# SYNTHESIS OF 3'-AZIDO- AND 3'-AMINO-2',3'-DIDEOXYNUCLEOSIDES FROM 2,4-QUINAZOLINEDIONES

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*Abstract* - 2,4-Quinazolinediones (**1**) were silylated and condensed with methyl 3-azido-5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-D-*erythro*-pentofuranoside (**3**) in the presence of TMS triflate to afford the corresponding 3'-azido nucleosides (**4**). Deprotection of **4** using $Bu_4NF$/THF at room temperature gave 1-(3-azido-2,3-dideoxy-α-D-*erythro*-pentofuranosyl)-2,4-quinazolinediones (**5**) and the corresponding β-anomers (**6**). Treatment of compound (**6b**) with triphenylphosphine in pyridine, followed by hydrolysis with aqueous ammonium hydroxide yielded 6-methyl-1-(3-amino-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-2,4-quinazolinedione (**7**) which was also obtained when silylated 6-methyl-2,4-quinazolinedione (**2b**) was condensed with 1,5-di-*O*-acetyl-2,3-dideoxy-3-phthalimido-β-D-*erythro*-*pentofuranose* (**8**) in acetonitrile followed by deprotection with $MeNH_2$/EtOH.

Since the discovery of human immunodeficiency virus (HIV) as the causative agent of AIDS,[1] and the identification of HIV as a retrovirus, much research has been aimed at developing agents that could control or block the HIV replication process.[2] Among the numerous candidates, the modified nucleoside 3'-azido-3'-deoxythymidine (AZT) is, at present, the only drug receiving wide clinical usage. Many structurally related

