Pergamon

Tetrahedron, Vol. 53, No. 2, pp. 447-456, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(96)01035-6

Nucleic Acid Related Compounds. 94. Remarkably High Stereoselective Reductions of 2'- and 3'-Ketonucleoside Derivatives To Give Arabino, Ribo, and Xylofuranosyl Nucleosides with Hydrogen Isotopes at C2' and C3'[1a]

Morris J. Robins,* Sanchita Sarker, Vicente Samano,[1b] and Stanislaw F. Wnuk

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602-5700

Abstract: Oxidation of 2',5'- and 3',5'-*O*-(*tert*-butyldimethylsilyl)-protected ribonucleosides gave the corresponding 3'-keto and 2'-keto derivatives, whose complete oxidation was assayed by total release of the heterocyclic base upon treatment with tetrabutylammonium fluoride/THF. Treatment of the protected ketones with sodium triacetoxyborohydride (generated in situ from sodium borohydride and acetic acid) in acetic acid resulted in hydride delivery at the α face with high stereoselectivity. The xylo/ribo (~49:1) and arabino/ribo (~49:1) diastereomers, respectively, were obtained in good to high overall yields upon deprotection. Selective removal of the TBDMS group from O5' (trifluoroacetic acid/water, 9:1, 0 °C) and treatment of these 5'-hydroxy-(3'- and 2')-ketones with sodium triacetoxyborohydride effected remarkably selective delivery of hydride at the β face. Deprotection gave the ribo/xylo (~99:1) and ribo/arabino (~99:1) nucleosides in high yields. Comparable results were obtained with sodium borodeuteride in acetic acid to give the four 2'[^{2}H] and 3'[^{2}H] arabino, ribo, and xylo isotopomers with >95% incorporation of deuterium. Development of efficient procedures and comparisons with previous methods are discussed.

Introduction

Ketonucleoside derivatives are useful intermediates for the synthesis of a variety of sugar-modified nucleosides.[2] They have been employed to change configurations[3-5] at C2' and C3', and to synthesize deuterio-labelled analogues from the parent ribonucleosides via oxidation-reduction sequences.[3,5-7] Hydride reductions of protected 2'- or 3'-ketonucleosides give epimeric mixtures of the corresponding nucleosides with stereoselectivities enhanced by proximity to the heterocyclic base.[3,8] Attack by hydride occurs predominantly at the α face of the sugar ring (trans to the base) with greater stereodifferentiation at the adjacent 2'-position. Thus, reductions of 2'-ketonucleoside derivatives usually give 80-95% of the arabino epimers, whereas lower ratios of xylo products are obtained from the analogous 3'-ketonucleosides.[3,8]

Ketonucleosides have usually been prepared by oxidation of suitably protected nucleosides with the Pfitzner-Moffatt[9] (DMSO/DCC),[4a,8] Garegg-Samuelsson[10] (CrO_3/pyridine/Ac_2O),[3] Swern[11] (DMSO/oxalyl

chloride),[6,12] Dess-Martin[13] (12-I-5-periodinane)[4d,5,14,15] and DMSO/Ac_2O reagents.[3,4d,8a] Uracil ketonucleoside derivatives have been deprotected and the 2'(and 3')-ketouridines have been isolated.[8a] However, protected purine 2'-ketonucleosides exist as equilibrium mixtures of ketones and ketone hydrates, and even the relatively stable 3'-ketoadenosine derivatives are transformed into a labile 3'-ketonucleoside upon deprotection.[8b] The 3'-*O*-pyruvoyl ester of 5'-*O*-tritylthymine was irradiated to provide the first isolated pyrimidine 2'-deoxy-3'-ketofuranosyl nucleoside.[16] A pyrrolopyrimidine 2'-deoxynucleoside derivative was oxidized under standard conditions to give its relatively stable 3'-keto product,[4b] but the first isolated purine 2'-deoxy-3'-ketonucleoside was prepared by careful Dess-Martin periodinane oxidation of 5'-*O*-(*tert*-butyldiphenylsilyl)-2'-deoxyadenosine.[14]

Reduction of 2'-keto[adenosine and 7-deazaadenosine (tubercidin)] derivatives with sodium borodeuteride gave the 2'-deuterio arabino precursors whose ribo epimers were then prepared via triflation and S_N2 inversion.[6] Several 2'(*S*)-[^{2}H]-2'-deoxynucleosides[7b] and other 2'-deuterionucleosides[17] (from the deuterioribose) were recently prepared by oxidation/reduction sequences. Addition of organocerium reagents to 5'-*O*-protected-2'-deoxy-3'-ketonucleosides occured at the α face to give 2'-deoxy-3'-C-substituted threo analogues.[15] However, treatment of selectively O5' deprotected[5] 3'-keto(uridine and adenosine) derivatives with organometallic reagents resulted in addition at the β face to give the 3'-C-substituted ribo epimers.[18]

We now report expanded studies on the stereocontrolled synthesis[5] of arabino and ribo epimers (and their 2'[^{2}H] isotopomers) by reduction of 2'-ketonucleoside derivatives with sodium triacetoxyboro(hydride and deuteride). The ribo and xylo diastereomers (and their 3'[^{2}H] isotopomers) were prepared from the analogous 3'-ketonucleoside derivatives.

