Ca^{2+}, 14127-61-8; Ba^{2+}, 22541-12-4; Pb^{2+}, 14280-50-3; Cu^{2+}, 15158-11-9; Ni^{2+}, 14701-22-5; Co^{2+}, 22541-53-3; Zn^{2+}, 23713-49-7; cyclam, 295-37-4; *N,N*-diethylchloroacetamide, 2315-36-8; ethyl chloroacetate, 105-39-5; chloroacetonitrile, 107-14-2; phenacyl bromide, 70-11-1; piperazine, 110-85-0; 1,4,7-triazacyclononane, 4730-54-5; 1,4,8,12-tetraazacyclopentadecane, 15439-16-4; 1,4,8,11-tetraazacyclotetradecane-5,7-dione, 63972-19-0; 1,4,7,10-tetraazacyclododecane tetrahydrochloride, 10045-25-7.

Supplementary Material Available: ^{1}H and/or ^{13}C NMR spectra for compounds **2b–d** (6 pages). Ordering information is given on any current masthead page.

Nucleic Acid Related Compounds. 70. Synthesis of 2′(and 3′)-Deoxy-2′(and 3′)-methyleneadenosines and Bis(methylene)furan 4′,5′-Didehydro-5′-deoxy-2′(and 3′)-methyleneadenosines. Inhibitors of *S*-Adenosyl-L-homocysteine Hydrolase and Ribonucleotide Reductase[1]

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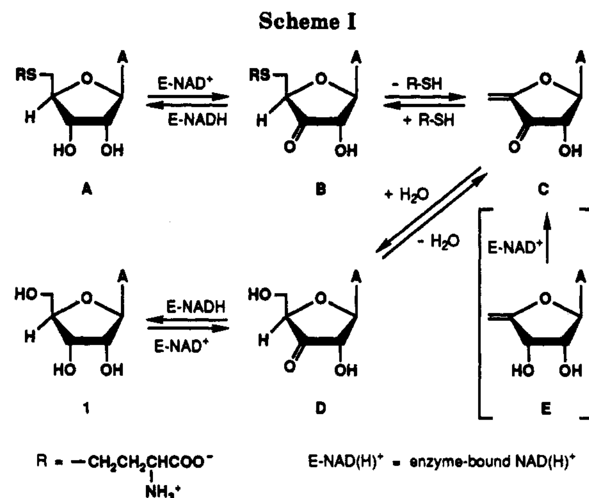
Wittig treatment of 3′,5′(or 2′,5′)-bis-*O*-silyl-2′(or 3′)-ketoadenosine derivatives with methylenetriphenylphosphorane and deprotection gave the 2′(or 3′)-deoxy-2′(or 3′)-methyleneadenosines, respectively. Enzymatic deamination afforded the 2′(or 3′)-deoxy-2′(or 3′)-methyleneinosines. Treatment of 2′-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-3′-methylene-5′-*O*-tosyladenosine (**14**) with sodium 2-methyl-2-butoxide and deprotection gave 9-(3,5-dideoxy-3-methylene-*β*-D-*glycero*-pent-4-enofuranosyl)adenine (**20**). Analogous treatment of a protected 2′,5′-dideoxy-5′-iodo-2′-methyleneadenosine derivative gave 9-(2,5-dideoxy-2-methylene-*β*-D-*glycero*-pent-4-enofuranosyl)adenine (**22**). Biochemical aspects of the putative mechanism-based inhibition of *S*-adenosyl-L-homocysteine hydrolase and ribonucleotide reductase by these compounds are discussed.

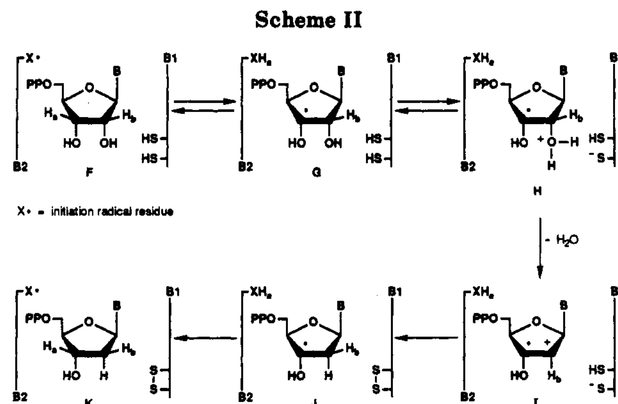
S-Adenosyl-L-homocysteine (AdoHcy) hydrolase (SAHase) (EC 3.3.1.1) and ribonucleoside diphosphate reductase (RDPR) (1.17.4.1) are important enzymes in the nucleic acid manifold. SAHase catalyzes the reversible hydrolysis of AdoHcy (A, Scheme I) to adenosine (1) and L-homocysteine.[2] This is crucial for continuing biosynthesis and cell division since the accumulation of AdoHcy results in feedback inhibition of important *S*-adenosylmethionine(AdoMet)-dependent transmethylation reactions.[3,4] Therefore, the targeted inhibition of SAHase is attractive for the development of pharmacologically active agents.[3,5,6] The accepted mechanism for SAHase[7] (Scheme I) is initiated by oxidation of the secondary alcohol function at C3′ of AdoHcy (A) by enzyme-bound NAD^+ to give 3′-ketonucleoside B. This activates H4′ for elimination of L-homocysteine to give enone C. Michael-type addition of water gives 3′-ketoadenosine (D) that is reduced by NADH to give adenosine (1). All steps in this sequence are reversible, and AdoHcy (A) is formed from adenosine and L-homocysteine in the presence of SAHase. It has been demonstrated[7b,c] that 9-(5-deoxy-*β*-D-*erythro*-pent-4-enofuranosyl)adenine (4′,5′-didehydro-5′-deoxyadenosine) (E) is oxidized at C3′ by the enzyme-bound NAD^+ of SAHase to give enone C directly.

Reduction of ribonucleoside 5′-diphosphates catalyzed by RDPR gives the essential 2′-deoxyribonucleotide building blocks for DNA synthesis in dividing cells.[8-10] Thus, RDPR plays a crucial role in cell growth. The

Scheme I



Scheme II



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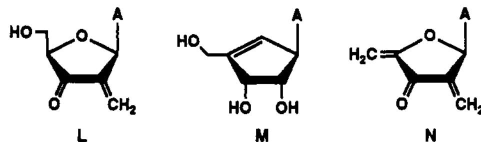
proposed mechanism[11] for RDPR (Scheme II) is initiated by abstraction of H3′(H_a) from a ribonucleoside 5′-diphosphate F by a radial species (X•) to give G. (A stabilized tyrosine oxy radical is contained in the B2 subunit of the enzyme.) Subsequent loss of water (the protonated 2′-hydroxyl group with general acid catalysis by a thiol pair present in the B1 subunit at the active site) from the resulting radical species H generates the radical cation I. "Hydride-equivalent" transfer from the dithiolate to I would give the reduced radical J. Return of H_a from the initiation complex to radical J produces the 2′-deoxynucleotide product K with concomitant regeneration of the initiating enzyme radical species (X•) to activate another ribonucleotide during the next catalytic cycle.

