Mannich-Type C-Nucleosidations with 7-Carba-purines and 4-Aminopyrimidines[1]

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Abstract: Regioselective Mannich-type C-nucleosidations of pyrroline derivatives **3** and **8** with 7-carba-purines and 4-aminopyrimidines occur under mild conditions to afford C(8)- and C(5)-azanucleosides, respectively.

Key words: C-azanucleosides, Mannich reaction, electrophilic substitution, heterocycles, 7-carba-purine, pyrimidines, pyrrolines

We have recently reported on Mannich-type electrophilic substitution reactions in the family of 5,8-diaza-7,9-dicarba-purines with cyclic iminium salts derived from 4-deoxy-4-amino-threose derivatives.[2,3] These reactions are regioselective C-nucleosidations proceeding efficiently under mild conditions to afford C(9)-nucleosides that are isosteric with corresponding N(9)-nucleosides of the natural series. Here, we report on C-nucleosidation reactions of 2,6-disubstituted 4-aminopyrimidines **1a**–**d**, and of 7-carba-purines **2a**–**d** (Figure 1).

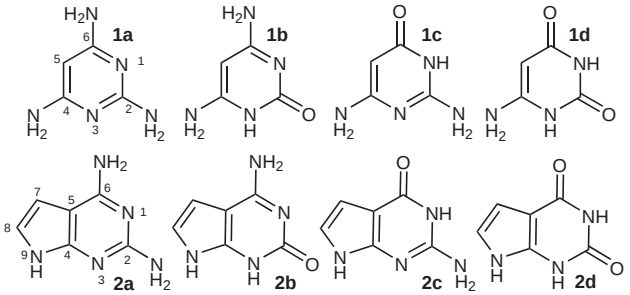


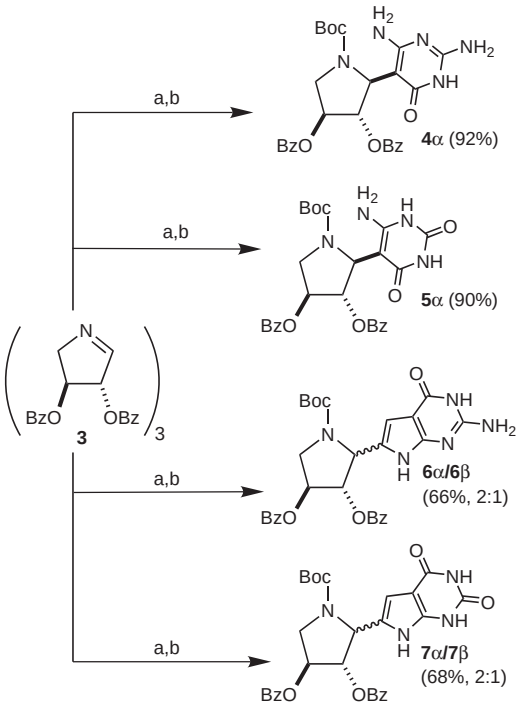
Figure 1 Purines and pyrimidines used in this C-nucleosidation study.

These heterocycles are expected (and known[4,5]) to have the ability to act as carbon-nucleophiles (at the C(5) position in **1a**–**d**, and at the C(8) position in **2a**–**d**), and therefore are anticipated to undergo Mannich-type reactions at these positions with pyrrolines of the type **3** and **8** which we used in our previous studies.[2]

While the pyrimidine bases **1a**–**d**[6] were available commercially (from Aldrich), the known 7-carba-purine bases **2a**–**d**[6] were synthesized according to literature procedures[7]; carba-purines **2a**,[7b] **2c**,[7b] and **2d**[7c] were easily obtained, albeit in modest yields, by the reaction of **1a** (31%), **1c** (68%) and **1d** (49%) with a solution of 50% aqueous chloroacetaldehyde in degassed water.[8]

Scheme 1 summarizes the acid-catalyzed C-nucleosidations with 2,3-di-*O*-benzoyl-pyrroline (as a trimer, **3**), under the conditions we have utilized for the previous C-nucleosidations[2,3] (products isolated after bocylation of the reaction mixture;[10] for conditions see caption of Scheme 1). Pyrimidine C(5)-azanucleosides **4α** and **5α** were isolated in excellent yields (>90%) as a single diastereoisomer (α-anomer only). In the carba-purine series, 2:1 mixtures of the α- and β-anomers **6α**/**β** and **7α**/**β** were obtained in moderate yields (>60%) and separated by column chromatography into the pure anomers.

The constitutional assignments of the C-azanucleosides were based on ^{1}H NMR and ^{13}C NMR spectral data, and were corroborated by ^{1}H–^{1}H and ^{1}H–^{13}C correlation experiments. The position of C-nucleoside bond in the C-



Scheme 1 C-Nucleosidation of pyrroline derivative **3**. *Reagents and conditions*: (a) 0.01–0.1 M (1 mol equiv) **3**, 0.1 (1) **1c** or **1d** or **2c** or 0.04 (2.7) **2d**, 0.04–0.1 (1–2.7) TsOH·H_2O, DMF, r.t., 2 h for **1c** and **1d**; 50 °C, 5 h for **2c**; r.t., 18 h for **2d**; (b) 0.16–0.4 (4–10) Et_3N, 0.04–0.1 (1–2.7) Boc_2O, DMF, r.t., 30 min to 2 h.

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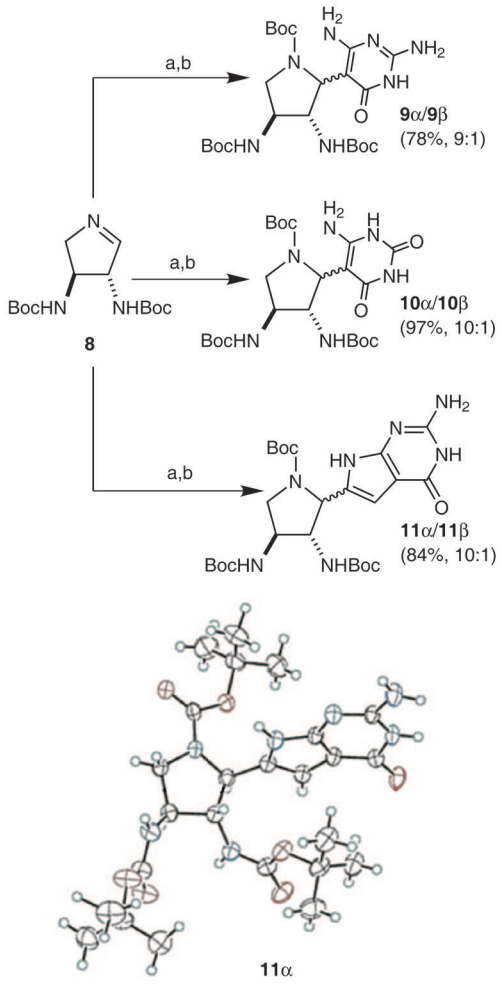
azanucleosides was revealed by the absence of H-C(5) proton signal in the pyrimidine derivatives **4α** and **5α** and the absence of H-C(8) proton in the carba-purine derivatives **6α**/**β** and **7α**/**β**. Configurational assignments of α- and β-anomers in the carba-purine series were made by NOE and ROESY measurements; e.g. for **7α**, a correlation between H-C(1′) at δ = 5.11 ppm and H-C(3′) at δ = 5.35 ppm was observed. While no such correlation was found for **7β**, a rather a strong correlation between H-C(1′) and H-C(2′) was detected, indicative of the *cis*-disposition of the geminal protons. In the case of pyrimidines **4α** and **5α**, assignment of the α-configuration is tentative, and is based on steric arguments and the predominance of the α-anomers in the carba-purine series.

