1,6,7,12-Tetramethoxy-4,9-dihydroxy-3,10-perylenequinone (26). A mixture of **23** (3.0 g, 4.73 mmol), sodium hydroxide (6.0 g), and water (2 mL) was heated in an oil bath. After the temperature was elevated gradually to 200 °C to remove water, it was further heated for 2 h at 250 °C. After cooling, water (50 mL) was added to dissolve the residue. Dimethyl sulfate (7.5 mL) was added dropwise over 30 min to the resulting solution. It was adjusted to pH 8–9 and stirred for 2 h at 50 °C. After cooling, the precipitate was collected and washed with water and acetone to afford **26** (450 mg, 21%): black amorphous; mp >300 °C dec; IR (KBr) 3450 (OH), 3140 (aromatic C—H), 1630 (quinone C═O), 1395 cm^{-1}. Anal. ($C_{24}H_{18}O_8$) C, H.

1,6,7,12-Tetraacetyl-4,9-dihydroxy-3,10-perylenequinone (27). Compound **25** (600 mg, 1.59 mmol) was suspended in acetic anhydride (30 mL) and pyridine (30 mL). The mixture was heated in an oil bath (100 °C) for 48 h. The solvent was removed in vacuo, and the residue was purified by column chromatography (SiO_2, 20 g) using chloroform–methanol (100:1) as eluant to furnish **27** (115 mg, 13%): yellow amorphous; mp 200–201 °C; IR (KBr) 3150 (aromatic C—H), 1680 (C═O of ester), 1625 (C═O of quinone), 1590 (C═C), 1482, 1397, 1376 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17, 2.18, 2.42 (all s, 6 H each, OAc × 6), 6.53 (s, 2 H, 2-H, 11-H), 7.14 (s, 2 H, 5-H, 8-H). Anal. ($C_{28}H_{18}O_{12}$) C, H.

Cytotoxic Assay. Assay for cytotoxicity in various tumor cells were carried out according to the procedures described previously.[8,9,10] The tumor cells included in this study were A-549 lung carcinoma, HCT-8 colon carcinoma, RPMI-7951 melanoma, TE-671 medulloblastoma, KB epidermoid carcinoma of nasopharynx, and P-388 lymphocytic leukemia cells.

Protein Kinase C Assay. The assay was performed by a modification of the mixed micelle assay as described elsewhere.[11] The reaction mixture in a total volume of 250 μL contained 0.3% Triton X-100 with 6 mol% phosphatidylserine (Avanti) and 0.5 mol% dioleoylglycerol (Avanti) in 29 mM Hepes buffer, pH = 7.5, 10 mM magnesium chloride, 100 μM calcium chloride, and 20 μM [^{32}P]ATP. Compound was dissolved in DMSO, and 10 μL was added to the assay. DMSO alone was added in the control assay reactions. The reaction was started with 20 μL of protein kinase C (PKC) (1 μg/mL). The reaction was terminated with 0.5 mL ice-cold trichloroacetic acid followed by 100 μL of bovine serum albumin (1 mg/mL). The precipitate was collected by vacuum filtration using GF/C filters and quantified by counting in a β scintillation counter.

Anti HSV-1/HSV-2 Assay. Confluent Vero cells were infected with 3PFU/Cell of HSV-1 (Kos) or HSV-2 (333) in RPMI-1640 medium containing 2% FCS. Two-fold serial dilutions of the drugs (final concentration: 100, 50, 25, 12.5 μg/mL) were added during the innoculation phase. After 24 h, the CPE was observed under the microscope.

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3′-Spiro Nucleosides, a New Class of Specific Human Immunodeficiency Virus Type 1 Inhibitors: Synthesis and Antiviral Activity of [2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-xylo- and -ribofuranose]-3′-spiro-5″-[4″-amino-1″,2″-oxathiole 2″,2″-Dioxide] (TSAO) Pyrimidine Nucleosides

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Instituto de Química Médica, Juan de la Cierva, 3. 28006 Madrid, Spain, and Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000, Leuven, Belgium. *Received January 27, 1992*

A series of 3′-spiro nucleosides have been synthesized and evaluated as anti-HIV-1 agents. Reaction of *O*-mesylcyanohydrins of furanos-3′-ulosyl nucleosides with base afforded [1-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-xylo- and -ribofuranosyl]]-3′-spiro-5″-[4″-amino-1″,2″-oxathiole 2″,2″-dioxide] derivatives of thymine, uracil and 4-*N*-acetylcytosine **11** and **12**. Desilylation of **11** and **12** gave the full deprotected 3′-spiro xylo- and ribofuranosyl nucleosides **13** and **14** or the partially 5′-O-deprotected-3′-spiro β-D-*xylo*- and -*ribo*-nucleosides **15** and **16**, or 2′-O-deprotected-3′-spiro β-D-*ribo*-nucleoside **17**. 2′-Deoxygenation of **17** afforded 2′-deoxy-3′-spiro β-D-*erythro*-pentofuranosyl derivative **18**. These 3′-spiro derivatives were evaluated for their anti-HIV-1 activity. All 3′-spiro nucleosides having a *xylo* configuration did not show any anti-HIV-1 activity. 3′-Spiro *ribo*-nucleosides with none or only one silyl group at C-2′ or C-5′ or the 2′-deoxy derivative were also inactive at subtoxic concentrations. However, 3′-spiro *ribo*-nucleosides having two silyl groups at C-2′ and C-5′ were potent and selective inhibitors of HIV-1. None of the nucleoside analogues that showed anti-HIV-1 activity proved inhibitory to the replication of HIV-2 or SIV.

Introduction

Azidothymidine (AZT, Retrovir) and DDI (dideoxyinosine) are, so far, the only drugs approved for the clinical treatment of acquired immunodeficiency syndrome (AIDS).[1-4] However, they also induce bone marrow suppression (AZT), peripheral neuropathy (DDI), pancreatitis (DDI), and other side effects.[3-6] AZT and DDI have

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‡ Rega Institute for Medical Research.