The design and synthesis of mechanism-based inhibitors[12] of SAHase and RDPR is the subject of this study. We had envisaged that functionalities present in the 2′(and 3′)-deoxy-2′(and 3′)-methyleneadenosines (**11** and **7**) and their corresponding 5′-deoxy-4′,5′-unsaturated derivatives **22** and **20** might be compatible with alternative substrate processing by SAHase and/or RDPR. Intermediates produced could be predicted to be reactive and/or tight-binding analogues that might result in the formation of covalently bonded or tightly associated inactivated enzyme complexes.

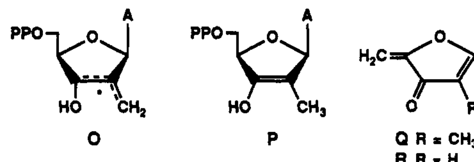
For example, 3′-deoxy-3′-methyleneadenosine (**7**) and its 4′,5′-unsaturated derivative **20** are crude "isosteric analogues" of intermediates D and C, respectively, in the SAHase mechanistic pathway (Scheme I). In these analogues, the sp^2 hybridized C3′ is bonded to a methylene carbon rather than a carbonyl oxygen. Such analogues would not be expected to react with the enzyme, but might be relatively tight-binding congeners. In contrast, oxidative removal of H3′ (hydride equivalent) from 2′-deoxy-2′-methyleneadenosine (**11**) by the enzyme-bound NAD^+ and proton loss from O3′ would generate the exocyclic enone species L that might function as an inactivating Michael acceptor.

It has been postulated that inactivation of SAHase by 2′-deoxyadenosine,[13a] 9-(β-D-arabinofuranosyl)adenine,[2] and neplanocin A[13b] (M) (a 4′-unsaturated "carbocyclic nucleoside" (cyclopentene) antibiotic) might result from oxidation at C3′ followed by β-elimination of adenine anion to give Michael-alkylating species (and might have occurred by direct enone formation with neplanocin A (M)). Borchardt since has shown that the likely mechanism of inhibition involves tightly bound NAD^+ cofactor depletion.[14]



For methylene analogue **11**, prior results[7b,c,14] suggested the possibility of alternative substrate oxidation of the secondary allylic alcohol function at C3′ by SAHase. The resulting exocyclic enone L would represent a new type of Michael acceptor with an electrophilic methylene group projecting outward from C2′ that would be generated by oxidation at C3′ without subsequent β-elimination. If analogous oxidation of the 4′,5′-didehydro-5′-deoxy-2′-methylene compound **22** occurred (or elimination of water from L), the cross-conjugated 2′,4′-bismethylen-3′-one species N would be generated with three contiguous sp^2-hybridized carbon atoms that might function as a potent alkylating agent at the active site of SAHase. Since SAHase accepts adenosine but not inosine analogues, an important biological consideration might favor the bismethylene analogues. The 2′(and 3′)-deoxy-2′(and 3′)-methyleneadenosines (**11** and **7**) are effective alternative substrates of adenosine aminohydrolase (EC 3.5.4.4) and are converted to their inactive inosine analogues (**12** and **8**), whereas the corresponding 4′,5′-didehydro-5′-deoxy analogues (**22** and **20**) are not deaminated. Adenosine aminohydrolase has broad substrate tolerance, but an intact 5′-hydroxymethyl group usually is required[15] by the mammalian enzyme.

The presence of a 5′-hydroxyl group also is necessary to allow formation of the 5′-diphosphate ester for RDPR. Abstraction of H3′ by the radical initiator (see Scheme II) at C3′ of 2′-deoxy-2′-methyleneadenosine 5′-diphosphate would result in the generation of an allylic radical species O. Hydrogen transfer to the exocyclic methylene carbon of O would produce enol P. Loss of its enol proton and conjugate elimination of adenine anion followed by β-elimination of H4′ and pyrophosphate would produce the 4-methyl-2-methylene-3(2*H*)-furanone (Q) analogue of Michael acceptor R that has been shown by Stubbe and co-workers to execute time-dependent irreversible inactivation of RDPR.[11]



Tronchet and Tronchet[16] prepared the first deoxymethylenenucleoside by condensation of a 3-methylene-α-D-*erythro*-pentofuranose derivative with 6-*N*-benzoyladenine chloromercury salt to give a mixture from which the β-anomer of 3′-deoxy-3′-methyleneadenosine (**7**) was obtained. Ueda and co-workers have prepared 2′-deoxy-2′-methyleneadenosine[17] (**11**) and various alkyl- and alkylidenenucleoside derivatives.[18,19] They recently reported the potent anticancer activity of 2′-deoxy-2′-methylenecytidine.[19,20] We have studied 2′- and 3′-ketonucleosides for several years,[21] and recently reported efficient conversion of uridine into the four exomethylene analogues of 2′- and 3′-deoxyuridine and -cytidine.[22] As we pre-

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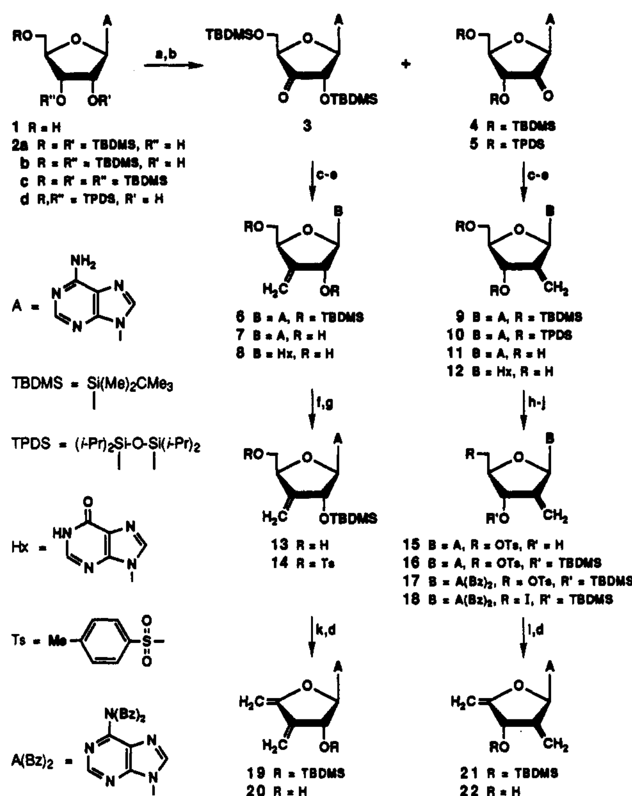
Scheme III[a]



[a] (a) TBDMSCl (or $TPDSCl_2$)/pyridine; (b) CrO_3/pyridine/Ac_2O; (c) $Ph_3PCH_3^+Br^-/Na^+\bar{O}C(Me)_2Et^-/Et_2O$/benzene; (d) $Bu_4N^+F^-$/THF; (e) Adenosine deaminase; (f) CF_3CO_2H/H_2O; (g) $TsCl/Et_3N$/DMAP; (h) TsCl/pyridine; (i) (i) TBDMSCl/imidazole/DMF, (ii) BzCl/pyridine; (j) NaI/acetone; (k) $Na^+OC(Me)_2Et^-$/benzene; (l) (i) DBN/DMF, (ii) NH_3/MeOH.

dicted, 2'-deoxy-2'-methylenecytidine 5'-diphosphate is a potent mechanism-based inhibitor of *Escherichia coli* ribonucleoside 5'-diphosphate reductase.[23] We now describe syntheses of 2'(and 3')-deoxy-2'(and 3')-methyleneadenosines, enzymatic deamination to give the inosine analogues, and the first syntheses of 9-(2,5-dideoxy-2-methylene-β-D-*glycero*-pent-4-enofuranosyl)adenine (**22**) and 9-(3,5-dideoxy-3-methylene-β-D-*glycero*-pent-4-enofuranosyl)adenine (**20**).

