Synthesis of New Nucleosides by Coupling of Chloropurines with 2- and 3-Deoxy Derivatives of *N*-Methyl-D-ribofuranuronamide

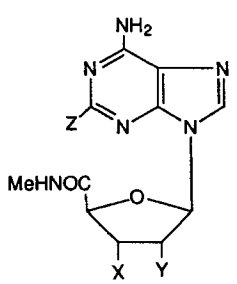
by **Rosaria Volpini, Emidio Camaioni, Sauro Vittori, Luciano Barboni, Catia Lambertucci,** and **Gloria Cristalli***

Dipartimento di Scienze Chimiche, Università di Camerino, I-62032 Camerino

The synthesis of new deoxyribose nucleosides by coupling chloropurines with modified D-ribose derivatives is reported. The methyl 2-deoxy-*N*-methyl-3-*O*-(*p*-toluoyl)-α-D-ribofuranosiduronamide (α-D-**8**) and the corresponding anomer β-D-**8** were synthesized starting from the commercially available 2-deoxy-D-ribose (**1**) (*Scheme 1*). Reaction of α-D-**8** with the silylated derivative of 2,6-dichloro-9*H*-purine (**9**) afforded regioselectively the N^9-(2′-deoxyribonucleoside) **10** as anomeric mixture (*Scheme 2*), whereas β-D-**8** did not react. Glycosylation of **9** or of 6-chloro-9*H*-purine (**17**) with 1,2-di-*O*-acetyl-3-deoxy-*N*-methyl-β-D-ribofuranuronamide (**13**) yielded only the protected β-D-anomers **14** and **18**, respectively (*Scheme 3*). Subsequent deacetylation and dechlorination afforded the desired nucleosides β-D-**11**, β-D-**12**, **15**, and **16**. The 3′-deoxy-2-chloroadenosine derivative **15** showed the highest affinity and selectivity for adenotin binding site *vs.* A_1 and A_{2A} adenosine receptor subtypes.

Introduction. – A low-affinity adenosine-binding protein named adenotin can be distinguished from the known adenosine receptor subtypes A_1, A_{2A}, A_{2B}, and A_3 [1–4]. Although adenotin shows amino-acid sequence homologies with heat-shock proteins, a calcium-binding protein, and a protein kinase, its physiological significance remains to be elucidated [5]. However, its high intracellular concentration (*ca.* 1% of protein in human placenta) suggests that adenotin could play an important role in the regulation of cellular functions (*e.g.*, cell proliferation, tumor growth).

Some adenosines and (1-adenin-9-yl)-*N*-alkyl-1-deoxy-β-D-ribofuranuronamides (Ade-Rib*f*Am5′R; Am = uronamide) have been reported to discriminate between A_1 and A_{2A} adenosine receptors [6–8]. On the other hand, 1-(2-chloroadenin-9-yl)-1-deoxy-*N*-methyl-β-D-ribofuranuronamide (cl^{2}Ade-Rib*f*Am5′Me) showed high affinity for both adenotin and adenosine receptors. Since removing OH groups from the 2′ and 3′ positions of adenosine derivatives greatly compromises adenosine receptor subtype affinity,



cl^{2}Ade–Rib*f*Am5′Me	X = OH, Y = OH, Z = Cl
β-D-**11**	X = OH, Y = H, Z = Cl
β-D-**12**	X = OH, Y = H, Z = H
15	X = H, Y = OH, Z = Cl
16	X = H, Y = OH, Z = H

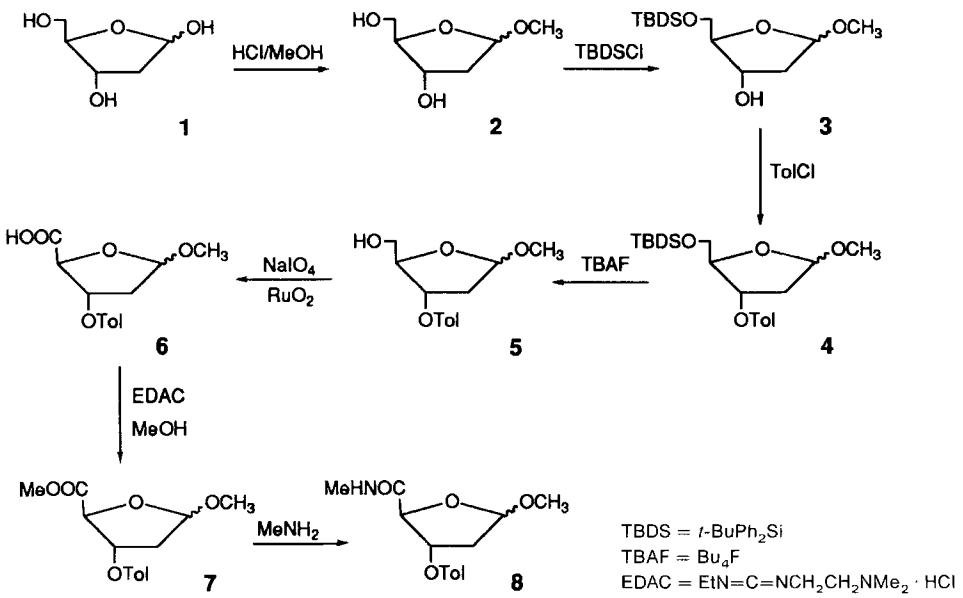
Fig. 1. *Target compounds* β-D-**11**, β-D-**12**, **15**, *and* **16** *derived from Ade-Rib*f*Am5′Me*

the synthesis of deoxy derivatives of Ade-Rib*f*Am5'Me (see *Fig.*) was carried out to characterize selective adenotin ligands.