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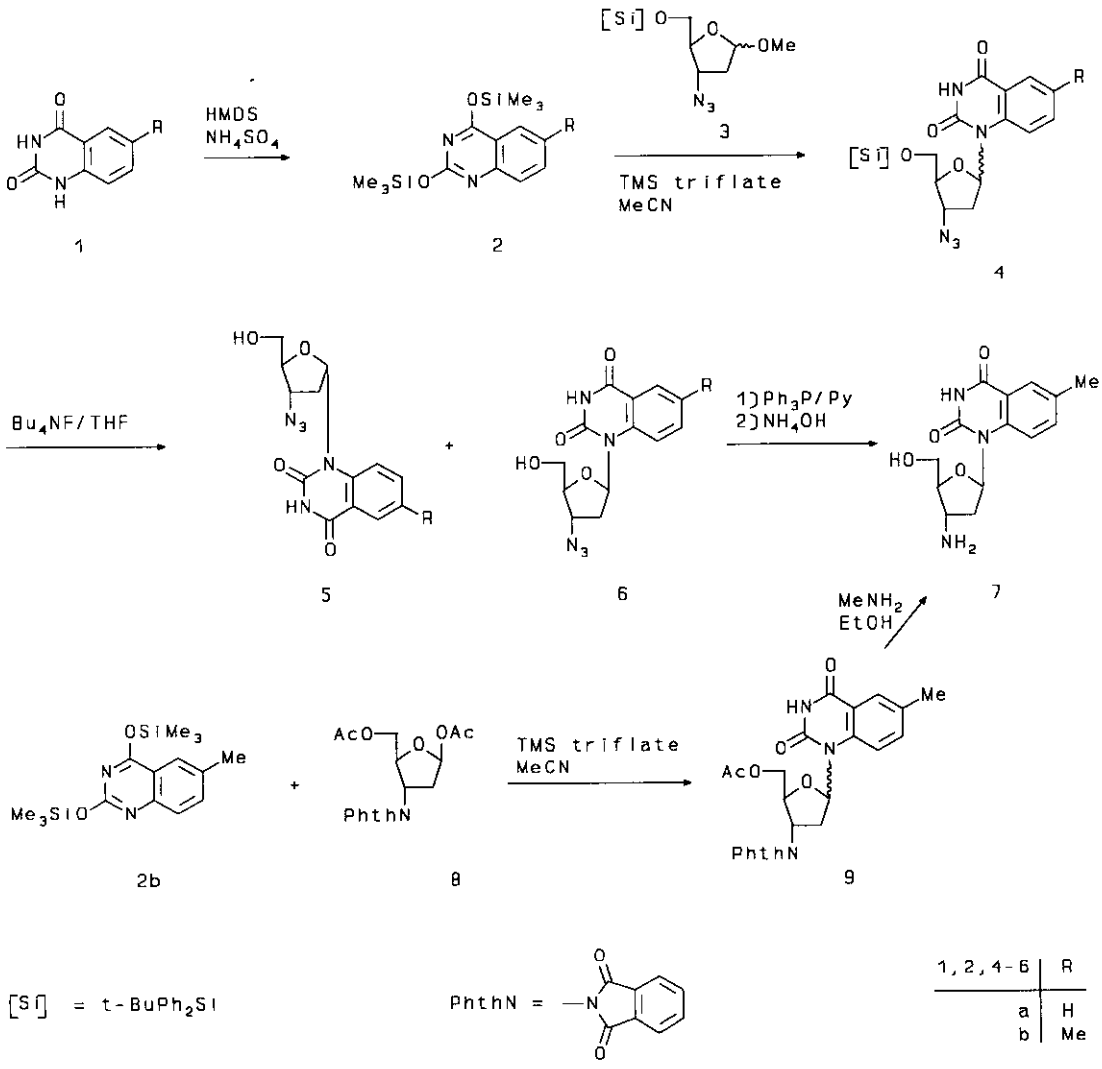
nucleosides have recently been synthesized leading to the 2',3'-dideoxynucleosides[3] as the most potent anti-HIV agents. The corresponding 3'-amino nucleosides have also shown biological activity. 3'-Amino-3'-deoxythymidine shows potent inhibitory activity against the replication of both murine sarcoma-180 and L 1210 murine leukemia *in vitro*[4,5] and *in vivo*.[6] The presence of 3-amino-3-deoxy-β-D-ribofuranose moiety in the antibiotic puromycin[7] has stimulated considerable interest in other amino sugar nucleosides and nucleotides as pharmacological agents. Furthermore, several types of 3'-amino-3'-deoxy nucleoside and nucleotide analogs have been reported to inhibit the synthesis of nucleic acid. Furthermore, 3'-amino nucleosides are useful starting materials for formation of a new type of antisense oligonucleotides with a modified backbone. These oligonucleotides are of interest in therapies utilizing antisense DNAs to interrupt protein synthesis or otherwise inactivate messenger RNA (mRNA) or double stranded DNA.[8]

One of the two methods we describe herein to prepare a 3'-amino nucleoside is the reduction of the corresponding 3'-azido nucleoside. Recently, *Dunkel and Pfleiderer*[9] have synthesized 1-(3-azido-2,3-dideoxy-β-D-ribofuranosyl)-2,4-quinazolinediones by treating 1-(2-deoxy-3-*O*-methanesulfonyl-5-*O*-monomethoxytrityl-β-D-xylofuranosyl)-2,4-quinazolinediones or 2,3'-anhydro-1-(5'-*O*-monomethoxytrityl-β-D-xylofuranosyl)-4-quinazolinones with lithium azide in DMF. Their starting material was synthesized in a linear route from the nucleoside which in turn was obtained by condensation of the nucleobases with sugars. However, we thought it more easy to synthesize this type of azido nucleosides by direct condensation of silylated 2,4-quinazolinediones with an appropriately protected 3-azido-2,3-dideoxypentofuranoside which in turn can be synthesized in only four steps from commercially available 2-deoxy-D-ribose as described by *Hansen and Pedersen*[10] by consecutive methyl glycosidation, 5-OH protection with *tert*-butylchlorodiphenylsilane, replacement of 3-OH with iodine, and finally replacement of iodine with azide.

