	1.25 (50–55)	84			171–172 (decomp.) (from Pr^iOH)
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. [b] A: 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.). [c] **a**: $CHCl_3$–MeOH; **b**: $CHCl_3$–MeOH–Et_3N; **c**: PhH–AcOEt; **d**: PhH–AcOEt–MeOH; **e**: PhH–AcOEt–Et_3N; **f**: PhH–AcOEt–Et_3N–MeOH; **g**: $CHCl_3$–AcOEt–Et_3N; **h**: water; **i**: water–MeOH; **j**: AcOEt–water–Pr^iOH. [d] Uncorrected; measured on a Yamato micro melting-point apparatus. [e] A combined yield of a mixture (86:14) of **3A** and its isomer. [f] Ref. 6b. [g] In addition, 9-(3-deoxy-α- and -β-D-*erythro*-pentofuranosyl)guanines were formed in ~20% yield. [h] Crystallized by trituration with EtOH. [i] Followed by treatment with KOH at r.t. for 5 min. [j] Followed by treatment with KOH at 0–5 °C for 8 min.

than O^6-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 N^1-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.] C	H	N	S	$[\alpha]_D$/° (c, $CHCl_3$)[c]	Temp. (°C)	UV[d] λ_{max}^{MeOH}/nm (ε/dm^3 mol^{-1} cm^{-1})	IR[e] ν_{max}^{KBr}/cm^{-1}
2U	[111–112 (Et_2O)][f]	65.1 [65.3	5.6 5.7	5.0 5.0][g]		+7.2 (0.91)	25	235 (23 600) 265 (11 900)	
2C	$C_{51}H_{49}N_3O_9$·0.3H_2O (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	$C_{52}H_{49}N_5O_9$·0.5H_2O (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_2O)][i]	66.4 [66.7	5.2 5.2	10.2 10.4][j]		−14.8 (1.06, DMF)	25	235 (21 400) [235 (21 400)][i]	
3U	$C_{36}H_{40}N_2O_{11}S$·1.6C_5H_{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	$C_{57}H_{59}N_3O_{12}S$ (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	$C_{58}H_{60}N_5O_{11}S$·0.5C_5H_{12}[k] (1071)	67.8 (67.8)	6.1 (6.2)	6.6 (6.5)	2.9 (3.0)				
3G	(not isolated)								
3H	(not isolated)								
4G	$C_{54}H_{53}N_5O_{13}S_2$ (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	$C_{32}H_{32}N_4O_{10}S_2$·0.3C_5H_{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	$C_{30}H_{30}N_2O_7$·1.0C_5H_{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	$C_{51}H_{51}N_3O_8$ (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	$C_{52}H_{49}N_5O_8$·0.5H_2O (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	$C_{30}H_{28}N_4O_5$·0.5H_2O (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^iOH)][l]	[144–145	(from EtOH)][m]			[+146 (0.8, water)	27	263 (10 300)][l]	
9C	[hygroscopic amorph.][l]								
9A	[195–196 (MeOH)][l]					[−24.3 (1.1, DMF)	20	259 (14 200)][l]	
9G	[>235 (from EtOH)][l]	43.8 [43.8	4.8 5.1	25.6 25.5][n]		[+8.7 (1.1, DMF)	20	253 (14 800) 271sh][l]	
9H	$C_{10}H_{12}N_4O_4$ (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	$C_{10}H_{12}N_4O_5$ (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	$C_{55}H_{55}N_5O_{15}S_3$·1.5C_5H_{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	$C_{33}H_{34}N_4O_{12}S_3$·0.9C_5H_{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	$C_{31}H_{30}N_4O_5$·0.3C_5H_{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	$C_{11}H_{14}N_4O_4$·0.1H_2O (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	$C_{31}H_{32}N_2O_9S$·0.9C_5H_{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	$C_{52}H_{53}N_3O_{10}S$·1.0C_5H_{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	$C_{52}H_{51}N_5O_{10}S$ (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	$C_{31}H_{30}N_4O_7S$·1.4C_5H_{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	$C_{30}H_{29}N_5O_6$·0.6C_5H_{12}·0.5H_2O (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	$C_{51}H_{50}N_6O_7$ (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	$C_{52}H_{48}N_8O_7$·0.5H_2O (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	$C_{30}H_{27}N_7O_4$·0.9C_5H_{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][q]		−17.5 (0.87, DMF)	20	262 (10 300) [263 (EtOH)	2 110 (N_3) (10 000) 2 140][p]
16C	$C_9H_{12}N_6O_3$·0.1H_2O (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.] C	H	N	S	$[\alpha]_D$/° (c, $CHCl_3$)[c]	Temp. (°C)	UV[d] λ_{max}^{MeOH}/nm (ε/dm^3 mol^{-1} cm^{-1})	IR[e] ν_{max}^{KBr}/cm^{-1}
