A Convenient Method for the Synthesis of 2′,3′-Didehydro-2′,3′-Dideoxy Nucleosides

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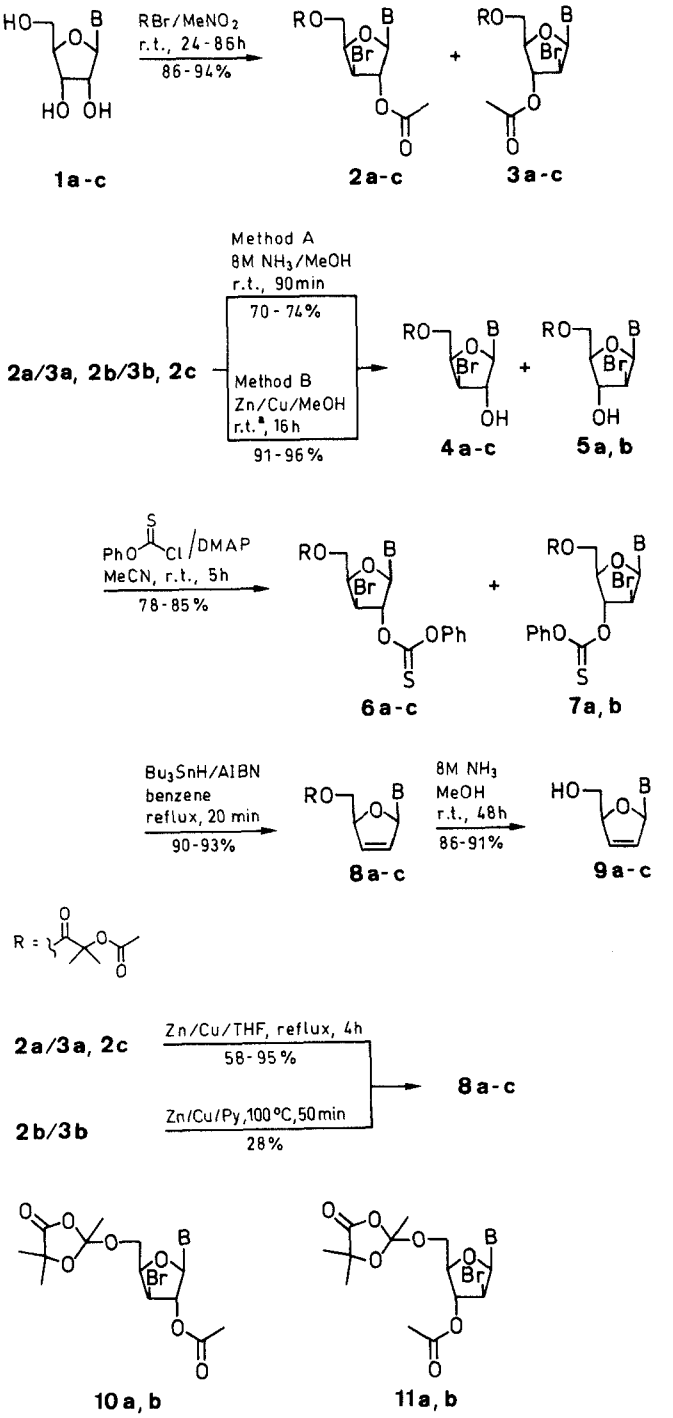
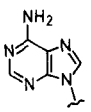
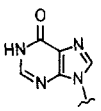
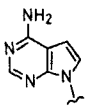
9-(2,3-Dideoxy-β-D-glyceropent-2-enofuranosyl)adenine (2′,3′-didehydro-2′,3′-dideoxyadenosine, **9a**), 9-(2,3-dideoxy-β-D-glyceropent-2-enofuranosyl)hypoxanthine (2′,3′-didehydro-2′,3′-dideoxyinosine, **9b**) and 4-amino-7-(2,3-dideoxy-β-D-glyceropent-2-enofuranosyl)pyrrolo[2,3-*d*]pyrimidine (2′,3′-didehydro-2′,3′-dideoxytubercidin, **9c**) were prepared via a free radical β-elimination of bromo and phenoxy(thiocarbonyl) leaving groups from appropriate 5′-*O*-(2-acetoxyisobutyryl)-2′(3′)-phenoxy(thiocarbonyl)-3′(2′)-bromo derivatives **6**, **7** of adenosine (**1a**), inosine (**1b**) and tubercidin (**1c**) with tributyltin hydride and subsequent deprotection of the resulting 5′-*O*-(2-acetoxyisobutyryl)-2′,3′-didehydro-2′,3′-dideoxynucleosides **8a**, **8b** and **8c**, respectively.

