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2′-AZIDO-2′-DEOXY- AND 2′-AMINO-2′-DEOXY-β-D-ARABINO-FURANOSYL PURINE NUCLEOSIDES*

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ABSTRACT

A general method for the preparation of 2′-azido-2′-deoxy- and 2′-amino-2′-deoxyarabinofuranosyl-adenine and -guanine nucleosides is described. Selective benzoylation of 3-azido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose afforded 3-azido-6-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**). Acid hydrolysis of **1**, followed by oxidation with sodium metaperiodate and hydrolysis by sodium hydrogencarbonate gave 2-azido-2-deoxy-5-*O*-benzoyl-D-arabinofuranose (**3**), which was acetylated to give 1,3-di-*O*-acetyl-2-azido-5-*O*-benzoyl-2-deoxy-D-arabinofuranose (**4**). Compound **4** was converted into the 1-chlorides **5** and **6**, which were condensed with silylated derivatives of 6-chloropurine and 2-acetamidohypoxanthine. The condensation reaction gave α and β anomers of both 7- and 9-substituted purine nucleosides. The structures of the nucleosides were determined by n.m.r. and u.v. spectroscopy, and by correlation of the c.d. spectra of the newly prepared nucleosides with those published for known purine nucleosides.

DISCUSSION

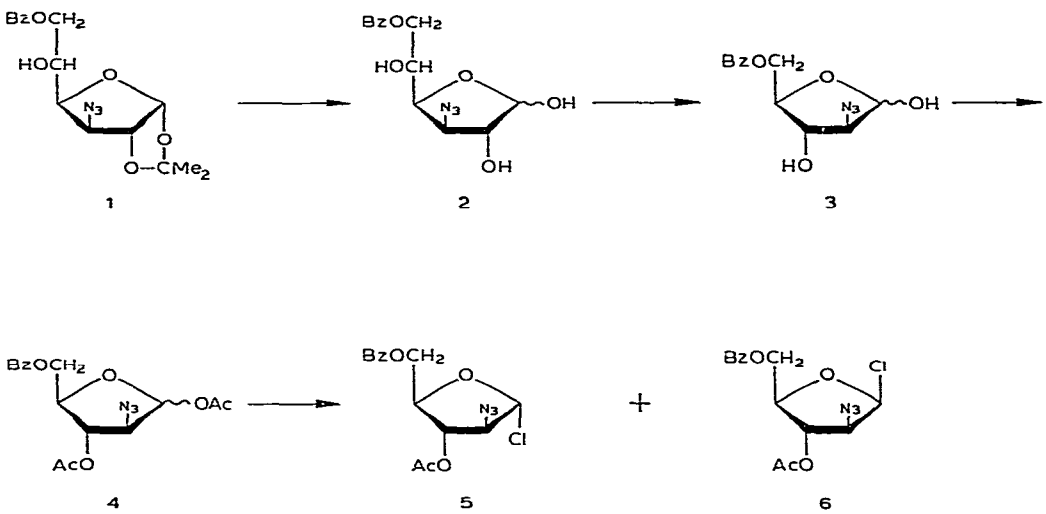
We have recently synthesized 2′-azido-2′-deoxy- and 2′-amino-2′-deoxy-β-D-arabinofuranosyl derivatives of uridine[1] and cytidine[2]; the cytidine derivatives are resistant to enzymic deamination and exhibit potent antitumor activity[2] *in vitro* and *in vivo*. In continuation of these studies on the chemical and biological properties of nucleosides possessing chemotherapeutic potential, this report now describes the synthesis of some purine nucleosides of 2-azido-2-deoxy- and 2-amino-2-deoxy-D-arabinofuranose by condensation of protected 2-azido-2-deoxy-D-arabinofuranosyl chlorides (**5**, **6**) with silylated derivatives of 6-chloropurine and 2-acetamidohypoxanthine.

The synthetic procedure first developed for the preparation of anomeric methyl 2-deoxy-4-thio-D-*erythro*-pentofuranosides[3] was adapted for synthesis of the sugar intermediates **4**. The starting material for the preparation of the glycosyl

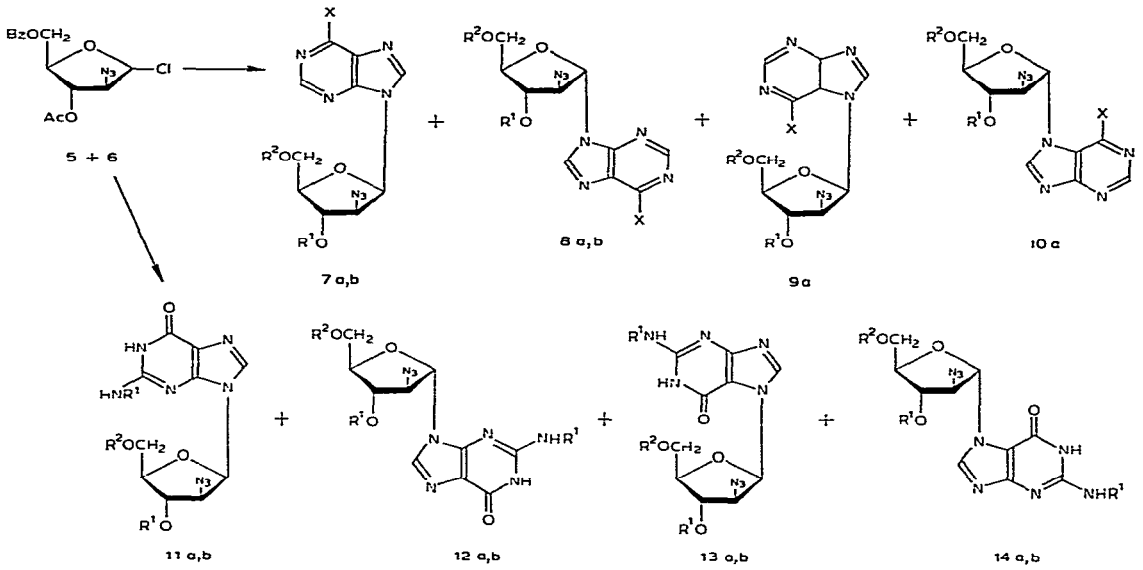
*Dedicated to Professor Roy L. Whistler.

