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Rare 2-Substituted Purine Nucleosides

Annual Report

October 18, 1986 to October 17, 1987

October 1987

Vasu Nair

Supported by

U. S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-86-C-6001

The University of Iowa
Iowa City, Iowa 52242

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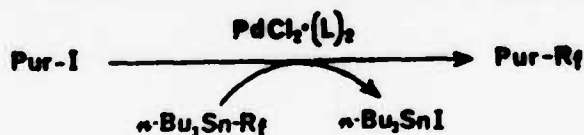
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→ This project is concerned with the synthesis of rare 2-substituted purine nucleosides with therapeutic potential against RNA viruses. In the second year of the contract, eleven rare 2-substituted purine nucleosides were synthesized, purified, fully characterized, and submitted to the Department of Antiviral Studies. Antiviral screening data have been received on a few of the compounds submitted and there are some very interesting and positive results. One compound (2-acetonylinosine, AVS-002159) has been found to have very high activity (TI >1000) against the SF virus. Another compound (2-vinylinosine, AVS-002716) has been found to have broad spectrum activity against a number of RNA viruses. Two other compounds (AVS-002883 and AVS-002884) have shown some activity against the RVF virus, and still another (AVS-002352) has shown activity against the YF virus. Five publications have appeared in 1987 on this work. Keywords: Rift Valley Fever virus; yellow fever virus;					
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3. Name of Principal Investigator: Vasu Nair
Professor of Chemistry
Phone: (319) 335-1364
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5. Description of Work In Progress:

In the second year of this contract, our goals were to utilize the procedures previously developed to synthesize a number of target molecules. A total of nine rare C-2 functionalized nucleosides (target compounds) were submitted to the Department of Antiviral Studies for biological evaluation between October 18, 1986 and October 17, 1987. In addition, two intermediates were submitted during this period. A description of the synthetic work done during this period, compounds submitted, biological test data, publications, personnel supported, and an executive summary are given in the pages following.

The starting point of our work during the second year of the contract was the synthesis of the 2-vinyl compounds 1 and 2. The rationale for the choice of these compounds as the starting point was that, in addition to being target molecules, they would also be key precursors for the synthesis of a variety of rare functionalized alkylated purine nucleosides. The general methodology for the introduction of carbon-carbon bonding at the 2-position of the hypoxanthine or purine ring systems developed in our laboratory under this contract is summarized in Scheme 1. The conversion apparently involves oxidative insertion of palladium into the carbon iodine bond of the iodopurine followed by coupling of the derived Pd(II) complex with the appropriate organostannane, trans-cis isomerization, and reductive elimination to give the coupled product with regeneration of the Pd(0). Only catalytic amounts of palladium are required for this reaction.



R_f = functionalized alkyl group

Scheme 1

The synthesis of 2-vinylinosine (1) commenced with guanosine (3) which was converted in two steps with the reagents shown to the 2-amino-6-chloropurine nucleoside (5) in 83% overall yield. Reaction of compound 5 with n-pentyl nitrite and diiodomethane in refluxing acetonitrile gave the 6-chloro-2-iodopurine nucleoside 6 in 71% yield. In the next step, this molecule was modified in preparation for the introduction of functionalized

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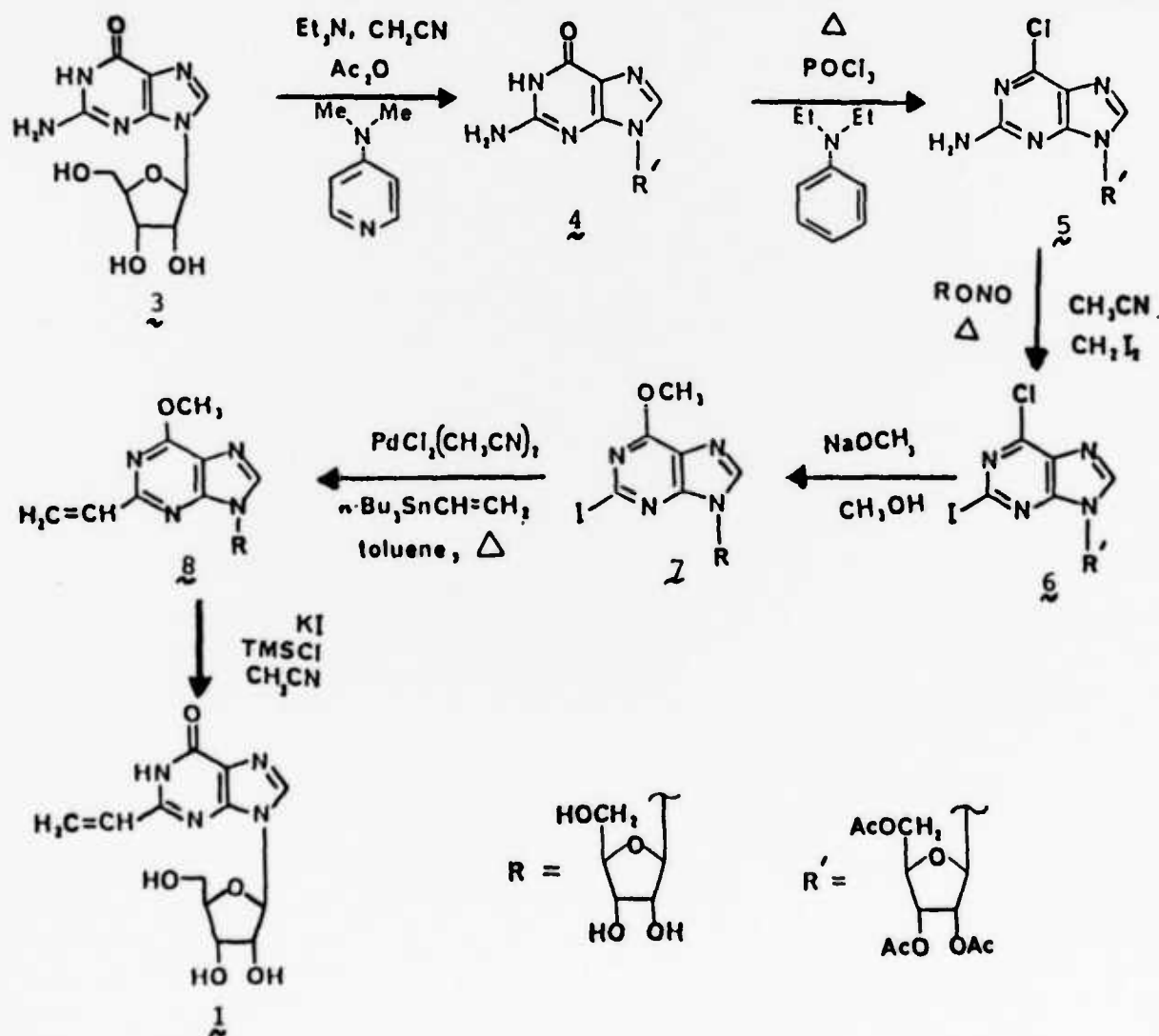
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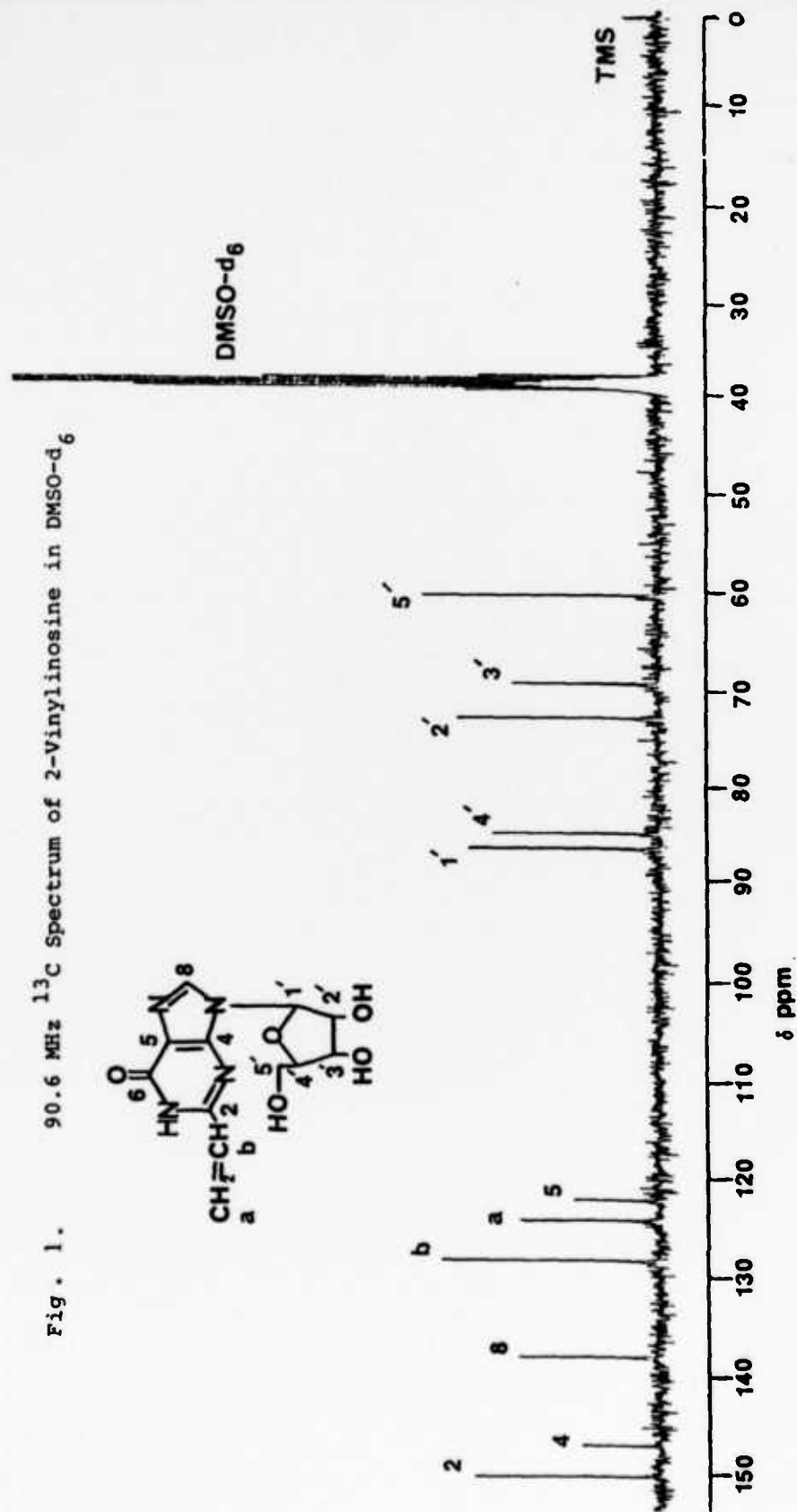
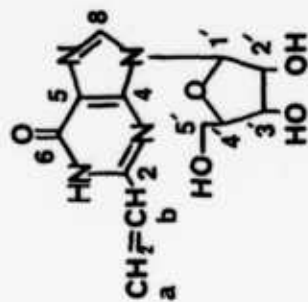
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alkylation at the 2-position. Thus it was treated with sodium methoxide in methanol. The 6-chloro group was replaced with methoxide to produce the masked base and the protecting acetyl groups on the carbohydrate moiety were cleaved. The product, nucleoside **7** (76%), was now properly constituted for the palladium-catalyzed cross-coupling reaction. Thus, reaction of **7** with tri-*n*-butylvinylstannane in the presence of palladium chloride gave **8** in > 80% yield. Deprotection of **8** with trimethylsilyl iodide in acetonitrile resulted in cleavage of the methyl group to give the target molecule **1** in about 50% yield after appropriate work up and purification (Scheme 2). Our procedure for masking the hypoxanthine base in this way will find wide application in purine nucleoside chemistry. Compound **1** was purified by high performance liquid chromatography (three passes) on Amberlite XAD-4 resin with ethanol-water as the eluting solvent. Complete characterization was carried out by UV, FTIR, high-field ^1H and ^{13}C NMR spectroscopy, and elemental analysis. The high-field ^{13}C NMR spectrum is enclosed (Fig. 1).

