Synthesis of [4,5-Bis(hydroxymethyl)-1,3-oxathiolan-2-yl]nucleosides as Potential Inhibitors of HIV via Stereospecific Base-Induced Rearrangement of a 2,3-Epoxy Thioacetate[1]

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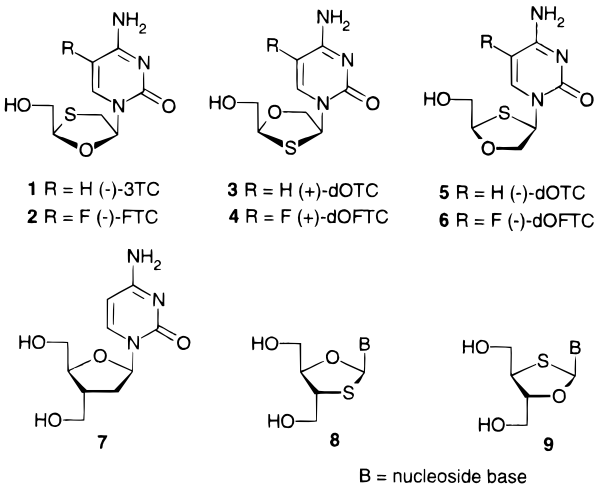
The synthesis of [4,5-bis(hydroxymethyl)-1,3-oxathiolan-2-yl]nucleosides is described. 2,3-Epoxy alcohol **10** was converted in one pot into thioacetate **11**. Treatment of **11** under mild alkaline conditions gave thiirane **12** with inversion of configuration at C-2. We also found that thioacetate **11** rearranges into thiirane **14** under mild acidic conditions. This rearrangement reaction was shown by independent synthesis to proceed with net retention of configuration at C-2. We have proposed a tentative mechanism which may explain the results obtained. Opening of thiiranes **12** and **14** followed by deprotection gave (2*R*,3*R*)-2-thiothreitol (**23**) and (2*S*,3*R*)-2-thioerythritol (**25**), respectively. Regioselective silylation of the primary hydroxyl groups of **23** followed by treatment with trimethyl orthoformate gave 2-methoxy-1,3-oxathiolanes **26** and **27**. Condensation with silylated bases followed by deprotection and separation of the anomers gave the oxathiolanyl-nucleosides. Compounds **29**−**31**, **34**, and **35** were found to be inactive when tested for inhibition of HIV-1 activity *in vitro*.

Introduction

In 1989, the first example of a new class of nucleosides was reported, in which the 3′-carbon atom was replaced by sulfur giving compounds with potent anti-HIV activity *in vitro*.[2] Further synthesis work[3] has resulted in the discovery of (−)-3TC (Lamivudine) (**1**), which currently is in advanced clinical trials for AIDS and HBV infections,[4] and its 5-fluoro analogue (−)-FTC (**2**).[5] Lamivudine and (−)-FTC are unusual in that they constitute the first examples of nucleosides where the L-configuration is more potent than the corresponding D-form. In addition, the L-nucleosides in these series were also generally found to be less toxic than their D-forms. Further investigations of this class of compounds have led to the structurally similar compounds **3**−**6** which have *in vitro* antiviral activity.[6]



As a part of our program[7] to prepare bioisosteres of **7**, a potent inhibitor of HIV activity *in vitro*,[8] we report the synthesis of oxathiolanylnucleosides **8** and **9**. In analogy with the corresponding 1,3-dioxolan-2-ylnucleosides,[9] compounds of this type have not been previously reported. Retrosynthetic analysis of **8** and **9** shows (2*R*,3*R*)-2-thiothreitol to be a common precursor, which to our knowledge has not been prepared previously in nonracemic form.[10] The principal methods for preparing chiral thiosugars with the sulfur atom attached to a secondary carbon involves displacement of a leaving group with a

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sulfur-containing nucleophile including opening of a terminal thiirane.[11] Indeed, the scope of these methods relies on naturally occurring carbohydrates as the source of chirality. The renewed interest in this area has resulted in *de novo* thiosugar synthesis using readily available chiral 2,3-epoxy alcohols as precursors.[12] However, opening of secondary 2,3-epoxy alcohols with sulfur nucleophiles usually proceed with low to moderate regioselectivity,[13] although high selectivity has been observed in the presence of titanium tetraisopropoxide[14] or by using triisopropoxytitanium thiobenzoate.[15] Highly regioselective openings of 2,3-epoxy alcohols with a sulfur nucleophile can be obtained using the C-1 hydroxyl group for intramolecular transfer of the sulfur nucleophile. This strategy has recently been successfully employed by Uenishi *et al.*[16] in the formation of a cyclic xanthate and by Gill *et al.*[17] with *in situ* formation and opening of a terminal thiiranium ion. During the preparation of this paper, Ko[18] reported on a new method for preparing chiral 2-thio 1,3-diols by rearrangement and subsequent reduction of cyclic thionocarbonates of 2,3-dihydroxy esters. We now report on a modified Payne-type rearrangement[19,20] involving a thiol group, as a new method for the regio- and stereospecifically introduction of sulfur into the 2-position of a 2,3-epoxy alcohol.

Results and Discussion

The hydroxyl group of chiral epoxy alcohol **10**[21] was substituted by thioacetate in a one-pot reaction using triphenylphosphine (PPh_3), diisopropyl azodicarboxylate (DIAD), and thioacetic acid in tetrahydrofuran to give **11** in 96% yield (Scheme 1) using a modified Mitsunobu procedure,[22] developed by Volante.[23] Treatment of **11** with sodium hydroxide (0.5 M) using standard conditions for the Payne rearrangement[20] failed to produce **12**, likely due to extensive polymerization of the terminal thiirane in the alkaline media.[24] Notably, high yields of **12** (89%) could be obtained using dilute solutions of ammonia in methanol (Table 1). No detectable amounts of starting material **11** or of the corresponding 2,3-epoxy thiol were observed. Compound **12** was unstable upon prolonged storage and was therefore used up immediately or acetylated to **13** for complete characterization. Surprisingly, we noted that **11**, during silica gel chromatography, slowly rearranged into thiirane **14** with net retention of configuration at C-2 (Scheme 2). This silica gel promoted rearrangement[25] of **11** was found to be a very clean reaction which could be optimized to give quantitative yield, either by stirring **11** in a slurry of silica gel in toluene or by adding compound **11** onto a column of silica gel in toluene and then allowing the solution to stand for 48 h after which the product (**14**) was eluted. Performing the rearrangement reaction under nonanhydrous conditions, i.e., stirring **11** in a slurry of silica gel in toluene without exclusion of moisture, gave a lower yield of **14** due to formation of a 1:1 mixture of two compounds, tentatively assigned as **15** and **16**, which

