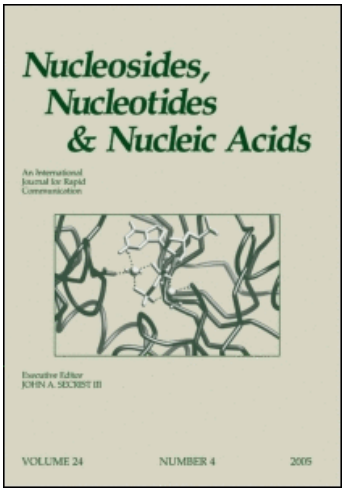

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

4-Substituted-5(3)-carbamoyl-3(5)-(2-deoxy-β-D-ribofuranosyl)pyrazoles. Application of Palladium Catalyzed Glycal Coupling Methodology to the Synthesis of Pyrazofurin Analogs

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To cite this Article Erion, Mark D. and Rydzewski, Robert M.(1997) '4-Substituted-5(3)-carbamoyl-3(5)-(2-deoxy-β-D-ribofuranosyl)pyrazoles. Application of Palladium Catalyzed Glycal Coupling Methodology to the Synthesis of Pyrazofurin Analogs', Nucleosides, Nucleotides and Nucleic Acids, 16: 3, 315 — 337
To link to this Article: DOI: 10.1080/07328319708001352
URL: http://dx.doi.org/10.1080/07328319708001352

NUCLEOSIDES & NUCLEOTIDES, 16(3), 315-337 (1997)

4-SUBSTITUTED-5(3)-CARBAMOYL-3(5)-(2-DEOXY-β-D-RIBO-FURANOSYL)PYRAZOLES. APPLICATION OF PALLADIUM CATALYZED GLYCAL COUPLING METHODOLOGY TO THE SYNTHESIS OF PYRAZOFURIN ANALOGS[1]

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Gensia, Inc., 9390 Towne Centre Drive, San Diego, CA 92121

ABSTRACT

Analogs of the C-nucleoside pyrazofurin were prepared in 7-9 steps using a key Pd(0)-catalyzed coupling reaction between protected iodopyrazoles **6a** and **6b** and glycal **8** to form the glycosyl bond. Conditions for this reaction were improved from those previously described for related reactions in order to maximize product yields and eliminate the need for triphenylarsine.

INTRODUCTION

C-nucleosides are nucleoside analogs in which the C-1 carbon of the ribose moiety is linked to the heterocyclic base via a carbon-carbon bond.[2] Interest in these compounds stems from their stability to deribosylations, an attribute which they share with carbocyclic nucleosides.[3] One C-nucleoside that has been extensively studied is **1**, the C-nucleoside analog of adenosine, formycin A.[4] In some cases, proteins which recognize adenosine also

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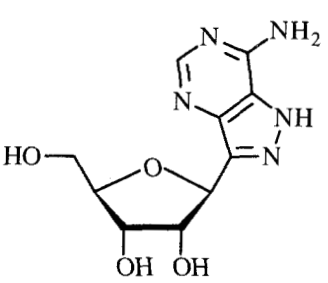

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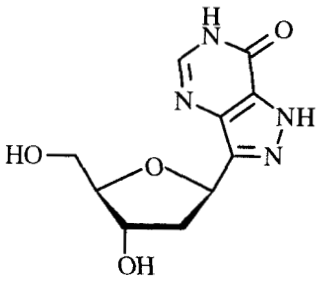

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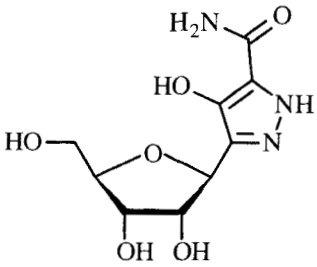

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recognize **1**, while in other cases the rather subtle difference in structures results in a dramatic change in biological activity. For example, **1** is an efficient substrate of adenosine kinase[5] but fails to bind to A1 or A2 receptors. Structural differences between nucleosides and their corresponding C-nucleoside analogs may account for the observed biological differences. X-ray structural studies of **1** indicate that the glycosyl bond is slightly longer than that observed for adenosine.[6] This increase in length is thought to increase rotation and therefore conformational freedom[7] about the glycosidic bond and may in turn account for the syn or the unusual "high anti" conformations often observed for C-nucleosides.[8]

Despite the potential of C-nucleosides as therapeutically important agents, relatively few analogs have been made due to the synthetic difficulty involved in forming the carbon-carbon glycosyl bond. In contrast to nucleoside synthesis strategies which generally involve Vorbrüggen couplings[9] or anionic displacements of 1-substituted sugars with heterocyclic bases, C-nucleosides have required longer, more arduous routes. Typically, the heterocyclic base is built up from ribose analogs substituted at C-1 by cyano,

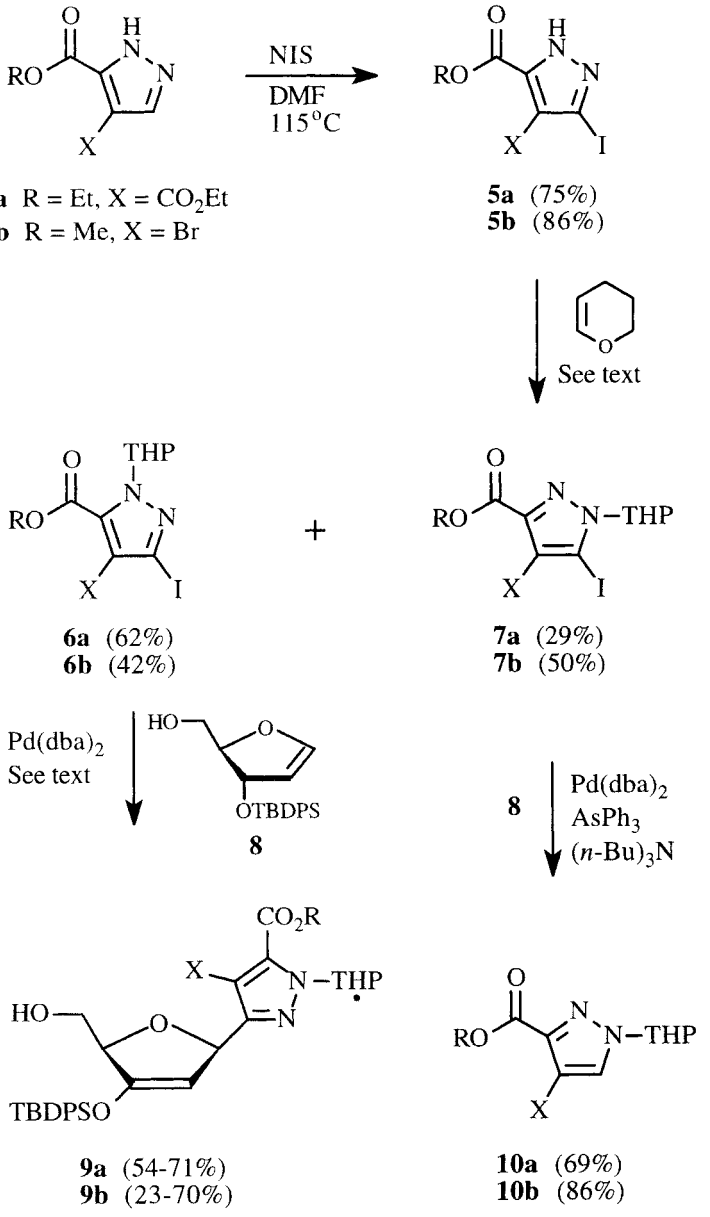
carboxyl, or malonyl groups. Overall yields are often low for these non-convergent approaches.

