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TETRAHEDRON

Nucleosides and Nucleotides. 191. Ring Expansion Reaction of 1-[2,3,5-Tri-*O*-TBS-4α-formyl-β-D-*ribo*-pentofuranosyl]uracil by Treating with (Methylene)triphenylphosphorane to Give a New Nucleoside Containing Dihydrooxepine Ring at the Sugar Moiety[1]

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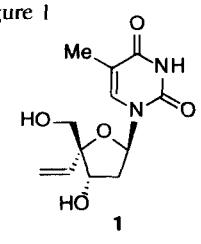
Abstract: When 1-[2,3,5-tri-*O*-TBS-4α-formyl-β-D-*ribo*-pentofuranosyl]uracil (**5**) was treated with (methylene)triphenylphosphorane in THF, an unusual ring-expansion reaction occurred to give a nucleoside (**7**) containing dihydrooxepine ring at the sugar moiety. A deuterium-label experiment showed that one carbon unit derived from the ylide was incorporated into the 5'-position of **7**. A ring cleavage between the C-3' and C-4' of **5** during the reaction was suggested.

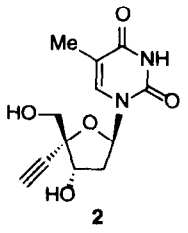
Key words: Nucleosides, Dihydrooxepine, Ring-expansion, Wittig reactions

Recent years, we have synthesized a series of nucleosides having various carbon-substituents at the 4'α-position and investigated their antitumor and antiviral activities.[2,3] Throughout these studies, we identified 2'-deoxynucleoside analogs having an unsaturated branched chain at the 4'α-position as potent antitumor and/or antiviral compounds. For instance, 4'α-ethenyl- and -ethynylthymidine (**1** and **2**, respectively) significantly inhibit the growth of both human immunodeficiency virus type-1 (HIV-1) and herpes simplex virus type-1 (HSV-1) *in vitro*,[2] and 4'α-ethyny-2'-deoxycytidine (**3**) shows a potent antileukemic activity *in vitro*.[3] These findings prompted us to synthesize the corresponding *ribo*-type nucleoside analogs having an unsaturated branched chain at the 4'α-position and to investigate their biological effects.

Figure 1



1



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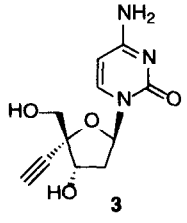

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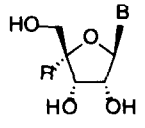

4

B: nucleobase
R: $HC{=}CH_2$
$C{\equiv}CH$

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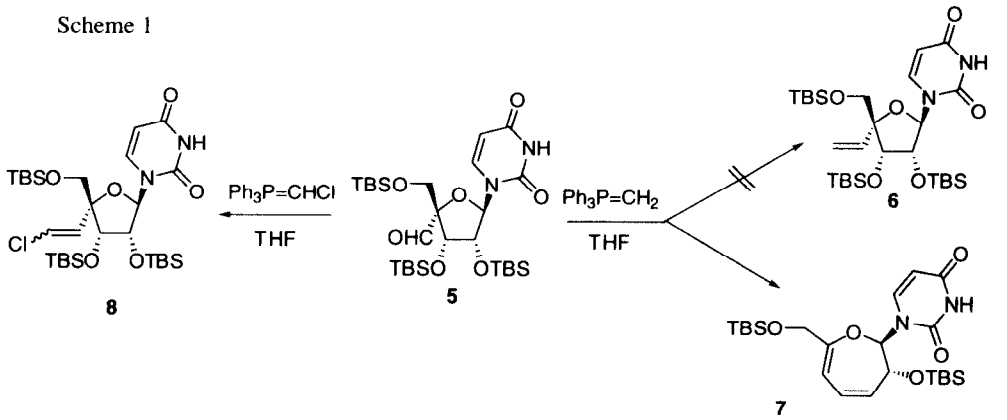
We planned to synthesize 4'α-ethenyl ribonucleoside analogs via Wittig reaction of 4'α-formyl ribonucleosides, which are readily prepared by a known method.[3] Reaction of 4'α-formyluridine derivative **5** with (chloromethylene)triphenylphosphorane gave the corresponding Wittig reaction product **8** in 80% yield.[3] However, when **5** was treated with (methylene)triphenylphosphorane in THF at -78 °C, the desired 4'α-ethenyl ribonucleoside **6** was not obtained at all, while an unexpected ring-expanded product **7** was obtained in 51% yield, after purification by silica gel column chromatography (Scheme 1). In this report, we describe this unusual ring-expansion reaction in detail.

