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SYNTHETIC APPROACHES TO NEW DOUBLY MODIFIED NUCLEOSIDES: CONGENERS OF CORDYCEPIN AND RELATED 2'-DEOXYADENOSINE

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Abstract: The syntheses of novel analogues of cordycepin (compounds **20-25**) and 2'-deoxyadenosine (compounds **11, 13-15, 18, 19**) are reported. In order to obtain entry into both the 3'-deoxy and 2'-deoxy isomeric series from a common starting compound, 2-amino-6-chloropurine ribonucleoside, this precursor was protected by conversion to a mixture of 2',5'- and 3',5'-bis-silyl compounds prior to modifications at the 2'- or 3'-positions of the carbohydrate moiety and the 2-position of the base component. Observation of silyl group isomerization is discussed. The other key transformations in the syntheses were radical deoxygenations (carbohydrate moiety), radical iodinations (tailoring of base for modification), and metal-mediated functionalization reactions (regio-specific modifications of base component). Structures of the final target molecules and their purities were established by UV, high-field ^{1}H and ^{13}C NMR, and FAB HRMS data. The synthetic approaches presented have generality and provide entry into a variety of doubly modified nucleosides.

Cordycepin (3'-deoxyadenosine) was originally isolated from Cordyceps militaris and Aspergillus nidulans.[1] Cordycepin is known to have antiviral activity against a number of RNA viruses.[2] The biochemical basis for this mechanism of action is thought to be the inhibition of viral RNA polymerase activity by cordycepin 5'-triphosphate.[3,4] The polynucleotide chain appears to be terminated at the point at which the cordycepin component is attached because of the absence of the 3'-hydroxyl group for further chain elongation. Biological activity has also been attributed to several 2'-

deoxyadenosines, particularly the 2-halo compounds.[5] Analogues of cordycepin and the related 2′-deoxyadenosine would therefore be of considerable potential antiviral and antitumor interest. However, very few examples of such compounds have been described.[6-8] This is in part due to limitations in methodologies that provide facile access to strategically modified analogues of these nucleosides. We report in this paper the development of approaches to the synthesis of novel 3′-deoxy and 2′-deoxy isomeric series of doubly modified nucleosides related to cordycepin.

The strategy for the synthesis of the novel deoxynucleosides was to start with readily available natural guanosine and to modify first the carbohydrate and then the base moiety in this compound. Modification of the carbohydrate moiety would involve regiospecific deoxygenation. Earlier methods of synthesis of deoxy nucleosides involved reaction of arabino halo sugar moieties with tin hydride.[9-11] Nucleoside 2′,3′-epoxides may be ring opened by hydride to form deoxy nucleosides.[12] Deoxygenation may also be carried out *via* a cyclic thiocarbonate by reaction with tributyltin hydride and AIBN according to the methodology originally developed by Barton and Subramanian.[13] However, reductive cleavage of the cyclic thiocarbonate gives mixtures of 2′- and 3′-deoxy nucleosides with the 2′-deoxy compound being the major product.[14] A more regiospecific deoxygenation, however, would be possible through the 3′-imidazolide.[14,15] If the imidazolides could be specifically prepared, entry to both the 3′-deoxy and the 2′-deoxy series could be achieved through related pathways but with the same initial precursor molecules.

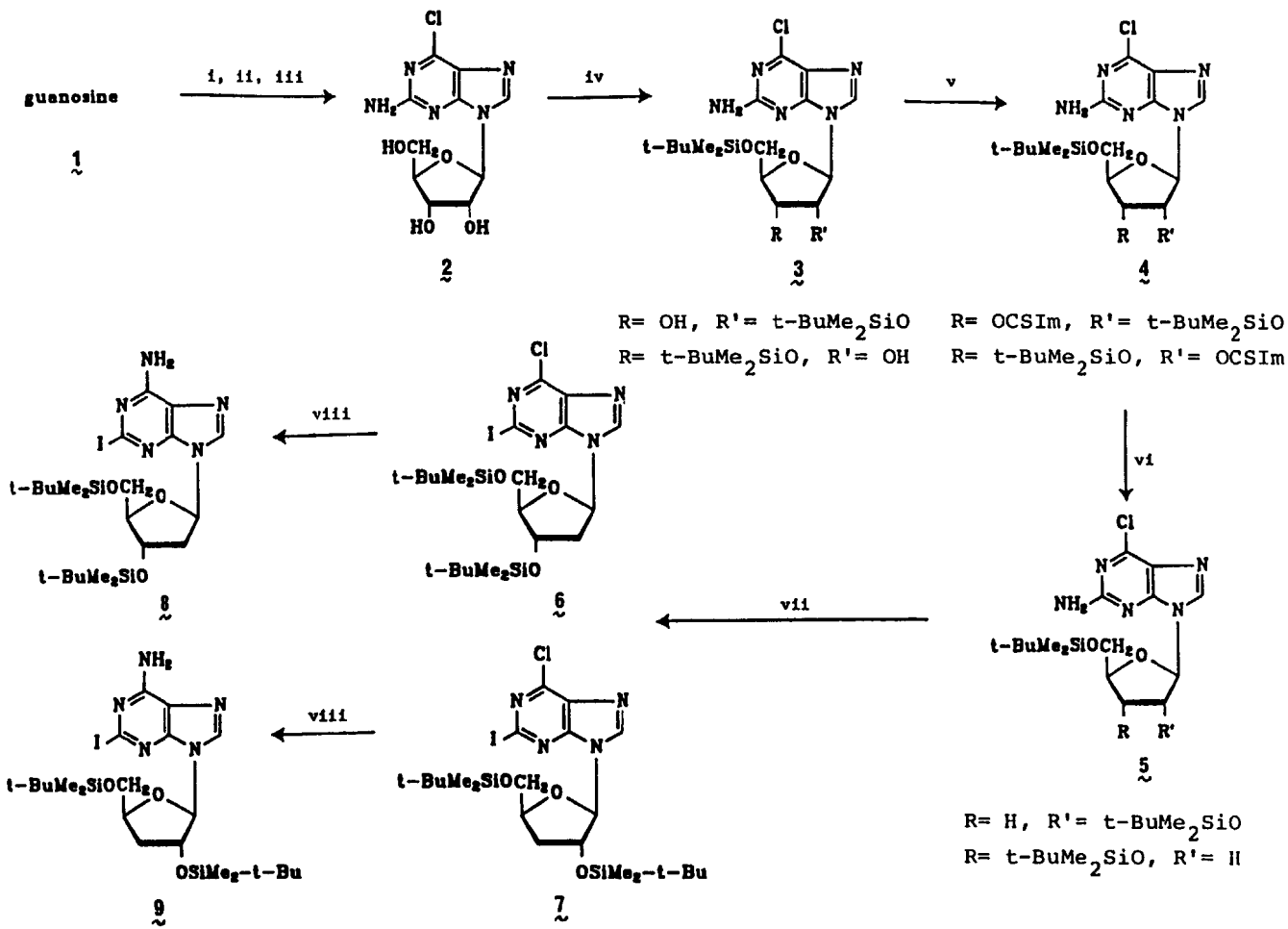
Guanosine **1** was converted in three known steps to 6-chloro-2-aminopurine ribonucleoside, **2**, in high yields.[16,17] When compound **2** was treated with 2.2 equivalents of t-butyldimethylsilyl chloride and 4.4 equivalents of imidazole in DMF at room temperature for 2 h, a mixture of 2′,5′- and 3′,5′-disilylated product **3** was obtained in 62% yield after

purification (Scheme I). The isolation of these compounds required chromatographic separation from two side products: the 5′-monosilylated compound (19 %) and the trisilylated material (5 %). All four compounds could be easily identified by mass spectrometry. The use of pyridine as base (cf. ref. 18) in this silylation reaction with this substrate is problematic in terms of yield, work up and purification. The isomer ratio also changes when pyridine is used in this reaction.[18] The mixture of the 2′,5′- and 3′,5′-disilylated compounds (regioisomer ratio approximately 1:1 by ^{1}H NMR data) may be separated into the individual isomers but with difficulty at this juncture or the mixture may be separated at a later stage in the synthetic pathway. We chose the latter as the more efficient approach.