The synthesis of 2′,3′-didehydro-2′,3′-dideoxy nucleosides has become particularly important in connection with the anti-HIV activity displayed by some of these compounds.[1] Recently a new approach to the synthesis of 2′,3′-didehydro-2′,3′-dideoxy nucleosides based on a free radical β-elimination of bromo and phenoxy(thiocarbonyl) groups was suggested.[2] Here we present a generalisation of that approach which was made possible by the finding that the reaction of 2-acetoxyisobutyryl bromide (1-bromocarbonyl-1-methylethyl acetate) with nucleosides, playing a crucial role in the introduction of bromo and then phenoxy(thiocarbonyl) group,[2] may be conducted in the way ensuring exclusive formation of the 5′-*O*-(2-acetoxyisobutyryl) derivatives. Depending on the starting nucleoside and the solvent the reaction of 2-acetoxyisobutyryl bromide with nucleosides was reported to give 5′-*O*-dioxolanyl or 5′-*O*-(2-acetoxyisobutyryl)-2′(3′)-acetoxy-3′(2′)-halo derivatives.[3–5] In particular the reactions of adenosine,[5–8] and inosine[9–11] led exclusively to 5′-*O*-dioxolanyl derivatives. The instability of the 5′-*O*-dioxolanyl group under mild acidic and alkaline conditions virtually precludes its application as a transient protection. On the other hand the 5′-*O*-(2-acetoxyisobutyryl) group may be employed during transformations of the sugar moiety such as removal of the 2′-*O*-acetyl group with 8 M methanolic ammonia.[3] We therefore reinvestigated the reactions of adenosine, inosine and tubercidin.[5,9,12] with 2-acetoxyisobutyryl bromide with the aim of preparing the 5′-*O*-(2-acetoxyisobutyryl) derivatives of those nucleosides, **2a**, **2b**, **2c**; **3a**, **3b**, **3c**, which could then be deacetylated to give compounds **4** and **5** and subsequently phenoxythiocarbonylated to give the key substrates **6** and **7** for deoxygenation reactions. It was noticed some time ago that the formation of the 5′-*O*-dioxolanyl derivatives appears to be controlled kinetically whereas that of 5′-*O*-(2-acetoxyisobutyryl) derivatives thermodynamically.[14] In order to investigate that problem we carried out a series of experiments and we established that it was indeed the case for adenosine (**1a**) and inosine (**1b**). When the nucleosides were allowed to react with 2-acetoxyisobutyryl bromide in nitromethane at room temperature for only 2–3 hours the starting material was disappearing and the 5′-*O*-dioxolanyl derivatives, **10a, b**, **11a, b**, were the only isolated products.



1–11	a	b	c
B			

[a] No deacetylation with Method B for **2b/3b** observed.

When the reaction time was extended to 86 hours (for **1a**) and 24 hours (for **1b**) the 5′-*O*-(2-acetoxyisobutyryl) derivatives, **2a/3a** and **2b/3b**, were isolated in 86–94% yield. Under the similar conditions tubercidin (**1c**) gave the 5′-*O*-(2-acetoxyisobutyryl) derivatives **2c/3c** after 30 minutes and further extension of the reaction time up to 24 hours did not affect the outcome of the reaction. The reactions of both adenosine (**1a**) and inosine (**1b**) resulted in inseparable mixtures of 3′-bromo-3′-deoxy and 2′-bromo-2′-deoxy isomers, **2a/3a** and **2b/3b** with the ratios **2a/3a** and **2b/3b** being 78:22 and 73:27, respectively. In the case of tubercidin (**1c**) only 3% of the 2′-bromo-2′-deoxy isomer **3c** was detected by ^{1}H NMR (Table 1). It was now possible to remove selectively the 2′-*O*-acetyl and 3′-*O*-acetyl groups from **2a/3a**, **2b/3b** or **2c** by the action of 8 M methanolic ammonia during 90 minutes at room temperature. The products of deacetylation **4a–c** and **5a, b** were isolated as a mixture of 2′-bromo-2′-deoxy and 3′-bromo-3′-deoxy isomers or as single isomers (Table 1) in 71–74% yield. When compounds **2a/3a, 2b/3b** and **2c** were allowed to react with zinc/copper couple in methanol at room temperature, the products of deacetylation **4a, 5a** and **4c**, identical to those obtained previously by reaction with 8 M methanolic ammonia, were obtained in excellent yields (91–96%, Table 1). Contrary to the earlier report[8,21] no products of reductive elimination such as **8a, 8b** or **8c** were detected and in the case of inosine derivatives **2b/3b** we observed neither deacetylation nor elimination.

