Synthesis and Anti-HIV Activity of D- and L-Thietanose Nucleosides

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Various D- and L-thietanose nucleosides were synthesized from D- and L-xylose. The four-membered thietane ring was efficiently synthesized by the cyclization of 1-thioacetyl-3-mesylate (**4**/**38**) under basic conditions. Condensation with various heterocyclic bases was conducted via Pummerer-type rearrangement to afford various nucleoside derivatives. Among the synthesized nucleosides, D-uridine (**23**), D-cytidine (**24**), D-5-fluorocytidine (**25**), and L-cytidine (**52**) analogues showed moderate anti-HIV activity, with EC_{50} = 6.9, 1.3, 5.8, and 14.1 μM, respectively. However, these four nucleoside analogues are cytotoxic in peripheral blood mononuclear and CEM cells. The other nucleosides are neither active nor cytotoxic. Interestingly, the oxetanocin A analogue **33** was not active. Comparison of the minimized reverse transcriptases (RTs) complexed with the corresponding triphosphates of the cytidine analogue **24** and the adenosine analogue **33** by molecular modeling studies showed that there is no difference in the binding mode of the triphosphate of the cytidine analogue **24** to the active site of HIV-1 RT from that of the triphosphate of the adenosine analogue **33**. Modeling studies on the initial monophosphorylation step by deoxycytidine kinase showed that the catalytic efficiency of phosphorylation through a nucleophilic attack of the 4′-hydroxyl group of thietanose on the γ-phosphate of ATP is diminished in the case of L-cytidine analogue (**52**) due to the increased distance between the 4′-hydroxyl group and the γ-phosphate.

Introduction

Nucleoside analogues have been well established as one of the richest sources of antiviral agents despite their toxicity[1] and drug resistance.[2] Various nucleosides have been reported as potent inhibitors against viruses such as human immunodeficiency virus (HIV),[3] herpes simplex virus (HSV),[4] hepatitis B virus (HBV),[5] varicella zoster virus (VZV),[6] and human cytomegalovirus (HCMV).[7] In the search for new antiviral nucleosides with favorable antiviral and toxicological profiles, numerous modifications have been conducted on naturally occurring nucleosides. A natural nucleoside, oxetanocin A, which has a four-membered oxetane ring instead of a five-membered ribose ring, showed antiviral and antitumor activity (Figure 1).[8] The unique structure as well as the interesting biological activity of oxetanocin A has prompted nucleoside chemists to explore the antiviral and antitumor activities of the nucleosides with four-membered-ring sugar-like moieties.[9] The study of structure−activity relationships (SARs) of oxetanocin A resulted in several bioactive analogues.[9] Oxetanocin T, in which the heterocyclic base is thymine, showed activity against VZV, HSV-1, and HSV-2,[10] and oxetanocin G, with guanine as the heterocyclic base, inhibited HBV replication in cell culture with an EC_{50} of 1.5 μM.[11] The carbocyclic analogue of oxetanocin A was also found to be active against HBV and HSV,[12] and the carbocyclic oxetanocin G was also active against HBV and HSV.[12] Additionally, thietanose nucleosides which have a four-membered thietane ring are of interest because the replacement of oxygen in the sugar ring with a sulfur usually increases the nucleoside's stability toward acidic hydrolysis as well as against phosphorylases which cleave the glycosyl bond, thus resulting in the inactivation of nucleosides.[13] However, only two synthetic methodologies for the synthesis of thietanose nucleosides have been reported in the literature, presumably due to the synthetic difficulties.[14] Formulation of the thietane ring as well as the condensation reaction with heterocyclic bases occurred in poor to moderate yield, which was not sufficient to conduct SAR studies of thietanose nucleosides. For the synthesis of various thietanose nucleosides, an efficient method of synthesis of a common intermediate is required, from which various analogues can be prepared for the study of the SARs of the thietanose nucleosides. Herein, we report the synthesis and anti-HIV activity of various D- and L-thietanose nucleosides, including D- and L-3′-thio analogues of oxetanocin A.

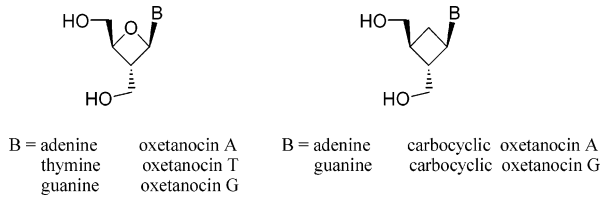

Figure 1. Oxetanocin A, T, and G and carbocyclic analogues oxetanocin A and G.

Results and Discussion

Chemistry. β-3-Hydroxythietanes, such as compound **7**, can serve as the key intermediate for the synthesis of various 2′-substituted thietanose nucleosides. The β-3-hydroxy group of **7** in the thietane ring can be derivatized to other desired moieties, such as methylene **9** or hydroxymethyl group **10**, under mild reaction conditions. To synthesize the key intermediate compound **7**, the substitution reaction of 1-thioacetyl-3-mesylate **4**, reported by several groups,[15] was adapted with some modifications. To synthesize the D-3′-thio analogues with various heterocyclic bases (**22**−**27**, **33**−**35**), D-xylose **1** was converted to the diol **2** in five steps by using the reported method (Scheme 1).[16] The diol **2** was mesylated with MsCl, TEA, and DMAP to give the 1,3-dimesylate **3** in 90% yield, which was selectively converted to the mono-thioacetate **4** by treatment with KSAc

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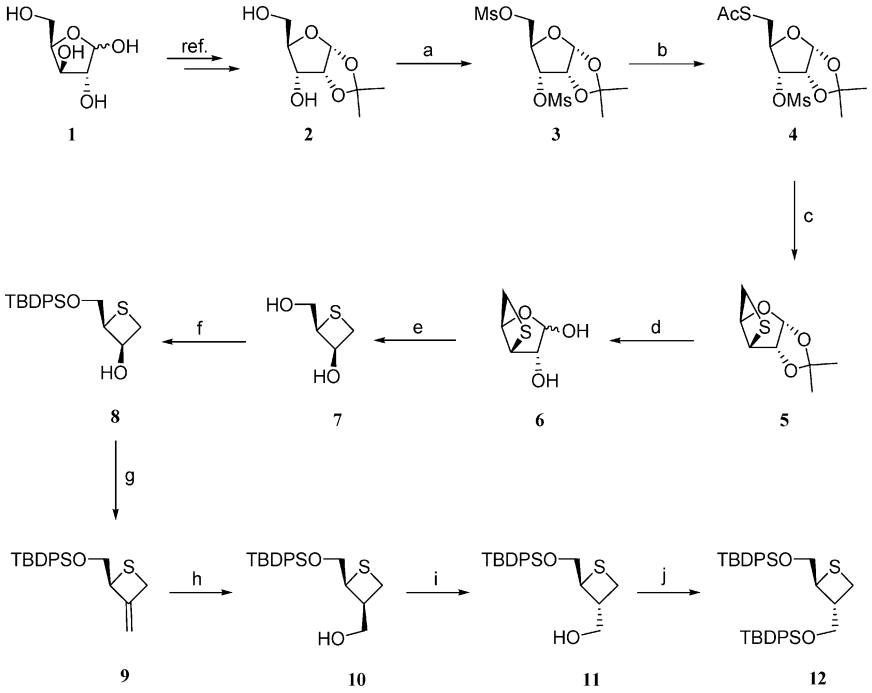
Scheme 1. Synthesis of the Key Intermediate **12**[a]



[a] Reagents and conditions: (a) MsCl, pyr, DMAP, CH_2Cl_2; (b) KSAc, DMF; (c) $NaHCO_3$, EtOH/H_2O, reflux; (d) 4% TFA, OH^- resin; (e) $NaIO_4$, $NaBH_4$, MeOH; (f) TBDPSCl, TEA, DMAP, CH_2Cl_2; (g) i. Ac_2O, DMSO, ii. Petasis reagent, THF/Et_2O (1:1), reflux; (h) BH_3SME_2, THF, H_2O_2, 1 N NaOH; (i) Swern oxidation, NaOMe, MeOH, $NaBH_4$; (j) TBDPSCl, imidazole, CH_2Cl_2.

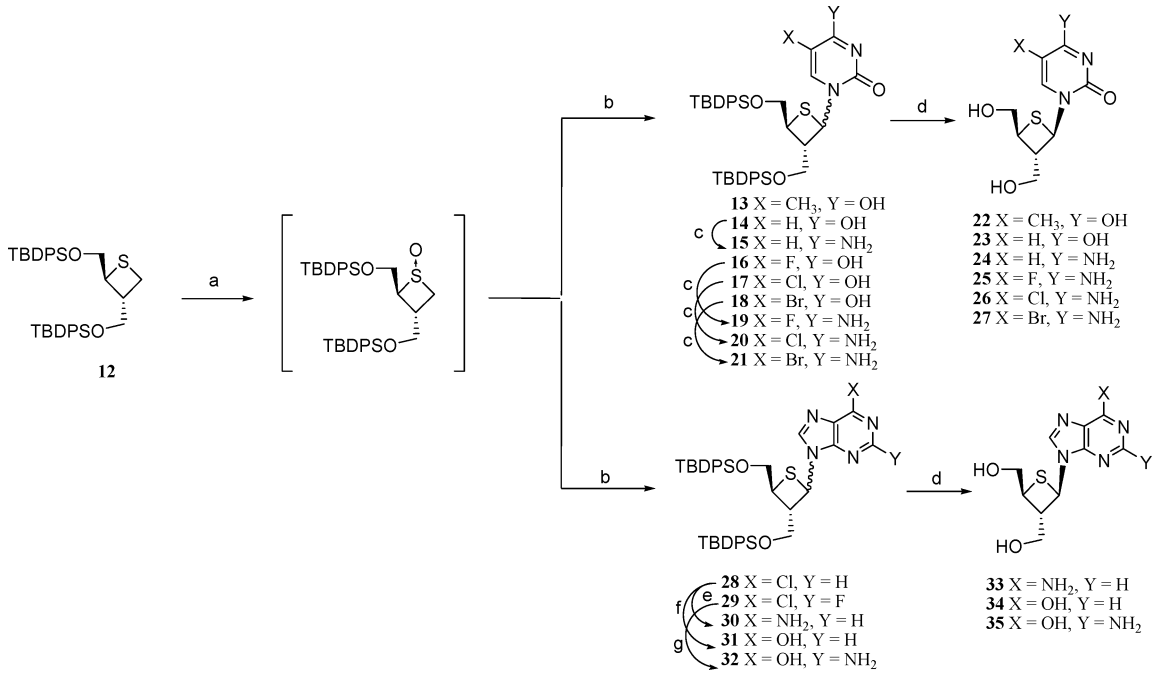
in DMF at room temperature in 80% yield. By employing a substitution reaction similar to one previously reported,[15] a solution of the mono-thioacetate **4** and $NaHCO_3$ in deoxygenated 95% aqueous EtOH was refluxed under nitrogen atmosphere for 6 h to give compound **5** in 92% yield. The compound **5** was deprotected by treatment with 4% TFA, followed by neutralization with Amberlite(OH^-) resin, to give the triol **6** in 90% yield. The compound **6** was oxidatively cleaved to give the key intermediate **7** in 70% yield, from which various 2′-substituted thietanose nucleosides were synthesized. For optimum yield of the 1,2-diol cleavage, several reaction conditions, such as the amount of $NaIO_4$ (1.2 equiv), vigorous stirring, reaction time (1 h), and temperature (0 °C), turned out to be critical.

The selective protection of the primary alcohol in compound **7** with TBDPSCl was explored with a few base catalysts, from which 2,4,6-collidine was found to give the highest selectivity between the primary and secondary hydroxyl groups. Thus, treatment of **7** with triethylamine and a catalytic amount of 2,4,6-collidine in CH_2Cl_2 gave the monoprotected compound **8** in 85% yield with no diprotected compound. Compound **8** was then oxidized under Moffatt-type conditions using DMSO and acetic anhydride to give a ketone as the intermediate, which was converted to the methylene derivative with Petasis reagent (Cp_2TiMe_2) to give compound **9** in 40% yield. Compound **9** underwent hydroboration upon treatment with $BH_3{\cdot}SMe_2$, followed by oxidation with 3% H_2O_2 and 1 N NaOH to give the undesired 2′-β-hydroxymethyl derivative **10** as the major product in 70% yield, along with the desired 2′-α-hydroxymethyl compound **11** in 12% yield. The sterically hindered nature of the β-side of compound **9**, caused by the bulky silyl protecting group, was probably unfavorable for the approach of BH_3 from the β-side, resulting in the formation of the undesired β-configuration of the 2′-hydroxymethyl group. This hypothesis is supported by the similar result obtained for the synthesis of (−)-cyclobut-A.[17] To obtain the intermediate with the correct configuration at the 2′-position, the major product **10** was oxidized to an aldehyde and equilibrated under basic conditions. Thus, Swern oxidation of compound **10**, followed by epimerization with NaOMe and reduction with $NaBH_4$, gave the desired product **11** in 47% overall yield in three steps. Compound **11** was protected by treatment with TBDPSCl and imidazole to give compound **12** in 90% yield.

Condensation of the thietanose derivative **12** with heterocyclic bases was conducted by the Pummerer-type rearrangement after formation of a sulfoxide with mCPBA (Scheme 2).[18] Silylated heterocyclic bases, such as thymine, uracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 6-chloropurine, and 6-chloro-2-fluoropurine, were obtained under reflux conditions using HMDS and acetonitrile, which were condensed with the corresponding sulfoxide of **12** in the presence of TMSOTf, triethylamine, and a catalytic amount of ZnI_2 to provide the protected nucleoside derivatives (**13**, **14**, **16**, **17**, **18**, **28**, and **29**) as α/β mixtures in 28−46% yield. For the pyrimidine nucleosides, α and β anomers cannot be separated from each other, while for the purine derivatives, it was possible to separate the desired β anomers from their α anomers by using silica gel column chromatography.

