Synthesis of sugar-modified 2,6-diaminopurine and guanine nucleosides from guanosine via transformations of 2-aminoadenosine and enzymatic deamination with adenosine deaminase[1]

Morris J. Robins, Ruiming Zou, Fritz Hansske, and Stanislaw F. Wnuk

Abstract: Treatment of 2,6-diaminopurine riboside (2-aminoadenosine) with α-acetoxyisobutyryl bromide in acetonitrile gave mixtures of the *trans* 2′,3′-bromohydrin acetates **2**. Treatment of **2** with zinc–copper couple effected reductive elimination, and deprotection gave 2,6-diamino-9-(2,3-dideoxy-β-D-*erythro*-pent-2-enofuranosyl)purine (**3***a*). Treatment of **2** with Dowex 1 × 2 (OH^-) resin in methanol gave the 2′,3′-anhydro derivative **4**. Stannyl radical-mediated hydrogenolysis of **2** and deprotection gave the 2′-deoxy **6***a* and 3′-deoxy **7***a* nucleosides. Treatment of the 3′,5′-*O*-(tetraisopropyldisiloxanyl) derivative (**5***a*) with trifluoromethanesulfonyl chloride – 4-(dimethylamino)pyridine gave 2′-triflate **5***c*. Displacement with lithium azide – dimethylformamide and deprotection gave the arabino 2′-azido derivative **8***a*, which was reduced to give 2,6-diamino-9-(2-amino-2-deoxy-β-D-arabinofuranosyl)purine (**8***b*). Sugar-modified 2,6-diaminopurine nucleosides were treated with adenosine deaminase to give the corresponding guanine analogues.

Key words: adenosine deaminase, 2,6-diaminopurine nucleosides, deoxygenation, guanine nucleosides, nucleosides.

Résumé : Le traitement du riboside de 2,6-diaminopurine (2-aminoadénosine) par du bromure d'α-acétoxyisobutyryle, dans l'acétonitrile, conduit à un mélange des acétates de la *trans*-2′,3′-bromohydrine (**2**). Le traitement de **2** par le couple zinc–cuivre provoque une élimination réductrice et une déprotection subséquente conduit à la 2,6-diamino-9-(2,3-didésoxy-β-D-*érythro*-pent-2-énofuranosyl)purine (**3***a*). Le traitement de **2** par de la résine Dowex 1 × 2 (OH^-) dans le méthanol conduit au dérivé 2′,3′-anhydro (**4**). Une hydrogénolyse du composé **2** catalysée par le radical stannyle, suivie d'une déprotection, fournit les nucléosides 2′-désoxy (**6***a*) et 3′-désoxy (**7***a*). Le traitement du dérivé 3′,5′-*O*-(tétraisopropyldisiloxanyl) (**5***a*) par du chlorure de trifluorométhanesulfonyle dans la 4-(diméthylamino)pyridine conduit au 2′-triflate (**5***c*). Un déplacement par de l'azoture de lithium dans le diméthylformamide, suivi d'une déprotection, conduit au dérivé 2′-azido-arabino (**8***a*) qui, par réduction, conduit à la 2,6-diamino-9-(2-amino-2-désoxy-β-D-arabinofuranosyl)purine (**8***b*). Les nucléosides de la 2,6-diaminopurine comportant des sucres modifiés ont été traités par de la désaminase d'adénosine pour conduire aux analogues guanines correspondantes.

Mots clés : désaminase d'adénosine, nucléosides de la 2,6-diaminopurine, désoxygénation, nucléosides de la guanine, nucléosides.

(Traduit par la rédaction)

Received October 21, 1996.

This paper is dedicated to Professor William A. Ayer, a most congenial, helpful, and knowledgable colleague, on the occasion of his 65th birthday.

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Introduction

Transformations of adenosine to give sugar-modified adenine nucleosides are well known (2, 3). However, analogous transformations of guanosine are plagued by experimental problems including poor solubility, instability, and formation of gels (4, 5). Vorbrüggen and Krolikiewicz reported an efficient transformation of the lactam functionality of guanosine into the cyclic amidine of 2,6-diamino-9-(β-D-ribofuranosyl)purine (**1**, 2,6-diaminopurine riboside, DAPR) (6), and DAPR (2-aminoadenosine) is a substrate (7) of calf intestinal adenosine deaminase (ADA; adenosine aminohydrolase, EC 3.5.4.4). Thus, conversion of the troublesome guanosine system into a chemical analogue of adenosine and subsequent enzymatic conversion of modified 2,6-diaminopurine nucleosides to their guanine counterparts allows convenient use of DAPR as a "masked guanosine" precursor for modifications of the sugar moiety (8). ADA also effects hydrolytic replacement of chloro and methoxy groups from 2-amino-6-chloropurine (9*a*) and 2-amino-6-methoxypurine (9*b*) nucleosides to give the corresponding guanine derivatives. The scope of such chemical/enzymatic syntheses is not limited to the specificity of mammalian ADA (10*a*) since this enzyme activity from *Aspergillus oryzae* has less stringent substrate requirements at C5′ (10*b*) and adenylic acid deaminase has broad tolerance for conversions to 6-oxopurine nucleosides (10*c*).

