Hydantoin Analogues of Thymidine

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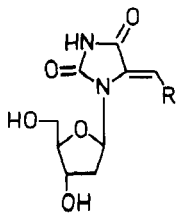
Hydantoin nucleosides were synthesized from a protected methyl 2-deoxy-D-ribofuranoside in a Friedel–Crafts catalyzed silyl-Hilbert–Johnson reaction as modified by Vorbrüggen. Atypical byproducts are accounted for by assuming the initial step being a ring opening of the sugar to give an acyclic glycos-1-yl cation.

Introduction

There should be an obvious interest in 1-glycosylated hydantoin derivatives because of their resemblance with natural nucleosides. In particular, we found the hydantoin nucleoside 1 with R equal to methyl interesting because of its deviation from thymidine only being ring contraction of the nucleobase by a *de facto* rearrangement of carbonyl from C5 to C6. Thymidine itself was isolated a long time



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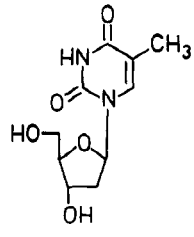
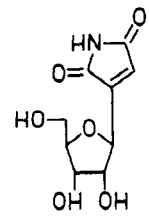


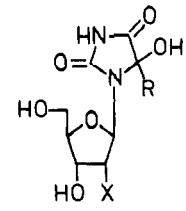
Thymidine



Showdomycin

ago from thymonucleic acid[1–4] and consequently there has been a great deal of interest in synthesizing modified thymidine nucleosides as potential drugs. A recent example is 3-azido-3-deoxythymidine (AZT) which was the first drug reported against human immunodeficiency virus (HIV).[5] The possibility of finding interesting five membered ring analogues of thymidine is best illustrated with showdomycin which is a broad spectrum antibiotic, first isolated from *Streptomyces showdoensis*.[6] This antibiotic has been found to exhibit definite activity against Ehrlich ascites tumor *in vivo* and against cultured HeLa cells.[7,8] This member of the C-nucleoside family has also been reported by other investigators because of its antibiotic and antitumor activities.[9,10]

Hydantoin nucleosides are seldomly described in the literature and derivatives like 1 seem unknown. Recently, the ozonolysis of cytidine, uridine, and thymidine has been reported[11,12] to afford 1-glycosylated 5-hydroxyhydantoins **2a** and **2b** in 9 and 16% yields, respectively. Also an N-3 hydantoin nucleoside has been prepared by glycosylation of a hydantoin derivative.[13]



2a R=H, X=OH
2b R=CH_3, X=H

Results and Discussion

Methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranoside (**5**) was prepared by treatment of 2-deoxy-D-ribose with HCl in methanol[14,15] and subsequently with *p*-toluoyl chloride in pyridine.[16] 5-Arylidenehydantoins (**3a–c,e,f**) were prepared by condensation of arylaldehydes with hydantoin in piperidine[17] whereas 5-ethylidenehydantoin (**3d**) was prepared by desulfurization of 5-ethylidene-2-thiohydantoin with aqueous chloroacetic acid.[18]

The silylation of the hydantoins (5-arylidene and 5-ethylidene-2,4-imidazolidinediones, **3**) was accomplished with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of a catalytic amount of ammonium sulfate. The trimethylsilylated derivatives **4** thus obtained were condensed as devised by Vorbrüggen et al.,[19,20] with methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranoside (**5**) in the presence of trimethylsilyl trifluoromethanesulfonate (TMS triflate) at −10 °C for 3 days. The nucleosides **6a–d** were isolated by silica gel column chromatography in 60–80% yield and no other nucleosides were detected in the reaction mixture as this was the only spot detected below the starting sugar when the TLC plate was sprayed with sulfuric acid. Removal of the protecting toluoyl groups from the glycon moiety of **6** with sodium methoxide in methanol at room temperature furnished 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-(substituted methylene)-2,4-imidazolidinediones **1** and the corresponding α anomer **7**.

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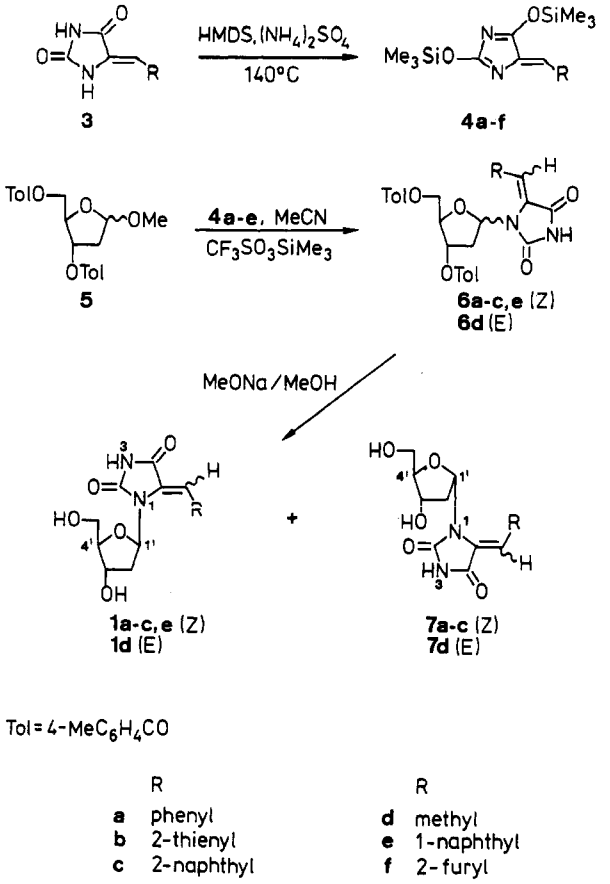
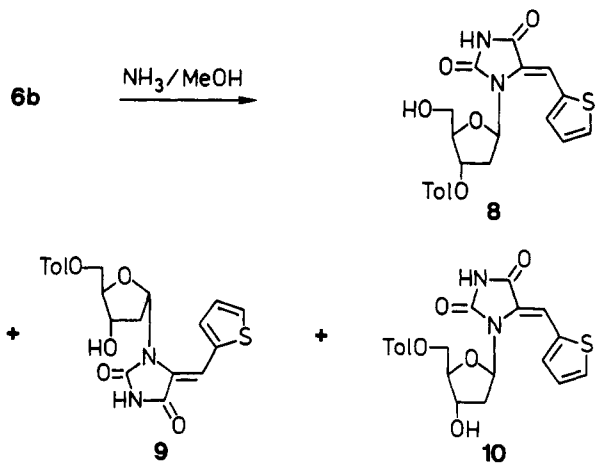
Scheme I



