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HYPOXANTHINE NUCLEOSIDE COUNTERPARTS OF THE ANTIBIOTIC, CORDYCEPIN

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Abstract: Analogues of 3'-deoxyinosine, although of potential RNA antiviral interest, are virtually unknown. This paper reports on approaches to the synthesis of base-modified hypoxanthine 3'-deoxynucleosides. All of the target compounds are new and contain functionality at the 2-position that can be further elaborated for the synthesis of a variety of other novel analogues of 3'-deoxyinosine. Intact natural guanosine was used as the precursor and the key transformations utilized were regioselective bis-silylation, thermal radical deoxygenation, regiospecific radical halogenation, metal-mediated functionalization, and selective ozonolysis. The synthetic approaches described have considerable generality in terms of entry to novel analogues of 3'-deoxyinosine.

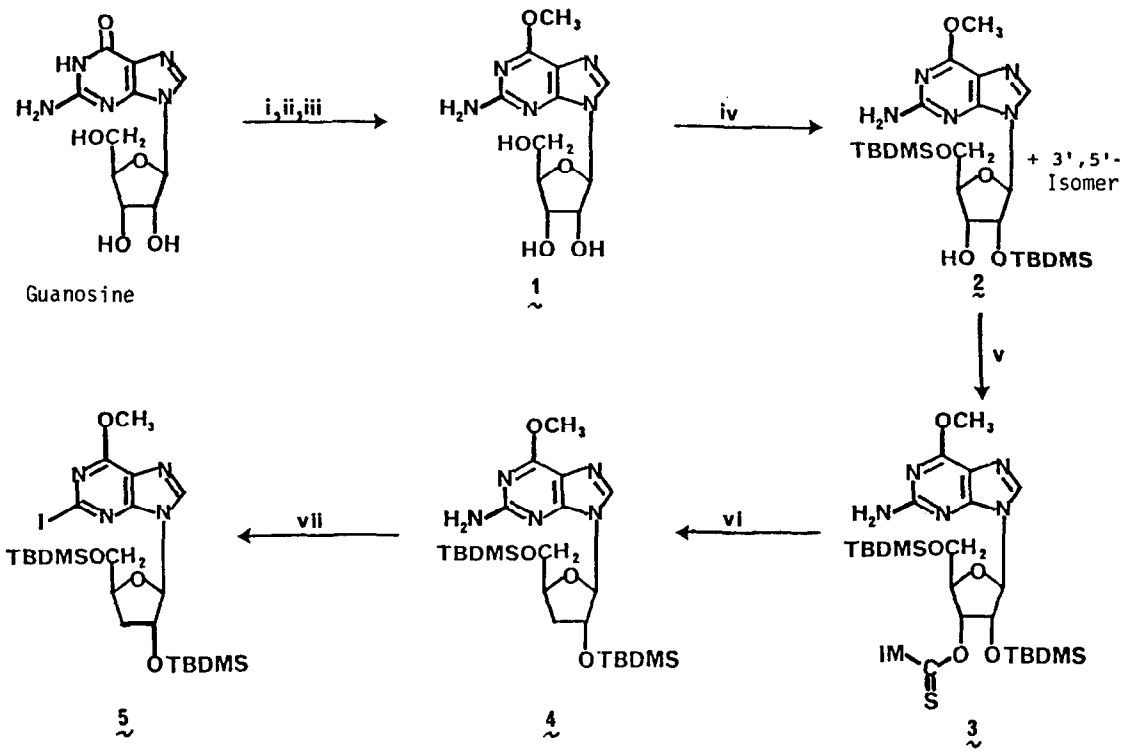
While numerous investigations have been carried out on the synthesis and modifications of purine ribonucleosides, the same cannot be said for their deoxygenated counterparts. This is particularly true for purine 3'-deoxynucleosides which are of potential biological interest as antiviral agents and as inhibitors of key purine metabolizing enzymes. For example, very little is known about hypoxanthine or guanine 3'-deoxynucleosides. The corresponding 2'-deoxynucleosides of the guanine family have received somewhat more attention.[2-5] 2'-Deoxyguanosine (presumably as its triphosphate) inhibits the growth of mouse lymphoma T-cell lines and is inhibitory to a number of viruses.[5-7] A derivative of this compound, N^2-phenyl-2'-deoxyguanosine, shows significant antiviral activity against the Herpes Simplex Virus (Type I).[8] 2'-Deoxyguanosine

and 2'-deoxyinosine are toxic to a number of microorganisms.[9-11] The triphosphate of 2'-deoxyguanosine is a potent inhibitor of mammalian ribonucleotide reductase.[12] In the adenine family of 3'-deoxynucleosides, the most studied of the few compounds known is the nucleoside antibiotic, cordycepin (3'-deoxyadenosine). This compound has RNA antiviral activity and is an inhibitor of viral RNA polymerase in its phosphorylated form.[13] This paper reports on the synthesis of analogues of the hypoxanthine counterpart of the antiviral compound, cordycepin. The doubly modified nucleosides have not been described before and are of interest, not only as potential antiviral agents (in their triphosphate forms), but also as potential inhibitors (in their monophosphate forms) of a key enzyme in purine metabolism, inosine monophosphate dehydrogenase.[14]

Two rational approaches can be envisaged for the synthesis of these compounds from intact ribonucleosides through modifications involving both the carbohydrate and aglycon moieties. Modifications may be carried out on the carbohydrate component first followed by alterations in the base moiety or this order may be reversed. We chose to use the first approach as several of the functional groups to be placed at the 2-position were expected to be sensitive to the reactions to be used for the alteration of the carbohydrate portion.

