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Carbohydrate Research 266 (1995) 87–94

CARBOHYDRATE
RESEARCH

Reaction of 2′-deoxyguanosine with glucose

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Received 11 May 1994; accepted 20 July 1994

Abstract

Glucose reacts with 2′-deoxyguanosine under physiological conditions to give the diastereomeric purine substituted trihydroxy-α-amino hexanoic acids **4** as main products. Hydrolysis of **4** leads to the guanine derivatives **6** which have been synthesized by an independent route.

1. Introduction

In a series of investigations, Cerami and his group have shown that DNA can react with glucose or glucose-6-phosphate [1]. The process is accelerated by an amino acid like lysine or arginine [2]. Probably glucose and the amino acid react to give an intermediate which adds to the amino groups of DNA, but so far the structures of the products remain unknown. Miksik et al. have shown that products obtained from glucose-6-phosphate and nucleotides can be detected by HPLC [3]. It has been hypothesized that glucose-DNA interaction may be responsible for strand breaks or more generally for processes associated with ageing [1].

Previously, we have shown that guanosine, glucose and propylamine, a model compound for protein–bound lysine, react in neutral solution under physiological conditions to give the stereoisomeric compounds **5a** and **5b** as main products [4]. The glycosyl derivatives, **2** and **3**, of guanosine and guanine have been isolated from heated mixtures of glucose and guanosine or 2′-deoxyguanosine, respectively. The latter reaction was carried out in unbuffered solution [5].

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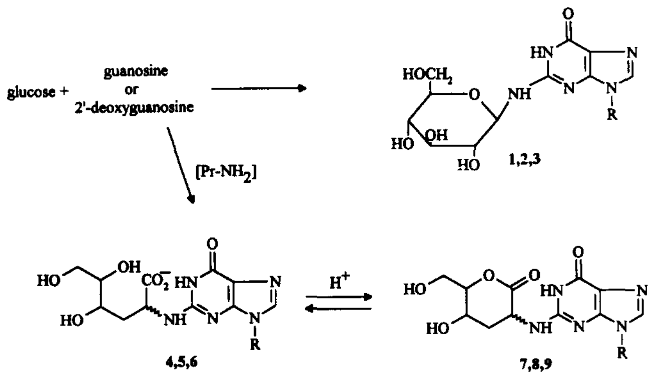
SSDI 0008-6215(94)00254-1



	R
1,4,7	2'-deoxy-β-D-ribofuranosyl
2,5,8	β-D-ribofuranosyl
3,6,9	H

a	2 (*R*)
b	2 (*S*)

Here, we report on a more detailed investigation of the reaction of 2′-deoxyguanosine with glucose, and a structural proof of the main new products by independent synthesis.

2. Results

When glucose and 2′-deoxyguanosine are heated in a phosphate buffered (pH 7) aqueous solution for several hours at 100°C, the glucosyl derivative **1** is obtained as the main product. When 2′-deoxyguanosine is allowed to react with glucose and propylamine in a phosphate buffered neutral aqueous solution at 40°C for several days, several products are formed which can be separated by HPLC on reversed phase material (Fig. 1). The stereoisomeric compounds **4a** and **4b** have been isolated as the main products, in