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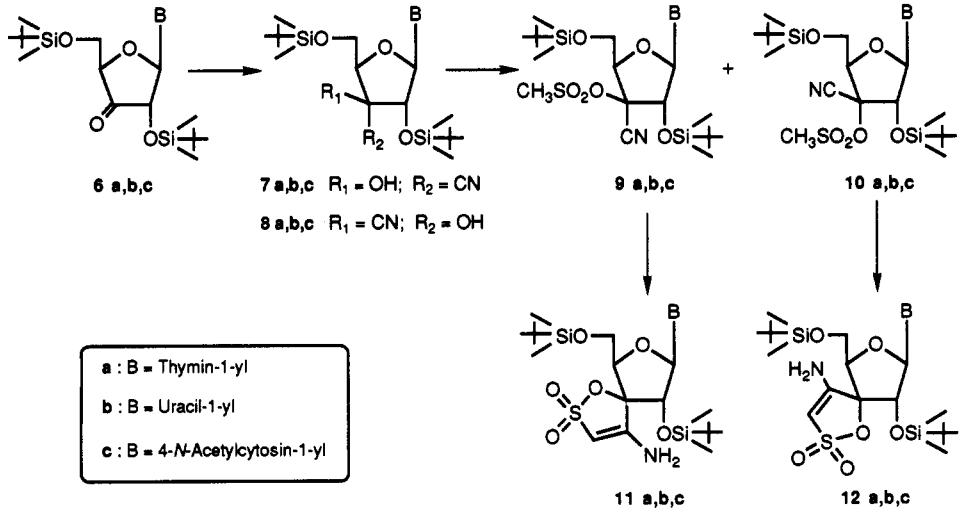
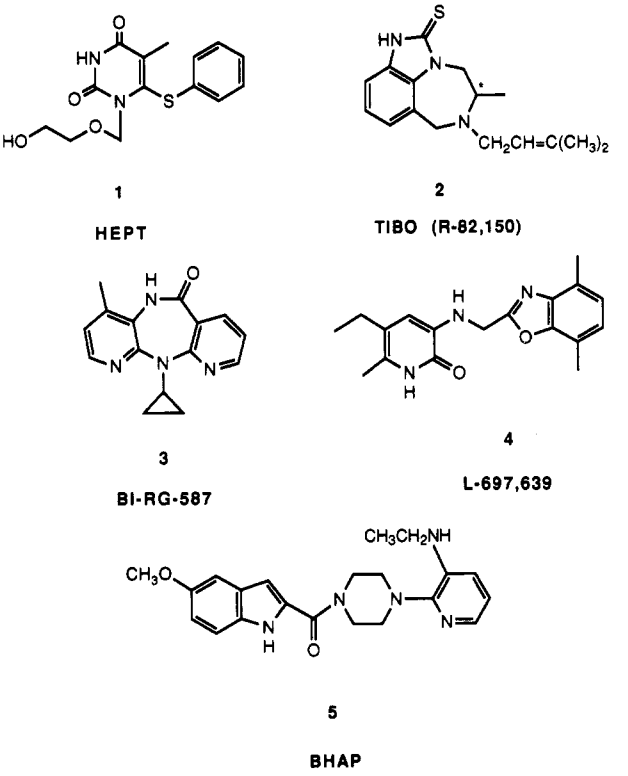
Scheme I



proved to be potent inhibitors of HIV reverse transcriptase.[7-9] The emergence of drug-resistant virus strains[10-12] together with the severe side effects that have been observed, justify the search for new compounds which are more potent and selective in their anti-HIV activity.

Recently, five new lead compounds have been identified as highly specific inhibitors of HIV-1 replication, i.e. the acyclouridine 1 (HEPT),[13-15] benzodiazepinone (TIBO) 2,[16,17] dipyridodiazepinone 3,[18,19] pyridinone 4,[20] and bis-

Chart I



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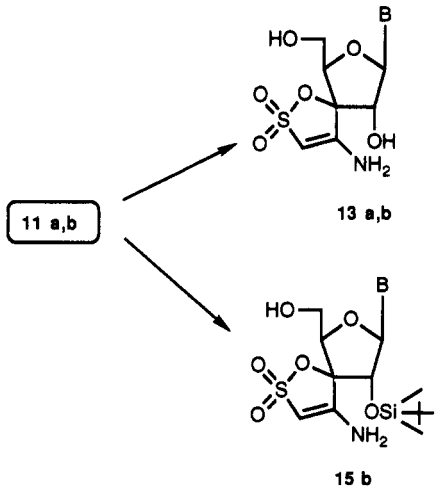
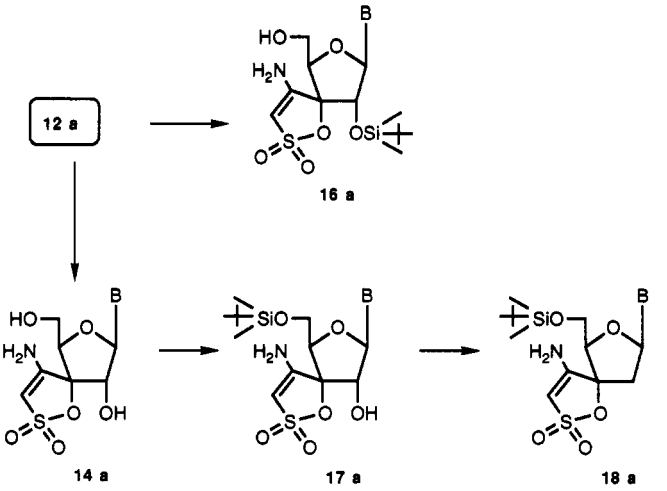
Scheme II



Scheme III



(heteroaryl)piperazine (BHAP) **5**.[21] All these compounds are highly specific for HIV-1. They do not inhibit HIV-2 or any other retroviruses. The specific HIV-1 inhibitors primarily interact with a nonsubstrate binding site at the HIV-1 reverse transcriptase (RT), but, in addition, their RT-inhibitory potency also depends on the type of the template used to monitor HIV-1 RT activity.[22-25]

In a previous paper[26] we described the synthesis of furanose-3-spiro-5'-[4'-amino-1',2'-oxathiole 2',2'-dioxide] derivatives by reaction of *O*-mesylcyanohydrins of furanos-3-uloses with base. The method involves abstraction of one proton from the mesylate methyl group, followed by nucleophilic attack of the carbanion thus formed at the nitrile carbon atom. We have used this procedure for the synthesis of a variety of furanose- and pyranose-3-spiro sugar derivatives.[27] Similar behavior was observed with *O*-mesylcyanohydrins of furanosid-3'-ulosylthymine which under basic conditions afforded the corresponding 3'-spiro nucleosides.[28] In order to prepare a new kind of highly functionalized branched chain nucleosides, we now extend the method to 3'-*C*-cyanomesylates of pyrimidine nucleosides, and here we report on the synthesis and anti-HIV-1 activity of a novel class of compounds, the [2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-pentofuranosyl]-3'-spiro-5''-[4''-amino-1'',2''-oxathiole 2'',2''-dioxide] (TSAO) pyrimidine derivatives.[29]

These spiro branched-chain nucleosides are potent and selective inhibitors of HIV-1, but not HIV-2, replication. They represent a new lead in the development of specific anti-HIV-1 agents. The lead compound **12a** is the first example of a nucleoside analogue which is highly specific for HIV-1.

