Synthesis of [4,5-Bis(hydroxymethyl)-1,3-dithiolan-2-yl]nucleosides as Potential Inhibitors of HIV[1]

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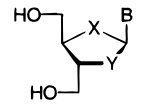
Received December 19, 1995[⊗]

The synthesis of [4,5-bis(hydroxymethyl)-1,3-dithiolan-2-yl]nucleosides is described. (2*S*,3*S*)-1,2:3,4-Diepoxybutane (**13**) was reacted with potassium thiocyanate to give (2*R*,3R)-1,2:3,4-diepithiobutane (**14**). Thiiranering opening with acetate followed by deacetylation gave (2*R*,3R)-2,3-dithiothreitol (**19**) which was silylated and treated with trimethyl orthoformate to give the 2-methoxy-1,3-dithiolane **20**. Condensation of **20** with silylated thymine, uracil, N^4-benzoylcytosine and 6-chloropurine using a modified Vorbrüggen procedure, followed by deprotection, gave the nucleoside analogues. Compounds **26**, **28**, and **30** were found to be inactive when tested for anti-HIV activity *in vitro*.

Introduction

We[2] and others[3] have reported 2′,3′-dideoxy-3′-*C*-(hydroxymethyl)cytidine (**1**) to be a potent inhibitor of HIV-1 activity *in vitro* and thus considered it to be a new interesting lead compound.[4] On the basis of the antiviral activities of several carbocyclic,[5] 4′-thio,[6] dioxolanyl[7] and oxathiolanyl nucleosides,[8] we have initiated a program to synthesize analogues of **1**. Previously, the syntheses of hydroxymethyl-substituted carbocyclic (**2**)[9] and 4′-thio nucleosides (**3**)[10] have been reported by us and other groups, and in the previous papers in this series, the synthesis of dioxolanyl (**4**)[11] and oxathiolanyl nucleosides (**5** and **6**)[12] is described. In the present paper, we report the synthesis of the corresponding 1,3-dithiolan-2-yl-nucleosides **7** (X = Y = S) as potential inhibitors of HIV. Although extensive synthetic work and structure−activity relationship investigations have been performed in the dioxolanyl[7] and oxathiolanyl nucleoside series,[8] to the best of our knowledge, the synthesis of nucleosides with two sulfur atoms in the carbohydrate moiety have previously not been reported.



B = Nucleoside base

	X	Y
1	O	CH_2
2	CH_2	CH_2
3	S	CH_2
4	O	O
5	O	S
6	S	O
7	S	S

For the synthesis of the dithiolanyl moiety of **7**, (2*R*,3*R*)-2,3-dithiothreitol was envisaged as a pivotal intermediate. Although several low molecular weight dithiol compounds are known, (2*R*,3*R*)-2,3-dithiothreitol and its enantiomer have, to our knowledge, not been prepared previously in isomerically pure form.[13] Compounds of this type are of potential interest as antidotes for heavy metal poisoning due to their metal-chelating properties,[14] and recently, 2,3-dithioerythritol prepared by reduction of *meso*-dimercaptosuccinic acid, was reported as a new potential arsenic antidote.[14] Furthermore, the 1,4-dithiol derivatives of threitol and erythritol (Clelands reagent) are commercially available and used

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⊗ Abstract published in *Advance ACS Abstracts,* May 1, 1996.

