2 H), 7.24 (d, J = 9 Hz, 2 H), 7.21 (s, 1 H), 2.82 (t, J = 9 Hz, 2 H), 2.60 (t, J = 9 Hz, 2 H), 2.30 (quint, J = 9 Hz, 2 H); MS (FAB) m/z 356 ($M^+ - 1$). Anal. ($C_{14}H_{13}ClN_2O_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-(4,5,6,7-tetrahydrobenzo[*c*]thiophene-yl-2-sulfonyl)urea (22).** Synthesized from 4,5,6,7-tetrahydrobenzo[c]thiophene-2-sulfonamide (prepared from 4,5,6,7-tetrahydrobenzo[c]thiophene[6] by method B) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 10.78 (bs, 1 H), 8.84 (s, 1 H), 7.54 (s, 1 H), 7.42 (d, J = 9 Hz, 2 H), 7.32 (d, J = 9 Hz, 2 H), 2.94 (m, 2 H), 2.64 (m, 2 H), 1.68 (m, 4 H); ^{13}C NMR (CD_3SOCD_3) δ 149.5, 143.1, 139.1, 137.2, 132.5, 128.6, 126.7, 126.6, 120.5, 25.7, 24.9, 22.0, 21.8; MS (FAB) m/z 371 (M^+). Anal. ($C_{15}H_{15}ClN_2O_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-(5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-yl-2-sulfonyl)urea (23).** Synthesized from 5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-2-sulfonamide (prepared from 5,6-dihydro-4*H*-cyclopenta[*b*]thiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 10.52 (bs, 1 H), 8.99 (s, 1 H), 7.57 (s, 1 H), 7.46 (d, J = 9 Hz, 2 H), 7.34 (d, J = 9 Hz, 2 H), 2.93 (t, J = 7 Hz, 2 H), 2.72 (t, J = 7 Hz, 2 H), 2.38 (quint, J = 7 Hz, 2 H); ^{13}C NMR δ 150.8, 149.2, 146.0, 140.8, 137.0, 128.8, 128.6, 126.9, 120.6, 29.0, 28.5, 27.6; MS (FAB) m/z 357 (M^+). Anal. ($C_{14}H_{13}ClN_2O_3S_2$) H, N, C: calcd, 47.12; found, 48.91.

***N*-(3,4-Dichlorophenyl)-*N'*-(4,5,6,7-tetrahydrobenzo[*b*]thiophene-yl-2-sulfonyl)urea (24).** Synthesized from 4,5,6,7-tetrahydrobenzo[b]thiophene-2-sulfonamide (prepared from 4,5,6,7-tetrahydrobenzo[b]thiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 9.18 (s, 1 H), 7.76 (d, J = 2 Hz, 1 H), 7.54 (d, J = 9 Hz, 1 H), 7.44 (s, 1 H), 7.30 (dd, J = 2, 9 Hz, 1 H), 2.76 (m, 2 H), 2.56 (m, 2 H), 1.74 (m, 4 H); ^{13}C NMR (CD_3SOCD_3) δ 141.4, 140.1, 134.8, 131.8, 130.8, 130.42, 130.39, 130.3, 123.0, 119.4, 118.5, 24.8, 24.5, 22.7, 22.0; MS (FAB) m/z 404 ($M^+ - 1$). Anal. ($C_{15}H_{14}Cl_2N_2O_3S_2$) C, H, N.

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Side-Chain Derivatives of Biologically Active Nucleosides. 1. Side-Chain Analogs of 3'-Azido-3'-deoxythymidine (AZT)[1]

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Starting from 3-*O*-mesyl-1,2-*O*-isopropylidene-α-D-allofuranose (**9**) the anomeric mixtures of the requisite carbohydrates 1,2-di-*O*-acetyl-6-*O*-benzoyl-5-deoxy-3-*O*-mesyl-D-allofuranoses **17Aα/β**, 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*O*-mesyl-D-allofuranoses **17Bα/β**, and 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*O*-mesyl-L-talofuranoses **17Cα/β** were synthesized. 1,2-Di-*O*-acetyl-5-*O*-benzoyl-6-deoxy-3-*O*-mesyl-D-allofuranoses **17Dα/β** and the corresponding L-talofuranoses **17Eα/β** were obtained from 6-deoxy-3,5-di-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-allofuranose (**12**) and the corresponding β-L-talofuranose **13**. Coupling of these sugar derivatives with thymine gave the β-nucleoside derivatives **18A–E**. Treatment of compounds **18A–E** with DBU produced the corresponding 2,3'-anhydro nucleosides **19A–E** with a free 2'-OH group. After deoxygenation of 2'-*O*-[[(4-methylphenyl)oxy]thiocarbonyl] compounds **20A–E** with tributyltin hydride the 2,3'-anhydro bridge of the 2'-deoxynucleosides **21A–E** was opened with LiN_3 to produce the protected 3'-azido-2,3'-dideoxynucleoside derivatives **22A–G**. Saponification with $NaOCH_3$ gave 1-(3'-azido-2',3',5'-trideoxy-β-D-allofuranosyl)thymine (**2**; homo-AZT), the 5'-*C*-(hydroxymethyl) derivatives of AZT 1-(3'-azido-2',3'-dideoxy-β-D-allofuranosyl)thymine (**3**) and 1-(3'-azido-2',3'-dideoxy-α-L-talofuranosyl)thymine (**4**), and the 5'-*C*-methyl derivatives of AZT 1-(3'-azido-2',3',6'-trideoxy-β-D-allofuranosyl)thymine (**5**) and 1-(3'-azido-2',3',6'-trideoxy-α-L-talofuranosyl)thymine (**6**). Compounds **2–6** were evaluated for their inhibitory effect on human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) replication in MT-4 cells and found inactive at subtoxic concentrations. Compounds **2–4** and **6** are not effective against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), vaccinia virus (VV), and vesicular stomatitis virus (VSV) at 400 μg/mL. **5** is slightly active against HSV-1, HSV-2, and VV at 150, 300, and 300 μg/mL, respectively.

Introduction

3'-Azido-3'-deoxythymidine (1; AZT) has been reported to be of marked benefit in the treatment of AIDS and AIDS-related complex.[2] The triphosphate analog inhibits the utilization of dTTP by reverse transcriptase and may be incorporated in the terminal position of DNA, thereby preventing elongation.[3,4] During long term treatment, AZT is significantly toxic to men.[5] The major drawbacks of AZT are (a) the low V_{max} (0.3% compared to the natural substrate thymidine monophosphate) for the introduction of the second phosphate residue by thymidylate kinase which results in the accumulation of AZT monophosphate;[3] (b) the short half-life in the body necessitates frequent

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(1) This work was presented in part as a poster at the 9th International Round Table—Nucleosides, Nucleotides & their Biological Applications, Uppsala, Sweden, July 30–August 3, 1990 and as a lecture at the 8th Symposium on the Chemistry of Nucleic Acid Components, Bechyne Castle, Czechoslovakia, September 17–21, 1990.

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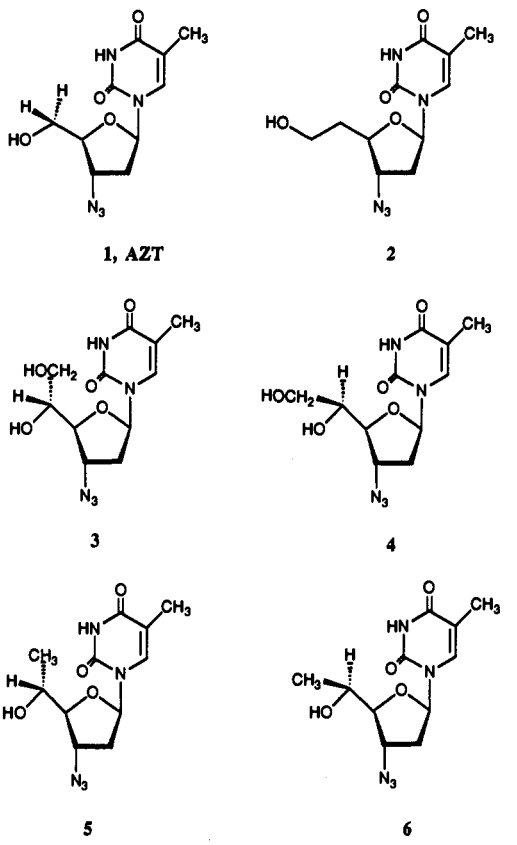
administration to maintain therapeutically effective levels;[2] (c) AZT cannot penetrate into the brain tissue from cerebrospinal fluid[6] and therefore may not be able to suppress viral replication in the brain. These problems stimulated the search for closely related nucleoside analogs[7-15] with

Scheme I



increased antiviral activity and decreased cytotoxicity. We were interested in the synthesis and structure–ac-