In this paper, we report a versatile synthesis of the target compounds β-D-**11**, β-D-**12**, **15**, and **16** in which the corresponding 2- and 3-deoxysugars were coupled to the commercially available 2,6-dichloro-9*H*-purine and 6-chloro-9*H*-purine. Using different amines in the deblocking step, it is possible to obtain a variety of N^6-substituted adenosine derivatives [9]. Furthermore, the presence of a Cl-atom at C(2) would allow the achievement of a number of 2,6-disubstituted purine derivatives.

Synthesis. – The methyl 2-deoxy-*N*-methyl-3-*O*-(*p*-toluoyl)-α-D-ribofuranosiduronamide (α-D-**8**) and the corresponding anomer β-D-**8** were synthesized starting from the commercially available 2-deoxy-D-ribose (**1**) (*Scheme 1*) which was at first treated with HCl/MeOH to give the sugar **2** as a 1:1 anomer mixture. Crude **2** was selectively protected at the 5-position by reaction with (*tert*-butyl)diphenylsilyl chloride yielding the anomer mixture α-D-**3**/β-D-**3** which was separated by flash chromatography (FC). The anomeric configuration of these compounds was assigned by ^{1}H-NOE difference spectroscopy in DMSO.

Scheme 1[a])



[a]) From compounds α- and β-D-**3** on all reactions were performed separately with the pure anomers.

Saturation of H–C(1) of α-D-**3** resulted in a NOE at the H–C(3) signal (0.9%) while there was none at the H–C(4) signal, and saturation of H–C(1) of β-D-**3** yielded a NOE at the H–C(4) signal (0.6%) while there was none at the H–C(3) signal, establishing the α-D- and β-D-configuration, respectively.

The derivative α-D-**3** was treated with *p*-toluoyl chloride (TolCl) to give α-D-**4**. Reaction α-D-**4** with tetrabutylammonium fluoride gave the 5-hydroxy derivative α-D-**5** which was oxidized using sodium periodate and ruthenium(IV) oxide. The resulting α-D-**6** was

esterified with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDAC) and MeOH and the resulting ester α-D-**7** was treated with methylamine to give amide α-D-**8**. Amide β-D-**8** was synthesized from β-D-**3** by the same procedure. The anomeric configuration of α-D- and β-D-**8** was again checked by ^{1}H-NOE difference spectroscopy before coupling to the base.

Saturation of H–C(4) was carried out since the H–C(1) signal was too close to the H–C(3) signal in both anomers **8**. The assignment of the α-D-configuration was confirmed by the absence of a NOE at H–C(1) which was present in the case of the β-D-anomer (0.6%).

Coupling of anomer α-D-**8** with the silylated derivative of 2,6-dichloro-9*H*-purine (**9**) using trimethylsilyl trifluoromethanesulfonate ($TfOSiMe_3$) as catalyst furnished the protected nucleoside **10** in 30% yield as a 1:1 anomer mixture (*Scheme 2*). When the same coupling was carried out using β-D-**8**, no reaction occurred. This fact can be due to the refusal of the β-oriented MeO group of β-D-**8** to behave as leaving group in the presence of $TfOSiMe_3$, according to the *Vorbrüggen* reaction [11]. This hypothesis is in agreement with our previous finding that the coupling between the β-D-anomer of the corresponding 3-deoxy sugar and the silylated derivative of **9**, under the same conditions, yielded two acyclic diastereoisomers in which the MeO group was still present at the C(1′) position [12]. Moreover, attempts to substitute the MeO group by other leaving groups (acetyl and halogen substituents) were unsuccessful. The anomers of **10** were separated by FC and reacted with liquid ammonia to give the corresponding 1-(2-chloroadenin-9-yl)-1,2-dideoxy-*N*-methyl-D-*erythro*-pentofuranuronamides **11**. The Cl-atom at C(2) was removed from both anomers by treatment with H_2 using 10% Pd/C as catalyst to give the adenine derivatives α-D- and β-D-**12** in 51 and 43% yield, respectively.

