171. 2,4-Disubstituted Pyrrolo[2,3-*d*]pyrimidine α-D- and β-D-Ribofuranosides Related to 7-Deazaguanosine

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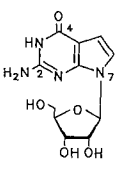
Nucleobase-anion glycosylation (KOH, tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1), MeCN) of the pyrrolo[2,3-*d*]pyrimidines **4a–d** with 5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-α-D-ribofuranosyl chloride (**5**) gave the protected β-D-nucleosides **6a–d** stereoselectively *(Scheme 1)*. Contrary, the β-D-halogenose **8** yielded the corresponding α-D-nucleosides (**9a** and **9b**) apart from minor amounts of the β-D-anomers. The deprotected nucleosides **10a** and **11a** were converted into 4-substituted 2-aminopyrrolo[2,3-*d*]-pyrimidine β-D-ribofuranosides **1**, **10c**, **12**, **14**, and **16** and into their α-D-anomers, respectively *(Scheme 2)*. From the reaction of **4b** with **5**, the glycosylation product **7** was isolated, containing two nucleobase moieties.

Introduction. – The convergent synthesis of pyrrolo[2,3-*d*]pyrimidine β-D-ribonucleosides is encountered with difficulties. When 2′-*O*-acyl-protected halogenoses are used during the glycosylation reaction, orthoamides are formed not rearranging to *N*-glycosides [1]. On the other hand, benzyl-*O*-protected halogenoses give rise to α-D-ribonucleosides, preferentially [2].



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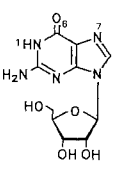

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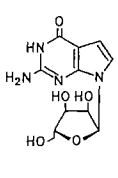

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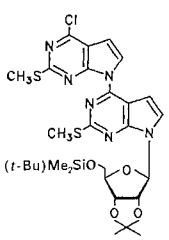

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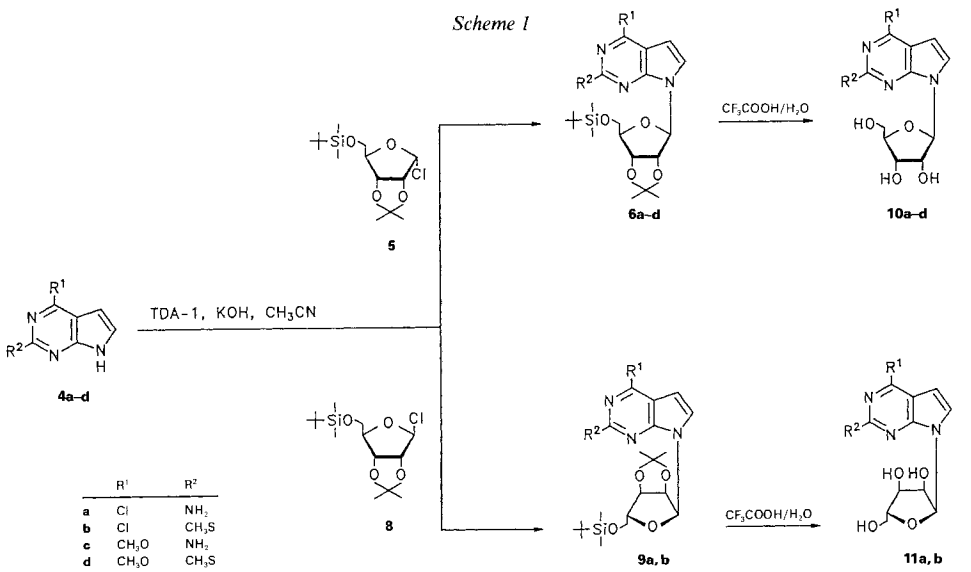
Recently, the halogenose **5** has been synthesized [3] and successfully used for the glycosylation of pyrrolo[2,3-*d*]pyrimidines [4–7]. It has been observed that an equimolar ratio of the sugar halide and the nucleobase can be used in case of 4-substituted pyrrolo[2,3-*d*]pyrimidines [5], but a two-fold excess of the nucleobase over the halogenose is necessary in other cases [4] [6]. As pyrrolo[2,3-*d*]pyrimidine ribonuclosides are isosteric to the parent purines (**1** *vs.* **2**) [8], they are useful building blocks for the synthesis of base-modified RNA fragments. In the following, we investigate the glycosylation of 2,4-disubstituted pyrrolo[2,3-*d*]pyrimidines in more detail. Moreover, studies are undertaken to employ the anomeric β-D-halogenose **8** for the synthesis of pyrrolo[2,3-*d*]-pyrimidine α-D-ribonucleosides (see *e.g.* **3**).

Results and Discussion. – Compounds **4a–d** have been chosen for the glycosylation experiments as the 4-Cl substituent of **4a** and **4b** or the 4-MeO group of **4c** and **4d** may be displaced later by nucleophiles leading to ribonucleosides with various substituents (H, OH, NH_2, =S) at C(4). On the other hand, a MeS group as found in **4b** and **4d** is useful for further displacement reaction at C(2) [9].

Compounds **4a–d** were synthesized as described earlier [10]. The halogenose **5** was prepared according to *Wilcox* and *Otoski* [3] and not isolated but directly used in the reaction [4]. Glycosylation of **4a–d** with **5** was carried out in MeCN with a 3-fold excess of powdered KOH and 0.1 equiv. of tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) under stirring at room temperature. An equimolar ratio as well as a two-fold excess of nucleobase over the halogenose **5** were used. Nucleoside formation (two-fold excess of nucleobase) was followed analytically by TLC scanning, and samples were taken every hour. In all cases, a reaction time of 20 h was necessary to reach a plateau value of nucleoside formation. This was much longer than in case of the toluoyl-protected 2′-deoxyhalogenose [11]. The analytically determined yields (TLC scanning) were the following: **6a** (80%), **6b** (80%), **6c** (40%), and **6d** (90%).

Scheme 1



Next, preparative-scale experiments were carried out: the products **6a–d** were purified by column chromatography and characterized by elemental analyses and ^{1}H-NMR spectroscopy. In all cases, β-D-anomers were formed which was confirmed by NOE difference spectroscopy using the NOE's of H–C(4′) upon irradiation of the anomeric proton [12].