chlorides **5** and **6**, 3-azido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose[4], was obtained by hydrolysis of 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with dilute acetic acid. This method gave a substantially higher yield (91%) of the product than that (50%) by the previously reported procedure[4], which used dilute hydrochloric acid in ethanol. Selective benzoylation of 3-azido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose according to the method of Nayak and Whistler[3] gave a high yield of 3-azido-6-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**, Scheme 1). Removal of the acetal group of **1** with Dowex 50 (H^+) gave **2** which was, without purification, oxidized with sodium metaperiodate. T.l.c. of the mixture indicated that the formyl group had been partially hydrolyzed from the intermediate obtained by periodate oxidation of **2** and, therefore, no attempts were made to isolate this intermediate; instead, the hydrolysis was completed with sodium hydrogencarbonate to give 2-azido-5-*O*-benzoyl-2-deoxy-D-arabinofuranose (**3**). Compound **3** was acetylated with pyridine–acetic anhydride to give an anomeric mixture (4:1 $\alpha:\beta$) as determined by n.m.r. spectroscopy[5] of 1,3-di-*O*-acetyl-2-azido-5-*O*-benzoyl-2-deoxy-D-arabinofuranoses (**4**). Compound **4** was converted into a mixture of 1-chlorides (**5** and **6**) by treatment with titanium tetrachloride in 1,2-dichloroethane at 0–4°.

Condensation of trimethylsilylated 6-chloropurine with 3-*O*-acetyl-2-azido-5-*O*-benzoyl-2-deoxy-D-arabinofuranosyl chlorides (**5** and **6**) in 1,2-dichloroethane at 50° and in the presence of mercuric acetate furnished four isomeric nucleosides (**7a–10a**, Scheme 2) which were separated by column chromatography on silica gel. The u.v. spectra exhibited by the four nucleosides were used to assign the site of the attachment of the sugar moiety. The u.v. spectra of **7a** and **8a** were similar to those of 6-chloro-9-(β-D-ribofuranosyl)purine[6] (λ_{max} 264), whereas the u.v. spectra of the



Scheme 1



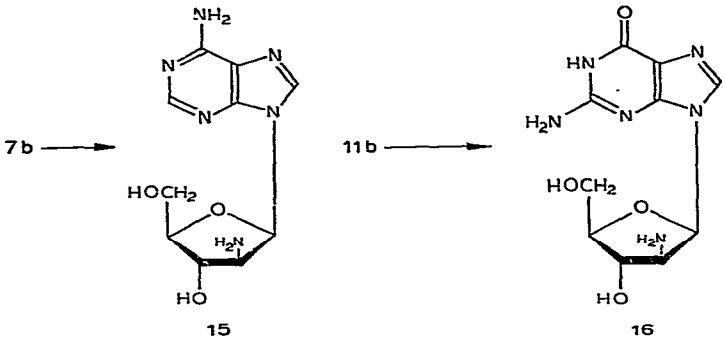
a: R^1 = Ac; R^2 = Bz, X = Cl
b: R^1, R^2 = H, X = NH_2

Scheme 2

7-substituted 6-chloropurines **9a** and **10a** showed broad maxima at 270 and shoulders at 283 nm.

Treatment of **7a** and **8a** with methanolic ammonia at 90° furnished 9-(2-azido-2-deoxy-β-D-arabinofuranosyl)adenine (**7b**) and its α anomer **8b**, respectively. The formation of traces of **7b** had previously been suggested to occur upon treatment of 9-(2,3-anhydro-5-*O*-benzoyl-β-D-ribofuranosyl)-*N*,*N*-dibenzoyladenine with sodium azide[7]. The u.v. spectra of **7b** and **8b** were similar to that of adenosine and, therefore, further supported the assignment of the site of glycosylation of the protected derivatives **7a–10a**. Compound **7b** was readily reduced by catalytic hydrogenation (Scheme 3) to 9-(2-amino-2-deoxy-β-D-arabinofuranosyl)adenine (**15**).

