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Synthesis of 2-Aminopurine Nucleosides via Regiocontrolled Glycosylation

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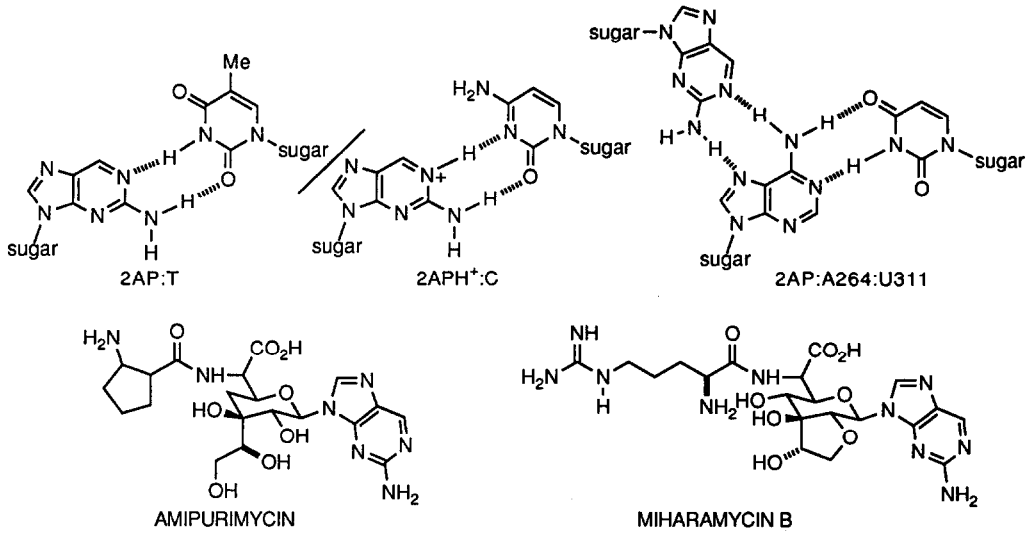
Abstract: *The stereo- and regiocontrolled synthesis of pyranosyl 2-aminopurine nucleosides is described. Coupling of bissilylated N^2-acetyl-2-aminopurine with peracetylated glucopyranosides ($SnCl_4$, $(CH_2Cl)_2$-MeCN, reflux) afforded good yields of the corresponding N^9-β-2-aminopurine nucleosides. Glycosylation of N^2-acetyl-2-amino-6-chloropurine could be made to produce either N^9-nucleosides (TMSOTf, $(CH_2Cl)_2$, reflux,) or N^7-nucleosides ($SnCl_4$/MeCN, room temperature) selectively. Application of Knapp's thioglycoside procedure (NIS + TfOH, $(CH_2Cl)_2$, room temperature) produced the N^9-nucleosides with either base. The 2-amino-6-chloropurine derivatives were converted to their corresponding 2-aminopurine nucleosides by hydrogenolysis (H_2, Pd/C). A convenient NOESY protocol for establishing base regiochemistry and anomeric stereochemistry is also presented.*

INTRODUCTION

2-Aminopurine (2AP) is an atypical nucleoside base with an interesting biological profile: 2AP itself induces transition mutations (A:T → G:C and G:C → A:T)[2] and the purported base-pair mismatches ($2APH^+$:T and 2AP:C) have been characterized by NMR.[3] The unique H-bonding properties of 2AP extend to the triple helix manifold and in this context it has been used to examine the guanosine binding site of an altered (G264:C311 → A264:U311) *Tetrahymena* group I ribozyme.[4] The inherent flourescence of 2AP nucleosides make them attractive analytical probes of local nucleic acid structure.[5] This base occurs naturally as a structural component of the *Streptomyces*-derived antifungal antibiotics amipurimycin[6] and the miharamycins.[7] Incorporation of 2AP into synthetic acyclic nucleoside analogs (in place of guanine) has led to the development of effective antiviral prodrugs such as 6-deoxyacyclovir[8] and famciclovir.[9] Finally, N^2-substituted 2AP nucleosides have been shown to inhibit mammalian DNA polymerase α.[10]

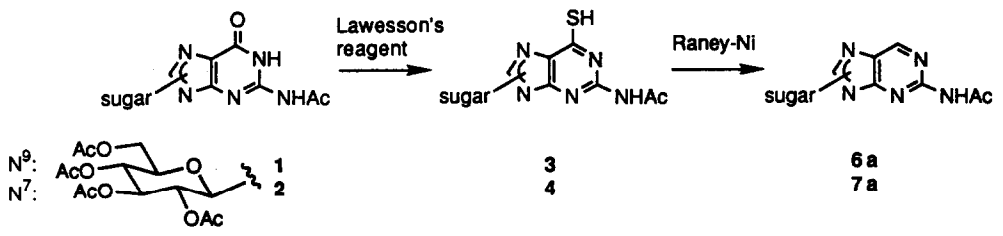
The synthesis of 2AP nucleosides has been largely restricted to the modification of guanosine and 2'-deoxyguanosine derivatives (or their related acyclic analogs). This approach generally involves Raney-Ni reduction of thioguanine derivatives which are available from the corresponding guanine nucleosides by thionation using P_4S_{10}.[11] A two-step route involving NaSH displacement of a 6-pyridyl species obtained by treatment of guanine with $(CF_3CO)_2O$/pyridine has been reported as well.[12] Alternatively, 2-amino-6-chloropurine (2A6CP) derivatives can be prepared from guanine nucleosides by treatment with phosphoryl chloride and reduced chemically (H_2/Pd-C[13,14] or $R_3NH^+HCO_2^-$/Pd-C),[5,15] photochemically (Et_3N, hν),[16] or electrochemically (-0.75 V, 0.25 M HCl)[17] to give 2AP nucleosides. These 2A6CP nucleosides can be converted to their 2-amino-6-thiopurine (2A6TP) and related derivatives via nucleophilic displacement.[13] The 9-β-2'-deoxyriboside of 2AP has also been synthesized by Ag_2O mediated oxidation of a 2-amino-6-hydrazinopurine derivative which was prepared from 2'-deoxyguanosine via its 6-sulfonate.[18]



