Nucleic Acid Related Compounds. 88. Efficient Conversions of Ribonucleosides into Their 2′,3′-Anhydro, 2′(and 3′)-Deoxy, 2′,3′-Didehydro-2′,3′-dideoxy, and 2′,3′-Dideoxynucleoside Analogues[1]

Morris J. Robins,* John S. Wilson, Danuta Madej, Nicholas H. Low, Fritz Hansske, and Stanislaw F. Wnuk

Department of Chemistry and Department of Medical Microbiology and Immunology, University of Alberta, Edmonton, Alberta, Canada, and Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602

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Treatment of purine, pyrimidine, and modified purine (antibiotic) ribonucleosides with 2-acetoxy-2-methylpropanoyl (α-acetoxyisobutyryl) bromide in acetonitrile gave mixtures of 2′,3′-bromohydrin acetates with different O5′ substituents. Significant amounts of 5′-unprotected (hydroxyl) bromo acetates were obtained in some cases, and formation of 2′,3′-*O*-isopropylidene derivatives as minor byproducts was detected for the first time. Acid-catalyzed nucleophilic displacement of chloride by bromide occurred with 2-amino-6-chloropurine riboside, but no substitution of fluoride by bromide was detected with 6-amino-2-fluoropurine riboside. Treatment of the trans bromo acetate mixtures obtained from purine-type nucleosides with Dowex 1 × 2 (OH^-) in methanol gave the 2′,3′-anhydro (ribo epoxide) compounds. Radical-mediated hydrogenolytic debromination and deprotection gave 2′- and 3′-deoxynucleosides. Treatment of the bromo acetate mixtures with zinc–copper couple or acetic acid-activated zinc effected reductive elimination, and deprotection gave 2′,3′-didehydro-2′,3′-dideoxy compounds which were hydrogenated to give 2′,3′-dideoxynucleosides. A number of these analogues have potent inhibitory activity against AIDS and hepatitis B viruses. New ^{13}C NMR data for several types of unsaturated-sugar nucleosides are tabulated. These procedures are directly applicable for the preparation of L-didehydro-dideoxy and L-dideoxy nucleoside analogues.

Introduction

The first pyrimidine 2′,3′-dideoxynucleoside, 3′-deoxythymidine, was described by Michelson and Todd in 1955.[2] Robins and Robins reported the first purine dideoxynucleoside, 2′,3′-dideoxyadenosine, in 1964[3] and predicted that "dideoxynucleoside-5′-phosphates should inhibit biosynthesis of DNA by acting as a polynucleotide chain terminator due to the absence of the 3′-hydroxyl group".[3a] This concept that dideoxynucleoside 5′-triphosphates could function as terminators of DNA biosynthesis was verified independently by Cohen[4] and Kornberg[5] and was developed by Sanger into the well-known methodology for DNA (gene) sequencing.[6]

The first syntheses of 2′,3′-didehydro-2′,3′-dideoxynucleosides, which are readily hydrogenated to give 2′,3′-dideoxynucleosides, employed base-promoted elimination of 3′-*O*-sulfonyl esters of 2′-deoxynucleosides.[7,8] Such 2′,3′-unsaturated nucleosides were later obtained from ribonucleosides by treatment with α-acetoxyisobutyryl halides,[9,10] followed by reductive elimination of the resulting 2′(3′)-acetoxy-3′(2′)-halogeno derivatives.[11,12] Treatment of ribonucleoside 2′,3′-*O*-ortho esters with pivalyl chloride/sodium iodide in pyridine gave trans vicinal iodohydrin esters whose derived iodo mesylates were subjected to reductive elimination with iodide to give 2′,3′-unsaturated derivatives.[13] An analogous route employed opening of 2′,3′-orthoacetates with acetyl bromide and reductive elimination of the bromohydrin acetates.[14] Vicinal diols have been converted to bis(xanthates) and subjected to radical-mediated elimination,[15,16] and elimination of vicinal bromo and phenoxy(thiocarbonyl) groups with tributylstannane or zinc–copper couple has been utilized.[17] Corey–Winter treat-

* Author to whom correspondence should be addressed at Brigham Young University.

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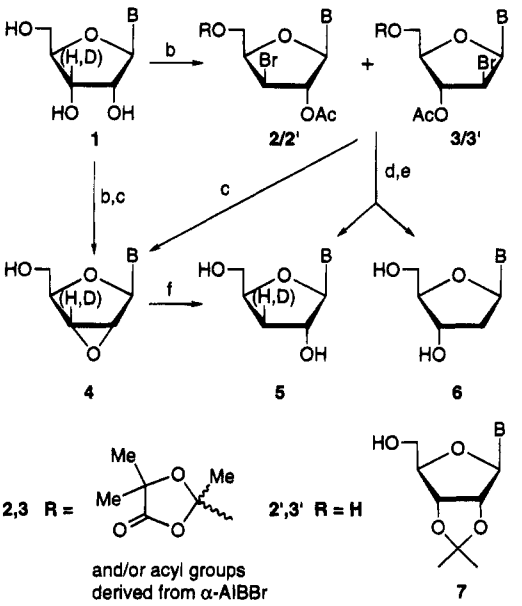
ment of 2′,3′-*O*-thiocarbonyl nucleosides with trialkyl phosphites[16,18] and thermolysis of uridine 2′,3′-ortho esters in acetic anhydride[19] gave 2′,3′-unsaturated derivatives. Barton procedures[20] and modifications[21] have converted nucleoside secondary alcohols to thiono esters which were deoxygenated with tributylstannane to give 2′,3′-dideoxynucleosides.[17a,22]

Treatment of ribonucleosides with α-acetoxyisobutyryl bromide gave 2′,3′ bromohydrin acetates[11,12,23] which have been subjected to reductive elimination with chromium(II) (3′-deoxynucleoside byproducts),[11] electrochemistry[24] (base loss and furan-opened byproducts[24a]), acetic acid-activated zinc,[25] and zinc–copper couple in DMF.[12] A 1994 report employed the Garegg–Samuelsson procedure (I_2/PPh_3/imidazole) to prepare pyrimidine 2′,3′-didehydro-2′,3′-dideoxynucleosides from O5′ protected precursors.[26] This elimination was successful (24–87%) with pyrimidines but failed with a purine (inosine) derivative. Their five-stage process gave 2′,3′-didehydro-3′-deoxythymidine (D4T, 38%) from 5-methyluridine.[26] By comparison the present three-stage methodology[12] gave 2′,3′-didehydro-2′,3′-dideoxyuridine (D4U, 67%) from uridine and the purine 2′,3′-didehydro-2′,3′-dideoxynucleosides D4I (70%) from inosine and D4A (86%) from adenosine. We and others have prepared a number of deoxy and dideoxynucleosides in this manner.[12,14,17b,27] The discovery[28] that dideoxynucleosides have potent activity against human immunodeficiency viruses ignited interest in their synthesis. Chemistry associated with AIDS-related dideoxynucleosides, derivatives, and analogues has been reviewed.[29] Dideoxynucleosides and analogues also were discovered[30] to be effective inhibitors of hepatitis B viruses.

