Synthesis and Properties of Flavin Ribofuranosides and Flavin Ribopyranosides

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Dedicated to Prof. *Albert Eschenmoser* on the occasion of his 75th birthday

Ribose-containing coenzymes like flavin mononucleotide (FMN) can be considered to be fossils of a prebiotic RNA world in which RNA encoded genetic information and catalyzed chemical reactions. To investigate the catalytic and base-pairing properties of FMN-containing oligonucleotides, the two cyclic flavin β-D-ribosides **3** and **4** derived from riboflavin **2** were synthesized (*Schemes 1* and *2*). These are both constitutionally strongly related to the nucleobase uridine and should be able to participate as catalytically competent and informational nucleobases in DNA, RNA, and p-RNA. Ribofuranoside **3** was too unstable to be isolated, but ribopyranoside **4** had the required stability, β-D-configuration, and *anti*-conformation of the glycosidic bond.

1. Introduction. – Genetic material is constructed from the standard nucleotides adenosine, guanosine, cytidine, thymidine, and uridine **1**. These building blocks are connected *via* phosphodiester bonds to give single-stranded oligonucleotides. Two such oligonucleotides form an antiparallel double strand in which the sequence of the four canonical bases represents the genetic information [1]. The fact that all organisms on earth use the same building blocks and the same principles for the construction of DNA and RNA as information-storing systems has stimulated tremendous interest to decipher the molecular origin of the genetic material [2]. Biochemical evidence suggests that RNA is the chemical precursor of DNA. Strong support for this so-called RNA-world hypothesis was derived from the discovery of ribozymes [3]. These are RNA molecules able to encode genetic information and to catalyze a chemical reaction [4]. Ribozymes fold like proteins into a defined three-dimensional structure, and they possess genotypic (information encoding) and phenotypic (catalytic) properties. These features connect RNA to the DNA and protein world.

The today popular RNA-world theory hence predicts that the evolution of the genetic system passed through a phase in which RNA molecules self-instructed catalytic competence, which was optimized along a gradient of increasing environmental pressure [2b].

In recent years, the RNA-world hypothesis has fueled the desire to find (or to select) new ribozymes with novel and interesting catalytic properties [3b]. With respect to the question of how to establish catalytic functions in an oligonucleotide environment, RNA-containing coenzymes deserve particular attention. Coenzymes comprise a

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small set of ubiquitously used small organic molecules, that catalyze chemical reactions within the active site of coenzyme-dependent enzymes. The protein environment in this interplay modulates through π-stacking, electrostatic forces, and H-bonding interactions the catalytic properties of the coenzyme to enable specific transformations. Some of the most important coenzymes like riboflavin (**2**) (present in flavin-adenine dinucleotide (FAD) and flavin mononucleotide (FMN)), ribodeazaflavin (present in F_{420}), nicotinamide (present in nicotinamide-adenine dinucleotide (NAD)), or folate derivatives contain a ribose-derived anchoring group. In addition, they possess H-bond donor and acceptor groups similar to the standard nucleobases. Both features establish a close constitutional relationship between coenzymes and the canonical nucleobases. These properties should allow participation of coenzymes as informational nucleobases with potential catalytic properties in an oligonucleotide environment [5].

To investigate the hypothesis that coenzymes embedded in oligonucleotides yield DNA and RNA strands with novel and interesting pairing and catalytic properties, we started a program aimed at the synthesis of coenzyme-derived nucleobases. Particular attention deserves the question of whether DNA or RNA is able to fine-tune the catalytic properties of embedded coenzymes similar to the surrounding protein in contemporary coenzyme-dependent enzymes [6]. Coenzymes like the riboflavin-containing FMN catalyze a variety of essential electron- and oxygen-transfer reactions [7]. Thus, incorporation of this coenzyme into oligonucleotides should yield DNA or RNA strands able to catalyze redox reactions. To increase the constitutional relationship between riboflavin (**2**) and the standard nucleobases, we designed the flavin β-D-ribofuranoside (**3**) and the flavin β-D-ribopyranoside (**4**) as the initial synthetic targets (see *Fig. 1*). In this paper, we disclose the synthesis and some properties of the riboflavin-derived nucleobases **3** and **4** [8]. Both compounds **3** and **4** are very close homologs of the nucleobase uridine **1**. They possess a cyclic ribose unit [8] that should allow the correct insertion of the flavin moiety as a catalytically competent base-pairing unit into DNA, RNA, or pyranosyl-RNA (p-RNA) [9].

2. Results and Discussion. – 2.1. *Synthesis and Properties of the Flavin Ribopyranoside* **4**. To the best of our knowledge, the only other report about the synthesis of flavin ribosides has been published by *Kuhn* and *Ströbele* in 1937 [8]. Neither the constitution nor the configuration of the flavin sugars obtained could be clarified. These open questions are now addressed in this investigation.

Towards the synthesis of the flavin β-D-ribopyranoside (**4**), D-ribose (**5**) was heated with a large excess of 3,4-dimethyl-2-nitroaniline (= nitroxylidine; **6**) in anhydrous EtOH (*Scheme 1*). The intensively orange-colored nitroxylidine riboside **7** was obtained after plug filtration through *Celite* as a 1:1 mixture of the α- and β-D-anomer. This mixture was subsequently esterified with Ac_2O in pyridine and furnished, surprisingly, only a single anomer **8**, which was isolated after column chromatography in 44% yield. Analysis of the crystal structure of the new compound **8** (*Fig. 2,a*[2])) established its α-D-configuration. The X-ray structure reveals a bifurcated H-bond

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[2]) The data were deposited at the *Cambridge Crystallographic Data Centre* (CCDC, 12 Union Road, Cambridge CB2 1EZ; e-mail: deposit@ccdc.cam.ac.uk). Deposition numbers: **4**, CCDC-130252; **8**, CCDC-130253; **18**, CCDC-44113.

