

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*]thiophene⁶ by method B) as outlined above: ¹H 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); ¹³C 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: ¹H 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); ¹³C 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: ¹H 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); ¹³C 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.

Acknowledgment. The authors would like to thank J. Jeffry Howbert for the synthesis of compounds 2 and an analog of 3, and Homer L. Pearce for encouragement and support throughout the course of this project.

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

Johann Hiebl,^{*,†,‡} Erich Zbiral,^{†,§} Jan Balzarini,^{||} and Erik De Clercq^{||}

Institut für Organische Chemie der Universität Wien, Währingerstrasse 38, A-1090 Wien, Austria, and Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium.

Received January 14, 1992

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 17A α / β , 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*O*-mesyl-D-allofuranoses 17B α / β , and 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*O*-mesyl-L-talofuranoses 17C α / β were synthesized. 1,2-Di-*O*-acetyl-5-*O*-benzoyl-6-deoxy-3-*O*-mesyl-D-allofuranoses 17D α / β and the corresponding L-talofuranoses 17E α / 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 LiN₃ to produce the protected 3'-azido-2,3'-dideoxynucleoside derivatives 22A-G. Saponification with NaOCH₃ 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 μ g/mL. 5 is slightly active against HSV-1, HSV-2, and VV at 150, 300, and 300 μ g/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

[†] Present address: Nycomed Drug Research, St. Peter-Strasse 25, A-4020 Linz, Austria.

[‡] Institut für Organische Chemie der Universität Wien.

[§] During the preparation of this manuscript Prof. Dr. Erich Zbiral deceased.

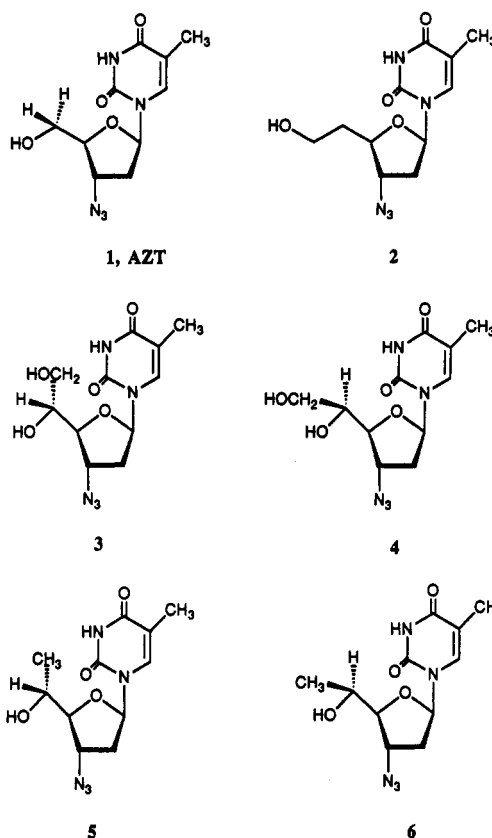
^{||} Rega Institute for Medical Research.

(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.

(2) (a) Fischl, M. A. New Developments in Dideoxynucleoside Antiretroviral Therapy for HIV Infection. In *Aids Clinical Review 1991*; Volberding, P., Jakobson, M. A., Eds.; Marcel Dekker, Inc.: New York, 1991; pp 197–214. (b) Klecker, R. W., Jr.; Collins, J. M.; Yarchoan, R.; Thomas, R.; Jenkins, J. F.; Broder, S.; Myers, C. E. Plasma and Cerebrospinal Fluid Pharmacokinetics of 3'-Azido-3'-deoxythymidine: A Novel Pyrimidine Analog with Potential Application for the Treatment of Patients with AIDS and Related Diseases. *Clin. Pharmacol. Ther.* 1987, 41, 407–412.

administration to maintain therapeutically effective levels;² (c) AZT cannot penetrate into the brain tissue from cerebrospinal fluid⁶ and therefore may not be able to suppress viral replication in the brain. These problems stimulated the search for closely related nucleoside analogs⁷⁻¹⁵ with

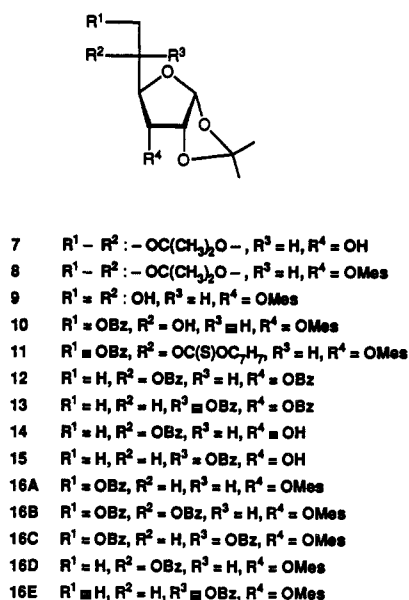
Scheme I



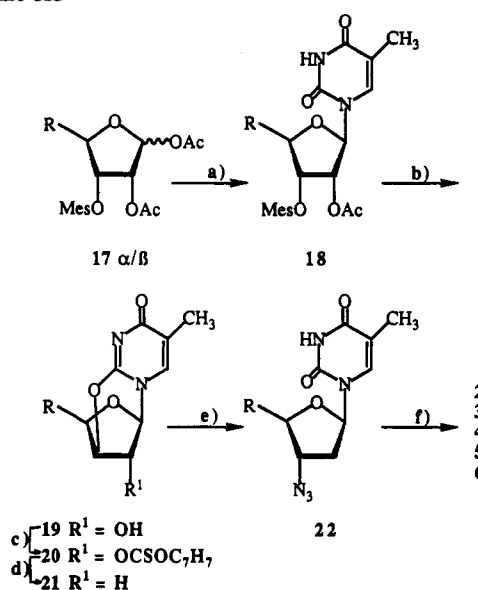
increased antiviral activity and decreased cytotoxicity. We were interested in the synthesis and structure-ac-

