Acknowledgment. We are indebted to the National Institutes of Health (GM-09706), the U.S. National Academy of Sciences, the Akademie der Wissenschaften der DDR, and the Milligen Division of Millipore Corporation for support of this work. The National Science Foundation is thanked for grants used to purchase the high-field NMR spectrometers used in this research. We thank U. Kertscher and H. Apelt for HPLC investigations, Dr. S. Katzwinkel, Ch. Salewski, and Rick Neves for amino acid analyses, Greg Dabkowski for microanalyses, and H. Hans and M. Dreissigacker for skillful technical assistance. Peter Coassin and Rick Neves of Milligen are thanked for software modifications needed to adapt the Milligen 9050 continuous flow instrument to acid chloride protocols. Mass spectral determinations were performed by the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility, and the Mass Spectral Laboratory of the Departments of Organic and Biochemistry, Czechoslovak Academy of Sciences. National Starch is thanked for Polyhipe resins and Protein Technologies, Inc., and Research Corporation Technologies for supplying a batch-style peptide synthesizer.

Registry No. 1, 91613-96-6; 2, 103321-53-5; 3, 124007-51-8; 4, 132438-33-6; 5, 132409-91-7; 8, 82361-40-8; 9, 58822-25-6; 10, 132409-92-8; 11, 132409-93-9; 12, 66851-75-0; 13, 106083-79-8; 14, 69-25-0; HOBt, 2592-95-2; Fmoc-Phe-Cl, 103321-57-9; BOC-Gly-OCs, 42538-64-7; Fmoc-Phe-OH, 35661-40-6; $BrCH_2COOH$, 79-08-3; Fmoc-Tyr(*t*-Bu)-OH, 71989-38-3; Fmoc-Tyr(*t*-Bu)-OMe, 132409-94-0; Fmoc-Gly-Cl, 103321-49-9; BOC-Nle-OH, 6404-28-0; Fmoc-Leu-Cl, 103321-59-1; H-Leu-OMe, 2666-93-5.

Regiospecific and Highly Stereoselective Electrophilic Addition to Furanoid Glycals: Synthesis of Phosphonate Nucleotide Analogues with Potent Activity against HIV

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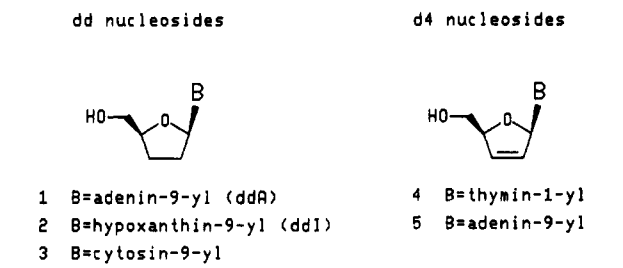
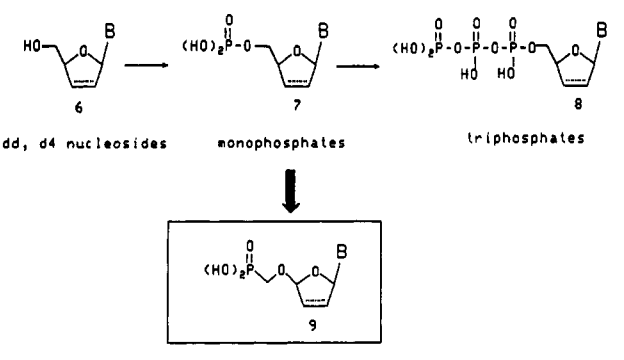
Regiospecific and highly stereoselective electrophilic addition to furanoid glycals has been used as a key step in the synthesis of phosphonate isosteres of nucleoside monophosphates. Using this methodology, phosphonate analogues of 1 (ddA), 4 (d4T), and 5 (d4A) monophosphates have been prepared. Present studies have also led to the development of a scheme for the synthesis of the phosphonate isostere of adenosine monophosphate. Despite the acetal structure, phosphonate derivatives 27 and 28 were substantially more acid stable than the corresponding nucleosides 1 and 5 with respect to glycosidic bond cleavage. The phosphonates 22 and 27 exhibited a potent antiretroviral activity comparable to that of 4 (d4T).

Most therapeutically useful antiviral agents selectively inhibit target enzymes produced in virus-infected cells. This selective inhibition of viral enzymes is the most important factor for the present wave of rapid development of novel nucleoside analogues as antiviral agents. Since the discovery of human immunodeficiency virus (HIV) as the causative agent of acquired immunodeficiency syndrome (AIDS),[1] there has been intense effort to find compounds that can selectively block the replication of HIV. Because 3′-azido-3′-deoxythymidine (AZT), which is currently the only licensed drug for the treatment of AIDS patients,[2] gives only limited prolongation of survival and suffers from some adverse toxicological effects,[3] there is an urgent need for other compounds that are at least as efficacious but less toxic in humans. In this regard two series of nucleoside analogues have emerged as a new class of potent and selective HIV inhibitors. They are characterized as 2′,3′-dideoxy (dd)[4] and 2′,3′-didehydro-2′,3′-dideoxy (d4)[5] nucleosides (Chart I). Several of these com-