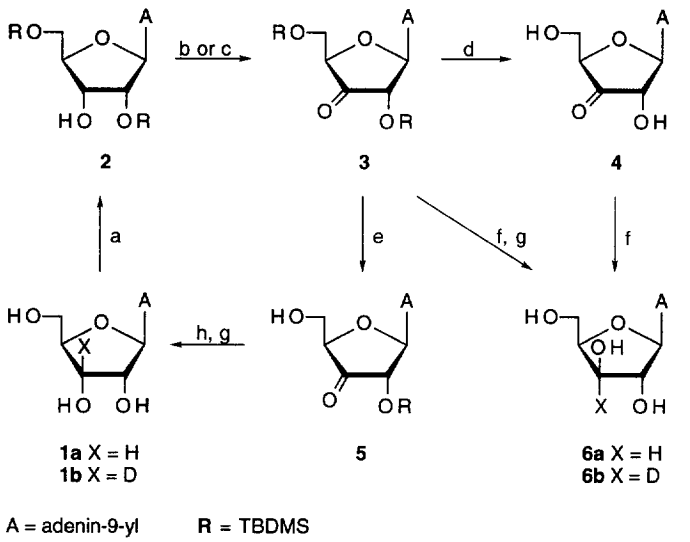
Results and Discussion

Adenosine (**1a**) was treated with *tert*-butyldimethylsilyl (TBDMS) chloride to give the 2',5'- (**2**) and 3',5'-bis-*O*-TBDMS-adenosine (**7a**) derivatives.[3,19] Oxidation of **2** with CrO_3/pyridine/Ac_2O or the Dess-Martin 12-I-5 periodinane (D-M-P) reagent[13] [1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one] gave crystalline 2',5'-bis-*O*-TBDMS-3'-ketoadenosine (**3**) in high yield[3,5] (Scheme 1). The D-M-P oxidation gave cleaner conversion of **2** → **3**, and isolation of the 2-iodobenzoic acid byproducts from **3** was achieved readily. However, the D-M-P reagent is sensitive to moisture and must be prepared with care in order to obtain a fully active oxidant.[13b,c] In some instances we and others[15] have observed incomplete oxidations and lower yields.

Treatment of **3** with excess sodium triacetoxyborohydride[20] (generated in situ from $NaBH_4$ and AcOH at <15 °C) resulted in predominant delivery of hydride at the α face to give the ribo and xylo diastereomers **1a/6a** (1:49, 95%) plus traces of adenine after deprotection (NH_4F/MeOH[21] or TBAF/THF). Analogous reduction of **3** with sodium triacetoxyborodeuteride gave 9-(3-deuterio-β-D-xylofuranosyl)adenine (**6b**, diastereoselectivity 49:1). Discrepencies in the **1a**:**6a** ratios in our laboratory,[3] and likely in literature values,[4a,8b] can result from unoxidized **2** carried forward with ketone **3** into the reduction step. The extent of oxidation of the 3'-hydroxyl to the 3'-keto function can be assayed by treatment of the ketone products with TBAF/THF. High quality **3**

underwent complete decomposition with release of adenine [*i.e.*, no adenosine (**1a**) was detected]. The purity of other ketones was routinely assayed by this procedure (*vide infra*). Subjection of these products to a second oxidation treatment was sometimes required to provide ketones that were uncontaminated with the original ribonucleoside.

Scheme 1[a]



[a] (a) TBDMSCl/pyridine. (b) CrO_3/Ac_2O/pyridine/CH_2Cl_2. (c) Dess-Martin periodinane/CH_2Cl_2. (d) TFA/H_2O/ambient temperature/20 h. (e) TFA/H_2O/1h/~0 °C. (f) $NaBH_4$ or $NaBD_4$/AcOH/~13 °C/ 48 h. (g) NH_4F/MeOH or Bu_4NF/THF. (h) $NaBH_4$ or $NaBD_4$/AcOH/ambient temperature/2 h.

