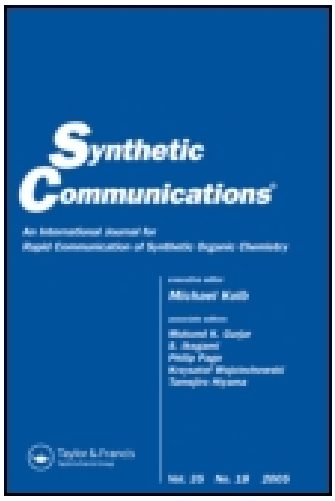

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SYNTHESIS OF 3′-AZIDO-2′,3′-DIDEOXY-4′-KETOHEXOPYRANOID ANALOGUES AS POSSIBLE ANTIVIRAL NUCLEOSIDES

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ABSTRACT

Peracetylated 2-deoxy-D-glucose was coupled with silylated bases. The product was deacetylated and the 4′,6′-hydroxy groups were then protected. An azido group was introduced at the 3′-carbon via tosylation, followed by deprotection, tritylation, and oxidation to give the final compound.

INTRODUCTION

Azidothymidine (AZT),[1] is the first clinically approved drug for treating acquired immunodeficiency syndrome (AIDS).[2] However, serious side

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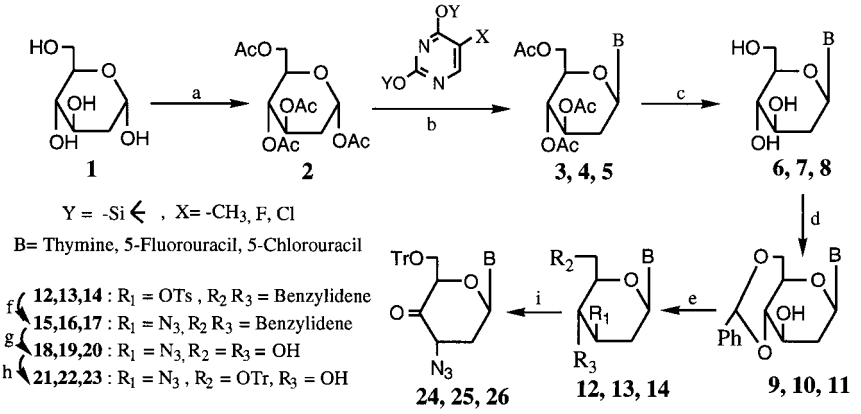
effects, such as short plasma half life[3] and bone marrow suppression,[4] were reported on clinical administration. In order to increase its therapeutic efficacy, several analogues of AZT were synthesized[5,6] and various steroidal carboxylic ester[7] and phosphotriester[8] conjugates of AZT were synthesized in our laboratory.

Recent synthesis in our laboratory and others of some pyrimidine nucleosides with unsaturated ketohexopyranosyl moiety,[9–12] which showed significant in vitro and in vivo anti-cancer and antiviral activities, stimulated our quest for more analogues of these compounds.

The study of the structure–activity relationship of unsaturated ketohexopyranosyl nucleosides has shown that the presence of an α,β-unsaturated keto system in the sugar ring plays a very important role for the biological activities[13] of these nucleosides.

Considering all these factors, we report here the synthesis of pyranoid analogues having an azido (N_3) group at the 3′-carbon and a keto group at the 4′-carbon with different pyrimidine bases in order to examine whether there is any potential for biological activity. While the evaluation of the biological activity of these compounds is in progress, the synthesis of other compounds in this series is continuing in our laboratory.



Reagent and Conditions: (a) Ac_2O, Pyridine (b) TMS-triflate, CH_3CN, 0°C → reflux (85°C), 3 h (c) NH_3/MeOH (d) $C_6H_5CH(OCH_3)_2$, HBF_4, DMF, 18–24 h, 75–80% (e) Tosyl chloride, DMAP, Pyridine, 32 h, 80% (f) NaN_3, DMF, 135°C, reflux, 4 h, 75–80% (g) 40% aq. trifluoroacetic acid, 4 h (h) Triphenylmethyl chloride, DMAP, Pyridine, 18–24 h, 62% (i) PDC, molecular sieves 3 Å, CH_2Cl_2, room temp., 6 h, 42%.