The methodology of Daves *et al.* [10] in which heteroaryl iodides were coupled to furanose glycals[11] using palladium(0) catalysis seemed attractive as a potential method of synthesizing pyrazole C-nucleosides, especially given the regio- and stereoselectivity of the reaction. Previously, 2'-deoxy formycin B (**2**) was prepared using this convergent strategy.[12] Furthermore, indications are that this approach may be quite versatile for heteroaryl iodides provided that suitable N-protection is employed.[13] As reported herein, we optimized this coupling reaction and used it to synthesize analogs of pyrazofurin (**3**), a natural product with antiviral and anticancer activity[14], thereby exploring the relatively short palladium catalyzed coupling route to pyrazole C-nucleosides.

RESULTS AND DISCUSSION

The preparation of the requisite iodopyrazoles began (Scheme 1) with the iodination of pyrazole **4a**[15] to give **5a**, which, although homogeneous by TLC, proved to have minor impurities by proton NMR and elemental analysis. Further purification, however, proved unnecessary, as crude **5a** was suitable for N-protection. As expected two products, (**6a** and **7a**) were obtained. The ratio of the two products varied somewhat with the reaction conditions, with the higher R_f product predominating under apparent kinetic conditions (CCl_4, 0°C, 10 min). NMR methods did not differentiate between the isomers, and indeed, the positive identification of alkylated pyrazole regioisomers has proven problematic in the past.[16] Structural assignments for **6a** and **7a** were therefore based on results obtained in the subsequent palladium catalyzed coupling of each compound with glycal **8.**[17]

Using the previously described and optimized coupling conditions,[12] the higher R_f pyrazole **6a** was treated with glycal **8** in the presence of triphenylarsine, bis(dibenzylideneacetone)palladium(0), and tri-*n*-butylamine in acetonitrile to give desired C-nucleoside **9a** in a 54% yield as an inseparable mixture of diastereomers epimeric at the



4a R = Et, X = CO_2Et
4b R = Me, X = Br

5a (75%)
5b (86%)

6a (62%)
6b (42%)

7a (29%)
7b (50%)

8

9a (54-71%)
9b (23-70%)

10a (69%)
10b (86%)

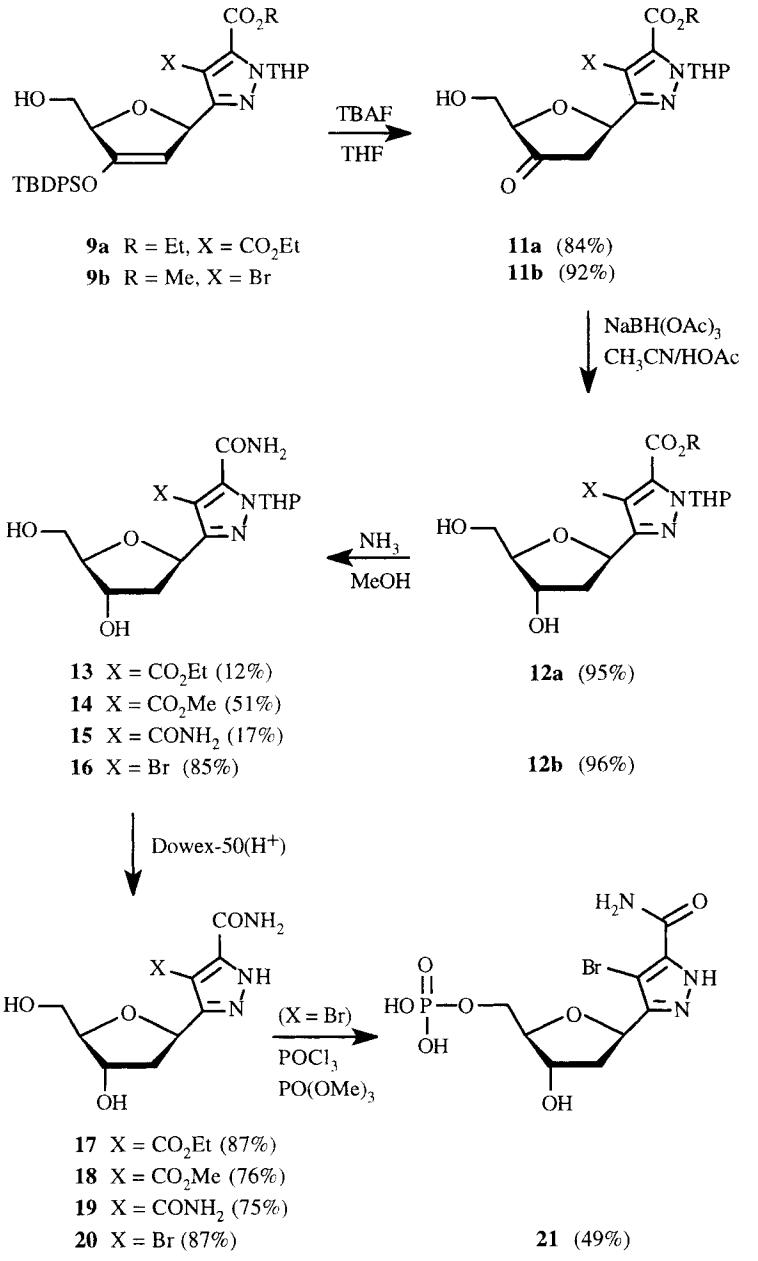
Scheme 1

THP chiral center . The lower R_f pyrazole **7a**, however, afforded only the des-iodo pyrazole **10a** under the same conditions. Dehalogenation occurs via the breakdown of the heteroaryl palladium adduct, and is frequently the major side reaction in insufficiently reactive palladium couplings. These results support the assigned structures for **6a** and **7a**, since the steric effect of the bulky THP group of the N-2 alkylated regioisomer **7a** is likely to hinder reactions at the adjacent carbon atom. Steric arguments have been used in the past to assign the structures of N-protected pyrazoles.[18]

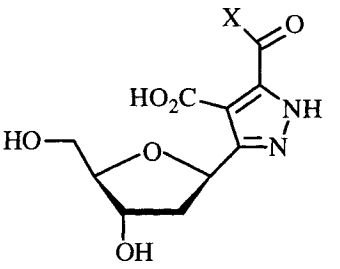
Transformations of the 2'-deoxyribose section of **9a** were straightforward, as shown in Scheme 2. Desilylation was followed by stereospecific reduction[12] of the resulting ketone **11a** to afford **12a**. At that point transformations of the pyrazole substituents were carried out. Ammonolysis of diester **12a** was expected to produce **13** regioselectively based on previous results for related *1H*-pyrazole-4,5-diesters.[15] Instead, treatment of **12a** with methanolic ammonia led to the formation of the expected product **13** (12%) along with two other, unanticipated products. The major product was methyl ester **14** (51%) which resulted from transesterification of the ester at C-4. The other product proved to be the bis-amide, **15**, a result of over-reaction. Deprotection of the amidopyrazoles with Dowex-50(H^+) resin gave C-nucleosides **17-19** in good yields.

