Synthesis of L-Dioxolane Nucleosides and Related Chemistry

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(+)-L- or (+)-(2*R*,4*S*)-1-[4-(hydroxymethyl)-1,3-dioxolan-2-yl]-5-fluorouracil (**25**) and other novel classes of 1,3-dioxolane nucleosides have been synthesized. Coupling of 2-methoxy-4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolane (**23**) or 2-methyl-1,3-dioxolane (**9**) with silylated 5-fluorouracil, thymine, cytosine, and 5-chlorocytosine in the presence of TMSOTf gave the corresponding 1,3-dioxolane nucleosides. These nucleosides were decomposed and rearranged to the ring-opened products in certain reaction conditions. It was found that 5-fluorouricil nucleosides (**12** and **25**) were relatively more stable than the thymine or cytosine derivatives (**10**, **13**, and **16**). Bulky protecting group (TBDPS) at the 1,3-dioxolane moiety in compound **24** may also contribute the stability to the 1,3-dioxolane nucleosides. The structures of these novel 1,3-dioxolane nucleosides and ring-opened products have been assigned by NMR spectra, and the mechanisms of decomposition and rearrangement to the ring opened products were discussed.

As a part of our continuing efforts to discover novel antiviral agents for human immunodeficiency virus (HIV) and hepatitis B virus (HBV), we have recently reported the asymmetric synthesis and antiviral activity of 1,3-dioxolane and 1,3-oxathiolane nucleosides.[1-5] In these reports, we have described dioxolane and oxathiolane nucleosides with the L-configuration or "L-like nucleoside" which exhibited potent anti-HIV and anti-HBV activities. (−)-β-L-(2R,5S)-1-[2-(Hydroxymethyl)oxathiolan-5-yl]cytosine (3TC), a compound with an unnatural nucleoside configuration, was found to be significantly more potent and less toxic than its racemate[6] or (+)-β-D-(2S,5R)-enantiomer[7] against HIV-1 in human peripheral blood mononuclear (PBM) cells. 1,3-Dioxolanylcytosines showed biological patterns similar to that of 1,3-oxathiolanylcytosine in that the (−)-β-L-(2*S*,4*S*)-enantiomer[2] with the unnatural nucleoside configuration was more potent than the (+)-β-D-(2R,4R)-enatiomer[3] with the natural nucleoside configuration. Interestingly, it was the first example of L-nucleosides being biologically more potent than the corresponding D-nucleosides (or the natural configuration).[7,8] However, these patterns were only applied to the cytosine derivatives in dioxolane and oxathiolane nucleosides.

Recently, several laboratories have also reported interesting biological activities of L-nucleosides such as FTC,[9] L-FddC,[10] and L-FMAU[11] as anti-HIV and anti-HBV agents. It was, therefore, of interest to extend the chemistry of L-nucleosides in the hope of discovering new and effective antiviral agents against HIV and HBV. We now wish to report some interesting chemistry related to the synthesis of β-L-1-[4-(hydroxymethyl)-1,3-dioxolan-2-yl]-5-fluorouracil and related 1,3-dioxolane nucleosides with heterocyclic bases substituted at 2-position in the dioxolane ring.

Our original approach was to synthesize the desired L-1,3-dioxolane nucleosides utilizing 1,6-anhydro-D-galactose (**1**)[12] to synthesize 2-acetoxy-4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolane (**8**) as the key intermediate for condensation with silylated bases (Scheme 1). However, this approach was unsuccessful due to the decomposition of **8** during condensation to form the L-1,3-dioxolane nucleosides. The similar decomposition of 1,3-dioxolane compounds was also reported in the literature.[13]

In order to find a viable synthetic approach for L-1,3-dioxolane nucleoside, we therefore decided to explore the chemistry of the 1,3-dioxolane system with a readily available compound, 2-methoxy-1,3-dioxolane, which can be condensed with heterocyclic bases. 2-Methoxy-1,3-dioxolane (**9**) was prepared from trimethyl orthoformate and ethylene glycol in the presence of catalytic amounts of benzoic acid as described.[14] In attempts to find optimal conditions for the condensation of 2-methoxy-1,3-dioxolane (**9**) with silylated bases, various Lewis acids (TMSOTf, $SnCl_4$, or $TiCl_4$), solvents (CH_3CN, CH_2Cl_2, or $ClCH_2CH_2Cl$), and reaction temperatures were investigated. In contrast to the other nucleosides, it was found

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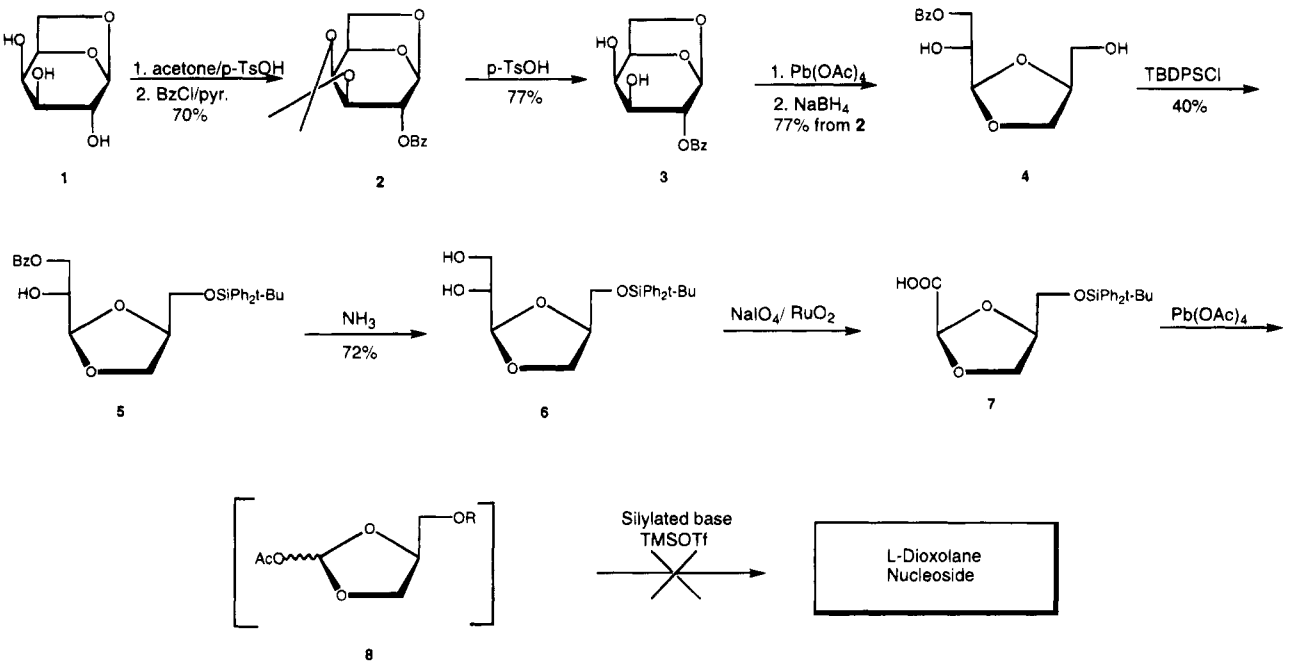
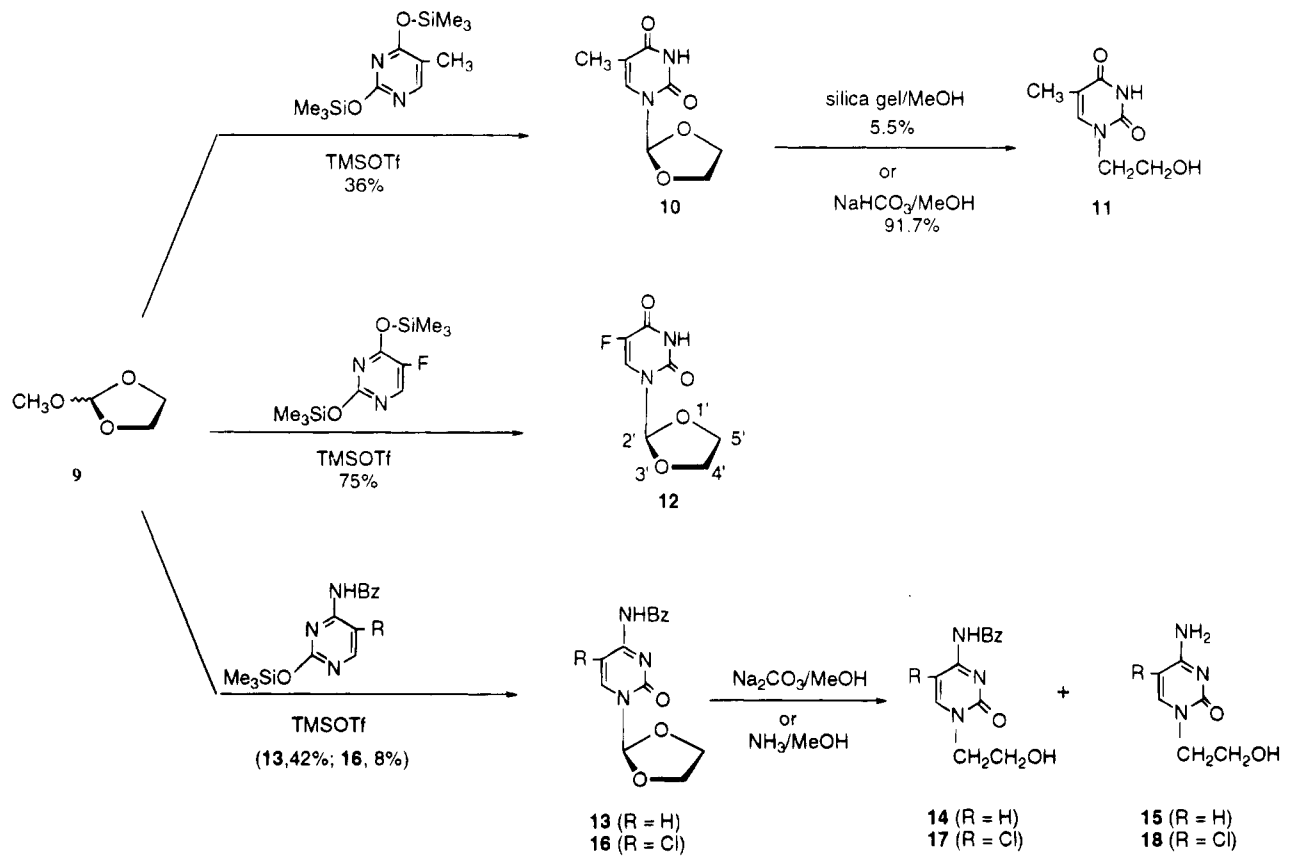
Scheme 1



