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THE UNIVERSITY OF ALBERTA

SYNTHETIC APPROACHES TO GUANINE NUCLEOSIDES AND ANALOGUES

A. SYNTHESES OF GUANINE NUCLEOSIDES VIA REGIOSELECTIVE GLYCOSYLATIONS.

B. SYNTHESES OF GUANINE NUCLEOSIDES VIA A COMBINATION OF CHEMICAL TRANSFORMATIONS AND ENZYMATIC DEAMINATION.

BY

RUIMING ZOU

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

DEPARTMENT OF CHEMISTRY

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submitted by RUIMING ZOU in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

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TO MY FAMILY

ABSTRACT

A general procedure for the regioselective synthesis of 9-glycosyl guanine nucleosides and analogues has been developed. Treatment of guanine with acetic anhydride in N,N-dimethylacetamide followed by O^6-diphenylcarbamoylation and 9-deacetylation gave N^2-acetyl-O^6-diphenylcarbamoylguanine in 83% overall yield. Trimethylsilylation of N^2-acetyl-O^6-diphenylcarbamoylguanine and subsequent coupling with glycosyl acetates or α-haloethers in toluene in the presence of trimethylsilyl triflate gave good yields of N9 substituted guanines without detected formation of the N7 isomers. For example, the coupling of silylated N^2-acetyl-O^6-diphenylcarbamoylguanine with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose afforded a 91% yield of the guanosine derivative, which was deprotected to give guanosine in 75% yield. This procedure has been applied to the coupling reactions of silylated N^2-acetyl-O^6-diphenylcarbamoylguanine with 1,2,3,5-tetra-O-acetyl-D-xylofuranose, 1,2,3,5-tetra-O-acetyl-D-arabinofuranose, 2,3,5-tri-O-benzyl-D-arabinofuranosyl chloride, 2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranosyl chloride, and (2-acetoxyethoxy)-methyl bromide to give the corresponding 9-glycosyl guanine nucleosides and analogues. X-ray crystallographic analysis of the coupling product from (2-acetoxyethoxy)methyl bromide confirmed the O^6-attachment of

the diphenylcarbamoyl group to the guanine moiety.

A complementary procedure has been found for the regioselective synthesis of 7-glycosyl guanines. Trimethylsilylation of N^2-acetylguanine followed by coupling [redacted] glycosyl acetates in 1,2-dichloroethane in the presence of stannic chloride at [redacted] temperature resulted in regioselective N7 glycosylation without significant formation of the N9 isomers. Application of these conditions to the coupling reactions of silylated N^2-acetylguanine with tetra-O-acetyl-D-furanosyl derivatives of ribose, xylose, and arabinose gave the corresponding N7 guanine nucleosides. The N7/N9 selectivity of these reactions was 15-20:1. Separation of the N7 glycosides from the minor N9 isomers was achieved by column chromatography on silica. Deprotection of the pure N7 isomers afforded the corresponding free N7 guanine nucleosides in good overall yields.

^{13}C NMR studies of our guanine derivatives have revealed that the C5 resonance peak of the N9 substituted guanines occurs at lower field than 114 ppm and that of the N7 isomers at higher field than 111 ppm. The C5 resonance regions of the two isomers do not overlap. Therefore, the C5 chemical shift, alone, can be used as a diagnostic index for differentiation between N7 and N9 guanine derivatives. The fact that the C5 chemical shift is very sensitive to changes o. N7 and N9 attachment and relatively insensitive to the nature of substituents on

the guanine moiety makes this method reliable for rapid determination of the site of attachment of N7 and N9 substituted guanines.

An indirect approach has been utilized for the synthesis of sugar-modified guanine nucleosides to avoid the inherent difficulties associated with direct transformations of guanosine. This approach involved three main steps: (1) a highly efficient chemical conversion of the experimentally uncooperative guanosine to 2,6-diamino-9-β-D-ribofuranosylpurine, (2) sugar transformation reactions on this 2,6-diaminopurine nucleoside, and (3) enzymatic deamination of the sugar-modified 2,6-diaminopurine compounds to return to their guanine counterparts. 2'-Deoxyguanosine, 3'-deoxyguanosine, 9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)guanine, 9-(2-amino-2-deoxy-β-D-arabinofuranosyl)guanine, and 9-β-D-xylofuranosylguanine have been synthesized using this approach.

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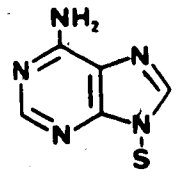
1. INTRODUCTION

Nucleic acids are of fundamental importance in storing and transmitting genetic information and controlling metabolism in living systems. The discovery of nucleic acids was reported more than a hundred years ago by Miescher[1]. He described the isolation of an acidic material containing a relatively high proportion of phosphorus and named it "nuclein". Altmann[2] later published a convenient and general method for the preparation of "nuclein" and introduced a new term "nucleic acid".

Nucleic acids are co-polymers of nucleotides that consist of three parts: (1) a heterocyclic base, (2) a pentose sugar, and (3) a phosphate residue. The combination of a heterocyclic base and a pentose is referred to as a "nucleoside", a term first introduced by Levene and Jacobs[3]. In a macromolecule of nucleic acid, nucleosides are joined together via phosphodiester linkages.

There are two general types of nucleic acids occurring in nature: (1) DNA (deoxyribonucleic acid) in which all of the sugar residues are 2-deoxy-D-ribose (2-deoxy-D-erythro-pentose) and (2) RNA (ribonucleic acids) in which all of the sugar residues are D-ribose. The four bases commonly found in DNA are adenine, guanine, cytosine, and thymine. In RNA, thymine is replaced by uracil (Scheme 1). DNA has been found to be the primary genetic substance in nature, except in cases of some viruses in which RNA takes its place.

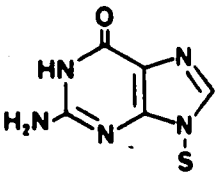
The genetic information is coded by the chemical structure of nucleic acids as specific sequences of the above mentioned bases along



S = H Adenine

S = R Adenosine

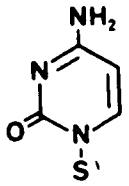
S = d-R 2'-Deoxyadenosine



S = H Guanine

S = R Guanosine

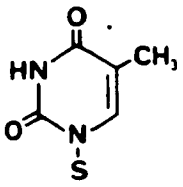
S = d-R 2'-Deoxyguanosine



S = H Cytosine

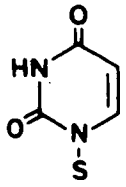
S = R Cytidine

S = d-R 2'-Deoxycytidine



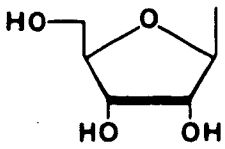
S = R Thymine

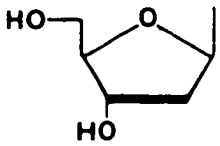
S = d-R Thymidine



S = H Uracil

S = R Uridine

R = 

d-R = 

SCHEME

the polynucleotide chain. Studies[4] of the macromolecular structure of these nucleic acids have revealed that the DNA molecule consists of two polynucleotide chains, wound together to form a double helix. This duplex has specific hydrogen bonds between purine and pyrimidine base pairs of guanine-cytosine and adenine-thymine.

DNA replication occurs during cell division. The genetic information is transmitted by the synthesis of complementary polynucleotide chains using the existing paired polynucleotide chains as templates. DNA also controls metabolic processes in cells. This is realized by the gene-controlled synthesis of specific enzymes to effect or alter these processes. Selective chemical inhibition of these important biological processes in bacterial-, virus-, or cancer-infected cells is a basis of chemotherapy for these diseases.

Nucleosides have proven to be a promising group of compounds in the search for new antiviral and anticancer agents. Nucleosides and their derivatives are required for nucleic acid biosynthesis, energy metabolism, and coenzyme functions. The biological importance of component nucleosides and the fact that a number of nucleoside analogues have shown good activity as antiviral or anticancer agents[5], have prompted considerable interest in the development of efficient new synthetic approaches to these compounds. Through the efforts of many researchers, a number of general methods[6-9] have been established and applied successfully to the synthesis of a wide variety of naturally occurring nucleosides and analogues. However, applications of these methods for the synthesis of guanine nucleosides are often much less satisfactory than in cases of adenine or pyrimidine nucleosides.

Guanine nucleosides are major components of nucleic acids of all types. Historically, guanosine was the first nucleoside to be isolated[10]. It gave guanine and a pentose on acid hydrolysis[11]. Extensive structural studies led to the conclusion that naturally occurring guanine nucleosides are 9-β-D-glycosyl compounds[12,13].

Sugar-modified guanine nucleosides have frequently been synthesized by condensation of a guanine derivative with an appropriately functionalized sugar. Specific chemical transformations on the sugar moiety of the intact nucleoside guanosine have also been employed. The alternative approach[14] involving the preparation of a glycosyl pyrimidine or imidazole with subsequent elaboration of the purine ring by cyclization requires more synthetic steps and is rarely used.

A. Syntheses of guanine nucleosides via sugar-base coupling reactions

Condensation of a heterocyclic base with a peracylated sugar is operationally simple and convenient. It is the most extensively used method for nucleoside syntheses. In practice, the reaction is performed by using one of the following general procedures.

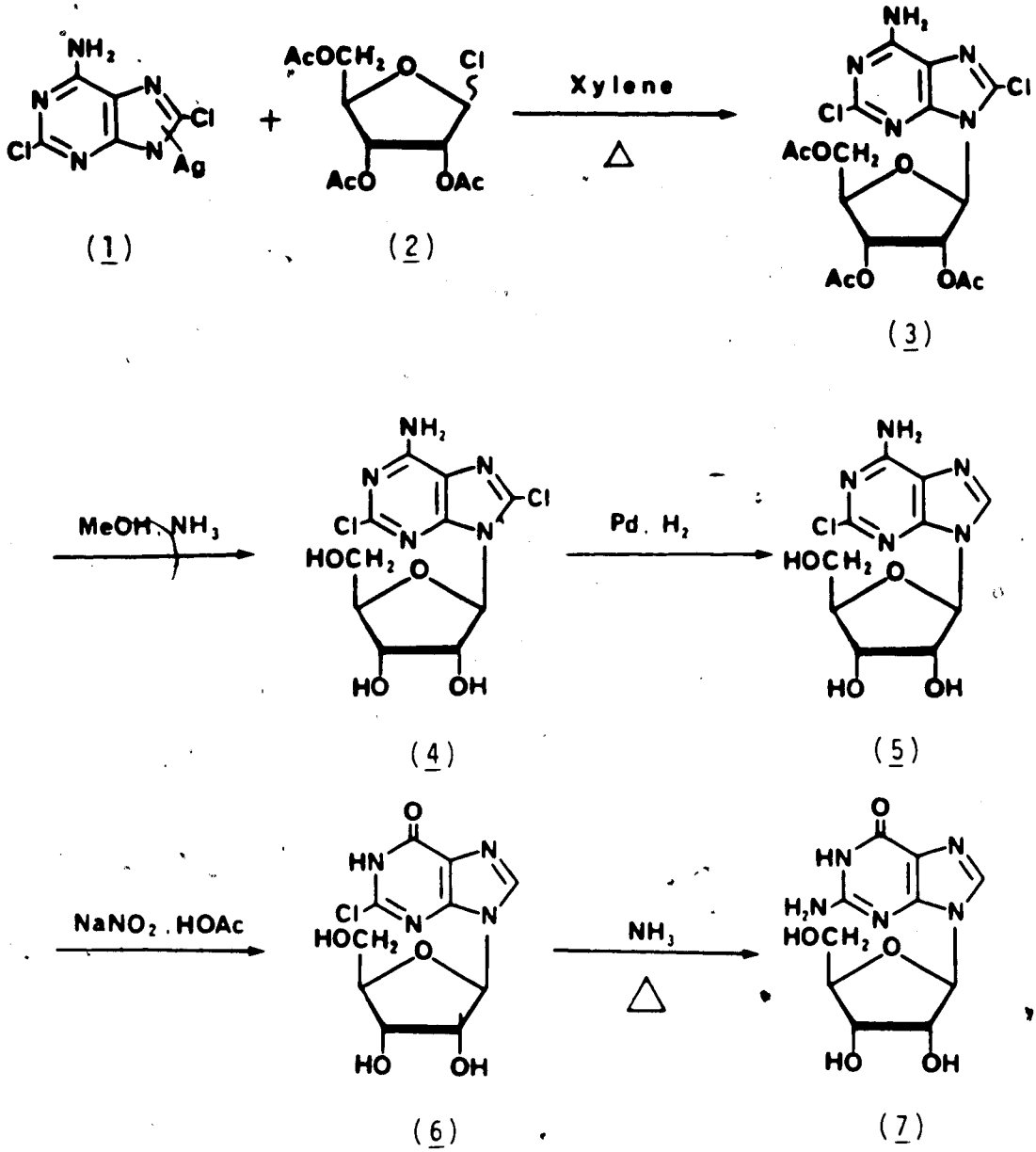
a. The heavy metal salt procedure

The heavy metal salt procedure was developed early in the nucleoside literature. In this procedure, the silver or mercury salt of a heterocyclic base is condensed with a protected glycosyl halide in hot xylene to afford the corresponding protected nucleoside.

Fischer and Helferich[15] achieved the first synthesis of nucleosides using the silver salt procedure with 2,3,4,6-tetra-O-acetyl-α-D-glycopyranosyl bromide. This procedure was later used by Todd and co-workers[13] for the first synthesis of guanosine (Scheme 2). Condensation of the silver salt of 2,8-dichloroadenine (1) with 2,3,5-tri-O-acetyl-D-ribofuranosyl chloride (2) followed by deacetylation yielded 2,8-dichloro-9-β-D-ribofuranosyladenine (4). The 8-chloro group was selectively removed by catalytic hydrogenolysis. Subsequent deamination with nitrous acid followed by amination at the 2-position gave guanosine (7). This synthetic compound was identical with the natural product guanosine. Adenosine also was synthesized from (4) by complete hydrogenolytic dechlorination[16].

Shabarova et al.[17] employed the related chloromercury procedure for the synthesis of 9-β-D-glucopyranosylguanine (13) using N^2-acetylguanine as the starting material (Scheme 3). Coupling of the mercury salt of N^2-acetylguanine (9) with 2,3,4,6-tetra-O-acetyl-α-D-glycopyranosyl bromide (10) was found to produce a mixture of N9 (11) and N7 (12) isomers with β configurations at the anomeric centres. The stereoselective formation of the β-anomers could be explained in terms of neighboring group participation[18]. Deprotection of the mixture gave a 27% yield of the corresponding free nucleosides (13) and (14), from which the N9 isomer (13) was isolated by repeated recrystallization.

This procedure was utilized by Walton and co-workers[19] for the preparation of 3'-deoxyguanosine. The formation of the N7 nucleoside isomer was again observed.


NH2
N
N
Cl
Cl
N
N
Ag
(1)
+
AcOCH2
O
Cl
AcO
OAc
(2)
Xylene
△
NH2
N
N
Cl
Cl
N
N
AcOCH2
O
AcO
OAc
(3)
MeOH, NH3
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HOCH2
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NaNO2 . HOAc
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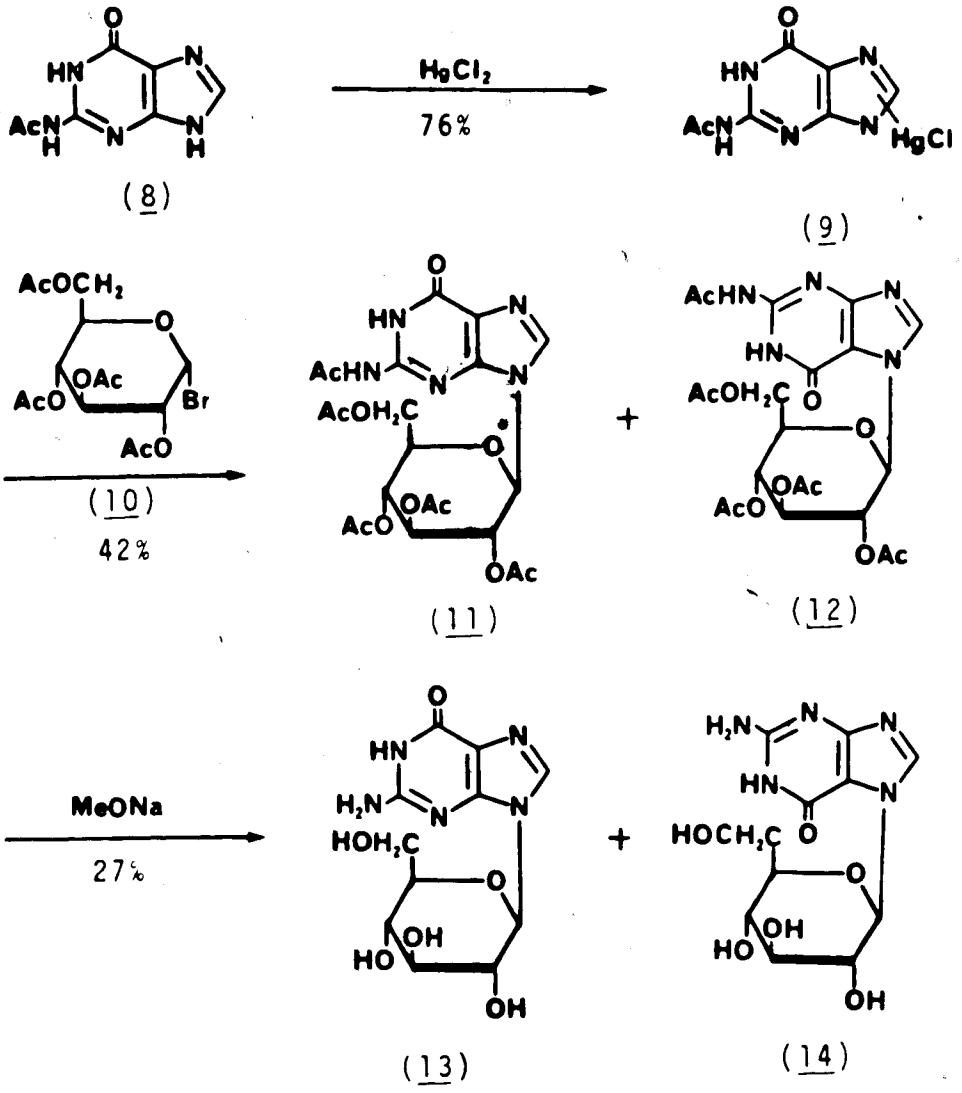
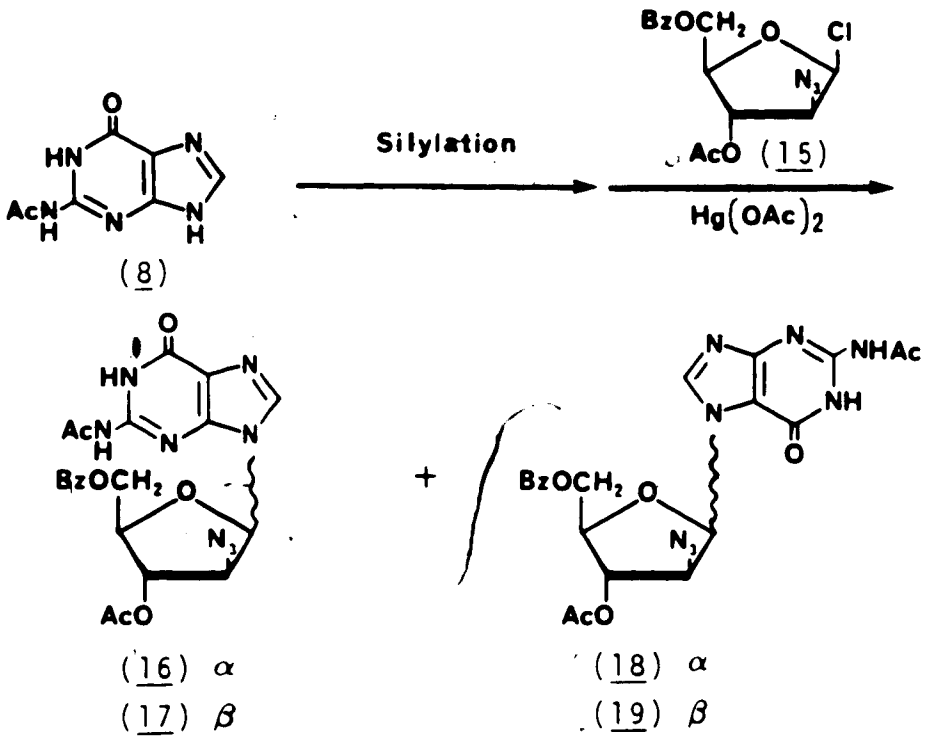
(7)

SCHEME 2



SCHEME 3

Mercuric salts also have been used to catalyse silyl Hilbert-Johnson reactions. Bobek[20] described the synthesis of 2'-azido guanosine derivatives via a mercury catalysed silyl Hilbert-Johnson reaction (Scheme 4). Condensation of the silyl derivative of N^2-acetylguanine with the chloro sugar (15) yielded not only N9 and N7 positional isomers, but also α and β anomers. The formation of β anomers was expected because of the absence of a participating group at the 2-position of the chloro sugar.



SCHEME 4

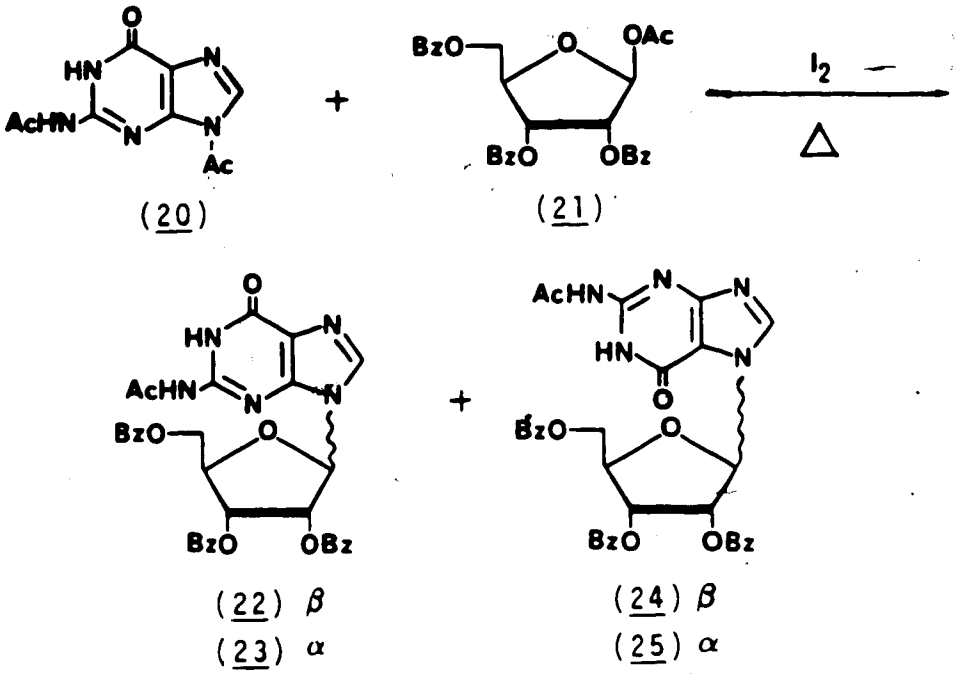
In addition to the chemical problems involving formation of side products using this procedure, mercury contamination of the nucleoside product is often a critical biological problem. Even trace amounts of mercury in the product can lead to false positive cytotoxicity

conclusions. For these reasons, the heavy metal salt procedure is seldom used in recent years.

b. **The fusion procedure**

The so-called fusion procedure was developed by Sato et al.[21,22] It involves heating a heterocyclic base with a peracylated sugar and a Lewis acid catalyst.

Imai and co-workers[23] applied this procedure to the synthesis of guanosine derivatives (Scheme 5). Fusion of N^2,9-diacetylguanine (20)



SCHEME 5

with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (21) in the presence of iodine afforded a mixture of acyl derivatives of guanine ribosides in 51% crude yield. Complete separation of the reaction products was not achieved. The unexpected formation of α anomers indicated that the fusion reaction did not follow Baker's trans rule[18].

Similar results were obtained by other investigators[24,25] in attempts to synthesize guanine nucleosides by fusion reactions.

A more detailed study[26] on the product distribution in fusion reactions employed glycosylations of N^2-acetylguanine with various fully acetylated sugars. The results showed that the anomeric configuration of the starting sugar had little effect on the product distribution. On the other hand, there was constancy in the ratio of N9 to N7 isomers observed in all the examples. This constancy also was apparent in fusion reactions of N^2-acetylguanine with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose using different catalysts. These observations suggested that the ratio of N9 to N7 isomers was dependent on the structure of the base derivative, but was not affected by the sugar or the catalyst under the specified fusion conditions. Subjection of individual nucleoside products to the fusion conditions was found to produce a similar mixture of positional isomers and anomers. This product ratio was similar to that observed in the initial fusion reactions. Therefore, it was concluded that the product distribution in these fusion reactions was determined by the thermodynamic stability of the products.

c. The silyl Hilbert-Johnson procedure

Modification of the original Hilbert-Johnson procedure with alkoxypyrimidines by using silylated bases in nucleoside synthesis overcame several disadvantages[6] of the classic method and further extended its applicability to the purine nucleoside series. Due to its superiority over other methods, the silyl procedure has been developed

as a general method for nucleoside synthesis.[8,27-34] Silylation transforms the normally insoluble bases into silylated derivatives that are very soluble in organic solvents. This ensures that the glycosylation reactions proceed in homogenous systems.

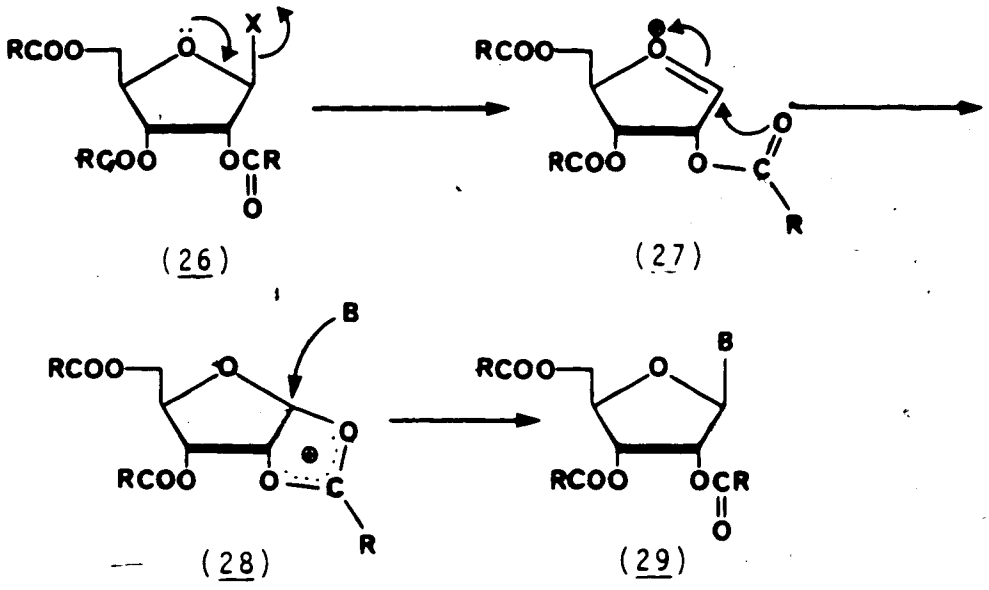
The silylated bases are readily obtained in near quantitative yields by treating heterocyclic bases with commercially available reagents such as hexamethyldisilazane (HMDS), trimethylsilyl chloride (TMSC), or N,O-bis(trimethylsilyl)acetamide (BSA). After the glycosyl condensation is completed, the trimethylsilyl groups are hydrolysed during the aqueous work-up procedure. These advantages contribute to making the silyl procedure one of the best for nucleoside syntheses.

In guanine nucleoside synthesis, the most frequently used base components have been N^2-substituted guanine derivatives since these compounds are more soluble than guanine and therefore undergo silylation more readily. Furthermore, the N^2-substituent improves the solubility of the nucleoside product and thus facilitates the work-up procedure. Guanine and its N^2-substituted derivatives are usually high melting compounds that often decompose before melting. They are almost completely insoluble in most solvents. In contrast, their silyl derivatives are viscous oils that can be distilled in some cases[35]. They are very soluble in most aprotic solvents.

The sugar components used in coupling reactions are usually peracylated glycosyl halides or acetates. Glycosyl halides are very reactive α-haloethers that permit generation of stabilized sugar cations under mild coupling reaction conditions. On the other hand, direct S_N2 displacement of the glycosyl halogen atom by lone-pair electrons of the

heterocyclic base is also possible. The amorphous furanosyl halides are rather unstable and decompose on standing. Hence, freshly prepared material is required for each condensation. The 1-O-acetyl sugars are much more convenient to use because they are quite stable. Some of them can be crystallized readily and are commercially available reagents. Under coupling reaction conditions, the 1-O-acetyl group reacts with the catalyst to generate a glycosyl cation that is attacked by the heterocyclic base to form a nucleoside.

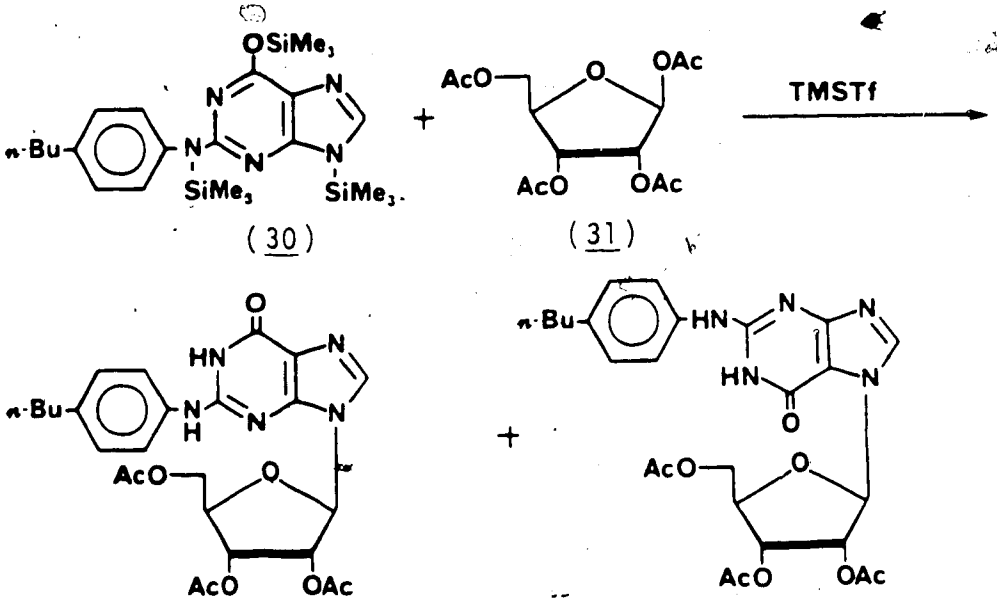
The anomeric configuration of the nucleoside product is primarily dependent upon the structure of the sugar component. Baker et al.[18] noted that when a participating group is present at C2 of the sugar component, the nucleoside is formed with a C1 to C2 trans configuration. The exclusive formation of the trans product was rationalized by the formation of an acyloxonium ion intermediate (28) by participation of the adjacent 2-acyloxy group (Scheme 6). Attack of



SCHEME 6

the heterocyclic base at C1 gives the nucleoside with C1 and C2 substituents trans to each other. However, if the glycosyl component is a 2-deoxy sugar or bears a nonparticipating group at C2, control of the anomeric configuration is usually lost. A mixture of nucleoside anomers is ordinarily produced presumably via attack of the heterocyclic base on a sugar cation analogous to (27) from either side, or by direct S_N2 displacement at C1 of the anomeric mixture of gylcosyl halides.