- (3) (a) Furman, P. A.; Fyfe, J. A.; St. Clair, M. H.; Weinhold, K.; Rideout, J. L.; Freeman, G. A.; Nusinoff-Lehrman, S.; Bolognesi, D. P.; Broder, S.; Mitsuya, H.; Barry, D. W. Phosphorylation of 3'-Azido-3'-deoxythymidine and Selective Interaction of the 5'-Triphosphate with Human Immunodeficiency Virus Reverse Transcriptase. *Proc. Natl. Acad. Sci. U.S.A.* 1986, 83, 8333-8337. (b) Huang, P.; Farquhar, D.; Plunkett, W. Selective Action of 3'-Azido-3'-deoxythymidine 5'-Triphosphate on Viral Reverse Transcriptases and Human DNA Polymerases. *J. Biol. Chem.* 1990, 265, 11914-11918.
- (4) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Nusinoff-Lehrman, S.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. 3'-Azidothymidine (BW A509U): An Antiviral Agent that Inhibits the Infectivity and Cytopathic Effect of Human T-Lymphotropic Virus Type III/Lymphadenopathy-Associated Virus in vitro. *Proc. Natl. Acad. Sci. U.S.A.* 1985, 82, 7096-7100.
- (5) Yarchoan, R.; Klecker, R. W.; Weinhold, K. J.; Markham, P. D.; Lyerly, H. K.; Durack, D. T.; Gelmann, E.; Nusinoff-Lehrman, S.; Blum, R. M.; Barry, D. W.; Shearer, G. M.; Fischl, M. A.; Mitsuya, H.; Gallo, R. C.; Collins, J. M.; Bolognesi, D. P.; Myers, C. E.; Broder, S. Administration of 3'-Azido-3'-deoxythymidine, an Inhibitor of HTLV-III/LAV Replication, to Patients with AIDS or AIDS-Related Complex. *Lancet* 1986, Vol. I, 575-580.
- (6) Terasaki, T.; Pardridge, W. M. Restricted Transport of 3'-Azido-3'-deoxythymidine and Dideoxynucleosides Through the Blood-Brain Barrier. *J. Infect. Dis.* 1988, 158, 630-632.
- (7) Enantiomeric form of 3'-azido-3'-deoxythymidine, L-AZT: Wengel, J.; Lau, J.; Pedersen, E. B.; Nielsen, C. M. Synthesis of L-3'-Azido-3'-deoxythymidine and its Stereoisomers. *J. Org. Chem.* 1991, 56, 3591-3594.
- (8) Exchange of the furanose oxygen by sulfur: (a) Secrist, J. A., III; Riggs, R. M.; Tiwari, K. N.; Montgomery, J. A. Synthesis and Anti-HIV Activity of 4'-Thio-2',3'-dideoxynucleosides. *J. Med. Chem.* 1992, 35, 533-538. (b) Dyson, M. R.; Coe, P. L.; Walker, R. T. The Synthesis and Antiviral Activity of Some 4'-Thio-2'-deoxy Nucleoside Analogs. *J. Med. Chem.* 1991, 34, 2782-2786. (c) Dyson, M. R.; Coe, P. L.; Walker, R. T. The Synthesis and Antiviral Properties of E-5-(2-bromovinyl)-4'-thio-2'-deoxyuridine. *J. Chem. Soc. Chem. Commun.* 1991, 741-742.
- (9) Replacement of the furanose oxygen by a methylene group: (a) Bodenteich, M.; Griengl, H. Synthesis of Enantiomerically Pure Carbocyclic 3'-Azido-2',3'-Dideoxythymidine, a Potential Anti-AIDS Drug. *Tetrahedron Lett.* 1987, 28, 5311-5312. (b) Mitsuya, H.; Matsukura, M.; Broder, S. Rapid in vitro Systems for Assessing Activity of Agents Against HTLV-III/LAV. In *AIDS, Modern Concepts and Therapeutic Challenges*; Broder, S., Ed.; Marcel Dekker Inc.: New York and Basel, 1987; pp 303-333.
- (10) Replacement of furanose oxygen by a fluoromethylene group: Highcock, R. M.; Hilpert, H.; Myers, P. L.; Roberts, S. M.; Storer, R. The Potential for Using Carbocyclic Nucleosides for the Treatment of AIDS. Part 1. Preparation of Some Analogues for Azidothymidine (AZT). *J. Chem. Soc. Perkin Trans. I* 1991, 1127-1134.