Scheme 2



that the 1,3-dioxolane nucleosides **10**, **12**, **13**, and **16** with bases substituted at the 2-position were unstable (Scheme 2). As a consequence, they easily decomposed to the ring-opened products **11**, **14**, **15**, **17**, and **18** under reaction conditions. However, after careful investigation, we were able to synthesize 1-(1,3-dioxolan-2-yl)thymine (**10**) from the condensation of **9** with silylated thymine in CH_3CN using TMSOTf (*vide infra*). After being stirred for 48 h at room temperature, the reaction was terminated by the addition of a saturated $NaHCO_3$ solution and ethyl acetate, and then the organic layer was immediately dried over anhyd Na_2SO_4. During the purification with silica gel column, the nucleoside **10** partially decomposed to 1-(2-hydroxyethyl)thymine (**11**), probably through a rearrangement reaction. The pure compound **10**, however, was only obtained by repeated recrystallization instead of separation by a silica gel column. 5-Fluorouracil nucleoside **12** was synthesized from silylated 5-fluorouracil and **9**. N^4-Benzoyl-5-chlorocytosine was also condensed with **9** to obtain the 5-chlorocytosine derivative

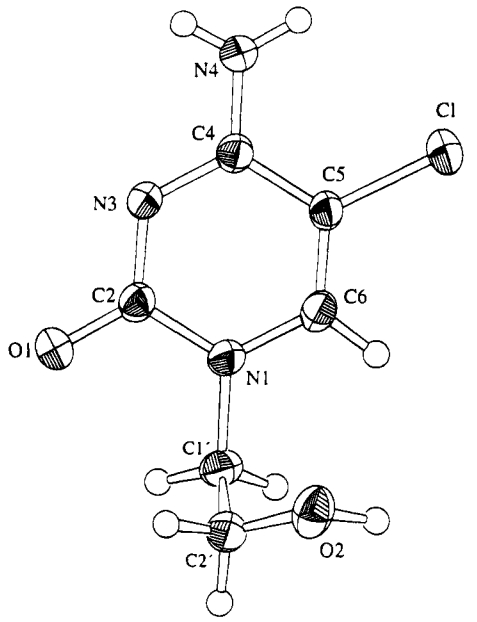


Figure 1. X-ray crystallographic computer-generated perspective drawing of 18.

16, which like the thymine nucleoside **10**, decomposed on a silica gel column to the ring-opened compound **17**. The pure **16** could only be obtained from repeated recrystallization. The hydrolysis of the N^4-benzoyl group in **16** to the corresponding cytosine-1,3-dioxolane nucleoside in $NaHCO_3$/MeOH solution only produced a mixture of **17** and **18**. Obviously, the weak base initially cleaved the 1,3-dioxolane ring system in **16**, instead of the hydrolysis of the benzamide bond, to form the hydroxyethyl derivative **17**, in which benzoyl group was then hydrolyzed to yield 5-chloro-1-(2-hydroxyethyl)cytosine (**18**). The structure of the decomposed product **18** was confirmed by X-ray crystallography (Figure 1)[21] as well as NMR spectroscopy. N^4-Benzoylcytosine nucleoside **13** was synthesized from the condensation of silylated N^4-benzoylcytosine with **9**. The pure **13** was obtained with the same procedure as **16**. Debenzoylation of **13** in an ammonia/methanol solution also resulted in the cleavage of 1,3-dioxolane ring system and benzamide to form compounds **14** and **15**. However, Na_2CO_3, instead of NH_3/MeOH, gave either **14** or **15** depending on the conditions. Condensations of **9** with other heterocyclic bases, such as cytosine, 5-fluorocytosine, and 6-chloropurine were unsuccessful under various reaction conditions.

After becoming experienced with the model system, we investigated the synthesis of 4-(hydroxymethyl)-1,3-dioxolane nucleoside **25**. 2-Methoxy-4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolane (**23**) was selected as an intermediate for the coupling with a silylated base (Scheme 3). Compound **23** was prepared from (R)-2,3-*O*-isopropylideneglyceraldehyde (**19**),[15] which was reduced by sodium borohydride to form 2,3-*O*-isopropylideneglycerol (**20**).[16] Compound **20** was protected by *tert*-butyldiphenylsilyl chloride to form **21**, and then the isopropylidene protecting group in **21** was removed in 90% acetic acid to give (*R*)-1-[(*tert*-butyldiphenylsilyl)oxy]-2,3-propanediol (**22**).[17,18] Upon cyclization with trimethyl orthoformate, compound **22** was converted to **23** in the presence of benzoic acid in 75% yield. After the liberated methanol was removed, sodium carbonate was added to the reaction mixture to neutralize benzoic acid which was chromatographically isolated as a 1:1 α,β-mixture, which had to be kept in an anhydrous condition due to its moisture sensitivity. The condensation of **23** with silylated 5-fluorouracil resulted in the desired product **24** (61.5%). It was found that compound **24** was significantly more stable than the above 1,3-dioxolane nucleosides **10**, **12**, **13**, or **16**. It was stable on a silica gel column as well as in an ammonia/methanol solution, indicating that the bulky protecting group such as TBDPS on the 1,3-dioxolane ring appeared to deter the decomposition (*vide infra*). However, attempts to condense **23** with various bases, such as 5-fluoro-N^4-benzoylcytosine, 5-fluorocytosine, thymine, or 6-chloropurine were unsuccessful.