It was known that primary silyloxy groups were cleaved more readily than their secondary counterparts under acidic conditions (80% AcOH/H_2O).[19a] We found that treatment of **3** with aqueous trifluroacetic acid (TFA/H_2O; 9:1) at 0 °C effected quantitative removal of the 5'-*O*- TBDMS group to give 2'-*O*-TBDMS-3'-ketoadenosine (**5**).[5] In remarkable contrast to the α face stereoselectivity with **3**, immediate treatment of the somewhat unstable β-hydroxy ketone **5** with $NaBH(OAc)_3$ (2 equiv.) at ambient temperature for 2 h resulted in stereoselective delivery of hydride from the β face to give adenosine (**1a**)/**6a** (99.5:0.5, RP-HPLC) in high yield after deprotection. Reduction of **5** with $NaBD(OAc)_3$ gave 3'-deuterioadenosine (**1b**, 93%) with <5% 3'[^{1}H]-incorporation (^{1}H NMR), which confirmed minimal exchange of ^{2}H in the borodeuteride reagent and its presumed O5'-ligand exchange intermediate. Sodium and tetramethylammonium triacetoxyborohydride have been used for chemoselective reduction of aldehydes[20,22] and for production of stereodirected diols from cyclic[23] and acylic[22,24] β-hydroxy ketones.

Treatment of **3** with TFA/H_2O at ambient temperature for 20 h gave mixtures of 2'-*O*-TBMDS-3'-ketoadenosine (**5**) and the labile[8b] 3'-ketoadenosine (**4**) plus adenine (**4/5**/adenine, ~2:1:2; TLC). This mixture

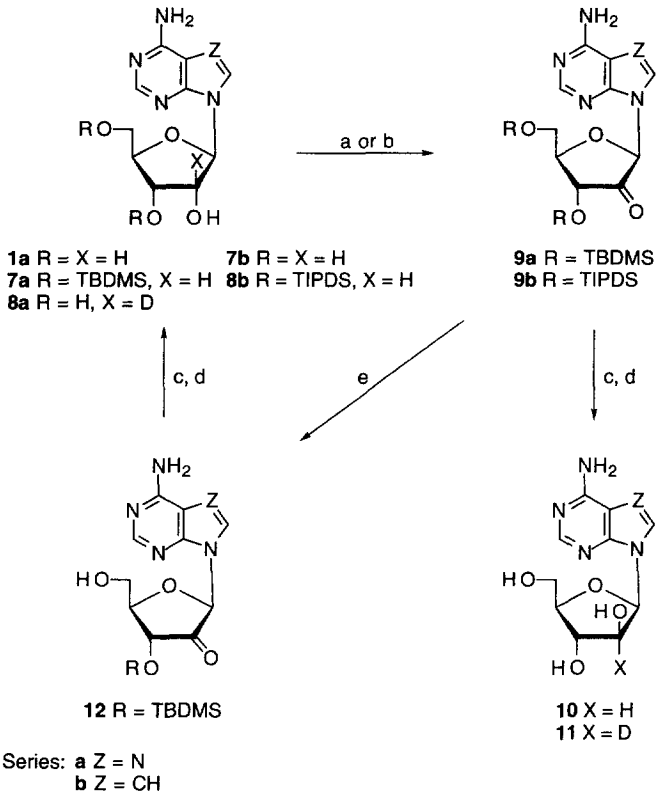
was treated immediately with $NaBH(OAc)_3$ and worked up. The organic layer contained products from the reduction of **5** (**1a** was the major component after deprotection). The water layer contained **1a/6a** (45:55, RP-HPLC) from the reduction of **4**, which might indicate competition between the directed intramolecular delivery of hydride involving O5' (β-hydroxy ketone) and O2' (α-hydroxy ketone). However, the influence of steric effects that promote attack from the α face (as observed with the 2',5'-*O*-diprotected 3'-ketone **3**) might contribute to the formation of **6a** from the deprotected 3'-ketone **4**. Stereodirected reductions of α-hydroxy ketones with triacetoxyborohydride reagents also are known,[25] but the reduction of a β-hydroxy ketone in the presence of an α-hydroxy ketone predominated in a complementary study.[23b] Reduction of 3'-ketoadenosine (**4**) with $NaBD_4/H_2O$ was reported to give a mixture of **1b/6b** (22:78).[8b]

Oxidation of 3',5'-bis-*O*-TBDMS-adenosine (**7a**) with CrO_3/pyridine/Ac_2O or the D-M-P reagent gave 9-(3,5-bis-*O*-TBDMS-β-D-*erythro*-pentofuran-3-ulosyl)adenine (**9a**) in high yield (Scheme 2). Reductions of protected 2'-ketoadenosine derivatives with $NaBH_4$ have been reported to give the arabino/ribo epimers with ratios of 96:6[3] and 75:25,[6] and reduction with $NaBD_4$ afforded the partially 2'-deuterated ribo epimers.[3,6] Such variable results are indicative of incomplete oxidation of the protected starting materials, since these ribonucleoside derivatives can be carried through the reaction sequences to give unchanged adenosine in the deprotected products. Several samples of homogeneous **9a** (complete oxidation of **7a** → **9a** was confirmed by total decomposition of a portion of this **9a** to adenine with TBAF/THF) were reduced [$NaBH(OAc)_3$] and deprotected (TBAF/THF). These experiments gave repeatable mixture of arabino (**10a**)/ribo (**1a**) epimers (49:1). Analogous treatment of **9a** with $NaBD(OAc)_3$ afforded the 2'[^{2}H]-arabino (**11a**)/ribo (**8a**) epimers (49:1, 71%) with >95% incorporation of deuterium.