We now report efficient general procedures for transformations of ribonucleosides into sugar-modified derivatives. Reactions were usually conducted at ambient temperature (19–22 °C) with readily available reagents and were easily adapted to base-modified nucleosides. Two 3′-deuterio analogues were prepared to clarify ^1H and ^{13}C NMR assignments, and new ^{13}C NMR data were obtained to characterize several types of unsaturated nucleosides.

Scheme 1[a]



(a) Scheme 2 has structures of B. (b) $(CH_3)_2C(OAc)COBr$/CH_3CN/(H_2O). (c) Dowex 1 × 2 (OH^-)/MeOH. (d) Bu_3SnH/AIBN/toluene/Δ. (e) NH_3/MeOH. (f) $LiEt_3BH$/THF/DMSO.

Results and Discussion

Moffatt and co-workers first applied the "abnormal" Mattocks reaction[9] of diols with 2-acetoxy-2-methylpropanoyl (α-acetoxyisobutyryl, α-AIB) halides to nucleosides.[10,11,23] Their treatment of adenosine with α-AIBCl in hot acetonitrile released adenine (≥20%) by acid-catalyzed glycosyl cleavage.[23a] The more reactive α-AIBBr at ambient temperature caused minimal glycosyl cleavage, but gave the 2′,3′,5′-tris(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl) byproducts (≥20%). Addition of traces of water suppressed this side reaction.

Our treatment of adenosine (**1a**) with α-AIBBr (4 equiv) in "moist" acetonitrile (dry acetonitrile with ~1 equiv of water added) at ambient temperature for 1 h gave mixtures of more slowly migrating (TLC) 9-(2-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (**2′a**) and 9-(3-*O*-acetyl-2-bromo-2-deoxy-β-D-arabinofuranosyl)-adenine (**3′a**) (**2′a**/**3′a**, ~3.2:1) plus more rapidly migrating 5′-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl) derivatives (**2a** and **3a**, Scheme 1). Minor byproducts included 2′,3′-*O*-isopropylideneadenosine (**7a**, ~1% isolated from a larger scale reaction). No **7a** was detected in the starting **1a** (HPLC, mass spectrometry) and no acetone was detected in the α-AIBBr or solvents which indicated that an isopropylidene synthon was generated in situ. Addition of the *measured* amount of water allowed high-yield conversion to the mixture of 2′,3′ bromo acetates without formation of appreciable quantities of the otherwise significantly contaminating 2′,3′,5′-tris(dioxolanon-2-yl) byproduct.

Treatment of the crude mixture containing **2a**/**3a**/**2′a**/**3′a** with Dowex 1 × 2 (OH^-) resin in dry methanol gave 2′,3′-anhydroadenosine (**4a**, 92% recrystallized). This

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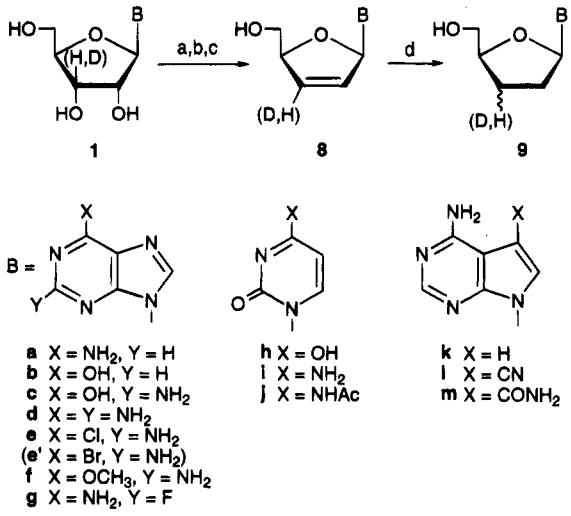
Scheme 2



(a) $(CH_3)_2C(OAc)COBr/CH_3CN/(H_2O)$. (b) Zn-Cu/DMF or Zn/HOAc/DMF. (c) Dowex 1 × 2 (OH^-) or NH_3/MeOH. (d) H_2/Pd•C/EtOH.

confirmed the efficient conversion of **1a** to 2′,3′-*trans* bromo acetates **2a/3a/2′a/3′a** with minimal glycosyl cleavage and byproduct formation. Subjection of 3′-deuterioadenosine[31] (**1a**-3′[^{2}H]) to the same sequence gave 9-(2,3-anhydro-3-deuterio-β-D-ribofuranosyl)adenine (**4a**-3′[^{2}H]) in similar yield. Lithium triethylborohydride (or deuteride) converted **4a** into cordycepin (**5a**) [or **5a**-3′-(*R*)[^{2}H]] (~90%) with no 2′-deoxy isomer detected.[32]

Treatment of the crude mixture containing **2a/3a/2′a/3′a** with Bu_3SnH/AIBN/toluene/Δ followed by deprotection and separation on a Dowex 1 × 2 (OH^-) column gave 2′-deoxyadenosine (**6a**, 16.5%) and 3′-deoxyadenosine (**5a**, 53%). The initial crude mixture was stirred with freshly prepared Zn−Cu couple in DMF for 1 h at ambient temperature. This suspension was filtered, and the concentrated filtrate was treated with NH_3/MeOH and evaporated. Chromatography of the residue on Dowex 1 × 2 (OH^-) and recrystallization gave 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)adenine (**8a**, 81% from **1a**). Reductive elimination (86%) also was performed with zinc dust/HOAc/DMF, with care being taken to avoid glycosyl cleavage during workup. Hydrogenation of **8a** (5% Pd•C/EtOH) gave 2′,3′-dideoxyadenosine **9a** (89%, recrystallized).

Subjection of 3′-deuterioadenosine[31] (**1a**-3′[^{2}H]) to the reductive elimination sequence gave **8a**-3′[^{2}H] (Scheme 2). The lower field vinyl proton signal was absent in ^{1}H NMR spectra of **8a**-3′[^{2}H] and the lower field vinyl carbon signal was diminished in ^{13}C NMR spectra. This demonstrated that the higher field signals resulted from H2′ and C2′ in contrast with usual spectra of saturated nucleosides. Hydrogenation of **8a**-3′[^{2}H] gave **9a**-3′[^{2}H] with reversed peak positions (*i.e.*, peaks for H2′,2″ and C2′ were at lower fields than those for H3′,3″ and C3′ in spectra of **9a**-3′[^{2}H]). Table 1 contains ^{13}C NMR data for various unsaturated and dideoxy nucleosides including those shown in Figure 1.