Plans for the further C-4 transformation of **14** were hindered by our inability to convert **14** to the pyrazole-4-carboxylic acid **22**. Saponification of **14** led to the formation of a *less polar* mixture of diastereomers by TLC and HPLC, which upon treatment with Dowex-50(H^+) resin gave a highly polar, granular, insoluble product. Proton NMR and electrospray mass spectroscopy indicated that this product was not the desired amido acid **22**, but was instead the crude diacid **23** which, due to its extreme insolubility, proved unusable for further reactions.[19]

The preparation of 4-bromopyrazole C-nucleoside **20** was therefore accomplished via total synthesis from **4b**. Using the elegant pyrazole metallation chemistry of Holzer et al. (Scheme 3), compound **24**[20] was regioselectively metallated and reacted with methyl chloroformate to afford ester **25** in an 82% yield. Deprotection of this N-benzene-



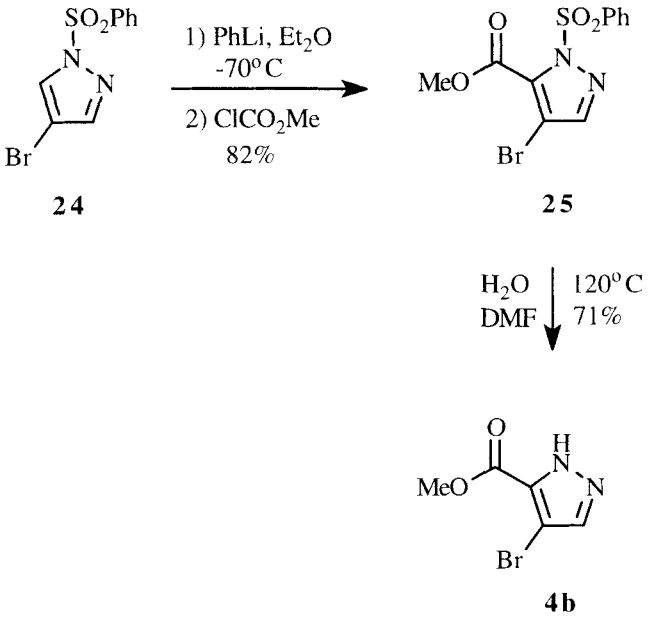
Scheme 2



22 X = NH_2
23 X = OH

sulfonylpyrazole to generate **4b** was accomplished under mild conditions by heating in moist DMF followed by recrystallization. Iodination of **4b** was followed by tetrahydropyranylation to give a mixture of two products, the higher R_f **6b** and the lower R_f **7b**. The structural assignments for these isomers were again determined by their subsequent reactivity in the coupling reaction. In this case, the best obtainable ratio of the desired N-1 product **6b** to the N-2 product **7b** was less favorable than for the previous analogs **6a** and **7a** (0.84:1 for the **b** series versus 2.1:1 for the **a** series). However, since the undesired N-2 product **7b** could be "recycled" in >90% yield by deprotection with Dowex-50(H^+) resin in methanol to regenerate the starting pyrazole **5b**, this was not an impediment to the synthesis of **20**.

Coupling **6b** with glycal **8** under the previously established conditions[12] gave two new products in a 1:1 ratio in relatively low yield (23% total). Chromatographic isolation of each product showed that the coupling of the 4-bromo-3-iodopyrazole **6b** occurred only at C-3 and not at C-4.[21] The products had nearly identical proton and carbon NMR spectra consistent with separable diastereomers of the desired **9b** epimeric at the THP chiral center. Why diastereomers of **9b** diverged in R_f value while diastereomers of **9a** did not is unclear. In any case, for operational simplicity, a mixture of the two separable diastereomers (and the small amount of **8** eluting between them) was used in the next step without adverse effect as shown in Scheme 2. Conversion of this mixture to **20** was readily accomplished in 4 steps with an overall yield of 65%.



Scheme 3

The low yield in the coupling reaction of **6b** and the use of toxic triphenylarsine were considered potential limitations in the syntheses of pyrazole C-nucleosides in this series, particularly upon scale-up. Consequently, alternative conditions for the iodopyrazole-glycal coupling reaction were explored in a series of microscale experiments where the palladium catalyst, ligand, and solvent were systematically varied and the results assessed qualitatively by TLC. The choice of solvent proved to be crucial. Coupling **6b** with **8** in either DMF or acetonitrile gave the desired product in a low yield and with many other minor side-products. The use of neat triethylamine as solvent, however, provided a more heterogeneous reaction mixture, but, to our surprise, gave a much cleaner reaction. This also allowed for replacement of the ligand triphenylarsine with the less toxic tri-*o*-tolylphosphine which was less effective in other solvents. Thus, the yield of **9b** diastereomers was increased to 70% under these conditions. An increase in the yield of **9a** under the modified conditions was significant but less pronounced (71% versus 54% under

the previous conditions). This indicates that these modified conditions may prove to have some general utility for palladium catalyzed iodoarene-glycal couplings.

Desilylation of the mixture of diastereomers of **9b** followed by reduction gave **12b** which upon treatment with methanolic ammonia gave amidopyrazole **16** with no evidence of competing addition-elimination at C-4.[22] Deprotection of **16** furnished the desired 4-bromo-C-nucleoside **20** in a 75% overall yield from **9b**.

For the sake of biochemical studies, **20** was phosphorylated with phosphoryl chloride in trimethyl phosphate. Reverse phase HPLC analysis indicated the formation of two new, faster eluting products, one of which converted to the other within several hours in aqueous solution. It was surmised that the transiently formed product is most likely an bisphosphorylated product phosphorylated at O-5' and N-1 or N-2 of the pyrazole ring. Like other N-phosphorylated nucleosides, this species would be expected to exhibit hydrolytic instability.[23] Preparative HPLC purification of the reaction mixture afforded **21** in a 49% yield, thus completing the synthesis of this series of 4-substituted-2'-deoxy-pyrazofurin analogs.

EXPERIMENTAL SECTION

General. Glassware was oven dried (125°C, 2h) and all reactions were performed with magnetic stirring under dry nitrogen. Acetonitrile, DMF, and CH_2Cl_2 were dried over activated 4A molecular sieves. THF was freshly distilled from sodium metal / benzophenone under nitrogen. Anhydrous Et_2O was purchased from Aldrich. Flash chromatography was done under nitrogen pressure using silica gel 60A (230-400 mesh). Silica gel GF analytical TLC plates (0.25mm) were purchased from Analtech, Inc., Newark, DE and were visualized at 254 nM or with phosphomolybdic acid. Melting points are uncorrected. UV spectra (220-400nM) were obtained in methanol followed by addition of 10 μL 6.0N NaOH to the 1.0 cc solvent cell, bringing the pH of neutral samples to approximately 14. ^1H and ^{13}C NMR spectra were obtained at 200 MHz and 50 MHz,

respectively and J values are given in Hertz. Owing to S/N, tautomeric, and diastereomeric considerations, some quaternary carbon signals are absent from the ^{13}C data. High resolution and LSIMS mass spectra were obtained at the Scripps Research Institute, San Diego, CA and electrospray mass spectra came from Mass Consortium, San Diego, CA.

Analytical HPLCs were run on an HPLC system equipped with a 4.6X250 mm YMC ODS-AQ 5μ column held at 40°C. The flow rate was 1.0 ml/min and the detector wavelength was 230 nM. Methanol was used as the organic eluent, with the initial concentration (30%) being held for 5.0 min followed by a 15.0 min linear gradient to the final concentration (60%), which was then held for 5.0 min

General Procedure for the Iodination of Pyrazoles 4a and 4b. The 3(5),4-disubstituted pyrazole (20 mmol) and N-iodosuccinimide (40 mmol) were dissolved in DMF (50 mL) and heated at an oil bath temperature of 115° C for 4.5 h. Rotary evaporation of the solvent was followed by partitioning of the residue between H_2O and CH_2Cl_2. Aqueous sodium thiosulfate was added to decolorize the layers. The organic phase was dried ($MgSO_4$), filtered, and evaporated, and the residue was flash chromatographed using the solvent system noted.

