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SRI-ORG-KM-90-128-6000-XVII

SYNTHESIS LABORATORY FOR THE U. S. ARMY MEDICAL RESEARCH INSTITUTE OF INFECTIOUS DISEASES SELECTION PANEL

ANNUAL PROGRESS REPORT

John A. Secrist III
Cecil D. Kwong
Charles A. Krauth
Angela G. Ford
Yajnanarayana H. R. Jois
Deborah A. Carter
Lisa K. Hanna
George S. McCaleb

FEBRUARY 5, 1990
(For the period 1 December 1988 - 30 November 1989)

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, MD 21701-5012

Contract No. DAMD17-86-C-6011

SOUTHERN RESEARCH INSTITUTE
2000 Ninth Avenue South
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Birmingham, Alabama 35255-5305

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SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION
Unclassified

1b. RESTRICTIVE MARKINGS

2a. SECURITY CLASSIFICATION AUTHORITY

3. DISTRIBUTION / AVAILABILITY OF REPORT
Distribution authorized to U. S. Government Agencies only; Proprietary Information February 1990 ATTN: SGRD-RMI-S

2b. DECLASSIFICATION / DOWNGRADING SCHEDULE

4. PERFORMING ORGANIZATION REPORT NUMBER(S)
SRI-ORG-KM-90-128-6000-XVII

5. MONITORING ORGANIZATION REPORT NUMBER(S)

6a. NAME OF PERFORMING ORGANIZATION
Southern Research Institute

6b. OFFICE SYMBOL (If applicable)

7a. NAME OF MONITORING ORGANIZATION

6c. ADDRESS (City, State, and ZIP Code)
2000 Ninth Avenue South
P. O. Box 55305
Birmingham, AL 35255-5305

7b. ADDRESS (City, State, and ZIP Code)

8a. NAME OF FUNDING / SPONSORING ORGANIZATION
U. S. Army Med. Research & Develop. Com.

8b. OFFICE SYMBOL (If applicable)

9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
Contract Number DAMD17-86-C-6011

8c. ADDRESS (City, State, and ZIP Code)
Fort Detrick
Frederick, MD 21701-5012

10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
63002A	3M2 63002D807	AD	064

11. TITLE (Include Security Classification)
Synthesis Laboratory for the U. S. Army Medical Research Institute of Infectious Diseases Selection Panel

12. PERSONAL AUTHOR(S) John A. Secrist III, Cecil D. Kwong, Charles A. Krauth, Angela G. Ford, Yajnanarayana H. R. Jois, Deborah A. Carter, George S. McCaleb, and Lisa K. Hanna

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Annual Report	FROM 12-1-88 TO 11-30-89	1990, February 5	50

16. SUPPLEMENTARY NOTATION

17. COSATI CODES		
FIELD	GROUP	SUB-GROUP
07	03	
06	15	

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
antiviral; synthesis laboratory; imidazole; adenosine; adenosine N^1-oxides; benzyloxyadenosines; tetraazadiphosphorines; selenadiazoles; triazolotriazoles; guanidines; pyrazoles; adamantanecarboxamides; adamantylthioureas; RAI

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

A synthesis laboratory has been established for the preparation of compounds to be evaluated against viruses of interest to U. S. Army Medical Research Institute of Infectious Diseases. The synthesis of known compounds as well as new compounds has been undertaken, and all compounds are being made in sufficient quantity to allow for full evaluation. Among the compounds prepared thus far are 1-benzyloxyadenosines, 9-substituted 1-benzyloxyadenines, 1,2,4,5,3,6-tetraazadiphosphorines, substituted imidazoles, selenadiazoles, triazoles, triazolotriazoles, guanidines, pyrazoles, adamantane derivatives, chloroquines, N^1-aminonucleosides, allopurinol acyclonucleosides, nucleotides of ribavirin and tiazofurin, and various other heterocyclic compounds. Keywords: antiviral agents (AT)

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT
☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS

21. ABSTRACT SECURITY CLASSIFICATION
Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL
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22c. OFFICE SYMBOL
SGRD-RMI-S

DD Form 1473, JUN 86 Previous editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE
Unclassified

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FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

Introduction

This report summarizes the activities supported by Contract No. DAMD17-86-C-6011 during Quarters 12-15 from 1 December 1988 through 30 November 1989. The purpose of this contract is to support the synthesis of a wide variety of compounds for evaluation in the USAMRIID viral screening program. These compounds will include: (1) known compounds that are needed in larger quantities for proper evaluation; and (2) new compounds whose structures have been determined by rational processes.

During this year, we submitted 33 more compounds for screening. Most of these were analogs of compounds that we either selected from the USAMRIID list of active antiviral compounds or found in our searches of the literature. We also synthesized and submitted a number of other compounds which had been specifically requested by Major Ussery or Dr. Gabrielsen. Thus far, we have addressed all but 2 of the compounds specifically requested by Major Ussery. We have also addressed 8 of the 12 compounds requested by Dr. Gabrielsen and we are actively synthesizing the remainder of these compounds. We are also preliminarily investigating a number of other compounds that we have discussed with Dr. Gabrielsen.

Personnel

During the year covered by this report, we have had the following personnel changes: Ms. Lisa K. Hanna has been working part-time since the end of the thirteenth quarter. Ms. Deborah A. Carter has been dividing her efforts between this project and another SRI project. Dr. Robert N. Comber temporarily joined us during the thirteenth and fourteenth quarters to synthesize a compound that was of interest to Dr. Gabrielsen.

The time charges made during the fourth year are listed below and are divided into various categories.

Name	Hours 1 Dec 88 - 30 Nov 89	Percent of Time
Project Supervision:		
Dr. J. A. Secrist III	194.5	11
Chemists:		
Dr. C. D. Kwong	1616.5	87
C. A. Krauth	1699.5	93
D. A. Carter	1582.5	85
G. S. McCaleb	1572.0	88
L. K. Hanna	1484.0	79
Dr. R. N. Comber	180.0	10
R. J. Gray	18.0	1
R. J. Remy	1.0	
Analytical Services:		
Dr. W. C. Coburn	147.75	8
Dr. J. M. Riordan	186.0	10
M. C. Kirk	264.5	14
C. Richards	227.5	13
M. D. Ochs	206.0	11
S. A. Campbell	12.0	1
A. D. Williams	20.0	1

Name	Hours 1 Dec 88 - 30 Nov 89	Percent of Time
Analytical Services: (cont'd)		
A. A. Beaty	21.5	1
L. M. Rose	11.0	1
D. M. McCain	105.0	6
Glassware Technicians:		
W. Johnson	133.0	7
J. Crow Robinson	398.5	22
A. Jackson	308.0	17

Compounds Submitted

The compounds that we submitted during the year for this annual report are shown on the following pages, in their approximate order of delivery. Our SRI numbers, AVS numbers (when available), and the amounts submitted are listed with each of these compounds. Of course, we can make additional quantities of any of these compounds, if warranted.

Chemistry

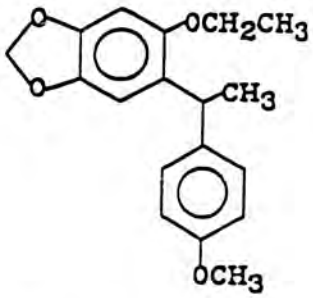
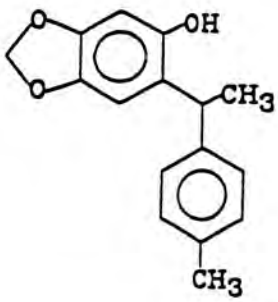
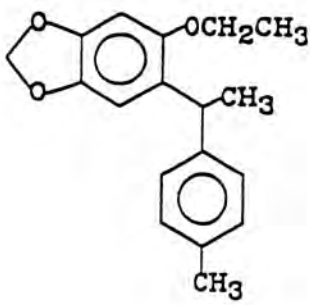
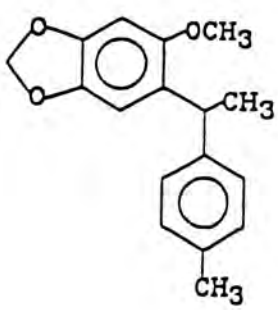
During this year, we continued to synthesize analogs of compounds which were either selected from the USAMRIID list of active antiviral compounds or found in the literature. Compound classes that we investigated include: N^1-benzyloxyadenosines [AVS-2875, 1986, 3679, 3607, 2911, and 4224]; 6-benzyl-1,3-dioxoles (as podophyllotoxin and Justicidin B analogs); 3-phenyl-1,4-benzothiazin-2-one oximes; and methanesulfonic acid derivatives. Other compounds that we synthesized include: formycin B 2',3',5'-triacetate [AVS-0096]; the free acid of ribavirin monophosphate; 1-ribofuranosyl-7-cyanoimidazo[1,2-*b*]pyrazole; 6-allylmercaptopurine riboside; 6-ethylmercaptopurine riboside [AVS-2700]; 4-amino-1-β-D-ribofuranosyl-pyrazolo[3,4-*d*]pyrimidine; 3-*t*-butyl-1-adamantylthiourea; 9-(2-phosphonylmethoxyethyl)adenine (PMEA); 5-(1,3-dihydroxy-2-propoxy)-4-hydroxy-1,2-pyrazole-3-carboxamide; N^1-aminoadenosine mesitylenesulfonate salt; and adenosine 5'-diethylthiocarbamate.

Scheme I shows the approa nes used to synthesize the six N^1-benzyloxyadenosines submitted this year (including multiple batches of AVS-2875 and 3679). As with the previously submitted N^1-benzyloxyadenosines, adenosine-N^1-oxide (**2**) was the precursor for compounds **3a-e**, and it was prepared by oxidizing adenosine (**1**) with *m*-chloroperbenzoic acid.[1-3] Alkylation of adenosine-N^1-oxide with appropriately substituted benzyl bromides gave the corresponding 1-benzyloxyadenosines which were then treated with ammonium perchlorate and isolated as their respective perchlorate salts **3a-e**. Since the procedures used to make these compounds were virtually identical, we have provided only the detailed procedure for the synthesis of 1-(2-cyanobenzyloxy)adenosine (**3f**) in the experimental section. No detailed synthetic procedures will be presented for compounds **3a-e**.

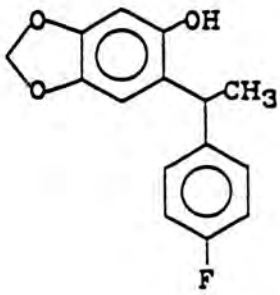
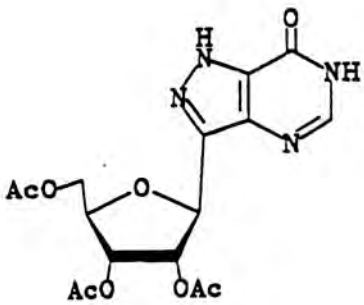
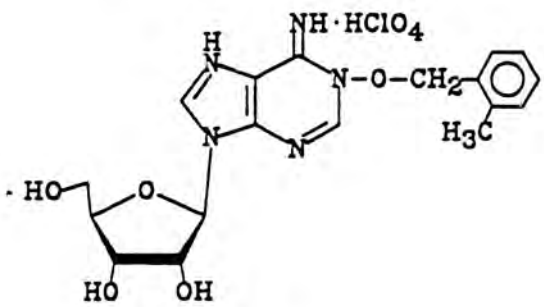
As shown in Scheme II and III, we synthesized nine 6-benzyl-1,3-dioxole derivatives[4] this year to complete a series of compounds that had been started last year. These structural analogs of podophyllotoxin and Justicidin B were selected, because they were bioactive compounds with antitumor

Compounds Submitted

December 1, 1988 to February 28, 1989

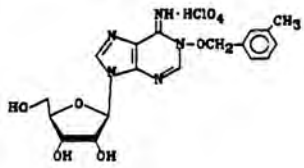
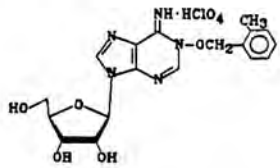
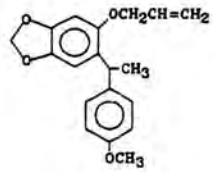
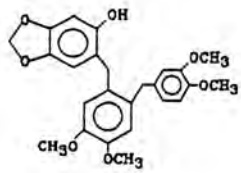
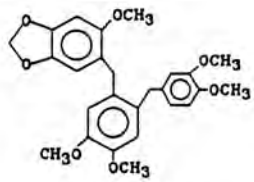
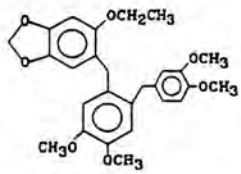
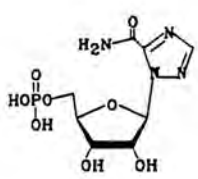
Compound	SoRI Number	AVS Number	Amount Submitted
	7369		1.2 g
	7370		1.2 g
	7371		1.2 g
	7372		1.2 g

Compounds Submitted (continued)

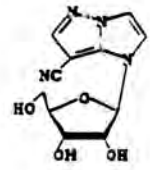
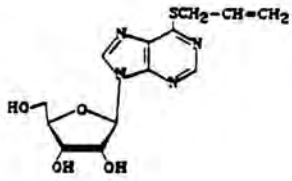
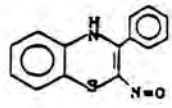
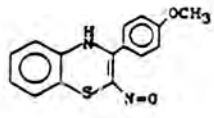
Compound	SoRI Number	AVS Number	Amount Submitted
	7373		1.2 g
	7367		5.0 g
	6887	002875	50 mg

Compounds Submitted

(March 1, 1988 - May 31, 1989)

Compound	SRI Number	AVS Number	Amount Submitted
	6767	001986	100 mg
	6887	002875	100 mg
	7394		700 mg
	7393		1.2 g
	7395		1.2 g
	7396		1.2 g
	7398		105 mg

Compounds Submitted - (continued)

Compound	SRI Number	AVS Number	Amount Submitted
$ClCH_2SO_2OCH_2CH_2CH_2CH_2OSO_2CH_2Cl$	6362		1 g
$CH_3SO_2CH_2SO_2OCH_2CH_2CH_2CH_2OSO_2CH_2SO_2CH_3$	6363		1 g
$ClCH_2SO_2OCH_2CH_2CH_2CH_2OSO_2CH_3$	6440		1 g
$CH_3SO_2CH_2SO_2OCH_2CH_2CH_2CH_2OSO_2CH_3$	6441		1 g
	7259		2 g
	1214		500 mg
	7426		2 g
	7427		1.2 g

Compounds Submitted - (continued)

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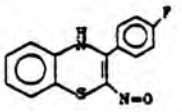
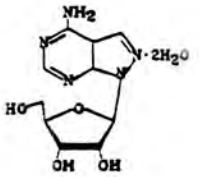
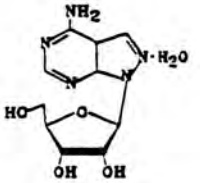
	7428		1.2 g
	7429		3 g
	7430		0.7 g

Compounds Submitted

(June 1, 1989 - August 31, 1989)

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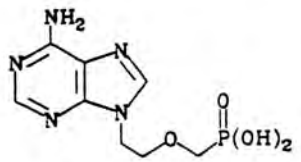	7496		1.9 g

Compounds Submitted

(September 1, 1989 - November 30, 1989)

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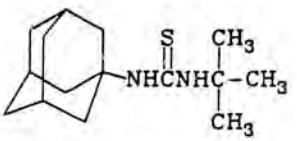
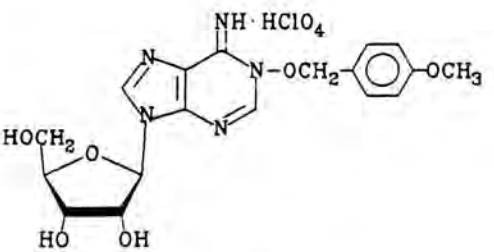
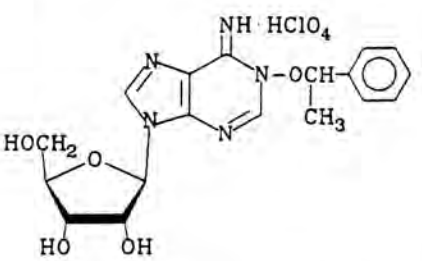
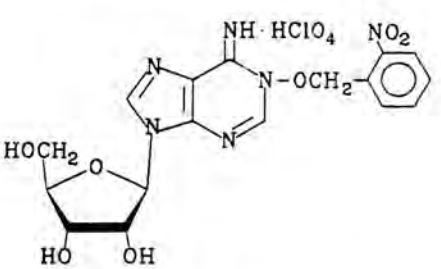
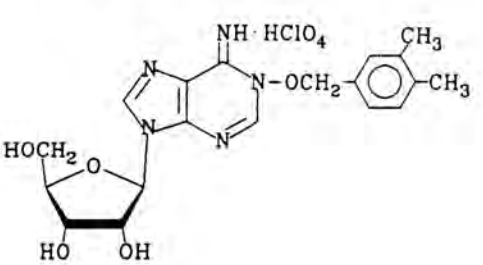
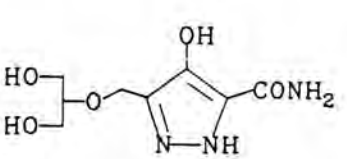
	6892	2885	3.3 g
	7037	3679	5.0 g
	7008	3607	2.0
	6927	2911	2.0 g
	7168	4224	2.0 g
	7494		90 mg

Compounds Submitted - (continued)

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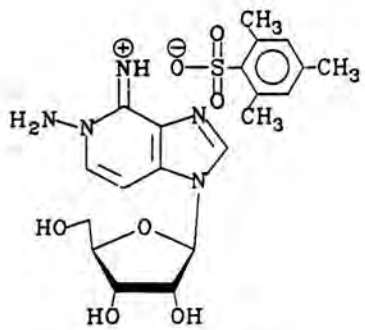
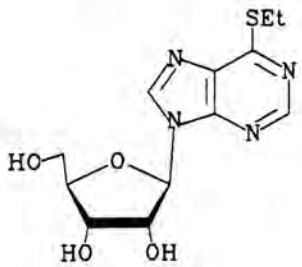
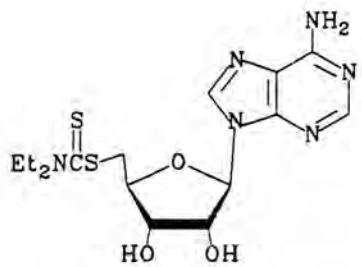
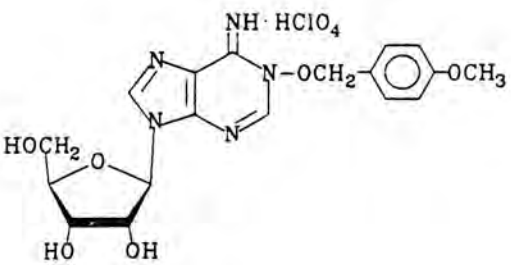
	7194	4588	2.0 g
	1215	2700	5.0 g
	7208	4618	2.0 g
	7037	3679 (second batch)	2.5 g

activity against the *in vivo* i.p. P388 murine lymphocytic leukemia. During this year, we synthesized **8b-c** as well as **9a-d**. The syntheses of compounds **8b-c** first required the synthesis of the appropriately substituted benzyl alcohols **5b-c** from the corresponding acetophenones. Then, **8b-c** were synthesized by condensing sesamol with benzyl alcohols **5b-c**, respectively. We also synthesized derivatives **9a-d** by alkylating previously synthesized **8a-b** with the appropriate alkyl bromides. Three other derivatives were also synthesized. As shown in Scheme III, compound **11** was obtained instead of the expected benzyldioxole **13** when we condensed sesamol (**6**) with 3,4-dimethoxybenzyl alcohol **10**. Ether derivatives **12a** and **b** were obtained by alkylating with either methyl iodide or ethyl iodide.

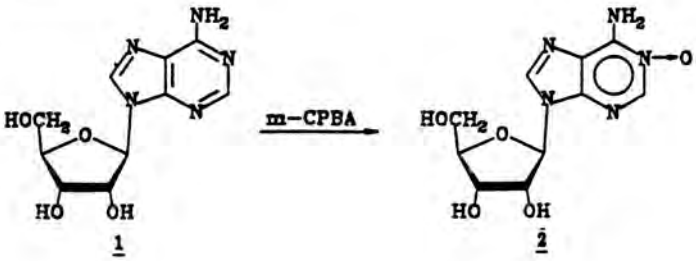
Three 3-phenyl-1,4-benzothiazin-2-one oximes were synthesized by the procedure shown in Scheme IV. Because our early attempts to reproduce the methods in the literature[5-7] (the conversion of appropriately substituted benzaldehydes via the corresponding nitrostyrenes to nitroacetophenone) were not successful, we developed another approach to these compounds. The appropriately substituted α-chloroacetophenones **13a-c** were first treated with *n*-butylnitrite and HCl[8,9] to give chloronitroso compounds **14a-c**. These intermediates was then reacted with 2-aminothiophenol to give the target phenylbenzothiazinone oximes **15a-c**.

