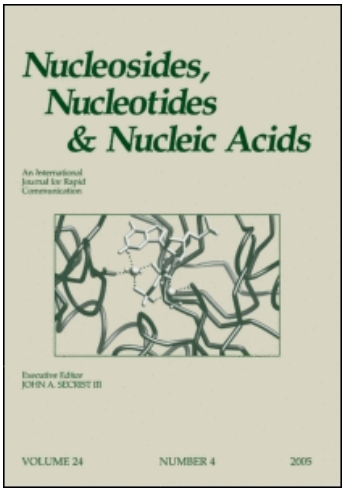

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STUDIES ON THE GLYCOSYLATION OF PYRROLO[2,3-*d*] PYRIMIDINES WITH 1-*O*-ACETYL-2,3,5-TRI-*O*-BENZOYL-β-D-RIBOFURANOSE: THE FORMATION OF REGIOISOMERS DURING TOYOCAMYCIN AND 7-DEAZAINOSINE SYNTHESES

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□ *Glycosylation of silylated 4-amino-6-bromo-5-cyano-7*H*-pyrrolo[2,3-*d*]pyrimidine (**9**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-*D*-ribofuranose (**10**) under "one-pot" glycosylation conditions (MeCN, TMSOTf) yielded the N-7 isomer **11** together with the N-1 compound **13** (ratio = 2:1). When the same conditions were applied to 4-hydroxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (**21**) the N-3 isomer **22** was the only glycosylation product formed in almost quantitative yield.*

Keywords Nucleosides; pyrrolo[2;3-*d*]pyrimidines; glycosylation; toyocamycin; 7-deazainosine; NMR-spectra

INTRODUCTION

The natural occurrence and the extraordinary biological and pharmacological properties of 7-deazapurine nucleosides have been the reason for studies on their synthesis, transformation, incorporation in nucleic acids, and the evaluation of their biochemical properties.[1–3] These subjects have already been treated in a number of reviews[4–12] (if not otherwise stated

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In honor and in celebration on the occasion of the 70th birthday of Morris J. Robins, a good friend and an outstanding scientist.

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systematic numbering is used throughout the manuscript). Pyrrolo[2,3-*d*]pyrimidine nucleosides are naturally occurring and have been isolated as monomers and as constituents of nucleic acids.[4,13] Among them are ribonucleosides such as tubercidin (**1a**) isolated from *Streptomyces tubercidicus* [14] as well as its 5-substituted derivatives toyocamycin (**1b**) and sangivamycin (**1c**) (Figure 1), which are produced by *Streptomyces toyocaensis* or other *Streptomyces* strains.[15,16] Other pyrrolo[2,3-*d*]pyrimidine nucleosides have been isolated from marine organisms, showing biological activity as metabolites or antimetabolites; some of them carry halogens at C-5-position of the pyrrolo[2,3-*d*]pyrimidine moiety such as 5′-deoxy-5-iodotubercidin (**2**).[17] Pyrrolo[2,3-*d*]pyrimidine ribonucleosides are also found as constituents of tRNA: Queuosine (**4b**) or archaeosine (**4c**) represent 7-subsituted 7-deazaguanine ribonucleosides, which are formed by post-modification of tRNA.[18] The parent compound 7-deazaguanosine (**4a**) does not occur in nature. It was synthesized in our laboratory in 1981.[19] Other naturally occurring pyrrolo[2,3-*d*]pyrimidine nucleoside antibiotics have been isolated, including mycalisines A (**3a**) and B (**3b**),[20,21] cadeguomycin (**4d**),[22] the antibiotic AB-116 (kanagawamicin, **5**),[23] and dapiramicin (**6**) (Figure 1).[24–26] Echiguanines A and B (**7a**,**b**) which can act as kinase

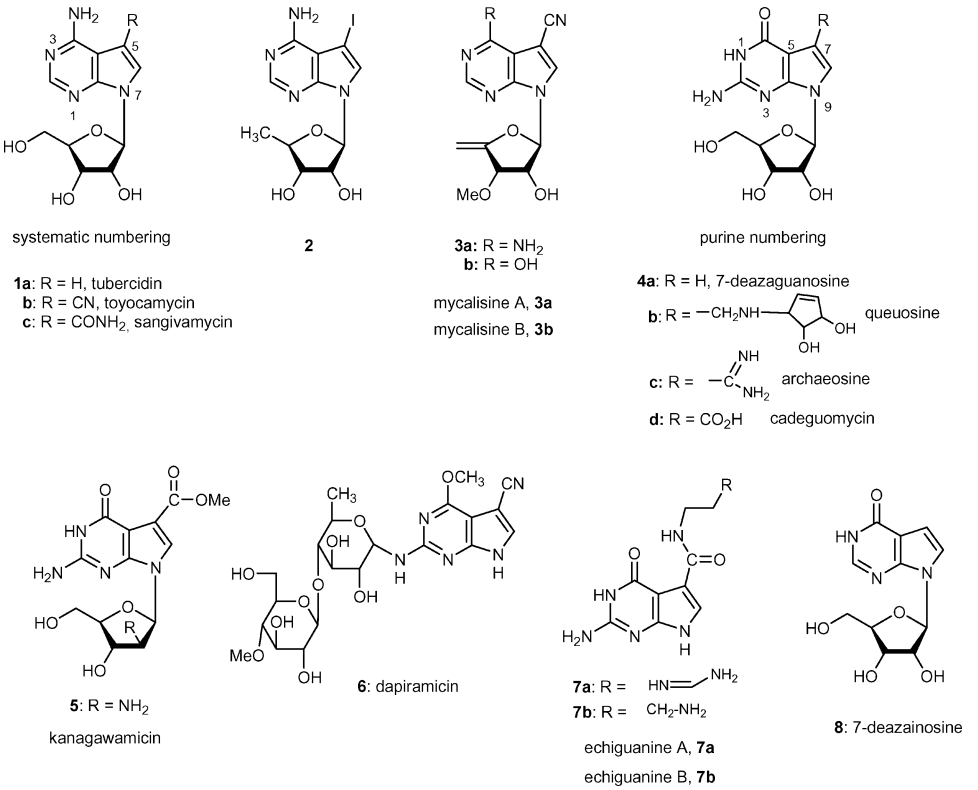


FIGURE 1

inhibitors have been isolated from *Streptomyces*[27] and were synthesized chemically,[28] 7-deazainosine (**8**) has been isolated from the ascidian *Aplidium pantherinum*[29] and was prepared in our laboratory as well as by others.[30, 31]