Chemistry

Treatment of the 3'-ketonucleosides derived from thymine **6a**,[30] uracil **6b**,[31] and 4-*N*-acetylcytosine **6c**[32] with

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sodium cyanide in a two phase ethyl ether/water system in the presence of sodium bicarbonate gave a mixture of the two epimeric nucleoside 3′-cyanohydrins **7** and **8**[30,31] (Scheme I). These cyanohydrins, on standing in solution, reversed to the corresponding ketonucleosides **6** used as starting materials. Thus, they were not isolated, and used without further purification in the next step. Reaction of the cyanohydrin mixture (**7** and **8**) with mesyl chloride in pyridine gave the respective 3′-*C*-cyano-3′-*O*-mesyl-*xylo* and -*ribo* derivatives of thymine **9a** (53%) and **10a** (10%), uracil **9b** (52%) and **10b** (11%), and 4-*N*-acetylcytosine **9c** (53%) and **10c** (15%). Treatment of the *xylo*-cyanomesylates **9a** and **9b** with Cs_2CO_3 and of **9c** with DBU afforded the spiro derivatives **11** [**11a** (87%); **11b** (80%); **11c** (63% yield)]. Similarly, reaction of the *ribo*-cyanomesylates **10a–c** with Cs_2CO_3 afforded the spiro nucleosides **12** [**12a** (85%); **12b** (39%); **12c** (70% yield)].

Treatment of **11a, 11b** (Scheme II) and **12a** (Scheme III) with tetrabutylammonium fluoride afforded the corresponding 3′-spiro 2′,5′-O-deprotected nucleosides **13a, 13b**, and **14a**. Attempts to deprotect the spiro derivatives of 4-*N*-acetylcytosine **11c** and **12c** gave complex reaction mixtures. Reaction of **11b** and **12a** with methanolic 0.1 N HCl gave the 5′-O-deprotected spiro derivatives **15b** and **16a**, respectively. Finally, treatment of **14a** with 1.1 equiv of *tert*-butyldimethylsilyl chloride gave the 5′-protected-2′-deprotected derivative **17a**. Deoxygenation[33] at the 2′ position of **17a** by treatment with *N,N*-thiocarbonyldiimidazole followed by reaction with tributyltin hydride in the presence of α,α'-azobis(isobutyronitrile) afforded the 2′-deoxy derivative of thymine **18a** in 50% yield.

Since no epimerization has been observed during mesylation of cyanohydrins,[26,27,34-36] the absolute configuration of the cyanomesylates **9** and **10** was assumed to be the same as that of the corresponding cyanohydrins **7** and **8**, and were assigned as *xylo* for the major compounds (**7a–c** and **9a–c**) and *ribo* for the minor compounds (**8a–c** and **10a–c**) based on the following criteria. Due to the deshielding effect of the adjacent mesyl group, H-2′ in **9a–c** (δ 4.87–5.17) appeared at lower field than in **10a–c** (δ 4.51–4.62), while H-4′ in compounds **10a–c** (δ 4.73–4.76) appeared at lower field than in compounds **9a–c** (δ 4.51–4.74). The stereochemical assignments are in agreement with the relative steric hindrance of the upper (β) or the lower (α) sides of the furanose ring. The *xylo* configuration of the major compounds **7a–c** and **9a–c** resulted from the approach of the CN^- ion to the uloses **6a–c** from the sterically less hindered α face of the furanose ring, opposite to the base and the 5′-O-substituent. This is in agreement with the stereochemistry observed for reactions of nucleophiles (RLi, RMgBr, and R_3Al) with **6b**.[37] The assignments of cyanomesylates **9a–c** and **10a–c** as *xylo* and *ribo*, respectively, were confirmed by NOE experiments carried out on the corresponding spiro derivatives **11a, 11c** and **12a, 12c** as shown below.

The ^1H NMR of the spiro derivatives **11a–c** and **12a–c** showed no signal for a mesylate group, but there were two new singlets at δ 6.31–6.95 (NH_2) and δ 5.56–5.63 (H-3″) for **11a–c**, and at δ 6.44–6.61 (NH_2) and δ 5.71–5.79 (H-3″) for **12a–c**.[38]

The absolute configurations at C-3′ for spiro derivatives **11a, 11c** and **12a, 12c** and thus, for the *xylo* (**9a, 9c**) and *ribo* (**10a, 10c**) cyanomesylates were unequivocally determined by NOE.[39,40] The signals of the NH_2 group of the compounds **11a, 11c** and **12a, 12c** were irradiated, and the magnitudes of NOE at all the protons were observed.[41] Thus irradiation of the NH_2 group of **11a, 11c** caused enhancements of the signals for H-1′, H-4′, and H-3″. Similarly, irradiation of the NH_2 group of **12a, 12c** influenced the signals for H-2′, H-5′a and H-3″.[41] The NOE values indicated that in nucleosides **11a, 11c** protons H-3″, H-4′, H-1′ and NH_2 are all "down", and thus, their structure is β-D-*xylo*. In compounds **12a, 12c** protons H-3″, H-2′, H-5′a and NH_2 are "up", thus, their structure is β-D-*ribo*.

The coupling constants of the furanose ring protons observed for the *xylo* derivatives **9a–c, 11a–c, 13a, 13b**, and **15b** ($J_{1',2'}$ = 1.2–5.7 Hz) are smaller than those observed for the *ribo*-pentofuranosyl nucleosides **10a–c, 12a–c, 14a, 16a, 17a**, and **18a** ($J_{1',2'}$ = 7.3–8.5 Hz). These couplings constants are also in a good agreement with those reported in the literature for 3′-C-branched-β-D-*xylo*-nucleosides ($J_{1',2'}$ = 2.0–5.1 Hz)[42] and 3′-C-branched-β-D-*ribo*-nucleosides ($J_{1',2'}$ = 7.5–8.0 Hz).[43-45] This suggests that these coupling constant values could be used to assign the C-3′-configuration of an unknown 3′-*C*-cyanomesylate or 3′-spiro nucleoside.

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Biological Results

A number of *xylo*- and *ribo*-nucleoside analogues with a 3'-spiro-5''-[4''-amino-1'',2''-oxathiole 2'',2''-dioxide] substituent in either (*S*) (*xylo*) or (*R*) (*ribo*) configuration and substituted at C-5' and/or C-2' by a *tert*-butyldimethylsilyl (tBDMS) group, were evaluated for their anti-HIV-1 activity in human MT-4 lymphocyte cells.

Compounds with silyl groups at C-2' and C-5' and a 3'-spiro moiety in the (*S*) configuration (**11a–c**) did not show any anti-HIV-1 activity at subtoxic concentrations. Their 50% cytotoxic concentration (CC_{50}) ranged from 3.1 to 18 μg/mL. Also, those thymine and uracil derivatives that contained a 3'-spiro group in the (*S*) configuration and no silyl group at C-2' and C-5' of the ribose moiety were devoid of any anti-HIV-1 activity. However, when the 3'-spiro moiety was in the (*R*) configuration (compounds **12a–c**), and silyl groups were present at C-2' and C-5', marked anti-HIV-1 activity was noted. The thymine derivative (**12a**) had an EC_{50} (50% effective concentration) of 0.034 μg/mL, whereas the uracil (**12b**) and 4-*N*-acetylcytosine (**12c**) derivatives were 3-fold less effective than their thymine congener **12a**. Interestingly, when only one silyl group was present, either at the C-2' position (**16a**) or C-5' position (**17**, **18**), the compounds were completely inactive. Also, when only the 3'-spiro moiety was present, as in **14a**, no inhibition was noted. The thymine derivative **14a** was not cytotoxic at 100 μg/mL, which indicates that the toxicity observed for compounds **12a–c** and **10a** could be attributed to the silyl groups at C-2' or C-5' rather than to the 3'-spiro group.