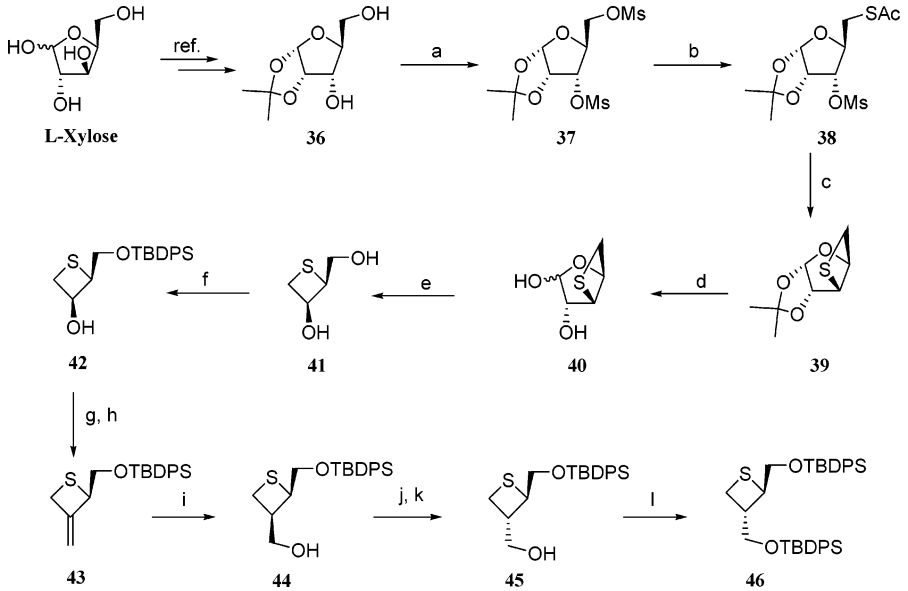
Condensation of compound **12** with thymine, uracil, 5-fluorouracil, 5-chlorouracil, and 5-bromouracil gave anomeric mixtures of protected nucleosides **13**, **14**, **16**, **17**, and **18** with β/α ratio of 2:1 in 46%, 40%, 37%, 32%, and 28% yield, respectively. The uracil, 5-fluorouracil, 5-chlorouracil, and 5-bromouracil derivatives **14**, **16**, **17**, and **18** were aminated by treatment with 2,4,6-triisopropylbenzenesulfonyl chloride, triethylamine, and DMAP in acetonitrile, followed by aqueous ammonia solution, to give the cytosine, 5-fluorocytosine, 5-chlorocytosine, and 5-bromocytosine derivatives **15**, **19**, **20**, and **21**, respectively. The nucleoside analogues **13**−**15**, **19**−**21** were treated with TBAF in THF at room temperature to afford pyrimidine thietanose nucleosides **22**−**27**.

Scheme 2. Synthesis of D-Thietanose Nucleosides[a]



[a] Reagents and conditions: (a) mCPMA, CH_2Cl_2; (b) pyrimidine or purine, HMDS, CH_3CN, TMSOTf, TEA, ZnI_2, toluene; (c) 2,4,6-triisopropylbenzenesulfonyl chloride, TEA, DMAP, CH_3CN, NH_4OH; (d) TBAF, THF; (e) i. NaN_3, DMF, ii. H_2, Pd(0), MeOH; (f) NaOMe, 2-mercaptoethanol, MeOH; (g) i. NaOMe, 2-mercaptoethanol, MeOH, ii. NH_3, EtOH, 60 °C.

Scheme 3. Synthesis of L-3′-Thio Analogues of Oxetanocin A[a]

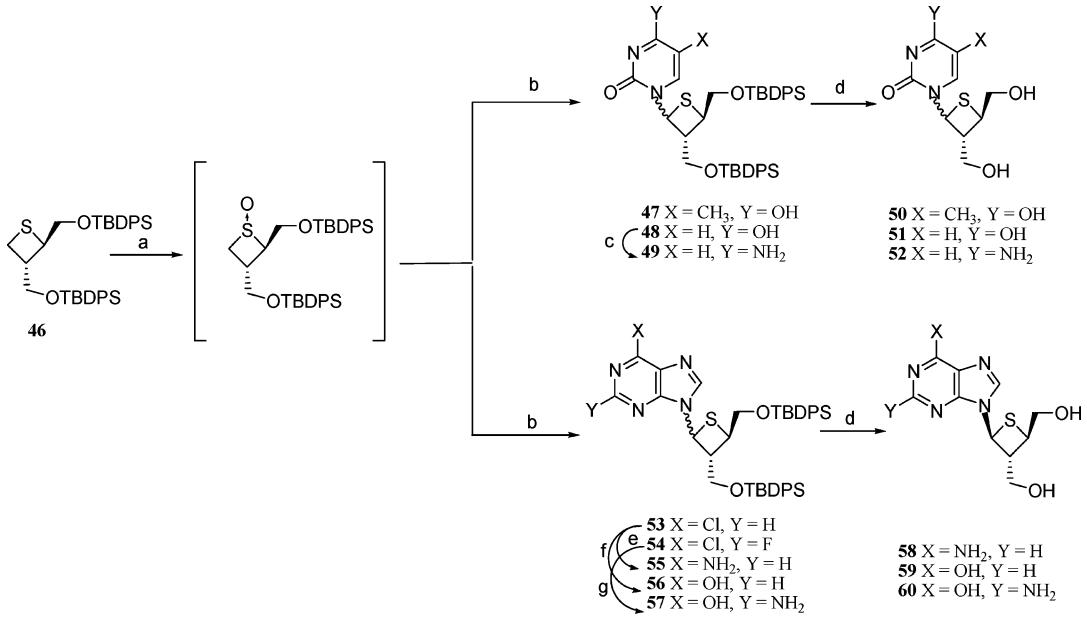


[a] Reagents and conditions: (a) MsCl, pyr, DMAP, CH_2Cl_2; (b) KSAc, DMF; (c) $NaHCO_3$, EtOH/H_2O, reflux; (d) 4% TFA, OH^- resin; (e) $NaIO_4$, $NaBH_4$, MeOH; (f) TBDPSCl, TEA, 2,4,6-collidine, CH_2Cl_2; (g) Ac_2O, DMSO; (h) Petasis reagent, (i) BH_3SMe_2, THF; (j) $(COCl)_2$, DMSO, NaOMe, MeOH; (k) $NaBH_4$, MeOH; (l) TBDPSCl, imidazole, CH_2Cl_2.

Compound **12** was condensed with 6-chloropurine and 6-chloro-2-fluoropurine to give compounds **28** and **29** as well as their α-isomers in 40−45% yield with a β/α ratio of 5:4 (Scheme 2). Compound **28** was converted to the adenine derivative **30** in 72% yield by using NaN_3 in DMF, followed by hydrogenation with 10% Pd(0) on carbon in methanol. Compound **28** was also converted to the inosine derivative **31** in 85% yield by treatment with NaOMe and 2-mercaptoethanol in methanol. On the other hand, the guanosine analogue **32** was obtained in 74% yield by treatment of **29** with NaOMe and 2-mercaptoethanol in methanol, followed by amination in ethanolic ammonia at 60 °C. Deprotection of compounds **30**−**32** by TBAF gave the purine thietanose nucleosides **33**−**35** in 89−94% yield.

The L-3′-thio analogues of oxetanocin A were also synthesized under similar reaction conditions starting from the opposite enantiomer, L-xylose (Scheme 3). L-Xylose was converted to the key intermediate **46**, the enantiomer of compound **12**, which was obtained through the thietane diol **41**, the enantiomer of compound **7**. After coupling of **46** with the appropriate silylated pyrimidine and purine bases, the L-3′-thio analogues (**50**−**52**, **58**−**60**) of oxetanocin A were obtained by using the same procedures employed for the synthesis of the D-isomers (Scheme 4).

Scheme 4. Synthesis of L-Thietanose Nucleosides[a]



[a] Reagents and conditions: (a) mCPBA, CH_2Cl_2; (b) pyrimidine or purine, HMDS, CH_3CN, TMSOTf, TEA, ZnI_2, toluene; (c) 2,4,6-triisopropylbenzenesulfonyl chloride, TEA, DMAP, CH_3CN, NH_4OH; (d) TBAF, THF; (e) i. NaN_3, DMF, ii. H_2, Pd(0), MeOH; (f) NaOMe, 2-mercaptoethanol, MeOH; (g) i. NaOMe, 2-mercaptoethanol, MeOH, ii. NH_3, EtOH, 60 °C.

Table 1. Anti-HIV Activity of D- and L-3′-Thio Thietanose Nucleoside Analogues

			HIV (PBM)		toxicity (IC_{50}, μM)		
compd	config	base	EC_{50} (μM)	EC_{90} (μM)	PBM	CEM	Vero
22	D	thymine	>100	>100	>100	>100	>100
23	D	uracil	6.9	23.1	8.5	4.9	>100
24	D	cytosine	1.3	5.3	≤1.0	4.3	54.8
25	D	5-fluorocytosine	5.8	13.9	<1.0	19.0	>100
26	D	5-chlorocytosine	>100	>100	>100	>100	>100
27	D	5-bromocytosine	11.5	41.9	>100	1.8	>100
33	D	adenine	>100	>100	>100	>100	>100
34	D	hypoxanthine	>100	>100	>100	>100	>100
35	D	guanine	>100	>100	>100	>100	>100
50	L	thymine	>100	>100	>100	>100	>100
51	L	uracil	>100	>100	>100	>100	>100
52	L	cytosine	14.1	47.6	13.1	45.6	>100
58	L	adenine	>100	>100	>100	>100	>100
59	L	hypoxanthine	>100	>100	>100	>100	>100
60	L	guanine	>100	>100	>100	>100	>100
AZT			0.004	0.01	>100	14.3	29.0

Anti-HIV Activity. The antiviral activity of the synthesized D- and L-thietanose nucleosides (**22**−**27**, **33**−**35**, **50**−**52**, **58**−**60**) was evaluated against HIV-1 in human peripheral blood mononuclear (PBM) cells in vitro using AZT as a positive control, and the results are summarized in Table 1. Among the synthesized nucleosides, D-uridine (**23**), D-cytidine (**24**), D-5-fluorocytidine (**25**), and L-cytidine (**52**) analogues show moderate anti-HIV activity, with EC_{50} = 6.9, 1.3, 5.8, and 14.1 μM, respectively. However, these four nucleoside analogues are also cytotoxic in PBM and CEM cells.

We synthesized the D-cytidine analogue in the early stages of this project, when some antiviral activity for the D-cytidine analogue (**24**, Table 1) was observed, and then we decided to explore the SAR at the 5-position of the pyrimidine ring. The addition of a halogen atom at the 5-position of the pyrimidine ring has been found to alter the kinetic parameters as well as the antiviral potency of the corresponding nucleoside analogues.[19] It is well known that modification of the 5-position of the cytosine ring with fluorine may result in reduced toxicity and in some cases increase the antiviral potency.[20] However, introduction of different halogens at the 5-position in this thietanose series (**25**−**27**) resulted in a decrease in antiviral potency (Table 1). The complete inactivity of **26** was unexpected. The other nucleosides showed neither anti-HIV activity nor cytotoxicity up to 100 μM. It is well known that nucleosides/nucleotides analogues can inhibit human DNA polymerases, which may cause side effects such as cytotoxicity, mitochondrial toxicity, etc.[21] Consequently, if compounds **24**, **25**−**27**, and **52** can be phosphorylated to triphosphates, the low selectivity of these nucleotides between the HIV reverse transcriptase (RT) and cellular polymerase may explain the observed antiviral activity as well as the cytotoxicity. Viral inhibition may also be due to the deleterious effect of the nucleosides on the cellular viability, caused by their metabolites to cellular machineries other than polymerase (e.g., ribonucleotide reductase, CTP synthase, etc.[22]). To confirm the hypothesis, however, more detailed experiments have to be conducted. As all the purine analogues, including the 3′-thio-oxetanocin A analogue **33**, showed no detectable anti-HIV activity while the compound **33** was found to have binding characteristics similar to those of the HIV RT by molecular modeling studies (vide infra), the purine thietanose nucleosides might have a low level

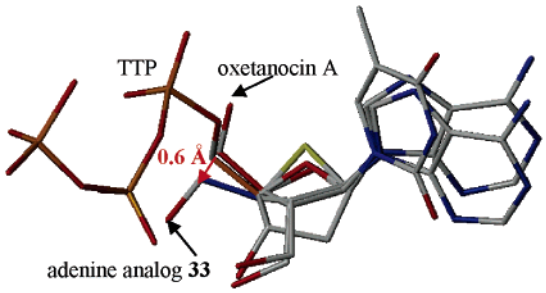


Figure 2. Superimposed structures of adenosine analogue **33**, oxetanocin A, and TTP, where the C3′−C4′ bond in adenosine analogue **33** is in blue, the C3′−C4′ bond in oxetanocin A is in red, and the C4′−C5′ bond in TTP is in orange.

of phosphorylation from the initial nucleoside kinase, which probably results in a low, if any, level of the triphosphate.

Molecular Modeling Studies. Molecular modeling studies on the synthesized thietanose adenosine derivative **33** as well as oxetanocin A were conducted to compare the conformations of these two nucleosides with that of thymidine triphosphate in the crystal structure of HIV-1 RT (PDB code 1RTD).[23] The most stable conformation of thietanose adenosine derivative **33** was obtained by a Monte Carlo conformational search using the molecular graphics and simulation program, MacroModel version 7.0 (Schrödinger, Inc.).[24] The crystal structure of oxetanocin A was obtained from the Cambridge Structural Database. The three conformations of thietanose adenosine derivative **33**, oxetanocin A, and TTP, were superimposed using Sybyl 6.7 (Figure 2). The C3′−C4′ bond (in blue) in thietanose adenosine derivative **33** is displaced by 0.6 Å from the C4′−C5′ bond (in orange) in TTP, and the 3′-sulfur atom in thietanose adenosine derivative **33** extrudes the 3′-oxygen in oxetanocin A and the 4′-oxygen in TTP. Another noticeable feature is that the 2′-hydroxymethyl groups of thietanose adenosine derivative **33** and oxetanocin A are completely overlapped with the 3′-hydroxy group of TTP. It is well known that the 3′-hydroxy pocket, composed of Asp113, Ala114, Tyr115, and Gln151, strengthens the binding of natural substrates to the active site of HIV-1 RT through hydrogen bonding, particularly with Tyr 115.[21] This 3′-hydroxy pocket also plays an important role in binding of AZTTP to HIV RT, which was demonstrated in our previous molecular modeling studies.[25] Thus, the 2′-hydroxymethyl groups of thietanose adenosine derivative **33** could be nicely accommodated at the 3′-OH pocket, which would favorably contribute to their binding affinity to RT.