Scheme 1

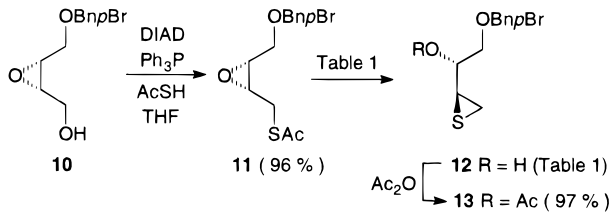
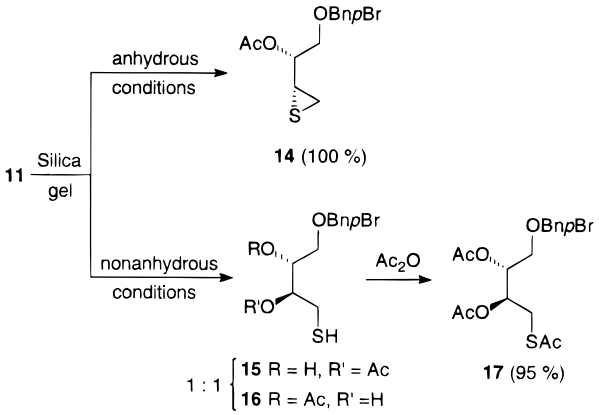


Table 1. Conversion of 2,3-Epoxy thioacetate 11 into Thiirane 12 under Alkaline Conditions

conditions[a]	time, h	yield[b] of **12**, %
0.5 M NaOH/THF 1:1	< 0.5	0
1 equiv of LiOH in THF/H_2O 3:1	< 0.5	0
1 equiv of K_2CO_3 in MeOH	1[c]	42
methanolic ammonia (sat.)	1[c]	49
methanolic ammonia (sat.)/ MeOH 1:10	3[c]	89

[a] The concentration of **11** was 50 mM. All reactions were carried out at 0 °C. [b] Referres to isolated yield. [c] The reaction was stopped when TLC showed complete disappearance of starting material **11**.

Scheme 2



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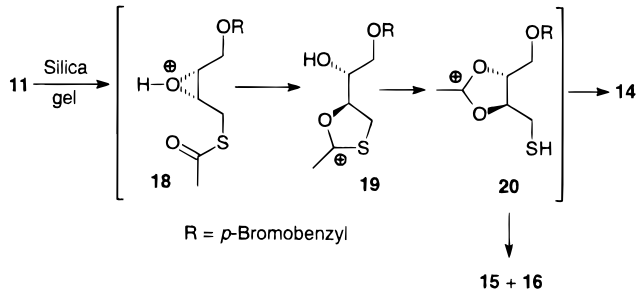
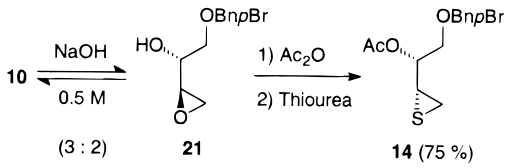
Scheme 3



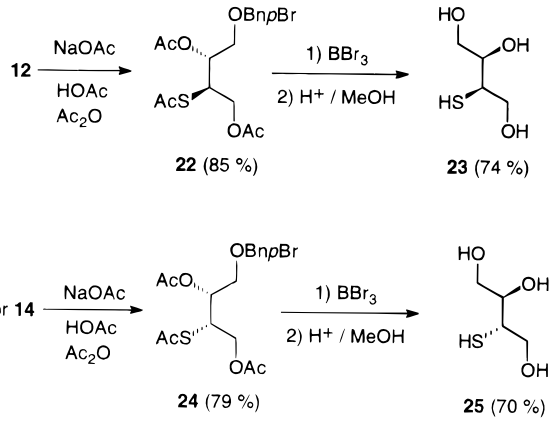
Scheme 4



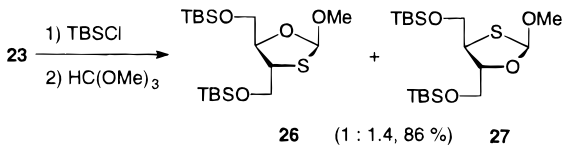
after acetylation gave **17** as a single diastereomer. The rearrangement of **11** could alternatively also be performed in glacial acetic acid−acetic anhydride (1:1) at 60 °C for 2 h to give **14** in an almost quantitative yield. A possible mechanism for the conversion of **11** into **14** under acidic conditions is depicted in Scheme 3. Opening of the activated epoxide **18** at C-2 by the thioacetate carbonyl oxygen gives 1,3-oxathiolan-2-ylium ion **19**, which rearranges into the more stable 1,3-dioxolan-2-ylium ion **20**.[26] A second inversion at C-2 is effected by nucleophilic substitution involving the thiol group at C-1 to give **14** with net retention of configuration at C-2. As in the case of the base-promoted rearrangement, the driving force of this rearrangement is likely due to the higher stability of thiiranes as compared to oxiranes.[27] Under nonanhydrous conditions, intermediate **20** will trap water and give a 1:1 mixture of **15** and **16**. The stereochemistry and optical purity of thiirane **14** was determined by independent synthesis (Scheme 4). Thus, Payne rearrangement[20] of **10** using sodium hydroxide (0.5 M) in tetrahydrofuran−water gave a 3:2 equilibrium mixture of **10** and **21** from which compound **21** was isolated by column chromatography. Acetylation of the hydroxyl group followed by conversion of the oxirane into the corresponding thiirane using thiourea[28] with inversion of configuration at C-2 gave **14** in 75% yield from **21**, in all aspects identical to the product obtained by the silica gel promoted rearrangement (*vide supra*).

Opening of thiirane **12** with sodium acetate in glacial acetic acid−acetic anhydride (1:1) gave **22** in 85% yield (Scheme 5). Deblocking of the *p*-bromobenzyl group of **22** using boron tribromide at −80 °C followed by deacetylation under acidic conditions to avoid thiirane formation and polymerization[24,29] gave (2*R*,3*R*)-2-thiothreitol (**23**) in 74% yield from **22**. Using the same methodology, the *erythro* derivative **24** was obtained from thiirane **14** in 79% yield. Deprotection gave (2*S*,3*R*)-2-thioerythritol (**25**) in 70% yield. Interestingly, starting from 2,3-epoxy thioacetate **11**, the rearrangement−opening procedure via thiirane **14** to **24** could be performed *in situ* as a one-pot reaction giving the same yield. Regioselective sily-

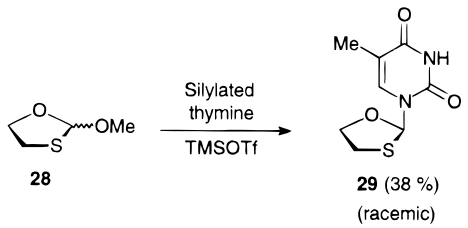
Scheme 5



Scheme 6



Scheme 7



lation of the primary hydroxyl groups of (2*R*,3*R*)-2-thiothreitol (**23**) using *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide, followed by treatment with trimethyl orthoformate and a catalytic amount of camphorsulfonic acid, gave a separable mixture of 2-methoxy-1,3-oxathiolanes **26** and **27**[30] in 86% total yield (Scheme 6).