Treatment of compound **3** with 1,1′-thiocarbonyldiimidazole in refluxing dichloroethane for about 4h afforded the thiocarbonyl ester mixture **4** in 87% yield. Longer reaction times led to decomposition products and lower yields. If DMAP is used in this reaction,[19] the yields drop to about 20% because of extensive decomposition of starting material. Interestingly, thermal isomerization of the silyl protecting groups occurred in the reaction, most likely prior to imidazolide formation, to produce a mixture of the 3′,5′- and 2′,5′-imidazolides in a 3:2 ratio, different from the original 1:1 ratio. In controlled thermal experiments monitored by ^{1}H NMR spectroscopy, we have shown that pure 2′,5′-disilyl compound in $CDCl_3$ containing imidazole rearranges slowly to a mixture containing both the 2′,5′- and the 3′,5′-isomer (cf. refs 20, 21). The rate of rearrangement increases with the addition of a small amount of water.

Deoxygenation of the chromatographically purified imidazolides was carried out with tributyltin hydride and AIBN in refluxing toluene for 1 h to give the deoxygenated products **5** in 86% yield (Scheme I). Iodination of the deoxygenated compounds with t-butyl nitrite, methylene diiodide, and

Scheme I[a]



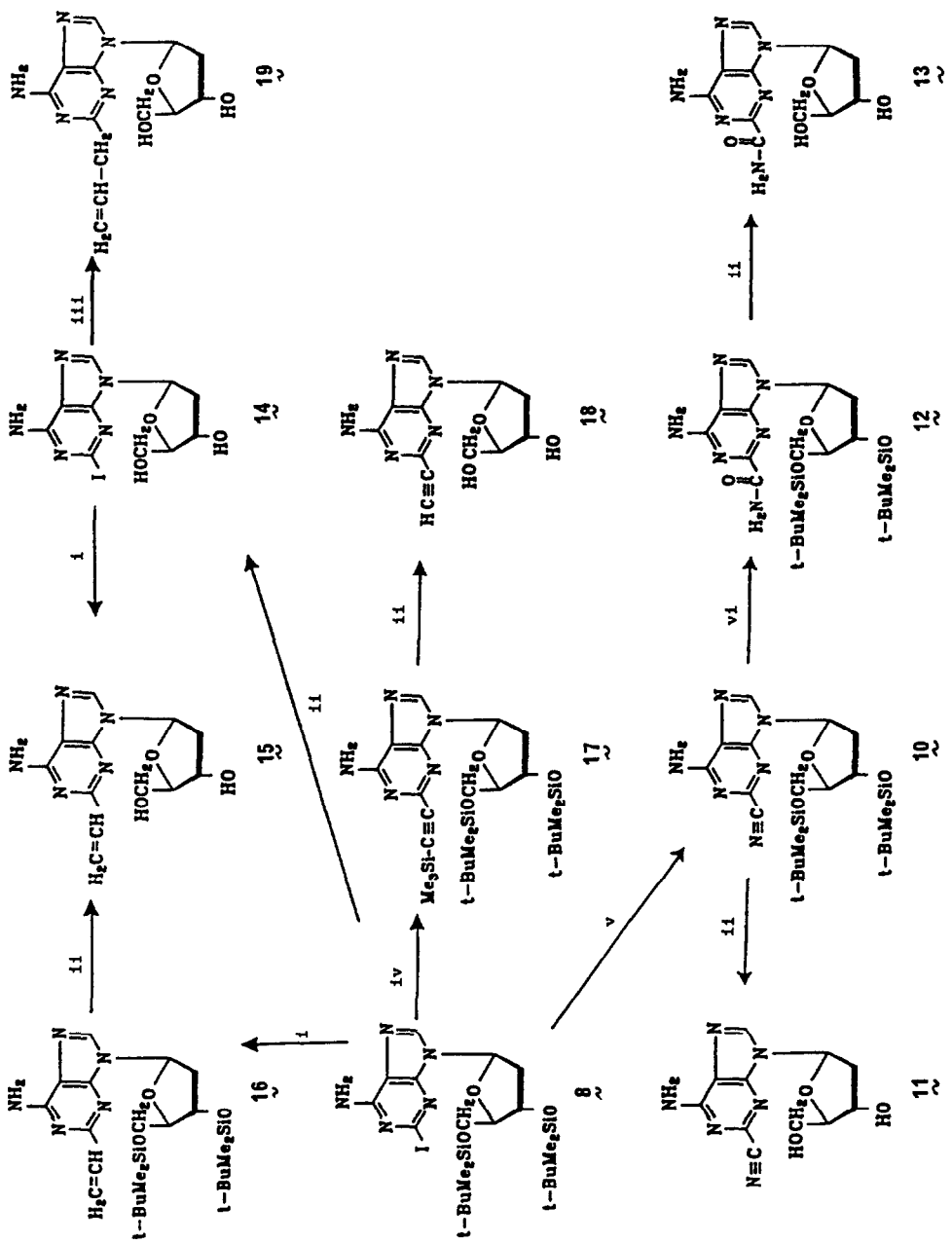
[a](i) Ac_2O, $(C_2H_5)_3N$, 4-(dimethylamino)pyridine, CH_3CN; (ii) $POCl_3$, N,N-diethylaniline, Δ; (iii) NH_3, MeOH; (iv) t-Bu$(CH_3)_2SiCl$, imidazole, DMF; (v) Im_2CS, $(CH_2Cl)_2$, Δ; (vi) n-Bu_3SnH, AIBN, toluene, Δ; (vii) n-$C_5H_{11}ONO$, CH_2I_2, $(CH_3)_3SiI$, hexane, Δ; (viii) NH_3, EtOH.

trimethylsilyl iodide in hexane gave the 2-iodo-6-chloro compounds **6** and **7** in a combined yield of 58 %. The iodination reaction of these substrates has to be conducted under carefully controlled conditions (dried redistilled reagents and solvents, N_2 atmosphere, optimum reaction time and temperature, catalytic amounts of TMSI, etc.) in order to obtain synthetically acceptable yields. Complete separation of the regioisomers was easily achieved at this stage of the synthesis by column chromatography on silica gel with hexane/ ethyl acetate (5:1) as the eluting solvent. The ratio of the two separated isomers was still 3:2 [2′-deoxy (**6**) : 3′-deoxy (**7**)] as shown by high-field ^1H NMR data (integration for H-1′, triplet for 2′-deoxy and doublet for 3′-deoxy).