Wright and Dudycz[36] have recently applied the silyl procedure to the synthesis of N^2-(p-n-butylphenyl)guanine nucleosides (Scheme 7). Coupling of silylated N^2-(p-n-butylphenyl)guanine (30) with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (31) using trimethylsilyl triflate as catalyst gave a mixture of N9 (69%) and N7 (11%) positional isomers. The anomeric configuration of both products was found to obey Baker's



(30) (31)

(32) 69% (33) 11%

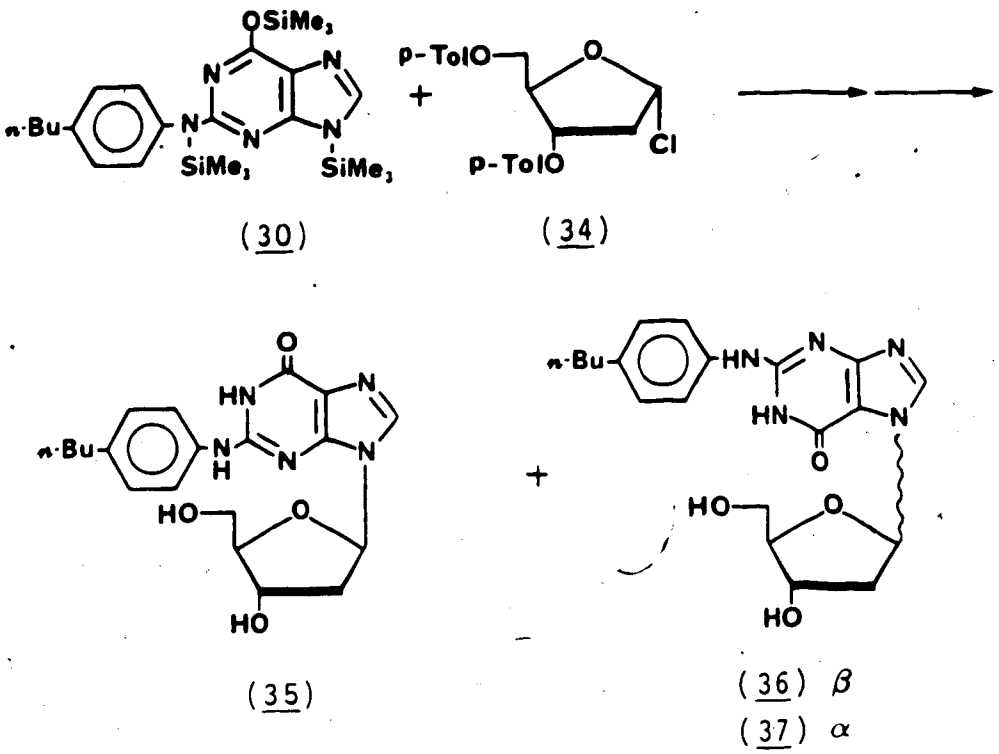
TMSTf = $CF_3SO_3SiMe_3$

SCHEME 7

trans rule. Mechanistic studies[37] of the glycosylation reaction showed that the 7-β isomer (33) was formed first and was subsequently isomerized to the more stable 9-β compound (32). A mixture of 9-β and 7-β isomers was obtained after a few hours with an isomeric ratio of 70-80:5-15. A similar mixture of 9-β and 7-β isomers was obtained upon subjection of each pure (9-β or 7-β) isomer to the glycosylation conditions. This N9⇌N7 interconversion is characteristic for guanine nucleoside syntheses effected at elevated temperatures and results in an equilibrium mixture of products.[6,38] The yield of a particular isomer under these conditions is dependent on the relative stability of that product. A 7,9-bis(ribosyl) nucleoside, which was isolated as a minor product of the glycosylation reaction, was postulated as an intermediate in the N9⇌N7 interconversion[37]. This was supported by the fact that the use of a two-fold excess of sugar in the glycosylation mixture accelerated the conversion of N7 to N9 isomers.

Coupling of the same base (30) with 2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranosyl chloride (34) allowed isolation of one α- and two β-anomers of the N7 and N9 isomeric 2'-deoxynucleoside products[36] (Scheme 8). The formation of α-anomer was expected because of the absence of a C2 participating group.

Applications of the silyl procedure to the synthesis of other guanine nucleosides have been reported.[31,39-42] The formation of N9 and N7 positional isomers was usually reported for these coupling reactions.



(30) (34)

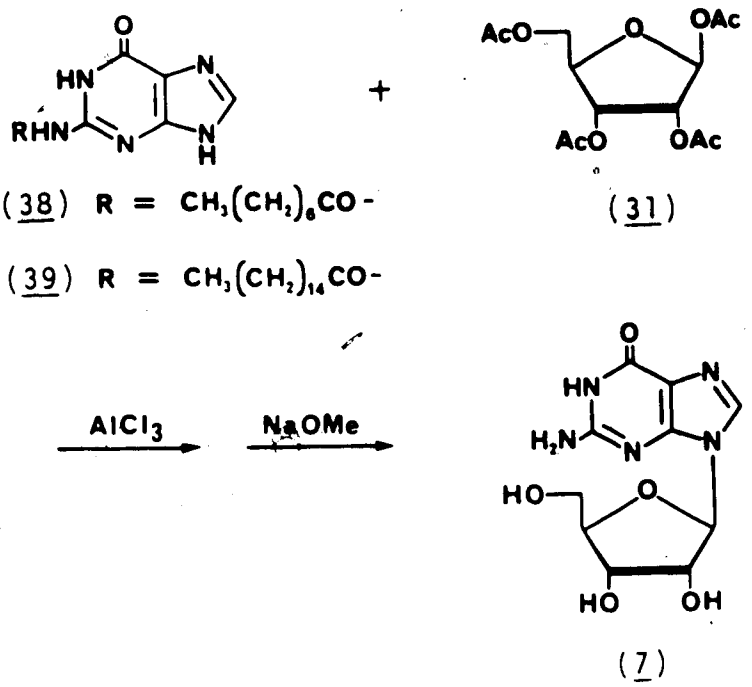
(35) (36) β (37) α

SCHEME 8

d. **The "Friedel-Crafts procedure"**

Since many coupling reactions involve attack of a sugar cation on an aromatic heterocycle, Friedel-Crafts catalysts have been evaluated and found to be effective. Furukawa and Honjo[43] studied the coupling of N^2-octanoylguanine (38) and N^2-palmitoylguanine (39) with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (31) in chlorobenzene in the presence of aluminium chloride (Scheme 9). These reactions afforded guanosine in 36% and 66% crude yields, respectively. Only a small amount of minor product was detected in the mother liquor. Its UV spectrum corresponded to that of 7-methylguanine.

A few years later, Lee et al.[44] attempted to apply this procedure for the preparation of "xylo-guanosine" derivatives using N^2-palmitoylguanine (39) and N^2-nonanoylguanine (40) (Scheme 10). It



(38) R = $CH_3(CH_2)_6CO$-

(39) R = $CH_3(CH_2)_{14}CO$-

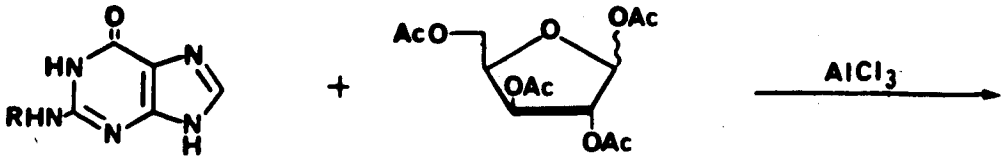
(31)

(7)

SCHEME 9

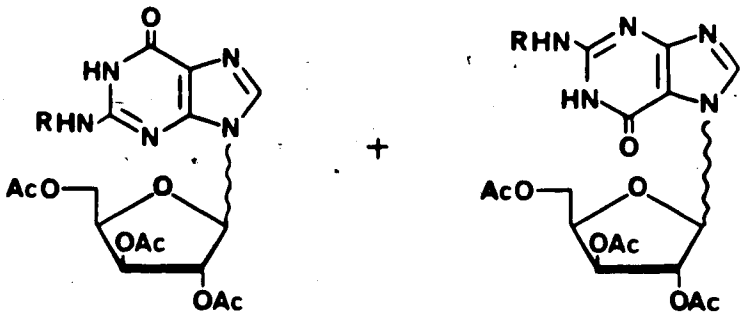
was reported that N^2-palmitoylguanine gave a higher ratio of N9 to N7 nucleosides than N^2-nonanoylguanine. This is surprising because one would expect that the bulkier group at the N^2-position would hinder the N9 position more than the N7 position. Moreover, it was found that α-anomers were formed in amounts equivalent to those of the β-anomers for both the N9 and N7 isomers and both N^2-acylguanines. A substantial improvement in the ratio of β-anomer (α:β=1:4) of the N9 isomer was realized by slow addition of the sugar (41) to the preformed complex of N^2-nonanoylguanine and aluminium chloride. However, the anomeric ratio of the N7 isomer remained unchanged[44].

Using the same procedure, treatment of N^2-nonanoylguanine with 1,2,3,5-tetra-O-acetyl-D-arabinofuranose afforded some N7 nucleoside with the N9 isomer as the major product[44]. The α-anomer was



(39) R = $CH_3(CH_2)_{14}CO$-

(40) R = $CH_3(CH_2)_7CO$-



(42) (43)

SCHEME 10

predominant for both the N9 and N7 isomers. The reaction with the preformed complex of N^2-nonanoylguanine and aluminium chloride did not alter the anomeric ratio of the nucleoside products. Although these experimental results are difficult to interpret, it is clear that the product distribution is affected by the structures of the base and sugar used.

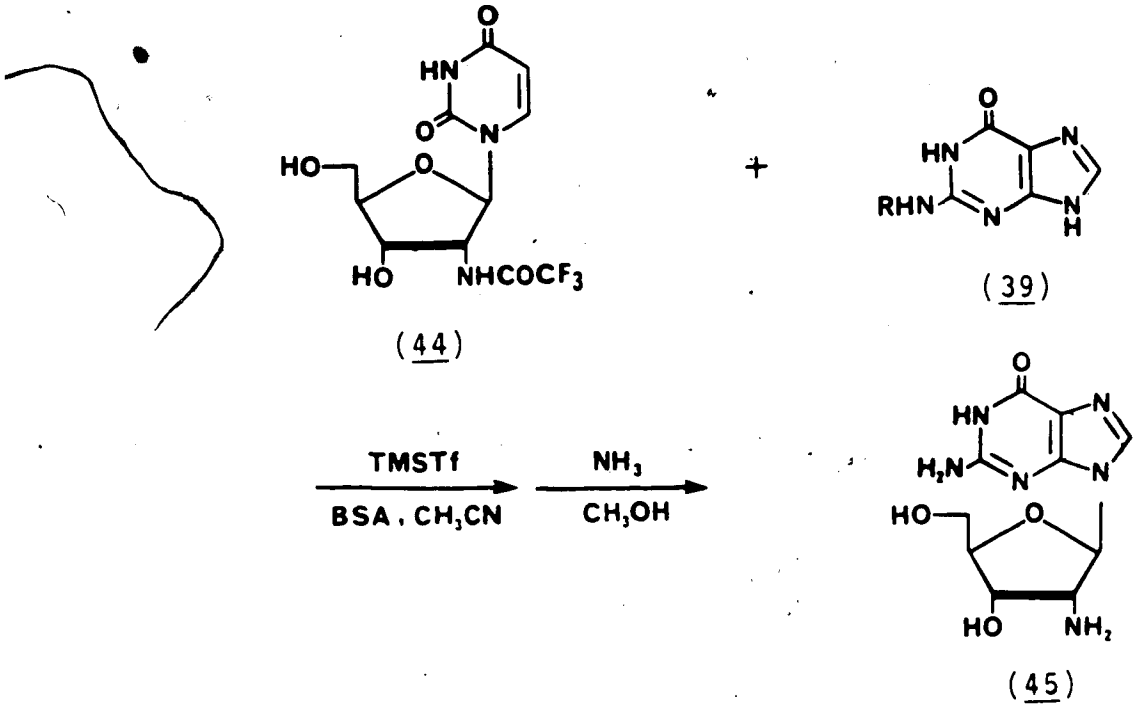
e. **Trimethylsilyl triflate and transnucleosidation**

In addition to the nature of the base and sugar derivative used in coupling reactions, the nature of the catalyst is important for the outcome of nucleoside syntheses.

Trimethylsilyl triflate, which was introduced by Vorbrüggen et al.,[30-34] was found to be an excellent catalyst for the silyl

Hilbert-Johnson reaction. It results in formation of higher ratios of the natural nucleosides that are more thermodynamically stable than other positional isomers. The use of this catalyst also facilitated the work-up procedure in comparison with stannic chloride catalysed silyl Hilbert-Johnson reactions, in which the formation of emulsions was often encountered.

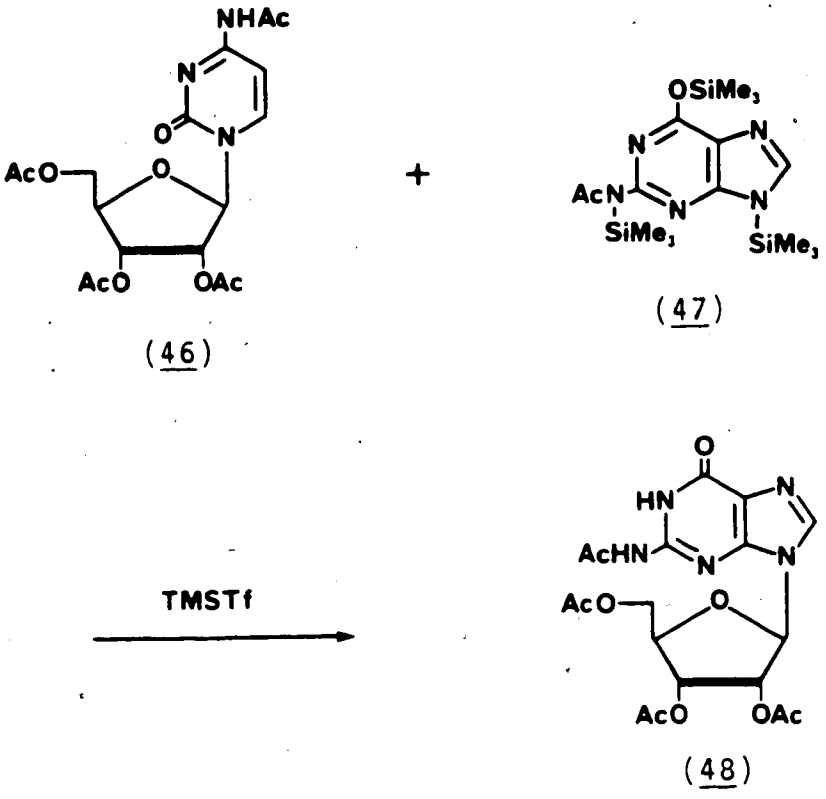
Studies also revealed that trimethylsilyl triflate catalysed the cleavage of some nucleosides with rearrangement to the more stable isomers[31]. This led to applications in transnucleosidation reactions in which the sugar moiety of a pyrimidine nucleoside was transferred to a purine base. Imazawa and Eckstein[45] applied this method successfully to the synthesis of 2'-amino-2'-deoxyguanosine (45) (Scheme 11).



SCHEME 11

Treatment of the uridine derivative (44) with silylated N^2-palmitoylguanine catalysed by trimethylsilyl triflate gave the desired N9 guanine nucleoside (45) in 60% yield after deblocking. This was superior to a previous method[46] which required several steps to get the modified sugar from an azidouridine derivative.

In another example[47], the sugar moiety from a cytidine derivative (46) was transferred to N^2-acetylguanine in the presence of trimethylsilyl triflate (Scheme 12). The yield of the 9-β nucleoside (48) was 66%. A minor product (- 2%) was assumed to be the N7 isomer from its UV spectrum.



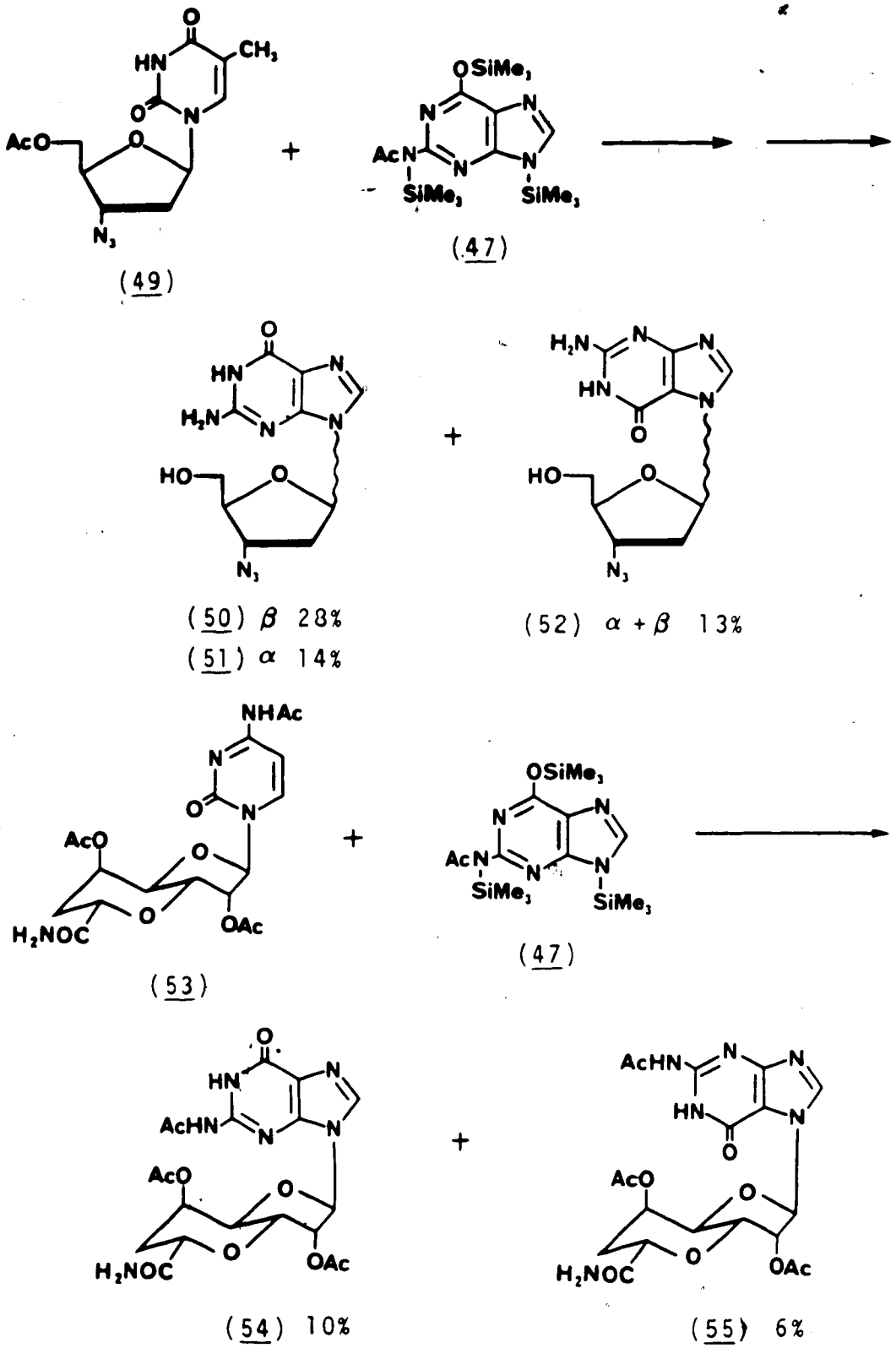
SCHEME 12

Transfers of certain other sugar moieties[47,48] to the N9 position of N^2-acetylguanine were less satisfactory since the N7 isomers were produced in considerable amounts (Scheme 13).

Mercuric bromide and stannic chloride also have been used to catalyse transnucleosidations[49], but the results were not as good as those with trimethylsilyl triflate. These transnucleosidation reactions clearly demonstrated the reversible nature of nucleoside synthesis by sugar-base condensations.

f. Syntheses of "acyclic guanine nucleosides"

In recent years, a number of acyclic nucleoside analogues of 2'-deoxyguanosine have been shown to possess a high degree of potency and selectivity against viruses of the herpes group. A typical example is 9-[(2-hydroxyethoxy)methyl]guanine (acycloguanosine, acyclovir). It contains an acyclic side chain which mimics the carbohydrate portion of natural nucleosides. Acycloguanosine is quite nontoxic to uninfected host cells, but it shows high antiviral activity in cells infected with herpes simplex viruses (HSV). This selective toxicity is attributed to phosphorylation of the acyclic nucleoside to monophosphate in infected cells by HSV-coded thymidine kinase. Subsequent phosphorylation to the di- and triphosphate levels is effected by host cell enzymes. The acyclic nucleoside triphosphate interferes with HSV replication by inhibition of the virus-specified DNA polymerase[50]. These findings have prompted tremendous efforts in the chemical synthesis of related acyclic nucleoside analogues. Examples of syntheses of certain acyclic guanine nucleosides are given in References 50-75.

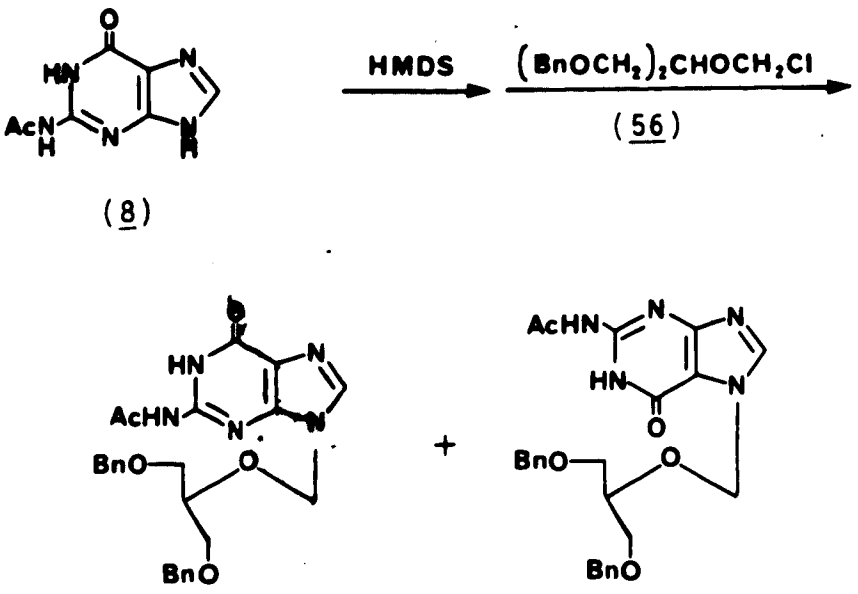


SCHEME 13

Generally, the synthesis of acyclic nucleosides can be achieved by alkylation of a base derivative. The use of alkyl halides (α-haloethers) is practical since they are reactive but fairly stable for storage. The corresponding alkyl acetates are less reactive under coupling conditions and require a Lewis acid catalyst. Reactions with alkyl halides (α-haloethers) may proceed via direct S_N2 displacement rather than by formation of an alkyl cation.

The silyl procedure has been employed extensively for the synthesis of acyclic nucleosides.[51-57] Ogilvie and co-workers[52] applied this procedure for the preparation of 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine, which is the most potent antiherpetic member in the group in certain systems (Scheme 14). Condensation of silylated N^2-acetylguanine with (1,3-dibenzyloxy-2-propoxy)methyl chloride (56) afforded a mixture of blocked nucleoside analogues with a N9 to N7 ratio of 1:1. Under similar conditions, the condensation using silylated guanine in place of silylated N^2-acetylguanine gave N9 and N7 isomers in 41% and 11% yields, respectively. The tedious step in this route was the silylation of guanine, which required four days at reflux in hexamethyldisilazane to complete. Separation of the positional isomers was difficult owing to their similar chromatographic mobilities in all solvents investigated. It was found that after deblocking they could be separated by repeated recrystallization[52].

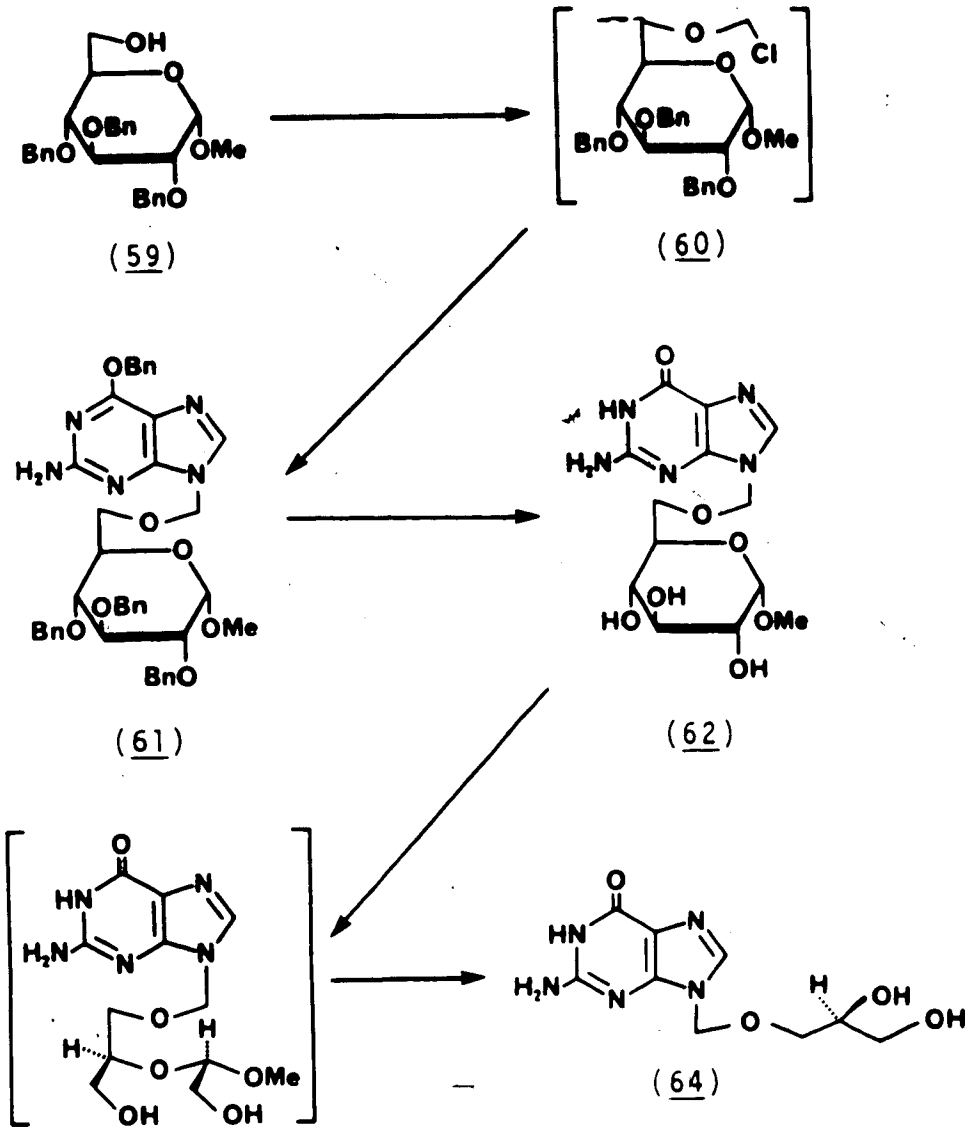
The fusion procedure also has been used for the synthesis of acyclic nucleosides.[58-60,72] The previously noted disadvantageous formation of anomeric mixtures with this procedure is not a concern



SCHEME 14

here since most acyclic nucleoside analogues do not have a chiral centre at the site of attachment to the base. Therefore, a simple mixture of N9 and N7 positional isomers is expected from the coupling of a guanine derivative under fusion conditions.

Recently, MacCoss et al.[62] described a new approach to the synthesis of an optically active acyclic nucleoside, (S)-9-[2, 3-dihydroxy-1-propoxy)methyl]guanine (64), starting from the readily available methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (59). This approach utilized the chirality of C5 of D-glucose to give a single enantiomer (64) (Scheme 15). The glucose derivative (59) was chloromethylated and subsequently coupled with the sodium salt of O^6-benzylguanine to afford the guanine nucleoside (62) after debenzylation. Periodate oxidation followed by sodium borohydride


OH
O
OBn
BnO
OMe
BnO
(59)
O
Cl
O
OBn
BnO
OMe
BnO
(60)
OBn
N
N
H2N
N
N
O
O
OBn
BnO
OMe
BnO
(61)
O
HN
N
H2N
N
N
O
O
OH
HO
OMe
OH
(62)
O
HN
N
H2N
N
N
O
H
O
OMe
OH
OH
(63)
O
HN
N
H2N
N
N
H
OH
O
OH
(64)

SCHEME 1

reduction cleaved the glucose ring and gave the acyclic derivative (63), which upon acid treatment provided the desired (S)-enantiomer (64). The (S)-enantiomer showed broad-spectrum antiviral activity whereas the (R)-enantiomer is inactive.

It is noteworthy that an O^6-protected guanine derivative was used in the coupling reaction. After chromatography, the desired N9 product (61) was obtained in 43% yield. Since O^6-protected guanine derivatives are rarely used in coupling reactions (probably due to their unavailability), it would be interesting to evaluate the influence of the O^6-protecting group on product distributions in coupling reactions. However, in this case, the side products of the coupling reaction were not reported.[62]

During the preparation of this thesis, a communication by Kjellberg and co-workers[75] claimed regioselective N9 alkylation of O^6-(β-methoxyethyl)guanine with a N9 to N7 ratio up to 15:1.

g. Syntheses of guanine nucleosides from 2,6-disubstituted purines

Direct condensations of guanine or N^2-substituted guanines with peracylated sugars normally lead to mixtures of N9 and N7 positional isomers. Further complication by formation of anomers is also observed in many cases. Separation of these positional and anomeric isomers is usually difficult because of their amphoteric nature, limited solubility, and similar chromatographic mobility. Therefore, indirect approaches have been explored to avoid these disadvantages.

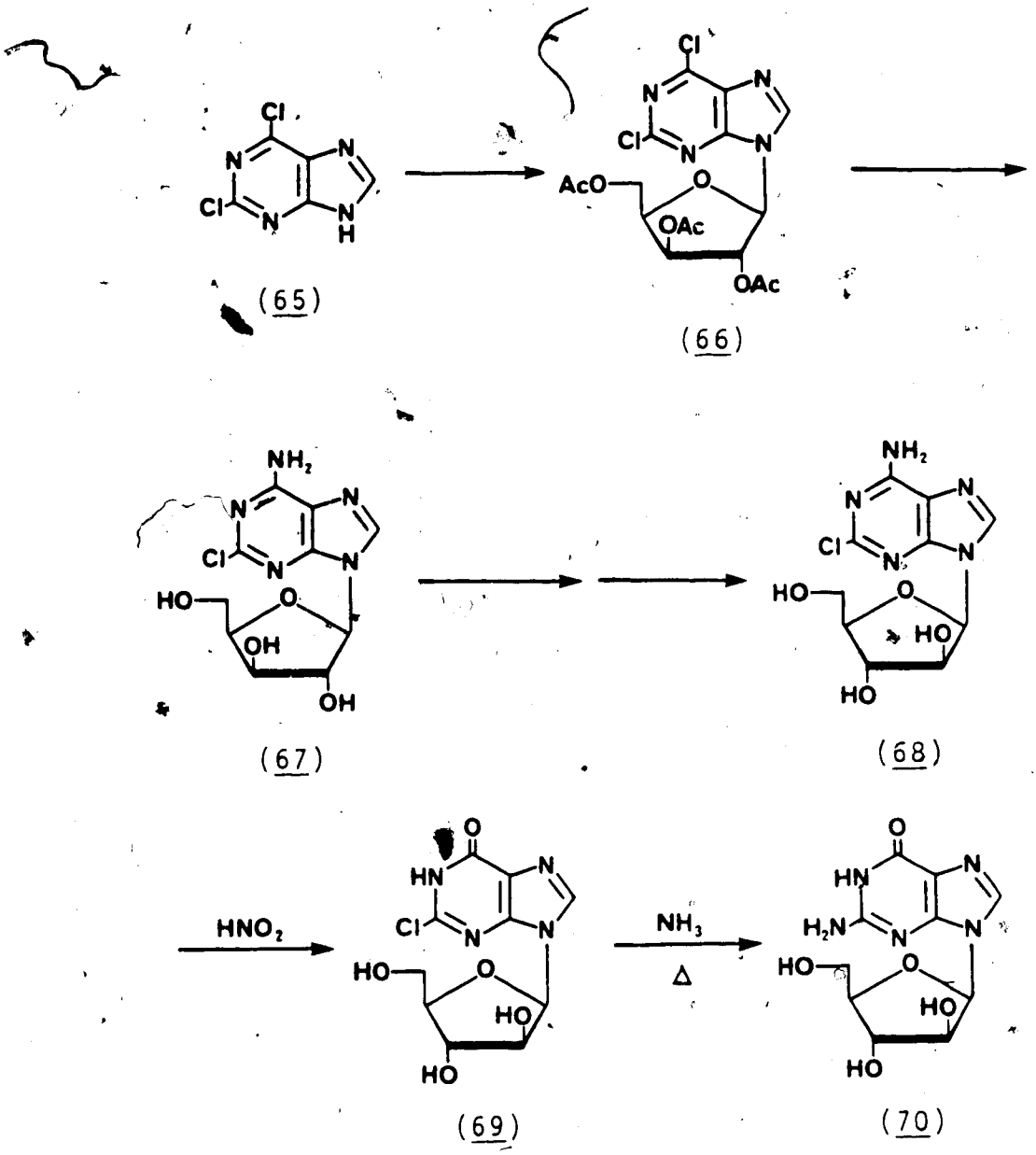
Indirect approaches have involved condensations using

2,6-disubstituted purines other than guanine or N^2-protected guanines and subsequent chemical conversions of the 2,6-disubstituted purine moiety to guanine. Such approaches have employed 2,6-dichloropurine, 2,6-diaminopurine, and 2-amino-6-chloropurine.

