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Nucleic Acid Related Compounds. 23. Transformation of Ribonucleoside 2′,3′-O-Ortho Esters into Unsaturated and Deoxy Sugar Nucleosides via Enol Ester-Substituted Iodo Intermediates[1,2]

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Abstract: Treatment of 2′,3′-*O*-methoxyethylideneadenosine (**1**) with sodium iodide and pivalic acid chloride in refluxing pyridine gave a mixture containing 6-*N*-pivalamido-9-(2-iodo-2-deoxy-3-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-5-*O*-pivalyl-β-D-arabinofuranosyl)purine (**2a**), the corresponding 3′-iodo-2′-*O*-(4,4-dimethyl-3-pivaloxypent-2-enoyl) (DMPP) xylo isomer (**3a**), 6-*N*-pivalylamido-9-(2-*O*-DMPP-5-*O*-pivalyl-3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)purine (**4a**), and 6-*N*-pivalamido-9-(5-pivaloxymethylfuran-2-yl)purine (**5**). These compounds were separated by column chromatography on activated carbon and fractional crystallization using solvent diffusion techniques. Deblocking of **4a** gave 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (**4b**), which was hydrogenated to give 3′-deoxyadenosine (**8**) plus its 4′-epimer (**9**). Both **2a** and **3a** gave **5** on prolonged heating in pyridine. A mixture containing **4a** + **5** was observed on heating **3a** in pyridine, and **4a** was rapidly converted to **5** at 180 °C. Silver acetate converted **3a** to **4a** quantitatively. Removal of the DMPP group was effected quantitatively using potassium permanganate in cold aqueous pyridine. Such treatment of **3a** gave **3b**, which was converted to the *trans*-3′-iodo-2′-mesylate (**3c**). Elimination with concomitant deblocking occurred upon addition of **3c** to aqueous sodium iodide and sodium hydroxide to give 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)adenine (**7**) in 81% yield. Deblocking of **5** gave 9-(5-hydroxymethylfuran-2-yl)adenine (**10a**) which was hydrogenated to give (D,L)-2′,3′-dideoxyadenosine (**13a**,**14a**). Hydrogenation of **7** gave authentic **13a** for comparison. Hydrogenolysis of the pivaloxy-methyl bond of **5** and deblocking gave 9-(5-methylfuran-2-yl)adenine (**10b**). Hydrogenation of **10b** gave (D,L)-2′,3′,5′-trideoxyadenosine (**13b**,**14b**). DMPP removal from **2a** gave **2b** which was converted to the trimethylsilyl-protected arabino iodohydrin **2c**. Elimination of hydrogen iodide was effected using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and the product (**6a**) was deblocked to give 9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)adenine (**6c**), the first 1′,2′-unsaturated nucleoside. Hydrogenation of **6c** gave 2′-deoxyadenosine (**11**) plus its α anomer (**12**). Spectroscopic identification of products and comparison of these procedures with other approaches in nucleoside chemistry are discussed.

Nucleoside antibiotics containing an unsaturated sugar moiety are known,[4] and unsaturated nucleoside intermediates have been postulated in biosynthetic pathways involving coenzyme B_{12} mediated reactions[5] as well as in deoxynucleoside biosynthesis.[6] Therefore, unsaturated nucleosides[7] are of interest as synthetic targets for biological investigations as well as being useful chemical intermediates for transformation into modified sugar nucleosides.

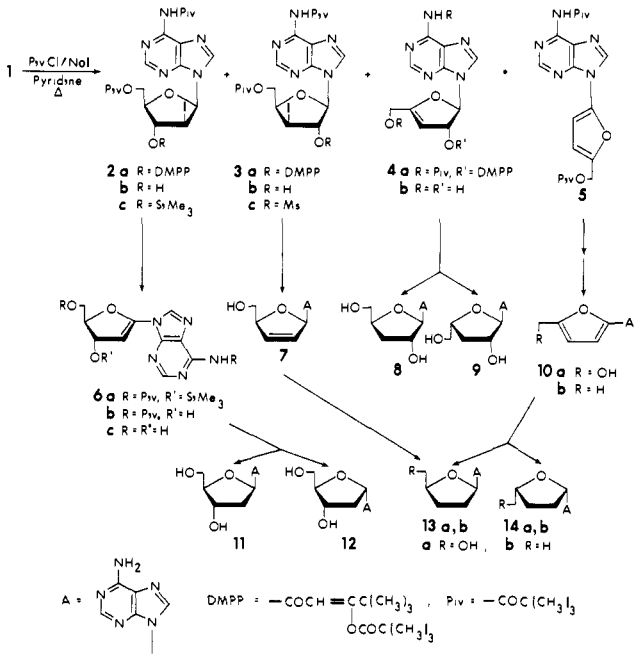
The exocyclic (4′-methylene) unsaturated products have been prepared in both the purine[8] and pyrimidine[9,10] riboside series. The antibiotic decoyinine (angustmycin A) was obtained from psicofuranine by elimination of the 6′-tosylate[8b] and a 4′,5′-unsaturated derivative of adenosine was the key intermediate in the synthesis of nucleocidin.[8c] Synthetic routes to 2′,3′-unsaturated nucleosides have generally employed pyrimidine cyclonucleoside chemistry[11] and/or naturally occurring 2′-deoxynucleosides.[12] Prior to our preliminary communication,[13] studies on 3′,4′-unsaturated nucleosides had involved C-5′ oxidized[7b,14a-c] (or electronegatively activated[14d]) derivatives. Although formation of a 1′,2′-unsaturated nucleoside by treatment of a 2′-bromo-2′-deoxyuridine derivative with reduced hydroxy cobalamine (vitamin B_{12s}) had been claimed,[15] the structure of that product was shown to be incorrect.[16]