Protection[24] of adenosine (**1**) with *tert*-butyldimethylsilyl (TBDMS) chloride gave 2',5'-bis- (**2a**, 56%), 3',5'-bis- (**2b**, 30%), and 2',3',5'-tris-*O*-(*tert*-butyldimethylsilyl)adenosine (**2c**, 4%) or 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[25] (TPDS dichloride) gave 3',5'-*O*-(tetraisopropyldisiloxanediyl)adenosine (**2d**) (Scheme III). Oxidation (chromium trioxide/pyridine/acetic anhydride[26] or the Dess-Martin[27] 12-I-5 periodinane[28,29]) gave ketoadenosines **3-5**. Methylenetriphenylphosphorane (methyltriphenylphosphonium bromide and sodium 2-methyl-2-butoxide[30] in diethyl ether/benzene at 0-4 °C) converted **3-5** to intermediates that showed no migration (TLC). ^1H and ^{31}P NMR spectra of an analogous Wittig reaction in the uridine series indicated formation of a single oxaphosphetane diastereomer.[22] These intermediates slowly disappeared with formation of the respective 2'- (**9**, 35%; **10**, 35%) and 3'-deoxy-3'-methylene (**6**, 80%) compounds. Deprotection (tetrabutylammonium fluoride/tetrahydrofuran (TBAF/THF)) and purification (Dowex 1 × 2 (OH^-)) gave crystalline **11** and **7**, respectively. Enzymatic deamination of **7** and **11** afforded 3'- (**8**) and 2'-deoxy-2'-methyleneinosine (**12**).

Syntheses of 4',5'-unsaturated nucleosides have employed elimination reactions[31] of 5'-iodonucleosides with silver fluoride/pyridine,[32] 5'-iodo(or 5'-*O*-tosyl)nucleosides with potassium *tert*-butoxide or 1,5-diazabicyclo[4.3.0]non-4-ene (DBN)[33-35] and thermal eliminations of 5'-selenoxides.[36] Our selective removal of 5'-*O*-TBDMS groups (aqueous trifluoroacetic acid at 0 °C)[28] converted **6** to 2'-*O*-(*tert*-butyldimethylsilyl)-3'-deoxy-3'-methyleneadenosine (**13**, 95%) that was treated with *p*-toluenesulfonyl chloride/4-(dimethylamino)pyridine/triethylamine to give its 5'-*O*-tosyl derivative **14** (84%). Treatment of **14** with sodium 2-methyl-2-butoxide[30b] in benzene gave 2'-*O*-(*tert*-butyldimethylsilyl)-4',5'-didehydro-3',5'-dideoxy-3'-methyleneadenosine (**19**, 80%) that was deprotected (TBAF/THF) and purified (Dowex 1 × 2 (OH^-)) to give crystalline 4',5'-didehydro-3',5'-dideoxy-3'-methyleneadenosine (**20**, 95%).

Attempted removal of the 5'-*O*-TBDMS group from **9** with aqueous trifluoroacetic acid at ≤0 °C resulted in rapid glycosyl bond cleavage. Treatment of **11** with tosyl chloride/pyridine at 5 °C gave a mixture of the 5'-*O*-tosyl (**15**, 52%) and 3',5'-di-*O*-tosyl (18%) derivatives. Successive treatment of **15** with TBDMS chloride/imidazole/DMF and benzoyl chloride/pyridine afforded the 6-*N*,*N*-dibenzoyl-3'-*O*-(*tert*-butyldimethylsilyl)-5'-*O*-tosyl compound **17** (60%). N-Benzoylation of **16** was required to prevent intramolecular attack[37] of N3 at C5'. Treatment of **17** with sodium 2-methyl-2-butoxide/benzene resulted in recovery of starting material plus debenzoylated products. Displacement of the 5'-tosyloxy group of **17** by iodide afforded **18** (54%). Successive treatment of the 5'-iodo derivative **18** with DBN/DMF and NH_3/MeOH gave the desired 4',5'-unsaturated compound **21** plus debenzoylated starting 5'-iodide (~4:1, ^1H NMR). Further deprotection of this mixture (TBAF/THF) and purification (HPLC) afforded **22** plus the completely deprotected 2',5'-dideoxy-5'-iodo-2'-methyleneadenosine.

It is noteworthy that our biomechanistic predictions were vindicated. Compound **11** is a time-dependent inactivator of purified SAHase, and **20** is a weak inhibitor.[38] The 2'-deoxy-2'-methylenecytidine analogue of compound **11** (as its 5'-diphosphate ester) is a potent time-dependent irreversible inhibitor of RDPR[23] that has antitumor ac-

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Table I. ^{13}C NMR Chemical Shift Data[a]

compd	C2	C4	C5	C6	C8	CH_2	C1′	C2′	C3′	C4′	C5′
6	153.71	147.98	120.13	156.16	139.56	109.00	88.21	77.56	150.88	81.89	66.49
7	153.06	149.71	119.60	156.61	140.49	108.39	88.51	74.00	148.61	81.75	64.70
8	146.30	148.76	124.58	156.94	139.27	108.61	87.76	74.53	148.04	81.52	64.19
9	153.80	149.51	120.14	155.90	139.39	113.28	85.42	150.50	70.75	83.22	61.40
10	153.76	148.04	120.45	156.18	139.02	112.26	83.69	150.23	71.69	83.02	61.66
11	153.04	149.32	119.01	156.32	139.67	111.92	85.44	150.28	70.11	82.79	61.06
12	146.19	148.25	124.40	156.91	139.09	112.47	85.52	149.83	69.99	82.95	60.91
13	153.37	149.36	121.69	156.56	141.12	108.74	92.15	74.91	147.54	83.59	66.26
19	154.04	150.54	120.60	156.11	139.32	111.63	89.60	75.74	156.99	142.24	83.48
20	153.34	149.80	119.20	156.26	140.05	110.88	88.25	72.45	156.73	142.58	82.10
22	153.26	148.96	119.18	156.21	140.20	113.98	83.48	163.38	69.10	146.04	83.27

[a] δ (Me_4Si internal) in $CDCl_3$ (**6, 9, 10, 13, 19**) or Me_2SO-d_6 (**7, 8, 11, 12, 20, 22**).

tivity in cell culture and animal models.[19,20] The adenosine analogue **11** is readily deaminated by adenosine aminohydrolase, which might result in such rapid conversion to the inactive inosine derivative **12** that biological activity in cellular or animal systems is precluded. However, **11** inactivates the purified SAHase under cell-free conditions, as predicted. The preparation of additional biologically active methylenenucleoside analogues and comprehensive biological activity results will be reported separately.

