Stereoselective Glycosylation of Nitrobenzimidazole Anions: Synthesis of 1,3-Dideaza-2′-deoxyadenosine and Related 2′-Deoxyribofuranosides

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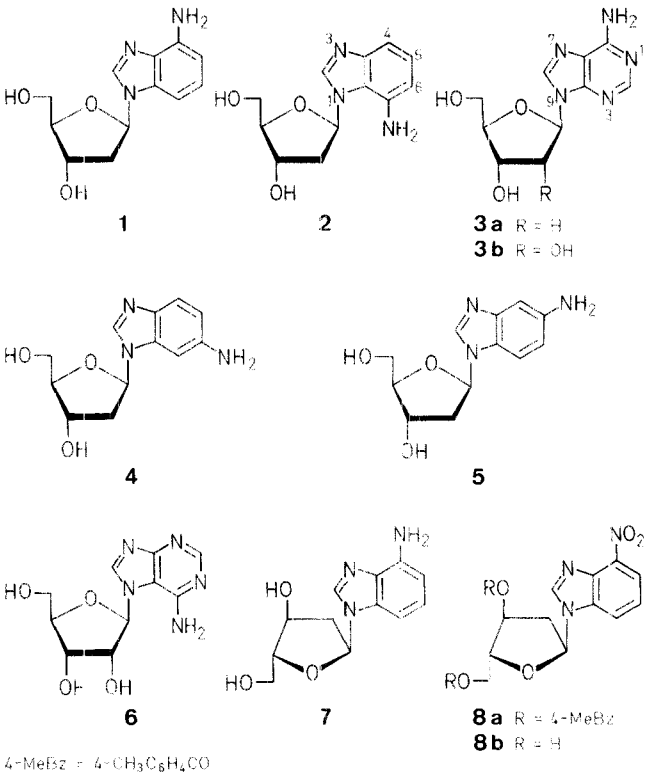
The synthesis of 1,3-dideaza-2′-deoxyadenosine (**1**) and related benzimidazole 2′-deoxyribonucleosides is described. Solid–liquid phase-transfer glycosylation of 5(6)-nitrobenzimidazole (**9**) or 4(7)-nitrobenzimidazole (**15**) in acetonitrile with 1-chloro-2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-α-D-*erythro*-pentofuranose (**10**) gave regioisomeric N-1 and N-3 β-D-2′-deoxyribofuranosides. The glycosylation yield, as well as the ratio of anomers and regioisomers, was altered by use of either tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) or [18]crown-6 as phase-transfer catalysts and potassium hydroxide or potassium carbonate as inorganic bases, respectively. Zemplén-deprotection and subsequent catalytic hydrogenation afforded the corresponding amino compounds **1**, **2**, **4**, **5** and **7**. Structural proof of anomeric and regioisomeric compounds was made on the basis of ^{1}H- and ^{13}C-NMR spectroscopy. The benzimidazole 2′-deoxyribofuranosides **4** and **5** exhibit strong fluorescence at λ_{max} = 362 and 395 nm, respectively. 1,3-Dideaza-2′-deoxyadenosine ($\varepsilon^1\varepsilon^3A_d$, **1**) is more stable in 1 N hydrochloric acid than dA (**3a**). Under alkaline conditions, compound **1** decomposes whereas the regioisomer **2** is stable. Compound **1** is no substrate for adenosine deaminase.

The synthesis of benzimidazole nucleosides was encouraged by the discovery, that 5,6-dimethyl-1-(α-D-*erythro*-pentofuranosyl)-benzimidazole is a constituent of vitamin B_{12}.[1] In addition benzimidazole nucleosides, such as 5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (DRB), are currently of interest due to their significant biological activity.[2] In view of this, and since the benzimidazole moiety is isosteric to the purine base, we decided to synthesize new benzimidazole 2′-deoxyribofuranosides structurally related to DNA-constituents.

The convergent synthesis of benzimidazole nucleosides, starting from an unsymmetrically substituted benzimidazole derivative and a suitably protected halosugar, is fraught with difficulties: such as to regio- and diastereoselectivity, as well as structural assignment of the reaction products. So far, benzimidazole nucleosides have been synthesized by conventional glycosylation techniques but in the series of 2′-deoxyribonucleosides only symmetrically substituted benzimidazoles were used for glycosylation reactions.[3]

In 1983 our laboratory developed a stereoselective 2′-deoxyribonucleoside synthesis using a nucleobase anion generated under liquid–liquid phase-transfer conditions.[4] Later, other laboratories used sodium hydride for anion generation in order to avoid deprotection of the sugar moiety, which occurred in case of heterocyclic bases being poorly soluble in the reaction mixture or exhibiting low nucleophilicity.[5] Using the sodium hydride-mediated reaction 5,6-disubstituted benzimidazole 2′-deoxyribofuranosides have recently been prepared.[6] We have shown that solid–liquid phase-transfer glycosylation is the adequate method for nucleobase anion generation, the cryptand complexes the counter ion of the base, thus accelerating the reaction rate.[7] As a result, glycosylation takes place rapidly at room temperature. Anhydrous conditions are not required and large scale preparations can easily be performed.

We now report on the synthesis and structural assignment of five regioisomeric aminobenzimidazole 2′-deoxyribofuranosides **1**, **2**, **4**, **5**, and **7** including 1,3-dideaza-2′-deoxyadenosine (**1**). Furthermore, it was of interest to control regio- and stereoselectivity by the phase-transfer catalyst or other parameters of the reaction.



In the beginning of our investigations glycosylation, of 5(6)-nitrobenzimidazole (**9**)[8,9] with the halogenose **10**[10] was studied (Scheme **A**). The reaction was carried out in acetonitrile containing a three-fold excess of powdered potassium hydroxide and 0.1 equivalent of the cryptand tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1). The reaction proceeded comparatively slowly to other heterocyclic bases, as compound **9** was poorly soluble in the reaction mixture. However, the reaction was complete within 2 h. TLC-monitoring indicated the formation of two glycosylation products, which were separated by flash-chromatography. A faster migrating material was isolated in 46% and a slower one in 39% yield. ^{1}H-, ^{13}C-NMR and UV spectra pointed to the regioisomers **11** and **12**. Following the empirical rules of Nuhn et al.,[11] the small chemical shift differences of H-4′ and 2 × H-5′ in the ^{1}H-NMR spectra suggested β-configuration; no α-nucleoside formation was observed.

