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SYNTHESIS OF NEW 2'-DEOXY-3'-SUBSTITUTED-α-L-*THREO*-PENTOFURANONUCLEOSIDES OF THYMINE AS POTENTIAL ANTIVIRAL AGENTS.

Corinne GÉNU-DELLAC, Gilles GOSSELIN and Jean-Louis IMBACH.*

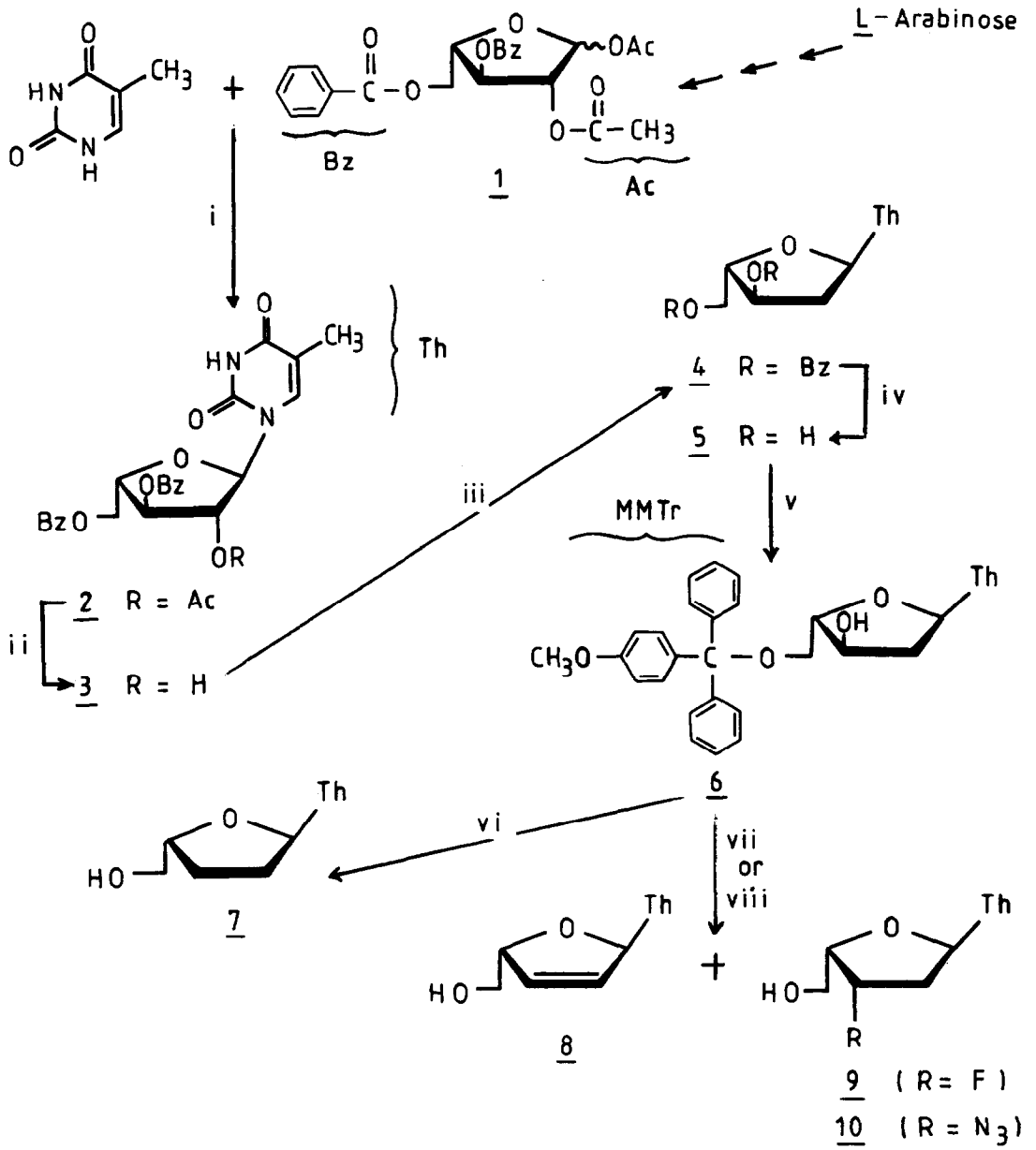
Université de Montpellier II, Sciences et Techniques du Languedoc, case courrier 008, Laboratoire de Chimie Bioorganique, Unité Mixte de Recherche Synthélabo-USTL-CNRS, Place Eugène Bataillon, 34095 MONTPELLIER Cedex 5, FRANCE.

Abstract: The title compounds, which are related to AZT and its congeners have been synthesized by a multi-step approach and their antiviral properties examined.

