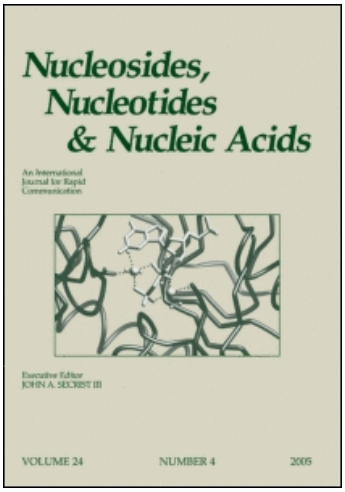

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John S. Cooperwood[a]; Vincent Boyd[a]; Giuseppe Gumina[a]; Chung K. Chu[a]
[a] Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, The University of Georgia, Athens, Georgia

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SYNTHESIS OF L-3'-HYDROXYMETHYLRIBONUCLEOSIDES

John S. Cooperwood, Vincent Boyd, Giuseppe Gumina and Chung K. Chu*

Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy,

The University of Georgia, Athens, Georgia 30602-2352

Dedicated to the memory of Gertrude B. Elion

Abstract: The target compounds were synthesized *via* the key intermediate carbohydrate **8**, which was synthesized by first selectively protecting the 1' - and 2'- hydroxyl groups followed by selective tosylation of the 5' -hydroxyl group to obtain compound **3**. The tosyl moiety was then replaced by a benzyl ether to obtain **4**. Compound **4** underwent Dess-Martin oxidation to afford the ketone **5**. Compound **5** was subjected to Wittig olefination to afford the alkene **6** followed by regioselective hydroboration to obtain **7**. Compound **7** was fully acetylated using acetic acid, acetic anhydride and sulfuric acid to obtain the key intermediate **8**.

INTRODUCTION

3'-Deoxy-3'-*C*-hydroxymethylribonucleosides are a known class of compounds originated with the synthesis of the D-adenosine analogue.[1] Following the discovery of

oxetanocins[1] and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG),[2] which are potent antiviral agents bearing a hydroxymethyl moiety in the 3' position or in an equivalent one, this class of compounds was revisited by Pudlo and Townsend[3] and Sterzychi *et.al.*[5] Pudlo and Townsend synthesized and evaluated the anti-HIV activity of the adenosine analogue, while Sterzychi *et al.* synthesized all of the natural bases analogues and evaluated their antiviral activity. Of this class of compounds, only 1-(3'-deoxy-3'-*C*-hydroxymethyl-1-β-D-ribofuranosyl)cytosine showed significant antiviral activity against HIV.

Since the report of the biological activity of 3TC,[6,7] L-nucleosides have received much interest. 3TC was found to have greater anti-HIV and anti-HBV activities than its D-counterpart. Interestingly, the L-isomer also exerts less cytotoxicity, which was the attractive feature as an antiviral agent for chronic diseases such as HIV and HBV infection. FTC, the 5-fluoro analogue of 3TC, was also found to have increased antiviral activity against HIV[8] and HBV[9] than its D-counterpart. Other L-nucleosides such as L-FddC[10], L-FMAU[11] and L-DAPD[12] have also shown more favorable antiviral activity profiles in comparison with their enantiomers. In view of these interesting biological features of L-nucleosides, we decided to synthesize the L-isomer of 3'-deoxy-3'-*C*-hydroxymethylribonucleosides in the hope to find compounds with enhanced antiviral activity in comparison with the D-isomers.