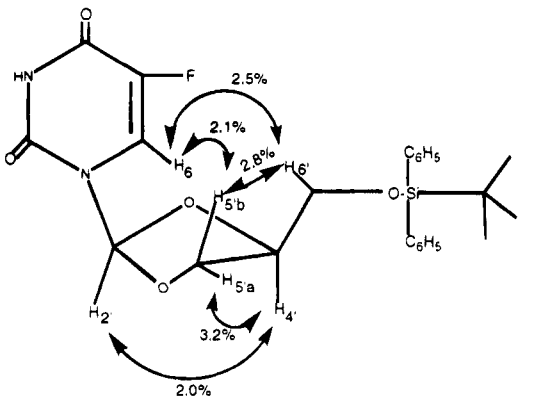


Figure 2. NOE experiment of (+)-(2*R*,4*R*)-1-[4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-2-yl]-5-fluorouracil (**24**).

The anomeric configuration of **24** was assigned by ^1H NMR and NOE experiments as shown in Figure 2, in which upon irradiation of H-2′ proton of **24** the signal for H-4′ (δ 5.24) was enhanced by 2.0%. NOE was also observed as a 2.1% increase between H-6 and H-5′$_b$; however, H-5′$_a$ was not affected due to the different orientation from H-5′$_b$. Similarly, the irradiation of H-6 proton (δ 7.30) increased the proton signal of H-6′ (δ 3.81) by 2.5%, indicating that H-6 was closer in space with H-6′ and H-5′$_b$ and the anomeric configuration of **24** must be β.

Treatment of **24** with n-Bu_4NF in anhydrous THF for 30 min gave a mixture containing desilylated product **25** and decomposed product **26**. Extending the reaction time (up to 1 h) only gave the decomposed product **26**. When the reaction mixture was purified by silica gel chromatography, desilylated product **25** was separated only in low yield due to the partial decomposition of **25** to the dihydroxypropyl derivative **26**. A modified approach by adding 1 equiv of acetic acid in the reaction mixture to neutralize the basicity of n-Bu_4NF was used, from which the pure product **25** was successfully isolated in high yield. The structure of the ring-opened product **26** was assigned as (+)-(2*R*)-1-(2,3-dihydroxypropyl)-5-fluorouracil with a specific rotation of $[\alpha]^{25}_D$ 79.58°. This assignment was based on the independent synthesis of (−)-(2*S*)-1-(2,3-dihydroxypropyl)-5-fluorouracil (**27**) with $[\alpha]^{25}_D$ −79.48°, the enantiomer of **26**, prepared from the condensation of 5-fluorouracil with (2*R*)-2,3-epoxy-1-

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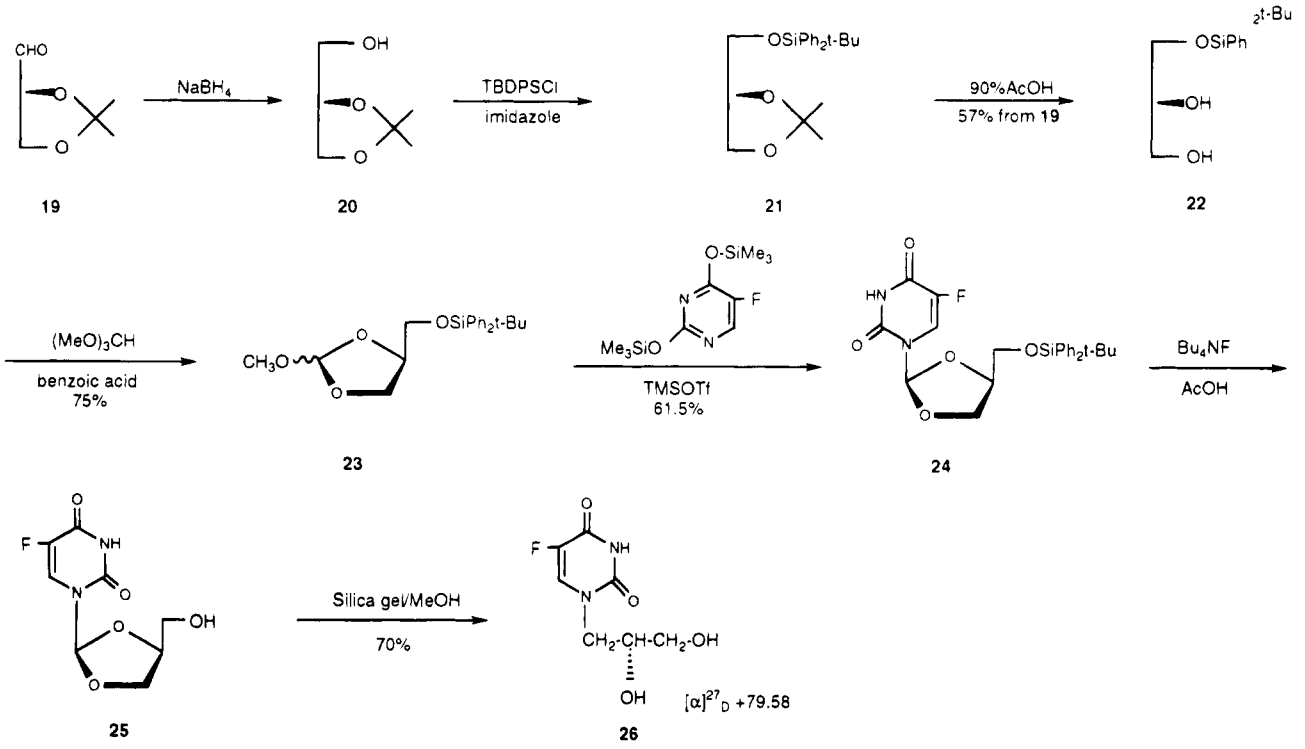
Scheme 3



propanol in the presence of trace amounts of K_2CO_3 using a modified Seita's method.[19]

Synthesis of the desired L-1,3-dioxolane nucleoside **25** required careful experiments to avoid decomposition. However, the mechanism of decomposition and rearrangement of the nucleoside **25** and other 1,3-dioxolane nucleosides to the acyclic compounds was interesting in that it may produce an enantiomerically pure isomer such as **26**. Although the proposed mechanism (Scheme 4) is tentative, it may partially explain the formation of **26**. The lone pair electrons on the oxygen atoms of the 1,3-dioxolane ring may contribute the glycosyl bond cleavage to give an anion **28** and a cation **29**, which may be stabilized as an ion pair. Sequentially, the anion **28** can preferably attack the C-5′ due to the less steric hindrance, compared to that of the tertiary carbon atom C-4′. Followed by silica gel catalyzed hydrolysis, formate **30** was converted to (+)-(2*R*)-1-(2,3-dihydroxypropyl)-5-fluorouracil (**26**) as the sole product. Supporting evidence for this mechanism was the finding that the chiral center at C-4′ in the nucleoside **25** was not involved in the rearrangement and its configuration was still retained in **26**. If the anion **28** had attacked the more sterically hindered C-4′ (in cation **29**), the rearrangement product would have been 1-(1,3-dihydroxyisoprop-2-yl)-5-fluorouracil (**31**). The proposed mechanism can also explain the added stability of compound **24**, in which the bulky [(*tert*-butyldiphenylsilyl)oxy]methyl group at C-4′ would block the nucleophilic attack of anion **28** at C-5′ or C-4′. This mechanism may also partially explain the base-catalyzed decomposition in which the transition state **29** may be attacked by a base at C-5′ as the 5-fluorouracil ion **28** does, which leads to **30**. The additional evidence for the proposed mechanism may be supported by the fact that 5-fluorouracil was also detected from the decomposition reaction.