Chart I



Scheme I



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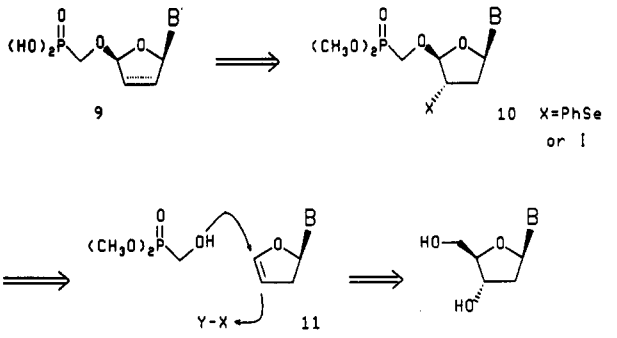
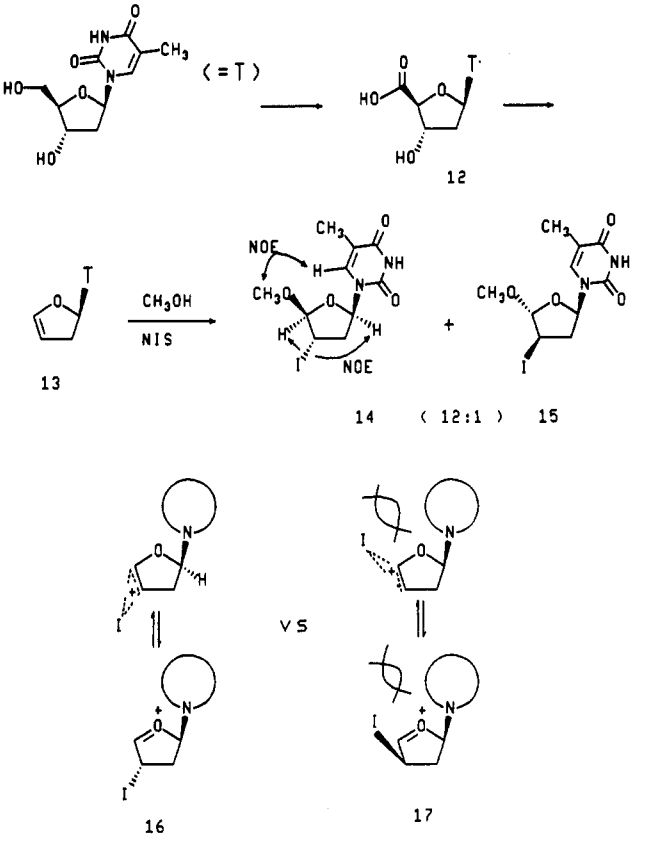
Scheme II



Scheme III



pounds, such as ddI (2),[6] ddC (3)[4] and d4T (4),[7] are currently in clinical trials.

Like AZT, these new antiviral nucleoside analogues do not directly exert antiviral activity, but rather are prodrugs of active phosphorylated metabolites, which are formed by the action of various kinases in cells. Ultimately the triphosphates of these drugs are responsible for actual antiviral activity by acting as inhibitors of HIV reverse transcripatase[8] (Scheme I). In addition to the inhibitory effect of the triphosphates 8 against HIV reverse transcriptase, the efficiency of the triphosphate formation in order to retain high level of active form in cells is a critical factor for these nucleoside analogues to be useful HIV agents.

One logical approach to the discovery of new and potent HIV inhibitors involves the design of phosphate analogues where the phosphate moiety is changed to isosteric and isoelectronic phosphonates. Those enzymatically and chemically stable phosphonate analogues, which mimic the nucleoside monophosphates, bypass the initial enzymatic phosphorylation and could potentially be more effective antiviral agents against HIV. Recently, a very successful phosphonate mimicking of the phosphate functionality has been realized in the series of (phosphonomethoxy)alkyl purine derivatives[9] as broad spectrum antiviral agents. In this case, the spacial location of the oxygen atom, namely the β-position from the phosphorus atom in the acyclic chain, has been demonstrated to play a critical role for antiherpesvirus and antiretrovirus activity.[10] The role of this oxygen atom for antiviral activity may be attributed to the increased binding capacity of the phosphonate analogues to target enzymes. The second factor of importance might involve the acidity of the phosphonates. Thus, the second pK_a value of the (phosphonomethoxy)-alkyl derivative is approximately 6.6, which is comparable to that of the phosphate.[10] This is to be compared with the second pK_a value of around 7.0 for the corresponding alkyl phosphonates. Taking into account that the phosphonomethoxy functionality (P–C–O) would be the closest chemical equivalent of the phosphonooxymethyl group (P–O–C) of the phosphate in the biological system, the new phosphonate structures 9 have emerged as the most promising isosteres of the monophosphates 7 (Scheme I).

The basic strategy envisioned for the assembly of the acetal functionality shown in 9 is depicted in Scheme II. This approach relies on the regio- and sterecontrolled addition of dimethyl (hydroxymethyl)phosphonate[11] to the chiral furanoid glycal 11, a process that could be mediated by electrophiles, such as halogens and phenylselenyl halides. In turn, the glycals (B = thymine, adenine, and uracil)[12] are derived from 2′-deoxy nucleosides, making this approach highly convergent. From a synthetic standpoint, the use of natural nucleosides as starting material enables the preparation of chiral 9 in which the asymmetry at C_5 would be relayed from the stereogenic glycosidic bond.

Since the literature offers no guidance on the stereochemical outcome in the electrophilic addition to the C_2-substituted furanoid glycals, an initial investigation of the addition reaction with a simple alcohol was performed with the aim of establishing the stereochemical course

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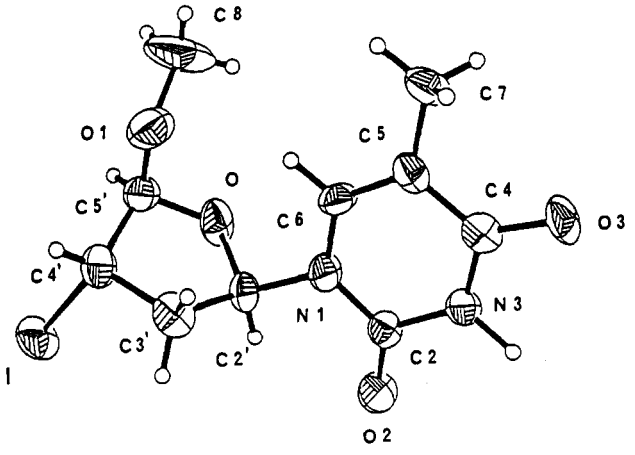


