

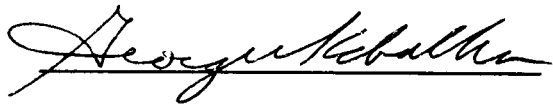
To the Graduate Council:

I am submitting herewith a dissertation written by Vivekanand Kamath entitled "Design and Synthesis of Analogs of Adenosine Deaminase Inhibitors and Potential Therapeutic Agents." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.



David C. Baker, Major Professor

We have read this dissertation
and recommend its acceptance:



Accepted for the Council:



Associate Vice Chancellor
and Dean of The Graduate School

**DESIGN AND SYNTHESIS OF ANALOGS OF ADENOSINE
DEAMINASE INHIBITORS AND POTENTIAL THERAPEUTIC
AGENTS**

A Dissertation

Presented for the

Doctor of Philosophy

Degree

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Vivekanand Kamath

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DEDICATION

This thesis is dedicated to the Almighty and to my dear parents

Mr. Amembal Pandurang Kamath

and

Mrs. Poornima P. Kamath

who have given me invaluable love, support, encouragement
and educational oppurtunities during all these years

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ABSTRACT

In the continued search for inhibitors of adenosine deaminase, the synthesis of seven- and eight-membered fused-ring imidazole compounds were carried out to probe the effect of ring size and replacement of N in the ring system on enzyme inhibition.

This research has accomplished the synthesis of analogs of 2'-deoxycoformycin, namely 1,4,5,6,7,8-hexahydroimidazo[4,5-*a*]cycloheptane (1), 4,5,6,7,8,9-hexahydro-1*H*-imidazo[4,5-*a*]cyclooctanone (2) and 4,5,8,9-tetrahydro-1*H*-imidazo[4,5-*a*]cycloocta-6-ene (3). The imidazole ring system being a π -electron rich system led to the formation of the unstable nucleosides. The sugar moiety upon being fixed to the N-1 of the imidazole ring was found to cleaved off almost immediately upon isolation of the compound.

This research has also accomplished the synthesis of the heterocyclic moiety of the nebularine analog, namely 3*H*-imidazo[4,5-*b*]pyridin-7-ol (5). Attempts to synthesize the eight-membered imidazole compound, namely 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*b*]cyclooctene-9-ol (6) along similar lines proved to futile.

The synthesis of 9-(2,3-dideoxy- β -D-*erythro*-pentofuranosyl)-6-methoxy-9*H*-purine was accomplished in excellent overall yields. The main aim of this research was to conduct a comparative study on the rate of deamination of dideoxyadenosine (ddA), as well as the dechlorination and demethoxylation, respectively, of 6-chloro- and 6-

methoxypurine dideoxynucleosides with respect to adenosine.

This research has also successfully accomplished the synthesis of 1,2,3,4,6,7,8,9-octahydro-1,3-dimethylpyrimido[2,1-*f*]purine-2,4,8-trione and methyl hexahydro-2-(hydroxymethyl)-2-methyl pyrrolo[1,2-*b*]isoxazole-3-carboxylate.

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LIST OF ABBREVIATIONS

ADA	adenosine deaminase
AIDS	acquired immunodeficiency syndrome
ara-A	9- β -D-arabinofuranosyladenine
AM1	austin model hamiltonian 1
Asp	aspartate residue
AZddU	3'-azido-2',3'-dideoxyuridine
AZT	3'-azido-3'-deoxythymidine
BTMAH	benzyltrimethylammonium hydroxide
CoF	coformycin
dAdo	deoxyadenosine
dATP	deoxyadenosine triphosphate
ddA	dideoxyadenosine
ddC	2',3'-dideoxycytidine
d4T	2',3'-didehydro-3'-deoxythymidine
ddI	2',3'-dideoxyinosine
dCF	2'-deoxycoformycin
DEPT	distortionless nuclei enhanced by polarization transfer

DHMPR	1,6-dihydro-6-(hydroxymethyl)-9-(β -D-ribofuranosyl)purine
DIBAL	diisobutylaluminium hydride
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
EHNA	(2 <i>R,S</i> ; 3 <i>S,R</i>)-3-(adenin-9-yl)-2-hydroxynonane
FAB	fast atom bombardment
HDPR	dihydropurine ribonucleoside
His	histidine residue
HMDS	hexamethyldisilazane
HOMO	highest-occupied molecular orbital
LUMO	lowest-unoccupied molecular orbital
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
PNPase	purine nucleoside phosphorylase
SCID	severe combined immunodeficiency syndrome
T.S.	transition-state
TBAF	tetrabutylammonium fluoride
TBDMSOTf	<i>tert</i> -butyldimethylsilyl trifluoromethylsulfonate
TBDPSCI	<i>tert</i> -butylchlorodiphenylsilane
TBDMSCI	<i>tert</i> -butylchlorodimethylsilane
TDA-1	tris[2-(2-methoxyethoxy)ethyl]amine

THF	tetrahydrofuran
TLC	thin-layer chromatography
TMSCl	trimethylchlorosilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPase	thymidine phosphorylase
XHCOR	hetronuclear shift correlation

PART I

**DESIGN AND SYNTHESIS OF ANALOGS OF ADENOSINE
DEAMINASE INHIBITORS**

I. INTRODUCTION

A. BIOLOGICAL ROLE OF ADENOSINE DEAMINASE

Adenosine deaminase (adenosine aminohydrolyase, EC 3.5.4.4, hereafter "ADA") is an enzyme present in virtually all mammalian cells that catalyzes the hydrolysis of amines, halides, alkoxides, oxygen and sulfur leaving groups from the C-6 position of purine ribonucleosides, most notably that of adenosine, to form inosine and ammonia (Figure 1). The function of ADA is critical in controlling the levels of adenosine, as adenosine itself is involved in various biological systems including, blood flow modulation, platelet aggregation, lipolysis, glycogenolysis, and neurotransmission.^{1,2}

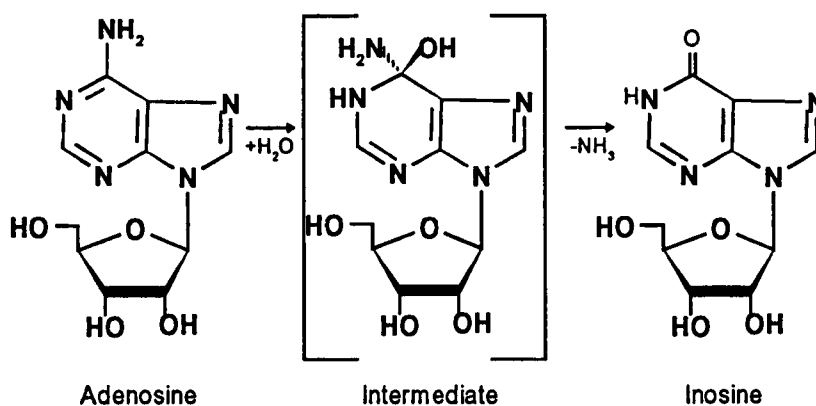


Figure 1. Proposed mechanism for ADA catalysis.

ADA plays a very important role in maintaining the competence of the immune system. It has been observed that the ADA levels change significantly during cellular dysfunctions such as leukemia, AIDS (acquired immunodeficiency syndrome)³ and SCID (severe combined immunodeficiency syndrome).⁴

ADA has proven to be a stumbling block in the path of antiviral and antitumor chemotherapy. Since many active nucleoside antiviral compounds are analogs of adenosine, these compounds are easily deaminated before they reach the target site, which is the virus-infected cell.

In the search for analogs of ADA inhibitors, one has to have sufficient knowledge about the enzyme itself, its mechanism, kinetics, and some knowledge of the structure of active site on the enzyme for binding. Over the years, a number of research groups have carried out studies in an attempt to get a clear view of the enzyme mechanism. That information will enable both chemists and biochemists to design and synthesize new enzyme inhibitors of ADA that would be beneficial for cancer chemotherapy, as well as in the search for new antiviral drugs.

B. DESIGN OF ADENOSINE DEAMINASE INHIBITORS

1. THEORY OF ENZYME CATALYZED REACTIONS

The basic function of an enzyme is like that of any catalyst, the $\Delta E_S^\ddagger$ of the transition-state of the reaction is lowered and is easier to reach. This could be possible

only if the enzyme has a certain affinity for the substrate in the transition-state (T.S.), which is at a higher energy level than the ground-state substrate.²

A general profile of an enzymatic reaction can be explained as shown in the following figure (Figure 2). According to the figure, E and S are free enzyme and substrate in the ground state, $ES^\ddagger$ is the transition-state achieved by affinity of the enzyme E to the substrate, and P is the final product.

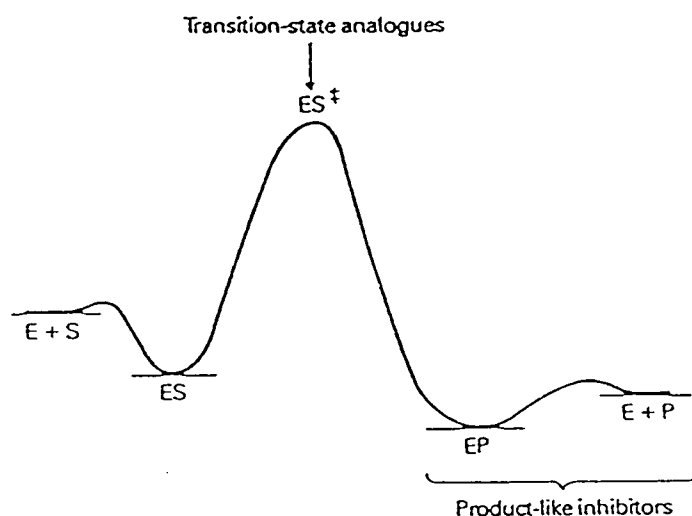
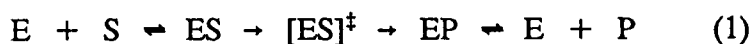


Figure 2. Reaction profile of a typical enzyme reaction.

The transition-state of ES to EP, which is $ES^\ddagger$, lies in the maximum energy range. The general pathway for an enzymatic pathway can be translated into an equation as shown in equation 1.



This theory of transition-state analogs was first proposed by Linus Pauling in 1946.³ The theory states that a higher affinity of the enzyme for the substrate is possible by altering or distorting the substrate, thereby lowering the energy of activation. Based

on this theory, one could explain the unusual effectiveness of certain enzyme inhibitors of ADA.⁴

Information about the enzyme-catalyzed mechanism and the position of the active binding site of ADA is very important due to the potential development of related applications in the area of medicinal chemistry. Studies on ADA over the past twenty years have revealed new information on the enzyme mechanism and kinetics. In the mid-sixties, preliminary studies showed that adenosine analogs were either substrates or inhibitors of ADA. Studies carried out by Cory and Suhadolnik⁵ to determine the structural requirements of these nucleosides for binding by ADA revealed that a significant difference existed between the binding of nucleosides to the enzyme by altering either the 6 or the 9 position of adenine. Later, studies carried out by Wolfenden⁶ revealed the possible mechanistic pathway for ADA catalysis, which was then later confirmed by Quijcho and co-workers based on the X-ray diffraction studies of dihydropurine ribonucleoside (HDPR) bound by ADA.¹⁶

2. ADENOSINE DEAMINASE INHIBITORS

Adenosine deaminase catalyzes the hydrolytic cleavage of several leaving groups from the C-6 position of the purine ribonucleoside. The deamination was thought to proceed either by direct water attack to eliminate ammonia or possibly by a double-displacement mechanism.⁷ Kinetic studies to determine the rate of deamination showed that leaving groups such as ammonia and chloride were hydrolysed at nearly the same limiting rates, even though there were vast differences in their bond energies to carbon

atom. The rate determining step in the reaction was thus a step other than the clipping of the scissile bond of the substrate.^{6,8} It was believed that the rate of the reaction could be determined by the hydrolysis of the intermediate formed by the enzymatic displacement of the leaving group. Later it was established that, if hydrolysis of the common intermediate were to be the rate-determining step, the reaction rates should differ for H₂O and D₂O solvent medium. The rate of hydrolysis in either case were found to be similar. Hence the reaction resembled to a non-enzymatic aromatic displacement reaction, where the transition state is reached early during the reaction, thereby leading to the formation of the tetrahedral intermediate at the C-6 position.^{9,10}

Studies by Kati and Wolfenden¹¹ based on the hydration of nebularine was analogous to the deamination of adenosine. Although nebularine lacked a substituent at the C-6 position, it was the unstable 1,6-hydrated complex (HDPR, hereafter), that bound very tightly to ADA and is reflected in the K_i value which is about 3×10^{-13} M.¹² Hence, the forces involved in the tight binding of the transition state of HDPR could be analogous to the enzymatic pathway during hydrolysis of adenosine (Figure 3).

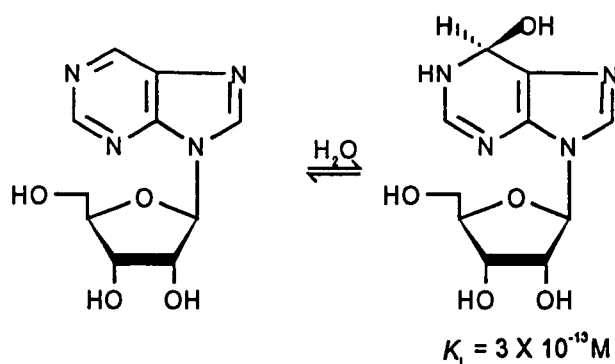


Figure 3. Wolfenden's HDPR inhibitor of ADA.

The tight binding nature of HDPR has been attributed to the presence of the hydroxy group at the C-6 position, suggesting that the hydroxy group is bound to the enzyme by more than one hydrogen bond.¹³

Further studies on the binding affinities of HDPR ($K_i = 3 \times 10^{-13}$ M)¹² and its analog, i.e, the 1,6-dihydropurine ribonucleoside ($K_i = 5.4 \times 10^{-6}$ M),¹³ suggested that this strong affinity in case of HDPR was largely due to the entropic effects.¹⁴ Based on these observations Kati and Wolfenden¹⁵ postulated an entropy-trap mechanism to explain the the hydration of purine ribonucleoside at the active ADA site (Figure 4).

This remarkable binding affinity of the C-6 hydroxy group to the enzyme has been further verified by Quioco and co-workers,¹⁶ based on the X-ray diffraction studies from a single crystal of HDPR bound to ADA. The crystal studies revealed some new findings. First of all, HDPR was shown to interact with two amino residues namely, His-238 and Asp-295, along with a Zn metal atom as a cofactor (Figure 5). All previous studies¹⁷ made no mention of cofactors required for ADA activity. Secondly, based on the atomic interaction of ADA and HDPR, a stereospecific S_N2 (substitution nucleophilic bimolecular) mechanism of ADA via a sp^3 -hybridized tetrahedral intermediate was evident, which further supported the earlier theories of ADA catalysis.^{9,10} Furthermore, the stereospecific attack of water was possible mainly due to the positioning of Zn metal, Asp-295 and His-238 on the B-face of the purine ring, thereby permitting the $-NH_2$ to leave from the A-face. The aromatic nature of the purine ring was reduced due to the participation of the lone pair of electrons of the N-1 atom, thereby making the C-6 position of the ring more susceptible to water attack (Figure 6).

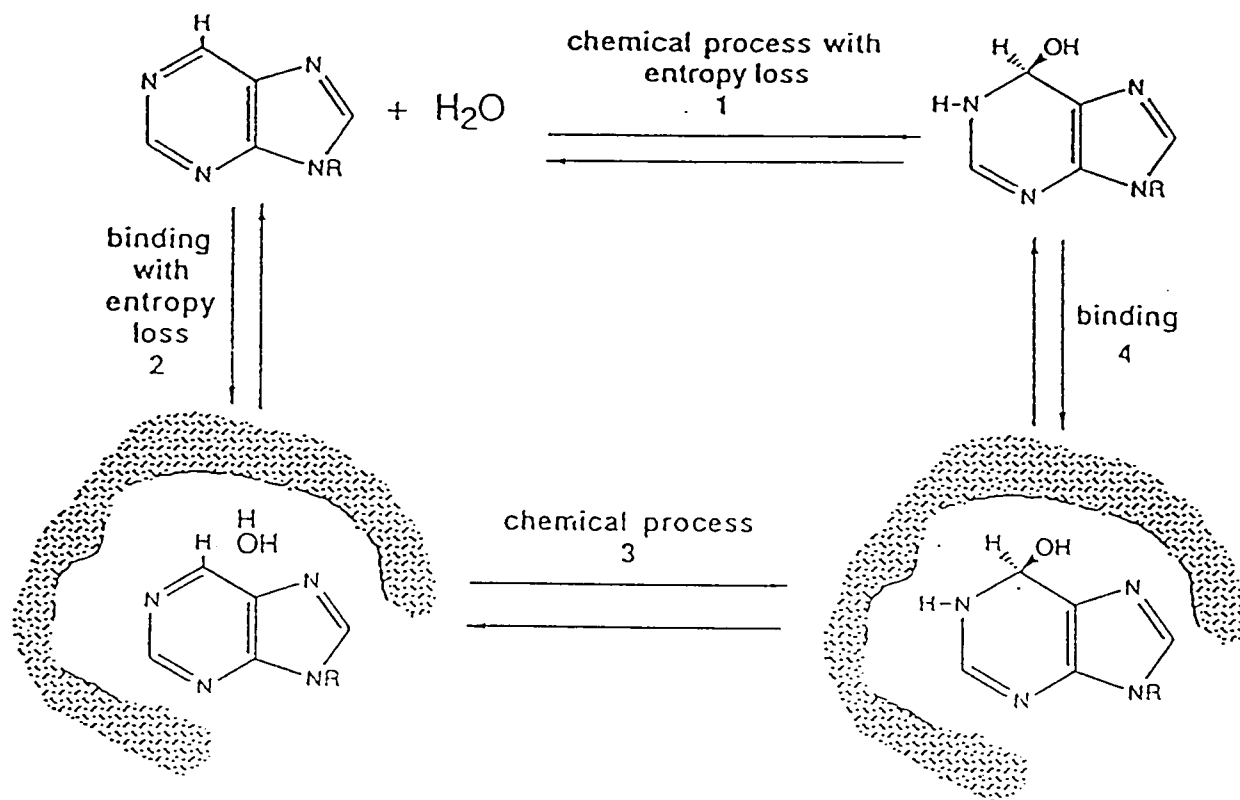


Figure 4. Entropy-trap mechanism for hydration of purine ribonucleoside at the active site of adenosine deaminase.

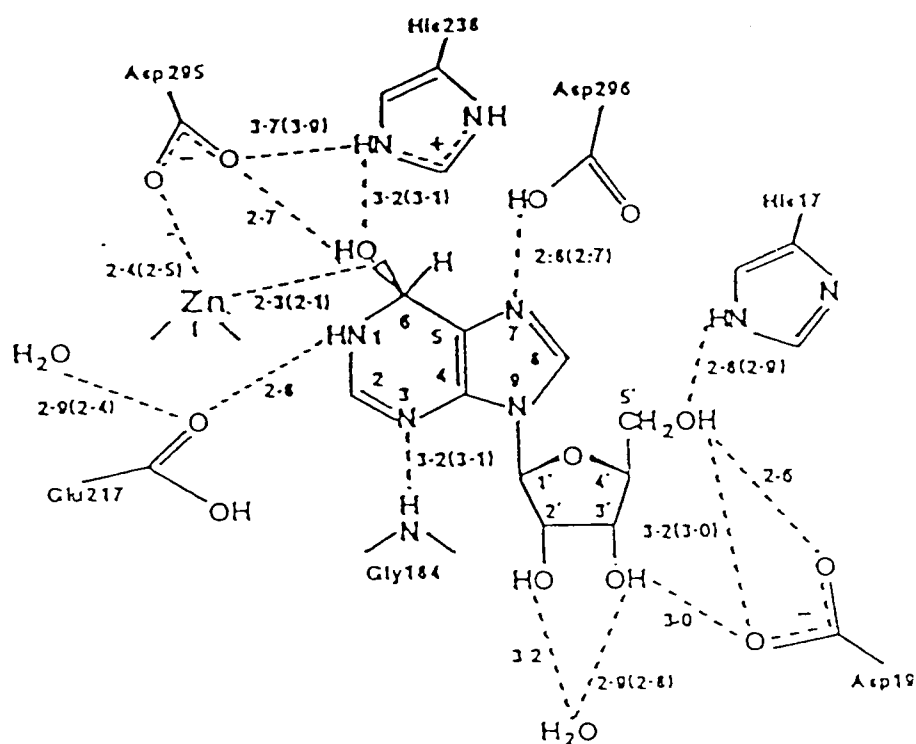


Figure 5. Schematic representation of the interaction between ADA and HDPR.

(As proposed by Quijcho and co-workers.)¹⁶

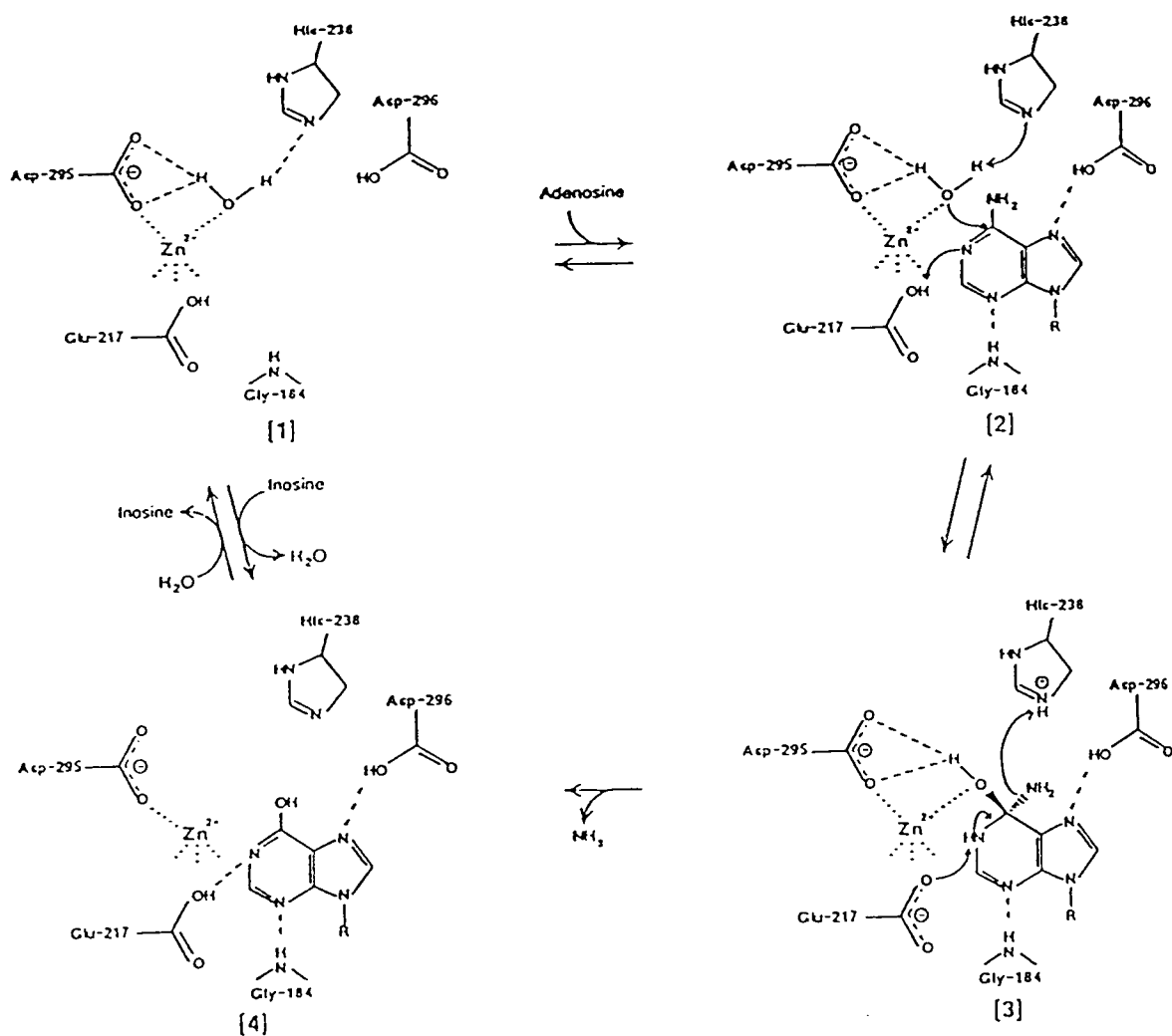


Figure 6. Proposed stereospecific S_N2 mechanism for ADA catalysis by Quiocho and co-workers.¹⁶

The stereospecific nature of the reaction has further confirmed the fact that the 6*R* diastereomer of HDPR is preferentially recognized by ADA. Prior to this paper, our group had confirmed this fact based on the molecular modelling studies¹⁸ carried out on SYBYL 5.41.

Over the years, a number of potent adenosine deaminase inhibitors have been have been designed and studied (Figure 7). Among them is 1,6-dihydro-6-(hydroxymethyl)-9-(β -D-ribofuranosyl)purine (DHMPR) (1, $K_i = 7.6 \times 10^{-7}$ M),¹⁹ which has been synthesized by the direct photochemical attack of methanol on 9- β -D-ribofuranosylpurine. Another less potent inhibitor, (2*R,S*; 3*S,R*)-3-(adenin-9-yl)-2-hydroxynonane (EHNA) (2, $K_i = 1.6 \times 10^{-9}$ M), was synthesized by Schaeffer and co-workers.²⁰ Coformycin and 2'-deoxycoformycin are two naturally occurring compounds that were isolated from fermentation of *Streptomyces antibioticus* by Woo et al.²⁴ and were found to be the most tight binding inhibitors of ADA. The synthesis of coformycin (CoF)²¹ was accomplished by Umezawa and co-workers using similar methodology used in the synthesis of DHMPR. This compound was found to be tightly bound to the enzyme ADA, which is reflected in its K_i value (3, $K_i = 2.2 \times 10^{-11}$ M). The synthesis of 2'-deoxycoformycin (2'-dCF) (4, $K_i = 5.1 \times 10^{-12}$ M)²² was accomplished by Baker and co-workers³⁰ in good yields. The potency of these compounds has been found to be defined by the stereochemistry at the C-8 position which bears the hydroxy group. It has been found that the 8*R* diastereomer binds $\approx 10^7$ times more strongly than the 8*S* diastereomer.²³

Since the topic of this dissertation is concerned with the design and synthesis of

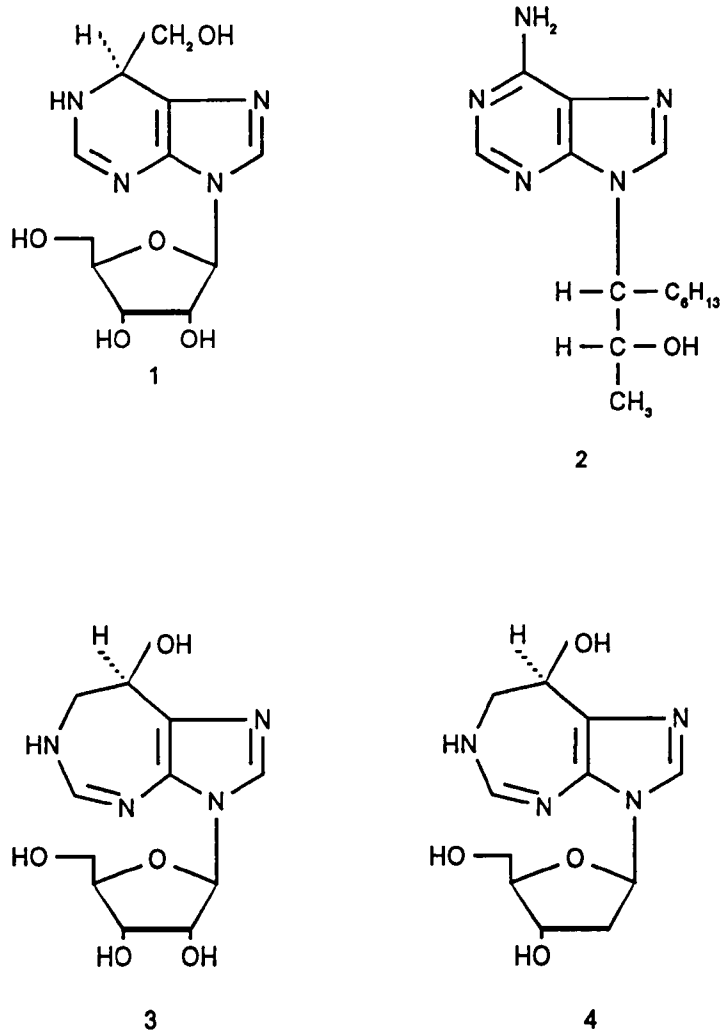


Figure 7. Inhibitors of adenosine deaminase.

analogs of 2'-dCF, it is important to understand first the molecular pharmacology of 2'-dCF and the need for designing analogs of 2'-dCF.

C. BIOLOGICAL ROLE OF 2'-DEOXYCOFORMYCIN ON ADENOSINE DEAMINASE

2'-dCF is an anticancer agent that has been recently approved by the Food and Drug Administration (FDA) for the treatment of interferon-refractory hairy cell leukemia. Studies are now in progress to test this drug in the treatment of cancer, diabetes, stroke-induced brain damage and possibly as a therapeutic agent for organ and bone-marrow transplants.

2'-Deoxycoformycin (2'-dCF) [(*R*)-3-(2-deoxy- β -D-*erythro*-pentofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol], as mentioned earlier, was first isolated in its natural form from a fermentation broth by Woo et al.²⁴ and was found to be a potent inhibitor of ADA, an enzyme which participates in the purine salvage metabolic pathway.

In the initial clinical trials, 2'-dCF was found to be extremely neurotoxic. Furthermore, lack of suitable preclinical models, where 2'-dCF could be adequately evaluated against cancer or as an immunotherapeutic agent, resulted in the sluggish progress of this drug toward development as a clinical agent. A lot of questions regarding the effect of 2'-dCF on clinical activity still remains to be resolved.²⁵

Based on the earlier studies of ADA catalysis, it was shown that the C-8 position of 2'-dCF mimics the sp^3 -hybridized tetrahedral carbon in the putative transition-state of the deamination reaction of adenosine.¹⁸

Clinical trials were carried out to study the activity of 2'-dCF on patients suffering from SCID.⁴ It was observed that the erythrocytes of these patients contained a ≥ 50 -fold amount of deoxyadenosine triphosphate (dATP), which was the toxic metabolite responsible for causing SCID. It was found that dATP was generated exclusively through deamination of deoxyadenosine (dAdo).^{26,27} Thus, inhibition of ADA by 2'-dCF results in the accumulation of dATP, resulting in an interruption of the salvage of deoxyribonucleotides via the phosphates.

Although, 2'-dCF alone lacks appreciable activity as a broad spectrum antitumor agent or as an antiviral, studies have shown that 2'-dCF in combination with other drugs improved its potential as a therapeutic drug. Studies by Lepage and co-workers²⁸ and others on ara-A, which is a potential anticancer agent, have shown that a combination of 2'-dCF and ara-A increased the half life of ara-A. ara-A alone has not been very effective as an anticancer agent, since it was subjected to deamination by ADA prior to reaching its target. This combination of 2'-dCF with ara-A was found to be useful in treating several types of leukemia and viral infections such as herpes.

Other *in vivo* and *in vitro* studies in combination with 2'-dCF and other adenosine analogs have shown significant immunological responses, such as cytotoxicity to T-cells and inhibition of lymphocytic-mediated cytolysis.²⁹ Furthermore, it has been shown that combination of 2'-dCF with cyclosporin increased the graft survival rate in skin

transplantation models. In view of the side effects of 2'-dCF present in the treatment of leukemia, no clinical studies have been carried out to test 2'-dCF as an immunosuppressive drug, which could be useful in bone marrow and organ transplants.

Thus 2'-dCF has attained a status as an "orphan drug" due to its limited use; there is a need to carry out further studies so as to maximize the potential of this drug. There has been an ongoing search for synthesizing other analogs of ADA inhibitors both in this laboratory and elsewhere.

D. SYNTHESIS OF 2'-DEOXYCOFORMYCIN

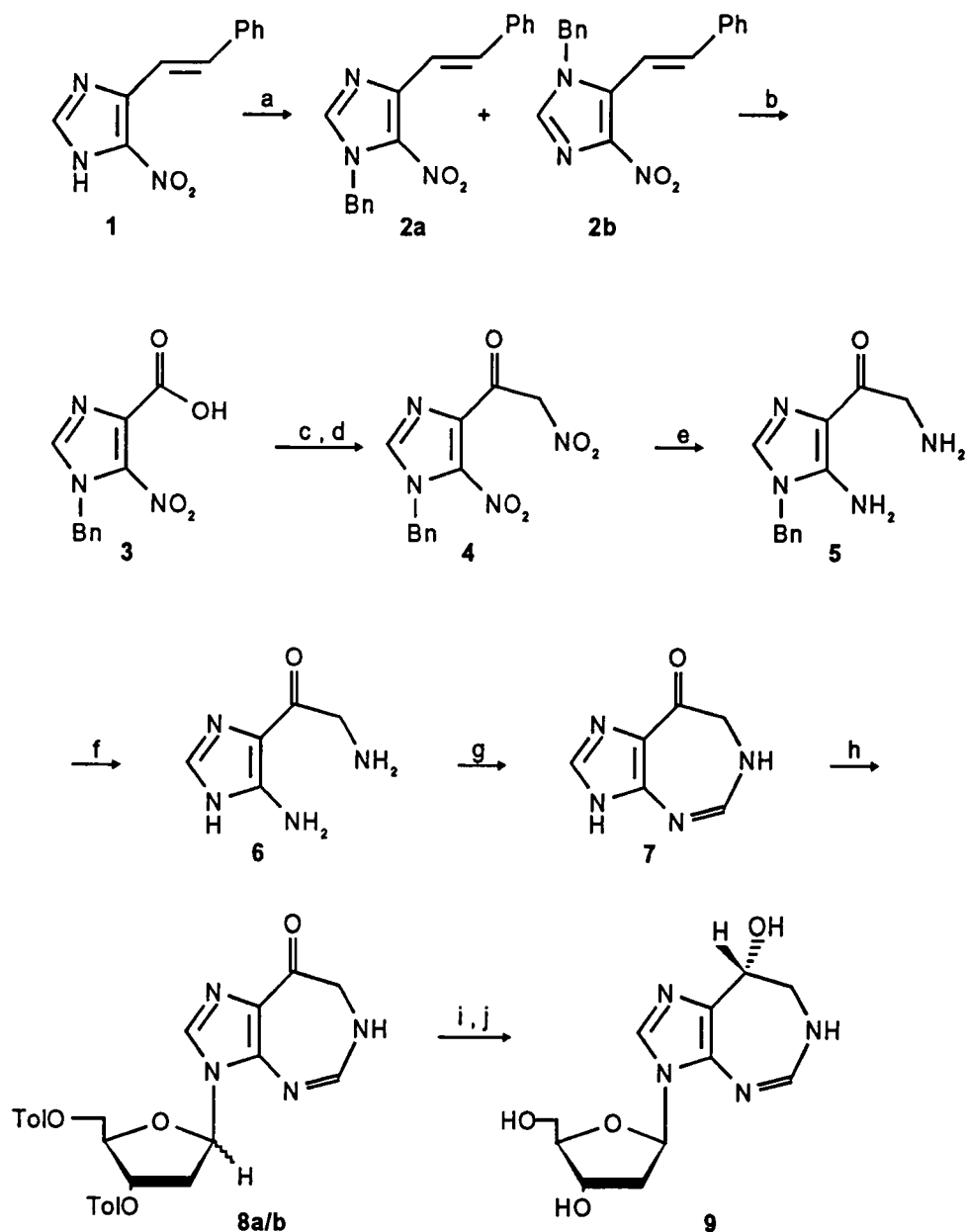
The first synthesis of 2'-dCF, also known as pentostatin, was first achieved by Baker and Putt³¹ in 1979. The general strategy was to first synthesize the heterocyclic aglycon unit with a functional group present at the C-8 position, which would then enable them to incorporate the fragile 2-deoxy sugar moiety using Vorbrüggen's methodology, thereby generating the title compound in good yields (Scheme 1).

Benzylation of the free imidazole 1, followed by ozonolysis of the styrene compound 2a/b, gave rise to free acid 3. This was followed by C-acylation using potassium nitromethanoate to generate the nitroketone 4. Reduction of the dinitro compound 4, followed by debenylation, generated the free amine 6. Ring cyclization with triethylorthoformate gave rise to the heterocyclic moiety 7. Using Vorbrüggen methodology the sugar moiety was coupled to the heterocycle, followed by deprotection

of the protecting groups on the sugar unit and reduction of the keto functionality, to generate the title compound **9a** after column chromatography in good yields.

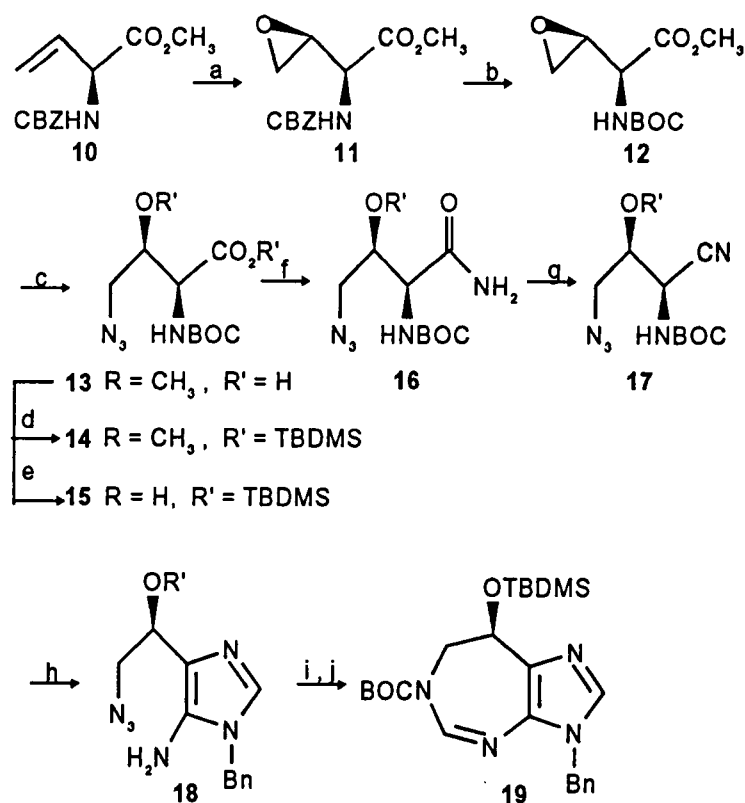
Recently, Rapoport³² published a stereo- and regiospecific synthesis of the aglycon moiety of 2'-dCF using L-vinylglycine as the chiral adduct (Scheme 2). Although, some of the compounds are of questionable value due to their unstable nature, the synthesis reflects some new approaches to generate the heterocyclic moiety.

The synthesis begins with a four-carbon core using L-vinylglycine **10**. Epoxidation of the glycine moiety gives rise to a mixture of diastereomers **11a/b** in ratio of 4:1. The *syn*-epoxide **11a** was then opened up to generate the azido alcohol **13**, followed by protection of the alcohol with *tert*-butylchlorodimethylsilane (TBDMSCl) and then hydrolysis of the ester to generate the free carboxylic acid **15**. Transformation of the acid to amide was possible by isobutyl chloroformate and ammonia at low temperatures so as to avoid any epimerization at the α -center. Dehydration of the amide **16**, followed by deprotection of the amine generated the free aminonitrile. The amino nitrile was then reacted with the *N*-benzylformimidate to generate the aminoimidazole **18**. The last phase of the synthesis was to effectively close the ring to generate the heterocyclic moiety. This was possible by preparation of the imidate using trimethylorthoformate, followed by reduction of the azido function, which then reacted spontaneously to generate the diazepine **19**.



Reagents: a. BnCl, K₂CO₃; b. O₃, [O]; c. 1,1'-carbonyldiimidazole; d. *tert*-BuOK, CH₃NO₂; e. SnCl₂, HCl; f. H₂, Pd/C; g. (EtO)₃CH, EtOH; h. (TMS)₂TFA, 2-deoxyribofuranosyl chloride; i. NaOMe; j. NaBH₄.

Scheme 1. Synthesis of 2'-deoxycoformycin by Baker and Putt.³¹



Reagents: a. *m*CPBA, CH₂Cl₂; b. H₂, Pd/C, (BOC)₂O; c. NaN₃, NH₄Cl; d. TBDMSCl, imidazole, DMF;

e. LiOH, H₂O/dioxane; f. ClCO₂C₄H₉/NH₃; g. TsCl, pyridine; h. 1. TFA, 0 °C; 2. *N*-

benzylformimidate; i. (MeO)₃CH; j. 1,3-propanedithiol, Et₃N.

Scheme 2. Regiospecific synthesis of aglycon moiety of 2'-deoxycoformycin by

Rapoport.³²

II. STATEMENT OF THE PROBLEM

A. DESIGN AND SYNTHESIS OF HETEROCYCLIC ANALOGS OF 2'-DEOXYCOFORMYCIN

In the process of synthesizing structural analogs of 2'-dCF, it is important to keep in mind a few salient points. Studies carried out by Montgomery et al.,³⁰ have revealed that the seven-membered ring of 2'-dCF is essential for ADA inhibition. Furthermore, the asymmetric carbon at the 8-position plays a key role in binding the enzyme tightly as was evident from the 8-keto compound, which had an inhibition constant about 10^7 times lower than that of 2'-dCF.²³

Based on the information available on ADA, we were interested in studying the effect of ring size and the replacement of N in 2'-deoxycoformycin on enzyme inhibition. We then designed the synthesis of seven- and eight-membered fused-ring imidazole compounds to probe the effect of ring size. We also wanted to probe the effect of enzyme inhibition on molecules having a hydroxy group in conjugation to the imidazole ring with no N atom in the ring.

Studies carried out by Wolfenden and co-workers¹¹ have shown that the K_i values for the hydrated form of nebularine (Figure 3) resembles the dissociation constant ($K_i = 10^{-13}$) of the enzyme-substrate complex in the deamination of adenosine. We were

interested in the synthesis of heterocyclic moiety of the nebularine analog having a hydroxy group at the C-6 position with replacement of N at the 1-position (purine numbering). This would allow us to probe the effect of the molecule on ADA inhibition and give some insight into the role of N-1. We also became interested in the synthesis of the eight-membered ring structure, having N at the 4 position, along with the hydroxy group at the 8 position, to study the ADA inhibition of this molecule.

III. SYNTHETIC STRATEGY

In our continued search for ADA inhibitors, the synthesis of seven- and eight-membered fused-ring imidazole compounds was designed to probe the effects of ring size and the replacement of N in the ring system on enzyme inhibition. We were also interested in the synthesis of compounds having hydroxy groups in the ring system to study the ADA activity of the molecule in the absence of an N atom.

The analogs of 2'-deoxycoformycin that were designed to probe ADA activity are shown in Figure 8.

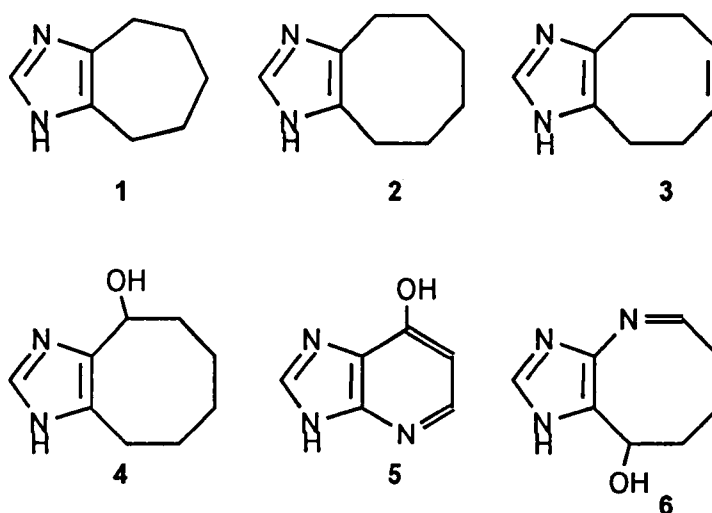
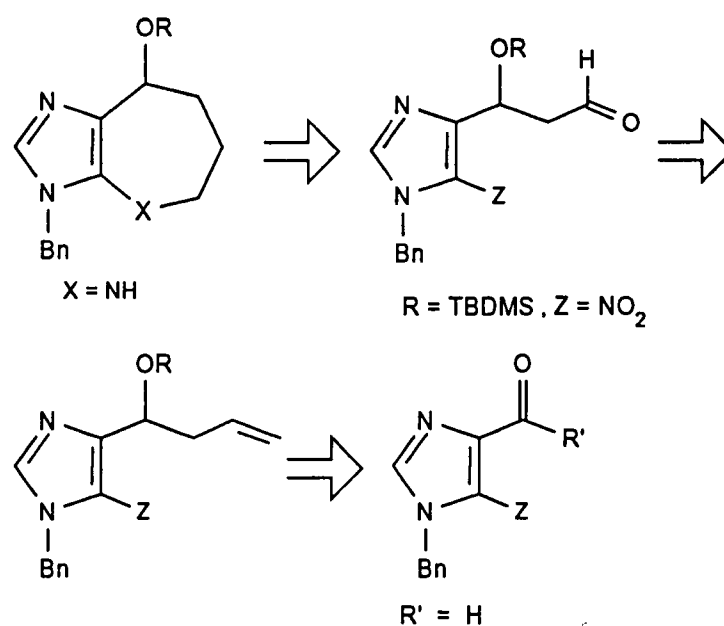


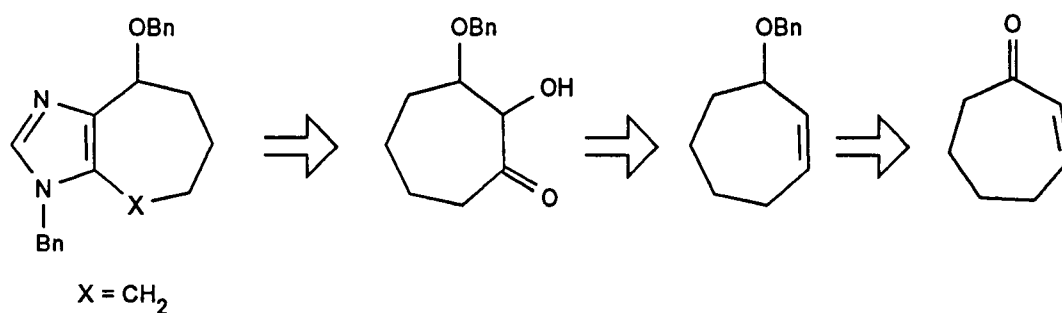
Figure 8. Analogs of 2'-deoxycoformycin.

Two strategies for the synthesis of these analogs were devised. A retrosynthetic scheme is shown in Schemes 3 and 4. According to these schemes one can generate the desired analogs using either method A or B. For the synthesis of compounds 1-5, method B was adopted. In this method (Scheme 4), one can generate the α,β -unsaturated ketone, using known methodology. This would be followed by subsequent reduction of the carbonyl functionality to furnish the alcohol, which would be later protected by a benzyl group using standard conditions. The cycloalkene would be then converted to a 1,2-diol using osmium tetroxide, followed by conversion of the diol to an α -ketol using dibutyltin oxide and bromine solution. The final step would be the conversion of an α -ketol to the fused-ring imidazole compound using the Bredereck reaction, where the α -ketol would be reacted with formamide at high temperature.