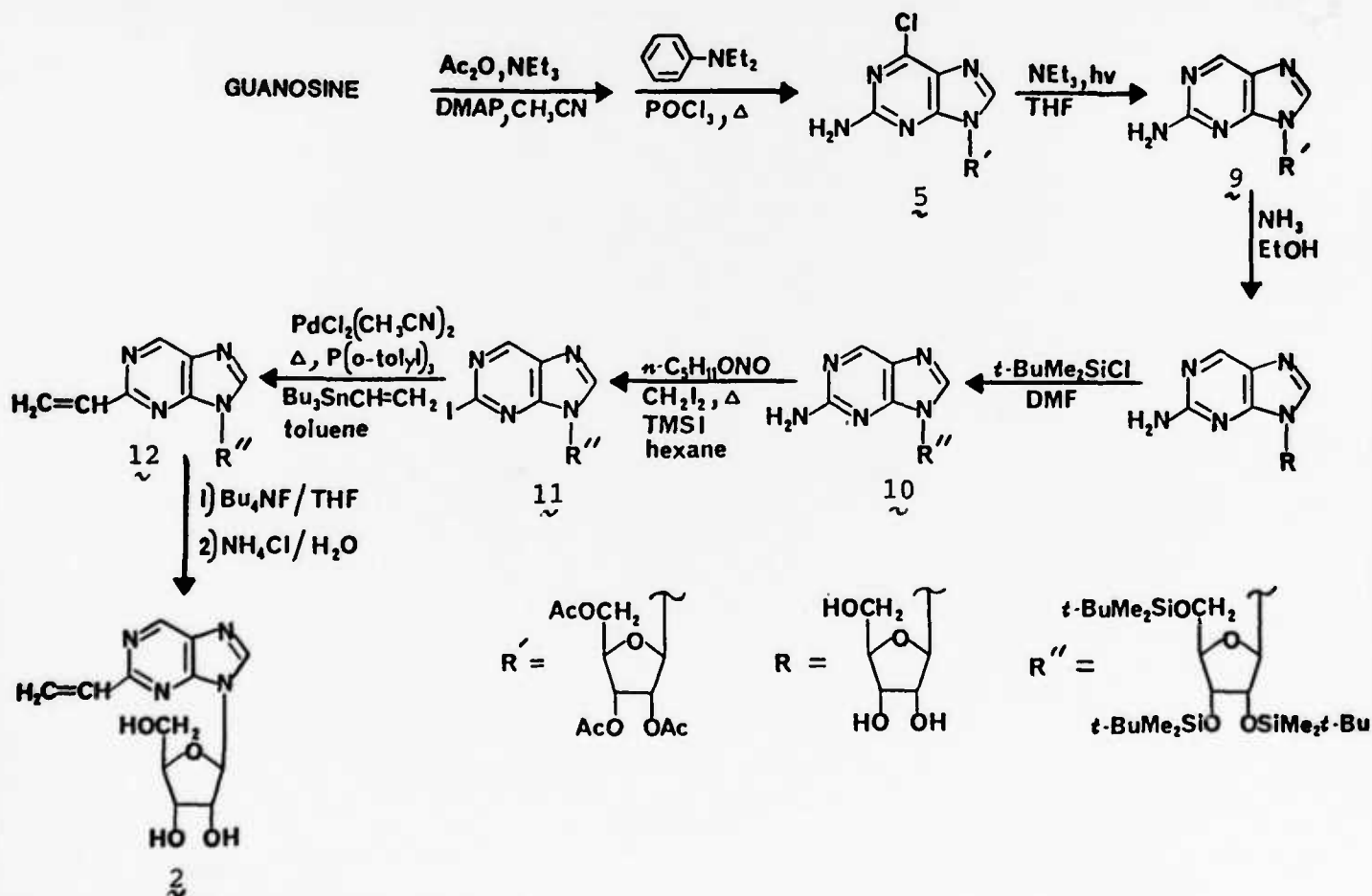


Scheme 2

Fig. 1. 90.6 MHz ^{13}C Spectrum of 2-Vinylinosine in DMSO-d_6

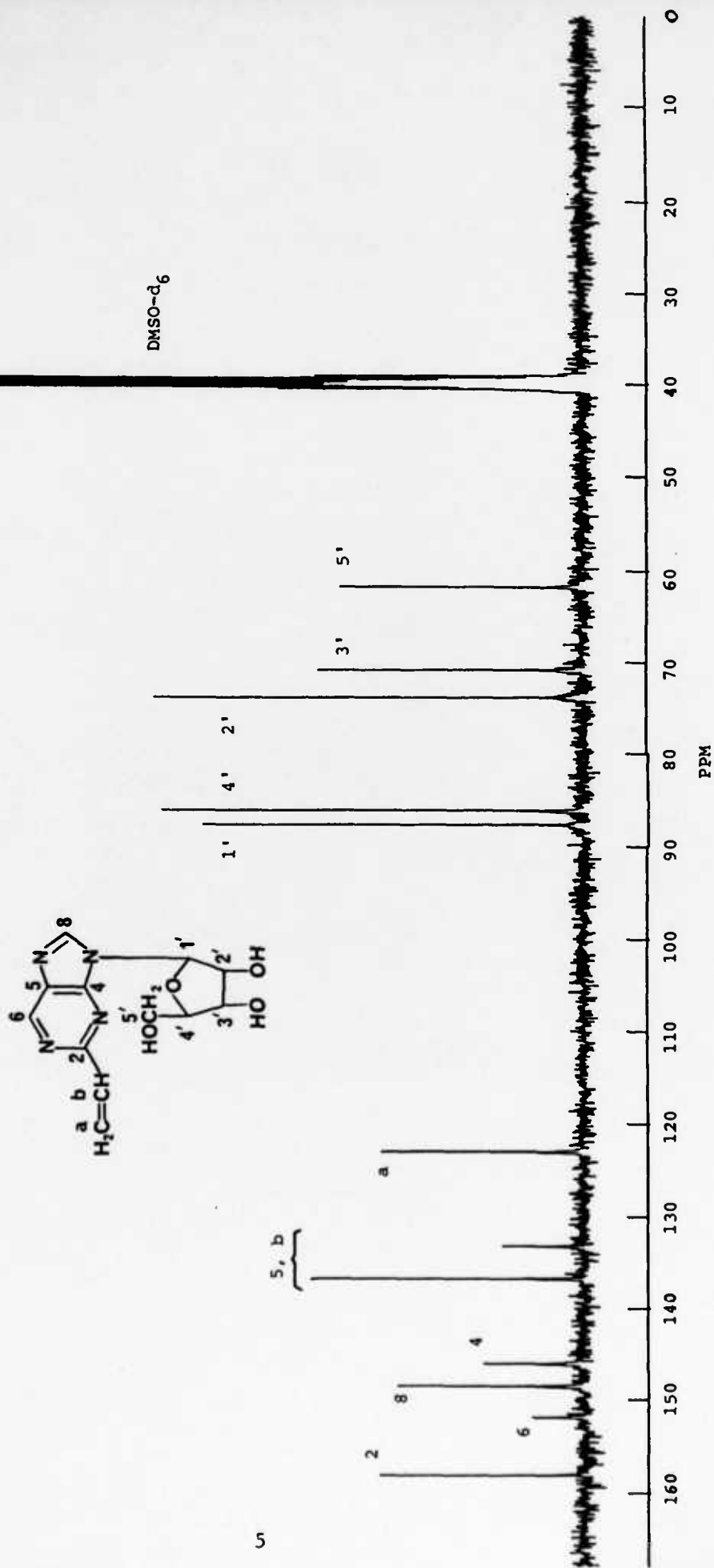


Compound **2** was synthesized using the sequence of reactions shown in Scheme 3. The starting material for the synthesis was the 6-chloropurine nucleoside **5**, prepared from guanosine in 83% yield as described above. In order to obtain entry into 2-substituted purine nucleosides, it was necessary to remove the 6-chloro group. This was done by a photoinduced reductive dehalogenation reaction with triethylamine in tetrahydrofuran as solvent. This photochemical dehalogenation is a new methodology in nucleoside chemistry and was developed in this project. It will find wide applicability in the nucleoside area. Attempted radical iodination of the 2-aminopurine **9** gave poor yields of the 2-iodinated product. However, when the protecting group was changed from acetate to hindered silyl group, then the radical iodination reaction proceeded in much higher yields to give **11**. Reaction of **11** with tri-*n*-butylvinylstannane under palladium catalysis gave the 2-vinylpurine nucleoside **12** which was deprotected with tetrabutylammonium fluoride to the target molecule **2**. The overall yield starting from guanosine was 12%. The crude product was purified by flash chromatography followed by HPLC and fully characterized as described above for **1**. The high-field ^{13}C NMR spectrum is shown in Fig. 2.

