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7-Functionalized 7-Deazapurine Ribonucleosides Related to 2-Aminoadenosine, Guanosine, and Xanthosine: Glycosylation of Pyrrolo[2,3-*d*]pyrimidines with 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose

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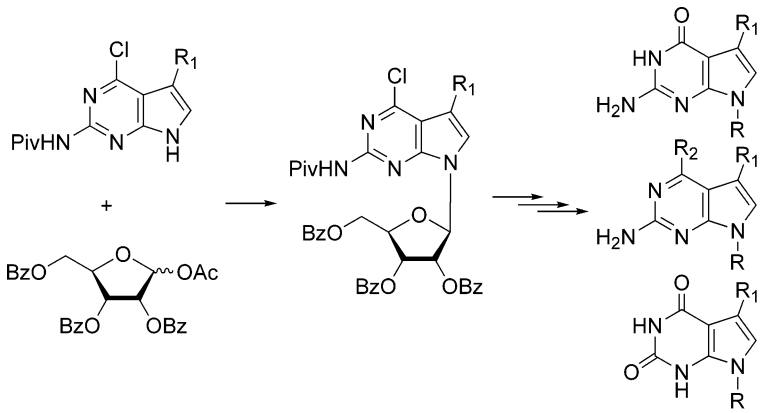

R = ribofuranosyl; R_1= Cl, Br, I, alkynyl, aminoalkynyl; R_2 = NH_2, Cl, OMe

The Silyl−Hilbert−Johnson reaction as well as the nucleobase−anion glycosylation of a series of 7-deazapurines has been investigated, and the 7-functionalized 7-deazapurine ribonucleosides were prepared. Glycosylation of the 7-halogenated 6-chloro-2-pivaloylamino-7-deazapurines **9b**−**d** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**5**) gave the *β*-D-nucleosides **11b**−**d** (73−75% yield), which were transformed to a number of novel 7-halogenated 7-deazapurine ribonucleosides (**2b**−**d**, **3b**−**d**, and **4b**−**d**) related to guanosine, 2-aminoadenosine, and xanthosine. 7-Alkynyl derivatives (**2e**−**i**, **3e**−**h**, or **4g**) have been prepared from the corresponding 7-iodonucleosides **2d**, **3d**, or **4d** employing the palladium-catalyzed Sonogashira cross-coupling reaction. The 7-halogenated 2-amino-7-deazapurine ribonucleosides with a reactive 6-chloro substituent (**18b**−**d**) were synthesized in an alternative way using nucleobase−anion glycosylation performed on the 7-halogenated 2-amino-6-chloro-7-deazapurines **13b**−**d** with 5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-α-D-ribofuranosyl chloride (**17**). Compounds **18b**−**d** have been converted to the nucleosides **19b**−**d** carrying reactive substituents in the pyrimidine moiety. Conformational analysis of selected nucleosides on the basis of proton coupling constants and using the program PSEUROT showed that these ribonucleosides exist in a preferred *S* conformation in solution.

Introduction

Several naturally occurring 7-deazapurine (pyrrolo[2,3-*d*]-pyrimidine) ribonucleosides, such as tubercidin (**1a**), toyocamycin (**1b**), and sangivamycin (**1c**; Scheme 1), exhibit a broad spectrum of biological activity (purine numbering is used throughout the general section).[1,2] The frequent natural occurrences and the biological properties of this class of compounds have promoted ample studies toward the synthesis, biological activity, and incorporation in oligonucleotides as well as the

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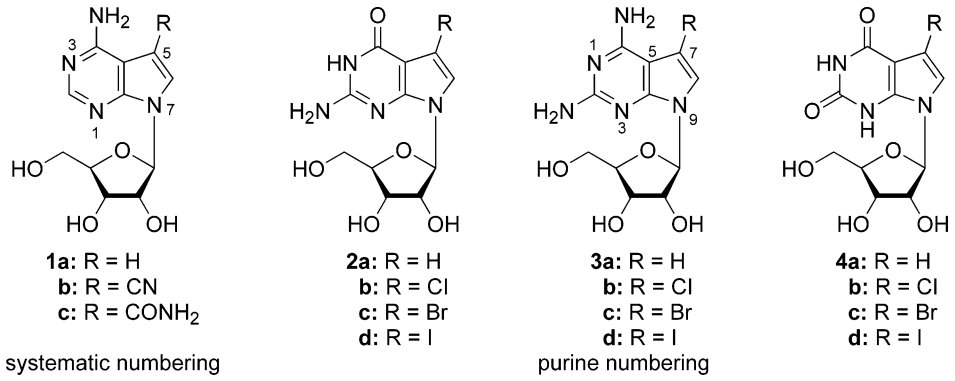
SCHEME 1. Structures of Nucleosides 1−4



chemically designed analogues.[3−7] The 7 position of 7-deazapurine is an ideal site for modifications that may lead to increasing antiviral activity,[1,8] to the introduction of reporter groups, to the modification of interference RNA, or to the enhancement of DNA or RNA duplex stability by substituents of moderate size, such as alkynyl residues or halogens.[4,7] Moreover, halogen-functionalized derivatives can be converted into biologically useful analogues by displacement reactions[9−14] or cross-coupling chemistry.[15−20] Thus, an efficient synthetic accessibility of the 7-functionalized 7-deazapurine ribonucleosides is of importance.

Considerable efforts have been expended in the development of methods for the chemical synthesis of the 7-deazapurine nucleosides related to tubercidin[3,6c] or 7-deazaguanosine.[6a,b] Different from the purine nucleoside, the synthesis by electrophilic glycosylation performed on the 7-deazapurines destroys the aromatic character of the pyrrole system. Consequently, the pyrrole nitrogen is rather inert against glycosylation with the result that the reaction is directed into the pyrimidine moiety[21a] or takes place at the pyrrole carbons.[21b,c] Therefore, the glycosylation reaction performed under acid-catalyzed conditions resulted in poor yields.[21,22] The development of stereoselective nucleobase−anion glycosylation made 7-deazapurine 2′-deoxyribonucleosides easily accessible.[23,24] This method was later applied to the synthesis of the 7-deazapurine ribonucleosides by using ribofuranosyl halides.[25−27] Unfortunately, ortho amides are formed by neighbor group participation when the sugar contains an acyl protecting group at the 2 position.[25,27a,b] This was circumvented when the nucleobase−anion glycosylation of a 7-deazapurine base was performed with a sugar halide protected at the 2,3-cis diol with an isopropylidene residue.[27c] By this means, 6-chloro- or 2-amino-6-chloro-7-deazapurine ribonucleosides were prepared under regio- and stereoselective control in good yield.[10,27a,28] As we became interested in the

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7-functionalized 7-deazapurine ribonucleosides, nucleobase−anion glycosylation was applied to the synthesis of such derivatives. However, it appeared that this protocol exhibited drawbacks for the synthesis of the 7-functionalized 7-deazapurine ribonucleosides, such as low coupling yields (Supporting Information) and a large consumption of nucleobases. This stimulated us to investigate the classical Silyl−Hilbert−Johnson reaction performed under Vorbrüggen conditions in more detail. Commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose was used as the sugar component.

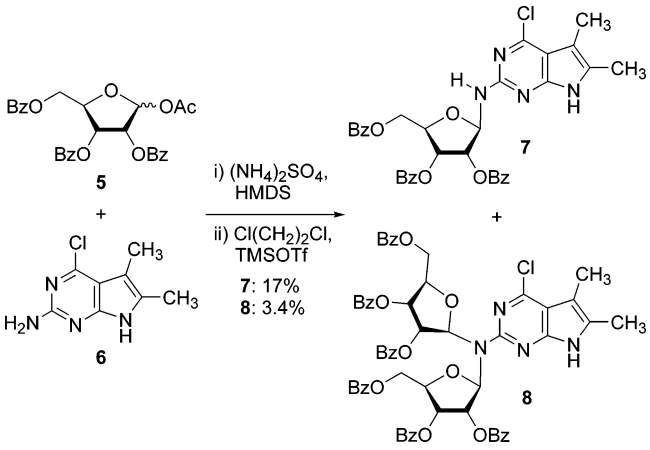
As previous work was concerned with the synthesis of the 7-deazapurine ribonucleosides related to tubercidin, this paper mainly focuses on the 7-functionalized 7-deazapurine ribonucleosides, such as the 7-deazaguanosines (**2b**−**d**), the 2-amino-7-deazaadenosines (**3b**−**d**), and the 7-deazaxanthosines (**4b**−**d**; Scheme 1). Two synthetic methods, nucleobase−anion glycosylation and Silyl−Hilbert−Johnson glycosylation, are compared. A rapid and efficient synthesis of 2-pivaloylamino-6,7-dihalogenated 7-deazapurine ribonucleosides is described. The resulting ribonucleosides were used in various displacement reactions to yield compounds **2b**−**d**, **3b**−**d**, and **4b**−**d**. Among those, the 7-iodo compounds **2d**, **3d**, or **4d** are particularly useful as intermediates for introducing alkynyl or aminoalkynyl groups via the Pd-catalyzed Sonogashira cross-coupling reaction.