Experimental Section

General Procedures. Ultraviolet (UV) spectra were determined with MeOH solutions unless specified otherwise. Low-resolution electron-impact mass spectra (MS) were determined at 20 eV. Flash evaporations were performed with a water aspirator or oil pump vacuum at <35 °C. Preparative HPLC was performed with PrepPAK-500/silica cartridges or a C_{18} reversed-phase column. TLC was performed on silica sheets. Flash chromatography was effected with E. Merck Kieselgel 60, 230–400 mesh. Unless specified otherwise the solvent system for all chromatography was hexane/EtOAc (3:7, v/v). Reagent-grade solvents and reagents were redistilled prior to use. Pyridine, Et_3N, and benzene were dried by refluxing with and distillation from CaH_2. Et_2O was distilled from sodium benzophenone ketyl. MeCN and DMF were distilled from P_4O_{10}.

Silylation of Adenosine.[24] TBDMSCl (17.0 g, 112.2 mmol) was added to a suspension of **1** (10.0 g, 37.4 mmol) in pyridine (75 mL) and stirred at ambient temperature for 48 h. Solvent was evaporated and the residue partitioned (ice-cold 5% HCl/H_2O//CH_2Cl_2). The organic phase was washed (saturated $NaHCO_3/H_2O$ and brine), dried (Na_2SO_4), and evaporated. Preparative HPLC (silica gel) of the white solid gave 2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)adenosine (**2c**, 0.80 g, 4%; R_f ~0.5), 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)adenosine (**2a**, 10.4 g, 56%; R_f ~0.3), and 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)adenosine (**2b**, 5.62 g, 30%; R_f ~0.15) as colorless powders with expected spectral properties.[24]

9-(2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuran-3-ulosyl)adenine (3). Procedure A.[26] Ac_2O (1.1 mL, 1.2 g, 12.1 mmol) and pyridine (1.9 mL, 1.85 g, 24.2 mmol) were added to an ice-cold suspension of CrO_3 (1.2 g, 12.1 mmol) in CH_2Cl_2 (25 mL) and stirred until homogeneous (~15 min) at ambient temperature. A suspension of **2a** (3.0 g, 6.0 mmol) in CH_2Cl_2 (5 mL) was added, stirring continued for 1.5 h, and the mixture poured into cold EtOAc (1 L) and filtered (glass microfiber filter, GF/A). Concentration of the filtrate (<25 °C) and purification (short column chromatography, EtOAc) gave **3** (2.4 g, 80%) as a colorless powder with expected properties.[26]

9-(3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuran-2-ulosyl)adenine (4). Oxidation of **2b** (3.0 g, 6.0 mmol, procedure A) gave light yellow amorphous **4** (1.8 g, 60%) with expected properties.[26]

9-(3,5-*O*-(Tetraisopropyldisiloxanediyl)-β-D-*erythro*-pentofuran-2-ulosyl)adenine (5). Oxidation of **2d**[25] (1.5 g, 2.9 mmol, procedure A) afforded light yellow amorphous **5** (0.89 g, 60%) with expected properties.[26]

9-(2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-methylene-β-D-*erythro*-pentofuranosyl)adenine (6). Procedure B.[30a] Sodium 2-methyl-2-butoxide (1.1 M in benzene, 5.4 mL, 6.0 mmol) was added to a suspension of methyltriphenylphosphonium bromide (2.4 g, 6.6 mmol) in dry Et_2O (180 mL) under N_2, and stirring of the yellow mixture was continued for 2 h. The mixture was cooled (−78 °C), **3** (1.0 g, 2.0 mmol) added, and the resulting mixture warmed to −10 °C over 1 h and stored at 4 °C for 48 h. Saturated NH_4Cl/H_2O was added and the aqueous layer extracted (Et_2O). The combined organic phase was washed (brine), dried, and evaporated. Column chromatography (hexane/EtOAc (2:3)) and crystallization (CH_2Cl_2/hexane) gave colorless needles of **6** (0.69 g, 80%): mp 121–122 °C; UV max 260 nm (ϵ 14 400); ^{1}H NMR ($CDCl_3$) δ 0.0–0.1 (4s, 12, 2SiMe$_2$), 0.80 and 0.90 (2s, 18, 2SiCMe$_3$), 3.77 (dd, $J_{5'-5''}$ = 11 Hz, $J_{5'-4'}$ = 3.4 Hz, 1, H5′), 3.93 (dd, $J_{5''-4'}$ = 3.4 Hz, 1, H5″), 4.69 (m, 1, H4′), 5.07 (d"q", $J_{2'-1'}$ = 6.6 Hz, $J_{'q'}$ = 1.8 Hz, 1, H2′), 5.16 (dd, J = 2.0, 2.4 Hz, 1, CH_AH_B), 5.24 (t, J = 2.0 Hz, 1, CH_AH_B), 5.86 (d, 1, H1′), 6.03 (br s, 2, NH_2), 8.14 (s, 1, H2), 8.31 (s, 1, H8); MS m/z 491 (4, M^+), 434 (100, M − CMe$_3$), 328 (30, M − B − CHO).

9-(3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-methylene-β-D-*erythro*-pentofuranosyl)adenine (9). Treatment of **4** (1.0 g, 2.0 mmol) by procedure B with chromatography (hexane/EtOAc (7:3)) gave colorless amorphous **9** (0.35 g, 35%): UV max 260 nm; ^{1}H NMR ($CDCl_3$) δ 0.0–0.1 (4s, 12, 2SiMe$_2$), 0.88 and 0.90 (2s, 18, 2SiCMe$_3$), 3.70–3.95 (m, 3, H4′,5′,5″), 4.98 (d"q", J = 5.0, 2.0 Hz, 1, H3′), 5.31 (dd, J = 2.2, 2.0 Hz, 1, CH_AH_B), 5.39 (t, J = 2.2 Hz, 1, CH_AH_B), 5.86 (br s, 2, NH_2), 6.72 ("q", $J_{'q'}$ = 1.4 Hz, 1, H1′), 7.95 (s, 1, H2), 8.34 (s, 1, H8); MS m/z 434 (100, M − CMe$_3$), 357 (4, M − B).

9-(2-Deoxy-3,5-*O*-(tetraisopropyldisiloxanediyl)-2-methylene-β-D-*erythro*-pentofuranosyl)adenine (10). Treatment of **5** (2.9 g, 5.8 mmol) by procedure B with chromatography (EtOH/$CHCl_3$, (1:24)) afforded light yellow amorphous **10** (1.0 g, 35%); UV max 260 nm; ^{1}H NMR ($CDCl_3$) δ 1.0–1.1 (m, 28, 2Si(i-Pr)$_2$), 3.78 (dt, $J_{4'-3'}$ = 8.4 Hz, $J_{4'-5'} \simeq J_{4'-5''}$ = 3.4 Hz, 1, H4′), 4.02 (dd, $J_{5'-5''}$ = 12.7 Hz, 1, H5′), 4.11 (dd, 1, H5″), 5.24 (d"q", $J_{'q'}$ = 1.7 Hz, 1, H3′), 5.41 (br s, 1, CH_AH_B), 5.48 (t, J = 1.7 Hz, 1, CH_AH_B), 6.02 (br s, 2, NH_2), 6.60 (br s, 1, H1′), 7.87 (s, 1, H2), 8.31 (s, 1, H8); MS m/z 462 (100, M − i-Pr), 371 (10, M − B), 328 (20, M − B − i-Pr).