For the synthesis of 1,3-oxathiolan-2-ylnucleosides, 2-methoxy-1,3-oxathiolane (**28**) was used as a model compound (Scheme 7). Condensation of **28** with silylated thymine and trimethylsilyl triflate under Vorbrüggen conditions[31] gave racemic **29** in 38% yield. No product arising from opening of the oxathiolane ring at C-4 or C-5 was detected. This reactivity is in sharp contrast to the corresponding dioxolanylnucleoside series.[9] Condensation of the diastereomeric mixture **26** and **27** with silylated thymine and trimethylsilyl triflate under Vorbrüggen conditions gave mainly dimeric products.[32] In dilute solutions, dimers were still formed, but the desired oxathiolanylnucleosides could be isolated in moderate yields. Desilylation followed by separation of the ano-

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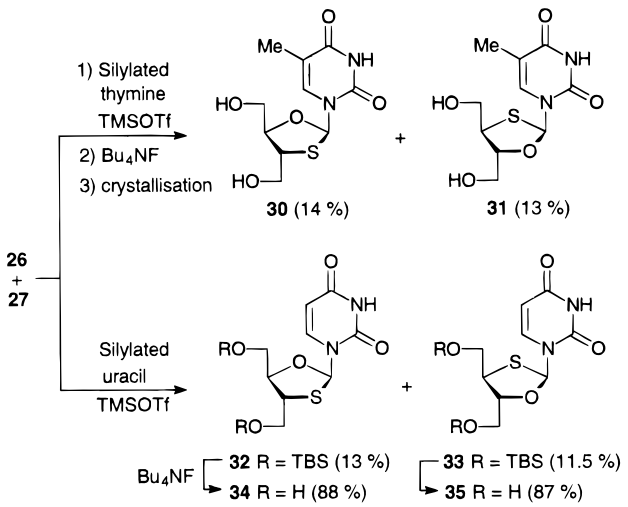
(30) Assignments of the 2(*S*,*R*) configuration of compounds **26** and **27** were based on ^{1}H NOE difference spectroscopy. In both **26** and **27**, H-4 and H-5 were easily distinguished by a large difference in chemical shift (0.6−0.7 ppm). Because of the higher electronegativity of oxygen compared to sulfur, it is assumed that H-5 appears at a higher chemical shift than H-4. Irradiation of H-5 in **26** gave enhancement of H-2 (1.3%) whereas irradiation of H-5 in **27** gave enhancement of the methoxy group (1.5%).

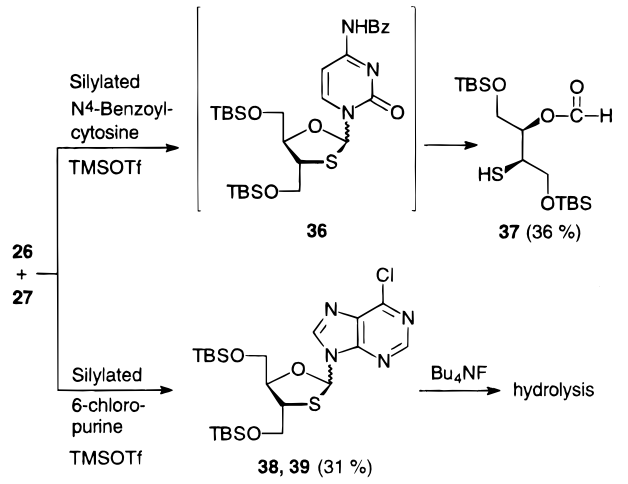
(31) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.

(32) For the acid-catalyzed formation of dimers from 2-methoxy-1,3-oxathiolane, see: Tanimoto, S.; Miyake, T.; Okano, M. *Bull. Inst. Chem. Res., Kyoto Univ.* **1977**, *55*, 276.

Scheme 8



Scheme 9



mers by fractional crystallization gave **30** and **31** in 14% and 13% yields, respectively (Scheme 8). The uracil derivatives **32** and **33** were prepared from silylated uracil in a similar way in 13% and 11.5% yields, respectively, after separation by column chromatography. Desilylation gave **34** and **35** in 88% and 87% yields, respectively. Condensation of the oxathiolanes **26** and **27** with silylated N^4-benzoylcytosine gave formate ester **37** in 36% yield but no detectable amounts of the desired nucleosides (Scheme 9). Interestingly, compound **37** was not formed during synthesis of the thymine or uracil derivatives, nor was it formed by treatment of **26** or **27** with trimethylsilyl triflate. It is likely that nucleoside **36** is formed in the coupling reaction but hydrolyzes spontaneously into formate ester **37** during quenching of the reaction. Condensation of the diastereomeric mixture **26** and **27** with silylated 6-chloropurine gave an unseparable mixture (1:1) of **38** and **39** in 31% total yield, which hydrolyzed upon desilylation.

Compounds **29**−**31**, **34**, and **35** were tested for inhibition of HIV-multiplication in a XTT assay in M4 cells.[33] All compounds were found to be inactive in the assay.

Structure Assignments

Assignments of the 2(*S*,*R*) configuration of uracil derivatives **32**−**35** were based on ^{1}H NOE difference spectroscopy which was performed on **40** and **41**, obtained

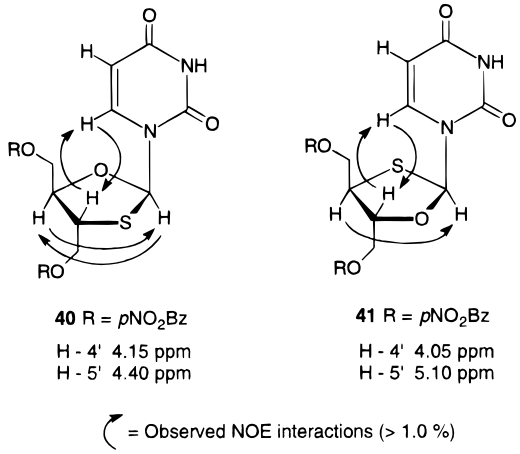


Figure 1.

from **34** and **35**, respectively, by *p*-nitrobenzoylation of the hydroxyl groups (Figure 1). In both **40** and **41**, H-4′ and H-5′ were well resolved and easily distinguished by a large difference in chemical shift. It is well-known that protons syn to the base are more deshielded than those which are anti.[34] The H-5′ proton of **40** appeared at a considerably higher field than that of **41**. A smaller reverse effect was observed for the H-4′ proton. These characteristic ^{1}H NMR features, which were also found in compounds **32**−**35**, were used to assign the 2(*S*,*R*) configuration of thymine derivatives **30** and **31**. Anomer **30** which had a downfield shift for H-5′ was assigned as (2*S*) and **31** assigned as (2*R*).

