Tetrahedron Letters, Vol.31, No.28, pp 4007-4010, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

1-(3′-AZIDO-2′,3′,5′-TRIDEOXY-β-D-ALLOFURANOSYL) THYMINE - A SIDE-CHAIN HOMOLOGUE OF 3′-AZIDO-3′-DEOXYTHYMIDINE

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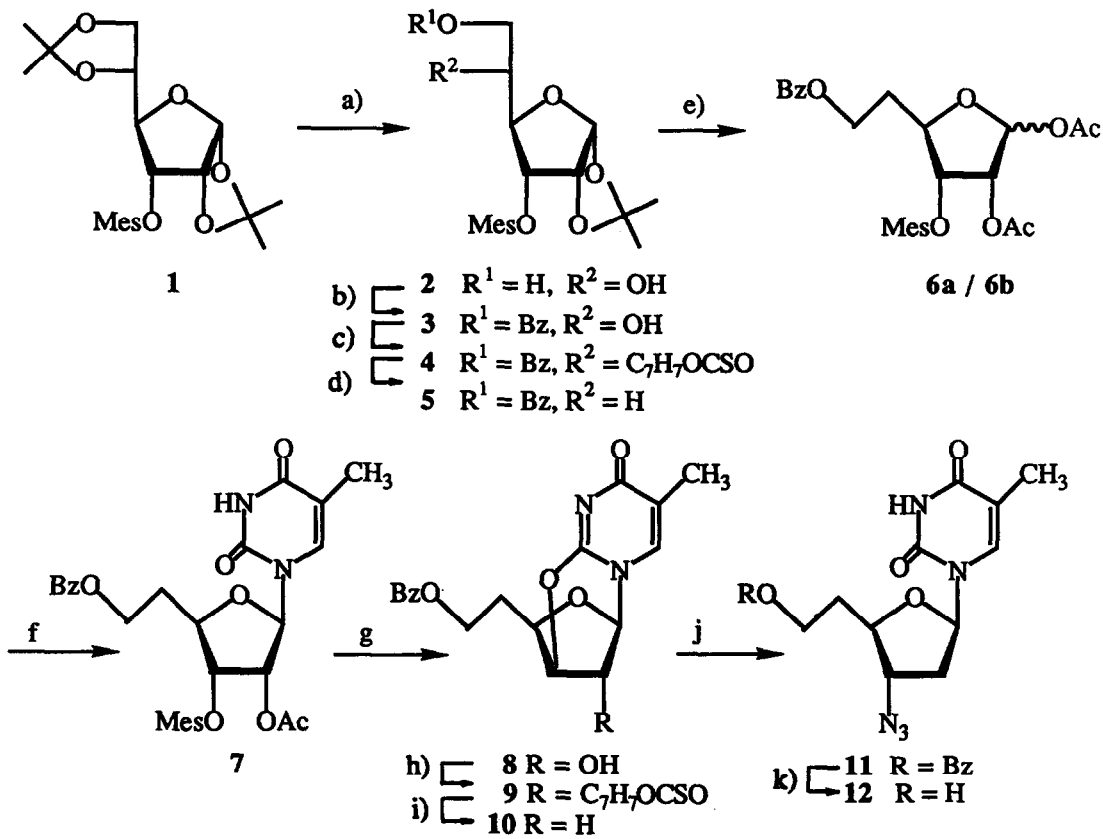
Summary: 1-(3′-Azido-2′,3′,5′-trideoxy-ß-D-allofuranosyl)thymine **12** (homo-AZT) was synthesized starting from 1,2;5,6-di-O-isopropylidene- 3-O-mesyl-α-D-allofuranose **1** in an eleven step sequence (overall yield: 4%).

The discovery of 3′-azido-3′-deoxythymidine (AZT, AzddThd) as an antiretroviral agent[1] represents the first important marking in the chemotherapy of AIDS. As the triphosphate analogue, AZT inhibits the utilization of dTTP by reverse transcriptase and may be incorporated in the terminal position of DNA, thereby preventing elongation[2]. AZT is the only drug approved to date by the Food and Drug Administration for treatment of AIDS and AIDS related complex (ARC) but is significantly toxic to many individuals receiving this drug[3]. Side effects include headaches, lowered white-cell counts, and suppression of bone marrow cell formation[4]. Additionally, its short half-life in the body nessitates frequent administration to maintain therapeutically effective levels[5].Therefore, the search continues for closely related nucleoside analogues[6] with increased antiviral activity and decreased cytotoxicity . Carbacyclic AZT[7], a sulphur analog of AZT prepared by selective oxygen - sulfur - exchange at the C-4 carbonyl moiety of thymine[8], phosphonate isostere of AZT-5′-phosphate[9], analogues of AZT formally obtained by substitution of 5-CH_3 by H, CF_3 or halogen atoms (Br, F, J)[10] and acyclic analogs of AZT[11,12] were synthesized.