RESULTS AND DISCUSSION

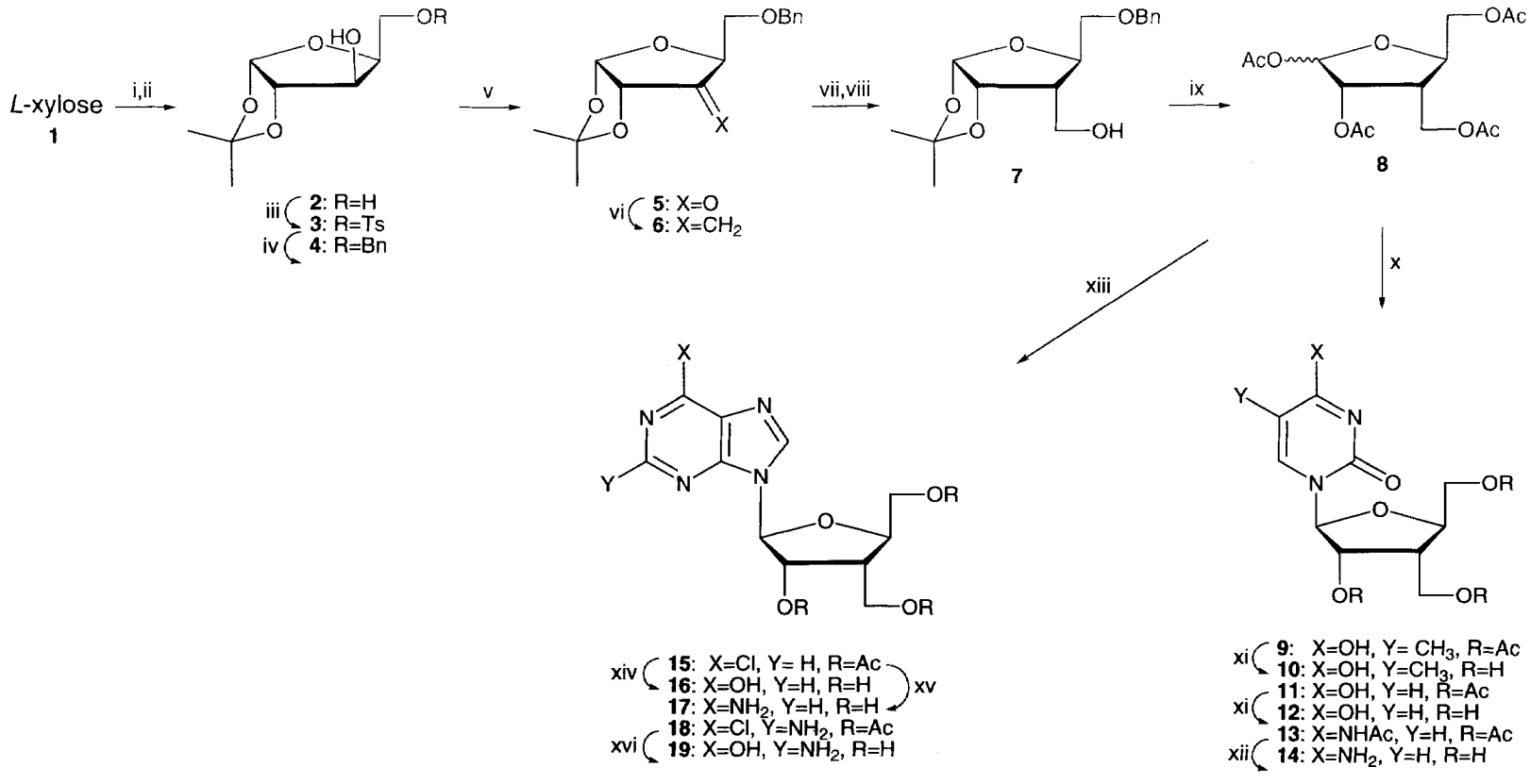
The key carbohydrate intermediate **8** was synthesized by a modification of the procedures used in the synthesis of the D- series by Sterzycki and co-workers. The

starting material, L-xylose was selectively protected to obtain 1,2-*O*-isopropylidene-L-xylofuranose **2** in 98% yield (Scheme). Since regioselective benzylation of the primary alcoholic functionality in **2** could not be achieved in satisfactory yield, the primary alcohol was selectively tosylated to afford **3** in 71% yield; this was treated with the sodium salt of benzyl alcohol at 100 °C to afford compound **4** in 85% yield. Oxidation of the benzyl ether **4** was carried out using the Dess-Martin procedure[13] to obtain the crude ketone **5**, which underwent Wittig olefination to obtain exo-olefin **6** in 71% yield. Hydroboration of **6** was carried out using BH_3-Me_2S/THF to obtain alcohol **7** in 79% yield, whose ^1H NMR and optical rotation data were consistent with those previously reported for the D-isomer.[14,15] NOE experiments confirmed the regioselectivity of the hydroboration reaction. Compound **7** was fully acetylated using AcOH, Ac_2O and a catalytic amount of H_2SO_4 to obtain key intermediate **8** in 82% yield (Scheme 1). Using Vorbrüggen-type glycosylation,[16] the anomeric mixture of **8** was condensed with various silylated bases using TMSOTf as catalyst to obtain exclusively the β anomer of the nucleosides. ^1H NMR spectrum displayed anomeric purity. The absence of any detectable amount of α anomer is due to the well-known neighboring group participatory effect of the 2'-acyl group.[17]

For the synthesis of pyrimidine nucleosides, compound **8** was condensed with silylated thymine and uracil to afford **9** and **11** in 80% and 86% yields, respectively. N^4-acetylcytosine was silylated and condensed with **8** to afford the N^4-acetylcytosine analogue **13** in 84% yield. Compounds **9**, **11** and **13** were deprotected in NH_3/MeOH to obtain thymine **10**, uracil **12** and cytosine **14** analogues in 53%, 49% and 45% yields, respectively.

Vorbrüggen conditions were also used in the synthesis of purine analogues. In the synthesis of the adenine analogue, 6-chloropurine was silylated and condensed with the

Scheme



i. acetone, H_2SO_4, $CuSO_4$, rt, 48 h. ii. 0.2% HCl/H_2O, rt 6 h. iii. TsCl, Py. rt, 17 h. iv. Na, BnOH, 100 °C. v. Dess-Martin periodinane, CH_2Cl_2, rt, 5 h. vi. methyltriphenylphosphonium bromide, phenyl lithium, THF, -78 °C - rt, 6 h. vii. BH_3-Me_2S, THF. viii. 30% H_2O_2, NaOH. ix. AcOH, AcO_2, H_2SO_4, rt. x. silylated uracil or thymine or N^4-acetylcytosine, TMSOTf, rt, 4h. xi. NH_3/MeOH, rt, 5 h. xii. NH_3/MeOH, rt, 5.5 h. xiii. silylated 6-chloropurine, TMSOTf, rt, 2h or silylated 2-amino-6-chloropurine, TMSOTf, rt, 3h. xiv. mercaptoethanol, NaOMe, MeOH, reflux, 7h. xv. conc. methanolic ammonia, 80 °C, 24h steel bomb. xvi. mercaptoethanol, NaOMe, MeOH, reflux, 16h.

key intermediate **8** to afford **15** in 57% yield. Intermediate **15** was treated with mercaptoethanol and sodium methoxide to obtain the inosine analogue **16** in 47% yield; the same intermediate, reacted with methanolic ammonia at 100 °C in a steel bomb, afforded adenine analogue **17** in 65% yield. 2-Amino-6-chloropurine was silylated and condensed with **8** to obtain **18** in 63% yield. Treatment of **18** with mercaptoethanol and sodium methoxide afforded the guanine analogue **19** in 45% yield.