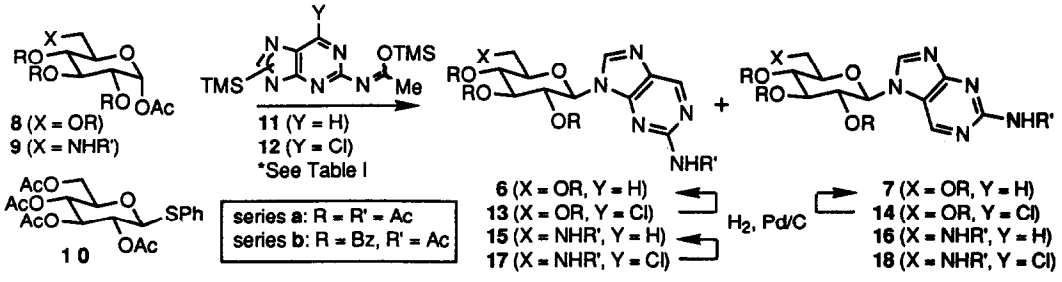
These procedures for the synthesis of 2AP nucleosides are most useful when the parent guanine derivative is readily available and does not possess functionality which is sensitive to the usual C-6 activation/reduction conditions (guanosine & acyclovir for example). When either or both of these conditions are not met, however, it may be necessary to introduce an already modified base (2AP or 2A6CP) directly via glycosylation. Such was the case with our synthetic approach to amipurimycin and miharamycin B which entailed glycosylation of a highly functionalized 6-amido-6-deoxyheptopyranose system at a rather late stage. In particular, one would not expect functionality such as a secondary amide and tertiary alcohol to withstand the guanine thionation[19] or chlorination[20] conditions outlined above. We now report that regio- and stereocontrolled syntheses of both β-D-glucopyranosyl as well as β-D-6'-amino-6'-deoxyglucopyranosyl 2-aminopurine nucleosides can be achieved via glycosylation.

RESULTS AND DISCUSSION

In order to secure authentic specimens of glucopyranosyl-2AP nucleosides at the outset, we began by converting the readily prepared N^9- and N^7-guanine nucleosides **1** and **2**[21] to their corresponding 2AP nucleosides **6a** and **7a** via a modification of the classical thionation/reduction sequence. Thus, treatment of **1** and **2** with Lawesson's thionation reagent ($(p\text{-}MeOC_6H_4P(S)S)_2$)[22] afforded the corresponding 2-aminopurine-6-thiol derivatives **3** and **4** in 65 and 60% yield respectively after flash chromatography. With the N^7-substituted guanine **2**, longer reaction times resulted in thionation of the N^2 acetyl group as well to give a dithionated species **5** (not shown) as a minor by-product. Increased steric hinderence about the C-6 carbonyl is apparently responsible for this side reaction with the N^7-substituted nucleoside **2** and it is even more pronounced when P_4S_{10} is used as the thionating agent. The use of Lawesson's reagent in place of P_4S_{10} represents an improvement for the synthesis of thionucleosides such as **3** and **4**.[23] Reductive desulfurization of **3** and **4** with Raney nickel afforded the corresponding N^9- and N^7-2AP nucleosides **6a** and **7a**.



We next looked at the Lewis acid catalyzed glycosylation of bissilylated N^2-acetyl-2AP **11** which we hoped would provide a direct route to 2AP nucleosides.[24] In spite of the interest in 2AP nucleosides over the years, there are only two reports of nucleosidation involving 2AP directly. Thus, condensation of chloromercuri-2-benzamidopurine with 2,3,5-tri-O-benzoylribofuranosyl chloride to give 2-amino-9-β-D-ribofuranosylpurine in 24% yield after deacylation.[25] The enzyme *nucleoside deoxyribosyltransferase* has also been used to effect a transnucleosidation between 2AP and 2'-deoxythymidine.[26] As far as the acyclic nucleoside analogs are concerned, alkylation of the sodium salt of 2AP with (2-acetoxyethoxy)methyl chloride afforded O-acetyl-6-deoxyacyclovir and the N^7-regiomer in 25 and 5% respectively.[15]



Compound **11** was prepared by treating its precursor, N^2-acetyl-2AP, with hot hexamethyldisilazane (HMDS) plus chlorotrimethylsilane (TMSCl). After removal of the volatiles, crude **11** was obtained as a moisture sensitive oil which was used directly without purification. As can be seen by the results gathered in Table I, this base reacted cleanly with peracetylated glucose **8a** and 6-amino-6-deoxyglucose **9a** under optimized conditons ($SnCl_4$, $(CH_2Cl)_2$-MeCN, reflux) to give good yields of the corresponding N^9-β-2AP nucleosides **6a** and **15a**. The glucose derived nucleoside **6a** was identical to the substance previously obtained by desulfurization of **3**. Only traces of the regioisomeric N^7-β-2AP nucleosides **7a** and **16a** could be detected by TLC and/or ^1H NMR analysis of the crude product mixtures. Coupling of **8a** with **11** using conditions known[21] to favor the formation of N^7-guanine nucleosides was very sluggish (presumably due to complexation of $SnCl_4$ with the more basic **11**)[27] and, in any event, gave N^9-substituted 2AP nucleoside **6a** as the sole product.

We also investigated an alternative route to 2AP nucleosides that involved glycosylation of the silylated 2A6CP derivative **12** followed by reductive dechlorination of the resulting nucleoside product (vide supra). Examples of glycosylation/alkylation of 2A6CP derivatives are known. Thus, reaction of **12** with 2,3,5-tri-O-acetyl-D-xylofuranosyl bromide in the presence of $Hg(CN)_2$ led to a 62% isolated yield of the corresponding N^9-β-2A6CP nucleoside.[28] More recently, the sodium salt of 2A6CP was shown to undergo a displacement

reaction with 1-chloro-2,3,5-tri-O-benzyl-α-D-arabinofuranose to give the corresponding β-N^9 and β-N^7 nucleosides in 68 and 11% yield respectively.[29] Base-mediated alkylation of 2A6CP with 2-benzoyloxyethoxymethyl chloride has also been used to synthesize of 6-deoxyacyclovir.[8] We felt that a general 2A6CP glycosylation protocol that did not involve stoichoimetric mercury (II) catalysis would be most useful.

