Articles

Ring-Expanded Nucleoside Analogues. 1,3-Dioxan-5-yl Pyrimidines

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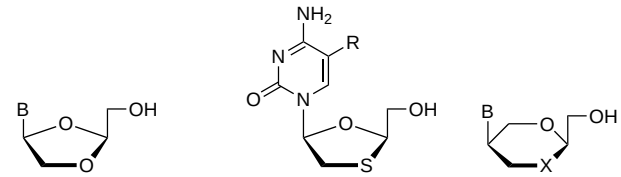
1,3-Dioxan-5-yl pyrimidine nucleoside analogues, higher homologues of antiviral and anticancer 1,3-dioxolanes, were prepared from bis-1,3-tritylglycerol and 3-benzoylated bases (uracil, 5-fluorouracil, thymine). Mitsunobu condensation, deprotection, and cycloacetalization gave cis/trans mixtures of 2,5-disubstituted-1,3-dioxanes in which the desired cis stereoisomers predominated. Cytosine derivatives could not be obtained in this manner; N^4-benzoylcytosine afforded an O-2 alkylated Mitsunobu product that rearranged to an O^2-(2,3-dihydroxypropyl)cytosine on detritylation with aqueous acetic acid. Cytosine and 5-fluorocytosine nucleosides were therefore prepared from the corresponding uracils via their 1,2,4-triazole derivatives. ^{1}H NMR data established the conformational preference for equatorial 2′-hydroxymethyl and axial 5′-base in the cis isomers; the trans compounds were diequatorial. Despite their conformations, the cis nucleosides showed no antiviral activity.

Introduction

The antiviral and anticancer activity of the L-nucleosides **1**[1,2] and **2**[3,4] prompted us to consider the properties of their higher homologues **3**. Formally derived from the 1,3-dioxolanes and 1,3-oxathiolanes by insertion of a methylene group between C1′ and the furanosyl O, these compounds and the corresponding 1,3-dithianes are of interest for several reasons. As with other dideoxy nucleosides (AZT, ddC, etc.) their lack of a secondary (3′) hydroxyl suggests potential activity as viral DNA polymerase inhibitors and/or chain terminators.[5] Compounds **3** also offer the opportunity to examine the effects of additional annular heteroatom substitution on the conformation and configuration (**3b**) of ring-expanded nucleoside analogues. The present paper describes the synthesis, conformational characteristics, and antiviral properties of *cis*-1,3-dioxan-5-yl pyrimidine nucleosides (**3a**).



1a B = thymin-1-yl
b B = cytosin-1-yl
c B = 5-fluorocytosin-1-yl

2a R = H (Lamivudine, 3TC)
b R = F (FTC)

3a X = O
b X = S

Although many six-membered ring nucleoside analogues (pyranose,[6] cyclohexanyl,[7] cyclohexenyl[8]) have been prepared, substantiated antiviral activity was not reported until 1993.

In that year Herdewijn and co-workers described a series of 1,5-anhydrohexitol nucleosides (**4**) that showed potent selective activity against several Herpes-type

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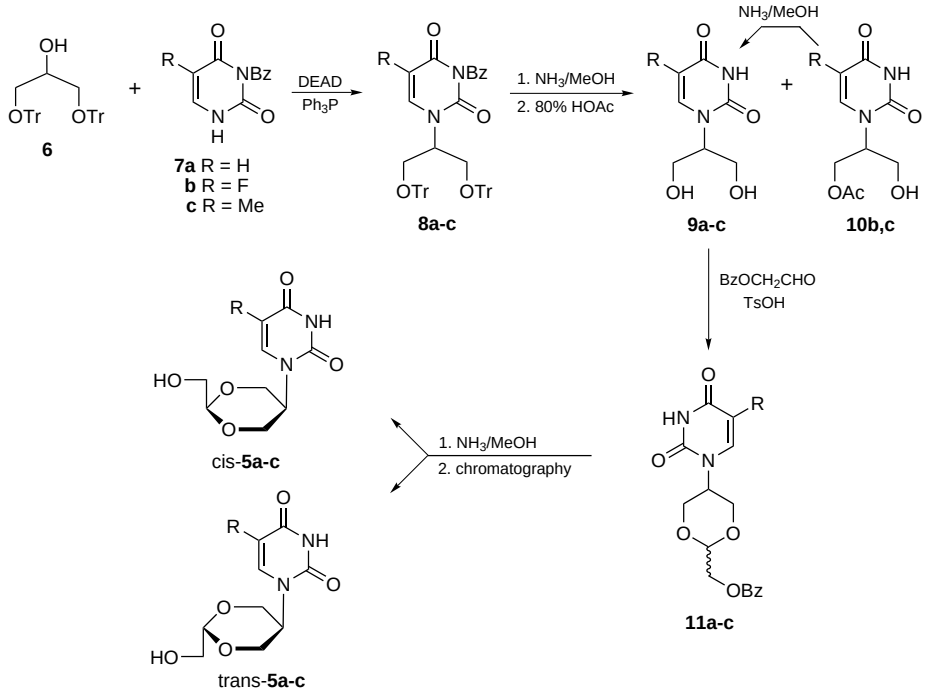
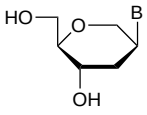
Scheme 1



viruses.[9] A notable structural feature of these compounds is the axial orientation of their bases. In previously described inactive six-membered nucleosides, bases occupied equatorial or pseudoequatorial positions, unfavorable for kinase mediated 5′-phosphorylation required for the initial step in viral DNA polymerase inhibitory activity.[9] However, conformational analysis supported by NMR data clearly established the preference for the axial base conformation of **4**, partially accounting for the antiviral activity. Molecular modeling showed **4** (with its axial base) to resemble closely natural nucleosides in size and shape,[7b,9a] thus facilitating enzymatic recognition.