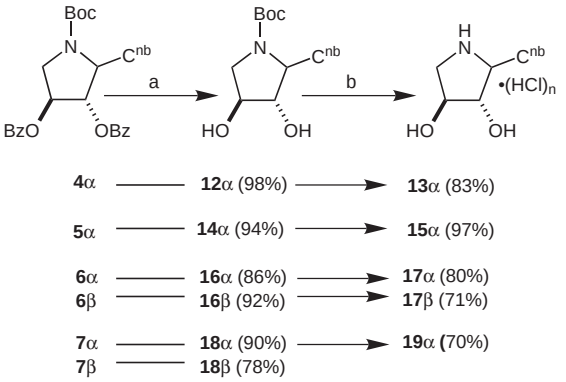
While the reaction with pyrimidine **1a**, under various conditions (0.03–0.1 M **1a** and **3**, 0.01–0.1 M TsOH·H_2O, DMF, r.t. to 50 °C, 6 h to 3 d), was inefficient,[11] no reaction at all was observed with either pyrimidine **1b** or carba-purine **2a**; starting materials were recovered unchanged.



Scheme 2 C-Nucleosidation of pyrroline derivative **8**. *Reagents and conditions*: (a) 0.12 M (1.2 mol equiv) **8**, 0.1 (1) **1c** or **1d** or **2c**, 0.1 (1) TsOH·H_2O, DMF, r.t., 2–4 h; (b) 0. 4 (4) Et_3N, 0.11–0.4 (1.1–4) Boc_2O, DMF, r.t., 30 min.

C-Nucleosidations with 2,3-di-*N*-boc-pyrroline derivative **8** as the substrate is summarized in Scheme 2. Again, C-nucleosidation was followed by bocylation to help in isolation of the products. Reaction of pyrimidines **1c** and **1d** with pyrroline **8** provided the C(5)-azanucleosides **9α**/**β** and **10α**/**β** in very good yields with the α-anomer dominating (>9:1) over the β-anomer. C-Nucleosidation was found to occur with 7-carbaguanine **2c** to afford C(8)-azanucleoside **11α**/**β** in 84% yield with a 10:1 preponderance of the α-anomer. Paralleling the observations made with the 2,4-di-*O*-pyrroline derivative **3**, no reaction of pyrroline **8** was observed with pyrimidines **1a** or **1b** and with carba-purine **2a**.[12]

The constitutional and configurational assignments for **9α**/**β** and **10α**/**β** are based on ^{1}H NMR and ^{13}C NMR spectral data and by comparison with spectral data of azanucleosides **4** and **5**. For C-azanucleoside **11α**, an X-ray[13] structural analysis provided the confirmation (Scheme 2).

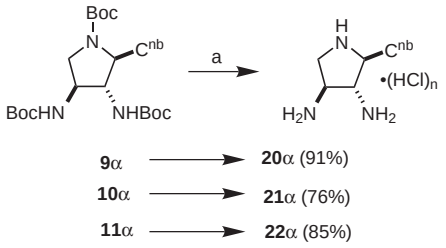


Scheme 3 Preparation of free C-azanucleosides. *Reagents and conditions*: (a) sat. NH_3 in MeOH, r.t., 24–48 h; (b) 2 M to sat. HCl in Et_2O, r.t., 1.5–2 h. Yields calcd for n = 2. C^{nb} = nucleobase.

Debenzoylation of C-azanucleosides **4**–**7**, by methanolic ammonia treatment, afforded the 2′,3′-dihydroxy derivatives **12**–**18** (Scheme 3) and exposure of azanucleosides **12**–**18** to dry HCl in anhydrous diethyl ether at room temperature gave the corresponding free C-azanucleosides **13**–**19** as the hydrochloride salts. The deprotections were found to proceed without epimerization at the anomeric center under these conditions. This was confirmed by converting **6α** and **6β**, separately, to the fully deprotected **17α** and **17β**, respectively (no epimers detected by ^{1}H NMR and TLC). Treatment of C-azanucleosides **9α**, **10α** and **11α** with dry HCl in anhydrous diethyl ether at room temperature afforded the hydrochloride salts of the debocylated C-azanucleosides **20α**, **21α** and **22α**, respectively, without the loss of stereochemical integrity at the anomeric center (Scheme 4).

The stability of these C-azanucleosides was probed in two specific cases. C-azanucleoside **21α**, as hydrochloride salt(s), was found to be constitutionally and configurationally stable under acidic conditions (0.1 M at pH 2.2 in D_2O, monitored by ^{1}H NMR for 15 h at r.t.). In contrast, under basic conditions (0.1 M, pH 10.0 in NaOD, r.t.),

epimerization to an almost 1:1 α/β mixture, accompanied by some decomposition, was observed after 9 hours (^{1}H NMR). The hydrochloride salt(s) of C-nucleoside **22α**, was found to be stable even after 6 months (0.1 M at pH 1.3 in D_2O, r.t., monitored by ^{1}H NMR).



Scheme 4 Preparation of free C-azanucleosides. *Reagents and conditions*: (a) 2 M to sat. HCl in Et_2O, r.t., 1.5–2 h. Yields calcd for n = 4. C^{nb} = nucleobase.

The lack of nucleophilic reactivity, observed in attempted C-nucleosidation of the heterocycles **1a**,**b** and **2a**, with pyrrolines **3** and **8** deserves a comment.[14,15] Among the four pyrimidines **1a**–**d**, reactivity towards electrophiles [at position C(5)] can be expected to follow the order **1a**>**1c**>**1b**>**1d**, what more or less agrees with the qualitative observations made in deuterium exchange studies.[16] However, the observed order of reactivity in C-nucleosidation reactions (**1c**≈**1d**>>>**1a**, no reaction of **1b**) are contrary to (our) expectation. The inefficient reactivity of pyrimidine **1a** (see also ref.[4b]) and the non-reactivity of pyrimidine **1b** may be a consequence of a combination of steric factors [hindrance between amino groups at C(4) and C(6) and bulky substituents at position C(5)] and the differing degree of aromaticity in these heterocycles (aromatic stabilization energy supposed to be higher in members that do not contain carbonyl functions). The notion that the difference in aromatic stabilization of the reactant is decisively influencing the relative ease of such nucleosidation reactions is supported by the lack of reactivity of purine **2a** as contrasted by the behavior of purine **2c** and **2d** which both contain carbonyl functions (no experiments were carried out with **2b**).

The regioselectivity observed in the cases of the 7-carba-purines **2c** and **2d** is notable – no C(7)-regioisomer is formed, in line with the (presumed) higher nucleophilicity at position C(8) as compared to C(7). The competing C(8)- vs. C(7)-regioselectivity in such 7-carba-purines has been addressed by various groups[5c–5e,17] in different contexts, and it has been reported that the C(8)-position is the preferred site of electrophilic attack.

The Mannich type C-nucleosidation reactions and products presented here add to the growing list of the repertoire of C-azanucleosides that deserve attention from various points of view.[18] Full experimental details and characterization of compounds are given below.[19]

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(8) Attempts to obtain the isoguanine analog **2b**[6] in this series, starting from **1b**, following this protocol were not successful. Instead, a compound identified as 5-aza-3,7-dicarbaguanine[9] was isolated in ca. 13% yield.
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(10) Bocylation also prevented the (unwanted) O→N migration of the 2′,3′-*O*-benzoyl groups.
(11) A minor product (ca. 10%) was isolated and was tentatively identified as the expected C(5)-azanucleoside; unreacted starting materials were recovered up to ca. 60%. In a follow-up experiment the C(5)-azanucleoside product from the reaction **1a** and **3** was debocylated (with sat. HCl in anhyd Et_2O) affording the NH-unprotected free C(5)-nucleoside; when this debocylated intermediate was subjected to the nucleosidation reaction conditions (condition a, Scheme 1), formation of the pyrimidine base **1a** was observed (TLC, ^{1}H NMR and MS).
(12) Reaction with carba-purine **2d** was not attempted.
(13) X-ray structure analysis of **11α** was carried out by Dr. Bernd Schweizer, ETHZ. Crystallographic data for the structure has been deposited with the Cambridge Crystallographic Data Centre as deposition no. CCDC 249544. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 union Road, Cambridge CB12 1EZ, UK [fax +44 (1233)3360333; e-mail: deposit@ccdc.cam.ac.uk].
(14) Pyrroline **3** is more reactive than pyrroline **8**; see footnote 13 of ref. 2b.