Two modifications of the purine ring were planned for the next stages of the syntheses; first, the conversion of the 6-chloro group to the 6-amino group, and second, the elaboration of the 2-position utilizing the carbon-iodine bond at this position. Transformation of the 2-iodo-6-chloropurine moiety in **6** and **7** to the 2-iodoadenine moiety could be easily brought about because of the nucleophilic lability of the 6-chloro group. Thus, treatment of the 2-iodo-6-chlorodeoxynucleosides **6** and **7** with ethanolic ammonia resulted in displacement of the 6-chloro group to furnish the deoxygenated adenine nucleosides **8** and **9**, respectively (Scheme I).

Carbon-carbon bond forming reactions leading to functionalization at the 2-position of the adenine moiety were carried out by palladium-catalyzed cross-coupling reactions with synthon bearing organostannanes. Thus, with the 2′-deoxy series, treatment of **8** with tri-n-butylcyanostannane and tetrakis(triphenylphosphine) palladium(0) in DMF at 120 ^oC gave the 2-cyanoadenine product **10** in 91% yield (Scheme II). Compound **10** can be converted to the deprotected novel target molecule **11** by treatment with tetraethylammonium fluoride. 2-Carboxamido-2′-deoxyadenosine **13**, another new nucleoside, can be synthesized from **10**

Scheme II[a]



[a](i) n-$Bu_3SnCH{=}CH_2$, $PdCl_2(CH_3CN)_2$, DMF, Δ; (ii) Et_4NF, CH_3CN; (iii) n-$Bu_3SnCH_2{-}CH{=}CH_2$, $Pd^0(Ph_3P)_4$, DMF, Δ; (iv) $(CH_3)_3SiC{\equiv}CH$, Et_3N, CuI, $Pd^0(Ph_3P)_4$, DMF, Δ; (v) n-Bu_3SnCN, $Pd^0(Ph_3P)_4$, DMF, Δ; (vi) Bu_4NHSO_4, CH_2Cl_2, NaOH, H_2O_2.

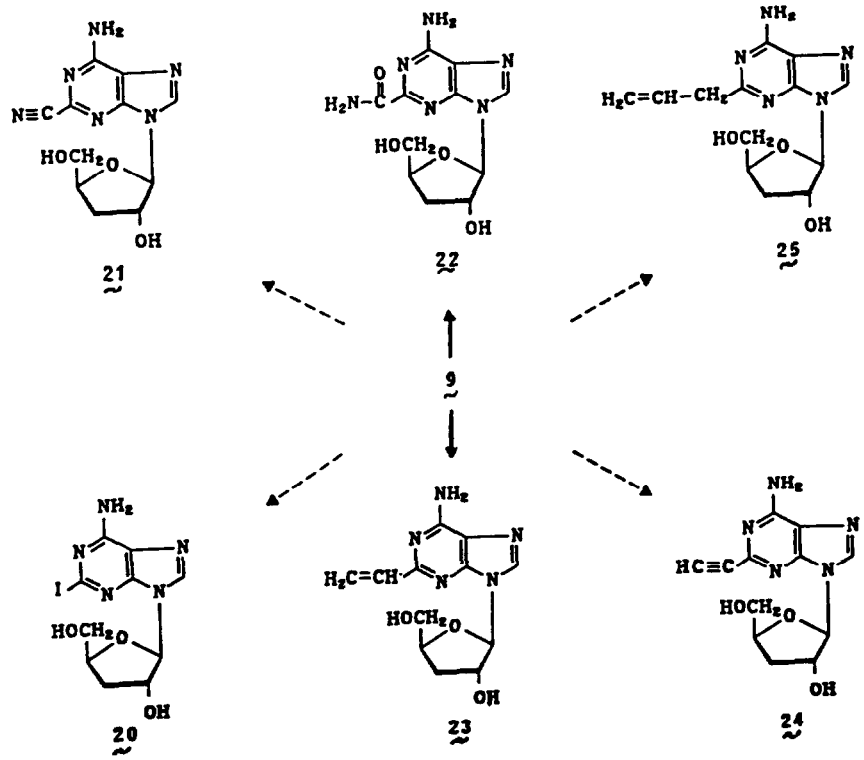
through hydrolysis and deprotection. The well established methods for effecting this functional group transformation involve hydrolysis under acidic or basic conditions or under basic conditions with hydrogen peroxide.[22] These methods appeared not to be useful for deoxy nucleosides because of the lability of their glycosidic bond under these conditions. However, the hydrolysis could be effectively carried out using a modification of the phase transfer conditions of Cacchi, Misiti and LaTorre[23] with aqueous sodium hydroxide and hydrogen peroxide to furnish the protected carboxamide **12** (89% yield). The novel target carboxamide **13** was obtained from **12** by deprotection (85%).

2-Iodo-2′-deoxyadenosine **14** has been reported recently to have antitumor activity.[24] Precursor **8** could be deprotected to this compound with fluoride ion in 97% yield. In this unprotected form, compound **14** can be converted to the new 2-vinyl compound **15** in 80% isolated yield by palladium-mediated cross-coupling with vinyl tri-n-butylstannane with heating in DMF.[25,26] Product **15** was also prepared from **8** by the palladium-catalyzed methodology followed by deprotection. Allylation reactions are also possible. Thus, unprotected **14** was converted to 2-allyl-2′-deoxyadenosine **19** by reaction with allyl tri-n-butylstannane and Pd(0) in DMF with heating. The temperature of this reaction was kept at 95 ^{o}C which is sufficient for the palladium-catalyzed carbon-carbon bond formation but not high enough for the isomerization of the allyl group on the base moiety to the thermodynamically more favorable 2-methylvinyl system. Introduction of the ethynyl group at the 2-position was also carried out but using a slightly different approach.[27] Treatment of **8** with trimethylsilyl acetylene in the presence of cuprous iodide, tetrakis(triphenylphosphine)palladium (0), and triethylamine in DMF gave **17** (> 90%) which could be deprotected directly to 2-ethynyl-2′-deoxyadenosine (**18**) (Scheme II). In contrast, palladium-catalyzed cross-coupling of **8** or

14 with ethynyl tri-n-butylstannane gave only low yields of the ethynyl products.

Using a related sequence of reactions, the 2-iodo-3′-deoxynucleoside 9 was converted to the following functionalized nucleosides: 2-iodo 20, 2-cyano 21, 2-carboxamide 22, 2-vinyl 23, 2-ethynyl 24 and 2-allyl 25 (Scheme III).