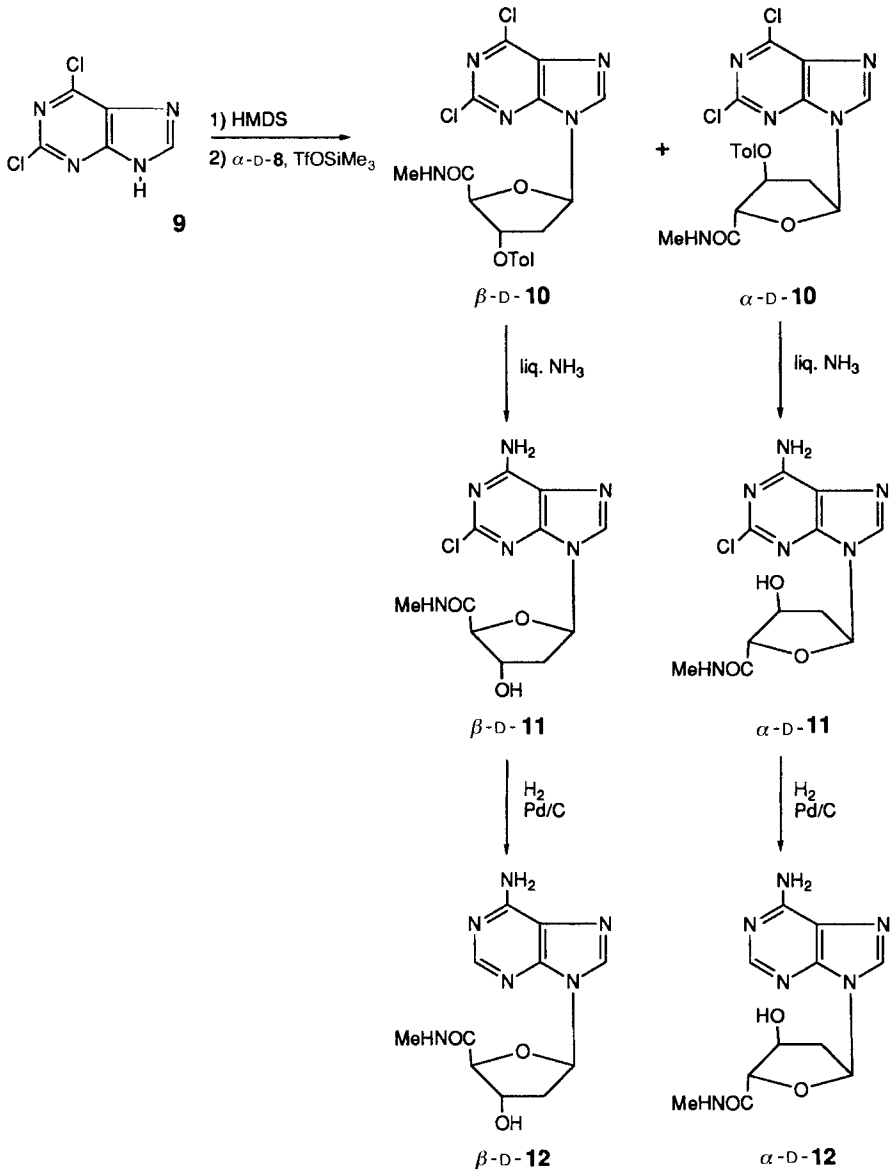
The anomeric configuration was assigned by applying the ^{1}H-NOE technique to the deprotected nucleosided α-D- and β-D-**11**. Saturation of H–C(1′) of β-D-**11** resulted in a NOE of 1.2% at H–C(4′), and saturation of the same proton gave a NOE of < 0.5% in the case of α-D-**11**.

The synthesis of 2-*O*-acetyl-1,3-dideoxy-1-(2,6-dichloro-9*H*-purin-9-yl)-*N*-methyl-β-D-ribofuranuronamide (**14**) was previously achieved in 32% yield by coupling methyl 2-*O*-acetyl-3-deoxy-*N*-methyl-β-D-ribofuranosiduronamide [10] to the silylated 2,6-dichloro-9*H*-purine (**9**). To improve the yield, the same base was coupled to 1,2-di-*O*-acetyl-3-deoxy-*N*-methyl-β-D-ribofuranuronamide (**13**) [13] (*Scheme 3*). Compound **14** was obtained in 66% yield only in the β-D-configuration, due to the presence of the neighboring 2-*O*-acetyl group on the sugar. The protected nucleoside **14** was treated with liquid ammonia to give the corresponding 2-chloroadenine derivative **15**. The synthesis of the dechlorinated nucleoside **16** was achieved by two different routes. Coupling of the silylated derivative of 6-chloro-9*H*-purine (**17**) with **13** gave the protected nucleoside **18** in 40% yield. The target **16** was then obtained either by treatmet of **18** with liquid ammonia or by a classical dechlorination of **15**.

The N(9)-isomer structure of the new nucleosides **12** and **16** was assigned on the basis of the UV spectra in comparison with those of adenosine.

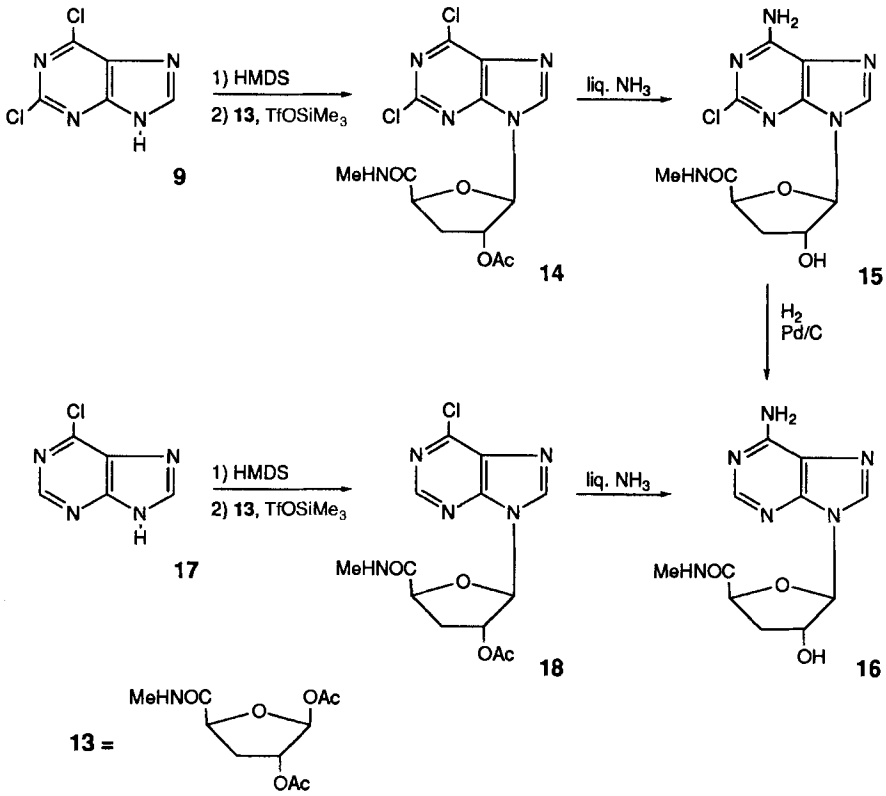
Conclusion. – Preliminary competition experiments for [^{3}H]NECA binding [4] showed that the new nucleosides β-D-**11**, β-D-**12**, **15**, and **16** possess high affinity for