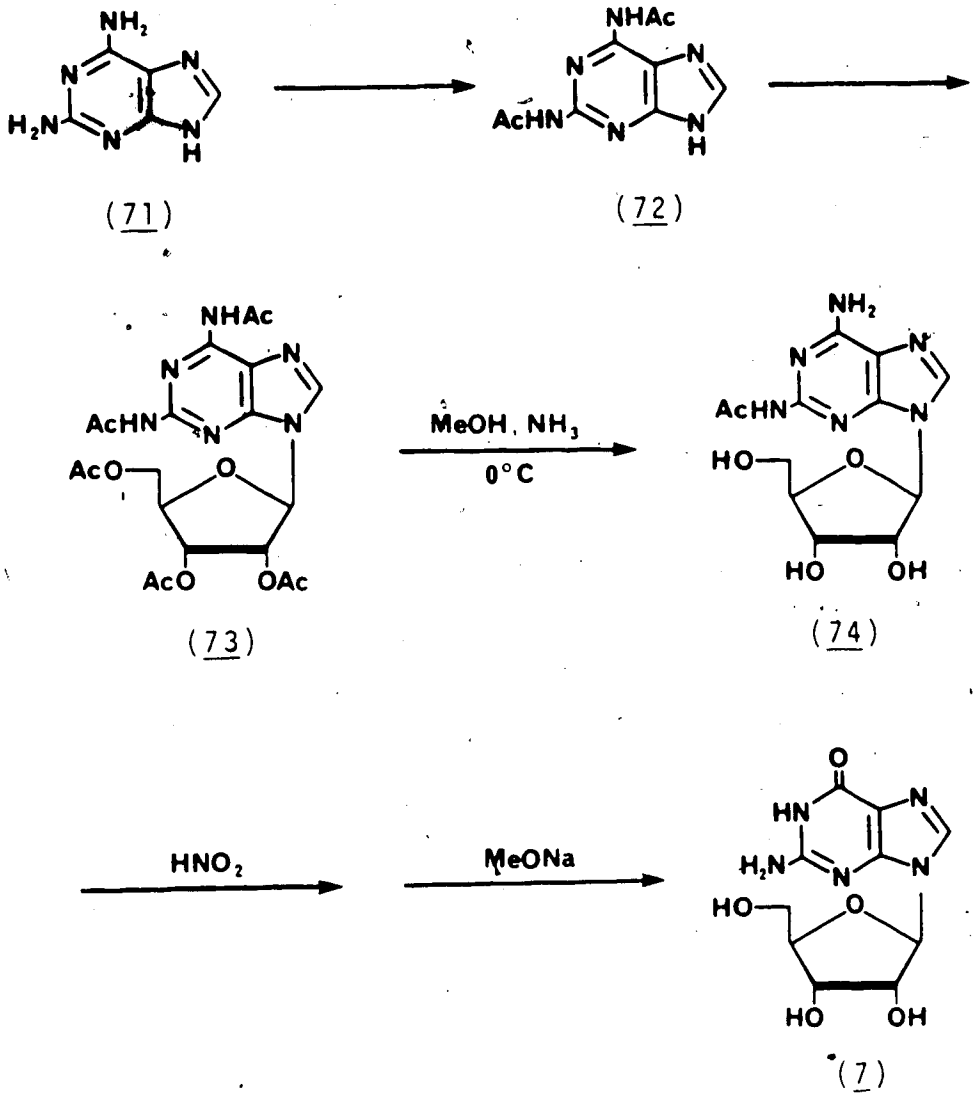
Reist and Goodman[76] have prepared 9-(β-D-arabinofuranosyl)guanine (70) from 2,6-dichloropurine (65) (Scheme. 16). Fusion of 2,6-dichloropurine (65) with 1,2,3,5-tetra-O-acetyl-D-xylofuranose afforded the desired N9 nucleoside (66). Subsequent treatment with methanolic ammonia resulted in replacement of the 6-chloro by an amino group and concomitant removal of the acetyl groups. After multistep transformation of the sugar moiety from xylose to arabinose, the resulting nucleoside (68) was deaminated with nitrous acid to give 2-chlorohypoxanthine arabinoside (69). Aminolysis of (69) at elevated temperature effected replacement of the 2-chloro by amino to afford the targeted guanine product.

Davoll and Lowy[77] employed 2,6-diaminopurine as a guanine precursor in the synthesis of guanosine (Scheme 17). Conversion of 2,6-diaminopurine (71) into 2,6-diacetamidopurine (72) was followed by formation of its mercury salt. This was condensed with 2,3,5-tri-O-acetyl-D-ribofuranosyl chloride to give the desired N9 nucleoside (73). Treatment of (73) with methanolic ammonia at 0°C preferentially removed the acetyl groups from the sugar moiety and the 6-amino group. This was the key step that allowed discrimination between the two acetamido groups. Deamination at the 6-position followed by removal of the remaining N^2-acetyl group gave guanosine.

Later, the same reaction sequence was applied successfully for the synthesis of 9-β-D-ribopyranosylguanine[78] and 9-(3-amino-3-deoxy-β-D-ribofuranosyl)guanine[79].

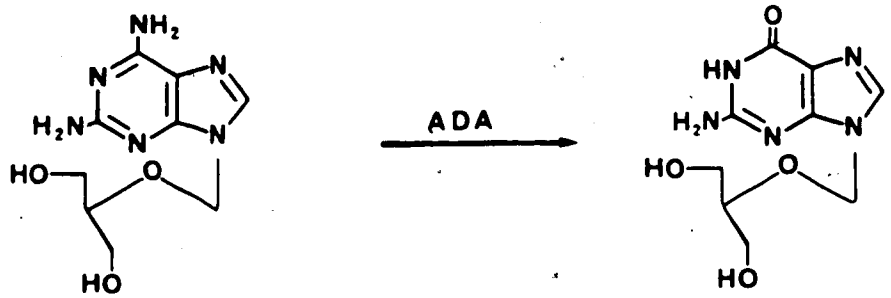


SCHEME 16


NH2
N
H2N
N
N
H
(71)
NHAc
N
AcHN
N
N
H
(72)
NHAc
N
AcHN
N
N
AcO
O
AcO
OAc
(73)
MeOH, NH3
0°C
NH2
N
AcHN
N
N
HO
O
HO
OH
(74)
HNO2
MeONa
O
HN
N
H2N
N
N
HO
O
HO
OH
(7)

SCHEME 17

With unprotected 2,6-diaminopurine nucleosides, chemical deamination with nitrous acid gave only isoguanine (6-aminopurin-2-one) nucleosides resulting from selective deamination at the 2-position.[77,79] However, exclusive deamination at the 6-position was effected using the enzyme adenosine deaminase (ADA) to give guanine nucleosides in high yields.[67,80-82] Thus, 2,6-diamino-9-[(1,3-dihydroxy-2-propoxy)-methyl]purine (75) was converted to the corresponding guanine counterpart (76) in near quantitative yield[67] (Scheme 18). Adenosine deaminase also was used to effect hydrolytic replacement of 6-substituents besides the amino group, such as chloro and methoxy groups to afford guanine nucleosides.[56,81,83]

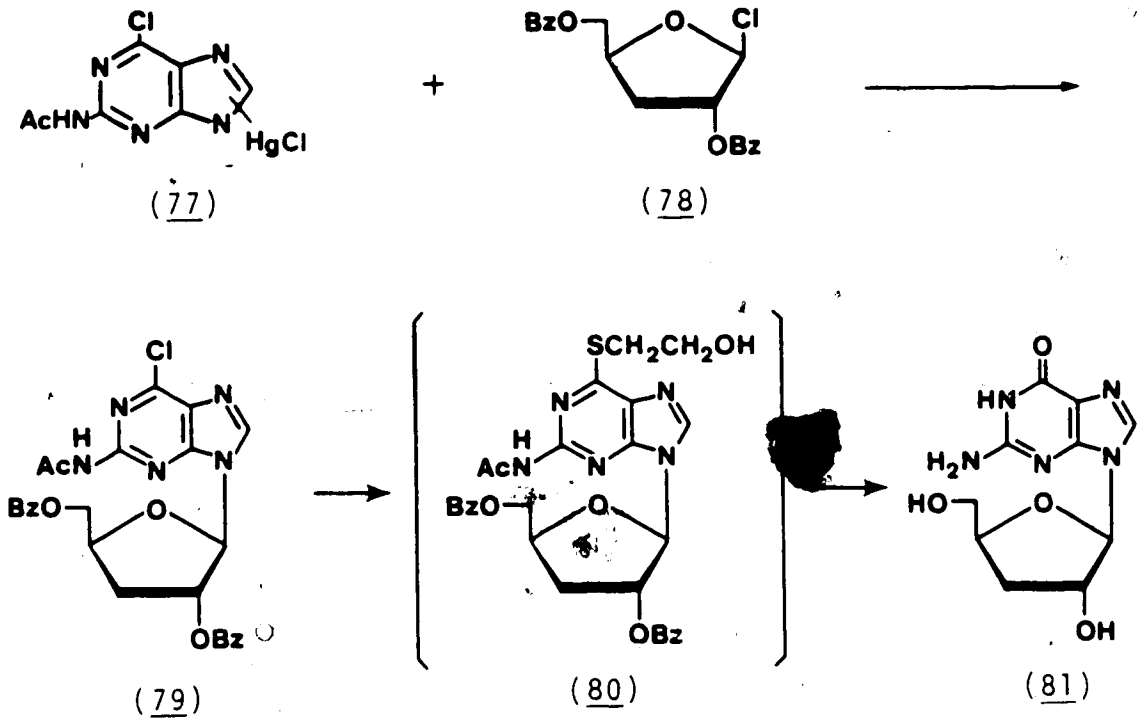


(75) (76)

ADA = Adenosine Deaminase

SCHEME 18

Another useful guanine precursor is 2-amino-6-chloropurine. Lee and Tong[84] prepared 3'-deoxyguanosine (81) starting with a derivative of this base (Scheme 19). Condensation of the mercury salt (77) with



SCHEME 19

chloro sugar (78) yielded the N9 nucleoside (79). This intermediate was converted to 3'-deoxyguanosine by treatment with methanolic sodium methoxide and 2-mercaptoethanol, which effected overall hydrolysis of the 6-chloro group and acyl deprotection.

2-Amino-6-chloropurine appears to have general applicability for the synthesis of N9 guanine nucleosides and analogues and has been

used by a number of researchers.[52,56,66,85-89] However, it is expensive and sometimes suffers from lower yields unless mercury salts are employed. Less generally applied syntheses of guanine nucleosides from other purine derivatives such as 2-chloro-6-iodopurine,[64] 6-amino-2-methylthiopurine,[90] 6-benzyloxy-2-flouropurine[91], and 6-amino-2,8-dichloropurine[13,92] have also been reported.

Unlike the coupling reactions with guanine or N^2-substituted guanines, condensations with 2,6-dichloropurine, 2,6-diaminopurine, or 2-amino-6-chloropurine afford N9 nucleosides in good yields without significant formation of N7 isomers. Reasons for the absence of the N7 isomers are not apparent. Perhaps such N7 substituted compounds have limited stability. Although these indirect approaches yield N9 guanine nucleosides, they suffer from the high costs of these 2,6-disubstituted purines and the subsequent steps required to produce the guanine base.

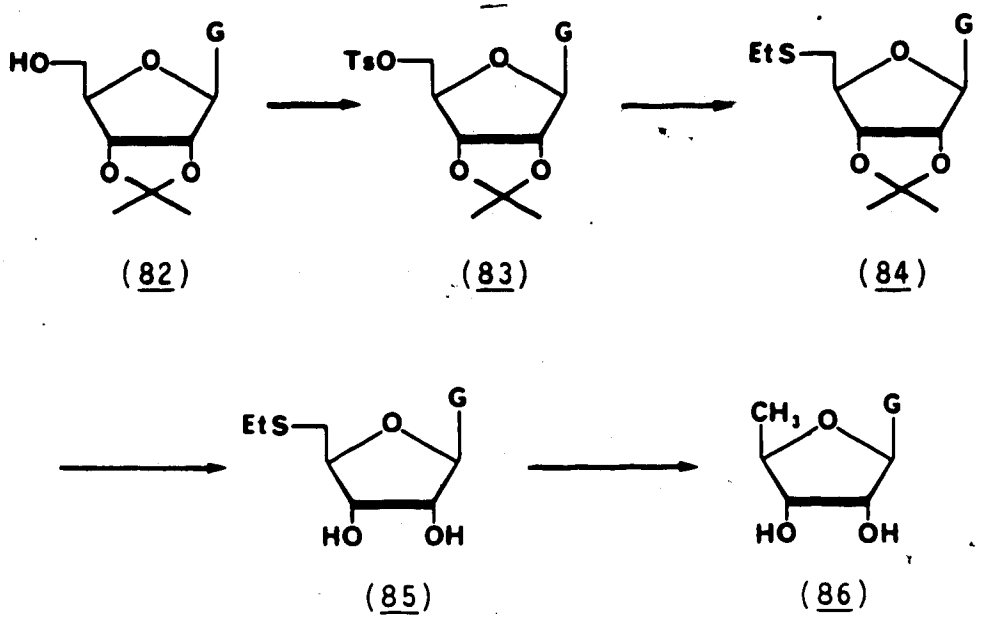
B. Syntheses of guanine nucleosides via chemical transformations

In addition to sugar-base coupling reactions, sugar transformation chemistry with intact nucleosides has proven to be another powerful method[9] for the synthesis of nucleoside analogues with modified carbohydrate moieties. However, transformations on the sugar portion of guanosine are much more difficult experimentally in comparison with such reactions on most other naturally occurring nucleosides. Poor solubility and self association (gelling) in various solvents, and the absence of convenient isolation and purification techniques are serious practical problems. The guanine base undergoes side reactions with a

number of reagents that are used for sugar transformations. These problems often contribute to lower yields for modified guanine nucleosides in parallel transformations. Also troublesome is the failure to isolate and purify the transformation products as a result of gelation during attempted recrystallization. Therefore, syntheses of guanine nucleosides via sugar transformations on guanosine have proven to be of limited applicability.

a. 5'-Modified guanine nucleosides

In order to introduce the desired modification at a specific position of the ribose moiety of a nucleoside, selective protection of other hydroxy groups is usually necessary. The 5'-OH as a primary alcohol differs greatly in reactivity from the 2'-OH and 3'-OH. Therefore, selective class protection can be achieved easily. Selective protection of the 2'-OH and 3'-OH is achieved via formation of 2',3'-O-isopropylidene derivatives. Many 2',3'-O-isopropylidene nucleosides are commercially available reagents. Various 5'-substituted nucleosides can be prepared readily starting with them. This can be illustrated by the synthesis of 5'-deoxyguanosine (86) (Scheme 20).[93] Commercial 2',3'-O-isopropylideneguanosine (82) was tosylated at the 5'-position to give (83). Displacement of the tosylate function from (83) was effected with sodium ethanethiolate. After successive deprotection and desulfurization, 5'-deoxyguanosine was obtained in 18% overall yield.



(82) (83) (84)

(85) (86)

SCHEME 20

Displacement of the 5'-tosylate (or similar leaving groups) from (83) with other external sulfur,[94] nitrogen,[95] or halogen[96] nucleophiles has been reported to give the corresponding 5'-alkylthio, 5'-amino, and 5'-halo-5'-deoxyguanosines. Displacements with internal nucleophiles have resulted in formation of N-3,5'- and X-8,5'-cyclonucleosides.[97-103]

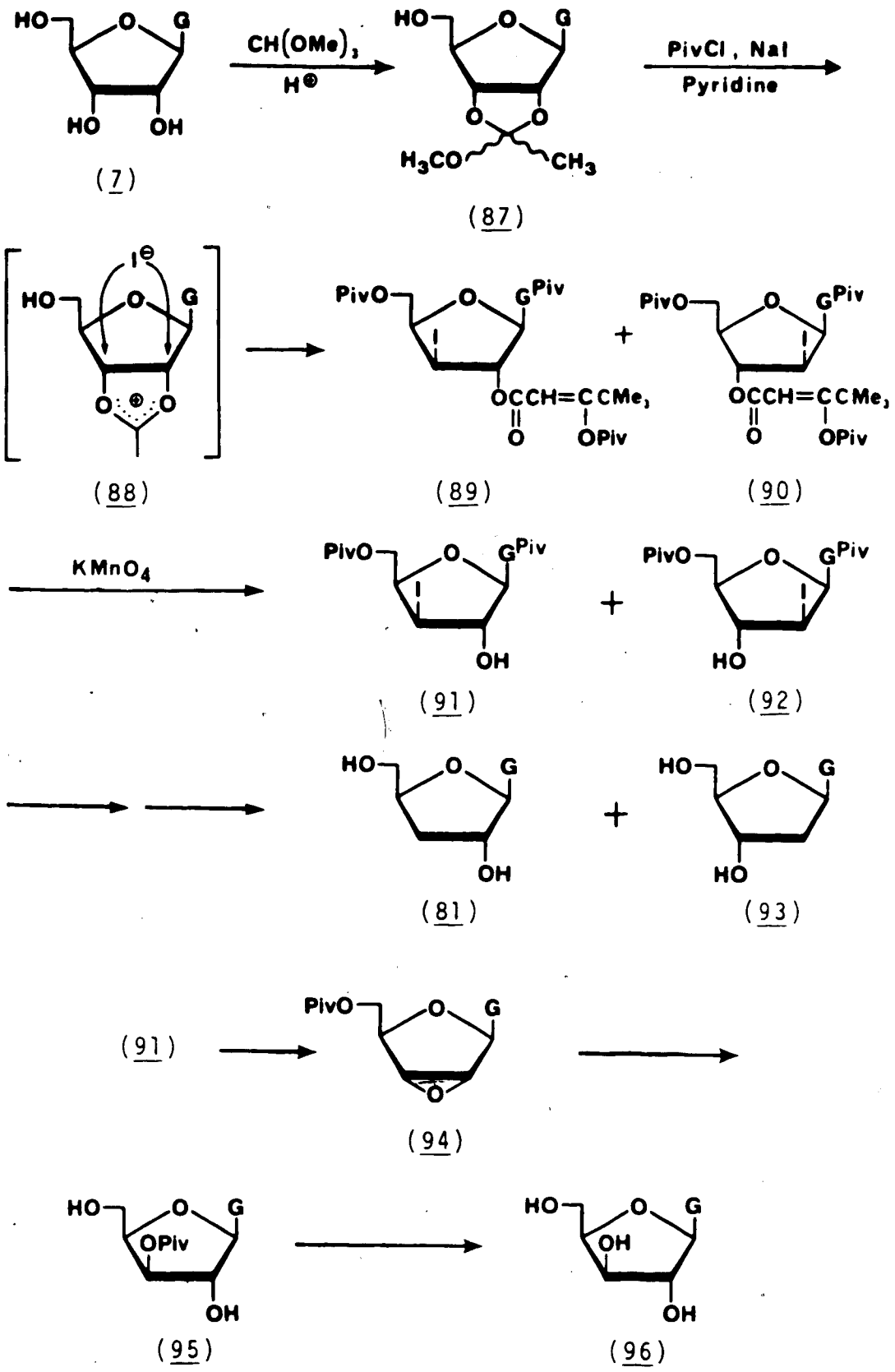
Nucleoside 5'-aldehydes are rather difficult to prepare and purify due to their inherent instability. However, a reasonably satisfactory solution to this problem has been developed using the Pfitzner-Moffatt oxidation method[104] and by manipulation of 1,3-diphenylimidazolidine[105] derivatives as protected aldehydes. Unlike most conventional oxidation methods, the Pfitzner-Moffatt method uses dimethylsulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) as oxidants and oxidizes the 5'-OH to

the aldehyde level without overoxidation. Isolation and purification of the free aldehydes have proven to be extremely difficult. The 5'-aldehyde undergoes partial epimerization at C4' and elimination of the C3' functional group readily. Conversion of the aldehyde to its 1,3-diphenylimidazolidine derivative allows isolation by direct crystallization[105]. Upon mild acid treatment, the aldehyde function is regenerated. Using this approach, guanosine 5'-aldehyde has been prepared.

For the preparation of nucleoside 5'-carboxylic acids, direct oxidation of the free nucleoside by oxygen with platinum catalyst has been successful. Guanosine 5'-carboxylic acid has been synthesized in 23% yield using this method.[106,107] Chemical oxidation of 2',3'-protected nucleosides with alkaline potassium permanganate is a useful alternative for many nucleosides. However, it has been reported to be unsuitable for guanosine derivatives.[108]

b. 3'-Modified guanine nucleosides

Chemical conversion of guanosine to its 3'-modified derivatives is difficult to accomplish due to the lack of an efficient method for selective derivatization of the 3'-OH. Mengel and Muhs[109,110] achieved the preparation of 3'-deoxyguanosine via a 3'-halo intermediate (Scheme 21). Treatment of the orthoester (87) with pivaloyl chloride and sodium iodide in hot pyridine gave an isomeric mixture of trans iodoesters (89 and 90) via the acetoxonium ion (88). Conversion of the isomeric iodides to the corresponding deoxy derivatives was effected by catalytic hydrogenolysis. The overall yields



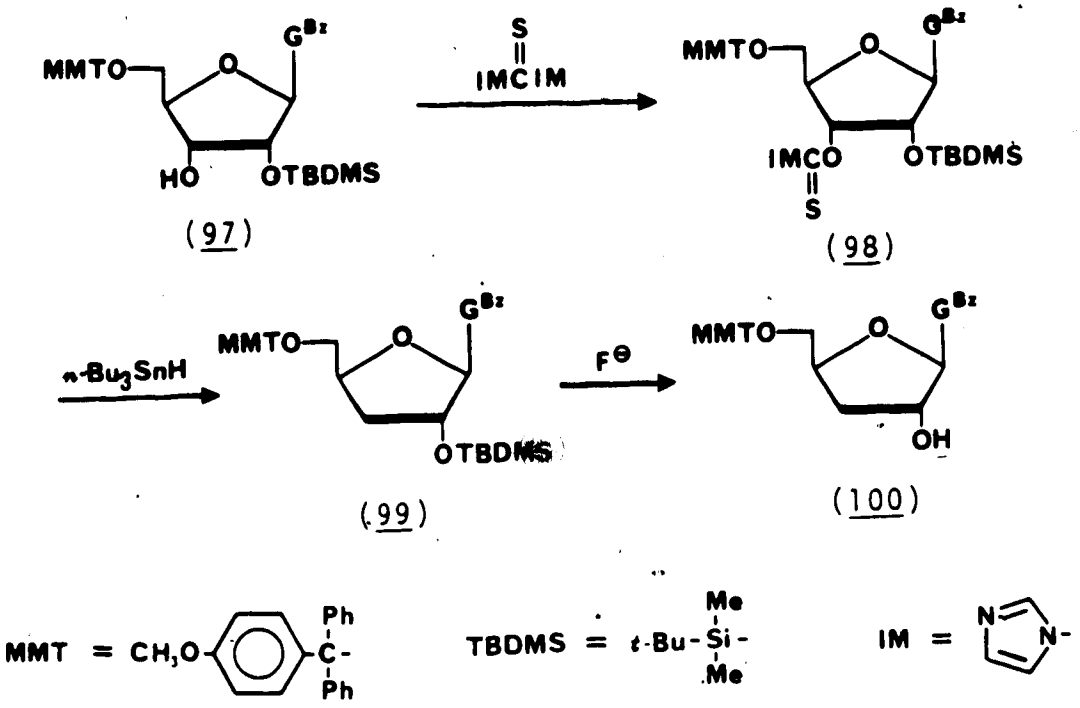
(7) (87) (88) (89) (90) (91) (92) (81) (93) (94) (95) (96)

SCHEME 21

of 3'-deoxy- and 2'-deoxyguanosine were 25% and 2%, respectively. Treatment of the trans hydroxy iodide (91) with base produced the epoxide (94). This was opened with boron trifluoride etherate to afford the xylo derivative (95) via migration of the 5'-pivaloyl group to the 3'-position. Epoxide opening with sodium benzoate in a hot methanol-water mixture led to the formation of the N-3,3'-cyclonucleoside.

Treatment of free nucleosides with α-acetoxyisobutyryl bromide afforded an isomeric mixture of nucleoside 2',3'-bromoacetates via a similar mechanism.[111-114] Reaction of this mixture with zinc-copper couple gave the 2',3'-unsaturated nucleosides.[113,114] Guanosine and adenosine were converted to the corresponding 2',3'-unsaturated nucleosides in 47% and 81% yields, respectively.[114]

Considerable effort[115-122] has been directed towards the development of chemical reactions that will discriminate between the 2'-OH and 3'-OH groups to give regioselective protection. Ogilvie et al.[117] reported procedures that claimed highly selective silylation of the 2',5'- or 3',5'-OH's of ribonucleosides. The procedures also claimed selective silylation at either the 2'- or 3'-position of 5'-O-dimethoxytritylribonucleosides. In the case of uridine, higher than 90% yields of the 2',5'- or 3',5'-disilyl nucleoside were reported. However, when this procedure was applied to guanosine or its N^2-acyl derivatives, the selectivity was very poor. Yields of the desired disilyl nucleosides were lower than 60%. Derivatization of the 3'-OH of the 2',5'-diprotected guanosine (97) was reported to require 70 hours to accomplish (Scheme 22)[123]. During this extended reaction period,



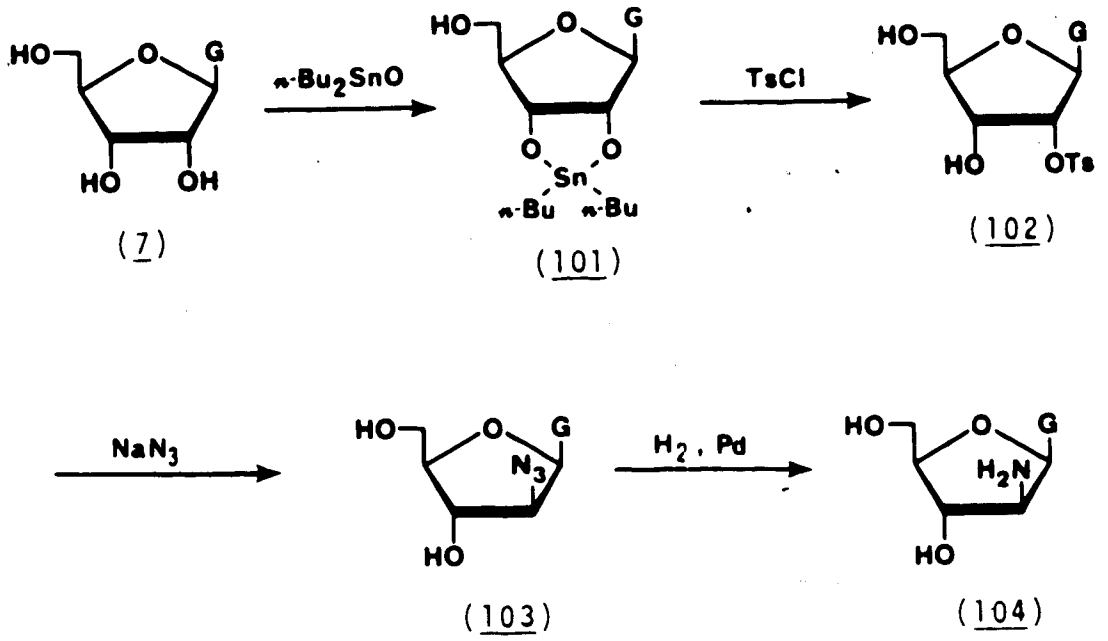
SCHEME 22

isomerization of the silyl groups occurred and a mixture of 2'- and 3'-acyl derivatives was obtained. Using this sequence, the three-step transformation afforded the 3'-deoxyguanosine derivative (100) in 8% overall yield.

c. **2'-Modified guanine nucleosides**

Chemical transformations at the 2'-position of ribonucleosides have proven to be more difficult than analogous reactions at the 3'-position. Both electronic and steric factors make the 2'-carbon more resistant to nucleophilic displacement. Hence, better leaving groups are required for activation of the 2'-OH. 2'-Tosylates have been a popular choice owing to their availability from regioselective tosylation. The method[124] for selective 2'-tosylation involves the use of di-n-butyltin oxide as the

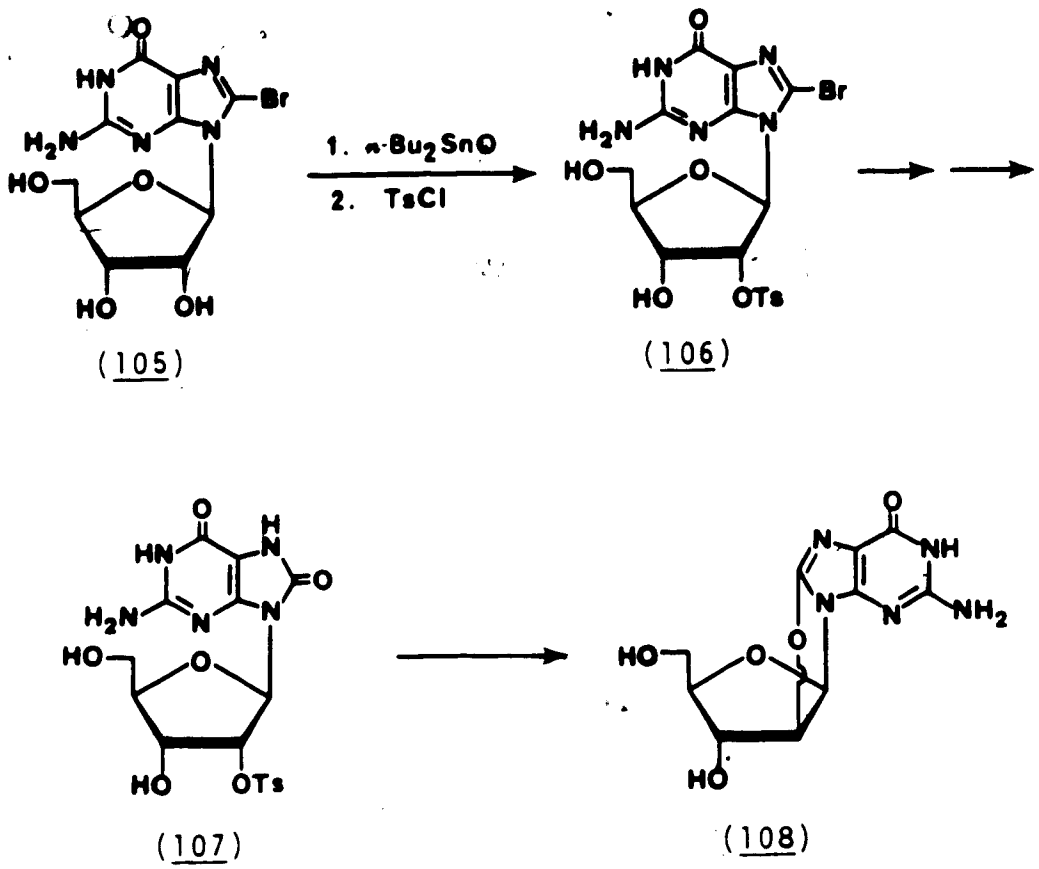
activating reagent. Utilizing this method, 2'-O-tosylguanosine (102) was prepared in 48% yield (Scheme 23).[125] Nucleophilic attack on tosylate (102) using sodium azide yielded the azido-nucleoside (103), which was hydrogenolyzed over palladium. The overall yield of the amino-nucleoside (104) was 4%.



(7) (101) (102) (103) (104)

SCHEME 23

Ikehara et al.[126,127] applied this method for the regioselective tosylation of 8-bromoguanosine. They prepared several X-8,2'-cyclonucleosides via displacement of the 8-bromo function with appropriate nucleophiles (Scheme 24). Intramolecular displacement of the 2'-tosylate from (107) with O-8 gave the O-8,2'-cycloguanosine



SCHEME 24

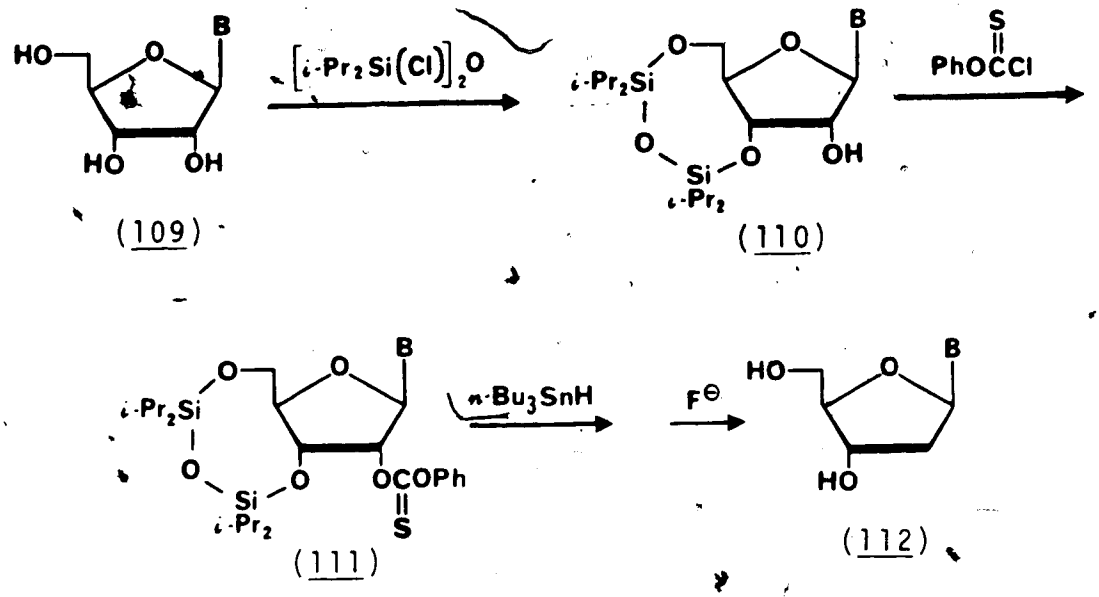
(108). Nucleophilic opening of the O-8, cyclonucleoside linkage with hydrazine or hydrogen sulfide produced 8-substituted 9-β-D-arabinofuranosylguanines, which could be converted into 9-β-D-arabinofuranosylguanine by removal of the 8-substituent.[128-132]

Displacement of the 2'-tosylate or other leaving groups with a sulfur nucleophile at the 8-position afforded S-8, 2'-thiocycloguanosine.[133-135] Direct desulfurization of this thiocycloguanosine provided a synthetic route to 2'-deoxyguanosine.