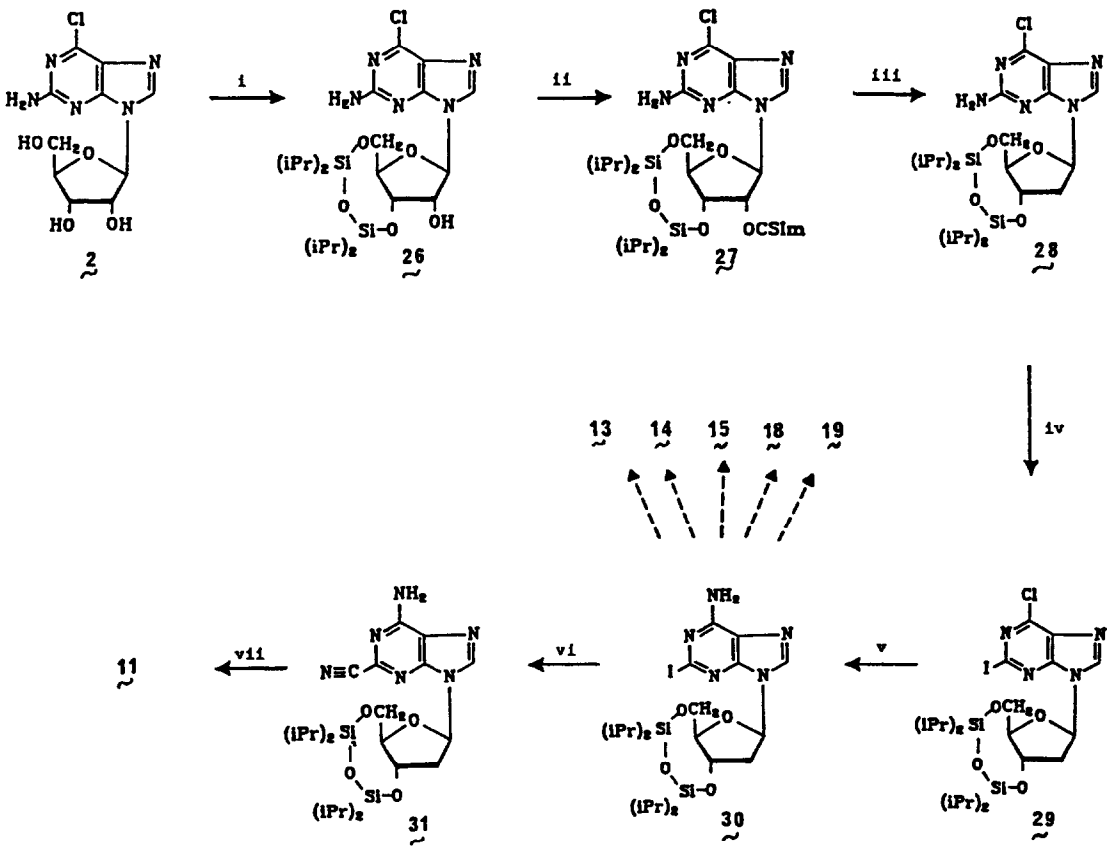
Scheme III



Finally, a regiospecific approach to functionalized 2′-deoxyadenosines may be realized through protection involving a 3′,5′-cyclic silyl group. Thus, nucleoside 2 can be converted to regiospecifically protected 26 in 62% yield by reaction with 1,3-dichloro-1,1,3,3-tetraisopropyl-1,3-disiloxane[28,29] and imidazole in DMF at room temperature (Scheme IV). Compound 26 was transformed into the key precursor for this series, the

protected 2-iodo-2′-deoxyadenosine, **30**, through a sequence of reactions similar to that described for the conversion of **3** to **8** and **9**. Conversion of **30** to the 2-cyano-2′-deoxyadenosine **11** (Scheme IV) is related to the conversion of **8** to **11** (see experimental description). Intermediate **30** may also be converted to the target molecules **13**, **14**, **15**, **18**, and **19** through the functionalization methodologies previously described (see Scheme II).

Scheme IV



[a](i) TPDS-Cl_2, imidazole, DMF; (ii) Im_2CS, $(CH_2Cl)_2$, Δ; (iii) n-Bu_3SnH, AIBN, toluene, Δ; (iv) n-$C_5H_{11}ONO$, CH_2I_2, $(CH_3)_3SiI$, hexane, Δ; (v) NH_3, EtOH; (vi) Pd°$(Ph_3P)_4$, n-Bu_3SnCN, DMF, Δ; (vii) Et_4NF, CH_3CN.

In summary, the synthesis of a series of doubly modified nucleosides, 2′- and 3′-isomeric analogues of the nucleoside antibiotic, cordycepin, is

described. All of the target compounds are new and contain functionality at the 2-position that can be exploited for further elaboration of these deoxygenated nucleosides. The key transformations used in these syntheses are regioselective bis-silylation, thermal radical deoxygenation and halogenation, and regiospecific metal-mediated carbon-carbon bond formation. The approaches presented have generality and can be extended for the synthesis of other new deoxygenated nucleosides functionalized in the base moiety.

Experimental Section

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 m 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. Preparative HPLC separations were also carried out with a Waters automated 600E system with photodiode array detector and FOXY fraction collector.

2-Amino-6-chloro-9-[3,5 and 2,5- bis-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]purine (3). A mixture of the nucleoside 2[16,17] (2.217 g, 7.35 mmol) , tert-butyldimethylsilyl chloride (2.436 g, 16.16 mmol), and imidazole (2.199 g, 32.33 mmol) in DMF (8 mL) was stirred at room temperature for 1.5 h. The solvent was removed under reduced pressure, the residue was partitioned between ethyl acetate (40 mL) and H_2O (40 mL), and the organic layer was re-extracted with H_2O (2 X 30 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography using $CHCl_3$ followed by 2-5% $CH_3OH/CHCl_3$ to give the 2',3',5'-tri-O-(tert-butyldimethylsilyl) derivative (0.250 g, 0.39 mmol, 5%), followed by **3** (2.428 g, 4.58 mmol, 62%). The mono-silylated derivative was removed from the column with 5% $CH_3OH/CHCl_3$ (0.591 g, 1.42 mmol, 19%). Data for **3a**: ^{1}H NMR ($CDCl_3$) δ 0.05-0.13 (m, 12H), 0.88-0.91 (m, 18H), 2.66 (d, 1H), 3.82 (dd, 1H), 3.95 (dd, 1H), 4.18 (m, 1H), 4.23 (q, 1H), 4.51 (t, 1H), 5.04 (s, 2H), 5.96 (d, 1H, J=5.2 Hz), 8.16 (s, 1H); UV (EtOH) λ_{max} 247, 308 nm. Data for **3b**: ^{1}H NMR ($CDCl_3$) δ 0.05-0.13 (m, 12H), 0.88-0.91 (m, 18H), 3.05 (d, 1H), 3.73 (dd, 1H), 3.90 (dd,

1H), 4.04 (m, 1H), 4.39 (q, 1H), 4.49 (t, 1H), 5.40 (s, 2H), 5.90 (d, 1H, J=4.3 Hz), 8.05 (s, 1H); UV (EtOH) λ_{max} 247, 308 nm.

