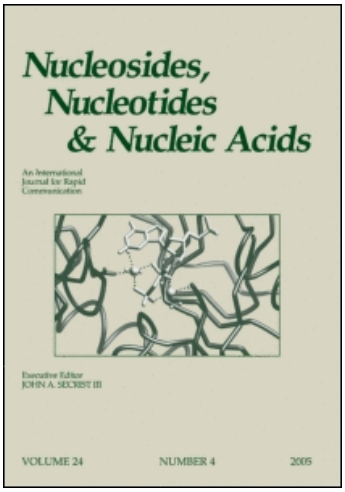

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Synthesis of 1-(3-Azido-2,3-Dideoxy-Beta-D-Ribo-Hexofuranosyl)Thymine

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SYNTHESIS OF 1-(3-AZIDO-2,3-DIDEOXY-BETA-D-RIBO-HEXOFURANOSYL)THYMINE

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ABSTRACT: The nucleoside derivative 1-(3-azido-2,3-dideoxy-beta-D-ribo-hexofuranosyl)thymine has been synthesized from 3-O-benzyl-1,2-O-isopropylidene-alpha-D-glucofuranose-5,6-carbonate in an overall yield of 16%. The key step in the synthesis involves the selective deacetylation of a nucleoside derivative having a cyclic carbonate moiety.

INTRODUCTION

Since the discovery that 3'-azido-3'-deoxythymidine (zidovudine) significantly inhibits the replication of HIV[1], significant effort has been directed toward the synthesis of nucleoside analogues with higher therapeutic indices. Systematic modifications of the 3'-azido-3'-deoxythymidine skeleton have been made in an attempt to develop a structure activity relationship and ultimately bring second generation RT inhibitors to the clinic. Modifications of the pyrimidine nucleus have been made at the 4- [2], 5- [3,4], and 6- [3] positions.

Several modifications of the furanose moiety have also been made. Griengl[5] has synthesized the enantiomerically pure carbocyclic analogue, while Scheiner[6] and Takaku[7] have synthesized acyclic analogues of 3'-azido-3'-deoxythymidine. Miyasaka[8] has synthesized the phosphonate isostere of 3'-azido-3'-deoxythymidine 5'-phosphate. Zbiral[9] has described the synthesis of 1-(3-azido-2,3,5-trideoxy-beta-D-allofuranosyl)thymine. The C-4' epimer of zidovudine has been synthesized by Czernecki[10]. Pyranoside analogues[11,12] of zidovudine have been reported. Most recently, Sztaricskai et al. have reported on the synthesis of the beta-L-ribo-hexopyranosyl analogues of zidovudine[13].

Holy[14] and Hieble[15] recently reported the synthesis of 1-(3-azido-2,3-dideoxy-beta-D-ribo-hexofuranosyl)thymine[16]. This publication describes an alternate synthesis which was in progress at the time that these publications appeared. The synthesis described herein differs significantly—the key step involves the selective deacetylation of a nucleoside derivative in the presence of a cyclic carbonate moiety. This methodology may find application in the broad fields of carbohydrate and nucleoside chemistry.

