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Synthesis of 3'-Azido-5'-Homothymidine Analogs

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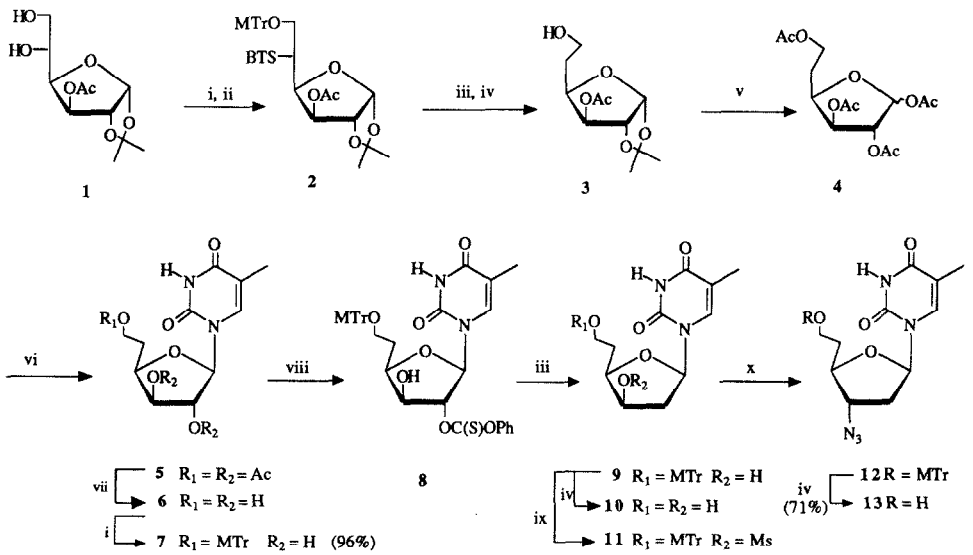
Abstract : 1-(3'-azido-2',3',5'-trideoxy-ß-D-allofuranosyl) thymine 13, and 1-(3'-azido-3',5'-dideoxy-ß-D-(glucofuranosyl) thymine 20 and its 2'-O-methyl ether 22 were synthesized starting from 1,2-O-isopropylidene-α-D-glucopyranose and from 1,2-O-isopropylidene-α-D-allofuranose, respectively.

Since the discovery of the human immunodeficiency virus (HIV) as the etiological agent of AIDS, intensive efforts are underway worldwide to find compounds that can block the replication of retroviruses. Therefore the enzyme reverse transcriptase, which plays a central role in the proliferation of the virus and is not found in the non-invaded host cell, is one of the major targets. Among the large number of 2',3'-dideoxy-nucleosides which have been synthesized and processed by this enzyme, 3'-azido-3'-deoxy-thymidine (AZT)[1] is the only FDA-approved drug available at the present time for the treatment of patients suffering from AIDS.

Since the brain may be an important site of HIV replication[2], we have investigated 5'-homonucleosides as lipophilic analogs of AZT. We report herein the synthesis of **13**, the 5'-homo analog of AZT and of **20** and **22**. Our versatile approach is based upon the preparation of the suitably functionalized hexofuranosyl moieties and their coupling with a silylated thymine in the key step. The formation of a 1,2-acyloxonium ion was used to minimize the formation of α anomers which are generally devoid of biological activity. Eventually 2'-deoxygenation was carried out.