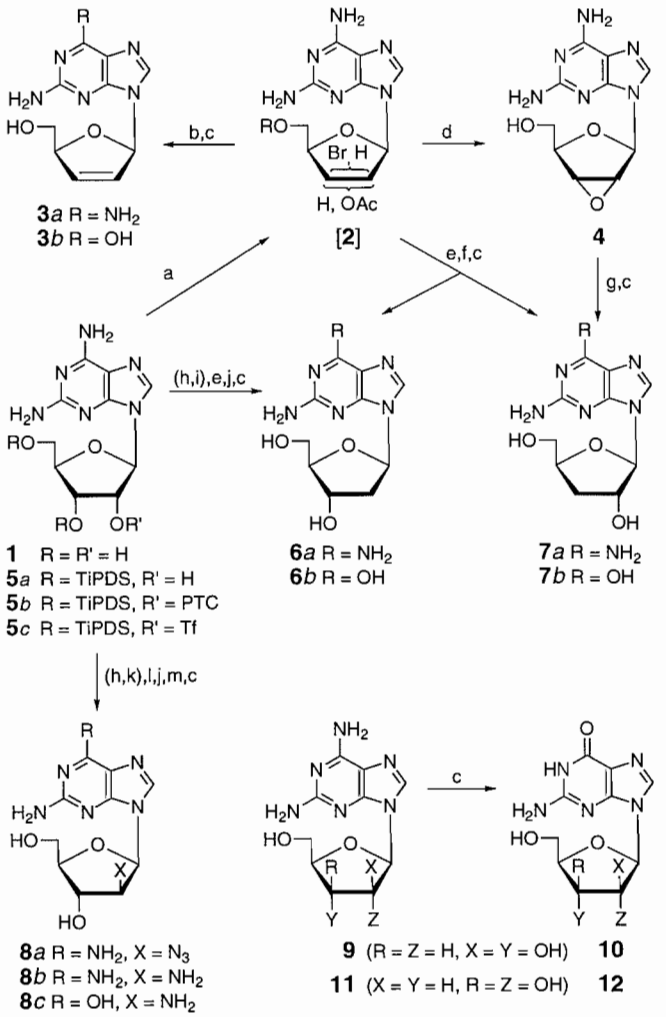
ADA is an ubiquitous human enzyme and sugar-modified 2,6-diaminopurine nucleosides are prodrugs of sugar-modified guanine nucleosides (11–13). Thus, 2,6-diamino-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)purine (2,6-diaminopurine 2′,3′-dideoxyriboside, ddDAPR) is an effective inhibitor of hepatitis B virus (11) and also has anti-HIV activity (12). We now report sugar modifications with DAPR and deaminations with ADA to give their guanine counterparts.

Results and discussion

DAPR (**1**, Scheme 1) was prepared from guanosine by modification (14) of the known method (6). Treatment of **1** with α-acetoxyisobutyryl bromide gave a mixture of *trans* bromo acetates **2** (R = H or 2,5,5-trimethyldioxolan-4-on-2-yl) (3, 15). Treatment of **2** with Dowex 1 × 2 (OH^-) resin in MeOH gave the 2′,3′-anhydro nucleoside **4** (81% from **1**). Lithium triethylborohydride effected selective cleavage (3, 16) of the epoxide O—C3′ bond of **4** to give 3′-deoxyDAPR (**7***a*, 85%). Treatment of **2** with tributyltin hydride and deprotection (NH_3–MeOH) gave 2′-deoxyDAPR (**6***a*, 16%) and 3′-deoxyDAPR (**7***a*, 59%), which were separated by ion-exchange chromatography with Dowex 1 × 2 (OH^-).

Treatment of **2** with zinc–copper couple in *N,N*-dimethylformamide (DMF) effected reductive elimination of bromide and acetate to give 2′,3′-didehydro-2′,3′-dideoxyDAPR (**3***a*), which was hydrogenated to give ddDAPR (3, 15*b*). A sample of DAPR containing 2′*R*[^{2}H] (~20% 2′[^{2}H]-**1**, obtained as the minor product from oxidation of **5***a* and reduction ($NaBD_4$) of the 2′-ketone (17)) was subjected to the sequence **1** → **2** → **3***a*. The product (containing 2′[^{2}H]-**3***a*) was analyzed by ^{1}H (3) and ^{13}C (Table 1) NMR. The higher field ^{1}H NMR signal at δ 6.10 (H2′) was diminished by ~20% relative to the signal at δ 6.42 (H3′) in agreement with the inverted signal positions observed with 3′[^{2}H]-adenosine as starting material (3, 15*a*). Also, the higher field vinyl ^{13}C signal was assigned to C2′ (δ 125.9) on the basis of selective ^{13}C–^{1}H decoupling and its reduced intensity relative to the signal at δ 134.5 (C3′).

Scheme 1.



(a) $(CH_3)_2C(OAc)COBr/CH_3CN/H_2O$; (b) Zn-Cu/DMF; (c) ADA/buffer; (d) Dowex 1 × 2 (OH^-)/MeOH; (e) Bu_3SnH/AIBN/toluene/Δ; (f) NH_3/MeOH; (g) $LiEt_3BH$/THF/DMSO; (h) $TiPDSCl_2$/pyridine; (i) PTCCl/DMAP/CH_3CN; (j) TBAF/THF; (k) TfCl/DMAP/CH_2Cl_2; (l) LiN_3/DMF; (m) N_2H_4/Raney Ni/EtOH.