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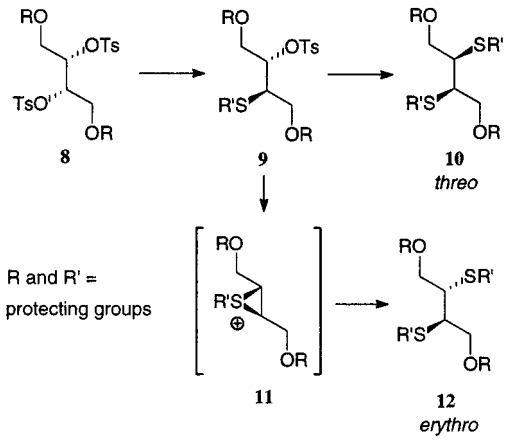
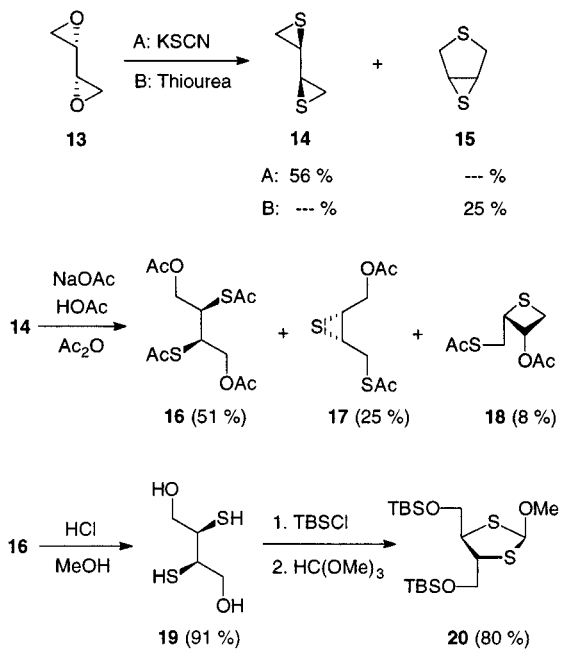
Scheme 1



Scheme 2



for the cleavage of disulfide bonds in proteins.[15] In principle, protected (2*R*,3*R*)-2,3-dithiothreitol (**10**) could be prepared from (2*S*,3*S*)-1,4-diprotected-2,3-ditosylthreitol **8** by disubstitution of the secondary tosylates with a sulfur-containing nucleophile via the monosubstituted intermediate **9** (Scheme 1). This methodology has previously successfully been used for the preparation of 2,3-diazido- and 2,3-diaminothreitol.[16] However, with sulfur as nucleophile, the stereochemical integrity might not be preserved when a second sulfur substituent is introduced.[17] Notably, in the preparation of 2,3-butanedithiol from 2,3-butanediol using this reaction sequence, partial epimerization occurred to at least 20% with the thiocyanate ion.[18] To circumvent this problem, we have developed a route to (2*R*,3*R*)-2,3-dithiothreitol (**19**) starting from (*S*,*S*)-diepoxybutane which involves the stereospecific introduction of sulfur with inversion of configuration at both chiral centers.

Results and Discussion

As starting material diepoxybutane was used, which is a versatile chiral building block,[19] readily available in both enantiomeric forms from diethyl D- or L-tartrate in five steps.[20,21] (*S*,*S*)-Diepoxybutane (**13**) was converted to the corresponding (*R*,*R*)-diepithio compound **14** with inversion of configuration at both chiral centers by treatment with potassium thiocyanate[22] in water, as described by Feit,[23] in 56% yield (Scheme 2). Compound **14** was obtained as a single diastereomer, indicating that no epimerization had occurred in this reaction. As reported,[23] diepithiobutane is prone to polymerization, due to the basicity of the reaction medium, and attempts to suppress polymerization[24] by dilution, cooling, neutralization with acid, or use of different solvents were not successful. Interestingly, substituting potassium thiocyanate for thiourea gave an increased rate of polymerization. However, one product could be isolated in 25% yield and identified as 3,6-dithiabicyclo[3.1.0]hexane (**15**).[25] Opening of diepithiobutane **14** with sodium acetate in acetic acid−acetic anhydride (1:1) at 120 °C gave tetraacetylated 2,3-dithiothreitol **16** in 51% yield. Compounds **17** and **18** were also formed in 25% and 8% yields, respectively.[26] Deprotection of **16** under acidic conditions to avoid thiirane formation and polymerization[27] gave white crystals of (2*R*,3*R*)-2,3-dithiothreitol (**19**) as a single diastereomer in 91% yield.[28] Selective protection of the hydroxyl groups of 2,3-dithiothreitol **19** as *tert*-butyldimethylsilyl ethers, followed by treatment with trimethyl orthoformate in the presence of camphorsulfonic acid (CSA) gave 2-methoxy-1,3-dithiolane **20** in 80% yield.

