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

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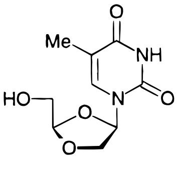
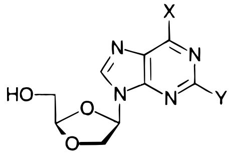
The synthesis of 1,3-dioxolan-2-ylnucleosides and related chemistry is described. We have shown that 2-methoxy-1,3-dioxolane (**6**) reacts with silylated thymine and trimethylsilyl triflate to give the acyclic formate ester 1-[2-(formyloxy)ethyl]thymine (**8**) rather than 1-(1,3-dioxolan-2-yl)thymine (**7**). A tentative mechanism which could explain this result is discussed. On the other hand, 2-methoxy-1,3-dioxolane **13c** reacts with silylated bases to give [4,5-bis(hydroxymethyl)-1,3-dioxolan-2-yl]nucleosides, thus representing the first examples of this novel class of compounds. The nature of the nucleobase and the hydroxyl protecting groups was found to have great influence on the reaction and on the stability of the nucleosides. Compounds **16** and **18** were found to be inactive when tested for anti HIV-1 activity *in vitro.*

Introduction

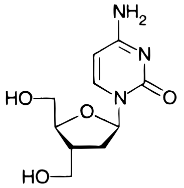
There are today four nucleoside analogues approved for the treatment of human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS),[1] AZT (Zidovudine),[2] ddC (Zalcitabine),[3] ddI (Didanosine),[3] and d4T (Stavudine).[4] A drawback with these compounds is their unfavorable toxicity profiles and that they are susceptible to the development of resistant strains of HIV.[1] In the search for therapeutically improved inhibitors of HIV, several novel classes of nucleosides have been investigated. Developments in this area have indicated that fundamental changes of the carbohydrate moiety can be compatible with potent antiviral activity.[5] An interesting approach involves the replacement of the 3′-carbon with oxygen or sulfur forming dioxolanyl- or oxathiolanylnucleosides, respectively. The first example of this class of compounds, racemic dioxolane T (**1**), was independently reported in 1989 by Norbeck *et al.*[6] and Belleau *et al.*[7] and was found to exhibit potent anti-HIV activity *in vitro.*[8] Extensive investigations of the structure−activity relationships for dioxolanylnucleosides have since then been performed.[9] Potent anti-HIV activity *in vitro* was found in both the purine and pyrimidine series, and for several derivatives, both enantiomers and some of the α-anomers were found to be active. Currently, (−)-(2*R*,4*R*)-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]guanine (DG) (**2**) and (−)-(2*R*,4*R*)-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]-2,6-diaminopurine (DAPD) (**3**) are undergoing preclinical evaluation as anti-HIV and anti-HBV agents, respectively.[10]



1 Dioxolane T



2 X = OH Y = NH$_2$ (DG)
3 X = NH$_2$ Y = NH$_2$ (DAPD)



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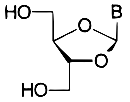

5 B = Nucleoside base

We[11] and others[12] have previously reported on the synthesis of 2′,3′-dideoxy-3′-*C*-(hydroxymethyl)cytidine

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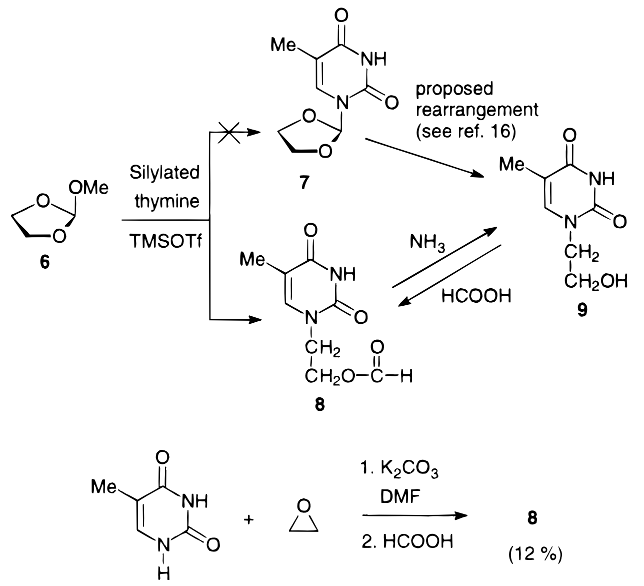
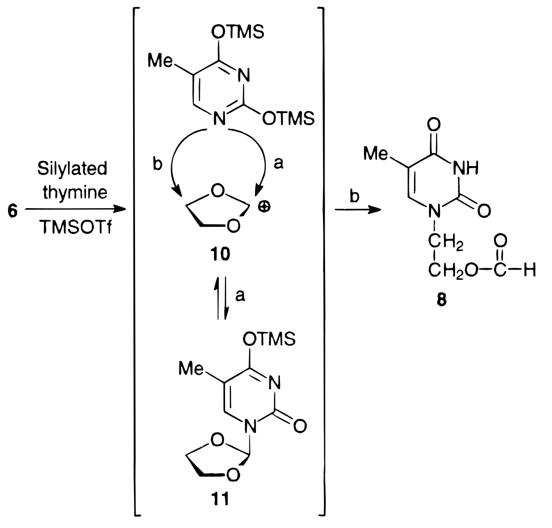
Scheme 1