Efforts to find anti-human immunodeficiency virus targeted against the virion-associated reverse transcriptase led up to the identification of several dideoxynucleosides endowed with potent antiviral activity,[1] like 1-(2,3-dideoxy-3-azido and 3-fluoro-β-D-*erythro*-pentofuranosyl)thymine (AZT[2] and FddThd[3]), 1-(β-D-5-hydroxymethyl-2-tetrahydrofuranyl)thymine (ddThd[4]) and 1-(2,3-β-D-*glycero*-pent-2-enofuranosyl)thymine (d4Thd[5]). However, the clinical usefulness of all of these compounds is compromised by their toxic side effects.

In this Communication, we report the synthesis of four hitherto unknown α-L-dideoxynucleosides **7-10** (*Scheme*). These nucleoside analogues show a close structural similarity to AZT and its congeners, the only difference lying in an inversion of configuration of the C-4'.

An appropriate synthetic plan to reach the compounds **8-10** appeared to first prepare a suitably protected 2'-deoxy-α-L-*erythro*-pentofuranonucleoside like **6** and to substitute its free 3'-hydroxy group with inversion of configuration. The intermediate 1-[5-O-(4-monomethoxytrityl)-2-deoxy-α-L-*erythro*-pentofuranosyl]thymine (**6**) was readily synthesized in five steps from 1,2-di-O-acetyl-3,5-di-O-benzoyl-L-arabinofuranose (**1**), hitherto unknown and specially prepared for our present purpose.[6] Thus, condensation of **1** with thymine by Vorbruggen procedure[7] gave 1-(2-O-acetyl-3,5-di-O-benzoyl-α-L-arabinofuranosyl)thymine (**2**) (64%) which was selectively 2'-O-deacylated with hydrazine hydrate in a buffered acetic acid-pyridine mixture[8] to afford **3** (67%). Treatment of this compound with phenyl chlorothionocarbonate[9] and 4-(dimethylamino)pyridine (DMAP) in methylene chloride gave the



Scheme. *Reagents and conditions* : i) $(CH_3)_3SiNHSi(CH_3)_3$, $(CH_3)_3SiCl$, $SnCl_4$/CH_3CN; ii)NH_2-$NH_2.H_2O$/CH_3CO_2H-C_5H_5N; iii)DMAP,C_6H_5OCSCl/CH_2Cl_2,then Bu_3SnH, AIBN/toluene; iv) NH_3/CH_3OH; v)MMTrCl/C_5H_5N; vi) DMAP,C_6H_5OCSCl/CH_2Cl_2,then Bu_3SnH, AIBN/toluene, then TFA/CH_2Cl_2; vii) DAST,C_5H_5N/CH_2Cl_2, then TFA/CH_2Cl_2, then OsO_4 , C_5H_5N/DMF-C_6H_6; viii) $(CF_3SO_2)O$/C_5H_5N, then NaN_3/DMF, then TFA/CH_2Cl_2.

corresponding 2'-O-(phenoxythiocarbonyl) derivative which was treated with tributyltin hydride and α,α'-azobisisobutyronitrile (AIBN) in toluene to afford the protected 2'-deoxygenated product 4 (64%). Removal of the benzoyl protecting groups with ammonia from 4 afforded 5 (82%), of which the 5'-hydroxy function was tritylated on reacting with 1.12 equivalents of 4-monomethoxytrityl chloride (MMTrCl) in pyridine for 14 h to afford 6 (95%).

The intermediate 6 was successively treated with phenyl chlorothionocarbonate and DMAP in methylene chloride, then with tributyltin hydride and AIBN in toluene, and finally with trifluoroacetic acid (TFA) in dichloromethane to yield 1-(α-L-5-hydroxymethyl-2-tetrahydrofuranyl)thymine (7) (69%).

Fluorination of 6 was effected using (diethylamino)sulfur trifluoride (DAST, 2 equiv.) in methylene chloride in the presence of pyridine at room temperature , and the crude reaction mixture was directly treated with TFA in methylene chloride to afford a mixture of 1-(2,3-dideoxy-α-L-*glycero*-pent-2-enofuranosyl)thymine (8) and 1-(2,3-dideoxy-3-fluoro-α-L-*threo*-pentofuranosyl)thymine (9) in a 53/47 molar ratio, the former resulting probably from a *trans*-elimination side reaction[10] with the favourably disposed H-2'. All attempts at this stage to separate these two compounds failed. To overcome this problem, we reacted the mixture of 8 and 9 with osmium tetroxide as oxidant[11] in order to convert the thymidinene 8 into the *cis*-glycol α-L-lyxo- and -ribofuranosyl stereoisomers. Thus, after OsO_4 treatment, pure 9 (15%) could be isolated by silica gel column chromatography.