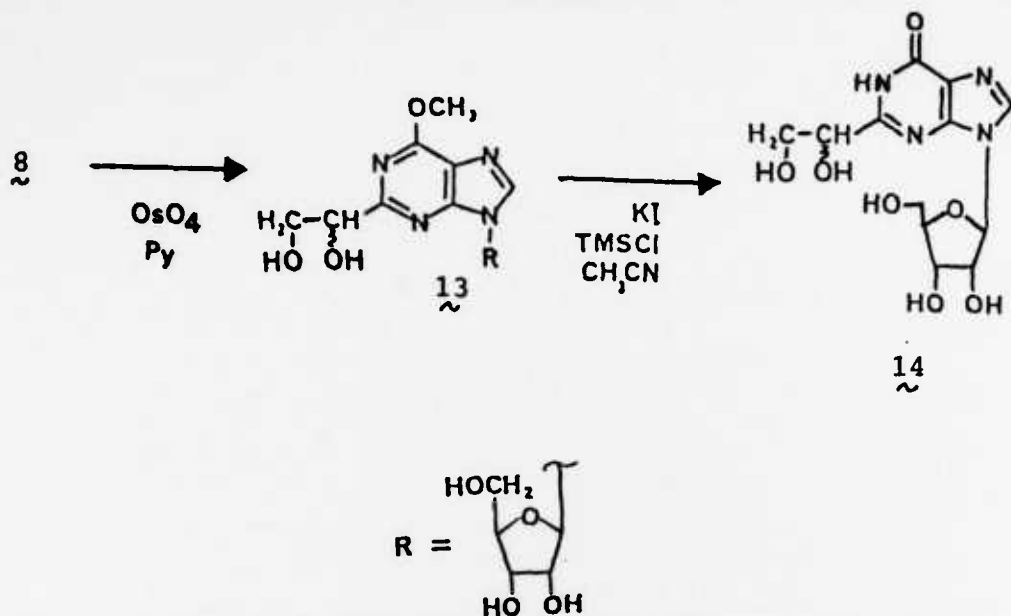


Scheme 3

Fig. 2. 90.6 MHz ^{13}C NMR of 2-Vinylnebularine in $\text{DMSO}-d_6$

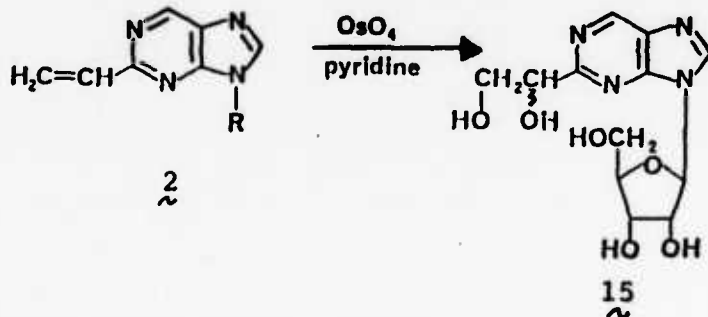


Hydroxylation of compound **8** with osmium tetroxide gave the 1,2-dihydroxyethyl compound **13** in 55 % yield. Deprotection of **13** with trimethylsilyl iodide in acetonitrile gave **14** in 50 % yield (Scheme 4). This target molecule was purified by HPLC on Amberlite XAD-4 resin. It was fully characterized by spectral methods and elemental analysis. The high-field ^{13}C NMR spectrum is enclosed (Fig. 3).



Scheme 4

Hydroxylation of compound **2** with osmium tetroxide followed by appropriate work-up and purification gave the target molecule **15** (Scheme 5). It was fully characterized by spectral methods and elemental analysis. The high-field ^{13}C NMR spectrum is shown in Fig. 4.



Scheme 5

Another target molecule synthesized and submitted was the 2-acetonylnébularine **17**. The immediate precursor for **17** was the silylated 2-iodopurine nucleoside **11**. When this compound was heated in toluene in the presence of palladium chloride, tri-*o*-tolylphosphine, tri-*n*-butyltin methoxide, and isopropenyl acetate, good yields of the expected 2-acetonyl

Fig. 3. 90.6 MHz ^{13}C Spectrum of 2-(1,2-Dihydroxyethyl)inosine in DMSO-d_6

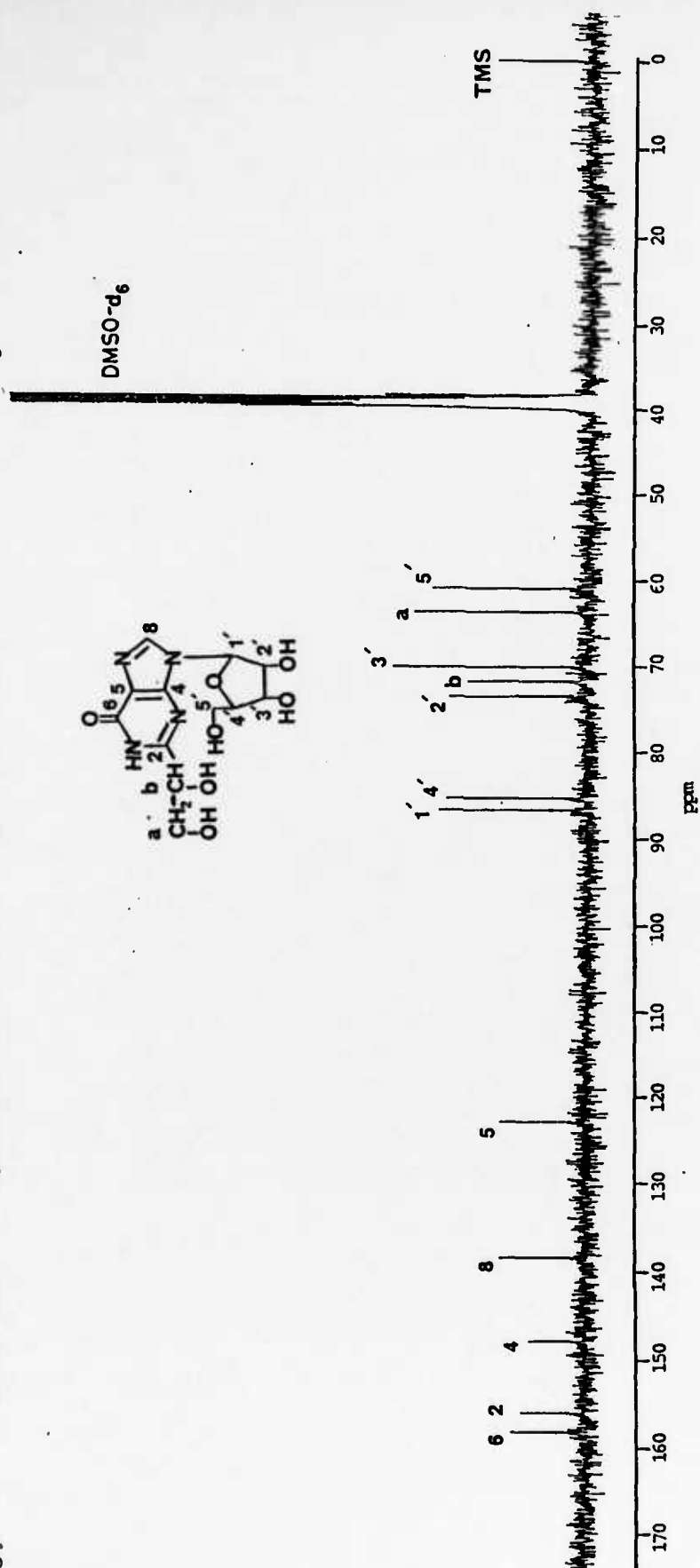
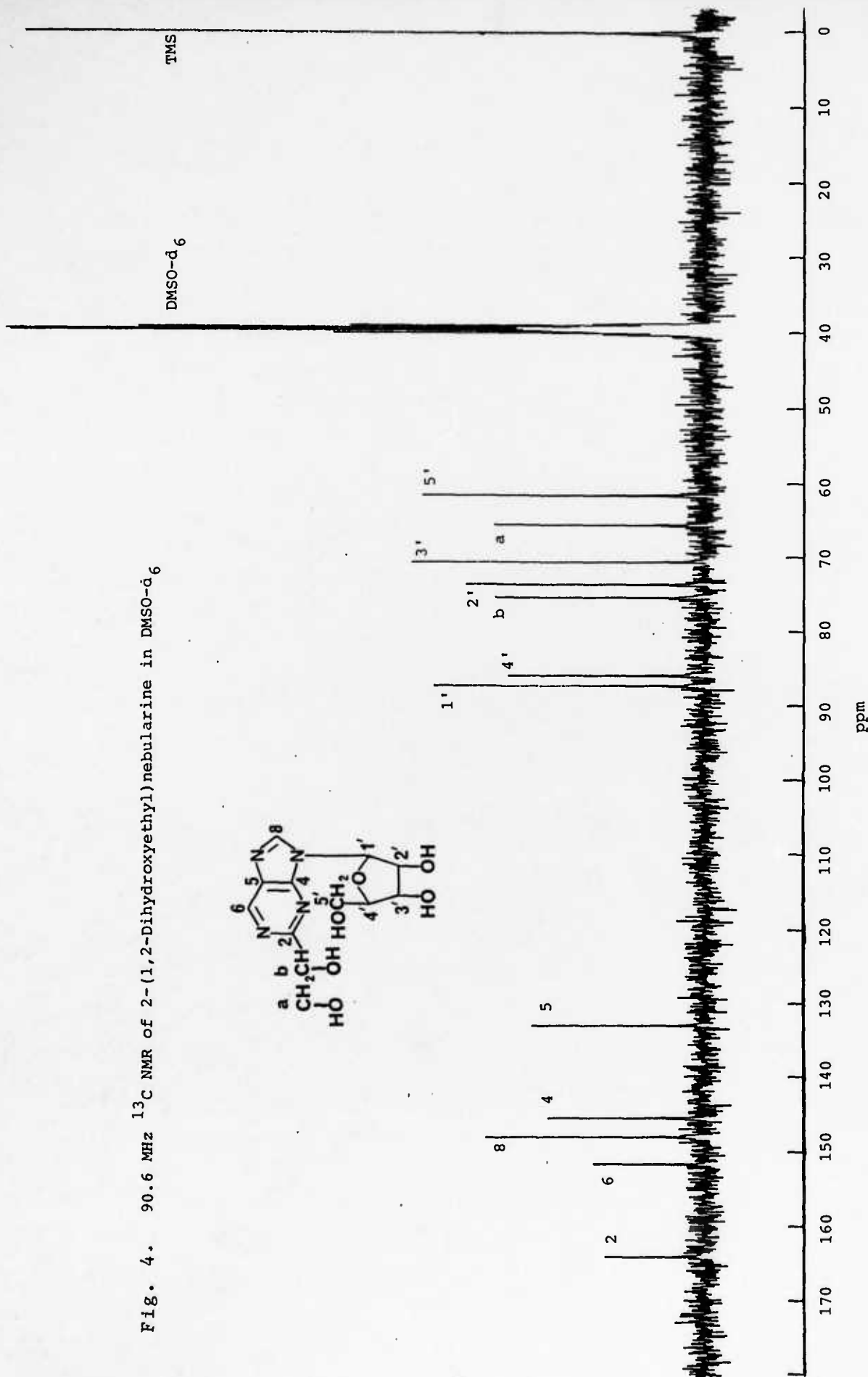
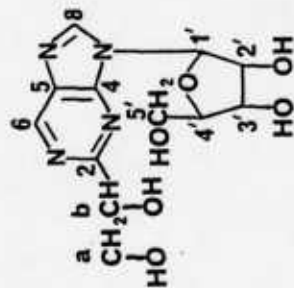
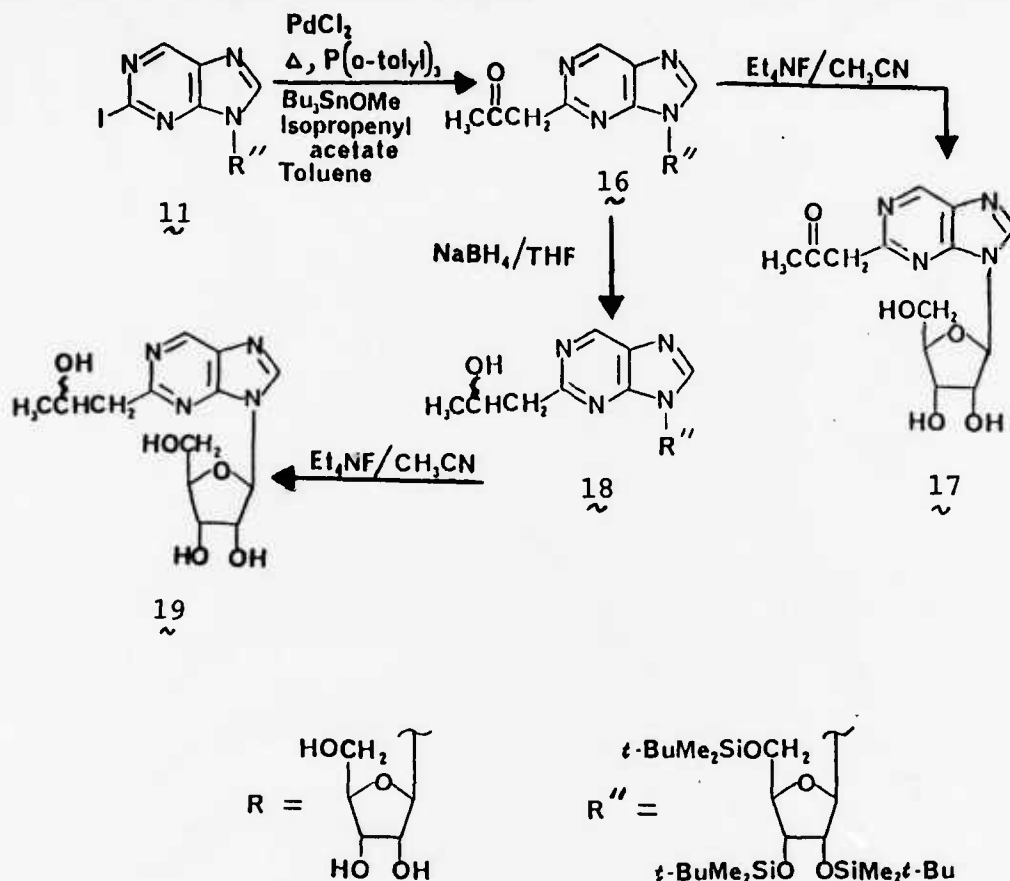