Scheme 2



(**4**), a potent inhibitor of HIV activity *in vitro,* considered as a new interesting lead compound.[13] As a part of our program to prepare analogues[14] of **4**, we became interested in applying the successful concept of substituting a methylene group in the pentofuranosyl moiety with an oxygen atom. Replacing C-2′ of **4** with an oxygen gives the nucleoside derivative **5**. To our knowledge, compounds of this novel type which basically can be viewed as cyclic orthoester derivatives, have not been previously reported.[15] In the present paper we describe the synthesis of some [4,5-bis(hydroxymethyl)-1,3-dioxolan-2-yl]-nucleosides and related chemistry.

Results and Discussion

During the preparation of this paper Chu *et al.*[16] reported that 2-methoxy-1,3-dioxolane (**6**) reacts with silylated thymine and trimethylsilyl triflate (TMSOTf) under Vorbrüggen conditions[17] to give 1-(1,3-dioxolan-2-yl)thymine (**7**) (Scheme 1). We have repeated their experiment and obtained a single product with analytical data identical with that reported[16] (mp and ^{1}H NMR).[18] However, on the basis of NMR data, we have assigned the product as 1-[2-(formyloxy)ethyl]thymine (**8**).[19] Consequently, we believe that the open chain formate ester **8** is formed rather than the dioxolanylnucleoside **7**.[20] Chu *et al.* also reported that the compound proposed to be **7** is unstable toward base and converts into 1-(2-hydroxyethyl)thymine (**9**) by a rearrangement reaction for which they have also proposed a mechanism.[16] When we treated **8** with base, hydrolysis of the formate ester occurred and we obtained **9** in all aspects identical with that reported.[16] To further confirm our assignment, we treated **9** with formic acid[21] at 70 °C and obtained the formate ester **8** in 79% yield. This compound was in all aspects identical to that obtained from the glycosylation reaction (*vide supra*). Further evidence for the assignment of compound **8** was obtained by reacting thymine with a large excess of ethylene oxide to give **9**, followed by treatment with formic acid. Compound **8** was obtained in 12% yield by separation from unreacted thymine and 1-(2-hydroxyethyl)thymine (**9**) and shown to be identical with that obtained above. We have proposed a tentative mechanism for the reaction of **6** with silylated bases under Vorbrüggen conditions,[17] which is based on the reported reactivity of 1,3-dioxolan-2-ylium ions[22] (Scheme 2). Generally, cyclic orthoesters react with Lewis acids in anhydrous media predominantly by loss of the exocyclic group over dioxolane ring cleavage with *in situ* formation of the corresponding 1,3-dioxolan-2-ylium ions.[23] This is also true for the formation of the

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(15) Compounds similar to **5** containing an additional methylene group inserted between the base and the dioxolane moiety have been prepared and evaluated as potential antiviral agents: (a) Efimtseva, E. V.; Mikhailov, S. N.; Meshkov, S. V.; Lönnberg, H. *Acta Chem. Scand.* **1992**, *46*, 1122. (b) Mikhailov, S. N.; Efimtseva, E. V.; Meshkov, S. V.; Kern, E. R. *Nucleosides Nucleotides* **1994**, *13*, 615.

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(18) The ^{13}C NMR spectrum is also identical with that reported except for the thymine C-5 methyl group which is not reported in ref 16. ^{1}H and ^{13}C NMR spectra are available as supporting information. See the Experimental Section for more details.

(19) Because of the symmetry of structure **7**, C-4 and C-5 in the dioxolanyl moiety are identical. However, in the ^{13}C NMR spectra of the compound obtained, two peaks corresponding to these carbons are found, indicating an asymmetric structure. Furthermore, one would expect C-2 in the dioxolanyl moiety of **7** to appear at ca. 90−115 ppm. For the compound obtained, the only peak present in this region is C-5 of thymine at 108.3 ppm. Compared to compound **9**, an additional signal at 161.7 ppm is found, which is in excellent agreement with a formate ester. This is also true for the proton singlet at 8.22 ppm. We have measured the C,H coupling constant for the carbon at 161.7 ppm in **8** to be 233 Hz. Formate esters usually have C,H coupling constants near 230 Hz, whereas the corresponding value for an orthoester derivative is expected to be below 200 Hz. The structure of **8** was further confirmed by H,C-COSY experiments, optimized for long-range C,H coupling constants of 3.5−5 Hz.