Scheme 2



adenotin combined with good selectivity *vs.* adenosine receptor subtypes. In fact, removing the 2′- or 3′-hydroxy group from cl^{2}Ade-Rib*f*Am5′Me greatly diminished A_1 and A_{2A} adenosine receptor affinity. In particular, cl^{2}Ade-d$^{3'}$Rib*f*Am5′Me (**15**) displayed high affinity and selectivity for the adenotin binding site (K_i = 13.7 nM; K_i (A_1) = 6800 nM; K_i (A_{2A}) = 5800 nM), thus being the most potent and selective adenotin ligand so far known.

Scheme 3



Experimental Part

General. Melting points *Büchi* apparatus, uncorrected. TLC: precoated TLC plates, silica gel *60 F-254* (*Merck*). Flash chromatography (FC): silica gel *60* (*Merck*). UV Spectra: *Perkin-Elmer-Coleman-575* spectrophotometer; $\lambda_{max}(\varepsilon)$ in nm. ^{1}H-NMR Spectra: *Varian-VXR-300* spectrometer; at 300 MHz; δ in ppm, J in Hz. Elemental analyses: *Carlo-Erba-1106* analyzer; $\pm 0.4\%$ of theor. values.

Methyl 5-O-[(tert-Butyl)diphenylsilyl]-2-deoxy-α and -β-D-ribofuranose (α-D- and β-D-**3** resp.). To a soln. of 2-deoxy-D-ribose (**1**; *Fluka*; 25 g, 186.39 mmol) in dry MeOH (450 ml), 1% HCl in MeOH (50 ml) was added, and the mixture was stirred at r.t. for 30 min. After the slow addition of Ag_2CO_3 (7 g, 25.4 mmol), the suspension was filtered over *Celite* and the filtrate evaporated: 30 g of *methyl 3-deoxy-*D*-ribofuranoside* (**2**) as a thick syrup. To an ice-cooled soln. of **2** (30 g) in dry CH_2Cl_2 (100 ml), dry Et_3N (30 ml) and 4-(dimethylamino)pyridine (1.5 g, 12.8 mmol) were added, followed by the dropwise addition of (*tert*-butyl)diphenylsilyl chloride (50 g, 182 mmol) in dry CH_2Cl_2 (100 ml). The mixture was allowed to stand at r.t. for 18 h and then evaporated. The residue was partitioned between H_2O and $CHCl_3$, the org. layer washed with brine, dried (Na_2SO_4), and evaporated, and the residue submitted to FC (silica gel, cyclohexane/AcOEt 95:5 → 70:30): less polar β-D-**3** (20.4 g, 28%) and more polar α-D-**3** (28.6 g, 40%), both as colorless oil.

α-D-**3**: ^{1}H-NMR ($CDCl_3$): 1.05 (*s*, *t*-Bu); 2.02 (*d*, J = 11.7, 1 H–C(2)); 2.20 (*m*, 1H–C(2)); 3.38 (*s*, MeO); 3.68 (*m*, 2 H–C(5)); 4.16 (*m*, H–C(4)); 4.30 (*m*, H–C(3)); 5.11 (*d*, J = 4.4, H–C(1)); 7.40 (*m*, 6 arom. H); 7.64 (*m*, 4 arom. H). Anal. calc. for $C_{22}H_{30}O_4Si$: C 68.36, H 7.82; found: C 68.57, H 7.99.

β-D-**3**: ^{1}H-NMR ($CDCl_3$): 1.08 (*s*, *t*-Bu); 2.00–2.27 (*m*, 2 H–C(2)); 3.27 (*s*, MeO); 3.74 (*m*, 2 H–C(5)); 3.95 (*m*, H–C(4)); 4.52 (*m*, H–C(3)); 5.05 (*dd*, J = 2,2, 5.2, H–C(1)); 7.40 (*m*, 6 arom. H); 7.69 (*m*, 4 arom. H). Anal. calc. for $C_{22}H_{30}O_4Si$: C 68.36, H 7.82; found: C 68.64, H 8.01.

*Methyl 5-O-[(*tert*-Butyl)diphenylsilyl]2-deoxy-3-O-(*p*-toluoyl)-α- and -β-*D*-ribofuranoside* (α-D- and β-D-**4**, resp.). To a soln. of α-D- *or* β-D-**3** (11.5 g, 29.8 mmol) in dry CH_2Cl_2 (300 ml) and dry pyridine (60 ml) cooled to 0°, *p*-toluoyl chloride (9 ml, 68 mmol) was added dropwise, and the mixture was allowed to stand at r.t. for 5 h. Ice and $CHCl_3$ (3 × 200 ml) were added, and the org. layer was separated and washed with H_2O, sat. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated. The residue was purified by FC (cyclohexane/$CHCl_3$/AcOEt 90:9:1): α-D-**4** (13.2 g, 88%) or β-D-**4** (13.1 g, 87%), resp., both as colorless oil.