Considerable work has been done in the development of methods for the chemical synthesis of pyrrolo[2,3-*d*]pyrimidine nucleosides related to tubercidin (**1a**)[32,33] and its derivatives such as toyocamycin (**1b**) as well as 7-deazainosine (**8**).[30,31,34] Different to purine nucleosides, the synthesis by electrophilic attack of a sugar cation on the nitrogen of the pyrrolo[2,3-*d*]pyrimidines affects the aromatic character of the pyrrole system. Consequently, the pyrrole nitrogen is rather inert against glycosylation with the result that the reaction might be directed into the pyrimidine moiety[35] or takes place at the pyrrole carbons.[36,37] Glycosylation reactions performed on pyrrolo[2,3-*d*]pyrimidines under acidic conditions results in poor yields when the pyrrole moiety is not functionalized.[35–38] The development of the stereoselective nucleobase anion glycosylation and/or using activated ribo sugar derivatives (ribofuranosyl halides) made pyrrolo[2,3-*d*]pyrimidine 2′-deoxyribonucleosides easily accessible, but in the case ribonucleosides the reaction shows drawbacks as ortho amides are formed in many cases due to neighbour-group participation of sugar acyl protecting groups at the 2-position.[39–43] The current work focuses on the outcome of the glycosylation of the silylated nucleobases of toyocamycin (**1b**) and 7-deazainosine (**8**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**10**) in an "one-pot" reaction employing TMSOTf as catalyst and MeCN as solvent.

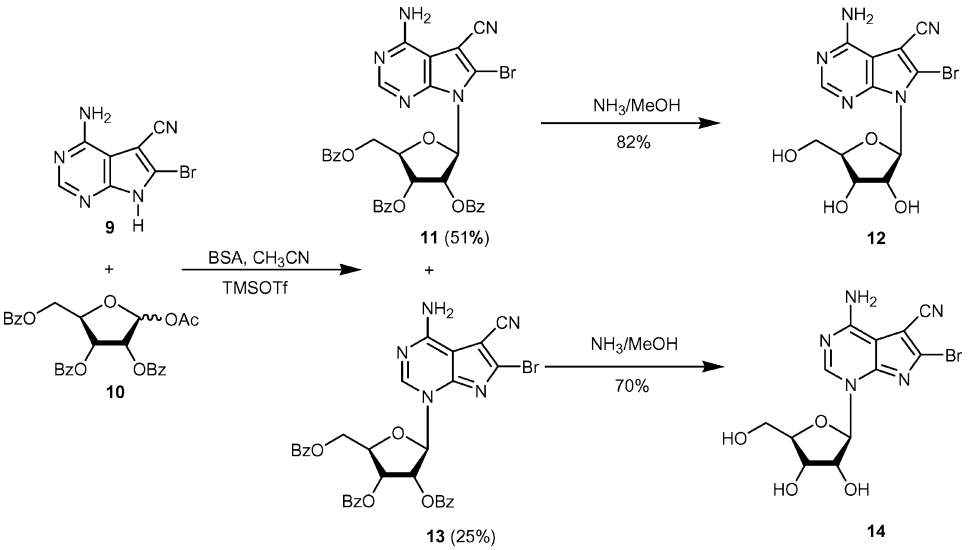
RESULTS AND DISCUSSION

1. Glycosylation of 4-amino-6-bromo-5-cyano-7*H*-pyrrolo [2,3-*d*]pyrimidine (9) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (10)

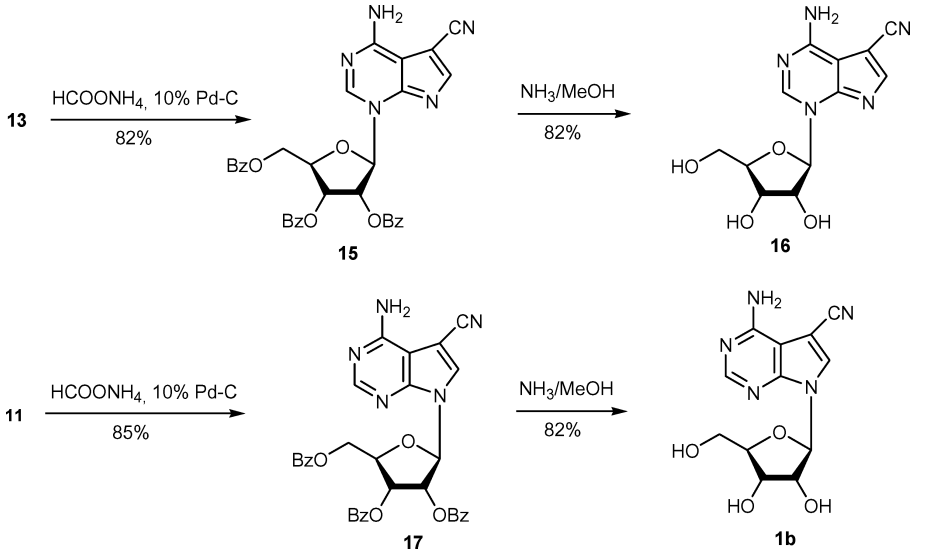
Earlier, the synthesis of toyocamycin (**1b**) was described by the laboratories of Bobek[44] and Townsend.[38,45] Both authors used 4-amino-6-bromo-5-cyano-7*H*-pyrrolo[2,3-*d*]pyrimidine (**9**) for the glycosylation and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**10**) as sugar component. Bobek employed a sequential silylation protocol with hexamethyldisilazane followed by trimethylsilyl chloride. The glycosylation of the silylated nucleobase was performed in dichloroethane with trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst at 80°C for 18 h resulting in a yield of 88% of compound **11**. Townsend described a "one-pot" procedure in which *N*,*O*-bis(trimethylsilyl)acetamide (BSA) was used as silylating agent, TMSOTf as catalyst and acetonitrile as solvent. Here, the reaction time was significantly shorter (3 hours at 80°C) and the yield was somewhat