- (11) Phosphonate isosteres of AZT-5'-phosphates: (a) Tanaka, H.; Fukui, M.; Haraguchi, K.; Masaki, M.; Miyasaka, T. Cleavage of a Nucleosidic Oxetan with Carbanions: Synthesis of a Highly Promising Candidate for Anti-HIV Agents-A Phosphonate Isostere of AZT-5'-Phosphate. *Tetrahedron Lett.* 1989, 30, 2567-2570. (b) Barton, D. H. R.; Géro, S. D.; Quiclet-Sire, B.; Samadi, M. Stereoselectivity in Radical Reactions of 2'-Deoxynucleosides. A Synthesis of an Isostere of 3'-Azido-3'-deoxythymidine-5'-monophosphate (AZT-5'-monophosphate). *Tetrahedron Lett.* 1989, 30, 4969-4972. (c) Balzarini, J.; Herdewijn, P.; Pauwels, R.; Broder, S.; De Clercq, E. α,β - and β,γ -Methylene 5'-Phosphonate Derivatives of 3'-Azido-2',3'-dideoxythymidine-5'-triphosphate. Correlation Between Affinity for Reverse Transcriptase, Susceptibility to Hydrolysis by Phosphodiesterases and Anti-Retrovirus Activity. *Biochem. Pharmacol.* 1988, 37, 2395-2403.
- (12) Acyclic AZT analogs: (a) Ogawa, T.; Takaku, H.; Yamamoto, N. A Convenient Approach to the Synthesis of Azido Acyclic Nucleosides. *Nucleosides Nucleotides* 1989, 8, 499-504. (b) Trinh, M.-C.; Florent, J.-C.; Grierson, D. S.; Monneret, C. Synthesis of Acyclic Analogs of Azidothymidine, Amino-thymidine, and Related Nucleosides. *Tetrahedron Lett.* 1991, 32, 1447-1448. (c) Scheiner, P.; Geer, A.; Bucknor, A.-M.; Imbach, J.-L.; Schinazi, R. F. Acyclic Analogues of 3'-Azido-3'-deoxythymidine as Potential Antiviral Agents. Nucleoside Synthesis by Michael Addition. *J. Med. Chem.* 1989, 32, 73-76. (d) Kumar, A.; Walker, R. T. The Chemistry of 2',3'-Secodeoxynucleosides IV. Synthesis and Reactions of 3'-Azido-2',3'-dideoxy-2',3'-secodeoxythymidine and Related Compounds. *Tetrahedron* 1990, 46, 3101-3110.
- (13) 2,5'-Anhydro derivative of AZT: Lin, T.-S.; Shen, Z.-Y.; August, E. M.; Brankovan, V.; Yang, H.; Ghazzouli, I.; Prusoff, W. H. Synthesis and Antiviral Activity of Several 2,5'-Anhydro Analogues of 3'-Azido-3'-deoxythymidine, 3'-Azido-2',3'-dideoxyuridine, 3'-Azido-2',3'-dideoxy-5-halouridines, and 3'-Deoxythymidine against Human Immunodeficiency Virus and Rauscher-Murine Leukemia Virus. *J. Med. Chem.* 1989, 32, 1891-1895.
- (14) AZT derivatives with fluorine at 2' position: (a) Watanabe, K. A.; Harada, K.; Zeidler, J.; Matulic-Adamic, J.; Takahashi, K.; Ren, W.-Y.; Cheng, L.-C.; Fox, J. J.; Chou, T.-C.; Zhu, Q.-Y.; Polsky, B.; Gold, J. W. M.; Armstrong, D. Synthesis and Anti-HIV-1 Activity of 2'-"Up"-Fluoro Analogues of Active Anti-AIDS Nucleosides 3'-Azido-3'-deoxythymidine (AZT) and 2',3'-Dideoxycytidine (DDC). *J. Med. Chem.* 1990, 33, 2145-2150. (b) Sterzycki, R. Z.; Ghazzouli, I.; Brankovan, V.; Martin, J. C.; Mansuri, M. M. Synthesis and Anti-HIV Activity of Several 2'-Fluoro-Containing Pyrimidine Nucleosides. *J. Med. Chem.* 1990, 33, 2150-2157. (c) Huang, J.-T.; Chen, L.-C.; Wang, L.; Kim, M.-H.; Warshaw, J. A.; Armstrong, D.; Zhu, Q.-Y.; Chou, T.-C.; Watanabe, K. A.; Matulic-Adamic, J.; Su, T.-L.; Fox, J. J.; Polsky, B.; Baron, P. A.; Gold, J. W. M.; Hardy, W. D.; Zuckerman, E. Fluorinated Sugar Analogues of Potential Anti-HIV-1 Nucleosides. *J. Med. Chem.* 1991, 34, 1640-1646.