We also submitted four methanesulfonic acid derivatives **18a-b** and **23a-b**[10-13] which had been synthesized as analogs of busulfan (**16**), a compound that is biologically active against Friend Leukemia virus.[14] As shown in Scheme V, compounds **18a** and **b** were synthesized by reacting the corresponding chloromethanesulfonyl chloride or (methylsulfonyl)methanesulfonyl chloride with 1,4-butanediol and triethylamine in ethyl acetate. Similarly, compounds **23a-b** were synthesized by reacting 4-benzyloxybutanol **20** (prepared by the method of Pistor[13]) with methanesulfonyl chloride to give intermediate **21**. This intermediate was catalytically hydrogenated to give 4-methylsulfonyloxybutanol **22**. Compound **22** was then immediately reacted with either chloromethanesulfonyl chloride or (methylsulfonyl)methanesulfonyl chloride to give **23a** and **b**.

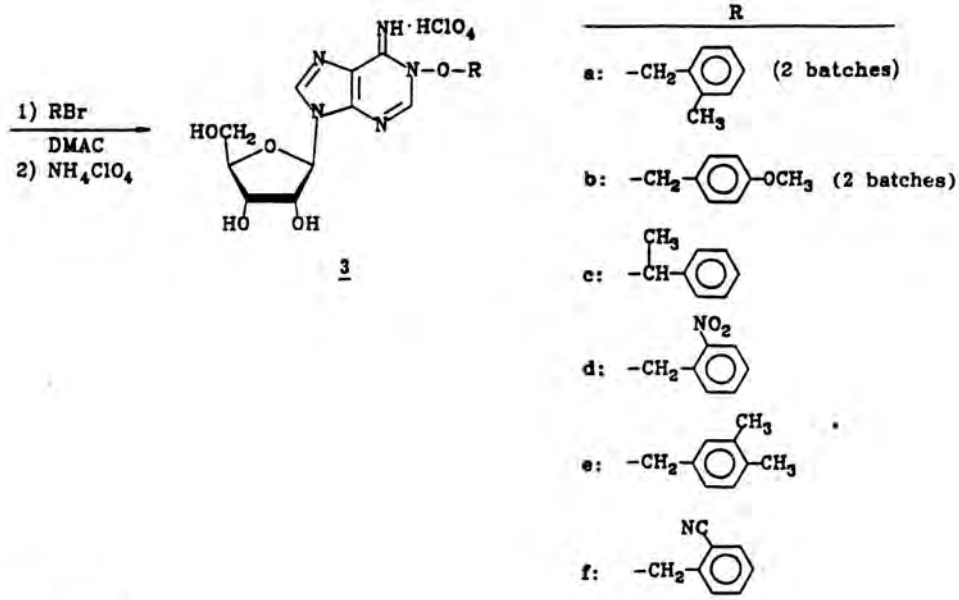
Other compounds submitted this year include: formycin B 2′,3′,5′-triacetate; the free acid of ribavirin monophosphate; 1-ribofuranosyl-7-cyanoimidazo[1,2-*b*]pyrazole, 6-allylmercaptopurine riboside; 6-ethylmercaptopurine riboside; 4-amino-1-β-D-ribofuranosyl-pyrazolo[3,4-*d*]pyrimidine; 3-*t*-butyl-1-adamantylthiourea; 9-(2-phosphonylmethoxyethyl)adenine (PMEA); 5-(1,3-dihydroxy-2-propoxy)-4-hydroxy-1,2-pyrazole-3-carboxamide; N^1-aminoadenosine mesitylenesulfonate; and adenosine 5′-diethylthiocarbamate.

Formycin B 2′,3′,5′-triacetate (**34**) was synthesized by adding acetic anhydride and pyridine to formycin B (**33**) which had been previously synthesized by the procedure shown in Scheme VI.[15,16] Ribofuranose 1-acetate-2,3,5-tribenzoate (**24**) was converted to cyanoester intermediate **29** by the following series of reactions. Ribofuranose **24** was treated with HBr and $Hg(CN)_2$ giving 1-cyanosugar **25**. Hydrolysis of **25** followed by treatment with thionyl chloride gave acid chloride **26**. This intermediate was then treated with HCN followed by ylide **28**, to give cyanoester **29**. (Ylide **28** was generated from *t*-butylacetyl-triphenylphosphorane HCl **27** with 10% sodium hydroxide in chloroform. Triphenylphosphorane HCl **27** was synthesized from chloroacetic acid and isobutene by treatment with sulfuric acid in benzene followed by triphenylphosphine.) Cyclization of cyanoester **29** with ethyl diazoacetate gave the ribosylated pyrazole

Scheme I

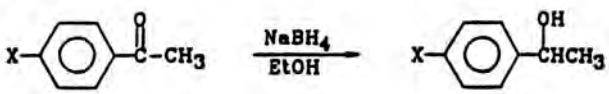


1 2



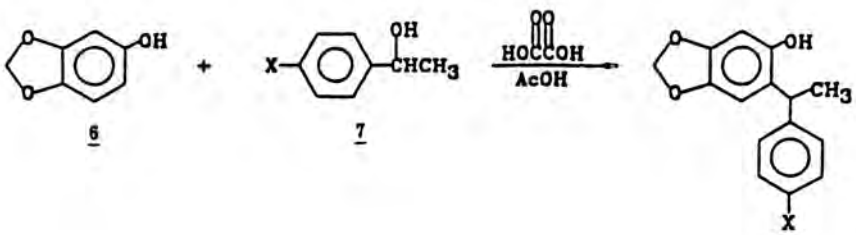
3

Scheme II



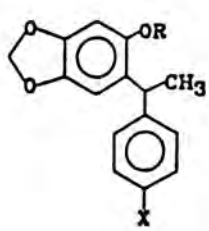
4 5

a) X = $-OCH_3$
b) X = $-CH_3$
c) X = $-F$



6 7 8

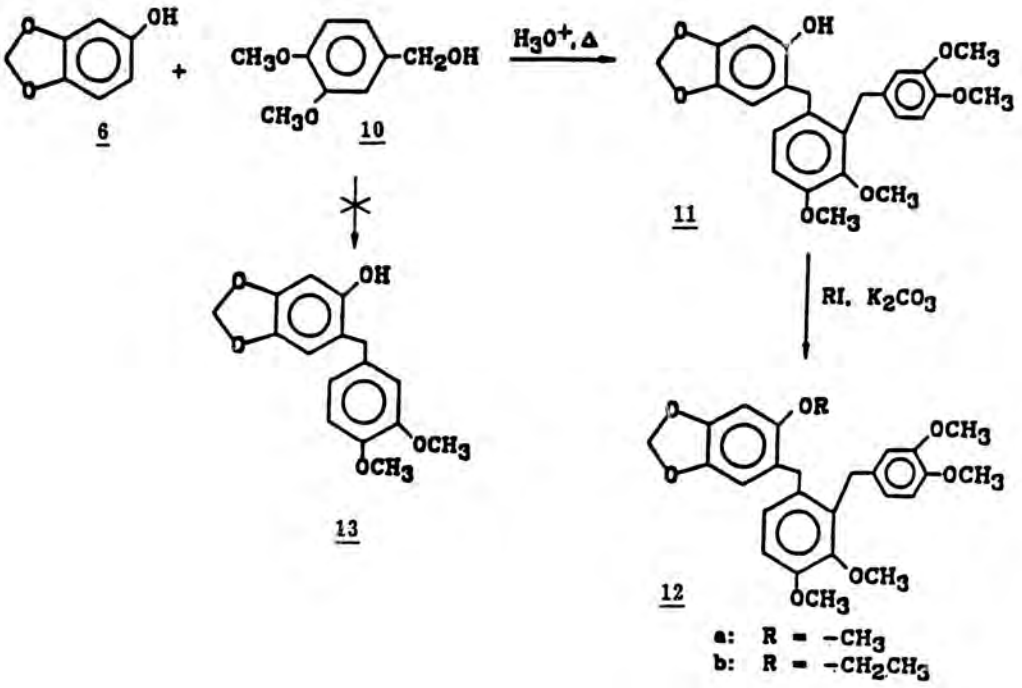
a) X = $-OCH_3$
b) X = $-CH_3$
c) X = $-F$



9

a) X = $-OCH_3$, R = $-Et$
b) X = $-CH_3$, R = $-CH_3$
c) X = $-CH_3$, R = $-Et$
d) X = $-OCH_3$, R = $-CH_2-CH=CH_2$

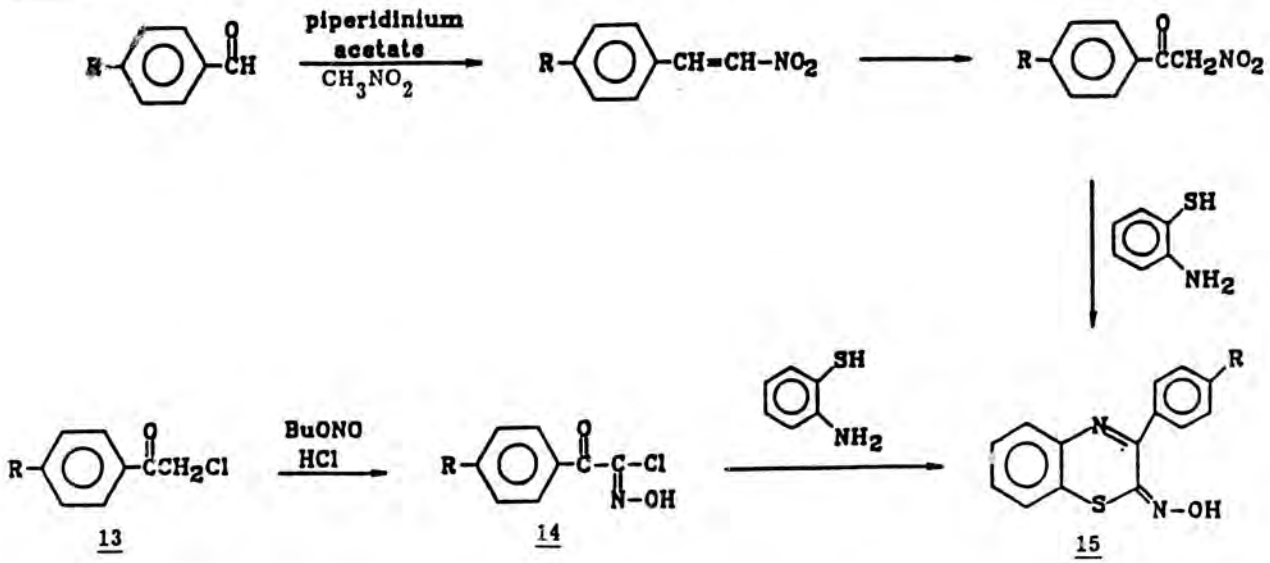
Scheme III



6 10 11 13 12

a: R = $-CH_3$
b: R = $-CH_2CH_3$

Scheme IV



13 14 15

a: R = H
b: R = F
c: R = OCH_3

Scheme V

busulfan, 16

1. RSO_2Cl + $HO(CH_2)_4OH$ → $RSO_2O(CH_2)_4OSO_2R$

17 18

a: R = $ClCH_2$–
b: R = $CH_3SO_2CH_2$–

2. ϕCH_2Cl + $HO(CH_2)_4OH$ $\xrightarrow[\Delta]{NaOH}$ $\phi CH_2O(CH_2)_4OH$

19 20

$\phi CH_2O(CH_2)_4OH$ $\xrightarrow[EtOAc]{Et_3N,\ CH_3SO_2Cl}$ $\phi CH_2O(CH_2)_4OSO_2CH_3$

21

$\phi CH_2O(CH_2)_4OSO_2CH_3$ $\xrightarrow[EtOAc]{H_2,\ Pd/C}$ $HO(CH_2)_4OSO_2CH_3$

22

$HO(CH_2)_4OSO_2CH_3$ $\xrightarrow[EtOAc]{Et_3N,\ RSO_2Cl}$ $RSO_2O(CH_2)_4OSO_2CH_3$

23

a: R = $ClCH_2$–
b: R = $CH_3SO_2CH_2$–

Scheme VI

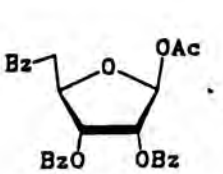
$ClCH_2COOH$ + $CH_3C(=CH_2)CH_3$ $\xrightarrow[H_2SO_4]{\phi H}$ $\xrightarrow[\phi NMe_2]{\phi_3P}$ $\phi_3\overset{\oplus}{P}-CH_2\overset{O}{\overset{\|}{C}}-O-C(CH_3)_3$ $Cl^{\ominus}$

27

$\xrightarrow[10\%\ NaOH]{CHCl_3}$

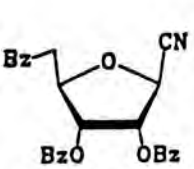
$\phi_3P{=}CH\overset{O}{\overset{\|}{C}}OC(CH_3)_3$

28



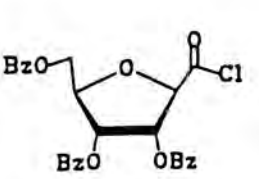
24

1) HBr, ϕCH_3
2) $Hg(CN)_2$



25

$\xrightarrow[\Delta]{HOAc,\ HCl}$ $\xrightarrow[\Delta]{SOCl_2,\ DMF}$



26

$\xrightarrow[0\ °C]{28,\ HCN}$

ring of Formycin B, thus giving pyrazolediester **30**. Sequential treatment of this intermediate with formic acid followed by 2,2,2-trichloroethanol, triethylamine, and diphenylphosphoryl azide gave carbamoyl ester **31**. Further treatment with zinc/acetic acid, and formamidine acetate effected cyclization, forming the necessary pyrimidine ring, thus giving 2′,3′,5′-tribenzoylated Formycin B (**32**). Deprotection with sodium methoxide in methanol to give Formycin B (**33**). Acetylation of **33** then gave the desired triacetate **34**.

The nucleoside of 7-cyanoimidazo[1,2-*b*]pyrazole (**40**)[17,18] was made by the procedure shown in Scheme VII. 2-Hydrazinoacetaldehyde diethylacetal (**35**) was made from hydrazine and chloroacetaldehyde diethylacetal. Reaction of diethylacetal (**35**) with ethoxymethylenemalononitrile gave 5-amino-1,3-(2,2-diethoxyethyl)-pyrazole-4-carbonitrile (**36**), which was cyclized to imidazolo-[1,2-*b*]pyrazole-7-carbonitrile (**37**) by treatment with 1 *N* HCl. Pyrazolecarbonitrile **37** was then ribosylated with 1-*O*-acetyl-2,3,5-tribenzoyl-D-ribofuranose and HMDS, giving a product mixture containing both protected nucleoside **38** and the isomeric nucleoside **39**. Chromatographic isolation of compound **38** followed by deprotection with methanolic ammonia gave the desired compound **40**.

Both 6-allylmercaptopurine riboside (**42a**) and the additional quantity of 6-ethylmercaptopurine riboside [AVS-2700] (**42b**) were prepared as shown in Scheme VIII. 6-Mercaptopurine riboside (**41**) was alkylated with either allyl bromide or ethyl bromide in DMAC and potassium carbonate to give these nucleoside analogs.[19,20]

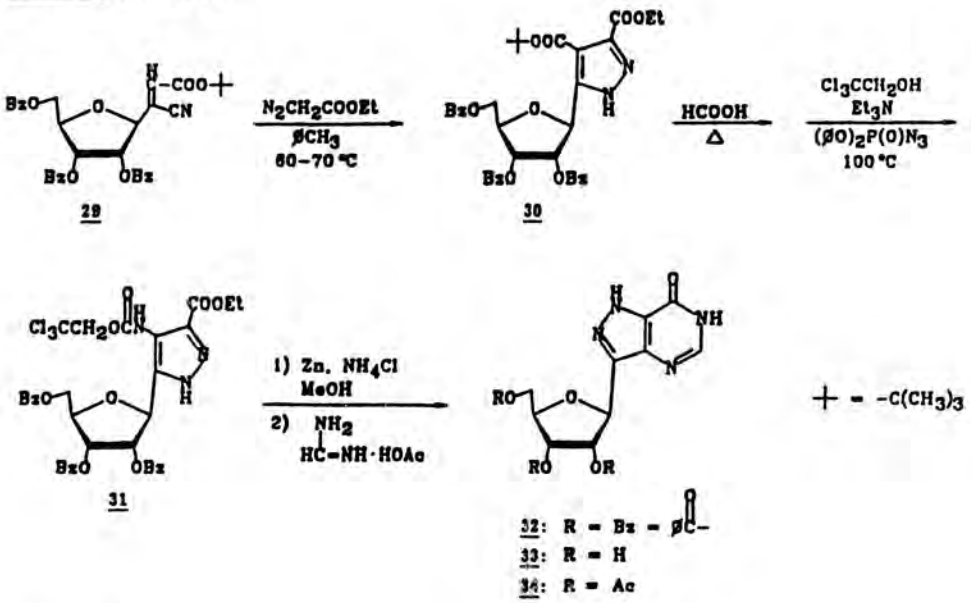
We were able to synthesize 4-amino-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (**48**)[21,22] by two similar approaches. Scheme IX shows the first approach in which allopurinol (**43**) was 3-brominated and then ribosylated with ribofuranose-1-acetate-2,3,5-tribenzoate to give protected nucleoside **45**. Thionyl chloride in DMF conversion of **45** to the 4-chloro analog **46** was followed by treatment with methanolic ammonia to deprotect the sugar and to displace the 4-chloro group, thus giving 3-bromonucleoside **47**. Catalytic reduction with palladium on carbon to remove the 3-bromo group then gave 4-amino-1-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (**48**), in low yield.

The second approach was developed to allow us to reduce our effort by one synthetic step. Starting with 4-aminopyrazolo-[3,4-*d*]pyrimidine (**49**), this approach offered an alternate route to common intermediate **47**. As is also shown in Scheme IX, **47** was obtained by the bromination of **49** followed by ribosylation and deprotection. Again, catalytic hydrogenolysis of **47** was again required to give nucleoside **48**.

Scheme X shows the approach that we again followed to synthesize 3-*t*-butyl-1-adamantylthiourea [AVS-2885] (**50**). 1-Adamantamine was dissolved in hexane and added to 3-*t*-butylisothiocyanate to give the desired compound **50**.

