Antitrypanosomal Activity of 5′-Deoxy-5′-(iodomethylene)adenosine and Related 6-*N*-Cyclopropyladenosine Analogues

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Received November 11, 2005

Treatment of the 6-*N*-cyclopropyl-2′,3′-di-*O*-isopropylideneadenosine 5′-aldehyde with sulfone-stabilized phosphonate or fluorophosphonate reagents followed by stannyldesulfonylations and subsequent iodo- or protiodestannylation gave 6-*N*-cyclopropyl-5′-deoxy-5′-(iodomethylene)adenosine **8b** or its 5′-fluoromethylene analogue **11**. Treatment of the 5′-aldehyde with hydroxylamine or dibromomethylene- or cyanomethylene-stabilized Wittig reagents and deprotections gave the oxime **4b**, 5′-cyanomethylene **5b**, and 5′-dibromomethylene **13b** analogues. Dehydrobromination of **13b** gave acetylenic compound **14b**. From the tested 6-*N*-cyclopropyladenosine analogues modified at the 5′ carbon, the 5′-iodomethylene **8b** had the most potent activity against *Trypanosoma brucei* in vitro with an IC_{50} of 12 μg/mL. The IC_{50} value was 19 μg/mL for both the 5′-fluoromethylene **11** and the 5′-cyanomethylene **5b** compounds. The (*E*)-5′-deoxy-5′-(iodomethylene)adenosine **2a**, a known inhibitor of AdoHcy hydrolase not modified with a cyclopropyl ring at 6-amino group, also inhibited *T. brucei* with an IC_{50} of 9 μg/mL. In contrast to some other adenosine analogues modified at C5′, the 6-*N*-cyclopropyladenosine analogues described here do not exhibit an inhibitory effect on AdoHcy hydrolase and displayed only marginal antiviral activity.

Introduction

The protozoan parasite *Trypanosoma brucei* is the causative agent of human African Trypanosomiasis, a disease that potentially threatens nearly 60 million people in sub-Saharan Africa.[1] The parasite is transmitted to the mammalian host through the bite of tsetse flies from *Glossina* genus and replicates in the bloodstream. Eventually the parasites cross the blood brain barrier and invade the central nervous system where they cause delirium, seizures, coma, and ultimately death if left untreated.[2] In the late 1970s, it was discovered that African trypanosomes were susceptible to treatment by the polyamine biosynthesis inhibitor, DL-α-difluoromethylornithine (DFMO, eflornithine), which inhibits ornithine decarboxylase, a key enzyme in the polyamine biosynthetic pathway.[3]

The pathways of methionine/*S*-adenosylmethionine (AdoMet)/decarboxylated AdoMet/*S*-adenosylhomocysteine (AdoHcy) and polyamine metabolism are closely related.[4] The success of DFMO against trypanosomiasis has raised interest in other enzymes of AdoMet/polyamine pathways as potential targets for the design of trypanocides. The nucleoside analogues (*Z*)-5′-[(4-amino-2-butenyl)methylamino]-5′-deoxyadenosine [**1a** (MDL73811); Figure 1], an inhibitor of AdoMet decarboxylase,[5] and 5′-*S*-(2-hydroxyethyl)-5′-thioadenosine (**1b**, HETA), a selective substrate of trypanosome MTA phosphorylase,[6] were found to be curative for various strains of African trypanosomiasis in vitro[5c,6] and animal models.[5b,c,6] The enhanced trypanocidal activity has been observed with O-acetylated purine nucleoside derivatives, including 2′,3′-di-*O*-acetyl-HETA (**1c**), presumably resulting from their improved uptake.[7] Inhibition of *T. brucei* has also been noted with phoshonogluconates dehydrogenase transition state analogues,[8] *s*-triazine substituted polyamines derivatives,[9a] and thiosemicarbazone cysteine protease inhibitors.[9b]

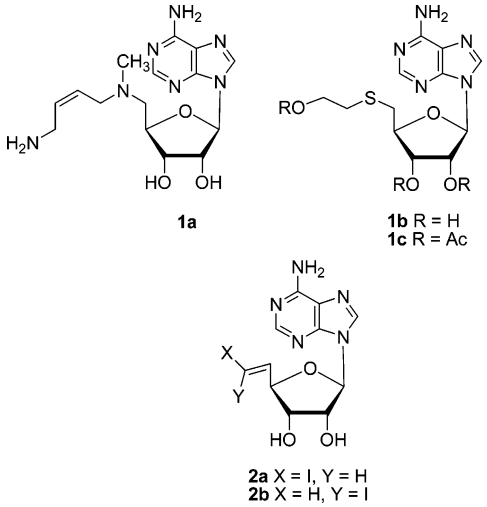

Figure 1.

The AdoHcy hydrolase effects hydrolytic cleavage of AdoHcy to adenosine (Ado) and L-homocysteine (Hcy).[10] Because the cellular level of the enzyme is critical and AdoHcy is a potent feedback inhibitor of crucial transmethylation enzymes, a number of inhibitors of AdoHcy hydrolase that utilize unusual spatial leniency within the enzyme occupied by C4′ constituents have been developed,[11−14] including 5′-deoxy-5′-(*E*)-(iodomethylene)adenosine **2a** [6′-(*E*)-iodohomovinyl derivative of adenosine, EIDDHA].[12a]

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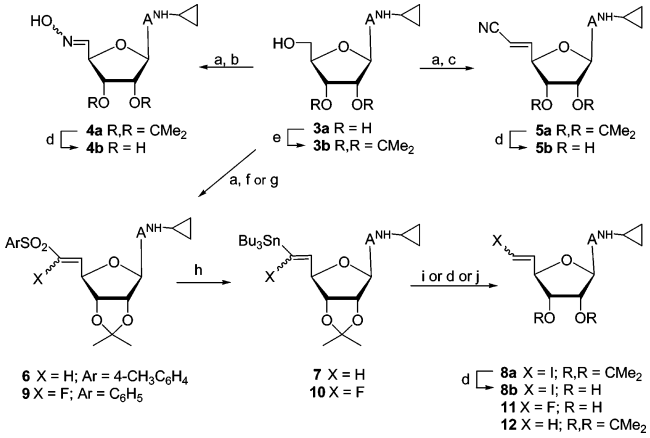
10.1021/jm0511379 CCC: $33.50
Published on Web 02/22/2006

Scheme 1[a]



[a] Reagents: (a) DMSO/DCC/Cl_2CHCO_2H; (b) NH_2OH/pyridine; (c) $Ph_3P{=}CHCN$; (d) TFA/H_2O; (e) $HC(OEt)_3/Me_2CO/H^+$; (f) $Ph_3P{=}CHTs$; (g) $PhSO_2CHFPO(OEt)_2$/LiHMDS/THF/−78 °C; (h) Bu_3SnH/AIBN/toluene/Δ; (i) NIS/CH_2Cl_2; (j) Selectfluor/MeCN/80 °C.

The 6-*N*-cycloalkyl (including cyclopropyl) derivatives of adenosine are known to be potent and a selective agonist of the A1 adenosine receptor.[15,16] Here, we report the antitrypanosomal activity of 5′-deoxy-5′-(*E*)-(iodomethylene)adenosine **2a**, which is a known inhibitor of AdoHcy hydrolase,[12a] and the synthesis and inhibition of *T. brucei* by a series of 6-*N*-cyclopropyladenosine analogues modified at carbon 5′ including halomethylene, acetylenic, and oxime derivatives.