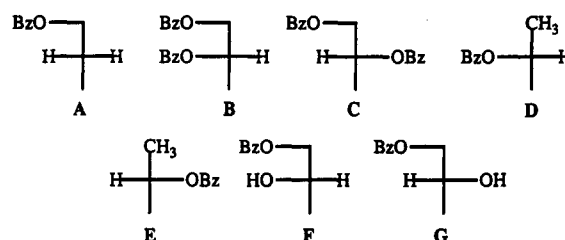
Scheme II



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

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) $NaOCH_3/MeOH$.

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

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). Deoxygenation¹⁹ yielded the desired 6-O-benzoyl-5-

- (15) Other derivatives: (a) Palomino, E.; Meltaner, B. R.; Kessel, D.; Horwitz, J. P. Synthesis and in Vitro Evaluation of Some Modified 4-Thiopyrimidine Nucleosides for Prevention or Reversal of AIDS-Associated Neurological Disorders. *J. Med. Chem.* 1990, 33, 258–263. (b) Lin, T.-S.; Guo, J.-Y.; Schinazi, R. F.; Chu, C. K.; Xiang, J.-N.; Prusoff, W. H. Synthesis and Antiviral Activity of Various 3'-Azido Analogues of Pyrimidine Deoxyribonucleosides against Human Immunodeficiency Virus (HIV-1, HTLV-III/LAV). *J. Med. Chem.* 1988, 31, 336–340. (c) Balzarini, J.; Baba, M.; Pauwels, R.; Herdewijn, P.; De Clercq, E. Anti-Retrovirus Activity of 3'-Fluoro- and 3'-Azido-Substituted Pyrimidine 2'-3'-Dideoxynucleoside Analogues. *Biochem. Pharmacol.* 1988, 37, 2847–2856. (d) Hrebabecky, H.; Holy, A.; De Clercq, E. Synthesis of 3'-Azido-2',3'-dideoxy-6-methyluridine, 2',3'-Dideoxy-6-methyluridine and 2',3'-Dideoxy-2',3'-didehydro-6-methyluridine. *Collect. Czech. Chem. Commun.* 1990, 55, 1801–1811. (e) Van Aerschot, A.; Everaert, D.; Gosselin, G.; Peeters, O.; Blaton, N.; De Ranter, C.; Imbach, J. L.; Balzarini, J.; De Clercq, E.; Herdewijn, P. 2'-Azido-2',3'-dideoxythymidine: Synthesis and Crystal Structure of a 2'-Substituted Dideoxynucleoside. *Antiviral Res.* 1990, 14, 357–369. (f) Prisbe, E. J.; Maag, H.; Verheyden, J. P. H. 4'-Azidothymidine (ADRT). A Member of a New Class of Nucleosides Having Potent Anti-HIV Activity. Presented at the 201st American Chemical Society National Meeting, Atlanta, GA, April 14–19, 1991. We thank E. J. Maag, H.; Chu, N.; Crawford-Ruth, D.; Eugui, E.; McRoberts, M. J.; Mirkovich, A.; Pettibone, M.; Prisbe, E. J.; Rydzewski, R. M.; Verheyden, J. P. H. 4'-Azidothymidine: Synthesis and in vitro Anti-HIV Activity. *Abstracts of the IVth International Conference on Antiviral Research*; New Orleans, LA, April 21–26, 1991. *Antiviral Res.* 1991, Suppl. 1, p 43. (h) Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. Synthesis and Anti-HIV Activity of 4'-Azido- and 4'-Methoxynucleosides. *J. Med. Chem.* 1992, 35, 1440–1451.

- (16) Hiebl, J.; Zbiral, E. 1-(3'-Azido-2',3',5'-trideoxy- β -D-allofuranosyl)thymine—A Side-Chain Homologue of 3'-Azido-3'-deoxythymidine. *Tetrahedron Lett.* 1990, 31, 4007–4010. (17) Baker, D. C.; Horton, D.; Tindall, C. G., Jr.; Preparation of Mono- and Disaccharides. D-Allose from 1,2:5,6-Di-O-isopropylidene- α -D-glucofuranose by Way of 1,2:5,6-Di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose Hydrate. *Methods Carbohydr. Chem.* 1985, 4, 3–6. (18) Zabacova, A.; Hermankova, V.; Jary, J. Reduction of Sulfonyl Esters of Aldoses with Sodium Hydrogen Bis(2-Methoxyethoxy)aluminate. *Collect. Czech. Chem. Commun.* 1977, 42, 2540–2548.

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 reaction²⁰ (triphenylphosphine(TPP)/diethyl azodicarboxylate (DEAD)/benzoic acid) of 6-*O*-monobenzoyle compound 10 yielded the dibenzoylated L-talose derivative 16C²¹ (85%, mp 94–96 °C).

The carbohydrate precursors 16D and 16E were prepared from the epimeric dibenzoylated compounds 12²² and 13²³ 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 Ac₂O, AcOH, and H₂SO₄ cat. led to the anomeric mixture of the 1,2-di-*O*-acetyl derivatives 17A α / β – 17E α / 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 deoxygenated¹⁹ 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 (EC₅₀) of 2 ng/mL, that is at a concentration that was 2000-fold lower than the 50% cytotoxic concentration, compounds 2–6 did not show any anti-HIV activity even at a concentration up to 200 μ g/mL. The CC₅₀ of compounds 2, 3, 5, and 6 was >200 μ g/mL; for compound 4, it was 17.7 \pm 0.5 μ g/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 μ g/mL. Compound 5 is slightly active against HSV-1 at 150 μ g/mL, against HSV-2 and VV at 300 μ g/mL, and against VSV at >400 μ g/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 ¹³C 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(NO₃)₄ in 2 N H₂SO₄ followed by heating at 200 °C. Flash chromatography³¹ was performed with 230–400