None of the nucleoside analogues that showed activity against HIV-1 replication in MT-4 cells proved inhibitory to the replication of HIV-2 (ROD), HIV-2 (EHO), or SIV (MAC_{251}) in vitro (data not shown). The TSAO class of anti-HIV-1 compounds represents the first example of nucleoside analogues, containing an intact ribose moiety, that are highly specific and selective inhibitors of HIV-1. In this respect, these compounds behave similarly to the non-nucleoside derivatives HEPT,[13-15] TIBO,[16,17] BI-RG-587 (nevirapin),[18,19] L-697,639, L697,661,[20] and BHAP.[21] The TSAO derivatives should be considered as novel candidate drugs that deserve further investigations for their therapeutic potential in the treatment of HIV-1 infections.

Table I. Inhibitory Effects of the Test Compounds on HIV-1-Induced Cytopathicity in MT-4 Cells

compound[a]	EC_{50}[b] (μg/mL)	CC_{50}[c] (μg/mL)	SI[d]
10a	>1.6	4.3 ± 1.8	<2.7
11a	>4	18 ± 16	<4.5
11b	>1.6	3.1 ± 0.5	<2
11c	>4	7.1 ± 2.7	<1.8
12a	0.034 ± 0.015	7.7 ± 1.5	227
12b	0.114 ± 0.023	8.3 ± 0.55	73
12c	0.097 ± 0.043	7.5 ± 2.2	77
13a	>500	≥500	≤1
13b	>80	320 ± 40	<4
14a	>100	>100	-
15b	>100	221 ± 5.0	<2
16a	>40	106 ± 17	<2.6
17a	>20	45 ± 2.6	<2.2
18a	>0.8	1.5 ± 0.04	<1.9
HEPT	5.5 ± 0.1	>200	>36
TIBO (R82150)	0.021 ± 0.011	>20	>952
BI-RG-587	0.038 ± 0.015	>20	>526

[a] Data represent the mean values of at least three to five independent experiments. [b] 50% effective concentration or compound concentration required to inhibit HIV-1-induced cytopathicity in MT-4 cells by 50%. [c] 50% cytotoxic concentration or compound concentration required to reduce MT-4 cell viability by 50%. [d] Selectivity index or ratio of CC_{50} to EC_{50}.

Experimental Section

Chemical Procedures. Melting points were measured with a Reichert-Junt Kofler micro hot stage apparatus and are uncorrected. Microanalyses were obtained with a Heareus CHN-O-RAPID instrument. ^{1}H NMR spectra were recorded with a Varian EM-390, a Varian XL-300, and a Bruker AM-200 spectrometer operating at 90, 300, and 200 MHz, and ^{13}C NMR spectra with a Bruker WP-80-SY, a Bruker AM-200, and a Varian XL-300 spectrometer operating at 20, 50, and 75 MHz, with Me_4Si as internal standard. IR spectra were recorded with a Shimadzu IR-435 spectrometer. Analytical TLC was performed on silica gel 60 F_{254} (Merck). Flash column chromatography was performed with silica gel 60 (230–400 mesh) (Merck).

Proximities were established conventionally on the basis of using NOE.

General Procedure for the Synthesis of 2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-3'-*C*-cyano-3'-*O*-mesyl-β-D-pentofuranosyl Nucleosides (9a–c and 10a–c). A mixture of the 3'-ketonucleoside **6a–c** (4 mmol), water (16 mL), ethyl ether (32 mL), sodium bicarbonate (0.64 g, 8 mmol), and sodium cyanide (0.2 g, 4 mmol) was stirred vigorously at room temperature for 16 h. The organic phase was separated, and the aqueous phase was washed with ethyl ether (2 × 50 mL). The combined ethereal phases were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue, a mixture of the two epimeric cyanohydrins, was dissolved in dry pyridine (8 mL). To this solution was added mesyl chloride (1.6 mL, 20 mmol). The mixture was stirred at 8–10 °C for 48 h, poured into ice and water, and extracted with chloroform (2 × 50 mL). The combined extracts were washed with 1 N HCl (50 mL), aqueous sodium hydrogen carbonate (50 mL), and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography.

1-[2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-3'-*C*-cyano-3'-*O*-mesyl-β-D-xylofuranosyl]thymine and 1-[2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-3'-*C*-cyano-3'-*O*-mesyl-β-D-ribofuranosyl]thymine (9a and 10a). The residue was chromatographed with ethyl acetate/hexane (1:4). The fastest moving fractions afforded 1.18 g (53%) of **9a** as a white foam: IR (KBr) 1375, 1185 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.96 (s, 3 H, CH_3-5), 3.33 (s, 3 H, CH_3SO_2), 4.05 (m, 2 H, H-5'), 4.51 (m, 1 H, H-4'), 4.87 (d, 1 H, H-2', $J_{1',2'}$ = 2 Hz), 6.03 (d, 1 H, H-1'), 7.28 (s, 1 H, H-6), 9.12 (bs, 1 H, NH-3); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 12.26 (CH_3-5), 40.24 (CH_3SO_2), 59.17 (C-5'), 81.51, 83.55 (C-2', C-4'), 82.51 (C-3'), 91.57 (C-1'), 111.87, 112.63 (CN, C-5), 134.68 (C-6), 150.22 (C-2), 163.55 (C-4). Anal. ($C_{24}H_{43}N_3O_8SSi_2$) C, H, N, S.

The slowest moving fractions afforded 0.22 g (10%) of **10a** as a white foam: IR (KBr) 1375, 1180 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.94 (s, 3 H, CH_3-5), 3.26 (s, 3 H, CH_3SO_2), 4.04 (m, 2 H, H-5', $J_{5'a,5'b}$ = 12, $J_{4',5'a}$ = 1.2, $J_{4',5'b}$ = 2.1 Hz), 4.51 (d, 1 H, H-2', $J_{1',2'}$ = 8.3 Hz), 4.73 (m, 1 H, H-4'), 6.24 (d, 1 H, H-1'), 7.38 (s, 1 H, H-6), 8.48 (bs, 1 H, NH-3); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 12.05 (CH_3-5), 40.33 (CH_3SO_2), 62.09 (C-5'), 80.34 (C-3'), 78.20, 84.10, 84.28 (C-2', C-4', C-1'), 112.24, 114.19 (C-5, CN), 133.68 (C-6), 150.42 (C-2), 163.18 (C-4). Anal. ($C_{24}H_{43}N_3O_8SSi_2$) C, H, N, S.