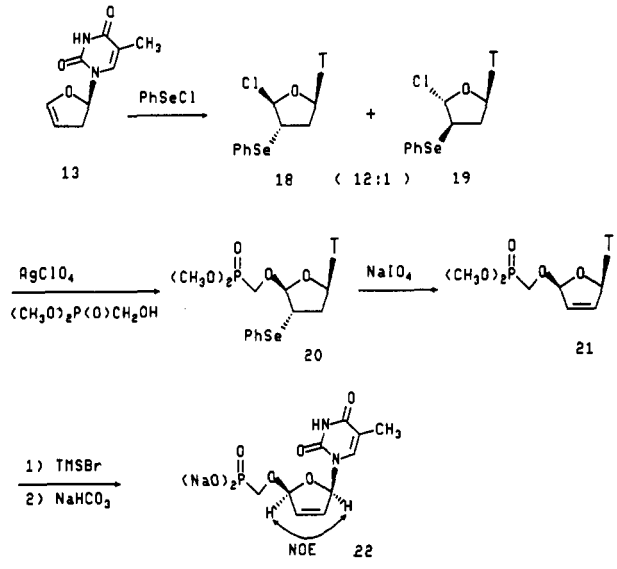
Figure 1. ORTEP drawing of compound **14**.

(Scheme III). The starting material for this study was the glycal **13**, which we readily prepared from thymidine via **12** in two steps by the procedure of Horwitz and coworkers.[12] The haloetherification reaction[13] of the glycal **13** with methanol mediated with *N*-iodosuccinimide gave a 12:1 mixture of two trans isomers **14** and **15** as assayed by NMR. The regiospecificity and the high stereoselectivity observed in this reaction are a consequence of the sterically favored α side approach of the electrophile to generate the energetically more stable halonium and/or oxonium transition intermediate **16** in preference to the less favorable **17**. In an NOE study of the isomer **14**, the methoxy protons showed a strong enhancement upon irradiation of the C_6 thymine proton in addition to a positive NOE between the 2-H and the 5-H. The stereochemical assignment of **14** was further ascertained by X-ray crystallography as shown in Figure 1. The crystallographic drawing of **14** also shows the preferred anti orientation for the thymine ring. This is consistent with the NOE observed between the methoxy protons and the C_6 thymine proton.

With the crucial C_5 stereochemistry of the tetrahydrofuran shown to favor the desired isomer, the synthesis of **22**, the phosphonate isostere of d4T (**4**) monophosphate, was next completed as illustrated in Scheme IV. When the glycal **13**[12] was reacted with phenylselenyl chloride at −70 °C, a 12:1 mixture of **18** and **19** was obtained in high yield. Treatment of this mixture with silver perchlorate in the presence of dimethyl (hydroxymethyl)phosphonate[11] afforded the phosphonate **20** in 41% overall yield. Assignment of the stereoarrangement in **20** was based on mechanistic considerations analogous to the stereoselective formation of **14**. The phosphonate **20** was transformed into the d4T phosphonate analogue **22** by the sequence (1) oxidation with sodium periodate in methanol to generate the olefin **21** and (2) removal of the phosphonate ester by treatment with bromotrimethylsilane in DMF followed by neutralization with sodium bicarbonate in overall 52% yield. The cis configuration in **22** is consistent with the NOE enhancement for the 5-H proton upon irradiation of the 2-H.

The chemistry now developed was next applied to the purine series. For this purpose, the glycal **23**[12] was prepared from 2′-deoxyadenosine by the procedure analogous

Scheme IV



to that described for synthesis of the glycal **13**. As illustrated in Scheme V, the (dimethylphosphono)methoxy funtionality was directly introduced to the glycal **23** with the aid of *N*-(phenylseleno)phthalimide or iodine bromide to give **24** (65%) or **25** (95%) in a regiospecific and a highly stereoselective manner. Oxidative elimination of the phenylselenyl group in **24** or base (DBU) promoted elimination of hydrogen iodide in **25** gave rise to the olefin **26** in high yield. The deblocking of the protecting groups in **26** in a similar manner described for conversion of **21** to **22** produced **27**, which is a phosphonate isostere of d4A (**5**) monophosphate. The tetrahydrofuranyl derivative **28**, a phosphonate isostere of ddA (**1**) monophosphate was also prepared by catalytic hydrogenation of the olefin **27**.

Bishyroxylation of the double bond in **26** was accomplished with catalytic osmium tetraoxide and *N*-methylmorpholine oxide[14] as the oxidant, and the diol **29** was generated as a single isomer in high yield. The stereochemistry of this diol is presumed to be as shown in **29**, based upon osmylation at the sterically more exposed α face of the double bond in the furan ring.[15] Removal of the protecting groups in **29** led to **30**, which is a phosphonate isostere of adenosine monophosphate. In compounds **27**, **28**, and **30**, a positive NOE was observed between the 2-H and 5-H, confirming the cis stereoarrangement of the adenine base and the phosphonomethoxy side chain.