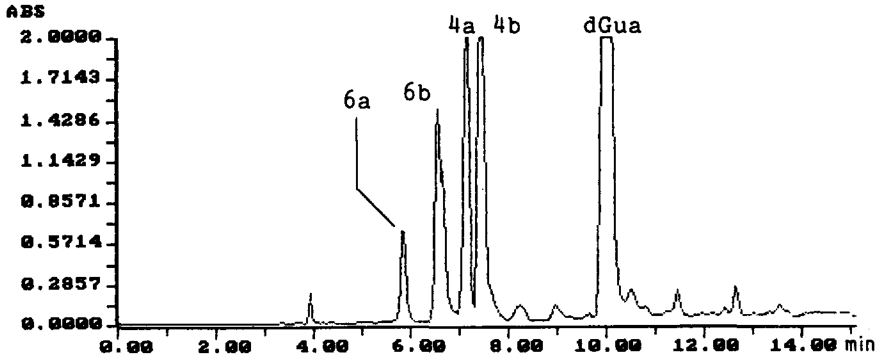
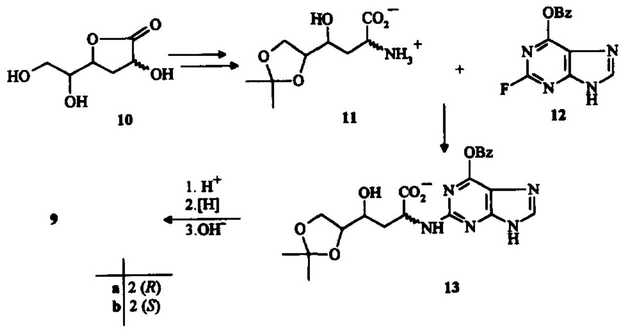


Fig. 1. High-pressure liquid-chromatogram of the mixture of glucose and 2′-deoxyguanosine (14 days, 40°C, pH 7.0, system 1, $\lambda = 278$ nm; dGua = 2′-deoxyguanosine)

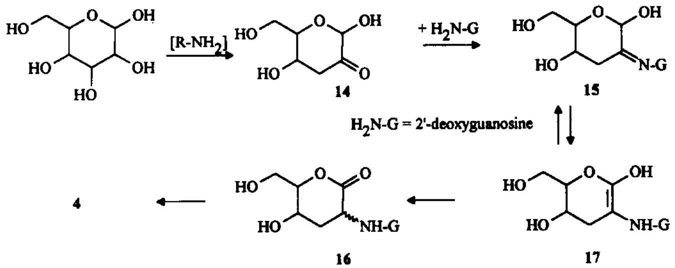
addition to the guanine derivatives **6a** and **6b** which are obviously formed by spontaneous hydrolysis of the 2′-deoxyribose-purine bond. As could be expected in slightly acidic solution, the amount of **6** increases at the expense of **4**. The same products can be isolated from mixtures of 3-deoxy-glucos-2-ulose and the nucleoside. Compound **6** is readily transformed into the lactone **9**, which reacts with hydroxylamine to give a hydroxamic acid detectable by a typical colour reaction with ferric chloride.

The structures of **1**, **4**, **6**, and **9** can be derived from spectroscopic data. For all compounds positive-ion FABMS data confirm the molecular weight. The UV maxima are shifted towards longer wavelengths compared to the starting compound. The NMR spectra display the presence of the intact guanine and 2′-deoxyguanosine moiety, respectively. For **1**, the ^{13}C NMR signal associated with C-1 of the glucosyl residue (δ 81 ppm) is consistent with an *N*,*O*-acetal structure [6]. Evidence for a β-glycosidic bond comes from ^{1}H NMR, which shows a coupling constant of 8.8 Hz for the H-1 of glucose. For **4** and **6** the ^{13}C NMR chemical shift of C-1 (δ 180 ppm) is characteristic for carboxylic acid anions. Signals for C-2 and C-3 are shifted upfield compared to glucose. The ^{13}C signal for C-2 (δ 54 ppm) is typical for α-amino acids. The ^{1}H NMR signals of **4** and **6** differ only for H-2 and H-3, which leads to the assumption that compounds **4a** and **4b**, and **6a** and **6b**, are diastereomers, respectively. The ^{1}H NMR signals for the methylene protons at C-3 for **4a** and **6a** are well resolved and are classified as a double double doublet and a double triplet, whereas in **4b** and **6b** the chemical shifts are similar and a multiplet is observed. The ^{1}H NMR spectrum of the lactones **9a** and **9b** show a downfield shift for all the ring protons of the glucose moiety. For **9a**, a coupling constant, $^{3}J_{H,H}$ 11.0, Hz is observed for H-2 which is typical for diaxial protons in six rings. Because of that, the absolute configuration at C-2 is *R*. Overall, **4a** and **6a** have the *ribo* configuration.