The glycosylation yields obtained with either an equimolar ratio or a two-fold excess of the nucleobase over halogenose **5** are shown in *Table 1:* they are strongly affected by the nucleobase substituents. Only **4a**, **4b**, and **4d** can be effectively used for glycosylation, whereas **4c**, the most appropriate precursor for a 2′-deoxyribonucleoside synthesis, is not suitable. Large quantities of unreacted **4c** were isolated from the reaction mixture.

Table 1. *Glycosylation Yields*[a]) *Employing the Halogenose* **5** *or* **8** *and the Nucleobases* **4a–d**

Halogenose	Nucleobase	Product	Glycosylation yields [%] **4**/Halogenose	
			1:1	2:1
5	**4a**	**6a**	34	65
5	**b**	**b**	53	78
5	**c**	**c**	21	31
5	**d**	**d**	59	82
8	**a**	**9a**	31 (+ 5% of **6a**)	31 (+ 11% of **6a**)

[a]) Referring to the amount of halogenoses **5** or **8**.

Regarding the glycosylation yields **6b** and **6d** appear to be candidates for further transformation. However, the displacement of the 2-MeS group proved to be difficult. As a result, compound **6a** was chosen for preparative-scale syntheses.

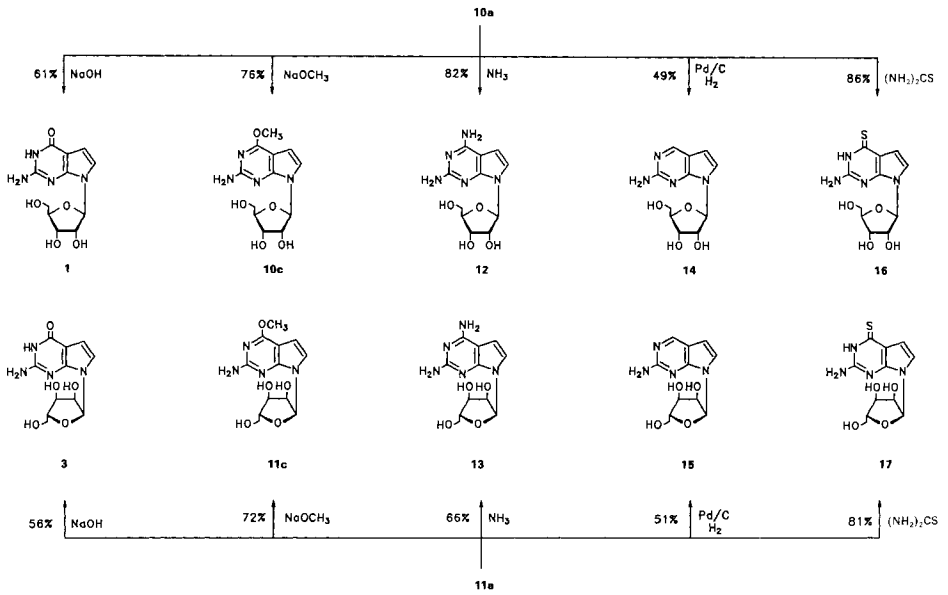
The reaction of **4b** and **5** gave rise to a by-product which was not observed in case of the other nucleobases. In particular an increase of the amount of the nucleobase **4b** over the halogenose **5** facilitated this reaction. It was considered that the 4-Cl substituent of **6b** was nucleophilically displaced by the nucleobase anion. The structure of **7** (7%) was established spectroscopically. Both ^{1}H- and ^{13}C-NMR spectra of **7** show two sets of nucleobase signals, while only one set of the sugar moiety appears. The MS of **7** gives an M^+ at 648 and an isotopic pattern which agrees with the calculated data. Signals at m/z 633 and 591 arise from the loss of the Me and *t*-Bu group, respectively, at the silyl moiety. This latter fragment loses the i-Pr and a further Me group ($\rightarrow m/z$ 533), while cleavage of the glyconic moiety [13] leads to m/z 445.

In order to obtain α-D-ribonucleosides, the β-D-halogenose **8**, also prepared according to *Wilcox* and *Otoski* [3], was used in glycosylation experiments with the nucleobases **4a** or **4b** under the same condition as reported for **5**. But contrary to **5**, the yield of glycosylation products was low and the α-D-ribonucleoside **9a** (31%; see *Table 1*) and **9b** (48%) were formed together with minor amounts of the β-D-anomers **6a** (11%) and **6b** (6%) respectively.

The most likely explanation for the non-stereoselective nucleobase-anion glycosylation employing **8** and the stereoselective route of **5** is a steric hindrance of the incoming nucleophile by the bulky isopropylidene group. This is supported by a slower α-D-nucleoside formation ($\rightarrow$**9**) as compared to that of the β-D-anomers ($\rightarrow$**6**; monitoring by TLC scanning). When the glycosylation velocity is increased by an excess of the nucleobase, selectivity should be decreased further. According to *Table 1*, the yield of α-D-ribonucleoside **9a** is not raised using a two-fold excess of nucleobase **4a** over **8**. The increase of the reaction product accounts solely for the β-D-ribonucleoside **6a**. The lower glycosylation yield of α-D-nucleosides as compared to their β-D-counterparts may be also due to steric shielding of the protecting group in case of **8**. Moreover, the steric hindrance reduces the attack of larger nucleophiles more strongly than that of small anions (OH^-) which can enhance side reactions.

The 5′-*O*-silyl group and the isopropylidene moiety of **6a** and **9a** were split off with CF_3COOH simultaneously, yielding crystalline **10a** and **11a**, respectively *(Scheme 1)*, which were then employed in various nucleophilic displacement reactions as shown in *Scheme 2*. Thus, reaction of **10a** and **11a** with aq. conc. NH_3 solution (pressure bottle, 80°) gave **12** (82%) and **13** (66%), respectively, catalytic hydrogenation (Pd/C) **14** (49%) and **15** (51%), respectively, and treatment with NaOMe **10c** (76%) and **11c** (72%), respectively. The synthesis of 7-deazaguanosine (**1**; 61%) and its 4-thiooxo analogue **16** (86%)

Scheme 2



and of the corresponding α-D-isomers **3** (56%) and **17** (81%) was accomplished directly from **10a** and **11a**, respectively, by one-step reactions.