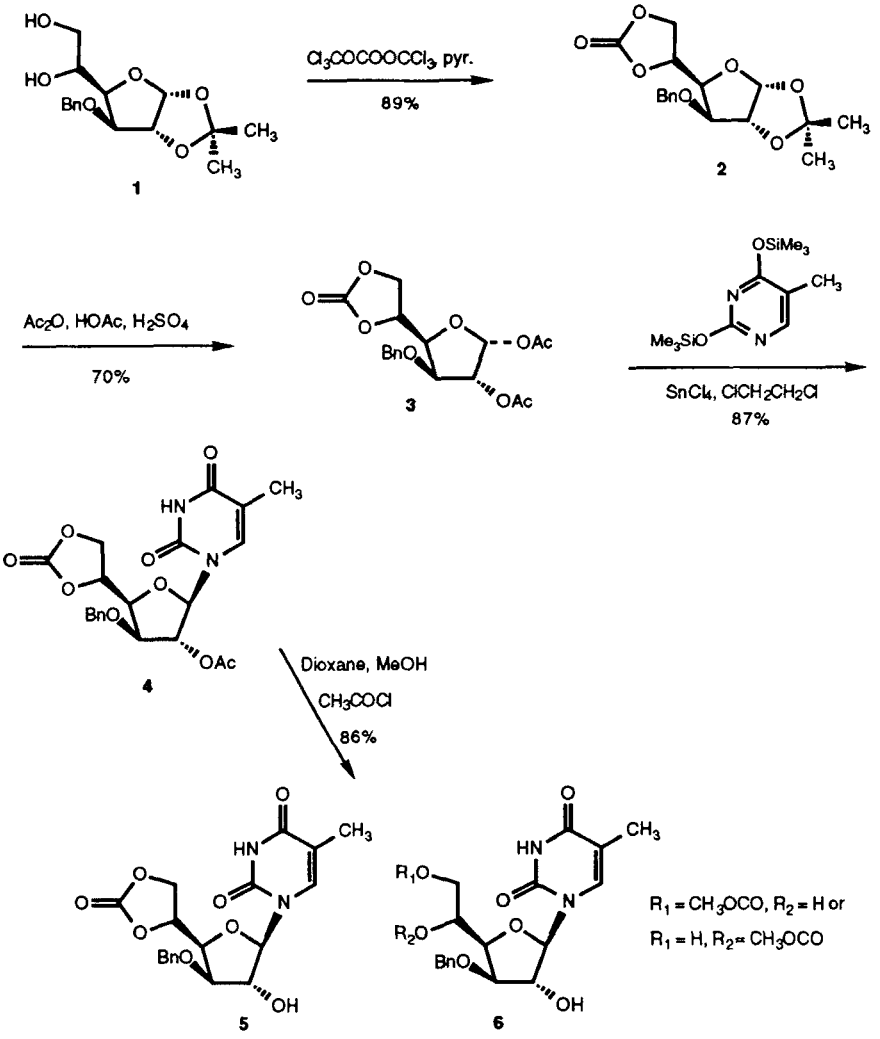

FIG. 1

CHEMISTRY

Initially, 3-O-benzyl-1,2-O-isopropylidene-alpha-D-glucofuranose **1**[17] was treated with dimethycarbonate and sodium methoxide according to the method of Fleet[18]. This procedure, although high yielding, presented some technical difficulties upon scale-up. Treatment of **1** with triphosgene in pyridine at + 5 °C generated the cyclic carbonate **2** in an 89% yield. In addition, this procedure was amenable to scale-up. The cyclic carbonate **2** was treated with a solution containing acetic anhydride, acetic acid, and sulfuric acid. The diacetate **3** was isolated in a 70% yield. The diacetate **3** was not stable for prolonged periods of time and because of this was used without complete characterization. The diacetate **3** was