Results and Discussion

This manuscript focuses on glycosylation reactions performed on the 7-deazapurines (pyrrolo[2,3-*d*]pyrimidines) with two different ribose derivatives, namely, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**5**) and 5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-α-D-ribofuranosyl chloride. The 7-deazapurines are functionalized at the 2, 6, and 7 positions. The exocyclic amino group is protected or nonprotected, depending on the protocol of the glycosylation reaction. The glycosylation protocols were altered (nucleobase−anion glycosylation vs Silyl−Hilbert−Johnson reaction) and the reaction conditions were changed to provide reliable and convenient procedures for the preparation of the 7-halogenated 7-deazapurine ribonucleosides. Although it will be shown that the Silyl−Hilbert−Johnson glycosylation can be applied efficiently to the 7-deazapurines with various substituents at different positions, reactive groups (e.g., halogen substituents) being present in the pyrimidine moiety are displaced during subsequent deprotection of the sugar or the base moiety. In these particular cases, it is still advisable to employ nucleobase−anion glycosylation with isopropylidene-protected sugar derivatives. This will be discussed in the second part of the manuscript, and examples will be given.

Glycosylation of the Nucleobases 9b−d with 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (5). Earlier, it has been shown for the 7-deazapurines nonfunctionalized at the 7 or 8 position that the acid-catalyzed glycosylation is directed to the pyrrole carbons.[21b,c] To prevent the unwanted side reaction, the 2-amino-7,8-dimethyl-7-deazapurine (**6**) was employed at first in the glycosylation studies. The coupling reaction of the base **6** with the sugar **5** was performed in dichloroethane using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the catalyst. Although the reaction proceeded smoothly, it resulted in a

SCHEME 2. Glycosylation of Compound 6 with Sugar Derivative 5



mixture of the N(2)-monoglycosylated nucleoside **7** and the N(2)-bis-glycosylated compound **8** (Scheme 2). The structural assignment of compounds **7** and **8** was made on the basis of ^{1}H and ^{13}C NMR spectra (Supporting Information). The ^{1}H NMR spectrum of the nucleoside **7** shows two N−H signals, a singlet at 11.46 ppm corresponding to the proton at N(9), and a doublet at 8.24 ppm corresponding to the proton at N(2). The spectrum of the nucleoside **8** shows two sets of sugar signals and only one for the base moiety; the ^{1}H NMR spectrum of compound **8** did not show a proton signal at 8.24 ppm, which is observed for nucleoside **7**. This confirms that the sugar is not attached directly to the nucleobase but is linked to the exocyclic amino group. After treatment of **7** and **8** with NH_3/MeOH, glycosylic bond cleavage was observed.

Therefore, the 2-amino group was protected with a sterically demanding pivaloyl residue (see compounds **9b**−**d**; Scheme 3).[14,29] The nucleobases were silylated with hexamethyldisilazane (HMDS), and the subsequent glycosylation was performed in dichloroethane with the sugar **5** using TMSOTf as the catalyst. Only the glycosylation of the 7-iodo compound **9d** with the sugar **5** afforded the β-D-nucleoside **11d** (45% yield, Supporting Information). The glycosylation of the 7-chloro or 7-bromo functionalized nucleobases **9b**,**c** with **5** failed.

Recently, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as the silylating reagent, CH_3CN as the solvent, and TMSOTf as the catalyst were employed for the synthesis of 7-fluoro-7-deazaadenosine, following the modified Vorbrüggen procedure.[30,31] Thus, the glycosylation of **9b**−**d** with the sugar **5** was performed under the same conditions. Nevertheless, the glycosylation reaction did not take place at room temperature. Therefore, the reaction was performed at different temperatures and reaction times. When the reaction was carried out at temperatures higher than 60 °C, the sugar decomposed and the glycosylation yield was low even when a large excess of the sugar component was consumed. Consequently, the temperature of the reaction was varied. It was found that, within a temperature range of 40−60 °C and using a twofold excess of the sugar component, the conditions were optimal and the nucleobases were completely

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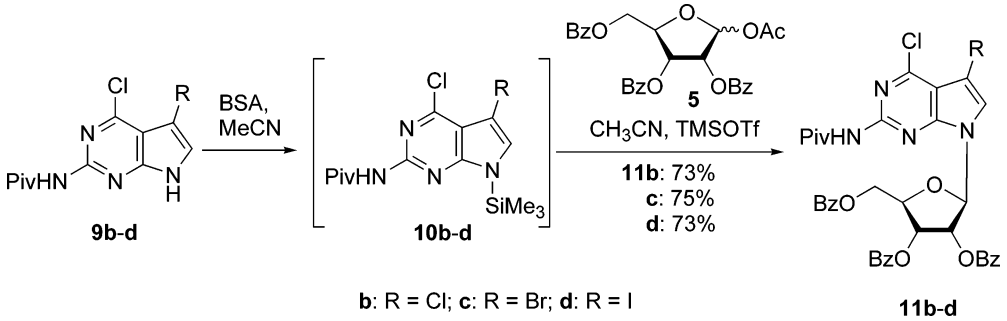
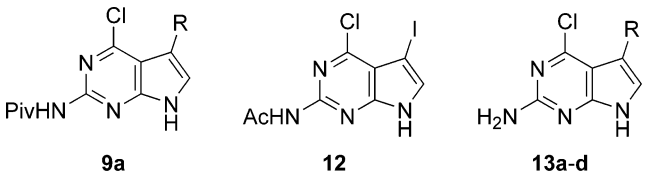
SCHEME 3. Synthesis of Nucleosides 11b−d



SCHEME 4. Structures of Nucleobases 9−13



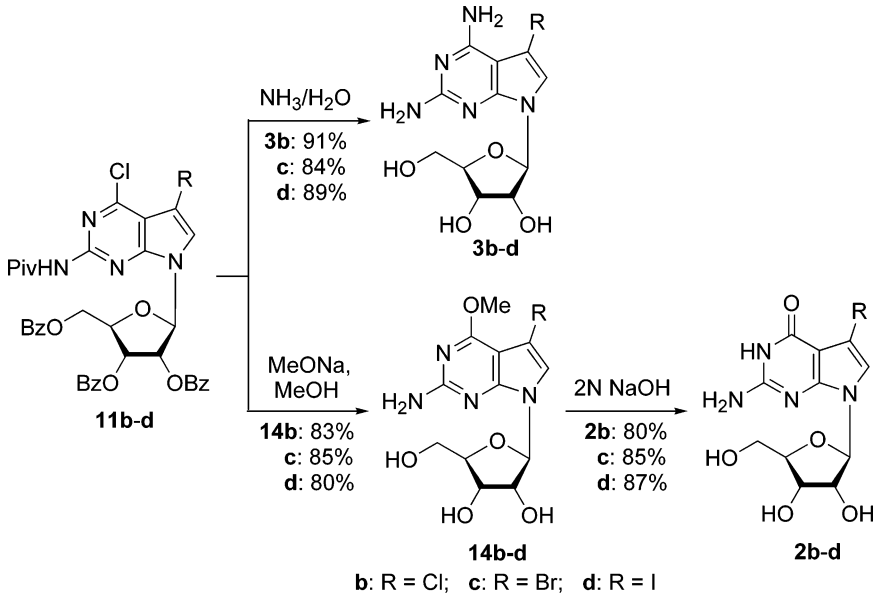
consumed within 24 h (TLC, CH_2Cl_2/MeOH, 99:1). This protocol afforded the highest glycosylation yields of the protected β-D-ribonucleosides **11b−d** (73−75%) when the nucleobases **9b−d** were employed (Scheme 3). Then, compounds **11b−d** were transformed to a series of ribonucleosides, namely, the guanosine analogues **2b−d**, the 2-amino-7-deazaadenosines **3b−d**, and the 7-deazaxathosine derivatives **4b−d**, by nucleophilic displacement reactions. This will be discussed in the next section.

Surprisingly, we were not able to perform the glycosylation under the same reaction conditions with compound **9a** not functionalized at the 7 position using the same protected ribofuranose **5**. Also, the glycosylation of nucleobase **12** protected at the 2-amino group with an acetyl residue or the 2-amino unprotected nucleobases **13a−d** failed (Scheme 4). Up to now, we have no good explanation for this finding. However, it seems likely that the electron-withdrawing 7-halogen substituents change the reactivity of the pyrrole nitrogens significantly, which might affect silylation as well as glycosylation.