An important precursor for the carbohydrate modification was the O^6-methylated guanosine **1**.[15] This compound can be prepared in three steps from guanosine with an overall yield of 80%.[15,16] The hydroxyl groups on the ribose were partially protected with tert-butyldimethylsilyl groups to give compound **2** and its 3',5'-isomer in a combined yield of 53%. An additional 31% of the total product was due to the 5'-monosilylated compound. In practice, this compound was recycled using 1.1 eq. of TBDMSCl, and 2.2 eq. of imidazole to produce additional disilyl compounds. Total conversions were over 80%. The desired 2',5'-disilylated compound **2**

was separated from its 3',5'-isomer by careful column chromatography on silica gel using a gradient of 20-50% ether/ hexanes as the eluting solvent. Compound **2** was deoxygenated *via* its imidazolides **3**. The latter could be synthesized in almost quantitative yield by reaction of **3** with thiocarbonyldiimidazole and DMAP in dry DMF at room temperature for 12 h. Treatment of compound **3** with tri-n-butyltin hydride and AIBN in refluxing toluene[17] furnished the deoxygenated, protected guanosine intermediate **4** in 98% yield (Scheme 1).



(i) Ac_2O, DMAP, Et_3N, CH_3CN; (ii) $POCl_3$, DEA, Δ; (iii) CH_3ONa, CH_3OH; (iv) TBDMSCl, IM, DMF; (v) Im_2CS, DMAP, DMF; (vi) n-Bu_3SnH, AIBN, Toluene, Δ; (vii) CH_2I_2, TMSI, RONO, hexane, Δ

