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Ring-opening mechanism in the glycosylation of 2,4(1*H*,3*H*)-quinazolinediones with *erythro*-3-*O*-tosyl and *threo*-3-iodo-2,3-dideoxypentofuranosides

Ahmed A El-Barbary#, Nasser R El-Brollosy#, Erik B Pedersen*

Department of Chemistry, Odense University, DK-5230 Odense M, Denmark

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Summary – 2,4(1*H*,3*H*)-Quinazolinediones **4** were silylated and condensed with methyl 5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-3-*O*-(4-methylbenzenesulfonyl)-D-*erythro*-pentofuranoside **2** in the presence of trimethylsilyl trifluoromethanesulfonate to afford the corresponding nucleosides **5** and acyclic nucleosides **6**. Treatment of **5** with *n*-Bu_4NF/THF at room temperature afforded 2,3′-anhydronucleosides **7** and the 5-*O*-deprotected α-nucleosides **8**, while **6** under the same reaction conditions afforded the 3′,4′-anhydro acyclic nucleoside **9**. A similar condensation of **4a** with methyl 5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-iodo-D-*threo*-pentofuranoside **3** yielded 1-(5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-iodo-β-D-*threo*-pentofuranosyl)-2,4(1*H*,3*H*)-quinazolinedione **10**, the corresponding α-anomer **11**, and the acyclic nucleoside **12**. Treatment of **10** with sodium methoxide in boiling MeOH gave the 3′,4′-didehydro nucleoside **13**. Reaction of **12** with *n*-Bu_4NF/THF at room temperature afforded the 3′,4′-anhydro acyclic nucleoside **16**.

2,3′-anhydronucleoside / 3′,4′-didehydronucleoside / nucleoside synthesis / acyclic nucleoside / 2,4(1*H*,3*H*)-quinazolinedione nucleoside

Résumé – Mécanisme d'ouverture du cycle dans la glycosylation de quinazoline-2,4(1*H*,3*H*)-diones avec l'*érythro*-3*O*-tosyl et le *thréo*-3-iodo-2,3-dideoxypentofuranosides. *Les quinazolines-2,4(1*H,3H*)-diones* **4** *ont été silylées et condensées avec le pentofuranoside de méthyle* **2** *en présence de triflate de triméthylsilyle pour conduire aux nucléosides* **5** *et nucléosides acycliques* **6**. *Le traitement de* **5** *par le n-Bu_4NF/THF à température ambiante fournit les 2,3-anhydronucléosides* **7** *et les α-nucléosides* **8** *déprotégés en 5, tandis que* **6** *dans les mêmes conditions de réaction conduit au nucléoside acyclique 3′,4′-anhydro* **9**. *Une condensation similaire de* **4a** *avec le pentofuranoside de méthyle* **3** *permet d'accéder à la quinazolinedione* **10**, *à l'anomère α correspondant* **11** *et au nucléoside acyclique* **12**. *Le traitement de* **10** *avec le méthanolate de sodium dans le méthanol bouillant donne le 3′,4′-didéshydronucléoside* **13**. *La réaction de* **12** *avec n-Bu_4F/THF à température ambiante conduit au 3′,4′-anhydronucléoside acyclique* **16**.

2,3′-anhydronucléoside / 3′,4′-didéhydronucléoside / synthèse de nucléoside / nucléoside acyclique / 2,4(1*H*,3*H*)-quinazolinedione nucléoside

Introduction

We recently reported that during the synthesis of nucleosides under the Vorbrüggen conditions [1] methyl arabinofuranosides could undergo a ring-opening reaction by cleavage of the endocyclic C–O bond to give an aminal type of acyclic nucleoside together with the expected conventional type of nucleoside [2, 3]. Hager and Liotta [4] have independently synthesized such an aminal type of acyclic nucleoside and shown that it can be cyclized into the conventional type of a nucleoside. We suggested that this new type of acyclic nucleoside is most likely an intermediate for the formation of the conventional nucleosides when methyl arabinosides are used as the substrate under the Vorbrüggen conditions. Moreover, we suggested this aminal type of acyclic nucleoside as a reaction intermediate when methyl 2-deoxy-D-pentofuranosides are used as substrates in the synthesis of nucleosides [5, 6]. The same type of mechanism has now been confirmed by Janardhanam and Nambiar when $SnCl_4$ is used as the catalyst for the nucleoside synthesis [7]. In the present investigation we also isolated the same type of acyclic nucleosides when 5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-3-*O*-(4-methylbenzenesulfonyl)-D-*erythro*-pentofuranoside **2** and methyl 5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-iodo-D-*threo*-pentofuranoside **3** are condensed with 2,4(1*H*,3*H*)-quinazolinediones to the corresponding nucleosides. Many natural as well as synthetic quinazolinedione derivatives exhibit significant biological activity [8] and their nucleosides have been of interest since Stout and Robins [9] prepared the uridine analogue 1-β-D-ribofuranosyl-2,4(1*H*,3*H*)-quinazolinedione in 1968. Dunkel and Pfleiderer

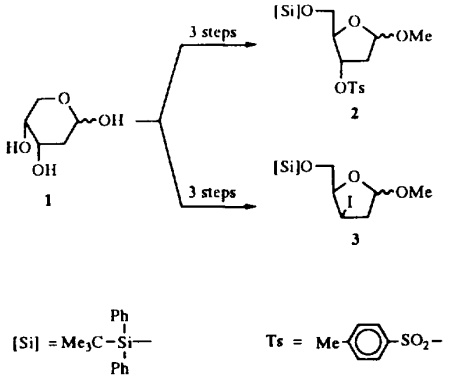
On leave from Chemistry Department, Faculty of Science, Tanta University, Tanta, Egypt