- (19) Barton, D. H. R.; McCombie, S. W. A New Method for the Deoxygenation of Secondary Alcohols. *J. Chem. Soc., Perkin Trans 1* 1975, 1574–1585.
- (20) Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* 1981, 1–28.
- (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.
- (23) Hiebl, J.; Zbiral, E. Synthesis of Glycofuranosyl Formamides, Isocyanides, and Isocyanates Starting from the Corresponding Glycosyl Azides. *Liebigs Ann. Chem.* 1988, 765–774.
- (24) We used 10 mol % NaOCH₃-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 CO₂. The yield of one cycle calculated on the reacted material was 70–80%.
- (25) Vorbrüggen, H.; Bennis, 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 mechanism²⁷ because this will only work for the acetyl residue. Although we used DBU stored over molecular sieves (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.

- (28) Verheyden, J. P. H.; Wagner, D.; Moffatt, J. G. Synthesis of Some Pyrimidine 2'-Amino-2'-deoxynucleosides. *J. Org. Chem.* 1971, 36, 250–254.
- (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.
- (30) Dr. H. Hrebabecky has presented another route to compound 3 at the Bechyn meeting.¹
- (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 transferred 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); ^1H 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. ($\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_{10}\text{S}$) 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); ^1H 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, $J_{6a,6b} = 12.0$ Hz, $J_{6a,5'} = 6.0$ 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, $J_{6b,5'} = 4.5$ 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. ($\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_{12}\text{S}$) C, H, N.

1-(2'-*O*-Acetyl-5',6'-di-*O*-benzoyl-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); ^1H 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, $J_{6a,6b} = 12.0$ Hz, $J_{6a,5'} = 6.0$ Hz, $J_{6b,5'} = 7.0$ 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. ($\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_{12}\text{S}$) 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); ^1H 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. ($\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_{14}\text{S}$) 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); ^1H 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, $J_{3,4'} = 3.0$ Hz, $J_{4,5'} = 4.5$ 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. ($\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_{10}\text{S}$) 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); ^1H 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. ($\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_6$) 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); ^1H NMR (400 MHz, d_6 -DMSO) δ 1.60 (s, 3, 5- CH_3), 4.55 (dd, 1, $J_{6a,6b} = 12.0$ Hz, $J_{6a,5'} = 6.0$ Hz, 6'- H_a), 4.75–4.80 (m, 2, $J_{6b,5'} = 2.5$ 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. ($\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_8$) 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-CHCl₃); R_f = 0.66 (CHCl₃-MeOH 5:1); ^1H NMR (400 MHz, d_6 -DMSO) δ 1.72 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 4.56 (dd, 1, $J_{8'a,8'b} = 12.0$ Hz, $J_{8'a,5'} = 7.0$ Hz, 6'-H_a), 4.67 (dd, 1, $J_{8'b,5'} = 4.0$ 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, D₂O-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. ($\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_8$) 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 (CHCl₃-MeOH 5:1); mp 258–261 °C (MeOH-CHCl₃); ^1H NMR (400 MHz, d_6 -DMSO) δ 1.38 (d, 3, J (CH₃, 5') = 7.0 Hz, CH₃), 1.61 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 4.42 (dd, 1, $J_{3',4'} = 2.5$ Hz, $J_{4',5'} = 7.0$ Hz, 4'-H), 4.72 (dd, after D₂O-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, D₂O 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. ($\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_8$) 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 (CHCl₃-MeOH); R_f = 0.45 (CHCl₃-MeOH 5:1); ^1H NMR (400 MHz, d_6 -DMSO) δ 1.36 (d, 3, J (CH₃, 5') = 6.5 Hz, CH₃), 1.74 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 4.56 (dd, 1, $J_{8'a,8'b} = 8.0$ Hz, $J_{4',5'} = 2.0$ 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, D₂O-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. ($\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_8$) 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 (CHCl₃-MeOH 5:1); ^1H NMR (400 MHz, d_6 -DMSO) δ 1.74 (s, 3, 5-CH₃), 3.80 (m, 1, 5'-H), 4.23 (dd, 1, $J_{8'a,8'b} = 12.0$ Hz, $J_{8'a,5'} = 5.5$ 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, $J_{OH,2'} = 6.0$ Hz, D₂O-exchangeable, 2'-OH), 6.44 (d, 1, $J_{OH,2'} = 4.0$ Hz, D₂O-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. ($\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_7$) 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 H₂O and CH₂Cl₂. The organic phase was separated, and the water phase was extracted with CH₂Cl₂ (6 × 50 mL). The combined organic phases were washed with 10% HCl solution and with water and dried with Na₂SO₄, concentrated, and purified (silica gel). For the purification of the raw material we used the following solvent systems: 20A CHCl₃-acetone 9:1; 20B MC-EA 5:2; 20C MC-EA 5:2; 20D CHCl₃-acetone 19:1; 20E CHCl₃-acetone 19:1. For experimental details see supplementary 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 CHCl₃-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 (CHCl₃-MeOH 5:1); ^1H NMR (400 MHz, d_6 -DMSO) δ 1.74 (d, 3, J (5-CH₃, 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}C 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. ($\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_5$) 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 (CHCl₃-MeOH 5:1); ^1H NMR (400 MHz, CD₂Cl₂) δ 1.79 (d, 3, J (CH₃, 6) = 2.0 Hz, 6-CH₃), 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'-H_a), 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, CD₂Cl₂) 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. ($\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_7$) C, H, N.