16G	$C_{10}H_{12}N_8O_3 \cdot 0.5H_2O$ (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	$C_{10}H_{11}N_7O_3$ (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	$C_{10}H_{11}N_7O_4 \cdot 0.8H_2O$ (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 CH_2Cl_2–pentane; all samples were dried at 60 °C for 4 h *in vacuo* over phosphorus pentaoxide. [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 $C_{30}H_{30}N_2O_8 \cdot 0.1Et_2O \cdot 0.3H_2O$ (559.4). [h] Ref. 6*b*. [i] Ref. 16. [j] Calc. for $C_{30}H_{28}N_4O_6$ (540.6). [k] A mixture (86:14) of **3A** and its isomer. [l] Ref. 7*b*. [m] Ref. 20. [n] Calc. for $C_{10}H_{13}N_5O_4 \cdot 0.4H_2O$ (274.4). [o] Dried at rt for 4 h over phosphorus pentaoxide. [p] Ref. 25. [q] Calc. for $C_9H_{11}N_5O_4 \cdot 0.1H_2O$ (255.0).

would take place by the attack of an anion on the N^1-position of species **4–8** to the methyl carbon of methyl methanesulfonate[23] 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 N^1- or O^6-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 N^2-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 ^{1}H 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 **16U**[25] 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 ^{1}H 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, F_{254}) 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-N^5′-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 cm^3) at room temperature (r.t.), after which dry pyridine (20 cm^3) was added, while compound **1U** (10 mmol) was dissolved in dry pyridine (40 cm^3). 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 cm^3), and the mixture was extracted with $CHCl_3$ (250 cm^3). The extract was washed successively with water (80 cm^3), aq. $NaHCO_3$ (50 cm^3), and water (2 × 80 cm^3), dried ($MgSO_4$), and evaporated. The pyridine was removed by co-evaporation with toluene. In the case of **1U**, **1G** or **1H**, the residue was triturated with Et_2O (100 cm^3), 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 cm^3). 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 ^{1}H 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)
	Others 2.9–3.2 (1 H, OH), 3.78 (6 H, s, 2 × OMe), 4.5–5.5 (very br s, OH), 6.8–7.4 (13 H, m, ArH), 9.6 (1 H, br s, NH)								
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)
	Others 3.42 (1 H, br s, OH), 3.69 and 3.70 (6 H, each s, 2 × OMe), 3.76 (6 H, s, 2 × OMe), 6.07 (1 H, br s, OH), 6.8–7.4 (14 H, m, ArH and NH)								
2G	B: 5.20 (3.8)	3.87	3.87 (m)		3.67–3.76	3.09 (m)			7.71
	Others 3.67 and 3.73 (12 H, each s, 4 × OMe), 4.87 (1 H, d, *J* 6.2, OH), 5.01 (1 H, d, *J* 5.1, OH), 6.79–7.52 (27 H, m, ArH and 2-NH), 10.6 [1 H, br s, N(1)-H]								
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
	Others 3.74 (3 H, s, OMe), 5.20 (1 H, br d, *J* 5.8, OH), 5.55 (1 H, br d, *J* 4.6, OH), 6.8–7.4 (14 H, m, ArH), 12.4 (1 H, br s, NH)								
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)
	Others 1.24 (9 H, s, Bu^t), 2.99 (3 H, s, SMe), 3.08 (6 H, s, OMe), 6.8–7.4 (13 H, m, ArH), 8.4 (1 H, br s, NH)								
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)
	Others 1.24 (9 H, s, Bu^t), 2.95 (3 H, s, SMe), 3.74 and 3.75 (12 H, each s, 4 × OMe), 6.7–7.3 (27 H, m, ArH and NH)								
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
	Others 1.19 (9 H, s, Bu^t), 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)								
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
	Others 1.22 (9 H, s, 3′-Bu^t), 3.08 (3 H, s, 2′-SMe), 3.76 and 3.77 (12 H, each s, 4 × OMe), 6.7–8.4 (27 H, ArH and NH)								
3G	not isolated								
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
	Others 2.96 and 3.29 (6 H, each s, 2 × SMe), 3.70 and 3.74 (12 H, each s, 4 × OMe), 6.84–7.59 (27 H, m, ArH and 2-NH), 10.7 [1 H, s, N(1)-H]								
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
	Others 3.05 and 3.09 (6 H, each s, 2 × SMe), 3.77 (3 H, s, OMe), 6.8–7.4 (14 H, m, ArH), 12.7 (1 H, br s, NH)								
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)
	Others 3.78 and 3.79 (6 H, each s, 2 × OMe), 3.82 (1 H, br d, *J* 6.4, OH), 6.8–7.4 (13 H, m, ArH), 9.04 (1 H, br d, NH)								
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 (7.6)
	Others 3.73, 3.74 and 3.75 (12 H, each s, 4 × OMe), 6.7–7.4 (27 H, m, ArH and NH)								
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