* Correspondence and reprints

[10] synthesized 2,3′-anhydronucleoside derivatives by treating 1-(2′-deoxy-β-D-ribofuranosyl)-6-methyl-2,4(1*H*,3*H*)-quinazolinediones with monomethoxytrityl chloride in dry pyridine followed by reaction with mesyl chloride and finally reaction with DBU (1,8-diazabicyclo[5.4.0]unde-7-ene) in THF. Their starting material was synthesized in a linear route from the nucleoside, which had been obtained by condensation of the nucleobase with sugar. We thought it more easy to synthesize this type of anhydronucleoside by direct condensation of silylated 2,4(1*H*,3*H*)-quinazolinediones with appropriately protected 2,3-dideoxy-3-*O*-tosylpentofuranoside followed by deprotection with tetrabutylammonium fluoride in THF.

Results and discussion

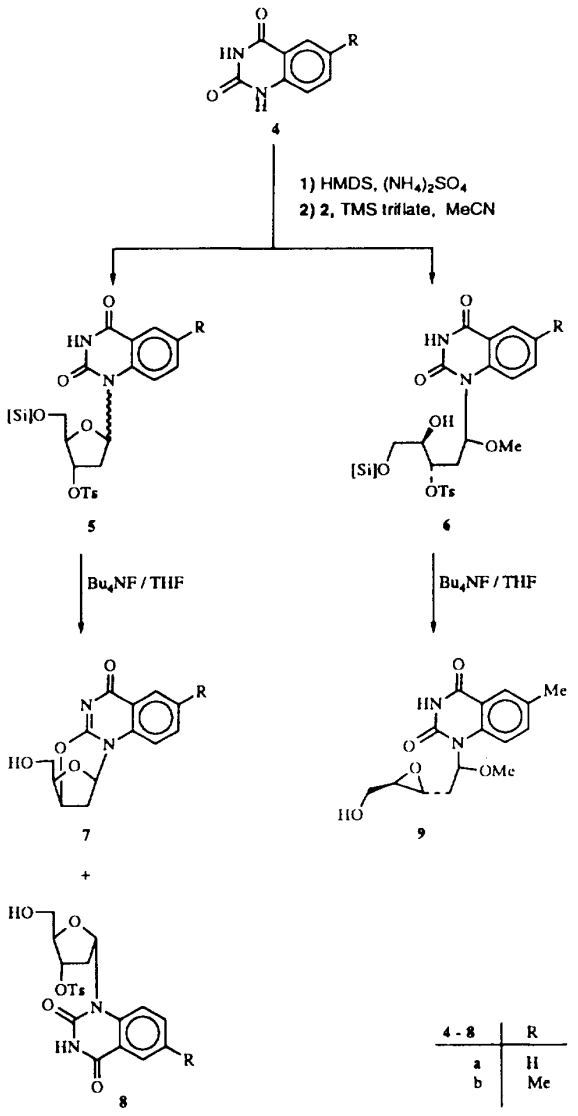
The tosylated sugar **2** was prepared from the commercially available 2-deoxy-D-ribose **1** by successive glycosidation with methanolic HCl, selective 5-*O*-silylation with *tert*-butyldiphenylchlorosilane and tosylation with 4-methylbenzenesulfonyl chloride in dry pyridine [11-14]. The iodo sugar **3** was prepared from **1** by glycosidation, silylation, and introduction of the 3-iodo substituent in a Mitsunobu reaction [11-13, 15].



Scheme 1

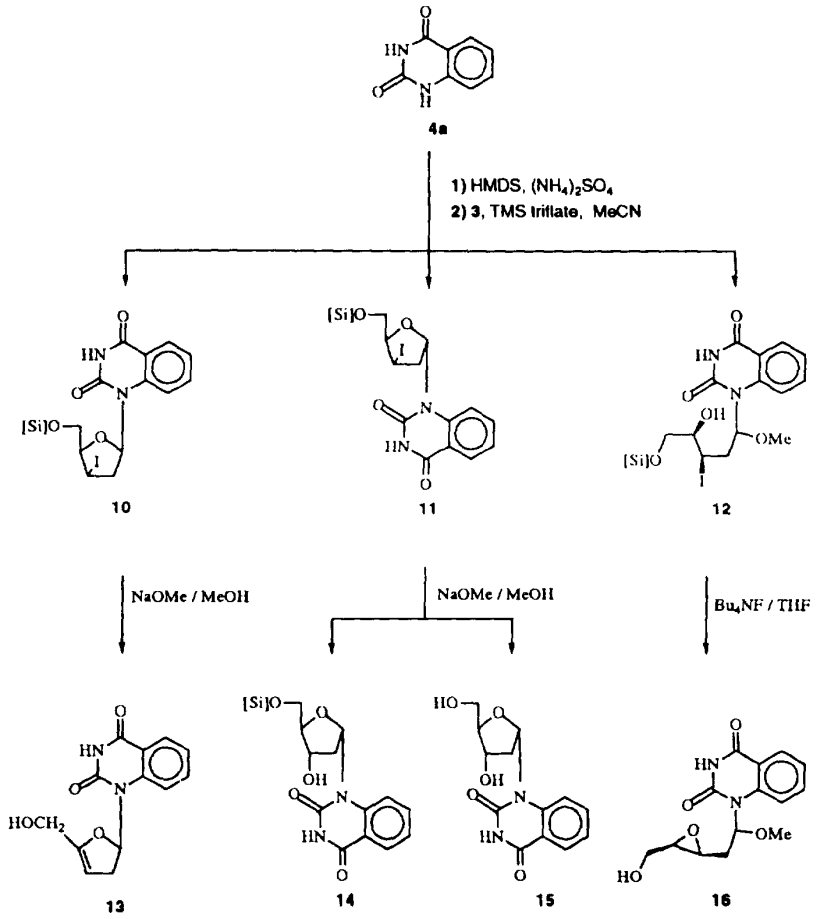
2,4(1*H*,3*H*)-Quinazolinediones **4** were prepared and silylated [16] with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of ammonium sulfate to give the corresponding trimethylsilylated derivatives, which were condensed with **2** in acetonitrile using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as the catalyst according to the method of Vorbrüggen et al [1] to give the corresponding α/β anomeric mixture of protected nucleosides **5** in good yields and the acyclic nucleosides **6** in 3–5% yields. Reaction of the anomeric mixture **5** with tetrabutylammonium fluoride in THF at room temperature afforded 2,3′-anhydronucleosides **7** in 46–76% yields, as the products formed from the β anomers, and the tosylated nucleosides **8** in 8–25% yields, as the products formed from the α anomers. Reaction of **6b** with the same reagent gave the epoxide **9** in 73% yield.