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It is interesting to note that the yields for **10** and **16** were higher than that of **12** and **16**. The observed yields may be related to the nucleophilicity of the heterocyclic moiety during the condensation of **9** with a hetercyclic moiety. Additional speculation for the lower yield of **12** and **16** may be related to the facilitated decomposition of **12** and **16** due to the elctronegativity of the 5-F and 5-Cl groups which promote the direct attack at the 4′-position by a solvent or a base in the absence of the bulky group at 4′-position.

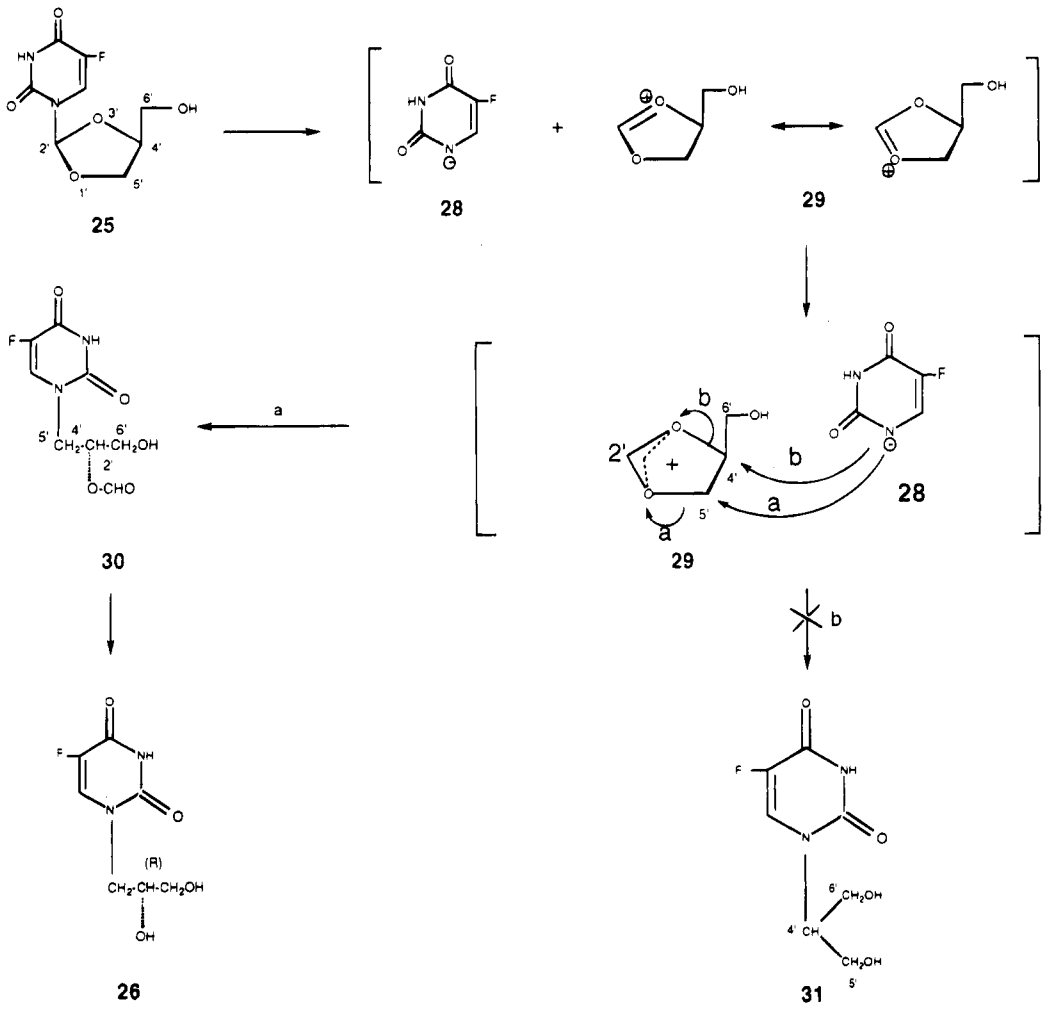
Biological evaluations of the synthesized compounds are in progress and will be reported elsewhere.

Experimental Section

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. Nuclear magnetic resonance spectra were recorded on Bruker 400 or 300 MHz spectrometers with tetramethylsilane as the internal reference; chemical shifts (δ) are reported in parts per million. UV spectra were obtained on a Beckman DU-7 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Mass spectra were obtained on a Ribermag R10-10C spectrometer. The silica gel used for vacuum flash column chromatography was purchased from Bodman (MN-Kieselgel G; particle size 2−20 μm). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. All reactions were monitored using thin layer chromatography on Analtech 250 μm silica gel GF plates.

(+)-2-*O*-Benzoyl-3,4-*O*-isopropylidene-1,6-anhydro-D-galactopyranose (2). 2,2-Dimethoxypropane (50 mL) and *p*-toluenesulfonic acid (0.5 g) were added to a solution of 1,6-anhydro-D-galactose[11] (**1**) (20 g, 0.123 mol), prepared from penta-*O*-acetyl-D-galactose in 200 mL of acetone, and the reaction mixture was stirred at room temperature for 16 h. A saturated $NaHCO_3$ solution was added to neutralize the acid, and the reaction mixture was concentrated to dryness. The residue was purified by chromatography on a silica gel column using EtOAc/hexane (2:3) as the eluant to give 3,4-*O*-isopropylidene-1,6-anhydro-D-galactose (19g, 79%), mp 140 °C: $[\alpha]_{25D}$ 32.6° (*c* 0.32, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.54 (s, 3H), 2.56 (m, 1H), 2.72 (dd, J = 4.8, 9.3 Hz, 1H), 2.85 (m,

Scheme 4



1H), 3.27 (m, 1H), 3.73 (dd, J = 2.7, 3.8 Hz, 1H), 4.30 (m, 1H), 4.57 (d, J = 3.8 Hz, 1H, D_2O exchangeable), 5.94 (d, J = 3.8 Hz, 1H); ^{13}C ($CDCl_3$) δ 105.6, 87.7, 77.4, 69.1, 44.6, 26.1, 26.8. Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.93. Found: C, 53.22; H, 6.90.

Benzoyl chloride (14 g, 0.1 mol) was added dropwise to 19 g (0.092 mol) of the above 3,4-*O*-isopropylidene-1,6-anhydro-D-galactose in 100 mL of pyridine, and the reaction mixture was stirred at room temperature for 3 h. After removal of pyridine, the residue was dissolved in EtOAc (100 mL), washed with H_2O, 5% H_2SO_4 solution, saturated aqueous $NaHCO_3$, and brine, and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified as a silica gel column (hexane/EtOAc, 3:1) to give product **2** (25 g, 89%), mp 110 °C: $[\alpha]^{26}_D$ 38.1° (*c* 0.47, MeOH); ^1H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.57 (s, 3H), 3.36 (m, 1H), 4.25 (m, 2H), 4.59 (m, 1H), 4.80 (m, 1H), 5.14 (s, 1H), 5.50 (s, 1H), 7.37–8.09 (m, 5H, Ar); ^{13}C ($CDCl_3$) δ 165.1, 133.4, 129.8, 128.4, 99.0, 73.9, 72.1, 71.7, 69.1, 63.3, 25.7, 24.2. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.88. Found: C, 62.70; H, 5.90.