Fig. 4. 90.6 MHz ^{13}C NMR of 2-(1,2-Dihydroxyethyl)nebularine in $\text{DMSO}-d_6$



product **16** was obtained. Compound **16** was deprotected to the target molecule **17** with tetraethylammonium fluoride. The overall yield starting from guanosine was 6.0%. Reduction of the carbonyl functionality in **16** with sodium borohydride gave **18** in about 30% yield (Scheme 6). The reduction reaction proceeded sluggishly and considerable decomposition of the starting material occurred in this step. Deprotection of **18** gave the target diastereoisomeric alcohols **19**. The ketone **17** and the alcohols **19** were purified by HPLC (Amberlite XAD-4 resin) and fully characterized. The ^{13}C NMR spectra of **17** and **19** are shown in Figs. 5 and 6.



Scheme 6

Access to the rare functionalized inosine analogue, 2-(2-hydroxyethyl) inosine **22**, was made possible through the availability of the 2-vinyl compound **8**. This compound was first protected by silylation to give **20**, which was then treated with 9-borabicyclo[3.3.1]nonane (9-BBN). Oxidative work-up of the resulting organoborane gave the alcohol **21** in 52% yield. It should be mentioned that hydroboration reactions have rarely been used to elaborate structures in nucleoside chemistry. The above mentioned reaction was regiospecific and only one isomer was isolated. Deprotection of **21** with trimethylsilyl iodide in acetonitrile followed by treatment with

Fig. 5. 90.6 MHz ^{13}C NMR of 2-Acetylnebularine in DMSO-d_6

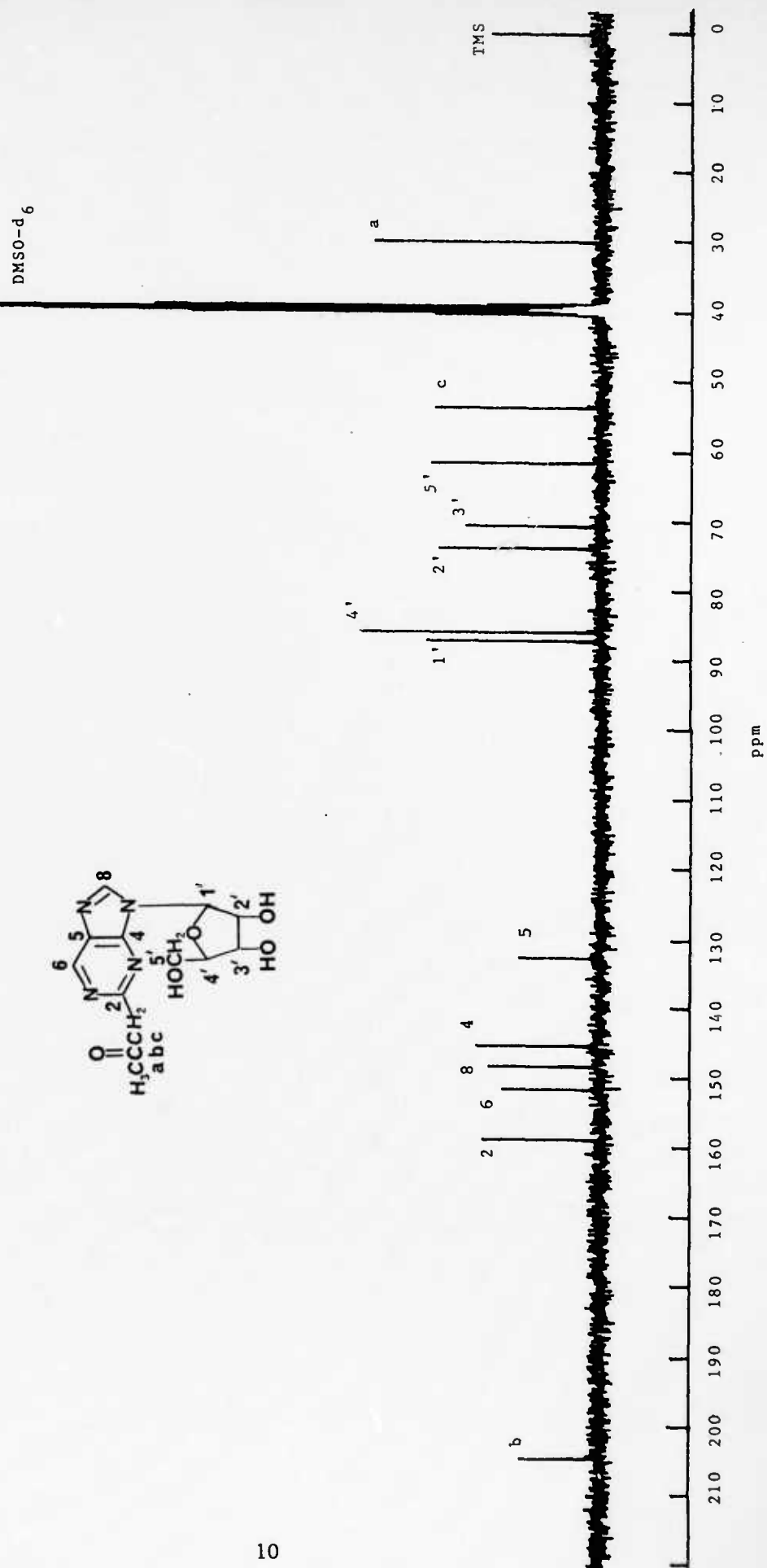
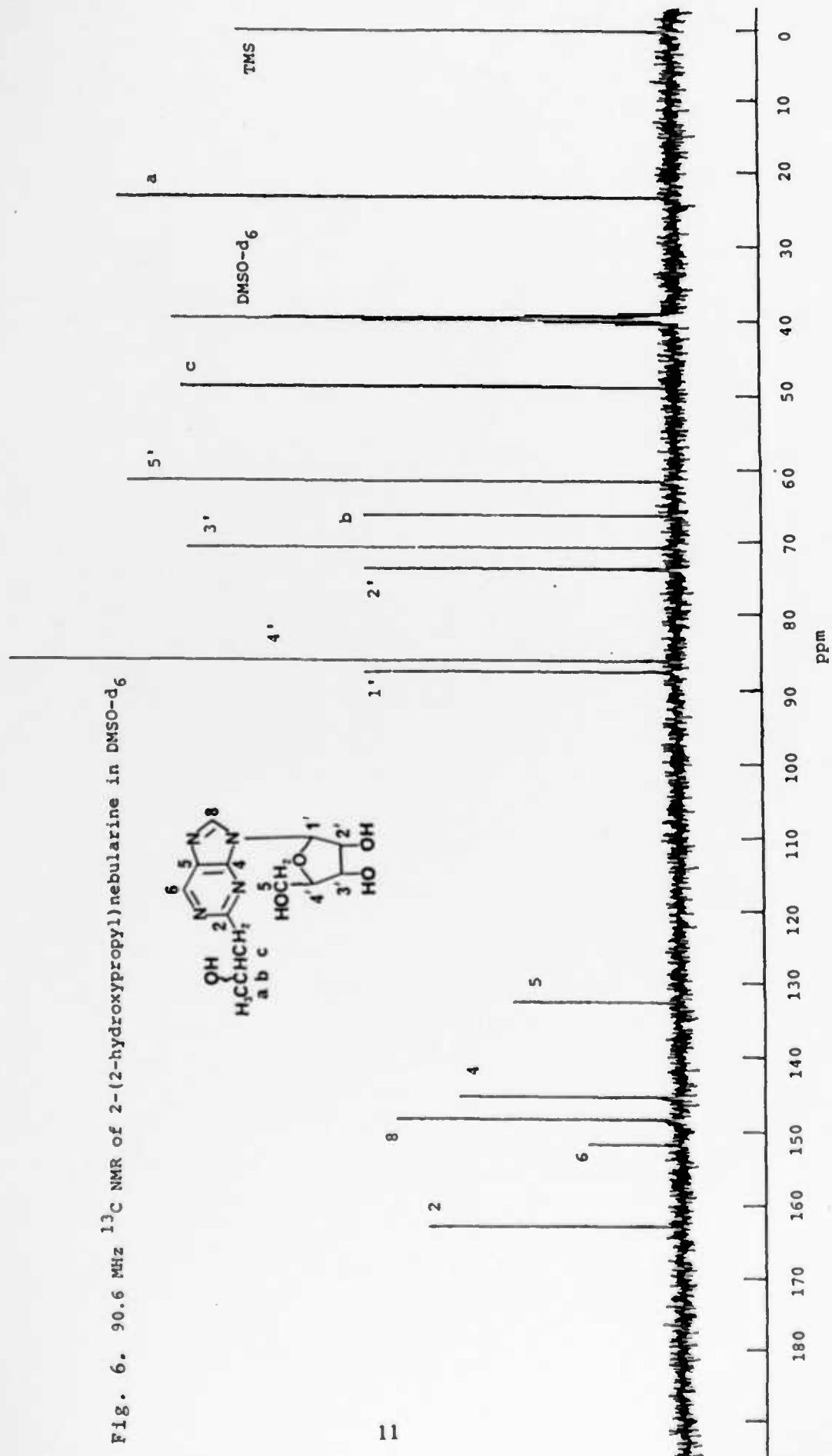
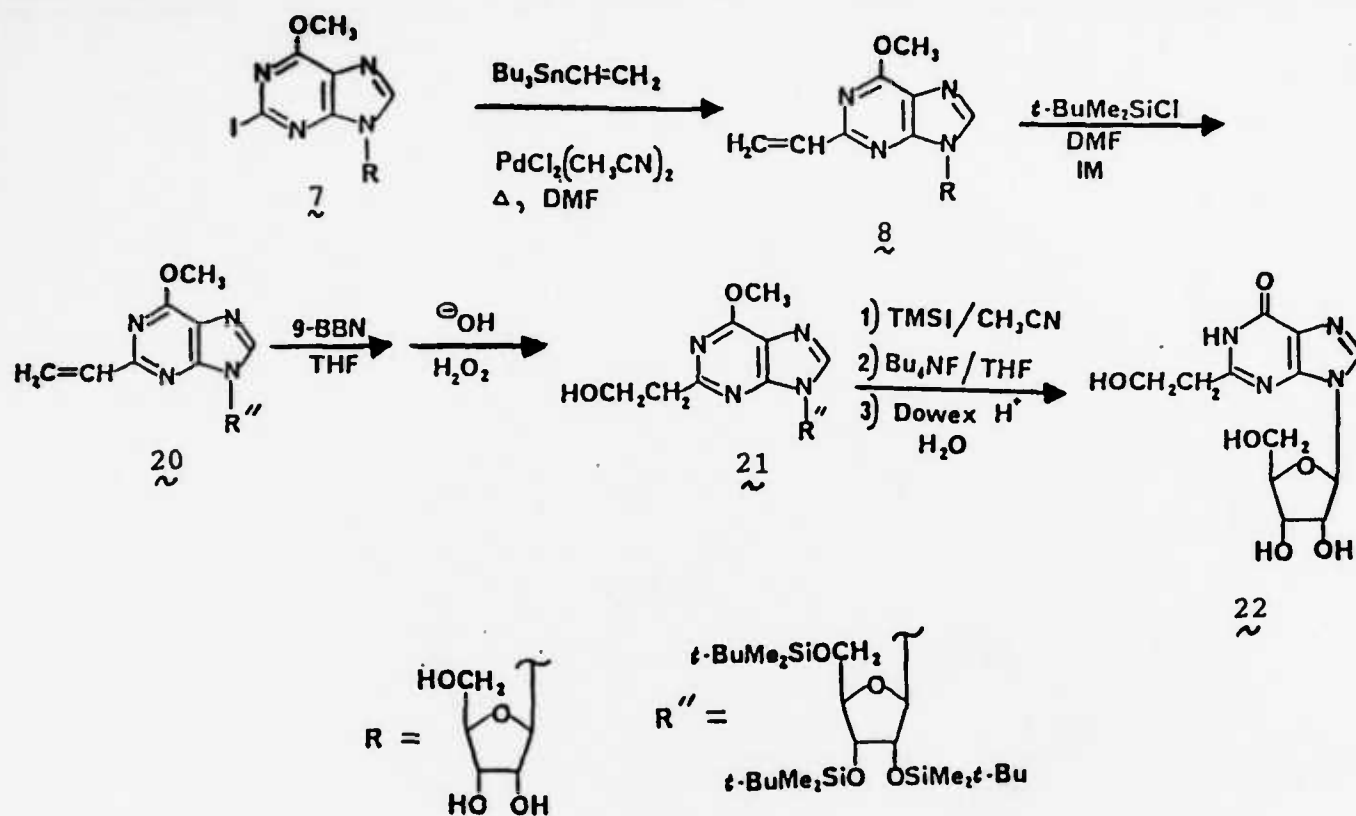