To further establish the structures, compounds **6a** and **6b** were synthesized by an independent route shown in Scheme 1. It is well documented that 1-benzyloxy-3-fluoropurine (**12**) is a suitable intermediate for the preparation of guanine derivatives. For instance, substitution of the fluorine atom in **12** by the amino group of alanine has been successfully performed [7]. The amino acid **11** is described in the literature [8]. We obtained a mixture of stereoisomeric products (**11a** and **11b**) from glucometasaccharinic acid lactone (**10**) by mesylation followed by an azide exchange reaction and catalytic



Scheme 1. Synthesis of **6a** and **6b**.



Scheme 2. Reaction mechanism for the formation of trihydroxy α-amino acids from glucose.

hydrogenation. When **11a**, **11b**, and **12** are heated in *N*-methylpyrrolidone in the presence of potassium carbonate, the substitution product **13** is formed in moderate yield. Acid hydrolysis followed by catalytic hydrogenation and alkali–induced opening of the lactone ring leads to compounds **9a** and **9b** which proved to be identical to the products obtained from glucose and 2′-deoxyguanosine.

It should be recognized that, during the reaction of glucose with 2′-deoxyguanosine, the aldohexose is transformed into a trihydroxy-α-amino hexanoic acid. This is a previously unknown mode of sugar degradation, resembling the formation of metasaccharinic acid.

A reaction mechanism is shown in Scheme 2. It is well established that the degradation of glucose, catalyzed by proteins, amino acids, or simple primary amines, leads to the formation of 3-deoxyglucosulose as an important intermediate [9]. A Schiff base of structure **15** could lead to the trihydroxy-α-amino hexanoic acid **4** by enamine-enol tautomerism via the enaminole **17** and the lactone **16**. The preferred reaction of the amino group of the nucleoside can be explained by the assumption that, for 3-deoxyhexosulose, cyclic structures like **14** are favoured at equilibrium. One might expect that *N*-substituted trihydroxy-α-amino hexanoic acids might be formed as well by interaction of glucose with primary aliphatic amines or lysine side chains of proteins. This would give a new insight into the Maillard reaction.

3. Experimental

General methods.—Melting points were determined in open capillaries in a Büchi apparatus and are uncorrected. ^1H NMR (400 MHz) and ^{13}C NMR (400 MHz) spectra were recorded with a Jeol 400 GSX spectrometer with $(CH_3)_4Si$ as internal standard. Chemical shifts are reported in ppm. Positive FABMS were obtained with a Kratos MS 80 RFA spectrometer. Column chromatography was performed on silica gel (0.063–0.200 mm, J.T. Baker, 0253; column size 20 × 3 cm, i.d.; elution with 1 : 1 : 0.1 EtOAc–MeOH–6 N ammonia) and monitoring was done with the same eluent by TLC (Silica gel 60-F_{254}, 0.2 mm, Merck, 5554). Analytical HPLC was performed with a Merck L-6200 gradient pump, a Merck D-6500 photodiode array detector including Merck DAD-Manager software, and a NEC pinwriter P60. UV-spectra were directly taken from this system (λ in nm).

For preparative chromatography, a Merck L-6000 pump, a Merck L-4000 UV-detector, and a Merck D-2500 chromato integrator were used. The water used for HPLC was distilled and filtered through a 0.45 μm nylon membrane. HPLC grade solvent (MeOH) was used without further purification. All solvents were degassed with He. System 1 (analytical): column: Hibar LiChrospher™ RP 18, 250 × 4.6 mm i.d., 5 μm with guard cartridge (25 × 4.6 mm i.d., 5 μm); UV-detection between 220 and 300 nm (DAD); eluent: gradient elution starting with 9:1 0.05 M triethylammonium acetate buffer pH 7–MeOH ending within 25 min with 2:8 buffer–MeOH at a flow rate of 0.8 mL/min. System 2 (preparative): column: Hibar LiChrosorb™ RP 18, 250 × 25 mm i.d., 7 μm; UV-detection at 270 nm. 2a, eluent: 5 mM ammonium formate, pH 7, at a flow rate of 7.0 mL/min. 2b, eluent: 3:7 20 mM ammonium formate buffer, pH 7–MeOH at a flow rate of 7.0 mL.