(15) In this context it is of interest to note that no, or inefficient, formation of C-nucleosides were observed when Schiff bases from aldosugar derivatives of L-α-di-*O*-benzoyl-threose or 2,3-acetonide of D-ribofuranose were used in place of pyrrolines **3** or **8** (see also Scheme 4 in ref. 2b).

(16) In a deuterium incorporation study (pH 5–6, CD_3CO_2D, DMSO-d_6, D_2O, r.t.) of the four pyrimidines **1a**–**d**, the H-C(5) proton was exchanged to D-C(5) most rapidly in **1a** (87% in 5 min), followed by **1c** (84% in 5 min), **1d** (69% in 5 min) and **1b** (2% in 5 min; 85% after 24 h).

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(19) **C-Nucleosidation of (3*S*,4*S*)-3,4-Dibenzoyloxypyrroline (Scheme 1). Representative Procedure.**

2,4-Diamino-5-[*N*-(*tert*-butyloxycarbonyl)-(2′*S*,3′*S*)-2′,3′-dibenzoyloxy-(1′*S*)-pyrrolidinyl]-6-oxopyrimidine (4α).

The amount of 927 mg (1.0 mmol) of pyrroline-trimer **3** and 190 mg (1.0 mmol) *p*-TsOH·H_2O was dissolved in 10 mL of DMF, to which 126 mg (1.0 mmol) of pyrimidine **1c** was added in one portion and stirred at r.t. for 2 h. TLC, (CH_2Cl_2–MeOH–25% aq NH_3) indicated that pyrimidine (R_f =0.25) totally disappeared, and a new UV active spot (R_f = 0.76) was formed. Then, 404 mg (4.0 mmol) of Et_3N and 250 mg (1.1 mmol) of Boc_2O was added to the above reaction solution and stirred at r.t. for 30 min. TLC (CH_2Cl_2–MeOH–25% aq NH_3) showed that the R_f = 0.76 spot was converted to another spot (R_f = 0.81). Evaporation of solvent under reduced pressure at 55 °C gave a light brown oil, which was purified by CC (silica gel, CH_2Cl_2–MeOH 100:8). Fractions 15–28 (10 mL each) were combined and evaporated under reduced pressure at 40 °C to give 492 mg (92%) of **4α** as amorphous light yellow solid; mp (EtOAc): >190 °C. TLC: R_f = 0.31 CH_2Cl_2–MeOH (10:1). ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ = 1.34 (s, 9 H, Me), 3.75 [dd, $^2J_{H\text{-}H}$ = 10.6 Hz, $^3J_{H\text{-}H}$ = 8.1 Hz, 1 H, H-C(4′)], 4.16 [dd, $^2J_{H\text{-}H}$ = 10.6 Hz, $^3J_{H\text{-}H}$ = 7.6 Hz, 1 H, H-C(4′)], 4.86 [d, J = 5.6 Hz, 1 H, H-C(1′)], 5.47 [ddd, $J_{trans\text{-}H4'\text{-}H3'} = J_{cis\text{-}H4'\text{-}H3'}$ = 7.9 Hz, $J_{H2'\text{-}H3'}$ = 6.2 Hz, 1 H, H-C(3′)], 5.62 (br s, NH_2, 2 H, exchanges with D_2O), 5.89 (br s, 2 H, NH_2, exchanges with D_2O), 6.15 [dd, $J_{H1'\text{-}H2} = J_{H3'\text{-}H2'}$ = 5.8 Hz, 1 H, H-C(2′)], 7.47–8.01 (m, 10 H, C_6H_5), 9.65 (s, 1 H, NH, exchanges with D_2O). ^{13}C NMR [75.45 MHz, DMSO-d_6): δ = 28.14 (q), 48.49 (t), 56.00 (d), 74.40 (d), 78.47 (d), 85.69 (s), 128.44 (d), 128.58 (d), 128.95 (s), 129.12 (d), 129.37 (d), 133.29 (d), 133.41 (d), 152.92 (s), 153.00 (s), 161.32 (s), 162.46 (s), 164.98 (s), 165.09 (s). MALDI-MS: *m/z* (%) = 558.1(51) [M + Na]$^+$, 536.2 (34) [M + H]$^+$), 458.1(33) [M – Boc + Na]$^+$, 436.1(100) [M – Boc + H]$^+$). HR-MALDI: *m/z* calcd for $C_{27}H_{29}N_5O_7Na$ [M + Na$^+$]: 558.1959; found: 558.1965. UV (c = 5·10^{-5} M in MeOH): λ_{max} = 273 nm (ε = 1.40·10^4), 230 (2.98·10^4), 215 (3.23·10^4); λ_{min} = 253 nm(6500), 224 (2.84·10^4), 206 (2.67·10^4). Anal. Calcd for $C_{27}H_{29}N_5O_7$: C, 60.55; H, 5.46; N, 13.08; Found C, 60.45; H, 5.57; N, 12.82.

4-Amino-5-[*N*-(*tert*-butyloxycarbonyl)-(2′*S*,3′*S*)-2′,3′-dibenzoyloxy-(1′*S*)-pyrrolidinyl]-2,6-dioxopyrimidine (5α).

Mp >200 °C(decomp). TLC: R_f = 0.33 (CH_2Cl_2–MeOH, 10:1). ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): 1.39 (s, 9 H, Me), 3.72 [dd, $^2J_{H\text{-}H}$ = 10.6 Hz, $^3J_{H\text{-}H}$ = 8.4 Hz, 1 H, H-C(4′)], 4.14 [dd, $^2J_{H\text{-}H}$ = 10.6 Hz, $^3J_{H\text{-}H}$ = 8.1 Hz,, 1 H, H-C(4′)], 4.83 [d, J = 6.0 Hz, 1 H, H-C(1′)], 5.45 ['q', $J_{H2'\text{-}H3'} = J_{cis\text{-}H4'\text{-}H3'} = J_{trans\text{-}H4'\text{-}H3'}$ = 8.7 Hz, 1 H, H-C(3′)], 6.01 (br s, 2 H, NH_2, exchanges with D_2O), 6.09 [dd, $J_{H1'\text{-}H2} = J_{H3'\text{-}H2'}$ = 6.3 Hz, 1 H, H-C(2′)], 7.49–7.80 (m, 10 H, C_6H_5), 9.97 (s, 1 H, NH, exchanges with D_2O), 10.36 (s, 1 H, NH, exchange with D_2O). ^{13}C NMR (75.45 MHz, DMSO-d_6): 28.1 (q), 48.4 (t), 56.0 (d), 74.5 (d), 78.5 (d), 85.8 (s), 128.6 (d), 128.8 (d), 129.1 (s), 129.3 (d), 129.6 (d), 133.5 (d), 133.6 (d), 153.1 (s), 153.7 (s), 161.6 (s), 162.7 (s), 165.2 (s), 165.3 (s). MALDI-MS: *m/z* (%) = 559.2(60) [M + Na]$^+$, 459.1(68) [M – C_6H_5]$^+$, 437.1(100) [M – Boc + H$^+$]. HR-MALDI: *m/z* calcd for $C_{27}H_{28}N_4O_8Na$ [M + Na$^+$]: 559.1719; found: 559.1811. UV (c = 5·10^{-5} M in MeOH): λ_{max} = 266 nm (ε = 1.83·10^4), 230 (3.26·10^4), λ_{min} = 249 (9500), 210 (1.18·10^4). Anal. Calcd for $C_{27}H_{30}N_4O_8·H_2O$: C, 58.48; H, 5.45; N, 10.10. Found: C, 58.71; H, 5.60; N, 10.14.

Data for C-nucleoside product isolated from reaction **1a** with **3**: ^{1}H NMR (600 MHz, DMSO-d_6, 70 °C): 1.30 (s, 9 H, Me), 3.76 [dd, 1 H, J = 6.8, 12.0, H-C(4′)], 4.14 [dd, 1 H, J = 7.9, 12.0 Hz, H-C(4′)], 5.14 [d, 1 H, J = 7.4 Hz, H-C(1′)], 5.30 (br s, 2 H, -NH_2), 5.49 [m, 5 H, H-C(3′), 2 NH_2], 5.82 [d, 1 H, J = 6.7 Hz, 1 H, H-C(2′)], 7.37–8.02 (m, 10 H, arom. H). EI-MS (pos., MeOH): *m/z* (%) = 557 (100) [M + Na]$^+$), 535 (40) [M + H]$^+$), 435 (20) [M – BOC]$^+$). EI-MS (neg., MeOH): *m/z* (%) = 569 (80) [M + Cl]$^-$.

