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This project is concerned with the biochemically-based rational design, synthesis, purification, complete spectral characterization, and antiviral evaluation of some unique adenine and hypoxanthine deoxynucleosides. A total of seven compounds were produced through complex multi-step syntheses and submitted for antiviral evaluation. The work at present is right on schedule and in complete accordance with the contract agreement. Based on previous results from our laboratory, information on the exotic RNA viruses and their key enzymes, rational design, and the current status of antiviral research in this and related areas, this project has a very high probability of producing antivirally active compounds of relevance and importance to the drug development program of the USAMRDC.

Ribonucleic acid

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Basic

FOREWORD

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Vasu Nair 2-28-90
PI - Signature DATE

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TABLE OF CONTENTS

INTRODUCTION

Alpha-, arena-, bunya-, and flavi- viruses are RNA viruses that cause serious fevers including the often fatal hemorrhagic fevers and some of these viruses also cause a variety of encephalitis (1-10). Rodents, mosquitoes, and ticks are the primary transporters of these viruses. The latter exist in one strain or another worldwide and this poses a particularly severe problem for the soldier in the field who may be constantly exposed to these viruses in the non-idealistic environments that military personnel are exposed to in times of conflict. The synthesis of broad spectrum antiviral agents to control these viruses would be of considerable benefit and significance to the military. Although the use of nucleoside analogues as antiviral agents has made significant advances in recent years, broad spectrum antiviral activity, particularly against RNA viruses, has not been generally observed.

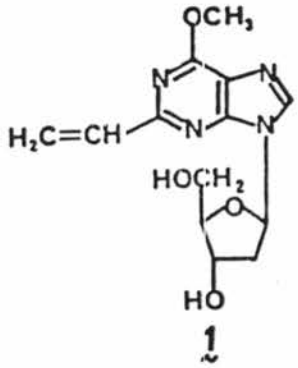
The major goal of this project is the biochemically-based rational design and synthesis of unique purine nucleosides that would have high therapeutic potential for broad spectrum antiviral activity, particularly against exotic RNA viruses that are etiologic agents for serious encephalitic and hemorrhagic diseases. The biological rationale for the choice of the target molecules includes considerations of *in vivo* phosphorylation by nucleoside and deoxynucleoside kinases, selective incorporation into viral RNAs and inhibition of viral RNA polymerases, inhibition of viral-specific mRNA capping enzymes, host cell toxicity, cellular stability (e.g. hydrolysis, breakdown by purine nucleoside phosphorylase and adenosine deaminase), and transport through the blood brain barrier. Important leads in the design of the proposed nucleosides were also derived from useful structure-activity correlations of active compounds from our previous USAMRIID project.

BODY:

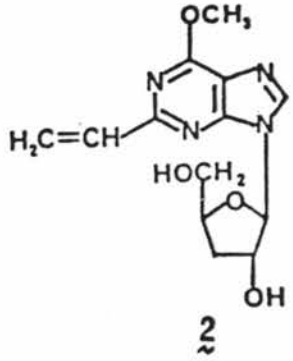
In the first seven and a half months of work on this contract, our goals were to develop rational procedures for the multi-step synthesis of the target molecules discussed in the proposal and to synthesize the first series of compounds for antiviral evaluation against the aforementioned exotic RNA viruses. This goal was successfully completed and the work done up to the present date is right on schedule. A total of seven new and rare nucleosides were synthesized, purified, characterized and submitted for antiviral evaluation. It should be emphasized that the synthetic work in this project was very complex and a considerable amount of extraordinary effort had to be expanded to achieve the aforementioned goals.

Synthesis of Novel Congeners of Deoxygenated Hypoxanthine Nucleosides

The starting point of our work during this period involved the preparation of multigram quantities of some basic precursors and investigation of feasible approaches to the synthesis of two compounds, 6-methoxy-2-vinyl-9-(2-deoxy-β-D-ribofuranosyl)purine (**1**) and 6-methoxy-2-vinyl-9-(3-deoxy-β-D-ribofuranosyl)purine (**2**). Choice of the methoxy group at the 6-position was based on the expectation that these compounds, if hydrolyzed in cellular systems, would behave as pro-drugs of the corresponding hypoxanthine nucleosides. Introduction of the vinyl functionality at the 2-position was based in part on the observation of broad spectrum RNA antiviral activity of 2-vinylinosine, a compound synthesized and submitted by us under the previous USAMRIID contract (11).



