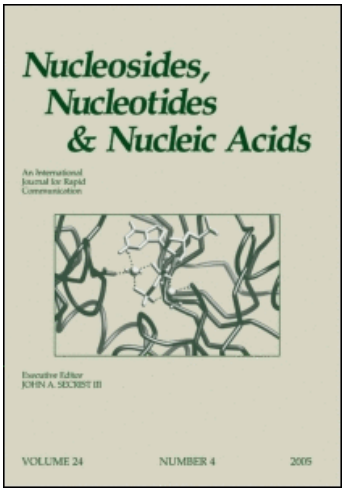

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Synthesis of Nucleoside Analogues Containing an Oxetane Ring Fused to the Furan Ring

Robert J. Hambalek[a]; George Just[a]
[a] Department of Chemistry, McGill University Montréal, Québec, Canada

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SYNTHESIS OF NUCLEOSIDE ANALOGUES CONTAINING AN OXETANE RING FUSED TO THE FURAN RING

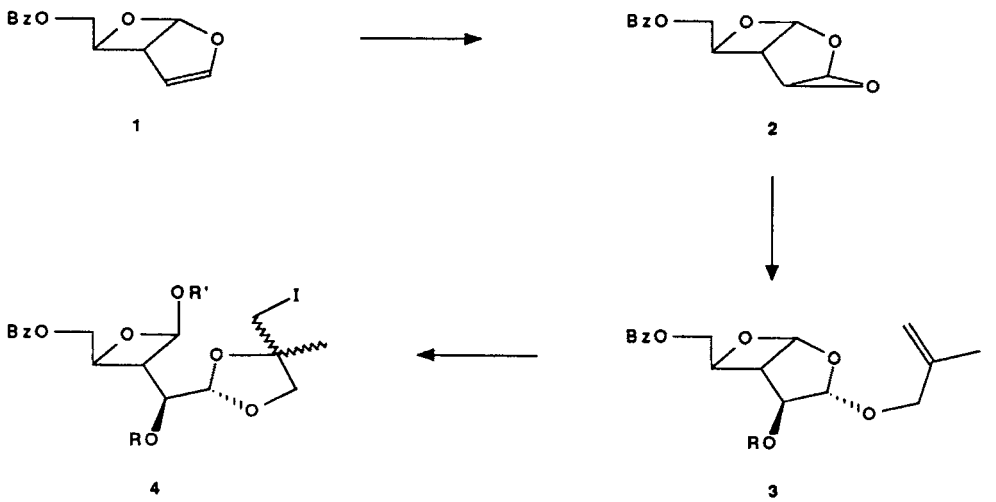
Robert J. Hambalek and George Just*

Department of Chemistry, McGill University
Montréal, Québec, Canada H3A 2K6

Abstract: The photo-adduct obtained from benzoyloxyacetaldehyde and furan was epoxidized, and the tricyclic compound was converted by reaction of persilylated thymine and cytosine in the presence of zinc chloride to thymidine and cytidine analogues containing a fused dioxabicyclo[3.2.0]heptane "sugar" portion, which were converted to furanosides of well defined stereochemistry.

INTRODUCTION

In the course of exploring the potential of the photo-adducts of aldehydes and furans as precursors for the synthesis of oxetanocin[1,2], we prepared racemic epoxide **2**. The latter could be opened



Scheme 1

by the action of methallyl alcohol to provide **3**, which was then transformed to substituted oxetanes **4**[3] by the adaptation of the method described by Fraser-Reid and Mootoo[4,5,6,7].

We now wish to report reaction of the racemic epoxide **2** with persilylated bases to provide novel types of nucleoside analogues with a well-defined stereochemistry.

RESULTS & DISCUSSION

After experimenting with various Lewis acids (tin tetrachloride, trimethylsilyl acetate, trimethylsilyl trifluoromethanesulfonate) and experiencing no success, it was found that by using zinc chloride as the Lewis acid catalyst in a variation of the procedure described by Danishefsky[8], nucleosides **5a** and **5b** were obtained stereospecifically in 67 and 66% yield, respectively, as shown in Scheme 2. It is interesting to note that the free hydroxyl group becomes silylated *in situ*, presumably by chlorotrimethylsilane generated by reaction of the silylated base with zinc chloride, and survives the work-up even when the reaction mixture is washed with 5% aqueous hydrochloric acid.