While the D-cytidine analogue **24** is moderately active against HIV, which has the same sugar conformation as D-adenosine analogue **33** based on the Monte Carlo conformational search, the D-adenosine analogue **33** does not show any anti-HIV activity. To understand the difference in anti-HIV activity between the cytidine analogue **24** and the adenosine analogue **33**, molecular modeling studies using the crystal structure of HIV-1 RT (PDB code 1RTD) were conducted, replacing TTP with the corresponding triphosphates of the nucleoside analogues **24** and **33**.[23] Each triphosphate was docked to the active site of HIV-1 RT, and the resulting complex was minimized using the Kollman all-atom force field. In the minimized structures, both nucleoside triphosphates are nicely accommodated at the active site of HIV-1 RT without any steric hindrance by amino acid residues from the active site of RT. As expected, each hydroxy moiety of the 2′-hydoxymethyl group (−CH_2OH) of the two thietanose nucleoside triphosphates is hydrogen-bonded to Tyr 115 of the 3′-hydroxy pocket in the active site of HIV RT as well as their own β-phosphate (Figure 3). From the molecular modeling studies, it is suggested that there would be no difference in the ability of both of the nucleoside triphosphates to bind to the active site of HIV RT. Thus, the lack of anti-HIV activity of the adenosine analogue **33** might have originated from the lack of phosphorylation by the initial kinase.

To investigate this possibility, we conducted molecular modeling studies of D- and L-thietanose cytidine analogues (**24**, **52**) with deoxycytidine kinase (dCK, PDB code 1P60).[26] Detailed analysis of the reported crystal structure (1P60.pdb) revealed that Glu53 and Arg128 are the acid−base pair which abstracts the proton and initiates the catalysis (Figure 4).[26] The distance between the nucleoside 5′-OH and Glu53 is critical for the phosphorylation. The 3′-OH is critical for activity; thus, if 3-OH is missing, the catalytic efficiency decreases.[27] The final minimized structures of **24** and **52** revealed that there is considerable preference for the D-thietanose analogue (**24**) over the L-thietanose analogue (**52**). The catalytic efficiency of phosphorylation through a nucleophilic attack of the 4′-hydroxyl group of thietanose on the γ-phosphate of ATP is diminished in the case of compound **52** due to the increased distance between the 4′-hydroxyl group and the γ-phosphate. Slight steric clashes are also observed between Leu82 and the 2′-hydroxy-

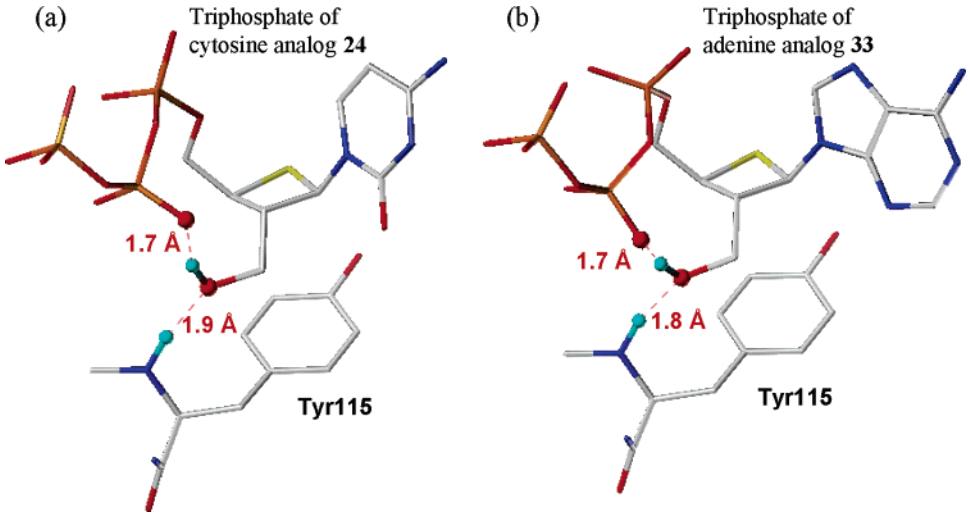


Figure 3. Minimized structures of HIV reverse transcriptase complexed with (a) the triphosphate of cytidine analogue **24** and (b) the triphosphate of adenosine analogue **33**, showing that both triphosphates are bound to the active site of HIV RT, interacting with Tyr115 and their own β-phosphate through hydrogen bonding.

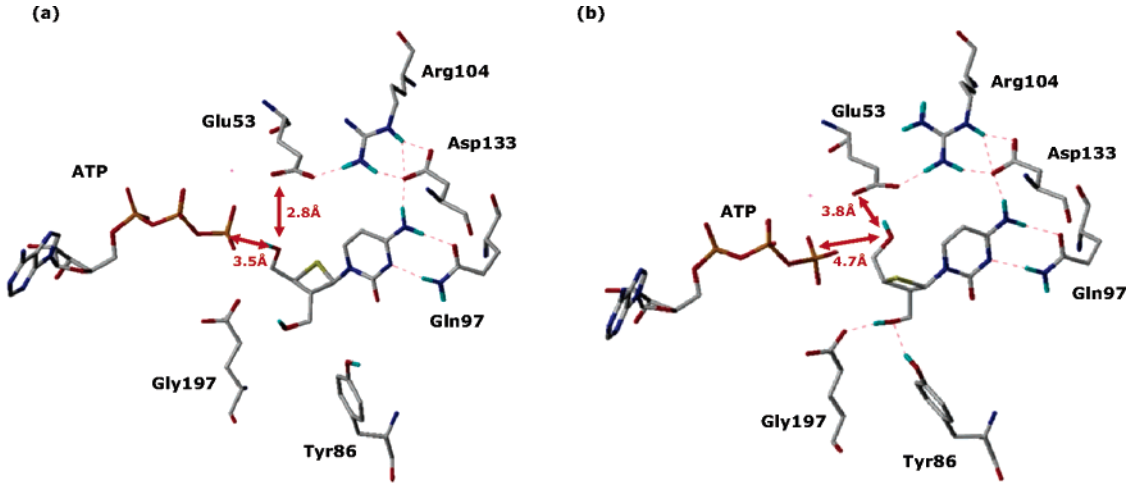


Figure 4. Minimized structures of deoxycytidine kinase (dCK) complexed with (a) the D-cytidine analogue **(24)** and (b) the L-cytidine analogue **(52)**, revealing the increased distance (1.2 Å) between the 4′-hydroxyl group and the γ-phosphate in the case of compound **52**, which may be responsible for the lower catalytic efficiency of phosphorylation through the nucleophilic attack.

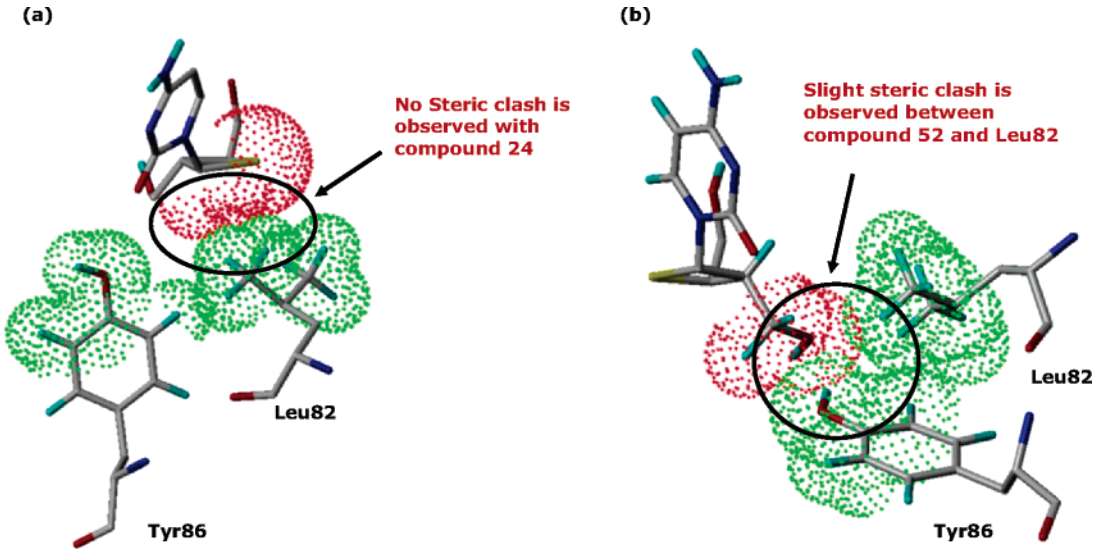


Figure 5. Steric clashes are observed between compound **52** and Leu82 but are absent in the case of compound **24**.

methyl group of **52** (Figure 5), which is due to the distinct binding mode of L-thietanose analogues. Thus, it can be concluded from the studies that the increased distance for nucleophilic attack on the γ-phosphate, coupled with the steric clashes observed for compound **52**, makes it less likely for **52** to be phosphorylated as efficiently as compound **24**, which may partially explain its lower anti-HIV activity.

In summary, various thietanose nucleosides, such as D- and L-3′-thio analogues of oxetanocin A and 2′-α- and 2′-β-hydroxythietanose nucleosides, were efficiently synthesized from D- and L-xylose. Among the synthesized nucleosides, D-uridine (**23**), D-cytidine (**24**), D-5-fluorocytidine (**25**), and L-cytidine (**52**) analogues show moderate anti-HIV activity as well as cytotoxicity. Molecular modeling studies show that the triphosphates of D-cytidine analogue **24** and adenosine analogue **33** are nicely accommodated at the active site of HIV RT through hydrogen-bonding interactions, but the initial kinase (dCK) may not efficiently phosphorylate compound **33**, resulting in a low level of its triphosphate, which in turn provides no anti-HIV activity.

Experimental Section

Melting points were determined on a Mel-temp II apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Inova 500 spectrometer at 500 MHz for ^{1}H NMR. Chemical shifts (δ) are reported as s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), m (multiplet), or br s (broad singlet). UV spectra were recorded on a Beckman DU-650 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Mass spectra were recorded on a Micromass Autospec high-resolution mass spectrometer. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either silica gel-60 (220−440 mesh) for flash chromatography or silica gel G (TLC grade, >440 mesh) for vacuum flash column chromatography. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

1,2-*O*-Isopropylidene-3,5-di-*O*-mesyl-α-D-ribofuranoside (3). A solution of compound **2** (33.2 g, 175 mmol) and pyridine (56.6 mL, 700 mmol) in CH_2Cl_2 (500 mL) was treated with MsCl (33.8 mL, 437 mmol) and DMAP (4.3 g, 35 mmol) at 0 °C for 18 h. The reaction mixture was diluted with CH_2Cl_2 (500 mL), washed with 1 N HCl, aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. The filtrate was concentrated and crystallized with a 1:10 mixture of CH_2Cl_2 and hexanes to give the product **3** (29.3 g, 0.0816 mol, 90%) as a white solid: mp 115−116 °C; $[\alpha]^{22}_D$ 77.8° (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.84 (d, J = 3.4 Hz, 1H), 4.82−4.74 (m, 2H), 4.55 (dd, J = 11.8, 1.9 Hz, 1H), 4.41−4.30 (m, 2H), 3.16 (s, 3H), 3.08 (s, 3H), 1.58 (s, 3H), 1.38 (s, 3H). Anal. ($C_{10}H_{18}O_9S_2$) C, H.

5-*S*-Acetyl-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-ribofuranoside (4). A solution of compound **3** (81.5 g, 235 mol) in DMF

(400 mL) was treated with KSAc (29.5 g, 258 mmol) at room temperature. After 16 h, the reaction mixture was diluted with EtOAc, washed with water (2 × 1 L), and dried over $MgSO_4$. The filtrate was concentrated and purified with 20% EtOAc in hexanes by silica gel column chromatography to give product **4** (61.4 g, 188 mmol, 80%) as a brownish solid: mp 112−113 °C; $[\alpha]^{23}_D$ 68.5° (*c* 0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.77 (d, J = 3.7 Hz, 1H), 4.75 (t, J = 4.2 Hz, 1H), 4.48 (dd, J = 8.8, 4.6 Hz, 1H), 4.31−4.25 (m, 1H), 3.35 (dd, J = 14.5, 4.1 Hz, 1H), 3.23 (J = 14.5, 5.1 Hz, 1H), 3.16 (s, 3H), 2.36 (s, 3H), 1.55 (s, 3H), 1.34 (s, 3H). Anal. ($C_{11}H_{18}O_7S_2$) C, H, S.

3,5-Thioanhydro-1,2-*O*-isopropylidene-α-D-xylofuranoside (5). A mixture of EtOH (100 mL) and water (5 mL) was refluxed under Ar for 2 h and cooled. Compound **4** (2.12 g, 6.50 mmol) and solid $NaHCO_3$ (1.09 g, 13.0 mmol) were added to the solvent, and the resulting mixture was refluxed for 8 h. The reaction mixture was cooled, diluted with Et_2O, filtered, and purified with 5% Et_2O in hexanes by silica gel column chromatography to give the product **5** (1.12 g, 5.98 mmol, 92%) as an oil: $[\alpha]^{22}_D$ 78.7° (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.41 (d, J = 3.4 Hz, 1H), 5.26 (t, J = 5.3 Hz, 1H), 4.71 (d, J = 3.4 Hz, 1H), 4.08 (d, J = 5.3 Hz, 1H), 3.49 (dd, J = 10.6, 5.4 Hz, 1H), 2.84 (d, J = 10.6 Hz, 1H), 1.43 (s, 3H), 1.36 (s, 3H). Anal. ($C_8H_{12}O_3S$) C, H, S.

3,5-Thioanhydro-α-D-xylofuranose (6). Compound **5** (1.10 g, 5.84 mmol) was treated with 4% solution of TFA in water at room temperature for 8 h, and then the reaction mixture was neutralized with Amberlite(OH) resin, which was prewashed with water (2 × 100 mL). After filtration, the filtrate was concentrated and purified with 50% EtOAc in hexanes by silica gel column chromatography to give the product **6** (0.75 g, 5.06 mmol, 87%): ^{1}H NMR ($CDCl_3$) for major δ 6.11 (d, J = 2.3 Hz, 1H), 5.16−5.12 (m, 1H), 4.17 (d, J = 2.5 Hz, 1H), 3.95 (d, J = 5.9 Hz, 1H), 3.50 (dd, J = 10.9, 6.3 Hz, 1H), 3.00 (d, J = 10.9 Hz, 1H), for minor δ 5.56 (s, 1H), 5.29−5.24 (m, 1H), 4.37 (s, 1H), 3.95 (d, J = 5.9 Hz, 1H), 3.64 (dd, J = 10.9, 6.1 Hz, 1H), 3.12 (d, J = 10.9 Hz, 1H). Anal. ($C_5H_8O_3S$) C, H, S.