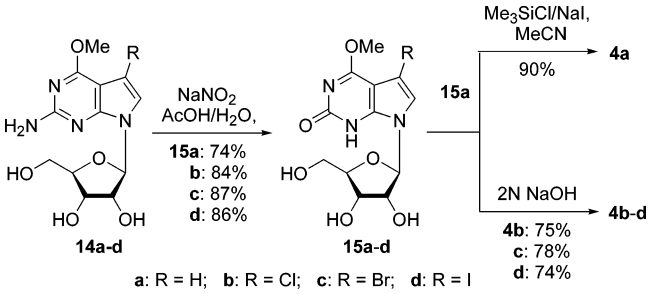
Conversion of Compounds 11b−d to the 7-Deazaguanine Ribonucleosides (2b−d), to the 2-Amino-7-deazaadenine Analogues (3b−d), and to the 7-Deazaxanthine Derivatives (4b−d). The 6- or 7-halogenated 2-amino-7-deazapurine nucleosides are useful intermediates for further manipulations using nucleophilic displacement reactions or palladium-catalyzed cross-coupling chemistry.[10,14,20,28] So, the transformation of the 6,7-dihalogenated 2-pivaloylamino-7-deazapurine ribonucleosides **11b−d** to several new 6,7-functionalized 2-amino-7-deazapurine ribonucleosides was studied. The 2,6-diamino ribonucleosides **3b−d** were obtained from compounds **11b−d** when treated with aq NH_3 (120 °C, 24 h, autoclave). Compounds **11b−d** were converted also to the 4-methoxy derivatives **14b−d** (0.5 M NaOMe, reflux, Supporting Information). The guanosine analogues **2b−d** became accessible from compounds **14b−d** (Scheme 5). The intermediately formed 4-methoxy nucleosides **14b−d** were converted to 7-deazaxanthine nucleosides **4b−d** (Scheme 6).

Next, the deamination of compounds **14b−d** or **14a**[10] with $NaNO_2$/AcOH was performed, resulting in the formation of the nucleosides **15a−d** (Scheme 6). Two methods, Me_3SiCl/NaI in CH_3CN or aq NaOH,[32] were employed for the demethylation (**15a−d** → **4a−d**). Compound **15a** was demethylated to give 7-deazaxanthosine **4a** with Me_3SiCl/NaI/CH_3CN (90% yield). However, this method cannot be applied to the conversion of the 7-halogenated nucleosides **15b−d** to 7-deazaxanthosine analogues **4b−d**. When compounds **15b**,**c** were treated with Me_3SiCl/NaI/CH_3CN, the 7-chloro or 7-bromo substituent was

SCHEME 5. Transformation of Intermediates 11b−d to the Nucleosides 2b−d and 3b−d



SCHEME 6. Transformation of 14a−d to the 7-Deazaxanthosine Derivatives 4a−d



partially displaced by iodine. Demethylation of **15d** with $Me_3SiCl/NaI/CH_3CN$ resulted in deiodination, and a mixture of **4a**,**d** (3:2) was formed. This was confirmed by ^1H and ^{13}C NMR spectra as well as by HPLC. Both ^1H and ^{13}C NMR spectra of the reaction products show two sets of nucleoside signals that correspond to the signals of pure **4a**,**d**, respectively. Furthermore, the HPLC profile of the reaction shows two product peaks that were identified using an artificial mixture of pure nucleosides **4a**,**d** (Figure 1). To avoid the unwanted side reactions occurring during demethylation of **15b**−**d**, the reaction was performed under alkaline conditions (2 N NaOH, reflux, 48 h). This resulted in a clean conversion of **15b**−**d** to the 7-deazaxanthosine derivatives **4b**−**d** (74−78% yield).

Palladium-Catalyzed Sonogashira Cross-Coupling Reaction. The introduction of alkynyl or aminoalkynyl side chains to the purine constituents of DNA or RNA has a major impact on their structure and stability,[33] their resistance to enzymatic degradation,[34] or an increased sensitivity of oligonucleotide detection by MALDI-TOF spectrometry.[35a,b] Also, the preparation of amino-functionalized oligonucleotides and their labeling with reporter groups has become an important tool of nucleic acid sequencing and diagnostics. The 7-iodo derivatives (**2d**, **3d**, and **4d**) of the 7-deazapurine ribonucleosides are particularly valuable intermediates for introducing alkynyl or aminoalkynyl groups because they can be used as starting materials in Pd-catalyzed cross-coupling reactions.[20] Thus, the 7-iodo-7-deazapurine ribonucleosides **2d**, **3d**, and **4d** were employed as precursors in the palladium-catalyzed Sonogashira cross-coupling reaction, yielding a number of novel 7-alkynyl or aminoalkynyl 7-deazapurine ribonucleosides **2e**−**i**, **3e**−**h**, or **4g** (Scheme 7). The coupling reaction was performed in anhydrous DMF with tetrakis(triphenylphosphine)palladium(0), copper(I) iodide, and triethylamine under argon and resulted in 50−92% yields of the alkynyl derivatives (Supporting Information).

Glycosylation of the Nucleobases 13b−d with 5-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-α-D-ribofuranosyl Chloride (17). As described above, the 7-functionalized 7-deazapurine ribonucleosides related to 2-amino-

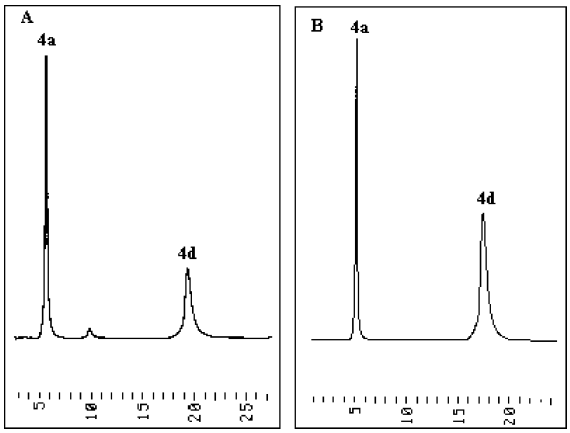


FIGURE 1. Reverse-phase HPLC (RP-18) profiles of (A) reaction products obtained after demethylation of **15d** using Me_3SiCl/NaI; (B) a mixture of nucleosides **4a**,**d** and the reaction products of the demethylation. The nucleoside mixtures were analyzed by reverse-phase HPLC at 260 nm on an RP-18 column (200 × 10 cm). Gradient: 0−20 min 100% A, 20−40 min 0−65% B in A, and 40−60 min 65−0% B in A. Flow rate = 0.7 mL/min [A, 0.1 M $(Et_3NH)OAc$ (pH 7.0)/MeCN, 95:5; B, MeCN].

noadenosine, guanosine, and xanthosine became easily accessible by using the 2-pivaloylamino nucleosides **11b**−**d** as precursors. However, the pivaloyl group of compounds **11b**−**d** is rather stable against hydrolysis and cannot be removed under mild basic conditions. Thus, nucleosides with labile residues at the 6 position of the pyrimidine moiety, such as a chloro substituent, cannot be prepared from these intermediates. Consequently, nucleobase−anion glycosylation was employed for the preparation of the 7-substituted 2-amino-6-chloro-7-deazapurine ribonucleosides.

It was found that the nucleobase−anion glycosylation of 2-pivaloylamino-7- deazapurines **9b**−**d** with the halogenose **17** did not occur. Also, 2-acetyl-protected nucleobase **12** gave a rather low yield (8%, Supporting Information). It is likely that the nucleophilicity of the pyrrole nitrogen is reduced when the 2-amino group is protected. Regarding the regioselectivity of the halogenation of the 2-amino-7-deazapurines, the protection of the 2-amino group is absolutely necessary.[14] As the trifluoroacetyl group is stable enough for such purposes and can be removed rather easily, we selected this group for the protection of compound **13a**. The latter was treated with trifluoroacetic anhydride in pyridine to give the protected derivative **16** (Scheme 8, Supporting Information). The regioselective 7-iodination of **16** with *N*-iodosuccinimide in CH_2Cl_2 followed by deprotection with NH_3/MeOH yielded the 7-iodo derivative **13d** (Supporting Information).