The title compound is a structurally most interesting congener of AZT. The elongation of the side-chain enhances the lipophilicity. The present report describes a convenient synthesis of this new analogue of AZT, which is illustrated in Scheme 1. We started with 1,2;5,6-di-O-isopropylidene-3-O-mesyl-α-D-allofuranose **1**[13], from which 1,2-O-isopropylidene-α-D-allofuranose **2**[13] was prepared by selective deblocking with 80% acetic acid (yield:79%). In the next step **2** was transformed selectively to 6-O-benzoyl derivative **3**[14] (68%, mp. 83-84°C). Then the 5′-O-(4-methylphenoxy)thiocarbonyl derivative **4** (yield: 82%) was deoxygenated with tributyltin hydride[15] to the 6-O-benzoyl-5-deoxy-1,2-O-isopropylidene-3-O-mesyl-α-D-allofuranose **5** (92%, mp. 69-70°C). Acetolysis (Ac_2O, AcOH, H_2SO_4 cat., 4°C, 16h) led to the anomeric mixture of 6-O-benzoyl-1,2-di-O-acetyl-3-O-mesyl-D-allofuranoses **6a/6b** (colorless oil,

88%). These sugar derivatives are most suited for the one pot procedure[16] of silyl-Hilbert- Johnson method. Using this strategy only the ß-nucleoside derivative 7[17] was formed in 46% yield. The formation of the 2,3´- anhydro derivative 8[18] was performed with DBU, proofing the ß - configuration of 7. The simultaneously selective saponification of the acetyl group at 2´- position with DBU[19] is noticeable. The 2´- O - (4-methylphenyloxy)-

Scheme 1



Scheme 1: a) AcOH : H_2O = 4 : 1, 16h, 25°C; b) BzCl, pyridine, 16h, -30 ->25°C; c) $CH_3C_6H_4OCSCl$, DMAP, CH_3CN, 16h, 25°C; d) Bu_3SnH, AIBN, toluene, 5h, 120°C; e) Ac_2O : AcOH = 2 : 1, H_2SO_4 cat., $CHCl_3$, 16h, 4°C; f) thymine, HMDS, TMS-Cl, CF_3SO_3H, CH_3CN, 5h, 80°C; g) 5 equiv. DBU, THF, 55h, 60°C; h) $CH_3C_6H_4OCSCl$, DMAP, CH_3CN, 16h, 25°C; i) Bu_3SnH, AIBN, toluene, 5h, 120°C; j) LiN_3, BzOH, DMF, 20h, 120°C; k) $NaOCH_3$, MeOH, 16h,

thiocarbonyl derivative 9[20] was deoxygenated with tributyltin hydride to yield compound 10[21]. Azidonucleoside derivative 11[22] was synthesized by opening of the 2,3'- anhydro-bridge of 10 with lithium azide / benzoic acid[23]. Deblocking of 11 with sodium methoxide yielded the desired title compound 12[24] (mp. 127-129°C).

Biological data and further experimental details will be published in a forthcoming paper.

Acknowledgment: This work was supported by the Fonds zur Förderung der wissenschaftlichen Forschung in Österreich - Project no. 7177. We thank Judith Humpelstetter for excellent technical assistance.

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17 compound 7: white foam, yield: 46%; MS (70ev, 220°C): m/e(%) = 496(1,M^+). ^{1}H-NMR (250 MHz,$CDCl_3$) : 1.90 (d, 3H, J(CH_3,6) = 1.0 Hz, 5-CH_3), 2.17 (s, 3H, $OCOCH_3$), 2.13-2.45(m, 2H, 5´-Ha, 5´-Hb), 3.10(s, 3H, OSO_2CH_3), 4.32(ddd, 1H, $J_{3´,4´}$ = 7.0Hz, J = 4.0 Hz, J = 9.0 Hz,4´-H), 4.38-4.60(m, 2H, 6´-Ha, 6´-Hb), 5.28(t,1H, $J_{1´,2´} = J_{2´,3´}$ = 7.0 Hz, 2´-H), 5.55-5.63(m, 2H, 1´-H, 3´- H), 6.98(d, 1H, 5-H), 7.44(2H), 7.57(1H), 8.04(2H), 9.40(br s, 1H, 3-H).