Earlier, Mizuno and co-workers[12] reported on the synthesis of the 5- and 6-nitrobenzimidazole β-D-ribofuranosides and found that the regioisomeric glycosylation products exhibit very similar UV-spectra. However, as they observed differences in the $\varepsilon_{240}/\varepsilon_{300}$ UV-ratios similar to those of already known 5- and 6-alkylated benzimidazoles, they used those differences for the assignment of the regioisomers. In earlier publications we have used ^{1}H-NMR NOE difference spectroscopy for both, anomeric assignment[13,14] and determination of the glycosylation position of 3,7-dideazapurine nucleosides.[14] This was also applied in the present work. For this purpose, compounds **11** and **12** were subjected to Zemplén-deprotection[15] yielding

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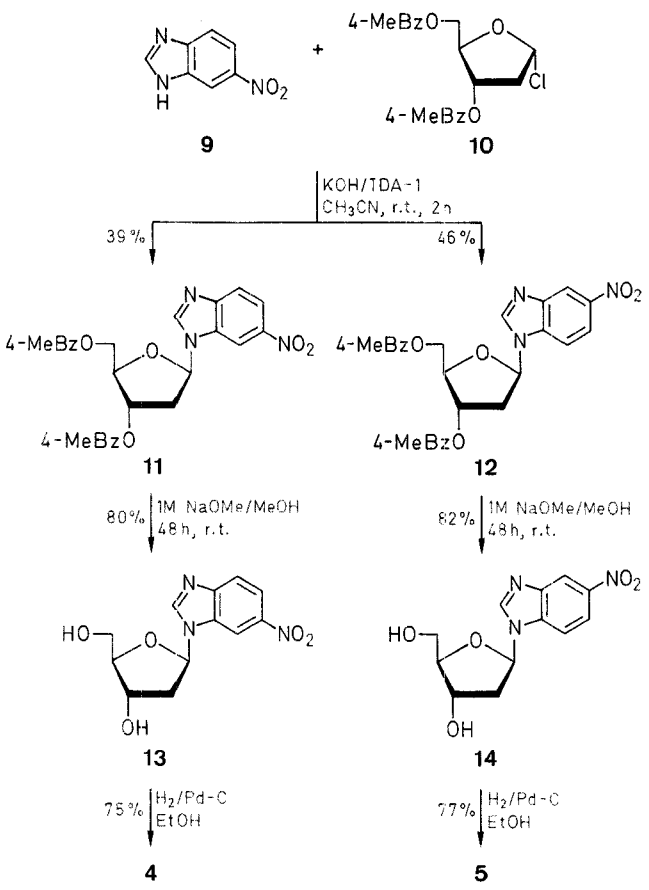
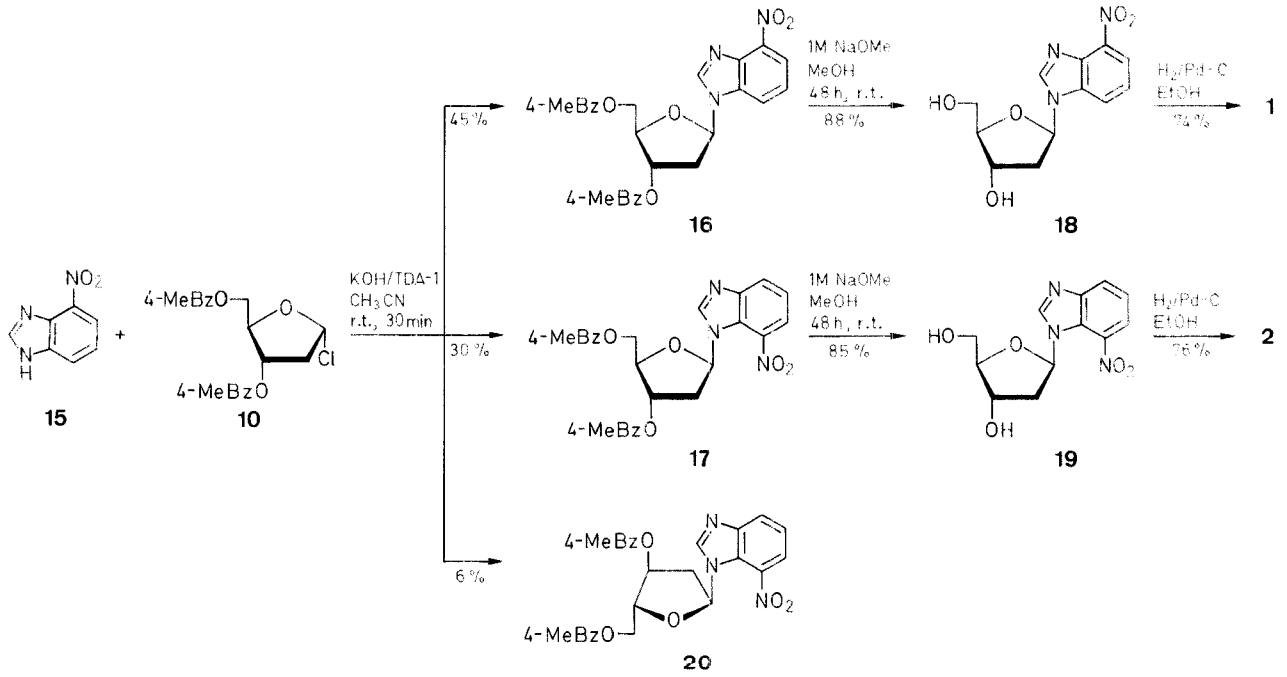
the crystalline 2′-deoxynucleosides **13** and **14** after chromatographic purification. From the NOE values of the 4′-H upon irradiation of the anomeric proton (Table 1) β-configuration was deduced. Moreover, the spatial proximity of the methine protons (H-7) to H-1′ was used as indicator for assignment of regioisomers. In the case of compound **13** a strong NOE (8.5%) was found for the proton in 7-position, represented by a small doublet ($J_{H\text{-}7,H\text{-}5}$ = 2.2 Hz) in the ^{1}H-NMR spectrum. For compound **14** a similar value (6.5%) was observed for the corresponding proton, displayed as a doublet with a larger coupling constant ($J_{H\text{-}7,H\text{-}6}$ = 9.0 Hz). Thus, the faster migrating isomer (46% yield) of the glycosylation reaction was compound **12**, whereas the slower one (39% yield) was compound **11**. The amino nucleosides **4** and **5**, were obtained by catalytic hydrogenation of **13** and **14**, respectively. Both compounds are strongly fluorescent; the emission maximum of compound **5** (Table 2) is bathochromically shifted as compared to its regioisomer **4**.



Scheme **A**

The glycosylation of 4(7)-nitrobenzimidazole (**15**)[8,16] was initially performed in the manner described for the 5(6)-isomer **9** (Scheme **B**). Purification of the reaction mixture on a silica gel column afforded two main glycosylation products **16** and **17** together with a small amount of a third reaction product **20**. The two main glycosylation products were deprotected yielding the 2′-deoxynucleosides **18** and **19**, the structures of which were then assigned again by ^{1}H-NMR NOE difference spectroscopy. According to Table 1 only the isomer **18** shows enhancements for H-7 and H-1′ upon irradiation of H-4′ indicating 1,4-substitution of the benzimidazole moiety and β-configuration. In order to establish the glycosylation position of compound **19** it was hydrogenated to give a crystalline material. Upon irradiation of H-1′ the amino group and H-4′ showed NOEs in agreement with formula **2**. Hydrogenation of **18** yielded 1,3-dideaza-2′-deoxyadenosine (**1**), which crystallized as colorless needles. As the aglycon of the third glycosylation product showed almost identical ^{13}C-NMR chemical shifts as compared to compound **17** (Table 3) but differences within those of the sugar moiety, it was assigned as α-nucleoside **20**. In addition to ^{1}H-NMR data all compounds described were characterized by ^{13}C-NMR data (Table 3). Assignment of ^{13}C-NMR signals was made on the basis of 2D [^{1}H, ^{13}C]-correlation spectra as well as 1D-gated-decoupled ^{13}C-NMR spectra (Table 4).