Initially, we used 2-methoxy-1,3-dithiolane (**21**)[29] as a simplified model system for the condensation of 2-methoxy-1,3-dithiolanes with silylated bases (Scheme 3). Condensation of **21** with silylated thymine under Vorbrüggen conditions[30] did not give the expected 1,3-dithiolan-2-ylnucleoside **22**, although dilute[12] conditions were used. Instead, 1,2-bis(1,3-dithiolan-2-yl)dithio-

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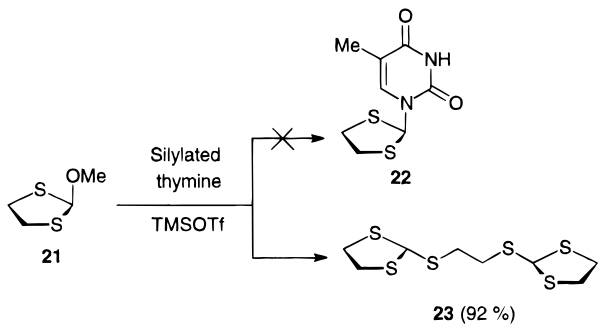
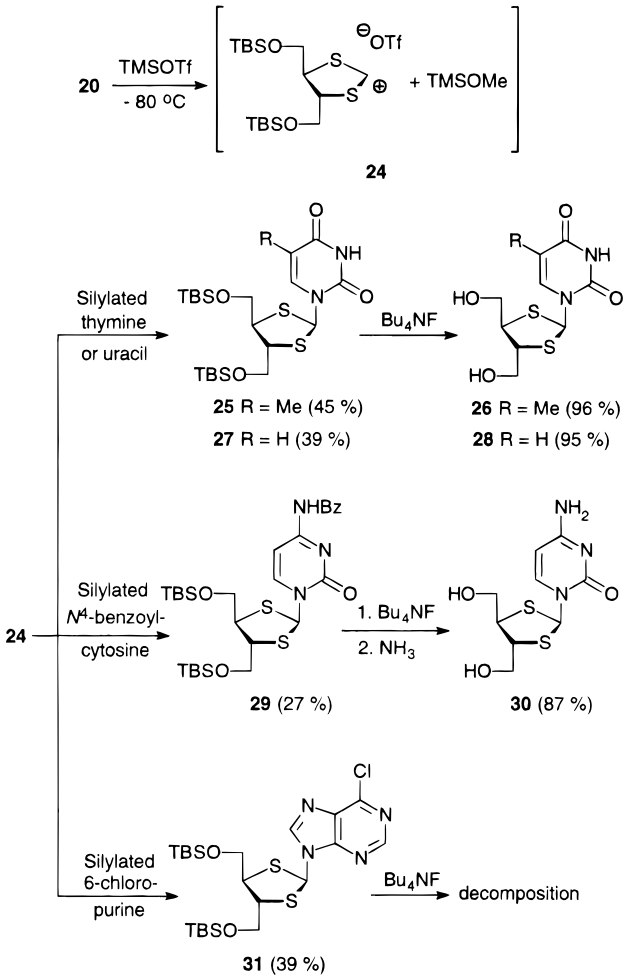
Scheme 3



Scheme 4



ethane (**23**)[31] was formed in 92% yield. Condensation of **20** with silylated thymine in the presence of trimethylsilyl triflate using dilute conditions gave the expected nucleoside **25** in yields of less than 10%. The yield of **25** was improved by preforming a dilute solution of the 1,3-dithiolan-2-ylium ion **24** by reacting **20** with trimethylsilyl triflate in dichloromethane at −80 °C. Adding this solution to an excess of silylated thymine in dichloromethane at −60 °C gave thymine derivative **25** in 45% yield (Scheme 4). Standard deprotection of the silyl protecting groups using tetrabutylammonium fluoride in tetrahydrofuran gave dithiolanylnucleoside **26** in 96% yield. The uracil derivatives **27** and **28** were obtained using the same methodology in 39% and 95% yields, respectively. In contrast to the corresponding 1,3-dioxolan-2-yl[11] and 1,3-oxathiolan-2-yl[12] series it was possible to condense **20** with silylated N^4-benzoylcytosine to give the protected cytosine derivative **29** in 27% yield. Deprotection of the silyl protecting groups followed by treatment with methanolic ammonia gave the cytosine derivative **30** in 87% yield. The 6-chloropurine derivative **31** was prepared from **20** and silylated 6-chloropurine using the methodology described above in 39% yield. However, we were not able to remove the silyl protecting groups of **31** under conditions that did not result in total decomposition.