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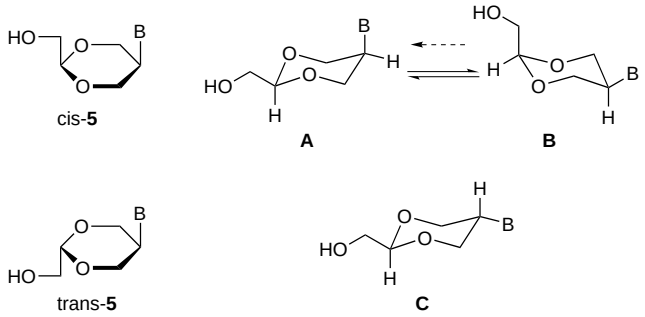
In principle, appropriate incorportion of heteroatoms in a cyclohexane ring could provide an alternative means for obtaining axially oriented bases. Conformational preferences of saturated six-membered heterocycles have been extensively investigated. For the target *cis*-2-hydroxymethyl-1,3-dioxan-5-yl nucleosides (cis-**5**), two effects are most important.[10] Substituents at the 2-position of 1,3-dioxanes favor the equatorial position to a greater extent than do the same substituents in cyclohexane, an effect attributed to enhanced 1,3-diaxial interactions resulting from the shorter C−O bond distance in the heterocycle.[11] On the other hand, "steric" requirements of annular O or S, including their axial lone pairs, are considerably less than those of C with an axial H. An axial substituent at the 5-position of a 1,3-dioxane is therefore less subject to unfavorable 1,3-diaxial interactions than it would be in cyclohexane. As a consequence, the preferred conformation of a *cis*-2,5-disubstituted-1,3-dioxane is determined primarily by the equatorial 2-substituent, not the 5-substituent. Accordingly, nucleosides cis-**5** should exist (predominantly) with their bases positioned axially (conformation **A** rather than **B**), as required for biological activity in the 1,5-anhydrohexitol (**4**) series. The diequatorial conformation **C** would of course be expected for the trans-**5** isomers.



As well as conformation, incorporation of various annular heteroatoms could also provide a measure of dimensional control in the design of ring-expanded nucleoside analogues. By virtue of their altered bond lengths and angles, the geometry of such nucleosides might be modified in predictable ways.[12]

The notable antiviral activity of several synthetic L ("unnatural") nucleosides, for example, **1** and **2**, has focused attention on chirality as an important parameter

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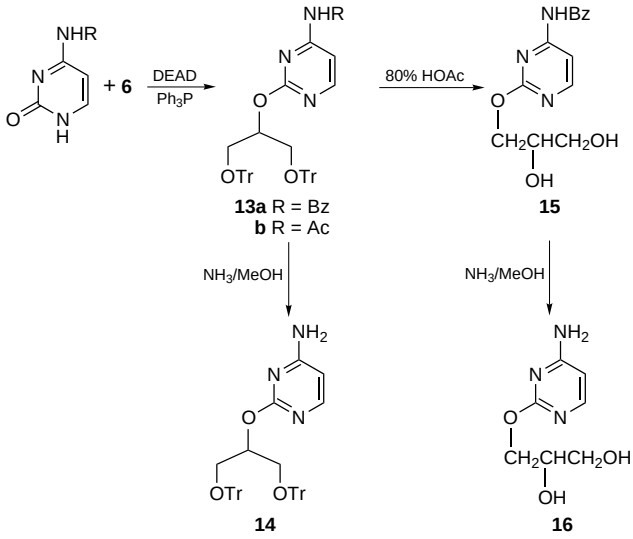
for antiviral activity and selectivity.[13−15] But unlike most other cyclic nucleoside analogues, the 1,3-dioxanes **5** are achiral, related to neither the D nor the L carbohydrate families. In view of the propensity of L nucleosides to select rapidly and completely for drug resistant virus strains,[16] the effect of the symmetry of **5** on biological activity was also of interest. Synthesis of cis-**5** was undertaken to explore these effects.

Results and Discussion

Preparation of cis-**5a**−**c** was accomplished in satisfactory overall yield (29−59%) as shown in Scheme 1. Mitsunobu condensation of bis-1,3-trityloxy-2-propanol[17] (**6**) with 3-benzoyluracil,[18] 3-benzoyl-5-fluorouracil,[19] and 3-benzoylthymine[18] (**7a**−**c**) gave products **8a**−**c**, respectively. Debenzoylation (ammonia in methanol, room temperature) followed by detritylation (80% acetic acid, 75 °C) afforded the necessary 1-(1,3-dihydroxy-2-propyl)-pyrimidines **9a**−**c**.[20] A minor side product (<6%) isolated from the detritylation of the 5-fluorouracil and thymine derivatives proved to be the half O-acetylated products (**10b**,**c**). The site of Mitsunobu alkylation, N-1 rather than O-2, was established by ^{1}H and ^{13}C NMR and comparison with previously reported spectra.[9,21] NMR examination of the crude Mitsunobu reaction mixtures revealed only trace amounts of isomeric products.