Next, the glycosylation of **13d** with 5-*O*-[(1,1-dimethylethyl)-dimethylsilyl]-2,3-*O*-(1-methylethylidene)-α-D-ribofuranosyl chloride (**17**)[27c,28c] was performed in CH_3CN with a twofold excess of powdered KOH and 0.1 equiv of tris[2-(2-methoxyethoxy)]-ethylamine (TDA-1) under stirring at room temperature. The desired nucleoside, **18d**, was obtained in 50% yield. Subsequent deprotection of **18d** with 90% CF_3COOH at room temperature afforded the ribonucleoside **19d** (90% yield). Encouraged by the successful synthesis of nucleoside **19d**, we then applied this protocol to the preparation of the 7-chlorinated and 7-brominated analogues. Nucleobase−anion glycosylation of **13b**,**c** (Supporting Information) with sugar chloride **17** yielded **18b**,**c** in 48−51% yield. Deprotection of the nucleosides **18b**,**c** under the conditions described for **18d** resulted in nearly quantitative

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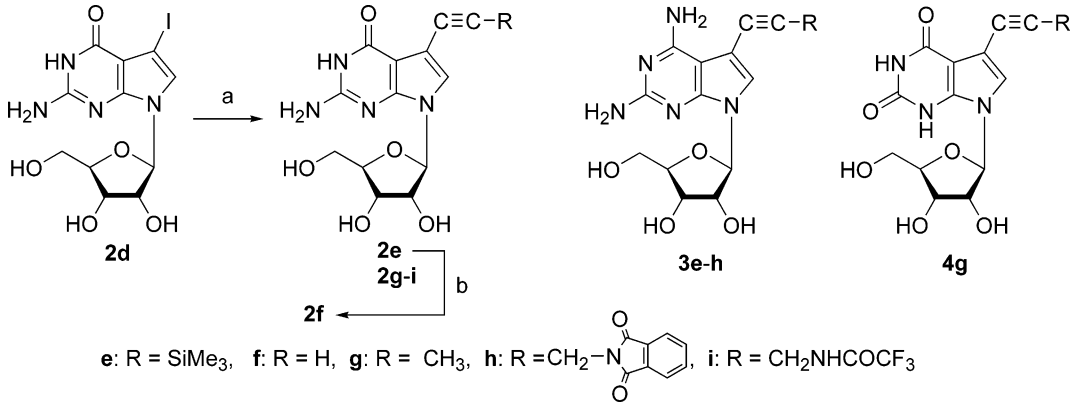
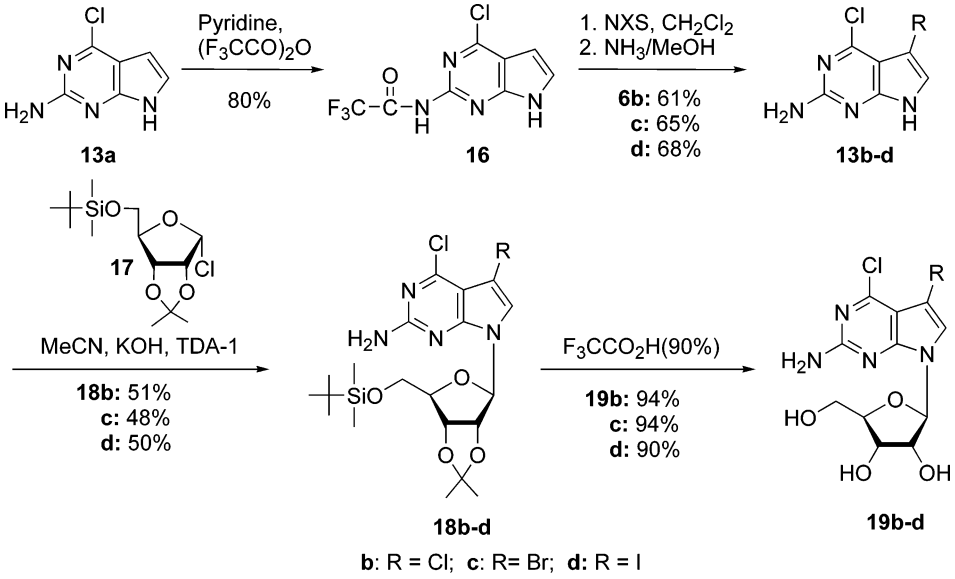
SCHEME 7. Synthesis of the 7-Alkynyl-7-Deazapurine Nucleosides (2e−i)[a]



[a] Reagents and conditions: (a) HC≡CR, anhydrous DMF, Pd(0)$(PPh_3)_4$, CuI, Et_3N; (b) MeOH, K_2CO_3.

SCHEME 8. Halogenation and Nucleobase−Anion Glycosylation



yields of compounds **19b**,**c**. The moderate glycosylation yield of the 7-halogenated bases **13b**−**d** with **17** is caused by the low solubility of compounds **13b**−**d**. Also, the electron-withdrawing property of the halogen atoms might reduce the electron-donating ability of the 7-deazapurine (pyrrolo[2,3-*d*]-pyrimidine) anion and decrease its nucleophilicity.

All compounds were characterized by ^{1}H NMR (Experimental Section and Supporting Information) and ^{13}C NMR spectra (Table 1) as well as by elemental analysis (Experimental Section). All nucleosides are assigned as β-D-anomers from the ^{1}H and ^{13}C NMR spectra, referring to earlier work.[10,28c,35c] The assignments of the ^{13}C NMR chemical shifts are made according to related compounds.[10,14,32] Compared to the nonfunctionalized compound, the C-7 signal is shifted upfield about 13 ppm upon bromination (**2c**, **3c**, **4c**, and **15c**), about 50 ppm upon iodination (**2d**, **3d**, **4d**, and **15d**), and 4 ppm upon alkynylation, but the signal is shifted downfield upon chlorination (about 3 ppm for **2b**, **3b**, **4b**, and **15b**).

Physical Properties of 7-Deazapurine Ribonucleosides (pK_a Values and Sugar Ring Conformation). The pK_a values and the conformational parameters of nucleosides can affect base pairing and duplex stability. Therefore, particular ribonucleosides were selected for data determination. The pK_a values of nucleosides **2**−**4** were measured by spectrophotometric titration[36] (pH 1.5−13.5) at 220−350 nm (Supporting Information). As shown in Table 2, the pK_a values of the 7-halogenated compounds **2b**−**d**, **3b**−**d**, and **4b**−**d** are lower than those of the corresponding nonfunctionalized nucleosides **2a**, **3a**, and **4a**, while the 7-alkynyl nucleosides **2f**,**g** show very similar pK_a values as the parent compounds.

A conformational analysis of the sugar moieties of nucleosides **2b**, **3c**, and **4b**,**c** was performed next on the basis of proton−proton coupling constants using the program PSEUROT (version 6.3).[37a,b] The default electronegativity values described in the manual PSEUROT 6.3 were used.[37a] The parameters *A* and *B* were taken from the published work of Altona and coworkers.[37c] In the PSEUROT program, a minimization of the

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TABLE 1. ^{13}C NMR Chemical Shifts of the 7-Deazapurine Ribonucleosides 2−19[a]

compd[b,c]	C(2)[d] C(2)	C(4)[d] C(6)	C(4a) C(5)	C(5) C(7)	C(6) C(8)	C(7a)[d] C(4)	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)
2a[10]	152.6	158.7	100.2	102.3	117.3	151.2	86.1	73.7	70.6	84.6	61.8
2b	153.0	157.4	97.1	106.2	114.3	150.4	85.6	73.6	70.4	84.7	61.5
2c	152.9	157.6	98.1	90.3	116.7	150.8	85.6	73.6	70.4	84.7	61.5
2d	152.6	158.0	99.8	55.1	122.0	151.2	85.6	73.6	70.5	84.7	61.5
3a[10]	159.7	157.9	96.5	100.1	118.3	152.8	86.9	73.7	70.8	84.7	62.0
3b	160.2	157.1	93.4	103.2	115.0	152.3	85.7	73.4	70.5	84.7	61.6
3c	160.0	157.2	94.5	87.4	117.5	152.7	85.8	73.4	70.5	84.7	61.6
3d	159.7	157.5	96.5	52.3	123.0	153.2	85.8	73.3	70.6	84.7	61.7
4a	150.8	159.6	99.7	103.1	118.4	138.4	85.5	74.0	70.7	89.3	61.4
4b	150.5	158.4	96.5	107.3	115.3	138.2	85.7	74.2	70.6	89.2	61.3
4c	151.1	158.7	97.3	91.1	117.5	140.1	85.7	74.0	70.6	89.1	61.3
4d	150.3	158.9	99.1	56.3	122.9	139.0	85.7	74.1	70.6	89.1	61.3
11b	152.3	150.6	110.0	103.4	125.9	150.5	87.6	71.2	73.9	79.2	63.6
11c	152.3	151.4	111.4	88.1	129.4	151.1	88.0	71.5	74.1	79.4	63.8
11d	151.7	151.5	113.2	54.0	128.3	151.2	87.5	71.2	73.8	79.1	63.6
14b	159.8	162.7	95.0	103.2	116.6	153.7	85.6	73.5	70.5	84.7	61.5
14c	159.7	162.8	96.3	87.2	119.1	154.2	85.6	73.5	70.5	84.8	61.5
14d	159.4	162.8	98.7	51.7	124.4	154.7	85.6	73.4	70.5	84.7	61.5
15a	159.3	164.0	98.5	99.4	121.2	*e*	85.0	73.7	70.6	85.0	61.5
15b	160.8	163.8	96.7	103.4	118.3	152.4	86.6	73.8	70.5	85.1	61.4
15c	160.5	163.8	98.2	87.3	120.8	152.3	86.5	73.8	70.5	85.1	61.4
15d	160.2	163.8	100.4	52.0	125.9	*e*	86.6	73.7	70.5	85.1	61.4
18b	159.5	150.7	105.0	103.3	120.8	152.5	88.4	80.4	83.6	86.2	63.3
18c	159.4	151.1	106.1	87.8	123.3	152.9	88.4	80.5	83.7	86.2	63.4
18d	159.1	151.8	108.1	53.7	128.7	153.3	88.5	80.5	83.7	86.1	63.4
19b	159.5	150.5	104.9	103.1	120.4	153.4	85.7	73.6	70.4	85.0	61.4
19c	159.4	150.9	106.0	87.5	122.9	153.7	85.8	73.6	70.4	85.0	61.4
19d	159.0	151.5	108.0	53.3	128.4	154.1	85.7	73.6	70.5	85.0	61.4

