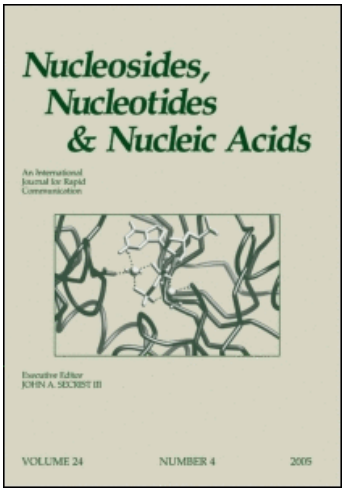

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

The Synthesis, Structure, and Conformation of 2'-Deoxy Analogues of „Fat" Xanthine Nucleosides, Containing the Imidazo[4,5-e][1,4]Diazepine Ring System

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To cite this Article Bhan, Anila and Hosmane, Ramachandra S.(1992) 'The Synthesis, Structure, and Conformation of 2'-Deoxy Analogues of „Fat" Xanthine Nucleosides, Containing the Imidazo[4,5-e][1,4]Diazepine Ring System', Nucleosides, Nucleotides and Nucleic Acids, 11: 6, 1175 — 1200
To link to this Article: DOI: 10.1080/07328319208018334
URL: http://dx.doi.org/10.1080/07328319208018334

NUCLEOSIDES & NUCLEOTIDES, 11(6), 1175-1200 (1992)

THE SYNTHESIS, STRUCTURE, AND CONFORMATION OF 2'-DEOXY ANALOGUES OF "FAT" XANTHINE NUCLEOSIDES, CONTAINING THE IMIDAZO[4,5-e][1,4]DIAZEPINE RING SYSTEM

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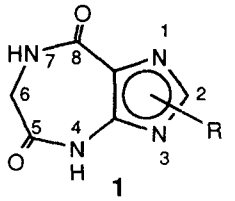
ABSTRACT

The syntheses of 1-(2-deoxy-β-D-erythro-pentofuranosyl)-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (**9β**), its 3-glycosyl regioisomer (**16β**), and their respective α anomers (**9α** and **16α**), are reported. Conformational and configurational studies, employing ^{1}H NMR NOE and CD spectroscopy, are described. The single-crystal X-ray structural analysis of **9β** is presented. The attempted enzymic glycosylation of the heterocyclic base **6** with a bacterial purine nucleoside phosphorylase was not successful.

INTRODUCTION

Ring-expanded ("fat") nucleosides and nucleotides are potentially useful in investigations of nucleic acid metabolism, structure, and function. With their structural similarity to natural purines, they are likely to be a rich source of substrates or inhibitors of enzymes of purine metabolism and of those requiring energy cofactors ATP or GTP. With their bulkier features as compared with the natural counterparts, "fat" nucleosides/-tides are also potential probes for steric and conformational constraints of the nucleic acid double helix. From a strictly chemical standpoint, studies relating to their structure, conformation, acid-base property, tautomerism, etc. would be interesting and rewarding.

We have recently reported the synthesis and biophysical characteristics of several ring-expanded purine nucleosides and nucleotides.[1] The 5′-diphosphate derivatives of **1a** and **1b**, the two regioisomeric nucleosides containing the 5:7-fused imidazo[4,5-e][1,4]diazepine nucleus, underwent facile enzymic polymerization with E. coli polynucleotide phosphorylase, but only the homopolymer derived from **1a** exhibited significant internal secondary structure with a stable helical conformation.[1b] The investigations of their primary structures later revealed that the two nucleosides had opposite base-ribose (syn/anti) and sugar pucker (exo/endo) conformations both in solid state and solution.[1b,1e] Nucleoside **2**, containing the imidazo[4,5-e][1,2,4]triazepine nucleus, is antiaromatic by the Hückel



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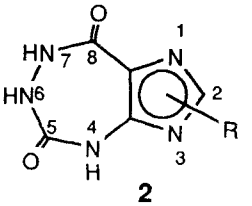

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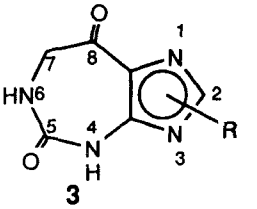

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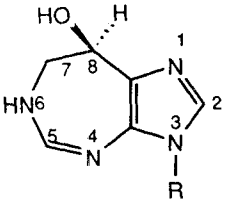
a; R = 1-β-D-ribofuranosyl
b; R = 3-β-D-ribofuranosyl



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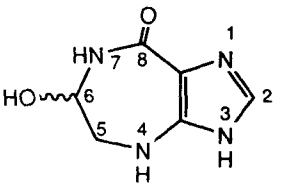


5

a; R = β-D-ribofuranosyl
b; R = 2-deoxy-β-D-ribofuranosyl

rule (4n + 2 Π electrons) due to the presence of 8 Π electrons in its seven-membered ring. Indeed, the attempted synthesis of an adenine analogue of **2** was riddled with opportunistic rearrangements,[2] while the synthesis of **2** itself proved to be far from trivial.[3] Ring-expanded heterocyclic bases and nucleosides have also been found in nature. The imidazo[4,5-d][1,3]diazepine ring system of the recently synthesized nucleoside **3**,[1g] is present in the naturally occurring synergistic

antitumor antibiotics, coformycin (**4a**) and pentostatin (**4b**),[4] which are the strongest known inhibitors of adenosine deaminase with a $K_i \simeq 10^{-11}$.[5] The ring system present in **1** has been recently discovered in another natural product called azepinomycin (**5**), a non-nucleoside which is reportedly an inhibitor of guanase.[6]

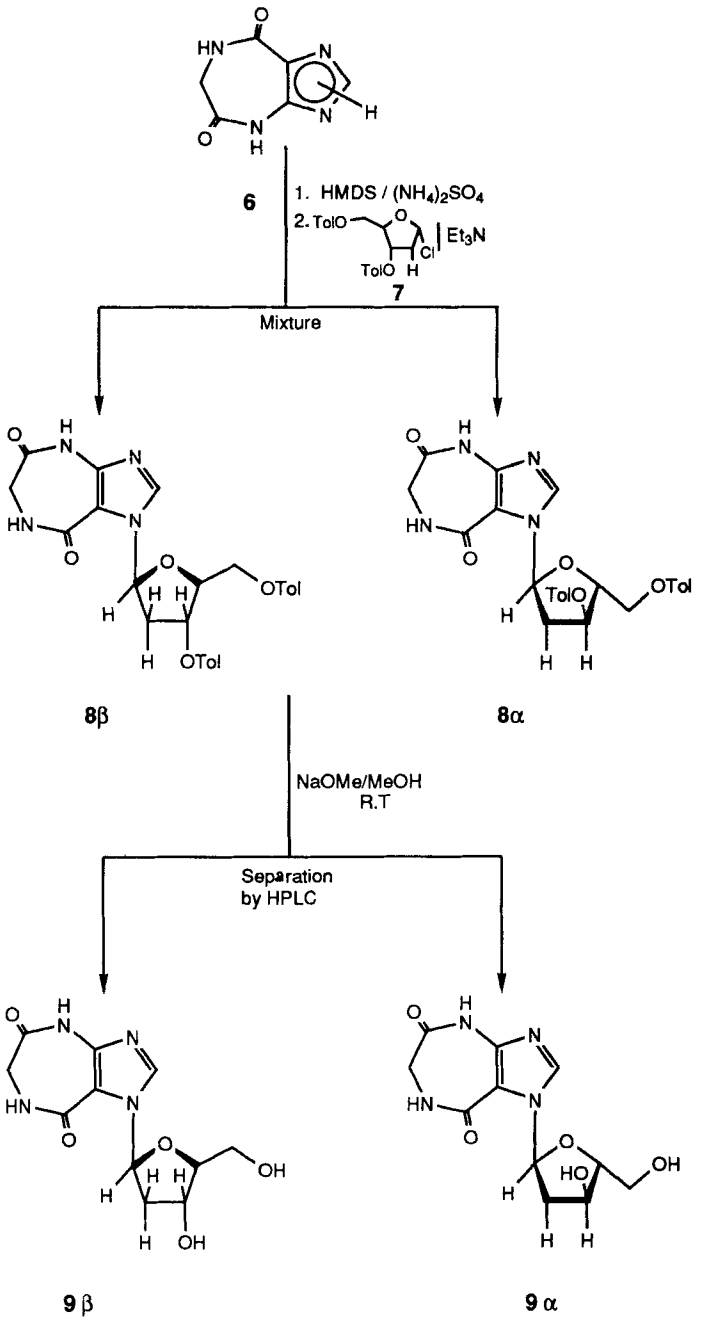
We report here the synthesis and conformational studies of the 2'-deoxy analogues of **1a** and **1b**, i.e. nucleosides **9β** and **16β**. These deoxy analogues are more appropriate than their ribose counterparts for probing the DNA metabolism. Also reported here are the respective α anomers, **9α** and **16α**, which are the side products of glycosylation. In addition, the single-crystal X-ray structural analysis of **9β** is presented. Finally, we report our results of the attempted enzymic glycosylation of the heterocyclic aglycon **6** with a bacterial purine nucleoside phosphorylase.