2-Amino-6-chloro-9[3-O-(1-imidazolyl)thiocarbonyl-2,5-bis-O-(tert-butyldimethylsilyl)- β -D-ribofuranosyl]purine 4a and Its Isomer 4b. A mixture of the nucleosides 3 (2.312 g, 4.36 mmol) and 1,1′-thiocarbonyldiimidazole (1.17 g, 6.54 mmol) in dry 1,2-dichloroethane was refluxed under a N_2 atmosphere with stirring for 2.5 h. The solvent was removed under reduced pressure, the residue partitioned between ethyl acetate (40 mL) and H_2O (40 mL) and the organic layer was re-extracted with saturated aqueous NaCl (30 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography with $CHCl_3$ followed by 2% $CH_3OH/CHCl_3$ to afford 4 (2.419 g, 3.78 mmol, 87%) as an off-white foam. Data for 4a: ^1H NMR ($CDCl_3$) δ 0.05-0.13 (m, 12H), 0.81-0.93 (m, 18H), 3.77 (dd, 1H), 3.95 (dd, 1H), 4.21 (m, 1H), 4.88 (m, 1H), 5.11 (s, 2H), 5.93 (m, 1H), 6.05 (d, 1H), 7.08 (s, 1H), 7.69 (s, 1H), 8.12 (s, 1H), 8.42 (s, 1H); UV (EtOH) λ_{max} 251, 281, 305 nm. Data for 4b: ^1H NMR ($CDCl_3$) δ 0.05-0.13 (m, 12H), 0.81-0.93 (m, 18H), 3.77 (dd, 1H), 3.94 (dd, 1H), 4.20 (m, 1H), 4.85 (m, 1H), 5.24 (s, 2H), 5.95 (t, 1H), 6.37 (d, 1H), 6.99 (s, 1H), 7.59 (s, 1H), 8.08 (s, 1H), 8.33 (s, 1H); UV (EtOH) λ_{max} 251, 281, 305 nm; mass spectrum (4), m/z (relative intensity) 582 (M^+-tBu-H, 0.5), 454 (M^+-tBu-OCSIm-2H, 0.8), 169 (B^++H, 23.9).

2-Amino-6-chloro-9-[3-deoxy-2,5-bis-O-(tert-butyldimethylsilyl)- β -D-ribofuranosyl]purine 5a and Its Isomer 5b. To a refluxing solution of the nucleosides 4 (2.445 g, 3.82 mmol) in toluene (40 mL) under N_2 was added a mixture of tributyltin hydride (1.08 mL, 4.01 mmol) and AIBN (0.313 g, 1.91 mmol) in N_2 purged toluene (40 mL) over a 40 min period. The reaction was allowed to reflux for an additional 5 min and then concentrated in vacuo. The residue was dissolved in chloroform/ hexanes and eluted through a short scrubber column with hexanes followed by chloroform. Further purification by flash chromatography with chloroform gave 5 as a white foam (1.682 g, 3.27 mmol, 86%). Data for 5a: ^1H NMR ($CDCl_3$) δ 0.05-0.13 (m, 12H), 0.81-0.94 (m, 18H), 1.83 (m, 1H), 2.19 (m, 1H), 3.82 (dd, 1H), 4.06 (dd, 1H), 4.49 (m, 2H), 5.06 (s, 2H), 5.85 (d, 1H), 8.25 (s, 1H); UV (EtOH) λ_{max} 247, 308 nm. Data for 5b: ^1H NMR ($CDCl_3$) δ 0.05-0.13 (m, 12H), 0.81-0.94 (m, 18H), 2.38 (m, 1H), 2.53 (m, 1H), 3.73 (dd, 1H), 3.79 (dd, 1H), 3.96 (m, 1H), 4.56 (m, 1H), 5.14 (s, 2H), 6.29 (t, 1H), 8.05 (s, 1H); UV (EtOH) λ_{max} 247, 308 nm; mass spectrum (5), m/z (relative intensity) 457 (M^+-tBu, 0.4), 169 (B^++H, 21.2), 171 ($B^+(^{37}Cl)$+H, 10.5).

2-Iodo-6-chloro-9-[2-deoxy-3,5-O-bis-(tert-butyldimethylsilyl)- β -D-ribofuranosyl]purine 6 and Its 3′-Deoxy Isomer 7. To a chilled (0°C) suspension of nucleoside 5 (0.685 g, 1.33 mmol) in N_2 purged hexane (30 mL) was added diiodomethane (0.43 mL, 5.33 mmol), tert-butyl nitrite (0.63 ml, 5.33 mmol), followed by SLOW addition of TMSI (0.04 mL, 0.26 mmol) via syringe. The reaction was stirred at 55°C under a N_2 atmosphere for 1.5 h and worked up by the addition of saturated aqueous Na_2SO_3 (5 mL). After the mixture was stirred for 5 min, the organic layer was separated and concentrated. The residue was purified by flash chromatography with 5:1 hexanes/ethyl acetate and afforded 0.193 g (0.31 mmol, 23%) of the 3′-deoxy regioisomer 7, followed by 0.295 g (0.35 mmol, 35%) of the 2′-deoxy isomer 6, both as viscous oils. Data for 7: ^1H NMR ($CDCl_3$) δ 0.05-0.13 (m, 12H), 0.81-0.92 (m, 18H), 1.82 (m, 1H), 2.16 (m, 1H), 3.75 (dd, 1H), 4.17 (dd, 1H). 4.59 (m, 2H), 5.97 (d, 1H), 8.63 (s, 1H); UV (EtOH) λ_{max} 254, 280nm; mass spectrum, m/z (relative intensity) 568 (M^+-tBu, 0.6), 280

(B^++H, 0.3). Data for **6**: ^{1}H NMR ($CDCl_3$) δ 0.05-0.13 (m, 12H), 0.81-0.92 (m, 18H), 2.46 (m, 1H), 2.57 (m, 1H), 3.74 (dd, 1H), 3.86 (dd, 1H), 4.00 (m, 1H), 4.60 (m, 1H), 6.41 (t, 1H), 8.36 (s, 1H); UV (EtOH) λ_{max} 254, 280 nm; mass spectrum, m/z (relative intensity) 568 (M^+-tBu, not observed), 280 (B^++H, 4.7).

2-Iodo-9-[2-deoxy-3,5-O-bis-(tert-butyldimethylsilyl)-β-D-ribofuranosyl] adenine (8). A chilled (0°C) solution of the deoxynucleoside **6** (0.429 g, 0.68 mmol) in absolute ethanol (40 mL) was saturated with NH_3 gas. The reaction mixture was allowed to proceed for 12 h with stirring at room temperature. The solvent was removed and the residue was dissolved in ethyl acetate (15 mL) and washed with H_2O (15 mL). The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and the residue was purified by flash chromatography with $CHCl_3$ followed by 5% $CH_3OH/CHCl_3$ to afford 0.358 g (0.59 mmol, 86%) of **8** as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.07-0.14 (m, 12H), 0.81-0.91 (m, 18H), 2.40 (m, 1H), 2.63 (m, 1H), 3.74 (dd, 1H), 3.85 (dd, 1H), 3.97 (m, 1H), 4.60 (m, 1H), 5.93 (s, 2H), 6.33 (t, 1H), 7.99 (s, 1H); UV (EtOH) λ_{max} 266 nm; mass spectrum, m/z (relative intensity) 548 (M^+-tBu, 1.7), 261 (B^++H, 42.6).