We have been interested in developing reactions and procedures for the defined chemical transformation of naturally occurring ribonucleosides into modified sugar products. Such routes should not be dependent upon specific structural features in the base nor on the position or type of glycosyl linkage. Application of these procedures to nucleoside antibiotics could

then proceed to give molecules of significant biological interest. A notable advantage of this approach (over the usual base-sugar coupling[17]) is that desired preexisting stereochemical integrity can be maintained. We now wish to present details of transformation of adenosine into each of the three possible (1′,2′; 2′,3′; and 3′,4′) endocyclic unsaturated nucleosides by uniquely defined routes.[13,18]

Treatment of 2′,3′-*O*-methoxyethylideneadenosine[19,20] (**1**) with excess sodium iodide and pivalic acid chloride (in situ generation of pivalyl iodide) in pyridine at reflux for ~5 min gave 6-*N*-pivalamido-9-(3-iodo-3-deoxy-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-5-*O*-pivalyl-β-D-xylofuranosyl)purine (**3a**) and its 2′-iodo-3′-*O*-(4,4-dimethyl-3-pivaloxypent-2-enoyl) (DMPP) isomer (**2a**) as major products in ~70% combined yield.[20] The 3′,4′-unsaturated compound (**4a**) and the fluorescent 6-*N*-pivalamido-9-(5-pivaloxymethylfuran-2-yl)purine (**5**) (see Scheme I) were formed in varying amounts

Scheme I



depending on reaction time. These products were separated by column chromatography on activated carbon and fractional crystallization at room temperature using solvent diffusion techniques.[20,21] The yields of **4a** and **5** increase at the expense of **3a** with longer reaction times. Heating purified **3a** in pyridine gave a mixture of **4a** + **5** (in addition to unreacted **3a**). Prolonged heating of this mixture (or of purified **4a**) in pyridine or as a neat melt gave **5**. Purified **2a** also gave **5** upon heating in pyridine. Treatment of **3a** with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) in pyridine gave a mixture of **4a** + **5** with **4a** predominating. However, silver acetate in pyridine effected selective elimination of hydrogen iodide from **3a** to give **4a** in 84% crystalline yield.

Hydrogenolysis of **2a** and **3a** followed by deblocking gave 2′-deoxyadenosine (**11**) and 3′-deoxyadenosine (cordycepin[22]) (**8**) in excellent overall yields.[20] Deblocking of **4a** gave 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (**4b**)[13,23] in over 90% crystalline yield. This 3′-ene was hydrogenated to give **8** plus its 4′-epimer, 9-(3-deoxy-α-L-*threo*-pentofuranosyl)adenine[14b] (**9**), in 70% yield. These diastereomers were cleanly separated on the Dekker anion exchange column[24] in a ratio of ~1.5:1 (**8**:**9**).

The unusually stable DMPP group[20] was selectively and quantitatively removed from **3a** using potassium permanganate in aqueous pyridine at 0 °C. The resulting 6-*N*-pivalamido-9-(3-iodo-3-deoxy-5-*O*-pivalyl-β-D-xylofuranosyl)purine (**3b**) was obtained crystalline in 86% yield. Treatment of **3b** with mesyl chloride in cold pyridine gave the somewhat labile 2′-mesylate (**3c**). Known elimination conditions used for converting vicinal carbohydrate iodo mesylates or tosylates to olefins[25] gave low to moderate yields. However, treatment of crude **3c** with cold aqueous base containing sodium iodide resulted in smooth elimination (initial iodine color fades to yellow hypoiodite) with concomitant deblocking to give 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)adenine[12,23a] (**7**) in 81% crystallized yield.

Deblocking of **5** gave 9-(5-hydroxymethylfuran-2-yl)adenine (**10a**). Hydrogenation of **10a** gave 9-(2,3-dideoxy-β-D,L-*glycero*-pentofuranosyl)adenine (**13a** and **14a**) in moderate yield. The spectral properties of this crystalline racemate were identical with those of 2′,3′-dideoxyadenosine (**13a**) prepared by hydrogenation of **7**.[12a] The indicated cis orientation of the adenine and hydroxymethyl groups was proven by heating the 5′-*O*-tosyl derivatives in acetone. The racemic $N^3 \rightarrow 5'$-cyclonucleoside salt was produced quantitatively as indicated by TLC and a 13-nm bathochromic shift in the ultraviolet maxima to 273 nm.[26] Hydrogenolysis of the pivaloxy-methyl bond of **5** occurred readily to give 6-*N*-pivalamido-9-(5-methylfuran-2-yl)purine which was deblocked to yield 9-(5-methylfuran-2-yl)adenine[12a] (**10b**). Hydrogenation of **10b** gave (D,L)-2′,3′,5′-trideoxyadenosine (**13b**,**14b**) as indicated spectroscopically.[12a,27]

The antibiotic angustmycin A (decoyinine[28a]) had originally been assigned a 1′,2′-unsaturated structure,[28b] and such intermediates had been considered in the biosynthesis of 2′-deoxynucleosides.[6] However, no authentic example of this structural type had been described. Direct treatment of **2a** with DBN or silver acetate gave primarily the furan derivative **5**. Removal of the DMPP group with potassium permanganate gave 6-*N*-pivalamido-9-(2-iodo-2-deoxy-5-*O*-pivalyl-β-D-arabinofuranosyl)purine (**2b**) in 75% yield. However, treatment of **2b** with DBN produced the $N^6,O^{5'}$-dipivalyl riboepoxide[29] in addition to the desired 1′-ene. Treatment of **2b** with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in pyridine gave the 3′-*O*-trimethylsilyl derivative **2c** in 95% yield which was quantitatively (TLC) converted to the 1′,2′-unsaturated product **6a** using DBN in pyridine. Methanolysis of **6a** gave 6-*N*-pivalamido-9-(2-deoxy-5-*O*-pivalyl-D-*erythro*-pent-1-enofuranosyl)purine (**6b**). Deblocking of **6b** gave 9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)adenine (**6c**) in 89% crystalline overall yield from **2b** when isolation of intermediates was omitted. The ^{1}H NMR resonance assigned to H-2′ (of **6c**) appeared at δ 5.69 as a doublet ($J_{2'3'}$ = 2.8 Hz), and there was no peak in the anomeric proton (H-1′) region. The remaining peaks corresponded to the sugar and base protons of such a deoxy nucleoside (see Experimental Section). The parent peak in the mass spectrum of **6c** was *m/e* 231.0752 (calcd for $M^+ - H_2O$: 231.0756) which suggested facile dehydration of **6c** to the furan derivative **10a** in the mass spectrometer. Heating a sample of **6c** slightly above its melting point resulted in formation of **10a**. Trimethylsilylation of **6c** gave a tris(trimethylsilyl) derivative with M^+ 465.2062 (calcd for $C_{19}H_{35}N_5O_3Si_3$: 465.2047). Elemental analyses were also in agreement with structure **6c**. The ultraviolet maximum of **6c** is blue shifted some 10 nm with respect to adenosine. The uv spectra of **6b** and **6c** resemble those of furan derivatives **10a** and **10b** with maxima at ~250 nm and long wavelength shoulders (~280, 290 nm). A bright blue-white fluorescence is observed with **10a** and **10b** on chromatograms under 2537 Å light. The 1′-ene (**6c**) also exhibits a less intense blue fluorescence.