For the synthesis of compounds 6 and 7, the first methodology, namely method A, was chosen. The retrosynthetic scheme is shown in Scheme 3. According to the retrosynthetic scheme 1-benzyl-5-nitro-1*H*-imidazo-4-carbaldehyde is first generated, starting with 4-methyl-5-nitro-1*H*-imidazole, using the known methodology of Baker and Putt.³¹ The aldehyde would then be reacted with allylboronic acid to extend the carbon chain by three carbons. Protection of the alcohol with silyl groups, followed by oxidative cleavage of the acyclic double bond, would furnish the desired aldehyde. In the case of compound 6, the carbon chain would be extended further by a Wittig reaction, reduction of the ester, and oxidation, to furnish the aldehyde. The final step would involve the cyclization of the molecule using hydrogenation methodology to afford the desired fused-ring imidazole compound.

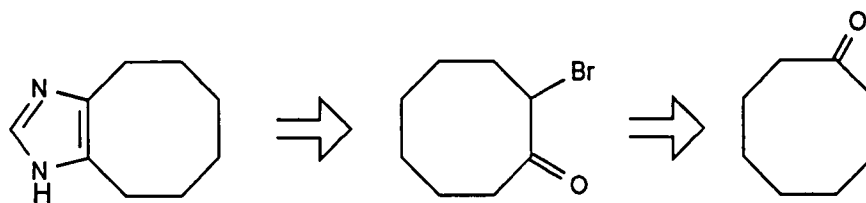


Scheme 3. Retrosynthetic scheme for 2'-deoxycoformycin analogs (Method A).



Scheme 4. Retrosynthetic scheme for 2'-deoxycoformycin analogs (Method B).

The general strategy for the synthesis of the seven- and eight-membered fused-ring imidazole compounds is as shown in Scheme 5. According to this scheme, the α -bromo ketone is synthesized from cycloketone using known methodology, followed by the Brederick reaction, to afford the desired fused-ring imidazole compounds.



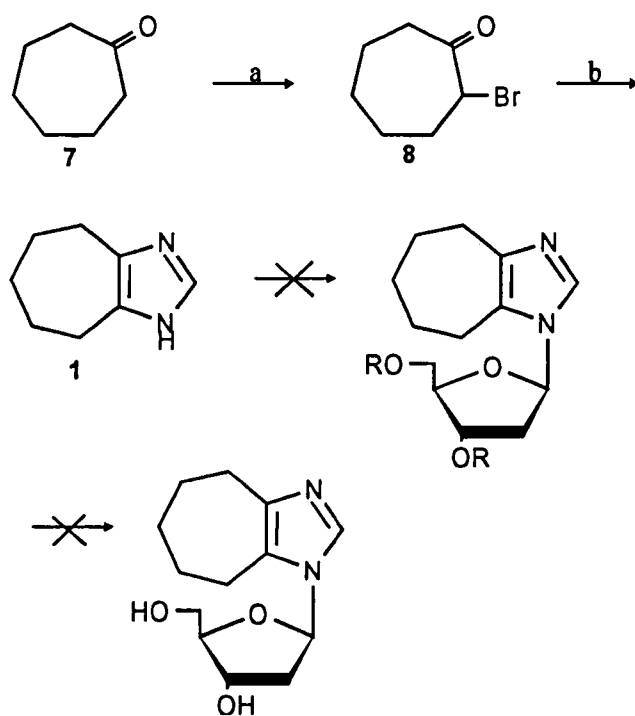
Scheme 5. Retrosynthetic scheme for seven- and eight-membered fused-ring imidazole compounds.

IV. RESULTS AND DISCUSSION

A. SYNTHESIS OF THE AGLYCON MOIETY OF 2'-DEOXYCOFORMYCIN ANALOGS

1. 1,4,5,6,7,8-Hexahydroimidazo[4,5-*a*]cycloheptane

The synthesis of the seven-membered fused-ring imidazo compound was achieved in a straightforward manner using known methodology (Scheme 6). In the first step the α -bromocycloheptanone was generated from cycloheptanone. The ketone was refluxed with *N*-bromosuccinimide (NBS) in the presence of a free-radical initiator for 0.5 h, followed by distillation of the crude product to afford 72% of the desired compound **8**. Compound **8** was identified by its boiling point and ^1H NMR spectrum.³³ The desired fused-ring imidazole compound was then obtained by reacting the α -bromocycloheptanone with formamide using the Bredereck reaction.³⁴ This is a classic method used in the synthesis of imidazole compounds. The haloketone was heated in the presence of formamide at 180 °C for 3 h to furnish the desired compound **1** in 42% yield as colorless crystals. The structure of compound **1** was confirmed by ^1H and ^{13}C NMR spectroscopy (see Appendix A). The resonance for H-2 proton appears at δ 7.32 as a singlet and the aliphatic protons as multiplets between δ 2.69–2.71 and 1.56–1.72 region.



Reagents: a. NBS, AIBN, CCl_4 , reflux; b. formamide, 180°C , 3 h.

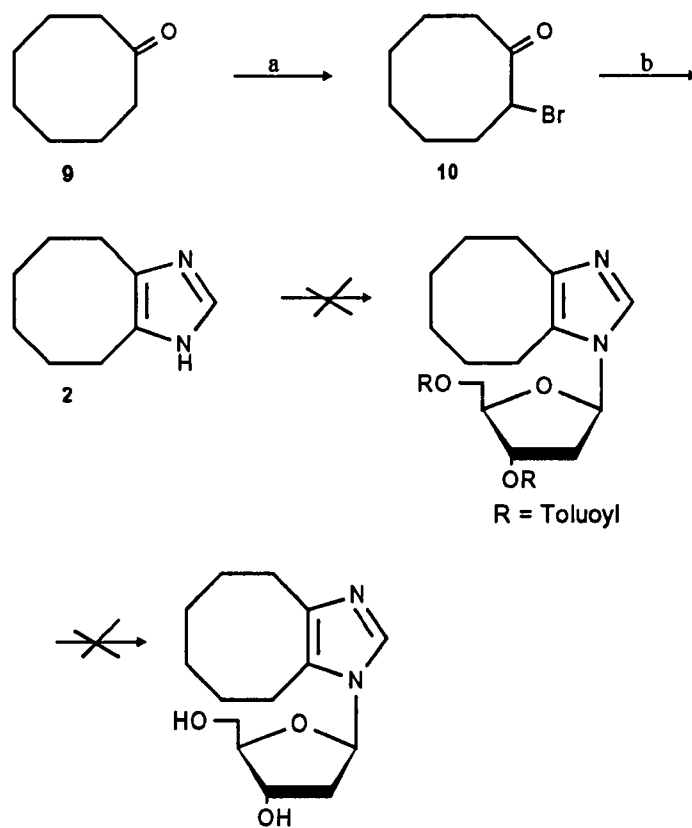
Scheme 6. Synthesis of 1,4,5,6,7,8-Hexahydroimidazo[4,5-a]cycloheptane 1.

2. 4,5,6,7,8,9-Hexahydro-1*H*-imidazo[4,5-*a*]cyclooctanone

The methodology used in the synthesis of the eight-membered fused-ring imidazole was similar to that used for the seven-membered compound as shown in Scheme 7. In this case cyclooctanone was reacted with *N*-bromosuccinimide to generate an α -bromoketone,³⁵ which then underwent the Bredereck reaction to furnish pale-yellow crystals of the desired compound 2 in 36% yield. The structure of compound 2 was confirmed by ¹H and ¹³C NMR spectroscopy (see Appendix A). The resonance for the H-2 proton appears at δ 7.26 as a singlet and the aliphatic proton resonance appears as multiplets between δ 1.47–2.79 region.

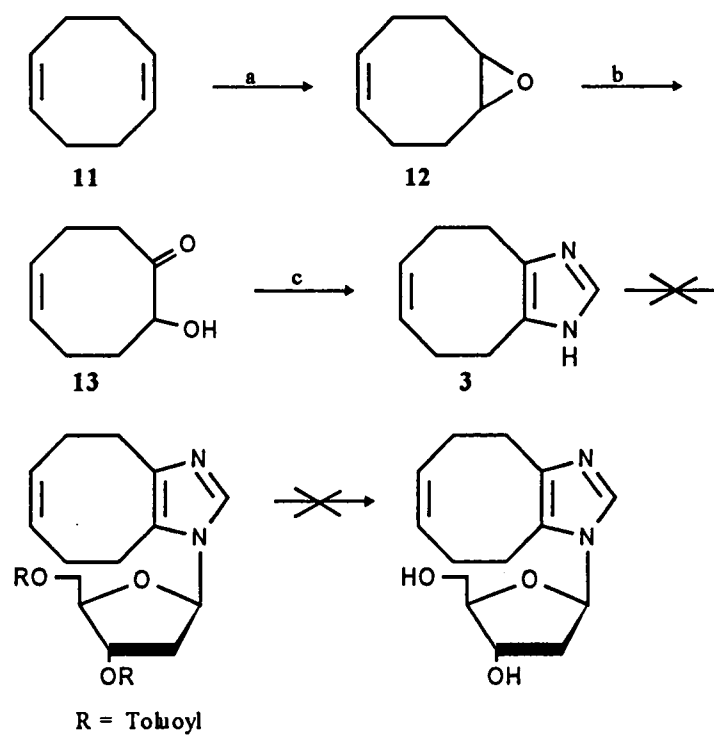
3. 4,5,8,9-Tetrahydro-1*H*-imidazo[4,5-*a*]cycloocta-6-ene

The synthesis of this eight-membered fused-ring compound (Scheme 8) was begun with the epoxidation of the (*Z,Z*)-1,5-cyclooctadiene 11 using 35% peroxyacetic acid and anhydrous sodium carbonate to generate the known epoxide 12 in 56% yield.³⁶ The epoxide was then reacted with boron trifluoride etherate (catalytic) in dimethyl sulfoxide at 100 °C to afford the α -ketol 13.³⁷ The α -ketol underwent the Bredereck reaction in presence of formamide and ammonium formate at 180 °C to furnish the desired compound 3, as pale brown crystals in 39% yield. The structure of compound 3 was



Reagents: **a**. NBS, AIBN, CCl_4 ; **b**. formamide, $180\text{ }^\circ\text{C}$, 3 h.

Scheme 7. Synthesis of 4,5,6,7,8,9-Hexahydro-1*H*-imidazo[4,5-*a*]cyclooctanone **2**.



Reagents: a. *m*CPBA; b. $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DMSO; c. formamide, ammonium formate, 180 °C.

Scheme 8. Synthesis of 4,5,8,9-Tetrahydro-1*H*-imidazo[4,5-*a*]cycloocta-6-ene 3.

confirmed by ^1H , ^{13}C , and DEPT spectrum (see Appendix A). The resonance for H-2 proton appears at δ 7.42 as a singlet while the aliphatic protons appears as multiplets between δ 2.42–3.01 region.

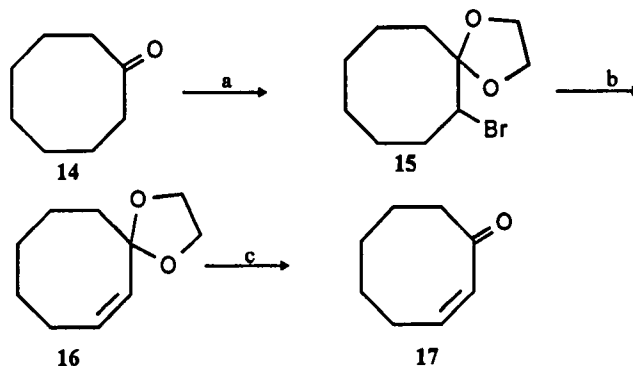
Attempts to introduce functional groups on the cyclooctene ring using sodium tungstate,³⁸ selenium dioxide,³⁹ potassium permanganate,⁴⁰ 2-cyanopyridine chlorochromate,⁴¹ chromyl chloride,⁴² silver acetate and iodine,⁴³ mercuric acetate,⁴⁴ and *m*-chloroperoxybenzoic acid⁴⁵ furnished only the starting material.

4. Attempted synthesis of 4,5,6,7,8,9-Hexahydro-1*H*-imidazo[4,5-*a*]cycloocta-4-ol

The synthesis of this eight-membered fused-ring imidazole compound was attempted using α,β -unsaturated cyclooctanone 14 as the key starting material. The synthesis of α,β -unsaturated carbonyl compounds has not been easy, mainly due to the vigorous conditions required. The most common method used in the synthesis of α,β -unsaturated carbonyl compound is the bromination–dehydrobromination method.⁴⁶ Direct dehydrogenations are also possible using a variety of reagents, including selenium dioxide,⁴⁷ dichlorodicyanoquinone,⁴⁸ periodic acid,⁴⁹ oxygen in presence of a transition-metal catalyst⁵⁰, and pyridine *N*-oxide–acetic anhydride.⁵¹ Although excellent procedures have been developed, the yields vary greatly. Also, there is a frequent problem with effective control of regioselectivity. Initially the synthesis of the α,β -unsaturated ketone was attempted using selenoxide elimination.⁵² But a review of the existing literature

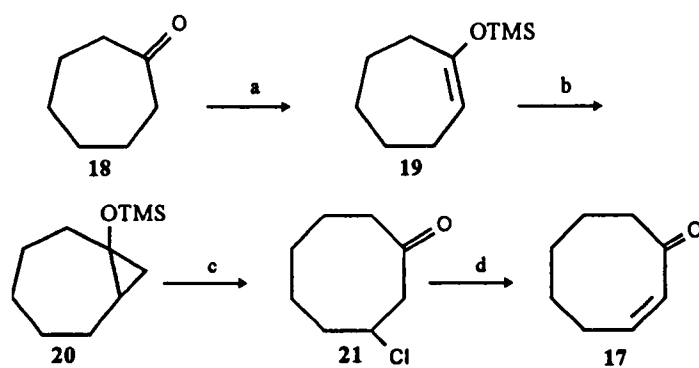
revealed that, although the reaction works fine in most cases, it fails in case of cyclic ketones giving rise to more side-products than the desired enone product.⁵³ To overcome this problem, Trost and Paraquette⁵⁴ have developed a convenient reagent for the synthesis of enones by the method of sulfinylation-dehydrosulfinylation using methyl 2-pyridinesulfinate. The unsaturated ketone was synthesized by two different methods using known methodology. In the first approach,⁵⁵ as outlined in Scheme 9, cyclooctanone was stirred with Br₂ in presence of ethylene glycol, followed by distillation to afford the ethylene ketal of 2-bromocyclooctanone. This was followed by elimination of bromine in presence of a base to furnish the ethylene ketal of 2-cycloctenone **16**.⁵⁶ Upon hydrolysis, the desired compound **17** was obtained in good yields. The structure of compound **17** was confirmed by its ¹H and ¹³C NMR spectra. The resonance for the H-2 proton appears at δ 6.37 as a multiplet and H-3 at δ 6.2 as a broad doublet of doublet ($J = 12.4$ Hz). The aliphatic protons appears in the region of δ 1.55–2.68 as multiplets.

In a second approach (Scheme 10), a one-carbon ring expansion methodology for the synthesis of the key cycloalkenone was employed.⁵⁷ 1-Trimethylsilyloxy cycloheptene was easily prepared from the corresponding ketone. Trimethylsilyl alkenyl ethers, which have an electron-rich double bond for carbenoid addition, are known to furnish the corresponding silyl cyclopropyl ether **20** in excellent yields, using the Simmons-Smith reagent.⁵⁸ Trimethylsilyloxybicyclo[5.1.0]octane was then oxidized in presence of anhydrous FeCl₃ to furnish the desired cyclooctenone via the intermediate



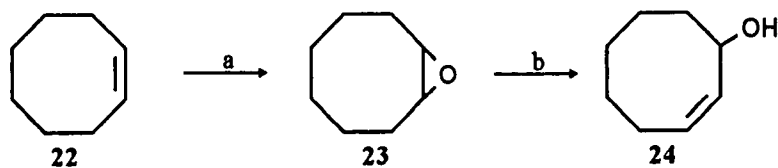
Reagents: a. Ethylene glycol, Br_2 ; b. NaOH , MeOH ; c. H^+ .

Scheme 9. Synthesis of 2-Cyclooctene-1-one (Method A).



Reagents: a. TMSCl , Et_3N ; b. Et_2Zn , CH_2I_2 , Et_2O ; c. FeCl_3 , DMF ; d. NaOH , MeOH .

Scheme 10. Synthesis of 2-Cyclooctene-1-one (Method B).



Reagents: a. *m*CPBA, CH_2Cl_2 , b. *tert*-BuOK, DMSO.

Scheme 11. Synthesis of Cycloocta-2-enol 24.

3-chlorocyclooctanone in good yields.⁵⁹ Another approach, which bypassed the formation of the key intermediate 17, was the synthesis of cycloocta-2-enol (24) in two steps starting from cyclooctene (Scheme 11).

Cyclooctene was epoxidized using *m*CPBA to generate the cyclooctene oxide in quantitative yields. The epoxide then underwent a base-catalyzed isomerization reaction using *tert*-BuOK in presence of DMSO to afford the desired compound 24. The spectral data and boiling point value obtained match with those in the literature.⁶⁰ The key intermediate 17 upon reduction with sodium borohydride generated cycloocta-2-enol 24.⁶¹ The next step involved the protection of the free hydroxy with a benzyl function using standard *O*-alkylation conditions (Scheme 12).⁶²

In the process of conversion of the cyclooctene to an α -ketol, two different synthetic pathways were attempted. In the first approach, cyclooctene was converted to *cis* 1,2-diol using osmium tetroxide solution in catalytic amount along with equimolar tertiary amine *N*-oxide.⁶³ The *N*-oxide used in the reaction helps in regenerating the osmium tetroxide, which has a high level of toxicity. The reaction proceeded in

excellent yields, 96%, to afford crystals of the diol **26**. The structure of compound **26** was confirmed by ^1H , and ^{13}C NMR spectroscopy. The resonances for H-1, H-2, and H-3 protons appears as multiplets between the region δ 3.64–4.09, while the aliphatic protons appear as multiplets at δ 1.32–2.01 region. The diol was then oxidized partially to afford the α -ketol which was generated either by Swern oxidation,⁶⁴ or dibutyltin oxide.⁶⁵ Both these methods gave excellent yields of 3-benzyloxy-2-hydroxy-cyclooctanone (**28**). A small fraction of the diol was protected with dimethoxyacetone to generate the isopropylidene ketal. ^1H NMR data of this compound revealed that the diol **26** generated was a mixture of cis/trans isomers (ratio of cis:trans 1:1). Comparison of the ^1H spectra of the diol **26** and the protected diol showed a distinct upfield shift in the H-3 proton at δ 3.67 as a multiplet, while the H-1 and H-2 protons appears at δ 4.10–4.20 as multiplets.

In the second approach, attempts were made to synthesize the α -ketol via an epoxide. According to the earlier synthesis of the eight-membered fused-ring imidazole compound **3**, an α -ketol had been furnished from the epoxide (refer Scheme 8). Similarly, cyclooctene **25** was first converted to the epoxide using *m*CPBA. Attempts were made to generate the α -ketol using a Lewis acid in DMSO, but unfortunately the ring would not open under any of these rather drastic conditions. It is presumed that this might be due to the conformation of the eight-membered ring structure, whereby the opening of the epoxide is prevented due to steric hinderances.

The epoxide **27** was modeled using SYBYL 6.0 molecular-modeling software (Tripos Associates, St. Louis, MO). Modeling studies were carried out on compound

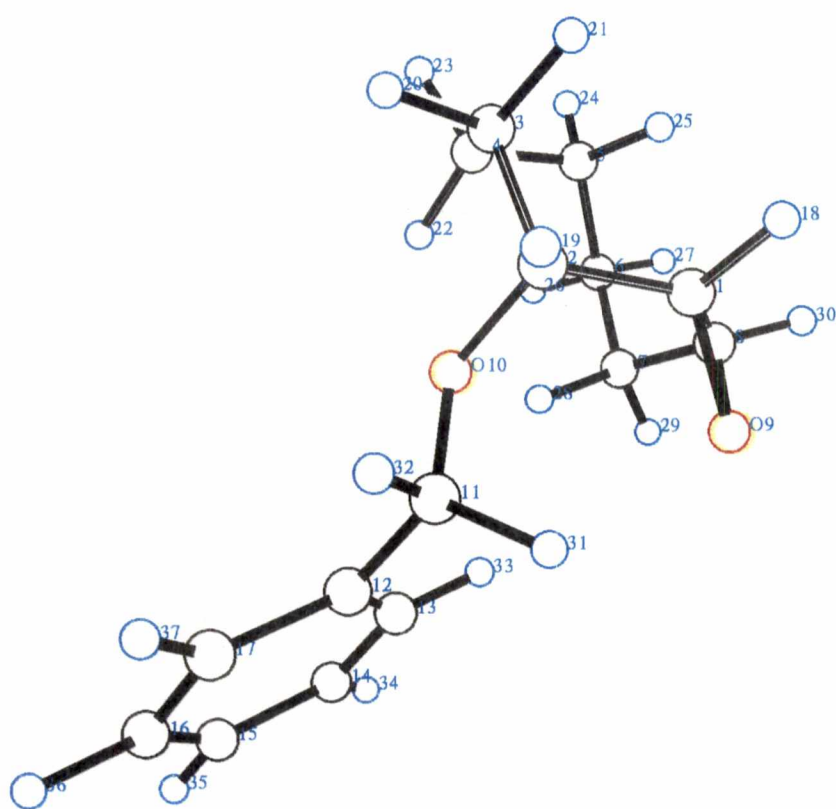


Figure 9. Molecular model generated for compound **27** using SYBYL 6.0.

Table 1. Interatomic distances for compound **27** generated by MOPAC.

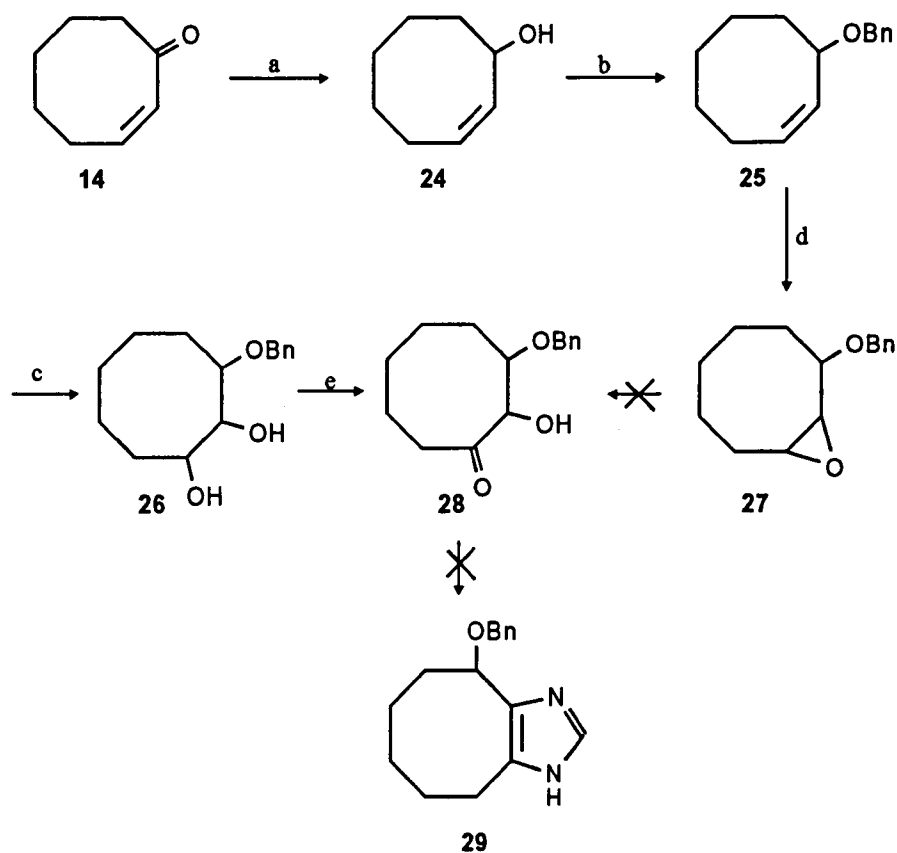
Bond	Length (Å)	Bond	Length (Å)
C-1-C-2	1.5124	C-14-C-15	1.3952
C-2-C-3	1.5287	C-15-C-16	1.3952
C-3-C-4	1.5151	C-16-C-17	1.3938
C-4-C-5	1.5142	C-17-C-12	1.3998
C-5-C-6	1.5153	O-10-O-9	2.8279
C-6-C-7	1.5154	O-9-H-30	2.1410
C-7-C-8	1.4987	O-9-H-18	2.1386
C-8-C-1	1.4916	O-9-H-28	2.6495
C-8-O-9	1.4397	O-9-H-29	2.9407
C-2-O-10	1.4250	O-10-H-19	2.0906
O-10-C-11	1.4321	O-10-H-31	2.0949
C-11-C-12	1.4936	O-10-H-32	2.0872
C-12-C-13	1.3985	O-10-C-12	2.3668
C-13-C-14	1.3940		

Table 2. Bond angles for compound **27** generated by MOPAC.

Bond angle	Degrees	Bond angle	Degrees
C-1-C-2-C-3	111.3018	C-2-C-1-H-18	111.9399
C-2-C-3-C-4	116.3629	C-1-C-2-H-19	106.7274
C-3-C-4-C-5	114.9804	C-2-C-3-H-20	107.1245
C-4-C-5-C-6	115.7703	C-2-C-3-H-21	107.5186
C-5-C-6-C-7	114.0375	C-3-C-4-H-22	108.5512
C-6-C-7-C-8	110.4961	C-3-C-4-H-23	107.3635
C-7-C-8-O-9	116.8593	C-4-C-5-H-24	108.4658
C-1-C-2-O-10	113.8877	C-4-C-5-H-25	109.5140
C-2-O-10-C-11	112.8713	C-5-C-6-H-26	109.4455
O-10-C-11-C-12	107.9692	C-5-C-6-H-27	108.1740
C-11-C-12-C-13	120.4269	C-6-C-7-H-28	109.9249
C-12-C-13-C-14	120.1028	C-6-C-7-H-29	109.8076
C-13-C-14-C-15	120.0921	C-7-C-8-H-30	114.4716
C-14-C-15-C-16	119.9297	O-10-C-11-H-31	109.4548
C-15-C-16-C-17	120.1455	O-10-C-11-H-32	108.8524

27 with the MOPAC package of semi-empirical method (Version 6.10)⁶⁶ using the Austin Model 1 (AM1) Hamiltonian⁶⁷ (Figure 9). The heat of formation of the most stable conformation of compound 27, was calculated to be -44.4 kcal/mole. Based on the interatomic distances and bond angle values (refer Tables 1 and 2), the stable conformer showed that the epoxide and the bulky benzyl group at the C-2 position appeared to move away from each other. Some of the data associated with the modeled compound 27 include the bond distances between C-7-C-8, C-8-C-1, C-8-O-9 and the rest of the aliphatic chain. The bond distance for C-7-C-8 was found to be 1.498 Å which was slightly shorter than the other aliphatic chains in the cyclooctane ring which had a bond length of 1.515 Å. Similarly, the bond distance for C-8-C-1 (containing the epoxide ring) was found to be 1.491 Å. However, this small difference in the bond lengths was not sufficient to induce any strain in the cyclooctane ring. Furthermore, molecular modeling studies carried out on the trans-isomer showed that the phenyl group positioned itself very close to the epoxide leading to steric hinderance in the molecule. This was evident from the heat of formation which was calculated to be 125.7 kcal/mole. Thus the molecular modeling studies on compound 27 could not explain the unreactive nature of this molecule.

Hence this approach had to be abandoned. Attempts were then made to synthesize the fused-ring compound using the Bredereck reaction via the α -ketol generated from the Swern oxidation⁶⁴ of the diol. The reaction did not proceed as expected due to the decomposition of the starting material. Several other known



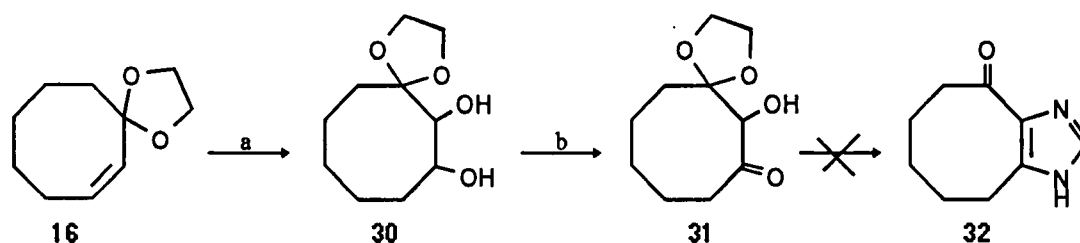
Reagents: a. NaBH_4 , MeOH; b. benzyl bromide, NaH, DMF; c. OsO_4 , NMO; d. *m*CPBA; e. oxalyl chloride, Et_3N , DMSO or Bu_2SnO , Br_2 .

Scheme 12. Attempted synthesis of 4,5,6,7,8,9-Hexahydro-1*H*-imidazo[4,5-*a*]cycloocta-4-ol 4.

procedures, such as the Weidenhagen procedure⁶⁸ and the modified Lipshutz method⁶⁹ were attempted without success.

5. Attempted synthesis of 1,5,6,7,8,9-hexahydroimidazo[4,5-*a*]cycloocta-4-one

Another approach towards the synthesis of compound **4** is outlined in Scheme 13. Compound **16** was reacted with a catalytic amount of osmium tetroxide in presence of tertiary amine *N*-oxide to generate the *cis* 1,2-diol **30** in excellent yields. The diol was further reacted with dibutyltin oxide to furnish the dibutylstannylene acetal, and then the crude was reacted with Br₂ to furnish the desired α -ketol **31** in excellent yield. Attempts to generate the desired fused-ring compound **4** using Brederick reaction proved futile.



Reagents: a. OsO₄, NMO; b. Bu₂SnO, Br₂.

Scheme 13. Attempted synthesis of 1,5,6,7,8,9-Hexahydroimidazo[4,5-*a*]cycloocta-4-one

6. 3*H*-imidazo[4,5-*b*]pyridine-7-ol

In a search for ADA inhibitors, considerable interest is vested in the synthesis of a hydroxylated analogue of nebularine that would resemble the hydrated form observed by Kati and Wolfenden¹¹ and which has been verified by Quioco and co-workers¹⁶ using single crystal X-ray diffraction studies from a 1:1 molecular adduct of HDPR to ADA (Figure 10). The literature is filled with information on the studies that have been carried out on nebularine itself; however, a review of the literature has also revealed that no attempts have been made to synthesize the hydroxylated analogs of nebularine, which might shed some light on the nature of the molecule and its binding affinity towards the enzyme.⁹⁻¹¹ Our approach toward the synthesis of the title compound, which lacks the N-1 of nebularine, is outlined in the retrosynthetic Scheme 14.

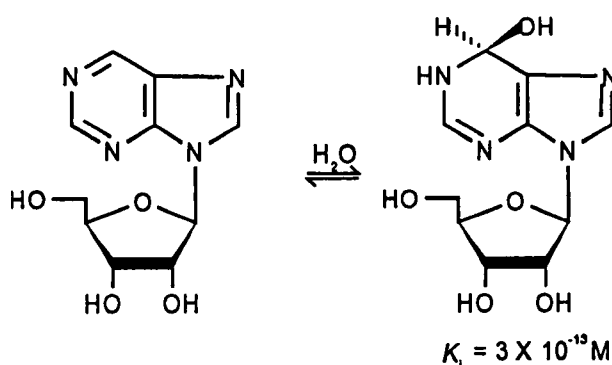
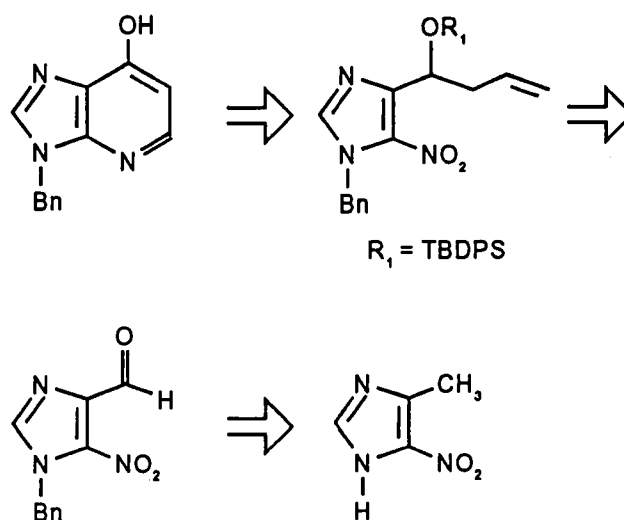


Figure 10. Wolfenden's HDPR inhibitor of ADA.

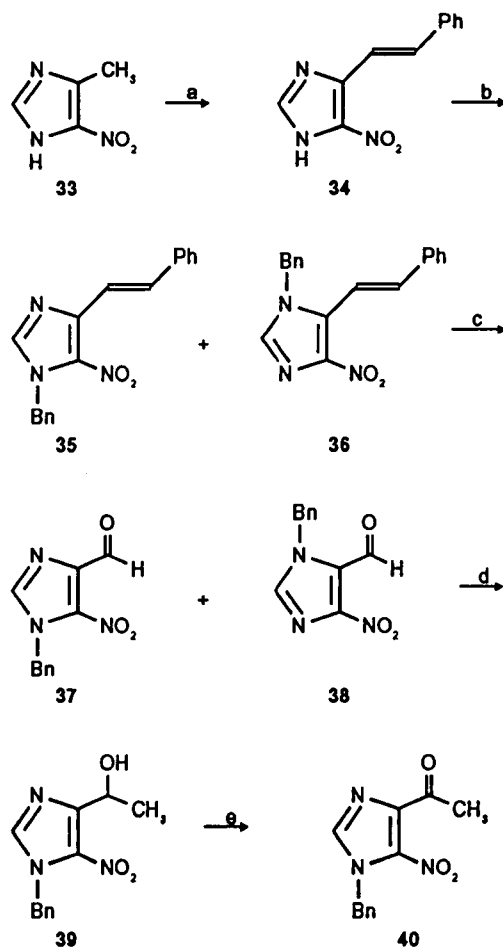


Scheme 14. Retrosynthetic scheme for synthesis of compound 5.

According to the retrosynthetic scheme for compound 5, the key starting material would be 1-benzyl-5-nitro-1*H*-imidazo-4-carbaldehyde **37**, which can be synthesized from 4-methyl-5-nitro-1*H*-imidazole **33**, using known methodology.⁷⁰ The methodology used in the synthesis of the aldehyde **37** is shown in Scheme 15. The imidazole **33** was first converted to the styryl compound by reacting with benzaldehyde and piperidine to afford a yellow solid in 78% yield. The spectral data obtained matched with those reported in the literature.⁷⁰ Then *N*-alkylation of the styryl compound furnished two isomers of the styryl compounds **35** and **36**. The isomers were separated by column chromatography using dichloromethane as the eluant. The styryl isomers were then subjected to ozonolysis, followed by workup with methyl sulfide, to furnish the corresponding aldehyde isomers **37** and **38**.

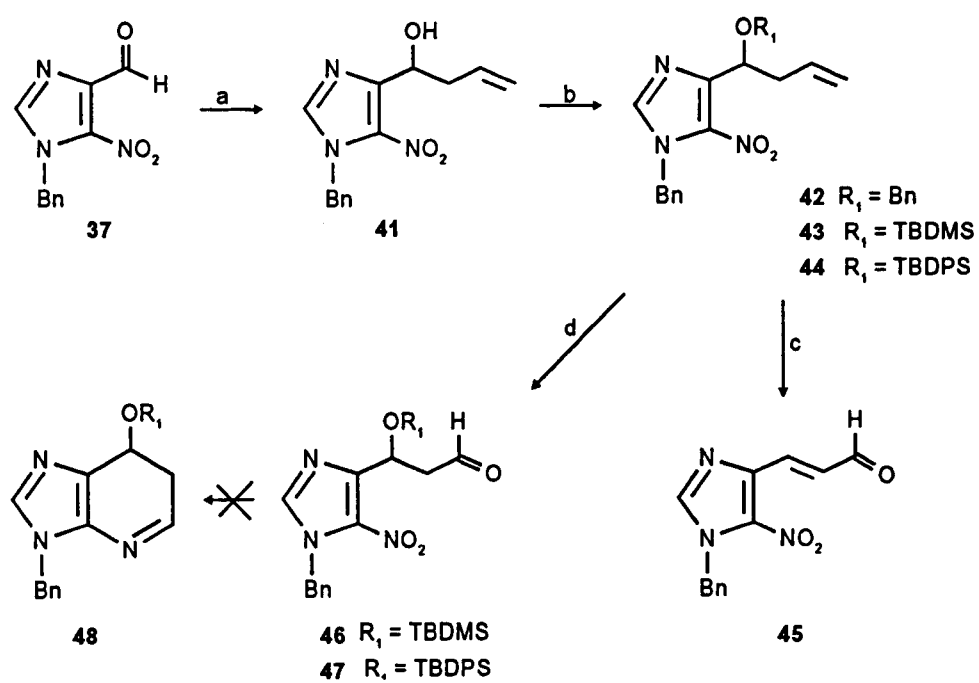
The aldehyde generated was now set up for a three-carbon chain extension. Initial studies on a one-carbon chain extension using methyllithium in presence of a Lewis acid such as TiCl_4 ⁷¹ proceeded to furnish the desired alcohol in excellent yields. Along the same lines, attempts were made to introduce the three-carbon chain extension, using allyllithium (*in situ*) and TiCl_4 . Unfortunately the reaction did not proceed as expected. Finally, the allylboronic acid methodology of Brown^{72, 73} worked out well to generate the allyl alcohol **41** in excellent yields (Scheme 16).

The free hydroxy group was protected using several protecting groups. Attempts to protect the free hydroxy group with a benzyl function met with little success as the reaction proceeded in poor yields. Furthermore the isolation of the protected compound was very difficult. Hence silyl protecting groups were used for the protection of the free hydroxy group, each generated from *tert*-butylchlorodimethylsilane (TBDMSCl),⁷⁴ or *tert*-butylchlorodiphenylsilane (TBDPSCI)⁷⁵ in the presence of imidazole in dry DMF. The silyl-protected allylic alcohol was then subjected to ozonolysis,⁷⁰ followed by workup with methyl sulfide, to generate the undesired compound **45**. The structure of compound **45** was confirmed by ^1H , ^{13}C NMR and XHCOR spectroscopy (see Appendix A). The resonance for the H-2' proton appears as a pseudo triplet at δ 7.14, while the H-1' proton appears slightly downfield at δ 8.00 as doublet ($J = 15.7$ Hz). Oxidative cleavage of the acyclic double bond with a catalytic amount of osmium tetroxide solution and sodium periodate (NaIO_4) furnished the desired aldehyde **46** and **47** in satisfactory yields.⁷⁶ The structure of the aldehyde **46** and **47** was confirmed by ^1H NMR spectroscopy (refer Table 3 and 4). The NMR spectrum of compound **46** showed a



Reagents: a. Benzaldehyde, piperidine; b. benzyl bromide, K_2CO_3 , DMF; c. O_3 , Me_2S , column chromatography; d. $TiCl_4$, $MeLi$; e. oxalyl chloride, Et_3N , DMSO.

Scheme 15. Synthesis of 1-(1-Benzyl-5-nitro-1H-imidazo-4-yl)ethanone 40.



Reagents: a. Allylboronic acid, Et_2O ; b. R_1Cl , DMF ($\text{R}_1 = \text{Bn}$, TBDMS, TBDPS); c. O_3 , Me_2S ; d.

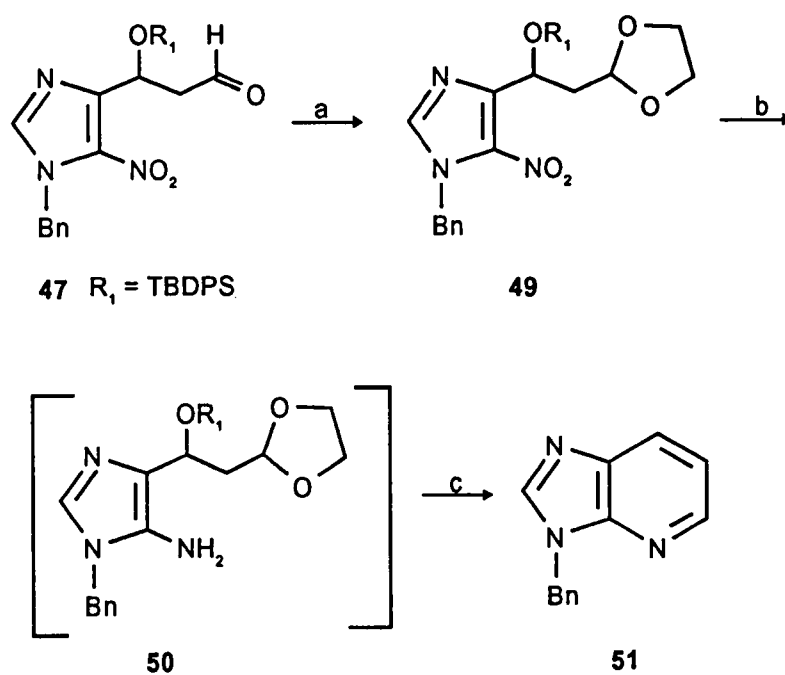
OsO_4 , NaIO_4 .

Scheme 16. Attempted synthesis of 3H-imidazo[4,5-b]pyridin-7-ol 5.

resonance for the H-3' proton at δ 9.93 as a singlet while in the case of compound 47 it appears as a triplet at δ 9.92 with a coupling constant $J = 2.1$ Hz. The final step was the ring cyclization where the nitro group would be first reduced to an amine, followed by intramolecular condensation. Various attempts to carry out the ring cyclization using 10% palladium-on-charcoal in absolute ethanol,⁷⁷ Raney nickel⁷⁸ and tin(II) chloride in ethanol⁷⁹ resulted in either no reaction or a mixture of compounds with partial reduction of the nitrogen-carbon double bond.

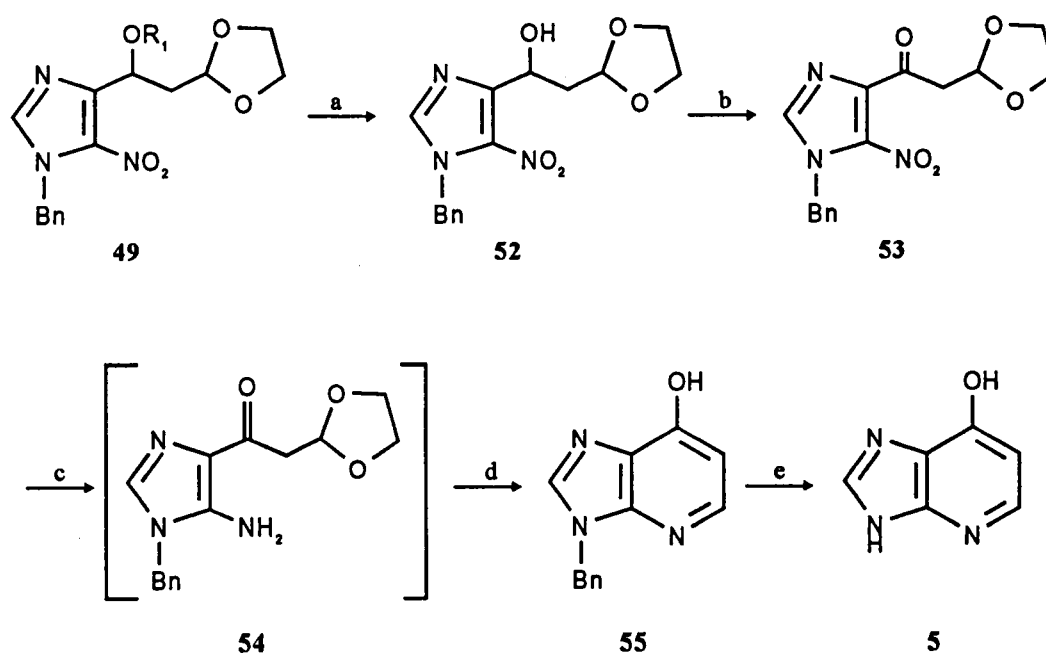
A different strategy was then attempted to synthesize the desired fused-ring imidazole compound (Scheme 17). According to this scheme, the aldehyde functionality was protected with ethylene glycol to furnish the desired acetal 49 in excellent yields.⁸⁰ Subsequent reduction of the nitro group by hydrogenolysis using H_2 , Pd/C at 50 psi and ambient temperature furnished the amine 50. The crude product was then refluxed in acetone:water (1:1) solvent mixture and *p*-toluene sulfonic acid (TsOH) for 16 h. Purification of the product by column chromatography furnished the aromatic compound 51. The structure of compound 51 was confirmed by ^1H , ^{13}C NMR spectroscopy and a decoupling experiment (see Appendix A). The resonance for the H-5 proton appears downfield at δ 8.45 as a doublet ($J = 4.6$ Hz) while the resonance for H-7 proton overlapped at δ 8.13 with the H-2 proton. The H-6 proton overlapped with the aromatic signals at δ 7.26–7.35 region.

A alternative route had to be used to synthesize the hydroxylated analog of nebularine starting from the acetal 49 (Scheme 18). The silyl protecting group was first removed by treating the acetal with tetrabutylammonium fluoride (TBAF, 1 M solution



Reagents: a. Ethylene glycol, TsOH, 50 °C; b. H_2 , Pd/C; c. TsOH, EtOH, reflux.

Scheme 17. Synthesis of 3-Benzyl-3H-imidazo[4,5-b]pyridine **51**.



Reagents: a. TBAF, THF; b. oxalyl chloride, DMSO, -78 °C; c. H₂, Pd/C; d. TsOH, EtOH, reflux; e.

H₂, Pd/C, cyclohexene, reflux.

Scheme 18. Synthesis of 3H-imidazo[4,5-b]pyridin-7-ol 5.

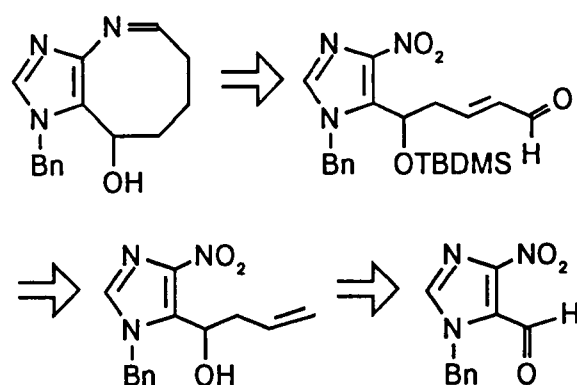
in THF)⁸¹ to furnish the free alcohol **52**. The alcohol was then subjected to oxidation using Swern oxidation⁶⁴ conditions to generate the desired ketone **53**. Reduction of the nitro group by hydrogenation using 10% palladium-on-charcoal in absolute ethanol furnished the amine **54**. This crude product was directly hydrolysed using *p*-toluene sulfonic acid (TsOH) to generate the cyclized product **55** in 63% yield. The structure of the cyclized compound **55** was confirmed by ¹H and ¹³C NMR spectroscopy. The resonance for the nitrogen-carbon double bond (H-5) appears at δ 8.25 as a doublet (J = 5.5 Hz) while the H-6 proton appears upfield at δ 6.79 as a doublet (J = 5.6 Hz).

Finally, the debenzylation of compound **55** was achieved by catalytic hydrogen transfer using 10% palladium-on-charcoal in presence of cyclohexene.⁸² The reaction was refluxed for 24 h and the crude product was purified by column chromatography to furnish the desired compound **5** in 56% yield. The structure of the final compound was confirmed by ¹H and ¹³C NMR spectroscopy (see Appendix A). The nitrogen-carbon double bond (H-5) appears at δ 7.80 as a doublet (J = 7.2 Hz) while the H-6 proton appears upfield at δ 6.40 as a doublet (J = 7.2 Hz).