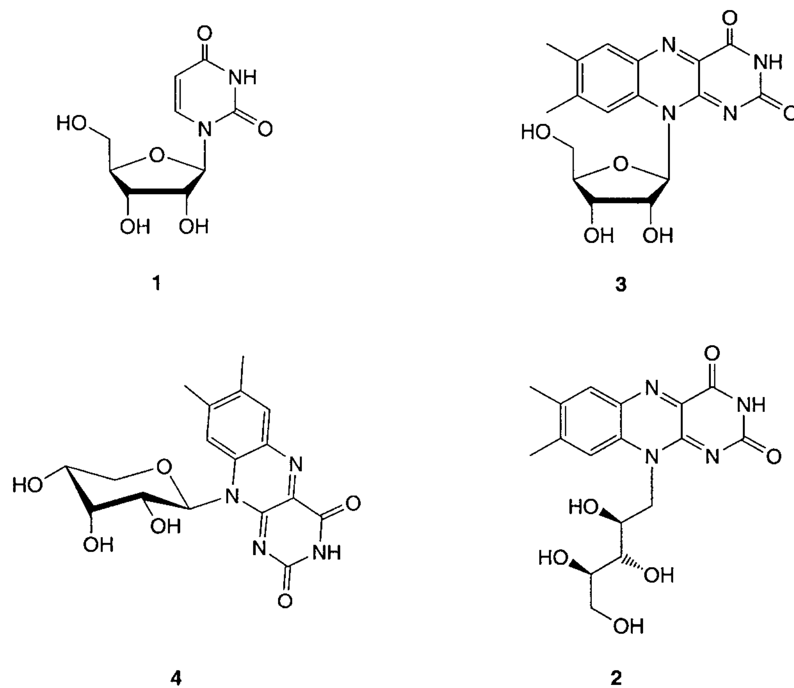
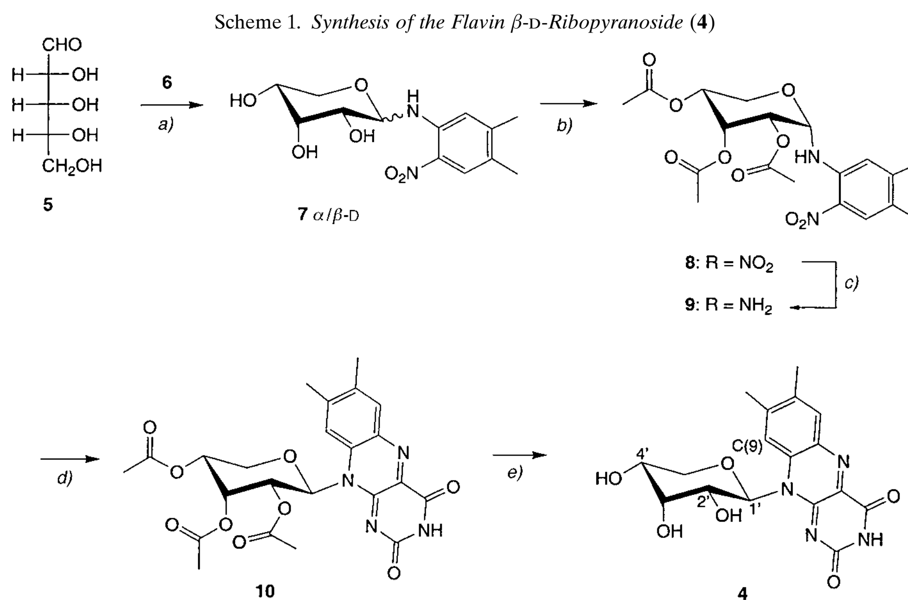


Fig. 1. *Structure of uridine* (**1**) *and of the constitutionally related flavin ribosides* **3** *and* **4**, *as well as of the riboflavin coenzyme* **2**

Scheme 1. *Synthesis of the Flavin β-*D*-Ribopyranoside* (**4**)



a) $Me_2(NO_2)C_6H_2NH_2$ (**6**), EtOH, NH_4Cl, reflux; 61%. *b*) Ac_2O, pyridine; 44%. *c*) PtO_2, H_2, Et_3N. *d*) Alloxan, boric acid, AcOH; 50%. *e*) NH_3, MeOH, r.t.; 48%.

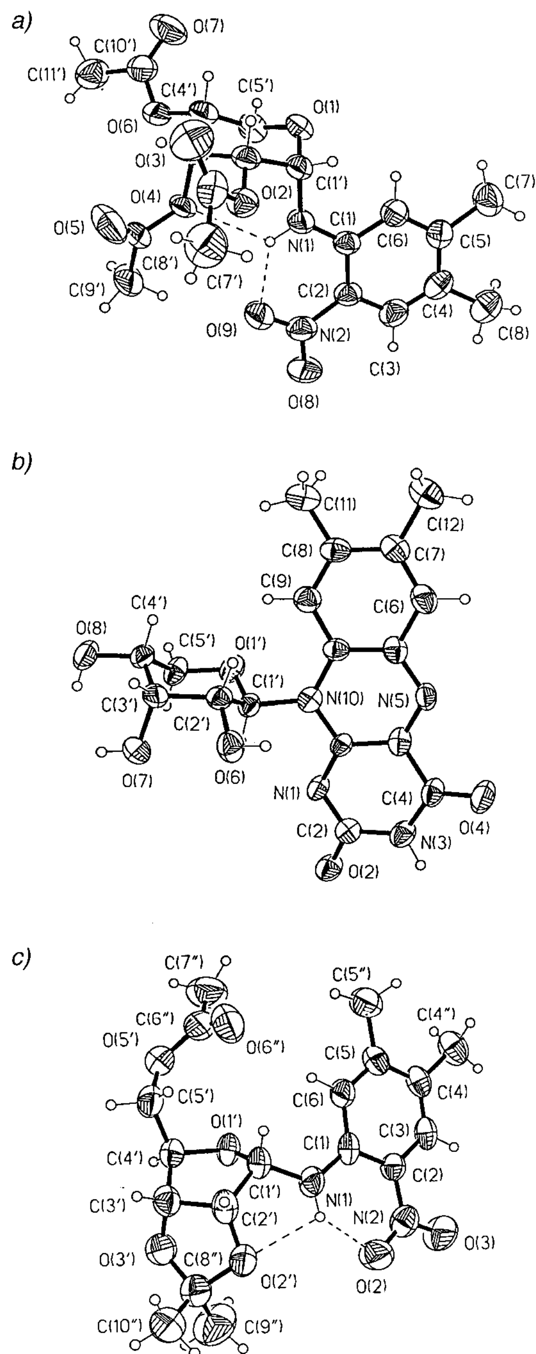


Fig. 2. *X-Ray crystal structures of* a) **8**, b) **4**, *and* c) **18**. ORTEP Plot of the molecular structure. Arbitrary numberings. Displacement ellipsoids are shown at the 50% probability level.