Hydrogenation of **6b** gave significant quantities of 6-*N*-pivalyladenine. Hydrogenation of **6c** in aqueous ethanol containing sodium bicarbonate gave **11** and 9-(2-deoxy-α-D-*erythro*-pentofuranosyl)adenine[30] (**12**) (5:1, respectively) in

82% yield. It is interesting that the β:α stereoselectivity is so high. Essentially equivalent amounts of α- and β-2′-deoxyuridine were produced upon hydrogenation of a derivative of the corresponding 1-(2-deoxy-D-*erythro*-pent-1-enofuranosyl) uracil in ethyl acetate.[16] The overall yield of **12** is prohibitively low owing to the formation of **2a** as the minor isomer in the initial step and the hydrogenation stereoselectivity for **11** in the last step. However, this route represents the transformation of a β-D-ribofuranosyl nucleoside to the corresponding 2′-deoxy-α-D structure while maintaining the glycosyl and $C_{1'}$–$O_{4'}$ linkages intact. Such transformations could prove unique in producing potentially useful[31] 2′-deoxy-α-D analogues of biologically potent nucleoside antibiotics.

It was observed that the NMR signals for the diastereotopic 5′,5″-protons of the unblocked β-deoxy nucleosides (C-5′ cis to adenine, **8, 11, 13a, 14a**) appear as a multiplet which is simplified by varying degrees upon exchange of the 5′-OH with D_2O. The corresponding signals for the α anomers (C-5′ trans to adenine, **9, 12**) collapse to an apparent doublet upon deuterium exchange. This effect (observed also in the tubercidin series) is presumably the result of base anisotropy and/or steric effects on the chemical shift difference of the 5′ and 5″ protons of the cis isomers. The nearly identical spin splitting patterns of the 2′ and 3′ methylene protons of **11** and **8**, respectively, suggest an *S* conformation[20] for **11** and an *N* conformation[20] for **8** with anisotropy effects remarkably constant in the volume of space enclosing the 2′,3′ region.

Moffatt and co-workers first applied the "abnormal Mattocks[32] reaction" of α-acetoxyisobutyryl halides to nucleosides and obtained 2′,3′-*trans*-acetoxyhalo nucleosides via an acetoxonium ion mediated process.[33] Treatment of their 3′-bromo-2′-*O*-acetyl product (obtained in 30–35% crystalline yields) with chromous acetate–ethylenediamine and deblocking gave **7** in 59% yield.[23a] However, 30% of **8** was simultaneously produced by functional hydrogenolysis of the 3′-bromo group. A 6% yield of **4b** as well as an unspecified quantity of **11** were additionally observed when their acetoxychloro nucleoside mixture[34] was subjected to this procedure. Even less favorable results were obtained using the crude iodo analogue mixture. This chromous amine complex procedure devised by Kochi et al.[35] and employed by Moffatt and co-workers[23a] is *conceptually facile*. However, the observed contamination of **7** by **4b** and **8**, and the somewhat involved preparation of reagents and techniques required, reduce its practical appeal. The fortuitous separation and crystallization of these closely related structures which appears preparatively feasible with adenosine[23a,34] was not achieved with guanosine or formycin.[23a] In contrast, the presently described sequence gives crystalline **7** in 33% overall yield from adenosine as the unique product of the final reactions. This route has been found to be directly applicable to antibiotic structures.[36]

The 3′-ene[13] (**4b**), which was noted as a side product in the above chromous complex reaction, was also prepared by Moffatt and co-workers using a crystalline acetoxy bromo derivative and DBN in hot acetonitrile. However, the ribo epoxide was also formed in "considerable amount" [23a] and **4b** was obtained in 59% yield after deblocking and purification. Lichtenthaler et al. have reported an analogous study using the 3′-iodo product and tetrahydropyranyl blocking to give **4b** in 61% yield.[23b] In the present study, **3a** was converted to **4a** (84% crystalline) selectively and quantitatively (TLC) using silver acetate in pyridine, and deblocking gave a 92% crystalline yield of **4b**.

Thus, reaction of the adenosine methyl orthoacetate **1** with sodium iodide/pivalyl chloride/pyridine has proven to be a source of versatile iodo-sugar intermediates. The interesting DMPP group[20] may be noted as a selectively removable blocking function since the smooth controlled oxidation by permanganate at 0 °C is very mild and would not affect usual protecting groups. Its use provides convenient and defined access into 2′,3′- and the previously unknown 1′,2′-unsaturated nucleoside series. Entry into the 3′,4′-unsaturated series was also selectively achieved. Hydrogenation of the 1′- and 3′-ene series allows epimeric nucleosides with cis and trans C-1′ and C-4′ substituents to be obtained while maintaining stereochemical integrity at the remaining centers. Manipulation and hydrogenation of 9-(furan-2-yl)adenine derivatives allows facile preparation of racemic di- and trideoxy nucleosides. High crystallization recovery has been achieved using solvent diffusion techniques.[20,21] Successful application of these procedures to obtain modified sugar products from the antibiotic tubercidin will be described separately.[36]

Experimental Section

General Methods. These are described in detail in ref 20. Furan protons in the NMR spectral data are given primed numbers corresponding to nucleoside–sugar numbering.