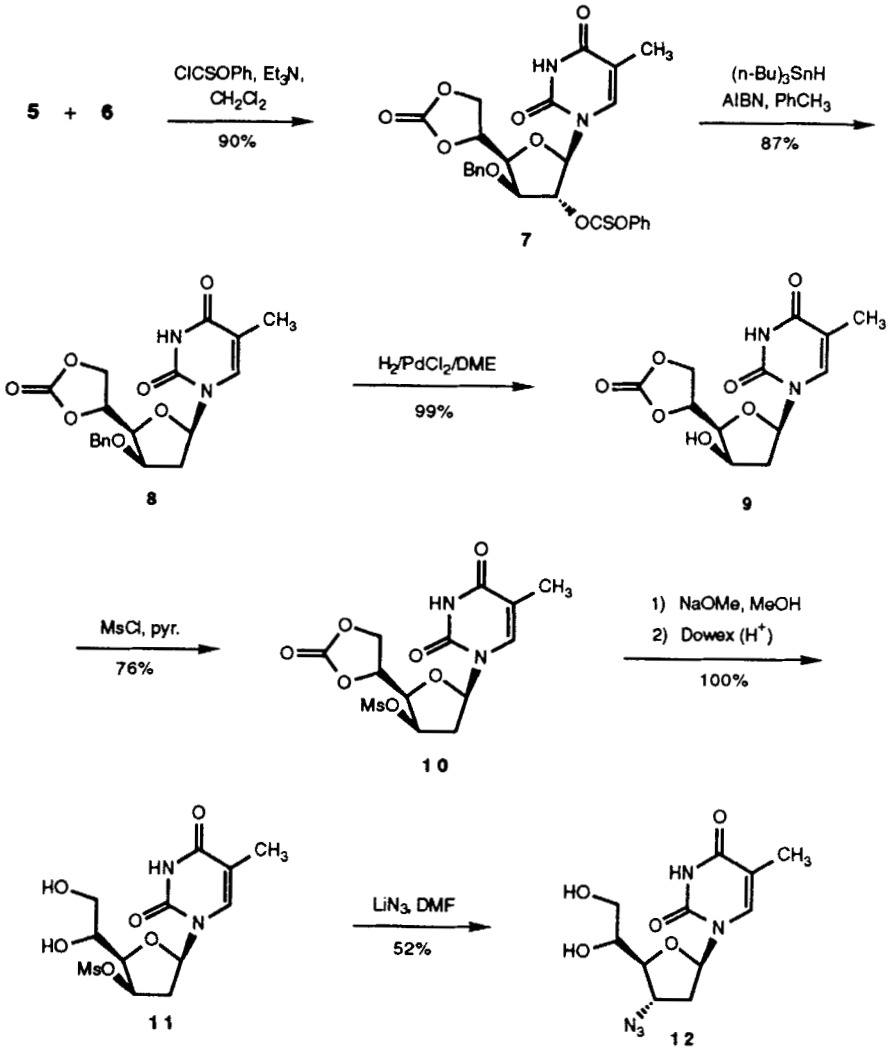

FIG. 1

Continued

condensed with silylated thymine according to the method of Vorbruggen[19]. Nucleoside derivative **4** was obtained in an 87% yield.

At this point in the synthesis it was necessary to hydrolyze the acetate at the 2'-position while leaving the cyclic carbonate intact. This was accomplished by heating at reflux for 24 h a solution containing compound **4**, dioxane, 25 equivalents of methanol, and 15 equivalents of acetyl chloride. The desired product **5** and an acyclic carbonate **6** were produced in an 86% combined yield. While the compounds were

inseparable by thin layer chromatography, an NMR spectrum revealed that the two compounds were present in a 95:5 ratio (**5**:**6**). The inseparable carbonates were treated with phenyl chlorothionocarbonate according to the method of Robins[20]. The cyclic carbonate **7** was the only product isolated in this reaction. The yield of this reaction was 90%. Treatment of **7** with tributyltin hydride led to the formation of 1-(3-O-benzyl-5,6-O-carbonyl-2-deoxy-beta-D-arabino-hexofuranosyl)thymine **8** in an 87% yield. Hydrogenolysis of the benzyl moiety using 10% palladium on carbon failed. Derivative **8** was successfully hydrogenolyzed in a 99% yield using palladium chloride in 1,2-dimethoxyethane. Compound **9** was converted to the corresponding mesylate using methanesulfonyl chloride in pyridine in a 76% yield. The carbonate was then hydrolyzed generating compound **11** in a 100% yield. The mesylate **11** was reacted with lithium azide in dimethyformamide, and the target compound **12** was obtained in a 52% yield. The product **12** was found to be identical by spectroscopic analysis to authentic material[14,15]. This chemistry is depicted in Fig 1.

EXPERIMENTAL

NMR spectra were recorded using samples prepared by dissolving 5 mg in 0.8 mL of 99.96% d_6-DMSO (Merck) after which the solution was filtered through cotton. All spectra were recorded using either Varian Unity 300 or VXR-500S spectrometers operating at observation frequencies for proton at 299.949 or 499.843 MHz, respectively. One-dimensional proton reference spectra were typically acquired with spectral widths of 4300 or 6360 Hz for 300 and 500 MHz, respectively; the spectra were digitized using 16K or 32K points, respectively. COSY spectra were typically acquired as 768 x 384 points, were zero-filled to 1024 x 1024 points during process, and were symmetrized. When necessary, heteronuclear chemical shift correlation spectra were recorded using the inverse-detected HMQC pulse sequence described by Bax and Subramanian[21]. The spectra were typically recorded as 384 x 64 points in a phase-sensitive manner using the hyper-complex method of States-Haberkorn. The instrument was equipped with a 5 mm Z-Spec inverse detection probe for these experiments obtained from Nalorac Cryogenics Corp., Martinez, CA. Unless stated otherwise, all chemicals were purchased from Aldrich Chemical Co. UV spectra were recorded on a Beckman DU-70 spectrophotometer. Melting points were taken on a Thomas Hoover melting point capillary melting point apparatus and are uncorrected. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA. Purification of compounds was accomplished using flash chromatography[22] or a modification of traditional flash chromatography as described by O'Neil[23].