The synthesized compounds were evaluated for anti-HIV-1 and anti-HBV activity in human peripheral blood mononuclear cells and 2.2.15 cells; no significant antiviral activity was detected up to 100 μM and 10 μM, respectively.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-temp II and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 AMX spectrometer for 400 MHz with Me_4Si as internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br s (broad singlet). Mass spectra were recorded on a Micromass Autospec high resolution mass spectrometer in fast atom bombardment (FAB) mode. Optical rotations were performed on a Jasco DIP-370 Digital Polarimeter. TLC were performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either silica gel 60 (220-440 mesh) for flash chromatography or silica gel G (TLC grade > 440 mesh) for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU-650 Spectraphotometer. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

1,2-*O*-(1-Methylethylidene)-L-xylofuranose (2). Concentrated H_2SO_4 (2.5 ml) and $CuSO_4$ (50 g, 313 mmol) were added to an ice-cooled suspension of L-xylose (25 g, 16.5 mmol) in acetone(700 ml), and stirred while allowing to warm to rt under a nitrogen atmosphere. After stirring for 36 h, the suspension was filtered and the solid was washed with acetone (100 ml). The filtrate was neutralized with 28% ammonium hydroxide (200 ml), filtered and the solid washed again with acetone (100 ml). The filtrate was concentrated *in vacuo* to dryness. A solution of 0.2% aqueous HCl (151 ml) was added to the residue and stirred until TLC indicated completion (*ca.* 6h). The mixture was concentrated *in vacuo* and purified by flash chromatography (gradient elution: 0-15% MeOH:$CHCl_3$) to afford 30.7 g (98%) of isopropylidene **2** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.97 (d, *J* = 3.7 Hz, 1H), 4.52 (d, *J* = 3.7 Hz, 1H), 4.30 (d, *J* = 2.7 Hz, 1H), 4.17 (m, 1H), 3.99 (m, 2H), 1.49 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 111.8, 104.8, 85.6, 79.1, 76.5, 60.8, 26.7, 26.2.

1,2-*O*-(1-Methylethylidene)-5-*O*-(*p*-toluenesulfonyl)-L-xylofuranose (3). To a solution of isopropylidene **2** (11.53 g, 61.1 mmol) in pyridine (50 ml) was added a solution of *p*-toluenesulphonyl chloride (11.85 g, 62.1 mmol) in chloroform (50 ml) and the mixture was maintained at rt under a nitrogen atmosphere overnight. After completion (indicated by TLC) the reaction was quenched with 15 ml of water and concentrated *in vacuo*. The resulting residue was redissolved in chloroform (300 ml), washed with water (2 x 100 ml), brine (50 ml), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-10% MeOH:$CHCl_3$,) to afford 15.7 g (71%) of tosylate **3** as a white solid: mp 135-136 °C; $[\alpha]^{25}_D$ 9.30° (*c* 1.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 5.87 (d, *J* = 3.6 Hz, 1H), 4.50 (d, *J* = 3.5 Hz, 1H), 4.4-4.2 (m, 3H), 4.14 (m, 1H), 2.80 (br s, 1H, D_2O exchangeable), 2.45 (s, 3H), 1.46 (s, 3H), 1.30 (s, 3H); ^{13}C NMR

($CDCl_3$) δ 149.4, 132.4, 130.0, 128.1, 112.1, 105.0, 85.1, 77.7, 74.3, 66.5, 26.8, 26.2, 21.7; FABMS *m/z* 345 $(M+H)^+$. Anal. Calcd for $C_{15}H_{21}O_7S_1$: C, 52.31; H, 5.85; S, 9.31. Found: C, 52.37; H, 5.87; S, 9.38.

1,2-*O*-(1-Methylethylidene)-5-*O*-benzyl-L-xylose (4). Sodium metal (4.6 g, 200.4 mmol) was added to benzyl alcohol (150 ml), heated to 100 °C and stirred until the metal was completely dissolved. Tosylate **3** (11.56 g, 33.4 mmol) was added to the solution and stirred for 17 h at 100 °C then cooled to rt. The reaction mixture was quenched with water (7.9 ml) and glacial acetic acid (9.7 ml) and stirred for 5 min. The mixture was diluted with diethyl ether (600 ml) and water (200 ml). The organic layer was washed with water (2 x 50 ml) and brine (70 ml), dried over magnesium sulfate and filtered. The volatile solvent was removed *in vacuo*, and the benzyl alcohol removed by vacuum distillation (76 °C, 0.5 mm of Hg). Azeotropic removal of trace amount of benzyl alcohol with water afforded a white solid. Recrystallization (1:2 EtOAc:Pentane) afforded 8.1 g (85%) of benzyl ether **4** as white needles: mp 61-62 °C; $[\alpha]^{25}_D$ -3.12° (*c* 0.59, $CHCl_3$); ^1H NMR (DMSO-d_6) δ 7.4-7.2 (m, 5H), 5.82 (d, *J* = 3.7 Hz, 1H), 5.25 (d, *J* = 5.0 Hz, 1H), 4.50 (s, 2H), 4.37 (d, *J* = 3.7 Hz, 1H), 4.13 (m, 1H), 3.97 (m, 1H), 3.67 (dd, *J* = 4.2, 10.4 Hz, 1H), 3.51 (dd, *J* = 7.0, 10.4 Hz, 1H), 1.37 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.1, 128.6, 128.1, 127.9, 111.6, 104.9, 85.4, 78.0, 76.6, 74.2, 68.3, 26.8, 26.2; FABMS *m/z* 281$(M+H)^+$. Anal. Calcd for $C_{15}H_{21}O_5$: C, 64.27; H, 7.19. Found: C, 64.37; H, 7.22.