5-[(1,3-Dihydroxy-2-propoxy)methyl]-4-hydroxy-1,2-pyrazole-3-carboxamide (**57**) is similar to AVS-0148 and to the pyrazolecarboxylates and pyrazolecarboxamides submitted in earlier report periods. 4-Hydroxypyrazolecarboxamides such as **57** had been originally pursued in another USAMRIID-sponsored project (DAMD17-86-C-6003), but the antiviral activities of these compounds were not determined until the funding for the original project had been depleted. Since Dr. Gabrielsen had also expressed an interest in compounds similar to these, we decided to support the synthesis of one more pyrazolecarboxamide with

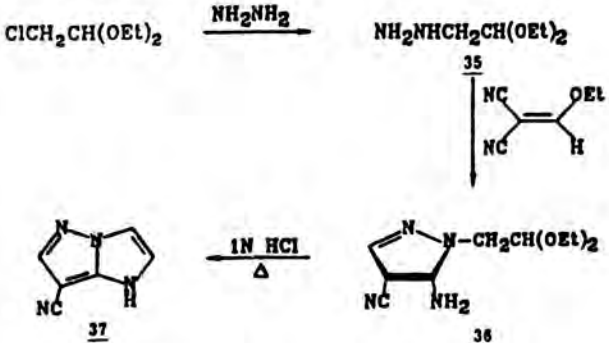
Scheme VI (continued)



29 30 31

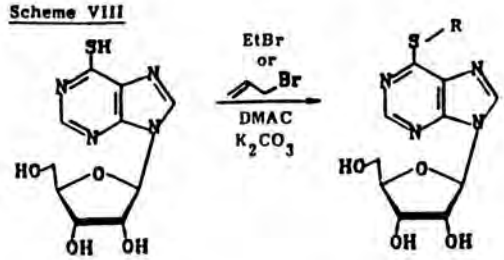
32: R = Bz = ØC–
33: R = H
34: R = Ac

Scheme VII



35 36 37 38 39 40

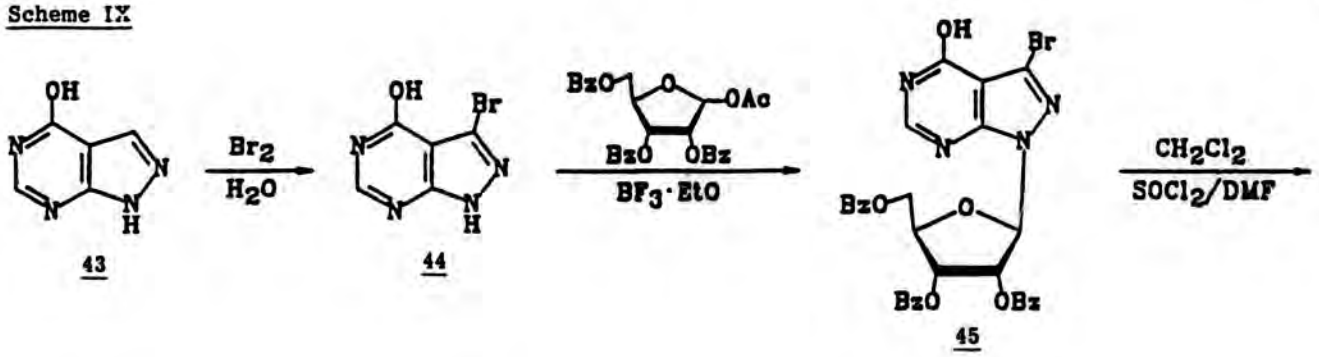
Scheme VIII



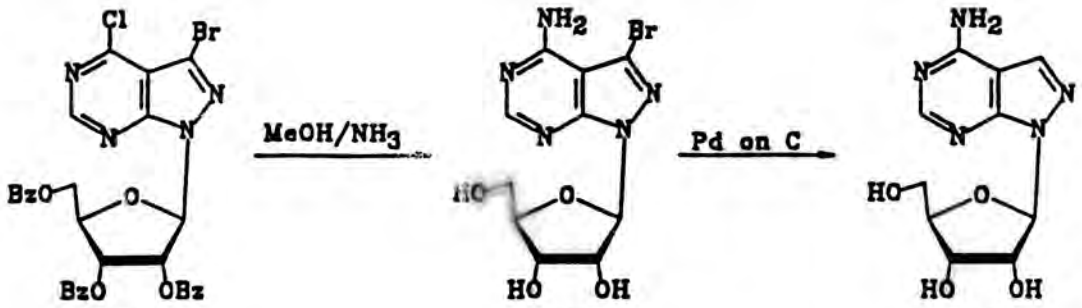
41 42

a) R = allyl
b) R = Et

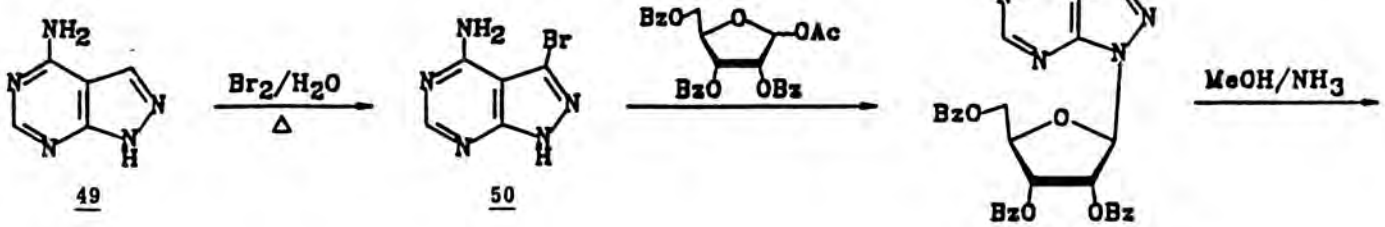
Scheme IX



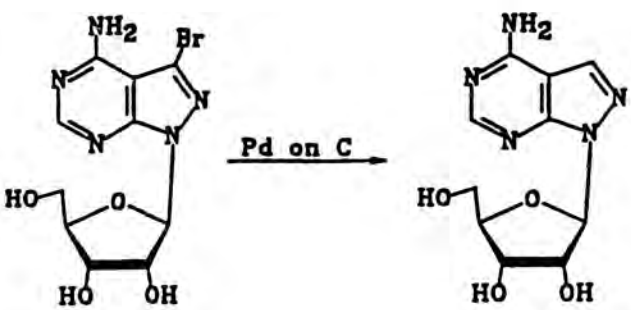
43 44 45



46 47 48

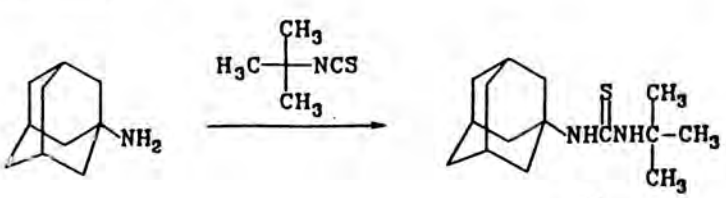


49 50 51



47 48

Scheme X



50

our project funds. As shown in Scheme XI, the synthesis of this compound started with methylpyruvate hydrazine (**51**), which had been prepared by reacting methylpyruvate with ethyl hydrazinoacetate.[23] Cyclization of adduct **51** with methanolic sodium methoxide gave **52**,[24] which was then acetylated with acetic anhydride/pyridine to give diacetate **53**. Bromination with NBS/carbon tetrachloride gave 5-bromomethyl compound **54**. This intermediate was then reacted with 1,3-di-*O*-benzyl-2-propanol and sodium hydride to give a mixture of products containing adduct **55**. Without isolating adduct **55**, the mixture was treated with methanolic ammonia to simultaneously convert the ester to the amide while deacetylating the N^1-blocked pyrazole. The resulting compound **56** was then catalytically hydrogenated with $Pd(OH)_2$ in ethanol to give pyrazolecarboxamide **57**.

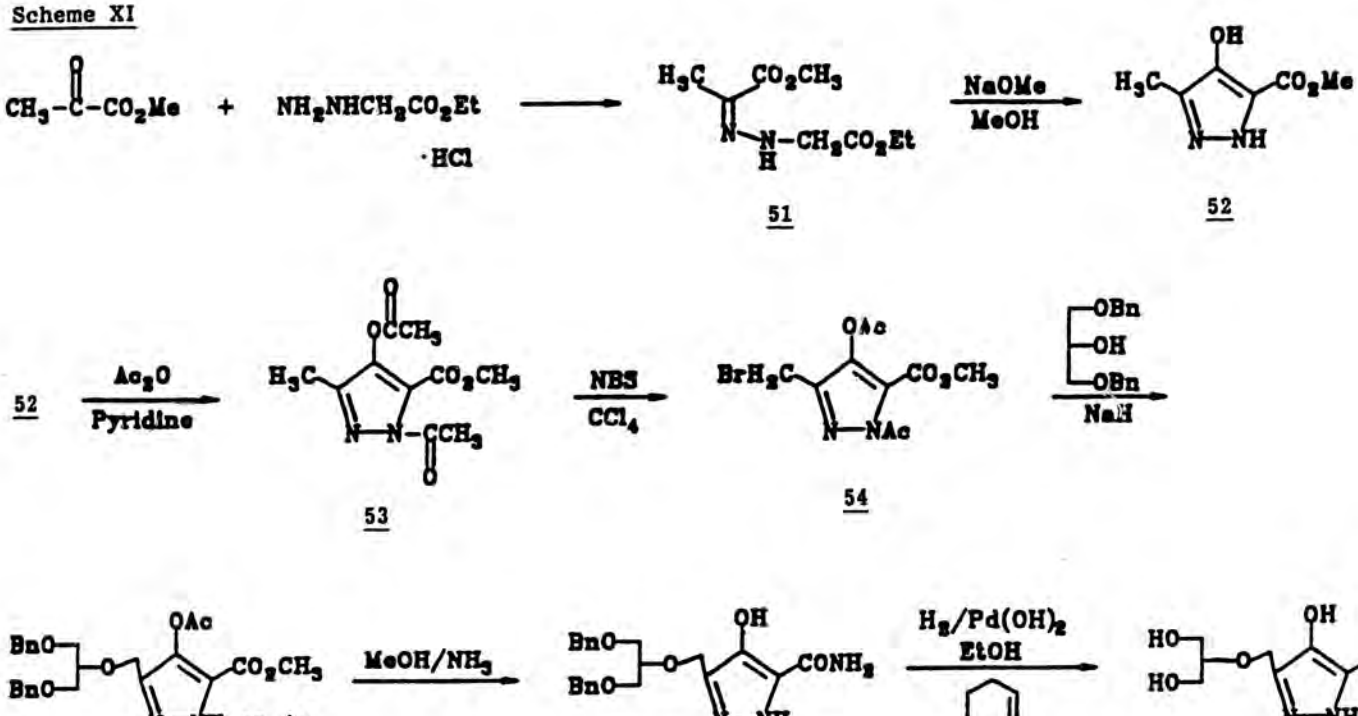
We synthesized an additional quantity of 1-aminoadenosine mesitylenesulfonate [AVS-4588] (**58**)[25] by the approach shown in Scheme XII. A solution of adenosine in methanol was treated with freshly prepared *O*-mesitylenesulfonylhydroxylamine to give the requested compound.

As shown in Scheme XIII, 5′-*N,N*-diethylthiocarbamate-5′-deoxy-5′-thioadenosine [AVS-4618] (**61**) was originally synthesized by reacting sodium diethyldithiocarbamate with 2′,3′-*O*-isopropylidine-5′-tosyladenosine (**59**) in DMF. For our resynthesis, we initially tried milder reaction conditions and were able to obtain a higher yield of the 2′,3′-*O*-blocked target compound **60**. However, we encountered unexpected difficulty while attempting the hydrolytic removal of the 2′,3′-*O*-blocking group. During our attempts to rectify this situation, we decided to simultaneously try a slight procedural modification. Since 5′-tosyladenosine (**62**) was commercially available, we investigated the direct reaction of this compound with sodium diethyldithiocarbamate under the same reaction conditions, and found that we obtained the desired 5′-*N,N*-diethylthiocarbamate-5′-deoxy-5′-thioadenosine (**61**) in good yield. The submitted 5′-*N,N*-diethylthiocarbamate-5′-deoxy-5′-thioadenosine (**61**) was prepared by this modified procedure.

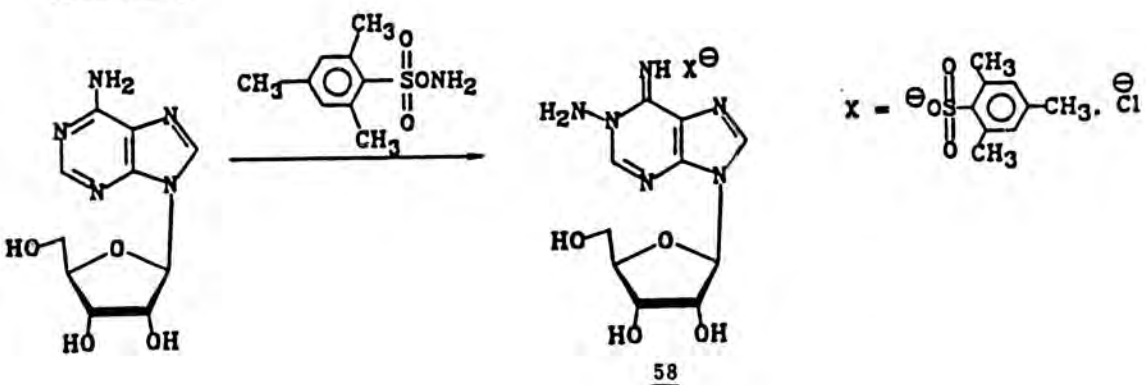
9-[2-(Phosphonylmethoxy)ethyl]adenine or PMEA (**69**)[26,27] was synthesized by the reaction sequence shown in Scheme XIV. The key acyclosugar sidechain precursor **67** was synthesized by following a procedure obtained from J. Bronson of Bristol-Myers. As shown in the scheme, dioxolane (**63**) was reacted with acetyl chloride and zinc chloride to give 2-(chloromethoxy)ethyl acetate (**64**). Treatment of **64** with triisopropylphosphite gave 2-(diisopropylphosphonylmethoxy)ethyl acetate (**65**). Hydrolysis of acetate **65** with HCl gave 2-(diisopropylphosphonylmethoxy)ethanol (**66**) which was then mesylated to give key intermediate **67**. Sodium hydride catalyzed coupling of **67** with adenine gave 9-(2-[diisopropylphosphonylmethoxy]ethyl)adenine (**68**), which gave PMEA **69** after hydrolysis with bromotrimethylsilane.

At the end of this year, we were continuing with our efforts to synthesize a number of other USAMRIID-requested compounds. Among these are: a second batch of 4-(4′-ethylamino-1′-methylbutylamino)-7-chloroquinoline [AVS-3980]; PMEG; PMEMAP; PMEDAP; ATP-N^1-oxide; ribavirin triphosphate; 1-(2-(phosphonylmethoxyethyl)-1,2,4-triazole-3-carboxamide; 6-carboxamidopurine riboside; 5-chloro-3-β-D-ribofuranosyl-*S*-triazolopyrimidin-7-one; additional batches of 3-(2′,3′,5′-tri-*O*-benzoyl-D-ribofuranosyl)amino-5*H*-*S*-triazolo[5,1-*c*]-*S*-triazole (AVS-4205) and 3-(β-D-ribofuranosyl)amino-5*H*-*S*-

Scheme XI



Scheme XII

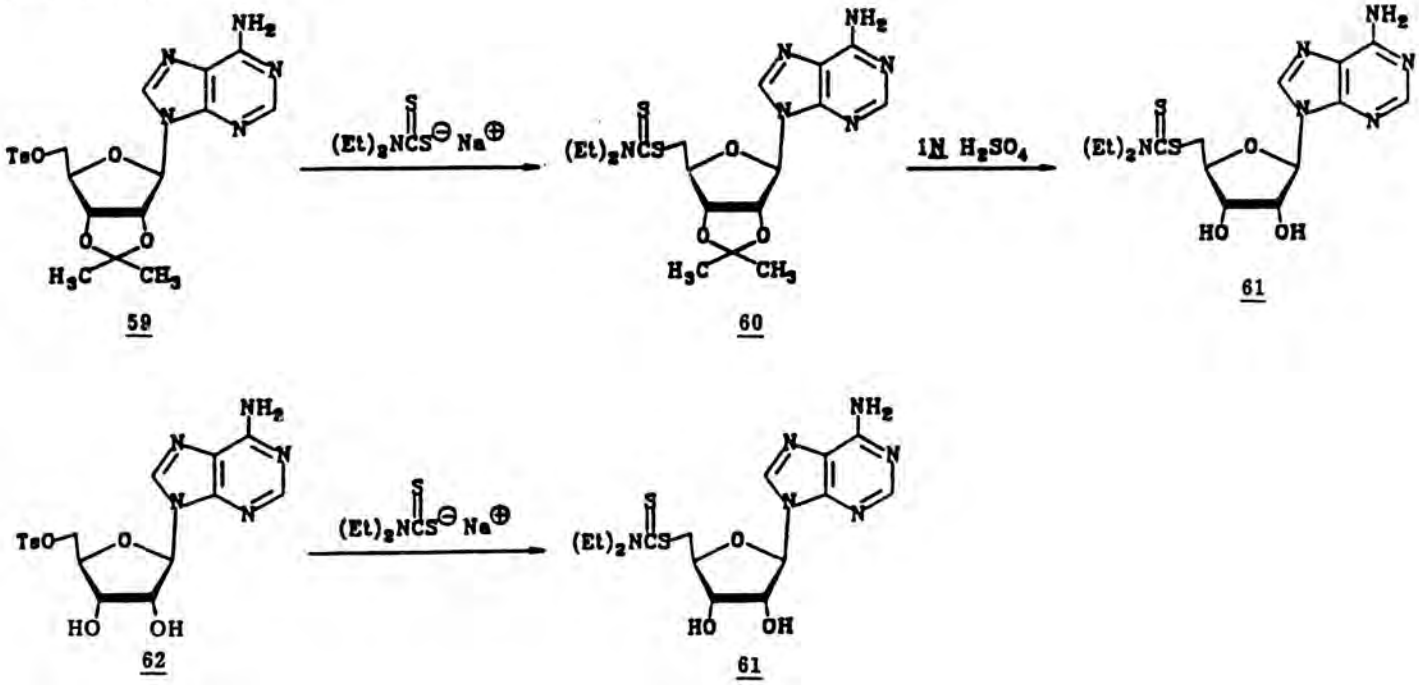


triazolo[5,1-*c*]-*S*-triazole (deblocked AVS-4205 for *in vivo* testing); and an additional batch of 3-acetamido-7-amino-6-methyl-7*H*-*S*-triazolo[5,1-*c*]-*S*-triazole (AVS-4206).

Scheme XV shows the approach followed to synthesize the additional quantity of 4-(4′-ethylamino-1′-methylbutylamino)-7-chloroquinoline (**73**).[28,29] Synthesis of this compound first required the synthesis of the sidechain precursor **71** by the reduction of 3-acetylpropanol (**70**) with $NaBH_3CN$ and ammonium acetate to give 4-aminopentanol (**71**). 4-Aminopentanol was then reacted with 4,7-dichloroquinoline to give **72** and was treated with HBr and ethylamine to give 4-(4′-ethylamino-1′-methylbutylamino)-7-chloroquinoline (**73**). Our synthesis by this method has yielded **73**, but our product still requires further purification.

Schemes XVI and XVII show the synthetic methods that we pursued in our attempts to synthesize 9-[2-(phosphonylmethoxy)ethyl]guanine or PMEG (**76**), an analog of recently submitted 9-[2-(phosphonylmethoxy)ethyl]adenine or PMEA (**69**). We began our investigation of the synthesis of PMEG (**76**) by the three approaches shown in Scheme XVI. The first mimicked the procedure for synthesizing PMEA (69).[30,31] As before, sidechain precursor **67** was first synthesized from dioxolane (**63**) by the following 4-step sequence. Dioxolane (**63**) was first treated with acetyl chloride and zinc chloride in ethyl ether. The resulting chloroacetate **64** was then reacted with triisopropylphosphite to give **65**. Hydrolysis of **65** in acetone-water (4:1) with concentrated HCl followed by mesylation then gave sidechain precursor **67**. The first of the approaches that we tried was the NaH-catalyzed coupling of 6-*O*-benzoylated guanine (**74**) with the sidechain precursor **67**. We also tried the HMDS-catalyzed alkylation of guanine (**77**) with sidechain precursor **67**, and we attempted the NaH-catalyzed coupling of 6-chloro-2-aminopurine (**79**) with the sidechain precursor **67**. We were especially interested in this third approach, because intermediate **80** would also be applicable to the synthesis of the other requested PMEA analogs 9-[2-(phosphonylmethoxy)ethyl]-2-aminopurine, PMEMAP (**81**) and 9-[2-(phosphonylmethoxy)ethyl]-2,6-diaminopurine, PMEDAP (**82**). Unfortunately, these early attempts met with little success, and therefore we decided to investigate a modified sidechain precursor **86** in conjunction with milder reaction conditions. We synthesized modified sidechain precursor **86**, diethylphosphonylmethoxyethyl tosylate more as a result of serendipity than rational strategy. As shown in Scheme XVII, the procedure for preparing this precursor was very similar to that for preparing **67**. In our earlier investigations into the synthesis of the sidechain precursor, we had synthesized a small amount of **83** by treating chloroacetate **64** with some triethylphosphite that we already had on hand. We had not pursued the conversion of this intermediate to a sidechain precursor, because the literature had suggested that the 9-[2-(diisopropylphosphonylmethoxyethyl)purine offered a slight advantage in later conversions of 2-amino-6-chloropurine moiety of intermediate **80**. However, during an interim while we were waiting for more starting materials for synthesizing **67**, we decided to proceed with **83** and to investigate a different leaving group in place of the mesyl group. Therefore, we hydrolyzed **83** with acetone-water (4:1) and concentrated HCl, and we treated the resulting diethylphosphonylmethoxyethanol (**85**) with tosyl chloride in methylene chloride and triethylamine to get precursor **86**.

