2-Deoxy-3-C-(hydroxymethyl)-D-pentofuranose Derivatives: Stereoselective Synthesis and Conversion into a Novel Class of Nucleoside Analogues

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Oxidation of pure anomers of 5-*O*-monoprotected methyl 2-deoxy-D-ribofuranosides **3**–**6** followed by Lombardo methylenation afforded the novel 3-*C*-methylene pentofuranosides **11**–**14**. Subsequent osmium tetraoxide-catalyzed dihydroxylations of **11**, **13**, and **14** afforded a mixture of *erythro*- and *threo*-configured 3-*C*-hydroxymethyl furanosides **15/16**, **18/19**, and **20/21**, respectively. However, analogous dihydroxylation of 5-*O*-(4-phenylbenzoyl)-protected β-anomer **12** proceeded with complete stereoselectivity to give 3-*C*-(hydroxymethyl)-β-D-*erythro* pentofuranoside **17** in 76% yield. Conversion of **17** to the corresponding primary tosylate **22**, followed by base-catalyzed nucleophilic attack by the nucleobases adenine and thymine, afforded after deprotection compounds **25** and **26**, respectively, as the first examples of a novel class of nucleoside analogues.

In the last decade, much research has been aimed at blocking uncontrolled cell proliferation or the replicative cycle of viruses by chemotherapy.[1-5] Although a large number of deoxynucleosides have been prepared and biologically evaluated in this context,[3-5] the discovery of more effective and selective analogues is of immense importance. Recently, there has been a growing interest in regioisomeric nucleoside analogues ("isonucleosides") as potential antiviral agents,[6] and structural examples are depicted in Figure 1 (structures **A**–**D**).

In this note, 2′-deoxynucleoside analogues **25** and **26** are reported as the first examples of a novel class of nucleoside analogues containing a one-atom linker between 3′-*C* of the pentofuranose ring and the nucleobase. The key synthon 3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranoside **17** was obtained from 2-deoxy-D-ribose in only five steps including a stereoselective dihydroxylation of 3-*C*-methylene pentofuranoside **12**. Additionally, **17** should be useful as a glycosyl donor in Vorbrüggen couplings[7] to give 3′-*C*-hydroxymethyl 2′-deoxynucleoside analogues containing different nucleobases. The interest in this class of nucleosides was recently stimulated by results showing that duplexes involving oligodeoxynucleotide analogues containing 3′-*C*-(hydroxymethyl)thymidine (**1**) (Figure 1) exhibit excellent thermal stabilities.[8]

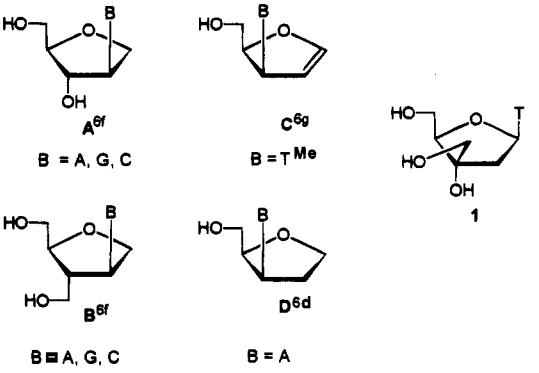

Figure 1. Structure of 3′-*C*-(hydroxymethyl)thymidine (**1**) and representative isonucleosides with the nucleobase attached to C-2′ (**A** and **B**) and C-3′ (**C** and **D**) of the sugar moiety.

Conversion of 2-deoxy-D-ribose to an anomeric mixture of methyl 2-deoxy-D-*erythro*-pentofuranosides **2** (Scheme 1) was obtained by acid-catalyzed glycoside formation under kinetic control as previously described.[9] Reaction of **2** with 1.1 mol equiv of 4-phenylbenzoyl chloride in anhydrous pyridine gave a mixture of the two 5-*O*-monoprotected anomers **3** and **4** as earlier reported.[9] However, we were able to isolate the pure β-anomer **4** in 24% yield by crystallization from petroleum ether followed by recrystallization from toluene. The yield of the β-anomer can be improved, as anomerization of the remaining mixture, mainly containing the α-anomer **3**, was performed by use of 0.05% HCl in MeOH.[10] Column chromatographic purification of the anomeric mixture remaining after β-crystallization afforded the α-anomer **4** in 35% yield together with additional β-anomer **4** in 3% yield. Reaction of **2** with 1.0 mol equiv of *tert*-butyldiphenylchlorosilane and imidazole in DMF[11] gave pure 5-*O*-silylated α-anomer **5** in 32% yield and the corresponding β-anomer **6** in 26% yield after column chromatographic purification. Assignment of anomeric configuration were for all four compounds **3**–**6** done by ^{1}H–^{1}H COSY and ^{1}H NOE experiments. Especially important were the mutual key NOE contacts between