Treatment of inosine (**1b**) and guanosine (**1c**) by conditions used for **1a** gave poor results, but α-AIBBr (8 equiv) in dry CH_3CN converted **1b** into **2b/3b/2′b/3′b**. Mixtures containing these 2′- or 3′-*trans* bromo acetates were converted into 2′,3′-anhydroinosine [**4b**, 81% from **1b**; Dowex 1 × 2 (OH^-)/MeOH]. Zn−Cu couple effected reductive elimination to give **8b** (70% from **1b**). A similar approach was recently reported to give **8b** (53%) which was hydrogenated to give the anti-HIV agent 2′,3′-dideoxyinosine (**9b**, 51% from **1b**).[27f] Treatment of **1c** with α-AIBBr in dry CH_3CN for 3 h at ambient temperature gave a favorable ratio of the bromo acetates **2c/3c/2′c/3′c** to starting **1c** plus guanine (after workup, UV analysis of the aqueous layer indicated ~30% of guanosine plus guanine, whereas ≤5% of hypoxanthine was observed with inosine). Treatment of the bromo acetates with Zn−Cu couple and deprotection gave the somewhat unstable 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-guanine (**8c**, 47% from **1c**).

Hepatitis B virus in vitro and in vivo (and HIV-1 in vitro) was strongly inhibited by 2,6-diamino-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)purine (2,6-diaminopurine 2′,3′-dideoxyriboside, ddDAPR, **9d**).[30,33] Treatment of 2,6-diamino-9-(β-D-ribofuranosyl)purine[34] (**1d**) with α-AIBBr in acetonitrile resulted in sluggish reaction of the insoluble hydrobromide salts and extensive glycosyl cleavage. Addition of molecular sieves aided formation of mixtures of bromo acetates **2d/3d/2′d/3′d** plus a soluble byproduct. This byproduct did not interfere with reductive elimination (Zn−Cu couple), and 2′,3′-unsaturated **8d** (68%; plus 20% of recovered **1d**) was obtained after deprotection and purification. Hydrogenation of **8d** gave ddDAPR (**9d**, 87%). The 2′,3′-*O*-isopropylidene derivative **7d** (~0.5%) was isolated from a larger scale experiment.

Treatment of 2-amino-6-chloro-9-(β-D-ribofuranosyl)-purine[35] (**1e**) with α-AIBBr (2.5 equiv) in dry acetonitrile gave mixtures with ^{1}H NMR spectra and TLC profiles consistent with the 5′-*O*-(2,5,5-trimethyldioxolan-4-on-2-yl) 2′,3′-bromo acetates **2e/3e** as major products. Small quantities (≤5%) of 2′,3′,5′-tris(dioxolan-2-yl) byproducts and 2-amino-6-chloropurine (~10%) were present. Treatment of this mixture with HOAc-activated zinc gave 2′,3′-unsaturated nucleosides which were cautiously deprotected to give the *presumed* 2-amino-6-chloro-9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)purine (**8e**). Attempts to hydrogenate (5% Pd•C) this material resulted in extensive decomposition. A moderate yield of *presumed* "**9e**" was obtained by hydrogenation of "**8e**" over 10% Rh•Al_2O_3, but significant glycosyl cleavage also occurred.

HPLC analysis of "**9e**" revealed a second product with identical TLC migration in several solvent systems and virtually identical UV and ^{1}H NMR spectra. Its mass spectrum was consistent with 2-amino-6-bromo-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)purine[36] (**9e′**). Thus, treatment of **1e** with α-AIBBr caused partial acid-catalyzed displacement of chloride by bromide. Treatment of **9e** (or **9e/e′**) with methanolic sodium methoxide effected displacement of chloride (or bromide) to give 2-amino-6-methoxy-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)purine (**9f**). Displacement of chloride/bromide from

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Table 1. ^{13}C NMR Spectral Data[a,b]

compound	C-1′	C-2′	C-3′	C-4′	C-5′	C-2	C-4	C-5	C-6	C-8/C-4a	C-7a
4b	82.05	57.73	58.48	81.25	60.79	147.93	145.85	124.06	156.44	138.70	
4k	81.86	57.86	58.75	80.41	61.12	151.90	157.50	100.11	121.76	102.69	149.96
8a	87.93	125.44	134.26	87.80	62.74	152.51	149.10	118.73	155.97	139.02	
8a-3′[^{2}H]	87.95	125.41	–	87.95	62.80	152.66	149.22	118.84	156.10	139.19	
8b	88.19	125.15	134.58	87.94	62.59	145.85	147.90	123.95	156.54	138.38	
8c	88.10	125.66	134.55	87.55	63.19	154.02	151.14	115.56	157.03	135.56	
8d	87.85	125.78	134.33	87.61	63.05	156.11	151.45	113.05	160.33	136.11	
8f[c]	87.85	125.40	134.31	87.31	62.83	159.89	153.79	113.69	160.65	137.64	
8h	89.45	126.08	135.40	87.74	62.59	152.12	163.54	101.88	142.48		
8i	89.72	126.67	133.89	87.00	62.62	155.31	165.60	93.98	141.46		
8k	87.57	126.15	133.63	87.08	63.50	151.71	157.46	99.70	121.10	102.64	149.84
8l[d]	88.13	125.37	134.62	87.95	62.59	153.57	156.90	82.81	132.07	101.00	149.81
8m[e]	87.55	125.38	134.41	87.55	63.70	152.82	158.00	111.08	124.80	100.87	150.60
9a	84.69	31.95	25.95	81.89	63.21	152.61	149.07	119.37	156.25	139.27	
9a-3′[^{2}H]	84.43	31.64	–	81.58	62.90	152.35	148.77	119.07	155.97	139.02	
9d	84.31	31.98	26.07	81.63	63.32	156.23	151.60	113.44	160.33	136.21	
9e	84.03	31.57	25.25	81.89	62.42	153.25	149.20	123.52	159.59	140.85	
9e′	83.76	31.27	24.95	81.61	62.13	151.69	141.55	125.72	159.14	140.37	
9f[f]	83.55	31.50	25.44	81.38	62.63	159.50	153.30	113.79	160.40	137.35	
9g	84.29	31.59	25.50	81.79	62.66	157.34	149.85	114.67	153.60	135.38	
9i	85.66	32.36	24.75	81.36	62.13	155.08	165.72	93.14	141.02		
9l[g]	84.01	31.89	26.03	81.47	64.01	153.27	157.00	83.56	131.89	100.53	149.55
9m[h]	83.56	31.64	26.41	81.30	63.49	152.76	158.05	110.73	124.73	100.91	150.37
A[i,j]	87.93	72.03	69.65	162.18	84.61	152.41	149.48	119.25	156.17	139.99	
B[i,k]	86.48	76.45	74.40	162.00	82.98	152.88	149.59	119.06	156.13	139.90	
C[i,l]	91.23	77.33	99.90	160.98	56.21	152.93	149.08	118.57	156.03	138.33	
D[i,m]	145.78	84.84	73.67	88.28	61.31	153.68	148.23	119.11	156.24	136.86	
E[i,n]	139.96	101.54	108.74	152.81	55.50	153.65	149.10	118.28	156.22	138.67	
F[i,o]	89.27	130.63	130.72	161.77	84.60	150.39	162.84	102.86	139.81		