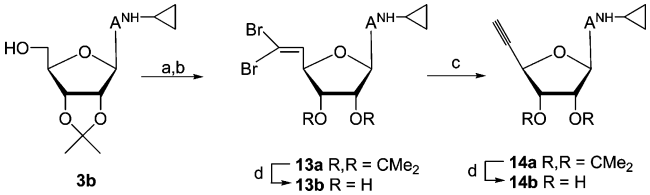
Chemistry

The 6-*N*-cyclopropyladenosine **3a** was prepared by nucleophilic displacement of the chloride from 6-chloro-9-(β-D-ribofuranosyl)purine[17] with cyclopropylamine[15] (pressure vial, 55 °C, 3 h; 90%). Standard protection of **3a** produced 6-*N*-cyclopropyl-2′,3′-*O*-isopropylideneadenosine **3b** (98%) that served as the substrate for the preparation of the selected 5′-modified 6-*N*-cyclopropyladenosine nucleosides (Scheme 1).

Moffatt oxidation[18] [dicyclohexylcarbodiimide (DCC)/DMSO/Cl_2CHCO_2H] of **3b** and treatment of the resulting crude 5′-aldehyde with $NH_2OH{\cdot}HCl$ gave oximes **4a** (*E*/*Z*, 72:28) in 89% yield. A stereochemical assignment was based on deshielding of H5′ signal (δ 7.50) cis to N−OH (*E*-isomer) relative to trans H5′ (δ 6.58) for the *Z* isomer and was in agreement with the literature value for other 5′-oxime derivatives.[14] Acid-catalyzed removal of the 2′,3′-*O*-isopropylidene group from **4a** and column chromatography gave **4b** (*E*/*Z*, 77:23; 57%). Analogous oxidation of **3b** and subsequent Wittig treatment with (triphenylphosphoranylidene)acetonitrile afforded **5a** as a single *E* isomer ($J_{5'-6'}$ = 16.3 Hz) in 85% yield. Deprotection of **5a** yielded 5′-cyanomethylene **5b** (85%). The multiplets in ^{1}H NMR spectra at δ ∼0.6, ∼0.9, and ∼3.0 (br s), and singlets at δ ∼7.0 and ∼22.0 in the ^{13}C NMR were diagnostic for the protons and carbons from the 6-*N*-cyclopropyl group. Also, a significant reduction in intensity for the C4 signal (δ ∼150.0) of the adenine ring was observed for 6-*N*-cyclopropyl analogues.

Oxidation of **3b** and treatment of the resulting crude 5′-aldehyde with the stabilized Wittig reagent [(*p*-toluenesulfonylmethylene)triphenylphosphorane] gave the *E*-vinyl 6′-sulfone **6** ($J_{6'-5'}$ = 15.0 Hz) in 70% yield. Radical stannyldesulfonylation of **6** with Bu_3SnH/AIBN afforded vinyl 6′-stannanes **7** (66%) as a mixture of *E*/*Z* isomers (88:12). Stereoselective halodestannylation of **7** with *N*-iodosuccinimide (NIS) provided **8a** (86%), which was deprotected with TFA/H_2O to give 5′-iodomethylene **8b** (*E*/*Z*, 89:11; 75%).

Scheme 2[a]



[a] Reagents: (a) DMSO/DCC/Cl_2CHCO_2H; (b) $Ph_3P/CBr_4/Zn/CH_2Cl_2$; (c) BuLi/THF/−78 °C; (d) TFA/H_2O.

Attempted fluorodestannylation[12a,19] of **7** with Selectfluor (CH_3CN/80 °C/1.5 h) effected protiodestannylation to give protected 6-*N*-cyclopropyl-5′-deoxy-5′-methyleneadenosine **12** (59%) in addition to a variable amount of byproduct(s) lacking the cyclopropyl ring (^{1}H NMR). On the other hand, Horner/Wittig-treatment of the 5′-aldehyde generated from **3b** with sulfone-stabilized fluorophosphonate reagent[20] yielded a mixture of 6′-fluorovinyl sulfones **9** (*E*/*Z*, 63:37; 59%). The coupling constants $J_{5'-F(trans)}$ = 32.6 Hz and $J_{5'-F(cis)}$ = 20.5 Hz were indicative of *E* and *Z* configurations. Stereoselective radical-mediated stannyldesulfonylation[12a,20a] of **9** with Bu_3SnH/AIBN produced 6′-fluorovinyl stannanes **10** (*E*/*Z*, 75:25, 62%). Treatment of **10** with TFA/H_2O affected protiodestannylation and deacetonization to give 5′-fluoromethylene **11** (*E*/*Z*, 26:74; 61%) with a stereochemical assignment in agreement with the literature values for similar nucleoside analogues[12a,21] [*E*-isomer, $J_{5'-6'(trans)}$ = 11.1 Hz, $J_{5'-F(cis)}$ = 19.9 Hz; *Z*-isomer, $J_{5'-6'(cis)}$ = 4.8 Hz, $J_{5'-F(trans)}$ = 41.3 Hz]. Protiodestannylation occurred with the retention of configuration, but the *E*/*Z* descriptors changed because of the change in Cahn−Ingold−Prelog priority at C6′.

Attempted oxidative-destannylation of **7** with lead tetraacetate in acetonitrile[12a,22] failed to produce the expected 5′-acetylenic product **14a**, giving instead the *N*-cyclopropyl cleaved byproducts. Opening of cyclopropyl ring upon treatment with $Pb(OAc)_4$[23a] and studies on N-decyclopropylation of *N*-cyclopropyl-*N*-alkylanilines by cytochrome P_{450}/PhIO have been reported.[23b] Nevertheless, oxidation of **3b** and Wittig-type olefination with dibromomethylene reagent[24] ($CBr_4/PPh_3/Zn$) gave **13a** (74%). Acid-catalyzed removal of the 2′,3′-isopropylidene group provided 5′-dibromomethylene **13b** (86%; Scheme 2). Treatment of **13a** with excess BuLi/hexane (THF/−78 °C) effected dehydrobromination[24] to give the acetylenic derivative **14a** (26%), which was deprotected to yield **14b** (74%). The signal at δ 3.73 (d, $J_{6'-4'}$ = 1.8 Hz) in ^{1}H NMR spectra of **14b** was diagnostic for an acetylenic proton.

Antitrypanosomal Activity

The 5′-deoxy-5′-(*E*)-(iodomethylene)adenosine **2a** and its 6-*N*-cyclopropyl analogue **8b** as well as other 5′-modified 6-*N*-cyclopropyladenosine analogues such as oximes **4b**, cyanomethylene **5b**, halomethylene **11** and **13b**, and acetylenic **14b** were tested against *T. brucei* in vitro. The 6-*N*-cyclopropyl-5′-deoxy-5′-(iodomethylene)adenosine **8b** (*E*/*Z*, 89:11) was the most potent inhibitor of *T. brucei* in vitro with an IC_{50} of 12 μg/mL (Table 1). In comparison, the IC_{50} value was 19 μg/mL for both 5′-fluoromethylene **11** (*E*/*Z*, 26:74) and 5′-cyanomethylene **5b** (*E*), while **4b** (*E*/*Z*, 77:23), **13b**, and **14b** did not show any significant effect against *T. brucei*.