2-*O*-Benzoyl-1,6-anhydro-D-galactopyranose (3). Compound **2** (20 g, 0.65 mol) was hydrolyzed by 6.6 mL of H_2SO_4 in 700 mL of H_2O/dioxane (1:1) at 80 °C for 16 h. $NaHCO_3$ was added to adjust the solution to pH 7. The solvents were removed *in vacuo*, and the residue was dissolved in EtOAc (800 mL), washed with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). After removal of the solvent, the residue was recrystallized from hexane/methylene chloride to afford **3** (13 g, 77%), mp 162–164 °C: $[\alpha]^{25}_D$ 45.3° (*c* 0.36, $CHCl_3$) [lit.[21] mp 154–157 °C, $[\alpha]_D$ 45.5° (*c* 0.8, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 3.03 (dd, J = 6.9 and 10.5 Hz, 1H), 3.24 (d, J = 10.5 Hz, 1H), 3.83 (m, 2H), 4.62 (m, 1H), 5.01 (s, 1H), 4.07 (m, 2H, D_2O exchangeable), 5.66 (d, J = 1.1 Hz, 1H), 7.44–8.06 (m, 5H); ^{13}C ($CDCl_3$) δ 165.1, 133.1, 129.2, 128.9, 80.6, 79.6, 74.3, 70.1, 68.9, 65.0. Anal. Calcd for $C_{13}H_{14}NO_5$: C, 55.32; H, 4.96; N, 11.35. Found: C, 55.22; H, 5.10; N, 11.12.

(1′*R*,2*R*,4*S*)-2-(2-*O*-Benzoyl-1-hydroxyethyl)-4-(hydroxymethyl)-1,3-dioxolane (4). A solution of $NaIO_4$ (11.7 g, 0.55 mol) in 400 mL of H_2O was added to **3** (13 g, 0.048 mol) in 95% EtOH (400 mL), and the mixture was stirred at room temperature for 1 h. After complete conversion of the diol to aldehyde by TLC, the reaction mixture was concentrated to half of its original volume and cooled to 5 °C. $NaBH_4$ (7.94 g, 0.209 mol) was then added portionwise to the mixture over a period of 5 min, and the reaction mixture was stirred for another 10 min. The resulting mixture was neutralized with glacial acetic acid and concentrated to dryness to give crude **4** as an oil, which was purified by silica gel chromatography ($CHCl_3$/MeOH, 10:0.3) to give **4** (9 g, 77%): $[\alpha]^{25}_D$ 24.5° (*c* 0.57, $CHCl_3$); ^1H NMR (DMSO-d_6) δ 3.44 (d, J = 4.3 Hz, 2H), 3.70–3.89 (m, 2H), 4.07 (m, 1H), 4.20–4.37 (dd, J = 5.7, 9.4 Hz, 2H), 4.74 (t, J = 5.7 Hz, 1H, D_2O exchangeable), 4.93 (d, J = 4.3 Hz, 1H), 5.43 (d, J = 5.6 Hz, 1H, D_2O exchangeable), 7.49–8.07 (m, 5H); ^{13}C (DMSO-d_6) δ 166.6, 133.1, 129.4, 129.1, 128.3, 101.1, 68.4, 66.3, 73.25, 63.9, 62.3.

(1′*R*,2*R*,4*R*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-(2-benzoyl-1-hydroxyethyl)-1,3-dioxolane (5). Imidazole (1.5 g, 22.38 mmol) and *tert*-butyldiphenylsilyl chloride (2.24 g, 8.2 mmol) were added to a solution of compound **4** (2 g, 7.46 mmol) in 40 mL of DMF and the reaction mixture stirred at

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(21) The author has deposited atomic coordinates for **18** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

room temperature for 2.5 h. After DMF was removed under reduced pressure, the residue was dissolved in EtOAc and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column using EtOAc/hexane (1:4) as the eluant to yield compound **5** (1.5 g, 40%) as an oil: $[\alpha]^{23}_D$ 28.14° (*c* 0.43, $CHCl_3$); ^1H NMR ($CDCl_3$) δ, 7.39–8.06 (m, 15H), 5.09 (d, J = 3.6 Hz, 1H), 4.46 (m, 2H), 4.23 (m, 1H), 3.72 (m, 2H), 1.06 (s, 9H); ^{13}C ($CDCl_3$) δ 167.2, 133.6, 135.4, 132.2, 101.4, 74.5, 68.6, 65.5, 63.2, 61.9 24.8. Anal. Calcd for $C_{29}H_{34}O_6Si \cdot 0.2H_2O$: C, 68.20; H, 6.74. Found: C, 68.18; H, 6.74.

(1′*R*,2*R*,4*R*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-(1,2-dihydroxyethyl)-1,3-dioxolane (6). A saturated NH_3/MeOH solution (50 mL) was added to **5** (1.5 g) at 0 °C, and the reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography using $CHCl_3$/MeOH (10:0.5) as the eluant to give compound **6** (0.8 g, 72%) as an oil: $[\alpha]^{25}_D$ 22.54° (*c* 0.25, MeOH); ^1H NMR (DMSO-d_6) δ 7.38–7.64 (m, 10H), 4.83 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 4.77 (d, J = 3.9 Hz), 4.49 (t, J = 5.2 Hz, 1H, D_2O exchangeable), 4.17 (m, 1H), 3.84 (m, 2H), 3.48 (m, 2H,), 3.43 (m, 2H), 0.97 (s, 9H); ^{13}C (DMSO-d_6) δ 135.4, 132.8, 133.5, 129.7, 127.6, 104.6, 79.5, 72.8, 66.6, 64.7, 62.7, 27.2. Anal. Calcd for $C_{22}H_{30}O_5Si \cdot 0.25H_2O$: C, 64.86; H, 7.49. Found: C, 64.86; H, 7.50.

(2*R*,4*R*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolane-2-carboxylic Acid (7). To a solution of **6** (0.75 g, 1.8 mmol) in CH_3CN (4 mL), CCl_4 (4 mL) and H_2O (6 mL) were added $NaIO_4$ (1.6 g, 7.44 mmol) and RuO_2 (4 mg), and the mixture was vigorously stirred at room temperature for 5 h. After methylene chloride (30 mL) was added, the mixture was separated and the aqueous layer was extracted with methylene chloride. The combined organic layer was washed with H_2O and dried (Na_2SO_4). The solvent was removed, and the crude product **7** (0.35 g) was used for the next reaction without further purification: ^1H NMR ($CDCl_3$) δ 7.66–7.39 (m, 10H), 5.33 (s, 1H), 3.87 (m, 2H), 3.70 (dd, J = 3.7 Hz, 2H), 1.10 (s, 9H); ^{13}C ($CDCl_3$) δ 172.2 (CO), 137.4, 134.2, 129.87, 100.9, 74.1, 69.3, 65.4, 28.7.

(2*R*,4*R*)- and (2*S*,4*R*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]-methyl]-2-acetoxy-1,3-dioxolane (8). To a solution of **7** (0.3 g, 0.77 mmol) in dry ethyl acetate (4 mL) and pyridine (0.5 mL) was added $Pb(OAc)_4$ (0.5 g, 1.2 mmol), and the mixture was stirred at room temperature for 15 h under argon. After filtration through a Celite pad, the solvent was removed under reduced pressure and the residue was purified by silica gel column (hexane/EtOAc, 3:1) to give **8** as an α,β mixture (50 mg, 17%): ^1H NMR ($CDCl_3$) δ 8.14–7.74 (m, 10H), 6.33, 6.21 (2 × s, 1H), 4.65 (m, 1H), 4.45 (m, 2H), 3.98 (m, 2H), 3.39, 3.41 (2 × s, 3H), 1.07 (s, 9H); ^{13}C ($CDCl_3$) δ 177.0, 133.2, 129.3, 128.2, 105.2, 70.3, 69.2, 64.8, 54.68, 26.9.