Scheme 1



The structure of **7** was confirmed by UV, ^{1}H-NMR, ^{13}C-NMR, ^{1}H-^{1}H COSY, HMQC, HMBC, NOESY, FAB-HRMS, and elemental analysis. The product gave a molecular-ion peak at *m/z* 481.2546 (*m/z* 481.2554 calculated for $C_{23}H_{41}N_2O_5Si_2$) in its FAB-HRMS. Elemental analysis data also supported molecular formula ($C_{23}H_{40}N_2O_5Si_2$) of the product. NMR data of the product **7** is summarized in Figure 2. From ^{1}H NMR data, this compound has protons of uracil moiety (H-5, δ 5.74, d, J = 7.6; H-6, δ 7.63, d, J = 7.6; and N^3-H, δ 10.14, br s), two *tert*-butyldimethylsilyl (TBS) groups, and four olefinic or anomeric protons (δ 5.41, 5.71, 5.82, and 5.88), which connect with different carbons respectively, from HMQC correlations. Furthermore, ^{1}H-^{1}H COSY correlations (H δ 5.71/ H δ 5.88, and H δ 5.88/ H δ 5.41) were observed. ^{1}H-^{1}H COSY, HMBC, and NOESY correlations were shown in Figure 2. HMBC correlations between (1) C-2' (δ 86.09)/H-3' (δ 4.73), (2) C-2', C-5', and C-6' (δ 86.09, 121.33, and 101.04)/ H-4' (δ 5.71), (3) C-4', C-5', C-7', and C-8' (δ 130.88, 121.33, 157.49, and 63.56)/ H-6' (δ 5.41), (4) C-3' and C-7' (δ 71.38 and 157.49)/H-2' (δ 5.82) allowed a dihydrooxepine ring system. The HMBC correlations were observed between C-2 and C-6 (δ 151.05 and 141.49)/H-2' (δ 5.82), C-2, C-4, C-5, and C-2' (δ 151.05, 163.02, 103.32, and 86.09)/H-6 (δ 7.63). These NMR data suggested that N^1-position of the uracil moiety was connected with the *C*-2-position of the dihydrooxepine ring. These data allowed assigning the gross structure as shown in Figure 2.

A correlation between H-6 and H-3' in NOESY spectrum and a coupling constant between H-2' and H-3' ($J_{2',3'}$ = 7.6 Hz) showed that the uracil ring at the 2'-position is in *trans* to the 3'-*O*-TBS group. From these data, the structure of 1'- and 2'-moieties of the starting material **5** was preserved in **7**, and accordingly the configuration at the 2'- and 3'-position is suggested as (2'*R*, 3'*R*). The assignment of the carbon and proton chemical shifts was shown in Figure 2C. All of the chemical shifts showed reasonable value for the structure.

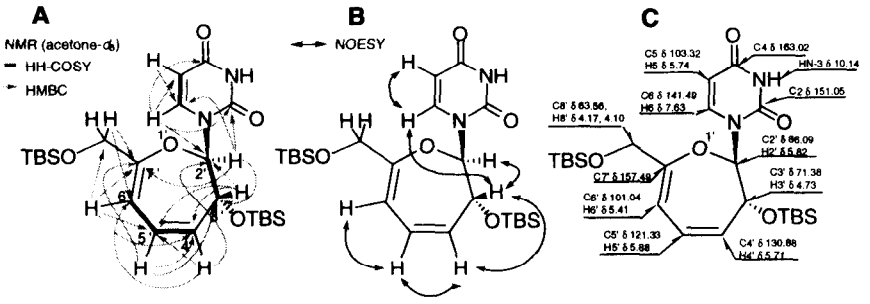
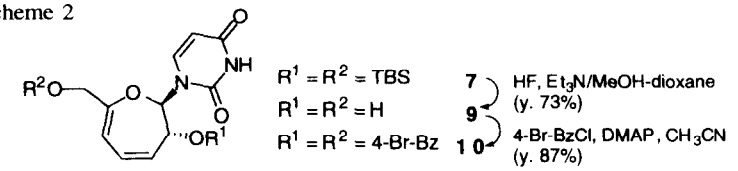


Figure 2. NMR data of **7**. A: ^{1}H-^{1}H COSY and HMBC correlations. B: NOESY correlations. C: ^{1}H- and ^{13}C-NMR chemical shifts.