8-[*N*-(*tert*-Butyloxycarbonyl)-(2′*S*,3′*S*)-2′,3′-(dibenzoyloxy)pyrrolidinyl]-7-carba-guanine (6α/β). Representative Procedure.

A mixture of 432.6 mg (0.47 mmol) of pyrroline-trimer **3** and 89.0 mg (0.47 mmol) of *p*-TsOH·H_2O was dissolved in 4.7 mL of dry DMF (molecular sieves), to which 70.6 mg (0.47 mmol) of purine **2c** was added in one portion and stirred at 50 °C for 5 h [after 5 h, TLC (CH_2Cl_2–MeOH–aq NH_3, 9:1:0.1) showed the disappearance of **2c** and presence of two spots (R_f = 0.22, 0.19)]. To this reaction mixture was added 0.27 mL (1.88 mmol) of Et_3N followed by 102.6 mg (0.47 mmol) of Boc_2O and stirred at 50 °C for next 2 h (after 2 h, spots at R_f = 0.22 and 0.19 disappeared and two new UV active spots at R_f = 0.3 and 0.27 were observed on TLC). Evaporation of the solvents (45 °C) under reduced pressure (rotavap.) followed by drying under high vacuum (0.3 mbar, 12 h) gave crude residue as yellow sticky solid, which was redissolved in CH_2Cl_2 and purified by CC (silica gel, CH_2Cl_2–MeOH 98:2 to 93:7). Fractions (33–70, 10 mL each) eluted with 3% MeOH in CH_2Cl_2 were combined and concentrated in vacuo to afford 89.4 mg (34%) of **6α** as off white solid. Fractions (71–103) eluted with 3–5% MeOH in CH_2Cl_2 were combined and concentrated in vacuo to give 139.2 mg (53%) of a mixture of epimers of **6**, which was re-purified by CC (silica gel, CH_2Cl_2–MeOH 98:2 to 94:6). Fractions (45–67) eluted with 2.5% MeOH in CH_2Cl_2 were combined and concentrated in vacuo to give 17.0 mg (6.5%) of **6α** [identical (^{1}H NMR) with the epimer of **6** isolated before] as an off-white solid. Fractions (72–115) eluted with 2.5–3.5% MeOH in CH_2Cl_2 were combined and concentrated in vacuo to afford 66.6 mg (25.4%) of the other β-epimer of **6.** Thus, overall isolated yields after two CCs are 40.5% for **6α** and 25.4% for **6β**. Purity was greater than 95% by ^{1}H NMR.

Analytical data of **6α**: TLC: R_f = 0.22 (MeOH–aq NH_3, 9:1:0.1). ^{1}H NMR (600 MHz, DMSO-d_6, 70 °C): δ = 1.38 (s, 9 H, 3 Me), 3.79 [dd, J = 2.7, 12.9 Hz, 1 H, H-C(4′)], 4.16 [dd, J = 6.2, 12.7 Hz, 1 H, H-C(4′)], 5.11 [br s, 1 H, H-C(2′)], 5.57 (dd, J = 3.2, 6.1 Hz, 1 H, H-C(3′)], 5.62 [br s, 1 H, H-C(1′)], 5.92 (s, 2 H, -NH_2), 6.14 [s, 1 H, H-C(7)], 7.37–8.02 (m, 10 H, arom. H), 10.19 (br s, 1, -NH-), 10.87 (br s, 1 H, -NH-). ^{13}C NMR (150.9 MHz, DMSO-d_6, 70 °C): δ = 28.89 (q, Me), 51.40 [d, C(4′)], 60.93 [d, C(2′)], 75.71 [d, C(3′)],

80.35 (s, CMe_3), 81.29 [d, C(1′)], 100.04 [d, C(7)], 101.01, 128.89, 129.27, 129.61, 129.92, 130.06, 130.26, 134.29, 134.53, 152.39, 153.22, 154.5 (arom. C), 159.41, 165.55 (2 s, C=O). ESI-MS (pos., MeOH): *m/z* (%) = 598 (25) [M + K]$^+$, 582 (100) [M + Na]$^+$. ESI-MS (neg., MeOH): *m/z* (%) = 594 (35) [M + Cl]$^-$, 558 (100) [M – H]$^-$.

Data for **6β**: TLC: R_f = 0.19 (MeOH–aq. NH_3, 9:1:0.1). ^{1}H NMR (600 MHz, DMSO-d_6, 70 °C): δ = 1.31 (s, 9 H, 3Me), 3.71 [dd, *J* = 3.2, 8.9 Hz, 1 H, H-C(4′)], 4.18 [dd, *J* = 5.8, 9.4 Hz, 1 H, H-C(4′)], 5.31 [d, *J* = 4.3 Hz, 1 H, H-C(2′)], 5.63 [m, 1 H, H-C(3′)], 5.77 [br m, 1 H, H-C(1′)], 5.79 (br s, 2 H, NH_2), 6.06 [s, 1 H, H-C(7)], 7.35–8.06 (m, 10 H, arom. H), 9.94 (br s, 1 H, -NH-), 10.84 (br s, 1 H, -NH-). ^{13}C NMR (150.9 MHz, DMSO-d_6, 70 °C): δ = 28.83 (q, Me), 49.82 [d, C(4′)], 57.39 [d, C(2′)], 75.29 [d, C(3′)], 76.75 [d, C(1′)], 80.17 (s, CMe_3), 100.84, 101.05 [d, C(7)], 127.41, 129.3, 129.60, 130.0, 130.09, 130.13, 130.17, 134.22, 134.5, 149.3, 152.18, 152.93, 154.61 (arom. C), 159.3, 165.4, 165.84 [s, C=O). ESI-MS (pos., MeOH): *m/z* (%) = 582 (10) [M + Na]$^+$), 560 (30) [M + H]$^+$). ESI-MS (neg., MeOH): *m/z* (%) = 558 (40) [M – H]$^-$.

8-[*N*-(*tert*-Butyloxycarbonyl)-(2′*S*,3′*S*)-2′,3′-(dibenzoyloxy)pyrrolidinyl]-7-carba-xanthine (7α/β).

Overall isolated yield of the two epimers, after purification by CC, is 67.5% (the ratio of the α- and β-epimers in the crude residue is 2:1).

Data for **7α**: TLC: R_f = 0.34 (CH_2Cl_2–MeOH, 19:1). ^{1}H NMR (600 MHz, DMSO-d_6, 70 °C): δ = 1.40 (s, 9 H, Me), 3.75 [dd, *J* = 2.3, 12.7 Hz, 1 H, H-C(4′)], 4.15 [dd, *J* = 5.9, 12.7 Hz, 1 H, H-C(4′)], 5.11 [s, 1 H, H-C(1′)], 5.59 [m, 1 H, H-C(3′)], 5.62 [s, 1 H, H-C(2′)], 6.19 [s, 1 H, H-C(7)], 7.39–8.03, (m, 10 H, arom. H), 10.13 (br s, NH, 0.6 H), 10.90 (br s, NH, 1 H). ^{13}C NMR (150.9 MHz, DMSO-d_6, 70 °C): δ = 28.86 (q, Me), 51.47 [t, C(4′)], 60.54 [d, C(1′)], 75.62 [d, (C3′)], 80.49 [d, C(2′)], 80.73 (s, CMe_3), 99.14 [s, C(5)], 101.21 [d, C(7)], 128.45 [s, C(8)], 128.45, 129.13, 129.46, 129.64, 129.76, 129.97, 130.09, 134.20, 134.45 (arom. C), 139.79 [s, C(4)], 151.47 [s, C(2)], 154.34 (arom. C), 160.12 [s, H(C6)], 165.19 (s, C=O), 165.27 (C=O), 173.0 (s, C=O). ESI-MS (pos., MeOH): *m/z* (%) = 599 (10) [M + K]$^+$), 583 (100) [M + Na]$^+$, 561 (25) [M + H]$^+$), 461 (20) [M – Boc + H]$^+$). ESI-MS (neg., MeOH): *m/z* (%) = 595 (10) [M + Cl]$^-$, 559 (80) [M – H]$^-$.