Treatment of **1** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TiPDSCl_2$) gave **5***a*, which was acylated with phenoxythiocarbonyl (PTC) chloride (18). Thionocarbonate **5***b* was reduced (tributyltin hydride) and deprotected (tetrabutylammonium fluoride, TBAF) to give 2′-deoxyDAPR (**6***a*, 41% from **1**). Triflation of **5***a* gave **5***c*, which was treated with lithium azide and deprotected (TBAF) to give the arabino 2′-azido analogue **8***a* (59%). Hydrogenolysis (Raney nickel) of **8***a* gave 2,6-diamino-9-(2-amino-2-deoxy-β-D-arabinofuranosyl)purine (**8***b*, 85%). Triflation of an analogously protected guanosine derivative had given a 2′,6-bis-*O*-(trifluoromethanesulfonyl) by-product (19) and other 6-*O*-triflyl derivatives of 2-deoxyguanosine have been reported (13*b*).

Enzymatic conversion of **3***a*, **6***a*, **7***a*, and **8***b* to their guanine counterparts **3***b*, **6***b*, **7***b*, and **8***c*, respectively, was effected with ADA in aqueous sodium phosphate buffer. Isolated

Table 1. ^{13}C NMR spectral data.[a,b]

Compound	C2	C4	C5	C6	C8	C1′	C2′	C3′	C4′	C5′
3*a*	156.3	151.6	113.2	160.5	136.5	88.1	125.9	134.5	87.9	63.2
3*b*	153.7	150.8	116.4	156.7	135.2	87.8	125.3	134.2	87.2	62.9
4	156.2	157.5	113.0	160.3	135.6	81.5	57.8	58.7	80.9	61.0
6*a*	156.1	151.2	113.5	160.0	135.7	83.1	39.4	71.0	87.6	61.9
6*b*	153.4	150.8	116.6	156.7	135.4	82.7	39.6	70.6	87.4	61.6
7*a*	156.2	151.2	113.4	160.1	135.8	90.2	74.4	34.5	80.2	62.9
7*b*	153.6	150.7	116.7	156.7	135.2	90.0	74.8	34.5	80.4	62.7
8*a*	156.1	151.6	112.8	160.4	136.2	81.1	67.5	71.9	83.4	59.8
8*b*	156.0	151.6	112.9	160.2	137.1	84.0	60.3	75.4	84.3	60.7
8*c*	153.4	150.9	116.2	156.8	136.5	84.0	60.0	75.1	84.1	60.4
9	155.9	151.6	112.4	160.1	136.9	83.1	75.5[c]	75.5	84.1	61.1
10	153.5	150.9	113.6	156.7	136.8	83.3	75.4	75.3	84.2	60.9
11	156.1	150.8	113.0	159.9	136.6	89.0	80.8	75.3	82.9	59.4
12	154.1	151.4	116.8	157.5	137.1	89.3	81.5	75.6	83.8	60.0

[a]Chemical shifts (δ) at 50 or 100 MHz (Me_4Si/Me_2SO-d_6).
[b]Proton-decoupled singlets.
[c]Signal absent in 2′*S*[^{2}H]-**9**.

yields of the guanine nucleosides were >80%, except for the 2′,3′-unsaturated nucleoside **3***b*. Complete deamination of **3***a* (a potent inhibitor of ADA (12)) required 10 days and the somewhat unstable **3***b* partially decomposed during the extended reaction period, which makes this route to **3***b* less appealing than direct deoxygenation of guanosine (3, 20). The arabino **9** and xylo **11** epimers of DAPR were subjected to deamination to give AraG (**10**) and XyloG (**12**), respectively, in high yields. An oxidation–reduction sequence at C2′ of protected guanosine (17) had given 9-(β-D-arabinofuranosyl)guanine (**10**). Coupling of 2-amino-6-chloropurine (followed by 7/9 isomer separation and base conversion to guanine (21*a*)) or 2-*N*-acetylguanine (followed by 7/9 isomer separation (21*b*)) (8) with xylofuranose derivatives had been employed to prepare 9-(β-D-xylofuranosyl)guanine (**12**).

In summary, this indirect approach (conversion of guanosine to DAPR, modification of the sugar, and enzymatic deamination to give the guanine nucleoside) is more experimentally convenient in many instances than direct sugar transformations with guanosine. Separation of isomers and purification of intermediates can be achieved readily since 2,6-diaminopurine nucleosides are amenable to ion-exchange chromatography with Dowex 1 × 2 (OH^-) resin and usually crystallize without difficulty.