[a] Chemical shifts (δ) at 75.5 MHz. [b] Proton-decoupled singlets. [c] Peak also at 53.17 (CH_3O). [d] Peak also at δ 115.30 (CN). [e] Peak also at δ 166.32 ($CONH_2$). [f] Peak also at δ 52.94 (CH_3O). [g] Peak also at δ 115.07 (CN). [h] Peak also at δ 166.41 ($CONH_2$). [i] Figure 1 has structures of **A**–**F**. [j] 9-(5-Deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (McCarthy, J. R., Jr.; Robins, R. K.; Robins, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 4993). [k] 9-(5-Deoxy-α-L-*threo*-pent-4-enofuranosyl)adenine (Srivastava, V. K.; Lerner, L. M. *J. Med. Chem.* **1979**, *22*, 24). [l] 9-(3-Deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine.[13b] [m] 9-(2-Deoxy-D-*erythro*-pent-1-enofuranosyl)adenine.[13b] [n] 9-[5-(Hydroxymethyl)furan-2-yl]adenine.[13b] [o] 2-Methylene-5(*R*)-(uracil-1-yl)-2,5-dihydrofuran (Wang, Y.; Hogenkamp, H. P. C. *J. Org. Chem.* **1978**, *43*, 3324).

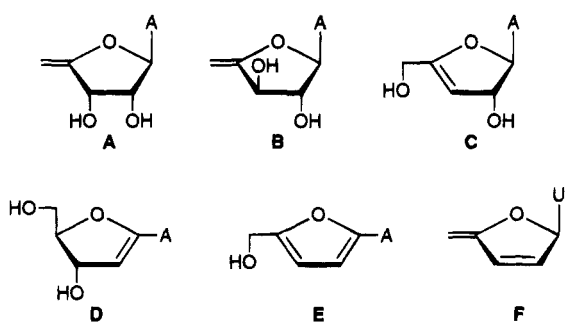

Figure 1. Structures for A and U can be found in Scheme 2: A, **a**; U, **h**.

8e/e′ by ammonia (and methoxide) followed by hydrogenation of the resulting **8d** (and **8f**) gave efficient alternative syntheses of **9d** (and **9f**).[37]

Analogous treatment of 6-amino-2-fluoro-9-(β-D-ribofuranosyl)purine[38] (**1g**) (α-AIBBr in acetonitrile) gave the somewhat unstable 6-amino-9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-2-fluoropurine (**8g**) in good overall yield with no evidence of displacement of 2-fluoro by bromide. Hydrogenation (Pd·C) of **8g** gave 6-amino-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-2-fluoropurine (**9g**, 72% from **1g**).

Treatment of uridine (**1h**) with α-AIBBr in acetonitrile at reflux[11] gave mixtures of 5′-*O*-(2-acetoxy-2-methylpropanoyl)-3′-*O*-acetyl- and 3′,5′-di-*O*-acetyl-2′-bromo-2′-deoxyuridine derivatives. Treatment of the mixture with Zn–Cu couple in NaOAc/AcOH buffer and deprotection gave 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-uracil (**8h**, 50%). Activated zinc dust in DMF and deprotection gave **8h** (67%), but extensive glycosyl cleavage again occurred. The *cis*-3′-*O*-acetyl-2′-bromo products are formed from uridine due to intermediate formation of O2–C2′ anhydro (cyclonucleoside) intermediates which are opened by nucleophilic attack of bromide at C2′ from the α face. Apparently, reductive trans elimination of bromide and uracil (from C2′ and C1′) competes effectively with cis elimination of bromide and acetate (from C2′ and C3′). Appreciable uracil formation also was noted with electrochemical reduction in this series.[24a] The trans–cis (1′-base-2′-bromo-3′-acetoxy) stereoelectronic arrangement in the 2′-bromo-2′-deoxyuridine (ribo) derivatives is absent from the trans 2′(3′)-acetoxy-3′(2′)-bromo (xylo and arabino) eliminations in the purine series.

Cytidine (**1i**) was known to react with α-acyloxyalkanoyl halides to give protected anhydronucleoside derivatives.[39] However, acylation of N4 markedly reduces the nucleophilicity of O2 in cytidine.[40] Treatment of 4-*N*-acetylcytidine[41] (**1j**) with α-AIBBr in "moist" acetonitrile followed by elimination (Zn–Cu couple) and deprotection gave 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)cytosine (**8i**, 70% from **1j**).[12b] Manchand et al. recently observed complex mixtures when **1i** was heated with α-AIBBr, but they also found that **1j** was converted to a mixture of vicinal bromo acetates that underwent reductive elimination (~75%, Zn–Cu couple; 42%, electrochemical) to give **8i**.[27e] Hydrogenation of **8i** gave the anti-

(37) Syntheses of various 2′,3′-dideoxynucleosides by nucleophilic displacements and other methods, inhibition of hepatitis B viruses, and effects on mammalian cells will be reported separately.

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(39) Russell, A. F.; Prystasz, M.; Hamamura, E. K.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 2182.

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HIV agent 2′,3′-dideoxycytidine. Others have treated uridine and 5-methyluridine with acetyl bromide to give 3′-*O*-acetyl-2′-bromo-2′-deoxy (ribo) derivatives.[27c,40] The 5-methyluridine product (97%) was treated with Zn–Cu couple to afford the anti-HIV agent 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (D4T) which was hydrogenated to 3′-deoxythymidine.[27c]

Treatment of the antibiotics tubercidin (**1k**), toyocamycin (**1l**), and sangivamycin (**1m**) by the reaction sequence used with adenosine gave the 2′,3′-unsaturated pyrrolo[2,3-*d*]pyrimidine analogues **8k** (90%), **8l** (81%; purified on silica to avoid hydrolysis of the 5-cyano function[27a]), and **8m** (80%), respectively. Tubercidin (**1k**) was converted to 2′,3′-anhydrotubercidin (**4k**, 91%) by treatment of crude **2/2′k** with Dowex 1 × 2 (OH^-) in dry MeOH, and hydrogenation of **8l** and **8m** gave the 2′,3′-dideoxy analogues **9l** and **9m**. It is noteworthy that essentially exclusive formation of 2′-*O*-acetyl-3′-bromo-3′-deoxy (xylo) products **2/2′k–m** occurs upon treatment of these 7-deaza analogues with α-AIB bromide,[23b,27a,b] whereas mixtures of 3′-bromo (xylo, major) and 2′-bromo (arabino) diastereomers are formed from purine ribonucleosides. The pyrazolo[4,3-*d*]pyrimidine nucleoside formycin, a C-glycosyl analogue with a longer glycosyl bond, gave more nearly equal mixture of 3′-bromo (xylo) and 2′-bromo (arabino) isomers.[23b,27a]

In summary, treatment of pyrimidine, purine, and base-modified nucleosides with α-AIB bromide gives mixtures of 2′,3′-bromohydrin acetates which undergo reductive elimination with zinc–copper couple or zinc powder in the presence of acetic acid. Removal of residual acyl groups with methanolic ammonia completes an efficient three-stage synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides from ribonucleosides with no need for protection/deprotection steps. These purified 2′,3′-didehydro compounds usually undergo hydrogenation readily to give 2′,3′-dideoxynucleosides. The crude bromohydrin acetates also serve as precursors for efficient synthesis of 2′,3′-anhydro (epoxide) intermediates and can be debrominated with tributylstannane to give 2′- and/or 3′-deoxy products. Formation of trace (<1%) quantities of 2′,3′-*O*-isopropylidene byproducts were observed for the first time in reactions of nucleosides with α-AIB bromide. NMR assignments have been clarified by deuterium substitution at C3′ and ^{13}C NMR data for various types of unsaturated-sugar nucleosides have been obtained. These procedures and spectral data are directly applicable for the synthesis of L-didehydro-dideoxy and L-dideoxy analogues of current interest[42] from L-ribonucleosides.