The configuration of nucleoside **5a**, and thus of **5b**, about H3' and H4' was confirmed by ^{1}H-NMR spectroscopy, which clearly showed couplings of ~ 0 Hz for $J_{H3'-H4'}$. This indicates that the nitrogenous base and protected hydroxyl function are *trans* to one another with a torsional angle of ~ 150°. Had the two subsituents been *cis*, a coupling between H3' and H4' would have been observed. The bicyclic structure was confirmed by a HETCOR carbon-hydrogen correlation which showed that the ^{13}C signal at 110.45 ppm was coupled to the proton (H1') at 6.28 ppm, and the ^{13}C signal at 99.02 ppm was coupled to the proton (H3') at 5.94 ppm. This indicates that the nitrogenous base is connected to C3' since O-C-O carbons are always more deshielded than O-C-N carbons.

We also investigated this reaction with purine bases. However, attempts to carry out the coupling reaction with *bis*-(trimethylsilyl)-N^6-benzoyladenine and zinc chloride proved to be unsuccessful, whether the silylated base was generated *in situ* using HMDS and chlorotrimethylsilane[9] or a stock solution of the silylated base in 1,2-dichloroethane was used. Further investigation of purine couplings to **2** have not been carried out.

Desilylation (Bu_4NF / THF) of nucleosides **5a** and **5b** proceded smoothly giving excellent yields (95 and 93%, respectively) of the desilylated nucleosides **6a** and **6b**. Fully deprotected **6b** was obtained by aminolysis (NH_3 / MeOH), followed by recrystallization from methanol, in 58% yield. Nucleoside **7a** was obtained in a similar manner[10] in 65% yield, except that it was purified by flash chromatography prior to recrystallization from methanol. The X-ray crystallographic structure of **7a** (FIGURE 1) confirmed our NMR analyses, clearly showing the nitrogenous base *trans* to the adjacent hydroxy group.

We also felt that these novel bicyclic nucleosides could be transformed into interesting furanosides simply by opening the oxetane ring, and this is known to proceed stereospecifically in many cases[11]. Reaction of **5a** with trifluoroacetic acid in methanol gave exclusively the ring opened nucleoside **8** in 89% yield. Its structure was confirmed ^{1}H and ^{13}C-NMR spectroscopy. Debenzoylation of **8** in methanolic ammonia, followed by flash chromatography and recrystallization from acetone /