*9-(2′-Deoxy-β-*D*-ribofuranosyl)-2-(β-*D*-glucopyranosylamino)-9*H*-purine-6(1*H*)-one* (**1**).—Glucose (7.2 g, 40 mmol) and 2′ deoxyguanosine monohydrate (1.14 g, 4 mmol) were kept in 2 M phosphate buffer (5 mL, pH 7.0) at 100°C for 5 h. Water (5 mL) was added and the mixture was filtered, after standing at 4°C, from unreacted material. Isolation of **1** was achieved by preparative HPLC (system 2a). This procedure was repeated several times; yield (20.8 mg, 1.2%); mp 180°C (dec); ^{1}H NMR (D_2O): δ 7.91 (s, 1 H, gua), 6.27 (t, 1 H, $J_{1,2}$ 7.3 Hz, H-1 derib), 5.20 (d, 1 H, $J_{1,2}$ 8.8 Hz, H-1 glc), 4.54 (m, 1 H, H-3 derib), 4.09 (m, 1 H, H-4 derib), 3.65–3.85 (m, 4 H, H-5a, H-5b derib, H-6a, H-6b glc), 3.50–3.55 (m, 2 H, H-3, H-5 glc), 3.38–3.40 (m, 2 H, H-2, H-4 glc), 2.85 (m, 1 H, H-2a derib), 2.42 (m, 1 H, H-2b derib); ^{13}C NMR: 158.8 (s, C-6 gua) 151.7 (s, C-2 gua), 150.3 (s, C-4 gua), 138.6 (d, C-8 gua), 118.4 (s, C-5 gua), 86.9 (d, C-4 derib), 83.9 (d, C-1, derib), 81.3 (d, C-1 glc), 77.3 (d, C-5 glc), 76.5 (d, C-3 glc), 72.1 (d, C-2 glc), 71.1 (d, C-3 derib), 69.2 (d, C-4 glc), 61.5 (t, C-5 derib), 60.4 (t, C-6 glc), 38.0 (t, C-2 derib). UV (H_2O, pH 7): λ_{max} 255; FABMS (Xe, 7 KV, glycerol, LiCl): m/z 430 ($M + H^+$).

Reaction of 2′-deoxyguanosine with glucose in the presence of propylamine.—Glucose (1.8 g, 10 mmol) and 2′-deoxyguanosine monohydrate (570 mg, 2 mmol) were heated at 40°C for 28 days in a mixture of 500 mg potassium dihydrogen phosphate, 648 mg di-sodium hydrogen phosphate dihydrate (3.7 mmol each), and propylamine (60 mg, 1 mmol) in 2.5 mL of water. The mixture was diluted with water (5 mL) and filtered for preparative HPLC (system 2a). The products were collected, lyophilisized and recrystallized from 3:1 EtOH–water.