## *RESULTS AND DISCUSSION*

2,4-Quinazolinediones (**1**) were prepared and silylated[11] with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of ammonium sulfate. The so formed trimethylsilylated derivatives (**2**) were condensed with methyl




3-azido-5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-D-*erythro*-pentofuranoside (**3**) in acetonitrile using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as the catalyst according to the method of *Vorbrüggen*[12] to give 1:1 α:β anomeric mixture of protected nucleosides (**4**) in good yields. This reaction most likely takes place by a complicated mechanism[13] in which the methyl glycoside in the initial step on treatment with TMS triflate undergoes a ring opening reaction at the anomeric center by a heterolytic cleavage of the ring C-O bond. Removal of the protecting group of **4** was achieved by treatment with tetrabutylammonium fluoride in tetrahydrofuran

at room temperature to afford 1-(3-azido-2,3-dideoxy-α-D-*erythro*-pentofuranosyl)-2,4-quinazolinediones (**5a,b**) in 39%, 40% yields, respectively, and the corresponding β-anomers (**6a,b**) in 35%, 36% yields, respectively.

The $^1$H-nmr and melting point of compounds (**6a**) and (**6b**) are in close agreement with the corresponding data reported[9] and the assingment of (**6b**) was confirmed, also, by $^1$H-$^1$H-homonuclear shift correlated (COSY) 2D-nmr and $^1$H-nuclear Overhauser effect ($^1$H-NOE difference spectroscopy). Most interestingly, irradiation of 8-H in the quinazoline ring resulted in a very strong NOE enhancement of 1'-H (15%) in the sugar moity which indicates a preference of *syn* conformation of the nucleobase around the glycosidic bond. However, strong enhancements of 3'-H (5%) and 2'β-H (4%) also on irradiation of 8-H prove that not only *syn*, but also *anti* conformation is considerably populated and the latter conformation is the same conformation as found in DNA for thymidine.

Treatment of compound (**6b**) with triphenylphosphine in pyridine,[14] followed by hydrolysis with ammonium hydroxide, yielded 6-methyl-1-(3-amino-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-2,4-quinazolinedione (**7**) in 66% yield. On the other hand, the trimethylsilylated derivative (**2b**) was condensed with 1,5-di-*O*-acetyl-2,3-dideoxy-3-phthalimido-β-*erythro*-pentofuranose (**8**) which was prepared as previously described[15] by reaction of phthalimide with unprotected 2-deoxy-D-ribose using the $P_4O_{10}/H_2O/n$-$Bu_3N$ reagent in $CHCl_3$ at 40 °C followed by acetylation. TMS triflate was used as the catalyst for the condensation reaction to give a 1:2 α:β-anomeric mixture of the protected nucleoside (**9**) in 85% yield, which was deprotected by treatment with 33% methylamine/ethanol to give **7**.

## *EXPERIMENTAL*

Nmr spectra were recorded on a Bruker 250 FT-NMR spectrometer. Mass spectra were recorded using electron ionization (EI) on a Varian Mat-311 A spectrometer, and fast atom bombardment (FAB) on a Kratos MS 50 spectrometer. Ir spectra were recorded on a Perkin Elmer 1720 spectrophotometer. The silica gel (0.040-0.063 mm) used for column chromatography was purchased from Merck.

*1-(3-Azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-D-erythro-pentofuranosyl)-2,4-quinazolinediones* (**4**).

A mixture of 2,4-quinazolinediones (**1**) (5 mmol), $(NH_4)_2SO_4$ (60 mg, 0.45 mmol) and HMDS (40 ml, 250 mmol) was refluxed at 140 °C overnight. The clear solution obtained was cooled and the solvent was removed *in vacuo*. The resulting residue (**2**) was dissolved in anhydrous MeCN (15 ml) and a solution of methyl 3-azido-2,3-dideoxy-5-*O*-*tert*-butyldiphenylsilyl-α,β-D-*erythro*-pentofuranoside (**3**) (1.23 g, 3 mmol) in anhydr. MeCN (15 ml) was added with stirring. The mixture was cooled to -50 °C and a solution of TMS triflate (0.75 ml, 3.9 mmol) in anhydr. MeCN (5 ml) was added dropwise during 5 min at -50 °C and the mixture was stirred for 2 h at -30 °C. The mixture was diluted with $CH_2Cl_2$ (200 ml), then washed with cold sat. aq. $NaHCO_3$ (150 ml), then with cold $H_2O$ (3 x 150 ml) and dried over anhydr. $Na_2SO_4$. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with $CHCl_3$ to afford **4a**, white foam, yield 1.09 g (69%, α:β 1:1) and **4b**, white foam, yield 1.17 g (72%, α:β 1:1).