1-[2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-3'-*C*-cyano-3'-*O*-mesyl-β-D-xylofuranosyl]uracil and 1-[2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-3'-*C*-cyano-3'-*O*-mesyl-β-D-ribofuranosyl]uracil (9b and 10b). The residue was chromatographed with ethyl acetate/hexane (1:4). The fastest moving fractions afforded 0.26 g (11%) of **10b** as a white foam: IR (KBr) 1375, 1180 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.23 (s, 3 H, CH_3SO_2), 4.03 (m, 2 H, H-5'), 4.56 (d, 1 H, H-2', $J_{1',2'}$ = 7.5 Hz), 4.73 (m, 1 H, H-4'), 5.76 (dd, 1 H, H-5), 6.26 (d, 1 H, H-1'), 7.80 (d, 1 H, H-6), 8.96 (bs, 1 H, NH-3); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 40.33 (CH_3SO_2), 62.46 (C-5'), 78.76, 80.50, 84.33, 84.93 (C-2', C-3', C-4', C-1'), 103.59 (C-5), 114.00 (CN), 138.73 (C-6), 150.27 (C-2), 162.55 (C-4). Anal. ($C_{23}H_{41}N_3O_8SSi_2$) C, H, N, S.

From the slowest moving fractions **9b** (1.25 g, 52%) was isolated as a white foam: IR (KBr) 1375, 1185 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.20 (s, 3 H, CH_3SO_2), 4.03 (m, 2 H, H-5'), 4.60 (m, 1 H, H-4'), 4.93 (d, 1 H, H-2', $J_{1',2'}$ = 1.5 Hz), 5.73 (d, 1 H, H-5), 5.86 (d, 1 H, H-1'), 7.46 (d, 1 H, H-6), 9.73 (bs, 1 H, NH-3);

^{13}C NMR ($CDCl_3$, 20 MHz) δ 40.01 (CH_3SO_2), 61.88 (C-5′), 77.71, 80.06, 82.51, 86.42 (C-2′, C-3′, C-4′, C-1′), 105.10 (C-5), 114.33 (CN), 139.10 (C-6), 149.69 (C-2), 163.00 (C-4). Anal. ($C_{23}H_{41}N_3O_8SSi_2$) C, H, N, S.

4-*N*-Acetyl-1-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-cyano-3′-*O*-mesyl-β-D-xylofuranosyl]cytosine and 4-*N*-Acetyl-1-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-cyano-3′-*O*-mesyl-β-D-ribofuranosyl]cytosine (9c and 10c). The residue was chromatographed with ethyl acetate/hexane (1:1). The fastest moving fractions afforded 1.3 g (53%) of **9c** as a white foam: IR (KBr) 1375, 1185 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.28 (s, 3 H, NAc), 3.17 (s, 3 H, CH_3SO_2), 4.10 (m, 2 H, H-5′), 4.76 (m, 1 H, H-4′), 5.17 (d, 1 H, H-2′, $J_{1',2'}$ = 1.2 Hz), 5.84 (d, 1 H, H-1′), 7.50 (d, 1 H, H-5), 7.82 (d, 1 H, H-6), 10.6 (bs, 1 H, NH-4); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 40.06 (CH_3SO_2), 59.11 (C-5′), 80.51 (C-3′), 81.57, 85.30 (C-2′, C-4′), 93.29 (C-1′), 96.75 (C-5), 112.78 (CN), 143.20 (C-6), 154.87 (C-2), 163.67 (C-4), 171.45 (4-NCO). Anal. ($C_{25}H_{44}N_4O_8SSi_2$) C, H, N, S.

The slowest moving fractions gave 0.37 g (15%) of **10c** as a white foam: IR (KBr) 1375, 1180 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.30 (s, 3 H, NAc), 3.24 (s, 3 H, CH_3SO_2), 4.04 (m, 2 H, H-5′), 4.62 (d, 1 H, H-2′, $J_{1',2'}$ = 8 Hz), 4.74 (m, 1 H, H-4′), 6.42 (d, 1 H, H-1′), 7.45 (d, 1 H, H-5), 8.23 (d, 1 H, H-6), 10.28 (bs, 1 H, NH-4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 40.36 (CH_3SO_2), 62.30 (C-5′), 80.70 (C-3′), 80.07, 84.46, 85.86 (C-1′, C-2′, C-4′), 97.81 (C-5), 114.10 (CN), 143.60 (C-6), 154.96 (C-2), 163.23 (C-4), 171.37 (4-NCO). Anal. ($C_{25}H_{44}N_4O_8SSi_2$) C, H, N, S.

General Procedure for the Synthesis of [2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-pentofuranose]-3′-spiro-5″-[4″-amino-1″,2″-oxathiole 2″,2″-Dioxide] Pyrimidine Nucleosides (11a–c and 12a–c). To a solution of the 3′-*C*-cyano-3′-*O*-mesylpentofuranosyl nucleoside **9a–c** or **10a–c** (1 mmol) in dry acetonitrile (10 mL) was added either Cs_2CO_3 (325 mg, 1 mmol) or DBU (0.15 mL, 1 mmol). The mixture was stirred at room temperature for 1–24 h and then filtered and evaporated to dryness. The residue was purified by column chromatography.

[1-[2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-xylofuranosyl]thymine]-3′-spiro-5″-[4″-amino-1″,2″-oxathiole 2″,2″-Dioxide] (11a). **9a** was treated with Cs_2CO_3 and stirred for 6 h at room temperature according to the general procedure. The residue was chromatographed with ethyl acetate/hexane (1:3) to give a white solid **11a** which was crystallized from hexane (0.57 g, 87%): mp >230 °C; IR (KBr) 3420, 3350 cm^{-1} (NH_2), 1655 (C=C—N); ^{1}H NMR [(CD_3)$_2$SO, 300 MHz] δ 1.81 (s, 3 H, CH_3-5), 3.79 (m, 2 H, H-5′, $J_{5'a,5'b}$ = 11.7 Hz), 4.43 (d, 1 H, H-2′, $J_{1',2'}$ = 5.7 Hz), 4.53 (dd, 1 H, H-4′, $J_{4',5'a}$ = 6.4, $J_{4',5'b}$ = 3.4 Hz) 5.56 (s, 1 H, H-3″), 6.07 (d, 1 H, H-1′), 6.95 (bs, 2 H, NH_2), 7.44 (s, 1 H, H-6), 11.52 (bs, 1 H, NH-3); ^{13}C NMR [(CD_3)$_2$CO, 50 MHz] δ 12.53 (CH_3-5), 61.53 (C-5′), 82.54, 84.35, 89.47, 90.05 (C-1′, C-2′, C-4′, C-3″), 93.22 (C-3′), 112.31 (C-5), 135.83 (C-6), 151.42, 153.57 (C-2, C-4″), 163.95 (C-4). Anal. ($C_{24}H_{43}N_3O_8SSi_2$) C, H, N.