Scheme 2



Further confirmation of the structure was tried by X-ray crystallographic analysis. Compound **7** was deprotected with HF-Et_3N in MeOH-dioxane to give **9**, whose hydroxyl groups were then 4-bromobenzoylated to give crystalline **10** (Scheme 2). An X-ray crystallography analysis of **10** was performed after it was recrystallized with EtOAc. An ORTEP drawing of the structure of compound **10** is shown in Figure 3. The compound **10** consisted of uracil and dihydrooxepine ring, whose observed bond length and the angle were shown in Table 1 and Table 2.

The 7'-*O*-bromobenzoyl group was disordered. The absolute structure of compound **10** was confirmed by Flack parameter method[4] (Flack parameter value: -0.143521(0.089641)). These results by studies of X-ray analysis of **10** are in good agreement with those by the NMR study described above.

To our best knowledge,[5] there is no precedent for this type of ring-expansion reaction to form a dihydrooxepine ring. A deuterium-label experiment with $Ph_3P{=}CD_2$ was performed to give **7D** (Scheme 3), whose the 5'-proton (δ 5.89) was replaced with a deuterium based on its ^{1}H NMR. This result showed that one carbon unit derived from the ylide was incorporated into the 5'-position of **7**. Therefore, a ring cleavage between the C-3' and C-4' during the reaction was suggested, and a possible reaction mechanism for this ring-expansion reaction is shown in Scheme 3. Compound **5** reacts with the ylide to form betaine **a**, and the 3'-*O*-TBS group is subsequently migrated to give **b**. A retro-aldol-type ring-cleavage between the C-3' and C-4' accompanied with an elimination of the silyloxy group to give **c**. Finally, an intramolecular Wittig reaction proceeds to give **7**.

As described above, when **5** was treated with (chloromethylene)triphenylphosphorane, the ring-expansion reaction did not occur to give usual Wittig product **8** (Scheme 1). In this case, it is likely that the elimination of triphenylphosphine oxide would occur before the migration of the 3'-*O*TBS group due to electron-withdrawing effect of the chlorine atom. On the other hand, when 2'-deoxycytidine derivative **11** was used as a substrate, a usual Wittig product **12** was obtained in high yield, even if (methylene)triphenylphosphorane was used (Scheme 4).[3] Therefore, the migration of the 3-*O*-TBS group may be facilitated due to the significant steric repulsion between adjacent bulky TBS groups on the 2',3'-*cis*-diol in *ribo*-type substrate **5**.

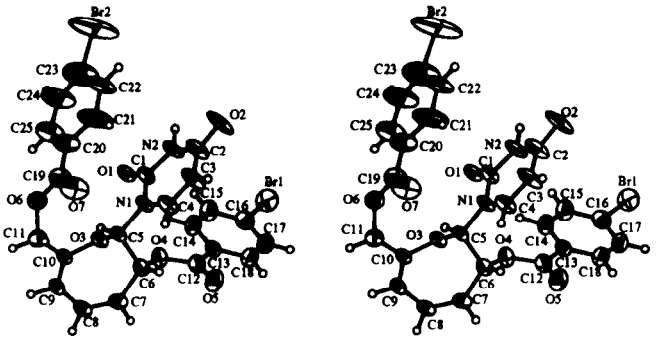


Figure 3. ORTEP drawing of compound **10** with the atomic numbering scheme.

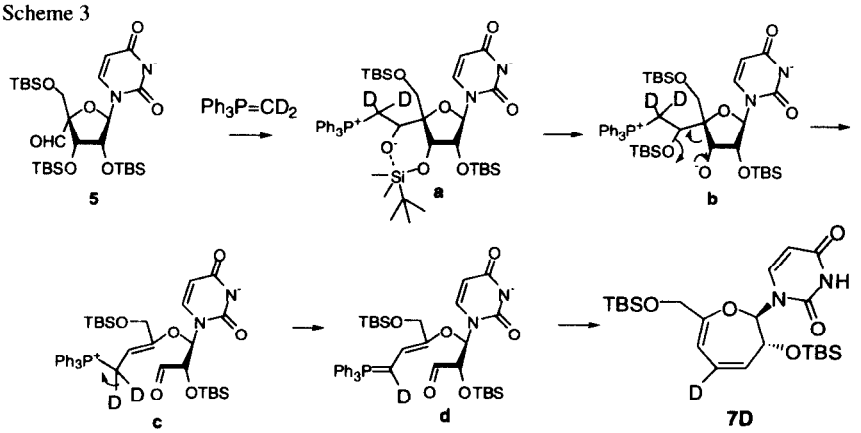
Table 1. Selected Bond Lengths of **10** (Å).