*1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-2,4-quinazolinedione* (**5a**) *and 1-(3-azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-2,4-quinazolinedione* (**6a**).

1 M $Bu_4N$/THF (0.65 ml, 0.71 mmol) was added to a stirred solution of **4a** (0.31 g, 0.57 mmol) in THF (10 ml) at room temperature. After complete reaction (2 h), the solvent was removed *in vacuo* and the residue was chromatographed on silica gel with the gradient 0-2% MeOH in $CHCl_3$ to give **5a** and **6a**.

Compound **5a**: yellowish solid, yield: 67 mg (39%). Ms: *m/z* (%) = 303 ($M^+$, 0.4). $^1$H-Nmr (250 MHz, DMSO-$d_6$): δ 2.57 (m, 2H, 2'-H), 3.56 (m, 2H, 5'-H), 4.29 (m, 2H, 3'-H, 4'-H), 5.02 (s, 1H, OH), 6.60 (t, $J$ = 7.7 Hz, 1H, 1'-H), 7.28 (t, $J$ = 7.6 Hz, 1H, 6-H), 7.58 (d, $J$ = 8.4 Hz, 1H, 8-H), 7.71-8.05 (m, 2H, 5-H, 7-H). $^{13}$C-Nmr (62.9 MHz, DMSO-$d_6$): δ 33.08 (C-2'), 60.23, 61.32 (C-3' and C-5'), 82.97 (C-4'), 84.42 (C-1'), 115.44, 116.31, 123.02, 127.66, 134.63, 139.54 ($C_{quin}$), 149.78 (C-2), 161.39 (C-4). Ir (KBr): υ = 2104 $cm^{-1}$ ($N_3$). Peak matching for $C_{13}H_{13}N_5O_4$: Calcd = 303.0968. Found = 303.0961.

Compound **6a**: yield: 61 mg (35%), mp: 168-170°C (decomp.), lit.,[9] mp: 169°C (decomp.).

*6-Methyl-1-(3-azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-2,4-quinazolinedione* (**5b**) *and 6-methyl-1-(3-azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-2,4-quinazolinedione* (**6b**).

The protected nucleoside (**4b**) (0.8 g, 1.4 mmol) was treated with 1 M $Bu_4N$/THF (1.6 ml, 1.74 mmol) as described in the preparation of **5a** and **6a**. Separation by column chromatography on silica gel with the gradient 0-2% MeOH in $CHCl_3$ gave **5b** and **6b**.

Compound **5b**: white solid, yield: 182 mg (40%); mp: 156°C. FAB ms (DMSO + glycerol): *m/z* (%) = 318 (M + $H^+$). $^1$H-Nmr (250 MHz, DMSO-$d_6$): δ 2.36 (s, 3H, $CH_3$), 2.62 (m, 2H, 2'-H), 3.58 (s, 2H, 5'-H), 4.29 (m, 2H, 3'-H, 4'-H), 5.03 (s, 1H, OH), 6.59 (t, *J* = 7.7, 1H, 1'-H), 7.47 (m, 2H, 7-H, 8-H), 7.83 (s, 1H, 5-H), 11.54 (s, 1H, NH). $^{13}$C-Nmr (62.9 MHz, DMSO-$d_6$): δ 19.74 ($CH_3$), 33.09 (C-2'), 60.26, 61.33 (C-3' and C-5'), 82.96, 84.38 (C-1' and C-4'), 115.39, 116.15, 127.29, 132.37, 135.44, 137.36 ($C_{quin}$), 149.75 (C-2), 161.38 (C-4). Ir (KBr): υ = 2104 $cm^{-1}$ ($N_3$).