[1-[2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-xylofuranosyl]uracil]-3′-spiro-5″-[4″-amino-1″,2″-oxathiole 2″,2″-Dioxide] (11b). **9b** was treated with Cs_2CO_3 and stirred at room temperature according to the general procedure for 8 h. The residue was chromatographed with chloroform/acetone (6:1) to give a solid **11b** which was crystallized from hexane (0.31 g, 80%): mp 128–130 °C; IR (KBr) 3450, 3370 cm^{-1} (NH_2), 1650 (C=C—N); ^{1}H NMR [(CD_3)$_2$CO, 300 MHz] δ 3.96 (d, 2 H, H-5′, $J_{4',5'}$ = 5.1 Hz), 4.58 (d, 1 H, H-2′, $J_{1',2'}$ = 3.9 Hz), 4.71 (t, 1 H, H-4′), 5.66 (s, 1 H, H-3″), 5.81 (dd, 1 H, H-5), 6.09 (d, 1 H, H-1′), 6.35 (bs, 2 H, NH_2), 7.69 (d, 1 H, H-6), 10.18 (bs, 1 H, NH-3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 60.13 (C-5′), 82.66, 83.37, (C-2′, C-4′), 90.29, 90.99, 91.50 (C-1′, C-3′, C-3″), 103.31 (C-5), 139.76 (C-6), 150.33, 151.62 (C-2, C-4″), 163.02 (C-4). Anal. ($C_{23}H_{41}N_3O_8SSi_2$) C, H, N.

[4-*N*-Acetyl-1-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-xylofuranosyl]cytosine]-3′-spiro-5″-[4″-amino-1″,2″-oxathiole 2″,2″-Dioxide] (11c). **9c** was treated with DBU according to the general procedure for 3 h. The residue was chromatographed with ethyl acetate/hexane (1:1) to give a white solid **11c** which was crystallized from hexane (0.22 g, 63%): mp >230 °C; IR (KBr) 3440, 3350 cm^{-1} (NH_2), 1650 (C=C—N); ^{1}H NMR [(CD_3)$_2$CO, 300 MHz] δ 2.22 (s, 3 H, NAc), 4.03 (m, 2 H, H-5′), 4.60 (d, 1 H, H-2′, $J_{1',2'}$ = 2.2 Hz), 4.88 (t, 1 H, H-4′, $J_{4',5'}$ = 5.3 Hz), 5.63 (s, 1 H, H-3″), 6.04 (d, 1 H, H-1′), 6.31 (bs, 2 H, NH_2), 7.42 (d, 1 H, H-5), 8.10 (d, 1 H, H-6), 9.90 (bs, 1 H, NH-4); ^{13}C NMR [(CD_3)$_2$CO, 50 MHz] δ 61.26 (C-5′), 83.52, 85.03, 89.57, 92.69 (C-2′, C-4′, C-1′, C-3″), 92.45 (C-3′), 96.82 (C-5), 145.50 (C-6), 153.40, 155.61 (C-2, C-4″), 163.93 (C-4), 171.43 (4-NCO). Anal. ($C_{25}H_{44}N_4O_8SSi_2$) C, H, N.

[1-[2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]thymine]-3′-spiro-5″-[4″-amino-1″,2″-oxathiole 2″,2″-Dioxide] (12a). According to the general procedure, **10a** was treated with Cs_2CO_3 for 24 h. The residue was chromatographed with ethyl acetate/hexane (1:3) to give 0.11 g (85%) of **12a** as an amorphous solid: IR (KBr) 3400, 3320 cm^{-1} (NH_2), 1645 (C=C—N); ^{1}H NMR [(CD_3)$_2$CO, 300 MHz] δ 1.90 (s, 3 H, CH_3-5), 4.06 (m, 2 H, H-5′, $J_{5'a,5'b}$ = 12.2 Hz), 4.31 (t, 1 H, H-4′, $J_{4',5'}$ = 3.6 Hz), 4.67 (d, 1 H, H-2′, $J_{1',2'}$ = 8.0 Hz), 5.75 (s, 1 H, H-3″), 6.00 (d, 1 H, H-1′), 6.47 (bs, 2 H, NH_2), 7.42 (s, 1 H, H-6), 10.32 (bs, 1 H, NH-3); ^{13}C NMR [(CD_3)$_2$CO, 50 MHz] δ 63.05 (C-5′), 72.12, 85.05, 87.62 (C-2′, C-4′, C-3″), 92.25, 92.31 (C-1′, C-3′), 112.20 (C-5), 136.22 (C-6), 151.60, 152.28 (C-2, C-4″), 163.72 (C-4). Anal. ($C_{24}H_{43}N_3O_8SSi_2$) C, H, N.

[1-[2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]uracil]-3′-spiro-5″-[4″-amino-1″,2″-oxathiole 2″,2″-Dioxide] (12b). According to the general procedure, **10b** was treated with Cs_2CO_3 for 24 h. The residue was chromatographed with ethyl acetate/hexane (1:2) to give 0.24 g (39%) of **12b** as an amorphous solid: IR (KBr) 3390, 3310, 3190 cm^{-1} (NH_2, NH), 1645 (C=C—N); ^{1}H NMR [(CD_3)$_2$CO, 300 MHz] δ 4.08 (m, 2 H, H-5′, $J_{4',5'a}$ = 3.2, $J_{4',5'b}$ = 2.9, $J_{5'a,5'b}$ = 12.4 Hz), 4.35 (dd, 1 H, H-4′), 4.59 (d, 1 H, H-2′, $J_{1',2'}$ = 8.1 Hz), 5.79 (s, 1 H, H-3″), 5.83 (d, 1 H, H-5), 6.08 (d, 1 H, H-1′), 6.44 (bs, 2 H, NH_2), 7.76 (d, 1 H, H-6), 10.30 (bs, 1 H, NH-3); ^{13}C NMR [(CD_3)$_2$SO, 75 MHz] δ 60.20 (C-5′), 74.50 (C-2′), 84.38, 84.58 (C-4′, C-3″), 89.50 (C-1′), 92.81 (C-3′), 103.23 (C-5), 139.91 (C-6), 150.92, 151.32 (C-2, C-4″), 162.73 (C-4). Anal. ($C_{23}H_{41}N_3O_8SSi_2$) C, H, N.

[4-*N*-Acetyl-1-[2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]cytosine]-3′-spiro-5″-[4″-amino-1″,2″-oxathiole 2″,2″-Dioxide] (12c). **10c** was treated with Cs_2CO_3 for 1 h according to the general procedure. The residue was chromatographed with chloroform/methanol (50:1) to give 0.14 g (70%) of **12c** as an amorphous solid: IR (KBr) 3410, 3320 cm^{-1} (NH_2), 1650 (C=C—N); ^{1}H NMR [(CD_3)$_2$CO, 300 MHz] δ 2.24 (s, 3 H, NAc), 4.07 (m, 2 H, H-5′), 4.29 (dd, 1 H, H-4′, $J_{4',5'a}$ = 3.09, $J_{4',5'b}$ = 4.66 Hz), 4.83 (d, 1 H, H-2′, $J_{1',2'}$ = 7.33 Hz), 5.71 (s, 1 H, H-3″), 5.97 (d, 1 H, H-1′), 6.61 (bs, 2 H, NH_2), 7.46 (d, 1 H, H-5), 8.17 (d, 1 H, H-6), 9.86 (bs, 1 H, NH-4); ^{13}C NMR [(CD_3)$_2$CO, 50 MHz] δ 62.97 (C-5′), 75.94, 85.25 (C-2′, C-4′), 91.12, 91.34, 91.50 (C-3′, C-3″, C-1′), 97.66 (C-5), 147.13 (C-6), 152.80, 155.80 (C-2′, C-4″), 164.08 (C-4), 171.64 (4-NCO). Anal. ($C_{25}H_{44}N_4O_8SSi_2$) C, H, N.