Experimental Section

Uncorrected melting points were determined on a microstage block. UV spectra were determined in H_2O (pH ~7) or other solvents as indicated. ^1H NMR spectra were determined at 200 or 400 MHz and ^{13}C NMR spectra at 50 or 100 MHz in Me_2SO-d_6 (Me_4S internal). High-resolution EI mass spectra were determined at 70 eV with direct sample introduction. Chemicals were reagent grade and solvents were distilled. Pyridine and acetonitrile were dried by reflux over and distillation from CaH_2. DMF was freshly distilled from BaO under reduced pressure for all zinc–copper couple reactions. TLC was performed on silica gel sheets with detection under a UV lamp (254 nm) and/or by spraying with H_2SO_4 and charring. Column chromatography was performed on fine mesh silica gel. "Diffusion crystallization" was performed as described.[13a] Elemental analyses were determined by the Microanalytical Laboratory at the University of Alberta.

Zinc–copper couple was prepared (per mmol of nucleoside substrate) as follows: Zn (3 g, 46 mmol) was suspended in H_2O (20 mL) and stirred while a saturated solution of $CuSO_4 \cdot 5H_2O$ (0.6 g, 2.4 mmol) was added. Stirring was continued for 10 min and the mixture was filtered. Care was taken that the liquid level did not reach the surface of the filter cake (markedly lowered efficiency of the reductive elimination results if the Zn–Cu couple is exposed to air). The filter cake was washed (H_2O and then thoroughly with DMF), and the submerged suspension was transferred immediately to a solution of nucleoside bromo acetates in DMF.

Acetic acid-activated zinc was prepared by stirring zinc dust in HOAc/95% EtOH (1:3) for ~5 min (at which time a granular appearance developed) and washing by decantation (EtOH, 3×; DMF, 2×). It was transferred to the reaction vessel as a submerged suspension in DMF.

General procedures illustrated with specific compounds are indicated in brackets after the bold-faced title of the experiment.

Treatment of Adenosine (1a) with α-AIBBr in "Moist" Acetonitrile To Give Mixtures Containing 2′-*O*-Acetyl-3′-bromo-3′-deoxy (Xylo) and 3′-*O*-Acetyl-2′-bromo-2′-deoxy (Arabino) Derivatives. [Procedure A]. A solution of H_2O/CH_3CN (1:9; 2 mL, 11 mmol) and then α-AIBBr (6 mL, 40 mmol) were added sequentially to a suspension of dried **1a** (2.67 g, 10 mmol) in dry CH_3CN (200 mL) and stirring was continued at ambient temperature. A clear solution resulted after ~45 min (and a fine colorless precipitate began to separate shortly thereafter). After 1 h, saturated $NaHCO_3$/H_2O (~250 mL) was added cautiously and the solution was extracted with EtOAc (2 × 250 mL). The combined organic phase was washed (brine), dried (Na_2SO_4), filtered, and evaporated to give a colorless solid foam. This crude product had a major rapidly migrating band (TLC) of **2a/3a** (≥3:1) and a more slowly migrating minor band (**2′a/3′a**, ~3.2:1; estimated from ^1H NMR spectra). Column chromatography gave **2a/3a** and **2′a/3′a** mixtures with data as reported[23a] plus 2′,3′-*O*-isopropylideneadenosine (**7a**; 20 mg, 0.7%) with TLC, mp, and spectral data identical to those of a commercial sample. The aqueous phase contained adenine (≤3%, UV analysis).

9-(2,3-Anhydro-β-D-ribofuranosyl)adenine (4a). [Procedure B]. Treatment of **1a** (1 mmol) by procedure A gave a colorless foam which was dissolved in dry MeOH (10 mL) and stirred for 1 h with 4 mL of Dowex 1 × 2 (OH^-) resin (previously washed with dry methanol). The resin was filtered and washed well with MeOH. Evaporation of the combined filtrate and crystallization of the residue (EtOH) gave microcrystalline **4a** (230 mg, 92%).

Treatment of **1a** (17.6 g, 66 mmol) by procedures A and B [500 mL of MeOH and 150 mL of Dowex 1 × 2 (OH^-) resin, monitored by TLC until complete] gave **4a** (15.3 g, 93%): mp 180–181 °C dec (lit.[23a] mp 180 °C dec); UV (MeOH) max 258 nm (ε 14 600); MS *m*/*z* 249.0858, calcd for M^+ 249.0862. Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.07; H, 4.46; N, 28.01.

9-(2,3-Anhydro-3-deuterio-β-D-ribofuranosyl)adenine (4a-3′[^{2}H]). Treatment of 3′-deuterioadenosine[31] (**1a**-3′[^{2}H]; 66.8 mg, 0.25 mmol) by procedures A and B gave **4a**-3′[^{2}H] (56 mg, 90%): mp 180 °C dec; MS *m*/*z* 250.0923, calcd for M^+ ($C_{10}H_{10}DN_5O_3$) 250.0925. ^1H NMR spectra of this product corresponded to those of the above **4a**[23a] except for the absence of a doublet at δ 4.22 (H3′) and collapse of the doublet at δ 4.44 to a singlet.

3′-Deoxyadenosine (5a) and 3′-Deuterio-3′-deoxyadenosine {5a-3′(*R*)[^{2}H]}. A solution of $LiEt_3BH$/THF (1 M; 25 mL, 25 mmol) was added dropwise to a cold (~4 °C, ice bath) deoxygenated (N_2, 30 min) solution of **4a** (498 mg, 2 mmol) in dry Me_2SO (50 mL) under N_2. Stirring was continued at ~4 °C for 1 h and at ambient temperature overnight. The reaction

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mixture was cautiously acidified (5% HOAc/H_2O, 50 mL), purged with N_2 for 1 h (fume hood) to remove *pyrophoric* triethylborane, and evaporated. The residue was chromatographed [Dowex 1 × 2 (OH^-); H_2O and 30% MeOH/H_2O] to give **5a** (492 mg, 98% after recrystallization from EtOH): mp 224–225 °C (lit.[23a] mp 225–226 °C); MS *m/z* 251.1018, calcd M^+ ($C_{10}H_{13}N_5O_3$) 251.1018. Reduction of **4a** (249 mg, 1 mmol) with $LiEt_3BD$ gave **5a**-3′(*R*)[^{2}H] (242 mg, 96%): mp 225 °C; MS *m/z* 252.1083, calcd M^+ ($C_{10}H_{12}DN_5O_3$) 252.1081.