Reaction of 1 with Sodium Iodide/Pivalyl Chloride/Pyridine at Reflux. Yields of products varied with reaction time. In each case, the quantities and procedures followed were those described in detail for a 4-min reaction.[20] Yields at various reflux times were as follows: for **2a,** 16% (2 min), 15% (4 min), 15% (6 min), 13% (8 min), and 15% (10 min); for the initial crystalline yield of **3a** (in the same time sequence), 41, 44, 38, 31, and 29%; for the total yield of **3a,** 46, 48, 45, 41, and 37%; and for **4a,** 2.4, 4, 8.8, 13, and 16%. The **4a** obtained in this series of reactions was identical with that prepared below by treatment of **3a** with AgOAc. The minor quantities of **5** can be eluted from the carbon column using $CHCl_3$.

6-*N*-Pivalamido-9-(3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-*glycero*-pent-3-enofuranosyl)purine (4a). A solution of 3.78 g (0.005 mol) of **3a** and 4.17 g (0.025 mol) of AgOAc in 150 ml of pyridine was stirred at 15 °C for ~17 h. The resulting dark solution was poured into 300 ml of 5% $NaHCO_3$. The mixture was extracted with Et_2O, and the combined organic phase was washed with H_2O and evaporated. The residue was coevaporated using toluene and then 98% EtOH, dissolved in $CHCl_3$, filtered through Celite, and evaporated to give **4a** as a pure (TLC, Et_2O) white solid foam (quantitative). This material was crystallized from 10 ml of Et_2O using pentane diffusion[20,21] to give 2.64 g (84%) of pure **4a**: mp 126–129 °C; uv (MeOH) max 271; 212 nm (ϵ 20 000; 41 800) min 243 nm (ϵ 11 600); NMR ($CDCl_3$) δ 1.17 (s, 9, C=C-*t*-Bu), 1.22 and 1.30 (s and s, 9 and 9, 5′-OPiv and C=COPiv), 1.44 (s, 9, 6-NPiv), 4.73 (s, 2, $H_{5'}$, $H_{5''}$), 5.43 (m, 1, $H_{3'}$), 5.74 (s, 1, CH=C) 6.08 (m, 1, $H_{2'}$), 6.62 (d, $J_{1'-2'}$ = 2.0 Hz, 1, $H_{1'}$), 8.08 (s, 1, H_8), 8.66 (br, 1, 6-NH) 8.78 (s, 1, H_2). Anal. ($C_{32}H_{45}N_5O_8$) C, H, N.

9-(3-Deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine[13,23] (4b). A solution of 1.26 g (0.002 mol) of **4a** and 0.5 g of NaOMe in 20 ml of MeOH was stirred at room temperature overnight, evaporated to dryness, dissolved in 125 ml of H_2O–95% EtOH (4:1), and filtered through Celite. Upon evaporating the solution to ~100 ml, 400 mg of **4b** crystallized. A second crop of 60 mg was obtained by concentration of the mother liquors to give 460 mg (92%) of **4b**: mp 227–230 °C; $[\alpha]^{26}D$ −354° (*c* 0.39, H_2O/DMF, 1:1); uv (MeOH) max 258 nm (ϵ 15 000) min 230 nm (ϵ 3500); NMR see ref 23a; [lit.[23a] mp 240–241 °C; $[\alpha]D$ 307° (*c* 0.1, H_2O)]. Anal. ($C_{10}h_{11}N_5O_3$) C, H, N.

3′-Deoxyadenosine (8) and 9-(3-Deoxy-α-L-*threo*-pentofuranosyl)adenine (9). A mixture of 249 mg (0.001 mol) of **4b**, 250 mg of 10% Pd/C, and 50 ml of H_2O–95% EtOH (1:1) was hydrogenated at 10 psi for 2 h, filtered through a Celite pad, the catalyst washed with 95% EtOH, and the filtrate evaporated to give 240 mg of a white powder. This material was dissolved in 30% MeOH/H_2O and applied to a column of Dowex 1-X2(OH^-) resin[24] (2.4 × 95 cm), packed and eluted with the same solvent mixture. Fractions from 2300 to 3000 ml contained 133 mg (53%) of **8.** Crystallization of this material from MeOH (Et_2O diffusion)[20] gave 104 mg of **8,** $[\alpha]^{26}D$ −47.2° (*c* 0.51, H_2O), identical with a known sample.[20] Anal. ($C_{10}H_{13}N_5O_3$) C, H, N.

Fractions from 4900 to 6000 ml contained 86 mg (35%) of solid. Crystallization of this material from MeOH (Et_2O diffusion)[20] gave 70 mg of **9**: mp 241–245 °C; $[\alpha]^{26}D$ −68.2° (*c* 0.54, H_2O); uv (MeOH) max 258 nm (ϵ 15 700) min 227 nm (ϵ 2900); NMR (Me_2SO-d_6) δ 1.85 ("quintet", $J_{3''-3'}$ = 13 Hz, $J_{3''-2'}$ = 6 Hz, $J_{3''-4'}$ = 8 Hz, 1, $H_{3''}$), 2.45 (m, $J_{3'-4'}$ = 7 Hz, 1, $H_{3'}$), 3.52 ("t", $J_{apparent}$ =

5 Hz; on D_2O exchange, d, $J_{5'\text{ and }5''\text{-}4'}$ = 4.5 Hz, 2, $H_{5'}$, $H_{5''}$), 4.50 (m, 1, $H_{4'}$), 4.90 (m, on D_2O exchange "quintet", $J_{2'\text{-}1'} \cong 4$ Hz, $J_{2'\text{-}3'} \cong J_{2'\text{-}3''}$ = 6.5 Hz, 2, $H_{2'}$, 5'-OH), 5.43 (d, $J_{OH\text{-}2'}$ = 5 Hz, 1, 2'-OH), 5.90 (d, $J_{1'\text{-}2'}$ = 4 Hz, 1, $H_{1'}$), 7.26 (s, 2, 6-NH_2), 8.19 (s, 1, H_2), 8.30 (s, 1, H_8); [lit.[14b] $[\alpha]^{25}D$ −52° (*c* 0.5, H_2O)]. Anal. ($C_{10}H_{13}N_5O_3$) C, H, N.