1-(1,3-Dioxolan-2-yl)thymine (10) and 1-(2-Hydroxyethyl)thymine (11). Method A. A mixture of thymine (2.0 g, 16 mmol) and ammonium sulfate (30 mg) in hexamethyldisilazane (HMDS) (50 mL) was refluxed for 4 h under argon. The clear solution was allowed to cool to room temperature and the HMDS removed under reduced pressure under anhydrous conditions. Dry CH_3CN (70 mL) was added to the silylated thymine base followed by the addition of **9** (1.5 g, 14.4 mmol) in 5 mL of dry CH_3CN. This suspension was cooled in an ice/water bath to 5 °C and treated with TMSOTf (3.0 mL, 16 mmol). The reaction mixture was stirred at room temperature for 48 h under argon and then poured into a saturated aqueous $NaHCO_3$ solution (20 mL) and ethyl acetate (50 mL). The organic layer was washed with H_2O (20 mL) and brine (20 mL), and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was purified as a silica gel column (hexane/EtOAc, 3:1) to give **10** (1.0 g, 36%) and **11** (136 mg, 5.5%). Compound **10** was recrystallized from EtOAc/hexane to yield white crystals, mp 168–170 °C: UV (H_2O) λ_{max} (pH 11) 271.5 nm (ϵ 2800), λ_{max} (pH 7) 273.0 (ϵ 4175), λ_{max} (pH 2) 271.0 (ϵ 5345); ^1H NMR (DMSO-d_6) δ 11.3 (s, 1H, D_2O exchangeable), 8.22, (s, 1H), 7.52 (s, 1H), 4.30 (t, J = 5.2 Hz, 2H), 3.91 (t, J = 5.2 Hz, 2H), 1.74 (s, 3H); ^{13}C (DMSO-d_6) δ 164.05, 161.66, 150.73, 141.41, 108.20, 60.60, 56.95; MS *m*/*e* 198 $(M)^+$. Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.44; H, 5.04; N, 14.14. Found: C, 48.39; H, 5.10; N, 14.26.

Compound **11** was recrystallized from MeOH/Et_2O, mp 180–181 °C: ^1H NMR (DMSO-d_6) δ 11.22 (s, 1H, D_2O exchangeable), 7.44, (s, 1H), 4.90 (t, J = 5.3 Hz, D_2O exchangeable), 3.68 (t, J = 4.9 Hz, 2H), 3.57 (m, 2H), 1.75 (s, 3H); ^{13}C (DMSO-d_6) δ 164.43, 150.90, 142.46, 107.55, 62.70, 58.56; MS *m*/*e* 170 $(M)^+$. Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.36; H, 5.88; N, 16.45. Found: C, 49.31; H, 5.88; N, 16.36.

1-(2-Hydroxyeth-1-yl)thymine (11). Method B. The mixture of **10** (15 mg), Na_2CO_3 (10 mg), and CH_3OH (3 mL) was stirred at room temperature for 10 h, and the solvent was then evaporated under reduced pressure. The residue was purified by preparative TLC ($CHCl_3$/MeOH, 10:1) to give white crystals of **11** (11 mg, 91.7%), mp 180–181 °C.

1-(1,3-Dioxolan-2-yl)-5-fluorouracil (12). A mixture of 5-fluorouracil (1.0 g, 7.69 mmol) and ammonium sulfate (10 mg) in hexamethyldisilazane (HMDS) (40 mL) was refluxed overnight under argon. The clear solution was allowed to cool to room temperature and the HMDS removed under reduced pressure under anhydrous conditions. Dry CH_3CN (30 mL) was added to the silylated 5-fluorouracil followed by **9** (0.92 g, 7.69 mmol) in dry CH_3CN (5 mL). This suspension was cooled in an ice/water bath to 5 °C and treated with TMSOTf (1.56 mL, 7.69 mmol). The reaction mixture was stirred at room temperature for 36 h under argon and then poured into a saturated aqueous $NaHCO_3$ solution (20 mL) and ethyl acetate (50 mL). The organic layer was washed with H_2O (20 mL) and brine (20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was separated by a silica gel column ($CHCl_3$/MeOH, 20:1) to afford **12** (150 mg, 7.5%) as white crystals, mp 145–146 °C: UV (H_2O) λ_{max} 272.0 nm (ϵ 5439) (pH 11), 270.5 (ϵ 7352) (pH 7), 270.5 (ϵ 7293) (pH 2); ^1H NMR (DMSO-d_6) δ 11.85 (s, 1H, D_2O exchangeable), 8.22, (s, 1H), 8.11 (d, J = 6.9 Hz, 1H), 4.39 (t, J = 5.1 Hz, 2H), 3.91 (t, J = 5.1 Hz, 2H); ^{13}C (DMSO-d_6) δ 161.82, 157.52, 149.50, 150.73, 141.41, 129.13, 60. 48, 46.63. Anal. Calcd for $C_7H_7FN_2O_4$: C, 41.56; H, 3.46; N, 13.85. Found: C, 41.70; H, 3.50; N, 13.82.

***N*⁴-Benzoyl-1-(1,3-dioxolan-2-yl)cytosine (13) and *N*⁴-Benzoyl-1-(2-hydroxyethyl)cytosine (14). Method A.** A mixture of *N*⁴-benzoylcytosine (1.14 g, 5.3 mmol) and ammonium sulfate (10 mg) in hexamethyldisilazane (HMDS) (30 mL) was refluxed for 4 h under argon. The clear solution was allowed to cool to room temperature and the HMDS removed under reduced pressure using anhydrous conditions. Dry CH_3CN (30 mL) was added to the silylated *N*⁴-benzoylcytosine base followed by **9** (0.63 g, 5.3 mmol) in dry CH_3CN (2 mL), which was cooled in an ice/water bath to 5 °C and treated with trimethylsilyl triflate (TMSOTf) (1.25 mL, 6.16 mmol). The reaction mixture was stirred at room temperature for 36 h under argon and was poured into saturated aqueous $NaHCO_3$ solution (20 mL) and ethyl acetate (30 mL). The organic layer was washed with H_2O (20 mL) and brine (20 mL) and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the yellowish solid was recrystallized twice from CH_2Cl_2 and ether to give **13** (600 mg, 42%), mp 165–166 °C: UV (MeOH) λ_{max} 258.5 nm; ^1H NMR (DMSO-d_6) δ 11.25 (s, 1H, D_2O exchangeable), 8.22, (s, 1H), 8.15 (d, J = 7.2 Hz, 1H), 7.54 (m, 5H), 7.33 (d, J = 7.2 Hz, 1H), 4.41 (t, J = 5.1 Hz), 4.14 (t, J = 5.1 Hz, 2H); ^{13}C (DMSO-d_6) δ 167.75, 163.79, 161.84, 150.72, 132.88, 128.38, 95.75, 60.32, 58.72; MS *m*/*e* 288 $(MH)^+$. Anal. Calcd for $C_{14}H_{13}N_3O_4$: C, 58.48; H, 4.53; N, 14.62. Found: C, 58.59; H, 4.55; N, 14.57.

