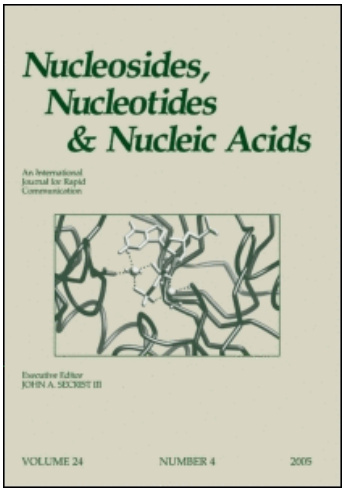


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Several 2'-Deoxy-3-Alkyl(ARYL)-3-Deazaguanosines: Mild Alkylation of a Cyanomethyl Imidazole with Electrophiles

Oscar L. Acevedo[a]; Robert S. Andrews[a]; P. Dan Cook[a]
[a] ISIS Pharmaceuticals, Carlsbad, CA

To cite this Article Acevedo, Oscar L. , Andrews, Robert S. and Cook, P. Dan(1993) 'Synthesis of Several 2'-Deoxy-3-Alkyl(ARYL)-3-Deazaguanosines: Mild Alkylation of a Cyanomethyl Imidazole with Electrophiles', Nucleosides, Nucleotides and Nucleic Acids, 12: 3, 403 — 416
To link to this Article: DOI: 10.1080/07328319308017835
URL: http://dx.doi.org/10.1080/07328319308017835

NUCLEOSIDES & NUCLEOTIDES, 12(3&4), 403-416 (1993)

SYNTHESIS OF SEVERAL 2'-DEOXY-3-ALKYL(ARYL)-3-DEAZAGUANOSINES: MILD ALKYLATION OF A CYANOMETHYL IMIDAZOLE WITH ELECTROPHILES

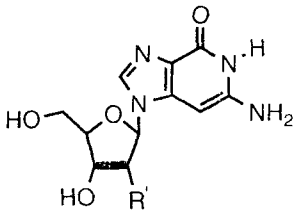
Oscar L. Acevedo*, Robert S. Andrews and P. Dan Cook
ISIS Pharmaceuticals, 2292 Faraday Avenue, Carlsbad, CA 92008

Abstract. The synthesis of several 2'-deoxy-3-alkyl(aryl)-3-deazaguanosines and of their heterocyclic aglycone is described. The 2-(1-napthyl)ethyl substituent group induces an unnatural 3'-endo/high-anti (-sc) conformation of the nucleoside.

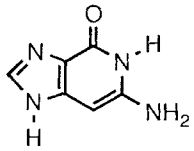
Introduction:

The syntheses[1] of 3-deazaguanine (6-aminoimidazo[4,5-c]pyridin-4(5H)-one, **2 a**) and of the nucleoside 2'-deoxy-3-deazaguanosine (6-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-c]pyridin-4(5H)-one, **1**, R'=H) have been previously described. 3-Deazaguanine is a potent guanine antimetabolite[2] with significant antitumor, antiviral, antibacterial and antiparasitic activities. 2'-Deoxy-3-deazaguanosine has exhibited a wide spectrum[2] of antiviral and antitumor activity in addition to antibacterial activity against E. coli.[3] Various ring,[4] peripheral[2,5] and sugar[2,6] modifications on 3-deazaguanine have been made resulting in a wide modulation of the biological activity of the heterocyclic ring system. However, to date no publications have appeared in which substitutions at the C-3 aromatic carbon have been described. Substitutions made at this carbon in the nucleoside are of interest since they would influence the range of rotation of the heterocycle about the glycosidic bond[7] thus potentially modifying biological activity.[8] Lipophilic substituents at this position could change the efficiency of transport of heterocycles and nucleosides across cellular membranes. We now report the synthesis of several 2'-deoxy-3-alkyl(aryl)-3-deazaguanosines and of their heterocyclic aglycone employing a mild alkylation procedure on an imidazole precursor to this ring system.

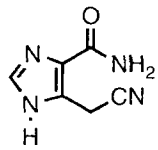
Synthesis: Nucleosides. The synthesis of the 3-deazaguanine ring system has been most widely achieved[1,2] *via* the base-catalysed cyclization of a 5(4)-cyanomethyl-imidazole-4(5)-carboxamide, (**4**, Fig 1). Both the 2'-deoxy- (**1**, R'= H) and the 3-deazaguanosines (**1**, R'=OH) have also been synthesized using a synthetic scheme which relies on this novel cyclization. The cyclization mechanism involves the attack of a carboxamide anion on the nitrile carbon followed by a prototropic shift. This mechanism should not change if the alpha carbon of the cyanomethyl group of



1



2 a



4

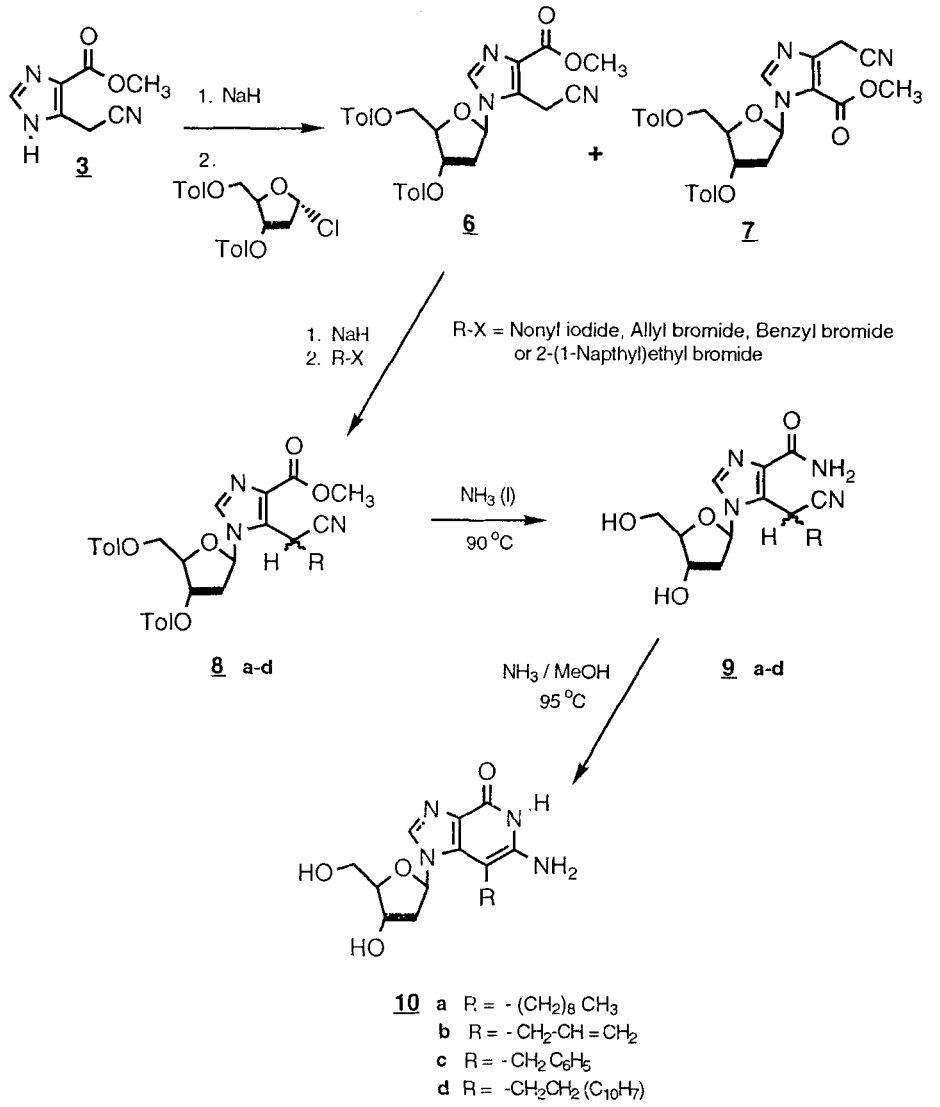
Fig 1.