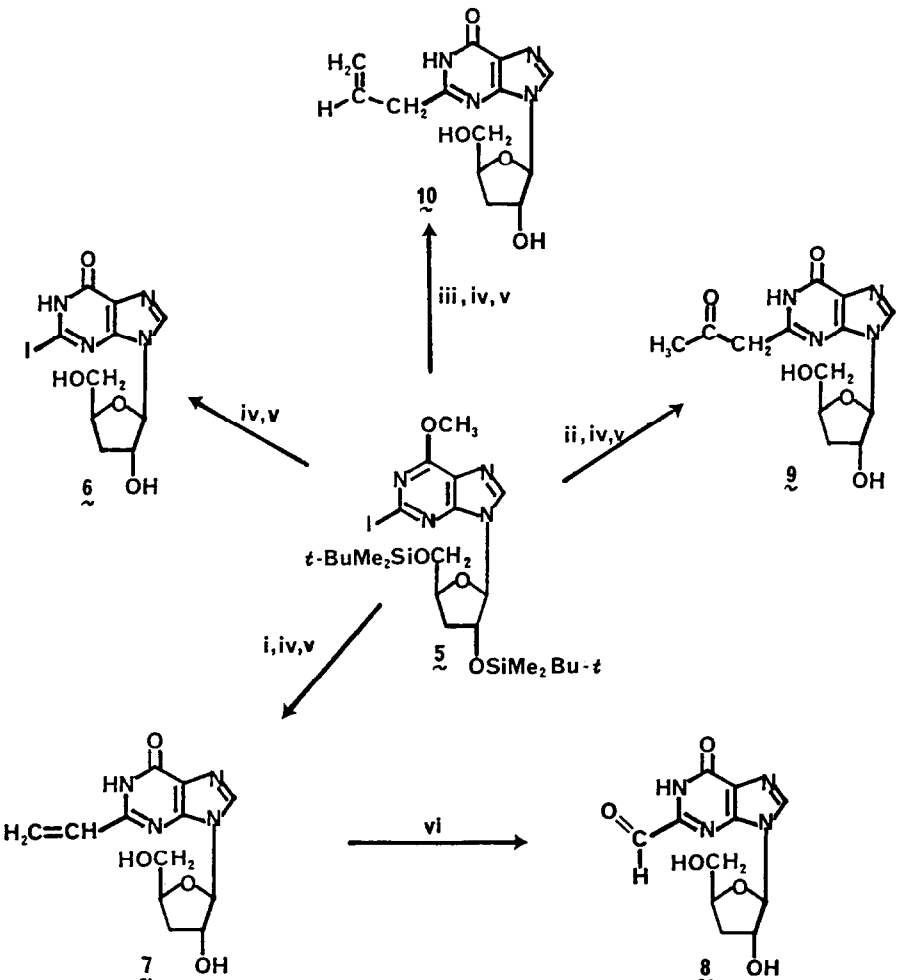
Scheme 1

The carbohydrate moiety having being modified, the next stage of the synthesis was to tailor the base moiety for alteration. This was done through the 2-iodo compound **5** which was prepared by treatment of **4** with diiodomethane, tert-butylnitrite, and trimethylsilyl iodide in dry hexane at 50 °C[18]. The 2-iodo intermediate **5** was the immediate precursor for the synthesis of the doubly modified hypoxanthine nucleosides. For example, the novel 2-iodo-3′-deoxyinosine (**6**) was synthesized from **5** by a two-step deprotection process: first, treatment of compound **5** with TMSCl and KI in acetonitrile resulted in demethylation at the O^6 position; second, treatment of the resulting product with tetraethylammonium fluoride in acetonitrile deprotected the silyl groups on the carbohydrate moiety. Compound **6** was isolated in a 39% overall yield from **5**.

Modification of the base moiety was carried out through palladium-catalyzed cross-coupling reactions on **5** with a variety of organostannanes.[19] Thus, treatment of compound **5** with $PdCl_2(CH_3CN)_2$ and $n\text{-}Bu_3SnCH{=}CH_2$ in dry toluene at 90 °C furnished the fully protected 2-vinyl compound in 97% yield. The two step deprotection gave 2-vinyl-2′-deoxyinosine **7** (Scheme 2).

Modified nucleosides bearing formyl groups on the base moiety have scarcely been investigated. 2-Formyl-3′-deoxyinosine (**8**), was easily synthesized from the 2-vinyl compound **7** in 77% yield by oxidation of the exocyclic ethylenic moiety with ozone. The high-field carbon-13 NMR data of **8** showed that it existed in two forms in equilibrium, the carbonyl and its hydrated (geminal diol) form. Interestingly, ozonolysis reactions have rarely been used for the elaboration of nucleosides.

Another novel deoxyinosine bearing a carbonyl group at the 2-position was also synthesized. This was 2-acetonyl-2′-deoxyinosine (**9**) which, like the 2-vinyl compound, was also prepared by metal-catalyzed methods (88% yield). In this case, the cross-coupling organostannane reagent, tri-n-



(i) n-$Bu_3SnCH{=}CH_2$, $PdCl_2(CH_3CN)_2$, $P(o\text{-tolyl})_3$, Toluene, Δ; (ii) n-Bu_3SnOCH_3, $P(o\text{-tolyl})_3$, $CH_3C(OAc){=}CH_2$, $PdCl_2(CH_3CN)_2$, Toluene, Δ; (iii) $PdCl_2(CH_3CN)_2$, $P(o\text{-tolyl})_3$, n-$Bu_3SnCH_2CH{=}CH_2$, Toluene, Δ; (iv) TMSCl, KI, CH_3CN; (v) $Et_4N^+F^-$, CH_3CN; (vi) O_3, H_2O

Scheme 2

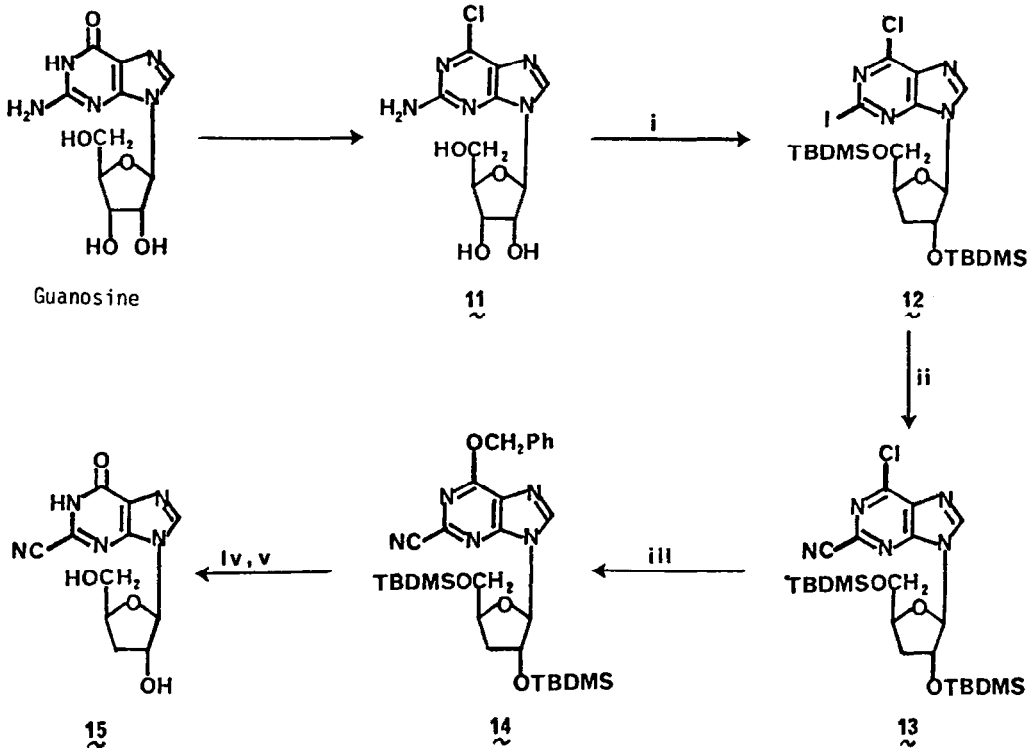
butylacetonylstannane, was generated in situ by reaction of tri-n-butyltin methoxide with isopropenyl acetate. Double deprotection gave the 2-acetonyl-3′-deoxyinosine **9**. The 2-allyl compound **10** was produced by using

allyltri-n-butylstannane as the transmetalation reagent in the palladium reaction followed by deprotection of the product. It is important in this reaction to maintain the temperature at about 95 °C, i.e. sufficient to surmount the barrier for the metal-mediated reaction, but not high enough for the isomerization of the allyl group in the product to the thermodynamically more stable methylvinyl system.