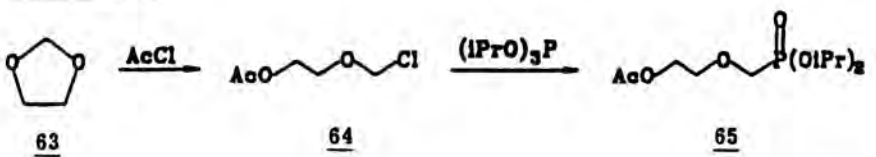
Scheme XIII



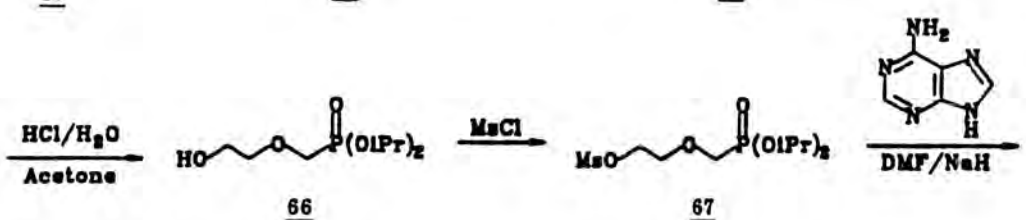
59 60 61

62 61

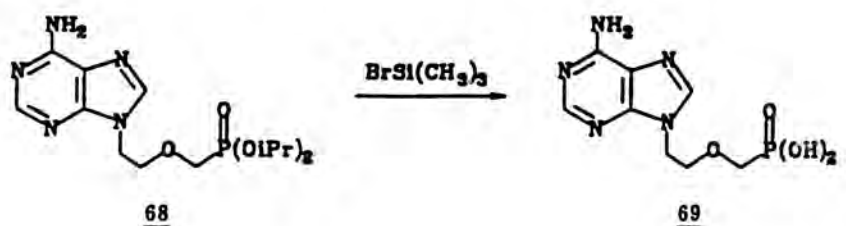
Scheme XIV



63 64 65

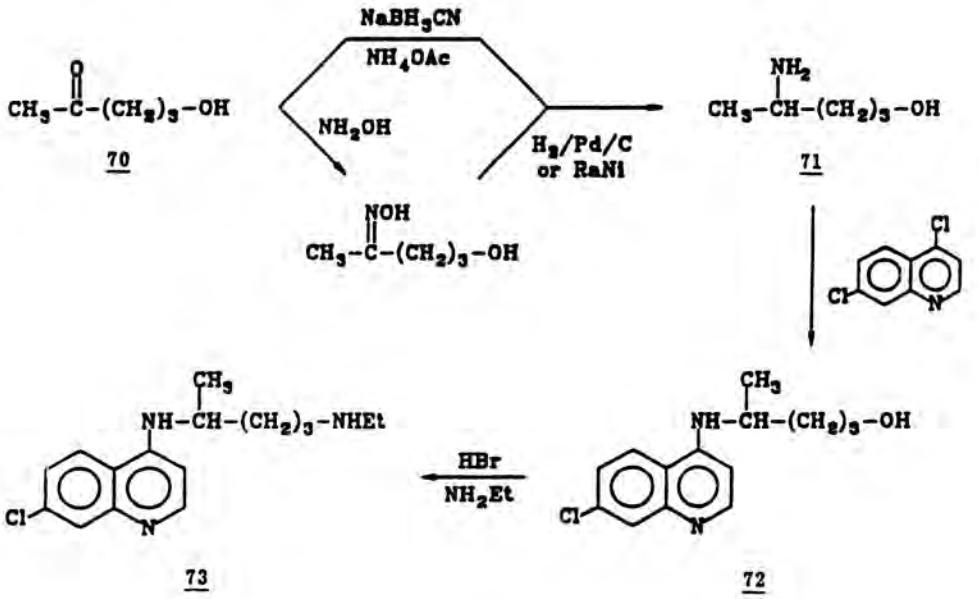


66 67

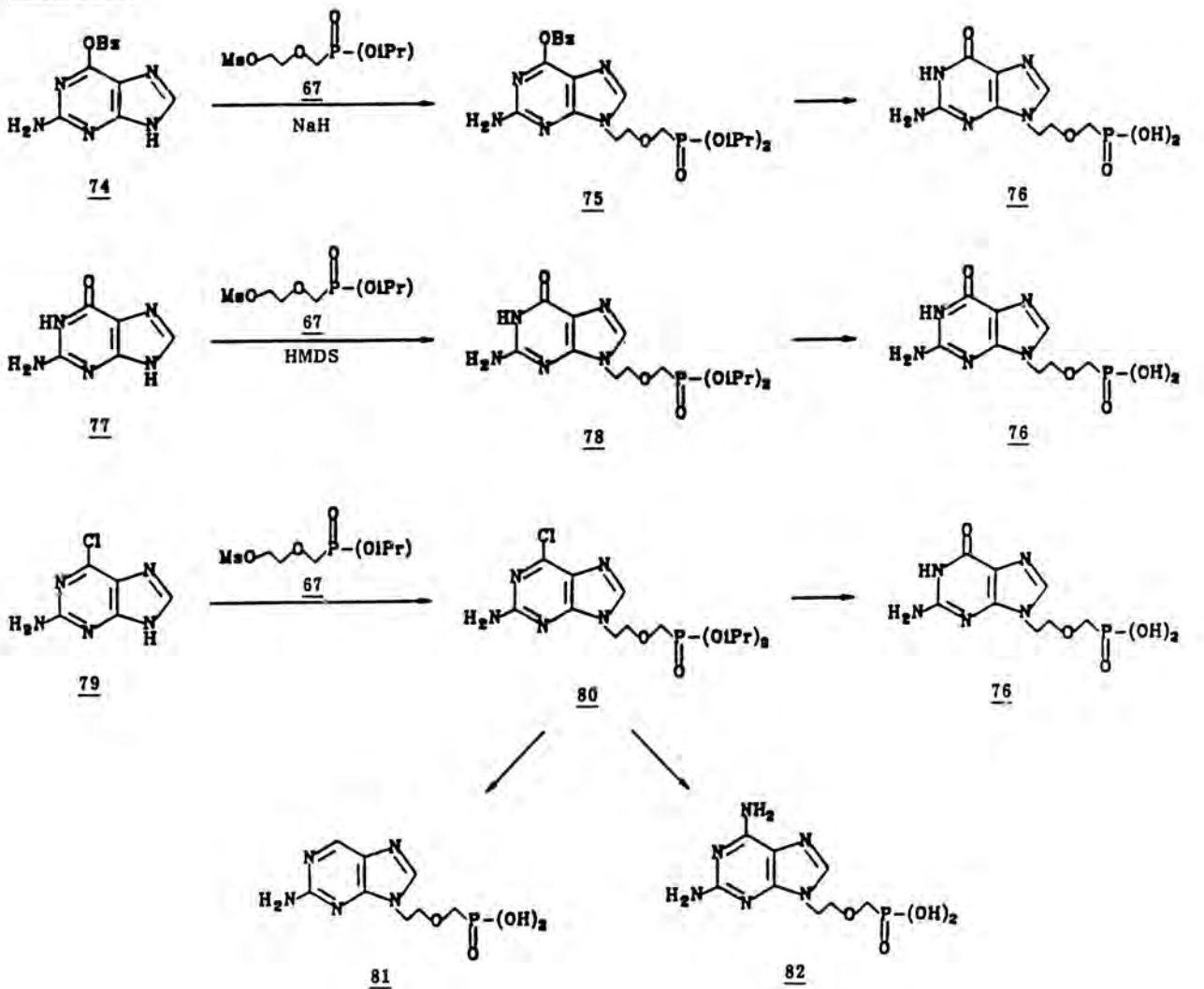


68 69

Scheme XV



Scheme XVI



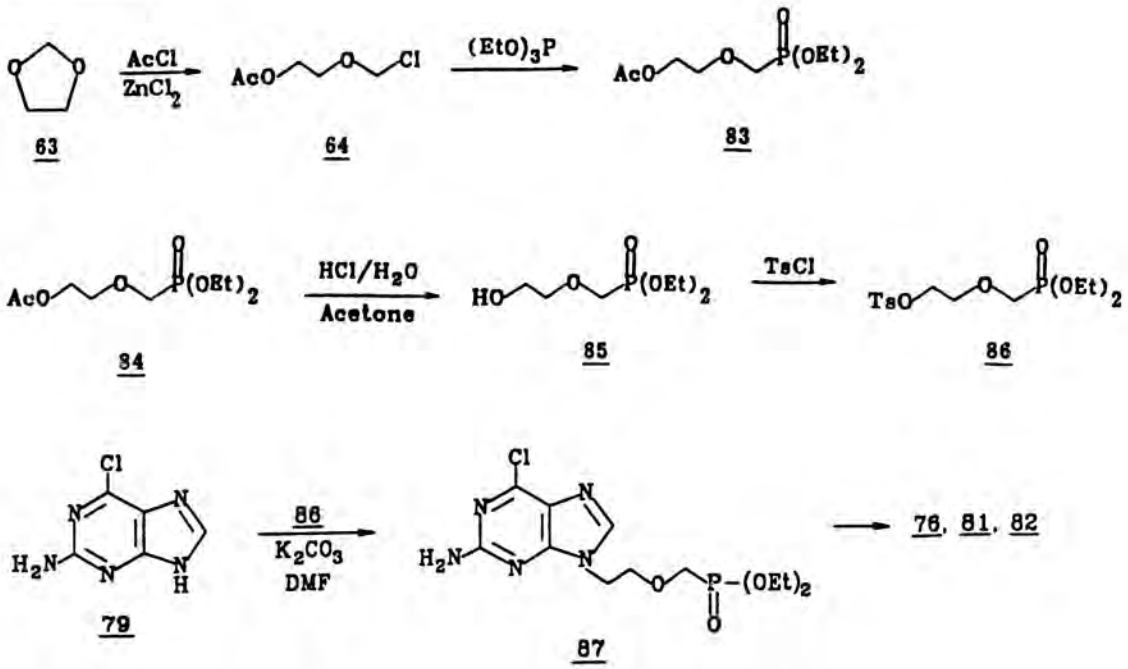
Using this new precursor with 2-amino-6-chloropurine and under milder reaction conditions (potassium carbonate and anhydrous DMF at room temperature for 3 days under argon),[32] we were able to prepare a small amount of the desired intermediate **87**. We have been able to convert the obtained **87** to PMEG, thus showing that we have a viable route to PMEG and probably to PMEMAP and PMEDAP.

Our efforts to synthesize ribavirin analog **90** also have shown promise. As shown in Scheme XVIII, our early approaches to synthesizing this PMEA analog began with methyl 1,2,4-triazole-3-carboxylate (**88**) generously supplied by Dr. Gabrielsen. We investigated the alkylation of methyl 1,2,4-triazole-3-carboxylate (**88**) with the acyclosugar precursor **67** with a number of reagents and reaction conditions (bis-*p*-nitrophenylphosphate/130 °C[33]; NaH/DMF/room temperature to 100 °C[34]; potassium carbonate/acetone or methanol; sodium methoxide/methanol or THF, etc.). All of these early attempts were unsuccessful, consistently yielding hydrolyzed sidechain precursor along with some recovered methyl 1,2,4-triazole-3-carboxylate. As is also shown in Scheme XVIII, we have recently been more successful as a result of our paralleling the PMEG work and using the combination of milder reaction conditions and the modified sidechain precursor **86**, 2-diethylphosphonylmethoxyethyl tosylate instead of 2-diisopropylphosphonylmethoxyethyl mesylate **67**. We have alkylated methyl 1,2,4-triazole-3-carboxylate with modified sidechain precursor **86** in anhydrous DMF with potassium carbonate at 90 °C under inert atmosphere[32] to get key intermediate **91**. The subsequent reactions, treatment of this intermediate with concentrated ammonium hydroxide followed by deesterification with bromotrimethylsilane occur in good overall yield to give the desired target compound **90**. Although analytical data confirms that we have synthesized **90**, it also indicates that our product is not analytically pure. The recrystallization procedure (from acetone/water) that had been effective for PMEA was ineffective for this compound, probably due to the extreme water solubility of this compound. We are evaluating isolation techniques that will provide us with pure compound.

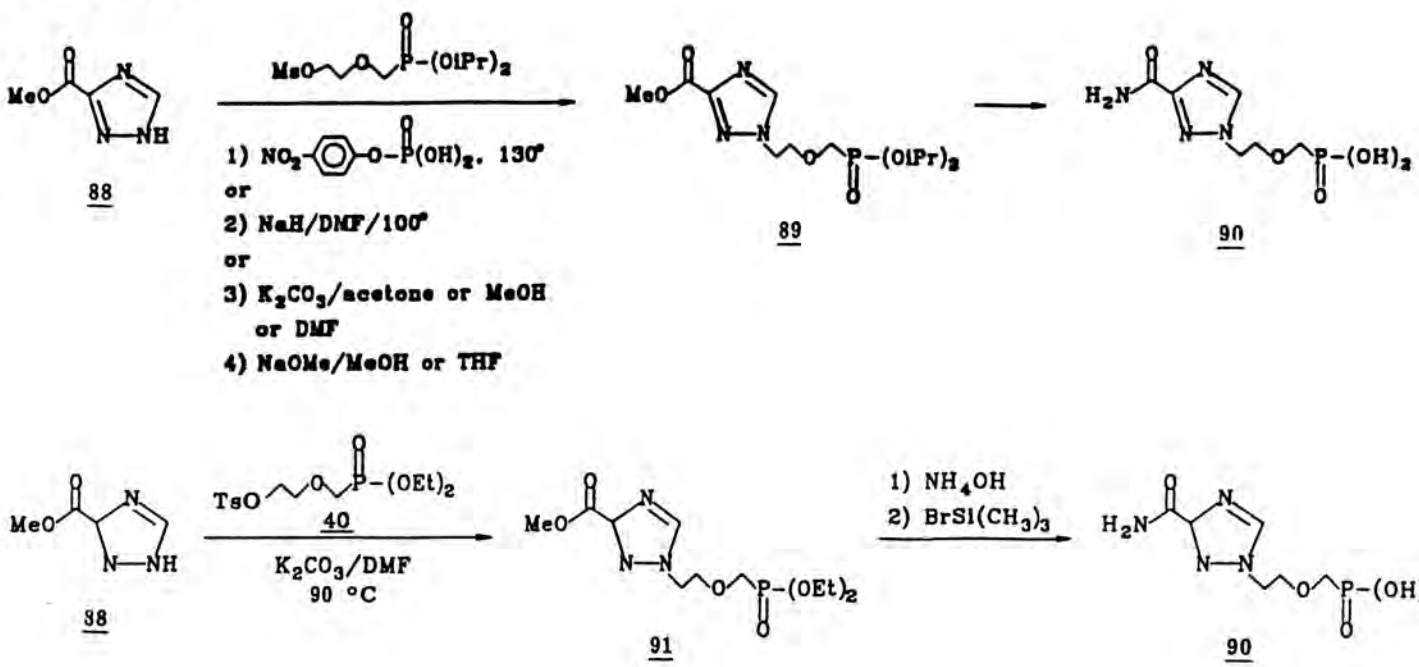
As previously reported, we were able to synthesize adenosine-N^1-oxide 5′-triphosphate (**92**) by the two methods shown in Scheme XIX: by the phosphorylation of adenosine-N^1-oxide (**2**); and by the direct N^1-oxidation of adenosine-5′-triphosphate (**93**) with *m*-chloroperoxybenzoic acid. Unfortunately, we have been unable to chromatographically remove a residual 5% adenosine-5′-triphosphate, and we have not been able to push the reaction any closer to completion. Therefore, our attempts to obtain pure product **92** have been unsuccessful.

The fourth ribavirin nucleotide requested by Major Ussery, ribavirin 5′-triphosphate (**96**) was synthesized according to the route shown in Scheme XX.[35] Ribavirin phosphate **97** was first made by treating ribavirin **94** with phosphoryl chloride and trimethylphosphate. Phosphate **97** was then converted to its morpholidate **98**, and subsequent treatment of the morpholidate in dry DMF with rigorously purified bis-tri-*n*-butylammonium pyrophosphate gave the desired triphosphate compound **96** without contamination with nucleoside di- and monophosphate. However, our synthetic procedure required a large excess (5x) of the pyrophosphate, and as a result, the isolated product contained a significant amount of pyrophosphate in addition to the desired triphosphate. The chromatographic systems that effectively purified the other

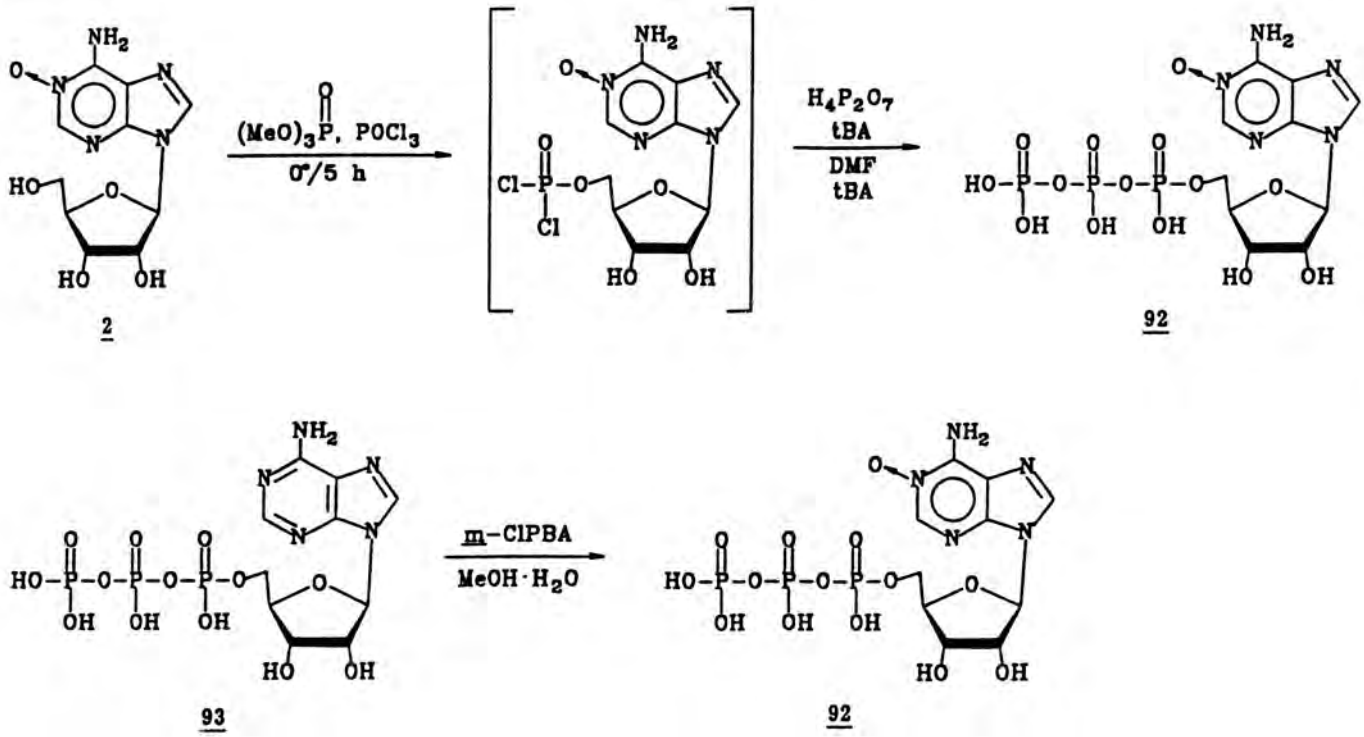
Scheme XVII



Scheme XVIII

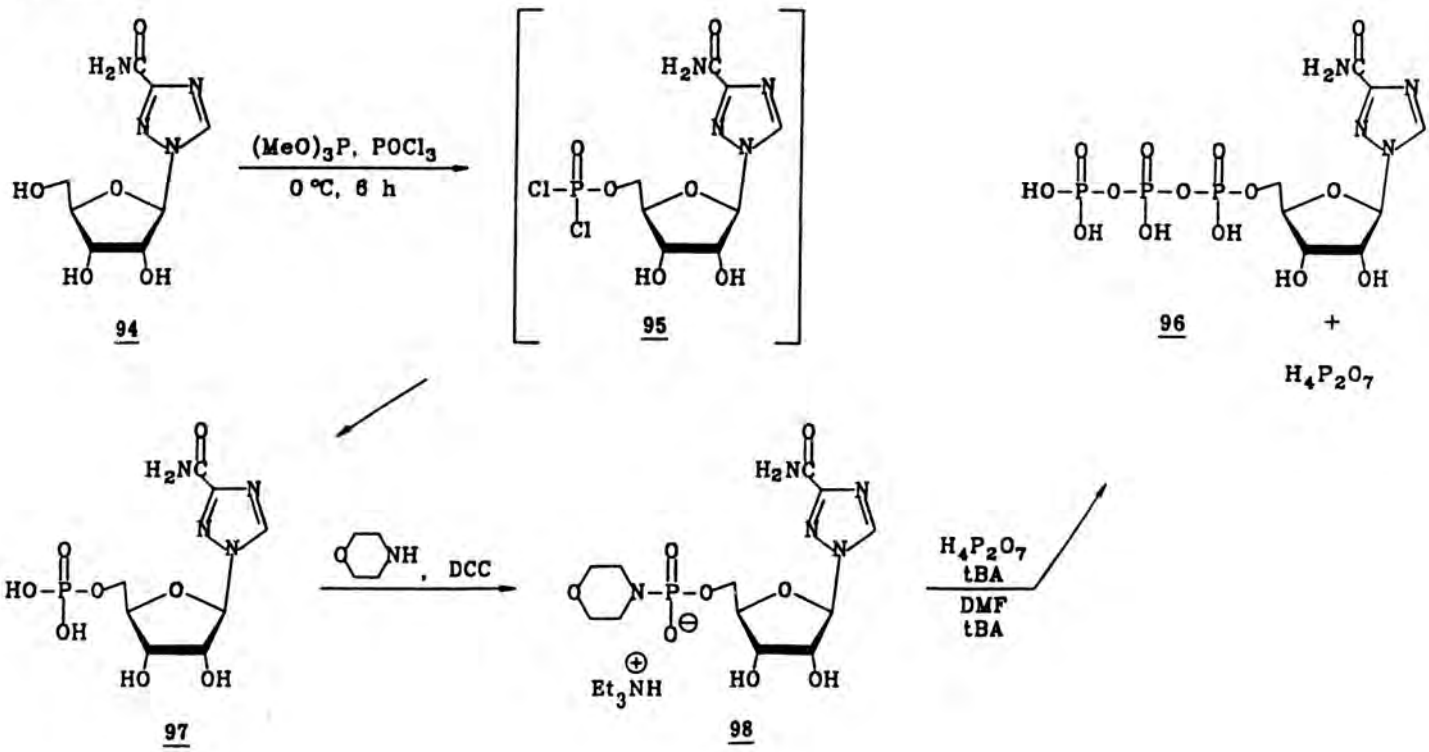


Scheme XIX



2 92 93 92

Scheme XX



94 95 96 + H4P2O7 97 98

ribavirin nucleotides from their corresponding reaction sideproducts were ineffective at separating ribavirin 5′-triphosphate from the residual pyrophosphate. We tried other approaches to remove or reduce the level of pyrophosphate from the product mixture, but none of our reaction condition modifications or chromatographic procedures have provided pure ribavirin 5′-triphosphate. Since it is unlikely that pyrophosphate would cause any harmful effects in antiviral screenings, we feel that this compound can be tested as is.