intermediate 4 were substituted with an alkyl or aryl substituent. Both 4 and its nucleoside counterpart, compound 9 (R=H, Scheme 1), may be obtained from the ammonolysis of the methyl 5-cyanomethylimidazole-4-carboxylates, 3 and 6. We chose to perform alkylations on the methylene carbon of 6 and on the protected ester 11 (Scheme 2), to convert the alkylated products to their carboxamide derivatives and to subsequenly cyclize the carboxamides using one of several available procedures.[1]

Thus, the compound 6[9] was equilibrated with an excess of NaH at room temperature in acetonitrile. A dilute solution of the electrophile (3-5 equivalents) in acetonitrile was introduced *via* syringe and the reaction mixtures stirred under an inert atmosphere for periods of 3-18 hr. Neutralization of the reaction media and isolation of products by flash-column chromatography yielded mixtures of diastereomeric products. In the case of the methyl 5-(cyano[2-(1-napthyl)ethyl]methyl)imidazole-4-carboxylate 2'-deoxynucleosides (8 d), the diasteromers were separated by flash-column chromatography and characterized by ^{1}H NMR. Individual isomers exhibited H-1' pseudotriplets at δ, 6.38 and 6.26 ppm and methine signals as doublet of doublets at δ, 4.82 and 5.17 ppm, indicative of a tertiary hydrogen[10] as part of an AM_2 system. In addition, these compounds exhibited nitrile absorption bands at 2220 to 2240 cm $^{-1}$ in their infrared spectra.

The methyl 5-(cyano[alkyl]methyl)-1-(2-deoxy-3,5-di-O-*p* -toluoyl-β-D-*erythro*-pentofuranosyl)imidazole-4-carboxylate nucleosides (8 **a-d**) were heated in liquid ammonia at 90 °C for 18-20 hr in a stainless steel vessel to afford moderate yields of the corresponding deprotected carboxamides (9 **a-d**). Treatment of the carboxamides with methanolic ammonia at 95 °C yielded the desired 2'-deoxy-3-alkyl (aryl)-3-deazaguanosines (10 **a-d**). This two step procedure furnished the cyclized products in better yields than by the prolonged heating of the methyl 5-cyanomethyl-imidazole-4-carboxylates (8 **a-d**) in liquid ammonia.[1a]

The 2'-deoxy-3-alkyl (aryl)-3-deazaguanosines (10 **a-d**) thus obtained have uv spectra with nearly identical maxima to that of the 2'-deoxy-3-deazaguanosine, 1 (R'=H). Also, their ^{1}H NMR exhibit H-2 (IUPAC numbering) aromatic resonances at δ



Scheme 1

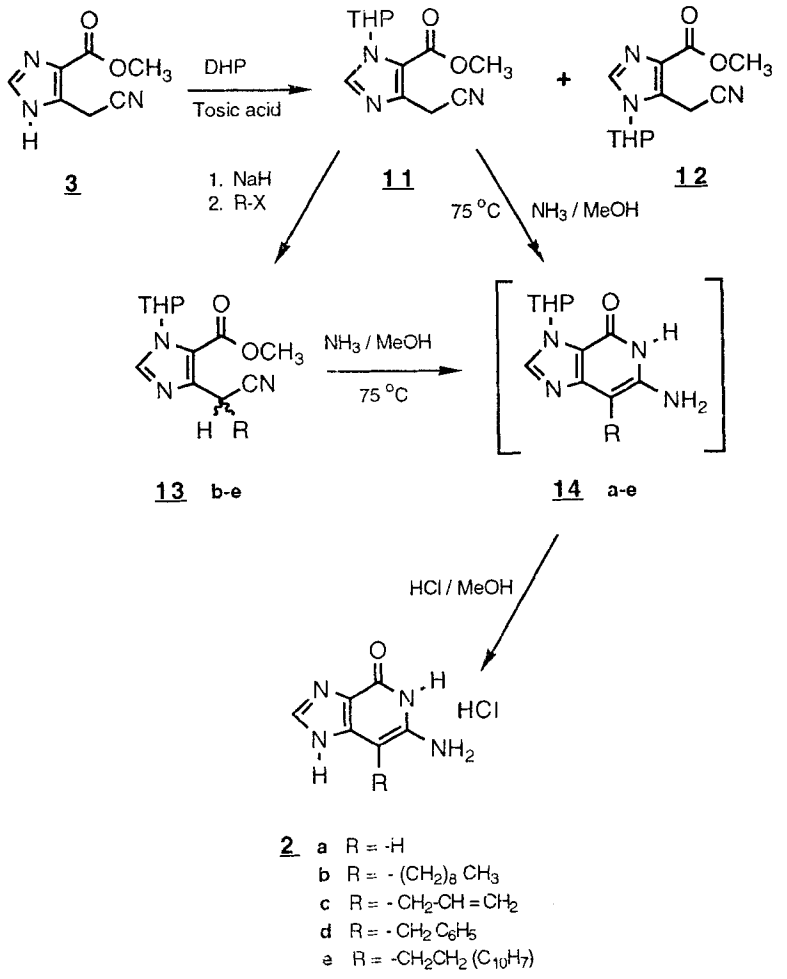
7.9 to 8.0 ppm, compared to 7.9 ppm for **1**, evidence of the nearly negligible electronic contributions from these substitutions to the overall purine ring current. However, the 2D-NOESY NMR spectrum of 2′-deoxy-3-(2-[1-napthyl]ethyl)-3-deazaguanosine, (7-(2-[1-napthyl]ethyl)-6-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-c]pyridin-4(5H)-one , **10** d), in DMSO-d_6 reveals some interesting features. The cross-peaks for the imidazole H-2 and sugar H-3′-protons are strong and there are weak cross peaks for the H-2 and H-2′ protons. In addition, the H-2″ (α) signal appears 0.4 ppm