Because of the fact that new phosphonate analogues **22**, **27**, **28**, and **30** described in this paper possess the unique acetal functionality adjacent to the glycosidic bond, the acid stability of these compounds was of concern for potential drug development. The acid sensitivity of ddA (**1**) and ddI (**2**) has been well documented.[16] As expected, when d4A (**5**) was dissolved in D_2O at pH = 1.8, NMR analysis showed the immediate formation of adenine and the furan derivative **32**. In contrast, the half-life of the d4A phosphonate **27** was approximately 3 h, indicating the greater acid stability of this class of compounds. Apparently, the presence of the electronegative oxygen atom at

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Scheme V

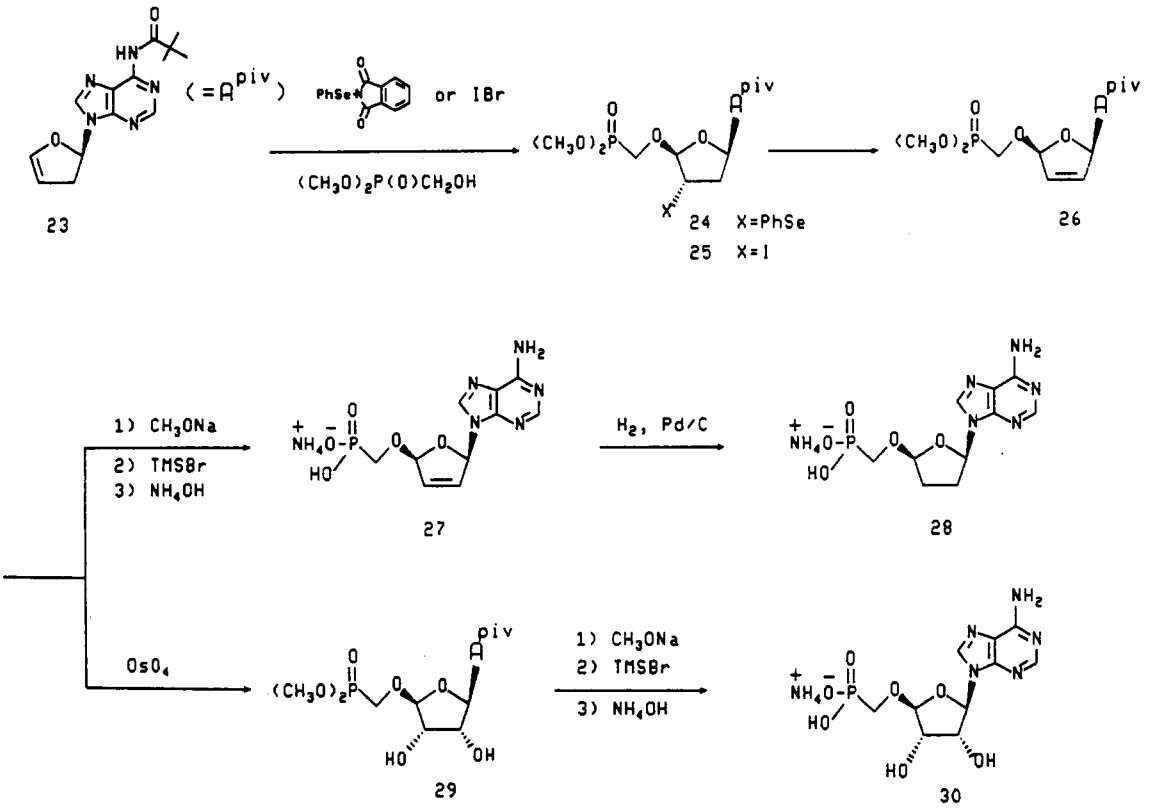
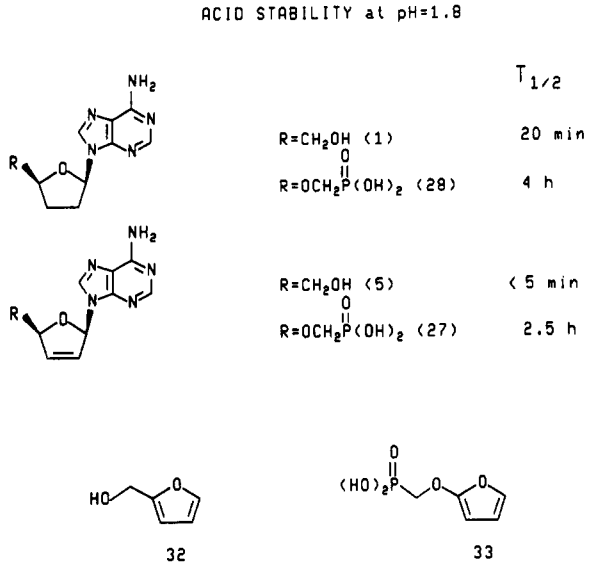


Chart II



the C_5 position in **27** makes the furan oxygen less capable to form the oxonium intermediate for cleavage of the glycosidic bond. Prolonged acid treatment of **27** eventually produced the furan derivative **33** and adenine (Chart II). A similar trend of the acid stability for compound **28** vs compound **1** (ddA) was also observed. In both compounds **27** and **28** no evidence of cleavage at the acetal portion was detected, indicating that the glycosidic bond is more susceptible than the acetal bond for the acid cleavage.

The phosphonate analogues **22** and **27** prepared in this study were evaluated for their inhibitory effect on the replication of retroviruses, including Rauscher-murine Leukemia virus (R-MuLV) and human immunodeficiency virus-1 (HIV-1). As seen in Table I, both **22** and **27** exerted very potent inhibition of HIV-induced cytopathogenicity in MT-4 cells comparable to that of compound **4** (d4T)

Table I. Antiretroviral and Anticellular Activities of the Cyclic Phosphonates in Tissue Culture

	ID_{50} (μM)		
virus or cell	**22**	**27**	**4** (d4T)
R-MuLV[a]	0.6	0.003	2.5
HIV-1[b]	12.0	1.5	1.2
MT-4 cells[c]	>600	>600	>600

[a] Rauscher-murine Leukemia virus: The R-MuLV in vitro assay was performed according to the published procedure, Rowe et al. *Virology* **1970**, *42*, 1136. [b] Fifty percent effective dose required to protect 50% of the HIV-1 infected MT-4 cells against cyytopathcity following a 5-day incubation period in the presence of the compound. [c] Fifty percent cytotoxic dose.

without any sign of cytotoxicity up to 600 μM. Furthermore, compound **27** was superior to d4T in inhibiting R-MuLV at 3 orders magnitude low concentration, indicating that the murine model might be useful to evaluate **27** for its in vivo efficacy against the retrovirus.[17] The finding obtained here for **22** and **27** suggests that these compounds are worthy of further biological evaluation for their potential as anti-HIV drugs.