Fig. 6. 90.6 MHz ^{13}C NMR of 2-(2-hydroxypropyl)nebularine in $\text{DMSO}-d_6$



fluoride ions gave the target alcohol **22** (Scheme 7). Purification and characterization were carried out as described for other target compounds. The high-field ^{13}C NMR spectrum of **22** is enclosed (Fig. 7).



Scheme 7

In the last part of the second year of support, four compounds were submitted for antiviral evaluation. Two of the compounds, **23** and **24**, were prepared by deprotection of key halogenated intermediates used in the syntheses previously described in this report. The other two compounds were target ketones **25** and **26** in which special emphasis was placed because of the potent antiviral activity of another ketone, 2-acetylinoine, previously synthesized by us in this program.

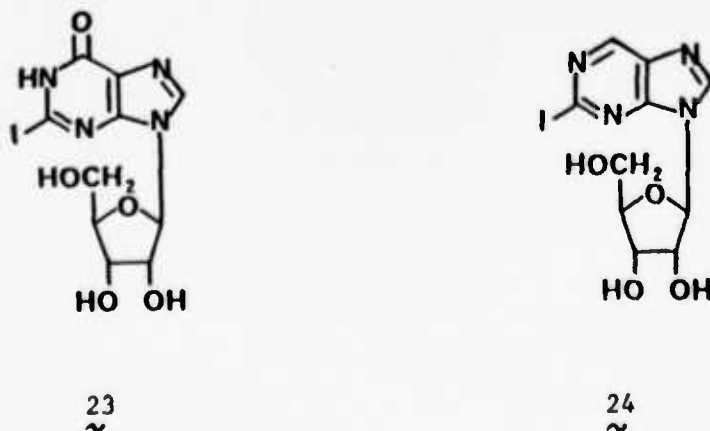
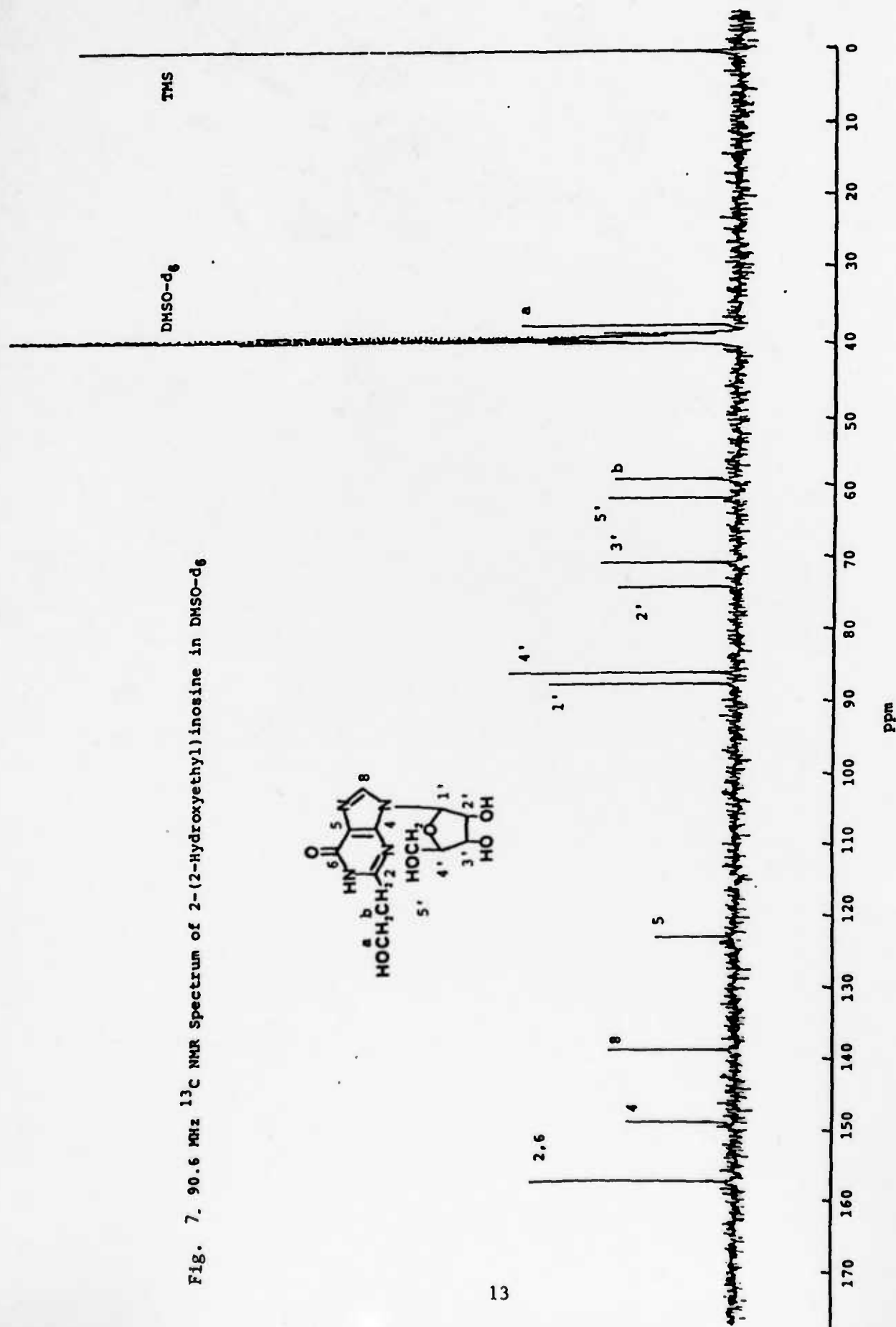
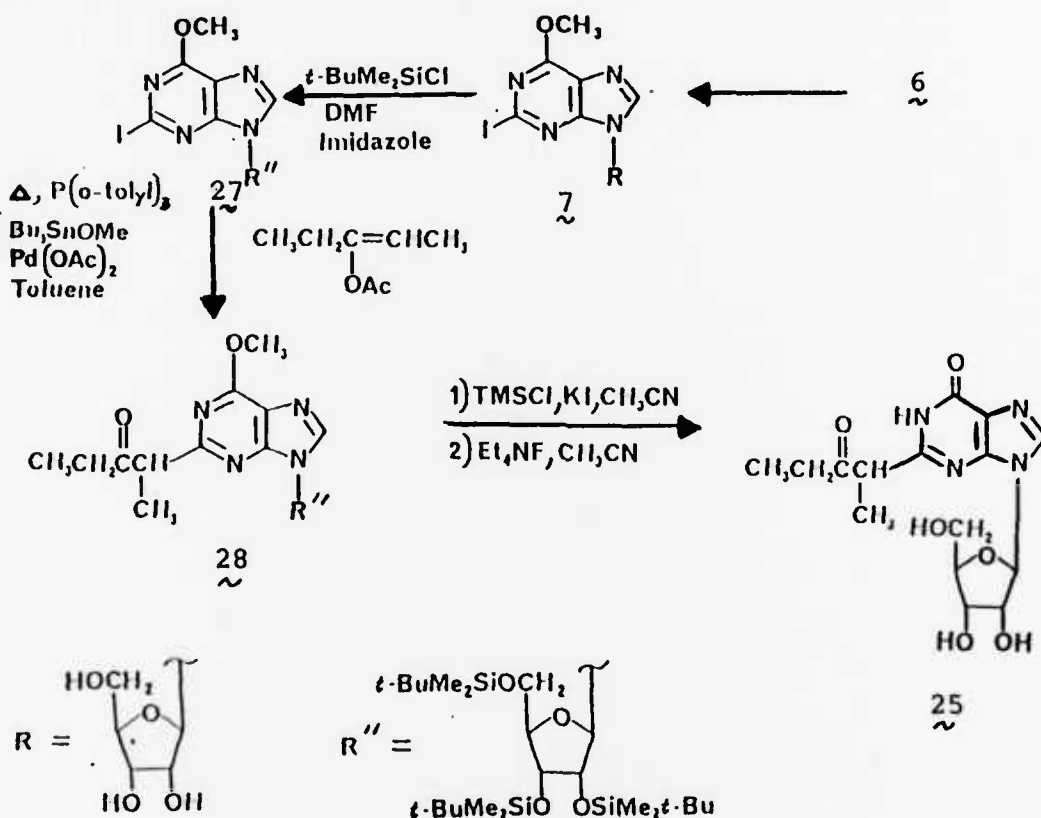


