100. Nucleosides

Part L[1])

Structure of Lumazine N^1-(2′-Deoxy-D-ribonucleosides) (= 1-(2′-Deoxy-D-ribofuranosyl)pteridine-2,4(1*H*,3*H*)-diones): A Revision of the Anomeric Configuration

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The anomeric configuration of the glycosidic bond in lumazine N^1-(2′-deoxy-D-ribonucleosides) **1–6** was investigated by NOE difference spectroscopy. The former configurational assignment of the α- and β-D-anomers **1** and **2**, **3** and **4**, and **5** and **6**, respectively, has to be reversed to be in agreement with the physical data. Additional proof is presented by X-ray analysis of **3** and **6**. Chemical interconversions of 1-(2′-deoxy-β-D-ribofuranosyl)-6,7-diphenyllumazine (**6**) into 2,3′-anhydrolumazine 2′-deoxyribonucleosides **16** and **17** are also in agreement with the revised anomeric configuration.

1. Introduction. – Lumazine N^1-ribonucleosides and N^1-(2′-deoxyribonucleosides) (= 1-(D-ribofuranosyl)- and 1-(2′-deoxy-D-ribofuranosyl)pteridine-2,4(1*H*,3*H*)-diones) can be regarded as structural analogs of uridine and thymidine, respectively, and were therefore, synthesized in our laboratory in 1970 [2], expecting some biological activity. However, so far no antibacterial, antiviral, or antitumor activity was found. The physical properties of these compounds are still of interest due to the fluorescence [3] [4] of the nucleobase.

The structural assignment of the *N*-glycosidic bond in the 1-(β-D-ribofuranosyl) lumazines synthesized *via* the *Hilbert-Johnson-Birkofer* procedure [5–7] was based on the *Baker-Tipson* rule [8] (β-D-ribonucleoside formation). Analogous glycosylations in the 2′-deoxyribofuranose series lacking the neighbouring-group-participation effect of the 2′-acyloxy function are less selective and lead usually to α,β-D-anomeric mixtures, which have to be separated by tedious chromatographical techniques.

In an earlier paper [2], the configuration of the glycosidic bond of the 1-(2′-deoxy-D-ribofuranosyl)lumazines was based upon simple chemical-shift data in analogy to the findings in the pyrimidine [9] [10] and purine 2′-deoxy-D-ribofuranoside series [11]. It was stated that the anomeric protons usually appearing as a *quadruplet* (*q*) at lower field is

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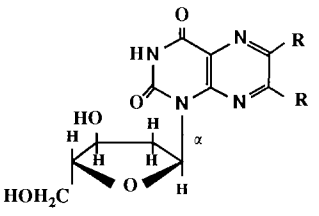
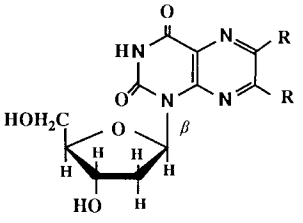
characteristic for the 2′-deoxy-α-D-ribofuranosides, whereas the β-D-anomer shows a *pseudo-triplet* ('*t*') at higher field. The validity of these assignments has now been questioned by recent studies with the former 1-(2′-deoxy-β-D-ribofuranosyl)-6,7-diphenyllumazine [12], which could not be converted into a 2,3′-anhydronucleoside in the usual manner. Reinvestigation of the configuration of the glycosidic bond became, therefore, necessary by an unambiguous method.

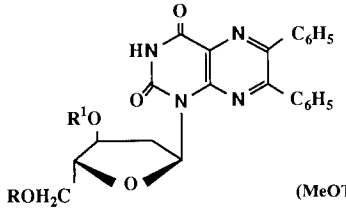
2. Results and Discussion. – The structures in question are the anomeric 1-(2′-deoxy-D-ribofuranosyl)lumazines (**1**/**2**) and its 6,7-dimethyl and 6,7-diphenyl derivatives **3**/**4** and **5**/**6**, respectively. Straightforward results on the assignment of anomeric configurations of nucleosides are available by NOE difference spectroscopy [13] which was now applied to our problem. *Dreiding* models show that in β-D-anomers, H–C(1′) and H–C(4′) are located in the whole range of N- to S-type conformations [14] in almost the same spacial