upfield of the H-2′ (β) signal, a configuration not normally registered for 2′-deoxynucleosides. Taken together, these observations indicate that the pseudorotation[7] of the sugar strongly favors 3′-endo (75 %)[11] and that this conformation forces the H-2″ proton into the shielding volume of the heterocyclic rings. An absence of NOE signals for the N-H imino and 3′-protons indicate that this and other nucleosides in this series appear to exist strictly in an anti conformation.[12] Further, because there is a strong NOE cross-peak from H-2 and H-1′, it appears that this nucleoside is virtually locked into a high-anti (-sc) conformation. In contrast, the 2D-NOESY spectrum for the 2′-deoxy-3-allyl-3-deazaguanosine (7-allyl-6-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-c]pyridin-4(5H)-one , **10 b**) exhibits strong cross-peaks for the imidazole H-2 and sugar H-2' protons and lesser cross peaks for H-2 and H-3′, indicating 2'-endo (62 %) as a predominant conformation for the deoxyribose sugar.

We believe that the unique preference of the deoxyribose for the 3'-endo conformation is caused by the steric crowding of the 2-(1-napthyl)ethyl group at the 3-position of the 3-deazaguanine with the sugar ring. Molecular models indicate that the 3′-endo/high-anti conformation best accomodates the steric bulk of the napthyl rings and avoids the close proximity of the H-2 and H-2′ protons of the 2′-deoxy-3-(2-[1-napthyl]ethyl)-3-deazaguanosine. In the case of the 2′-deoxy-3-allyl-3-deazaguanosine the steric crowding is less and the nucleoside adopts a 2′-endo/anti (-ac) conformation.

Heterocyles. We chose to protect the imidazole[1a] of the methyl 5(4)-cyanomethyl-imidazole-4(5)-carboxylate, (3), with a tetrahydropyranyl group (Scheme 2). A reaction with 2,3-dihydropyran in the presence of tosic acid yielded the tetrahydropyranyl positional isomers **11** and **12** in roughly 2:1 ratio. These isomers were separated in order to isolate the isomer with a tetrahydropyranyl protecting group in a position removed from the proposed site of alkylation. It was our desire to work with the more abundant isomer **11** and, upon alkylation, to characterize a simpler mixture of alkylated products based on one chiral center and a racemic tetrahydropyranyl group. We expected that the alkylated cyanomethylimidazoles obtained from our methodology would likely cyclize efficiently in methanolic ammonia to yield the 7-alkyl(aryl)-6-amino-3-tetrahydropyranyl-1,5-dihydroimidazo-[4,5-c]pyridin-4-one ring system. The cyclization of positional isomers methyl 4-cyanomethyl-imidazole-5-carboxylates (**11**) and (7) has been shown to occur more readily[2] than that of the isomers **12** and **6**. This cyclization is undoubtedly hindered by the presence of a tetrahydropyranyl or 2′-deoxyribo group at the imidazole nitrogen adjacent to the cyanomethyl substitutent.

Thus, compound **11** was alkylated using a procedure identical to that for the nucleosides. The alkylated products **13 b-e** were subsequently treated with methanolic ammonia and heated at 75 °C in a sealed vessel for 72 hours.[13] After this time, the reaction mixtures were evaporated under reduced pressure to afford light colored solids which decomposed rapidly when exposed to air and moisture. Though the 7-alkyl (aryl)-6-amino-3-tetrahydropyranyl-imidazo[4,5-c]pyridin-4(5H)-one (**14 b-e**) products



2 **a** R = -H
b R = - $(CH_2)_8 CH_3$
c R = - CH_2-CH = CH_2
d R = - $CH_2 C_6H_5$
e R = -CH_2CH_2 ($C_{10}H_7$)

Scheme 2

were undoubtedly part of these reaction mixtures, we were not able to isolate them under any circumstances. Instead, the crude reaction products were thoroughly rid of all ammonia and then treated with 1 N HCl in methanol for several hours; these conditions removed the tetrahydropyranyl protecting group and gave the 7-alkyl(aryl)-6-amino-1,5-dihydroimidazo[4,5-c]pyridin-4-one (**2 b-e**) products as hydrochloride salts.[4a] Similarly, compound **11** was cyclized in methanolic ammonia and the product treated with methanolic HCl to afford **2 a** directly.

As previously mentioned, the products of ammonolysis **14 b-e** decomposed rapidly in the course of isolation or during attempts at crystallization. We do not yet understand why these products would be unstable under these conditions. Since we

did not characterize the numerous products seen on thin-layer chromatography plates, we are unable to comment on the mechanism of decomposition. Fortunately, the instability of these intermediates was surmounted and the desired final products were isolated by an immediate treatment with methanolic HCl. The hydrochloride salts **2 b-e** gave satisfactory C,H,N analyses (see Experimental) and ^{1}H NMR spectra after months of storage, attesting to their long-term stability.

Discussion: We have described a mild alkylation procedure on the methylene carbon of a cyanomethyl imidazole precursor to 3-deazaguanine. The alkylated products obtained were subsequently cyclized to the 3-alkyl (aryl)-3-deazaguanines by sequential treatments with methanolic ammonia and methanolic HCl. The corresponding nucleosides were synthesized *via* the mild alkylation of the methyl 5-cyanomethyl-1-(2-deoxy-β-D-*erythro* -pentofuranosyl)imidazole-4-carboxylate with various electrophiles. Cyclized products were obtained using a two-step procedure employing liquid and then methanolic ammonia.