Scheme II

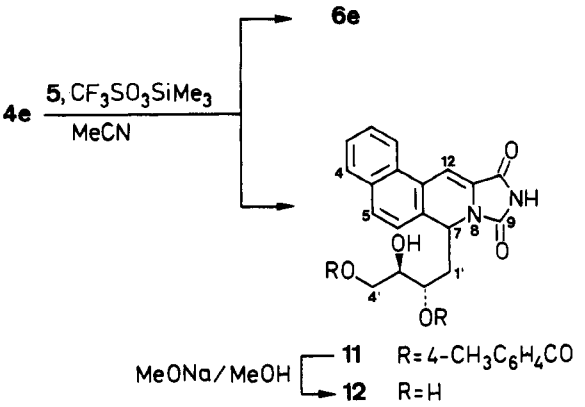


Deprotection of **6** to give the free nucleosides **1** was preferentially done with sodium methoxide in methanol since removal of the protecting toluoyl groups of the glycon moiety of **6b** with saturated methanolic ammonia at room temperature was incomplete even after 3 days and the compounds **8–10** were formed. Characteristic downfield shifts were observed for H5′ in the ^{1}H-NMR spectrum of the α/β mixture **9** + **10** when compared with the shifts of H5′ in the 5′-*O* deprotected compound **8**.

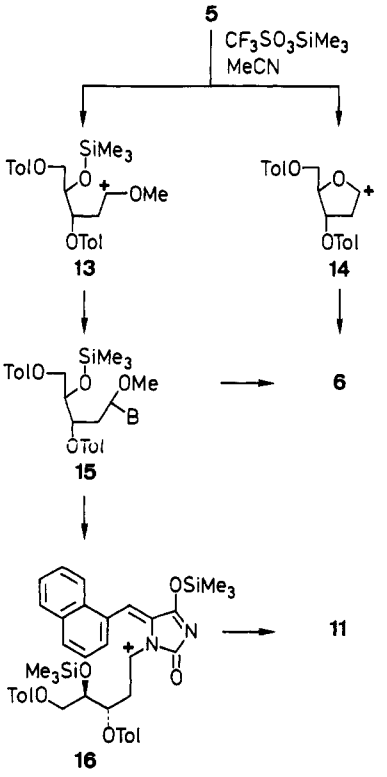
When the trimethylsilyl derivative **4e** was condensed with **5** in the presence of TMS triflate at −10 °C for 3 days, the reaction products **6e** and **11** were isolated by silica gel chromatography in 20 and 50% yields, respectively.

Since it is difficult to explain formation of the acyclic compound **11** *via* the cyclic carbonium ion **14**, its formation

Scheme III



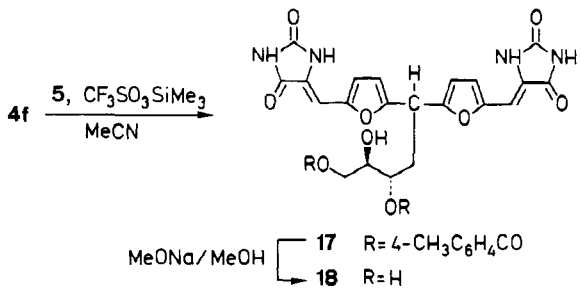
Scheme IV



is explained by a mechanism in which the ring oxygen of the sugar is silylated making endocyclic cleavage possible with formation of the acyclic carbonium ion **13** which in turn can condense with the silylated nucleobase **4e** to give **15**. Silylation of the methoxy group in **15** will cause formation of the carbonium ion **16** which can undergo an intramolecular electrophilic substitution reaction to form the final product **11** after hydrolysis. More intriguing, according to Jørgensen et al.,[21] proposing an acyclic route for the formation of nucleosides from methyl glycosides, the intermediate **15** may represent an important route for formation of nucleosides **6**. This is in contrast with the generally accepted idea that such nucleosides should be formed from the cyclic carbonium ion **14** generated *via* exocyclic silylation of the glycoside **5**. An isolated yield about 50% of the acyclic nucleoside **11** shows formation of the acyclic carbonium ion **13** to be strongly favored. Therefore, it is most likely that all the nucleosides **6** are formed mainly through the acyclic carbonium ion **13**, since

(21) Jørgensen, P. T.; Pedersen, E. B.; Nielsen, C. *Synthesis* **1992**, 1299.

Scheme V



it is hard to believe that the substitution pattern of the silylated hydantoins **4** should determine whether the acyclic carbonium ion **13** or the cyclic carbonium ion **14** is intermediately formed. In support of a mechanism with the aminal **15** as an intermediate that can produce the nucleosides **6** we have found in the literature that Hager and Liotta[22] have synthesized a similar aminal from an acetal and shown that it can cyclize to 3′-azido-3′-deoxythymidine (AZT) under acidic conditions. Removal of the protecting toluoyl groups from the glycon moiety of **11** with sodium methoxide in methanol at room temperature furnished **12**. Due to the induction of a new asymmetric carbon in the dihydropyridine ring, two epimers of **12** could be isolated. In ^{1}H NMR spectra of **11** and **12** the chemical shifts of H7 and H12 were in good agreement with those of similar protons in 2*H*,5*H*-imidazo-[1,5-*b*]isoquinoline-1,3-diones.[23,24]

The trimethylsilyl derivative **4f** was condensed with **5** in the presence of TMS triflate at −10 °C for 3 days. The product **17** was isolated by silica gel chromatography in 21% yield. Formation of acyclic sugar **17** is again explained by a mechanism in which the acyclic carbonium ion **13** is playing the major role. Instead of *N*-glycosylation, the reactive furan ring undergoes an electrophilic aromatic substitution reaction with the electrophile **13**. This is repeated by splitting off the methoxy group and subsequent formation of **17**. Removal of the toluoyl groups of the glycone moiety of **17** with sodium methoxide at room temperature furnished **18**.