Compound **6b**: yield: 166 mg (36%); mp: 210-212°C (decomp.), lit.,[9] mp: 201-202°C (decomp.).

*6-Methyl-1-(3-amino-2,3-dideoxy-β-D-erythro-pentofuranosyl)-2,4-quinazolinedione* (**7**).

6-Methyl-1-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-2,4-quinazolinedione (**6b**) (250 mg, 0.79 mmol) and triphenylphosphine (340 mg, 1.3 mmol) were dissolved in pyridine (3 ml) and kept at room temperature for 1 h. Conc. ammonium hydroxide was added and the reaction mixture was allowed to stand for an additional 2 h. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with the gradient 5-15% MeOH in $CHCl_3$ to obtain the title compound (**7**) as a white solid; yield: 152 mg (66%); mp: 203-206 °C. Ms: *m/z* (%) = 291 ($M^+$, 2). $^1$H-Nmr (250 MHz, DMSO-$d_6$): δ 1.86 (m, 1H, 2'-H), 2.34 (s, 3H, $CH_3$), 2.57 (m, 1H, 2'-H), 3.54 (m, 4H, 3'-H, 4'-H, and 5'-H), 6.64 (t, *J* = 7.6 Hz, 1H, 1'-H), 7.48 (d, *J* =8.5 Hz, 1H, 7-H), 7.64 (d, J = 8.7 Hz, 1H, 8-H), 7.81 (s, 1H, 5-H). $^{13}$C-Nmr (62.9 MHz, DMSO-$d_6$): δ 19.79 ($CH_3$), 36.77 (C-2'), 51.22 (C-3'), 60.77 (C-5'), 82.79 (C-4'), 86.42 (C-1'), 116.19, 116.75, 126.98, 132.23, 135.18, 137.03 ($C_{quin}$), 149.85 (C-2), 161.45 (C-4). Peak matching for $C_{14}H_{17}N_3O_4$: Calcd: 291.1219. Found: 291.1211.

*6-Methyl-1-(5-O-acetyl-2,3-dideoxy-3-phthalimido-D-erythro-pentofuranosyl)-2,4-quinazolinedione* (**9**).

A mixture of 6-methyl-2,4-quinazolinedione (**1b**) (0.88 g, 5 mmol), $(NH_4)_2SO_4$ (60 mg, 0.45 mmol) and HMDS (40 ml, 250 mmol) was refluxed at 140°C overnight. The clear solution obtained was cooled and the solvent was removed *in vacuo*. The resulting residue was dissolved in anhydr. MeCN (15 ml) and a solution of 1,5-di-*O*-acetyl-2,3-dideoxy-3-phthalimido-β-D-*erythro*-pentofuranose (**8**) (0.95 g, 3 mmol) in anhydr. MeCN (15 ml) was added with stirring. The mixture was cooled to -50 °C and a solution of TMS triflate (0.75 ml, 3.9 mmol) in anhydr. MeCN (5 ml) was added dropwise during 5 minutes at -50 °C. The mixture was stirred for 1 h at -30 °C. The mixture was diluted with $CH_2Cl_2$ (200 ml), washed with cold sat. aq. $NaHCO_3$ (150 ml) and with cold $H_2O$ (3 x 150 ml) and dried over anhydr. $Na_2SO_4$. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with $CHCl_3$ to give **9** as a white foam, yield: 1.24 g (84%, α:β 1:2).

*Deprotection of compound* **9** *to give* **7**.

A 33% solution of $MeNH_2$ in absolute EtOH (10 ml) was added to a stirred suspension of compound (**9**) (200 mg, 0.43 mmol) in abs. EtOH (5 ml) at room temperature. After 5 min the clear solution obtained was refluxed for 30 min. The mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel using 0-5% MeOH in $CHCl_3$ to give compound (**7**), yield: 32 mg (25 %) as crystals and 69 mg (55 %) as a mixture of **7** and its corresponding α anomer.

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