lower (75%). Both authors described compound **11** as the only reaction product.

We performed the same reaction at exactly the same conditions as described by Townsend. For this purpose, 4-amino-6-bromo-5-cyano-7*H*-pyrrolo[2,3-*d*]pyrimidine (**9**) was prepared as described.[46a–c] Nucleobase **9** was silylated by the addition of 2 equivalents of BSA in dry acetonitrile at room temperature. Then, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**10**, 1 equivalent) and trimethylsilyl trifluoromethanesulfonate (3 equivalents) were added resulting in a clear yellow solution which was heated at 80°C for 3 hours. The formation of two main products (R_F 0.45, 0.64) was indicated by TLC (solvent CH_2Cl_2/EtOAc). Both compounds were separated by flash chromatrography and the slower migrating compound was characterized as compound **11** by comparison of the ^{1}H-NMR spectra according to data taken from the literature.[44,45] In our hands, compound **11** was isolated in 51% yield. Another compound, tentatively assigned as compound **13** was obtained in 25% (ratio = 2:1). The reaction was repeated several times under the same conditions to confirm a 2:1 ratio for the formation of the nucleosides **11** and **13**. Next, compounds **11** and **13** were treated with saturated methanolic ammonia furnishing the nucleoside **12** and the tentatively assigned **14** in 82% and 70% yield, respectively (Scheme 1). The formation of two regioisomeric glycosylation products was supported by a work of Bobek[47] on the same base **9**, but using an azido sugar in the glycosylation reaction. Two glycosylation products were obtained and their structures were assigned to N-7 and N-1 isomers.



SCHEME 1



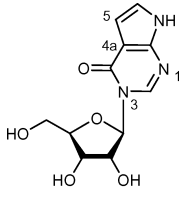
SCHEME 2

For debromination, the protected compounds **11** and **13** were refluxed in hot ethanol for 3 h with ammonium formate and 10% Pd/C to give the dehalogenated compounds **17** and **15**. Toyocamycin (**1b**) and the tentatively assigned isomer **16** were formed after debenzoylation in methanolic ammonia (Scheme 2). All compounds were characterized by ^{1}H- and ^{13}C- NMR spectra and elemental analyses. However, the structures of **16** and its precursors are still ambiguous. For assignment, ^{13}C-NMR spectra (Table 1) were measured and coupling constants (Table 2) were determined from gated-decoupled spectra. The signal for the C-2 was unambiguously assigned based on the ^{1}J (C-2, H-C-2) coupling (>200 Hz). Furthermore, the C-2 carbon of nucleoside **16** shows a ^{3}J (C-2, H-C-1′) coupling (3.8 Hz) to the anomeric proton giving a clear indication that the sugar is attached to the pyrimidine moiety. The C-4 signal is assigned by the ^{3}J (C-4, H-C-2) coupling (>11 Hz) to H-C-2. The C-4a signal appears as a singlet in case of the brominated nucleosides **12** and **14**. After removal of the bromine atom new couplings are observed to the H-C-6. C-4a shows a ^{3}J (C-4a, H-C-6) coupling (4.5 Hz) (compound **16**). For the C-5 carbon a ^{2} J (C-5, H-C-6) coupling (10.9 Hz) (compound **16)** is observed and the C-6 carbon gives a ^{1}J (C-6, H-C-6) coupling (188 Hz). The C-7a carbon shows a complex splitting pattern in all nucleosides due to a variety of proximal protons. Here, ^{3}J couplings are possible to either H-C-1′, H-C-2 or H-C-6 (Table 2).

From Table 1, it is apparent that all C-2 carbon signals are shifted upfield by about 10 ppm in the case of the N-1 isomers (**13**, **14**, **15**, **16**) compared to the N-7 glycosylated compounds (**11**, **12**, **17**, **1b**). Similarly, a downfield shift of about 10 ppm is observed for C-6 while the signal of C-4

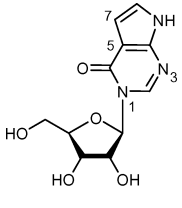
TABLE 1 ^{13}C-NMR chemical shifts (δ [ppm]) of pyrrolo[2,3-*d*]pyrimidine nucleosides and precursors[a]

