reflect the views or policies of the Department of Health and Human Services, nor does the mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Registry No. 1, 69-33-0; 2 free base, 136947-20-1; 2 HCl salt, 135362-83-3; 3 free base, 64526-34-7; 3 HCl salt, 136947-12-1; 4, 136947-13-2; 5, 7126-44-5; 6, 5991-01-5; 7, 135362-84-4; 8, 135362-85-5; 9, 135362-86-6; 10, 135362-87-7; 11, 135362-88-8; 12, 135362-89-9; 13, 4060-34-8; 14, 136947-14-3; 15, 136947-15-4; 16, 136947-16-5; 17, 136947-17-6; 18, 136947-18-7; 19, 136947-19-8; 5-bromotubercidin, 21193-80-6.

Synthesis and Anti-HIV Activity of 4′-Thio-2′,3′-dideoxynucleosides†

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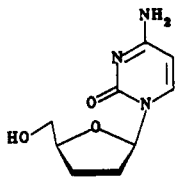
A series of 2′,3′-dideoxy-4′-thionucleoside analogues of purines and pyrimidines, including 4′-thioddI (17), 4′-thioddC (27), and 4′-thioAZT (34), were synthesized and evaluated for their inhibitory activity against human immunodeficiency virus (HIV). A stereospecific synthesis of the 2,3-dideoxy-4-thioribofuranosyl carbohydrate precursor 11 starting with L-glutamic acid is described. 2′,3′-Dideoxy-4′-thiocytidine (27) displayed significant, but modest activity in vitro against human immunodeficiency virus.

The 2′,3′-dideoxynucleosides are among the most potent and selective agents for the treatment of AIDS.[1,2] Within this series of compounds dideoxycytidine (1) and dideoxyinosine (2) have emerged as the most promising analogues and are currently undergoing clinical trials. The suggested mode of action of these analogues and 3′-azido-3′-deoxythymidine (AZT, 3), the present drug of choice, requires that they be metabolized sequentially via the monophosphate to the triphosphate, and the triphosphate then inhibits reverse transcriptase and/or terminates the growing DNA chain.[3]



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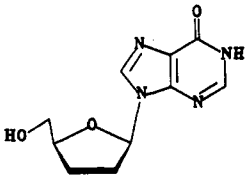

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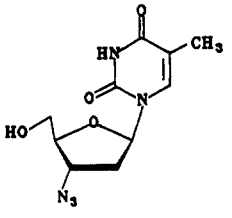
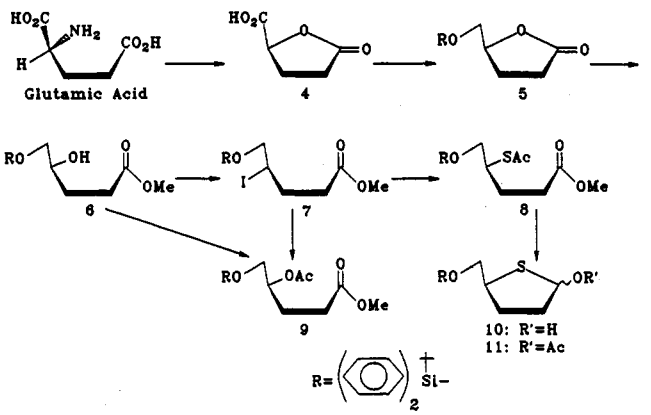


3

In hopes of finding better therapeutic agents for AIDS, a wide variety of sugar-modified nucleosides have been prepared. Thionucleosides in which oxygen of the sugar ring has been replaced by sulfur have shown interesting biological activities.[4-7] It has been demonstrated that 4′-thioadenosine, which is a potent inhibitor of *S*-adenosylhomocysteine hydrolase,[8] rapidly undergoes phosphorylation to its triphosphate. The resistance of several 4′-thioribonucleosides to bacterial cleavage[8] and of 4′-thioinosine to cleavage by purine nucleoside phosphorylase[9] has been reported. No 2′,3′-dideoxy-4′-thionucleosides have been reported, but it is logical to assume that such nucleosides would also be resistant to phosphorolytic cleavage. As part of an ongoing effort in our

Scheme I



† Presented at the Third International Conference on Antiviral Research, Brussels, Belgium, April 22–27, 1990.

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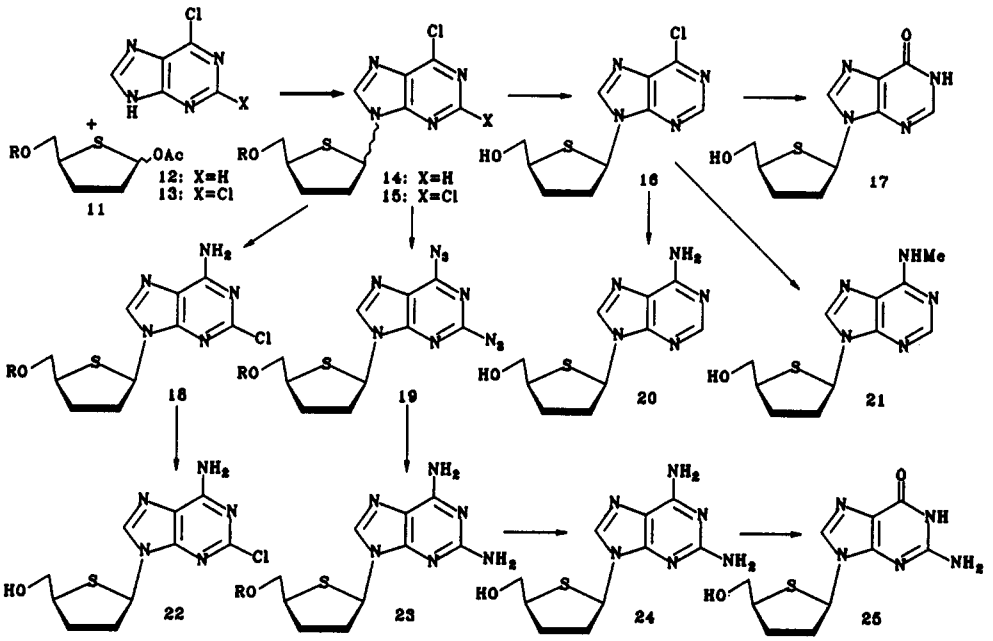
Scheme II