The residual solution of **13** was purified by a silica gel column with $CHCl_3$/MeOH (15:1), and the white solid was recrystallized from EtOAc/MeOH to yield **14** (50 mg, 4.4%), mp 207–209°C: ^1H NMR (DMSO-d_6) δ 11.19 (s, 1H, D_2O exchangeable), 7.62 (d, J = 7.1 Hz, 1H), 7.26 (d, J = 7.1 Hz, 1H), 7.59 (m, 5H), 4.96 (t, J = 5.4 Hz, 1H, D_2O exchangeable), 3.88 (t, J = 4.9 Hz, 2H), 3.63 (m, 2H); ^{13}C (DMSO-d_6) δ 163.20, 151.76, 133.30, 132.30, 128.45, 95.30, 58.15, 52.36. Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.17; H, 5.02; N, 16.19. Found: C, 60.04; H, 5.09; N, 16.14.

N^4-Benzoyl-1-(2-hydroxyethyl)cytosine (14). Method B. The mixture of **13** (10 mg, 0.0386 mmol), Na_2CO_3 (6 mg, 0.057 mmol), and anhydrous CH_3OH (1 mL) was stirred at room temperature for 20 h, and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC ($CHCl_3$/MeOH, 10:1) to yield white crystals of **14** (6 mg, 66.7%), mp 207–209 °C.

1-(2-Hydroxyethyl)cytosine (15). The mixture of **13** (20 mg, 3.48 mmol), Na_2CO_3 (12 mg, 13.8 mmol), and anhydrous CH_3OH (1 mL) was stirred at room temperature for 36 h, and then the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC ($CHCl_3$/MeOH, 10:1) to give white crystals of **15** (10 mg, 90.9%), mp 229–230°C: ^1H NMR (DMSO-d_6) δ 7.37 (s, 2H, D_2O exchangeable), 7.48 (d, J = 7.0 Hz, 1H), 5.60 (d, J = 7.0 Hz, 1H), 4.85 (t, J = 5.2 Hz, 1H, D_2O exchangeable), 4.06 (t, J = 5.3 Hz, 2H), 3.94 (m, 2H); ^{13}C (DMSO-d_6) δ 166.08, 92.56, 58.95, 51.41. Anal. Calcd for $C_6H_9N_3O_2$: C, 46.41; H, 5.80; N, 27.07. Found: C, 46.43; H, 5.88; N, 26.99.

N^4-Benzoyl-5-chloro-1-(1,3-dioxolan-2-yl)cytosine (16). A mixture of N^4-benzoyl-5-chlorocytosine (1.0 g, 4.0 mmol) and ammonium sulfate (10 mg) in hexamethyldisilazane (HMDS) (40 mL) was refluxed for 4 h under argon. The clear solution was allowed to cool to room temperature and the HMDS removed under reduced pressure using anhydrous condition. Dry CH_3CN (40 mL) was added to the silylated base followed by **9** (0.48 g, 4 mmol) in dry CH_3CN (2 mL). This suspension was cooled in an ice/water bath to 5 °C and treated with TMSOTf (0.9 mL, 4 mmol). The reaction mixture was stirred at room temperature for 36 h under argon and was poured into a mixture of saturated aqueous $NaHCO_3$ solution (10 mL) and ethyl acetate (30 mL). The organic layer was washed with H_2O (20 mL) and brine (20 mL) and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was separated by a silica gel column (EtOAc/hexane, 2:1) to give **16**, which was recrystallized from EtOAc/hexane three times to yield white crystals (100 mg, 8%), mp 174–176 °C: UV (MeOH) λ_{max} 258.5 nm; ^1H NMR (DMSO-d_6) δ 10.91 (s, 1H, D_2O exchangeable), 8.25, (s, 1H), 6.22 (s, 1H), 4.37 (t, J = 4.7 Hz, 2H), 4.09 (m, 2H); ^{13}C (DMSO-d_6) δ 161.78, 156.50, 149.50, 146.20, 135.00, 132.58, 129.01, 128.25, 105.39, 60.32, 58.04. Anal. Calcd for $C_{14}H_{12}N_3O_4Cl$·0.15 H_2O: C, 51.77; H, 4.04; N, 12.94. Found: C, 51.67; H, 4.33; N, 12.92.

N^4-Benzoyl-5-chloro-1-(2-hydroxyethyl)cytosine (17) and 5-Chloro-1-(2-hydroxyethyl)cytosine (18). A mixture of **16** (50 mg) and saturated ammonia in CH_3OH (5 mL) was stirred at room temperature for 2 h, and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC ($CHCl_3$/MeOH, 10:1) to give white solids **17** and **18**. Compound **17** was recrystallized from EtOAc/MeOH to yield 22 mg (48.9%), mp 190–191°C: ^1H NMR (DMSO-d_6) δ 11.00 (s, 1H, D_2O exchangeable), 8.14 (s, 1H), 4.92 (t, J = 5.3 Hz, 1H, D_2O exchangeable), 4.05 (t, J = 5.1 Hz, 2H), 3.62 (m, 2H); ^{13}C (DMSO-d_6) δ 164.43, 149.23, 140.40, 130.11, 128.98, 105.15, 62.78, 58.56. Anal. Calcd for $C_{13}H_{12}N_3O_3Cl$: C, 53.10; H, 4.12; N, 14.29. Found: C, 53.13; H, 4.42; N, 14.01.

Compound **18** was recrystallized from EtOAc/MeOH to give white crystals (12 mg, 41.3%), mp 232–235°C: ^1H NMR (DMSO-d_6) δ 7.66 (bs, 1H, D_2O exchangeable), 7.86, (s, 1H), 4.87 (t, J = 5.3 Hz, 1H, D_2O exchangeable), 3.53 (t, J = 5.1 Hz, 2H), 3.70 (m, 2H); ^{13}C (DMSO-d_6) δ 161.84, 154.33, 145.11, 97.12, 58.47, 51.42. Anal. Calcd for $C_6H_8N_3O_2Cl$: C, 38.10; H, 4.23; N, 22.22. Found: C, 38.22; H, 4.32; N, 22.28.

(+)-(4*R*)-2,2-Dimethyl-4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolane (21). To a solution of imidazole (21.0 g, 0.31 mol) in DMF (35 mL) were added *tert*-butyldiphenylsilyl chloride (40.0 g, 0.145 mol) and **20**[16] (17.5 g, 0.132 mol), and the mixture was stirred for 4 h and quenched with cold saturated $NaHCO_3$ (20 mL). Ether (100 mL) was added, and the organic layer was separated, washed with 1 N HCl (40 mL), H_2O (20 mL), and brine (20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a colorless oil, which was used for the next reaction without further purification.

(+)-(4*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2,3-propanediol (22). Compound **21** prepared above was dissolved in 200 mL of 90% AcOH, and the solution was refluxed for 1 h. After cooling, the reaction mixture was neutralized with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 (4 × 100 mL), and dried (Na_2SO_4). The compound was separated by silica gel column (hexane/EtOAc, 3:1), and the solvents were evaporated to obtain a colorless syrup. Hexane (400 mL) was added to the syrup to obtain white crystals (25 g, 57.1%), mp 56.5–57 °C: $[\alpha]^{24}_D$ 6.85 (*c* 2.2, MeOH) [lit.[17] $[\alpha]^{20}_D$ 6.50, (*c* 2.0, MeOH)]; ^1H NMR ($CDCl_3$) δ 7.41 (m, 10 H), 3,71 (m, 5H), 2.65 (d, J = 5.0 Hz, 1H, D_2O exchangeable), 2.09 (t, J = 6.3 Hz, 1H, D_2O exchangeable), 1.07 (s, 9 H); ^{13}C ($CDCl_3$) δ 135.52, 132.61, 129.94, 127.84, 71.80, 65.22, 63.82, 26.85.