Introduction of a cyano group at the 2-position of 3'-deoxyinosine was of interest because of the potential of this group to be a precursor for the corresponding carboxylic acid, amide, amine, amidine, and other functionalities. Initially, we had attempted to use compound **5** as an immediate precursor for the introduction of the cyano group. While this reaction was successful, considerable decomposition of product occurred at the demethylation step with trimethylsilyl iodide. An alternative masking group for the lactam carbonyl, the benzyl group, was then chosen. This group can be removed by catalytic hydrogenation using Pd/C thus eliminating the aforementioned complications. The 2-iodo-6-chloro-3'-deoxy precursor **12** was prepared in four steps from 2-amino-6-chloropurine ribonucleoside (**11**),[15] using the series of reactions described for the conversion of **1** to **5**. Treatment of **12** with n-Bu_3SnCN, $Pd(PPh_3)_4$ in toluene at 100 °C produced the 2-cyano-6-chloro compound **13** in 77% yield (Scheme 3). For the introduction of oxygen at the 6-position, compound **13** was treated with the sodium salt of benzyl alcohol which furnished the 6-benzyl derivative **14** in 85% yield. Catalytic hydrogenation of **14** with 10% Pd/C and H_2 (65% yield) followed by desilylation of the deoxyribose moiety with fluoride ions (76% yield) furnished the novel 2-cyano-3'-deoxyinosine.**15**

In summary, the synthesis of some novel analogues of 3'-deoxyinosine is described. The approaches presented have sufficient generality that they can be applied to the synthesis of many other deoxygenated hypoxanthine nucleosides functionalized in the base moiety. Biological

studies pertaining to the RNA antiviral activities of these compounds will be reported elsewhere.



(i) see 1→5; (ii) *n*-Bu_3SnCN, $Pd(PPh_3)_4$, Toluene, Δ ; (iii) $PhCH_2OH$, Na, DMF ; (iv) H_2, Pd/C, 10%; (v) $Et_4N^+F^-$, CH_3CN

Scheme 3

EXPERIMENTAL

Melting points reported are uncorrected and were determined on a Thomas-Hoover melting point apparatus fitted with a microscope. Nuclear magnetic resonance spectra were recorded on Bruker Models WM360, MSL300, and AC300 pulse Fourier transform spectrometers. Mass spectra were determined on a VG ZAB-HF high resolution mass spectrometer with FAB

capability or a VG TRIO single quadrupole GC/MS system. Ultraviolet spectra were recorded on a Varian Cary Model 219 or a Gilford Response spectrophotometer. Infrared spectra were recorded on a Mattson Cygnus 25 Fourier transform instrument. Lyophilizations were performed with a Virtis freezemobile 3 unit. Preparative layer chromatography plates were prepared by coating six 20 cm x 20 cm plates with a slurry made from 150 g of E. Merck PF_{254} silica gel in 400 mL of water. The silica gel plates were allowed to dry slowly and were then activated for 3 h at 135°C. Flash chromatography was carried out using glass columns packed with 230-400 mesh silica gel. High performance liquid chromatography was done at 80 psi using Altex columns packed with 40-60 μm Amberlite XAD-4 resin (Rohm and Haas). Fractions were monitored by a Pharmacia UV-2 ultraviolet monitor and products were collected on a Gilson FC-100 fraction collector.

2-Amino-6-methoxy-9-(2',5'-di-O-tert-butyldimethylsilyl-β-D-ribofuranosyl) purine (2). Guanosine was converted to 6-chloro-2-amino purine nucleoside as previously described[15,16]. To a solution of 12.200 g (28.5 mmol) of this product in 100 mL of dry methanol, was added 7.700 g (142.6 mmol) of sodium methoxide. The solution was stirred at room temp. for 15 h., when it was shown to be complete by UV spectral examination. The solvents were removed in vacuo, and the residue was adsorbed on 5 g of silica gel to form a plug for column chromatography. The residue was purified on silica gel using 15% methanol/chloroform as the eluent to give 8.085 g (27.2 mmol, 96%) of compound **1** as an off-white solid: m.p. 131-133°C (lit[15] m.p.133-135°C); UV λ_{max}(EtOH) 247, 280 nm; ^{1}H NMR (DMSO-d_6) δ : 8.08 (s, 1H), 6.41 (brs, 2H), 5.75 (d, 1H), 5.35 (d, 1H), 5.08 (m, 2H), 4.45 (m, 1H), 4.08 (m, 1H), 3.96 (s, 3H), 3.90 (m, 1H), 3.55 (m, 2H).