Data for **7β**: TLC: R_f = 0.29 (CH_2Cl_2–MeOH, 19:1). ^{1}H NMR (600 M Hz, DMSO-d_6, 70 °C): δ = 1.32 (s, 9 H, Me), 3.75 [dd, *J* = 3.54, 12.15 Hz, 1 H, H-C(4′)], 4.13 [dd, *J* = 5.52, 12.05 Hz, 1 H, H-C(4′)], 5.34 [m, 1 H, H-C(1′)], 5.58 [m, 1 H, H-C(3′)], 5.78 [m, 1 H, H-C(2′)], 6.09 [s, 1 H, H-C(7)], 7.43–8.00, [m, 10 H, arom. H), 10.02 (br s, 0.7 H), 10.98 (br s, 1 H). ESI-MS (pos., MeOH): *m/z* (%) = 583 (100) [M + Na]$^+$, 561 (25) [M + H]$^+$), 461(25) [M – Boc + H]$^+$). ESI-MS (neg., MeOH): *m/z* (%) = 595 (5) [M + Cl]$^-$, 559 (100) [M – H]$^-$).

C-Nucleosidation of (3*R*,4*S*)-3,4-Di(*tert*-butyloxycarbonylamino)pyrroline (Scheme 2). Representative Procedure. 2,4-Diamino-5-[*N*-(*tert*-butyloxycarbonyl)-(2′*R*,3′S)-2′,3′-di(*tert*-butyloxycabonylamino)-(1′*S*)-pyrrolidinyl]-6-oxopyrimidine (9α/β).

A mixture of 360 mg (1.2 mmol) of compound **8** and 190 mg (1.0 mmol) of *p*-TsOH·H_2O was dissolved in 10 mL of DMF, to which 126 mg (1.0 mmol) of pyrimidine **1c** was added all in one portion and the mixture was stirred at r.t. for 2 h. TLC (CH_2Cl_2–MeOH–25% aq NH_3, 4:1:0.2) showed the total consumption of **1c** (R_f = 0.21) and the formation of a new main spot (R_f = 0.32). Then, 404 mg (4.0 mmol) of Et_3N and 250 mg (1.1 mmol) of Boc_2O were added and the reaction mixture was stirred at r.t. for 30 min. TLC (CH_2Cl_2–MeOH–25% aq NH_3, 4:1:0.2) showed that the spot (R_f = 0.24) was converted to another spot (R_f = 0.88). After evaporation of the solvent under reduced pressure (at 55 °C), 250 mL of EtOAc was added, the organic layer washed with H_2O (3 × 50 mL) and dried (Na_2SO_4). Removal of solvent gave a light brown solid, which was purified by CC (silica gel, CH_2Cl_2–MeOH. 100:10). Fractions 16–35 (5 mL each) were combined and evaporated under reduced pressure at 40 °C to give 413 mg (78%, α/β = 9:1, by ^{1}H NMR) of **9α/β** as light yellow solid. Crystallization of 400 mg of epimeric mixture from EtOAc–hexane gave 203 mg (51%) of pure **9α**. Mp >202 °C (decomp.). TLC: R_f = 0.09 (CH_2Cl_2–MeOH, 100:10). ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ = 1.31 (s, 9 H, 3 CH_3), 1.38 (s, 9 H, 3 CH_3), 1.39 (s, 9 H, 3 CH_3), 3.24 [dd, $^2J_{H\text{-}H}$ = 10.0 Hz, $^3J_{H\text{-}H}$ = 8.8 Hz, 1 H, *trans*-H-C(4′)], 3.78 [m, 2 H, *cis*-H-C(4′) and H-C(3′)], 4.05 [m, 1 H, H-C(2′)], 4.42 (d, *J* = 5.6 Hz, 1 H, H-1′), 5.63 (br s, 2 H, NH_2), 5.85 (br s, 2 H, NH_2), 6.68 (br s, 1 H, NHBoc), 6.75 (br s, 1 H, NHBoc), 9.67 (br s, 1 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ = 28.19 [q, $(CH_3)_3C$], 50.34 [t, C(4′)], 54.21 (d), 57.73 (d), 59.95 (d), 78.88 (s, Me_3C), 78.29 (s, Me_3C), 87.52 (s, C-6), 153.18 (s), 153.35 (s), 154.87 (s), 155.62 (s), 161.41 (s), 162.38 (s). UV (c = 5·10^{-5} M in MeOH): λ_{max} = 213 nm (ε = 2.32·10^5), 274 (1.18·10^5). MALDI-MS: *m/z* (%) = 548.3(100) [M + Na]$^+$), 448.2(46), [M – Boc + Na]$^+$), 348.2(10) [M – 2 Boc + Na]$^+$).

4-Amino-5-[*N*-(*tert*-butyloxycarbonyl)-(2′*R*,3′*S*)-2′,3′-di(*tert*-butyloxycabonylamino)-(1′*S*)-pyrrolidinyl]-2,6-dioxopyrimidine (10α/β).

TLC: R_f = 0.29 (CH_2Cl_2–MeOH, 100:10). Mp 205 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ = 1.32–1.39 (s, 27 H, 9 × CH_3), 3.21 [dd, *J* = 9.7, 8.1 Hz, 1 H, H-C(4′)], 3.78 [m, 2 H, H-C(4′) and H-C(3′)], 4.19 [pseudo q, $J_{H\text{-}2'\text{-}H\text{-}1'}$ = $J_{H\text{-}2'\text{-}H\text{-}3'}$ = $J_{H\text{-}2'\text{-}NH}$ = 8.0 Hz, 1 H, H-C(2′)], 4.36 [d, *J* = 7.1 Hz, 1 H, H-C(1′)], 5.75 (br s, 2 H, NH_2), 6.45 (br s, 1 H, 2 × NHBoc), 9.74, 9.83 (br s, 2 H, NH-1 and NH-3). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ = 28.16 [q, $(CH_3)_3C$], 28.20 [q, $(CH_3)_3C$], 48.53 (t, C-4′), 49.88 (q, CH_3OH), 53.82 (d), 56.28 (d), 58.94 (d), 77.99 (s), 78.07(s), 78.23 (s), 84.73 (s), 149.65 (s), 152.17 (s), 153.07(s), 154.99 (s), 155.44 (s), 162.72 (s). UV (c = 5·10^{-5} M in MeOH): λ_{max} = 268 (ε = 1.48·10^5), 224 (ε = 5.01·10^4). ESI-MS: *m/z* (%) = 549.3(96) [M + Na]$^+$, 449.2(100) [M – Boc + Na]$^+$, 349.2(38) [M – 2 Boc + Na]$^+$). HR-MALDI: *m/z* calcd for $C_{23}H_{38}N_6O_8Na$: 549.2643; found: 549.2653. Anal. Calcd for $C_{23}H_{38}N_6O_8$·MeOH: C, 51.60; H, 7.57; N, 15.04. Found C, 51.50; H, 7.28; N, 14.86.

7-Carba-8-[*N*-(*tert*-butyloxycarbonyl)-(2′*R*,3′*S*)-2′,3′-di(*tert*-butyloxycabonylamino)-(1′*S*)-pyrrolidinyl]guanine (11α/β).