Treatment of the trimethylsilylated derivative of 2-acetamidohypoxanthine with the glycosyl chlorides **5** and **6** gave anomers of both the 9- and 7-isomers (**11a**, **12a**, and **13a**, **14a**, Scheme 2) of 2-acetamido-9-(3-*O*-acetyl-2-azido-5-*O*-benzoyl-2-deoxy-D-arabinofuranosyl) (hypoxanthine). These were separated by chromatography on silica gel and were deprotected in methanolic sodium methoxide to give the corresponding guanine derivatives **11b**, **13b**, and **14b**. The assignment of the position of attachment of the sugar moiety in the guanine derivatives **11b**, **13b**, and **14b** was made on the basis of a comparison of their u.v. absorption with those of 7- and 9-substituted (glycofuranosyl)guanines[8]. The purity of compounds was verified by elemental analyses. Compounds **5** and **6** were not analyzed because of their lability, and satisfactory analytical data could not be obtained for the protected nucleosides **12a** and



Scheme 3

14a. However, the product **14b** obtained after deprotecting **14a** gave satisfactory data. The anomeric configuration of **7b**, **8b**, **13b**, and **14b** was established by c.d. data which, therefore, also confirmed the configuration of the corresponding protected nucleosides **7a**, **8a**, **13a**, and **14a** and the amino nucleoside **15**. The c.d. spectrum of 7-(2-azido-2-deoxy-β-D-arabinofuranosyl)guanine (**13b**) was almost identical to that published for 7-ribosylguanine[9], whereas that of the corresponding α anomer (**14b**) showed a maximum of opposite sign in the region of 288 nm. The c.d. spectra of the adenine derivatives **7b** and **8b** exhibited a negative Cotton effect for **7b**, which is characteristic of the β-configuration of glycofuranosyladenine nucleosides[10], and a positive one for the corresponding α anomer **8b**.

The 9-substituted guanine nucleoside **11b** gave a c.d. spectrum different from that of 9-(β-D-arabinofuranosyl)guanine[11] and, as interpretation of the spectra of guanosine nucleosides is complicated, no conclusion could be drawn in this instance. The assignment of configuration of **9a**, **10a**, **11a**, **11b**, and **12a** was based on the empirical rule[12,13] that states that H-1 resonates at lower field when the 1′,2′-substituents are *cis* than when they are *trans*. Although this rule has been used for assignments of the anomeric configuration of a variety of nucleosides[5,14], a recent finding[15] of an exception to it, in the case of some adenine and imidazole nucleosides of lyxo- and manno-furanoses, suggests that some caution should be exercised when using the chemical shift of the anomeric protons for determination of the anomeric configuration. The validity of this rule to the foregoing assignments appears to be confirmed by correlation of the anomeric configurations of **7a**, **7b**, **8a**, **8b**, **13a**, and **13b** with the chemical shifts of H-1′ (Table I), as well as by a similar correlation of some 2′-azido-2′-deoxyarabinofuranosyl pyrimidine nucleosides[1,2]. The coupling constants $J_{1',2'}$ for **11a** (5.5) and **12a** (3.0 Hz, Table I) provide further support for the assigned configuration. Values for $J_{1',2'}$ within this range have been considered indicative of the anomeric configuration[5,16].

Whereas a number of methods[14b,17,18] have been developed for the synthesis of 2′-amino-2′-deoxy-β-D-ribofuranosyl nucleosides, the synthesis of 2′-amino-2′-deoxy nucleosides that have the amino group in the "up" (*arabino*) configuration has proved

TABLE I

100-MHz PROTON-N.M.R. CHEMICAL SHIFTS (δ) AND FIRST-ORDER COUPLINGS (Hz) FOR THE ANOMERIC PROTONS

Compound	*Solvent*	*H-1*	*H-1'*	$J_{1,2}$	$J_{1',2'}$
1	$CDCl_3$	5.93d		3.5	
3 α anomer	$CDCl_3$–CD_3OD	5.89s		—	
β anomer		5.99d		4.5	
4 α anomer	$CDCl_3$	6.20s		—	
β anomer		6.39d		4.5	
5	$CDCl_3$	6.13s		—	
6	$CDCl_3$	6.25d		4.5	
7a	$CDCl_3$		6.57d		4.5
7b	Me_2SO-d_6		6.45d		6.5
8a	$CDCl_3$		6.21d		3.5
8b	Me_2SO-d_6		5.92d		7.0
9a	$CDCl_3$		6.67d		5.0
10a	$CDCl_3$		6.28d		4.0
11a	$CDCl_3$		6.30d		5.5
11b	Me_2SO-d_6		6.14d		6.0
12a	$CDCl_3$		5.95d		3.0
13a	$CDCl_3$		6.78d		4.5
13b	Me_2SO-d_6		6.58d		6.0
14a	$CDCl_3$		6.29d		3.2
14b	Me_2SO-d_6		5.96d		6.5
15	Me_2SO-d_6		6.31d		6.0
16	Me_2SO-d_6		6.00d		6.0

rather elusive[19,20]. The synthetic procedure described here, and our previous reports on the synthesis of the corresponding pyrimidine nucleosides[1,2], constitute a general method for their preparation and make them now available for biochemical and biological studies.

A method utilizing 1,3,5-tri-*O*-acetyl-2-azido-2-deoxyribose and stannic chloride has been recently reported for the synthesis of 2'-azido-2'-deoxy and 2'-amino-2'-deoxyribofuranosylpurines[17]. However, initial experiments showed that, in the case of the 1-*O*-acetyl derivatives **4**, this method afforded only traces of the β anomers, the major products being the α anomers.