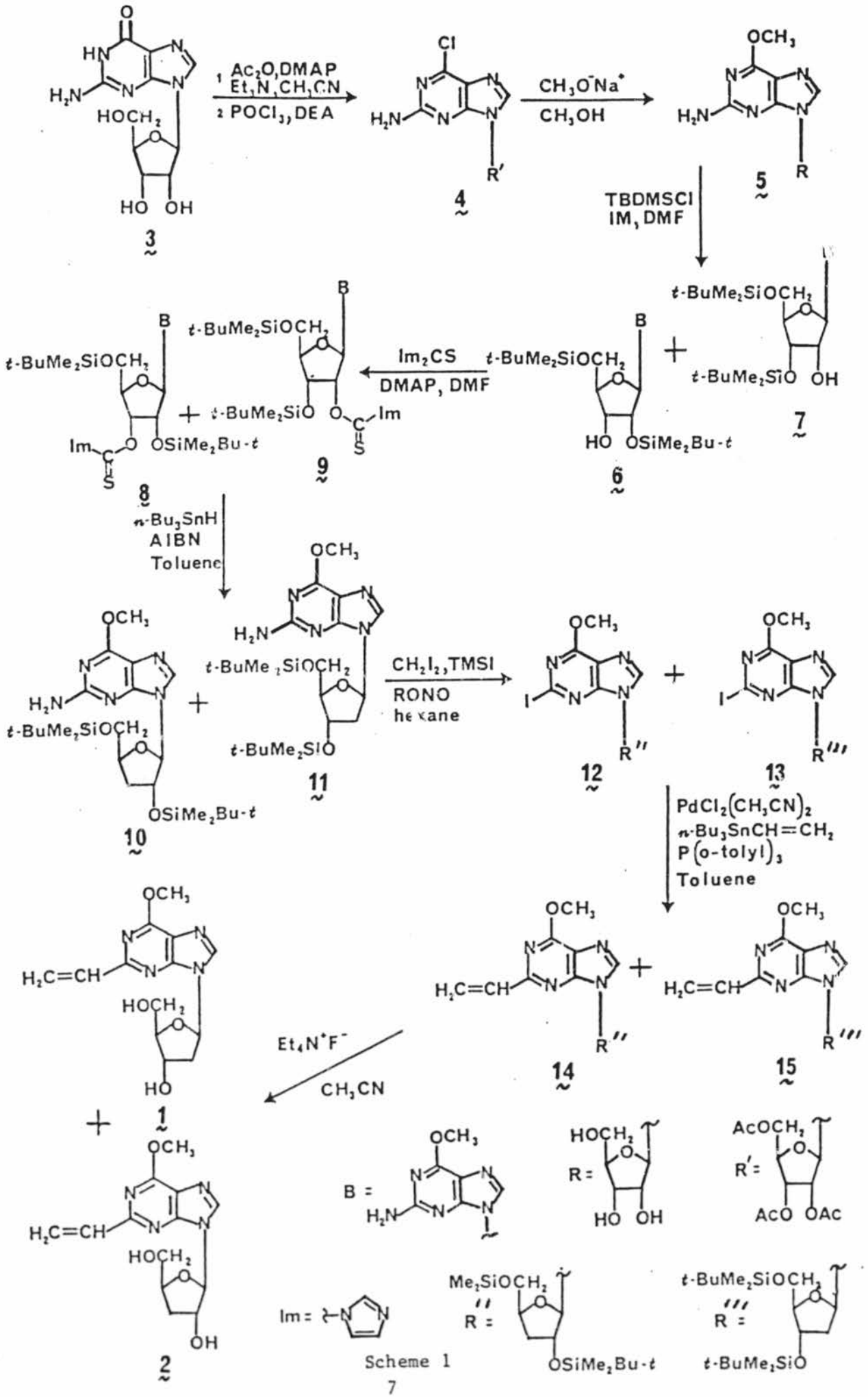
1



2

Natural guanosine, the starting compound, was converted in two steps to the known 6-chloro-2-aminopurine ribonucleoside **4** (Scheme 1). Treatment of **4** with sodium methoxide in methanol gave **5** in 75 % yield. Silylation of **5** with approximately 2 equivalents of t-butyldimethylsilyl chloride in DMF in the presence of imidazole gave a mixture of the 2',5'- and 3',5'-disilylated nucleosides **6** and **7** in a combined yield of 68%. The deoxygenations of these compounds were carried out in two steps. This methodology is related to Barton's procedure for deoxygenations of carbohydrates but has been developed specifically for modified nucleosides by us (12). In the first step, compounds **6** and **7** were converted to their thioimidazolides **8** and **9**, respectively, by reaction with thiocarbonylimidazole and dimethylaminopyridine in DMF (66%). Radical deoxygenation of **8** and **9** with tributyltin hydride and AIBN in refluxing toluene gave the mixture of 2'- and 3'-deoxy compounds **10** and **11** in 98% yield !

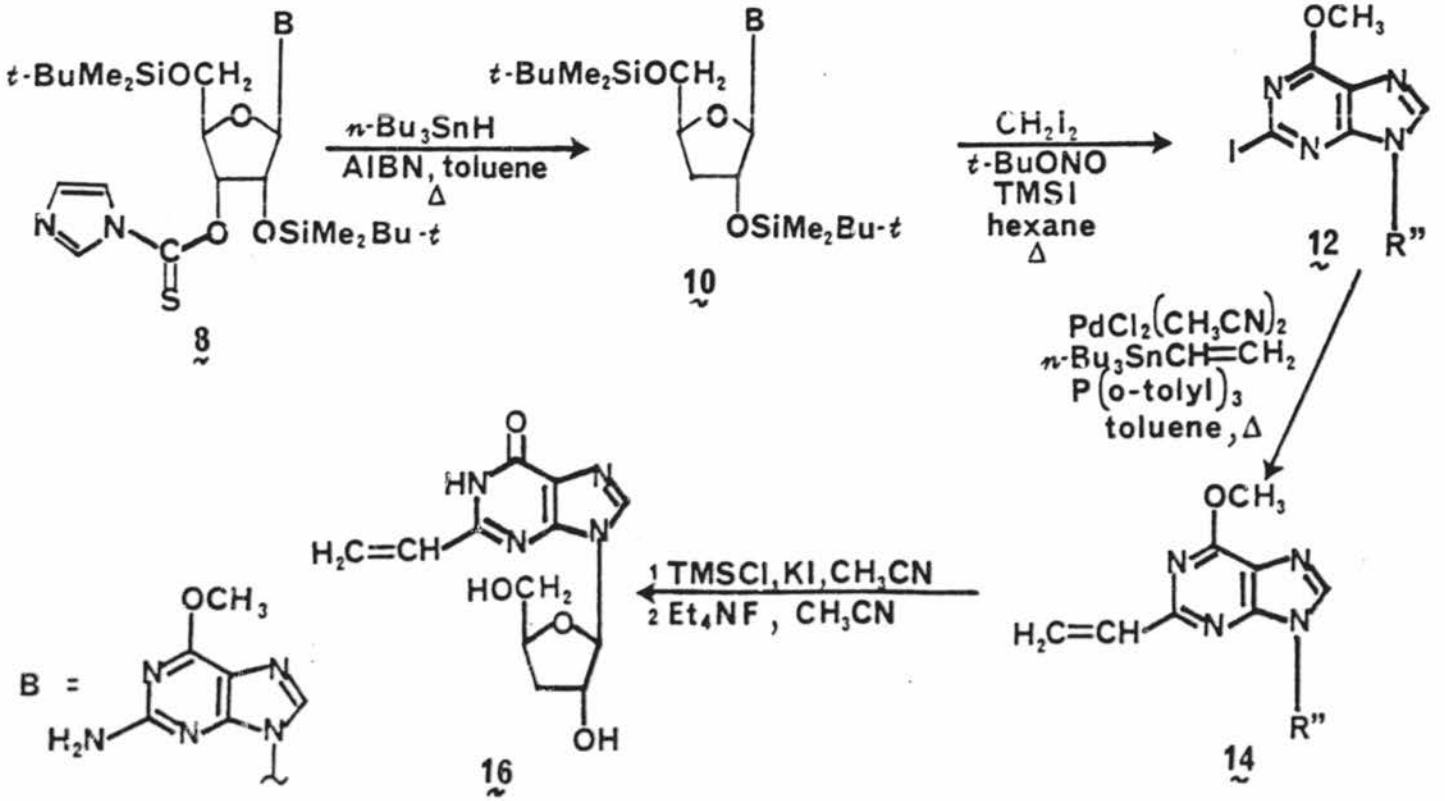
The deoxygenation having been achieved, the next modification was the functionalization of the 2-position of the base moiety. In order to prepare compounds **10** and **11** for this transformation, they were first tailored to their 2-iodo derivatives **12** and **13**, by a radical deamination/halogenation procedure with n-pentyl nitrite, diiodomethane, and trimethylsilyliodide in hexane. This procedure has been previously described by us (13). Although separation of the two isomeric compounds could be achieved at various stages in this synthetic sequence, the most practical point of separation based on R_f differences, is after the iodination reaction.


1 Ac2O,DMAP
Et3N,CH3CN
2 POCl3, DEA
CH3O⁻Na⁺
CH3OH
TBDMSCl
IM, DMF
Im2CS
DMAP, DMF
n-Bu3SnH
AIBN
Toluene
CH2I2,TMSI
RONO
hexane
PdCl2(CH3CN)2
n-Bu3SnCH=CH2
P(o-tolyl)3
Toluene
Et4N⁺F⁻
CH3CN
B =
R =
R' =
Im =
R'' =
R''' =

Scheme 1

The iodo compounds **12** and **13** were converted in separate runs to the vinyl compounds **14** and **15** through a palladium-catalyzed cross-coupling reaction with bis(acetonitrile)palladium chloride, vinyl tributyltin and tri-o-tolylphosphine in refluxing toluene. This reaction has also been developed recently in our laboratory (14). The yield in both cases was about 86%. Deprotection of **14** and **15** with tetraethylammonium fluoride in acetonitrile removed the silyl protecting groups completely in each case to give the target compounds **1** and **2**. The target compounds were purified by preparative layer chromatography (twice) followed by crystallization. The high-resolution fast atom bombardment mass spectrometry (FAB HRMS) established the molecular weights accurately at 292.115. The UV spectrum in ethanol showed absorption at about 262 nm (9,700). The high-field ^{1} NMR spectra (Figures 1 and 2 in Appendix)) clearly showed the presence of the methylene protons in the carbohydrate moiety and the presence of the vinyl protons in the base moiety in each case, as well as all of the other protons. No impurities were detected. Both target compounds were submitted for antiviral evaluation.