9-(3-Deoxy-3-methylene-β-D-*erythro*-pentofuranosyl)adenine (3′-Deoxy-3′-methyleneadenosine) (7). Procedure C. TBAF/THF (1 M, 2.4 mL, 2.4 mmol) was added to a stirred solution of **6** (0.60 g, 1.2 mmol) in THF (20 mL). After 3 h solvent was evaporated and the residue partitioned (Et_2O/H_2O). The aqueous layer was washed (Et_2O), concentrated (<35 °C), and chromatographed (Dowex 1 × 2 (OH^-) resin, H_2O). Elution ($MeOH/H_2O$ (1:1)), evaporation of appropriate fractions, and recrystallization (EtOH) gave colorless solid **7** (0.32 g, 99%): mp 182–183 °C; UV (H_2O, pH 7) max 260 nm (ϵ 14 700); ^{1}H NMR (Me_2SO-d_6) δ 3.56 (ddd, $J_{5'-5''}$ = 12.0 Hz, $J_{5'-OH}$ = 7.4 Hz, $J_{5'-4'}$ = 4.2 Hz, 1, H5′), 3.69 (ddd, $J_{5''-OH}$ = 4.4 Hz, $J_{5''-4'}$ = 3.4 Hz, 1, H5″), 4.65 (br s, 1, H4′), 5.13 (t"q", $J_{2'-1'}$ = $J_{2'-OH}$ = 6.6 Hz, $J_{'q'}$ = 1.8 Hz, 1, H2′), 5.21 (dd, J = 2.0, 1.8 Hz, 1, CH_AH_B), 5.25 (dd, J = 2.2, 2.0 Hz, 1, CH_AH_B), 5.39 (dd, 1, OH5′), 5.70 (d, 1, H1′), 5.94 (d, 1, OH2′), 7.37 (br s, 2, NH_2), 8.14 (s, 1, H2), 8.37 (s, 1, H8); MS m/z 263 (16, M^+), 233 (30, M − CH_2O), 164 (100, BHCHO), 136 (80, BH_2). Anal. Calcd for $C_{11}H_{13}N_5O_3 \cdot 0.25H_2O$: C, 49.34; H, 5.08; N, 26.16. Found: C, 49.09; H, 4.94; N, 26.22.

9-(2-Deoxy-2-methylene-β-D-*erythro*-pentofuranosyl)adenine (2′-Deoxy-2′-methyleneadenosine) (11). Treatment of **9** (0.80 g, 1.6 mmol) by procedure C with recrystallization

($MeOH/H_2O$) gave colorless prisms of **11** (0.42 g, 99%): mp 204–205 °C dec; UV (H_2O, pH 7) max 260 nm (ε 14700); ^1H NMR (Me_2SO-d_6) δ 3.5–3.8 (m, 3, H4′,5′,5″), 4.77 (t"q", $J_{3'-4'} \cong J_{3'-OH}$ = 7 Hz, $J_{q'}$ = 1.6 Hz, 1, H3′), 5.00 (t, J = 5.4 Hz, 1, OH5′), 5.20 (dd, J = 2.0, 2.2 Hz, 1, CH_AH_B), 5.38 (dd, J = 2.0, 1.6 Hz, 1, CH_AH_B), 5.71 (d, 1, OH3′), 6.61 ("q", $J_{q'}$ = 2.0 Hz, 1, H1′), 7.29 (br s, 2, NH_2), 8.13 (s, 1, H2), 8.21 (s, 1, H8); MS m/z 263 (16, M^+), 232 (100, M – CH_2OH). Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.98; N, 26.60. Found: C, 49.93; H, 4.97; N, 26.51. Compound **11** also was obtained from **10** by procedure C in an equivalent yield.

9-(3-Deoxy-3-methylene-β-D-*erythro*-pentofuranosyl)hypoxanthine (3′-Deoxy-3′-methyleneinosine) (8). Procedure D. Adenosine deaminase (30 mg, Sigma type II) was added to a solution of **7** (100 mg, 0.38 mmol) in aqueous phosphate buffer (0.05 M, pH 7.5; 25 mL) and the mixture stirred at ambient temperature for 8 h. The suspension was concentrated and chromatographed (Amberlite XAD-4, H_2O). Elution (H_2O, 600 mL; MeOH, 100 mL), evaporation of appropriate fractions, and recrystallization (MeOH) gave colorless needles of **8** (100 mg, quant): mp 212–213 °C dec; UV (H_2O, pH 7) max 248 nm (ε 12200); ^1H NMR (Me_2SO-d_6) δ 3.55–3.70 (m, 2, H5′,5″), 4.63 (br s, 1, H4′), 5.02 (br m, 1, H2′), 5.03 (t, J = 5.8 Hz, 1, OH5′), 5.21 (dd, J = 2.0, 1.5 Hz, 1, CH_AH_B), 5.25 (dd, J = 2.0, 1.6 Hz, 1, CH_AH_B), 5.69 (d, $J_{1'-2'}$ = 7 Hz, 1, H1′), 5.97 (d, $J_{OH-2'}$ = 6.2 Hz, 1, OH2′), 8.10 (s, 1, H2), 8.39 (s, 1, H8), 12.43 (br m, 1, NH); MS m/z 264 (20, M^+), 165 (40, BHCHO), 136 (100, BH). Anal. Calcd for $C_{11}H_{12}N_4O_4 \cdot 0.25H_2O$: C, 49.16; H, 4.69; N, 20.85. Found: C, 49.55; H, 4.39; N, 20.78.

9-(2-Deoxy-2-methylene-β-D-*erythro*-pentofuranosyl)hypoxanthine (2′-Deoxy-2′-methyleneinosine) (12). Treatment of **11** (110 mg, 0.41 mmol) by procedure D (1 h) and recrystallization ($MeOH/H_2O$) gave colorless solid **12** (110 mg, quant); mp 119–120 °C (softening); UV (H_2O, pH 7) max 248 nm (ε 11900); ^1H NMR (Me_2SO-d_6) δ 3.58 (dd, $J_{5'-5''}$ = 12.5 Hz, $J_{5'-4'}$ = 5.2 Hz, 1, H5′), 3.65–3.80 (m, 2, H4′,5″), 4.73 (d, $J_{3'-4'}$ = 6.5 Hz, 1, H3′), 4.95 (br s, 1, OH), 5.25 (dd, J = 2.0, 1.6 Hz, 1, CH_AH_B), 5.41 (t, J = 2.0 Hz, 1, CH_AH_B), 5.75 (br s, 1, OH), 6.59 (d, J = 1.2 Hz, 1, H1′), 8.03 (s, 1, H2), 8.09 (s, 1, H8), 12.15 (br m, 1, NH); MS m/z 246 (8, M – H_2O), 136 (100, BH). Anal. Calcd for $C_{11}H_{12}N_4O_4 \cdot 0.5H_2O$: C, 48.35; H, 4.80; N, 20.50. Found: C, 48.05; H, 4.52; N, 20.18.