The biological activity of these compounds will be reported elsewhere.

EXPERIMENTAL

General methods. — Solutions were dried with anhydrous sodium sulfate and evaporated under diminished pressure using a Buchler rotary evaporator. ^{1}H-N.m.r. spectra were determined in solutions as specified, with Me_4Si as internal standard, by using a Varian XL-100 spectrometer. Chemical shifts are reported in p.p.m. (δ) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (complex multiplet). Coupling constants are first-order. C.d. data were measured with a

Jasco-5 spectropolarimeter at room temperature. U.v. spectra were recorded with Cary-14 and Aminco spectrophotometers. Melting points were determined on a Fisher–Johns block and are uncorrected.

*3-Azido-3-deoxy-1,2-*O*-isopropylidene-α-*D*-glucofuranose.* — 3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (145.0 g; 508 mmol) was dissolved in 60–70% acetic acid (2 L). The solution was heated for 6 h at 45–50° and evaporated to a syrup that was taken up in toluene (500 mL). The solution was evaporated and the syrupy residue crystallized from ethanol–ether–petroleum ether (~1:1:3) to give 82 g of the product, m.p. 85–86°; lit.[4] m.p. 84–85°. The filtrate was evaporated to a syrup that was purified on silica gel in 1:1 chloroform–ether to give 32 g of product; m.p. 86°; total yield 114 g (91.4%).

*3-Azido-6-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**1**). — 3-Azido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (109.5 g; 446 mmol) was dissolved in a mixture of pyridine (200 mL) and dichloromethane (500 mL), and the solution was cooled to −30°. Benzoyl chloride (68 g; 483 mmol) in dichloromethane (200 mL) was added dropwise with stirring, keeping the temperature at −30°. The mixture was kept overnight at −20°. Cold water (50 mL) was added and the mixture evaporated. Toluene (1 L) and water (200 mL) were added to the syrupy residue. The toluene solution was extracted with water (2 × 200 mL) and evaporated. A portion (~1 g) of the syrupy residue was purified by chromatography on silica gel (3:1 chloroform–ether) to give **1** as a colorless syrup; n.m.r. ($CDCl_3$): δ 7.36–8.18 (m, 5, aromatic), 5.93 (d, 1, $J_{1,2}$ 3.5 Hz, H-1), 4.67 (d, 1, $J_{1,2}$ 3.5 Hz, H-2), 4.25–4.80 (m, 5, H-3,4,5,6), 1.50, and 1.33 (2s, 6, $2CH_3$).

Anal. Calc. for $C_{16}H_{19}N_3O_6$: C, 55.01; H, 5.48; N, 12.03. Found: C, 55.42; H, 5.72; N, 11.80.

*2-Azido-5-*O*-benzoyl-2-deoxy-*D*-arabinofuranose* (**3**). — Crude **1** from the preceding experiment, containing a small proportion of the 5,6-dibenzoate (~5%) and a trace of the 5-benzoate of 3-azido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose, was dissolved in 1,4-dioxane–water (1:1, 2 L). Dowex-50 (H^+) resin (150 mL) was added to the solution and the mixture was stirred for 52–60 h at 80–85° (at which point t.l.c., developed in 2:1 chloroform–ether, showed the disappearance of **1**). The mixture was filtered and the resin washed with 1,4-dioxane (300 mL). Sodium metaperiodate (100 g; 467 mmol) in water (600–800 mL) was added slowly with stirring while the temperature of the mixture was kept below 25°. Additional sodium metaperiodate (30 g; 140 mmol) in water (200 mL) was added after 1 h and the mixture was stirred for another 1 h at room temperature. Sodium hydrogencarbonate (45 g; 535 mmol) was added in small portions and the mixture stirred overnight. The mixture was filtered and the precipitate washed with 1,4-dioxane (200 mL). The combined filtrates were concentrated to 200 mL and extracted with dichloromethane (1 × 800 and 2 × 100 mL). The dichloromethane solution was evaporated and the residue dissolved in methanol (~400 mL). Sodium hydrogencarbonate (~0.5 g) was added and the mixture was stirred overnight at room temperature to complete hydrolysis of the 3-*O*-formyl group. The solution was evaporated

and the syrupy residue purified by column chromatography on silica gel in 3:1 dichloromethane–ether. Pure **3** (78.5 g, 63%) was obtained as a colorless syrup; n.m.r. ($CDCl_3$–CD_3OD): 7.40–8.20 (m, 5, aromatic), 5.99 (d, $J_{1,2}$ 4.5 Hz, H-1), and 5.89 (s, H-1).

Anal. Calc. for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.91; H, 4.81; N, 14.78.