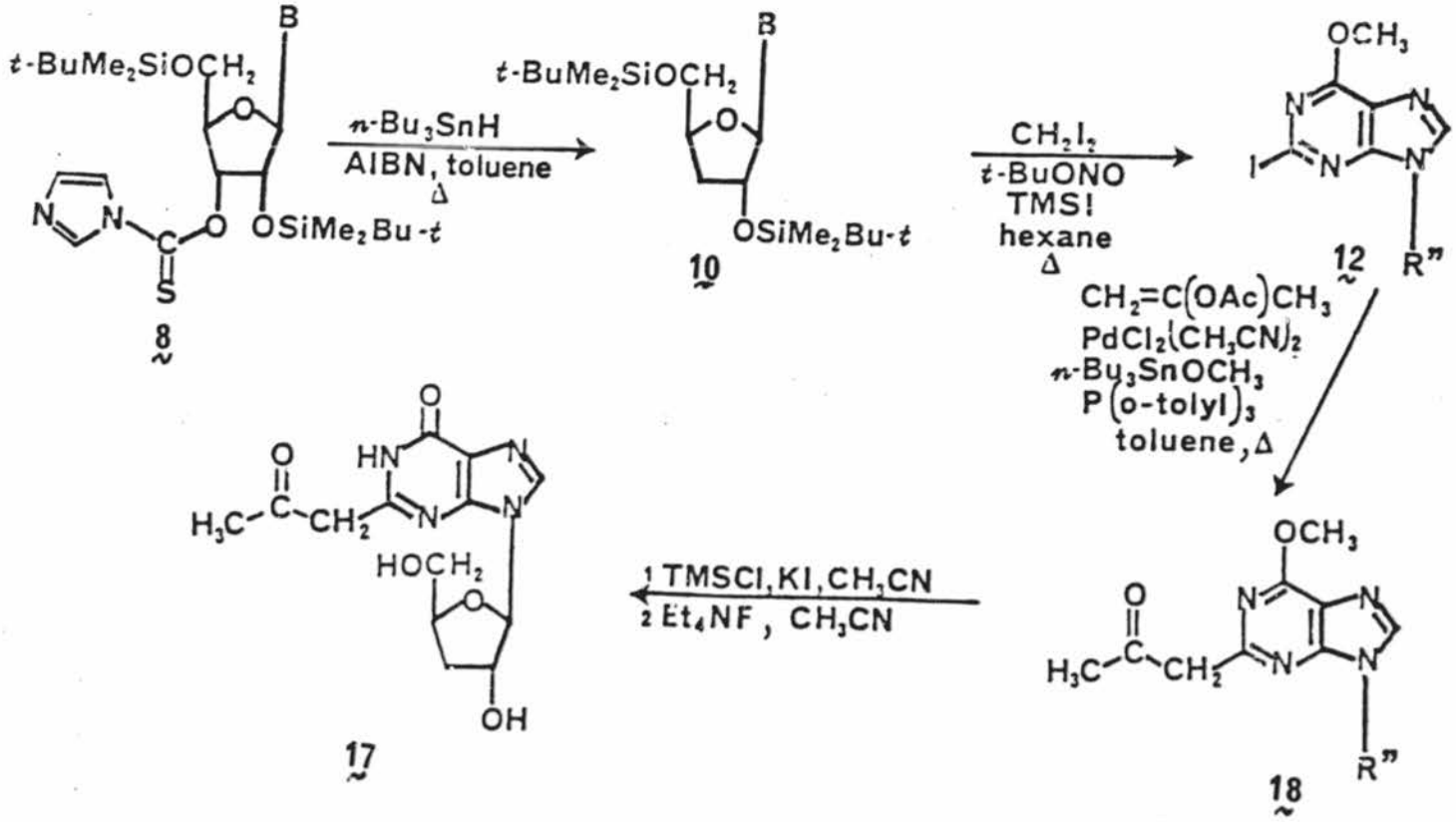
The procedure outlined in Scheme 1 can be extended for the synthesis of 2-vinyl-3'-deoxyinosine (**16**) by deprotection of **14** with trimethylsilyl iodide followed by desilylation with fluoride ions (Scheme 2). This compound was purified by HPLC, characterized by UV, high-field NMR data (Figures 3 and 4 in Appendix) and FAB HRMS and submitted for antiviral evaluation.



Scheme 2

In the previous contract, we had discovered that the introduction of an acetonyl group at the 2-position of a hypoxanthine ribonucleoside resulted in a compound which showed very high and specific antiviral activity (TI > 1000) against the Sandfly Fever Virus. With this structure-activity data in mind, we synthesized the corresponding 3'-deoxy analogue with this expectation that this compound would be as efficiently phosphorylated as the ribonucleoside but would be even more active against this (and perhaps other) virus(es). Because of the absence of the 3'-hydroxy group and the presence of the 2'-hydroxyl group, the triphosphate of this target compound would be recognized by the RNA polymerase as a ribonucleotide but, after incorporation, chain termination would occur because of the absence of the 3'-hydroxyl group. The design of this compound was therefore based on solid biochemical grounds.

Synthesis of 2-acetonyl-3'-deoxyinosine (**17**) utilized precursor **12**, the synthesis of which was described in Scheme 1. Palladium-catalyzed cross-coupling of **12** with tributyltin enolate of acetone (14) gave the 2-acetonyl compound **18** in 85% yield (Scheme 3). Double deprotection of **18** by previously described methods gave the target compound **17**. After multiple HPLC purification, the compound was in the ultra pure state for antiviral evaluation and was submitted. Its high-field ^{13}NMR spectrum is shown in Figure 5 (Appendix).