1,2-*O*-(1-Methylethylidene)-5-*O*-benzyl-L-xylulose (5). To a solution of benzyl ether **4** (43 g, 154 mmol) in methylene chloride (700 ml) was added Dess-Martin periodinane (98 g, 231 mmol), and the mixture was stirred at rt until TLC (4:1 x 3 Hexane:EtOAc) indicated completion (*ca.* 3.5 h). The resulting suspension was filtered through a silica gel pad, and the solid washed with diethyl ether (350 ml). The filtrate

was washed with saturated aqueous sodium bicarbonate (250 ml), water (120 ml), brine (150 ml), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 42.5 g (99%) of crude ketone **5** as a yellow oil. A small amount was purified by silica gel chromatography (20% Hexanes:EtOAc) for characterization. The remaining crude was used in the following Wittig reaction: $[\alpha]^{27}_{D}$ -149.23° (*c* 1.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.4-7.2 (m, 5H), 6.13 (d, *J* = 4.4 Hz, 1H), 4.6-4.4 (m, 3H), 4.34 (d, *J* = 4.5 Hz 1H), 3.71 (m, 2H), 1.45 (s, 3H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 210.0, 137.4, 128.5,, 127.8, 127.5, 114.1, 103.5, 79.9, 76.8, 73.6, 70.0, 27.6, 27.1; FABMS *m/z* 279 [$(M+H)^+$, calcd for $C_{15}H_{19}O_5$: 279]. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.84; H, 6.58.

1,2-*O*-(1-Methylethylidene)-3-deoxy-3-methylene-5-*O*-benzyl-L-xylofuranose (6). To a suspension of methyltriphenylphosphonium bromide (111.5 g, 312.6 mmol) in THF (750 ml) was added 1.8 M solution of phenyl lithium in THF (163 ml) dropwise and the yellowish mixture was stirred for 1 h, then allowed to warm to rt. Upon recooling to -78 °C, the crude ketone **5** (25 g, 11.6 mmol) in THF (150 ml) was added by cannula over a 15 min period. The reaction was allowed to warm to rt and stirred for 1 h, then heated to 55 °C and stirred for an additional 2 h. Upon completion, as indicated by TLC, the resulting dark mixture was cooled to 0 °C and quenched with saturated ammonium chloride (75 ml). The aqueous phase was separated and extracted with EtOAc (3 x 150 ml), and the combined organic layers were washed in brine (40 ml), dried over magnesium sulfate and filtered. The crude product was concentrated *in vacuo* and purified by silica gel chromatography (gradient elution: 5% -10% Hexanes:EtOAc) to afford 24.8 g (71%) of alkene **6** as a colorless oil: $[\alpha]^{27}_{D}$ -119.60° (*c* 1.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.4-7.2 (m, 5H), 5.87 (d, *J* = 4.0 Hz, 1H), 5.41 (d, *J* = 1.1 Hz, 1H), 5.18 (d, *J* = 1.4 Hz, 1H), 4.89 (m, 2H), 4.58 (s, 2H), 3.67 (dd, *J* = 3.7, 10.4 Hz, 1H), 3.55 (dd,

J = 5.0, 10.4 Hz, 1H), 1.50 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 146.7, 137.9, 128.4, 127.6, 112.4, 111.8, 104.6, 81.8, 78.6. 73.4, 71.6, 27.4, 27.2; FABMS *m/z* 277 $(M+H)^+$. Anal. Calcd for $C_{16}H_{20}O_4 \cdot 0.25\ H_2O$: C, 68.43; H, 7.30. Found: C, 68.13; H, 7.53.