In *Table 2*, NOE data obtained after irradiation of the anomeric proton H–C(1′) are summarized for some of the synthesized compounds; the data confirm the attributed anomeric configurations [12].

Table 2. *NOE Data of Pyrrolo[2,3-d]pyrimidine* D-*Ribonucleosides in* (D_6)*DMSO after Irradiation at H–C(1′)*

	Observed NOE (%)
10b (β)	H–C(6) (3.0), OH–C(2′) (4.3), OH–C(3′) (1.5), H–C(2′) (1.6), H–C(4′) (2.1)
11a (α)	H–C(6) (10.8)[a]), H–C(2′) (6.9), H–C(3′) (1.7)
11c (α)	H–C(6) (2.7), H–C(2′) and H–C(3′) (15.6)
3 (α)	H–C(6) (4.0)[a]), H–C(2′) and H–C(3′) (7.1)
1 (β)	H–C(6) (1.8), H–C(2′) (2.1), H–C(4′) (2.2)
13 (α)	H–C(6) (1.9), H–C(2′) and H–C(3′) (10.7)
15 (α)	H–C(6) (2.0), H–C(2′) (8.9), H–C(3′) (2.8)
17 (α)	H–C(6) (0.8), H–C(2′) (7.6), H–C(3′) (1.8)
16 (β)	H–C(4′) (1.3)

[a]) Simultaneous saturation of H–C(1′) and H–C(5′).

^{13}C-NMR chemical shifts are summarized in *Table 3*. Data were assigned by gated-decoupled or INAPT spectroscopy or by using earlier unequivocal assignments. In case of the protected nucleosides **6a–d**, the order of sugar signals is C(1′), C(4′), C(3′), C(2′), and C(5′) (decreasing δ values) which was confirmed by gated-decoupled and 2D-^{1}H,^{13}C-correlation spectra and which is in agreement with earlier findings [14]. The nucleobase signals of **6a–d** show no significant differences to those of the corresponding aglycons

Table 3. *^{13}C-NMR Chemical Shifts of Pyrrolo[2,3-d]pyrimidines and Related Nucleosides in (D_6)DMSO*[a])

Compound	C(2)	C(4)	C(4a)	C(5)	C(6)	C(7a)	CH_3O	CH_3S	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)
4a	159.4	151.0	108.7	98.8	123.2	154.7							
b	162.8	150.5	113.3	99.0	126.7	152.8		13.7					
c[b])	159.5	162.9	97.0	98.0	119.3	155.1	52.9						
d	161.8	162.2	101.3	98.1	122.7	153.5	53.3	13.6					
6a(β)[c])	159.5	151.1	108.9	100.1	123.4	153.6			88.6	80.8	83.6	86.0	63.5
b(β)	163.8	151.4[d])	114.1	100.2	127.8	151.0[d])		13.9	89.6	80.9	83.6	86.0	63.2
c(β)[b])	159.7	163.1	97.3	99.5	120.3	154.3	52.9		88.2	80.8	83.6	85.5	63.5
d(β)	161.8	163.0	101.9	99.3	123.9	152.2	53.6	13.7	88.9	81.0	83.4	85.4	63.4
9a(α)[c])	159.3	151.1	108.7	98.7	125.1	153.4			84.1	81.9	79.5	82.3	64.3
b(α)	163.3	150.5[d])	112.3	98.7	128.2	151.0[d])		13.7	85.1	81.9	79.5	82.4	65.2
10a(β)	159.5	151.2	109.0	99.9	124.1	154.4			86.1	73.7	70.7	84.9	61.7
b(β)[e])	163.4	150.6	114.0	100.0	127.2	152.1		13.9	86.9	74.1	70.5	85.4	61.5
c(β)[b])	159.9	163.0	97.3	99.1[f])	120.0[f])	154.9	52.9[f])		86.2[f])	73.5[f])	70.7[f])	84.7[f])	61.8[f])
d(β)	163.4	152.1	113.9	100.0	127.2	150.6	53.6	15.8	86.9	74.1	70.1	85.4	61.4
11a(α)	159.1	150.7	108.5	98.2[f])	126.7[f])	154.0			83.1[f])	70.9[f])	70.6[f])	84.1[f])	61.5[f])
b(α)[g])	163.1	150.4	113.7	98.4	130.2	152.2		13.7	84.0	70.9	70.7	85.0	61.6
c(α)	159.3	162.9	96.8	97.6[f])	123.2[f])	154.6	52.8		82.9[f])	71.0[f])	70.8[f])	83.6[f])	61.6[f])
1(β)[b])[h])	152.6	158.7	100.2	102.3	117.3	151.2			86.1	73.7	70.6	84.6	61.8
3(α)[b])	152.9	159.2	99.5	100.7[f])	120.6[f])	150.9			83.1[f])	71.1[f])	70.7[f])	83.6[f])	62.8[f])
12(β)[b])[h])	159.7	157.9	96.5	100.1	118.3	152.8			86.9	73.7	70.8	84.7	62.0
13(α)[b])	159.8	157.9	95.8	98.8[f])	120.9[f])	152.9			83.0[f])	71.2[f])	70.8[f])	83.4[f])	61.9[f])
14(β)[b])[h])	160.0	150.8	111.3	100.7	122.7	153.5			85.6	73.5	70.7	84.7	61.8
15(α)[b])	159.7	150.1[f])	110.8	99.0[f])	125.9[f])	153.1			82.3[f])	70.9[f])	73.7[f])	83.7[f])	61.5[f])
16(β)	152.1	175.7	113.1	104.3	120.5	147.7			84.7	73.7	70.5	85.9	61.5
17(α)	152.1	175.3	112.9	102.8[f])	124.0[f])	147.3			83.2[f])	71.1[f])	70.7[f])	84.1[f])	61.5[f])

[a]) TMS as internal standard.
[b]) Assignment of aglycone signals according to the 2′-deoxyribonucleoside [15] [16].
[c]) INAPT spectroscopy.
[d]) Tentative.
[e]) Gated-decoupled spectra.
[f]) Assigned by ^{1}H,^{13}C-correlation spectroscopy.
[g]) [17].
[h]) [14].