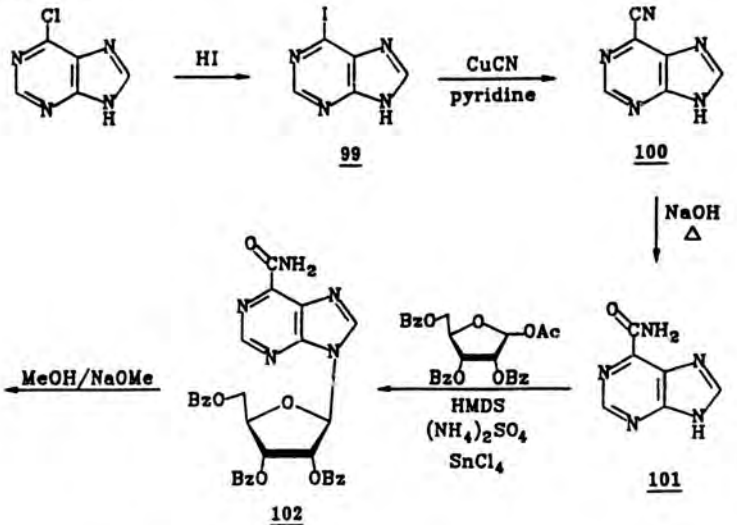
Our efforts to synthesize 9-ribofuranosylpurine-6-carboxamide (**103**)[36-38] are shown in Scheme XXI. 6-Iodopurine (**99**) was converted to 6-cyanopurine (**100**) by treatment with CuCN in pyridine. We have been having difficulty with the hydrolysis of 6-cyanopurine (**100**) to 6-carboxamidopurine (**101**), but we recently determined reaction conditions that will allow this conversion in better yield. We will be preparing more 6-carboxamidopurine and will begin investigating the ribosylation of this compound to give **102** and eventually **103**. We will also be pursuing the amidine analog of **103** by following a similar reaction scheme.

We also investigated the synthesis of 5-chloro-3-β-D-ribofuranosyl-*S*-triazolopyrimidin-7-one (**109**).[39] As shown in Scheme XXII, our approach to this compound began with the condensation and cyclization of diethylmalonate with 3-amino-1,2,4-triazole (**104**) to give triazolopyrimidin-5,7-dione (**105**). Dione **105** was then converted to the dichlorotriazolopyrimidine **106** by treatment with phosphorus oxychloride. **106** was then hydrolyzed to give the required heterocyclic intermediate **107**. Coupling of **107** with 2,3,5-tribenzoylribofuranose 1-acetate then gave protected nucleoside **108a** which after deblocking should give the desired product **109**. We had difficulty in completely debenzoylating **108a**, especially the removal of the final 5′-benzoyl group. We investigated ethanolic sodium methoxide, ethanolic ammonia, and LiOH/EtOH as potential deblocking conditions, but we had little success. As a result, we pursued the coupling of 1,2,3,5-tetraacetylribofuranose with **107**, and we have recently found that deprotection of the triacetate analog **108b** occurs more readily. We are currently scaling up our efforts and will also be attempting to synthesize the 7-thione analog of **109**.

We also began our synthesis of the additional quantity of 3-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)amino-5*H*-*S*-triazolo[5,1-*c*]-*S*-triazole [AVS-4205] (**114**) and 3-(β-D-ribofuranosyl)amino-5*H*-*S*-triazolo[5,1-*c*]-*S*-triazole (**116**). Scheme XXIII shows the approach that we are again following to synthesize this compound. 3-Amino-1,2,4-triazole (**104**) will first be nitrated to 3-nitroamino-1,2,4-triazole (**110**) by treatment with fuming nitric acid.[40] Reduction of **110** with zinc dust and acetic acid will give 3-hydrazino-1,2,4-triazole (**111**). Compound **111** will then be treated with cyanogen bromide to give 3-amino-5*H*-*S*-triazolo[5,1-*c*]-*S*-triazole (**112**).[41] Fusion with 2,3,5-tri-*O*-benzoyl-D-ribofuranose 1-acetate and $SnCl_4$ will then give the indicated mixture of products of which target compound **114** will be one of three major components. Deprotection of **114** will then give the second requested compound, **116**.

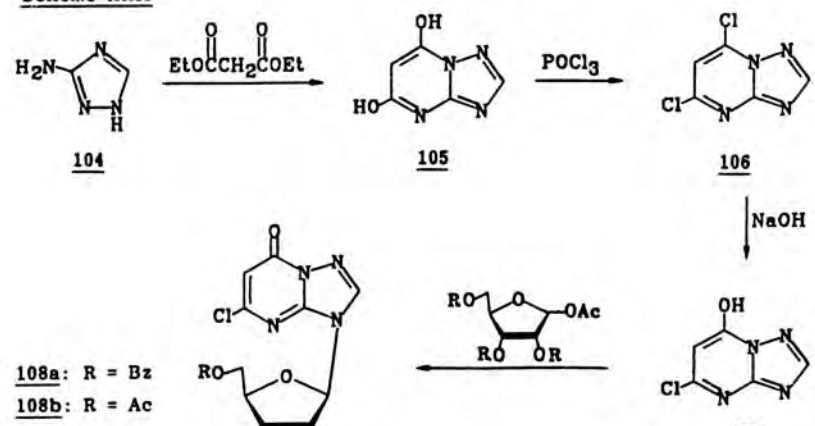
We are also resynthesizing an additional quantity of 3-acetamido-7-amino-6-methyl-7*H*-*S*-triazolo[5,1-*c*]-*S*-triazole [AVS-4206] (**120**). As shown in Scheme XXIV, the required precursor for this compound, 3,7-diamino-6-methyl-7*H*-*S*-triazolo[5,1-*c*]-*S*-triazole (**119**) was synthesized from triaminoguanidine (**117**). Sequential treatment of triaminoguanidine with acetic acid and hydrochloric acid gave triazole **118**.[42] This

Scheme XXI

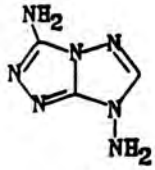


103

Scheme XXII

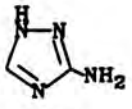


Scheme XXIII

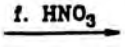


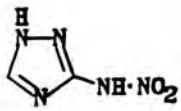
11

(AVS-000245)



104





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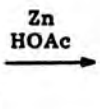

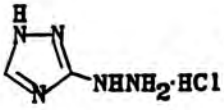

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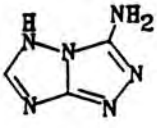

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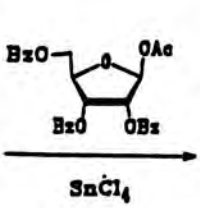
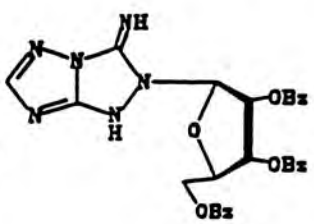
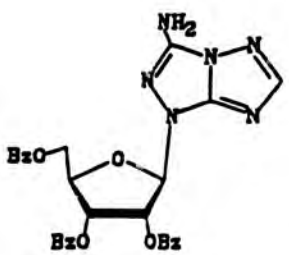
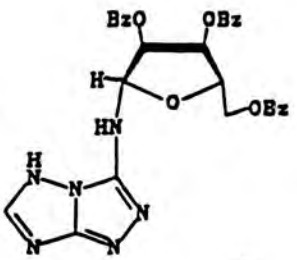




113



114



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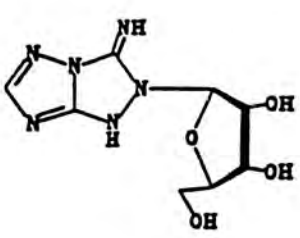
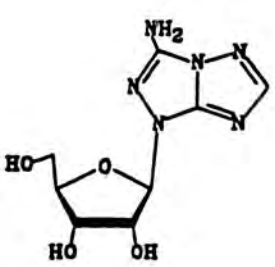
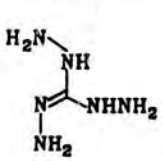




116

Scheme XXIV



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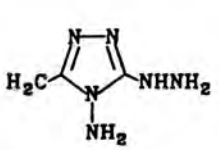

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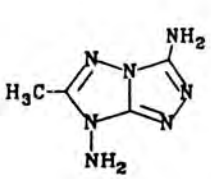
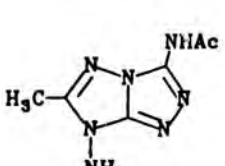


119



120

intermediate was then further cyclized by treatment with cyanogen bromide to give precursor **119**,[41] which after acetylation with acetic anhydride gave **120**. This compound is in the final stages of purification and analytical verification, and it should be submitted in the next few weeks.

During this year, we terminated our efforts directed toward the synthesis of three compounds: N^1-(4-*N,N*-dimethylaminobenzyloxy)adenosine; Justicidin B; and 4-Amino-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine 5′-acetate. Our efforts were showing little signs of success, and therefore we decided to dedicate our time to other more promising compounds.

Experimental

All solvents and materials were reagent grade and were either used as received or purified as required. ^{1}H NMR and ^{13}C NMR spectra were run with a Nicolet NMC NT-300 NB spectrometer operating at 300.65 MHz with tetramethylsilane as an internal reference. Chemical shifts (δ) for multiplets were measured from the appropriate centers. The mass spectral data were obtained from a Varian MAT 311A mass spectrometer in fast atom bombardment (FAB) or electron-impact (EI) mode (direct probe temperature 20 °C), as indicated. Infrared data were obtained with a Nicolet 10-MX spectrometer. In most cases, only strong or medium peaks in the 1800-600 cm^{-1} range were reported. UV absorption spectra were determined in the appropriate pH 1 (0.1 *N* HCl), pH 7 buffer, and pH 13 (0.1 *N* NaOH) solutions with either a Cary 17 spectrometer or a Perkin Elmer Model Lambda 9 UV/VIS/NIR spectrophotometer. Melting point data was obtained with a Mel-Temp Capillary Melting Point apparatus, and all melting points were uncorrected. Elemental analysis data were obtained from either an in-house Perkin Elmer Model 240 Elemental Analyzer or from Atlantic Microlab of Atlanta, Georgia.

1-(2-Methylbenzyloxy)adenosine, Perchloric Acid Salt [AVS-2875] (3a). In a 100-mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate drying tube was placed 2.5 g (8.83 mmol) of adenosine-N^1-oxide, 50 mL of molecular sieve (4A) dried *N,N*-dimethyl acetamide (DMAC), and 9.8 g (44.2 mmol) of 2-methylbenzyl bromide. The mixture was stirred at room temperature. Since solution was not complete after 20 min, 2.0 mL more DMAC was added. Solution was achieved within 10 min, and the light, yellow solution was stirred for 2 h. The reaction mixture was stirred until the gum stuck to the walls of the flask, leaving a nearly clear liquid phase which was decanted. The gummy residue was washed with 400 mL of ether, decanted, recovered with 400 mL of ether, and ground to a powder. The powder was allowed to settle, the ether was decanted, and the residue was dried in a stream of argon. The residue was dissolved in 25 mL of H_2O and added with stirring to a warm solution of 5 g (42.6 mmol) of ammonium perchlorate dissolved in 25 mL of H_2O. The product crystallized upon scratching and chilling. One recrystallization from water yielded 4.0 g (77%); UV λ_{max} 259 nm (13,420) at pH 1; 259 (13,260) at pH 7; 258 (13,210) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR 1687, 1510, 1415, 1225, 1127, 1083, 916, 880, 767, 690, 623 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.47 (s, 3, CH_3), 3.57, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5′), 3.99 (apparent q, 1, H-4′), 4.15 (apparent t, 1, $J_{3',4'}$ = 3.8 Hz, H-3′), 4.43-4.53 (br s, 1, $J_{2',3'}$ = 4.9 Hz, H-2′), 4.98-5.14 (br s, 1, 5′-OH), 5.24-5.38 (br s, 1,

3'-OH), 5.46 (s, 2, OCH_2Ar), 5.54-5.64 (br s, 1, 2'-OH), 5.92 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.20-7.50 (m, 4, H-Ar), 8.61 (s, 1, H-2), 8.83 (s, 1, H-8), 9.70-9.88 (br s, 1, H-$\overset{\oplus}{N}H_2$), 10.38-10.54 (br s, 1, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 18.64 (CH_3), 60.83 (C-5'), 69.92 (C-3'), 74.46 (C-2'), 79.56 (OCH_2Ar), 85.83 (C-4'), 87.74 (C-1'), 119.84 (C-5), 125.84 (Ar-C3), 129.93 (Ar-C6), 130.45 (Ar-C4), 131.34 (Ar-C2), 138.13 (Ar-C1), 142.84 (C-8), 144.40 (C-2), 145.17 (C-4), 148.32 (C-6). *Anal.* Calcd for $C_{18}H_{22}ClN_5O_9 \cdot 0.75H_2O$: C, 43.12; H, 4.72; N, 13.97. Found: C, 43.18; H, 4.67; N, 14.18.

1-(4-Methoxybenzyloxy)adenosine, Perchloric Acid Salt [AVS-3679] (3b). The general procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed, using the following reagent quantities: 2 x 2.5 g (2 x 8.83 mmol) adenosine-N^1-oxide; 2 x 4 mL 4-methoxybenzyl bromide; 2 x 30 mL DMAC. The hydrobromide was treated with 50 mL H_2O and only partially dissolved. The mixture was added to the warm solution of NH_4ClO_4 (2 x 4g). As the lumps were ground while trying to effect solution, product began to crystallize. The mixture was chilled in an ice bath, and the lumps were pulverized as much as possible. After 1 h in the ice bath, the precipitate was collected. The product was dissolved in 300 mL hot EtOH, cooled, treated with silica gel to remove salts, filtered through a silica gel plug, and diluted with hexane. The white product was collected, washed with hexane, and dried at 56 °C for 5 h over phosphorus pentoxide, yield 5.1 g (29%); UV λ_{max} 258 nm (13,900) at pH 1; 259 (12,100) at pH 7; 259 (11,400) at pH 13; MS (FAB) *m/e* 404 (M + 1); IR 1684, 1610, 1516, 1252, 1229, 1180, 1100 broad, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.70 (2 m, 2, CH_2-5'), 3.79 (s, 3, OCH_3), 3.99 (apparent q, 1, H-4'), 4.16 (apparent q, 1, H-3'), 4.49 (apparent q, 1, H-2'), 5.09 (apparent t, 1, OH-5'), 5.33 (apparent d, 1, OH-3'), 5.35 (s, 2, OCH_2Ar), 5.60 (d, 1, OH-2'), 5.93 (d, 1, H-1'), 6.99 (d, 2, Ar-H-3,5), 7.59 (d, 2, Ar-H-2,6), 8.80 (s, 1, H-8), 8.74 (s, 1, H-2), 10.02 (br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{18}H_{22}ClN_5O_{10} \cdot H_2O$: C, 41.43; H, 4.64; N, 13.42. Found: C, 41.42; H, 4.62; N, 13.19. *Anal.* Calcd for $C_{18}H_{22}ClN_5O_{10} \cdot 0.75H_2O$: C, 41.79; H, 4.58; N, 13.54. Found: C, 41.86; H, 4.62; N, 13.37.

1-(1-Phenylethyloxy)adenosine, Perchloric Acid Salt [AVS-3607] (3c). The general procedure of 1-(2-cyanobenzyloxy)adenosine was followed using the following reagent quantities: 4 g (14.1 mmol) adenosine-N^1-oxide; 8 mL 1-bromoethylbenzyl bromide; 80 mL DMAC; 8 g NH_4ClO_4. Because it took 1 h for the N^1-oxide to go into solution, the reaction mixture was stirred for 4 h before it was worked up. Also, since crystallization did not occur upon chilling and scratching, small spots were frozen on the flask with dry ice and scratched. After crystals had grown, the flask was stored overnight in the refrigerator. The product was collected, washed with ice water and dried at 56 °C for 6 h over phosphorus pentoxide, yield 3.0 g (43%); UV λ_{max} 259 nm (12,400) at pH 1; 259 (12,500) at pH 7; 258 (12,900) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR 1691, 1510, 1430, 1400, 1325, 1225, 1100 broad, 875, 720, 705, 635, 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.80 (d, 3, CH_3), 3.55, 3.65 (2 m, 2, CH_2-5'), 3.95 (apparent q, 1, H-4'), 4.12 (apparent t, 1, H-2'), 5.07, 5.31, 5.68 (3 apparent s, 3, OH-5',3',2'), 5.71 (apparent q, 1, O*CH*Ar), 5.90 (m, 1, H-1'), 7.42, 7.59 (2 m, 5, Ar-H), 8.77 (apparent t, 2, H-8,2), 9.53, 10.32 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 18.61 (C-(CH_3)$_3$), 60.80 (C-5'), 69.88 (C-3'), 74.39 (C-2'), 85.83 (C-4'), 87.65 (C-1'), 88.60 (OCH_2Ar), 118.97 (C-5), 128.49, 128.54 (Ar-C-2,3,5,6), 129.85 (Ar-C-4), 136.05 (Ar-C-1), 142.83 (C-8), 144.72

(C-2), 144.89 (C-4), 148.61 (C-6). *Anal.* Calcd for $C_{18}H_{22}ClN_5O_9 \cdot H_2O$: C, 42.74; H, 4.78; N, 13.84. Found: C, 42.69; H, 4.59; N, 13.81.

1-(2-Nitrobenzyloxy)adenosine, Perchloric Acid Salt [AVS-2911] (3d). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed with the following reagent quantities: 4 g (14.1 mmol) of adenosine-N^1-oxide; 9.5 g (45 mmol) 2-nitrobenzyl bromide; 80 mL DMAC; 8 g NH_4ClO_4. Two recrystallizations from water followed by drying at 78 °C over phosphorus pentoxide for 18 h yielded 6.0 g (82%); UV λ_{max} 259 nm (18,170) at pH 1; 259 (18,090) at pH 7; 257 (16,890) at pH 13; MS (FAB) *m/e* 419 (M + 1); IR 1685, 1538, 1530, 1510, 1347, 1105 broad, 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.7 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.1 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.08 (br s, 1, 5'-OH), 5.32 (br s, 1, 3'-OH), 5.60 (br s, 1, 2'-OH), 5.76 (s, 2, OCH_2Ar), 5.95 (d, 1, $J_{1',2'}$ = 5.35 Hz, H-1'), 7.75 (m, 1, Ar-H-4), 7.90 (m, 1, Ar-H-5), 7.99 (apparent d, 1, Ar-H-3), 8.22 (apparent d, 1, Ar-H-6), 8.83 (s, 1, H-8), 8.94 (s, 1, H-2), 9.80, 10.46 (2 br s, 2, H-$\overset{\oplus}{N}H_2$; ^{13}C NMR (Me_2SO-d_6) δ 60.83 (C-5'), 69.92 (C-3'), 74.46 (C-2'), 77.01 (OCH_2Ar), 85.84 (C-4'), 87.77 (C-1'), 119.54 (C-5), 124.81 (Ar-C-3), 128.32 (Ar-C-1), 130.29 (Ar-C-4), 131.11 (Ar-C-5), 134.03 (Ar-C-6), 142.79 (C-8), 144.45 (C-2), 145.21 (C-4), 147.54 (Ar-C-2), 148.36 (C-6). *Anal.* Calcd for $C_{17}H_{19}ClN_6O_{11} \cdot 1.5\,H_2O$: C, 36.62; H, 4.05; N, 15.32. Found: C, 36.48; H, 3.78; N, 15.62.

1-(3,4-Dimethylbenzyloxy)adenosine, Perchloric Acid Salt [AVS-4224] (3e). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was used with the following reagent quantities: 4 g (14.1 mmol) adenosine-N^1-oxide; 9 mL of 3,4-dimethylbenzyl bromide; 80 mL DMAC; 8 g NH_4ClO_4. Yield, 5.9 g (83%); mp 139-142 °C (cap. dec.); UV λ_{max} 259 nm (13,300) at pH 1; 259 (13,300) at pH 7; 258 (13,600) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR 1691, 1510, 1100 (broad), 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.25 (s, 6, Ar-CH_3), 3.58, 3.69 (2 m, 2, $J_{4',5'a}$ = $J_{4',5'b}$ = 3.87 Hz, $J_{5'a,5'b}$ = 12.1 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.85 Hz, H-3'), 4.49 (apparent q, 1, $J_{2',3'}$ = 4.88 Hz, H-2'), 5.09 (br s, 1, OH-5'), 5.33 (s, 2, OCH_2Ar), 5.60 (br d, 1, $J_{2',2'\text{-OH}}$ = 4.57 Hz, OH-2'), 5.94 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 8.81 (s, 1, H-8), 8.91 (s, 1, H-2), 9.72, 10.41 (2 br s, 2, H-$\overset{\oplus}{N}H_2$. *Anal.* Calcd for $C_{19}H_{24}ClN_5O_9 \cdot H_2O$: C, 43.89; H, 5.04; N, 13.47. Found: C, 43.78; H, 5.06; N, 13.40.