Our results are consistent with those reported by Gonzalez et al.[15] who employed zinc/copper couple in methanol to the selective deacetylation of certain aromatic acetates. Compounds **4a/5a, 4b/5b** and **4c** reacted with *O*-phenylchlorothionoformate[16] in the presence of dimethylaminopyridine. The resulting inseparable mixtures **6a/7a, 6b/7b** and compound **6c** obtained in 78–85% yield were deoxygenated with tributyltin hydride in the presence of 2,2′-azobisisobutyronitrile (AIBN) to give the corresponding 5′-*O*-(2-acetoxyisobutyryl)-2′,3′-didehydro-2′,3′-dideoxynucleosides **8a–c** in virtually quantitative yields (Table 2). The formation of the double bond was clear from the ^{1}H NMR spectrum which showed characteristic signals at $\delta = 6-7$ corresponding to the olefinic protons (Table 2).

Finally the 5′-*O*-(2-acetoxyisobutyryl) group was removed from **8a–c** with (8 M methanolic ammonia during 48 hours at room temperature to give 2′,3′-didehydro-2′,3′-dideoxyadenosine (**9a**); 2′,3′-didehydro-2′,3′-dideoxyinosine (**9b**) and 2′,3′-didehydro-2′,3′-dideoxytubercidin (**9c**) (Table 2). The structures of the nucleosides were confirmed by the spectroscopic data which agreed with the literature values.[10,17–19] The compounds **2a/3a** and **2c/3c** were also converted directly into **8a** and **8c** in 58% and 95% respectively using zinc/copper couple in tetrahydrofuran. However, we were unable to convert the inosine derivatives **2b/3b** into **8b** using zinc/copper couple in tetrahydrofuran or dimethylformamide. Only when pyridine was employed as a solvent[11] was it possible to obtain **8b** although in rather low yield (28%).

The use of 2-acetoxyisobutyryl bromide for the transformation of the sugar moiety of nucleosides in the way ensuring exclusive formation of 5′-*O*-(2-acetoxyisobutyryl) derivatives in very high yield combined with almost quantitative free radical β-elimination of bromo and phenoxy(thiocarbonyl) leaving groups resulted in a convenient method for the synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides.

Although that method comprises more steps than some of the methods suggested previously the overall yields – d4A-46%; d4I-43% and d4Tub-65% – are similar or higher than those reported for the same nucleosides.[8,18,19]

Due to the fact that the crucial steps involving 2′,3′-didehydro-2′,3′-dideoxy nucleosides are carried out under mild conditions and proceed consistently in nearly quantitative yields our approach appears to be suited particularly for the synthesis of such nucleosides as d4I – whose preparation via zinc/copper couple mediated elimination gives only poor yields.

Melting points were determined on a Reichert micro hot stage apparatus and are uncorrected. UV spectra were measured in 95% EtOH with a Pye-Unicam SP-8-150 UV-Vis spectrometer. ^{1}H NMR spectra were recorded at 250 MHz with a Bruker WH 250 spectrometer with TMS as an internal standard and DMSO-d_6 as a solvent. In the cases where analytical data are given for hydrates the presence of H_2O was confirmed by ^{1}H NMR: the protons of 2′-OH, 3′-OH, NH_2, NH and H_2O were exchangeable with D_2O. Mass spectra were obtained using a VG 7070 H with either EI or FAB ionisation. HPTLC was run on Merck silica gel 60 F_{254} analytical plates in the following solvent systems: (A) $CHCl_3$/EtOH (19:1), (B) $CHCl_3$/EtOH (9:1), (C) $CHCl_3$/EtOH (4:1). Short column chromatography was carried out on silica gel 60 H (Merck). The solvents were removed in vacuo at 30–40°C unless otherwise indicated.

HPLC analysis was performed on the system comprising Waters model 510 pump, model 680 automated gradient controller, model 46 K injector and model 490 programmable wavelength detector. Retention times (t_R) were determined on a Trilab 3000 multichannel chromatography data system (Trivector). The column – 5 μm APEX ODS 250 × 4.6 mm, Jones Chromatography U.K., was eluted with 0.025 M NH_4OAc buffer/3:1) (D) and (17:3) (E) under isocratic conditions. *O*-Phenylchlorothionoformate, dimethylaminopyridine, tributyltin hydride and 2-acetoxyisobutyryl bromide (1-bromocarbonyl-1-methylethyl acetate) were purchased from Aldrich.