O(3)–C(5)	1.404(8)
C(5)–C(6)	1.52(1)
N(1)–C(5)	1.455(7)
O(4)–C(6)	1.439(8)
C(6)–C(7)	1.495(10)
C(7)–C(8)	1.32(1)
C(8)–C(9)	1.45(1)
C(9)–C(10)	1.32(1)
C(10)–C(11)	1.48(1)
O(3)–C(10)	1.384(8)

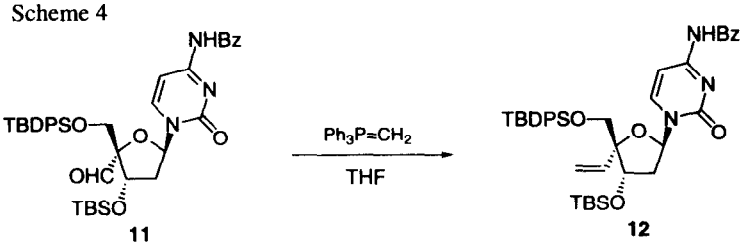
Table 2. Selected Bond Angles of **10** (deg).

C(5)–O(3)–C(10)	117.9(5)
O(3)–C(5)–N(1)	106.2(5)
O(3)–C(5)–C(6)	111.1(5)
N(1)–C(5)–C(6)	109.7(5)
O(4)–C(6)–C(5)	105.1(5)
O(4)–C(6)–C(7)	107.9(6)
C(5)–C(6)–C(7)	115.6(6)
C(6)–C(7)–C(8)	128.3(7)
C(7)–C(8)–C(9)	129.6(6)
C(8)–C(9)–C(10)	128.1(6)
O(3)–C(10)–C(9)	124.0(7)
O(3)–C(10)–C(11)	111.0(6)
C(9)–C(10)–C(11)	124.9(6)

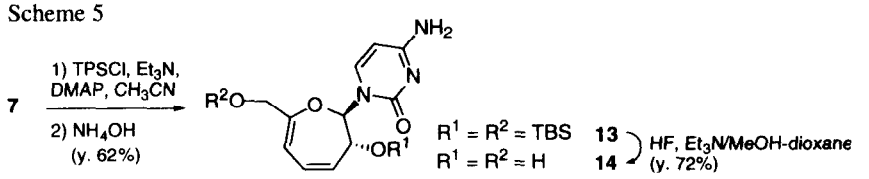
Scheme 3



Scheme 4



Scheme 5



The nucleosides having dihydrooxepine ring at the sugar moiety have not been reported yet. We are interested in their biological activities. Thus, with using a TPSCl-Et_3N-DMAP system,[6] compound **7** was transformed into the corresponding cytosine derivative **13**, which was then deprotected with HF-Et_3N in MeOH-dioxane to give **14** (Scheme 5). The cytotoxicities of **9** and **14** against L1210 and KB cells and anti-HIV-1 activities were examined, however, no activities were observed up to 100 μg/mL.

In conclusion, we found a novel ring-expansion reaction of 4'α–formyluridine derivative **5** to give a nucleoside **7** containing a dihydrooxepine ring at the sugar moiety.

Experimental

General methods: Melting points were measured on a Yanagimoto MP-3 micromelting point apparatus and are not corrected. The ^1H NMR spectra were recorded on a Jeol AL-400 (400 MHz) or Jeol JNM-EX 270 (270 MHz) spectrometer with tetramethylsilane (0.00 ppm) or DMSO (2.49 ppm) as an internal standard. Chemical shifts were reported in parts per million (δ), and signals were expressed as a s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by disappearance on the addition of D_2O. ^{13}C NMR spectra were recorded on a Jeol AL-400 (400 MHz) or Jeol JNM-EX 270 (270 MHz) spectometer. Fast atom bombardment mass spectrometry (FAB-MS) was done on a JEOL JMS-HX110 instrument at an ionizing voltage of 70 eV. TLC was done on Merck Silica gel 60 F_{254} pre-coated plates. The silica gel used for column chromatography was Merck Silica gel 60 (70-230 mesh).