Experimental

Uncorrected melting points were obtained with a hotstage apparatus. UV spectra were determined with solutions in MeOH unless otherwise noted. ^1H (200 or 400 MHz) and ^{13}C (50 or 100 MHz, Table 1) NMR spectra (Me_4Si–Me_2SO-*d6*) were recorded with Bruker spectrometers. Mass spectra (EI MS, CI, FAB) were determined at 20 or 70 eV. Solvents were purified, dried (CaH_2 or $LiAlH_4$), and distilled before use. Pyridine was dried by refluxing with and distillation from CaH_2. Reagent grade chemicals were used without further purification. TLC was performed with silica gel 60 F_{254} sheets, and silica gel (200–425 mesh) was used for column chromatography. Elemental analyses were determined by the Microanalytical Laboratory at the University of Alberta. Calf intestinal adenosine deaminase (ADA, 2.7 units/mg protein) was obtained from Sigma.

2,6-Diamino-9-(2,3-anhydro-β-D-ribofuranosyl)purine 4

Amorphous solid **2** (prepared (3, 15*b*) from **1** (2 mmol)) was dissolved in a minimal volume of MeOH and the solution was applied to a column of Dowex 1 × 2 (OH^-) resin previously soaked in and washed with MeOH. The column was allowed to stand for 1 h at ambient temperature and the product was eluted with MeOH (crystallization occurred in early fraction-collecting tubes). Evaporation of appropriate fractions and recrystallization (MeOH) gave **4** (427 mg, 81% from **1**); mp ~180°C (dec.); UV max: 255, 280 nm (ε 9900, 10 300); ^1H NMR δ: 3.55 (m, *J* = 11.5, 5.5, 5.0 Hz, 2H), 4.15 (t, *J* = 5.0 Hz, 1H), 4.17 (d, *J* = 2.5 Hz, 1H), 4.37 (d, *J* = 2.5 Hz, 1H), 5.09 (t, *J* = 5.0 Hz, 1H), 5.85 (s, 2H), 6.01 (s, 1H), 6.77 (s, 2H), 7.92 (s, 1H); MS *m/z*: 264.0968 (23, M^+ = 264.0971). Anal. calcd. for $C_{10}H_{12}N_6O_3$: C 45.45, H 4.58, N 31.80; found: C 45.35, H 4.75, N 31.48.

2,6-Diamino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-purine 6*a* and 2,6-diamino-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)purine 7*a*

Amorphous solid **2** (prepared (3, 15*b*) from **1** (2 mmol)) was dissolved in deoxygenated toluene (80 mL), AIBN (64 mg, 0.4 mmol) and Bu_3SnH (2.2 mL, 2.38 g, 8.2 mmol) were added, and the solution was refluxed for 1 h. Volatiles were evaporated, the residue was dissolved in CH_3CN–H_2O (100 mL, 1:1), and this solution was washed with pentane (100 mL) and then evaporated. The residue was stirred with NH_3–MeOH (50 mL, saturated at −10°C) at ambient temperature for 4 h and volatiles were evaporated. The residue was chromatographed (Dowex 1 × 2 (OH^-), H_2O) and recrystallized (MeOH) to give **6***a* (85 mg, 16% from **1**); mp 154–155°C (lit. (22) mp 147–149°C); UV max: 256, 280 nm (ε 10 100, 10 600); ^1H NMR δ: 2.20 (m, *J* = 13.0, 6.0, 3.0 Hz, 1H); 2.62 (m, *J* = 13.0, 8.0, 5.5

Hz, 1H), 3.54 (m, J = 12.0, 6.0, 4.0 Hz, 1H), 3.60 (m, J = 12.0, 5.0 Hz, 1H), 3.86 (m, J = 2.0 Hz, 1H), 4.37 (m, J = 4.0 Hz, 1H), 5.26 (d, J = 4.0 Hz, 1H), 5.29 (dd, J = 6.0, 5.0 Hz, 1H), 5.76 (s, 2H), 6.19 (dd, J = 8.0, 6.0 Hz, 1H), 6.76 (s, 2H), 7.92 (s, 1H); MS *m/z*: 266.1128 (12, M^+ = 266.1127). Anal. calcd. for $C_{10}H_{14}N_6O_3$: C 45.11, H 5.30, N 31.56; found: C 45.01, H 5.41, N 31.31.

Further elution of the ion-exchange column (30% MeOH–H_2O) and recrystallization of the residue (MeOH) gave **7***a* (316 mg, 59% from **1**); mp 198–199°C; MS *m/z*: 266.1129 (11, M^+ = 266.1127); other data identical to those with **7***a* prepared by the following reduction of **4**.