	C(2)[b] C(2)[c]	C(4) C(6)	C(4a) C(5)	C(5) C(7)	C(6) C(8)	C(7a) C(4)	C≡N	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)
9	149.1	155.5	103.2	83.9	124.5	149.6	115.5	—	—	—	—	—
11	153.8	156.0	101.8	88.1	121.3	150.1	114.0	89.1	69.9	73.1	78.8	62.4
13	144.6	156.0	104.4	83.8	132.2	144.5	115.7	92.2	70.5	73.7	79.7	63.4
12	153.2	156.1	102.2	87.5	121.7	150.0	114.2	91.1	71.2	70.7	86.6	62.1
14	143.5	155.8	104.3	83.6	131.9	145.0	115.8	92.7	73.7	69.4	85.8	60.4
9a	153.0	156.8	101.5	81.0	134.3	152.3	116.8	—	—	—	—	—
17	153.8	157.1	101.4	83.9	133.3	150.0	114.9	87.2	70.6	73.5	79.2	63.3
15	145.0	157.4	103.2	82.0	146.4	145.6	117.1	92.9	70.3	73.5	79.4	63.2
1b	153.6	157.0	101.2	83.0	132.4	150.2	115.4	87.8	74.2	70.2	85.5	61.2
16	144.3	157.3	103.3	81.8	145.6	145.6	117.1	94.1	73.0	70.2	86.8	61.1
22	144.7	157.2	106.7	102.5	121.6	147.0	—	90.3	74.0	70.7	81.6	63.6
23	143.1	157.6	106.3	102.4	121.1	147.0	—	87.3	74.8	69.7	84.7	60.7
8[29]	144.1	158.6	108.7	102.8	121.5	148.1	—	87.2	74.6	70.9	85.4	61.9



systematic numbering

23



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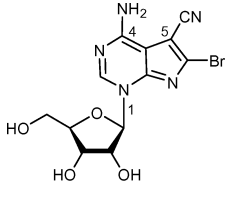

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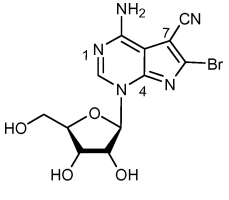


purine numbering

14

[a]Measured in DMSO-d_6 at 298 K.

[b]First heading row = systematic numbering.

[c]Second heading row = purine numbering.

TABLE 2 Coupling constants $J_{C,H}$ [Hz] of pyrrolo[2,3-*d*]pyrimidine nucleosides[a,b]

		12	14	16
C(2)	^{1}J(C2, H-C2)	211	202	210
C(2)	^{3}J(C2, H-C1′)	n.d.	—	3.8
C(4)	^{3}J(C4, H-C2)	11.6	11.1	12.0
C(4a)	^{3}J(C4a, H-C6)	s	s	4.5
C(5)	^{2}J(C5, H-C6)	s	s	10.9
C(6)	^{1}J(C6, H-C6)	s	s	188
C(7a)	^{3}J(C7a, H-C1′) or	m		m
	^{3}J(C7a, H-C2) or		6.7	
	^{3}J(C7a, H-C6)		5.5	
C(1′)	^{1}J(C1′, H-C1′)	171	164	169
C(2′)	^{1}J(C2′, H-C2′)	149	149	149
C(3′)	^{1}J(C3′, H-C3′)	147	150	149
C(4′)	^{1}J(C4′, H-C4′)	148	147	148
C(5′)	^{1}J(C5′, H-C5′)	140	139	140
C≡N	^{3}J(CN, H-C6)	s	s	1.4

[a]Measured in DMSO-d_6 at 298 K.
[b]Systematic numbering. s = singlet. m = multiplet.
n.d. = not determined.

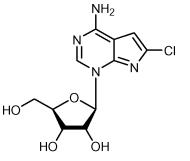
stays almost unaffected. According to observations made on other isomeric pyrrolo[2,3-*d*]pyrimidine nucleosides, N-7 was established as glycosylation site for the sugar residues linked to the pyrrole moiety and N-1 for the isomers with the sugar attached to the pyrimidine system.[43,48] In both series of isomers, the removal of the bromine substituent (**15**, **17**) induces a downfield shift for the C-6 (ca. 10 ppm) and an upfield shift of C-5 (Table 1). In addition, the amino group of the isonucleosides (**13–16**) shows two signals for their exchangeable protons in the ^{1}H-NMR spectrum. This indicates the nonequivalence of these protons; a hindered rotation has been reported for N-1 alkylated pyrrolo[2,3-*d*]pyrimidines.[49] Analogously, the structure of the N-1 compound was assigned to formula **16**. This structure was further evidenced by single crystal x-ray analysis which is published elsewhere.[50]

Next, UV-data were measured. From Table 3, it is obvious that a change of the glycosylation position causes changes in the UV-spectra. When the UV-spectra of the N-1 nucleosides **14** and **16** are compared to their N-7 counterparts **12** and **1b** (toyocamycin), an additional maximum around 312 nm appears, a finding which was already reported for other pyrrolo[2,3-*d*]pyrimidines with a functionalized pyrrole moiety (compounds **27**, **28**[48]).

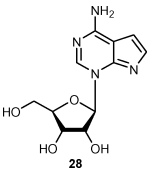
The formation of the N-1 isomer in the course of glycosylation is in line with methylation experiments performed in our laboratory on the tubercidin base **18** treated under neutral conditions with MeI in dimethylacetamide.[51] In this case, two regiosiomeric methylation products—the N-3 isomer **20a** and the N-1 derivative **19a** were obtained (Scheme 3). Analogously, neutral alkylation conditions with

TABLE 3 UV data of pyrrolo[2,3-*d*]pyrimidine nucleosides[a]

Cpd (λ_{max})	Wavelength [nm]	Extinction coefficient (ε)
12[38]	284	18300
	288(sh)	9800
1b	231	9300
	278	15100
27[48]	219	25400
	250	6900
	282	9900
	313	7000
8	259	9100
14	220	25700
	260	11000
	285	12200
	312	9600
16	230	13500
	260	11300
	278	12900
	313	6200
28[48]	216	22600
	272	8700
	292	10000
23	261	8000