9-(2-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-methylene-β-D-*erythro*-pentofuranosyl)adenine (13). To a solution of trifluoroacetic acid/H_2O (9:1, 20 mL) at 0 °C was added **6** (1.2 g, 2.44 mmol) and stirring continued at 0 °C for 30 min. The mixture was evaporated in vacuo (<25 °C) and partitioned (ice-cold EtOAc (40 mL)//saturated $NaHCO_3/H_2O$ (30 mL)). The aqueous layer was extracted (EtOAc, 2 × 40 mL) and the combined organic phase washed (H_2O, 30 mL; brine), dried, and evaporated. Crystallization (EtOAc/hexane) gave colorless needles of **13** (0.87 g, 95%): mp 195–196 °C; UV max 259 nm (ε 17000); ^1H NMR ($CDCl_3$) δ –0.20 (s, 3, SiMe), –0.10 (s, 3, SiMe), 0.80 (s, 9, $SiCMe_3$), 3.65 (td, $J_{5'-5''} \cong J_{5'-OH}$ = 12.0 Hz, $J_{5'-4'}$ = 1.5 Hz, 1, H5′), 4.02 (br d, 1, H5″), 4.77 (br m, J = 1.5 Hz, 1, H4′), 5.22 (dd, J = 2.5, 1.5 Hz, 1, CH_AH_B), 5.28 (dd, J = 2.5, 2.0 Hz, 1, CH_AH_B), 5.38 (dm, $J_{2'-1'}$ = 7.3 Hz, J_m = 2.5 Hz, 1, H3′), 5.49 (d, 1, H1′), 5.85 (br s, 2, NH_2), 6.35 (br d, 1, OH5′), 7.80 (s, 1, H2), 8.35 (s, 1, H8); MS m/z 377 (2, M^+), 347 (20, M – CH_2O), 320 (100, M – CMe_3), 242 (40, M – BH). Anal. Calcd for $C_{17}H_{27}N_5O_3Si_2$: C, 54.09; H, 7.21; N, 18.55. Found: C, 54.20; H, 7.13; N, 18.65.

9-(2-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-methylene-5-*O*-(*p*-toluenesulfonyl)-β-D-*erythro*-pentofuranosyl)adenine (14). Portions of tosyl chloride (0.27 g, 1.42 mmol) were added slowly to a stirred solution of **13** (0.27 g, 0.71 mmol), Et_3N (1.0 mL, 0.726 g, 7.1 mmol), and DMAP (0.017 g, 0.14 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The mixture was stirred at ambient temperature for 2.5 h and poured into ice-cold saturated $NaHCO_3/H_2O$ (5 mL). The aqueous layer was extracted (CH_2Cl_2, 2 × 10 mL) and the combined organic phase washed (brine, 10 mL), dried, evaporated, and flash chromatographed (EtOAc/hexane (1:1)) to give light yellow amorphous **14** (0.32 g, 84%): UV max 260 nm; ^1H NMR ($CDCl_3$) δ –0.40 (s, 3, SiMe), –0.10 (s, 3, SiMe), 0.75 (s, 9, $SiCMe_3$), 2.39 (s, 3, ArMe), 4.26 (dd, $J_{5'-5''}$ = 10.6 Hz, $J_{5'-4'}$ = 4.0 Hz, 1, H5′), 4.33 (dd, $J_{5''-4'}$ = 5.0 Hz, 1, H5″), 4.86 (m, 1, H4′), 5.24 (br s, 1, CH_AH_B), 5.33 (br s, 1, CH_AH_B), 5.35 (m, 1, H2′), 5.67 (br s, 2, NH_2), 5.71 (d, $J_{1'-2'}$ = 6.6 Hz, 1, H1′), 7.22 (d, J = 8.0 Hz, 2, Ar), 7.72 (d, J = 8.0 Hz, 2, Ar), 7.89 (s, 1, H2), 8.22 (s, 1, H8); MS m/z 474 (2, M – CMe_3), 359 (15, M – TsOH), 302 (20, M – TsOH – CMe_3), 135 (100, BH).

9-(2-*O*-(*tert*-Butyldimethylsilyl)-3,5-dideoxy-3-methylene-β-D-*glycero*-pent-4-enofuranosyl)adenine (19). Sodium 2-methyl-2-butoxide (1.9 M in benzene; 0.35 mL, 0.68 mmol) was added to a cold (6 °C) solution of **14** (0.25 g, 0.47 mmol) in benzene (25 mL), and stirring was continued at ambient temperature for 1 h. The mixture was poured into ice-cold saturated $NaHCO_3/H_2O$ (15 mL) and the organic layer washed (brine), dried, evaporated, and flash chromatographed ($CHCl_3$/EtOH (97:3)) to give a colorless solid foam that was crystallized (CH_2Cl_2/hexane) to give needles of **19** (0.135 g, 80%): mp 120 °C (softening); UV max 258 nm (ε 19500); ^1H NMR ($CDCl_3$) δ –0.20 (s, 3, SiMe), 0.00 (s, 3, SiMe), 0.82 (s, 9, $SiCMe_3$), 4.50 (d, $J_{5'-5''}$ = 2.6 Hz, 1, H5′), 4.63 (d, 1, H5″), 5.30 (d, J = 2.2 Hz, 1, CH_AH_B), 5.35 (dt, $J_{2'-1'}$ = 4.7 Hz, J = 2.2 Hz, 1, H2′), 5.69 (d, J = 2.2 Hz, 1, CH_AH_B), 5.77 (br s, 2, NH_2), 5.99 (d, 1, H1′), 7.83 (s, 1, H2), 8.37 (s, 1, H8); MS m/z 359 (30, M^+), 302 (100, M – CMe_3), 224 (97, M – BH), 167 (40, M – BH – CMe_3). Anal. Calcd for $C_{17}H_{25}N_5O_2Si \cdot 0.5H_2O$: C, 55.41; H, 7.11; N, 19.00. Found: C, 55.52; H, 7.29; N, 18.65.

9-(3,5-Dideoxy-3-methylene-β-D-*glycero*-pent-4-enofuranosyl)adenine (4′,5′-Didehydro-3′,5′-dideoxy-3′-methyleneadenosine) (20). TBAF/THF (1 M; 1.0 mL, 1.0 mmol) was added to a solution of **19** (0.20 g, 0.55 mmol) in THF (20 mL) at 0 °C. The solution was allowed to warm to ambient temperature, stirred for 30 min, cooled to 0 °C, neutralized with AcOH/THF (1:1), concentrated (~4 mL), and chromatographed (Dowex 1 × 2 (OH^-), H_2O). Elution ($MeOH/H_2O$ (1:1) followed by MeOH), evaporation of appropriate fractions, and crystallization ($MeOH/Et_2O$) gave colorless solid **20** (0.129 g, 95%): mp 240 °C dec; UV (H_2O, pH 7) max 259 nm (ε 17000); ^1H NMR (Me_2SO-d_6) δ 4.31 (d, $J_{5'-5''}$ = 2.3 Hz, 1, H5′), 4.65 (d, 1, H5″), 5.37 (d, J = 2.3 Hz, 1, CH_AH_B), 5.47 (br m, 1, H2′), 5.78 (d, J = 2.5 Hz, 1, CH_AH_B), 5.98 (d, $J_{1'-2'}$ = 6.0 Hz, 1, H1′), 6.24 (br d, J = 5.6 Hz, 1, OH2′), 7.39 (br s, 2, NH_2), 8.15 (s, 1, H2), 8.39 (s, 1, H8); MS m/z 245 (34, M^+), 164 (55, BCH_2O), 136 (100, BH_2). Anal. Calcd for $C_{11}H_{11}N_5O_2$: C, 53.87; H, 4.52; N, 28.56. Found: C, 54.00; H, 4.72; N, 28.44.