Assignment of α and β configurations was determined from the deshielding effect of the nucleobase which generates a downfield shift of H5′ in the β anomers **1**, **6**(β), and **10** when compared with the corresponding α anomers **7**, **6**(α), and **9**, respectively. Furthermore, H4′ of the α anomer appears downfield from that observed for the β anomer.[25,26]

The protons in the ^{1}H-NMR spectra were assigned by ^{1}H–^{1}H-homonuclear shift-correlated (COSY) 2D-NMR. ^{1}H-Nuclear Overhauser effects (NOE difference spectroscopy) also proved α anomeric configurations of **7b–d** and β of **1b–d**, **6e**(β), and **8**. A typical decisive feature for β configurations was irradiations of H2′ at the α site and H2′ at the β site which resulted in strong NOE enhancements in H1′ and H3′, respectively. In the ^{1}H-NMR spectrum of compound **7c** neither H3′ and H4′ nor H2′ to the α site and H2′ to the β site were overlapping. This made it possible to assign α configuration by strong NOE

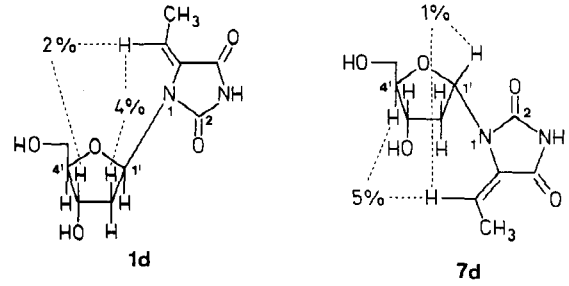


Figure 1. NOE enhancements as obtained upon irradiation of the vinylic hydrogen in compounds **1d** and **7d**. The NOE contacts indicate *E* configuration and anti orientation of the nucleobase, in both **1d** and **7d**.

enhancements in both H1′ and H3′ when H2′ to the β site was irradiated. *Z* configuration and N^1-glycosylation of the arylidene derivatives were proven by strong NOE enhancements in one or two (ortho) aromatic protons when H1′ was irradiated. Besides, this NOE contact between H1′ and the aromatic protons indicated, in both α and β anomers, indicates predominant syn orientation of the nucleobase in the arylidene derivatives.

The site of glycosylation on the hydantoin **3** could also be assigned by comparing the ^{1}H-NMR shift values of NH of the nucleosides **1** and **7** with those of the parent hydantoins. In the ^{1}H-NMR spectrum of **3a** in DMSO-d_6 N^1-H was found at 10.57 ppm and N^3-H at 11.15 ppm.[27] The ^{1}H-NMR spectrum of **1a** in DMSO-d_6 showed a signal at 11.60 ppm which was assigned to N^3-H, identifying the nucleoside **1** as the N^1 glycosylated derivative. Originally, the assignments of N^1-H and N^3-H were done by observing the shifts of NH in the corresponding methylated hydantoins. Also, it should be emphasized that *O*-glycosylation was easily excluded because the C1′ resonance was found at the typical ppm value of *N*-nucleosides[28] and not ~20 ppm at lower field as normally found for glycofuranosides.

NOE difference spectroscopy of the ethylidene derivatives **7d** and **1d** proved not only N^1 glycosylation and the anomeric configuration as α or β, but also isomerization of the exocyclic double bond from *Z* to *E* configuration during the nucleoside synthesis.

Figure 1 schematically shows the NOE enhancements that were observed for the glycosyl protons upon specific irradiation of the vinylic proton. For the β anomer **1d** the largest NOE enhancement was found for the H2′β resonance (4%), which clearly indicates predominant anti orientation of the nucleobase. This is an interesting result since this nucleoside then resembles the corresponding pyrimidine nucleosides which generally have a pronounced preference for anti conformation around the glycosidic bond[29] and this may by of decisive importance with respect to its biological activity since a viewpoint although debatable[30,31] is that the conformational feature of a particular nucleoside analogue is important.[32]

Figure 1 also shows anti conformation of the nucleobase in the α anomer **7d** as a consequence of the NOE enhancement observed for H4′ when the vinylic proton was irradiated. The multiplet of both H2′ protons also

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showed an enhancement, but this was not used for any stereochemical conclusions, except for assignment of anti conformation, because the signals of these two protons were overlapping.

In order to gain insight into the isomerization of the double bond during the synthesis of the ethylidene nucleoside **6d**, the synthesis was in one experiment investigated after 6 h, before completion of the reaction. In the ^{13}C-NMR spectra of the crude product mixture we assigned two lines at 115.0 and 115.4 ppm to the exocyclic vinylic carbons of an anomeric mixture of **6d** having *Z* configurations. The corresponding *E* isomers were found at 117.7 and 118.0 ppm in agreement with the findings of Tan *et al.*[27] who reported the exocyclic vinylic carbons in (*Z*)-methylenehydantoins at higher fields than those of the corresponding *E* isomers. After reaction for further a 18 h, no *Z* isomer could be detected which indicated that a *Z* hydantoin nucleoside could rearrange into the corresponding *E* isomer under the conditions of the glycosylation reaction.

Experimental Section

Silylation of the Hydantoins 3. General Procedure. A mixture of the hydantoin **3a–f** (8.0 mmol), anhydrous $(NH_4)_2SO_4$ (0.04 mmol), and 1,1,1,3,3,3-hexamethyldisilazane (60 mL) was refluxed overnight. The clear solution obtained was cooled and the solvent was evaporated *in vacuo* to give the silylated compounds **4a–f** as pale yellow oils.

(*Z*)-1-[2-Deoxy-3,5-bis-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranosyl]-5-(phenylmethylene)-2,4-imidazolidinedione (6a). A solution of the sugar **5** (2.06 g, 5.4 mmol) in anhydrous MeCN (20 mL) was added to a stirred solution of the silylated compound **4a** in anhydrous MeCN (30 mL) and the mixture was cooled to -50 °C. A solution of trimethylsilyl trifluoromethanesulfonate (1.08 mL, 6 mmol) in anhydrous MeCN (10 mL) was added dropwise during 5 min at −50 °C and the mixture was stirred at −30 °C for 4 h and then at −10 °C for 3 days. The reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with cold saturated aqueous $NaHCO_3$ (200 mL) and water (2 × 100 mL), and dried over anhydrous Na_2SO_4. The mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel with the gradient 0–2% MeOH in $CHCl_3$ to afford 0.41 g (19%) of **6aα** as a white foam and 1.19 g (55%) of **6aβ** as a white foam.