3-O-Benzyl-1,2-O-isopropylidene-alpha-D-glucofuranose-5,6-carbonate (2). A three-neck round bottom flask was charged with 3-O-benzyl-1,2-O-isopropylidene-alpha-D-glucofuranose[18] (35.94 g, 115.84 mmol) and dry pyridine (110 mL). The solution was cooled to an internal temperature of +5 °C, and triphosgene (11.50 g, 38.76 mmol) was added in portions using a solids addition funnel over an 80 min period. Stirring was then continued for 1 h. The reaction was diluted with chloroform (550 mL) and washed with water (1 X 220 mL, 1 X 150 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was azeotroped with toluene (2 X 60 mL) and dried in vacuo overnight. The product was purified on a flash chromatography column which

was eluted with EtOAc : hexanes (25:75 to 100:0) in increasingly polar increments. The appropriate fractions were combined and concentrated. The product was isolated in an 89% yield. A small sample was rechromatographed for analysis. Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.70; H, 5.99. Found: C, 60.73; H, 6.02.

1,2-Di-O-acetyl-3-O-benzyl-alpha-D-glucofuranose-5,6-carbonate (3). A three-neck round bottom flask was charged with 3-O-benzyl-1,2-O-isopropylidene-alpha-D-glucofuranose-5,6-carbonate (24.96 g, 74.26 mmol) and acetic anhydride (63 mL). The suspension was cooled in an ice bath, and acetic acid (88.5 mL) was added dropwise over a 40 min period. Sulfuric acid (5.3 mL) was next added over a 7 min period. The bath was removed, and the reaction was stirred overnight at room temperature before being poured onto ice (270 g). The reaction was extracted with chloroform (1 X 125 mL, 1 X 175 mL) and ethyl acetate (1 X 100 mL). The organic fractions were combined, concentrated to a volume of 200 mL, and extracted with a saturated sodium bicarbonate solution (3 X 50 mL). The organic layer was passed through phase separatory paper and concentrated in vacuo. The crude product was diluted with toluene (2 X 50 mL) and concentrated in vacuo. The product was purified according to the method of O'Neil[23] using EtOAc: hexanes (1: 2 to 1:1). The appropriate fractions were combined and concentrated. The product was isolated in a 70% yield. The product was used immediately without complete characterization.