7. Attempted synthesis of 6,7,8,9-Tetrahydro-1*H*-imidazo[4,5-*b*]cyclooctene-9-ol

The synthesis of the desired compound was attempted using the methodology outlined in the retrosynthetic scheme (Scheme 19). According to this scheme, the key starting material was the alternate isomer of the aldehyde, compound **38**, which was

generated by ozonolysis of the styryl compound **36**. A three-carbon chain extension using allylboronic acid followed by ozonolysis of the acyclic bond, would furnish the desired aldehyde. This would be followed by a two-carbon chain extension using the Wittig reaction. Reduction of the ester, followed by oxidation and hydrogenolysis, would furnish the desired compound **6**.

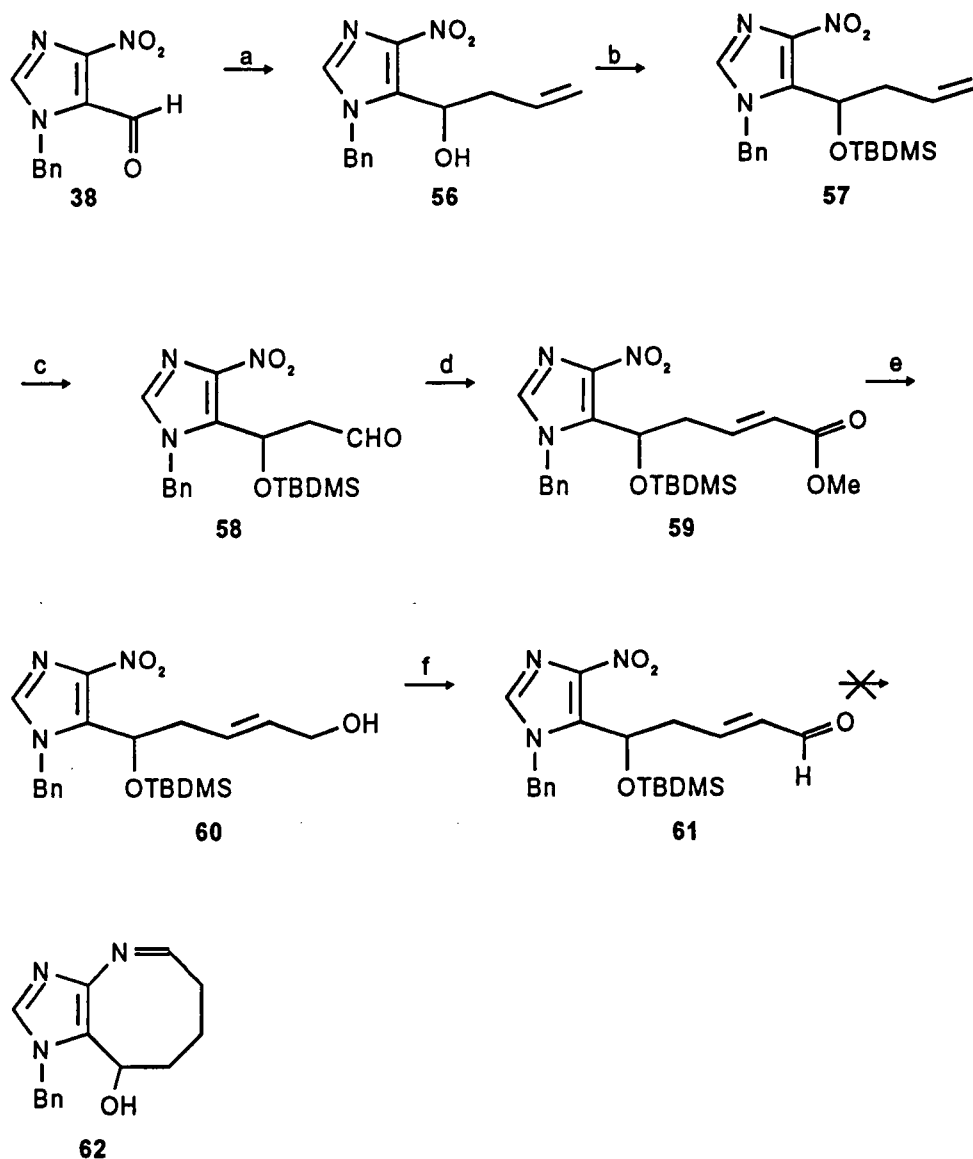


Scheme 19. Retrosynthetic scheme for synthesis of compound **6**.

The aldehyde **38**, upon reaction with the allylboronic acid, furnished the desired allylic alcohol **56** in excellent yields (Scheme 20). Comparison of the ^1H NMR spectra of the two allylic alcohol isomers **41** and **56** (refer Tables 3 and 7) showed that the signals for all the protons in compound **41** are slightly downfield with respect to the other isomer. Protection of the alcohol with *tert*-butylchlorodimethylsilane (TBDMSCl)⁷² furnished the compound **57** in excellent yields. Ozonolysis of the acyclic double bond, followed by workup with methyl sulfide, generated the desired aldehyde **58**. Further extension of the carbon chain was achieved by a Wittig reaction using methyl(triphenyl

phosphoranylidene)acetate⁸³ to furnish the ester **59**. The structure of the compound was confirmed by ¹H, ¹³C, DEPT, decoupling and XHCOR spectroscopy (see Appendix A). The ¹H spectra confirmed that only the trans isomer was obtained. The resonance for the H-3' proton appears at δ 6.82 as a doublet, while the H-4' proton appears upfield at δ 5.72 as a doublet ($J = 15.7$ Hz) which is a characteristic coupling constant value for the trans isomer. Reduction of the ester using diisobutylaluminium hydride (DIBAL)⁸⁴ furnished the alcohol **60**. The alcohol was then oxidized using Swern oxidation,⁶⁴ to generate aldehyde **61** as a gum. The structure of the aldehyde **61** was confirmed by ¹H, ¹³C, DEPT, decoupling and XHCOR spectroscopy (see Appendix A). The ¹H NMR confirmed that the structure obtained was indeed the trans isomer as reflected in the coupling constant values for the α,β -unsaturated aldehyde. The resonance for H-3' proton appears at δ 6.74 as a multiplet while the H-4' proton appears at δ 5.87 as a doublet of doublet ($J = 7.7, 15.4$ Hz).

The final step involved the ring cyclization which could be achieved by first reducing the nitro group to an amine followed by intramolecular condensation. Attempts to carry out the ring cyclization by hydrogenolysis using various catalysts such as 10% palladium-on-charcoal and Raney nickel resulted in a complicated reaction. Finally, in an attempt to carry out the ring cyclization, excessive amounts of tin(II) chloride in absolute ethanol were used and the reaction was refluxed for 24 h. The cyclization reaction did not proceed as expected.



Reagents: a. Allylboronic acid, Et_2O ; b. TBDMSCl, DMF; c. O_3 , Me_2S ; d. $\text{Ph}_3\text{P}^+\text{CHCO}_2\text{Me}$; e. DIBAL-H; f. oxalyl chloride, Et_3N , DMSO.

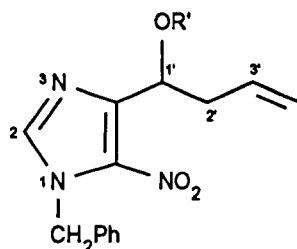
Scheme 20. Attempted synthesis of 6,7,8,9-Tetrahydro-1*H*-imidazo[4,5-*b*]cyclooctene-9-ol 6.

B. SPECTROMETRIC IDENTIFICATION OF INTERMEDIATES OF THE TARGET MOLECULES

The structures for all the intermediates for the target molecules **6** and **7** were identified by proton nuclear magnetic resonance (^1H NMR) spectroscopy using a Bruker AC 250 MHz spectrometer. The spectra were recorded using chloroform-*d* as the solvent with tetramethylsilane for internal standard. ^1H and ^{13}C NMR data for all the intermediates for the target molecules **6** and **7** are shown in Tables 3–10. Some additional spectra are shown in Appendix A for further reference.

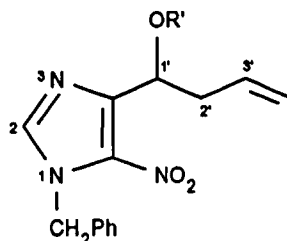
The structures for all these intermediates were identified by ^1H , ^{13}C NMR spectroscopy. Apart from that, distortionless nuclei enhanced by polarization transfer (DEPT), decoupling experiment, and heteronuclear shift correlation (XHCOR) spectroscopy were used in the identification of structures for some of the intermediates. The ^1H and ^{13}C NMR data for intermediates **41–44**, **46–47**, **56–58** and **59–61** are shown in Tables 3–10.

The chemical shifts for compounds **41–47** are in accordance with the expected values. The H-2', H-3' and H-4' protons for compounds **41–44** (see Table 3–6 for numbering) are shown as multiplets. The olefinic protons appear between δ 5–6 as multiplets. The aromatic region in all these compounds appears between δ 7–7.6. The H-1' proton of the molecule appears as a triplet around δ 5.2–5.5, which is predicted by the $n+1$ rule, with the exception of compound **43**. The H-2 proton appears as a singlet

Table 3. ^1H NMR data for compounds 41–44.^a

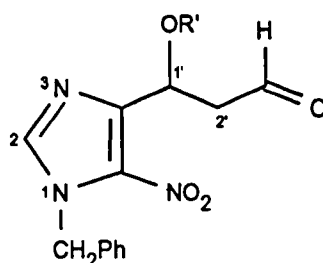
Position	41	42	43	44
	$\text{R}' = \text{H}$	$\text{R}' = {}^i\text{CH}_2\text{Ph}$	$\text{R}' = \text{TBDMS}$	$\text{R}' = \text{TBDPS}$
1	5.52 (s)	5.44 (dd) ^b	5.52 (m)	5.25 (d) ^c
2	7.54 (s)	7.56 (s)	7.67 (s)	7.72 (m)
1'	5.27 (t) ^d	5.20 (t) ^e	5.52 (m)	5.49 (t) ^f
2'	2.59 (m)	2.57–2.82 (m)	2.64 (m)	2.69 (m)
3'	5.85 (m)	5.85 (m)	5.84 (m)	5.73 (m)
4'	5.10 (m)	4.98 (m)	5.05 (m)	4.96 (m)
5'	-	4.53 (q) ^g	-	-
Aryl	7.11–7.42 (m)	7.12–7.36 (m)	7.11–7.36 (m)	7.03–7.63 (m)
Silyl Group	-	-	0.0–0.2 (s)- Me 0.9 (s)- <i>t</i> -Bu	1.05 (s)- <i>t</i> -Bu

^aSpectra were recorded at 250 MHz using CDCl_3 as solvent. The chemical shifts are reported in ppm, and first-order multiplicities (d, doublet; dd, doublet of doublets; m, multiplet; q, quartet; s, singlet; t, triplet) immediately follow in parenthesis. ^b $J = 5.3, 7.2$ Hz; ^c $J = 3.3$ Hz; ^d $J = 6.2$ Hz; ^e $J = 6.7$ Hz; ^f $J = 6.6$ Hz; ^g $J = 1.9$ Hz.

Table 4. ^{13}C NMR data for compounds 41–44.^a

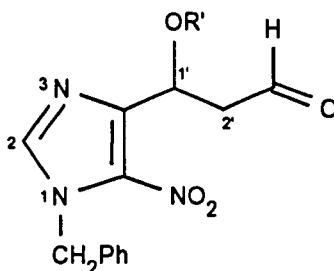
Position	41	42	43	44
	R' = H	R' = $^i\text{CH}_2\text{Ph}$	R' = TBDMS	R' = TBDPS
1	51.8	51.7	51.7	51.4
2	139.4	139.9	139.9	139.4
4	134.1	137.9	134.4	134.2
5	162.4	147.4	149.2	148.6
1'	67.3	73.5	67.6	67.7
2'	40.7	39.1	41.9	41.8
3'	133.5	133.7	133.8	133.7
4'	118.1	117.4	117.2	117.6
5'	-	71.6	-	-
Aryl	127.4, 128.7, 129.1	127.3, 127.4, 127.7, 128.0, 128.6, 129.0, 134.1	126.6, 128.1, 128.6	127.0, 127.4, 127.6, 128.6, 129.0, 129.3, 129.5, 134.7, 135.6, 135.7
Silyl Group	-	-	-4.9, -4.8, 18.2, 25.7	26.5, 26.9

^aSpectra were recorded at 62.5 MHz using CDCl_3 as solvent. Chemical shifts are reported in ppm.

Table 5. ^1H NMR data for compounds 46 and 47.^a

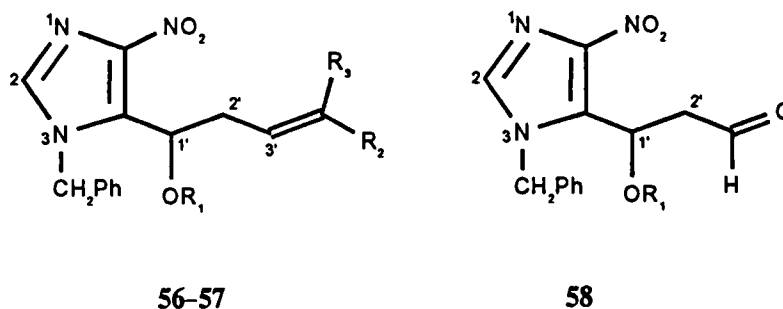
Position	46	47
	R' = TBDMS	R' = TBDPS
1	5.57 (s)	5.24 (s)
2	7.62 (s)	7.26 (s)
1'	5.95 (t) ^b	5.91 (t) ^c
2'	3.02 (m)	2.94 (m)
3'	9.93 (s)	9.92 (t) ^d
Aryl	7.11–7.53 (m)	7.08–7.60 (m)
Silyl Group	-0.00–0.12 (s)- Me	1.00 (s)- <i>t</i> -Bu
	0.89 (s)- <i>t</i> -Bu	

^aSpectra were recorded at 250 MHz using CDCl_3 as solvent. Chemical shifts are reported in ppm, and first-order multiplicities (s, singlet; t, triplet). ^b $J = 6.0$ Hz. ^c $J = 5.9$ Hz. ^d $J = 2.1$ Hz.

Table 6. ^{13}C NMR data for compounds 46 and 47.*

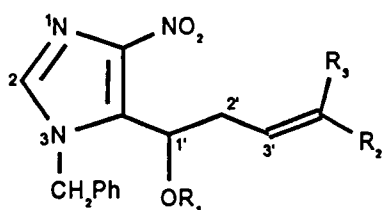
Position	46	47
	R' = TBDMS	R' = TBDPS
1	51.7	50.1
2	140.0	139.2
4	127.8	133.8
5	134.3	146.8
1'	67.6	64.1
2'	52.1	51.6
3'	200.6	200.7
Silyl Group	-5.2, -4.9, 18.2, 25.8	19.3, 26.8
Aryl	127.5, 129.0, 129.4	127.6, 127.7, 128.8, 129.1, 129.5, 129.8, 132.8, 135.5, 135.6

*Spectra were recorded at 62.5 MHz using CDCl_3 as solvent. Chemical shifts are reported in ppm.

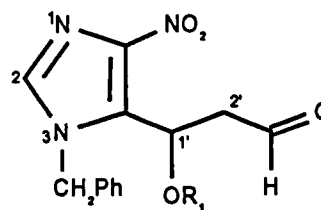
Table 7. ^1H NMR data for compounds 56–58.^a

Position	56	57	58
	$R_1 = R_2 = R_3 = \text{H}$	$R_1 = \text{TBDMS}, R_2 = R_3 = \text{H}$	$R_1 = \text{TBDMS}$
2	7.11–7.42 (m)	7.22 (s)	7.18–7.40 (m)
3	5.28–5.34 (m)	5.55 (bdd) ^b	5.60 (bdd) ^c
1'	5.28–5.34 (m)	6.03 (t) ^d	6.49 (dd) ^e
2'	2.40 (m)	2.44 (m)	2.78 (m)
3'	5.71 (m)	5.70 (m)	9.69 (s)
4'	4.93–5.13 (m)	4.98 (m)	-
Aryl	7.15–7.39 (m)	7.14–7.39 (m)	7.18–7.46 (m)
Silyl Group	-	-0.03– 0.12 (s) - Me 0.87 (s) - <i>t</i> -Bu	-0.00–0.19 (s) - Me 0.91 (s) - <i>t</i> -Bu

^aSpectra were recorded at 250 MHz using CDCl_3 as solvent. The chemical shifts are reported in ppm, and first-order multiplicities (dd, doublet of doublets; m, multiplet; s, singlet; t, triplet). ^b $J = 5.4, 21.7$ Hz. ^c $J = 5.5, 25.0$ Hz. ^d $J = 7.1$ Hz. ^e $J = 4.5, 8.9$ Hz.

Table 8. ^{13}C NMR data for compounds 56–58.^a

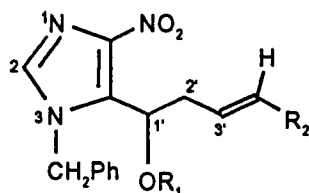
56–57



58

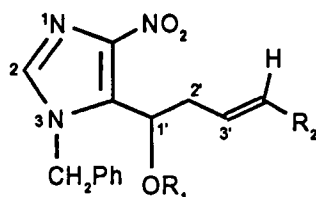
Position	56	57	58
	$R_1 = R_2 = R_3 = \text{H}$	$R_1 = \text{TBDMS}, R_2 = R_3 = \text{H}$	$R_1 = \text{TBDMS}$
2	135.8	136.1	136.6
3	51.0	51.0	50.7
4	134.4	133.7	132.7
5	137.3	134.6	134.3
1'	65.7	66.7	61.7
2'	40.3	41.9	49.7
3'	132.6	132.4	197.6
4'	119.3	118.7	-
Aryl	127.3, 128.9, 129.3	127.4, 128.8, 129.3	127.2, 128.9, 129.4
Silyl Group	-	-5.1, -4.9, 17.5, 25.7	-5.4, -5.0, 17.7, 25.4

^aSpectra were recorded at 62.5 MHz using CDCl_3 as solvent. The chemical shifts are reported in ppm.

Table 9. ^1H NMR data for compounds 59–61.^a

Position	59	60	61
	$R_1 = \text{TBDMS},$ $R_2 = {}^5\text{COOMe}^{5a}$	$R_1 = \text{TBDMS},$ $R_2 = {}^5\text{CH}_2\text{OH}$	$R_1 = \text{TBDMS},$ $R_2 = {}^5\text{CHO}$
2	7.17–7.43 (m)	7.18–7.44 (m)	7.49 (s)
3	5.63 (dd) ^b	5.57 (m)	5.56 (bq)
1'	6.06 (t) ^c	5.98 (t) ^d	6.07 (t) ^e
2'	2.51 (t) ^f	2.43 (m)	2.65 (m)
3'	6.82 (m)	5.59 (m)	6.74 (m)
4'	5.72 (d) ^g	5.59 (m)	5.87 (dd) ^h
5'	3.68 (s) - OMe	3.96 (d) ⁱ - CH ₂	9.50 (d) ^j - CHO
Aryl	7.17–7.43 (m)	7.18–7.44 (m)	7.20–7.47 (m)
Silyl Group	-0.01–0.13 (s) - Me	-0.05–0.09 (s) - Me	-0.02–0.13 (s) - Me
	0.90 (s) - <i>t</i> -Bu	0.85 (s) - <i>t</i> -Bu	0.89 (s) - <i>t</i> -Bu

^aSpectra were recorded at 250 MHz using CDCl_3 as solvent. Chemical shifts are reported in ppm, and first-order multiplicities (d, doublet; dd, doublet of doublets; m, multiplet; bq, broad quartet; s, singlet; t, triplet) immediately follow in parenthesis. ^b $J = 5.5, 40.5$ Hz. ^c $J = 6.5$ Hz. ^d $J = 7.0$ Hz. ^e $J = 6.8$ Hz. ^f $J = 7.2$ Hz. ^g $J = 15.7$ Hz. ^h $J = 7.7, 15.4$ Hz. ⁱ $J = 4.1$ Hz. ^j $J = 7.8$ Hz.

Table 10. ^{13}C NMR data for compounds 59–61.^a

Position	59	60	61
	R ₁ = TBDMS, R ₂ = ⁵ COOMe ^{5a}	R ₁ = TBDMS, R ₂ = ⁵ CH ₂ OH	R ₁ = TBDMS, R ₂ = ⁵ CHO
2	136.4	136.2	136.7
3	50.5	50.9	51.0
4	133.2	134.0	132.9
5	134.5	134.7	134.5
1'	66.2	66.7	65.8
2'	39.1	40.1	40.3
3'	142.6	133.3	150.9
4'	124.3	126.0	135.4
5'	165.5	62.7	192.9
5'a	50.8	-	-
Aryl	127.1, 128.7, 129.1	127.4, 128.8, 129.3	127.1, 129.0, 129.4
Silyl Group	-5.4, -5.1, 18.1, 25.7	-5.1, -4.9, 17.9, 25.6	-5.2, -5.0, 18.1, 25.7

^aSpectra were recorded at 62.5 MHz using CDCl₃ as solvent. Chemical shifts are reported in ppm.

around δ 7.54–7.72 region. In case of compound **44**, the H-2 proton is hidden beneath the aromatic protons and hence it is difficult to identify its exact position. The methylene protons of the N-1 protected benzyl group appear as either a doublet or a multiplet in case of compounds **42–44**.

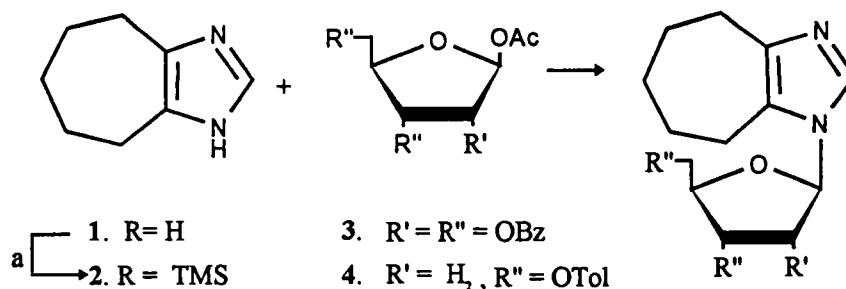
In case of the intermediates of the other compound **7**, the structures were identified by both ^1H and ^{13}C NMR spectroscopy. Compounds **56–58** showed similar spectral characteristics to the other intermediates of compound **6**. Further extension of the carbon chain at the H-3' position in compound **58** furnished intermediates **59–61**. Based on the observed J values of the olefinic bond, it was shown that the intermediate **59** was a trans isomer. Reduction of the ester furnished the alcohol **60**, which was evident from the position of the H-5' protons. The olefinic protons could not be identified clearly as they overlapped with the methylene protons of the N-3 protected benzyl group. The NMR data obtained from **61**, revealed that the compound was a trans isomer based on the coupling constant values of the olefinic protons. The H-3' and the H-4' protons of intermediates **59** and **61**, were identified by heteronuclear shift correlation (XHCOR) spectroscopy. It was observed in compounds **59–61**, that the H-3' proton was much more downfield than the H-4' proton. The β -proton (H-3') of an α,β -unsaturated ester is generally more downfield than the α -proton (H-4') because of the lower value of electron density at the β -position resulting from the delocalization of the electrons. A similar argument could be made in the case of the undesired product **45**, where the H-1' proton was downfield relative to the H-2' proton.

The silyl groups appear as singlets between δ 0.0–0.12 for methyl and as a singlet at 0.9 ppm for the *tert*-butyl group in case of both TBDMS and TBDPS protective groups.

C. APPROACH TOWARDS THE SYNTHESIS OF 2'-DEOXYNUCLEOSIDES

In our attempts to synthesize various ADA inhibitors, the syntheses of seven- and eight-membered fused-ring imidazole compounds were accomplished. Attempts were made to synthesize the nucleoside by attaching the 2'-deoxyribose unit to the N-1 of the imidazole using methodology that is commonly used in the synthesis of nucleosides. Unfortunately, the imidazole ring system is a π -electron rich system, thereby leading to formation of unstable nucleosides. The sugar moiety upon being affixed to the N-1 position of the imidazole was found to be cleaved off almost immediately upon isolation of the compound. Although the presence of the coupled product could be identified by TLC and by ^1H NMR spectroscopy in the case of the seven-membered fused-ring compound, it was difficult to purify the compound. Column chromatography of the compound resulted in glycosylic cleavage of the product.

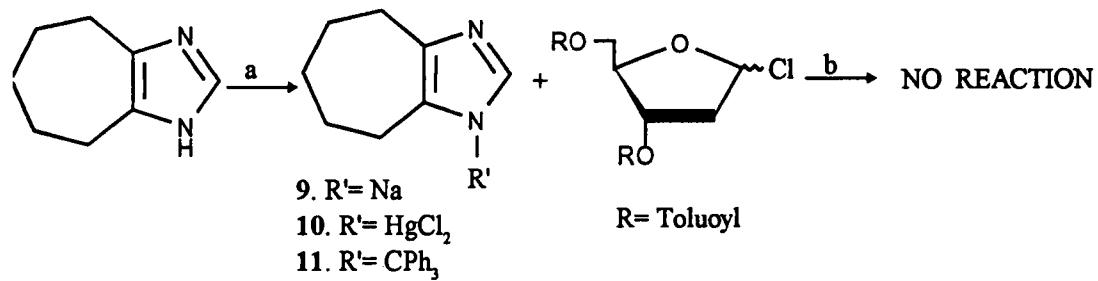
Several methods were used to couple the sugar moiety to the heterocycle (Scheme 21). Using the classical approach in nucleoside synthesis with per(trimethylsilyl)ated heterocycle 2 in presence of a Lewis acid namely tin(IV) chloride,^{85, 86} attempts were made to couple the sugar moiety with different concentrations of Lewis acid.



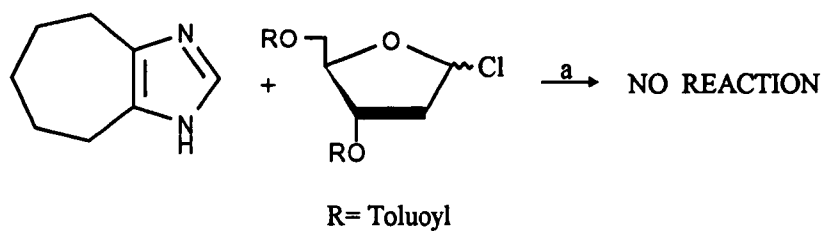
a. CF₃, [=NTMS]OTMS or HMDS, Pyridine

1. 3, SnCl₄, (-30 °C → R.T), CH₃CN
Lewis acid: 10 mole%, 50 mole%, 1,2,3, and 4 equiv.
2. 3, TMSCl, triflic acid, CH₃CN, R.T
3. 3, TMSOTf, dichloroethane, R.T
4. 3, SnCl₄, dichloroethane, bis(trimethylsilyl)acetamide, reflux, 72 h
5. 3, TMSOTf, dichloroethane, reflux
6. 3, TBDMSOTf, CH₃CN, reflux
7. 3, Iodine, 180 °C, (24 torr) fusion reaction
8. 3, TsOH, 180 °C, (26 torr) fusion reaction

Scheme 21. Methods attempted for coupling sugar moiety to the heterocycle.⁹⁸



9. a. NaH , CH_3CN ; b. CH_3CN , R.T.
10. a. HgCl_2 ; b. Celite, CdCO_3 , toluene
11. a. TrCl , pyridine; b. liq. SO_2 , 100°C , sealed tube



12. a. KOH , tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1), CH_3CN

Scheme 21. (continued).

Unfortunately, none of them worked. Various other Lewis acids such as triflic acid,⁸⁷ trimethylsilyl trifluoromethanesulfonate (TMSOTf),⁸⁸ and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf)⁸⁹ were used without any success. A new approach using bis(trimethylsilyl)acetamide was used in an attempt to couple the sugar unit to the heterocycle.⁹⁰ The advantage this method had over the other existing methods was that it was a one-pot procedure for nucleoside synthesis without the need for removal of the silylating agent. Furthermore this silylating reagent was much superior to hexamethyldisilazane (HMDS). The reaction mixture was refluxed for 72 h under dry conditions. Workup of the reaction, followed by purification of the crude product by column chromatography, afforded the nucleoside as a mixture of α , β anomers in about 7% yield. Attempts to purify this compound proved to be futile as the compound disintegrated to afford the heterocycle with the sugar being clipped off. Further attempts to use the fusion reaction with iodine⁹¹ or in presence of *p*-toluene sulfonic acid (TsOH)⁹² under reduced pressure and high temperature conditions furnished a gum. Attempts to isolate the product again proved to be futile. Robins method using sodium salt of the imidazole was also unsuccessful.⁹³ Coupling of the sugar moiety was also attempted using the mercuric salt of the imidazole without any success.⁹⁴ Using the trityl derivative of the imidazole compound and reacting it in the presence of liquid SO₂ in a sealed tube at 100 °C with the imidazole, also proved useless.⁹⁵ Seela's procedure,⁹⁶ using a strong base like potassium hydroxide with a catalytic amount of tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) was tried but gave no results. Finally, an attempt

to couple the sugar unit to the heterocycle using an enzyme-catalyzed glycosyl transferase reaction was carried out without any success.⁹⁷

V. EXPERIMENTAL

General Methods: NMR spectra were obtained using a Bruker AC 250 MHz spectrometer. Chemical shifts are reported in δ -units downfield from an internal tetramethylsilane standard in chloroform-*d* and dimethylsulfoxide-*d*₆. First-order coupling constants are given in Hz and multiplicities are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; m, multiplet; q, quartet; t, triplet. ¹³C NMR spectra were recorded at 62.5 MHz on a Bruker AC 250 MHz, at 90 MHz on a Bruker AM 360 MHz. Thin-layer chromatography was carried out using Silica Gel GF₂₅₄ (E. Merck) aluminum-backed plates. TLC visualizations were carried out using either iodine solution [I₂ (1 g); KI (10 g) in 2 mL acetic acid and 98 mL of water] or anisaldehyde-sulfuric acid dip/heating. Column chromatography was carried out using Silica Gel 60 (E. Merck) products [70–200 mesh for open columns and 230–400 mesh for medium pressure (flash)]. Melting points were determined using a Thomas-Hoover "unimelt" capillary melting point apparatus equipped with a Cole-Parmer model 8520-50 Digi-Sense digital thermocouple combination that was calibrated with known standards. Optical rotations were measured in the indicated solvent and the concentration at the sodium D line in a 1-dm cell at ambient temperatures (21–27 °C), on a Perkin-Elmer model 241 spectropolarimeter. UV absorbance was determined in appropriate solvents using a Shimadzu model UV-2101PC spectrophotometer. Electron-impact (EI⁺) and

negative-ion fast-atom bombardment (FAB) mass spectrometry were carried out on a VG ZAB-EQ (VG Analytical, Manchester, England) instrument at the Mass Spectrometry Center of The University of Tennessee.

All solvents and reagents were reagent grade and were used directly unless noted otherwise. *N,N*-Dimethylformamide (DMF) and acetonitrile were distilled from calcium hydride at ca. 20 torr and at atmospheric pressure, respectively. Methanol was distilled from magnesium turnings, and tetrahydrofuran (THF) was distilled from potassium-benzophenone ketyl at atmospheric pressure. All dry solvents were stored over appropriately activated molecular sieves. Evaporation of solvents was carried out at ca. 40 °C under aspirator vacuum. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA.

Preparation of α -Bromocycloheptanone (8)

To a mixture of cycloheptanone (20 g, 0.17 mol) in 100 mL of anhydrous CCl_4 was added *N*-bromosuccinimide (NBS) (35 g, 0.19 mol), and a catalytic amount of 2,2'-azobis(2-methylpropionitrile) (200 mg). The solution was refluxed for 30 min. The reaction mixture was cooled, and filtered. The volume of the carbon tetrachloride filtrate was reduced in vacuo, the residue was treated with pentane (50 mL), and the solution was then cooled to -50 °C to afford two layers. The organic layer contained the desired compound. Further extraction of the residue with pentane at -50 °C, followed by evaporation of the solvent, afforded a crude product. Distillation of the crude product under reduced pressure at 51–55 °C (0.5 torr) [lit.³³ bp 72–73 °C, 1.5 torr], afforded

24 g (72%) of the desired product **8**: ^1H NMR data (CDCl_3 , 250 MHz): δ 1.0–3.0 (m, 10 H, aliphatic CH_2), 4.06 (m, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 24.9, 26.8, 29.5, 34.2, 39.3, 53.7, 206.1.

1,4,5,6,7,8-Hexahydroimidazo[4,5-*a*]cycloheptane (1)

A solution of α -bromocycloheptanone (11.0 g, 57.5 mmol) in 100 mL of formamide was heated at 170–180 °C for 3 h. The solution was cooled and poured into 125 mL of 10% HCl and decolorized with activated carbon. The filtrate was made basic with ammonium hydroxide and extracted with CHCl_3 (3 $\times$ 40 mL). The organic extracts were washed with water (3 $\times$ 100 mL) and brine solution. The organic extracts were dried (MgSO_4). The solvent was removed under reduced pressure and triturated with EtOAc to afford white crystals of **1** (4.06 g, 52%): mp 198 °C; ^1H NMR data (250 MHz, CDCl_3): δ 1.6–1.8 (m, 6 H, H-5, H-6, H-7), 2.69–2.71 (m, 4 H, H-4, H-8), 7.32 (s, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 27.7, 27.8, 30.7, 130.7; IR data (KBr): 3018 cm^{-1} , 2930 cm^{-1} , 1215 cm^{-1} ; UV data (methanol): 223.30 nm (ϵ 4517.5).

Anal. Calcd for $\text{C}_8\text{H}_{12}\text{N}_2$: C, 70.55; H, 8.88. Found: C, 70.30; H, 8.83.

Preparation of α -Bromocyclooctanone (10)

To a solution of cyclooctanone (14 g, 0.12 mol) in 200 mL of anhydrous CCl_4 , was added *N*-bromosuccinimide (28 g, 0.13 mol), and a catalytic amount of 2,2'-azobis(2-methylpropionitrile) (200 mg). The solution was refluxed for 2 h after which time the reaction mixture was cooled and filtered. The filtrate was evaporated in vacuo, and the residue was distilled under reduced pressure at 55–60 °C (0.15 torr Hg) [lit.³⁵ bp 65–73 °C, 0.2–0.5 torr] to afford 6.4 g (28%) of the desired product **10**: ^1H NMR

data (CDCl₃, 250 MHz): δ 1.0–3.0 (m, 12 H, aliphatic CH₂), 4.27 (dd, 1 H, J = 5.7 Hz, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 23.9, 25.4, 26.5, 28.6, 33.2, 36.2, 54.2, 205.9.

4,5,6,7,8,9-Hexahydro-1*H*-imidazo[4,5-*a*]cyclooctanone (2)

To a solution of α -bromocyclooctanone (13 g, 63 mmol) in formamide (200 mL) was heated to 170–180 °C for 3 h. The reaction was cooled and poured into 100 mL of 10% HCl and decolorized with activated carbon. The filtrate was made basic with ammonium hydroxide and extracted with CHCl₃ (3 $\times$ 30 mL). The combined organic extracts were then washed with water (3 $\times$ 60 mL) and brine solution. The organic extracts were dried (MgSO₄), evaporated and triturated with EtOAc to afford 3.4 g (36%) of pale-yellow crystals of 2: mp 145–146 °C; ¹H NMR data (CDCl₃, 250 MHz): δ 1.47–1.5 (m, 4 H, H-6, H-7), 1.6–1.8 (m, 4 H, H-5, H-8), 2.73–2.78 (m, 4 H, H-4, H-9), 7.26 (s, 1 H, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 25.0, 25.7, 28.1, 131.6; IR data (KBr): 3018 cm⁻¹, 2930 cm⁻¹, 1215 cm⁻¹; UV data (methanol): 224.20 nm (ϵ 3993.3).

Anal. Calcd for C₉H₁₄N₂·0.01CHCl₃: C, 71.47; H, 9.33. Found: C, 71.40; H, 9.27.

Preparation of (Z)-1,2-Epoxy-5-cyclooctene (12)

To an ice-cold stirred solution of (Z,Z)-1,5-cyclooctadiene (54.0 g, 520 mmol) in 600 mL of CH₂Cl₂ was added anhydrous sodium carbonate (213 g, 2.01 mol), followed by dropwise addition of 35% peroxyacetic acid (108 g, 52.3 mmol) [pretreated with a small amount of sodium acetate]. The reaction mixture was stirred at room temperature

for 12 h. The solid salts were removed by suction and washed well with CH_2Cl_2 . The solvent was removed in vacuo, and the crude product was distilled under reduced pressure to afford 34.5 g (55.7%) of the desired product 12: bp 47 °C (0.75 torr) [lit.³⁶ bp 52 °C, 0.8 torr]: ^1H NMR data (CDCl_3 , 250 MHz): δ 2.0–2.49 (m, 8 H, H-2, H-3, H-6, H-7), 3.03 (m, 2 H, H-1, H-8), 5.57 (m, 2 H, H-4, H-5); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 23.6, 28.1, 56.6, 128.8.

Preparation of (Z)-2-Hydroxy-5-cycloocten-1-one (13)

To a solution of epoxide 12 (13.2 g, 102 mmol) in 40 mL of dry dimethyl sulfoxide (DMSO) was added boron trifluoride etherate (130 μL , 1.02 mmol), and the reaction mixture was heated under an inert atmosphere of nitrogen at 100 °C overnight. After completion of the reaction the solution was cooled and poured into ice water. The solution was extracted with CHCl_3 (3 $\times$ 40 mL) and further washed with cold water, dried (MgSO_4), and evaporated in vacuo to afford a pale yellowish oil. The crude product was purified by fractional distillation under reduced pressure (bp 60–62 °C, 0.2 torr) to afford a colorless oil 13 (10.6 g, 56%): [lit.³⁷ bp 55 °C, 0.1 torr]; ^1H NMR data (CDCl_3 , 250 MHz): δ 2.0–3.0 (m, 8 H, H-3, H-4, H-7, H-8), 4.33 (m, 1 H, H-2), 5.67 (m, 2 H, H-5, H-6); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 20.9, 28.0, 41.0, 43.0, 129.9, 130.6, 203.2.

4,5,8,9-Tetrahydro-1*H*-imidazo[4,5-*a*]cycloocta-6-ene (3)

To a solution of α -ketol 13 (15 g, 0.10 mol) in 75 mL of formamide was added ammonium formate (15 g, 0.23 mol). The reaction mixture was heated to 170–180 °C for 3 h. The reaction was cooled in an ice bath and acidified to pH 2 using 100 mL of

10% HCl. The reaction mixture was made basic to pH 8 using ammonium hydroxide, and later extracted with CHCl_3 (3×25 mL). The organic extract was washed with water and then with brine solution, dried (MgSO_4) evaporated in vacuo to afford a brown syrup. The syrup was triturated with EtOAc-hexane and scratched hard to afford pale-brown crystals of **3** (5.7 g, 38%): mp 160–161 °C; ^1H NMR data (CDCl_3 , 250 MHz): δ 2.4–2.6 (m, 4 H, H-5, H-8), 2.8–3.0 (m, 4 H, H-4, H-9), 5.5–5.6 (m, 2 H, H-6, H-7), 7.45 (s, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 25.5, 25.7, 70.1, 131.7; IR data (KBr): 3018 cm^{-1} , 2399 cm^{-1} , 1215.4 cm^{-1} ; UV data (methanol): 221.4 nm (ϵ 4344), 281.4 nm (ϵ 300.8).

Anal. Calcd for $\text{C}_9\text{H}_{12}\text{N}_2$: C, 72.94; H, 8.16. Found: C, 72.80; H, 8.12.

Preparation of the Ethylene Ketal of 2-Cyclooctanone (16)

To a solution of cyclooctanone (8.6 g, 68 mmol) in 70 mL of ethylene glycol was added 3 drops of bromine, and the solution stirred at room temperature for 15 min. The yellow color dissappeared slowly. The solution was cooled to 15 °C and bromine (11 g, 68 mmol) was added slowly. The resulting yellow solution was warmed to room temperature. The completion of the reaction was indicated by loss of yellow color. The solution was poured into a suspension of 25 g of Na_2CO_3 in 120 mL of hexane. After 10 min. 100 mL of water was added, and the organic layer separated, dried (Na_2SO_4) and concentrated. The crude residue was distilled to afford 13 g (79%) of the crude ethylene ketal of 2-bromocyclooctanone **15**: bp 93–95 °C (0.6 torr) [lit.⁴⁸ bp 87–89 °C, 0.5 torr]; ^1H NMR data (CDCl_3 , 250 MHz): δ 1.0–2.3 (m, 12 H, aliphatic CH_2), 3.7–4.4 (m, 4 H, CH_2O), 4.5 (m, 1 H, H-2).

mmol) of sodium hydroxide in 50 mL of MeOH. The solution was refluxed for 72 h and then partitioned between hexane and brine solution. The organic layer was dried (Na_2SO_4) and concentrated. The crude liquid was distilled to afford 5.9 g (65%) of the desired product **16**: bp 70–72 °C (1.5 torr) [lit.⁴⁸ bp 67–69 °C, 1.4 torr]; ^1H NMR data (CDCl_3 , 250 MHz): δ 1.26–2.44 (m, 10 H, aliphatic CH_2), 3.92 (s, 4 H, CH_2O), 5.60 (m, 2 H, vinyl CH); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 21.7, 23.9, 24.5, 27.8, 39.2, 63.9, 131.4, 133.3.

Preparation of 2-Cycloocten-1-one (**17**)

To a solution of **16** (1.7 g, 9.9 mmol) in 20 mL of MeOH was added 10 mL of 10% HCl, and the mixture was refluxed overnight. The reaction mixture was cooled and extracted with ether (3×20 mL), washed with saturated NaHCO_3 solution, dried (Na_2SO_4), concentrated and purified by column chromatography using 1:3 (v/v) EtOAc–hexane to afford 0.74 g (60%) of the desired product **17** as a colorless liquid: bp 62–64 °C (2.4 torr) [lit.⁴⁸ bp 70–71.5 °C, 2.8 torr]; ^1H NMR data (CDCl_3 , 250 MHz): δ 1.55–2.68 (m, 10 H, aliphatic CH_2), 6.03 (d, 1 H, $J = 2.4$ Hz, H-3), 6.37 (m, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 22.5, 23.1, 25.3, 28.5, 42.7, 132.4, 141.5, 208.3.

Preparation of 1-Trimethylsilyloxycycloheptene (**19**)

To a flame-dried three-necked round-bottomed flask was added 60 mL of *N,N*-dimethylformamide (DMF) (previously distilled over calcium hydride) and triethylamine (15 g, 0.15 mol). The solution was stirred for a while and then trimethylchlorosilane (8.56 g, 0.07 mol) and cycloheptanone (7.3 g, 60 mmol) were injected into the flask.

The reaction mixture was refluxed for 6 h under an inert atmosphere of nitrogen. The reaction was cooled down and diluted with 100 mL of pentane. The precipitate of triethylamine hydrochloride was filtered. The organic extract was successively washed with saturated NaHCO_3 solution (3×40 mL), brine (2×30 mL), dried (Na_2SO_4) and concentrated to a colorless liquid. The residual liquid was distilled under reduced pressure to afford 9.2 g (77%) of the desired product **19**: bp 81–82 °C (20 torr) [lit.⁵⁰ bp 82–83 °C, 20 torr]; ^1H NMR data (CDCl_3 , 250 MHz): δ 0.15 (s, 9 H, $3 \times \text{Me}$), 1.47–2.24 (m, 10 H, aliphatic CH_2), 5.01 (t, 1 H, $J = 6.5$ Hz, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 0.27, 25.2, 25.3, 27.8, 31.5, 35.5, 108.6.

Preparation of 1-Trimethylsilyloxybicyclo[5.1.0]octane (20)

To a flame-dried three-necked flask maintained under an inert atmosphere of nitrogen was charged with 50 mL of dry ether, 1-trimethylsilyloxycycloheptane (2.18 g, 11.8 mmol) and diethylzinc (2.04 g, 16.6 mmol). The reaction mixture was stirred at room temperature for 0.5 h. Diiodomethane (4.72 g, 17.7 mmol) was added slowly to the reaction mixture over a period of 1 h. The reaction mixture was refluxed for 8 h. After completion of the reaction the flask was cooled in ice-bath, and 0.8 mL of NH_4Cl solution was added slowly. Upon hydrolysis a white solid was formed. The salt was filtered, and the organic extract was washed successively with saturated NH_4Cl solution (3×30 mL), brine (2×30 mL), dried (Na_2SO_4) and concentrated to afford a colorless liquid. The residual liquid was distilled under reduced pressure to afford 2.17 g (93%) of the desired product **20**: bp 85–87 °C (13 torr) [lit.⁵⁰ bp 97–99 °C, 16 torr]; ^1H NMR data (CDCl_3 , 250 MHz): δ 0.12 (s, 9 H, $3 \times \text{Me}$), 0.39 (ψ t, 1 H, endo H at C-8),

0.79–1.77 (m, 10 H, aliphatic CH₂), 2.08–2.2 (m, 2 H, aliphatic CH₂); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 1.39, 25.5, 30.4, 31.2, 31.4, 32.0, 37.6, 43.8.

Preparation of 2-Cycloocten-1-one (17)

To a flame-dried three-neck flask maintained under nitrogen atmosphere was charged with anhydrous iron(III) chloride (20 g, 0.12 mol). The flask was immersed in an ice–water bath, followed by slow addition of 70 mL of *N,N*-dimethylformamide (DMF). Upon complete dissolution of the iron(III) chloride, compound **20** (13.6 g, 600 mmol) was slowly added to the reaction vessel while the internal temperature was maintained 0–5 °C. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was poured into 200 mL of 1 N HCl, and the aqueous solution was extracted with CHCl₃ (3 × 60 mL). The organic extract was washed successively with 50 mL of 1 N HCl, saturated NaHCO₃ solution (2 × 40 mL) and brine (2 × 30 mL). The extract was dried (Na₂SO₄) and evaporated to afford 11 g of the crude product **21**.

The crude product was dissolved in 60 mL of dry MeOH saturated with sodium acetate and refluxed for 3 h. The solution was cooled and concentrated. The residue was extracted with ether (3 × 30 mL), and the extract was washed with water (2 × 30 mL), dried (Na₂SO₄), evaporated to afford 3.6 g (43%) of compound **17**: bp 65–67 °C (2.5 torr).

Preparation of Cyclooctene Oxide (23)

To a solution of cyclooctene (6.4 g, 6.0 mmol) in 50 mL of dry CH₂Cl₂ was added 80% *m*-chloroperoxybenzoic acid (18.5 g, 8.50 mmol). The reaction mixture was stirred at room temperature for 1 h and later refluxed for 12 h under an inert atmosphere

of N₂. After completion of the reaction as indicated by TLC (R_f = 0.94, 0.5:9.5 (v/v) MeOH-CHCl₃), the reaction mixture was cooled to 0 °C. The precipitate of *m*-chlorobenzoic acid was filtered, and the filtrate was concentrated to a colorless oil. The crude product was purified by fractional distillation to afford 7.5 g (99%) of the desired product **23**: bp 40–42 °C (1 torr) [lit.⁵² bp 67–69 °C, 9.8 torr]; ¹H NMR data (CDCl₃, 250 MHz): δ 1.25–2.17 (m, 12 H, aliphatic CH₂), 2.9 (m, 2 H, H-1, H-8); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 25.5, 26.2, 26.5, 55.6.