1,2-*O* -(1 -Methylethylidene)-3-deoxy-3-(hydroxymethyl)-5-*O* -benzyl-L-ribofuranose (7). To an ice-cooled solution of alkene **6** (2 g, 7.2 mmol) in THF (7.2 ml) was added a 2 M solution of BH_3-Me_2S in THF (8.0 ml, 15.92 mmol) and the solution was stirred while allowing to warm to rt. After 1 h, the reaction mixture was cooled to 0 °C, then diluted slowly with a 1:1 solution of THF:H_2O (7.2 ml). A 2 M solution of sodium hydroxide (22.4 ml), followed by a solution of 30% hydrogen peroxide (11.3 ml), were added to the cooled mixture and the reaction was stirred at rt until the TLC indicated completion (*ca.* 3 h). The volatiles were concentrated *in vacuo*, and the resulting residue was diluted with ethyl acetate (75 ml) and brine (75 ml). The aqueous phase was separated and extracted with ethyl acetate (3 x 100 ml) and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (gradient elution: 20-30% Hexanes:EtOAc) afforded 1.67 g (79%) of **7** as a white solid: mp 67-70 °C [lit. mp 67-70]; $[\alpha]^{25}_D$ -33.9° [lit. $[\alpha]^{25}_D$ +36°] (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H), 5.81 (d, J = 3.7 Hz, 1H), 4.72 (t, J = 4.4 Hz, 1H), 4.59 (q, J = 12.0 Hz, 2H), 4.17 (m, 1H), 3.79 (m, 2H), 3.64 (m, 2H), 3.10 (br s, 1H, D_2O), 2.16 (m, 1H), 1.50 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.9, 129.3, 128.9, 128.32, 112.4, 105.3, 82.3, 79.1, 74.1, 70.5, 59.5, 48.9, 27.0, 26.6; FABMS *m/z* 237 $[(M+H-(CH_3)_2CO)^+]$. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.12; H, 7.45.

3-Deoxy-1,2,5-tri-*O*-acetyl-3-[(*O*-acetyl)-methyl]-L-ribofuranose (8). To a stirring solution of alcohol **7** (7.62 g, 25.8 mmol) in acetic acid (100 ml) was added acetic anhydride (15 ml) and H_2SO_4 (4 ml) dropwise at 0 °C. The ice-cooled solution was

stirred and allowed to warm to rt. Upon completion (*ca.* 24 h, as indicated by TLC) the reaction mixture was neutralized with saturated sodium bicarbonate solution and extracted with EtOAc (3 x 300 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography (elution gradient: 20-30% EtOAc:Hexanes) of the crude afforded 8.1 g (94%) of **8** as a yellow syrup: ^{1}H NMR ($CDCl_3$) δ 6.11 (s, 1H), 5.30 (d, J = 4.8 Hz, 1H), 4.34-4.21 (m, 2H), 4.15-4.05 (m, 2H), 2.74 (m, 1H) 2.12 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.7, 138.3, 128.6, 128.5, 99.4, 82.6, 73.5, 73.3, 72.1, 66.3, 42.1, 21.5, 21.1; FABMS *m/z* 273 [(M +H -AcOH)$^+$, Anal. calcd for $C_{12}H_{16}O_7 \cdot 0.3$ EtOAc: C, 50.89; H, 6.36. Found: C, 51.12; H, 6.04.

General procedure for the condensation of key intermediate (8) with the corresponding silylated bases.

A suspension of anhydrous base (1.5 equiv.), anhydrous ammonium sulfate (0.03 equiv.) and hexamethyldisilazane (70 equiv.) was refluxed under a dry nitrogen atmosphere for 1 h. After cooling to rt, the solution was concentrated *in vacuo*, then placed under a dry nitrogen atmosphere. A solution of acetate **8** in dichloroethane was added by cannula to the silylated base, and the resulting suspension was stirred and cooled to -20 °C. Trimethylsilytriflate (0.3 equiv.) was added dropwise, and the mixture was maintained at -20 °C for 15 min then allowed to warm to rt. After 4 h, the homogeneous mixture was poured onto a mixture of cold EtOAc (25 ml) and saturated sodium bicarbonate solution (15 ml) and stirred for 10 min. The aqueous phase was separated and extracted with EtOAc (3 x 50 ml). The organic layers were combined, washed with brine (2 x 25 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was then purified by silica gel chromatography.

1-{3-Deoxy-1, 2, 5-tri-*O*-acetyl-3-[(*O*-acetyl)-methyl]-β-L-ribofuranosyl}thymine (9). Using the general procedure for the condensation of the key intermediate with silylated base, the fully protected thymine analogue **9** was synthesized and purified by silica gel chromatography (0-3% MeOH:EtOAc) in 80% yield as a colorless syrup: $[\alpha]^{27}_D$ -10.1°(*c* 2.0, $CHCl_3$); UV ($CHCl_3$) λ_{max} 264 nm; ^{1}H NMR ($CDCl_3$) δ 8.31 (br s, 1H), 7.20 (s, 1H), 5.71 (d, *J* = 2.5 Hz, 1H), 5.50 (dd, *J* = 2.5, 2.5 Hz, 1H), 4.4-4.2 (m, 4H), 4.1 (m, 1H), 2.8 (m, 1H), 2.16 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.8 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.7, 170.1, 150.1, 136.3, 111.5, 91.7, 80.7, 76.8, 64.3, 60.2, 41.0, 21.2, 21.1, 21.0, 13.0. FABMS*m/z* 399 $(M+H)^+$. Anal. calcd for $C_{17}H_{22}O_9N_2$·0.35 EtOAc: C, 51.49; H, 5.78; N, 6.53. Found: C, 51.85; H, 5.66; N, 6.89.