Diethyl 3(5)-iodopyrazole-4,5(3)-dicarboxylate (5a). Chromatography with 3% MeOH/CH_2Cl_2 gave 5.08g (75%) slightly impure **5a** as an oil that was used without further purification. Analytical TLC (5%MeOH/CH_2Cl_2) R_f 0.43. UV (MeOH) sh. 230; (MeOH+NaOH) λ_{max} 256 (6,700); ^1H NMR ($CDCl_3$) δ 4.42 (m, 4H, OCH_2), 1.41 (m, 6H, CH_3); MS (electrospray) $(M-H)^-$ 337.

Methyl 4-Bromo-3(5)-iodopyrazole-5(3)-carboxylate (5b). Chromatography with 30-35% EtOAc/hexane gave 5.72g (86%) of crystalline **5b**, mp 136.5-137.5 °C. Analytical TLC (30% EtOAc/hexane) R_f 0.40. UV (MeOH) λ_{max} 234 (8,800), λ_{min} 224, sh. 255; (MeOH+NaOH) λ_{max} 247 (10,900), λ_{min} 228; ^1H NMR (DMSO-d_6) δ 3.85 (s, 3H, Me); MS (LSIMS) (MH^+) 331/333. Anal. Calcd for $C_5H_4BrIN_2O_2$: C, 18.15; H, 1.22; N, 8.47; Br, 24.15; I, 38.35. Found: C, 18.31; H, 1.21; N, 8.38; Br, 23.98; I, 38.08.

General procedure for the N-protection of 5a and 5b. To a solution of the trisubstituted pyrazole (3.0 mmol), 3,4-dihydro-2*H*-pyran (1.01g, 12 mmol), and the appropriate solvent (35 mL) at the desired temperature was added a solution of p-toluenesulfonic acid monohydrate (.015 g, .079 mmol) dissolved in THF (3.0 mL). After 3 h, the acid was neutralized with triethylamine and the solvent was removed *in vacuo*. Flash chromatography furnished the N1- and N2- substituted products as noted below.

Diethyl 3-Iodo-1-(tetrahydropyran-2-yl)pyrazole-4,5-dicarboxylate (6a) and Diethyl 5-Iodo-1-(tetrahydropyran-2-yl)pyrazole-3,4-dicarboxylate (7a). CCl_4 was the solvent, and the reaction was carried out at 0-5°C. Chromatography with 20-25% EtOAc/hexane afforded the faster eluting **6a** (0.785g, 62%), an oil. Analytical TLC (20% EtOAc/hexane) R_f 0.52. ^1H NMR ($CDCl_3$) δ 5.71 (dd, J=2.6, 8.2, 1H, OCHN), 4.36 (m, 4H, CH_2), 3.85 (m, 1H, THP), 3.62 (m, 1H, THP), 2.36 (m, 1H, THP), 2.03 (m, 2H, THP), 1.61 (m, 3H, THP), 1.36 (m, 6H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.4, 159.8, 137.0, 119.1, 97.1, 86.7, 67.2, 62.8, 61.3, 29.1, 24.8, 21.5, 14.3, 14.1; MS (electrospray) $(MH)^+$ 423. Anal. Calcd for $C_{14}H_{19}IN_2O_5$: C, 39.83; H, 4.54; N, 6.63. Found: C, 39.59; H, 4.50; N, 6.43.

Also obtained was the slower eluting **7a** (0.366g, 29%) as an oil. Analytical TLC (20% EtOAc/hexane) R_f 0.38. ^1H NMR ($CDCl_3$) δ 5.57 (dd, J=2.8,9.7, 1H, OCHN), 4.38 (m, 4H, CH_2), 4.11 (m, 1H, THP), 3.70 (m, 1H, THP), 2.50 (m, 1H, THP), 1.58-2.22 (m, 5H, THP), 1.37 (m, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 162.1, 145.0, 120.2, 88.5, 87.7, 68.0, 62.0, 61.5, 29.3, 24.8, 22.4, 14.3. Anal. Calcd for $C_{14}H_{19}IN_2O_5$: C, 39.83; H, 4.54; N, 6.63. Found: C, 39.44; H, 4.46; N, 6.39.

Methyl 4-Bromo-3-iodo-1-(tetrahydropyran-2-yl)-pyrazole-5-carboxylate (6b) and Methyl 4-Bromo-5-iodo-1-(tetrahydropyran-2-yl)pyrazole-3-carboxylate (7b). THF was used at ambient temperature. Chromatography with 15-25% EtOAc/hexane gave 0.523g (42%) of the faster eluting **6b**, mp 107-108° C. Analytical TLC (15% EtOAc/hexane) R_f 0.63. ^1H NMR ($CDCl_3$) δ 6.13 (dd, J=2.6, 9.5,

1H, OCHN), 3.90-4.12 (m, 1H, THP), 3.95 (s, 3H, OMe), 3.60-3.81 (m, 1H, THP), 2.30-2.58 (m, 1H, THP), 1.89-2.21 (m, 2H, THP), 1.50-1.89 (m, 3H, THP); ^{13}C NMR ($CDCl_3$) δ 158.0, 131.9, 109.6, 103.6, 86.3, 68.1, 52.8, 29.1, 25.0, 22.5. Anal. Calcd for $C_{10}H_{12}BrIN_2O_3$: C, 28.94; H, 2.91; N, 6.75; Br, 19.25; I, 30.58. Found: C, 28.94; H, 2.94; N, 6.69; Br, 19.44; I, 30.81.

Also obtained was 0.621g (50%) of the slower eluting **7b**, mp 110-111° C. Analytical TLC (15% EtOAc/hexane) R_f 0.43. ^{1}H NMR ($CDCl_3$) δ 5.45 (dd, J=2.7, 9.7, 1H, OCHN), 3.94-4.15 (m, 1H, THP), 3.95 (s, 3H, OMe), 3.64-3.80 (m, 1H, THP), 2.48-2.64 (m, 1H, THP), 1.51-2.25 (m, 5H, THP); ^{13}C NMR ($CDCl_3$) δ 160.7, 141.6, 107.6, 91.9, 88.6, 68.1, 52.5, 29.0, 24.7, 22.3. Anal. Calcd for $C_{10}H_{12}BrIN_2O_3$: C, 28.94; H, 2.91; N, 6.75; I, 30.58. Found: C, 28.98; H, 2.75; N, 6.71; I, 30.61.

General Procedures for the Coupling of Iodopyrazoles with 8.

Method A[12]**:** A mixture of bis(dibenzylideneacetone)palladium(0) (0.195g, 0.34 mmol) and triphenylarsine (0.208g, 0.51 mmol) was stirred at rt for 0.5 h, then added to a solution of **8**[17] (1.50g, 4.2 mmol), the iodopyrazole (3.4 mmol), and tri-*n*-butylamine (1.21 mL, 5.1 mmol) in acetonitrile (20 mL). The reaction mixture was heated to reflux under Ar for 12-20 h, then cooled and rotary evaporated. The residue was flash chromatographed using the solvent system noted.

Method B : A mixture of the bis(dibenzylideneacetone)palladium(0) (0.128g, 0.22 mmol) and tri-*o*-tolylphosphine (0.135g, 0.44 mmol) in triethylamine (50 mL) was stirred at rt for 0.25 h, and the iodopyrazole (2.77 mmol) and a solution of **8** (0.786g, 2.22 mmol) in triethylamine (5 mL) were added. The reaction mixture was heated at bath temperature 85°C under Ar for 15 h, then cooled and rotary evaporated. The residue was flash chromatographed using the solvent system noted.