6-*N*-Pivalamido-9-(3-iodo-3-deoxy-5-*O*-pivalyl)-β-D-xylofuranosyl)purine (3b). To a solution of 3.95 g (0.025 mol) of $KMnO_4$ in 75 ml of pyridine–H_2O (2:1) stirred at 0 °C was added 3.78 g (0.005 mol) of **3a**. Stirring was continued at 0 °C for 2 h and 100 ml of 95% EtOH was added. After an additional 18 h at 0–4 °C, the reaction was filtered through Celite and the filter cake was washed with 95% EtOH. The combined filtrate was evaporated to a yellow gum, dissolved in 500 ml of Et_2O, and washed with 50 ml of 5% $NaHCO_3$ and 2 × 50 ml of H_2O. The organic phase was evaporated and coevaporated successively using toluene and 98% EtOH to give a white solid foam (quantitative). This material was dissolved in 50 ml of Et_2O and 2.08 g (76%) of **3b** rapidly crystallized. The mother liquors were evaporated, dissolved in 5 ml of Et_2O, and placed in a desiccator containing pentane. A further 0.26 g of **3b** crystallized for a yield of 2.34 g (86%): mp 104–105 °C; uv (MeOH) max 272 nm (ε 18 200) min 233 nm (ε 4500); NMR (Me_2SO-d_6) δ 1.18 (s, 9, 5'-OPiv), 1.31 (s, 9, 6-NPiv), 3.36 (br, 1, 2'-OH), 4.18–4.58 (m, 4, $H_{3'}$-$H_{5''}$), 5.12 (d of d, $J_{2'\text{-}1'}$ = 4.5 Hz, $J_{2'\text{-}3'}$ = 5.5 Hz, 1, $H_{2'}$), 5.99 (d, $J_{1'\text{-}2'}$ = 4.5 Hz, 1, $H_{1'}$), 8.63 (s, 1, H_8), 8.75 (s, 1, H_2), 10.10 (br, 1, 6-NH). Anal. ($C_{20}H_{28}IN_5O_5$) C, H, I, N.

6-*N*-Pivalamido-9-(3-iodo-3-deoxy-2-*O*-mesyl-5-*O*-pivalyl-β-D-xylofuranosyl)purine (3c). To a solution of 545 mg (0.001 mol) of **3b** in 2.5 ml of pyridine at 0 °C was added 0.5 ml (0.0065 mol) of mesyl chloride. After 2 h the reaction was poured into 100 ml of 5% $NaHCO_3$, extracted with Et_2O, washed with H_2O, and evaporated to give 605 mg (97%) of **3c** as a yellow solid foam: uv (MeOH) max 271 nm, min 233 nm; NMR ($CDCl_3$) δ 1.20 (s, 9, 5'-OPiv), 1.36 (s, 9, 6-NPiv), 3.33 (s, 3, 2'-OMs), 4.06–4.66 (m, 4, $H_{3'}$-$H_{5''}$), 5.83 (m, 1, $H_{2'}$), 6.20 (d, $J_{1'\text{-}2'}$ = 1.5 Hz, 1, $H_{1'}$), 8.31 (br, 1, 6-NH) 8.39 (s, 1, H_8), 8.71 (s, 1, H_2); ir (Nujol) 1175 cm^{-1} (OSO_2R).

9-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)adenine (7). A 1.09-g (0.002 mol) portion of **3b** was mesylated as above for 2 h, and the reaction mixture containing **3c** was then poured into a stirred solution of 1.8 g (0.045 mol) of NaOH and 1.5 g (0.010 mol) of NaI in 25 ml of H_2O at 0 °C. The reaction was continued at 0 °C for 1 h and then at room temperature for 16 h. The solution was evaporated to dryness, dissolved in H_2O, and applied to a column (3 × 83 cm) of Dowex 1-X2(OH^-) resin packed in H_2O. The column was eluted with H_2O (600 ml), 10% (200 ml), 20% (200 ml), and 30% (900 ml) of MeOH/H_2O. Evaporation of fractions from 900 to 1900 ml gave 414 mg (89%) of **7**. Crystallization of this material from 200 ml of MeOH (Et_2O diffusion)[20] gave 380 mg (81%) of **7** in two crops as large prisms: mp 196–200 °C; resolidifies, 280–310 °C dec; $[\alpha]^{23}D$ 20.6° (*c* 0.39, MeOH); uv (MeOH) max 258 nm (ε 15 400) min 226 nm (ε 3000); NMR see ref 23a; [lit.[12a] mp 187–190 °C dec (resolidifies, did not remelt <300 °C); $[\alpha]^{23}D$ 19.1° (*c* 1.0, MeOH)]. Anal. ($C_{10}H_{11}N_5O_2$) C, H, N.

6-*N*-Pivalamido-9-(5-pivaloxymethylfuran-2-yl)purine (5). A 627-mg (0.001 mol) sample of **4a** was heated in an oil bath at 180 °C for 3 min. The residue was dissolved in $CHCl_3$, evaporated, and dissolved in 10 ml of Et_2O. Crystallization of 304 mg (76%) of **5** occurred in two crops: mp 141–143 °C; uv (MeOH) max 261; 212 nm (ε 26 200; 18 900) min 228 nm (ε 14 400); NMR ($CDCl_3$) δ 1.19 (s, 9, 5'-OPiv), 1.40 (s, 9, 6-NPiv), 5.08 (s, 2, $H_{5'}$, $H_{5''}$), 6.57 (d, $J_{3'\text{-}2'}$ = 4 Hz, 1, $H_{3'}$), 6.77 (d, $J_{2'\text{-}3'}$ = 4 Hz, 1, $H_{2'}$), 8.34 (s, 1, H_8), 8.57 (br, 1, 6-NH), 8.81 (s, 1, H_2). Anal. ($C_{20}H_{25}N_5O_4$) C, H, N.