27



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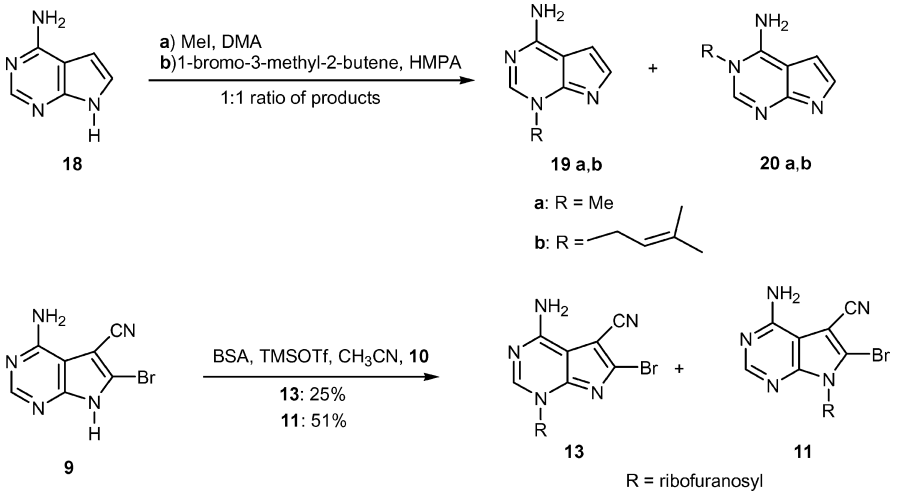
[a]Measured in methanol.

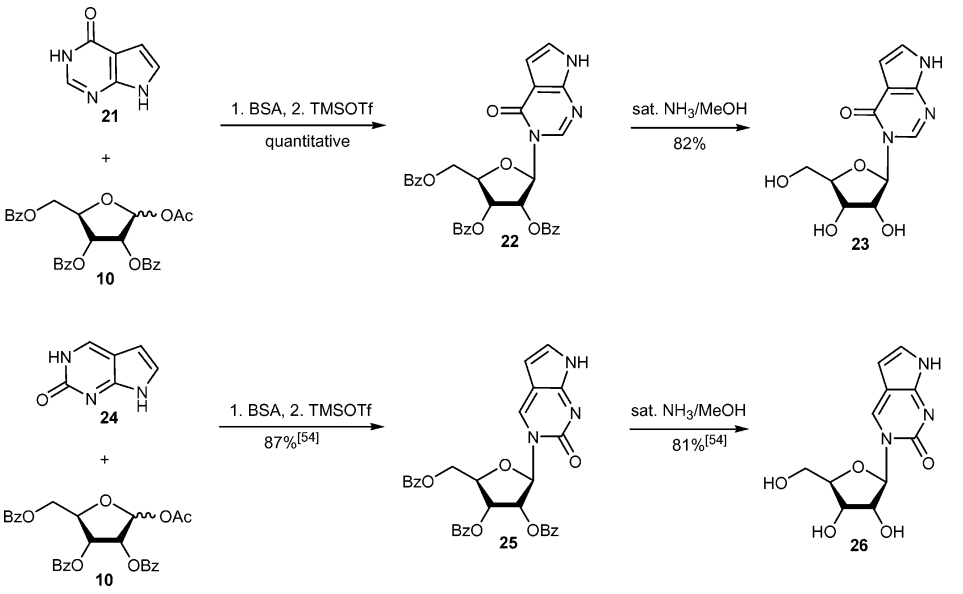


SCHEME 3

isopentenylbromide in HMPA were employed for the synthesis of the 7-deazapurine derivatives of naturally occurring triacanthine **19b**,[49] (Scheme 3), showing similar results. The different outcome of the glycosylation reaction performed on the toyocamycin base **9** employing the ribo sugar **10** is the result of the electron-withdrawing character of the pyrrole substituents which changes the nucleophilic character of the ring nitrogens. Consequently, N-7 becomes the most nucleophilic site whereas N-1 is still nucleophilic enough to form the side product **13**. N-3 has lost its nucleophilicity due to the influence of the pyrrole substituents.

2. Glycosylation of 4-hydroxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (21) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (10)

The outcome of an "one-pot" glycosylation changes when 4-hydroxypyrrolo[2,3-*d*]pyrimidine (**21**) is used. Now, an exclusive glycosylation at N-3 is observed leading to the protected derivative **22** in quantitative yield which was deblocked in methanolic ammonia furnishing **23** (Scheme 4). This compound was already prepared under HgO catalysis resulting in a significant lower yield at the glycosylation step (25%)[52]; a similar outcome has been reported for a related derivative.[53] Nucleoside **25** (pyrroloC)[54] is also formed in almost quantitative yield when the nucleobase **24** is used and the "one-pot" glycosylation is employed (Scheme 4). The deprotected nucleoside **26** is highly fluorescent and is introduced as fluorescence reporter in single- and double-stranded oligonucleotides.[54]



SCHEME 4

A number of 4,5-halogenated pyrrolo[2,3-*d*]pyrimidine ribonucleosides were prepared by the "one-pot" glycosylation using TMSOTf/BSA.[55] Also, nucleobase anion glycosylation was successful for the synthesis of 6-halogenated derivatives reported by Kazimierczuk[41] and Anderson.[48]

CONCLUSION

The 4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidines such as **9** form the N-7 isomer **11** as main product with the N-1 derivatives as minor component (**13**), when "one-pot" glycosylation conditions (MeCN, silylated base, TMSOTf) are employed. The corresponding 4-hydroxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (**21**) or 2-hydroxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (**24**) give the N-3 isomers almost exclusively. A selective N-7 glycosylation is only accomplished with 5-substituted 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidines,[55] or 4-phthalimido derivatives[56] bearing electron-withdrawing substituents at C-5 (e.g., halogens) while in the absence of electron-withdrawing substituents the reaction fails. Here, isoproylidene-protected halogenoses have to be used and nucleobase anion glycosylation has to be employed.[42,43] The glycosylation reaction is selective when pyrrole precursors[57] are used instead of pyrrolo[2,3-*d*]pyrimidines.