Table I. Glycosylation of 2AP and 2A6CP Derivatives.

entry	sugar substrate	silylated base	coupling conditions[a]	nucleoside products	N^9:N^7 ratio	combined yield, %
1	**8a**	**11**	A	**6a/7a**	98:2	78
2	**8a**	**11**	B	**6a/7a**	96:4	51
3	**8a**	**11**	C	**6a/7a**	100:0	11[b]
4	**8a**	**12**	A	**13a/14a**	50:50	66
5	**8a**	**12**	B	**13a/14a**	83:17	67
6	**8a**	**12**	C	**13a/14a**	12:88	68
7	**8b**	**12**	B	**13b/14b**	98:2	71
8	**8b**	**12**	C	**13b/14b**	10:90	65
9	**9a**	**11**	A	**15a/16a**	>98:2	67
10	**9a**	**12**	B	**17a/18a**	75:25	64
11	**9a**	**12**	C	**17a/18a**	59:41	22[c]
12	**10**	**11**	D	**6a/7a**	>98:2	60
13	**10**	**12**	D	**13a/14a**	>98:2	64

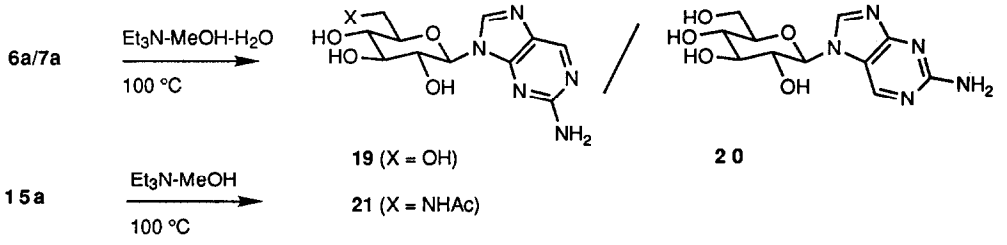
[a]Procedure A: $SnCl_4/CH_3CN$-$(CH_2Cl)_2$, reflux; B: trimethylsilyl triflate (TMSOTf)/$(CH_2Cl)_2$, reflux; C: $SnCl_4/CH_3CN$, room temperature; D: N-iodosuccinimide (NIS), triflic acid (TfOH)/$(CH_2Cl)_2$, room temperature. [b]Crude NMR showed 89 mol% of unreacted **8a**. [c]Corrected yield based on 33% recovered **9a**.

The silylated 2A6CP derivative **12** (prepared from 2A6CP by a sequence identical to the one used for **11**) was coupled with **8a** to give good yields of either the N^9-substituted nucleoside **13a** (TMSOTf, $(CH_2Cl)_2$, reflux) or the N^7 regioisomer **14a** ($SnCl_4$, MeCN, room temperature) regioselectively. In this sense, the Lewis acid catalyzed glycosylation of silylated 2A6CP **12** resembles that of trissilylated N^2-acetylguanine since the N^9/N^7 regioselectivity can be controlled in both cases by simply adjusting the reaction conditions so as to favor either thermodynamic ($\rightarrow N^9$) or kinetic ($\rightarrow N^7$) control.[21] As expected, use of the O-benzoylated glucose derivative **8b** resulted in an improved N^9:N^7 ratio. While **9a** could be coupled with **12** to give the N^9-substituted nucleoside **17a** selectively, the 6-acetamido group appeared to have a deleterious effect ($SnCl_4$ complexation?) on the N^7-selective nucleosidation conditions.

Recently, Knapp reported a mild procedure for nucleoside synthesis that involved iodonium-mediated activation of O-peracetylated 1-thioglycosides followed by trapping with the requisite silylated base.[30] The fact that these glycosylations proceeded readily at room temperature encouraged us to try this procedure with 2AP and 2A6CP since relatively harsh conditions had been required to access the desired N^9-2AP and N^9-2A6CP nucleosides. Both **11** and **12** were coupled to the β-thioglucoside **10**[31] (NIS, TfOH, $(CH_2Cl)_2$, room

temperature) to give good yields the N^9-nucleosides **6a** and **13a**. No more than a trace of the N^7-regioisomer could be detected in the crude reaction mixtures by TLC. These results could have bearing on our projected syntheses of amipurimycin and miharamycin B since both of these targets incorporate sensitive functionality (3° alcohol) which may not survive the combination of strong Lewis acids and elevated reaction temperatures.

Hydrogenolysis (H_2, Pd/C) of the resulting 2A6CP nucleosides proceeded uneventfully to give high yields of the corresponding 2AP nucleosides **6a**, **7a**, and **15a**. The 2AP nucleosides **6a** and **7a** were heated in Et_3N-MeOH-H_2O (bath T = 100 °C) to give the fully deprotected nucleosides **19** and **20** in 64% and 44% yield respectively. Likewise, methanolysis of **15a** resulted in the clean production of compound **21** (68% yield) in which the 6'-acetamide linkage remained intact (recall that both amipurimycin & miharamycin B have analogous peptide linkages). In each case, the deacetylated 2AP nucleosides could be purified to homogeneity using reverse phase HPLC.



The characterization of nucleosides prepared by glycosylation centers around determining the anomeric configuration of the sugar (stereoselectivity) and point of attachment to the heterocyclic base (regioselectivity). For the $^4C_1$ pyranosyl nucleosides described in this paper, the β-D-gluco configuration (expected on mechanistic grounds)[27] was readily deduced from ^1H NMR vicinal coupling data ($J_{1',2'}$ = 9-10 Hz). The point of attachment to the purine ring (N^9 or N^7) can be established using a set of empirical rules based on relative ^1H and ^{13}C NMR chemical shift differences wherein the signals for H-8 (excepting **13** and **14**), C-4, C-8, & C-1' are shielded and C-5 & C-6 deshielded in the N^9-substituted purines relative to their N^7-substituted counterparts.[32] An alternative 2D NMR based protocol for the characterization of 2AP nucleosides was also examined (Figure 1). *Both* the anomeric configuration and purine regiochemistry of these nucleosides could be readily deduced from NOESY experiments which established proximity between H-8 and H-1', H-2' for β-N^9 2AP nucleosides **6a** and **15a** but showed additional off-diagonal interactions between H-6 and H-1', H-2' for the β-N^7 2AP nucleoside **7a**.