	Others 3.70, 3.71, and 3.73 (12 H, each s, 4 × OMe), 5.08 (1 H, d, *J* 4.5, OH), 6.83–7.52 (27 H, m, ArH and 2-NH), 10.6 [1 H, s, N(1)-H]								
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
	Others 3.74 (3 H, s, OMe), 5.45 (1 H, br d, *J* 3, OH), 6.8–7.2 (13 H, m, ArH), 12.3 (1 H, br s, NH)								
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)
	Others 5.15 (1 H, br d, *J* 6.6, 2′-OH), 5.03 (1 H, br s, 5′-OH), 6.99 (2 H, br d, *J* 38, NH_2)								
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
	Others 5.11 (1 H, br t, *J* 5.3, 5′-OH), 5.39 (1 H, br d, *J* 5.6, 2′-OH), 12.3 (1 H, br s, NH)								
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
	Others 5.2–5.7 (2 H, very br s, 2 × OH), 10.7 (1 H, s, NH), 11–12 (~0.5 H, very br s, NH)								
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
	Others 3.22 and 3.32 (6 H, each s, 2 × SMe), 3.76 (3 H, s, 6-SMe), 3.77 and 3.78 (12 H, each s, 4 × OMe), 6.83–7.32 (26 H, m, ArH)								
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
	Others 3.07 and 3.08 (6 H, each s, 2 × SMe), 3.66 (3 H, s, 1-SMe), 3.79 (3 H, s, OMe), 6.8–7.4 (14 H, m, ArH)								
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
	Others 3.51 (3 H, s, NMe), 3.74 (3 H, s, OMe), 5.45 (1 H, d, *J* 4.9, OH), 6.8–7.4 (14 H, m, ArH)								
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
	Others 3.51 (3 H, s, NMe), 5.10 (1 H, br t, 5′-OH), 5.38 (1 H, br d, *J* 5, 2′-OH)								

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,	3.47 (3.4, 10.7)	5.50 (dd, 1.7, 8.2)	7.75 (8.2)
	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)								
14C	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)
	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)								
14G	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
	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]								
14H	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
	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)								
15U	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)
	Others 3.80 (6 H, s, 2 × OMe), 6.8–7.4 (13 H, m, ArH), 8.49 (1 H, br s, NH)								
15C	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)
	Others 3.73 and 3.74 (12 H, each s, 4 × OMe), 6.7–7.3 (27 H, m, ArH and NH)								
15G	B: 5.39 (1.4)	4.19	1.63 (m)	1.73 (m)	4.19	3.01 (br d, 4)			7.66
	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]								
15H	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
	Others 3.79 (3 H, s, OMe), 6.8–7.5 (14 H, m, ArH), 12.9 (1 H, br s, NH)								
16U	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)
	Others 5.17 (1 H, br s, OH), 11.4 (1 H, br s, NH)								
16C	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)
	Others 5.14 (1 H, very br t, OH), 7.14 (2 H, br d, *J* 7.5, NH_2)								
16G	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
	Others 5.07 (1 H, br t, OH), 6.48 (2 H, br s, NH_2)								
16H	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
	Others 5.12 (1 H, br s, OH), 12.4 (1 H, br s, NH)								
16X	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
	Others 1.8–3.5 (very br s, NH and OH), 10.7 (1 H, br s, NH)								

[a] Obtained with a JEOL JNM-GX 500 spectrometer. [b] Determined in $CDCl_3$ (A), $(CD_3)_2SO$ (B), or $(CD_3)_2CO$ (C) with Me_4Si 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 cm^3) was added to quench the reaction, and the mixture was extracted with $CHCl_3$ (250 cm^3). The extract was washed successively with water (80 cm^3), aq. $NaHCO_3$ (50 cm^3), and water (80 cm^3), dried ($MgSO_4$), 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 CH_2Cl_2 (50 cm^2) and pyridine (7.5 cm^3). To this solution at 0–5 °C was added PivCl (1.85 cm^3, 15 mmol), then the mixture was stirred at this temperature for 15 min. MsCl (1.17 cm^3, 15 mmol) was added, followed by addition of triethylamine (4 cm^3), after which the mixture was stirred at 0–5 °C for 10 min. The reaction was then quenched with 50% aq. pyridine (2 cm^3) and the mixture was extracted with $CHCl_3$ (250 cm^3). The extract was washed successively with water (80 cm^3), aq. $NaHCO_3$ (50 cm^3), and water (80 cm^3), dried ($MgSO_4$), 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 cm^3, 7.5 mmol) was added to a stirred solution of compound **2G** (2.22 g, 2.5 mmol) in a mixture of dry Et_3N (2.5 cm^3) and CH_2Cl_2 (20 cm^3) 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 $CHCl_3$ (200 cm^3). The extracts were washed successively with water (60 cm^3), aq. $NaHCO_3$ (2 × 40 cm^3), and water (60 cm^3), dried ($MgSO_4$), and evaporated. The residual Et_3N was removed by co-evaporation with benzene (30 cm^3) 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 CH_2Cl_2 (5 cm^3) 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 cm^3). The mixture was stirred at this temperature for 10 min, diluted