6aα: ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.37 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.72 (td, 1H, *J* = 7.8, 13.7 Hz, H2′), 2.92 (td, 1H, *J* = 6.7, 13.7 Hz, H2′), 4.35 (m, 2H, H5′), 4.62 (q, 1H, *J* = 4.4 Hz, H4′), 5.30 (q, 1H, *J* = 6.6 Hz, H3′), 5.65 (t, 1H, *J* = 7.2 Hz, H1′), 6.70 (s, 1H, =CH), 7.23–7.89 (m, 13H, H_{arom}), 11.64 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 21.11, 21.14 (2 CH_3), 33.89 (C2′), 64.52 (C5′), 73.90 (C3′), 79.99 (C4′), 83.77 (C1′), 111.02 (=CH), 126.44, 126.51, 128.39, 128.47, 129.09, 129.19, 129.34, 129.48, 132.44, 143.67, 143.84 (C5, C_{arom}), 154.54 (C2), 163.83 (C4), 165.31, 165.41 (2 × C=O); IR (KBr) 3252, 3062, 2958, 1775, 1724, 1659, 1612 cm^{-1}; MS (EI) *m/z* 540 (1.43, M$^+$). Anal. Calcd for $C_{31}H_{28}N_2O_7$: C, 68.88; H, 5.22; N, 5.18. Found: C, 68.83; H, 5.46; N, 4.81.

6aβ: ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.32 (m, 1H, H2′), 2.37 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.25 (m, 1H, H2′), 4.18 (m, H4′), 4.39 (dd, 1H, *J* = 5.8, 11.5 Hz, H5′), 4.47 (dd, 1H, *J* = 5.9, 11.5 Hz, H5′), 5.56 (m, 1H, H3′), 5.66 (t, 1H, *J* = 7.1 Hz, H1′), 6.75 (s, 1H, =CH), 7.29–7.92 (m, 13H, H_{arom}), 11.72 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 21.11 (2 CH_3), 32.68 (C2′), 63.85 (C5′), 74.73 (C3′), 80.56 (C4′), 84.13 (C1′), 111.11 (=CH), 126.26, 126.64, 128.54, 129.11, 129.15, 129.31, 129.83, 132.49, 143.63, 143.93 (C5, C_{arom}), 154.35 (C2), 163.63 (C4), 164.75, 165.41 (2 × C=O); IR (KBr) 3247, 3061, 2958, 1775, 1724, 1660, 1612 cm^{-1}; MS (FAB, 3-$O_2NC_6H_4CH_2OH$) *m/z* 541 (M + H$^+$). Anal. Calcd for $C_{31}H_{28}N_2O_7$. 0.5 H_2O: C, 67.75; H, 5.32; N, 5.10. Found: C, 67.45; H, 5.34; N, 4.60.

(*Z*)-1-[2-Deoxy-3,5-bis-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranosyl]-5-(2-thienylmethylene)-2,4-imidazolidinedione (6b). The anomeric mixture **6b** was prepared as described for **6a**. The mixture was chromatographed on silica gel with the gradient 0–2% MeOH in $CHCl_3$ to yield 2.35 g (80%) of **6b** as a pale yellow foam (α/β = 1:2); IR (KBr) 3245, 3069, 1773, 1719, 1650, 1612; MS (FAB, 3-$O_2NC_6H_4CH_2OH$) *m/z* 547 (M + H$^+$). Anal. Calcd for $C_{29}H_{26}N_2O_7S$. 0.5 H_2O: C, 62.69; H, 4.90; N, 5.04. Found: C, 62.55; H, 4.76; N, 4.88.

(*Z*)-1-[2-Deoxy-3,5-bis-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranosyl]-5-(2-naphthylmethylene)-2,4-imidazolidinedione (6c). The anomeric mixture **6c** was prepared as described for **6a**. The mixture was chromatographed on silica gel with the gradient 0–2% MeOH in $CHCl_3$ to yield 2.50 g (78%) of **6c** as a pale yellow foam: IR (KBr) 2356, 1775, 1724, 1658 cm^{-1}; MS (EI) *m/z* 590 (3.3, M$^+$). Anal. Calcd for $C_{31}H_{28}N_2O_7$. 1.5 H_2O: C, 68.06; H, 5.39; N, 4.54. Found: C, 68.39; H, 4.92; N, 4.48.

(*E*)-1-[2-Deoxy-3,5-bis-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranosyl]-5-ethylidene-2,4-imidazolidinedione (6d). The anomeric mixture **6d** was prepared as described for **6a**. The mixture was chromatographed on silica gel with the gradient 0–2% MeOH in $CHCl_3$ to yield 1.96 g (63%) of **6d** as a pale yellow foam.

(*Z*)-1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-(phenylmethylene)-2,4-imidazolidinedione (1a). To a stirred suspension of the protected nucleoside **6aβ** (0.30 g, 0.55 mmol) in anhydrous MeOH (15 mL) was added portionwise NaOMe (0.059 g, 1.1 mmol) in anhydrous MeOH (15 mL) at room temperature and the solution was stirred overnight. After evaporation of the solvent *in vacuo*, H_2O (15 mL) was added and the mixture extracted several times with CH_2Cl_2 to remove the ester formed during deprotection. To the resulting aqueous solution was added an ion exchange resin (Dowex 50W × 2, H$^+$-form), previously washed with MeOH. After stirring for 5 min, the solution was filtered and evaporated *in vacuo* and the residue chromatograped on silica gel with the gradient 2–5% MeOH in $CHCl_3$ to afford **1a**: yield 0.147 g (88%) as a white solid; mp 170 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.89 (ddd, 1H, *J* = 3.6, 7.1, 13.2 Hz, H2′), 2.82 (td, 1H, *J* = 6.7, 13.4 Hz, H2′), 3.34–3.50 (m, 3H, H4′ and H5′), 4.16 (m, 1H, H3′), 4.60 (s, 1H, 5′-OH), 4.95 (s, 1H, 3′-OH), 5.51 (t, 1H, *J* = 7.1, H1′), 6.67 (s, 1H, =CH), 7.36–7.50 (m, 5H, H_{arom}), 11.60 (s, 1H, NH); ^{13}C NMR (DMSO) δ 36.01 (C2′), 61.92 (C5′), 70.47 (C3′), 83.99 (C1′), 86.85 (C4′), 110.91 (=CH), 128.47, 128.51, 129.21, 129.85, 132.50 (C5, C_{arom}), 154.50 (C2), 163.83 (C4); IR (KBr) 3436, 1764, 1727, 1658 cm^{-1}; MS (EI) *m/z* 304 (4, M$^+$). Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.20; H, 5.30; N, 9.20. Found: C, 58.95; H, 5.27; N, 9.13.