EXPERIMENTAL SECTION

All coupling reactions were performed under Ar atmosphere. TLC analysis was performed on Merck silica gel 60 F-254 plates and visualized first by UV illumination and then by charring with 5% anisaldehyde in (95:5:1) EtOH-AcOH-H_2SO_4. Melting points are uncorrected. ^1H NMR signal assignments were based on selective homonuclear decoupling experiments while the ^{13}C assignments were based on APT (attached proton test) experiments. High resolution mass spectral data (EI unless stated otherwise) are reported in units of m/e. Acetonitrile and 1,2-dichloroethane were distilled from CaH_2 and P_2O_5, respectively, while trimethylsilyl triflate and tin tetrachloride were distilled under Ar just prior to use.

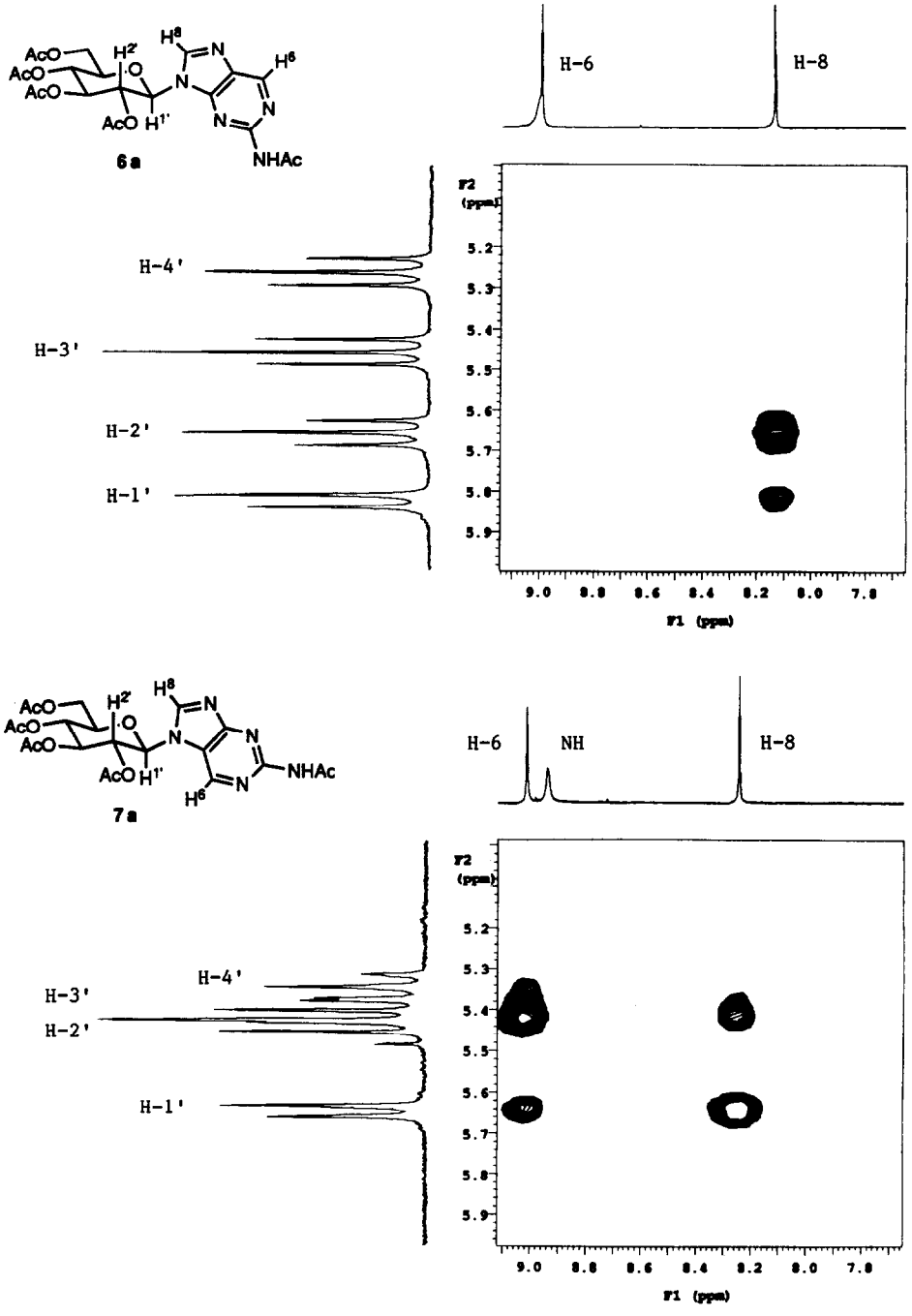


Figure 1. Relevent portions of the 300 MHz ^{1}H NMR NOESY spectra obtained for compounds **6a** and **7a** in $CDCl_3$ showing interactions between H-8, H-6 and H-1', H-2'. The data were collected at ambient T with a 270-ms mixing time, 1D = 2D sweep width = 4000 Hz, pulse width = 20.5 degrees, number of transients = 32, number of increments = 256, and fourier transform size = 4 x 0.5 K.

General Procedure for Nucleoside Thiation

Lawesson's reagent (1.9 equiv) was added to a solution of **1** or **2** in toluene (0.01 M) and the mixture was stirred at 100 °C for 2 h, at which time the TLC in 14:1 EtOAc-MeOH showed the formation of product, at the expense of the starting material. Concentration followed by flash chromatography (SiO_2, 4:1 EtOAc-hexanes) afforded the corresponding 2A6TP nucleosides **3** or **4** as yellow solids.

N^2-Acetyl-2-amino-9-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)thioguanine (3). 65% yield; *Rf* 0.61 (14:1 EtOAc-MeOH); amorphous solid, mp 167-169 °C; $[\alpha]_D^{24}$ -19.7° (*c* 1.82, $CHCl_3$); IR ($CHCl_3$) 1755, 1610, 1550, 1220 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.17 (s, NHAc), 7.83 (s, H-8), 5.77 (t, J = 9.2 Hz, H-2'), 5.51 (d, J = 9.5 Hz, H-1'), 5.36 (t, J = 9.2 Hz, H-3'), 5.24 (t, J = 9.5 Hz, H-4'), 4.28 (dd, J = 12.5, 5.1 Hz, H-6'a), 4.15 (dd, J = 12.6, 2.5 Hz, H-6'b), 4.03 - 3.97 (m, H-5'), 2.34 (s, NHAc), 2.07, 2.05, 2.02, 1.83 (s, 4 x OAc); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.76, 171.98, 170.55, 170.03, 169.44 (5 x C=O), 169.04 (C-6), 147.05 (C-4), 144.09 (C-2), 139.58 (C-8), 132.79 (C-5), 81.39 (C-1'), 74.82 (C-2'), 73.05 (C-3'), 69.44 (C-4'), 67.70 (C-5'), 61.70 (C-6'), 24.53, 20.70, 20.53, 20.36, 20.32 (5 x $COCH_3$); HRMS calcd for $C_{21}H_{25}N_5O_{10}S$ (M^+) 539.1322, found 539.1310.