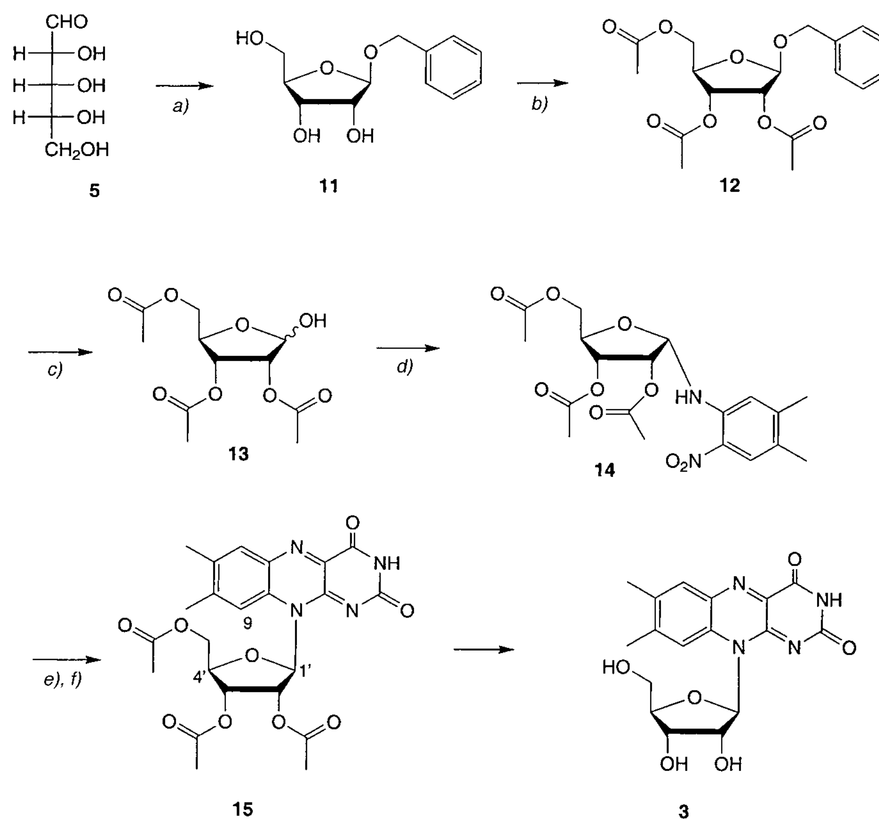
between HN(1) as the H-bond donor and the acceptor centers O(4) and O(9). We believe that formation of this H-bond furnishes the driving force for the exclusive formation of the α-D-anomer **8**. Subsequent hydrogenolytic reduction of the nitro group in **8** and filtration of the solution containing the diamine **9** directly into a suspension of alloxan (= pyrimidine-2,4,5-6(1*H*,3*H*)-tetrone) and boric acid in AcOH furnished a new flavin riboside in 50% yield, whose structure was established by NMR investigations as flavin β-D-ribopyranoside **10**. During the flavin synthesis, the configuration at the anomeric center apparently switches from α-D in **8** to β-D in **10**. The AcOH medium probably allows ring opening of the N,O-acetal of intermediate **9** to the corresponding imine. Condensation of **9** with alloxan to give **10** seems to proceed preferentially with the β-D-configurated educt **9**. Compound **10** contains the large tricyclic flavin moiety and two of the three AcO groups in the thermodynamically favored equatorial position. Finally, cleavage of the three acetyl protecting groups of **10** with NH_3 in anhydrous methanol gave **4** as a stable yellow compound in 48% isolated yield (6.5% overall yield) without further purification.

To elucidate the conformation of the glycosidic bond and to get an initial insight into the potential of **4** to form a catalytically active base-pairing unit in p-RNA [9a], an X-ray crystal structure of **4** was determined (*Fig. 2*,*b*[2])). Thus, compound **4** has a β-D-ribopyranoside structure, exists in the expected chair conformation, and has a torsion angle of the glycosidic bond of $-122.1°$ (*anti*). This *anti*-conformation is strictly required if **4** is intended to mimic a standard nucleobase in a p-RNA double strand [9]. NOE Experiments (performed with **10** in $CDCl_3$) showed that the essential *anti*-conformation of the flavin β-D-ribopyranoside (**4**) could dominate also in solution (irradiation at the H–C(9) signal → strong NOE at the signals of the axially oriented H–C(2′) and H–C(4′), but no NOE at the H–C(1′) signal). These NOE experiments, together with the X-ray crystal structure, strongly suggest that the flavin β-D-ribopyranoside (**4**) possesses *a*) the correct pyranoside constitution, *b*) the required β-D-configuration at the anomeric center, and *c*), even the desired *anti*-conformation of the glycosidic bond. All three properties should enable the participation of **4** as an informational nucleobase in a p-RNA double helix [9].

2.2. *Synthesis and Properties of the Flavin Ribofuranoside* **3**. For the preparation of the flavin β-D-ribofuranoside (**3**), a ribose precursor fixed as a furanosidic constitutional isomer was condensed with nitroxylidene **6** (*Scheme 2*). To obtain this furanose precursor, D-ribose (**5**) was first converted to the *O*-acetyl-protected ribofuranose **13** *via* **11** and **12** by standard procedures [10]. The ribofuranose **13** was subsequently heated with a large excess of nitroxylidine **6** to give the *O*-acetyl-protected nitroxylidine ribofuranoside **14** in 55% yield. The NMR data of **14** again pointed to the α-D-configuration at the anomeric center. Unfortunately, all attempts to crystallize **14** to establish the formation of a bifurcated H-bond failed.

Hydrogenolytic reduction of the nitro group in **14** and filtration of the product mixture directly into a solution of alloxan and boric acid in AcOH afforded the new *O*-acetyl-protected flavin ribofuranoside **15**. The yield of this step varied strongly between 5 and 20% depending on the hydrogenation time. After a minimum of 1–3 min at 2 bar H_2, and after medium-pressure chromatography, **15** could be obtained in yields up to 20% as a brilliant yellow powder. Longer reduction times, however, reduced the yield

Scheme 2. *Synthesis of the Flavin β-*D*-Ribofuranoside* **15** *and Attempts to Deprotect* **15** *to Give* **3**



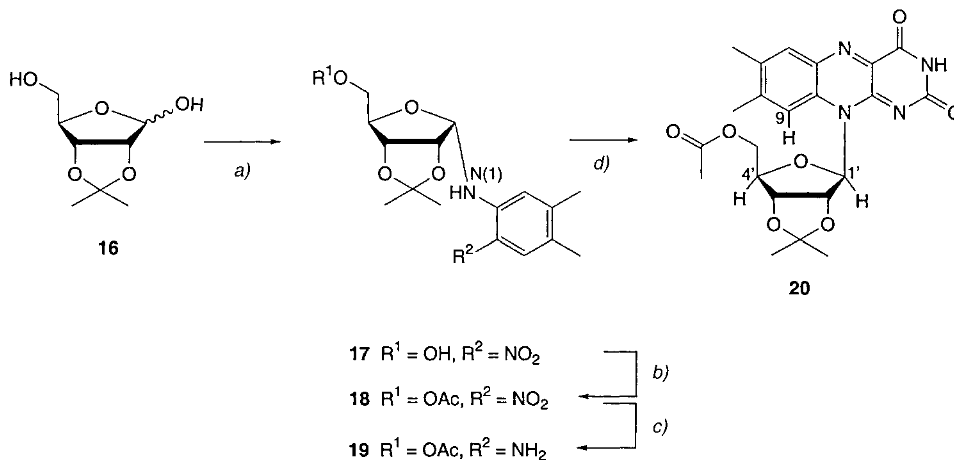
a) Benzyl alcohol, 1% HCl soln.; 30%. *b*) Ac_2O, pyridine; quant. *c*) H_2, Pd/C, MeOH; quant. *d*) $Me_2(NO_2)C_6H_2NH_2$ (**6**), EtOH, NH_4Cl, reflux; 55%. *e*) PtO_2, H_2, Et_3N. *f*) Alloxan, boric acid, AcOH; max. 20%.

to *ca.* 5% only. Under all circumstances, an additional flavin ribofuranoside was obtained in yields of 2–5%.