α-D-**4**: ^{1}H-NMR ($CDCl_3$): 1.05 (*s*, *t*-Bu); 2.13 (*m*, 1 H–C(2)); 2.41 (*s*, *Me*C_6H_4); 2.54 (*m*, 1 H–C(2)); 3.42 (*s*, MeO); 3.84, 3.95 (2*m*, 2 H–C(5)); 4.31 (*m*, H–C(4)); 5.19 (*d*, *J* = 4.4, H–C(1)); 5.48 (*m*, H–C(3)); 7.21–7.95 (*m*, 14 arom. H). Anal. calc. for $C_{30}H_{36}O_5Si$: C 71.4, H 7.19; found: C 71.68, H 7.30.

β-D-**4**: ^{1}H-NMR ($CDCl_3$): 1.05 (*s*, *t*-Bu); 2.27 (*m*, H–C(2)); 2.42 (*s*, *Me*C_6H_4); 2.46 (*m*, 1 H–C(2)); 3.34 (*s*, MeO); 3.80 (*m*, 2 H–C(5)); 4.30 (*m*, H–C(4)); 5.18 (*m*, H–C(1)); 5.58 (*m*, H–C(3)); 7.22–7.96 (*m*, 14 arom. H). Anal. calc. for $C_{30}H_{36}O_5Si$: C 71.4, H 7.19; found: C 71,57, H 7.32.

*Methyl 2-Deoxy-3-O-(*p*-toluoyl)-α- and β-*D*-ribofuranoside* (α-D- and β-D-**5**, resp.). A mixture of α-D- or β-D-**4** (12 g, 23.8 mmol) and 1M Bu_4NF in THF (26 ml) was stirred at r.t. for 1 h and then evaporated. Purification by FC (cyclohexane/AcOEt 70:30) gave α-D-**5** (5.83 g, 92%) or β-D-**5** (4.12 g, 65%), resp.

α-D-**5**: Colorless powder. ^{1}H-NMR ($CDCl_3$): 2.20 (*m*, 1 H–C(2)); 2.41 (*s*, *Me*C_6H_4); 2.48 (*m*, 1 H–C(2)); 3.41 (*s*, MeO); 3.86 (*m*, 2 H–C(5)); 4.25 (*m*, H–C(4)); 5.16 (*d*, *J* = 4.4, H–C(1)); 5.32 (*m*, H–C(3)); 7.24 (*d*, *J* = 8.2, 2 arom. H); 7.94 (*d*, *J* = 8.3, 2 arom. H). Anal. calc. for $C_{14}H_{18}O_5$: C 63.15, H 6.81; found: C 63.38, H 6.94.

β-D-**5**: Light-yellow oil. ^{1}H-NMR ($CDCl_3$): 2.32–2.57 (*m*, 2 H–C(2), *Me*C_6H_4); 3.45 (*s*, MeO); 3.81 (*d*, *J* = 3.3, 2 H–C(5)); 4.38 (*m*, H–C(4)); 5.25 (*m*, H–C(1)); 5.55 (*m*, H–C(3)); 7.24 (*d*, *J* = 8.2, 2 arom. H); 7.91 (*d*, *J* = 8.3, 2 arom. H). Anal. calc. for $C_{14}H_{18}O_5$: C 63.15, H 6.81; found: C 63.37, H 6.98.

*Methyl (2-Deoxy-3-O-(*p*-toluoyl)-α- and β-*D*-ribofuranosiduronic Acid)* (α-D- and β-D-**6**, resp.). A mixture of α-D- or β-D-**5** (4.0 g, 15 mmol), ruthenium(IV) oxide (150 mg), and sodium periodate (16 g, 75 mmol) in $CHCl_3$/MeCN/H_2O 2:2:3 (270 ml) was vigorously stirred at r.t. for 16 h and then filtered over *Celite*. The filtrate was partitioned between H_2O and $CHCl_3$ and the org. layer dried (Na_2SO_4), filtered, and evaporated: 4.15 g of α-D-**6** or 4.4 g of β-D-**6**, resp. The dark syrups were used without further purification in the following step. Anal. samples were obtained by prep. TLC ($CHCl_3$/MeOH 8:2).

α-D-**6**: ^{1}H-NMR ($CDCl_3$): 1.98 (*d*, *J* = 14.5, 1 H–C(2)); 2.40 (*m*, *Me*C_6H_4, 1 H–C(2)); 3.33 (*s*, MeO); 4.58 (*d*, *J* = 2.9, H–C(4)); 5.24 (*d*, *J* = 5.4, H–C(1)); 5.44 (*m*, H–C(3)); 7.37 (*d*, *J* = 8.2, 2 arom. H); 7.87 (*d*, *J* = 8.3, 2 arom. H). Anal. calc. for $C_{14}H_{16}O_6$: C 60.0, H 5.75; found: C 60.32, H 5.93.

β-D-**6**: ^{1}H-NMR ($CDCl_3$): 2.30–2.60 (*m*, 2 H–C(2), *Me*C_6H_4); 3.52 (*s*, MeO); 4.77 (*d*, *J* = 2.6, H–C(4)); 5.35 (*dd*, *J* = 2.4, 5.2, H–C(1)); 5.81 (*m*, H–C(3)); 7.26 (*m*, 2 arom. H); 7.93 (*m*, 2 arom. H). Anal. calc. for $C_{14}H_{16}O_6$: C 60.0, H 5.75; found: C 60.32, H 5.93.