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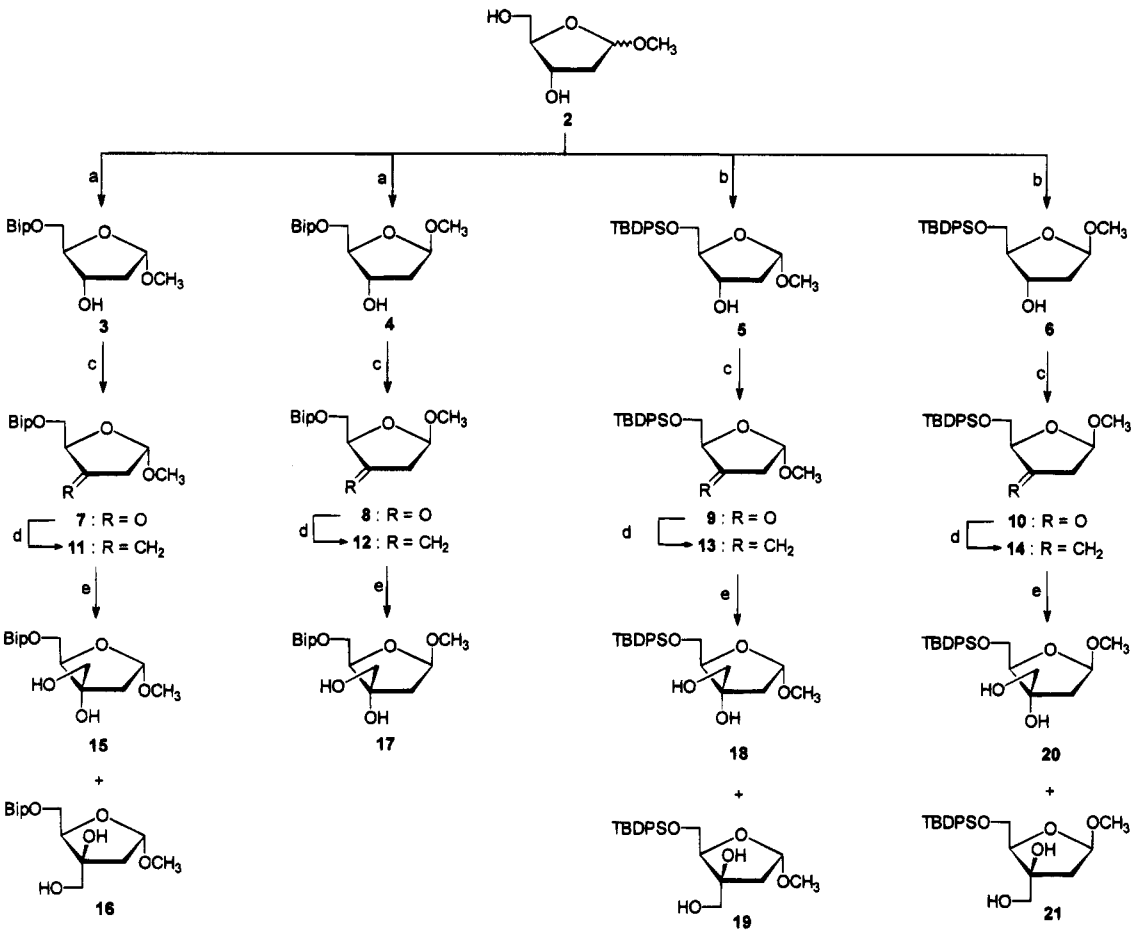
Scheme 1[a]



[a] (a) 4-Phenylbenzoyl chloride (BipCl), pyridine; (b) *tert*-butyldiphenylchlorosilane (TBDPSCl), imidazole, DMF; (c) CrO_3, pyridine, acetic anhydride, CH_2Cl_2; (d) Zn, CH_2Br_2, $TiCl_4$, THF, CH_2Cl_2; (e) OsO4, *N*-methylmorpholine *N*-oxide, pyridine, H_2O, *tert*-butanol.

H-1 and H-4 which were observed for the β-anomers but not for the α-anomers. Oxidation of **3-6** with chromium trioxide/pyridine/acetic anhydride reagent[12,13] gave the corresponding 3-uloses **7-10** which were used in the next step without purification. Wittig methylenation[14] was attempted for the 5-*O*-silyl protected compounds **9** and **10**, but analytical TLC indicated formation of several products (not identified) and incomplete conversion of the starting ketones. Consequently, only minor amounts of the expected 3′-*C*-methylene products were isolated. Therefore, we used the electrophilic organometallic reagent consisting of $Zn/CH_2Br_2/TiCl_4$ in THF[15,16] ("Lombardo methylenation"), and 3-*C*-methylene products **11**–**14** were obtained in 58–71% yield. Compared to the published procedure for synthesis of ethyl 2,3-dideoxy-3-*C*-methylene-D-*glycero*-pentofuranoside in six steps from 3-methyl-2-butenal,[17] we have accomplished an only four-step synthesis of analogous 5-*O*-protected methyl 2,3-dideoxy-3-*C*-methylene-D-*glycero*-pentofuranosides **11**-**14** from 2-deoxy-D-ribose.

To synthesize 3-*C*-hydroxymethyl pentofuranoside derivatives, we used catalytic amounts of osmium tetraoxide[18,19] in basic aqueous *tert*-butyl alcohol using *N*-methylmorpholine *N*-oxide as cooxidant. *N*-Methylmorpholine *N*-oxide is a preferable cooxidant compared to a variety of other known cooxidants,[18-21] because it retards overoxidation. When 5-*O*-(4-phenylbenzoyl)-protected β-D-pentofuranoside **12** was used as substrate, the desired β-D-*erythro* isomer **17** was isolated in 76% yield after column chromatographic purification. As no other product (except unreacted starting material **12**) was isolated or detected (analytical TLC), the dihydroxylation of **12** proceeded with complete stereoselectivity. When the same reaction was done on the corresponding α-anomer **11**, both the *erythro* isomer (**15**, 18% yield) and the *threo* isomer (**16**, 47% yield) were obtained after column chromatographic purification. Thus, the effect of the configuration around the anomeric center on the stereochemical outcome of the dihydroxylations is pronounced. The positioning of both the 5-*O*-acyl protective group and the glycosidic bond at the β-face of the pentofuranose ring directs the dihydroxylation to proceed exclusively from the less sterically hindered α-face. Dihydroxylation of methyl 5-*O*-*tert*-butyldiphenylsilyl-protected pentofuranoside **14** afforded after column chromatographic purification 5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranoside **20** in 22% yield plus a large fraction consisting of a mixture (7:1) of the

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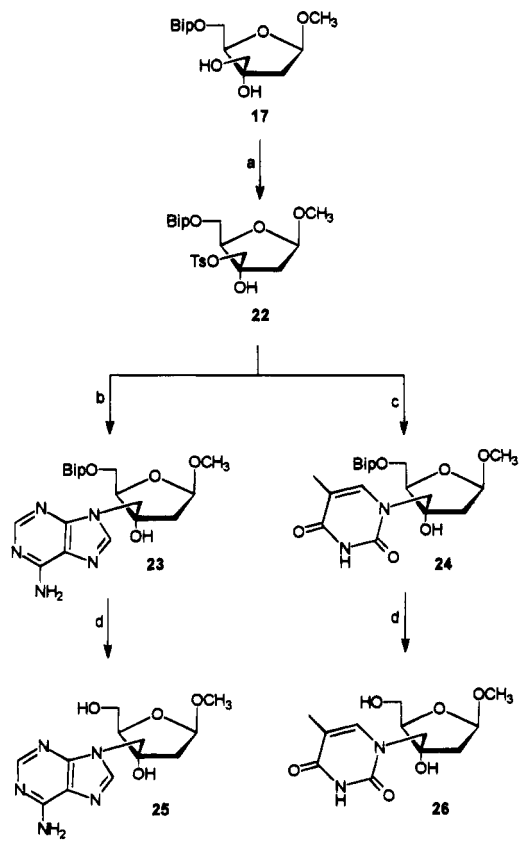
Scheme 2[a]