2-Substituted-1,3-dioxanes (also 1,3-dithianes, 1,3-oxathianes) are conveniently prepared by cycloacetalization of aldehydes with 1,3-diols (or 1,3-dithiols, 3-mercapto alcohols). Benzoyloxyacetaldehyde,[22] a protected α-hydroxyaldehyde, reacted well with the 1,3-dihydroxy-2-propyl-substituted pyrimidines (**9a**−**c**) to afford cis/trans mixtures of the 1,3-dioxanes **11a**−**c**. Under the conditions employed (no solvent, TsOH catalyst, 80 °C, 2−3 mmHg), the desired cis stereoisomers were the major products, constituting 70−86% of the crude cyclization mixtures. Although a kinetic preference for the formation of *cis*-2,5-dialkyl-1,3-dioxanes has been previously noted,[23] the cis isomers (cis-**11**) might also be thermodynamically more stable than the trans due to intramolecular H-bonding between the 2-hydroxy pyrimidine tautomers and the dioxanyl oxygens. Similar stabilization has been invoked to account for the greater thermodynamic stability of *cis*-(axial)-5-hydroxymethyl-2-isopropyl-1,3-dioxane as compared with its trans (diequatorial) isomer,[24] as well as for the axial preference of 5-hydroxy-1,3-dithianes.[25]

Scheme 2



Acid-catalyzed equilibration of the thymine derivatives (cis- and trans-**5c**) supported this supposition. Approached from both directions using pure cis-**5c** and a 25% cis−75% trans mixture (DMSO solvent, 60−65 °C, BF_3 etherate catalyst, degassed and sealed in NMR tubes), the same equilibrium mixture was obtained: 75% cis−25% trans, corresponding to an energy difference $\Delta G = 0.78$ (±0.08) kcal/mol.

Debenzoylation of **11** (NH_3/MeOH) and silica gel chromatography gave the major product cis-**5**; pure samples of the minor product trans-**5**, on the other hand, could not be obtained by either column chromatography or HPLC. Attempts to isolate the (minor) trans isomers were therefore not pursued. NMR data described for these compounds were obtained from later column fractions, mixtures rich (>70%) in the trans isomers but in all cases contaminated with the cis.

Attempts to prepare the *cis*-cytosin-1-yl nucleoside (**5d**) via the method of Scheme 1 failed. Mitsunobu condensation of N^4-benzoylcytosine and **6** gave predominantly O-2 alkylated product **13a** (Scheme 2). NMR analysis of the crude product indicated a ratio of ca. 8:1 (O-2:N-1 alkylation), in general agreement with other Mitsunobu alkylations reported for this base.[8c,21b] Predominant O-2 alkylation also occurred with N^4-acetylcytosine and **6** to give **13b**. Verification of the O-2 assignment was obtained by ^{13}C and ^{1}H NMR; the H-2′ (OC*H*) chemical shifts of **13a**,**b** (δ 5.53, 5.46, respectively) were appreciably downfield from those of the N-1 Mitsunobu products **8a**−**c** (δ 4.92−4.99). Debenzoylation of **13a** gave **14**, a compound that permitted direct comparison with ^{13}C spectra reported for other O-2 alkylated cytosines.[8c,21a,b] The values observed for C5, C6, and C2

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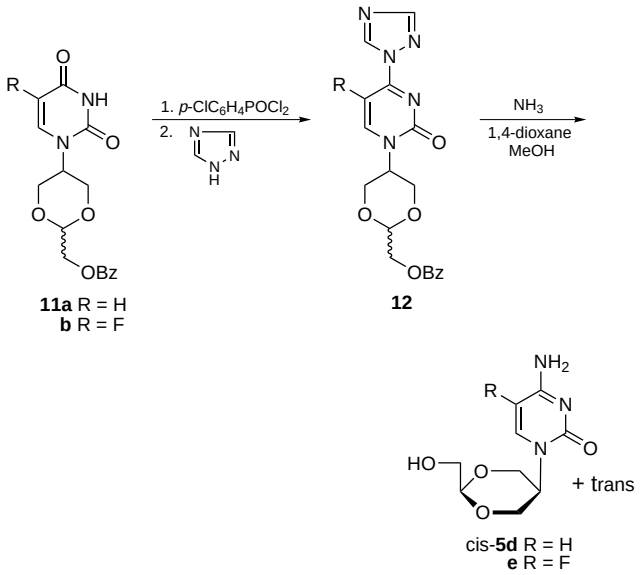
Scheme 3



11a R = H
b R = F

12

cis-**5d** R = H
e R = F

(δ 99.1, 157.4, and 164.8, respectively) are consistent with O-2 but not N-1 alkylation.

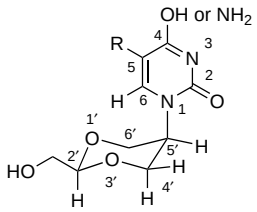
In contrast to the N-1 substituted pyrimidines **8a**−**c** (Scheme 1), **13a** produced a rearranged product, N^4-benzoyl-O^2-(2,3-dihydroxypropyl)cytosine (**15**), on treatment with 80% acetic acid (Scheme 2). Deacylation of the rearranged product gave the O-2 alkylated cytosine **16**.

The properties (NMR, mp) of **15** and **16** differed markedly from those reported for the corresponding N-1 alkylated isomers.[26] Although the migration of trityl groups under acidic conditions has been reported,[27] the present rearrangement is plausibly explained by intramolecular nucleophilic attack of 1° hydroxyl on C-2, followed by ring opening of the dioxolane intermediate. Alternatively, a pathway involving nucleophilic attack by cytosine on a glycidyl intermediate, similar to that recently proposed in a different context,[28] might be involved. Further investigation may clarify the nature of the rearrangement.

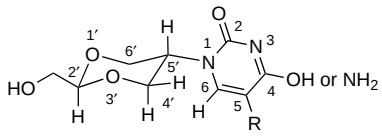
Because of O-2 alkylation, the cytosine and 5-fluorocytosine nucleosides (cis-**5d**,**e**) were prepared from the corresponding 2-benzoyloxymethyl-1,3-dioxanyluracil and 5-fluorouracil derivatives **11a**,**b**, respectively, by the 1,2,4-triazole method[29] (Scheme 3). The major cis stereoisomers were again isolated chromatographically.