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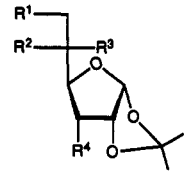
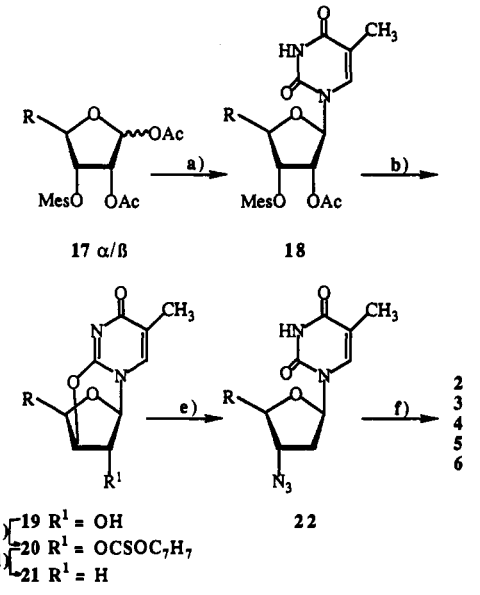
Scheme II



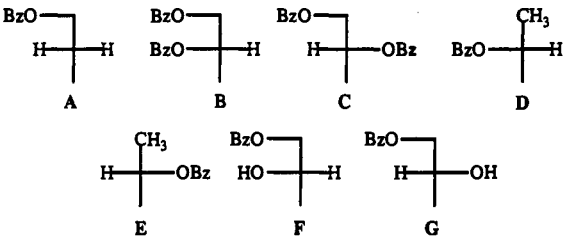
7	$R^1 - R^2 : -OC(CH_3)_2O-$, $R^3 = H$, $R^4 = OH$
8	$R^1 - R^2 : -OC(CH_3)_2O-$, $R^3 = H$, $R^4 = OMes$
9	$R^1 = R^2 : OH$, $R^3 = H$, $R^4 = OMes$
10	$R^1 = OBz$, $R^2 = OH$, $R^3 = H$, $R^4 = OMes$
11	$R^1 = OBz$, $R^2 = OC(S)OC_7H_7$, $R^3 = H$, $R^4 = OMes$
12	$R^1 = H$, $R^2 = OBz$, $R^3 = H$, $R^4 = OBz$
13	$R^1 = H$, $R^2 = H$, $R^3 = OBz$, $R^4 = OBz$
14	$R^1 = H$, $R^2 = OBz$, $R^3 = H$, $R^4 = OH$
15	$R^1 = H$, $R^2 = H$, $R^3 = OBz$, $R^4 = OH$
16A	$R^1 = OBz$, $R^2 = H$, $R^3 = H$, $R^4 = OMes$
16B	$R^1 = OBz$, $R^2 = OBz$, $R^3 = H$, $R^4 = OMes$
16C	$R^1 = OBz$, $R^2 = H$, $R^3 = OBz$, $R^4 = OMes$
16D	$R^1 = H$, $R^2 = OBz$, $R^3 = H$, $R^4 = OMes$
16E	$R^1 = H$, $R^2 = H$, $R^3 = OBz$, $R^4 = OMes$

tivity relationship (SAR) of side-chain analogs of AZT, in which the 4′-*C*-(hydroxymethyl) group of AZT is replaced by a hydroxyethyl group (**2**, homo-AZT, see Scheme I), and one of the diastereotopic protons at 5′-C is substituted by a hydroxymethyl group (5′-*C*-(hydroxymethyl) AZT derivatives **3** and **4**) or by a methyl group (5′-*C*-methyl AZT derivatives **5** and **6**). The elongation of the side chain by a methyl group or by a hydroxymethyl group generates an additional asymmetric center at the 5′-position and changes the primary hydroxy group to a secondary one. The aforementioned compounds open a way to study the influence of the methyl group and the hydroxymethyl group in antiviral activity studies. For this program we developed a general strategy useful for the preparation of side-chain analogs of biologically active 2′,3′-dideoxynucleoside derivatives.[16]

Scheme III[a]



Definition of the side chain residue R:



[a] (a) Thymine, $(CH_3)_3SiNHSi(CH_3)_3$, $(CH_3)_3SiCl$, CF_3SO_3H, CH_3CN, reflux; (b) equiv DBU, toluene, 90 °C (oil bath); (c) $ClC(S)OC_7H_7$, DMAP, CH_3CN, 25 °C, 16 h; (d) Bu_3SnH, AIBN, toluene, 120 °C, 16 h; (e) LiN_3, BzOH, DMF, 120 °C, 16 h; (f) $NaOCH_3$/MeOH.

Chemistry

1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose (**7**)[17] was the starting material for the requisite carbohydrate precursors (Scheme II). 1,2-*O*-Isopropylidene-3-*O*-mesyl-α-D-allofuranose (**9**) (91%, mp 87–90 °C) was prepared by selectively removing the 5,6-*O*-isopropylidene group of 1,2:5,6-di-*O*-isopropylidene-3-*O*-mesyl-α-D-allofuranose (**8**).[18] Compound **9** was transformed to mono-6-*O*-benzoyl derivative **10** (66%, mp 83–84 °C). The remaining free OH group in **10** was transformed to the 5-*O*-[[(4-methylphenyl)oxy]thiocarbonyl] derivative **11** (82%, mp 161 °C). Deoxygenation[19] yielded the desired 6-*O*-benzoyl-5-

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deoxy-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-allofuranose (**16A**) (92%, mp 69–70 °C).

The 5'-epimeric sugar units **16B** and **16C** could be obtained from compounds **9** and **10**, respectively (Scheme II). Treatment of compound **9** with 2.2 equivs of benzoyl chloride gave 5,6-di-*O*-benzoyl-3-*O*-mesyl-1,2-*O*-isopropylidene-α-D-allofuranose (**16B**) (83%, mp 143–145 °C). Mitsunobu reaction[20] (triphenylphosphine(TPP)/diethyl azodicarboxylate (DEAD)/benzoic acid) of 6-O-monobenzoylated compound **10** yielded the dibenzoylated L-talose derivative **16C**[21] (85%, mp 94–96 °C).

The carbohydrate precursors **16D** and **16E** were prepared from the epimeric dibenzoylated compounds **12**[22] and **13**[23] by selective deblocking of the 3-*O*-benzoyl group.[24] The sugar derivatives **14** (mp 95–97 °C) and **15** (mp 152–153 °C) with a free 3-OH group were reacted with mesyl chloride to give **16D** (93%, mp 125–125.5 °C) and **16E** (97%, mp 102–103 °C).

Replacing the 1,2-*O*-isopropylidene group of compounds **16A–E** with acetyl groups by treatment with Ac_2O, AcOH, and H_2SO_4 cat. led to the anomeric mixture of the 1,2-di-*O*-acetyl derivatives **17Aα/β – 17Eα/β** (Scheme III). These sugar derivatives are most suited for the one-pot procedure of silyl Hilbert–Johnson method.[25]

The coupling of these sugar derivatives with silylated thymine (Scheme III) yielded only the β-nucleoside derivatives **18A–E** (46–69%). Treatment of the nucleosides **18A–18E** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) produced the corresponding 2,3'-anhydronucleosides **19A–E** with a free 2'-OH group, proving the β-configuration of **18A** ($J_{1',2'}$ = 7.5 Hz), **18B** ($J_{1',2'}$ = 6.5 Hz), **18C** ($J_{1',2'}$ = 5.0 Hz), **18D** ($J_{1',2'}$ = 7.2 Hz), and **18E** ($J_{1',2'}$ = 6.5 Hz). The simultaneous selective deblocking of the acetyl group at the 2'-position with DBU is noticeable. The best results for this transformation were obtained in toluene at 90 °C oil-bath temperature.[26] The 2'-*O*-[[(4-methylphenyl)-oxy]thiocarbonyl] derivatives **20A–E** were deoxygenated[19] to yield compounds **21A–E**. The azidonucleoside derivatives **22A–E** were synthesized by opening of the 2,3'-anhydro bridge of **21A–E** with lithium azide/benzoic acid.[28] In the case of 5'-*C*-(hydroxymethyl) derivatives of AZT (**21B** and **21C**) the opening of the 2,3'-anhydro bridge gave two products. The more lipophilic compounds bear two benzoyl groups (**22B, 22C**). In the other compounds (**22F, 22G**) only one benzoyl group was present and located at the 6'-O-position as indicated by NMR. Saponification of the azidonucleoside derivatives **22A–G** yielded 1-(3'-azido-2',3',5'-trideoxy-β-D-allofuranosyl)thymine (**2**; homo-AZT)[16,29] 1-(3'-azido-2',3'-dideoxy-β-D-allofuranosyl)thymine (**3**),[30] 1-(3'-azido-2',3'-dideoxy-α-L-talofuranosyl)thymine (**4**), 1-(3'-azido-2',3',6'-trideoxy-β-D-allofuranosyl)thymine (**5**), and 1-(3'-azido-2',3',6'-trideoxy-α-L-talofuranosyl)thymine (**6**), respectively. NOE experiments with the AZT analogs **2–6** confirmed the ribo configuration of the 3'-azido group.