3′-Deoxyadenosine (5a) and 2′-Deoxyadenosine (6a). Bu_3SnH (1.08 mL, 1.16 g, 4 mmol) and AIBN (32 mg, 0.2 mmol) were added to a solution of the crude mixture [from treatment of **1a** (2 mmol) by procedure A] in deoxygenated toluene (40 mL) and the solution was refluxed for 2 h and evaporated. The residue was stirred with NH_3/MeOH overnight and the solution was evaporated. The residue was partitioned (Et_2O/H_2O), and the aqueous layer was concentrated to ~5 mL and chromatographed [Dowex 1 × 2 (OH^-); H_2O]. Evaporation of fractions and crystallization of the residue (EtOH) gave **6a** (83 mg, 16.5%): mp 191–192 °C (lit.[21] mp 191–192 °C); UV (H_2O) max 260 nm (ε 15 200); MS *m/z* 251.1017, calcd M^+ 251.1018. Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.21; N, 27.87. Found: C, 47.53; H, 5.20; N, 27.88. Further elution of the column (MeOH/H_2O, 3:7), evaporation of fractions, and crystallization of the residue (EtOH) gave **5a** (265 mg, 53%): mp 224–225 °C (lit.[23a] mp 225–226 °C); UV (H_2O) max 260 nm (ε 14 900); MS *m/z* 251.1015. Anal. Found: C, 47.67; H, 5.20; N, 27.80.

9-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)adenine (8a). [Procedure C]. Zn–Cu couple was added to a solution of the crude mixture [from treatment of **1a** (2 mmol) by procedure A] in DMF (25 mL), and the suspension was stirred for 1 h at ambient temperature and filtered with Celite. The filter cake was washed (DMF), the combined filtrate was evaporated (<30 °C), and the residue was stirred with NH_3/MeOH overnight and evaporated. The residue was chromatographed [Dowex 1 × 2 (OH^-); H_2O], and the product was "diffusion-crystallized" (MeOH/Et_2O) to give **8a** (377 mg, 81%): mp 194–196 °C (lit.[11] mp 194–195 °C); UV (MeOH) max 259 nm (ε 14 900); MS *m/z* 233.0915, calcd for M^+ 233.0912. Anal. Calcd for $C_{10}H_{11}N_5O_2$: C, 51.49; H, 4.75; N, 30.03. Found: C, 51.35; H, 4.75; N, 30.03.

[Procedure D]. Zn dust (10 g, 150 mmol) and HOAc (1 mL) were added to a solution of the crude mixture [from treatment of **1a** (10 mmol) by procedure A] in DMF (50 mL), and the suspension was stirred for 30 min at ambient temperature. Workup as in procedure C gave **8a** (2.01 g, 86% from **1a**): mp 194–196 °C.

9-(2,3-Dideoxy-3-deuterio-β-D-*glycero*-pent-2-enofuranosyl)adenine (8a-3′[^{2}H]). Treatment of 3′-deuterioadenosine[31] (**1a**-3′[^{2}H]; 66.8 mg, 0.25 mmol) by procedures A and C gave **8a**-3′[^{2}H] (44.5 mg, 76%): mp 193–194 °C; MS *m/z* 234.0974, calcd for M^+ ($C_{10}H_{10}DN_5O_2$) 234.0976. ^{1}H NMR spectra of **8a**-3′[^{2}H] had chemical shifts corresponding to those of the above **8a**[11] (H2′ and H3′ assignments are reversed). The peak for H3′ at δ 6.48 was absent, and splittings of the peaks[11] for H1′, H2′, and H4′ were simplified.

9-(2,3-Dideoxy-β-D-*glycero*-pentofuranosyl)adenine (9a). [Procedure E]. Hydrogenation (5% Pd·C, 100 mg) of **8a** (233 mg, 1 mmol) in 98% EtOH (100 mL) at 10 psi for 5 h at ambient temperature followed by filtration, evaporation of the filtrate, and recrystallization of the residue (abs EtOH) gave **9a** (212 mg, 89%): mp 185–187 °C (lit.[3a] mp 184–186 °C); MS *m/z* 235.1067, calcd for M^+ ($C_{10}H_{13}N_5O_2$) 235.1069.

9-(2,3-Dideoxy-3-deuterio-β-D-*glycero*-pentofuranosyl)adenine (9a-3′[^{2}H]). Treatment of **8a**-3′[^{2}H] (15 mg, 0.065 mmol) by procedure E gave **9a**-3′[^{2}H] (12 mg, 80%): MS *m/z* 236.1135, calcd for M^+ ($C_{10}H_{12}DN_5O_2$) 236.1132. ^{1}H NMR spectra of **9a**-3′[^{2}H] corresponded to those of the above **9a** with one-half reduction in integrated intensity (and shifting of the center) of the upfield H3′,3″ multiplet and simplification in the splitting of other peaks.[3b,22b]

Treatment of Inosine (1b) with α-AIBBr in Acetonitrile To Give Mixtures Containing 2′-*O*-Acetyl-3′-bromo-3′-deoxy (Xylo) and 3′-*O*-Acetyl-2′-bromo-2′-deoxy (Arabino) Derivatives. [Procedure F]. α-AIBBr (1.2 mL, 9 mmol) was added to a suspension of dry **1b** (268 mg, 1 mmol) in dry CH_3CN (20 mL), and stirring was continued for 3 h at ambient temperature (a clear solution resulted after ~15 min). Saturated $NaHCO_3$/H_2O (40 mL) was added cautiously, and the solution was extracted (EtOAc, 2 × 50 mL). The combined organic phase was washed (brine), dried (Na_2SO_4), filtered, and evaporated to give a solid foam.[11,27f] TLC migrations and ^{1}H NMR data for this material were similar to those from the parallel reaction with **1a**. The aqueous phase contained hypoxanthine (≤5%, UV analysis).

9-(2,3-Anhydro-β-D-ribofuranosyl)hypoxanthine (4b). The impregnated resin [from treatment of **1b** (1 mmol) by procedure F and then B] was added to a column and washed (MeOH). Product was eluted (30 mM aqueous $Et_3NH{\cdot}HCO_3$), and the eluant was evaporated (<30 °C). The residue was chromatographed (silica gel, 3% MeOH/$CHCl_3$) and crystallized (EtOH) to give **4b** (202 mg, 81%) with ^{1}H NMR data as reported:[43] mp 210 °C dec (lit.[43] mp 226–230 °C dec); UV (MeOH) max 249 nm (ε 12 700); MS *m/z* 250.0697, calcd for M^+ 250.0702. Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.03; N, 22.39. Found: C, 48.12; H, 4.07; N, 22.26.