1-(2-O-Acetyl-3-O-benzyl-5,6-O-carbonyl-beta-D-glucofuranosyl)thymine (4). A three-neck 1-L round bottom flask equipped with a condenser, an addition funnel, and a stopper was charged with thymine (7.20 g, 57.1 mmol), anhydrous 1,2-dichloroethane (300 mL), and bis(trimethylsilyl)acetamide (30.2 mL, 0.121 mol). The suspension was heated in a 65-70 °C oil bath while being maintained under a nitrogen atmosphere. The resulting solution was then cooled in an ice bath to 5 °C followed by the rapid addition of 1,2-di-O-acetyl-3-O-benzyl-alpha-D-glucofuranose-5,6-carbonate (20.0 g, 52.6 mmol) in 1,2-dichloroethane (250 mL). After 15 minutes, 99% stannic chloride (8.8 mL, 75 mmol) was added dropwise to the reaction, which was then stirred for 30 min at 5 °C, 30 min at room temperature, and finally heated at reflux for 12 h. The dark mixture was cooled to 5 °C, and a saturated solution of potassium sodium tartrate (300 mL) was added. After stirring for 45 min, the resulting suspension was filtered through Celite. The solids were then washed with EtOAc (300 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to give a dark red oil. Flash chromatography over silica gel using hexane : ethyl acetate (1:1 to 1:4) in increments of increasing polarity provided a white foam (20.3 g, 45.6 mmol, 87%). 1H nmr (d_6-DMSO): δ 11.41 (s, NH), 7.36 (m, benzyl aromatics and H6), 6.03 (d, J = 2.5 Hz, H1'), 5.29 (dd, J = 2.7, 0.8 Hz, H2'), 5.23 (ddd, J = 8.4, 6.5, 4.2 Hz, H5'), 4.76 and 4.56 (AB quartet, J = 11.2 Hz, benzyl CH_2), 4.53 (dd, J = 8.6, 8.6 Hz, H6'), 4.473 (dd, J = 8.2, 6.4 Hz, H6"), 4.471 (dd, J = 4.0, 4.0 Hz, H4'), 4.30 (dd, J = 4.2, 1.0 Hz, H3'), 2.09 (s, acetyl Me), 1.57 (d, J = 1.2 Hz, 5-Me). All resonance assignments were made from 300 MHz data except for the H4' and H6", which were differentiated using 500 MHz data. Carbon resonance assignments for the saccharide carbons were obtained from the HMQC spectrum and are as follows: C1', 86.7; C2', 76.5; C3',

81.1; C4', 79.6; C5', 85.3; C6', 66.0; benzyl CH_2, 70.5. Anal. calcd. for $C_{21}H_{22}N_2O_9$: C, 54.31; H, 5.21; N, 6.03. Found: C, 54.01; H, 4.94; N, 5.79. UV (10% EtOH/pH 7): 264.5 nm (8400).

1-(3-O-benzyl-5,6-O-carbonyl-2-hydroxy-beta-D-glucofuranosyl)thymine (5 and 6). Acetyl chloride (36 mL) was added dropwise to a solution of 1-(2-O-acetyl-3-O-benzyl-5,6-O-carbonyl-beta-D-glucofuranosyl)thymine (22.7 g, 50.8 mmol) in anhydrous 1,4-dioxane (800 mL) and anhydrous methanol (51 mL) in a three-neck 1-L round bottom flask under a nitrogen atmosphere and equipped with a condenser topped by a nitrogen inlet, an additional funnel, and a stopper. The reaction was heated at reflux for 24 h and allowed to cool before being concentrated in vacuo to a brown foam. Flash chromatography over silica gel using chloroform : methanol (98:2 to 95:5) in increments of increasing polarity afforded the product as a white foam (17.7 g, 43.8 mmol). Proton nmr analysis revealed the compound as a mixture of two alcohols: one with the cyclic carbonate intact, **5**, and one as the result of the carbonate ring opened by methanol, **6**, in a 95:5 ratio respectively. 1H nmr (d_6-DMSO): δ 11.44 (s, NH), 7.38 (m, benzyl aromatics/H6), 6.05 (d, J = 4.3 Hz, H1'), 5.88 (dd, J = 4.1, 0.8 Hz, H2'), 5.22 (ddd, J = 8.4, 6.6, 4.4 Hz, H5'), 4.74 and 4.54 (AB quartet, J = 11.3 Hz, benzyl CH_2), 4.53 (dd, J = 7.6, 7.6 Hz, H6'), 4.41 (m, H6", H4'), 4.10 (dd, J = 4.2, 1.0 Hz, H3'), 3.73 (s, Me of the ring-opened carbonate **6**, a diagnostic peak for determining the amount of the minor product), 1.59 (s, 5-Me).