Experimental Section

General methods were the same as those previously described.[9]

(2*R*,3*R*)-1-*S*-Acetyl-4-[(*p*-bromobenzyl)oxy]-2,3-epoxy-1-butanethiol (11). Diisopropyl azodicarboxylate (DIAD) (13.3 g, 65.8 mmol) was added to an efficiently stirred solution of triphenylphosphine (21.6 g, 82.4 mmol) in tetrahydrofuran (180 mL) at 0 °C. After the solution was stirred at 0 °C for 30 min, a white precipitate formed. Compound **10**[21] (9.00 g, 32.9 mmol) and thioacetic acid (5.00 g, 65.8 mmol) in tetrahydrofuran (75 mL) were slowly added over 10 min, and the mixture was stirred for an additional 2 h at 0 °C. During this time the precipitate was dissolved and a clear yellow solution was obtained. The solvent was evaporated, and the solid residue was dissolved in hot toluene and set in a freezer overnight to precipitate most of the triphenylphosphine oxide formed. The solids were filtered off and washed with cold toluene. The solvent was evaporated, and the crude product was purified by flash column chromatography (toluene/ethyl acetate 20:1) to give **11** (10.4 g, 96%) as a colorless oil. It was important to make sure that the product was eluted as rapidly as possible to minimize the exposure to silica gel. **11**: $[\alpha]^{22}_D$ +8.5° (*c* 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.07 (2d, J = 5.5 and 6.9 Hz, 2H), 3.13 (ddd, J = 6.9, 5.5, 4.1 Hz, 1H), 3.25 (dt, J = 6.2, 4.1 Hz, 1H), 3.58 (dd, J = 11.3, 6.2 Hz, 1H), 3.76 (dd, J = 11.3, 4.1 Hz, 1H), 4.54 (2d, J = 12.0 Hz, 2H), 7.2−7.5 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 27.6, 30.5, 54.4, 56.0, 68.0, 72.5, 121.7, 129.4, 131.6, 136.8, 194.6. Anal. Calcd for $C_{13}H_{15}O_3SBr$: C, 47.14; H, 4.56; S, 9.68. Found: C, 47.05; H, 4.62; S, 9.46.

(2*R*,3*S*)-2-*O*-Acetyl-1-[(*p*-bromobenzyl)oxy]-3,4-epithio-2-butanol (13). To a solution of **11** (4.60 g, 13.9 mmol) in methanol (120 mL) was added methanolic ammonia (12 mL,

(33) Vial, J. M.; Johansson, N. G.; Wrang, L. Chattopadhyaya, J. *Antiviral Chem. Chemother.* **1990**, *1*, 183.

(34) See, for example: Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1988**, *53*, 4780.

saturated) at 0 °C, and the solution was stirred at this temperature for 3 h. The mixture was diluted with dichloromethane, washed with water, dried, filtered, and evaporated. The residue was purified by column chromatography (toluene/ethyl acetate 9:1) to give (2*R*,3*S*)-1-[(*p*-bromobenzyl)oxy]-3,4-epithio-2-butanol **12** (3.57 g, 89%) as a colorless oil. **12**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.20 (d, J = 8.0 Hz, 1H), 2.40 (dd, J = 5.6, 0.8 Hz, 1H), 2.44 (dd, J = 6.5, 0.8 Hz, 1H), 3.26 (ddd, J = 6.5, 5.6, 4.0 Hz, 1H), 3.53 (dd, J = 9.5, 5.8 Hz, 1H), 3.61 (dd, J = 9.5, 5.6 Hz, 1H), 3.85 (ddd, J = 8.0, 5.7, 4.0 Hz, 1H), 4.57 (s, 2H), 7.2−7.5 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.2, 38.1, 69.6, 72.8, 74.1, 121.7, 129.3, 131.6, 136.9. Compound **12** polymerized easily, which precluded further characterization, and was consequently used immediately in the next reactions. A small sample of **12** (18 mg, 0.0623 mmol) was treated with acetic anhydride (0.5 mL) in pyridine (1 mL) at room temperature for 30 min. The solvent was evaporated and coevaporated with added toluene, and the residue was purified by column chromatography (toluene/ethyl acetate 20:1) to give **13** (20 mg, 97%) as a colorless syrup. **13**: $[\alpha]^{22}_D$ −3.5° (*c* 2.2, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.30 (dd, J = 5.4, 1.3 Hz, 1H), 2.52 (dd, J = 6.5, 1.3 Hz, 1H), 3.18 (ddd, J = 7.2, 6.5, 5.4 Hz, 1H), 3.65 (d, J = 5.1 Hz, 2H), 4.50 (2d, J = 12.3 Hz, 2H), 4.81 (dt, J = 7.2, 5.1 Hz, 1H), 7.15−7.5 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.0, 22.2, 33.9, 70.9, 72.6, 74.9, 121.7, 129.2, 131.6, 136.8, 170.0. Anal. Calcd for $C_{13}H_{15}O_3SBr$: C, 47.14; H, 4.56; S, 9.68. Found: C, 47.01; H, 4.53; S, 9.50.