The nitro nucleoside **18** exhibits a UV maximum at λ_{max} = 310 nm, whereas that of the regioisomer **19** shows a bathochromic shift to λ_{max} = 318 nm. Comparing these values to the



Scheme **B**

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known 4-nitrobenzimidazole N-1 β-D-ribofuranoside (λ_{max} = 317 nm)[29] it should be noted that a difference exists between our UV data and those of Mizuno.[12]

The glycosylation experiments carried out under solid–liquid phase-transfer conditions (Table 5) show that nucleobase anion glycosylation of **9** proceeds stereoselectively if the reaction is carried out in acetonitrile with excess potassium hydroxide and TDA-1 as catalyst. The regioisomers **11** and **12** were formed in about the same quantitiy demonstrating that the nitro group does not perceptibly influence the glycosylation position if it is located in the 5- or 6-position of the benzimidazole moiety. It is conspicuous that in case of compound **15** traces of only one α-anomeric glycosylation product **20** was formed using potassium hydroxide as inorganic base. However, if [18]crown-6 was used instead of TDA-1 the glycosylation yield was increased from 81% to 89% but the ratio of glycosylation products (**16**:**17**:**20** = 7.5:5:1) was found to be equal (Table 5).

Table 1. 1-D-NOE Difference Data (%) of Benzimidazole 2′-Deoxyribofuranosides upon Irradiation of H-1′[a,b]

Compound	H_α-2′	H_β-2′	H-3′	H-4′	H-5′	H-2	H-7 H-8	NH_2
1	4.5	0	0	2.8	0	5.2	6.2	0
2	10.0	0	0	3.2	0	6.1	–	4.2
8b	0	9.5	4.2	0	13.0	3.0	6.6	–
13	9.7	0	0	1.8	0	5.3	8.5	–
14	8.6	0	0	1.8	0	4.8	6.5	–
18	5.9	0	0	1.9	0	5.7	6.1	–
19	6.8	1	0	1.8	0	0.5	–	–

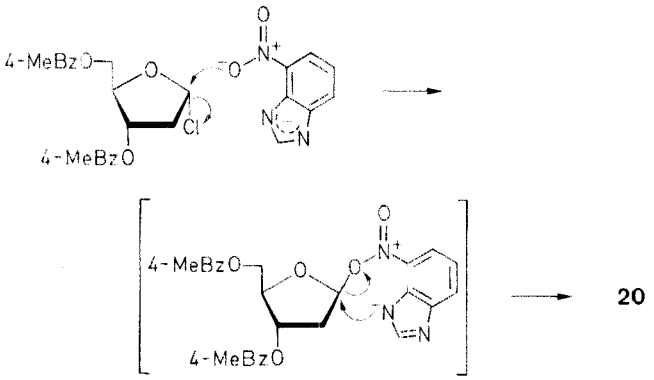
[a] Spectra measured in DMSO-d_6.
[b] Purine numbering in parentheses.

Table 2. Fluorescence-Data of Benzimidazole 2′-Deoxyribofuranosides[a]

Compound	Excitation Wavelength λ (nm)	Emission Maximum λ (nm)
4	330	362
5	340	395

[a] In H_2O.

Compound **15** is easily deprotonated with potassium hydroxide, the N-1/N-3 anion thus formed attacks the 1′-carbon of the halogenose **10** resulting in the β-configurated nucleosides **16** and **17** with inversion of configuration. The formation of the α-nucleoside **20** during glycosylation reactions of **15** may be due to the peculiarity of the nitro group. As outlined in Scheme **C**, nitro group could act as nucleophile in the first glycosylation step followed by an intramolecular S_N2-displacement with repeated inversion of configuration. As a consequence compound **20** is formed. In case of pyrazolo[3,4-*d*]-pyrimidines[17] not carrying a nitro group the formation of an α-anomer was also observed for only one of the regioisomeric glycosylation products. It is not clear whether the tendency towards anomerization is due to differences in the nucleophilicity of the nitrogens or to a reaction intermediate as depicted in Scheme **C**.



Scheme C

If potassium hydroxide is replaced by potassium carbonate upon glycosylation of **15** reaction yields are strongly decreased (Table 5). However, the glycosylation becomes regioselective for N-9[18] but the α-anomer **8a** was now the main reaction product. This demonstrates that by use of K_2CO_3 the reaction of the more nucleophilic N-9 anion[18] of **15** is preferred. The formation of the α-anomer **8a** is likely to be a consequence of *in situ* equilibration of the halogenose probably due to the prolonged reaction time.

Table 3. ^{13}C-NMR Chemical Shifts (δ) of Benzimidazole 2′-Deoxyribofuranosides[a,b]

Compound	C-2 (C-8)	C-4 (C-6)	C-5	C-6 (C-2)	C-7	C-3a[c] (C-5)	C-7a[c] (C-4)	C-1′	C-2′	C-3′	C-4′	C-5′	2-C=O	2-CH_3
1	139.1	132.4[e]	104.8	123.8	98.7	133.7	140.4	84.4	–[e]	70.6	87.4	61.7		
2	141.4	108.7[d]	109.2	122.9[d]	123.0[e]	135.2	145.9	84.9	–[e]	70.0	87.5	61.6		
4	139.0	119.5	111.5	135.6[e]	94.1	134.2	145.1	83.9	–[e]	70.6	87.2	61.7		
5	141.2	102.6	125.3[e]	112.3	111.1	144.2	144.9	84.3	–[e]	70.5	87.2	61.6		
7	139.5	132.2[e]	104.6	123.6	98.5	133.7	140.3	84.4	–[e]	70.5	87.6	61.5		
8b	146.1	135.6[e]	118.7	122.2	118.3	136.8	138.6	85.7	–[e]	70.7	88.9	61.8		
11	146.7	120.2	118.0	132.7[e]	108.6	143.3	148.1	82.0	36.7	74.9	85.2	64.2	165.4/.5	21.3/.3
12	145.9	116.0	137.3[e]	118.3	112.3	143.1	143.0	81.9	36.6	74.7	85.3	64.0	165.4/.5	21.3/.3
13	147.3	120.0	117.7	132.3[e]	108.8	143.1	148.3	85.1	–[e]	70.2	87.8	61.2		
14	146.0	115.7	137.3[e]	118.2	112.0	142.9	143.0	85.1	–[e]	70.2	87.8	61.2		
16	145.3	135.4[e]	119.0	122.3	118.5	136.8	138.8	81.8	36.5	74.5	85.2	63.9	165.3/.4	21.1/.2
17	144.1	126.3[d]	121.9	120.3[d]	147.0[e]	124.6	136.7	81.6	37.3	74.2	86.7	63.7	165.2/.2	21.1/.2
18	145.5	135.7[e]	118.7	122.2	118.5	136.8	138.6	85.0	–[e]	70.3	87.8	61.2		
19	144.6	126.3[d]	121.6	120.2[d]	124.6[e]	136.4	147.1	86.9	–[e]	69.7	87.5	60.8		
20	145.4	126.3[d]	121.9	121.8[d]	147.8	124.4[e]	136.6	83.9	38.2	75.0	89.2	64.1	165.1/.5	21.2/.3