1-[(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-7-(*tert*-butyldimethylsilyloxymethyl)-1,2-dihydrooxepin-2-yl]uracil (7). To a suspension of Ph_3PCH_3Br (3.22 g, 9.00 mmol) in THF (30 mL) was added 1.58 M BuLi solution in hexane (5.69 mL, 9.00 mmol) at -78 °C under an Ar atmosphere. After stirring the mixture for 30 min at 0 °C, a solution of **5** [3] (1.85 g, 3.00 mmol) in THF (20 mL) was added, and the resulting mixture was stirred for 2 h at room temperature. Saturated NH_4Cl solution (80 mL) was added to the mixture, which was extracted with EtOAc (100 mL). The extract was washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified on a silica gel column with 11% EtOAc in $CHCl_3$ to give a crude product, which was crystallized from EtOAc-hexane to give pure **7** (742 mg, 51% as colorless plates): mp 194–195 °C; UV (MeOH) λ_{max} 258 nm (ε 16600); ^1H NMR (acetone-d_6) 10.14 (1H, br s, 3-NH), 7.63 (1H, d, H-6, $J_{6,5}$ = 8.2

Hz), 5.88 (1H, ddd, H-5', $J_{5',3'}$ = 2.3, $J_{5',4'}$ = 11.7, $J_{5',6'}$ = 7.6 Hz), 5.82 (1H, d, H-2', $J_{2',3'}$ = 7.6 Hz), 5.74 (1H, d, H-5, $J_{5,6}$ = 8.2 Hz), 5.71(1H, dd, H-4', $J_{4',3'}$ = 2.4, $J_{4',5'}$ = 11.7 Hz), 5.41 (1H, d, H-6', $J_{6',5'}$ = 7.6 Hz), 4.73 (1H, ddd, H-3', $J_{3',2'}$ = 7.6, $J_{3',4'}$ = 2.4, $J_{3',5'}$ = 2.3 Hz), 4.17 (1H, d, H-8'a, J_{gem} = 14.4 Hz), 4.10 (1H, d, H-8'b, J_{gem} = 14.4 Hz), 0.87, 0.81 (each 9H, each s, $(CH_3)_3CSiMe_2 \times 2$), 0.14 (3H, s, CH_3Si), 0.06 (6H, s, $CH_3Si \times 2$), 0.05 (3H, s, CH_3Si); ^{13}C NMR (acetone-d_6) 163.01, 157.49, 151.04, 141.48, 130.87, 121.32, 103.31, 101.03, 86.07, 71.38, 63.55, 26.06, 25.83, 18.74, 18.21, -4.01, -4.62, -5.24, -5.32; FAB-MS *m/z* 481 (MH^+); FAB-HRMS *m/z* 481.2546, calcd. for $C_{23}H_{41}N_2O_5Si_2$ *m/z* 481.2554. Anal. calcd. for $C_{23}H_{40}N_2O_5Si_2$: C, 57.46; H, 8.39; N, 5.83. Found: C, 57.20; H, 8.34; N, 5.92.

1-[(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-7-(*tert*-butyldimethylsilyloxymethyl)-[5-^{2}H]-1,2-dihydrooxepin-2-yl]uracil (7D). Compound **7D** (56.7 mg, 39%; 85% of the 5'-position was replaced with deuterium based on its ^1H NMR) was obtained from **5** (185 mg, 0.30 mmol) as described above for the synthesis of **7**, with Ph_3PCD_3Br instead of Ph_3PCH_3Br: ^1H NMR (acetone-d_6) 10.12 (1H, br s, 3-NH), 7.63 (1H, d, H-6, $J_{6,5}$ = 8.2 Hz), 5.88 (0.15H, ddd, H-5', $J_{5',3'}$ = 2.4, $J_{5',4'}$ = 11.7, $J_{5',6'}$ = 7.8 Hz), 5.82 (1H, d, H-2', $J_{2',3'}$ = 7.6 Hz), 5.74 (1H, d, H-5, $J_{5,6}$ = 8.2 Hz), 5.72(1H, d, H-4', $J_{4',3'}$ = 2.0 Hz), 5.42 (1H, s, H-6'), 4.73 (1H, dd, H-3', $J_{3',2'}$ = 7.6, $J_{3',4'}$ = 2.0 Hz), 4.17 (1H, d, H-8'a, J_{gem} = 14.4 Hz), 4.10 (1H, d, H-8'b, J_{gem} = 14.4 Hz), 0.87, 0.81 (each 9H, each s, $(CH_3)_3CSiMe_2 \times 2$), 0.14 (3H, s, CH_3Si), 0.06 (6H, s, $CH_3Si \times 2$), 0.05 (3H, s, CH_3Si); FAB-MS *m/z* 482 (MH^+); FAB-HRMS *m/z* 482.2622, calcd. for $C_{23}H_{40}DN_2O_5Si_2$ *m/z* 482.2622.