Fig. 7. 90.6 MHz ^{13}C NMR Spectrum of 2-(2-Hydroxyethyl)inosine in DMSO- d_6



The immediate precursor for the synthesis of the 2-ketoinosine **25** was the silylated 2-iodo compound **27**, prepared from 2-iodo-6-methoxypurine nucleoside **7** (see synthesis of **7** in Scheme 2). When compound **27** was heated under reflux in toluene with palladium acetate, tri-*o*-tolylphosphine, tri-*n*-butyltin methoxide, and 2-pentene-3-acetate, very good yields of the keto compound **28** was isolated. The latter was deprotected to the target molecule **25** in two steps, first by reaction with trimethylsilyl iodide and then with tetraethylammonium fluoride (Scheme 8). Target compound **25** was purified by reversed-phase HPLC. The overall yield of **25** starting from guanosine was 10.8 %. It was fully characterized by spectral methods and by high-resolution fast atom bombardment mass spectrometry (FAB HRMS). The high-field ^{13}C NMR spectrum is shown in Fig. 8.



Scheme 8

Synthesis of the ketonebularine **26** was achieved using the silylated 2-iodopurine nucleoside **11** as the immediate precursor. Compound **11** can be prepared in six steps from guanosine as previously presented in Scheme 3. The palladium-catalyzed cross-coupling reaction of **11** to give **29** was carried out as described above for the conversion of **27** to **28**. Excellent yields of product were obtained in this conversion. Deprotection of **29** (tetraethylammonium fluoride) followed by purification of the resulting material by HPLC, gave target molecule **26** (13.7% overall yield from guanosine). Compound **26** was fully characterized. The high-field ^{13}C NMR spectrum of **26** is shown in Fig. 9.

Fig. 8. 90.6 MHz ^{13}C NMR of 2-(1-Methyl-2-oxobutyl)-9-(β -D-ribofuranosyl)hypoxanthine in $\text{DMSO}-d_6$

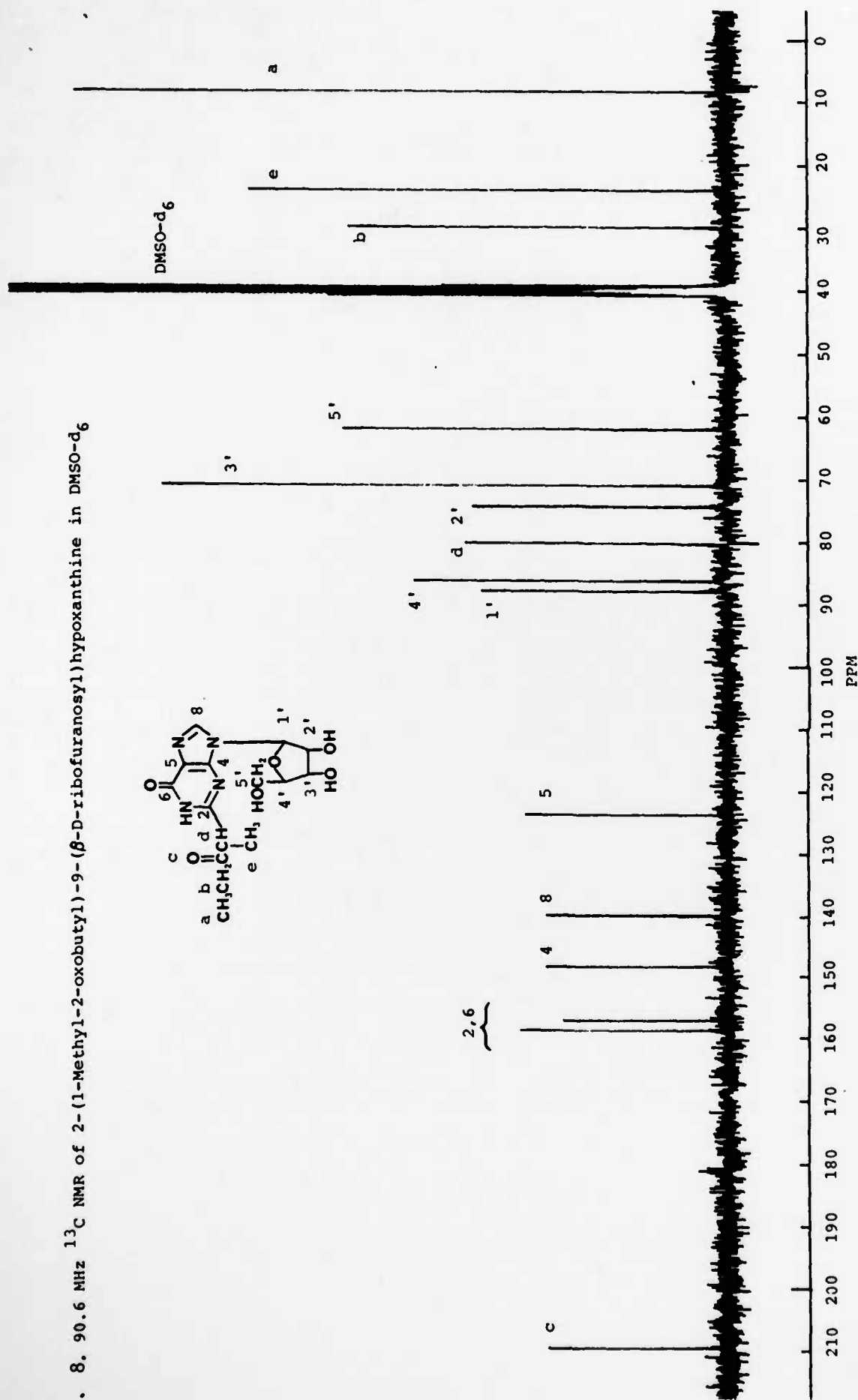
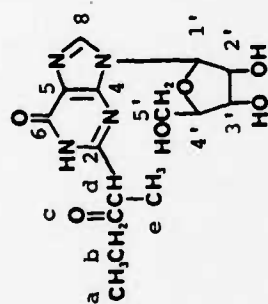
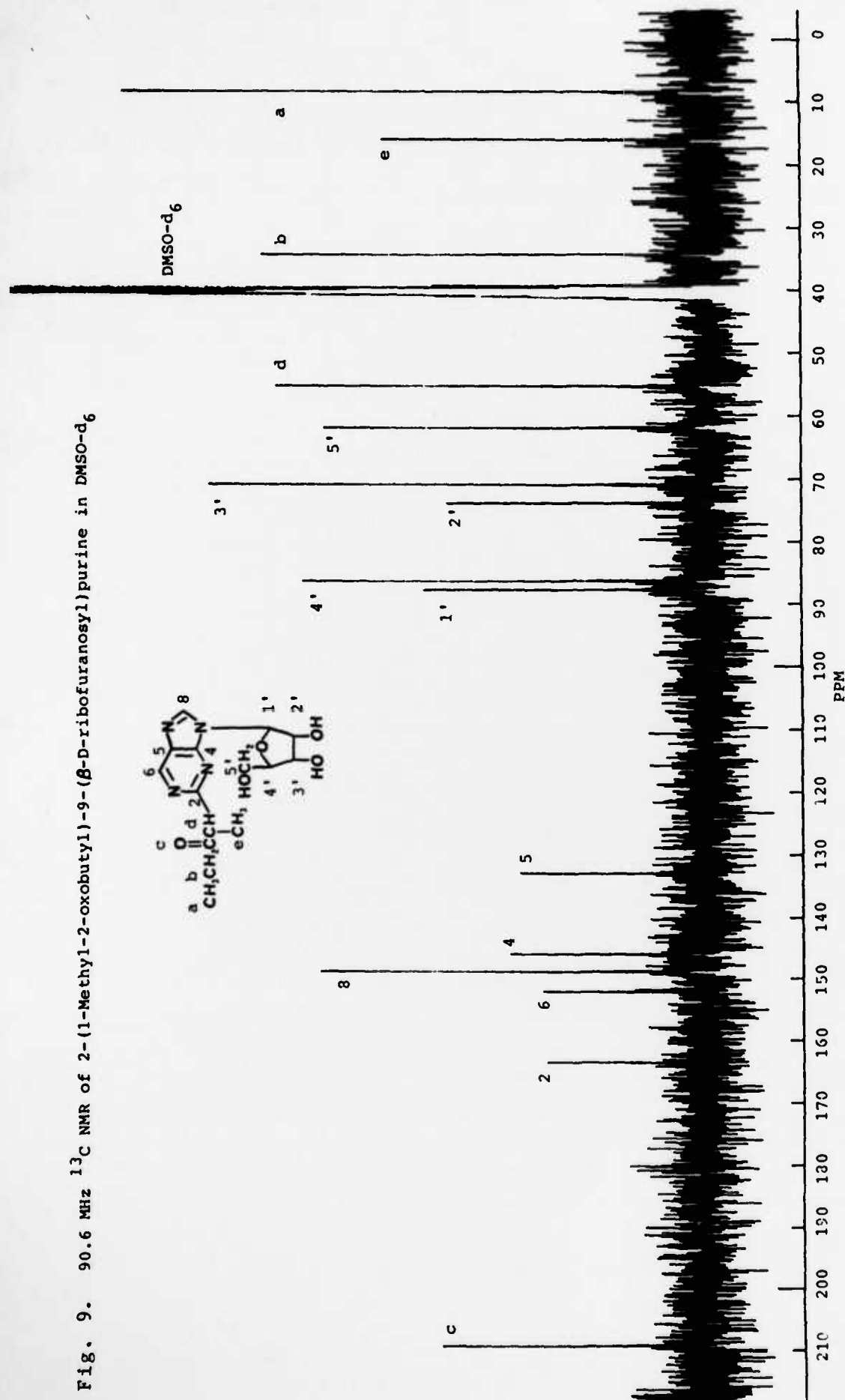
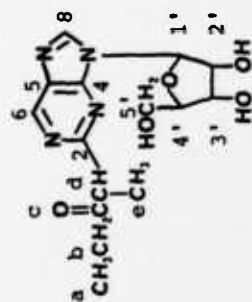
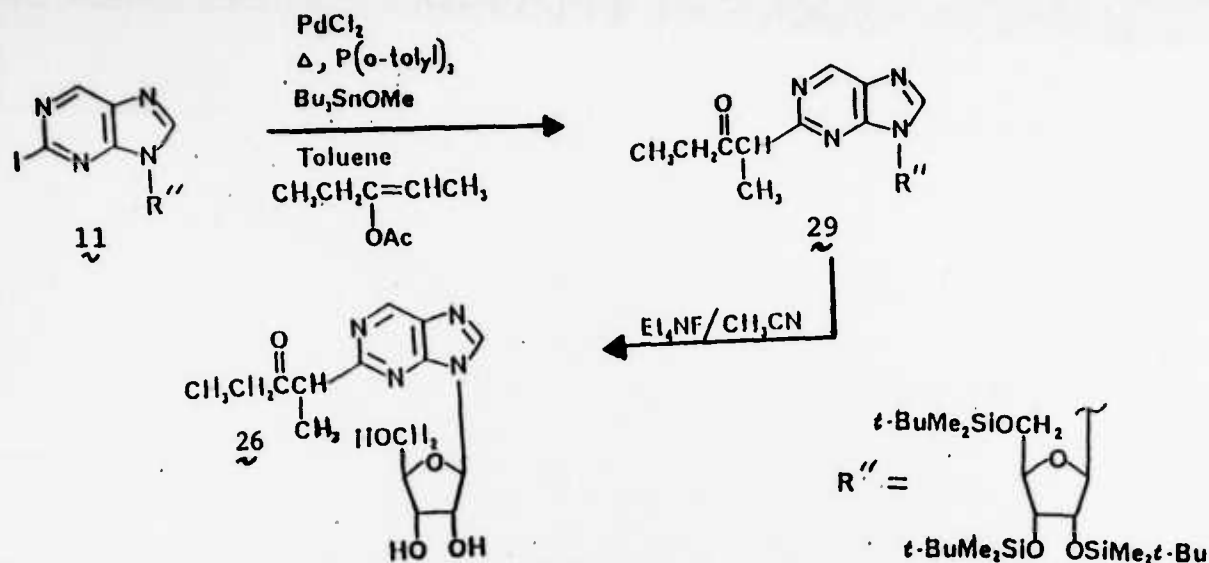