1-(2-Cyanobenzyloxy)adenosine, Perchloric Acid Salt [AVS-2889] (3f). In a 100-mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate drying tube was placed 2.5 g (8.83 mmol) of adenosine-N^1-oxide, 50 mL of molecular sieve (4A) dried *N,N*-dimethyl acetamide (DMAC), and 5.2 g (26.5 mmol) of α-bromo-*o*-cyano toluene. The mixture was stirred at room temperature and stirred for 2 h after complete solution was achieved. The reaction solution was poured into 300-500 mL of anhydrous ether with slight swirling. After the product stuck to the walls of the flask, the supernatant was decanted. The gummy residue was washed with 400 mL of ether, decanted, again covered with 400 mL of ether, and ground to a powder. The powder was allowed to settle, the ether was decanted, and the residue was dried in a stream of argon. The residue was dissolved in 25 mL of H_2O and added with stirring to a warm solution of 5 g (42.6 mmol) of ammonium perchlorate dissolved in 25 mL of H_2O. The product crystallized upon scratching and chilling. One recrystallization from water and drying at 78 °C over

phosphorus pentoxide yielded 3.5 g (79%); UV λ_{max} 260 nm (12,700) at pH 1; 259 (12,560) at pH 7; 257 (12,160) at pH 13; MS (FAB) *m/e* 399 (M + 1); IR 2250, 1684, 1505, 1222, 1100 (broad), 772, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.8 Hz, H-2'), 5.0 (br s, 1, 5'-OH), 5.33 (br s, 1, 3'-OH), 5.60 (br s, 1, 2'-OH), 5.60 (s, 2, OCH_2Ar), 5.94 (apparent d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.70 (t, 1, Ar-H4), 7.87, 7.90 (2 m, 2, Ar-H3,5), 7.99 (d, 1, Ar-H6), 8.81 (s, 1, H-2), 8.83 (s, 1, H-8), 9.8-10.6 (br, 2H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.81 (C-5'), 69.89 (C-3'), 74.44 (C-2'), 78.56 (OCH_2Ar), 85.83 (C-4'), 87.74 (C-1'), 112.53 (Ar-C2), 117.12 (*C*CN), 119.58 (C-5), 130.50, 131.71, 133.20, 133.38 (Ar-C3,4,5,6), 135.16 (Ar-C1), 142.81 (C-8), 144.23 (C-2), 145.16 (C-4) 148.38 (C-6). *Anal.* Calcd for $C_{18}H_{19}ClN_6O_9 \cdot 0.25H_2O$: C, 42.95; H, 3.90; N, 16.70. Found: C, 42.84; H, 3.92; N, 16.63.

5-Ethoxy-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxol (9a). 6-[1-(4-Methoxyphenyl)ethyl]-1,3-benzodioxol-6-ol **8a** (1.9 g, 0.007 mol) and ethyl iodide (3.3 mL, 0.041 mol) were added to acetone (20 mL) with stirring. Potassium carbonate (7 g, 0.05 mol) was added, and the reaction mixture was refluxed for 48 h. The potassium salts were then removed by filtration and rinsed thoroughly with acetone. Evaporation of the solvent gave a brownish solid which was recrystallized using hot methanol. The desired compound was isolated as white, needle-like crystals (1.3 g, mp 90-90.5 °C). MS (EI) *m/e* 300 (M^+); ^1H NMR (Me_2SO-d_6) δ 7.13 (m, 2, H-Ar), 6.80 (m, 2, H-Ar), 5.90, 5.92 (2 d, 2, -OCH_2O-), 4.37 (q, 1, -*CH*CH_3), 3.88 (m, 2, -OCH_2CH_3), 3.70 (s, 3, -OCH_3), 1.45 (d, 3, -CHCH_3), 1.26 (t, 3, -OCH_2CH_3); IR (KBr) 1504, 1484, 1478, 1430, 1178, 1041, 986, 853, 819, 349 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 157.1, 150.2, 145.4, 140.6, 138.2, 128.0, 127.3, 113.3, 106.9, 100.6, 96.1, 64.5, 54.8, 35.9, 20.9, 14.7. *Anal.* Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.85; H, 6.84.

6-[1-(4-Methylphenyl)ethyl]-1,3-benzodioxol-5-ol (8b). 4-Methylacetophenone (13.4 g, 0.1 mol) was dissolved in 50 mL of ethanol. Sodium borohydride (1.9 g, 0.05 mol) was slowly added, and the mixture was stirred for 3 h. An excess of water was added to precipitate an oil which was isolated by extracting with ether. The ether was removed by vacuum evaporation, and the resulting oil (13.5 g) was refluxed with sesamol (13.8 g, 0.1 mol), oxalic acid (1 g, 0.008 mol), acetic acid (30 mL), and water (2.5 mL) for 5 h. An excess of water was again added to precipitate a solid. Extracting with ether, drying with sodium sulfate, and solvent evaporation gave an off-white solid (6.4 g, mp 116-8 °C). MS (EI) *m/e* 256 (M^+); ^1H NMR (Me_2SO-d_6) δ 9.05 (s, 1, -OH), 7.12 (m, 2, H-Ar), 7.05 (m, 2, H-Ar), 6.62 (s, 1, H-Ar), 6.41 (s, 1, H-Ar), 6.36, 6.34 (2 d, 2, -OCH_2O-), 4.36 (q, 1, -*CH*CH_3), 2.24 (s, 3, CH_3-Ar), 1.44 (d, 3, -CHCH_3); IR (KBr) 3462, 1512, 1437, 1233, 1182, 1175, 1039, 925, 854, 823 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 148.6, 145.0, 143.4, 139.6, 134.3, 128.5, 127.1, 124.5, 106.9, 100.3, 97.4, 20.7, 20.5. *Anal.* Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C,74.99; H, 6.43.

5-Methoxy-6-[1-(4-methylphenyl)ethyl]-1,3-benzodioxol (9b). 6-[1-(4-Methylphenyl)ethyl]-1,3-benzodiol-5-ol **8b** (1.8 g, 0.007 mol) and methyl iodide (3 mL, 0.041 mol) were added to acetone (20 mL) with stirring. Potassium carbonate (7 g, 0.05 mol) was added, and the mixture was stirred for 48 h. An excess of water was added to precipitate an oil which was extracted with ether. The ether was dried

with sodium sulfate and evaporated to give a pale yellow oil (1.2 g) MS (EI) *m/e* 270 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 7.08 (m, 2, H-Ar), 7.04 (m, 2, H-Ar), 6.72 (2 s, 2, H-Ar), 5.81, 5.89 (2 d, 2, -OCH_2O-), 4.37 (q, 1, -CHCH$_3$), 3.67 (s, 3, -OCH$_3$), 2.23 (s, 3, CH_3-Ar), 1.43 (d, 3, -CHCH_3); IR (KBr) 1505, 1483, 1465, 1423, 1192, 1170, 1158, 1040, 854, 349 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 151.2, 145.6, 143.2, 140.6, 134.4, 128.6, 127.0, 126.8, 107.1, 100.7, 95.2, 56.4, 36.1, 20.9, 20.5. *Anal.* Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.81. Found: C, 75.56; H, 6.90.

5-Ethoxy-6-[1-methylphenyl)ethyl]-1,3-benzodioxol (9c). 6-[1-(4-Methylphenyl)ethyl]-1,3-benzodioxol-5-ol **8b** (1.8 g, 0.007 mol) and ethyl iodide (3.3 mL, 0.041 mol) were added to acetone (20 ml) while stirring. Potassium carbonate (7 g, 0.05 mol) was added, and the reaction mixture was refluxed for 48 h. The potassium salts were removed by filtration and rinsed thoroughly with acetone. Evaporation of the solvent gave a dark oil. Water (50 mL) was added, the oil was extracted with ether, dried with sodium sulfate, and the solvent evaporated to give the desired compound as a golden oil (1.3 g). MS (EI) *m/e* 284 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 7.10 (m, 2, H-Ar), 7.04 (m, 2, H-Ar), 6.76 (s, 1, H-Ar), 6.69 (s, 1, H-Ar), 5.91, 5.89 (2 d, 2, -OCH_2O-), 4.37 (q, 1, -CHCH$_3$), 3.89 (m, 2, -OCH_2CH$_3$), 2.24 (s, 3, CH_3-Ar), 1.45 (d, 3, -CHCH_3), 1.25 (t, 3, -OCH$_2$$CH_3$); IR (KBr) 1504, 1484, 1478, 1431, 1178, 1041, 936, 853, 819, 349 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 150.2, 145.5, 143.2, 140.6, 134.3, 128.5, 127.1, 127.0, 106.9, 100.6, 96.1, 64.5, 36.3, 20.8, 20.5, 14.6. *Anal.* Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.71; H, 7.18.

6-[1-(4-Fluorophenyl)ethyl]-1,3-benzodioxol-5-ol (8c). 4-Fluoroacetophenone (13.8 g, 0.1 mol) was dissolved in 50 mL of ethanol. Sodium borohydride (1.9 g, 0.05 mol) was slowly added and the mixture was stirred overnight. An excess of water was added to precipitate an oil which was isolated by extracting with ether. The resulting oil was refluxed overnight with sesamol (13.8 g, 0.1 mol), oxalic acid (1 g, 0.008 mol), acetic acid (30 mL), and water (2.5 mL). An excess of water was added to precipitate a solid which was isolated by filtration. Toluene (200 mL) was then added and evaporated to remove residual acetic acid. The solid was then recrystallized with ether/petroleum ether to give the desired compound as a brown solid (1.4 g, 109.5-111.0 °C). MS (EI) *m/e* 260 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 9.09 (s, 1, -OH), 7.25 (m, 2, H-Ar), 7.06 (m, 2, H-Ar), 6.69 (s, 1, H-Ar), 6.41 (s, 1, H-Ar), 5.85 (d, 2, -OCH_2O-), 4.39 (q, 1, -CHCH$_3$), 1.45 (d, 3, -CHCH_3); IR (KBr) 3436, 1508, 1434, 1218, 1169, 1143, 1037, 836, 816, 543 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 162.0, 158.8 ($^1J_{C,F}$ = 241.3 Hz), 148.7, 145.4, 142.7, 142.6 ($^4J_{C,F}$ = 2.95 Hz), 139.9, 128.9, 128.8 ($^3J_{C,F}$ =7.8 Hz), 124.2, 114.6, 114.4 ($^2J_{C,F}$ = 20.9 Hz), 106.9, 100.4, 97.7, 36.1, 20.7. *Anal.* Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.71; H, 7.18.

5-(2-Propenyloxy)-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxole (9d). 6-[1-(4-Methoxyphenyl)ethyl]-1,3-benzodioxol-6-ol **8a** (1.9 g, 0.007 mol) and allyl iodide (1.17 g, 0.041 mol) were added to acetone (20 mL) with stirring. Potassium carbonate (1.74 g, 0.012 mol) was added, and the reaction mixture was refluxed for 24 h. An excess of water was added to precipitate an oil which was extracted with ether. The ether solution was dried with sodium sulfate and evaporated to give an oil. The desired compound was isolated as an off-white solid (0.7 g, mp 50-51 °C). MS (EI) *m/e* 312 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 7.12 (d, 2, H-Ar), 6.80 (d, 2, H-Ar), 6.74 (s, 1, H-Ar), 6.71 (s, 1, H-Ar), 5.98 (d, 1, -CH=CH$_2$), 5.90

(d, 2, -OCH_2O-), 5.35 (d, 1, -CH=CH_2), 5.21 (d, 1, -CH=CH_2), 4.43 (m, 2, -OCH_2-CH=CH_2), 4.39 (q, 1, -$CH$$CH_3$), 3.68 (s, 3, -O$CH_3$), 1.44 (d, 3, -CH$CH_3$); IR (KBr) 1508, 1485, 1429, 1271, 1235, 1196, 1182, 1037, 929, 835 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 157.2, 149.7, 145.4, 140.8, 138.1, 133.8, 128.0, 127.5, 116.7, 113.4, 107.0, 100.6, 96.5, 69.5, 54.9, 35.8, 20.9. *Anal.* Calcd for $C_{19}H_{20}O_4$: C, 72.81; H, 6.80. Found: C, 73.06; H, 6.45.

6-[1-(2-(3,4-Dimethoxybenzyl)-4,5-dimethoxyphenyl)methyl]-1,3-benzodioxol-5-ol (11). 3,4-Dimethoxybenzyl alcohol (16.8 g, 0.1 mol) was refluxed with sesamol (13.8 g, 0.1 mol), oxalic acid (1 g, 0.008 mol), acetic acid (30 mL), and water (2.5 mL) for 5 h. An excess of water was added to precipitate an oil. Extraction with ether, drying with sodium sulfate, filtering, and solvent evaporation gave an off-white solid (5.4 g); mp 132-133 °C. MS (EI) *m/e* 438 (M^+); ^1H NMR (Me_2SO-d_6) δ 9.18 (s, 1, -OH), 6.80 (d, 1, H-Ar''), 6.75 (s, 1, H-Ar'), 6.73 (s, 1, H-Ar'), 6.68 (s, 1, H-Ar), 6.57 (m, 1, H-Ar''), 6.44 (s, 1, H-Ar), 6.18 (s, 1, H-Ar), 5.81 (2 d, 2, -OCH_2O-), 3.75 (s, 4, -CH_2-), 3.57 (m, 12, -OCH_3); IR (KBr) 1514, 1506, 1436, 1257, 1232, 1228, 1176, 1159, 1138, 1028 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 149.1, 148.6, 147.11, 147.10, 145.4, 139.6, 133.6, 131.4, 131.1, 120.3, 118.9, 114.4, 114.3, 112.5, 111.8, 108.8, 100.4, 97.4, 55.6, 55.5, 55.4, 55.3, 37.2, 31.5. *Anal.* Calcd. for $C_{25}H_{26}O_7$: C, 68.48; H, 5.98. Found: C,68.45; H, 6.07.

5-Methoxy-6-[1-(2-(3,4-dimethoxybenzyl)-4,5-dimethoxyphenyl)methyl]-1,3-benzodioxole (12a). 6-[1-(2-(3,4-dimethoxybenzyl)-4,5-dimethoxyphenyl)methyl]-1,3-benzodiol-5-ol **11** (2.0 g, 0.004 mol) and methyl iodide (3 mL, 0.041 mol) were added to acetone (20 mL) with stirring. Potassium carbonate (7 g, 0.05 mol) was added, and the mixture was stirred for 48 h. An excess of water was added to precipitate a yellow solid which was collected by filtration. The solid was recrystallized using hot methanol. The desired product was isolated as white crystals (1.7 g); mp 107-108 °C. MS (EI) *m/e* 452 (M^+); ^1H NMR (Me_2SO-d_6) δ 6.79 (d, 1, H-Ar''), 6.79 (s, 1, H-Ar'), 6.78 (s, 1, H-Ar), 6.71 (s, 1, H-Ar'), 6.68 (s, 1, H-Ar''), 6.56 (d, 1, H-Ar''), 6.28 (s, 1, H-Ar), 5.90 (s, 2 -OCH_2O-), 3.70 (m, 19, -OCH_3 and -CH_2-); IR (KBr) 1515, 1508, 1484, 1262, 1222, 1196, 1163, 1139, 1024, 869 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 151.5, 148.2, 147.0, 146.9, 145.8, 140.3, 133.4, 131.2, 130.6, 120.9, 120.1, 114.3, 114.2, 112.4, 111.7, 108.9, 100.7, 94.8, 56.2, 55.55, 55.48, 55.4, 55.3, 37.1, 31.4. *Anal.* Calcd for $C_{26}H_{28}O_7$: C, 69.01; H, 6.24. Found: C, 68.95; H, 6.61.

5-Ethoxy-6-[1-(2-(3,4-dimethoxybenzyl)-4,5-dimethoxyphenyl)methyl]-1,3-benzodioxole (12b). 6-[1-(2-(3,4-dimethoxybenzyl)-4,5-dimethoxyphenyl)methyl]-1,3-benzodioxole **11** (2.0 g, 0.004 mol) and ethyl iodide (3.3 mL, 0.041 mol) were added to acetone (20 mL) while stirring. Potassium carbonate (7 g, 0.05 mol) was added, and the reaction mixture was refluxed for 72 h. An excess of water was added to precipitate a solid which was filtered and recrystallized with hot methanol. The desired compound was isolated as a white solid (1.2 g); mp 105-6 °C. MS (EI) *m/e* 466 (M^+); ^1H NMR (Me_2SO-d_6) δ 6.79 (d, 1, H-Ar''), 6.75 (s, 1, H-Ar'), 6.72 (s, 1, H-Ar), 6.70 (s, 1, H-Ar'), 6.65 (m, 1, H-Ar''), 6.52 (m, 1, H-Ar''), 6.30 (s, 1, H-Ar), 5.87 (s, 2, -OCH_2O-), 3.94 (q, 2, -$CH_2$$CH_3$), 3.78, 3.70 (2 s, 4, -$CH_2$-), 3.66 (m, 12, -O$CH_3$), 1.24 (t, 3, -O$CH_2$$CH_3$); IR (KBr) 1514, 1489, 1475, 1254, 1229, 1148, 1138, 1101, 1038, 1030 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 150.6, 148.5, 146.9, 146.88, 145.7, 140.3, 133.4, 131.1, 130.7, 121.3, 120.1, 114.2, 112.3, 111.7, 108.9, 100.6, 95.8, 64.3, 55.53, 55.46, 55.42, 55.3, 37.1, 31.4, 14.7. *Anal.* Calcd for $C_{27}H_{30}O_7$: C, 69.51; H, 6.48. Found: C, 69.35; H, 6.76.

3-Phenylbenzo-1,4-thiazin-2-one oxime (15a). α-Chloroisonitrosoacetophenone (2 g, 0.011 mol) and 2-aminothiophenol (1.38 g, 0.011 mol, 1.17 mL) were dissolved in benzene, and the mixture was cooled in an ice bath. Sodium methoxide (0.65 g, 0.012 mol) was slowly added with stirring, and the reaction mixture was allowed to slowly warm to room temperature. The mixture was then heated at reflux for 2 h and cooled. The yellow solid was collected and dried. Recrystallization from boiling ethanol gave yellow needle-like crystals (3.7 g); mp 220-221 °C. MS (FAB) *m/e* 255 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 12.92 (s, 1, -OH or -NH), 7.78 (m, 2, H-Ar), 7.60 (m, 1, H-Ar), 7.46 (m, 4, H-Ar), 7.36 (m, 2, H-Ar). IR (KBr) 3053, 3037, 3024, 2904, 2768, 2730, 1145, 1004, 994, 696 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 153.5 (C-5'), 140.5 (C-2), 137.9 (C-3'), 137.6 (Ph-C-1), 131.2 (C-5), 129.5 (Ph-C-4), 129.2 (Ph-C-2), 128.5 (C-6), 127.5 (Ph-C-3), 127.1 (C-7), 125.7 (C-8), 122.5 (C-8'). *Anal.* Calcd for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.01. Found: C, 65.94; H, 4.28; N, 11.09.

3-(4-Fluorophenyl)-benzo-1,4-thiazin-2-one oxime (14b). 2-Aminothiophenol (1.25 g, 0.01 mol) was added to methanol (100 mL) with stirring. The solution was cooled in an ice bath, and sodium methoxide (0.54 g, 0.01 mol) and α-chloroisonitroso-4'-fluoroacetophenone (2 g, 0.01 mol) were slowly added. After 24 h of stirring, the solvent was removed by distillation, leaving a solid which was recrystallized with ethanol. The desired compound was isolated as a yellow solid (2.3 g); mp 243-244 °C. MS (EI) *m/e* 272 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 12.92 (s, 1, -OH or -NH), 7.86 (m, 2, H-Ar), 7.60 (m, 1, H-Ar), 7.47 (m, 1, H-Ar), 7.36 (m, 2, H-Ar), 7.26 (m, 2, H-Ar); IR (KBr) 3049, 3024, 2763, 1600, 1508, 1412, 1238, 998, 831, 754 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 164.4, 161.2, 152.3, 140.5, 137.8, 133.94, 133.90, 131.7, 131.6, 131.2, 128.5, 127.1, 125.7, 122.6, 114.6, 114.3. *Anal.* Calcd for $C_{14}H_9FN_2OS$: C, 61.75; H, 3.33; N, 10.29. Found: C, 61.73; H, 3.57; N, 10.18.

3-[4-Methoxyphenyl]-benzo-1,4-thiazin-2-one oxime (14c). 2-Aminothiophenol (1.12 g, 0.009 mol) was added to methanol (100 mL) with stirring. The solution was cooled in an ice bath, and sodium methoxide (0.48 g, 0.009 mol) and α-chloroisonitroso-4'-fluoroacetophenone (2 g, 0.01 mol) were slowly added. After 24 h of stirring, the solvent was removed by distillation, leaving a solid which was recrystallized with methanol. The desired compound was isolated as a yellow solid (1.2 g); mp 199-200 °C. MS (EI) *m/e* 284 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 12.88 (s, 1, -OH or -NH), 7.74 (m, 2, H-Ar), 7.59 (m, 1, H-Ar), 7.46 (m, 1, H-Ar), 7.32 (m, 2, H-Ar), 7.00 (m, 2, H-Ar), 3.83 (s, 3, CH_3); IR (KBr) 3137, 3057, 2908, 1606, 1510, 1442, 1253, 1179, 994, 828 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 160.6, 152.4, 140.6, 138.2, 131.2, 131.0, 129.8, 128.0, 126.9, 125.6, 122.5, 112.9, 55.2. *Anal.* Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.26; N, 9.85. Found: C, 63.08; H, 4.57; N, 10.07.