To a solution of 2.490g (8.39 mmol) of **1** in dry DMF (5 mL) was added 2.790 g (18.45 mmol) of TBDMSCl and 2.510 g (36.9 mmol) of imidazole. The reaction flask was sealed under N_2 and allowed to stand at room temperature

for 15 h. The solvent was removed in vacuo, and the residue was partitioned between ether and water. The organic layer was separated and the aqueous layer was washed with ether (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, purified and separated on silica gel using gradient elution with 20-50% ether/hexanes as solvent. The bis-silyl compound **2** was obtained as a clear glass (0.930 g, 1.77 mmol, 21%). The 3',5'-di-O-silyl isomer of **2** was the major product (1.400 g, 2.66 mmol, 32%). In addition, 1.080 g (2.64 mmol, 31%) of the 5'-silyl derivative was obtained. This material was recycled through the reaction using 1.1 equivalents of TBDMSCl and 2.2 equivalents of imidazole. Spectral data for **2**: UV λ_{max}(EtOH) 247, 280 nm; mass spectrum, m/z (rel. intensity) 468 [$(M-tBu)^+$,16.92]; ^1H NMR (DMSO-d_6) δ : 8.31 (s, 1H), 8.24 (s, 1H), 6.92 (m, 2H), 5.87 (d, 1H), 5.81 (d, 1H), 5.43 (d, 1H), 5.10 (d, 1H), 4.55 (m, 1H), 4.27 (m, 1H), 4.03 (m, 1H), 3.80 (m, 2H), 0.90, 0.06, (m, 30H).

2-Iodo-6-methoxy-9-[3'-deoxy-2',5'-di-O-tert-butyldimethylsilyl- β -D-ribofuranosyl]purine (5). To a solution of **2** (0.580g, 1.11mmol) in dry DMF (5 mL) was added, under N_2, thiocarbonyldiimidazole (0.297g , 1.67mmol), and DMAP (0.339 g, 2.78 mmol). The reaction was sealed under N_2, and allowed to stand at room temp. for 24 h. The volatiles were removed in vacuo, and the residue was purified on silica gel using 2% methanol/chloroform. Compound **3** was obtained as an oil (0.697g, 1.097mmol, 99%): UV λ_{max}(EtOH) 248, 280 nm; mass spectrum, m/z (rel. intensity) 635 (M^+,0.15), 578 [$(M-tBu)^+$, 9.04], 152 ($Base^+$, 0.29), 153 [$(Base+H)^+$, 2.86]; ^1H NMR (DMSO-d_6) δ : 8.56 (s, 1H), 8.05 (s, 1H), 7.87 (s, 1H), 7.11 (s, 1H), 6.51 (d, 1H), 6.27 (brs, 2H), 5.02 (t, 1H), 3.98 (m, 6H), 1.03, 0.84 (m, 30H).

A solution consisting of 6.89 mL (25.71 mmol) of n-Bu_3SnH, 0.675 g (4.11 mmol) of AIBN, and 25 mL of dry toluene was purged (N_2 ,30 min), then added dropwise to a boiling solution of 3.260 g (5.15 mmol) of **3** in 100 mL of toluene. The reaction was stirred under N_2 at 110°C for 2 h. The

reaction mixture was concentrated, and the resulting oil was chromatographed on silica gel using hexanes followed by 70% ether/hexanes as the eluent. Compound **4** was obtained as a clear glass (2.550 g, 5.02mmol, 98%); UV λ_{max}(EtOH) 247, 280 nm; mass spectrum, m/z (rel. intensity) 452 [$(M-tBu)^+$, 12.85], 287 [$(Sugar-tBu)^+$, 5.05], 165 [$(Base+H)^+$, 9.60], 194 [$(Base+CHO)^+$, 4.17]; ^1H NMR (DMSO-d_6) δ: 8.25 (s, 1H), 8.05 (s, 1H), 6.30 (t, 1H), 5.84 (d, 1H), 5.07 (m, 1H), 4.57 (m, 1H), 4.00 (m, 1H), 3.80 (m, 2H), 2.40-1.80 (m, 4H), 0.90, 0.09 (m, 30H).

To an ice-cold, N_2 purged solution of **4** (1.592g, 3.13 mmol) in 100 mL of hexane (distilled from $LiAlH_4$) was added 2.53 mL (31.3 mmol) of diiodomethane, 3.72 mL (31.3 mmol) of tert-butylnitrite, and 0.89 mL (6.26 mmol) of iodotrimethylsilane. The reaction was stirred at 60°C under a nitrogen atmosphere for 2 h and concentrated. The resulting residue was partitioned between ether and saturated aqueous Na_2SO_3. The organic layer was set aside, and the aqueous layer was extracted with ether (3 x 50mL). The combined organic layers were dried (Na_2SO_4), concentrated, and chromatographed on silica gel using hexanes followed by chloroform as the eluent. Compound **5** (1.017 g, 1.640 mmol, 53%) was obtained as an oil: UV λ_{max}(EtOH) 258 nm; mass spectrum, m/z (rel. intensity) 563 [$(M-tBu)^+$, 15.95], 287 [$(Sugar-tBu)^+$,13.49], 277 [$(Base+2H)^+$, 5.26), 304 [$(Base+CHO)^+$, 0.07]; ^1H NMR (DMSO-d_6) δ: 8.44 (s, 1H), 5.89 (d, 1H), 4.71 (m, 1H), 4.42 (m, 1H), 4.07 (s, 3H), 3.91 (dd, 2H), 2.10 (m, 2H), 0.87, 0.06 (m, 30H).