1,3-Di-O-acetyl-2-azido-5-O-benzoyl-2-deoxy-D-arabinofuranose (**4**). — Compound **3** (70 g; 250 mmol) was acetylated with pyridine–acetic anhydride (2:1, 500 mL) overnight at room temperature. The mixture was evaporated and xylene (2 × 200 mL) was evaporated from the syrupy residue; yield 86 g (94.4%). This product was sufficiently pure for the preparation of nucleosides. A portion (~1 g) of it was purified by chromatography on silica gel in 6:1 benzene–ethyl acetate. Compound **4** was a syrupy mixture of α and β anomers in $\alpha:\beta \simeq 4:1$ ratio (as determined by n.m.r.); n.m.r. ($CDCl_3$) for the α anomer: δ 7.42–8.36 (2m, 5, aromatic), 6.20 (s, 1, H-1), 5.14 (dd, $J_{2,3}$ 1.5, $J_{3,4}$ 2.0 Hz, H-3), and 4.20 (d, 1, $J_{2,3}$ 1.5 Hz, H-2); for the β anomer of **4**: δ 7.42–8.36 (2m, 5, aromatic), 6.39 (d, 1, $J_{1,2}$ 4.5 Hz, H-1), 5.56 (dd, 1, $J_{2,3}$ 8.0, $J_{4,3}$ 6 Hz, H-3), and 4.09 (dd, 1, $J_{1,2}$ 4.5, $J_{2,3}$ 8 Hz, H-2).

Anal. Calc. for $C_{16}H_{17}N_3O_7$: C, 52.89; H, 4.71; N, 11.56. Found: C, 53.20; H, 4.98; N, 11.33.

3-O-Acetyl-2-azido-5-O-benzyl-2-deoxy-D-arabinofuranosyl chlorides (**5** and **6**). — Compound **4** (7.5 g; 20 mmol) was dissolved in dichloromethane (200 mL) and the solution cooled to 0–4°. Titanium tetrachloride (3.5–4 mL; 31–36 mmol) was added dropwise with stirring and the mixture kept for 3–4 h at 0–4°. It was then poured, with stirring, into a cold (0–4°) saturated solution of sodium hydrogencarbonate (~200 mL) and filtered (Celite). The dichloromethane solution was then separated and dried. Silica gel (~10 g) was added and the mixture was filtered and evaporated. T.l.c. (8:1 toluene–ethyl acetate) showed 2 spots of **5** and **6** and a trace of **4**. The syrupy mixture of **5** and **6** was used without further purification for synthesis of the nucleosides. The ratio of **5**:**6**, about 4:1, was determined by n.m.r.; n.m.r. ($CDCl_3$) for compound **5**: δ 7.32–8.20 (2m, 5H, aromatic), 6.13 (s, 1, H-1), 5.10 (d, 1, *J* 4.5 Hz, H-3), and 2.16 (s, 3H, Ac); for **6**: δ 7.32–8.20 (2m, 5, aromatic), 6.25 (d, 1, $J_{1,2}$ 4.5 Hz, H-1), 5.65 (dd, 1, $J_{2,3}$ 8.5, $J_{3,4}$ 6.0 Hz, H-3), 4.31 (dd, 1, $J_{1,2}$ 4.5, $J_{2,3}$ 8.5 Hz, H-2), and 2.13 (s, 3H, Ac).

9-(3-O-Acetyl-2-azido-5-O-benzoyl-2-deoxy-β-D-arabinofuranosyl)-6-chloropurine (**7a**), *9-(3-O-acetyl-2-azido-5-O-benzoyl-2-deoxy-α-D-arabinofuranosyl)-6-chloropurine* (**8a**), *7-(3-O-acetyl-2-azido-5-O-benzoyl-2-deoxy-β-D-arabinofuranosyl)-6-chloropurine* (**9a**), *and 7-(3-O-acetyl-2-azido-5-O-benzoyl-2-deoxy-α-D-arabinofuranosyl)-6-chloropurine* (**10a**). — 6-Chloropurine (3.5 g; 22.6 mmol) was silylated by boiling with hexamethyldisilazane (~15 mL) and chlorotrimethylsilane (~1 mL) in toluene (~80 mL) for 3 h with stirring under reflux. The clear solution was evaporated and toluene evaporated from the crystalline residue. A solution of the glycosyl chlorides **5** and **6** (prepared from 7.3 g; 20 mmol of **4**) in 1,2-dichloroethane (200 mL) and mercuric acetate (6.5 g; 25 mmol) were added to the silylated 6-chloro-

purine and the mixture was stirred for 2 days at 45–50°. The solution was washed with 20% potassium iodide solution (2 × 100 mL) and water (100 mL). It was dried, evaporated, and resolved on a column of silica gel with chloroform–ethyl ether as the eluant. The compounds were eluted from the column in the following order **8a**, **7a**, **10a**, and **9a**. Compound **8a** (1.25 g, 13.7%) was obtained as a white solid foam; λ_{max}^{EtOH} 264 nm; n.m.r. ($CDCl_3$): δ 8.85, 8.32 (2s, 2, H-2, H-8), 7.44–8.20 (2m, 5, aromatic), 6.21 (d, 1, $J_{1',2'}$ 3.5 Hz, H-1'), 5.46 (t, $J_{3',4'} = J_{2',3'} = 4$ Hz, H-3'), 5.22 (q, $J_{2',3'}$ 4, $J_{1',2'}$ 3.5 Hz, H-2'), 4.89–4.62 (2m, 3, H-4', H-5'), and 2.07 (s, 3, acetyl).

Anal. Calc. for $C_{19}H_{16}ClN_7O_5$: C, 49.84; H, 3.52; N, 21.41. Found: C, 50.12; H, 3.49; N, 21.15.