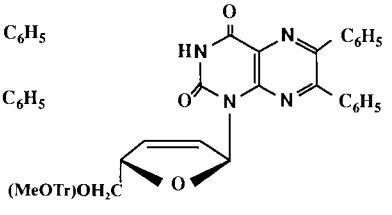


1 R = H
3 R = Me
5 R = Ph



2 R = H
4 R = Me
6 R = Ph





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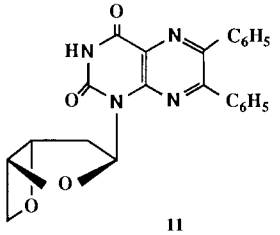

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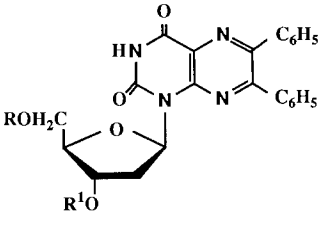
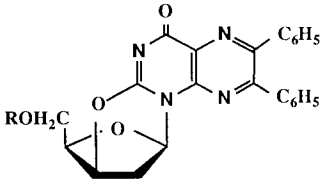
7 R = MeOTr, R′ = H
8 R = MeOTr, R′ = $MeSO_2$
9 R = H, R′ = $MeSO_2$



12 R = MeOTr, R′ = H
13 R = MeOTr, R′ = $MeSO_2$
14 R = 4-MeC_6H_4CO, R′ = H
15 R = 4-MeC_6H_4CO, R′ = CF_3SO_2



16 R = MeOTr
17 R = 4-MeC_6H_4CO

MeOTr = monomethoxytrityl

proximity on the same side (α) of the sugar moiety. Consequently, H_β–C(2′) and H_β–C(3′) are positioned on the opposite face. Analogous considerations on 2′-deoxy-α-D-ribonucleosides, bearing H–C(1′) and H–C(3′) on the β-side of the ribofuranose ring, indicate that the S-type puckered conformation causes a large *H*–C(1′), *H*–C(3′) distance which is shortened on pseudorotational interconversion towards the N-type conformation.

Saturation of the ^{1}H-NMR signal ((D$_6$)DMSO) of the anomeric H–C(1′) in the 1-(2′-deoxy-β-D-ribofuranosyl)lumazines **2**, **4**, and **6** causes characteristic NOE's on H–C(4′) (1.5–2.7%) and H_α–C(2′) (5.5–7.9%), whereas no signal enhancement is observed for H–C(3′) and H_β–C(2′) (see *Table 1*). The corresponding α-D-anomers **1**, **3**, and **5** exhibit consequently typical NOE's on H–C(3′) (1.5–2.8%) and H_β–C(2′) (5.5–7.1%) and no signal changes for H–C(4′) and H_α–C(2′).

Table 1. *NOE Data and Chemical Shifts of 2 H–C(2′) of 1-(2′-Deoxy-α- and -β-D-ribofuranosyl)lumazines in (D$_6$)DMSO*

	NOE [%] on irradiation of H–C(1′)				Chemical shift δ [ppm]		$\Delta\delta$
	H_α–C(2′)	H_β–C(2′)	H–C(3′)	H–C(4′)	H_α–C(2′)	H_β–C(2′)	
1	0	6.7	2.8	0	2.70	2.36	0.34
2	7.9	0	0	2.7	2.03	2.83	0.80
3	0	6.1	2.8	0	2.75	2.35	0.40
4	6.3	0	0	1.5	2.03	2.85	0.82
5	0	5.5	1.5	0	2.83	2.40	0.43
6	5.5	0	0	1.5	2.07	2.95	0.88

A more simple possibility to assign the anomeric configuration in pteridine 2′-deoxy-D-ribonucleosides consists in the analysis of the chemical-shift difference of the H_α–C(2′) and H_β–C(2′) signals. In the α-D-anomers, these differences are always smaller than in the β-D-anomers [15] (see *Table 1*), which seems to be an indication of a more favoured and more restricted S-type puckered conformation in the β-D-anomer and a more flexibel situation in the α-D-anomer.