Selective removal of the 5'-*O*-TBDMS group from **9a** gave 3'-*O*-TBDMS-2'-ketoadenosine (**12a**) as a colorless powder (97%). The O5'-directed reduction [$NaBH(OAc)_3$] of this γ-hydroxy ketone **12a** followed by deprotection (TBAF/THF) gave adenosine (**1a**, 79%). RP-HPLC indicated that this **1a** contained ~1% of the arabino epimer **10a**. Stereocontrolled reductions of γ-hydroxy ketones with $NaBH(OAc)_3$ have been reported,[26] including transannular delivery with a borohydride reagent in a synthesis of 13-*epi*-taxol.[27] Analogous treatment of **12a** with $NaBD(OAc)_3$ gave 2'[^{2}H]-adenosine (**8a**, 86%).

Our directed-transfer results compare favorably with Perlman's route[6] in which 2'[^{2}H]-adenosine (**8a**) was prepared from the 2'[^{2}H]-arabino epimer **11a**. His **8a** was obtained by reduction of a 2'-ketoadenosine derivative with $NaBD_4$, followed by triflation of the resulting arabino O2', displacement of 2'-triflate with cesium propionate, and deprotection. His 2'[^{2}H]-**8a** had high deuterium content, but it was obtained in a lower overall yield. Our approach also provides an efficient direct alternative to the coupling synthesis beginning with 2[^{2}H]-ribose.[17] Thus, our present oxidations of selectively protected adenosine derivatives followed by stereocontrolled reductions of the 2'- and 3'-ketone derivatives provide convenient access to the 2'[^{2}H]- and 3'[^{2}H]-adenosines, and their arabino and xylo diastereomers, with high deuterium incorporation and generally in high yields.

Scheme 2[a]



[a] (a) CrO_3/Ac_2O/pyridine/CH_2Cl_2. (b) Dess-Martin periodinane/CH_2Cl_2. (c) $NaBH_4$ or $NaBD_4$/AcOH/~13 °C/72 h. (d) NH_4F/MeOH or Bu_4NF/THF. (e) TFA/H_2O/~0 °C/2 h.

Perlman recently noted[6] that Swern oxidation of the tubercidin derivative **8b**[28] followed by reduction with $NaBD_4$ gave an arabino/ribo (85:15) mixture in which the arabino epimer was deuteriated at C2', but the ribo epimer was only partially C2'-deuteriated.[6] This is consistent with our observations (*vide supra*) that incomplete oxidation results in quantities of starting material (2'[^{1}H]) being carried to the product stage. We have successfully applied our oxidation/reduction sequence to the inversion of stereochemistry at C2' of tubercidin (**7b**). Oxidation of **8b** (CrO_3/pyridine/Ac_2O) gave the 2'-ketone **9b** (complete oxidation was verified by total decomposition of a sample of **9b** with TBAF/THF to give 4-aminopyrrolo[2,3-*d*]pyrimidine). Treatment of **9b** with sodium triacetoxyborohydride (or deuteride) and deprotection gave the arabino epimers **10b** or 2'[^{2}H]-**11b** (each contained ~3% of the ribo epimers **7b** or 2'[^{2}H]-**7b**). This confirms that the *complete* oxidation of suitably protected ribonucleosides followed by stereocontrolled reduction with borohydride reagents affords an efficient route for the synthesis of arabino, ribo, and xylo diastereomers. High levels of deuterium can be incorporated at any of the four regio/stereo positions on C2' and C3'.

Experimental

^{1}H NMR spectra (Me_2SO-d_6 unless otherwise noted) were recorded at 200 MHz. 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. Isocratic analytical RP-HPLC was performed with a Dynamax C_{18} reversed-phase column (CH_3CN/H_2O, 4.5:95.5; 1 mL/min). Adenosine (**1a**) was treated with TBDMSCl as reported[19] to give **2** (60%) and **7a** (29%) [separated by gradient flash chromatography (50% hexanes/EtOAc → EtOAc)].