(2*R*,3*R*)-2-*O*-Acetyl-1-[(*p*-bromobenzyl)oxy]-3,4-epithio-2-butanol (14). Compound **11** (792 mg, 2.39 mmol) in toluene was allowed to stand in a column of silica gel for several days, after which it was eluted (toluene/ethyl acetate 9:1). Evaporation of the solvent gave a colorless oil of **14** (788 mg, 100%) as a single diastereomer. Alternatively, compound **11** (92 mg, 0.278 mmol) in glacial acetic acid/acetic anhydride (1:1, 2 mL) was stirred at 60 °C for 2 h. The solvent was evaporated and coevaporated with added toluene, and the residue was purified by column chromatography (toluene/ethyl acetate 20:1) to give **14** (90 mg, 98%) in all aspects identical with that obtained above. **14**: $[\alpha]^{22}_D$ +39.6° (*c* 0.7, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.43 (dd, J = 5.2, 1.1 Hz, 1H), 2.50 (dd, J = 6.2, 1.1 Hz, 1H), 3.12 (ddd, J = 8.2, 6.2, 5.2 Hz, 1H), 3.75 (2d, J = 3.8 and 4.7 Hz, 2H), 4.53 (2d, J = 12.3 Hz, 2H), 4.62 (dt, J = 8.2, 4.1 Hz, 1H), 7.2−7.5 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.1, 23.8, 32.1, 71.1, 72.5, 76.3, 121.6, 129.2, 131.6, 136.9, 170.2. Anal. Calcd for $C_{13}H_{15}O_3SBr$: C, 47.14; H, 4.56; S, 9.68. Found: C, 47.25; H, 4.49; S, 9.44.

(2*S*,3*R*)-1-*S*,2,3-*O*-Triacetyl-4-(*p*-bromobenzyl)-1-thiothreitol (17). Compound **11** (363 mg, 1.10 mmol) in a slurry of silica gel in wet toluene was stirred at room temperature for 5 days without exclusion of moisture. The silica gel was filtered off, and the solvent was evaporated. The residue was purified by column chromatography (toluene/ethyl acetate 5:1) to give compound **14** and a mixture (1:1) of **15** and **16** (264 mg, 69%) that could not be separated by column chromatography. **15** and **16**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.46 (t, J = 8.8 Hz, 1H), 1.55 (t, J = 8.7 Hz, 1H), 2. 05, 2.09 (2s, 6H), 2.50−2.95 (m, 6H), 3.46 (dd, J = 9.6, 6.1 Hz, 1H), 3.50 (dd, J = 9.6, 4.7 Hz, 1H), 3.63 (dd, J = 10.5, 5.3 Hz, 1H), 3.69 (dd, J = 10.5, 5.5 Hz, 1H), 3.87 (m, 1H), 4.11 (m, 1H), 4.45 (m, 4H), 4.94 (dt, J = 3.1, 6.6 Hz, 1H), 5.13 (dt, J = 3.6, 5.1 Hz, 1H), 7.1−7.5 (m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.0, 21.9, 24.5, 27.9, 69.3, 71.4, 72.2, 72.5, 72.6, 72.8, 74.9, 121.8, 129.3, 129.4, 131.6, 136.5, 136.6, 170.6. A small sample of the mixture of **15** and **16** (45 mg, 0.129 mmol) was treated with acetic anhydride (1 mL) in pyridine (1 mL) for 3 h. The solvent was evaporated, and the residue was purified by column chromatography (toluene/ethyl acetate 9:1) to give syrupy **17** (53 mg, 95%) as a single diastereomer. **17**: $[\alpha]^{22}_D$ +19° (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.03, 2.10 (2s, 6H), 2.33 (s, 3H), 2.90 (dd, J = 14.0, 6.8 Hz, 1H), 3.31 (dd, J = 14.0, 5.2 Hz, 1H), 3.50 (dd, J = 10.3, 5.0 Hz, 1H), 3.56 (dd, J = 10.3, 5.3 Hz, 1H), 4.44 (s, 2H), 5.1−5.2 (m, 2H), 7.1−7.5 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.7, 20.9, 29.2, 30.4, 68.1, 70.2, 71.0, 72.5, 121.7, 129.3, 131.6, 136.6, 169.9, 170.2, 194.3. Anal. Calcd for $C_{17}H_{21}O_6SBr$: C, 47.12; H, 4.88; S, 7.40. Found: C, 47.05; H, 4.85; S, 7.23.

(2*R*,3*R*)-1-[(*p*-Bromobenzyl)oxy]-3,4-epoxy-2-butanol (21). To a solution of **10** (250 mg, 0.916 mmol) in tetrahydrofuran (5 mL) was added sodium hydroxide (5 mL, 0.5 M), and the resulting mixture was stirred at room temperature for 3 h. Ammonium sulfate was added, and the mixture was extracted with diethyl ether. The organic phase was dried, filtered, and concentrated to give a mixture of starting material **10** and **21** (3:2) which was separated by column chromatography (toluene/ethyl acetate 1:1) to give **21** (96 mg, 38%) as a colorless oil. **21**: $[\alpha]^{22}_D$ −9.7° (*c* 0.7, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.30 (d, J = 6.2 Hz, 1H), 2.78 (dd, J = 5.0, 2.9 Hz, 1H), 2.81 (t, J = 5.0 Hz, 1H), 3.13 (dt, J = 2.9, 3.9 Hz, 1H), 3.59 (dd, J = 9.6, 6.1 Hz, 1H), 3.63 (dd, J = 9.6, 4.8 Hz, 1H), 3.79 (m, 1H), 4.53 (s, 2H), 7.15−7.55 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 44.0, 52.7, 69.6, 71.9, 72.7, 121.7, 129.3, 131.6, 136.8. Anal. Calcd for $C_{11}H_{13}O_3Br$: C, 48.37; H, 4.80. Found: C, 48.12; H, 4.80.

Preparation of (2*R*,3*R*)-2-*O*-Acetyl-1-[(*p*-bromobenzyl)-oxy]-3,4-epithio-2-butanol (14) from (2*R*,3*R*)-1-[(*p*-Bromobenzyl)oxy]-3,4-epoxy-2-butanol (21). To a solution of compound **21** (43 mg, 0.157 mmol) in pyridine (1 mL) was added acetic anhydride (1 mL). After 30 min at room temperature, the solvent was evaporated and coevaporated with added toluene. The residue was dissolved in dichloromethane, washed with hydrogen chloride (1 M) and saturated aqueous sodium hydrogen carbonate, dried, filtered, and concentrated. The crude product was dissolved in methanol, thiourea was added, and the mixture was stirred at room temperature for 3 h. The solvent was evaporated, and the residue was suspended in dichloromethane and washed with water. The organic phase was dried, filtered, concentrated, and purified by column chromatography (toluene/ethyl acetate 20:1) to give **14** (39 mg, 75%), in all aspects identical with that obtained above.