1-[3-Deoxy-3-(hydroxymethyl)-β-L-ribofuranosyl]thymine (10). Compound **9** (120 mg, 0.3 mmol) was dissolved in methanolic ammonia and stirred at rt. After 5 h, the reaction mixture was concentrated *in vacuo*, and the residue was recrystallized in MeOH/H_2O to obtain 43 mg (53%) of **10** as a white solid: mp 186 °C; $[\alpha]^{25}_D$ -23.55 °(*c* 0.5, H_2O); UV (H_2O) λ_{max} 269 (log ε 3.66, pH = 2), 267 (log ε 3.64, pH = 7), 266 (log ε 3.58, pH = 11); ^{1}H NMR (DMSO-d_6) δ 11.26 (s, 1H), 7.98 (s, 1H), 5.64 (d, *J* = 2.5 Hz, 1H), 5.55 (d, *J* = 4.8 Hz, 1H), 5.15 (t, *J* = 4.88 Hz, 1H), 4.50 (t, *J* = 4.9 Hz, 1H), 4.14 (m, 1H), 3.94 (d, *J* = 8.9 Hz, 1H), 3.77 (m, 1H), 3.6 (m, 2H), 3.4 (m, 1H), 2.21 (m, 1H), 1.7 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 164.3, 150.8, 136.8, 108.8, 90.7, 83.2, 75.4, 61.5, 57.6, 43.6, 12.6. FABMS*m/z* 273 $(M+H)^+$. Anal. calcd for $C_{11}H_{16}O_6N_2$: C, 48.52; H, 5.88; N, 10.29. Found: C, 48.48; H, 5.86; N, 10.28.

1-{3-Deoxy-1,2,5-tri-*O*-acetyl-3-[(*O*-acetyl)-methyl]-β-L-ribofuranosyl}uracil (11). Using the general procedure for the condensation of the key intermediate with silylated base, the fully protected uracil analogue **11** was synthesized and purified by

silica gel chromatography (0-3% MeOH:EtOAc) in 86% yield as a clear syrup: $[\alpha]^{26}_{D}$ -30.29° (*c* 2.0, $CHCl_3$); UV ($CHCl_3$) λ_{max} 266 nm; ^{1}H NMR ($CDCl_3$) δ 8.48 (br s, 1H), 7.47 (d, *J* = 8 Hz, 1H), 5.74 (d, *J* = 8 Hz, 1H) 5.69 (d, *J* = 2.2 Hz, 1H), 5.50 (dd, *J* = 2.5, 2.5 Hz, 1H), 4.5-4.3 (m, 4H), 4.08 (m, 1H), 2.79 (m, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.7, 170.1, 149.9, 140.4, 102.9, 92.1, 81.0, 64.1, 60.1, 41.0, 21.2, 21.1, 21.0. FABMS *m/z* 385 $(M+H)^+$. Anal. calcd for $C_{16}H_{20}O_9N_2 \cdot 0.2\ H_2O$: C, 49.42; H, 5.28; N, 7.20. Found: C, 49.47; H, 5.36; N, 6.93.

1-[3-Deoxy-3-(hydroxymethyl)-β-L-ribofuranosyl]uracil (12). Compound **11** (150 mg, 0.39 mmol) was dissolved in methanolic ammonia and stirred at rt. After 5 h, the reaction mixture was concentrated *in vacuo*, and the residue recrystallized from MeOH/H_2O to obtain 49 mg (49%) of **12** as a white solid: mp 200 °C; $[\alpha]^{25}_{D}$ -54.93 °(*c* 0.53, H_2O); UV (H_2O) λ_{max} 263 (log ε 3.72, pH = 2), 263 (log ε 3.67, pH = 7), 263 (log ε 3.49, pH = 11); ^{1}H NMR (DMSO-d_6) δ 11.29 (s, 1H), 8.09 (d, *J* = 8 Hz, 1H), 5.65 (d, *J* = 1.7 Hz, 1H), 5.57 (m, 2H), 5.14 (br s, 1H), 4.54 (br s, 1H), 3.97 (m, 1H), 3.78 (d, *J* = 12 Hz, 1H), 3.6 (m, 1H), 3.56 (d, *J* = 12 Hz, 1H), 3.4 (m, 1H), 2.5 (m, 1H), 2.1 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 164.4, 150.7, 141.2, 101.0, 91.1, 83.2, 75.4, 61.3, 57.3, 43.4. FABMS *m/z* 259 $(M+H)^+$. Anal. calcd for $C_{10}H_{14}O_6N_2$: C, 46.51; H, 5.42; N, 10.85. Found: C, 46.45; H, 5.44; N, 10.81.

1-{3-Deoxy-1, 2, 5-tri-*O*-acetyl-3-[(*O*-acetyl)-methyl]-β-L-ribofuranosyl}-N^4-acetylcytosine (13). Using the general procedure for the condensation of the key intermediate with silylated base, the fully protected N^4-cytosine analogue**13** was synthesized and purified by silica gel chromatography (0-5% MeOH:EtOAc) in 84% yield as a yellow syrup: $[\alpha]^{26}_{D}$ -25.91° (*c* 0.53, $CHCl_3$); UV ($CHCl_3$) λ_{max} 248 and 288 nm; ^{1}H NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.02 (d, *J* = 7.5 Hz, 1H) 7.43 (d, J = 7.5 Hz, 1H), 5.81 (s,

1H) 5.65 (d, J = 5.2 Hz, 1H), 5.50 (dd, J = 2.5, 2.5 Hz, 1H), 4.5-4.3 (m, 4H), 4.02 (m, 1H), 2.70 (m, 1H), 2.25 (s, 3H), 2.14 (br s, 6H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.6, 169.5, 163.0, 144.7, 96.7, 92.8, 81.7, 63.7, 59.9, 40.6, 25.3, 21.2, 21.1. FABMS*m/z* 426 $(M+H)^+$. Anal. calcd for $C_{18}H_{23}O_9N_3$ 0.2 MeOH: C, 50.34; H, 5.66; N, 9.52. Found: C, 50.12; H, 5.52; N, 9.32.