Preparation of Cycloocta-2-enol (**24**)

Method A. Base-catalyzed isomerization using potassium *tert*-butoxide

To a solution of **23** (7.5 g, 59 mmol) in 40 mL of anhydrous dimethyl sulfoxide (DMSO) was added potassium *tert*-butoxide (8.0 g, 71 mmol), and the reaction mixture was heated under a nitrogen atmosphere for 22 h. TLC showed no further progress in the reaction and so the heating was stopped and the reaction was cooled. To the cooled solution was added 4 mL of water and dry ice to neutralize the solution. The reaction mixture was extracted in ether (3 × 30 mL), and the ether extract was washed with water (3 × 20 mL), dried (MgSO₄) and concentrated to generate the crude product. The compound was purified by short-path distillation to afford 1.8 g (25%) of **24**: bp 60–62 °C (0.94 torr) [lit.⁵² bp 74 °C, 2 torr], along with 5.0 g of the unreacted epoxide; overall yield (92%).

Method B. Reduction of an α,β -unsaturated ketone using sodium borohydride

To a solution of **17** (1.0 g, 8.0 mmol) in MeOH was added sodium borohydride (0.31 g, 8.0 mmol). The reaction was exothermic and went to completion in 1.5 min.

The reaction was monitored by TLC ($R_f = 0.57$, 0.5:9.5 (v/v) MeOH-CHCl₃) and the reaction was worked upon completion. The mixture was neutralized with 20 mL of 1% HCl and extracted into ether (3 × 15 mL), and the ether extract was dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography using 3:2 (v/v) EtOAc-hexane to afford 0.97 g (96%) of compound **24**: ¹H NMR data (CDCl₃, 250 MHz): δ 1.2–2.2 (m, 10 H, aliphatic CH), 4.64 (m, 1 H, CHOH), 5.48–5.62 (m, 2 H, -CH=CH-); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 23.6, 25.9, 26.2, 29.0, 38.6, 68.4, 128.6, 134.9.

Preparation of 3-Benzyloxycyclooctene (**25**)

To a solution of **24** (2.46 g, 19.5 mmol) in 50 mL of dry *N,N*-dimethylformamide (DMF) was added 60% sodium hydride (850 mg, 21.4 mmol), and the reaction mixture was stirred under an inert atmosphere of nitrogen at room temperature. To this mixture was added benzyl bromide (3.99 g, 23.4 mmol) very slowly, and the reaction mixture was stirred for 18 h. After completion of the reaction, the solvent was removed under reduced pressure, and the residue was dissolved in CHCl₃. The organic extract was washed with water (3 × 30 mL), dried (MgSO₄) and concentrated to a syrup. The crude product was purified by column chromatography using 1:2 (v/v) EtOAc-hexane to afford 3.15 g (89%) of compound **25**: ¹H NMR data (CDCl₃, 250 MHz): δ 1.25–2.33 (m, 8 H, aliphatic CH), 4.33–4.38 (m, 1 H, H-3), 4.40–4.64 (m, 2 H, -OCH₂Ph), 5.54–5.76 (m, 2 H, -CH=CH-), 7.25–7.35 (m, 5 H, aryl); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 23.7, 26.3, 26.5, 35.8, 70.5, 75.9, 127.3, 127.7, 128.3, 130.4.

Anal. Calcd for C₁₅H₂₀O: C, 83.29; H, 9.32. Found: C, 83.37; H, 9.29.

3-Benzyloxycyclooctane-1,2-diol (26)

To a solution of **25** (19.6 g, 90.7 mmol) in water:*tert*-BuOH:THF (1:3:10) solvent mixture was added 4-methylmorpholine-*N*-oxide (11.0 g, 94.0 mmol). The reaction was stirred at room temperature for 5 min. A catalytic amount of osmium tetroxide solution (6 mL) (1 g/125 mL of *tert*-BuOH) was added, and the reaction stirred at room temperature for 18 h. After completion of the reaction as indicated by TLC (R_f = 0.50, 1:9 (v/v) MeOH-CHCl₃), the mixture was poured into a slurry of magnesium silicate (12 g) and 1 g of sodium hydrosulfite in 50 mL of water. The reaction was acidified to pH 2 using conc H₂SO₄ and extracted with EtOAc (3 × 30 mL). The organic extracts were washed with brine (2 × 30 mL), dried (Na₂SO₄) and concentrated to a colorless syrup. The crude product was purified by column chromatography using 4:1 (v/v) EtOAc-hexane as the eluant to afford 21.7 g (96%) of compound **26**. The crude product was recrystallized from hexane at -4 °C to afford 18.09 g of the pure product: mp 47–49 °C; ¹H NMR data (CDCl₃, 250 MHz): δ 1.3–2.0 (m, 10 H, aliphatic CH), 3.64–3.92 (m, 2 H, H-1, H-3), 3.94–4.09 (m, 1 H, H-2), 4.37–4.72 (m, 2 H, -OCH₂Ph), 7.23–7.43 (m, 5 H, aryl); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 22.0, 23.1, 27.8, 29.7, 30.0, 70.6, 71.3, 74.6, 78.3, 127.8, 128.5.

Anal. Calcd for C₁₅H₂₁O₃: C, 71.97; H, 8.86. Found: C, 72.17; H, 8.73.

2-Benzyloxy-9-oxa-bicyclo[6.1.0]nonane (27)

To a solution of **25** (2.38 g, 11.0 mmol) in 40 mL of dry CH₂Cl₂ was added (80%) *m*-chloroperoxybenzoic acid (2.97 g, 13.7 mmol) very slowly over a period of 1 h. The solution was refluxed for 3 h under an inert atmosphere of nitrogen. The

solution was cooled and the precipitate of *m*-chlorobenzoic acid was filtered. The organic extract was washed with 10% sodium bisulfite (3 × 25 mL), saturated NaHCO₃ (2 × 25 mL), brine (2 × 25 mL), dried (Na₂SO₄) and concentrated to afford the crude product. The crude product was purified by column chromatography using 1:9 (v/v) EtOAc–hexane to afford 2.46 g (97%) of **27**: [*R_f* = 0.98, 3:7 (v/v) EtOAc–hexane]; ¹H NMR data (CDCl₃, 250 MHz): δ 1.2–2.2 (m, 10 H, aliphatic CH), 2.97 (m, 2 H, H-1, H-2), 3.4 (m, 1 H, H-3), 4.57–4.87 (m, 2 H, -OCH₂Ph), 7.25–7.4 (m, 5 H, aryl); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 23.6, 25.3, 26.5, 26.8, 33.6, 53.4, 59.1, 71.2, 78.4, 125.2, 127.3, 127.7, 128.2.

Anal. Calcd for C₁₅H₂₀O₂: C, 77.52; H, 8.68. Found: C, 77.28; H, 8.57.

3-Benzoyloxy-2-hydroxycyclooctanone (**28**)

Method A. Using dibutyltin oxide

A mixture of compound **26** (470 mg, 1.88 mmol) and dibutyltin oxide (560 mg, 2.25 mmol) in 20 mL of dry benzene was refluxed for 48 h with azeotropic removal of water using the Dean–Stark apparatus. The solvent was evaporated to afford the crude stannylene product which was used without any further purification. The crude product was dissolved in 10 mL of dry benzene along with 0.2 g of 4 Å molecular sieves. To this a solution of bromine (290 mg, 1.88 mmol) in 2 mL of CH₂Cl₂ was added dropwise at ambient temperature. The completion of the reaction was indicated by the discoloration of the reaction mixture. The solvent was evaporated and the crude product was purified by column chromatography using 9:1 (v/v) EtOAc–hexane to afford 350 mg (75%) of **28** (as a mixture of diastereomers).

Method B. Using the Swern oxidation

A solution of oxalyl chloride (3.50 g, 27.7 mmol) in 30 mL of dry CH_2Cl_2 was cooled under an inert atmosphere of nitrogen to $-60\text{ }^\circ\text{C}$. To this a solution of dimethyl sulfoxide (DMSO) (4.16 g, 53.2 mmol) was added, and the resulting mixture was stirred for 10 min at the same temperature. A solution of **26** (5.32 g, 21.3 mmol) in 10 mL of CH_2Cl_2 was added to the above solution, and the reaction mixture was stirred at $-60\text{ }^\circ\text{C}$ for 15 min. To this mixture was added dry triethylamine (15.0 g, 149 mmol), and the reaction mixture was warmed to room temperature over a period of 1 h. The reaction was quenched with 30 mL of water and stirred for 10 min. The organic layer were separated and the aqueous layer was further extracted with CH_2Cl_2 ($2 \times 25\text{ mL}$). The combined organic layers was dried (MgSO_4) and concentrated to afford a syrup. The crude product was purified by column chromatography using 1:9 (v/v) $\text{MeOH}-\text{CHCl}_3$ to afford 4.98 g (94%) of the desired product **28** (as a mixture of diastereomers): ^1H NMR data (CDCl_3 , 250 MHz): δ 1.0–2.1 (m, 10 H, aliphatic CH_2), 3.0 (m, 1 H, H-3), 4.34 (bdd, 1 H, $J = 1.8\text{ Hz}$, H-2), 4.70 (d, 2 H, $-\text{OCH}_2\text{Ph}$), 7.25–7.38 (m, 5 H, aryl); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 21.0, 24.6, 27.2, 28.3, 39.0, 71.0, 82.7, 127.6, 128.4, 192.3.

Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_3 \cdot 0.14\text{CHCl}_3$: C, 68.51; H, 7.65. Found: C, 68.67; H, 7.35.

Attempted synthesis of 4-Benzyloxy-4,5,6,7,8,9-hexahydro-1*H*-imidazo[4,5-*a*]cyclooctanone (29**)**

To a solution of **28** (1.44 g, 5.80 mmol) in 4.6 mL of formamide was added

ammonium formate (3.66 g, 5.80 mmol), and the reaction mixture was heated to 150 °C for 8 h. The reaction mixture was cooled and made basic (pH 9) using ammonium hydroxide. The aqueous solution was extracted with CHCl_3 (3×30 mL), and the extract was washed with water (3×20 mL), dried (MgSO_4) and concentrated to afford 400 mg of brown crystals. NMR data of this compound resembled to that of α -amino alcohol.

Ethylene Ketal of Cycloocta-1-one-2,3-diol (30)

To a mixture of 4-methylmorpholine-*N*-oxide (700 mg, 6.54 mmol) in acetone- H_2O (1:2, v/v) and catalytic amount of osmium tetroxide solution (4.08 mL) (10 mg/1 mL *tert*-BuOH) was added 16 (1.00 g, 5.95 mmol). The reaction was stirred at room temperature for 36 h. The completion of the reaction was indicated by TLC (R_f = 0.23, 9:1 (v/v) EtOAc-hexane). A slurry of 3 g of magnesium silicate and 0.2 g of sodium hydrosulfite in 15 mL of water was added to the reaction mixture. Upon filtration of the silicate, the filtrate was acidified to pH 2 using conc H_2SO_4 , extracted with EtOAc (3×25 mL). The organic extracts were dried (Na_2SO_4) and concentrated to afford a syrup. The crude product was purified by column chromatography using 8:2 (v/v) EtOAc-hexane to afford 1.09 g (91%) of the desired product 30 as colorless crystals (recrystallized from Et_2O): mp 68–70 °C; ^1H NMR data (CDCl_3 , 250 MHz): δ 1.2–2.16 (m, 10 H, aliphatic CH_2), 2.63–2.85 (bs, 2 H, $2 \times \text{OH}$), 3.86–4.14 (m, 6 H, H-6, H-7, $-\text{O}(\text{CH}_2)_2\text{O}-$); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 22.0, 22.5, 28.9, 32.5, 34.2, 64.3, 65.9, 72.6, 73.3, 111.7.

Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_4$: C, 59.39; H, 8.97. Found: C, 59.67; H, 9.11.

Ethylene Ketal of 2-Hydroxycycloocta-1,3-dione (31)

To a mixture of **30** (430 mg, 2.12 mmol) in 20 mL of dry benzene was added dibutyltin oxide (630 mg, 2.55 mmol), and the mixture was refluxed 48 h using a Dean-Stark apparatus for azeotropic removal of water. The solvent was evaporated to afford a crude stannylene derivative. The crude product was dissolved in 5 mL benzene, and 0.3 g of 4 Å molecular sieves was added to remove any traces of water. Bromine (310 mg, 2.12 mmol) dissolved in 2 mL of dry CH_2Cl_2 was added slowly to the crude product, and the reaction was stirred at room temperature for 0.5 h. The completion of the reaction was indicated by the discoloration of the reaction mixture. The solvent was evaporated to give the crude product, which was purified by column chromatography using 1:9 (v/v) MeOH-CHCl_3 to afford 330 mg (80%) of **31** as an oil: ^1H NMR data (CDCl_3 , 250 MHz): δ 1.35–2.0 (m, 8 H, aliphatic CH_2), 2.63 (m, 1 H, H-8''), 2.79 (m, 1 H, H-8'), 3.9–4.2 (m, 4 H, $-\text{O}(\text{CH}_2)_2\text{O}-$), 4.1–4.2 (m, 1 H, H-6); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 22.3, 23.6, 33.7, 38.6, 40.3, 66.1, 66.2, 72.6, 81.5, 209.1.

Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_4 \cdot 0.12\text{CHCl}_3$: C, 56.52; H, 7.55. Found: C, 56.85; H, 7.26.

Attempted synthesis of 1,5,6,7,8,9-hexahydroimidazo[4,5-*a*]cycloocta-4-one (32)

To a solution of **31** (330 mg, 1.65 mmol) in 4 mL of formamide was added ammonium formate (520 mg, 8.25 mmol), and the reaction mixture was heated to 120 °C for 8 h. The reaction mixture was cooled and made basic (pH 9) using ammonium hydroxide. The aqueous solution was extracted with CHCl_3 (3 $\times$ 25 mL), and the extract was washed with water (3 $\times$ 10 mL), dried (MgSO_4) and concentrated to afford

55.0 mg of brown crystals. The NMR data of this compound resembled to that of the α -ketol with the elimination of the ethylene ketal group.

Preparation of 5-Nitro-4-styryl-1*H*-imidazole (34)

A flame-dried three-neck flask was charged with 4-methyl-5-nitro-1*H*-imidazole (33) (5.0 g, 39 mmol) maintained under inert atmosphere of nitrogen. To this was added benzaldehyde (12 g, 0.11 mol) and piperidine (3.0 g, 35 mmol) to form a thick slurry. The reaction was heated to 95 °C on a oil bath for 22 h, during which time the product crystallized out as a yellow solid. To the solid was added 100 mL of *N,N*-dimethylformamide and 200 mL of 2-propanol. The slurry was filtered to afford 6.6 g (78%) of the desired compound 34 [R_f = 0.32, 1:9 (v/v) MeOH-CHCl₃]: mp 257 °C (dec) [lit. mp 260 °C]; ¹H NMR data (DMSO-*d*₆, 250 MHz): δ 3.3 (s, 1 H, NH), 7.3–7.8 (m, 7 H, aryl, -CH=CH-), 7.9 (s, 1 H, H-2); ¹³C NMR data (DMSO-*d*₆, 62.5 MHz): δ 127.5, 129.1, 129.2, 135.2, 136.1, 147.2.

Preparation of 1-Benzyl-5-nitro-4-styryl-1*H*-imidazole (35) and 3-Benzyl-5-nitro-4-styryl-3*H*-imidazole (36)

To a flame-dried three-neck flask containing 34 (25 g, 0.11 mol) in 500 mL of dry *N,N*-dimethylformamide was added anhydrous potassium carbonate (24 g, 0.17 mol), and the reaction mixture was stirred under an inert atmosphere of nitrogen for 5 min. To this mixture was added benzyl bromide (23 g, 0.13 mol) in one portion, and the reaction mixture was heated to 75 °C for 8 h. The completion of the reaction was indicated by TLC [R_f = 0.70 (35), R_f = 0.65 (36) 1:9 MeOH-CHCl₃]. The reaction was cooled in an ice-bath and the solid that formed was filtered, washed with CH₂Cl₂ and

the filtrate was evaporated to afford a brown syrup. The residue was dissolved in CHCl_3 , and the extract was washed with water (3×40 mL), dried (MgSO_4) and concentrated to afford the crude product. The crude product was purified by column chromatography using CH_2Cl_2 as the eluant to separate the two isomers, 22 g (65%) and 12 g (35%) of compound **35** and **36**. Both the isomers were recrystallized from EtOAc.

Compound **35**: mp 91°C [lit. mp $92\text{--}94^\circ\text{C}$]; ^1H NMR data ($\text{DMSO}-d_6$, 250 MHz): δ 5.6 (s, 2 H, H-1), 7.17–7.79 (m, 13 H, aryl, $-\text{CH}=\text{CH}-$, H-2); ^{13}C NMR data ($\text{DMSO}-d_6$, 62.5 MHz): δ 50.6, 117.8, 126.7, 127.3, 127.8, 128.8, 129.0, 129.1, 136.3, 142.7.

Compound **36**: mp 104°C [lit. mp 105°C]; ^1H NMR data ($\text{DMSO}-d_6$, 250 MHz): δ 5.34 (s, 2 H, H-3), 7.2–7.5 (m, 12 H, aryl, $-\text{CH}=\text{CH}-$), 7.95 (s, 1 H, H-2); ^{13}C NMR data ($\text{DMSO}-d_6$, 62.5 MHz): δ 48.3, 112.8, 126.9, 127.0, 127.1, 128.0, 128.9, 135.6, 136.1.

Preparation of 1-Benzyl-5-nitro-1*H*-imidazo-4-carbaldehyde (**37**)

To a flame-dried three-neck flask was added **35** (22 g, 70 mmol) in 200 mL of dry CH_2Cl_2 along with 1.5 equiv of dry MeOH (4.4 mL). The solution was maintained at -78°C under an inert atmosphere of nitrogen. The ozone generated in a Welsbach ozonizer (1.96 CFM, 6 psi, 110 V) was bubbled in for ca. 1.5 h until a distinct blue color indicated excess ozone. The flask was flushed with dry nitrogen until the blue color dissappeared. To this clear solution was added methyl sulfide (9.0 g, 0.14 mol), and the reaction was slowly warmed to -10°C over a period of 1 h. The reaction was further warmed to room temperature and stirred for 1 h. The solvent was then removed

under reduced pressure to afford a yellow syrup. The crude product was purified by column chromatography using 0.3:9.7 (v/v) MeOH-CHCl₃ as the eluant. The appropriate fractions were collected and concentrated to give a yellow solid which was recrystallized from Et₂O to afford 13 g (78%) of the desired product **37**: [*R_f* = 0.42, 1:9 MeOH-CHCl₃]; mp 100–102 °C; ¹H NMR data (DMSO-*d*₆, 250 MHz): δ 5.62 (s, 2 H, H-1), 7.25–7.35 (m, 5 H, aryl), 8.38 (s, 1 H, H-2), 10.1 (s, 1 H, -CHO); ¹³C NMR data (DMSO-*d*₆, 62.5 MHz): δ 50.5, 127.0, 128.1, 128.8, 135.3, 141.7, 184.0.

Preparation of 3-Benzyl-5-nitro-3*H*-imidazo-4-carbaldehyde (38**)**

To a solution of **36** (22.6 g, 70.1 mmol) in 400 mL of dry CH₂Cl₂ and 4.52 mL of dry MeOH at -78 °C for 2 h until a blue color indicated excess ozone. Removal of the excess ozone and workup was similar to the one used in the synthesis of the other isomer (previous paragraph). The solid obtained after column was recrystallized from Et₂O to afford 13.0 g (76%) of the desired product **38**: [*R_f* = 0.49, 1:9 MeOH-CHCl₃]; mp 86–87 °C; ¹H NMR data (DMSO-*d*₆, 250 MHz): δ 5.64 (s, 2 H, H-3), 7.3–7.37 (m, 5 H, aryl), 8.42 (s, 1 H, H-2), 10.27 (s, 1 H, CHO); ¹³C NMR data (DMSO-*d*₆, 62.5 MHz): δ 50.4, 127.2, 127.9, 128.6, 140.5, 181.5.

1-(1-Benzyl-5-nitro-1*H*-imidazol-4-yl)ethanol (39**)**

A flame-dried two-neck flask maintained under an argon atmosphere was charged with 30 mL of dry THF and titanium tetrachloride (TiCl₄) (4.52 g, 23.0 mmol) at -60 °C. To this was added methyllithium (MeLi, 1.4 M sol) (17 mL, 23 mmol) very slowly. The reaction was stirred for 15 min at -60 °C and the temperature was raised slowly to -30 °C. A solution of the aldehyde **37** (3.68 g, 12.0 mmol) in 20 mL of dry THF was

slowly introduced into the flask. The reaction mixture was stirred at $-30\text{ }^{\circ}\text{C}$ for 5 h, poured into cold water, and stirred for 10 min. The organic layer was separated and washed with saturated NaHCO_3 solution ($2 \times 20\text{ mL}$), dried (MgSO_4) and concentrated to a brown syrup. The crude product was purified by column chromatography using 0.5:9.5 (v/v) MeOH-CHCl_3 as eluant to afford 2.21 g (56%) of the desired product **39** as a yellow gum: [$R_f = 0.51$, 1:9 MeOH-CHCl_3]; ^1H NMR data (CDCl_3 , 250 MHz): δ 1.54 (d, 3 H, $J = 0.6\text{ Hz}$, Me), 5.30 (m, 1 H, $-\text{CHOH}$), 5.52 (s, 2 H, H-1), 7.19–7.39 (m, 5 H, aryl), 7.56 (s, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 22.0, 51.8, 64.2, 127.6, 128.8, 129.1, 133.9, 139.3.

Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.33; H, 5.32; N, 16.90.

1-(1-Benzyl-5-nitro-1*H*-imidazol-4-yl)ethanone (**40**)

A solution of oxalyl chloride (1.46 g, 11.0 mmol) in 40 mL of dry CH_2Cl_2 was cooled under inert an atmosphere of nitrogen to $-60\text{ }^{\circ}\text{C}$. To this solution was added dimethyl sulfoxide (1.74 g, 22.0 mmol), and the resulting mixture was stirred at $-60\text{ }^{\circ}\text{C}$ for 10 min. A solution of alcohol **39** (2.21 g, 8.92 mmol) in 10 mL of CH_2Cl_2 was added, and the resulting mixture stirred further for 20 min. To this mixture was added dry triethylamine (5.87 g, 50.0 mmol), and the reaction mixture was allowed to warm to room temperature over a period of 1.5 h. Upon completion of the reaction as indicated by TLC [$R_f = 0.65$, 1:9 (v/v) MeOH-CHCl_3], 30 mL of water was added to the reaction mixture and stirred further for 10 min. The aqueous layer was extracted with CH_2Cl_2 ($3 \times 30\text{ mL}$), and the organic extract was washed with water ($3 \times 20\text{ mL}$),

dried (MgSO_4) and concentrated to a brown syrup. The crude product was purified by column chromatography using 2:3 (v/v) EtOAc–hexane to afford 1.51 g (69%) of the desired product **40** as brown gum: ^1H NMR data (CDCl_3 , 250 MHz): δ 2.60 (s, 3 H, Me), 5.40 (s, 2 H, H-1), 7.26–7.39 (m, 5 H, aryl), 7.49 (s, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 28.2, 45.8, 127.8, 129.2, 129.4, 136.9, 189.2.

Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.74; H, 4.52; N, 17.11.

1-(1-Benzyl-5-nitro-1*H*-imidazol-4-yl)but-3-en-1-ol (41)

A flame-dried flask maintained under an inert atmosphere of nitrogen at $-78\text{ }^\circ\text{C}$ was charged with trimethoxyborane (4.04 g, 38.0 mmol) in 100 mL of dry ether. To this was added allylmagnesium bromide (1.0 M) (42.8 mL, 42.0 mmol) very slowly, and the mixture was stirred at this temperature for 3 h. At the end of 3 h, the dry ice–acetone bath was replaced by an ice bath, and 45 mL (90 mmol) of 2 N HCl was slowly added to the above mixture and stirred under nitrogen at $0\text{ }^\circ\text{C}$ for 1 h. The ether layer was separated, and the aqueous layer was extracted with Et_2O ($2 \times 30\text{ mL}$), dried (Na_2SO_4) and concentrated to 1/3 volume. This solution was transferred via cannula to a dry flask containing compound **37** (3.01 g, 12.1 mmol) in 20 mL of dry CH_2Cl_2 . The reaction was stirred under a nitrogen atmosphere for 24 h at room temperature. The solution was concentrated to a syrup, and the residue was extracted in CH_2Cl_2 ($3 \times 30\text{ mL}$), and the organic extract was washed with water ($3 \times 20\text{ mL}$), dried (Na_2SO_4) and concentrated to a pale brown syrup. The crude compound was purified by column chromatography using 3:7 EtOAc–hexane as the eluant to afford 2.50 g (70%) of the

desired compound **41** (recrystallized in Et₂O): [*R_f* = 0.53, 1:9 MeOH-CHCl₃]; mp 91–93 °C; for ¹H and ¹³C NMR data, see Tables 3 and 4, respectively.

Anal. Calcd for C₁₄H₁₅N₃O₃: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.61; H, 5.55; N, 15.31.

1-Benzyl-4-(1-benzyloxy-but-3-enyl)-5-nitro-1*H*-imidazole (42)

A flame-dried flask was charged with 60% sodium hydride (0.37 g, 9.4 mmol) in 50 mL of dry THF, and the mixture was stirred at room temperature under an inert atmosphere of nitrogen. To this mixture, compound **41** (2.0 g, 7.3 mmol) was added in one portion, followed by addition of benzyl bromide (1.3 g, 8.0 mmol) and a catalytic amount of tetrabutylammonium iodide (0.27 g, 0.71 mmol). The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in CH₂Cl₂. The organic phase was washed with water, dried (MgSO₄) and concentrated to a syrup. The crude product was purified by column chromatography using 1:5 (v/v) EtOAc-hexane to afford 1.1 g (42%) of the desired product **42** as a brown gum: [*R_f* = 0.85, 1:9 MeOH-CHCl₃], along with 0.61 g (30%) of unreacted starting material. For ¹H and ¹³C NMR data, see Tables 3 and 4, respectively.

Anal. Calcd for C₂₁H₂₁N₃O₃·0.16C₆H₁₂: C, 69.99; H, 6.13; N, 11.15. Found: C, 70.16; H, 5.91; N, 10.94.

1-Benzyl-4-[1-(*tert*-butyldimethylsilyloxy)but-3-enyl]-5-nitro-1*H*-imidazole (43)

To a solution of **41** (0.68 g, 2.5 mmol) in 30 mL of dry *N,N*-dimethylformamide was added imidazole (0.26 g, 3.7 mmol), and the solution was stirred under an inert

atmosphere of nitrogen for 5 min. To the above mixture, *tert*-butylchlorodimethylsilane (0.41 g, 2.7 mmol) was added in one portion, and the reaction mixture was stirred for 24 h at room temperature. After the reaction had gone to completion (as indicated by TLC), the solvent was removed under reduced pressure, and the residue was treated with 20 mL saturated NaHCO₃ solution to make the solution basic. The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL), and the extract was dried (MgSO₄) and evaporated to a syrup. The crude product was purified by column chromatography using 1:1 EtOAc–hexane to furnish 0.71 g (74%) of the desired compound **43** as a colorless gum: [*R_f* = 0.77, 1:9 (v/v) MeOH–CHCl₃]. For ¹H and ¹³C NMR data, see Tables 3 and 4, respectively.

Anal. Calcd for C₂₀H₂₉N₃O₃Si: C, 62.00; H, 7.54; N, 10.85. Found: C, 62.02; H, 7.50; N, 10.73.

1-Benzyl-4-[1-(*tert*-butyldiphenylsilyloxy)but-3-enyl]-5-nitro-1*H*-imidazole (44)

To a solution of **41** (2.49 g, 9.12 mmol) in 40 mL of dry *N,N*-dimethylformamide was added imidazole (740 mg, 10.9 mmol), and the reaction was stirred under a nitrogen atmosphere for 5 min. To the above solution was added *tert*-butylchlorodiphenylsilane (2.75 g, 10.1 mmol), and the reaction was stirred at room temperature for 18 h. The reaction was worked up in a similar manner to that for compound **43**. Purification of the crude product by column chromatography using 1:1 EtOAc–hexane furnished the desired compound **44** as a colorless gum, 4.18 g (90%): [*R_f* = 0.76, 1:9 (v/v) MeOH–CHCl₃]. For ¹H and ¹³C NMR data, see Tables 3 and 4, respectively.

Anal. Calcd for C₃₀H₃₃N₃O₃Si: C, 70.44; H, 6.50; N, 8.21. Found: C, 70.24;

H, 6.61; N, 8.06.

3-(1-Benzyl-5-nitro-1*H*-imidazo-4-yl)prop-2-enal (45)

To a solution of **44** (5.48 g, 10.7 mmol) in 50 mL of dry CH_2Cl_2 was added 1.5 equiv of dry MeOH (0.65 mL), and the reaction mixture was maintained under a nitrogen atmosphere at $-78\text{ }^\circ\text{C}$. Ozone (generated from Welsbach ozonizer) [2.9 CFM, 5 psi, 110 V] was bubbled into the solution for 0.5 h until a distinct blue color indicated excess ozone. The reaction was flushed with dry nitrogen until the blue color disappeared. To this solution was added methyl sulfide (1.33 g, 21.4 mmol), and the solution was allowed to warm to room temperature over a period of 1 h. The solution was concentrated to a pale yellow syrup which was then purified by column chromatography using 1:1 EtOAc-hexane to afford the undesired compound **45**, 502 mg (18%), which was recrystallized from Et_2O : [R_f = 0.56, 1:9 (v/v) MeOH- CHCl_3]; mp $123\text{--}125\text{ }^\circ\text{C}$; ^1H NMR data (CDCl_3 , 250 MHz): δ 5.55 (s, 2 H, H-1), 7.14 (ψ t, 1 H, H-2'), 7.2–7.4 (m, 5 H, aryl), 7.61 (s, 1 H, H-2), 8.00 (d, 1 H, J = 15.7 Hz, H-1'), 9.79 (d, 1 H, J = 7.9 Hz, H-3'); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 52.2 (C-1), 127.6, 129.1 and 129.3 (Ar), 132.7 (C-4), 133.8 (C-5), 134.1 (C-2'), 139.5 (C-2), 140.5 (C-1'), 193.2 (C-3').

Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 59.92; H, 4.31; N, 15.59.

3-(1-Benzyl-5-nitro-1*H*-imidazo-4-yl)-3-(*tert*-butyldimethylsilyloxy)propionaldehyde (46)

To a solution of **43** (0.23 g, 6.1 mmol) in 15 mL of 1:1 dioxane-water was added

sodium periodate (0.18 g, 8.5 mmol) along with a catalytic amount of osmium tetroxide solution (0.3 mL) [1g/125 mL of dioxane], and the reaction mixture was stirred for 18 h at room temperature. A white precipitate was formed that was filtered off and the precipitate was repeatedly washed with CHCl_3 . The organic phase was later dried (Na_2SO_4) and concentrated to a syrup. The crude product was purified by column chromatography using 3:2 EtOAc–hexane as the eluant to furnish 0.14 g (62%) of the desired product **46**: [R_f = 0.61, 1:9 (v/v) MeOH– CHCl_3]. For ^1H and ^{13}C NMR data, see Tables 5 and 6, respectively.

Anal. Calcd for $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_4\text{Si}$: C, 58.60; H, 6.99; N, 10.79. Found: C, 58.15; H, 6.92; N, 10.61.

3-(1-Benzyl-5-nitro-1*H*-imidazo-4-yl)-3-(*tert*-butyldiphenylsilyloxy)propionaldehyde (47)

To a solution of **44** (7.2 g, 14 mmol) in 100 mL of 1:1 dioxane–water was added sodium periodate (6.0 g, 28 mmol), along with osmium tetroxide solution (30 mL) [1 g/125 mL of dioxane], and the reaction was stirred at room temperature for 18 h. The reaction was worked up on same lines as for compound **46**. Purification of the crude product by column chromatography using 3:2 EtOAc–hexane afforded 3.6 g (49%) of the desired compound **47**: [R_f = 0.5, 1:9 (v/v) MeOH– CHCl_3]. For ^1H and ^{13}C NMR data, see Tables 5 and 6, respectively.

Anal. Calcd for $\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_4\text{Si}$: C, 67.83; H, 6.08; N, 8.18. Found: C, 67.54; H, 6.05; N, 8.00.

1-Benzyl-4-[1-(*tert*-butyldiphenylsilyloxy)-2-(1,3-dioxolan-2-yl)ethyl]-5-nitro-1*H*-

imidazole (49)

To a solution of **47** (1.29 g, 2.51 mmol) in 20 mL of 1:1 ethylene glycol–benzene was added catalytic amount of *p*-toluene sulfonic acid (50.1 mg, 0.251 mmol), and the reaction mixture was stirred at 50 °C for 8 h under an inert atmosphere of N₂. After the reaction had gone to completion (as indicated by TLC), 20 mL of saturated NaHCO₃ solution was added to the reaction mixture (pH 8). The aqueous layer was extracted with CHCl₃ (3 × 25 mL), and the organic extract was dried (MgSO₄) and concentrated to a syrup. The crude product was purified by column chromatography using 4:1 (v/v) EtOAc–hexane to afford 1.34 g (96%) of the desired product **49** as a colorless gum: [*R*_f = 0.69, 1:9 MeOH–CHCl₃]; ¹H NMR data (CDCl₃, 250 MHz): δ 1.05 (s, 9 H, *tert*-Bu), 2.15–2.50 (m, 2 H, H-2', H-2''), 3.72–3.89 (m, 4 H, -O(CH₂)₂O-), 5.04 (dd, 1 H, *J* = 3.7 Hz and *J* = 5.3 Hz, H-3'), 5.23 (dd, 2 H, *J* = 4.9 Hz and *J* = 13.4 Hz, H-1), 5.72 (t, 1 H, *J* = 6.5 Hz, H-1'), 7.02–7.62 (m, 16 H, aryl, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 19.3, 22.5, 26.9, 51.3, 64.6, 64.9, 101.7, 127.0, 127.3, 127.4, 128.5, 129.0, 129.1, 129.4, 133.3, 133.7, 134.2, 135.5, 139.2, 148.2.

Anal. Calcd for C₃₁H₃₅N₃O₅Si: C, 66.78; H, 6.33; N, 7.54. Found: C, 66.84; H, 6.40; N, 7.43.

3-Benzyl-3*H*-imidazo[4,5-*b*]pyridine (51)

A suspension of **49** (1.29 g, 2.32 mmol) and 10% palladium-on-charcoal (129 mg) in 30 mL of absolute ethanol, was stirred under 55 psi hydrogen for 6 h, at which time TLC revealed completion of the reaction. The reaction mixture was filtered through Celite and washed with copious amount of ethanol. The solvent was evaporated to give

0.60 g of compound **50** as a syrup. Compound **50** was then taken directly to the next step without any further purification.

Compound **50** (600 mg, 1.14 mmol) was dissolved in 20 mL of 1:1 acetone–water. To this was added *p*-toluene sulfonic acid (550 mg, 2.85 mmol), and the reaction mixture was refluxed for 16 h. After the reaction had gone to completion (as indicated by TLC), 20 mL of saturated NaHCO₃ solution was added to the reaction mixture (pH 8). The aqueous layer was extracted with CHCl₃ (3 × 20 mL), and the organic extract was washed with brine (3 × 15 mL), dried (MgSO₄) and concentrated to a brown syrup. The crude product was purified by column chromatography using 1:9 (v/v) MeOH–CHCl₃ to afford 59.1 mg (24%) of compound **51** as a syrup.

Data for compound **50**: [*R*_f = 0.52, 1:9 MeOH–CHCl₃]; ¹H NMR data (CDCl₃, 250 MHz): δ 1.00 (s, 9 H, *tert*-Bu), 2.09–2.50 (m, 2 H, H-2', H-2''), 3.65–3.89 (m, 4 H, O(CH₂)₂O), 4.73 (s, 2 H, H-1), 4.94 (t, 1 H, *J* = 5.0 Hz, H-1'), 7.22–7.74 (m, 6 H, aryl, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 19.2, 26.5, 26.7, 46.7, 64.4, 102.4, 126.3, 126.8, 127.3, 127.5, 128.3, 128.7, 129.4, 130.8, 131.4, 133.6, 134.8, 135.7, 135.8, 136.0, 136.2.

Data for compound **51**: [*R*_f = 0.56, 1:9 MeOH–CHCl₃]; ¹H NMR data (CDCl₃, 250 MHz): δ 5.50 (s, 2 H, H-3), 7.26–7.35 (m, 6 H, aryl, H-6), 8.04 (s, 1 H, H-2), 8.10 (dd, 1 H, *J* = 1.1 Hz and *J* = 8.0 Hz, H-7), 8.47 (dd, 1 H, *J* = 1.2 Hz and *J* = 4.8 Hz, H-5); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 47.2, 118.7, 127.8, 128.4, 129.0, 130.1, 135.5, 143.2.

Anal. Calcd for C₁₃H₁₁N₃·0.3C₃H₆O: C, 73.65; H, 5.69; N, 18.54. Found: C,

73.35; H, 5.49; N, 18.81.

1-(1-Benzyl-5-nitro-1*H*-imidazo-4-yl)-2-(1,3-dioxolan-2-yl)ethanol (52)

To a solution of **49** (980 mg, 1.73 mmol) in 20 mL of dry THF was added 4.30 mL (4.32 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF. The reaction mixture was stirred at room temperature for 18 h, at which time TLC revealed complete reaction. The solution was partitioned between 30 mL of water and 40 mL of Et₂O. The aqueous layer was extracted with Et₂O (3 × 30 mL), the combined organic extract was washed with brine (3 × 10 mL), dried (Na₂SO₄) and concentrated to a syrup. The crude product was purified by column chromatography using 1:1 (v/v) EtOAc–hexane as eluant to afford 520 mg (96%) of the desired product **52** as a solid: [*R*_f = 0.38, 1:9 MeOH–CHCl₃]; mp 80–82 °C; ¹H NMR data (CDCl₃, 250 MHz): δ 2.20–2.28 (m, 2 H, H-2'), 3.36 (bs, 1 H, OH, exchanges with D₂O), 3.85–3.98 (m, 4 H, -O(CH₂)₂O-), 5.13 (ψt, 1 H, H-1'), 5.47 (t, 1 H, *J* = 4.3 Hz, H-3'), 5.50 (s, 2 H, H-1), 7.16–7.36 (m, 5 H, aryl), 7.57 (s, 1 H, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 39.4, 51.8, 64.7, 64.8, 102.4, 127.4, 128.7, 129.1, 134.0, 139.4, 149.2.

Anal. Calcd for C₁₅H₁₇N₃O₅: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.17; H, 5.42; N, 12.89.

1-(1-Benzyl-5-nitro-1*H*-imidazo-4-yl)-2-(1,3-dioxolan-2-yl)ethanone (53)

A solution of oxalyl chloride (310 mg, 2.41 mmol) in 20 mL of dry CH₂Cl₂ was cooled under an inert atmosphere of nitrogen to -68 °C. To this solution was added dimethyl sulfoxide (360 mg, 4.01 mmol), and the resulting mixture was stirred at -60 °C for 10 min. A solution of alcohol **52** (520 mg, 1.63 mmol) in 10 mL of CH₂Cl₂ was

added, and the resulting mixture stirred further for 20 min. To this mixture was added dry triethylamine (1.06 g, 10.5 mmol), and the reaction mixture was allowed to warm to room temperature over a period of 1.5 h. Upon completion of the reaction as indicated by TLC, 30 mL of water was added to the reaction mixture and stirred further for 10 min. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL), and the organic extract was washed with water (3×20 mL), dried (MgSO_4) and concentrated to a pale-brown syrup. The crude product was purified by column chromatography using 2:3 (v/v) EtOAc-hexane to afford 402 mg (79%) of the desired product as a brown solid: [R_f = 0.58, 1:9 (v/v) MeOH- CHCl_3]; mp 134–136 °C; ^1H NMR data (CDCl_3 , 250 MHz): δ 3.39 (d, 2 H, J = 4.8 Hz, H-2'), 3.71–3.97 (m, 4 H, $-\text{O}(\text{CH}_2)_2\text{O}-$), 5.39 (s, 2 H, H-1), 5.44 (t, 1 H, J = 4.6 Hz, H-3'), 7.20–7.40 (m, 5 H, aryl), 7.46 (s, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 45.1, 51.3, 64.9, 100.9, 127.8, 129.3, 129.4, 136.8, 198.3; HRFABMS Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_5$ ($\text{M} + \text{H}^+$): 318.1089. Found: 318.1092.

3-Benzyl-3*H*-imidazo[4,5-*b*]pyridin-7-ol (55)

A suspension of **53** (380 mg, 1.21 mmol) and 10% palladium-on-charcoal (40 mg) in 15 mL of absolute ethanol was stirred under 55 psi hydrogen at room temperature for 2 h, at which time TLC revealed complete reaction. The suspension was filtered with Celite, and the filter cake was washed with copious amount of ethanol. The solvent was evaporated to give 335 mg (96%) of compound **54** as a syrupy residue. The residue was taken directly to the next step without any further purification.

To a solution of **54** (130 mg, 0.460 mmol) in 10 mL of 1:1 acetone–water was added *p*-toluene sulfonic acid (220 mg, 1.11 mmol), and the reaction mixture was

refluxed for 8 h, at which time TLC revealed complete reaction. The reaction mixture quenched with water and the aqueous layer was extracted with EtOAc (3×10 mL). The extract was dried (Na_2SO_4) and concentrated to afford 66.1 mg (63%) of the desired product **55** as a pale-brown solid.

Data for compound **54**: [$R_f = 0.38$, 1:9 (v/v) MeOH- CHCl_3]; ^1H NMR data (CDCl_3 , 250 MHz): δ 3.23 (d, 2 H, $J = 5.3$ Hz, H-2'), 3.83–3.98 (m, 4 H, $-\text{O}(\text{CH}_2)_2\text{O}-$), 4.93 (s, 2 H, H-1), 5.46 (t, 1 H, $J = 5.2$ Hz, H-3'), 5.58 (bs, 2 H, NH_2), 7.12–7.33 (m, 6 H, aryl, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 47.0, 64.7, 100.3, 125.8, 127.7, 128.4, 129.1, 145.6, 191.2.

Data for compound **55**: [$R_f = 0.44$, 1:9 (v/v) MeOH- CHCl_3]; mp 170–172 °C; ^1H NMR data (CDCl_3 , 250 MHz): δ 5.44 (s, 2 H, H-3), 6.79 (d, 1 H, $J = 5.5$ Hz, H-6), 7.26–7.31 (m, 5 H, aryl), 7.97 (s, 1 H, H-2), 8.27 (d, 1 H, $J = 4.5$ Hz, H-5); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 47.4, 106.9, 123.9, 127.9, 128.4, 129.0, 141.0, 146.9, 156.6.

Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_1 \cdot 0.5\text{C}_3\text{H}_6\text{O}$: C, 68.42; H, 4.60; N, 16.34. Found: C, 68.13; H, 5.43; N, 16.22.

3H-imidazo[4,5-b]pyridin-7-ol (5)

A suspension of **55** (30 mg, 0.13 mmol) and 10% palladium-on-charcoal (20 mg) in 4 mL of absolute ethanol and 1 mL of cyclohexene was refluxed for 24 h, at which time TLC revealed complete reaction. The suspension was filtered through Celite, and the filter cake was washed with copious amount of ethanol. The solvent was evaporated to a brown residue. The residue was purified by column chromatography using 1:9 (v/v)

MeOH-CHCl₃ as eluant to furnish 10 mg (56%) of the desired product **5** as a white solid: [*R_f* = 0.18, 1.5:8.5 (v/v) MeOH-CHCl₃]; mp 184–186 °C; ¹H NMR data (CD₃OD, 250 MHz): δ 6.40 (d, 1 H, *J* = 7.2 Hz, H-6), 7.80 (d, 1 H, *J* = 7.2 Hz, H-5), 8.14 (s, 1 H, H-2); ¹³C NMR data (CD₃OD, 62.5 MHz): δ 111.4, 136.4, 142.2; HRFABMS Calcd for C₆H₅N₃O₁ (M - SiO₂ + H⁺): 136.0841. Found: 136.0894.

1-(3-Benzyl-5-nitro-3*H*-imidazol-4-yl)but-3-en-1-ol (56)

A flame-dried flask was charged with trimethoxyborane (4.5 g, 43 mmol) in 50 mL of dry ether, and the solution was maintained under nitrogen atmosphere at -78 °C. To this was added allylmagnesium bromide (1 M, 45 mL, 45 mmol), and the reaction was stirred at -78 °C for 3 h. The dry ice-acetone bath was replaced by an ice bath, and 2 N HCl (35 mL, 70 mmol) was added slowly and the reaction mixture was stirred at 0 °C for 1 h. The organic layer was separated, and the aqueous layer was extracted with Et₂O (2 × 30 mL). The extract was dried (Na₂SO₄) and concentrated to 1/3 volume.

The allylboronic acid solution was transferred via cannula to a dry flask charged with compound **38** (5.0 g, 22 mmol) in 30 mL of dry CH₂Cl₂. The reaction was stirred under a nitrogen atmosphere at room temperature for 18 h. At the end of the reaction the solvent was evaporated to a brown syrup. The residue was made basic (pH 8) by addition of 30 mL of saturated NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL), and the extract was dried (Na₂SO₄), concentrated and purified by column chromatography using 3:2 (v/v) EtOAc-hexane to furnish 5.0 g (85%) of the desired product **56**, which was recrystallized from Et₂O: [*R_f* = 0.51, 1:9 (v/v) MeOH-CHCl₃]; mp 91–93 °C. For ¹H and ¹³C NMR data, see Tables 7 and 8, respectively.

Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.63; H, 5.60; N, 15.37.

1-Benzyl-5-[1-(*tert*-butyldimethylsilyloxy)but-3-enyl]-4-nitro-1*H*-imidazole (57)

To a solution of **56** (1.1 g, 3.9 mmol) in 40 mL of dry *N,N*-dimethylformamide was added imidazole (0.62 g, 9.1 mmol), followed by *tert*-butylchlorodimethylsilane (0.71 g, 4.7 mmol), and the reaction mixture was stirred at room temperature for 18 h under a nitrogen atmosphere. After the reaction was complete, the solvent was removed under reduced pressure, and the residue was made basic by addition of 20 mL of saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL), and the extract was dried (Na_2SO_4) and concentrated to a colorless syrup. The crude product was purified by column chromatography using 3:2 (v/v) EtOAc-hexane to afford 1.3 g (86%) of the desired product **57**, which was recrystallized from Et_2O : [R_f = 0.78, 1:9 (v/v) MeOH- $CHCl_3$]; mp 66–67 °C. For ^1H and ^{13}C NMR data, see Tables 7 and 8, respectively.

Anal. Calcd for $C_{20}H_{29}N_3O_3Si$: C, 62.00; H, 7.54; N, 10.85. Found: C, 61.96; H, 7.58; N, 10.79.

3-(3-Benzyl-5-nitro-3*H*-imidazo-4-yl)-3-(*tert*-butyldimethylsilyloxy)propionaldehyde (58)

To a solution of **57** (4.01 g, 10.4 mmol) in 200 mL of dry CH_2Cl_2 was added 1.1 equiv of dry MeOH (0.47 mL), and the reaction mixture was stirred under a nitrogen atmosphere at -78 °C. Ozone (generated from a Welsbach ozonizer) was bubbled into the reaction flask [3.0 CFM, 5.8 psi, 110 V] for 0.5 h until a distinct blue color

indicated excess ozone. The solution was purged with dry nitrogen until the blue color disappeared. To the above mixture, methyl sulfide (840 mg, 13.5 mmol) was added, and the reaction mixture was slowly allowed to attain room temperature over a period of 1 h. The solvent was evaporated, and the crude product was purified by column chromatography using 3:2 (v/v) EtOAc–hexane to afford 3.24 g (81%) of the desired product **58**, as a colorless gum: [R_f = 0.54, 1:9 (v/v) MeOH–CHCl₃]. For ¹H and ¹³C NMR data, see Tables 7 and 8, respectively.