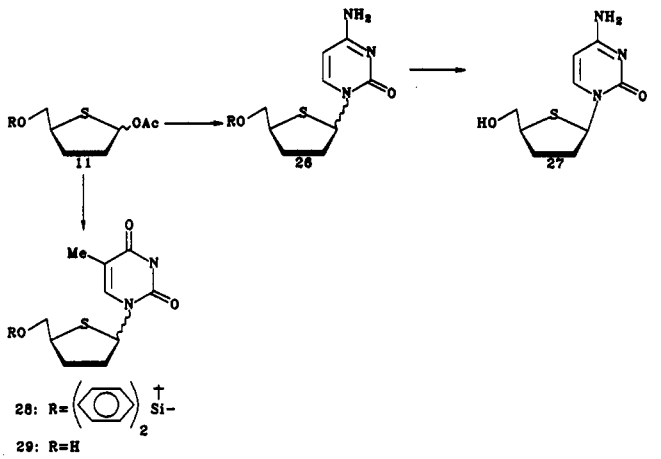


laboratory to develop new potential therapeutic agents against AIDS, we initiated a program to synthesize certain 2′,3′-dideoxy-4′-thioribonucleosides. Because of the lengthy sequence required to synthesize, by conventional methods, the 4-thio carbohydrate precursor needed for conversion into the corresponding 2,3-dideoxy nucleosides, we devised a new, short stereospecific route to the 2,3-dideoxy-4-thiosugar moiety from L-glutamic acid. 3′-Azido-3′-deoxy-4′-thiothymidine, the 4′-thio analogue of AZT, was synthesized from 4′-thiothymidine.[10]

Chemistry

The work of Okabe et al.[11] employing a 5-*tert*-butyldimethylsilyl dideoxyribose derivative in the synthesis of dideoxycytidine provided a useful precedent for our synthetic approach (Scheme I). The 5-*tert*-butyldiphenylsilyl-protected lactone **5** was synthesized in the three steps from L-glutamic acid using known methodology.[12,13] The lactone **5** was opened with sodium hydroxide and converted to the 4(*S*)-hydroxy ester **6**, which was transformed into the 4(*R*)-iodo ester **7** by treatment with triphenylphosphine, imidazole, and iodine.[14] Displacement of the iodo group of **7** by thioacetate in toluene occurred readily to give **8**, which was treated with 2 equiv of DIBAL-H to reductively deprotect the sulfur and reduce the methyl ester to an aldehyde, thereby giving rise to the thiolactol **10** via spontaneous cyclization. Sugar **11** was obtained by the acetylation of the thiolactol **10**, employing standard conditions.

Scheme III



The enantiospecificity of the iodination reaction was determined by comparison of the optical rotations and other physical data of **9** obtained by two different routes. Direct acetylation of **6** gave **9** $[\alpha]^{25}_D$ −20.1°). S_N2 displacement of the iodo group of **7** by acetate ion also afforded **9** ($[\alpha]^{25}_D$ −17.3°), essentially identical to the sample obtained by direct acetylation.

Sugar **11** was coupled to 6-chloropurine (**12**) by a modification of the method of Niedballa and Vorbruggen[15] with

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Table I. Comparative Potency and Selectivity of 2',3'-Dideoxy-4'-thionucleoside Analogues as Inhibitors of HIV Replication in MT-2 and CEM Cells[a]

compd	cell line	IC_{50} (μg/mL)	TC_{25} (μg/mL)	SI	TAI
20	MT-2	80	>100	1.3	>17
24	CEM	37	97	2.6	21
25	CEM	I	>100		
	MT-2	98	>200	1.6	11
27	CEM	1.0	>100	>100	>65
	MT-2	38	>100	>2.4	>23
AZT	MT-2	0.14	9.3	>160	>82
	CEM	<0.03	>10	>300	>93
DDC	MT-2	0.44	>9.8	>25	>52
	CEM	0.05	5.3	120	>63

[a] All data represents the means of several experiments. IC_{50} represents the minimum drug concentration (μg/mL) that inhibited CPE by 50%, calculated by using a regression analysis program for semilog curve fitting. I indicates compounds that did not inhibit CPE by 50%. TC_{25} represents the minimum drug concentration (μg/mL) that reduced cell viability by 25%. SI is calculated by dividing the TC_{25} by the ID_{50}. TAI (total viral) index is the area between the cytotoxicity and the antiviral activity curves.

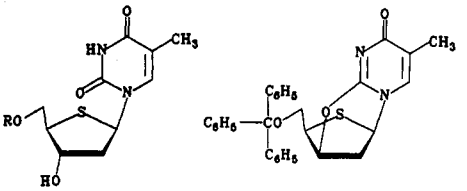
diethylaluminum chloride as the catalyst at 0–5 °C to give **14** as a 1:1 α/β anomeric mixture in 60% yield (Scheme II). Coupling of **11** and 2,6-dichloropurine (**13**) gave **15** in an approximate 2:3 α/β anomeric ratio in 60% yield. Cytosine and thymine were successfully coupled with **11** by a modification of the Vorbruggen and Bennua procedure[16] (Scheme III). Cytosine, **11**, HMDS, TMSCl, and potassium nonafluorobutanesulfonate afforded **26** in 60% as a 4:3 α/β mixture; thymine in similar fashion gave **28** in 90% yield in the same anomeric ratio. Proton assignments and anomeric ratio determinations were made by NMR including decoupling experiments.

Obtaining the target nucleosides from **14**, **15**, **26**, and **28** was difficult because of the anomeric separations required (Schemes II and III). Deprotection of **14** afforded the anomers of **16**, which were tediously separated by preparative TLC to provide the pure β-anomer. As expected, treatment of α,β-**16** with adenosine deaminase converted only the β-anomer to the dideoxyinosine analogue **17**, which was easily separated from unreacted α-**16**. Ammonia treatment of α,β-**16** provided α,β-**20**, which was separated by ion-exchange chromatography to give a modest yield of β-**20**. Nucleoside β-**21** was obtained by treatment of α,β-**16** with 40% aqueous methylamine followed by separation of the anomers on a Dekker column.[17] The lack of activity of these nucleosides against HIV precluded further efforts to improve the separations.

Since attempted separation of α,β-**27** by a variety of techniques was unsuccessful, the precursor mixture (α,β-**26**) was separated by preparative TLC. Deprotection of β-**26** and removal of tetrabutylammonium salts afforded **27** as an amorphous solid in 64% yield. In contrast, only a partial separation of α,β-**28** (3:1 β/α by HPLC) was achieved chromatographically. Unfortunately, crystallization of this partially pure β-anomer gave a crystalline material enhanced in the α-anomer. Again, the lack of biological activity of **29** made further efforts to obtain the pure β-nucleoside untenable.

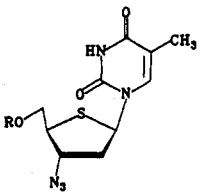
The separation of α,β-**15** was facile using preparative TLC. The pure β-**15** was treated with lithium azide to give, in quantitative yield, the diazido nucleoside **19**, which was reduced within lithium aluminum hydride to provide **23** in 80% yield, and deprotection and tetrabutylammonium salt removal gave **24** in 75% yield after recrystallization. Amination at C-6 of β-**15** by ethanolic ammonia gave **18** in good yield. Deprotection of **18** was carried out in the usual manner to obtain compound **22**. The guanosine analogue **25** was obtained by enzymatic deamination of **24** with adenosine deaminase followed by crystallization.