The β-D-configuration at the anomeric center and the *syn*-conformation of the glycosidic bond of the main product **15** were established by NMR spectroscopy (strong NOE for H–C(1′)/H–C(4′) and H–C(9)/H–C(1′), very weak NOE for H–C(9)/H–C(2′) and H–C(3′)). This *syn*-conformation of the glycosidic bond would compromise the ability of the flavin β-D-ribofuranoside (**3**) to participate as a base-pairing unit in a standard DNA or RNA double strand. Cleavage of the *O*-acetyl groups of **15** to give the flavin ribofuranoside **3** was subsequently attempted under mild basic conditions. However, in sharp contrast to the formation of the isomeric pyranoside **4**, from **10**, we observed under all circumstances rapid decomposition of ribofuranoside **3**, which was accompanied by the formation of dimethyl-alloxazin and accelerated in the presence of light. Although stepwise cleavage of all *O*-acetyl protecting groups, including AcO–C(2′), could be followed by TLC, isolation of the target **3** was not possible (even under exclusion of light) due to its surprisingly high instability.

To circumvent the possibly harmful basic saponification step **15** → **3**, we alternatively reacted the acid-labile isopropylidene-protected ribofuranose **16** with nitroxylidene **6** (*Scheme 3*), which furnished nitroxylidine riboside **17** in 66% yield. The latter was immediately acetylated with Ac_2O in pyridine, giving **18** in 98% yield as a yellow powder. Crystals of compound **18** suitable for X-ray analysis were obtained after recrystallization from EtOH. The X-ray crystal structure (*Fig. 2,c*[2])) established the existence of a bifurcated H-bond between the H-bond donor HN(1) and the acceptor centers O(2) and O(2′) as well as the α-D-configuration at the anomeric center. Reduction of the nitro group of **18** furnished the diamino compound **19**, which was immediately reacted with alloxan in boric acid to give the isopropylidene-protected flavin ribofuranoside **20** in 22% yield in a clean and reproducible reaction. All attempts, however, to cleave the isopropylidene group, now under acidic conditions, failed again. Treatment of **20** with various acids caused always rapid decomposition. The detection of alloxazin as one of the products indicated that the rapid decomposition was again caused by the cleavage of the glycosidic bond.

Scheme 3. *Synthesis of the Flavin* β-D-*Ribofuranoside* **19** *and Attempts to Deprotect* **19** *to Give* **3**



a) $Me_2(NO_2)C_6H_2NH_2$ (**6**), EtOH, NH_4Cl, reflux; 66%. *b*) Ac_2O, pyridine; 98%. *c*) Pd/C, H_2, MeOH. *d*) Alloxan, boric acid, AcOH; 22%.

The rapid decomposition of compound **3** under basic and acidic conditions is surprising. The observed instability of the N(10)-linked flavin ribofuranoside **3** [11] is particularly interesting when we take into account that all known N(1)-linked alloxazin ribofuranosides, prepared by the *Pfleiderer* group and others [12], are stable compounds. These alloxazin ribofuranosides could be chemically manipulated and were even incorporated into DNA single and double strands as novel fluorescent nucleobases. Our target compound **3**, however, contains an N(10)-linked flavin chromophore that is able to participate in a single-electron- and hydride-transfer reaction. In contrast to the N(1)-linked alloxazin compounds, the N(10)-linked flavin systems possess the special reactivity of the flavin coenzyme. This reactivity is, in our opinion, responsible for the observed instability. Based on the known properties of the

flavin heterocycle to abstract H-atoms from organic substrates, we can speculate that such a H-abstraction process from the ribose moiety (preferentially H–C(2′)) could be responsible for the observed rapid cleavage of the glycosidic bond. Surprisingly, the more stable pyranoside form of the ribose sugar in the flavin β-D-ribopyranoside **4** seems to protect this constitutional isomer from the rapid decomposition process.

3. Conclusions. – The hitherto unknown configurations and constitutions of the flavin ribosides, obtained upon treatment of pyranosidic and furanosidic ribose precursors with nitroxylidine by *Kuhn* and *Ströbele* in 1937, could be elucidated.

The observed large stability differences between the flavin ribopyranoside **4** and the isomeric flavin ribofuranoside **3** is an unexpected result, which sets, however, the frame for the potential of both flavin ribosides to function as informational nucleobases in DNA/RNA or in a p-RNA environment [9].

The flavin β-D-ribopyranoside (**4**) clearly possesses the stability and the correct *anti*-conformation of the glycosidic bond required for an informational nucleobase with catalytic properties in p-RNA double-strand environment and, hence, for the construction of catalytically active flavin-containing p-RNA strands. It now awaits its incorporation into p-RNA single and double strands [13].

The instability and the preferred *syn*-conformation of the isomeric flavin β-D-ribofuranoside (**3**), however, strongly compromises the potential of **3** to participate as an informational base-pairing unit in DNA or RNA. DNA and RNA strands containing **3** should suffer from rapid strand cleavage, in particular under aerobic conditions and in the presence of light [11][14][3]).

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Experimental Part

General. All materials were obtained from commercial suppliers and were used without further purification. Solvents of technical quality were distilled prior to use. For reactions under an inert gas atmosphere, N_2 of standard quality was used. TLC: precoated silica-gel plates (*Merck 60-F254*); staining of sugar compounds with anisaldehyde (0.5 ml) in AcOH (50 ml) and sulfonic acid (1 ml), followed by heating at 100°. Flash chromatography (FC): silica gel (*Merck*; 0.040–0.063 mm) and silica-gel-*H* (*Fluka*; 0.005–0.040 mm). MPLC: *Knauer* HPLC instrument with pumps *64*, *Knauer* variable-wavelength UV detector, and *Knauer* degasser. M.p.: uncorrected; *Büchi Smp 20*. IR Spectra: *Perkin-Elmer 1600 FT-IR*, KBr pellets or $CHCl_3$ solns.; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Varian Gemini 200* (200 MHz (^1H), 50 MHz (^{13}C)), *Varian Gemini 300* (300 MHz (^1H), 75 MHz (^{13}C)), and *Bruker AM-500* (500 MHz (^1H), 125 MHz (^{13}C)); chemical shift δ in ppm downfield from $SiMe_4$ (=0 ppm), or alternatively, residual solvent protons as reference. MS: EI, ESI, and FAB spectra were measured by the staff of the mass-spectrometry facilities of the ETH Zürich; *Hitachi-Perkin-Elmer VG TRIBRID*, 70 eV ionization energy (EI); *ZAB-2 SEQ*, 3-nitrobenzyl alcohol as matrix (FAB); *m*/*z* (rel. %). Elemental analyses were performed by the microanalysis laboratory of the ETH Zürich.