9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuran-3-ulosyl]adenine (3). ***Procedure A.*** Pyridine (1.90 mL, 1.85 g, 24.2 mmol) and Ac_2O (1.1 mL, 1.2 g, 12.1 mmol) were added consecutively to an ice-cold suspension of CrO_3 (1.2 g, 12.1 mmol) in CH_2Cl_2 (30 mL), and stirring at ambient temperature under an Ar atmosphere was continued until a homogeneous solution was obtained (~10 min). A solution of **2** (3.0 g, 6.0 mmol) in CH_2Cl_2 (25 mL) was added dropwise via a syringe, and stirring was continued for 2h. The reaction mixture was poured into cold EtOAc and the resulting precipitate was filtered (glass microfibre filter). The filtrate was concentrated and flash chromatographed (EtOAc/hexanes, 1:1) to give **3** (2.35g, 78%) as a colorless powder with reported properties.[3] {One batch by procedure A, assayed by procedure C, showed a mixture of adenine (t_R = 8.2 min; from decomposition of ketone **3**) and**1a** (t_R =16.0 min; from unoxidized **2**) (adenine/**1a**, 91:9). That **2/3** mixture (235 mg, ~0.48 mmol) was treated again by procedure A [CrO_3 (0.25 mmol)] to give **3** (193 mg, 82%), which was assayed by procedure C and showed adenine only [RP-HPLC: adenine (t_R = 8.3 min) with no peak at t_R ~ 16 min].}

Procedure B. *CAUTION*![13b-d] A solution of **2** (0.50 g, 1 mmol) in CH_2Cl_2 (10 mL) was added to a solution of the D-M-P reagent[13b,c] (2.00 g, 4.68 mmol) in CH_2Cl_2 (10 mL) at 0 °C under Ar. Stirring was continued at 0 °C for 15 min followed by warming to ambient temperature, and reaction progress was monitored (TLC). After ~4 h, Et_2O (60 mL) was added and the mixture was poured into ice-cold saturated $NaHCO_3/H_2O$ (60 mL) containing $Na_2S_2O_3$•5 H_2O (6.0 g, 24 mmol). This mixture was shaken for 5 min, and the separated organic phase was washed (saturated $NaHCO_3/H_2O$, H_2O, and brine), dried (Na_2SO_4), and concentrated in vacuo at ambient temperature to give **3** (0.41 g, 82%) as a slightly yellow powder with spectral data identical to those from procedure A. Assay of this **3** by procedure C showed adenine only.

Assay of the Extent of Oxidation to Ketones. ***Procedure C.*** TBAF/THF (1 M, 1 mL) was added to a solution of **3** (25 mg, 0.05 mmol) in THF (1 mL) and the solution was stirred overnight at ambient temperature and then evaporated. The residue was partitioned (EtOAc/H_2O), and the aqueous layer was subjected to RP-HPLC analysis.

9-[2-*O*-(*tert*-Butyldimethylsilyl)-β-D-*erythro*-pentofuran-3-ulosyl]adenine (5). ***Procedure D.*** Ketone **3** (0.2 g, 0.40 mmol) was added to a solution of TFA/H_2O (9:1, 4 mL) at 0 °C and stirring was continued for 1 h. The mixture was evaporated in vacuo (< 25 °C) and partitioned (ice-cold EtOAc//$NaHCO_3/H_2O$). The aqueous layer was extracted with EtOAc (2×) and the combined organic layer was

washed (H_2O, brine), dried (Na_2SO_4), and evaporated to give **5**[5] (140 mg, 91%): ^{1}H NMR ($CDCl_3$) δ -0.01, 0.00 (2 s, 3 and 3), 0.75 (s, 9), 3.89-3.99 (m, 2), 4.36 (m, 1), 5.15 (d, *J* = 8.0 Hz, 1), 5.84 (d, *J* = 8.0 Hz, 1), 6.47 (br s, 2), 7.90 (s, 1), 8.35 (s, 1).

Adenosine (1a). ***Procedure E.*** Ketone **5** (70 mg, 0.18 mmol) was added to a solution of $NaBH(OAc)_3$/AcOH [generated in situ by addition of $NaBH_4$ (58 mg, 1.53 mmol) to AcOH (4 mL) and stirring for 2 h at <15 °C]. After 5 min, the reaction mixture was allowed to warm to ambient temperature, and stirring was continued for 2 h (TLC). Volatiles were evaporated, the residue was partitioned (EtOAc//$NaHCO_3$/H_2O), and the aqueous layer was extracted with EtOAc. The combined organic phase was washed (H_2O, brine), dried ($MgSO_4$), filtered, and evaporated. The oily residue (66 mg, 94%) was dissolved in NH_4F/MeOH (34 mg, 0.92 mmol/3 mL) and the solution was refluxed for 2 h [alternatively the residue was dissolved in THF (5 mL) and stirred with Bu_4NF/THF (1M, 0.5 mL) for 16 h at ambient temperature]. Volatiles were evaporated, the residue was partitioned (EtOAc/H_2O), and the aqueous layer was evaporated. RP-HPLC indicated a mixture of **6a** (t_R = 12.6 min)/**1a** (t_R = 15.5 min) (0.5:99.5). Ion exchange chromatography [Dowex 1 × 2 (OH^-), H_2O → 70% MeOH/H_2O] gave **1a/6a** (99.5:0.5; 40 mg, 83%) with spectral data identical to those of a commercial sample of **1a**.