4'-Thiothymidine (**30**)[10] was converted to its 5'-*O*-trityl derivative **31**, which by reaction with DAST in dichloromethane afforded 5'-*O*-trityl-4'-thio-2,3'-anhydrothymidine (**32**). Treatment of **32** with sodium azide in a mixture of dimethylformamide–water under reflux for 8 h gave **33** which, after deprotection, provided 4'-thioAZT (**34**).



30: R=H
31: R=$(C_6H_5)_3C$-

32



33: R=$-C(C_6H_5)_3$
34: R=H

Biological Evaluation

The 2',3'-dideoxy-4'-thiopurine and 2',3'-dideoxy-4'-thiopyrimidine nucleoside analogues were evaluated for biological activity against the human immunodeficiency virus (HIV-1) in vitro. MT-2 cells,[18] a cell line that naturally expresses CD4 receptors and is therefore highly susceptible to HIV infections, and CEM cells, clone SS (CEM-SS),[19] were used as target cell lines. HTLV-IIIB strain of HIV-1 used for studies described herein was obtained from Dr. R. Gallo's laboratory, NIH, Bethesda, MD. Viral stocks were prepared by propagating the virus in H_9 cells, and all viral stocks were stored at temperatures <80 °C. The 50% tissue culture infective dose ($TCID_{50}$) per milliliter of each cell-free virus pool (stock) was determined by end-point titration using MT-2 cells. End-point titers of the virus stocks were calculated using the method of Reed and Muench.[20] MT-2 cells were infected at a multiplicity of infection of 0.03 (MOI = 0.03); at this MOI, 80–90% of the target cells are killed due to the viral cytopathogenic effect (CPE) within 7 days. Test compounds were added to preinfected cells in half-log concentrations ranging from 100 μg/mL to 0.32 μg/mL. All tests were conducted in triplicate at each concentration using 96-well microtiter plates, and drug cytotoxicity was measured in duplicate on uninfected cultures at parallel concentrations. Cell controls (uninfected, untreated cells) and virus controls (infected, untreated cells) were plated in replicates

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of six wells each. Test plates were incubated at 37 °C in an atmosphere of 5% CO_2 and moisture. At day 7 postinfection, 450 μg/mL of MTT, a tetrazolium salt used for measuring cell viabilities,[21] was added to each well (20 μL/well) and allowed to incubate for 4 h (this was calculated to be the optimum time for linear release of formazan produced by the viable cells). The cells were solubilized with 10% SDS and 0.1 N HCl to release formazan, and optical density (OD) values were read on a Vmax plate reader at a wavelength of 570 nm.

The IC_{50} and TC_{25} values of compounds active against HIV are listed in Table I. The anti-HIV activity of each compound is expressed as a selectivity index (SI) and total viral index (TAI). In these test systems, 2',3'-dideoxy-4'-thiocytidine (**27**) showed significant activity. Larger quantities of **27** are being prepared for further studies. Three of the purine nucleosides (**20**, **24**, and **25**) showed slight activity, whereas the other target compounds (**16**, **17**, **21**, and **30**) were inactive.

Experimental Section

All evaporations were carried out in vacuo with a rotary evaporator or by short-path distillation into a dry ice–acetone-cooled receiver under high vacuum. Analytical samples were normally dried in vacuo over P_2O_5 at room temperature for 16 h. Analtech precoated (250 μm) silica gel G(F) plates were used for TLC analyses; the spots were detected by irradiation with a mineral light and/or by charring after spraying with saturated $(NH_4)_2SO_4$. All analytical samples were TLC homogeneous. Melting points were determined with a Kofler-Heizbank apparatus unless otherwise specified. Purifications by flash chromatography were carried out on Merck silica gel 60 (230–400 mesh) using the slurry method of column packing. The UV absorption spectra were determined in 0.1 N HCl (pH 1), pH 7 buffer, and 0.1 N NaOH (pH 13) with a Cary 17 spectrophotometer. The maxima are reported in nanometers ($\epsilon \times 10^{-3}$ M^{-1} cm^{-1}). The NMR spectra in Me_2SO-d_6 or $CDCl_3$ with tetramethylsilane as an internal reference were determined with a Nicolet NT 300 NB spectrometer operating at 300.635 MHz. Chemical shifts (δ) quoted in the case of multiplets were measured from the approximate center. Where necessary, the chemical shift and coupling constant values for the non-first-order parts of the spectra were obtained from simulated spectra by employing the General Electric/Nicolet ITRACAL program for iterative analysis. The mass spectral data were obtained with a Varian-MAT 311A mass spectrometer in the fast atom bombardment mode. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

5-[(*tert*-Butyldiphenylsilyl)oxy]-4(*S*)-hydroxypentanoic Acid, Methyl Ester (6). To lactone **5** (5 g, 14.1 mmol) dissolved in 250 mL of ethanol was added a solution of NaOH (564 mg, 14.1 mmol) in 14.5 mL of water. The reaction was stirred 1 h, and then the solvent was removed azeotropically with toluene. The residue was redissolved in 50 mL of dimethyl sulfoxide and 10 mL of toluene and treated with dimethyl sulfate (1.6 mL, 17 mmol). After stirring 2 h at 25 °C, the reaction was poured into 200 mL of ice–water and extracted with 2 × 75 of ethyl ether and 1 × 50 mL of toluene. The organic phase was washed with 4 × 100 mL of water and dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was filtered through a 40-g silica pad with 3:1 hexane/ethyl acetate. Solvent removal afforded 5.30 g (97%) of a viscous oil: FAB MS 329 (M – *tert*-butyl)$^+$; ^{1}H NMR (CCl_4) δ 7.8–7.2 (m, 10 H, ArH), 3.7 (m, 1 H, H-4), 3.65 (s, 3 H, OCH_3), 3.6 (m, 1 H, OH), 3.4 (m, 2 H, CH_2), 2.4 (m, 2 H, CH_2), 1.8 (m, 2 H, CH_2), 1.1 (s, 9 H, *tert*-butyl). Anal. ($C_{22}H_{30}O_4Si \cdot 0.125H_2O$) C, H.