6-*N*-Pivalamido-9-(5-methylfuran-2-yl)purine. A mixture of 798 mg (0.002 mol) of **5**, 336 mg (0.004 mol) of $NaHCO_3$, 400 mg of 5% Pd/C, and 60 ml of 95% EtOH–H_2O (5:1) was hydrogenated at 10 psi for 1 h, filtered through Celite, and the catalyst was washed with H_2O, EtOH, and $CHCl_3$. After evaporation of the combined filtrate, the residue was partitioned between H_2O and $CHCl_3$. The organic layer was evaporated to give 580 mg of a white solid foam, which was chromatographed using a column of silica gel (2.2 × 12.5 cm, 25 g) packed in and eluted with $CHCl_3$. Evaporation of fractions from 50 to 315 ml gave 490 mg (82%) of white foam. Crystallization from EtOH–H_2O gave 260 mg of crystals: mp 109–111 °C; uv (MeOH) max 262; 210 nm (ε 26 400; 23 000) min 228 nm (ε 13 500); NMR ($CDCl_3$) δ 1.40 (s, 9, 6-NPiv), 2.35 (s, 3, 5'-CH_3), 6.14 (m, 1, $H_{3'}$), 6.57 (d, $J_{2'\text{-}3'}$ = 3 Hz, 1, $H_{2'}$), 8.25 (s, 1, H_2), 8.81 (s, 1, H_8), 8.55 (br, 1, 6-NH). Anal. ($C_{15}H_{17}N_5O_2$) C, H, N.

9-(5-Methylfuran-2-yl)adenine (10b). A 150-mg (0.0005 mol) sample of the above 6-*N*-pivalamide was dissolved in 100 ml of MeOH–Et_3N–H_2O (45:10:45), stirred at room temperature for 2 days, evaporated to dryness, and crystallized from 10 ml of MeOH to give 95 mg (88%) of **10b**: mp 238–239 °C; uv (MeOH) max 248 nm (ε 23 000) shoulder 280 nm (ε 7400) min 220 nm (ε 12 800); NMR (Me_2SO-d_6) δ 2.35 (s, 3, 5'-CH_3), 6.29 (m, 1, $H_{3'}$), 6.57 (d, $J_{2'\text{-}3'}$ = 3 Hz, 1, $H_{2'}$), 7.41 (s, 2, 6-NH_2), 8.21 (s, 1, H_2), 8.38 (s, 1, H_8); [lit.[12a] mp 236–237 °C]. Anal. ($C_{10}H_9N_5O$) C, H, N.

9-(5-Hydroxymethylfuran-2-yl)adenine (10a). A solution of 798 mg (0.002 mol) of **5** and 250 mg of NaOMe in 20 ml of MeOH was stirred at room temperature for 17 h, evaporated to dryness, triturated with 25 ml of H_2O, and filtered. The filter cake was washed with H_2O until the filtrate was neutral (~15 ml) and then with MeOH and Et_2O to leave 432 mg (92%) of **10a** as a white solid: mp 253–255 °C dec; uv (MeOH) max 247 nm (ε 23 000) shoulder 280 nm (ε 8000) min 218 nm (ε 14 000); NMR (Me_2SO-d_6) δ 4.44 (d, $J_{5'\text{ and }5''\text{-}OH}$ = 5.5 Hz, 2, $H_{5'}$, $H_{5''}$), 5.31 (t, $J_{OH\text{-}5'\text{ and }5''}$ = 5.5 Hz, 1, 5'-OH), 6.49 (d, $J_{3'\text{-}2'}$ = 3 Hz, 1, $H_{3'}$), 6.64 (d, $J_{2'\text{-}3'}$ = 3 Hz, 1, $H_{2'}$), 7.41 (s, 2, 6-NH_2), 8.21 (s, 1, H_2), 8.40 (s, 1, H_8). Anal. ($C_{10}H_9N_5O_2$) C, H, N.

9-(2,3-Dideoxy-β-DL-*glycero*-pentofuranosyl)adenine (13a,14a). A mixture of 231 mg (0.001 mol) of **10a**, 252 mg (0.003 mol) of $NaHCO_3$, 460 mg of 10% Pd/C, and 50 ml of MeOH–H_2O (4:1) was hydrogenated at 60 psi for 30 h. The mixture was filtered through Celite, and the catalyst was washed with 50 ml of MeOH. The filtrate was evaporated, dissolved in H_2O, and applied to a column of Dowex 1-X2(OH^-) resin (1.3 × 37 cm) packed in H_2O. The column was eluted with H_2O (70 ml), 30% MeOH/H_2O (120 ml), and 0.1 *M* NH_4HCO_3 (500 ml). Fractions from 70 to 150 ml gave 149 mg (64%) of **13a,14a** and those from 530 ml to 690 ml contained 18 mg of adenine (by uv). Crystallization of a 75-mg sample of **13a,14a** from MeOH gave 52 mg: mp 165–167 °C; uv (MeOH) max 258 nm (ε 15 900) min 226 nm (ε 2900); NMR (Me_2SO-d_6) δ 2.08 (m, 2, $H_{3'}$, $H_{3''}$), 2.41 (m, 2, $H_{2'}$, $H_{2''}$), 3.59 (m, 2, $H_{5'}$, $H_{5''}$), 4.10 ("septet", $J_{4'\text{-}5'\text{ and }5''}$ = $J_{4'\text{-}3'}$ = $J_{4'\text{-}3''}$ = 7.0 Hz, 1, $H_{4'}$), 5.04 (t, $J_{OH\text{-}5'\text{ and }5''}$ = 5.5 Hz, 1, 5'-OH), 6.22 (t, $J_{1'\text{-}2'\text{ and }2''}$ = 5.0 Hz, 1, $H_{1'}$), 7.23 (s, 2, 6-NH_2), 8.16 (s, 1, H_2), 8.36 (s, 1, H_8). The NMR and mass spectra of a sample of pure **13a** prepared by hydrogenation of **7** were identical with the spectra obtained for this racemate. Anal. ($C_{10}H_{13}N_5O_2$) C, H, N.