3'-Deuterioadenosine (3'[^{2}H]-1b). Treatment of **5** (38 mg, 0.1 mmol) by procedure E ($NaBD_4$ rather than $NaBH_4$) gave **1b** (25 mg, 93%): ^{1}H NMR δ 3.52 (ddd, *J* = 12.0, 7.2, 4.0 Hz, 1), 3.67 (dt, *J* = 12.0, 4.0 Hz, 1), 3.94 (t, *J* = 4.0 Hz, 1), 4.59 (t, *J* = 6.2 Hz, 1), 5.15 (s, 1), 5.41 (dd, *J* = 7.2, 4.0 Hz, 1), 5.43 (d, *J* = 6.2 Hz, 1), 5.86 (d, *J* = 6.2 Hz, 1), 7.33 (br s, 2), 8.13 (s, 1), 8.34 (s, 1); MS *m/z* 268 (10, [^{2}H]M$^+$), 238 (20), 178 (28), 164 (100), 135 (68, BH).

9-(β-D-Xylofuranosyl)adenine (6a). ***Procedure F.*** Ketone **3** (70 mg, 0.14 mmol) (purity checked by procedure B) was added to a stirred solution of $NaBH(OAc)_3$/AcOH [generated in situ by addition of $NaBH_4$ (58 mg, 1.53 mmol) to AcOH (4 mL) and stirring for 2 h at <15 °C] and stirring was continued for 48 h at 13 °C. Volatiles were evaporated in vacuo and the residue was partitioned (EtOAc//$NaHCO_3$/H_2O). The aqueous layer was extracted with EtOAc, and the combined organic phase was washed (brine), dried ($MgSO_4$), filtered, and evaporated. The residual white solid was treated with NH_4F/MeOH (81 mg, 2 mmol/4 mL) or Bu_4NF/THF as described in Procedure E to give **6a/1a** (98:2, RP-HPLC). Chromatography [Dowex 1 × 2 (OH^-), H_2O → 40% MeOH/H_2O) and crystallization of the residue from pooled fractions gave **6a/1a** (98:2; 36 mg, 95%) with data[4a] identical to those of a commercial sample of **6a**.

9-(3-Deuterio-β-D-xylofuranosyl)adenine (3'[^{2}H]-6b). Treatment of **3** (70 mg, 0.14 mmol) by procedure F [$NaBD_4$ (65 mg, 1.55 mmol) in AcOH (6 mL)] gave **6b/1b** (98:2; 30 mg, 79%): RP-HPLC (**6b**: t_R = 14.09 min; **1b**: t_R = 17.40 min); ^{1}H NMR δ 3.75 (m, 2), 4.16 (t, *J* = 7.2 Hz, 1), 4.33 (s, 1), 5.88 (s, 1), 7.36 (br s, 2), 8.17 (s, 1), 8.26 (s, 1); HRMS (CI) *m/z* 269.1103 (MH$^+$, 100; [$C_{10}H_{13}DN_5O_4$] = 269.1109).

Treatment of 9-(β-D-*erythro*-pentofuran-3-ulosyl)adenine (4) with $NaBH(OAc)_3$. Ketone **3** (100 mg, 0.20 mmol) was added to a solution of TFA/H_2O (9:1; 2 mL) and stirring was continued at ambient temperature for 20 h to give **5/4**/adenine (~1:2:2, TLC). Volatiles were evaporated in vacuo to give a dark-colored oily residue (49 mg, 89%). No attempt was made to purify this mixture owing to the known lability of **4**.[8b] Treatment of the mixture with $NaBH(OAc)_3$ [$NaBH_4$ (0.12 g, 3.20 mmol) in AcOH (6 mL)] by procedure E gave a residue that was partitioned (EtOAc/H_2O) and the aqueous layer was evaporated. RP-HPLC indicated a mixture of **6a/1a** (55:45) plus adenine.

9-[3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuran-2-ulosyl]adenine (9a). Oxidation of **7a** (1.50 g, 1.00 mmol) with CrO_3 (1.20 g, 2.00 mmol)/pyridine (0.32 mL, 0.31 g, 3.96 mmol)/Ac_2O (0.18 mL, 0.19 g, 1.76 mmol)/CH_2Cl_2 (10 mL) by procedure A gave **9a** (0.40 g, 81%) as a colorless powder with the same properties as reported.[3]

Oxidation of **7a** (0.50 g, 1.00 mmol) with the D-M-P reagent[13] (1.80 g, 4.22 mmol) by procedure B gave **9a** (0.42 g, 84%) as an orange glass.