[a] In DMSO-d_6 relative to TMS.
[b] Purine numbering in parenthesis.
[c,d] Tentative assignment.
[e] Superimposed by DMSO-d_6.

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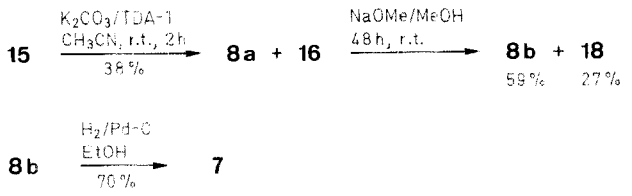

Compound **8a** could not be separated chromatographically from its β-anomer **16** so that the ratio of anomers (**8a**: **16** = 2:1) had to be estimated from the integrals of the H-2 singlets in the ^{1}H-NMR spectrum. Deprotection of the anomeric mixture **16/8a** with 1 M NaOMe/MeOH solution gave the crystalline nucleosides **18** and **8b** which were now obtained separately upon chromatographic purification. The structure of the α-nucleoside **8b** was confirmed by spectroscopic data including ^{1}H-NMR NOE difference spectroscopy (Table 1). Hydrogenation of **8b** yielded the α-anomer of 1,3-dideaza-2′-deoxyadenosine **(7)** obtained crystalline from ethanolic solution.

Table 4. $J_{C,H}$ Coupling Constants (Hz) of Benzimidazole 2′-Deoxyribofuranosides[a,b]

$J_{C,H}$	1	2	4	5	13	14	18	19
C-2,H-2	208.6	208.2	208.2	207.1	211.4	212.2	212.0	213.5
H-1′	4.0	3.4	3.0	3.8	3.6	3.7	3.4	3.1
C-4,H-4	m	162.4	158.8	157.3	196.3	169.0	m	164.7
H-6	–	8.1	–	5.1	–	4.6	–	8.2
C-5,H-5	150.5	156.3	156.7	m	169.4	m	166.8	165.9
H-7	5.8	–	5.5	–	4.2	–	–	–
C-6,H-4	–	–	–	5.6	–	4.5	–	–
H-6	156.9	157.1	m	157.1	m[b]	169.1	166.1	167.1
C-7,H-5	8.3	m	5.7	–	5.0	–	8.5	m
H-7	165.1	–	159.9	161.9	171.8	170.6	167.1	–
C-3a	m	m	m	m	m	m	m	m
C-7a	m	m	m	m	m	m	m	m
C-1′,H-1′	162.7	164.8	163.2	162.0	167.7	165.8	165.8	172.0
C-2′,H-2′[c]	–	–	–	–	–	–	–	
C-3′,H-3′	148.0	150.7	151.5	150.3	148.6	148.5	150.7	148.6
C-4′,H-4′	148.0	148.5	146.7	146.2	147.8	146.4	146.6	147.9
C-5′,H-5′	138.7	139.7	139.4	139.6	139.5	140.5	139.1	139.4

[a] Spectra recorded in DMSO-d_6.
[b] Multiplets are unresolved.
[c] Superimposed by solvent signals.

Table 5. Glycosylation of compound **15**: Influence of Inorganic Base and Phase-transfer Catalyst on the Ratio (%) of Anomers and Regioisomers

Reaction Conditions	Product (Yield, %)	Reaction Time (min)
KOH/TDA-1	**16** (45), **17** (30), **20** (6)	30
KOH/[18]-6	**16** (49), **17** (32), **20** (8)	30
K_2CO_3/TDA-1	**16** (12), **8a** (26)	120
K_2CO_3/[18]-6	**16** (14), **8a** (27)	120

Table 6. Half-life Values and First Order Rate Constants (k) for the Hydrolysis of Benzimidazole 2′-Deoxyribofuranosides[a]

Compound	1 N HCl			1 N NaOH
	40 °C	60 °C	70 °C	40 °C
1	49 (1.41)	25 (2.77)	– –	60 (1.16)
2	– –	539 (0.12)	155 (0.45)	stable

[a] $\tau/2$ (min); k ($\times 10^{-2} \times$ min^{-1}).

The hydrolytic stability of benzimidazole 2′-deoxyribonucleosides to acid- and base-catalyzed hydrolysis was followed by UV-spectrophotometry. According to Table 6 the benzimidazole 2′-deoxynucleoside **1** hydrolyzes much slower in 1 N hydrochloric acid than the parent compound dA (**3a**, 25 °C, k = 2000 min^{-1}, $\tau/_2$ = 3.5 min).[19] This is in accordance with recently published results, benzimidazole nucleosides are generally more stable against acid than purine nucleosides.[20] Measurement of the pK_a led to values of approximately 0.7 and 4.5 (compound **1**) and 4.6 (compound **2**), whereas that of dA is 3.8.[21] The first protonation site of dA is N-1[22] whereas the site of protonation of **1** has to be different, most likely N-3 (first protonation) and NH_2 (second protonation). Within the regioisomers **1** and **2**, the hydrolysis rate of the latter is further increased by a factor of 20 (Table 6). The different stability of glycosylic bonds of regioisomeric nucleosides has already been reported for adenosine **(3b)** and its N-7 regioisomer **6**.[23] In contrast to **3b** and **6**, where greater stability was exhibited by the N-9 isomer, compound **2** was more stable compared to **1**.

Under alkaline conditions (1 N sodium hydroxide) compound **1** decomposes rapidly, whereas compound **2** is stable. If one assumes that alkaline degradation starts with nucleophilic attack of hydroxide ion at C-2 (C-8 in purine numbering) followed by ring opening as reported for adenosine,[24] the stability of **2** vs **1** could be explained by the lower electron density at C-2 in the case of **2**. This can be demonstrated by the canonical structures, which do not allow formation of a species with a positively charged C-2.