CHEMISTRY

Acetylated α-2-deoxy-D-glucose **2** was coupled with silylated bases in the presence of TMS-triflate to yield the β-isomer of tri-*o*-acetylated nucleosides **3**, **4**, **5**.[6]

Deacetylation of **3**, **4**, **5** in methanolic ammonia gave compounds **6**, **7**, **8** in quantitative yield. These compounds were then treated with benzaldehydedimethyl acetal and tetrafluoroboric acid[14] in anhydrous DMF to protect 4′,6′-hydroxyl groups to give **9**, **10** and **11**. The protected benzylidene nucleosides were treated with tosyl chloride in pyridine with DMAP to give **12**, **13** and **14**. These then reacted with NaN_3 in DMF to afford compounds **15**, **16** and **17**. The 4′,6′-benzylidene groups of these nucleosides were cleaved in 40% aq. trifluoroacetic acid in a small amount of ethanol to afford **18**, **19** and **20** which were then dried well overnight and treated with well-dried triphenylmethyl chloride in pyridine in the presence of DMAP, giving the 6′-*o*-trityl nucleosides **21**, **22** and **23**. Finally, oxidation of **21**, **22** and **23** with pyridinium dichromate in the presence of molecular sieves (3Å) in dry CH_2Cl_2 gave the target compounds **24**, **25** and **26** which were characterized by the absence of the H-4′ proton in their NMR and by IR spectrum.

EXPERIMENTAL SECTION

α-2-Deoxy-glucose, nucleobases, DMF, acetonitrile of anhydrous grade, and all other chemicals used were purchased from Adrich Chemical Co. THF and CH_2Cl_2 were distilled from Na/benzophenone and CaH respectively under N_2 atmosphere. Melting point (uncorrected) was recorded using Mel-Temp apparatus. Thin layer chromatography (TLC) was performed on precoated silica gel plastic TLC sheets $60F_{254}$ (0.2 mm) EM reagents. Compound visualization was effected with a UV lamp (254 nm) and confirmed by spraying a 5% solution of H_2SO_4 in EtOH, followed by heating. ^{1}H NMR spectra were recorded on a Brucker/IBM-5Y2000 spectrometer at 300 MHz with Me_4Si as internal standard and are expressed in ppm. Silica gel 60 (70–230 mesh ASTM) was used for column chromatography. Molecular sieves (3 Å) used for oxidation was finely powdered, heated to about 375–400°C just before the experiment in a vacuum system (specially designed) in the vicinity of P_2O_5 and then cooled to room temperature. All the reactions were carried out under N_2 atmosphere.

1-(2,3-Dideoxy-3,4,6-tri-*o*-acetyl-β-D-glycero-hexopyranosyl)thymine 3: A mixture of thymine (17.0 g, 134.79 mmol) and saccharine (50 mg) in hexamethyldisilazane (HMDS) (30 ml) and 1,2-dichloroethane (20 ml) was

heated under reflux for 3 h to get a clear solution. Excess HMDS was removed by evaporation under vacuum and the reaction assembly was flushed with dry N_2 gas. A solution of **2** (17.76 g, 53.49 mmol) in dry CH_3CN (50 ml) was then added to the silylated base. The reaction mixture was then cooled to 0°C in an ice bath. The stirred, cooled reaction mixture was finally treated dropwise with TMS-triflate (10 ml, 44.99 mmol). After complete addition, the reaction mixture was stirred at room temperature for 30 min and then heated at 85°C for 3 h. Later, it was cooled in an ice bath (below 5°C) and neutralized with methanolic ammonia solution. The solvent was evaporated and the residue obtained was mixed with EtOAc. The precipitate separated was filtered and washed with excess of ethyl acetate. The combined filtrate was concentrated and purified by column chromatography (silica gel) using hexane : EtOAc (3 : 2) as eluant. Yield, 92%, m.p. 188°C. ^{1}H NMR ($CDCl_3$): δ 8.59 (s, 1H,-NH proton); 7.15 (brs, 1H, H-6); 5.88 and 5.84 (dd, 1H, H-1′, $J = 10$ Hz and 7 Hz); 5.15 (m, 1H, H-3′); 5.02 (m, 1H, H-4′); 4.28 and 4.24 (dd, 1H, H-6′b, $J = 12$ Hz and 4 Hz); 4.10 and 4.06 (dd, 1H, H-6′a, $J = 12$ Hz and 4.5 Hz); 3.80 (m, 1H, H-5′); 2.42 (m, 2H, H-2′); 2.08, 2.05, 2.01 (each s, each 3H, 3 × OAc); 1.93 (s, 3H,-CH_3). Anal. calcd for $C_{17}H_{22}O_9N_2$: C, 51.25; H, 5.53; N, 7.04. Found: C, 51.82; H, 5.06; N, 7.18.