2,3'-Anhydro-1-(5',6'-di-*O*-benzoyl-2'-deoxy- α -L-idofuranosyl)thymine (21C): yield 94%; colorless crystals, mp 213–218 °C (CHCl₃-PE); R_f = 0.41 (CHCl₃-MeOH 5:1); ^1H NMR (400 MHz, d_6 -DMSO) δ 1.65 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 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'-H_b, 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. ($\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_7$) 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 (CHCl₃-MeOH 5:1); ^1H NMR (400 MHz, d_6 -DMSO) δ 1.37 (d, 3, J (CH₃, 5') = 6.5 Hz, CH₃), 1.64 (s, 3, 5-CH₃), 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. ($\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_5$) 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 (CHCl₃-MeOH 5:1); ^1H NMR (400 MHz, d_6 -DMSO) δ 1.36 (d, 3, J (CH₃, 5') = 6.5 Hz, CH₃), 1.74 (d, 3, J (5-CH₃, 6) = 1.5 Hz, 5-CH₃), 2.51 (dt, 1, $J_{2'a,2'b} = 13.0$ Hz, $J_{2'a,1'} = J_{2'a,3'} = 4.0$ Hz, 2'-H_a), 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. ($\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_5$) C, H, N.

Synthesis of 3'-Azido-2,3'-dideoxynucleosides Derivatives 22A–G. The 2,3'-anhydro-2'-deoxynucleoside derivative (2.213 mmol), LiN₃ (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 H₂O (5 mL) and CH₂Cl₂ (50 mL). The organic phase was separated, and the water phase was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phases were dried with Na₂SO₄