Biological Results and Discussion

Compounds **2–6** were evaluated for their activity against human immunodeficiency virus (HIV) type 1 and type 2. Under conditions where AZT inhibited HIV replication at a 50% effective concentration (EC_{50}) of 2 ng/mL, that is at a concentration that was 2000-fold lower than the 50% cytotoxic concentration, compounds **2–6** did not shown any anti-HIV activity even at a concentration up to 200 μg/mL. The CC_{50} of compounds **2, 3, 5,** and **6** was >200 μg/mL; for compound **4**, it was 17.7 ± 0.5 μg/mL. Compounds **2–6** were also evaluated for their inhibitory effect on herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), vaccinia virus (VV), and vesicular stomatitis virus (VSV), respectively. **2–4** and **6** are not effective against HSV-1, HSV-2, VV, and VSV at 400 μg/mL. Compound **5** is slightly active against HSV-1 at 150 μg/mL, against HSV-2 and VV at 300 μg/mL, and against VSV at >400 μg/mL, respectively.

These structure–activity relationship studies reveal that the elongation of the 5'-C side chain of AZT results in loss of activity. The inactivity of the 3'-azido-substituted 1-β-D-allo- and 1-α-L-talofuranosylthymine derivatives as antiviral agents may be ascribed to the fact that they are either poorly recognized as substrates for the activating (phosphorylation) enzymes (e.g. thymidine kinase) and/or have little substrate affinity for the viral polymerases (e.g. reverse transcriptase).

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker WM 250 or Bruker WM 400 spectrometer. The deuterated solvent will be given for each compound. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Precoated Merck silica gel F 254 plates were used for TLC, and the spots were examined with UV light and by spraying with a solution of 2% $Ce(NO_3)_4$ in 2 N H_2SO_4 followed by heating at 200 °C. Flash chromatography[31] was performed with 230–400

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(21) Seven equivalents of the reagents were necessary to complete the reaction because of competitive formation of the N-benzoylated hydrazoester.

(22) Hiebl, J.; Zbiral, E. Transformation of β-Glycofuranosyl Isocyanides into Tetrahydrofurans. *Monatsh. Chem.* **1990**, *121*, 683–690.

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(24) We used 10 mol % $NaOCH_3$–MeOH and carefully monitored the reaction by TLC (PE–EA 1:1). After the first appearance of fully deblocked material, the reaction was stopped with solid CO_2. The yield of one cycle calculated on the reacted material was 70–80%.

(25) Vorbrüggen, H.; Bennua, B. A New Simplified Nucleoside Synthesis. *Chem. Ber.* **1981**, *114*, 1279–1286.

(26) The reaction times using THF and 2.5 equiv of DBU are in the range of 3–5 days. Using refluxing toluene, the reaction is completed within 2 h. At this high temperature side reactions take place. Besides **19A** we could isolate compound **19F** with an additional free OH group in the 5'-position excluding a ketene mechanism[27] because this will only work for the acetyl residue. Although we used DBU stored over molesieves (3Å) we cannot exclude the presence of small amounts of water. Saponification of the benzoyl group could be achieved by traces of DBU hydroxide, formed from DBU in the presence of water.

(27) Baptistella, L. H. B.; Dos Santos, J. F.; Ballabio, K. C.; Marsaioli, A. J. 1,8-Diazabicyclo[5.4.0]undec-7-ene as a Mild Deprotective Agent for Acetyl Groups. *Synthesis* **1989**, 436–438.

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(29) During the preparation of this paper a different route to compound **2** appeared in the literature: Gautier, C.; Leroy, R.; Monneret, C.; Roger, P. Synthesis of 3'-Azido-5'-homothymidine Analogues. *Tetrahedron Lett.* **1991**, *32*, 3361–3364.

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(31) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.

mesh silica gel from E. Merck. Infrared spectra were recorded with a Perkin-Elmer 377 spectrophotometer. The source of the anhydrous solvents was as follows: tetrahydrofuran was obtained by distillation after reflux with potassium–benzophenone; toluene was dried by distillation after it had been refluxed in the presence of sodium; acetonitrile, dioxane, dimethylformamide (DMF), and pyridine were refluxed over CaH_2 and distilled; dichloromethane was refluxed over phosphorus pentoxide and distilled; methanol was dried with magnesium pieces. Methanesulfonyl chloride and benzoyl chloride were distilled before use. Thymine and [[(4-methylphenyl)oxy]thiocarbonyl chloride were purchased from Fluka, 1,8-diazabicyclo[5.4.0]undec-7-ene from Merck. Abbreviations used are AIBN (2,2'-azobis(2-methylpropionitrile), DEAD (diethyl azodicarboxylate), EA (ethyl acetate), FC (flash chromatography), MC (dichloromethane), PE (petroleum ether), t_R (reaction time), TPP (triphenylphosphine), TPPO (triphenylphosphine oxide).

Synthesis of the Nucleosides 18A–E. The 3-*O*-mesyl-1,2-*O*-isopropylidene-protected carbohydrate (10 mmol) was dissolved in CH_2Cl_2 (50 mL). Then Ac_2O–AcOH 2:1 (200 mL) was added to 0 °C (ice bath). After addition of two drops of concentrated sulfuric acid from a Pasteur pipette, the reaction was stored at 4 °C for 16 h. In the case of incomplete reaction more concentrated sulfuric acid was added, and the mixture was stored at room temperature. After complete reaction (TLC control), the mixture was poured into ice-cold water and stirred for 30 min. The product was extracted with cold CH_2Cl_2 (3 × 100 mL). The organic phase was transfered into a separatory funnel, and ice–water (200 mL) was added. Cold concentrated NaOH solution (50% in water) was added very slowly (ice was used for cooling) the water phase was alkaline (pH control) after shaking well. The organic phase was separated, washed with brine (100 mL), then dried with Na_2SO_4 and concentrated. The α- and the β-anomers could be separated by flash chromatography: **17A** PE–EA 1:5, ratio of α:β = 1:3; **17B** PE–EA 1:2, ratio of α:β = 1:5; **17C** PE–EA 1:3, ratio of α:β = 3:1; **17D** PE–EA 1:3, ratio of α:β = 1:3; **17E** PE–EA 1:2, ratio of α:β = 3:1. The purified (flash chromatography) anomeric mixture of 1,2-di-*O*-acetyl-3-*O*-mesyl sugar derivatives (10 mmol) was dissolved in dry acetonitrile (50 mL). Thymine (12 mmol, 1.51 g), hexamethyldisilazane (12 mmol, 2.53 mL), chlorotrimethylsilane (14 mmol, 1.78 mL), and trifluoromethanesulfonic acid (14 mmol, 1.24 mL) were added, and the suspension was heated to reflux.[25] After the reaction was completed, the solution was concentrated to the half of the volume, poured into saturated $NaHCO_3$ solution, and stirred for 30 min. The organic phase was separated, and the water phase was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, concentrated, and purified by flash chromatography. The appropriate reaction time (t_R) and the solvent system used for flash chromatography (FC) will be given for the corresponding compounds.

1-(2'-*O*-Acetyl-6'-*O*-benzoyl-5'-deoxy-3'-*O*-mesyl-β-D-allofuranosyl)thymine (18A): reaction time (t_R) 4 h; flash chromatography (FC) PE–EA 1:1; yield 46%; colorless crystals, mp 132–132.5 °C (EA–PE); R_f = 0.60 (EA); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.90 (d, 3, J (CH_3, 6) = 1.0 Hz, 5-CH_3), 2.17 (s, 3, CH_3CO), 2.13–2.45 (m, 2, 5'-H_a, 5'-H_b), 3.10 (s, 3, OSO_2CH_3), 4.32 (ddd, 1, $J_{3',4'}$ = 7.0 Hz, J = 4.0, 9.0 Hz, 4'-H), 4.38–4.60 (m, 2, 6'-H_a, 6'-H_b), 5.28 (t, 1, $J_{1',2'} = J_{2',3'}$ = 7.0 Hz, 2'-H), 5.55–5.63 (m, 2, 1'-H, 3'-H), 6.98 (d, 1, 6-H), 7.44 (m, 2, aromatic-H), 7.57 (m, 1, aromatic-H), 8.04 (m, 2, aromatic-H), 9.40 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.216, 20.460, 31.293, 37.923, 60.912, 72.518, 77.547, 78.693, 91.265, 111.726, 128.292, 129.491, 129.865, 132.988, 137.395, 150.292, 163.746, 166.336, 169.910. Anal. ($C_{21}H_{24}N_2O_{10}S$) C, H, N.

1-(2'-*O*-Acetyl-5',6'-di-*O*-benzoyl-3'-*O*-mesyl-β-D-allofuranosyl)thymine (18B): t_R 12 h; FC PE–EA 1:1; yield 68.5%, colorless crystals, mp 146–148 °C (EA–PE), R_f = 0.75 (PE–EA 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (d, 3, J (CH_3, 6) = 1.0 Hz, 5-CH_3), 2.17 (s, 3, CH_3CO), 3.05 (s, 3, OSO_2CH_3), 4.57 (dd, 1, $J_{6'a,6'b}$ = 12.0 Hz, $J_{6'a,5'}$ = 6.0 Hz, 6'-H_a), 4.65 (dd, 1, $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 4.5 Hz, 4'-H), 4.82 (dd, 1, $J_{6'b,5'}$ = 4.5 Hz, 6'-H_b), 5.48 (dd, $J_{1',2'}$ = 6.5 Hz, $J_{2',3'}$ = 6.0 Hz, 2'-H), 5.67 (dd, 1, 3'-H), 5.80 (dt, 1, 5'-H), 5.98 (d, 1, 1'-H), 6.85 (d, 1, 6-H), 7.40–7.65 (m, 6, aromatic-H), 8.00–8.15 (m, 4, aromatic-H), 8.55 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.897, 20.466, 38.338, 62.271, 70.960, 71.807, 75.590, 81.124, 87.567, 112.239, 128.445, 128.733, 128.810, 129.271, 129.678, 129.843, 133.314, 133.927, 135.393, 150.474, 163.463, 165.223, 165.980, 169.956. Anal. ($C_{28}H_{28}N_2O_{12}S$) C, H, N.