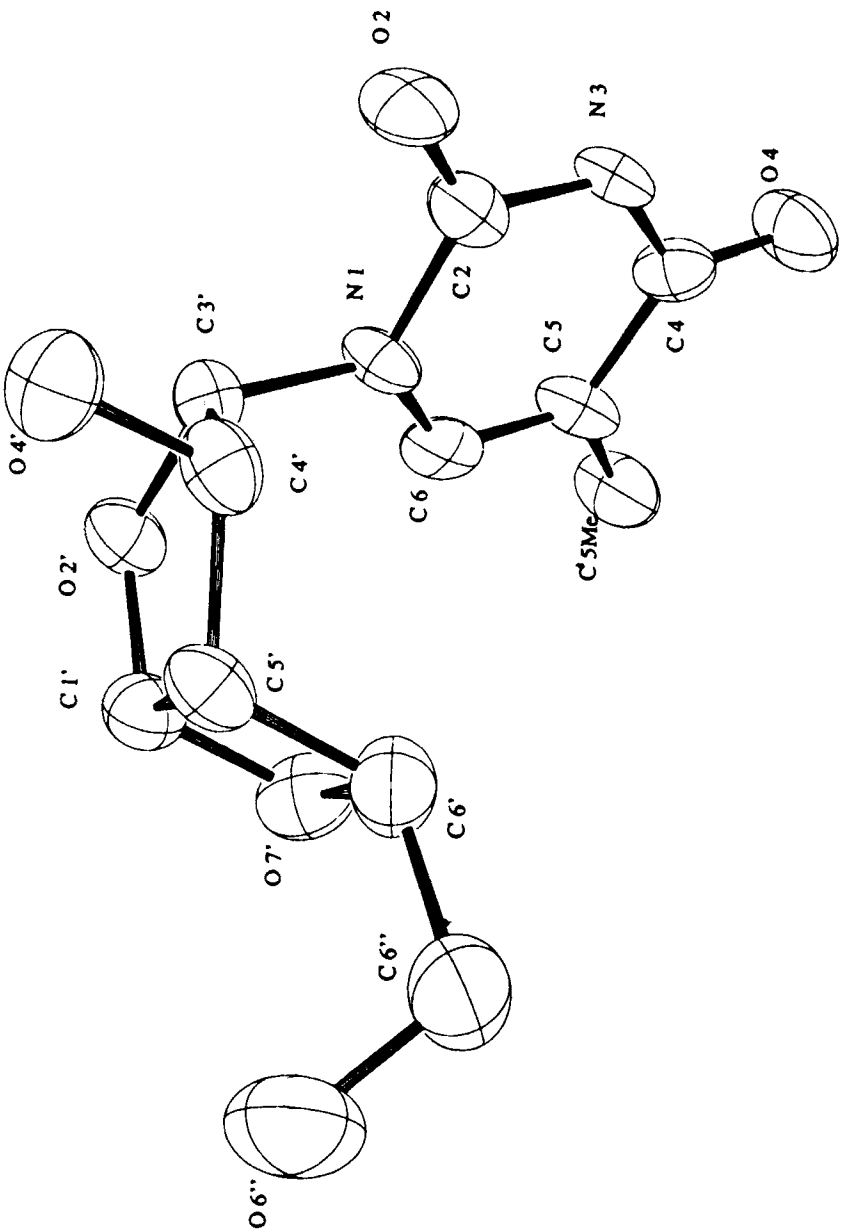
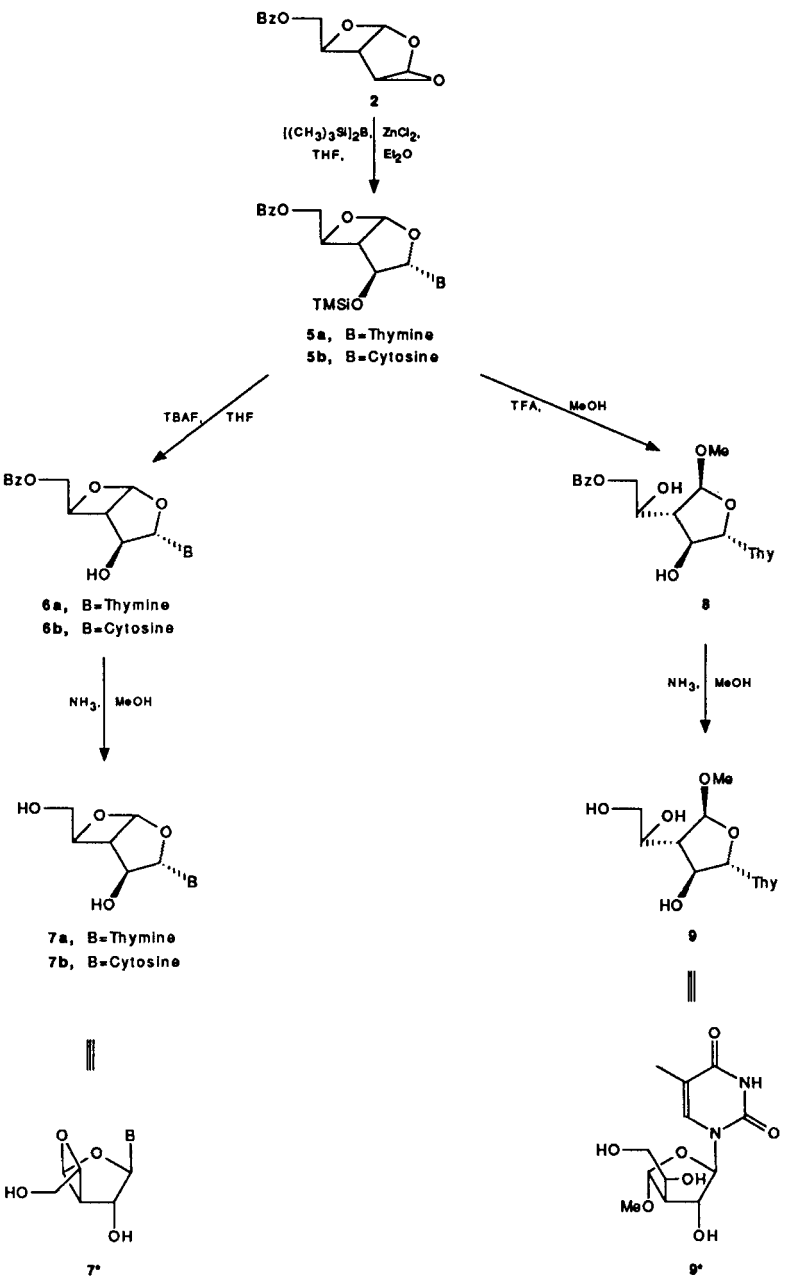