RESULTS AND DISCUSSION

Synthesis

The simplest approach to the synthesis of target nucleosides was to perform selective 2'-deoxygenation of the corresponding ribonucleosides, **1a** and **1b**,[1b,1c] using the well-established literature procedures.[7] The procedure normally calls for sequential reactions involving protection of the 3',5'-OH groups with a silyl moiety, conversion of the 2'-OH to a thiocarbonyl ester, reduction with tin hydride, and removal of the silyl function with fluoride. In this regard, while we succeeded[1e] in preparing the bis(3',5'-OH)-protected nucleoside derivative of **1b** by treatment with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane,[8] all our subsequent efforts to prepare the corresponding 2'-thiocarbonyl ester derivative by reaction with phenoxythiocarbonyl chloride produced only intractable reaction mixtures. Therefore, this route to the synthesis of the target 2'-deoxynucleosides was abandoned.

The synthesis of **9β** (**Scheme I**) proceeded from the heterocyclic base **6**,[1d] which was glycosylated by sequential reactions involving silylation with hexamethyldisilazane (HMDS)/ammonium sulfate, and condensation with the freshly prepared 2-deoxy-3,5-di-O-(p-toluoyl)-α-D-erythro-pentofuranosyl chloride (**7**), employing the procedure of Hubbard, et al,[9] with modifications of Kawakami, et al.[10] The product

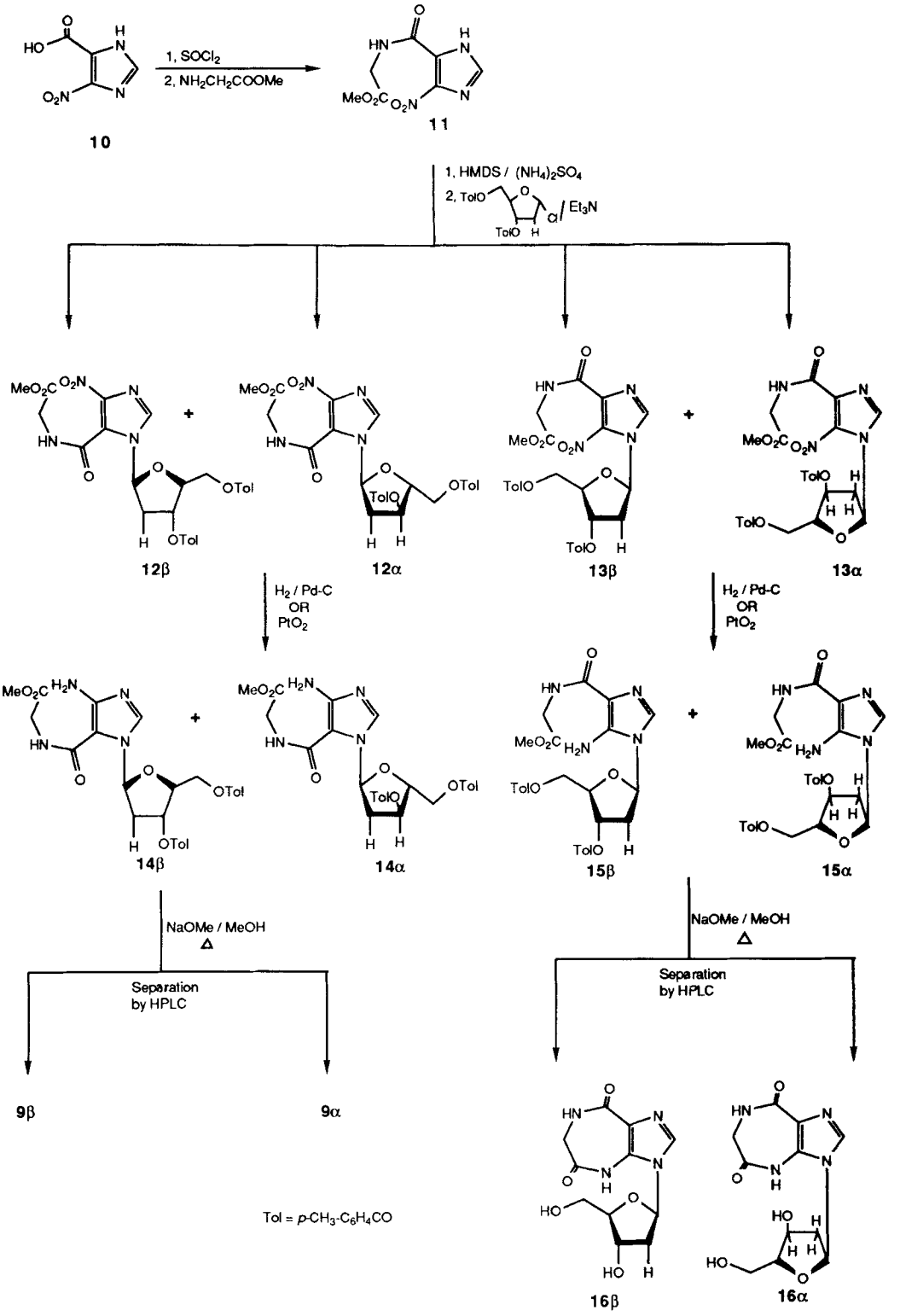


Tol = *p*-CH_3-C_6H_4CO

SCHEME I

8, obtained in 65-70% yield, was a single regioisomer, but a mixture of α and β anomers that were indistinguishable by TLC. Furthermore, most of the signals corresponding to the two anomers overlapped in the ^{1}H NMR spectrum of the product. However, the ^{13}C NMR spectrum of the product revealed two distinct sets of signals for most of the carbons of the two anomers. The product was assigned as the 1-glycosyl regioisomer, based upon comparison of ^{1}H NMR and UV spectral data of the subsequent OH-deprotected product **9** with those of the corresponding ribosyl analogue **1a**.[1b] The distinctive ^{1}H NMR signal between **1a** & **1b** is that of the imidazole H-2 which appears at >8.0 δ in **1a** but at <8.0 δ in **1b**.[1b] The ^{1}H NMR spectrum of **9α** exhibited this signal at δ 8.03 and **9β** at δ 8.16. The electron-withdrawing C-8 carbonyl functionality of **1a** or **9** causes the respective imidazole H-2 to be deshielded via resonance relative to the H-2 of **1b** or **16**, respectively, which experiences the electron-donating mesomeric effects of an $\underline{N}^{4}$-H. Similar observations have been noted in the case of N-7 and N-9 alkylated purines.[11b] Likewise, the distinctive UV absorption between **1a** and **1b** is the peak in the region of λ_{max} 250 nm in basic pH (≃12-13), which is present in **1b** but absent in **1a**. This peak was conspicuously absent in the UV of both **8** (α + β) and **9** (α or β). The anomers **8α** and **8β** were inseparable by silica gel flash chromatography or by fractional recrystallization from a variety of solvent systems. On the other hand, the target anomers **9α** and **9β**, obtained by treatment of the anomeric mixture of **8** with sodium methoxide in methanol, could be conveniently separated by reverse phase HPLC on a C-18 column or by rotating disc chromatography on a Chromatotron plate of silica gel. The two anomers, obtained in 26% (α) and 41% (β) yields, were distinguished from each other by the reported characteristic ^{1}H NMR coupling pattern of anomeric protons of α, β anomers.[11a] Compound **9β** exhibited its H-1′ as a pseudo triplet at δ 6.48 with $\underline{J}_{1',2'a} \simeq \underline{J}_{1',2'b} \simeq 6.0$ Hz, while the H-1′ of **9α** was revealed as a doublet of doublets at δ 6.52 with two unequal coupling constants, $\underline{J}_{1',2'a} = 1.5$ Hz and $\underline{J}_{1',2'b} = 7.0$ Hz. In addition, the chemical shift difference between the H-5′ and H-4′ signals was considerably smaller in the β-anomer as compared with that in the α-anomer, consistent with the reported pattern of these sugar signals in 2′-deoxynucleoside anomers.[11c]

The synthesis of **16β** necessitated a longer route than that described above for **9β**. This approach (**Scheme II**) employed 4(5)-nitro-