Scheme 3

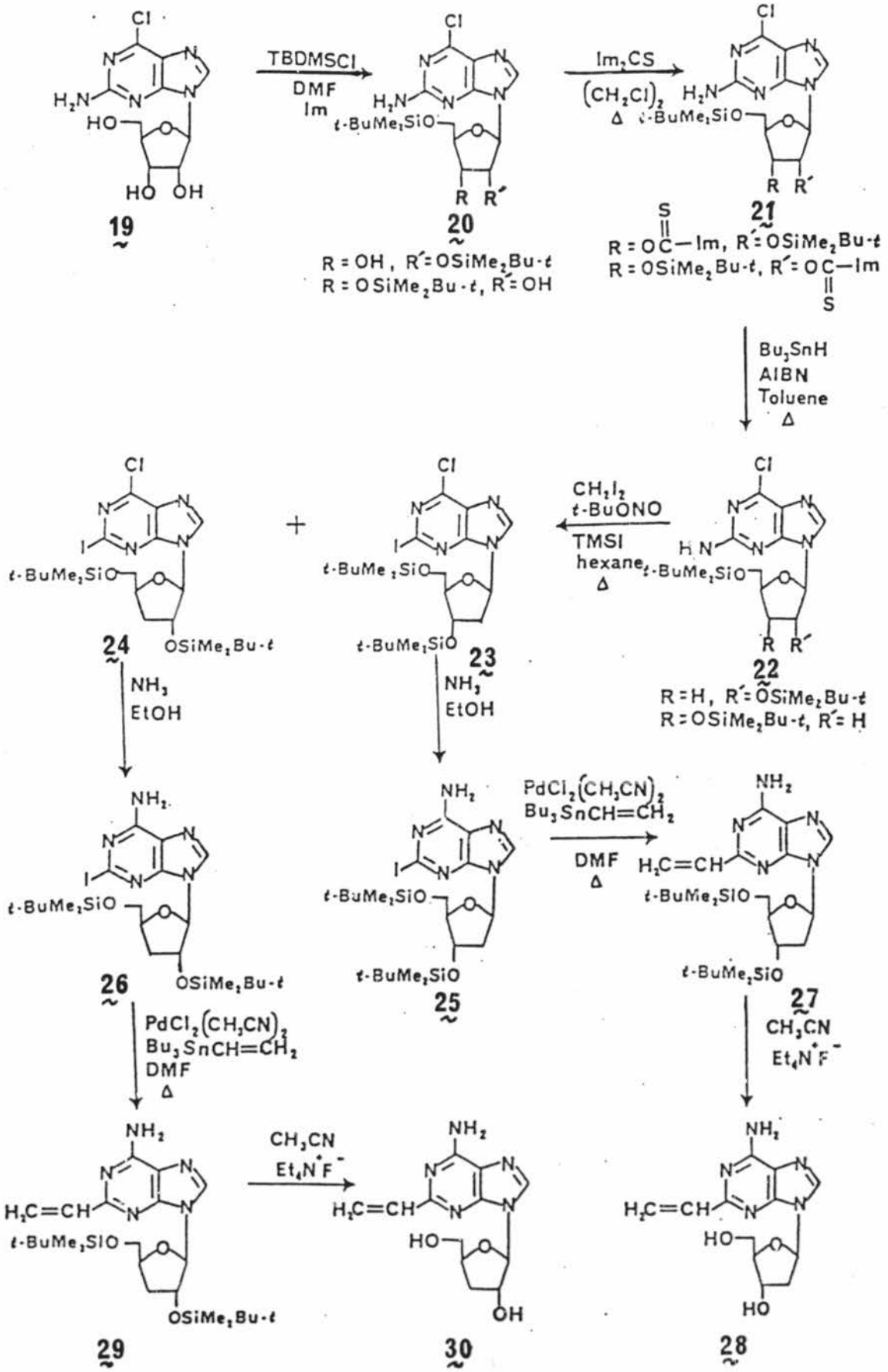
Synthesis of Novel Congeners of Cordyceoin

Cordycepin (3'-deoxyadenosine) is known to have antiviral activity against a number of RNA viruses (15). The biochemical basis for this mechanism of action is thought to be a result of the inhibition of the viral RNA polymerase activity by cordycepin 5'-triphosphate (16-18). The polynucleotide chain appears to be terminated at the point at which the cordycepin component is added because of the absence of the 3'-hydroxyl group for further chain elongation. Analogues of cordycepin (i.e. both 3'-deoxy and 2'-deoxy) would therefore be of considerable potential antiviral interest.

The strategy for the synthesis of the novel 2'-deoxy and 3'-deoxy nucleoside congeners of cordycepin involved starting with readily available natural guanosine and modifying both the carbohydrate and base moieties in this compound. Modification of the carbohydrate moiety involves regiospecific deoxygenation. Earlier methods of synthesis of deoxy nucleosides involved reaction of arabino halo sugar moieties with hydride (19,20). Nucleoside 2',3'-epoxides may be ring opened by hydride to form deoxy nucleosides (20). Deoxygenation may also be carried out via a cyclic thiocarbonate by reaction with tributyltin hydride and AIBN according to the methodology originally developed by Barton and Subramanian (21). However, reductive cleavage of the cyclic thiocarbonate gives mixtures of 2'- and 3'-deoxy nucleosides with the 2'-deoxy compound being the major product (12). A more regiospecific deoxygenation, however, would be possible through the 3'-imidazolide (12,22). If the imidazolides could be specifically prepared, entry to both the 3'-deoxy and the 2'-deoxy series could be achieved through related pathways but with the same initial precursor molecules.

Guanosine **3** was converted in three known steps to 6-chloro-2-aminopurine ribonucleoside, **19** (11) in high yields. When this compound was treated with 2.2 equivalents of t-butyldimethylsilyl chloride and 4.4 equivalents of imidazole in DMF at room temperature for 2 h, a 64% isolated yield of a mixture of 2',5'- and 3',5'-disilylated product **20** was obtained (Scheme 4). The isolation of these compounds required separation by flash chromatography from two minor side products: the monosilylated compound and the trisilylated material. The three could be identified by mass spectrometry. The mixture of the 2',5'- and 3',5'-disilylated compounds (regioisomer ratio approximately 1:1 by ^{1}H NMR data) may be separated into the individual isomers at this juncture or the mixture may be separated at a later stage in the synthetic pathway. We chose the latter as the more efficient approach.

Treatment of compound **20** with 1,1'-thiocarbonyldiimidazole in refluxing dichloroethane (12) for about 5h afforded the thiocarbonyl ester mixture **21** in about 80% yield. Longer reaction times led to decomposition products and lower yields. If DMAP is used in this reaction, the yields drop to about 20% because of extensive decomposition of starting material. Deoxygenation of the chromatographically purified imidazolides was carried out with


TBDMSCl
DMF
Im
Im₂CS
(CH₂Cl)₂
Δ
Bu₃SnH
AIBN
Toluene
Δ
CH₂I₂
t-BuONO
TMSI
hexane
Δ
NH₃
EtOH
PdCl₂(CH₃CN)₂
Bu₃SnCH=CH₂
DMF
Δ
CH₃CN
Et₄N⁺F⁻
19
20
21
22
23
24
25
26
27
28
29
30
R = OH, R´= OSiMe₂Bu-t
R = OSiMe₂Bu-t, R´= OH
R = OC(=S)—Im, R´= OSiMe₂Bu-t
R = OSiMe₂Bu-t, R´= OC(=S)—Im
R = H, R´= OSiMe₂Bu-t
R = OSiMe₂Bu-t, R´= H