18 compound 8: white foam, yield: 83%; MS (70ev, 300°C): m/e(%) = 358(12, M^+). ^{1}H-NMR (400 MHz, d_6-DMSO) : 1.75(d, 3H, J(CH_3,6) = 0.80 Hz, 5-CH_3), 1.94(m,1H, 5´-Ha), 2.09(m,1H, 5´-Hb), 4.31-4.46(m, 2H, 6´-Ha, 6´-Hb), 4.61(ddd, 1H, J = 2.2Hz, J = 6.0Hz, J = 9.0Hz,4´-H),4.75(br s, 1H, 2´-H), 5.02(br s, 1H, 3´-H), 5.52(s, 1H, 1´-H),6.38(br s, 1H, 2´- OH, D_2O exchangeable), 7.56(d, 1H, 6-H), phenyl protons: 7.51(2H), 7.65(1H), 7.95(2H).

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20 compound 9: white foam, yield:83%; ^{1}H-NMR (250 MHz, $CDCl_3$) : 2.00(s,3H, 5-CH_3), 2.28(m,2H, 5´-Ha, 5´- Hb), 2.38(s, 3H, CH_3), 4.50(m, 2H, 6´-Ha, 6´-Hb), 4.79(ddd, 1H, J = 2.0 Hz, J = 4.0 Hz, J = 8.0 Hz, 4´-H), 5.20(br s, 1H, 3´-H), 5.71(s, 1H, 1´-H), 5.97(s, 1H, 2´- H), 7.00(s, 1H, 6-H), tolyl protons: 6.98(d, 2H), 7.22(d,2H), phenyl protons: 7.45(2H), 7.58(1H), 8.05(2H).

21 compound 10: white foam, yield: 89%; MS (70ev, 200°C): m/e(%) = 342(9,M^+). ^{1}H-NMR (250 MHz, $CDCl_3$) : 1.97(d, 3H, J(CH_3,5) = 0.8Hz), 2.18(m,2H, 5´-Ha, 5´-Hb), 2.50(ddd, 1H, $J_{1´,2´a}$ = 3.3Hz, $J_{2´a,2´b}$= 12.0Hz, $J_{2´a,3´}$= 1.8Hz, 2´-Ha), 2.68(d, 1H, 2´-Hb),4.45(m, 3H, 4´-H, 6´-Ha, 6´-Hb), 5.18(m, 1H,3´-H), 4.48(d, 1H, 1´-H), 6.90(d, 1H, 6-H), phenyl protons: 7.45(2H), 7.58(1H), 8.33(2H).

22 compound 11: white foam, yield: 50%; MS (70ev, 200°C): m/e(%) = 385(2,M^+). ^{1}H-NMR (250MHz, $CDCl_3$) : 1.93(d, 3H, J(CH_3,5) = 1.2Hz), 2.21(m,2H, 5´-Ha, 5´-Hb), 2.43(m,2H, 2´- Ha, 2´-Hb), 4.10(m,2H, 6´-Ha, 6´-Hb), 4.56(dt, 1H, $J_{3´,4´}$ = 11.0Hz, $J_{2´,3´}$ = 6.0Hz, 3´-H), 6.05(t, 1H, $J_{1´,2´}$ = 6.0Hz, 1´- H), phenyl protons: 7.45(2H), 7.75(1H), 8.05(2H), 8.75(br s, 1H, 3-H).

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24 compound 12: mp. 127-129°C, yield: 82%; IR(KBr): ν =2102cm^{-1}; MS (70ev, 180°C): m/e(%) = 281(3, M^+). ^{1}H-NMR (250MHz, $CDCl_3$) : 1.95(s, 3H, 5-CH_3), 2.00(m, 2H, 5´-Ha, 5´- Hb), 2.43(pseudo t, 2H, 2´- Ha, 2´- Hb), 2.75(br s, 1H, 5´- OH, D_2O exchangeable), 3.85(m, 2H, 6´-Ha, 6´-Hb), 3.95(m, 1, 4´-H), 4.11(q, 1H, $J_{3´,2´a} = J_{3´,2´b} = J_{3´,4´}$ = 7.0Hz, 3´-H), 6.05(t, 1H, $J_{1´,2´a} = J_{1´,2´b}$ = 7.0Hz), 7.12(s, 1H, 6-H), 8.87(br s, 1H, 3-H, D_2O exchangeable).

(Received in Germany 18 April 1990)