4a–d. The sugar signals of the corresponding protected α-D-anomers **9a, b** are in the order C(1'), C(4'), C(2'), C(3'), and C(5'), as determined by INAPT spectroscopy.

The ^{13}C-NMR aglycone signals of **10a–d** are also similar to those of **4a–d**, and the order of the sugar signals is the same as found for **6a–d**. For the chemical shifts of the α-D-anomers **11a–c** it is apparent that C(6) is strongly shifted downfield as compared to **4a–c**. This is due to the anisotropic effect of the 2'-OH group being in close proximity to this particular C-atom in the α-D-series. Anomeric 2'-deoxyribonucleosides do not show this behaviour [5].

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Experimental Part

General. See [4]. Solvent systems: *A* = AcOEt/light petroleum ether 2:8, *B* = AcOEt/light petroleum ether 4:6, *C* = CH_2Cl_2/MeOH 9:1, *D* = CH_2Cl_2/MeOH 95:5, *E* = H_2O/i-PrOH 9:1, *F* = CH_2Cl_2/MeOH 8:2, *G* = $CHCl_3$/MeOH 95:5, *H* = Et_2O/light petroleum ether 2:8, *I* = $CHCl_3$/MeOH 9:1, *J* = CH_2Cl_2/MeOH 6:4.

4-Chloro-7-{5'-O-[(1,1-dimethylethyl)dimethylsilyl]-2',3'-O-(1-methylethylidene)-β-D-ribofuranosyl}-7H-pyrrolo[2,3-d]pyrimidin-2-amine (**6a**). Powdered KOH (1.40 g, 25.0 mmol) was stirred for 10 min in anh. MeCN (60 ml). TDA-1 (52 µl, 0.16 mmol) was added and stirring was continued for another 10 min. Then, the mixture was treated with solid 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine [18] (**4a**; 1.35 g, 8.0 mmol). After 10 min, freshly prepared 5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-α-D-ribofuranosyl chloride [3] (**5**; 4.0 mmol, calculated on the basis of 100% yield of **5**) was added to the stirred suspension, and stirring was continued for 20 h at r.t. Insoluble material was filtered off and the residue chromatographed (silica gel, column 5 × 15 cm, *A*). Evaporation of the solvent gave a yellow gum (1.18 g, 65%). TLC (silica gel, *B*): R_f 0.8. UV (MeOH): 235 (26000), 258 (3800), 317 (5000). ^{1}H-NMR ((D$_6$)DMSO): −0.04 (*s*, Me_2Si); 0.82 (*s*, *t*-BuSi); 1.32, 1.52 (2*s*, 2 Me); 3.70 (*m*, CH_2(5')); 4.08 (*m*, H–C(4')); 4.96 (*m*, H–C(3')); 5.16 (*m*, H–C(2')); 6.12 (*d*, *J* = 2.6, H–C(1')); 6.38 (*d*, *J* = 3.8, H–C(5)); 6.80 (*s*, NH_2); 7.30 (*d*, *J* = 3.8, H–C(6)). Anal. calc. for $C_{20}H_{31}ClN_4O_4Si$ (455.0): C 52.79, H 6.87, N 12.31; found: C 52.97, H 6.99, N 12.18.

4-Chloro-7-{5'-O-[(1,1-dimethylethyl)dimethylsilyl]-2',3'-O-(1-methylethylidene)-β-D-ribofuranosyl}-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine (**6b**). Compound **6b** was prepared from **4b** (800 mg, 4.0 mmol) as described for **6a**. After chromatography (silica gel, column 5 × 20 cm, *H*), a light yellow gum (760 mg, 78%) was isolated from the faster migrating zone. TLC (silica gel, *H*): R_f 0.57. UV (MeOH): 261 (21400), 275 (7800), 309 (6300). ^{1}H-NMR ((D$_6$)DMSO): −0.05 (*s*, Me_2Si); 0.80 (*s*, *t*-BuSi); 1.33, 1.54 (2*s*, 2 Me); 2.58 (*s*, MeS); 3.69 (*m*, CH_2(5')); 4.18 (*m*, H–C(4')); 4.92 (*m*, H–C(3')); 5.31 (*m*, H–C(2')); 6.28 (*d*, *J* = 2.6, H–C(1')); 6.64 (*d*, *J* = 3.8, H–C(5)); 7.70 (*d*, *J* = 3.8, H–C(6)). Anal. calc. for $C_{21}H_{32}N_3O_4SSi$ (486.1): C 50.67, H 6.80, N 8.86; found: C 50.99, H 6.82, N 8.80.

7-{5'-O-[(1,1-Dimethylethyl)dimethylsilyl]-2',3'-O-(1-methylethylidene)-β-D-ribofuranosyl}-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-amine (**6c**). Compound **6c** was prepared from **4c** (1.31 g, 8.0 mmol) as described for **6a**. Chromatography (silica gel, column 5 × 15 cm, *A*) yielded a light yellow sirup (560 mg, 31%). TLC (silica gel, *B*): R_f 0.7. UV (MeOH): 260 (9100), 284 (6800). ^{1}H-NMR ((D$_6$)DMSO): 0.02 (*s*, Me_2Si); 0.84 (*s*, *t*-BuSi); 1.32, 1.52 (2*s*, 2 Me); 3.71 (*m*, CH_2(5')); 3.92 (*s*, MeO); 4.11 (*m*, H–C(4')); 4.94 (*m*, H–C(3')); 5.13 (*m*, H–C(2')); 6.11 (*d*, *J* = 2.8, H–C(1')); 6.28 (*d*, *J* = 3.7, H–C(5)); 6.30 (*s*, NH_2); 7.04 (*d*, *J* = 3.7, H–C(6)). Anal. calc. for $C_{21}H_{34}N_4O_5Si$ (450.6): C 55.98, H 7.61, N 12.43; found: C 55.79, H 7.78, N 12.19.