Due to the electron withdrawing effect of the adjacent electron-deficient anomeric centre, the 2'-OH of ribonucleosides is slightly more acidic than the 3'-(and 5'-) hydroxyl function. Accordingly, the 2'-ester is hydrolysed more readily than the others and selective deprotection of O2' can be achieved with retention of the 3'- and 5'-esters. Partial deprotection of 2-N-,2',3',5'-tri-O-benzoylguanosine with hydrazine in acetic acid-pyridine gave 2-N-,3',5'-di-O-benzoylguanosine in 63% yield.[136] Such N2,3',5'-protected guanosines are used as starting materials for 2'-transformations.[137]

The most useful method for protection of the 3'-OH and 5'-OH functions of nucleosides utilizes the 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane reagent developed by Markiewicz and Wiewiorowski.[138,139] Silylation of nucleosides occurs selectively at the 3'- and 5'-positions to give the corresponding 3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl) (3',5'-O-TPDS) derivatives in high yields.

Taking advantage of this new method, Robins and Wilson developed a general procedure for transformation of ribonucleosides to their corresponding 2'-deoxyribonucleosides (Scheme 25).[140-143] The 3'- and 5'-OH's of ribonucleosides (109) were protected as their 3',5'-O-TPDS derivatives (110). Functionalization of the 2'-OH with phenoxythiocarbonyl chloride gave the 2'-thionocarbonates (111). Reduction with tributyltin hydride followed by deprotection with fluoride afforded the 2'-deoxyribonucleosides in good overall yields. For example, adenosine and guanosine were converted into their 2'-deoxy counterparts in 78% and 57% yields, respectively. The relatively lower



SCHEME 25

yield for guanosine resulted from its poor solubility and side reactions in the silylation step. It is noteworthy that this procedure employed a biomimic free radical mechanism for the 2'-deoxygenation and thus avoided an energetically unfavorable heterolysis of the C2'-O2' bond.

Transformations of the 3',5'-O-TPDS derivatives (110) by successive oxidation and reduction have led to β-arabinonucleosides,[144] which are difficult to prepare by coupling reactions. Coupling reactions with arabinose derivatives with a C2 participating group give a mixture of α- and β-anomers or exclusively the α-anomer. The exclusive formation of α-anomers by coupling silylated bases with 1,2,3,5-tetra-O-acetyl-D-arabinofuranose was utilized for the synthesis of α-arabinonucleosides[143]. Applications of the Robins-Wilson deoxygenation procedure to the deprotected α-arabinonucleosides opened a general stereo-controlled route to these α-2'-deoxy compounds.

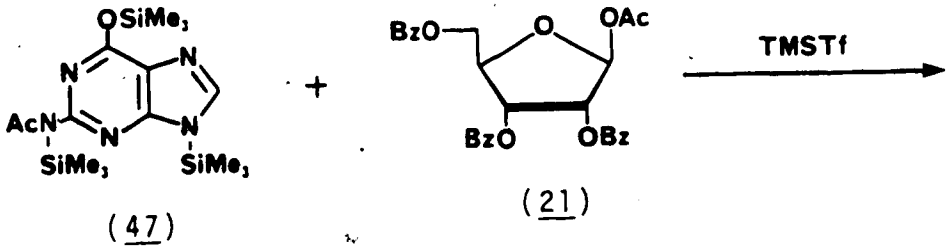
2. RESULTS AND DISCUSSION

A. Syntheses of guanine nucleosides via regioselective glycosylations

Guanine is an inexpensive, commercially available heterocycle that can be converted to its N^2-acylated derivatives via simple chemical reactions. Because of their availability, N^2-acylated guanine derivatives have been used extensively as starting materials for guanine nucleoside syntheses in glycosylation reactions. However, the problems of formation of positional isomers and the difficulty in separating them have rendered the glycosylation method much less efficient for guanine nucleoside syntheses. Therefore, new coupling procedures that allow regioselective glycosylation are desirable.

a. Regioselective glycosylation leading to N9 guanine nucleosides

In 1981, Vorbrüggen et al.[31] studied the behavior of trimethylsilyl triflate as a catalyst in nucleoside synthesis. This catalyst was found to favor the formation of the more thermodynamically stable isomer. Guanosine was reported to be obtained in 66% overall yield from N^2-acetylguanine using this catalyst. However, no analytical data were reported for the product, which comigrated with naturally occurring guanosine on TLC. To evaluate this method for guanine nucleoside synthesis, we reinvestigated Vorbrüggen's procedure (Scheme 26). The literature conditions were followed carefully and the nucleoside products were analysed by 400 MHz ^{1}H NMR spectroscopy at both the intermediate protected stage and the deprotected product. The ^{1}H NMR spectrum of the crude protected product showed that a significant



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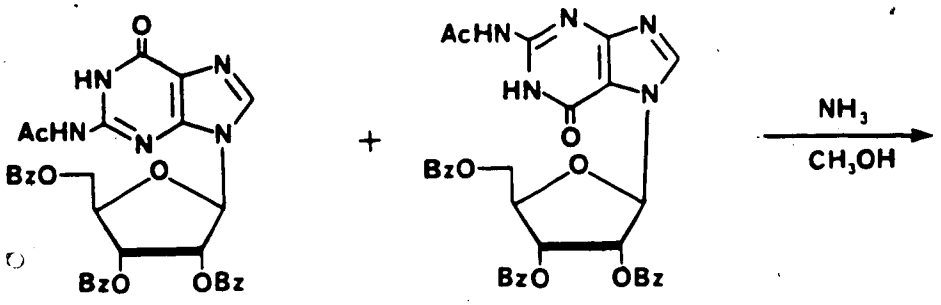

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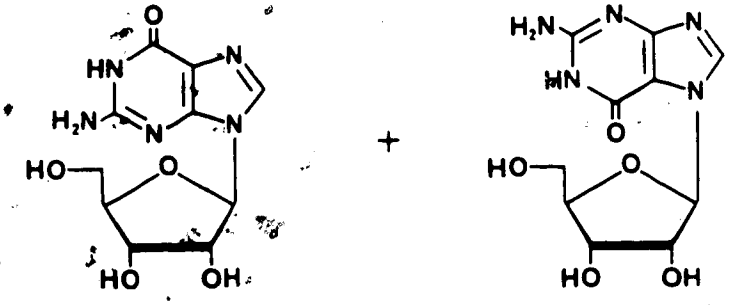


(7) (113)

SCHEME 26

amount of the N7 isomer (24) was produced together with the major N9 nucleoside (22) (N9 to N7 3:1). The minor product was assigned as the N7 isomer on the basis of its characteristic downfield shifts relative to the N9 isomer for the H8 and H1' resonances [δ 8.58 (H8), δ 6.63 (H1') for the N7 isomer and δ 8.30 (H8), δ 6.42 (H1') for the N9 isomer]. Formation of the N7 isomer was further confirmed by the ^{1}H NMR spectrum of the deprotected product which showed signals at δ 8.28 (H8) and δ 5.95 (H1') for the N7 isomer [δ 7.92 (H8) and δ 5.68 (H1') for the N9 isomer].

Similar reaction conditions were applied to the glycosylations of silylated N^2-acetylguanine with three different 1,2,3,5-tetra-O-acetyl-D-pentofuranoses. ^{1}H NMR analysis of the crude coupling products at the protected stage indicated that both the N9 and N7 isomers were produced in all cases. The N9 to N7 ratios ranged from approximately 5:1 to 2:1. These results were in agreement with the literature that equilibrium mixtures of positional isomers were produced from glycosylations with N^2-substituted guanines. Alterations of reaction conditions by using various catalysts, solvents, sugar derivatives, or N^2-acyl substituents had limited effects on product ratios. It is quite clear that the product ratio is mainly dependent upon the isomeric products' relative stability, which is in turn related to the structure of the guanine derivative used for the glycosylation. Little work has been done to alter the structure of the starting guanine derivatives except for N^2-substituents. However, the N^2-substituent is distant from the glycosylation sites and is attached to an exocyclic amino group. Hence, it should have limited electronic or steric effects on the glycosylation

reaction. We expected that an O^6-protecting group would shift the activation barriers to favor the N9 isomer more effectively since the O^6-substituent adjacent to N7 should hinder the attack of a sugar cation on this position kinetically. In a thermodynamic equilibrium system, the larger steric interaction between the O^6-substituent and the N7 sugar residue would make it less stable and facilitate its rearrangement to the more stable N9 isomer. In addition, the electronic structure of the O^6-protected guanine derivative would be more like those of 2-amino-6-chloropurine and 2,6-diaminopurine, which are known to undergo regioselective N9 glycosylation. Our first challenge involved studies on the synthesis of O^6-protected guanine derivatives.

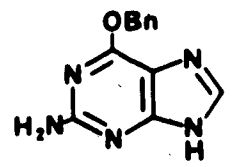
Novak and Sorm[145] had reported that treatment of guanine with acetic anhydride in hot N,N-dimethylacetamide (DMAc) gave N^2-acetylguanine in 73% yield from the cooled reaction mixture. We found that the deposited product was actually N^2,9-diacetylguanine (20). With slight modifications of this procedure, we were able to obtain N^2,9-diacetylguanine in 90% yield. Attempts to recrystallize this material from ethanol or an ethanol/water mixture resulted in cleavage of the 9-acetyl group to afford crystalline N^2-acetylguanine. This lability of the 9-acetyl group under recrystallization conditions might explain the previously reported results[146] of selective acetylation of the 2-amino group of 2-amino-6-substituted purines. The selectivity was probably not due to monoacetylation of the 2-amino group, but rather to the selective deacetylation of the 9-acetyl group during work-up or recrystallization. In fact, we found that treatment of 2-amino-6-benzyloxypurine (114) with acetic anhydride in N,N-dimethylacetamide

at 150°C for 30 min gave the 9-acetylated product (115) in 75% yield. Therefore, the 9-position of guanine may also be the first site to be acylated.

Several methods[147-153] were known to provide O^6-protection in the guanosine series. We next examined the applicability of such methods for guanine derivatives. Hata and co-workers[152,153] reported that treatment of appropriately protected guanosines with diphenylcarbamoyl (DPC) chloride in pyridine gave the O^6-DPC derivatives in high yields. We studied the acylation of N^2-acetylguanine with DPC chloride under similar conditions. It was found that the first DPC group was bound to the N9 or N7 position of N^2-acetylguanine. Using a modified acylation procedure, a mixture of 9- and 7-DPC isomers (116/117 ~ 1.2:1) was obtained in excellent yield. Although a second DPC group could be introduced at the O^6-position under forcing conditions, the 9- and 7-DPC groups of the products (118,119) were resistant to hydrolysis under conditions that removed the 9-acetyl group from N^2,9-diacetylguanine.

Acylation of N^2-acetyl-O^6-benzylguanine (120) with DPC chloride afforded the corresponding 9- and 7-DPC derivatives (121,122) in 82% and 15% yields, respectively. The much higher selectivity for the N9 isomer in comparison with that of the acylation of N^2-acetylguanine indicated the significant effect of the O^6-benzyl group on the product ratio.

It was clear that protection of the more reactive N9 (or N7) position was a necessary prerequisite for introduction of the O^6-DPC group. In consideration of the ready availability of N^2,9-diacetyl-



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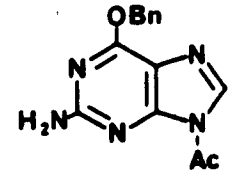

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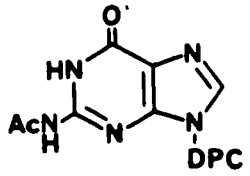

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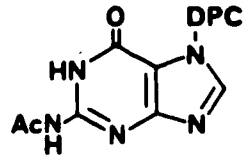

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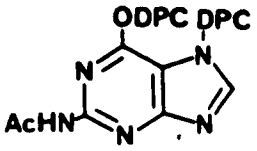

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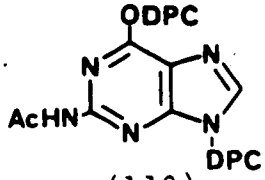

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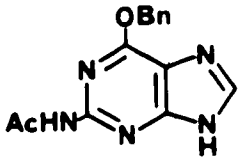

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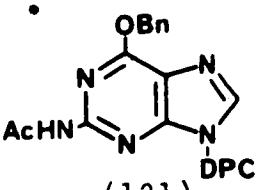

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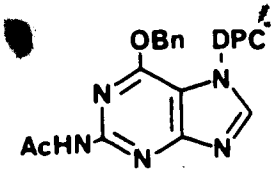

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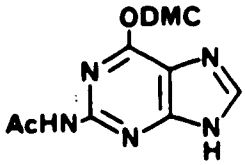

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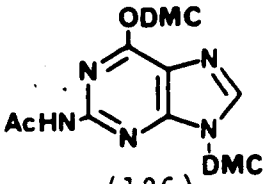

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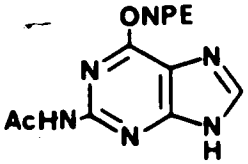

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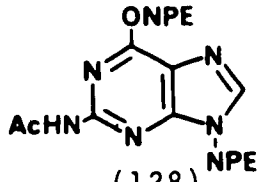

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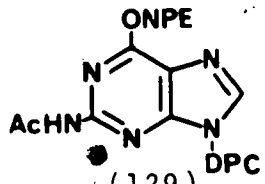

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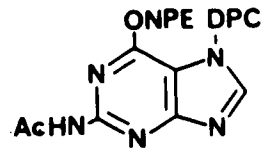

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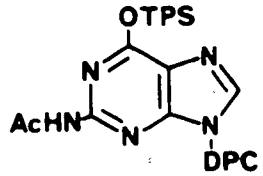

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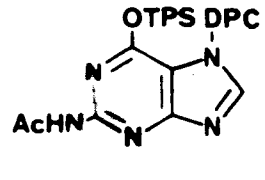

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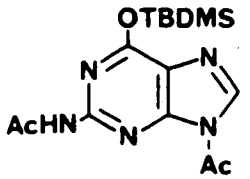
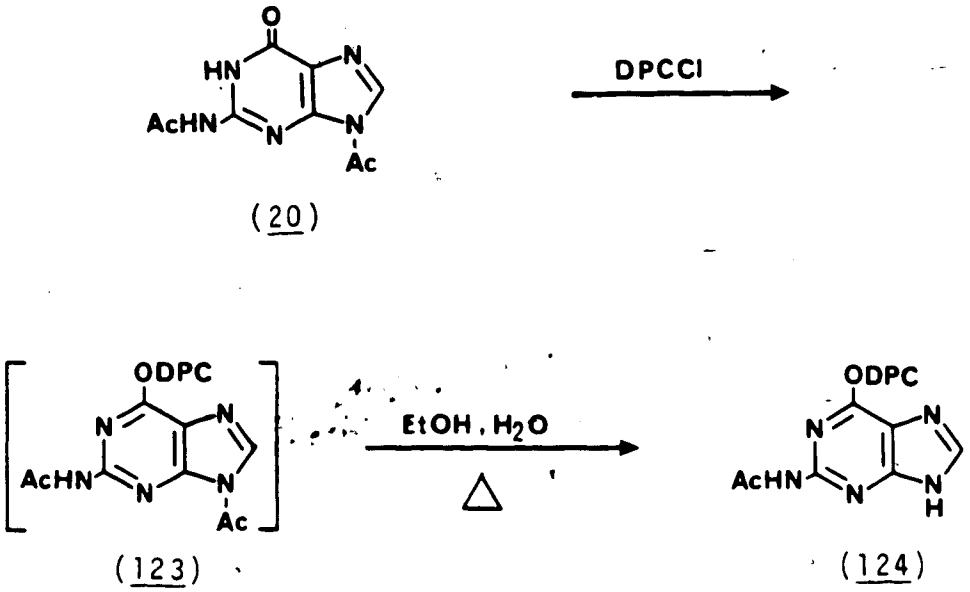


(133)

SCHEME 27

guanine and the lability of its 9-acetyl group, we applied Hata's diphenylcarbamoylation procedure[152,153] to this 9-protected N^2-acetylguanine derivative (Scheme 28). A suspension of N^2,9-diacetylguanine in dry pyridine was treated with 1.1 equivalents of DPC



(20)

(123)

(124)

SCHEME 28

chloride and 2 equivalents of diisopropylethylamine to give a red solution. This solution was evaporated and the residue was heated in an ethanol/water mixture to effect 9-deacetylation. Filtration of the resulting suspension and washing of the solid product with ethanol gave the analytically pure compound (124) in 92% overall yield. The intermediate product (123) was isolable with a careful work-up procedure.

Similar treatment of N^2,9-diacetylguanine with dimethylcarbamoyl (DMC) chloride resulted in a mixture of two products, which probably were (125) and (126) according to their ^1H and ^{13}C NMR spectra. Formation of the bis(DMC) derivative (126) indicated that the 9-acetyl group of N^2,9-diacetylguanine was cleaved during the reaction. This cleavage also was observed in attempts to prepare the O^6-p-nitrophenylethyl (NPE) derivative (127) by a reported method.[151] Owing to the greater stability of the 9-(and 7-)DPC group, O^6-protection of N^2-acetyl-9-(and 7-)diphenylcarbamoylguanine with NPE and TPS (2,4,6-triisopropylphenylsulfonyl) groups was achieved to afford the corresponding trisubstituted guanines (129,130,131,132) in high yields.

Reaction of N^2,9-diacetylguanine with t-butyldimethylsilyl (TBDMS) chloride proceeded smoothly and gave the O^6-TBDMS derivative (133). Glycosylation of (133) with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose in the presence of trimethylsilyl triflate yielded a mixture of N9 and N7 isomers similar to that obtained by glycosylation of silylated N^2-acetylguanine. Parallel direct glycosylation reactions with the guanine derivatives (116), (117), (118), (124), (131), and (132) gave unsatisfactory results.

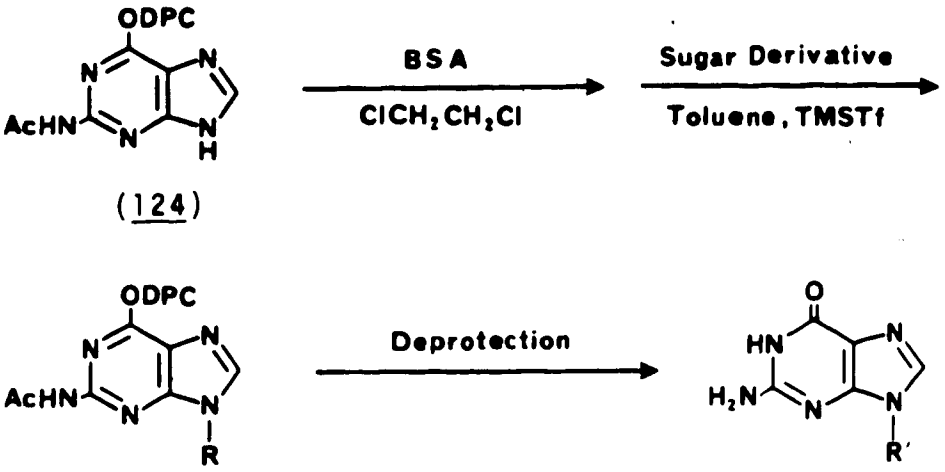
Various coupling conditions were tested for the glycosylation of N^2-acetyl-O^6-diphenylcarbamoylguanine (124) with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose. Compound (124) was chosen for the tests for several reasons. A convenient high-yield synthesis of (124) was at hand. Our preliminary results showed that the O^6-DPC group was fairly stable under certain coupling reaction conditions and required no extra deprotection steps to give the free nucleoside. Furthermore, it was

expected that the bulkier O^6-DPC group would have a greater steric effect on N7 and improve the solubility of the base component.

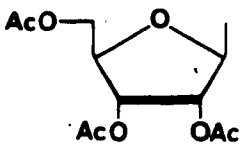
Treatment of a suspension of the O^6-DPC derivative (124) in 1,2-dichloroethane with N,O-bis(trimethylsilyl)acetamide at 80°C gave a homogeneous solution in 10-15 min. After removal of volatile materials by evaporation at reduced pressure, the residual silyl derivative was dissolved in dry toluene. Glycosylation of the silyl derivative with 1.2 equivalents of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose in the presence of trimethylsilyl triflate at 80°C proceeded cleanly as indicated by TLC. This coupling reaction was completed in 30 min - 1 h and gave the N9 nucleoside (134) in 91% yield after chromatographic purification on silica (Scheme 29). A minor product was obtained in about 2% yield. By using 2.5 equivalents of the sugar component in the glycosylation reaction, we were able to isolate this minor product. It was characterized as a bis(ribofuranosyl) derivative (147) (see Scheme 30) from its NMR and mass spectral data.

Removal of all protecting groups from the major N9 product (134) was effected with methanolic ammonia. The free nucleoside (7) was obtained as a hemihydrate after recrystallization from H_2O. The overall yield of guanosine (7) from the O^6-DPC guanine derivative (124) was 68%. Although this yield was only slightly higher than that reported by Vorbrüggen et al.[31], our final product was free of contamination with the N7 isomer.

In this coupling procedure, the mild silylation conditions using N,O-bis(trimethylsilyl)acetamide were necessary. Alternative silylation with hexamethyldisilazane required much higher temperatures and longer



(124)

R = 

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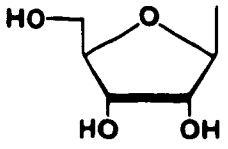
R' = 

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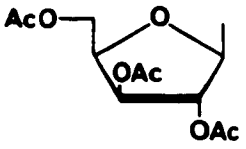
R = 

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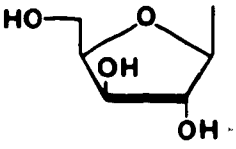
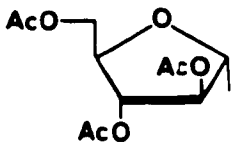
R' = 

(96)

R = 

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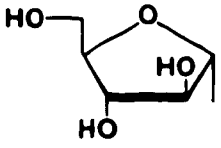
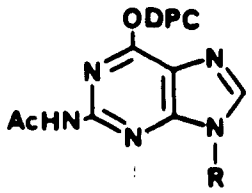
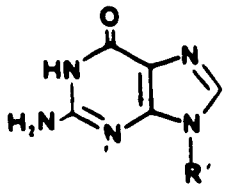
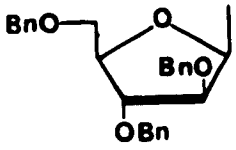
R' = 

(137)

SCHEME 29





R = 

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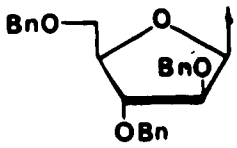
R' = 

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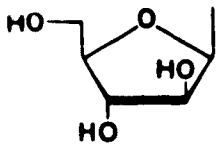
R' = 

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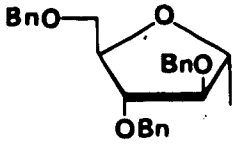
R = 

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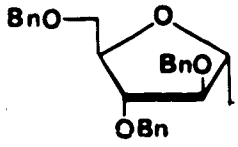
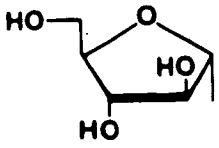
R' = 

(141)

R' = 

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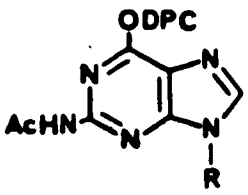
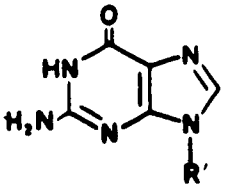
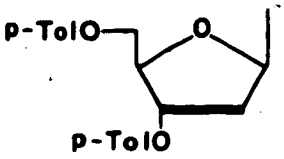




R = 

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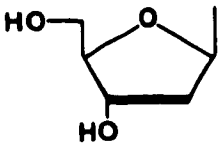
R' = 

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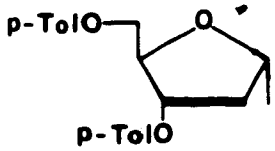
R = 

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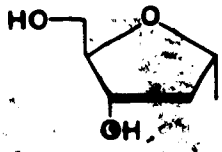
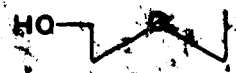
R' = 

(144)

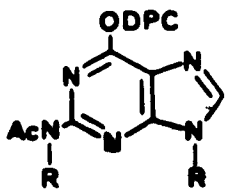
R = 

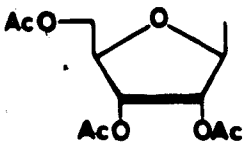
(145)

R' = 

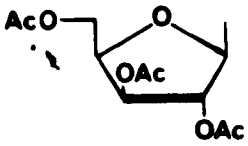
(146)

SCHEME 29 (continue



R = 

(147)

R = 

(148)

R = 

(149)

SCHEME 30

reaction times and was found to cause partial decomposition of the base component (124). The choice of toluene as solvent for the coupling reaction also was important. Parallel coupling reactions in acetonitrile or 1,2-dichloroethane resulted in formation of several minor products as indicated by TLC.

The coupling procedure we used for the synthesis of guanosine was found to be a general method for regioselective N9 glycosylation of N^2-acetyl-O^6-diphenylcarbamoylguanine (124) with various sugar components. Its application to the glycosylation of (124) with an anomeric mixture of 1,2,3,5-tetra-O-acetyl-D-xylofuranose gave the desired N9 nucleoside (135) in 86% yield. About 4% of a bis(xylosyl) derivative (148) was isolated as a minor product. Saponification of (135) afforded 9-β-D-xylofuranosylguanine (96) in 67% yield. The

relatively lower yield for the deblocking step was due primarily to the lower recovery of (96) in recrystallization.

The same coupling procedure was followed for the glycosylation reaction of (124) with an anomeric mixture of 1,2,3,5-tetra-O-acetyl-D-arabinofuranose. This gave the expected 9-α nucleoside (136) in 82% yield. Formation of the corresponding bis(arabinosyl) by-product was not detected in this case. After deprotection, the free nucleoside, 9-α-D-arabinofuranosylguanine (137), was obtained in 84% yield.

Glycosylation of (124) with 1-O-p-nitrobenzoyl-2,3,5-tri-O-benzyl-β-D-arabinofuranose using the same coupling procedure required 5 hours to accomplish owing to the low reactivity of the sugar component. This reaction gave a mixture of 9-β and 9-α nucleoside anomers (138,140) in low yields. Several side products were detected on TLC. One of them was isolated and identified as the deacetylated derivative of (140). Modification of the coupling procedure by using 2,3,5-tri-O-benzyl-D-arabinofuranosyl chloride as the sugar component accelerated the glycosylation reaction and gave the N9 nucleoside anomers (138,140). After chromatographic separation on silica, the pure anomers (~1:1) were obtained in 61% combined yield.

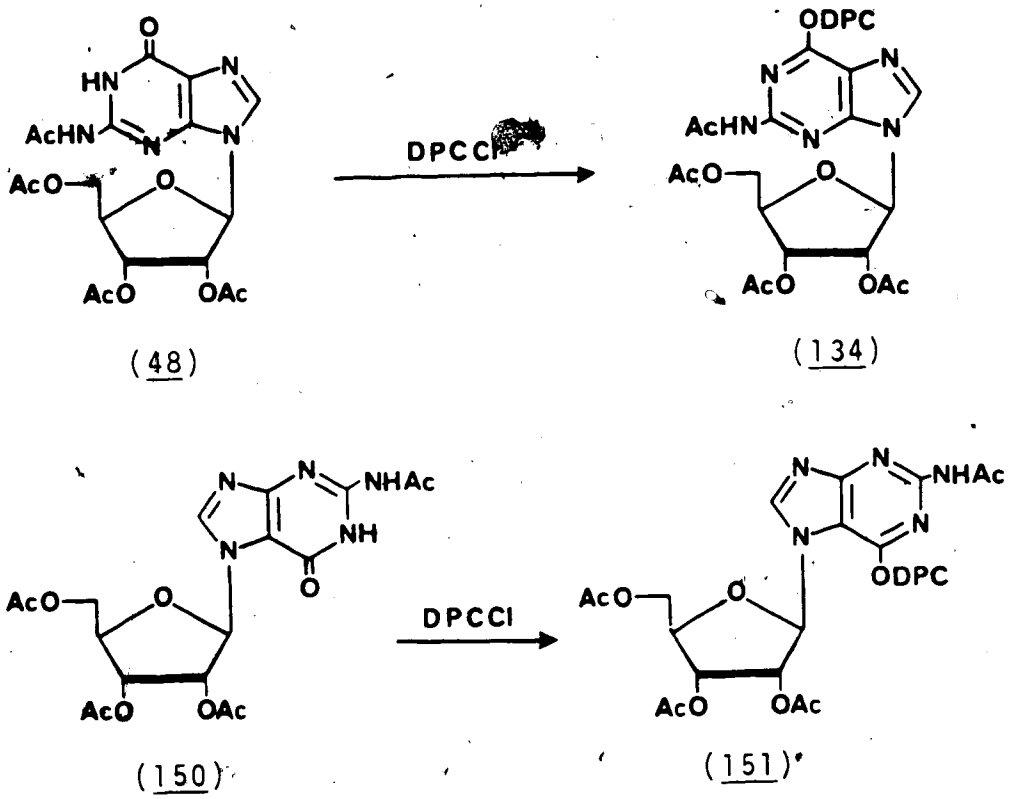
Complete deprotection of (138) and (140) in one step was attempted with sodium metal in liquid ammonia. These reactions resulted in partial deblocking and afforded 2-N-acetyl-9-D-arabinofuranosylguanines in moderate yields. In view of the difficulty of cleaving the N^2-acetyl group and the potential risk of reducing the guanine moiety under more severe conditions, the attempted one-step deprotection of (138) and (140) was abandoned.

Removal of acyl groups from (138) and (140) was effected by treatment in aqueous ammonia/methanol. The corresponding β- and α-anomers (139,141) of 9-(2,3,5-tri-O-benzyl-D-arabinofuranosyl)guanine were obtained in 88% yields after chromatographic purification. Debenzylation of (139) and (141) by hydrogenolysis over palladium was found to be difficult. MacCoss et al.[62] had reported that removal of benzyl protective groups from a glucose derivative (61) under those hydrogenolysis conditions could be achieved by addition of one equivalent of p-toluenesulfonic acid per benzyl group. However, parallel results were not observed in the cases of (139) and (141). Reductive debenzylation of the β-anomer (139) with sodium metal in liquid ammonia was known[89] to give the free nucleoside (70) in 78% yield. This approach was successfully applied to the crude deacylation product of (138). Thus, saponification of (138) followed by debenzylation gave (70) in 81% overall yield without isolation of intermediate (139). The α-anomer (137) was obtained in 71% yield from (140) in a similar manner. Successive saponification of (140) and debenzylation of (141) with boron trichloride afforded (137) in 65% yield.

Coupling of (124) with 3,5-di-O-p-toluoyl-2-deoxy-α-D-erythro-pentofuranosyl chloride (34) using our coupling procedure gave an anomeric mixture of the N9 nucleosides. After chromatographic separation the pure β (142) and α (143) anomers were recovered in 31% and 36% yields, respectively. Subjection of each pure anomer to saponification yielded the corresponding 2'-deoxyguanosine (93) and its α-anomer (144).

Analogous coupling of (124) with (2-acetoxyethoxy)methyl bromide[56] proceeded smoothly at room temperature without any catalyst. The pure N9 alkylated guanine product (145) was obtained in 63% yield after chromatographic purification and crystallization from acetonitrile with diffusion of ether. A minor product was isolated in about 3% yield which was identified as the bis(alkyl) derivative (149). Treatment of the crystalline (145) with aqueous ammonia/methanol at 60°C gave acycloguanosine (146) in 91% yield.

In order to analyze the regioselectivity of this N9 glycosylation procedure, we prepared DPC derivative (134) and its N7 isomer (151) from 2-N-,2',3',5'-tri-O-acetylguanosine (48) and its N7 isomer (150), respectively, utilizing Hata's procedure[152,153] (Scheme 31).



(48) (134)

(150) (151)

SCHEME 31

Comparison of the 400 MHz ^{1}H NMR spectra of the products of Hata's acylation procedure with that of the crude product obtained from our N9 glycosylation procedure showed that our product was identical with the DPC derivative of the N9 nucleoside (134) and was free of the N7 isomer (151).

It is known that kinetic formation of N7 nucleosides is observed in coupling reactions with N^2-substituted guanines. However, attempts to isolate the N7 isomer (151) as a coupling product under mild conditions failed. Glycosylation of silylated N^2-acetyl-O^6-diphenylcarbamoylguanine (124) with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose in toluene solution with trimethylsilyl triflate catalyst at room temperature for 4 days gave the N9 nucleoside (134) in good yield.

Coupling of the same base and sugar components in 1,2-dichloroethane at room temperature using stannic chloride as catalyst was also examined. This reaction gave the N9 isomer in 40% yield as the only significant product. The low yield of this reaction resulted from partial decomposition of the DPC-base by stannic chloride. It is noteworthy that this combination of catalyst, solvent, and reaction temperature normally favours formation of the kinetic product. It has been used by us as standard conditions for regioselective N7 glycosylation of silylated N^2-acetylguanine (see part b of this chapter).