(2'*R*)-*cis*-3-[2,5-Dihydro-4[[(1,1dimethylethyl)diphenylsilyl]oxy]-5-(hydroxymethyl)-2-furanyl]-4,5-bis(carboethoxy)-1-(tetrahydro-pyran-2-yl)pyrazole (9a) (Mixture of diastereomers). Method A yield: 54%, Method B yield: 71%. Chromatography with 25-32.5% EtOAc/hexane gave an oil. Analytical TLC

(25% EtOAc/hexane) R_f 0.43. ^1H NMR ($CDCl_3$) δ 7.70-7.84 (m, 4H, Ph), 7.22-7.49 (m, 6H, Ph), 6.10 (m, 1H, 1'), 5.59 (m, 1H, OCHN), 4.87 (m, 1H, THP), 4.78 (m, 1H, 2'), 4.25-4.48 (m, 3H, 4',OCH_2), 3.52-4.21 (m, 5H, 5', OCH_2 , THP), 1.39-2.48 (m, 6H, THP), 1.33 (apparent dt, J=2.0, 7.0, 6H, CH_3), 1.06 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 161.6, 160.5, 154.5, 154.3, 149.1, 149.0, 137.1, 136.6, 135.6, 135.3, 131.8, 131.1, 130.0, 127.8, 127.5, 127.4, 111.3, 110.9, 102.5, 86.4, 86.3, 84.1, 78.1 (2 peaks), 66.7, 66.4, 62.3, 60.6, 60.5, 28.5, 28.2, 26.3, 24.7, 24.6, 21.2, 20.9, 19.2, 13.8. Anal. Calcd for $C_{35}H_{44}N_2O_8Si \cdot 1/4\ H_2O$: C, 64.34; H, 6.87; N, 4.29. Found: C, 64.38; H, 6.60; N, 4.19.

(2'*R*)-*cis*-3-[2,5-Dihydro-4[[(1,1dimethylethyl)diphenylsilyl]oxy]-5-(hydroxymethyl)-2-furanyl]-4-bromo-5-carbomethoxy-1-(tetrahydropyran-2-yl)pyrazole (9b High R_f diastereomer and 9b Low R_f diastereomer).

9b High R_f diastereomer Method A yield: 11%, Method B yield: 35%.

Chromatography with 25% EtOAc/hexane gave an oil. Analytical TLC (2.5% acetone/toluene) R_f 0.39. ^1H NMR ($CDCl_3$) δ 7.58-7.87 (m, 4H, Ph), 7.36-7.52 (m, 6H, Ph), 6.07 (dd, J=1.6, 7.5, 1H, OCHN), 5.79 (dd, J=1.7, 3.1, 1H, 1'), 4.79 (m, 1H, 2'), 4.44 (m, 1H, THP), 4.31 (m, 1H, 4'), 3.87-4.03 (m, 5H, 5', OMe), 3.72 (m, 1H, THP), 2.27-2.58 (m, 1H, THP), 1.90-2.25 (m, 2H, THP), 1.54-1.82 (m, 3H, THP), 1.08 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 158.8, 152.2, 149.9, 135.9, 135.6, 135.0, 132.0, 131.2, 130.4, 130.3, 128.1, 128.0, 101.7, 99.4, 86.4, 84.4, 77.4, 68.0, 62.6, 52.6, 28.4, 26.8, 26.6, 25.2, 22.7, 19.5; HRMS calcd for $C_{31}H_{37}BrN_2O_6Si$: $(m+Cs)^+$ 773.0659, found 773.0680.

9b Low R_f diastereomer Method A yield: 12%, Method B yield: 35%.

Chromatography with 25% EtOAc/hexane gave an oil. Analytical TLC (2.5% acetone /toluene) R_f 0.32. ^1H NMR ($CDCl_3$) δ 7.68-7.90 (m, 4H, Ph), 7.26-7.51 (m, 6H, Ph), 6.06 (dd, J=2.5,10, 1H, OCHN), 5.75 (dd, J=1.7,3.0, 1H, 1'), 4.78 (m, 1H, 2'), 4.61 (m, 1H, THP), 4.26 (m, 1H, 4'), 3.89-4.10 (m, 5H, 5', OMe), 3.70 (m, 1H, THP), 2.26-2.51 (m, 1H, THP), 1.92-2.24 (m, 2H, THP), 1.53-1.85 (m, 3H, THP), 1.05 (s,

9H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 159.1, 152.1, 150.0, 136.0, 135.6, 135.0, 131.8, 131.4, 130.4, 130.2, 128.1, 127.8, 101.7, 98.6, 86.3, 84.4, 77.7, 68.1, 62.6, 52.6, 28.7, 26.6, 25.1, 22.8, 19.5; HRMS calcd for $C_{31}H_{37}BrN_2O_6Si$: $(m+Cs)^+$ 773.0659, found 773.0678.

Diethyl 1-(tetrahydropyran-2-yl)pyrazole-3,4-dicarboxylate (10a). Method A yield: 69%. Chromatography with 22.5% EtOAc/hexane gave an oil. Analytical TLC (25% EtOAc/hexane) R_f 0.29. ^1H NMR ($CDCl_3$) δ 8.13 (s, 1H, ArH), 5.45 (dd, J=2.9, 9.0, 1H, OCHN), 4.43 (q, J=7.0, 2H, OCH_2), 4.31 (q, J=7.2, 2H, OCH_2), 4.07 (m, 1H, THP), 3.70 (m, 1H, THP), 1.60-2.22 (m, 6H, THP), 1.41 (t, J=7.0, 3H, CH_3), 1.35 (t, J=7.2, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 162.1, 161.9, 143.6, 132.2, 115.4, 88.5, 68.0, 61.8, 60.9, 31.1, 24.9, 22.0, 14.4. Anal. Calcd for $C_{14}H_{20}N_2O_5 \cdot 1/4\ H_2O$: C, 55.89; H, 6.87; N, 9.31. Found: C, 55.75; H, 6.63; N, 9.01.

Methyl 4-Bromo-1-(tetrahydropyran-2-yl)pyrazole-3-carboxylate (10b). Method A yield: 86%. Chromatography with 25% EtOAc/hexane gave an oil. Analytical TLC (25% EtOAc/hexane) R_f 0.32. ^1H NMR ($CDCl_3$) δ 7.75 (s, 1H, ArH), 5.44 (dd, J=2.6, 9.1, 1H, OCHN), 4.08 (m, 1H, THP), 3.95 (s, 3H, OMe), 3.70 (m, 1H, THP), 1.88-2.21 (m, 3H, THP), 1.57-1.85 (m, 3H, THP); ^{13}C NMR ($CDCl_3$) δ 161.6, 140.3, 130.4, 97.0, 89.1, 68.1, 52.3, 31.0, 24.8, 22.0. Anal. Calcd for $C_{10}H_{13}BrN_2O_3$: C, 41.54; H, 4.53; N, 9.69; Br, 27.64. Found: C, 41.53; H, 4.50; N, 9.46; Br, 27.93.

General Procedure for the Deprotection of Deoxynucleoside Silyl Enol Ethers 9a and 9b. A solution of the enol ether (2.0 mmol) and THF (25 mL) was cooled to 0-5°C and acetic acid (0.46mL, 8.0mmol) was added. The solution of 1.0M tetrabutylammonium fluoride in THF (4.0mL, 4.0 mmol) was added dropwise. After 10 min, the solvent was evaporated *in vacuo* and the residue was triturated with 50% EtOAc/hexane (5.0 mL) and filtered. The filtrate was flash chromatographed using the solvent system noted. Products obtained showed a tendency to decompose with time and were quickly used without further purification for the subsequent reactions.