9-(2-Deoxy-2-methylene-5-*O*-(*p*-toluenesulfonyl)-β-D-*erythro*-pentofuranosyl)adenine (15). Tosyl chloride (1.45 g, 7.6 mmol) was added in portions to a suspension of **11** (1.0 g, 3.8 mmol) in pyridine (150 mL) at 0 °C. The mixture was allowed to stand at 5 °C for 48 h, and additional tosyl chloride (0.36 g, 1.8 mmol) was added. After 24 h at 5 °C, the mixture was evaporated in vacuo (<20 °C) and the residue chromatographed. Elution ($MeOH/CHCl_3$ (1:19), 250 mL) gave the 3′,5′-di-*O*-tosyl compound (0.40 g, 18%) that crystallized ($CHCl_3$) as a pale yellow solid: mp 125 °C dec; UV max 260, 226 nm; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3, ArMe), 2.45 (s, 3, ArMe), 4.08 (dd, $J_{5'-5''}$ = 11.0 Hz, $J_{5'-4'}$ = 3.5 Hz, 1, H5′), 4.16 (dd, $J_{5''-4'}$ = 3.5 Hz, 1, H5″), 4.33 (dt, $J_{4'-3'}$ = 4.4 Hz, 1, H4′), 5.29 (dd, J = 3.2, 1.8 Hz, 1, CH_AH_B), 5.50 (dd, J = 3.2, 1.8 Hz, 1, CH_AH_B), 5.60 (d m, J_m = 1.6 Hz, 1, H3′), 5.98 (br s, 2, NH_2), 6.64 ("q", J = 1.6 Hz, 1, H1′), 7.18–7.85 (4d, J = 8.0 Hz, 8, ArH), 7.85 (s, 1, H2), 8.25 (s, 1, H8).

Elution ($MeOH/CHCl_3$, (1:9), 250 mL) gave **15** (0.82 g, 52%) that crystallized (MeOH) as a colorless solid: mp 190 °C dec; UV max 260 nm; ^1H NMR (Me_2SO-d_6) δ 2.31 (s, 3, ArMe), 3.88 (td, $J_{4'-3'} \cong J_{4'-5'}$ = 6.5 Hz, $J_{4'-5''}$ = 3.0 Hz, 1, H4′), 4.27 (dd, $J_{5'-5''}$ = 11.0 Hz, 1, H5′), 4.35 (dd, 1, H5″), 4.84 (br t, $J_{3'-OH}$ = 6.5 Hz, 1, H3′), 5.24 (s, 1, CH_AH_B), 5.39 (s, 1, CH_AH_B), 5.92 (d, 1, OH3′), 6.57 (s, 1, H1′), 7.25 (d, J = 8.0 Hz, 2, ArH), 7.32 (br s, 2, NH_2), 7.75 (d, J = 8.0 Hz, 2, ArH), 8.08 (s, 1, H2), 8.15 (s, 1, H8); MS m/z 245 (5, M – TsOH), 227 (25, M – TsOH – H_2O), 135 (100, BH).

6-*N*,*N*-Dibenzoyl-9-(3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-methylene-5-*O*-(*p*-toluenesulfonyl)-β-D-*erythro*-pentofuranosyl)adenine (17). TBDMSCl (0.71 g, 4.74 mmol) was added to a stirred solution of **15** (0.66 g, 1.58 mmol) and imidazole (1.13 g, 16.6 mmol) in pyridine (3.5 mL) at 0 °C. After 2 h at ambient temperature the mixture was evaporated in vacuo (<20 °C) and the residue was partitioned (ice-cold saturated $NaHCO_3/H_2O$ (30 mL)//$CHCl_3$ (50 mL)). The aqueous layer was extracted ($CHCl_3$, 30 mL) and the combined organic phase washed

(brine, 30 mL), dried, and evaporated. The colorless powder (**16**, 0.75 g) was dissolved in pyridine (7 mL), cooled to 0 °C, treated with benzoyl chloride (0.92 mL, 1.11 g, 7.9 mmol), and stirred at ambient temperature for 1 h. The solution was evaporated in vacuo (<25 °C) and the residue coevaporated (EtOAc, 3 × 10 mL) and flash chromatographed (EtOAc/hexane (3:7)) to give colorless amorphous **17** (0.69 g, 60%): UV max 273, 250, 224 nm (ϵ 19 700, 24 500, 33 900); ^{1}H NMR ($CDCl_3$) δ 0.15 (s, 3, SiMe), 0.17 (s, 3, SiMe), 0.90 (s, 9, $SiCMe_3$), 2.37 (s, 3, ArMe), 4.00 (dt, $J_{4'-3'}$ = 6.4 Hz, $J_{4'-5'} \cong J_{4'-5''}$ = 3.4 Hz, 1, H4′), 4.24 (d, 2, H5′,5″), 4.95 (d"q", $J_{\text{"q"}}$ = 1.6 Hz, 1, H3′), 5.33 (s, 1, CH_AH_B), 5.48 (s, 1, CH_AH_B), 6.70 ("q", J = 1.4 Hz, 1, H1′), 7.20–8.10 (m, 14, ArH), 8.18 (s, 1, H2), 8.60 (s, 1, H8); MS *m/z* 568 (2, M – OTs), 342 (15, B), 223 (100, M – TsOH – BH_2). Anal. Calcd for $C_{17}H_{25}N_5O_2Si$: C, 61.68; H, 5.59; N, 9.47. Found: C, 61.70; H, 5.59; N, 9.47.

6-*N*,*N*-Dibenzoyl-9-(3-*O*-(*tert*-butyldimethylsilyl)-2,5-dideoxy-5-iodo-2-methylene-β-D-*erythro*-pentofuranosyl)adenine (18). A mixture of **17** (0.67 g, 0.90 mmol), dry NaI (0.50 g, 3.3 mmol), and dry Me_2CO (16 mL) was refluxed for 20 h while protected from light. Solvent was evaporated and the residue partitioned (5% $NaHSO_3/H_2O$ (30 mL)//$CHCl_3$ (50 mL)). The organic layer was washed (5% $NaHSO_3/H_2O$ (2 × 20 mL)) and the combined aqueous phase back-extracted ($CHCl_3$ (2 × 30 mL)). The combined organic phase was dried, evaporated, and flash chromatographed (EtOAc/hexane, (7:3)) to give colorless amorphous **18** (0.34 g, 54%): UV max 274, 250 nm; ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 3, SiMe), 0.19 (s, 3, SiMe), 0.92 (s, 9, $SiCMe_3$), 3.38 (dd, $J_{5'-5''}$ = 12.4 Hz, $J_{5'-4'}$ = 5.0 Hz, 1, H5′), 3.57 (m, 2, H4′,5″), 4.76 (d"q", $J_{3'-4'}$ = 6.2 Hz, $J_{\text{"q"}}$ = 1.6 Hz, 1, H3′), 5.38 (s, 1, CH_AH_B), 5.48 (dd, J = 2.0, 1.6 Hz, 1, CH_AH_B), 6.79 ("q", J = 1.6 Hz, 1, H1′), 7.30–7.90 (m, 10, ArH), 8.31 (s, 1, H2), 8.65 (s, 1, H8); MS *m/z* 637 (1, M – 1 – CMe_3), 239 (12, AdeBz).