1-[3-O-Benzyl-5,6-O-carbonyl-2-O-(phenoxythiocarbonyl)-beta-D-glucofuranosyl]thymine (7). A solution of phenyl chlorothionoformate (7.0 mL, 50 mmol) in dichloromethane (50 mL) was added dropwise to a 0 °C solution of 1-(3-O-benzyl-5,6-O-carbonyl-2-hydroxy-beta-D-glucofuranosyl)thymine (as the mixture of cyclic and ring-opened carbonates) (17.0 g, 42 mmol) and triethylamine (75 mL) in anhydrous dichloromethane (600 mL) in a three-neck 1-L round bottom flask equipped with a nitrogen inlet, an addition funnel, and a stopper. The ice bath was removed, and the reaction was stirred for 4 h before being concentrated in vacuo. Ethyl acetate (300 mL) and water (100 mL) were added to the residue, and the layers were separated. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to an orange glass. Addition of 200 mL of hexane : ethyl acetate (4:1) allowed the glass to be pulverized into a free-flowing precipitate that was filtered to give the thiocarbonate as a pale yellow solid, which was azeotroped with toluene (20.3 g, 38 mmol, 90%). 1H nmr (d_6-DMSO): δ 11.45 (s, NH), 7.3 (m, benzyl aromatics, H6, and phenylthiocarbonate aromatics), 6.22 (d, J = 2.3 Hz, H1'), 5.76 (d, J = 2.2 Hz, H2'), 5.29 (ddd, J = 8.5, 6.7, 3.7, H5'), 4.85 (d, J = 11.1 Hz, benzyl CH2) and 4.64 (d, J = 11.0 Hz, benzyl CH_2), 4.60 (m, H3' and H4'), 4.57 (dd, J = 8.4, 8.4 Hz, H6'), 4.52 (dd, J = 8.4, 6.6 Hz, H6"), 1.56 (d, J = 1.2 Hz, 5-Me). Carbon resonance assignments were obtained for some of the protonated carbons from the HMQC spectrum and were as follows: C1', 87.5; C2', 86.4; C3' and C4' had identical carbon chemical shifts of 79.7; C6', 65.7; benzyl CH_2, 71.4. Anal. cald. for $C_{26}H_{24}N_2O_9S$ (0.2 mol H_2O, 0.4 mol toluene): C, 59.54; H, 4.79; N, 4.82; S, 5.52. Found: C, 59.45; H, 4.74; N, 4.81; S, 5.48.

1-(3-O-Benzyl-5,6-O-carbonyl-2-deoxy-beta-D-arabino-hexofuranosyl)thymine (8). A 2-L round bottom flask was equipped with a condenser (topped by a nitrogen inlet) and two stoppers.

The flask was charged with 1-[3-O-benzyl-5,6-O-carbonyl-2-O-(phenoxythiocarbonyl)-beta-D-glucofuranosyl]thymine (20.3 g, 37.5 mmol) and toluene (800 mL). The solution was degassed with nitrogen for 15 min. Then 97% tributyltin hydride (24.1 mL, 86.9 mmol) and AIBN [Fluka] (1.0 g) were added. The reaction was heated at 85-90 °C for 1 h, cooled, and concentrated in vacuo. The oily residue was dissolved in acetonitrile (500 mL) and washed with several portions of hexanes (6 x 200 mL) to remove organotin compounds. The acetonitrile layer was concentrated in vacuo, and the crude product was purified on a flash chromatography column using hexane: ethyl acetate (2:1 to 1:3) in increments of increasing polarity to provide the deoxy-nucleoside as a white foam, which was azeotroped with toluene (12.7 g, 0.032.6 mmol, 87%). 1H nmr (d6-DMSO): δ 11.34 (s, NH), 7.47 (q, J = 1.2 Hz, H6), 7.35 (m, benzyl aromatics), 6.28 (dd, J = 8.8, 3.0 Hz, H1'), 5.25 (ddd, J = 8.4; 6.5, 3.8 Hz, H5'), 4.59 (d, J = 11.5 Hz, benzyl CH_2), 4.53 (dd, J = 8.7, 8.7 Hz, H6'), 4.44 (d, J = 11.5 Hz, benzyl CH_2), 4.32 (dd, J = 5.1, 3.9 Hz, H3'), 4.26 (dd, J = 3.7, 3.7 Hz, H4'), 2.60 (ddd, J = 15.4, 8.9, 5.4 Hz, H2'), 2.31 (dd, J = 15.4, 3.4 Hz, H2"), 1.51 (d, J = 1.2 Hz, 5-Me). UV (10% EtOH/pH 7): 266 nm (7013). Anal. calcd. for $C_{19}H_{20}N_2O_7$ (0.1 mol H_2O and 0.2 mol toluene): C, 59.97; H, 5.38; N, 6.86. Found; C, 59.98; H, 5.48; N, 6.77.