1-(2'-*O*-Acetyl-5',6'-di-*O*-benzyl-3'-*O*-mesyl-α-L-talofuranosyl)thymine (18C): t_R 8 h; FC PE–EA 1:1; yield 69%, white foam; R_f = 0.22 (PE–EA 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 3, J (CH_3, 6) = 1.0 Hz, 5-CH_3), 2.14 (s, 3, CH_3CO), 3.13 (s, 3, OSO_2CH_3), 4.63 (dd, 1, $J_{3',4'}$ = 7.0 Hz, $J_{4',5'}$ = 3.0 Hz, 4'-H), 4.71 (ABX system, 2, $J_{6'a,6'b}$ = 12.0 Hz, $J_{6'a,5'}$ = 6.0 Hz, $J_{6'b,5'}$ = 7.0 Hz, 6'-H_a, 6'-H_b), 5.40–5.46 (m, 2, 2'-H, 3'-H), 5.85 (m, 1, 5'-H), 5.87 (d, 1, $J_{1',2'}$ = 5.0 Hz, 1'-H), 7.18 (d, 1, 6-H), 7.37–7.47 (m, 4, aromatic-H), 7.52–7.58 (m, 2, aromatic-H), 7.96–8.08 (m, 4, aromatic-H), 9.66 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.334, 20.448, 38.046, 62.619, 69.380, 72.339, 74.915, 80.436, 88.954, 112.139, 128.402, 128.564, 128.821, 129.222, 129.654, 129.771, 133.311, 133.720, 135.855, 150.343, 163.408, 165.696, 165.948, 169.843. Anal. ($C_{28}H_{28}N_2O_{12}S$) C, H, N.

1-(2'-*O*-Acetyl-5'-benzoyl-6'-deoxy-3'-*O*-mesyl-β-D-allofuranosyl)thymine (18D): t_R 10 h; FC PE–EA 1:1; yield 68%, white foam; R_f = 0.24 (PE–EA 1:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 1.52 (d, 3, J (CH_3, 5') = 6.5 Hz, CH_3), 2.18 (s, 3, CH_3CO), 3.15 (s, 3, OSO_2CH_3), 4.42 (dd, 1, $J_{3',4'}$ = 2.5 Hz, $J_{4',5'}$ = 6.0 Hz, 4'-H), 5.42 (m, 1, 5'-H), 5.48 (dd, 1, 2'-H), 5.62 (dd, 1, $J_{2',3'}$ = 2.2 Hz, 3'-H), 6.21 (d, 1, $J_{1',2'}$ = 7.2 Hz, 1'-H), 6.75 (d, 1, 6-H), 7.45–7.57 (m, 2, aromatic-H), 7.59–7.69 (m, 1, aromatic-H), 8.10–8.18 (m, 2, aromatic-H), 8.75 (s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.359, 15.913, 20.201, 38.414, 70.158, 71.235, 74.283, 84.260, 84.653, 112.051, 128.668, 128.881, 129.340, 133.585, 133.824, 150.199, 162.857, 164.898, 169.666. Anal. ($C_{21}H_{24}N_2O_{14}S$) C, H, N.

1-(2'-*O*-Acetyl-5'-*O*-benzoyl-6'-deoxy-3'-*O*-mesyl-α-L-talofuranosyl)thymine (18E): t_R 7 h; FC PE–EA 1:1; yield 53%, white foam; R_f = 0.79 (EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, 3, J (CH_3, 5') = 6.5 Hz, CH_3), 1.87 (d, 3, J (5-CH_3, 6) = 0.5 Hz, 5-CH_3), 2.15 (s, 3, CH_3CO), 3.10 (s, 3, OSO_2CH_3), 4.38 (dd, 1, $J_{5',4'}$ = 3.0 Hz, $J_{4',3'}$ = 4.5 Hz, 4'-H), 5.33 (dd, 1, $J_{2',3'}$ = 6.5 Hz, 3'-H), 5.42 (t, 1, 2'-H), 5.50 (m, 1, 5'-H), 6.02 (d, 1, $J_{1',2'}$ = 6.5 Hz, 1'-H), 7.25 (d, 1, 6-H), 7.42–7.48 (m, 4, aromatic-H), 7.54–7.60 (m, 1, aromatic-H), 8.02–8.07 (m, 2, aromatic-H), 9.62 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.389, 16.494, 20.444, 38.207, 69.006, 72.376, 75.416, 83.757, 87.447, 112.130, 128.555, 129.495, 133.447, 135.395, 150.440, 163.515, 165.712, 169.845. Anal. ($C_{21}H_{24}N_2O_{10}S$) C, H, N.

Synthesis of 2,3'-Anhydronucleoside Derivatives 19A–E. The 2'-*O*-acetyl-3'-*O*-mesyl derivatives of the corresponding nucleosides **18A–E** (0.71 mmol) were dissolved in dry toluene (10 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.076 mL, 0.51 mmol) was added, and the mixture was kept at 90 °C. The required reaction time will be given for the corresponding derivative. After the reaction was completed (TLC control: $CHCl_3$–MeOH 5:1, or $CHCl_3$–acetone 1:3), palmitic acid (43.5 mg, 0.34 mmol) was added. After 15 min the solvent was removed and the residue was applied onto silica gel. The column was eluted first with 500 mL of $CHCl_3$, then 500 mL of $CHCl_3$:MeOH 39:1, 500 mL of $CHCl_3$–MeOH 19:1, and then the product was eluted with $CHCl_3$–MeOH 9:1.

2,3'-Anhydro-1-(6'-*O*-benzoyl-5'-deoxy-β-D-glucofuranosyl)thymine (19A): t_R 2 h; yield 83%; colorless crystals, mp 218–223 °C ($CHCl_3$–MeOH); R_f = 0.58 ($CHCl_3$–MeOH 5:1); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.75 (d, 3, J (5-CH_3, 6) = 0.8 Hz, 5-CH_3), 1.94 (m, 1, 5'-H_a), 2.09 (m, 1, 5'-H_b), 4.31–4.46 (m, 2, 6'-H_a, 6'-H_b), 4.61 (ddd, 1, J = 2.2 Hz, J = 6.0, 9.0 Hz, 4'-H), 4.75 (br s, 1, 2'-H), 5.02 (br s, 1, 3'-H), 5.52 (s, 1, 1'-H), 6.38 (br s, 1, 2'-OH, D_2O exchangeable), 7.56 (d, 1, 6-H), 7.51 (m, 2, aromatic-H), 7.65 (m, 1, aromatic-H), 7.95 (m, 2, aromatic-H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 13.102, 29.006, 61.755, 69.965, 80.143, 80.777, 89.288, 116.237, 128.852, 129.259, 129.726, 133.463, 137.030, 153.205, 165.699. Anal. ($C_{18}H_{18}N_2O_6$) C, H, N.

2,3'-Anhydro-1-(5',6'-di-*O*-benzoyl-β-D-glucofuranosyl)thymine (19B): t_R 1.5 h (the reaction was stopped after the first appearance of **19F**); yield 63%; colorless crystals, mp 209–214 °C; R_f = 0.65 ($CHCl_3$–MeOH 5:1); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.60 (s, 3, 5-CH_3), 4.55 (dd, 1, $J_{6'a,6'b}$ = 12.0 Hz, $J_{6'a,5'}$ = 6.0 Hz, 6'-H_a), 4.75–4.80 (m, 2, $J_{6'b,5'}$ = 2.5 Hz, 6'H_b, 2'-H), 4.85 (dd, 1, $J_{3',4'}$ = 2.0 Hz, $J_{4',5'}$ = 9.0 Hz, 4'-H), 5.12 (d, 1, 3'-H), 5.56 (m, 1,

5'-H), 5.60 (s, 1, 1'-H), 6.54 (d, 1, $J_{OH,2'}$ = 4.0 Hz, 2'-OH), 7.47 (s, 1, 6-H), 7.40–7.54 (m, 4, aromatic-H), 7.58–7.67 (m, 2, aromatic-H), 7.85–7.95 (m, 4, aromatic-H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 12.902, 63.014, 68.674, 69.797, 78.545, 80.470, 89.224, 116.155, 128.652, 128.771, 129.121, 129.326, 133.523, 136.535, 152.718, 164.689, 165.278, 170.882. Anal. ($C_{25}H_{22}N_2O_8$) C, H, N.