Compound **7a** (2.04 g, 22.3%) was obtained as a white solid foam; λ_{max}^{EtOH} 264 nm; n.m.r. ($CDCl_3$): δ 8.78, 8.45 (2s, 2, H-8, H-2), 7.43–8.2 (2m, 5, aromatic), 6.57 (d, 1, $J_{1',2'}$ 4.5 Hz, H-1'), 5.51 (q, 1, $J_{2',3'}$ 1.5 Hz, H-3'), 4.77 (d, 2, $J_{4',5'}$ 5.0 Hz, H-5'), and 4.51 (m, 2, H-2', H-4').

Anal. Calc. for $C_{19}H_{16}ClN_7O_5$: C, 49.84; H, 3.52; N, 21.41. Found: C, 50.22; H, 3.78; N, 21.12.

Compound **10a** (94.0 mg, 10.3%) had m.p. 167–168° (ether–petroleum ether); λ_{max}^{EtOH} 270 and 283 nm (sh); n.m.r. ($CDCl_3$): δ 9.76, 8.43 (2s, 2H, H-8, H-2), 7.40–8.20 (2m, 5H, aromatic). 6.28 (d, 1, $J_{1',2'}$ 4 Hz, H-1'), 5.50 (t, 1, $J_{2',3'} = J_{3',4'} = 4.0$ Hz, H-3'), 5.29 (t, 1, $J_{1',2'} = J_{2',3'} = 4$ Hz, H-2'), 4.68–4.94 (m, 3H, H-4', H-5'), and 2.10 (s, 3, acetyl).

Anal. Calc. for $C_{19}H_{16}ClN_7O_5$: C, 49.84, H, 3.52, N, 21.41. Found: C, 50.17; H, 3.77; N, 21.52.

Compound **9a** (150 mg, 1.64%) was obtained as a colorless syrup; λ_{max}^{EtOH} 270 and 283 nm(sh); n.m.r. ($CDCl_3$): δ 9.81, 8.57 (2s, 2, H-8, H-2), 7.48–8.22 (2m, 5H, aromatic, 6.67 (d, 1, $J_{1',2'}$ 5 Hz, H-1'), 5.52 (m, 1, H-3'), 4.80 (d, 2, $J_{4',5'}$ 4.5 Hz, H-5'), 4.60 (m, 2, H-2',4'), and 2.24 (s, 3, acetyl).

Anal. Calc. for $C_{19}H_{16}ClN_7O_5$: C, 49.84; H, 3.52; N, 21.41. Found: C, 50.20; H, 3.69; N, 21.17.

9-(2-Azido-2-deoxy-β-D-arabinofuranosyl)adenine (**7b**). — Compound **7a** (1.9 g; 4 mmol) was treated with methanolic ammonia (150 mL, saturated at room temperature) in a sealed flask for 18 h at 90–95°. The solution was cooled and evaporated. The crystalline residue was extracted with hot benzene (2 × 80 mL) to remove benzamide. It was stirred with ethanol (50 mL), filtered, and the crystals were washed with ethanol and ether to give 540 mg of **7b**; m.p. 205–206°. The filtrate was concentrated to ~15 mL and crystallized to furnish 320 mg of **7b**; m.p. 194–196°. This filtrate was evaporated and purified by chromatography on silica gel in 6:1 chloroform–methanol to give an additional 170 mg of **7b**; yield 1.03 g (85%). The analytical sample of **7b** was recrystallized from water; $\lambda_{max}^{H_2O}$ pH 7.4 259 nm (ε 13,600); c.d. λ_{max} (H_2O) 261 nm ([Θ] −15,400); n.m.r. (Me_2SO-d_6): δ 8.38, 8.21 (2s, 2, H-2, H-8), 7.37 (s, 2, NH_2), 6.45 (d, 1, $J_{1',2'}$ 6.5 Hz, H-1'), and 6.07 (d, 3'-OH).

Anal. Calc. for $C_{10}H_{12}N_8O_3$ (292.26): C, 41.09; H, 4.14; N, 38.34. Found: C, 41.50; H, 4.28; N, 38.14.

9-(2-Azido-2-deoxy-α-D-arabinofuranosyl)adenine (**8b**). — Compound **8a** (1.1 g; 2.4 mmol) was treated with methanolic ammonia under the conditions described for the preparation of **7b**. The crude **8b** was purified by chromatography on silica gel in 6:1 chloroform–methanol and crystallization from ethanol; yield 460 mg (65.4%); m.p. 152–154°; $\lambda_{max}^{H_2O}$ (pH 7.4) 259 nm (ε 12,600); c.d. λ_{max} (H_2O) 260 nm ([Θ] +4,000); n.m.r. (Me_2SO-d_6): δ 8.44, 8.23 (2s, 2, H-2, H-8), 7.37 (s, 2, NH_2), 6.16 (d, 1,3′-OH), 5.92 (d, 1, $J_{1',2'}$ 7 Hz, H-1′), 5.08 (m, 1, H-2′), 4.94 (t, 1, *J* 5.5 Hz, 5′-OH), and 4.23 (m, 2, H-3′, H-4′).

Anal. Calc. for $C_{10}H_{12}N_8O_3$ (292.26): C, 41.09; H, 4.14; N, 38.34. Found: C, 41.49; H, 4.23; N, 38.03.