N^2-Acetyl-2-amino-7-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)thioguanine (4). 60% yield; *Rf* 0.70 (14:1 EtOAc-MeOH); amorphous solid, mp 150-153 °C; $[\alpha]_D^{23}$ -78.3° (*c* 3.26, $CHCl_3$); IR ($CHCl_3$) 1760, 1620, 1560, 1375, 1220 cm-1; ^1H NMR (200 MHz, $CDCl_3$) δ 10.38 (s, NHAc), 8.21 (s, H-8), 7.32 (d, J = 9.3 Hz, H-1'), 5.53 (t, J = 9.1 Hz, H-2'), 5.43 (t, J = 9.1 Hz, H-3'), 5.21 (t, J = 9.6 Hz, H-4'), 4.27 (dd, J = 12.6, 4.8 Hz, H-6'a), 4.16 (dd, J = 12.7, 2.4 Hz, H-6'b), 4.15 - 4.05 (m, H-5'), 2.41 (s, NHAc), 2.04, 2.00, 1.87 (s, 4 x OAc); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.44, 170.59, 169.86, 169.63 (5 x C=O), 169.47 (C-6), 153.10 (C-4), 148.13 (C-2), 144.08 (C-8), 122.73 (C-5), 80.93 (C-1'), 74.39 (C-2'), 73.30 (C-3'), 69.73 (C-4'), 67.82 (C-5'), 61.46 (C-6'), 24.67, 20.74, 20.50, 20.39 (5 x $COCH_3$); HRMS calcd for $C_{21}H_{26}N_5O_{10}S$ (M^+) 539.1322, found 539.1349.

General Procedure for Desulfurization

W-2 Raney Ni (ca 20 equiv)[33] was added to a solution of **3** or **4** in (1:1) EtOH-H_2O (0.005 M) and the mixture was stirred at 100 °C for 30 min, at which time the TLC in (14:1) EtOAc-MeOH showed the clean formation of product at the expense of the starting material. Concentration followed by flash chromatography (SiO_2, 30:1 EtOAc-MeOH) afforded the corresponding 2AP nucleosides **6a** or **7a** as white solids.

N^2-Acetyl-2-amino-9-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)purine (6a). 54% yield; *Rf* 0.54 (14:1 EtOAc-MeOH); crystalline solid, mp 116-117 °C; $[\alpha]_D^{25}$ -7.2° (*c* 0.47, $CHCl_3$); IR ($CHCl_3$) 1760, 1680, 1630, 1590 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.92 (s, H-6), 8.29 (s, NHAc), 8.10 (s, H-8), 5.81 (d, J = 9.4 Hz, H-1'), 5.64 (t, J = 9.3 Hz, H-2'), 5.45 (t, J = 9.2 Hz, H-3'), 5.25 (t, J = 9.6 Hz, H-4'), 4.29 (dd, J = 12.6, 4.8 Hz, H-6'a), 4.15 (dd, J = 12.6, 2.4 Hz, H-6'b), 4.01 (ddd, J = 9.9, 4.8, 2.4 Hz, H-5'), 2.56 (s, NHAc), 2.06, 2.02, 1.77 (s, 4 x OAc); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.44, 169.90, 169.33, 168.95 (5 x C=O), 153.21 (C-4), 152.17 (C-2), 150.15 (C-6), 142.18 (C-8), 130.43 (C-5), 80.45 (C-1'), 75.06 (C-2'), 72.78 (C-3'), 69.90 (C-4'), 67.64 (C-5'), 61.46 (C-6'), 29.67, 25.23, 20.66, 20.52, 20.13 (5 x $COCH_3$); HRMS calcd for $C_{21}H_{25}N_5O_{10}$ (M^+) 507.1601, found 507.1611; Anal. Calcd for $C_{21}H_{25}N_5O_{10}\cdot H_2O$: C, 48.00; H, 5.18; N, 13.33. Found: C, 48.08; H, 5.29; N, 13.12.

N^2-Acetyl-2-amino-7-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)purine (7a). 63% yield; *Rf* 0.34 (14:1 EtOAc-MeOH); crystalline solid, mp 148-150 °C; $[\alpha]_D^{25}$ -61.4° (*c* 1.82, $CHCl_3$); IR ($CHCl_3$) 1760, 1675, 1630, 1560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, NHAc), 9.06 (s, H-6), 8.21 (s, H-8), 5.59 (d, J = 8.6 Hz, H-1'), 5.44 (t, J = 8.9 Hz, H-2'), 5.39 (t, J = 8.9 Hz, H-3'), 5.31 (t, J = 9.1 Hz, H-4'), 4.33 (dd, J = 12.7, 4.8 Hz, H-6'a), 4.21 (dd, J = 12.7, 1.9 Hz, H-6'b), 4.04 (m, H-5'), 2.58 (s, NHAc), 2.10, 2.07, 2.01, 1.83 (s, 4 x OAc); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.46, 169.94, 169.31, 168.50 (5 x C=O), 162.24 (C-4), 154.17 (C-2), 146.52 (C-8), 142.64 (C-6), 120.50 (C-5), 84.18 (C-1'), 75.39 (C-2'), 72.39 (C-3'), 70.24 (C-4'), 67.53 (C-5'), 61.45 (C-6'), 25.21, 20.66, 20.46, 20.04 (5 x $COCH_3$); HRMS calcd for $C_{21}H_{25}N_5O_{10}$ (M^+) 507.1601, found 507.1600.