The trimethylsilylated derivative of **4a** was condensed with methyl 5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-iodo-D-*threo*-pentofuranoside **3** according

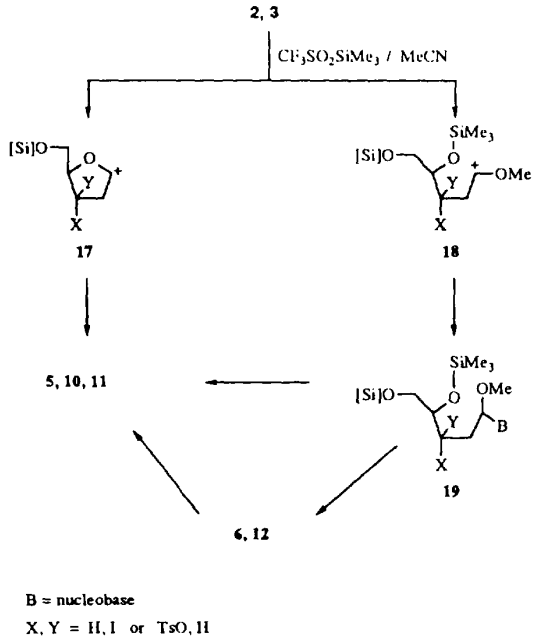


Scheme 2

to the method of Vorbrüggen et al [1] to afford the corresponding β anomer **10** in 20% yield, the α anomer **11** in 29% yield, and the acyclic nucleoside **12** in 12% yield. Treatment of **10** with 10 equiv of sodium methoxide in methanol under reflux gave 3′,4′-didehydro nucleoside **13** in 60% yield, while compound **11** under the same conditions afforded the protected nucleoside **14** and the deprotected nucleoside **15** in 11 and 57% yields, respectively. The α anomer **11** is believed to form an 2,3′-anhydro intermediate by action of sodium methoxide in methanol. Subsequent hydrolysis due to moisture in methanol could then afford **14** and **15**. Another explanation could be that on treatment with sodium methoxide the 2,3′-anhydro intermediate undergoes a substitution reaction on the pyrimidine ring to give a 2-*O*-methyl nucleoside which is subsequently demethylated by action of the sodium methoxide. The acyclic nucleoside **12** reacted with tetrabutylammonium fluoride in THF to form the epoxide **16** in 83% yield.



Scheme 3



Scheme 4

Formation of the acyclic nucleosides **6** and **12** can be explained by a mechanism [12, 17] in which the ring oxygen of the sugar is silylated making ring opening possible with formation of the acyclic carbonium ion **18**, which, in turn, can condense with the silylated nucleobase to give **19**, an intermediate which produces the acyclic nucleoside **6** or **12** on hydrolysis. When the acyclic nucleoside **6a** was treated with TMS triflate under the same reaction conditions as used in the preparation of **5a** and **6a**, TLC analysis of the reaction mixture confirmed formation of the cyclic nucleoside **5a** together with decomposition products. The decomposition may be ascribed to the use of nonsilylated acyclic nucleoside **6a** instead of its silylated analogue which is actually the primarily formed intermediate in the reaction mixture during the nucleoside synthesis. From these findings, we conclude that the acyclic nucleoside may represent an important route for the formation of the nucleosides **5**, **10** and **11**. This is in contrast with the generally accepted idea that such nucleosides should be formed from the cyclic carbonium ion **17** generated via exocyclic silylation of the methoxy group of the glycosides **2** and **3**.

The protons in the ^1H NMR spectra were assigned by ^1H-^1H homonuclear shift correlated (COSY) 2D-NMR. The NMR chemical shift values of 3′-H, 4′-H, C-3′ and

C-4′ of compounds **9** and **16** were found at high magnetic fields in agreement with values that have been reported for epoxides [18, 19]. There was no coupling between 3′-H and 4′-H in the (COSY) 2D-NMR spectrum of **9** and consequently, compound **9** is assumed to be in the *trans* form. The compounds **8a** and **11** were selected for ^{1}H nuclear Overhauser effect (^{1}H-NOE difference spectroscopy) to assign the site of glycosylation on the quinazoline ring and the anomeric configuration. N^1-Glycosylation of the quinazoline derivatives was proven by strong NOE enhancements in 8-H (6% in **8a** and 12% in **11**) when 1′-H was irradiated. A typical decisive feature for α configuration of **8a** was irradiation of 2′-H at the β site which resulted in strong NOE enhancement in 1′-H (8%) and 3′-H (7%). The α configuration of **11** was proven by irradiation of 2′-H at the α site and 2′-H at the β site, which resulted in strong enhancements in 3′-H (7%) and 1′-H (7%), respectively. In compound **8a**, irradiation of 1′-H generated NOE in $2'_\beta$-H (4%); irradiation of 3′-H generated NOEs in $2'_\beta$-H (3%) and 4′-H (2%). In compound **11**, irradiation of 1′-H generated a large NOE in $2'_\beta$-H (6%); irradiation of 3′-H generated NOEs in $2'_\alpha$-H (4%) and 4′-H (6%).