3-O-acetyl-2,3-O-isopropylidene-α-D-glucofuranose **1**[3] was selectively protected as its 5-methoxytrityl ether (87%) and subsequently treated with S-benzothiazoledisulfide[4] to afford compound **2**[5] in 73% yield (scheme 1). Radical deoxygenation of **2** followed by deprotection of the primary OH led to the 5-deoxyglucofuranose derivative **3** (50%). Acetolysis of **3**[6] and then coupling of the anomeric mixture of **4** with silylated thymine by the procedure of Vorbrüggen[7] (CH_3CN, TMSOTf) gave **5**[8]. After transesterification (79% overall yield for the two

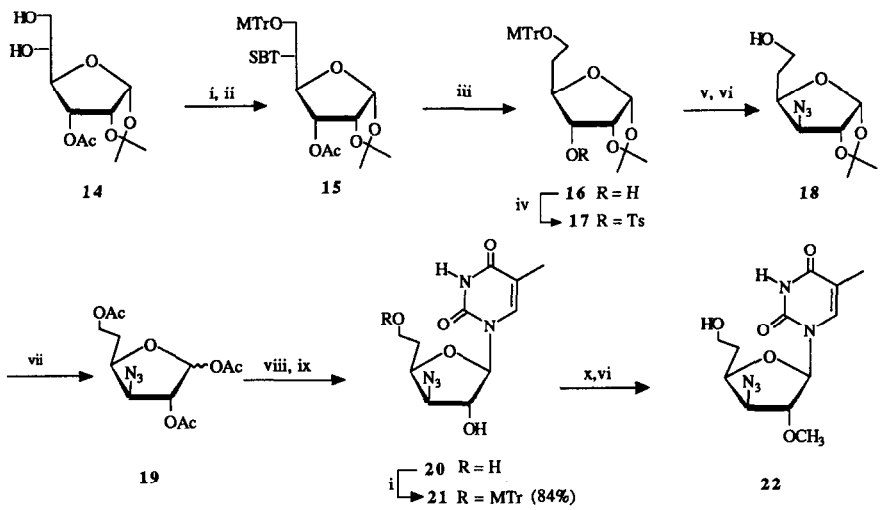
steps) and selective protection of **6**, the 2'-deoxy corresponding analog **9** was easily obtained through a highly selective thiocarbonylation of **7** with phenyl chlorothionoformate (4 equiv.) and radical deoxygenation of the phenylthiocarbonate **8** (Bu_3SnH, AIBN). Mild acidolysis of **9** gave **10**[9] and finally, the azido group as present in **13**[10], (recently reported by Hiebl and Zbiral[11]), was introduced after mesylation of **9**, azidolysis of **11** in DMF under reflux and deprotective treatment (overall yield ≈ 65%) of **12**.



SCHEME 1

To obtain the 3'-azido-2'-O-methyl derivative of arabino configuration **22** (scheme 2) the starting compound was the 3-O-acetyl-1,2-O-isopropylidene-α-D-allohexofuranose **14**[12]. Selective 5'-OH protection of **14** followed by 5-benzothiazoledisulfide treatment afforded **15** which after radical deoxygenation led to **16**. Then tosylation of **16** and azidolysis of **17** gave **18**. The anomeric mixture of 1,2,6-tri-O-acetyl-3-azido-3,5-dideoxy-D-glucofuranose **19** resulting from acetolysis of **18** was condensed with the silylated thymine to afford stereoselectively after transesterification the ß-nucleoside **20**[13]. Finally, compound

22 was obtained after successive protection of the 5'-OH as a methoxytriphenylether, methylation and deblocking (**20** → **21** → **22**)[14].



14 **15** **18** **19** **22**

i: MTrCl, pyridine, R.T. 2h ,(88%); ii: S-benzothiazolyl disulfide, Bu_3P, toluene, reflux, 1.5h (92%); iii:Bu_3SnH, AIBN,toluene, reflux, 48h(77%); iv: TsCl, pyridine, RT, 18h (89%); v: NaN_3, DMF, reflux, 7h (79%);vi: TsOH 2% in CH_2Cl_2-MeOH, 70/30, 30 min. (83%):vii: Ac_2O-AcOH-H_2SO_4, 0°C-> RT, 18h (77%); viii: silyl thymine, TMSOTf, CH_3CN, R.T. (41%); ix: MeONa-MeOH, R.T. (75%); x: ICH_3, NaH, THF, 8h.