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); $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 1.93 (d, 3, J (5-CH₃, 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, $J_{2',3'} = 6.0$ 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); $^{13}\text{C NMR}$ (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. ($\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_5$) 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: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.71 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 2.36 (ddd, 1, $J_{2',3'} = 14.0$ Hz, $J_{2',1'} = 7.0$ Hz, $J_{2',3'} = 7.0$ Hz, 2'-H_a), 2.49 (ddd, 1, $J_{2',1'} = 6.0$ Hz, $J_{2',3'} = 3.0$ 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, $J_{6',5'} = 12.0$ Hz, $J_{6',4'} = 6.5$ Hz, 6'-H_a), 4.84 (dd, 1, $J_{6',5'} = 4.0$ 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); $^{13}\text{C NMR}$ (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. ($\text{C}_{25}\text{H}_{23}\text{N}_5\text{O}_7$) 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: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.87 (d, 3, J (5-CH₃, 6) = 1.5 Hz, 5-CH₃), 2.22 (ddd, 1, $J_{2',3'} = 14.0$ Hz, $J_{2',1'} = 7.0$ Hz, $J_{2',3'} = 7.0$ Hz, 2'-H_a), 2.47 (ddd, 1, $J_{2',1'} = 6.5$ Hz, $J_{2',3'} = 5.0$ 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, $J_{6',5'} = 12.0$ Hz, $J_{6',4'} = 4.5$ Hz, 6'-H_a), 4.75 (dd, 1, $J_{6',5'} = 7.5$ 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); $^{13}\text{C NMR}$ (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. ($\text{C}_{25}\text{H}_{23}\text{N}_5\text{O}_7$) 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); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.47 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 1.48 (d, 3, J (CH₃, 5') = 7.0 Hz, CH₃), 2.25 (ddd, 1, $J_{2',3'} = 14.0$ Hz, $J_{2',1'} = 8.0$ Hz, $J_{2',3'} = 8.0$ Hz, 2'-H_a), 2.56 (ddd, 1, $J_{2',1'} = 6.0$ Hz, $J_{2',3'} = 4.0$ 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); $^{13}\text{C NMR}$ (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. ($\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_5$) 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); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.52 (d, 3, J (CH₃, 5') = 7.0 Hz, CH₃), 1.89 (d, 3, J (5-CH₃, 6) = 1.5 Hz, 5-CH₃), 2.23 (m, 1, $J_{2',3'} = 14.0$ Hz, $J_{2',1'} = 7.0$ Hz, $J_{2',3'} = 7.0$ Hz, 2'-H_a), 2.48 (ddd, 1, $J_{2',1'} = 6.0$ Hz, $J_{2',3'} = 4.5$ 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); $^{13}\text{C NMR}$ (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. ($\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_5$) 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); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.90 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 2.37 (ddd, 1, $J_{2',3'} = 14.0$ Hz, $J_{2',1'} = 7.0$ Hz, $J_{2',3'} = 4.0$ Hz, 2'-H_a), 2.52 (ddd, 1, $J_{2',1'} = 7.0$ Hz, $J_{2',3'} = 7.0$ Hz, 2'-H_b), 3.96 (br s, 1, 5'-OH, D₂O-exchangeable), 4.01 (t, 1, $J_{4',5'} = J_{4',3'} = 4.0$ Hz, 4'-H), 4.25 (br s, after D₂O-exchange dt, 1, 5'-H), 4.41 (dd, 1, $J_{6',5'} = 12.0$ Hz, $J_{6',4'} = 6.0$ Hz, 6'-H_a), 4.53-4.60 (m, 2, $J_{6',5'} = 4.0$ 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); $^{13}\text{C NMR}$ (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. ($\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_7$) 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); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.92 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 2.37 (ddd, 1, $J_{2',3'} = 14.0$ Hz, $J_{2',1'} = 6.5$ Hz, $J_{2',3'} = 4.0$ Hz, 2'-H_a), 2.61 (ddd, 1, $J_{2',1'} = 6.5$ Hz, $J_{2',3'} = 6.5$ Hz, 2'-H_b), 3.56 (d, 1, $J_{5',6'} = 6.0$ 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, $J_{6',5'} = 11.5$ Hz, $J_{6',4'} = 5.0$ Hz, 6'-H_a), 4.49 (dt, 1, 3'-H), 4.54 (dd, 1, $J_{6',5'} = 7.0$ 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); $^{13}\text{C NMR}$ (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. ($\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_7$) 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 NaOCH₃ in MeOH were added. After the reaction was completed, solid CO₂ 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 crystals, mp 127-129 °C (EA-PE); $R_f = 0.33$ (EA); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.94 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 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, D₂O 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, D₂O exchangeable); $^{13}\text{C NMR}$ (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. ($\text{C}_{11}\text{H}_{15}\text{N}_5\text{O}_4$) 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); $^1\text{H NMR}$ (400 MHz, CD_3OD) δ 1.88 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 2.32 (ddd, 1, $J_{2',3'} = 13.5$ Hz, $J_{2',1'} = 6.0$ Hz, $J_{2',3'} = 4.0$ Hz, 2'-H_a), 2.36 (ddd, 1, $J_{2',1'} = 7.0$ Hz, $J_{2',3'} = 7.0$ Hz, 2'-H_b), 3.64 (ABX system, 2, $J_{6',5'} = 11.0$ Hz, $J_{6',4'} = 6.0$ Hz, $J_{6',5'} = 5.0$ 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); $^{13}\text{C NMR}$ (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. ($\text{C}_{11}\text{H}_{15}\text{N}_5\text{O}_5$) 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); $^1\text{H NMR}$ (400 MHz, CD_3OD) δ 1.87 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 2.36 (ddd, 1, $J_{2',3'} = 14.0$ Hz, $J_{2',1'} = 6.5$ Hz, $J_{2',3'} = 5.0$ Hz, 2'-H_a), 2.43 (ddd, 1, $J_{2',1'} = 6.5$ Hz, $J_{2',3'} = 7.0$ Hz, 2'-H_b), 3.63 (d, 2, $J_{6',5'} = 7.0$ Hz, 6'-H_a, 6'-H_b), 3.79 (dt, 1, $J_{4',5'} = 2.0$ Hz, $J_{5',6'} = J_{5',4'} = 7.0$ 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). $^{13}\text{C NMR}$ (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. ($\text{C}_{11}\text{H}_{15}\text{N}_5\text{O}_5$) 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); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.22 (d, 3, J (CH₃, 5') = 6.5 Hz, CH₃), 1.84 (d, 3, J (5-CH₃, 6) = 1.5 Hz, 5-CH₃), 2.27 (ddd, 1, $J_{2',3'} = 14.0$ Hz, $J_{2',1'}$

= 6.5 Hz, $J_{2a,3} = 3.5$ Hz, 2'-H_a), 2.47 (ddd, 1, $J_{2b,1} = 7.0$ Hz, $J_{2b,3} = 7.0$ Hz, 2'-H_b), 2.95 (br s, 1, 5'-OH, D₂O-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); ¹³C NMR (100 MHz, CDCl₃) δ 12.453, 19.098, 36.971, 59.314, 67.152, 86.953, 88.123, 111.350, 137.057, 150.363, 163.693. IR (CH₂Cl₂) 2115 (N₃) cm⁻¹. Anal. (C₁₁H₁₅N₅O₄) 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, CDCl₃) δ 1.34 (d, 3, J (CH₃, 5') = 6.2 Hz, CH₃), 1.92 (d, 3, J (5-CH₃, 6) = 1.0 Hz, 5-CH₃), 2.36 (ddd, 1, $J_{2a,2b} = 14.0$ Hz, $J_{2a,1} = 7.0$ Hz, $J_{2a,3} = 5.0$ Hz, 2'-H_a), 2.54 (ddd, 1, $J_{2b,1} = 7.0$ Hz, $J_{2b,3} = 7.0$ 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); ¹³C NMR (100 MHz, CDCl₃) δ 12.513, 20.256, 36.901, 61.121, 67.476, 86.538, 87.366, 111.268, 136.854, 150.250, 163.640; IR (CH₂Cl₂) 2115 (N₃) cm⁻¹. Anal. (C₁₁H₁₅N₅O₄) 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-III_B) at 400 CCID₅₀/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 hemacytometer following the trypan blue exclusion procedure.