Experimental section

NMR spectra were recorded on a Bruker 250 FT NMR spectrometer, with TMS as internal standard. 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. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from Merck.

*1-[5-*O*-*tert*-Butyldiphenylsilyl-2-deoxy-3-*O*-(4-methylbenzenesulfonyl)-α,β-*D*-*erythro*-pentofuranosyl]-2,4(1*H*,3*H*)-quinazolinediones* **5** *and 5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-1-*O*-methyl-3-*O*-(4-methylbenzenesulfonyl)-1-*C*-(1,2,3,4-tetrahydro-2,4-dioxoquinazolin-1-yl)-*D*-*erythro*-pentitol* **6**

A mixture of 2,4(1*H*,3*H*)-quinazolinedione **4** (8 mmol), $(NH_4)_2SO_4$ (100 mg) and 1,1,1,3,3,3-hexamethyldisilazane (60 mL) was refluxed overnight. The clear solution obtained was cooled to room temperature and the solvent was removed under reduced pressure. The resulting residue was dissolved in anhydrous MeCN (20 mL) and a solution of methyl 5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-3-*O*-(4-methylbenzenesulfonyl)-D-*erythro*-pentofuranoside **2** (2.9 g, 5.4 mmol) in anhydrous MeCN (20 mL) was added with stirring. The mixture was cooled to −50 °C and a solution of trimethylsilyl trifluoromethanesulfonate (1.3 mL, 6.5 mmol) in anhydrous MeCN (5 mL) was added dropwise and the mixture was stirred for 5 h at −30 °C. The reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with a cold saturated aqueous $NaHCO_3$ (150 mL), cold H_2O (3 × 150 mL), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was chromatographed on silica gel with 0–2% MeOH in $CHCl_3$ to afford **5** and **6** as white foams.

Compound **5a**

Yield 1.94 g (54%, α:β 2:3).

^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H, *t*-Bu), 2.30 (m, 1H, 2′-H), 2.42 (s, 3H, CH_3), 2.67 (m, 2H, 2′-H), 2.91 (m, 2′-H), 3.65–3.98 (m, 5′-H), 4.14 (q, 1H, J = 3.7 Hz, 4′-H), 4.50 (m, 1H, 4′-H), 5.39 (m, 1H, 3′-H), 5.46 (m, 1H, 3′-H), 6.61 (t, 1H, J = 7.4 Hz, 1′-H), 6.98 (t, 1H, J = 7.8 Hz, 1′-H), 7.25–8.23 (m, H_{arom}), 8.73 (s, 1H, NH), 8.76 (s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ 18.99, 19.29 (Me_3C), 26.67, 26.85 [$(CH_3)_3C$], 34.19, 34.80 (C-2′), 62.21, 64.40 (C-5′), 78.06, 80.07 (C-3′), 83.33, 83.42, 83.87, 85.34 (C-1′, C-4′), 116.14, 116.27, 116.43, 116.61, 123.60, 123.65, 127.64, 127.69, 127.79, 127.95, 128.57, 128.80, 129.52, 129.68, 129.81, 129.89, 129.94, 132.30, 133.12, 133.17, 134.85, 135.12, 135.22, 135.37, 135.47, 138.75, 139.50, 145.10, 145.24 (C_{arom}), 149.65, 149.91 (C-2), 161.55 (C-4).

Anal $C_{36}H_{38}N_2O_7SSi{\cdot}2.0H_2O$, calc: C 61.17, H 5.99, N 3.96. Found: C 61.16, H 5.58, N 3.85.

Compound **5b**

Yield 1.81 g (49%, α:β 1:9).

^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9H, *t*-Bu), 2.25 (s, 3H, CH_3), 2.27 (m, 1H, 2′-H), 2.41 (s, 3H, CH_3), 2.88 (m, 1H, 2′-H), 3.83 (dd, 1H, J = 3.6, 11.6 Hz, 5′-H), 3.94 (dd, 1H, J = 2.2, 11.6 Hz, 5′-H), 4.13 (m, 1H, 4′-H), 5.45 (td, 1H, J = 4.0, 8.0 Hz, 3′-H), 6.61 (t, 1H, J = 7.4 Hz, 1′-H), 6.76 (m, 1H, H_{arom}), 7.25–7.94 (m, 17H, H_{arom}), 9.05 (s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ 19.32 (Me_3C), 20.14 (CH_3), 21.51 (CH_3), 26.89 [$(CH_3)_3C$], 34.21 (C-2′), 62.24 (C-5′), 78.14 (C-3′), 83.31, 83.89 (C-1′, C-4′), 116.19, 116.25, 127.63, 127.69, 127.81, 128.23, 129.64, 129.77, 129.93, 132.37, 133.30, 133.38, 133.51, 135.29, 135.49, 136.14, 137.30, 145.07 (C_{arom}), 149.63 (C-2), 161.64 (C-4).