Reaction of Nucleosides 1a, 1b, 1c with 1-Bromocarbonyl-1-methylethyl Acetate; General Procedure; Products 2, 3:

To a suspension of adenosine (**1a**), inosine (**1b**) or tubercidin (**1c**) (6 mmol) in dry $MeNO_2$ (45 mL) a solution of 1-bromocarbonyl-1-methylethyl acetate (4.98 g, 24 mmol) in dry $MeNO_2$ (15 mL) was added. The resulting pale-yellow solution which became clear after 1–2 h is stirred at r.t. for 24 h (for **1b, 1c**) or 86 h (for **1a**). The solvent was removed in vacuo, the residue partitioned between EtOAc/5% aq $NaHCO_3$ (1:1, 250 mL) and the aqueous layer was extracted further with EtOAc (3 × 40 mL). The combined EtOAc extracts were dried (Na_2SO_4), concentrated under reduced pressure, dissolved in a small amount of $CHCl_3$ and applied to a short column of silica gel. Elution of the column with $CHCl_3$/EtOH (97:3) afforded the mixtures **2a/3a, 2b/3b** and **2c/3c** as a colourless froth. Analytical samples were obtained when the crude products (0.25 g, ~0.5 mmol) were dissolved in a small amount of $CHCl_3$ (~1 mL) and added dropwise to stirred petroleum ether (bp 30–40°C) (50 mL). The resulting colourless precipitate is collected by centrifugation and dried in a desiccator (Table 1).