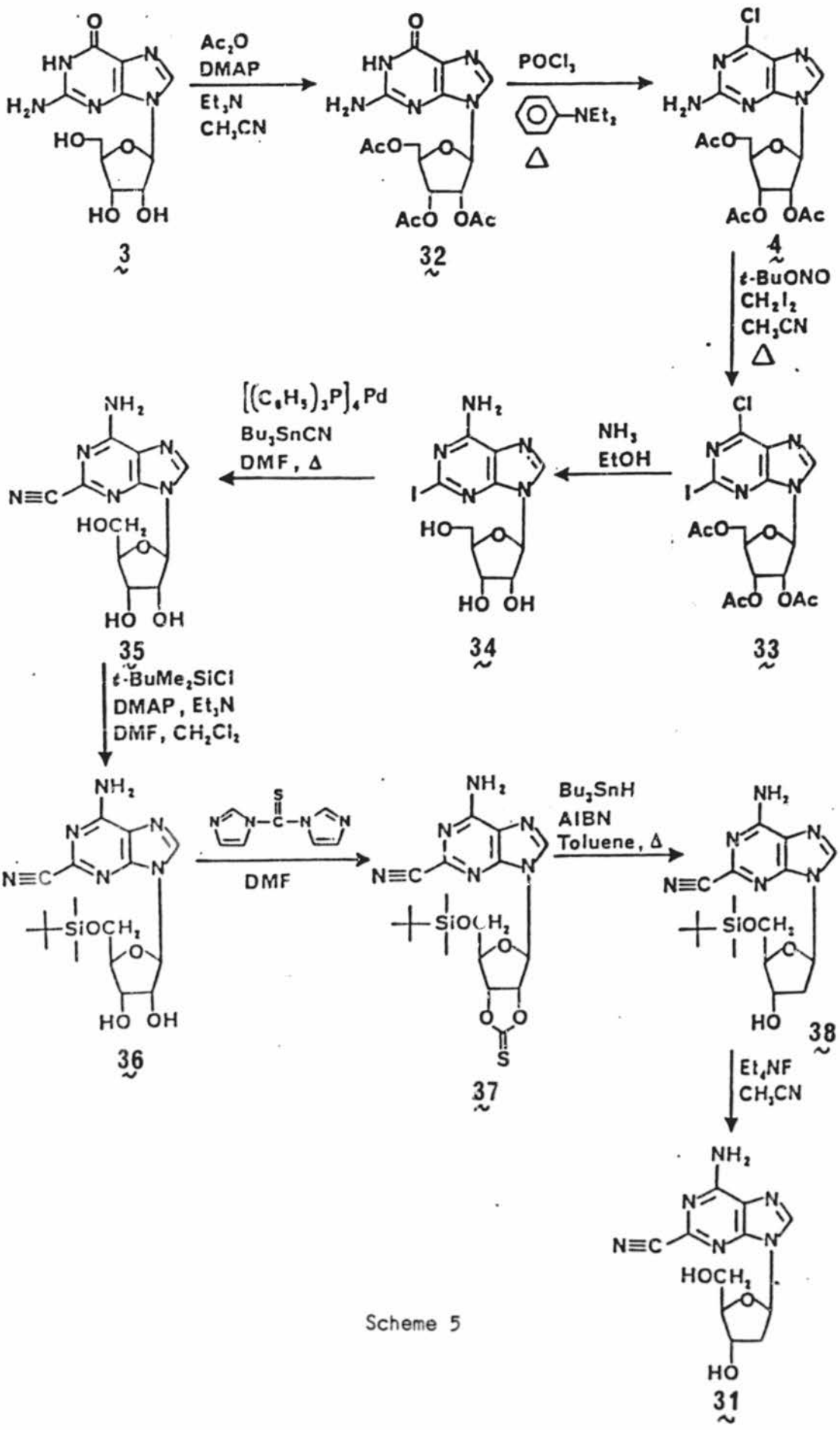
Scheme 4

tributyltin hydride and AIBN in refluxing toluene for 1 h to give the deoxygenated products **22** in 86% yield (Scheme 4). Iodination of the deoxygenated compounds with t-butyl nitrite, methylene diiodide, and trimethylsilyl iodide in hexane gave the 2-iodo-6-chloro compounds in a combined yield of 58 %. The iodination reaction of these substrates has to be conducted under carefully controlled conditions (dried redistilled reagents and solvents, N_2 purging and atmosphere, optimum reaction time and temperature) in order to obtain synthetically acceptable yields. Complete separation of the regioisomers was easily achieved at this stage of the synthesis by column chromatography on silica gel with hexane/ ethyl acetate (4:1) as the eluting solvent. The ratio of the two separated isomers is 3:2 [2'-deoxy (**23**) : 3'-deoxy (**24**)] as shown by high-field ^{1}H NMR data.

Two modifications of the purine ring were planned for the next stages of the syntheses; first, the conversion of the 6-chloro group to the 6-amino group, and second, the elaboration of the 2-position utilizing the carbon-iodine bond at this position. Transformation of the 2-iodo-6-chloropurine moiety in **23** and **24** to the 2-iodoadenine moiety could be easily brought about with ammonia because of the nucleophilic lability of the 6-chloro group. Thus, treatment of the 2-iodo-6-chlorodeoxynucleosides **23** and **24** with ethanolic ammonia resulted in displacement of the 6-chloro group to furnish the deoxygenated adenine nucleosides **25** and **26**, respectively (Scheme 4).

Carbon-carbon bond forming reactions leading to functionalization at the 2-position of the adenine moiety were carried out by palladium-catalyzed cross-coupling reactions with synthon bearing organostannanes (11,14). Thus, compound **25** was converted to the protected new 2-vinyl compound **27** in 70% isolated yield by palladium-mediated cross-coupling with vinyl tri-n-butylstannane with heating in DMF. Fluoride ion deprotection gave the target compound **28** in 98% yield. 2-Vinyl-3'-deoxyadenosine **30** was prepared from **26** by the palladium-catalyzed methodology followed by deprotection. Both target compounds (**28** and **30**) were purified by HPLC, characterized, and then submitted for antiviral evalaution. The high field NMR data for these compounds are shown in Figures 6, 7, and 8 (Appendix).

One additional novel analogue of cordycepin was also synthesized. This was 2-cyano-2'-deoxyadenosine (**31**). A key precursor for this synthesis was 2-iodoadenosine **34** (23). This compound, on treatment with tri-n-butylcyanostannane and tetrakis(triphenylphosphine) palladium(0) in DMF at 120 ^{o}C gave the 2-cyanoadenine product **35** in 80% yield (Scheme 5). Compound **35** was deoxygenated and converted to the novel target molecule **31** using a procedure recently developed in our laboratory (12). The structure of the purified 2-cyano product **31** was confirmed by spectral data: high-field ^{1}H and ^{13}C NMR, FTIR, UV, and FAB HRMS. Its high-field ^{13}C NMR spectrum is shown in Figure 9 (Appendix). This interesting compound was also submitted for antiviral evaluation.


Ac2O
DMAP
Et3N
CH3CN
POCl3
NEt2
Δ
t-BuONO
CH2I2
CH3CN
Δ
NH3
EtOH
[(C6H5)3P]4Pd
Bu3SnCN
DMF, Δ
t-BuMe2SiCl
DMAP, Et3N
DMF, CH2Cl2
DMF
Bu3SnH
AIBN
Toluene, Δ
Et4NF
CH3CN
3
32
4
33
34
35
36
37
38
31