Subjection of the N7 nucleoside (151) to our standard N9 glycosylation conditions resulted in complete conversion of (151) to its N9 isomer (134). This isomerization required two hours at 80°C to complete. The slower reaction rate and the failure to isolate the N7 nucleoside (151) as a coupling product under mild conditions implied

that the N7 isomer (151) was not an intermediate in the regioselective N9 glycosylation reaction.

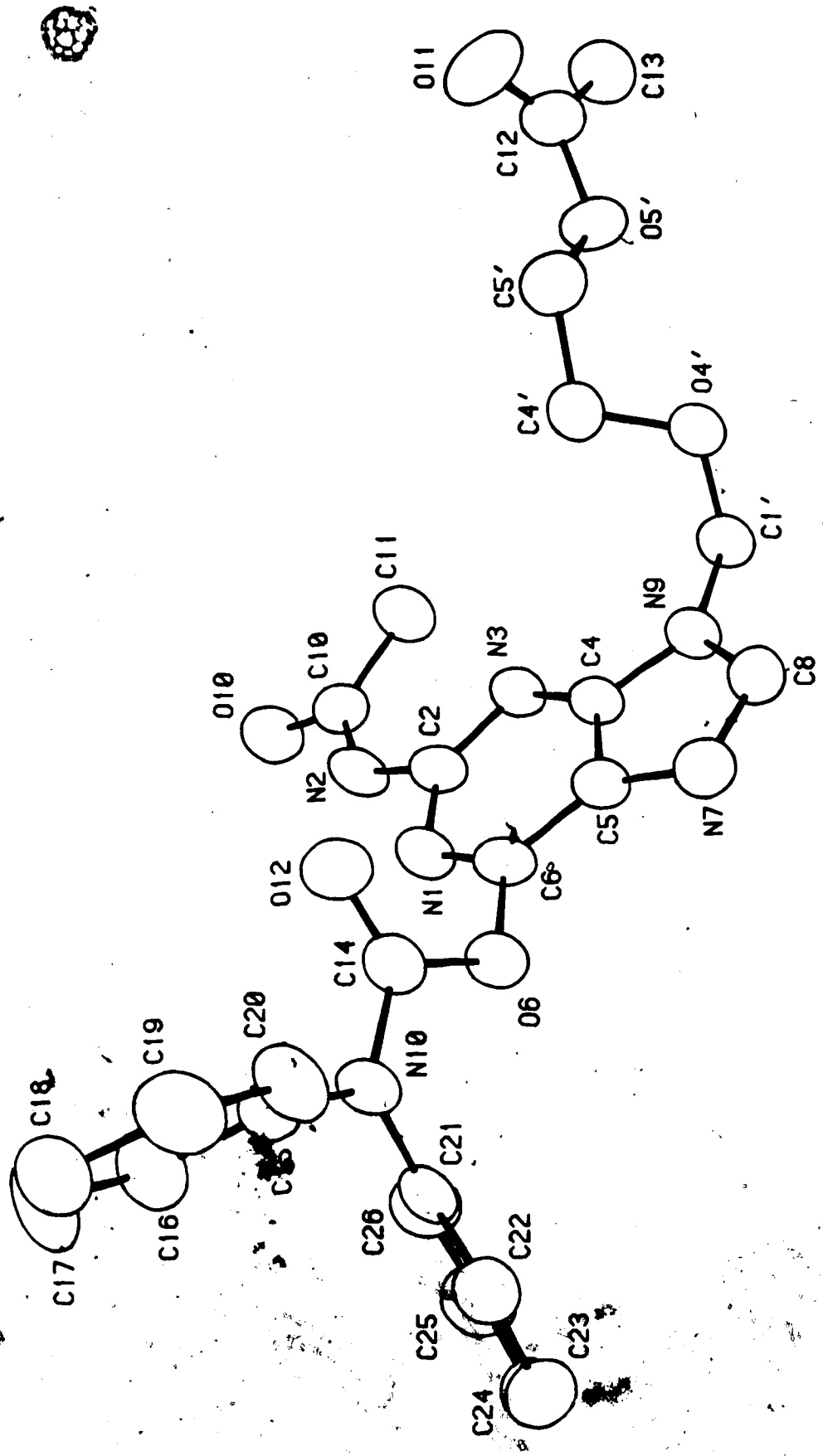
The bis(xylofuranosyl) derivative (148) was assumed to be a N9 nucleoside on the basis of its ^{13}C NMR data (see Part c of this chapter). This attachment was further confirmed by the fact that hydrolysis of (148) gave 9-β-D-xylofuranosylguanine (96) as the major product. Attachment of the second xylosyl residue to the 2-amino nitrogen was assigned on the basis of the ^{13}C-^{1}H coupled ^{13}C NMR spectrum. The signal for C2 was split into a doublet by H1' of the second sugar residue. The other bis-substituted compounds (147, 149) are probably linked at N^2 and N9 as well since they are formed under chemically analogous conditions. Therefore, it is concluded that this coupling procedure gives regioselective N9 glycosylation without formation of the N7 isomer (the amount of the N7 isomer, if any, is below the detectable limit of our 400 MHz ^{1}H NMR spectrometer).

In the above discussion, the DPC group was assumed to be attached at O^6 of the guanine derivative (124). However, this O^6-attachment of the DPC group had not been proven. Hata et al.[152,153] had prepared DPC derivatives of guanine nucleosides and reported them as O^6-DPC compounds by analogy of the DPC acylation procedure to other methods that give O^6-substituted guanosine derivatives.

Mass spectra of (124) and other DPC compounds had no peaks for M-Ph_2NCOO fragments. ^{1}H NMR spectroscopy did not differentiate between possible O^6-DPC and N1-DPC derivatives. Ultraviolet spectroscopy is useful for the determination of sites of attachment of

groups on many heterocyclic bases. However, it is not useful for our DPC derivatives since the DPC group absorbs UV light in the same region as the guanine base. The site of attachment of the DPC group was determined to be at O^6 by X-ray crystallographic analysis[154] of DPC derivative (145). The computer-generated structure and structural parameters are shown on the following pages (Scheme 32, Table 1-3).

Since the DPC derivative (134) prepared by coupling with N^2-acetyl-O^6-diphenylcarbamoylguanine (124) was identical with that prepared by Hata's diphenylcarbamoylation procedure, we assume that all of our DPC derivatives from coupling with (124), as well as Hata's diphenylcarbamoylation products, have the same O^6 attachment.


O11
C13
C12
O5'
C5'
C4'
O4'
C1'
N9
C8
C4
N3
C2
C11
C10
O10
N2
C5
N7
C6
N1
O12
C14
O6
N10
C20
C19
C18
C21
C26
C22
C25
C23
C24
C17
C16

SCHEME 32

Table 1. Bond distances Of (145) In Ångstroms

Atom1	Atom2	Distance	Atom1	Atom2	Distance	Atom1	Atom2	Distance
O4'	C1'	1.396 (2)	N3	C4	1.340 (2)	C15	C16	1.373 (3)
O4'	C4'	1.437 (2)	N7	C5	1.387 (2)	C15	C20	1.371 (3)
O5'	C5'	1.458 (2)	N7	C8	1.300 (2)	C16	C17	1.364 (3)
O5'	C12	1.336 (2)	N9	C1'	1.456 (2)	C17	C18	1.393 (3)
O6	C6	1.374 (2)	N9	C4	1.367 (2)	C18	C19	1.352 (3)
O6	C14	1.373 (2)	N9	C8	1.374 (2)	C19	C20	1.406 (3)
O10	C10	1.227 (2)	N10	C14	1.355 (2)	C21	C22	1.378 (3)
O11	C12	1.180 (3)	N10	C15	1.440 (2)	C21	C26	1.387 (3)
O12	C14	1.204 (2)	N10	C21	1.439 (2)	C22	C23	1.374 (3)
N1	C2	1.350 (2)	C4	C5	1.388 (2)	C23	C24	1.382 (3)
N1	C6	1.320 (2)	C4'	C5'	1.482 (3)	C24	C25	1.369 (3)
N2	C2	1.401 (2)	C5	C6	1.389 (3)	C25	C26	1.384 (3)
N2	C10	1.373 (2)	C10	C11	1.503 (3)			
N3	C2	1.325 (2)	C12	C13	1.500 (3)			

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 2. Bond Angles Of (145) In Degrees

Atom1	Atom2	Atom3	Angle
C1'	O4'	C4'	113.8 (1)
C5'	O5'	C12	116.3 (2)
O6	O6	C14	115.7 (1)
C2	N1	C6	117.1 (2)
C2	N2	C10	131.7 (2)
C2	N3	C4	111.8 (1)
C5	N7	C8	103.5 (1)
C1'	N9	C4	126.7 (2)
C1'	N9	C8	127.4 (2)
C4	N9	C8	105.8 (1)
C14	N10	C15	118.0 (2)
C14	N10	C21	124.3 (1)
C15	N10	C21	117.7 (1)
O4'	C1'	N9	113.2 (2)
N1	C2	N2	119.9 (2)
N1	C2	N3	127.8 (2)
N2	C2	N3	120.2 (2)
N3	C4	N9	127.2 (2)
N3	C4	C5	127.4 (2)
N9	C4	C5	105.4 (1)
O4'	C4'	C5'	108.9 (2)
O5'	C5'	C4'	108.0 (2)
N7	C5	C4	110.9 (2)
N7	C5	C6	135.5 (2)
C4	C5	C6	113.6 (2)
O6	C6	N1	117.2 (2)
O6	C6	C5	120.2 (2)
N1	C6	C5	122.4 (2)
N7	C8	N9	114.3 (2)
O10	C10	N2	117.0 (2)
O10	C10	C11	121.6 (2)
N2	C10	C11	121.5 (2)
O5'	C12	O11	123.8 (2)
O5'	C12	C13	110.9 (2)
O11	C12	C13	125.3 (2)
O6	C14	O12	123.1 (2)
O6	C14	N10	110.6 (2)
O12	C14	N10	126.2 (2)
N10	C15	C16	119.7 (2)
N10	C15	C20	119.9 (2)
C16	C15	C20	120.3 (2)
C15	C16	C17	120.4 (2)
C16	C17	C18	120.0 (2)
C17	C18	C19	119.9 (2)
C18	C19	C20	120.2 (2)
C15	C20	C19	119.1 (2)
N10	C21	C22	119.0 (2)
N10	C21	C26	121.4 (2)
C22	C21	C26	119.5 (2)
C21	C22	C23	120.5 (2)
C22	C23	C24	120.0 (2)
C23	C24	C25	119.7 (2)
C24	C25	C26	120.6 (2)
C21	C26	C25	119.6 (2)

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 3. Torsional Angles Of (145) In Degrees

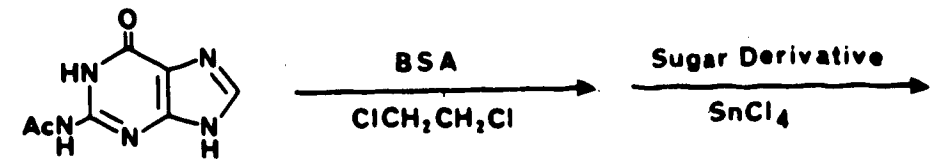
Atom 1	Atom 2	Atom 3	Atom 4	Angle
C4'	O4'	C1'	N9	-66.21
C1'	O4'	C4'	C5'	-173.97
C12	O5'	C5'	C4'	161.39
C5'	O5'	C12	O11	-1.82
C5'	O5'	C12	C13	177.87
C14	O6	C6	N1	-67.07
C14	O6	C6	C5	117.82
C6	O6	C14	O12	-23.62
C6	O6	C14	N10	158.78
C6	N1	C2	N2	179.27
C6	N1	C2	N3	0.20
C2	N1	C6	O6	-176.27
C2	N1	C6	C5	-1.27
C10	N2	C2	N1	177.49
C10	N2	C2	N3	-3.37
C2	N2	C10	O10	177.46
C2	N2	C10	C11	-2.80
C4	N3	C2	N1	0.10
C4	N3	C2	N2	-178.89
C2	N3	C4	N9	179.18
C2	N3	C4	C5	0.68
C8	N7	C5	C4	-0.06
C8	N7	C5	C6	-179.23
C5	N7	C8	N9	-0.18
C4	N9	C1'	O4'	97.20
C8	N9	C1'	O4'	-83.39
C1'	N9	C4	N3	0.40
C1'	N9	C4	C5	179.17
C	N9	C4	N3	-179.11
C8	N9	C4	C5	-0.34
C1'	N9	C8	N7	-179.16
C4	N9	C8	N7	0.34
C15	N10	C14	O6	168.97
C15	N10	C14	O12	-8.54
C21	N10	C14	O6	-11.55
C21	N10	C14	O12	170.94
C14	N10	C15	C16	111.57
C14	N10	C15	C20	-70.79
C21	N10	C15	C16	-67.95
C21	N10	C15	C20	109.70
C14	N10	C21	C22	127.00
C14	N10	C21	C26	-54.67
C15	N10	C21	C22	-53.52
C15	N10	C21	C26	124.81
N3	C4	C5	N7	179.02
N3	C4	C5	C6	-1.61
N9	C4	C5	N7	0.26
N9	C4	C5	C6	179.63
O4'	C4'	C5'	O5'	67.82
N7	C5	C6	O6	-4.13
N7	C5	C6	N1	-178.98
C4	C5	C6	O6	176.71
C4	C5	C6	N1	1.86
N10	C15	C16	C17	178.72
C20	C15	C16	C17	1.08
N10	C15	C20	C19	-179.14
C16	C15	C20	C19	-1.50
C15	C16	C17	C18	-0.61
C16	C17	C18	C19	0.60
C17	C18	C19	C20	-1.04
C18	C19	C20	C15	1.50
N10	C21	C22	C23	178.77
C26	C21	C22	C23	0.40
N10	C21	C26	C25	179.77
C22	C21	C26	C25	-1.90
C21	C22	C23	C24	0.54
C22	C23	C24	C25	0.03
C23	C24	C25	C26	-1.56
C24	C25	C26	C21	2.50

b. Regioselective glycosylation leading to N7 guanine nucleosides

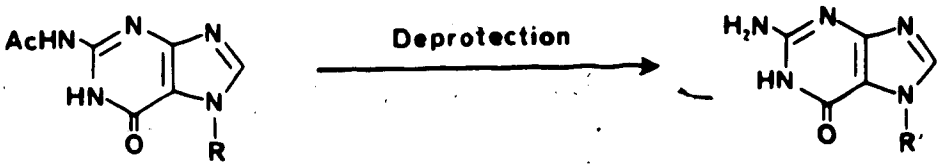
Naturally occurring purine nucleosides are N9 glycosyl compounds. This N9 attachment is also common to most biologically active purine nucleoside analogues. Therefore, in purine nucleoside syntheses by coupling reactions, the N9 glycoside is normally the target and any N7 isomer appears as an unwanted side product. This is particularly true in guanine nucleoside syntheses. Major efforts have been devoted to raising the ratio of N9/N7 guanine nucleosides. Few attempts have been made to do the opposite.

In the exploration of regioselective glycosylation approaches for guanine nucleoside synthesis, we examined the coupling reactions of silylated N^2-acetylguanine with three different peracetylated pentofuranoses using various reaction conditions. It was found that when the coupling reaction was conducted at room temperature in 1,2-dichloroethane in the presence of stannic chloride, the N7 nucleoside was produced predominantly without significant formation of the N9 isomer. ^{1}H NMR analysis of the crude coupling reaction products showed that the N7/N9 selectivity was 15-20:1 (calculated from ^{1}H NMR integration of the H8 signal of the products). The sequential procedure involved silylation of N^2-acetylguanine, addition of stannic chloride to form a complex with the silylated base, glycosylation with a peracetylated sugar derivative, and removal of protective groups to give the free N7 nucleoside.

Thus, treatment of a suspension of N^2-acetylguanine in 1,2-dichloroethane with N,O-bis(trimethylsilyl)acetamide at 80°C gave a homogeneous solution of the silylated base (Scheme 33). This solution



(8)



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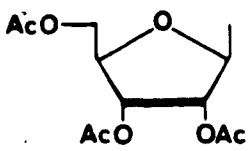

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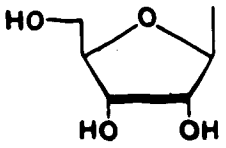

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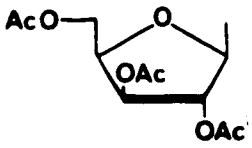

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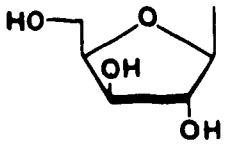

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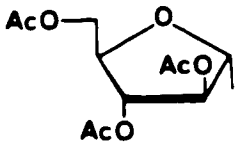

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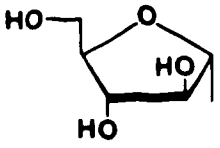
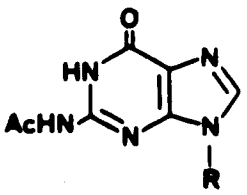
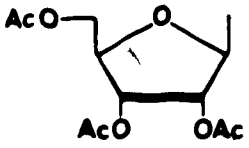


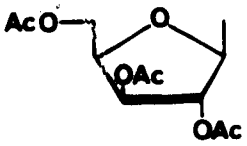
(155)

SCHEME 33

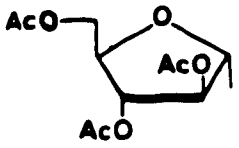


R = 

(48)

R = 

(156)

R = 

(157)

SCHEME 34

was cooled to room temperature and then was stirred with 2.14 equivalents of stannic chloride for 30 min. 1.1 Equivalents of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose was added and the glycosylation reaction was allowed to proceed at room temperature for 1 day. After a standard work-up procedure and chromatographic purification, the pure N7 nucleoside (150) was obtained in 70% yield. Deprotection of (150) was effected with methanolic ammonia. The yield of the N7 isomer (113) of guanosine was 78%.

In this coupling procedure, the silylation of N^2-acetylguanine also can be achieved by treatment with hexamethyldisilazane. However, the use of N,O-bis(trimethylsilyl)acetamide is preferable since it allows more facile silylation and enables combination of the silylation and glycosylation steps into a "one-pot" procedure.

A practical problem frequently encountered in stannic chloride-catalysed coupling reactions was formation of emulsions during work-up. We found that this problem could be minimized by addition of a small amount of methanol prior to the liquid-liquid extraction procedure.

Application of this N7 glycosylation procedure to the coupling of (8) with an anomeric mixture of 1,2,3,5-tetra-O-acetyl-D-xylofuranose gave the corresponding N7 "xylo-guanosine" derivative (152) in 76% yield after separation on silica. About 3% of the N9 nucleoside (156) was isolated as a minor product. Deprotection of (152) with aqueous ammonia/methanol afforded 7-β-D-xylofuranosylguanine (153) in 86% yield.

Glycosylation of (8) with an anomeric mixture of 1,2,3,5-tetra-O-acetyl-D-arabinofuranose using the same coupling procedure gave the expected 7-α nucleoside (154) in 72% yield. The free 7-α-D-arabinofuranosylguanine (156) was obtained in 85% yield by removal of protective groups.

c. A convenient method for determination of the site of glycosyl attachments of guanine nucleosides

The position of attachment of the glycosyl linkage of natural purine nucleosides was first established by comparison of their UV spectra.[12,155-158] It was found that the UV spectra of 9-methylguanine were similar to those of natural guanine nucleosides and were considerably different from those of 7-methylguanine in neutral and alkaline solutions. Guanosine and 2'-deoxyguanosine were assigned as N9 glycosides on this basis. Later, UV criteria were used extensively

to distinguish between positional isomers of guanine nucleosides obtained from glycosylation reactions. However, this method is restricted to free nucleosides or substituents that are UV transparent.

Structure assignment of positional isomers of guanine nucleosides by ^{1}H NMR spectroscopy is often more reliable and can be applied to protected nucleosides. Ashton et al.[59] have observed that downfield shifts of the H8 and H1' resonances of N7 isomers relative to their N9 isomers are characteristic. ^{1}H NMR studies of our guanine derivatives are generally in agreement with this observation. The H8 and H1' chemical shifts of isomeric pairs of guanine derivatives are listed in Table 4. The data show that the H8 resonances of N7 isomers are approximately 0.3 ppm downfield relative to those of their N9 isomers. The H1' signals are also shifted downfield to a similar extent. The downfield shift of the H1' resonances of the N7 isomers, attributed to carbonyl group anisotropy, has been shown to be a reliable indicator for the site of glycosylation in other nucleosides.[159-162]

An exception to this trend is (151), whose H1' resonance is 0.17 ppm upfield relative to that of its N9 isomer (134). Two factors that may contribute to this are the absence of the guanine carbonyl anisotropy and adoption of an anti conformation in which the H1' resides within a shielding area of the DPC group.

Structure assignments of N7 and N9 guanine derivatives by ^{1}H NMR spectroscopy are straightforward when identical positional isomers are available for comparison. However, this analysis becomes complicated when anomers are involved. Inversion of configuration at the anomeric center sometimes results in shifts of the H8 and H1'

Table 4. H8 (and H1') Chemical Shifts[a] Of Isomeric Pairs Of Substituted Guanines

Compound	Attachment[c]	H8	H1'	Compound	Attachment[c]	H8	H1'
(7)	N9	7.96	5.71	(129)	N9[d]	8.40	
(113)	N7	8.30	5.98	(130)	N7[d]	8.70	
(22)	N9	8.30	6.42	(131)	N9[d]	8.61	
(24)	N7	8.58	6.63	(132)	N7[d]	8.88	
(48)	N9	8.25	6.08	(131)	N9[d]	8.09[b]	
(150)	N7	8.52	6.31	(132)	N7[d]	8.26[b]	
(96)	N9	7.83	5.66	(134)	N9	8.61	6.26
(153)	N7	8.12	6.08	(151)	N7	8.91	6.09
(116)	N9	8.12		(137)	N9	7.90	5.65
(117)	N7	8.60		(155)	N7	8.16	5.91
(119)	N9[d]	8.42		(156)	N9	8.18	5.97
(118)	N7[d]	8.60		(152)	N7	8.40	6.36
(121)	N9[d]	7.94[b]		(157)	N9	8.24	6.17
(122)	N7[d]	8.25[b]		(154)	N7	8.44	6.36

a. Measurements were made in DMSO-d_6 unless otherwise specified.

b. Measured in $CDCl_3$.

c. Assignments have been corroborated by other means except for those marked with d.

d. Assignments were based on relative H8 resonances of positional isomers.

resonances similar to those between N7 and N9 pairs.

Previous studies[163-169] have shown that ^{13}C NMR spectroscopy provides valuable information in determination of the site of N-substitution on nitrogen heterocycles. This spectral method relies on changes in chemical shifts of those carbon atoms α and β to the site of N-substitution. An improved method[169] has utilized a combination of the α- and β-carbon chemical shift data with certain long-range two- and three-bond ^{13}C-^{1}H coupling constants. The key spin-spin coupling of Cα and H1' allows an unambiguous assignment of the site of N-glycosylation. However, it requires much longer accumulation times and larger sample sizes to obtain such ^{13}C-^{1}H coupled spectra.

In attempts to distinguish between N7 and N9 purine nucleoside isomers by ^{13}C NMR spectroscopy, Schmidt and co-workers[170,171] noted that the purine carbon shift pattern of N9 isomers was similar, but distinct from another compatible pattern for the N7 isomers. These patterns were considered to provide unequivocal assignment of the site of glycosyl linkages. Although this criterion was applicable to many guanine derivatives, difficulties were encountered when the guanine carbon shift pattern was complicated by additional signals from substituents.

^{13}C NMR studies of our guanine derivatives have revealed that the C5 resonance peak of the N9 substituted guanines occurs at lower field than 114 ppm and that of the N7 isomers at higher field than 111 ppm. The C5 resonance regions of the two isomers do not overlap (see Table 5). Therefore, the C5 chemical shift, alone, can be used as a diagnostic index for differentiation between N7 and N9 guanine derivatives.

Table 5. C5 Chemical Shifts Of N9 And N7 Guanine Derivatives

N9 derivative	C5 shift	N9 derivative	C5 shift	N9 derivative	C5 shift	N7 derivative	C5 shift
(7)	116.68	(126)	119.70	(141)	120.60	(113)	107.67
(20)	121.38	(134)	120.26	(142)	120.55	(117)	110.40
(48)	120.33	(135)	119.69	(143)	120.42	(150)	110.49
(70)	115.76	(136)	120.09	(144)	116.50	(151)	110.59
(93)	116.84	(137)	116.60	(145)	119.54	(152)	110.55
(96)	116.24	(138)	119.54	(146)	116.43	(153)	107.41
(115)	114.46	(139)	115.76	(148)	122.59	(154)	110.45
(116)	119.12	(140)	120.13	(156)	119.81	(155)	107.49
(123)	120.77						

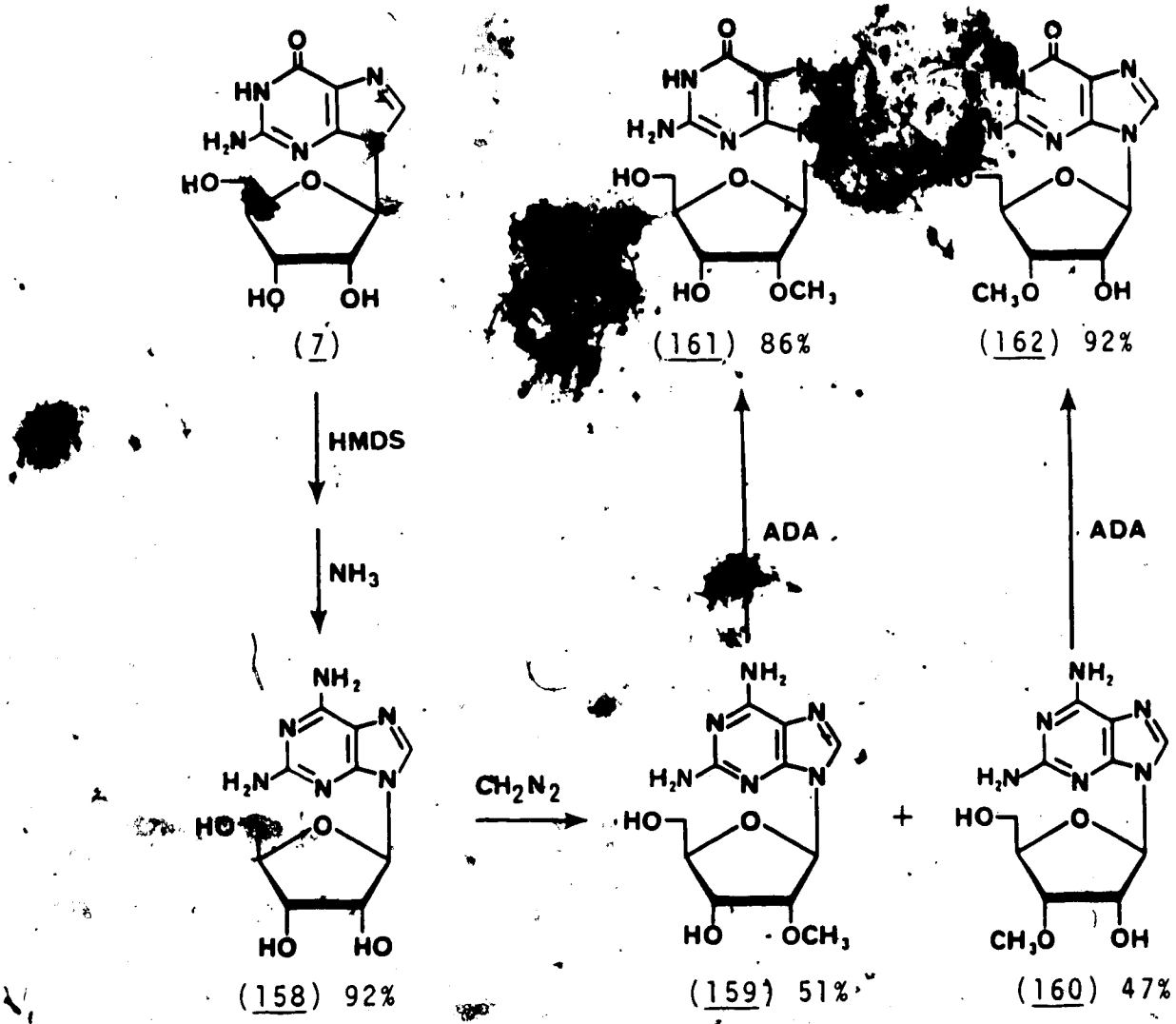
Use of the C5 chemical shift index offers several advantages: (1) Among the five guanine carbon peaks, the C5 signal is usually the easiest to identify. It appears at the highest field and in a region normally free of other signals. (2) C5 is close to the glycosylation sites, hence its chemical shift is sensitive to changes of glycosyl attachment. In fact, the C5 chemical shifts of N7 substituted guanines are 8-10 ppm upfield from those of their N9 isomers. (3) C5 signals are relatively insensitive to the nature of N^2- and O^6-substituents. The shifts caused by N^2- and O^6-substituents are normally within 4 ppm. (4) The C5 chemical shift index does not require the other isomer for comparison and allows rapid evaluation of the position of the glycosyl linkage without assignment of the other ^{13}C NMR signals. All of these features contribute to making this a convenient and general method for determination of the site of glycosyl attachment of N7 vs. N9 guanine nucleosides.

The ^{13}C NMR spectra of guanine derivatives with unsubstituted imidazole nitrogens such as (8), (120), (124) and (125) have a common feature in that most of the guanine carbon signals are broadened and/or depleted. The existence of tautomers other than the 9-H isomer and equilibration between them[172] may account for this observation.

B. Syntheses of guanine nucleosides via a combination of chemical transformations and enzymatic deamination

In 1981, a convenient approach for the synthesis of sugar-modified guanine nucleosides via sugar transformations was reported by our research group.[80] Guanosine was converted to 2,6-diamino-9-β-D-

ribofuranosylpurine (158), which upon methylation afforded a mixture of 2'-O- and 3'-O-methylated 2,6-diaminopurine nucleosides (159) and (160) (Scheme 35). Treatment of (159) and (160) with



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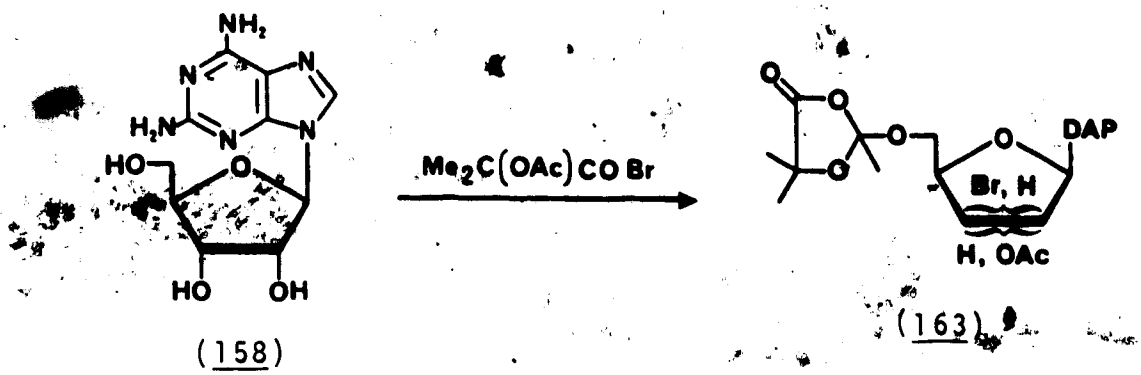
adenosine deaminase (adenosine aminohydrolase; E.C.3.5.4.4) gave the corresponding sugar-modified guanine nucleosides (161 and 162) in high overall yields. This approach featured a highly efficient chemical conversion of the experimentally uncooperative guanosine to

2,6-diamino-9-β-D-ribofuranosylpurine followed by sugar transformation chemistry on this "2-aminoadenosine" nucleoside and then enzymatic deamination of the sugar-modified 2,6-diaminopurine compounds to return to their guanine counterparts.

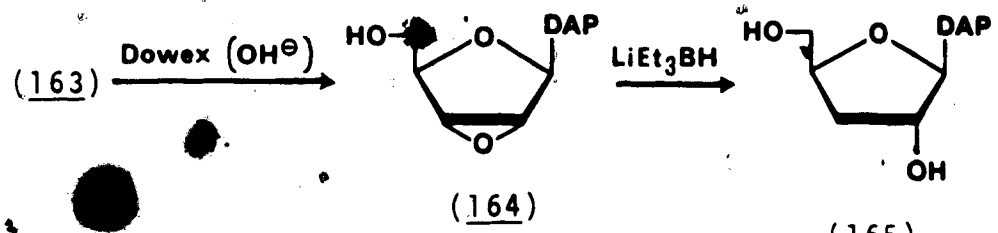
We have extended this indirect approach to the synthesis of several sugar-modified guanine nucleosides. 2,6-Diamino-9-β-D-ribofuranosylpurine (158) was prepared from guanosine (7) using a modification[80] of the known method.[173] Treatment of (158) with α-acetoxyisobutyryl bromide[111-114] yielded an isomeric mixture of trans bromo acetates (163) (Scheme 36). Application of this mixture to a column of Dowex 1X2 (OH^-) and elution with methanol gave the 2',3'-anhydro nucleoside (164) in 81% yield from (158). Reductive opening of the epoxide ring of (164) with lithium triethylhydridoborate resulted in selective cleavage of the O-C3' bond to give the 3'-deoxy nucleoside (165) in 85% yield.