Stereochemical and conformational assignments were facilitated by the ^{1}H NMR correlations developed by Eliel and co-workers for 1,3-dioxanes and 1,3-dithianes.[30] The relative chemical shifts of the H-5′ (dioxanyl) protons and the H-6 (pyrimidinyl) protons were particularly informative, as were the H-4′(6′)−H-5′ coupling constants. In the cis isomers (cis-**5a**−**e**) signals for the equatorial H-5′ occurred at higher field ($\Delta\delta$ = 0.19−0.28 ppm) than those of the axial H-5′ of the corresponding trans isomers (trans-**5a**−**e**), due to deshielding of the latter by the ring oxygens. For the same reason, the pyrimidinyl H-6 of the axially oriented bases in the cis compounds appeared downfield ($\Delta\delta$ = 0.23−0.55 ppm) from that of the corresponding trans isomers. Relevant chemical shifts are given in Table 1.

Table 1. Selected ^{1}H Chemical Shifts (in δ) for cis- and trans-5[a]



cis-**5**



trans-**5**

compd	base	H-4′(6′)$_{ax}$	H-4′(6′)$_{eq}$	H-5′	H-6[b]
cis-**5a**	U	4.14	4.21	4.29	8.16
b	5FU	4.13	4.21	4.31	8.39
c	T	4.08	4.22	4.30	8.08
d	C	4.05	4.18	4.32	8.12
e	5FC	4.08	4.19	4.30	8.27
trans-**5a**	U	3.89−4.04 (m)		4.51	7.71
b	5FU	3.94 (t)	4.04 (dd)	4.50	8.16
c	T	3.88−4.10 (m)		4.53	7.53
d	C	3.85 (t)	3.99 (dd)	4.60	7.65
e	5FC	3.88−4.02 (m)		4.55	8.01

[a] 400 MHz, DMSO-d_6 solvent, TMS reference. [b] All doublets (J = 7.2−7.8 Hz) except cis- and trans-**5c**, singlets.

Table 2. H-4′(6′), H-5′ Coupling Constants (in hertz) for cis- and trans-5c

compd	$J_{4'(6')ax,4'(6')eq}$	$J_{4'(6')ax,5'}$	$J_{4'(6')eq,5'}$
cis-**5c**	11.0	1.8	1.6
trans-**5c**	10.5	11.0	6.0

A distinctive, easily recognizable pattern for H-4′(6′) and H-5′ was observed for the cis products (cis-**5a**−**e**). The H-5′ signals appeared as somewhat broadened single peaks reflecting the small but similar magnitudes of $^3J_{4a,5}$ and $^3J_{4e,5}$ (ca. 1.7 Hz). In agreement with earlier observations,[30c] the equatorial H-4′(6′) signals of the cis and trans compounds were downfield from the axial H-4′(6′) signals ($\Delta\delta$ = 0.07−0.14 ppm). At 400 MHz, both H-4′(6′)$_e$ and H-4′(6′)$_a$ in the cis isomers appeared as characteristic distorted doublets. The partial experimental spectrum (H-4′(6′), H-5′) of cis-**5c** was accurately reproduced by ^{1}H NMR simulation[31] using the δ-values given in Table 1 and the coupling constants (^3J) tabulated in Table 2. Similar simulations were effected for the other cis isomers.

Spectra of the minor trans isomers (trans-**5**) were entirely different; axial H-5′ appeared as well-defined multiplets, while H-4′(6′)$_e$ in trans-**5b**,**d** appeared as a doublet of doublets and H-4′(6′)$_a$ as a distorted triplet,

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as previously described for other 1,3-dioxanes.[32] Overlapping signals made it difficult to discern this pattern in trans-**5a**,**c**,**e**. The partial spectrum of trans-**5c**, representative of the trans isomers, was simulated with the data in Tables 1 and 2. The observed coupling constants agree well with those of other *cis*- and *trans*-2,5-disubstituted-1,3-dioxanes reported by Eliel and co-workers.[30,32] As anticipated, the bases are axially positioned in cis-**5a**−**e**.

Antiviral Testing. Cis nucleosides **5a**−**e** were evaluated for activity against the following viruses, HSV-1, HSV-2, HBV, EBV, and HIV-1, by previously described procedures.[33] None of the compounds showed significant antiviral activity: HSV-1 and -2 and HIV-1, $ED_{50} > 100$ μM; EBV and $ED_{50} > 50$ μM; HBV, $ED_{50} > 10$ μM. No cytotoxicity was observed.

Conclusions

An efficient synthesis of ring-expanded achiral 1,3-dioxan-5-yl nucleosides containing pyrimidine bases has been developed. Under the cyclization conditions employed, the cis stereoisomers, analogous to natural β-anomers, were preferentially formed. As predicted from conformational considerations, the cis products (**5a**−**e**) possess equatorial 2′-hydroxymethyl substituents and axial 5′-bases, confirming the potential of annular heteroatom substitution for conformational control in ring-expanded nucleoside analogues. Despite their axial bases, cis-**5a**−**e** did not show the antiviral activity of the conformationally related 1,5-anhydrohexitols (**4**). Additional factors, such as the 2° hydroxyl group of **4**,[34] may be necessary for antiviral activity.