2,3'-Anhydro-1-(5',6'-di-*O*-benzoyl-α-L-idofuranosyl)thymine (19C): t_R 1.5 h; yield 50%, colorless crystals, mp 218–221 °C (MeOH–$CHCl_3$); R_f = 0.66 ($CHCl_3$–MeOH 5:1); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.72 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 4.56 (dd, 1, $J_{6'a,6'b}$ = 12.0 Hz, $J_{6'a,5'}$ = 7.0 Hz, 6'-H_a), 4.67 (dd, 1, $J_{6'b,5'}$ = 4.0 Hz, 6'H_b), 4.77 (d, 1, $J_{3',4'}$ = 2.0 Hz, 3'H), 4.81 (dd, 1, $J_{4',5'}$ = 8.0 Hz, 4'-H), 5.18 (s, 1, 2'-H), 5.61 (s, 1,1'-H), 5.66 (m, 1,5'-H), 6.55 (br s, 1, D_2O-exchangeable, 2'-OH), 7.58 (d, 1, 6-H), 7.38–7.50 (m, 4, aromatic-H), 7.56–7.65 (m, 2, aromatic-H), 7.77–7.89 (m, 4, aromatic-H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 12.995, 63.393, 69.553, 69.891, 78.991, 81.210, 89.289, 116.226, 128.506, 128.742, 128.938, 129.006, 129.136, 133.480, 133.540, 136.719, 152.734, 164.668, 165.192. Anal. ($C_{25}H_{22}N_2O_8$) C, H, N.

2,3'-Anhydro-1-(5'-*O*-benzoyl-6'-deoxy-β-D-glucofuranosyl)thymine (19D): t_R 7 h; yield 81%; R_f = 0.57 ($CHCl_3$–MeOH 5:1); mp 258–261 °C (MeOH–$CHCl_3$); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.38 (d, 3, J (CH_3, 5') = 7.0 Hz, CH_3), 1.61 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 4.42 (dd, 1, $J_{3',4'}$ = 2.5 Hz, $J_{4',5'}$ = 7.0 Hz, 4'-H), 4.72 (dd, after D_2O-exchange d, 1, $J_{2',3'}$ = 0.8 Hz, 2'-H), 5.06 (br s, 1, 3'-H), 5.22 (m, 1, 5'-H), 5.55 (s, 1, 1'-H), 6.48 (d, 1, D_2O exchangeable, $J_{2',OH}$ = 6.0, 2'-OH), 7.66 (d, 1, 6-H), 7.40–7.50 (m, 2, aromatic-H), 7.58–7.63 (m, 1, aromatic-H), 7.82–7.87 (m, 2, aromatic-H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 12.884, 16.730, 67.596, 69.854, 78.382, 84.106, 89.305, 116.125, 128.590, 129.166, 129.198, 133.310, 136.553, 152.903, 164.813, 170.896. Anal. ($C_{18}H_{18}N_2O_6$) C, H, N.

2,3'-Anhydro-1-(5'-*O*-benzoyl-6'-deoxy-α-L-idofuranosyl)thymine (19E): t_R 1.5 h; yield 95%; colorless crystals, mp 222–225 °C ($CHCl_3$–MeOH); R_f = 0.45 ($CHCl_3$–MeOH 5:1); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.36 (d, 3, J (CH_3, 5') = 6.5 Hz, CH_3), 1.74 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 4.56 (dd, 1, $J_{5',4'}$ = 8.0 Hz, $J_{4',3'}$ = 2.0 Hz, 4'-H), 4.76 (s, 1, 3'-H), 5.08 (s, 1, 2'-H), 5.14 (m, 1, 5'-H), 5.56 (s, 1, 1'-H), 6.55 (br s, 1, D_2O-exchangeable, 2'-OH), 7.57 (d, 1, 6-H), 7.44–7.50 (m, 2, aromatic-H), 7.60–7.66 (m, 1, aromatic-H), 7.84–7.90 (m, 2, aromatic-H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 12.996, 16.808, 69.870, 69.893, 78.909, 84.915, 89.487, 116.186, 128.643, 129.175, 129.472, 133.442, 136.950, 152.916, 164.861. Anal. ($C_{18}H_{18}N_2O_6$) C, H, N.

2,3'-Anhydro-1-(6'-*O*-benzoyl-β-D-glucofuranosyl)thymine (19F). Compound **19F** could be isolated as a side product in the synthesis of compound **19B**. After refluxing for 16 h the yield was 40%: colorless crystals, mp 235–240 °C dec; R_f = 0.45 ($CHCl_3$–MeOH 5:1); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.74 (s, 3, 5-CH_3), 3.80 (m, 1, 5'-H), 4.23 (dd, 1, $J_{6'a,6'b}$ = 12.0 Hz, $J_{6'a,5'}$ = 5.5 Hz, 6'-H_a), 4.35–4.47 (m, 2, 6'H_b, 4'-H), 4.75 (br s, 1, 2'-H), 4.94 (d, 1, 3'-H), 5.58 (s, 1, 1'-H), 5.76 (d, 1, $J_{OH,5'}$ = 6.0 Hz, D_2O-exchangeable, 5'-OH), 6.44 (d, 1, $J_{OH,2'}$ = 4.0 Hz, D_2O-exchangeable, 2'-OH), 7.56 (s, 1, 6-H), 7.46–7.70 (m, 3, aromatic-H), 7.94–8.01 (m, 2, aromatic-H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 1.302, 66.238, 66.688 (C'-6), 69.583, 79.131, 82.837, 89.381, 116.033, 128.667, 129.257, 129.650, 133.317, 136.808, 153.085, 165.601, 170.889. Anal. ($C_{18}H_{18}N_2O_7$) C, H, N.

Synthesis of 2,3'-Anhydro-2'-deoxynucleosides 21A–E. The 2,3'-anhydronucleoside (0.59 mmol) and (dimethylamino)pyridine (0.187 g, 1.53 mmol) were dissolved in dry acetonitrile (80 mL). [(4-Methylphenyl)oxy]thiocarbonyl chloride (0.118, 0.77 mmol) was added at once with a syringe. The reaction was stirred overnight, concentrated to one-third of the volume, and partitioned between H_2O and CH_2Cl_2. The organic phase was separated, and the water phase was extracted with CH_2Cl_2 (6 × 50 mL). The combined organic phases were washed with 10% HCl solution and with water and dried with Na_2SO_4, concentrated, and purified (silica gel). For the purification of the raw material we used the following solvent systems: **20A** $CHCl_3$–acetone 9:1; **20B** MC–EA 5:2; **20C** MC–EA 5:2; **20D** $CHCl_3$–acetone 19:1; **20E** $CHCl_3$–acetone 19:1. For experimental details see supplamentary material. The 2,3'-anhydro-2'-*O*-[(4-methylphenyl)oxy]thiocarbonyl nucleoside derivatives **20A–E** (0.683 mmol) were dissolved in toluene (50 mL). Tributyltin hydride (0.362 mL, 1.266 mmol) and a catalytical amount of AIBN (20 mg) were added.[19] Then the reaction was kept at 120 °C for 6 h. After the reaction was completed, the mixture was allowed to cool down and concentrated. The residue was purified from the tin contaminations by flash chromatography (silica gel). First, EA was used, and then the product was eluted with $CHCl_3$–MeOH 5:1.

2,3'-Anhydro-1-(6'-*O*-benzoyl-2',5'-dideoxy-β-D-glucofuranosyl)thymine (21A): yield 89%; white foam, R_f = 0.58 ($CHCl_3$–MeOH 5:1); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.74 (d, 3, J (5-CH_3, 6) = 1.0 Hz), 1.88 (m, 1, 5'-H_a), 2.05 (m, 1, 5'-H_b), 2.60 (dd, 1, $J_{2'a,2'b}$ = 12.0 Hz, $J_{2'a,3'}$ = 2.0 Hz, 2'-H_b, 2'-H_a under DMSO signal), 4.35 (m, 3, 4'-H, 6'-H_a, 6'-H_b), 5.25 (br s, 1, 3'-H), 5.82 (d, 1, $J_{1',2'a}$ = 3.0 Hz, 1'-H), 7.58 (d, 1, 6-H), 7.40–8.00 (m, 5, aromatic-H); ^{13}NMR (100 MHz, d_6-DMSO) δ 13.000, 29.519, 32.865, 61.590, 77.868, 82.215, 86.599, 116.034, 128.720, 129.204, 129.636, 133.354, 136.714, 153.523, 165.617, 170.948. Anal. ($C_{18}H_{18}N_2O_5$) C, H, N.

2,3'-Anhydro-1-(5',6'-di-*O*-benzoyl-2'-deoxy-β-D-glucofuranosyl)thymine (21B): yield 85%; colorless crystals, mp 235–240 °C (MeOH), R_f = 0.37 ($CHCl_3$–MeOH 5:1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.79 (d, 3, J (CH_3, 6) = 2.0 Hz, 6-CH_3), 2.54 (ddd, 1, $J_{2'a,2'b}$ = 12.0 Hz, $J_{2'a,1'}$ = 4.0 Hz, $J_{2'a,3'}$ = 2.5 Hz, 2'-Ha), 2.62 (dd, 1, $J_{2'b,3'}$ = 2.0 Hz, 2'-H_b), 4.60 (dd, 1, $J_{6'a,6'b}$ = 13.0 Hz, $J_{6'a,5'}$ = 5.0 Hz, 6'-H_a), 4.64 (dd, 1, $J_{3',4'}$ = 2.5 Hz, $J_{4',5'}$ = 9.0 Hz, 4'-H), 4.81 (dd, 1, $J_{6'b,5'}$ = 3.0 Hz, 6'-H_b), 5.28 (t, 1, 3'-H), 5.55 (m, 2, 1'-H, 5'-H), 6.93 (d, 1, 6-H), 7.40–7.46 (m, 4, aromatic-H), 7.54–7.60 (m, 2, aromatic-H), 7.96–8.01 (m, 4, aromatic-H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 13.299, 34.013, 63.219, 69.321, 76.661, 82.924, 87.861, 118.880, 128.769, 128.780, 129.434, 129.859, 130.000, 133.568, 133.730, 135.178, 153.368, 165.182, 166.130, 171.678. Anal. ($C_{25}H_{22}N_2O_7$) C, H, N.