Reduction of (163) with tri-n-butyltin hydride followed by deprotection gave a mixture of the 2'-deoxy and 3'-deoxy nucleosides (165 and 166). After separation on a Dowex 1X2 (OH^-) column, the pure 2'-deoxy and 3'-deoxy isomers were obtained in 16% and 59% yields, respectively.

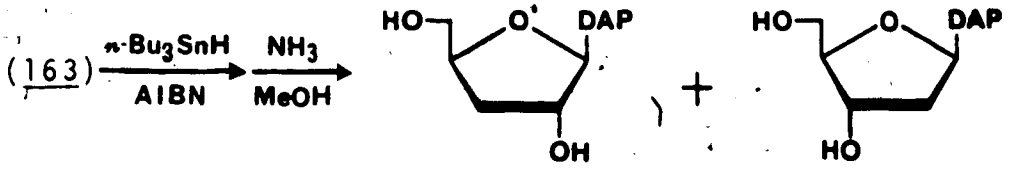
Treatment of (163) with zinc-copper couple in N,N-dimethylformamide[114] effected smooth reductive elimination of bromide and acetate from (163). The 2',3'-unsaturated nucleoside (167) was obtained after deprotection. Assignment of the vinylic proton and carbon resonance peaks of (167) was complicated by the tightly coupled spin system. An experiment using a labeled compound was designed to distinguish the signals of H2' and C2' from those of H3' and C3'.



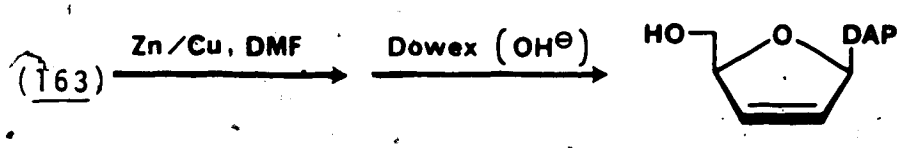
(158) (163)



(164) (165)



(165) (166)



(167)

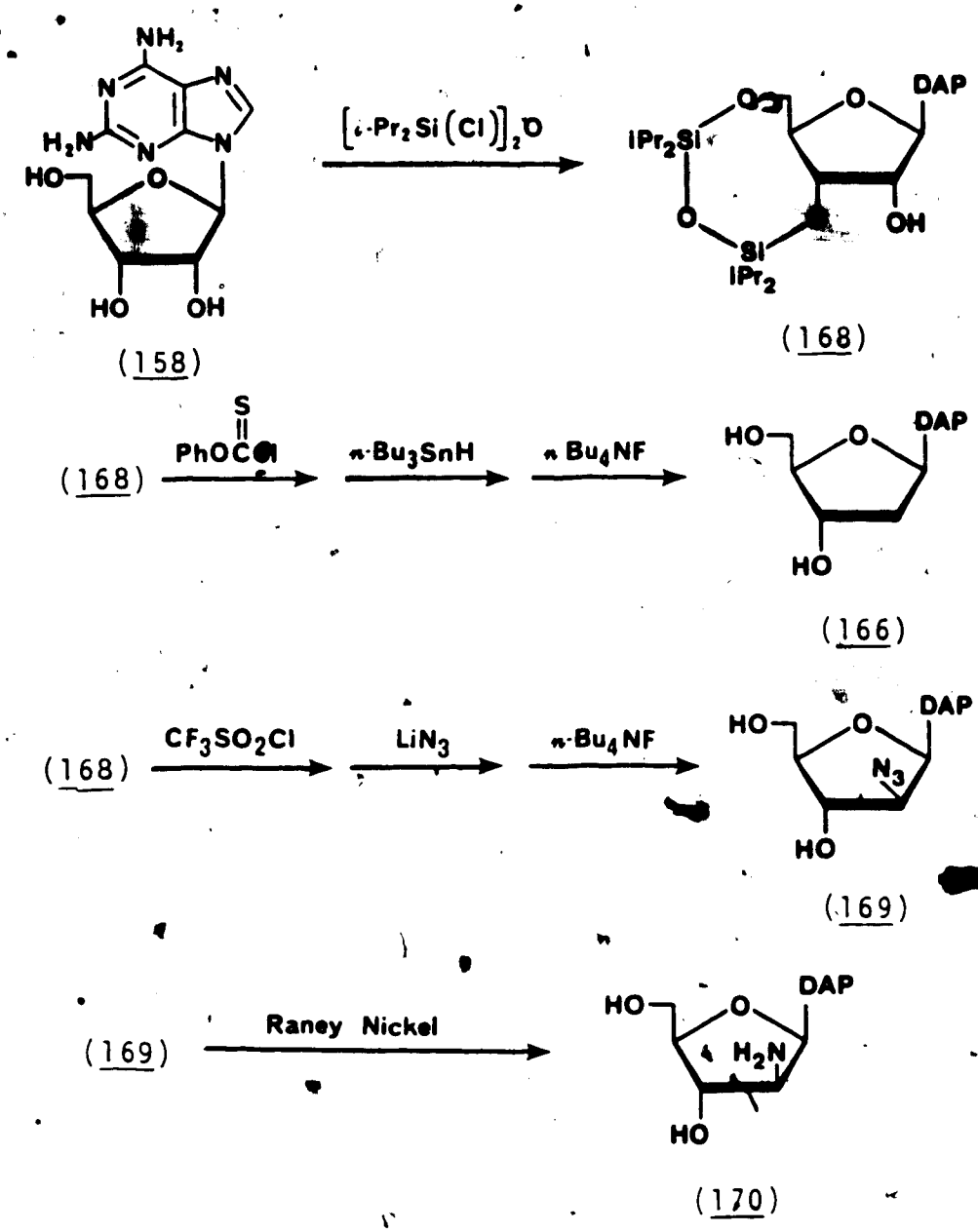
SCHEME 36

Subjection of 2,6-diamino-9-(2-deuterio-β-D-ribofuranosyl)purine[174] [2'-D-(158)] (~16% ^{2}H) to this reaction sequence gave the corresponding 2',3'-unsaturated nucleoside with the 2'-position partially labeled [2'-D-(167)]. The ^{1}H NMR spectrum of this product showed two vinyl proton signals at 6.10 ppm and 6.44 ppm. The higher-field signal was ~16% less intense than the lower. Therefore, the signal at 6.10 ppm was assigned to H2' and that at 6.44 ppm to H3'. The higher field vinyl carbon signal was assigned to C2' on the basis of selective ^{13}C-^{1}H decoupling experiments. These assignments of H2' and C2' to higher field were in harmony with the ordering for other 2',3'-unsaturated nucleosides.[113,114]

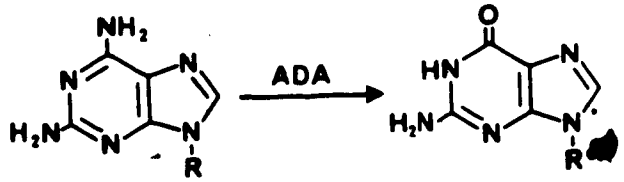
Treatment of (158) with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane under the literature conditions[140,141] gave (168) in high yield (Scheme 37). The crude product (168) was acylated with phenoxythiocarbonyl chloride and the resulting thionocarbonate was reduced with tri-n-butyltin hydride. After removal of the silyl protecting group, the 2'-deoxy nucleoside (166) was obtained in 41% overall yield from (158).

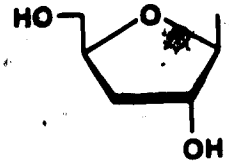
Triflation of (168) followed by displacement with azide and deprotection with fluoride afforded the 2'-azido nucleoside (169). This compound was converted to the 2'-amino nucleoside (170) by hydrogenolysis with Raney nickel.

Conversion of these sugar-modified 2,6-diaminopurine nucleosides (165, 166, 167, 170, 172) to their guanine nucleoside counterparts was effected in aqueous sodium phosphate buffer solution using adenosine deaminase (Scheme 38). The reaction process was monitored by

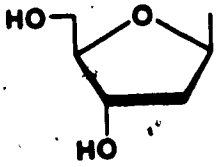

NH2
N
N
H2N
N
N
HO
O
HO
OH
(158)
[i-Pr2Si(Cl)]2O
i-Pr2Si
O
O
O
DAP
OH
Si
iPr2
(168)
(168)
PhOC(=S)Cl
n-Bu3SnH
n-Bu4NF
HO
O
DAP
HO
(166)
(168)
CF3SO2Cl
LiN3
n-Bu4NF
HO
O
DAP
N3
HO
(169)
(169)
Raney Nickel
HO
O
DAP
H2N
HO
(170)

SCHEME 37



R = 

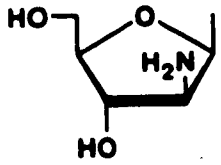
(165) (81)

R = 

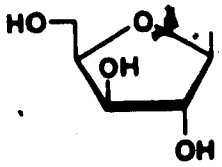
(166) (93)

R = 

(167) (171)

R = 

(170) (104)

= 

(172) (96)

SCHEME 38

electrophoresis. The isolated yields of the corresponding guanine nucleosides were higher than 80% except for the unsaturated nucleoside (171). In this case, the enzymatic deamination required 10 days for completion and the somewhat unstable unsaturated nucleosides partially decomposed during the extended reaction period.

In general, this indirect approach for the synthesis of sugar-modified guanine nucleosides is considerably more favorable to carry out experimentally than the direct sugar transformations of guanosine. Separation and purification of the intermediate reaction products are easily achieved because these 2,6-diaminopurine nucleosides are amenable to ion-exchange chromatography on Dowex 1X2 (OH^-) resin and usually crystallize readily. This approach offers better overall yields in certain cases than the direct transformation method and thus provides a useful alternative route to sugar-modified guanine nucleosides.

3. EXPERIMENTAL

A. General Procedures

Melting points (mp) were determined on a Reichert micro stage apparatus and are uncorrected. Mass spectra (MS) were determined by the Mass Spectrometry Laboratory of this department. High resolution MS measurements were done on a Kratos MS-50 instrument with computer processing at 70 eV using a direct probe for sample introduction. Fast atom bombardment (FAB) MS were recorded on a Kratos MS-9 instrument at low resolution. Nuclear magnetic resonance (NMR) spectra were determined on Bruker WH-400 or Bruker WH-200 spectrometers operating in the FT mode, with Me_4Si as internal standard in Me_2SO-$\underline{d}_6$ solutions. Ultraviolet (UV) spectra were recorded on a Hewlett Packard 8450A diode array spectrophotometer and infrared (IR) spectra on a Nicolet 7199 FT (IR) instrument. Elemental analyses were determined by the Microanalytical Laboratory of this department or by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. X-Ray crystallographic analysis was done on an Enraf-Nonius CAD4 automated diffractometer by the Structure Determination Laboratory of this department.

All solvents used were of reagent grade and were purified according to the methods described in reference 175 if used as reaction media. Solvents used for chromatography, extraction, and other purposes were purified by simple distillation. All dried solvents were stored over Davison 3 Å and 4 Å molecular sieves purchased from the Fisher Scientific Company.

Buffer solutions used for enzymatic deamination reactions were formulated to 0.1 M from monosodium phosphate. pH values were adjusted to the desired values (pH 7.4 or pH 6.5) by addition of NaOH solution using a Corning pH meter model 7 calibrated with a Fisher certified standard buffer solution (pH 7.00).

Enzymatic deamination reactions were monitored by thin layer electrophoresis (TLE) on Polygram CEL 300 pre-coated plastic sheets (layer thickness 0.1 mm) on a Brinkmann instrument operating at 800 V, pH 3.5 (sodium formate buffer solution) for 30 min. The other reactions were followed by thin layer chromatography (TLC) on Merck silica gel $60F_{254}$ pre-coated plastic sheets (layer thickness 0.2 mm). The TLE and TLC sheets were observed under UV light (2537 Å). Preparative TLC was performed on glass plates coated with Merck silica gel $60PF_{254}$. The solvents used for TLC were different ratios of MeOH:$CHCl_3$ (1:50, 1:19, 1:9), EtOAc : Skelly B (2:8, 4:6, 6:4), SSE (the upper phase of EtOAc:n-PrOH:H_2O, 4:1:2), and i-PrOH:H_2O:NH_4OH (7:2:1). Silica gel column chromatography was performed using Terochem silica gel (100 mesh up: 5%, 100-200 mesh: 47.6%, 200 mesh down: 47.4%) or Merck silica gel 60 (230-400 mesh). Anion exchange chromatography was carried out on Dowex 1 X 2 resin in the hydroxide form.

Evaporations were effected using a Buchi rotating evaporator equipped with a Dewar "dry ice" condenser under water aspirator or mechanical oil pump vacuum at 40°C or cooler. The specified reaction temperatures were direct readings of the bath temperatures.

Abbreviations used are: ADA = adenosine deaminase (adenosine

aminohydrolase; EC 3.5.4.4); AIBN = azobisisobutyronitrile; BSA = N,O-bis(trimethylsilyl)acetamide; DMAc = N,N-dimethylacetamide; DMAP = 4-(dimethylamino)pyridine; DMF = N,N-dimethylformamide; DMSO = dimethyl sulfoxide; THF = tetrahydrofuran; TMSTf = trimethylsilyl triflate; TPDSCl = 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane; s = singlet; d = doublet; t = triplet; m = multiplet; br = broad; abs = absolute; dec = decomposition; Lit = Literature; Sh = shoulder peak. Skelly B represents the petroleum ether fraction which boils between 60-90°C.

B. Syntheses

N^2,9-Diacetylguanine (20)

To 30.22 g (0.2 mol) of guanine in 250 mL of dry DMAc was added 50 mL (54.1 g, 0.528 mol) of Ac_2O. The suspension was stirred at 160°C for 7 h to give a brown solution. The oil bath was removed and the reaction mixture was allowed to stand at ambient temperature overnight. The resulting crystals were collected by filtration and washed with 250 mL of cold 95% EtOH. The filtrate and washings were kept at 5°C overnight to give an additional crop. The combined yield was 42.53 g (90%) of (20): mp 270°C (dec) (Lit[22] mp 261-263°C); MS m/z 235.0706 (12%, M^+ = 235.0706); ^1H NMR δ 2.20 (s, 3, AcN^2), 2.80 (s, 3, AcN9), 8.42 (s, 1, H8), 11.70-12.20 (br, 2, H1, HN^2); ^{13}C NMR δ 173.47 (CON^2), 167.75 (CON9), 154.45 (C6), 148.25 (C2), 147.68 (C4), 137.14 (C8), 121.38 (C5), 24.40 ($\underline{C}H_3CON^2$), 23.65 ($\underline{C}H_3CON9$); Anal. Calcd. for $C_9H_9N_5O_3$: C 45.96, H 3.86, N 29.78. Found: C 45.77, H 3.83, N 29.79; UV (MeOH) Max 252 and 292 nm.

N^2-Acetylguanine (8)

A suspension of 2.35 g (10 mmol) of N^2,9-diacetylguanine (20) in 100 mL of 50% EtOH was heated on a steam bath for 2 h and then kept at 5°C overnight. The crystals were collected by filtration and washed with 50 mL of 95% EtOH to give 1.89 g (98%) of (8): mp > 290°C (Lit[17,145] mp 260°C); MS m/z 193.0600 (24%, M^+ = 193.0600); ^1H NMR

δ 2.16 (s, 3, Ac), 8.02 (s, 1, H8), 11.60-12.40 (br, 3, HN1, HN^2, $HN9^{176}$); Anal. Calcd. for $C_7H_7N_5O_2$: C 43.53, H 3.65, N 36.26. Found: C 43.16, H 3.61, N 36.41; UV (H_2O) max 259 nm (ε 15,600); (0.1 N HCl) max 260 nm (ε 16,600); (pH 9) max 264 nm (ε 11,300). [Lit[177] UV (H_2O) max 260 nm (ε 15,290); (0.1 N HCl) max 261 nm (ε 15,930); (pH 9.1) max 264 nm (ε 11,800)].

2-Acetamido-6-diphenylcarbamoyloxy-9-acetylpurine (N^2,9-diacetyl-O^6-diphenylcarbamoylguanine) (123)

To a stirred suspension of 0.47 g (2 mmol) of N^2,9-diacetylguanine (20) and 0.7 mL (4 mmol) of diisopropylethylamine in 20 mL of dry pyridine was added portionwise 0.51 g (2.2 mmol) of diphenylcarbamoyl chloride. The reaction mixture was stirred at room temperature for 1 h. During this period, the solid material disappeared and a dark red solution was obtained. Volatile materials were evaporated and coevaporated with toluene (5 mL x 3). The residue was suspended in CH_3CN and filtered. The solid product was washed with portions of CH_3CN and dried to give 0.63 g (73%) of (123) as a powder: mp 224-228°C (dec); MS m/z 430.1379 (18%, M^+ = 430.1390); ^1H NMR δ 2.24 (s, 3, AcN^2), 2.93 (s, 3, AcN9), 7.28-7.62 (m, 10, Ph_2), 8.88 (s, 1, H8), 10.92 (s, 1, HN^2); ^{13}C NMR δ 168.56 (CON^2), 167.45 (CON9), 155.48 (C6), 153.47 (C4), 152.85 (C2), 149.61 (COO^6), 142.28 (C8), 141.33, 129.15, 127.10, 126.66 (Ph_2), 120.77 (C5), 24.41 (2 X $\underline{C}H_3CO$); UV (MeOH) max 263 nm.

2-Acetamido-6-diphenylcarbamoyloxypurine (N^2-acetyl-O^6-diphenylcarbamoylguanine) (124)

The procedure outlined in the preparation of (123) was followed using 5.88 g (25 mmol) of N^2,9-diacetylguanine (20), 120 mL of dry pyridine, 8.7 mL (50 mmol) of diisopropylethylamine, and 6.37 g (27.5 mmol) of diphenylcarbamoyl chloride. After stirring the reaction mixture at room temperature for 1 h, H_2O (10 mL) was added and stirring was continued for 10 min. Volatile materials were evaporated and coevaporated with toluene (20 mL x 3). The residue was heated on a steam bath in 300 mL of 50% EtOH for 1.5 h. The mixture was allowed to cool and then filtered. The solid product was washed with portions of 98% EtOH until washings were colorless and dried to give 8.93 g (92%) of (124) as a powder: mp 254-256°C (fast heating, dec); MS m/z 388.1283 (7.5%, M^+ = 388.1284); ^1H NMR δ 2.18 (s, 3, Ac), 7.26-7.56 (m, 10, Ph_2), 8.46 (s, 1, H8), 10.66 (s, 1, HN^2), 13.02 (br, 1, $HN9^{176}$); Anal. Calcd. for $C_{20}H_{16}N_6O_3$: C 61.85, H 4.15, N 21.64. Found: C 61.84, H 4.24, N 21.51; UV (MeOH) max 224 and 278 nm.

2-Acetamido-6-diphenylcarbamoyloxy-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine (134) from (124)

To a suspension of 388 mg (1 mmol) of (124) in 10 mL of dry 1,2-dichloroethane was added 0.5 mL (2 mmol) of BSA. The reaction mixture was stirred in a stoppered flask at 80°C for 15 min to give a

clear solution. Volatile materials were evaporated and the residue was dissolved in 5 mL of dry toluene. To this solution were added 0.25 mL (1.3 mmol) of TMSTf and a solution of 382 mg (1.2 mmol) of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose in 5 mL of toluene. The reaction mixture was stirred at 80°C for 1 h and then cooled. EtOAc (50 mL) was added and the organic phase was washed successively with saturated $NaHCO_3/H_2O$ (50 mL x 2), saturated $NaCl/H_2O$ (50 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed on a silica column (25 g, 2 x 15 cm) using Et_2O and 8:2 Et_2O/Me_2CO as eluants. Evaporation of appropriate fractions gave 589 mg (91%) of (134) as a white foam: MS (FAB) m/z 647 (2.9%, M+1); ^1H NMR δ 1.99, 2.05, 2.12 (3 X s, 3 X 3, 3 X AcO), 2.18 (s, 3, AcN^2), 4.33 (d of d, $J_{5''-5'}$ = 11.0 Hz, $J_{5''-4'}$ = 6.0 Hz, 1, H5"), 4.38 (m, $J_{4'-5'}$ = 3.5 Hz, $J_{4'-3'}$ = 5.5 Hz, 1, H4'), 4.43 (d of d, 1, H5'), 5.78 (t, $J_{3'-2'}$ = 5.5 Hz, 1, H3'), 5.95 (t, $J_{2'-1'}$ = 5.0 Hz, 1, H2'), 6.26 (d, 1, H1'), 7.28-7.54 (m, 10, Ph_2), 8.61 (s, 1, H8), 10.77 (s, 1, HN^2); ^{13}C NMR δ 169.75, 169.01, 168.29 (4 X $\underline{C}OCH_3$), 155.25 (C6), 153.98 (C4), 152.16 (C2), 149.77 (COO^6), 144.10 (C8), 141.41, 129.19, 127.10, 126.77 (Ph_2), 120.26 (C5), 86.27 (C1'), 79.76 (C4'), 72.16 (C2'), 70.25 (C3'), 63.04 (C5'), 24.26 ($NCO\underline{C}H_3$), 20.21, 20.09, 19.96 (3 X $OCO\underline{C}H_3$); UV (MeOH) max 225 and 278 nm.

2-[N-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)acetamido]-6-diphenylcarbamoyloxy-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine (147)

The silylation conditions used in the synthesis of (134) were

applied to 388 mg (1 mmol) of (124), 15 mL of 1,2-dichloroethane, and 0.5 mL (2 mmol) of BSA. To the resulting clear solution were added 796 mg (2.5 mmol) of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose and 0.4 mL (2.1 mmol) of TMSTf. Stirring was continued at 80°C for 3 h. The identical work-up procedure was followed and the residue was chromatographed on a silica column (25 g, 2 x 15 cm) using 3:97 and then 10:90 $Me_2CO/CHCl_3$ as eluants. Evaporation of fractions 11-14 gave 26 mg of pure (147) as a white foam: MS (FAB) m/z 905 (0.2%, M+1); ^1H NMR δ 1.60, 1.95, 2.04, 2.06, 2.12, 2.14, (6 X s, 7 X 3, 7 X Ac), 3.83, 4.18, 4.23, 4.37 (4 X m, 6, 2 X H4' and 2 X H5',5"), 5.28, 5.60, 5.80, 5.97 (t, t, m, t, 4, 2 X H2' and 2 X H3'), 6.11, 6.36 (2 X d, 2, 2 X H1'), 7.30-7.60 (m, 10, Ph_2), 8.85 (s, 1, H8); UV (MeOH) max 228 (Sh) and 263 (Sh) nm.

Evaporation of fractions 23-40 yielded 160 mg of pure (134). Fractions 15-22 contained 115 mg of a white foam, which was a mixture of (134) and (147).

Guanosine (7)

A mixture of 647 mg (1 mmol) of (134) in 20 mL of NH_3/MeOH (saturated at -10°C) was stirred in a sealed flask at room temperature for 1 day. Volatile materials were evaporated. The solid residue was extracted twice with $CHCl_3$ and then recrystallized from H_2O to give 220 mg (75%) of (7) as a hemihydrate: mp 265°C (dec) [Lit[178] mp > 235°C (dec)]; MS (FAB) m/z 284 (23%, M+1); ^1H NMR δ 3.52 (m, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = 4.0 Hz, $J_{5"-5'OH}$ = 5.5 Hz, 1, H5"), 3.62 (m, $J_{5'-4'}$ = 4.0 Hz, $J_{5'-5'OH}$ = 5.5 Hz, 1, H5'), 3.88 (m, $J_{4'-3'}$ = 4.0 Hz, 1,

H4'), 4.08 (m, $J_{3'-2'}$ = 5.0 Hz, $J_{3'-3'OH}$ = 4.5 Hz, 1, H3'), 4.40 (m, $J_{2'-1'}$ = 6.0 Hz, $J_{2'-2'OH}$ = 6.5 Hz, 1, H2'), 5.10 (t, 1, HO5'), 5.17 (d, 1, HO3'), 5.44 (d, 1, HO2'), 5.71 (d, 1, H1') 6.49 (s, 2, H_2N^2), 7.96 (s, 1, H8), 10.69 (s, 1, HN1); ^{13}C NMR δ 156.77 (C6), 153.63 (C2), 151.28 (C4), 135.60 (C8), 116.68 (C5), 86.42 (C1'), 85.21 (C4'), 73.69 (C2'), 70.36 (C3'), 61.40 (C5'); Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C 41.10, H 4.83, N 23.96. Found: C 41.03, H 4.63, N 23.99; UV (H_2O) max 252 nm (ε 13,800); (0.1 N HCl) max 255 nm (ε 12,300); (0.1 N KOH) max 264 nm (ε 11,500).

2-Acetamido-6-diphenylcarbamoyloxy-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)purine (135) and 2-[N-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-acetamido]-6-diphenylcarbamoyloxy-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)purine (148)

The conditions and work-up used for the synthesis of (134) were applied to the preparation of (135) using 388 mg (1 mmol) of (124) and 382 mg (1.2 mmol) of anomeric 1,2,3,5-tetra-O-acetyl-D-xylofuranose.[179] The residue was chromatographed on a silica column (25 g, 2 x 15 cm) using $CHCl_3$ and 1:99 MeOH/$CHCl_3$ as eluants. Evaporation of fractions 22-32 gave 553 mg (86%) of (135) as a white foam: MS (FAB) m/z 647 (3.8%, M+1); ^1H NMR δ 2.01, 2.09, 2.10 (3 X s, 3 X 3, 3 X AcO), 2.22 (s, 3, AcN^2), 4.29 (m, $J_{5''-5'}$ = 12.0 Hz, $J_{5''-4'}$ = 7.0 Hz, $J_{5'-4'}$ = 4.0 Hz, 2, H5', 5"), 4.61 (m, $J_{4'-3'}$ = 4.5 Hz, 1, H4'), 5.55 (d of d, $J_{3'-2'}$ = 2.5 Hz, 1, H3'), 5.81 ("t", $J_{2'-1'}$ = 3.5 Hz, 1, H2'), 6.18 (d, 1, H1'), 7.28-7.56 (m, 10, Ph_2), 8.59 (s, 1, H8), 10.74 (s, 1, HN^2); ^{13}C NMR δ 169.69, 168.97, 168.83 (4 X

$\underline{C}OCH_3$), 155.12 (C6), 154.23 (C4), 152.33 (C2), 149.77 (COO^6), 143.18 (C8), 141.41, 129.17, 127.07, 126.68 (Ph_2), 119.69 (C5), 86.15 (C1'), 78.25 (C2'), 77.69 (C4'), 73.98 (C3'), 61.11 (C5'), 24.35 ($NCO\underline{C}H_3$), 20.26, 20.18, 20.15 (3 X $OCO\underline{C}H_3$); UV (MeOH) max 226 and 278 nm.

Evaporation of fractions 17-20 gave 40 mg (4%) of (148) as a white foam: MS (FAB) m/z 905 (5.7%, M+1); ^1H NMR δ 1.43, 1.90, 1.96, 2.02, 2.10 (5 X s, 7 X 3, 7 X Ac), 3.88, 4.03, 4.30, 4.62 (4 X m, 2 X H4' and 2 X H5', 5"), 5.22, 5.52, 5.75, 5.80 (4 X m, 4, 2 X H2' and 2 X H3'), 6.14, 6.29 (2 X d, 2, 2 X H1'), 7.30-7.60 (m, 10, Ph_2), 8.83 (s, 1, H8); ^{13}C NMR δ 170.13, 169.75, 169.63, 169.09, 168.83 (7 X $\underline{C}OCH_3$), 155.17 (C6), 154.12 (C4), 151.82 (C2), 149.62 (COO^6), 145.73 (C8), 141.35, 129.24, 127.21, 126.72 (Ph_2), 122.59 (C5), 87.72, 86.83 (2 X C1'), 78.40, 78.07, 76.94, 75.54, 74.79, 74.13 (2 X C2', 2 X C3', 2 X C4'), 61.20, 61.02 (2 X C5'), 23.28 ($NCO\underline{C}H_3$), 20.28, 20.15, 19.27 (6 X $OCO\underline{C}H_3$); UV (MeOH) max 228 (Sh) and 263 (Sh) nm.

9-β-D-xylofuranosylguanine (96) from (135)

To 647 mg (1 mmol) of (135) in 20 mL of MeOH was added 20 mL of NH_3/H_2O (28-30%). The reaction mixture was stirred in a sealed flask at 60°C for 1 day. Volatile materials were evaporated. The solid residue was extracted twice with $CHCl_3$ and then recrystallized from H_2O to give (two crops) 197 mg (67%) of (96) as a hemihydrate: mp 250°C (dec) [Lit[24,42] mp 241-243°C (dec)]; MS (FAB) m/z 284 (14%, M+1); ^1H NMR δ 3.62 (m, $J_{5"-5'}$ = 11.5 Hz, $J_{5"-4'}$ = 6.0 Hz, $J_{5"-5'OH}$ =

5.5 Hz, 1, H5"), 3.72 (m, $J_{5'-4'}$ = 5.0 Hz, $J_{5'-5'OH}$ = 5.5 Hz, 1, H5'), 4.01 (m, $J_{3'-4'}$ = 3.5 Hz, $J_{3'-2'}$ = 1.5 Hz, $J_{3'-3'OH}$ = 4.5 Hz, 1, H3'), 4.08 (m, 1, H4'), 4.19 (m, $J_{2'-1'}$ = 1.5 Hz, $J_{2'-2'OH}$ = 4.5 Hz, 1, H2'), 4.69 (t, 1, HO5'), 5.56 (d, 1, HO3'), 5.66 (d, 1, H1'), 5.80 (d, 1, HO2'), 6.47 (s, 2, H_2N^2), 7.83 (s, 1, H8), 10.63 (s, 1, HN1); ^{13}C NMR δ 156.52 (C6), 153.51 (C2), 150.63 (C4), 135.89 (C8), 116.24 (C5), 88.52 (C1'), 83.06 (C4'), 80.92 (C2'), 75.08 (C3'), 59.33 (C5'); Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C 41.10, H 4.83, N 23.96. Found: C 40.97, H 4.52, N 23.83; UV (H_2O) max 252 nm (ε 13,700).

2-Acetamido-6-diphenylcarbamoyloxy-9-(2,3,5-tri-O-acetyl-α-D-arabinofuranosyl)purine (136)

The procedure and work-up used for the synthesis of (134) was followed using 388 mg (1 mmol) of (124) and 382 mg (1.2 mmol) of anomeric 1,2,3,5-tetra-O-acetyl-D-arabinofuranose.[179] The residue was applied to a silica column (25 g, 2 x 15 cm) and the product was eluted with 8:2 Et_2O/Me_2CO. Evaporation of appropriate fractions gave 531 mg (82%) of (136) as a white foam: MS (FAB) m/z 647 (0.8%, M+1); ^1H NMR δ 2.04 (s, 9, 3 X AcO), 2.22 (s, 3, AcN^2), 4.20 (d of d, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = 5.5 Hz, 1, H5"), 4.32 (d of d, $J_{5'-4'}$ = 3.5 Hz, 1, H5'), 5.00 (m, $J_{4'-3'}$ = 6.5 Hz, 1, H4'), 5.40 (d of d, $J_{3'-2'}$ = 5.0 Hz, 1, H3'), 6.04 ("t", $J_{2'-1'}$ = 4.0 Hz, 1, H2'), 6.32 (d, 1, H1'), 7.26-7.56 (m, 10, Ph_2), 8.59 (s, 1, H8), 10.76 (s, 1, HN^2); ^{13}C NMR δ 169.80, 169.45, 169.32, 168.69, (4 X $COCH_3$), 155.18 (C6), 153.99 (C4), 152.18 (C2), 149.77 (COO^6), 143.95 (C8), 141.40, 129.17, 127.08, 126.67

(Ph_2), 120.09 (C5), 86.71 (C1'), 80.18 (C4'), 78.26 (C2'), 74.87 (C3'), 62.56 (C5'), 24.37 ($NCO\underline{C}H_3$), 20.30, 20.26, 20.15 (3 X $O\underline{C}OCH_3$); UV (MeOH) max 226 and 278 nm.

9-α-D-arabinofuranosylguanine (137) from (136)

The deprotection conditions and work-up used for the preparation of (96) from (135) were applied to 647 mg (1 mmol) of (136). The crude product was recrystallized from H_2O to give 246 mg (84%) of (137): mp 290°C (dec); MS (FAB) m/z 284 (16%, M+1); ^1H and ^{13}C NMR spectra were identical with those of the product obtained from deprotection of (140). Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C 41.10, H 4.83, N 23.96. Found: C 41.23, H 4.57, N 24.08; UV (H_2O) max 252 nm (ε 13,000).