Experimental Section

General methods were the same as previously described.[35] UV spectra were recorded with a Perkin-Elmer Lambda 2 UV/vis spectrophotometer; ^{1}H NMR spectra were determined with a Varian Inova 400 MHz spectrometer (^{13}C at 100 MHz) or a Brucker 200 MHz (^{13}C at 50 MHz). Unless otherwise specified UV spectra were obtained in methanol solutions and spectra were recorded on DMSO-d_6 solutions with TMS as internal standard. Column and thin-layer chromatography utilized silica gel; eluents were methylene chloride with increasing amounts of methanol. Melting points are uncorrected. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

General Procedure for Mitsunobu Condensation and Deprotection. 1-(1,3-Dihydroxy-2-propyl)pyrimidines (9a−c). Diethyl azodicarboxylate (DEAD) (4.40 g, 25.3 mmol) dissolved in anhydrous tetrahydrofuran (40 mL) was added dropwise at room temperature, under a nitrogen atmosphere, to a stirred solution or suspension of triphenylphosphine (6.56 g, 25.0 mmol), bis-1,3-trityloxy-2-propanol (**6**)[17] (5.77 g, 10.0 mmol), and the appropriate base[18,19] (20.0 mmol) in anhydrous 1,4-dioxane (200 mL). After addition, the stoppered flask was stirred at room temperature for 16−23 h, and then solvent was removed under reduced pressure. Products (**8a**−**c**) were isolated by column chromatography, dissolved in methanol (250 mL), cooled to 0 °C, saturated with gaseous ammonia and stirred for 16−20 h. Solvent and ammonia were removed under reduced pressure, and the residue was stirred with 80% acetic acid (200 mL) at 70−75 °C until the original suspensions became clear and TLC indicated completion of the reaction (4−8 h). Following solvent removal and re-evaporation with added toluene (2 × 50 mL) under reduced pressure, the resulting white to beige mixtures were suspended in water (60 mL) and extracted with methylene chloride (3 × 50 mL). Evaporation of the water layer gave **9a**−**c**, purified further by either column chromatography (elution with 3% methanol in methylene chloride) or recrystallization from chloroform−methanol mixtures.

1-(1,3-Dihydroxy-2-propyl)uracil (9a): 68%. Mp: 153−155 °C. UV: λ_{max} 266 nm. ^{1}H NMR: δ 3.60−3.63 (m, 4H), 4.42 (m, 1H), 4.92 (s, 2H), 5.52 (d, 1H, $J = 8$ Hz), 7.58 (d, 1H, $J = 8$ Hz), 11.17 (s, 1H). ^{13}C NMR: δ 59.1, 100.2, 143.7, 151.5, 163.3. Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.26; H, 5.36; N, 15.12.

1-(1,3-Dihydroxy-2-propyl)-5-fluorouracil (9b): 41%. Mp: 175−176 °C. UV: λ_{max} 273 nm. ^{1}H NMR: δ 3.58−3.65 (m, 4H), 4.44 (m, 1H), 4.95 (t, 2H, $J = 4.2$ Hz), 7.98 (d, 1H, $J = 7.2$ Hz), 11.68 (br s, 1H). ^{13}C NMR: δ 59.2, 59.7, 128.5 (d, $^2J = 33.2$ Hz), 139.8 (d, $^1J = 227.2$ Hz), 150.6, 157.4 (d, 2H, $^2J = 26.7$ Hz). Anal. Calcd for $C_7H_9FN_2O_4$: C, 41.18; H, 4.44; N, 13.72. Found: C, 41.29; H, 4.41; N, 13.71.

1-(1-Acetyloxy-3-hydroxy-2-propyl)-5-fluorouracil (10b): isolated (6%) during the column chromatography of **9b**. ^{1}H NMR: δ 1.99 (s, 3H), 3.66 (m, 2H), 4.27 (d, 2H, $J = 5.6$ Hz), 4.66 (m, 1H), 5.16 (t, 1H, $J = 8.4$ Hz), 8.16 (d, 1H, $J = 5.6$ Hz), 11.43 (s, 1H). Treatment with methanolic ammonia (room temperature, 15 h) quantitatively converted **10b** to **9b**.

1-(1,3-Dihydroxy-2-propyl)thymine (9c): 78%. Mp: 227−229 °C. UV: λ_{max} 271 nm. ^{1}H NMR: δ 1.77 (s, 3H), 3.58−3.64 (m, 4H), 4.43 (m, 1H), 4.90 (t, 2H, $J = 7.7$ Hz), 7.47 (s, 1H), 11.15 (s, 1H). ^{13}C NMR: δ 12.1, 58.8, 59.0, 107.8, 139.2, 151.5, 163.9. Anal. Calcd for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 13.99. Found: C, 48.08; H, 6.02; N, 14.00.

1-(1-Acetyloxy-3-hydroxy-2-propyl)thymine (10c): isolated (4%) during column chromatography of **9c**. ^{1}H NMR: δ 1.77 (s, 3H), 1.98 (s, 3H), 3.65 (m, 2H), 4.28 (m, 2H), 4.63 (m, 1H), 5.10 (t, 1H, $J = 5.6$ Hz), 7.58 (s, 1H), 11.23 (s, 1H). ^{13}C NMR: δ 12.0, 20.4, 55.8, 58.9, 61.5, 108.5, 138.6, 151.4, 163.7, 170.0. Treatment with methanolic ammonia (room temperature, 13 h) quantitatively converted **10c** to **9c**.

***N*^{4}-Benzoyl-*O*^{2}-(bis-1,3-trityloxy-2-propyl)cytosine (13a).** Mitsunobu condensation of **6** and *N*^{4}-benzoylcytosine (as above) gave, after column chromatography, **13a** (36%) contaminated with ca. 6% of isomeric material (presumably the N-1 alkylated isomer). Pure product was obtained by rechromatography. Mp: 107−110 °C. ^{1}H NMR ($CDCl_3$): δ 3.40−3.52 (m, 4H), 5.53 (quint., 1H, $J = 5.2$ Hz), 7.2−7.4 (m, 30H), 7.49−7.66 (m, 3H), 7.85 (d, 1H, $J = 5.6$ Hz), 8.02 (d, 2H, $J = 7.7$ Hz), 8.49 (d, 1H, $J = 5.6$ Hz), 11.13 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 61.9, 74.9, 86.6, 103.9, 127.3, 127.7, 128.7, 129.1, 132.9, 133.3, 143.9, 159.0, 160.7, 164.3, 165.9. Anal. Calcd for $C_{52}H_{43}N_3O_4$: C, 80.69; H, 5.60; N, 5.43. Found: C, 80.58; H, 5.67; N, 5.38.