5-[(*tert*-Butyldiphenylsilyl)oxy]-4(*R*)-iodopentanoic Acid, Methyl Ester (7). To a solution of **6** (4.33 g, 11.2 mmol) in 250 mL of toluene were added triphenylphosphine (5.9 g, 22.4 mmol), imidazole (2.3 g, 33.6 mmol), and iodine (4.26 g, 16.8 mmol) under a nitrogen atmosphere. The reaction mixture was lowered into a preheated heating mantle and refluxed for 1 h. The reaction mixture was quenched by pouring into 200 mL of saturated $NaHCO_3$ solution. Excess triphenylphosphine was destroyed by the addition of iodine until an iodine coloration persisted in the organic phase. The organic phase was then washed with a 5% sodium thiosulfate solution (2 × 100 mL) and 2 × 200 mL water. The product was purified by flash chromatography with 6:1 hexane/ethyl acetate: yield 4.75 g (85%) of a viscous oil; $[\alpha]^{25}_D$ +6.7° (*c* = 1, $CHCl_3$); FAB MS 497 (M + H)$^+$, 439 (M – *tert*-butyl)$^+$; ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 4 H, ArH), 7.4 (m, 6 H, ArH), 4.15 (m, 1 H, H-4), 3.85 (m, 2 H, CH_2), 3.7 (s, 3 H, OCH_3), 2.5 (m, 2 H, CH_2), 2.25 (m, 1 H, H-2), 2.1 (m, 1 H, H-2), 1.1 (s, 9 H, *tert*-butyl). Anal. ($C_{22}H_{29}IO_3Si$) C, H.

4(*S*)-(Acetylthio)-5-[(*tert*-butyldiphenylsilyl)oxy]pentanoic Acid, Methyl Ester (8). A 1 M solution of tetrabutylammonium hydroxide in methanol (11 mL, 11 mmol) with a washing of 1 mL of methanol was added to thioacetic acid (1 mL, 13.2 mmol) in 20 mL of toluene under a nitrogen atmosphere. The methanol was removed azeotropically with toluene, and the residual salt was redissolved in 30 mL of toluene. The salt solution with a washing of 20 mL of toluene was added to a solution of **7** (4.75 g, 9.6 mmol) in 50 mL of toluene, and the mixture was stirred under nitrogen for 18 h. After removal of solvent and precipitated salts, the crude product was purified by flash chromatography with 6:1 hexane/ethyl acetate: yield 3.47 g (81%) of a viscous oil; $[\alpha]^{25}_D$ −16.0° (*c* = 0.7 $CDCl_3$); FAB MS 445 (M + H)$^+$, 387 (M – *tert*-butyl)$^+$; ^{1}H NMR ($CDCl_3$) δ 7.65 (m, 4 H, ArH), 7.4 (m, 6 H, ArH), 3.8 (m, 1 H, H-4), 3.7 (s, 3 H, OCH_3), 3.7 (m, 2 H, CH_2), 2.35 (m, 2 H, CH_2), 2.3 (s, 3 H, acetyl CH_3), 2.2 (m, 1 H, H-2), 1.9 (m, 1 H, H-2), 1.05 (s, 9 H, *tert*-butyl). Anal. ($C_{24}H_{32}O_4SSi$) C, H.

4(*S*)-Acetoxy-5-[(*tert*-butyldiphenylsilyl)oxy]pentanoic Acid, Methyl Ester (9). (a) A mixture of **6** (0.15 g, 0.39 mmol), pyridine (0.1 mL, 1.3 mmol), acetic anhydride (74 μL, 0.78 mmol), and a catalytic amount of DMAP was stirred in 3 mL of dichloromethane at 25 °C overnight. The mixture was washed with dilute $NaHCO_3$ solution, and the dichloromethane solution was dried ($MgSO_4$). The solvent was removed in vacuo, and the crude product was purified by preparative TLC (6:1 hexane/ethyl acetate) to give 140 mg (84%) of **9**: $[\alpha]^{25}_D$ −20.1° (*c* = 1.2, $CHCl_3$).

(b) Following the procedure for **8**, acetic acid (34 μL, 0.6 mmol), 1 M tetrabutylammonium hydroxide in methanol (0.4 mL, 0.4 mmol), and the iodo compound **7** (0.1 g, 0.2 mmol), after preparative TLC (6:1 hexane/ethyl acetate), gave 65 mg (80%) of **9**: $[\alpha]^{25}_D$ −17.3° (*c* = 0.7, $CHCl_3$); FAB MS 429 (M + H)$^+$; ^{1}H NMR ($CDCl_3$) δ 7.65 (m, 4 H, ArH), 7.4 (m, 6 H, ArH), 5.0 (m, 1 H, H-4), 3.68 (m, 2 H, CH_2), 3.66 (s, 3 H, OCH_3), 2.35 (t, 2 H, CH_2), 2.05 (s, 3 H, acetyl CH_3), 1.94 (m, 2 H, CH_2), 1.05 (s, 9 H, *tert*-butyl). Anal. ($C_{24}H_{32}O_5Si$) C, H.

1-*O*-Acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-4-thioribofuranose (11). A solution of **8** (1 g, 2.25 mmol) in 14 mL of dry hexane and 2 mL of toluene was cooled to −78 °C under nitrogen. A 1.5 M toluene solution of DIBAL-H (3.03 mL, 4.5 mmol) was added over a 2-min period with stirring continued for an additional 30 min. The reaction was quenched with 1.2 mL of methanol and allowed to warm to 25 °C. Then 2.5 mL of saturated $NaHCO_3$ solution was added followed by 15 mL of ethyl acetate, and the mixture was dried with $MgSO_4$. The solids were removed by filtration and washed with ethyl acetate. After removal of solvent in vacuo, the residue **10** was redissolved in 20 mL of dichloromethane and treated with DMAP (10 mg), pyridine (0.8 mL, 10 mmol), and acetic anhydride (0.47 mL, 5 mmol) with stirring under nitrogen overnight. The reaction mixture was shaken with 50 mL of water and then 50 mL of 1% $NaHCO_3$. After drying ($MgSO_4$), the solvent was removed in vacuo, and the residue was purified by flash chromatography with 8:1 hexane/ethyl acetate: yield 0.78 g (83%) of a viscous oil: FAB MS 357 (M – *tert*-butyl)$^+$; ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 4 H, ArH), 7.4 (m, 6 H, ArH), 6.0 (m, 1 H, anomeric H's), 3.75 (m, 1 H, H-5), 3.5 (m, 1 H, H-4), 3.5 (m, 1 H, H-5), 2.15 (m, 2 H, CH_2), 2.0 (2 s, 3 H, anomeric acetyl's), 1.9 (m, 2 H, CH_2), 1.05 (s, 9 H, *tert*-butyl). Anal. ($C_{23}H_{30}O_3SSi$) C, H.