2-Acetamido-6-diphenylcarbamoyloxy-9-(2,3,5-tri-O-benzyl-α-D-arabinofuranosyl)purine (140) and 2-acetamido-6-diphenylcarbamoyloxy-9-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)purine (138)

The procedure and work-up used for the synthesis of (134) was applied to 388 mg (1 mmol) of (124) and anomeric 2,3,5-tri-O-benzyl-D-arabinofuranosyl chloride[180] prepared from 684 mg (1.2 mmol) of 1-O-p-nitrobenzoyl-2,3,5-tri-O-benzyl-β-D-arabinofuranose. The residue was chromoatographed on a silica column (30 g, 2 x 18 cm) with Skelly B and then 3:7 EtOAc/Skelly B as eluants. Evaporation of

fractions 18-31 gave 262 mg (33%) of (140) as a white foam: MS (FAB) m/z 791 (8.8%, M+1); ^{1}H NMR δ 2.18 (s, 3, AcN^2), 3.65 ("d", $J_{5'-4'}$ = 5.5 Hz, 2, H5', 5"), 4.23 ("t", $J_{3'-4'}$ = 4.5 Hz, $J_{3'-2'}$ = 3.5 Hz, 1, H3'), 4.55, 4.56, 4.68 (s, m, m, 3 X 2, benzylic), 4.77 (m, 1, H4'), 4.89 (t; $J_{2'-1'}$ = 3.0 Hz, 1, H2'), 6.26 (d, 1, H1'), 7.14-7.58 (m, 25, 5 X Ph), 8.54 (s, 1, H8), 10.72 (s, 1, HN^2); ^{13}C NMR δ 168.69 (N<u>C</u>OCH$_3$), 155.01 (C6), 153.85 (C4), 151.98 (C2), 149.85 (COO^6), 143.33 (C8), 141.47, 137.94, 137.41, 137.28, 129.15, 128.01, 127.97, 127.94, 127.51, 127.36, 127.26, 127.05, 126.85, 126.70 (5 X Ph), 120.13 (C5), 87.97 (C1'), 84.66 (C2'), 83.01 (C4'), 82.34 (C3'), 72.24, 71.54, 71.13 (benzylic), 69.50 (C5'), 24.38 (Me); UV (MeOH) max 228 and 279 nm.

Evaporation of fractions 33-50 gave 225 mg (28%) of (138) as a white foam: MS (FAB) m/z 791 (17%, M+1); ^{1}H NMR δ 2.18 (s, 3, AcN^2), 3.77 (m, $J_{5"-5'}$ = 11.0 Hz, $J_{5"-4'}$ = 4.5 Hz, $J_{5'-4'}$ = 5.0 Hz, 2, H5', 5"), 4.18 (m, $J_{4'-3'}$ = 5.5 Hz, 1, H4'), 4.28, 4.47 (d, d, 2, benzylic), 4.53 (s, 2, benzylic), 4.56 (t, $J_{2'-3'}$ = $J_{2'-1'}$ = 5.5 Hz, 1, H2'), 4.68 (m, 3, H3' and benzylic), 6.45 (d, 1, H1'), 6.86-7.60 (m, 25, 5 X Ph), 8.45 (s, 1, H8), 10.72 (s, 1, HN^2); ^{13}C NMR δ 168.47 (N<u>C</u>OCH$_3$), 155.01 (C6), 154.34 (C4), 152.01 (C2), 149.91 (COO^6), 144.23 (C8), 141.51, 137.94, 137.87, 136.79, 129.21, 128.11, 128.03, 127.95, 127.46, 127.40, 127.36, 127.29, 127.11, 126.76 (5 X Ph), 119.54 (C5), 82.64 (C1'), 81.59 (C2'), 80.81 (C3'), 80.12 (C4'), 72.16, 71.83, 71.35 (benzylic), 69.49 (C5'), 24.37 (Me); UV (MeOH) max 228 and 278 nm.

9-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)guanine (139)

To 791 mg (1 mmol) of (138) in 20 mL of MeOH was added 20 mL of NH_3/H_2O (28-30%). The reaction mixture was stirred in a sealed flask at 60°C for 1 day. Volatile materials were evaporated and the residue was purified on a silica column (25 g, 2 x 15 cm) using $CHCl_3$ and 3:97 $MeOH/CHCl_3$ as eluants. Evaporation of appropriate fractions gave 488 mg (88%) of (139) as a white foam: MS (FAB) m/z 554 (12%, M+1); ^1H NMR δ 3.67 ("d", $J_{5'-4'}$ = 5.0 Hz, 2, H5', 5"), 4.12 (m, $J_{4'-3'}$ = 5.0 Hz, 1, H4'), 4.27 (d, 1, benzylic), 4.30 (t, $J_{3'-2'}$ = 5.0 Hz, 1, H3'), 4.35 (t, $J_{2'-1'}$ = 5.0 Hz, 1, H2'), 4.43 (d, 1, benzylic), 4.52 (s, 2, benzylic), 4.63 (m, 2, benzylic), 6.17 (d, 1, H1'), 6.53 (s, 2, H_2N^2), 7.04, 7.24-7.40 (m, m, 15, 3 X Ph), 7.72 (s, 1, H8), 10.66 (s, 1, HN1); ^{13}C NMR δ 156.62 (C6), 153.78 (C2), 150.92 (C4), 138.03, 137.77, 137.10 (Ph's), 136.25 (C8), 128.22, 128.17, 127.61, 127.44, 127.42 (Ph's), 115.76 (C5), 81.91 (C1'), 81.21 (C2'), 80.87 (C3'), 79.89 (C4'), 72.22, 71.56, 71.16 (benzylic), 69.45 (C5'); UV (MeOH) max 254 nm. [Lit[89] UV (EtOH) max 254 nm].

9-(2,3,5-tri-O-benzyl-α-D-arabinofuranosyl)guanine (141)

Application of the procedure used for the preparation of (139) to 791 mg (1 mmol) of (140) gave 489 mg (88%) of (141) as a white foam: MS (FAB) m/z 554 (9.0%, M+1); ^1H NMR δ 3.60 ("d", $J_{5'-4'}$ = 5.0 Hz, 2, H5', 5"), 4.19 ("t", $J_{3'-4'}$ = 4.5 Hz, $J_{3'-2'}$ = 3.5 Hz, 1, H3'), 4.54

(s, 2, benzylic), 4.58 (m, 3, H4' and benzylic), 4.61 (s, 2, benzylic), 4.66 (t, $J_{2'-1'}$ = 3.5 Hz, 1, H2'), 6.00 (d, 1, H1'), 6.52 (s, 2, H_2N^2), 7.20-7.40 (m, 15, 3 X Ph), 7.86 (s, 1, H8), 10.68 (s, 1, HN1); ^{13}C NMR δ 156.46 (C6), 153.51 (C2), 150.57 (C4), 137.94, 137.46, 137.22 (Ph's), 135.08 (C8), 128.01, 127.48, 127.44, 127.38, 127.33, 127.24 (Ph's), 116.60 (C5), 86.64 (C1'), 85.48 (C2'), 82.30 (C4'), 82.27 (C3'), 72.23, 71.21, 71.14 (benzylic), 69.52 (C5'); UV (MeOH) max 255 nm.

9-β-D-arabinofuranosylguanine (70)

The saponification procedure used for the preparation of (139) was followed using 791 mg (1 mmol) of (138). Volatile materials were evaporated. The crude product was coevaporated twice with THF and then dissolved in 5 mL of THF. The solution was cooled to -60°C and NH_3 gas was admitted. After about 25 mL of NH_3 was condensed, small pieces of sodium metal were added at -40°C until a persistent blue color was retained. The blue solution was stirred at -40°C for an additional 15 min and the bath temperature was lowered to -60°C. Solid NH_4Cl was added in small portions until the blue color was discharged. The cooling bath was removed and NH_3 was vented with a stream of N_2. The residual mixture was evaporated to dryness in vacuo and then extracted twice with benzene. The solid product was dissolved in 10 mL of H_2O and the solution was acidified to pH 7 with AcOH. The precipitate (two crops) was collected and recrystallized from H_2O to give (three crops) 236 mg (81%) of (70) as a hemihydrate: mp 280°C (dec) [Lit[89] mp 290°C (dec)]; MS (FAB) m/z 284 (7.3%, M+1); ^1H NMR

δ 3.60 (m, $J_{5''-5'}$ = 11.5 Hz, $J_{5''-4'}$ = 5.0 Hz, $J_{5''-5'OH}$ = 5.5 Hz, $J_{5'-4'}$ = 4.5 Hz, $J_{5'-5'OH}$ = 5.5 Hz, 2, H5', 5"), 3.73 (m, $J_{4'-3'}$ = 4.0 Hz, 1, H4'), 4.02 (m, $J_{2'-3'}$ = 4.0 Hz, $J_{2'-2'OH}$ = 5.5 Hz, $J_{2'-1'}$ = 4.5 Hz, 1, H2'), 4.04 (m, $J_{3'-3'OH}$ = 4.0 Hz, 1, H3'), 5.04 (t, 1, HO5'), 5.48 (d, 1, HO3'), 5.59 (d, 1, HO2'), 6.00 (d, 1, H1'), 6.46 (s, 2, H_2N^2), 7.75 (s, 1, H8), 10.60 (s, 1, HN1); ^{13}C NMR δ 156.59 (C6), 153.47 (C2), 150.83 (C4), 136.65 (C8), 115.76 (C5), 84.22 (C4'), 83.31 (C1'), 75.44 (C2', C3'), 60.96 (C5'); Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C 41.10, H 4.83, N 23.96. Found: C 41.03, H 4.73, N 24.01; UV (H_2O) max 252 nm (ε 14,100).

9-α-D-arabinofuranosylguanine (137) from (140)

The deprotection procedure and work-up used for the preparation of (70) was applied to 791 mg (1 mmol) of (140). The residue was recrystallized from H_2O to give (two crops) 208 mg (71%) of (137) as a hemihydrate: mp 290°C (dec); MS (FAB) m/z 284 (18%, M+1); ^1H NMR δ 3.44 (m, $J_{5''-5'}$ = 12.0 Hz, $J_{5''-4'}$ = $J_{5''-5'OH}$ = 5.5 Hz, 1, H5"), 3.56 (m, $J_{5'-4'}$ = 3.5 Hz, $J_{5'-5'OH}$ = 5.5 Hz, 1, H5'), 3.94, (m, $J_{3'-4'}$ = $J_{3'-2'}$ = $J_{3'-3'OH}$ = 5.5 Hz, 1, H3'), 4.05 (m, 1, H4'), 4.45 (m, $J_{2'-1'}$ = 5.0 Hz, $J_{2'-2'OH}$ = 5.5 Hz, 1, H2'), 4.85 (t, 1, HO5'), 5.49 (d, 1, HO3'), 5.65 (d, 1, H1'), 5.71 (d, 1, HO2'), 6.44 (s, 2, H_2N^2), 7.90 (s, 1, H8), 10.62 (s, 1, HN1); ^{13}C NMR δ 156.56 (C6), 153.41 (C2), 151.01 (C4), 135.76 (C8), 116.60 (C5), 87.54 (C1'), 85.13 (C4'), 79.73 (C2'), 75.44 (C3'), 61.11 (C5'); Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C 41.10, H 4.83, N 23.96. Found: C 41.13, H 4.54, N 24.05; UV (H_2O) max 252 nm (ε 13,700).

2-Acetamido-6-diphenylcarbamoyloxy-9-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)purine (142) and 2-acetamido-6-diphenylcarbamoyloxy-9-(2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranosyl)purine (143).

The procedure and work-up used for the synthesis of (134) was applied to 388 mg (1 mmol) of (124) and 466 mg (1.2 mmol) of 2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranosyl chloride.[181] The residue was chromatographed on a silica column (30 g, 2 x 18 cm) using $CHCl_3$ and 1:99 $CH_3CN/CHCl_3$ as eluants. Evaporation of fractions 21-35 gave 231 mg (31%) of (142) as a white foam: MS (FAB) m/z 741 (2.4%, M+1); ^1H NMR δ 2.18 (s, 3, AcN^2), 2.34, 2.40 (2 X s, 2 X 3, 2 X Me), 2.78 (m, $J_{2''-2'}$ = 14.5 Hz, $J_{2''-1'}$ = 7.0 Hz, $J_{2''-3'}$ = 3.0 Hz, 1, H2"), 3.40 (m, $J_{2'-1'} = J_{2'-3'}$ = 7.0 Hz, 1, H2'), 4.59 (m, 2, H5', 5"), 4.68 (m, 1, H4'), 5.90 (m, 1, H3'), 6.54 (t, 1, H1'), 7.20-7.60 (m, 14, Aromatic), 7.80, 7.94 (2 X d, 2 X 2, Aromatic), 8.61 (s, 1, H8), 10.70 (s, 1, HN^2); ^{13}C NMR δ 168.43 ($NCOCH_3$), 165.33, 165.09 (2 X $OCOPhCH_3$), 155.18 (C6), 154.11 (C4), 152.03 (C2), 149.98 (COO^6), 144.38 (C8), 143.99, 143.61, 141.52, 129.37, 129.32, 129.25, 129.15, 127.20, 126.87, 126.80, 126.57, 126.49 (Aromatic), 120.54 (C5), 84.39 (C1'), 81.90 (C4'), 74.95 (C3'), 64.03 (C5'), 35.29 (C2'), 24.41 ($NCOCH_3$), 21.13, 21.06 (2 X Me); UV (MeOH) max 229, 238, and 277 nm.

Evaporation of fractions 38-55 gave 264 mg (36%) of (143) as a white foam: MS (FAB) m/z 741 (4.0%, M+1); ^1H NMR δ 2.18 (s, 3, AcN^2), 2.30, 2.40 (2 X s, 2 X 3, 2 X Me), 3.02 (m, $J_{2''-2'}$ = 14.0 Hz,

$J_{2"-1'}$ = 6.5 Hz, $J_{2"-3'}$ = 7.0 Hz, 1, H2"), 3.14 (m, $J_{2'-1'}$ = 2.0 Hz, 1, H2'), 4.55 (m, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = $J_{5'-4'}$ = 4.5 Hz, 2, H5', 5"), 5.08 (m, 1, H4'), 5.64 (m, 1, H3'), 6.59 (d of d, 1, H1'), 7.16 (d, 2, Aromatic), 7.30-7.60 (m, 14, Aromatic), 7.92 (d, 2, Aromatic), 8.62 (s, 1, H8), 10.66 (s, 1 HN^2); ^{13}C NMR δ 168.46 ($N\underline{C}OCH_3$), 165.28, 164.86 (2 X $O\underline{C}OPhCH_3$), 154.95 (C6), 153.82 (C4), 151.87 (C2), 149.91 (COO^6), 143.61, 143.53 (Aromatic), 143.16 (C8), 141.47, 129.10, 128.89, 126.97, 126.67, 126.47, 126.15 (Aromatic), 120.42 (C5), 85.73 (C1'), 83.14 (C4'), 74.39 (C3'), 63.72 (C5'), 36.75 (C2'), 24.25 ($NCO\underline{C}H_3$), 20.90 (2 X Me); UV (MeOH) max 229, 238 (Sh), and 278 nm.

2'-Deoxyguanosine (93) from (142)

The deprotection and work-up procedure outlined in the preparation of (96) from (135) was applied to 741 mg (1 mmol) of (142). The crude product was recrystallized from H_2O to give (two crops) 205 mg (74%) of (93): mp 240°C (dec) (Lit[178] mp 250°C); MS (FAB) m/z 268 (22%, M+1); ^1H NMR δ 2.20 (m, $J_{2"-2'}$ = 13.0 Hz, $J_{2"-3'}$ = 3.0 Hz, $J_{2"-1'}$ = 6.0 Hz, 1, H2"), 2.50 (m, $J_{2'-3'}$ = 5.5 Hz, $J_{2'-1'}$ = 7.5 Hz, 1, H2'), 3.52 (m, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = $J_{5'-4'}$ = 4.5 Hz, $J_{5"-5'OH}$ = $J_{5'-5'OH}$ = 5.5 Hz, 2, H5', 5"), 3.80 (m, $J_{4'-3'}$ = 2.5 Hz, 1, H4'), 4.34 (m, $J_{3'-3'OH}$ = 4.0 Hz, 1, H3'), 4.95 (t, 1, HO5'), 5.26 (d, 1, HO3'), 6.12 (d of d, 1, H1'), 6.46 (s, 2, H_2N^2), 7.92 (s, 1, H8), 10.64 (s, 1, HN1); ^{13}C NMR δ 156.92 (C6), 153.53 (C2), 150.93 (C4), 135.64 (C8), 116.84 (C5), 87.59 (C4'), 83.01 (C1'), 70.84 (C3'), 61.78 (C5'), 39.76 (C2'); Anal. Calcd. for $C_{10}H_{13}N_5O_4 \cdot 0.5H_2O$: C 43.48, H 5.11, N

25.35. Found: C 43.22, H 4.88, N 25.58; UV (H_2O) max 252 nm (ε 13,600).

9-(2-Deoxy-α-D-erythro-pentofuranosyl)guanine (144)

Application of the deprotection procedure outlined in the preparation of (96) from (135) to 741 mg (1 mmol) of (143) and recrystallization of the crude product from H_2O gave 233 mg (84%) of (144): mp 250°C (dec); MS (FAB) m/z 268 (6.7%, M+1); ^{1}H NMR δ 2.20 (m, $J_{2"-2'}$ = 14.0 Hz, $J_{2"-3'}$ = $J_{2"-1'}$ = 3.0 Hz, 1, H2"), 2.67 (m, $J_{2'-3'}$ = 7.0 Hz, $J_{2'-1'}$ = 8.0 Hz, 1, H2'), 3.44 (m, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = $J_{5'-4'}$ = 4.5 Hz, $J_{5"-5'OH}$ = $J_{5'-5'OH}$ = 5.5 Hz, 2, H5', 5"), 4.06 (m, $J_{4'-3'}$ = 2.5 Hz, 1, H4'), 4.27 (m, $J_{3'-3'OH}$ = 4.0 Hz, 1, H3'), 4.86 (t, 1, HO5'), 5.51 (d, 1, HO3'), 6.10 (d of d, 1, H1'), 6.45 (s, 2, H_2N^2), 7.97 (s, 1, H8), 10.63 (s, 1, HN1); ^{13}C NMR δ 156.79 (C6), 153.54 (C2), 150.79 (C4), 135.97 (C8), 116.50 (C5) 88.19 (C4'), 82.85 (C1'), 70.71 (C3'), 61.67 (C5'), 40.34 (C2'); Anal. Calcd. for $C_{10}H_{13}N_5O_4 \cdot 0.5H_2O$: C 43.48, H 5.11, N 25.35. Found: C 43.59, H 4.99, N 25.52; UV (H_2O) max 252 nm (ε 14,000). [Lit[91] UV (MeOH) max 253 nm (ε 12,000)].

2-Acetamido-6-diphenylcarbamoyloxy-9-[(2-acetoxyethoxy)methyl]purine (145) and 2-{N-[(2-acetoxyethoxy)methyl]acetamido}-6-diphenylcarbamoyloxy-9-[(2-acetoxyethoxy)methyl]purine (149)

The procedure and work-up used for the synthesis of (134) was

applied to the preparation of (145) using 388 mg (1 mmol) of (124) and 0.158 mL (1.2 mmol) of (2-acetoxyethoxy)methyl bromide[56] except no TMSTf catalyst was used and the coupling reaction was conducted at room temperature for 1.5 h. The residue was applied to a silica column (25 g, 2 x 15 cm). The column was eluted with Et_2O and then 3:7 Me_2CO/Et_2O. Evaporation of fractions 18-32 gave a white foam that was recrystallized from CH_3CN/Et_2O (diffusion) to afford 319 mg (63%) of (145) as white crystals: mp 136-138°C; MS m/z 504.1770 (0.7%, M^+ = 504.1757); (FAB) m/z 505 (25%, M+1); ^1H NMR δ 191 (s, 3, OAc), 2.22 (s, 3, NAc), 3.78 (m, 2, $AcOCH_2C\underline{H}_2O$), 4.08 (m, 2, $AcOC\underline{H}_2CH_2O$), 5.62 (s, 2, OCH_2N), 7.30-7.56 (m, 10, ph_2), 8.60 (s, 1, H8), 10.76 (s, 1, HN^2); ^{13}C NMR δ 169.83 ($O\underline{C}OCH_3$), 168.62 ($N\underline{C}OCH_3$), 155.04 (C6), 154.88 (C4), 152.33 (C2), 149.81 (COO^6), 145.36 (C8), 141.43, 129.08, 126.97, 126.64 (Ph_2), 119.54 (C5), 72.47 (NCH_2O), 67.20 ($AcOCH_2\underline{C}H_2O$) 62.44 ($AcO\underline{C}H_2CH_2O$), 24.27 ($NCO\underline{C}H_3$), 20.16 ($OCO\underline{C}H_3$); UV (MeOH) max 225, 278 nm (ε 37,800, 13,600).

Evaporation of fractions 14-16 gave 20 mg (3%) of (149), which was repurified on a silica plate (5 x 20 cm, developed twice with 3:7 Me_2CO/Et_2O) before NMR analysis. ^1H NMR δ 1.85, 1.86 (2 X s, 2 X 3, 2 X AcO), 2.28 (s, 3, AcN^2), 3.66, 3.74 (2 X m, 2 X 2, 2 X $AcOCH_2C\underline{H}_2O$), 4.03 (m, 4, 2 X $AcOC\underline{H}_2CH_2O$), 5.42, 5.68 (2 X s, 2 X 2, 2 X OCH_2N), 7.30-7.60 (m, 10, Ph_2), 8.73 (s, 1, H8).

9-[(2-Hydroxyethoxy)methyl]guanine (acycloguanosine, acyclovir) (146)

A 504 mg (1 mmol) sample of crystalline (145) was subjected to the deprotection and work-up procedure used for the preparation of (96) from (135). The crude product was recrystallized from H_2O to give

(two crops) 212 mg (91%) of (146) as a hemihydrate: mp 250-253°C (Lit[56] mp 265-266°C for an anhydrous sample); MS m/z 225.0865 (7.2%, M^+ = 225.0862); (FAB) m/z 226 (80%, M+1); ^{1}H NMR δ 3.46 (s, 4, OCH_2CH_2O), 4.67 (br s, 1, HO), 5.35 (s, 2, NCH_2O), 6.51 (s, 2, H_2N^2), 7.81 (s, 1, H8), 10.64 (s, 1, HN1); ^{13}C NMR δ 156.76 (C6), 153.78 (C2), 151.39 (C4), 137.71 (C8), 116.43 (C5), 72.01 (OCH_2N), 70.34 ($HOCH_2CH_2O$), 59.88 ($HOCH_2$); Anal. Calcd. for $C_8H_{11}N_5O_3 \cdot 0.5H_2O$: C 41.03, H 5.16, N 29.90. Found: C 41.21, H 4.99, N 29.92; UV (H_2O) max 251 nm (ε 13,200).

2-Acetamido-7-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)hypoxanthine (150)

A suspension of 193 mg (1 mmol) of N^2-acetylguanine (8) and 0.5 mL (2 mmol) of BSA in 10 mL of dry 1,2-dichloroethane was stirred in a stoppered flask at 80°C until a clear solution resulted (~2.5 h). The solution was cooled, 0.25 mL (557 mg, 2.1 mmol) of $SnCl_4$ was added, and the reaction mixture was stirred at room temperature for 30 min. A solution of 350 mg (1.1 mmol) of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose in 5 mL of 1,2-dichloroethane was added. Stirring was continued at room temperature for 1 day. MeOH (5 mL) was added and the reaction mixture was diluted with 50 mL of $CHCl_3$. The solution was washed successively with saturated $NaCl/H_2O$ (50 mL), saturated $NaHCO_3/H_2O$ (50 mL x 2), and saturated $NaCl/H_2O$ (50 mL). The organic layer was dried (Na_2SO_4), filtered, and the filtrate evaporated. The residue was chromatographed on a silica column (25 g, 2 x 15 cm) using Et_2O and 9:1 Et_2O/MeOH as eluants. Evaporation of appropriate fractions gave 317 mg (70%) of (150) as a white foam: MS m/z 451.1331

(6.2%, M^+ = 451.1339); ^1H NMR δ 2.04 (s, 6, AcO), 2.11 (s, 3, AcO), 2.17 (s, 3, AcN^2), 4.24 (d of d, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = 6.0 Hz, 1, H5"), 4.32 (m, $J_{4'-5'}$ = 4.0 Hz, $J_{4'-3'}$ = 5.0 Hz, 1, H4'), 4.42 (d of d, 1, H5'), 5.44 (d of d, $J_{3'-2'}$ = 6.0 Hz, 1, H3'), 5.80 (t, $J_{2'-1'}$ = 6.0 Hz, 1, H2'), 6.31 (d, 1, H1'), 8.52 (s, 1, H8), 11.66, 12.24 (2 X br s, 2, HN^2 and HN1); ^{13}C NMR δ 173.18 ($N\underline{C}OCH_3$), 169.77, 169.08, 168.88 (3 X $O\underline{C}OCH_3$), 158.26 (C4), 152.07 (C6), 147.35 (C2), 143.85 (C8), 110.49 (C5), 87.50 (C1'), 79.40 (C4'), 73.00 (C2'), 69.58 (C3'), 62.79 (C5'), 23.48 ($NCO\underline{C}H_3$), 20.24, 20.07, 19.88 (3 X $OCO\underline{C}H_3$); UV (MeOH) max 221 and 263 nm.

7-β-D-ribofuranosylguanine (113)

The deprotection and work-up conditions outlined in the synthesis of (7) were applied to 451 mg (1 mmol) of (150). The crude product was recrystallized from H_2O to give 228 mg (78%) of (113) as a hemihydrate: mp 275°C (dec) [Lit[182] mp 230-265° (dec)]; MS m/z 283.0910 (6.3%, M^+ = 283.0917); (FAB) m/z 284 (12%, M+1); ^1H NMR δ 3.53 (m, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = 4.0 Hz, $J_{5"-5'OH}$ = 6.0 Hz, 1, H5"), 3.66 (m, $J_{5'-4'}$ = 4.0 Hz, $J_{5'-5'OH}$ = 4.5 Hz, 1, H5'), 3.89 (m, $J_{4'-3'}$ = 4.0 Hz, 1, H4'), 4.07 (m, $J_{3'-2'}$ = 5.5 Hz, $J_{3'-3'OH}$ = 5.0 Hz, 1, H3'), 4.36 (m, $J_{2'-1'}$ = 5.5 Hz, $J_{2'-2'OH}$ = 6.0 Hz, 1, H2'), 5.01 (t, 1, HO5'), 5.10 (d, 1, HO3'), 5.36 (d, 1, HO2'), 5.98 (d, 1, H1'), 6.25 (s, 2, H_2N^2), 8.30 (s, 1, H8), 10.96 (br s, 1, HN1); ^{13}C NMR δ 160.63 (C4), 154.31 (C6), 152.87 (C2), 142.36 (C8), 107.67 (C5), 89.10 (C1'), 85.17 (C4'), 74.39 (C2'), 69.69 (C3'), 61.12 (C5'); Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C 41.10, H 4.83, N 23.96. Found: C 41.13, H 4.50, N 23.71; UV (H_2O) max 286 nm (ε 6,800).

2-Acetamido-7-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)hypoxanthine (152) and 2-acetamido-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)hypoxanthine (156)

The procedure and work-up outlined in the synthesis of (150) was applied to 193 mg (1 mmol) of (8) and 350 mg (1.1 mmol) of anomeric 1,2,3,5-tetra-O-acetyl-D-xylofuranose.[179] The residue was chromatographed on a silica column (25 g, 2 x 15 cm). The column was eluted with $CHCl_3$ and then 2:98 MeOH/$CHCl_3$. Evaporation of fractions 15-24 gave 341 mg (76%) of (152) as a white foam: MS m/z 451.1338 (8.7%, M^+ = 451.1339); ^1H NMR δ 2.05, 2.06, 2.10 (3 X s, 3 X 3, 3 X AcO), 2.18 (s, 3, AcN^2), 4.34 (m, $J_{5''-5'}$ = 12.0 Hz, $J_{5''-4'}$ = 7.0 Hz, $J_{5'-4'}$ = 4.5 Hz, 2, H5', 5''), 4.61 (m, $J_{4'-3'}$ = 4.5 Hz, 1, H4'), 5.48 (d of d, $J_{3'-2'}$ = 2.5 Hz, 1, H3'), 5.58 (t, $J_{2'-1'}$ = 3.0 Hz, 1, H2'), 6.36 (d, 1, H1'), 8.40 (s, 1, H8), 11.63, 12.20 (2 X br s, 2, HN^2 and HN1); ^{13}C NMR δ 173.01 ($N\underline{C}OCH_3$), 169.55, 168.74, 168.54 (3 X $O\underline{C}OCH_3$), 157.35 (C4), 152.10 (C6), 147.00 (C2), 142.02 (C8), 110.55 (C5), 88.16 (C1'), 79.35 (C2'), 77.96 (C4'), 73.89 (C3'), 60.96 (C5'), 23.37 ($NCO\underline{C}H_3$), 20.15, 20.01 (3 X $OCO\underline{C}H_3$); UV (MeOH) max 221 and 264 nm.

Evaporation of fractions 28-30 gave 13 mg (3%) of (156): ^1H NMR δ 2.02, 2.08, 2.10 (3 X s, 3 X 3, 3 X AcO), 2.18 (s, 3, AcN^2), 4.28 (m, $J_{5''-5'}$ = 11.5 Hz. $J_{5''-4'}$ = 7.0 Hz, $J_{5'-4'}$ = 4.5 Hz, 2, H5', 5''), 4.56 (m, $J_{4'-3'}$ = 4.5 Hz, 1, H4'), 5.52 (d of d, $J_{3'-2'}$ = 2.5 Hz, 1, H3'), 5.58 (t, $J_{2'-1'}$ = 3.0 Hz, 1, H2'), 5.97 (d, 1, H1'), 8.18 (s, 1, H8), 11.70, 12.10 (2 X br s, 2, HN^2 and HN1); ^{13}C NMR δ173.20 ($N\underline{C}OCH_3$), 169.60, 168.88, 168.84 (3 X $O\underline{C}OCH_3$), 154.50 (C6), 148.33

(C4), 147.97 (C2), 136.98 (C8), 119.81 (C5), 85.58 (C1'), 78.82 (C2'), 77.74 (C4'), 73.86 (C3'), 60.92 (C5'), 23.52 ($NCOC\underline{H}_3$), 20.19, 20.14 (3 X $OCOC\underline{H}_3$); UV (MeOH) max 258 and 280 nm.

7-β-D-xylofuranosylguanine (153)

The deprotection and work-up procedure used for the synthesis of (96) from (135) was applied to 451 mg (1 mmol) of (152). The crude product was recrystallized from H_2O to give (two crops) 251 mg (86%) of (153) as a hemihydrate: mp 285°C (dec) [Lit[42] mp > 220°C (dec)]; MS (FAB) m/z 284 (26%, M+1); ^1H NMR δ 3.67 (m, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = 6.5 Hz, $J_{5"-5'OH}$ = 5.5 Hz, 1, H5"), 3.74 (m, $J_{5'-4'}$ = 3.0 Hz, $J_{5'-5'OH}$ = 5.5 Hz, 1, H5'), 4.01 (m, $J_{3'-4'}$ = 3.5 Hz, $J_{3'-2'}$ = 1.5 Hz, $J_{3'-3'OH}$ = 4.5 Hz, 1, H3'), 4.15 (m, 1, H4'), 4.23 (m, $J_{2'-1'}$ = 1.0 Hz, $J_{2'-2'OH}$ = 4.0 Hz, 1, H2'), 4.73 (t, 1, HO5'), 5.45 (d, 1, HO3'), 5.80 (d, 1, HO2'), 6.08 (d, 1, H1'), 6.25 (s, 2, H_2N^2), 8.12 (s, 1, H8), 10.98 (s, 1, HN1); ^{13}C NMR δ 159.98 (C4), 154.36 (C6), 152.60 (C2), 141.75 (C8), 107.41 (C5), 91.11 (C1'), 83.44 (C4'), 81.39 (C2'), 75.11 (C3'), 59.31 (C5'); Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C 41.10, H 4.83, N 23.96. Found: C 41.01, H 4.58, N 23.78; UV (H_2O) max 285 (ε 7,300).

2-Acetamido-7-(2,3,5-tri-O-acetyl-α-D-arabinofuranosyl)-hypoxanthine (154)

The procedure and work-up outlined in the synthesis of (150) was

followed using 193 mg (1 mmol) of (8) and 350 mg (1.1 mmol) of anomeric 1,2,3,5-tetra-O-acetyl-D-arabinofuranose.[179] The residue was purified on a silica column (25 g, 2 x 15 cm). The column was eluted successively with Et_2O, 5:95, and then 10:90 MeOH/Et_2O. Evaporation of appropriate fractions gave 326 mg (72%) of (154) as a white foam: MS m/z 451.1328 (3.6%, M^+ = 451.1339); ^1H NMR δ 2.03, 2.04, 2.06 (3 X s, 3 X 3, 3 X AcO), 2.16 (s, 3, AcN^2), 4.18 (d of d, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = 6.0 Hz, 1, H5"), 4.28 (d of d, $J_{5'-4'}$ = 3.5 Hz, 1, H5'), 4.83 (m, $J_{4'-3'}$ = 6.0 Hz, 1, H4'), 5.37 (t, $J_{3'-2'}$ = 5.0 Hz, 1, H3'), 5.93 (t, $J_{2'-1'}$ = 5.0 Hz, 1, H2'), 6.36 (d, 1, H1'), 8.44 (s, 1, H8), 11.66, 12.23 (2 X br s, 2, HN^2 and HN1); ^{13}C NMR δ 173.47 ($NCOCH_3$), 170.13, 169.75, 169.39 (3 X $OCOHCH_3$) 158.42 (C4), 152.48 (C6), 147.48 (C2), 143.80 (C8), 110.45 (C5), 88.18 (C1'), 79.86 (C4'), 79.01 (C2'), 74.54 (C3'), 63.08 (C5'), 23.72 ($NCOCH_3$), 20.54, 20.51, 20.37 (3 X $OCOCH_3$); UV (MeOH) max 221 and 263 nm.