Treatment of the racemate with tosyl chloride/pyridine followed by heating the product in acetone gave quantitative (TLC) cyclonucleoside formation, uv (H_2O) max 273 nm.[26]

Hydrogenation of 10b. This was effected analogously to the conversion of **10a** → **13a,14a** described above. The racemic product **13b,14b** had spectroscopic properties consistent with those of 2',3',5'-trideoxyadenosine.[12a,27]

6-*N*-Pivalamido-9-(2-iodo-2-deoxy-5-*O*-pivalyl-β-D-arabinofuranosyl)purine (2b). To a stirred solution of 790 mg (0.005 mol) of $KMnO_4$ in 15 ml of pyridine–H_2O (2:1) at 0 °C was added 755 mg (0.001 mol) of **2a**. After 2 h at 0 °C 20 ml of 95% EtOH was added, and stirring was continued for 16 h at 0 °C. The mixture was filtered using a Celite pad, and the filter cake was washed with 95% EtOH. The filtrate was evaporated, dissolved in EtOAc and washed with 5% $NaHCO_3$ and H_2O. The organic layer was evaporated to a white powder, stirred with Et_2O, and filtered to give 410 mg (75%) of **2b**. Recrystallization of a sample of this material from MeOH gave **2b**·monohydrate: mp 216–217 °C dec; uv (MeOH) max 272; 211 nm (ε 17 400; 19 000) min 231 nm (ε 3600); NMR ($CDCl_3$) δ 1.18 (s, 9, 5'-OPiv), 1.31 (s, 9, 6-NPiv), 3.95 (br m, 1, $H_{4'}$), 4.43 (m, 2, $H_{5'}$, $H_{5''}$), 4.78 (m, 2, $H_{2'}$, $H_{3'}$), 6.16 (m, 1, 3'-OH), 6.45 (d, $J_{1'\text{-}2'}$ = 4.8 Hz, 1, $H_{1'}$), 8.55 (s, 1, H_8), 8.60 (br, 1, 6-NH), 8.72 (s, 1, H_2), 3.30 (s, 2, H_2O). Anal. ($C_{20}H_{28}IN_5O_5{\cdot}H_2O$) C, H, I, N.

6-*N*-Pivalamido-9-(2-iodo-2-deoxy-3-*O*-trimethylsilyl-5-*O*-pivalyl-β-D-arabinofuranosyl)purine (2c). A solution of 55 mg (0.0001 mol) of **2b**·H_2O in 1 ml of pyridine and 0.05 ml of BSA was stirred at room temperature for 1 h. An additional 0.05 ml of BSA was added, and stirring was continued for 1 h.

MeOH (1 ml) was added, the solution was evaporated to dryness, dissolved in Et_2O, and washed with H_2O. Evaporation of the organic layer gave 94 mg of a gum which was chromatographed using a silica column (0.8 × 13.5 cm, 2.5 g) packed in and eluted with $CHCl_3$. Evaporation of the fractions comprising 8 to 20 ml gave 59 mg (95%) of **2c** as a white solid foam: uv (CH_3CN) max 272; 212 nm (ε 272/ε 212 = 0.88), min 237 nm (ε 272/ε 237 = 4.92); NMR ($CDCl_3$) δ 0.24

(s, 9, $SiMe_3$), 1.27 (s, 9, 5′-OPiv), 1.41 (s, 9, 6-NPiv), 4.11 (m, 1, $H_{4'}$), 4.47 ("d", $J_{apparent}$ = 4.5 Hz, 2, $H_{5'}$, $H_{5''}$), 4.66 ("q", $J_{2'-1'}$ = 5.5 Hz, $J_{2'-3'}$ = 4.5 Hz, 1, $H_{2'}$), 4.84 ("t", $J_{3'-2'} = J_{3'-4'}$ = 4.5 Hz, 1, $H_{3'}$), 6.11 (d, $J_{1'-2'}$ = 5.5 Hz, 1, $H_{1'}$), 8.25 (s, 1, H_8), 8.35 (s, 1, 6-NH), 8.78 (s, 1, H_2); mass spectrum calcd for M^+ ($C_{23}H_{36}IN_5O_5Si$): 617.1531, found: *m/e* 617.1506.

6-*N*-Pivalamido-9-(2-deoxy-5-*O*-pivalyl-D-*erythro*-pent-1-enofuranosyl)purine (6b). A 165-mg (0.0003 mol) sample of **2b**·H_2O was treated with BSA/pyridine as described above for the conversion of **2b**·H_2O → **2c** to the end of the first paragraph. DBN (0.15 ml) was then added, and stirring was continued for 2 h. MeOH (1.5 ml) was added, and stirring was continued for 30 min. The solution was evaporated, the residue was partitioned between EtOAc and H_2O, and the combined organic layers were evaporated.

The residue was chromatographed using a silica column (0.8 × 15 cm, 2.8 g) packed in and eluted with $CHCl_3$. Fractions comprising 35 to 165 ml were evaporated to give 123 mg (98%) of **6b** as a waxy solid: uv (MeOH) max 264; 248 nm (ε 18 600; 19 200) shoulder 216 nm (ε 15 900) min 257; 227 nm (ε 18 500; 13 200); NMR ($CDCl_3$) δ 1.21 (s, 9, 5′-OPiv), 1.31 (s, 9, 6-NPiv), 4.32 (m, 2, $H_{5'}$, $H_{5''}$), 4.69 (m, 1, $H_{4'}$), 4.92 (m, 1, $H_{3'}$), 5.57 (d, $J_{OH-3'}$ = 6.0 Hz, 1, 3′-OH), 5.82 (d, $J_{2'-3'}$ = 2.8 Hz, 1, $H_{2'}$), 8.60 (br, 1, 6-NH), 8.56 (s, 1, H_8), 8.86 (s, 1, H_2). Anal. ($C_{20}H_{27}N_5O_5$) C, H, N.