General Procedure for Removal of the Protecting Groups of the 2′,5′-Bis-*O*-silyl-protected 3′-Spiro β-D-xylo- and -ribofuranosyl Nucleosides (11a,b and 12a). To a solution of the protected nucleoside **11a,b** or **12a** (1 mmol) in THF (15 mL) was added tetrabutylammonium fluoride trihydrate (Bu_4NF) (0.63 g, 2 mmol), and the mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through a column of silica gel using THF as the eluent. The filtrate was evaporated to dryness, and the residue was purified by column chromatography.

[1-(β-D-Xylofuranosyl)thymine]-3′-spiro-5″-[4″-amino-1″,2″-oxathiole 2″,2″-Dioxide] (13a). Following the general procedure, **11a** was reacted with Bu_4NF for 24 h. The residue was chromatographed with chloroform/methanol (100:15) to afford 0.09 g (73%) of **13a** as an amorphous solid: IR (KBr) 3420, 3400, 3320 cm^{-1} (NH_2, NH, OH), 1620 (C=C—N); ^{1}H NMR [(CD_3)$_2$SO, 300 MHz] δ 1.82 (s, 3 H, CH_3-5), 3.62 (m, 2 H, H-5′), 4.31 (m, 1 H, H-2′), 4.50 (m, 1 H, H-4′), 5.10 (t, 1 H, OH-5′) 5.57 (s, 1 H, H-3″), 5.89 (d, 1 H, H-1′, $J_{1',2'}$ = 3.6 Hz), 6.79 (d, 1 H, OH-2′), 6.83 (bs, 2 H, NH_2), 7.39 (s, 1 H, H-6), 11.47 (bs, 1 H, NH-3). Anal. ($C_{12}H_{15}N_3O_8S$) C, H, N.

[1-(β-D-Xylofuranosyl)uracil]-3′-spiro-5″-[4″-amino-1″,2″-oxathiole 2″,2″-Dioxide] (13b). According to the general procedure, **11b** was reacted with Bu_4NF for 24 h. The residue was chromatographed with chloroform/acetone (3:1) to give 0.11 g (62%) of **13b** as a white solid: mp 240–242 °C dec; IR (KBr) 3480 cm^{-1} (OH), 3320, 3300, 3220 (NH_2, NH), 1650 (C=C—N); ^{1}H NMR [(CD_3)$_2$SO, 300 MHz] δ 3.78 (dd, 1 H, H-5′a, $J_{5'a,5'b}$ = 11.5, $J_{4',5'a}$ = 4.4 Hz), 3.87 (dd, 1 H, H-5′b, $J_{4',5'b}$ = 6.2 Hz), 4.24 (d, 1 H, H-2′, $J_{1',2'}$ = 2.6 Hz), 4.60 (dd, 1 H, H-4′), 5.55 (s, 1 H,

H-3''), 5.73 (d, 1 H, H-5), 5.82 (d, 1 H, H-1'), 6.81 (bs, 2 H, NH_2), 7.51 (d, 1 H, H-6). Anal. ($C_{11}H_{13}N_3O_8S$) C, H, N.

[1-(β-D-Ribofuranosyl)thymine]-3'-spiro-5''-[4''-amino-1'',2''-oxathiole 2'',2''-Dioxide] (14a). Following the general procedure **12a** was reacted with Bu_4NF for 24 h. The residue was chromatographed with chloroform/methanol (10:1) to give 0.32 g (60%) of **14a** as a white solid: mp 170 °C dec; IR (KBr) 3400, 3300, 3200 cm^{-1} (NH_2, OH), 1660 (C=C—N); ^1H NMR [$(CD_3)_2SO$, 300 MHz] δ 1.80 (s, 3 H, CH_3-5), 3.54–3.72 (m, 2 H, H-5'), 4.16 (t, 1 H, H-4', $J_{4',5'}$ = 3.1 Hz), 4.52 (dd, 1 H, H-2', $J_{1',2'}$ = 8.5 Hz), 5.71 (s, 1 H, H-3''), 5.87 (d, 1 H, H-1'), 6.03 (t, 1 H, OH-5'), 6.17 (d, 1 H, OH-2'), 6.81 (bs, 2 H, NH_2), 7.77 (s, 1 H, H-6), 11.45 (bs, 1 H, NH-3); ^{13}C NMR [$(CD_3)_2SO$, 50 MHz] δ 12.29 (CH_3-5), 60.21 (C-5'), 72.63 (C-2'), 84.24, 84.37, 88.92 (C-4', C-3'', C-1'), 93.23 (C-3'), 110.17 (C-5), 135.71 (C-6), 151.05, 152.07 (C-2, C-4''), 163.51 (C-4). Anal. ($C_{12}H_{15}N_3O_8S$) C, H, N.

[1-[2'-O-(tert-Butyldimethylsilyl)-β-D-xylofuranosyl]-uracil]-3'-spiro-5''-[4''-amino-1'',2''-oxathiole 2'',2''-Dioxide] (15b). The protected nucleoside **11b** (0.13 g, 0.22 mmol) was stirred with methanolic 0.1 N HCl (15 mL) at room temperature for 30 min. The solution was neutralized with 1 N NaOH–MeOH, and the solvent was evaporated to dryness. The residue was purified by column chromatography using chloroform/acetone (3:1) to afford 0.09 g (86%) of **15b** as an amorphous solid: IR (KBr) 3550, 3450, 3350 cm^{-1} (OH, NH_2), 1645 (C=C—N); ^1H NMR [$(CD_3)_2CO$, 300 MHz] δ 3.80 (m, 2 H, H-5', $J_{5'a,5'b}$ = 12.3, $J_{4',5'a}$ = 6.5, $J_{4',5'b}$ = 3.7 Hz), 4.13 (dd, 1 H, OH-5'), 4.60 (d, 1 H, H-2, $J_{1',2'}$ = 4.2 Hz), 4.68 (dd, 1 H, H-4'), 5.68 (s, 1 H, H-3''), 5.81 (d, 1 H, H-5), 6.09 (d, 1 H, H-1'), 6.36 (bs, 2 H, NH_2), 7.72 (d, 1 H, H-6), 10.20 (bs, 1 H, NH-3). Anal. ($C_{17}H_{27}N_3O_8SSi$) C, H, N.