Table 1. Products **2, 3**; **4, 5** and **6, 7** Prepared

Product[b]	Yield (%) (ratio)	Molecular Formula[a] or Lit. mp (°C)	R_f: Solvent Systems A, B, C	UV (95% EtOH) λ_{max} (nm) (log ε)	^{1}H NMR (DMSO-d_6/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
2a/3a	86 (78 : 22)	$C_{18}H_{22}BrN_5O_7$ (500.3)	0.22, 0.43, 0.75	259 (4.12)	1.48, 1.49 (2s, 6H, $C(CH_3)_2$), 2.00 (s, 3H, $C(O)CH_3$), 2.11 (s, 3H, $C(O)CH_3$), 4.40 (m, 2H, H-5'a, H-5'b), 4.55 (m, 1H, H-4'), 4.92 (m, 1H, H-3'), 5.91 (m, 1H, H-2'), 6.17 (m, 1H, H-1'), 7.38 (s, 2H, NH_2), 8.16, 8.28 (2s, 2H, H-2, H-8) The 2'-bromo isomer **(3a)** can be recognised by its H-1' (6.47, d, J = 6.19) and H-2' (5.15, t, J = 6.4) signals	500 (M^+, 20), 136 (81)
2b/3b	92 (73 : 27)	$C_{18}H_{21}BrN_4O_8$ (501.3)	0.18, 0.39, 0.72	245 (3.97), 250 (3.97)	1.49 (s, 6H, $C(CH_3)_2$), 2.00, 2.12 (2s, 6H, $2C(O)CH_3$), 4.42 (m, 2H, H-5'a, H-5'b), 4.57 (m, 1H, H-4'), 4.92 (m, 1H, H-3'), 5.85 (t, 1H, J = 3.03, H-2'), 6.16 (d, 1H, J = 3.08, H-1'), 8.10, 8.24 (2s, 2H, H-2, H-8), 12.41 (br s, 1H, NH) The 2'-bromo isomer **3b** can be recognised by its H-1' (6.47, d, J = 6.15) and H-2' (5.14, t, J = 6.3) signals	5502 (M^+, 7), 279 (83), 137 (100)
2c/3c	94 (97 : 3)	No mp is quoted[13]	0.35, 0.44, 0.74	269 (4.09)	The spectrum of **2c** agreed with the literature[13] The 2'-bromo isomer **3c** can be recognised by its H-1' (6.56, d, J = 6.2) and H-2' (5.07, t, J = 6.2) signals	500 (M^+, 34), 163 (100), 134 (100)
4a	54[c]; 70[d]	$C_{16}H_{20}BrN_5O_6$ (458.3)	0.12, 0.34, 0.68	259 (4.14)	1.48 (s, 6H, $C(CH_3)_2$), 1.98 (s, 3H, $C(O)CH_3$), 4.42 (m, 2H, H-5'a, H-5'b), 4.58 (m, 2H, H-3', H-4'), 4.98 (m, 1H, H-2'), 5.89 (d, 1H, J = 4.03, H-1'), 6.30 (d, 1H, J = 4.9, 2'-OH), 7.27 (s, 2H, NH_2), 8.17, 8.27 (2s, 2H, H-2, H-8)	458 (M^+, 18), 135 (100)
5a	16[c]; 21[d]	$C_{16}H_{20}BrN_5O_6$ (458.3)	0.06, 0.32, 0.66	259 (4.13)	1.49 (s, 6H, $C(CH_3)_2$), 1.99 (s, 3H, $C(O)CH_3$), 3.98 (m, 1H, H-4'), 4.43 (m, 1H, H-3'), 4.43 (m, 2H, H-5'a, H-5'b), 4.67 (m, 1H, H-3'), 4.82 (t, 1H, J = 7.4, H-2'), 6.26 (d, 1H, J = 5.34, 3'-OH), 6.46 (d, 1H, J = 6.60, H-1'), 7.34 (s, 2H, NH_2), 8.16, 8.24 (2s, 2H, H-2, H-8)	
4b	17	$C_{16}H_{19}BrN_4O_7$ (459.2)	0.05, 0.18, 0.57	245 (4.02) 249 (4.02)	1.49 (s, 6H, $C(CH_3)_2$), 2.00 (s, 3H, $C(O)CH_3$), 4.30 (m, 2H, H-5'a, H-5'b), 4.42 (m, 1H, H-4'), 4.59 (m, 1H, H-3'), 4.68 (m, 1H, H-2'), 6.08 (d, 1H, J = 4.23, H-1'), 6.39 d, 1H, J = 4.79, 3'-OH), 6.67 (d, 1H, J = 3.62, H-7), 7.07 (s, 2H, NH_2), 7.32 (d, 1H, J = 3.65, H-8), 8.08 (s, 1H, H-2)	459 (M^+, 9), 137 (100)
4b/5b	57 (67 : 33)	$C_{16}H_{19}BrN_4O_7$ (459.2)	0.05, 0.18/ 0.20, 0.57/ 0.60	245 (4.02) 249 (4.02)	The 2'-bromo isomer **5b** can be recognised by its H-1' (6.55, d, J = 5.15), H-2' (4.81, t, J = 7.5) and H-4' (3.99, m) signals	
4c	73[c]; 96[d]	$C_{17}H_{21}BrN_4O_6$ (457.3)	0.32, 0.40, 0.74	268 (4.04)	1.49 (s, 6H, $C(CH_3)_2$), 2.00 (s, 3H, $C(O)CH_3$), 4.30 (m, 2H, H-5'a, H-5'b), 4.42 (m, 1H, H-4'), 4.59 (m, 1H, H-3'), 4.68 (m, 1H, H-2'), 6.08 (d, 1H, J = 4.23, H-1'), 6.39 (d, 1H, J = 3.62, H-7), 7.07 (s, 2H, NH_2), 7.32 (d, 1H, J = 3.65, H-8), 8.08 (s, 1H, H-2)	457 (M^+, 37), 163 (65), 134 (29)
6a/7a	78 (74 : 26)	$C_{23}H_{24}BrN_5O_7S$ (594.4)	0.22, 0.50, 0.78	257 (4.18)	1.50 (s, 6H, $C(CH_3)_2$), 2.03 (s, 3H, $C(O)CH_3$), 4.40 (m, 2H, H-5'a, H-5'b), 4.60 (m, 1H, H-4'), 5.20 (m, 1H, H-3'), 6.34 (m, 1H, H-2'), 6.43 (d, 1H, J = 2.49, H-1'), 7.44 (m, 7H, ArH, NH_2), 8.19, 8.32 (2s, 2H, H-2, H-8) The 2'-bromo isomer **(7a)** can be recognised by its H-1' (6.54, d, J = 5.98) and H-2' (5.40, t, J = 5.59) signals	594 (M^+, 9), 136 (100)
6b/7b	79 (72 : 28)	$C_{23}H_{23}BrN_4O_8S$ (595.4)	0.27, 0.45, 0.75	243 (4.18)	1.51 (s, 6H, $C(CH_3)_2$), 2.02 (s, 3H, $C(O)CH_3$), 4.45 (m, 2H, H-5'a, H-5'b), 4.65 (m, 1H, H-4'), 5.19 (m, 1H, H-3'), 6.28 (m, 1H, H-2'), 6.42 (d, 1H, J = 2.82, H-1'), 7.36 (m, 5H, ArH), 8.15, 8.28 (2s, 2H, H-2, H-8), 12.40 (br s, 1H, NH) The 2'-bromo isomer **(7b)** can be recognised by its H-1' (6.53, d, J = 5.65) and H-2' (5.38, t, J = 5.46) signals	595 (M^+, 6), 233 (25), 137 (73)
6c	85	$C_{24}H_{25}BrN_4O_7S$ (593.4)	0.43, 0.47, 0.78	267 (4.12)	1.51 (s, 6H, $C(CH_3)_2$), 2.02 (s, 3H, $C(O)CH_3$), 4.36 (m, 2H, H-5'a, H-5'b), 4.53 (m, 1H, H-4'), 5.17 (m, 1H, H-3'), 6.03 (m, 1H, H-2'), 6.56 (d, 1H, J = 3.38, H-1'), 6.73 (d, 1H, J = 3.93, H-7), 7.20 (s, 2H, NH_2), 7.37 (d, 1H, J = 3.67, H-8), 7.40 (m, 5H, ArH), 8.13 (s, 1H, H-2)	594 (M^+, 4), 163 (80), 134 (100)

[a] Satisfactory microanalyses obtained: C ±0.4, H ±0.2, N ±0.5; exception **5b** N ±0.6, **6b** C ±0.6.
[b] The products were obtained as amorphous powders having indefinite melting points.
[c] Deprotection with 8M NH_3/MeOH.
[d] Deprotection with Zn/Cu couple in MeOH.