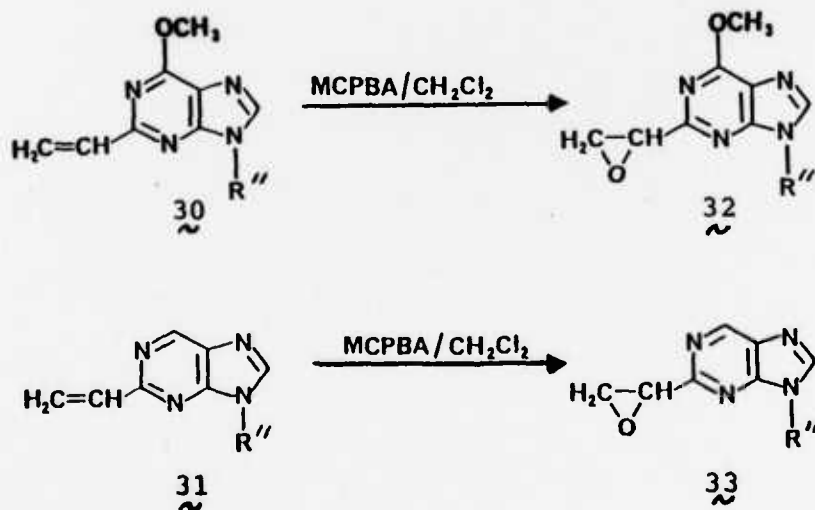
Fig. 9. 90.6 MHz ^{13}C NMR of 2-(1-Methyl-2-oxobutyl)-9-(β -D-ribofuranosyl)purine in DMSO-d_6





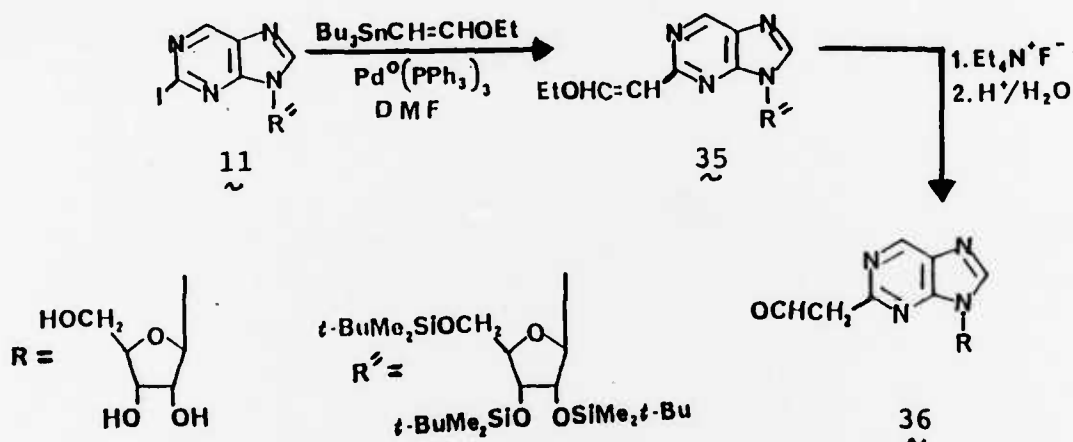
Scheme 9

Epoxy substituted purine nucleosides are very rare compounds and only one example of a purine system with an epoxy group at the 6-position is known (Nair and Chamberlain, *J. Am. Chem. Soc.* 1985, 107, 2183). The approach to the 2-epoxy compounds of the inosine and nebularine series was through the corresponding vinyl compound precursors (30 and 31) whose synthesis have been described previously in this report. Although epoxidation of these vinyl compounds appeared to have proceeded as expected to give the epoxides 32 and 33 (Scheme 10), isolation of the epoxide products was extremely difficult because of their inherent instability. Several different procedures for isolation and deprotection were attempted, but all were unsuccessful.

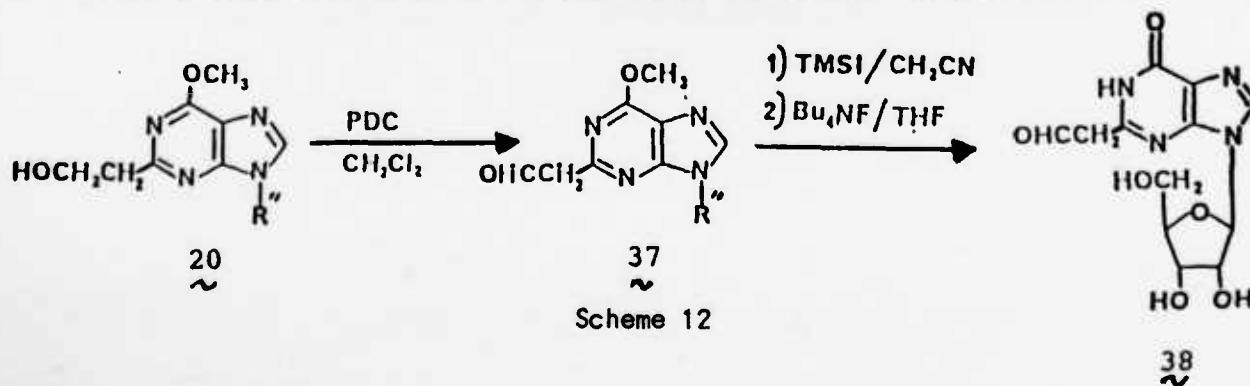


Scheme 10

During this second year of the contract, we have also been involved in the development of approaches to the synthesis of analogues of nebularine and inosine that contain aldehyde functionalized carbon-carbon bonding at the 2-position. The initial approach for the nebularine series was to synthesize the 2-(2-hydroxyethyl)purine system and selectively oxidize this primary hydroxyl group to the aldehyde. Although the synthetic procedure for the preparation of the 2-hydroxyethyl derivative of inosine had previously been developed by us, application of this (i.e. hydroboration followed by oxidative work-up) resulted in the formation of the 2-ethyl compound through reduction of the intermediate organoborane. An alternative procedure involved direct introduction of a masked aldehyde moiety at the C-2 position. This was achieved through the use of ethyl vinyltributyltin ether **34**. The organostannane **34** was prepared by the radical coupling of tributyltin hydride with ethyl ethynyl ether. Palladium-catalyzed coupling of the organostannane **34** with protected 2-iodopurine nucleoside **11** gave the (E)- and (Z)- mixture of the expected product **35** in about 70% yield (Scheme 11). We are currently working on the removal of the protecting groups from **35** which would give us the target molecule **36**.

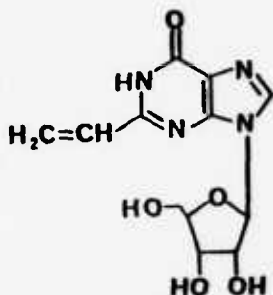


Synthesis of the protected aldehyde **37** through oxidation of **20** (a difficult reaction) was also successfully investigated. The deprotection step, which may pose some difficulties because of the sensitive nature of this aldehyde functionality, remains to be worked out (Scheme 12).