SCHEME II

5(4)-carboxyimidazole[1d] (**10**) as the starting material. The reaction of **10** with thionyl chloride, followed by treatment with glycine methyl ester, provided the amide **11** in 76% yield. The latter was glycosylated with **7**, using the procedure described above for **6**, to obtain a mixture of regio- and stereoisomers, **12** (α + β) and **13** (α + β). The two regioisomers **12** and **13**, each a mixture of anomers, could be easily separated by silica gel flash chromatography, with **12** eluting faster than **13**. The yields of **12** and **13** were 18% and 29%, respectively. The two regioisomers were differentiated by ^{1}H NMR, based upon the anticipated and observed enhanced deshielding effect of the nitro group on the imidazole H-2 (resonance effect) and the anomeric H-1' (inductive effect) of **13** as compared with those of **12**. While the two anomers of **12** were mostly indistinguishable by ^{1}H NMR, those of **13** exhibited distinct signals. However, no attempts were made to separate the α,β anomers until after the final synthetic step. Compounds **12** and **13** were reduced by catalytic hydrogenation to the corresponding amino compounds, **14** and **15** in 80% yield each. The latter were ring-closed with sodium methoxide/methanol with concomitant hydroxyl deprotection to yield the final products **9** (α + β) and **16** (α + β), respectively. The separation and distinction of α,β anomers of **9** and **16** were accomplished in an analogous manner as described above for the anomeric mixture of **9** obtained by direct method of glycosylation of the heterocyclic base. The separated anomers **9α** (16%) and **9β** (24%) were identical in all respects with those obtained by direct glycosylation. The yields of the separated anomers **16α** and **16β** were 19% and 26%, respectively. As in the case of **9α** and **9β**, the anomeric proton of **16β** was a triplet at δ 6.03 with nearly equal coupling constants, $J_{1',2'a} \simeq J_{1',2'b} \simeq 6.5$ Hz, whereas the anomeric proton of **16α** was a doublet of doublets at δ 6.05 with $J_{1',2'a} = 2.5$ Hz and $J_{1',2'b} = 7.5$ Hz. The regioisomeric assignment of **9** and **16** was corroborated by ^{1}H NMR chemical shift of H-2; it was at >8.0 δ in **9α** (8.05) and **9β** (8.16), but at <8.0 δ in **16α** (7.89) and **16β** (7.88). Further support for the accuracy of regioisomeric assignment of **9** and **16** was provided by the respective H-1' chemical shifts-- **9α** (δ 6.52) and **9β** (δ 6.48) absorbed at lower fields as compared with **16α** (δ 6.05) and **16β** (δ 6.03). While the H-1' of **9** experiences the electron-withdrawing inductive effect of the C-8 carbonyl function, that of **16** feels the electron-donating inductive effect of the NH group at position 4.

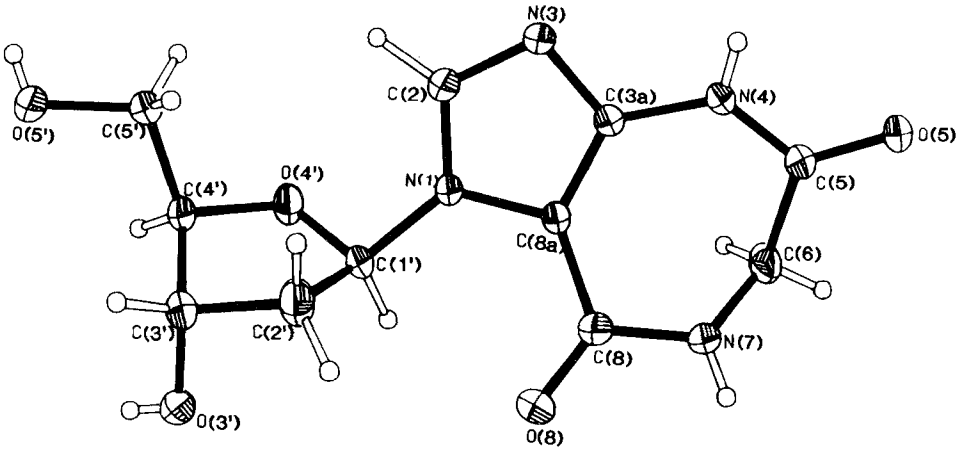


Figure 1: ORTEP view of **9β** showing the employed atom numbering scheme.

Single-Crystal X-Ray Diffraction Analysis of 9β

Despite extensive spectral evidence, the structural confirmation of at least one of the four final products by single-crystal X-ray diffraction analysis was warranted, especially in view of a number of errors in the reportedly alleged seven-membered and larger ring heterocycles that were later found to be only 5- or 6-membered ring systems.[12] The structure of **9β** was confirmed by single-crystal X-ray diffraction analysis. The ORTEP view of **9β**, along with the atom numbering scheme is shown in **Figure 1**. As anticipated, the seven-membered ring of **9β** is puckered. The two lactam N-C(=O) bonds deviate by 25 ± 2° from planarity, and the C5(C=O) to C8(C=O) torsional angle is ≃ 82°. The base-ribose conformational relationship is anti ($\chi_{C,N}$ = 26.5°), and the sugar pucker is C2'-endo-C3'-exo, which is opposite to the sugar pucker found in the corresponding ribosyl analogue **1a**. The glycosyl bond length, 1.474 (4) Å, is comparable to that found in purine nucleosides,[13] and is slightly shorter than that found in **1a** [1.488 (3) Å].[1b]

Conformational and Configurational Analyses by NOE

The α/β configuration and syn/anti conformation of the target nucleosides **9** and **16** were investigated by ^{1}H NMR Nuclear Overhauser

Table I: NOE enhancements (%) of nucleosides **9α, 9β, and 16α, 16β** in DMSO-d_6 at 25 °C.

Compd. No.	Protons Observed	Protons Irradiated H-2	H-1'	H-4'
9α	H-2	---	3.5	3.0
	H-1'	5.0	---	0.0
	H-4'	10.0	0.0	---
9β	H-2	---	0.0	0.0
	H-1'	0.0	---	ND
	H-4'	0.0	6.0	---
16α	H-2	---	<3.0	0.0
	H-1'	7.0	---	0.0
	H-4'	0.0	0.0	---
16β	H-2	---	30.0	0.0
	H-1'	30.0	---	ND
	H-4'	0.0	7.0	---

(ND = not determined)

Effect (NOE) difference spectroscopy.[14] The data are collected in **Table I.**

The two β-anomers, **9β** and **16β**, exhibited a sizeable NOE between the spatially proximal H-4' and H-1', whereas no such NOE was observed in the respective α-anomers, **9α** and **16α**. Likewise, a pronounced NOE existed between H-2 and H-1' in **16β**, pointing to its syn conformation in solution. The observed large NOE in **16β** is comparable to that found earlier in compound **1b**,[1e] which possesses the syn conformation both in solid state[1b] and in solution.[1e] The single-crystal X-ray structural analysis of **1b** revealed that the compound is frozen into syn conformation by the presence of a strong hydrogen bond between the sugar 5'-hydroxyl group and the N^4-H of the diazepine ring. Nucleoside **9β**, by contrast, showed little NOE between H-2 and H-1', indicating its anti conformation. The same conformation was discovered earlier in the corresponding ribonucleoside **1a**.[1e] A conspicuous conformational contrast between the two α-anomers, **9α** and **16α**, was reflected in their respective NOE's between H-2 and H-4'. While **9α** exhibited a measurable

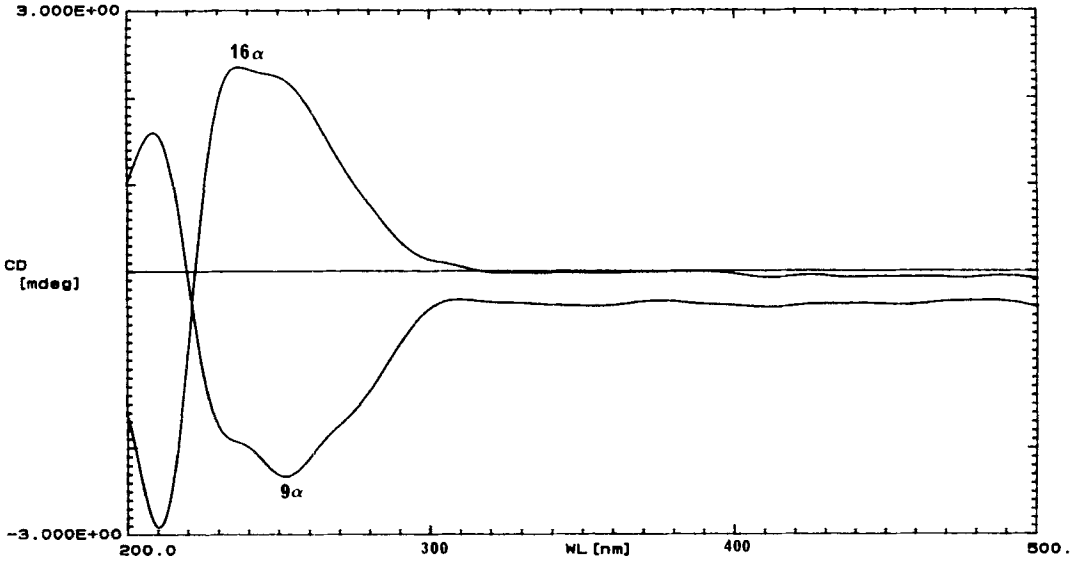


Figure 2: CD spectra of Compounds **9α** and **16α** in H_2O.