Preparation of Silylated Bases 11 and 12

A suspension of 2AP or 2A6CP in acetic anhydride (0.45 mmol/mL) was refluxed under an N_2 atm for 25 min. During this time the reaction became homogeneous. The solution was cooled to room temperature and diluted with Et_2O whereupon a precipitate formed and was collected by suction filtration. This precipitate was suspended in 50% aqueous EtOH (0.2 mmol/mL) and refluxed for 15 min. The mixture became homogenous after 5 min and within 15 min, a new precipitate began to form. Upon cooling to room temperature, the desired N^2-monoacetates of 2AP and 2A6CP were collected by suction filtration. [Ac2AP: 38% overall yield; amorphous solid, mp >300 °C (dec), ^1H NMR (200 MHz, DMSO-d_6): δ 10.50 (s, NH), 8.96 (s, H-6), 8.46 (s, H-8), 2.51 (s, NHAc). Ac2A6CP: 41% overall yield; amorphous solid, mp >300 °C (dec), ^1H NMR (200 MHz, DMSO-d_6): δ 10.78 (s, NH), 8.51 (s, H-8), 2.17 (s, NHAc).] To a solution of N^2-acetylated base in CH_3CN (0.1 M) was added HMDS (12 equiv) and TMSCl (2.8 equiv) at room temperature. The resulting mixture was heated under reflux at 135 °C for 1 h, then cooled to room temperature. Excess solvent and reagents were distilled off at atmospheric pressure and residual oil was pumped at 50 °C for 2 h, then used for coupling reactions without purification.

General Coupling Procedures

Method A. To a solution of silylated base (2.1 equiv, 0.66 M in CH_3CN) was added a solution of acylated sugar (1.0 equiv, 0.11 M in $(CH_2Cl)_2$) followed by $SnCl_4$ (3.3 equiv). The reaction mixture was heated under reflux at 135 °C until judged complete by TLC (30 min to 1 h). The mixture was cooled to room temperature, poured into saturated $NaHCO_3$ solution, and extracted with $CHCl_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude nucleosides which were purified by flash chromatography (SiO_2).

Method B. To a solution of silylated base (2.0 equiv, 0.14 M in $(CH_2Cl)_2$) was added a solution of acylated sugar (1 equiv, 0.09 M in $(CH_2Cl)_2$) followed by TMSOTf (2 equiv). The reaction mixture was heated under reflux at 135 °C until judged complete by TLC (5 to 16 h) then processed as described above.

Method C. To a solution of silylated base (2.2 equiv, 1.2 M in CH_3CN) was added a solution of acylated sugar (1.0 equiv, 0.22 M in CH_3CN) followed by $SnCl_4$ (5.1 equiv). The reaction mixture was stirred at room temperature until judged complete by TLC (ca 16 h) then processed as described above.

Method D. To a solution of silylated base (2.0 equiv, 0.1 M in $(CH_2Cl)_2$) were added $(CH_2Cl)_2$ solutions of thioglucoside (1.0 equiv, 0.07 M), NIS (3.0 equiv, 0.04 M), and TfOH (1.2 equiv, 0.5 M). The reaction mixture was stirred at room temperature until judged complete by TLC (ca 3 h) then diluted with CH_2Cl_2, washed with 10% $Na_2S_2O_3$ solution, and processed further as described above.

8a + 11 → 6a/7a. Procedure A. Flash chromatography (97:3 $CHCl_3$-MeOH); **6a:** 76% isolated yield. **7a:** 2% isolated yield.

10 + 11 → 6a. Procedure D. Flash chromatography (97:3 $CHCl_3$-MeOH); 60% isolated yield.

8a + 12 → N^2-Acetyl-2-amino-6-chloro-9-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)purine (13a). Procedure B. Flash chromatography (EtOAc); 56% isolated yield; *Rf* 0.65 (EtOAc); crystalline solid, mp 170-171.5 °C (from MeOH); $[\alpha]_D^{25}$ -7.5° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 1760, 1700, 1340, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, NHAc), 8.18 (s, H-8), 5.83 (d, J = 9.5 Hz, H-1'), 5.68 (t, J = 9.3 Hz, H-2'), 5.47 (t, J = 9.4 Hz, H-3'), 5.27 (t, J = 9.6 Hz, H-4'), 4.30 (dd, J = 12.6, 4.6 Hz, H-6'$_a$), 4.14 (bd, J = 12.6 Hz, H-6'$_b$), 4.04 (m, H-5'), 2.58 (s, NHAc), 2.08, 2.07, 2.04, 1.82 (s, 4 x OAc); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.42, 169.87, 169.30, 168.98 (5 x C=O), 152.55 (C-4), 152.39 (C-2), 151.86 (C-6), 142.13 (C-8), 127.82 (C-5), 80.86 (C-1'), 75.06 (C-2'), 72.69 (C-3'), 69.82 (C-4'), 67.57 (C-5'), 61.43 (C-6'), 25.25, 20.64, 20.52, 20.47, 20.17 (5 x $COCH_3$); HRMS calcd for $C_{21}H_{24}N_5O_{10}Cl$ (M^+) 541.1212, found 541.1280; Anal. Calcd for $C_{21}H_{25}N_5O_{10}Cl \cdot 1/2H_2O$: C, 45.78; H, 4.57; N, 12.71. Found: C, 45.82; H, 4.22; N, 12.51. **14a:** 11% isolated yield.

10 + 12 → 13a. Procedure D. Flash chromatography (EtOAc); 64% isolated yield.

8a + 12 → N^2-Acetyl-2-amino-6-chloro-7-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)purine (14a). Procedure C. Flash chromatography (EtOAc); 56% isolated yield; *Rf* 0.38 (EtOAc); crystalline solid, mp 129-131 °C (from MeOH); $[\alpha]_D^{25}$ -18.9° (*c* 0.70, $CHCl_3$); IR ($CHCl_3$) 1755, 1690, 1480, 1370, 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, NHAc), 8.18 (s, H-8), 6.08 (bd, J = 7.9 Hz, H-1'), 5.69 (t, J = 9.3 Hz, H-2'), 5.47 (t, J = 9.4 Hz, H-3'), 5.28 (t, J = 9.8 Hz, H-4'), 4.29 (dd, J = 12.6, 5.0 Hz, H-6'$_a$), 4.19 (dd, J = 12.6, 2.1 Hz, H-6'$_b$), 4.07 (ddd, J = 10.1, 4.9, 2.2 Hz, H-5'), 2.60 (s, NHAc), 2.09, 2.06, 1.91 (s, 4 x OAc); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.02, 170.41, 169.92, 169.25, 169.01 (5 x C=O), 152.93 (C-4), 163.42 (C-2), 147.06 (C-8), 143.31 (C-6), 118.50 (C-5), 82.62 (C-1'), 74.97 (C-2'), 72.89 (C-3'), 69.73 (C-4'), 67.49 (C-5'), 61.38 (C-6'), 25.21, 20.65, 20.50, 20.22 (5 x $COCH_3$); HRMS calcd for $C_{21}H_{24}N_5O_{10}Cl$ (M^+) 541.1212, found 541.1122; Anal. Calcd for $C_{21}H_{25}N_5O_{10}Cl \cdot 3/2H_2O$: C, 44.45; H, 4.53; N, 12.34. Found: C, 44.73; H, 4.13; N, 11.84. **13a:** 12% isolated yield.