Compound **11α**: mp 225 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ = 1.30 (s, 9 H, 3 × CH_3), 1.35 (s, 9 H, 3 × CH_3), 1.40 (s, 9 H, 3 × CH_3), 3.21 [dd, *J* = 10.3, 8.0 Hz, 1 H, H-C(4′)], 3.80 [dd, *J* = 10.3, 7.6 Hz, 1 H, H-C(4′)], 3.93 [m, 1 H, H-C(3′)], 4.05 [pseudo q, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = $J_{H\text{-}3'\text{-}H\text{-}2'}$ = $J_{H\text{-}2'\text{-}NH}$ = 8.0 Hz, 1 H, H-C(2′)], 4.51 (*d*, *J* = 7.5, 1H, H-C(1′)], 5.77 (br s, 2 H, NH_2), 6.05 [d, $J_{H\text{-}7\text{-}NH\text{-}9}$ = 2.2 Hz, 1 H, H-C(7)], 8.35 (br d, *J* = 7.5 Hz, 1 H, NHBoc), 6.76 (br s, 1 H, NHBoc), 9.93 (br s, 1 H, NH-3), 10.41 (br s, 1 H, NH-9). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ = 28.06 [q, $(CH_3)_3C$], 28.16 [q, $(CH_3)_3C$], 28.20 [q, $(CH_3)_3C$], 48.98 [t, C(4′)], 53.48 [d, C(3′)], 58.43 [d, C(1′)], 61.23 [d, C(2′)], 78.14 [s, $(CH_3)_3C$], 78.21 [s, $(CH_3)_3C$], 78.83 [s, $(CH_3)_3C$], 99.23 [d, C(7)], 99.86 [s, C(5)], 130.31 [s, C(8)], 150.97 [s, C(4)], 151.94 [s, C(2)], 153.43 (s, C=O of N-Boc), 154.93 (s, C=O of NHBoc-3′), 155.10 (s, C=O of NHBoc-2′), 158.29 [s, C(6)]. UV (c = 5·10^{-5} M in MeOH): λ_{max} = 262 nm

($\varepsilon = 1.55 \cdot 10^4$), λ_{min} = 233 nm ($\varepsilon = 3200$), 216 ($\varepsilon = 2.05 \cdot 10^4$). MALDI-MS: *m/z* (%) = 572.3(100) $[M + Na]^+$, 472.2(48), 432.2(60), 372.2(10), 227.1 (88), 151.1 (46). HR-MALDI: *m/z* calcd for $C_{25}H_{39}N_7O_7Na$: 572.2803; found: 572.2804. Anal. Calcd for $C_{25}H_{39}N_7O_7$: C, 54.63; H, 7.15; N, 17.84. Found: C, 54.58; H, 7.01; N, 17.87.

Preparation of Free C-Azanucleosides (Scheme 3).

Representative Procedure for Step a: 2,4-Diamino-5-[*N*-(*tert*-butyloxycarbonyl)-(2′*S*,3′*S*)-2′,3′-dihydroxy-(1′*S*)-pyrrolidinyl]-6-oxopyrimidine (12α).

The amount of 333 mg (0.62 mmol) of **4α** was dissolved in 50 mL of sat. NH_3 in MeOH and stirred at r.t. for 24 h. TLC (CH_2Cl_2–MeOH, 8:1) showed the consumption of starting material **4α** (R_f = 0.50) and the formation of a new UV active spot (R_f = 0.05). Evaporation of the solvent afforded a yellow oil residue that was purified by CC (silica gel, CH_2Cl_2–MeOH, 8:1). Fractions 29–41 (5 mL each) were combined and evaporated under reduced pressure at 30 °C to give 198 mg (98%) of **12α** as white solid. TLC: R_f = 0.21 (CH_2Cl_2–MeOH, 4:1). ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ = 1.30 (s, 9 H, 3 Me), 3.29 [dd, *J* = 11.2, 3.8 Hz, 1 H, H-C(4′)], 3.59 [dd, *J* = 10.8, 6.9 Hz, 1 H, H-C(4′)], 3.76, 3.93 [br s, 2 H, H-C(2′), H-C(3′)], 4.32 (d, *J* = 2.8 Hz, 1 H, H-1′), 4.81 (br s, 1 H, OH, exchanges with D_2O), 5.67 (br s, 2 H, NH_2, exchanges with D_2O), 5.91 (br s, 2 H, NH_2, exchanges with D_2O), 6.19 (br d, *J* = 7.5 Hz, 1 H, OH, exchanges with D_2O), 9.75 (br s, 1 H, OH). ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C): δ = 28.08 (q), 52.96 (br t), 61.07 (d), 73.62 (d), 77.45 (s), 82.06 (br d), 87.41 (s), 153.08 (s), 153.37 (s), 162.61 (s), 162.53 (s). ESI-MS: *m/z* (%) = 676.9 (32) [2 M + Na]$^+$, 366.0(20) $[M + K]^+$), 350.0(100) $[M + Na]^+$. UV (c = $5 \cdot 10^{-5}$ M in MeOH): λ_{max} = 274 nm ($\varepsilon = 1.16 \cdot 10^4$), 213 ($\varepsilon = 2.24 \cdot 10^4$), λ_{min} = 251 nm (ε = 3500).

4-Amino-5-[*N*-(*tert*-butyloxycarbonyl)-(2′*S*,3′*S*)-2′,3′-dihydroxy-(1′*S*)-pyrrolidinyl]-2,6-dioxopyrimidine (14α).

TLC: R_f = 0.42 (CH_2Cl_2–MeOH, 4:1]. ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C): δ = 1.32 (s, 9 H, 3 Me), 3.29 [dd, *J* = 10.8, 5.1 Hz, 1 H, H-C(4′)], 3.57 [dd, *J* = 10.8, 6.3 Hz, 1 H, H-C(4′)], 3.80 (br s, 1 H, H-C(3′)], 4.01 [br s, 1 H, H-C(2′)], 4.32 [d, *J* = 3.9 Hz, 1 H,), 4.83 [br s, 1 H, HO-C(2′)], 5.46 [br s, 2 H, HO-C(3′)], 5.89 (br s, 2 H, NH_2, exchanges with D_2O), 9.85 (br s, 2 H, 2 NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.11 (q), 51.66 [br t, C-(4′)], 58.91 [d, C-(1′)], 73.55 [d, C-(3′)], 77.74 (s, Me_3C), 80.11 [br d, C-(2′)], 84.97 [s, C-(5)], 150.05 (s), 152.48 (s), 153.53 (s), 163.42 (s). ESI-MS: *m/z* (%) = 679.0(8) [2 M + Na]$^+$), 366.9(12) [M + K]$^+$, 351.0(100) $[M + Na]^+$). HR-MALDI: *m/z* calcd for $C_{13}H_{20}N_4O_6Na$ [M + Na$^+$]: 351.1275; found: 351.1272. UV (c = $5 \cdot 10^{-5}$ M in MeOH): λ_{max} = 269 nm ($\varepsilon = 1.62 \cdot 10^4$), 222 ($\varepsilon$ = 5300), λ_{min} = 242 (ε = 3200), 215 (ε = 5220).

8-[*N*-(*tert*-Butyloxycarbonyl)-(2′*S*,3′*S*)-2′,3′-dihydroxy-(1′*S*)-pyrrolidinyl]-7-carba-guanine (16α).

^{1}H NMR (600 MHz, DMSO-d_6, 70 °C): δ = 1.31 (s, 9 H, 3 Me), 3.35 [dd, *J* = 3.2, 11.4 Hz, 1 H, H-C(4′)], 3.66 [dd, *J* = 5.5, 11.4 Hz, 1 H, H-C(4′)], 3.99 [br s, 1 H, H-C(2′), exchanges with D_2O), 4.00 (br s, 1 H, H-C(3′), exchanges with D_2O), 4.47 [br s, 1 H, H-C(1′)], 5.22 [d, *J* = 3.3 Hz, 1 H, HO-C(2′)], 5.39 [br s, 1 H, OH-C(3′)], 5.85 (br s, 2 H, NH_2), 6.05 [d, *J* = 1.8 Hz, 1 H, H-C(7)], 10.02 (br s, 1 H, NH), 10.22 (br s, 1 H, NH). ^{13}C NMR (150.9 MHz, DMSO-d_6, 70 °C): δ = 28.96 (q, Me), 53.47 [d, C(4′)], 63.50 [d, C(1′)], 75.13 [d, C(3′)], 79.37 (s, CMe_3), 81.58 [d, C(2′)], 100.71 [s, C(7)], 118.14, 13.05, 151.77 [s, C(4)], 153.07 [s, C(2)], 154.94 (s, C=O), 159.49 [s, C(6)]. ESI-MS (pos., MeOH): *m/z* (%) = 374 (10) $[M + Na]^+$, 352 (40) $[M + H]^+$. ESI-MS (neg., MeOH): *m/z* (%) = 386 (30) $[M + Cl]^-$), 350 (100) $[M – H]^-$.