The work described in this paper summarizes the highlights of our synthetic work on a new class of phosphonate isosteres of nucleoside monophosphates. A high stereoselectivity observed for the electrophilic addition to the C_2-substituted furanoid glycals is unprecedented. This finding will lead to further development of the furanoid glycals for the stereoselective natural product synthesis. The potent anti-HIV activity exhibited by the d4T and d4A phosphonate analogues **22** and **27** clearly demonstrates that not only these phosphonates may act as biologically equivalent isosteres of corresponding nucleoside mono-

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phosphates, but also they are taken up enough be cells to exert antiviral activity. As shown in the synthesis of compound **30**, a phosphonate isostere of adenosine monophosphate, the synthetic approach described herein should be applicable for other phosphonate mimics[18] of many natural and unnatural nucleosides monophosphates, which are often active metabolites or intermediates of the biological significance.

Experimental Section

Melting points are uncorrected. All reactions were performed under nitrogen.

(2*R*,4*S*,5*S*)-1-(Tetrahydro-4-iodo-5-methoxy-2-furanyl)thymine (14). To a cooled (−20 °C) solution of the glycal **13**[12] (388 mg, 2.0 mmol) in CH_2Cl_2 (4 mL) and MeOH (1 mL) was added portionwise *N*-iodosuccinimide (450 mg, 2.0 mmol). After being stirred at 0 °C for 45 min, the reaction mixture was diluted with ether (25 mL), washed with water and brine, dried ($MgSO_4$), and then evaporated in vacuo to dryness. The residue, on recrystallization from benzene, gave **14** (650 mg, 92%) as white needles: mp 132–135 °C; ^1H NMR ($CDCl_3$) δ 1.91 (s, 3 H), 2.5–2.68 (m, 2 H), 3.45 (s, 3 H), 4.22 (d, J = 7.2 Hz, 1 H), 5.27 (s, 1 H), 6.71 (t, J = 6.3 Hz, 1 H), 7.31 (s, 1 H), 8.58 (broad s, 1 H). Anal. Calcd for $C_{10}H_{13}N_2O_4I$: C, 34.11; H, 3.72; N, 7.96. Found: C, 34.21; H, 3.92; N, 7.89.

(2*R*,4*S*,5*S*)-1-[Tetrahydro-4-(phenylselenyl)-5-[(dimethoxyphosphinyl)methoxy]-2-furanyl]thymine (20). To a solution of the glycal **13** (1.94 g, 10 mmol) in CH_2Cl_2 (30 mL) at −70 °C was added dropwise a solution of phenylselenyl chloride (1.92 g, 10 mmol) in CH_2Cl_2 (5 mL). After the mixture was stirred at −70 °C for 1 h, the solvent was removed in vacuo to give a 12:1 mixture of **18** and **19** as a yellow oil: ^1H NMR ($CDCl_3$) of **18** δ 1.95 (s, 3 H), 2.5–2.8 (m, 2 H), 4.18 (d, J = 6.5 Hz, 1 H), 6.20 (s, 1 H), 6.55 (dd, J = 6.0, 7.5 Hz, 1 H), 7.1–7.7 (m, 6 H), 9.30 (br s, 1 H). Without further purification, the mixture of **18** and **19** was dissolved in CH_2Cl_2 (20 mL), and dimethyl (hydroxymethyl)phosphonate[11] (4.6 g, 22 mmol) was added. The solution was cooled to −70 °C, and silver perchlorate (2.3 g, 11 mmol) in acetonitrile (4 mL) was added dropwise over 3 min. The mixture was allowed to warm to 0 °C and was then poured into aqueous $NaHCO_3$. The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2–5% MeOH as eluent to give **20** (1.7 g, 41%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.93 (s, 3 H), 2.4–2.5 (m, 2 H), 3.70 (dd, J = 8.0, 8.4 Hz, 1 H), 3.75 (d, J = 12.0 Hz, 6 H), 3.85 (d, J = 6.9 Hz, 1 H), 3.90 (dd, J = 8.0, 8.4 Hz, 1 H), 4.2 (m, 1 H), 5.10 (s, 1 H), 6.52 (t, J = 7.0 Hz, 1 H), 7.1–7.6 (m, 5 H), 8.86 (br s, 1 H).

(2*R*,5*R*)-1-[2,5-Dihydro-5-[(dimethoxyphosphinyl)methoxy]-2-furanyl]thymine (21). To a solution of **20** (6.0 g, 12.2 mmol) in MeOH (20 mL) was added dropwise a suspended solution of sodium bicarbonate (1.8 g, 21 mmol) and sodium periodate (3.2 g, 15 mmol) in water (20 mL). After being stirred at room temperature for 1 h, the mixture was heated at 80 °C for 45 min. Volatiles were removed in vacuo, and the residue was suspended in CH_2Cl_2, filtered through Celite, and dried ($MgSO_4$). After the volatiles were evaporated in vacuo, the residue was chromatographed on silica gel using CH_2Cl_2–5% MeOH as eluent to give **21** (3.4 g, 85%) as a white amorphous solid: ^1H NMR ($CDCl_3$) δ 1.86 (s, 3 H), 3.75 (d, J = 12.8 Hz, 3 H), 3.81 (d, J = 12.8 Hz, 3 H), 3.83 (dd, J = 8.4, 8.9 Hz, 1 H), 3.90 (dd, J = 8.4, 8.9 Hz, 1 H), 5.71 (s, 1 H), 6.07 (d, J = 5.7 Hz, 1 H), 6.23 (d, J = 5.7 Hz, 1 H), 6.92 (s, 1 H), 7.13 (s, 1 H), 8.95 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.339, 52.889, 52.976, 53.080, 60.491, 62.738, 87.837, 108.402, 108.569, 111.653, 130.613, 131.675, 135.435, 150.480, 163.603. Anal. Calcd for $C_{12}H_{17}N_2O_7P$: C, 43.38; H, 6.16; N, 8.43. Found: C, 43.53; H, 6.20; N, 8.26.