6. List of Target Compounds and Intermediates Submitted:

- (I) 2-Vinyl-9-(β -D-ribofuranosyl)hypoxanthine or 2-Vinylinosine



AVS Identifying No: AVS-002716

Contractor's Identifying Code No: VN-1-103

Report Reference: This Annual Report, Scheme 2

- (II) 2-Vinyl-9-(β -D-ribofuranosyl)purine or 2-Vinylnebularine

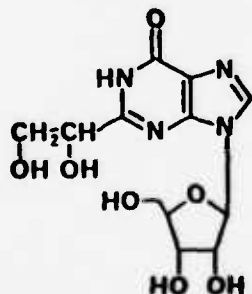


AVS Identifying No: AVS-002694

Contractor's Identifying Code No: VN-1-104

Report Reference: This Annual Report, Scheme 3

- (III) 2-(1,2-Dihydroxyethyl)-9-(β -D-ribofuranosyl)hypoxanthine or 2-(1,2-Dihydroxyethyl)inosine

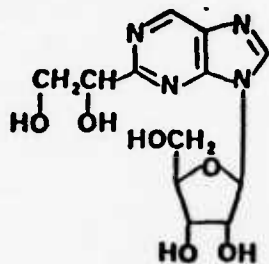


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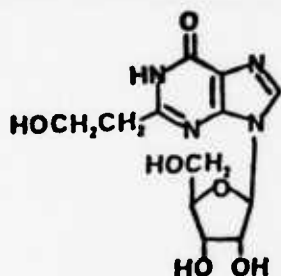
Report Reference: This Annual Report, Scheme 4

- (iv) 2-(1,2-Dihydroxyethyl)-9-(β -D-ribofuranosyl)purine or
2-(1,2-Dihydroxyethyl)nebularine



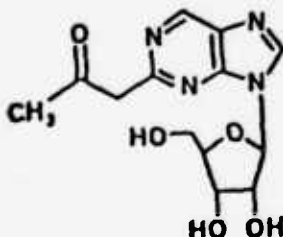
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Contractor's Identifying Code No: VN-1-106
Report Reference: This Annual Report, Scheme 5

- (v) 2-(2-Hydroxyethyl)-9-(β -D-ribofuranosyl)hypoxanthine or
2-(2-Hydroxyethyl)inosine



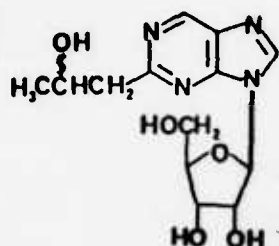
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Contractor's Identifying Code No: VN-1-107
Report Reference: This Annual Report, Scheme 7

- (vi) 2-Acetyl-9-(β -D-ribofuranosyl)purine or 2-Acetylnebularine



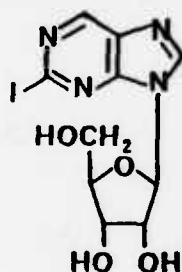
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Contractor's Identifying Code No: VN-1-108
Report Reference: This Annual Report, Scheme 6

- (vii) 2-(2-Hydroxypropyl)-9-(β -D-ribofuranosyl)purine or 2-(2-Hydroxypropyl)nebularine



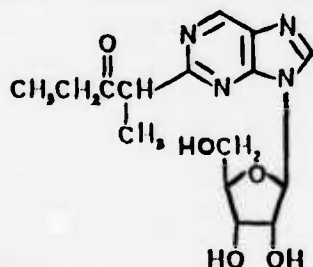
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Report Reference: This Report, Scheme 6

- (viii) 2-Iodo-9-(β -D-ribofuranosyl)purine or 2-Iodonebularine (Intermediate)



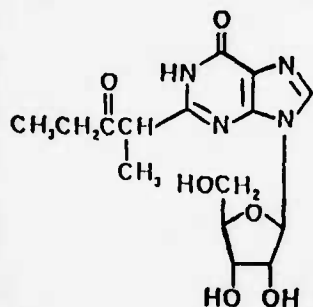
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Contractor's Identifying Code No: VN-I-110
Report Reference: This Annual Report, Scheme 3

- (ix) 2-(1-Methyl-2-oxobutyl)-9-(β -D-ribofuranosyl)purine



AVS Identifying No: AVS-003924
Contractor's Identifying Code No: VN-I-111
Report Reference: This Annual Report, Scheme 9

(x) 2-(1-Methyl-2-oxobutyl)-9-(β -D-ribofuranosyl)hypoxanthine

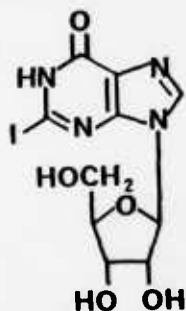


AVS Identifying No: AVS-003921

Contractor's Identifying Code No: VN-I-112

Report Reference: This Annual Report, Scheme 8

(xi) 2-Iodo-9-(β -D-ribofuranosyl)hypoxanthine or 2-Iodoinosine



AVS Identifying No: AVS-003922

Contractor's Identifying Code No: VN-I-113

Report Reference: This Annual Report, Scheme 2

7. Antiviral Screening Data:

AVS Identifying Number
Contractor's Code Number

Antiviral Drug Screening
Data

AVS-002159
VN-I-101

Very active, specific
TI >1000 (in vitro, SF)
HIV results not available
Toxic in CCHF suckling mouse

AVS-002352
VN-I-102

Some activity against YF
Not active against VSV, AD2, VV,
HIV, SF, JE in vitro
in vivo data not available

AVS-002716
VN-I-103

Some broad spectrum activity
(in vitro) against YF, JE,
AD2, VV, PT, RVF, not active
against VEE, VSV, HIV
in vivo data not available

AVS-002694
VN-I-104

Not active (in vitro)
in vivo data not available

AVS-002695
VN-I-105

Not active (in vitro)
in vivo data not available

AVS-002883
VN-I-106

Some activity against RVF
Not active (in vitro)
against other viruses
HIV results not available
in vivo data not available

AVS-002884
VN-I-107

Some activity against RVF
Not active (in vitro)
against other viruses
HIV results not available
in vivo data not available

AVS-003039
VN-I-108

Not active against AD2, JE,
VSV, VV, RVF

AVS-003582
VN-I-109

Screening data not available

AVS-003923
VN-I-110

Screening data not available

AVS-003924
VN-I-111

Screening data not available

AVS-003921
VN-I-112

Screening data not available

AVS-003922
VN-I-113

Screening data not available

8. Bibliography of Publications, Patents, and Presentations:

- (i) V. Nair, D. A. Young, and R. DeSilvia, Jr., 2-Halogenated Purine Nucleosides: Synthesis and Reactivity, Journal of Organic Chemistry, 1987, 52, 1344 (4 copies furnished to SGRD-RMS).
- (ii) V. Nair, D. A. Young, and R. DeSilvia, Jr., 2-Amino-9-(β -D-ribofuranosyl)purine. Photoinduced Reductive Dehalogenation: A General Approach to 2-Aminopurine and Related Systems, An Invited Article In "Nucleic Acid Chemistry", Part 4, Edited by L. B. Townsend and R. S. Tipson, 1987 (4 copies furnished to SGRD-RMS).
- (iii) V. Nair, S. D. Chamberlain, R. DeSilvia, Jr., and G. S. Buenger, Synthetic Approaches to Rare 2-Substituted Purine Nucleosides, Nucleosides and Nucleotides, 1987, 6, 229 (4 copies furnished to SGRD-RMS).
- (iv) V. Nair and D. A. Young, Conformational Correlation of Purine Nucleosides by High-Field Carbon-13 NMR Data, Magnetic Resonance in Chemistry, 1987, 25, 937 (4 copies furnished to SGRD-RMS).
- (v) V. Nair, G. A. Turner, and S. D. Chamberlain, Novel Approaches to Functionalized Nucleosides via Palladium-Catalyzed Cross-Coupling with Organostannanes, Journal of the American Chemical Society, 1987, 109, 7223 (4 copies furnished to SGRD-RMS).
- (vi) V. Nair, Alkylated Inosines as Antiviral Agents, Patent Serial Number 67,498 filed with U. S. Patent Office, June 1987.
- (vii) V. Nair, D. A. Young, S. D. Chamberlain, and G. S. Buenger, 2-Aminopurine Nucleosides: Synthesis, Biological Activity, and Reactivity, 21st Midwest Regional Meeting of the American Chemical Society, Kansas City, Missouri, November, 1986.
- (viii) V. Nair, G. A. Turner, G. S. Buenger, and A. G. Lyons, Synthetic Approaches to New, Biologically-Active Purine Nucleosides, 194th National Meeting of the American Chemical Society, New Orleans, Louisiana, September, 1987.
- (ix) V. Nair and G. S. Buenger, Novel 2-Substituted Purine Nucleosides, 99th Session of the Iowa Academy of Science, Grinnell, Iowa, April 1987.
- (x) V. Nair and A. G. Lyons, Functionalization of Inosine, 99th Session of the Iowa Academy of Science, Grinnell, Iowa, April, 1987.

- (xi) V. Nair, Rare 2-Substituted Purine Nucleosides, USAMRIID Department of Antiviral Studies Program Review, August, 1987.
- (xii) V. Nair, Eight Invited Research Seminars on "The Search for New Antiviral Compounds: Rare 2-Substituted Purine Nucleosides", presented at major Universities in Sydney, Melbourne, and Adelaide, Australia, July, 1987, as part of an Award as Distinguished Visiting Professor/Scholar.

9. Personnel Supported:

Gregory A. Turner, Graduate Student, Ph.D. Degree, May 1987
Greg S. Buenger, Graduate Student
Arthur G. Lyons, Graduate Student
Brian J. Hettrick, Graduate Student

10. Summary:

In the second year of this contract, we have had considerable success in our synthetic work and a total of eleven rare 2-substituted purine nucleosides (nine target compounds and two intermediates) were synthesized, purified, characterized, and submitted to the Department of Antiviral Studies. Our progress on this contract is now right on schedule. Although screening data are not available as yet on several of the compounds submitted, some very interesting and positive data have been received. One compound (2-acetonylinosine, AVS-002159) has been found to have very high activity ($TI > 1000$) against the Sandfly Fever Virus (Phlebovirus). Another compound (2-vinylinosine, AVS-002716) has been found to have low but broad spectrum activity against a number of RNA viruses. Two other compounds (AVS-002883 and AVS-002884) have shown some activity against the Rift Valley Fever Virus, and still another (AVS-002352) has shown activity against the Yellow Fever Virus. Five publications have appeared in 1987 on this work. In addition, a patent has been filed on some of the inosine analogues synthesized. Various aspects of the synthetic work have also been presented as invited and contributed papers and research seminars at regional, national, and international scientific meetings and occasions.

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