5-Fluoro-1-(2,3-dideoxy-3,4,6-tri-*o*-acetyl-β-D-glycero-hexopyranosyl)uracil 4: Following the procedure as described for the synthesis of **3**, 5-fluorouracil (10 g, 76.88 mmol) was silylated with HMDS (22 ml) and saccharine (30 mg), and then silylated base was condensed with **2** (9.2 g, 27.71 mmol) in presence of TMS-triflate (6.0 ml, 26.99 mmol) in dry acetonitrile (40 ml). Worked up followed by column chromatography (3 : 2, hexane : ethyl acetate) of the reaction mixture afforded compound **4** as crystalline solid. Yield 88%. ^{1}H NMR ($CDCl_3$): δ 8.68 (s, 1H,-NH proton); 7.25 (brs, 1H, H-6); 5.78 and 5.75 (dd, 1H, H-1′, $J = 12$ Hz and 8 Hz); 5.15–5.08 (m, 2H, H-3′ and H-4′); 4.26 and 4.21 (dd, 1H, H-6′b, $J = 12$ Hz and 6 Hz); 4.12 and 4.05 (dd, 1H, H-6′a, $J = 10$ Hz and 4.5 Hz); 3.76 (m, 1H, H-5′); 2.45 (m, 2H, H-2′); 2.06, 2.04, 2.01 (each s, each 3H, 3 × OAc). ^{19}F NMR ($CDCl_3$): −116.35. Anal. calcd for $C_{16}H_{19}O_9N_2F$: C, 47.76; H, 4.73; N, 6.97. Found: C, 47.02; H, 4.73; N, 6.82.

5-Chloro-1-(2,3-dideoxy-3,4,6-tri-*o*-acetyl-β-D-glycero-hexopyranosyl)uracil 5: Following the procedure as described for the synthesis of **3**, 5-chlorouracil (8.0 g, 54.60 mmol) was silylated with HMDS (12 ml) and saccharine (20 mg), and then silylated base was condensed with **2** (7.0 g, 21.08 mmol) in the presence of TMS-triflate (4.5 ml, 20.25 mmol) in dry acetonitrile (40 ml). Worked up followed by column chromatography (3 : 2, hexane : ethyl acetate) of the reaction mixture afforded compound **5** as crystalline solid. Yield 89%. m.p. 132–135°C. ^{1}H NMR was in accordance with the structure

of the compound. Anal. calcd for $C_{16}H_{19}O_9N_2Cl$: C, 45.93; H, 4.55; N, 6.70. Found: C, 45.81; H, 4.53; N, 6.06.

1-(2,3-Dideoxy-β-D-glycero-hexopyranosyl)thymine 6: Yield 95%; m.p. 218–220°C; ^{1}H NMR (CD_3OD): δ 8.88 (brs, 1H, -NH proton); 7.18 (brs, 1H, H-6); 5.88 and 5.84 (dd, 1H, H-1′, $J = 10$ Hz and 7 Hz); 5.15 (m, 1H, H-3′); 5.02 (m, 1H, H-4′); 4.28 and 4.19 (dd, 2H, H-6, $J = 12$ Hz and 6 Hz); 3.80 (m, 1H, H-5′); 2.42 (m, 2H, H-2′); 1.93 (s, 3H, -CH_3).

Compound **7**: Yield 94%; m.p. 215–219°C.

Compound **8**: Yield 93%; m.p. 220–222°C.

1-(2,3-Dideoxy-4,6-*o*-benzylidene-β-D-glycero-hexopyranosyl)thymine 9: Yield 75%; m.p. 149–152°C; ^{1}H NMR ($CDCl_3$): δ 8.65 (brs, 1H, -NH proton); 7.23–7.16 (m, 6H, -C_6H_5 and H-6); 6.68 (d, 1H, H-1′, $J = 10$ Hz); 5.51 (m, 1H, H-3′); 5.12 (m, 1H, H-4′); 4.48 and 4.32 (two dd, 2H, H-6′, $J = 12$ Hz and 4 Hz); 3.51 (m, 1H, H-5′); 2.46 and 2.40 (two m, 2H, $J_{gem} = 12.7$ Hz, $J_{vic} = 3.05$, 1.65 Hz, H-2′); 1.92 (s, 3H, CH_3).

Compound **10**: Yield 72%; m.p. 154–155°C.

Compound **11**: Yield 71%; m.p. 158–161°C.