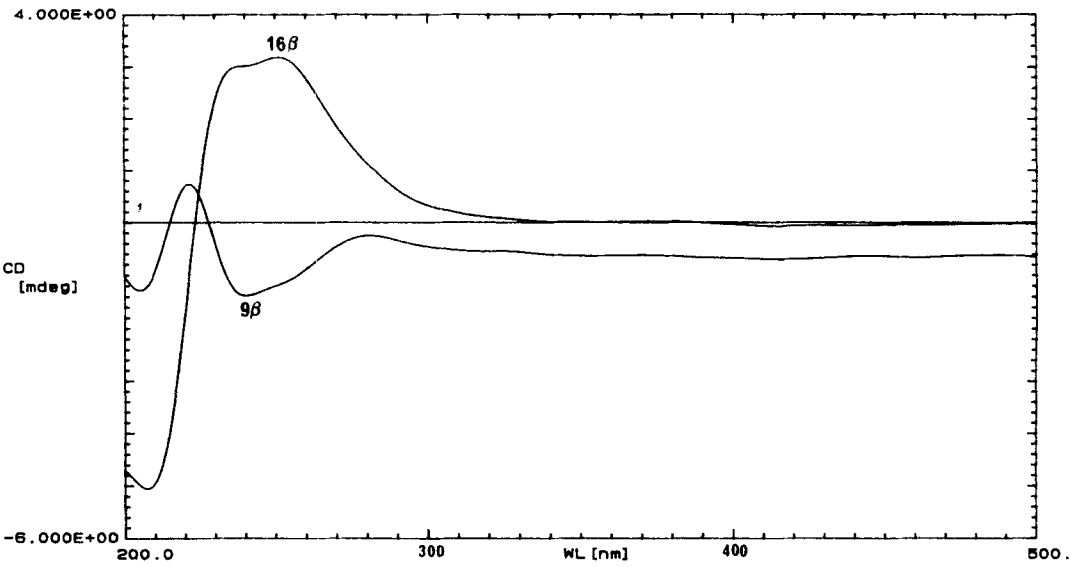


Figure 3: CD spectra of Compounds **9β** and **16β** in H_2O.

Table II: CD and UV data of **9α**, **9β**, **16α**, and **16β**, along with those of xanthosine for comparison, in H_2O at 25 °C

Compound Number	UV λmax nm	ε	CD λmax nm	θ m deg	cm^2 [θ] λmax deg/dmole	Δε
Xanthosine	262.5	9000	265.0	-3.1	-1484	-0.45
9α	268.0	7000	252.0	-2.33	-12,939	-3.90
9β	267.5	7900	240.0	-1.39	-6,794	-2.05
16α	263.0	5100	237.0	+2.35	+8,747	+2.65
16β	264.0	5800	251.0	+3.18	+11,761	+3.50

NOE between the latter protons, no NOE could be detected between H-4' and H-2 of **16α**. Molecular models indicate that an anti sugar conformation of **9α** places its sugar H-4' in proximity to the base H-2.

Circular Dichroism (CD) Spectra of Nucleosides in Water

The anti/syn conformational contrasts existing between the pair of anomers, **9α** & **16α** and **9β** & **16β**, as revealed by the above NOE data, were corroborated by their respective CD spectra in H_2O. As shown in **Figures 2** and 3, and by data in **Table II**, each pair of anomers exhibited opposite Cotton effects. We had earlier observed a similar phenomenon in the CD spectra of the corresponding ribonucleosides **1a** and **1b**.[1e] The calculated molar ellipticity [θ] data for the anomers, along with that of xanthosine for comparison, are listed in **Table II**.

Attempted Enzymic Glycosylation of 6 with Purine Nucleoside Phosphorylase

In view of multiple nucleoside products obtained by chemical methods of glycosylation, as described above, it was of interest to see if an enzymic glycosylation would produce a single regio- and stereoisomer. In this respect, purine nucleoside phosphorylase (PNP, EC 2.4.2.1) was a logical choice for carrying out enzymic glycosylation. PNP catalyzes the reversible degradation of a wide variety of ribo- and 2'-deoxyribonucleosides, and has been extensively

employed in recent years to synthesize various ^{15}N- and radiolabeled nucleosides from the corresponding heterocyclic bases.[15] However, as most of the reported studies are limited to 5:6-fused ring systems, an a priori assessment of PNP acceptance of the 5:7-fused **6** could not be made. Employing a literature procedure,[15b] **6** was subjected to enzymic glycosylation with a bacterial PNP (Sigma), using either 2-deoxy-α-D-ribose-1-phosphate or α-D-ribose-1-phosphate. As a control, glycosylation of adenine to adenosine was monitored under identical conditions. The products were analyzed by HPLC. While the conversion of adenine to adenosine could be detected, there was no trace of any of the ribo- or 2-deoxyribonucleoside products of **6** in the chromatogram. It follows, therefore, that **6** is not a substrate for the employed PNP.

EXPERIMENTAL

^1H NMR spectra were recorded at 80, 300 or 500 MHz, on an IBM NR/80 or a GE QE-300 or a GE GN-500 spectrometer, respectively. The ^{13}C NMR spectra were recorded on the above GE QE-300 instrument. The reported spectral data are relative to Me_4Si as an internal reference standard. Multiplicity is designated by the abbreviation, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. Deuterium oxide was used to verify the presence of exchangeable protons. Electron impact (EI) or chemical ionization (CI) mass spectra were recorded at 70 eV on a Hewlett Packard 5988A mass spectrometer. 2-Methylpropane was the reagent gas used in CI mass spectral determinations. Infrared spectra were obtained on a Perkin-Elmer 1420 ratio recording instrument. Ultraviolet spectra were recorded on a Gilford Response UV/VIS spectrophotometer. Circular dichroism measurements were made on a JASCO J-720 spectrometer, using a pathlength of 0.1 cm. X-Ray diffraction analyses were carried out at the Department of Chemistry, Southern Methodist University, Dallas, TX on an automatic Nicolet R_{3m}/V diffractometer. Elemental microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. Melting points are uncorrected. Dry solvents were prepared as follows: ether, toluene, and xylene were distilled over sodium; acetonitrile was distilled from CaH_2, followed by distillation over P_2O_5; DMF and DMSO were distilled under reduced

pressure from CaH_2; THF was first dried over KOH and then distilled over sodium. All dry solvents were stored over 3 or 4 Å molecular sieves.

1-(2-Deoxy-3,5-di-O-p-toluoyl-α/β-D-erythro-pentofuranosyl)-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (8α + 8β).

A suspension of **6**[1d] (1.0 g, 6.0 mmol) and $(NH_4)_2SO_4$ (50 mg) in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (60 mL) was refluxed under N_2 for 6-8 h, and a clear, dark-brown solution was formed. Evaporation *in vacuo* afforded a syrup, which was co-evaporated with dry toluene (2 x 20 mL). The residue was dissolved in dry $CHCl_3$ (100 mL), and the solution was maintained under N_2 at 0 °C, using an ice water-salt bath. The separately prepared 2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranosyl chloride (**7**)[16] (2.5 g, 6.4 mmol) was added to the solution, followed by Et_3N (1.0 mL, 7.1 mmol). The reaction mixture was stirred for 1 h, when a TLC (silica gel, $CHCl_3$:MeOH, 10:1) showed the formation of a UV absorbing compound with a higher Rf than the starting material. The reaction mixture was poured into 100 mL of H_2O, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 250 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate was evaporated to dryness. The residue was purified by flash chromatography on a column of silica gel (particle size 40-63 μm), eluting with a mixture of $CHCl_3$-MeOH (250:1). Evaporation of the appropriate UV absorbing fractions gave **8** as a white solid, which was a mixture of α and β anomers. The solid was recrystallized from MeOH as white crystals, yield 2.0-2.18 g (65-70%), mp 229-231 °C: ^1H NMR (DMSO-d_6) δ 10.82 (s, 1 H, NH), 8.11 (s, H-2 of minor isomer), 8.08 (br s, 2 H, H-2 + NH), 7.89 (d, J = 8.0 Hz, 2 H, Ar-H), 7.81 (d, J = 7.5 Hz, 2 H, Ar-H), 7.61 (d, J = 8.1 Hz, Ar-H of minor isomer), 7.35 (d, J = 8.0 Hz, 2 H, Ar-H), 7.30 (d, J = 7.5 Hz, 2 H, Ar-H), 6.6 (app t, J = 6.5 Hz, 1 H, H-1'), 5.6 (br s, 1 H, sugar H), 5.54 (d, J = 6.3 Hz, sugar H of minor isomer), 4.55 (m, 3 H, sugar CH_2 + H), 4.53-4.48 (m, sugar CH_2 + H of minor isomer), 3.65-3.59 (m, 2 H, ring CH_2), 2.77 (m, 2 H, H-2'+ H-2"), 2.49 (br s, H-2' of minor isomer), 2.38 (s, 3 H, CH_3), 2.36 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6) (major anomer) δ 168.88 (>C=O), 165.79 (>C=O), 165.55 (>C=O), 162.13 (>C=O), 144.43 (>C=), 144.22 (>C=), 143.58 (>C=), 137.36 (=CH-), 126.85 (>C=), 126.77 (>C=), 111.19 (>C=), 129.75 (=CH-), 129.68 (=CH-), 129.59 (=CH-), 86.18 (>CH-), 82.28 (>CH-), 75.11 (>CH-), 64.43 (>CH_2), 46.15