Two-dimensional NMR experiments (2D-NOESY) indicate that the substituted 2'-deoxy-3-deazaguanosines prefer the anti-conformation. Though this observation seems intuitively obvious, it may be noted that a high syn (+ac) conformational preference was observed for a related 2'-deoxy-7-deazaguanosine substituted with an isopropyl group at the N-3 position.[12] Additionally, the bulky substituent in 2'-deoxy-3-(2-[1-napthyl]ethyl)-3-deazaguanosine appears to force the sugar into an unusual 3'-endo conformation. We expect that gradually decreasing the size of these substituents would increase the equilibrium population of the nucleoside towards 2'-endo. Though 2D-NOESY experiments were not performed on all nucleosides, the spectra of 2'-deoxy-3-allyl-3-deazaguanosine and of 2'-deoxy-3-deazaguanosine[14] indicate a preponderance of 2'-endo conformation for these compounds. We do not know whether these structural changes can be correlated with any biological activity. However, it is reasonable to expect that the 2'-deoxy-3-alkyl (aryl)-3-deazaguanosines bearing the larger substituents might be enhanced substrates for viral kinases due to their preference for the anti-conformation.[15]

Biological Evaluation: The 2'-deoxy-3-alkyl (aryl)-3-deazaguanosines and their heterocyclic aglycone were screened for their anti-HIV activity in an MTT assay utilizing CEM and MT-2 cells. No anti-HIV activity was detected with these compounds in either cell line. These compounds were also screened for activity against Influenza A virus in MDCK cells and showed no activity. Finally, all compounds showed no antitumor activity against the following tumor cell lines: CCRF-SB (leukemia), HCT-116 (colon), HOP-62 (lung), RPMI-7951 (melanoma), SF-539 (CNS), and SN12K1 (renal).

Experimental Section:

Silica gel used for flash chromatography was ICN 60 (Costa Mesa, CA), 32-63 mesh. Materials not soluble in the solvent system used for flash chromatography (FC) were coevaporated onto E. Merck silica gel 100 (Darmstadt, Republic of Germany), 70-230 mesh, using a suitable solvent. The dry materials were then applied to the top of a FC column. TLC was performed on prescored E. Merck Kieselgel 60 F_{254} plates. Compounds were visualized by illuminating TLC plates under UV light (254 nm) and/or by spraying with 10 % methanolic H_2SO_4 followed by heating. Evaporations were carried out at 40-50 °C using a rotary evaporator and a vacuum pump coupled to a vacuum controller. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, N.J. ^1H NMR spectra were obtained at 400 MHz in DMSO-d_6 unless otherwise noted. Where relevant, treatment of samples with D_2O recorded exchangeable hydrogens. Infrared spectra were recorded on a Perkin-Elmer 16PC FT-IR spectrophotometer. Solvent system A = ethyl acetate-hexanes, 3:2; B = ethyl acetate-methanol, 9:1, v/v.

A large scale synthesis of the methyl 5-(cyanomethyl)-1-(2'-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-erythro-pentofuranosyl)imidazole-4-carboxylate (**6**), a starting material for this work was carried out according to the sodium-salt glycosylation procedure described in Reference 2. Likewise, the methyl 5-cyanomethyl-3-tetrahydropyranyl-imidazole-4-carboxylate (**11**) was prepared and separated from its positional isomer according to the procedure given in Reference 1b. A small scale synthesis of the 2'-deoxy-3-deazaguanosine (6-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-c]pyridin-4(5H)-one, **1**, R'=H) yielded material identical in every respect with that reported in Reference 2. The alkylation procedures described below yield diastereomeric mixtures differing in configuration at the alkylated (methine) carbon. For the nucleosides, these mixtures exhibit well-resolved signals for their H-2, methine, H-1' and other protons in their 400 MHz ^1H NMR spectra.

General Method: Alkylation. Methyl 5-(cyano[nonyl]methyl)-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)imidazole-4-carboxylate (8 a).
A solution of **6** (5.7 g, 11 mmol) in anhydrous acetonitrile (75 mL) was treated with sodium hydride (0.88 g, 60% in oil, washed with hexanes) at room temperature and under an atmosphere of argon. This suspension was stirred for 15 minutes and then treated with iodononane (7.5 mL, 37.4 mmol) *via* syringe. The reaction mixture was stirred under these conditions for 6 hr; thin layer chromatography showed the disapperance of starting material nucleoside (Rf = 0.45, solvent A) and the appearance of two closely migrating and faster products (Rf = 0.65, avg). The reaction was quenched with the addition of glacial acetic acid to pH 5 and then evaporated to dryness *in vacuo* to afford a yellow syrup. The syrup was redissolved in dichloromethane (150 mL) and the solution was washed with cold 0.1 N HCl, water,

and then dried over magnesium sulfate. Filtration and evaporation of the organic layer afforded a yellow gum which was purified using FC on silica gel (120 g) using a gradient of ethyl acetate in hexanes (20 to 50 %). Fractions corresponding to the alkylated products were pooled and evaporated to yield (8 **a**) as a foam, 2.9 g (47 %). ^{1}H NMR: δ, 8.18 and 8.15 (2 s; 1 H; H-2); 6.48 and 6.37 (2 t; 1 H; H-1'); 4.68 and 4.36 (2 m; 1 H; methine); 3.32 (s; 3 H; $COOCH_3$); 2.05, 1.75, 1.18 and 0.90 (4 m; 19 H; nonyl). IR (film): 2240 cm^{-1} (CN). *Anal*. Calcd for $C_{37}H_{45}N_3O_7$ (643.778): C, 69.03, H, 7.04, N, 6.53. Found: C, 68.77, H, 6.97, N, 6.39.

Methyl 5-(allyl[cyano]methyl)-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)imidazole-4-carboxylate (8 b).

A solution of 6 (5.0 g, 9.7 mmol) in anhydrous acetonitrile (75 mL) was treated with sodium hydride (0.46 g, 11.6 mmol) and then allyl bromide (2.5 mL, 29 mmol). Workup of the reaction and purification of the products on silica gel (75 g) as described in the General Method afforded 8 **b** as a yellowish foam, 3.7 g (68 %). ^{1}H NMR (200 MHz): δ, 8.15 and 8.13 (2 s; 1 H; H-2); 6.38 (m; 1 H; H-1'); 5.75 and 5.08 (2 m; 3 H; vinyl); 3.79 (s; 3 H; $COOCH_3$). *Anal*. Calcd for $C_{32}H_{31}N_3O_7$ (557.60): C, 66.77, H, 5.60, N, 7.53. Found: C, 66.43; H, 5.59, N, 7.38.

Methyl 5-(benzyl[cyano]methyl)-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)imidazole-4-carboxylate (8 c).