7-{5'-O-[(1,1-Dimethylethyl)dimethylsilyl]-2',3'-O-(1-methylethylidene)-β-D-ribofuranosyl}-4-methoxy-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine (**6d**). Compound **6d** was prepared from **4d** (1.55 g, 8.0 mmol) as described for **6a**. Chromatography (silica gel, column 5 × 20 cm, *H*) yielded a colourless sirup (1.58 g, 82%). TLC (silica gel, *H*): R_f 0.6. UV (MeOH): 236 (11600), 281 (10200). ^{1}H-NMR ((D$_6$)DMSO): −0.03 (*s*, Me_2Si); 0.82 (*s*, *t*-BuSi); 1.33, 1.55 (2*s*, 2 Me); 2.57 (*s*, MeS); 3.69 (*m*, CH_2(5')); 4.02 (*s*, MeO); 4.14 (*m*, H–C(4')); 4.93 (*m*, H–C(3')); 5.29 (*m*, H–C(2')); 6.25 (*d*, *J* = 2.8, H–C(1')); 6.52 (*d*, *J* = 3.6, H–C(5)); 7.41 (*d*, *J* = 3.6, H–C(6)). Anal. calc. for $C_{22}H_{35}N_3O_5SSi$ (481.7): C 54.86, H 7.32, N 8.72; found: C 54.97, H 7.43, N 8.84.

4-(4″-Chloro-2″-(methylthio)-7″H-pyrrolo[2,3-d]pyrimidin-7″-yl)-7-{5′-O-[(1,1-dimethylethyl)dimethylsilyl]-2′,3′-O-(1-methylethylidene)-β-D-ribofuranosyl}-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine (**7**). See synthesis of **6b**: The slower migrating zone yielded compound **7** as a yellow gum (195 mg, 7.5%). TLC (silica gel, *H*): R_f 0.45. ^{1}H-NMR ((D$_6$)DMSO): −0.01 (*s*, Me_2Si); 0.83 (*s*, *t*-BuSi); 1.35, 1.57 (2*s*, 2 Me); 2.63 (*s*, MeS); 3.74 (*m*, H–C(5′)); 4.19 (*m*, H–C(4′)); 4.95 (*dd*, *J* = 6.2, 3.2, H–C(3′)); 5.30 (*dd*, *J* = 6.2, 2.7, H–C(2′)); 6.37 (*d*, *J* = 2.7, H–C(1′)); 6.83 (*d*, *J* = 3.9, H–C(5)); 6.88 (*d*, *J* = 3.9, H–C(5″)); 7.69 (*d*, *J* = 3.9, H–C(6)); 8.09 (*d*, *J* = 3.9, H–C(6″)). ^{13}C-NMR ((D$_6$)DMSO): 63.3 (C(5′)); 80.9 (C(2′)); 83.6 (C(3′)); 85.7 (C(4′)); 89.1 (C(1′)); 102.5 (C(5)); 103.5 (C(5″)); 107.6, 115.3 (C(4a), C(4a″)); 126.1, 128.5 (C(6), C(6″)); 147.3, 151.3 (C(7a), C(7a″)); 151.4, 153.6 (C(4), C(4″)); 163.6, 165.0 (C(2), C(2″)). MS: 648 (3, M^+), 633 (3), 591 (28), 533 (20), 445 (70).

4-Chloro-7-{5′-O-[(1,1-dimethylethyl)dimethylsilyl]-2′,3′-O-(1-methylethylidene)-α-D-ribofuranosyl}-7H-pyrrolo[2,3-d]pyrimidin-2-amine (**9a**). Compound **9a** was prepared from **4a** (675 mg, 4.0 mmol) as described for **6a**, except that β-halogenose **8** (4.0 mmol, calculated on the basis of 100% yield of **8**) was used. Chromatographic workup (column 2.5 × 65 cm, *A*) followed by crystallization (MeOH) afforded colourless needles (560 mg, 31%). M.p. 123–124°. TLC (silica gel, *A*): R_f 0.4. UV (MeOH): 235 (26400), 260 (3700), 317 (4900). ^{1}H-NMR ((D$_6$)DMSO): 0.10 (*s*, Me_2Si); 0.93 (*s*, *t*-BuSi); 1.40, 1.25 (2*s*, 2 Me); 3.76 (*d*, *J* = 3.6, H–C(5′)); 4.29 (*m*, H–C(4′)); 4.80 (*m*, H–C(2′), H–C(3′)); 6.32 (*d*, *J* = 3.8, H–C(5)); 6.43 (*d*, *J* = 4.1, H–C(1′)); 6.51 (*s*, NH_2); 7.19 (*d*, *J* = 3.8, H–C(6)). Anal. calc. for $C_{20}H_{31}ClN_4O_4Si$ (455.0): C 52.79, H 6.87, N 12.31, Cl 7.79; found: C 52.80, H 6.79, N 11.98, Cl 7.52.

4-Chloro-7-{5′-O-[(1,1-dimethylethyl)dimethylsilyl]-2′,3′-O-(1-methylethylidene)-α-D-ribofuranosyl}-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine (**9b**). Compound **9b** was prepared from **4b** (1.60 g, 8.0 mmol) as described for **9a**. Chromatography (silica gel, column 5 × 20 cm, *A*) yielded a yellow gum (935 mg, 48%). TLC (silica gel, *H*): R_f 0.62. UV (MeOH): 251 (21400), 275 (7900), 309 (6400). ^{1}H-NMR ((D$_6$)DMSO): 0.10 (*s*, Me_2Si); 0.93 (*s*, *t*-BuSi); 1.24, 1.39 (2*s*, 2 Me); 3.81 (*m*, H–C(5′)); 4.39 (*m*, H–C(4′)); 4.90 (*m*, H–C(2′), H–C(3′)); 6.57 (*d*, *J* = 3.8, H–C(5)); 6.68 (*d*, *J* = 4.0, H–C(1′)); 7.69 (*d*, *J* = 3.8, H–C(6)).