***N*^{4}-Acetyl-*O*^{2}-(bis-1,3-trityloxy-2-propyl)cytosine (13b):** prepared as for **13a**, 29%. Mp: 231−232 °C. ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H), 3.42−3.55 (m, 4H), 5.46 (quint., 1H, $J = 5.2$ Hz), 7.2−7.4 (m, ca. 30H), 7.72 (d, 1H, $J = 5.6$ Hz), 7.84 (s, 1H), 8.33 (d, 1H, $J = 5.6$ Hz). Anal. Calcd for $C_{47}H_{41}N_3O_4$: C, 79.30; H, 5.81; N, 5.90. Found: C, 79.03; H, 5.87; N, 5.78.

***O*^{2}-(Bis-1,3-trityloxy-2-propyl)cytosine (14).** A sample of **13a** (70 mg, 0.09 mmol) dissolved in methanol (20 mL), cooled to 0 °C, saturated with ammonia, and allowed to stand for 36 h at room temperature deposited fine white crystals (47 mg, 78%). Recrystallized from aqueous MeOH, mp 117−121 °C. ^{1}H NMR ($CDCl_3$): δ 3.42 (dd, 2H, $J = 9.6$, 7.6 Hz), 3.53 (dd, 2H, $J = 9.6$, 4.8 Hz), 4.89 (s, 2H), 5.45 (quint., 1H, $J = 5.2$ Hz), 6.00 (d, 1H, $J = 5.6$ Hz), 7.2−7.4 (m, Tr H's), 7.93 (d, 1H, $J = 5.6$ Hz). ^{13}C NMR ($CDCl_3$): δ 62.0, 74.0, 86.4, 99.1, 126.8, 127.7, 128.8, 144.0, 157.4, 164.7, 164.8. Anal. Calcd

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for $C_{45}H_{39}N_3O_3 \cdot 0.5H_2O$: C, 79.62; H, 5.94; N, 6.19. Found: C 79.50; H, 6.17; N, 6.20.

***N*⁴-Benzoyl-*O*²-(2,3-dihydroxypropyl)cytosine (15).** A sample of **13a** (1.31 g, 1.70 mmol) was dissolved in 80% (aqueous) acetic acid (50 mL) and heated for 11 h at 60−65 °C. After removal of the solvent and re-evaporation with added 1-butanol and then toluene, the residue was shaken with a mixture of water and methylene chloride (50 mL each). The aqueous layer was evaporated under reduced pressure to give **15** (0.305 g, 62%), further purified by recrystallization from ethyl acetate−methanol (5:1). Mp: 156−158 °C. ^{1}H NMR: δ 3.49 (t, 2H, J = 5.6 Hz), 3.85 (m, 1H), 4.27 (dd, 1H, J = 10.8, 6.4 Hz), 4.37 (dd, 1H, J = 6.4, 4.4 Hz), 4.70 (t, 1H, J = 5.6 Hz), 4.90 (d, 1H, J = 5.2 Hz), 7.54 (t, 2H, J = 7.6 Hz), 7.62 (t, 1H, J = 7.2 Hz), 7.87 (d, 1H, J = 5.4 Hz), 8.04 (d, 2H, J = 8.0 Hz), 8.52 (d, 1H, J = 5.4 Hz), 11.14 (s, 1H). ^{13}C NMR: 62.7, 68.5, 69.5, 104.3, 128.2, 128.3, 132.4, 133.3, 160.1, 160.2, 164.5, 167.0. Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.11; H, 5.23; N, 14.53. Found: C, 57.88; H, 5.30; N, 14.37.

***O*²-(2,3-Dihydroxypropyl)cytosine (16).** Compound **15** (0.134 g, 0.464 mmol) treated with methanolic ammonia as for **14** gave a quantitative yield of **16**, mp = 129−131 °C from ethyl acetate−MeOH (4:1). ^{1}H NMR: δ 7.84 (d, 1H, J = 7.2 Hz), 6.81 (br s, 2H), 6.06 (d, 1H, J = 7.2 Hz), 4.89 (d, 1H, J = 4.8 Hz), 4.61 (t, 1H, J = 6.0 Hz) 4.16 (dd, 1H, J = 10.8, 4.4 Hz), 4.05 (dd, 2H, J = 10.4, 6.0 Hz), 3.73 (m, 1H), 3.40 (t, 2H, J = 6.0 Hz). ^{13}C NMR: δ 62.7, 67.6, 69.6, 99.1, 156.0, 164.8, 165.1. Anal. Calcd for $C_7H_{11}N_3O_3$: C, 45.40; H, 5.99; N, 22.69. Found: C, 45.47; H, 5.99; N, 22.74.