A solution of 6 (5.0 g, 9.6 mmol) in anhydrous acetonitrile (75 mL) was treated with sodium hydride (0.46 g, 11 mmol) under argon and stirred at room temperature for 15 minutes. The mixture was cooled to 4 ^{o}C in an ice bath and a solution of benzyl bromide (1.26 mL, 10.6 mmol) in acetonitrile (15 mL) was added dropwise over 70 min. The ice bath was removed and the reaction further stirred at room temperature for 2.5 hr. Workup of the reaction and purification of the products on silica gel (100 g) as described in the General Method afforded 8 **c** as a white foam, 3.4 g (58 %). ^{1}H NMR: δ, 8.12 and 8.05 (2 s; 1 H; H-2); 8.0-7.10 (m; 13 H; aromatic); 6.33 and 6.01 (2 t; 1 H; H-1'); 5.22 and 5.02 (2 t; 1 H; methine); 3.80 (s; 3 H; $COOCH_3$). IR (film): 2240 cm^{-1} (-CN). *Anal*. Calcd for $C_{35}H_{33}N_3O_7$ (607.66): C, 69.18; H, 5.47; N, 6.92. Found: C, 69.15; H, 5.43; N, 6.82.

Methyl 5-(cyano[2-(1-napthyl)ethyl]methyl)-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)imidazole-4-carboxylate (8 d).

A solution of 6 (7.43 g, 14.3 mmol) in anhydrous acetonitrile (50 mL) was treated with sodium hydride (1.15 g, 28.7 mmol) under argon and stirred at room temperature for 15 minutes. The 2-(1-napthyl)ethyl bromide (16.9 g, 71.5 mmol) was added neat and the reaction stirred for 18 hr. Workup of the reaction as described in the General Method and purification of the products on silica gel (150 g) using a gradient of ethyl acetate in hexanes (20 to 60 %) yielded three major fractions. Fraction 1 (1.55 g) contained the

faster isomer; fraction 2 (0.90 g) contained a mixture of both isomers; fraction 3 (1.53 g) contained the slower isomer. Overall yield of **8 d**, 3.9 g, 42 %. Fraction 1. ^{1}H NMR: δ, 8.17 (s; 1 H; H-2); 7.9-7.1 (m; 15 H; aromatic); 6.38 (t; 1 H; H-1'); 5.17 (t; 1 H; methine); 3.72 (s; 3 H; $COOCH_3$). Fraction 3. δ, 8.15 (s; 1 H; H-2); 7.9-7.1 (m; 15 H; aromatic); 6.26 (t; 1 H; H-1'); 4.82 (t; 1 H; methine); 3.77 (s; 3 H; $COOCH_3$). *Anal.*. (Mixture of diastereomers). Calcd for $C_{40}H_{37}N_3O_7$ (671.75): C, 71.52; H, 5.55; N, 6.26. Found: C, 71.76; H, 5.54; N, 6.02.

General Method. Ammonolysis. 5-(Cyano[nonyl]methyl)-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazole-4-carboxamide (9 a).

The nucleoside **8 a** (2.98 g, 4.6 mmol) was dissolved in anhydrous methanol (5 mL) and transferred to a stainless steel vessel. The solution was cooled to -78 °C and then treated with anhydrous liquid ammonia (45 mL). The bomb was sealed and then heated to 100 °C in an oil bath for 21 hr. TLC (solvent B) exhibited products Rf = 0.45, and toluamide Rf = 0.85, indicating a complete removal of the toluoyl protecting groups. Ammonia was evaporated at room temperature and the amber gum which resulted was flash chromatographed on silica gel (80 g) using a gradient of methanol in ethyl acetate (5 to 10 %). Fractions corresponding to the products were pooled and evaporated *in vacuo* to yield **9 a** as a white foam, 1.2 g (63 %). ^{1}H NMR: δ, 8.09 and 8.05 (2 s; 1 H; H-2); 6.14 (t; 1 H: H-1'); 5.45 and 5.32 (2 dd; 1 H; methine); 2.10, 1.80, 1.40-1.05 and 0.82 (4 m; 19 H; nonyl). *Anal*. Calcd. for $C_{20}H_{32}N_4O_4$ (392.50): C, 61.20; H, 8.22; N, 14.27. Found: C, 60.97; H, 8.24; N, 13.98.

5-(Allyl[cyano]methyl)-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-imidazole-4-carboxamide (9 b).

The nucleoside **8 b** (3.95g, 7.08 mmol) was treated with liquid ammonia and heated to 100 °C in a stainless steel bomb for 8 hr. The products of this reaction were worked up and purified on silica gel (80 g) as described in the General Method.. The deprotected compound **9 b** was isolated as a white foam, 1.3 g (58 %). ^{1}H NMR: δ, 8.09 and 8.05 (2 s; 1 H; H-2); 6.15 (t; 1 H; H-1'); 5.75 and 5.10 (2 m; 3 H; vinyl); 5.42 and 5.34 (2 t; 1 H; methine). *Anal.* Calcd for $C_{14}H_{18}N_4O_4$ (306.33): C, 54.89; H, 5.92; N, 18.29. Found: C, 54.58; H, 5.92; N, 17.93.

5-(Benzyl[cyano]methyl)-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-imidazole-4-carboxamide (9 c).

The nucleoside **8 c** (3.0 g, 4.93 mmol) was treated with liquid ammonia and heated to 100 °C in a stainless steel bomb for 6 hr. The products of this reaction were worked up and purified on silica gel (80 g) as described in the General Method. The deprotected compound **9 c** was isolated as a white foam, 1.0 g (59 %). ^{1}H NMR: δ, 8.05 and 8.03 (2 s; 1 H; H-2); 7.25 (m; 5 H; phenyl); 6.17 and 6.07 (2 t; 1 H; H-1'); 5.50 and 5.42 (2 t; 1 H; methine). *Anal.* Calcd for $C_{18}H_{33}N_3O_7$ (357.39): C, 60.49; H, 5.92; N, 15.68. Found: C, 60.65; H, 5.69; N, 15.23.

5-(Cyano[2-(1-napthyl)ethyl]methyl)-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-imidazole-4-carboxamide (9 d).

The nucleoside **8 d** (3.78 g, 5.76 mmol) was treated with liquid ammonia and then heated to 100 °C in a stainless steel bomb for 20 hr. The products of this reaction were worked up and purified on silica gel (86 g) as described in the General Method. The deprotected compound **9 d** was isolated as a white foam, 1.2 g (49 %). ^{1}H NMR: δ, 8.14 and 8.08 (2 s; 1 H; H-2); 8.0-7.3 (m; 7 H; napthyl); 6.22 and 6.19 (2 t; 1 H; H-1'); 5.55 and 5.30 (2 t; 1 H; methine). *Anal.* Calcd for $C_{23}H_{24}N_4O_4$ (420.47): C, 65.70; H, 5.75; N, 13.32. Found: C, 65.78; H, 5.72; N, 13.05.