The 1-(2′-deoxy-α-D-ribofuranosyl)-6,7-dimethyllumazine (**3**) and the 1-(2′-deoxy-β-D-ribofuranosyl)-6,7-diphenyllumazine (**6**) could be crystallized and their structures established unambiguously by X-ray analyses (see *Figs. 1* and *2* and *Table 2*).

The data were collected on a *Nicolet-R3m* four-circle diffractometer fitted with a *LT1* cooling apparatus. The structures were determined by direct methods using the SHELXTL PLUS (VAX II) system. The coordinates and geometrical data were deposited at the *Cambridge Crystallographic Data Centre*, University Chemical Laboratory, Cambridge CB2 1EW, UK.

The correct structural assignments of **5** and **6** enabled us to perform also a series of intramolecular interconversions which could not be achieved before. Thus, α-D-anomer **5** was first converted into 5′-*O*-monomethoxytrityl derivative **7** [15] and then mesylated (→**8**). Treatment of **8** with Et_3N, NaOMe, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) did not result in any reaction, but *t*-BuOK treatment afforded the elimination product **10**. Acid detritylation of **8** to **9** and subsequent treatment with *t*-BuOK in DMF led to 3′,5′-anhydro derivative **11**.

In an analogous series of reactions, β-D-anomer **6** was transformed *via* the 5′-*O*-monomethoxytrityl derivative **12** [15] into its 5′-*O*-(monomethoxytrityl)-3′-*O*-mesyl

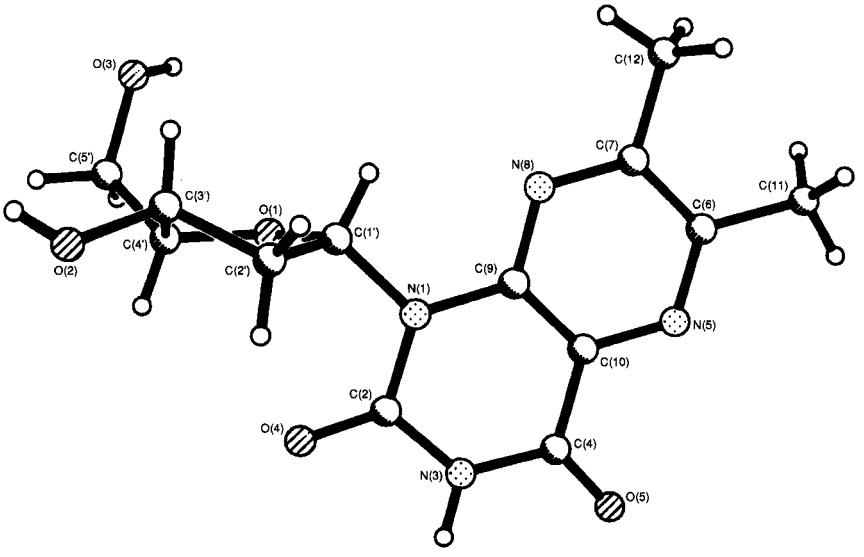


Fig. 1. *Crystal structure of 1-(2'-deoxy-α-D-ribofuranosyl)-6,7-dimethyllumazine* (**3**). Arbitrary numbering.