Acknowledgment. This work was supported by the Fonds zur Förderung der wissenschaftlichen Forschung in Österreich—Project No. 7177 and P6537C (400 MHz NMR), the AIDS Basic Research Programme of the European Community, and the Belgian Fonds voor Geneeskundig Wetenschappelijk Onderzoek (Project No. 3.0097.87). We thank Ann Absillis, Wolfgang Binder, Frieda Demeyer, Martina Drescher, Judith Humpelstetter, Dirk Trauner and Anita Van Lierde for technical assistance and Hanspeter Kählig for 400-MHz spectra.

Registry No. 1, 30516-87-1; 2, 130481-61-7; 3, 136011-36-4; 4, 142003-05-2; 5, 134018-71-6; 6, 141980-84-9; 7, 2595-05-3; 8, 14728-80-4; 9, 64993-88-0; 10, 130481-52-6; 11, 130481-53-7; 12, 89128-39-2; 13, 114978-51-7; 14, 141980-85-0; 15, 141980-86-1; 16a, 130481-54-8; 16b, 141980-87-2; 16c, 141980-88-3; 16d, 141980-89-4; 16e, 141980-90-7; α-17a, 130481-55-9; β-17a, 130481-62-8; α-17b, 142036-32-6; β-17b, 142036-33-7; α-17c, 142036-34-8; β-17c, 142036-35-9; α-17d, 141980-91-8; β-18d, 141980-92-9; α-17e, 141980-93-0; β-17e, 141980-94-1; 18a, 130481-56-0; 18b, 141980-95-2; 18c, 141980-96-3; 18d, 141980-97-4; 18e, 141980-98-5; 19a, 130481-57-1; 19b, 141980-99-6; 19c, 142036-36-0; 19d, 141981-00-2; 19e, 142036-37-1; 19f, 141981-01-3; 20a, 130481-58-2; 20b, 141981-02-4; 20c, 142036-38-2; 20d, 141981-03-5; 20e, 142128-33-4; 21a, 130481-59-3; 21b, 141981-04-6; 21c, 142036-39-3; 21d, 141981-05-7; 21e, 142036-40-6; 22a, 130481-60-6; 22b, 142003-12-1; 22c, 141981-06-8; 22d, 141981-07-9; 22e, 141981-08-0; 22f, 141981-09-1; 22g, 141981-10-4; ClC(S)OC₇H₇, 937-63-3; thymine, 65-71-4.

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 ¹³C NMR data of 17Aα/β–17Eα/β (8 pages). Ordering information is given on any current masthead page.

- (32) Balzarini, J.; Pauwels, R.; Baba, M.; Robins, M. J.; Zou, R.; Herdewijn, P.; De Clercq, E. The 2',3'-Dideoxyribose of 2,6-Diaminopurine Selectively Inhibits Human Immunodeficiency Virus (HIV) Replication in vitro. *Biochem. Biophys. Res. Commun.* 1987, 145, 269–276.
- (33) Balzarini, J.; Naesens, L.; Herdewijn, P.; Rosenberg, I.; Holy, A.; Pauwels, R.; Baba, M.; Johns, D. G.; De Clercq, E. Marked in vivo Antiretrovirus Activity of 9-(2-Phosphonylmethoxyethyl)adenine, a Selective Anti-Human Immunodeficiency Virus Agent. *Proc. Natl. Acad. Sci. U.S.A.* 1989, 332–336.

Dispiro-1,2,4,5-tetraoxanes: A New Class of Antimalarial Peroxides¹

Jonathan L. Vennerstrom,^{*,†} Hong-Ning Fu,[†] William Y. Ellis,[‡] Arba L. Ager, Jr.,[§] James K. Wood,^{||} Steven L. Andersen,[‡] Lucia Gerena,[‡] and Wilbur K. Milhous[†]

College of Pharmacy, University of Nebraska Medical Center, 600 South 42nd Street, Omaha, Nebraska 68198-6025, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100, Department of Chemistry, University of Nebraska at Omaha, 60th and Dodge Street, Omaha, Nebraska 68182-0109, and Center for Tropical Parasitic Diseases, Department of Microbiology and Immunology, University of Miami School of Medicine, 12500 Southwest 152nd Street, Miami, Florida 33177. Received March 16, 1992

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 ED₅₀'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 IC₅₀'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 ef-

fective peroxide-containing antimalarial. Most work, however, has centered around artemisinin (1), the proto-

[†] University of Nebraska Medical Center.

[‡] Walter Reed Army Institute of Research.

[§] University of Miami.

^{||} University of Nebraska at Omaha.

- (1) Presented in part at the 40th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Boston, MA, 1991.
- (2) Vennerstrom, J. L.; Eaton, J. W. Oxidants, Oxidant Drugs and Malaria. *J. Med. Chem.* 1988, 31, 1269–1277, and references cited therein.
- (3) Vennerstrom, J. L.; Acton, N.; Lin, A. J.; Klayman, D. L. Peroxides as Oxidant Antimalarials. *Drug Des. Delivery* 1989, 4, 45–54.