8-[*N*-(*tert*-Butyloxycarbonyl)-(2′*S*,3′*S*)-2′,3′-dihydroxy-(1′*R*)-pyrrolidinyl]-7-carba-guanine (16β).

TLC: R_f = 0.14 (CH_2Cl_2–MeOH, 8.5:1.5). ^{1}H NMR (600 MHz, DMSO-d_6, 343 °K): δ = 1.26 (s, 9 H, Me), 3.22 [dd, *J* = 3.7, 11.0 Hz, 1 H, H-C(4′)], 3.67 [dd, *J* = 5.4, 11.0 Hz, 1 H, H-C(4′)], 3.93 [t, *J* = 5.1 Hz, 1 H, H-C(2′)], 4.00 [dd, *J* = 4.5 Hz, 1 H, 9.2, H-C(3′)], 4.75 [d, *J* = 5.9 Hz, 1 H, H-C(1′)], 5.77 (br s, 2 H, NH_2), 5.93 [s, 1 H, H-C(7)]. ^{13}C NMR (150.9 MHz, DMSO-d_6, measured at 343 K): δ = 28.92 (q, Me), 52.39 [t, C(4′)], 58.93 [d, C(1′)], 73.91 [d, C(3′)], 77.82 [d, C(2′)], 79.06 (s, CMe_3), 100.22 [d, C(7)], 100.86, 129.44, 151.78, 152.94, 155.03, 159.76. ESI-MS (pos., MeOH): *m/z* (%) = 374 (100) $[M + Na]^+$), 352 (30) $[M + H])^+$. ESI-MS (neg., MeOH): 386 (20) $[M + Cl]^-$, 350(100) $[M – H]^-$).

8-[*N*-(*tert*-Butyloxycarbonyl)-(2′*S*,3′*S*)-2′,3′-dihydroxy-(1′*S*)-pyrrolidinyl]-7-carba-xanthine (18α).

TLC: R_f = 0.47 (CH_2Cl_2–MeOH, 4:1). ^{1}H NMR (600 MHz, DMSO-d_6, 70 °C): δ = 1.33 (s, 9 H, Me), 3.35 [d, *J* = 11.5 Hz, 1 H, H-C(4′)], 3.62 [dd, *J* = 4.8, 11.5 Hz, 1 H, H-C(4′)], 3.99 (s, 1 H), 4.03 (m, 1 H), 4.50 (s, 1 H), 5.29 (br s, 1 H, OH), 6.10 [s, 1 H, H-C(7)], 10.07 (br s, 1 H, NH). ^{13}C NMR (150.9 MHz, DMSO-d_6, 70 °C): *d* = 28.94 (q, Me), 53.83 [*t*, C(4′)], 63.50 [d, C(1′)], 79.64 [d, (C3′)], 98.81 [s, C(5)], 102.34 [d, C(7)], 130.42 [s, C(8)], 139.76 [s, C(4)], 151.47 [s, C(2)], 160.56 [s, H(C6)]. ESI-MS (positive, MeOH): *m/z* (%) = 727 (10) [2 M + Na]$^+$), 705(2) [2 M + H]$^+$), 398 (100) [M + 2 Na]$^+$, 375 (40) [M + Na]$^+$, 353 (40) [M + H]$^+$). ESI-MS (neg., MeOH): *m/z* (%) = 387 (5) $[M + Cl]^-$, 351 (100) $[M – H]^-$.

8-[*N*-(*tert*-Butyloxycarbonyl)-(2′*S*,3′)-2′,3′-dihydroxy-(1′*R*)-pyrrolidinyl]-7-carba-xanthine (18β).

TLC: R_f = 0.39 (CH_2Cl_2–MeOH, 4:1). ^{1}H NMR (600 MHz, DMSO-d_6, 70 °C): 1.27 (s, 9 H, Me), 3.26 [dd, *J* = 11.2 Hz, 1 H, 2.98, H-C(4′)], 3.61 [dd, *J* = 5.1, 11.2 Hz, 1 H, H-C(4′)], 3.94 (m, 1 H), 3.97 (s, 1 H), 4.75 (d, *J* = 5.4 Hz, 1 H), 5.02 (br s, 1 H, OH), 6.00 [s, 1 H, H-C(7)], 10.06 (br s, 1 H, NH), 10.35 (br s, OH, 0.5 H). ESI-MS (positive, MeOH): *m/z* (%) = 375 (10) $[M + Na]^+$), 353 (5) $[M + H]^+$). ESI-MS (neg., MeOH): *m/z* (%) = 387(50) $[M + Cl]^-$, 351 (100) $[M – H]^-$.

Representative Procedure for Step b: 2,4-Diamino-5-[(2′*S*,3′*S*)-2′,3′-dihydroxy-(1′*S*)-pyrrolidinyl]-6-oxo-pyrimidine Hydrochloride (13α).

The amount of 151 mg (0.46 mmol) of **12α** was suspended in 50 mL of sat. HCl in Et_2O and stirred at r.t. for 2 h. The off white solid in the reaction mixture was filtered, washed with 20 mL Et_2O and dried to give 113 mg (83%, calcd according to 2HCl salt) of **13α** as white solid. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.35 [dd, *J* = 4.5, 12.2 Hz, 1 H, H-C(4′)], 3.53 [dd, *J* = 5.6, 12.2 Hz, 1 H, H-C(4′)], 4.25 [ddd, $J_{cis\text{-}H\text{-}4'\text{-}H\text{-}3'}$ = 5.6 Hz, $J_{trans\text{-}H\text{-}4'\text{-}H\text{-}3'} = J_{H\text{-}2'\text{-}H\text{-}3'}$ = 4.2 Hz, 1 H, H-C(3′)], 4.44 [dd, *J* = 3.5, 7.5 Hz, 1 H, H-C(2′)], 4.55 [d, *J* = 7.5 Hz, 1 H, H-C(1′)]. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 48.30 (t), 57.95 (d), 74.01(d), 76.49 (d), 80.38 (s), 151.88 (s), 155.47 (s), 160.75 (s). ESI-MS: *m/z* (%) = 228.0(100) $[M + H]^+$). HR-MALDI: *m/z* calcd for $C_8H_{14}N_5O_3$ $[M + H]^+$: 228.1091; found: 228.1089.

4-Amino-5-[(2′*S*,3′*S*)-2′,3′-dihydroxy-(1′*S*)-pyrrolidinyl]-2,6-dioxopyrimidine Hydrochloride (15α).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.08 [d, *J* = 5.1 Hz, 1 H, H-C(4′)], 3.24 [dd, *J* = 6.3, 11.7 Hz, 1 H, H-C(4′)], 3.98 [d, *J* = 4.8 Hz, 1 H, H-C(1′)], 4.28 (m, 2 H, H-2′ and H-3′), 5.69 (br s, 2 H, NH_2), 7.01 (br s, 2 H, NH_2), 8.45 (br s, 1 H, OH), 9.56 (br s, 1 H, OH), 10.71, 10.72 (s, 2 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 48.16 (t), 58.16 (d), 73.99 (d), 76.48 (d), 77.44 (s), 149.34 (s), 154.42 (s), 164.00 (s).

ESI-MS: 229.0(100) [M + H]$^+$). HR-MALDI: *m/z* calcd for $C_8H_{14}N_5O_3$ [M + H]$^+$: 229.0937; found: 229.0927.

8-[(2′*S*,3′)-2′,3′-Dihydroxy-(1′*S*)-pyrrolidinyl]-7-carbaguanine Hydrochloride (17*α*).