(2*R*,5*R*)-1-[2,5-Dihydro-5-(phosphonomethoxy)-2-furanyl]thymine Disodium Salt (22). To a solution of **21** (916 mg, 2.76 mmol) in DMF (4 mL) at 0 °C was added bromotrimethylsilane (3 mL). After the mixture was stirred at 0 °C for 4 h, the volatiles were removed in vacuo and the residue was dissolved in aqueous $NaHCO_3$ and then evaporated in vacuo to dryness. The residual solid was purified by C_{18} reverse-phase column chromatography under 8 psi of pressure using water as eluent to give **22** (656 mg, 61%) as a white solid: mp 23–237 °C; UV max (H_2O) 266 nm (ϵ 10134); ^1H NMR (D_2O) δ 1.85 (s, 3 H), 3.56 (dd, J = 8.4, 8.7 Hz, 1 H), 3.74 (dd, J = 8.4, 8.7 Hz, 1 H), 5.99 (s, 1 H), 6.18 (d, J = 6.0 Hz, 1 H), 6.43 (d, J = 6.0 Hz, 1 H), 6.82 (s, 1 H), 7.38 (s, 1 H); ^{13}C NMR (D_2O) δ 13.921, 67.870, 69.848, 89.868, 111.242, 111.364, 113.908, 131.177, 134.655, 139.350. Anal. Calcd for $C_{10}H_{11}N_2O_7Na_2P\cdot H_2O$: C, 32.61; H, 3.51; N, 7.61. Found: C, 32.31; H, 3.63; N, 7.35.

9-[2,3-Dihydro-2(*R*)-furanyl]-6-*N*-pivaloyladenine (23). To a solution of 2(*R*)-adenin-9-yl-2,3-dihydrofuran[12] (2.0 g, 10 mmol) in 1,2-dichloroethane (10 mL) and pyridine (1 mL) was added pivaloyl chloride (1.5 g, 12 mmol) and (dimethylamino)-pyridine (170 mg). After the mixture was heated at 55–60 °C for 6 h, volatiles were evaporated in vacuo. The residual oil was taken up in CH_2Cl_2, washed with water, 20% H_3PO_4, and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified on silica gel using CH_2Cl_2–3% MeOH as eluent to give **23** (2.5 g, 85%) as a white powder: ^1H NMR ($CDCl_3$) δ 1.24 (s, 9 H), 2.29 (ddd, J = 3.5, 5.0, 17.1 Hz, 1 H), 3.33 (dddd, J = 2.4, 5.0, 9.4, 17.1 Hz, 1 H), 5.24 (dd, J = 2.4, 5.0 Hz, 1 H), 6.41 (dd, J = 3.5, 9.4 Hz, 1 H), 6.48 (dd, J = 2.4, 5.0 Hz, 1 H), 8.18 (s, 1 H), 8.73 (s, 1 H). Anal. Calcd for $C_{14}H_{17}N_5O_2$: C, 58.54; H, 17.14; N, 24.39. Found: C, 58.61; H, 16.98; N, 24.02.

(2*R*,4*S*,5*R*)-6-*N*-Pivaloyl-9-[tetrahydro-4-(phenylselenyl)-5-[(dimethoxyphosphinyl)methoxy]-2-furanyl]-adenine (24). To a solution of the glycal **23** (8.0 g, 28 mmol) and dimethyl (hydroxymethyl)phosphonate[11] (9.8 g, 70 mmol) in 1,2-dichloroethane (60 mL) at 23 °C was added *N*-(phenylseleno)phthalimide (19 g, 56 mmol). After 15 min, the mixture was heated at 85 °C for 2 h. The resulting yellow solution was diluted with CH_2Cl_2 (300 mL), washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2–3% MeOH as eluent to give **24** (10.8 g, 65%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.25 (s, 9 H), 2.61 (ddd, J = 2.7, 6.6, 14.4 Hz, 1 H), 2.96 (ddd, J = 6.6, 7.5, 14.4 Hz, 1 H), 3.68 (d, J = 11 Hz, 6 H), 3.7–4.0 (m, 3 H), 3.98 (dd, J = 2.7, 7.5 Hz, 1 H), 5.24 (s, 1 H), 6.63 (t, J = 6.6 Hz, 1 H), 8.27 (s, 1 H), 8.67 (s, 1 H).

(2*R*,4*S*,5*R*)-6-*N*-Pivaloyl-9-[tetrahydro-4-iodo-5-[(dimethoxyphosphinyl)methoxy]-2-furanyl]adenine (25). To a solution of the glycal **23** (861 mg, 3.0 mmol) and dimethyl (hydroxymethyl)phosphonate[11] (1.5 g, 11 mmol) in CH_2Cl_2 (7 mL) at −25 °C was added a solution of iodine bromide (1.2 g, 6.0 mmol) in CH_2Cl_2 (10 mL) over a period of 5 min. After being stirred at −25 °C for 45 min, the mixture was diluted with CH_2Cl_2 and aqueous $NaHCO_3$. The organic phase was washed with aqueous bisulfite, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2–3% MeOH as eluent to give **25** (1.5 g, 92%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.32 (s, 9 H), 2.84 (dd, J = 6.5, 14.9 Hz, 1 H), 3.16 (ddd, J = 5.9, 6.5, 14.9 Hz, 1 H), 3.76 (d, J = 10.5 Hz, 6 H), 3.7–4.0 (m, 2 H), 4.45 (d, J = 5.9 Hz, 1 H), 5.46 (s, 1 H), 6.83 (t, J = 6.5 Hz, 1 H), 8.27 (s, 1 H), 8.51 (s, 1 H), 8.69 (s, 1 H).