2-Methoxy-4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolane (23). A mixture of **22** (1.0 g, 3.03 mmol), trimethyl orthoformate (0.5 g, 4.7 mmol), and benzoic acid (11 mg) was heated at 130 °C in an oil bath for 1.5 h. The reaction was stopped when TLC (hexane/EtOAc; 4:1) showed the absence of starting material. The reaction mixture was then treated with 20 mg of Na_2CO_3 powder, and excess trimethyl orthoformate was removed under reduced pressure. The residue was purified by silica gel column (hexane/EtOAc; 20:1) to yield a colorless oil (0.85 g, 75.4%) as an α,β mixture: ^1H NMR ($CDCl_3$) δ 7.67–7.35 (m, 10H), 5.74, 5.73 (2 × s, 1H), 3.46–4.40 (m, 5H), 3.32, 3.30 (2 × s, 3H), 1.07 (s, 9H); ^{13}C ($CDCl_3$) δ 135.56, 133.12, 129.80, 119.31, 116.20, 76.48, 66.58, 64.03, 53.21, 51.51, 26.74. Anal. Calcd for $C_{21}H_{28}O_4Si$: C, 67.64; H, 7.51. Found: C, 67.74; H, 7.51.

(+)-(2*R*,4*R*)-1-[4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-2-yl]-5-fluorouracil (24). A mixture of 5-fluorouracil (0.6 g, 4.5 mmol) and ammonium sulfate (10 mg) in hexamethyldisilazane (HMDS) (20 mL) was refluxed for 16 h under argon. The clear solution obtained was concentrated to dryness, and the oily residue was dissolved in dry CH_3CN (30 mL) followed by addition of TMSOTf (0.9 mL, 4 mmol) and **23** (1.48 g, 4.5 mmol) in dry CH_3CN (5 mL). The reaction mixture was stirred at room temperature for 36 h under argon and was poured into a mixture of saturated aqueous $NaHCO_3$ (10 mL) and ethyl acetate (30 mL). The organic layer was separated, washed with H_2O (10 mL) and brine (10 mL), and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was purified by silica gel column (hexane/EtOAc; 5:1) to give a white solid, which was recrystallized from ethyl ether to yield **24** (650 mg, 61.5%), mp 154–155 °C: $[\alpha]^{22}_D$ 40.93° (*c* 0.16, MeOH); UV (MeOH) λ_{max} 271.0 nm; ^1H NMR ($CDCl_3$) δ 8.80 (s, 1H, D_2O exchangeable), 7.93 (s, 1H), 7.37–7.65 (m, 10H), 7.30 (d, J = 5.3 Hz, 1H), 5.24 (m, 1H), 4.29 (d, d, J = 3.6, 10.9 Hz, 1H), 3.75 (m, 1H), 3.81 (d, J = 4.1 Hz, 2H), 1.08 (s, 9H); ^{13}C ($CDCl_3$) δ 159.82, 149.18, 135.53, 132.37,127.95, 129.34, 128.82, 137.5, 142.3, 71.34, 62.38, 48.99, 26.81. Anal. Calcd for $C_{24}H_{27}FN_2O_5Si$: C, 61.28; H, 5.73; N, 5.95. Found: C, 61.01; H, 5.71; N, 6.03.

(+)-(2*R*,4*S*)-1-[4-(Hydroxymethyl)-1,3-dioxolan-2-yl]-5-fluorouracil (25). Compound **24** (0.5 g, 1.06 mmol) in anhydrous THF (20 mL) was treated with 1 M n-Bu_4NF/THF solution (1.06 mL, 1.06 mmol) and glacial acetic acid (0.063 g, 1.06 mmol) for 30 min at room temperature. After evaporation of the solvent at 20 °C, the residue was purified by a silica gel column twice using EtOAc/hexane (2:1) to give **25** (220 mg, 92.3%) as an oil, which was solidified under high vacuum in 3 days. The white solid was recrystallized with ethyl acetate/hexane to yield hydroscopic white crystals: $[\alpha]^{23}_D$ 23.88° (*c* 0.16, MeOH); UV (MeOH) λ_{max} 270.3 mn; ^1H NMR (DMSO-d_6) δ 11.78 (s, 1H, D_2O exchangeable), 8.25 (s, 1H), 7.96 (d, J = 6.8 Hz, 1H), 5.49 (s, 1H, D_2O exchangeable), 4.05–3.53 (m, 5H); ^{13}C (DMSO-d_6) δ 162.52, 158.10, 157.67, 141.38, 137.75, 131.91, 131.38, 66.18, 65.47, 51.04. Anal. Calcd for $C_8H_9FN_2O_5$: C, 41.35; H, 3.88; N, 12.06. Found: C, 41.22; H, 3.97; N, 12.18.

(2*R*)-1-(2,3-Dihydroxypropyl)-5-fluorouracil (26). A solution of **24** (0.1 g, 0.213 mmol) in anhydrous THF (5 mL) was treated with 1 M n-Bu_4NF/THF solution (0.3 mL, 0.3 mmol) by stirring for 1 h at room temperature. After evaporation of the solvent at 20 °C, the residue was separated by a silica gel column using EtOAc/MeOH (10:1) to give a white solid which

was recrystallized from EtOAc/Et_2O to yield **26** as white crystals (30 mg, 70%), mp 148–150 °C: $[\alpha]^{27}_D$ 79.58° (*c* 0.11, MeOH); UV (H_2O) λ_{max} 270.0 nm (ϵ 5383) (pH 11), 271.0 (ϵ 5725) (pH 7), 271.5 (ϵ 6317) (pH 2); ^1H NMR (DMSO-d_6) δ 11.80 (s, 1H, D_2O exchangeable), 7.88 (d, J = 6.8 Hz, 1H), 5.01 (d, J = 5.0 Hz, 1H, D_2O exchangeable), 4.68 (t, J = 5.0 Hz, 1H, D_2O exchangeable), 3.68 (m, 2H), 3.35 (m, 3H); ^{13}C (DMSO-d_6) δ 157.79, 157.40, 149.75, 140.84, 137.33, 131.79, 131.25, 68.78, 63.55, 51.35. Anal. Calcd for $C_7H_9FN_2O_4$: C, 41.14; H, 4.41; N, 13.72. Found: C, 41.09; H, 4.44; N, 13.63.

(−)-(2*S*)-1-(2,3-Dihydroxypropyl)-5-fluorouracil (27). A mixture of 5-fluorouracil (1.29 g, 10 mmol) and (2*R*)-2,3-epoxy-1-propanol (0.74 g, 10 mmol) in DMF (50 mL) containing anhydrous K_2CO_3 (20 mg) was stirred at 130 °C for 12 h. The solvent was evaporated to dryness under reduced pressure, and the residue was purified by a silica gel column (benzene/methanol, 10:1). The product was recrystallized from benzene/methanol to give compound **27** (0.2 g, 11%), mp 150 °C: $[\alpha]^{27}_D$ −79.47 (*c* 0.11, MeOH); UV (H_2O) λ_{max} 270.0 nm (ϵ 5421) (pH 11), 271.0 (ϵ 5747) (pH 7), 271.0 (ϵ 6511) (pH 2); ^1H NMR (DMSO-d_6) δ 11.71 (s, 1H, D_2O exchangeable), 7.91 (d, J = 6.9 Hz, 1H), 5.02 (d, J = 5.0 Hz, 1H, D_2O exchangeable), 4.69 (t, J = 5.0 Hz, 1H, D_2O exchangeable), 3.71 (m, 2H), 3.36 (m, 3H); ^{13}C (DMSO-d_6) δ 157.78, 156.40, 149.74, 140.85, 137.36, 131.78, 131.27, 68.75, 63.53, 51.32. Anal. Calcd for $C_7H_9FN_2O_4$: C, 41.14; H, 4.41; N, 13.72. Found: C, 41.02; H, 4.52 N, 13.62.

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