EXPERIMENTAL PART

General

All chemicals were purchased from Acros (Geel, Belgium), Fluka (Taufkirehen, Germany), or Sigma-Aldrich (Sigma-Aldrich Chemie GmbH, Deisenhofen, Germany). Solvents were of laboratory grade. Thin layer chromatography (TLC): aluminium sheets, silica gel 60 F254 (0.2 mm; Merck, Darmstadt, Germany). Flash column chromatography (FC): silica gel 60 (VWR, Darmstadt, Germany) at 0.4 bar; sample collection with an Ultra Rac II (Bromma, Sweden) fractions collector (LKB Instruments, Sweden). UV spectra: U-3200 spectrometer (Hitachi, Tokyo, Japan); NMR spectra: Avance-DPX-300 spectrometer (Bruker, Rheinstetten, Germany), at 300 MHz for ^{1}H and ^{13}C; δ in ppm relative to Me_4Si as internal standard. The J values are given in Hz. Elemental analyses were performed by Mikroanalytisches Laboratorium Beller (Göttingen, Germany).

4-Amino-6-bromo-5-cyano-7*H*-pyrrolo[2,3-*d*]pyrimidine (**9**): Compound **9** was prepared as described.[46] Analytical data: TLC (SiO_2, CH_2Cl_2/MeOH 9:1): R_f 0.57. ^{1}H-NMR (DMSO-d_6): 8.22 (s, 1H, H-C(2)); 7.21 (s, 2H, NH_2). Analytical data are identical with those obtained earlier.[46]

4-Amino-5-cyano-7*H*-pyrrolo[2,3-*d*]pyrimidine (**9a**): Compound **9a** was prepared as described.[46] TLC (SiO_2, CH_2Cl_2/MeOH 9:1): R_f 0.4. ^{1}H-NMR

(DMSO-d_6): 8.16 (s, 1H, H-C(2)); 8.09 (s, 1H, H-C(6)); 6.60 (s, 2H, NH_2). Analytical data are identical with those obtained earlier.[46]

Glycosylation of 4-amino-6-bromo-5-cyano-7*H*-pyrrolo[2,3-*d*]pyrimidine (9) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (10): The glycosylation was performed as described earlier by Townsend et al.[45] Compound **9** (2.4 g, 10 mmol) was suspended in dry acetonitrile. *N*,*O*-Bis(trimethylsilyl)acetamide (4.1 g, 2.9 ml, 20 mmol) was added and the mixture was stirred for 15 minutes. Then, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (5.0 g, 10 mmol) and trimethylsilyl trifluoromethanesulfonate (6.7 g, 5.4 ml, 30 mmol) were added. Within 10 minutes, the suspension became a clear yellow solution. This solution was heated at 80°C for 3 h, cooled and extracted with ethyl acetate. The organic layer was washed with saturated bicarbonate solution and brine, dried, evaporated and applied to FC (silica gel, column 20 × 5 cm, $CH_2Cl_2 \rightarrow CH_2Cl_2$/EtOAc 4:1). After flash chromatography (FC) two main zones were obtained. The fast migrating zone furnished compound **13** (25%) and the slower migrating zone furnished compound **11** (51%).

4-Amino-6-bromo-5-cyano-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (13): From the faster migrating zone compound **13** (1.7g, 25%) was isolated as colorless foam. TLC (SiO_2, CH_2Cl_2/EtOAc 4:1): R_f 0.64. UV (MeOH): λ_{max} 315 (ε 8200), 283 (ε 4900), 266 (ε 12900), 231 (ε 53700). ^{1}H-NMR (DMSO-d_6): 8.79 (bs, 1H, NH), 8.69 (s, 1H, H-C(2)), 7.91, 7.64, 7.46 (3m, 16H, arom.H, NH), 6.63 (d, J = 2.4, 1H, H-C(1′)), 6.31 (m, 2H, H-C(2′), H-C(3′)), 4.79 (m, 3H, H-C(4′), H-C(5′)). Anal. Calc. for $C_{33}H_{24}BrN_5O_7$ (682.48): C 58.08, H 3.54, N 10.26; found C 58.10, H 3.65, N 10.20.

4-Amino-6-bromo-5-cyano-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7-pyrrolo[2,3-*d*]pyrimidine (11): From the slower migrating zone compound **11** (3.5g, 51%) was isolated as colorless foam. TLC (SiO_2, CH_2Cl_2/EtOAc 4:1): R_f 0.45. ^{1}H-NMR (DMSO-d_6): 8.16 (s, 1H, H-C(2)), 7.90, 7.85, 7.45 (3m, 15H, arom.H), 7.12 (s, 2H, NH_2), 6.61 (m, H-C(1′)), 6.43 (m, 2H, H-C(2′), H-C(3′)), 4.87 (m, 2H, H-C(5′)), 4.60 (m, 1H, H-C(4′)). Analytical data are identical to those reported earlier.[45]