(20) Chu *et al.* (ref 16) also report the preparation of the fluorouracil and cytosine analogue of **7** and some [4-(hydroxymethyl)-1,3-dioxolan-2-yl]nucleosides. Since these compounds have the same spectral characteristics (NMR) as compound **8**, we believe that the open chain formate esters are formed in these cases as well.

(21) Primary and secondary alcohols react with formic acid without catalyst to give the corresponding formate ester: (a) Ringold, H. J.; Löken, B.; Rosenkranz, G.; Sondheimer, F. *J. Am. Chem. Soc.* **1956**, *78*, 816. (b) Werner, W. *J. Chem. Res.* **1980**, 196.

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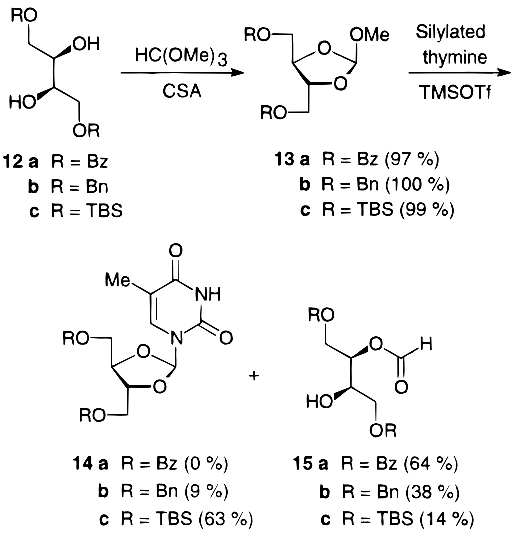
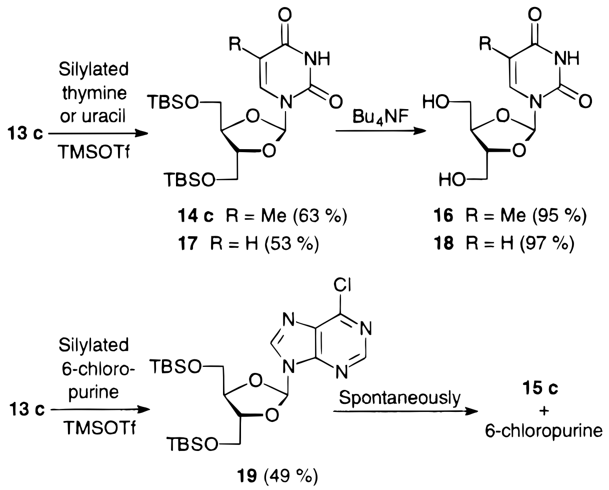
Scheme 3



Scheme 4



1,3-dioxolan-2-ylium ion (**10**).[23] Ions of this type are ambidentate cations which can react with nucleophiles in two ways depending on the reaction conditions. Under kinetic control the nucleophile is expected to react at C-2, the atom of greatest electron deficiency (path a). Attack at C-4, in a thermodynamically controlled reaction, proceeds with alkylation of the nucleophile to give the carboxylic ester (path b). The preferred route and thus the product distribution depend mainly on the nature of the nucleophile, the stability of the ambident cation, the reaction temperature, and the reaction time. If the kinetic product is stable enough, dissociation back to the cation may be avoided and the kinetic product can be isolated. Although some exceptions have been reported, products from the kinetically controlled reaction can usually only be isolated when strongly nucleophilic or basic reagents are used.[22] We believe that the C-2 substituted product **11** might be formed initially but under the reaction conditions used this compound should be in equilibrium with ion **10**, allowing the reaction to proceed to the thermodynamic product **8**.