2,3'-Anydro-1-(5',6'-di-*O*-benzoyl-2'-deoxy-α-L-idofuranosyl)thymine (21C): yield 94%, colorless crystals, mp 213–218 °C ($CHCl_3$–PE); R_f = 0.41 ($CHCl_3$–MeOH 5:1); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.65 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 2.47 (dd, 1, $J_{2'a,2'b}$ = 13.0 Hz, $J_{2'a,1'}$ = 2.0 Hz, 2'-H_a), 2.55 (d, 1, 2'-H_b), 4.47 (dd, 1, $J_{6'a,6'b}$ = 12.0 Hz, $J_{6'a,5'}$ = 6.5 Hz), 4.58 (m, 2, 6'-Hb, 4'), 5.44 (s, 1, 3'-H), 5.50 (m, 1, 5'-H), 5.82 (d, 1, 1'-H), 7.50 (d, 1, 6-H), 7.30–7.59 (m, 6, aromatic-H), 7.68–7.84 (m, 4, aromatic-H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 12.974, 32.989, 63.203, 69.932, 76.826, 82.527, 86.711, 116.116, 128.516, 128.693, 128.924, 129.040, 129.113, 129.191, 133.478, 133.516, 136.536, 153.135, 164.641, 165.208, 170.623. Anal. ($C_{25}H_{22}N_2O_7$), C, H, N.

2,3'-Anhydro-1-(5'-*O*-benzoyl-2',6'-dideoxy-β-D-glucofuranosyl)thymine (21D): yield 80%; colorless crystals, mp 233–235 °C (MeOH–EA); R_f = 0.43 ($CHCl_3$–MeOH 5:1); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.37 (d, 3, J (CH_3, 5') = 6.5 Hz, CH_3), 1.64 (s, 3, 5-CH_3), 2.50 (m, 1, $J_{2'a,2'b}$ = 13.0 Hz, 2'-H_a), 2.57 (d, 1, 2'-H_b), 4.40 (dd, 1, $J_{3',4'}$ = 2.0 Hz, $J_{4',5'}$ = 7.5 Hz, 4'-H), 5.12 (m, 1, 5'-H), 5.44 (d, 1, 3'-H), 5.86 (d, 1, $J_{1',2'a}$ = 4.5 Hz, 1'-H), 7.49 (s, 1, 6-H), 7.43–7.47 (m, 2, aromatic-H), 7.46–7.65 (m, 1, aromatic-H), 7.85–7.90 (m, 2, aromatic-H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 12.905, 16.791, 32.759, 67.911, 76.262, 85.500, 86.816, 116.063, 128.623, 129.203, 133.362, 136.445, 153.348, 164.776, 170.990. Anal. ($C_{18}H_{18}N_2O_5$) C, H, N.

2,3'-Anhydro-1-(5'-*O*-benzoyl-2',6'-dideoxy-α-L-idofuranosyl)thymine (21E): yield 77%; colorless crystals, mp 258–264 °C (MeOH); R_f = 0.37 ($CHCl_3$–MeOH 5:1); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.36 (d, 3, J (CH_3, 5') = 6.5 Hz, CH_3), 1.74 (d, 3, J (5-CH_3, 6) = 1.5 Hz, 5-CH_3), 2.51 (dt, 1, $J_{2'a,2'b}$ = 13.0 = Hz, $J_{2'a,1'}$ = $J_{2'a,3'}$ = 4.0 Hz, 2'-Ha), 2.73 (dd, 1, $J_{2'b,3'}$ = 1.5 Hz, 2'-H_b), 4.40 (dd, 1, $J_{3',4'}$ = 2.5 Hz, $J_{4',5'}$ = 8.5 Hz, 4'-H), 5.06 (dq, 1, 5'-H), 5.42 (ddd, 1, 3'-H), 5.85 (d, 1, 1'-H), 7.57 (d, 1, 6-H), 7.45–7.50 (m, 2, aromatic-H), 7.61–7.66 (m, 1, aromatic-H), 7.84–7.88 (m, 2, aromatic-H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 13.020, 16.768, 32.955, 70.270, 76.808, 86.240, 86.900, 116.064, 128.671, 129.142, 129.440, 133.466, 136.795, 153.332, 164.834, 170.866. Anal. ($C_{18}H_{18}N_2O_5$) C, H, N.

Synthesis of 3'-Azido-2',3'-dideoxynucleosides Derivatives 22A–G. The 2,3'-anhydro-2'-deoxynucleoside derivative (2.213 mmol), LiN_3 (1 g, 20.4 mmol), and benzoic acid (0.27 g, 2.213 mmol) were dissolved in dry DMF (50 mL).[28] The reaction mixture was kept at 120 °C (oil bath temperature) for 16 h. Then the solvent was removed in vacuo, and the residue was dissolved in H_2O (5 mL) and CH_2Cl_2 (50 mL). The organic phase was separated, and the water phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried with Na_2SO_4

and purified by flash chromatography.

1-(3′-Azido-6′-*O*-benzoyl-2′,3′,5′-trideoxy-β-D-allofuranosyl)thymine (22A): FC EA–PE 1:1; yield 50%; foam, R_f = 0.80 (EA); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.93 (d, 3, J (5-CH_3, 6) = 1.2 Hz), 2.21 (m, 2, 5′-H_a, 5′-H_b), 2.43 (m, 2, 2′-H_a, 2′-H_b), 4.10 (m, 2, 6′-H_a, 6′-H_b), 4.44 (m, 1, 4′-H), 4.56 (dt, 1, $J_{3',4'}$ = 11.0 Hz, $J_{2'a,3'}$ = $J_{2'b,3'}$ = 6.0 Hz, 3′-H), 6.05 (t, 1, $J_{1',2'}$ = 6.0 Hz, 1′-H), 7.11 (d, 1, 6-H), 7.45 (m, 2, aromatic-H), 7.75 (m, 1, aromatic-H), 8.05 (m, 2, aromatic-H), 8.75 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.363, 32.604, 36.903, 61.231, 63.302, 80.765, 85.415, 111.252, 128.174, 128.307, 129.410, 129.755, 129.755, 133.032, 135.713, 150.220, 164.087, 166.260; IR (CH_2Cl_2) 2115 (N_3) cm^{-1}. Anal. ($C_{18}H_{19}N_5O_5$) C, H, N.

1-(3′-Azido-5′,6′-di-*O*-benzoyl-2′,3′-dideoxy-β-D-allofuranosyl)thymine (22B). Opening of the 2,3′-anhydro bridge of **21B** gave two products, which could be separated by FC (PE–EA 1:1). The more lipophilic compound **22B** (yield 45%; R_f = 0.85 (EA)) had both benzoyl groups. The other compound **22F** (yield 41%; R_f = 0.66 (EA)) had only one benzoyl group at the 6′-O position as indicated by NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 2.36 (ddd, 1, $J_{2'a,2'b}$ = 14.0 Hz, $J_{2'a,1'}$ = 7.0 Hz, $J_{2'a,3'}$ = 7.0 Hz, 2′-H_a), 2.49 (ddd, 1, $J_{2'b,1'}$ = 6.0 Hz, $J_{2'b,3'}$ = 3.0 Hz, 2′-H_b), 4.24 (dd, 1, $J_{4',5'}$ = 4.0 Hz, $J_{4',3'}$ = 5.5 Hz, 4′-H), 4.52 (m, 1, 3′-H), 4.55 (dd, 1, $J_{6'a,6'b}$ = 12.0 Hz, $J_{2'a,5'}$ = 6.5 Hz, 6′-H_a), 4.84 (dd, 1, $J_{6'b,5'}$ = 4.0 Hz, 6′-H_b), 5.74 (m, 1, 5′-H), 6.21 (dd, 1, 1′-H), 7.05 (d, 1, 6-H), 7.41–7.50 (m, 4, aromatic-H), 7.54–7.64 (m, 2, aromatic-H), 7.98–8.09 (m, 4, aromatic H), 9.31 (br s, 1,3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.138, 37.014, 61.120, 63.144, 71.375, 82.418, 85.309, 111.886, 128.547, 128.796, 128.915, 129.360, 129.697, 129.789, 133.407, 133.941, 134.904, 150.200, 163.590, 165.519, 166.094; IR (CH_2Cl_2) 2118 (N_3) cm^{-1}. Anal. ($C_{25}H_{23}N_5O_7$) C, H, N.