***(2R,3S)*-2-Hydroxymethyl-thietan-3-ol (7).** A solution of compound **6** (1.92 g, 12.9 mmol) in MeOH (50 mL) was treated with an aqueous solution of $NaIO_4$ (3.04 g, 14.2 mmol) in water (25 mL) dropwise at 0 °C for 10 min with vigorous stirring. After 20 min, well-ground $NaBH_4$ was added portionwise to the reaction mixture at 0 °C. After 30 min, the resulting mixture was filtered, and the filtrate was neutralized with 1 N HCl and concentrated. The residue was dissolved in a mixture of CH_2Cl_2 and MeOH (1:1), and the white solid was filtered off. The filtrate was concentrated and purified with 3−5% MeOH in CH_2Cl_2 by silica gel column chromatography to give the products **7** (1.08 g, 9.0 mmol, 70%): $[\alpha]^{24}_D$ 166.2° (*c* 0.63, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.00 (quin., J = 8.1 Hz, 1H), 4.09−3.98 (m, 2H), 3.85 (d, J = 8.9 Hz, 1H), 3.76−3.71 (m, 1H), 3.37−3.24 (m, 3H). Anal. ($C_4H_8O_2S\cdot 0.35H_2O$) C, H, S.

(2*R*,3*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-thietan-3-ol (8). A solution of compound **7** (5.00 g, 41.6 mmol), triethylamine (11.6 mL, 83.2 mmol), and 2,4,6-collidine (0.46 mL, 4.2 mmol) in CH_2Cl_2 was treated with TBDPSCl (11.45 mL, 43.7 mmol) at 0 °C for 2 h. The resulting mixture was concentrated and purified with 5% EtOAc in hexanes by silica gel column chromatography to give the product **8** (11.9 g, 33.2 mmol, 82%) as an oil: $[\alpha]^{20}_D$ 74.1° (*c* 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.84−7.38 (m, 10H), 5.06 (quin., J = 8.1 Hz, 1H), 4.19−4.10 (m, 2H), 3.88 (d, J = 9.7 Hz, 1H), 3.73−3.67 (m, 1H), 3.54 (t, J = 8.3 Hz, 1H), 3.33 (t, J = 8.3 Hz, 1H), 1.12 (s, 9H). Anal. ($C_{20}H_{26}O_2SSi$) C, H, S.

***tert*-Butyl-[(2*S*)-3-methylene-thietan-2-ylmethoxy]-diphenyl-silane (9).** Compound **8** (10.9 g, 30.4 mmol) was treated with DMSO (45 mL) and Ac_2O (30 mL) at room temperature overnight. The reaction mixture was quenched with ice, diluted with Et_2O (500 mL), and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with 3% EtOAc in hexanes by silica gel column chromatography to give the intermediate ketone (10.0 g, 28.1 mmol, 92%) as an oil.

A mixture of titanocene dichloride (38.7 g, 115 mmol) in Et_2O (1 L) was treated with 1.6 M MeLi solution (214 mL) in Et_2O at room temperature for 2 h. The reaction mixture was quenched with ice and extracted with Et_2O. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. This reagent (Petasis reagent) was dissolved in THF (80 mL). A solution of the intermediate ketone (10.0 g, 28.1 mmol) in Et_2O (50 mL) was treated with the freshly prepared Petasis reagent solution. The resulting mixture was refluxed at 60 °C bath temperature. After 48 h, the reaction mixture was cooled to room temperature, diluted with hexanes, and filtered through the silica gel pad. The filtrate was concentrated and purified with 2% EtOAc in hexanes by silica gel column chromatography to give the product **9** (4.12 g, 11.6 mmol, 41%) as an oil: $[\alpha]^{22}_D$ 73.6° (*c* 0.80, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.72−7.65 (m, 4H), 7.47−7.37 (m, 6H), 4.86 (d, J = 2.1 Hz, 1H), 4.71 (d, J = 2.1 Hz, 1H), 4.44−4.37 (m, 1H), 4.00 (dd, J = 10.3, 6.8 Hz, 1H), 3.87 (dd, J = 10.3, 6.8 Hz, 1H), 3.84−3.74 (m, 2H), 1.06 (s, 9H). Anal. ($C_{21}H_{26}OSSi$) C, H, S.

[(2*S*,3*R*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-thietan-3-yl]-methanol (10). A solution of compound **9** (4.12 g, 11.6 mmol) in THF (200 mL) was treated with 2 M BH_3SMe_2 solution (11.5 mL) in THF at 0 °C for 30 min. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with 3% H_2O_2 (26 mL) and 1 N NaOH (23 mL). After 2 h, the reaction mixture was treated with saturated $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The filtrate was concentrated and purified with 10% EtOAc in hexanes by silica gel column chromatography to give the product **10** (3.35 g, 8.13 mmol, 70% yield) as well as compound **11** (0.51 g, 1.37 mmol, 12% yield): $[\alpha]^{22}_D$ 43.4° (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.78−7.32 (m, 10H), 4.28 (t, J = 10.1 Hz, 1H), 4.01 (t, J = 9.9 Hz, 1H), 3.80−3.42 (m, 5H), 3.02−2.83 (m, 2H), 1.07 (s, 9H). Anal. ($C_{21}H_{28}O_2SSi$) C, H, S.

[(2*R*,3*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-thietan-3-yl]-methanol (11). Oxalyl chloride (1.56 mL, 17.9 mmol) was added dropwise to a solution of DMSO (1.90 mL, 26.8 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After 10 min, a solution of compound **10** (3.33 g, 8.94 mmol) in CH_2Cl_2 (20 mL) was added to the reaction mixture at −78 °C. After 20 min, TEA (5.0 mL, 36 mmol) was added at −78 °C. After 10 min, the reaction mixture was warmed to room temperature for 1 h. The resulting mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. The aldehyde was dissolved in MeOH (30 mL) and treated with NaOMe (1.45 g, 26.8 mmol) for 16 h. The resulting mixture was treated with $NaBH_4$ (1.01 g, 26.7 mmol) for 2 h. The reaction mixture was neutralized with 1 N HCl, concentrated to a tenth volume of the solution, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, concentrated, filtered, and purified by silica gel column chromatography with 10% EtOAc in hexanes to give the product **11** (1.58 g, 4.24 mmol, 47% yield): $[\alpha]^{24}_D$ 40.7° (*c* 0.81, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.70−7.36 (m, 10H), 3.82−3.58 (m, 5H), 3.22−3.10 (m, 1H), 3.01−2.93 (m, 2H), 1.06 (s, 9H). Anal. ($C_{21}H_{28}O_2SSi$) C, H, S.

(2*R*,3*S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietane (12). A solution of compound **11** (2.00 g, 5.37 mmol) and imidazole (0.77 g, 11 mmol) in CH_2Cl_2 was treated with TBDPSCl (1.54 mL, 5.92 mmol) at room temperature for 3 h. The reaction mixture was concentrated and purified with 2% EtOAc in hexanes to give the product **12** (2.95 g, 4.83 mmol, 90%) as an oil: $[\alpha]^{22}_D$ 45.0° (*c* 0.38, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.70−7.33 (m, 20H), 3.90 (dd, J = 9.7, 6.1 Hz, 1H), 3.77 (dd, J = 10.2, 6.6 Hz, 1H), 3.73−3.65 (m, 3H), 3.16−2.95 (m, 3H), 1.05 (s, 9H), 1.04 (s, 9H). Anal. ($C_{37}H_{46}O_2SSi_2$) C, H, S.

1-[(2*R*,3*S*,4*R*/*S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-thymine (13). A solution of compound **12** (0.250 g, 0.409 mmol) in CH_2Cl_2 was treated with a solution of 77% mCPBA (0.092 g, 0.411 mmol) in CH_2Cl_2 dropwise at −78 °C. The mixture was stirred at −78 °C for 30 min. The reaction was quenched with aqueous $Na_2S_2O_3$, diluted with CH_2Cl_2, washed with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. The

filtrate was concentrated to dryness. The crude sulfoxide was used for the next reaction without further purification. A mixture of thymine (0.155 g, 1.23 mmol) in acetonitrile (10 mL) and HMDS (10 mL) was refluxed for 3 h until the solution became clear. After evaporation, the residue was treated successively with a solution of the crude sulfoxide in toluene (10 mL), triethylamine (0.11 mL, 0.79 mmol), TMSOTf (0.16 mL, 0.88 mmol), and ZnI_2 (0.039 g, 0.12 mmol) at 0 °C. After 24 h, the reaction was quenched with water at 0 °C, and the reaction mixture was diluted with CH_2Cl_2. The organic layer was dried over $NaSO_4$, filtered, concentrated, and purified with 30% EtOAc in hexane by preparative TLC to give the product **13** (0.138 g, 0.188 mmol, 46%) as an α/β mixture (1:3): UV (CH_2Cl_2) λ_{max} 270.0 nm; ^{1}H NMR ($CDCl_3$) δ 9.03, 8.99 (2br s, 1H), 7.98, 7.80 (2s, 1H), 7.72−7.30 (m, 20H), 6.30 (d, J = 6.8 Hz, 0.75H), 6.20 (d, J = 7.7 Hz, 0.25H), 3.88 (dd, J = 9.8, 5.9 Hz, 0.25H), 3.81−3.45 (m, 5H), 3.26−3.19 (m, 0.75H), 1.87, 1.83 (2s, 3H), 1.07, 1.044, 1.036, 0.98 (4s, 18H). Anal. ($C_{42}H_{50}N_2O_4SSi_2$) C, H, N, S.

1-[(2*R*,3*S*,4*R/S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-uracil (14). See the procedure for compound **13** for the condensation reaction with thymine. The title compound **14** was obtained on a 0.301-mmol scale in 40% yield: UV (CH_2Cl_2) λ_{max} 265.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.58, 8.53 (2br s, 1H), 8.19 (d, J = 7.8 Hz, 0.3H), 8.16 (d, J = 7.8 Hz, 0.7H), 7.70−7.33 (m, 20H), 6.24 (d, J = 6.8 Hz, 0.7H), 6.20 (d, J = 7.8 Hz, 0.3H), 5.69 (d, J = 8.8 Hz, 0.3H), 5.60 (d, J = 7.8 Hz, 0.7H), 3.85 (dd, J = 10.7, 5.8 Hz, 0.3H), 3.77−3.46 (m, 5H), 3.26−3.20 (m, 0.7H), 1.07, 1.05, 1.03, 0.98 (4s, 18H). Anal. ($C_{41}H_{48}N_2O_4SSi_2$) C, H, N, S.

1-[(2*R*,3*S*,4*R/S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-cytosine (15). A solution of compound **14** (0.120 g, 0.166 mmol) in acetonitrile was treated with triethylamine (0.07 mL, 0.50 mmol), 2,4,6-triisopropylbenzenesulfonyl chloride (0.151 g, 0.499 mmol), and DMAP (0.061 g, 0.50 mmol) at room temperature. After 16 h, ammonia water was added to the resulting mixture. After 3 h, the mixture was diluted with CH_2Cl_2 (50 mL), and the organic layer was washed with brine, dried over Na_2SO_4, concentrated, and purified by column chromatography with 5% MeOH in CH_2Cl_2 to give an α/β mixture of compound **15** (0.090 g, 0.125 mmol, 75% yield): UV (CH_2Cl_2) λ_{max} 285.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 7.8 Hz, 0.3H), 8.25 (d, J = 7.8 Hz, 0.7H), 7.69−7.28 (m, 20H), 6.26 (d, J = 6.8 Hz, 0.7H), 6.24 (d, J = 7.8 Hz, 0.3H), 5.62 (d, J = 6.8 Hz, 0.3H), 5.58 (d, J = 6.8 Hz, 0.7H), 3.92 (dd, J = 10.7, 5.8 Hz, 0.3H), 3.83−3.46 (m, 5H), 3.18−3.11 (m, 0.7H), 1.07, 1.03, 1.00 (3s, 18H). Anal. ($C_{41}H_{49}N_3O_3SSi_2$) C, H, N, S.

1-[(2*R*,3*S*,4*R/S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-5-fluorouracil (16). See the procedure for compound **13** for the condensation reaction with thymine. The title compound **16** was obtained on a 0.389-mmol scale in 37% yield: UV (CH_2Cl_2) λ_{max} 271 nm; ^{1}H NMR ($CDCl_3$) δ 8.58, 8.53 (2br s, 1H), 8.19 (d, J = 7.8 Hz, 0.3H), 8.16 (d, J = 7.8 Hz, 0.7H), 7.70−7.33 (m, 20H), 6.24 (d, J = 6.8 Hz, 0.7H), 6.20 (d, J = 7.8 Hz, 0.3H), 5.69 (d, J = 8.8 Hz, 0.3H), 5.60 (d, J = 7.8 Hz, 0.7H), 3.85 (dd, J = 10.7, 5.8 Hz, 0.3H), 3.77−3.46 (m, 5H), 3.26−3.20 (m, 0.7H), 1.07, 1.05, 1.03, 0.98 (4s, 18H); HRMS (ESI, M + Na^+) calcd for $C_{41}H_{47}FN_2O_4SSi_2Na$ 761.2677, found 761.2671.

1-[(2*R*,3*S*,4*R/S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-5-chlorouracil (17). See the procedure for compound **13** for the condensation reaction with thymine. The title compound **17** was obtained on a 0.291-mmol scale in 32% yield: UV (CH_2Cl_2) λ_{max} 273.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.58, 8.53 (2br s, 1H), 8.19 (d, J = 7.8 Hz, 0.3H), 8.16 (d, J = 7.8 Hz, 0.7H), 7.70−7.33 (m, 20H), 6.24 (d, J = 6.8 Hz, 0.7H), 6.20 (d, J = 7.8 Hz, 0.3H), 5.69 (d, J = 8.8 Hz, 0.3H), 5.60 (d, J = 7.8 Hz, 0.7H), 3.85 (dd, J = 10.7, 5.8 Hz, 0.3H), 3.77−3.46 (m, 5H), 3.26−3.20 (m, 0.7H), 1.07, 1.05, 1.03, 0.98 (4s, 18H); HRMS (ESI, M + Na^+) calcd for $C_{41}H_{47}ClN_2O_4SSi_2Na$ 777.2382, found 777.2378.