General Method: Cyclization. 6-Amino-7-nonyl-1-(2-deoxy-β-D-*erythro*-pento-furanosyl)imidazo[4,5-c]pyridin-4(5H)-one (2'-Deoxy-3-nonyl-3-deazaguanosine, 10 a).

A solution of the nucleoside **9 a** (250 mg) in 35 mL methanolic ammonia(methanol saturated with liquid ammonia at -20 °C) was heated to 95 °C in a sealed vessel for 18 hr. The mixture was evaporated to afford a dark solid which was redissolved in hot ethanol. The solid which separated upon cooling was filtered and dried *in vacuo* for 18 hr to afford **10 a** (180 mg, 72 %) as an amorphous solid. MP 150 °C dec. ^{1}H NMR: δ, 10.3 (bs; 1 H; N-H); 7.90 (s; 1 H; H-2); 6.08 (pseudo t; 1 H; H-1', J=6.0 Hz); 5.15 (bs; 2 H; NH_2); 2.52, 1.30 and 1.82 (3 m; 19 H; nonyl). UV, λ_{max}, nm, (log ε): MeOH, 312 (4.001), 278 (4.040); pH 1, 322 (3.687), 296 (3.845); pH 7, 308 (2.811), 276 (2.842); pH 12, 290 (3.978). *Anal.* Calcd for $C_{20}H_{32}N_4O_4$ (392.50): C, 61.20; H, 8.22; N, 14.27. Found: C, 61.02; H, 8.20; N, 14.22.

7-Allyl-6-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-*c*]pyridin-4(5H)-one (2'-deoxy-3-allyl-3-deazaguanosine, 10 b).

The nucleoside **9 b** (250 mg) was cyclized and purified according to the General Procedure described above to yield **10 b** (190 mg, 76 %) as an amorphous solid. MP.155 °C dec. ^{1}H NMR (200 MHz): δ, 10.4 (bs; 1 H; N-H); 7.98 (s; 1 H; H-2); 6.05 (pseudo t; 1 H; H-1', J=5.4 Hz); 5.92, 5.02 and 4.88 (3 m; 3 H; vinylic); 5.34 (s; 2 H; NH_2); 3.40 and 3.19 (2 m; 2 H; allylic). UV, λ_{max}, nm, (log ε): MeOH, 310 (3.996), 276 (4.060); pH 1, 320 (3.891), 292, (4.064); pH 7, 306 (3.963), 274 (4.011); pH 12, 288 (4.160). *Anal.* Calcd for $C_{14}H_{18}N_4O_4$ (306.32): C, 54.89; H, 5.92; N, 18.29. Found: C, 54.58; H, 5.92; N, 18.09.

6-Amino-7-benzyl-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo-[4,5-*c*]pyridin-4(5H)-one (2'-deoxy-3-benzyl-3-deazaguanosine, 10 c).

The nucleoside **9 c** (250 mg) was cyclized and purified by trituration with hot ethanol as described in the General Method to yield **10 c** (200 mg, 80 %) as a white solid. MP 140 °C dec. ^{1}H NMR: δ 10.4 (bs; 1 H; N-H); 7.84 (s; 1 H; H-2); 7.3-7.1 (m, 5 H, phenyl); 6.04 (pseudo t; 1 H; H-1', J= 6.3 Hz); 5.07 (bs; 2 H; NH_2); 4.07 and 3.88 (dd; 2 H; benzylic, J = 17 Hz). UV, λ_{max}, nm, (log ε): MeOH, 310 (3.950), 276 (4.002); pH 1, 320 (3.835), 294 (3.988); pH 7 308 (3.923), 274 (3.959); pH 12, 310 (3.930). *Anal.* Calcd for $C_{18}H_{20}N_4O_4$ (356.38): C, 60.66; H, 5.66; N, 15.72. Found: C, 60.55; H, 5.60; N, 15.51.

6-Amino 7-(2-[1-napthyl]ethyl)-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-c]pyridin-4(5H)-one (2'-deoxy-3-(2-[1-napthyl]ethyl)-3-deazaguanosine, 10 d).
The nucleoside 9 d (250 mg) was cyclized and purified from hot ethanol as described in the General Method to yield **10 d** (200 mg, 80 %) as an off-white solid. MP 195 °C dec. ^{1}H NMR: δ, 10.5 (bs; 1 H; N-H); 7.98 (s; 1 H; H-2); 8.2-7.4 (m; 7 H; napthyl); 6.21 (pseudo t; 1 H; H-1', J=6.9 Hz); 5.32 (bs; 2 H; NH_2); 3.3-2.8 (m; 4 H; ethylene); 2.60 (m; 1 H; H-2"); 2.20 (m; 1 H; H-2'). UV, λ_{max}, nm, (log ε): MeOH, 310 (4.019), 289 (4.180); pH 1, 324 (3.805), 290 (4.114); pH 7, 310 (3.611), 284 (3.834); pH 12, 286 (4.185). *Anal.* Calcd for $C_{23}H_{24}N_4O_4$ (420.47): C, 65.70; H, 5.75; N, 13.32. Found: C, 65.80; H, 5.72; N, 13.05.

General Method: Alkylation. Methyl 5-(cyano[nonyl]methyl)-3-tetrahydropyranyl-imidazole-4-carboxylate (13 b).
The cyanomethyl imidazole **11** (5.0 g, 20 mmol) was alkylated using NaH (1.2 g, 60 % in oil, washed with hexanes) and iodononane (7.6 g, 30 mmol) as described in the General Procedure for the nucleosides. The products were purified by FC using a gradient of ethyl acetate in hexanes (20 to 50 %). Evaporation of the fractions containing the products yielded **13 b** (5.0 g, 67 %) as a yellow foam . ^{1}H NMR (200 MHz): δ, 8.22 (s; 1 H; H-2); 5.87 (m; 1 H; H-2' tetrahydropyranyl); 4.58 (m; 1 H; methine); 3.85 (s; 3 H; $COOCH_3$); 1.30 and 0.88 (2 m; 19 H; nonyl). *Anal.* Calcd for $C_{21}H_{33}N_3O_3$ (375.51): C, 67.17; H, 8.86; N, 11.19. Found: C, 67.47; H, 8.95; N, 11.21.