2-Iodo-9-(3'-deoxy-β-D-ribofuranosyl)hypoxanthine (6). To a solution consisting of 0.090 g (0.145 mmol) of compound **5**, and 0.029 g (0.174 mmol) of dry KI in dry acetonitrile (20 mL) was added chlorotrimethylsilane (0.020 mL, 0.174 mmol). The solution was stirred under N_2 for 3 hr. The solvents were removed and the residue was dried overnight on the vacuum pump. This residue was then dissolved in dry acetonitrile (10mL), purged (N_2, 10 min), and treated with 0.87 mL (0.435 mmol) of tetraethylammonium fluoride/acetonitrile solution. The reaction mixture was stirred under N_2

for 4 hr. Upon completion of the reaction (TLC), the solvents were removed and the residue was partitioned between water and chloroform. The aqueous layer was extracted with ether, the combined organic layers back-extracted with 10 mL of water. The aqueous layers were combined and concentrated. The residue was purified by HPLC with 2% ethanol/water as the eluting solvent. 2-Iodo-3'-deoxyinosine **6** was recovered as a clear solid (0.021g, 0.056 mmol, 39%): m.p. >200°C dec; UV $\lambda_{max}(H_2O)$ 253 (ε=15341), 272 nm (sh, ε=11900); ^1H NMR (Me_2SO-d_6) δ: 2.1 - 2.4 (m, 2H), 3.58 (m, 2H), 3.93 (m, 2H), 4.46 (m, 1H), 5.00 (t, 1H), 5.50 (d, 1H), 5.92 (d, 1H), 8.24 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 34.3, 62.7, 74.1, 80.0, 90.1, 122.6, 124.4, 135.3, 149.4, 164.6; FAB(HRMS) calcd for $C_{10}H_{11}N_4O_4I$: 378.9903 (M^++H), found: 378.9900 (M^++H).

2-Vinyl-9-(3'-deoxy-β-D-ribofuranosyl)hypoxanthine (**7**). A solution consisting of 0.180g (0.29 mmol) of **5**, 0.005 g (0.02 mmol) of $PdCl_2(MeCN)_2$, 0.018 g (0.06 mmol) of P(o-Tolyl)$_3$, and 0.10 mL (0.319 mmol) of n-$Bu_3SnCH=CH_2$ in dry toluene (50 mL) was purged (N_2, 30 min.) and then heated at 100 °C for 1 hr. The solvent was removed under vacuum and the residue remaining was purified on silica gel with 30% ether/hexanes to give the protected vinyl compound as an oil (0.146g, 0.281 mmol, 97%). This compound was subjucted to the two-step deprotection as described for the conversion of **5** to **6** to give 0.026 g. (0.093 mmol, 33%) of **7** as a white solid: m.p. 115-117 °C; UV $\lambda_{max}(H_2O)$ 207 (ε=22724), 260 (ε=9088), 290 (ε=7669); ^1H NMR (DMSO-d_6) δ: 12.3 (brs, 1H), 8.32 (s, 1H), 6.60 (m, 2H), 5.89 (d, 1H), 5.80 (dd, 1H), 5.70 (s, 1H), 5.00 (s, 1H), 4.56 (m, 1H), 4.35 (m, 1H), 3.58 (m, 2H), 2.27, 1.92 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 157.0, 151.8, 148.1, 138.9, 129.7, 125.3, 123.3, 90.7, 81.1, 75.2, 62.6, 34.3; FAB (HRMS) calcd for $C_{12}H_{15}N_4O_4$: 279.1093 (M^++H), found: 279.1112 (M^++H);

2-Formyl-9-(3'-deoxy-β-D-ribofuranosyl)hypoxanthine (**8**). A solution consisting of 0.015g (0.054 mmol) of compound **8** in distilled water (350 mL)

was cooled down to ice-bath temp. and ozonized for 1 min. Air was then bubbled through the solution for 12 h, while slowly allowing the solution to reach room temp. The solvent was removed *in vacuo* and the residue purified by HPLC column using 9% EtOH/H_2O as the eluent. The title compound **8** was obtained (0.0117 g, 0.042 mmol, 77%) as a white crystalline solid: m.p. 162-165 °C; UV $\lambda_{max}(H_2O)$ 249 (ε=9991), 272 nm (ε=4823); ^1H NMR (DMSO-D_6) δ : 9.56 (s,1H), 8.53 (s,1H), 5.93 (d,1H), 5.67 (m,1H), 5.00 (m,1H), 4.54 (m,1H), 4.38 (m,1H), 3.59 (m,2H), 2.27, 1.97 (m,2H). ^{13}C NMR (DMSO-d_6)δ : (33.9, 34.1), (62.4, 62.7), (75.0, 75.5), (81.4, 81.5), (91.0, 91.2), 97.5, (123.2, 124.4), (139.6, 139.9), (146.4, 147.2), (149.2, 151.8), (153.3, 155.0), 186.1; FAB(HRMS) calcd for $C_{11}H_{12}N_4O_5$: 281.0886 (M^++H), found: 281.0851 (M^++H).