2,6-Diamino-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-purine 7*a*

$LiEt_3BH$–THF (1 M; 25 mL, 25 mmol) was added dropwise to a stirred solution of **4** (528 mg, 2 mmol) in DMSO (40 mL) at 10°C under N_2. The cooling bath was removed after 1 h and the reaction mixture was stirred at ambient temperature for 3 days. H_2O (60 mL) was added carefully and the solution was purged vigorously with N_2 to remove *pyrophoric* triethylborane. Volatiles were evaporated in vacuo (~0.5 Torr; 1 Torr = 133.3 Pa) at <60°C and the residue was chromatographed (Dowex 1 × 2 (OH^-), H_2O followed by 30% MeOH–H_2O) and recrystallized (MeOH) to give **7***a* (453 mg, 85%), mp 198–199°C, mp 122–123°C (from H_2O) (lit. (23) mp 120–121°C (from H_2O)); UV max: 255, 280 nm (ε 10 200, 10 700); ^{1}H NMR δ: 1.92 (m, J = 13.0, 6.5, 3.5 Hz, 1H), 2.24 (m, J = 13.0, 8.0, 6.0 Hz, 1H), 3.50 (m, J = 11.5, 5.5, 4.0 Hz, 1H), 3.65 (m, J = 11.5, 5.5, 3.5 Hz, 1H), 4.30 (m, 1H), 4.51 (m, J = 4.5, 2.5 Hz, 1H), 5.18 (t, J = 5.5 Hz, 1H), 5.56 (d, J = 4.5 Hz, 1H), 5.70 (d, J = 2.5 Hz, 1H), 5.78 (s, 2H), 6.75 (s, 2H), 7.92 (s, 1H); MS *m/z*: 266.1124 (16, M^+ = 266.1127). Anal. calcd. for $C_{10}H_{14}N_6O_3$: C 45.11, H 5.30, N 31.56; found: C 44.90, H5.31, N 31.52.

2,6-Diamino-9-(3,5-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-β-D-ribofuranosyl)purine 5*a*

$TiPDSCl_2$ (4 mL, 3.88 g, 12.3 mmol) was added to a stirred suspension of **1** (2.82 g, 10 mmol) in dried pyridine (50 mL) at ambient temperature. EtOH (5 mL) was added after 6 h and volatiles were evaporated. Toluene was added and evaporated several times and the residue was partitioned ($CHCl_3$–H_2O, 1:1; 600 mL). The organic layer was concentrated and chromatographed (silica gel, 10% MeOH–$CHCl_3$) to give **5***a* (5.12 g, 97%) as an amorphous solid with data as reported (24); ^{1}H NMR δ: 1.94–2.14 (m, 28H), 3.90–4.14 (m, 3H), 4.31 (m, J = 5.0, 1.5 Hz, 1H), 4.45 (dd, J = 8.0, 5.0 Hz, 1H), 5.61 (d, J = 5.0 Hz, 1H), 5.72 (d, J = 1.5 Hz, 1H), 5.79 (s, 2H), 6.79 (s, 2H), 7.78 (s, 1H); MS *m/z*: 524.2602 (8, M^+ ($C_{22}H_{40}N_6O_5Si_2$) = 524.2599).

2,6-Diamino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-purine 6*a*

PTCCl (0.40 mL, 380 mg, 2.2 mmol) was added to a suspension of **5**a (obtained from **1** (2 mmol)) in dried CH_3CN (20 mL) containing DMAP (489 mg, 4 mmol) at ambient temperature. Stirring was continued for 1 h and the resulting solution was diluted (EtOAc, 100 mL), washed (AcOH–H_2O, $NaHCO_3$–H_2O), dried (Na_2SO_4), evaporated, and coevaporated successively with toluene, $CHCl_3$, and Et_2O. The resulting amorphous **5***b* was dried in vacuo at ambient temperature for 2 h and dissolved in toluene (20 mL). AIBN (66 mg, 0.4 mmol) and Bu_3SnH (0.85 mL, 920 mg, 3.2 mmol) were added and the solution was deoxygenated (N_2, 30 min) and heated at 80°C overnight. TBAF–THF (1 M; 4 mL, 4 mmol) was added and heating was continued for 3 h. Volatiles were evaporated and the residue was partitioned (H_2O–Et_2O, 1:1; 200 mL). The aqueous phase was concentrated and applied to a column of Dowex 1 × 2 (OH^-). Elution (H_2O) and recrystallization (MeOH) of the residue gave **6***a* (216 mg, 41% from **1**); mp 154–155°C; MS *m/z*: 266.1124 (15, M^+ = 266.1127) with data identical to those with **6***a* from debromination of **2**.

2,6-Diamino-9-(2-azido-2-deoxy-β-D-arabinofuranosyl)-purine 8*a*

CF_3SO_2Cl (0.15 mL, 237 mg, 1.4 mmol) was added to a cold (~0°C) stirred suspension of **5***a* (525 mg, 1 mmol) and DMAP (367 mg, 3 mmol) in dried CH_2Cl_2 (10 mL). $CHCl_3$ (50 mL) was added after 30 min and the solution was washed (2% HOAc–H_2O, brine), dried (Na_2SO_4), and evaporated. The residue was successively coevaporated with toluene, $CHCl_3$, and Et_2O to give amorphous **5***c*, which was dried in vacuo at ambient temperature for 4 h. A solution of this **5***c* and dried LiN_3 (196 mg, 4 mmol) in dried DMF (10 mL) was stirred at ambient temperature overnight and volatiles were evaporated. The residue was dissolved (EtOAc, 50 mL) and the solution was washed (brine) and evaporated. The residue was dissolved (THF, 10 mL) and stirred with TBAF–THF (1 M; 3 mL, 3 mmol) at ambient temperature overnight. Evaporation of volatiles and chromatography of the residue (Dowex 1 × 2 (OH^-), H_2O and then 20% MeOH–H_2O) gave crystalline **8***a* (181 mg, 59%); mp ~262°C (dec.); UV max: 255, 280 nm (ε 10 300, 10 800); ^{1}H NMR δ: 3.64 (m, J = 12.0, 5.5, 4.5 Hz, 1H), 3.72 (m, J = 12.0, 5.5, 3.0 Hz, 1H), 3.76 (m, J = 7.5 Hz, 1H), 4.35 (m, J = 7.5, 5.5 Hz, 1H), 4.49 (dd, J = 7.5, 6.5 Hz, 1H), 5.20 (t, J = 5.5 Hz, 1H), 5.83 (s, 2H), 5.99 (d, J = 5.5 Hz, 1H), 6.19 (d, J = 6.5 Hz, 1H), 6.78 (s, 2H), 7.90 (s, 1H); MS *m/z*: 307.1141 (13, M^+ = 307.1141). Anal. calcd. for $C_{10}H_{13}N_9O_3$: C 39.09, H 4.25, N 41.03; found: C 38.85, H 4.35, N 40.63.