For the synthesis of [4,5-bis(hydroxymethyl)-1,3-dioxolan-2-yl]nucleosides, the 1,4-diprotected derivatives of D-threitol (**12a**−**c**) were used as starting materials (Scheme 3). The corresponding 2-methoxy-1,3-dioxolanes **13a**−**c** were prepared in almost quantitative yields by treatment with trimethyl orthoformate in the presence of camphorsulfonic acid (CSA). Condensations of these compounds with silylated thymine in the presence of trimethylsilyl triflate gave mixtures of the desired nucleosides **14a**−**c**[24] and the formate esters **15a**−**c**.[25] Formation of products arising from attack at C-4 could not in any case be detected, probably due to the steric hindrance exerted by the hydroxymethyl groups. We found that the product distribution was highly dependent on the hydroxyl protecting groups used. We were not able to isolate any detectable amounts of the dibenzoyl derivative **14a** although several reaction conditions were used. In contrast, the dibenzyl derivative **14b** was isolated in a small but reproducible yield. A considerably higher yield of the desired nucleoside was obtained using the bulky *tert*-butyldimethylsilyl group. The thymine derivative **14c** was isolated in 63% yield as a stable solid which could be stored for months (Scheme 4). Desilylation of **14c** using tetrabutylammonium fluoride in tetrahydrofuran gave the thymine derivative **16** in 95% yield. This compound was surprisingly stable and could be purified by standard silica gel chromatography without detectable hydrolysis. The corresponding uracil derivatives **17** and **18** were obtained in a similar way in 53% and 97% yields, respectively. Condensation of **13c** with silylated 6-chloropurine under normal Vorbrüggen conditions[17] was not successful. However, if the reaction was quenched with pyridine after addition of 0.3 equiv of trimethylsilyl triflate, **19** could be isolated in 49% yield. Unfortunately, compound **19** was not stable enough for full characterization and spontaneously hydrolyzed into formate ester **15c** and 6-chloropurine. All attempts to condense **13c** with silylated cytosine or N^4-benzoylcytosine were unsuccessful, giving the formate ester **15c** as the main product. Neither was it possible to convert the uracil derivative **17** into cytosine using 1,2,4-triazole and *p*-chlorophenyl phosphodichloridate.[26]

Compounds **16** and **18** were tested for inhibition of HIV multiplication in a XTT assay in M4 cells.[27] Both compounds were found to be inactive in the assay.[28]

Experimental Section

Concentrations were performed under diminished pressure (1−2 kPa) at a bath temperature not exceeding 40 °C. ^{1}H NMR and ^{13}C NMR spectra were measured at 250 and 62.9 MHz, respectively, using $CDCl_3$, MeOH-d_4, or DMSO-d_6 solutions with TMS as internal standard. The shifts are reported in ppm (δ scale). TLC was performed on precoated silica gel plates. Spots were visualized by UV light and/or charring with ethanol/sulfuric acid/*p*-anisaldehyde/acetic acid (90:4:4:2). Column chromatography was performed using silica gel (0.040−0.063 mm). Organic phases were dried over anhydrous magnesium sulfate.

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(24) Because of the C-2 symmetry of the intermediate 1,3-dioxolan-2-ylium ion, only one diastereomer is formed in the glycosylation reaction.

(25) The formate esters **15a**−**c** were also formed from dioxolanes **13a**−**c** when stored without exclusion of moisture.

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(28) Compounds **16** and **18** are expected to be very sensitive to acid-catalyzed hydrolysis. Although stable for at least 24 h in a neutral methanol solution, it cannot be ruled out that these compounds might hydrolyze during the biological evaluation.

General Procedure for Silylation of Nucleoside Bases. A suspension of thymine, uracil, cytosine, N^4-benzoylcytosine, or 6-chloropurine (10 mmol) and a small crystal of ammonium sulfate in a mixture of hexamethyldisilazane (20 mL) and trimethylchlorosilane (2 mL) was refluxed until a clear solution was obtained. Volatile matters were evaporated off, the residue was coevaporated with toluene and dissolved in dichloromethane (10 mL) to give stock solutions (1.0 M) of silylated bases for direct use in the coupling reactions.

1-[2-(Formyloxy)ethyl]thymine (8). 2-Methoxy-1,3-dioxolane (**6**)[29] was condensed with silylated thymine using 1.1 equiv of trimethylsilyl triflate as described by Chu *et al.*[16] to give **8** as a white solid. ^{1}H NMR was in agreement with that reported. **8**: mp 169−170 °C (lit.[16] mp 168−170 °C); ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.77 (d, $J = 1.1$ Hz, 3H), 3.92 (t, $J = 5.2$ Hz, 2H), 4.31 (t, $J = 5.2$ Hz, 2H), 7.52 (d, $J = 1.1$ Hz, 1H), 8.22 (s, 1H), 11.1 (bs, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 11.8, 46.2, 60.7, 108.3, 141.4, 150.8, 161.7, 164.1.

1-(2-Hydroxyethyl)thymine (9). Compound **8** (35 mg, 0.177 mmol) was treated with methanolic ammonia (3 mL, saturated) for 5 h. The solvent was evaporated, and the residue purified by column chromatography (ethyl acetate/methanol 4:1) to give **9** (28 mg, 94%) as a white solid. ^{1}H NMR was in agreement with that reported. **9**: mp 179−180 °C (lit.[16] mp 180−181 °C); ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.76 (s, 3H), 3.57 (q, $J = 5.2$ Hz, 2H), 3.69 (t, $J = 5.2$ Hz, 2H), 4.91 (t, $J = 5.4$ Hz, 1H), 7.44 (s, 1H), 11.2 (bs, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 11.8, 49.8, 58.5, 107.5, 142.3, 150.8, 164.3.