General Procedure for Cycloacetalization and Deprotection. *cis*-1-(2-Hydroxymethyl-1,3-dioxan-5-yl)pyrimidines (cis-5a−c). In a one-necked 10 mL flask with a vacuum takeoff adapter, a stirred mixture of a 1-(1,3-dihydroxy-2-propyl)pyrimidine (**9**, 5.00 mmol), freshly distilled benzoyloxyacetaldehyde[22] (2.46 g, 15.0 mmol), and ca. 25 mg of *p*-toluenesulfonic acid was heated (oil bath) at 75−80 °C and 1−2 mmHg. The suspension became clear after about 1 h. When TLC of the mixture (chloroform−methanol, 9.5:0.5) showed no pyrimidine starting material and a new product spot (2−3 h), heating was discontinued, and the cooled mixture was taken up in methylene chloride (50 mL), extracted with saturated $NaHCO_3$ solution (25 mL) and water (25 mL), and dried over $MgSO_4$. Removal of the solvent gave ca. 3.9 g of crude material (product + aldehyde) that was chromatographed over silica gel (75 g), affording **11** (3.1−4.6:1, cis:trans, by NMR) on elution with 2% methanol in methylene chloride. Product **11**, a cis/trans mixture, was dissolved in methanol (200 mL), cooled to 0 °C, saturated with ammonia, and stirred at room temperature for 15−22 h. Evaporation of the solvent gave a mixure of **5** and benzamide, separated easily by passage through a silica gel column (60 g) and elution with 2% methanol in methylene chloride. Pure cis-**5** eluted first, followed by mixtures of cis- and trans-**5**. The cis products were recrystallized from chloroform−methanol mixtures. A small sample (~2 mg) of trans-**5c** was obtained by thick layer chromatography (silica gel, eluent chloroform−methanol 9:1, 100 mL + 2 mL benzene and 1 drop of acetic acid); similar attempts to isolate pure samples of the other trans-**5** compounds were unsuccessful. Isolated yields of cis-**5** are given below; yields of trans-**5** are estimated from the NMR spectra of the crude cis/trans mixtures, using the integrated values of the pyrimidinyl C-5 signals of the cis and trans compounds and the isolated yields of the cis. NMR data for the trans compounds were obtained from binary mixtures rich in trans-**5**, by subtraction of the pure cis isomer.

***cis*-1-(2-Hydroxymethyl-1,3-dioxan-5-yl)uracil (cis-5a):** 62%. Mp: 191−192 °C. UV: λ_{max} 266 nm. ^{1}H NMR: δ 3.39 (m, 2H), 4.14 (apparent d, 2H), 4.21 (apparent d, 2H), 4.29 (br s, 1H), 4.70 (t, 1H, J = 3.7 Hz), 4.92 (t, 1H, J = ca. 2 Hz, exchangeable), 5.60 (d, 1H, J = 7.9 Hz), 8.16 (d, 1H, J = 7.9 Hz), 11.32 (s, 1H). ^{13}C NMR: δ 47.5, 62.4, 67.7, 100.6, 101.1, 143.7, 150.9, 163.2. Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.35; H, 5.30; N, 12.28. Found: C, 47.47; H, 5.30; N, 12.18.

***trans*-1-(2-Hydroxymethyl-1,3-dioxan-5-yl)uracil (trans-5a)** (estimated, 11%). ^{1}H NMR: δ 3.89−4.05 (m, 4H), 4.51 (m, 1H), 4.71 (s, 1H), 4.92 (t, 1H, J = ca. 2 Hz, exchangeable), 5.58 (d, 1H, J = 7.6 Hz), 7.71 (d, 1H, J = 7.6 Hz), 11.34 (br s, 1H).

***cis*-5-Fluoro-1-(2-hydroxymethyl-1,3-dioxan-5-yl)uracil (cis-5b):** 71%. Mp: 207−208 °C. UV: λ_{max} 266 nm. ^{1}H NMR: δ 3.43 (m, 2H), 4.13 (apparent d, 2H), 4.21 (apparent d, 2H), 4.31 (s, 1H), 4.71 (t, 1H, J = 4.0 Hz), 4.98 (t, 1H, J = 6.0 Hz), 8.39 (d, 1H, J = 7.6 Hz), 11.94 (s, 1H). ^{13}C NMR: δ 47.5, 62.5, 67.7, 101.0, 128.3 (d, ^2J = 34 Hz), 139.3 (d, ^1J = 227 Hz), 149.6, 156.9 (d, ^2J = 26 Hz). Anal. Calcd for $C_9H_{11}FN_2O_5$: C, 43.91; H, 4.50; N, 11.38. Found: C, 43.99; H, 4.51; N, 11.36.

***trans*-5-Fluoro-1-(2-hydroxymethyl-1,3-dioxan-5-yl)uracil (trans-5b)** (estimated, 15%). ^{1}H NMR: δ 3.94 (t, 2H, J = 11.0 Hz), 4.04 (dd, 2H, J = 10.8, 4.8 Hz), 4.50 (m, 1H), 4.58 (t, 1H, J = 4.4 Hz, exchangeable), 4.95 (t, 1H, J = 6.4 Hz), 8.16 (d, 1H, J = 7.2 Hz), 11.85 (s, 1H).

***cis*-1-(2-Hydroxymethyl-1,3-dioxan-5-yl)thymine (cis-5c):** 76%. Mp: 230−231 °C. UV: λ_{max} 271 nm. ^{1}H NMR: δ 1.79 (s, 3H), 3.43 (m, 2H), 4.08 (apparent d, 2H), 4.22 (apparent d, 2H), 4.30 (s, 1H), 4.71 (t, 1H, J = 4.0 Hz), 4.97 (t, 1H, J = 6.4 Hz), 8.08 (s, 1H), 11.33 (s, 1H). ^{13}C NMR: δ 12.3, 47.1, 62.5, 67.8, 101.0, 107.9, 139.4, 151.0, 163.7. Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.47; H, 5.77; N, 11.49.

***trans*-1-(2-Hydroxymethyl-1,3-dioxan-5-yl)thymine (trans-5c)** (estimated, 18%). ^{1}H NMR: δ 1.74 (s, 3H), 3.40 (m, 2H), 3.88−4.10 (m, 4H), 4.53 (m, 1H), 4.59 (t, 1H, J = 4.6 Hz), ~5 (v br s), 7.53 (s, 1H). ^{13}C NMR: δ 12.2, 47.0, 62.4, 66.5, 100.9, 109.0, 137.6, 151.7, 164.9.