*Ammonium 2-(*N^2*-2′-deoxyguanosyl)-2,3-dideoxy-*D-ribo*-hexonate* (**4a**).—Yield, 30.5 mg (3%); mp 226–230°C (dec); ^{1}H NMR (D_2O): δ 7.90 (s, 1 H, gua), 6.29 (t, 1 H, $J_{1,2}$ 6.6 Hz, H-1 derib), 4.65 (m, H-3 derib), 4.38 (t, 1 H, $J_{2,3}$ 6.6 Hz, H-2), 4.11 (m, 1 H, H-4 derib), 3.77–3.93 (m, 3 H, H-5a derib, H-4, H-6a), 3.65–3.77 (m, 3 H, H-5b derib, H-5, H-6b), 2.89 (m, 1 H, H-2a derib), 2.36 (m, 1 H, H-2b derib), 2.15 (ddd, 1 H, $J_{3,4}$ 2.5, $J_{2,3}$ 6.6, J_{gem} 12.5 Hz, H-3a), 1.83 (m, 1 H, H-3b); ^{13}C NMR: 179.3 (s, C-1), 158.9 (s, C-6 gua), 151.9 (s, C-2 gua), 151.4 (s, C-4 gua, 138.7 (d, C-8 gua), 116.7 (s, C-5 gua), 87.0 (d, C-4 derib), 84.7 (d, C-1 derib), 75.0 (d, C-5), 71.3 (d, C-3 derib), 70.2 (d, C-4), 62.8 (t, C-5 derib), 61.9 (t, C-6), 55.4 (d, C-2), 38.0 (t, C-2 derib), 35.1 (t, C-3); UV (H_2O, pH 7): λ_{max} 255.6, 278.5 (sh); FABMS (Xe, 7 KV, glycerol): m/z 430 ($M + H^+$) for the free acid.

*Ammonium 2-(*N^2*-2'-deoxyguanosyl)-2,3-dideoxy-*D-arabino*-hexonate* (**4b**).—Yield, 29.3 mg (3%); mp 230–240°C (dec); ^{1}H NMR (D_2O): δ 7.90 (s, 1 H, gua), 6.27 (t, 1 H, $J_{1,2}$ 6.6 Hz, H-1 derib), 4.63 (m, 1 H, H-3 derib), 4.54 (dd, 1 H, $J_{2,3a}$ 4.5, $J_{2,3b}$ 8.5 Hz, H-2), 4.09 (m, 1 H, H-4 derib), 3.79–3.84 (m, 3 H, H-5a derib, H-4, H-6a), 3.65–3.75 (m, 3 H, H-5b derib, H-5, H-6b), 2.93 (m, 1 H, H-2a derib), 2.53 (m, 1 H, H-2b derib), 2.09 (m, 2 H, H-3a, H-b); ^{13}C NMR: 179.3 (s, C-1), 159.6 (s, C-6 gua), 153.0 (s, C-6 gua), 152.0 (s, C-4 gua), 139.2 (d, C-8 gua), 117.0 (s, C-5 gua), 87.5 (d, C-4 derib), 84.8 (d, C-1 derib), 75.4 (d, C-5), 71.7 (d, C-3 derib), 69.5 (d, C-4), 63.3 (t, C-5 derib, 62.4 (t, C-6), 54.4 (d, C-2), 38.7 (t, C-2 derib), 35.5 (t, C-3); UV (H_2O, pH 7): λ_{max} 255.6 278.5 (sh); FABMS (Xe, 7 KV, glycerol): m/z 430 ($M + H^+$) for the free acid.

Reaction of 2'-deoxyguanosine with 3-deoxy-glucos-2-ulose.—3-Deoxy-glucos-2-ulose (600 mg, 3.7 mmol) [10] and 2'-deoxyguanosine monohydrate (700 mg, 2.6 mmol) in 0.5 M phosphate buffer (6 mL) were stored at 70°C for 4 days. Samples were taken daily and assayed by analytical HPLC (system 1a). The new products proved to be identical to **4a** and **4b**. On prolonged heating (overall 8 days), two new compounds appeared which were isolated by HPLC. After dilution with 5 mL of water and filtration, the mixture was chromatographed (system 2a). The fractions were lyophilisized and recrystallized from EtOH.