Methyl 5-(allyl[cyano]methyl)-3-tetrahydropyranyl-imidazole-4-carboxylate (13 c).
The cyanomethyl imidazole **11** (5.0 g, 20 mmol) was alkylated using NaH (1.2 g)and allyl bromide (3.6 g, 30 mmol) and purified according to the General Method described above. White foam, 3.9 g, 67 %. ^{1}H NMR (200 MHz): δ, 8.23 (s; 1 H,;H-2); 5.87 (m; 1 H; H-2' tetrahydropyranyl); 5.77 and 5.15 (2 m; 3 H; vinylic); 5.68 (m; 1 H; methine); 3.86 (s; 3 H; $COOCH_3$). *Anal.* Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.27; H, 6.62; N, 14.54.

Methyl 5-(benzyl[cyano]methyl)-3-tetrahydropyranyl-imidazole-4-carboxylate (13 d).
The cyanomethyl imidazole **11** (5.0 g, 20 mmol) was alkylated using NaH (1 2 g) and benzyl bromide (5.1 g, 30 mmol) and purified according to the General Method described above. White foam, 4.8 g, 71 %. ^{1}H NMR (200 MHz): δ, 8.25 (s; 1H; H-2); 7.29 (m; 5 H; phenyl); 6.83 (m; 1 H; H-2' tetrahydropyranyl); 4.84 (m; 1 H; methine); 3.84 and 3.80 (2 s; 3 H; $COOCH_3$); 3.19 (m; 2 H; benzylic).*Anal.* Calcd. for $C_{19}H_{21}N_3O_3$ (339.39): C, 67.24; H, 6.24; N, 12.38. Found: C, 67.21; H, 6.19; N, 12.02.

Methyl 5-(cyano[2-(1-napthyl)ethyl]methyl)-3-tetrahydropyranyl-imidazole-4-carboxylate (13 e).
The cyanomethyl imidazole **11** (5.0 g, 20 mmol) was alkylated using NaH (1.2 g) and 2-(1-napthyl)ethyl bromide (7.1 g, 30 mmol, Frinton Labs, Vineland, N.J.) and purified

according to the General Method described above. White foam, 5.0 g, 62 %. ^{1}H NMR (200 MHz): δ, 8.23 (s; 1 H; H-2); 8.1-7.3 (m; 7 H; napthyl); 5.80 (m; 1 H; H-2' tetrahydropyranyl); 4.58 (m; 1 H; methine); 3.57 (s; 3 H; $COOCH_3$). *Anal.* Calcd for $C_{24}H_{35}N_3O_3$ (403.48): C, 71.44; H, 6.24; N, 10.41. Found: 71.38; H, 6.16; N, 10.45.

General Method: Cyclization. 6-Amino-7-nonyl-1,5-dihydroimidazo[4,5-c]pyridin-4-one Hydrochloride salt (2 b).

The compound **13 b** (2.5 g, 6.7 mmol) was dissolved in 50 mL methanolic ammonia (saturated at -20 °C) in a stainless steel vessel. The mixture was stirred at 75 °C for 72 hr and then evaporated to dryness *in vacuo*. The resulting solid was coevaporated with methanol (45 mL) and then immediately stirred with methanolic 1 N HCl (50 mL) for 12 hr. After this time, the reaction mixture was evaporated to afford a light yellow gum. This gum was precipitated by repeated coevaporation with methanol. Amorphous solid, 1.1 g, 53 %. MP 225 darkens; 240 °C dec. ^{1}H NMR: δ, 10.8 (bs;1 H; N-H); 8.72 (s; 1 H; H-2); 5.80 (bs; 2 H; NH_2); 2.0, 0.9 and 0.4 (3 m; 19 H; nonyl). UV, λ_{max}, nm, (log ε): MeOH, 310 (3.935), 270 (3.969). *Anal.* Calcd. for $C_{15}H_{25}N_4OCl$ (312.84): C, 57.59; H, 8.05; N, 17.90. Found: C, 57.53; H, 8.05; N, 17.87.

7-Allyl-6-amino-1,5-dihydroimidazo[4,5-c]pyridin-4-one Hydrochloride salt (2 c).

The compound **13 c** (2.5 g, 8.6 mmol) was cyclized and isolated according to the General Method described above. Amorphous solid, 1.3 g, 67 %. MP 210 °C dec. ^{1}H NMR: δ, 11.0 (bs; 1 H; N-H); 8.49 (s; 1 H; H-2); 5.80 and 4.98 (2 m; 3 H; vinylic); 5.80 (bs; 2 H; NH_2); 3.26 (m; 2 H,;allylic). UV, λ_{max}, nm, (log ε): MeOH, 310 (3.927), 268 (3.985). *Anal.* Calcd for $C_9H_{11}N_4OCl$ (226.66): C, 47.69; H, 4.89; N, 24.72. Found: C, 48.04; H, 5.02; N, 24.76.

6-Amino-7-benzyl-1,5-dihydroimidazo[4,5-c]pyridin-4-one Hydrochloride salt (2 d).

The compound **13 d** (2.5 g, 7.4 mmol) was cyclized and isolated according to the General Method described above. Amorphous solid, 1.9 g, 92 %. MP 196 °C dec. ^{1}H NMR: δ, 11.5 (bs; 1 H; N-H); 9.20 (s; 1 H; H-2); 7.17 (m; 5 H; phenyl); 6.20 (bs; 2 H; NH_2); 3.95 (s; 2 H; benzylic). UV, λ_{max}, nm, (log ε): MeOH, 310 (3.958), 268 (3.988). *Anal.* Calcd for $C_{13}H_{13}N_4OCl$ (276.72): C, 56.42; H, 4.73; N, 20.25. Found: C, 56.40; H, 4.71; N, 20.03.

6-Amino-7-(2-[1-napthyl]ethyl)-1,5-dihydroimidazo[4,5-c]pyridin-4-one Hydrochloride salt (2 e).

The compound **13 e** (2.5 g, 6.2 mmol) was cyclized and isolated according to the General Method described above. Amorphous solid, 1.64 g, 78 %. MP 260 darkens, 273 °C dec. ^{1}H NMR: δ, 11.4 (bs; 1 H; N-H); 9.20 (s; 1 H; H-2); 8.1-7.4 (m; 7 H; napthyl); 6.10 (bs; 2 H; NH_2); 3.15 and 3,02 (2 m; 4 H; ethylene). UV, λ_{max}, nm, (log ε): MeOH, 308 (3.930), 272 (4.137). *Anal.* Calcd for $C_{18}H_{17}N_4OCl$ (340.81): C, 63.18; H, 4.95; N, 16.28. Found: C, 63.18; H, 4.95; H, 16.28.