2,6-Diamino-9-(2-amino-2-deoxy-β-D-arabinofuranosyl)-purine 8*b*

Hydrazine (95%, 1 mL) was added to a stirred suspension of **8***a* (307 mg, 1 mmol) in EtOH–H_2O (3:1, 20 mL) containing Raney Ni (100 mg) at ambient temperature. The reaction mixture was filtered after 6 h and the solid was washed (EtOH–H_2O, 8:2). The filtrate and washings were combined, concentrated, and chromatographed (Dowex 1 × 2 (OH^-), H_2O) to give crystalline **8***b* (238 mg, 85%); mp 289–292°C; UV (H_2O) max: 255, 280 nm (ε 9 800, 10 300); ^{1}H NMR δ: 1.20–1.80 (br s, 2H), 3.40 (t, J = 6.5 Hz, 1H), 3.58 (dd, J = 12.5, 4.5 Hz, 1H), 3.68 (dd, J = 12.5, 2.5 Hz, 1H), 3.70 (m, 1H), 4.01 (m, 1H), 4.60–5.60 (br s, 1H), 5.39 (d, J = 4.5 Hz, 1H), 5.76 (s, 2H), 6.02 (d, J = 6.5 Hz, 1H), 6.68 (s, 2H), 7.88 (s, 1H); MS *m/z*: 281.1232 (10, M^+ = 281.1236). Anal. calcd. for $C_{10}H_{15}N_7O_3$: C 42.70, H 5.38, N 34.86; found: C 42.56, H 5.38, N 34.87.

2′-Deoxyguanosine 6*b* (deamination procedure)

ADA (10 mg; Sigma, 2.7 units/mg protein) was added to a solution of **6***a* (266 mg, 1 mmol) in DMSO (5 mL) and aque-

ous sodium phosphate buffer (0.1 M, 25 mL; pH 7.4) and stirring was continued at ambient temperature overnight (reaction progress was monitored by thin-layer electrophoresis). Volatiles were evaporated in vacuo and the residue was applied to a column of Dowex 1 × 2 (OH^-), which was washed successively with H_2O, 80% MeOH–H_2O, and H_2O. The product was then eluted (30 mM aqueous $Et_3NH{\cdot}HCO_3$) and fractions were evaporated, coevaporated several times with H_2O, and recrystallized (H_2O) to give **6***b* (250 mg, 91%); mp ~250°C (dec.) (lit. (18) mp 251–252°C); UV (H_2O) max: 252 nm (ε 13 400); ^1H NMR δ: 2.20 (m, J = 13.0, 6.0, 3.0 Hz, 1H), 2.50 (m, J = 13.0, 7.5, 5.5 Hz, 1H), 3.52 (m, J = 12.0, 5.5, 4.5, Hz, 2H), 3.80 (m, 1H), 4.34 (m, 1H), 4.95 (t, J = 5.5 Hz, 1H), 5.26 (d, J = 4.0 Hz, 1H), 6.12 (dd, J = 7.5, 6.0 Hz, 1H), 6.46 (s, 2H), 7.92 (s, 1H), 10.64 (s, 1H); MS (FAB) *m/z*: 268 (6, MH^+). Anal. calcd. for $C_{10}H_{13}N_5O_4{\cdot}0.5H_2O$: C 43.48, H 5.11, N 25.35; found: C 43.42, H 4.90, N 25.62.

3′-Deoxyguanosine 7*b*

Treatment of **7***a* (266 mg, 1 mmol) with ADA (as described for **6***b*) and recrystallization (H_2O) gave **7***b* (239 mg, 87%) as a hemihydrate; mp ~250°C (dec.) (lit. (25) mp >300°C (dec.)); UV (H_2O) max: 252 nm (ε 13 600); ^1H NMR δ: 1.89 (m, J = 13.5, 6.5, 3.0 Hz, 1H), 2.20 (m, J = 13.5, 9.0, 5.5 Hz, 1H), 3.51 (dd, J = 12.0, 4.5 Hz, 1H), 3.64 (dd, J = 12.0, 3.5 Hz, 1H), 4.31 (m, 1H), 4.46 (m, 1H), 4.60–5.90 (br s, 2H), 5.70 (d, J = 2.0 Hz, 1H), 6.49 (s, 2H), 7.94 (s, 1H), 10.65 (s, 1H); MS (FAB) *m/z*: 268 (6, MH^+). Anal. calcd. for $C_{10}H_{13}N_5O_4{\cdot}0.5H_2O$: C 43.48, H 5.11, N 25.35; found: C 43.38, H 4.89, N 25.39.