($>CH_2$), 38.97 ($>CH_2$), 21.56 ($-CH_3$), 21.52 ($-CH_3$); ^{13}C NMR (DMSO-d_6) (minor isomer) δ 168.73 (>C=O), 165.36 (>C=O), 165.34 (>C=O), 162.42 (>C=O), 144.31 (>C=), 144.25 (>C=), 143.95 (>C=), 137.79 (=CH-), 126.90 (>C=), 126.70 (>C=), 110.65 (>C=), 129.75 (=CH-), 129.68 (=CH-), 129.59 (=CH-), 88.27 (>CH-), 84.29 (>CH-), 75.29 (>CH-), 65.32 ($>CH_2$), 46.15 ($>CH_2$), 38.97 ($>CH_2$), 21.57 ($-CH_3$), 21.48 ($-CH_3$); IR (KBr) 3400-2900 (br), 1730-1650 (br) cm^{-1}; MS (CI) m/z 519 (MH^+, 100%), 383, 353, 247, 167; UV λ_{max} (MeOH-H_2O) 266.5 nm (ε 11.5 x 10^3), 243 sh (ε 39 x 10^3), (pH 13.5) 296.5 (ε 8.5 x 10^3), (pH 0.3) 266 (ε 12 x 10^3), 243 sh (ε 40 x 10^3).

Anal. Calcd for $C_{27}H_{26}O_7N_4$: C, 62.55; H, 5.05; N, 10.80. Found: C, 62.61; H, 5.10; N, 10.73.

1-(2-Deoxy-α-D-erythro-pentofuranosyl)-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (9α) and 1-(2-Deoxy-β-D-erythro-pentofuranosyl)-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]-diazepine-5,8-dione (9β).

Method A: By OH-Deprotection of 8 (α + β), followed by Separation of Anomers. Dry MeOH (25 mL) was placed in a 100-mL three-neck flask, maintained under a stream of N_2. Freshly cut Na metal (50 mg, 2.1 mg-atom) was carefully added while stirring to form a clear solution. The above mixture of **8** (α + β) (1.0 g, 1.9 mmol) was added, and the reaction mixture was stirred at room temperature for 2-3 h. A TLC (silica gel, $CHCl_3$:MeOH, 4:1) indicated the formation of a UV absorbing compound with a lower Rf than the starting material. The reaction mixture was cooled in an ice bath, neutralized with 0.5 N HCl, and evaporated to dryness. The residue was purified by flash chromatography on a column of silica gel (particle size 40-63 μm), eluting with a gradient of $CHCl_3$-MeOH (8:1 → 6:1). Evaporation of appropriate fractions afforded a white solid, whose ^1H NMR indicated it to be a mixture of α and β anomers.

The α, β anomers were separated either by reverse phase HPLC on a Bondapak C-18 column (Waters), using H_2O as the eluent, or by rotating disc chromatography on a Chromatotron plate of silica gel, eluting with a gradient of $CHCl_3$-MeOH. The 9α anomer was the first compound to elute by the HPLC (C-18 column) method, whereas it was the second compound to elute by the Chromatotron (silica gel plate) method. Evaporation of the appropriate fractions gave a solid which was recrystallized from MeOH-

Et_2O to give **9α** as a white amorphous powder, yield 140 mg (26%), mp >250 °C (gradual dec. >220 °C): ^1H NMR (DMSO-d_6) δ 10.75 (s, 1 H, NH), 8.05 (t, J = 5.0 Hz, 1 H, NH-7), 8.03 (s, 1 H, H-2), 6.52 (dd, J = 7.0 Hz & 1.5 Hz, 1 H, H-1'), 5.32 (d, J = 2.5 Hz, 1 H, 3'-OH), 4.90 (t, J = 5.5 Hz, 1 H, 5'-OH), 4.22 (d, J = 3.5 Hz, 1 H, H-3'), 4.12 (m, 1 H, H-4'), 3.63 (m, 2 H, ring CH_2), 3.40 (m, 2 H, H-5'), 2.6 (app t, J = 7.0 Hz, 1 H, H-2'), 2.12 (dd, J = 14.5 Hz & <1.0 Hz, 1 H, H-2"); IR (KBr) 3400 (br, OH/NH), 1690 (C=O), 1650 (C=O) cm^{-1}; UV λ_{max} (H_2O) 268 nm (ε 7 x 10^3), (pH 13.5) 295 (ε 7.8 x 10^3), (pH 0.25) 254 (ε 7.2 x 10^3).

Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 4.99; N, 19.85. Found: C, 46.92; H, 5.04; N, 19.79.

The anomer **9β**, which eluted slower in the reverse phase HPLC method (C-18 column), but faster in the rotating disc (Chromatotron) method (silica gel plate), was collected as a white solid after evaporation of the appropriate fractions, redissolving the residue in MeOH, and precipitation with Et_2O. The solid was recrystallized as colorless crystals from MeOH, yield 220 mg (41%), mp >275 °C (gradual dec. >230 °C): ^1H NMR (DMSO-d_6) δ 10.76 (s, 1 H, NH), 8.16 (s, 1 H, H-2), 8.03 (t, J = 5.5 Hz, 1 H, NH-7), 6.48 (t, J = 6.0 Hz, 1 H, H-1'), 5.23 (d, J = 4.5 Hz, 1 H, 3'-OH), 4.98 (t, J = 5.5 Hz, 1 H, 5'-OH), 4.24 (d, J = 4.0 Hz, 1 H, H-3'), 3.79 (d, J = 3.5 Hz, 1 H, H-4'), 3.67-3.50 (m, 4 H, ring CH_2 + sugar CH_2), 2.33-2.24 (m, 2 H, H-2'+ H-2"); IR (KBr) 3400-3300 (br, OH/NH), 1690 (C=O), 1650 (C=O) cm^{-1}; MS (CI) m/z 283 (MH^+), 167, 117; UV λ_{max} (H_2O) 267.5 nm (ε 7.9 x 10^3), (pH 13.5) 294 (ε 8.5 x 10^3), (pH 0.4) 252.5 (ε 7.7 x 10^3).

Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 4.99; N, 19.85. Found: C, 46.90; H, 5.04; N, 19.75.

Method B: Ring-Closure of 14 (α + β), followed by Separation of Anomers. Dry MeOH (25 mL) was introduced to a 100-mL three-neck flask, maintained under a stream of N_2. Freshly cut Na metal (100 mg, 4.3 mg.atom) was added with stirring, to form a clear solution. Compound **14** (α + β) (0.5 g, 0.9 mmol) was introduced, and the reaction mixture was heated at reflux for 6-8 h. The reaction mixture was cooled, neutralized with 0.5 N HCl, and rotary evaporated to dryness. The residue was purified by flash chromatography (silica gel, particle size 40-63 μm), eluting with a mixture of $CHCl_3$-MeOH (8:1). Evaporation of the appropriate UV-absorbing fractions gave **9** as a mixture of α and β

anomers. Separation of the 9α and 9β anomers was accomplished as described above in Method A, yield of 9α = 40 mg (15.8%), 9β = 60 mg (23.6%). The spectral data of 9α and 9β were superimposable with those of 9α and 9β, obtained by Method A.

5-(N-((Methoxycarbonyl)methyl)carbamoyl)-4-nitro-1H-imidazole (11).

In a flame-dried three-neck round bottom (r.b.) flask, fitted with a $CaCl_2$ guard tube, was placed **10** [1d] (5 g, 31.8 mmol). Thionyl chloride (20 mL, 0.27 mol) was introduced through a serum cap and the reaction mixture was heated to 50 °C with continuous stirring for 24 h. The mixture was rotary evaporated under anhydrous conditions, and the residue was co-evaporated with dry toluene three times, when a highly hygroscopic yellow powder--the acid chloride--was obtained. Without further purification, this powder was placed in a three-neck r.b.flask, maintained under N_2. Dry CH_3CN (15 mL) was added, followed by the addition of a cold CH_2Cl_2 solution of glycine methyl ester (3 g, 33 mmol) which was freshly liberated from the corresponding hydrochloride salt in 20 mL of CH_2Cl_2 by treatment with triethylamine at 0 °C. The reaction mixture was stirred at room temperature for 10 h. The mixture was evaporated to dryness on a rotary evaporator, and the residue was dissolved in boiling MeOH (100 mL), treated with decolorizing charcoal, and filtered. Concentration and cooling of the filtrate afforded a solid which was recrystallized from MeOH as off-white shining crystals of **11** (5.5 g, 76%), mp 221-223 °C (lit.[1d] 221-223 °C): ^1H NMR (Me_2SO-d_6) δ 9.22-9.20 (t, J = 4.5 Hz, 1 H, NH), 7.88 (s, 1 H, imidazole CH); 4.11 (d, J= 5.5 Hz, 2, CH_2), 3.67 (s, 3 H, OMe); IR (KBr) 3318, 1732, 1656, 1510, 1508 cm^{-1}; MS (EI) m/z 228 (M^+), 197, 169, 140; UV λ_{max} (MeOH) 303 nm.