6-Amino-1,5-dihydroimidazo[4,5-c]pyridin-4-one (3-Deazaguanine) Hydrochloride salt (2 a).

The compound **11** (2.5 g, 10 mmol) was cylized and the product isolated according to the General Method described above. This product gave a satisfactory ^{1}H NMR but proved unstable during purification and did not fit C,H,N analysis as a hydrochloride salt.[4a] ^{1}H NMR: δ, 10.5 (bs; 1 H; N-H); 8.18 (s; 1 H; H-2); 5.4 (bs; 2 H; NH_2); 4.6 (s; 1 H; H-7).

REFERENCES

1 (a) Cook, P.D.; Rousseau, R.J.; Mian, A.M.; Meyer, R.B., Jr.; Dea, P.; Ivanovics, G.; Streeter, D.G.; Witkowski, J.T.; Stout, M.G.; Simon, L.N.; Sidwell, R.W.; Robins, R.K. **J. Am. Chem. Soc.** 1975, **97**, 2916. (b) Cook, P.D.; Allen, L.B.; Streeter, D.G.; Huffman, J.H.; Sidwell, R.W.; Robins, R.K. **J. Med. Chem.** 1978, **21**, 1212 and references contained therein.

2 Revankar, G.R.; Gupta, P.K.; Adams, A.D.; Dalley, N.K.; McKernan, P.A.; Cook, P.D.; Canonico, P.G.; Robins, R.K. **J. Med. Chem.** 1984, **27**, 1389.

3 Burman, S.R.; Mian, A.M.; Khwaja, T.A. **Chem. Scripta** 1986, **26**, 155.

4 (a) Hartman, J.D.; Alks, V.; Huang, C.C.; Cook, P.D. **J. Labelled Compd. Radiopharm.** 1985, **23**, 35. (b) Pickering, M.V.; Campbell, M.T.; Witkowski, J.T.; Robins, R.K. **J. Heterocycl. Chem.** 1977, **14**, 697. (c) Ehler, K.W. ; Robins, R.K.; Meyer, R.B., Jr. **J.Med. Chem.** 1977. 20, 317. (d)Meyer, R.B., Jr.; Revankar, G.R.; Cook, P.D.; Ehler, K.W.;Schweizer, M.P.; Robins, R.K. **J. Heterocycl. Chem.** 1980, **17**, 159. (e) Schneller, S.W.; Luo, J.-K.; Hosmane, R.S. **Tetrahedron Lett.** 1980, **21**, 3135. (f) Berry, D.A.; Bilbertsen, R.B.; Cook, P.D. J. Med. Chem. 1986, 29, 2034.

5 (a) Cook, P.D.; Robins, R.K. **J. Org. Chem.** 1978, **43**, 289.

6 (a) Poonian, M.S.; McComas, W.W.; Kramer, M.J. **J. Med. Chem.** 1979, **22**, 958. (b) Gupta, P.K.; Bhakuni, D.S. **Indian J. Chem. sect.B** 1981, 20B, 702. (c) McGee, D.P.C.; Martin, J.C.; Smee, D.F. ; Verheyden, J.P.H. **Nucleosides and Nucleotides**, 1990, **9**, 815.

7 Saenger, W. "Principles of Nucleic Acid Structure", Cantor, C.R., Ed., Springer-Verlag, New York, 1983,.

8 (a) Saran, A.; Chatterjee , C.L.; **Int. J. Quantum Chem.** 1984, **25**, 743. (b) Miles, D.L.; Miles, D.W.; Redington, P.; Eyring, H. **J. Theor. Biol.** 1977, 67, 499.

9 The synthetic intermediate **6** was obtained from the sodium salt glycosylation of methyl 5(**4**)-cyanomethyl-imidazole-4(5)carboxylate (**3**) with 1-chloro-2-deoxy-3,5-di-O-*p* -toluoyl-α-D-*erythro* -pentofuranose (chlorosugar) in acetonitrile. Positional isomers corresponding to methyl 5-cyanomethyl-1-(2-deoxy-3,5-di-O-*p* -toluoyl-β-D-*erythro* -pentofuranosyl)-imidazole-4-carboxylate (**6**) and methyl 4-cyanomethyl-1-(2-deoxy-3,5-di-O-*p* -toluoyl-β-D-*erythro* -pentofuranosyl)-imidazole 5-carboxylate (**7**) were obtained in 1:1.5 ratios and in good overall yields. We found that the most favorable ratio of positional isomers was obtained when the chlorosugar used in the condensation was free of acidic contaminants and anhydrous conditions were maintained during the course of the reaction.[2]

10 Pretsch, E.; Seibl, J.; Simon, W. Spectral Data for Structure Determination of Organic Compounds, 2nd Edition, Fresenius, W.; Huber, J.F.K.; Pungor, E.; Rechnitz, G.A.; Simon, W.; West. T.S., Eds.; Springer-Verlag, New York, 1989, p. H-15.

11 The relative populations of 2'-and 3'-endo conformations of the nucleosides were determined from their 2D-NOESY spectra, by a measurement of the volume of the cross peaks of H-2 and H-2' (β) versus H-2 and H-3' and divided by the sum of both cross-peak volumes.

12 Rosenmeyer, H.; Toth, G.; Golankiewicz, B.; Kazimierczuk, Z.; Bourgeois, W.; Kretschmer, U.; Muth, H.-P.; Seela, F. J. Org. Chem. 1990, 55, 5784.

13 Curiously, when the ammonolysis was conducted at 100 °C, there was extensive decomposition and no products could be isolated.

14 The 2D-NOESY spectrum of the 2'-deoxy-3-deazaguanosine indicates it prefers an 2'-endo/anti conformation.

15 At room temperature, nucleosides in solution exist in discrete *syn* or *anti*-conformational ranges about the glycosidic bond. Though the barrier between these ranges is low (= 25 kJ/mol), structural changes like those described in this paper would raise this barrier. If in an enzymatic reaction the initial encounter between an enzyme and its substrate is fast compared to the conformational interchange, the enzyme can distinguish between the different conformers. See: Birnbaum, G.I.; Shugar, D. "Biologically Active Nucleosides and Nucleotides: Conformational Features and Interactions with Enzymes" in Nucleic Acid Structure, Part 3, S. Neidle, Ed. VCH Publishers, 1987.

Received 10/22/92
Accepted 3/3/93