Anal $C_{37}H_{40}N_2O_7SSi{\cdot}1.5H_2O$, calc: C 62.43, H 6.09, N 3.93. Found: C 62.08, H 5.69, N 3.91.

Compound **6a**

Yield 113 mg (3%).

^{1}H NMR ($CDCl_3$): δ 1.04 (s, 9H, *t*-Bu), 2.34 (s, 3H, CH_3), 2.37 (m, 1H, 2′-H), 2.69 (m, 1H, 2′-H), 2.93 (d, 1H, J = 4.8 Hz, OH), 3.32 (s, 3H, OCH_3), 3.49 (dd, 1H, J = 6.2, 10.5 Hz, 5′-H), 3.62 (dd, 1H, J = 4.5, 10.5 Hz, 5′-H), 3.91 (m, 1H, 4′-H), 4.79 (m, 1H, 3′-H), 6.53 (t, 1H, J = 6.2 Hz, 1′-H), 7.18–8.22 (m, 18H, H_{arom}), 8.96 (s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ 19.07 (Me_3C), 21.49 (CH_3), 26.66 [$(CH_3)_3C$], 33.93 (C-2′), 56.03 (OCH_3), 63.98 (C-5′), 71.62 (C-3′), 78.36 (C-4′), 84.70 (C-1′), 116.69, 116.82, 123.49, 127.66, 127.69, 127.72, 128.56, 129.64, 129.81, 132.63, 133.35, 134.74, 134.83, 135.40, 135.44, 144.73 (C_{arom}), 150.50 (C-2), 161.54 (C-4).

Anal $C_{37}H_{42}N_2O_8SSi{\cdot}1.5H_2O$, calc: C 60.88, H 6.21, N 3.84. Found: C 60.86, H 5.86, N 3.86.

FAB MS: m/z 703 ($M + H^+$).

Compound **6b**

Yield 192 mg (5%).

^{1}H NMR ($CDCl_3$): δ 1.02 (s, 9H, *t*-Bu), 2.34 (s, 3H, CH_3), 2.36 (m, 1H, 2′-H), 2.39 (s, 3H, CH_3), 2.85 (m, 1H, 2′-H), 2.91 (d, 1H, J = 4.8 Hz, OH), 3.31 (s, 3H, OCH_3), 3.51 (dd, 1H, J = 6.2, 10.5 Hz, 5′-H), 3.63 (dd, 1H, J = 4.6, 10.7 Hz, 5′-H), 3.94 (m, 1H, 4′-H), 4.8 (m, 1H, 3′-H), 6.53 (m, 1H, 1′-H), 7.15–8.00 (m, 17H, H_{arom}), 8.85 (s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ 19.09 (Me_3C), 20.34 (CH_3), 21.49 (CH_3), 26.71 [$(CH_3)_3C$], 34.03 (C-2′), 55.96 (OCH_3), 64.06 (C-5′), 71.71 (C-3′), 78.47 (C-4′), 84.62 (C-1′), 116.75, 127.71, 127.73, 128.27, 129.63, 129.81, 132.72,

133.36, 133.52, 135.42, 135.47, 135.89, 144.69 (C_{arom}), 150.44 (C-2), 161.85 (C-4).

Anal $C_{38}H_{44}N_2O_8SSi$, calc: C 63.66, H 6.19, N 3.91. Found: C 63.42, H 6.37, N 3.81.

*2,3'-Anhydro-1-(2-deoxy-β-D-*threo*-pentofuranosyl)-4(1H)- quinazolone* **7a** *and 1-[2-deoxy-3-O-(4-methylbenzenesulfonyl)-α-D-*erythro*-pentofuranosyl]-2,4(1H,3H)-quinazolinedione* **8a**

One molar Bu_4NF/THF (3.7 mL, 4 mmol) was added to a stirred solution of **5a** (1.2 g, 1.8 mmol) in THF (15 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 0–5% MeOH in $CHCl_3$ to give **7a** and **8a**.

Compound **7a**

Yield 215 mg (46%), mp 223–224 °C.

^{1}H NMR (DMSO-d_6): δ 2.49 (m, 2H, 2'-H), 3.45 (m, 2H, 5'-H), 4.27 (dt, 1H, J = 2.2, 6.1 Hz, 4'-H), 4.99 (t, 1H, J = 5.3 Hz, 3'-H), 5.34 (s, 1H, OH), 6.69 (d, 1H, J = 4.0 Hz, 1'-H), 7.10–8.04 (m, 4H, H_{arom}).

^{13}C NMR (DMSO-d_6): δ 31.99 (C-2'), 58.75 (C-5'), 76.29 (C-3'), 80.42 (C-4'), 84.37 (C-1'), 112.88, 117.57, 123.88, 126.53, 132.63, 137.71 (C_{quin}), 154.17 (C-2), 167.45 (C-4).

Anal $C_{13}H_{12}N_2O_4 \cdot 0.5H_2O$, calc: C 57.99, H 4.87, N 10.40. Found: C 57.44, H 4.48, N 10.18.

EI MS: m/z (relative intensity) 260 (M^+, 41).

Compound **8a**

Yield 190 mg (25%), mp 148–150 °C (decomp).

^{1}H NMR (DMSO-d_6): δ 2.42 (s, 3H, CH_3), 2.54 (m, 2H, 2'-H), 3.38 (m, 2H, 5'-H), 4.40 (q, 1H, J = 3.7 Hz, 4'-H), 5.06 (t, 1H, J = 5.3 Hz, OH), 5.12 (m, 1H, 3'-H), 6.66 (t, 1H, J = 7.8 Hz, 1'-H), 7.29–8.03 (m, 8H, H_{arom}), 11.65 (s, 1H, NH).