9-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)guanine 3*b*

Treatment of **3***a* (248 mg, 1 mmol; prepared as described (3, 15b)) with ADA (reaction mixture stirred at ambient temperature for 10 days with additions of ADA (20 mg) every second day) gave a residue that was chromatographed (Dowex 1 × 2 (OH^-), $Et_3NH{\cdot}HCO_3$–H_2O) and recrystallized (H_2O (gentle heating)) to give **3***b* (130 mg, 50%) with data as reported (3, 20); mp ~200°C (dec.); UV (H_2O) max: 252 nm (ε 13 800); MS (FAB) *m/z*: 250 (16, MH^+). Anal. calcd. for $C_{10}H_{11}N_5O_3{\cdot}0.5H_2O$: C 46.51, H 4.68, N 27.12; found: C 46.20, H 4.58, N 27.07.

9-(2-Amino-2-deoxy-β-D-arabinofuranosyl)guanine 8*c*

Treatment of **8***b* (141 mg, 0.5 mmol) with ADA (pH 6.5, stirred at ambient temperature for 15 days with addition of ADA (8 mg) every second day) gave a residue that was chromatographed (Dowex 1 × 2 (OH^-), $Et_3NH{\cdot}HCO_3$–H_2O) to give **8***c* as a mixed salt and free 2′-amine. Further ion-exchange chromatography and recrystallization (H_2O) gave **8***c* (131 mg, 90%) with data as reported (26); mp ~230°C (dec.) (lit. (26) mp 193–196°C (dec.)); UV (H_2O) max: 252 nm (ε 13 000); MS (FAB) *m/z*: 283 (57, MH^+). Anal. calcd. for $C_{10}H_{14}N_6O_4{\cdot}0.5H_2O$: C 41.24, H 5.19, N 28.85; found: C 41.38, H 4.93, N 28.68.

9-(β-D-Xylofuranosyl)guanine 12

Treatment of **11** (282, 1 mmol) (prepared by coupling ($SnCl_4$–CH_3CN (27)) 2,6-diacetamidopurine (28*a*) with 1,2,3,5-tetra-*O*-acetyl-D-xylofuranose and deprotection (NH_3–MeOH), with data as reported (28*b*, 29); mp 159-161°C (lit. (28*b*) mp 160–163°C); MS *m/z*: 282.1080 (8, M^+ ($C_{10}H_{14}N_6O_4$) = 282.1076)) with ADA (stirred at ambient temperature for 3 days with addition of ADA (20 mg) each day) gave a residue that was chromatographed (Dowex 1 × 2 (OH^-), $Et_3NH{\cdot}HCO_3$–H_2O) and recrystallized (H_2O) to give **12** (242 mg, 83%); mp ~250°C (dec.) (lit. (21*a*) mp 236–240°C); UV (H_2O) max: 252 nm (ε 13 300); MS (FAB) *m/z*: 284 (28, MH^+); and other data as reported (21*a*). Anal. calcd. for $C_{10}H_{13}N_5O_5{\cdot}0.5H_2O$: C 41.10, H 4.83, N 23.96; found: C 41.01, H 4.63, N 23.63.

9-(β-D-Arabinofuranosyl)guanine 10

Deamination of **9** (17) proceeded analogously to give **10** with data identical to those of a sample prepared previously (17).

Acknowledgements

We thank the Natural Sciences and Engineering Research Council, the University of Alberta, and Brigham Young University for support and Mrs. Jeanny K. Gordon for assistance with the manuscript.