*Methyl (Methyl 2-Deoxy-3-O-(*p*-toluoyl)-α- and -β-*D*-ribofuranosiduronate)* (α-D- and β-D-**6**; resp.). To 4.15 g of crude α-D- or β-D-**6** in dry MeOH (45 ml), EDAC (6.7 g, 34.5 mmol) was added, and the mixture was stirred at r.t. for 4 h. The solvent was evaporated, the residue partitioned between H_2O and $CHCl_3$ and the org. layer dried (Na_2SO_4) and evaporated: α-D-**7** or 3.6 g of β-D-**7**, resp., which were used without further purification in the following step. An anal. sample of α-D-**7** was obtained by prep. TLC (cyclohexane/AcOEt 9:1). ^{1}H-NMR ($CDCl_3$): 2.17 (*m*, 1 H–C(2)); 2.42 (*s*, *Me*C_6H_4); 2.52 (*m*, 1 H–C(2)); 3.45 (*s*, MeO); 3.81 (*s*, COOMe); 4.76 (*d*, *J* = 3.3, H–C(4)); 5.32 (*d*, *J* = 4.8, H–C(1)); 5.53 (*m*, H–C(3)); 7.25 (*d*, *J* = 7.7, 2 arom. H); 7.95 (*d*, *J* = 8.2, 2 arom. H). Anal. calc. for $C_{15}H_{18}O_6$: C 61.22, H 6.16; found: C 61.01, H 5.97.

*Methyl 2-Deoxy-*N*-methyl-3-O-(*p*-toluoyl)-α- and β-*D*-ribofuranosiduronamide* α-D- *and* β-D-**8**. To a soln. of crude α-D-**7** (4.3 g) or β-D-7 (3.6 g) in THF (25 ml), 2M $MeNH_2$ in THF (15 ml) was added. The mixture was stirred for 2 h at −20° and then 16 h at r.t. The solvent was evaporated and the residue purified by FC (cyclohexane/AcOEt 7:3): α-D-**8** (1.6 g, 37% from α-D-**5**) or β-D-**8** (1.1 g, 25% from β-D-**5**), resp., as white solids.

α-D-**8**: M.p. 124–126°. ^{1}H-NMR ($CDCl_3$): 2.19 (*m*, 1 H–C(2)); 2.38 (*m*, *Me*C_6H_4, 1 H–C(2)); 2.87 (*d*, *J* = 4.9, *Me*NH); 3.42 (*s*, MeO); 4.73 (*d*, *J* = 2.7, H–C(4)); 5.25 (*d*, *J* = 4.4, H–C(1)); 5.51 (*m*, H–C(3)); 6.65 (*m*, NH); 7.23 (*d*, *J* = 8.1, 2 arom. H); 7.95 (*d*, *J* = 8.3, 2 arom. H). Anal. calc. for $C_{15}H_{19}NO_5$: C 61.42, H 6.53, N 4.78; found: C 61.74, H 6.75, N 4.49.

β-D-**8**: M.p. 104–106°. ^{1}H-NMR ($CDCl_3$): 2.27 (*m*, 1 H–C(2)); 2.39 (*m*, *Me*C_6H_4, 1 H–C(2)); 2.87 (*d*, *J* = 4.8, *Me*NH); 3.55 (*s*, MeO); 4.69 (*s*, H–C(4)); 5.36 (*t*, *J* = 5.3, H–C(1)); 5.70 (*m*, H–C(3)); 7.20 (*d*, *J* = 8.6, 2 arom. H); 7.65 (*m*, NH); 7.91 (*d*, *J* = 8.2, 2 arom. H). Anal. calc. for $C_{15}H_{19}NO_5$: C 61.42, H 6.53, N 4.78; found: C 61.78, H 6.72, N 4.50.

*1,2-Dideoxy-1-(2,6-dichloro-9*H*-purin-9-yl)-*N*-methyl-3-O-(*p*-toluoyl)-β- and* -α-D-erythro-*pentofuranuronamide* (β-D- and α-D-**10**, resp.). A mixture of 2,6-dichloro-9*H*-purine (**9**; 0.280 g, 1.48 mmol), ammonium sulfate

(cat. amount), and hexamethyldisilazane (HMDS; 5 ml) was refluxed for 3 h under N_2. The solvent was evaporated under exclusion of moisture and the residue dissolved in dry CH_2Cl_2 (5 ml). After the addition of α-D-**8** (0.322 g, 1.48 mmol) in dry CH_2Cl_2 (5 ml), $TfOSiMe_3$ (0.287 ml, 1.48 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise and the mixture stirred for 16 h at r.t. Then a sat. $NaHCO_3$ soln. (10 ml) was added and the org. phase dried (Na_2SO_4) and evaporated. Purification by FC ($CHCl_3$/cyclohexane/MeCN 86:10:4) gave β-D-**10** (0.175 g, 32%) and α-D-**10** (0.175 g, 32%) as white oily solids.