9-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-4-thio-α,β-D-ribofuranosyl]-6-chloropurine (14). A mixture of **11** (0.43 g, 1.04 mmol) and 6-chloropurine (**12**) (0.24 g, 1.56 mmol) in 17

(21) Tada, H.; Shiho, O.; Kuroshima, K.; Koyama, M.; Tsukamoto, K. An improved colorimetric assay for interleukin 2. *J. Immunol. Methods* **1986**, *93*, 157–165.

mL of acetonitrile was cooled to 0 °C, and a 1.8 M toluene solution of diethylaluminum chloride (0.59 mL, 1.06 mmol) was added over 1 min. Stirring was continued at 0 °C for 5 min and at 25 °C for 10 min. The reaction mixture was quenched by pouring into a mixture of 20 mL of dichloromethane and 10 mL of saturated $NaHCO_3$. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was flash chromatographed with 9:1 hexane/ethyl acetate followed by 4:1 hexane/ethyl acetate. Solvent removal gave a 1:1 α/β anomeric mixture: yield 0.315 g (59%); FAB MS 509 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 8.7 (s, 1 H, H-2), 8.45 (s, 1 H, H-8), 7.7 (m, 4 H, ArH), 7.4 (m, 6 H, ArH), 6.27 (m, 1 H, 1'-H), 3.95 (m, 1 H, 5'-H), 3.85 (m, 2 H, 4'-H, 5'-H), 2.45 (m, 2 H, 2'-H's), 2.25 (m, 1 H, 3'-H), 1.85 (m, 1 H, 3'-H), 1.1 (s, 9 H, *tert*-butyl). Anal. ($C_{26}H_{28}N_4ClOSSi$) C, H, N.

9-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-4-thio-α,β-D-ribofuranosyl]-2,6-dichloropurine (15). Following the procedure for **14**, compound **11** (0.25 g, 0.6 mmol), 2,6-dichloropurine (**13**, 0.142 g, 0.75 mmol), and 1.8 M diethylaluminum chloride in toluene (0.345 mL, 0.62 mmol) gave 0.196 g (60%) of **19** as a 2:3 α/β anomeric mixture. The β-anomer was separated by prep TLC with 15:1 toluene/ethyl acetate: yield 105 mg; FAB MS 543 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 8.47 (s, 1 H, H-8), 7.7 (m, 4 H, ArH), 7.45 (m, 6 H, ArH), 6.22 (m, 1 H, 1'-H), 3.97 (m, 1 H, 5'-H), 3.85 (m, 2 H, 4'-H, 5'-H), 2.45 (m, 2 H, 2'-H's), 2.25 (m, 1 H, 3'-H), 1.82 (m, 1 H, 3'-H), 1.1 (s, 9 H, *tert*-butyl). Anal. ($C_{26}H_{28}Cl_2N_4OSSi$) C, H, N.

9-(2,3-Dideoxy-4-thio-α,β-D-ribofuranosyl)-6-chloropurine (16). A solution of **14** (0.315 g, 0.62 mmol), acetic acid (36 μL, 0.63 mmol), and 1 M tetrabutylammonium fluoride in methanol (0.65 mL, 0.65 mmol) in 3 mL of tetrahydrofuran was stirred for 10 min under nitrogen. The solvent was removed in vacuo, and the residue was flash chromatographed with dichloromethane followed by 19:1 chloroform/methanol to give 0.164 g (98%) of the anomers. The anomers were separated by centrifugal chromatography with 19:1 chloroform/methanol: yield 10 mg of β anomer; mp 125–128 °C; $[\alpha]^{25}_D$ +2.5° (c = 0.1, CH_3OH); FAB MS 271 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 9.0 (s, 1 H, H-2), 8.8 (s, 1 H, H-8), 6.3 (m, 1 H, 5'-OH), 3.8 (m, 1 H, 5'-H), 3.65 (m, 2 H, 4'-H, 5'-H), 2.6 (m, 1 H, 2'-H), 2.45 (m, 1 H, 2'-H), 2.2 (m, 1 H, 3'-H), 2.0 (m, 1 H, 3'-H). Anal. ($C_{10}H_{11}ClN_4OS$) C, H, N.

2',3'-Dideoxy-4'-thioinosine (17). To a solution of the α-/β-anomers of **16** (82 mg, 0.3 mmol) in 20 mL of a 0.75 M TEAB buffer was added 5 μL of adenosine deaminase. The reaction was stirred 34 h followed by lyophilization. The residue was purified by preparative TLC with 6:1 chloroform/methanol containing 1% acetic acid. The crude product was recrytallized from methanol/carbon tetrachloride to give 30.5 mg (79%) of **17**: mp 195–197 °C; $[\alpha]^{25}_D$ −13.9° (c = 0.1, H_2O); FAB MS 253 $(M + H)^+$; ^1H NMR (D_2O) δ 8.5 (s, 1 H, H-2), 8.2 (s, 1 H, H-8), 6.2 (m, 1 H, 1'-H), 3.95 (m, 1 H, 5'-H), 3.8 (m, 2 H, 4'-H, 5'-H), 2.5 (m, 2 H, 2'-H's), 2.3 (m, 1 H, 3'-H), 1.9 (m, 1 H, 3'-H). Anal. ($C_{10}H_{13}O_2S$·0.75CH_3OH·0.125CCl_4) C, H.

5'-*O*-(*tert*-Butyldiphenylsilyl)-2-chloro-2',3'-dideoxy-4'-thioadenosine (18). A mixture of β-**15** (150 mg) and saturated ethanolic ammonia (50 mL) was heated at 50 °C in a glass-lined stainless-steel pressure vessel for 48 h. The reaction mixture was evaporated to dryness to afford a syrup which was purified on two silica gel thick plates (Analtech, GF, 1000 μm) that were developed in 99:1 $CHCl_3$/MeOH. The product was eluted with $CHCl_3$, and the solution was evaporated. The residue was crystallized from EtOAc/cyclohexane to give pure **18** (125 mg, 86%): mp 123–125 °C; FAB MS 524 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 8.14 (s, 1 H, H-8), 7.72 (m, 4 H, ArH), 7.42 (m, 6 H, ArH), 6.02 (br s, 2 H, NH_2), 6.16 (m, 1'-H), 3.93 (m, 1 H, 5'-H), 3.84 (m, 1 H, 5'-H), 3.73 (m, 1 H, 4'-H), 2.36 (m, 2 H, 2'-H), 2.18 (m, 1 H, 3'-H), 1.90 (m, 3'-H), 1.1 (s, 9 H, *tert*-butyl). Anal. ($C_{26}H_{30}ClN_5OSSi$) C, H, N.