(2*R*,3*R*)-1,3-*O*,2-*S*-Triacetyl-4-(*p*-bromobenzyl)-2-thiothreitol (22). To a solution of **12** (4.70 g, 16.3 mmol) in acetic acid (25 mL) and acetic anhydride (25 mL) was added sodium acetate (6.70 g, 81.3 mmol), and the reaction mixture was heated at 60 °C for 1 h to give the acetylated compound **13**. The reaction was further heated at 130 °C for 48 h and allowed to attain room temperature. Toluene was added, the solids were filtered off, and the filtrate was evaporated. The residue was purified by column chromatography (toluene/ethyl acetate 9:1) to give **22** (6.04 g, 85%) as a colorless syrup. **22**: $[\alpha]^{22}_D$ −4.4° (*c* 0.85, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.05, 2.06 (2s, 6H), 2.36 (s, 3H), 3.51 (dd, J = 10.0, 6.0 Hz, 1H), 3.59 (dd, J = 10.0, 6.1 Hz, 1H), 4.06 (dd, J = 9.4, 4.3 Hz, 1H), 4.18 (ddd, J = 7.6, 4.3, 2.8 Hz, 1H), 4.24 (dd, J = 9.4, 7.6 Hz, 1H), 4.46 (s, 2H), 5.45 (dt, J = 2.8, 6.0 Hz, 1H), 7.1−7.5 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.8, 30.6, 43.3, 63.2, 66.9, 69.8, 72.5, 121.7, 129.4, 131.6, 136.7, 169.9, 170.5, 193.5. Anal. Calcd for $C_{17}H_{21}O_6SBr$: C, 47.12; H, 4.88; S, 7.40. Found: C, 47.21; H, 4.85; S, 7.26.

(2*R*,3*R*)-2-Thiothreitol (23). To a solution of **22** (490 mg, 1.13 mmol) in dichloromethane (10 mL) was added BBr_3 (0.13 mL, 1.36 mmol) at −80 °C. The mixture was slowly allowed to warm to −20 °C (2 h) and stirred at this temperature for 30 min. The mixture was again cooled to −80 °C and quenched by the dropwise addition of methanol/pyridine (1:1, 8 mL). The mixture was allowed to attain room temperature, and the solvent was evaporated. The residue was suspended in toluene, and the solids were filtered off and were thoroughly washed with toluene. Evaporation of the solvent gave an oily residue which was applied onto a short column of silica gel and eluted with toluene/ethyl acetate (1:1). The appropriate fractions were combined, evaporated, and treated with 5% hydrogen chloride in methanol for 14 h. Evaporation of the solvent, coevaporation with added toluene, and purification of the residue by column chromatography (ethyl acetate/methanol 5:1) gave **23** (115 mg, 74%) as a colorless oil. **23**: $[\alpha]^{22}_D$ −38.7° (*c* 2.7, MeOH); ^{1}H NMR (250 MHz, MeOH-d_4) δ 2.95−3.05 (m, 1H), 3.60−3.80 (m, 4H), 3.98 (dt, J = 2.5, 6.3 Hz, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 45.1, 64.8, 66.1, 71.4. Anal.

Calcd for $C_4H_{10}O_3S$: C, 34.77; H, 7.29; S, 23.20. Found: C, 34.90; H, 7.33; S, 22.96.

(2*S*,3*R*)-1,3-*O*,2-*S*-Triacetyl-4-(*p*-bromobenzyl)-2-thioerythritol (24). To a solution of **14** (2.05 g, 6.19 mmol) in acetic acid (10 mL) and acetic anhydride (10 mL) was added sodium acetate (2.50 g, 30.5 mmol), and the reaction mixture was heated at 130 °C for 48 h and then allowed to attain room temperature. Toluene was added, the solids were filtered off, and the filtrate was evaporated. The residue was purified by column chromatography (toluene/ethyl acetate 9:1) to give **24** (2.13 g, 79%) as a colorless syrup. **24**: $[\alpha]^{22}_D$ +19° (*c* 1.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.02, 2.05 (2s, 6H), 2.33 (s, 3H), 3.62 (d, J = 4.9 Hz, 2H), 4.1−4.35 (m, 3H), 4.40 (d, J = 12.2 Hz, 1H), 4.50 (d, J = 12.2 Hz, 1H), 5.26 (q, J = 5.0 Hz, 1H), 7.1−7.5 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.7, 20.9, 30.6, 42.9, 63.0, 69.1, 70.9, 72.5, 121.7, 129.3, 131.5, 136.6, 169.9, 170.5, 193.4. Anal. Calcd for $C_{17}H_{21}O_6SBr$: C, 47.12; H, 4.88; S, 7.40. Found: C, 47.00; H, 4.83; S, 7.30.

(2*S*,3*R*)-2-Thioerythritol (25). Compound **25** was prepared from **24** (77 mg, 0.177 mmol) following the same methodology as described for the preparation of 2-thiothreitol (**23**) to give **25** (17 mg, 70%) as a colorless oil. **25**: $[\alpha]^{22}_D$ +5.9° (*c* 1.7, MeOH); ^{1}H NMR (250 MHz, MeOH-d_4) δ 2.96 (q, J = 5.5 Hz, 1H), 3.60−3.90 (m, 5H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 44.8, 65.1, 65.4, 75.6. Anal. Calcd for $C_4H_{10}O_3S$: C, 34.77; H, 7.29; S, 23.20. Found: C, 34.86; H, 7.15; S, 23.12.

(2*R*,4*R*,5*R*)- and (2*S*,4*R*,5*R*)-2-Methoxy-4,5-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-oxathiolanes (26 and 27). A solution of **23** (192 mg, 1.39 mmol), *tert*-butyldimethylsilyl chloride (460 mg, 3.06 mmol), and imidazole (245 mg, 3.61 mmol) in dimethyl formamide (2 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with toluene and washed with saturated sodium hydrogen carbonate. The organic phase was dried, filtered, and concentrated. The residue was dissolved in dichloromethane/trimethyl orthoformate (1:1, 20 mL), and camphorsulfonic acid (30 mg) was added. After being stirred at room temperature for 1 h, the mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate. The organic phase was dried, filtered, and concentrated to give a mixture of **26** and **27** which was separated by column chromatography (toluene/ethyl acetate 50:1) to give **26** and **27** (488 mg, 86%) in a ratio of 1:1.4 as colorless oils. **26**: $[\alpha]^{22}_D$ +10.5° (*c* 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.053, 0.070 (2s, 12 H), 0.88, 0.89 (2s, 18H), 3.37 (s, 3H), 3.5−3.6 (2d, J = 8.1 and 6.0 Hz, 2H), 3.67 (ddd, J = 8.5, 5.7, 2.8 Hz, 1H), 3.72 (dd, J = 10.1, 5.3 Hz, 1H), 3.85 (dd, J = 10.1, 7.6 Hz, 1H), 4.33 (ddd, J = 7.6, 5.3, 2.8 Hz, 1H), 6.16 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.3, 18.2, 25.8, 52.1, 54.6, 63.7, 65.2, 85.2, 110.9. Anal. Calcd for $C_{18}H_{40}O_4SSi_2$: C, 58,89; H, 9.86; S, 13.74. Found: C, 59.01; H, 9.97; S, 13.46. **27**: $[\alpha]^{22}_D$ −0.7° (*c* 2.7, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.052, 0.063 (2s, 12 H), 0.88, 0.90 (2s, 18H), 3.36 (s, 3H), 3.54 (dt, J = 8.2, 6.3 Hz, 1H), 3.7−3.9 (m, 4H), 4.25 (dt, J = 6.3, 5.1 Hz, 1H), 6.11 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.3, 18.3, 25.9, 51.2, 54.4, 63.8, 66.0, 84.9, 110.4. Anal. Calcd for $C_{18}H_{40}O_4SSi_2$: C, 58,89; H, 9.86; S, 13.74. Found: C, 58.96; H, 10.07; S, 13.52.