^{13}C NMR (DMSO-d_6): δ 20.99 (CH_3), 33.78 (C-2'), 61.04 (C-5'), 80.27 (C-3'), 82.87 (C-4'), 84.46 (C-1'), 115.66, 116.42, 123.06, 127.49, 127.62, 130.16, 132.55, 134.34, 139.13, 145.42 (C_{arom}), 149.82 (C-2), 161.34 (C-4).

FAB MS: m/z 433 ($M + H^+$).

*2,3'-Anhydro-1-(2-deoxy-β-D-*threo*-pentofuranosyl)-6-methyl- 4(1H)-quinazolone* **7b** *and 1-[2-deoxy-3-O-(4-methylbenzenesulfonyl)-α-D-*erythro*-pentofuranosyl]-6-methyl-2,4(1H,3H)-quinazolinedione* **8b**

The protected nucleoside **5b** (0.5 g, 0.73 mmol) was treated with 1 M Bu_4NF/THF (1.5 mL, 1.62 mmol) as described in the preparation of **7a** and **8a**. Separation by column chromatography on silica gel with the gradient 0–5% MeOH in $CHCl_3$ gave **7b** and **8b**.

Compound **7b**

Yield 152 mg (76%), mp 237–239 °C (decomp).

^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 2.50 (m, 1H, 2'-H), 2.66 (d, 1H, J = 12.6 Hz, 2'-H), 3.47 (m, 2H, 5'-H), 4.26 (dt, 1H, J = 2.3, 6.4 Hz, 4'-H), 4.98 (t, 1H, J = 5.3 Hz, OH), 5.32 (d, 1H, J = 1.2 Hz, 3'-H), 6.65 (d, 1H, J = 4.0 Hz, 1'-H), 7.56 (dd, 1H, J = 1.7, 8.6 Hz, 8-H), 7.73 (d, 1H, J = 8.7 Hz, 7-H), 7.83 (s, 1H, 5-H).

^{13}C NMR (DMSO-d_6): δ 20.11 (CH_3), 32.78 (C-2'), 59.47 (C-5'), 77.02 (C-3'), 81.18 (C-4'), 85.17 (C-1'), 113.62, 118.29, 126.91, 134.15, 134.34, 136.44 (C_{quin}), 154.73 (C-2), 168.25 (C-4).

Anal $C_{14}H_{14}N_2O_4 \cdot 0.5H_2O$, calc: C 59.36, H 5.34, N 9.89. Found: C 59.36, H 5.14, N 9.67.

EI MS: m/z (relative intensity) 274 (M^+, 63).

Compound **8b**

Yield 25 mg (8%), white foam.

^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.53 (m, 2H, 2'-H), 3.61 (dd, 1H, J = 3.2, 12.1 Hz, 5'-H), 3.80 (dd, 1H, J = 2.3, 12.3 Hz, 5'-H), 4.55 (m, 1H, 4'-H), 5.18 (m, 1H, 3'-H), 6.75 (t, 1H, J = 7.8 Hz, 1'-H), 7.20–7.83 (m, 6H, H_{arom}), 7.96 (s, 1H, 5-H).

^{13}C NMR ($CDCl_3$): δ 20.26 (CH_3), 21.57 (CH_3), 34.33 (C-2'), 62.11 (C-5'), 79.06 (C-3'), 83.19, 84.77 (C-1', C-4'), 115.78, 116.50, 127.87, 128.53, 130.01, 133.72, 135.94, 136.57, 145.35 (C_{arom}), 150.21 (C-2), 161.54 (C-4).

FAB MS: m/z 447 ($M + H^+$).

*3,4-Anhydro-2-deoxy-1-O-methyl-1-C-(6-methyl-1,2,3,4-tetrahydro-2,4-dioxoquinazolin-1-yl)-D-*threo*-pentitol* **9**

The protected acyclic nucleoside **6b** (100 mg, 0.14 mmol) was treated with 1 M Bu_4NF/THF (0.35 mL, 0.32 mmol) in a similar way to that described in the preparation of **7a** and **8a**. Purification by column chromatography on silica gel with the gradient 0–5% MeOH in $CHCl_3$ afforded 31 mg (73%) of **9** as a white foam.

^{1}H NMR ($CDCl_3$): δ 2.19 (m, 1H, 2'-H), 2.40 (s, 3H, CH_3), 2.43 (m, 1H, 2'-H), 2.90 (dd, 1H, J = 2.9, 6.3 Hz, 3'-H), 3.09 (m, 1H, 4'-H), 3.40 (s, 3H, OCH_3), 3.64 (dd, 1H, J = 4.0, 12.7 Hz, 5'-H), 3.79 (dd, 1H, J = 3.1, 12.7 Hz, 5'-H), 6.46 (t, 1H, J = 6.9 Hz, 1'-H), 7.41 (dd, 1H, J = 2.2, 8.7 Hz, 8-H), 7.80 (d, 1H, J = 8.7 Hz, 7-H), 8.01 (s, 1H, 5-H).

^{13}C NMR ($CDCl_3$): δ 20.34 (CH_3), 35.16 (C-2'), 52.16 (C-3'), 56.15 (OCH_3), 57.79 (C-4'), 61.23 (C-5'), 86.13 (C-1'), 116.58, 128.40, 133.59, 135.96, 136.13, 136.83 (C_{quin}), 150.92 (C-2), 161.61 (C-4).

FAB MS: m/z 307 ($M + H^+$).