3-(β-D-*glycero*-Pentofuran-3-ulos-1-yl)-4,5-bis(carboethoxy)-1-(tetrahydropyran-2-yl)pyrazole (11a) (Mixture of diastereomers). Reaction of **9a** followed by chromatography with 60% EtOAc/hexane gave **11a** (0.687g, 84%) as an oil. Analytical TLC (50% EtOAc/hexane) R_f 0.36. ^{1}H NMR ($CDCl_3$) δ 5.85 (m, 1H, 1'), 5.66 (m, 1H, OCHN), 4.26-4.55 (m, 4H, OCH_2), 4.13 (bs, 1H, 5'), 3.72-4.03 (m, 3H, 4', 5', THP), 3.56-3.71 (m, 1H, THP), 2.79-3.08 (m, 2H, 2'), 2.18-2.43 (m, 1H, THP), 1.86-2.17 (m, 2H, THP), 1.53-1.86 (m, 3H, THP), 1.40 (t, J=7.2, 3H, CH_3), 1.33 (t, J=7.1, 3H, CH_3).

3-(β-D-*glycero*-Pentofuran-3-ulos-1-yl)-4-bromo-5-(carbomethoxy)-1-(tetrahydropyran-2-yl)pyrazole (11b) (Mixture of diastereomers). Reaction of the **9b** diastereomeric mixture followed by chromatography with 50% EtOAc/hexane gave **11b** (0.745g, 92%) as an oil. ^{1}H NMR (DMSO-d_6) δ 6.00 (dd, J=2.2, 11, 1H, OCHN), 5.35 (m, 1H, 1'), 4.89 (m, 1H, 5'-OH), 4.03 (m, 1H, 4'), 3.92 (s, 3H, OMe), 3.85 (m, 1H, THP), 3.59 (m, 3H, 5', THP), 2.71-3.05 (m, 2H, 2'), 1.47-2.28 (m, 6H, THP).

General Procedure for the Reduction of 3'-Ketodeoxynucleosides 11a and 11b. To a solution of the ketodeoxynucleoside (1.2 mmol) in acetonitrile/HOAc (20 mL of each) at -15°C was added the sodium triacetoxyborohydride (0.339g, 1.6 mmol). After 15 min, the reaction mixture was warmed and rotary evaporated. The residue was treated with 10% MeOH/CH_2Cl_2 (2 mL), filtered, and the filtrate was flash chromatographed using the specified solvent system.

3-(2-Deoxy-β-D-ribofuranosyl)-4,5-bis(carboethoxy)-1-(tetrahydropyran-2-yl)pyrazole (12a) (Mixture of diastereomers). Chromatography with 7.5% MeOH/CH_2Cl_2 gave an oil (0.472g, 95%). Analytical TLC (5% MeOH/CH_2Cl_2) R_f 0.41. ^{1}H NMR ($CDCl_3$) δ 5.51-5.68 (m, 2H, 1', OCHN), 4.51 (m, 1H, 3'), 4.15-4.35 (m, 4H, OCH_2), 3.99 (m, 1H, THP), 3.76-3.94 (m, 2H, 4', 5'), 3.47-3.68 (m, 2H, 5', THP), 3.43 (s, 1H, OH), 1.43-2.42 (m, 8H, 2', THP), 1.31 (t, J=7.0, 3H, CH_3), 1.25 (t, J=7.0, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 162.4, 160.5, 154.5, 154.3, 137.2, 112.2, 111.9, 87.4, 86.8, 86.6, 74.1, 73.9, 72.4, 72.3, 67.3, 62.6, 61.2, 42.3, 29.1, 28.9,

24.8, 21.6, 14.3, 14.2; HRMS calcd for $C_{19}H_{28}N_2O_8$: $(m+Na)^+$ 435.1743. Found: 435.1775.

3-(2-Deoxy-β-D-ribofuranosyl)-4-bromo-5-(carbomethoxy)-1-(tetrahydropyran-2-yl)pyrazole (12b) (Mixture of diastereomers). Chromatography with 5-7.5% MeOH/CH_2Cl_2 gave an oil (0.469g, 96%). Analytical TLC (5% MeOH/CH_2Cl_2) R_f 0.29. ^1H NMR (DMSO-d_6) δ 6.00 (dd, J=2.2, 7.6, 1H, OCHN), 5.10 (dd, J=5.8, 9.8, 1H, 1'), 4.24 (dd, J=2.6, 5.8, 1H, 3'), 3.91 (s, 3H, Me), 3.82 (m, 2H, THP), 3.58 (m, 1H, 4'), 3.39 (pseudo t, J=5.1, 2H, 5'), 2.28-2.49 (m, 1H, 2'), 2.10-2.28 (m, 1H, THP), 1.79-2.08 (m, 3H, 2', THP), 1.43-1.78 (m, 3H, THP). Proton decoupling at 3' (δ4.24) changed the multiplicity at H-2' (δ2.28-2.49), while decoupling at OCHN (δ6.00) simplified the resonance at δ2.10-2.28 (THP). ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.4, 151.8, 151.6, 87.7, 87.6, 86.2, 73.4, 73.3, 73.0, 68.2, 68.1, 63.1, 63.0, 52.6, 41.5, 41.4, 28.9, 25.0, 22.7; HRMS calcd for $C_{15}H_{21}BrN_2O_6$: $(m+Na)^+$ 427.0481. Found: 427.0497.

General Procedure for the Ammonolysis of 5-carboxyalkylpyrazoles 12a and 12b. A solution of the pyrazole (1.0 mmol) and 9.5 M methanolic ammonia (5.0 mL) was stirred at the specified temperature for the specified time. The solution was then rotary evaporated and the residue was flash chromatographed using the solvent system specified.

3-(2-Deoxy-β-D-ribofuranosyl)-4-carboethoxy-5-carbamoyl-1-(tetrahydropyran-2-yl)pyrazole (13) (Mixture of diastereomers). The reaction of **12a** was carried out at ambient temperature for 48 h. Chromatography using 7.5-20% MeOH/CH_2Cl_2 gave the fastest eluting product as a foam (0.046g, 12%). Analytical TLC (7.5% MeOH/CH_2Cl_2) R_f 0.47. ^1H NMR (DMSO-d_6) δ 8.21 (bs, 1H, NH), 7.95 (bs, 1H, NH), 5.40-5.58 (m, 2H, 1', OCHN), 5.06 (d, J=4.1, 1H, 3'-OH), 4.65 (m, 1H, 5'-OH), 4.09-4.22 (m, 3H, 3', OCH_2), 3.88 (m, 1H, THP), 3.72 (m, 1H, 4'), 3.35-3.56 (m obscured by H_2O, 3H, 5', THP), 1.42-2.40 (m, 8H, 2', THP), 1.24 (t, J=7.0, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 162.0, 160.9, 151.8, 142.1, 109.7, 108.9, 87.2, 84.5, 72.1,

71.1, 71.0, 66.5, 62.0, 59.7, 41.5, 28.5, 24.0, 21.5, 13.6; HPLC: t_r 16.6 min (43.7%), t_r 17.4 min (51.7%). Anal. Calcd for $C_{17}H_{25}N_3O_7 \cdot 1/2\ H_2O$: C, 52.03; H, 6. 55; N, 10.71. Found: C, 51.87; H, 6.57; N, 10.54.