9-(2-Amino-2-deoxy-β-D-arabinofuranosyl)adenine (**15**). — Compound **7b** (292 mg; 1 mmol) in methanol (100 mL) was reduced for 1 h with hydrogen at room temperature and atmospheric pressure with 10% Pd–C as the catalyst. The catalyst was filtered off and the filtrate evaporated. The residue was crystallized from methanol; yield 226 mg (85%); m.p. 220–222°; $\lambda_{max}^{H_2O}$ (pH 7.4) 259.5 nm (ε 13,000); c.d. λ_{max} (H_2O) 258 nm ([Θ] −5,900); n.m.r. (Me_2SO-d_6): δ 8.37, 8.20 (2s, 2, H-2, H-8), 7.31 (s, 2, NH_2), and 6.31 (d, 1, $J_{1',2'}$ 6 Hz, H-1′).

Anal. Calc. for $C_{10}H_{14}N_6O_3$ (266.26): C, 45.11; H, 5.30; N, 31.56. Found: C, 45.45; H, 5.42; N, 31.26).

9-(3-O-Acetyl-2-azido-5-O-benzoyl-2-deoxy-β-D-arabinofuranosyl)-2-acetamidohypoxanthine (**11a**), *9-(3-O-acetyl-2-azido-5-O-benzoyl-2-deoxy-α-D-arabinofuranosyl)-2-acetamidohypoxanthine* (**12a**), *7-(3-O-acetyl-2-azido-5-O-benzoyl-2-deoxy-β-D-arabinofuranosyl)-2-acetamidohypoxanthine* (**13a**), *and 7-(3-O-acetyl-2-azido-5-O-benzoyl-2-deoxy-α-D-arabinofuranosyl)-2-acetamidohypoxanthine* (**14a**). — A mixture of tris(trimethylsilyl)-2-acetamidohypoxanthine[21] [prepared from 4.5 g (23.3 mmol) of 2-acetamidohypoxanthine], the glycosyl chlorides **5** and **6** [prepared from 7.3 g (20 mmol) of **4**], and mercuric acetate (6.5 g; 25 mmol) in 1,2-dichloroethane (250 mL) was kept for 4 days at room temperature. The solution was washed with 20% potassium iodide solution (2 × 100 mL), and water, and then dried. It was evaporated, and the residue separated on silica gel with 25:1 chloroform–methanol as the solvent. The protected nucleosides were eluted from the column in the following order **13a**, **14a**, **12a**, and **11a**.

Compound **13a** was crystallized from chloroform–methanol; yield 1.560 g (15.7%) m.p. 199–201°; n.m.r. ($CDCl_3$): δ 12.44 (brs, 1, NH), 11.26 (s, 1, NH), 8.21 (s, 1, H-8), 7.44–8.18 (2m, 5, aromatic), 6.78 (d, 1, $J_{1',2'}$ 4.5 Hz, H-1′), 5.34 (q, 1, $J_{2',3'}$ 1.5, $J_{3',4'}$ 3.0 Hz, H-3′), 2.44, and 2.20 (2s, 6H, 2 acetyl groups).

Anal. Calc. for $C_{21}H_{20}N_8O_7$ (496.44): C, 50.80; H, 4.06; N, 22.57. Found: C, 51.03; H, 4.16; N, 22.43.

Compound **12a** was obtained as a syrup; yield 120 mg (1.2%); n.m.r. ($CDCl_3$): δ 12.27 (brs, 1, NH), 10.57 (s, 1, NH), 7.33–8.09 (m, 5, aromatic), 5.95 (d, 1, $J_{1',2'}$

3 Hz, H-1'), 5.34 (t, 1, *J* 4 Hz, H-3'), 4.43–5.0 (2m, 3H, H-2',4',5'), 2.31, and 2.05 (2s, 6H, 2 acetyl groups).

Anal. Calc. for $C_{21}H_{20}N_8O_7$: C, 50.80; H, 4.06; N, 22.57. Found: C, 51.36; H, 4.38; N, 22.06.

Compound **11a** was crystallized from chloroform–methanol; yield 760 mg (7.65%); m.p. 126–127°; n.m.r. ($CDCl_3$): δ 12.20 (s, 1, NH), 10.26 (s, 1, NH), 7.40–8.12 (2m, 5, aromatic), 7.88 (s, 1, H-8), 6.30 (d, 1, $J_{1',2'}$ 5.5 Hz, H-1'), 7.76 (t, 1, *J* 4.5 Hz, H-3'), 2.37, and 1.99 (2s, 6H, 2 acetyl groups).

Anal. Calc. for $C_{21}H_{20}N_8O_7$ (496.44): C, 50.80, H, 4.06, N, 22.57. Found: C, 51.04; H, 4.26; N, 22.40.

Compound **14a** was obtained as a syrup; yield 140 mg (1.4%); n.m.r. ($CDCl_3$): δ 12.50 (br.s, 1, NH), 11.04 (s, 1, NH), 8.06 (s, 1, H-8), 7.42–8.20 (2m, 5, aromatic), 6.29 (d, 1, $J_{1',2'}$ 3.2 Hz, H-1'), 5.37 (t, 1, $J_{2',3'} = J_{3',4'} = 3.6$ Hz, H-3'), 4.95 (m, 2, $J_{2'3'}$ 3.6, $J_{3',4'}$ 3.6 $J_{4',5'} \simeq 5$ Hz, H-2',4'), 4.63 (d, 2, $J_{4',5'}$ 5.1 Hz, H-5'), 2.40, and 2.00 (2s, 6, 2 acetyl groups).