Anal. Calcd for C₁₉H₂₇N₃O₄: C, 58.60; H, 6.99; N, 10.79. Found: C, 58.09; H, 6.94; N, 10.69.

5-(3-Benzyl-5-nitro-3*H*-imidazo-4-yl)-5-(*tert*-butyldimethylsilyloxy)pent-2-enoic acid, methyl ester (59**)**

To a solution of **58** (3.20 g, 8.31 mmol) in 60 mL of dry CH₂Cl₂ was added methyl(triphenylphosphoranylidene)acetate (5.56 g, 16.6 mmol), and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 16 h. The solvent was evaporated, and the crude product was purified by column chromatography using 2:3 EtOAc–hexane to afford 4.09 g (97%) of the desired compound **59**, as a gum: [R_f = 0.68, 1:9 (v/v) MeOH–CHCl₃]. For ¹H and ¹³C NMR data, see Tables 9 and 10, respectively.

Anal. Calcd for C₂₂H₃₁N₃O₅Si: C, 59.32; H, 7.01; N, 9.43. Found: C, 59.15; H, 7.12; N, 9.32.

5-(3-Benzyl-5-nitro-3*H*-imidazo-4-yl)-5-(*tert*-butyldimethylsilyloxy)pent-2-enol (60**)**

To a solution of **59** (4.1 g, 9.1 mmol) in 30 mL of dry THF was added excess

of diisobutylaluminum hydride (1.5 M, 61 mL, 91 mmol), and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ under a nitrogen atmosphere for 2 h. To the above solution, saturated Rochelle's salt solution (30 mL) was added, and the mixture was allowed to warm to room temperature. Water (10 mL) was added and the aqueous layer was separated and extracted with CH_2Cl_2 ($3 \times 30\text{ mL}$). The organic extract was dried (MgSO_4) and evaporated to afford the crude product. Purification of the crude product by column chromatography using 1:1 (v/v) EtOAc-hexane furnished 2.9 g (78%) of the desired compound **60**, as a pale yellow solid which was recrystallized from Et_2O : [$R_f = 0.55$, 1:9 (v/v) MeOH- CHCl_3]; mp $76\text{--}78\text{ }^{\circ}\text{C}$. For ^1H and ^{13}C NMR data, see Tables 9 and 10, respectively.

Anal. Calcd for $\text{C}_{21}\text{H}_{31}\text{N}_3\text{O}_4\text{Si}$: C, 60.42; H, 7.48; N, 10.07. Found: C, 60.18; H, 7.65; N, 9.79.

5-(3-Benzyl-5-nitro-3H-imidazo-4-yl)-5-(*tert*-butyldimethylsilyloxy)pent-2-enal (61)

To a solution of oxalyl chloride (1.2 g, 9.0 mmol) in 30 mL of dry CH_2Cl_2 was added dry dimethyl sulfoxide (1.4 g, 16 mmol) at $-78\text{ }^{\circ}\text{C}$, and the reaction mixture was stirred for 10 min under a nitrogen atmosphere. To the above mixture, **60** (2.6 g, 6.3 mmol) dissolved in 10 mL of dry CH_2Cl_2 was added slowly, and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 0.5 h. Dry triethylamine (4.1 g, 41 mmol) was then introduced into the reaction mixture, and the solution was allowed to warm to room temperature over a period of 1 h. The reaction was quenched with 20 mL of water, and the aqueous layer was separated. The aqueous layer was extracted with CH_2Cl_2 ($3 \times 25\text{ mL}$), and the organic extract was dried (MgSO_4) and evaporated to afford the crude product. The

crude product was purified by column chromatography using 1:9 MeOH-CHCl₃ to afford 2.4 g (95%) of the desired compound **61**, as a pale yellow gum: [*R_f* = 0.67, 1:9 (v/v) MeOH-CHCl₃]. For ¹H and ¹³C NMR data, see Tables 9 and 10, respectively.

Anal. Calcd for C₂₁H₂₉N₃O₄Si·0.2CHCl₃: C, 57.96; H, 6.70; N, 9.56. Found: C, 57.77; H, 6.76; N, 9.34.

VI. CONCLUSION

This research has accomplished the synthesis of analogs of 2'-deoxycoformycin, namely 1,4,5,6,7,8-hexahydroimidazo[4,5-*a*]cycloheptane (1), 4,5,6,7,8,9-hexahydro-1*H*-imidazo[4,5-*a*]cyclooctanone (2) and 4,5,8,9-tetrahydro-1*H*-imidazo[4,5-*a*]cycloocta-6-ene (3). These compounds were designed to probe the effect of ring size on enzyme inhibition. Attempts to couple the 2'-deoxyribose unit to the N-1 of the imidazole failed completely. The imidazole ring system being a π -electron rich system led to the formation of unstable nucleosides. The sugar moiety, upon being affixed to the N-1 position of the imidazole, was found to be cleaved off almost immediately upon isolation of the compound. Attempts to use enzyme-catalyzed glycosyl transferase reaction also proved to be futile.

Attempts to synthesize 4,5,6,7,8,9-hexahydro-1*H*-imidazo[4,5-*a*]cycloocta-4-ol (4), proved to be unsuccessful. This was due to the fragile nature of the α -ketol that was subjected to high temperature conditions. The lessons learned during the synthesis of this imidazo compound might be of use to chemists hoping to synthesize these analogs of 2'-dCF.

This research has also accomplished the synthesis of the heterocyclic moiety of nebularine analog, namely 3*H*-imidazo[4,5-*b*]pyridine-7-ol (5). Extension of the carbon chain on aldehyde (37) and cyclization of the intermediate using different procedures

generated the desired compound (5).

Attempts were made to synthesize the eight-membered imidazole compound, namely 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*b*]cyclooctene-9-ol (6) using a similar approach. Extension of the carbon chain at the aldehyde (38), followed by ozonolysis and Wittig reaction, furnished the ester. However, attempts to carry out the ring cyclization by various approaches proved futile.

Although, there have been setbacks in the progress towards the synthesis of 2'-dCF analogs, the chemistry that has been explored in the process may shed some light on the nature of these heterocyclic systems.

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**PART II. DESIGN AND SYNTHESIS OF POTENTIAL THERAPEUTIC
AGENTS**

**A. DESIGN AND SYNTHESIS OF 6-ALKOXPURINE-2', 3'-
DIDEOXYNUCLEOSIDE**

I. INTRODUCTION

About a decade ago, many believed that infectious diseases were no longer a threat in the developed world. Heart disease, cancer and degenerative diseases were thought to be the only challenges remaining to be overcome. But the early 1980's saw the advent of a new incurable disease known as AIDS (acquired immunodeficiency syndrome),¹ caused by a class of infectious agents namely, retroviruses. This has triggered, in the scientific community, a search for a cure for this deadly disease. So far, the most successful antiviral agents against HIV infection have been inhibitors of viral reverse transcriptase.

Among these, a class of nucleoside analogues known as dideoxynucleosides have gained special importance.¹⁴ It appears that the 2',3'-dideoxynucleosides are taken up by the T lymphocytes and thereby undergo *in vivo* phosphorylation to generate 2',3'-dideoxynucleoside 5'-triphosphates. These analogues are then incorporated into the DNA strand, and the absence of the 3'-OH group in the sugar moiety leads to premature chain termination. Hence, retroviral reverse transcriptases are sensitive to dideoxynucleosides, which results in the therapeutic usefulness of these compounds. Up to this time, there have been very few drugs that have been synthesized and found to be clinically useful against AIDS (Figure 1). The dideoxynucleosides such as ddC (2',3'-dideoxycytidine, 1), ddI (2',3'-dideoxyinosine, 2), and AZT (3'-azido-3'-deoxythymidine, 3) have been

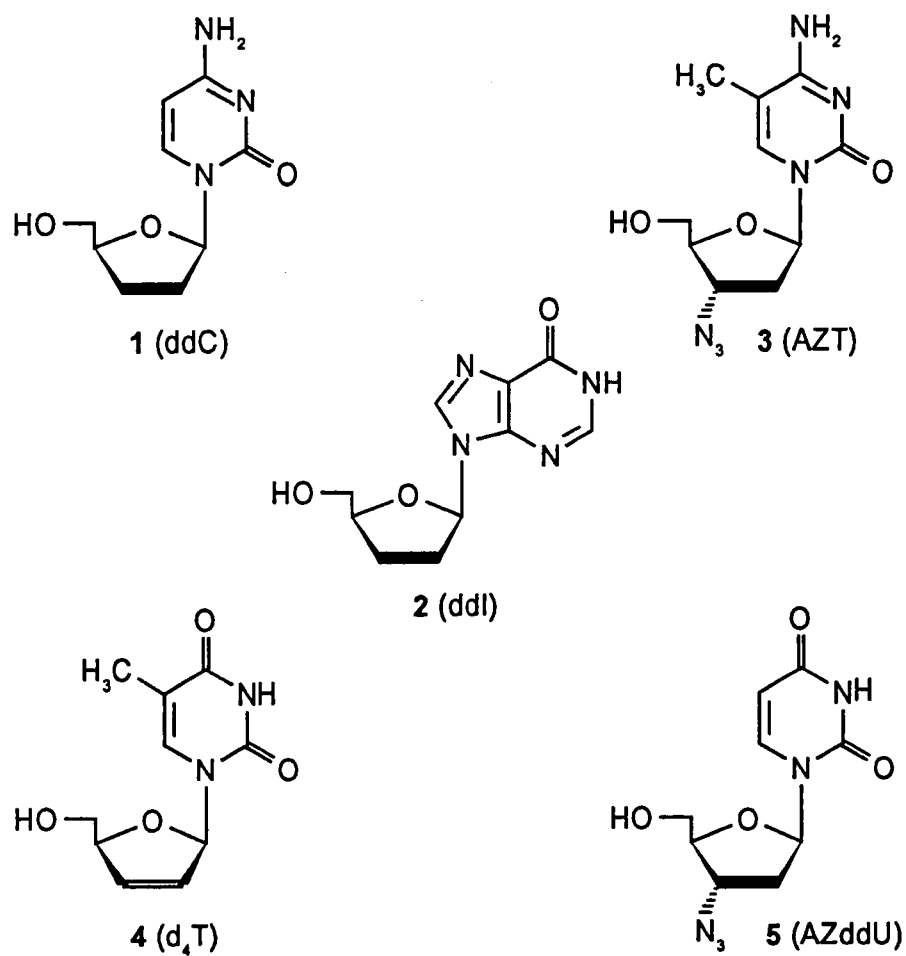


Figure 1. Potential drugs for AIDS.

found to be the most effective therapeutic agents for the treatment of AIDS²; however, these drugs are only palliative in their action and do not represent a cure for the disease.

Several other drugs of this dideoxynucleoside family have passed the preliminary clinical stage of evaluations. A few examples of these are d4T (2',3'-didehydro-3'-deoxythymidine, 4) and AZddU (3'-azido-2',3'-dideoxyuridine, 5).

During the search for a cure for AIDS, a number of nucleosides were tested for activity. Studies conducted earlier showed that certain compounds, especially the 2- and 6- substituted purine ribonucleosides, were readily hydrolyzed by adenosine deaminase (ADA, EC 3.5.4.4).³ So a plan was drawn to find out whether these corresponding dideoxynucleosides, which were being tested for AIDS activity, could also be substrates for ADA.

Adenosine deaminase (ADA) is a key enzyme in the purine metabolism and it helps in catalyzing the irreversible hydrolysis of adenosine or deoxyadenosine to its respective inosine product and ammonia.⁴ ADA is present in all mammalian cells and helps in maintaining essential functions of the immune system (Figure 2).

Statistical studies by Craig,⁵ using structure-activity correlations as a tool for a better understanding of the biological mechanism of action, and studies carried out by Mitsuya and co-workers⁷ on 2',3'-dideoxypurine nucleosides for increasing the lipophilic character of the drug based on substitution patterns at the C-6 position of the purine ring, prompted our interest in the synthesis of 6-alkoxypurine-2',3'-dideoxynucleosides.

Our main goal was to carry out a comparative study on the rate of deamination

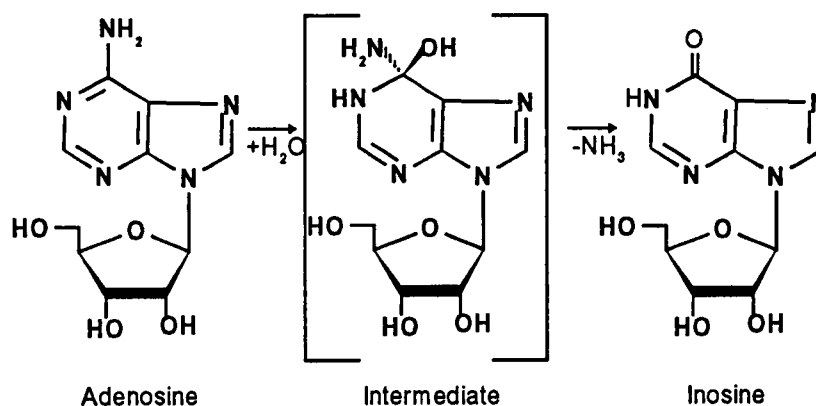


Figure 2. Proposed mechanism for ADA catalysis.

of dideoxyadenosine (ddA), 6-chloro- and 6-methoxypurine dideoxynucleosides with respect to adenosine. The 6-alkoxypurine 2',3'-dideoxynucleoside, which can undergo dealkoxylation at the C-6 position of the purine ring, could also serve as a prodrug for ddI (dideoxyinosine). These studies would give us the comparative K_m and relative V_{max} values for adenosine deaminase activity (ADA). The ratio of V_{max} to the K_m value will give an approximate idea on the relative efficiencies of deamination.

During the process of our synthesis of the 6-methoxy dideoxynucleoside, the Burroughs-Wellcome group reported the enzymatic synthesis of a series of 6-alkoxy dideoxynucleosides.⁶ These compounds were tested for anti-HIV activity in MT4 cells, along with cytotoxicity and adenosine deaminase activity.

II. STATEMENT OF THE PROBLEM

Our main interest in the synthesis of the compound, 9-(2,3-dideoxy- β -D-*erythro*-pentofuranosyl)-6-methoxy-9*H*-purine, **12**, was to conduct a comparative study on the rate of deamination of dideoxyadenosine (ddA), 6-chloro-, and 6-methoxypurine dideoxynucleosides with respect to adenosine. These studies would give us a comparative K_m and relative V_{max} values for adenosine deaminase activity (ADA). Prior to the studies carried out by the Burroughs-Wellcome group,⁶ we also wanted to investigate the anti-HIV activity on MT4 cells.

Based on the earlier published data⁷ describing the anti-HIV activity of the lipophilic halogenated 2',3'-dideoxypurine nucleosides, it was presumed that the lipophilic nature of the nucleoside would be increased by introduction of the phenolic oxygen at the C-6 position of the purine ring, although, improvement in the lipophilic nature of the drug may or may not improve the therapeutic index. These issues can only be resolved by carrying out *in vivo* studies. Hence we devised a methodology to carry out the synthesis of the title compound in multigram quantities.

III. SYNTHETIC STRATEGY

In our attempt to synthesize 9-(2,3-dideoxy- β -D-*erythro*-pentofuranosyl)-6-methoxy-9H-purine, **12**, use was made of the existing methodology that has been used in the synthesis of nucleosides.

During the process of synthesis of the title compound, the Burroughs-Wellcome group published⁶ an article describing the synthesis of several 6-alkoxypurine 2',3'-dideoxynucleosides using an enzymatic method. Pentose-1-phosphate is generated *in situ* from 2',3'-dideoxythymidine and inorganic phosphate using thymidine phosphorylase (TPase). The resulting 2',3'-dideoxy sugar 1-phosphate is coupled *in situ* with the appropriate purine base using purine nucleoside phosphorylase (PNPase). The net result was the transfer of the 2',3'-dideoxy sugar moiety from thymidine dideoxy nucleoside phosphorylase onto a purine with net retention of the β -configuration in the nucleoside. The enzymatic approach is a one-step process that affords the title compound in satisfactory yields. The main drawback of the process was the use of excessive amounts of a specially cloned enzyme, which was very expensive and not universally available (Figure 3).

The first step in the chemical approach would be a glycosylation procedure which involved introduction of a sugar moiety onto a purine ring. There have been several well-established methods in nucleoside chemistry to carry out this glycosylation. Our goal

was to afford the desired anomer in maximum yields without encountering any problems in the separation of the anomers. Among the existing methods, Robins methodology⁸ using a sodium salt glycosylation procedure would be useful enough to generate only two anomers that could later be separated easily by column chromatography. Although several other methods were tried, the Robins method gave excellent yields of the 9β anomer using the sodium salt of the purine and 2-deoxy-3,5-(di-*O-p*-toluoyl)- α -D-erythro-pentofuranosyl chloride 2. The rest of the steps would involve simple protection of the hydroxy group of the sugar moiety, followed by dehydroxylation of the C-3' hydroxy group using the Barton-McCombie procedure.⁹ Finally, deprotection of the primary hydroxy group would afford us the final desired 2',3'-dideoxy nucleoside.

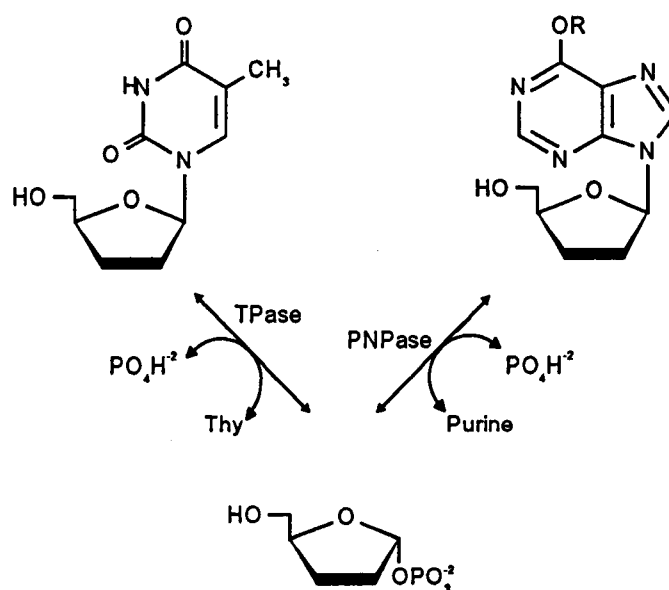


Figure 3. Enzymatic approach by the Burroughs-Wellcome group.⁶

IV. RESULTS AND DISCUSSION

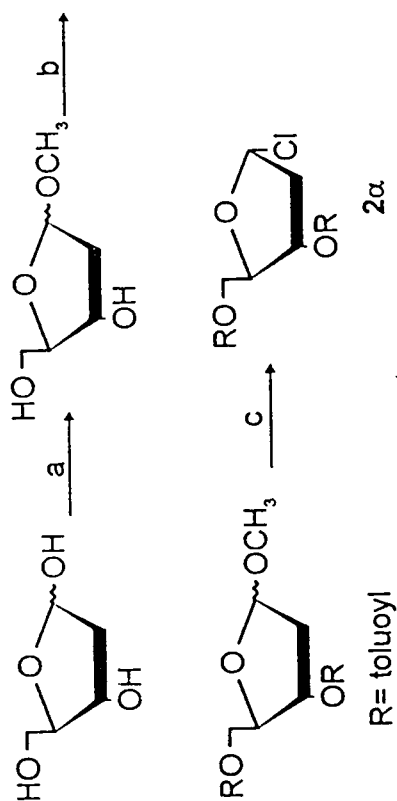
The synthesis of 9-(2,3-dideoxy- β -D-*erythro*-pentofuranosyl)-6-methoxy-9H-purine **12** was accomplished using the R. K. Robins stereospecific, single-phase, sodium salt glycosylation procedure which involved using the sodium salt of the purine with a suitably protected 2-deoxyribosyl halide.⁸

During the synthesis of this compound, the Burroughs-Wellcome group published a paper⁶ describing the synthesis of a series of 6-alkoxypurine 2',3'-dideoxynucleosides using an enzymatic method. Dideoxy sugar 1-phosphate is generated *in situ* from 2',3'-dideoxythymidine via thymidine phosphorylase (TPase). The resulting 2',3'-dideoxy sugar 1-phosphate is coupled *in situ* with the appropriate purine base using purine nucleoside phosphorylase (PNPase). The method, however simple, was not economically viable, as the reactions were carried out using large quantities of the phosphorylase enzyme. Biological testing of these compounds was carried out with respect to anti-HIV activity in MT4 cells and adenosine deaminase assay. However, the biological testing results were not encouraging enough. Nevertheless, synthesis of the title compound was carried out using the chemical approach (Scheme 2 and 3).

Several approaches to carry out the glycosylation of the 6-methoxypurine ring were attempted. The Vorbrüggen procedure using various Lewis acids¹⁰ such as trimethylsilyltrifluoroacetic acid (TMSOTf), tin(IV) chloride, and titanium(IV) chloride

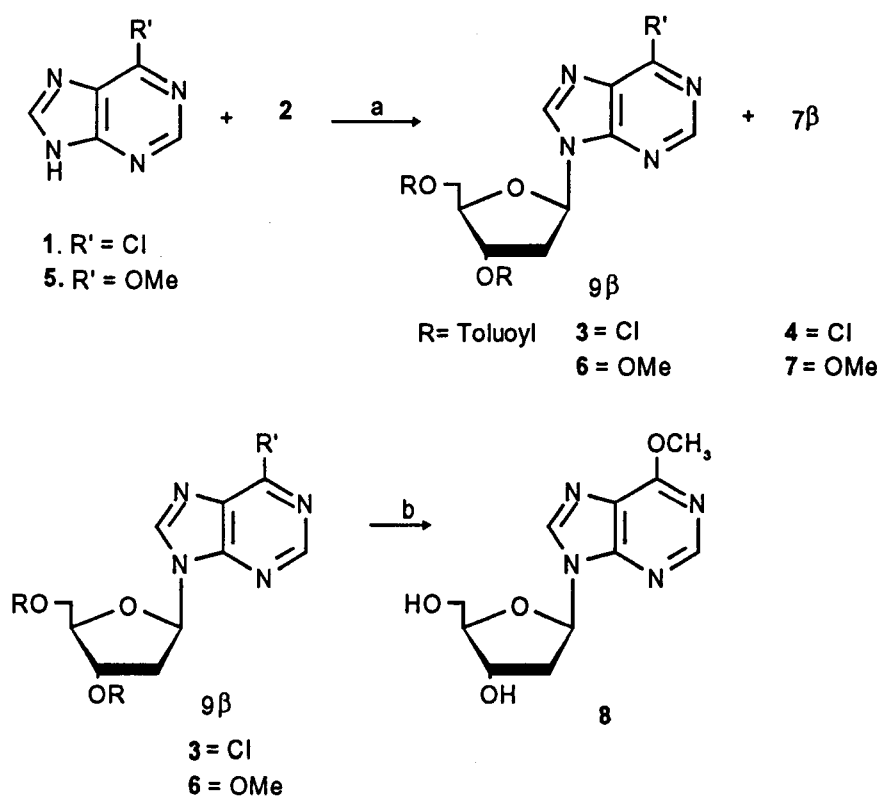
on silylated purines and suitably protected 2-deoxyribose gave a mixture of products which proved difficult to separate on column chromatography. Other methodologies such as the Fraser-Reid¹¹ methodology using pentenyl ribose to couple with the purine ring also suffered from the same drawback. Finally, the Robins⁸ method using a stereospecific, single-phase sodium salt glycosylation procedure proved to be very successful for the synthesis of 3 and 6.

Treatment of the sodium salt of 6-chloropurine with 2-deoxy-3,5-di-*O-p*-toluoyl- α -D-*erythro*-pentofuranosyl chloride,¹² 2, furnished 59% yield of the protected nucleoside. This method gave only the 9 β and the 7 β anomers of the nucleoside which could be separated easily by column chromatography. Similar methodology was used for the synthesis of the 6-methoxy nucleoside to afford the desired anomers in 74% yield. Comparison of the ¹H NMR spectra of the 9 β and 7 β anomers revealed the resonance for the H-1' proton at δ 6.58 and 6.65 ppm respectively (see Appendix B). The *p*-toluoyl protecting group was easily removed in both the 6-chloro- and 6-methoxy nucleoside using sodium methoxide to afford excellent yields of the 6-methoxypurine 2-deoxynucleoside 8. The primary hydroxy group on the 2-deoxy sugar at the C-5' position was protected¹³ using *tert*-butylchlorodimethylsilane (TBDMSCl) to afford 9 in 83% yield. The hydroxy group at the C-3' position was deoxygenated using the Barton-McCombie procedure⁹ to afford 11 in 90% yield (two steps). The ¹H NMR spectrum of compound 11 revealed the resonance for the C-2' and C-3' position as a multiplet at δ 2.5 ppm. Finally, removal of the silyl protecting group was accomplished using tetrabutylammonium fluoride (TBAF) in dry tetrahydrofuran to afford the final



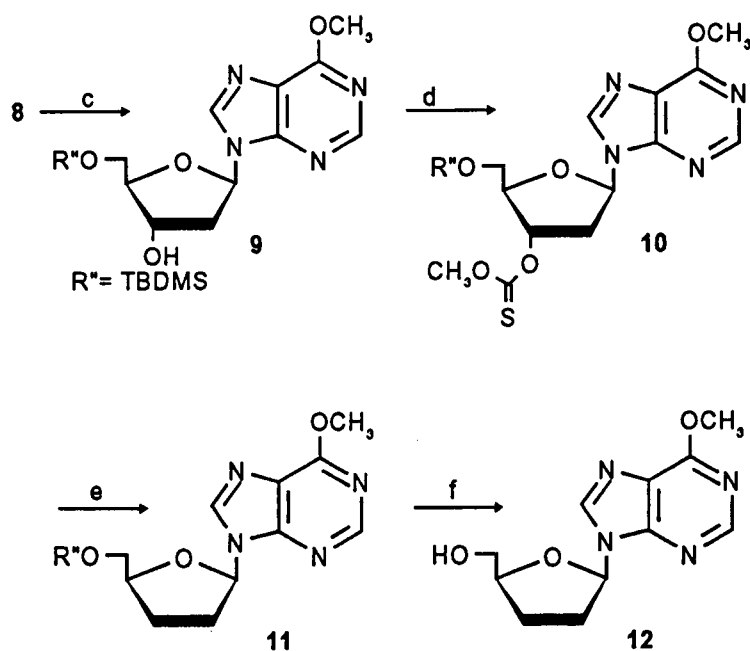
Reagents: a. MeOH, H⁺; b. *p*-toluoyl chloride, pyridine; c. HCl, glacial acetic acid.

Scheme 1. Synthesis of 2-deoxy-3,5-di-*O*-*p*-toluoyl- α -D-*erythro*-pentofuranosyl chloride 2.



Reagents: a. NaH (60%), CH_3CN , reflux; b. NaOMe

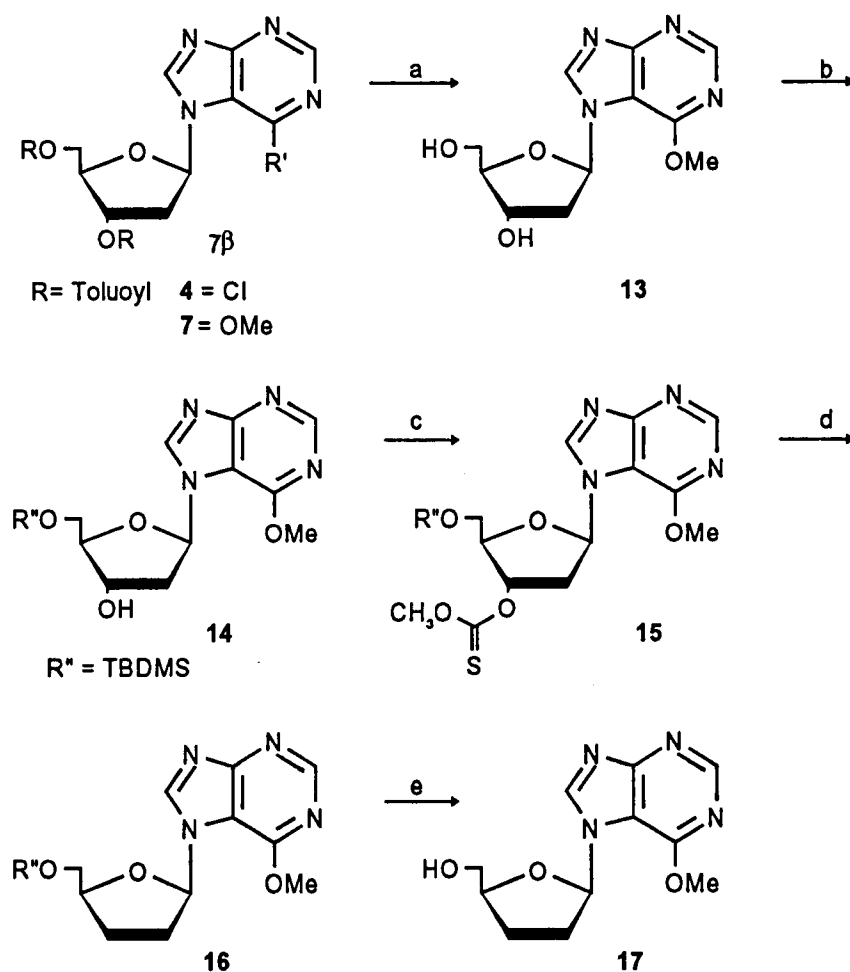
Scheme 2. Synthesis of 9-(2-Deoxy- β -D-erythro-pentofuranosyl)-6-methoxy-9H-purine 8.



Reagents: c. TBDMSCl, pyridine; d. (1) 1,1'-thiocarbonyldiimidazole, DMF; (2) MeOH, reflux; e.

Bu₃SnH, AIBN; f. TBAF, THF.

Scheme 3. Synthesis of 9-(2,3-Dideoxy-β-D-*erythro*-pentofuranosyl)-6-methoxy-9H-purine 12.



Reagents: a. NaOMe; b. TBDMSCl, pyridine; c. (1) 1,1'-thiocarbonyl-diimidazole, DMF; (2) MeOH, reflux; d. Bu_3SnH , AIBN; f. TBAF, THF.

Scheme 4. Synthesis of 7-(2,3-Dideoxy- β -D-*erythro*-pentofuranosyl)-6-methoxy-7H-purine 17.

compound **12** in 60% yield. The structure of the final compound was confirmed by ^1H , ^{13}C NMR, mp and specific rotation values. The NMR data obtained matches with those reported in the literature⁶ (see Appendix B). This methodology was also used to synthesize 7β anomer of the final compound (Scheme 4).

This is the first example of the total synthesis of a 6-alkoxypurine 2',3'-dideoxy nucleosides using a chemical approach. The main aim for carrying out the synthesis of this compound was to conduct a comparative study on the rate of deamination of dideoxyadenosine (ddA), 6-chloro- and 6-methoxypurine dideoxynucleosides with respect to adenosine. These studies would give us the comparative K_m and relative $V_{\max}$ values for adenosine deaminase activity (ADA).

V. EXPERIMENTAL

General methods: NMR spectra were obtained using a Bruker AC 250 MHz spectrometer. Chemical shifts are reported in δ -units downfield from an internal tetramethylsilane standard in chloroform-*d* and dimethylsulfoxide-*d*₆. Thin-layer chromatography was carried out using Silica Gel GF₂₅₄ (E. Merck) aluminum-backed plates. Column chromatography was carried out using Silica Gel 60 (E. Merck) products [70–200 mesh for open columns and 230–400 mesh for medium pressure (flash)]. Melting points were determined using a Thomas-Hoover "unimelt" capillary melting point apparatus equipped with a Cole-Parmer model 8520–50 Digi-Sense digital thermocouple combination that was calibrated with known standards. Optical rotations were measured in the indicated solvent and the concentration at the sodium D line in a 1-dm cell at ambient temperatures (21–27 °C), on a Perkin-Elmer model 241 spectropolarimeter. UV absorbance was determined in appropriate solvents using a Shimadzu model UV-2101PC spectrophotometer. Electron-impact (EI⁺) and negative-ion fast atom-bombardment (FAB) mass spectrometry were carried out on a VG ZAB-EQ (VG Analytical, Manchester, England) instrument at the Mass Spectrometry Center of The University of Tennessee.

All solvents and reagents were reagent grade and were used directly unless noted otherwise. *N,N*-Dimethylformamide and acetonitrile were distilled from calcium hydride

at ca. 20 torr and at atmospheric pressure, respectively. Methanol was distilled from magnesium turnings, and tetrahydrofuran was distilled from potassium-benzophenone ketyl at atmospheric pressure. Evaporation of solvents was generally carried out at ca. 40 °C under aspirator vacuum. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA.

Preparation of 2-deoxy-3,5-di-*O-p*-toluoyl- α -D-*erythro*-pentofuranosyl chloride (2)

To a solution of 2-deoxy-D-*erythro*-pentose (1.0 g, 7.3 mmol) in 20 mL of dry methanol was added 4 mL of 1% hydrogen chloride in methanol. The reaction mixture was refluxed under an inert atmosphere of nitrogen for 3 h. The reaction mixture was cooled down and 0.75 g of silver carbonate was added to the reaction mixture with additional stirring for 10 min. The mixture was filtered and the clear solution was evaporated under reduced pressure to afford 1.0 g of a colorless syrup.

The syrup was dissolved in 25 mL of dry pyridine and the solution was cooled to 0 °C. To this solution was added *p*-toluoyl chloride (2.5 g, 16 mmol), and the reaction was stirred at room temperature for 2 h. The mixture was poured onto crushed ice and the aqueous phase was extracted thoroughly with ether (3 $\times$ 30 mL). The organic layer was washed successively with water, 5% sulfuric acid, and aqueous sodium bicarbonate. The organic extract was dried (Na₂SO₄) and evaporated to afford 2.1 g (76%) of the crude compound as a syrup.

The syrup was dissolved in 10 mL of glacial acetic acid presaturated with dry hydrogen chloride gas at 10 °C. Hydrogen chloride gas was passed into the reaction

mixture for 15 min., whereupon the chloride **2** solidified to a thick crystalline mass. The crystals were filtered off by suction and washed with dry ether. The crystals were stored in a vacuum desiccator containing soda-lime and phosphorous pentaoxide, yield 1.4 g (63%).

Data for compound **2**: mp 106 °C [lit.¹² mp 109 °C]; ¹H NMR data (CDCl₃, 250 MHz): δ 2.41 (s, 3 H, Me), 2.42 (s, 3 H, Me), 2.71–2.93 (m, 2 H, H-2', H-2''), 4.55–4.72 (m, 2 H, H-5', H-5''), 4.85 (m, 1 H, H-4'), 5.55 (dd, 1 H, J = 2.8 Hz, H-3'), 6.47 (d, 1 H, J = 4.9 Hz, H-1'), 7.22–8.01 (m, 8 H, aryl); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 21.7, 44.3, 63.4, 73.5, 84.6, 95.2, 129.2, 129.6, 129.9, 190.1.

Preparation of 6-Chloro-9-(2-deoxy-3,5-di-*O-p*-toluoyl- β -D-*erythro*-pentofuranosyl)purine (3**)**

To a suspension of sodium hydride (60% in oil, 421 mg, 10.5 mmol) in anhydrous acetonitrile (60 mL) was added 6-chloropurine **1** (1.35 g, 8.78 mmol), and the mixture was then stirred under a nitrogen atmosphere for 30 min at room temperature. Dry, powdered 2-deoxy-3,5-di-*O-p*-toluoyl- α -D-*erythro*-pentofuranosylchloride¹² **2** (3.49 g, 8.95 mmol) was added in portions and then stirred at room temperature for 20 h. The completion of the reaction was determined by TLC, and the reaction was filtered to remove a small amount of insoluble material, followed by evaporation of the solvent to give a brown oil. The crude product was purified by column chromatography using 0.2:9.8 (v/v) MeOH–CHCl₃ as eluant. Evaporation of the appropriate fractions furnished compound **3** [R_f = 0.46, 1:9 MeOH–CHCl₃], which was recrystallized from absolute EtOH to yield 2.23 g (50%) of **3**.

Data for compound 3: mp 107–108 °C (dec.) [lit.⁸ mp 107–109 °C]; $[\alpha]_D^{22} = -37.87^\circ$ (c 0.47, MeOH); ^1H NMR data (DMSO- d_6 , 250 MHz): δ 2.37–2.41 (s, 6 H, 2 $\times$ Me), 3.43 (m, 2 H, H-2', H-2''), 4.5–4.7 (m, 3 H, H-4', H-5', H-5''), 5.85 (ψ t, 1 H, $J = 2.7$ Hz, 3.2 Hz, H-3'), 6.65 (t, 1 H, $J = 6.8$ Hz, H-1'), 7.3–7.9 (m, 8 H, aryl), 8.73 (s, 1 H, H-8), 8.91 (s, 1 H, H-2); ^{13}C NMR data (DMSO- d_6 , 62.5 MHz): δ 21.1, 35.6, 63.7, 74.5, 81.9, 84.6, 126.4, 129.1, 129.2, 129.4, 146.1, 151.5, 165.1, 165.3.

Anal. Calcd for $\text{C}_{26}\text{H}_{23}\text{ClN}_4\text{O}_5$: C, 61.60; H, 4.57; N, 11.05. Found: C, 61.71; H, 4.61; N, 10.99.

Preparation of 6-Chloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl- β -D-*erythro*-pentofuransoyl)purine (4)

Purification of the crude product by column chromatography, followed by evaporation of the appropriate fractions furnished compound 4 [$R_f = 0.38$, 1:9 MeOH- CHCl_3] which was then recrystallized from absolute EtOH to yield 0.39 g (8.9%).

Data for compound 4: mp 148–150 °C [lit.⁸ mp 152–153 °C]; $[\alpha]_D^{22} = -16.76^\circ$ (c 0.365, MeOH); ^1H NMR data (DMSO- d_6 , 250 MHz): δ 2.37–2.41 (s, 6 H, 2 $\times$ Me), 3.0–3.2 (m, 2 H, H-2', H-2''), 4.5–4.7 (m, 3 H, H-4', H-5', H-5''), 5.74 (d, 1 H, $J = 0.5$ Hz, H-3'), 6.89 (t, 1 H, $J = 6.3$ Hz, H-1'), 7.27–7.9 (m, 8 H, aryl), 8.86 (s, 1 H, H-8), 9.16 (s, 1 H, H-2); ^{13}C NMR data (DMSO- d_6 , 62.5 MHz): δ 21.1, 30.3, 63.8, 74.8, 82.1, 85.6, 126.3, 129.1, 129.3, 129.4, 147.4, 151.9, 163.5, 165.2.

Anal. Calcd for $\text{C}_{26}\text{H}_{23}\text{ClN}_4\text{O}_5$: C, 61.60; H, 4.57; N, 11.05. Found: C, 61.70;

H, 4.61; N, 10.96.

9-(2-Deoxy-3,5-di-*O-p*-toluoyl- β -D-*erythro*-pentofuranosyl)-6-methoxy-9*H*-purine (6)

To a suspension of sodium hydride (60% in oil, 301 mg, 7.68 mmol) in dry acetonitrile (50 mL) was added 6-methoxypurine **5** (960 mg, 6.40 mmol), and the mixture was then stirred under a nitrogen atmosphere for 30 min at ambient temperature. Dry, powdered 2-deoxy-3,5-di-*O-p*-toluoyl- α -D-*erythro*-pentofuranosyl chloride **2** (2.54 g, 6.52 mmol) was added in one portion, and then refluxed for 24 h. The completion of the reaction was determined by TLC. Workup of the reaction as described above, followed by column chromatography using 1:9 MeOH-CHCl₃, generated compound **6** as glass, [*R_f* = 0.53, 1:9 MeOH-CHCl₃]; yield: 1.23 g (38%). The unreacted starting material (6-methoxypurine) was also recovered (180 mg, 19% yield).

Data for compound **6**: $[\alpha]_D^{22} = -19.75^\circ$ (*c* 1.62, MeOH); ¹H NMR data (CDCl₃, 250 MHz): δ 2.4–2.44 (s, 6 H, 2 $\times$ Me), 2.8 (m, 1 H, H-2''), 3.14 (m, 1 H, H-2'), 4.18 (s, 3 H, OMe), 4.70 (m, 2 H, H-5', H-5''), 4.74 (m, 1 H, H-4'), 5.81 (d, 1 H, *J* = 6.5 Hz, H-3'), 6.58 (dd, 1 H, *J*_{1,2''} = 5.64 Hz, *J*_{1,2'} = 8.18 Hz, H-1'), 7.3–7.9 (m, 8 H, aryl), 8.08 (s, 1 H, H-8), 8.51 (s, 1 H, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 21.6, 21.68, 37.8, 54.1, 63.9, 75.0, 83.0, 84.8, 129.2, 129.5, 129.7, 140.2, 144.0, 144.4, 152.2, 165.8, 166.1.

Anal. Calcd for C₂₇H₂₆N₄O₆·0.06CHCl₃: C, 63.77; H, 5.15; N, 10.99. Found: C, 63.95; H, 5.39; N, 10.44.

7-(2-Deoxy-3,5-di-*O-p*-toluoyl- β -D-*erythro*-pentofuranosyl)-6-methoxy-7*H*-purine (7)

Purification of the crude product by column chromatography, followed by

evaporation of the appropriate fractions, furnished compound 7 as glass, [R_f = 0.34, 1:9 MeOH-CHCl₃]; yield: 1.13 g (35%).

Data for compound 7: $[\alpha]_D^{22} = -8.90^\circ$ (c 1.045, MeOH); ¹H NMR data (CDCl₃, 250 MHz): δ 2.39–2.4 (s, 6 H, 2 × Me), 2.63–2.84 (m, 2 H, H-2', H-2''), 4.1 (s, 3 H, OMe), 4.2–4.6 (m, 3 H, H-4', H-5', H-5''), 5.67 (d, 1 H, J = 3.5 Hz, H-3'), 6.65 (ψt, 1 H, J = 6.1 Hz, 7.4 Hz, H-1'), 7.27–7.9 (m, 8 H, aryl), 8.39 (s, 1 H, H-8), 8.68 (s, 1 H, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ 21.5, 21.6, 29.1, 40.2, 54.2, 63.7, 74.3, 82.9, 87.0, 126.3, 129.2, 129.3, 129.4, 129.6, 142.8, 144.2, 152.3, 156.6, 165.7, 166.0.

Anal. Calcd for C₂₇H₂₆N₄O₆: C, 64.53; H, 5.21; N, 11.15. Found: C, 64.25; H, 5.25; N, 11.00.

9-(2-Deoxy-β-D-erythro-pentofuranosyl)-6-methoxy-9H-purine (8)

To a solution of 3 (1.78 g, 3.51 mmol) in 20 mL of anhydrous MeOH was added 2.5 equiv of sodium metal, and the reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Upon completion of the reaction, the solvent was evaporated to give a syrup. This syrup was columned in 0.5:9.5 (v/v) MeOH-EtOAc to afford quantitative yields of compound 8 [R_f = 0.31, 1:9 MeOH-CHCl₃] as glass.

A similar procedure was carried out on compound 6 (1.17 g, 2.33 mmol), with the exception that the reaction was refluxed for 1 h. The solvent was evaporated to give a syrup. This syrup was columned in 0.5:9.5 (v/v) MeOH-EtOAc to afford compound 8 in quantitative yields.

Data for compound 8: $[\alpha]_D^{22} = -11.4^\circ$ (c 0.175, MeOH); UV (MeOH): (pH 1)

248.7, 209.5, (pH 7) 246.4, 211, (pH 12) 248.1, 214.4; ^1H NMR data (CDCl_3 , 250 MHz): δ 2.37 (dd, 1 H, $J = 5.15$ Hz, $J = 13.05$ Hz), 2.8–2.9 (m, 1 H, H-2''), 3.7–3.9 (m, 3 H, H-4', H-5', H-5''), 4.1 (s, 3 H, OMe), 4.17 (bs, 1 H, H-3'), 6.39 (ψ t, 1 H, H-1'), 8.14 (s, 1 H, H-8), 8.41 (s, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 40.7, 54.3, 62.8, 72.2, 86.9, 89.0, 122.4, 141.8, 150.4, 151.6, 161.1; HRFABMS Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_4$ ($\text{M} - 2\text{H}_2\text{O} + \text{H}^+$): 267.1091; found : 267.1102.

Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 42.93; H, 5.00; N, 17.70.

7-(2-Deoxy- β -D-erythro-pentofuranosyl)-6-methoxy-7H-purine (13)

Deprotection of **4** and **7** (7β anomers) was carried out in similar manner using sodium methoxide to afford compound **13**, [$R_f = 0.17$, 1:9 MeOH– CHCl_3], which was recrystallized from EtOAc– Et_2O (few drops) to afford a colorless solid in quantitative yield.

Data for compound **13**: mp 149 °C; $[\alpha]_D^{22} = +28.26^\circ$ (c 0.45, MeOH); UV (MeOH): (pH 1) 255.4, 216.5, (pH 7) 258.3, 217.3, (pH 12) 258.6, 218.6; ^1H NMR data (CDCl_3 , 250 MHz): δ 2.4–2.6 (m, 2 H, H-2', H-2''), 4.0–4.1 (m, 3 H, H-4', H-5', H-5''), 4.17 (s, 3 H, OMe), 4.86 (d, 1 H, $J = 7.9$ Hz, H-3'), 6.52 (d, 1 H, $J = 6.2$ Hz, H-1'), 9.35 (s, 1 H, H-8), 9.68 (s, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 40.4, 41.2, 54.3, 61.2, 70.2, 86.5, 88.1, 11.8, 144.7, 151.6, 156.7, 161.4; HRFABMS Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_4$ ($\text{M} + \text{H}^+$): 267.1094; found : 267.1093.

Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 40.49; H, 4.88; N, 16.60.

9-(5-*O*-(*tert*-Butyldimethylsilyl)-2-deoxy- β -D-*erythro*-pentofuranosyl)-6-methoxy-9H-purine (9)

To a solution of **8** (784 mg, 2.94 mmol) in 15 mL of dry *N,N*-dimethylformamide (DMF) was added imidazole (600 mg, 6.82 mmol) and the mixture was stirred under an inert argon atmosphere for 15 min. This was followed by slow addition of *tert*-butylchlorodimethylsilane (480 mg, 3.24 mmol), and the mixture was then stirred at room temperature for 18 h. The solvent was removed under reduced pressure. After extraction with CHCl_3 (3×20 mL) the organic layer was washed with water, dried (MgSO_4) and evaporated. Purification of the crude product by flash chromatography using 4:1 EtOAc-hexane afforded compound **9** as glass [$R_f = 0.47$, 1:9 MeOH- CHCl_3]; yield: 930 mg, (83%).

Data for compound **9**: $[\alpha]_D^{22} = -3.91^\circ$ (c 0.465, MeOH); ^1H NMR data (CDCl_3 , 250 MHz): δ 0.0–0.2 (s, 6 H, $2 \times \text{Me}$), 0.9 (s, 9 H, *tert*-Bu), 2.4–2.7 (m, 2 H, H-2', H-2''), 3.8 (d, 2 H, $J = 4.0$ Hz, H-5', H-5''), 4.08 (dd, 1 H, $J = 0.5$ Hz, $J = 3.6$ Hz, H-4'), 4.18 (s, 3 H, OMe), 4.61 (m, 1 H, H-3'), 6.53 (t, 1 H, $J = 6.4$ Hz, H-1'), 8.29 (s, 1 H, H-8), 8.42 (s, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ -5.1, -4.8, 18.1, 22.3, 25.6, 41.2, 53.8, 63.1, 71.2, 84.3, 87.3, 121.4, 140.5, 151.6, 160.6.

Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{N}_4\text{O}_4\text{Si}$: C, 53.65; H, 7.41; N, 14.72. Found: C, 53.55; H, 7.44; N, 14.65.

7-(5-*O*-(*tert*-Butyldimethylsilyl)-2-deoxy- β -D-*erythro*-pentofuranosyl)-6-methoxy-7H-purine (14)

The primary hydroxy group at the C-5' position of compound **13** (400 mg, 1.53

mmol) was protected using *tert*-butylchlorodimethylsilane (230 mg, 1.56 mmol) to afford compound **14** as a colorless solid, which was recrystallized from Et₂O; yield: 300 mg, (85%) [*R_f* = 0.33, 1:9 MeOH-CHCl₃].

Data for compound **14**: mp 123–125 °C; [α]_D²² = +2.0° (c 0.5, MeOH); ¹H NMR data (CDCl₃, 250 MHz): δ 0.0–0.2 (s, 6 H, 2 $\times$ Me), 0.9 (s, 9 H, *tert*-Bu), 2.4–2.6 (m, 2 H, H-2', H-2''), 3.89 (d, 2 H, *J* = 3.5 Hz, H-5', H-5''), 4.1–4.12 (m, 1 H, H-4'), 4.16 (s, 3 H, OMe), 4.65 (dd, 1 H, *J* = 1.9 Hz, *J* = 5.9 Hz, H-3'), 6.62 (t, 1 H, *J* = 6.1 Hz, H-1'), 8.53 (s, 1 H, H-8), 8.64 (s, 1 H, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ -5.0, -4.7, 18.3, 25.9, 43.0, 54.1, 63.3, 71.8, 87.0, 87.3, 143.1, 152.1, 162.1.

Anal. Calcd for C₁₇H₂₆N₄O₄Si: C, 53.65; H, 7.41; N, 14.72. Found : C, 53.55; H, 7.43; N, 14.66.

9-(5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy- β -D-*erythro*-pentofuranosyl)-6-methoxy-9*H*-purine (11)

To a solution of **9** (850 mg, 2.23 mmol) in 20 mL of dry *N,N*-dimethylformamide (DMF) was added 1, 1'-thiodicarbonyldiimidazole (590 mg, 3.35 mmol), and the reaction mixture was heated for 1 h at 80 °C. The solution was cooled down and concentrated under reduced pressure. The brown residue was dissolved in dry MeOH and heated for 2 h at 60 °C. Evaporation of the solvent gave a brown residue. The residue was extracted with CH₂Cl₂ (3 $\times$ 15 mL) and the extract was washed with water, dried (Na₂SO₄) and evaporated to afford compound **10** as a colorless oil; yield: 890 mg (88%) [*R_f* = 0.56, 1:9 MeOH-CHCl₃].

Compound **10** was then taken directly to the next step without any further purification. To a solution of **10** (890 mg, 1.95 mmol) in 20 mL of dry toluene was added tributyltin hydride (1.05 mL, 3.91 mmol), along with a catalytic amount of 2,2'-azobis(2-methylpropionitrile) (AIBN). The reaction mixture was refluxed for 1 h and then cooled. The solvent was evaporated to afford a syrup. Purification of the residue by flash chromatography using 1:4 MeOH-CHCl₃ furnished 660 mg (92%) of compound **11** [*R_f* = 0.61, 1:9 MeOH-CHCl₃].

Data for compound **10**: ¹H NMR data (CDCl₃, 250 MHz): δ 0.0–0.2 (s, 6 H, 2 × Me), 0.9 (s, 9 H, *tert*-Bu), 2.8 (m, 2 H, H-2', H-2''), 4.0 (dd, 2 H, *J* = 3.7 Hz, *J* = 6.5 Hz, H-5', H-5''), 4.08 (s, 3 H, -CSOMe), 4.19 (s, 3 H, OMe), 4.42 (bs, 1 H, H-4'), 5.84 (bs, 1 H, H-3'), 6.61 (ψt, 1 H, H-1'), 8.37 (s, 1 H, H-8), 8.53 (s, 1 H, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ -5.1, -4.6, 18.1, 25.7, 38.9, 53.9, 59.6, 63.7, 83.4, 84.3, 85.2, 140.0, 151.9, 160.8, 195.2.

Data for compound **11**: mp 60–62 °C; [*α*]_D²² = -8.57° (c 0.4, MeOH); ¹H NMR data (CDCl₃, 250 MHz): δ 0.2 (s, 6 H, 2 × Me), 0.9 (s, 9 H, *tert*-Bu), 2.5 (m, 4 H, H-2', H-2'', H-3', H-3''), 3.9 (ddd, 2 H, *J* = 2.9 Hz, *J* = 11.4 Hz, *J* = 14.2 Hz, H-5', H-5''), 4.18 (s, 3 H, OMe), 4.2–4.3 (m, 1 H, H-4'), 6.4 (dd, 1 H, *J* = 2.3 Hz, *J* = 6.1 Hz, H-1'), 8.48 (s, 1 H, H-8), 8.52 (s, 1 H, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ -5.1, -4.7, 24.8, 25.7, 33.3, 53.8, 63.8, 82.0, 85.3, 121.7, 140.8, 150.9, 151.5.

Anal. Calcd for C₁₇H₂₈N₄O₃Si · 0.07CHCl₃: C, 55.00; H, 7.59; N, 15.03. Found: C, 55.52; H, 7.75; N, 14.50.

7-(5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy- β -D-*erythro*-pentofuranosyl)-6-methoxy-7*H*-purine (16)

Using similar methodology deoxygenation of compound 14 (0.13 g, 0.35 mmol) afforded 70 mg (100%) of compound 16. The spectral data of compound 15 and 16 are as shown below.

Data for compound 15: [R_f = 0.29, 1:9 MeOH-CHCl₃]; ¹H NMR data (CDCl₃, 250 MHz): δ 0.0–0.2 (s, 6 H, 2 $\times$ Me), 0.9 (s, 9 H, *tert*-Bu), 2.5–2.7 (m, 2 H, H-2', H-2''), 3.9–3.98 (m, 2 H, H-5', H-5''), 4.06 (s, 3 H, -CSOMe), 4.12 (s, 3 H, OMe), 4.39 (s, 1 H, H-4'), 5.76 (s, 1 H, H-3'), 6.6 (bs, 1 H, H-1'), 8.53 (s, 1 H, H-8), 8.6 (s, 1 H, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ -5.0, -4.7, 18.2, 25.8, 40.7, 54.1, 59.8, 63.8, 83.3, 85.8, 87.3, 142.9, 152.0, 156.6, 162.2, 195.2.

Data for compound 16: [R_f = 0.28, 1:9 MeOH-CHCl₃]; [α]_D²² = +13.13° (c 0.44, MeOH); ¹H NMR data (CDCl₃, 250 MHz): δ 0.2 (s, 6 H, 2 $\times$ Me), 0.9 (s, 9 H, *tert*-Bu), 1.9–2.5 (m, 4 H, H-2', H-2'', H-3', H-3''), 3.9 (ddd, 2 H, J = 3 Hz, J = 11.4 Hz, J = 14.3 Hz, H-5', H-5''), 4.12 (s, 3 H, OMe), 4.23 (m, 1 H, H-4'), 6.42 (dd, 1 H, J = 1.9 Hz, J = 6.3 Hz, H-1'), 8.6 (s, 1 H, H-8), 8.64 (s, 1 H, H-2); ¹³C NMR data (CDCl₃, 62.5 MHz): δ -5.0, -4.7, 18.4, 24.3, 25.9, 34.8, 54.0, 63.8, 82.7, 88.0, 143.4, 145.0, 150.4, 151.9, 153.4.

Anal. Calcd for C₁₇H₂₈N₄O₃Si $\cdot$ 0.10CHCl₃: C, 54.58; H, 7.53; N, 14.89. Found: C, 54.99; H, 7.76; N, 14.31.

9-(2,3-Dideoxy- β -D-*erythro*-pentofuranosyl)-6-methoxy-9*H*-purine (12)

To a solution of 11 (660 mg, 1.81 mmol) in dry THF (20 mL) was added 1 M

solution of tetrabutylammonium fluoride (TBAF) (3.6 mL, 3.6 mmol), and the reaction mixture was stirred at room temperature for 1 h. The solution was concentrated, and the resulting syrup was purified by flash chromatography using 1.5:8.5 (v/v) MeOH-CHCl₃ to afford 260 mg (60%) of 12 [*R_f* = 0.52, 1.5:8.5 MeOH-CHCl₃]. The spectroscopic data of the final compound matched with the ¹H, mp and [α]_D²² values published previously.⁶

Data for compound 12: mp 109–110 °C [lit.⁶ mp 122–123 °C]; [α]_D²² = -22.0° (c 0.5, DMF) [lit.⁶ [α]_D²⁰ = -22.4° (c 0.5, DMF)]; ¹H NMR data (DMSO-*d*₆, 250 MHz): δ 2.0–2.1 (m, 2 H, H-3', H-3''), 2.4–2.5 (m, 2 H, H-2', H-2''), 3.4–3.6 (m, 2 H, H-5', H-5''), 4.09 (s, 3 H, OMe), 4.12–4.18 (m, 1 H, H-4'), 4.97 (t, 1 H, *J* = 5.5 Hz, OH), 6.32 (dd, 1 H, *J*_{1,2''} = 3.9 Hz, *J*_{1,2'} = 6.1 Hz, H-1'), 8.53 (s, 1 H, H-8), 8.62 (s, 1 H, H-2); ¹³C NMR data (DMSO-*d*₆, 62.5 MHz): δ 25.4, 31.7, 53.8, 62.5, 81.9, 84.6, 141.7, 151.4.

7-(2,3-Dideoxy- β -D-erythro-pentofuranosyl)-6-methoxy-7H-purine (17)

To the solution of 16 (55 mg, 0.15 mmol) in dry THF (5 mL) was added 1 M tetrabutylammonium fluoride (0.60 mL, 0.61 mmol), and the reaction mixture was stirred for 1 h. Evaporation of the solvent, followed by flash chromatography, furnished 34 mg (89%) of compound 17.

Data for compound 17: [*R_f* = 0.47, 1.5:8.5 MeOH-CHCl₃]; mp 120–122 °C (softens); [α]_D²² = +13.33° (c 0.15, MeOH); ¹H NMR data (CDCl₃, 250 MHz): δ 1.9–2.5 (m, 4 H, H-2', H-2'', H-3', H-3''), 3.8–4.12 (ddd, 2 H, *J* = 3.2 Hz, *J* = 12.1 Hz, *J* = 15.4 Hz, H-5', H-5''), 4.12 (s, 3 H, OMe), 4.3 (m, 1 H, H-4'), 6.4 (dd, 1 H,

$J = 1.7 \text{ Hz}$, $J = 6.7 \text{ Hz}$, H-1'), 8.57 (s, 1 H, H-8), 8.94 (s, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 62.5 MHz): δ 24.5, 29.6, 34.6, 54.2, 62.9, 82.7, 87.9, 143.7, 152.1.

Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_3 \cdot 0.07\text{CHCl}_3$: C, 52.34; H, 5.81; N, 20.99. Found: C, 52.41; H, 5.90; N, 20.77.

VI. CONCLUSION

This research has accomplished the synthesis of 9-(2,3-dideoxy- β -D-*erythro*-pentofuranosyl)-6-methoxy-9*H*-purine in excellent overall yield. The main aim of this research was to conduct a comparative study on the rate of deamination of ddA, 6-chloro- and 6-methoxypurine dideoxynucleosides with respect to adenosine. The synthesis of the title compound was accomplished earlier by the Burroughs-Wellcome group⁶ using excessive amounts of a specially cloned enzyme, which was very expensive.

The use of the R. K. Robins stereospecific, single-phase, sodium salt glycosylation procedure,⁸ generated the 9 β and 7 β anomers of the nucleoside. The anomers were separated by column chromatography and the title compound was then synthesized using known methodology.

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VII. REFERENCES

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PART II

B. SYNTHESIS OF 1,2,3,4,6,7,8,9-OCTAHYDRO-1,3-DIMETHYLPYRIMIDO[2,1-f]PURINE-2,4,8-TRIONE

I. INTRODUCTION

During the last decade or so, considerable research activity has been focused on derivatives of theophylline. This has led to the synthesis of pharmacologically important compounds with diuretic, cardiotonic, hypotensive, bronchospasmolytic and antihistamine activity.¹

Based on the results of pharmacological research, these heterocyclic systems have attained a unique position with regards to their biological activity. A wide variety of theophylline derivatives have been synthesized and examined for their involvement in a wide spectrum of biochemical and biological processes. A cursory glance at the wide spectrum of theophylline derivatives having biological activity shows substitution patterns at the N-7 and the C-8 position (Figure 1). A general example of some of the derivatives of theophylline having biological importance is the N-(ψ -haloalkyl)xanthines. These compounds have a general formula shown in Figure 1.

According to the literature data, the xanthines are often synthesized in two stages. The first involves hydroxyalkylation using an alkylene oxide, and the second, the replacement of the hydroxy group with a halogen using thionyl chloride or phosphorous tribromide solution in a dry solvent. These compounds have been found to be useful as intermediates in the synthesis of diuretic and cardiotonic drugs.

Other examples of theophylline derivatives have shown to be useful as

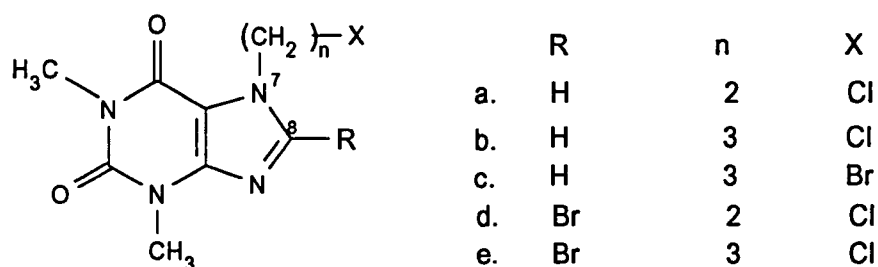


Figure 1. Haloalkylxanthines as 7,8-disubstituted derivatives.

cardiovascular drugs.² A fine example among them is bamiphyline, which is the hydrochloride of 7 β -(*N*-2'-hydroxyethyl-*N*-ethyl)-aminoethyl-8-benzyltheophylline. This compound has found extensive use as a therapeutic agent and is known to stimulate the action of myocardium by exerting a dilatory action on the coronary and the bronchial blood vessels.

The synthesis of these compounds has been achieved using a strategy utilized in the synthesis of compounds shown in Figure 1. In this method, catalytic addition of appropriate alkanes to 8-benzylamino derivatives gave rise to the compounds which are shown in Figure 2.

The examples cited above are basically those which depict the substitution patterns at N-7 and C-8 position. The literature also reveals derivatives of theophylline having a third ring attached at N-7 and C-8 position.^{4,5} Some of these compounds, upon biological testing, have been found to be excellent cardiac stimulants. Among the few

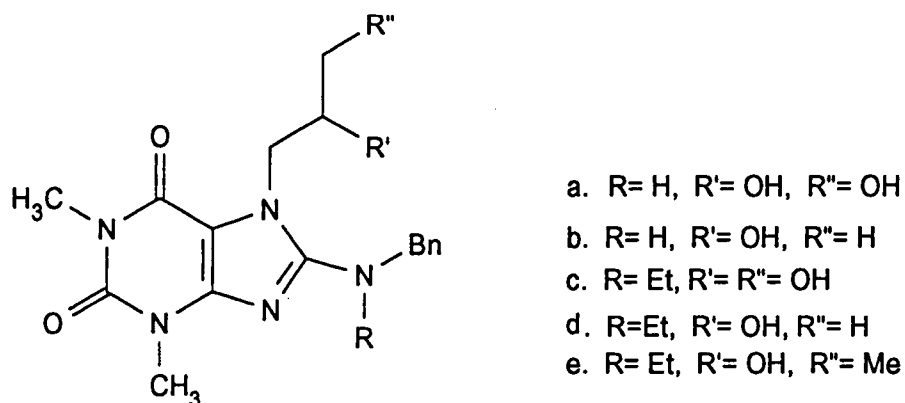


Figure 2. 7,8-disubstituted theophylline derivatives as cardiovascular drugs.

examples presented in Figure 3, compound (d) has been found to lower blood pressure, increase breathing rate and increase the coronary blood flow at 0.5–2.0 mg/kg dosage.

Generally, it has been found that most of the compounds which have shown promising activity are those which have substitution pattern at the N-7 and C-8 position. Hence, it was deduced that there is a structure–activity relationship which could give

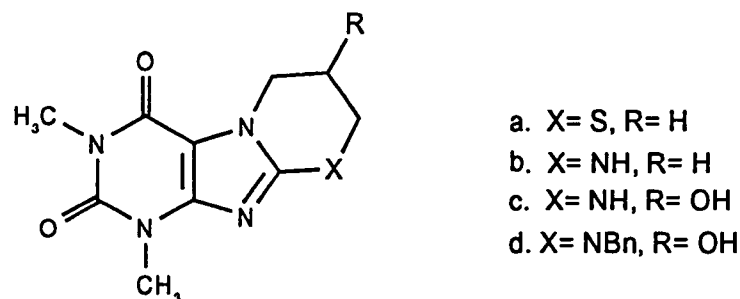


Figure 3. Other theophylline derivatives of pharmaceutical importance.

rise to compounds of therapeutic importance. The pharmacological evaluation of a hexahydropyrimidine[2,3-*f*]theophylline compound prompted us to investigate the synthesis and its biological activity of the title compound **1**, NSC-632302.

II. STATEMENT OF THE PROBLEM

The structure-activity relationship of the 7,8-disubstituted theophylline derivatives,⁵ as well as the pharmacological evaluation of a hexahydropyrimidine[2,3-*f*]theophylline prompted our interest in the biological evaluation and in a simple, workable synthesis of 1,2,3,4,6,7,8,9-octahydro-1,3-dimethylpyrimido[2,1-*f*]purine-2,4,8-trione (1) in gram quantity.

A considerable amount of effort was expended in the preparation of the title compound as described by Pawlowski³ which, in our hands, resulted in failure. Hence a new and simple synthetic strategy was designed to synthesize the title compound in excellent yields. The retrosynthetic scheme for the synthesis of the title compound is shown in Scheme 1. According to this scheme, we attempted to carry out the N-7 alkylation of the bromotheophylline. The introduction of the amino group at the C-8 position would enable us to carry out the ring cyclization.

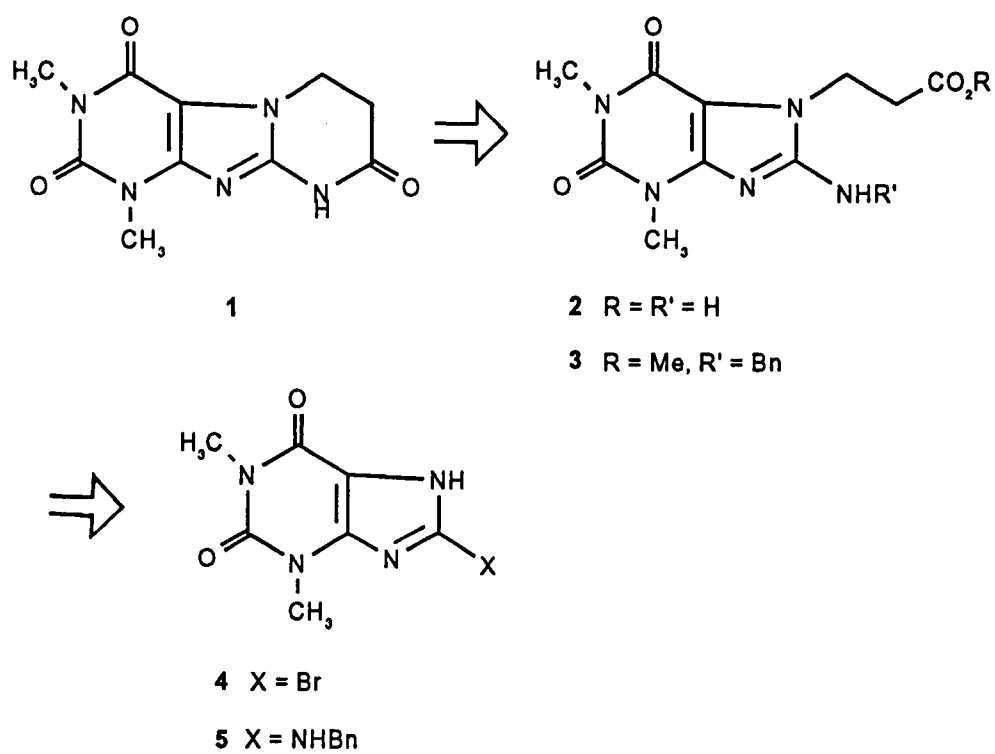
III. SYNTHETIC STRATEGY

Our interest in the biological evaluation of 1,2,3,4,6,7,8,9-octahydro-1,3-dimethylpyrimido[2,1-*f*]purine-2,4,8-trione 1 (NSC-632302) required its preparation in gram quantity.

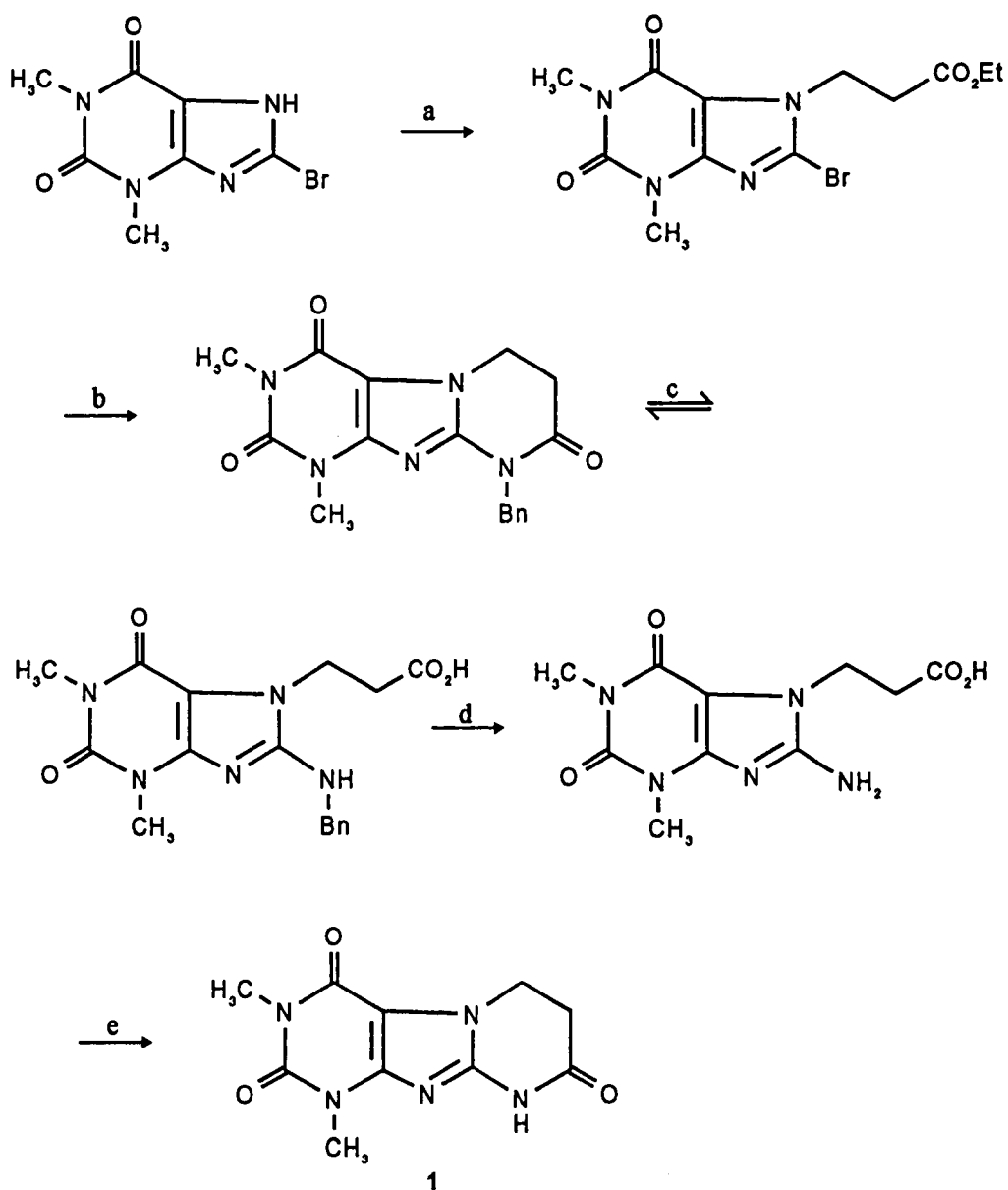
The general approach towards the synthesis of 1 is as shown in the retrosynthetic analysis in Scheme 1. According to this scheme, the N-7 alkylation of the 8-bromotheophylline would be attempted first, followed by subsequent introduction of the amino group at the C-8 position. This would hopefully allow to do the ring closure leading to the title compound.

Pawlowski described³ a synthetic methodology to synthesize the title compound as shown in Scheme 2. A considerable amount of effort was expended in repeating the synthesis described by Pawlowski but, at least in our hands, the procedure always resulted in failure. In fact none of the reactions could be repeated. This prompted us to devise a simple and workable strategy for the synthesis of the title compound.

The N-7 alkylation of the bromotheophylline, as described by Pawlowski, using ethyl acrylate gave a low-yielding product. A number of reactions were carried out for the N-7 alkylation, but unfortunately none of the reactions worked. Finally, N-7 alkylation was achieved using acrylonitrile and Triton B in xylenes, to furnish the desired



Scheme 1. Retrosynthetic analysis of compound 1.



Reagents: a. Ethyl acrylate, DMF, reflux; b. benzylamine, EtOH; c. 10% NaOH; d. 90% H₂SO₄; e. EtOH, H₂SO₄.

Scheme 2. Synthesis of 1,2,3,4,6,7,8,9-octahydro-1,3-dimethylpyrimido[2,1-f]purine-2,4,8-trione, by Pawlowski.³

compound in excellent yields.

After introduction of the amino group at the C-8 position, the ring closure under basic conditions was to be attempted, whereby the 8-amino group would react with the cyano function to generate the amidine 10, followed by hydrolysis to generate the title compound. Although there were a number of precedents for this approach, the ring closure did not proceed as expected. Hence, a benzylamino group was introduced at the C-8 position. Attempts to repeat the cyclization reaction as reported by Pawlowski³ failed completely. A different approach using an azide group was attempted, whereby the azide group would be reduced to the amine, followed by esterification of the cyano group which would be conducive for ring cyclization of 12 under reflux conditions to afford the title compound.

IV. RESULTS AND DISCUSSION

The synthesis of the the title compound has been reported³ using a ring closure of either a 3-(8-aminotheophyllin-7-yl)propionic acid, **2**, or a methyl 3-[8-(benzylamino)theophyllin-7-yl]propanoate, **3**. This was then followed by debenzylation in the latter sequence as shown in Scheme 2.

Pawlowski reported that N-7 alkylation of 8-bromotheophylline **4** using ethyl acrylate gave only a 39% yield, and the alkylation of the 8-(benzylamino)theophylline **5** with ethyl 3-chloropropanoate gave an 84% yield.

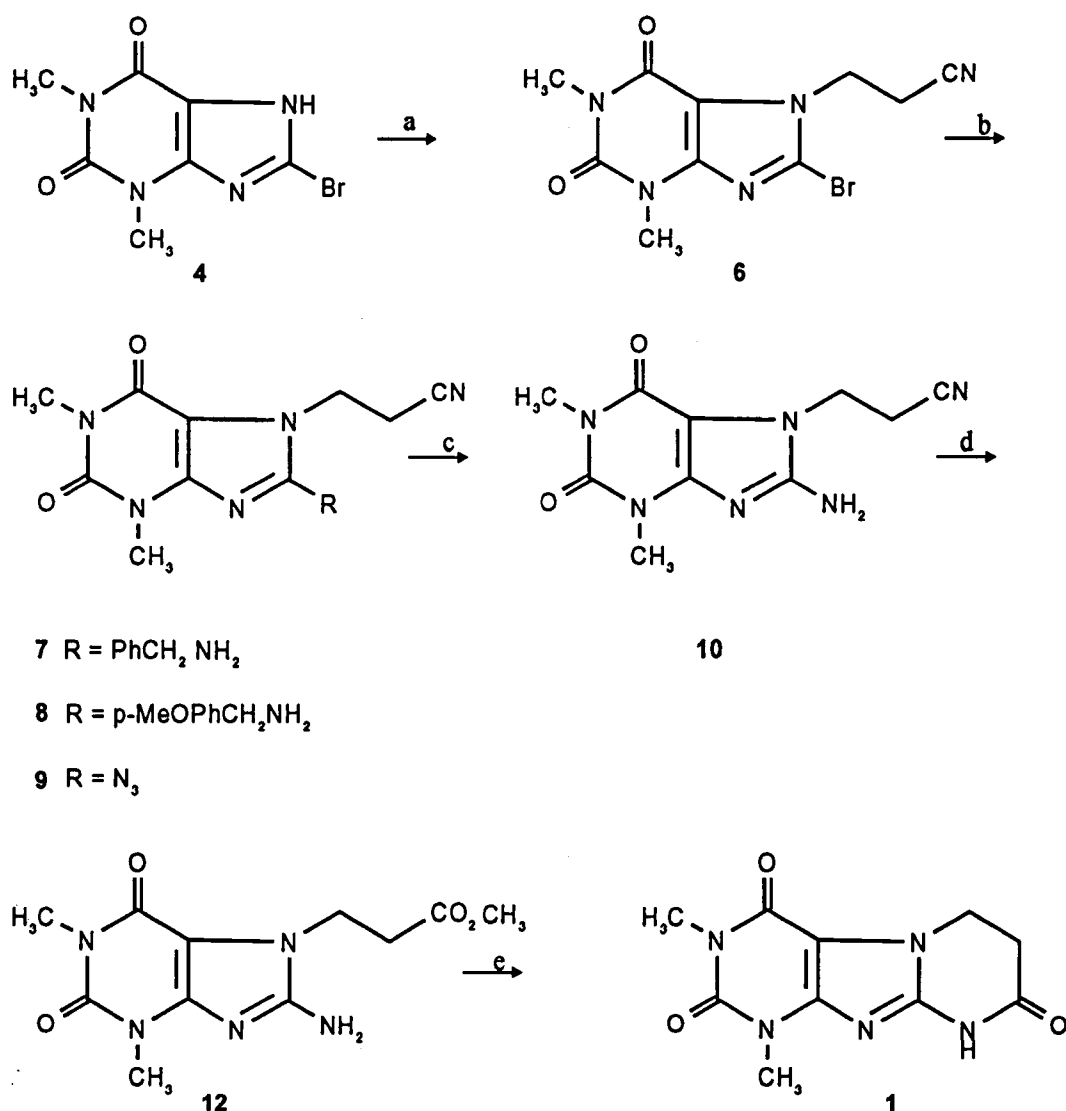
In an attempt to duplicate and expand upon these procedures, compound **4** was alkylated with ethyl 3-bromopropanoate, 3-chloropropionic acid or 3-bromopropionitrile under a variety of conditions. These procedures yielded very little, if any product. Similarly, several attempts to accomplish the alkylation of **4** via conjugate addition of ethyl acrylate were unsuccessful. Furthermore, no product was obtained from the 8-benzylamino compound **5** when it was heated with ethyl 3-bromopropionate.

However, when a refluxing solution of **4** and acrylonitrile (Scheme 3) in 1,4-dioxane was treated with benzyltrimethylammonium hydroxide (Triton B) periodically over a period of 10 h, 8-bromo-7-(2-cyanoethyl)theophylline, (**6**), was formed in a 64% yield. This N-alkylation could be achieved successfully only when Triton B was added dropwise using a long dropper tube that allowed the reagent to be admitted directly into

the refluxing solution. If the Triton B dripped onto the walls of the reaction vessel or came in contact with the vapors, the acrylonitrile would polymerize, resulting in no alkylation as observed by TLC. A further improvement in the reaction was achieved by changing the solvent to xylenes. The yields were found to improve to ca. 95% of the desired N-alkylated product. The ^1NMR spectrum of this compound revealed two triplets at δ 4.61 and 3.01 ppm respectively for the two methylene groups. The IR spectrum of this compound showed the presence of a band at 2250 cm^{-1} which is characteristic of a cyano group.

The strategy was then altered whereby the 6-bromo group of **6** was replaced with the amino function and, hopefully under the basic conditions of the reaction, the 8-amino group would react with the cyano function to furnish the amidine **11** in a single step. The latter compound could then be hydrolysed to furnish the title compound **1** (Scheme 4). Although there are quite a few examples for this type of approach,⁶ attempts to displace the bromo group at the C-8 position of compound **6** failed and gave quantitatively 8-bromotheophylline, (**4**), by the process of a reverse Michael reaction. This meant that other methods were required to introduce the amino group at the C-8 position.

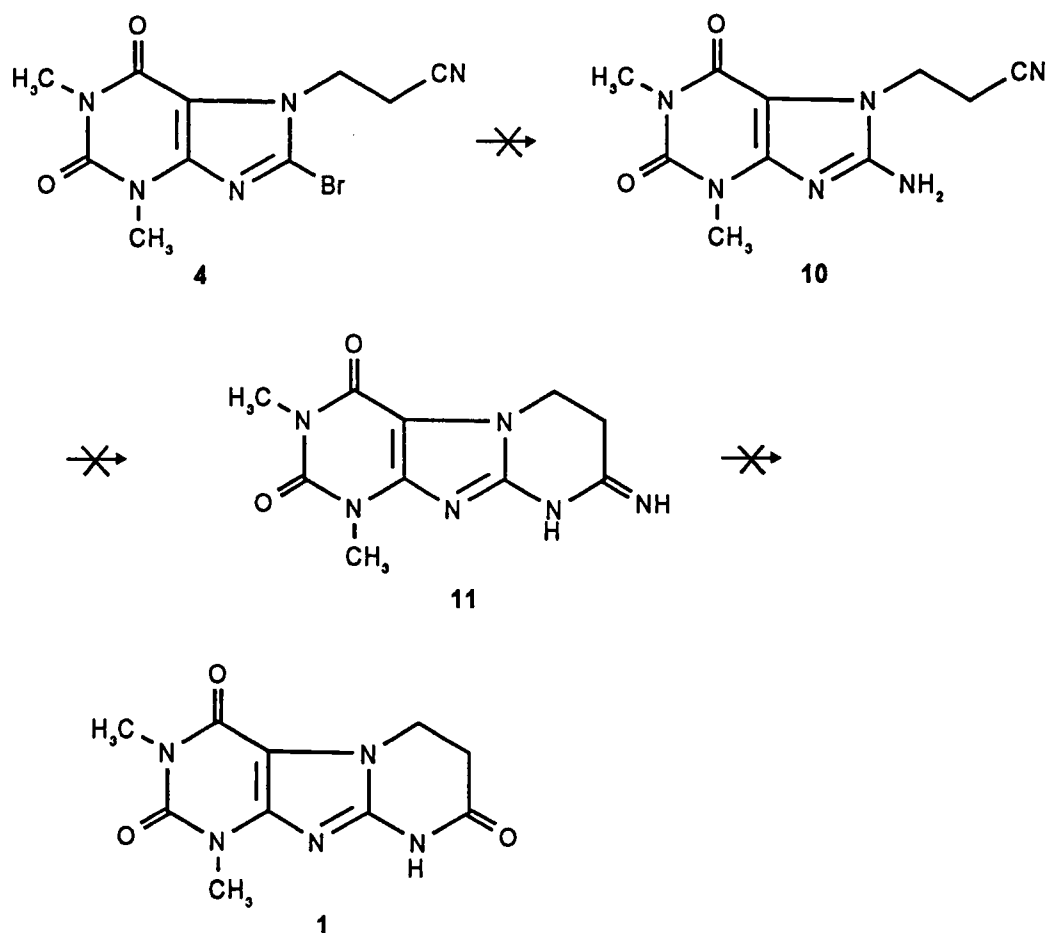
Compound **6** was then treated with benzylamine to afford the 8-benzyamino derivative **7**. However, compound **7** did not cyclize under the conditions reported by Pawlowski,³ nor did it cyclize under a variety of acidic or basic conditions. Furthermore, removal of the benzyl protecting group to furnish the free amine **11**, which could be further used in the cyclization, was found to be fruitless as one obtained only



Reagents: a. Acrylonitrile, Triton B; b. sodium azide, DMSO; c. Lindlar's catalyst; d. HCl, MeOH; e. triethylamine, DMF.

Scheme 3. Synthesis of 1,2,3,4,6,7,8,9-octahydro-1,3-dimethylpyrimido[2,1-f]purine-

2,4,8-trione 1.¹¹



Scheme 4. Attempted synthesis of compound 1.

low yields of **10**. Compound **6** was then refluxed with *p*-methoxybenzylamine and triethylamine in 95% ethanol for 36 h furnished compound **8** in 75% yield. However, the oxidative removal of the *p*-methoxybenzyl group with ammonium cerium(IV) nitrate was low yielding.

Finally compound **6** was reacted with sodium azide in dimethyl sulfoxide at 60 °C for 2 h to furnish a highly crystalline 8-azide-7-(2-cyanoethyl)theophylline, (**9**), in 60% yield.⁷ Reduction of the azide function was accomplished using Lindlar's catalyst in 2:3 ethanol-1,4-dioxane under a hydrogen atmosphere.⁸ Other methods which were tried, namely with triphenylphosphine⁹ and nickel boride,¹⁰ furnished compound **10** in only a 64% and a 30% yields respectively. The structure of this compound was identified by both ¹H NMR and IR spectroscopy. The IR spectrum showed a broad absorption band at 3350 cm⁻¹ which is characteristic in case of primary amines.

Attempts to obtain either the amidine **11** or the amide **1** directly from **10** was unsuccessful under a variety of conditions. Therefore, **10** was converted to the methyl ester **12** by refluxing in a solution of methanolic hydrogen chloride at 100 °C for 24 h in a sealed tube. Efforts to cyclize **12** using the literature protocol with methanol and concentrated acid under reflux conditions failed to produce any detectable **1**. However, the cyclization of **12** was found to proceed smoothly in *N,N*-dimethylformamide and triethylamine to furnish the title compound **1** in a 64% yield. The product obtained had a mp ≥350 °C and was fully characterized by ¹H, and ¹³C NMR spectroscopy and by elemental analysis¹¹ (see Appendix B).

V. EXPERIMENTAL

General Methods: NMR spectra were obtained using either a Nicolet NT 200 (200 MHz for ^1H) or a Bruker WM 360 (360 MHz for ^1H or 90 MHz for ^{13}C). Chemical shifts are reported on the δ -scale (ppm) downfield from an internal standard of tetramethylsilane. Multiplicities are first-order values in Hz and are indicated as: br, broad; s, singlet; d, doublet; t, triplet. Infrared spectroscopy was performed using either a Perkin-Elmer 710B or 283B spectrophotometer. Thin-layer chromatography was carried out using Silica Gel GF₂₅₄ (E. Merck) aluminum-backed plates. TLC visualizations were carried out using anisaldehyde-sulfuric acid dip/heating and with 3% solution of phosphomolybdic acid in ethanol. Column chromatography was performed using Silica Gel 60 (E. Merck) products [70–230 mesh for open columns and 230–400 mesh for medium pressure (flash)]. Evaporation of solvent was generally carried out at 40 °C under aspirator vacuum on a Büchi Rotovapor. Melting points were determined using a Thomas-Hoover "unimelt" capillary melting point apparatus equipped with a Cole-Parmer model 8520-50 Digi-Sense digital thermocouple combination that was calibrated with known standards. All solvents and reagents were reagent grade and were used directly unless noted otherwise. *N,N*-Dimethylformamide (DMF) was distilled from calcium hydride at ca. 20 torr. Methanol was distilled from magnesium turnings. All other solvents were distilled from calcium hydride at atmospheric pressure and stored

over 4Å molecular sieves. 3Å Molecular sieves were used in the case of methanol. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA.

8-Bromo-7-(2-cyanoethyl)theophylline (6)

To a suspension of 8-bromotheophylline **4** (15 g, 57 mmol) in 350 mL of dry xylenes was added 30 mL (0.45 mol) of freshly distilled acrylonitrile, and the mixture was heated under reflux. At this point, 2.0 mL (4.4 mmol) of 40% benzyltrimethylammonium hydroxide (BTMAH) in MeOH was carefully added directly into the reaction mixture without dripping the reagent on the walls of the reaction flask. (A long dropping tube which extended into boiling xylenes was used). Additional amounts of acrylonitrile [30 (0.45 mol), 20 (0.30 mol), and 20 mL (0.30 mol)] and BTMAH [2.0 (4.4 mmol), 2.0 (4.4 mmol), and 3.0 mL (6.6 mmol)] were added at 2 h intervals. The completion of the reaction as determined by TLC (5:95 MeOH-CHCl₃) was about 10 h. The mixture was cooled, and the solvent was evaporated to give a brownish colored residue. The residue was diluted with water and extracted with CHCl₃. The organic extracts were combined together, washed with brine solution, dried (MgSO₄), and then evaporated on to give the crude product, which was then crystallized from MeOH-CHCl₃ to give 14 g (95%) of **6**: mp 192–194 °C; IR (KBr): 2250 cm⁻¹; ¹NMR data (CDCl₃, 200 MHz): δ 3.00 (t, *J*_{1',2'} = 6.5 Hz, 2 H, H-2'), 3.41 (s, 3 H, NMe), 3.56 (s, 2 H, NMe), 4.61 (t, *J*_{1',2'} = 6.5 Hz, 2 H, H-1').

Anal. Calcd for C₁₀H₁₀BrN₅O₂: C, 38.48; H, 3.23; N, 22.44. Found: C, 38.55; H, 3.28; N, 22.35.

8-Benzylamino-7-(2-cyanoethyl)theophylline (7)

To a stirred solution of **6** (0.10 g, 0.32 mmol) in 8 mL of anhydrous ethanol, was added benzylamine (68 mg, 0.63 mmol), and the solution was refluxed for 20 h. After the reaction had gone to completion, the mixture was cooled and the solvent was evaporated. The crude mixture was triturated with hexane several times and then crystallized from EtOAc to give needle-shaped crystals, 64 mg (60%) of **7**: mp 234–236 °C; ¹NMR data (CDCl₃, 200 MHz): δ 3.00 (t, $J_{1,2}$ = 6.5 Hz, 2 H, H-2'), 3.38 (s, 3 H, NMe), 3.58 (s, 3 H, NMe), 4.45 (t, $J_{1,2}$ = 6.5 Hz, 2 H, H-1'), 5.17 (s, 2 H, CH₂Ph), 7.1–7.5 (m, 5 H, Ph).

Anal. Calcd for C₁₇H₁₈N₆O₂·0.12CHCl₃: C, 59.86; H, 5.10; N, 20.82. Found: C, 59.64; H, 5.04; N, 20.62.

8-(4-Methoxybenzylamino)-7-(2-cyanoethyl)theophylline (8)

To a stirred solution of **6** (10.0 g, 31.8 mmol) in 60 mL of anhydrous ethanol was added *N,N*-diisopropylethylamine (12.3 g, 95.5 mmol), followed by addition of 4-methoxybenzylamine (5.45 g, 39.7 mmol). The reaction was then refluxed for 36 h. Upon completion of the reaction, the solution was cooled and the solvent was evaporated to give a solid precipitate. The crude product was recrystallized from EtOAc to afford **8** as white crystals, 8.80 g (75%): mp 234–235 °C; ¹NMR data (CDCl₃, 200 MHz): δ 3.00 (t, $J_{1,2}$ = 6.5 Hz, 2 H, H-2'), 3.4 (s, 3 H, NMe), 3.57 (s, 3 H, NMe), 4.0 (s, 3 H, OMe), 4.45 (t, $J_{1,2}$ = 6.5 Hz, 2 H, H-1'), 5.2 (s, 2 H, CH₂Ph), 7.1–7.5 (m, 5 H, Ph).

Anal. Calcd for C₁₈H₂₀N₆O₃·0.5CHCl₃: C, 59.98; H, 5.07; N, 20.81. Found:

C, 59.88; H, 4.99; N, 20.67.

8-Azide-7-(2-cyanoethyl)theophylline (9)

To a stirred solution of **6** (6.0 g, 19 mmol) in 100 mL of dry dimethyl sulfoxide was added 1.9 g (29 mmol) of sodium azide, and the solution was heated at 60–65 °C for 2 h. The reaction mixture was cooled and diluted with 40 mL of water. The resulting solid was filtered and dried by suction on a Buchner funnel. The crude product obtained was recrystallized from methanol to give 3.2 g (61%) of **9**: mp 310–312 °C; IR (KBr): 2150 cm^{-1} ; ^1NMR data (CDCl_3 , 200 MHz): δ 3.00 (t, $J_{1,2} = 6.5$ Hz, 2 H, H-2'), 3.40 (s, 3 H, NMe), 3.57 (s, 3 H, NMe), 4.37 (t, $J_{1,2} = 6.5$ Hz, 2 H, H-1').

Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_8\text{O}_2$: C, 43.80; H, 3.68; N, 40.86. Found: C, 43.84; H, 3.69; N, 40.78.

8-Amino-7-(2-cyanoethyl)theophylline (10)

Using Lindlar's catalyst. A solution of **9** (2.7 g, 9.8 mmol) in 60 mL of EtOH and 90 mL of 1,4-dioxane containing 1.5 g of Lindlar's catalyst (Pd/ CaCO_3 poisoned with lead, Aldrich, cat. no. 20,573-7) was hydrogenated at 50–60 psi at an ambient temperature for 18 h. The mixture was filtered through Celite, and the residue was washed with EtOH. The combined filtrate and the washings were concentrated, and the residue was diluted with water and acidified to pH 2 using 10% HCl. The mixture was washed with Et_2O , and the aqueous layer was adjusted to pH 8 using 10% aq NaOH. The solution was thoroughly extracted with dichloromethane. The combined extracts were then washed with brine, dried (MgSO_4), and evaporated. The solid obtained was then recrystallized from 2-methoxyethanol to give 2.0 g (84%) of **10**.

Using triphenylphosphine. To a stirred solution of **9** (0.10 g, 0.36 mmol) in 8 mL of dry THF was added triphenylphosphine (95 mg, 0.36 mmol), and the mixture was stirred at room temperature for 2 h. To this was then added water (0.5 mL) with stirring for 16 h. The reaction mixture was then acidified to pH 6 and extracted with ether. The aqueous layer was basified to pH 10 using 10% NaOH and extracted with chloroform. The organic extracts were dried (MgSO_4), and evaporated. The solid obtained was recrystallized from 2-methoxyethanol to give 58 mg (64%) of **10**.

Using nickel chloride and sodium borohydride. To a solution of **9** (0.14 g, 0.51 mmol) in 10 mL of MeOH was added nickel chloride hexahydrate (0.56 g, 2.4 mmol) at 0 °C. Sodium borohydride (0.15 g, 4.0 mmol) was then added slowly to the reaction mixture to avoid any excess frothing. The reaction went to completion in 15 min. The reaction mixture was acidified with acetic acid, diluted with water and basified to pH 9 using 10% K_2CO_3 . The aqueous solution was thoroughly extracted with chloroform, dried (MgSO_4) and evaporated. The crude solid obtained was recrystallized from 2-methoxyethanol to give 37 mg (30 %) of **10**.