2-Acetonyl-9-(3'-deoxy-β-D-ribofuranosyl)hypoxanthine (9). In a 50 mL RBF were mixed 5 mL of dry toluene (from NaH), 0.050 mL (0.425 mmol) of isopropenyl acetate, and 0.122 mL (0.425 mmol) of tri-butyltin methoxide. This flask was sealed under N_2 and stirred for 1 h at 50°C. The iodo compound **5** (0.211 g, 0.340 mmol), 0.006g (0.024 mmol) of $PdCl_2(MeCN)_2$, and 0.021g (0.068 mmol) of P(o-tolyl)$_3$ were combined in a 100 mL RBF and evacuated briefly on the vacuum line. The 100 mL RBF was then sealed under N_2, and the contents dissolved in toluene (25 mL). This solution was purged (N_2, 30 min), and the preformed acetonyl tin reagent was added to the 100 mL RBF *via* double-tipped needle. The reaction mixture was stirred for 2 h under N_2 at 90°C and then concentrated. The residue was purified on silica gel using hexanes followed by 30% ether/hexanes as the eluent. The protected 2-acetonyl compound (0.165 g, 0.300 mmol, 88%) was isolated and then subjected to the two-step deprotection reaction described for the conversion of **5** to **6** to give **9** (0.105 g, 0.341 mmol, 40%) as a white solid: m.p. 112-114 °C; UV $\lambda_{max}(H_2O)$ 249 (ε=10900), 266 (ε=6440); FTIR (KBr) 3400, 1699, 1550 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ :12.4 (s, 1H), 8.28 (s, 1H), 5.80

(d, 1H), 5.64 (m, 1H), 4.97 (m, 1H), 4.50 (m, 1H), 4.35 (m, 1H), 3.90 (m, 2H), 3.60 (m, 2H), 2.22-1.99 (m, 5H); ^{13}C NMR (Me_2SO-d_6) δ :202.8, 156.8, 152.7, 147.8, 138.0, 122.5, 90.3, 80.8, 74.9, 62.3, 49.0, 34.1, 29.8 ; FAB(HRMS) calcd for $C_{13}H_{16}N_4O_5$: 309.1199 (M^++H), found: 309.1221 (M^++H).

2-Allyl-9-(3'-deoxy- β -D-ribofuranosyl)hypoxanthine (10). A solution consisting of 0.377g (0.608 mmol) of **5**, 0.011g (0.042 mmol) of $PdCl_2(MeCN)_2$, 0.21 mL (0.669 mmol) of n-$Bu_3SnCH_2CH{=}CH_2$, and 0.037 g. (0.122 mmol) of P(o-tolyl)$_3$, in dry toluene (40 mL) was heated under a nitrogen atmosphere at 95°C for 28 h. The reaction mixture was concentrated and the residue was purified on a silica gel column using 40% ether/hexanes as the eluting solvent. The protected 2-allyl compound was obtained in 48% yield (0.157g, 0.294 mmol) together with 0.109 g. (0.176 mmol, 29%) starting material. The product was subjected to the two step deprotection procedure (see conversion of **5** to **6**) to give **10** (0.029 g, 0.126 mmol, 43%) as a white solid: m.p. 138-140°C; UV λ_{max}(H_2O) 249 nm (ε=7848); ^1H NMR (DMSO-d_6) δ : 2.1-2.6 (m, 2H), 3.42 (d, 2H), 3.60 (m, 2H), 3.97 (m, 1H), 4.52 (m, 1H), 5.10 (m, 4H), 5.84 (d, 1H), 6.07 (m, 1H), 8.25 (s, 1H), 12.04 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ : 34.6, 38.8, 62.8, 75.1, 81.1, 90.7, 118.2, 122.6, 133.1, 138.4, 148.4, 156.5, 156.8; FAB(HRMS) calcd for $C_{13}H_{16}N_4O_4$: 293.1250 (M^++H), found: 293.1225 (M^++H).