4-Amino-5-cyano-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7*H*-pyrrolo [2,3-*d*]pyrimidine (17): The compound was prepared according to a procedure published earlier[45] with **11** (1.0 g, 1.46 mmol) and ammonium formate (1.0 g, 15 mmol) and 10% Pd on activated charcoal. After FC (column 20 × 5 cm, $CH_2Cl_2 \rightarrow CH_2Cl_2$/EtOAc 4:1) compound **17** (750 mg, 85%, Lit.[45]: 85%) was obtained as colorless foam. TLC (SiO_2, CH_2Cl_2/EtOAc 4:1): R_f 0.25. ^{1}H-NMR (DMSO-d_6): 8.52 (s, 1H, H-C(6)), 8.17 (s, 1H, H-C(2)), 7.92, 7.86, 7.46 (3m, 15H, arom.H), 6.99 (s, 2H, NH_2), 6.61 (d, J = 4.6, 1H, H-C(1′)), 6.33 (t, J = 4.7, 1H, H-C(2′)), 6.18 (t, J = 5.8, 1H, H-C(3′)), 4.85 (m, 2H, H-C(5′)), 4.67 (m, 1H, H-C(4′)). Analytical data are identical to those reported earlier.[45]

4-Amino-6-bromo-5-cyano-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*] pyrimidine (**14**): Compound **13** (1.0 g, 1.47 mmol) was stirred in MeOH saturated with ammonia (50 ml) overnight. The solvent was evaporated and the residual foam was adsorbed on silica gel (20 g) and applied to FC (silica gel, column 15 × 5 cm, $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 95:5). Evaporation of the main zone afforded **14** (380 mg, 70%) as colorless foam. Recrystallisation from MeOH furnished colorless crystals. m.p.: 195–198°C, dec. TLC (SiO_2, CH_2Cl_2/MeOH 95:5): R_f 0.20. UV (MeOH): λ_{max} 285 (ε 19000); (Lit.[38] 284 (ε 18300)). ^{1}H-NMR (DMSO-d_6): 8.20 (s, 1H, H-C(2)), 7.08 (s, 2H, NH_2), 5.93 (d, J = 6.5, 1H, H-C(1′)), 5.46 (d, J = 6.1, 1H, HO-C(2′)), 5.33 (m, 1H, HO-C(3′)), 5.25 (d, J = 4.7, 1H, HO-C(5′)), 5.05 (d, J = 6.1, 1H, H-C(2′)), 4.21 (d, J = 2.7, H-C(3′)), 3.97 (d, J = 2.9, 1H, H-C(4′)), 3.70, 3.54 (2m, 2H, H-C(5′)). Analytical data are identical to those reported earlier.[38]

4-Amino-5-cyano-7-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (toyocamycin, (**1b**)): As described earlier[45] with compound **17** (0.6 g, 1 mmol) and saturated methanolic ammonia (50 ml). Compound **1b** was obtained as colorless solid (240 mg, 82%). TLC (SiO_2, CH_2Cl_2/MeOH 9:1) R_f 0.35. ^{1}H-NMR (DMSO-d_6): 8.45 (s, 1H, H-C(2)), 8.22 (s, 1H, H-C(6)), 6.92 (s, 2H, NH_2), 6.05 (d, J = 5.6, 1H, H-C(1′)), 5.48 (d, J = 6.0, 1H, HO-C(2′)), 5.22 (m, 2H, HO-C(3′), HO-C(5′)), 4.36 (d, J = 6.1, H-C(2′)), 4.09 (d, J = 2.7, 1H, H-C(3′)), 3.92 (d, J = 3.5, 1H, H-C(4′)), 3.62 (m, 2H, H-C(5′)). Analytical data are identical to those reported earlier.[38,44,45]

4-Amino-5-cyano-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7*H*-pyrrolo [2,3-*d*] pyrimidine (**15**): Compound **13** (1.32 g, 1.9 mmol) was suspended in EtOH (40 ml). Then, ammonium formate (1.0 g, 15 mmol) and 10% Pd on activated charcoal (100 mg) was added and the solution was stirred for 3 hours under reflux. The solution was filtrated through a bed of Celite and the Celite was washed with hot EtOH (2 × 50 ml). The solvent of the filtrate was evaporated and the remaining residue was dissolved in CH_2Cl_2, adsorbed on silica gel (25 g) and applied to FC (silica gel, column 20 × 5 cm, $CH_2Cl_2 \rightarrow CH_2Cl_2$/EtOAc 4:1). Evaporation of the main zone furnished compound **15** (960 mg, 82%) as colorless foam. TLC (SiO_2, CH_2Cl_2/EtOAc 4:1): R_f 0.50. UV (MeOH): λ_{max} 314 (ε 6500), 283 (ε 12200), 268 sh (ε 10200), 231 (ε 44700). ^{1}H-NMR (DMSO-d_6): 8.69 (s, 2H, H-C(2), NH), 7.90, 7.62, 7.45 (3m, 17H, arom.H, H-C(6), NH), 6.61 (m, 1H, H-C(1′)), 6.42 (m, 2H, H-C(2′), H-C(3′)), 4.80 (m, 3H, H-C(4′), H-C(5′)). Anal Calc. for $C_{33}H_{25}N_5O_7$ (603.58): C 65.67, H 4.17, N 11.60; found C 65.58, H 4.18, N 11.52.

4-Amino-6-bromo-5-cyano-1-(β-D-ribofuranosyl)-7H-pyrrolo[2,3-*d*] pyrimidine (**14**): Compound **13** (600 mg, 0.88 mmol) was suspended in saturated methanolic ammonia (50 ml) and the mixture was stirred for 12 hours. The solvent was evaporated and the foamy residue was adsorbed on silica gel (25 g) and applied to FC (silica gel, column 20 × 5 cm,

$CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 95:5). Evaporation of the main zone afforded **14** as amorphous solid (250 mg, 77%). TLC (SiO_2, CH_2Cl_2/MeOH 9:1): R_f 0.22. UV (MeOH): λ_{max} 312 (ε 9600), 285 (ε 12200), 260 (ε 11000), 220 (ε 25700). ^{1}H-NMR (DMSO-d_6): 8.79 (s, 1H, H-C(2)), 8.57 (bs, 1H, NH), 7.39 (bs, 1H, NH), 6.07 (d, J = 4.3, 1H, H-C(1′)), 5.62 (d, J = 5.5, 1H, HO-C(2′)), 5.49 (m, 1H, HO-C(3′)), 5.22 (d, J = 5.1, 1H, HO-C(5′)), 4.45 (m, 1H, H-C(2′)), 4.13 (m, 1H, H-C(3′)), 4.02 (m, 1H, H-C(4′)), 3.77, 3.61 (2m, 2H, H-C(5′)). Anal Calc. for $C_{12}H_{12}BrN_5O_4$ (370.16): C 38.94, H 3.27, N 18.92; found C 38.85, H 3.30, N, 18.81.