2-Iodo-9-[3-deoxy-2,5-bis-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl] adenine (9) was prepared from **7** as described above for the preparation of **8**. The product was obtained as a white foam (86% yield): ^{1}H NMR ($CDCl_3$) δ 0.07-0.14 (m, 12H), 0.81-0.91 (m, 18H), 1.76 (m, 1H), 2.13 (m, 1H), 3.73 (dd, 1H), 4.10 (dd, 1H), 4.57 (m, 2H), 5.88 (d, 1H), 6.38 (s, 2H), 8.22 (s, 1H); UV (EtOH) λ_{max} 266 nm; mass spectrum, m/z (relative intensity) 548 (M^+-tBu, 30.1), 262 (B^++2H, 6.8).

2-Cyano-9-[2-deoxy-3,5-O-bis-(tert-butyldimethylsilyl)-β-D-ribofuranosyl] adenine (10). A mixture of the 2-iodo deoxynucleoside **8** (0.351 g, 0.58 mmol), tetrakis(triphenylphosphine)palladium(0) (0.080 g, 0.07 mmol), and tributyltin cyanide (0.202 g, 0.64 mmol) in DMF (10 mL) was stirred at 120°C for 40 min under a N_2 atmosphere. The solvent was removed under reduced pressure and the residue initially purified on a short silica gel scrubber column with hexanes followed by ethyl acetate. Final purification by flash chromatography with chloroform afforded 0.267 g (0.53 mmol, 91%) of **10** as an off-white foam: ^{1}H NMR ($CDCl_3$) δ 0.06-0.13 (m, 12H), 0.85-0.94 (m, 18H), 2.43 (m, 1H), 2.63 (m, 1H), 3.74 (dd, 1H), 3.88 (dd, 1H), 3.99 (m, 1H), 4.07 (m, 1H), 6.36 (t, 1H), 6.49 (s, 2H), 8.27 (s, 1H); UV (EtOH) λ_{max} 259, 264, 296 nm; mass spectrum, m/z (relative intensity) 447 (M^+-tBu, 0.5), 160 (B^++H, 41.4).

2-Cyano-9-(2-deoxy-β-D-ribofuranosyl)adenine (11). To a solution of **10** (0.156 g, 0.31 mmol) in dry CH_3CN (7 mL) was added tetraethylammonium fluoride in acetonitrile (0.5M, 1.86 mL, 0.93 mmol) *via* syringe. The reaction was stirred at room temperature for 1.5 h. The solvent was removed under reduced pressure and the residue was purified on silica gel plates with 12% $CH_3OH/CHCl_3$ as the mobile phase. The band at R_f 0.47 afforded 0.079 g (0.28 mmol, 92%) of almost pure product **11**. Further purification was carried out by reversed-phase HPLC on Amberlite XAD-4 resin employing 12% ethanol/water as the mobile phase: mp 205-207 °C; ^{13}C NMR (Me_2SO-d_6) δ 38.6, 61.4, 70.4, 83.6, 87.9, 116.7, 120.5, 136.5, 141.6, 148.0, 156.0; ^{1}H NMR (Me_2SO-d_6) δ 2.34 (m, 1H), 2.65 (m, 1H), 3.51 (m, 1H), 3.61 (m, 1H), 3.87 (m, 1H), 4.41 (m, 1H), 4.96 (t, 1H), 5.36 (m, 1H), 6.33 (t, 1H), 7.97 (s, 2H), 8.58 (s, 1H); UV (H_2O) λ_{max} 261 (ε 9000), 265.5 (9600), 296 nm (6300); FAB HRMS obsd (M^++H) 277.1076, calcd for $C_{11}H_{13}N_6O_3$ 277.1049.

2-Carboxamido-9-[2-deoxy-3,5-O-bis-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]adenine (12). To a solution of **10** (0.216 g, 0.43 mmol) in CH_2Cl_2 (20mL) was added 30% hydrogen peroxide (0.21 mL, 1.71 mmol), tetrabutylammonium hydrogen sulfate (0.029 g, 0.085 mmol), and 0.5M aqueous sodium hydroxide (1.03 mL, 0.51 mmol). The reaction mixture was stirred at room temperature for 3 h. Water (20 mL) and CH_2Cl_2 (10 mL) were then added. The organic layer was separated, washed with saturated aqueous NaCl (10 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified on preparative silica gel plates with 8% $CH_3OH/CHCl_3$ as the mobile phase. The band at R_f 0.46 afforded 0.201 g (0.38 mmol, 89%) of **12** as a white foam: ^1H NMR ($CDCl_3$) δ 0.04-0.13 (m, 12H), 0.85-0.94 (m, 18H), 2.42 (m, 1H), 2.65 (m, 1H), 3.77 (dd, 1H), 3.85 (dd, 1H), 3.98 (m, 1H), 4.57 (m, 1H), 6.38 (s, 2H), 6.52 (t, 1H), 6.62 (s, 1H), 7.77 (s, 1H), 8.27 (s, 1H); UV (EtOH) λ_{max} 261, 265, 284 nm; mass spectrum, m/z (relative intensity) 523 (M^+, 0.9), 465 (M^+-tBu, 4.8), 178 (B^++H, 11.6).

2-Carboxamido-9-(2-deoxy-β-D-ribofuranosyl)adenine (13). Deprotection of **12** was carried out as described for the conversion of **10** to **11**. The product was obtained as a solid after preparative thin layer chromatography on silica gel and was recrystallized from methanol/water (85% yield): mp > 240 °C (decomp); ^{13}C NMR (Me_2SO-d_6) δ 40.9, 61.5, 70.6, 83.2, 87.7, 119.3, 140.7, 149.1, 152.7, 155.5, 164.9; ^1H NMR (Me_2SO-d_6) δ 2.30 (m, 1H), 2.71 (m, 1H), 3.57 (m, 2H), 3.87 (m, 1H), 4.43 (m, 1H), 4.93 (t, 1H), 5.33 (d, 1H), 6.42 (t, 1H), 7.50 (s, 2H), 7.54 (s, 1H), 7.81 (s, 1H), 8.47 (s, 1H); UV (H_2O) λ max 259 (ε 8600), 264 (8900), 291.5 (4900); FTIR (KBr) 1685 cm^{-1}; FAB HRMS obsd (M^++H) 295.1147, calcd for $C_{11}H_{14}N_6O_4$ 295.1154.

2-Iodo-9-(2-deoxy-β-D-ribofuranosyl)adenine (14). The silylated 2-iodo deoxynucleoside **8** (0.173 g, 0.28 mmol) was dissolved in dry CH_3CN (7 mL) and deprotected with fluoride as described for **10** -> **11** to afford 0.105 g (0.28 mmol, 97%) of **14** as a white solid: mp >215 °C (decomp); ^1H NMR (Me_2SO-d_6) δ 2.27 (m, 1H), 2.63 (m, 1H), 3.52 (m, 1H), 3.57 (m, 1H), 3.85 (m, 1H), 4.38 (m, 1H), 4.94 (t, 1H), 5.31 (d, 1H), 6.24 (t, 1H), 7.70 (s, 2H), 8.27 (s, 1H); UV (EtOH) λ_{max} 266 nm.