1-(2,3-Dideoxy-4,6-*o*-benzylidene-3-*o*-tosyl-β-D-glycero-hexopyranosyl)-thymine 12: Yield 75%; ^{1}H NMR ($CDCl_3$): δ 8.70 (brs, 1H,-NH proton); 7.28–7.17 (m, 11H, 2x-C_6H_5 and H-6); 5.98 (d, 1H, H-1′, $J = 12$ Hz); 5.52–5.33 (m, 2H, H-3′ and H-4′); 4.46 and 4.31 (two dd, 2H, H-6′, $J = 12$ Hz and 4 Hz); 3.60 (m, 1H, H-5′); 2.45 and 2.41 (two m, 2H, $J_{gem} = 12.7$ Hz, $J_{vic} = 3.05$, 1.65 Hz, H-2′); 1.91 and 1.93 (two s, 6H, 2×- CH_3).

Compound **13**: Yield 75–78%; Syrup.

Compound **14**: Yield 76–80%; Syrup.

1-(3-Azido-2,3-dideoxy-4,6-*o*-benzylidene-β-D-glycero-hexopyranosyl)thymine 15: Yield 75%; m.p. 110–112°C; ^{1}H NMR ($CDCl_3$): δ 8.63 (brs, 1H, -NH proton); 7.48–7.22 (m, 6H, -C_6H_5 and H-6); 6.65 (d, 1H, H-1′, $J = 12$ Hz); 5.65–5.51 (m, 2H, H-3′ and H-4′); 4.58 and 4.41 (two dd, 2H, H-6′, $J = 10$ Hz and 4 Hz); 3.54 (m, 1H, H-5′); 2.46 and 2.40 (two m, 2H, $J_{gem} = 12.8$ Hz, $J_{vic} = 3.08$, 1.80 Hz, H-2′); 1.93 (s, 3H, CH_3). IR (KBr): 2125 cm^{-1} (N_3 group).

Compound **16**: Yield 72–78%; IR(Neat): 2120 cm^{-1} (N_3 group).

Compound **17**: Yield 75–80%; IR(Neat): 2122 cm^{-1} (N_3 group).

1-(3-Azido-2,3-dideoxy-β-D-glycero-hexopyranosyl)thymine 18: Yield 90%; m.p. 182–185°C; ^{1}H NMR ($CDCl_3$): δ 8.62 (brs, 1H, -NH proton); 7.50 (brs, 1H, H-6); 6.68 (d, 1H, H-1′, $J = 10$ Hz); 5.64–5.46 (m, 2H, H-3′ and H-4′); 4.52 and 4.38 (two dd, 2H, H-6′, $J = 12$ Hz and 4 Hz); 3.62 (m, 1H, H-5′); 2.48 and 2.32 (two m, 2H, H-2′); 1.92 (s, 3H, CH_3). IR (KBr): 2125 cm^{-1} (N_3 group).

Compound **19**: Yield 85–90%; IR(Neat): 2120 cm^{-1} (N_3 group); ^{19}F NMR ($CDCl_3$): − 117.65.

Compound **20**: Yield 85%; IR(Neat): 2122 cm^{-1} (N_3 group).

1-(3-Azido-2,3-dideoxy-6-*o*-trityl-β-D-glycero-hexopyranosyl)thymine 21: Yield 55–60%; ^1H NMR ($CDCl_3$): δ 8.60 (brs, 1H, -NH proton); 7.58–7.18 (m, 16H, 3x-C_6H_5 and H-6); 6.62 (d, 1H, H-1′, $J = 10$ Hz); 4.92–4.72 (m, 2H, H-3′ and H-4′); 4.46 and 4.31 (two dd, 2H, H-6′, $J = 10$ Hz and 4 Hz); 3.55 (m, 1H, H-5′); 2.43 and 2.38 (two m, 2H, H-2′); 1.91 (s, 3H, -CH_3). IR (KBr): 2122 cm^{-1} (N_3 group).

Compound **22**: Yield 60–62%; IR(Neat): 2125 cm^{-1} (N_3 group).

Compound **23**: Yield 58–60%; IR(Neat): 2124 cm^{-1} (N_3 group).