Adenosine deaminase, which rapidly converts dA into dI, does not deaminate $c^1c^3A_d$ (**1**; data not shown). This result supports earlier findings that the pyrimidine nitrogens (N-1, N-3) are required for enzymatic reaction.[25]

Compound **1** has about the same spatial requirements as the DNA-constituent 2′-deoxyadenosine (dA) but can form only one hydrogen bond of a regular Watson–Crick base pair with dT. Moreover, ligand binding is restricted via the minor groove at position-3[18] within a DNA-duplex. Therefore, its incorporation into oligonucleotides is of interest. Conversion of $c^1c^3A_d$ **(1)** into a suitable building block for automated oligonucleotide synthesis is in progress.

NMR spectra were recorded on a AC-250-Bruker spectrometer; operational frequencies 250.134 (^{1}H) and 62.898 (^{13}C) MHz; δ values relative to TMS as internal standard. UV spectra were measured on a 150-20-spectrophotometer (Hitachi, Japan). Melting points were determined on a Büchi-SMP-20 apparatus (Büchi, Switzerland) and are uncorrected. Microanalyses were performed by Mikroanalytisches Laboratorium Beller, Göttingen, FRG. Analytical TLC was performed on glass plates coated with a 0.25 mm layer of silica gel Sil G-25 with fluorescent indicator UV_{254} (Merck, FRG). Column flash chromatography (0.8 bar) was performed on silica gel 60 H (Merck, FRG). The columns were connected with a Uvicord S detector and an UltroRac II fraction collector (LKB Instruments, Sweden); solvent systems: A, CH_2Cl_2/EtOAc (8:2); B, $CHCl_3$/MeOH (8:2); C, $CHCl_3$/MeOH (9:1); D, CH_2Cl_2/EtOAc (1:1). The pK_a values were determined spectrophotometrically in Teorell–Stenhagen buffer[26]: compound **1** [0.7 (λ = 286 nm); 4.5 (λ = 250 nm)]; compound **2** [4.6 (λ = 261 nm)]. CH_3CN was distilled from CaH_2. Adenosine deaminase from calf intestine mucosa (EC 3.5.4.4; 5 mg/mL glycerol; 1 mg ≙ 200 units) was purchased from Boehringer, Mannheim. Deamination experiments were performed at 22 °C in a Hitachi 150-20 spectrophotometer with cuvettes of 1 cm light path length. Deamination was followed at λ_{max} = 265 nm.[28] The incubation mixture (1 mL) of 0.067 M Sörensen

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phosphate buffer (pH 7.0) contained 0.001 units adenosine deaminase; the concentration of the nucleoside was 0.04 μM. The acid- and alkaline catalyzed hydrolyses of **1** and **2** were followed UV spectrophotometrically on a Hitachi-3200 UV-spectrophotometer at $\lambda = 243$ nm and 253 nm, respectively.

Glycosylation of 5(6)-Nitrobenzimidazole (9) with 1-Chloro-2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-α-D-erythro-pentofuranose (10):

A suspension of 5(6)-nitrobenzimidazole[8,9] (**9**; 980 mg, 6.0 mmol) in anhydrous CH_3CN (300 mL) containing KOH (1.013 g, 18.0 mmol) and TDA-1[27] (178 mg, 0.6 mmol) is stirred at r.t. for 30 min. Compound **10**[10] (2.45 g, 6.3 mmol) is added and the stirring is continued for 2 h. Insoluble material is filtered off and the filtrate is adsorbed onto silica gel 60 (3 g). The dry residue is applied on the top of a silica gel column (50 × 5.5 cm). Compounds **11** and **12** are isolated by elution with solvent A.

1-[2-Deoxy-3,5-bis-O-(4-methylbenzoyl)-β-D-erythro-pentofuranosyl]-6-nitrobenzimidazole (**11**): From the slower migrating zone a colorless foam is isolated; yield: 1.2 g (39%); $R_f = 0.4$ (solvent A).

$C_{28}H_{25}N_3O_7$	calc.	C 65.24	H 4.89	N 8.15
(515.5)	found	65.31	5.01	8.03

UV (MeOH): $\lambda_{max} = 238$, 287 (sh), 298, 339 (sh) nm (log ε = 4.65, 3.96, 3.99, 3.46).

^{1}H-NMR (DMSO-d_6): δ = 2.36, 2.42 (2 s, 6 H, 2 CH_3); 2.89 (m, 1 H, H-2'$_b$); 3.11 (m, 1 H, H-2'$_a$); 4.56 (m, 2 H, H-5'); 4.66 (m, 1 H, H-4'); 5.73 (m, 1 H, H-3'); 6.78 (dd, 1 H, $J = 6.1$, 7.5 Hz, H-1'); 7.88 (d, 1 H, $J = 8.9$ Hz, H-4); 8.14 (dd, 1 H, $J = 2.1$, 8.9 Hz, H-5); 8.78 (d, 1 H, $J = 2.1$ Hz, H-7); 8.87 (s, 1 H, H-2); and H_{arom} of the protecting groups.

1-[2-Deoxy-3,5-bis-O-(4-methylbenzoyl)-β-D-erythro-pentofuranosyl]-5-nitrobenzimidazole (**12**): From the faster migrating zone colorless crystals are obtained after evaporation of the solvent; yield: 1.42 g (46%); mp 143–145°C; $R_f = 0.55$ (solvent A).

$C_{28}H_{25}N_3O_7$	calc.	C 65.24	H 4.89	N 8.15
(515.5)	found	65.16	4.86	8.11

UV (MeOH): $\lambda_{max} = 239$, 286 (sh), 298 nm (log ε = 4.71, 3.91, 3.95).

^{1}H-NMR (DMSO-d_6): δ = 2.38, 2.41 (2 s, 6 H, 2 CH_3); 2.88 (m, 1 H, H-2'$_b$); 3.11 (m, 1 H, H-2'$_a$); 4.59 (m, 3 H, H-4', 5'); 5.74 (m, 1 H, H-3'); 6.68 (dd, 1 H, $J = 6.1$, 8.0 Hz, H-1'); 7.96 (d, 1 H, $J = 8.8$ Hz, H-7); 8.04 (dd, 1 H, $J = 2.1$, 8.8 Hz, H-6); 8.55 (d, 1 H, $J = 2.1$ Hz, H-4); 8.80 (s, 1 H, H-2); and H_{arom} of the protecting groups.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-nitrobenzimidazole (13):

A solution of compound **11** (600 mg, 1.16 mmol), dissolved in a mixture of MeOH (20 mL) and 1 M NaOMe/MeOH (2.5 mL) is stirred for 48 h at r.t. The solid residue, obtained after evaporation of the solvent, is chromatographed (column 3 × 20 cm, solvent B); crystallization from MeOH affords colorless crystals; yield: 260 mg (80%); mp 211–212°C; $R_f = 0.5$ (solvent B).

$C_{12}H_{13}N_3O_5$	calc.	C 51.61	H 4.69	N 15.05
(279.3)	found	51.45	4.67	15.00

UV (MeOH): $\lambda_{max} = 234$, 299 nm (log ε = 4.19, 3.98).