[a] Measured in d_6-DMSO. [b] First heading row = systematic numbering. [c] Second heading row = purine numbering. [d] Tentative. [e] Not detected.

TABLE 2. pK_a Values of the 7-Deazapurine Ribonucleosides 2−4[a]

compd	wavelength[b] (nm)	pK_a	compd	wavelength[b] (nm)	pK_a
2a	304	10.2	**3b**	285	4.9
2b	304	9.7	**3c**	285	4.8
2c	304	9.8	**3d**	287	4.9
2d	304	9.7	**4a**	260	6.5
2f	307	10.1	**4b**	260	6.0
2g	305	10.2	**4c**	260	6.1
3a	285	5.7	**4d**	260	6.1

[a] Measured in phosphate buffer (7.8 g $NaH_2PO_4 \cdot H_2O$ in 500 mL H_2O) from pH 1.5 to pH 13.5. [b] Wavelength with the most significant absorbance change.

differences between the experimental and the calculated couplings is accomplished by a nonlinear Newton−Raphson minimization; the quality of the fit is expressed by the root-mean-square (rms) difference. This procedure presupposes the existence of a two-state *N*/*S* equilibrium (Figure 2). The input contained the following coupling constants: *J*(H1′,H2′), *J*(H2′,H3′), and *J*(H3′,H4′). During the iterations, the puckering amplitudes of both conformers were constrained. The coupling constants *J*(H1′,H2′), *J*(H2′,H3′), and *J*(H3′,H4′) and the pseudorotational parameters are shown in Table 3. For detailed procedures of the PSEUROT calculation, refer to refs 29 and 37b.

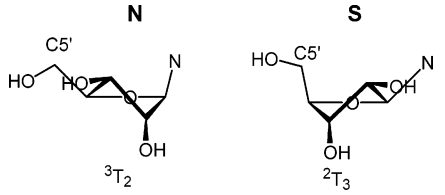

FIGURE 2. *N* and *S* conformers of ribonucleosides.

TABLE 3. $^3J_{H,H}$ Coupling Constant of the Sugar Moieties and Conformer Population of the Ribonucleosides Guanosine (G), 2b, 3c, and 4b,c[a]

	$^3J_{H,H}$ [Hz]			pseudorotational parameters[b]				
compd	1′,2′	2′,3′	3′,4′	%*S*	%*N*	P_S (deg)	P_N (deg)	rms (Hz)
G[c]	6.00	5.20	3.60	66	34	141.3	−13.4	0.000
2b	5.96	5.33	3.59	66	34	137.8	−20.8	0.000
3c	6.30	5.39	3.00	69	31	186.9	56.3	0.000
4b	6.32	5.64	2.70	69	31	198.1	76.3	0.000
4c	6.16	5.56	2.82	70	30	196.5	67.5	0.000

[a] Measured in D_2O. [b] Ψ_N (deg) = 32 and Ψ_S (deg) = 35 were fixed during the final minimization. [c] Electronegativities are taken from PSEUROT, version 6.3; parameters *A* and *B* are taken from Altona et al.;[37c] and experimental coupling constants are taken from Chattopadhyaya et al.[38e]

According to Table 3, it is apparent that the 7-halogenated 7-deazapurine ribonucleosides show a preferred *S* conformer population in solution, which is similar to the corresponding 2′-deoxyribonucleosides.[14,29,32] This is also in line with the sugar conformation of tubercidin (**1a**) and toyocamycin (**1b**) found in the crystalline state adopting an *S*-type pucker.[38a−d] Compared to the 2-amino-7-deazaadenosine derivative **3c** or the 7-deaza-xanthosine analogues **4b**,**c**, 7-deazaguanine ribonucleoside **2b** shifts the $N \leftrightarrows S$ equilibrium toward the *N* conformation (Table 3). Our data are similar to those of the corresponding canonical purine ribonucleosides described by Chattopadhyaya and co-workers.[38e] This suggests that purine or the 7-deazapurine ribonucleosides prefer the *S* conformation in solution while the *N* conformation is found for pyrimidine ribonucleosides (such

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as cytidine)[38e] or for purine ribonucleosides with the 5′-hydroxyl groups being phosphorylated, as reported by Altona and Sundaralingam.[38a]

Conclusion

According to the literature, the synthesis of the 7-deazapurine ribonucleosides is accomplished with difficulties.[21a,39] This results from the reactivity differences of the pyrrole versus the imidazole systems. While imidazole nitrogens are easily attacked by electrophilic sugar cations, the free electron pair of the pyrrole nitrogen is rather inert, as its electron pair is part of the aromatic π system. Even though a number of methods have been developed for the synthesis of the 7-deazapurine ribonucleosides using activated sugar halides such as the chloromercury salt procedure,[40] fusion reactions,[22,39] the indoline−indole method,[41] the Wittenburg procedure,[21a,42] the nucleobase−anion glycosylation,[25−27] and so forth, the outcome of these procedures is disappointing.[3] The glycosylation was directed into the pyrimidine moiety,[21a] takes place at the pyrrole carbons,[21b,c] or resulted in poor yields.[22,40,41]

In the present investigation it was observed that the TMSOTf-catalyzed glycosylation of the 7-deazapurines with the ribosugar **5** depends strongly on the silylation reagent,[31] the substituents of the base moiety, and a carefully selected temperature. As a result of the inertness of the pyrrole nitrogen, the silylating step becomes important. When the silylation was carried out with BSA in MeCN and the glycosylation was performed in the same solution (one-pot reaction), the yields were generally high. This was not the case in the two-step protocol—silylation with HMDS/$(NH_4)_2SO_4$ and the removal of the reagent by distillation (first step), followed by the glycosylation in dichloroethane (second step). The two-step procedure even failed in some cases. To avoid the exocyclic amino group competing with the pyrrole nitrogen in the glycosylation reaction, a bulky group was provided for the protection of the 2-amino group (**9b**−**d**). Electron-withdrawing substituents (such as halogens) on the 7-deazapurine moiety facilitate the glycosylation reaction; 7-deazapurines without 7-substituents resist glycosylation. A temperature range of 40−60 °C was optimal; higher temperatures caused extensive decomposition of the sugar. When all parameters were carefully chosen, the synthesis of the 7-functionalized 7-deazapurine ribonucleosides became efficient. Glycosylation of the 2-pivaloylamino-6,7-dihalogenated 7-deazapurines **9b**−**d** with the sugar **5** afforded the β-D-nucleosides **11b**−**d** in excellent yields (73−75%). The 7-deazaguanosine analogues **2b**−**d**, the 2-amino-7-deazaadenosines **3b**−**d**, and the 7-deazaxanthosine derivatives **4b**−**d** were prepared from **11b**−**d** by nucleophilic displacement reactions. The 7-iodo compounds **2d**, **3d**, or **4d** were converted to the 7-alkynyl or 7-aminoalkynyl derivatives (**2e**−**i**, **3e**−**h**, or **4g**) by palladium-catalyzed cross-coupling chemistry. Conformational analysis of the sugar moieties of nucleosides **2b**, **3c**, and **4b**,**c** disclose that these ribonucleosides prefer the *S* conformation in aq solution.