Preparation of 8 from 9. A solution of compound **9** (18 mg, 0.106 mmol) in formic acid (85%, 2 mL) was heated at 70 °C for 2 h. The solvent was evaporated and coevaporated with toluene. The solid residue was purified by column chromatography (ethyl acetate) to give **8** (16.5 mg, 79%) as a white solid, identical to that obtained above.

Preparation of Compound 8 from Thymine and Ethylene Oxide.[30] To a suspension of thymine (1.00 g, 7.93 mmol) and potassium carbonate (40 mg) in dimethylformamide (10 mL) was added ethylene oxide (6.0 g, 150 mmol). The mixture was refluxed at 60 °C overnight. Excess ethylene oxide and residual solvents were evaporated, and the solid residue was dissolved in formic acid (85%, 5 mL) and heated at 70 °C for 2 h. After evaporation of the solvent and coevaporation with toluene, the crude product was purified by column chromatography (ethyl acetate) to give **8** (188 mg, 12%) as a white solid identical to that described above. Further elution with ethyl acetate/methanol (4:1) gave a mixture of **8**, **9**, and thymine.

1,4-Bis-*O*-(*tert*-butyldimethylsilyl)-D-threitol (12c). To a stirred solution of D-threitol (1.55 g, 12.7 mmol) in dimethylformamide (30 mL) were added imidazole (1.73 g, 25.4 mmol) and *tert*-butyldimethylsilyl chloride (3.84 g, 25.4 mmol). The resulting mixture was stirred overnight at room temperature. The solution was diluted with toluene and washed with saturated aqueous sodium hydrogen carbonate. The organic phase was dried, filtered, concentrated, and purified by column chromatography (toluene/ethyl acetate 9:1) to give **12c** (3.25 g, 73%) as a colorless oil which solidified on standing. **12c**: $[\alpha]^{22}_{\mathrm{D}}$ −4.4° (c 1.2, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ 0.082 (s, 12H), 0.90 (s, 18H), 2.8 (m, 2H), 3.75 (m, 6H); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ −5.47, 18.2, 25.8, 65.0, 71.4. Anal. Calcd for $C_{16}H_{38}O_4Si_2$: C, 54.81; H, 10.92. Found: C, 54.67; H, 10.73.

(4*R*,5*R*)-2-Methoxy-4,5-bis[(benzoyloxy)methyl]-1,3-dioxolane (13a). To a solution of 1,4-di-*O*-benzoyl-D-threitol (**12a**) (3.00 g, 9.09 mmol) in trimethyl orthoformate/dichloromethane (40 mL, 1:1) was added camphorsulfonic acid (45 mg, 0.18 mmol). After being stirred at room temperature for 1 h, the reaction mixture was diluted with dichloromethane and washed with saturated aqueous sodium hydrogen carbonate. The organic phase was dried, filtered, and concentrated to give **13a** (3.28 g, 97%) as a colorless oil which was used in the following steps without further purification. **13a**: $[\alpha]^{22}_{\mathrm{D}}$ +16.5° (c 1.3, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ 3.36 (s, 3H), 4.4−4.65 (m, 6H), 5.88 (s, 1H), 7.4−7.6 (m, 6H), 8.0−8.1 (m, 4H); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 52.0, 63.9, 64.9, 75.7, 76.0, 116.8, 128.5, 129.7, 133.2, 133.2, 166.1. Anal. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.29; H, 5.34.

(4*R*,5*R*)-2-Methoxy-4,5-bis[(benzyloxy)methyl]-1,3-dioxolane (13b). Compound **13b** was prepared from 1,4-di-*O*-benzyl-D-threitol (**12b**) (300 mg, 0.99 mmol) using the same methodology as described for the preparation of compound **13a**. Compound **13b** (348 mg, 100%) was obtained as a colorless oil which was used in the following steps without further purification. **13b**: $[\alpha]^{22}_{\mathrm{D}}$ −10° (c 1.2, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ 3.31 (s, 3H), 3.60 (dd, $J = 11.5$, 5.0 Hz, 1H), 3.65−3.70 (m, 2H), 3.73 (dd, $J = 10.0$, 5.8 Hz, 1H), 4.1−4.3 (m, 2H), 4.55, 4.56 (2s, 4H), 5.79 (s, 1H), 7.2−7.4 (m, 10 H); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 51.6, 70.0, 71.4, 73.5, 77.3, 116.4, 127.6, 128.4, 137.9, 138.0. Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.48; H, 6.98.