^{1}H-NMR (DMSO-d_6): δ = 2.38 (m, 1 H, H-2'$_b$); 2.63 (m, 1 H, H-2'$_a$); 3.58 (m, 2 H, H-5'); 3.92 (m, 1 H, H-4'); 4.44 (m, 1 H, H-3'); 5.06 (m, 1 H, 5'-OH); 5.39 (m, 1 H, 3'-OH); 6.53 (pt, 1 H, $J = 6.3$ Hz, H-1'); 7.86 (d, 1 H, $J = 8.9$ Hz, H-4); 8.13 (dd, 1 H, $J = 2.2$, 8.9 Hz, H-5); 8.78 (d, 1 H, $J = 2.2$ Hz, H-7); 8.83 (s, 1 H, H-2).

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-nitrobenzimidazole (14):

In the same manner as described for the preparation of **13**, a solution of compound **12** (500 mg, 0.97 mmol) in MeOH (130 mL) and 1 M NaOMe/MeOH (2 mL) is stirred for 48 h at r.t. Silica gel 60 (2 g) is added and the solvent evaporated *in vacuo*. The dry material is applied on the top of a silica gel column (20 × 3.5 cm). Elution with solvent B furnishes a colorless foam (222 mg, 82%); $R_f = 0.6$ (solvent B).

$C_{12}H_{13}N_3O_5$	calc.	C 51.61	H 4.69	N 15.05
(279.3)	found	51.41	4.69	15.00

UV (MeOH): $\lambda_{max} = 238$, 300, 339 (sh) nm (log ε = 4.35, 3.93, 3.29).

^{1}H-NMR (DMSO-d_6): δ = 2.37 (m, 1 H, H-2'$_b$); 2.62 (m, 1 H, H-2'$_a$); 3.58 (m, 2 H, H-5'); 3.91 (m, 1 H, H-4'); 4.43 (m, 1 H, H-3'); 5.05 (t, 1 H, $J = 5.2$ Hz, 5'-OH); 5.41 (d, 1 H, $J = 4.1$ Hz, 3'-OH); 6.46 (pt, 1 H, $J = 6.6$ Hz, H-1'); 7.98 (d, 1 H, $J = 9.0$ Hz, H-7); 8.17 (dd, 1 H, $J = 2.1$, 9.0 Hz, H-6); 8.56 (d, 1 H, $J = 2.1$ Hz, H-4); 8.79 (s, 1 H, H-2).

6-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)benzimidazole (4):

A solution of compound **13** (120 mg, 0.43 mmol) in EtOH (60 mL) is hydrogenated in the presence of Pd/C (25 mg, 10% Pd) at room temperature and atmospheric pressure for 6 h. The catalyst is removed by filtration, and silica gel 60 (0.5 g) is added to the filtrate. The solvent is evaporated *in vacuo* and the dry residue applied onto a silica gel column (20 × 3 cm). Elution with solvent B and recrystallization from MeOH affords colorless crystals; yield: 80 mg (75%); mp 201–203°C (dec); $R_f = 0.2$ (solvent B).

$C_{12}H_{15}N_3O_3$	calc.	C 57.82	H 6.07	N 16.86
(249.3)	found	57.65	6.24	16.79

UV (MeOH): $\lambda_{max} = 220$ (sh), 257, 300 nm (log ε = 4.29, 3.81, 3.79).

^{1}H-NMR (DMSO-d_6): δ = 2.24 (m, 1 H, H-2'$_b$); 2.56 (m, 1 H, H-2'$_a$); 5.53 (m, 2 H, H-5'); 3.84 (m, 1 H, H-4'); 4.96 (t, 1 H, $J = 5.4$ Hz, 5'-OH); 5.02 (br s, 2 H, NH_2); 5.38 (d, 1 H, $J = 4.2$ Hz, 3'-OH); 6.13 (dd, 1 H, $J = 6.1$, 7.6 Hz, 1 H, H-1'); 6.54 (dd, 1 H, $J = 1.9$, 8.5 Hz, H-5); 6.69 (d, 1 H, $J = 1.9$ Hz, H-7); 7.30 (d, 1 H, $J = 8.5$ Hz, H-4); 8.09 (s, 1 H, H-2).

5-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)benzimidazole (5):

Hydrogenation of compound **14** (120 mg, 0.43 mmol) as described for the preparation of compound **4** affords colorless crystals from Et_2O; yield: 83 mg (77%); mp 156–157°C; $R_f = 0.25$ (solvent B).

$C_{12}H_{15}N_3O_3$	calc.	C 57.82	H 6.07	N 16.86
(249.3)	found	57.89	6.19	16.76

UV (MeOH): $\lambda_{max} = 259$ (sh), 309, 339 (sh) (log ε = 3.57, 3.56, 2.78).

^{1}H-NMR (DMSO-d_6): δ = 2.22 (m, 1 H, H-2'$_b$); 2.57 (m, 1 H, H-2'$_a$); 3.55 (m, 2 H, H-5'); 3.85 (m, 1 H, H-4'); 4.37 (m, 1 H, H-3'); 4.97 (m, 3 H, 5'-OH and NH_2); 5.36 (m, 1 H, 3'-OH); 6.23 (dd, 1 H, $J = 6.2$, 7.5 Hz, H-1'); 6.62 (dd, 1 H, $J = 1.9$, 8.6 Hz, H-6); 6.80 (d, 1 H, $J = 1.9$ Hz, H-4); 7.35 (d, 1 H, $J = 8.6$ Hz, H-7); 8.22 (s, 1 H, H-2).

Glycosylation of 4(7)-Nitrobenzimidazole (15) with 1-Chloro-2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-α-D-*erythro*-pentofuranose (10) in the Presence of KOH:

A solution of 4(7)-nitrobenzimidazole[8,16] (**15**; 980 mg, 6.0 mmol) in CH_3CN (175 mL) containing KOH (1.013 g, 18.0 mmol) and TDA-1 (178 mg, 0.6 mmol) is stirred at r.t. for 30 min. Compound **10** (2.45 g, 6.3 mmol) is added and stirring is continued for 30 min. Purification is achieved by flash-column chromatography (50 × 5.5 cm). Solvent A elutes three zones from which the compounds **16**, **17**, and **20** are isolated. (The same reaction is conducted with [18]crown-6 (159 mg, 0.6 mmol) instead of TDA-1; yields are summarized in Table 5).

1-[2-Deoxy-3,5-bis-O-(4-methylbenzoyl)-β-D-erythro-pentofuranosyl]-4-nitrobenzimidazole (**16**): From the slow migrating zone a yellowish foam is obtained; yield: 1.42 g (45%); $R_f = 0.50$ (solvent A).

$C_{28}H_{25}N_3O_7$	calc.	C 65.24	H 4.89	N 8.15
(515.5)	found	64.92	4.98	8.21

UV (MeOH): $\lambda_{max} = 239$, 278 (sh), 285, 309, 339 (sh) nm (log ε = 4.55, 3.77, 3.81, 3.91, 3.64).