Experimental Section

4,5-Dichloro-2-pivaloylamino-7-[(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (11b). General Procedure for the Preparation of 11b−d. Into a stirred suspension of 4,5-dichloro-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*] pyrimidine[14] (**9b**, 574 mg, 2.0 mmol) in anhydrous MeCN (14 mL) was added BSA (97%, 0.6 mL, 2.41 mmol) at room temperature. After stirring for 5 min, TMSOTf (0.50 mL, 2.59 mmol) was added and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose[43] (**5**; 2.02 g, 4.0 mmol) was introduced in three portions (once per 8 h). In total, the reaction was stirred at 50 °C (oil bath) for 24 h, cooled to room temperature, and diluted with CH_2Cl_2 (50 mL). The solution was washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a syrup, which was applied to flash chromatography (FC) on silica gel (column 4 × 12 cm, solvent CH_2Cl_2). The main zone afforded compound **11b** as a yellowish foam (1.07 g, 73%). TLC (silica gel, CH_2Cl_2/MeOH, 99:1): R_f 0.30. UV (MeOH): λ_{max} 231 nm (ϵ 48 100), 254 nm (ϵ 34 500), 275 nm (ϵ 8800), 281 nm (ϵ 8700). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 1.19 (s, 9H, 3Me), 4.61−4.86 [m, 3H, H−C(4′), H−C(5′)], 6.35−6.38 and 6.41−6.44 [2m, 2H, H−C(3′), H−C(2′)], 6.52 [d, J = 3.7 Hz, 1H, H−C(1′)], 7.42−7.49 (m, 6H, aromatic), 7.63−7.65 (m, 3H, aromatic), 7.88−7.96 (m, 6H, aromatic), 8.03 [s, 1H, H−C(6)], 10.39 (s, 1H, NH). Anal. Calcd for $C_{37}H_{32}Cl_2N_4O_8$ (731.58): C, 60.74; H, 4.41; N, 7.66. Found: C, 60.72; H, 4.30; N, 7.65.

5-Bromo-4-chloro-2-pivaloylamino-7-[(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (11c). Compound **11c** was prepared as described for **11b** using 5-bromo-4-chloro-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*] pyrimidine[14] (**9c**, 663 mg, 2.0 mmol) and **5** (2.02 g, 4.0 mmol). Compound **11c** was obtained as a pale yellow foam (1.17 g, 75%). TLC (silica gel, CH_2Cl_2/MeOH, 99:1): R_f 0.30. UV (MeOH): λ_{max} 232 nm (ϵ 48 200), 254 nm (ϵ 34 600), 275 nm (ϵ 8200), 281 nm (ϵ 8100). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 1.16 (s, 9H, 3Me), 4.60−4.84 [m, 3H, H−C(4′), H−C(5′)], 6.34−6.37 and 6.42−6.47 [2m, 2H, H−C(3′), H−C(2′)], 6.50 [d, J = 3.6 Hz, 1H, H−C(1′)], 7.40−7.49 (m, 6H, aromatic), 7.62−7.65 (m, 3H, aromatic), 7.86−7.93 (m, 6H, aromatic), 8.01 [s, 1H, H−C(6)], 10.38 (s, 1H, NH). Anal. Calcd for $C_{37}H_{32}ClBrN_4O_8$ (776.03): C, 57.27; H, 4.16; N, 7.22. Found: C, 57.57; H, 4.01; N, 7.08.

4-Chloro-5-iodo-2-pivaloylamino-7-[(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (11d). As described for **11b**, compound **11d** was prepared from 4-chloro-5-iodo-2-pivaloylamino-7*H*-pyrrolo[2,3-*d*] pyrimidine[14] (**9d**, 757 mg, 2.0 mmol) and **5** (2.02 g, 4.0 mmol). Compound **11d** was obtained as a yellowish foam (1.2 g, 73%). TLC (silica gel, CH_2Cl_2/MeOH, 99:1): R_f 0.30. UV (MeOH): λ_{max} 230 nm (ϵ 48 000), 253 nm (ϵ 34 600), 273 nm (ϵ 9300), 283 nm (ϵ 9300). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 1.18 (s, 9H, 3Me), 4.62−4.85 [m, 3H, H−C(4′), H−C(5′)], 6.33−6.37 [m, 1H, H−C(3′)], 6.44−6.48 [m, 1H, H−C(2′)], 6.52 [d, J = 3.7 Hz, 1H, H−C(1′)], 7.42−7.47 (m, 6H, aromatic), 7.62−7.64 (m, 3H, aromatic), 7.89−7.94 (m, 6H, aromatic), 8.06 [s, 1H, H−C(6)], 10.34 (s, 1H, NH). Anal. Calcd for $C_{37}H_{32}ClIN_4O_8$ (823.03): C, 54.00; H, 3.92; N, 6.81. Found: C, 54.14; H, 4.30; N, 6.63.

5-Chloro-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2,4-diamine (3b). General Procedure for the Preparation of 3b−d. A suspension of **11b** (732 mg, 1.0 mmol) in dioxane (30 mL) and 25% aq NH_3 (70 mL) was introduced into an autoclave and stirred at 120 °C for 24 h. The volume of the clear solution was reduced to 10 mL and kept in the refrigerator for 24 h, affording

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colorless needles (287 mg, 91%), mp = 238 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 9:1): R_f 0.20. UV (MeOH): λ_{max} 228 nm (ϵ 34 800), 268 nm (ϵ 16 200), 289 nm (ϵ 9600). Anal. Calcd for $C_{11}H_{14}ClN_5O_4$ (315.71): C, 41.85; H, 4.47; N, 22.18. Found: C, 41.45; H, 4.35; N, 21.99.

5-Bromo-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2,4-diamine (3c). Compound **3c** was prepared from **11c** (512 mg, 0.66 mmol) as described for **3b**, affording colorless crystals (200 mg, 84%), mp = 238 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 9:1): R_f 0.20. UV (MeOH): λ_{max} 229 nm (ϵ 32 900), 269 nm (ϵ 11 100), 289 nm (ϵ 9000). Anal. Calcd for $C_{11}H_{14}BrN_5O_4$ (360.16): C, 36.68; H, 3.92; N, 19.44. Found: C, 36.87; H, 3.78; N, 19.34.

5-Iodo-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2,4-diamine (3d). Compound **11d** (1.14 g, 1.39 mmol) was converted to **3d** as described for **3b**, affording colorless crystals (500 mg, 89%), mp = 236 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 9:1): R_f 0.20. UV (MeOH): λ_{max} 231 nm (ϵ 35 000), 269 nm (ϵ 11 200), 289 nm (ϵ 9800). Anal. Calcd for $C_{11}H_{14}IN_5O_4$ (407.16): C, 32.45; H, 3.47; N, 17.20. Found: C, 32.59; H, 3.51; N, 17.36.

2-Amino-5-chloro-7-(β-D-ribofuranosyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (2b). General Procedure for the Preparation of 2b−d. Compound **14b** (149 mg, 0.45 mmol) was dissolved in 2 N NaOH (40 mL) and 1,4-dioxane (6 mL). The mixture was stirred under reflux for 3 h. After neutralization with 2 N HCl, the volume was reduced by 50%. The solution was applied to a Serdolit AD-4 column (3 × 12 cm, resin 0.1−0.2 mm). Salt was removed by elution with H_2O (150 mL), and the product was eluted with H_2O/*i*-PrOH (9:1, 500 mL). The fractions containing compound **2b** were combined; the solvent was evaporated to about 50 mL. Crystallization occurred overnight affording colorless crystals (114 mg, 80%), mp > 290 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 5:1): R_f 0.22. UV (MeOH): λ_{max} 220 nm (ϵ 22 400), 263 nm (ϵ 12 600), 287 nm (ϵ 6900). Anal. Calcd for $C_{11}H_{13}ClN_4O_5$ (316.70): C, 41.72; H, 4.14; N, 17.69. Found: C, 41.92; H, 4.46; N, 17.52.

2-Amino-5-bromo-3,7-dihydro-7-(β-D-ribofuranosyl)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (2c). Compound **14c** (199 mg, 0.53 mmol) was converted to **2c** as described for **2b**, affording colorless crystals (163 mg, 85%), mp > 290 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 5:1): R_f 0.23. UV (MeOH): λ_{max} 222 nm (ϵ 26 000), 262 nm (ϵ 12 300), 287 nm (ϵ 8200). Anal. Calcd for $C_{11}H_{13}BrN_4O_5$ (361.15): C, 36.58; H, 3.63; N, 15.51. Found: C, 37.02; H, 3.82; N, 15.11.

2-Amino-5-iodo-3,7-dihydro-7-(β-D-ribofuranosyl)-4*H*-pyrrolo-[2,3-*d*]pyrimidin-4-one (2d). Nucleoside **2d** was prepared from **14d** (422 mg, 1.0 mmol) as described for **2b**, affording colorless crystals (355 mg, 87%), mp > 239 °C (H_2O, decomposition) TLC (silica gel, CH_2Cl_2/MeOH, 5:1): R_f 0.28. UV (MeOH): λ_{max} 266 nm (ϵ 12 000), 287 nm (ϵ 8200). Anal. Calcd for $C_{11}H_{13}IN_4O_5$ (408.15): C, 32.37; H, 3.21; N, 13.73. Found: C, 32.58; H, 3.19; N, 13.67.