Anal. Calc. for $C_{21}H_{20}N_8O_7$ (496.44): C, 50.80; H, 4.06; N, 22.57. Found: C, 51.42, H, 4.48; N, 22.11.

*9-(2-Azido-5-*O*-benzoyl-2-deoxy-β-*D*-arabinofuranosyl)guanine* (**11b**). — Compound **11a** (500 mg; 1 mmol) was heated for 18 h at 45–50° in methanol containing a catalytic amount of sodium methoxide. The solution was carefully made neutral with a small amount of Dowex-50 (H^+) ion-exchange resin. The resin was filtered off and washed with methanol. The filtrate was evaporated and the residue crystallized from water–ethanol to give 270 mg (87%) of **11b**, which decomposed without melting when heated; $\lambda_{max}^{H_2O}$ 253 (ε 11,260) and 273 nm (infl.) (8,010); c.d. λ_{max} (H_2O) 283 ([Θ] −1080) and 247 nm (+6,400); n.m.r. (Me_2SO-d_6):δ 10.64 (br.s, 1, NH), 7.92 (s, 1, H-8), 6.49 (s, 2, NH_2), 6.14 (d, 1, $J_{1',2'}$ 6 Hz, H-1'), 5.99 (d, 1, $J_{3',OH}$ 4 Hz, 3'-OH), 5.13 (t, 1, *J* 5 Hz, 5'-OH), 4.40 (m, 2, H-2',3'), and 3.72 (m, 3, H-4',5').

Anal. Calc. for $C_{10}H_{12}N_8O_4$ (308.26): C, 38.96; H, 3.92; N, 36.35. Found: C, 39.10, H, 4.08; N, 36.03.

*7-(2-Azido-2-deoxy-β-*D*-arabinofuranosyl)guanine* (**13b**). — Compound **13a** (1.2 g; 2.4 mmol) was deprotected as described for **11b**, and was crystallized from methanol; yield 650 mg (87%); it decomposed without melting when heated; $\lambda_{max}^{H_2O}$ 285 (ε 6,700), 241 (infl.) (6,350) and 218 nm (17,330); c.d. λ_{max} (H_2O) 287 nm ([Θ] +6,000); n.m.r. (Me_2SO-d_6): δ 11.8 (br.s, 1, NH), 8.35 (s, 1, H-8), 6.58 (d, 1, $J_{1',2'}$ 6 Hz, H-1'), 6.30 (s, 2, NH_2), 5.99 (d, 1, $J_{3'OH}$ 5 Hz, 3'-OH), 5.24 (t, 1, $J_{5',OH}$ 5 Hz, 5'-OH), 4.50 (q, 1, $J_{1',2'}$ 6, $J_{2',3'}$ 1.5 Hz, H-2'), and 4.22 (m, 1, H-3').

Anal. Calc. for $C_{10}H_{12}N_8O_4$ (308.26): C, 38.96; H, 3.92; N, 36.35. Found: C, 38.81; H, 4.10; N, 36.15.

*7-(2-Azido-2-deoxy-α-*D*-arabinofuranosyl)guanine* (**14b**). — Compound **14a** (100 mg; 0.2 mmol) was deprotected as described for **11b** and crystallized from methanol; yield 45 mg (72%); it decomposed without melting when heated above 220°; $\lambda_{max}^{H_2O}$ 286 (ε 6,350), 241 (infl.) (4,040), and 218 nm (ε 13,870); c.d. λ_{max} (H_2O) 288 nm ([Θ] −3,000); n.m.r. (Me_2SO-d_6): δ 10.9 (br.s, 1, NH), 8.26 (s, 1, H-8), 6.26

(s, 2, NH_2), 5.96 (d, 1, $J_{1',2'}$ 6.5 Hz, H-1'), 4.83 (t, 1, $J_{1',2'} = J_{2',3'} = 6.5$ Hz, H-2'), and 4.22 (m, 2, H-3', H-4').

Anal. Calc. for $C_{10}H_{12}N_8O_4$ (308.26): C, 38.96; H, 3.92; N, 36.35. Found: C, 39.08; H, 4.10; N, 36.08.

9-(2-Amino-2-deoxy-β-D-arabinofuranosyl)guanine (**16**). — Compound **11b** (154 mg; 0.5 mmol) was reduced with hydrogen in 1:1 methanol–water (100 mL) at room temperature and atmospheric pressure for 2 h with 10% Pd–C. The catalyst was filtered off and washed with 10:1 methanol–conc. ammonium hydroxide (50 mL). The filtrate was evaporated and the residue crystallized from methanol; yield 110 mg (81%); m.p. >250 (dec.); $\lambda_{max}^{H_2O}$ 253 (ε 13,400) and 273 nm (infl.) (9,600); n.m.r. (Me_2SO-d_6): δ 7.86 (s, 1, H-8), 6.71 (s, 2, NH_2), and 6.00 (d, 1, $J_{1',2'}$ 6 Hz, H-1').

Anal. Calc. for $C_{10}H_{14}N_6O_4$ (282.21): C, 42.55; H, 5.00; N, 29.76. Found: C, 42.36; H, 5.23; N, 29.38.

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