(2*R*,5*R*)-6-*N*-Pivaloyl-9-[2,5-dihydro-5-[(dimethoxyphosphinyl)methoxy]-2-furanyl]adenine (26). To a mixture of **24** (10.2 g, 17.5 mmol) and $NaHCO_3$ (5 g, 60 mmol) in dioxane (100 mL) at 5 °C was added dropwise 30% H_2O_2 (6.0 mL) over a period of 3 min. After the mixture was stirred at room temperature for 4 h, volatiles were evaporated in vacuo. The residual oil was taken up in CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified on silica gel column using CH_2Cl_2–5% MeOH as eluent to give **26** (6.1 g, 82%) as a white oil.

Alternatively, to a solution of **25** (1.2 g, 2.1 mmol) in THF (10 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (610 mg, 4 mmol), and the solution was heated at 65 °C for 50 min. The solvent was removed in vacuo, and the residual oil was taken in CH_2Cl_2, washed with 20% H_3PO_4 and brine, and concentrated in vacuo. The oily residue was chromatographed on silica gel using CH_2Cl_2–5% MeOH as eluent to give **26** (580 mg, 65%): ^1H NMR ($CDCl_3$) δ 1.31 (s, 9 H), 3.64 (d, J = 10.8 Hz, 3 H), 3.71 (d, J = 10.8 Hz, 3 H), 3.84 (dd, J = 8.7, 9.9 Hz, 1 H), 3.92 (dd, J = 8.7,

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9.9 Hz, 1 H), 5.87 (s, 1 H), 6.27 (d, J = 6.0 Hz, 1 H), 6.34 (dd, J = 1.5, 6.0 Hz, 1 H), 7.0 (d, J = 1.5 Hz, 1 H), 8.04 (s, 1 H), 8.66 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.524, 40.607, 53.318 (d, J = 6.2 Hz), 61.598 (d, J = 165 Hz), 86.247, 109.202, 123.406, 130.657, 132.679, 141.966, 150.205, 152.056, 176.547. Anal. Calcd for $C_{17}H_{24}N_5O_6P$: C, 48.00; H, 5.67; N, 16.47. Found: C, 39.66; H, 6.01; N, 16.09.

(2*R*,5*R*)-9-[2,5-Dihydro-5-(phosphonomethoxy)-2-furanyl]adenine Ammonium Salt (27). To a solution of **26** (979 mg 2.3 mmol) in MeOH (3 mL) at 0 °C was added 25% sodium methoxide in MeOH (2 mL). After being stirred at 25 °C for 5 h, the reaction mixture was carefully neutralized to pH = 8.0 by dropwise addition of 2 N HCl in an ice bath. Volatiles were removed in vacuo to dryness to give a white solid which was dried in high vacuum over P_2O_5. Without further purification, this material was dissolved in DMF (15 mL), and freshly distilled bromotrimethylsilane (6 mL) was added to 0 °C. The solution was stirred for 1 h at 0 °C and for 2 h at 25 °C. Volatiles were removed in vacuo, and the residual oil was diluted with concentrated NH_4OH (7 mL) and reevaporated in vacuo. The solid residue was purified by C_{18} reverse-phase column using water as eluent under 8 psi of pressure to give **27** (608 mg, 80%) as a white amorphous powder: UV max (H_2O) 260 nm (ϵ 14 982); ^{1}H NMR (D_2O) δ 3.59 (dd, J = 9.3, 13.2 Hz, 1 H), 3.69 (dd, J = 9.3, 13.2 Hz, 1 H), 5.99 (s, 1 H), 6.46 (d, J = 6.0 Hz, 1 H), 6.50 (d, J = 6.0 Hz, 1 H), 6.82 (s, 1 H), 7.87 (s, 1 H), 8.13 (s, 1 H); ^{13}C NMR (D_2O) δ 70.756 (d, J = 150 Hz), 93.065, 116.510, 122.434, 136.579, 139.835, 147.763, 155.424, 158.990, 161.809. Anal. Calcd for $C_{10}H_{15}N_6O_5P\cdot 3H_2O$: C, 31.25; H, 5.46; N, 21.87. Found: C, 31.32; H, 5.85; N, 22.15.

(2*R*,5*R*)-9-[Tetrahydro-5-(phosphonomethoxy)-2-furanyl]adenine Ammonium Salt (28). A solution of **27** (280 mg, 0.9 mmol) in EtOH–water (4:1) (30 mL) was hydrogenated in the presence of 10% Pd/C (100 mg) at 25 psi for 6 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by C_{18} reverse-phase column using water as eluent under 8 psi of pressure to give **28** (220 mg, 82%) as white powder: UV max (H_2O) 260 nm (ϵ 14 774); ^{1}H NMR (D_2O) δ 2.2–2.7 (m, 4 H), 3.48 (dd, J = 9.6, 13.2 Hz, 1 H), 3.56 (dd, J = 9.0, 13.2 Hz, 1 H), 5.36 (t, J = 3.9 Hz, 1 H), 6.33 (t, J = 6.3 Hz, 1 H), 8.08 (s, 1 H), 8.30 (s, 1 H); ^{13}C NMR (D_2O) δ 36.201, 38.125, 69.471 (d, J = 158 Hz), 91.210, 113.875 (d, J = 11.8 Hz), 124.675, 147.475, 154.80, 159.022, 161.995. Anal. Calcd for $C_{10}H_{17}N_6O_5P\cdot 2H_2O$: C, 32.60; H, 5.71; N, 22.82. Found: C, 37.41; H, 6.05; N, 22.39.