3-(2-Deoxy-β-D-ribofuranosyl)-4-carbomethoxy-5-carbamoyl-1-(tetrahydropyran-2-yl)pyrazole (14) (Mixture of diastereomers). The second product obtained from chromatography of the **12a** reaction mixture as described above was a foam (0.188g, 51%). Analytical TLC (7.5% MeOH/CH_2Cl_2) R_f 0.40. ^{1}H NMR (DMSO-d_6) δ 8.22 (bs, 1H, NH), 7.95 (bs, 1H, NH), 5.46 (m, 2H, 1', OCHN), 5.06 (d, J=5.2, 1H, 3'-OH), 4.64 (apparent dt, J=2.4, 4.0, 1H, 5'-OH), 4.22 (m, 1H, 3'), 3.82-3.97 (m, 1H, THP), 3.71 (s, 4H, 4', OCH_3), 3.23-3.64 (m, 2H, 5', THP), 3.17 (d, J=5.1, 1H, 5'), 1.43-2.44 (m, 8H, 2', THP); MS (electrospray) $(MH)^+$ 370; HPLC: t_r 14.0 min (48.1%), t_r 14.6 min (49.1%).

3-(2-Deoxy-β-D-ribofuranosyl)-4,5-bis(carbamoyl)-1-(tetrahydropyran-2-yl)pyrazole (15) (Mixture of diastereomers). The last product obtained from chromatography of the **12a** reaction mixture as described above was a foam (0.059g, 17%). Analytical TLC (7.5% MeOH/CH_2Cl_2) R_f 0.14. ^{1}H NMR (DMSO-d_6) δ 8.53 (bd, 1H, NH), 7.93 (bs, 1H, NH), 7.67 (bs, 2H, NH), 5.86 (pseudo t, J=7, 1H, 1'), 5.22 (dd, J=3.8, 5.9 Hz, OCHN), 5.14 (d, J=4.3, 1H, 3'-OH), 4.74 (m, 1H, 5'-OH), 4.21 (m, 1H, 3'), 3.88 (bd, J=12, 1H, THP), 3.75 (m, 1H, 4'), 3.29-3.63 (m, 2H, 5', THP), 3.17 (d, J=5.3, 1H, 5'), 1.44-2.52 (m, 8H, 2', THP); HPLC: t_r 13.1 min (45.9%), t_r 13.8 min (53.7%).

3-(2-Deoxy-β-D-ribofuranosyl)-4-bromo-5-carbamoyl-1-(tetrahydro-pyran-2-yl)pyrazole (16) (Mixture of diastereomers). Reaction of **12b** was carried out in a sealed tube at bath temperature 60°C for 20 hr. Chromatography with 10% MeOH/CH_2Cl_2 gave a brittle foam (0.333g, 85%). Analytical TLC (7.5% MeOH/CH_2Cl_2) R_f 0.29. ^{1}H NMR (DMSO-d_6) δ 7.99 (bs, 2H, NH), 5.66 (dd, J=2.5, 9.4, 1H, OCHN), 5.10 (d, J=5.3, 1H, 3'-OH), 5.04 (dd, J=5.9, 9.9, 1H, 1'), 4.67 (apparent q, J=3.2, 1H, 5'-OH), 4.23 (m, 1H, 3'), 3.66-3.92 (m, 2H, THP), 3.52 (m, 1H, 4'), 3.39 (m obscured

by H_2O, 2H, 5'), 1.44-2.47 (m, 8H, 2', THP); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.1, 160.0, 150.9, 150.8, 135.2, 95.6, 95.2, 87.7, 87.6, 86.1, 73.3, 73.0, 72.9, 72.8, 68.2, 68.0, 63.1, 63.0, 41.0, 28.8, 24.9, 22.6. HRMS calcd for $C_{14}H_{20}BrN_3O_5$: $(m+Na)^+$ 412.0484. Found: 412.0499.

General Procedure for the Deprotection of 1-(Tetrahydropyran-2-yl) pyrazoles 13, 14, 15, and 16. A mixture of the pyrazole (0.50 mmol), 95% MeOH (10 mL) for **14**, **15**, and **16** or 95% EtOH (10 mL) for **13** and Dowex 50X8-200 resin (0.700g) (which had been rinsed with the appropriate alcohol and briefly air dried) was stirred at rt for 7 h. The reaction mixture was filtered, the resin rinsed with more alcohol, and the combined filtrate evaporated *in vacuo* . Recrystallization from the specified solvent gave the pure products.

3(5)-(2-Deoxy-β-D-ribofuranosyl)-4-carboethoxy-5(3)-carbamoylpyrazole (17). Reaction of **13** as described above, followed by recrystallization from acetonitrile/ethanol gave the crystalline product (0.130g, 87%), mp 207-208°C. UV (MeOH) sh. 224; (MeOH+NaOH) λ_{max} 257 (8,000), λ_{min} 234; ^1H NMR (DMSO-d_6) δ 13.19 (bs, 1H, pyrazole NH), 7.35-8.50 (bd, 2H, NH), 5.44 (dd, J=5.9, 9.6, 1H, 1'), 5.18 (d, J=3.7, 1H, 3'-OH), 4.83 (t, J=6.1, 1H, 5'-OH), 4.13-4.26 (m, 3H, 3', OCH_2), 3.80 (bs, 1H, 4'), 3.40-3.61 (m, 2H, 5'), 2.17-2.38 (m, 1H, 2'), 1.73-1.97 (m, 1H, 2'), 1.27 (t, J=7.0, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 163.6, 148.1, 87.8, 72.5, 71.3, 61.8, 59.9, 41.7, 13.8; HPLC: t_r 11.8 min (96.3%); HRMS calcd for $C_{12}H_{17}N_3O_6$: $(m+Cs)^+$ 432.0172. Found: 432.0175.

3(5)-(2-Deoxy-β-D-ribofuranosyl)-4-carbomethoxy-5(3)-carbamoyl-pyrazole (18). Reaction of **14** as described above, followed by recrystallization from methanol gave desired product (0.108g, 76%) mp 218.5-219.5°C. UV (MeOH) sh. 224; (MeOH+NaOH) λ_{max} 257 (8,000), λ_{min} 234; ^1H NMR (DMSO-d_6) δ 13.20 (bs, 1H, pyrazole NH), 8.08 (bs, 1H, 1'), 7.58 (bs, 1H, NH), 5.42 (dd, J=5.9, 9.5, 1H, 1'), 5.16 (d, J=3.9, 1H, 3'-OH), 4.80 (bs, 1H, 5'-OH), 4.19 (m, 1H, 3'), 3.72-3.87 (m, 4H, 4', Me), 3.47 (d, J=4.8, 1H, 5'), 3.37 (m, 1H, overlapping H_2O, 5'), 2.19 (m, 1H, 2'),

1.86-2.06 (m, 1H, 2'); ^{13}C NMR (DMSO-d_6) δ 163.2, 147.7, 107.4, 87.2, 72.1, 71.1, 61.4, 51.2, 41.3; MS (LSIMS) (MH^+) 286; HPLC: t_r 11.9 min (98.1%). Anal. Calcd for $C_{11}H_{15}N_3O_6$: C, 46.32; H, 5.30; N, 14.73. Found: C, 46.37; H, 5.05; N, 14.58.