X-Ray Crystal-Structure Data of **4**[2]). Yellow needles (MeOH); $C_{17}H_{18}N_4O_6 \cdot 2$ MeOH (M_r 438.44). Triclinic space group *P*1, $D_c = 1.440$ g/cm^{-3}; $Z = 1$; $a = 5.206$ (3), $b = 8.894$ (5), $c = 11.103$ (6) Å; $\lambda = 93.14$ (5), $\beta = 99.71$ (5), $\gamma = 91.08$ (5); $V = 505.8$ (5) Å^3; α 1.54178 Å radiation, $4.0 \geq 2\Theta \leq 49.9°$, 1037 unique reflections, *T* 293 K. The crystal structure was solved by direct methods (SHELXTL PLUS) and refined by full-matrix least-squares analysis on the basis of experimental weights (heavy atoms anisotropic; H-atoms refined isotropically).

[3]) The reduced flavin coenzyme is a strong electron donor and drives a photochemical electron transfer to repair UV-light-induced lesions in DNA photolyases.

Final $R(F) = 0.040$, $wR(F) = 0.100$ for 285 variables and 1037 observed reflections with $F > 4.0\sigma(F)$. Diffractometer: *Picker-Stoe.*

X-Ray Crystal-Structure Data of **8**[2]). Yellow needles (H_2O); $C_{19}H_{24}N_2O_9$ (M_r 424.40). Monoclinic space group $P2$, $D_c = 1.354$ g/cm^{-3}; $Z = 2$; $a = 9.141$ (4), $b = 8.148$ (5), $c = 14.365$ (11) Å; $\alpha = 90$, $\beta = 103.40$ (5), $\gamma = 90$; $V = 1040.8$ (11) Å^3; λ 0.71073 Å radiation, $2.29 \geq 2\Theta \leq 26.54°$, 2474 unique reflections, T 293 K. The crystal structure was solved by direct methods (SHELXTL PLUS) and refined by full-matrix least-squares analysis on the basis of experimental weights (heavy atoms anisotropic; H-atoms refined isotropically). Final $R(F) = 0.036$, $wR(F) = 0.087$ for 277 variables and 2330 observed reflections with $F > 4.0\sigma(F)$. Diffractometer: *Picker-Stoe.*

X-Ray Crystal-Structure Data of **18**[2]). Yellow needles (H_2O); $C_{18}H_{24}N_2O_7$ (M_r 380.39). Monoclinic space group $P2$, $D_c = 1.306$ g/cm^{-3}; $Z = 2$; $a = 9.133$ (11), $b = 9.852$ (12), $c = 11.247$ (12) Å; $\alpha = 90$, $\beta = 107.15$ (8), $\gamma = 90$; $V = 967$ (2) Å^3; λ 0.71073 Å radiation, $2.33° \geq 2\Theta \leq 20.04$, 1034 unique reflections, T 293 K. The crystal structure was solved by direct methods (SHELXTL PLUS) and refined by full-matrix least-squares analysis on the basis of experimental weights (heavy atoms anisotropic; H-atoms refined isotropically). Final $R(F) = 0.030$, $wR(F) = 0.068$ for 249 variables and 972 observed reflections with $F > 4.0\sigma(F)$. Diffractometer: *Picker-Stoe.*

*4,5-Dimethyl-2-nitro-*N*-(α/β-D-ribopyranosyl)benzenamine* (**7**). To D-ribose (**5**; 0.50 g, 3.33 mmol) in abs. EtOH (15 ml) under Ar, 3,4-dimethyl-2-nitrobenzenamine (= nitroxylidine, **6**; 2.80 g, 16.65 mmol) and a cat. amount of NH_4Cl were added. The orange soln. was heated to reflux for 1.5 h, then allowed to cool to r.t., and filtered. *Celite* was added to the soln. and the mixture evaporated *in vacuo* until a dry powder was obtained. The material was added to the soln. on top of a silica-gel column, and residual **6** was eluted with $CHCl_3$. The product was subsequently eluted with MeOH/$CHCl_3$ 1:25: 0.60 g (61%) of **7** (α/β-D 1:1). Orange powder. M.p. > 66° (dec.). R_f (silica gel, CH_2Cl_2/MeOH 25:1) 0.13 and 0.23 (α- and β-D). IR (KBr): 3386, 2922, 1630, 1570, 1506, 1439, 1411, 1328, 1239, 1194, 1150, 1078, 889. ^{1}H-NMR (300 MHz, $CDCl_3$; α/β-D-isomers): 2.19 (*s*, Me); 2.20 (*s*, Me); 2.28 (*s*, Me); 2.29 (*s*, Me); 3.41 – 4.17 (*m*, 10 H, H–C(2′), H–C(3′), H–C(4′), CH_2(5′)); 4.86 – 4.90 (*m*, 1 H, H–C(1′) (α)); 5.10 – 5.15 (*m*, 1 H, H–C(1′) (β)); 6.78 (*s*, 1 arom. H, (α)); 7.92 (*s*, 1 arom. H (α)); 6.92 (*s*, 1 arom. H (β)); 7.94 (*s*, 1 arom. H (β)); 8.14 (*d*, *J* = 7.5, NH (β)); 8.86 (*d*, *J* = 8.7, NH (α)). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$, α/β-D-isomers): 18.07; 18.10; 20.14; 30.65; 61.12; 63.66; 66.89; 67.16; 68.89; 70.01; 70.36; 70.83; 80.27; 82.04; 115.64; 115.89; 125.22; 125.30; 125.36; 126.1; 129.99; 130.08; 142.09; 142.60; 146.89; 147.35. ESI-MS (neg. mode; 5M HN_4OAc): 357 (40, $[M + OAc]^-$), 333 (100), 335 (20, $[M + Cl]^-$), 297 (52, M^-). Anal. calc. for $C_3H_{18}N_2O_6$ (298.30): C 52.35, H 6.08, N 9.39; found: C 52.18, H 5.82, N 9.11.