The 5′-deoxy-5′-(*E*)-(iodomethylene)adenosine **2a** (not modified with cyclopropyl ring at 6-amino group) also inhibited the growth of *T. brucei* with an IC_{50} of 9 μg/mL. The inhibition of *T. brucei* by **2a** (known inhibitor of AdoHcy hydrolase[12a]) shows that **2a** and the 6-*N*-cyclopropyl inhibitors described herein are

Table 1. In Vitro Antitrypanosomal Activity of 5′-Modified Adenosine Derivatives

compound	IC_{50} (μg/mL)[a]
2a	9
2b	45
4b[b]	no effect
5b	19
8b[c]	12
11[d]	19
13b	no effect
14b	marginal
4′-thioAdo	14
3-deazaAdo	no effect

[a] The concentration required to inhibit the growth of trypanosomes by 50%. [b] (*E*/*Z*, 77:23). [c] (*E*/*Z*, 89:11). [d] (*E*/*Z*, 26:74).

comparable in their potency against *T. brucei*. In contrast, 3-deazaadenosine (classical AdoHcy hydrolase inhibitor[10]), at 100 μg/mL, did not inhibit *T. brucei* in vitro, whereas the 4′-thioadenosine (moderate inhibitor of AdoHcy hydrolase) showed an IC_{50} of 14 μg/mL. Interestingly, the 5′-deoxy-5′-(*Z*)-(iodomethylene)adenosine analogue **2b** showed lower potency against *T. brucei* (IC_{50} of 45 μg/mL). This observation correlates with the more pronounced antiviral and cytostatic activities of the 5′-(*E*)-halomethylene analogues than their *Z* counterparts.[12a] The adenosine analogue **1a** displays potent inhibition of trypanosomal growth with an IC_{50} of 0.02−0.08 μg/mL,[5c] while MTA analogues **1b** and **1c** had IC_{50} values of 0.16 and 0.12 μg/mL, respectively.[6,7]

The *N*-cyclopropyl analogues **4b**, **5b**, **8b**, **11**, and **13b** do not exhibit inhibitory effects on human, trypanosomal, or plasmodium forms of AdoHcy hydrolase (data not shown); thus they must be producing their antitrypanosomal activity via a mechanism different from that of **2a**. These results also suggest that because the 5′-modified analogues are unlikely converted to ATP analogues, the effect could be on polyamine pathways or the purine salvage pathway because they are dependent on exogenous purines. The utilization of adenosine analogues as anti-parasitics should be explored as a therapeutic paradigm, as it has been shown previously that inhibitors of AdoHcy hydrolase are also very potent inhibitors against the growth of *Plasmodium falciparum*.[25]

Antiviral Activity

When tested against vesicular stomatitis virus (VSV; RNA virus) grown in BHK cells, this class of 6-*N*-cyclopropyl adenosine analogues modified at carbon 5′ was found to display marginal antiviral activity (data not shown). Also, no specific antiviral effects (i.e., minimal antiviral effective concentration >5-fold lower than minimal cytotoxic concentration) were noted for **4b**, **8b**, **11**, and **13b** against other viruses [in HeLa cell cultures (vesicular stomatitis virus, Coxsackie B4 virus, or respiratory syncytial virus); in Vero cell cultures (parainfluenza virus type 3, reovirus type 1, Sindbis virus, Coxsackie B4 virus, or Punta Toro virus); in E_6SM cell cultures (herpex simplex virus (HSV-1, KOS strain; HSV-2, G strain), vaccinia virus, or vesicular stomatitis virus)] (data not shown). Interestingly, the unmodified at 6-amino position analogue **2a** showed quite potent antiviral (IC_{50} of 2 μg/mL against VSV) and cytotoxic activity.[12a]

Despite its activity against *T. brucei*, the lack of antiviral activity by this class of adenosine analogues modified at C5′ was surprising. This is in contrast to the well-established effect by adenosine analogues on RNA viruses.[10b] On the other hand, the lack of effect of 3-deazaadenosine on the growth of *T. brucei* suggests a kinetic difference between different kinds of AdoHcy hydrolases and the malarial enzyme, which may be reflected by structural differences. This unique difference among the AdoHcy hydrolases of different species suggests a selective therapeutic paradigm to discover *T. brucei* specific inhibitors as described here. *T. brucei* is unable to synthesize purines de novo and can only survive by transporting the preformed purines from its hosts.[26] The 6-*N*-cyclopropyl compounds may also interfere with the nucleoside permeases of the parasites and thus exert growth inhibition. A strain-specific effect of adenosine on *T. brucei* has been observed.[27] A plausible explanation for the lack of antiviral activity of the 6-*N*-cyclopropyl-Ado analogues is their inability to be converted to ATP analogues. Previous observations with the 3-deazaadenosine analogues on the HIV virus,[28a,b] as well as formation of nucleotide analogues of neplanocin A in malarial parasites, support this hypothesis.[28c]

Summary and Conclusions

The novel 6-*N*-cyclopropyladenosine analogues modified at carbon 5′ including cyano- **5b** and halomethylene **8b**, **11**, and **13b**, as well as acetylenic **14b** and oxime **4b** derivatives, the parental adenosine analogues of which are known inhibitors of AdoHcy hydrolase,[12−14] were prepared using Wittig-type homologations or related chemistry. Thus, Horner/Wittig-treatment of 6-*N*-cyclopropyladenosine 5′-aldehyde with a sulfone-stabilized fluorophosphonate reagent followed by stannyldesulfonylation and protiodestannylation/deacetonization sequence yielded the 5′-fluoromethylene analogue **11**. The 5′-deoxy-5′-(*E*)-(iodomethylene)adenosine **2a** (EIDDHA) and its 6-*N*-cyclopropyl analogue **8b** were found to inhibit the growth of *T. brucei* in vitro at the level of IC_{50} at 9 and 12 μg/mL, respectively. This class of 6-*N*-cyclopropyl adenosine analogues modified at carbon 5′, whose unmodified at 6-amino position analogues are potent inhibitor of AdoHcy hydrolase, does not exhibit an inhibitory effect on human or parasite forms of the enzyme and displays only marginal antiviral activity.

Experimental Section

Uncorrected melting points were determined with a capillary apparatus. UV spectra were measured with solutions in MeOH. ^{1}H (Me_4Si) NMR spectra were determined with solutions in $CDCl_3$ at 400 MHz, ^{13}C (Me_4Si) at 100.6 MHz, and ^{19}F (CCl_3F) at 376.4 MHz unless otherwise noted. Mass spectra (MS) were obtained by atmospheric pressure chemical ionization (APCI) techniques unless otherwise noted. Reagent grade chemicals were used, and solvents were dried by reflux over and distillation from CaH_2, except THF (potassium), under an argon atmosphere. Selectfluor fluorinating reagent (>95% active [F^+]) was purchased from Aldrich. TLC was performed on Merck Kieselgel 60-F_{254} with MeOH/$CHCl_3$ (1:9, 1:19), EtOAc/hexane (2:1), or EtOAc/*i*-PrOH/H_2O (4:1:2, upper layer; S1) as developing systems, and products were detected with 254 nm light. Merck Kieselgel 60 (230−400 mesh) was used for column chromatography. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN.

6-*N*-Cyclopropyl-2′,3′-*O*-isopropylideneadenosine (3b). A solution of **3a**[15] (0.58 g, 1.9 mmol) and *p*-toluenesulfonic acid (413 mg, 2.2 mmol) in acetone (20 mL) was stirred for 30 min at ambient temperature, and then triethyl orthoformate (1.45 mL, 1.29 g, 8.7 mmol) was added. After 3 h, volatiles were evaporated and the residue was partitioned ($NaHCO_3$/H_2O//$CHCl_3$). The separated organic layer was washed (brine), dried (Na_2SO_4), and evaporated to give **3b** (0.64 g, 98%) as a white foam: ^{1}H NMR δ 0.64−0.69 (m, 2, *c*-Pr), 0.93−0.97 (m, 2, *c*-Pr), 1.38 (s, 3, CH_3), 1.65 (s, 3, CH_3), 3.02 (br s, 1, *c*-Pr), 3.80 (d, J = 11.8 Hz, 1, H5′), 3.98 (d, J = 12.6 Hz, 1, H5″), 4.54 (s, 1, H4′), 5.13 (d, J = 5.8 Hz, 1, H3′), 5.22 ("t", J = 5.3 Hz, 1, H2′), 5.84 (d, J = 4.9 Hz, 1, H1′), 6.70 (br s, 1, NH), 7.78 (s, 1, H2), 8.41 (s, 1, H8); MS *m*/*z* 348 (MH^+).