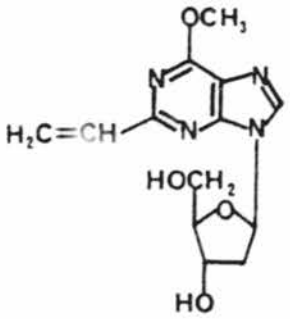
Scheme 5

Summary of Novel Compounds Submitted for RNA Antiviral Evaluation

1. 6-Methoxy-2-vinyl-9-(2-deoxy-β-D-ribofuranosyl)purine

VN-I-201

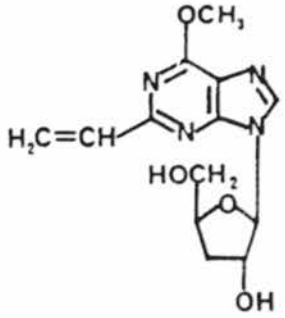
AVS-005911



2. 6-Methoxy-2-vinyl-9-(3-deoxy-β-D-ribofuranosyl)purine

VN-I-202

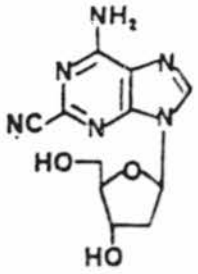
AVS-005912



3. 2-Cyano-9-(2-deoxy-β-D-ribofuranosyl)adenine
or 2-Cyano-2'-deoxyadenosine

VN-I-203

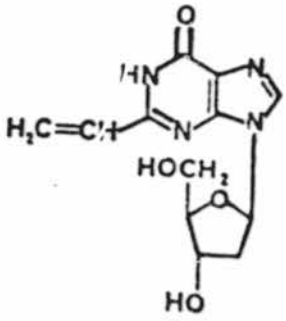
AVS-006231



4. 2-Vinyl-9-(2-deoxy-β-D-ribofuranosyl)hypoxanthine
or 2-Vinyl-2'-deoxyinosine

VN-I-204

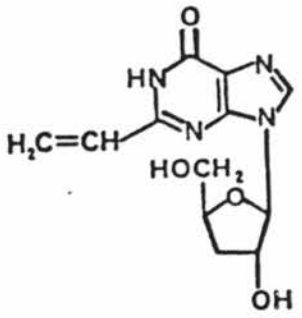
AVS-006232



5. 2-Vinyl-9-(3-deoxy-β-D-ribofuranosyl)hypoxanthine

VN-I-205

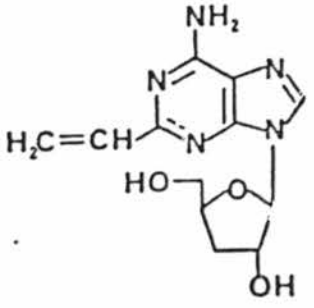
AVS-006305



6. 2-Vinyl-9-(3-deoxy-β-D-ribofuranosyl)adenine
or 2-Vinyl-3'-deoxyadenosine

VN-I-206

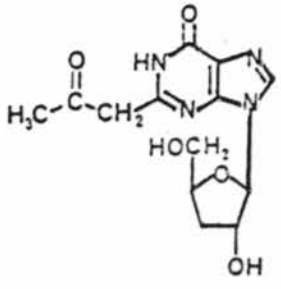
AVS-006507



7. 2-Acetonyl-9-(3-deoxy-β-D-ribofuranosyl)hypoxanthine

VN-I-207

AVS-006508



CONCLUSIONS:

This project is concerned with the biochemically-based rational design, synthesis, purification, complete spectral characterization, and antiviral evaluation of some unique adenine and hypoxanthine deoxynucleosides. A total of seven compounds were produced through complex multi-step syntheses and submitted for antiviral evaluation. The work at present is right on schedule and in complete accordance with the contract agreement. Based on previous results from our laboratory, information on the exotic RNA viruses and their key enzymes, rational design, and the current status of antiviral research in this and related areas, this project has a very high probability of producing antivirally active compounds of relevance and importance to the drug development program of the USAMRDC.

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5. V. Nair and G. S. Buenger, Base Modified Deoxyadenosines: Synthesis and Enzymology, 198th National Meeting of the American Chemical Society, Miami Beach, Florida, September, 1989.

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PERSONNEL SUPPORTED

Ph.D. Degree Graduate Students

Greg S. Buenger	Arthur G. Lyons
Todd B. Sells	David F. Purdy

APPENDIX

Spectral data for target compounds are enclosed.

Figure 1.

300 MHz ^{1}H NMR spectrum of 6-Methoxy-2-Vinyl-9-(3'-deoxy-β-D-ribofuranosyl)purine in DMSO-d_6

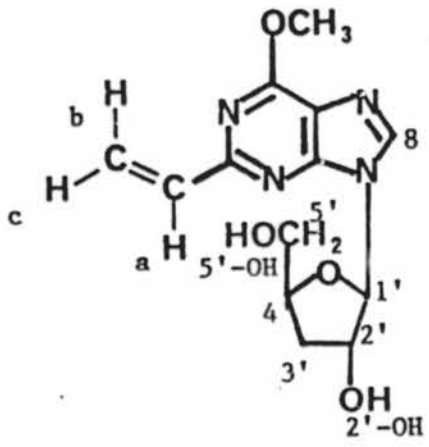

Figure 2

300 MHz ^{1}H NMR spectrum of 6-Methoxy-2-Vinyl-9-(2'-deoxy-β-D-ribofuranosyl)purine in DMSO-d_6

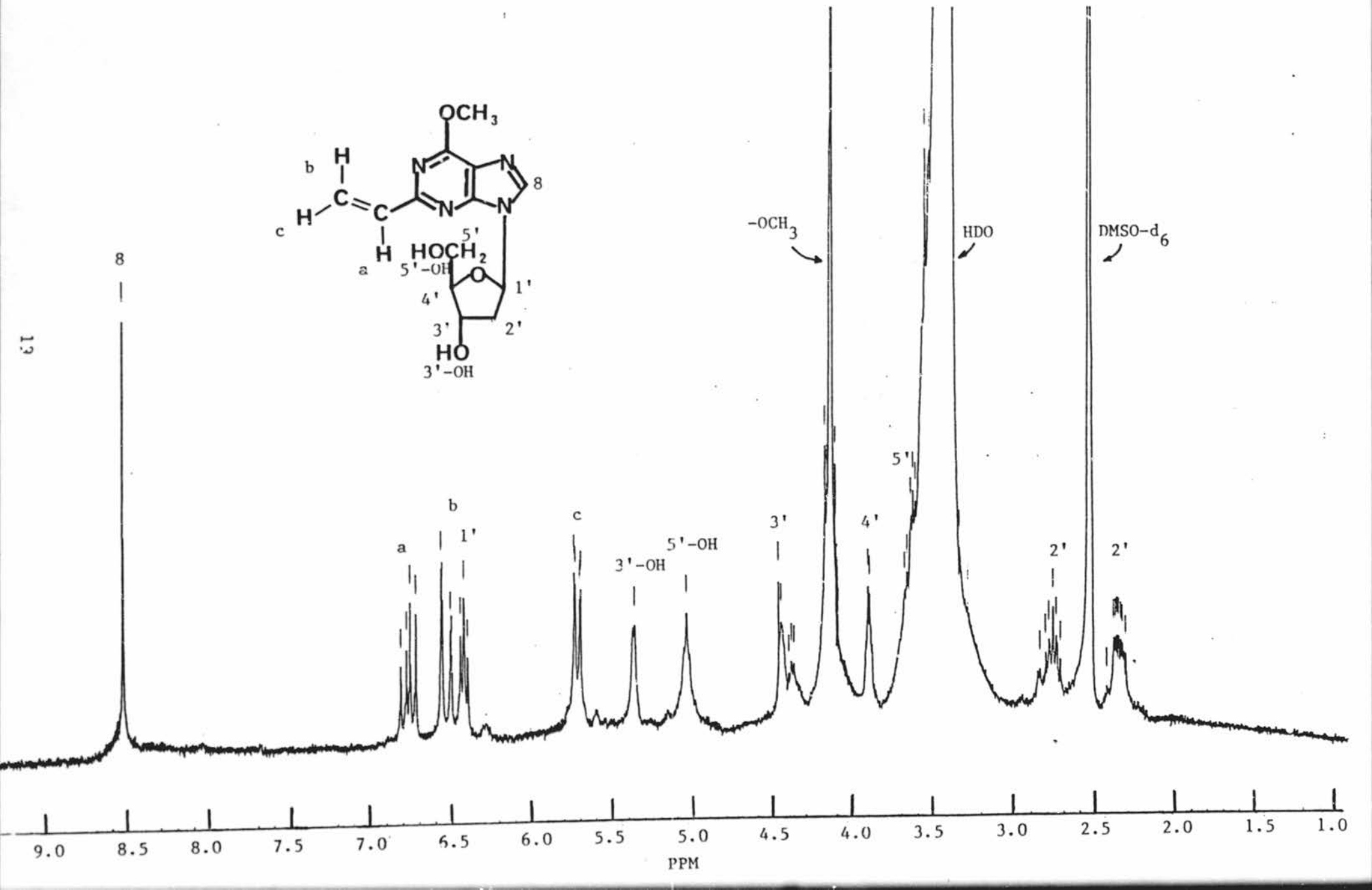

Figure 3

90.6 MHz ^{13}C NMR Spectrum of 2-Vinyl-9-(3-deoxy-β-D-ribofuranosyl)hypoxanthine in DMSO-d_6

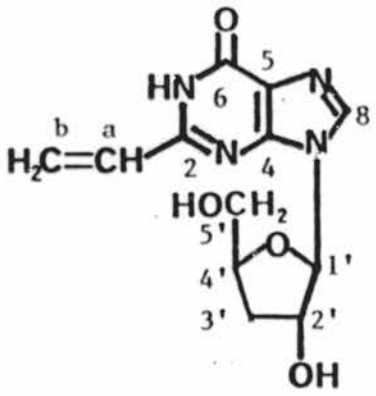

Figure 4.