1-[(2*S*,3*R*)-3-Hydroxy-7-hydroxymethyl-1,2-dihydrooxepin-2-yl]uracil (9). Compound **7** (245 mg, 0.400 mmol) was added to a mixture of 48% HF (0.059 mL, 1.8 mmol), Et_3N (0.251 mL, 1.8 mmol), and dioxane (0.3 mL) in CH_3CN (1.5 mL). The whole was stirred for 14 h at 60 °C and cooled to room temperature. Silica gel was added to the mixture, and the whole was successively evaporated, which was purified on a silica gel column with 7–8% MeOH in $CHCl_3$ to give **9** (55 mg, 73% as a white solid): mp 136.5–138 °C; UV (H_2O) λ_{max} 257 nm (ε 20200): ^1H NMR (DMSO-d_6) 11.41 (1H, br s, 3-NH), 7.72 (1H, d, H-6, $J_{6,5}$ = 8.1 Hz), 5.79 (1H, ddd, H-5', $J_{5',3'}$ = 2.4, $J_{5',4'}$ = 12.0, $J_{5',6'}$ = 7.8 Hz), 5.73 (1H, d, 3'-OH, $J_{OH,3'}$ = 7.1 Hz), 5.69 (1H, dd, H-4', $J_{4',3'}$ = 1.7, $J_{4',5'}$ = 12.0 Hz), 5.66 (1H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,3}$ = 2.0 Hz), 5.58 (1H, d, H-2', $J_{2',3'}$ = 7.8 Hz), 5.30 (1H, d, H-6', $J_{6',5'}$ = 7.8 Hz), 5.19 (1H, t, 8'-OH, $J_{OH,8'}$ = 6.1 Hz), 4.55 (1H, m, H-3'), 3.86 (1H, d, H-8'a, J_{gem} = 15.1, $J_{8'a,OH}$ = 6.1 Hz), 3.82 (1H, d, H-8'b, J_{gem} = 15.1, $J_{8'b,OH}$ = 6.1 Hz); ^{13}C NMR (DMSO-d_6) 162.84, 157.50, 150.60, 141.69, 130.56, 120.00, 102.08, 99.40, 84.89, 67.95, 61.04; FAB-MS *m/z* 253 (MH^+). Anal. calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.02; H, 4.82; N, 11.48.

1-[(2*S*,3*R*)-3-(4-Bromobenzoyloxy)-7-(4-bromobenzoyloxymethyl)-1,2-dihydrooxepin-2-yl]uracil (10). To a suspension of **9** (76 mg, 0.30 mmol) in CH_3CN (2.5 mL) were added 4-DMAP (92 mg, 0.75 mmol) and 4-bromobenzoyl chloride (151 mg, 0.69 mmol), and the mixture was stirred for 1 h at room temperature. After addition of MeOH, the mixture was diluted with $CHCl_3$ (50 mL) and washed with H_2O (50 mL × 2). The organic phase was dried (Na_2SO_4), filtered, and evaporated. The residue was purified on a silica gel column with 20% EtOAc in $CHCl_3$ to give a crude product, which was crystallized from Et_2O to give **10** (161 mg, 87%): mp 206–207 °C; ^1H NMR (DMSO-d_6) 11.47 (1H, s, N^3H), 7.89 (1H, d, H-6, $J_{6,5}$ = 8.0 Hz), 7.83 (2H, d, *p*-BrBz, *J* = 8.5 Hz), 7.74 (4H, br s, *p*-BrBz), 7.73 (2H, d, *p*-BrBz, *J* = 8.5 Hz), 6.16 (1H, br d, H-3', $J_{3',2'}$ = 7.8 Hz), 6.08 (1H, d, H-2', $J_{2',3'}$ = 7.8 Hz), 6.08 (1H, ddd, H-5', $J_{5',3'}$ = 2.0, $J_{5',6'}$ = 7.8, $J_{5',4'}$ =12.0 Hz), 5.92 (1H, dd, H-4', $J_{4',3'}$ = 2.0, $J_{4',5'}$ =12.0 Hz), 5.73 (1H, d, H-6', $J_{6',5'}$ = 7.8 Hz), 5.62 (1H, dd, H-5, $J_{5,3}$ = 2.0, $J_{5,6}$ = 8.0 Hz), 4.92 (1H, d, H-8'a, J_{gem} = 13.7 Hz), 4.85 (1H, d, H-8'b, J_{gem} = 13.7 Hz); ^{13}C NMR (DMSO-d_6) 164.33, 163.23, 162.38, 152.35, 150.08, 140.86, 132.01, 131.81, 130.98, 128.22, 128.04, 127.65, 127.60, 126.71, 122.54, 105.17, 102.78, 83.23, 70.20, 64.22; FAB-MS *m/z* 619 (MH^+). Anal. calcd. for $C_{25}H_{18}Br_2N_2O_7$: C, 48.57; H, 2.93; N, 4.53. Found: C, 48.47; H, 2.95; N, 4.38.