1-[3-Deoxy-3-(hydroxymethyl)-β-L-ribofuranosyl]cytosine (14).

Compound **13** (130 mg, 0.31 mmol) was dissolved in methanolic ammonia and stirred. After 6 h, the reaction mixture was concentrated *in vacuo*, and the residue was recrystallized in MeOH/H_2O to obtain 35 mg (45%) of **14** as a white solid: mp 226 °C; $[\alpha]^{25}_D$ -199.99 °(*c* 0.51, H_2O); UV (H_2O) λ_{max} 263 (log ε 3.77, pH = 2), 263 (log ε 3.60, pH = 7), 263 (log ε 3.56, pH = 11); ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 7.2 Hz, 1H), 7.10 (br s,1H), 7.00 (br s, 1H), 5.66 (d, J = 7.4 Hz, 1H), 5.61 (s, 1H), 5.53 (d, J = 4.8 Hz, 1H), 5.07 (t, J = 5.16 Hz, 1H), 4.47 (t, J = 5.04, 1H), 4.08 (m, 1H), 3.79 (m, 1H), 3.9 (m, 1H), 3.6 (m, 2H), 3.4 (m, 1H), 2.1 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 164.2, 154.1, 139.7, 91.7, 90.4, 81.6, 74.2, 59.5, 55.5, 41.7. FABMS*m/z* 258 $(M+H)^+$. Anal. calcd for $C_{10}H_{15}O_5N_3$: C, 46.69; H, 5.83; N, 16.34. Found: C, 46.40; H, 6.02; N, 16.05.

6-Chloro-9-{3-deoxy-1,2,5-tri-*O*-acetyl-3-[(*O*-acetyl)-methyl]-β-L-ribofuranosyl}-9*H*-purine (15). Using the general procedure for the condensation of the key intermediate with silylated base, the fully protected 6-chloro purine analogue **15** was synthesized and purified by silica gel chromatography (0-5% MeOH:EtOAc) in 57% yield as a cloudy syrup: $[\alpha]^{26}_D$ 3.87°(*c* 0.8, $CHCl_3$); UV ($CHCl_3$) λ_{max} 264 nm; ^{1}H NMR ($CDCl_3$) δ 8.78 (s, 1H), 8.35 (s, 1H) 6.10 (d, J = 1.28 Hz, 1H), 5.87 (dd, J = 1.2, 1.2 Hz, 1H) 4.43 (m, 4H) 4.19 (m, 1H), 3.29 (m, 1H), 2.19 s, 3H), 2.08 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 170.3,169.7., 152.1, 151.4, 150.7, 143.8, 132.3, 89.9, 81.3, 63.6,

59.6, 40.7, 20.7, 20.65, 20.60. FABMS*m/z* 427 $(M+H)^+$. Anal. calcd for $C_{17}H_{19}O_7N_4Cl$: C, 47.89; H, 4.46; N, 13.14. Found: C, 48.06; H, 4.71; N, 12.87.

9-[3-Deoxy-3-(hydroxymethyl)-β-L-ribofuranosyl]hypoxanthine (16). A mixture of 6-chloropurine **15** (250 mg, 0.58 mmol), sodium methoxide (5 mg, 0.037 mmol), mercaptoethanol (165 ml, 2.29 mmol) and methanol (30 ml) was refluxed under a nitrogen atmosphere for 4 h. After cooling to 0 °C, the solution was acidified with acetic acid (5 ml), diluted with water (50 ml), and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (30 ml), saturated sodium bicarbonate (40 ml), brine (15 ml) then dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by preparative TLC (20% MeOH:$CHCl_3$) to obtain 77 mg (47%) of **16** as a white solid: mp >200 °C dec; $[\alpha]^{27}_D$ 26.62° (*c* 0.62, MeOH); UV (H_2O) λ_{max} 249 (log ε 5.58, pH = 2), 249 (log ε 5.49, pH = 7), 253 (log ε 5.58, pH = 11); ^{1}H NMR (DMSO-d_6) δ 12.43 (br s, 1H), 8.40 (s, 1H), 8.06 (s, 1H), 5.89 (s, 1H), 5.81 (br s, 1H) 5.15 (br s, 1H) 4.66 (br s, 1H), 4.47 (d, J = 4.7 Hz, 1H), 4.04 (m, 1H), 3.8-3.6 (m, 2H), 3.6-3.4 (m, 2H), 2.4 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 157.0, 147.9, 146.1, 138.2, 124.7, 90.7, 83.6, 75.9, 62.1, 57.6, 44.3. FABMS*m/z* 283 $(M+H)^+$. Anal. calcd for $C_{11}H_{15}O_5N_4$.: C, 46.07; H, 5.10; N, 19.54. Found: C, 46.16; H, 4.95; N, 19.33.