1-[(2*R*,3*S*,4*R/S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-5-bromouracil (18). See the procedure for compound **13** for the condensation reaction with thymine. The title compound **18** was obtained on a 0.375-mmol scale in 28% yield: UV (CH_2Cl_2) λ_{max} 278.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.58, 8.53 (2br s, 1H), 8.19 (d, J = 7.8 Hz, 0.3H), 8.16 (d, J = 7.8 Hz, 0.7H), 7.70−7.33 (m, 20H), 6.24 (d, J = 6.8 Hz, 0.7H), 6.20 (d, J = 7.8 Hz, 0.3H), 5.69 (d, J = 8.8 Hz, 0.3H), 5.60 (d, J = 7.8 Hz, 0.7H), 3.85 (dd, J = 10.7, 5.8 Hz, 0.3H), 3.77−3.46 (m, 5H), 3.26−3.20 (m, 0.7H), 1.07, 1.05, 1.03, 0.98 (4s, 18H); HRMS (ESI, Mona$^+$) calcd for $C_{41}H_{47}BrN_2O_4SSi_2Na$ 821.1876, found 821.1867.

1-[(2*R*,3*S*,4*R/S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-5-fluorocytosine (19). See the procedure for compound **14** for the amination reaction with the uridine analogue. The title compound **19** was obtained on a 0.284-mmol scale in 73% yield: UV (CH_2Cl_2) λ_{max} 285 nm; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 7.8 Hz, 0.3H), 8.25 (d, J = 7.8 Hz, 0.7H), 7.69−7.28 (m, 20H), 6.26 (d, J = 6.8 Hz, 0.7H), 6.24 (d, J = 7.8 Hz, 0.3H), 5.62 (d, J = 6.8 Hz, 0.3H), 5.58 (d, J = 6.8 Hz, 0.7H), 3.92 (dd, J = 10.7, 5.8 Hz, 0.3H), 3.83−3.46 (m, 5H), 3.18−3.11 (m, 0.7H), 1.07, 1.03, 1.00 (3s, 18H); HRMS (ESI, M + Na^+) calcd for $C_{41}H_{48}FN_3O_3SSi_2Na$ 760.2837, found 760.2845.

1-[(2*R*,3*S*,4*R/S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-5-chlorocytosine (20). See the procedure for compound **14** for the amination reaction with the uridine analogue. The title compound **20** was obtained on a 0.318-mmol scale in 68% yield: UV (CH_2Cl_2) λ_{max} 277 nm; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 7.8 Hz, 0.3H), 8.25 (d, J = 7.8 Hz, 0.7H), 7.69−7.28 (m, 20H), 6.26 (d, J = 6.8 Hz, 0.7H), 6.24 (d, J = 7.8 Hz, 0.3H), 5.62 (d, J = 6.8 Hz, 0.3H), 5.58 (d, J = 6.8 Hz, 0.7H), 3.92 (dd, J = 10.7, 5.8 Hz, 0.3H), 3.83−3.46 (m, 5H), 3.18−3.11 (m, 0.7H), 1.07, 1.03, 1.00 (3s, 18H); HRMS (ESI, M + Na^+) calcd for $C_{41}H_{48}FN_3O_3SSi_2Na$ 776.2541, found 776.2533.

1-[(2*R*,3*S*,4*R/S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-5-bromocytosine (21). See the procedure for compound **14** for the amination reaction with the uridine analogue. The title compound **21** was obtained on a 0.338-mmol scale in 63% yield: UV (CH_2Cl_2) λ_{max} 292 nm; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 7.8 Hz, 0.3H), 8.25 (d, J = 7.8 Hz, 0.7H), 7.69−7.28 (m, 20H), 6.26 (d, J = 6.8 Hz, 0.7H), 6.24 (d, J = 7.8 Hz, 0.3H), 5.62 (d, J = 6.8 Hz, 0.3H), 5.58 (d, J = 6.8 Hz, 0.7H), 3.92 (dd, J = 10.7, 5.8 Hz, 0.3H), 3.83−3.46 (m, 5H), 3.18−3.11 (m, 0.7H), 1.07, 1.03, 1.00 (3s, 18H); HRMS (ESI, M + Na^+) calcd for $C_{41}H_{48}BrN_3O_3SSi_2Na$ 820.2036, found 820.2027.

1-[(2*R*,3*S*,4*R*)-2,3-Dihydroxymethyl-thietan-4-yl]-thymine (22). A solution of compound **13** (0.130 g, 0.177 mmol) in THF (10 mL) was treated with 0.35 mL of 1 M TBAF solution in acetonitrile at 0 °C. After 3 h, the reaction mixture was concentrated and purified by preparative TLC with 7% MeOH in CH_2Cl_2 to give compound **22** (0.029 g, 0,112 mmol, 63% yield) and the α-isomer (0.011 g, 0.043 mmol, 24% yield): mp > 200 °C (dec); $[\alpha]^{26}_D$ −86.8 ° (*c* 0.075, DMSO); UV (H_2O) λ_{max} 264.0 nm (ϵ 9400, pH 2), 262.0 nm (ϵ 9900, pH 7), 265.5 nm (ϵ 7100, pH 11); ^{1}H NMR (MeOH) δ 8.30 (s, 1H), 6.08 (d, J = 6.8 Hz, 1H), 3.76 (dd, J = 11.7, 3.9 Hz, 1H), 3.72 (dd, J = 11.7, 4.9 Hz, 1H), 3.58 (d, J = 3.9 Hz, 2H), 3.54−3.49 (m, 1H), 3.32−3.26 (m, 1H), 1.95 (s, 3H). Anal. ($C_{10}H_{14}N_2O_4S$) C, H, N, S.

1-[(2*R*,3*S*,4*R*)-2,3-Dihydroxymethyl-thietan-4-yl]-uracil (23). See the procedure for compound **22** for the deprotection reaction with 1 M TBAF solution. The title compound **23** was obtained on a 0.083-mmol scale in 59% yield: mp > 200 °C (dec); $[\alpha]^{22}_D$ −35.4° (*c* 0.17, MeOH); UV (H_2O) λ_{max} 265.5 nm (ϵ 9200, pH 2), 265.5 nm (ϵ 8500, pH 7), 265.5 nm (ϵ 6900, pH 11); ^{1}H NMR (MeOH) δ 8.46 (d, J = 7.8 Hz, 1H), 6.07 (d, J = 6.8 Hz, 1H), 5.81 (d, J = 7.8 Hz, 1H), 3.76 (dd, J = Hz, 1H), 3.71 (dd, J = Hz, 1H), 3.60 (d, J = Hz, 2H), 3.54−3.49 (m, 1H), 3.28−3.21 (m, 1H). Anal. ($C_9H_{12}N_2O_4S$) C, H, N, S.

1-[(2*R*,3*S*,4*R*)-2,3-Dihydroxymethyl-thietan-4-yl]-cytosine (24). See the procedure for compound **22** for the deprotection reaction with 1 M TBAF solution. The title compound **24** was obtained on a 0.118-mmol scale in 59% yield: mp 125−126 °C; $[\alpha]^{23}_D$ −59.2° (*c* 0.14, MeOH); UV (H_2O) λ_{max} 282.5 nm (ϵ 12 500, pH 2), 274.5 nm (ϵ 9700, pH 7), 275.5 nm (ϵ 9600, pH 11); ^{1}H NMR (MeOH) δ 8.43 (d, J = 6.8 Hz, 1H), 6.04 (s, J = 6.8 Hz, 1H), 6.00 (d, J = 7.8 Hz, 1H), 3.75 (dd, J = 11.7, 4.9 Hz, 1H), 3.69 (dd, J = 11.7,

5.6 Hz, 1H), 3.66−3.58 (m, 1H), 3.51−3.47 (m, 1H), 3.14 (quin., J = 6.8 Hz, 1H). Anal. ($C_9H_{12}N_2O_4S$) C, H, N, S.

1-[(2*R*,3*S*,4*R*)-2,3-Dihydroxymethyl-thietan-4-yl]-5-fluorocytosine (25). See the procedure for compound **22** for the deprotection reaction with 1 M TBAF solution. The title compound **25** was obtained on a 0.109-mmol scale in 51% yield: mp 125−126 °C; $[\alpha]^{26}_D$ −53.3 ° (*c* 0.30, MeOH); UV (H_2O) λ_{max} 272 nm (ϵ 9226, pH 2), 288 nm (ϵ 14 146, pH 7), 278 nm (ϵ 12 588, pH 11); ^{1}H NMR (MeOH) δ 8.65 (d, J = 6.8 Hz, 1H), 6.04 (dd, J = 6.6, 2.2 Hz, 1H), 3.76 (dd, J = 9.0, 4.4 Hz, 2H), 3.67 (dd, J = 5.6, 3.9 Hz, 2H), 3.55−3.51 (m, 1H), 3.24−3.20 (m, 1H). Anal. ($C_9H_{12}N_2O_4S$) C, H, N, S.

1-[(2*R*,3*S*,4*R*)-2,3-Dihydroxymethyl-thietan-4-yl]-5-chlorocytosine (26). See the procedure for compound **22** for the deprotection reaction with 1 M TBAF solution. The title compound **26** was obtained on a 0.112-mmol scale in 46% yield: mp 125−126 °C; $[\alpha]^{25}_D$ −43.4° (*c* 0.22, MeOH); UV (H_2O) λ_{max} 297 nm (ϵ 5486, pH 2), 291 nm (ϵ 4567, pH 7), 291 nm (ϵ 6903, pH 11); ^{1}H NMR (MeOH) δ 8.61 (s, 1H), 5.87 (d, J = 6.3 Hz, 1H), 3.62 (dd, J = 8.5, 4.1 Hz, 2H), 3.55 (dd, J = 5.6, 2.9 Hz, 1H), 3.42−3.38 (m, 1H), 3.13−3.07 (m, 1H). Anal. ($C_9H_{12}N_2O_4S$) C, H, N, S.

1-[(2*R*,3*S*,4*R*)-2,3-Dihydroxymethyl-thietan-4-yl]-5-bromocytosine (27). See the procedure for compound **22** for the deprotection reaction with 1 M TBAF solution. The title compound **27** was obtained on a 0.105-mmol scale in 37% yield: mp 125−126 °C; $[\alpha]^{23}_D$ −25.3 ° (*c* 0.14, MeOH); UV (H_2O) λ_{max} 302 nm (ϵ 8311, pH 2), 293 nm (ϵ 6585, pH 7), 293 nm (ϵ 7005, pH 11); ^{1}H NMR (MeOH) δ 8.83 (s, 1H), 6.00 (s, J = 6.4 Hz, 1H), 3.74 (dd, J = 8.1, 4.1 Hz, 2H), 3.68 (dd, J = 5.6, 3.2 Hz, 2H), 3.56−3.52 (m, 1H), 3.33−3.28 (m, 1H). Anal. ($C_9H_{12}N_2O_4S$) C, H, N, S.

9-[(2*R*,3*S*,4*R*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-6-chloropurine (28). See the procedure for compound **13** for the condensation reaction with thymine. The title compound **28** as well as the α-isomer were obtained on a 0.622-mmol scale in 45% yield as a 5:4 mixture of compound **28** and the α-isomer: $[\alpha]^{23}_D$ 16.8 ° (*c* 0.65, $CHCl_3$); UV (CH_2Cl_2) λ_{max} 264.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.87 (s, 1H), 8.86 (s, 1H), 7.66−7.27 (m, 20H), 6.56 (d, J = 7.1 Hz, 1H), 3.82−3.62 (m, 5H), 3.39−3.31 (m, 1H), 1.06 (s, 9H), 1.02 (s, 9H). Anal. ($C_{42}H_{47}ClN_4O_2SSi_2$) C, H, N, S.

9-[(2*R*,3*S*,4*R*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-6-chloro2-fluoropurine (29). See the procedure for compound **13** for the condensation reaction with thymine. The title compound **29** as well as the α-isomer were obtained on a 0.797-mmol scale in 40% yield as a 5:4 mixture of compound **29** and the α-isomer: $[\alpha]^{24}_D$ 9.3 ° (*c* 0.21, $CHCl_3$); UV (CH_2Cl_2) λ_{max} 254.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1H), 7.64−7.24 (m, 20H), 6.47 (d, J = 6.8 Hz, 1H), 3.83−3.65 (m, 5H), 3.36−3.28 (m, 1H), 1.06 (s, 9H), 1.03 (s, 9H). Anal. ($C_{42}H_{46}ClFN_4O_2SSi_2$) C, H, N, S.

9-[(2*R*,3*S*,4*R*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-adenine (30). A solution of compound **28** (0.202 g, 0.265 mmol) in DMF (2 mL) was treated with NaN_3 (0.172 g, 2.65 mol) at room temperature for 16 h. The resulting mixture was directly filtered through a silica gel pad using as eluent a 1:1 mixture of hexanes and EtOAc. The filtrate was concentrated to dryness. A solution of the crude azide in MeOH (15 mL) was treated with 0.030 g of Pd(0)/C and H_2 balloon for 48 h. The resulting mixture was filtered through a Celite pad, and the filtrate was concentrated and purified by column chromatography with 2% MeOH in CH_2Cl_2 to give the product **30** (0.143 g, 0.192 mmol, 72% yield): $[\alpha]^{23}_D$ 41.5° (*c* 0.17, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 272.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.44 (s, 1H), 7.85 (s, 1H), 7.66−7.30 (m, 20H), 6.06 (br s, 2H), 6.03 (d, J = 8.6 Hz, 1H), 3.91−3.83 (m, 2H), 3.74−3.54 (m, 3H), 3.43−3.34 (m, 1H), 1.09 (s, 9H), 1.05 (s, 9H). Anal. ($C_{42}H_{49}N_5O_2SSi_2$) C, H, N, S.