*4,5-Dimethyl-2-nitro-*N*-(2′,3′,5′-tri-*O*-acetyl-α-D-ribopyranosyl)benzenamine* (**8**). To **7** (0.80 g, 2.68 mmol) in pyridine (10 ml), Ac_2O (3 ml) was added. The mixture was stirred for 12 h at r.t. and then heated for 30 min to 50°. After evaporation, the brownish solid residue was submitted to FC (silica gel, CH_2Cl_2/MeOH 25:1): 0.50 g (44%) of **8**, after recrystallization from EtOH. Yellow needles. M.p. 149°. R_f (silica gel, toluene/AcOEt 5:1) 0.50. IR (KBr): 3378, 2941,1752, 1632, 1572, 1508, 1411, 1376, 1227, 1027, 879. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.02 (*s*, Me); 2.04 (*s*, Me); 2.21 (*s*, Ac); 2.29 (*s*, Ac); 2.37 (*s*, Ac); 3.61 (*dd*, *J* = 5.3, 11.2, 1 H–C(5′)); 3.90 (*t*, *J* = 11.2, 1 H–C(5′)); 5.08 (*qd*, *J* = 3.2, 5.2, H–C(4′)); 5.16 – 5.30 (*m*, H–C(2′)); 5.45 – 5.49 (*m*, H–C(3′)); 5.73 – 5.75 (*m*, *J* = 3.1, H–C(1′)); 6.90 (*s*, H–C(6)); 7.98 (*s*, H–C(3)); 8.93 (*d*, *J* = 6.8, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 18.68; 20.46; 20.64; 20.68; 20.86; 55.80; 66.06; 66.17; 67.90; 76.77;115.53; 115.73; 127.04; 131.51; 141.47; 147.42; 169.56; 169.57; 170.38. FAB-MS (pos. mode): 425 (100 MH^+). Anal. calc. for $C_{19}H_{24}N_2O_9$ (424.41): C 53.77, H 5.70, N 6.60; found: C 53.70, H 5.72, N 6.53.

*7,8-Dimethyl-10-(2′,3′,5′-tri-*O*-acetyl-β-D-ribopyranosyl)benzo[*g*]pteridine-2,4(3*H*,10*H*)-dione* (**10**). To a soln. of **8** (0.10 g, 0.24 mmol) in AcOEt (3 ml), Et_3N (0.17 g, 1.65 mmol) and PtO_2 (0.05 g, 0.20 mmol) were added. The resulting suspension was stirred under H_2 at 2 bar in an autoclave until a colorless soln. was obtained (*ca.* 1 h). The soln. containing **9** was filtered under exclusion of light into a suspension of alloxan monohydrate (0.07 g, 0.42 mmol) and boric acid (0.07 g, 1.07 mmol) in AcOH (30 ml). The colorless soln. turned immediately green and, subsequently, upon stirring, yellow-brown. After 2 h of stirring, H_2O (50 ml) was added, the mixture extracted with $CHCl_3$ (3 ×), the combined org. phase washed with H_2O (4 ×), dried (Na_2SO_4), and evaporated. The residue showed 3 yellow (irradiation at 366 nm) flavin spots on TLC. The main β-D-isomer **10** was isolated by FC (silica gel-*H*, CH_2Cl_2/MeOH 10:1). Prep. MPLC ($CHCl_3$/MeOH 100:0 → 75:25 within 1 h) allowed removal of the minor α-D-isomer: 0.60 g (50%) of **10**. M.p. 177°. R_f (silica gel, CH_2Cl_2/MeOH 25:1) 0.25. IR (neat): 3278, 2933, 1750, 1583, 1539, 1367, 1233, 1083, 1044. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.75 (*s*, Ac); 2.10 (*s*, Ac); 2.30 (*s*, Ac); 2.42 (*s*, Me); 2.55 (*s*, Me); 4.13 – 4.24 (*m*, 2 H–C(5′)); 4.19 (*qd*, *J* = 11, H–C(4′)); 5.80 – 5.85 (*m*, H–C(2′), H–C(3′)); 7.69 (*d*, *J* = 10.7, H–C(1′)); 7.95 (*s*, H–C(6 or 9)); 7.96 (*s*, H–C(6 or 9)); 8.63 (*s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.45; 20.22; 20.61; 20.90; 22.09; 64.46; 65.77; 65.85; 67.99; 80.72; 117.65; 129.26; 133.30; 134.95; 135.50; 137.27; 148.05; 151.46; 154.53; 158.97; 168.97; 169.59; 170.22. FAB-MS (pos. mode): 501 (46, MH^+), 405 (22), 259 (100). FAB-HR-MS (pos. mode): 501.1629 ($C_{23}H_{25}N_4O_9^+$; MH^+; calc. 501.1621).

7,8-Dimethyl-10-(β-D-ribopyranosyl)benzo[g]pteridine-2,4(3H,10H)-dione (**4**). A soln. of **10** (55 mg, 0.11 mmol) in abs. MeOH was saturated with NH_3 (50 ml) and stirred for 3 h at r.t. Evaporation gave **4** (20 mg, 48%). Yellow powder. M.p. 187°. R_f (silica gel, MeOH): 0.66. IR (neat): 3360, 2944, 1721, 1667, 1542, 1449, 1390, 1275, 1099, 104. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.35, 2.45 (2*s*, 2 Me); 3.68 (*m*, CH_2(5′)); 4.04 (br., H−C(4′), H−C(3′)); 4.34 (br. *s*, H−C(2′)); 4.91 (br. *s*, 2 OH), 5.15 (br. *s*, 1 OH); 7.11 (*d*, H−C(1′)); 7.84, 7.95 (2*s*, H−C(9), H−C(6)). ^{13}C-NMR (300 MHz, (D_6)DMSO): 18.58; 20.76; 65.67; 65.90; 66.24; 71.16; 83.13; 118.75; 129.25; 131.25; 134.00; 135.52; 136.86; 144.95; 151.75; 155.25; 159.44. ESI-MS (MeOH): 787 (15, $[2M+K]^+$), 771 (100, $[2M+Na]^+$), 413 (25, $[M+K]^+$), 397 (100, $[M+Na]^+$), 375 (58, MH^+). FAB-HR-MS (pos. mode): 375.1301 ($C_{17}H_{19}N_4O_6^+$; MH^+; calc. 375.1304).

2′,3′,5′-Tri-O-acetyl-1′-O-benzyl-β-D-ribofuranose (**12**). To benzyl β-D-ribofuranoside (**11**; 1.00 g, 4.16 mmol) in pyridine (10 ml), Ac_2O (3 ml) was added. The mixture was stirred for 8 h at r.t. and then heated for additional 1.5 h to 50°. EtOH (10 ml) and Et_2O (100 ml) were added, and the mixture was extracted with H_2O (3 × 100 ml). The combined org. phase was dried (Na_2SO_4) and evaporated and the residue dried under high vacuum: 1.5 g (quant.) of **12**. Colorless solid material. M.p. 60–65°. R_f (silica gel, CH_2Cl_2/MeOH 10:1) 0.84. IR (KBr): 3356, 3022, 2900, 1747, 1433, 1381, 1220, 1083, 967, 745, 702, 626. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.05 (*s*, Ac); 2.07 (*s*, Ac); 2.11 (*s*, Ac); 4.10–4.41 (*m*, H−C(4′)); CH_2(5′)); 4.53 (*d*, J = 12, 1 H, $PhCH_2$); 4.77 (*d*, J = 12, 1 H, $PhCH_2$); 5.41 (*s*, H−C(1′)); 5.09–5.51 (*m*, H−C(2′), H−C(3′)); 7.33–7.38 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.53; 20.61; 20.77; 64.43; 69.42; 71.54; 74.86; 78.65; 104.24; 127.92 (2 ×); 127.94; 128.48 (2 ×); 136.82; 169.64; 169.70; 170.71. FAB-MS (pos. mode): 625 (10, $[M+259]^+$), 389 (10, $[M+Na]^+$), 367 (12, MH^+), 259 (100). Anal. calc. for $C_{18}H_{22}O_8$ (366.37): C 59.01, H 6.05; found: C 59.05, H 5.96.