1-[(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-7-(*tert*-butyldimethylsilyloxymethyl)-1,2-dihydrooxepin-2-yl]cytosine (13). TPSCl (303 mg, 1.00 mmol) was added to a mixture of **7** (240 mg, 0.50 mmol), DMAP (122 mg, 1.00 mmol), and Et_3N (0.139 mL, 1.00 mmol) in CH_3CN (3.0 mL). After stirring for 45 min at room

temperature, 28% NH_4OH (1.5 mL) and CH_3CN (3.0 mL) were added to the mixture, which was then stirred for 30 min at room temperature. The mixture diluted with EtOAc (50 mL) was washed with H_2O (50 mL), 0.1 N HCl (50 mL), and saturated $NaHCO_3$ solution (50 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified on a silica gel column with 4% MeOH in $CHCl_3$ to give a crude product, which was crystallized from Et_2O to give **13** (149 mg, 62%): mp 205–207 °C (decomp.); UV (MeOH) λ_{max} 254 nm (ε 18000); ^{1}H NMR (DMSO-d_6) 7.59 (1H, d, H-6, $J_{6,5}$ = 7.3 Hz), 5.85 (1H, ddd, H-5', $J_{5',3'}$ = 2.0, $J_{5',4'}$ = 11.7, $J_{5',6'}$ = 7.8 Hz), 5.78 (1H, d, H-2', $J_{2',3'}$ = 7.6 Hz), 5.75 (1H, d, H-5, $J_{5,6}$ = 7.3 Hz), 5.63 (1H, dd, H-4', $J_{4',3'}$ = 2.1, $J_{4',5'}$ = 11.7 Hz), 5.32 (1H, d, H-6', $J_{6',5'}$ = 7.8 Hz), 4.69 (1H, ddd, H-3', $J_{3',2'}$ = 7.6, $J_{3',4'}$ = 2.1, $J_{3',5'}$ = 2.0 Hz), 4.06 (1H, d, H-8'a, J_{gem} = 14.5 Hz), 4.03 (1H, d, H-8'b, J_{gem} = 14.5 Hz), 0.82, 0.71 (each 9H, each s, $(CH_3)_3CSiMe_2$ × 2), 0.05, 0.00, -0.01, -0.07 (3H, s, CH_3Si × 4); ^{13}C NMR (DMSO-d_6) 165.23, 156.66, 154.75, 141.86, 130.21, 120.34, 99.84, 94.57, 85.13, 70.11, 62.63, 25.70, 25.43, 17.94, 17.41, -4.21, -4.83, -5.39, -5.44; FAB-MS *m/z* 480 (MH^+). Anal. calcd. for $C_{23}H_{41}N_3O_4Si_2$: C, 57.58; H, 8.61; N, 8.76. Found: C, 57.36; H, 8.56; N, 8.70.