300 MHz ^{1}H NMR spectrum of 6-Methoxy-2-Vinyl-9-(2'-deoxy-β-D-ribofuranosyl)purine in DMSO-d_6

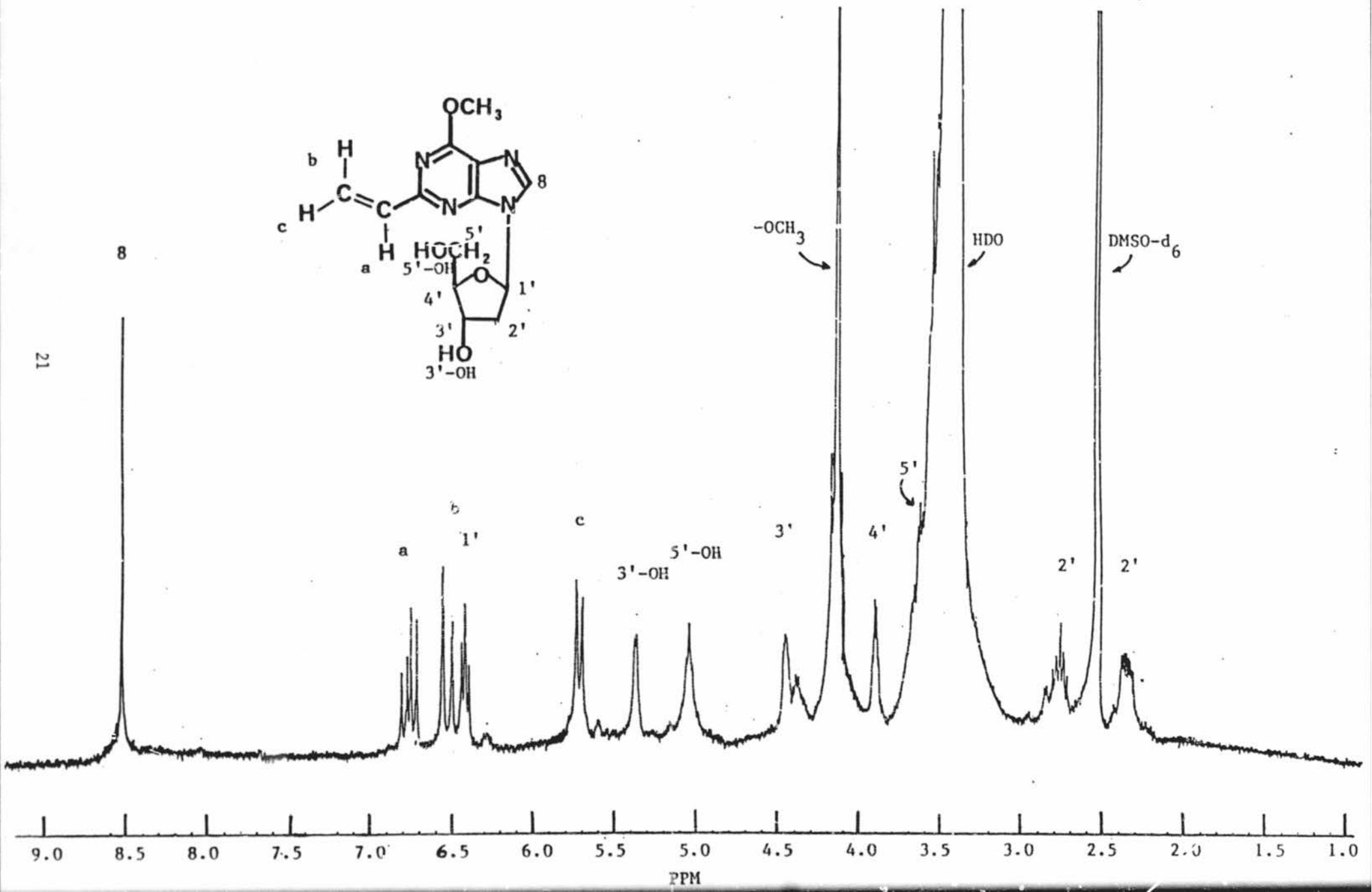

Figure 5.