Compounds **26**, **28**, and **30** were tested for inhibition of HIV multiplication in a XTT assay in M4 cells.[32] All compounds were found to be inactive in the assay.

Experimental Section

General methods were the same as those previously described.[11]

(2*R*,3*R*)-1,2:3,4-Diepithiobutane (14). Compound **14** was prepared from (2*S*,3*S*)-1,2:3,4-diepoxybutane (**13**)[20,33] (1.20 g, 13.9 mmol) according to the method of Feit[23] and purified by column chromatography (hexane/chloroform 1:1) to give **14** (918 mg, 56%) as a white solid. Mp and $[\alpha]^{22}_D$ were in agreement with those reported.[23] **14**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.2−2.3 (m, 2H), 2.45−2.55 (m, 2H), 3.15−3.25 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 23.8, 36.9.

3,6-Dithiabicyclo[3.1.0]hexane (15). To a solution of (2*S*,3*S*)-1,2:3,4-diepoxybutane (**13**)[20,33] (294 mg, 3.42 mmol) in methanol (10 mL) was added thiourea (1.56 g, 20.5 mmol) at 0 °C. After 5 h at 0 °C, water was added and the mixture was extracted with dichloromethane. The organic phase was dried, filtered, and evaporated to give **15** (101 mg, 25%) as a colorless oil: bp 108−111 °C (10 mmHg), lit. 45 °C (0.1 mmHg).[25] **15**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.17 (d, J = 12.6 Hz, 2H), 3.28 (dd, J = 12.6, 2.0 Hz, 2H), 3.47 (d, J = 2.0 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 34.8, 42.0.

(2*R*,3*R*)-1,4-*O*,2,3-*S*-Tetraacetyl-2,3-dithiothreitol (16). A mixture of **14** (500 mg, 4.24 mmol), acetic anhydride (5 mL), acetic acid (5 mL), and sodium acetate (3.0 g, 42.4 mmol) was heated at 120 °C for 20 h. After the solution was cooled to room temperature, toluene was added and the solids were filtered off and washed with toluene. The solvent was evaporated, and the residue was purified by column chromatography (toluene/ethyl acetate 20:1) to give **17** (233 mg, 25%) and **18** (56 mg, 6%) as colorless oils. Further elution with toluene/ethyl acetate (9:1) gave **16** (696 mg, 51%) as a colorless oil which solidified on standing. **16**: $[\alpha]^{22}_D$ −3.4° (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.07 (s, 6H), 2.36 (s, 6H), 4.04 (dd, J = 15.0, 9.7 Hz, 2H), 4.2−4.3 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.7, 30.6, 43.0, 63.7, 170.4, 193.0. Anal. Calcd for $C_{12}H_{18}O_6S_2$: C, 44.71; H, 5.63; S, 19.89. Found: C, 44.61; H, 5.50; S, 19.95. **17**: $[\alpha]^{22}_D$ + 30 ° (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.37 (s, 3H), 3.0 (dd, J = 13.8, 7.9 Hz, 1H), 3.15−3.3 (m, 2H), 3.45 (dd, J = 13.8, 5.0 Hz, 1H), 4.15 (dd, J = 12.1, 7.4 Hz, 1H), 4.45 (dd, J = 12.1, 5.7 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.8, 30.1, 30.4, 36.4, 37.9, 63.8, 170.4, 194.6. Anal. Calcd for $C_8H_{12}O_3S_2$: C, 43.61; H, 5.49; S, 29.11. Found: C, 43.55; H, 5.51; S, 28.93. **18**: $[\alpha]^{22}_D$ −95° (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.33 (s, 3H), 3.35 (ddd, J = 9.1, 8.2, 0.8 Hz, 1H), 3.42 (d, J = 7.3 Hz, 1H), 3.45 (d, J = 7.9 Hz, 1H), 3.5 (t, J = 8.7 Hz, 1H), 3.75 (dq, J = 0.8, 7.5 Hz, 1H), 5.8 (q, J = 8.0 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.7, 30.5, 30.8, 32.6, 48.0,

(31) The instability of 2-methoxy-1,3-dithiolane (**21**) to form 1,2-bis-(1,3-dithiolan-2-yl)dithioethane (**23**), especially under acidic conditions, has been well-documented, see: Coffen, D. L.; Chambers, J. Q.; Williams, D. R.; Garrett, P. E.; Canfield, N. D. *J. Am. Chem. Soc.* **1971**, *93*, 2258 and ref 29.