9-[(2*R*,3*S*,4*R*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-hypoxanthine (31). A solution of compound **28** (0.134 g, 0.176 mmol), 2-mercaptoethanol (0.049 mL, 0.70 mmol), and NaOMe (0.038 g, 0.70 mmol) in MeOH was refluxed for 6 h. The mixture was cooled to room temperature, neutralized with AcOH, concentrated, and purified by column chromatography with 2% MeOH in CH_2Cl_2 to give the product **31** (0.112 g, 0.150 mmol, 85% yield): $[\alpha]^{24}_D$ 27.9° (*c* 0.21, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 262.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 7.72 (s, 1H), 7.68−7.12 (m, 20H), 6.56 (d, J = 5.9 Hz, 1H), 3.89 (dd J = 10.7, 5.9 Hz, 1H), 3.85−3.68 (m, 4H), 3.39−3.32 (m, 1H), 1.05 (s, 9H), 1.01 (s, 9H). Anal. ($C_{42}H_{48}N_4O_3SSi_2$) C, H, N, S.

9-[(2*R*,3*S*,4*R*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-guanine (32). A solution of compound **29** (0.138 g, 0.177 mmol), 2-mercaptoethanol (0.049 mL, 0.70 mmol), and NaOMe (0.019 g, 0.35 mmol) in MeOH was refluxed for 4 h. The mixture was cooled to room temperature, neutralized with AcOH, concentrated, and filtered through a silica gel pad. The filtrate was concentrated to dryness. The residue was treated with ethanolic ammonia at 60 °C for 6 h. The reaction mixture was concentrated and purified by column chromatography with 2% MeOH in CH_2Cl_2 to give the product **32** (0.115 g, 0.151 mmol, 74% yield): $[\alpha]^{24}_D$ 17.8 ° (*c* 0.12, $CHCl_3$); UV (CH_2Cl_2) λ_{max} 264.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H), 7.75−7.24 (m, 20H), 6.36 (d, J = 6.8 Hz, 1H), 3.95−3.63 (m, 5H), 3.37−3.30 (m, 1H), 1.04 (s, 9H), 0.99 (s, 9H). Anal. ($C_{42}H_{49}N_5O_3SSi_2$) C, H, N, S.

9-[(2*R*,3*S*,4*R*)-2,3-Dihydroxymethyl-thietan-4-yl]-adenine (33). See the procedure for compound **22** for the deprotection reaction with 1 M TBAF solution. The title compound **33** was obtained on a 0.188-mmol scale in 94% yield: mp > 200 °C; $[\alpha]^{25}_D$ 95.2° (*c* 0.057, MeOH); UV (H_2O) λ_{max} 272.5 nm (ϵ 15 000, pH 2), 270.5 nm (ϵ 10 000, pH 7), 271.5 nm (ϵ 10 000, pH 11); ^{1}H NMR (MeOH) δ 8.84 (s, 1H), 8.24 (s, 1H), 6.17 (d, J = 6.6 Hz, 1H), 3.80 (d, J = 4.6 Hz, 2H), 3.73 (dd, J = 11.7, 6.6 Hz, 1H), 3.69 (dd, J = 11.7, 5.1 Hz, 1H), 3.62−3.56 (m, 1H), 3.55−3.48 (m, 1H). Anal. ($C_{10}H_{13}N_5O_2S$) C, H, N, S.

9-[(2*R*,3*S*,4*R*)-2,3-Dihydroxymethyl-thietan-4-yl]-hypoxanthine (34). See the procedure for compound **22** for the deprotection reaction with 1 M TBAF solution. The title compound **34** was obtained on a 0.150-mmol scale in 89% yield: mp 213−214 °C; $[\alpha]^{26}_D$ 22.0° (*c* 0.13, MeOH); UV (H_2O) λ_{max} 256.5 nm (ϵ 7600, pH 2), 258.0 nm (ϵ 7200, pH 7), 263.0 nm (ϵ 7600, pH 11); ^{1}H NMR (MeOH-d_4) δ 8.91 (s, 1H), 8.02 (s, 1H), 6.36 (d, J = 5.9 Hz, 1H), 3.83 (dd, J = 11.7, 4.9 Hz, 1H), 3.78 (dd, J = 11.7, 4.9 Hz, 1H), 3.77−3.70 (m, 2H), 3.60 (q, J = 4.9 Hz, 1H), 3.48 (quin., J = 5.9 Hz, 1H). Anal. ($C_{10}H_{12}N_4O_3S$) C, H, N, S.

9-[(2*R*,3*S*,4*R*)-2,3-Dihydroxymethyl-thietan-4-yl]-guanine (35). See the procedure for compound **22** for the deprotection reaction with 1 M TBAF solution. The title compound **35** was obtained on a 0.132-mmol scale in 91% yield: mp > 200 °C (dec); $[\alpha]^{23}_D$ −73.7° (*c* 0.11, DMSO); UV (H_2O) λ_{max} 251.5 nm (ϵ 7300, pH 2), 266.0 nm (ϵ 6900, pH 7), 266.0 nm (ϵ 7100, pH 11); ^{1}H NMR (DMSO-d_6) δ 13.48 (br s, 1H), 8.79 (s, 1H), 6.23 (d, J = 6.8 Hz, 1H), 5.07 (t, J = 4.9 Hz, 1H), 4.99 (br s, 1H), 3.79−3.46 (m, 5H), 3.30−2.26 (m, 1H). Anal. ($C_{10}H_{13}N_5O_3S$) C, H, N, S.

(−)-[2*R*,3*R*,4*S*,5*S*]-Methanesulfonic Acid 5-Methanesulfonyloxymethyl-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-6-yl Ester (37). Using the same procedure described for the preparation of compound **3**, the title compound was prepared on a 81.6-mmol scale in 90% yield as a white solid: mp 115−116 °C; $[\alpha]^{22}_D$ −80.2° (*c* 0.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.84 (d, J = 3.4 Hz, 1H), 4.82−4.74 (m, 2H), 4.55 (dd, J = 11.8, 1.9 Hz, 1H), 4.41−4.30 (m, 2H), 3.16 (s, 3H), 3.08 (s, 3H), 1.58 (s, 3H), 1.38 (s, 3H). Anal. ($C_{10}H_{18}O_9S_2$) C, H.

(−)-[2*R*,3*R*,4*S*,5*S*]-Thioacetic acid *S*-(6-methanesulfonyloxy-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-ylmethyl) ester (38) was prepared from compound **37** on a 14.0-mmol scale in 80% yield as a brownish solid by the same procedure described for **4**: mp 112−113 °C; $[\alpha]^{23}_D$ −70.0° (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.77 (d, J = 3.7 Hz, 1H), 4.75 (t, J = 4.2 Hz, 1H), 4.48 (dd, J = 8.8, 4.6 Hz, 1H), 4.31−4.25 (m, 1H), 3.35 (dd, J = 14.5, 4.1 Hz, 1H), 3.23 (J = 14.5, 5.1 Hz, 1H), 3.16 (s, 3H), 2.36 (s, 3H), 1.55 (s, 3H), 1.34 (s, 3H). Anal. ($C_{11}H_{18}O_7S_2$) C, H, S.

(−)-4,4-Dimethyl-tetrahydro-3,5,6-trioxa-2-thia-cyclobuta[*a*]-pentalene (39) was prepared from compound **38** on a 30.85-mmol scale in 95% yield as a yellowish oil by the same procedure described for **5**: $[\alpha]^{23}_D$ −89.4° (*c* 1.76, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 6.41 (d, J = 3.4 Hz, 1H), 5.26 (t, J = 5.3 Hz, 1H), 4.71 (d, J =

3.4 Hz, 1H), 4.08 (d, J = 5.3 Hz, 1H), 3.49 (dd, J = 10.6, 5.4 Hz, 1H), 2.84 (d, J = 10.6 Hz, 1H), 1.43 (s, 3H), 1.36 (s, 3H). Anal. ($C_8H_{12}O_3S$) C, H, S.

(−)-2-Oxa-6-thia-bicyclo[3.2.0]heptane-3,4-diol (40) was prepared from compound **39** on a 27.77-mmol scale in 90% yield as a yellowish oil (anomeric mixture) by the same procedure described for **6**.

(−)-[2*R*,3*S*]-2-Hydroxymethyl-thietan-3-ol (41) was prepared from compound **40** on a 10.11-mmol scale in 70% yield as a yellowish oil by the same procedure described for **7**: $[\alpha]^{24}_D$ −173.5° (*c* 0.84, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.00 (quin., J = 8.1 Hz, 1H), 4.09−3.98 (m, 2H), 3.85 (d, J = 8.9 Hz, 1H), 3.76−3.71 (m, 1H), 3.37−3.24 (m, 3H). Anal. ($C_4H_8O_2S\cdot 0.35H_2O$) C, H, S.

(−)-[2*R*,3*R*]-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-thietan-3-ol (42) was prepared from compound **41** on a 17.10-mmol scale in 85% yield as a yellowish oil by the same procedure described for **8**: $[\alpha]^{22}_D$ −78.6° (*c* 0.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.84−7.38 (m, 10H), 5.06 (quin., J = 8.1 Hz, 1H), 4.19−4.10 (m, 2H), 3.88 (d, J = 9.7 Hz, 1H), 3.73−3.67 (m, 1H), 3.54 (t, J = 8.3 Hz, 1H), 3.33 (t, J = 8.3 Hz, 1H), 1.12 (s, 9H). Anal. ($C_{20}H_{26}O_2SSi$) C, H, S.

(−)-[2*R*]-*tert*-Butyl-(3-methylene-thietan-2-ylmethoxy)-diphenyl-silane (43) was prepared from compound **42** on a 5.32-mmol scale in 40% yield as a yellowish oil by the same procedure described for **9**: $[\alpha]^{23}_D$ −71.8° (*c* 1.60, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.72−7.65 (m, 4H), 7.47−7.37 (m, 6H), 4.86 (d, J = 2.1 Hz, 1H), 4.71 (d, J = 2.1 Hz, 1H), 4.44−4.37 (m, 1H), 4.00 (dd, J = 10.3, 6.8 Hz, 1H), 3.87 (dd, J = 10.3, 6.8 Hz, 1H), 3.84−3.74 (m, 2H), 1.06 (s, 9H). Anal. ($C_{21}H_{26}OSSi$) C, H, S.

(−)-[2*R*,3*R*]-[2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-thietan-3-yl]-methanol (44) was prepared from compound **43** on a 4.43-mmol scale in 64% yield as a yellowish oil by the same procedure described for **10**: $[\alpha]^{22}_D$ −32.1° (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.78−7.32 (m, 10H), 4.28 (t, J = 10.1 Hz, 1H), 4.01 (t, J = 9.9 Hz, 1H), 3.80−3.42 (m, 5H), 3.02−2.83 (m, 2H), 1.07 (s, 9H). Anal. ($C_{21}H_{28}O_2SSi$) C, H, S.

(−)-[2*R*,3*S*]-[2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-thietan-3-yl]-methanol (45) was prepared from compound **44** on a 2.27-mmol scale in 45% yield as a yellowish oil by the same procedure described for **11**: $[\alpha]^{22}_D$ −39.5° (*c* 0.91, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.70−7.36 (m, 10H), 3.82−3.58 (m, 5H), 3.22−3.10 (m, 1H), 3.01−2.93 (m, 2H), 1.06 (s, 9H). Anal. ($C_{21}H_{28}O_2SSi$) C, H, S.

(−)-[2*R*,3*S*]-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietane (46) was prepared from compound **45** on a 2.16-mmol scale in 92% yield as a yellowish oil by the same procedure described for **12**: $[\alpha]^{24}_D$ −44.7° (*c* 0.43, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.70−7.33 (m, 20H), 3.90 (dd, J = 9.7, 6.1 Hz, 1H), 3.77 (dd, J = 10.2, 6.6 Hz, 1H), 3.73−3.65 (m, 3H), 3.16−2.95 (m, 3H), 1.05 (s, 9H), 1.04 (s, 9H). Anal. ($C_{37}H_{46}O_2SSi_2$) C, H, S.

1-[(2*S*,3R,4*R/S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-thymine (47) was prepared from the coupling of sulfoxide, which was obtained from the oxidation of compound **46** with silylated thymine, on a 0.18-mmol scale in 44% yield (α/β mixture, α:β = 1:3 as determined by NMR) by the same procedure described for **13**: UV (CH_2Cl_2) λ_{max} 270.0 nm. Anal. ($C_{42}H_{50}N_2O_4SSi_2$) C, H, N, S.

1-[(2*S*,3*R*,4*R/S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-uracil (48). Using a condensation procedure similar to that for the preparation of compound **13**, the title compound **48** was obtained on a 0.325-mmol scale in 40% yield as an α/β mixture (α:β = 1:2 as determined by NMR): UV (CH_2Cl_2) λ_{max} 265.0 nm. Anal. ($C_{41}H_{48}N_2O_4SSi_2$) C, H, N, S.

1-[(2*S*,3*R*,4*R/S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-cytosine (49). Using a condensation procedure similar to that for the preparation of compound **15**, the title compound **49** was obtained on a 0.16-mmol scale in 75% yield as an α/β mixture: UV (CH_2Cl_2) λ_{max} 285.5 nm. Anal. ($C_{41}H_{49}N_3O_3SSi_2$) C, H, N, S.

1-[(2*S*,3*R*,4*S*)-2,3-Dihydroxymethyl-thietan-4-yl]-thymine (50) was prepared from compound **47** on a 0.043-mmol scale in 63% yield as white solid by the same procedure described for **22**: mp > 200 °C (dec); $[\alpha]^{26}_D$ 82.8° (*c* 0.13, DMSO); UV (H_2O) λ_{max} 264.0 nm (ϵ 9400, pH 2), 262.0 nm (ϵ 9900, pH 7), 265.5 nm (ϵ 7100, pH 11); ^{1}H NMR (MeOH) δ 8.30 (s, 1H), 6.08 (d, J = 6.8 Hz, 1H), 3.76 (dd, J = 11.7, 3.9 Hz, 1H), 3.72 (dd, J = 11.7, 4.9 Hz, 1H), 3.58 (d, J = 3.9 Hz, 2H), 3.54−3.49 (m, 1H), 3.32−3.26 (m, 1H), 1.95 (s, 3H). Anal. ($C_{10}H_{14}N_2O_4S$) C, H, N, S.