Data for compound **10**: mp 260–263 °C; IR (KBr): 3350, 2200 cm^{-1} ; ^1NMR data (CDCl_3 , 200 MHz): δ 2.95 (t, $J_{1',2'} = 6.9$ Hz, 2 H, H-2'), 3.37 (s, 3 H, NMe), 3.49 (s, 3 H, NMe), 4.40 (t, $J_{1',2'} = 6.9$ Hz, 2 H, H-1'), 5.90 (br s, 2 H, NH_2).

Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_6\text{O}_2$: C, 48.38; H, 4.87; N, 33.85. Found: C, 48.44; H, 4.88; N, 33.79.

Methyl-3-(8-aminotheophyllin-7-yl)propanoate (12)

A solution of **10** (1.9 g, 7.6 mmol) in 100 mL of dry MeOH saturated with HCl

was heated in a sealed tube for 24 h at 100 °C. After cooling the solution to room temperature, the mixture was concentrated. The residue was adjusted to pH 8 with 1N Na₂CO₃ and thoroughly extracted with CHCl₃. The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated to give a solid which was recrystallized from 2-methoxyethanol to afford 1.4 g (68%) of 12: mp >320 °C; IR (KBr): 3400, 1730 cm⁻¹; ¹H NMR data (CDCl₃, 200 MHz) δ 3.05 (t, *J*_{2',3'} = 5.2 Hz, 2 H, H-2'), 3.39 (s, 3 H, NMe), 3.51 (s, 3 H, NMe), 3.72 (s, 3 H, OMe), 4.29 (t, *J*_{1',2'} = 5.2 Hz, 2 H, H-3'), 5.37 (br s, 2 H, NH₂).

Anal. Calcd for C₁₁H₁₅N₅O₄: C, 46.96; H, 5.38; N, 24.90. Found: C, 46.70; H, 5.34; N, 24.84.

1,2,3,4,6,7,8,9-Octahydro-1,3-dimethylpyrimido[2,1-*f*]purine-2,4,8-trione (1)

A solution of 12 (0.70 g, 2.5 mmol) in 30 mL of dry *N,N*-dimethylformamide containing 0.90 mL of (6.4 mmol) of triethylamine was maintained under a nitrogen atmosphere and heated under reflux for 20 h. The mixture was concentrated, and the residue was thoroughly extracted with CHCl₃. The combined organic extracts were washed with water, brine solution, dried (MgSO₄), and then evaporated to give a white solid which was recrystallized from 2-methoxyethanol to yield 0.42 g (64%) of 1: mp >350 °C [lit.₂ mp >340 °C]; ¹H NMR data (Me₂SO-*d*₆, 500 MHz): δ 2.84 (t, *J*_{6,7} = 7.2 Hz, 2 H, H-7), 3.21 (s, 3 H, NMe), 3.38 (s, 3 H, NMe), 4.32 (t, *J*_{6,7} = 7.2 Hz, 2 H, H-6), 8.23 (s, 1 H, NH); ¹³C NMR data (Me₂SO-*d*₆, 125 MHz): δ 26.8, 28.9, 29.3, 38.4, 102.3, 146.7, 147.5, 150.7, 153.1, 162.0, 166.7.

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.21; H, 4.46; N, 28.04.

VI. CONCLUSION

This research has resulted in the synthesis of the title compound **1**. A considerable amount of effort was expended in the synthesis of the title compound as described by Pawlowski,³ at least in our hands, which resulted in failure. So a new and simple strategy was designed by which the compound 1,2,3,4,6,7,8,9-octahydro-1,3-dimethylpyrimido[2,1-*f*]purine-2,4,8-trione was synthesized in excellent overall yields.

The crucial step in the synthesis was the N-7 alkylation of the bromotheophylline which was accomplished by careful addition of Triton B to the reaction mixture, thereby resulting in a 95% yield of the desired product.

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VII. REFERENCES

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PART II

C. SYNTHESIS OF METHYL HEXAHYDRO-2-(HYDROXYMETHYL)-2-METHYL PYRROLO[1,2-b]ISOXAZOLE-3-CARBOXYLATE

I. INTRODUCTION

Alkaloids have been isolated from plant species and alkaloids from the genres Senecio, Crotalaria and Heliotropium are of special interest. Pyrrolizidine alkaloids, also known as Senecio alkaloids,¹ fall basically into three main categories, monoesters of the "necine" with a monocarboxylic "necic acids", diesters of the necine with two different monocarboxylic acids and finally, cyclic diesters of the necine with a dicarboxylic necic acid. Among these three categories, the last one represents a highly interesting group of compounds.

An important feature relating to the constitution of the pyrrolizidine alkaloids which has gained importance is the presence of the alkaloid *N*-oxides in plants. Some examples of *N*-oxides alkaloids are: europine, heleurine, heliotrine, lasiocarpine, platphylline, retrosine, rosmarinine, sarracine, seneciphylline and supinine. Detailed investigations of the *N*-oxide content in the plant at various stages of growth of the plant have revealed that the *N*-oxides form a convenient oxidation-reduction system, and play a useful role in the plant metabolism. These Senecio alkaloids have been found to be toxic and cause liver tumors and lung damage in animals feeding on plants containing these compounds.²

A representative example of this class of alkaloids is as shown in Figure 1. The alkaloid consists basically of a pyrrolizidine ("necine") base and a carboxylic ("necic")

acid coupled by a ester linkage. The "necine" base embodies the pyrrolizidine nucleus with one or more hydroxyl groups as shown in Figure 1. It is believed that the unsaturated pyrrolizidine alkaloids are responsible for the hepatotoxicity of these compounds.

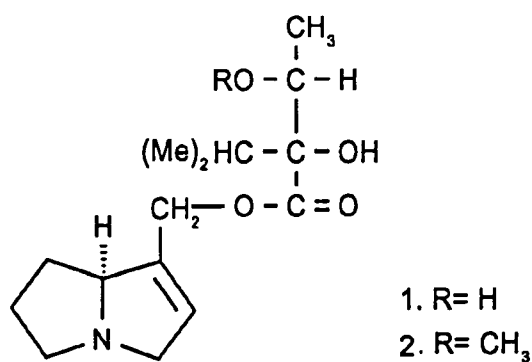


Figure 1. Senecio Alkaloids

Many research groups have have successfully accomplished the total synthesis of the alkaloids which belong to this class.³⁻⁷ Hence we adopted a known methodology from the literature to synthesize the title compound **7a/b**.

II. STATEMENT OF THE PROBLEM

The title compound belongs to the class of pyrrolizidine alkaloids, also referred to as the Senecio alkaloids were of considerable interest to us. Based on the biological activity of the compound, we were prompted to carry out an efficient synthesis of methyl hexahydro-2-(hydroxymethyl)-2-methylpyrrolo[1,2-*b*]isoxazole-3-carboxylate **7a/b**, NCI-607620 in milligram quantities.

III. SYNTHETIC STRATEGY

The title compound was synthesized using known methodology which has been used previously in the synthesis of alkaloids containing the pyrrolizidine ring. The key step in the synthesis of the title compound was the 1,3-dipolar cycloaddition reaction of the nitron 6 and the alcohol 4a/b.

A number of review articles have been published in the last two decades on the 1,3-dipolar cycloaddition reaction.⁸ 1,3-Dipolar cycloadditions are susceptible to electronic and steric influences, which affect the nature of the transition state. Generally the cycloaddition reactions have been classified into three categories based on whether the dominant interaction is: a. between the dipole-HOMO and the dipolarophile-LUMO, b. between the dipole-LUMO and the dipolarophile-HOMO and c. both interactions a and b being equally significant. The frontier-orbital interactions account for the regioselectivity of the cycloaddition reaction. Based on the available information, the title compound was to be synthesized in one step using this key 1,3-dipolar cycloaddition reaction. The nitron, which is generally unstable in nature, would be generated *in situ*, followed by the addition of the alcohol, thereby leading to the synthesis of the title compound. Using the methodology of Murahashi,^{9,10} the nitron was synthesized in satisfactory yields, followed by the 1,3-dipolar cycloaddition to the alcohol to generate the title compound 7a/b.

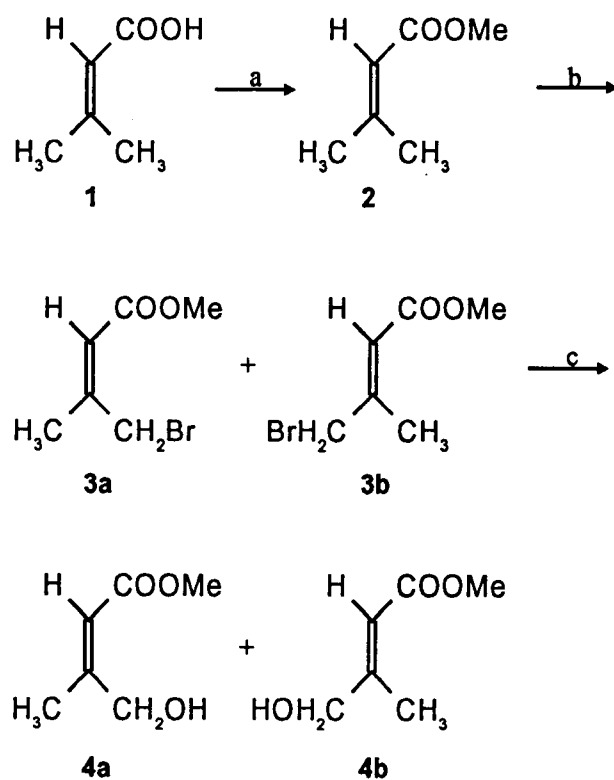
IV. RESULTS AND DISCUSSION

The synthesis of the title compound published earlier¹¹ had drawbacks which prompted the current effort to devise a more efficient synthesis. The key step in the synthesis of the title compound was the 1,3-dipolar cycloaddition reaction of the nitron and the alcohol. This methodology had been used earlier in the synthesis of the pyrrolozidine class of alkaloids.²

The synthesis of the alcohol **4a/b** was carried out as shown in Scheme 1. Dimethylacrylic acid was first esterified using known procedure to furnish methyl 3-methyl crotonate **2** in excellent yields. Bromination of the acrylate ester was then carried out using *N*-bromosuccinimide in presence of a free radical initiator, purification by distillation to afford a mixture of two isomers, methyl (*Z*)- and (*E*)-4-bromo-3-methyl-2-butenate (**3a/b**) in the ratio of 1.3:1.

Various methods were then tried to generate the desired alcohol (**4a/b**), since the published procedure mentioned only 35% yield of the alcohol using silver oxide and silver nitrate method. Excellent yields up to 70% were obtained when the bromo ester was reacted with mercuric oxide and tetrafluoroborate¹² to generate the mixture of alcohols **4a/b** in the ratio of 1.25:1.

The synthesis of nitron **6** was then carried out by the methodology of Murahashi, using sodium tungstate⁹ or selenium dioxide¹⁰ and 30% hydrogen peroxide in ca 48%



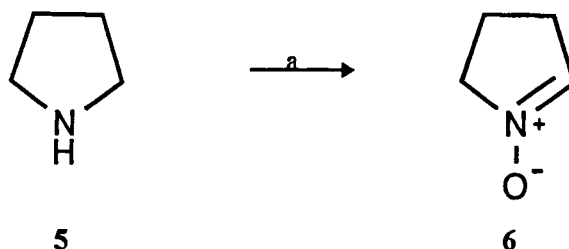
Reagents: a. MeOH, HCl; b. NBS, AIBN, CCl₄; c. HgO, 35% HBF₄, 1,4-dioxane.

Scheme 1. Synthesis of methyl (*E,Z*)-4-hydroxy-2-methyl-2-butenate **4a/b**.

yield (Scheme 2). Due to the unstable nature of the nitron, it was generated *in situ*, followed by the addition of the alcohol to synthesize the title compounds **7a/b** as an inseparable mixture in approximately 30% yield (Scheme 3). The ^1H NMR data for all the intermediates described above were in accordance with published data.¹¹

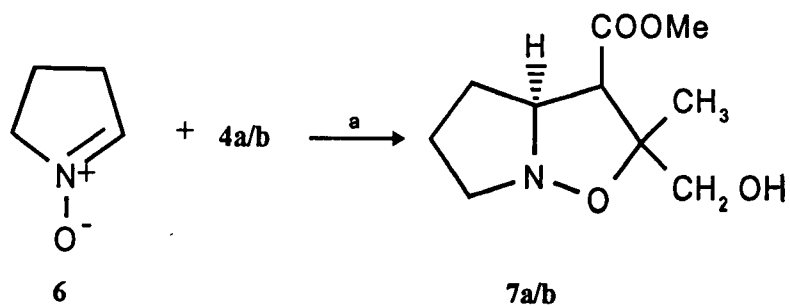
Although the methodology used in the synthesis of the title compound was similar to the published article,¹¹ there were two improvements in our procedure. First of all there was a significant improvement in the yield of the desired alcohol **4a/b** using mercuric oxide and tetrafluoroborate. Secondly, the desired compound could be furnished in one step by the generation of the unstable nitron **6** (*in situ*), and then followed by a 1,3-dipolar cycloaddition reaction by addition of the alcohol to the nitron.

This work was supported in part by a contract from the Drug Synthesis and Chemistry Branch of the National Cancer Institute (Project 331 under Master Order Agreement NO1-CM-607620).



Reagents: a. SeO_2 , 30% H_2O_2 .

Scheme 2. Synthesis of 1-pyrroline-*N*-oxide 6.



Reagents: a. CHCl_3 , N_2 atm, R.T $\rightarrow$ reflux

Scheme 3. Synthesis of methyl hexahydro-2-(hydroxymethyl)-2-methyl pyrrolo[1,2-*b*]isoxazole-3-carboxylate 7a/b.

V. EXPERIMENTAL

General Methods: NMR spectra were obtained using either a Nicolet NT 200 (200 MHz for ^1H) or a Bruker WM 360 (360 MHz for ^1H or 90 MHz for ^{13}C). Chemical shifts are reported on the δ -scale (ppm) downfield from an internal standard of tetramethylsilane. Multiplicities are first-order values and are indicated as: s, singlet; d, doublet; t, triplet. Thin-layer chromatography was carried out using Silica Gel GF₂₅₄ (E. Merck) aluminum-backed plates. TLC visualizations were carried out using anisaldehyde-sulfuric acid dip/heating and with Drangedorffs reagent. Column chromatography was carried out using Silica Gel 60 (E. Merck). Evaporation of solvents were carried out at 40 °C under aspirator vacuum on a Büchi Rotovapor. All solvents and reagents were reagent grade and were used directly unless noted otherwise.

Preparation of Methyl (*E,Z*)-3-methyl-2-butenolate (2)

To a solution of 3,3-dimethylacrylic acid **1** (20 g, 0.21 mole) in 100 mL of dry MeOH was added dropwise boron trifluoride etherate (13 mL, 0.24 mole). The reaction mixture was heated to 60 °C under nitrogen atmosphere for 20 h. The reaction mixture was cooled and concentrated. The concentrate was extracted with ether (3 × 30 mL), dried (Na_2SO_4), evaporated to give a pale yellow oil. Distillation of the crude oil at atmospheric pressure (bp 132–135 °C) afforded a colorless oil **2**; yield: 17 g (86%).

Data for compound 2: ^1H NMR data (CDCl_3 , 200 MHz): δ 1.89 (s, 3 H, Me), 2.17 (s, 3 H, Me), 3.68 (s, 3 H, OMe), 5.68 (s, 1 H, H-2); ^{13}C NMR data (CDCl_3 , 50 MHz): δ 20.1, 27.3, 50.7, 115.6, 198.8.

Preparation of Methyl (*E,Z*)-4-bromo-3-methyl-2-butenolate (3a/b)

To a solution of 2 (1.00 g, 8.76 mmol) in 20 mL of dry CCl_4 was added *N*-bromosuccinimide (NBS) (1.92 g, 10.5 mmol), along with a catalytic amount of 2,2'-azobis(2-methylpropionitrile) (AIBN) (24.8 mg, 0.151 mmol). The reaction mixture was heated for 3 h at 80 °C. The reaction mixture was cooled and the solid was filtered. The solvent was evaporated to give a crude brownish oil. Distillation of the crude under reduced pressure (bp 80–82 °C at 12 torr) [lit.¹¹ bp 89–90 °C at 12 torr] to afford a colorless oil as a mixture of two isomers 3a/b; yield: 1.18 g (70%). The ratio of 3a/b isomers was 1.3:1 as shown by ^1H NMR spectroscopy.

Data for compound 3a: ^1H NMR data (CDCl_3 , 200 MHz): δ 2.27 (d, 3 H, J = 1.5 Hz, H-5), 3.70 (s, 3 H, H-6), 3.92 (s, 2 H, H-4), 5.93 (d, 1 H, J = 1.5 Hz, H-2).

Data for compound 3b: ^1H NMR data: δ 2.05 (d, 3 H, J = 1.5 Hz, H-5), 3.70 (s, 3 H, H-6), 4.57 (s, 2 H, H-4), 5.73 (d, 1 H, J = 1.5 Hz, H-2).

Preparation of Methyl (*E,Z*)-4-hydroxy-2-methyl-2-butenolate (4a/b)

To a solution of mercuric oxide (HgO) (20.2 g, 93.0 mmol) was added 35% tetrafluoroborate (HBF_4) (46.5 g, 186 mmol), in 200 mL of 1,4-dioxane. To this was added dropwise the bromo compound 3a/b (35.8 g, 186 mmol). The reaction was stirred for 24 h. The solution was made alkaline (pH 8.5) by addition of 3N KOH solution. The solid was filtered off and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 40 mL),

dried (MgSO_4) and concentrated to afford a colorless oil. The crude oil was distilled under reduced pressure to afford **4a/b**, as a colorless oil, yield: 18.6 g (70%) (bp 75–77 °C, 0.6 torr) [lit.¹¹ bp 95–100 °C, at 6.2 torr]. The ratio of **4a/b** isomers was 1.25:1 as shown by ^1H NMR spectroscopy.

Data for compound **4a**: ^1H NMR data (CDCl_3 , 200 MHz): δ 2.08 (m, 3 H, H-5), 3.70 (s, 3 H, H-6), 4.12 (d, 2 H, $J = 4$ Hz, H-4), 6.0 (m, 1 H, H-2).

Data for compound **4b**: ^1H NMR data: δ 2.15 (m, 3 H, H-5), 3.70 (s, 3 H, H-6), 4.74 (m, 2 H, $J = 4$ Hz, H-4), 5.86 (m, 1 H, H-2).

Preparation of 1-Pyrroline *N*-oxide (**6**)

To a solution of pyrrolidine **5** (1.0 g, 14 mmol) in 30 mL of acetone was added selenium dioxide (78 mg, 0.70 mmol) at room temperature. 30% H_2O_2 solution (4.6 g, 41 mmol) was added dropwise, and the temperature was maintained at 0 °C as the reaction is exothermic in nature. The reaction went to completion in 3 h. The solvent was removed under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL), dried (Na_2SO_4) and concentrated. The crude mixture was purified using column chromatography with acetone as eluant. Evaporation of the appropriate fractions afforded the nitron **6** as a colorless oil, yield: 0.70 g (60%).

Data for compound **6**: ^1H NMR data (CDCl_3 , 200 MHz): δ 2.2–2.37 (m, 2 H, H-4), 2.7–2.8 (m, 2 H, H-3), 3.92–4.03 (m, 2 H, H-5), 6.8–6.9 (m, 1 H, $-\text{CH}=\text{N}-$).

Preparation of Methyl hexahydro-2-(hydroxymethyl)-2-methyl pyrrolo[1,2-*b*]isoxazole-3-carboxylate (**7a/b**)

To a solution of **4a/b** (2.0 mL, 1.5 mmol) in 20 mL of dry CHCl_3 was added

slowly freshly prepared nitron 6 (0.70 g, 8.2 mmol). The reaction was maintained under an inert atmosphere of nitrogen and stirred at room temperature for 4 h and then refluxed for 10 h. The reaction mixture was cooled and the solvent evaporated under reduced pressure to give a oily residue. The crude oil was purified using column chromatography with CHCl_3 (2.0 L), CHCl_3 -EtOAc (1:1, 1.0 L), EtOAc (1.0 L) and acetone (2.0 L) as eluant. The TLC was developed using Dragendorff's reagent. Evaporation of the appropriate fractions afforded a brown oil **7a/b**; yield: 0.52 g, (30%). The two isomers could not be separated by column chromatography. The ^1H NMR data of the reported compound matches exactly with the compound synthesized.¹¹

Data for compound **7a/b**: ^1H NMR data (CDCl_3 , 200 MHz): δ 1.2 (s, 3 H, H-10), 1.9 (m, 4 H, H-6,7), 3.0 (m, 2 H, H-8), 3.31 (d, 1 H, $J = 7$ Hz, H-4), 3.68 (s, 2 H, H-9), 3.73, 3.74 (s, 3 H, H-12), 4.28 (m, 1 H, H-5).

VI. CONCLUSION

This research has resulted in the synthesis of the title compound using known methodology.¹¹ However there were two modifications in the existing procedure. First of all the yield of the alcohol **4a/b** was improved significantly by reacting the bromoester with mercuric oxide and tetrafluoroborate.

Secondly, the nitron was generated *in situ* followed by addition of the alcohol in the same pot to furnish the title compounds **7a/b** by 1,3-dipolar cycloaddition reaction.

LIST OF REFERENCES

VII. REFERENCES

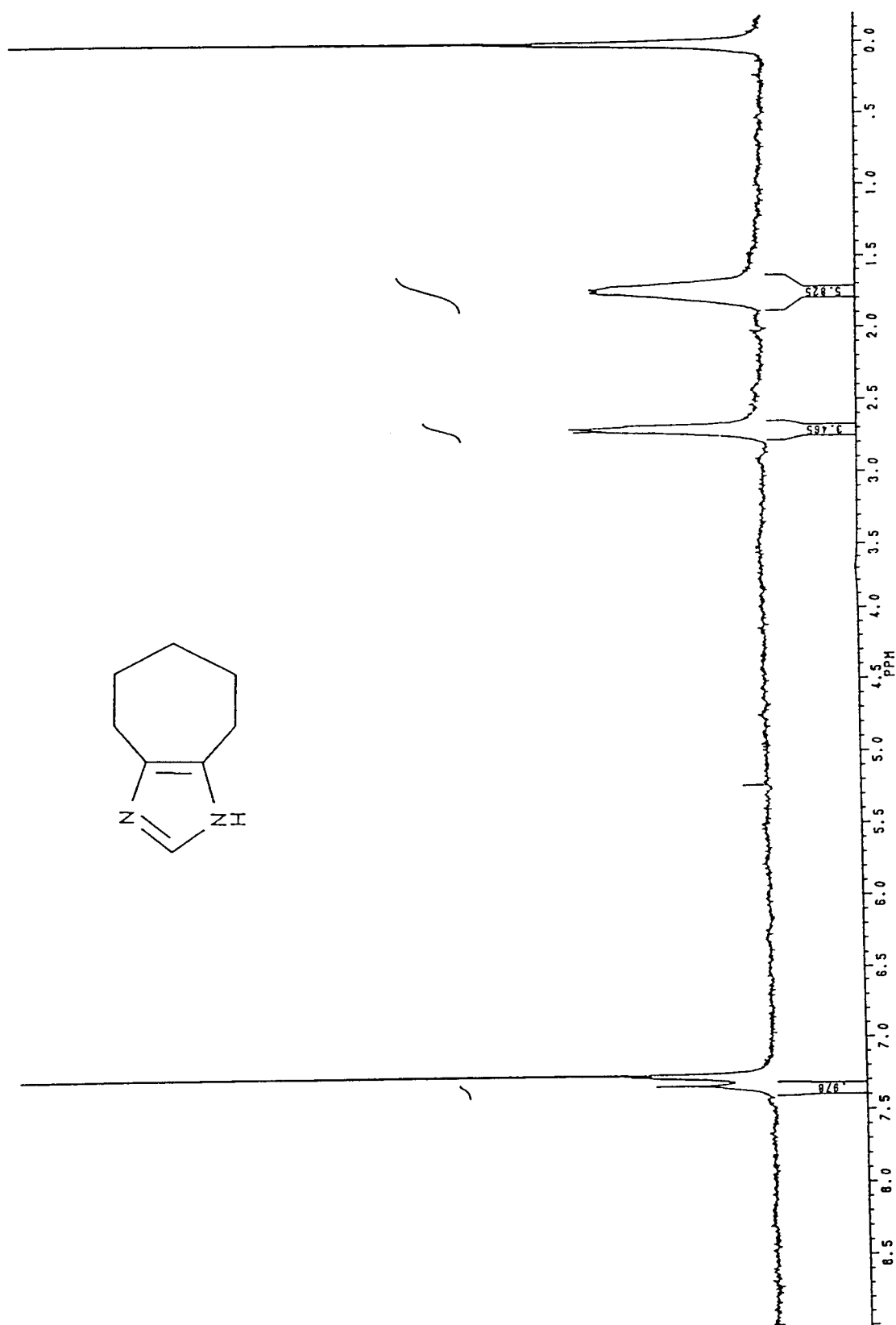
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APPENDICES

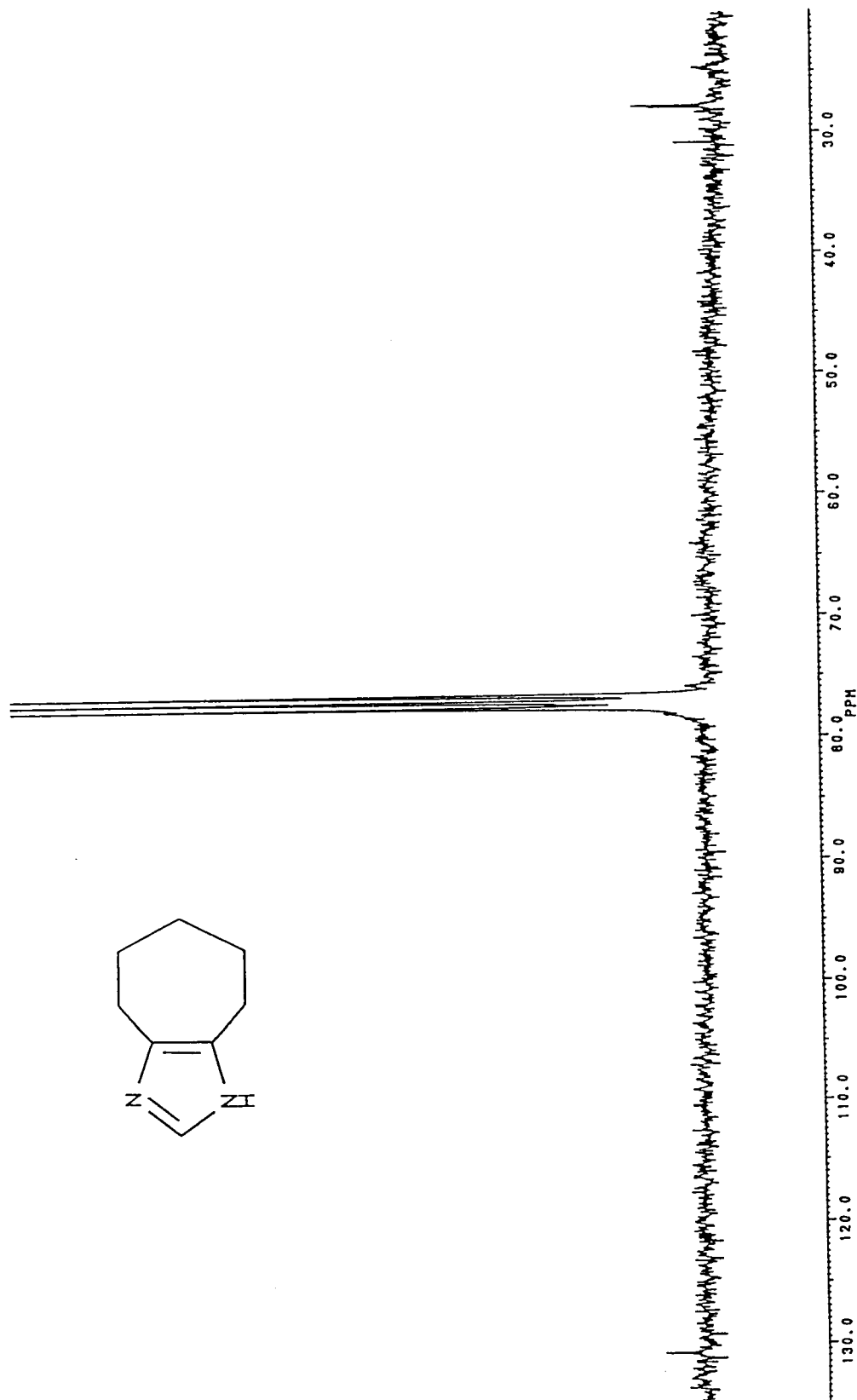
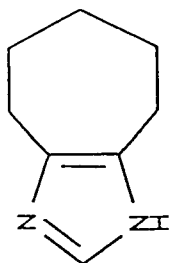
APPENDIX A

^1H , ^{13}C , DEPT. 135, and 2-D NMR

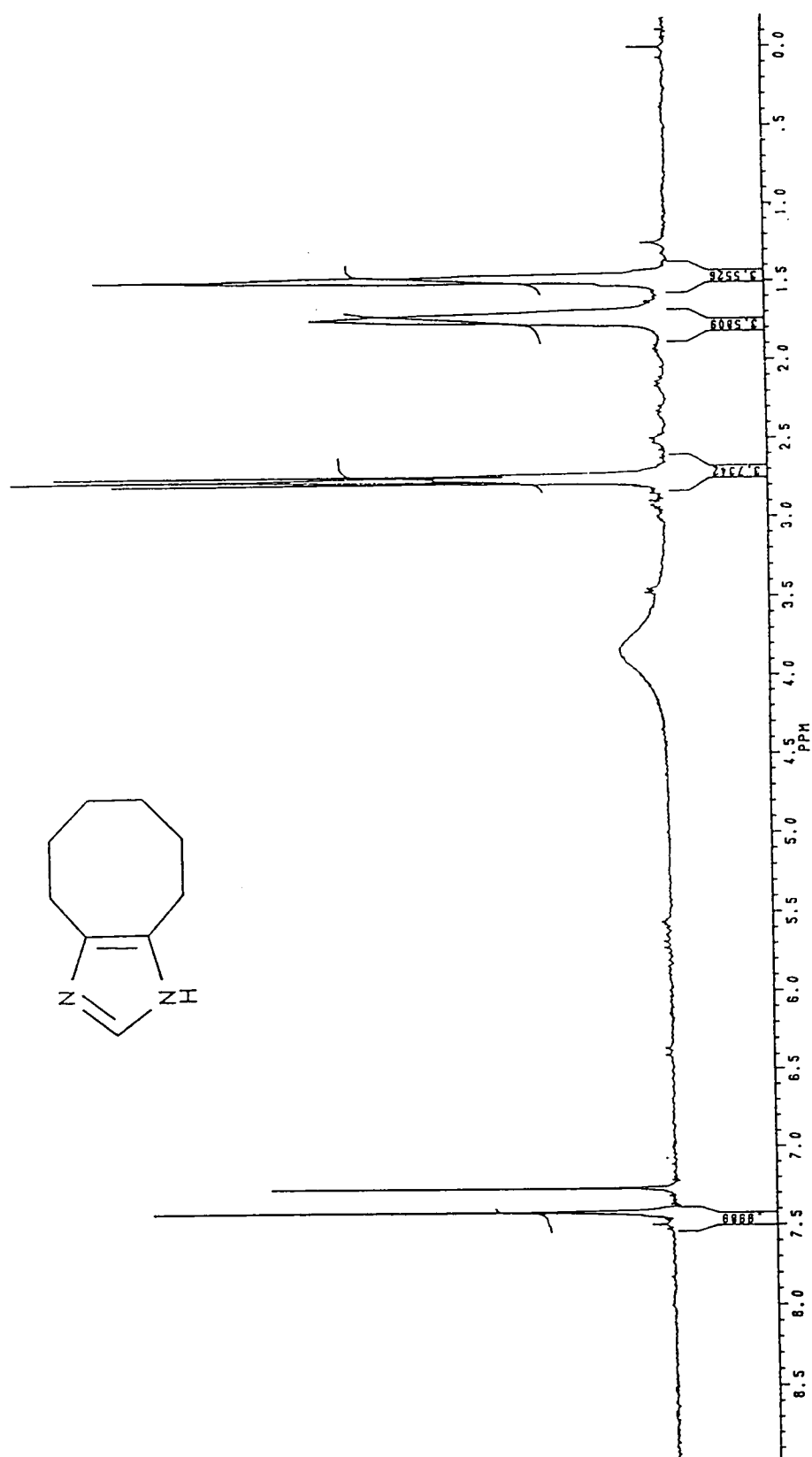
Spectra for Selected Compounds



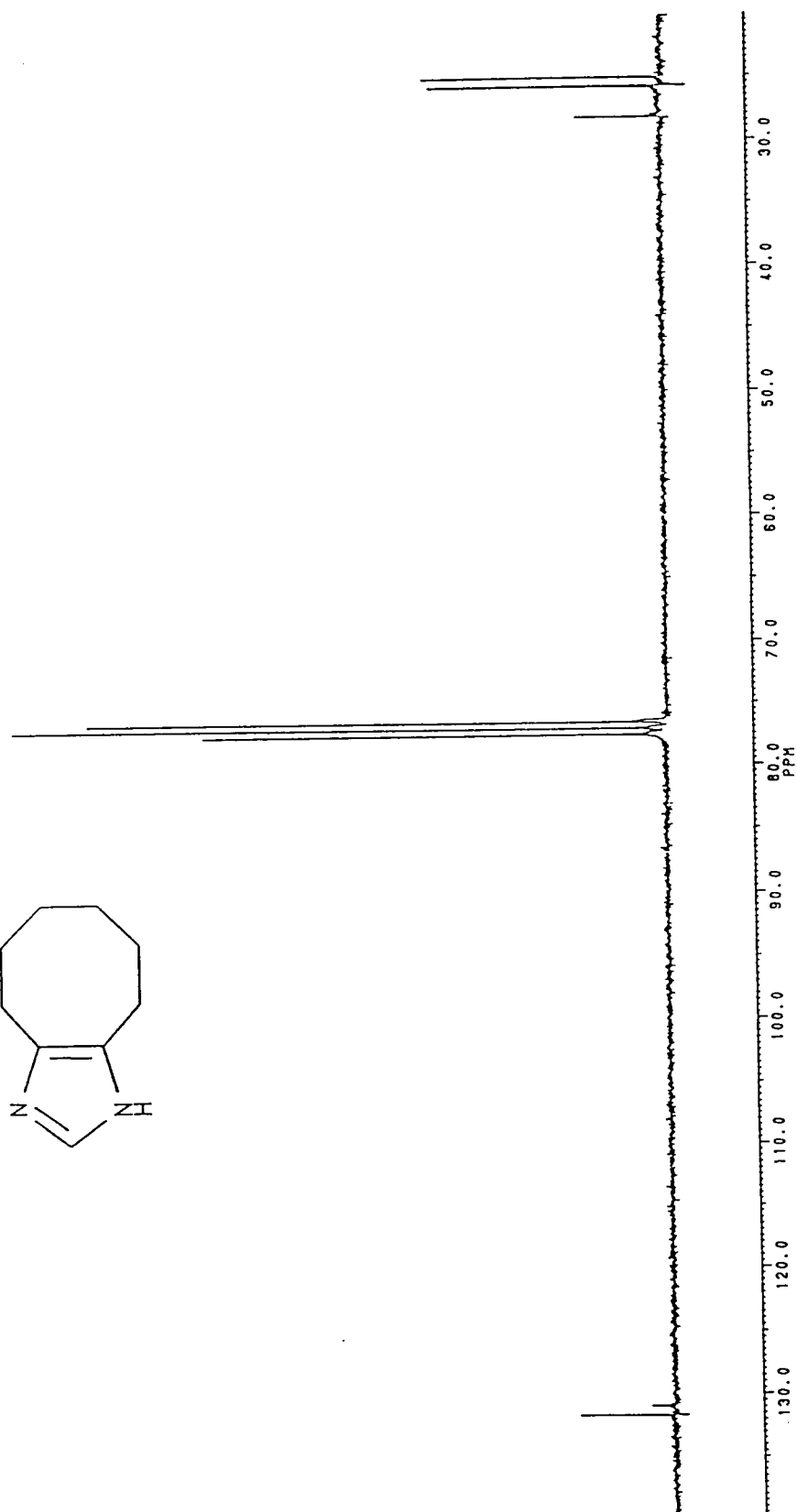
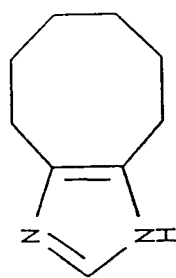
^1H NMR (CDCl_3 , 250 MHz) Spectrum of 1,4,5,6,7,8-Hexahydroimidazo[4,5-a]cycloheptane (1)



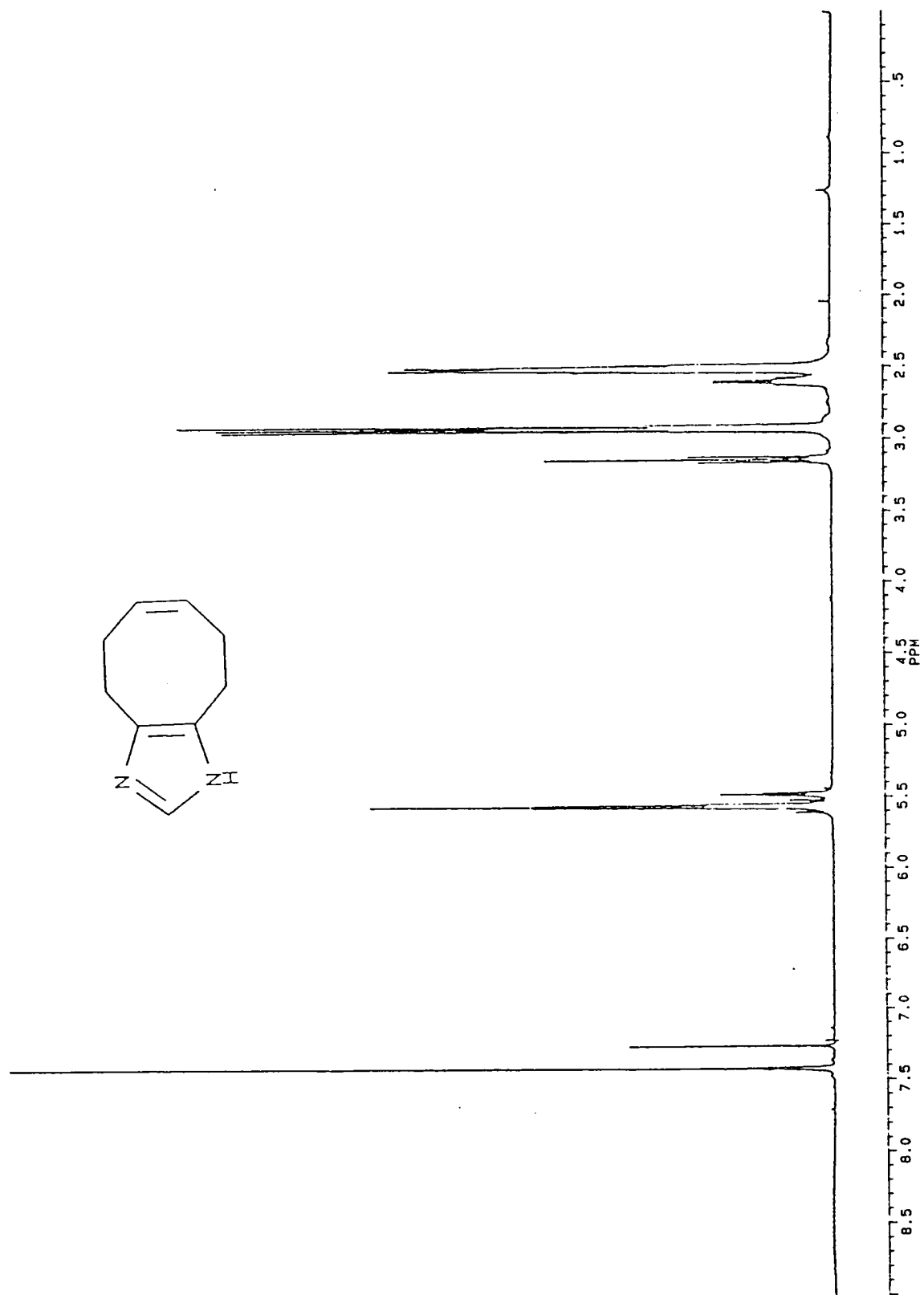
^{13}C NMR (CDCl_3 , 62.5 MHz) Spectrum of 1,4,5,6,7,8-Hexahydroimidazo[4,5-a]cycloheptane (1)



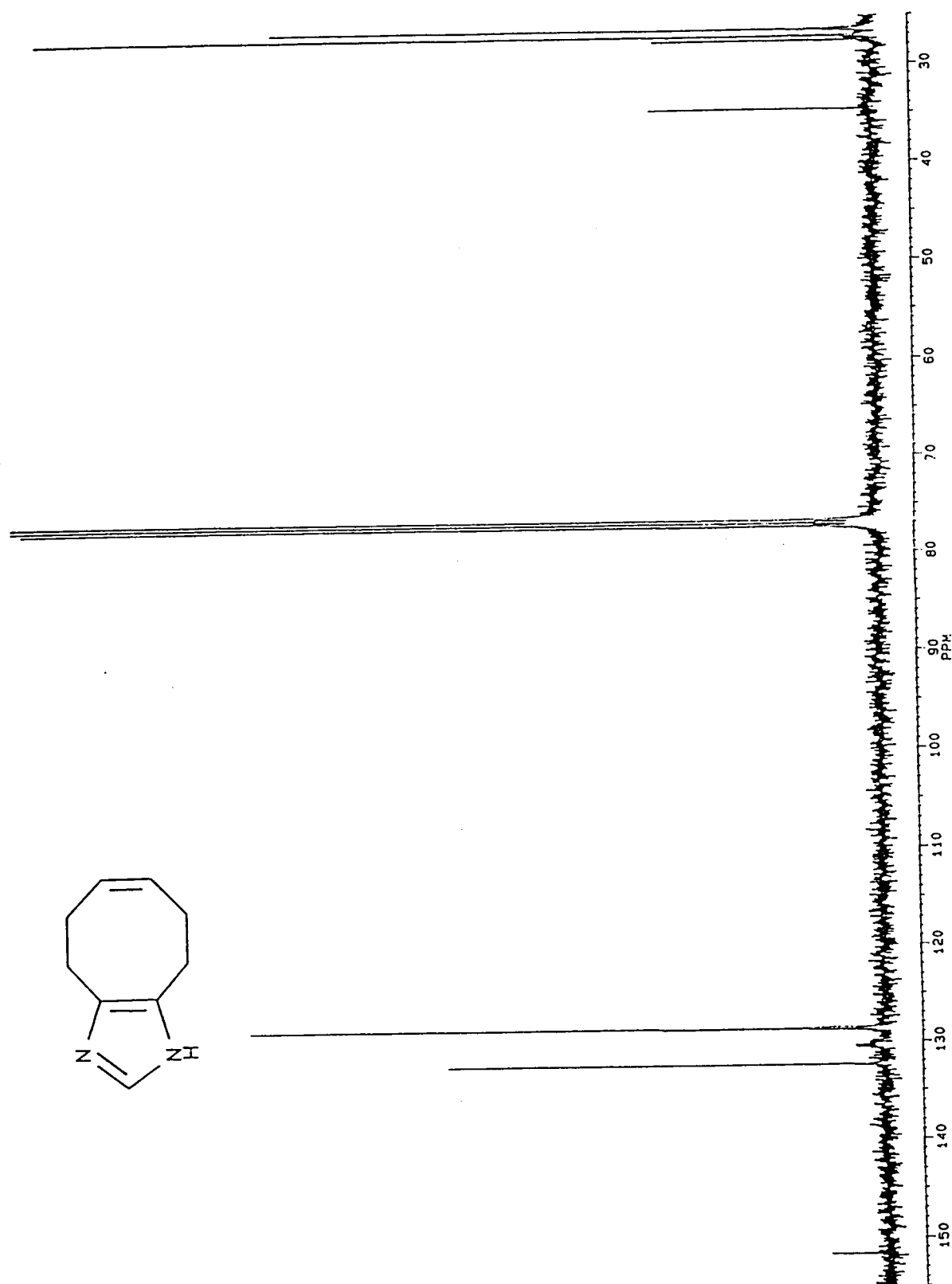
^1H NMR (CDCl_3 , 250 MHz) Spectrum of 4,5,6,7,8,9-Hexahydro-1H-imidazo[4,5-a]cyclooctanone (2)



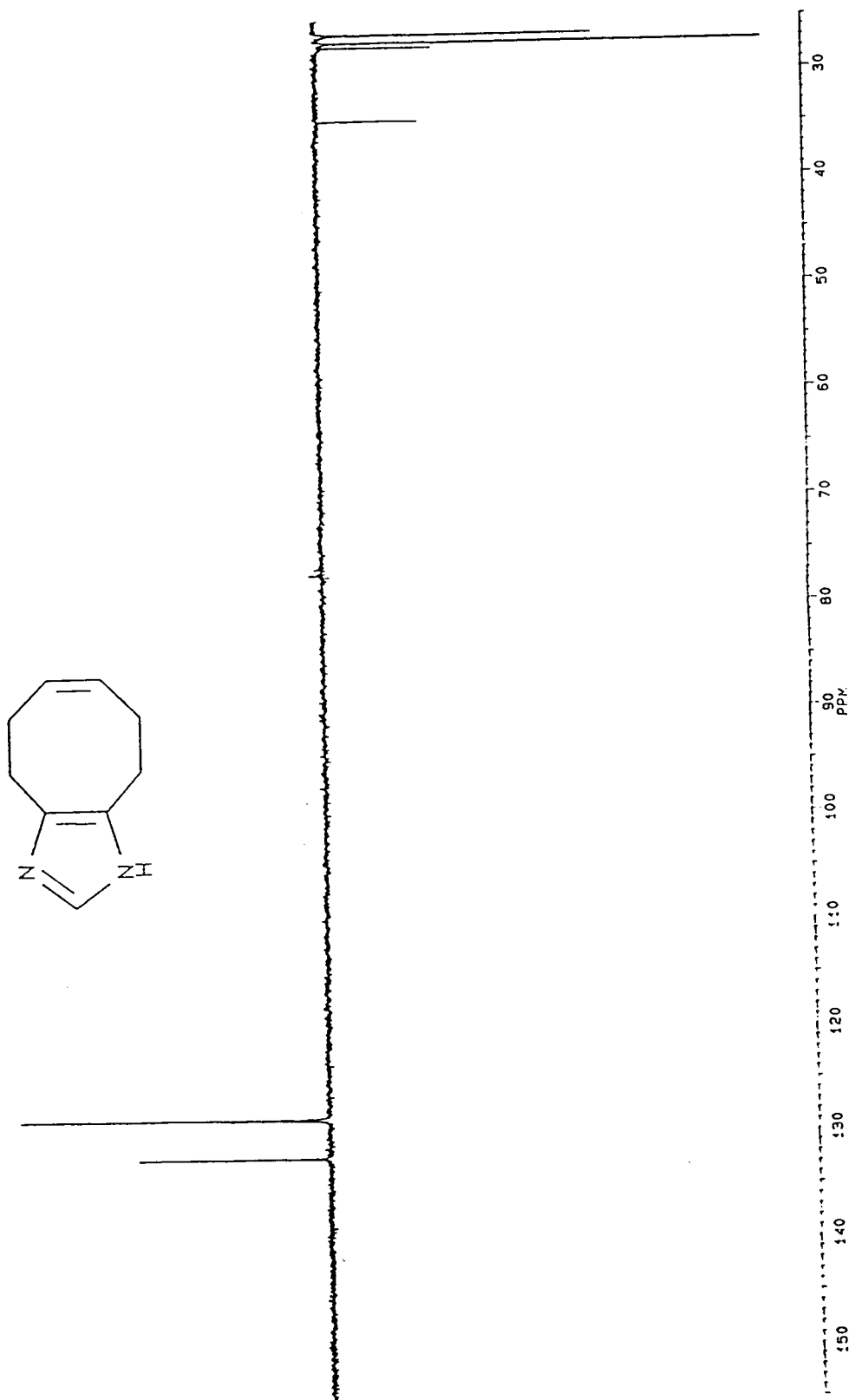
¹³C NMR (CDCl₃, 62.5 MHz) Spectrum of 4,5,6,7,8,9-Hexahydro-1H-imidazo[4,5-a]cyclooctanone (2)