[a] (a) *p*-Toluenesulfonyl chloride, pyridine; (b) adenine, K_2CO_3, 18-crown-6, DMF; (c) Na-salt of thymine, K_2CO_3, 18-crown-6, DMF; (d) NH_3 in MeOH.

erythro and *threo* isomers (**20** and **21**, respectively) in 56% yield. $^1H-^1H$ COSY and ^1H NOE difference experiments confirmed **15**, **17**, and **20** as being *erythro* isomers. Thus, *e.g.* mutual NOE contact between 3-*C*-CH_2 and H-5 were observed. Analogously, mutual NOE contacts between H-2α, 3-*C*-CH_2, and H-4 confirmed the *threo*-configuration of compound **16**. Using the same dihydroxylation procedure, the α-anomer **13** afforded **18** and **19** as an inseperable mixture (approximately 1:1) in a total yield of 83%. From these results (Scheme 1) it is clear, due to the advantageous crystallization of the β-anomer **4** and subsequent stereoselective dihydroxylation of 3-*C*-methylene derivative **12**, that the synthetic route **2** → **4** → **8** → **12** → **17** represents an attractive strategy for preparation of β-D-erythro configurated 3-*C*-hydroxymethyl 2-deoxyfuranose derivatives.

As the first step in syntheses of the novel nucleoside analogues **25** and **26** (Scheme 2), furanoside **17** was reacted with *p*-toluenesulfonyl chloride in pyridine at room temperature to afford **22** in 86% yield after column chromatography. The tosylated compound **22** was subsequently reacted with either adenine or the sodium salt of thymine,[22] potassium carbonate, and 18-crown-6 in anhydrous DMF at 65 °C. In both cases, complete conversion of the starting material to a less polar product was observed by analytical TLC after 1 h reaction. Isolation of this product failed, but NMR and EI-MS of the crude material indicated it to be a 3(*R*)-spiro-epoxide. Accordingly, when the reaction mixture was heated at 95 °C, formation of the expected nucleobase-alkylated products commenced, and after 48 h the reactions were completed. In the case of thymine, we observed ~20% of the *N*-1,*N*-3 dialkylated compound but no *N*-3 monoalkylated product. The reaction with adenine afforded exclusively the desired *N*-9 alkylated product. Isolation of the 5′-*O*-protected nucleoside analogues by use of column chromatography afforded adenine derivative **23** in 65% yield and thymine derivative **24** in 42% yield. The structural assignment of the adenine nucleoside **23** was done by comparison with structurally related compounds,[6c] whereas the *N*-1 alkylated structure of the thymine nucleoside **24** was confirmed by $^1H-^1H$ COSY and ^1H NOE experiments (*e.g.* mutual NOE effects between H-6 and 3′-*C*-CH_2/H-2′β). Deprotection using ammonia in methanol gave after column chromatographic purification the novel nucleoside analogues **25** and **26** in 65% and 94% yield, respectively. Thus, this methodology offers easy access to this novel class of nucleoside analogues that, besides their potential as possible biologically active compounds, are interesting as possible monomeric substitutes in modified oligonucleotide analogues. In addition, other nucleophiles than nucleobases could be used in syntheses of a large variety of hitherto unknown carbohydrate derivatives.

In summary, an effective and stereoselective synthetic route from 2-deoxy-D-ribose to the corresponding methyl 2-deoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranoside **17** in only five steps has been developed. A new class of nucleoside analogues has been introduced by use of furanoside **17** and tosylate **22** as key synthetic intermediates.

Experimental Section

General. NMR spectra were recorded at 250 and 500 MHz for ^1H NMR and 62.9 and 125 MHz for ^{13}C NMR. ^1H NMR chemical shifts are in ppm relative to tetramethylsilane as internal standard. ^1H NMR peak assignments for compounds **11**, **12**, **15**–**17**, **20**, and **22**–**26** were derived from $^1H-^1H$ COSY and NOE (compounds **15**–**17**, **20**, **24**, and **25**) NMR experiments. ^{13}C NMR peak assignment for compound **17** were derived from INEPT and $^1H-^{13}C$ COSY experiments. Microanalyses were performed at Department of Chemistry, University of Copenhagen. The silica gel used for column chromatography (0.040–0.063 mm) was purchased from Merck.

Methyl 2-Deoxy-5-*O*-(4-phenylbenzoyl)-α-D-*erythro*-pentofuranoside (3)[9] and Methyl 2-Deoxy-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside (4).[9] 4-Phenylbenzoyl chloride (16.09 g, 0.075 mol) was added in small portions to a stirred solution of methyl 2-deoxy-D-*erythro*-pentofuranoside (**2**)[9] (10.08 g, 0.068 mol) in anhydrous pyridine (125 mL) at −20 °C. The mixture was allowed to warm to 0 °C and stirring was continued for 4 h. The reaction mixture was poured into crushed ice and extracted with CH_2Cl_2 (4 × 200 mL). The combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (4 × 100 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was coevaporated with toluene (2 × 40 mL). The resulting pale yellow solid was dissolved in CH_2Cl_2 (35 mL) and cooled to 0 °C. After addition of petroleum ether (100 mL), the β-anomer **4** crystallized. Recrystallization from toluene gave analytically pure **4**. Yield 5.30 g (24%). R_f = 0.25 (5% MeOH in CH_2Cl_2, v/v). Mp 116–118 °C. After evaporation, the remaining product was chromatographed on silica gel (30% petroleum ether in CH_2Cl_2, v/v) to give the α-anomer **3** as a gum. Yield 7.84 g (35%). R_f = 0.38 (5% MeOH in CH_2Cl_2, v/v). Additional β-anomer **4** (0.74 g, 3%) was obtained as the more polar product. ^1H NMR and ^{13}C NMR for both isomers were in accordance with published data.[9]