SCHEME 2

References and Notes

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8. Compound **5** : ^{1}H-NMR ($CDCl_3$, 100 MHz) : 1,5-2,0 ppm (14H, m, CH_3-5, H5', H5", Acetyl) ; 4,0-4,5 ppm (3H, m, H4', H6', H6") ; 5,12 ppm (1H, d, J = 2,3Hz, H2') ; 5,27 ppm (1H, d, H3', J = 3,5Hz) ; 6,03 ppm (1H, d, J = 2,3Hz, H1') ; 7,24 ppm (1H, d, J = 1,0Hz, H6) ; 8,37 ppm (s, NH).

9. Compound **10** : ^{1}H-NMR (d4-MeOH , 100 MHz) : 1,87 ppm (3H, d, J = 1,2 Hz, CH_3-5) ; 1,9-2,1 ppm (3H, m, H2', H5',H5") ; 2,65 ppm (1H, ddd, J = 5,3Hz, 8,3 Hz, 14,9 Hz, H2") ; 3,73 ppm (2H, t, J = 6,4 Hz, H6', H6") ; 4,00 ppm (1H, dt, J = 3,0Hz, 6,8 Hz, H4') ; 4,24 ppm (1H, dd, J = 3,0Hz, 5,0Hz, H3') ; 6,11 ppm (1H, dd, J = 2,4 Hz, 8,3Hz, H1') ; 7,87 ppm (1H, d, J = 1,2Hz, H6). mp < 50°C.

10. Compound **13** : MS(DIC/NH_3) : m/z 282 $(M + H)^+$. ^{1}H-NMR ($CDCl_3$, 100MHz) : 1,57 ppm (s, 6'-OH) ; 1,94 ppm (3H, d, J = 1,2 Hz, CH_3-5) ; ≈ 2,0 ppm (2H, m, H5',H5") ; 2,41 ppm (2H, pseudo t, J = 6,5 Hz, H2', H2") ; 3,8-4,2 ppm (4H, m, H3', H4', H6', H6") ; 6,04 ppm (1H, t, J = 6,3 Hz, H1') ; 7,11 ppm (1H, d, J = 1,2 Hz, H6) ; 8,43 ppm (s, NH). IR (KBr) : ν = 2106 cm^{-1}. mp : 136-138°C.

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13. Compound **20** : MS(DIC/NH_3) : m/z 298 $(M + H)^+$. ^{1}H-NMR (d4-MeOH , 100 MHz) : 1,89 ppm (3H, d, J = 1,2Hz, CH_3-5) ; 2,02 ppm (2H, pseudo q, J = 6,4 Hz, H5', H5") ; 3,74 ppm (2H, t, J = 6,3 Hz, H6', H6") ; 4,03 ppm (1H, dd, J = 1,5 Hz, 3,9 Hz, H3') ; 4,28 ppm (1H, pseudo t, J = 1,6Hz, H2') ; 4,47 ppm (1H, dt, J = 3,9Hz, 6,6Hz, H4') ; 5,73 ppm (1H, d, J = 1,8 Hz, H1') ; 7,46 ppm (1H, d, J = 1,2 Hz, H6).

14. Compound **22** : MS(DIC/NH_3) : m/z 312 $(M + H)^+$. ^{1}H-NMR ($CDCl_3$, 100 MHz) : 1,94 ppm (3H, d, J = 1,1Hz, CH_3-5) ; 2,06 ppm (2H, q, J = 5,6 Hz, H5', H5") ; 3,53 ppm (3H, s, CH_3-O 2') ; 3,8 ppm (3H, m, H2', H6', H6") ; 4,02 ppm (1H, d, J = 3,4 Hz, H3') ; 4,40 ppm (1H, dt, J = 3,4 Hz, 6,6 Hz, H4') ; 5,89 ppm (1H, d, J = 1,4 Hz, H1') ; 7,32 ppm (1H, d, J = 1,1 Hz, H6) ; 8,78 ppm (s, NH).

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