2',3'-Dideoxy-4'-thioadenosine (20). A mixture of the α-/β-anomers **16** (80 mg, 0.3 mmol) and 50 mL of saturated ammonia/methanol was heated at 80 °C for 3 days. The solvent was removed in vacuo, and the residue was purified by preparative TLC with 9:1 chloroform/methanol to give 55 mg (73%) of the anomers. The anomeric mixture was separated on a Dowex-50W-X8 glutamate (200–400) column (elution with water) to give, after recrystallization from ethanol/ethyl acetate, 7.5 mg of β-anomer: mp 179–182 °C; ^1H NMR (DMSO-d_6) δ 8.4 (s, 1 H, H-2), 8.15 (s, 1 H, H-8), 7.25 (s, 2 H, NH_2), 6.15 (m, 1 H, 1'-H), 5.15 (br s, 1 H, 5'-OH), 3.75 (m, 1 H, 5'-H), 3.6 (m, 2 H, 4'-H, 5'-H), 2.4 (m, 2 H, 2'-H's), 2.15 (m, 1 H, 3'-H), 2.0 (m, 1 H, 3'-H). Anal. ($C_{10}H_{13}N_5OS$·0.75H_2O·0.25EtOAc) C, H, N.

2',3'-Dideoxy-N^6-methyl-4'-thioadenosine (21). The anomeric mixture of **16** (0.132 g, 0.49 mmol) in a steel bomb was stirred with 20 mL of 40% methylamine in water at 80 °C overnight. After solvent removal in vacuo, the residue was purified by preparative TLC with 9:1 chloroform/methanol to give 100 mg (77%) of the anomeric mixture. The anomers were partially separated by a Dowex (OH^-) column (four passes) with 10% aqueous methanol to give 37 mg of impure β-anomer which was recrystallized from hexane/ethyl acetate to afford 22.5 mg of pure β-anomer by HPLC: mp 131–134 °C; FAB MS 266 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 8.4 (s, 1 H, H-2), 8.2 (s, 1 H, H-8), 7.7 (br s, 1 H, NH), 6.2 (m, 1 H, 1'-H), 5.15 (m, 1 H, 5'-OH), 3.75 (m, 1 H, 5'-H), 3.6 (m, 2 H, 4'-H, 5'-H), 2.95 (s, 3 H, CH_3), 2.4 (m, 2 H, 2'-H's), 2.15 (m, 1 H, 3'-H), 2.0 (m, 1 H, 3'-H). Anal. ($C_{11}H_{15}N_5OS$·0.33H_2O) C, H, N.

2-Chloro-2',3'-dideoxy-4'-thioadenosine (22). To a solution of **18** (100 mg, 0.19 mmol) in 5 mL of THF was added CH_3COOH (14 μL, 0.24 mmol) and a 1 M solution of tetrabutylammonium fluoride in MeOH (0.4 mL, 0.4 mmol) followed by stirring for 1 h. One drop of pyridine was added, and then solvent was evaporated in vacuo. The residue was purified by preparative TLC using 90:10 $CHCl_3$/MeOH as eluant to afford crude **22**, which was crystallized by EtOH to give a pure sample (38 mg, 70%): mp 125–127 °C; FAB MS 286 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 8.45 (s, 1 H, H-2), 7.80 (br s, 2 H, NH_2), 6.10 (m, 1 H, 1'-H), 5.12 (m, 1 H, 5'-OH), 3.75 (m, 1 H, 4'-H), 3.61 (m, 2 H, 5'-H), 2.40 (m, 2 H, 2'-H), 2.15 (m, 1 H, 3'-H), 2.0 (m, 1 H, 3'-H). Anal. ($C_{10}H_{12}ClN_5OS$) C, H, N.

2-Amino-5'-*O*-(*tert*-butyldiphenylsilyl)-2',3'-dideoxy-4'-thioadenosine (23). A solution of β-**15** (117.5 mg, 0.22 mmol) and lithium azide (54 mg, 1.1 mmol) in 10 mL of 95% ethanol was refluxed for 2 h. The solvent was removed in vacuo, and the residue was partitioned between dichloromethane and water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to a residue which was redissolved in 15 mL of ethyl ether. The ethereal solution was then treated with LAH (0.1 g, 2.6 mmol) for 0.5 h at 25 °C. The excess LAH was decomposed by the addition of 20% water/tetrahydrofuran followed by the addition of Celite and filtration. The residue was washed with ethyl ether, and the filtrates were concentrated to give the crude diamino compound. The product was purified by preparative TLC with 95:5 chloroform/methanol to afford 90 mg (80%) of **23**: FAB MS 505 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 7.83 (s, 1 H, H-8), 7.68 (m, 4 H, ArH), 7.42 (m, 6 H, ArH), 6.02 (m, 1 H, 1'-H), 5.4 (br s, 2 H, NH_2), 4.68 (br s, 2 H, NH_2), 3.93 (m, 1 H, 5'-H), 3.83 (m, 1 H, 5'-H), 3.72 (m, 1 H, 4'-H), 2.35 (m, 2 H, 2'-H's), 2.17 (m, 1 H, 3'-H), 1.88 (m, 1 H, 3'-H), 1.8 (br s, CH_3OH), 1.43 (s, CH_3OH), 1.1 (s, 9 H, *tert*-butyl). Anal. ($C_{26}H_{32}N_6OSSi$·CH_3OH) C, H, N.

2-Amino-2',3'-dideoxy-4'-thioadenosine (24). A mixture of **23** (50 mg, 0.1 mmol), acetic acid (7 μL, 0.12 mmol), and 0.17 mL of 1 M tetrabutylammonium fluoride in THF (0.17 mmol) was stirred in 10 mL of tetrahydrofuran overnight. Water (2 mL) and 15 mL of ether were added followed by stirring for 5 min. The organic phase was extracted with 2 mL water, and then the combined aqueous solution was washed with 15 mL of ether. The aqueous extract was concentrated in vacuo to 1 mL and then applied to a 4 mL Dowex 100–200 (OH^-) column (four passes) to remove tetrabutylammonium salts by eluting with water followed by 20% aqueous methanol. The solvent was removed in vacuo, and the product was recrystallized from ethanol/ethyl acetate to afford 19.5 mg (54%) of **10**: mp 187–90 °C dec; FAB MS 267 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 8.0 (s, 1 H, H-8), 6.68 (br s, 2 H, NH_2), 5.95 (m, 1 H, 1'-H), 5.71 (br s, 2 H, NH_2), 5.22 (m, 1 H, 5'-OH), 3.73 (m, 1 H, 5'-H), 3.57 (m, 2 H, 4'-H, 5'-H), 2.4 (m, 1 H, 2'-H), 2.32 (m, 1 H, 2'-H), 2.12 (m, 1 H, 3'-H), 1.98 (m, 1 H, 3'-H). Anal. ($C_{10}H_{14}N_6OS$·0.25H_2O·0.125EtOAc) C, H. N.