1-[(2*S*,3*R*,4*S*)-2,3-Dihydroxymethyl-thietan-4-yl]-uracil (51) was prepared from compound **48** on a 0.043-mmol scale in 59% yield as a white solid by the same procedure described for **23**: mp > 200 °C (dec); $[\alpha]^{24}_D$ 33.2° (*c* 0.23, MeOH); UV (H_2O) λ_{max} 265.5 nm (ϵ 9200, pH 2), 265.5 nm (ϵ 8500, pH 7), 265.5 nm (ϵ 6900, pH 11); ^{1}H NMR (MeOH) δ 8.46 (d, J = 7.8 Hz, 1H), 6.07 (d, J = 6.8 Hz, 1H), 5.81 (d, J = 7.8 Hz, 1H), 3.76 (dd, J = Hz, 1H), 3.71 (dd, J = Hz, 1H), 3.60 (d, J = Hz, 2H), 3.54−3.49 (m, 1H), 3.28−3.21 (m, 1H). Anal. ($C_9H_{12}N_2O_4S$) C, H, N, S.

1-[(2*S*,3*R*,4*S*)-2,3-dihydroxymethyl-thietan-4-yl]-cytosine (52) was prepared from compound **49** on a 0.043-mmol scale in 56% yield as a white solid by the same procedure described for **24**: mp 126−127 °C; $[\alpha]^{25}_D$ 61.7° (*c* 0.11, MeOH); UV (H_2O) λ_{max} 282.5 nm (ϵ 12 500, pH 2), 274.5 nm (ϵ 9700, pH 7), 275.5 nm (ϵ 9600, pH 11); ^{1}H NMR (MeOH) δ 8.43 (d, J = 6.8 Hz, 1H), 6.04 (s, J = 6.8 Hz, 1H), 6.00 (d, J = 7.8 Hz, 1H), 3.75 (dd, J = 11.7, 4.9 Hz, 1H), 3.69 (dd, J = 11.7, 5.6 Hz, 1H), 3.66−3.58 (m, 1H), 3.51−3.47 (m, 1H), 3.14 (quin., J = 6.8 Hz, 1H). Anal. ($C_9H_{12}N_2O_4S$) C, H, N, S.

9-[(2*S*,3*R*,4*S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-6-chloropurine (53). Using the same condensation procedure as for the preparation of compound **28**, the title compound **53** was obtained on a 0.370-mmol scale in 40% yield, together with its α anomer (α:β = 4:5): $[\alpha]^{22}_D$ −16.8° (*c* 0.58, $CHCl_3$); UV (CH_2Cl_2) λ_{max} 264.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.87 (s, 1H), 8.86 (s, 1H), 7.66−7.27 (m, 20H), 6.56 (d, J = 7.1 Hz, 1H), 3.82−3.62 (m, 5H), 3.39−3.31 (m, 1H), 1.06 (s, 9H), 1.02 (s, 9H). Anal. ($C_{42}H_{47}ClN_4O_2SSi_2$) C, H, N, S.

9-[(2*S*,3*R*,4*S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-6-chloro2-fluoropurine (54). Using the same condensation procedure as for compound **29**, the title compound **54** was obtained on a 0.797-mmol scale in 23% yield, together with its α anomer (α:β = 4:5): $[\alpha]^{24}_D$ −10.1° (*c* 0.54, $CHCl_3$); UV (CH_2Cl_2) λ_{max} 254 nm; ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1H), 7.64−7.24 (m, 20H), 6.47 (d, J = 6.8 Hz, 1H), 3.83−3.65 (m, 5H), 3.36−3.28 (m, 1H), 1.06 (s, 9H), 1.03 (s, 9H). Anal. ($C_{42}H_{46}ClFN_4O_2SSi_2$) C, H, N, S.

9-[(2*S*,3*R*,4*S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-adenine (55) was prepared from compound **53** on a 0.078-mmol scale in 74% yield as a white solid by the same procedure described for **30**: $[\alpha]^{23}_D$ −40.7° (*c* 0.15, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 272.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.44 (s, 1H), 7.85 (s, 1H), 7.66−7.30 (m, 20H), 6.06 (br s, 2H), 6.03 (d, J = 8.6 Hz, 1H),;3.91−3.83 (m, 2H), 3.74−3.54 (m, 3H), 3.43−3.34 (m, 1H), 1.09 (s, 9H), 1.05 (s, 9H). Anal. ($C_{42}H_{49}N_5O_2SSi_2$) C, H, N, S.

9-[(2*S*,3*R*,4*S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-hypoxanthine (56) was prepared from compound **53** on a 0.11-mmol scale in 84% yield as a white solid by the same procedure described for **31**: $[\alpha]^{24}_D$ 26.9° (*c* 0.13, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 262.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 7.72 (s, 1H), 7.68−7.12 (m, 20H), 6.56 (d, J = 5.9 Hz, 1H), 3.89 (dd J = 10.7, 5.9 Hz, 1H), 3.85−3.68 (m, 4H), 3.39−3.32 (m, 1H), 1.05 (s, 9H), 1.01 (s, 9H). Anal. ($C_{42}H_{48}N_4O_3SSi_2$) C, H, N, S.

9-[(2*S*,3*R*,4*S*)-2,3-Bis(*tert*-butyl-diphenyl-silanyloxymethyl)-thietan-4-yl]-guanine (57) was prepared from compound **54** on a 0.11-mmol scale in 84% yield as a white solid by the same procedure described for **32**: $[\alpha]^{22}_D$ 17.8° (*c* 0.29, $CHCl_3$); UV (CH_2Cl_2) λ_{max} 264.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H), 7.75−7.24 (m, 20H), 6.36 (d, J = 6.8 Hz, 1H), 3.95−3.63 (m, 5H), 3.37−3.30 (m, 1H), 1.04 (s, 9H), 0.99 (s, 9H). Anal. ($C_{42}H_{49}N_5O_3SSi_2$) C, H, N, S.

9-[(2*S*,3*R*,4*S*)-2,3-Dihydroxymethyl-thietan-4-yl]-adenine (58). Using the same procedure as for deprotection of compound **33**, the title compound **58** was obtained on a 0.094-mmol scale in 84% yield: mp > 200 °C; $[\alpha]^{25}_D$ −93.3° (*c* 0.11, MeOH); UV (H_2O)

λ_{max} 272.5 nm (ϵ 15 000, pH 2), 270.5 nm (ϵ 10 000, pH 7), 271.5 nm (ϵ 10 000, pH 11); ^{1}H NMR (MeOH) δ 8.84 (s, 1H), 8.24 (s, 1H), 6.17 (d, J = 6.6 Hz, 1H), 3.80 (d, J = 4.6 Hz, 2H), 3.73 (dd, J = 11.7, 6.6 Hz, 1H), 3.69 (dd, J = 11.7, 5.1 Hz, 1H), 3.62−3.56 (m, 1H), 3.55−3.48 (m, 1H). Anal. ($C_{10}H_{13}N_5O_2S$) C, H, N, S.

9-[(2*S*,3*R*,4*S*)-2,3-Dihydroxymethyl-thietan-4-yl]-hypoxanthine (59). Using the same procedure as for the deprotection of compound **33**, the title compound **59** was obtained on a 0.145-mmol scale in 86% yield: mp 213−214 °C; $[\alpha]^{27}_D$ −23.9° (*c* 0.15, MeOH); UV (H_2O) λ_{max} 256.5 nm (ϵ 7600, pH 2), 258.0 nm (ϵ 7200, pH 7), 263.0 nm (ϵ 7600, pH 11); ^{1}H NMR (MeOH-d_4) δ 8.91 (s, 1H), 8.02 (s, 1H), 6.36 (d, J = 5.9 Hz, 1H), 3.83 (dd, J = 11.7, 4.9 Hz, 1H), 3.78 (dd, J = 11.7, 4.9 Hz, 1H), 3.77−3.70 (m, 2H), 3.60 (q, J = 4.9 Hz, 1H), 3.48 (quin., J = 5.9 Hz, 1H). Anal. ($C_{10}H_{12}N_4O_3S$) C, H, N, S.

9-[(2*S*,3*R*,4*S*)-2,3-Dihydroxymethyl-thietan-4-yl]-guanine (60). Using the same procedure as for the deprotection of compound **25**, the title compound **35** was obtained on a 0.124-mmol scale in 86% yield: mp > 200 °C (dec); $[\alpha]^{23}_D$ 70.7° (*c* 0.12, DMSO); UV (H_2O) λ_{max} 251.5 nm (ϵ 7300, pH 2), 266.0 nm (ϵ 6900, pH 7), 266.0 nm (ϵ 7100, pH 11); ^{1}H NMR (DMSO-d_6) δ 13.48 (br s, 1H), 8.79 (s, 1H), 6.23 (d, J = 6.8 Hz, 1H), 5.07 (t, J = 4.9 Hz, 1H), 4.99 (br s, 1H), 3.79−3.46 (m, 5H), 3.30−2.26 (m, 1H). Anal. ($C_{10}H_{13}N_5O_3S$) C, H, N, S.

Antiviral Assay. Human PBM cells (obtained from Atlanta Red Cross) were isolated by Ficoll-Hypaque discontinuous gradient centrifugation from healthy seronegative donors. Cells were stimulated with phytohemagglutinin A (Difco, Sparks, MD) for 2−3 days prior to use. HIV-1_{LAI}, obtained from the Centers for Disease Control and Prevention (Atlanta, GA), was used as the standard reference virus for the antiviral assays. The molecular infectious clones HIV-1_{xxBru} were obtained from Dr. John Mellors (University of Pittsburgh). Infections were done in bulk for 1 h, either with 100 $TCID_{50}$/1 × 10^7 cells for a flask (T25) assay or with 200 $TCID_{50}$/6 × 10^5 cells/well for a 24-well plate assay. Cells were added to a plate or flask containing a 10-fold serial dilution of the test compound. Assay medium was RPMI-1640, supplemented with heat-inactivated 16% fetal bovine serum, 1.6 mM L-glutamine, 80 IU/mL penicillin, 80 μg/mL streptomycin, 0.0008% DEAE-Dextran, 0.045% sodium bicarbonate, and 26 IU/mL recombinant interleukin-2 (Chiron Corp., Emeryville, CA). AZT was used as a positive control for the assay. Untreated and uninfected PBM cells were grown in parallel at equivalent cell concentrations as controls. The cell cultures were maintained in humidified 5% CO_2 air at 37 °C for 5 days, and supernatants were collected for determination of RT activity.

Supernatants were centrifuged at 12 000 rpm for 2 h to pellet the virus. The pellet was solubilized with vortexing in 100 μL of virus solubilization buffer (VSB) containing 0.5% Triton X-100, 0.8 M NaCl, 0.5 mM phenylmethylsulfonyl fluoride, 20% glycerol, and 0.05 M Tris, pH 7.8. Ten-microliter portions of each sample were added to 75 μL of RT reaction mixture (0.06 M Tris, pH 7.8, 0.012 M $MgCl_2$, 0.006 M dithiothreitol, 0.006 mg/mL poly(rA)$_n$ oligo(dT)$_{12-18}$, 96 μg/mL dATP, and 1 μM of 0.08 mCi/mL ^{3}H-thymidine triphosphate (Moravek Biochemicals, Brea, CA)) and incubated at 37 °C for 2 h. The reaction was stopped by the addition of 100 μL of 10% trichloroacetic acid containing 0.05% sodium pyrophosphate. The acid-insoluble product was harvested onto filter paper using a Packard harvester (Meriden, CT), and the RT activity was read on a Packard direct beta counter (Meriden, CT). The RT results were expressed in counts per minute (CPM) per milliliter. The antiviral 50% effective concentration (EC_{50}) and 90% effective concentration (EC_{90}) were determined from the concentration−response curve using the median effect method.[28]

Cytotoxicity Assays. The compounds were evaluated for their potential toxic effects on uninfected PHA-stimulated human PBM cells, in CEM (T-lymphoblastoid cell line obtained from American Type Culture Collection, Rockville, MD) and Vero (African green monkey kidney) cells. PBM cells were obtained from whole blood of healthy seronegative donors (HIV-1 and hepatitis B virus) by single-step Ficoll-Hypaque discontinuous gradient centrifugation. Log phase Vero, CEM, and PHA-stimulated human PBM cells were seeded at a density of 5 × 10^3, 2.5 × 10^3, and 5 × 10^4 cells/well, respectively. All of the cells were plated in 96-well cell culture plates containing 10-fold serial dilutions of the test drug. The cultures were incubated for 3, 4, and 5 days for Vero, CEM, and PBM cells, respectively, in humidified 5% CO_2 air at 37 °C. At the end of incubation, MTT tetrazolium dye solution (Cell titer 96, Promega, Madison, WI) was added to each well and incubated overnight. The reaction was stopped with stop-solubilization solution (Promega, Madison, WI). The plates were incubated for 5 h to ensure that the formazan crystals were dissolved. The plates were read at a wavelength of 570 nm using an ELISA plate reader (Bio-tek instruments, Inc., Winooski, VT, model EL 312e). The 50% inhibition concentration (IC_{50}) was determined from the concentration−response curve using the median effect method.[28]

Molecular Modeling Studies. (a) Conformational Analysis. The initial conformations of D-cytidine analogue **24** and D-adenosine analogue **33** were constructed and geometrically optimized through a Monte Carlo conformational search using MMFF94s force field in Macromodel, version 7.0 (Schrödinger, Inc.).

(b) Binding Affinity Study to HIV-1 Reverse Transcriptase. All molecular modeling of the enzyme−substrate complexes was carried out using Sybyl 6.7 (Tripos Associates, St. Louis, MO) on a Silicon Graphics Octane2 workstation. The enzyme site of the enzyme−ligand complex was constructed on the basis of the X-ray structure of the covalently trapped catalytic complex of HIV-1 RT with TTP and primer−template duplex (PDB code 1rtd). A model of the NRTI binding site was constructed which consisted of residues between Lys1 and Pro243 in the p66 subunit and a 7:4 (template−primer) duplex. The geometrically optimized structures of each inhibitor, obtained from the geometry optimization study, were used as the initial Cartesian coordinates. The heterocyclic moiety of the (n + 1)-th nucleotide in template overhang was modified to the base complementary to the incoming NRTIs. Thus, the adenine moiety which was in the original X-ray structure (1rtd) was modified to guanine. The inhibitor triphosphates were manually docked to the active site of the enzyme by adjusting the torsional angles to those found in the X-ray structure. Gästeiger−Hückel charge was given to the enzyme−ligand complex with formal charges (+2) to two Mg atoms in the active site. Then, Kollman all-atom charges were loaded to the enzyme site from the biopolymer module in Sybyl. To eliminate local strains resulting from merging inhibitors and/or point mutations, residues less than 6 Å from the merged inhibitors and mutated residues were annealed until the energy change from one iteration to the next was less than 0.05 kcal/mol. The annealed enzyme−inhibitor complexes were minimized by using the Kollman all-atom force field until the iteration number reached 5000.