2′,3′,5′-Tri-O-acetyl-α/β-D-ribofuranose (**13**) [10]. A soln. of **12** (1.48 g, 4.04 mmol) in AcOEt (20 ml) and 10% Pd/C (1.00 g) was stirred under H_2 at 4.5 bar. The soln. was filtered through *Celite* and evaporated and the residue subjected to FC (silica gel, CH_2Cl_2/MeOH 15:1): 1.10 g (quant.) of **13**. Colorless oil. R_f (silica gel, CH_2Cl_2/MeOH 10:1) 0.34. ^{1}H-NMR (300 MHz, $CDCl_3$); mixture of the α/β-D-isomers): 2.07 (*s*, 3 H, Ac); 2.10 (*s*, 3 H, Ac); 2.10 (*s*, 3 H, Ac); 2.11 (*s*, 3 H, Ac); 2.13 (*s*, 3 H, Ac); 2.14 (*s*, 3 H, Ac), 3.05–3.25 (*m*, 2 OH); 4.13–4.42 (*m*, 6 H); 5.08–5.40 (*m*, 6 H). ESI-MS (CH_2Cl_2): 294 (100, $[M+NH_4]^+$), 259 (24, $[MH]^+$).

4,5-Dimethyl-2-nitro-N-(2′,3′,5′-tri-O-acetyl-α-D-ribofuranosyl)benzenamine (**14**). Under Ar, **13** (1.00 g, 3.62 mmol) was dissolved in EtOH (15 ml). Then, **6** (3.62 g, 18.1 mmol, 5 equiv.) and a cat. amount of NH_4Cl (0.03 g) were added. The orange mixture was heated to reflux for 2.5 h, then allowed to cool to r.t., and filtered. *Celite* was added to the soln., and the mixture was evaporated. The solid material was added ontop of a silica gel column, and residual **6** was eluted with CH_2Cl_2. The product was then eluted with CH_2Cl_2/MeOH 25:1: 0.85 g (55%) of **14** (with traces of the corresponding β-D-isomer). Yellow oil. R_f (silica gel, CH_2Cl_2/MeOH 10:1) 0.38. IR (neat): 3372, 2934, 1747, 1627, 1572, 1506, 1433, 1372, 1232, 1058. ^{1}H-NMR (300 MHz, $CDCl_3$; α-D-isomer): 2.13 (*s*, Ac); 2.14 (*s*, Ac); 2.21 (*s*, Ac); 2.22 (*s*, Me); 2.29 (*s*, Me); 4.20–4.34 (*m*, CH_2(5′), H−C(4′)); 5.27–5.31 (*m*, H−C(3′)); 5.39–5.42 (*m*, H−C(2′)); 5.75–5.80 (*m*, H−C(1′)); 6.95 (*s*, 1 arom. H); 7.96 (*s*, 1 arom. H); 8.74 (*d*, J = 7.8, NH). ^{13}C-NMR (125 MHz, $CDCl_3$; α-D-isomer): 18.59; 20.36; 20.53; 20.58; 20.74; 63.48; 69.75; 71.45; 78.91; 82.05; 115.43; 126.29; 126.91; 131.42; 141.12; 147.31; 169.40; 169.97; 170.44. FAB-MS (pos. mode): 424 (100, M^+), 259 (87), 139 (42). Anal. calc. for $C_{19}H_{24}N_2O_9$ (424.40): C 53.77, H 5.70, N 6.60; found: C 53.87, H 5.78, N 6.42.

7,8-Dimethyl-10-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)benzo[g]pteridine-2,4(3H,10H)-dione (**15**). To a soln. of **14** (0.30 g, 0.70 mmol) in AcOEt (3 ml), Et_3N (0.49 g, 4.90 mmol) and PtO_2 (0.06 g, 0.27 mmol) were added. The suspension was briefly (!) stirred under H_2 at 2 bar in an autoclave until a colorless soln. was obtained. The mixture was filtered into a suspension of alloxan monohydrate (0.20 g, 1.24 mmol) and boric acid (0.20 g, 3.17 mmol) in AcOH (10 ml) under exclusion of light. Upon stirring at r.t., the initially green suspension changed into a green-brown soln. After 2 h, the mixture was worked up as described for **10** (CH_2Cl_2 instead of $CHCl_3$). The main β-D-isomer **15** was isolated by FC (silica gel-*H* (CH_2Cl_2/MeOH 10:1; 3 spots on TLC). Separation of the two minor products was achieved by MPLC (silica gel, $CHCl_3$/MeOH 100:0 → 75:25 within 1 h): 24 mg (18%) of **15**. R_f (silica gel, CH_2Cl_2/MeOH 10:1) 0.71. IR (KBr): 3455, 2367, 1750, 1733, 1683, 1655, 1578, 1544, 1394, 1377, 1233, 1050. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.08 (*s*, Ac); 2.12 (*s*, Ac); 2.16 (*s*, Ac); 2.43 (*s*, Me); 2.53 (*s*, Me); 4.45–4.56 (*m*, CH_2(5′), H−C(4′)); 5.80–5.85 (*m*, H−C(3′)); 5.98 (*dd*, J = 4.0, 6.7, H−C(2′)); 6.92 (*d*, J = 3.8, H−C(1′)); 7.51 (*s*, 1 arom. H); 8.04 (*s*, 1 arom. H); 8.39 (*s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.37; 20.35; 20.42; 20.80; 21.86; 62.78; 69.72; 71.83; 80.20; 90.11; 115.40; 129.89; 133.39; 134.94; 136.47; 137.12; 147.89; 153.66; 156.10; 158.84; 169.48; 170.02; 170.45. FAB-MS (pos. mode): 501 (15, MH^+), 393 (100). FAB-HR-MS (pos. mode): 501.1629 ($C_{23}H_{24}N_4O_9^+$, MH^+; calc. 501.1622).