*1-(5-O-*tert*-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-β-D-*threo*-pentofuranosyl)-2,4(1H,3H)-quinazolinedione* **10**, *1-(5-O-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-iodo-α-D-*threo*-pentofuranosyl)-2,4(1H,3H)-quinazolinedione* **11** *and 5-O-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-iodo-1-O-methyl-1-C-(1,2,3,4-tetrahydro-2,4-dioxoquinolin-1-yl)-D-*threo*-pentitol* **12**

A mixture of 2,4-(1*H*,3*H*)-quinazolinedione **4a** (1.3 g, 8 mmol), HMDS (60 mL) and $(NH_4)_2SO_4$ (100 mg) was refluxed overnight, cooled and the solvent was removed in vacuo. The resulting residue was dissolved in anhydrous MeCN (20 mL) and a solution of methyl 5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-3-iodo-D-*threo*-pentofuranoside **3** (2.67 g, 5.4 mmol) in anhydrous MeCN (20 mL) was added with stirring. The mixture was cooled to −50 °C and a solution of TMS triflate (1.3 mL, 6.5 mmol) in anhydrous MeCN (5 mL) was added dropwise. The mixture was stirred for 1 h at −35 °C. The mixture was

diluted with CH_2Cl_2 (200 mL), washed with a cold saturated aqueous $NaHCO_3$ (150 mL) and with cold H_2O (3 × 150 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was chromatographed on silica gel with the gradient 20–30% $CHCl_3$ in petroleum ether to give **10–12** as white foams.

Compound **10**

Yield 690 mg (20%).

^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H, *t*-Bu), 2.85 (m, 2H, 2′-H), 3.47 (q, 1H, J = 5.7 Hz, 4′-H), 3.89 (dd, 1H, J = 5.5, 10.8 Hz, 5′-H), 4.04 (dd, 1H, J = 5.9, 10.8 Hz, 5′-H), 4.63 (m, 1H, 3′-H), 6.68 (t, 1H, J = 8.3 Hz, 1′-H), 7.24–8.24 (m, 14H, H_{arom}), 9.22 (s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ 19.15 (Me_3C), 21.52 (C-3′), 26.79 [(CH_3)$_3$C], 39.21 (C-2′), 69.22 (C-5′), 79.03 (C-4′), 83.48 (C-1′), 116.68, 117.89, 123.87, 127.65, 127.67, 128.59, 129.69, 129.74, 132.97, 133.18, 134.71, 135.52, 135.57, 138.39 (C_{arom}), 150.29 (C-2), 161.39 (C-4).

FAB MS: m/z 627 (M + H$^+$).

Compound **11**

Yield 975 mg (29%).

^{1}H NMR ($CDCl_3$): δ 1.09 (s, 9H, *t*-Bu), 2.80 (ddd, 1H, J = 4.5, 7.3, 13.8 Hz, 2′$_\beta$-H), 3.56 (td, 1H, J = 6.8, 13.5 Hz, 2′$_\alpha$-H), 3.80 (dd, 1H, J = 5.4, 10.7 Hz, 5′-H), 4.05 (dd, 1H, J = 4.1, 10.8 Hz, 5′-H), 4.18 (q, 1H, J = 4.7 Hz, 4′-H), 4.95 (td, 1H, J = 2.4, 4.5 Hz, 3′-H), 6.49 (t, 1H, J = 6.8 Hz, 1′-H), 7.23–8.23 (m, 14H, H_{arom}), 9.33 (s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ 19.09 (Me_3C), 26.07 (C-3′), 26.77 [(CH_3)$_3$C], 41.89 (C-2′), 69.13 (C-5′), 82.62 (C-4′), 86.73 (C-1′), 114.24, 116.30, 123.57, 127.57, 127.64, 128.86, 129.70, 132.87, 133.18, 134.70, 135.28, 135.42, 135.57, 141.31 (C_{arom}), 149.34 (C-2), 161.91 (C-4).

FAB MS: m/z 627 (M + H$^+$).

Compound **12**

Yield 430 mg (12%).

^{1}H NMR ($CDCl_3$): 1.06 (s, 9H, *t*-Bu), 2.34 (m, 2′-H), 2.78 (m, 2′-H), 3.20 (s, OH), 3.39, 3.43 (2 × s, OCH_3), 3.61 (m, 4′-H, 5′-H), 4.56 (m, 3′-H), 6.46 (m, 1′-H), 7.23–8.24 (m, H_{arom}), 9.20, 9.31 (2 × s, NH).

^{13}C NMR ($CDCl_3$): δ 19.11 (Me_3C), 26.73 [(CH_3)$_3$C], 29.54, 29.58 (C-3′), 39.56, 40.88 (C-2′), 56.36, 56.72 (OCH_3), 67.45, 67.92 (C-5′), 72.21, 73.93 (C-4′), 87.20, 88.29 (C-1′), 116.67, 123.54, 123.71, 127.74, 128.69, 128.76, 129.78, 129.84, 132.71, 132.92, 134.89, 134.95, 135.39, 135.52 (C_{arom}), 150.47 (C-2), 161.69 (C-4).

1-(3,4-Didehydro-2,3-dideoxy-β-D-pentofuranosyl)-2,4(1H,3H)-quinazolinedione **13**

A mixture of the protected nucleoside **10** (400 mg, 0.64 mmol) and sodium methoxide (346 mg, 6.4 mmol) was refluxed in MeOH (25 mL) for 5 h. The reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel with the gradient 0–5% MeOH in $CHCl_3$ to afford 99 mg (60%) of **13**; mp 225 °C (decomp).

^{1}H NMR (DMSO-d_6): δ 2.75 (m, 2H, 2′-H), 3.98 (d, 1H, J = 5.2 Hz, 5′-H), 5.15 (m, 2H, OH, 3′-H)), 7.26–8.09 (m, 5H, 1′-H, H_{arom}), 11.70 (s, 1H, NH).