Samples of ketone **9a** (15 mg, 0.03 mmol) were dissolved in THF (1 mL), treated with Bu_4NF/THF (1.0 M, 0.05 mL) for 1 h at 45 °C, and evaporated. The dark-colored residues were partitioned (EtOAc/H_2O), and the aqueous layers were analyzed by RP-HPLC. Only adenine (t_R = 8.2 min) was detected, which confirmed complete oxidation of **7a** → **9a**.

9-(β-D-Arabinofuranosyl)adenine (10a). Treatment of **9a** (65 mg, 0.13 mmol) by procedure F [$NaBH_4$ (58 mg, 1.53 mmol) in AcOH (5 mL)] gave **10a/1a** (98:2; 27 mg, 77%) with spectral data[3] identical to those of a commercial sample of **10a**.

9-(2-Deuterio-β-D-arabinofuranosyl)adenine (2'[^{2}H]-11a). Treatment of **9a** (70 mg, 0.14 mmol) by procedure F [$NaBD_4$ (69 mg, 1.65 mmol) in AcOH (6 mL)] gave **11a/8a** [98:2; 27 mg, 71%; RP-HPLC: **11a** (t_R = 11.9 min), **8a** (t_R = 15.4 min)] with data as reported[6] for **11a**: ^{1}H NMR δ 3.60 - 3.68 (m, 2), 3.78 (m, 1), 4.16 (d, *J* = 4.8 Hz, 1), 5.51 (br s, 3), 6.26 (s, 1), 7.25 (br s, 2), 8.14 (s, 1), 8.19 (s, 1); HRMS (CI) *m/z* 269.1100 (MH^+, 100; [$C_{10}H_{13}DN_5O_4$] = 269.1109).

Adenosine (1a). Treatment of **9a** (0.10 g, 0.20 mmol) with TFA/H_2O (9:1, 3 mL) by procedure D gave 9-[3-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuran-2-ulosyl]adenine (**12a**; 75 mg, 97%) as a colorless powder.

Treatment of **12a** (59 mg, 0.15 mmol) by procedure E [$NaBH_4$ (50 mg, 1.32 mmol) in AcOH (4 mL)] gave **1a/10a** (99:1; 33 mg, 79%) with spectral data identical to those of a commercial sample of **1a**.

2'-Deuterioadenosine (2'[^{2}H]-8a). Treatment of **12a** (50 mg, 0.13 mmol) by procedure E [$NaBD_4$ (44 mg, 1.05 mmol) in AcOH (4 mL)] gave **8a/11a** (99:1; 30 mg, 86%; RP-HPLC: **8a** (t_R = 14.9 min), **11a** (t_R = 12.1 min) with data as reported[6,17] for **8a**: ^{1}H NMR δ 3.59 (dd, *J* = 14.5, 2.6 Hz, 1), 3.67 (dd, *J* = 14.5, 3.9 Hz, 1), 3.98 (q, *J* = 2.9 Hz, 1), 4.15 (d, *J* = 2.6, Hz, 1) 5.41 (br s, 3), 5.88 (s, 1), 7.37 (br s, 2), 8.15 (s, 1), 8.36 (s, 1); HRMS *m/z* 269.1111 (MH^+, 100; [$C_{10}H_{13}DN_5O_4$] = 269.1109).

4-Amino-7-[3,5-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-β-D-pentofuran-2-ulosyl]pyrrolo[2,3-*d*]pyrimidine (9b). Oxidation of **8b**[28] (1.30 g, 2.55 mmol) with CrO_3 (0.4 g, 4 mmol)/pyridine (0.64 mL, 0.63 g, 7.91 mmol)/Ac_2O (0.36 mL, 0.39 g, 3.61 mmol)/CH_2Cl_2 (34 mL) by procedure A gave **9b**[3,6] (0.68 g, 53%) as a colorless powder (complete oxidation of **8b** → **9b** was confirmed by procedure C): ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 28), 3.97-4.18 (m, 3), 5.56 (d, *J* = 9.5 Hz, 1), 5.69 (s, 1), 6.42 (d, *J* = 3.6 Hz, 1), 6.56 (br s, 2), 6.96 (d, *J* = 3.6 Hz, 1) 8.08 (s, 1); ^{13}C NMR ($CDCl_3$) δ 207.49, 156.72, 151.32, 150.54, 125.39, 104.21, 100.39, 82.80, 78.92, 73.24, 61.75, 17.79, 17.29, 13.84, 13.46, 13.04, 12.93.

4-Amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine (10b). Treatment of **9b** (0.406 g, 0.80 mmol) by procedure F [$NaBH_4$ (0.22 g, 5.81 mmol) in AcOH (20 mL)] gave **10b/7b** [~97:3 (^{1}H NMR); 0.12 g, 56%] with data as reported[3] for **10b**.