TLC: R_f = 0.08 (CH_2Cl_2–MeOH, 8:2). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.15–3.17 [br m, 1 H, H-C(4′)], 3.40 [m, 1 H, H-C(4′)], 4.14 (dd, *J* = 3.5, 7.3 Hz, 1 H, H-C(3′)], 4.24 [t, *J* = 4.0 Hz, 1 H, H-C(2′)], 4.36 [dd, *J* = 6.0, 11.5 Hz, 1 H, H-C(1′)], 6.49 [s, 1 H, H-C(7)], 9.15 (br s, 1 H, -NH), 10.02 (br s, 1 H, -NH), 10.73 (br s, 1 H, -NH), 11.21 (br s, 1 H, -NH). ^{13}C NMR (150.9 MHz, DMSO-d_6): δ = 41.35 [d, C(4′)], 61.64 [d, C(1′)], 74.96 [d, C(3′)], 79.84 [d, C(2′)], 101.01 [s, C(5)], 104.81 [d, C(7)], 125.0 [s, C(8)], 152.91 [s, C(2)], 158.21 [s, C(6)] (one carbon signal is not observable). ESI-MS (pos., MeOH): *m/z* (%) = 503 (20) [2 M + H]$^+$), 252 (100) [M + H]$^+$). ESI-MS (neg., MeOH): *m/z* (%) = 537 (10) [2 M + Cl]$^-$, 286 (50) [M + Cl]$^-$), 250 (100) [M – H]$^-$.

8-[(2′*S*,3′*S*)-2′,3′-Dihydroxy-(1′*R*)-pyrrolidinyl]-7-carbaguanine Hydrochloride (17β).

TLC: R_f = 0.08 (CH_2Cl_2–MeOH, 8:2). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.01–3.04 (br m, 1 H, H-4′), 3.53–3.57 [m, 1 H, H-C(4′)], 4.08 [br s, H-C(2′)], 4.24 [d, *J* = 4.3 Hz, 1 H, H-C(3′)], 4.70 [dd, *J* = 2.5, 8.7 Hz, 1 H, H-C(1′)], 6.59 (d, *J* = 1.9 Hz, 1 H, H-C(7)], 9.24 (br s, 1 H, NH), 10.38 (br s, 1 H, NH), 11.48 (br s, 1 H, NH), 11.56 (br s, 1 H, -NH). ^{13}C NMR (150.9 MHz, DMSO-d_6): δ = 51.32 [d, C(4′)], 58.46 [d, C(1′)], 74.92 [d, C(2′)], 76.79 [d, C(3′)], 100.98 [d, C(5)], 105.35 [d, C(7)], 122.56 [d, C(8)], 152.64 [s, C(2)], 157.97 [d, C(6)] (one carbon-signal not observable). ESI-MS (pos., MeOH): δ = 503(10) [2 M + H]$^+$, 252 (100) [M + H]$^+$). EI-MS (neg., MeOH): δ = 537 (10) [2 M + Cl]$^-$, 286 (40) [M + Cl]$^-$, 250 (100) [M – H]$^-$.

8-[(2′*S*,3′*S*)-2′,3′-Dihydroxy-(1′*S*)-pyrrolidinyl]-7-carbaxanthine Hydrochloride (19*α*).

TLC: R_f = 0.56 (CH_2Cl_2–MeOH–aq NH_3, 5:5:0.5). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.43 [dd, *J* = 11.95, 5.06 Hz, 1 H, H-C(4′)], 4.19 [m, 1 H, H-C(3′)], 4.23 [m, 1 H, H-C(2′)], 4.45 [d, *J* = 4.32 Hz, 1 H, H-C(1′)], 6.48 [s, 1 H, H-C(7)], 9.11 (br s, 0.5 H, NH), 9.94 (br s, 0.5 H, NH), 10.27 (br s, 1 H, OH,), 10.86 (br s, 1 H, OH), 11.30 (br s, 0.6 H, NH). ^{13}C NMR (150.9 MHz, DMSO-d_6): δ = 50.93, 62.43, 75.26, 79.93, 99.54, 105.78, 123.71, 140.91, 151.52, 160.39. ESI-MS (pos., MeOH): *m/z* (%) = 275 (10) [M + Na]$^+$), 253 (100) [M + H]$^+$). ESI-MS (neg., MeOH): *m/z* (%) = 287 (5) [M + Cl]$^-$, 251 (10) [M – H]$^-$.

Preparation of Free C-Azanucleosides (Scheme 4). Representative Procedure. 2,4-Diamino-5-[(2′*R*,3′)-2′,3′-diamino-(1′*S*)-pyrrolidinyl]-6-oxopyrimidine Hydrochloride (20*α*).

The amount of 132 mg (0.25 mmol) of **9α** was suspended in 20 mL of sat. HCl in Et_2O and stirred at r.t. for 2 h. The off white solid in the reaction mixture was filtered, washed with 20 mL Et_2O and dried to give 85 mg of **20α** (91%, calcd according to 4HCl salt) as white solid. ^{1}H NMR (300 MHz, CD_3COOD–D_2O, 5:2): δ = 4.01 [dd, *J* = 4.7, 13.7 Hz, 1 H, H-C(4′)], 4.23 [dd, *J* = 8.1, 13.7 Hz, 1 H, H-C(4′)], 4.67 [ddd, *J* = 8.0, 5.0, 5.0 Hz, 1 H, H-C(3′)], 4.90 (dd, *J* = 5.6, 7.5 Hz, 1 H, H-2′), 5.20 [d, *J* = 7.8 Hz, 1 H, H-C(1′)]. ^{13}C NMR (75 MHz, DMSO-d_6): 44.54, 50.11, 51.98, 55.07, 76.86, 156.56, 157.12, 161.06. ESI-MS (MeOH): *m/e* (%) = 226.1 (100) [M + H$^+$], 450.9 (13) [2 M + H$^+$].

4-Amino-5-[(2′*R*,3′)-2′,3′-diamino-(1′*S*)-pyrrolidinyl]-2,6-dioxopyrimidine Hydrochloride (21*α*).

^{1}H NMR (300 MHz, CD_3COOD–D_2O, 2:1; contaminated with 6% of the corresponding β-epimer): δ = 4.02 [dd, *J* = 4.6, 13.4 Hz, 1 H, H-C(4′)], 4.24 [dd, *J* = 8.1, 13.4 Hz, 1 H, H-C(4′)], 4.67 (ddd, *J* = 8.1, 5.2, 5.2 Hz, 1 H, H-3′), 4.89 [dd, *J* = 5.6, 8.1 Hz, 1 H, H-C(2′)], 5.14 (d, *J* = 7.8 Hz, 1 H, H-1′). ^{13}C NMR (75 MHz, DMSO-d_6–D_2O): 47.67, 53.19, 55.68, 58.87, 77.07, 152.46, 156.82, 166.30. ESI-MS (MeOH): *m/e* (%) = 227.1 (100) [M + H$^+$], 453.0 (32) [2 M + H$^+$].

7-Carba-8-[(2′*R*,3′*S*)-2′,3′-diamino-(1′*S*)-pyrrolidinyl]guanine Hydrochloride (22*α*).

^{1}H NMR (400 MHz, D_2O): δ = 3.60 [dd, *J* = 7.3, 13.4 Hz, 1 H, H-C(4′)], 3.97 [dd, *J* = 9.1, 13.4 Hz, 1 H, H-C(4′)], 4.35 [ddd, $J_{\text{trans-H-4′-H-3′}}$ = 7.3 Hz, $J_{cic\text{-H-4′-H-3′}}$ = 9.1 Hz, $J_{\text{H-2′-H-3′}}$ = 8.3 Hz, 1 H, H-C(3′)], 4.50 [dd, *J* = 8.3, 10.4 Hz, 1 H, H-C(2′)], 5.03 (d, *J* = 10.5 Hz, 1 H, H-1′), 5.03 [d, *J* = 0.5 Hz, 1 H, H-C(7)]. ^{13}C NMR (100 MHz, D_2O): δ = 45.29 [t, C(4′)], 50.49 [d, C(3′)], 54.95 [d, C(2′)], 56.82 [d, C(1′)], 101.00 [s, C(5)], 106.65 [d, C(7)], 119.59 [s, C(8)], 145.08 (s), 151.99 (s), 160.01 (s). ESI-MS (MeOH): *m/e* (%) = 250.2 (20) [M + H$^+$], 499.3 (37) [2 M + H$^+$], 537.3 (100) [2 M + K$^+$].