6-*N*-Cyclopropyl-2′,3′-*O*-isopropylideneadenosine-5′-aldehyde Oximes [6-*N*-Cyclopropyl-9-(2,3-*O*-isopropylidene-*β*-D-*ribo*-pentodialdo-1,4-furanosyl)adenine Oximes] (4a). Step a: Cl_2CHCO_2H (12.4 μL, 19 mg, 0.15 mmol) was added to the stirred solution of **3b** (92 mg, 0.26 mmol) in DMSO (1.5 mL) containing dicyclohexylcarbodiimide (DCC; 217 mg, 1.04 mmol), at ambient temperature, under N_2, and stirring was continued for 90 min. Step b: Pyridine (0.5 mL) and NH_2OH·HCl (209 mg, 3.0 mmol) were added to the above crude 5′-aldehyde, and stirring was continued for 14 h. Oxalic acid dihydrate (98 mg, 0.78 mmol) in MeOH (2 mL) was added, and the reaction mixture was kept at ∼0 °C for 30 min. The precipitated dicyclohexylurea (DCU) was filtered off, and the mother liquor was partitioned (1% $CH_3CO_2H/H_2O//CHCl_3$). The aqueous layer (∼50 mL) was separated and neutralized to pH ∼8 by addition of $NaHCO_3/H_2O$ and was then extracted with $CHCl_3$ (5 ×15 mL) [to improve efficiency of extraction MeOH (5 mL) was also added]. The combined organic washings were dried (Na_2SO_4), evaporated, and column chromatographed (0 → 2% MeOH/EtOAc) to give **4a** (*E*/*Z*, 72:28, 85 mg, 89%). Compound **4a** (*E*) had: ^{1}H NMR δ 0.55−0.64 (m, 2, *c*-Pr), 0.83−0.91 (m, 2, *c*-Pr), 1.48 (s, 3, CH_3), 1.62 (s, 3, CH_3), 2.94 (br s, 1, *c*-Pr), 4.95 (dd, *J* = 2.0, 5.9 Hz, 1, H4′), 5.38 (dd, *J* = 2.0, 6.0 Hz, 1, H3′), 5.60 (d, *J* = 6.0 Hz, 1, H2′), 6.16 (s, 1, H1′), 6.92 (br s, 1, NH), 7.50 (d, *J* = 5.9 Hz, 1, H5′), 7.85 (s, 1, H2), 8.42 (s, 1, H8), 11.55 (br s, 1, OH). Compound **4a** (*Z*) had: ^{1}H NMR δ 0.55−0.64 (m, 2, *c*-Pr), 0.83−0.91 (m, 2, *c*-Pr), 1.48 (s, 3, CH_3), 1.62 (s, 3, CH_3), 2.94 (br s, 1, *c*-Pr), 5.36−5.45 (m, 2, H3′,4′), 5.60 (d, *J* = 5.9 Hz, 1, H2′), 6.13 (s, 1, H1′), 6.58 (d, *J* = 4.1 Hz, 1, H5′), 6.92 (br s, 1, NH), 7.92 (s, 1, H2), 8.58 (s, 1, H8), 12.10 (br s, 1, OH); MS *m*/*z* 361 (MH^+).

6-*N*-Cyclopropyladenosine-5′-aldehyde Oximes [6-*N*-Cyclopropyl-9-(*β*-D-*ribo*-pentodialdo-1,4-furanosyl)adenine Oximes] (4b). A solution of **4a** (85 mg, 0.24 mmol) in TFA/H_2O (9:1, 5 mL) was stirred at ∼0 °C (ice bath) for 1 h. Volatiles were evaporated (<15 °C) and then coevaporated with toluene (2×) and with ethanol under an oil-pump vacuum. The residue was chromatographed (flash column 0 → 20% S1/EtOAc) to give crude **4b** (57 mg, 75%). Further purification on RP-HPLC (preparative C_{18} column; gradient program 30 → 70% CH_3CN/H_2O for 30 min followed by 70 → 100% CH_3CN/H_2O for the next 10 min at 2.5 mL/min; t_R 27.2 min) gave **4b** (*E*/*Z*, 77:23, 43 mg, 57%) as a white powder: mp 154−157 °C; UV max 269 nm (ε 17 600), min 231 nm (ε 2900). Compound **4b** (*E*) had: ^{1}H NMR (DMSO-d_6) δ 0.58−0.65 (m, 2, *c*-Pr), 0.70−0.76 (m, 2, *c*-Pr), 3.02 (br s, 1, *c*-Pr), 4.32 (br s, 1, H3′), 4.40 (dd, *J* = 4.1, 7.6 Hz, 1, H4′), 4.73 (br s, 1, H2′), 5.53 (br s, 1, OH2′), 5.60 (br s, 1, OH3′), 5.95 (d, *J* = 5.3 Hz, 1, H1′), 7.61 (d, *J* = 7.6 Hz, 1, H5′), 8.00 (br s, 1, NH), 8.27 (s, 1, H2), 8.38 (s, 1, H8), 11.10 (s, 1, OH); ^{13}C NMR (DMSO-d_6) δ 7.98 (*c*-Pr, C2/2′), 22.18 (*c*-Pr, C1), 73.96, 74.29 (C2′/3′), 83.02 (C4′), 89.09 (C1′), 120.84 (C5), 141.28 (C8), 149.25 (C5′), 150.92 (br s, C4), 153.96 (C2), 156.88 (C6). Compound **4b** (*Z*) had: ^{1}H NMR (DMSO-d_6) δ 0.58−0.65 (m, 2, *c*-Pr), 0.70−0.76 (m, 2, *c*-Pr), 3.02 (br s, 1, *c*-Pr), 4.13 (d, *J* = 7.0 Hz, 1, H3′), 4.87−4.94 (m, 1, H4′), 5.00 (d, *J* = 5.3 Hz, 1, H2′), 5.53 (br s, 1, OH2′), 5.65 (br s, 1, OH3′), 5.95 (d, *J* = 5.3 Hz, 1, H1′), 7.23 (d, *J* = 5.5 Hz, 1, H5′), 8.00 (br s, 1, NH), 8.27 (s, 1, H2), 8.43 (s, 1, H8), 11.35 (s, 1, OH); MS *m*/*z* 321 (MH^+). HRMS (FAB) calcd for ($C_{13}H_{15}N_6O_6$ + H^+) 321.1311; found 321.1311. Anal. $C_{13}H_{16}N_6O_4$·H_2O (338.32) C, H, N.

6-*N*-Cyclopropyl-9-[5,6-dideoxy-6-cyano-2,3-*O*-isopropylidene-*β*-D-*ribo*-hex-5-(*E*)-enofuranosyl]adenine (5a). (Triphenylphosphoranylidene)acetonitrile (199 mg, 0.66 mmol) was added to the reaction mixture containing crude 5′-aldehyde [generated from **3b** (92 mg, 0.26 mmol) as described for **4a** (step a)], and stirring was continued for 14 h. Oxalic acid dihydrate (98 mg, 0.78 mmol) in MeOH (2 mL) was added, and DCU was filtered off. The residue was partitioned ($H_2O/CHCl_3$), and the separated organic layer was washed ($NaHCO_3/H_2O$, brine), dried (Na_2SO_4), evaporated, and chromatographed (65 → 90% EtOAc/hexane) to give **5a** (66 mg, 67%) as a white foam: ^{1}H NMR δ 0.67−0.72 (m, 2, *c*-Pr), 0.95−0.98 (m, 2, *c*-Pr), 1.42 (s, 3, CH_3), 1.63 (s, 3, CH_3), 3.06 (br s, 1, *c*-Pr), 4.76 (ddd, *J* = 1.8, 3.7, 5.2 Hz, 1, H4′), 5.24 (dd, *J* = 3.7, 6.2 Hz, 1, H3′), 5.38 (dd, *J* = 1.8, 16.3 Hz, 1, H6′), 5.55 (dd, *J* = 1.5, 6.2 Hz, 1, H2′), 6.07 (br s, 1, NH), 6.12 (d, *J* = 1.5 Hz, 1, H1′), 6.84 (dd, *J* = 5.2, 16.3 Hz, 1, H5′), 7.80 (s, 1, H2), 8.44 (s, 1, H8); MS *m*/*z* 369 (MH^+).