(c) Binding Affinity Study to Deoxycytidine Kinase (dCK). All molecular modeling of the enzyme−substrate complexes was carried out using Sybyl 6.7 (Tripos Associates, St. Louis, MO) on a Silicon Graphics Octane2 workstation. The enzyme site of the enzyme−ligand complex was constructed on the basis of the X-ray structure of the catalytic complex of dCK with dC and adenosine diphosphate (ADP) (PDB code 1P60).[26] Terminal residues were capped with acetyl and methyl groups, Mg^{2+} atom was added, and γ-phosphate was added. Substrate coordinates of **24** and **52** were constructed and geometrically optimized through a Monte Carlo conformational search using MMFF94s force field in Macromodel, version 7.0 (Schrödinger, Inc.). Substrates were docked into the binding pocket on the basis of the coordinates of dC. Gästeiger−Hückel charges and Kollman all-atom charge were loaded to the ligands and dCK, respectively, with formal charges (+2) to Mg atom in the active site. And the residues less than 6 Å (hot region, 6 Å; interesting region, 12 Å) from the substrate were annealed until the energy change from one iteration to the next was less than 0.05 kcal/mol. The annealed dCK−substrate complex was fully minimized by using the Kollman all-atom force field for 5000 iterations.

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Supporting Information Available: Elemental analyses data of compounds **3**−**15**, **22**−**60**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Petersen, E. A.; Ramirez-Ronda, D. H.; Hardy, W. D.; Schwartz, R.; Sacks, H. S.; Follansbee, S.; Peterson, D. M.; Cross, A.; Anderson, R. E. Dunkle, L. M. Dose-related activity of stavudine in patients infected with human immunodeficiency virus. *J. Infect. Dis.* **1995**, *171 (Suppl. 2)*, S131−S139. (b) Yarchoan, R.; Pluda, J. M.; Thomas, R. V.; Mitsuya, H.; Brouwers, P.; Wyvill, K. M.; Hartman, N.; Johns, D. G.; Broder, S. Long-term toxicity/activity profile of 2′,3′-dideoxyinosine in AIDS or AIDS-related complex. *Lancet* **1990**, *336*, 526−529.

(2) Larder, B. A. Viral resistance and the selection of antiretroviral combinations. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* **1995**, *10 (Suppl. 1)*, S28−S33.

(3) (a) Schinazi, R. F. Competitive inhibitors of human immunodeficiency virus reverse transcriptase. *Perspect. Drug Discuss. Des.* **1993**, *1*, 151−180. (b) De Clercq, E. Toward improved anti-HIV chemotherapy: Therapeutic strategies for intervention with HIV infections. *J. Med. Chem.* **1995**, *38*, 2492−2517. (c) el Kouni, M. H. Trends in the design of nucleoside analogs as anti-HIV drugs. *Curr. Pharm. Des.* **2002**, *8*, 581−593.

(4) (a) De Clercq, E. Strategies in the design of antiviral drugs. *Nature Rev.* **2002**, *1*, 12−25. (b) Herdewijn, P. A. M. M. 5-Substituted-2′deoxyuridines as anti-HSV-1 agents: synthesis and structure activity relationship. *Antiviral Chem. Chemother.* **1994**, *5*, 131−146. (c) Guenther, S,; Balzarini, J.; De Clercq, E.; Nair, V. A Thymidine Phosphorylase-Stable Analogue of BVDU with Significant Antiviral Activity. *J. Med. Chem.* **2002**, *45*, 5426−5429.

(5) (a) De Clercq, E. Perspectives for the treatment of hepatitis B virus infections. *Int. J. Antimicrob. Chemother.* **1999**, *12*, 81−95 and references therein. (b) Gumina, G.; Song, G. Y.; Chu, C. K. Advances in antiviral agents for hepatitis B virus. *Antiviral Chem. Chemother.* **2001**, *12 (Suppl. 1)*, S93−S117. (c) Hong, J. H.; Choi, Y.; Chun, B. K.; Chu, C. K. Current status of anti-HBV chemotherapy. *Arch. Pharm. Res.* **1998**, *21*, 89−105.

(6) (a) Snoeck, R.; Andrei, G.; De Clercq, E. Current pharmacological approaches to the therapy of varicella zoster virus infection: a guide to treatment. *Drugs* **1999**, *57*, 187. (b) Wutzler, P. Antiviral therapy of herpes simplex and varicella-zoster virus infections. *InterVirology* **1997**, *40*, 343.

(7) (a) McGigan, D.; Pathirana, R. N. Snoeck, R. Andrei. G.; De Clercq, E. Balzarini, J.; Discovery of a new family of inhibitors of human cytomegalovirus (HCMV) based upon lipophilic alkyl furano pyrimidine dideoxy nucleosides: Action via a novel non-nucleosidic mechanism. *J. Med. Chem.* **2004**, *47*, 1847−1851. (b) Faulds, D.; Heel, R. C. Ganciclovir: A review of its antiviral activity, pharmacokinetic properties and theraperutic efficacy in cytomegalovirus infections. *Drugs* **1990**, *39*, 597−638. (c) Lea, A. P.; Bryson, H. M. Cidofovir. *Drugs* **1996**, *52*, 225−230.

(8) (a) Shimada, N.; Hasegawa, S.; Harada, T.; Tomisiwa, T.; Fujii, A.; Takita, T. Oxetanocin, a novel nucleoside from bacteria. *J. Antibiot.* **1986**, *39*, 1623−1625. (b) Hoshino, H.; Shimizu, N.; Shimada, N.; Takeuchi, T. Inhibition of infectivity of human immunodeficiency virus by oxetanocin. *J. Anibiot.* **1987**, *40*, 1077−1078.

(9) (a) Masuda, A.; Kitagawa, M.; Tanaka, A.; Saito, S.; Shimada, N.; Ikeda, R.; Hoshino, H.; Daikoku, T.; Nishiyama, Y. Synthesis and antiviral activity of adenosine deaminase-resistant oxetanocin A derivatives-2-halogeno-oxetanocin-A. *J. Antibiot.* **1993**, *46*, 1034−1037. (b) Branalt, J.; Kvarnstrom, I.; Classon, B.; Samuelsson, B. Synthesis of [4,5-bis(hydroxymethyl)-1,3-dioxolan-2-yl]nucleosides as potential inhibitors of HIV. *J. Org. Chem.* **1996**, *61*, 3599−3603. (c) Ichikawa, E.; Yamamura, S.; Kato, K. Synthesis of 2′,3′-dideoxy-3′-C-(hydroxymethyl)-4′-thiopentofuranosyl nucleosides as potential antiviral agent. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1113−1114.

(10) Alder, J.; Mitten, M.; Norbeck, D.; Marsh, K.; Kern E. R.; Clement, J. Efficacy of A- 73209, a potent orally active agent against VZV and HSV infections *Antiviral Res.* **1994**, *23*, 93.a

(11) Nagahata, T. Kitagawa, M.; Matsubara, K. Effect of oxetanocin-G, a novel nucleoside analog, on DNA-synthesis by hepatitis B virus virions. *Antimicrob. Agents Chemother.* **1994**, *38*, 707−712.

(12) Mansour, T. S.; Storer, R. Antiviral nucleosides. *Curr. Pharm. Des.* **1997**, *3*, 227−264.

(13) Parks, R. E., Jr.; Stoeckler, J. D.; Cambor, C.; Savarese, T. M.; Crabtree, G. W.; Chu, S.-H.; Purine nucleoside phosphorylase and 5′-methylthioadenosine phosphorylase: Targets of chemotherapy. In *Molecular Actions and Targets for Cancer Chemotherapeutic Agents*; Sartorelli, A. C., Lazo, J. S., Bertino, J. R., Eds.; Academic Press: New York, 1981; pp 229−252.

(14) (a) Nishizono, N.; Koike, N.; Yamagata, Y.; Fujii, S.; Matsuda, A. Nucleosides and nucleotides. 159. Synthesis of thietane nucleosides via the pummerer reaction as a key step. *Tetrahedron Lett.* **1996**, *42*, 7569−7572. (b) Ichikawa, E.; Yamamura, S.; Kato, K. Synthesis of enantiomerically pure 9-[(1′R,2′R,3′S)-bis(hydroxymethyl)thietan-1′-yl] adenine, 3′-thio analog of oxetanocin A. *Tetrahedron Lett.* **1999**, *40*, 7385−7388.

(15) (a) Adiwidjaja, G.; Brunck, J. S.; Polchow, K.; Voss, J. Thiosugars, Part 3 Preparation of methyl 2,3-di-*O*-mesyl-4,6-thioanhydro-α-D-galactopyranoside and methyl 2-*O*-mesyl-4,6-thioanhydro- α-D-gulopyranoside. *Carbohydr. Res.* **2000**, *325*, 237−244. (b) Payre, C.; Mourabit, A. A.; Merckle, L.; Ahond, A.; Poupat, C.; Potier, P. Semisynthesis of D-ring-modified taxoids: thietane derivatives from taxine B. *Tetrahedron Lett.* **2000**, *41*, 4891−4894. (c) Ohuchida, S.; Hamanaka, N.; Hayashi, M. Synthesis of thromboxane-A2 analog dl-(9,11),(11,12)-dideoxa-(9,11)-epithio-(11,12)-methylene-thromboxane-A2. *Tetrahedron Lett.* **1981**, *22*, 1349−1352. (d) Ohuchida, S.; Hamanaka, N.; Hayashi, M. A convenient route to (+)-(9,11)-epithia-(11,12)-methano-thromboxane-A2 from prostaglandin E2-methyl ester. *Tetrahedron Lett.* **1981**, *22*, 5301−5302.

(16) Ma, T.; Pai, S. B.; Zhu, Y. L.; Lin, J. S.; Shanmuganathan, K.; Du, J,; Wang, C.; Kim, H.; Newton, M. G.; Cheng, Y. C.; Chu, C. K. Structure−activity relationships of 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)pyrimidine nucleosides as anti-hepatitis B virus agents. *J. Med. Chem.* **1996**, *39*, 2835−2843.

(17) Brown, B.; Hegedus, L. S. Optically active cyclobutanone chemistry: Synthesis of (−)-cyclobut-A and (±)-3′-epi-cyclobut-A. *J. Org. Chem.* **1998**, *63*, 8012−8018.

(18) O'Neil, I. A.; Hamilton, K. M. A novel method for the coupling of nucleoside bases with tetramethylene sulfoxide. *Synlett* **1992**, 791−792.

(19) Ray, A. S.; Schinazi, R F.; Murakami, E.; Basavapathruni, A.; Shi, J.; Zorca, S. M.; Chu, C. K.; Anderson, K. S. Probing the mechanistic consequences of 5-fluorine substitution on cytidine nucleotide analogue incorporation by HIV-1 reverse transcriptase. *Antiviral Chem. Chemother.* **2003**, *14*, 115−125.

(20) (a) Schinazi, R. F.; McMillan, A.; Cannon, D.; Mathis, R.; Lloyd, R. M.; Peck, A.; Sommadossi, J P.; Stclair, M.; Wilson, J.; Furman, P. A.; Painter, G.; Choi, W. B.; Liotta, D. C. Selective inhibition of human immunodeficiency viruses by racemates and enantiomers of *cis*-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. *Antimicrob. Agents Chemother.* **1992**, *36*, 2423−2431. (b) Ma, T. W.; Pai, S. B.; Hu, Y. L.; Lin, J. S.; Shanmuganathan, K.; Du, J. F.; Wang, C. G.; Kim, H.; Newton, M. G.; Cheng, Y. C.; Chu, C. K. Structure−activity relationships of 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)pyrimidine nucleosides as anti-Hepatitis B virus agents. *J. Med. Chem.* **1996**, *39*, 2835−2843. (c) Lee, K.; Choi, Y.; Gllen, E.; Schlueter-Wirtz, S.; Schinazi, R. F.; Cheng, Y. C.; Chu, C. K. Synthesis and anti-HIV and anti-HBV activities of 2′-fluoro-2′,3′-unsaturated L-nucleosides. *J. Med. Chem.* **1999**, *42*, 1320. (d) Chong, Y.; Choo, H.; Chu, C. K. Effects of fluorine substitution of cytosine analogues on the binding affinity to HIV-1 reverse transcriptase, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 437−440.

(21) Lewis, W.; Day, B. J.; Copeland, W. C. Mitochondrial toxicity of NRTI antiviral drugs: An integrated cellular perspective. *Nat. Rev. Drug. Discovery* **2003**, *2*, 812−822.

(22) Galmarini, C. M.; Mackey, J. R.; Dumontet, C. Nucleoside analogues and nucleobases in cancer treatment. *Lancet Oncol.* **2002**, *3*, 415−424.

(23) Huang, H.; Chopra, R.; Verdine, G. L.; Harrison, S. C. Structure of a covalently trapped catalytic complex of HIV-1 reverse transcriptase: Implications for drug resistance. *Science* **1998**, *282*, 1669−1675.

(24) Chong, Y.; Chu, C. K. Understanding the unique mechanism of L-FMAU(clevudine) against hepatitis B virus: Molecular dynamics studies. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3459−3462.

(25) (a) Chong, Y.; Borroto-Esoda, K.; Furman, P. A.; Schinazi, R. F.; Chu, C. K. Molecular mechanism of DAPD/DXG against zidovudine- and lamivudine- drug resistant mutants: a molecular modeling approach. *Antiviral Chem. Chemother.* **2002**, *13*, 115−128. (b) Lee,

K.; Chu, C. K. Molecular modeling approach to understanding the mode of action of L-nucleosides as antiviral agents. *Antimicrob. Agents Chemother*. **2001**, *45*, 138−144.
(26) Sabini, E.; Ort, S.; Monnerjahn, C.; Konrad, M.; Lavie, A. Structure of human dCK suggests strategies to anticancer and antiviral therapy. *Nat. Struct. Biol.* **2003**, *10*, 513−519.
(27) Johansson N. G.; Eriksson S. Structure−activity relationships for phosphorylation of nucleoside analogs to monophosphates by nucleoside kinases, *Acta Biochem. Pol.* **1996**, *43*, 143−160.
(28) Belen'kii, S. M.; Schinazi, R. S. Multiple drug effect analysis with confidence interval. *Antiviral Res.* **1994**, *25*, 1−11.

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