(*Z*)-1-(2-Deoxy-α-D-*erythro*-pentofuranosyl)-5-(phenylmethylene)-2,4-imidazolidinedione (7a). The protected nucleoside **6aα** (0.3 g, 0.55 mmol) was treated similarly as described for the preparation of **1a**. Purification by column chromatography on silica gel with the gradient 2–5% MeOH in $CHCl_3$ afforded **7a**: yield 0.15 g (90%); mp 170 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.40 (m, 1H, H2′), 2.69 (m, 1H, H2′), 3.24 (dd, 1H, *J* = 4.8, 11.8 Hz, H5′), 3.44 (d, 1H, *J* = 11.6 Hz, H5′), 3.78–3.93 (m, 2H, H3′ and H4′), 4.53 (s, 1H, 5′-OH), 5.17 (s, 1H, 3′-OH), 5.32 (t, 1H, *J* = 7.4 Hz, H1′), 6.67 (s, 1H, =CH), 7.34–7.46 (m, 5H, H_{arom}), 11.63 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) 36.45 (C2′), 60.78 (C5′), 69.59 (C3′), 83.59 (C1′), 85.65 (C4′), 110.93 (=CH), 128.56, 128.98, 129.16, 130.08, 132.59 (C5 and C_{arom}), 155.33 (C2), 163.92 (C4); IR (KBr) 3436, 1728, 1656 cm^{-1}; MS (EI) *m/z* 304 (4.3, M$^+$). Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.20; H, 5.30; N, 9.20. Found: C, 59.27; H, 5.36; N, 9.16.

(*Z*)-1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-(2-thienylmethylene)-2,4-imidazolidinedione (1b) and (*Z*)-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-5-(2-thienylmethylene)-2,4-imidazolidinedione (7b). The protected nucleoside **6b** (1 g, 1.8 mmol) was treated similarly as described in the preparation of **1a**. The mixture was chromatographed on silica gel with the

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gradient 0–5% MeOH in $CHCl_3$ to yield 0.25 g (46%) of **1b** as a white solid, mp 182 °C, and 0.20 g (36%) of **7b** as a white solid, mp 196 °C.

1b: ^1H NMR (250 MHz, DMSO-d_6) δ 2.01 (ddd, 1H, J = 3.7, 7.1, 13.1 Hz, H2′α), 2.91 (td, 1H, J = 6.7, 13.3 Hz, H2′β), 3.36–3.54 (m, 2H, H5′), 3.63 (m, 1H, H4′), 4.23 (m, 1H, H3′), 4.64 (s, 1H, 5′-OH), 5.05 (s, 1H, 3′-OH), 5.93 (t, 1H, J = 7.0 Hz, H1′), 6.74 (s, 1H, =CH), 7.17 (dd, 1H, J = 3.7, 5.0 Hz, H4″), 7..46 (d, 1H, J = 3.6 Hz, H3″), 7.77 (dd, 1H, J = 1.0, 5.0 Hz, H5″), 11.53 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 36.01 (C2′), 61.95 (C5′), 70.61 (C3′), 83.94 (C1′), 87.02 (C4′), 104.16 (=CH), 128.36 (C3″), 128.62 (C5), 129.71 (C4″), 130.75 (C5″), 134.54 (C2″), 154.52 (C2), 163.88 (C4); IR (KBr) 3431, 1761, 1724, 1650 cm^{-1}; MS (EI) m/z 310 (2, M^+). Anal. Calcd for $C_{13}H_{14}N_2O_5S$: C, 50.32; H, 4.55; N, 9.02. Found: C, 50.58; H, 4.77; N, 8.72.

7b: ^1H NMR (250 MHz, DMSO-d_6) δ 2.53 (td, 1H, J = 6.4, 12.8 Hz, H2′β), 2.77 (m, 1H, H2′α), 3.31 (m, 1H, H5′), 3.51 (d, 1H, J = 11.9, H5′), 3.94 (m, 2H, H3′ and H4′), 4.58 (t, 1H, J = 5.1 Hz, 5′-OH), 5.20 (d, 1H, J = 5.0 Hz, 3′-OH), 5.73 (t, 1H, J = 7.5 Hz, H1′), 6.75 (s, 1H, =CH), 7.16 (dd, 1H, J = 3.7, 5.1 Hz, H4″), 7.42 (d, 1H, J = 3.7 Hz, H3″), 7.75 (dd, 1H, J = 0.9, 5.1 Hz, H5″), 11.63 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 36.56 (C2′), 60.86 (C5′), 69.61 (C3′), 83.57 (C1′), 85.75 (C4′), 104.35 (=CH), 128.32 (C3″), 128.86 (C5), 129.56 (C4″), 130.82 (C5″), 134.52 (C2″), 155.37 (C2), 163.87 (C4); IR (KBr) 3431, 1761, 1724, 1650 cm^{-1}; MS (EI) m/z 310 (7, M^+). Anal. Calcd for $C_{13}H_{14}N_4O_5S$: C, 50.32; H, 4.55; N, 9.02. Found: C, 50.68; H, 4.68; N, 8.65.

(*Z*)-1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-(2-naphthylmethylene)-2,4-imidazolidinedione (1c) and (*Z*)-1-(2-Deoxy-α-D-*erythro*-pentofuranosyl)-5-(2-naphthylmethylene)-2,4-imidazolidinedione (7c). The protected nucleside **6c** (1.5 g, 2.5 mmol) with an 1:1 α/β ratio was treated similarly as described in the preparation of **1a**. The mixture was chromatographed on silica gel with the gradient 0–5% MeOH in $CHCl_3$ to yield 0.38 g (42%) of **1c** as a white solid, mp 195 °C, and 0.35 g (40%) of **7c** as a white solid, mp 182 °C.

1c: ^1H NMR (250 MHz, DMSO-d_6) δ 1.92 (ddd, 1H, J = 3.8, 7.1, 13.0 Hz, H2′α), 2.90 (td, 1H, J = 6.8, 13.5 Hz, H2′β), 3.37–3.55 (m, 3H, H4′ and H5′), 4.16 (m, 1H, H3′), 4.61 (s, 1H, 5′-OH), 4.87 (d, 1H, 3′-OH), 5.60 (t, 1H, J = 7.1 Hz, H1′), 6.83 (s, 1H, =CH), 7.50–8.33 (m, 7H, H_{arom}), 11.58 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 36.15 (C2′), 61.95 (C5′), 70.42 (C3′), 84.15 (C1′), 86.80 (C4′),110.93 (=CH), 126.53, 126.69, 127.55, 127.92 128.01, 128.78, 129.68, 130.02, 130.15, 132.44, 132.55 (C5, C_{arom}), 154.58 (C2), 163.92 (C4); IR (KBr) 3431, 1762, 1724, 1655 cm^{-1}; MS (EI) m/z 354 (5, M^+). Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.90. Found: C, 64.06; H, 5.25; N, 7.54.