1-(2-Deoxy-3,5-di-O-p-toluoyl-α/β-D-erythro-pentofuranosyl)-5-(N-((methoxycarbonyl)methyl)carbamoyl)-4-nitroimidazole (12 α + 12 β) and 1-(2-Deoxy-3,5-di-O-p-toluoyl-α/β-D-erythro-pentofuranosyl)-4-(N-((methoxycarbonyl)methyl)carbamoyl)-5-nitroimidazole (13 α + 13 β).

A mixture of **11** (1.0 g, 4.38 mmol), $(NH_4)_2SO_4$ (50 mg), and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (100 mL) was heated under reflux for 24 h, and a clear brown solution was formed. The reaction mixture was evaporated to dryness in vacuo under anhydrous conditions, and the residue was co-evaporated with dry toluene (2 x 30 mL). The

residue was dissolved in dry $CHCl_3$ (100 mL), and the solution was maintained at 0 °C using an ice water–salt bath. The separately prepared compound **7** (1.8 g, 4.63 mmol) was added to the solution, followed by Et_3N (0.7 mL, 5.0 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water (100 mL), and extracted with CH_2Cl_2 (2 x 500 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate evaporated to dryness. The residue was purified by flash chromatography over silica gel (particle size 40–63 μm), eluting with a gradient of $CHCl_3$:acetone (1:0 → 10:1).

Compound **12** (α + β) eluted first. Evaporation of the appropriate UV-absorbing fractions gave a white solid, yield 700 mg (18%). An analytical sample was prepared by recrystallization from MeOH as colorless crystals, mp 163–165 °C: ^{1}H NMR (DMSO-d_6) δ 9.56 (t, J = 5.0 Hz, 1 H, NH), 8.18 (s, 1 H, imidazole CH), 7.94 (d, J = 8.0 Hz, 2 H, Ar-H), 7.84 (d, J = 8.0 Hz, 2 H, Ar-H), 7.32 (m, 4 H, Ar-H), 6.28 (app t, J = 7.0 Hz, 1 H, H-1'), 5.62 (br s, 1 H, sugar H), 4.63–4.57 (m, 3 H, sugar H), 4.05 (dd, J = 5.5 Hz & 1.5 Hz, 2 H, CH_2), 3.59 (s, 3 H, OMe), 2.81 (m, 2 H, H-2' + H-2"), 2.38 (s, 3 H, Ar-Me), 2.36 (s, 3 H, Ar-Me); ^{13}C NMR (DMSO-d_6) δ 169.69 (>C=O), 165.70 (>C=O), 165.36 (>C=O), 158.62 (>C=O), 144.31 (>C=), 144.12 (>C=), 143.57 (>C=), 133.74 (=CH-), 129.67 (=CH-), 129.46 (=CH-), 129.37 (=CH-), 126.68 (>C=), 126.60 (>C=), 125.93 (>C=), 86.93 (>CH-), 82.95 (>CH-), 74.97 (>CH-), 64.18 ($>CH_2$), 51.94 (OCH_3), 41.18 ($>CH_2$), 38.95 ($>CH_2$), 21.2 ($-CH_3$), 21.23 ($-CH_3$); IR (KBr) 3300 (NH), 1742 (C=O), 1720 (C=O), 1648 (C=O) cm^{-1}; MS (CI) m/z 581 (MH^+), 551, 353, 229, 199, 137; UV λ_{max} (MeOH-H_2O) 240 nm, 275 (sh), 285 sh, (pH 13) 296 (sh), 274.5 (sh), 239, (pH 0.5) 281.5, 274, 240.

Anal. Calcd for $C_{28}H_{28}N_4O_{10}$: C, 57.93; H, 4.82; N, 9.65. Found: C, 58.02; H, 4.89; N, 9.66.

The slower eluting **13** (α + β) was obtained as a solid after evaporation of appropriate chromatographic fractions. The solid was recrystallized from MeOH as light yellow flakes, yield 1.1 g (29%), mp 95–98 °C: ^{1}H NMR (DMSO-d_6) δ 8.87 (t, J = 5.5 Hz, 1 H, NH), 8.39 (s, 0.5 H, imidazole CH), 8.30 (s, 0.5 H, imidazole CH), 7.91 (m, 2 H, Ar-H), 7.77 (d, J = 8.0 Hz, 1 H, Ar-H), 7.59 (d, J = 8.0 Hz, 1 H, Ar-H), 7.37–7.26 (m, 4 H, Ar-H), 6.67 (app d, J = 6.5 Hz, 0.5 H, H-1'), 6.53

(app t, J = 6.5 Hz, 0.5 H, H-1'), 5.62 (br s, 0.5 H, sugar H), 5.59 (d, J = 6.0 Hz, 0.5 H, sugar H), 5.15 (t, J = 3.5 Hz, 0.5 H, sugar H), 4.66 (d, J = 3.5 Hz, 0.5 H, sugar H), 4.54 (d, J = 4.5 Hz, 1 H, sugar H), 4.49 (d, J = 4.5 Hz, 1 H, sugar H), 4.02 (d, J = 5.5 Hz, 1 H, CH_2), 3.98 (d, J = 5.0 Hz, 1 H, CH_2), 3.66 (s, 1.5 H, OMe), 3.64 (s, 1.5 H, OMe), 3.05 (m, 0.5 H, H-2'), 2.94 (m, 1 H, H-2' + H-2"), 2.75 (app d, J = 15.5 Hz, 0.5 H, H-2"), 2.38 (s, 3 H, Ar-Me), 2.36 (s, 1.5 H, Ar-Me), 2.35 (s, 1.5 H, Ar-Me); IR (KBr) 3400 (NH), 1750 (C=O), 1710 (C=O), 1670 (C=O) cm^{-1}; MS (CI) m/z 581 (MH^+), 551, 353, 229, 137; UV λ_{max} ($MeOH-H_2O$) 240 nm, (pH 13) 238.5, (pH 0.6) 239.

Anal. Calcd for $C_{28}H_{28}N_4O_{10}$: C, 57.93; H, 4.82; N, 9.65. Found: C, 57.82; H, 4.86; N, 9.66.

4-Amino-1-(2-deoxy-3,5-di-O-p-toluoyl-α/β-D-erythro-pentofuranosyl)-5-(N-((methoxycarbonyl)methyl)carbamoyl)imidazole (14 α + 14 β)

A mixture of **12** (α + β) (1.0 g, 1.7 mmol) in abs. MeOH (150 mL) and $PtO_2 \cdot H_2O$ (100 mg) was hydrogenated in a Parr hydrogenator at 40 psi for 35 min. The reaction mixture was filtered twice through Celite, and the filtrate was evaporated to dryness. The residual syrup was purified by rotating disc chromatography on a Chromatotron plate, made of silica gel (particle size 15 μm, 2 mm thickness), eluting with a gradient of $CHCl_3$:acetone (50:1 → 10:1). Evaporation of appropriate UV absorbing fractions gave **14** (α + β) as a foam, yield 0.76 g (80%). An analytical sample of **14** (α + β) was prepared by dissolving the foam in Et_2O, followed by precipitation with hexane: ^1H NMR (DMSO-d_6 + D_2O) δ 7.89 (d, J = 8.0 Hz, 2 H, Ar-H), 7.79 (d, J = 8.0 Hz, 2 H, Ar-H), 7.33 (s, 1 H, imidazole CH), 7.29 (m, 4 H, Ar-H), 6.03 (dd, J = 8.0 Hz & 6.0 Hz, 1 H, H-1'), 5.57 (d, J = 6.0 Hz, 1 H, sugar H), 4.53-4.44 (m, 3 H, sugar H), 3.89 (s, 2 H, CH_2), 3.57 (s, 3 H, OMe), 2.73-2.60 (m, 2 H, H-2' + H-2"), 2.33 (s, 3 H, Ar-Me), 2.32 (s, 3 H, Ar-Me). Note: The NH_2 and NH signals appear at δ 5.35 and 7.68, respectively, if the spectrum is run in DMSO-d_6 without D_2O; ^{13}C NMR (DMSO-d_6) δ 170.75 (>C=O), 165.52 (>C=O), 165.30 (>C=O), 161.03 (>C=O), 152.19 (>C=), 144.09 (>C=), 143.88 (>C=), 135.73 (=CH-), 126.54 (>C=), 126.47 (>C=), 104.77 (>C=), 85.70 (>CH-), 81.70 (>CH-), 74.72 (>CH-), 64.11 ($>CH_2$), 51.73 (OCH_3), 41.01 ($>CH_2$), 38.27 ($>CH_2$), 21.19 ($-CH_3$), 21.17 ($-CH_3$); IR (KBr) 3360 (NH), 1740 (C=O), 1720 (C=O), 1630, 1610 cm^{-1}; MS (CI) m/z 551 (MH^+), 479, 419, 353, 271, 199, 137; UV λ_{max} ($MeOH-H_2O$) 273.5 nm, 239.5, (pH 12.5) 270.5 (sh), 237.5, (pH 0.8) 270 (sh), 240.5.