1-[(2*S*,3*R*)-3-Hydroxy-7-hydroxymethyl-1,2-dihydrooxepin-2-yl]cytosine (14). Compound **14** (125 mg, 0.260 mmol) was added to a mixture of Et_3N (0.22 mL, 1.6 mmol), 48% HF (0.051 mL, 1.6 mmol), and dioxane (0.26 mL) in CH_3CN (1.3 mL). The mixture was stirred for 16 h at 60 °C and cooled to room temperature. The mixture was diluted with MeOH and silica gel was added to the mixture, which was then evaporated. The mixture was purified on a silica gel column with 17–25% MeOH in $CHCl_3$ to give a solid, which was crystallized from MeOH-CH_3CN to give **21** (47.2 mg, 72% as a white solid): mp 186–187 °C; UV (H_2O) λ_{max} 257 nm (ε 21900); ^{1}H NMR (DMSO-d_6) 7.58 (1H, d, H-6, $J_{6,5}$ = 7.6 Hz), 7.23, 7.17 (each 1H, each br s, 4-NH_2), 5.65–5.80 (4H, m, H-2',H-4', H-5', H-5), 5.53 (1H, d, 3'-OH, $J_{OH,3'}$ = 7.6 Hz), 5.28 (1H, d, H-6', $J_{6',5'}$ = 7.6 Hz), 5.13 (1H, dd, 8'-OH, $J_{OH,8'a}$ = 6.1, $J_{OH,8'b}$ = 5.9 Hz), 4.47 (1H, br d, H-3'), 3.84 (1H, d, H-8'a, J_{gem} = 15.2, $J_{8'a,OH}$ = 6.1 Hz), 3.82 (1H, d, H-8'b, J_{gem} = 15.2, $J_{8'b,OH}$ = 5.9 Hz); ^{13}C NMR (DMSO-d_6) 165.43, 158.04, 155.28, 142.12, 130.76, 119.97, 99.12, 94.47, 85.35, 68.05, 61.07; FAB-MS *m/z* 252 (MH^+). Anal. calcd. for $C_{11}H_{13}N_3O_4$: C, 52.58; H, 5.22; N, 16.73. Found: C, 52.21; H, 5.28; N, 16.49.

X-ray crystallography of 10 *Data Collection*:Formula $C_{25}H_{18}O_7N_2Br_2$, M=618.23, monoclinic, space group $P2_1$(#4), a=13.640(2), b=7.150(2), c=14.720(2)Å, β=116.006(8)°, V=1290.2(4)Å^3, Z=4, D_{cal}=1.59 g/cm^3, F(000)= 616, μ(Cu-Kα)=43.96 cm^{-1}, Cu-Kα Radiation, λ=1.54178Å. A colorless prismatic crystal of **10** having approximate dimensions of 0.25 × 0.05 × 0.38 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Cu-Kα radiation and a rotating anode generator. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 20 carefully centered reflections in the range 33.61 < 2θ < 39.62° corresponded to a primitive monoclinic cell. The data were collected at a temperature of 20±1°using the ω-2θ scan technique to a maximum 2θ value of 138.2°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.42° with a take-off angle of 6.0°. Scans of (1.73+0.30tanθ)° were made at a speed of 8.0°/min (in omega). The weak reflections (I <10.0σ(I)) were rescanned (maximum of 3 scans) and the counts were accumulated to ensure good couting statistics. Stationary background counts were recorded on each side of the reflection. the ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm, the crystal to detector distance was 258 mm.

Data Reduction Of the 2687 reflections which were collected, 2581 were unique (R_{int}=0.019). The intensities of three representative reflection were measured after every 150 reflections. No decay correction was applied. The linear absorption coefficient, μ, for Cu-Kα radiation is 44.0 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.51 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 7.35470e-07).

Structure Solution and Refinement The structure was solved by direct methods (SHELXS-97) and expanded using Fourier techniques (DIRDIF94). The non-hydrogen atoms were refined anisotropically.

Hydrogen atoms were placed on a calculated positions. The final cycle of full-matrix least-squares refinement was based on 2111 observed reflections ($I > 2.00\sigma(I)$) and 327 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweigthed and weighted agreement factors of: $R=\sum||Fo|-|Fc||/\sum|Fo|=0.056$. $Rw=[\sum w(|Fo|-|Fc|)^2/\sum wFo^2]^{1/2}=0.077$. The standard deviation of an observation of unit weight was 1.73. The weighting scheme was based on counting statistics and included a factor ($p=0.069$) to downweight the intense reflections. Plots of $\sum w(|Fo|-|Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.68 and -0.46$e^-/Å^3$, respectively. Neutral atom scattering factors were taken from Cromer and Waber[7]. Anomalous dispersion effects were included in Fcalc[8]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[9]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[10]. All calculations were performed using the teXsan[11] crystallographic software package of Molecular Structure Corporation.

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