9-(3-*O*-(*tert*-Butyldimethylsilyl)-2,5-dideoxy-2-methylene-β-D-*glycero*-pent-4-enofuranosyl)adenine (21). DBN (70 μL, 70 mg, 0.56 mmol) in DMF (0.25 mL) was added to a solution of **18** (0.20 g, 0.28 mmol) in DMF (4 mL) at 0 °C. The mixture was stirred at ambient temperature for 2 h, and additional DBN (70 μL, 70 mg, 0.56 mmol) in DMF (0.25 mL) added. After 1.5 h, NH_3/MeOH (17 mL) was added, stirring continued at ambient temperature for 18 h, and the mixture evaporated in vacuo. The residue was flash chromatographed (EtOAc/hexane, (4:1)) to give a light yellow powder (34 mg) whose ^{1}H NMR spectrum indicated a mixture (~4:1, respectively) of **21** [^{1}H NMR ($CDCl_3$) δ 0.18, 0.19 (2 s, 6, $SiMe_2$), 0.97 (s, 9, $SiCMe_3$), 4.28 (dd, $J_{5'-5''}$ = 2.2 Hz, $J_{5'-3'}$ = 1.6 Hz, 1, H5′), 4.53 (t, $J_{5''-3'}$ = 2.2 Hz, 1, H5″), 5.40 (s, 1, CH_AH_B), 5.53 (m, 1, H3′), 5.56 (s, 1, CH_AH_B), 5.73 (br s, 2, NH_2), 6.78 ("q", J = 1.6 Hz, 1, H1′), 7.80 (s, 1, H2), 8.33 (s, 1, H8)] and the debenzoylated 5′-iodo starting material [^{1}H NMR ($CDCl_3$) δ 0.15, 0.17 (2, s, 6, $SiMe_2$), 0.95 (s, 9, $SiMe_3$), 3.40–3.60 (m, 3, H4′,5′,5″), 4.78 (d"q", $J_{3'-4'}$ = 6.0 Hz, $J_{\text{"q"}}$ = 2.0 Hz, 1, H3′), 5.30 (t, J = 1.7 Hz, 1, CH_AH_B), 5.45 (t, J = 2.0 Hz, 1, CH_AH_B), 5.73 (br s, 2, NH_2), 6.74 ("q", J = 1.7 Hz, 1, H1′), 7.83 (s, 1, H2), 8.40 (s, 1, H8)]. Lower yields of **21** resulted from extended treatment with DBN.

9-(2,5-Dideoxy-2-methylene-β-D-*glycero*-pent-4-enofuranosyl)adenine (4′,5′-Didehydro-2′,5′-dideoxy-2′-methyleneadenosine) (22). TBAF/THF (1 M; 0.1 mL, 0.1 mmol) was added to the above mixture (**21** and the 5′-iodo compound; 34 mg, ~0.09 mmol) in THF (1.5 mL) at 0 °C, and stirring was continued at 0 °C for 30 min. Solvent was evaporated (<20 °C) and the residue flash chromatographed (MeOH/CH_2Cl_2 (7:93)) to give a light yellow viscous oil (12 mg) that contained **22** and the deprotected 5′-iodo compound (~4:1). Preparative HPLC (C_{18}; CH_3CN/H_2O (1:4)) and crystallization (MeOH/Et_2O) gave pale yellow solid **22** (6 mg): mp 137–138 °C; UV (H_2O, pH 7) max 260 nm (ϵ 14 600); ^{1}H NMR (Me_2SO-d_6) δ 4.20 (s, 1, H5′), 4.33 (s, 1, H5″), 5.43 (s, 1, CH_AH_B), 5.51 (s, 1, CH_AH_B), 5.61 (s, 1, H3′), 6.10 (br s, 1, OH3′), 6.89 (s, 1, H1′), 7.31 (br s, 2, NH_2), 8.13 (s, 1, H2), 8.25 (s, 1, H8); MS *m/z* 245 (30, M^+), 203 (10, M – C_2H_2O), 134 (90, B), 110 (30, M – BH), 84 (100, M – B – C_2H_3). Anal. Calcd for $C_{11}H_{11}N_5O_2$: C, 53.87; H, 4.52; N, 28.56. Found: C, 53.47; H, 4.80; N, 28.22.

The 2′,5′-dideoxy-5′-iodo-2′-methyleneadenosine (2 mg) had ^{1}H NMR (Me_2SO-d_6): δ 3.43 (dd, $J_{5'-5''}$ = 10.0 Hz, $J_{5'-4'}$ = 6.2 Hz, 1, H5′), 3.60–3.70 (m, 2, H4′,5″), 4.70 (br m, 1, H3′), 5.23 (dd, J = 2.0, 1.7 Hz, 1, CH_AH_B), 5.42 (t, J = 2.0 Hz, 1, CH_AH_B), 5.95 (br d, J = 5.0 Hz, 1, OH3′), 6.66 (m, J = 1.7 Hz, 1, H1′), 7.32 (br s, 2, NH_2), 8.15 (s, 1, H2), 8.23 (s, 1, H8).

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Electrochemical and Enzyme-Mediated Oxidations of Tetrahydropapaveroline

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The electrochemically driven and enzyme-mediated oxidations of the alkaloid tetrahydropapaveroline (THP) have been studied in aqueous solution. The electrochemical oxidation of THP is a 4e/4H^+ reaction giving diquinone **6** as the intermediate. In the absence of strong nucleophiles **6** undergoes an internal Michael reaction to give 5,6-dihydrodibenz[*b*,*g*]indolizine-2,3,9,10-tetrol (**2**) as the initial isolated product. Ceruloplasmin/O_2, peroxidase/H_2O_2, and tyrosinase/O_2 all cause a very rapid oxidation of THP to give **2**. In the presence of the intraneuronal nucleophile glutathione putative diquinone intermediate **6** reacts to give 1,2,3,4-tetrahydro-1-[(6-*S*-glutathionyl-3,4-dihydroxyphenyl)methyl]-6,7-isoquinolinediol (**5**). The latter conjugate can be further oxidized and attacked by a second molecule of glutathione to give 1,2,3,4-tetrahydro-[6-*S*-glutathionyl-3,4-dihydroxyphenyl)methyl]-8-*S*-glutathionyl-6,7-isoquinolinediol (**4**) and 1,2,3,4-tetrahydro-1-[(6-*S*-glutathionyl-3,4-dihydroxyphenyl)methyl]-5-S-glutathionyl-6,7-isoquinolinediol (**3**). The possible role of the oxidation of THP in the neurodegenerative aspects of chronic alcoholism are discussed.

The normal metabolism of the catecholaminergic neurotransmitter dopamine (DA) in the central nervous system is initiated by monoamine oxidase (MAO) which catalyzes oxidative deamination of the transmitter to 3,4-dihydroxyphenylacetaldehyde (DOPAL). Subsequently, DOPAL is rapidly oxidized in the presence of

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