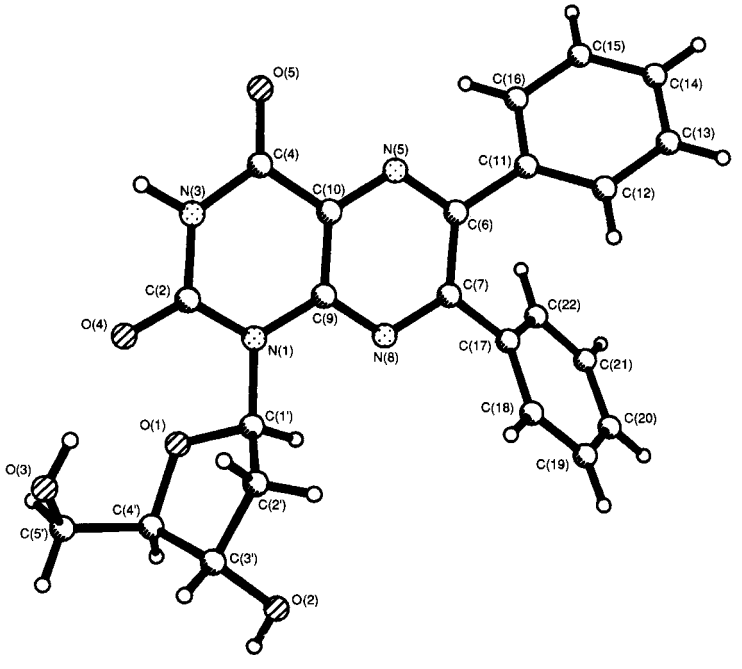


Fig. 2. *Crystal structure of 1-(2'-deoxy-β-D-ribofuranosyl)-6,7-diphenyllumazine* (**6**). Arbitrary numbering.

Table 2. *Crystallographic Data of 1-(2′-Deoxy-α-D-ribofuranosyl)-6,7-dimethyllumazine* (**3**) *and 1-(2′-Deoxy-β-D-ribofuranosyl)-6,7-diphenyllumazine* (**6**)

	3	**6**
Crystal Data		
Empirical formula	$C_{13}H_{16}N_4O_5$	$C_{23}H_{20}N_4O_5$
Colour, habit	colourless, prismatic	colourless, prismatic
Crystal size [mm]	0.25 × 0.4 × 0.4	0.25 × 0.25 × 0.4
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit-cell dimensions a [Å]	6.604 (3)	9.523 (5)
b [Å]	10.907 (5)	10.461 (4)
c [Å]	18.975 (8)	21.038 (10)
V [Å^3]	1366.8 (11)	2095.8 (17)
Z	4	4
Molecular weight	308.3	432.4
Density (calc.) [Mg/m^3]	1.498	1.370
Absorption coefficient	0.110 mm^{-1}	0.092 mm^{-1}
F(000)	648	904
Radiation MoK_α λ [Å]	0.71073	0.71073
Data Collection		
T [K]	183	183
2Θ range	0.56°	0.56°
Scan type	ω	ω
Scan speed (variable)	0.50–14.65°/min in ω	0.92–14.65°/min in ω
Scan range (ω)	0.76°	1.10°
Standard reflections	2 measured every 120 reflections	2 measured every 120 reflections
Index ranges	$0 \leq h \leq 8, 0 \leq k \leq 14, 0 \leq l \leq 25$	$-12 \leq h \leq 0, 0 \leq k \leq 13, -27 \leq l \leq 0$
Reflections collected	1945	2925
Independent reflections	1921 (R_{int} 0.00%)	2892 (R_{int} 8.24%)
Observed reflections	1839 ($F > 5.0\,\sigma(F)$)	2127 ($F > 5.0\,\sigma(F)$)
Number of parameter	211	297
Final R index (obs. data)	4.06	4.37

derivative **13**. Treatment of **13** with DBU in $CHCl_3$ under reflux afforded the anticipated 2,3′-anhydro-xylonucleoside **16** in 87% yield. A similar sequence of reactions took place when **6** was first acylated to its 5′-*O*-(4-toluoyl) derivative **14**, which reacted with trifluoromethane sulfonic anhydride in 1,2-dichloroethane/pyridine *via* **15** directly to the 2,3′-anhydro-xylonucleoside **17**.

3. Conclusions. – All structures of the formerly published 1-(2′-deoxy-α- and β-D-ribofuranosyl)lumazines [2] [5] [13] have to be revised from α-D- to β-D-configuration and *vice versa*, according to NOE difference spectroscopic studies, X-ray analyses, and some chemical interconversions.

We would like to thank Mr. *P. Iaiza* for excellent technical assistance.