7c: ^1H NMR (250 MHz, DMSO-d_6) δ 2.40 (m, 1H, 2H′β), 2.77 (m, 1H, H2′α), 3.18–3.46 (m, 2H, H5′), 3.85 (m, 1H, H3′), 3.95 (m, 1H, H4′), 4.49 (s, 1H, 5′-OH), 5.18 (s, 1H, 3′-OH), 5.42 (t, 1H, J = 7.5 Hz, H1′), 6.84 (s, 1H, =CH), 7.53–8.06 (m, 7H, H_{arom}), 11.67 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 36.68 (C2′), 60.95 (C5′), 69.63 (C3′), 83.92 (C1′), 85.72 (C4′), 111.01 (=CH), 126.47, 126.75, 126.90, 127.60, 127.94, 128.02, 128.76, 130.14, 130.38, 132.44, 132.55 (C5, C_{arom}), 155.42 (C2), 163.94 (C4); IR (KBr) 3431, 1762, 1724, 1655 cm^{-1}; MS (EI) m/z 354 (5.3, M^+). Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.90. Found: C, 64.42; H, 5.22; N, 7.77.

(*E*)-1-(2-Deoxy-β-D-erythro-pentofuranosyl)-5-ethylidene-2,4-imidazolidinedione (1d) and (E)-1-(2-Deoxy-α-D-erythro-pentofuranosyl)-5-ethylidene-2,4-imidazolinedione (7d). The protected nucleoside **6d** (0.4 g, 0.83 mmol) was treated similarly as described in the preparation of **1a**. The mixture was chromatographed on silica gel with the gradient 2–5% MeOH in $CHCl_3$ to yield 70 mg (35%) of **1d** as a colorless oil and 50 mg (25%) of a mixture of **7d** and **1d** (ratio 3:2) as a colorless oil.

1d: ^1H NMR (500 MHz, CD_3OD) δ 2.15 (ddd, 1H, J = 3.5, 6.9, 13.4 Hz, H2′α), 2.32 (d, 3H, J = 7.6 Hz, CH_3), 2.95 (td, 1H, J = 6.8, 13.6 Hz, H2′β), 3.80 (dd, 1H, J = 4.8, 12.1 Hz, H5′), 3.88 (dd, 1H, J = 3.5, 11.9 Hz, H5′), 3.93 (dd, 1H, J = 3.9, 8.5 Hz, H4′), 4.53 (td, 1H, J = 3.8, 7.5 Hz, H3′), 6.07 (t, 1H, J = 7.4 Hz, H1′), 6.22 (q, 1H, J = 7.6 Hz, =CH); ^{13}C NMR (CD_3OD) δ 12.20 (CH_3), 37.07 (C2′), 63.15 (C5′), 72.16 (C3′), 82.97 (C1′), 87.76 (C4′), 118.05 (=CH), 129.43 (C5), 154.64 (C2), 165.15 (C4); MS (EI) m/z 242 (5, M^+). Anal. Calcd for $C_{10}H_{14}N_2O_5$: 242.0903. Found: 242.0903.

7d: ^1H NMR (500 MHz, CD_3OD) δ 2.35 (d, 3H, J = 7.6 Hz, CH_3), 2.60–2.71 (m, 2H, H2′), 3.74 (dd, 1H, J = 4.8, 12 Hz, H5′), 3.81 (dd, 1H, J = 3.4, 12.0 Hz, H5′), 4.15 (m, 1H, H4′), 4.52 (m, 1H, H3′), 6.07 (t, 1H, J = 7.3 Hz, H1′), 6.26 (q, 1H, J = 7.7 Hz, =CH); ^{13}C NMR (CD_3OD) δ 12.26 (CH_3), 37.41 (C2′), 63.18 (C5′), 72.47 (C3′), 82.96 (C1′), 87.80 (C4′), 117.64 (=CH), 129.44 (C5), 155.93 (C2), 166.00 (C4).

(*Z*)-1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-(1-naphthylmethylene)-2,4-imidazolidenedione (1e). The protected nucleoside (**6eβ**) (0.3 g, 0.51 mmol) was treated similarly as described for the preparation of **1a**. The mixture was chromatographed on silica gel with the gradient 2–5% MeOH in $CHCl_3$ to yield 0.15 g (85%) of **1e** as a pale yellow foam: ^1H NMR (250 MHz, CD_3OD) δ 1.64 (ddd, 1H, J = 4.1, 7.3, 13.4 Hz, H2′), 2.77 (td, 1H, J = 6.8, 13.5 Hz, H2′), 3.46 (m, 1H, H4′), 3.52–3.67 (m, 2H, H5′), 4.24 (m, 1H, H3′), 5.34 (t, 1H, J = 7.1 Hz, H1′), 7.20 (s, 1H, =CH), 7.46–7.93 (m, 7H, H_{arom}); ^{13}C NMR (CD_3OD) δ 38,48 (C2′), 64.06 (C5′), 72.60 (C3′), 85.82 (C1′), 88.26 (C4′), 111.52 (=CH), 126.07, 126.56, 127.84, 128.26, 128.53, 130.07, 130.72, 131.35, 132.85, 133.01, 135.32 (C5, C_{arom}), 156.45 (C2), 165.73 (C4); IR (KBr) 3436, 1762, 1724, 1655 cm^{-1}; MS (EI) m/z 354 (7, M^+). Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.90. Found: C, 64.01; H, 5.11; N, 7.47.

(*Z*)-1-[2-Deoxy-3-*O*-(4-methylbenzoyl)-β-*erythro*-pentofuranosyl]-5-(2-thienylmethylene)-2,4-imidazolidinedione (8), (*Z*)-1-[2-Deoxy-5-*O*-(4-methylbenzoyl)-α-D-*erythro*-pentofuranosyl]-5-(2-thienylmethylene)-2,4-imidazolidinedione (9) and (*Z*)-1-[2-Deoxy-5-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-5-(2-thienylmethylene)-2,4-imidazolidinedione (10). The protected nucleoside **6b** (0.5 g, 0.91 mmol) was stirred in saturated NH_3/MeOH (25 mL) at room temperature for 3 days. The solvent was removed *in vacuo* and the residue was chromatograped on silica gel with the gradient 0–2% MeOH in $CHCl_3$ to afford 155 mg (40%) of **8** as a pale yellow solid, mp 175 °C, 40 mg (10%) of **9** as a pale yellow foam, and 30 mg (8%) of **10** as a pale yellow foam.