*Ammonium 2,3-dideoxy-2-(*N^2*-guanyl)-*D-ribo*-hexonate* (**6a**).—Yield, 47 mg (6%); mp 230°C (dec); ^{1}H NMR (D_2O): δ 7.90 (s, 1H, gua), 4.35 (t, 1 H, $J_{2,3}$ 7 Hz, H-2), 3.87 (dd, 1H, $J_{5,6}$ 2, J_{gem} 12 Hz, H-6a), 3.79 (dd, 1 H, $J_{5,6}$ 5, J_{gem} 12 Hz, H-6b), 3.63–3.72 (m, 2 H, H-4, H-5), 2.25 (ddd, $J_{3,4}$ 2.5, $J_{2,3}$ 5.5, J_{gem} 12.5 Hz, H-3a), 1.93 (m, 1 H, H-3b); ^{13}C NMR: 179.4 (s, C-1), 159.9 (s, C-6 gua), 151.8 (s, C-2 gua), 151.3 (s, C-4 gua), 138.5 (d, C-8 gua), 116.5 (s, C-5 gua), 75.4 (d, C-5), 70.2 (d, C-4), 61.0 (t, C-6), 55.4 (d, C-2), 35.1 (t, C-3); UV (H_2O, pH 7): λ_{max} 249.2, 279.6; FABMS (Xe, 7 KV, glycerol): m/z 313 ($M + H^+$) for the free acid.

*Ammonium 2,3-dideoxy-2-(*N^2*-guanyl)-*D-arabino*-hexonate* (**6b**).—Yield, 45 mg (6%); mp 220°C (dec); ^{1}H NMR (D_2O): δ 7.90 (s, 1 H, gua), 4.54 (dd, 1 H $J_{2,3a}$ 4.5, $J_{2,3b}$ 8.5 Hz, H-2), 3.88 (m, 1 H, $J_{5,6}$ 2.2, J_{gem} 12 Hz, H-6a), 3.79 (dd, 1 H, $J_{5,6}$ 5, J_{gem} 12 Hz, H-6b), 3.63–3.72 (m, 2 H, H-4, H-5), 2.09 (m, 2 H, H-3a, H-3b); ^{13}C NMR: 179.3 (s, C-1), 159.6 (s, C-6 gua), 153.0 (s, C-2 gua), 152.0 (s, C-4 gua), 139.2 (d, C-8 gua), 117.0 (s, C-5 gua), 75.4 (d, C-5), 69.5 (d, C-4), 62.4 (t, C-6), 54.4 (d, C-2), 35.5 (t, C-3); UV (H_2O, pH 7): λ_{max} 249.2, 279.6; FABMS (Xe, 7 KV, glycerol): m/z 313 ($M + H^+$) for the free acid.

Lactonisation of **6**.—Water was evaporated from the 2'-deoxyguanosine–3-deoxyglucos-2-ulose mixture and 5 : 1 MeOH–HCl (5 mL) was added. The mixture was filtered and stirred for 1 h at room temperature. Semi-preparative HPLC (system 2a) was applied to isolate the lactones.

*2,3-Dideoxy-2-(*N^2*-guanyl)-*D-ribo*-hexono-1,5-lactone* (**9a**).—Yield, 39 mg (5%). ^{1}H NMR (CD_3OD): δ 7.93 (s, 1H, gua), 5.01 (dd, 1 H, $J_{2,3eq}$ 8.8, $J_{2,3ax}$ 11.7 Hz, H-2), 3.85–4.01 (m, 2 H, H-6a, H-6b), 3.70–3.78 (m, 2 H, H-4, H-5), 2.70 (m, H-3a), 2.45 (m, H-3b); UV (H_2O, pH 7): λ_{max} 248.8, 278.5; FABMS (Xe, 7 KV, glycerol): m/z 296 ($M + H^+$).

*2,3-Dideoxy-2-(*N^2*-guanyl)-*D-arabino*-hexono-1,5-lactone* (**9b**).—Yield, 42 mg (5%). ^{1}H NMR (CD_3OD): δ 7.94 (s, 1 H, gua), 5.03 (dd, 1 H, $J_{2,3eq}$ 4.4, $J_{2,3ax}$ 8.8 Hz, H-2), 3.84–3.99 (m, 2 H, H-6a, H-6b) 3.67–3.73 (m, 2 H, H-4, H-5) 2.60 (m, 2 H, H-3a, H-3b); UV (H_2O, pH 7): λ_{max} 248.8, 278.5; FABMS (Xe, 7 KV, glycerol): m/z 296 ($M + H^+$):

*Synthesis of the diastereomeric mixture of 2-amino-2,3-dideoxy-5,6-*O*-isopropylidene-*D-erythro-*hexonic acid* (**11a** *and* **11b**).—The procedure was adopted from the known synthesis of the enantiomerically pure amino acid derivatives [8]. The starting compound was D-glucometasaccharinic acid-1,4-lactone **10** (6 g, 37 mmol) [11], which was protected and further treated as described to yield 2.24 g (10.2 mmol; 27% overall yield) of the title compounds.