Methyl 2-Deoxy-5-*O*-(4-phenylbenzoyl)-α-D-*glycero*-pentofuranosid-3-ulose (7).[12] To a stirred mixture of an-

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hydrous pyridine (5.3 mL, 0.065 mol) and anhydrous CH_2Cl_2 (60 mL) under argon was added CrO_3 (3.20 g, 0.032 mol), and stirring was continued at rt for 15 min. Compound **3** (2.90 g, 8.8 mmol) was dissolved in CH_2Cl_2 (25 mL) and added to the above mixture. Immediate addition of acetic anhydride (3.2 mL, 0.033 mol) followed. After 15 min, the dark brown solution was carefully added to stirred ethyl acetate (450 mL) and filtered through silica. The resulting pale yellow solution was evaporated to dryness and coevaporated with toluene (2 × 50 mL) to give ketone **7** as a pale yellow solid which was used for preparation of **11** without further purification. Yield 2.62 g (91%). R_f = 0.72 (10% MeOH in CH_2Cl_2, v/v). ^{1}H NMR and ^{13}C NMR were in accordance with published data.[12]

Methyl 2-Deoxy-5-*O*-(4-phenylbenzoyl)-β-D-*glycero*-pentofuranosid-3-ulose (8).[12] To a stirred solution of anhydrous pyridine (4.0 mL, 0.050 mol), in anhydrous CH_2Cl_2 (55 mL) was added CrO_3 (2.46 g, 0.025 mol), and stirring was continued at rt for 15 min. Compound **4** (3.20 g, 9.7 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) and added to the above mixture. Immediate addition of Ac_2O (2.3 mL, 0.025 mol) followed. Reaction and workup as described for **7** afforded **8** as a pale yellow solid which was used for preparation of **12** without further purification. Yield 2.79 g (88%). R_f = 0.69 (10% MeOH in CH_2Cl_2, v/v). ^{1}H NMR and ^{13}C NMR were in accordance with published data.[12]

Methyl 5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-α-D-*glycero*-pentofuranosid-3-ulose (9). To a stirred solution of anhydrous pyridine (5.2 mL, 0.064 mol) in anhydrous CH_2Cl_2 (70 mL) was added CrO_3 (3.21 g, 0.032 mol), and stirring was continued at rt for 15 min. Compound **5** (4.13 g, 10.7 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) and added to the above mixture. Immediate addition of Ac_2O (3.0 mL, 0.032 mol) followed. Reaction and workup as described for **7** afforded **9** as a yellow oil which was used for preparation of **13** without further purification. Yield 3.91 g (95%). R_f = 0.85 (15% EtOAc in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$) δ 1.01 (9H, s), 2.43 (1H, d, J = 17.6 Hz), 2.68 (1H, dd, J = 5.4, 17.7 Hz), 3.45 (3H, s), 3.87 (1H, dd, J = 1.7, 10.6 Hz), 3.91–3.99 (2H, m), 5.41 (1H, d, J = 5.1 Hz), 7.34–7.70 (10H, m). ^{13}C NMR ($CDCl_3$) δ 19.10, 26.55, 44.25, 54.79, 62.88, 78.64, 101.47, 127.59, 127.61, 129.60, 129.65, 132.73, 132.86, 135.46, 135.48, 212.25. Anal. Calcd for $C_{22}H_{28}SiO_4$: C, 68.71; H, 7.34. Found: C, 68.53; H, 7.38.

Methyl 5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-β-D-*glycero*-pentofuranosid-3-ulose (10). To a stirred solution of anhydrous pyridine (4.3 mL, 0.053 mol) in anhydrous CH_2Cl_2 (60 mL) was added CrO_3 (2.68 g, 0.027 mol), and stirring was continued at rt for 15 min. Compound **6** (3.35 g, 8.87 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) and added to the above mixture. Immediate addition of Ac_2O (2.5 mL, 0.027 mol) followed. Reaction and workup as described for **7** afforded **10** as a pale yellow oil which was used for preparation of **14** without further purification. Yield 2.98 g (89%). R_f = 0.79 (5% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s), 2.43 (1H, d, J = 18.3 Hz), 2.74 (1H, dd, J = 5.6, 18.3 Hz), 3.39 (3H, s), 3.81 (1H, dd, J = 5.9, 11.1 Hz), 3.90 (1H, dd, J = 3.2, 11.1 Hz), 4.14 (1H, dd, J = 3.2, 5.6 Hz), 5.33 (1H, dd, J = 2.0, 5.6 Hz), 7.34–7.71 (10H, m). ^{13}C NMR ($CDCl_3$) δ 19.13, 26.58, 43.56, 54.89, 64.86, 81.84, 102.13, 127.57, 127.64, 129.50, 129.61, 129.72, 132.99, 133.08, 135.51, 135.56, 211.79.

Methyl 2,3-Dideoxy-3-*C*-methylene-5-*O*-(4-phenylbenzoyl)-α-D-*glycero*-pentofuranoside (11). To a stirred solution of ketone **7** (1.46 g, 4.6 mmol) in anhydrous CH_2Cl_2 (65 mL) under argon at 0 °C was added three portions of the slurry reagent[15] (3 × 15 mL; 10 min intervals) prepared from Zn (7.5 g, 120 mmol), CH_2Br_2 (2.7 mL, 38 mmol), and $TiCl_4$ (3.15 mL, 29 mmol) in anhydrous THF (70 mL). After stirring for 15 min, the reaction mixture was allowed to warm to rt, stirred for 45 min, and then poured into a mixture of ice and a saturated aqueous solution of $NaHCO_3$ (500 mL). The mixture was stirred for 10 min with $CHCl_3$ (300 mL) and filtered through silica gel on a glass filter. The organic phase was separated, dried (Na_2SO_4), and evaporated. Purification using silica gel column chromatography (0–0.5% MeOH in CH_2Cl_2, v/v) afforded **11** as a white solid. Yield 0.87 g (58%). R_f = 0.53 (50% EtOAc in petroleum ether, v/v). ^{1}H NMR ($CDCl_3$) δ 2.56–2.63 (1H, m, H-2a), 2.75–2.86 (1 H, m, H-2b), 3.40 (3H, s, OCH_3), 4.41 (1H, dd, J = 5.7, 11.7 Hz, H-5a), 4.55 (1H, dd, J = 3.4, 11.7 Hz, H-5b), 5.11–5.13 (1H, m, H-4), 5.16–5.20 (3H, m, H-1, 3-*C*-CH_2a, 3-*C*-CH_2b), 7.36–8.14 (9H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 39.58, 54.59, 66.58, 77.23, 103.96, 107.39, 126.96, 127.16, 128.05, 128.63, 128.82, 130.09, 139.88, 145.16, 145.68, 166.19. EI-MS m/z = 324 (M^+, 1.1%). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.95; H, 6.09.