Experimental Part

General. TLC: precoated silica-gel thin-layer sheets *F 1550 LS 254* and cellulose thin-layer sheets *F 1440* from *Schleicher & Schüll*. Prep. TLC: silica gel *60 PF_{254}* (*Merck*). Prep. column chromatography: silica gel (*Merck 60*, 0.063–0.2 mesh). M.p.: *Büchi* apparatus, model Dr. *Tottoli*; no corrections. UV: *Uvikon 820*, *Kontron*, and *Perkin-Elmer, Lambda 5*; λ_{max} in nm (lg ε). ^{1}H-NMR: *Bruker WM 250* and *Bruker AC-250* with *Aspect-3000* computer and array processor; δ in ppm rel. to TMS; for the NOE measurements, the (D_6)DMSO solns. (0.1M) were degassed, and typical spectral conditions were as follows: number of data points 32 K; pre-irradiation delay 1.6 s; relaxation delay 4.5 s; an irradiation time of 1.5 s with an irradiation power of 40–50 dB below 0.2 W yielded a saturation of $\geq$ 95%; evaluation by the NOEDIFF mode of the *Bruker* software package.

1. *1-[2′-Deoxy-3′-O-mesyl-5′-O-(4-monomethoxytrityl)-α-D-ribofuranosyl]-6,7-diphenylpteridine-2,4(1H,3H)-dione* (**8**). A soln. of 1.4 g (2 mmol) of 1-[2′-deoxy-5′-*O*-(4-monomethoxytrityl)-α-D-ribofuranosyl]-6,7-diphenylpteridine-2,4(1*H*,3*H*)-dione (**7**) [15] in 15 ml of abs. pyridine was treated with 0.4 ml $MeSO_2Cl$ for 19 h. The mixture was poured on ice, the precipitate collected and then dissolved in $CHCl_3$, the soln. washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue crystallized from 20 ml of EtOH: 1.39 g (88%). Colourless crystals. M.p. 168–171°. UV (MeOH): 360 (4.08), 275 (4.18), 228 (sh, 4.53). ^{1}H-NMR ((D_6)DMSO): 12.07 (*s*, NH); 7.07 (*t*, H–C(1′)); 6.81–7.52 (*m*, 24 arom. H); 5.17 (*q*, H–C(3′)); 4.68 (*m*, H–C(4′)); 3.71 (*s*, MeO); 3.46 (*m*, CH_2(5′)); 3.11 (*s*, Me); 3.08 (*m*, H_α–C(2′)); 2.83 (*m*, H_β–C(2′)). Anal. calc. for $C_{44}H_{38}N_4O_8$ (782.8): C 67.51, H 4.89, N 7.16; found: C 67.32, H 4.93, N 7.11.

2. *1-(2′-Deoxy-3′-O-mesyl-α-D-ribofuranosyl)-6,7-diphenylpteridine-2,4(1H,3H)-dione* (**9**). To a soln. of 0.2 g of TsOH in 10 ml of CH_2Cl_2/MeOH 4:1 were added 0.078 g (0.1 mmol) of **8** and stirred for 2 h. Then H_2O (5 ml) was added, the mixture neutralized by a $NaHCO_3$ soln. and extracted twice with CH_2Cl_2, and the org. layer washed with H_2O, dried (Na_2SO_4), and evaporated: 0.042 g (82%). Colourless solid. M.p. 149–150°. UV (MeOH): 360 (4.16), 275 (4.23), 223 (4.47). ^{1}H-NMR ((D_6)DMSO): 12.07 (*s*, NH); 7.32–7.52 (*m*, 10 arom. H); 7.05 (*t*, H–C(1′)); 5.18 (*t*, H–C(3′)); 4.94 (*t*, OH–C(5′)); 4.44 (*m*, H–C(4′)); 3.41–3.61 (*m*, CH_2(5′)); 3.24 (*s*, MeO); 3.13 (*m*, H_α–C(2′)); 2.84 (*m*, H_β–C(2′)). Anal. calc. for $C_{24}H_{22}N_4O_7 \cdot 0.5\ H_2O$ (519.5): C 55.48, H 4.46, N 10.78; found: C 55.75, H 4.40, N 10.75.