1,7-Dihydro-4-methoxy-7-(β-D-ribofuranosyl)-2*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (15a). General Procedure for the Preparation of 15a−d. To a solution of **14a** (297 mg, 1.0 mmol) in a mixture of glacial acetic acid and H_2O (v/v, 1:7, 60 mL) was added a solution of $NaNO_2$ (170 mg, 2.46 mmol) in H_2O (2.0 mL) dropwise while stirring at room temperature. The stirring was continued for 30 min, and the pH of the yellow solution was adjusted to 7.0 with 25% aq NH_3. The solution was applied to a Serdolit AD-4 column (4 × 20 cm, resin 0.1−0.2 mm). Salt was removed by washing with H_2O (200 mL), and the product was eluted with H_2O/MeOH (1:1, 300 mL). The volume of the combined fractions was reduced to about 20%, thereby forming colorless needles (220 mg, 74%), mp = 203 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 5:1): R_f 0.53. UV (MeOH): λ_{max} 223 nm (ϵ 26 000), 288 nm (ϵ 6900). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 3.50−3.64 [m, 2H, H−C(5′)], 3.87−3.89 [m, 1H, H−C(4′)], 3.95 (s, 3H, OMe), 4.04−4.05 [m, 1H, H−C(3′)], 4.27−4.29 [m, 1H, H−C(2′)], 5.11−5.29 [m, 3H, OH−C(5′), OH−C(3′), OH−C(2′)], 5.93 [d, J = 6.1 Hz, 1H, H−C(1′)], 6.37 [d, J = 3.5 Hz, 1H, H−C(5)], 7.22 [d, J = 3.5 Hz, 1H, H−C(6)], 11.39 (s, 1H, NH). Anal. Calcd for $C_{12}H_{15}N_3O_6$ (297.26): C, 48.48; H, 5.09; N, 14.14. Found: C, 48.56; H, 5.12; N, 14.08.

5-Chloro-1,7-dihydro-4-methoxy-7-(β-D-ribofuranosyl)-2*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (15b). By an identical procedure as described for **15a**, the deamination of **14b** (331 mg, 1.0 mmol) was performed yielding colorless needles of **15b** (279 mg, 84%), mp = 219 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 5:1): R_f 0.57. UV (MeOH): λ_{max} 229 nm (ϵ 22 700), 285 nm (ϵ 6200). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 3.51−3.62 [m, 2H, H−C(5′)], 3.86−3.87 [m, 1H, H−C(4′)], 3.98 (s, 3H, OMe), 4.04−4.05 [m, 1H, H−C(3′)], 4.26−4.28 [m, 1H, H−C(2′)], 5.10−5.12 [m, 2H, OH−C(5′), OH−C(3′)], 5.32 [d, J = 5.9 Hz, 1H, OH−C(2′)], 5.97 [d, J = 6.2 Hz, 1H, H−C(1′)], 7.44 [s, 1H, H−C(6)], 11.62 (s, 1H, NH). Anal. Calcd for $C_{12}H_{14}ClN_3O_6$ (331.71): C, 43.45; H, 4.25; N, 12.67. Found: C, 43.29; H, 4.15; N, 12.52.

5-Bromo-1,7-dihydro-4-methoxy-7-(β-D-ribofuranosyl)-2*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (15c). For the preparation of **15c**, compound **14c** (375 mg, 1.0 mmol) was treated as descibed for **15a**, yielding colorless crystals (327 mg, 87%), mp = 220 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 5:1): R_f 0.57. UV (MeOH): λ_{max} 226 nm (ϵ 23 600), 287 nm (ϵ 6400). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 3.44−3.62 [m, 2H, H−C(5′)], 3.85−3.87 [m, 1H, H−C(4′)], 3.98 (s, 3H, OMe), 4.04−4.05 [m, 1H, H−C(3′)], 4.26−4.28 [m, 1H, H−C(2′)], 5.10−5.12 [m, 2H, OH−C(5′), OH−C(3′)], 5.32 [br s, 1H, OH−C(2′)], 5.97 [d, J = 6.2 Hz, 1H, H−C(1′)], 7.48 [s, 1H, H−C(6)], 11.62 (s, 1H, NH). Anal. Calcd for $C_{12}H_{14}BrN_3O_6$ (376.16): C, 38.32; H, 3.75; N, 11.17. Found: C, 38.43; H, 3.86; N, 11.23.

1,7-Dihydro-5-iodo-4-methoxy-7-(β-D-ribofuranosyl)-2*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (15d). Compound **15d** was obtained by the deamination of **14d** (422 mg, 1.0 mmol) in the same way as described for **15a**, affording colorless needles (364 mg, 86%), mp = 220 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 5:1): R_f 0.57. UV (MeOH): λ_{max} 229 nm (ϵ 23 500), 287 nm (ϵ 6200). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 3.55−3.58 [m, 2H, H−C(5′)], 3.86−3.87 [m, 1H, H−C(4′)], 3.97 (s, 3H, MeO), 4.03−4.05 [m, 1H, H−C(3′)], 4.26−4.28 [m, 1H, H−C(2′)], 5.08−5.11 [br d, 2H, OH−C(5′), OH−C(3′)], 5.30 [d, J = 5.8 Hz, 1H, OH−C(2′)], 5.94 [d, J = 5.1 Hz, 1H, H−C(1′)], 7.48 [s, 1H, H−C(6)], 11.52 (s, 1H, NH). Anal. Calcd for $C_{12}H_{14}IN_3O_6$ (423.16): C, 34.06; H, 3.33; N, 9.93. Found: C, 33.98; H, 3.40; N, 9.87.

7-(β-D-Ribofuranosyl)-1,3,7-trihydro-2*H*,4*H*-pyrrolo[2,3-*d*]pyrimidin-2,4-dione (4a). To a suspension of **15a** (148 mg, 0.50 mmol) in MeCN was added NaI (113 mg, 0.75 mmol) and Me_3SiCl (99 μL, 0.78 mol) at room temperature while stirring. Stirring was continued for 1 h. The precipitated product was filtered and washed with MeCN to give **4a** as a colorless solid (127 mg, 90%). TLC (silica gel, CH_2Cl_2/MeOH, 5:1): R_f 0.38. UV (0.1 M NaH_2PO_4 in H_2O): λ_{max} 219 nm (ϵ 24 600), 252 nm (ϵ 10 400), 281 nm (ϵ 7300). Anal. Calcd for $C_{11}H_{13}N_3O_6$ (283.24): C, 46.65; H, 4.63; N, 14.84. Found: C, 46.54; H, 4.48; N, 14.81.

5-Chloro-7-(β-D-ribofuranosyl)-1,3,7-trihydro-2*H*,4*H*-pyrrolo-[2,3-*d*]pyrimidin-2,4-dione (4b). General Procedure for the Preparation of 4b−d. A solution of compound **15b** (200 mg, 0.60 mmol) in 2 N NaOH (40 mL) and 1,4-dioxane (6 mL) was stirred under reflux for 48 h. After neutralization with 2 N HCl and reducing the volume to 1/3, the solution was applied to a Serdolit AD-4 column (3 × 12 cm, resin 0.1−0.2 mm). The column was washed with H_2O (150 mL) to remove the salt, and the product was eluted with MeOH (200 mL). The fractions containing compound **4b** were combined, the volume was reduced to 20% of its original value, and compound **4b** was crystallized from H_2O as colorless crystals (143 mg, 75%), mp = 240 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 5:1): R_f 0.40. UV (0.1 M

NaH_2PO_4 in H_2O): λ_{max} 220 nm (ϵ 24 800), 255 nm (ϵ 10 500), 286 nm (ϵ 6400). Anal. Calcd for $C_{11}H_{12}ClN_3O_6$ (317.68): C, 41.59; H, 3.81; N, 13.23. Found: C, 41.15; H, 4.08; N, 13.20.

5-Bromo-7-(β-D-ribofuranosyl)-1,3,7-trihydro-2*H*,4*H*-pyrrolo-[2,3-*d*]pyrimidin-2,4-dione (4c). Compound **4c** was prepared from **15c** (188 mg, 0.5 mmol) as described for **4b**, yielding colorless crystals (141 mg, 78%), mp = 220 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 5:1): R_f 0.40. UV (0.1 M NaH_2PO_4 in H_2O): λ_{max} 222 nm (ϵ 24 000), 256 nm (ϵ 10 200), 285 nm (ϵ 6500). Anal. Calcd for $C_{11}H_{12}BrN_3O_6$ (362.13): C, 36.48; H, 3.34; N, 11.60. Found: C, 36.54; H, 3.46; N, 11.54.