^{1}H-NMR (DMSO-d_6): δ = 2.37, 2.41 (2 s, 6 H, 2 CH_3); 2.88 (m, 1 H, H-2'$_b$); 3.14 (m, 1 H, H-2'$_a$); 4.51–4.68 (m, 3 H, H-4', 5'); 5.76 (m, 1 H, H-3'); 6.70 (dd, 1 H, $J = 5.9$, 7.9 Hz, H-1'); 8.07 (d, 1 H, $J = 7.9$ Hz, H-5); 8.21 (d, 1 H, $J = 7.9$ Hz, H-7); 8.81 (s, 1 H, H-2).

1-[2-Deoxy-3,5-bis-O-(4-methylbenzoyl)-β-D-erythro-pentofuranosyl]-7-nitrobenzimidazole (**17**): From the second zone colorless crystals are obtained by crystallization from Et_2O; yield: 950 mg (30%); mp 124–125°C; $R_f = 0.55$ (solvent A).

$C_{28}H_{25}N_3O_7$	calc.	C 65.24	H 4.89	N 8.15
(515.5)	found	65.25	4.95	8.14

UV (MeOH): $\lambda_{max} = 240$, 273, 282, 321, 339 (sh) nm (log ε = 4.56, 3.59, 3.59, 3.67, 3.54).

^{1}H-NMR (DMSO-d_6): δ = 2.37, 2.40 (2 s, 6 H, 2 CH_3); 2.96 (m, 1 H, H-2'$_b$); 3.20 (m, 1 H, H-2'$_a$); 4.15 (dd, 1 H, $J = 6.1$, 12.1 Hz, H-5'); 4.42 (dd, 1 H, $J = 3.8$, 12.1 Hz, H-5''); 4.53 (m, 1 H, H-4'); 5.61 (m, 1 H, H-3'); 6.60 (pt, 1 H, $J = 5.8$ Hz, H-1'); 7.24–7.42 (m, 5 H, 4 toluoyl-H and H-6); 8.78 (s, 1 H, H-2); and H_{arom} of the protecting groups.

1-[2-Deoxy-3,5-di-O-(4-methylbenzoyl)-α-D-erythro-pentofuranosyl]-7-nitrobenzimidazole (**20**): From the fast zone a yellow foam is isolated; yield: 190 mg (6%); $R_f = 0.6$ (solvent A).

$C_{28}H_{25}N_3O_7$	calc.	C 65.24	H 4.89	N 8.15
(515.5)	found	65.21	4.92	8.13

UV (MeOH): $\lambda_{max} = 239$, 272 (sh); 282, 324, 339 (sh) nm (log ε = 4.53, 3.48, 3.46, 3.70, 3.60).

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^{1}H-NMR (DMSO-d_6): δ = 2.35, 2.40 (2 s, 6 H, 2 CH_3); 2.98 (m, 2 H, H-2'$_{a,b}$); 4.48 (m, 2 H, H-5'); 4.75 (m, 1 H, H-4'); 5.58 (M, 1 H, H-3'); 6.77 (d, 1 H, J = 5.2 Hz, H-1'); 7.44 (t, 1 H, J = 7.8 Hz, H-5); 8.02 (d, 1 H, J = 7.8 Hz, H-6); 8.15 (d, 1 H, J = 7.8 Hz, H-4); 8.86 (s, 1 H, H-2); and H_{arom} of the protecting groups.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-4-nitrobenzimidazole (18):
Using same route as described for the preparation of compound **13**, compound **18** is obtained from compound **16** (650 mg, 1.26 mmol), 1 M NaOMe/MeOH (2.6 mL) and MeOH (150 mL). The residue is purified on a silica gel column (20 × 3 cm) with solvent B. The product obtained from the main zone crystallizes from EtOH in colorless crystals; yield: 310 mg (88%); mp 159–161 °C; R_f = 0.6 (solvent B).

$C_{12}H_{13}N_3O_5$	calc.	C 51.61	H 4.69	N 15.05
(279.3)	found	51.48	4.76	15.11

UV (MeOH): λ_{max} = 218 (sh), 310 nm (log ϵ = 3.99, 3.91).

^{1}H-NMR (DMSO-d_6): δ = 2.40 (m, 1 H, H-2'$_b$); 2.66 (m, 1 H, H-2'$_a$); 3.59 (m, 2 H, H-5'); 3.93 (m, 1 H, H-4'); 4.45 (m, 1 H, H-3'); 5.06 (t, 1 H, J = 5.2 Hz, 5'-OH); 5.43 (d, 1 H, J = 4.1 Hz, 3'-OH); 6.49 (pt, 1 H, J = 6.6 Hz, H-1'); 7.48 (t, 1 H, J = 8.1 Hz, H-6); 8.08 (d, 1 H, J = 8.1 Hz, 1 H, H-5); 8.24 (d, 1 H, J = 8.1 Hz, H-7); 8.80 (s, 1 H, H-2).

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-7-nitrobenzimidazole (19):
Compound **19** is prepared as described for **13** by using compound **17** (650 mg, 1.26 mmol), 1 M NaOMe/MeOH (2.6 mL) and MeOH (150 mL). The residue is purified on a silica gel column (25 × 4 cm) with solvent C. Colorless needles from 2-propanol; yield: 299 mg (85%); mp 160–161 °C; R_f = 0.6 (solvent B).

$C_{12}H_{13}N_3O_5$	calc.	C 51.61	H 4.69	N 15.05
(279.3)	found	51.75	4.76	15.13

UV (MeOH): λ_{max} = 226 (sh), 318, 339 (sh) nm (log ϵ = 3.88, 3.78, 3.65).

^{1}H-NMR (DMSO-d_6): δ = 2.41–2.65 (m, 2 H, H-2'$_{a,b}$); 3.43 (m, 2 H, H-5'); 3.83 (m, 1 H, H-4'); 4.33 (m, 1 H, H-3'); 4.95 (t, 1 H, J = 5.1 Hz, 5'-OH); 5.36 (d, 1 H, J = 4.3 Hz, 3'-OH); 6.42 (pt, 1 H, J = 5.8 Hz, H-1'); 7.43 (t, 1 H, J = 8.0 Hz, H-5); 7.99 (d, 1 H, J = 8.0 Hz, H-6); 8.12 (d, 1 H, J = 8.0 Hz, H-4); 8.85 (s, 1 H, H-2).

4-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)benzimidazole (1,3-dideaza-2'-deoxyadenosine (1):
Hydrogenation of **18** (160 mg, 0.57 mmol) as described for the preparation of compound **4** gives colorless needles upon crystallization from EtOH; yield: 105 mg (74%); mp 180–181 °C; R_f = 0.3 (solvent B).