1-(3′-Azido-5′,6′-di-*O*-benzoyl-2′,3′-dideoxy-α-L-talofuranosyl)thymine (22C). Opening of the 2,3′-anhydro bridge of **21C** gave two products, which could be separated by FC (PE–EA 1:1). The more lipophilic compound **22C** (yield 40%; R_f = 0.19 (PE–EA 1:1)) had both benzoyl groups. The other compound **22G** (yield 41%; R_f = 0.12 (PE–EA 1:1)) had only one benzoyl group at the 6′-O position as indicated by NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (d, 3, J (5-CH_3, 6) = 1.5 Hz, 5-CH_3), 2.22 (ddd, 1, $J_{2'a,2'b}$ = 14.0 Hz, $J_{2'a,1'}$ = 7.0 Hz, $J_{2'a,3'}$ = 7.0 Hz, 2′-H_a), 2.47 (ddd, 1, $J_{2'b,1'}$ = 6.5 Hz, $J_{2'b,3'}$ = 5.0 Hz, 2′-H_b) 4.23 (dd, 1, $J_{4',5'}$ = 3.0 Hz, $J_{4',3'}$ = 5.0 Hz, 4′-H), 4.29 (dt, 1, 3′-H), 4.66 (dd, 1, $J_{6'a,6'b}$ = 12.0 Hz, $J_{6'a,5'}$ = 4.5 Hz, 6′-H_a), 4.75 (dd, 1, $J_{6'b,5'}$ = 7.5 Hz, 6′-H_b), 5.82 (ddd, 1, 5′-H), 6.25 (dd, 1, 1′-H), 7.34 (d, 1, 6-H), 7.38–7.65 (m, 6, aromatic-H), 7.95–8.06 (m, 4, aromatic-H), 8.50 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.440, 37.483, 60.546, 63.153, 70.704, 82.529, 84.666, 111.608, 128.438, 128.472, 128.502, 128.677, 128.754, 128.814, 129.239, 129.642, 129.708, 133.346, 133.952, 134.688, 150.098, 163.519, 165.469, 165.834, 166.008; IR (CH_2Cl_2) 2115 (N_3) cm^{-1}. Anal. ($C_{25}H_{23}N_5O_7$) C, H, N.

1-(3′-Azido-5′-*O*-benzoyl-2′,3′,6′-trideoxy-β-D-allofuranosyl)thymine (22D): FC PE–EA 1:1; yield 56%; foam, R_f = 0.19 (PE–EA 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 1.48 (d, 3, J (CH_3, 5′) = 7.0 Hz, CH_3), 2.25 (ddd, 1, $J_{2'a,2'b}$ = 14.0 Hz, $J_{2'a,1'}$ = 8.0 Hz, $J_{2'a,3'}$ = 8.0 Hz, 2′-H_a), 2.56 (ddd, 1, $J_{2'b,1'}$ = 6.0 Hz, $J_{2'b,3'}$ = 4.0 Hz, 2′-H_b), 4.02 (t, 1, $J_{3',4'}$ = 4.0 Hz, $J_{4',5'}$ = 4.0 Hz, 4′-H), 4.45 (dt, 1, 3′-H), 5.48 (m, 1, 5′-H), 6.21 (dd, 1, 1′-H), 6.94 (d, 1, 6-H), 7.46–7.65 (m, 3, aromatic-H), 8.02–8.06 (m, 2, aromatic-H), 8.98 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.871, 16.637, 37.643, 60.181, 70.177, 84.341, 85.799, 111.562, 128.201, 128.784, 129.452, 133.724, 134.319, 150.060, 163.369, 165.371; IR (CH_2Cl_2) 2113(N_3) cm^{-1}. Anal. ($C_{18}H_{19}N_5O_5$) C, H, N.

1-(3′-Azido-5′-*O*-benzoyl-2′,3′,6′-trideoxy-α-L-talofuranosyl)thymine (22E): FC PE–EA 1:1; yield 58%; foam, R_f = 0.85 (EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, 3, J (CH_3, 5′) = 7.0 Hz, CH_3), 1.89 (d, 3, J (5-CH_3, 6) = 1.5 Hz, 5-CH_3), 2.23 (m, 1, $J_{2'a,2'b}$ = 14.0 Hz, $J_{2'a,1'}$ = 7.0 Hz, $J_{2'a,3'}$ = 7.0 Hz, 2′-H_a), 2.48 (ddd, 1, $J_{2'b,1'}$ = 6.0 Hz, $J_{2'b,3'}$ = 4.5 Hz, 2′-H_b), 3.99 (dd, 1, $J_{3',4'}$ = 5.0 Hz, $J_{4',5'}$ = 4.0 Hz, 4′-H), 4.18 (ddd, 1, 3′-H), 5.48 (m, 1, 5′-H), 6.24 (dd, 1, 1′-H), 7.40 (d, 1, 6-H), 7.44–7.50 (m, 2, aromatic-H), 7.59–7.64 (m, 1, aromatic-H), 8.01–8.04 (m, 2, aromatic-H), 8.88 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.508, 17.080, 29.670, 37.767, 60.757, 69.900, 84.529, 85.772, 111.440, 128.677, 129.496, 129.568, 133.628, 134.825, 150.042, 163.467, 165.841; IR (CH_2Cl_2) 2114(N_3) cm^{-1}. Anal. ($C_{18}H_{19}N_5O_5$) C, H, N.

1-(3′-Azido-2′,3′-dideoxy-6′-*O*-benzoyl-β-D-allofuranosyl)thymine (22F): yield 41%; white foam, R_f = 0.66 (EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 2.37 (ddd, 1, $J_{2'a,2'b}$ = 14.0 Hz, $J_{2'a,1'}$ = 7.0 Hz, $J_{2'a,3'}$ = 4.0 Hz, 2′-H_a), 2.52 (ddd, 1, $J_{2'b,1'}$ = 7.0 Hz, $J_{2'b,3'}$ = 7.0 Hz, 2′-H_b), 3.96 (br s, 1, 5′-OH, D_2O-exchangeable), 4.01 (t, 1, $J_{4',5'}$ = $J_{4',3'}$ = 4.0 Hz, 4′-H), 4.25 (br s, after D_2O-exchange dt, 1, 5′-H), 4.41 (dd, 1, $J_{6'a,6'b}$ = 12.0 Hz, $J_{2'a,5'}$ = 6.0 Hz, 6′-H_a), 4.53–4.60 (m, 2, $J_{6'b,5'}$ = 4.0 Hz, 3′-H, 6′-H_b), 6.21 (t, 1, 1′-H), 7.35 (d, 1, 6-H), 7.43–7.49 (m, 2, aromatic-H), 7.56–7.62 (m, 1, aromatic-H), 8.03–8.08 (m, 2, aromatic-H), 9.53 (br s, 1,3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.451, 37.033, 60.608, 66.103, 70.296, 84.777, 86.910, 111.483, 128.543, 129.430, 129.763, 133.481, 136.821, 150.505, 163.912, 166.883; IR (CH_2Cl_2) 2115 (N_3) cm^{-1}. Anal. ($C_{18}H_{18}N_5O_7$) C, H, N.

1-(3′-Azido-2′,3′-dideoxy-6′-*O*-benzoyl-α-L-talofuranosyl)thymine (22G): yield 41%; white foam, R_f = 0.12 (PE–EA 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 2.37 (ddd, 1, $J_{2'a,2'b}$ = 14.0 Hz, $J_{2'a,1'}$ = 6.5 Hz, $J_{2'a,3'}$ = 4.0 Hz, 2′-H_a), 2.61 (ddd, 1, $J_{2'b,1'}$ = 6.5 Hz, $J_{2'b,3'}$ = 6.5 Hz, 2′-H_b), 3.56 (d, 1, $J_{5',5'\text{-OH}}$ = 6.0 Hz, 5′-OH), 4.03 (dd, 1, $J_{4',5'}$ = 1.5 Hz, $J_{4',3'}$ = 4.0 Hz, 4′-H), 4.49 (dt, 1, 3′-H), 4.44 (dd, 1, $J_{6'a,6'b}$ = 11.5 Hz, $J_{6'a,5'}$ = 5.0 Hz, 6′-H_a), 4.49 (dt, 1, 3′-H), 4.54 (dd, 1, $J_{6'b,5'}$ = 7.0 Hz, 6′-H_b), 6.06 (t, 1, 1′-H), 7.45 (d, 1, 6-H), 7.43–7.48 (m, 2, aromatic-H), 7.56–7.62 (m, 1, aromatic-H), 8.03–8.07 (m, 2, aromatic-H), 8.58 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.441, 36.837, 61.221, 66.292, 69.430, 84.161, 86.705, 111.173, 128.412, 128.463, 129.489, 129.654, 133.327, 136.967, 150.451, 164.005, 164.181, 166.751; IR (CH_2Cl_2) 2115 (N_3) cm^{-1}. Anal. ($C_{18}H_{18}N_5O_7$) C, H, N.