General Procedure for the Silylation of Nucleoside Bases. Stock solutions of silylated bases (1.0 M in dichloromethane) were prepared as described previously.[9]

***rac*-1-(1,3-Oxathiolan-2-yl)thymine (29).** To a stirred solution of racemic 2-methoxy-1,3-oxathiolane **28**[32] (166 mg, 1.38 mmol) in dichloromethane (90 mL) were added silylated thymine (1.7 mL of a 1.0 M solution in dichloromethane) and trimethylsilyl triflate (0.28 mL, 1.52 mmol). The resulting solution was stirred at room temperature overnight. The reaction was neutralized by the addition of pyridine, poured onto a column of silica gel, and eluted with dichloromethane/ethyl acetate (1:1). Further purification by column chromatography (toluene/ethyl acetate 1:1) gave racemic **29** (113 mg, 38%) as a colorless solid. **29**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.95 (d, J = 0.8 Hz, 3H), 3.18 (ddd, J = 10.3, 5.6, 3.1 Hz, 1H), 3.32 (ddd, J = 10.3, 9.0, 5.7 Hz, 1H), 3.99 (dt, J = 5.6, 9.2 Hz, 1H), 4.52 (ddd, J = 9.3, 5.7, 3.1 Hz, 1H), 7.31 (s, 1H), 7.34 (d, J = 0.8 Hz, 1H), 8.9 (bs, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.6, 33.1, 71.5, 90.4, 111.9, 135.0, 150.4, 163.7. Anal. Calcd for $C_8H_{10}O_3SN_2$: C, 44.85; H, 4.71; S, 14.91; N, 13.08. Found: C, 44.78; H, 4.58; S, 14.91; N, 12.99.

1-[(4*R*,5*R*)-4,5-Bis(hydroxymethyl)-1,3-oxathiolan-2-yl]thymines (30 and 31). To a stirred solution of compounds **26** and **27** (240 mg, 0.588 mmol) in dichloromethane (40 mL) were added silylated thymine (0.35 mL of a 1.0 M solution in dichloromethane) and trimethylsilyl triflate (0.12 mL, 0.647 mmol). The resulting solution was stirred at room temperature overnight, neutralized by the addition of pyridine, poured onto a column of silica gel, and eluted with ethyl acetate to give an anomeric mixture (1:1) of protected **30** and **31** which could not be separated by column chromatography: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.054, 0.067 (2s, 24 H), 0.90 (s, 36 H), 1.94, 1.97 (2d, J = 0.9 Hz, 6H), 3.65−4.05 (m, 11H), 4.53 (dt, J = 2.4, 5.1 Hz, 1H), 7.31, 7.34 (2s, 2H), 7.46, 7.49 (2d, J = 0.9 Hz, 2H). The anomeric mixture was dissolved in tetrahydrofuran (5 mL), tetrabutylammonium fluoride (1.0 mL of a 0.5 M solution in tetrahydrofuran) was added, and the resulting solution was stirred at room temperature for 1 h. The solvent was evaporated, and the crude product was filtered through a short column of silica gel to give a 1:1 mixture of **30** and **31**. Fractional crystallization from methanol gave **30** (22.5 mg, 14%) as white crystals and **31** (21 mg, 13%) as a colorless syrup. **30**: $[\alpha]^{22}_D$ +8.3° (*c* 0.3, MeOH); ^{1}H NMR (250 MHz, MeOH-d_4) δ 1.92 (d, J = 0.9 Hz, 3H), 3.7−3.85 (m, 3H), 3.90−3.95 (m, 2H), 4.02 (ddd, J = 8.0, 4.3, 3.1 Hz, 1H), 7.3 (s, 1H), 7.77 (d, J = 0.9 Hz, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 12.4, 52.8, 62.4, 63.9, 87.1, 89.8, 112.5, 137.4, 151.8, 166.1. Anal. Calcd for $C_{10}H_{14}O_5SN_2$: C, 43.79; H, 5.15; N, 10.22; S, 11.67. Found: C, 43.60; H, 4.91; N, 9.93; S, 11.36. **31**: $[\alpha]^{22}_D$ −5.0° (*c* 0.2, MeOH); ^{1}H NMR (250 MHz, MeOH-d_4) δ 1.91 (d, J = 0.9 Hz, 3H), 3.65−3.85 (m, 5H), 4.54 (dt, J = 4.2, 5.2 Hz, 1H), 7.26 (s, 1H), 8.01 (d, J = 0.9 Hz, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 12.5, 53.2, 62.9, 64.3, 86.8, 91.4, 111.9, 137.2, 152.2, 166.2. Anal. Calcd for $C_{10}H_{14}O_5SN_2$: C, 43.79; H, 5.15; N, 10.22; S, 11.67. Found: C, 43.80; H, 5.17; N, 9.81; S, 11.52.

1-[(4*R*,5*R*)-4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-oxathiolan-2-yl]uracils (32 and 33). To a stirred solution of compounds **26** and **27** (290 mg, 0.711 mmol) in dichloromethane (50 mL) were added silylated uracil (1.4 mL of a 0.6 M solution in dichloromethane) and trimethylsilyl triflate (0.14 mL, 0.782 mmol). The resulting solution was stirred at room temperature overnight, neutralized by the addition of pyridine, poured onto a column of silica gel, and eluted with toluene/ethyl acetate (1:1). Further purification by column chromatography (toluene/ethyl acetate 3:1) gave **32** (45 mg, 13%) and **33** (40 mg, 11.5%). **32**: $[\alpha]^{22}_D$ +38° (*c* 0.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.078 (s, 12H), 0.90, 0.91 (s, 18H), 3.75−4.05 (m, 6H), 5.79 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 8.95 (bs, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.45, 18.3, 25.8, 50.9, 62.7, 64.6, 86.1, 89.0, 103.2, 139.9, 149.8, 162.8. Anal. Calcd for $C_{21}H_{40}O_5SN_2Si_2$: C, 51.62; H, 8.26; S, 6.54; N, 5.74. Found: C, 51.39; H, 8.10; S, 6.73; N, 5.88. **33**: $[\alpha]^{22}_D$ −27° (*c* 0.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.082, 0.092 (2s, 12H), 0.91 (s, 18H), 3.65−3.85 (m, 5H), 4.50 (dt, J = 3.2, 5.0 Hz, 1H), 5.79 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 8.2 (bs, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.45, −5.35, 18.2, 18.3, 25.8, 52.1, 63.5, 64.7, 84.5, 90.5, 102.9, 139.7, 149.9, 162.7. Anal. Calcd for $C_{21}H_{40}O_5SN_2Si_2$: C, 51.62; H, 8.26; S, 6.54; N, 5.74. Found: C, 51.37; H, 8.11; S, 6.62; N, 5.75.