^{13}C NMR (DMSO-d_6): δ 31.61 (C-2′), 56.02 (C-5′), 85.50 (C-1′), 95.93 (C-3′), 115.24, 116.53, 123.19, 127.88, 134.60, 138.25 (C_{quin}), 150.08 (C-2), 157.03 (C-4′), 161.27 (C-4).

Anal $C_{13}H_{12}N_2O_4 \cdot 1.25H_2O$, calc: C 55.20, H 5.08, N 9.91. Found: C 55.15, H 4.74, N 9.81.

FAB MS: m/z 261 (M + H$^+$).

1-(5-O-tert-Butyldiphenylsilyl-2-deoxy-α-D-erythro-pentofuranosyl)-2,4(1H,3H)-quinazolinedione **14** *and 1-(2-deoxy-α-D-erythro-pentofuranosyl)-2,4(1H,3H)-quinazolinedione* **15**

The protected nucleoside **11** (626 mg, 1 mmol) was refluxed with sodium methoxide (540 mg, 10 mmol) in MeOH (30 mL) as described in the preparation of **13**. Separation by column chromatography on silica gel with the gradient 0–5% MeOH in $CHCl_3$ afforded **14** and **15**.

Compound **14**

Yield 56 mg (11%), white foam.

^{1}H NMR ($CDCl_3$): δ 1.10 (s, 9H, *t*-Bu), 2.63 (dd, 1H, J = 1.0, 14.5 Hz, 2′-H), 2.88 (m, 1H, 2′-H), 3.82 (dd, 1H, J = 2.4, 11.2, 5′-H), 3.84 (dd, 1H, J = 3.0, 11.2 Hz, 5′-H), 4.38 (m, 1H, 4′-H), 4.57 (t, 1H, J = 8.8 Hz, 3′-H), 4.86 (d, 1H, J = 10.5 Hz, OH), 6.35 (dd, 1H, J = 3.5, 9.0 Hz, 1′-H), 7.25–8.25 (m, 14H, H_{arom}), 9.22 (s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ 19.16 (Me_3C), 26.80 [(CH_3)$_3$C], 39.44 (C-2′), 65.62 (C-5′), 73.88 (C-3′), 87.80, 89.36 (C-1′, C-4′), 114.78, 116.43, 123.84, 127.73, 127.76, 128.72, 129.78, 129.86, 132.77, 133.12, 134.78, 135.41, 135.47, 141.35 (C_{arom}), 149.83 (C-2), 161.76 (C-4).

FAB MS: m/z 517 (M + H$^+$).

Compound **15**

Yield 158 mg (57%), mp 166–167 °C.

^{1}H NMR (DMSO-d_6): δ 2.37 (m, 2H, 2′-H), 3.47 (m, 2H, 5′-H), 4.08 (m, 1H, 4′-H), 4.32 (m, 1H, 3′-H), 4.81 (t, 1H, J = 5.3 Hz, OH), 5.38 (d, 1H, J = 4.9 Hz, OH), 6.65 (t, 1H, J = 8.0 Hz, 1′-H), 7.27 (t, 1H, J = 7.3 Hz, 7-H), 7.68 (m, 1H, 6-H), 7.86 (d, 1H, J = 8.6 Hz, 8-H), 8.02 (d, 1H, J = 7.8 Hz, 5-H), 11.59 (s, 1H, NH).

^{13}C NMR (DMSO-d_6): δ 36.24 (C-2′), 61.67 (C-5′), 70.40 (C-3′), 84.20, 85.93 (C-1′, C-4′), 116.43, 116.61, 122.92, 127.51, 134.31, 139.05 (C_{quin}), 150.04 (C-2), 161.42 (C-4).

EI MS: m/z (relative intensity) 278 (M$^+$, 30).

3,4-Anhydro-2-deoxy-1-O-methyl-1-C-(1,2,3,4-tetrahydro-2,4-dioxoquinazolin-1-yl)-D-erythro-pentitol **16**

The protected acyclic nucleoside **12** (250 mg, 0.38 mmol) was treated with 1 M Bu_4NF/THF (0.42 mL, 0.46 mmol) in a similar way to that described in the preparation of **7a** and **8a**. The residue was chromatographed on silica gel with the gradient 0–5% MeOH in $CHCl_3$ to give 92 mg (83%) of **16** as a white foam.

^{1}H NMR ($CDCl_3$): (*predominant isomer*): δ 2.17 (m, 1H, 2′-H), 2.56 (m, 1H, 2′-H), 3.17 (m, 1H, 4′-H), 3.33 (m, 4H, 3′-H, OCH_3), 3.59 (m, 2H, 5′-H), 5.07 (broad s, 1H, OH), 6.41 (t, 1H, J = 6.7 Hz, 1′-H), 7.26 (t, 1H, J = 3.3 Hz, 7-H), 7.61–8.00 (m, 2H, 6-H, 8-H), 8.17 (d, 1H, J = 7.6 Hz, 5-H).

^{13}C NMR ($CDCl_3$): (*predominant isomer*): δ 31.65 (C-2′), 52.86 (C-3′), 55.83 (C-4′), 56.11 (OCH_3), 59.42 (C-5′), 86.27 (C-1′), 116.38, 123.43, 128.34, 134.61, 138.61, 138.92 (C_{quin}), 150.99 (C-2), 161.83 (C-4).

Peak matching: $C_{14}H_{16}N_2O_5$, calc: 292.1059. Found: 292.1061.

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