Table 2. Products **8** and **9** Prepared

Product	Yield (%)	Molecular Formula[a] or Lit. mp (°C)	R_f: Solvent Systems A, B, C	UV (95% EtOH) λ_{max} (nm) (log ε)	^{1}H NMR (DMSO-d_6/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
8a	90, 58[c]	$C_{16}H_{19}N_5O_5$ (361.3)	0.11, 0.41, 0.66	259 (4.02)	1.45, 1.46 (2s, 6H, $C(CH_3)_2$), 1.99 (s, 3H, $(CO)CH_3$), 4.24 (m, 2H, H-5'a, H-5'b), 5.08 (m, 1H, H-4'), 6.27 (d, 1H, J = 5.61, H-3'), 6.41 (d, 1H, J = 5.92, H-2'), 6.97 (m, 1H, H-1'), 7.30 (s, 2H, NH_2), 8.11, 8.17 (2s, 2H, H-2, H-8)	362 (M^+, 100)
8b	91, 28[c]	$C_{16}H_{18}N_4O_6$ (362.3)	0.09, 0.30, 0.60	249 (3.94)	1.44, 1.46 (2s, 6H, $C(CH_3)_2$), 2.00 (s, 3H, $C(CO)CH_3$), 4.21 (m, 2H, H-5'a, H-5'b), 5.09 (m, 1H, H-4'), 6.27 (d, 1H, J = 5.81, H-3'), 6.44 (d, 1H, J = 6.01, H-2'), 6.94 (m, 1H, H-1'), 8.06, 8.10 (2s, 2H, H-2, H-8), 12.40 (br s, 1H, N–H)	363 (M^+, 2), 166 (68), 137 (100)
8c	93, 95[c]	$C_{17}H_{20}N_4O_5$ (360.4)	0.23, 0.33, 0.70	270 (4.03)	1.48 (s, 6H, $C(CH_3)_2$), 1.99 (s, 3H, $C(O)CH_3$), 4.18 (d, 2H, J = 4.05, H-5'a, H-5'b), 4.99 (m, 1H, H-4'), 6.14 (d, 1H, J = 5.78, H-3'), 6.36 (d, 1H, J = 5.95, H-2'), 6.65 (d, 1H, J = 3.34, H-7), 7.14 (s, 4H, H-1', H-8, NH_2), 8.11 (s, 1H, H-2)	361 (M^+, 2), 166 (68), 137 (100)
9a	86	194–195,[10] 184–186[19]	–, 0.08, 0.21	259 (4.04)	[10, 19]	234 (M^+, 18), 185 (46), 136 (87)
9b	88	> 300,[10] > 310[19]	–, 0.03, 0.19	250 (4.18)	[10, 19]	235 (M^+, 6), 137 (100)
9c	91	206–208,[17] 204–205[18]	0.06, 0.11, 0.35	270 (3.95)	[17, 18]	232 (M^+, 11), 134 (100), 107 (94)

[a] Satisfactory microanalysis obtained: C ±0.4, H ±0.2, N ±0.4 for **8a**, **8b**, **8c**.

[b] **8a**, **8b**, **8c** were obtained as amorphous powders having indefinite melting points; **9a** had m.p. 190–191 °C (MeOH), **9b** > 300 °C (MeOH) and **9c** 207–208 °C (acetone).

[c] Obtained from **2** and **3** via elimination with Zn/Cu couple in THF or pyridine.

Reaction of Nucleosides 1a, 1b, 1c with 1-Bromocarbonyl-1-methylethyl Acetate; General Procedure; Products 10, 11 and 2c/3c.

The nucleosides **1a**, **1b** or **1c** reacted with 1-bromocarbonyl-1-methylethyl acetate in $MeNO_2$ under conditions identical to those described for products **2**, **3** but the reaction was conducted for 2.5 h (for **1b**, **1c**) or 6–48 h (for **1a**). After the same work-up and chromatographic separation as described above the products **10a/11a**, **10b/11b** and **2c/3c** were obtained as a colourless froth having the spectroscopic data which agreed well with the literature values;[3,5,6,9,10,13] the IR spectra of **10a/11a** and **10b/11b** showed an intense band at 1805 cm^{-1} characteristic of alkoxydioxolanones.[4]

Deacetylation of the Products 2a/3a, 2b/3b and 2c/3c; General Procedures;

Method A (with 8 M methanolic ammonia):