β-D-**10**: ^{1}H-NMR ($(D_6)Me_2SO$): 2.43 (*s*, *Me*C_6H_4); 2.62 (*d*, *J* = 4.5, *Me*NH); 2.77 (*m*, 1 H–C(2′)); 3.22 (*m*, 1 H–C(2′)); 4.77 (*s*, H–C(4′)); 5.84 (*d*, *J* = 5.3, H–C(3′)); 6.59 (*t*, *J* = 7.1, H–C(1′)); 7.41 (*d*, *J* = 8.2, 2 arom. H); 7.99 (*d*, *J* = 8.2, 2 arom. H); 8.02 (*m*, NH); 9.05 (*s*, H–C(8)). Anal. calc. for $C_{19}H_{16}Cl_2N_5O_4$: C 50.8, H 3.59, N 15.59; found: C 51.04, H 3.76, N 15.22.

α-D-**10**: ^{1}H-NMR ($(D_6)Me_2SO$): 2.31 (*s*, *Me*C_6H_4); 2.70 (*d*, *J* = 4.7, *Me*NH); 2.94 (*m*, 2 H–C(2′)); 5.16 (*s*, H–C(4′)); 5.66 (*d*, *J* = 5.3, H–C(3′)); 6.76 (*m*, H–C(1′)); 7.25 (*d*, *J* = 8.2, 2 arom. H); 7.65 (*d*, *J* = 8.2, 2 arom. H); 8.30 (*m*, NH); 8.94 (*s*, H–C(8)). Anal. calc. for $C_{19}H_{16}Cl_2N_5O_4$: C 50.8, H 3.59, N 15.59; found: C 51.07, H 3.79, N 15.20.

*1-(6-Amino-2-chloro-9*H*-purin-9-yl)-1,2-dideoxy*-N-*methyl-β- and* -α-D-erythro-*pentofuranuronamide* (β-D- and α-D-**11**, resp.). Nucleoside β-D-**10** (0.340 g, 0.76 mmol) or α-D-**10** (0.380 g, 0.85 mmol) was treated with liq. NH_3 (20 ml) at r.t. for 48 h in a steel tube. After evaporation, the residue was crystallized from MeOH: β-D-**11** (0.125 g, 53%) or α-D-**11** (0.135 g, 51%), resp. both as white solid.

β-D-**11**: M.p. 170–172°. ^{1}H-NMR ($(D_6)Me_2SO$): 2.25 (*m*, H–C(2′)); 2.59–2.72 (*m*, *Me*NH, 1 H–C(2′)); 4.28 (*s*, H–C(4′)); 4.48 (*m*, H–C(3′)); 6.41 (*dd*, *J* = 5.1, 8.6, H–C(1′)); 7.93 (*s*, NH_2); 8.22 (*m*, NH); 8.46 (*s*, H–C(8)). Anal. calc. for $C_{11}H_{13}ClN_6O_3$: C 42.25, H 4.19, N 26.87; found: C 42.59, H 4.41, N 26.56.

α-D-**11**: M.p. 165–166°. ^{1}H-NMR ($(D_6)Me_2SO$): 2.29 (*d*, *J* = 14.7, 1 H–C(2′)); 2.59 (*m*, 1 H–C(2′)); 2.64 (*d*, *J* = 4.4, *Me*NH); 4.50 (*m*, H–C(3′)); 4.58 (*s*, H–C(4′)); 6.56 (*d*, *J* = 7.2, H–C(1′)); 7.88 (*s*, NH_2); 8.12 (*m*, NH); 8.46 (*s*, H–C(8)). Anal. calc. for $C_{11}H_{13}ClN_6O_3$: C 42.25, H 4.19, N 26.87; found: C 42.61, H 4.38, N 26.59.

*1-(6-Amino-9*H*-purin-9-yl)-1,2-dideoxy*-N-*methyl-β- and* α-D-erythro-*pentofuranuronamide* (β-D- and α-D-**12**, resp.). To β-D-**11** (0.670 g, 2.1 mmol) or α-D-**11** (0.070 g, 0.22 mmol) in abs. EtOH (30 ml), 2N NaOH (1 ml) and 10% Pd/C (10 mg) were added. The mixture was hydrogenated at 40 psi for 6 h. The catalyst was removed by filtration and the filtrate evaporated. Purification by FC ($CHCl_3$/MeOH 97:3) gave β-D-**12** (0.260 g, 43%). White solid. M.p. 194–196°. UV (MeOH): 258 (10100); pH 2: 257 (9700); pH 12: 258 (9900). ^{1}H-NMR ($(D_6)Me_2SO$): 2.24 (*dd*, *J* = 4.9, 12.2, 1 H–C(2′)); 2.63–2.77 (*m*, *Me*NH, 1 H–C(2)); 4.29 (*s*, H–C(4′)); 4.47 (*m*, H–C(3′)); 6.47 (*dd*, *J* = 5.2, 9.6, H–C(1′)); 7.43 (*s*, NH_2); 8.24 (*s*, H–C(2)); 8.43 (*s*, H–C(8)); 8.81 (*m*, NH). Anal. calc. for $C_{11}H_{14}N_6O_3$: C 47.48, H 5.07, N 30.20; found: C 47.17, H 5.31, N 30.56.

α-D-**12**: M.p. 193–195°. UV (MeOH): 258 (8600); pH 2: 257 (8400); pH 12: 258 (10900). ^{1}H-NMR ($(D_6)Me_2SO$): 2.31 (*d*, *J* = 14.3, H–C(2′)); 2.59–2.74 (*m*, *Me*NH, 1 H–C(2′)); 4.59 (*m*, H–C(3′)); 4.58 (*s*, H–C(4′)); 6.61 (*dd*, *J* = 2.1, 8.1, H–C(1′)); 7.36 (*s*, NH_2); 8.13 (*m*, NH); 8.19 (*s*, H–C(2)); 8.42 (*s*, H–C(8)). Anal. calc. for $C_{11}H_{14}N_6O_3$: C 47.48, H 5.07, N 30.20; found: C 47.21, H 4.98, N 30.49.