8b + 12 → N^2-Acetyl-2-amino-6-chloro-9-(2',3',4',6'-tetra-O-benzoyl-β-D-glucopyranosyl) purine (13b). Procedure B. Flash chromatography (2:1 EtOAc-hexanes); 69% isolated yield; *Rf* 0.67 (3:1 EtOAc-hexanes); crystalline solid, mp 125-129 °C; $[\alpha]_D^{25}$ +57.4° (*c* 5.23, $CHCl_3$); IR ($CHCl_3$) 1740, 1600, 1575, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, NHAc), 8.23 (s, H-8), 7.98-7.15 (m, 4 x Ph), 6.17-6.09 & 5.88 (m & t, J = 9.0 Hz, H-1', H-2', H-3', H-4'), 4.70-4.49 (m, H-5', H-6'$_a$, H-6'$_b$), 2.49 (s, NHAc); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.45, 165.97, 165.53, 165.07, 164.79 (5 x C=O), 152.64 (C-4), 152.29 (C-2), 151.66 (C-6), 142.16 (C-8), 127.81 (C-5), 133.79, 133.72, 133.51, 133.35, 129.84, 129.71, 128.51, 128.34, 129.20, 127.52 (4 x Ph), 82.35 (C-1'), 75.53 (C-2'), 72.76 (C-3'), 71.01 (C-4'), 68.74 (C-5'), 62.46 (C-6'), 25.13 ($COCH_3$); Anal. Calcd. for $C_{41}H_{32}N_5O_{10}Cl \cdot 1/2H_2O$: C, 61.62; H, 4.16; N, 8.76. Found: C, 61.52; H, 4.17; N, 7.96. **14b:** 1% isolated yield.

8b + 12 → N^2-Acetyl-2-amino-6-chloro-7-(2',3',4',6'-tetra-O-benzoyl-β-D-glucopyranosyl) purine (14b). Procedure C. Flash chromatography (2:1 EtOAc-hexanes); 59% isolated yield;

Rf 0.36 (3:1 EtOAc-hexanes); crystalline solid, mp 140-144 °C; $[\alpha]_D^{25}$ +41.2° (*c* 3.91, $CHCl_3$); IR ($CHCl_3$) 1740, 1600, 1550, 1490, 1260 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.63 (s, NHAc), 8.20 (s, H-8), 8.04-7.24 (m, 4 x Ph), 6.49-5.87 (m, H-1', H-2', H-3', H-4'), 4.76-4.51 (m, H-5', H-6'a, H-6'b), 2.55 (s, NHAc); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.06, 165.99, 165.59, 165.03, 164.83 (5 x C=O), 163.37 (C-4), 152.81 (C-2), 147.42 (C-8), 143.20 (C-6), 118.58 (C-5), 134.08, 133.77, 133.61, 133.38, 129.81, 129.71, 129.15, 128.40, 128.12, 127.29 (4 x Ph), 82.96 (C-1'), 75.46 (C-2'), 73.02 (C-3'), 70.60 (C-4'), 68.64 (C-5'), 62.47 (C-6'), 25.14 ($COCH_3$); Anal. Calcd. for $C_{41}H_{32}N_5O_{10}Cl$: C, 62.32; H, 4.08; N, 8.86. Found: C, 62.42; H, 4.35; N, 9.03. **13b:** 7% isolated yield.

9a + 11 → N^2-Acetyl-2-amino-9-(2',3',4'-tri-O-acetyl-6'-acetamido-6'-deoxy-β-D-glucopyranosyl)purine (15a). Procedure A. Flash chromatography (20:1 EtOAc-MeOH). 67% isolated yield; *Rf* 0.14 (14:1 EtOAc-MeOH); crystalline solid, mp 140-141 °C; $[\alpha]_D^{25}$ -18.9° (*c* 1.69, $CHCl_3$); IR ($CHCl_3$) 1760, 1675, 1510, 1370, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 2-NHAc), 8.95 (s, H-6), 8.07 (s, H-8), 6.26 (m, 6'-NHAc), 5.76 (d, J = 9.4 Hz, H-1'), 5.65 (t, J = 9.4 Hz, H-2'), 5.43 (t, J = 9.3 Hz, H-3'), 5.13 (t, J = 9.8 Hz, H-4'), 3.93 (m, H-5'), 3.65-3.59 (m, H-6'a), 3.50-3.41 (m, H-6'b), 2.51 (s, NHAc), 2.09, 2.01, 1.95, 1.77 (s, 4 x Ac); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.42, 169.89, 169.72, 168.95 (5 x CO), 153.21 (C-4), 152.10 (C-2), 150.05 (C-6), 142.13 (C-8), 130.36 (C-5), 80.87 (C-1'), 76.05 (C-2'), 72.69 (C-3'), 69.85 (C-4'), 68.35 (C-5'), 39.16 (C-6'), 25.19, 23.01, 20.63, 20.50, 20.13 (5 x $COCH_3$).