3. *1-[2′,3′-Didehydro-2′,3′-dideoxy-5′-O-(4-monomethoxytrityl)-α-D-*glycero*-pentofuranosyl]-6,7-diphenylpteridine-2,4(1H,3H)-dione* (**10**). To a soln. of 0.1 g (0.125 mmol) of **8** in 5 ml of abs. DMF, a soln. of 0.2 g of *t*-BuOK in 2 ml of *t*-BuOH was added. The mixture was heated to 90° for 1 h and then evaporated under high vacuum. The residue was chromatographed (silica gel, column 0.7 × 6 cm, $CHCl_3$): 0.072 g (82%). Colourless solid. M.p. 125–127°. UV (MeOH): 361 (4.05), 275 (4.13), 226 (4.49). ^{1}H-NMR ((D_6)DMSO): 12.1 (*s*, NH); 8.30 (*d*, H–C(1′)); 6.83–7.64 (*m*, 24 arom. H); 6.40 (*d*, H–C(3′)); 6.06 (*d*, H–C(2′)); 5.12 (*m*, H–C(4′)); 3.71 (*s*, MeO); 3.05–3.48 (*m*, CH_2(5′)). Anal. calc. for $C_{43}H_{34}N_4O_5 \cdot 0.5\ H_2O$ (695.7): C 74.23, H 5.07, N 8.05; found: C 74.03, H 5.35, N 8.13.

4. *1-(3′,5′-Anhydro-2′-deoxy-α-D-xylofuranosyl)-6,7-diphenylpteridine-2,4(1H,3H)-dione* (**11**). A soln. of 0.52 g (1 mmol) of **9** in 15 ml of abs. DMF was treated with 0.6 g of *t*-BuOK in 2 ml of *t*-BuOH at r.t. for 30 min and then 5 h at 100°. The solvents were evaporated under high vacuum, and the residue was chromatographed (silica gel, column 0.7 × 20 cm, $CHCl_3$/MeOH 49:1): 0.22 g (56%). Colourless solid. M.p. 193–196°. UV (MeOH): 360 (4.16), 274 (4.24), 223 (sh, 4.46). ^{1}H-NMR ((D_6)DMSO): 12.0 (*s*, NH); 7.37–7.52 (*m*, H–C(1′), 10 arom. H); 5.48 (*t*, H–C(3′)); 5.04 (*d*, H–C(4′)); 4.16–4.62 (*m*, CH_2(5′)); 2.81 (*m*, H_α–C(2′)); 2.56 (*m*, H_β–C(2′)). Anal. calc. for $C_{23}H_{18}N_4O_4 \cdot 0.5\ H_2O$ (423.5): C 65.27, H 4.52, N 13.24; found: C 65.04, H 4.38, N 12.95.

5. *1-[2′-Deoxy-3′-O-mesyl-5′-O-(4-monomethoxytrityl)-β-D-ribofuranosyl]-6,7-diphenylpteridine-2,4(1H,3H)-dione* (**13**). A soln. of 1.3 g (1.8 mmol) of 1-[2′-deoxy-5′-*O*-(4-monomethoxytrityl)-β-D-ribofuranosyl]-6,7-diphenylpteridine-2,4(1*H*,3*H*)-dione (**12**) [13] in 15 ml of abs. pyridine was treated dropwise with 0.2 ml of $MeSO_2Cl$. After stirring at r.t. for 2 h, the mixtures was poured on ice, the precipitate filtered off and dissolved in 20 ml of $CHCl_3$, and the soln. washed with H_2O, dried (Na_2SO_4), evaporated to a small volume, and then added dropwise into 50 ml of pentane: 1.15 g (82%). Colourless powder. M.p. 138–141°. UV (MeOH): 357 (4.09), 274 (4.14), 225 (sh, 4.50). ^{1}H-NMR ($CDCl_3$): 9.58 (*s*, NH); 6.69–7.47 (*m*, H–C(1′), 24 arom. H); 5.38 (*q*, H–C(3′)); 4.18 (*q*, H–C(4′)); 3.73 (*s*, MeO); 3.30 (*m*, CH_2(5′)); 3.13 (*m*, H_β–C(2′)); 2.83 (*s*, $MeSO_2$); 2.78 (*m*, H_α–C(2′)). Anal. calc. for $C_{44}H_{38}N_4O_8S$ (791.8): C 67.20, H 4.96, N 7.12; found: C 67.51, H 4.89, N 7.16.