FIGURE 1. X-ray crystallographic structure of nucleoside 7a.



Scheme 2

hexanes gave the deprotected nucleoside 9[12] in 86% yield. All efforts to obtain crystals large enough for X-ray diffraction studies proved to be unsuccessful.

EXPERIMENTAL

General Methods.

Melting points (m.p.) were determined on a Gallenkamp block and are uncorrected. Low-resolution chemical ionization mass spectra were obtained on an HP-5980A quadrapole mass spectrometer in the direct-inlet mode. High-resolution chemical ionization and FAB mass spectra (low-resolution and high-resolution) were obtained on a VG ZAB-2F-HS sector mass spectrometer in the direct-inlet mode. The measurements were carried out at a resolving power (res) of 10000, unless otherwise indicated. Elemental analyses were performed by Guelph Chemical Laboratories Ltd. (Guelph, Ontario, Canada). All compounds were shown to be homogeneous by tlc and to have a purity of >95% by high-field NMR.

^{1}H-NMR spectra were obtained on either a Varian XL-200 or Varian XL-300 spectrometer at 200 MHz and 300 MHz respectively and the peak assignments were made, in some cases, with the aid of homonuclear decoupling and/or COSY experiments. Chemical shifts are given in the scale of parts per million (ppm). The residual proton signals of chloroform, methanol and methylene chloride (assigned values of δ 7.24, 3.30 and 5.32 ppm, respectively) were used as reference in these solvents. The multiplicities are recorded using the following abbreviations: **s**, singlet; **d**, doublet; **t**, triplet; **m**, multiplet; **br**, broad; **ex**, exchangeable. ^{13}C-NMR spectra were obtained on a Varian XL-300 spectrometer at 75.4 MHz and the peak assignments were made, in some cases, with the aid of APT and/or HETCOR experiments. The ^{13}C signals of $CDCl_3$, CD_3OD and CD_2Cl_2 (assigned values of δ 77.00, 49.00 and 53.80 ppm, respectively) were used as reference in these solvents.

Tetrahydrofuran was distilled from sodium benzophenone ketyl. Methylene chloride was distilled from P_2O_5. Methanol was distilled from magnesium. Thin-layer chromatography (tlc) was performed on silica gel (Kieselgel 60 F_{254}) aluminum-backed plates (0.2 mm thickness) and visualized by UV and/or dipping into a solution of 2.5 g ammonium molybdate and 1 g ceric sulfate in 10 mL sulphuric acid / 90 mL water, followed by heating. Kieselgel 60 (Merck 230-400 mesh) silica gel was used for column chromatography.

(±)-6'-*exo*-Benzoyloxymethyl-3'-*endo*-thymin-1-yl-4'-*exo*-trimethylsilyloxy-2',7'-dioxabicyclo[3.2.0]-heptane (5a).