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(33) **Caution!** Diepoxybutane is highly mutagenic. Diepithiobutane might have similar properties. All handling with these compounds was performed in a well-ventilated fume hood.

67.6, 169.4, 194.9. Anal. Calcd for $C_8H_{12}O_3S_2$: C, 43.61; H, 5.49; S, 29.11. Found: C, 43.80; H, 5.56; S, 28.72.

(2*R*,3*R*)-2,3-Dithiothreitol (19). A solution of **16** (638 mg, 1.98 mmol) in methanol (10 mL) containing hydrogen chloride (5%, w/w) was stirred at room temperature for 24 h. The solvent was evaporated, and residual solvents were coevaporated with added toluene. The solid residue was recrystallized from chloroform to give **19** (277 mg, 91%) as white crystals. **19**: mp 114.8−115.3 °C; $[\alpha]^{22}_D$ −6.3° (*c* 2.0, EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.60 (d, J = 9.5 Hz, 2H), 2.22 (dd, J = 7.8, 4.6 Hz, 2H), 3.3−3.4 (m, 2H), 3.75 (ddd, J = 11.3, 7.8, 6.8 Hz, 2H), 3.85 (dt, J = 11.3, 5.0 Hz, 2H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 43.9, 66.3. Anal. Calcd for $C_4H_{10}O_2S_2$: C, 31.15; H, 6.53; S, 41.57. Found: C, 31.09; H, 6.38; S, 41.71.

(4*R*,5*R*)-2-Methoxy-4,5-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-dithiolane (20). A solution of **19** (340 mg, 2.21 mmol), *tert*-butyldimethylsilyl chloride (733 mg, 4.86 mmol), and imidazole (450 mg, 6.62 mmol) in dimethylformamide (3 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with toluene and washed with saturated aqueous sodium hydrogen carbonate. The organic phase was dried, filtered, and concentrated. The oily residue was dissolved in dichloromethane/trimethyl orthoformate (1:1, 20 mL) followed by the addition of camphorsulfonic acid (30 mg). After being stirred at room temperature for 1 h, the mixture was diluted with dichloromethane and washed with saturated aqueous sodium hydrogen carbonate. The organic phase was dried, filtered, and concentrated. The residue was purified by flash column chromatography (hexane/toluene 1:1) to give **20** (750 mg, 80%) as a colorless oil. **20**: $[\alpha]^{22}_D$ +34° (*c* 0.4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.052, 0.068 (2s, 12 H), 0.89 and 0.90 (2s, 18 H), 3.31 (s, 3H), 3.52 (dd, J = 10.1, 5.6 Hz, 1H), 3.60−3.75 (m, 2H), 3.80−3.95 (m, 2H), 4.15 (dd, J = 9.6, 5.6 Hz, 1H), 6.01 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.33, −5.26, 18.2, 25.9, 56.0, 56.8, 57.8, 65.0, 94.9. Anal. Calcd for $C_{18}H_{40}O_3S_2Si_2$: C, 50.89; H, 9.49; S, 15.10. Found: C, 50.64; H, 9.29; S, 14.87.

General Procedure for Silylation of Nucleoside Bases. Stock solutions of silylated bases in dichloromethane (1.0 M) were prepared as described previously.[11]

Isolation of 1,2-Bis(1,3-dithiolan-2-yl)dithioethane (23) during the Attempted Preparation of Compound 22. To a solution of 2-methoxy-1,3-dithiolane (**21**)[29] (500 mg, 3.68 mmol) in dichloromethane (250 mL) were added silylated thymine (5.5 mL of a 1.0 M solution in dichloromethane) and trimethylsilyl triflate (0.74 mL, 4.04 mmol). After 12 h at room temperature, the reaction mixture was neutralized with pyridine, applied to a column of silica gel, and eluted with toluene/ethyl acetate (9:1) to give **23** (340 mg, 92%) as a white solid. Mp and ^{1}H NMR were in agreement with those reported.[29,31] **23**: ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 34.1, 38.4, 58.0.