3(5)-(2-Deoxy-β-D-ribofuranosyl)-4,5(3)-bis(carbamoyl)pyrazole (19). Reaction of **15** as described above, followed by recrystallization from methanol gave desired product (0.102g, 75%) mp 210-211°C. ^1H NMR (DMSO-d_6) δ 13.25 (bs, 1H, pyrazole NH), 9.95 (bs, 1H, NH), 7.99 (bs, 1H, NH), 7.77 (bs, 1H, NH), 7.20 (bs, 1H, NH), 5.65 (dd, J=5.9, 8.9, 1H, 1'), 5.11 (d, J=4.0, 1H, 3'-OH), 4.90 (t, J=5.6, 1H, 5'-OH), 4.13 (bd, J=2.6, 1H, 3'), 3.76 (m, 1H, 4'), 3.53 (bs, 2H, 5'), 2.29-2.45 (m, 1H, 2'), 1.63-1.82 (m, 1H, 2'); HPLC: t_r 5.6 min (99.0%). Anal. Calcd for $C_{10}H_{14}N_4O_5$: C, 44.44; H, 5.22; N, 20.73. Found: C, 44.45; H, 5.00; N, 20.43.

3(5)-(2-Deoxy-β-D-ribofuranosyl)-4-bromo-5(3)-carbamoylpyrazole (20). Reaction of **16** as described above, followed by recrystallization from acetonitrile afforded product (0.127g, 87%) mp 171.5-173°C. Analytical TLC (15% MeOH/CH_2Cl_2) R_f 0.25. UV (EtOH) sh. 237; (EtOH+NaOH) λ_{max} 247 (7,200), λ_{min} 230; ^1H NMR (DMSO-d_6) δ 7.50 (bs, 1H, NH), 7.28 (bs, 1H, NH), 5.18 (d, J=3.7, 1H, 3'-OH), 5.09 (dd, J=5.8, 9.8, 1H, 1'), 4.22 (bs, 1H, 3'), 3.78 (m, 1H, 4'), 3.46 (d, J=5.2, 2H, 5'), 2.08 (m, 2H, 2'); MS (electrospray) $(m-H)^-$ 304/306; HPLC: t_r 7.7 min (95.9%). Anal. Calcd for $C_9H_{12}BrN_3O_4$: C, 35.28; H, 3.85; N, 13.76. Found: C, 35.31; H, 3.95; N, 13.73.

4-Bromo-5(3)-carbamoyl-3(5)-(2-Deoxy-β-D-ribofuranosyl)pyrazole 5'-Monophosphate (21). A solution of **20** (0.050g, 0.17 mmol) and $POCl_3$ (55.0 μL, 0.60 mmol) in trimethyl phosphate (3.0 mL) was kept at 0-5°C for 16 hr, then poured onto ice (30g) and the pH was maintained at 8-9 by additon of 1M NaOH over the course of 1 h. After an additional 1.5 h, the reaction mixture was washed with ether and the aqueous phase was rotary evaporated (1 torr, bath temperature 60°C) to give a moist white solid. Preparative HPLC on a 10x250 mm YMC ODS-AQ column, eluting with 12-75% MeOH / 0.1 M HOAc (detector at 250nM) afforded **21** (0.032g, 49%) as a hygroscopic solid. UV (H_2O) sh. 237; (H_2O+NaOH) λ_{max} 246 (8,000), λ_{min} 222; ^1H NMR (DMSO-d_6) δ 7.48

(bs, 1H, NH), 7.33 (bs, 1H, NH), 5.13 (pseudo t, J=8.0, 1H, 1'), 4.27 (bs, 1H, 3'), 3.74-4.04 (m, 3H, 4', 5'), 1.97-2.23 (m, 2H, 2'); ^{13}C NMR (DMSO-d_6 + D_2O) δ 162.5 (CO), 143.6 (3), 141.5 (5), 91.6 (4), 88.8 (d, J=5.5, 4'), 72.1 (1' or 3'), 71.7 (1' or 3'), 66.0 (5'), 41.1 (2'); HPLC: t_r 11.5 min (95.6%); MS (LSIMS) (MH^+) 386/388. Anal. Calcd for $C_9H_{13}BrN_3O_7P \cdot 3/2\ H_2O$: C, 26.16; H, 3.90; N, 10.17. Found: C, 25.96; H, 3.94; N, 9.99.

Saponification and Deprotection of 4-carbomethoxypyrazole 14. A solution of **14** (.075g, .20 mmol) and NaOH (.082g, 2.0 mmol) in 50% aqueous MeOH (5.0 mL) was heated to reflux for 8 h. After cooling, Dowex 50X8-200 (2.0 g, freshly rinsed with MeOH and air dried) and more solvent (15 mL) were added with stirring. Filtration and rinsing of the resin with more solvent was followed by evaporation of the combined filtrate. The resulting hard, crystalline residue was triturated with acetonitrile and filtered to give crude **3(5)-(2-Deoxy-β-D-ribo-furanosyl)-pyrazole-bis-4,5(3)-carboxylic acid (23)** (0.048g). ^1H NMR (DMSO-d_6) δ 4.0-6.4 (broad singlet, exchangeable with D_2O), 5.52 (dd, J=5.8, 9.5, 1H, 1'), 4.17 (m, 1H, 3'), 3.78 (m, 1H, 4'), 3.48 (d, J=4.8, 2H, 5'), 2.19-2.32 (m, 1H, 2'), 1.83-1.97 (m, 1H, 2'); MS (electrospray) $(m-H)^-$ 270; HPLC: t_r 6.4 min (65.2%).

Methyl 4-Bromo-1-phenylsulfonylpyrazole-5-carboxylate (25). A suspension of **24**[20] (5.74 g, 20 mmol) in anhydrous ether (100 ml) was cooled to -70°C and 1.8M phenyllithium in cyclohexane-ether (11.1 mL, 20 mmol) was added. The mixture was warmed to 0°C over the course of 2h, then re-cooled to -70°C and methyl chloroformate (1.70 mL, 22 mmol) was slowly added. After 30 min, the mixture was warmed to 0°C and sat. $NaHCO_3$ (50 mL) was carefully added. Separation of the organic phase was followed by washing with brine and drying. Filtration and solvent evaporation followed by flash chromatography on silica gel (1% acetone/toluene) afforded **25** (5.66g, 82%) as a yellow solid, mp 55-58°C. Analytical TLC (15% EtOAc/hexane) R_f 0.35. ^1H NMR (DMSO-d_6) δ 8.22 (s, 1H, ArH), 7.60-8.12 (m, 5H, Ph), 4.01 (s, 3H, Me) ; ^{13}C NMR (DMSO-d_6) δ 159.0, 145.2, 136.0, 135.3, 130.2, 128.2, 99.5, 54.0. Anal. Calcd for

$C_{11}H_9BrN_2O_4S$: C, 38.38; H, 2.64; N, 8.14; Br, 23.15. Found: C, 38.02; H, 2.45; N, 8.06; Br, 23.49.

Methyl 4-Bromopyrazole-3(5)-carboxylate (4b). A solution of **25** (2.00 g, 5.8 mmol) and water (156 mL, 8.7 mmol) in DMF (20 mL) was heated at bath temperature 120°C for 1h. Cooling, rotary evaporation, and recrystallization from CH_3CN (10 mL) gave crystalline **4b** (0.843 g, 71%), mp 202-203°C. Analytical TLC (50% EtOAc/hexane) R_f 0.49. UV (MeOH) sh. 242 ; (MeOH+NaOH) λ_{max} 244 (10,300), λ_{min} 221; ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 1H, ArH), 3.83 (s, 3H, Me). Anal. Calcd for $C_5H_5BrN_2O_2$: C, 29.29; H, 2.46; N, 13.66; Br, 38.98. Found: C, 29.46; H, 2.48; N, 13.68; Br, 39.20.

ACKNOWLEDGEMENT

We wish to thank Dr. Bhima Ugarkar for helpful discussions and Wesley Jacobs for the expert preparation of intermediates.

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Received November 27, 1996
Accepted January 24, 1997