(4*R*,5*R*)-2-Methoxy-4,5-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-dioxolane (13c). Compound **13c** was prepared from **12c** (3.25 g, 9.29 mmol) using the same methodology as described for the preparation of compound **13a**. Compound **13c** (3.62 g, 99%) was obtained as a colorless oil which was used in the following steps without further purification. **13c**: $[\alpha]^{22}_{\mathrm{D}}$ +4.8° (c 2.0, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ 0.066 (s, 12H), 0.89 (s, 18H), 3.31 (s, 3H), 3.65−3.8 (m, 3H), 3.83 (dd, $J = 10.2$, 5.2 Hz, 1H), 4.01 (dt, $J = 5.2$, 6.3 Hz, 1H), 4.09 (dt, $J = 4.2$, 6.3 Hz, 1H), 5.75 (s, 1H); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ −5.42, 18.3, 25.8, 51.2, 63.6, 64.6, 78.1, 78.8, 116.2. Anal. Calcd for $C_{18}H_{40}O_5Si_2$: C, 55.06; H, 10.27. Found: C, 54.82; H, 10.13.

Isolation of 1,4-Di-*O*-benzoyl-2-*O*-formyl-D-threitol (15a) during the Attempted Preparation of 14a. To a stirred solution of **13a** (500 mg, 1.27 mmol) in dichloromethane (10 mL) were added silylated thymine (4 mL of a 1.0 M solution in dichloromethane) and trimethylsilyl triflate (0.26 mL, 1.40 mmol). The resulting solution was stirred at room for 5 min. The reaction mixture was neutralized by the addition of pyridine, poured onto a silica gel column, and eluted with toluene/ethyl acetate (5:1). Further purification by column chromatography (toluene/ethyl acetate 3:1) gave **15a** (290 mg, 64%) as a colorless solid. **15a**: $[\alpha]^{22}_{\mathrm{D}}$ −8.1° (c 0.6, CHCl$_3$); mp 152.4−152.8 °C (EtOAc/hexane); ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.2 (bs, 1H), 4.28 (dd, $J = 11.1$, 5.2 Hz, 1H), 4.33 (dd, $J = 11.1$, 6.5 Hz, 1H), 4.49 (dd, $J = 11.9$, 7.8 Hz, 1H), 4.62 (dd, $J = 11.9$, 3.4 Hz, 1H), 5.42 (m, 1H), 5.73 (bs, 1H), 7.5−7.8 (m, 6H), 7.9−8.05 (m, 4H), 8.40 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 63.6, 64.8, 66.8, 71.2, 128.7, 128.8, 129.2, 129.3, 129.6, 133.5, 133.6, 161.9, 165.5, 165.6. Anal. Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06. Found: C 63.61; H, 5.11.

(4*R*,5*R*)-1-[4,5-Bis[(benzyloxy)methyl]-1,3-dioxolan-2-yl]thymine (14b) and 1,4-Di-*O*-benzyl-2-*O*-formyl-D-threitol (15b). To a stirred solution of **13b** (200 mg, 0.58 mmol) in dichloromethane (10 mL) were added silylated thymine (4 mL of a 1.0 M solution in dichloromethane) and trimethylsilyl triflate (0.12 mL, 0.64 mmol). The resulting solution was stirred at room temperature for 5 min. The reaction mixture was neutralized by the addition of pyridine, poured onto a silica gel column, and eluted with toluene/ethyl acetate (5:1). Further purification by column chromatography (toluene/ethyl acetate 3:1) gave **15b** (72 mg, 38%) and **14b** (22 mg, 9%) as colorless syrups. **14b**: $[\alpha]^{22}_{\mathrm{D}}$ −5.2° (c 0.4, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ 1.67, (d, $J = 1.1$ Hz, 3H), 3.55−3.70 (m, 2H), 3.99 (dd, $J = 11.0$, 2.9 Hz, 1H), 4.30 (dt, $J = 3.0$ Hz, 1H), 4.45−4.60 (m, 2H), 4.59 (s, 4H), 6.99 (s, 1H), 7.3−7.4 (m, 10 H), 7.52 (d, $J = 1.1$ Hz, 1H), 8.2 (bs, 1H); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 12.1, 68.7, 69.8, 73.7, 76.1, 78.3, 102.1, 111.1, 127.6−128.6, 134.8, 137.3, 137.4, 150.2, 163.4. Anal. Calcd for $C_{24}H_{26}O_6N_2$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.89; H, 5.92; N, 6.19. **15b**: $[\alpha]^{22}_{\mathrm{D}}$ −11.3° (c 0.7, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ 2.74 (d, $J = 5.1$ Hz, 1H), 3.49 (dd, $J = 9.7$, 6.0 Hz, 1H), 3.54 (dd, $J = 9.7$, 4.9 Hz, 1H), 3.67 (dd, $J = 10.6$, 5.3 Hz, 1H), 3.72 (dd, $J = 10.6$, 4.4 Hz, 1H), 4.07 (dt, $J = 5.0$ Hz, 1H), 4.45−4.60 (m, 4H), 5.25 (m, 1H), 7.25−7.40 (m, 10 H), 8.11 (s, 1H); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 69.0, 69.7, 70.6,

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(29) Baganz, H.; Domaschke, L. *Chem. Ber.* **1958**, *91*, 650.