Deblocking of the Benzoyl Groups of the Nucleosides Derivatives. The benzoylated 3′-azido-2′,3′-dideoxynucleoside derivative (0.262 mmol) was dissolved in dry methanol (10 mL). Then 3 mL of 0.1 M $NaOCH_3$ in MeOH were added. After the reaction was completed, solid CO_2 was added. The solvent was removed, and the residue was purified by flash chromatography (FC).

1-(3′-Azido-2′,3′,5′-trideoxy-β-D-allofuranosyl)thymine (2): FC EA; yield 82%; colorless cyrstals, mp 127–129 °C (EA–PE); R_f = 0.33 (EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 2.00 (m, 2, 5′-H_a, 5′-H_b), 2.43 (pseudo, t, 2, J = 7.0 Hz, 2′-H_a, 2′-H_b), 2.75 (br s, 1, 5′-OH, D_2O exchangeable), 3.85 (m, 2, 6′-H_a, 6′-H_b), 3.95 (m, 1, 4′-H), 4.11 (q, 1, J = 7.0 Hz, 3′-H), 6.05 (t, 1, $J_{1',2'}$ = 7.0 Hz, 1′-H), 7.12 (d, 1, 6-H), 8.87 (br s, 1, 3-H, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) δ 12.585, 35.621, 37.032, 59.602, 63.260, 82.226, 85.423, 111.487, 135.724, 150.067, 163.565; IR (KBr) 2102 (N_3) cm^{-1}. Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

1-(3′-Azido-2′,3′-dideoxy-β-D-allofuranosyl)thymine (3). Deblocking of compounds **22B** and **22F** gave **3**: FC EA; yield 89%; colorless crystals, mp 163–165 °C (EA); R_f = 0.27 (EA); ^{1}H NMR (400 MHz, CD_3OD) δ 1.88 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 2.32 (ddd, 1, $J_{2'a,2'b}$ = 13.5 Hz, $J_{2'a,1'}$ = 6.0 Hz, $J_{2'a,3'}$ = 4.0 Hz, 2′-H_a), 2.36 (ddd, 1, $J_{2'b,1'}$ = 7.0 Hz, $J_{2'b,3'}$ = 7.0 Hz, 2′-H_b), 3.64 (ABX system, 2, $J_{6'a,6'b}$ = 11.0 Hz, $J_{6'a,5'}$ = 6.0 Hz, $J_{6'b,5'}$ = 5.0 Hz, 6′-H_a, 6′-H_b), 3.84 (m, 1, 5′-H), 3.93 (t, 1, $J_{4',3'}$ = 4.0 Hz, $J_{4',5'}$ = 4.0 Hz, 4′-H), 4.46 (dt, 1,3′-H), 6.16 (dd, 1, 1′-H), 7.66 (d, 1, 6-H); ^{13}C NMR (100 MHz, CD_3OD) δ 10.922, 36.447, 59.869, 62.499, 71.183, 84.006, 84.140, 110.184, 135.937, 150.291, 164.287; IR (CH_2Cl_2) 2115 (N_3) cm^{-1}. Anal. ($C_{11}H_{15}N_5O_5$) C, H, N

1-(3′-Azido-2′,3′-dideoxy-α-L-talofuranosyl)thymine (4). Deblocking of compounds **22C** and **22G** gave **4**: FC EA; yield 80%; mp 135–137 °C (EA/PE), R_f = 0.51 (EA); ^{1}H NMR (400 MHz, CD_3OD) δ 1.87 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 2.36 (ddd, 1, $J_{2'a,2'b}$ = 14.0 Hz, $J_{2'a,1'}$ = 6.5 Hz, $J_{2'a,3'}$ = 5.0 Hz, 2′-H_a), 2.43 (ddd, 1, $J_{2'b,1'}$ = 6.5 Hz, $J_{2'b,3'}$ = 7.0 Hz, 2′-H), 3.63 (d, 2, $J_{6',5'}$ = 7.0 Hz, 6′-H_a, 6′-H_b), 3.79 (dt, 1, $J_{5',4'}$ = 2.0 Hz, $J_{5',6'a}$ = $J_{5',6'b}$ = 7.0 Hz, 5′-H), 4.00 (dd, 1, $J_{3',4'}$ = 5.0 Hz, 4′-H), 4.42 (dt, 1, 3′-H), 6.20 (t, 1, 1′-H), 7.97 (d, 1, 6-H). ^{13}C NMR (100 MHz, CD_3OD) δ 12.476, 38.188, 62.466, 64.240, 72.446, 85.116, 85.941, 111.565, 138.282, 152.353, 166.398; IR (CH_2Cl_2) 2115 (N_3) cm^{-1}. Anal. ($C_{11}H_{15}N_5O_5$) C, H, N.

1-(3′-Azido-2′,3′,6′-trideoxy-β-D-allofuranosyl)thymine (5): FC PE–EA 2:1; yield 94%; foam, R_f = 0.54 (EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, 3, J (CH_3, 5′) = 6.5 Hz, CH_3), 1.84 (d, 3, J (5-CH_3, 6) = 1.5 Hz, 5-CH_3), 2.27 (ddd, 1, $J_{2'a,2'b}$ = 14.0 Hz, $J_{2'a,1'}$

= 6.5 Hz, $J_{2'a,3'}$ = 3.5 Hz, 2'-H_a), 2.47 (ddd, 1, $J_{2'b,1'}$ = 7.0 Hz, $J_{2'b,3'}$ = 7.0 Hz, 2'-H_b), 2.95 (br s, 1, 5'-OH, D_2O-exchangeable, 5'-OH), 3.72 (dd, 1, $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 3.0 Hz, 4'-H), 4.04 (m, 1, 5'-H), 4.35 (dt, 1,3'-H), 5.94 (dd, 1, 1'-H), 7.25 (d, 1, 6-H), 9.10 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.453, 19.098, 36.971, 59.314, 67.152, 86.953, 88.123, 111.350, 137.057, 150.363, 163.693. IR (CH_2Cl_2) 2115 (N_3) cm^{-1}. Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

1-(3'-Azido-2',3',6'-trideoxy-α-L-talofuranosyl)thymine (6): FC EA; yield 80%; colorless crystals, mp 110-111 °C (EA-PE); R_f = 0.51 (EA); ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, 3, J (CH_3, 5') = 6.2 Hz, CH_3), 1.92 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 2.36 (ddd, 1, $J_{2'a,2'b}$ = 14.0 Hz, $J_{2'a,1'}$ = 7.0 Hz, $J_{2'a,3'}$ = 5.0 Hz, 2'-H_a), 2.54 (ddd, 1, $J_{2'b,1'}$ = 7.0 Hz, $J_{2'b,3'}$ = 7.0 Hz, 2'-H_b), 3.75 (dd, 1, $J_{3',4'}$ = 5.0 Hz, $J_{4',5'}$ = 3.0 Hz, 4'-H), 3.99 (dq, 1, 5'-H), 4.34 (dt, 1, 3'-H), 6.07 (t, 1, 1'-H), 7.43 (d, 1, 6-H), 9.00 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$ δ 12.513, 20.256, 36.901, 61.121, 67.476, 86.538, 87.366, 111.268, 136.854, 150.250, 163.640; IR (CH_2Cl_2) 2115 (N_3) cm^{-1}. Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

Anti-HIV Assays. The HIV cytopathicity assay in human T-lymphocyte MT-4 cells has been described previously.[32,33] Briefly, MT-4 cells, subcultured 1 day before the start of the experiment, were adjusted to 5×10^5 cells/mL and infected with HIV ($HTLV\text{-}III_B$) at 400 $CCID_{50}$/mL. Then, 100 μL of the infected cell suspension was transferred to wells of a microtiter tray containing 100 μL of varying dilutions of the test compounds. After 5 days of incubation at 37 °C, the number of viable cells was recorded microscopically in a hematocytometer following the trypan blue exclusion procedure.

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Supplementary Material Available: Full experimental details and ^1H NMR data of compounds **8-11**, **14**, **15**, **16A-E**, **17Aα/β-17Eα/β**, and **20A-20E** and ^{13}C NMR data of **17Aα/β-17Eα/β** (8 pages). Ordering information is given on any current masthead page.

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Dispiro-1,2,4,5-tetraoxanes: A New Class of Antimalarial Peroxides[1]

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Dispiro-1,2,4,5-tetraoxanes **2-4** were synthesized as potential peroxide antimalarial drugs. They had curative activity against *Plasmodium berghei* in vivo at single doses of 320 and 640 mg/kg which confirms earlier unpublished data. Moreover, artemisinin (**1**) and **4** had equivalent ED_{50}'s against *P. berghei* in vivo in the multiple-dose Thompson test; neither showed any evidence of acute toxicity at total doses of more than 12 g/kg. Dispiro-1,2,4,5-tetraoxane **4** had IC_{50}'s comparable to those of **1** against *Plasmodium falciparum* clones in vitro. These results confirm the potential of dispiro-1,2,4,5-tetraoxanes as a new class of inexpensive peroxide antimalarial drugs.

As a result of an apparent association between the peroxide functional group and antimalarial activity,[2] a substantial effort has been devoted to developing new peroxide antimalarials. Our early attempts[3,4] in this regard led us to conclude that an endoperoxide ketal is a minimum but insufficient structural requirement for an effective peroxide-containing antimalarial. Most work, however, has centered around artemisinin (**1**), the proto-

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