General Procedure for the Preparation of Cytosin-1-yl Derivatives (cis-5d,e). A solution of **11a** or **11b** (7.10 mmol) and 1,2,4-triazole (6.83 g, 98.9 mmol) in anhydrous pyridine (45 mL) was cooled to 0 °C. Under an atmosphere of dry nitrogen, 4-chlorophenyl dichlorophosphate (5.0 g, 20.4 mmol) was added dropwise over 5 min to the cold, stirred solution. After 4 h at 0 °C the ice bath was removed and the orange solution was stirred at room temperature for 20 h. Removal of solvent under reduced pressure gave tarry dark material that was re-evaporated three times with added toluene, dissolved in methylene chloride (100 mL), and extracted with four portions of water (50 mL each). The aqueous layers were re-extracted twice with methylene chloride (50 mL each), and the combined organic layers were dried ($MgSO_4$) and evaporated to give a brownish solid. Chromatography (silica gel, 50 g) gave the triazole derivative cis/trans-**12** which was used without additional purification. Product **12** was stirred at room temperature with concentrated ammonium hydroxide (15 mL) and 1,4-dioxane (30 mL) for 20 h; solvent was removed and the residue treated with saturated methanolic ammonia (50 mL) for 24 h and then evaporated to give cis/trans-**5**. Pure samples of cis-**5d**,**e** were obtained by chromatography and elution with 2% methanol in methylene chloride, along with cis/trans mixtures. Small amounts of the uracil derivatives cis-**5a** and cis-**5b** were also isolated.

***cis*-1-(2-Hydroxymethyl-1,3-dioxan-5-yl)cytosine (cis-5d):** 38%. Mp: 245−247 °C. UV: λ_{max} 275 nm. ^{1}H NMR: δ 3.37 (m, 2H), 4.05 (apparent d, 2H), 4.18 (apparent d, 2H), 4.32 (s, 1H), 4.69 (t, 1H, J = 10.2 Hz), 4.94 (t, 1H, J = 6.4 Hz), 5.73 (d, 1H, J = 7.2 Hz), 6.99, 7.16 (br s's, 2H, exchangeable), 8.12 (d, 1H, J = 7.2 Hz). ^{13}C NMR: δ 47.8, 62.7, 67.9, 93.0, 101.2, 144.0, 155.4, 165.4. Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.63; H, 5.74; N, 18.46.

***trans*-1-(2-Hydroxymethyl-1,3-dioxan-5-yl)cytosine (trans-5d)** (estimated, 7%). ^{1}H NMR: δ ~3.4 (ca. 2H, partially covered), 3.85 (t, 2H, J = 10.4 Hz), 3.93 (dd, 2H, J = 10.4, 7.2 Hz), 4.59 (t, 1H, J = 4.8 Hz), 4.60 (m, 1H), 4.93 (t, 1H, J = 4.8 Hz), 5.71 (d, 1H, J = 7.4 Hz), 7.13, 7.26 (br s's, 2H, exchangeable), 7.65 (d, 1H, J = 7.4 Hz).

***cis*-5-Fluoro-1-(2-hydroxymethyl-1,3-dioxan-5-yl)cytosine (cis-5e):** 39%. Mp: 253−255 °C. UV: λ_{max} 283 nm. ^{1}H NMR: δ 3.42 (dd, 2H, J = 4.0, 6.0 Hz), 4.08 (apparent d, 2H), 4.19 (apparent d, 2H), 4.30 (s, 1H), 4.70 (t, 1H, J = 4.0 Hz), 4.94 (t, 1H, J = 6.2 Hz), 7.50, 7.65 (br s's, 2H), 8.27 (d, 1H, J = 7.6 Hz). ^{13}C NMR: δ 48.2, 62.5, 67.8, 101.1, 128.8 (d,

^2J = 32 Hz), 138.4 (d, ^1J = 239 Hz), 153.7, 156.9(d, ^2J = 13 Hz). Anal. Calcd for $C_9H_{12}FN_3O_4$: C, 44.08; H, 4.93; N, 17.14. Found: C, 44.15; H, 4.92; N, 17.18.

***trans*-5-Fluoro-1-(2-hydroxymethyl-1,3-dioxan-5-yl)cytosine (trans-5e):** (estimated, 9%). ^{1}H NMR: δ 3.38 (m, 2H), 3.88−4.02 (m, 4H), 4.55 (m, 1H), 4.57 (t, 1H, J = 2.8 Hz, exchangeable), 4.91 (t, 1H, J = 6.0 Hz), 7.65, 7.75 (br s's, 2H), 8.01 (d, 1H, J = 7.2 Hz).

Acid-Catalyzed Equilibration of *cis*- and *trans*-1-(2-Hydroxymethyl-1,3-dioxan-5-yl)thymines. A solution of cis-**5c** in hexadeuteriodimethyl sulfoxide (0.1 mmol in 0.75 mL) was placed in an NMR tube with TMS and boron trifluoride etherate (ca. 50 μL each). The tube and its contents were degassed by two freeze−thaw cycles, sealed, and maintained in a water bath at 60−65 °C (tube A). An NMR tube containing a mixture of 75% trans-**5c** and 25% cis-**5c** was similarly prepared (tube B). Periodically, the C-6 proton signals (singlets: δ 8.08 (cis), δ 7.53 (trans)) were integrated. After 29 days, tube A, 83% cis, 17% trans; tube B, 70% cis, 30% trans. After 47 days both tubes contained 75% cis, 25% trans, a ratio that did not change further with time. No additional products were detected.

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Supporting Information Available: ^{1}H NMR spectra of compounds cis-**5a**−**e**, **8a**−**c**, **9a**,**b**,**c**, **10b**,**c**, **12a**,**b**, **13**−**16**; ^{13}C NMR of cis-**5a**−**e**, **9a**,**b**,**c**, **10c**, **12a**, **13**−**16** (36 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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