To a stirred solution of epoxide **2** (263 mg, 1.06 mmol) in dry tetrahydrofuran (5 mL) at room temperature under an atmosphere of nitrogen was added *bis*(trimethylsilyl)thymine (860 mg, 3.18 mmol) and zinc chloride (1.0M solution in ether, 1.06 mL, 1.06 mmol). After 18 h, the reaction mixture was

poured into cold saturated aqueous sodium bicarbonate (50 mL), extracted with methylene chloride (5 x 50 mL) and washed with brine (5 x 50 mL). The combined organic phases were then dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to yield a clear syrup which was chromatographed over silica gel (methylene chloride / methanol, 100:1 v/v) affording nucleoside **5a** (312 mg, 66% yield) as a white foam. {^{1}H-NMR (200 MHz, CD_2Cl_2): δ 0.18 (s, 9H, Me_3Si), 1.92 (d, 3H, CH_3 at C5), 3.34 (t, 1H, H5'), 4.35 (ddd, 1H, H6'), 4.41 (A of ABX, 1H, H6"$_a$), 4.52 (B of ABX, 1H, H6"$_b$), 4.74 (s, 1H, H4'), 5.94 (s, 1H, H3'), 6.28 (d, 1H, H1'), 7.43 - 7.65 (m, 3H, Ph), 7.95 (d, 1H, H6), 8.02 - 8.08 (m, 2H, Ph), 9.69 (s, br, ex, 1H, NH), $J_{H1'-H5'}$ = 4.1 Hz, $J_{H5'-H6'}$ = 4.4 Hz, $J_{H6'-H6"a}$ = 3.4 Hz, $J_{H6'-H6"b}$ = 3.4 Hz, $J_{H6"a-H6"b}$ = -11.8 Hz, J_{H6-Me} = -1.1 Hz; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ -0.12 [$(\mathbf{CH_3})_3$Si], 12.52 [$\mathbf{CH_3}$ at C5], 50.97 [C5'], 65.15 [C6"], 76.76 [C6'], 78.11 [C4'], 99.02 [C3'], 109.47 [C5], 110.45 [C1'], 128.39, 129.52 and 133.32 [aromatic **CH**], 129.17 [aromatic **C**], 135.68 [C6], 151.00 [C2], 164.55 [C4], 165.96 [**CO**]; LRMS (CI-NH_3): m/e 464 ([M + NH_4^+], 28.6%), 447 ([MH^+], 100%), 357 ([MH^+ - Me_3SiOH], 78.9%); HRMS (CI-NH_3): m/e calcd. for $C_{12}H_{27}N_2O_7Si$ [MH^+], 447.1589; found, 447.1587}.

(±)-6'-*exo*-Benzoyloxymethyl-3'-*endo*-cytosin-1-yl-4'-*exo*-trimethylsilyloxy-2',7'-dioxabicyclo[3.2.0]-heptane (5b).

Epoxide **2** and *bis*(trimethylsilyl)cytosine afforded nucleoside **5b** in 58% yield by a procedure similar to the one used for the preparation of nucleoside **5a**. {^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.16 (s, 9H, Me_3Si), 3.25 (t, 1H, H5'), 4.23 (ddd, 1H, H6'), 4.38 (A of ABX, 1H, H6"$_a$), 4.51 (B of ABX, 1H, H6"$_b$), 4.74 (s, 1H, H4'), 5.78 (d, 1H, H5), 5.95 (s, 1H, H3'), 6.24 (d, 1H, H1'), 7.35 (s, br, ex, 2H, NH_2), 7.39 - 7.61 (m, 3H, Ph), 8.00 - 8.06 (m, 2H, Ph), 8.11 (d, 1H, H6), $J_{H1'-H5'}$ = 4.3 Hz, $J_{H5'-H6'}$ = 4.0 Hz, $J_{H6'-H6"a}$ = 3.8 Hz, $J_{H6'-H6"b}$ = 3.9 Hz, $J_{H6"a-H6"b}$ = -12.4 Hz, J_{H5-H6} = 7.6 Hz; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 0.07 [$(\mathbf{CH_3})_3$Si], 51.08 [C5'], 65.24 [C6"], 76.74 [C6'], 77.76 [C4'], 93.85 [C5], 99.85 [C3'], 110.56 [C1'], 128.48, 129.64 and 133.39 [aromatic **CH**], 129.31 [aromatic **C**], 141.16 [C6], 156.32 [C2], 165.90 [C4], 166.07 [Ph**CO**]; LRMS (CI-NH_3): m/e 432 ([MH^+], 25.3%)}.