9-[3-Deoxy-3-(hydroxymethyl)-β-L-ribofuranosyl]adenine (17). 6-Chloropurine derivative **15** (280 mg, 0.65 mmol) was heated at 80 °C in a bomb under pressure in the presence of concd. methanolic ammonia (15 ml) for 24 h. Upon cooling to rt, the volatiles were removed *in vacuo* and the resulting white solid purified by preparative TLC (20% MeOH:$CHCl_3$) to 120 mg (65%) of **17** as a white solid: mp 216 °C [lit. mp 213-214 °C]; $[\alpha]^{27}_D$ -25.77° (*c* 0.58, DMSO) [lit. $[\alpha]^{22}_D$ 26 (*c* 1, H_2O)]; UV (H_2O) λ_{max} 258 (log ε 3.81, pH = 2), 260 (log ε 3.89, pH = 7), 260 (log ε 3.83, pH = 11); ^{1}H

NMR (DMSO-d_6) δ 8.42 (s, 1H), 8.15 (s, 1H), 7.31 (s, 2H), 5.91 (d, *J* = 2.4 Hz, 1H), 5.73 (d, *J* = 5.0 Hz, 1H) 5.26 (t, *J* = 5.5 Hz, 1H) 4.61 (t, *J* = 5.2 Hz, 1H), 4.56 (m, 1H), 4.07 (m, 1H), 3.8-3.6 (m, 2H), 3.6-3.5 (m, 2H), 2.4 (m, 1H); ^{13}C NMR (DMSO- d_6) δ 156.3, 152.8, 149.0, 139.6, 119.4, 90.7, 83.5, 75.5, 62.4, 57.7, 44.5. FABMS *m/z* 283 $(M+H)^+$. Anal. calcd for $C_{11}H_{15}O_4N_5$ 0.437: C, 45.69; H, 5.53; N, 24.22. Found: C, 45.58; H, 5.18; N, 23.96.

2-Amino-6-chloro-9-{3-deoxy-1,2,5-tri-*O*-acetyl-3-[(*O*-acetyl)-methyl]-β-L-ribofuranosyl}-9*H*-purine (18). Using the general procedure for the condensation of the key intermediate with silylated base, the fully protected 2-amino-6-chloro purine analogue **18** was synthesized and purified by silica gel chromatography (0-5% MeOH:EtOAc) in 63% yield as a clear syrup: $[\alpha]^{24}_D$ -7.78° (*c* 0.5, $CHCl_3$); UV ($CHCl_3$) λ_{max} 309 nm; ^{1}H NMR ($CHCl_3$) δ 7.9 (s, 1H), 5.9 (s, 1H) 5.86 (d, *J* = 5.96 Hz, 1H), 5.2 (br s, 1 H) 4.5 (dd, *J* = 2.5, 2.2 Hz, 1H), 4.3 (m, 4H), 4.1 (m, 2H), 3.6 (br s, 1H) 3.3 (m, 1H), 2.17 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.5, 170.4, 170.1., 160.2, 153.7, 150.1, 141.8, 123.8, 88.1, 80.4, 76.8, 64.2, 60.1, 40.9, 20.9, 20.8, 20.7. FABMS*m/z* 443 $(M+H)^+$. Anal. calcd for $C_{17}H_{21}O_7N_5Cl \cdot 0.9$ EtOAc: C, 47.48; H, 5.26; N, 13.44. Found: C, 47.22; H, 5.15; N, 13.42.

9-[3-Deoxy-3-(hydroxymethyl)-β-L-ribofuranosyl]guanine (19). A mixture of 2-amino-6-chloropurine **18** (331 mg, 0.75 mmol), sodium methoxide (5 mg, 0.09 mmol), mercaptoethanol (165 ml, 2.29 mmol) and methanol (30 ml) was refluxed under a nitrogen atmosphere for 6 h. After cooling to 0 °C, the solution was acidified with acetic acid (5 ml), diluted with water (50 ml) and extracted with EtOAc (3 x 100 ml). The combined organic layers were washed with water (30 ml), saturated sodium bicarbonate (40 ml), brine (15 ml), then dried over magnesium sulfate, filtered and concentrated *in*

vacuo. The residue was purified by reverse phase high performance liquid chromatography (HPLC) (5% MeOH:H_2O) to obtain 100 mg (45%) of **19** as a white solid: mp >200 °C dec; $[\alpha]^{27}_D$ 26.21° (*c* 0.62, MeOH); UV (H_2O) λ_{max} 255 (log ε 3.75, pH = 2), 253 (log ε 3.78, pH = 7), 269 (log ε 3.23, pH = 11); ^{1}H NMR (DMSO-d_6) δ 10.48 (s, 1H), 7.8 (s, 1H) 6.34 (br s, 1H), 5.59 (d, *J* = 2.3 Hz, 1H), 5.46 (d, J = 5.2 Hz, 1H) 4.9 (t, *J* = 5.4 Hz, 1H), 4.4 (t, *J* = 5 Hz, 1H), 4.2 (br s, 1H), 3.8 (m, 1H), 3.5 (m, 2H), 3.4 (m, 2H), 2.3 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 153.7, 151.1, 135.6., 116.9, 89.5, 83.1, 75.5, 62.3, 57.7, 44.5. FABMS*m/z* 298 $(M+H)^+$. Anal. calcd for $C_{11}H_{15}O_5N_5 \cdot 0.5\ H_2O$: C, 43.23; H, 5.27; N, 22.87. Found: C, 43.23; H, 5.26; N, 22.78.

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