4-Amino-7-(2-deuterio-β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine (2'[^{2}H]-11b). Treatment of **9b** (0.116 g, 0.23 mmol) by procedure F [$NaBD_4$ (62 mg, 1.48 mmol) in AcOH (7 mL)] gave **11b/2'[^{2}H]-7b** (~97:3; 32 mg, 51%) with data as reported[6] for **11b**: ^{1}H NMR δ 3.57-3.77 (m, 3), 4.08 (d, *J* = 4.0 Hz, 1), 5.10 (br s, 1), 5.47 (br s, 2), 6.42 (s, 1), 6.54 (d, *J* = 3.8 Hz, 1), 6.97 (br s, 2), 7.31 (d, *J* = 3.8 Hz, 1), 8.05 (s, 1); HRMS (CI) *m/z* 268.1143 (MH^+, 100; [$C_{11}H_{14}DN_4O_4$] = 268.1156).

Acknowledgments. We thank the American Cancer Society (Grant No. DHP-34) and Brigham Young University development funds for support, and Mrs. Jeanny Gordon for assistance with the manuscript.

References and Notes

1. (a) Part 93: Robins, M. J.; Zou, R.; Guo, Z.; Wnuk, S. F. *J. Org. Chem.*, In press. (b) Present address: GlaxoWellcome, Inc., 3030 Cornwallis Road, Research Triangle Park, NC 27709
2. (a) Moffatt, J. G. In *Nucleoside Analogues: Chemistry, Biology, and Medical Applications*; Walker, R. T., De Clercq, E., Eckstein, F., Eds; Plenum Press: New York, 1979; pp. 71-164. (b) Ueda, T. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed; Plenum Press: New York, 1988; Vol 1, pp 1-112.
3. Hansske, F.; Madej, D.; Robins, M. J. *Tetrahedron* **1984**, *40*, 125.
4. (a) Cheng, X.; Zhang, J.-D.; Zhang, L.-H. *Synthesis* **1989**, 383. (b) Rosemeyer, H.; Seela, F. *Helv. Chim. Acta* **1989**, *72*. 1084. (c) Zhang, H.-C.; Daves, G. D., Jr. *J. Org. Chem.* **1992**, *57*, 4690. (d) Rozners, E.; Bizdena, E. *Nucleosides Nucleotides* **1995**, *14*, 2009.
5. Robins, M. J.; Samano, V.; Johnson, M. D. *J. Org. Chem.* **1990**, *55*, 410.
6. Perlman, M. E. *Nucleosides Nucleotides* **1993**, *12*, 73.
7. (a) Wu, J.-C.; Bazin, H.; Chattopadhyaya, J. *Tetrahedron* **1987**, *43*, 2355. (b) Kawashima, E.; Aoyama, Y.; Radwan, M. F.; Miyahara, M.; Sekine, T.; Kainosho, M.; Kyogoku, Y.; Ishido, Y. *Nucleosides Nucleotides* **1995**, *14*, 333.
8. (a) Cook, A. F.; Moffatt, J. G. *J. Am. Chem. Soc.* **1967**, *89*, 2697. (b) Crews, R. P.; Baker, D. C. *Nucleosides Nucleotides* **1983**, *2*, 275.

9. Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661.
10. Garegg, P. J.; Samuelsson, B. *Carbohydr. Res.* **1978**, *67*, 267.
11. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
12. Ueda, T.; Shuto, S.; Satoh, M.; Inoue, H. *Nucleosides Nucletides* **1985**, *4*, 401.
13. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (d) Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, July 16, 3.
14. Samano, V.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 5186.
15. Bender, S. L.; Moffett, K. K. *J. Org. Chem.* **1992**, *57*, 1646.
16. Binkley, R. W.; Hehemann, D. G.; Binkley, W. W. *J. Org. Chem.* **1978**, *43*, 2573.
17. Cook, G. P.; Greenberg, M. M. *J. Org. Chem.* **1994**, *59*, 4704.
18. Jung, P. M. J.; Burger, A.; Biellmann, J.-F. *Tetrahedron Lett.* **1995**, *36*, 1031.
19. (a) Ogilvie, K. K.; Beaucage, S. L.; Schifman, A. L.; Theriault, N. Y.; Sadana, K. L. *Can. J. Chem.* **1978**, *56*, 2768. (b) Samano, V.; Robins, M. J. *J. Org. Chem.* **1991**, *56*, 7108.
20. Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535.
21. Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177.
22. Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 4287.
23. (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449.
24. (a) Evans, D. A.; Chapman K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. (b) Hoveyda, A. H.; Evans, E. A.; Fu, G. C. *Chem. Rev.* **1993**,*93*, 1307.
25. Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662.
26. Adams, J.; Poupart, M.-A.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753.
27. Hoemann, M. Z.; Velde, D. V.; Aubé, J.; Georg, G. I. *J. Org. Chem.* **1995**, *60*, 2918.
28. Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.

(*Received in USA* 10 *September* 1996; *revised* 1 *November* 1996; *accepted* 2 *November* 1996)