Chloromethanesulfonic Acid, 1,4-Butanediyl Ester (18a). Into a 100-mL three-necked round-bottomed flask equipped with an addition funnel, magnetic stirring bar, and a calcium sulfate drying tube was added chloromethanesulfonyl chloride[10-12] (15.5 g, 0.105 mol) dissolved in ethyl acetate (50 mL), with stirring and chilling in a salt-ice bath. A solution of triethylamine (17.3 mL, 0.125 mol) and 1,4-butanediol (4.7 g, 0.052 mol) was dissolved in ethyl acetate (10 mL) and added dropwise over 45 min with stirring. The reaction mixture was stirred for 2 h and then stored in a refrigerator overnight. The triethylamine hydrochloride was removed by filtration and washed with ethyl acetate. The filtrate was washed with brine

solution (3 x 25 mL), dried over $MgSO_4$, filtered, and evaporated. The solid residue was triturated with ethyl acetate and dried over phosphorus pentoxide; yield, 6.4 g (39%); IR (KBr) 1361, 1172, 1141, 1137, 1029, 937, 882, 855, 544 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.80 (m, 4, -$OCH_2CH_2CH_2CH_2O$-), 4.37 (m, 4, -$OCH_2CH_2CH_2CH_2O$-), 5.35 (s, 4, $ClCH_2SO_2$). *Anal.* Calcd for $C_6H_{12}Cl_2O_6S_2$: C, 22.86; H, 3.84. Found: C, 22.96; H, 3.97.

(Methylsulfonyl)methanesulfonic Acid, 1,4-Butanediyl Ester (18b). Into a 100-mL round-bottomed flask equipped with an addition funnel, calcium sulfate drying tube, and a magnetic stirring bar was added methylsulfonylmethanesulfonyl chloride[10-12] (7 g, 36.3 mmol) and ethyl acetate (50 mL). The reaction solution was chilled in an ice bath and a solution of 1,4-butanediol (1.64 g, 18.2 mmol) and triethylamine (4.4 g, 43.6 mmol) in ethyl acetate (10 mL) was added dropwise over 10-15 minutes. The mixture was stirred for 4 h in the ice bath before the insoluble precipitate was collected and washed with more ethyl acetate. The filtrate was washed with brine (3 x 25 mL), dried over $MgSO_4$, filtered, and evaporated: yield 1.0 g (14%). The previously separated EtOAc insoluble residue was treated with water, and the insoluble material was collected, washed again with water, and dried, yield 4.4 g (60%). The two crops were combined, dissolved in acetonitrile, filtered, diluted with benzene until cloudy, and scratched to initiate crystallization. The product was collected and dried at room temperature over phosphorus pentoxide, yield, 3.6 g (49%); mp 135-137 °C cap; IR (KBr) 1350, 1333, 1319, 1229, 1183, 1175, 1170, 1123, 929, 865 cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 1.98 (m, 4, -$OCH_2CH_2CH_2CH_2O$-), 3.25 (s, 6, SO_2CH_3), 4.53 (m, 4, -$OCH_2CH_2CH_2CH_2O$-), 5.25 (s, 4, -$SO_2CH_2SO_2$-). *Anal.* Calcd for $C_8H_{18}O_{10}S_4$: C, 23.87; H, 4.51. Found: C, 23.73; H, 4.70.

Chloromethanesulfonic Acid, 4-[(Methanesulfonyl)oxy]butyl Ester (23a). 4-Benzyloxybutanol [20] (10 g, 55.6 mmol) and triethylamine (6.73 g, 66.7 mmol) dissolved in ethyl acetate (10 mL) was added dropwise over 40 min to a chilled solution of methanesulfonyl chloride[10-12] (6.37 g, 55.6 mmol) in ethyl acetate (20 mL). The mixture was stirred in an ice bath for 4 h before the triethylamine hydrochloride was removed by filtration. The residue was washed with ethyl acetate, and the filtrate and washings were washed with brine, dried over $MgSO_4$, filtered, and evaporated. A yellow oil was obtained which was passed through a column of silica gel (300 g) and eluted with 2:1 hexane:ethyl acetate. The appropriate fractions, as identified by TLC, were combined and evaporated, giving 9.2 g of **23a** from two crops. Both crops were dissolved in ethyl acetate (100 mL), and the benzyl group was removed by hydrogenation at atmospheric pressure using 10% Pd/C as catalyst. The catalyst was removed by filtration through a Celite pad. The filtrate was then chilled in an ice bath and treated with triethylamine (4.3 g, 42.5 mmol). A solution of chloromethanesulfonyl chloride (5.2 g, 0.035 mol) in ethyl acetate (10 mL) was added dropwise over 25 min. The mixture was stirred for 0.5 h and stored at 6-10 °C overnight. The triethylamine hydrochloride was removed by filtration and washed with ethyl acetate. The filtrate was washed with brine, dried over $MgSO_4$, filtered, and evaporated; crude yield 7.4 g.

After two recrystallizations from ethyl acetate: hexane, 2.6 g (27%) of pure product was obtained; mp 44-46 $°C_{cap}$; IR (KBr) 1364, 1351, 1338, 1170, 1982, 938, 925, 879, 856, 532 cm^{-1}; ^1H NMR ($CDCl_3$)

δ 1.9 (m, 4, -$OCH_2CH_2CH_2CH_2O$-), 3.02 (s, 3, SO_2CH_3), 4.29, 4.46 (2 m, 4, -$OCH_2CH_2CH_2CH_2O$-), 4.62 (s, 2, SO_2CH_2Cl). *Anal.* Calcd for $C_6H_{13}ClO_6S_2$: C, 25.67; H, 4.67. Found: C, 25.80; H, 4.75.

(Methylsulfonyl)methanesulfonic Acid, 4-[(Methylsulfonyl)oxy]butyl Ester (23b). 4-Benzyloxybutanol (20)[13] (10 g, 55.6 mmol) and triethylamine (6.7 g, 66.7 mmol) were dissolved in ethyl acetate (15 mL) and added dropwise with stirring to a cold solution of methanesulfonyl chloride[10-12] in ethyl acetate (25 mL) in an ice bath. The reaction mixture was stirred for 2 h and stored overnight in a refrigerator. The triethylamine hydrochloride was removed by filtration and washed with ethyl acetate. The filtrate was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified with a silica gel (300 g) column using 2:1 hexane-ethyl acetate. yield, 9.2 g (64%). The sulfonate ester was dissolved in ethyl acetate (100 mL) and hydrogenated at atmospheric pressure with 10% Pd/C. The catalyst was removed by filtration through a Celite pad. Triethylamine (4.3 g, 42.5 mmol) was added to the filtrate (and washings) with good stirring in an ice bath followed by the addition of a solution of (methylsulfonyl)methanesulfonyl chloride[10-12] (5.4 g, 28.3 mmol) in ethyl acetate (25 mL). The reaction mixture was stirred for 1 h at 0 °C and stored overnight in the refrigerator. The triethylamine hydrochloride was removed by filtration, washed with ethylacetate, and the filtrate (and washings) was washed with brine, dried over $MgSO_4$, filtered, and evaporated. After two recrystallizations from ethyl acetate-hexane, a pure product was obtained, yield, 3.6 g (39%); mp 97-98.5 °C; IR (KBr) 1370, 1351, 1339, 1330, 1309, 1177, 1160, 934 (broad), 854, 527 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.92 (m, 4, -$OCH_2CH_2CH_2CH_2O$-), 3.19 (s, 3, -OSO_2CH_3), 3.25 (s, 3, $CH_2SO_2CH_3$), 4.31, 4.51 (2 m, 4, -$OCH_2CH_2CH_2CH_2O$-), 5.22 (s, 2, $CH_3SO_2CH_2$). *Anal.* Calcd for $C_7H_{16}O_8S_3$: C, 25.92; H, 4.97. Found: C, 26.02; H, 4.94.

2′,3′,5′-O-Acetylformycin B (3-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidin-7-one, 34). Formycin B (33) was suspended with stirring in 100 mL of dry pyridine and 100 mL of acetic anhydride. The reaction mixture was protected from moisture with an argon atmosphere. (No exothermic heat was detectable.) The reaction mixture was chilled briefly in an ice bath, stored in the refrigerator, and shaken occasionally. Complete solution was achieved in less than 24 h. Since TLC indicated the reaction was complete, the solvents were removed at reduced pressure. The resulting syrup was treated with 50 mL of ethanol and refluxed for 15 min. The ethanol was evaporated, and additional portions of ethanol were evaporated until a foam was obtained. The foam was dissolved in chloroform and washed with 2 x 50 mL portions of 1 *N* HCl, water, saturated $NaHCO_3$, and brine. The $CHCl_3$ solution was dried, filtered, and evaporated to a foam. The foam was dissolved in 50 mL of hot water, filtered, and allowed to cool. Because oiling occurred, the mixture was warmed and the solution was decanted. The warm solution was cooled slowly, and the sides of the flask were scratched with a glass rod to induce crystallization. The white product was collected and dried over phosphorus pentoxide; yield, 5.3 g (36%); mp 171-172 °C cap; UV λ_{max} 274 nm (7,600), 217 (15,400) at pH 1; 277 (7,600), 217 (15,700) at pH 7; 291 (8,700), 229 (15,900) at pH 13; MS (FAB) *m/e* 394 (M + 1); IR KBr) 1745, 1728, 1699, 1679, 1590, 1377, 1254, 1230, 1041, 924 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.00, 2.02, 2.09 (3 s, 9, -$COCH_3$), 4.10, 4.34 (2 m, 2, CH_2-5′),

4.27 (apparent q, 1, H-4′), 5.21 (d, 1, H-1′), 5.48 (t, 1, H-3′), 5.78 (t, 1, H-2′), 7.92 (s, 1, H-2). *Anal.* Calcd for $C_{16}H_{18}N_4O_8$: C, 48.73; H. 4.60; N, 14.21. Found: C, 48.66; H, 4.74; N, 14.26.

1-β-D-Ribofuranosylimidazo[1,2-*b*]pyrazole-7-carbonitrile (40). A suspension of 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*b*]pyrazole-7-carbonitrile (**39**, 13 g, 0.023 mol) in about 500 mL of methanolic ammonia (saturated at 0 °C) was allowed to stand with occasional stirring at room temperature in a bomb for 3 days. The ammonia was then allowed to escape and the solution was evaporated to a yellow gum. The residue was extracted with hot benzene (4 x 500 mL) to remove benzamide. The residue was recrystallized from ethanol and the product was collected and dried at room temperature over phosphorus pentoxide, yield, 3,7 g; UV λ_{max} 243 nm (16,100) at pH 1; 243 (15,800) at pH 7; 244 (15,700) at pH 13; MS (FAB) *m/e* 265 (M + 1); IR (KBr) 1614, 1499, 1305, 1210, 1186, 1135, 1120, 1105, 1060, 1047, 1020, 870, 855, 700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.60 (m, 2, CH_2-5′), 3.94 (apparent q, 1, H-4′), 4.06 (apparent q, 1, H-3′), 4.35 (q, 1, H-2′), 5.03 (t, 1, OH-5′), 5.31 (d, 1, OH-3′), 5.59 (d, 1, OH-2′), 5.65 (d, 1, H-1′), 7.68 (d, 1, H-2), 7.98 (d, 1, H-3), 8.15 (d, 1, H-6). *Anal.* Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 50.24; H, 4.88; N, 20.90.

6-Ethylthiopurine Riboside [AVS-2700] (42a). In a 250-mL round-bottomed flask stoppered with a calcium sulfate drying tube was mixed 6-mercaptopurine riboside (11 g, 38.7 mmol), freshly dried potassium carbonate (5.9 g, 42.6 mmol), and dry *N,N*-dimethylacetamide. To this well-stirred mixture was added ethylbromide (4.2 g, 38.7 mmol), dropwise over 3-5 min under nitrogen atmosphere. After 1.5 h at room temperature, thin-layer chromatography indicated mostly product along with some starting 6-MPR. The reaction mixture was heated at 55-60 °C for 1 h and filtered hot through a Celite pad. The flask and residue were washed with several portions of acetone, and the combined filtrate and washings were evaporated *in vacuo* to a syrup at <50 °C. The syrup was treated twice with 150 mL portions of EtOH and evaporated. The syrup was then pumped at maximum vacuum for several hours. The residue was dissolved in 150 mL of hot acetone, filtered, concentrated to ~100 mL, cooled, and scratched to induce crystallization. The white product was collected, washed with a little acetone, and dried at 65 °C for 18 h over phosphorus pentoxide; yield, 6.0 g (50%); mp 100-107 °C cap; UV λ_{max} 294 nm (17,600) 225 nm (10,300) at pH 1; 292 (19,300), 225 (10,800) at pH 7; 292 (19,400), 225 (10,700) at pH 13; MS (FAB) *m/e* 313 (M + 1); IR 1567, 1435, 1420, 1335, 1211, 1170, 1127, 1119, 1084, 1058, 944 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.37 (t, 3, SCH_2CH_3), 3.36 (q, 2, SCH_2CH_3), 3.57, 3.70 (2 m, 2, CH_2-5′), 3.98 (apparent q, 1, H-4′), 4.18 (apparent q, 1, H-3′), 4.61 (q, 1, H-2′), 5.13 (t, 1, OH-2′), 5.24 (d, 1, OH-3′), 5.53 (d, 1, OH-5′), 6.00 (d, 1, H-1′), 8.71 (s, 1, H-8), 8.74 (s, 1, H-2). *Anal.* Calcd for $C_{12}H_{16}N_4O_4S$: C, 46.14; H, 5.16; N, 17.94. Found: C, 45.90; H, 5.31; N, 17.80.

6-Allylthiopurine Riboside (42b). Into a 100-mL round-bottomed flask stoppered with a calcium drying tube was mixed 6-mercaptopurine riboside (1.9 g, 6.69 mmol), freshly dried potassium carbonate (1.02, 7.36 mmol), and *N,N*-dimethylacetamide (60 mL). Allyl bromide (0.81 g, 6.85 mmol) was added dropwise to this well-stirred mixture, and the reaction mixture was stirred for 2 h at room temperature. When TLC showed the reaction to be complete, it was evaporated *in vacuo* at less than 40 °C, and then ethanol (75 mL) was added and evaporated twice. The resulting gummy material was dissolved in

chloroform-methanol and passed through a silica gel flash column with 19:1 chloroform:methanol as eluent. Appropriate fractions (TLC) were combined and evaporated. This material was again column chromatographed on 150 g silica gel with 9:1 $CHCl_3$-MeOH as solvent. The proper fractions were combined and evaporated to give a glassy, hygroscopic solid (750 mg, 36%); UV λ_{max} 293 nm (18,900) at pH 1; 292 (20,300) at pH 7; 292 (20,400) at pH 13; MS (FAB) *m/e* 325 (M + 1); IR (KBr) 1568, 1334, 1207, 1120, 1080, 1051 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.70 (2 m, 2, CH_2-5'), 3.98 (apparent q, 1, H-4'), 4.07 (d, 2, $SCH_2CH{=}CH_2$), 4.19 (apparent q, 1, H-3'), 4.60 (apparent q, 1, H-2'), 5.10 (m, 1, OH-5'), 5.14 (m, 2, $CH{=}CH_2$), 5.21 (d, 1, OH-3'); 5.36 (m, 2, $CH{=}CH_2$), 5.52 (d, 1, OH-2'), 6.00 (d, 1, H-1'), 6.00 (m, 1, $SCH_2CH{=}CH_2$), 8.72, 8.75 (2 s, 2, H-2,8). *Anal.* Calcd for $C_{13}H_{16}N_4O_4S \cdot 0.15EtOH \cdot 0.05CHCl_3$: C, 47.19; H, 5.07; N, 16.61. Found: C, 47.10; H, 5.50; N, 16.52.

4-Amino-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (48). The 10% Pd/C catalyst (200 mg) was added to a solution of 4-amino-3-bromoribofuranosylpyrazolopyrimidine **47** (2.3 g, 6.4 mmol) and 50% aqueous ethanol (150 mL), and the mixture was hydrogenated at 40 psi at room temperature for 48 h. The reaction mixture was the filtered through a Celite pad, and the filtrate was evaporated to give a residual solid (0.7 g, 37.6%); mp 205-210 °C; MS (EI) *m/e* 267 (M^+); IR (KBr) 3424, 3258, 3221, 3165, 3157, 3151, 1658, 1603, 1573, 1041; ^1H NMR (Me_2SO-d_6) δ 3.44 (m, 1, H-5'), 3.56 (m, 1, H-5'), 3.92 (m, 1, H-4'), 4.22 (m, 1, H-3') 4.62 (m, 1, H-2'), 4.88 (t, 1, OH), 5.12 (d, 1, OH), 5.36 (d, 1, OH), 6.08 (d, 1, H-1'), 7.76 (br s, 2, NH_2), 8.2 (d, 1, H-Ar); ^{13}C NMR (Me_2SO-d_6) δ 133.2 (C-3), 100.4 (C-4), 157.9 (C-5), 153.8 (C-7), 155.9 (C-9), 88.5 (C-1'), 73.1 (C-2'), 70.8 (C-3'), 85.0 (C-4'), 62.3 (C-5). *Anal.* Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.53. Found: C, 42.10; H, 5.42; N, 24.42. A second batch of 4-amino-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine was prepared by the reduction of **47** (2.2 g, 6.3 mmol) with $Pd/BaSO_4$ (200 mg) in ethanol to give 0.7 g (41.6%). MS (EI) *m/e* 267 (M^+). *Anal.* Calcd for $C_{10}H_{13}N_5O_4 \cdot 2H_2O$: C, 39.60; H, 5.65; N, 23.05. Found: C, 39.20; H, 5.40; N, 23.03. All other analytical data was essentially the same.

1-Adamantyl, 3-*t*-Butylthiourea [AVS-2885] (50). 1-Adamantamine (49) (10 g, 66 mmol) was dissolved in 150 mL hexane. Insoluble material was filtered out and then *t*-butylisothiocyanate (8.4 mL, 66 mmol) was added. After stirring for 3 h, solvent was removed yielding 10.7 g in two batches of white solid. Submitted batch mp 137-139 °C; ^1H NMR ($CDCl_3$) δ 5.8 (br s, 1, NH), 5.6 (br s, 1, NH), 2.15 (s, 9, CH, CH_2), 1.7 (s, 4, CH_2), 1.45 (s, 9, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 179.5 (s, 1, C=S), 54.2, 53.2 (2 s, 2, C-NH), 42.2 (s, 3, adamantyl C), 36.2 (s, 3, adamantyl C), 29.5 (s, 3, adamantyl C), 29.4 (s, 3 $C(CH_3)_3$); IR 3274, 2907, 1537, 1391, 1356, 1324, 1310, 1299, 1201 cm^{-1}. *Anal.* Calcd for $C_{15}H_{26}N_2S$: C, 67.64; H, 9.84; N, 10.52. Found: C, 67.36; H, 9.99; N, 10.35.

Methyl 2-[(2-Ethoxy-2-oxoethyl)hydrazono]propanoate [AVS-2909] (51). Sodium acetate (6.36 g, 77.6 mmol) was dissolved in a mixed solvent system consisting of MeOH (97 mL) and water (32 mL). Ethyl hydrazinoacetate monohydrochloride (12 g, 77.6 mmol) was added as a solid and the reaction mixture was stirred at room temperature for 48 h. The solvents were then evaporated to dryness and the residue was dissolved in chloroform and washed with water. The pH 5 water layer was then adjusted to pH 7 with 1 *N* NaOH. The aqueous layer was then extracted twice with chloroform. The chloroform layers were

combined, dried with $MgSO_4$, filtered, and evaporated. After drying *in vacuo* over P_2O_5, the resulting yellow oil crystallized giving a pale yellow solid in from 80-100% yield. Crystallization from ether-petroleum ether (30-60 °C) (5:1) provided **51** as a white crystalline solid. MS (EI) *m/e* 202 (M^+); mp 65 °C; ^1H NMR (Me_2SO-d_6) δ 1.22 (t, 3, $COOCH_2CH_3$), 1.87 (s, 4, CH_3C=N), 3.64 (s, 3, $COOCH_3$), 4.05 (d, 2, $NHCH_2CO_2$), 4.11 (q, 2, $COOCH_2CH_3$), 7.67 (t, 1, NH). *Anal.* Calcd for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.30; H, 6.97; N, 13.90.