(30) **Caution!** All handling with ethylene oxide was performed in a well-ventilated fume hood.

72.2, 73.5, 73.6, 127.7, 127.9, 128.2, 128.5, 137.5, 137.6, 160.6. Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.22; H, 6.80.

(4*R*,5*R*)-1-[4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-dioxolan-2-yl]thymine (14c) and 1,4-Di-*O*-(*tert*-butyldimethylsilyl)-2-*O*-formyl-D-threitol (15c). Compound **14c** was prepared from **13c** (500 mg, 1.27 mmol) using the same methodology as described for the preparation of compound **14b**. Compound **15c** (67 mg, 14%) was obtained as a colorless syrup, and compound **14c** (0.381 g, 63%) as a colorless syrup which solidified on standing. **14c**: $[\alpha]^{22}_{D}$ −3.5° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.081, 0.10 (2s, 12H), 0.91, 0.92 (2s, 18H), 1.92 (d, $J = 1.1$ Hz, 3H), 3.72 (dd, $J =$ 11.0, 3.4 Hz, 1H), 3.78, (dd, $J = 11.4, 2.3$ Hz, 1H), 3.84 (dd, $J = 11.0, 4.4$ Hz, 1H), 3.98 (dd, $J = 11.4, 3.4$ Hz, 1H), 4.21 (dt, $J = 6.4, 3.1$ Hz, 1H), 4.30 (ddd, $J = 6.4, 4.4, 3.4$ Hz, 1H), 6.93 (s, 1H), 7.37 (d, $J = 1.1$ Hz, 1H) 9.05 (bs, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.54, −5.42, −5.35, 18.2, 18.4, 25.8, 25.9, 62.2, 63.3, 77.2, 78.9, 101.7, 111.2, 134.4, 150.3, 163.8. Anal. Calcd for $C_{22}H_{42}O_6N_2Si_2$: C, 54.29; H, 8.70; N, 5.76. Found: C, 54.41; H, 8.41; N, 5.82. **15c**: $[\alpha]^{22}_{D}$ −15.5° (*c* 1.2, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.056, 0.063 (2s, 12H), 0.88 (s, 18H), 2.90 (d, $J = 4.9$ Hz, 1H), 3.6−3.7 (m, 2H), 3.82 (dd, $J = 11.1, 5.1$ Hz, 1H), 3.91 (dd, $J = 11.1, 4.5$ Hz, 1H), 3.9−4.0 (m, 1H), 5.07 (q, $J = 4.5$ Hz, 1H), 8.14 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.54, 18.1, 18.2, 25.7, 25.8, 62.5, 63.4, 70.9, 73.3, 160.6. Anal. Calcd for $C_{17}H_{38}O_5Si_2$: C, 53.92; H, 10.12. Found: C, 54.06; H, 10.00.

(4*R*,5*R*)-1-[4,5-Bis(hydroxymethyl)-1,3-dioxolan-2-yl]thymine (16). Compound **14c** (27 mg, 0.057 mmol) was dissolved in tetrahydrofuran (2 mL), tetrabutylammonium fluoride (0.57 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 purified by column chromatography (ethyl acetate/methanol 4:1) to give **16** (14 mg, 95%) as a white solid. **16**: $[\alpha]^{22}_{D}$ +15° (*c* 0.4, MeOH); ^1H NMR (250 MHz, MeOH-d_4) δ 1.88 (d, $J = 1.1$ Hz, 3H), 3.64 (dd, $J = 12.3, 4.1$ Hz, 1H), 3.73 (dd, $J = 12.5, 3.6$ Hz, 1H), 3.79 (dd, $J = 12.3, 3.5$ Hz, 1H), 3.91 (dd, $J = 12.5, 3.1$ Hz, 1H), 4.19 (dt, $J = 7.0, 3.3$ Hz, 1H), 4.33 (dt, $J = 7.0, 3.9$ Hz, 1H), 6.93, (s, 1H), 7.77 (d, $J = 1.1$ Hz, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 12.4, 61.7, 62.6, 79.4, 80.5, 103.4, 111.8, 136.8, 152.4, 166.3. Anal. Calcd for $C_{10}H_{14}O_6N_2$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.24; H, 5.34; N, 10.68.