6. *1-[2′-Deoxy-5′-O-(4-toluoyl)-β-D-ribofuranosyl]-6,7-diphenylpteridine-2,4(1H,3H)-dione* (**14**). A soln. of 0.7 ml (5 mmol) of 4-toluoyl chloride in 10 ml of 1,2-dichloroethane was added at 0° dropwise to 2.15 g (5 mmol) of 1-(2′-deoxy-β-D-ribofuranosyl)-6,7-diphenylpteridine-2,4(1*H*,3*H*)-dione (**6**) [2] [5] in 40 ml of abs. pyridine and stirred for 1 h. The mixture was poured on ice and extracted by $CHCl_3$, the soln. washed with $NaHCO_3$ soln., dried

(Na_2SO_4), and evaporated, and the residue purified by column chromatography (3 × 10 cm, silica gel, toluene/AcOEt 1:2): 2.14 g (77%). Colourless solid. M.p. 159–161°. UV (MeOH): 359 (4.09), 274 (4.11), 230 (4.43). ^{1}H-NMR ((D_6)DMSO): 12.04 (*s*, NH); 7.26–7.84 (*m*, 14 arom. H); 7.17 (*dd*, H–C(1′)); 5.39 (*d*, OH–C(3′)); 4.01–4.60 (*m*, H–C(3′), H–C(4′), CH_2(5′)); 2.95 (*m*, H_β–C(2′)); 2.37 (*s*, Me); 2.25 (*m*, H_α–C(2′)). Anal. calc. for $C_{31}H_{26}N_4O_6 \cdot 0.5\ H_2O$ (559.6): C 66.54, H 4.86, N 10.02; found: C 66.82, H 4.82, N 10.33.

7. *2,3′-Anhydro-1-[2′-deoxy-5′-*O*-(4-monomethoxytrityl)-β-*D*-xylofuranosyl]-6,7-diphenylpteridine-2,4(1*H*,3*H*)-dione* (**16**). A soln. of 0.95 g (1.2 mmol) of **13** in 30 ml of abs. $CHCl_3$ was treated with 0.5 ml of DBU and then refluxed for 4 h. The mixture was washed twice with H_2O, dried (Na_2SO_4), and evaporated: 0.72 g (87%). Chromatographically pure colourless solid. M.p. 154–156°. UV (MeOH): 360 (4.14), 271 (4.14), 228 (4.52). ^{1}H-NMR ((D_6)DMSO): 6.71–7.55 (*m*, H–C(1′), 24 arom. H); 5.56 (*s*, H–C(3′)); 4.57 (*m*, H–C(4′)); 3.66 (*s*, MeO); 3.19 (*m*, CH_2(5′)); 2.75 (*m*, H_β–C(2′)); 2.54 (*m*, H_α–C(2′)). Anal. calc. for $C_{43}H_{35}N_4O_5 \cdot 0.5\ H_2O$ (695.7): C 74.23, H 5.07, N 8.05; found: C 74.22, H 5.45, N 8.00.

8. *2,3′-Anhydro-1-[2′-deoxy-5′-*O*-(4-toluoyl)-β-*D*-xylofuranosyl]-6,7-diphenylpteridine-2,4(1*H*,3*H*)-dione* (**17**). To a mixture of 0.28 g (0.5 mmol) of **14** in 10 ml of 1,2-dichloroethane and 1 ml of abs. pyridine was added dropwise a soln. of 0.09 ml (0.5 mmol) of trifluoromethanesulfonic anhydride in 10 ml of 1,2-dichloroethane. After stirring for 10 min, H_2O was added, the org. layer dried (Na_2SO_4) and evaporated, and the residue crystallized from 3 ml of EtOH: 0.23 g (86%). Colourless crystals. M.p. 173–177°. UV (MeOH): 359 (4.09), 269 (sh, 4.09), 230 (4.45). ^{1}H-NMR ((D_6)DMSO): 7.19–7.84 (*m*, 14 arom. H); 7.11 (*d*, H–C(1′)); 5.63 (*s*, H–C(3′)); 4.70 (*m*, CH_2(5′)); 4.43 (*m*, H–C(4′)); 2.76 (*m*, CH_2(2′)); 2.29 (*s*, Me). Anal. calc. for $C_{31}H_{24}N_4O_5$ (534.4): C 68.75, H 4.84, N 10.34; found: C 68.75, H 4.73, N 10.46.

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