6-*N*-Cyclopropyl-9-[5,6-dideoxy-6-cyano-*β*-D-*ribo*-hex-5-(*E*)-enofuranosyl]adenine (5b). Deprotection of **5a** (55 mg, 0.15 mmol), as described for **4b** [column chromatography (0 → 20% S1/EtOAc)] gave **5b** (42 mg, 85%). RP-HPLC (preparative C_{18} column; gradient program 30 → 70% CH_3CN/H_2O for 30 min followed by gradient program from 70% CH_3CN/H_2O → 100% CH_3CN for 10 min at 2.5 mL/min; t_R 28.6 min) gave **5b** (15 mg, 30%) as a white powder, mp 148−152 °C; UV max 269 nm (ε 16 400), min 238 nm (ε 4000): ^{1}H NMR (DMSO-d_6) δ 0.58−0.65 (m, 2, *c*-Pr), 0.69−0.76 (m, 2, *c*-Pr), 3.02 (br s, 1, *c*-Pr), 4.25 ("q", *J* = 4.5 Hz, 1, H3′), 4.51−4.56 (m, 1, H4′), 4.70 ("q", *J* = 5.3 Hz, 1, H2′), 5.66 (d, *J* = 5.5 Hz, 1, OH2′), 5.68 (d, *J* = 5.5 Hz, 1, OH3′), 5.92 (dd, *J* = 1.5, 16.3 Hz, 1, H6′), 5.97 (d, *J* = 5.5 Hz, 1, H1′), 7.14 (dd, *J* = 5.5, 16.3 Hz, 1, H5′), 8.00 (br s, 1, NH), 8.26 (s, 1, H2), 8.38 (s, 1, H8); ^{13}C NMR (DMSO-d_6) δ 7.36 (*c*-Pr, C2/2′), 24.71 (*c*-Pr, C1), 73.26, 74.21 (C2′/3′), 83.75 (C4′), 88.54 (C1′), 101.40 (C6′), 118.57 (C7′), 120.61 (C5), 140.90 (C8), 150.12 (br s, C4), 153.14 (C5′), 153.56 (C2), 156.60 (C6); MS *m*/*z* 328 (MH^+). HRMS (FAB) calcd for ($C_{15}H_{16}N_6O_3$ + H^+) 329.1362; found 329.1360. Anal. $C_{15}H_{16}N_6O_3$·H_2O (346.34) C, H, N.

6-*N*-Cyclopropyl-9-[5,6-dideoxy-6-(*p*-toluenesulfonyl)-2,3-*O*-isopropylidene-*β*-D-*ribo*-hex-5-(*E*)-enofuranosyl]adenine (6). The (*p*-toluenesulfonylmethylene)triphenylphosphorane[29] (155 mg, 0.36 mmol) was added to the reaction mixture containing crude 5′-aldehyde [generated from **3b** (92 mg, 0.26 mmol) as described for **4a** (step a)], and stirring was continued for 14 h. Oxalic acid dihydrate (98 mg, 0.78 mmol) in MeOH (2 mL) was added, and DCU was filtered off. The mother liquor was partitioned ($NaHCO_3/H_2O//CHCl_3$), and the separated organic layer was washed ($NaHCO_3/H_2O$, brine), dried (Na_2SO_4), evaporated, and chromatographed (50 → 80% EtOAc/hexane) to give **6** (92 mg, 70%) as a foam: ^{1}H NMR δ 0.65−0.70 (m, 2, *c*-Pr), 0.92−0.95 (m, 2, *c*-Pr), 1.48 (s, 3, CH_3), 1.60 (s, 3, CH_3), 2.42 (s, 3, CH_3), 3.03 (br s, 1, *c*-Pr), 4.80−4.85 (m, 1, H4′), 5.20 (dd, *J* = 3.6, 6.2 Hz, 1, H3′), 5.49 (dd, *J* = 1.5, 6.2 Hz, 1, H2′), 6.07 (d, *J* = 1.5 Hz, 1, H1′), 6.35 (dd, *J* = 1.8, 15.0 Hz, 1, H6′), 6.98 (dd, *J* = 4.6, 15.0 Hz, 1, H5′), 7.29 (d, *J* = 8.5 Hz, 2, Ar), 7.47 (d, *J* = 8.5 Hz, 2, Ar), 7.77 (s, 1, H2), 8.28 (s, 1, H8); MS *m*/*z* 499 (MH^+).

6-*N*-Cyclopropyl-9-[5,6-dideoxy-6-(tributylstannyl)-2,3-*O*-isopropylidene-*β*-D-*ribo*-hex-5-(*E*/*Z*)-enofuranosyl]adenine (7). A suspension of **6** (*E*; 456 mg, 0.91 mmol) in toluene (20 mL) was deoxygenated (N_2, 15 min), and Bu_3SnH (0.4 mL, 436 mg, 1.5 mmol) was added. Deoxygenation was continued for 15 min, and AIBN (32 mg, 0.2 mmol) was added. The solution was heated at 75 °C for 6 h [TLC (95:5, $CHCl_3$:MeOH) showed formation of less polar products] and was evaporated. The residue was column chromatographed [well washed with hexane followed by slow elution (0 → 40% EtOAc/hexane)] to give **7** (*E*/*Z*, 88:12; 387 mg, 66%) as a transparent oil: ^{1}H NMR δ 0.55−0.61 (m, 2, *c*-Pr), 0.72−0.88 (m, 11, *c*-Pr, Bu_3Sn), 1.13−1.40 (m, 18, Bu_3Sn), 1.35 (s, 3, CH_3), 1.55 (s, 3, CH_3), 2.97 (br s, 1, *c*-Pr), 4.41 (d, *J* = 5.9 Hz, 0.12, H4′), 4.61−4.65 (m, 0.88, H4′), 4.91−4.95 (m, 0.12, H3′), 4.98−5.03 (m, 0.88, H3′), 5.47 (d, *J* = 6.2 Hz, 0.12, H2′), 5.55 (d, *J* = 6.1 Hz, 0.88, H2′), 5.96 (dd, *J* = 6.0, 19.1 Hz, 0.88, H5′), 6.08 (s, 0.88, H1′), 6.15 (d, *J* = 19.1 Hz, 0.88, H6′), 6.03−6.23 (m, 0.36, H1′,5′,6′), 6.50 (br s, 1, NH), 7.79 (s, 1, H2), 8.39 (s, 1, H8); MS *m*/*z* 634 (100, MH^+, ^{120}Sn), 632 (76, MH^+, ^{118}Sn), 630 (41, MH^+, ^{116}Sn).

6-*N*-Cyclopropyl-9-[5,6-dideoxy-6-iodo-2,3-*O*-isopropylidene-*β*-D-*ribo*-hex-5-(*E*/*Z*)-enofuranosyl]adenine (8a). A solution of NIS (56 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of **7** (*E*/*Z*, 89:11; 120 mg, 0.19 mmol) in CH_2Cl_2/CCl_4 (10 mL, 1:1) at ∼0 °C (ice bath). After 1 h, the slightly pink mixture was poured into a saturated solution of $NaHCO_3/H_2O$ and extracted ($CHCl_3$). The combined organic fraction was washed with diluted $NaHSO_3/H_2O$ (to effect decolorization) and