8: ^1H NMR (250 MHz, DMSO-d_6) δ 2.33 (m, 1H, H2′α), 2.39 (s, 3H, CH_3), 3.23 (td, 1H, J = 7.8, 15.6 Hz, H2′β), 3.58 (m, 2H, H5′), 3.97 (dt, 1H, J = 5.7, 2.4 Hz, H4′), 4.77 (t, 1H, J = 5.8 Hz, 5′-OH), 5.47 (m, 1H, H3′), 6.04 (t, 1H, J = 7.1 Hz, H1′), 6.76 (s, 1H, =CH), 7.15–7.78 (m, 7H, H_{arom}), 11.67 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 21.05 (CH_3), 33.07 (C2′), 61.58 (C5′), 75.02 (C3′), 83.68, 83.99 (C1′, C4′), 104.04 (=CH), 126.55, 128.15, 128.71, 129.10, 129.12, 129.45, 130.52, 134.25, 143.77 (C5, C_{arom}), 154.37 (C2), 163.54 (C4), 164.79 (C=O); IR (KBr) 3407, 3221, 1767, 1724, 1650 cm^{-1}; MS (EI) m/z (1.4, M^+). Anal. Calcd for $C_{21}H_{20}N_2O_6S$, 0.25 H_2O: C, 58.26; H, 4.77; N, 6.37. Found: C, 58.67; H, 5.13; N, 5.87.

9: ^1H NMR (250 MHz, $CDCl_3$) δ 2.39 (s, 3H, CH_3), 2.53 (d, 1H, J = 14.4 Hz, H2′), 2.80 (m, 1H, H2″), 4.35 (m, 2H, H5′), 4.47 (m, 1H, H4′), 4.62 (m, 1H, H3′), 5.31 (d, 1H, J = 11 Hz, 3′-OH), 6.12 (dd, 1H, J = 3.3, 9.3 Hz, H1′), 6.93 (s, 1H, =CH), 7.16–7.95 (m, 7H, H_{arom}), 9.07 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.57 (CH_3), 39.06 (C2′), 64.91 (C5′), 73.25 (C3′), 84.49 (C1′), 86.33 (C4′), 107.73 (=CH), 127.61, 128.14, 129.07, 129.27, 129.42, 129.59, 130.67, 134.00, 143.88 (C5, C_{arom}), 154.56 (C2), 162.94 (C4), 166.18 (C=O); MS (FAB, $CHCl_3$ + 1% AcOH in 3-$O_2NC_6H_4CH_2OH$) m/z 429 (M + H^+).

10: ^1H NMR (250 MHz, $CDCl_3$) δ 2.26 (m, 1H, H2′), 2.35 (s, 3H, CH_3), 3.04 (m, 1H, H2′), 4.04 (m, 1H, H4′), 4.54 (m, 2H, H5′), 4.79 (q, 1H, J = 6.7 Hz, H3′), 6.08 (dd, 1H, J = 4.7, 8.2 Hz, H1′), 6.87 (s, 1H, =CH), 7.06–7.94 (m, 7H, H_{arom}), 9.30 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.54 (CH_3), 37.29 (C2′), 64.45 (C5′), 71.48 (C3′), 83.35, 83.63 (C1′, C4′), 106.85 (=CH), 126.85, 127.87. 128.17, 128.96, 129.09, 129.71, 130.50, 134.49, 143.77 (C5, C_{arom}), 153.64 (C2), 163.49 (C4), 166.75 (C=O); MS (FAB, $CHCl_3$ + 1% AcOH in 3- $O_2NC_6H_4CH_2OH$) m/z 429 (M + H^+).

(*Z*)-1-[2-Deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-5-(1-naphthylmethylene)-2,4-imidazolidinedione (6eβ) and 7-[2,4-bis-*O*-(4-methylbenzoyl)-1-deoxy-D-erythrit-1-yl]benz[*f*]imidazo[1,5-*b*]isoquinoline-9,11(7*H*,10*H*)-dione (11). The reaction was performed as described for the preparation of **6a**. The mixture was chromatographed on silica gel with the gradient 0–2% MeOH in $CHCl_3$ to afford 0.63 g (20%) of **6eβ** as a pale yellow foam and 1.6 g (50%) of **11** as a yellow foam with an epimeric ratio 3:2: IR

(KBr) 3250, 1720, 1723, 1667 cm^{-1}; MS (EI) m/z 590 (39, M^+). Anal. Calcd for $C_{35}H_{30}N_2O_7$, 0.5 H_2O: C, 70.11; H, 5.21; N, 4.67. Found: C, 69.69; H, 5.08; N, 4.90.

6eβ: ^1H NMR (250 MHz, DMSO-d_6) δ 1.81 (m, 1H, H2′), 2.36 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.15 (m, 1H, H2′), 3.95 (m, 1H, H4′), 4.30 (dd, 1H, J = 5.9, 11.6 Hz, H5′), 4.38 (dd, 1H, J = 5.8, 11.6 Hz, H5′), 5.22 (t, 1H, J = 7.1 Hz, H1′), 5.38 (m, 1H, H3′), 7.10 (s, 1H, =CH), 7.27–8.00 (m, 15H, H_{arom}), 11.73 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 21.01 (CH_3), 21.08 (CH_3), 32.82 (C2′), 63.72 (C5′), 74.59 (C3′), 80.52 (C4′), 83.99 (C1′), 108.33 (=CH), 124.84, 125.23, 126.07, 126.41, 126.60, 126.90, 127.02, 128.48, 128.81, 128.99, 129.05, 129.21, 129.59, 130.44, 131.40, 132.93 143.52, 143.84 (C5, C_{arom}), 153.99 (C2), 163.22 (C4), 164.50 (5′-OC=O), 165.30 (3′-OC=O); IR (KBr) 3256, 1775, 1724, 1659 cm^{-1}; MS (EI) m/z 590 (0.7, M^+). Anal. Calcd for $C_{35}H_{30}N_2O_7$, H_2O: C, 69.07; H, 5.30; N, 4.60. Found: C, 69.29; H, 5.05; N, 4.66.

7-(1-Deoxy-D-erythrit-1-yl)benz[*f*]imidazo[1,5-*b*]isoquinoline-9,11(7*H*,10*H*)-dione (12). The synthesis was performed as described for **6a**. The residue was chromatographed on silica gel with the gradient 2–10% MeOH in $CHCl_3$ to yield 0.05 g (21%) of the less-polar epimer of **12** as a pale yellow solid, mp 200 °C, and 0.14 g (59%) of the more polar epimer of **12** as a pale yellow solid, mp 227 °C.