Mass spectrum of the 3′-*O*-trimethylsilyl derivative (**6a**) calcd for M^+ ($C_{23}H_{35}N_5O_5Si$): 489.2407; found: *m/e* 489.2425.

9-(2-Deoxy-D-*erythro*-pent-1-enofuranosyl)adenine (6c). A 1.13-g (0.002 mol) sample of **2b**·H_2O was treated with BSA/pyridine and then DBN as in the above preparation of **6b** to the end of the first paragraph.

The residue was treated with 500 mg of NaOMe in 20 ml of MeOH overnight at room temperature, evaporated, and dissolved in 25 ml of H_2O. Crystallization occurred rapidly to give 474 mg (89%) of **6c**·monohydrate in two crops. A sample for analysis was dried over P_2O_5 at 110 °C (0.1 mm Hg) to give **6c**: mp 196–198 °C, resolidifies at 202–210 °C and melts with decomposition at 224–235 °C; $[\alpha]^{27}$D 100.5° (*c* 0.96, DMF); uv (MeOH) max 250 nm (ε 16 500) shoulder 281; 290 nm (ε 7200; 4700) min 222 nm (ε 10 700); NMR (Me_2SO-d_6) δ 3.59 ("t", $J_{apparent}$ = 6 Hz, 2, $H_{5'}$, $H_{5''}$), 4.43 ("sextet", $J_{4'-5' \text{ and } 5''}$ = 5.0 Hz, $J_{4'-3'}$ = 3.0 Hz, 1, $H_{4'}$), 4.84 ("quintet", $J_{3'-2'}$ = 2.8 Hz, $J_{3'-4'}$ = 3.0 Hz, $J_{3'-OH}$ = 6.0 Hz, 1, $H_{3'}$), 5.03 (t, $J_{OH-5' \text{ and } 5''}$ = 6.0 Hz, 1, 5′-OH), 5.35 (d, $J_{OH-3'}$ = 6.0 Hz, 1, 3′-OH), 5.69 (d, $J_{2'-3'}$ = 2.8 Hz, 1, $H_{2'}$), 7.47 (s, 2, 6-NH_2), 8.30 and 8.34 (s and s, 1 and 1, H_2 and H_8); pK_a ~ 3.31. Anal. ($C_{10}H_{11}N_5O_3$) C, H, N.

Mass spectrum calcd for $M^+ - H_2O$ ($C_{10}H_9N_5O_2$): 231.0756; found: *m/e* 231.0752; tris(trimethylsilyl) derivative of **6c**, calcd for M^+ ($C_{19}H_{35}N_5O_3Si_3$): 465.2047; found: *m/e* 465.2062.

2′-Deoxyadenosine (11) and 9-(2-Deoxy-α-D-*erythro*-pentofuranosyl)adenine (12). A mixture of 267 mg (0.001 mol) of **6c**·H_2O, 84 mg (0.001 mol) of $NaHCO_3$, 100 mg of 5% Pd/C, and 50 ml of 95% EtOH–H_2O (4:1) was hydrogenated at 3 psi for 2 h, filtered using a Celite pad, the filter cake washed with EtOH and H_2O, and the filtrate evaporated. The residue was dissolved in H_2O and applied to a column of Dowex 1-X2(OH^-) resin (2.2 × 58 cm) packed in and eluted with H_2O. Evaporation of the fractions from 1650 to 2050 ml gave 34 mg (14%) of solid. "Diffusion crystallization"[20] of this product (MeOH/Et_2O) gave 30 mg of **12**: mp 216–217 °C; $[\alpha]^{23}$D 70.8° (*c* 0.92, H_2O); NMR (Me_2SO-d_6) δ 2.31 (d of "t", $J_{2''-2'}$ = 14 Hz, $J_{2''-3'}$ = 3 Hz, $J_{2''-1'}$ = 3 Hz, 1 $H_{2''}$), 2.72 ("sextet", $J_{2'-2''}$ = 14 Hz, $J_{2'-3'}$ = 7 Hz, $J_{2'-1'}$ = 8 Hz, 1, $H_{2'}$), 3.46 ("t", $J_{apparent}$ = 5 Hz; on D_2O exchange, d, $J_{5' \text{ and } 5''-4'}$ = 4.5 Hz, 2, $H_{5'}$, $H_{5''}$), 4.12 (m, 1, $H_{4'}$), 4.30 (m, 1, $H_{3'}$), 4.81 (t, $J_{OH-5' \text{ and } 5''}$ = 5 Hz, 1, 5′-OH), 5.75 (d, $J_{OH-3'}$ = 4.5 Hz, 1, 3′-OH), 6.33 ("q", $J_{1'-2'}$ = 8 Hz, $J_{1'-2''}$ = 3 Hz, 1, $H_{1'}$), 7.22 (s, 2, 6-NH_2), 8.16 (s, 1, H_2), 8.38 (s, 1, H_8); [lit.[30] mp 211–213.5 °C; $[\alpha]^{27}$D 69.8° (*c* 0.9, H_2O)]. Anal. ($C_{10}H_{13}N_5O_3$) C, H, N.

Evaporation of fractions comprising 2350 to 4050 ml gave 181 mg (68%) of **11**·H_2O. Crystallization of this material from MeOH (Et_2O diffusion)[20] gave 143 mg: mp 192–193 °C; $[\alpha]^{23}$ D −26.7° (*c* 1.10, H_2O); NMR spectrum identical with that of an authentic sample.[20] Anal. ($C_{10}H_{13}N_5O_3$·H_2O) C, H, N.

References and Notes

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