The mixtures **2a/3a**, **2b/3b** or **2c/3c** in the ratio of 78:22, 73:27 and 97:3, respectively (2 mmol) were dissolved in 8 M methanolic NH_3 (17 mL) and the colourless solution was stirred at r.t. for 90 min. The solvent was removed in vacuo and each residue was dissolved in a small amount of $CHCl_3$ and applied to a short column of silica gel. The product was eluted with $CHCl_3$/EtOH (97:3) for **4a** and **5a** (23:2) for the mixture **4b/5b** (67:33) and **4b** and (95.5:4.5) for **4c**. The fractions containing the product were combined and concentrated under reduced pressure to give the product as a colourless froth; analytical samples were prepared as described for compounds **2** and **3** (Table 1).

Method B (wth Zn/Cu couple in MeOH):

The mixtures **2a/3a**, **2b/3b** and **2c/3c** in the ratio of 78:22, 73:27 and 97:3, respectively, (1 mmol) were dissolved in MeOH (20 mL) and freshly prepared[20] Zn/Cu couple (0.96 g) was added to the solution. The resulting suspensions were stirred at r.t. for 16 h. The catalyst was filtered off, the solvent was evaporated in vacuo and each residue was applied to a short column of silica gel. The product was eluted with $CHCl_3$/EtOH at the same polarity as described above for the same products of deacetylation with 8 M methanolic NH_3 to give **4a**, **5a** and **4c** as a colourless froth (Table 1). No desired products of deacetylation were isolated in the case of inosine derivatives **2b/3b**.

Acylation of the Nucleosides 4a/5a, 4b/5b and 4c with *O*-Phenylchlorothionoformate; General Procedure:

To a stirred suspension of the nucleoside **4a/5a** (77:23), **4b/5b** (67:33) or **4c** (1 mmol) and DMAP (2 mmol) in anhydr. MeCN (11 mL) a solution of *O*-phenylchlorothionoformate (1.5 mmol) in anhydr. MeCN (5 mL) was added in one portion. The resulting pale yellow solution was stirred at r.t. for 5 h. The solvent was removed under reduced pressure and the residue partitioned between EtOAc/H_2O (4:1, 100 mL). The organic phase was washed with cold M HCl (2 × 20 mL), H_2O (20 mL), 5% aq $NaHCO_3$ (20 mL), H_2O (20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was applied to a short column of silica gel. The product was eluted with CH_2Cl_2/EtOH (24:1) for **6a/7a** (74:26), (47:3) for **6b/7b** (72:28) and (95.5:4.5) for **6c**. The fractions containing the product were combined and evaporated to give the product as a colourless froth (Table 1); analytical samples were prepared as described for compounds **2** and **3**.

Reaction of Phenoxy(thiocarbonyl) Nucleosides 6a/7a, 6b/7b and 6c; with Tributyltin Hydride; General Procedure:

To a solution of the nucleoside **6a/7a** (74 : 26), **6b/7b** (72 : 28) or **6c** (1 mmol) in benzene (40 mL) Bu_3SnH (1.1 mL; 4 mmol) and AIBN (0.050 g, 0.025 mmol) were added. The stirred reactants were heated under reflux for 20 min. The solvent was removed under reduced pressure and the residue was applied to a short column of silica gel. The product was eluted with $CHCl_3$/EtOH (95.5:4.5) for **8a** and **8b** and (97:3) for **8c**. The fractions containing the product were combined and concentrated under reduced pressure to give the product as a colourless froth; analytical samples were prepared as described for compounds **2** and **3** (Table 2).

Reaction of Nucleosides 2a/3a, 2b/3b and 2c/3c with Zn/Cu Couple in THF or Pyridine; General Procedure:
To a solution of the nucleoside **2a/3a** (78:22) or **2c/3c** (97:3) (1 mmol) in anhydr. THF (15 mL) or **2b/3b** (73:27) in anhydr. pyridine (15 mL), freshly prepared Zn/Cu couple[20] (0.96 g) was added and the stirred suspension was heated under reflux for 4 h (for **2a/3a, 2c/3c**) or at 100 °C for 50 min (for **2b/3b**). The catalyst was filtered off, the solvent was removed in vacuo and the residue was applied to a short column of silica gel. The product was eluted with $CHCl_3$/EtOH at the same polarity as described for the same products of deoxygenation with Bu_3SnH to give **8a, 8b** and **8c** as a colourless froth (Table 2).