2-Iodo-6-chloro-9-(3'-deoxy-2',5'-di-O-tert-butyldimethylsilyl- β -D-ribofuranosyl)purine (12). The silylation of compound **11**[15] (1.02 g, 3.36 mmol) was carried out as described for compound **1**. The final product was worked-up, purified and separated as described for compound **2** to give 0.552 g (1.04 mmol, 31%) of the 2',5'-disilylated compound. This compound was converted to its 3'-deoxy analogue by the procedure described for the conversion of **2** to **4**. Data for 2-amino-6-chloro-9-(3'-deoxy-2',5'-di-O-TBDMS- β -D-ribofuranosyl)purine: UV λ max (EtOH) 246, 305 nm; ^1H NMR (DMSO-d_6) δ : 8.25 (s, 1H), 8.05 (s, 1H), 6.30 (t, 1H), 5.84 (d, 1H), 5.07

(m, 1H), 4.57 (m, 1H), 4.00 (m, 1H), 3.80 (m, 2H), 2.40-1.80 (m, 4H), 0.90, 0.09 (m, t-BuSi); mass spectrum, m/z (rel. intensity) 456 [$(M\text{-}t\text{-}Bu)^+$, 1.98], 169 ($Base^+$, 25.6), 134 ($Base^+$ -Cl, 23.1).

Compound **12** was prepared from the 2-amino-6-chloro-3'-deoxy compound by radical deamination-halogenation as described previously for the conversion of **4** to **5**. Data for **12**: UV λ_{max}(EtOH) 248, 281 nm; ^1H NMR (DMSO-d_6) δ: 8.36 (s, 1H), 8.62 (s, 1H), 6.42 (t, 1H), 5.97 (d, 1H), 4.60 (m, 2H), 4.00 (m, 1H), 3.82 (m, 2H), 2.60-1.80 (m, 4H), 0.90, 0.10 (m, 30H); mass spectrum, m/z (rel.intensity) 567 [$(M\text{-}t\text{-}Bu)^+$, 2.3].

2-Cyano-9-(3'-deoxy-β-D-ribofuranosyl)purine (15). Compound **12** (0.238g, 0.381 mmol), 0.031g (0.027 mmol) of $Pd(PPh_3)_4$, 0.132 g (0.419 mmol) of n-Bu_3SnCN, and 0.023g (0.076 mmol) of P(o-tolyl)$_3$ were mixed in a 50 mL RBF in a glove box under a N_2 atmosphere.. The contents were dissolved in toluene (15 ml, dried from NaH). The solution was purged (N_2, 30 min), and the reaction mixture then allowed to stir under N_2 at 90°C for 8 h and then concentrated. The residue was purified on silica gel using 1:1 ether/hexanes as the eluent. The protected 2-cyano compound **13** was isolated as an oil (0.154 g, 0.294 mmol, 77%): UV λ_{max}(EtOH) 273 nm; ^1H NMR (DMSO-d_6) δ : 9.08 (s, 1H), 6.47 (t, 1H), 4.72 (m, 1H), 3.80 (m, 3H), 2,50 (m, 2H), 0.85, 0.13 (m, 30H); mass spectrum m/z (rel. intensity) 466 [$(M\text{-}t\text{-}Bu)^+$, 7.42], 468 [$[M(^{37}Cl)\text{-}t\text{-}Bu]^+$, 3.30], 179 [$(Base+H)^+$, 41.02], 181 [$[Base(^{37}Cl)+H]^+$, 13.77].

To 0.5 mL of benzyl alcohol was added 0.007 g (0.281 mmol) of metallic sodium under a N_2 atmosphere. When all the sodium had been consumed, a solution of the nucleoside **13** (0.113 g, 0.216 mmol) in dry DMF (5 mL) was added under N_2 via a double-tipped needle. The nucleoside flask was rinsed out with DMF (2 mL) and this was added to the reaction flask. The resulting solution was stirred at room temperature for 6 h, concentrated, and the residue was purified on a silica gel column using 30% ether/hexanes as the eluting solvent. The 6-benzyloxy compound **15** was isolated

as an oil (0.086 g, 0.145 mmol, 85%): UV λ_{max}(EtOH) 260, 272 nm; mass spectrum: m/z (rel. intensity) 538 [$(M-t-Bu)^+$, 9.84].

A solution of 0.130 g (0.220 mmol) of compound **14** in absolute ethanol (200 mL) was purged (N_2, 20 min). Approximately 0.065 g of 10% Pd/C was added to the reaction vessel. This mixture was hydrogenated on a Parr apparatus for 12 h, using 35 psi of H_2. The palladium was then filtered off, and the filtrate was concentrated in vacuo. This residue was dried on the vacuum line overnight and was then treated with 1.32 mL (0.660 mmol) of a 0.5 M tetraethylammonium fluoride/acetonitrile solution to deprotect the silyl groups. The title compound **15** was purified by HPLC to give 0.015g (0.054 mmol, 25% for the two steps) of purified product as a solid: m.p. 170 °C (dec); UV λ_{max}(H_2O) 296 (ε=5299), 257 (ε=6206), 252 nm (ε=6214); FTIR (KBr): 2260 cm^{-1} (CN stretch); ^{1}NMR (DMSO-d_6) δ: 1.91, 2.21 (m, 2H), 3.65 (m, 2H), 4.33 (m, 1H), 4.50 (m, 1H), 5.12 (m, 1H), 5.75 (d, 1H), 8.11 (s, 1H); FAB(HRMS) calcd for $C_{11}H_{12}N_5O_4$: 278.1789 (M^++H), found: 278.1759 (M^++H).

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