(4*R*,5*R*)-1-[4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-diothiolan-2-yl]thymine (25). A solution of **20** (120 mg, 0.283 mmol) in dichloromethane (20 mL) was cooled to −80 °C, and trimethylsilyl triflate (0.056 mL, 0.311 mmol) was added dropwise. The resulting solution was slowly added to silylated thymine (1.0 mL of a 1.0 M solution in dichloromethane) in dichloromethane (2 mL) at −60 °C, and the solution was stirred for 30 min. Pyridine was added, and the mixture was filtered through a short column of silica gel. The solvent was evaporated, and the residue was purified by column chromatography (toluene/ethyl acetate 3:1) to give **25** (66 mg, 45%) as a colorless syrup which solidified on standing. **25**: $[\alpha]^{22}_D$ +48° (*c* 0.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.08, 0.10 (2s, 12 H), 0.90, 0.92 (2s, 18 H), 1.97 (d, J = 0.8 Hz, 3H), 3.69 (dd, J = 9.6, 5.9 Hz, 1H), 3.77 (t, J = 9.0 Hz, 1H), 3.80 (dd, J = 9.0, 5.3 Hz, 1H), 3.86 (t, J = 9.6 Hz, 1H), 3.94 (ddd, J = 9.6, 5.3, 2.3 Hz, 1H), 4.02 (ddd, J = 9.0, 5.8, 2.3 Hz, 1H), 7.25 (s, 1H), 7.63 (d, J = 0.8 Hz, 1H), 8.34 (bs, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.34, −5.22, 12.8, 18.2, 25.8, 57.6, 58.1, 64.8, 65.1, 66.2, 112.0, 135.8, 150.2, 162.9. Anal. Calcd for $C_{22}H_{42}O_4N_2S_2Si_2$: C, 50.92; H, 8.16; N, 5.40; S, 12.36. Found: C, 50.74; H, 8.22; N, 5.47; S, 12.09.

(4*R*,5*R*)-1-[4,5-Bis(hydroxymethyl)-1,3-diothiolan-2-yl]-thymine (26). Compound **25** (40 mg, 0.079 mmol) was dissolved in tetrahydrofuran (3 mL), tetrabutylammonium fluoride (0.80 mL of a 0.5 M solution in tetrahydrofuran) was added, and the resulting solution was stirred for 1 h at room temperature. The solvent was evaporated, and the crude product was purified by column chromatography (ethyl acetate/methanol 4:1) to give **26** (22 mg, 96%) as a white solid. **26**: $[\alpha]^{22}_D$ +55° (*c* 0.4, MeOH); ^{1}H NMR (250 MHz, MeOH-d_4) δ 1.92 (s, 3H), 3.6−4.1 (m, 6H), 7.20 (s, 1H), 7.98 (s, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 12.6, 59.6, 59.8, 64.6, 64.8, 67.0, 112.5, 137.8, 152.3, 166.0. Anal. Calcd for $C_{10}H_{14}O_4N_2S_2$: C, 41.37; H, 4.86; N, 9.65; S, 22.09. Found: C, 41.09; H, 4.67; N, 9.85; S, 22.01.