2',3'-Didehydro-2',3'-dideoxyadenosine (9a), 2',3'-Didehydro-2',3'-dideoxyinosine (9b) and 2',3'-Didehydro-2',3'-dideoxytubercidin (9c):
A compound **8a, 8b** or **8c** (1 mmol) was dissolved in 8 M methanolic NH_3 (10 mL) and the colourless solution was stirred at r.t. for 48 h. The solvent was removed in vacuo, the residue was dissolved in MeOH (50 mL), silica gel (0.5 g) was added to the solution, and the resulting suspension was evaporated to dryness. The residue was treated with a small amount of $CHCl_3$/MeOH (24:1) for **9a** (19:1) for **9b** and $CHCl_3$/EtOH (19:1) for **9c**. Each resulting slurry was applied to a short column of silica gel (5 g, 20 × 32 mm). Elution of the column with $CHCl_3$/MeOH (49:6), (17:3) and $CHCl_3$/EtOH (17:3) afforded the products **9a**, **9b** and **9c**, respectively as colourless glasses. Each colourless glass was dissolved in a small amount of H_2O and lyophilised to give the products as colourless powders (Table 2) homogenous on HPLC; t_R (sec): **9a**-149 (D), 114 (E); **9b**-123 (D), 110 (E); **9c**-210 (D); 133 (E).

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(1) De Clercq, E.; Aerschot Van, A.; Herdewijn, P.; Baba, H.; Pauwels, R.; Balzarini, J. *Nucleosides, Nucleotides* **1989**, 659.
(2) Serafinowski, P. *Synthesis* **1990**, 411.
(3) Jain, T.C.; Russell, A.J.; Moffatt, J.G. *J. Org. Chem.* **1973**, 3179.
(4) Greenberg, S.; Moffatt, J.G. *J. Am. Chem. Soc.* **1973**, *95*, 4016.
(5) Russell, A.F.; Greenberg, S.; Moffatt, J.G. *J. Am. Chem. Soc.* **1973**, *95*, 4025.
(6) Robins, M.J.; Hansske, F.; Low, N.H.; Park, J.I. *Tetrahedron Lett.* **1984**, 367.
(7) Although it is claimed[8] that 5'-*O*-(2-acetoxyisobutyryl) derivative of adenosine is formed along with 5'-*O*-dioxolanyl and 5'-OH derivatives no analytical or spectroscopic data are quoted to substantiate the claim.
(8) Mansuri, M.M.; Starrett, J.E.; Wos, J.A.; Tortolani, D.R.; Brodfuehrer, P.R.; Howell, H.G.; Martin, J.C. *J. Org. Chem.* **1989**, 4780.
(9) Lichtenthaler, F.W.; Kitahara, J.; Strobel, K. *Synthesis* **1974**, 860.
(10) Jain, T.C.; Jenkins, I.D.; Russell, A.F.; Verheyden, J.P.H.; Moffatt, J.G. *J. Org. Chem.* **1974**, 30.
(11) Yoshioka, H.; Kojima, E.; Ishida, S.; Yoshioka, H.; Murakami, K.Jpn Patent, JP0291,096[9091,096] (a, CO7H19/16) 30 Mar, 1990, Appl. 88/240,876, 28 Sep. 1988; 6pp. *Chem. Abstr.* **1990**, *113*, 132718.
(12) Reaction of tubercidin with 2-acetoxyisobutyryl bromide in acetonitrile is reported to give either 5'-*O*-dioxolanyl[3] or 5'-*O*-(2-acetoxyisobutyryl)[13] derivatives depending on the time of the reaction.
(13) Hobbs, F.W.; Cocuzza, A.J. European Patent Appl. 0251786, 1988; *Chem. Abstr.* **1988**, *109*, 93540.
(14) Serafinowski, P. *Nucleic Acid. Res.* **1987**, 1121.
(15) Gonzalez, A.G.; Jorge, Z.D.; Lopez Dorta, H. *Tetrahedron Lett.* **1981**, 335.
(16) Robins, H.J.; Wilson, J.S. *J. Am. Chem. Soc.* **1981**, 932.
(17) Robins, M.J.; Jones, R.A.; Mengel, R. *Can. J. Chem.* **1977**, 1251.
(18) Krawczyk, S.H.; Townsend, L.B. *Nucleosides, Nucleotides* **1989**, 97.
(19) Chu, C.K.; Bhadti, V.S.; Doboszewski, B.; Gu, Z.P.; Kosugi, Y.; Pullaiah, K.C.; Roey Van, P. *J. Org. Chem.* **1989**, 2217.
(20) Smith, R.D.; Simmons, H.E. *Organic Synthesis Coll. Vol V*, **1973**, 855.
(21) A discrepancy between our results and those reported by Mansuri et al.[8] is probably due to their use of the mixture of 5'-*O*-(2-acetoxyisobutyryl), 5'-*O*-dioxolanyl and 5'-OH derivatives in an unspecified ratio as starting materials and MeOH with some CH_2Cl_2 and MeCN as a solvent. (Ref. 8, p 4784).