with CH_2Cl_2 (70 cm^3), and then washed with water (3 × 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 × 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-N^1*-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; ~1.3 cm^3), then diluted with $CHCl_3$ (40 cm^3). The mixture was washed with water (3 × 20 cm^3), dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column with $CHCl_3$–MeOH (99:1 ⟶ 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 × 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 × 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 × 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*]-N^1-*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 ⟶ 95:5 ⟶ 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 × 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*)-N^1-*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 cm^3) and then with EtOH–water (1:1; 60 cm^3). 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 cm^3; for **8C**, 6 cm^3). 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 cm^3). The mixture was extracted with $CHCl_3$ (75 cm^3), and the extract was washed successively with water (30 cm^3), aq. $NaHCO_3$ (30 cm^3), and water (30 cm^3), dried ($MgSO_4$), 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 CH_2Cl_2 (25 cm^3) and Et_3N (2 cm^3). To this stirred solution at 0–5 °C was added MsCl (0.44 cm^3, 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 cm^3) was added to cleave the 6-*O*-methanesulfonyl group. The progress of the reaction was monitored by TLC with $CHCl_3$–MeOH (95:5). After the mixture had been stirred at r.t. for 5 min, it was diluted with CH_2Cl_2 (70 cm^3). The solution was washed with brine (3 × 40 cm^3), dried ($MgSO_4$), 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 cm^3). To this stirred solution at 0–5 °C was added MsCl (0.12 cm^3, 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 $CHCl_3$-MeOH (85:15). After the mixture had been cooled to 0–5 °C, it was quenched with 50% aq. pyridine (1 cm^3) and extracted with $CHCl_3$ (250 cm^3). The extract was washed with water (25 cm^3) and then cooled to 0–5 °C. To this solution was added a solution of KOH (140 mg, 2.5 mmol) in MeOH (4 cm^3), and the mixture was stirred at 0–5 °C for 8 min to cleave the N^1-methanesulfonyl group of the trismethanesulfonate. The progress of the reaction was monitored by TLC with the same solvent system as described above. The $CHCl_3$ solution was washed with cold brine (3 × 70 cm^3), dried ($MgSO_4$), 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 MMTr-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 cm^3). 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 Et_2O–$CHCl_3$ (8:2; 100 cm^3) and washed with water (4 × 30 cm^3), dried ($MgSO_4$), 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 cm^3; for **15C**, 30 cm^3; for **15G**, 13 cm^3; for **15H**, 60 cm^3) 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 Et_2O (for **15U** and **H**, 100 cm^3; for **15G**, 50 cm^3) and water (20 cm^3), and the organic layer was extracted several times with water (20 cm^3) 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 CH_2Cl_2 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 cm^3) at r.t. was gradually added 88% formic acid (4 cm^3) 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 cm^3) was refluxed for 10 min. After the mixture had been cooled, the resin was removed by filtration and washed with MeOH (5 cm^3). 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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