2-Vinyl-9-[2-deoxy-3,5-O-bis-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]adenine (16). To a mixture of **8** (0.312 g, 0.52 mmol), and bis(acetonitrile)palladium (II) chloride (0.007g, 0.025 mmol) in DMF (4 mL) was added vinyltributyltin (0.16 mL, 0.57 mmol). The reaction was allowed to proceed for 45 min at 90°C under N_2 and then cooled, concentrated under reduced pressure, and purified on silica gel plates with 5% $CH_3OH/CHCl_3$ as the developing solvent. The band at R_f 0.42 afforded 0.179 g (0.35 mmol, 69%) of **16** as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.05-0.13 (m, 12H), 0.82-0.93 (m, 18H), 2.38 (m, 1H), 2.69 (m, 1H), 3.74 (dd, 1H), 3.85 (dd, 1H), 3.96 (m, 1H), 4.59 (m, 1H), 5.54 (dd, 1H), 5.98 (s, 2H), 6.43 (m, 2H), 6.71 (dd, 1H), 8.04 (s, 1H); UV (EtOH) λ_{max} 265, 272, 295(s) nm; mass spectrum, m/z (relative intensity) 448 (M^+-tBu, 0.15), 161 (B^++H, 29.7).

2-Vinyl-9-(2-deoxy-β-D-ribofuranosyl)adenine (15). Deprotection of **16** was carried out as described for the conversion of **10** -> **11**. The product **15** was obtained as white crystals (98% yield). (Characterization described below).

2-Vinyl-9-(2-deoxy-β-D-ribofuranosyl)adenine (15). Unprotected **14** was converted to **15** as described for the conversion of **8** -> **16** to give **15** as a white solid (80% yield): mp 181-183°C; ^{13}C NMR (Me_2SO-d_6) δ 39.8, 61.8, 70.9, 83.7, 87.9, 118.3, 120.9, 137.0, 134.8, 149.3, 155.5, 157.6; ^{1}H NMR (Me_2SO-d_6) δ 2.26 (m, 1H), 2.73 (m, 1H), 3.53 (m, 1H), 3.61 (m, 1H), 3.88 (m, 1H), 4.41 (m, 1H), 5.21 (t, 1H), 5.31 (d, 1H),5.54 (dd, 1H, 2.3, 10.4 Hz), 6.34 (m, 2H), 6.60 (dd, 1H, J=10.4, 17.2 Hz), 7.26 (s, 2H), 8.31 (s, 1H); UV (H_2O) λ_{max} 265.5 (ε10990), 270 (10820), 292(s) nm (5500); FAB HRMS obsd (M^++H) 278.1266, calcd for $C_{12}H_{16}N_5O_3$ 278.1253.

2-Ethynyl-9-(2-deoxy-β-D-ribofuranosyl)adenine (18). A mixture of the nucleoside **8** (0.102 g, 0.169 mmol), tetrakis(triphenylphosphine) palladium (0) (0.010 g, 0.008 mmol) and cuprous iodide (0.002 g, 0.013 mmol) was dissolved in DMF (5 mL) and triethylamine (1 mL). Trimethylsilylacetylene (0.05 ml, 0.338 mmol) was subsequently added dropwise *via* syringe to the reaction mixture, which was then stirred under nitrogen at 80° C for 70 min. Upon removal of the solvents under reduced pressure, the residue was taken up in ethyl acetate (20 mL) and extracted with 10% Na_2EDTA (2 X 15 mL). The organic layer was washed with aqueous NaCl (15 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in $CHCl_3$ and eluted through a short silica gel scrubber column with chloroform followed by ethyl acetate to afford **17** as a brown oil. The crude product in dry CH_3CN (6 mL) was treated with 0.646 mmol of tetraethylammonium fluoride (TEAF) in CH_3CN (0.5 M solution) and stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue purified on silica gel plates with 14 % MeOH/$CHCl_3$ as the developing solvent. The band at R_f 0.50 gave 0.036 g (0.130 mmol, 77%) as a clear glass which was crystallized from CH_3CN to give the title nucleoside **18** as white needles: mp 187-189 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.29 (m, 1H), 2.68 (m, 1H), 3.54 (m, 1H), 3.59 (m, 1H), 3.88 (m, 1H), 3.96 (s, 1H), 4.40 (m, 1H), 4.99 (s, 1H), 5.27 (t, 1H), 6.31 (dd, 1H), 7.42 (s, 2H), 8.39 (s, 1H); UV (H_2O) λ_{max} 263 (ε 10300), 268 (10800), 287 nm (6600); FAB HRMS obsd (M^++H) 276.1122, calcd for $C_{12}H_{14}N_5O_3$ 276.1096.

2-Allyl-9-(2-deoxy-β-D-ribofuranosyl)adenine (19). To a solution containing the unprotected nucleoside **14** (0.044 g, 0.118 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.010 g, 0.009 mmol) in DMF (4 mL) was added allyltributyltin (0.04mL, 0.130 mmol) dropwise *via* syringe. The reaction mixture was stirred under nitrogen for 30h at 95°C and the solvent was removed under reduced pressure and the residue was purified on silica gel plates with ether followed by 14 % MeOH/ $CHCl_3$ as the developing solvent. The band at R_f 0.43 gave 0.028g (0.096 mmol, 82%) of the title nucleoside as a white solid: mp 75-77°C; ^{1}H NMR (Me_2SO-d_6) δ 2.25 (m, 1H), 2.71 (m, 1H), 3.42 (dm, 2H), 3.53 (m, 1H), 3.63 (m, 1H), 3.89 (m, 1H), 4.40 (m, 1H), 5.07 (ddm, 2H), 5.25 (m, 2H), 6.10 (m, 1H), 6.32 (dd, 1H), 7.17 (s, 2H), 8.24 (s, 1H); UV (H_2O) λ_{max} 262 nm (ε 11000); FAB HRMS obsd (M^++H) 292.1415, calcd for $C_{13}H_{18}N_5O_3$ 292.1409.

2-Iodo-9-(3-deoxy-β-D-ribofuranosyl)adenine (20). The silylated nucleoside **9** (0.173 g, 0.28 mmol) was dissolved in dry CH_3CN (7 mL) and treated with a 0.5 M TEAF solution (1.00 mL, 0.497 mmol) in CH_3CN. The reaction proceeded at room temp for 2 h. The solvent was removed under reduced pressure and the residue purified on a silica gel plate with 12% methanol/chloroform as the developing solvent. The band at R_f 0.44 afforded 0.057 g (0.152 mmol,

92%) of product which was recrystallized from acetonitrile to afford the title nucleoside **20**[30] as a white solid: mp 207-208 °C; ^{13}C NMR (Me_2SO-d_6) δ 33.9, 62.3, 74.6, 80.7, 90.4, 118.7, 120.6, 138.6, 149.1, 155.7; ^{1}H NMR (Me_2SO-d_6) δ 1.94 (m, 1H), 2.24 (m, 1H), 3.52 (m, 1H), 3.68 (m, 1H), 4.34 (m, 1H), 4.53 (m, 1H), 4.94 (m, 1H), 5.62 (s, 1H), 5.79 (d, 1H, J=2.25 Hz), 7.62 (s, 2H), 8.27 (s, 1H); UV (H_2O) λ_{max} 262 nm (ε 12700).