4-Amino-5-cyano-1-(β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**16**): Compound **15** (750 mg, 1.2 mmol) was suspended in saturated methanolic ammonia (50 ml). The solution was stirred for 12 hours, then the solvent was evaporated and the remaining residue was adsorbed on silica gel (25 g). FC (silica gel, column 15 × 4 cm, $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 95:5) furnished compound **16** (300 mg, 82%) as colorless solid. Crystallisation from MeOH gave colorless crystals: m.p.: 189–192°C, dec. TLC (SiO_2, CH_2Cl_2/MeOH 9:1): R_f 0.41. UV (MeOH): λ_{max} 313 (ε 6200), 278 (ε 12900), 260 (ε 11300), 230 (ε 13500). ^{1}H-NMR (DMSO-d_6): 8.73 (s, 1H, H-C(2)), 8.49 (bs, 1H, NH), 7.85 (s, 1H, H-C(6)), 7.20 (bs, 1H, NH), 6.23 (m, 1H, H-C(1′)), 6.02 (d, J = 5.5, 1H, HO-C(2′)), 5.60 (d, J = 5.8, 1H, HO-C(3′)), 5.21 (d, J = 4.5, 1H, HO-C(5′)), 4.65 (m, 1H, H-C(2′)), 4.10 (m, 2H, H-C(3′)), H-C(4′)), 3.60 (m, 2H, H-C(5′)). Anal Calc. for $C_{12}H_{13}N_5O_4$ (291.26): C 49.48, H 4.50, N 24.04; found C 49.49, H 4.61, N 23.90.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-one (**22**): To a suspension of 3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**21**) (220 mg, 1.63 mmol) in dry acetonitrile, *N*,*O*-bis(trimethylsilyl)acetamide (1.6 g, 1.1 ml, 4.43 mmol) was added and the mixture stirred for 10 minutes at room temperature Then, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**10**) (1.34 g, 2.65 mmol) and trimethylsilyl trifluoromethanesulfonate (430 mg, 0.35 ml, 1.79 mmol) were introduced. The mixture was stirred for another 15 minutes at room temperature During this time the suspension became a clear yellow solution. This solution was heated at 80°C for 3h in a preheated oil-bath. The solution was cooled and diluted with ethyl acetate. The organic layer was washed with saturated bicarbonate solution and brine, dried, evaporated and applied to FC (silica gel, column 20 × 5 cm, CH_2Cl_2/acetone 15:1). From FC one main zone was obtained. The solvent was evaporated and the title compound **22** was obtained as colorless foam (920 mg, 98%). TLC (SiO_2, CH_2Cl_2/EtOAc 4:1): R_f 0.4. UV (MeOH): λ_{max} 262 (ε 18000), 228 (ε 84000). ^{1}H-NMR (DMSO-d_6): 12.11 (s, 1H, NH), 8.33 (s, 1H, H-C(2)), 8.04–7.42 (4m, 15H, arom. H), 7.13 (d, J = 2.8, 1H, H-C(6)), 6.55 (d, J = 2.8, 1H, H-C(5)), 6.38 (d, J = 2.3, 1H, H-C(1′)), 6.12 (m, 2H, H-C(2′), H-C(3′)), 4.73 (m, 3H, H-C(4′), H-C(5′)). Anal Calc. for

$C_{32}H_{25}N_3O_8$ (579.56): C 66.32, H 4.35, N 7.25; found C 66.24, H 4.19, N 7.19.

3- (β-D-Ribofuranosyl)- 3,7- dihydro- 4*H*-pyrrolo [2,3-*d*]pyrimidin-4-one (**23**): Compound **22** (1.08 g, 1.86 mmol) was suspended in saturated methanolic ammonia (40 ml) and the mixture was stirred for 12 hours. The solvent was evaporated and the residual foam was adsorbed on silica gel (20 g) and applied to FC (silica gel, column 15 × 5 cm, CH_2Cl_2/MeOH 20:1→CH_2Cl_2/MeOH 4:1). Evaporation of the main zone afforded **23** (410 mg, 82%) as colorless foam. TLC (SiO_2, CH_2Cl_2/MeOH 9:1): R_f 0.20. UV (MeOH): λ_{max} 261 (ε 16000). ^{1}H-NMR (DMSO-d_6): 11.87 (s, 1H, NH), 8.43 (s, 1H, H-C(2)), 7.07 (d, J = 2.9, 1H, H-C(6)), 6.48 (m, 2H, H-C(5)), 6.15 (d, J = 4.7, 1H, H-C(1′)), 5.38 (d, J = 5.5, 1H, HO-C(3′)), 5.14 (t, J = 5.0, 1H, HO-C(5′)), 5.11 (d, J = 6.9, 1H, HO-C(2′)), 4.13 (m, 2H, H-C(2′), H-C(3′)), 3.91 (m, 1H, H-C(4′)), 3.68, 3.61 (2m, 2H, H-C(5′)). Anal Calc. for $C_{11}H_{13}N_3O_5$ (267.24): C 49.44, H 4.90, N 15.72; found C 49.53, H 4.82, N 15.61.

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