4'-Thio-2',3'-dideoxyguanosine (25). To a solution of **24** (50 mg, 0.18 mmol) in 20 mL of a 0.75 M TEAB buffer was added 6 μL of adenosine deaminase. The reaction was stirred for 12 days followed by lyophilization. The residue was purified by preparative TLC with 4:1 $CHCl_3$–MeOH. The crude product was

recrystallized from hot EtOH to give **25** (40 mg, 80%): mp 180–183 °C, FAB MS 268 (M + H)$^+$; ^{1}H NMR (DMSO-d_6) δ 10.8 (br s, 1 H, NH), 8.0 (s, 1 H, H-8), 6.6 (s, 2 H, NH_2), 5.90 (m, 1 H, 1′-H), 5.12 (br s, 1 H, 5′-OH), 3.72 (m, 1 H, 4′-H), 3.55 (m, 2 H, 5′-H), 2.35 (m, 2 H, 2′-H), 2.15 (m, 1 H, 3′-H), 1.95 (m, 1 H, 3′-H). Anal. ($C_{10}H_{13}N_5O_2S\cdot1.0H_2O\cdot0.25EtOH$) C, H, N.

1-[5-*O*-(*tert*-Butyldiphenyl)-2,3-dideoxy-4-thio-α,β-D-ribofuranosyl]cytosine (26). A mixture of **11** (0.26 g, 0.63 mmol), cytosine (0.105 g, 0.95 mmol), and potassium nonafluorobutanesulfonate (0.77 g, 2.3 mmol) was suspended in 12 mL of dry acetonitrile under nitrogen. HMDS (0.135 mL, 0.63 mmol) and TMSCl (0.37 mL, 2.9 mmol) were added sequentially via syringe, and the reaction was stirred at 25 °C overnight. The reaction was poured into a mixture of 20 mL of dichloromethane and 15 mL of saturated $NaHCO_3$ and shaken. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The anomers were separated by preparative TLC with $CHCl_3$/MeOH (93:7) in an ammonia atmosphere. Yield: β-anomer, 78 mg; α-anomer, 117 mg; total yield of 195 mg (66.5%); FAB MS 466 (M + H)$^+$; ^{1}H NMR ($CDCl_3$) of α/β mixture, δ 8.12 (d, 1 H, 6-H), 7.7 (m, 4 H, ArH), 7.4 (m, 6 H, ArH), 6.32 (m, 1 H, 1′-H), 5.9–5.3 (hump, 1 H, NH_2), 5.75 (d, 1 H, 5-H), 5.45 (d, 1 H, 5-H), 3.75 (m, 3 H, 4′-$H_{\alpha,\beta}$, 5′-$H_{\alpha,\beta}$'s), 2.0 (m, 4 H, 2′-$H_{\alpha,\beta}$'s, 3′-$H_{\alpha,\beta}$'s); ^{13}C NMR ($CDCl_3$) C-2 (165.56, 165.51), C-4 (156.3, 156.2), C-6 (142.1, 141.7), phenyl C_{ortho} (135.6, 135.5), phenyl C-1 (133.2, 133.1), phenyl C_{para} (129.85, 129.82), phenyl C_{meta} (127.8, 127.7), C-5 (95.1, 94.6), C-5′ (66.8, 66.4), C-4′ (65.2, 64.8), C-3′ (30.1, 29.9), *tert*-butyl CH_3 (26.87, 26.81), *tert*-butyl C (19.26, 19.22). Anal. ($C_{25}H_{31}N_3O_2SSi\cdot H_2O$) C, H, N.

2′,3′-Dideoxy-4′-thiocytidine (27). The β-anomer of **26** (78 mg, 0.17 mmol) was dissolved in a mixture of 4 mL of tetrahydrofuran and 0.2 mL (0.2 mmol) of 1 M tetrabutylammonium fluoride in THF and acetic acid (11.5 μL, 0.2 mmol) with subsequent stirring at 25 °C overnight. The reaction was diluted with 10 mL of water and 10 mL of ethyl ether followed by stirring for 5 min. The aqueous phase was washed with 20 mL of ethyl ether and concentrated in vacuo to 1 mL. The residue was eluted from a 5 mL Dowex (OH^-) column (four times) with water to remove the tetrabutylammonium salts. The product (33 mg, 87%) precipitated as an amorphous solid from ethyl acetate and ethyl ether to afford 26.5 mg (69%) of **8**: mp 83–85 °C; FAB MS 228 (M + H)$^+$; ^{1}H NMR (DMSO-d_6) δ 8.0 (d, 1 H, H-6), 7.1 (br d, 2 H, NH_2), 6.15 (m, 1 H, 1′-H), 5.74 (d, 1 H, H-5), 5.1 (br s, 1 H, 5′-OH), 4.2 (q, EtOAc), 3.64 (m, 1 H, 5′-H), 3.5 (m, 2 H, 4′-H, 5′-H), 2.18 (m, 1 H, 2′-H), 2.0 (m, 2 H, 2′-H, 3′-H), 1.99 (s, EtOAc), 1.82 (m, 1 H, 3′-H), 1.18 (t, EtOAc). Anal. ($C_9H_{13}N_3O_2S\cdot0.66H_2O\cdot0.125EtOAc$) C, H, N.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-4-thio-α,β-D-ribofuranosyl]thymine (28). Using the procedure for **26**, compound **11** (0.35 g, 0.83 mmol), thymine (0.13 g, 1.05 mmol), potassium nonafluorobutanesulfonate (0.875 g, 2.54 mmol), HMDS (0.175 mL, 0.83 mmol), and TMSCl (0.4 mL, 3.2 mmol), following purification by preparative TLC (8:1 dichloromethane/acetonitrile), afforded 371 mg (92.5%) of **28** as a 4:3 α/β anomeric mixture: FAB MS 481 (M + H)$^+$; ^{1}H NMR ($CDCl_3$) δ 9.65 (s, 1 H, NH), 7.7 (m, 4 H, ArH), 7.4 (m, 6 H, ArH), 6.3 (m, 1 H, 1′-$H_{\alpha,\beta}$), 3.88 (m, 1 H, 4′-H_α), 3.82 (d, 1 H, 5′-H_β), 3.66 (d + m, 2, 4′-H_β, 5′-H_α), 2.4–1.85 (m, 4 H, 2′-$H_{\alpha,\beta}$'s, 3′-$H_{\alpha,\beta}$'s), 1.95 (s, 3 H, 5_β-CH_3), 1.77 (s, 3 H, 5_β-CH_3), 1.11 (s, 9 H, β-*tert*-butyl), 1.07 (s, 9 H, α-*tert*-butyl); ^{13}C NMR ($CDCl_3$) C-4 (163.8), C-2 (150.9, 150.8), C-6 (136.4, 136.3), phenyl-C (135.54, 135.48), phenyl-C (133.19, 133.14), phenyl-C (129.9, 129.8), phenyl-C (127.8, 127.7), C-5 (110.9, 110.7), C-5′ (66.93), C-4′ (63.8, 63.5), C-1′ (51.97, 51.88), C-2′ (36.8, 36.5), C-3′ (30.9, 30.6), *tert*-butyl CH_3 (26.86, 26.8), *tert*-butyl C (19.3, 19.24), CH_3 (12.7, 12.6). Anal. ($C_{26}H_{32}N_2O_3SSi\cdot0.33H_2O$) C, H, N.