brine, dried (Na_2SO_4), and evaporated. Column chromatography (0 → 70% EtOAc/hexane) gave **8a** (*E*/*Z*, 89:11; 74 mg, 86%) as a white solid powder. Compound **8a** (*E*) had: ^{1}H NMR δ 0.56−0.62 (m, 2, *c*-Pr), 0.91−0.96 (m, 2, *c*-Pr), 1.41 (s, 3, CH_3), 1.62 (s, 3, CH_3), 3.05 (br s, 1, *c*-Pr), 4.64 (dd, J = 3.1, 6.8 Hz, 1, H4′), 5.13 (dd, J = 3.1, 6.1 Hz, 1, H3′), 5.58 (dd, J = 1.6, 6.1 Hz, 1, H2′), 6.04 (br s, 1, NH), 6.08 (d, J = 1.6 Hz, 1, H1′), 6.36 (d, J = 14.5 Hz, 1, H6′), 6.70 (dd, J = 6.8, 14.5 Hz, 1, H5′), 7.81 (s, 1, H2), 8.51 (s, 1, H8). Compound **8a** (*Z*) had: ^{1}H NMR δ 0.56−0.62 (m, 2, *c*-Pr), 0.91−0.96 (m, 2, *c*-Pr), 1.41 (s, 3, CH_3), 1.62 (s, 3, CH_3), 3.05 (br s, 1, *c*-Pr), 4.10−4.15 (m, 1, H4′), 5.03 (dd, J = 4.1, 7.7 Hz, 1, H3′), 5.67 (d, J = 4.1 Hz, 1, H2′), 6.04 (br s, 1, NH), 6.09 (s, 1, H1′), 6.43 ("t", J = 7.8 Hz, 1, H5′), 6.49 (d, J = 7.9 Hz, 1, H6′), 7.81 (s, 1, H2), 8.49 (s, 1, H8); MS *m*/*z* 470 (MH^+).

6-*N*-Cyclopropyl-9-[5,6-dideoxy-6-iodo-*β*-D-*ribo*-hex-5-(*E*/*Z*)-enofuranosyl]adenine (8b). Deprotection of **8a** (62 mg, 0.13 mmol), as described for **4b** [column chromatography (0 → 20% MeOH/EtOAc)] gave crude **8b** (42 mg, 75%). RP-HPLC purification (preparative C_{18} column; gradient program 30 → 70% CH_3CN/H_2O for 30 min followed by 70 → 100% CH_3CN/H_2O for next 10 min at 2.5 mL/min; t_R 28.6 min) gave **8b** (*E*/*Z*, 89:11; 15 mg, 30%) as a white powder: mp 186−192 °C; UV max 269 nm (ϵ 16 400), min 238 nm (ϵ 3800). Compound **8b** (*E*) had: ^{1}H NMR (DMSO-d_6) δ 0.58−0.64 (m, 2, *c*-Pr), 0.69−0.76 (m, 2, *c*-Pr), 3.01 (br s, 1, *c*-Pr), 4.16−4.22 (m, 1, H3′), 4.33 (dd, J = 4.5, 7.5 Hz, 1, H4′), 4.69 ("q", J = 5.1 Hz, 1, H2′), 5.48 (d, J = 5.4 Hz, 1, OH3′), 5.61 (d, J = 5.5 Hz, 1, OH2′), 5.91 (d, J = 5.0 Hz, 1, H1′), 6.67 (d, J = 14.5 Hz, 1, H6′), 6.85 (dd, J = 7.5, 14.5 Hz, 1, H5′), 8.00 (br s, 1, NH), 8.22 (s, 1, H2), 8.37 (s, 1, H8); ^{13}C NMR (DMSO-d_6) δ 7.33 (*c*-Pr, C2/2′), 24.10 (*c*-Pr, C1), 73.59, 73.82 (C3′/2′), 83.12 (C4′), 86.70 (C6′), 88.68 (C1′), 120.56 (C5), 140.81 (C5′), 144.63 (C8), 149.10 (br s, C4), 153.51 (C2), 156.57 (C6). Compound **8b** (*Z*) had: ^{1}H NMR (DMSO-d_6) δ 0.58−0.64 (m, 2, *c*-Pr), 0.69−0.76 (m, 2, *c*-Pr), 3.01 (br s, 1, *c*-Pr), 4.13−4.17 (m, 1, H3′), 4.54 (dd, J = 3.0, 7.8 Hz, 1, H4′), 4.84 ("q", J = 5.5 Hz, 1, H2′), 5.57 (d, J = 5.1 Hz, 1, OH3′), 5.62 (d, J = 4.8 Hz, 1, OH2′), 5.94 (d, J = 6.1 Hz, 1, H1′), 6.72 (d, J = 7.8 Hz, 1, H6′), 6.80 (t, J = 7.8 Hz, 1, H5′), 8.00 (br s, 1, NH), 8.22 (s, 1, H2), 8.37 (s, 1, H8); MS *m*/*z* 430 (MH^+). Anal. $C_{14}H_{16}IN_5O_3 \cdot 0.33H_2O$ (435.22) C, H, N.

6-*N*-Cyclopropyl-9-[5,6-dideoxy-6-fluoro-6-phenylsulfonyl-2,3-*O*-isopropylidene-*β*-D-*ribo*-hex-5-(*E*/*Z*)-enofuranosyl]adenine (9). LiHMDS (1 M/THF; 0.3 mL, 0.3 mmol) was added dropwise to the stirred solution of diethyl fluoro(phenylsulfonyl)-methylephosphonate[20b] (93 mg, 0.3 mmol) in THF (2.5 mL) at −78 °C. The resulting mixture was stirred for 30 min, and the crude 5′-aldehyde [generated from **3b** (92 mg, 0.26 mmol) as described for **4a** (step a)] was added dropwise. After 15 min, the reaction mixture was allowed to warm to −30 °C over 1.5 h and was quenched with NH_4Cl/H_2O (0.5 mL). Oxalic acid dihydrate (98 mg, 0.78 mmol) in MeOH (2 mL) was added, and DCU was filtered off. The residue was partitioned ($NaHCO_3/H_2O$//$CHCl_3$), and the separated organic layer was washed ($NaHCO_3/H_2O$, brine), dried (Na_2SO_4), evaporated, and chromatographed [EtOAc/hexane (8:2) → EtOAc followed by 0 → 40% S1/EtOAc] to give **9** (*E*/*Z*, 63:37; 82 mg, 59%) as a white foam. Compound **9** (*E*) had: ^{1}H NMR δ 0.65−0.73 (m, 2, *c*-Pr), 0.91−0.97 (m, 2, *c*-Pr), 1.47 (s, 3, CH_3), 1.62 (s, 3, CH_3), 3.06 (br s, 1, *c*-Pr), 5.10 ("d", J = 8.2 Hz, 1, H4′), 5.26 ("d", J = 5.9 Hz, 1, H3′), 5.59 (d, J = 5.6 Hz, 1, H2′), 6.06 (s, 1, H1′), 6.27 (s, 1, NH), 6.55 (dd, J = 8.2, 32.6 Hz, 1, H5′), 7.58 (t, J = 8.1 Hz, 2, Ar), 7.66−7.72 (m, 1, Ar), 7.84 (d, J = 8.1 Hz, 2, Ar), 7.96 (s, 1, H2), 8.40 (s, 1, H8); ^{19}F NMR δ −122.46 (d, J = 32.6 Hz, 0.63F). Compound **9** (*Z*) had: ^{1}H NMR δ 0.65−0.73 (m, 2, *c*-Pr), 0.91−0.97 (m, 2, *c*-Pr), 1.47 (s, 3, CH_3), 1.62 (s, 3, CH_3), 3.06 (br s, 1, *c*-Pr), 5.26 ("d", J = 5.9 Hz, 1, H3′), 5.54 (d, J = 4.8 Hz, H2′), 6.09 (s, 1, H1′), 6.20−6.30 (m, 3, H4′,5′ & NH), 7.58−7.84 (m, 5, Ar), 7.99 (s, 1, H2), 8.46 (s, 1, H8); ^{19}F NMR δ −112.13 (d, J = 20.5 Hz, 0.37F); MS *m*/ *z* 502 (MH^+).