4-Chloro-7-(β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (**10a**). A soln. of **6a** (650 mg, 1.4 mmol) in 90% aq. CF_3COOH soln. (3 ml) was stirred for 1 h at r.t. The mixture was evaporated, and traces of CF_3COOH were removed by repeated coevaporation with MeOH. The residue was chromatographed (silica gel, column 6 × 10 cm, *C*). From the main zone, colourless needles (330 mg, 77%) were obtained after crystallization from MeOH/H_2O. M.p. 170–172°. TLC (silica gel, *C*): R_f 0.45. UV (MeOH): 235 (26700), 259 (3900), 317 (5200). ^{1}H-NMR ((D$_6$)DMSO): 3.55 (*m*, H–C(5′)); 3.85 (*m*, H–C(4′)); 4.05 (*m*, H–C(3′)); 4.31 (*m*, H–C(2′)); 4.99 (*t*, *J* = 5.3, OH–C(5′)); 5.10 (*d*, *J* = 6.2, OH–C(3′)); 5.30 (*d*, *J* = 4.5, OH–C(2′)); 5.99 (*d*, *J* = 6.4, H–C(1′)); 6.38 (*d*, *J* = 3.8, H–C(5′)); 6.71 (*s*, NH_2); 7.39 (*d*, *J* = 3.9, H–C(6)). Anal. calc. for $C_{11}H_{13}ClN_4O_4$ (300.7): C 43.94, H 4.36, N 18.63; found: C 44.13, H 4.52, N 18.45.

4-Chloro-2-(methylthio)-7-(β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine (**10b**). Compound **10b** was prepared from **6b** (1.0 g, 2.1 mmol) as described for **10a**. The crude product was crystallized from MeOH: colourless needles (490 mg, 70%). M.p. 191–193°. TLC (silica gel, *I*): R_f 0.4. UV (MeOH): 251 (22600), 276 (6300), 310 (6500). ^{1}H-NMR ((D$_6$)DMSO): 2.60 (*s*, MeS); 3.60 (*m*, H–C(5′)); 3.94 (*m*, H–C(4′)); 4.13 (*m*, H–C(3′)); 4.44 (*m*, H–C(2′)); 5.44 (*d*, *J* = 6.4, OH–C(3′)); 6.14 (*d*, *J* = 6.1, H–C(1′)); 6.68 (*d*, *J* = 3.7, H–C(5)). Anal. calc. for $C_{12}H_{14}N_3O_4ClS$ (331.8): C 43.44, H 4.25, N 12.67; found: C 43.60, H 4.36, N 12.58.

4-Methoxy-7-(β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (**10c**). Compound **10c** [7] was prepared from **6c** (1.08 g, 2.4 mmol) as described for **10a**. Crystallization (*G*) afforded colourless needles (480 mg, 68%).

A soln. of **10a** (200 mg, 0.67 mmol) in 1.0M NaOMe/MeOH was stirred for 24 h at r.t. The mixture was neutralized with AcOH and evaporated. The residue was suspended in CH_2Cl_2 and filtered. The filtrate was dried (Na_2SO_4), and, after evaporation, chromatographed (silica gel, column 2.5 × 13 cm, *D*). From the main zone, colourless crystals of **10c** (150 mg, 76%) were obtained. M.p. 168°. TLC (silica gel, *D*): R_f 0.51. UV (MeOH): 260 (8600), 286 (6700). ^{1}H-NMR ((D$_6$)DMSO): 3.54 (*m*, H–C(5′)); 3.83 (*m*, H–C(4′)); 3.92 (*s*, MeO); 4.05 (*m*, H–C(3′)); 4.30 (*m*, H–C(2′)); 5.04 (*m*, OH–C(5′), OH–C(3′)); 5.23 (*d*, *J* = 6.3, OH–C(2′)); 5.97 (*d*, *J* = 6.3, H–C(1′)); 6.20 (*s*, NH_2); 6.28 (*d*, *J* = 3.7, H–C(5)); 7.11 (*d*, *J* = 3.7, H–C(6)). Anal. calc. for $C_{12}H_{16}N_4O_5$ (296.3): C 48.65, H 5.44, N 18.91; found: C 48.94, H 5.51, N 18.61.

4-Methoxy-2-(methylthio)-7-(β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine (**10d**). Compound **10d** was prepared from **6d** (240 mg, 0.4 mmol) as described for **10a**. Crystallization (MeOH) afforded colourless needles (130 mg, 80%). TLC (silica gel, *C*): R_f 0.3. UV (MeOH): 236 (11400), 281 (10000). ^{1}H-NMR ((D$_6$)DMSO): 2.54 (*s*, Me); 3.56 (*m*, CH_2(5′)); 3.87 (H–C(4′)); 4.04 (*m*, H–C(3′)); 4.40 (*m*, H–C(2′)); 5.11 (*t*, OH–C(5′)); 5.26 (*d*, *J* = 4.7, OH–C(3′)); 5.39 (*d*, *J* = 6.4, OH–C(2′)); 6.06 (*d*, *J* = 6.2, H–C(1′)); 6.49 (*d*, *J* = 3.7, H–C(8)); 7.45 (*d*, *J* = 3.7, H–C(6)). Anal. calc. for $C_{13}H_{17}N_3O_5S$ (327.4): C 47.69, H 5.23, N 12.83; found: C 47.95, H 5.40, N 12.73.

4-Chloro-7-(α-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (**11a**). Compound **11a** was prepared from **9a** (300 mg, 0.66 mmol) as described for **10a**. Chromatography (silica gel, column 5 × 10 cm, *I*) followed by crystallization (i-PrOH) afforded colourless needles (143 mg, 72%). M.p. 93–95°. TLC (silica gel, *I*): R_f 0.35. UV (MeOH): 235 (27200), 260 (3900), 318 (4900). ^{1}H-NMR ((D$_6$)DMSO): 3.50 (*m*, CH_2(5′)); 4.00 (*m*, H–C(4′)); 4.14 (*t*, *J* = 5.1, H–C(3′)); 4.27 (*t*, *J* = 5.1, H–C(2′)); 6.30 (*d*, *J* = 3.8, H–C(5)); 6.33 (*d*, *J* = 5.1, H–C(1′)); 6.66 (*s*, NH_2); 7.45 (*d*, *J* = 3.8, H–C(6)). Anal. calc. for $C_{11}H_{13}ClN_4O_4$ (300.7): C 43.94, H 4.36, N 18.63, Cl 11.79; found: C 44.05, H 4.36, N 18.49, Cl 11.89.