1-(5,6-O-Carbonyl-2-deoxy-beta-D-arabino-hexofuranosyl)thymine (9). To a solution of 1-(3-O-benzyl-5,6-O-carbonyl-2-deoxy-beta-D-arabino-hexofuranosyl)thymine (12.5 g, 32.2 mmol) in anhydrous 1,2-dimethoxyethane (170 mL) in a Parr bottle was added palladium(II) chloride (5.3 g, 29.9 mmol). The vessel was then put on a Parr shaker where it was agitated for 3 h under 40 psi of hydrogen gas. The reaction was filtered through Celite and washed with several portions of 95% ethanol. After the solvents were removed in vacuo, the resulting solid was collected and washed with 100 mL of chloroform : ethyl acetate (2:1) to provide the alcohol as a white powder (9.5 g, 31.9 mmol, 99%). 1H nmr (d_6-DMSO): δ 11.34 (s, NH), 7.77 (q, J = 1.3 Hz, H6), 6.20 (dd, J = 8.7, 3.3 Hz, H1'), 5.23 (ddd, J = 8.4, 6.6, 3.6 Hz, H5'), 4.55 (dd, J = 8.6, 8.6 Hz, H6'), 4.46 (dd, J = 8.4, 6.6 Hz, H6"), 4.36 (dd, J = 8.9, 3.7 Hz, H3'), 4.20 (dd, J = 3.6, 3.6 Hz, H4'), 2.64 (ddd, J = 14.8, 8.8, 5.7 Hz, H2'), 1.89 (dd, J = 15.0, 3.3 Hz, H2"), 1.76 (d, J = 1.2 Hz, 5-Me). The 3'-OH resonance was not observed.

Anal. calcd. for $C_{12}H_{14}N_2O_7$ (0.8 EtOAc): C, 49.51; H, 5.58; N, 7.60. Found: C, 49.77; H, 5.51; N, 7.88. UV (10% EtOH/pH 7): 264.5 nm (9420).

1-(5,6-O-Carbonyl-2-deoxy-3-O-mesyl-beta-D-arabino-hexofuranosyl)thymine (10). A 100 mL three-neck round bottom flask under a nitrogen atmosphere equipped with a stopper, a nitrogen inlet, and a septum, was charged with 1-(5,6-O-carbonyl-2-deoxy-beta-D-arabino-hexofuranosyl)thymine (1.0 g, 3.35 mmol) and dry pyridine (40 mL). The solution was cooled to 0 °C, and mesyl chloride (0.39 mL, 5.03 mmol) was added dropwise. The pale yellow solution was brought to room temperature and was stirred overnight. The reaction was then concentrated in vacuo, and toluene was used to azeotrope residual pyridine. The crude mesylate was partitioned between ethyl acetate (200 mL) and water (50 mL), and the organic layer was washed with brine (25 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to a beige solid. The product was purified on a flash chromatography column, which was eluted with hexane: ethyl acetate (2:1 to 1:3) in increments of increasing polarity. The mesylate was obtained as a

white powder (0.96 g, 2.55 mmol, 76%). ^{1}H nmr (d_6-DMSO): δ 11.41 (s, NH), 7.39 (q, J = 1.3 Hz, H6), 6.22 (dd, J = 8.3, 4.5 Hz, H1'), 5.40 (ddd, J = 5.9, 3.8, 1.3 Hz, H3'), 5.19 (ddd, J = 8.5, 6.3, 4.2 Hz, H5'), 4.64 (dd, J = 8.4, 8.4 Hz, H6'), 4.49 (dd, J = 8.4, 6.3 Hz, H6"), 4.39 (dd, J = 3.8, 3.8 Hz, H4'), 3.31 (s, 4-mesyl Me), 2.89 (ddd, J = 15.8, 8.4, 6.1 Hz, H2'), 2.32 (ddd, J = 15.7, 4.4, 1.3 Hz, H2"), 1.78 (d, J = 1.2 Hz, 5-Me). Anal. calcd. for $C_{13}H_{16}N_2O_9S$ (0.40 H_2O): C, 40.71; H, 4.41; N, 7.30; S, 8.36. Found: C, 40.53; H, 4.15; N, 7.13; S, 8.23.