5-Iodo-7-(β-D-ribofuranosyl)-1,3,7-trihydro-2*H*,4*H*-pyrrolo-[2,3-*d*]pyrimidin-2,4-dione (4d). The preparation of **4d** followed the protocol described for **4b** employing **15d** (351 mg, 0.83 mmol). Colorless crystals of **4d** were obtained (251 mg, 74%), mp = 230 °C (H_2O, decomposition). TLC (silica gel, CH_2Cl_2/MeOH, 5:1): R_f 0.40. UV (0.1 M NaH_2PO_4 in H_2O): λ_{max} 224 nm (ϵ 21 800), 258 nm (ϵ 9700), 285 nm (ϵ 6800). Anal. Calcd for $C_{11}H_{12}IN_3O_6$ (409.13): C, 32.29; H, 2.96; N, 10.27; I, 31.02. Found: C, 32.41; H, 3.12; N, 10.20; I, 30.74.

4,5-Dichloro-7-{5′-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2′,3′-*O*-(1-methylethylidene)-β-D-ribofuranosyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (18b). General Procedure for the Preparation of 18b−d. A suspension of powdered KOH (760 mg, 13.57 mmol) and TDA-1 (0.2 mL, 0.63 mmol) in MeCN (100 mL) was stirred for 10 min at room temperature. Compound **13b** (1.62 g, 7.98 mmol) was added, and the stirring was continued for 1 h. Then, freshly prepared 5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-α-D-ribofuranosyl chloride[27c,28c] (**17**, 1.29 mg, 4.0 mmol, calculated on the basis of 100% yield of **17**) was added to the stirred suspension, and the stirring was continued for 20 h at room temperature. Insoluble material was filtered off, the filtrate was evaporated to dryness, and the residue was applied to FC (silica gel, column 5 × 12 cm, elution with CH_2Cl_2). The fractions containing the desired material were collected and evaporated to dryness to give compound **18b** as a colorless foam (0.99 g, 51%). TLC (silica gel, CH_2Cl_2/MeOH, 99:1): R_f 0.17. UV (MeOH): λ_{max} 240 nm (ϵ 29 000), 265 nm (ϵ 3700), 324 nm (ϵ 5000). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.00 (s, 6H, Me_2Si), 0.84 (s, 9H, *t*-BuSi), 1.33 and 1.53 (2s, 6H, 2Me), 3.70−3.76 [m, 2H, H−C(5′)], 4.11−4.14 [m, 1H, H−C(4′)], 4.94−4.96 [dd, J = 3.3, 6.1 Hz, 1H, H−C(3′)], 5.13−5.14 [dd, J = 2.1, 6.1 Hz, 1H, H−C(2′)], 6.14 [d, J = 2.1 Hz, 1H, H−C(1′)], 7.03 (s, 2H, NH_2), 7.48 [s, 1H, H−C(6)]. Anal. Calcd for $C_{20}H_{30}Cl_2N_4O_4Si$ (489.45): C, 49.08; H, 6.18; N, 11.45. Found: C, 49.47; H, 6.05; N, 11.18.

5-Bromo-4-chloro-7-{5′-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2′,3′-*O*-(1-methylethylidene)-β-D-ribofuranosyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (18c). The procedure described for **18b** was applied to **18c** using **13c** (1.98 g, 8.0 mmol) and freshly prepared **17** (1.29 g, 4.0 mmol), yielding a yellowish foam (1.03 g, 48%). TLC (silica gel, CH_2Cl_2/MeOH, 99:1): R_f 0.17. UV (MeOH): λ_{max} 241 nm (ϵ 29 200), 267 nm (ϵ 3600), 324 nm (ϵ 4900). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.00 (s, 6H, Me_2Si), 0.84 (s, 9H, *t*-BuSi), 1.32 and 1.52 (2s, 6H, 2Me), 3.71−3.77 [m, 2H, H−C(5′)], 4.09−4.15 [m, 1H, H−C(4′)], 4.93−4.96 [dd, J = 3.4, 6.2 Hz, 1H, H−C(3′)], 5.11−5.15 [dd, J = 2.1, 6.2 Hz, 1H, H−C(2′)], 6.14 [d, J = 2.1 Hz, 1H, H−C(1′)], 7.00 (s, 2H, NH_2), 7.51 [s, 1H, H−C(6)]. Anal. Calcd for $C_{20}H_{30}BrClN_4O_4Si$ (533.93): C, 44.99; H, 5.66; N, 10.49. Found: C, 45.46; H, 5.76; N, 10.76.

4-Chloro-7-{5′-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2′,3′-*O*-(1-methylethylidene)-β-D-ribofuranosyl}-5-iodo-7*H*-pyrrolo[2,3-*d*]-pyrimidin-2-amine (18d). The procedure described for **18b** was applied to **18d** employing **13d** (2.36 g, 8.0 mmol) and freshly prepared **17**, resulting in a pink foam (1.16 g, 50%). TLC (silica gel, CH_2Cl_2/MeOH, 99:1): R_f 0.17. UV (MeOH): λ_{max} 244 nm (ϵ 29 700), 268 nm (ϵ 3700), 324 nm (ϵ 4900). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.00 (s, 6H, Me_2Si), 0.84 (s, 9H, *t*-BuSi), 1.31 and 1.51 (2s, 6H, 2Me), 3.65−3.70 [m, 2H, H−C(5′)], 4.09−4.12 [m, 1H, H−C(4′)], 4.90−4.95 [m, 1H, H−C(3′)], 5.08−5.12 [m, 1H, H−C(2′)], 6.12 [d, J = 2.0 Hz, 1H, H−C(1′)], 6.92 (s, 2H, NH_2), 7.51 [s, 1H, H−C(6)]. Anal. Calcd for $C_{20}H_{30}ClIN_4O_4Si$ (580.92): C, 41.35; H, 5.21; N, 9.64. Found: C, 41.16; H, 5.39; N, 9.60.

2-Amino-4,5-dichloro-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (19b). General Procedure for the Preparation of 19b−d. A solution of **18b** (979 mg, 2.0 mmol) in 90% aq CF_3-OOH solution (5 mL) was stirred for 1 h at room temperature. The mixture was evaporated, and traces of CF_3OOH were removed by coevaporation with MeOH. The residue was crystallized from MeOH, yielding colorless crystals (630 mg, 94%), mp = 185 °C. TLC (silica gel, CH_2Cl_2/MeOH, 9:1): R_f 0.29. UV (MeOH): λ_{max} 241 nm (ϵ 27 500), 267 nm (ϵ 3200), 324 nm (ϵ 4600). Anal. Calcd for $C_{11}H_{12}Cl_2N_4O_4$ (335.14): C, 39.42; H, 3.61; N, 16.72. Found: C, 39.43; H, 3.76; N, 16.33.

2-Amino-5-bromo-4-chloro-7-(β-D-ribofuranosyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidine (19c). Compound **18c** (902 mg, 1.69 mmol) was converted to the nucleoside **19c** as described for **19b**, yielding colorless crystals (603 mg, 94%), mp = 180 °C (MeOH). TLC (silica gel, CH_2Cl_2/MeOH, 9:1): R_f 0.29. UV (MeOH): λ_{max} 242 nm (ϵ 27 600), 268 nm (ϵ 3100), 325 nm (ϵ 4500). Anal. Calcd for $C_{11}H_{12}BrClN_4O_4$ (379.59): C, 34.80; H, 3.19; N, 14.76. Found: C, 34.90; H, 3.24; N, 14.44.

2-Amino-4-chloro-5-iodo-7-(β-D-ribofuranosyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidine (19d). Compound **19d** was prepared from **18d** (999 mg, 1.72 mmol) as described for **19b**, affording colorless crystals (660 mg, 90%), mp = 180 °C (MeOH). TLC (silica gel, CH_2Cl_2/MeOH, 9:1): R_f 0.30. UV (MeOH): λ_{max} 244 nm (ϵ 26 700), 268 nm (ϵ 3500), 324 nm (ϵ 4400). Anal. Calcd for $C_{11}H_{12}ClIN_4O_4$(426.59): C, 30.97; H, 2.84; N, 13.13. Found: C, 31.22; H, 3.00; N, 13.02.

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Supporting Information Available: The synthesis and characterization for compounds **6**−**8** and **12**; the procedures for the glycosylation of **8** with sugar chloride **17**; experimental details of the Pd-catalyzed cross-coupling reaction of **2d**, **3d**, and **4d**; characterization of compounds **2e**−**i**, **3e**−**h**, and **4g**; the synthesis and characterization of compounds **14b**−**d** from **11b**−**d**; the synthesis and characterization of the 7-halogenated bases **13b**−**d**; tables of ^{1}H NMR data; and pK_a measurements of compounds **2**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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