6-*N*-Cyclopropyl-9-[5,6-dideoxy-6-fluoro-6-(tributylstannyl)-2,3-*O*-isopropylidene-*β*-D-*ribo*-hex-5-(*E*/*Z*)-enofuranosyl]adenine (10). Reaction of **9** (*E*/*Z*, 63:37; 127 mg, 0.25 mmol) with Bu_3SnH, as described for **7** [column chromatography: hexane followed by elution with 0 → 80% EtOAc/hexane)], gave **10** (*E*/*Z*, 75:25; 102 mg, 62%) as a transparent oil. Compound **10** (*E*) had: ^{1}H NMR δ 0.65−0.68 (m, 2, *c*-Pr), 0.84−0.96 (m, 11, *c*-Pr, Bu_3-Sn), 1.24−1.46 (m, 18, Bu_3Sn), 1.42 (s, 3, CH_3), 1.63 (s, 3, CH_3), 3.02 (br s, 1, *c*-Pr), 5.03 (dd, J = 2.6, 6.1 Hz, 1, H3′), 5.10 (dd, J = 8.8, 51.5 Hz, 1, H5′), 5.33 (dd, J = 2.5, 8.5 Hz, 1, H4′), 5.66 (d, J = 1.6, 6.2 Hz, 1, H2′), 6.05 (d, J = 1.6 Hz, 1, H1′), 6.13 (br s, 1, NH), 7.84 (s, 1, H2), 8.47 (s, 1, H8); ^{19}F NMR δ −95.66 (d, J = 52.0 Hz, 84% of 0.75F) & (ddd, J = 4.7, 52.0, 215.0 Hz, 16% of 0.75F). Compound **10** (*Z*) had: ^{1}H NMR δ 0.65−0.68 (m, 2, *c*-Pr), 0.84−0.96 (m, 11, *c*-Pr, Bu_3Sn), 1.24−1.46 (m, 18, Bu_3Sn), 1.42 (s, 3, CH_3), 1.63 (s, 3, CH_3), 3.02 (br s, 1, *c*-Pr), 4.49 ("dt", J = 2.9, 10.7 Hz, 1, H4′), 5.01 (dd, J = 3.3, 6.3 Hz, 1, H3′), 5.48 (dd, J = 1.6, 6.3 Hz, 1, H2′), 6.03 (d, J = 1.6 Hz, 1, H1′), 6.04 (dd, J = 10.1, 34.0 Hz, 1, H5′), 6.13 (br s, 1, NH), 7.82 (s, 1, H2), 8.49 (s, 1, H8); ^{19}F NMR δ −89.07 ("d", J = 34.0 Hz, 0.25F); MS *m*/*z* 652 (100, M + 1, ^{120}Sn), 650 (75, MH^+, ^{118}Sn), 648 (38, MH^+, ^{116}Sn).

6-*N*-Cyclopropyl-9-[5,6-dideoxy-6-fluoro-*β*-D-*ribo*-hex-5-(*E*/*Z*)-enofuranosyl]adenine (11). A solution of **10** (*E*/*Z*, 75:25; 90 mg, 0.14 mmol) in TFA/H_2O (9:1, 3 mL) was stirred at ∼0 °C (ice bath) for 50 min. Volatiles were evaporated (<15 °C) and coevaporated with toluene (2×) and ethanol under vacuum. The residue was chromatographed (hexane followed by elution with 0 → 20% S1/EtOAc) to give **11** (*E*/*Z*, 26:74; 41 mg, 61%) as a white powder: mp 184−187 °C; UV max 269 nm (ϵ 17 400), min 231 nm (ϵ 3000). Compound **11** (*E*) had: ^{1}H NMR (MeOH-d_4) δ 0.63−0.69 (m, 2, *c*-Pr), 0.87−0.93 (m, 2, *c*-Pr), 2.96 (br s, 1, *c*-Pr), 4.30 (t, J = 4.9 Hz, 1, H3′), 4.44 (dd, J = 4.7, 8.8 Hz, 1, H4′), 4.78 (t, J = 4.6 Hz, 1, H2′), 5.73 (ddd, J = 8.8, 11.1, 19.9 Hz, 1, H5′), 6.00 (d, J = 4.0 Hz, 1, H1′), 6.95 (dd, J = 11.1, 83.7 Hz, 1, H6′), 8.22 (s, 1, H2), 8.32 (s, 1, H8); ^{19}F NMR (MeOH-d_4) δ −126.53 (dd, J = 19.9, 83.7 Hz, 0.26F); ^{13}C NMR (MeOH-d_4) δ 8.97 (*c*-Pr, C2/2′), 25.95 (*c*-Pr, C1), 76.31 (C2′), 77.05 (C3′), 82.62 (d, J = 14.8 Hz, C4′), 91.84 (C1′), 113.09 (d, J = 11.6 Hz, C5′), 122.42 (C5), 142.47 (C8), 151.31 (br s, C4), 153.93 (d, J = 260.6 Hz, C6′), 155.19 (C2), 158.53 (C6). Compound **11** (*Z*) had: ^{1}H NMR (MeOH-d_4) δ 0.63−0.69 (m, 2, *c*-Pr), 0.87−0.93 (m, 2, *c*-Pr), 2.96 (br s, 1, *c*-Pr), 4.29 (t, J = 5.1 Hz, 1, H3′), 4.85 (t, J = 5.0 Hz, 1, H2′), 5.01 (dd, J = 4.6, 9.1 Hz, 1, H4′), 5.36 (ddd, J = 4.8, 9.1, 41.3 Hz, 1, H5′), 6.01 (d, J = 4.9 Hz, 1, H1′), 6.73 (ddd, J = 1.0, 4.8, 83.7 Hz, 1, H6′), 8.22 (s, 1, H2), 8.32 (s, 1, H8); ^{19}F NMR (MeOH-d_4) δ −127.15 (dd, J = 41.3, 83.7 Hz, 0.74F); ^{13}C NMR (MeOH-d_4) δ 8.97 (*c*-Pr, C2/2′), 25.95 (*c*-Pr, C1), 76.27 (C2′), 77.59 (C3′), 79.65 (d, J = 6.6 Hz, C4′), 91.80 (C1′), 112.48 (C5′), 122.68 (C5), 142.69 (C8), 151.31 (br s, C4), 155.20 (C2), 155.22 (d, J = 263.3 Hz, C6′), 158.53 (C6); MS *m*/*z* 322 (MH^+). Anal. $C_{14}H_{16}FN_5O_3$ (321.31) C, H, N.

6-*N*-Cyclopropyl-9-(6,6-dibromo-5,6-dideoxy-2,3-*O*-isopropylidene-*β*-D-*ribo*-hex-5-enofuranosyl)adenine (13a). A mixture of CBr_4 (299 mg, 0.9 mmol) and PPh_3 (236 mg, 0.9 mmol) and zinc dust (59 mg, 0.9 mmol) in CH_2Cl_2 (3 mL) was stirred for 3 h at ambient temperature. A solution of crude 5′-aldehyde [generated from **3b** (92 mg, 0.26 mmol) as described for **4a** (step a)] was added dropwise to the brown reaction mixture of ylide, and stirring was continued for 14 h [TLC ($CHCl_3$/MeOH, 95:5) showed less polar **13a** comigrated with Ph_3PO]. Oxalic acid dihydrate (98 mg, 0.78 mmol) in MeOH (2 mL) was added, and DCU was filtered off. The mother liquor was partitioned ($NaHCO_3/H_2O$//$CHCl_3$), and the separated organic layer was washed (brine), dried (Na_2SO_4), evaporated, and chromatographed (50 → 90% EtOAc/hexane) to give **13a** (97 mg, 74%) as a white foam: ^{1}H NMR δ 0.63−0.69 (m, 2, *c*-Pr), 0.91−0.96 (m, 2, *c*-Pr), 1.40 (s, 3, CH_3), 1.63 (s, 3, CH_3), 3.04 (br s, 1, *c*-Pr), 4.96 (dd, J = 2.4, 8.1 Hz, 1, H4′), 5.21 (dd, J = 2.4, 4.1 Hz, 1, H3′), 5.58 (d, J = 4.1 Hz, 1, H2′), 6.07 (s, 1, H1′), 6.18 (br s, 1, NH), 6.70 (d, J = 8.1 Hz, 1, H5′), 7.81 (s, 1, H2), 8.47 (s, 1, H8); MS *m*/*z* 502 (MH^+).