1-(3-Azido-2,3-dideoxy-6-*o*-trityl-β-D-glycero-hexopyranose-4-ulosyl)thymine 24: 1.0 gm (1.90 mmol) of **21** and (1.78 g, 4.73 mmol) of PDC were dried with THF. 4.0 g of molecular seive (3Å), freshly activated at 375°C over P_2O_5 in vacuum, was cooled and added to the flask, followed by 40 ml of anhyd. CH_2Cl_2. After 6 h stirring at room temperature, the mixture was diluted with equal volume of EtOAc and stirred further for 30 min. It was then filtered over a bed of silica gel and celite and washed copiously with CH_2Cl_2. Combined filterate was concentrated and purified by column chromatography using hexane : EtOAc (3 : 2) as eluant to obtain pure compound. Yield: 42%; m.p. 145°C; ^1H NMR ($CDCl_3$): δ 8.62 (brs, 1H, -NH proton); 7.50–7.20 (m, 16H, $3 \times$-C_6H_5 and H-6); 6.68 (d, 1H, H-1′, $J = 10$ Hz); 5.51 (m, 1H, H-3′); 4.48 and 4.32 (two dd, 2H, H-6′, $J = 12$ Hz and 4 Hz); 3.51 (m, 1H, H-5′); 2.46 and 2.40 (two m, 2H, $J_{gem} = 12.7$ Hz, $J_{vic} = 3.05$, 1.65 Hz, H-2′); 1.92 (s, 3H, CH_3). IR (KBr): 2125 cm^{-1} (N_3 group), 1720 cm^{-1} (keto group). Anal. calcd for $C_{30}H_{27}O_5N_5$: C, 67.04,; H, 5.03; N, 13.04. Found: C, 67.31; H, 5.08; N, 13.21.

5-Fluoro-1-(3-azido-2,3-dideoxy-6-*o*-trityl-β-D-glycero-hexopyranose-4-ulosyl)uracil 25: Following the procedure as described for the synthesis of **24**, 1.10 g (2.02 mmol) of **22** and (2.05 mg, 5.45 mmol) of PDC were reacted in anhydrous dichloromethane (45 ml) in presence of 3.0 gm of cooled molecular seive (3Å), freshly activated at 375°C over P_2O_5 in vacuum. Worked up and purified by column chromatography using hexane : EtOAc (3 : 2) as eluant to obtain pure compound. Yield: 45%; ^1H NMR ($CDCl_3$): δ 8.80 (brs, 1H,-NH proton); 7.55–7.21 (m, 16H, $3 \times C_6H_5$ and H-6); 5.58 (d, 1H, H-1′, $J = 10$ Hz); 5.32 (m, 1H, H-3′); 4.38 and 4.25 (two dd, 2H, H-6′, $J = 11$ Hz and 4.5 Hz); 3.48 (m, 1H, H-5′); 2.44 and 2.42 (two m, 2H, $J_{gem} = 11$ Hz, $J_{vic} = 3.00$, 1.66 Hz, H-2′); ^{19}F NMR ($CDCl_3$) : − 117.60. IR (Neat): 2126 cm^{-1} (N_3 group), 1722 cm^{-1} (keto group). Anal. calcd for $C_{29}H_{24}O_5N_5F$: C, 64.33; H, 4.45; N, 12.94. Found: C, 64.89; H, 4.42; N, 12.94.

5-Chloro-1-(3-azido-2,3-dideoxy-6-*o*-trityl-β-D-glycero-hexopyranose-4-ulosyl)uracil 26: Following the procedure as described for the synthesis of **24**, 0.98 g (1.75 mmol) of **23** and (1.68 g, 4.46 mmol) of PDC were reacted in

anhydrous dichloromethane (45 ml) in presence of 3.0 g of cooled molecular seive (3 Å), freshly activated at 375°C over P_2O_5 in vacuum. Worked up and purified by column chromatography using hexane : EtOAc (3 : 2) as eluant to obtain pure compound. Yield: 44%; ^{1}H NMR ($CDCl_3$): δ 8.75 (brs, 1H,-NH proton); 7.48–7.00 (m, 16H, $3 \times C_6H_5$ and H-6); 6.12 (d, 1H, H-1′); 5.48 (m, 1H, H-3′); 4.58 and 4.37 (m, 2H, H-6′); 3.36 (m, 1H, H-5′); 2.46 and 2.41 (two m, 2H, $J_{gem} = 12$ Hz, $J_{vic} = 3.06$, H-2′); IR (Neat): 2124 cm^{-1} (N_3 group), 1719 cm^{-1} (keto group). Anal. calcd for $C_{29}H_{24}O_5N_5Cl$: C, 62.48; H, 4.31; N, 12.57. Found: C, 61.98; H, 4.31; N, 12.21.

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