Methyl 2,3-Dideoxy-3-*C*-methylene-5-*O*-(4-phenylbenzoyl)-β-D-*glycero*-pentofuranoside (12). To a stirred solution of ketone **8** (2.79 g, 8.5 mmol) in anhydrous CH_2Cl_2 (65 mL) under argon at 0 °C was added three portions of the slurry reagent[15] (3 × 15 mL; 10 min intervals) prepared from Zn (15 g, 240 mmol), CH_2Br_2 (5.2 mL, 74 mmol), and $TiCl_4$ (6.3 mL, 58 mmol) in anhydrous THF (150 mL). Reaction, workup, and purification as described for **11** afforded **12** as a white solid. Yield 1.95 g (71%). R_f = 0.55 (50% EtOAc in petroleum ether, v/v). ^{1}H NMR ($CDCl_3$) δ 2.65 (1H, dd, J = 3.6, 14.8 Hz, H-2a), 2.80–2.94 (1H, m, H-2b), 3.38 (3H, s, OCH_3), 4.39 (1H, dd, J = 7.6, 11.5 Hz, H-5a), 4.50 (1H, dd, J = 4.2, 11.5 Hz, H-5b), 4.84–4.87 (1H, m, H-4), 5.10–5.17 (2H, m, 3-*C*-CH_2a, 3-*C*-CH_2b), 5.19 (1H, m, H-1), 7.38–8.18 (9H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 39.99, 54.58, 68.31, 78.71, 104.54, 107.49, 127.03, 127.25, 128.10, 128.89, 130.23, 140.03, 145.51, 145.72, 166.32. EI-MS m/z = 324 (M^+, 2.1%). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.92; H, 6.30.

Methyl 5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-3-*C*-methylene-α-D-*glycero*-pentofuranoside (13). To a stirred solution of ketone **9** (1.88 g, 4.9 mmol) in anhydrous CH_2Cl_2 (80 mL) under argon at 0 °C was added three portions of the slurry reagent[15] (3 × 25 mL, 10 min intervals) prepared from Zn (8.1 g, 124 mmol), CH_2Br_2 (2.9 mL, 41 mmol) and $TiCl_4$ (3.4 mL, 31 mmol) in anhydrous THF (80 mL). Reaction and workup as described for **11** followed by purification using silica gel column chromatography (15% EtOAc in petroleum ether, v/v) afforded **13** as a colorless oil. Yield 1.24 g (66%). R_f = 0.91 (15% EtOAc in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s), 2.50 (1H, d, J = 15.9 Hz), 2.69–2.79 (1H, m), 3.37 (3H, s), 3.73–3.76 (2H, m), 4.52 (1H, dd, J = 2.0, 4.0 Hz), 4.96–4.97 (1H, m), 5.07–5.11 (2H, m), 7.33–7.73 (10H, m). ^{13}C NMR ($CDCl_3$) δ 19.27, 26.81, 39.97, 54.47, 66.70, 80.32, 103.99, 106.48, 127.60, 129.60, 133.53, 133.60, 135.69, 146.39. Anal. Calcd for $C_{23}H_{30}SiO_3$: C, 72.21; H, 7.90. Found: C, 72.31; H, 8.09.

Methyl 5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-3-*C*-methylene-β-D-*glycero*-pentofuranoside (14). To a stirred solution of ketone **10** (1.16 g, 3.0 mmol) in anhydrous CH_2Cl_2 (70 mL) under argon at 0 °C was added three portions of the slurry reagent[15] (3 × 20 mL, 10 min intervals) prepared from Zn (5.1 g, 78 mmol), CH_2Br_2 (1.8 mL, 26 mmol), and $TiCl_4$ (2.1 mL, 19 mmol) in anhydrous THF (60 mL). Reaction and workup as described for **11** followed by purification using silica gel column chromatography (CH_2Cl_2) afforded **14** as a colorless oil. Yield 0.69 g (60%). R_f = 0.90 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 1.08 (9H, s), 2.49–2.57 (1H, m), 2.78 (1H, ddd, J = 2.0, 4.7, 16.4 Hz), 3.26 (3H, s), 3.72–3.76 (2H, m), 4.57–4.62 (1H, m), 5.02–5.04 (3H, m), 7.34–7.72 (10H, m). ^{13}C NMR ($CDCl_3$) δ 19.16, 26.72, 40.00, 54.35, 68.21, 81.38, 104.09, 106.73, 127.54, 129.50, 129.52, 133.47, 133.57, 135.52, 146.34. Anal. Calcd for $C_{23}H_{30}SiO_3$: C, 72.21; H, 7.90. Found: C, 72.15; H, 7,74.

Methyl 2-Deoxy-3-*C*-(hydroxymethyl)-5-*O*-(4-phenylbenzoyl)-α-D-*erythro*-pentofuranoside (15) and Methyl 2-Deoxy-3-*C*-(hydroxymethyl)-5-*O*-(4-phenylbenzoyl)-α-D-*threo*-pentofuranoside (16). To a solution of compound **11** (526 mg, 1.62 mmol) in *tert*-butyl alcohol (15 mL) was added *N*-methylmorpholine *N*-oxide (1.31 g, 11.22 mmol), pyridine (0.7 mL, 8.6 mmol), H_2O (0.95 mL), and osmium tetraoxide (75 μL of a 2.5% solution in *tert*-butyl alcohol, 6 μmol). The reaction mixture was stirred under argon at 76 °C for 5 h, cooled to rt, and treated with a 20% aqueous solution of sodium bisulfite (4 mL). The mixture was evaporated to dryness under reduced pressure, a saturated aqueous solution of NaCl (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried (Na_2SO_4) and evaporated. Purification using silica gel column chromatography (0–2.5% MeOH in CH_2Cl_2, v/v) gave **15** as an off-white