References

1. M.J. Robins, Z. Guo, and S.F. Wnuk. J. Am. Chem. Soc. **119**, 3637 (1997).
2. (*a*) J.G. Moffatt. *In* Nucleoside analogues: chemistry, biology, and medical applications. *Edited by* R.T. Walker, E. De Clercq, and F. Eckstein. Plenum Press, New York. 1979. pp. 71–164; (*b*) P.C. Srivastava, R.K. Robins, and R.B. Meyer, Jr. *In* Chemistry of nucleosides and nucleotides. Vol. 1. *Edited by* L.B. Townsend. Plenum Press, New York. 1988. pp. 113–281.
3. M.J. Robins, J.S. Wilson, D. Madej, N.H. Low, F. Hansske, and S.F. Wnuk. J. Org. Chem. **60**, 7902 (1995).
4. R. Mengel and W. Muhs. Chem. Ber. **112**, 625 (1979).
5. T.C. Jain, I.D. Jenkins, A.F. Russell, J.P.H. Verheyden, and J.G. Moffatt. J. Org. Chem. **39**, 30 (1974).
6. H. Vorbrüggen and K. Krolikiewicz. Liebigs Ann. Chem. 745 (1976).
7. H.-P. Baer, G.I. Drummond, and E.L. Duncan. Mol. Pharmacol. **2**, 67 (1966).
8. M.J. Robins, R. Zou, F. Hansske, D. Madej, and D.L.J. Tyrrell. Nucleosides Nucleotides, **8**, 725 (1989).
9. (*a*) V. Nair and T.B. Sells. Synlett, 753 (1991); (*b*) M.R. Almond, J.L. Collins, B.E. Reitter, J.L. Rideout, G.A. Freeman, and M.H. St. Clair. Tetrahedron Lett. **32**, 5745 (1991).
10. (*a*) A. Bloch, M.J. Robins, and J.R. McCarthy, Jr. J. Med. Chem. **10**, 908 (1967); (*b*) S.F. Wnuk, J.D. Stoeckler, and M.J. Robins. Nucleosides Nucleotides, **13**, 389 (1994); (*c*) A.L. Margolin, D.R. Borcherding, D. Wolf-Kugel, and N. Margolin. J. Org. Chem. **59**, 7214 (1994).
11. (*a*) S. Suzuki, B. Lee, W. Luo, D. Tovell, M.J. Robins, and D.L.J. Tyrrell. Biochem. Biophys. Res. Commun. **156**, 1144 (1988); (*b*) B. Lee, W. Luo, S. Suzuki, M.J. Robins, and D.L.J. Tyrrell. Antimicrob. Agents Chemother. **33**, 336 (1989).
12. (*a*) J. Balzarini, R. Pauwels, M. Baba, M.J. Robins, R. Zou, P. Herdewijn, and E. De Clercq. Biochem. Biophys. Res. Commun. **145**, 269 (1987); (*b*) J. Balzarini, M.J. Robins, R. Zou, P. Herdewijn, and E. De Clercq. Biochem. Biophys. Res. Commun. **145**, 277 (1987); (*c*) R. Pauwels, M. Baba, J. Balzarini, P. Herdewijn, J. Desmyter, M.J. Robins, R. Zou, D. Madej, and E. De Clercq. Biochem. Pharmacol. **37**, 1317 (1988).
13. (*a*) J. Balzarini, M. Baba, R. Pauwels, P. Herdewijn, S.G. Wood, M.J. Robins, and E. De Clercq. Mol. Pharmacol. **33**, 243 (1988); (*b*) P. Herdewijn and A. Van Aerschot. Tetrahedron

Lett. **30**, 855 (1989); (*c*) M.J. Robins, S.G. Wood, N.K. Dalley, P. Herdewijn, J. Balzarini, and E. De Clercq. J. Med. Chem. **32**, 1763 (1989).
14. M.J. Robins, F. Hansske, and S.E. Bernier. Can. J. Chem. **59**, 3360 (1981).
15. (*a*) M.J. Robins, F. Hansske, N.H. Low, and J.I. Park. Tetrahedron Lett. **25**, 367 (1984); (*b*) M.J. Robins, D. Madej, N.H. Low, F. Hansske, and R. Zou. *In* Nucleic acid chemistry: improved and new synthetic procedures, methods and techniques. Vol 4. *Edited by* L.B. Townsend and R.S. Tipson. John Wiley & Sons, New York. 1991. pp. 211–219.
16. F. Hansske and M.J. Robins. Tetrahedron Lett. **26**, 4295 (1985).
17. F. Hansske, D. Madej, and M.J. Robins. Tetrahedron, **40**, 125 (1984).
18. M.J. Robins, J.S. Wilson, and F. Hansske. J. Am. Chem. Soc. **105**, 4059 (1983).
19. M.J. Robins, S.D. Hawrelak, A.E. Hernández, and S.F. Wnuk. Nucleosides Nucleotides, **11**, 821 (1992).
20. C.K. Chu, V.S. Bhadti, B. Doboszewski, Z.P. Gu, Y. Kosugi, K.C. Pullaiah, and P. Van Roey. J. Org. Chem. **54**, 2217 (1989).
21. (*a*) G. Gosselin, M.-C. Bergogne, J. De Rudder, E. De Clercq, and J.-L. Imbach. J. Med. Chem. **29**, 203 (1986); (*b*) J. Med. Chem. **30**, 982 (1987).
22. L.F. Christensen, A.D. Broom, M.J. Robins, and A. Bloch. J. Med. Chem. **15**, 735 (1972).
23. E. Walton, F.W. Holly, G.E. Boxer, R.F. Nutt, and S.R. Jenkins. J. Med. Chem. **8**, 659 (1965).
24. M.J. Robins, J.S. Wilson, L. Sawyer, and M.N.G. James. Can. J. Chem. **61**, 1911 (1983).
25. G.L. Tong, K.J. Ryan, W.W. Lee, E.M. Acton, and L. Goodman. J. Org. Chem. **32**, 859 (1967).
26. A. Sato, R. Imai, N. Nakamizo, and T. Hirata. Chem. Pharm. Bull. **27**, 821 (1979).
27. M. Saneyoshi and E. Satoh. Chem. Pharm. Bull. **27**, 2518 (1979).
28. (*a*) J. Davoll and B.A. Lowy. J. Am. Chem. Soc. **73**, 1650 (1951); (*b*) J. Am. Chem. Soc. **74**, 1563 (1952).
29. J.A. Montgomery and K. Hewson. J. Org. Chem. **34**, 1396 (1969).