(±)-6'-*exo*-Benzoyloxymethyl-4'-*exo*-hydroxy-3'-*endo*-thymin-1-yl--2',7'-dioxabicyclo[3.2.0]heptane (6a).

To a stirred solution of nucleoside **5a** (322 mg, 0.722 mmol) in dry tetrahydrofuran (20 mL) at room temperature under an atmosphere of nitrogen was added tetra-*n*-butylammonium fluoride (1.0M solution in tetrahydrofuran, 1.08 mL, 1.08 mmol). After 1 h, the solvent was removed *in vacuo* to yield a white solid which was chromatographed over silica gel (methylene chloride / methanol, 20:1 v/v) affording nucleoside **6a** as a white solid (246 mg, 91% yield). {^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.91 (d, 3H, CH_3 at C5), 3.29 (t, 1H, H5'), 3.48 (s, br, ex, 1H, OH), 4.33 (ddd, 1H, H6'), 4.46 (A of ABX, 1H, H6"$_a$), 4.57 (B of ABX, 1H, H6"$_b$), 5.92 (s, 1H, H3'), 6.27 (d, 1H, H1'), 7.41 - 7.63 (m, 3H, Ph), 7.92 (d, 1H, H6), 8.02 - 8.14 (m, 2H, Ph), 10.20 (s, br, ex, 1H, NH), $J_{H1'-H5'}$ = 4.1 Hz, $J_{H5'-H6'}$ = 4.2 Hz, $J_{H6'-H6"a}$

= 4.1 Hz, $J_{H6'-H6"b}$ = 3.8 Hz, $J_{H6"a-H6"b}$ = -12.3 Hz, J_{H6-Me} = -1.1 Hz; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 12.64 [CH_3 at C5], 49.61 [C5'], 65.08 [C6"], 77.53 [C6'], 78.89 [C4'], 100.02 [C3'], 110.50 [C5], 110.97 [C1'], 128.56, 129.72, 133.48 [aromatic CH], 129.35 [aromatic C], 135.71 [C6], 151.48 [C2], 164.55 [C4], 166.12 [PhCO]; LRMS (CI-NH_3): m/e 392 ([M + NH_4^+], 8.4%), 375 ([MH^+], 100%), 357 ([MH^+ - H_2O], 49.1%); HRMS (CI-NH_3): m/e calcd. for $C_{18}H_{19}N_2O_7$ [MH^+], 375.1192; found, 375.1192}.

(±)-6'-*exo*-Benzoyloxymethyl-3'-*endo*-cytosin-1-yl-4'-*exo*-hydroxy-2',7'-dioxabicyclo[3.2.0]heptane (6b).

Nucleoside **6b** was obtained in 96% yield as a white foam by a procedure identical to the one described for the preparation of nucleoside **6a**. {^{1}H-NMR (200 MHz, CD_3OD): δ 3.41 (t, 1H, H5'), 4.34 (A of ABX, 1H, H6"$_a$), 4.39 (ddd, 1H, H6'), 4.44 (B of ABX, 1H, H6"$_b$), 4.65 (s, 1H, H4'), 5.88 (d, 1H, H5), 6.00 (s, 1H, H3'), 6.26 (d, 1H, H1'), 7.47 - 7.68 (m, 3H, Ph), 8.04 - 8.10 (m, 2H, Ph), 8.24 (d, 1H, H6), $J_{H1'-H5'}$ = 4.4 Hz, $J_{H5'-H6'}$ = 4.9 Hz, $J_{H6'-H6"a}$ = 4.1 Hz, $J_{H6'-H6"b}$ = 2.8 Hz, $J_{H6"a-H6"b}$ = -12.5 Hz, J_{H5-H6} = 7.5 Hz; LRMS (CI - NH_3): m/e 377 ([M + NH_4^+], 1.3%), 360 ([MH^+], 100%), 249 ([MH^+ - cytosine], 20.2%); HRMS (CI - NH_3): m/e calcd. for $C_{17}H_{18}N_3O_6$ [MH^+], 360.1196; found, 360.1195}.

(±)-4'-*exo*-Hydroxy-6'-*exo*-hydroxymethyl-3'-*endo*-thymin-1-yl-2',7'-dioxabicyclo[3.2.0]heptane (7a).