2-Cyano-9-(3-deoxy-β-D-ribofuranosyl)adenine (21) was synthesized from the protected 2-iodo-3′-deoxyadenosine (**9**) by the palladium catalyzed procedure followed by deprotection described for the conversion of **8** to **11**. Product **21** crystallized from CH_3CN as white needles (87% yield): mp 189-191 °C; ^{13}C NMR (Me_2SO-d_6) δ 33.7, 62.1, 75.0, 81.3, 90.9, 116.9, 120.6, 136.7, 141.3, 149.9, 156.1; ^{1}H NMR (Me_2SO-d_6) δ 1.91 (m, 1H), 2.21 (m, 1H), 3.53 (m, 1H), 3.71 (m, 1H), 4.38 (m, 1H), 4.53 (m, 1H), 5.04 (t, 1H), 5.73 (s, 1H), 5.89 (d, 1H), 7.96 (s, 2H), 8.61 (s, 1H); UV (H_2O) λ_{max} 261 (ε 8740), 265.5 (9200), 296 nm (6000); FAB HRMS obsd (M^++H) 277.1059, calcd for $C_{11}H_{13}N_6O_3$ 277.1049.

2-Carboxamido-9-(3-deoxy-β-D-ribofuranosyl)adenine (22) was synthesized by the phase transfer hydrolysis of the silylated 2-cyano compound synthesized from **9** followed by deprotection. The procedure is similar to the preparation of **13** from **8**. Crystallization of **22** from CH_3OH/H_2O afforded white needles (49% yield for 3 steps): mp 227-229 °C; ^{13}C NMR (Me_2SO-d_6) δ33.6, 62.1, 74.8, 80.8, 90.5, 119.2, 140.2, 148.8, 152.2, 155.5, 164.9; ^{1}H NMR (Me_2SO-d_6) δ 1.91 (m, 1H), 2.26 (m, 1H), 3.52 (m, 1H), 3.72 (m, 1H), 4.36 (m, 1H), 4.57 (m, 1H), 5.03 (t, 1H), 5.72 (s, 1H), 5.95 (d, 1H), 7.49 (s, 2H), 7.57 (s, 1H), 7.86 (s, 1H), 8.48 (s, 1H); UV (H_2O) λ_{max} 259 (ε 8000),264 (8300), 291.5 nm (4500); FAB HRMS obsd (M^++H) 295.1118, calcd for $C_{11}H_{14}N_6O_4$ 295.1154.

2-Vinyl-9-(3-deoxy-β-D-ribofuranosyl)adenine (23) was synthesized from **9** in a procedure similar to the conversion of **8** to **15**. Purification by reverse-phase HPLC with 11% ethanol/water followed by 15% ethanol/water afforded 0.039g (0.14 mmol, 72%) of the title nucleoside **23** as a white solid (63% yield for 2 steps): mp 86-88 °C; ^{13}C NMR (Me_2SO-d_6) δ 34.2, 62.7, 74.2, 80.3, 90.5, 118.1, 120.8, 137.1, 139.5, 149.3, 155.5, 157.6; ^{1}H NMR (Me_2SO-d_6) δ 1.95 (m, 1H), 2.30 (m, 1H), 3.52 (m, 1H), 3.65 (m, 1H), 4.34 (m, 1H), 4.61 (m, 1H), 5.14 (t, 1H), 5.54 (dd, 1H), 5.64 (s, 1H), 5.86 (d, 1H), 6.36 (dd, 1H), 6.61 (dd, 1H), 7.23 (s, 2H), 8.32 (s, 1H); UV (H_2O) λ_{max} 265.5 (ε 11300), 270 (11200), 292(s) nm (6300); FAB HRMS obsd (M^++H) 278.1278, calcd for $C_{12}H_{16}N_5O_3$ 278.1253.

2-Ethynyl-9-(3-deoxy-β-D-ribofuranosyl)adenine (24) was prepared in 72% yield from **9** as described above for the conversion of **8** to **18**: mp 122-124 °C; ^{1}H NMR (Me_2SO-d_6) δ1.92 (m, 1H), 2.23 (m, 1H), 3.41 (m, 1H), 3.53 (m, 1H), 3.96 (s, 1H), 4.37 (m, 1H), 4.54 (m, 1H), 5.01 (t, 1H), 5.63 (s, 1H), 5.85 (d, 1H, J=2.1 Hz), 7.42 (s, 2H), 8.42 (s, 1H); UV (H_2O) λ_{max} 263 (ε 9600),268 (10 000), 287 nm (6300); FAB HRMS obsd (M^++H) 276.1128, calcd for $C_{12}H_{14}N_5O_3$ 276.1096.

2-Allyl-9-(3-deoxy-β-D-ribofuranosyl)adenine (25) was prepared in 79% yield from **20** as described for the conversion of **14** to **19**: mp 73-75 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.97 (m, 1H), 2.30 (m, 1H), 3.43 (dm, 2H), 3.67 (m, 1H), 3.79 (m, 1H), 4.32 (m, 1H), 4.60 (m, 1H), 5.11 (ddm, 2H), 5.22 (t, 1H), 5.61 (d, 1H), 5.82 (d, 1H, J=2.85 Hz), 6.11 (m, 1H), 7.22 (s, 2H), 8.26 (s, 1H); UV

(H_2O) λ_{max} 262 nm (ε 11000); FAB HRMS obsd (M^++H) 292.1422, calcd for $C_{13}H_{18}N_5O_3$ 292.1409.

2-Amino-6-chloro-9-(3,5-O-tetraisopropyldisiloxane-β-D-ribofuranosyl) purine (26). To a stirred mixture of the nucleoside **2** (1.934 g, 6.47 mmol), imidazole (0.990 g, 14.56 mmol) in dry DMF was added 2.14 ml (2.14 g, 6.80 mmol) of TPDS-Cl_2. The mixture was stirred at room temp for 45 min. The solvent was removed under reduced pressure, the residue dissolved in ether (40 mL) and extracted with H_2O (2 X 40 mL). The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography with $CHCl_3$ followed by 2% MeOH / $CHCl_3$ to afford 2.162 g (3.97 mmol, 62%) of product as a white foam: ^1H NMR ($CDCl_3$) δ 1.07 (m, 28H), 3.03 (s, 1H), 4.06 (m, 3H), 4.48 (m, 1H), 4.75 (m, 1H), 5.11 (s, 2H), 5.89 (d, 1H, J=1.6 Hz), 7.92 (s, 1H); UV (EtOH) λ_{max} 247, 308 nm; mass spectrum, m/z (relative intensity) 544 (M^+, 5.3), 501 (M^+-iPr, 64.4).

2-Iodo-9-(2-deoxy-3,5-O-tetraisopropyldisiloxane-β-D-ribofuranosyl) adenine (30). Nucleoside **26** was deoxygenated, iodinated, and aminated as described for the conversion of **4** to **8**. The overall yield from **26** to **30** was 25%: ^1H NMR ($CDCl_3$) δ 1.07 (m, 28H), 2.65 (m, 2H), 3.85 (m, 1H), 4.01 (d, 2H, J=4.0 Hz), 4.85 (q, 1H), 5.68 (s, 2H), 6.20 (dd, 1H),7.89 (s, 1H); UV (EtOH) λ_{max} 266 nm.

2-Cyano-9-(2-deoxy-β-D-ribofuranosyl)adenine (11) was prepared from **30** as described for the conversion of **8** to **11**.

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