7-α-D-arabinofuranosylguanine (155)

The deprotection and work-up procedure outlined in the synthesis of (7) was applied to 451 mg (1 mmol) of (154). The crude product was recrystallized from H_2O to give 249 mg (85%) of (155) as a hemihydrate: mp 250°C (dec); MS (FAB) m/z 284 (12%, M+1); ^1H NMR δ 3.47 (m, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = $J_{5"-5'OH}$ = 5.5 Hz, 1, H5"), 3.58 (m, $J_{5'-4'}$ = 3.5 Hz, $J_{5'-5'OH}$ = 5.5 Hz, 1, H5'), 3.93 (m, $J_{3'-4'}$ = 6.5 Hz, $J_{3'-2'}$ = 5.5 Hz, $J_{3'-3'OH}$ = 5.0 Hz, 1, H3'), 4.19 (m, 1, H4'), 4.49 (m, $J_{2'-1'}$ = 5.0 Hz, $J_{2'-2'OH}$ = 5.5 Hz, 1, H2'), 4.84 (t, 1, HO5'),

5.45 (d, 1, HO3'), 5.68 (d, 1, HO2'), 5.91 (d, 1, H1'), 6.24 (s, 2, H_2N^2), 8.16 (s, 1, H8), 10.92 (s, 1, HN1); ^{13}C NMR δ 160.66 (C4), 154.28 (C6), 152.83 (C2), 142.44 (C8), 107.49 (C5), 90.33 (C1'), 84.82 (C4'), 80.26 (C2'), 75.03 (C3'), 61.13 (C5'); Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C 41.10, H 4.83, N 23.96. Found: C 41.35, H 4.83, N 24.18; UV (H_2O) max 286 nm (ε 7,500).

2-N-,2',3',5'-tri-O-acetylguanosine (48)

The acylation and work-up conditions specified in the synthesis of 2-N-,2',3',5'-tri-O-propionylguanosine by Hata et al.[152,153] were applied to 283 mg (1 mmol) of guanosine and 1.42 mL (1.54 g, 15 mmol) of acetic anhydride. The residue was purified on a silica column (25 g, 2 x 15 cm) using $CHCl_3$, and 3:97 MeOH/$CHCl_3$ as eluants. Evaporation of appropriate fractions gave 255 mg (57%) of (48) as a white foam: MS m/z 451.1348 (11%, M^+ = 451.1339); ^1H NMR δ 2.03, 2.05, 2.12 (3 X s, 3 X 3, 3 X AcO), 2.20 (s, 3, AcN^2), 4.26-4.44 (m, 3, H4', H5', 5"), 5.48 (d of d, $J_{3'-4'}$ = 4.0 Hz, $J_{3'-2'}$ = 6.0 Hz, 1, H3'), 5.81 (t, $J_{2'-1'}$ = 6.0 Hz, 1, H2'), 6.08 (d, 1, H1'), 8.25 (s, 1, H8), 11.70, 12.08 (2 X br s, 2, HN^2 and HN1); ^{13}C NMR δ 173.35 ($NCOCH_3$), 169.91, 169.25, 169.05 (3 X $OCOCH_3$), 154.61 (C6), 148.50 (C4), 148.11 (C2), 137.68 (C8), 120.33 (C5), 84.59 (C1'), 79.78 (C4'), 72.10 (C2'), 70.23 (C3'), 62.95 (C5'), 23.73 ($NCOCH_3$), 20.35, 20.21, 19.99 (3 X $OCOCH_3$); UV (MeOH) max 258 and 280 nm. [Lit[183] UV (95% EtOH) max 258, 282 nm. (ε 14,600, 12,500)]

2-Acetamido-6-diphenylcarbamoyloxy-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine (134) from (48)

The diphenylcarbamoylation conditions of Hata et al.[152,153] were applied to 177 mg (0.39 mmol) of (48). Excess reagent was destroyed by addition of 1 mL of H_2O. The reacton mixture was evaporated and the residue was dissolved in 40 mL of $CHCl_3$. The $CHCl_3$ solution was washed with $NaHCO_3/H_2O$ (40 mL x 2), $NaCl/H_2O$ (40 mL), and evaporated. The residue was purified on a silica column (20 g, 2 x 12 cm) using $CHCl_3$ and 1:99 $MeOH/CHCl_3$ as eluants. Evaporation of appropriate fractions gave 194 mg (77%) of (134) as a white foam. The ^1H and ^{13}C NMR and UV spectra of this material were identical with those of (134) prepared from (124) via a coupling reaction. The two samples comigrated in three different TLC systems.

2-Acetamido-6-diphenylcarbamoyloxy-7-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine (151)

The diphenylcarbamoylation procedure and work-up outlined in the synthesis of (134) from (48) was applied to 226 mg (0.5 mmol) of (150). The reaction was allowed to proceed at room temperature for 3 h. The residue was purified on a silica column (20 g, 2 x 12 cm) using $CHCl_3$ and 2:98 $MeOH/CHCl_3$ as eluants. Evaporation of appropriate fractions gave 264 mg (82%) of (151) as a white foam: MS (FAB) m/z 647 (25%, M+1); ^1H NMR δ 1.95, 2.00, 2.16 (3 X s, 3 X 3, 3 X AcO), 2.20 (s, 3,

AcN^2), 4.21 (d of d, $J_{5''-5'}$ = 12.0 Hz, $J_{5''-4'}$ = 6.0 Hz, 1, H5''), 4.32 (d of d, $J_{5'-4'}$ = 3.5 Hz, 1, H5'), 4.47 (m, $J_{4'-3'}$ = 4.5 Hz, 1, H4'), 5.44 ("t", $J_{3'-2'}$ = 6.5 Hz, 1, H3'), 5.68 (t, $J_{2'-1'}$ = 6.0 Hz, 1, H2'), 6.09 (d, 1, H1'), 7.30-7.65 (m, 10, Ph_2), 8.91 (s, 1, H8), 10.70 (s, 1, HN^2); ^{13}C NMR [184] δ 169.91, 169.29, 168.96, 168.72 (4 X $\underline{C}OCH_3$), 164.84 (C4), 152.33 (C6), 150.32 (COO^6), 149.19 (C2), 147.73 (C8), 141.23, 129.43, 127.55, 127.30, 127.24, 127.12 (Ph_2), 110.59 (C5), 87.21 (C1'), 80.00 (C4'), 72.86 (C2'), 69.87 (C3'), 62.95 (C5'), 24.39 (NCO$\underline{C}H_3$), 20.35, 19.96 (3 X OCO$\underline{C}H_3$); UV (MeOH) max 230 and 286 nm.

2,6-Diamino-9-[2-O-acetyl-3-bromo-3-deoxy-5-O-(2,5,5-trimethyldioxolan-4-on-2-yl)-β-D-xylofuranosyl]purine and 2,6-diamino-9-[3-O-acetyl-2-bromo-2-deoxy-5-O-(2,5,5-trimethyldioxolan-4-on-2-yl)-β-D-arabino-furanosyl]purine as a crude mixture (163)

To a suspension of 564 mg (2 mmol) of (158)[80] in 40 mL of dry CH_3CN were added 4 mL of CH_3CN/H_2O (99:1) and 1.2 mL (1.67 g, 8 mmol) of α-acetoxyisobutyryl bromide.[111,114] The reaction mixture was stirred at room temperature for 4 h. $NaHCO_3/H_2O$ (30 mL) was added and the solution was extracted with 200 mL of EtOAc. The organic layer was washed with 30 mL of saturated $NaCl/H_2O$, dried (Na_2SO_4), filtered, and evaporated to give (163) as a white foam. This crude product was used directly in further transformation reactions.

2,6-Diamino-9-(2,3-anhydro-β-D-ribofuranosyl)purine (164)

The crude foam (163) prepared from 2 mmol of (158) was dissolved in a minimal volume of MeOH and the solution was applied to a Dowex 1 X 2 (OH^-) column (3 x 20 cm, previously washed with MeOH). The column was allowed to stand for 1 h at ambient temperature and the title compound was eluted with MeOH. Crystallization occurred in the early fraction-collecting tubes. Crystals were collected by filtration and the filtrate and appropriate fractions were concentrated and chilled to give an additional crop of product. The total yield of (164) was 427 mg [81% from (158)]: mp 180°C (dec); MS m/z 264.0968 (23%, M^+ = 264.0971); ^1H NMR δ 3.55 (m, $J_{5"-5'}$ = 11.5 Hz, $J_{5"-4'}$ = $J_{5"-5'OH}$ = $J_{5'-5'OH}$ = 5.0 Hz, $J_{5'-4'}$ = 5.5 Hz, 2, H5', 5"), 4.15 ("t", 1, H4'), 4.17 (d, $J_{3'-2'}$ = 2.5 Hz, 1, H3'), 4.37 (d, 1, H2'), 5.09 (t, 1, HO5'), 5.85 (s, 2, H_2N^2), 6.01 (s, 1, H1'), 6.77 (s, 2, H_2N^6), 7.92 (s, 1, H8); ^{13}C NMR δ 160.33 (C6), 156.17 (C2), 151.48 (C4), 135.63 (C8), 112.98 (C5), 81.49 (C1'), 80.89 (C4'), 61.04 (C5'), 58.67 (C3'), 57.76 (C2'); Anal. Calcd. for $C_{10}H_{12}N_6O_3$: C 45.45, H 4.58, N 31.80. Found: C 45.35, H 4.75, N 31.48; UV (MeOH) max 255, 280 nm (ε 9,900, 10,300).

2,6-Diamino-9-(3-deoxy-β-D-erythro-pentofuranosyl)purine (165) from (164)

To a stirred solution of 528 mg (2 mmol) of (164) in 40 mL of DMSO was added 25 mL of 1 M $LiEt_3BH$/THF at 10°C under N_2

protection. After 1 h the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 3 days. H_2O (60mL) was added carefully and a strong N_2 stream was passed through the solution to remove the pyrophoric triethylboron. Solvents were evaporated at 50-60°C in vacuo (~ 0.5 mm Hg) and the yellowish residue was chromatographed on a Dowex 1 X 2 (OH^-) column (3 x 24 cm) using H_2O and 3:7 MeOH/H_2O as eluants. Evaporation of appropriate fractions and recrystallization of the residue from MeOH gave 453 mg (85%) of (165): mp 198-199°C, mp 122-123°C (from H_2O) [Lit[185] mp 120-121°C (from H_2O)]; MS m/z 266.1124 (16%, M^+ = 266.1127); ^1H NMR δ 1.92 (m, $J_{3"-3'}$ = 13.0 Hz, $J_{3"-4'}$ = 6.5 Hz, $J_{3"-2'}$ = 3.5 Hz, 1, H3"), 2.24 (m, $J_{3'-4'}$ = 8.0 Hz, $J_{3'-2'}$ = 6.0 Hz, 1, H3'), 3.50 (m, $J_{5"-5'}$ = 11.5 Hz, $J_{5"-4'}$ = 4.0 Hz, $J_{5"-5'OH}$ = 5.5 Hz, 1, H5"), 3.65 (m, $J_{5'-4'}$ = 3.5 Hz, $J_{5'-5'OH}$ = 5.5 Hz, 1, H5'), 4.30 (m, 1, H4'), 4.51 (m, $J_{2'-1'}$ = 2.5 Hz, $J_{2'-2'OH}$ = 4.5 Hz, 1, H2'), 5.18 (t, 1, HO5'), 5.56 (d, 1, HO2'), 5.70 (d, 1, H1'), 5.78 (s, 2, H_2N^2), 6.75 (s, 2, H_2N^6), 7.92 (s, 1, H8); ^{13}C NMR δ 160.11 (C6), 156.17 (C2), 151.23 (C4), 135.76 (C8), 113.38 (C5), 90.18 (C1'), 80.19 (C4'), 74.38 (C2'), 62.93 (C5'), 34.51 (C3'); Anal. Calcd. for $C_{10}H_{14}N_6O_3$: C 45.11, H 5.30, N 31.56. Found: C 44.90, H 5.31, N 31.52; UV (MeOH) max 255, 280 nm (ε 10,200, 10,700).

2,6-Diamino-9-(3-deoxy-β-D-erythro-pentofuranosyl)purine (165) and 2,6-Diamino-9-(2-deoxy-β-D-erythro-pentofuranosyl)purine (166) from (163)

The crude foam (163) prepared from 2 mmol of (158) was dissolved

in 80 mL of oxygen-free toluene. After addition of 64 mg (0.4 mmol) of AIBN and 2.2 mL (2.38 g, 8.2 mmol) of n-Bu_3SnH, the reaction mixture was refluxed for 1 h. Toluene was removed by evaporation and the residue was dissolved in 100 mL of 1:1 CH_3CN/H_2O. The solution was washed with 100 mL of n-pentane and then evaporated. The residue was treated with 50 mL of NH_3/MeOH (saturated at -10°C) at ambient temperature for 4 h. Volatile materials were evaporated and the residue was chromatographed on a Dowex 1 X 2 (OH^-) colum (3 x 30 cm). Elution with H_2O, evaporation of appropriate fractions, and recrystallization from MeOH gave 85 mg [16% from (158)] of (166): mp 154-155°C (Lit[186] mp 147-149°C); MS m/z 266.1128 (12%, M^+ = 266.1127); ^1H NMR δ 2.20 (m, $J_{2"-2'}$ = 13.0 Hz, $J_{2"-3'}$ = 3.0 Hz, $J_{2"-1'}$ = 6.0 Hz, 1, H2"), 2.62 (m, $J_{2'-3'}$ = 5.5 Hz, $J_{2"-1'}$ = 8.0 Hz, 1, H2'), 3.54 (m, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = 4.0 Hz, $J_{5"-5'OH}$ = 6.0 Hz, 1, H5"), 3.60 (m, $J_{5'-4'}$ = $J_{5'-5'OH}$ = 5.0 Hz, 1, H5'), 3.86 (m, $J_{4'-3'}$ = 2.0 Hz, 1, H4'), 4.37 (m, $J_{3'-3'OH}$ = 4.0 Hz, 1, H3'), 5.26 (d, 1, HO3'), 5.29 (d of d, 1, HO5'), 5.76 (s, 2, H_2N^2), 6.19 (d of d, 1, H1'), 6.76 (s, 2, H_2N^6), 7.92 (s, 1, H8); ^{13}C NMR δ 159.98 (C6), 156.14 (C2), 151.17 (C4), 135.75 (C8), 113.48 (C5), 87.63 (C4'), 83.10 (C1'), 70.98 (C3'), 61.95 (C5'), 39.37 (C2'); Anal. Calcd. for $C_{10}H_{14}N_6O_3$: C 45.11, H 5.30, N 31.56. Found: C 45.01, H 5.41, N 31.31; UV (MeOH) max 256, 280 nm (ε 10,100, 10,600).

Further elution with 3:7 MeOH/H_2O, evaporation of appropriate fractions, and recrystallization from MeOH gave 316 mg [59% from (158)] of (165): mp 198-199°C; MS m/z 266.1129 (11%, M^+ = 266.1127). This product was identical with that prepared by reduction of (164).

2,6-Diamino-9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)purine (167)

The crude foam (163) obtained from a 2 mmol reaction of (158) was dissolved in 40 mL of DMF and treated with freshly prepared Zn/Cu couple [187] at room temperature for 30 min. Solid materials were removed by filtration. The filtrate was evaporated and the oily residue was partitioned between 100 mL of saturated $NaHCO_3/H_2O$ and 100 mL of EtOAc. The organic layer was washed with 100 mL of saturated $NaCl/H_2O$, evaporated, and applied to a Dowex 1 X 2 (OH^-) column (3 x 30 cm, previously washed with MeOH). Elution with MeOH, evaporation of appropriate fractions, and recrystallization from $MeOH/Et_2O$ (diffusion) gave 396 mg [79% from (158)] of (167): mp 157-160°C; MS m/z 248.1020 (3.9%, M^+ = 248.1022); ^1H NMR δ 3.57 (d, $J_{5'-4'}$ = 4.0 Hz, 2, H5', 5"), 4.85 (m, $J_{4'-3'}$ = 1.5 Hz, $J_{4'-2'}$ = 2.0 Hz, $J_{4'-1'}$ = 3.0 Hz, 1, H4'), 5.10 (br s, 1, HO5'), 5.82 (s, 2, H_2N^2), 6.10 (m, $J_{2'-3'}$ = 6.0 Hz, $J_{2'-1'}$ = 1.5 Hz, 1, H2'), 6.44 (m, $J_{3'-1'}$ = 1.5 Hz, 1, H3'), 6.76 ("s", 2, H_2N^6), 6.77 (m, 1, H1'), 7.76 (s, 1, H8); ^{13}C NMR δ 160.38 (C6), 156.18 (C2), 151.53 (C4), 136.15 (C8), 134.36 (C3'), 125.84 (C2'), 113.19 (C5), 87.89 (C1'), 87.71 (C4'), 63.14 (C5'); Anal. Calcd. for $C_{10}H_{12}N_6O_2 \cdot 0.2H_2O$: C 47.69, H 4.96, N 33.37. Found (The sample was repurified by recrystallization from MeOH): C 47.59, H 5.06, N 33.38; UV (MeOH) Max 255, 280 nm (ε 9,900, 10,300).

2,6-Diamino-9-[3,5-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-β-D-ribofuranosyl]purine[188] (168)

A stirred suspension of 2.82 g (10 mmol) of (158) in 50 mL of dry pyridine was treated with 4 mL (3.88 g, 12.3 mmol) of TPDSCl at ambient temperature for 6 h. After addition of 5 mL of EtOH, the reaction mixture was evaporated. The residue was coevaporated several times with toluene and then partitioned between 300 mL of $CHCl_3$ and 300 mL of H_2O. The organic layer was concentrated and applied to a silica column (225 g, 6 x 15 cm). Elution with 1:9 MeOH/$CHCl_3$ and evaporation of appropriate fractions gave 5.12 g (97%) of (168) as a foam: MS m/z 524.2602 (8.2%, M^+ = 524.2599); ^1H NMR δ 1.94-2.14 (m, 28, i-Pr), 3.90-4.14 (m, 3, H4', H5', 5"), 4.31 (m, $J_{2'-3'} = J_{2'-2'OH}$ = 5.0 Hz, $J_{2'-1'}$ = 1.5 Hz, 1, H2'), 4.45 (d of d, $J_{3'-4'}$ = 8.0 Hz, 1, H3'), 5.61 (d, 1, HO2') 5.72 (d, 1, H1'), 5.79 (s, 2, H_2N^2), 6.79 (s, 2, H_2N^6), 7.78 (s, 1, H8); UV (MeOH) max 257 and 281 nm.

2,6-Diamino-9-(2-deoxy-β-D-erythro-pentofuranosyl)purine (166) from (168)

The foam (168) obtained from a 2 mmol reaction of (158) was suspended in 20 mL of dry CH_3CN and treated with 489 mg (4 mmol) of DMAP and 0.4 mL (380 mg, 2.2 mmol) of phenoxythiocarbonyl chloride[189] at ambient temperature for 1 h. The resulting solution was diluted with 100 mL of EtOAc, washed with 100 mL of 2% AcOH/H_2O,

100 mL of saturated $NaHCO_3/H_2O$, 100 mL of saturated $NaCl/H_2O$, dried (Na_2SO_4), and evaporated. The residue was coevaporated successively with toluene, $CHCl_3$, and Et_2O. The resulting foam was dired in vacuo at room temperature for 2 h and then dissolved in 20 mL of toluene. After addition of 66 mg (0.4 mmol) of AIBN and 0.85 mL (920 mg, 3.2 mmol) of n-Bu_3SnH, the reaction mixture was purged with oxygen-free nitrogen and heated at 80°C overnight. Addition of 4 mL of 1 M n-Bu_4NF/THF was followed by stirring at 80°C for 3 h. Volatile materials were evaporated and the residue was partitioned between 100 mL of H_2O and 100 mL of Et_2O. The aqueous phase was concentrated and applied to a Dowex 1 X 2 (OH^-) column (3 x 30 cm). Elution with H_2O, evaporation of appropriate fractions, and recrystallization from MeOH gave 216 mg [41% from (158)] of (166): mp 154-155°C; MS M/z 266.1124 (15%, M^+ = 266.1127). This material was identical with the minor product (166) prepared by debromination of (163).

2,6-Diamino-9-(2-azido-2-deoxy-β-D-arabinofuranosyl)purine (169)

To a suspension of 525 mg (1 mmol) of (168) in 10 mL of dry CH_2Cl_2 were added 367 mg (3 mmol) of DMAP and 0.15 mL (237 mg, 1.4 mmol) of CF_3SO_2Cl. The reaction mixture was stirred at 0°C for 30 min, 50 mL of $CHCl_3$ was added, and the solution was washed with 2% $HOAc/H_2O$ (2 x 30 mL), saturated $NaCl/H_2O$ (2 x 30 mL) and dried (Na_2SO_4). Filtration, evaporation of the filtrate, and successive coevaporation with toluene, $CHCl_3$, and Et_2O gave a foam. This was dried in vacuo at ambient temperature for 4 h and then treated with 196

mg (4 mmol) of dry LiN_3 in 10 mL of dry DMF at ambient temperature overnight. The residue obtained after evaporation was dissolved in 50 mL of EtOAc. The solution was washed with saturated $NaCl/H_2O$ (3 x 50 mL) and evaporated. The resulting foam in 10 mL of THF was treated with 3 mL of 1 M n-Bu_4NF/THF at ambient temperature overnight. THF was evaporated and the residue was chromatographed on a column of Dowex 1 X 2 (OH^-) resin (3 x 10 cm) using H_2O and 8: 2 MeOH/H_2O as eluants. Evaporation of appropriate fractions gave 181 mg (59%) of (169) as a crystalline solid: mp 262°C (dec); MS m/z 307.1141 (13%, M^+ = 307.1141); ^1H NMR δ 3.64 (m, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = 4.5 Hz, $J_{5"-5'OH}$ = 5.5 Hz, 1, H5"), 3.72 (m, $J_{5'-4'}$ = 3.0 Hz, $J_{5'-5'OH}$ = 5.5 Hz, 1, H5'), 3.76 (m, $J_{4'-3'}$ = 7.5 Hz, 1, H4'), 4.35 (m, $J_{3'-2'}$ = 7.5 Hz, $J_{3'-3'OH}$ = 5.5 Hz, 1, H3'), 4.49 (d of d, $J_{2'-1'}$ = 6.5 Hz, 1, H2'), 5.20 (t, 1, HO5'), 5.83 (s, 2, H_2N^2), 5.99 (d, 1, HO3'), 6.19 (d, 1, H1'), 6.78 (s, 2, H_2N^6), 7.90 (s, 1, H8); ^{13}C NMR δ 160.37 (C6), 156.09 (C2), 151.60 (C4), 136.20 (C8), 112.78 (C5), 83.11 (C4'), 81.43 (C1'), 71.91 (C3'), 67.54 (C2'), 59.85 (C5'); Anal. Calcd. for $C_{10}H_{13}N_9O_3$: C 39.09, H 4.26, N 41.03. Found: C 38.85, H 4.35, N 40.63; UV (MeOH) max 255, 280 nm (ε 10,300, 10,800).

2,6-Diamino-9-(2-amino-2-deoxy-β-D-arabinofuranosyl)purine (170)

A suspension of 307 mg (1 mmol) of (169) in 15 mL of 98% EtOH and 5 mL of H_2O was treated with 100 mg of Raney nickel and 1 mL of 95% NH_2NH_2 at room temperature for 6 h. The reaction mixture was filtered and the solid was washed with 8:2 EtOH/H_2O. The filtrate and

washings were combined, concentrated, and applied to a Dowex 1 X 2 (OH^-) column (3 x 10 cm). Elution with H_2O and evaporation of appropriate fractions gave 238 mg (85%) of crystalline (170): mp 289-292°C; MS m/z 281.1232 (10%, M^+ = 281.1236); ^1H NMR δ 1.20-1.80 (br s, 2, H_2N2'), 3.40 (t, $J_{2'-3'} = J_{2'-1'}$ = 6.5 Hz, 1, H2'), 3.58 (d of d, $J_{5''-5'}$ = 12.5 Hz, $J_{5''-4'}$ = 4.5 Hz, 1, H5"), 3.68 (m, $J_{5'-4'}$ = 2.5 Hz, 1, H5'), 3.70 (m, $J_{4'-3'}$ = 6.5 Hz, 1, H4'), 4.01 (m, $J_{3'-3'OH}$ = 4.5 Hz, 1, H3'), 4.60-5.60 (br, 1, HO5'), 5.39 (d, 1, HO3'), 5.76 (s, 2, H_2N^2), 6.02 (d, 1, H1'), 6.68 (s, 2, H_2N^6), 7.88 (s, 1, H8); ^{13}C NMR δ 160.17 (C6), 156.02 (C2), 151.63 (C4), 137.10 (C8), 112.92 (C5), 84.29 (C4'), 84.03 (C1'), 75.41 (C3'), 60.70 (C5'), 60.31 (C2'); Anal. Calcd. for $C_{10}H_{15}N_7O_3$: C 42.70, H 5.38, N 34.86. Found: C 42.56, H 5.38, N 34.87; UV (H_2O) max 255, 280 nm (ε 9,800, 10,300).

3'-Deoxyguanosine (81)

To 266 mg (1 mmol) of (165) dissolved in 5 mL of DMSO and 25 mL of 0.1 M sodium phosphate buffer solution (pH 7.4) was added 10 mg of ADA (2.7 units/mg protein). The reaction mixture was stirred at room temperature overnight. Solvents were evaporated in vacuo and the residue was applied to a Dowex 1 X 2 (OH^-) column (2 x 10 cm). The column was washed successively with H_2O, 8+2 MeOH/H_2O, and H_2O. The product was eluted with 0.03 M [Et_3NH^+][HCO_3^-] solution. Evaporation of appropriate functions gave a white solid, which was coevaporated with H_2O several times and then recrystallized from H_2O to afford 239 mg (87%) of (81) as a hemihydrate: mp 250°C

(dec)[Lit[84] mp 240°C (dec), Lit[86] mp 250°C (dec)]; MS (FAB) m/z 268 (5.6%, M+1); ^{1}H NMR δ 1.89 (m, $J_{3"-3'}$ = 13.5 Hz, $J_{3"-4'}$ = 6.5 Hz, $J_{3"-2'}$ = 3.0 Hz, 1, H3"), 2.20 (m, $J_{3'-4'}$ = 9.0 Hz, $J_{3'-2'}$ = 5.5 Hz, 1, H3'), 3.51 (d of d, $J_{5"-5'}$ = 12.0 Hz, $J_{5"-4'}$ = 4.5 Hz, 1, H5"), 3.64 (d of d, $J_{5'-4'}$ = 3.5 Hz, 1, H5'), 4.31 (m, 1, H4'), 4.46 (m, $J_{2'-1'}$ = 2.0 Hz, 1, H2'), 4.60-5.90 (br, 2, HO5' and HO2'), 5.70 (d, 1, H1'), 6.49 (s, 2, H_2N^2), 7.94 (s, 1, H8), 10.65 (s, 1, HN1); ^{13}C NMR δ 156.58 (C6), 153.43 (C2), 150.63 (C4), 135.04 (C8), 116.60 (C5), 89.85 (C1'), 80.27 (C4'), 74.68 (C2'), 62.56 (C5'), 34.40 (C3'); Anal. Calcd. for $C_{10}H_{13}N_5O_4 \cdot 0.5H_2O$: C 43.48, H 5.11, N 25.35. Found: C 43.38, H 4.89, N 25.39; UV (H_2O) max 252 nm (ε 13,600).

2'-Deoxyguanosine (93)

The enzymatic deamination procedure outlined in the preparation of (81) was followed using 266 mg (1 mmol) of (166) and 20 mg of ADA (1 unit/mg protein). Chromatographic purification of the product on a Dowex 1 X 2 (OH^-) column (2 x 10 cm) and recrystallization from H_2O gave 250 mg (91%) of (93): mp 250°C (dec) (Lit[178] mp 250°C); MS (FAB) m/z 268 (6.5%, M+1); ^{1}H and ^{13}C NMR Spectra were identical with those of (93) prepared from (142) by deprotection. Anal. Calcd. for $C_{10}H_{13}N_5O_4 \cdot 0.5H_2O$: C 43.48, H 5.11, N 25.35. Found: C 43.42, H 4.90, N 25.62; UV (H_2O) max 252 nm (ε 13,400).

9-(2,3-Dideoxy-β-D-glycero-pent-2-enofuranosyl)guanine (171)

The deamination procedure used for the preparation of (81) was applied to 248 mg (1 mmol) of (167) and 20 mg of ADA (1 unit/mg protein). The reaction mixture was stirred at room temperature for 10 days with additions of 20 mg of fresh ADA every other day. After chromtographic purification on Dowex 1 X 2 (OH^-) resin, the product was recrystallized from H_2O (gentle heating) to give 130 mg (50%) of (171): mp 200°C (dec); MS (FAB) m/z 250 (16%, M+1); ^1H NMR δ 3.54 (d, $J_{5'-4'}$ = 4.0 Hz, 2, H5', 5"), 4.83 (m, $J_{4'-3'}$ = 2.0 Hz, $J_{4'-2'}$ = 1.5 Hz, $J_{4'-1'}$ = 3.0 Hz, 1, H4'), 4.93 (br, 1, HO5'), 6.09 (m, $J_{2'-3'}$ = 6.0 Hz, $J_{2'-1'}$ = 1.5 Hz, 1, H2'), 6.44 (m, $J_{3'-1'}$ = 1.5 Hz, 1, H3'), 6.50 (s, 2, H_2N^2), 6.70 (m, 1, H1'), 7.72 (s, 1, H8), 10.67 (br s, 1, HN1), ^{13}C NMR δ 156.70 (C6), 153.69 (C2), 150.81 (C4), 135.22 (C8), 134.22 (C3'), 125.34 (C2'), 116.43 (C5), 87.77 (C1'), 87.23 (C4'), 62.87 (C5'); Anal. Calcd. for $C_{10}H_{11}N_5O_3 \cdot 0.5H_2O$: C 46.51, H 4.68, N 27.12. Found: (The sample was repurified by recrystallization from H_2O): C 46.20, H 4.58, N 27.07; UV (H_2O) max 252 nm (ε 13,800) [Lit[114] UV (H_2O) max 253 nm (ε 14,000)].

9-(2-Amino-2-deoxy-β-D-arabinofuranosyl)guanine (104)

The deamination procedure outlined in the preparation of (81) was applied to 141 mg (0.5 mmol) of (170), 10 mL of 0.1 M sodium phosphate buffer solution (pH 6.5), and 8 mg of ADA (1 unit/mg protein). The reaction mixture was stirred at ambient temperature for

15 days with additions of 8 mg of fresh ADA every other day. After chromtographic purification on a Dowex 1 X 2 (OH^-) column (2 x 10 cm), the desired product (104) was obtained in both a free 2'-amino form and as a salt. This salt was converted into the free 2'-amino form by repeated Dowex 1 X 2 (OH^-)chromatography. Recrystallization of the free 2'-amino product from H_2O gave 131 mg (90%) of (104): mp 230°C (dec) [Lit[125] mp 193-196°C (dec)]; MS (FAB) m/z 283 (57%, M+1); ^1H NMR δ 0.50-5.00 (br, 3, H_2N2' and HO5'), 3.43 (t, $J_{2'-3'}$ = $J_{2'-1'}$ = 6.0 Hz, 1, H2'), 3.60 (d of d, $J_{5''-5'}$ = 12.5 Hz, $J_{5''-4'}$ = 4.5 Hz, 1, H5'), 3.68 (m, 2, H4' and H5'), 3.99 (m, 1, H3'), 5.41 (br s, 1, HO3'), 5.98 (d, 1, H1'), 6.46 (s, 2, H_2N^2), 7.87 (s, 1, H8), 10.56 (s, 1, HN1); ^{13}C NMR δ 156.91 (C6), 153.50 (C2), 151.09 (C4), 136.70 (C8), 116.31 (C5), 84.22 (C4'), 84.17 (C1'), 75.21 (C3'), 60.54 (C5'), 60.17 (C2'); Anal. Calcd. for $C_{10}H_{14}N_6O_4 \cdot 0.5H_2O$: C 41.24, H 5.19, N 28.85. Found: (The sample was repurified by recrystallization from H_2O): C 41.38, H 4.93, N 28.68; UV (H_2O) max 252 nm (ε 13,000).

9-β-D-xylofuranosylguanine (96) from (172)

The deamination conditions outlined in the preparation of (81) were followed using 282 mg (1 mmol) of (172)[190] and 20 mg of ADA (1 unit/mg protein). The reaction mixture was stirred at room temperature for 3 days with additions of 20 mg of ADA every day. Purification of the product on Dowex 1 X 2 (OH^-) resin and recrystallization from H_2O gave 242 mg (83%) of (96): mp 250°C (dec);

MS (FAB) m/z 284 (28%, M+1); ^{1}H and ^{13}C NMR spectra were identical with those of the product (96) obtained from deprotection of (135). Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C 41.10, H 4.83, N 23.96. Found: C 41.01, H 4.63, N 23.63; UV (H_2O) max 252 nm (ε 13,300).

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