12 (less polar epimer): ^1H NMR (250 MHz, CD_3OD) δ 1.29 (m, 1H, H1′), 2.50 (m, 1H, H1′), 3.31 (m, 2H, H2′, H3′), 3.48 (dd, 1H, J = 5.5, 11.1 Hz, H4′), 3.60 (dd, 1H, J = 3.40, 11.1 Hz, H4′), 5.84 (dd, 1H, J = 3.1, 11.1 Hz, H7), 6.86 (s, 1H, H12), 7.42-7.86 (m, 6H, H_{arom}); ^{13}C NMR (CD_3OD) δ 39.92 (C1′), 57.07 (C4′), 64.86 (C2′), 70.26 (C3′), 76.19 (C7), 115.32 (C12), 127.22, 127.68, 129.45, 130.30, 131.05, 131.61, 132.01, 132.19, 135.35, 137.35, 137.68 (C11a, C_{arom}), 156.61 (C9), 165.99 (C11); IR (KBr) 3431, 1752, 1723, 1667 cm^{-1}; MS (EI) m/z (%) = 354 (M^+, 41). Anal. Calcd for $C_{19}H_{18}N_2O_5$, 0.25 H_2O: C, 63.59; H, 5.20; N, 7.81. Found: C, 63.97; H, 5.31; N, 7.48.

12 (more polar epimer): ^1H NMR (250 MHz, DMSO-d_6) δ 1.65 (m, 1H, H1′), 1.94 (dd, 1H, J = 8.2, 12.9 Hz, H1′), 2.88 (m, 1H, H2′), 3.06 (m, 1H, H3′), 3.16 (dd, 1H, J = 5.7, 10.8 Hz, H4′), 3.30 (dd, 1H, J = 3.8, 10.9 Hz, H4′), 4.32 (s, 2H, 3′-OH, 4′-OH), 4.52 (d, J = 5.5 Hz, 2′-OH), 5.70 (t, 1H, J = 7.3 Hz, H7), 6.83 (s, 1H, H12), 7.48–7.87 (m, 6H, H_{arom}), 11.39 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 37.23 (C1′), 56.69 (C4′), 62.81 (C2′), 69.45 (C3′), 74.64 (C7), 111.53 (C12), 125.81, 128.58, 128.95, 129.19, 129.47, 129.67, 130.00, 130.14, 133.28, 134.62, 135.28 (C11a, C_{arom}), 154.40 (C9), 163.89 (C11); IR (KBr) 3431, 1752, 1723, 1667 cm^{-1}; MS (EI) m/z (%) = 354 (M^+, 46). Calcd for $C_{19}H_{18}N_2O_5 \cdot 1/3\ H_2O$: C, 63.33; H, 5.22; N, 7.77. Found: C, 63.62; H, 5.32; N, 7.27.

(2*R*,3*S*)-1,3-Bis-*O*-(4-methylbenzoyl)-5,5-bis[5-[(2,4-oxo-5-imidazolidinylidene)methyl]furan-2-yl]pentane-1,2,3-triol (17). The synthesis was performed as described for **6a**. The residue was chromatographed on silica gel with the gradient 0–2% MeOH in $CHCl_3$ to afford 0.8 g (21%) of **17** as a brown foam: ^1H NMR (250 MHz, DMSO-d_6) δ 2.35 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.51–2.74 (m, 2H, H4), 4.08 (quint, 1H, J = 5.3 Hz, H2), 4.25 (m, 2H, H1), 4.65 (dd, 1H, 6.1, 8.9 Hz, H3), 5.17 (s, 1H, 3-OH), 5.62 (d, 1H, J = 5.5 Hz, H5), 6.14, 6.18 (2 × s, 2H, =CH), 6.40, 6.46 (2 × d, 2H, J = 3.5 Hz, $H3_{furan}$), 6.81, 6.84 (2 × d, 2H, J = 3.4, $H4_{furan}$), 7.26, 7.79 (2 × m, 8H, H_{arom}), 10.02, 10.04 (2 × s, 2H, $H1_{hydantoin}$), 11.14 (s, 2H, $H3_{hydantoin}$); ^{13}C NMR (DMSO-d_6) δ 21.00 (2 × CH_3), 31.94 (C4), 34.98 (C1), 64.89 (C3), 69.16 (C2), 72.73 (C5), 96.48, 109.09, 109.58, 114.06, 125.00, 125.06, 126.71, 126.78, 128.81, 128.93, 129.08, 129.26, 143.31, 143.38, 154.76, 154.81 (=CH, $C5_{hydantoin}$, C_{arom}), 155.85, 156.48 ($C2_{hydantoin}$), 164.71 ($C4_{hydantoin}$), 165.06 (C=O), 165.34, (C=O); IR (KBr) 3441, 1724, 1665 cm^{-1}.

(2*R*,3*S*)-5,5-Bis[5-[(2,4-oxo-5-imidazolidinylidine)methyl]-furan-2-yl]pentane-1,2,3-triol (18). The synthesis was performed as described for **6a**. The residue was chromatographed on silica gel with the gradient 2–10% MeOH in $CHCl_3$ to afford 150 mg (75%) of **18** as a brown solid, mp 180 °C dec; ^1H NMR (250 MHz, CD_3OD) δ 2.60 (m, 1H, H4), 3.07 (t, 1H, J = 12.5 Hz, H4), 3.80 (m, 1H, H3), 4.00-4.27 (m, H1, H2), 5.24 (dd, 1H, J = 3.7, 11.2 Hz, H5), 6.72 (2 × s, 2H, =CH), 6.91 (m, 2H, $H3_{furan}$), 7.15, 7.21 (2 × d, 2H, J = 3.4 Hz, $H4_{furan}$); ^{13}C NMR (CD_3OD) δ 36.87 (C4), 37.35 (C1), 64.58 (C3), 70.80 (C2), 76.42 (C5), 99.36 ($C3_{furan}$), 109.81, 111.13 (=CH), 116.21, 116,27 ($C4_{furan}$), 126.39, 126.62 ($C5_{hydantoin}$), 150.31, 150.51 ($C2_{furan}$), 156.6 ($C5_{furan}$), 158.10, 159.85 ($C2_{hydantoin}$), 166.86 ($C4_{hydantoin}$); IR (KBr) 3430, 1719, 1662; MS (FAB, DMSO + 1% CF_3COOH in glycerol) m/z 473 (M + H^+). Anal. Calcd for $C_{21}H_{20}N_4O_9 \cdot 1.5\ H_2O$: C, 50.50; H, 4.33; N, 11.21. Found: C, 50.53; H, 4.64; N, 10.94.