1-(2-Deoxy-3-O-mesyl-beta-D-arabino-hexofuranosyl)thymine (11). To a solution of 1-(5,6-O-carbonyl-2-deoxy-3-O-mesyl-beta-D-arabino-hexo-furanosyl)thymine (0.45 g, 1.2 mmol) in anhydrous methanol (40 mL) in a 100 mL round bottom flask under a nitrogen atmosphere was added rapidly a solution of commercial 95% sodium methoxide in anhydrous methanol (10 mL). The resulting solution was stirred overnight at room temperature before being adjusted with Dowex acidic resin (50X8-400) to pH 6-7. The reaction was filtered, the Dowex resin was washed with several portions of methanol, and the combined washings were concentrated in vacuo to a beige foam (0.42 g, 1.2 mmoL, 100%). ^{1}H nmr (d_6-DMSO): δ 11.35 (s, NH), 7.38 (q, J = 1.3 Hz, H6), 6.15 (dd, J = 8.6, 2.7 Hz, H1'), 5.21 (dd, J = 4.9, 2.9 Hz, H3'), 3.88 (dd, J = 9.0, 2.7 Hz, H4'), 3.72 (ddd, J = 9.4, 5.5, 2.4 Hz, H5'), 3.59 (dd, J = 11.4, 2.4 Hz, H6'), 3.38 (dd, J = 11.4, 5.4 Hz, H6"), 3.31 (s, 4'-mesyl Me), 2.86 (ddd, J = 15.9, 8.7, 5.2 Hz, H2'), 2.24 (dd, J = 15.9, 2.8 Hz, H2"), 1.76 (d, J = 1.2 Hz, 5-Me).

Anal. calcd. for $C_{12}H_{18}N_2O_8S$ (0.90 H_2O): C, 39.32; H, 5.44; N, 7.64. Found: C, 39,33; H, 5.32; N, 7.56.

1-(3-Azido-2,3-dideoxy-beta-D-ribo-hexofuranosyl)thymine (12). To a solution of 1-(2-deoxy-3-O-mesyl-beta-D-arabino-hexofuranosyl)thymine (8.80 g, 25.1 mmol) in anhydrous dimethylformamide (70 mL) in a 250 mL round bottom flask equipped with a condenser topped by a nitrogen inlet was added lithium azide (3.55 g, 72.5 mmol) portionwise. The reaction was heated at reflux for 20 h, cooled to room temperature, and concentrated in vacuo. The residue was purified on a flash chromatography column using chloroform : methanol (98:2 to 95:5) in increments of increasing polarity to provide the azide as a white powder (3.86 g, 13 mmol, 52%), m.p. 164-165 °C, lit. m.p. 164-165 °C[14], m.p. 163-165 °C[15]. ^{1}H nmr (d_6-DMSO): δ 11.31 (s, NH), 7.64 (q, J = 1.3 Hz, H6), 6.06 (dd, J = 7.3, 6.3 Hz, H1'), 5.32 (d, J = 5.5, 4.0 Hz, 5'-OH), 4.70 (dd, J = 5.5, 5.5 Hz, 6'-OH), 4.49 (ddd, J = 7.0, 3.5, 3.5 Hz, H3'), 3.84 (dd, J = 5.5, 4.0 Hz, H4'), 3.65 (dddd, J = 5.5, 5.5, 5.5, 5.5 Hz, H5'), 3.44 (dd, J = 11.1, 5.5 Hz, H6'), 3.40 (dd, J = 11.0, 5.3 Hz, H6"), 2.30 (ddd, J = 13.8, 7.1, 7.1 Hz, H2'), 2.19 (ddd, J = 13.8, 6.3, 3.8 Hz, H2"), 1.79 (d, J = 1.2 Hz, 5-Me). Anal. calcd. for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56. Found: C, 44.55; H, 5.10; N, 23.46. UV (10% EtOH/pH 7): 265 nm (10,300).

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