$C_{12}H_{15}N_3O_3$	calc.	C 57.82	H 6.07	N 16.86
(249.27)	found	58.02	6.21	16.97

UV (MeOH): λ_{max} = 221, 266, 291 nm (log ϵ = 4.40, 3.88, 3.73).

^{1}H-NMR (DMSO-d_6): δ = 2.26 (m, 1 H, H-2'$_b$); 2.57 (m, 1 H, H-2'$_a$); 3.55 (m, 2 H, H-5'); 3.85 (m, 1 H, H-4'); 4.37 (m, 1 H, H-3'); 4.95 (t, 1 H, J = 5.3 Hz, 5'-OH); 5.28 (s, 2 H, NH_2); 5.34 (d, 1 H, J = 4.2 Hz, 3'-OH); 6.24 (pt, 1 H, J = 7.0 Hz, H-1'); 6.39 (d, 1 H, J = 7.8 Hz, H-5); 6.78 (d, 1 H, J = 7.8 Hz, H-7); 6.93 (t, 1 H, J = 7.8 Hz, H-6); 8.23 (s, 1 H, H-2).

7-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)benzimidazole (2):
Compound **2** is prepared according to the procedure described for **4** from compound **19** (160 mg, 0.57 mmol), EtOH (70 mL) and Pd/C (35 mg, 10% Pd). Purification by column chromatography (2.5 × 5 cm, solvent B) and crystallization from 2-propanol yielded colorless crystals; yield: 109 mg (76%); mp 165–166 °C; R_f = 0.3 (solvent B).

$C_{12}H_{15}N_3O_3$	calc.	C 57.82	H 6.07	N 16.86
(249.3)	found	57.87	6.06	16.84

UV (MeOH): λ_{max} = 219, 265, 287 (sh) nm (log ϵ = 4.45, 3.86, 3.64).

^{1}H-NMR (DMSO-d_6): δ = 2.29, (m, 1 H, H-2'$_b$); 2.65 (m, 1 H, H-2'$_a$); 3.52 (m, 2 H, H-5'); 3.88 (m, 1 H, H-4'); 4.38 (m, 1 H, H-3'); 5.00 (t, 1 H, J = 5.2 Hz, 5'-OH); 5.15 (s, 2 H, NH_2); 5.36 (d, 1 H, J = 4.4 Hz, 3'-OH); 6.42 (dd, 1 H, J = 5.8, 7.9 Hz, H-1'); 6.55 (t, 1 H, J = 4.3 Hz, H-5); 6.92 (d, 2 H, J = 4.3 Hz, H-4, H-6); 8.27 (s, 1 H, H-2).

Glycosylation of 15 with 10 in the Presence of K_2CO_3. Anomeric 4-Nitro-1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranosyl]benzimidazoles (16/8a):
Compound **15** (980 mg, 6.0 mmol) is glycosylated as described except that K_2CO_3 (2.49 g, 18.0 mmol) is used instead of KOH with a reaction time of 2 h. Purification of the reaction mixture on a silica gel column (40 × 4 cm, solvent A) affords one main zone as yellowish foam; yield: 1.20 g (38%); contains compounds **16** and **8a**, as indicated by the ^{1}H-NMR spectrum; R_f = 0.5 (solvent A).

$C_{28}H_{25}N_3O_7$	calc.	C 65.24	H 4.89	N 8.15
(515.5)	found	65.10	4.96	8.02

^{1}H-NMR (DMSO-d_6): δ = 6.70 (dd, 1 H, J = 5.9, 7.9 Hz, H-1'$_\beta$), 6.78 (m, 1 H, H-1'$_\alpha$); 8.81 (s, 1 H, H-2$_\beta$), 8.84 (s, 1 H, H-2$_\alpha$).

1-(2-Deoxy-α-D-*erythro*-pentofuranosyl)-4-nitrobenzimidazole (8b):
The glycosylation mixture of **15** (1.20 g, 2.33 mmol) is dissolved in MeOH (250 mL) and then 1 M NaOMe/MeOH (5.1 mL) is added. Stirring is continued for 48 h and the solution evaporated to dryness. The residue is chromatographed on a silica gel 60 column (60 × 4 cm). Solvent B affords two zones, from which the content of the faster one (177 mg, 27%) is characterized as compound **18**. The content of the slower zone **8b** is crystallized from EtOH in light yellowish needles: yield: 382 mg (59%); mp 170–171 °C; R_f = 0.55 (solvent B).

$C_{12}H_{13}N_3O_5$	found	51.61	4.69	15.05
(279.3)	found	51.70	4.87	15.03

UV (MeOH): λ_{max} = 220 (sh), 312, 339 (sh) nm (log ϵ = 3.94, 3.86, 3.62).

^{1}H-NMR (DMSO-d_6): δ = 2.43 (dt, 1 H, J = 2.6, 14.3 Hz, H-2'$_b$); 2.78 (pq, 1 H, J = 7.2 Hz, H-2'$_a$); 3.49 (m, 2 H, 5'-H); 4.13 (m, 1 H, H-4'); 4.39 (m, 1 H, H-3'); 4.91 (t, 1 H, J = 5.6 Hz, 5'-OH); 5.46 (d, 1 H, J = 3.5 Hz, 3'-OH); 6.51 (dd, 1 H, J = 2.7, 7.3 Hz, H-1'); 7.51 (t, 1 H, J = 8.1 Hz, H-6); 8.09 (d, 1 H, J = 8.1 Hz, H-5); 8.20 (d, 1 H, J = 8.1 Hz, H-7); 8.75 (s, 1 H, H-2).

4-Amino-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)benzimidazole (7):
Hydrogenation of **8b** (200 mg, 0.72 mmol) gives **7** as colorless crystals; yield: 125 mg (70%); mp 180–182 °C (EtOH); R_f = 0.3 (solvent B).

$C_{12}H_{15}N_3O_3$	calc.	C 57.82	H 6.07	N 16.86
(249.3)	found	57.97	6.14	17.00

UV (MeOH): λ_{max} = 221, 266, 291 nm (log ϵ = 4.41, 3.89, 3.72).

^{1}H-NMR (DMSO-d_6): δ = 2.35 (dt, 1 H, J = 3.7, 14.0 Hz, H-2'$_b$); 2.73 (pq, 1 H, J = 6.9 Hz, H-2'$_a$); 3.50 (m, 2 H, H-5'); 4.02 (m, 1 H, H-4'); 4.34 (m, 1 H, H-3'); 4.87 (t, 1 H, J = 5.7 Hz, 5'-OH); 5.31 (br s, NH_2); 5.45 (d, 1 H, J = 3.9 Hz, 3'-OH); 6.24 (dd, 1 H, J = 7.4, 3.7 Hz, H-1'); 6.40 (d, 1 H, J = 7.2 Hz, H-5); 6.82 (d, 1 H, J = 7.2 Hz, H-6); 8.26 (s, 1 H, H-2).

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(29) Taken from the UV-curve in ref. 12.

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