Anal. Calcd for $C_{28}H_{30}N_4O_8$: C, 61.09; H, 5.48; N, 10.17. Found: C, 60.97; H, 5.47; N, 10.16.

5-Amino-1-(2-deoxy-3,5-di-O-p-toluoyl-α/β-D-erythro-pentofuranosyl)-4-(N-({methoxycarbonyl}methyl)carbamoyl)imidazole (15 α + 15 β)

The procedure used is analogous to the one described above for **14** (α + β), except for the following changes: (1) the catalyst used was 5% Pd-C (100 mg) for 1.0 g of **13** (α + β). (2) Hydrogenation took 1.5 h instead of 35 min. (3) The thickness of the silica gel plate was 1 mm. (4) The eluting solvent used was a mixture of $CHCl_3$:acetone (100:1). Compound **15** (α + β) was obtained as a foam, yield 0.75 g (80%): ^{1}H NMR (DMSO-d_6 + D_2O) δ 7.85 (d, J = 8.0 Hz, 2 H, Ar-H), 7.75 (d, J = 8.0 Hz, 2 H, Ar-H), 7.68 (s, 1 H, imidazole CH), 7.30 (d, J = 8.0 Hz, 2 H, Ar-H), 7.27 (d, J = 8.0 Hz, 2 H, Ar-H), 6.37 (t, J = 6.5 Hz, 1 H, H-1'), 5.49 (m, 1 H, sugar H), 4.53-4.45 (m, 3 H, sugar H), 3.93 (s, 2 H, CH_2), 3.56 (s, 3 H, OMe), 2.68-2.63 (m, 2 H, H-2' + H-2"), 2.32 (s, 3 H, Ar-Me), 2.31 (s, 3 H, Ar-Me). Note: The NH_2 and NH signals appear at δ 5.35 and 7.68, respectively, if the spectrum is run in DMSO-d_6 without D_2O; IR (KBr) 3410 (NH), 1750 (C=O), 1720 (C=O), 1630, 1610 cm^{-1}; MS (CI) m/z 551 (MH^+), 353, 289, 245, 199, 161; UV λ_{max} (MeOH-H_2O) 262 nm, 241, (pH 13) 262 (sh), 240.5, (pH 0.5) 266 (sh), 243.

Anal. Calcd for $C_{28}H_{30}N_4O_8$: C, 61.09; H, 5.48; N, 10.17. Found: C, 61.01; H, 5.51; N, 10.04.

3-(2-Deoxy-α-D-erythro-pentofuranosyl)-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (16α) and 3-(2-Deoxy-β-D-erythro-pentofuranosyl)-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (16β).

The title compounds were obtained as a mixture by the NaOMe-catalyzed ring-closure of **15** (α + β) (0.5 g, 0.9 mmol), using an analogous procedure described above for the preparation of **9** (α + β) from **14** (α + β) (Method B). The two anomers, **16α** and **16β**, were separated by the rotating disc chromatography as described for **9α** and **9β**.

Compound **16α** was recrystallized as a white powder from MeOH-Et_2O, yield 60 mg (19%), mp gradual dec. >200 °C: ^{1}H NMR (DMSO-d_6) δ 10.79 (br s, 1 H, NH-4), 7.89 (s, 1 H, H-2), 7.84 (t, J = 5.0 Hz, 1 H, NH-7), 6.05 (dd, J = 7.5 Hz & 2.5 Hz, 1 H, H-1'), 5.58 (br s, 1 H, 3'-OH), 4.86 (t, J = 6.0 Hz, 1 H, 5'-OH), 4.28 (d, J = 6.5 Hz, 1 H, H-3'), 4.07

(dd, J = 6.5 Hz & 3.5 Hz, 1 H, H-4'), 3.61 (dd, J = 14.5 Hz & 5.0 Hz, 2 H, ring CH_2), 3.40 (m, 2 H, H-5'), 2.66 (app t, J = 7.0 Hz, 1 H, H-2'), 2.14 (m, 1 H, H-2"); IR (KBr) 3500-3000 (br, OH/NH), 1690 (C=O), 1652 (C=O), 1648, 1460 cm^{-1}; MS (CI) m/z 283 (MH^+), 167, 117, 99; UV λ_{max} (H_2O) 263 nm (ε 5.1 x 10^3), 230 sh (ε 7.6 x 10^3), (pH 13.1) 293.5 (ε 7.2 x 10^3), 245.5 (ε 8.9 x 10^3), (pH 0.4) 254.5 sh (ε 6.5 x 10^3), 217.5 (ε 10.9 x 10^3).

Anal. Calcd for $C_{11}H_{14}N_4O_5 \cdot 1\frac{1}{2}\ H_2O$: C, 42.73; H, 5.05; N, 18.12. Found: C, 42.68; H, 4.83; N, 18.11.

Compound **16β** was recrystallized as a white powder from MeOH-Et_2O, yield 75 mg (26%), mp gradual dec. >200 °C: ^1H NMR (DMSO-d_6) δ 10.74 (br s, 1 H, NH-4), 7.88 (s, 1 H, H-2), 7.85 (t, J = 5.0 Hz, 1 H, NH-7), 6.03 (app t, J = 6.5 Hz, 1 H, H-1'), 5.32 (d, J = 4.0 Hz, 1 H, 3'-OH), 4.32 (m, 1 H, H-3'), 3.80 (br s, 1 H, H-4'), 3.67 (m, 1 H, one H of ring CH_2), 3.55 (m, 3 H, one H of ring CH_2 + two H-5'), 2.37 (m, 1 H, H-2'), 2.24 (m, 1 H, H-2"); IR (KBr) 3500-3000 (br, OH/NH), 1705 (C=O), 1655 (C=O), 1545, 1370 cm^{-1}; MS (CI) m/z 283 (MH^+), 223, 167, 117, 99; UV λ_{max} (H_2O) 264 nm (ε 5.8 x 10^3), (pH 13.2) 293.5 (ε 7.1 x 10^3), 247 (ε 8.7 x 10^3), (pH 0.5) 255.5 sh (ε 6.5 x 10^3), 217.5 (ε 10.9 x 10^3).

Anal. Calcd for $C_{11}H_{14}N_4O_5 \cdot 1\ H_2O$: C, 43.97; H, 5.32; N, 18.65. Found: C, 43.97; H, 4.97; N, 18.57.

Single Crystal X-ray Diffraction Analysis of Compound 9.

Colorless crystals of **9β** were grown through slow crystallization from MeOH. The unit cell dimensions were obtained by a least-squares fit of the angles of 24 accurately centered reflections in the range of 15° <2θ <25°. Intensity data were collected by using a θ-2θ scan type in the range of 2.5° ≤2θ ≤50° at room temperature, using graphite monochromated Mo·Kα (λ = 0.71073 Å) radiation. Three standard reflections monitored after every 150 reflections did not show any significant change in intensity during data collection. Intensities were corrected for Lorentz and polarization effects but not for absorption. The structures were determined by direct methods and all non-hydrogen atoms were found by using the program package SHELXTL-PLUS[17] and subsequent difference Fourier techniques. Full-matrix least-squares refinements were performed. Neutral-atom scattering factors and anomalous scattering correction terms were taken from the

Table III: Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2x10^3$) for **9β**.

Atom	x	y	z	U(eq)
O(8)	5572(2)	2220	3251(2)	48(1)
O(5)	111(2)	743(4)	5085(2)	40(1)
O(4')	6027(2)	-2532(4)	516(2)	33(1)
O(3')	8960(2)	-307(4)	771(3)	58(1)
O(5')	8832(2)	-6312(4)	724(3)	53(1)
N(1)	4755(2)	-1666(4)	2310(2)	31(1)
C(8a)	3932(2)	-443(4)	3035(2)	26(1)
C(8)	4330(3)	1535(4)	3361(2)	32(1)
N(7)	3237(3)	2533(4)	3853(3)	39(1)
C(6)	1609(3)	2092(5)	3504(3)	37(1)
C(5)	1119(2)	518(4)	4379(2)	29(1)
N(4)	1793(2)	-1178(4)	4317(2)	35(1)
C(3a)	2891(3)	-1619(4)	3508(3)	33(1)
N(3)	3046(3)	-3448(4)	3119(3)	56(1)
C(2)	4174(3)	-3414(5)	2390(3)	51(1)
C(1')	6024(2)	-1160(4)	1591(2)	27(1)
C(2')	7582(3)	-1290(5)	2523(3)	38(1)
C(3')	8595(3)	-1946(5)	1514(3)	36(1)
C(4')	7546(2)	-3309(5)	577(2)	28(1)
C(5')	7564(3)	-5353(5)	1105(3)	36(1)

*Equivalent isotropic U is one third of the trace of the orthogonalized U_{ij} tensor

International Tables for X-ray Crystallography.[18] The hydrogen atoms were located from difference Fourier maps and were included in the final refinement with fixed isotropic thermal factors (U=0.08 $Å^2$). The weight had the form, $\underline{w} = [\sigma^2(F_o) + g(F_o)^2]^{-1}$ where $g = 1.3 \times 10^{-5}$. Final cycles of refinement converged at $\underline{R} = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.037$, and $R_w = [\Sigma\underline{w}(|F_o| - |F_c|)^2/\Sigma\underline{w}(|F_o|)^2]^{\frac{1}{2}} = 0.039$. The largest parameter shifts were less than 0.01 of their estimated standard deviations. A final difference Fourier showed no features greater than $0.25\underline{e}/Å^3$. The final atomic coordinates, bond lengths, bond angles, and selected torsion angles for **9β** are collected in **Tables III-VI.** Anisotropic displacement coefficients, H-atom coordinates with isotropic displacement coefficients, and the calculated and observed structure factors for **9β** are collected in **Supplementary Tables 1-3,** and are available from authors upon request.