solid. Yield 102 mg (18%). R_f = 0.62 (10% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$) δ 2.07–2.23 (2H, m, H-2α, H-2β), 2.88 (1H, s), 3.42 (3H, s, OCH_3), 3.80 (1H, d, J = 17.5 Hz, 3-*C*-CH_2a), 3.85 (1H, d, J = 17.5 Hz, 3-*C*-CH_2b), 4.04 (1H, br s), 4.34 (1H, dd, J = 4.9, 11.8 Hz, H-5a), 4.44–4.48 (1H, m, H-4), 4.61 (1H, dd, J = 3.8, 11.8 Hz, H-5b), 5.15 (1H, d, J = 3.9 Hz, H-1), 7.36–8.12 (9H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 42.69, 55.01, 63.42, 64.74, 80.87, 85.04, 104.44, 126.99, 127.10, 128.07, 128.29, 128.79, 129.97, 130.09, 139.69, 145.76, 165.99. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 66.99; H, 6.51. As the more polar product, **16** was obtained as an off-white solid. Yield 271 mg (47%). R_f = 0.53 (10% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$) δ 2.07 (1H, dd, J = 2.1, 14.3 Hz, H-2α), 2.29 (1H, dd, J = 5.7, 14.3 Hz, H-2β), 3.14 (1H, s), 3.29 (1H, br s), 3.36 (3H, s, OCH_3), 3.79 (1H, d, J = 17.6 Hz, 3-*C*-CH_2a), 3.85 (1H, d, J = 17.6 Hz, 3-*C*-CH_2b), 4.22 (1H, dd, J = 3.8, 6.4 Hz, H-4), 4.45 (1H, dd, J = 6.4, 11.9, H-5a), 4.77 (1H, dd, J = 3.8 Hz, 11.9 Hz, H-5b), 5.16 (1H, dd, J = 2.1, 5.7 Hz, H-1), 7.38–8.12 (9H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 44.72, 54.99, 64.49, 67.76, 80.28, 80.90, 103.39, 126.97, 127.13, 128.09, 128.31, 128.82, 130.13, 139.71, 145.83, 166.84. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 66.79; H, 6.47.

Methyl 2-Deoxy-3-*C*-(hydroxymethyl)-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside (17). To a solution of compound **12** (1.95 g, 5.98 mmol) in *tert*-butyl alcohol (55 mL) was added *N*-methylmorpholine *N*-oxide (4.85 g, 41.51 mmol), pyridine (2.6 mL, 31.8 mmol), H_2O (3.6 mL) and osmium tetraoxide (275 μL of a 2.5% solution in *tert*-butyl alcohol, 22 μmol). Reaction and workup as described for **15/16** afforded **17** as a white solid after silica gel column chromatography (0–2.5% MeOH in CH_2Cl_2, v/v). Yield 1.62 g (76%). R_f = 0.35 (10% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$) δ 2.04 (1H, dd, J = 3.4, 14.2 Hz, H-2α), 2.33 (1H, dd, J = 5.9, 14.2 Hz, H-2β), 2.94 (1H, br s), 3.37 (3H, s, OCH_3), 3.44 (1H, s), 3.83–3.89 (2H, m, 3-*C*-CH_2a, 3-*C*-CH_2b), 4.33 (1H, dd, J = 4.5, 6.5 Hz, H-4), 4.40 (1H, dd, J = 6.5, 11.1 Hz, H-5a), 6.61 (1H, dd, J = 4.5, 11.1 Hz, H-5b), 5.20 (1H, dd, J = 3.4, 5.9 Hz, H-1), 7.25–8.13 (9H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 43.18 (C-2), 55.48 (OCH_3), 64.41 (C-5), 64.99 (3-*C*-CH_2), 81.61 (C-4), 84.51 (C-3), 105.13 (C-1), 127.08, 127.22, 128.15, 128.54, 128.89, 130.18, 139.86, 145.88 (Ar), 166.39 (C=O). EI-MS: *m/z* (%) = 358 (M^+, 0.3%). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 66.66; H, 6.28.

Methyl 5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-3-*C*-(hydroxymethyl)-α-D-*erythro*-pentofuranoside (18) and Methyl 5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-3-*C*-(hydroxymethyl)-α-D-*threo*-pentofuranoside (19). To a solution of **13** (0.437 g, 1.14 mmol) in *tert*-butyl alcohol (15 mL) was added *N*-methylmorpholine *N*-oxide (0.93 g, 7.9 mmol), pyridine (0.6 mL, 7.4 mmol), H_2O (0.7 mL, 38.9 mmol), and OsO_4 (60 μL of a 2.5% solution in *tert*-butyl alcohol, 4.8 μmol). Reaction and workup as described for **15/16** afforded an inseparable mixture of **18** and **19** (1:1) as a solid white material after silica gel column chromatography (25% cyclohexane in EtOAc, v/v). Yield 395 mg (83%). R_f = 0,56 (10% MeOH in CH_2Cl_2, v/v). ^{13}C NMR ($CDCl_3$) δ 19.06, 19.11, 26.66, 26.76, 42.66, 44.99, 54.98, 62.97, 63.08, 64.87, 67.80, 81.08, 81.16, 81.30, 87.46, 103.43, 104.62, 127.72, 127.82, 127.90, 129.82, 129.90, 130.02, 130.06, 132.12, 132.31, 132.59, 132.71, 135.49, 135.52, 135.64. Anal. Calcd for $C_{23}H_{32}SiO_5$ (1:1 mixture): C, 66.31; H, 7.74. Found: C, 66.49; H, 7.78.