90.6 MHz ^{13}C NMR Spectrum of 2-Acetonyl-9-(3-deoxy-β-D-ribofuranosyl)hypoxanthine in DMSO-d_6

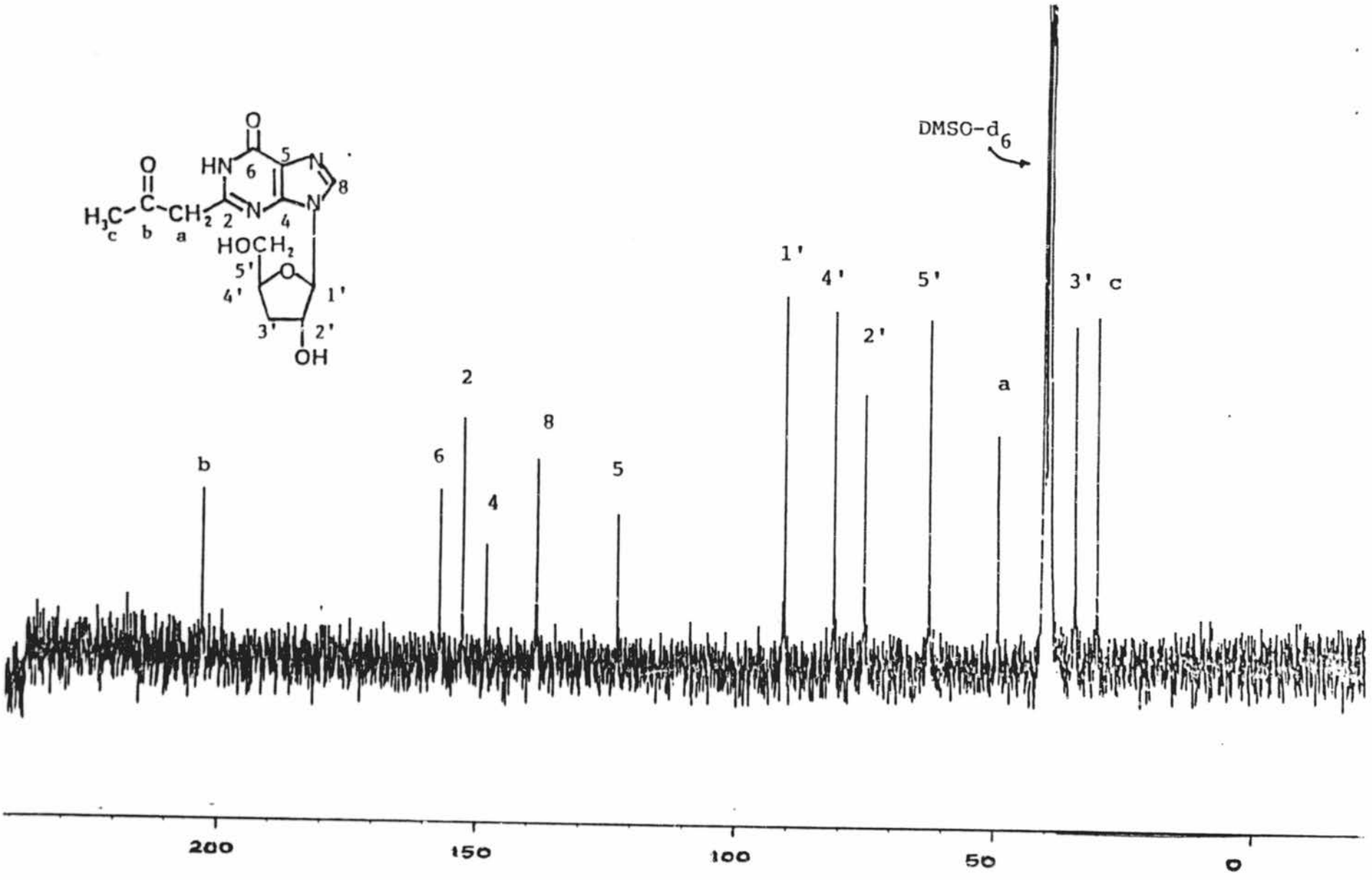

Figure 6. 300 MHz ^{1}H spectrum of 2-Vinyl-9-(2-deoxy-β-D-ribofuranosyl)adenine in DMSO-d_6.

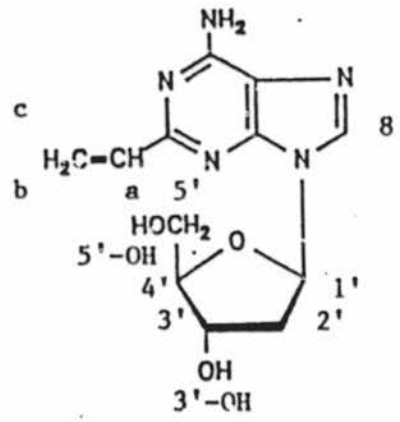

Figure 7. 300 MHz ^{1}H NMR Spectrum of

2-Vinyl-9-(3-deoxy-β-D-ribofuranosyl)adenine in DMSO-d_6.

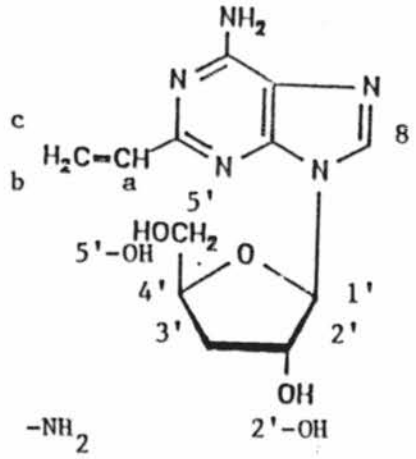

Figure 8. 90.56 MHz ^{13}C NMR Spectrum of

2-Vinyl-9-(3-deoxy-β-D-ribofuranosyl)adenine in DMSO-d_6.

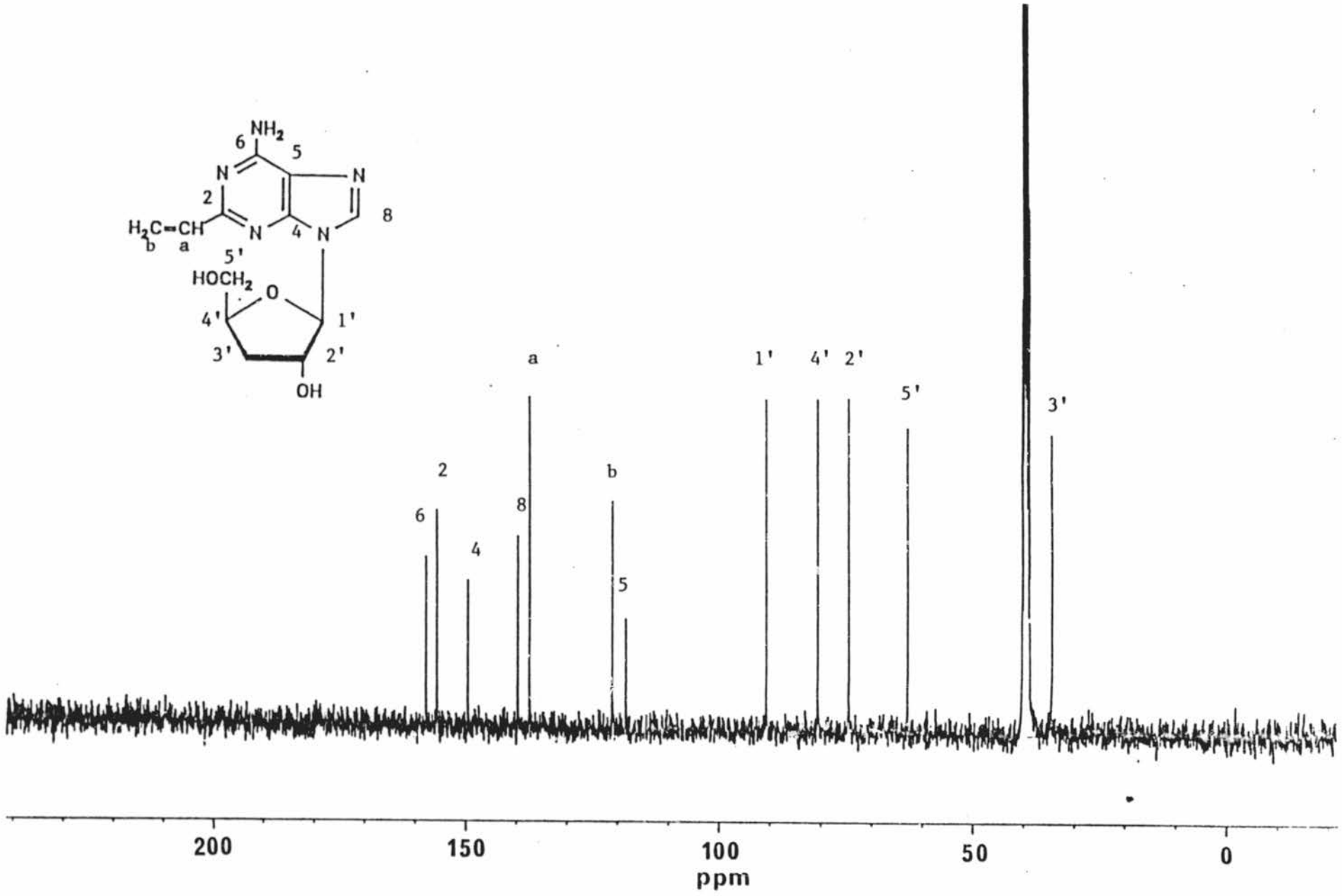

Figure 9.

90.56 MHz ^{13}C NMR Spectrum of 2-Cyano-2'-deoxyadenosine in DMSO-d_6.