Finally, treatment of the 3'-O-trifluoromethanesulfonate derivative of 6 (prepared *in situ*) with sodium azide in dimethylformamide (DMF), followed by acidic deblocking of the trityl protecting group, afforded a mixture of 1-(2,3-dideoxy-3-azido-α-L-*threo*-pentofuranosyl)thymine (10) (43%) and of the 2',3'-didehydroderivative 8 (10%) which could be separately isolated pure by preparative h.p.l.c. It is worth noting that, after this work was finished, we became aware of a communication relating an independent synthesis of 10.[12]

Compounds 7-10 were characterized by elemental analyses, ^1H n.m.r., u.v., fast atom bombardment mass spectrometry and where appropriate, ^{19}F n.m.r.[13] They were tested for their *in vitro* inhibitory effects on the replication of a number of DNA and RNA viruses, including HIV-1. Unfortunately, none of them showed a marked antiviral effect or host cell morphology at the highest concentration tested (1 mM).

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References :

1. (a) R. Yarchoan and S. Broder, *Pharmac. Ther.*, **1989**,*40*,329; (b) M. Nasr, C. Litterst and J. McGowan, *Antiviral Res.* **1990**, *14*, 125.
2. H. Mitsuya, K.J. Weinhold, P.A. Furman, M.H. St Clair, S.N. Lehrman, R.C. Gallo, D. Bolognesi, D.W. Barry and S. Broder, *Proc. Natl. Acad. Sci. U.S.A.*, **1985**,*82*,7096.
3. (a) P. Herdewijn, J. Balzarini, M. Baba, R. Pauwels, A. Van Aerschot, G. Janssen and E. De Clercq, *J. Med. Chem.*, **1988**,*31*,2040 ; (b) E. Matthes, C. Lehmann, D. Scholz, H.A. Rosenthal and P. Langen, *Biochem. Biophys. Res. Commun.*, **1988**,*153*,825 ; (c) J. Balzarini, M. Baba, R. Pauwels, P. Herdewijn and E. De Clercq, *Biochem. Pharmacol.*, **1988**,*37*,2847.
4. H. Mitsuya and S. Broder, *Proc. Natl. Acad. Sci. U.S.A.*, **1986**,*83*,1911.
5. (a) J. Balzarini, G.-J. Kang, M. Dalal, P. Herdewijn, E. De Clercq, S. Broder and D.G. John, *Mol. Pharmacol.*, **1987**, *32*,162. (b) Y. Hamamoto, H. Nakashima, T. Matsui, A. Matsuda, T. Ueda and N. Yamamoto, *Antimicrob. Agents Chemother.*, **1987**,*31*,907 ; (c) T.S. Lin, R.F. Schinazi and W.H. Prusoff, *Biochem. Pharmacol.*,**1987**,*36*,2713.
6. C. Génu-Dellac, G. Gosselin and J.-L. Imbach, *manuscript in preparation*.
7. (a) H. Vorbruggen, K. Krolikiewicz and B. Bennua, *Chem. Ber.*, **1981**,*114*,1234 ; (b) H. Vorbruggen and B. Bennua, *Chem. Ber.*, **1981**,*114*,1279.
8. Y. Ishido, N. Nakazaki and N. Sakairi, *J. Chem. Soc. Perkin Trans.I*, **1979**, 2088.
9. M.J. Robins, D. Madej, F. Hansske, J.S. Wilson, G. Gosselin, M.-C. Bergogne, J.-L. Imbach, J. Balzarini and E. De Clercq, *Canad. J., Chem.*, **1988**,*66*,1258.
10. T.J. Tewson and M.J. Welch, *J. Org. Chem.*,**1978**,*43*,1090.
11. V. Skaric and J. Matulic-Adamic, *Helv. Chim. Acta*, **1980**,*63*,2179.
12. J. Wengel, J. Lau, K. Walczak and E.B. Pedersen, *9th International Round Table, Nucleosides, Nucleotides and their Biological Applications*, July 30-August 3, **1990**, Uppsala, Sweden.
13. Physical properties of **10**: Mp 172-173°C (crystallized from MeOH); UV (EtOH) λ_{max} 268 nm (9,000), λ_{min} 234 nm (2,100); ^{1}H NMR (Me_2SO-d_6), δ (relative to Me_2SO-d_5 set at 2.49 ppm) 11.24 (s, 1H, NH-3), 7.54 (s, 1H, H-6), 6.07 (t, 1H, H-1'; $J_{1',2'}$ = 7.0 Hz), 4.9 (br s, 1H, OH-5'), 4.5 (m, 1H, H-3'), 4.4 (m, 1H, H-4'), 3.55 (d, 2H, H-5',5"; J = 5.1 Hz), 2.6-2.4 (m, 2H, H-2',2"), 1.78 (s, 3H, CH_3-5); mass spectra (matrix, glycerol-thioglycerol 50:50, v/v) FAB>0: 268 $(M+H)^+$, FAB<0: 266 $(M-H)^-$; $[\alpha]_D^{20}$ +12.8° (c 0.94, Me_2SO). Anal. calcd. for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.54; H, 5.08; N, 26.08.

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