4-Methoxy-7-(α-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (**11c**). Compound **11c** was prepared from **11a** (250 mg, 0.83 mmol) as described for **10c** from **10a**. The crude product was purified on silica gel (column 2.5 × 20 cm, *F*): yellow foam (176 mg, 72%). TLC (silica gel, *F*): R_f 0.69. UV (MeOH): 225 (23400), 260 (8800), 287 (6900). ^{1}H-NMR ((D$_6$)DMSO): 3.50 (*m*, CH_2(5′)); 3.92 (*s*, MeO); 3.99 (*m*, H–C(4′)); 4.11 (*m*, H–C(3′)); 4.18 (*m*, H–C(2′)); 4.80 (*t*, OH–C(5′)); 5.15 (*d*, *J* = 5.3, OH–C(2′)); 5.24 (*d*, *J* = 5.6, OH–C(3′)); 6.16 (*s*, NH_2); 6.19 (*d*, *J* = 3.7, H–C(5)); 6.31 (*d*, *J* = 4.7, H–C(1′)); 7.21 (*d*, *J* = 3.7, H–C(6)). Anal. calc. for $C_{12}H_{16}N_4O_5$ (296.3): C 48.65, H 5.44, N 18.91; found: C 48.77, H 5.75, N 18.96.

2-Amino-7-(β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one (**1**). Compound **10a** (70 mg, 0.23 mmol) was dissolved in 2N NaOH (30 ml). After addition of 1,4-dioxane (5 ml), the mixture was heated under reflux for 3 h. After neutralization with AcOH and evaporation, the crude product was chromatographed on *Amberlite XAD-4* (mesh 20–50; column 2 × 20 cm, *E*): 40 mg (61%) of colourless crystals, after recrystallization from MeOH. M.p. 310–312°. TLC (silica gel, *E*): R_f 0.33. UV (MeOH): 218 (20200), 258 (12700), 280 (7800). ^{1}H-NMR ((D$_6$)DMSO): 3.54 (*m*, CH_2(5′)); 3.80 (*m*, H–C(4′)); 4.03 (*m*, H–C(3′)); 4.24 (*m*, H–C(2′)); 4.97 (*t*, *J* = 5.4, OH–C(5′)); 5.05 (*d*, *J* = 4.4, OH–C(3′)); 5.24 (*d*, *J* = 6.2, OH–C(2′)); 5.87 (*d*, *J* = 6.2, H–C(1′)); 6.24 (*s*, NH_2); 6.28 (*d*, *J* = 3.6, H–C(5)); 6.94 (*d*, *J* = 3.6, H–C(6)); 10.33 (*s*, NH). See also [6].

2-Amino-7-(α-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one (**3**). Compound **3** was prepared from **11a** (250 mg, 0.83 mmol) as described for **1** yielding 130 mg (56%) of colourless crystals upon crystallization from i-PrOH. M.p. 98–100°. TLC (silica gel, *E*): R_f 0.41. UV (MeOH): 218 (24600), 260 (13200), 278 (8800). ^{1}H-NMR ((D$_6$)DMSO): 3.44 (*m*, CH_2(5′)); 3.97 (*m*, H–C(4′)); 4.10 (*m*, H–C(3′)); 4.13 (*m*, H–C(2′)); 6.15 (*d*, *J* = 3.7, H–C(5)); 6.17 (*d*, *J* = 6.4, H–C(1′)); 6.62 (*s*, NH_2); 7.02 (*d*, *J* = 3.6, H–C(6)); 11.30 (*s*, NH). Anal. calc. for $C_{11}H_{14}N_4O_5$ (282.3): C 46.81, H 5.00, N 19.85; found: C 46.94, H 5.20, N 19.75.

7-(β-D-Ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine (**12**). Compound **10a** (200 mg, 0.67 mmol) was dissolved in 25% aq. NH_3 soln. (150 ml) and heated in a steel bomb for 20 h at 80°. The mixture was evaporated and purified on silica gel (column 2.5 × 13 cm, *E*). From the main zone, **12** [7] was isolated as a colourless gum (155 mg, 82%). TLC (silica gel, *E*): R_f 0.46. UV (MeOH): 264 (8700), 285 (6800). ^{1}H-NMR ((D$_6$)DMSO): 3.54 (*m*, CH_2(5′)); 3.82 (*m*, H–C(4′)); 4.04 (*m*, H–C(3′)); 4.11 (*m*, OH–C(5′)); 4.32 (*m*, H–C(2′)); 5.04 (*d*, *J* = 4.4, OH–C(3′)); 5.20 (*m*, OH–C(2′)); 5.59, 6.69 (2*s*, $2NH_2$); 5.84 (*d*, *J* = 6.4, H–C(1′)); 6.39 (*d*, *J* = 3.6, H–C(5)); 6.90 (*d*, *J* = 3.7, H–C(6)). Anal. calc. for $C_{11}H_{15}N_5O_4$ (281.3): C 46.97, H 5.38; found: C 46.82, H 5.44.

7-(α-D-Ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine (**13**). Compound **13** was prepared from **11a** (250 mg, 0.83 mmol) as described for **12**. Chromatographic workup (column 2.5 × 13 cm, *J*) gave colourless crystals (155 mg, 66%). M.p. 205–206°. TLC (silica gel, *J*): R_f 0.43. UV (MeOH): 222 (23700), 264 (8900), 284 (7200). ^{1}H-NMR ((D$_6$)DMSO): 3.45 (*m*, CH_2(5′)); 3.97 (*m*, H–C(4′)); 4.10 (*m*, H–C(3′)); 4.14 (*m*, H–C(2′)); 4.82 (*t*, *J* = 5.6, OH–C(5′)); 5.21 (*d*, *J* = 4.8, OH–C(2′)); 5.27 (*d*, *J* = 5.7, OH–C(3′)); 5.51 (*s*, NH_2–C(4)); 6.20 (*d*, *J* = 4.5, H–C(1′)); 6.29 (*d*, *J* = 3.6, H–C(5)); 6.50 (*s*, NH_2–C(2)); 7.00 (*d*, *J* = 3.7, H–C(6)). Anal. calc. for $C_{11}H_{15}N_5O_4$ (281.3): C 46.97, H 5.38, N 24.90; found: C 47.15, H 5.37, N 24.86.