An ice-cold solution of nucleoside **6a** (381 mg, 1.02 mmol) in anhydrous methanol (20 mL) was saturated with ammonia gas and allowed to warm to room temperature. After 20 h, the reaction was heated to boiling for 0.5 h, allowed to cool and the solvent removed under reduced pressure to yield a white solid which was washed repeatedly with ether. Recrystallization from methanol yielded bone white crystals of nucleoside **7a** (226 mg, 82% yield, m.p. 194-196°C). {^{1}H-NMR (200 MHz, CD_3OD): δ 1.86 (d, 3H, CH_3 at C5), 3.28 (t, 1H, H5'), 3.63 (A of ABX, 1H, H6"$_a$), 3.69 (B of ABX, 1H, H6"$_b$), 4.14 (ddd, 1H, H6'), 4.59 (s, 1H, H4'), 5.97 (s, 1H, H3'), 6.17 (d, 1H, H1'), 8.05 (d, 1H, H6), $J_{H1'-H5'}$ = 4.2 Hz, $J_{H5'-H6'}$ = 4.4 Hz, $J_{H6'-H6"a}$ = 3.8 Hz, $J_{H6'-H6"b}$ = 3.2 Hz, $J_{H6"a-H6"b}$ = -12.6 Hz, J_{H6-Me} = -1.2 Hz; ^{13}C-NMR (75.4 MHz, CD_3OD): δ 13.57 [CH_3 at C5], 51.42 [C5'], 65.22 [C6"], 80.06 [C6'], 82.63 [C4'], 101.48 [C3'], 110.92 [C5], 112.86 [C1'], 138.38 [C6], 153.42 [C2], 167.46 [C4]; LRMS (CI-NH_3): m/e 271 ([MH^+], 100%), 253 ([MH^+ - H_2O], 7.7%); HRMS (CI-NH_3): m/e calcd. for $C_{11}H_{15}N_2O_6$ [MH^+], 271.0931; found, 271.0930}. Anal. calcd. for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37; found: C, 48.52; H, 5.49; N, 10.46.

(±)-3'-*endo*-Cytosin-1-yl-4'-*exo*-hydroxy-6'-*exo*-hydroxymethyl-2',7'-dioxabicyclo[3.2.0]heptane (7b).

Nucleoside **7b** was obtained in 77% yield as a white powder by a procedure identical to the one described for the preparation of nucleoside **7a**. {^{1}H-NMR (200 MHz, CD_3OD): δ 3.24 (t, 1H, H5'), 3.62 (A of ABX, 1H, H6"$_a$), 3.67 (B of ABX, 1H, H6"$_b$), 3.98 (ddd, 1H, H6'), 4.52 (s, 1H, H4'), 5.83 (d, 1H, H5), 5.94 (s, 1H, H3'), 6.13 (d, 1H, H1'), 8.21 (d, 1H, H6), $J_{H1'-H5'}$ = 4.1 Hz, $J_{H5'-H6'}$ = 4.6 Hz, $J_{H6'-H6"a}$ =

4.1 Hz, $J_{H6'-H6"b}$ = 3.2 Hz, $J_{H6"a-H6"b}$ = -12.6 Hz, J_{H5-H6} = 7.5 Hz; ^{13}C-NMR (75.4 MHz, CD_3OD): δ 50.41 [C5'], 64.41 [C6"], 79.05 [C4'], 81.73 [C6'], 95.07 [C5], 101.41 [C3'], 112.10 [C1'], 142.17 [C6], 158.76 [C2], 167.99 [C4]; LRMS (FAB - glycerol): m/e 278 ([M + Na^+], 23.2%), 256 ([MH^+], 35.4%); HRMS (FAB - glycerol): m/e calcd. for $C_{10}H_{14}N_3O_5$ [MH^+], 256.0933; found, 256.0933}.

(±)-3'β-Hydroxy-4'α-(1-hydroxy-2-benzoyloxyethyl)-5'β-methoxy-2'α-thymin-1-yl-tetrahydrofuran (8).