N-*(2′,3′-O-Isopropylidene-α-D-ribofuranosyl)-4,5-dimethyl-2-nitrobenzenamine* (**17**). Under Ar, **16** (0.53 g, 2.76 mmol) was dissolved in EtOH (15 ml). Then **6** (3.30 g, 13.8 mmol, 5 equiv.) and a cat. amount of NH_4Cl

(70 mg) were added. The orange mixture was heated to reflux for 2.5 h. After 10 min, 3 Å molecular sieves were added. The mixture was allowed to cool to r.t. and filtered. *Celite* was added to the soln. and the slurry evaporated. The residue was added to the soln. on top of a silica gel column, and **6** was eluted with CH_2Cl_2. The product was eluted with CH_2Cl_2/MeOH 15 : 1: 0.59 g (66%) of **17** (α/β-D 12 : 1). Yellow oil. R_f (silica gel, CH_2Cl_2/MeOH 25 : 1) 0.36. IR (neat): 3370, 2933, 2300, 1627, 1567, 1506, 1406, 1327, 1272, 1239, 1094, 856. ^{1}H-NMR (300 MHz, $CDCl_3$; α-D-isomer): 1.38 (*s*, 3 H, Me_2C); 1.59 (*s*, 3 H, Me_2C); 2.20 (*s*, Me); 2.29 (*s*, Me); 3.71 – 3.77 (*m*, $CH_2(5')$); 4.33 – 4.36 (*m*, H–C(4')); 4.70 (*dd*, *J* = 2.5, 5.9, H–C(3')); 4.92 (*dd*, *J* = 1.9, 6.1, H–C(2')); 5.45 (*dd*, *J* = 1.5, 9.5, H–C(1')); 6.96 (*s*, 1 arom. H); 7.93 (*s*, 1 arom. H); 8.35 (*d*, *J* = 9.1, NH). ^{13}C-NMR (100 MHz, $CDCl_3$; α-D-isomer): 18.59; 20.57; 24.92; 26.13; 63.29; 79.66; 81.43; 81.43; 84.36; 114.51; 116.09; 126.29; 126.39; 131.32; 141.28; 146.91. FAB-MS (pos. mode): 677 (7, 2 MH$^+$), 391 (33), 362 (28, $[M + Na]^+$, 339 (100), 339 (MH$^+$).

N-*(5'*-O-*Acetyl-2',3'*-O-*isopropylidene-α-*D*-ribofuranosyl)-4,5-dimethyl-2-nitrobenzenamine* (**18**). To a soln. of **17** (0.86 g, 2.53 mmol) in pyridine (10 ml), Ac_2O (3 ml) was added and the mixture stirred for 3 h at r.t. and then heated for 8 h at 50°. EtOH (10 ml) and Et_2O (100 ml) were added, and the mixture was washed with H_2O (3 × 100 ml). The org. phase was dried (Na_2SO_4) and evaporated and the residue (yellow powder) dried under high vacuum for 2 days: 0.95 g (98%) of **18**. An anal. sample of **18** was obtained by recrystallization from EtOH. Yellow needles. M.p. 157 – 161°. R_f (silica gel, CH_2Cl_2/MeOH 10 : 1) 0.73. IR (neat): 3367, 2933, 1742, 1627, 1567, 1508, 1433, 1372, 1239, 1094, 1033, 861. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.44 (*s*, 3 H, Me_2C); 1.68 (*s*, 3 H, Me_2C); 1.14 (*s*, Ac); 2.20 (*s*, Me); 2.29 (*s*, Me); 4.13 – 4.16 (*m*, 1 H–C(5')); 4.31 – 4.40 (*m*, H–C(4'), 1 H–C(5')); 4.73 (*dd*, *J* = 1.8, 6.6, H–C(3')); 4.89 (*dd*, *J* = 3.3, 4.9, H–C(2')); 5.49 (*dd*, *J* = 4.8, 7.6, H–C(1')); 6.93 (*s*, 1 arom. H); 7.95 (*s*, 1 arom. H); 8.77 (*d*, *J* = 7.5, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.64; 20.53; 20.96; 25.16; 26.19; 63.87; 79.27; 79.49; 81.57; 84.29; 114.79; 116.18; 126.33; 126.59; 131.50; 141.08; 146.99; 170.58. FAB-MS (pos. mode): 381 (34, MH$^+$), 289 (41). Anal. calc. for $C_{18}H_{24}N_2O_7$ (380.40): C 56.83, H 6.36, N 7.36; found: C 56.86, H 6.36, N 7.36.

10-(5'-O-*Acetyl-2',3'*-O-*isopropylidene-β-*D*-ribofuranosyl)-7,8-dimethylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione* (**20**). To a soln. of **18** (0.30 g, 0.79 mmol) in AcOEt (9 ml) and Et_3N (0.59 g, 5.53 mmol), PtO_2 (0.07 g, 0.31 mmol) was added and the mixture stirred under H_2 at 2 bar in an autoclave until a colorless soln. was obtained (1 h). The mixture containing **19** was filtered under exclusion of light into a suspension of alloxan monohydrate (0.22 g, 1.40 mmol) and boric acid (0.22 g, 3.58 mmol) in AcOH (30 ml). The mixture turned immediately green and, upon stirring at r.t., yellow-brown. After 2 h, the mixture was worked up as described for **10** (2 × $CHCl_3$). The main β-D-isomer **20** was isolated by FC (silica gel *H*, CH_2Cl_2/MeOH 10 : 1; 3 spots on TLC). Separation of the two minor products was achieved by MPLC (silica gel, $CHCl_3$/MeOH 100 : 0 → 75 : 25 within 1 h): 80 mg (22%) of **20**. M.p. 142°. R_f (silica gel, CH_2Cl_2/MeOH 10 : 1) 0.74. IR (neat): 3178, 2933, 2811, 1717, 1657, 1578, 1542, 1395, 1256, 1156, 1078. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.38 (*s*, 3 H, Me_2C); 1.63 (*s*, 3 H, Me_2C); 2.04 (*s*, Ac); 2.44 (*s*, Me); 2.55 (*s*, Me); 4.47 – 4.57 (*m*, $CH_2(5')$, H–C(4')); 5.41 (*dd*, *J* = 4.0, 6.3, H–C(3')); 5.57 (*dd*, *J* = 1.2, 6.5, H–C(2')); 6.68 (*s*, H–C(1')); 7.66 (*s*, 1 arom. H); 8.05 (*s*, 1 arom. H); 8.35 (*s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.40; 20.81; 21.64; 25.27; 27.25; 64.60; 82.77; 84.24; 88.35; 92.83; 114.79; 114.97; 130.75; 133.08; 135.03; 136.72; 137.18; 148.42; 149.03; 153.40; 158.87; 170.48. ESI-MS: 456 (10, M^+), 243 (100). FAB-HR-MS (pos. mode): 457.1727 ($C_{22}H_{25}N_4O_7^+$, MH$^+$; calc. 457.1723).

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