9-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)hypoxanthine (8b). The impregnated Dowex 1 × 2 (OH^-) column [from treatment of **1b** (2 mmol) by procedure F and then C] was eluted (30 mM aqueous $Et_3NH{\cdot}HCO_3$) and pooled fractions were evaporated. The yellow product was chromatographed (silica gel, 3% MeOH/$CHCl_3$) and "diffusion crystallized" (MeOH/Et_2O) to give **8b** (328 mg, 70%) with ^{1}H NMR data as reported[11] (peak assignments for H2′ and H3′ are reversed): mp >300 °C (lit.[11] mp >300 °C); UV (MeOH) max 250 nm (ε 12 500); MS *m/z* 234.0757, calcd for M^+ 234.0753. Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.02; H, 4.31; N, 23.86.

9-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)guanine (8c). Treatment of **1c** (283 mg, 1 mmol) by procedure F (suspension remained throughout the 3 h reaction time) gave a mixture that was treated by procedure C (and worked up, purified, and crystallized as described for **8b**) to give **8c** (117 mg, 47%) with ^{1}H NMR data as reported:[16] mp >300 °C (lit.[16] mp >250 °C); UV (H_2O) max 253 nm (ε 14 000); MS *m/z* 249.0852, calcd for M^+ 249.0862. Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 47.76; H, 4.41; N, 27.58.

2,6-Diamino-9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)purine (8d). Treatment of dried **1d**[34] (282 mg, 1 mmol) by procedure A (with addition of powdered, dried 4 Å molecular sieves, 2 h at ambient temperature) and procedure C gave **8d** (169 mg, 68%): mp 168–169 °C; UV (MeOH) max 282, 256 nm (ε 9500, 8600), min 266, 237 nm (ε 6900, 5300); ^{1}H NMR δ 3.54 (m, 2, H5′,5″), 4.83 (m, 1, H4′), 5.05 (t, 1, OH5′), 5.77 (br s, 2, 6-NH_2), 6.08 (m, 1, H2′), 6.42 (m, 1, H3′), 6.70 (br s, 2, 2-NH_2), 6.73 (m, 1, H1′), 7.72 (s, 1, H8); MS *m/z* 248.1020, calcd for M^+ 248.1022. Anal. Calcd for $C_{10}H_{12}N_6O_2$: C, 48.38; H, 4.87; N, 33.85. Found: C, 48.38, H, 4.54; N, 33.87. Further elution of the column with MeOH/H_2O (3:2) recovered **1d** (57 mg, 20%). [Byproduct **7d** (216 mg, 0.5%) was isolated from a 15 mmol reaction: mp 242–244 °C; MS *m/z* 322.1391, calcd for M^+ ($C_{13}H_{18}N_6O_4$) 322.1390.]

2,6-Diamino-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-purine (9d). Hydrogenation of **8d** (485 mg, 1.95 mmol) by procedure E (20 h) gave a product that was filtered through a short column of Dowex 1 × 2 (OH^-) (prewashed with MeOH, eluted with MeOH until no product remained). Evaporation of the eluate and recrystallization of the residue (MeOH) gave **9d** (424 mg, 87%): mp 194–195 °C; UV (MeOH) max 282, 256 nm (ε 9500, 8400), min 266, 237 nm (ε 6400, 5400); ^{1}H NMR δ 2.02 (m, 2, H3′,3″), 2.30 (m, 2, H2′,2″), 3.54 (m, 2, H5′,5″), 4.05 (m, 1, H4′), 5.05 (t, 1, OH5′), 5.74 (br s, 2, 6-NH_2), 6.01 ("t", 1, H1′), 6.68 (br s, 2, 2-NH_2), 7.92 (s, 1, H8); MS *m/z* 250.1180, calcd for M^+ 250.1178. Anal. Calcd for $C_{10}H_{14}N_6O_2{\cdot}0.5H_2O$: C, 46.33; H, 5.83; N, 32.41. Found: C, 46.70; H, 5.50; N, 32.40.

2-Amino-6-bromo/chloro-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)purine (9e′/9e). Treatment of finely powdered **1e**[35] (5.0 g, 16.6 mmol) by procedure F [α-AIBBr (60 mL,

(43) Lichtenthaler, F. W.; Kitahara, K.; Strobel, K. *Synthesis* **1974**, 860.

40 mmol), 1 h, ambient temperature (solution obtained after ~45 min)] and procedure D (with activated Zn) gave a suspension that was neutralized with 1 M KOH/H_2O (10 mL) and filtered. The filtrate was evaporated, the residue was dissolved in MeOH (20 mL), and saturated K_2CO_3/H_2O (100 mL) was added. The suspension was stirred for 2 h and extracted (EtOAc, 5 × 50 mL). The aqueous phase contained the 2-amino-6-bromo/chloropurine chromophore (≤10%, UV analysis). The combined organic phase was dried (Na_2SO_4) and evaporated. Crystallization of the residue (H_2O) gave **8e/8e′** (3.1 g, ~60%) as a granular solid with ^1H NMR data as reported[44] for **8e**: **8e/8e′** mp 113 °C dec (lit.[44] **8e** mp 167 °C). Hydrogenation of **8e/8e′** (536 mg, ~2 mmol) in MeOH (200 mL) at atmospheric pressure over 10% Rh·Al_2O_3 for 5 h resulted in significant glycosyl cleavage (≥25%, TLC). The suspension was filtered with Celite and the filtrate was evaporated. Column chromatography of the residue (silica gel, 5% MeOH/$CHCl_3$) and crystallization of the product (toluene/THF) gave **9e/9e′** (270 mg, ~50%) as needle clusters with ^1H NMR data as reported for **9e**.[44] Preparative reversed-phase HPLC [Whatman C_{18} column (1 × 25 cm), MeCN/H_2O (12.5:87.5), 2 mL/min] gave partial separation of **9e** and **9e′**, and the leading and trailing fractions were passed through the column a second time to give clean products. A sample of **9e** had mp 139–141 °C (lit.[44] mp 129–133 °C; lit.[45] mp 139–141 °C); MS *m/z* 271.0654 (3, M^+ [^{37}Cl] 271.0651), 269.0678 (9, M^+ [^{35}Cl] 269.0680). Anal. Calcd for $C_{10}H_{12}ClN_5O_2$: C, 44.60; H, 4.50; N, 26.03. Found: C, 44.64; H, 4.76; N, 25.72. ^1H NMR and UV spectra of **9e** and amorphous **9e′** [36] were virtually identical: MS *m/z* 315.0149 (14, M^+ [^{81}Br] 315.0154), 313.0023 (16, M^+ [^{79}Br] 313.0174).