3(5)-Carbomethoxy-4-hydroxy-5(3)-methylpyrazole (52).[22] Sodium (3.1 g, 135 mmol) was added to cold (5 °C) MeOH (200 mL). After the sodium had reacted, crude methyl pyruvate hydrazone (**51**) (10.4 g, 51.4 mmol) was added in one aliquot, and the solution was heated at reflux for 4 h. The solution was chilled in an ice bath and then, concentrated HCl (11.2 mL) was added slowly over 10 min. (If necessary, more HCl or $NaHCO_3$ is added to adjust the pH to near neutral by pH paper.) Most of the MeOH was then evaporated, and the residue was dissolved in water. After readjusting the pH to near 7, the product was extracted with ethyl acetate (7 x 40 mL). The ethyl acetate layers were combined, dried with sodium sulfate, filtered, and evaporated to dryness. The crude product (7.22 g, 90% yield) was used in the next step without further purification. An analytical sample was obtained by column chromatography on 400 mesh silica gel with chloroform-methanol (9:1) as the eluant. MS (EI) *m/e* 156 (M^+); mp 154-155 °C; ^1H NMR (Me_2SO-d_6) δ 2.10 (s, 3, CH_3), 3.77 (s, 3, $COOCH_3$), 8.35, 12.75 (br s, 2, OH and NH). *Anal.* Calcd for $C_6H_8O_3N_2$: C, 46.15; H, 5.16; N, 17.94. Found: C, 45.82; H, 5.36; N, 17.89.

Methyl 1-Acetyl-4-acetyloxy-3-methyl-1*H*-pyrazole-5-carboxylate [AVS-2956] (53). Crude **52** (5.78 g, 37 mmol) was dissolved in acetic anhydride (50 mL) and pyridine (27 mL), and the mixture was then heated at 90 °C for 3 h. After cooling, the solvents were removed by vacuum, and the residue was dissolved in diethyl ether and washed with water (2 x 30 mL). The ether layer was dried with sodium sulfate, filtered, and evaporated to give an orange-tinted residue. Trituration with cold ether, filtering, and drying gave 7.55 g of **53** (two crops, 85%) as fine white needles. MS (EI) *m/e* 240 (M^+); mp 75-77 °C; ^1H NMR (Me_2SO-d_6) δ 2.33 (s, 3, $COCH_3$), 2.4 (s, 3, $COCH_3$), 2.68 (s, 3, CH_3), 3.84 (s, 3, $COOCH_3$); ^{13}C NMR (Me_2SO-d_6) δ 10.64 (3-CH_3), 20.03, 22.39 ($OCOCH_3$ and $NCOCH_3$), 52.10 ($COOCH_3$), 134.38, 134.56, 136.61 (C-3, C-4, C-5), 160.25 ($COOCH_3$), 168.33, 171.38 (NCO-, OCO-). *Anal.* Calcd for $C_{10}H_{12}N_2O_5$: C, 50.02; H, 5.00; N, 11.67. Found: C, 49.73; H, 5.15; N, 11.66.

Methyl 1-Acetyl-4-acetyloxy-3-bromomethyl-1*H*-pyrazole-5-carboxyate [AVS 2996] (54). Compound **53** (3.0 g, 12.5 mmol), benzoyl peroxide (250 mg, 1.03 mmol), *N*-bromosuccinimide (4.90 g, 27.5 mmol) and potassium carbonate (1.0 g, 7.23 mmol) were added to CCl_4 (120 mL) and refluxed for 2 h. After chilling the mixture to 5-10 °C, the solution was filtered and evaporated *in vacuo*. Trituration of the residue with isopropanol crystallized the product which was filtered and dried to give 3.28 g (82%) of **54** as a white solid; mp 94-96 °C; MS (FAB) *m/e* 319 (M + 1); ^1H NMR (Me_2SO-d_6) δ 2.38 (s, 3, $OCOCH_3$), 2.73 (s, 3, $NCOCH_3$), 3.87 (s, 3, $COOCH_3$), 4.86 (s, 2, CH_2Br). *Anal.* Calcd for $C_{10}H_{11}BrN_2O_5$: C, 37.64; H, 3.47; N, 8.78. Found: C, 37.73; H, 3.63; N, 8.64.

3(5)-[(1,3-Dibenzyloxy-2-propoxy)methyl]-4-hydroxy-1*H*-pyrazole-5(3)-carboxamide (56) Via Methyl 3(5)-[(1,3-Dibenzyloxy-2-propoxy)methyl]-4-hydroxy-1*H*-pyrazole-5(3)-carboxylate (55). Di-*O*-benzylglycerol (17.07

g, 62.66 mmol) in dry THF (20 mL) was added dropwise over 0.5 h at room temperature to a stirred suspension of 60% NaH (2.51 g, 62.64 mmol) in dry THF (60 mL). Approximately 1 h after the addition was complete, bromomethylpyrazole **54** (4.5 g, 14.1 mmol) in dry THF (20 mL) was added in one aliquot at room temperature under nitrogen. After stirring 15 min at room temperature, the temperature was raised to 60 °C for 0.5 h. The reaction was immediately cooled in an ice bath, and acetic acid (3.76 g, 62.66 mmol) was added dropwise, resulting in the reaction mixture acquiring a deep red color. The solvents were evaporated, and the residue was partitioned between water and ethyl acetate. The resulting emulsion was treated with a small amount of acetic acid and extracted with ethyl acetate (4 x 100 mL). The ethyl acetate extracts were combined and evaporated to dryness to give a semisolid residue that was chromatographed on silica gel (70-230 mesh) eluting first with chloroform to remove excess di-*O*-benzylglycerol and then with ethyl acetate to elute product **55** as part of a complex mixture. The combined product-containing fractions were evaporated to dryness giving 4.5 g of a residue which was added to cold saturated methanolic ammonia (~25 mL) and transferred to a steel bomb. The mixture was heated at 95 °C for 5 h, cooled, and evaporated to dryness. After being dissolved in a small amount of chloroform and filtering, the filtrate was chromatographed on silica gel (230-400 mesh) with a $CHCl_3$-MeOH gradient (98-95%). An additional 1.4 g of di-*O*-benzylglycerol and a small amount of unreacted **55** were obtained by eluting with $CHCl_3$/MeOH (98:2). Switching the gradient to 95:5 resulted in the elution of product **56** as a clear oil which solidified on standing, 740 mg (35% per step over two steps); MS (FAB) *m/e* 412 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 3.52 (m, 4, -CH_2CHCH_2-), 3.80 (br s, 1, -CHO-CH_2-), 4.47 (s, 4, -CH_2Ph), 4.56 (s, 2, -CHOCH_2-), 7.31 (m, 10, Ph), 7.33-7.7 (m, 2, $CONH_2$), 8.69, 9.38 (br s, 1, 4-OH), 12.89, 12.96 (br s, 1, NH, mixture of tautomers).

3(5)-[(1,3-Dihydroxy-2-propoxy)methyl]-4-hydroxy-1*H*-pyrazole-5(3)-carboxamide (57). Compound **56** (520 mg, 1.26 mmol) and palladium hydroxide on carbon (100 mg) were added to EtOH-cyclohexene (1:1) and heated at reflux for 16 h. Because the reaction was incomplete, additional catalyst (20 mg) was added and reflux was continued for 8 h. The reaction mixture was cooled, filtered through Celite, and the filtrate was evaporated to dryness. Acetone was added and evaporated away several times to produce a white solid which was filtered and dried to give 239 mg of the desired product (82% in two crops); mp 134-136 °C; MS (FAB) *m/e* 232 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 3.42 (m, 5, -CH_2CHCH_2-), 4.56 (s, 2, -CH_2OCH-), 6.86 (br s, 1, $CONH_2$), 7.44 (br s, 2, 4-OH, $CONH_2$), 12.84 (br s, 1, NH). *Anal.* Calcd for $C_8H_{13}N_3O_5$: C, 41.56; H, 5.67; N, 18.17. Found: C, 41.10, H, 5.83; N, 18.29.

1-Aminoadenosinium Mesitylene Sulfonate [AVS-4610] (58). Freshly prepared *O*-mesitylenesulfonylhydroxylamine (6 g) was added to a solution of adenosine (2.67 g) in methanol (200 mL). The solution was stirred at room temperature for 30 min and then immersed in a dry ice-isopropanol bath. The precipitate (2.7 g) was collected and dried; mp 193-194 °C; MS (FAB) *m/e* 283 (M + 1); UV λ_{max} 258 (12,740) at pH 1, 258 (12,790) at pH 7, 258 (13,460) at pH 13; IR 3282, 3149, 3650-2800 (broad, NH_2, NH, OH, SO_3H), 2930, 1692 (SO_3H) 1635, 1605 (aromatic), 1560, 1510, 1420, 1230, 1210, 1175, 1120, 1085, 1065, 1015, 905, 860 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 10.15-10.05 and 9.25-9.15 (br s, 2, C=NH and MesOH), 6.65-6.50 (br s, 2, NH_2), 5.95 (d, 1, J = 5 Hz, C_1,2-H), 4.52 (t, 1, C_2,-

H), 4.18 (t, 1, $C_{3'}$-H), 4.0 (q, 1, $C_{4'}$-H), 3.64 (2 q, 2, $C_{5'}$-H), 2.5 (s, 6, ortho protons of MesOH), 2.15 (s, 3, para protons of MesOH); ^{13}C NMR (Me_2SO-d_6) δ 151.4 (C-6), 148.9 (C-2, $^1J_{CH}$ = 218.8 Hz), 145.7 (C-4, $^3J_{C_{4'},H_8}$ = 13.15 Hz, $^3J_{C_{4'},H_2}$ = 5.1 Hz), 142.5 (C-8, $^1J_{C_{8'},H_{8'}}$ = 217.8 Hz, $^3J_{C_{8'},H_{1'}}$ = 4.05 Hz), 142.2 (C-SO_3H), 136.3 (Ph-C-4), 135.7 (Ph-C-2), 129.7 (Ph-C-3), 118.5 (C-5), 87.7 (C-1', $^1J_{C_{1'},H_{1'}}$ = 167.2 Hz), 85.8 (C-4'), 74.3 (C-2'), 70.0 (C-3'), 60.9 (C-5'), 22.6 (*o*-CH_3), 20.2 (*p*-CH_3). *Anal.* Calcd for $C_{19}H_{26}N_6SO_7$: C, 46.84; H, 5.49; N, 17.27. Found: C, 46.93; H, 5.53; N, 17.46.

5'-Deoxyadenosine, 5'-*N,N*-Diethylthiocarbamate [AVS-4618] (61). A hot, stirred solution of 5'-tosyladenosine **62** (3.15 g, 7.47 mmol) in ethanol (300 mL) was treated with sodium diethyldithiocarbamate (2.36 g, 10.46 mmol). This reaction solution was heated at reflux for 4 h. The solvent was removed under reduced pressure, and the residual solid was stirred in cold water (50 mL). The white solid product was collected, washed with cold water, and dried *in vacuo* (P_2O_5). Yield, 2.34 g, 78%); mp 168-170 °C; MS (FAB) *m/e* 399 (M + 1); UV λ_{max} 258 (23,470) at pH 7, 258 (24,400) at pH 13; IR 3500, 3129, 2975, 2925, 3450-2800 (broad) [NH_2, OH and CH], 1672 (C=S), 1642, 1602 (aromatic), 1575, 1489, 1470, 1421, 1415, 1335, 1295, 1270, 1206 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.37 (s, 1, H-8), 8.16 (s, 1, H-2), 7.3 (br s, 2, NH_2), 5.9 (d, 1, J = 6 Hz, H-1'), 5.53 (d, 1, J = 6 Hz, OH-2'), 5.4 (d, 1, J = 5 Hz, OH-3'), 4.86 (d d, 1, H-2'), 4.18 (d d, 1, H-3'), 4.14-4.04 (m, 1, H-4'), 3.97 (q, 2, -CH_2N-), 3.87-3.68 and 3.68-3.52 (m, 4, H-5' and -CH_2N-), 1.18 and 1.15 (t, 6, CH_3). *Anal.* Calcd for $C_{15}H_{22}N_6O_3S_2 \cdot 0.75H_2O \cdot 0.25EtOH$: C, 43.95; H, 5.95; N, 19.84. Found: C, 43.97; H, 6.34; N, 19.99.

[For the syntheses of compounds **64-67**, we relied only on MS and ^1H NMR for confirmation of their identifications. We felt that full characterization of all intermediates was unnecessary since we were closely following a procedure provided by J. Bronson of Bristol-Myers. However, in the experimental section, we have included all of the analytical data supplied to us in the Bronson procedure.]

2-Chloromethoxyethyl Acetate (64). Into a 500-mL round-bottomed flask a solution of acetyl chloride (17.4 g, 220 mmol) in 80 mL of anhydrous ether was added dropwise via an additional funnel, over 1 h to a mixture of 1,3-dioxolane (15 g, 202 mmol) and zinc chloride (0.109 g, 80 mmol) in 100 mL of anhydrous ether at room temperature under nitrogen. [The 1,3-dioxolane was predistilled to remove any triethylamine inhibitor.] The reaction mixture was then stirred at room temperature for 25 h and evaporated *in vacuo* to remove any volatile materials. The resulting light brown oil was purified by distillation under reduced pressure to afford a colorless oil (21.2 g, bp 54-55 °C at 0.8 mmHg); MS (EI) *m/e* 152 (M^+); ^1H NMR (200 MHz, $CDCl_3$) δ 5.50 (s, 2, -CH_2Cl), 4.25 (t, 2, J = 7 Hz, -CH_2-), 3.80 (t, 2, J = 7 Hz, -CH_2-), and 2.05 (s, 3, -CH_3); IR (thin film): 2980, 2950, 1740(s), 1460, 1380, 1235, 1140, 1080, and 650 cm^{-1}.

2-(Diisopropylphosphonylmethoxy)ethyl Acetate (65). 2-(Chloromethoxy)ethyl acetate (64) (21.2 g, 0.150 mol) and triisopropyl phosphite (25 g, 25.8 mL, 0.139 mol) were combined in a 200-mL three-necked round-bottomed flask equipped with a reflux condenser and a gas inlet adapter. The reaction mixture was heated at around 100-110 °C for 18 h. (Bubbling was noted when the temperature initially reached 105 °C.) The reaction mixture was then allowed to cool to room temperature and the volatile residuals were removed *in vacuo*. The residual oil was purified by vacuum distillation (bp 133-138 °C,

0.7-0.8 mmHg) yielding a colorless liquid (16.5 g); MS (EI) *m/e* 282 (M^+); ^{1}H NMR ($CDCl_3$) δ 4.79 (apparent octet, 2, J = 6.5 Hz, -CH-), 4.24 (t, 2, J = 4.5 Hz, -CH_2-), 3.81 (t, 2, J = 4.5 Hz, -CH_2-), 3.79 (d, 2, J = 8.2 Hz, -CH_2-), 2.08 (s, 3, -CH_3), and 1.35 (d, 12, J = 6.5 Hz, -CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.85, 71.10 (d, J = 7 Hz), 70.88 (d, J = 11 Hz), 65.99 (d, J = 170 Hz), 63.28, 24.09 (d, J = 4 Hz), 23.96 (d, J = 4 Hz), and 20.84; IR (thin film) 2981, 2938, 2880, 1742(s), 1468, 1456, 1387, 1377, 1242(s), 1180, 1132, 1109, 1057, 991(s), and 890 cm^{-1}.

2-Diisopropylphosphonylmethoxy-1-ethanol (66). A solution of 2-diisopropylphosphonylmethoxyethyl acetate (**65**) (79.9 g) in 500 mL of acetone-water (4:1) was treated with concentrated HCl (42.8 mL). The reaction mixture was stirred at 50-55 °C for 72 h. The resulting solution was concentrated *in vacuo* and the residue was co-evaporated with toluene (3 x 150 mL) to afford a crude dark yellow oil (80 g) which was used without further purification.

2-(Diisopropylphosphonylmethoxy)ethylmethanesulfonate (67). 2-Diisopropylphosphonylmethoxy-1-ethanol (**66**) (100 g, 0.471 mol, accumulated from combined runs) was dissolved in 850 mL of anhydrous methylene chloride (dried over activated molecular sieves) and the solution was cooled to 0 °C. After 15 min, the methanesulfonyl chloride was added rapidly (55.8 g, 37.5 mL, 0.490 mol) followed by dropwise addition of triethylamine (81.56 g, 125 mL, 0.806 mol) over 1 h. The resulting clear yellow solution was stirred at room temperature for 18 h and then 200 mL water was added. The reaction mixture was stirred for 10 min before the organic layer was separated and the aqueous layer was extracted with 300 mL methylene chloride. The combined organic portions were washed with saturated sodium chloride solution (2 x 300 mL). The compound was isolated by evaporation *in vacuo* to yield a yellow oil and was purified by column chromatography in silica gel (5:1), eluting with a gradient of 3-5% methanol/methylene chloride. MS (FAB) *m/e* 319 (M + 1); ^{1}H NMR ($CDCl_3$) δ 4.78 (d of septet, 2, J = 5, 6.2 Hz, -CH-), 4.38-4.42 (m, 2, -CH_2-), 3.86-3.90 (m, 2, -CH_2-), 3.80 (d, 2, J = 8.6 Hz, -CH_2-), 3.09 (s, 3, -CH_3), and 1.36 (d, 12, J = 6.2 Hz, -CH_3); ^{13}C NMR ($CDCl_3$) δ 71.21 (d, J = 7 Hz), 70.75 (d, J = 11 Hz), 68.71, 66.12 (d, J = 170 Hz), 37.73, 24.07 (d, J = 4 Hz), and 23.99 (d, J = 4 Hz); IR (thin film) 2983, 2937, 2881, 1739, 1468, 1456, 1414, 1376, 1355(s), 1253, 1177(s), 1133, 1108, 988(s), 926, 836, 808, 755, and 727 cm^{-1}.

9-(2-Diisopropylphosphonylmethoxyethyl)adenine (68). Sodium hydride (1.2 g, 0.05 mol) was added to a stirred slurry of adenine (2.0 g, 0.014 mol) in 100 mL of anhydrous dimethylformamide in a 200-mL three-necked round-bottomed flask equipped with an overhead mechanical stirrer and an argon inlet adapter. The reaction mixture was heated at 80 °C for 2 h to give a thick, white slurry. A solution of 2-(diisopropylphosphonylmethoxy)ethylmethanesulfonate (67) (7.7 g, 0.024 mol) in 10 mL of anhydrous DMF was then added over 10 min to the hot slurry and the reaction mixture was raised to 100 °C. The reaction mixture was stirred at 100-105 °C for 14 h, allowed to cool to room temperature, and filtered to remove insoluble material. The filtrate was concentrated *in vacuo* and the gummy, semi-solid residue was suspended in 100 mL of 10% isopropanol in methylene chloride. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give an orange, viscous residue. Purification by column chromatography on silica gel (10:1), eluting with a gradient of 3-10% methanol in methylene chloride afforded 2.11 g (24.6% yield) of a white crystalline solid. This material was purified further by recrystallization from ethyl

acetate/toluene. MS (EI) *m/e* 358 (M^+); ^1H NMR ($CDCl_3$) δ 8.15 (s, 1), 8.09 (s, 1), 7.21 (br s, 2), 4.50 (apparent octet, 2, J = 6.5 Hz, -CH-), 4.34 (t, 2, J = 4.8 Hz, $-CH_2-$), 3.91 (t, 2, J = 4.8 Hz, $-CH_2-$), 3.79 (d, 2, J = 8.4 Hz, $-CH_2-$), 1.18 (d, 6, J = 6.5 Hz, $-CH_3$), and 1.13 (d, 6, J = 6.5 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ 155.86, 152.23, 149.46, 140.90, 118.57, 70.22 (d, J = 10 Hz), 70.05 (d, J = 12 Hz), 64.50 (d, J = 165 Hz), 42.35, 23.61 (d, J = 7 Hz), and 23.52 (d, J = 7 Hz).

9-(2-Phosphonylmethoxyethyl)adenine (69). A solution of 9-(2-diisopropylphosphonylmethoxyethyl)adenine **(68)** (2.11 g, 0.060 mol) in 20 mL of anhydrous acetonitrile was treated with bromotrimethylsilane (8.29 g, 0.054 mol), and the resulting clear, yellow solution was stirred at room temperature under argon for 16 h. The reaction mixture was concentrated *in vacuo* and the yellow residue was placed under high vacuum for 5 h. Water (15 mL) was added next, causing immediate formation of a white precipitate. Acetone (15 mL) was added, and the pale yellow slurry was stirred at room temperature for 14 h. The solid was collected by filtration, washed twice with 10 mL of acetone and once with 10 mL of anhydrous ether. An additional portion of solid was collected from the filtrate. The combined solids were recrystallized from water to afford 1.41 g (86%) of an off-white crystalline solid; mp >250 °C; MS (EI) *m/e* 273 (M^+); ^1H NMR (Me_2SO-d_6) δ 8.14 (s, 1), 8.13 (s, 1), 7.27 (br s, 2), 4.32 (t, 2, J = 5 Hz, $-CH_2-$), 3.87 (t, 2, J = 5 Hz, $-CH_2-$), and 3.59 (d, 2, J = 8.8 Hz, $-CH_2-$); ^{13}C NMR (Me_2SO-d_6) δ 151.10, 148.70, 146.28, 143.80, 118.05, 69.94 (d, J = 10 Hz), 66.27 (d, J = 160 Hz), and 43.15. *Anal.* Calcd for $C_8H_{12}N_5O_4P \cdot 0.5H_2O$: C, 34.04; H, 4.64; N, 24.82. Found: C, 33.90; H, 4.76; N, 24.86.

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