Methyl 5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranoside (20) and Methyl 5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-3-*C*-(hydroxymethyl)-β-D-*threo*-pentofuranoside (21). To a solution of compound **14** (0.526 g, 1.62 mmol) in *tert*-butyl alcohol (55 mL) was added *N*-methylmorpholine *N*-oxide (4.85 g, 41.51 mmol), pyridine (2.6 mL, 31.8 mmol), H_2O (3.6 mL), and osmium tetraoxide (275 μL of a 2.5% solution in *tert*-butyl alcohol, 22 μmol). Reaction and workup as described for **15/16** afforded **20** as a white solid after silica gel column chromatography (25% cyclohexane in EtOAc, v/v). Yield 117 mg (20%). R_f = 0.70 (10% MeOH in CH_2Cl_2, v/v). ^{1}H NMR (DMSO-d_6) δ 1.00 (9H, s, *tert*-butyl), 1.92 (1H, dd, J = 4.8, 13.4 Hz, H-2β), 2.04 (1H, dd, J = 5.6, 13.4 Hz, H-2α), 3.30 (3H, s, OCH_3), 3.51–3.54 (2H, m, 3-*C*-CH_2a, 3-*C*-CH_2b), 3.65 (1H, dd, J = 6.1, 10.8 Hz, H-5a), 3.82 (1H, dd, J = 4.3, 10.8 Hz, H-5b), 3.93 (1H, dd, J = 4.5, 5.8 Hz, H-4), 4.58 (1H, t, 3-*C*-CH_2OH, J = 5.5 Hz), 4.80 (1H, s), 5.09–5.13 (1H, m, H-1), 7.39–7.72 (10H, m, Ar). ^{13}C NMR (DMSO-d_6) δ 18.65, 26.42, 42.21, 54.91, 63.82, 64.04, 80.49, 87.06, 104.91, 127.66, 127.68, 129.64, 132.94, 132.96, 134.98, 135.01. Anal. Calcd for $C_{23}H_{32}SiO_5$·0.25 H_2O: C, 65.60; H, 7.78. Found: C, 65.89; H, 7.77. Besides, a 7:1 mixture of **20** and **21** was isolated as a white solid material. Yield 327 mg (56%). Data for **21**: ^{13}C NMR (DMSO-d_6) δ 18.63, 26.50, 42.83, 54.03, 64.82, 64.89, 74.59, 80.08, 104.80, 129.59, 132.92, 133.03, 134.95, 135.02. Anal. Calcd for $C_{23}H_{32}SiO_5$·0.25 H_2O (7:1 mixture): C, 65.60; H, 7.78. Found: C, 65.44; H, 7.82.

Methyl 2-Deoxy-5-*O*-(4-phenylbenzoyl)-3-*C*-((*p*-toluenesulfonyloxy)methyl)-β-D-*erythro*-pentofuranoside (22). To a stirred solution of compound **17** (0.300 g, 0.85 mmol) in anhydrous pyridine (5 mL) was added *p*-toluenesulfonyl chloride (0.250 g, 1.3 mmol) at 0 °C. After 1 h, the reaction mixture was allowed to warm to rt, and stirring was continued for 18 h. Additional *p*-toluenesulfonyl chloride (0.05 g, 0.26 mmol) was added, and stirring was continued at rt for another 18 h. The reaction mixture was diluted with EtOAc (25 mL), washed with a saturated aqueous solution of $NaHCO_3$ (3 × 10 mL), dried (Na_2SO_4), and evaporated. Purification using silica gel column chromatography (0–1% MeOH in CH_2Cl_2, v/v) afforded tosylate **22** as a white solid. Yield 0.39 g (86%). R_f = 0.70 (5% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$) δ 2.10 (1H, dd, J = 3.1, 14.0 Hz, H-2a), 2.32 (1H, dd, J = 5.7, 14.0 Hz, H-2b), 2.38 (3H, s, CH_3), 2.87 (1H, s), 3.29 (3H, s, OCH_3), 4.26–4.52 (3H, m, H-4, H-5a, H-5b), 5.14 (1H, dd, J = 3.1, 5.7 Hz, H-1), 7.25–8.09 (13H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 21.61, 43.29, 55.48, 63.14, 72.34, 79.47, 83.92, 104.76, 127.07, 127.24, 128.01, 128.23, 128.45, 128.96, 129.99, 130.19, 139.88, 145.31, 145.86, 165.84. Anal. Calcd for $C_{27}H_{28}O_8S$·H_2O: C, 61.12; H, 5.70; S, 6.04. Found: C, 61.11; H, 5.54; S, 6.37.

Methyl 3-*C*-(Adenin-9-ylmethyl)-2-deoxy-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside (23). Compound **17** (282 mg, 0.55 mmol) was dissolved in anhydrous DMF (5 mL), and the solution was stirred under argon. K_2CO_3 (0.37 g, 2.2 mmol), 18-crown-6 (0.150 g, 0.55 mmol), and adenine (0.148 g, 1.1 mmol) were added. Stirring was continued at 65 °C for 24 h and subsequently at 90 °C for another 24 h. The solvent was evaporated, and the residue was redissolved in EtOAc (15 mL). The mixture was washed with saturated aqueous solutions of $NaHCO_3$ (3 × 10 mL) and water (2 × 10 mL). The organic phase was dried (Na_2SO_4) and evaporated. Purification using silica gel column chromatography (1–5% MeOH in CH_2Cl_2, v/v) afforded **23** as a white solid. Yield 175 mg (65%). R_f = 0.30 (10% MeOH in CH_2Cl_2, v/v). ^{1}H NMR ($CDCl_3$) δ 1.85 (1H, d, J = 13.8 Hz, H-2'β), 2.11 (1H, dd, J = 5.5, 13.8 Hz, H-2'α), 3.40 (3H, s, OCH_3), 4.40 (1H, dd, J = 4.4, 6.3 Hz, H-4), 4.46 (1H, d, J = 14.1 Hz, 3'-*C*-CH_2a), 4.58 (1H, dd, J = 6.3, 11.7 Hz, H-5'a), 4.70 (1H, dd, J = 4.4, 11.7 Hz, H-5'b), 4.78 (1H, d, J = 14.1 Hz, 3'-*C*-CH_2b), 5.07 (1H, d, J = 5.5 Hz, H-1), 6.07 (2H, s), 6.69 (1H, s), 7.38–7.69 (7H, m, Ar), 7.83 (1H, s, H-2), 8.15–8.17 (2H, m, Ar), 8.32 (1H, s, H-8). ^{13}C NMR ($CDCl_3$) δ 42.96, 50.62, 55.45, 63.05, 79.48, 83.65, 104.22, 119.73, 127.15, 127.29, 128.23, 128.52, 128.95, 130.26, 139.94, 142.25, 146.00, 150.13, 152.54, 155.80, 166.15. HRMS Calcd. for $C_{25}H_{25}N_5O_5$: 475.1856. Found: 475.1853. Anal. Calcd. for $C_{25}H_{25}N_5O_5$·0.9H_2O: C, 61.07; H, 5.49; N, 14.24. Found: C, 61.11; H, 5.30; N, 14.09.