6-*N*-Cyclopropyl-9-(6,6-dibromo-5,6-dideoxy-*β*-D-*ribo*-hex-5-enofuranosyl)adenine (13b). Treatment of **13a** (90 mg, 0.18 mmol)

with TFA/H_2O (9:1, 2 mL) as described for **4b** and column chromatography (65 → 95% EtOAc/hexane followed by 0 → 20% S1/EtOAc) gave **13b** (71 mg, 86%) as a white powder: mp 198−200 °C; UV max 269 nm (ϵ 17 600), min 233 nm (ϵ 3100); ^{1}H NMR (DMSO-d_6) δ 0.59−0.65 (m, 2, *c*-Pr), 0.70−0.77 (m, 2, *c*-Pr), 3.03 (br s, 1, *c*-Pr), 4.22 ("t", J = 3.9 Hz, 1, H3′), 4.52 (dd, J = 3.4, 8.5 Hz, 1, H4′), 4.78 ("t", J = 5.0 Hz, 1, H2′), 5.64 (br s, 2, OH2′,3′), 5.94 (d, J = 5.6 Hz, 1, H1′), 7.14 (d, J = 8.5 Hz, 1, H5′), 8.12 (br s, 1, NH), 8.28 (s, 1, H2), 8.41 (s, 1, H8); ^{13}C NMR (DMSO-d_6) δ 7.15 (*c*-Pr, C2/2′), 25.01 (*c*-Pr, C1), 73.76, 74.64 (C2′/3′), 84.94 (C4′), 88.62 (C1′), 93.60 (C6′), 120.64 (C5), 137.20 (C5′), 141.98 (C8), 149.74 (C4), 153.31 (C2), 156.50 (C6); MS *m*/*z* 462 (MH^+). Anal. $C_{14}H_{15}Br_2N_5O_3$ (461.11) C, H, N.

6-*N*-Cyclopropyl-9-(5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-ynofuranosyl)adenine (14a). BuLi/hexane (1.6 M; 1.21 mL, 1.94 mmol) was added dropwise to a solution of **13a** (120 mg, 0.24 mmol) in THF (4 mL) at −78 °C under N_2. After 20 min [TLC ($CHCl_3$/MeOH, 95:5) showed the presence of four more polar products], the reaction mixture was neutralized with AcOH (pH ∼6) and volatiles were evaporated. The residue was partitioned ($NaHCO_3$/H_2O//$CHCl_3$), and the organic layer was washed ($NaHCO_3$/H_2O, brine), dried (Na_2SO_4), evaporated, and column chromatographed (50 → 90% EtOAc/hexane) to give **14a** (21 mg, 26%) as an oil: ^{1}H NMR δ 0.63−0.68 (m, 2, *c*-Pr), 0.91−0.96 (m, 2, *c*-Pr), 1.42 (s, 3, CH_3), 1.61 (s, 3, CH_3), 2.49 (d, J = 1.8 Hz, 1, H6′), 3.04 (br s, 1, *c*-Pr), 5.05 (s, 1, H4′), 5.13 (d, J = 5.6 Hz, 1, H3′), 5.72 (d, J = 5.6 Hz, 1, H2′), 6.16 (br s, 1, NH), 6.23 (s, 1, H1′), 8.00 (s, 1, H2), 8.48 (s, 1, H8); MS *m*/*z* 342 (MH^+).

Note: The major byproduct isolated (∼25%) from the reaction mixture was the corresponding 6′-bromohomovinyl analogue (e.g., **8a** if X = Br): ^{1}H NMR δ 6.33 (d, J = 14.0 Hz, 1, H6′), 6.37 (dd, = 7.0, 14.0 Hz, 1, H5′); MS *m*/*z* 424 (100, MH^+, ^{81}Br), 422 (100, MH^+, ^{79}Br).

6-*N*-Cyclopropyl-9-(5,6-dideoxy-β-D-*ribo*-hex-5-ynofuranosyl)adenine (14b). Deprotection of **14a** (33 mg, 0.1 mmol) with TFA/H_2O (9:1, 1 mL) as described for **4b** gave **14b** (22 mg, 74%) as a white powder: mp 196−198 °C (dec); UV max 269 nm (ϵ 15 400), min 232 nm (ϵ 2400); ^{1}H NMR (DMSO-d_6) δ 0.59−0.65 (m, 2, *c*-Pr), 0.71−0.77 (m, 2, *c*-Pr), 3.02 (br s, 1, *c*-Pr), 3.73 (d, J = 1.9 Hz, 1, H6′), 4.36 (q, J = 4.6 Hz, 1, H3′), 4.53−4.57 (m, 1, H4′), 4.77 (q, J = 5.0 Hz, 1, H2′), 5.71 (d, J = 5.9 Hz, 1, OH2′), 5.74 (d, J = 5.7 Hz, 1, OH3′), 5.94 (d, J = 5.0 Hz, 1, H1′), 7.98 (br s, 1, NH), 8.27 (s, 1, H2), 8.32 (s, 1, H8); ^{13}C NMR (DMSO-d_6) δ 7.07 (*c*-Pr, C2/2′), 14.87 (*c*-Pr, C1), 73.91, 74.39 (C2′/3′), 76.09 (C6′), 79.53 (C5′), 82.03 (C4′), 88.25 (C1′), 120.27 (C5), 139.99 (C8), 150.07 (br s, C4), 153.58 (C2), 156.55 (C6). MS *m*/*z* 302 (MH^+). HRMS (FAB) calcd for ($C_{14}H_{14}N_5O_3$+H^+) 302.1253; found 302.1251.

Culturing of Parasites. The bloodstream form of *Trypanosoma brucei* 427 strain was maintained under the standard cell culture conditions (37 °C, 5% CO_2). The parasites were grown in complete HMI-9 medium containing 10% FBS, 10% Serum Plus, and 1× penicillin/streptomycin.[30]

Luciferase Assay. Luciferase assay was used to measure ATP-bioluminescence in *T. brucei* cultured in 96-well plates at 37 °C for 48 h. Parasites were diluted to 1.0×10^5 cells/mL in complete HMI-9 medium. One hundred microliters (100 μL) of the diluted parasites was aliquoted into sterile 96-well flat white opaque culture plates (Greiner). Each compound was serially diluted from 10 to 0.1 μM in DMSO and then mixed in the appropriate wells containing parasites. The treated parasites were then incubated for 48 h at 37 °C with 5% CO_2 before monitoring viability. To measure the viability of the parasites after treatment with each compound, the parasites were lysed in the wells by adding 100 μL of CellTiter-Glo (Promega). After lysis, the ATP bioluminescence of the 96-well plates was measured with a SpectraFluor Plus multidetection plate reader (Tecan).[31]

Antiviral Activity. Antiviral activity was determined by exposing BHK cells for 6 h to growth medium containing inhibitors (10 and 100 μg/mL) before infecting with VSV (Indiana serotype) at a multiplicity of infection of 10 plaque-forming units/cell. Infections were allowed to proceed in the continuing presence of inhibitors for ∼24 h. Yields of infectious virus from control and inhibitor-treated cells were determined by plaque assay on BHK cells as described.[32]

Acknowledgment. We wish to thank Professor Ronald T. Borchardt and Sumin Cai (University of Kansas) for their testing of 6-*N*-cyclopropyl analogues against AdoHcy hydrolase, and Professor Erik De Clercq (Rega Institute for Medical Research) for antiviral assays. This work was supported by NIH/NIGMS S06GM08205 (S.F.W.), by Drugs for Neglected Diseases Initiative (J.H.M.), and by a RSUM to NIAID TDRU AI35707 (Z.B.M.).

Supporting Information Available: Experimental procedures and characterization data for compounds **3a** and **12**, and elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM0511379