2-Amino-6-methoxy-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)purine (9f). A solution of **9e/9e′** (88 mg, ~0.33 mmol) in NaOMe/MeOH [prepared from Na (10 mg, 0.43 mmol) and MeOH (2 mL)] was stirred at ambient temperature for 24 h and evaporated. The residue was chromatographed [Dowex 1 × 2 (OH^-); H_2O] and crystallized (H_2O) to give **9f** (52 mg, 59%): mp 76–78 °C; UV (MeOH) max 282, 248 nm (ε 9200, 9500), min 261, 226 nm (ε 4600, 4000); ^1H NMR δ 2.00 (m, 2, H3′,3″), 2.33 (m, 2, H2′,2″), 3.53 (m, 2, H5′,5″), 3.94 (s, 3, OCH_3), 4.06 (m, 1, H4′), 4.94 (t, $J_{OH\text{-}5',5''}$ = 5.5 Hz, 1, OH5′), 6.07 ("t", $J_{1'\text{-}2',2''}$ ~6.4 Hz, 1, H1′), 6.43 (br s, 2, NH_2), 8.10 (s, 1, H8); MS *m/z* 265.1171, calcd for M^+ 265.1172. Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot 0.5H_2O$: C, 48.17; H, 5.88; N, 25.53. Found C, 48.48; H, 5.95; N, 25.76.

6-Amino-2-fluoro-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)purine (9g). Treatment of finely powdered **1g**[38] (4.75 g, 16.7 mmol) by procedure F [α-AIBBr (60 mL, 50 mmol); 2 h, ambient temperature] gave a mixture of bromo acetates (7.27 g). A suspension of this material (1.9 g) and activated Zn–Cu (the usual Zn–Cu couple filter cake was washed with 0.5% HOAc/H_2O) in DMF (34 mL) was stirred for 1 h at ambient temperature and filtered, and the filtrate was evaporated. The residue was deprotected (NaOMe/MeOH), and the crude **8g** was filtered rapidly through a silica column (glycosyl cleavage occurred on silica gel). The purified material was dissolved in MeOH (5 mL) and hydrogenated at atmospheric pressure (5% Pd·C, 50 mg) overnight. The mixture was filtered and the filtrate was evaporated to give **9g** (500 mg, 72% from **1g**) with ^1H NMR data as reported:[44] UV (MeOH) max 261 nm (ε 10 800); mp 199–200 °C (lit.[44] mp 200–202 °C); MS *m/z* 253.0971, calcd for M^+ 253.0975. Anal. Calcd for $C_{10}H_{12}FN_5O_2$: C, 47.43; H, 4.78; N, 27.66. Found: C, 47.10; H, 4.59; N, 27.50.

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-uracil (8h). Treatment of **1h** (488 mg, 2 mmol) in dry CH_3CN (45 mL) by a modified procedure F [α-AIBBr (1.2 mL, 6 mmol) heated at reflux for 3 h], then procedure D [Zn dust (2g, 30 mmol), HOAc (0.5 mL), dry DMF (30 mL); 2 h at ambient temperature], and deprotection (NH_3/MeOH) gave a residue that was chromatographed (silica gel, 5% MeOH/$CHCl_3$) and "diffusion crystallized" (EtOH/Et_2O) to give **8h** (276 mg, 67%) with ^1H NMR data as reported:[18,44] mp 156–158 °C (lit.[11] mp 154.5–155.5 °C); UV (H_2O) max 261 nm (ε 9700); MS *m/z* 210.0637, calcd for M^+ 210.0641. Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.19; H, 4.78; N, 13.22.

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)cytosine (8i). Treatment of **1j**[41] (570 mg, 2 mmol) by procedures A and C gave a residue that was "diffusion crystallized" (MeOH/Et_2O) to give **8i** (294 mg, 70%) with ^1H NMR data as reported:[16] mp 162–163 °C (lit.[16] mp 167–169 °C); UV max 271 nm (ε 8800); MS *m/z* 210.0884, calcd for MH^+ 210.0879. Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.40; H, 5.73; N, 19.91.

4-Amino-7-(2,3-anhydro-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (4k). Treatment of **1k** (266 mg, 1 mmol) by procedures A and B gave a residue that was "diffusion crystallized" (95% EtOH/Et_2O) to give **4k** (255 mg, 91%) with ^1H NMR data as reported:[23b] mp 170–172 °C (lit.[23b] mp 145–176 °C dec); UV (MeOH) max 271 nm (ε 12 100); MS *m/z* 248.0911, calcd for M^+ 248.0909. Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.86; N, 22.57. Found: C, 53.02; H, 4.80; N, 22.51.

4-Amino-7-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)pyrrolo[2,3-*d*]pyrimidine (8k). Treatment of **1k** (1 mmol) by procedures A and C gave **8k** (209 mg, 90%) with ^1H NMR data as reported:[27b] mp 210–211 °C (lit.[27b] mp 204–205 °C); UV (EtOH) max 270 nm (ε 12 000); MS *m/z* 232.0965, calcd for M^+ 232.0960. Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.13. Found: C, 56.74; H, 5.29; N, 24.07.

4-Amino-5-cyano-7-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)pyrrolo[2,3-*d*]pyrimidine (8l). Treatment of **1l** (291 mg, 1 mmol) by procedures A and C (to deprotection with NH_3/MeOH) gave a residue that was chromatographed (silica gel, 3% MeOH/$CHCl_3$) and "diffusion crystallized" (EtOH/Et_2O) to give **8l** (206 mg, 81%) with ^1H NMR data as reported:[27b] mp 192–194 °C (lit.[27b] 201–202 °C); UV (MeOH) max 278 nm (ε 15 300); MS *m/z* 257.0915, calcd for M^+ 257.0913. Anal. Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 56.17; H, 4.29; N, 27.06.

4-Amino-5-cyano-7-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (9l). Hydrogenation of **8l** (129 mg, 0.5 mmol) by procedure E gave a residue that was "diffusion crystallized" (EtOH/Et_2O) to give **9l** (115 mg, 89%) with ^1H NMR data as reported:[27b] mp 185–186 °C (lit.[27b] 197–197.5 °C); UV (MeOH) max 278 nm (ε 15 600); MS *m/z* 259.1063, calcd for M^+ 259.1069. Anal. Calcd for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.36; H, 5.09; N, 26.84.

4-Amino-5-carboxamido-7-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)pyrrolo[2,3-*d*]pyrimidine (8m). Treatment of **1m** (309 mg, 1 mmol) by procedures A and C gave **8m** (220 mg, 80%) with ^1H NMR data as reported:[27b] mp ~220 °C dec (lit.[27b] 240 °C dec); UV (MeOH) max 278 nm (ε 12 500); MS *m/z* 275.1020, calcd for M^+ 275.1018. Anal. Calcd for $C_{12}H_{13}N_5O_3$: C, 52.36; H, 4.76; N, 25.44. Found: C, 52.09; H, 4.75; N, 25.26.

4-Amino-5-carboxamido-7-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (9m). Hydrogenation of **8m** (138 mg, 0.5 mmol) by procedure E gave a residue that was "diffusion crystallized" (EtOH/Et_2O) to give **9m** (128 mg, 92%) with ^1H NMR data as reported:[27b] mp 205–206 °C (lit.[27b] 207–208 °C); UV (MeOH) max 279 nm (ε 12 700); MS *m/z* 277.1177, calcd for M^+ 277.1175. Anal. Calcd for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 51.75; H, 5.41; N, 25.11.

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