To a stirred solution of nucleoside **5a** (322 mg, 0.72 mmol) in anhydrous methanol (22 mL) under an atmosphere of nitrogen at room temperature was added trifluoroacetic acid (63 mL, 0.72 mmol). After 30 min, the solution was evaporated to dryness. The residue was redissolved in methylene chloride (100 mL), washed with saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to yield the title comnpound in quantitative (493 mg) yield as a white foam. {^{1}H-NMR (200 MHz, CD_2Cl_2): δ 1.82 (d, 3H, CH_3 at C5), 2.45 (ddd, 1H, H4'), 3.42 (s, 3H, MeO), 4.31 - 4.45 (m, 5H, H3', H4", $H4'''_a$, $H4'''_b$, OH), 5.33 (d, ex, 1H, OH), 5.34 (d, 1H, H5'), 5.94 (d, 1H, H2'), 7.34 - 7.62 (m, 3H, Ph), 7.49 (d, 1H, H6), 8.03 - 8.08 (m, 2H, Ph), 10.39 (s, br, ex, 1H, NH), $J_{H2'-H3'}$ = 5.2 Hz, $J_{H4'-H5'}$ = 4.5 Hz, $J_{OH-H3' \text{ or } H4"}$ = 0.8 Hz, J_{H6-Me} = -0.8 Hz; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 12.36 [$\mathbf{CH_3}$ at C5], 54.26 [C4'], 56.26 [$\mathbf{CH_3O}$], 67.71 [C4'''], 67.86 [C4"], 77.28 [C3'], 90.90 [C2'], 105.40 [C3'], 109.96 [C5], 128.41, 129.76, 133.26 [aromatic **CH**], 129.66 [aromatic **C**], 136.64 [C6], 151.87 [C2], 164.32 [C4], 166.84 [PhCO]; LRMS (CI-NH_3): m/e 424 ([M + NH_4^+], 2.6%), 407 ([MH^+], 22.2%), 375 ([MH^+ - MeOH], 100%), 281 ([MH^+ - thymine], 12.3%); HRMS (CI-NH_3): m/e calcd. for $C_{19}H_{23}N_2O_8$ [MH^+], 407.1455; found, 407.1454}.

(±)-4'α-(1,2-Dihydroxyethyl)-3'β-hydroxy-5'β-methoxy-2'α-thymin-1-yl-tetrahydrofuran (9).

Nucleoside **9** was obtained in 86% yield as a white powder by a procedure identical to the one described for the preparation of nucleoside **7a**. {^{1}H-NMR (200 MHz, CD_3OD): δ 1.85 (d, 3H, CH_3 at C5), 2.19 (ddd, 1H, H4'), 3.39 (s, 3H, MeO), 3.51 (A of ABX, 1H, $H4'''_a$), 3.56 (B of ABX, 1H, $H4'''_b$), 3.85 (ddd, 1H, H4"), 4.16 (t, 1H, H3'), 5.10 (d, 1H, H5'), 6.01 (d, 1H, H2'), 7.52 (d, 1H, H6), $J_{H2'-H3'}$ = 7.2 Hz, $J_{H3'-H4'}$ = 8.2 Hz, $J_{H4'-H4"}$ = 4.4 Hz, $J_{H4"-H4'''a}$ = 7.4 Hz, $J_{H4"-H4'''b}$ = 4.4 Hz, $J_{H4'''a-H4'''b}$ = -10.9 Hz, $J_{H4'-H5'}$ = 4.2 Hz, J_{H6-Me} = -1.3 Hz; ^{13}C-NMR (75.4 MHz, CD_3OD): δ 12.36 [$\mathbf{CH_3}$ at C5], 55.29 [C4'], 56.14 [$\mathbf{CH_3O}$], 65.93 [C4'''], 71.24 [C4"], 75.91 [C3'], 88.63 [C2'], 105.18 [C5'], 112.18 [C5], 137.82 [C6], 152.77 [C2], 166.11 [C4]; LRMS (CI-NH_3): m/e 303 ([MH^+], 39.1%), 271 ([MH^+ - MeOH], 100%); HRMS (CI-NH_3): m/e calcd. for $C_{12}H_{19}N_2O_7$ [MH^+], 303.1191; found, 303.1192}. Anal. calcd. for $C_{12}H_{18}N_2O_7 \cdot H_2O$: C, 45.00; H, 6.29; N, 8.75; found: C, 44.83; H, 6.19; N, 8.67.

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