(4*R*,5*R*)-1-[4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-dioxolan-2-yl]uracil (17). To a stirred solution of **13c** (500 mg, 1.27 mmol) in dichloromethane (10 mL) were added silylated uracil (4.0 mL of a 1 M solution in dichloromethane) and trimethylsilyl triflate (0.26 mL, 1.40 mmol). The resulting solution was stirred at room temperature for 5 min. The reaction mixture was neutralized by the addition of pyridine, poured onto a silica gel column, and eluted with toluene/ethyl acetate (5:1). Further purification by column chromatography (toluene/ethyl acetate 3:1) gave **17** (318 mg, 53%) as a colorless syrup which solidified on standing. **17**: $[\alpha]^{22}_{D}$ +7.5° (*c* 2.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.085, 0.099 (2s, 12H), 0.91, 0.92 (2s, 18H), 3.73 (dd, $J = 11.0, 3.6$ Hz, 1H), 3.77 (dd, $J = 11.5, 2.6$ Hz, 1H), 3.82 (dd, $J = 11.0, 4.6$ Hz, 1H), 4.00 (dd, $J = 11.5, 2.9$ Hz, 1H), 4.23 (dt, $J = 6.2, 2.6$ Hz, 1H), 4.33 (ddd, $J = 6.2, 4.6, 3.6$ Hz, 1H), 5.70 (d, $J = 8.4$ Hz, 1H), 6.98 (s, 1H), 7.81 (d, $J = 8.4$ Hz, 1H), 9.75 (bs, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.55, −5.45, 18.2, 18.3, 21.4, 25.8, 62.2, 63.3, 76.9, 79.5, 102.0, 102.7, 139.4, 150.5, 163.5. Anal. Calcd for $C_{21}H_{40}O_6N_2Si_2$: C, 53.36; H, 8.53; N, 5.93. Found: C, 53.19; H, 8.34; N, 6.01.

(4*R*,5*R*)-1-[4,5-Bis(hydroxymethyl)-1,3-dioxolan-2-yl]uracil (18). Compound **17** (53 mg, 0.112 mmol) was dissolved in tetrahydrofuran (4 mL), tetrabutylammonium fluoride (1.12 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 purified by column chromatography (ethyl acetate/methanol 4:1) to give **18** (26.5 mg, 97%) as a white solid. **18**: $[\alpha]^{22}_{D}$ +17° (*c* 0.4, MeOH); ^1H NMR (250 MHz, MeOH-d_4) δ 3.64 (dd, $J = 12.3, 4.0$ Hz, 1H), 3.72 (dd, $J = 12.4, 3.6$ Hz, 1H), 3.80 (dd, $J = 12.3, 3.4$ Hz, 1H), 3.89 (dd, $J = 12.4, 3.1$ Hz, 1H), 4.20 (dt, $J = 6.9, 3.4$ Hz, 1H), 4.32 (dt, $J = 6.9, 3.8$ Hz, 1H), 5.71 (d, $J = 8.0$ Hz, 1H), 6.93 (s, 1H), 7.94 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 61.7, 62.6, 79.6, 80.6, 103.1, 103.5, 141.3, 152.2, 166.0. Anal. Calcd for $C_9H_{12}O_6N_2$: C, 44.27; H, 4.95; N, 11.47. Found: C, 44.06; H, 5.01; N, 11.24.

(4*R*,5*R*)-9-[4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-dioxolan-2-yl]-6-chloropurine (19). To a stirred solution of **13c** (250 mg, 0.637 mmol) in dichloromethane (4 mL) were added silylated 6-chloropurine (1.0 mL of a 1.0 M solution in dichloromethane) and trimethylsilyl triflate (0.035 mL, 0.19 mmol). The resulting solution was stirred at room temperature for 15 min, neutralized by the addition of pyridine, poured onto a silica gel column, and eluted with toluene/ethyl acetate (9:1) containing 2% pyridine. Further purification by column chromatography (toluene/ethyl acetate 9:1 + 2% pyridine) gave **19** (160 mg, 49%) as a colorless syrup. **19**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.05 (s, 12 H), 0.84, 0.86 (2s, 18 H), 3.5−4.5 (m, 6H), 7.12 (s, 1H), 8.54 (s, 1H), 8.66 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.62, −5.51, 18.0, 18.2, 25.6, 25.7, 61.9, 62.5, 77.3, 80.1, 101.8, 131.5, 142.4, 150.3, 151.7, 152.0. Compound **19** was too unstable for further characterization.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compound **8** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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