9a + 12 → N^2-Acetyl-2-amino-6-chloro-9-(2',3',4'-tri-O-acetyl-6'-acetamido-6'-deoxy-β-D-glucopyranosyl)purine (17a). Procedure B. Flash chromatography (14:1 EtOAc-MeOH). 48% isolated yield; *Rf* 0.39 (14:1 EtOAc-MeOH); amorphous solid, mp 155-157 °C; $[\alpha]_D^{25}$ +12.3° (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 1760, 1670, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 2-NHAc), 8.12 (s, H-8), 6.21 (bm, 6'-NHAc), 5.75 (d, J = 9.4 Hz, H-1'), 5.67 (t, J = 9.3 Hz, H-2'), 5.43 (t, J = 9.3 Hz, H-3'), 5.16 (t, J = 9.7 Hz, H-4'), 3.94 (m, H-5'), 3.60-3.52 (m, H-6'a & H-6'b), 2.50 (s, NHAc), 2.11, 2.03, 1.99, 1.83 (s, 4 x Ac); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.52, 169.89, 169.80, 169.71, 168.97 (5 x C=O), 152.47 (C-4), 152.22 (C-2), 151.77 (C-6), 142.12 (C-8), 127.99 (C-5), 81.43 (C-1'), 75.87 (C-2'), 72.60 (C-3'), 69.82 (C-4'), 68.20 (C-5'), 39.13 (C-6'), 25.15, 23.02, 20.63, 20.50, 20.17 (5 x $COCH_3$); HRMS calcd for $C_{21}H_{25}N_6O_9Cl$ (M^+) 540.1371, found 540.1395. **18a:** 16% isolated yield.

General Procedure for Dechlorination

To a solution of 2A6CP nucleoside in EtOAc (ca. 0.05 M) was added Et_3N (1.1 equiv) and 10% Pd/C (300 mg/mmol). The mixture was stirred under an H_2 atmosphere at room temperature for 3 h, at which time, the TLC in (14:1) EtOAc-MeOH showed the reaction to be complete. The mixture was filtered through a Celite pad, washed with 50 mL of boiling EtOAc, and the filtrate was evaporated to a white solid. Purification by flash chromatography (SiO_2, 25:1 EtOAc-MeOH) afforded the 2AP nucleosides as white solids.
13a → 6a: 94% yield. **14a → 7a:** 86% yield. **17a → 15a:** 97% yield.

General Procedure for Nucleoside Deacylation

The protected nucleoside was suspended in 2:1:1 Et_3N-MeOH-H_2O (**6a** and **7a**, ≈ 0.01 M) or 1:1 Et_3N-MeOH (**15a**, ≈ 0.05 M) and heated at 100 °C for 1 day (dissolution occurred). The reaction mixture was cooled

to room temperature and evaporated to give crude product. Semi-preparative HPLC (Rainin Dynamax-60A 8µm C18) gave analytically pure material.

6a → 2-Amino-9-(β-D-glucopyranosyl)purine (19). 64% yield; t_r 15.1 min (analytical column, H_2O, 1 mL/min); amorphous solid, mp 235 °C (dec); $[\alpha]_D^{25}$ -7.4° (*c* 0.35, H_2O); UV (H_2O) λ_{max} 304 nm (ε 4738), 243 (4890); (0.1 N HCl) 308 (10853), 243 (9526); (0.1 N NaOH) 308 (9987), 239 (9868); IR (KBr) 1640, 1585, 1430 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 8.58 (s, H-6), 8.19 (s, H-8), 6.37 (s, NH_2), 5.34 (d, J = 9.4 Hz, H-1'), 5.19, 5.07, 4.95, 4.42 (m's, 4 x OH), 3.95 (m, H-2'), 3.70 (m, H-3'), 3.53-3.19 (m, H-4', H-5', H-6'a, H-6'b); ^{13}C NMR (50.4 MHz, DMSO-d_6) δ 160.51 (C-2), 153.28 (C-4), 149.06 (C-6), 141.01 (C-8), 126.78 (C-5), 81.98 (C-1'), 80.05 (C-2'), 77.31 (C-3'), 71.02 (C-4'), 69.68 (C-5'), 60.85 (C-6'); HRMS (FAB/glycerol) calcd for $C_{11}H_{16}N_5O_5$ ([M+H]$^+$) 298.1151, found 298.1457.

7a → 2-Amino-7-(β-D-glucopyranosyl)purine (20). 44% yield; t_r 10.8 min (analytical column, H_2O, 1 mL/min); amorphous solid, mp 255-258 °C (dec); $[\alpha]_D^{25}$ -1° (*c* 0.90, H_2O); UV (H_2O) λ_{max} 315 nm (ε 3084), 248 (3503), (0.1 N HCl) 328 (6755), 260 (7142), (0.1 N NaOH) 314 (2954), 249 (3175); IR (KBr) 1635, 1580, 1430 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 8.64 (s, H-6), 8.34 (s, H-8), 6.05 (s, NH_2), 5.36 (d, J = 8.9 Hz, H-1'), 5.32 (bs, OH), 5.02 (m, 2 x OH), 4.46 (m, OH), 3.73-3.22 (m, H-2', H-3', H-4', H-5', H-6'a, H-6'b); ^{13}C NMR (50.4 MHz, DMSO-d_6) δ 162.66 (C-2), 160.90 (C-4), 146.45 (C-8), 142.96 (C-6), 117.73 (C-5), 85.65 (C-1'), 79.83 (C-2'), 76.84 (C-3'), 71.77 (C-4'), 69.44 (C-5'), 60.81 (C-6'); HRMS (FAB/glycerol) calcd for $C_{11}H_{16}N_5O_5$ ([M+H]$^+$) 298.1151, found 298.0920.

14a → 2-Amino-9-(6'-acetamido-6'-deoxy-β-D-glucopyranosyl)purine (21). 68% yield; t_r 20.8 min (analytical column, 40:1 H_2O-MeOH, 1 mL/min); amorphous solid, mp 175-180 °C (dec); $[\alpha]_D^{25}$ -16.5° (ε 1.40, MeOH); IR (MeOH) 3560-3000, 1620, 1580 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 8.58 (s, H-6), 8.21 (s, H-8), 7.74 (bs, 6-NHAc), 6.39 (s, NH_2), 5.33 (d, J = 9.4 Hz, H-1'), 5.26 (m, OH), 5.11 (m, 2 x OH), 3.95 (m, H-2'), 3.60 (m, H-3'), 3.47-3.17 (m, H-4', H-5', H-6'a, H-6'b); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 169.77 (6-NH<u>Ac</u>), 160.54 (C-2), 153.28 (C-4), 149.09 (C-6), 141.06 (C-8), 126.76 (C-5), 82.05 (C-1'), 77.78 (C-2'), 76.59 (C-3'), 71.21 (C-4'), 71.07 (C-5'), 38.89 (C-6'), 22.43 (CO<u>C</u>H$_3$).

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