1-[(2*R*,4*R*,5*R*)-4,5-Bis(hydroxymethyl)-1,3-oxathiolan-2-yl]uracil (34). To a solution of **32** (30 mg, 0.0614 mmol) in tetrahydrofuran (3 mL) was added tetrabutylammonium fluoride (0.60 mL of a 0.5 M solution in tetrahydrofuran). The resulting solution was stirred at room temperature for 1 h. The solvent was evaporated, and the residue was purified by column chromatography (ethyl acetate/methanol 5:1) to give **34** (14 mg, 88%) as an amorphous solid. **34**: $[\alpha]^{22}_D$ +89° (*c* 0.7, MeOH); ^{1}H NMR (250 MHz, MeOH-d_4) δ 3.71 (dd, J = 11.2, 6.1 Hz, 1H), 3.75−3.95 (m, 4H), 4.03 (ddd, J = 8.1, 4.5, 3.2 Hz, 1H), 5.77 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 52.9, 62.5, 63.9, 87.4, 90.1, 103.7, 141.9, 151.7, 165.8. Anal. Calcd for

$C_9H_{12}O_5N_2S$: C, 41.53; H, 4.65; N, 10.76; S, 12.32. Found: C, 41.86; H, 4.69; N, 10.44; S, 12.07.

1-[(2*S*,4*R*,5*R*)-4,5-Bis(hydroxymethyl)-1,3-oxathiolan-2-yl]uracil (35). Compound **33** (26 mg, 0.0532 mmol) was deprotected using the same method as described for compound **34**, to give **35** (12 mg, 87%) as an amorphous solid. **35**: $[\alpha]^{22}_D$ −63° (*c* 0.6, MeOH); ^{1}H NMR (250 MHz, MeOH-d_4) δ 3.65−3.80 (m, 5H), 4.54 (dt, J = 4.2, 5.2 Hz, 1H), 5.75 (d, J = 8.1 Hz, 1H), 7.24 (s, 1H), 8.07 (d, J = 8.1 Hz, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 53.1, 62.9, 64.4, 87.1, 91.7, 103.0, 141.6, 152.0, 165.9. Anal. Calcd for $C_9H_{12}O_5N_2S$: C, 41.53; H, 4.65; N, 10.76; S, 12.32. Found: C, 41.64; H, 4.72; N, 10.56; S, 12.18.

Isolation of (2*R*,3*R*)-1,4-Bis-*O*-(*tert*-butyldimethylsilyl)-3-*O*-formyl-2-thiothreitol (37) during the Attempted Preparation of Compound 36. To a solution of compounds **26** and **27** (120 mg, 0.294 mmol) in dichloromethane (20 mL) were added silylated N^4-benzoylcytosine (0.30 mL of a 1.0 M solution in dichloromethane) and trimethylsilyl triflate (0.060 mL, 0.323 mmol). The resulting solution was stirred at room temperature overnight. The reaction mixture was neutralized by the addition of pyridine, poured onto a silica gel column, and eluted with toluene/ethyl acetate (3:1). Further purification of by column chromatography (toluene/ethyl acetate 20:1) gave **37** (42 mg, 36%) as a colorless syrup. **37**: $[\alpha]^{22}_D$ −10.5° (*c* 0.4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.052, 0.069 (2s, 12 H), 0.88, 0.89 (2s, 18H), 1.60 (d, J = 10.6 Hz, 1H), 3.16 (dddd, J = 10.6, 8.1, 4.8, 3.4 Hz, 1H), 3.58 (dd, J = 10.2, 8.1 Hz, 1H), 3.75−3.9 (m, 3H), 5.27 (dt, J = 3.4, 6.0 Hz, 1H), 8.10 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.45, 18.2, 25.8, 41.5, 61.7, 65.0, 73.2, 160.4. Anal. Calcd for $C_{17}H_{38}O_4SSi_2$: C, 51.73; H, 9.70; S, 8.12. Found: C, 51.62; H, 9.49; S, 7.95.

1-[(4*R*,5*R*)-4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-oxathiolan-2-yl]-6-chloropurines (38 and 39). To a stirred solution of compounds **26** and **27** (114 mg, 0.279 mmol) in dichloromethane (20 mL) were added silylated 6-chloropurine (0.35 mL of a 1.0 M solution in dichloromethane) and trimethylsilyl triflate (0.057 mL, 0.307 mmol). The resulting solution was stirred at room temperature overnight, neutralized by the addition of pyridine, poured onto a column of silica gel, and eluted with toluene/ethyl acetate (1:1). Further purification by column chromatography (toluene/ethyl acetate 9:1) gave a 1:1 mixture of **38** and **39** (46 mg, 31%) which could not be separated by column chromatography. **38** and **39**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.050−0.124 (7s, 24 H), 0.88−0.92 (4s, 36H), 3.75−4.0 (m, 9H), 4.07 (q, J = 6.3 Hz, 1H), 4.26 (dt, J = 6.6, 4.3 Hz, 1H), 4.43 (q, J = 5.0 Hz, 1H), 7.46 (2s, overlapping, 2H), 8.60, 8.73, 8.76, 8.77 (4s, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.4, 18.3, 18.4, 25.8, 52.2, 53.4, 62.9, 63.0, 63.7, 64.3, 84.3, 86.7, 87.8, 88.1, 132.2, 132.4, 143.5, 143.9, 151.2, 151.3, 151.5, 152.3, 152.4. Anal. Calcd for a mixture of **38** and **39** ($C_{22}H_{39}O_3N_4SClSi_2$): C, 49.74; H, 7.40; N, 10.54; S, 6.04. Found: C, 49.83; H, 7.66; N, 10.22; S, 5.88.

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