7-(β-D-Ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (**14**). To a soln. of **10a** (120 mg, 0.04 mmol) in MeOH (20 ml), 25% aq. NH_3 soln. (1 ml) was added, and the mixture was hydrogenated in the presence of 10% Pd/C (130 mg) for 4 h at r.t. The catalyst was filtered off and the filtrate evaporated. After chromatography (silica gel, column 2 × 10 cm, *D*) and crystallization from MeOH/H_2O, colourless needles (52 mg, 49%) were obtained. M.p. 162–164°. TLC (silica gel, *C*): R_f 0.24. UV (MeOH): 234 (28000), 256 (4200), 314 (5100). ^{1}H-NMR ((D$_6$)DMSO): 3.53 (*m*, CH_2(5′)); 3.83 (*m*, H–C(4′)); 4.05 (*m*, H–C(3′)); 4.32 (*m*, H–C(2′)); 5.00 (*t*, *J* = 5.4, OH–C(5′)); 5.08 (*d*, *J* = 4.4, OH–C(3′)); 5.26 (*d*, *J* = 6.2, OH–C(2′)); 6.02 (*d*, *J* = 6.3, H–C(1′)); 6.23 (*s*, NH_2); 6.37 (*d*, *J* = 3.6, H–C(5)); 7.28 (*d*, *J* = 3.7, H–C(6)); 8.46 (*s*, H–C(4)). Anal. calc. for $C_{11}H_{14}N_4O_4$ (266.3): C 49.62, H 5.30, N 21.04; found: C 49.81, H 5.39, N 20.98.

7-(α-D-Ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (**15**). Compound **15** was prepared from **11a** (250 mg, 0.83 mmol) as described fro **14**. After hydrogenation for 2 h (r.t., 1 atm) and evaporation, the crude product was chromatographed on silica gel (column 2.5 × 10 cm, *F*). From the main zone, colourless needles (114 mg, 51%) were obtained. M.p. 219–220°. TLC (silica gel, *F*): R_f 0.52. UV (MeOH): 234 (30100), 255 (4200), 314 (5000). ^{1}H-NMR ((D$_6$)DMSO): 3.50 (*m*, CH_2(5′)); 4.00 (*m*, H–C(4′)); 4.10 (*q*, *J* = 5.5, H–C(3′)); 4.25 (*q*, *J* = 5.2,

H–C(2')); 4.86 (*t*, *J* = 5.6, OH–C(5')); 5.22 (*d*, *J* = 5.6, OH–C(2')); 5.29 (*d*, *J* = 5.6, OH–C(3')); 6.21 (*s*, NH_2); 6.30 (*d*, *J* = 3.8, H–C(5)); 6.39 (*d*, *J* = 4.9, H–C(1')); 7.40 (*d*, *J* = 3.8, H–C(6)); 8.46 (*s*, NH). Anal. calc. for $C_{11}H_{14}N_4O_4$ (266.3): C 49.62, H 5.30, N 21.04; found: C 49.72, H 5.44, N 20.84.

*2-Amino-7-(β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-4(3*H*)-thione* (**16**). To a soln. of **10a** (250 mg, 0.83 mmol) and thiourea (200 mg, 2.6 mmol) in H_2O (25 ml), HCO_2H (1 drop) was added and the mixture heated under reflux for 15 min. Aq. NH_3 soln. (25%) was added until the pH rose to 3.0. After another 10 min of heating, the mixture was evaporated and the residue chromatographed (silica gel, column 3 × 15 cm, *C*). From the main zone, colourless needles (213 mg, 86%) were obtained. M.p. 225–228°. TLC (silica gel, *C*): R_f 0.28. UV (MeOH): 235 (18900), 271 (12600), 345 (18700). ^{1}H-NMR ((D_6)DMSO): 3.56 (*m*, CH_2(5')); 3.84 (*m*, H–C(4')); 4.05 (*m*, H–C(3')); 4.27 (*m*, H–C(2')); 4.94 (*t*, *J* = 5.3, OH–C(5')); 5.05 (*d*, *J* = 4.5, OH–C(3')); 5.26 (*d*, *J* = 6.1, OH–C(2')); 5.88 (*d*, *J* = 6.2, H–C(1')); 6.43 (*d*, *J* = 3.7, H–C(5)); 6.62 (*s*, NH_2); 7.16 (*d*, *J* = 3.7, H–C(6)); 11.77 (*s*, NH). Anal. calc. for $C_{11}H_{14}N_4O_4S$ (298.3): C 44.29, H 4.73, N 18.78, S 10.75; found: C 44.47, H 4.90, N 18.87, S 10.79.

*2-Amino-7-(α-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-4(3*H*)-thione* (**17**). Compound **17** was prepared from **11a** (250 mg, 0.83 mmol) as described for **16**. Chromatography (silica gel, column 3 × 12 cm, *C*) furnished yellow needles (200 mg, 81%). M.p. 207–209°. TLC (silica gel, *C*): R_f 0.2. UV (MeOH): 235 (19200), 270 (12400), 345 (17700). ^{1}H-NMR ((D_6)DMSO): 3.43 (*m*, CH_2(5')); 4.01 (*m*, H–C(4')); 4.10 (*q*, *J* = 5.3, H–C(3')); 4.19 (*m*, H–C(2')); 4.85 (*t*, *J* = 5.6, OH–C(5')); 5.19 (*d*, *J* = 5.6, OH–C(3')); 5.26 (*d*, *J* = 5.6, OH–C(2')); 6.18 (*d*, *J* = 4.9, H–C(1')); 6.33 (*d*, *J* = 3.7, H–C(5)); 6.58 (*s*, NH_2); 7.15 (*d*, *J* = 3.7, H–C(6)); 11.74 (*s*, NH). Anal. calc. for $C_{11}H_{14}N_4O_4S$ (298.3): C 44.29, H 4.73, N 18.78, S 10.75; found: C 44.30, H 4.69, N 18.63, S 10.89.

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