[1-[2'-O-(tert-Butyldimethylsilyl)-β-D-ribofuranosyl]-thymine]-3'-spiro-5''-[4''-amino-1'',2''-oxathiole 2'',2''-Dioxide] (16a). The protected nucleoside **12a** (0.16 g, 0.27 mmol) was stirred with methanolic 0.1 N HCl (10 mL) at room temperature for 2 h. The solution was neutralized with 1 N NaOH–MeOH and the solvent was evaporated to dryness. The residue was purified by column chromatography using chloroform/acetone (4:1) to give 0.11 g (90%) of **16a** as an amorphous solid: IR (KBr) 3400, 3350, 3200 cm^{-1} (OH, NH_2, NH); ^1H NMR [$(CD_3)_2CO$, 200 MHz] δ 1.86 (s, 3 H, CH_3-5), 3.79–4.03 (m, 2 H, H-5', $J_{5'a,5'b}$ = 12.8 Hz), 4.33 (dd, 1 H, H-4', $J_{4',5'a}$ = 2.5, $J_{4',5'b}$ = 1.3 Hz), 4.97 (d, 1 H, H-2, $J_{1',2'}$ = 8.1 Hz), 5.74 (s, 1 H, H-3''), 5.79 (bs, 1 H, OH-5'), 5.84 (d, 1 H, H-1'), 6.61 (bs, 2 H, NH_2), 7.86 (s, 1 H, H-6), 10.24 (bs, 1 H, NH-3); ^{13}C NMR [$(CD_3)_2CO$, 50 MHz] δ 12.36 (CH_3-5), 61.76 (C-5'), 74.92 (C-2'), 85.95, 89.70 (C-4', C-3''), 92.55 (C-1'), 94.62 (C-3'), 112.18 (C-5), 138.50 (C-6), 151.83, 152.12 (C-2, C-4''), 163.82 (C-4). Anal. ($C_{18}H_{29}N_3O_8SSi$) C, H, N.

[1-[5'-O-(tert-Butyldimethylsilyl)-β-D-ribofuranosyl]-thymine]-3'-spiro-5''-[4''-amino-1'',2''-oxathiole 2'',2''-dioxide] (17a). To a solution of **14a** (0.33 g, 0.91 mmol) in dry pyridine (6 mL) *tert*-butyldimethylsilyl chloride (0.15 g, 1 mmol) was added. The resulting mixture was stirred at room temperature for 24 h and then evaporated to dryness. The residue was purified by column chromatography using chloroform/methanol (20:1) to yield 0.37 g (83%) of **17a** as an amorphous solid: IR (KBr) 3410, 3330, 3200 cm^{-1} (OH, NH_2), 1650 (C=C—N); ^1H NMR [$(CD_3)_2CO$, 300 MHz] δ 1.89 (s, 3 H, CH_3-5), 4.07 (m, 2 H, H-5', $J_{4',5'}$ = 3.7 Hz), 4.31 (t, 1 H, H-4'), 4.79 (d, 1 H, H-2', $J_{1',2'}$ = 8.3 Hz), 5.26 (bs, 1 H, OH-2'), 5.72 (s, 1 H, H-3''), 5.98 (d, 1 H, H-1'), 6.44 (bs, 2 H, NH_2), 7.55 (s, 1 H, H-6), 10.12 (bs, 1 H, NH-3); ^{13}C NMR [$(CD_3)_2CO$, 50 MHz] δ 12.42 (CH_3-5), 63.02 (C-5'), 74.03 (C-2'), 84.95, 87.89 (C-4', C-3''), 91.31 (C-1'), 92.60 (C-3'), 111.64 (C-5), 136.85 (C-6), 151.87, 153.04 (C-2, C-4''), 164.02 (C-4). Anal. ($C_{18}H_{29}N_3O_8SSi$) C, H, N.

[1-[5'-O-(tert-Butyldimethylsilyl)-2'-deoxy-β-D-erythro-pentofuranosyl]thymine]-3'-spiro-5''-[4''-amino-1'',2''-oxathiole 2'',2''-Dioxide] (18a). To a solution of **17a** (0.29 g, 0.61 mmol) in toluene/acetonitrile (8 mL) was added *N,N'*-thiocarbonyldiimidazole (0.12 g, 0.67 mmol). The mixture was heated at 80 °C for 30 min, and the solvent was evaporated. The residue was dissolved in ethyl acetate (50 mL) and washed with (5%) HCl (25 mL), water, until the pH of the organic phase was neutral, and brine (50 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was suspended in dry acetonitrile (10 mL), α,α'-azobis(isobutyronitrile) (0.02 g, 0.12 mmol) and tributyltin hydride (0.26 mL, 0.92 mmol) were added under argon, and the mixture was heated at 80 °C for 3 h. After cooling, the solvent was evaporated. The residue was washed with hexane and purified by column chromatography with chloroform/methanol (30:1) to give 0.14 g (50%) of **18a** as an amorphous solid: IR (KBr) 3430, 3320, 3200 cm^{-1} (NH_2, NH), 1640 (C=C—N); ^1H NMR [$(CD_3)_2CO$, 300 MHz] δ 1.85 (s, 3 H, CH_3-5), 2.69 (m, 1 H, H-2'b, $J_{1',2'b}$ = 5.8, $J_{2'a,2'b}$ = 14.3 Hz), 2.96 (m, 1 H, H-2'a, $J_{1',2'a}$ = 9.0 Hz), 4.03 (m, 2 H, H-5'), 4.24 (dd, 1 H, H-4', $J_{4',5'a}$ = 3.5, $J_{4',5'b}$ = 5.3 Hz), 5.65 (s, 1 H, H-3''), 6.12 (dd, 1 H, H-1'), 6.50 (bs, 2 H, NH_2), 7.58 (s, 1 H, H-6), 10.21 (bs, 1 H, NH-3); ^{13}C NMR [$(CD_3)_2CO$, 50 MHz] δ 12.43 (CH_3-5), 40.82 (C-2'), 62.90 (C-5'), 62.90 (C-5'), 86.42, 86.99, 90.03 (C-4', C-3'', C-1'), 93.02 (C-3'), 111.14 (C-5), 138.03 (C-6), 151.38, 154.77 (C-2, C-4''), 164.07 (C-4). Anal. ($C_{18}H_{30}N_3O_7SSi$) C, H, N.

Antiretrovirus Assays. HIV-1 (HTLV-III_B) was obtained from persistently HIV-infected H9 cells as described previously.[46] Virus stocks were prepared from the supernatants of HIV-1 (III_B)-infected MT-4 cells.

MT-4 cells were infected with HIV-1 as previously described.[47] Briefly, 5×10^5 MT-4 cells/mL were infected with HIV-1 at 100 $CCID_{50}$ (50% cell culture infective dose) per mL cell suspension. Then, 100 μL of the infected cell suspension was transferred to microtiter plate wells and mixed with 100 μL of the appropriate dilutions of the test compounds. After 5 days, the number of viable cells was determined by trypan blue staining. The 50% effective concentration (EC_{50}) and 50% cytotoxic concentration (CC_{50}) were defined as the compound concentrations required to reduce by 50% the number of viable cells in the virus-infected and mock-infected cell cultures, respectively.

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