Methyl 2-Deoxy-5-*O*-(4-phenylbenzoyl)-3-*C*-(thymin-1-ylmethyl)-β-D-*erythro*-pentofuranoside (24). Compound **17** (300 mg, 0.58 mmol) was dissolved in anhydrous DMF (5 mL), and the solution was stirred under argon. K_2CO_3 (0.40 g, 2.38 mmol), 18-crown-6 (0.150 g, 0.55 mmol), and the sodium salt of thymine[22] (0.250 g, 1.7 mmol) were added. Stirring was continued at 65 °C for 5 h and subsequently at 90 °C for 48 h. The solvent was evaporated, and the residue was redissolved in EtOAc (15 mL). The mixture was washed with saturated aqueous solutions of $NaHCO_3$ (3 × 10 mL) and water (2 × 10 mL). The organic phase was dried (Na_2SO_4) and evaporated. Purification using silica gel column chromatography (1–5% MeOH in CH_2Cl_2, v/v) afforded **24** as a white solid. Yield 116

mg (42%). R_f = 0.33 (7.5% MeOH in CH_2Cl_2, v/v). ^1H NMR ($CDCl_3$) δ 1.90 (3H, s, CH_3), 2.18 (1H, dd, J = 1.9, 14.0 Hz, H-2′α), 2.28 (1H, dd, J = 5.4, 14.0 Hz, H-2′β), 3.40 (3H, s, OCH_3), 3.99 (1H, d, J = 14.4 Hz, 3′-*C*-CH_2a), 4.30−4.32 (1H, m, H-4′), 4.35 (1H, d, J = 14.4 Hz, 3′-*C*-CH_2b), 4.50 (1H, dd, J = 6.1, 11.9 Hz, H-5′a), 4.63 (1H, dd, J = 5.1, 11.9 Hz, H-5′b), 4.79 (1H, br s), 5.11 (1H, dd, J = 1.9, 5.4 Hz, H-1′), 7.22 (1H, s, H-6), 7.35−8.15 (10H, m, Ar, H-6). ^{13}C NMR ($CDCl_3$) δ 12.30, 42.22, 53.17, 55.45, 62.89, 80.31, 83.75, 104.12, 111.04, 127.09, 127.21, 128.18, 128.40, 128.89, 130.20, 139.81, 142.14, 145.89, 153.45, 164.13, 166.05. EI-MS: m/z (%) = 466 (M^+, 0.7%). Anal. Calcd for $C_{25}H_{26}N_2O_7 \cdot 0.5H_2O$: C, 63.15; H, 5.72; N, 5.89. Found: C, 63.22; H, 5.66; N, 5.89.

Methyl 3-*C*-(Adenin-9-ylmethyl)-2-deoxy-β-D-*erythro*-pentofuranoside (25). Compound **23** (110 mg, 0.23 mmol) was dissolved in methanol saturated with NH_3 (75 mL), and stirring at rt under argon was continued for 2 h. The solvent was evaporated under reduced pressure, and the residue was purified using silica gel column chromatography (0−10% MeOH in CH_2Cl_2, v/v) affording **25** as a white solid. Yield 45 mg (65%). R_f = 0.14 (10% MeOH in CH_2Cl_2, v/v). ^1H NMR (CD_3OD) δ 1.98 (1H, dd, J = 5.7, 13.9 Hz, H-2a), 2.23 (1H, dd, J = 4.2, 13.9 Hz, H-2b), 3.48 (3H, s, CH_3), 3.80 (1H, dd, J = 5.4, 11.7 Hz, H-5′a), 3.90 (1H, dd, J = 6.0, 11.7 Hz, H-5′b), 4.09 (1H, dd, J = 5.4, 6.0 Hz, H-4′), 4.46 (1H, d, J = 14.4 Hz, 3′-*C*-CH_2a), 4.74 (1H, d, J = 14.4 Hz, 3′-*C*-CH_2b), 5.17 (1H, dd, J = 4.2, 5.7 Hz, H-1′), 8.24 (1H, s), 8.30 (1H, s). ^{13}C NMR (CD_3OD) δ 44.48, 49.85, 56.04, 62.95, 81.69, 88.88, 106.44, 119.57, 143.94, 151.19, 153.59, 157.24. HRMS Calcd for $C_{12}H_{17}N_5O_4$: 295.1281. Found: 295.1296. Anal. Calcd for $C_{12}H_{17}N_5O_4 \cdot 0.25\ H_2O$: C, 48.08; H, 5.88; N, 22.68. Found: C, 47.90; H, 5.94; N, 22.49.

Methyl 2-Deoxy-3-*C*-(thymin-1-yl)methyl)-β-D-*erythro*-pentofuranoside (26). Compound **24** (98 mg, 0.21 mmol) was dissolved in methanol saturated with NH_3 (65 mL), and stirring at rt under argon was continued for 8 h. The solvent was evaporated, and the residue was purified using silica gel column chromatography (0−10% MeOH in CH_2Cl_2, v/v) affording **26** as a white solid. Yield 60 mg (94%). R_f = 0.32 (10% MeOH in CH_2Cl_2, v/v). ^1H NMR (DMSO-d_6) δ 1.74 (3H, s, CH_3), 1.90−2.07 (2H, m, H-2′a, H-2′b), 3.30 (3H, s, OCH_3), 3.39−3.50 (2H, m, H-5′a, H-5′b), 3.55 (1H, d, J = 14.2 Hz, 3′-*C*-CH_2a), 3.75−3.79 (1H, m, H-4′), 4.22 (1H, d, J = 14.2 Hz, 3′-*C*-CH_2b), 4.99 (1H, t, J = 5.4 Hz, H-1′), 7.42 (1H, s, H-6), 11.17 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 11.93, 42.26, 50.74, 54.95, 61.49, 80.79, 87.43, 104.82, 107.23, 142.92, 151.33, 164.19. HRMS Calcd for $C_{12}H_{18}N_2O_6$: 286.1165. Found: 286.1158. Anal. Calcd for $C_{12}H_{18}N_2O_6 \cdot H_2O$: C, 47.65; H, 6.60; N, 9.26. Found: C, 47.94; H, 6.30; N, 9.55.

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