Table IV: Bond lengths (Å) for **9β**.

O(8)-C(8)	1.226 (3)	O(5)-C(5)	1.232 (4)
O(4')-C(1')	1.422 (4)	O(4')-C(4')	1.448 (3)
O(3')-C(3')	1.426 (4)	O(5')-C(5')	1.418 (4)
N(1)-C(8a)	1.398 (4)	N(1)-C(2)	1.339 (4)
N(1)-C(1')	1.474 (4)	C(8a)-C(8)	1.453 (5)
C(8a)-C(3a)	1.379 (4)	C(8)-N(7)	1.353 (4)
N(7)-C(6)	1.459 (4)	C(6)-C(5)	1.506 (4)
C(5)-N(4)	1.339 (4)	N(4)-C(3a)	1.394 (4)
C(3a)-N(3)	1.352 (5)	N(3)-C(2)	1.328 (5)
C(1')-C(2')	1.516 (3)	C(2')-C(3')	1.518 (4)
C(3')-C(4')	1.520 (4)	C(4')-C(5')	1.522 (5)

Table V: Bond angles (°) for **9β**.

C(1')-O(4')-C(4')	110.5(2)	C(8a)-N(1)-C(2)	106.9(2)
C(8a)-N(1)-C(1')	127.3(3)	C(2)-N(1)-C(1')	125.8(3)
N(1)-C(8a)-C(8)	124.5(2)	N(1)-C(8a)-C(3a)	104.1(3)
C(8)-C(8a)-C(3a)	130.6(2)	O(8)-C(8)-C(8a)	122.9(2)
O(8)-C(8)-N(7)	122.9(3)	C(8a)-C(8)-N(7)	114.1(2)
C(8)-N(7)-C(6)	123.6(3)	N(7)-C(6)-C(5)	113.6(2)
O(5)-C(5)-C(6)	122.3(3)	O(5)-C(5)-N(4)	121.0(3)
C(6)-C(5)-N(4)	116.7(2)	C(5)-N(4)-C(3a)	126.0(3)
C(8a)-C(3a)-N(4)	129.4(3)	C(8a)-C(3a)-N(3)	111.5(3)
N(4)-C(3a)-N(3)	119.0(3)	C(3a)-N(3)-C(2)	104.9(3)
N(1)-C(2)-N(3)	112.5(3)	O(4')-C(1')-N(1)	106.8(2)
O(4')-C(1')-C(2')	106.0(2)	N(1)-C(1')-C(2')	113.4(2)
C(1')-C(2')-C(3')	102.5(2)	O(3')-C(3')-C(2')	107.4(3)
O(3')-C(3')-C(4')	112.0(2)	C(2')-C(3')-C(4')	101.9(2)
O(4')-C(4')-C(3')	104.8(2)	O(4')-C(4')-C(5')	108.8(2)
C(3')-C(4')-C(5')	115.0(2)	O(5')-C(5')-C(4')	108.7(2)

Table VI: Selected torsion angles (°) for **9β**.

C(4')-O(4')-C(1')-N(1)	-130.0(2)	C(4')-O(4')-C(1')-C(2')	-8.8(3)
C(1')-O(4')-C(4')-C(3')	-15.1(3)	C(1')-O(4')-C(4')-C(5')	108.3(2)
C(2)-N(1)-C(8a)-C(8)	171.3(2)	C(2)-N(1)-C(8a)-C(3a)	0.2(3)
C(1')-N(1)-C(8a)-C(8)	-8.6(3)	C(1')-N(1)-C(8a)-C(3a)	-179.7(2)
C(8a)-N(1)-C(2)-N(3)	-0.6(3)	C(1')-N(1)-C(2)-N(3)	179.3(2)
C(8a)-N(1)-C(1')-O(4')	-153.6(2)	C(8a)-N(1)-C(1')-C(2')	90.0(3)
C(2)-N(1)-C(1')-O(4')	26.5(3)	C(2)-N(1)-C(1')-C(2')	-89.9(3)
N(1)-C(8a)-C(8)-O(8)	-13.4(4)	N(1)-C(8a)-C(8)-N(7)	169.2(2)
C(3a)-C(8a)-C(8)-O(8)	155.2(2)	C(3a)-C(8a)-C(8)-N(7)	-22.1(3)
N(1)-C(8a)-C(3a)-N(4)	178.7(2)	N(1)-C(8a)-C(3a)-N(3)	0.3(3)
C(8)-C(8a)-C(3a)-N(4)	8.3(4)	C(8)-C(8a)-C(3a)-N(3)	-170.1(2)
O(8)-C(8)-N(7)-C(6)	154.9(3)	C(8a)-C(8)-N(7)-C(6)	-27.8(4)

Table VI (Contd.): Selected torsion angles (°) for **9β**.

C(8)-N(7)-C(6)-C(5)	82.3(3)	N(7)-C(6)-C(5)-O(5)	122.8(3)
N(7)-C(6)-C(5)-N(4)	-59.7(3)	O(5)-C(5)-N(4)-C(3a)	177.0(2)
C(6)-C(5)-N(4)-C(3a)	-0.6(3)	C(5)-N(4)-C(3a)-C(8a)	26.8(4)
C(5)-N(4)-C(3a)-N(3)	-154.9(2)	C(8a)-C(3a)-N(3)-C(2)	-0.6(3)
N(4)-C(3a)-N(3)-C(2)	-179.2(2)	C(3a)-N(3)-C(2)-N(1)	0.8(3)
O(4')-C(1')-C(2')-C(3')	29.0(3)	N(1)-C(1')-C(2')-C(3')	145.9(3)
C(1')-C(2')-C(3')-O(3')	80.8(3)	C(1')-C(2')-C(3')-C(4')	-37.1(3)
O(3')-C(3')-C(4')-O(4')	-82.0(3)	O(3')-C(3')-C(4')-C(5')	158.6(2)
C(2')-C(3')-C(4')-O(4')	32.5(3)	C(2')-C(3')-C(4')-C(5')	-86.9(3)
O(4')-C(4')-C(5')-O(5')	160.3(2)	C(3')-C(4')-C(5')-O(5')	-82.5(3)

Crystallographic Data for Compound 9β: $C_{11}H_{14}N_4O_5$, M_r = 282.3, D_x = 1.57 g. cm^{-3}, space group $P2_1$, a = 8.393 (3) Å, b = 7.017 (3) Å, c = 9.721 (4), β = 100.35 (2), U = 596.7 (4) $Å^3$, μ_{calcd} = 1.35 cm^{-1}. Final R = 3.7%, R_w = 3.9%, for 1751 observed [$I \geq 3\sigma(I)$] reflections, out of 1984 unique reflections.

Attempted Enzymic Glycosylation of 6 with Purine Nucleoside Phosphorylase.

A mixture (total volume 285 μL) containing 6^{1d} (88 μM) or adenine (88 μM, used as a control), Tris-HCl (pH 7.4, 175 mM), dithiothreitol (DTT, 8.8 mM), α-D-ribose-1-phosphate or 2-deoxy-α-D-ribose-1-phosphate (877 μM), bovine serum albumin (219 μg/mL), and PNP (bacterial, Sigma, 1.75 μg /mL), was incubated at 37 °C for 1.5 h. The reaction mixture was analyzed by an analytical HPLC (ISCO), using a C18 column (5 x 250 mm, ISCO) and water as an eluting solvent (flow rate 1 mL/min). The effluent was monitored at 254 nm. In the control reaction, both adenine (retention time = 11.5 min) and adenosine (r.t. = 6.5 min) were detected on the chromatogram [eluent = H_2O-MeOH (85:15), flow rate = 1.5 mL/min], but only 6 (r.t. = 10.6 min) was present in the sample reaction mixture.

ACKNOWLEDGMENTS

This research was supported by a grant (# CA 36154) from the National Institutes of Health. We are grateful to Dr. Hongming Zhang and Dr. Narayan Hosmane of the Southern Methodist University, Dallas, Texas for single-crystal X-ray diffraction data of Compound 9.

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Received 8/23/91
Accepted 12/27/91