1-(2,3-Dideoxy-4-thio-α,β-D-ribofuranosyl)thymine (29). To a solution of **28** (0.136 g, 0.28 mmol) in 3 mL of tetrahydrofuran were added acetic acid (17 μL, 0.3 mmol) and 0.3 mL (0.3 mmol) of 1 M tetrabutylammonium fluoride in methanol, followed by stirring for 1 h. One drop of triethylamine was added, and then the solvent was removed in vacuo. The residue was flash chromatographed with dichloromethane followed by 95:5 chloroform/methanol to afford a quantitative yield of the anomeric mixture, which could not be separated: FAB MS 243 (M + H)$^+$; ^{1}H NMR (DMSO-d_6) δ 11.3 (br s, 1 H, NH), 7.88, 7.73 (2 s, 1 H, H_α-6, H_β-6), 6.15 (m, 1 H, 1′-$H_{\alpha,\beta}$), 5.15, 5.0 (2 m, 1 H, 5′-$OH_{\alpha,\beta}$), 3.73 (m, 0.5 H, 4′-H_β), 3.68 (m, 0.5 H, 5′-H_β), 3.62–3.42 (m, 1.5 H, 4′-H_α, 5′-H_α, 5′-H_β), 3.56 (m, 0.5 H, 5′-H_α), 2.3 (m, 0.5 H, 2′-H_β), 2.24–2.04 (m, 2.5 H, 2′-H_α, 2′-$H_{\alpha,\beta}$, 3′-$H_{\alpha,\beta}$), 2.04–1.8 (m, 1 H, 3′-$H_{\alpha,\beta}$), 1.8 (2 s, 3 H, $5_{\alpha,\beta}$-CH_3). Anal. ($C_{10}H_{14}N_2O_3S\cdot0.125H_2O$) C, H, N.

5′-*O*-Trityl-4′-thiothymidine (31). 4′-Thiothymidine (**30**)[10] (257 mg, 1 mmol) was treated with trityl chloride (334 mg, 1.2 mmol) in dry pyridine (15 mL) at 100 °C for 0.5 h, and the reaction mixture was poured on ice water (60 mL). The precipitated solid was filtered, washed with generous quantities of water, and dried in vacuo to afford an amorphous powder: yield 425 mg (85%); FAB MS 501 (M + H)$^+$; ^{1}H NMR ($CDCl_3$) δ 9.02 (s, 1 H, H-3), 7.14–7.50 (m, 16 H, H-6 and phenyls of trityl), 6.44 (t, 1 H, H-1′, J = 3.5 Hz), 4.48 (br s, 1 H, H-3′), 3.50–3.60 (m, 2 H, H-4′ and H-5′), 3.18–3.22 (m, 1 H, H-5′), 2.82 (br s, 1 H, 3′-OH), 2.40–2.48 (m, 1 H, H-2′), 1.94–2.04 (m, 1 H, H-2′), 1.42 (s, 3 H, CH_3).

5′-*O*-Trityl-4′-thio-2,3′-anhydrothymidine (32). To a solution of **31** (400 mg, 0.8 mmol) in 15 mL of CH_2Cl_2 was added (diethylamido)sulfur trifluoride (161.2 mg, 1.0 mmol) at −78 °C, and the solution was stirred at that temperature for 15 min. The reaction mixture was cooled to room temperature, and 25 mL of water was added. The aqueous solution was extracted with dichloromethane, and the organic phase was dried ($MgSO_4$) and evaporated to dryness to afford a yellow syrup which was purified by column chromatography to yield **32** (290 mg, 75%): FAB MS 483 (M + H)$^+$; ^{1}H NMR ($CDCl_3$) δ 7.30–7.44 (m, 15 H, phenyl of trityl), 6.80 (s, 1 H, H-6), 5.35 (br s, 1 H, H-3′), 5.20 (br s, 1 H, H-1′), 3.66–3.72 (m, 2 H, H-4′ and H-5′), 3.42–3.50 (m, 1 H, H-5′), 2.92–2.98 (m, 1 H, H-2′), 2.40–2.50 (m, 1 H, H-2′), 1.90 (s, 3 H, CH_3).

3′-Azido-3′-deoxy-4′-thio-5′-*O*-tritylthymidine (33). To a solution of **32** (241 mg, 0.5 mmol) in dimethylformamide (10 mL) were added sodium azide (120 mg, 1.85 mmol) and water (3 mL), and the resulting homogeneous solution was heated under reflux for 2 days after which time the reaction was essentially complete. The dimethylformamide was removed in vacuo at room temperature, and the resulting syrup was purified by column chromatography to afford **33** as a colorless syrup (171.6 mg, 65%): FAB MS 526 (M + H)$^+$; ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 1 H, H-3), 7.20–7.50 (m, 16 H, H-6 and phenyls of trityl), 6.37 (t, 1 H, H-1′, J = 3.5 Hz), 4.26–4.32 (m, 1 H, H-3′), 3.48–3.56 (m, 2 H, H-5′), 3.22–3.30 (m, 1 H, H-4′), 2.44–2.52 (m, 1 H, H-2′), 2.0–2.10 (m, 1 H, H-2′), 1.66 (s, 3 H, CH_3).

3′-Azido-3′-deoxy-4′-thiothymidine (34). Compound **33** (105 mg, 0.2 mmol) was dissolved in aqueous 80% acetic acid (10 mL), and the mixture was heated for 2 h on a steam bath before the solution was evaporated to dryness under vacuum. The residue was purified by preparative thin-layer chromatography to afford 38 mg of amorphous solid which was crystallized from 2-propanol and ethyl acetate to give 31 mg of **34** (55% yield): mp 120–121 °C; FAB MS 284 (M + H)$^+$; ^{1}H NMR ($CDCl_3$) δ 11.34 (s, 1 H, H-3), 7.84 (s, 1 H, H-6), 6.18 (s, 1 H, H-1′, J = 3.5 Hz), 5.32–5.38 (m, 1 H, 5′-OH), 4.50–4.52 (m, 1 H, H-3′), 3.60–3.66 (m, 2 H, H-5′), 3.34–3.42 (m, 1 H, H-4′), 1.80 (s, 3 H, CH_3). Anal. ($C_{10}H_{13}N_5O_3S\cdot0.25H_2O\cdot0.40EtOAc$) C, H, N.

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