*2-O-Acetyl-1,3-dideoxy-1-(2,6-dichloro-9*H*-purin-9-yl)*-N-*methyl-β-*D-*ribofuranuronamide* (**14**). A mixture of **9** (0.285 g, 1.51 mmol), ammonium sulfate (cat. amount), and HMDS (5 ml) was refluxed for 3 h under N_2. The solvent was evaporated under exclusion of moisture and the residue dissolved in dry CH_2Cl_2 (5 ml). After addition of **13** [13] (0.300 g, 1.22 mmol), $TfOSiMe_3$ (0.29 ml, 1.51 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise and the mixture stirred 16 h at r.t. Then sat. $NaHCO_3$ soln. (10 ml) was added and the org. phase dried (Na_2SO_4) and evaporated. Purification by FC (AcOEt/cyclohexane 7:3) gave only **14** (0.306 g, 67%). White solid. M.p. 84–86°. ^{1}H-NMR ($(D_6)Me_2SO$): 2.13 (*s*, MeCO); 2.40–2.81 (*m*, *Me*NH, 2 H–C(3′)); 4.74 (*m*, H–C(4′)); 5.69 (*d*, *J* = 5.5, H–C(2′)); 6.37 (*s*, H–C(1′)); 8.00 (*m*, NH); 9.07 (*s*, H–C(8)). Anal. calc. for $C_{13}H_{13}Cl_2N_5O_4$: C 41.73, H 3.5, N 18.72; found: C 41.92, H 3.71, N 18.48.

*1-(6-Amino-2-chloro-9*H*-purin-9-yl)-1,3-dideoxy*-N-*methyl-β-*D-*ribofuranuronamide* (**15**). As described for **11**, with **14** (0.456 g, 1.22 mmol) and NH_3 (20 ml; 16 h): **15** (0.294 g, 74%). White solid. M.p. 248–250° (MeOH; dec.). ^{1}H-NMR ($(D_6)Me_2SO$): 2.14–2.42 (*m*, 2 H–C(3′)); 2.67 (*d*, *J* = 4.5, *Me*NH); 4.56 (*m*, H–C(2′)); 4.67 (*t*, H–C(4′)); 5.90 (*d*, *J* = 2.4, H–C(1′)); 7.88 (*s*, NH_2); 8.20 (*m*, NH); 8.56 (*s*, H–C(8)). Anal. calc. for $C_{11}H_{13}ClN_6O_3$: C 42.25, H 4.19, N 26.87; found: C 42.62, H 4.34, N 26.51.

*1-(6-Amino-9*H*-purin-9-yl)-1,3-dideoxy*-N-*methyl-β-*D-*ribofuranuronamide* (**16**). As described for **12**, with **15** (0.200 g, 0.64 mmol), EtOH (30 ml), 2N NaOH (2.0 ml), and 10% Pd/C (30 mg): **16** (0.083 g, 45%) as white solid.

From **18**: Compound **18** (0.080 g, 0.24 mmol) was treated with liq. NH_3 (10 ml) for 16 h at r.t. Purification by FC ($CHCl_3$/MeOH 97:3) gave **16** (0.041 g, 60%). White solid. M.p. 195–197° (dec.). UV (MeOH): 258 (11600); pH 2: 257 (11500); pH 12: 258 (11000). ^{1}H-NMR ($(D_6)Me_2SO$): 2.15–2.41 (*m*, 2 H–C(3′)); 2.65

(*d*, J = 4.3, *Me*NH); 4.52–4.60 (*m*, H–C(2'), H–C(4')); 5.93 (*s*, H–C(1')); 7.33 (*s*, NH_2); 8.17 (*s*, H–C(2)); 8.37 (*m*, NH); 8.48 (*s*, H–C(8)). Anal. calc. for $C_{11}H_{14}N_6O_3$: C 47.48, H 5.07, N 30.20; found: C 47.61, H 5.26, N 29.93.

*2-O-Acetyl-1-(6-chloro-9H-purin-9-yl)-1,3-dideoxy-*N*-methyl-β-*D*-ribofuranuronamide* (**18**). As described for **14**, with **17** (0.080 g, 0.52 mmol), ammonium sulfate (cat. amount), HM-DS (5 ml), CH_2Cl_2 (5 ml), **13** [13] (0.128 g, 0.52 mmol), $TfOSiMe_3$ (0.1 ml, 0.52 mmol), CH_2Cl_2 (2 ml), and sat. $NaHCO_3$ soln. (4 ml): **18** (0.118 g, 67%). White solid. M.p. 78–80°. ^{1}H-NMR ($(D_6)Me_2SO$): 2.13 (*s*, MeCO); 2.40–2.84 (*m*, *Me*NH, 2 H–C(3')); 4.74 (*m*, H–C(4')); 5.75 (*d*, J = 5.7, H–C(2')); 6.40 (*s*, H–C(1')); 8.05 (*m*, NH); 8.84 (*s*, H–C(2)); 9.04 (*s*, H–C(8)). Anal. calc. for $C_{13}H_{14}ClN_5O_4$: C 45.96, H 4.15, N 20.61; found: C 46.22, H 4.31, N 20.28.

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