(4*R*,5*R*)-1-[4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-diothiolan-2-yl]uracil (27). A solution of **20** (112 mg, 0.264 mmol) in dichloromethane (20 mL) was cooled to −80 °C, and trimethylsilyl triflate (0.053 mL, 0.290 mmol) was added dropwise. The resulting solution was slowly added to silylated uracil (1,0 mL of a 1.0 M solution in dichloromethane) in dichloromethane (2 mL) at −60 °C, and the solution was stirred for 30 min. Pyridine was added, and the mixture was filtered through a short column of silica gel. The solvent was evaporated, and the residue was purified by column chromatography (toluene/ethyl acetate 3:1) to give **27** (52 mg, 39%) as a colorless syrup. **27**: $[\alpha]^{22}_D$ +54° (*c* 0.4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.08, 0.10 (2s, 12 H), 0.90, 0.91 (2s, 18 H), 3.69 (dd, J = 10.1, 5.7 Hz, 1H), 3.74 (dd, J = 9.6, 8.1 Hz, 1H), 3.78 (dd, J = 9.6, 5.5 Hz, 1H), 3.83 (dd, J = 10.1, 7.9 Hz, 1H), 3.95 (ddd, J = 8.1, 5.5, 2.8 Hz, 1H), 4.00 (ddd, J = 7.9, 5.7, 2.8 Hz, 1H), 5.84 (dd, J = 8.0, 0.5 Hz, 1H), 7.22 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 9.0 (bs, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.41, −5.32, −5.27, 18.2, 25.8, 57.9, 58.0, 64.7, 64.9, 66.5, 103.5, 140.4, 150.3, 162.6. Anal. Calcd for $C_{21}H_{40}O_4N_2S_2Si_2$: C, 49.96; H, 7.99; N, 5.55; S, 12.70. Found: C, 50.11; H, 8.23; N, 5.50; S, 12.59.

(4*R*,5*R*)-1-[4,5-Bis(hydroxymethyl)-1,3-diothiolan-2-yl]-uracil (28). Compound **27** (34 mg, 0.067 mmol) was dissolved in tetrahydrofuran (3 mL), tetrabutylammonium fluoride (0.68 mL of a 0.5 M solution in tetrahydrofuran) was added, and the resulting solution was stirred for 1 h at room temperature. The solvent was evaporated, and the crude product was purified by column chromatography (ethyl acetate/methanol 4:1) to give **28** (18 mg, 95%) as a white solid. **28**: $[\alpha]^{22}_D$ +69° (*c* 1.0, MeOH); ^{1}H NMR (250 MHz, MeOH-d_4) δ 3.67 (dd, J = 11.3, 6.1 Hz, 1H), 3.73 (dd, J = 11.0, 6.3 Hz, 1H), 3.79 (dd, J = 11.0, 7.6 Hz, 1H), 3.85 (dd, J = 11.3, 7.2 Hz, 1H), 3.94 (ddd, J = 7.2, 6.1, 3.4 Hz, 1H), 4.03 (ddd, J = 7.6, 6.3, 3.4 Hz, 1H), 5.80 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 59.8, 64.6, 64.9, 67.5, 103.5, 142.4, 152.2, 165.7. Anal. Calcd for $C_9H_{12}O_4N_2S_2$: C, 39.12; H, 4.38; N, 10.14; S, 23.21. Found: C, 39.04; H, 4.44; N, 10.35; S, 22.98.

(4*R*,5*R*)-*N*^{4}-Benzoyl-1-[4,5-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-diothiolan-2-yl]cytosine (29). A solution of **20** (25 mg, 0.295 mmol) in dichloromethane (20 mL) was cooled to −80 °C, and trimethylsilyl triflate (0.059 mL, 0.324 mmol) was added dropwise. The resulting solution was slowly added to silylated *N*^{4}-benzoylcytosine (1.0 mL of a 1.0 M solution in dichloromethane) in dichloromethane (2 mL) at −60 °C, and the solution was stirred for 30 min. Pyridine was added, and the mixture was filtered through a short column of silica gel. The solvent was evaporated, and the residue was purified by column chromatography (toluene/ethyl acetate 1:1) to give **29** (48 mg, 27%) as a white solid. **29**: $[\alpha]^{22}_D$ +64° (*c* 0.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.09 (s, 12 H), 0.91, 0.92 (2s, 18 H), 3.70 (dd, J = 9.8, 5.4 Hz, 1H), 3.75 (dd, J = 9.0, 5.8 Hz, 1H), 3.80 (dd, J = 9.0, 5.4 Hz, 1H), 3.86 (dd, J = 9.8, 4.8 Hz, 1H), 3.95−4.05 (m, 2H), 6.33 (d, J = 7.7 Hz, 1H), 7.26 (s, 1H), 7.45−7.55 (m, 3H), 8.00−8.05 (m, 2H), 8.27 (d, J = 7.7 Hz, 1H), 9.45 (bs, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.39, −5.27, 18.2, 25.8, 57.6, 57.9, 64.7, 64.8, 68.3, 106.5, 127.6, 128.7, 131.8, 135.6, 140.9, 156.3, 165.3, 172.7. Anal. Calcd for $C_{28}H_{45}O_4N_3S_2Si_2$: C, 55.32; H, 7.46; N, 6.91; S, 10.55. Found: C, 55.34; H, 7.28; N, 6.77; S, 10.29.