Coupling reaction of (**11a** *and* **11b**) *with 2-fluoro-6-benzyloxypurine* (**12**).—2-Fluoro-6-benzyloxypurine [7] (260 mg, 1.06 mmol) was dissolved in 3 mL of 1-methyl-2-pyrrolidone. The solution was added to a suspension of protected amino acid **11** (463 mg, 2.13 mmol) and potassium carbonate (213 mg, 2.13 mmol) in 3 mL of water. The mixture was stirred at 70°C for 5 days. After cooling, chromatography on silica gel was applied to remove excess starting compounds. The separation of the two diastereomeric acids were achieved by semipreparative HPLC (system 2b).

*Ammonium 2,3-dideoxy-2-*N^2*-(*O*-benzylguanyl)-5,6-*O*-isopropylidene-*D-ribo-*hexonate* (**13a**).—Yield, 147 mg (33%); ^{1}H NMR (D_2O): δ 7.89 (s, 1 H, gua), 7.33–7.21 (m, 5 H, CH_2Ar), 4.60 (s, 2 H, OCH_2Ar), 4.34 (t, 1 H, J 7 Hz, H-2), 4.15–3.60 (m, 4 H, H-4, H-5, H-6a, H-6b), 2.20 (ddd, 1 H, $J_{3,4}$ 2.8, $J_{2,3}$ 5.5, J_{gem} 13.5 Hz, H-3a), 1.93 (m, 1 H, H-3b), 1.43 (s, 3 H, C–CH_3), 1.33 (s, 3 H, C–CH_3); UV (H_2O, pH 7): λ_{max} 247.6, 291.2; FABMS (Xe, 7 KV, glycerol): m/z 404 ($M + H^+$).

*Ammonium 2,3-dideoxy-2-*N^2*-(*O*-benzylguanyl)-5,6-*O*-isopropylidene-*D-arabino-*hexonate* (**13b**).—Yield, 26 mg (28%); ^{1}H NMR (D_2O): δ 7.91 (s, 1 H, gua), 7.35–7.24 (m, 5 H, CH_2–Ar), 4.64 (s, 2 H, OCH_2Ar), 4.54 (t, 1 H $J_{2,3}$ 7 Hz, H-2), 4.11–3.58 (m, 4 H, H-4, H-5, H-6a, H-6b), 2.07 (m, 2 H, H-3a, H-3b), 1.43 (s, 3 H, C–CH_3), 1.32 (s, 3 H, C–CH_3); UV (H_2O, pH 7): λ_{max} 247.6, 291.2; FABMS (Xe, 7 KV, glycerol): m/z 404 ($M + H^+$).

Synthesis of **9a**.—Compound **13a** (100 mg, 0.24 mmol) was refluxed in 1 : 1 THF–1 N HCl. (10 mL) for 1 h. The solvent was evaporated, the residue was re-dissolved in 1 : 1 EtOH–water (10 mL), and 10% Pd–C (0.3 g) was added to the solution. The mixture was then stirred under 1 atm of H_2 for 12 h and filtered. The filtrate was evaporated to dryness and the residue was refluxed with 6 N ammonia (10 mL) for 1 h. After concentration, the product was purified by semipreparative HPLC (system 2a). Chromatographic and spectroscopic data revealed the identity of the synthesized product to be that of the isolated product **9a**. Yield, 28.8 mg (37%).

Synthesis of **9b**.—Compound **13b** (100 mg) was treated in the same manner as described above. Yield, 26.3 mg, 34%.

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