(2*R*,3*R*,4*S*,5*R*)-6-*N*-Pivaloyl-9-[tetrahydro-3,4-dihydroxy-5-[(dimethoxyphosphinyl)methoxy]-2-furanyl]adenine (29). To a solution of phenylboric acid (860 mg, 7.0 mmol) and 4-methylmorpholine *N*-oxide (900 mg, 7.5 mmol) in CH_2Cl_2 (20 mL) was added at 23 °C osmium tetraoxide (25 mg) followed by **26** (2.75 g, 6.4 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred 2 h, and 10% sodium bisulfite (4 mL) was added. After the mixture was stirred for 1 h, the CH_2Cl_2 was separated, washed with brine, and dried over $MgSO_4$. Evaporation of solvent gave a white oil which was dissolved in acetone (15 mL) and 1,3-dipropanol (760 mg, 10 mmol). All volatiles were removed in vacuo, and the resulting oil was chromatographed on silica gel using CH_2Cl_2–7% MeOH as eluent to give **29** (2.3 g, 76%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H), 3.72 (d, J = 10.5 Hz, 6 H), 3.73 (dd, J = 1.1, 13.5 Hz, 1 H), 3.95 (d, J = 10.6, 13.5 Hz, 1 H), 4.91 (dd, J = 4.5, 6.3 Hz, 1 H), 4.33 (d, J = 4.5 Hz, 1 H), 5.09 (s, 1 H), 6.38 (d, J = 6.3 Hz, 1 H), 8.35 (s, 1 H), 8.49 (s, 1 H), 8.83 (br s, 1 H).

(2*R*,3*R*,4*S*,5*R*)-9-[Tetrahydro-3,4-dihydroxy-5-(phosphonomethoxy)-2-furanyl]adenine Ammonium Salt (30). To a solution of **29** (2.2 g, 4.8 mmol) in MeOH (30 mL) at 0 °C was added 25% sodium methoxide in MeOH (5 mL). After being stirred at 25 °C for 7 h, the reaction mixture was neutralized to pH = 8.0 by dropwise addition of 2 N HCl in an ice bath. Volatiles were removed in vacuo to dryness to give a white solid that was dried in high vacuum over P_2O_5. Without further purification, this material was dissolved in DMF (30 mL), and freshly distilled bromotrimethylsilane (7 mL) was added at 0 °C. After the mixture was stirred for 1 h at 0 °C and for 6 h at 25 °C, volatiles were removed in vacuo. The residual oil was diluted with concentrated NH_4OH (3 mL) and reevaporated in vacuo. The solid residue was purified by C_{18} reverse-phase column using water as eluent under 8 psi of pressure to give **30** (1.1 g, 65%) as a white amorphous solid: UV max (H_2O) 262 nm (ϵ 12 640); ^{1}H NMR (D_2O) δ 3.56 (dd, J = 10.0, 12.9 Hz, 1 H), 3.79 (dd, J = 10.0, 12.9 Hz, 1 H), 4.31 (d, J = 11.0 Hz, 1 H), 4.92 (dd, J = 6.0, 11.0 Hz, 1 H), 5.17 (s, 1 H), 6.08 (d, J = 6.0 Hz, 1 H), 8.24 (s, 1 H), 8.25 (s, 1 H); ^{13}C NMR (D_2O) δ 66.296 (d, J = 157 Hz), 75.881, 88.982, 111.148, 119.927, 142.208, 150.689, 153.560, 156.330. Anal. Calcd for $C_{10}H_{17}N_6O_7P\cdot 2H_2O$: C, 30.05; H, 5.26; N, 21.03. Found: C, 30.09; H, 5.06; N, 20.38.

Crystallography. Crystals of compound **14** for structure analysis were grown from benzene. Single crystals of $C_{10}H_{13}N_2O_4I$ are orthorhombic, at 20 + 1 °C, space group $P2_12_12_1$-D_2^4 (no. 19) with a = 5.674 (1) Å, b = 14.401 (3) Å, c = 15.513 (3) Å, V = 1268 (1) Å^3, and z = 4 [d_{calcd} = 1.845 g cm^{-3}; μ_a(Mo Kα) – 2.50 mm^{-1}]. A total of 1705 independent absorption-corrected reflections having 2θ(Mo Kα) < 55.0° (the equivalent of 1.0 limiting Cu Kα spheres) were collected on a computer-controlled Nicolet autodiffractometer using full (0.90° wide) scans and graphite-monochromated Mo Kα radiation. The structure was solved using "heavy atom" techniques with the Nicolet SHELXTL software package as modified at Crystalytics Co. The resulting structural parameters have been refined to convergence [R_1 (unweighted, based on F) = 0.039 for 1176 independent absorption-corrected reflections having 2θ(Mo Kα) < 55.0° and $I > 3\sigma(I)$] using counter-weighted full-matrix least-squares techniques and a structural model which incorporated anisotropic thermal parameters for all non-hydrogen atoms and isotropic thermal parameters for all hydrogen atoms. Hydrogen atom H_{3N} was located from a difference Fourier map and refined as an independent isotropic atom. The methyl groups were included in the refinement as idealized sp^3-hybridized rigid rotors and gave final values for the O–C–H and C–C–H angles which ranged from 103° to 118°. The remaining hydrogen atoms were fixed at idealized sp^2- or sp^3-hybridized positions with a C–H bond length of 0.96 Å. The correctness of the enantiomeric description was verified in cycles of least-squares refinement in which the multiplier of $\Delta f''$ was varied; this multiplier refined to a final value of 1.1(1).

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