(4*R*,5*R*)-1-[4,5-Bis(hydroxymethyl)-1,3-diothiolan-2-yl]-cytosine (30). Compound **29** (30 mg, 0.049 mmol) was dissolved in tetrahydrofuran (2 mL), tetrabutylammonium fluoride (0.50 mL of a 0.5 M solution in tetrahydrofuran) was

added, and the resulting solution was stirred for 1 h at room temperature. The solvent was evaporated, and the crude product was purified by column chromatography (ethyl acetate/methanol 4:1). The appropriate fractions were combined, evaporated and treated with methanolic ammonia (saturated, 4 mL), and the solution was stirred at room temperature for 24 h. The solvent was evaporated, and the residue was purified by column chromatography (chloroform/methanol 3:1) to give **30** (12 mg, 87%) as a foam. **30**: $[\alpha]^{22}_D$ +36° (*c* 0.6, MeOH); ^{1}H NMR (250 MHz, MeOH-d_4) δ 3.63 (dd, J = 11.2, 6.1 Hz, 1H), 3.69 (dd, J = 10.9, 5.8 Hz, 1H), 3.76 (dd, J = 11.2, 7.8 Hz, 1H), 3.83 (dd, J = 10.9, 7.4 Hz, 1H), 3.91 (ddd, J = 7.4, 5.8, 3.2 Hz, 1H), 3.99 (ddd, J = 7.8, 6.1, 3.2 Hz, 1H), 6.00 (d, J = 7.7 Hz, 1H), 7.20 (s, 1H), 8.25 (d, J = 7.7 Hz, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 59.6, 59.7, 64.7, 65.0, 68.4, 97.0, 142.9, 158.3, 167.4. Anal. Calcd for $C_9H_{11}O_3N_3S_2$: C, 39.55; H, 4.06; N, 15.37; S, 23.46. Found: C, 40.04; H, 4.36; N, 15.22; S, 23.13.

(4*R*,5*R*)-1-[4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-diothiolan-2-yl]-6-chloropurine (31). A solution of **20** (125 mg, 0.295 mmol) in dichloromethane (20 mL) was cooled to −80 °C, and trimethylsilyl triflate (0.059 mL, 0.324 mmol) was added dropwise. The resulting solution was slowly added to silylated 6-chloropurine (1,0 mL of a 1.0 M solution in dichloromethane) in dichloromethane (2 mL) at −60 °C, and the solution was stirred for 30 min. Pyridine was added, and the mixture was filtered through a short column of silica gel. The solvent was evaporated, and the residue was purified by column chromatography (toluene/ethyl acetate 9:1) to give **31** (63 mg, 39%) as a white solid. **31**: $[\alpha]^{22}_D$ +39° (*c* 0.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.10 (s, 12H), 0.92 (s, 18H), 3.73 (dd, J = 10.2, 5.6 Hz, 1H), 3.78 (dd, J = 10.3, 5.7 Hz, 1H), 3.84 (dd, J = 10.3, 8.9 Hz, 1H), 3.91 (dd, J = 10.2, 8.6 Hz, 1H), 4.09 (ddd, J = 8.9, 5.7, 2.8 Hz, 1H), 4.21 (ddd, J = 8.6, 5.6, 2.8 Hz, 1H), 7.21 (s, 1H), 8.69 (s, 1H), 8.77 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.31, 18.2, 25.8, 58.1, 58.8, 64.0, 64.4, 64.6, 132.3, 143.5, 151.2, 151.4, 152.1. Anal. Calcd for $C_{22}H_{39}O_2N_4S_2Si_2Cl$: C, 48.28; H, 7.18; N, 10.24; S, 11.72. Found: C, 48.13; H, 7.05; N, 10.07; S, 11.48.

Acknowledgment. We thank the National Swedish Board for Technical Development, Medivir AB and Stipendium Berzelianum for financial support, and Medivir AB for the biological testings.

JO952228O