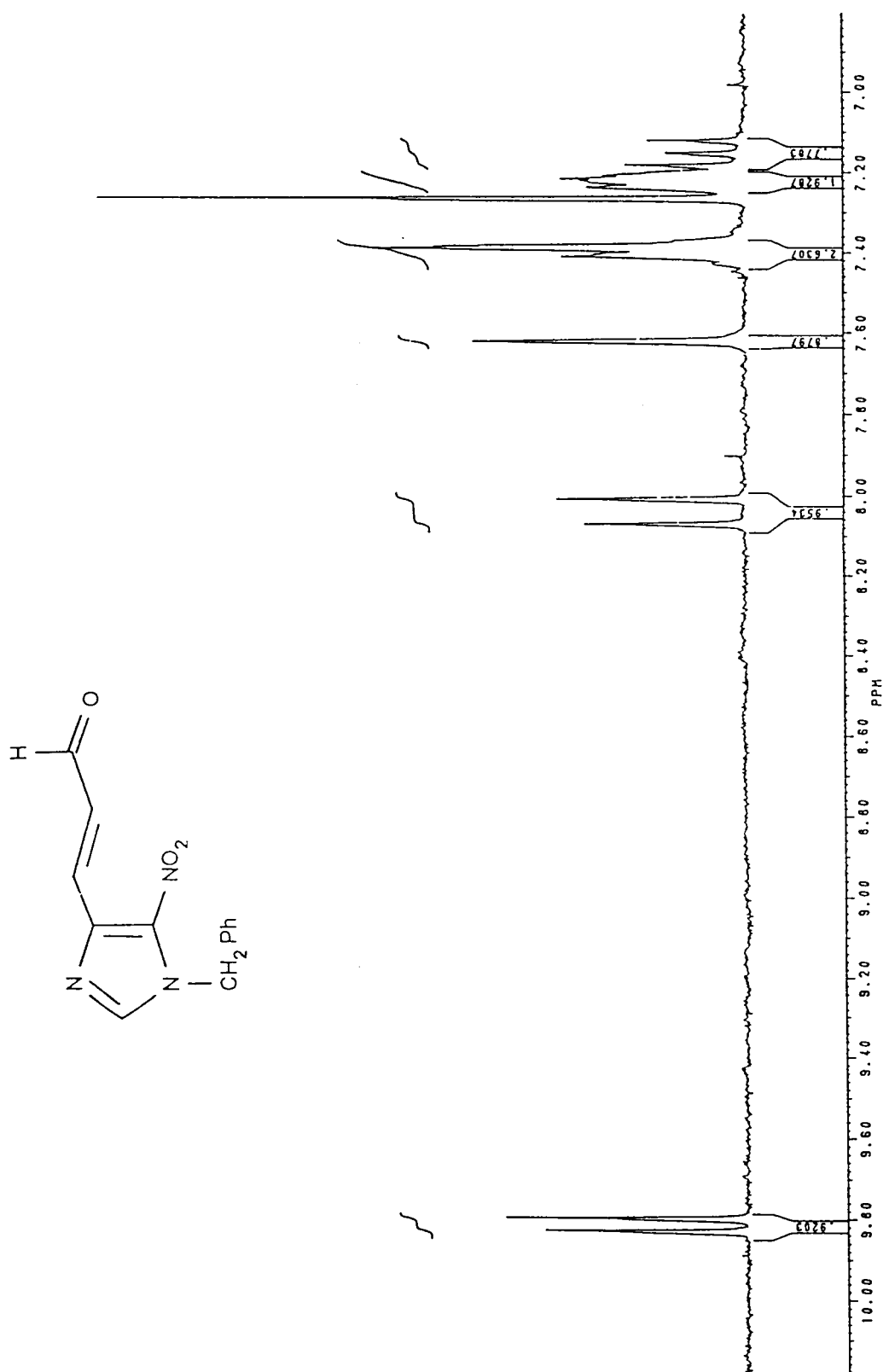
^1H NMR (CDCl_3 , 360 MHz) Spectrum of 4,5,8,9-Tetrahydro-1H-imidazo[4,5-a]cycloocta-6-ene (3)



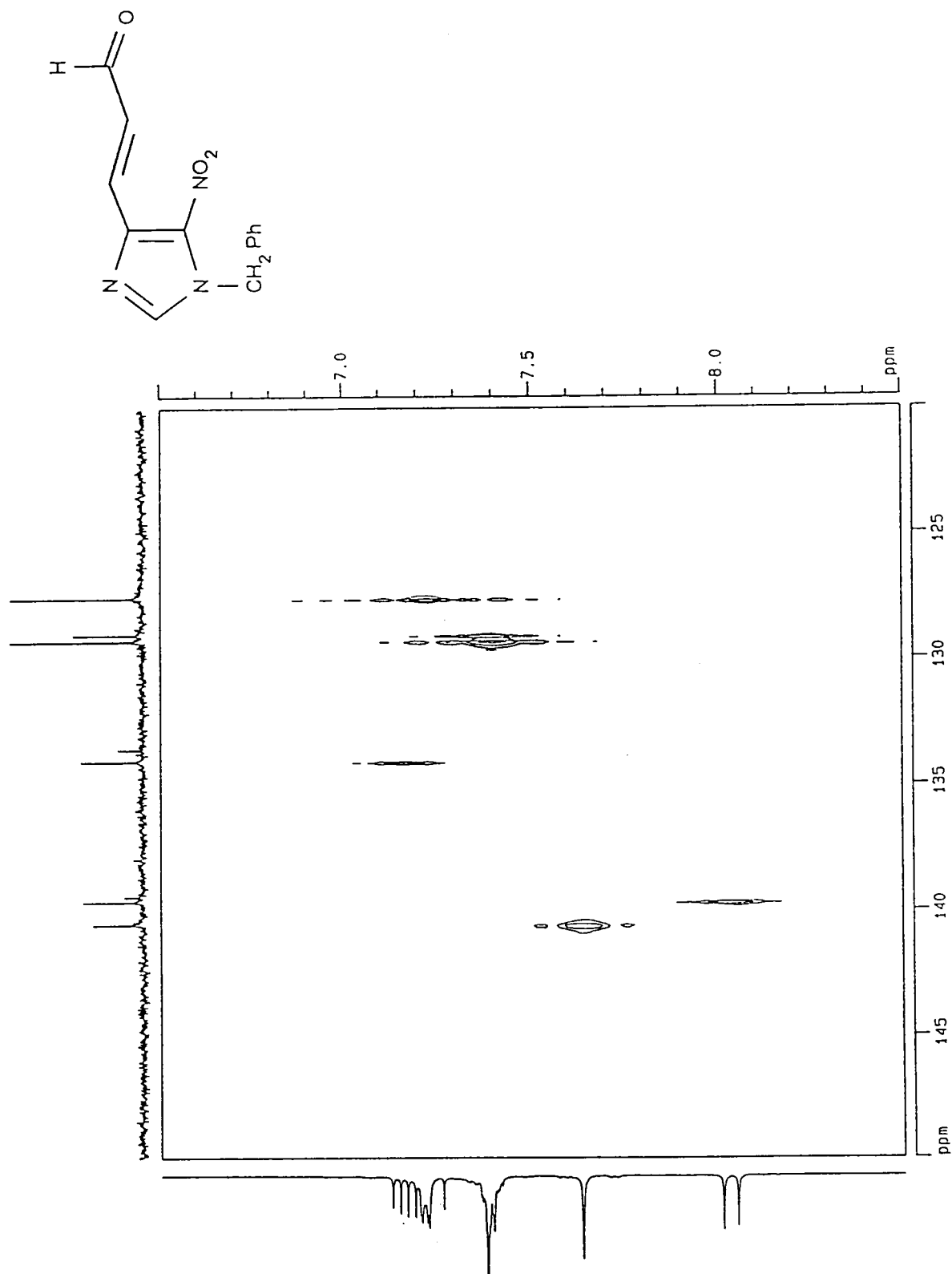
^{13}C NMR (CDCl_3 , 90 MHz) Spectrum of 4,5,8,9-Tetrahydro-1H-imidazo[4,5-a]cycloocta-6-ene (3)



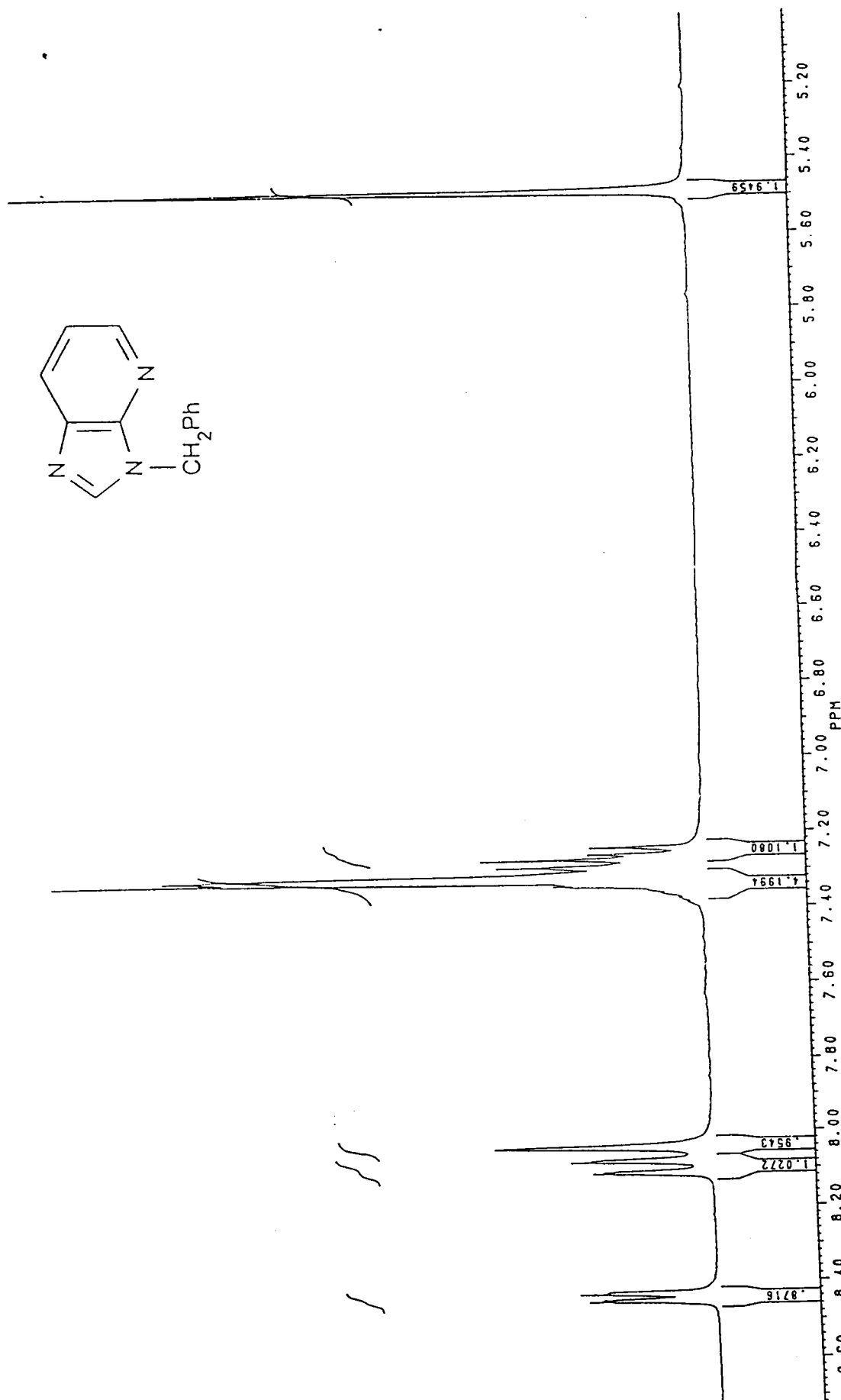
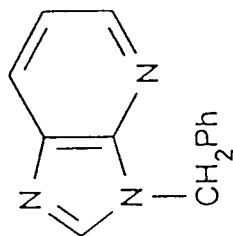
DEPT. 135 (CDCl₃, 360 MHz) Spectrum of 4,5,8,9-Tetrahydro-1H-imidazo[4,5-a]cycloocta-6-ene (3)

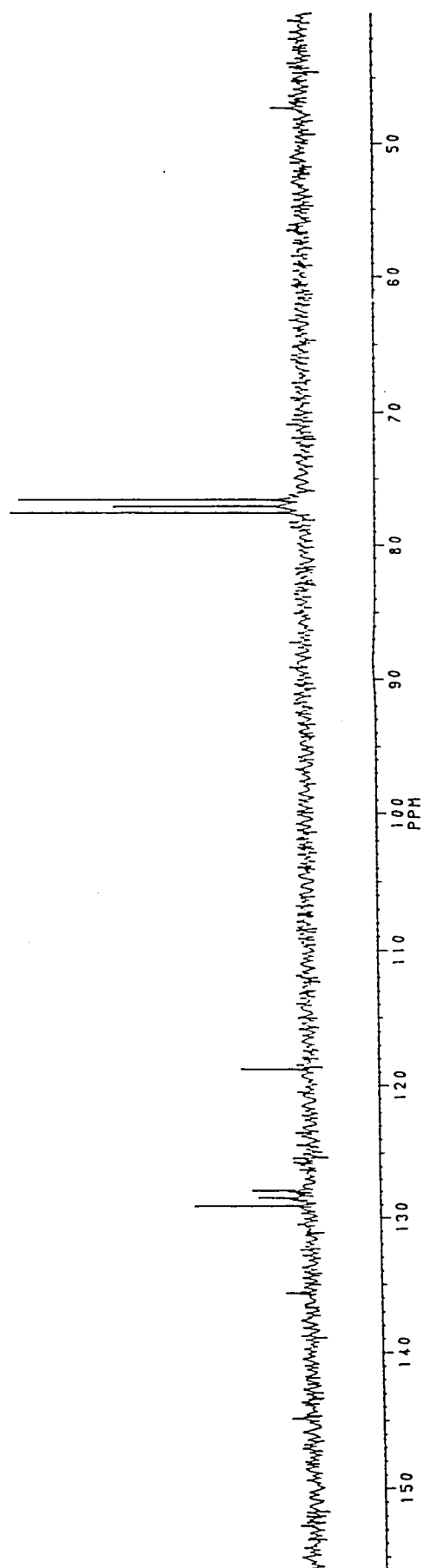
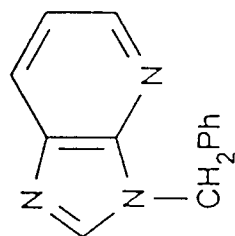


Partial ¹H NMR (CDCl₃, 250 MHz) Spectrum of 3-(1-Benzyl-5-nitro-1H-imidazol-4-yl)prop-2-enal (45)

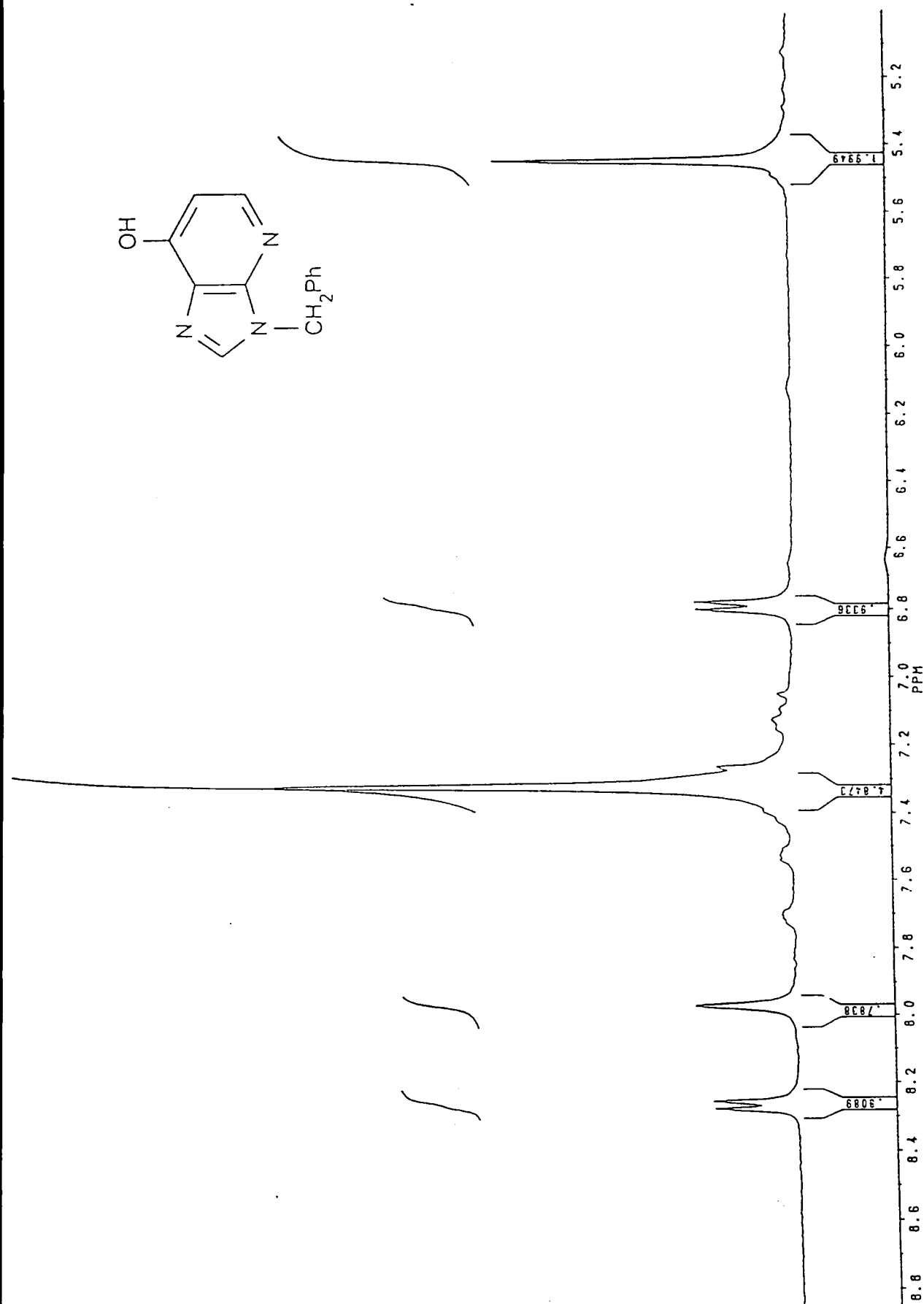
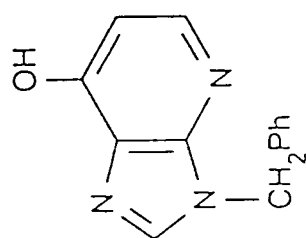


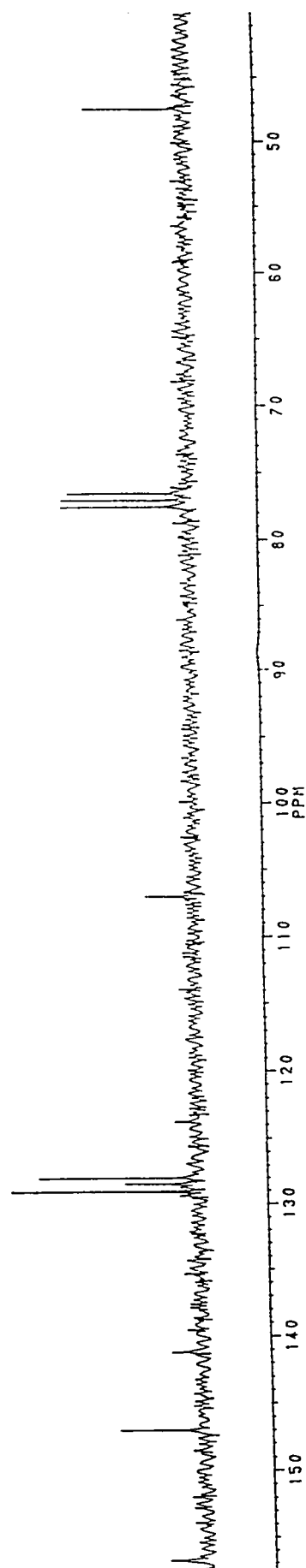
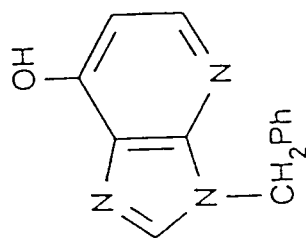
Partial XHCOR (CDCl₃, 400 MHz) Spectrum of 3-(1-Benzyl-5-nitro-1H-imidazol-4-yl)prop-2-enal (45)



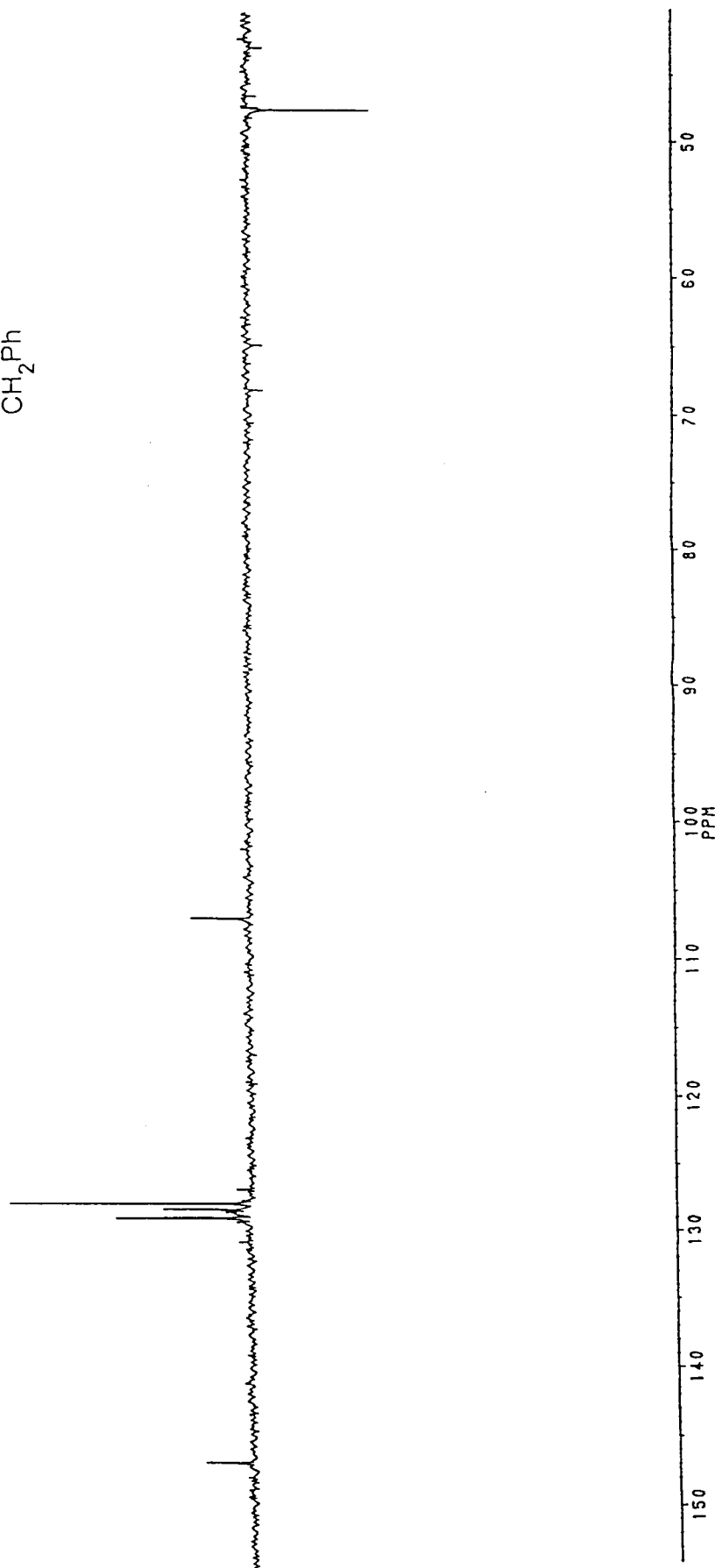
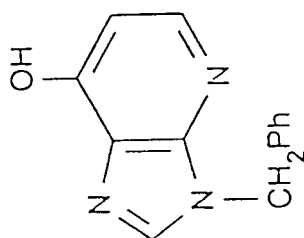


¹³C NMR (CDCl₃, 62.5 MHz) Spectrum of 3-Benzyl-3H-imidazo[4,5-b]pyridine (51).

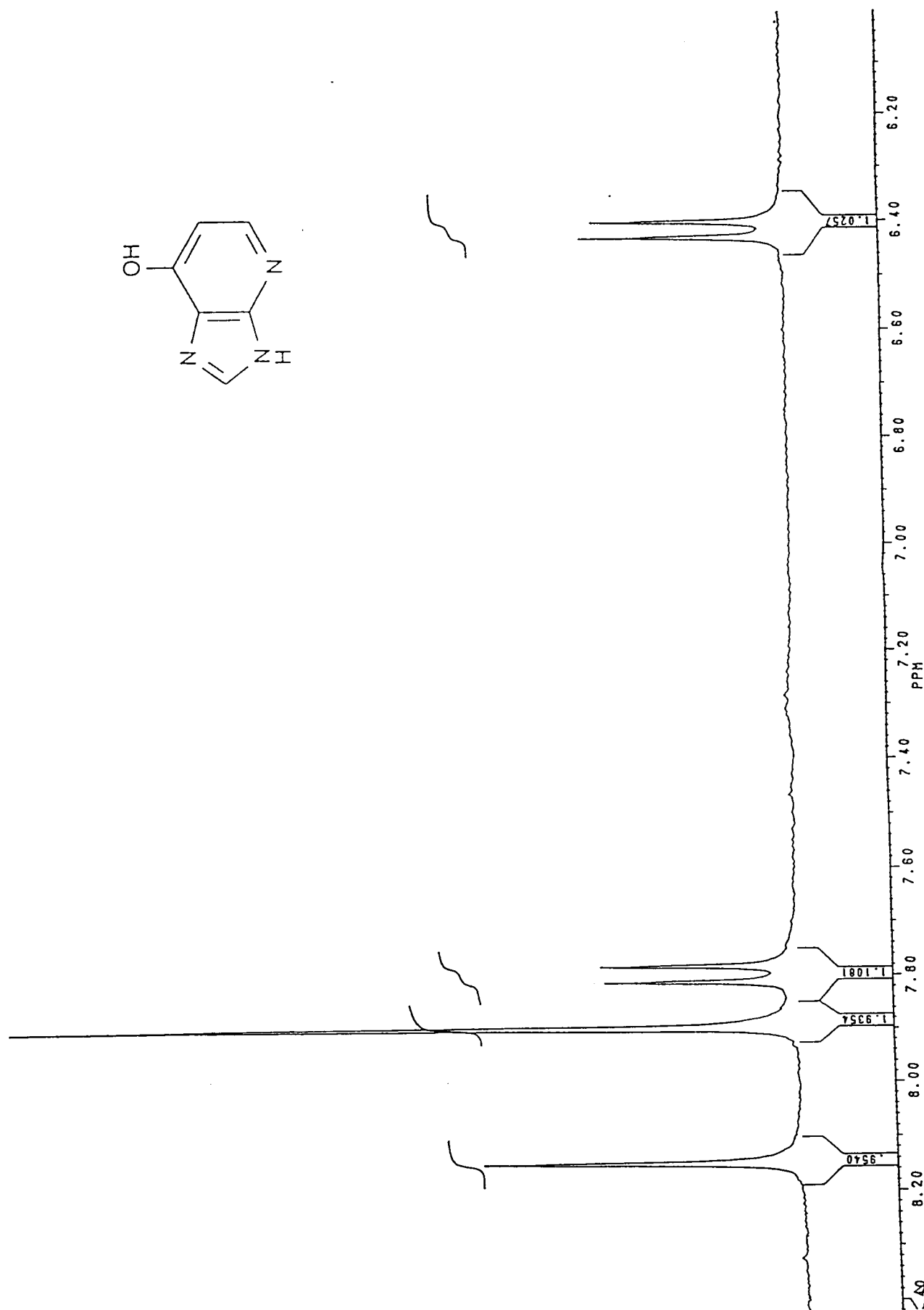
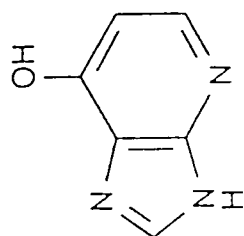


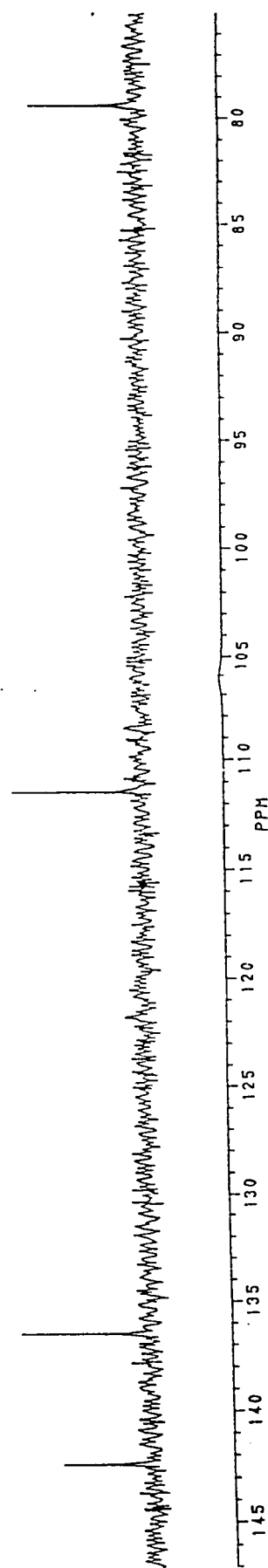
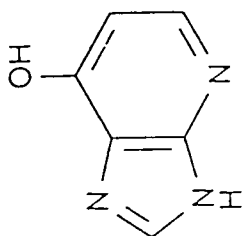


^{13}C NMR (CDCl_3 , 62.5 MHz) Spectrum of 3-Benzyl-3H-imidazo[4,5-b]pyridin-7-ol (55).

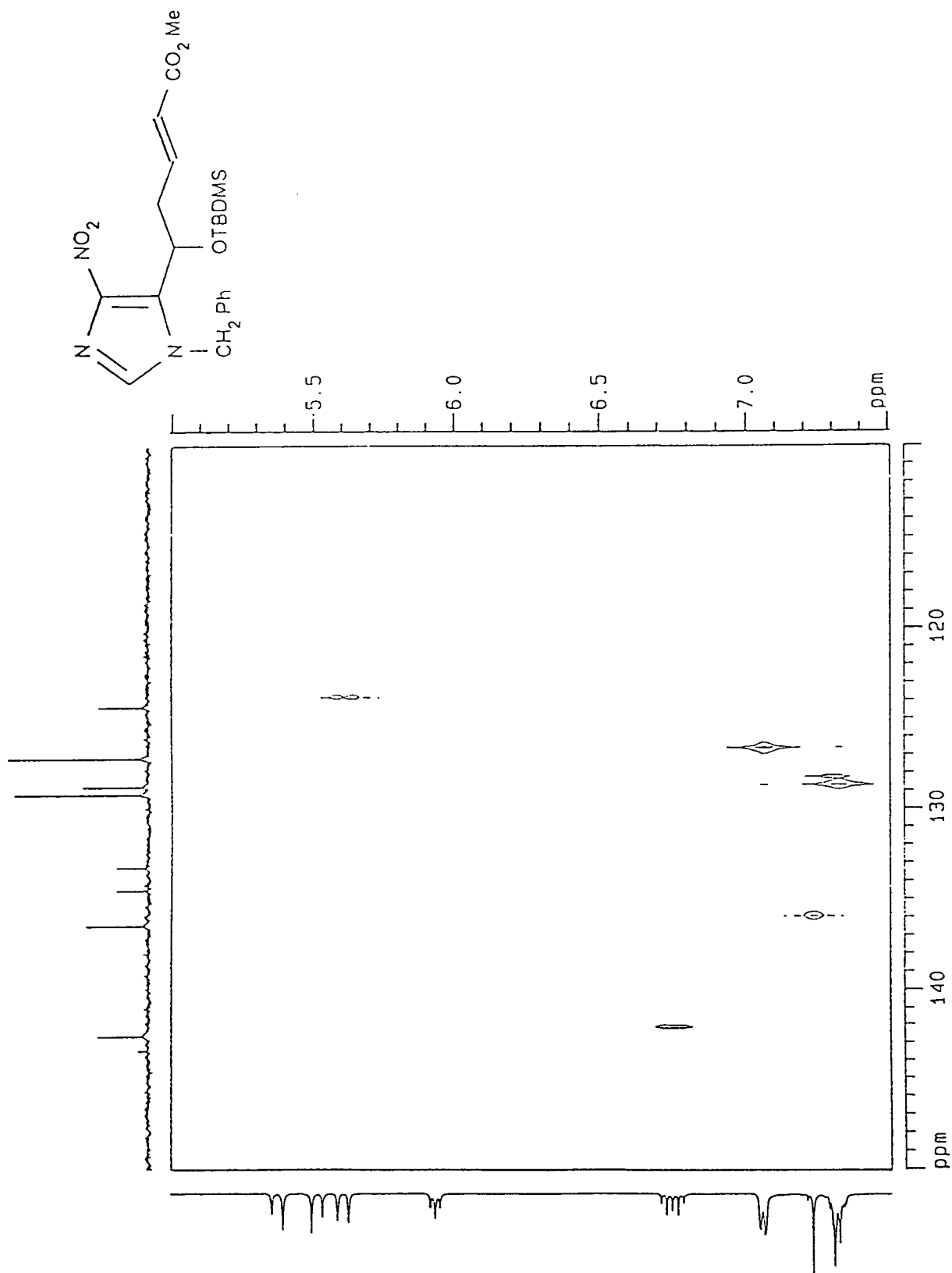


DEPT.135 (CDCl₃, 250 MHz) Spectrum of 3-Benzyl-3H-imidazo[4,5-b]pyridin-7-ol (55).

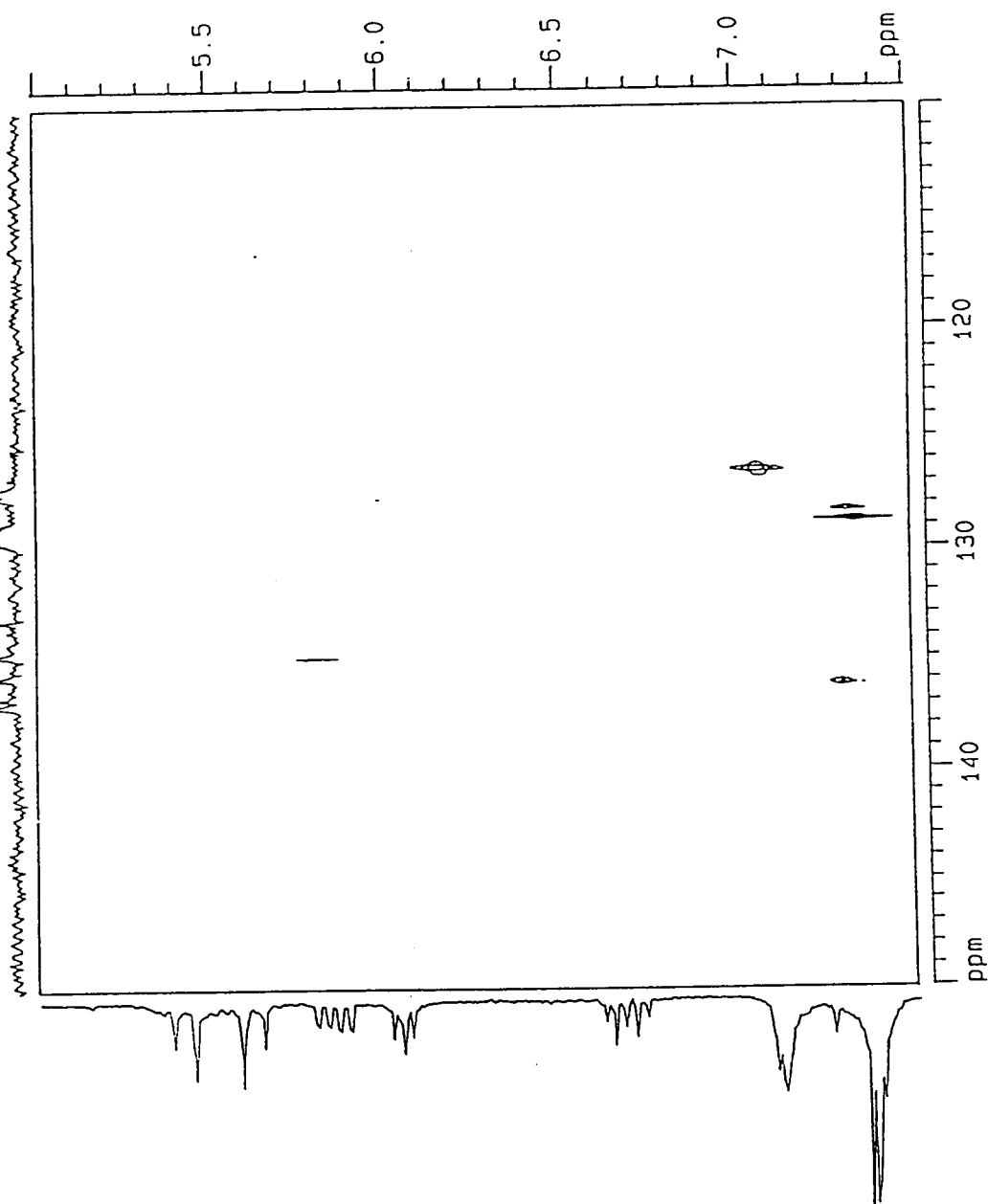
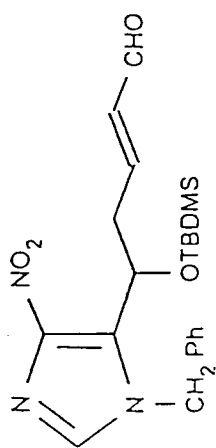




Partial ^{13}C NMR (CD_3OD , 250 MHz) Spectrum of 3H-imidazo[4,5-b]pyridin-7-ol (5).



Partial XHCOR (CDCl₃, 400 MHz) Spectrum of 5-(3-Benzyl-5-nitro-3*H*-imidazol-4-yl)-5-(*tert*-butyldimethylsilyloxy)pent-2-enoic acid, methyl ester (59). 203



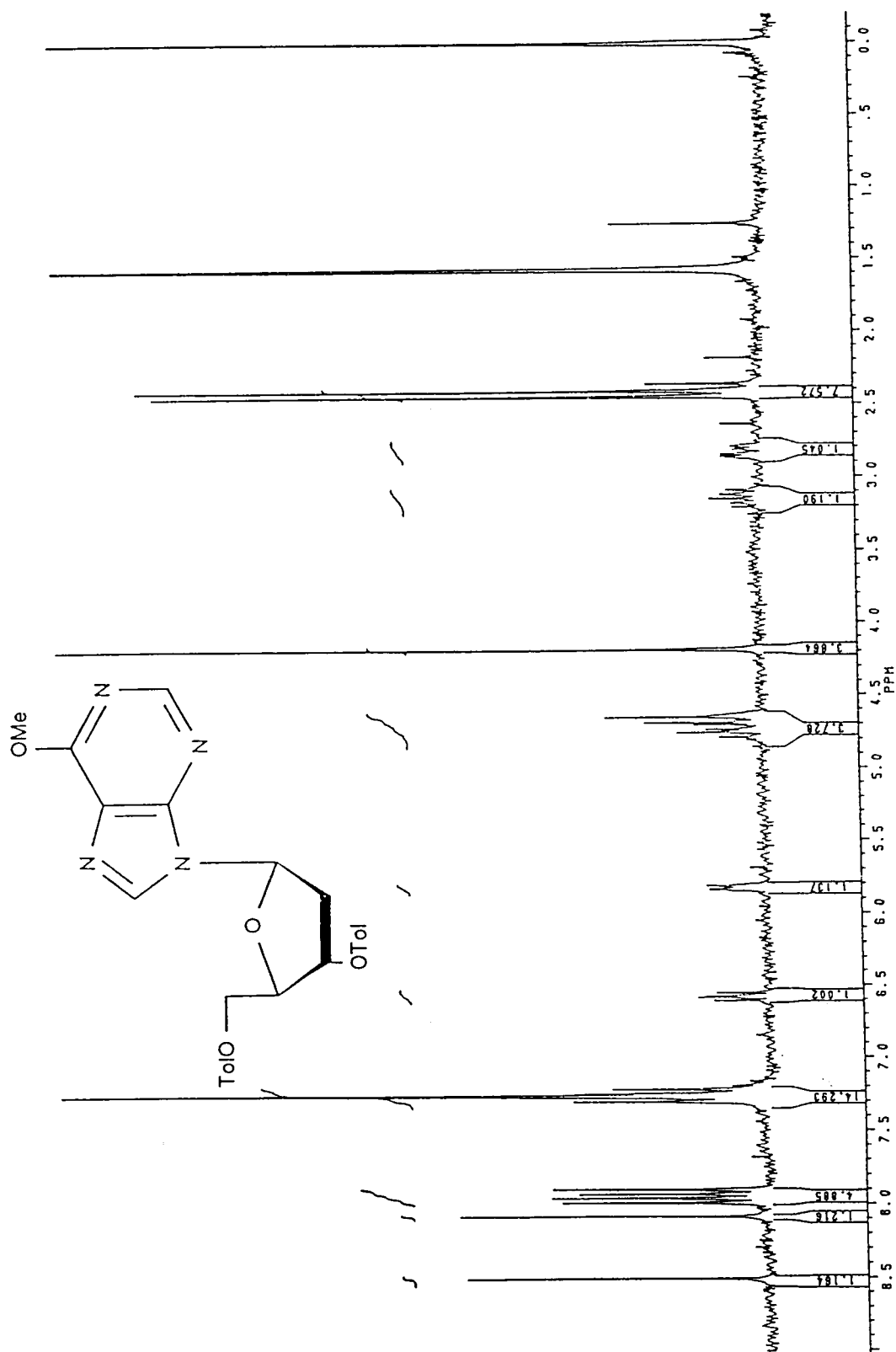
Partial XHCOR (CDCl_3 , 400 MHz) Spectrum of 5-(3-Benzyl-5-nitro-1*H*-imidazol-4-yl)-5-(*tert*-butyldimethylsilyloxy)pent-2-enal

(61).

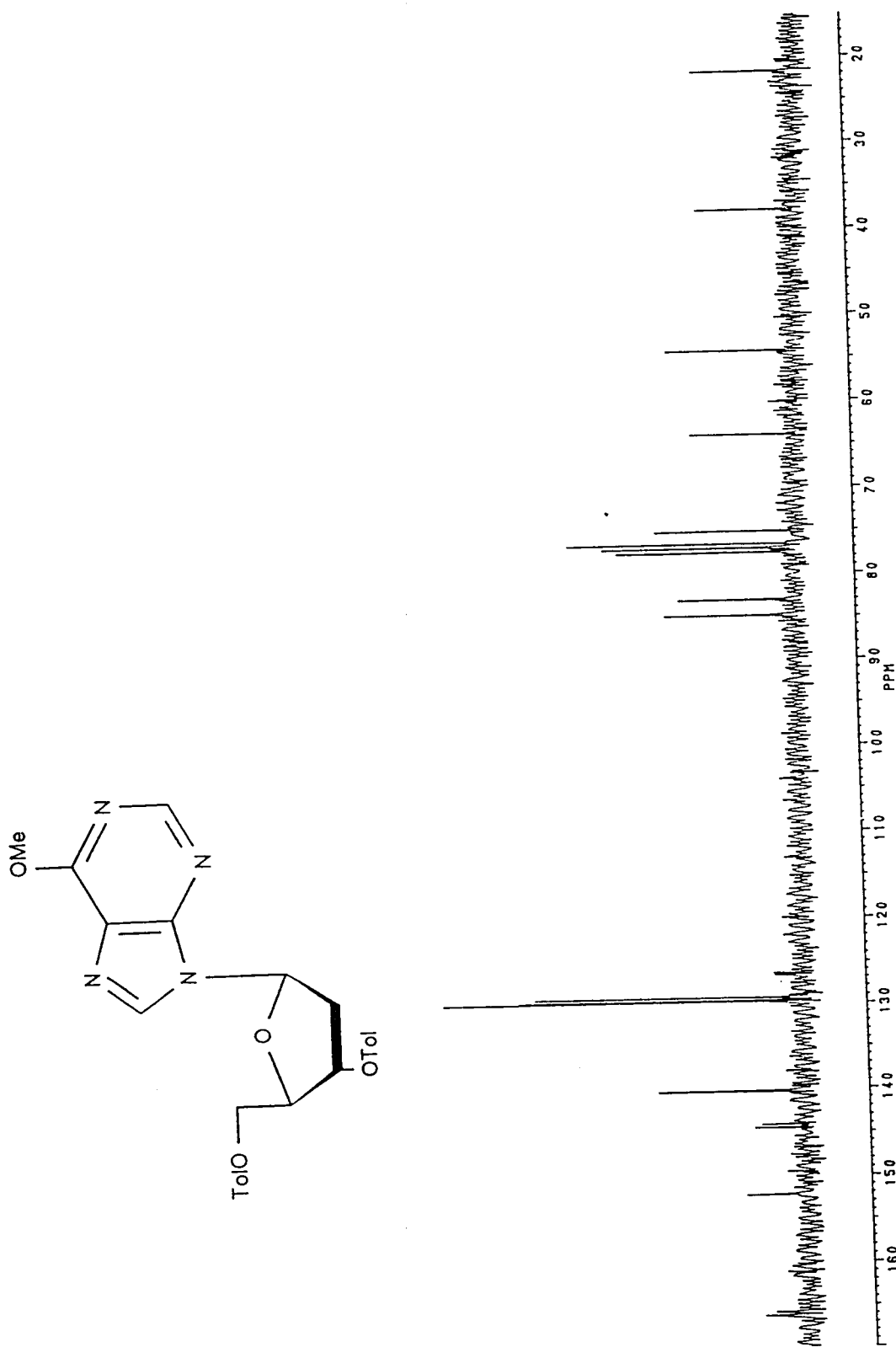
APPENDIX B

^1H , ^{13}C , DEPT. 135 and 2-D NMR

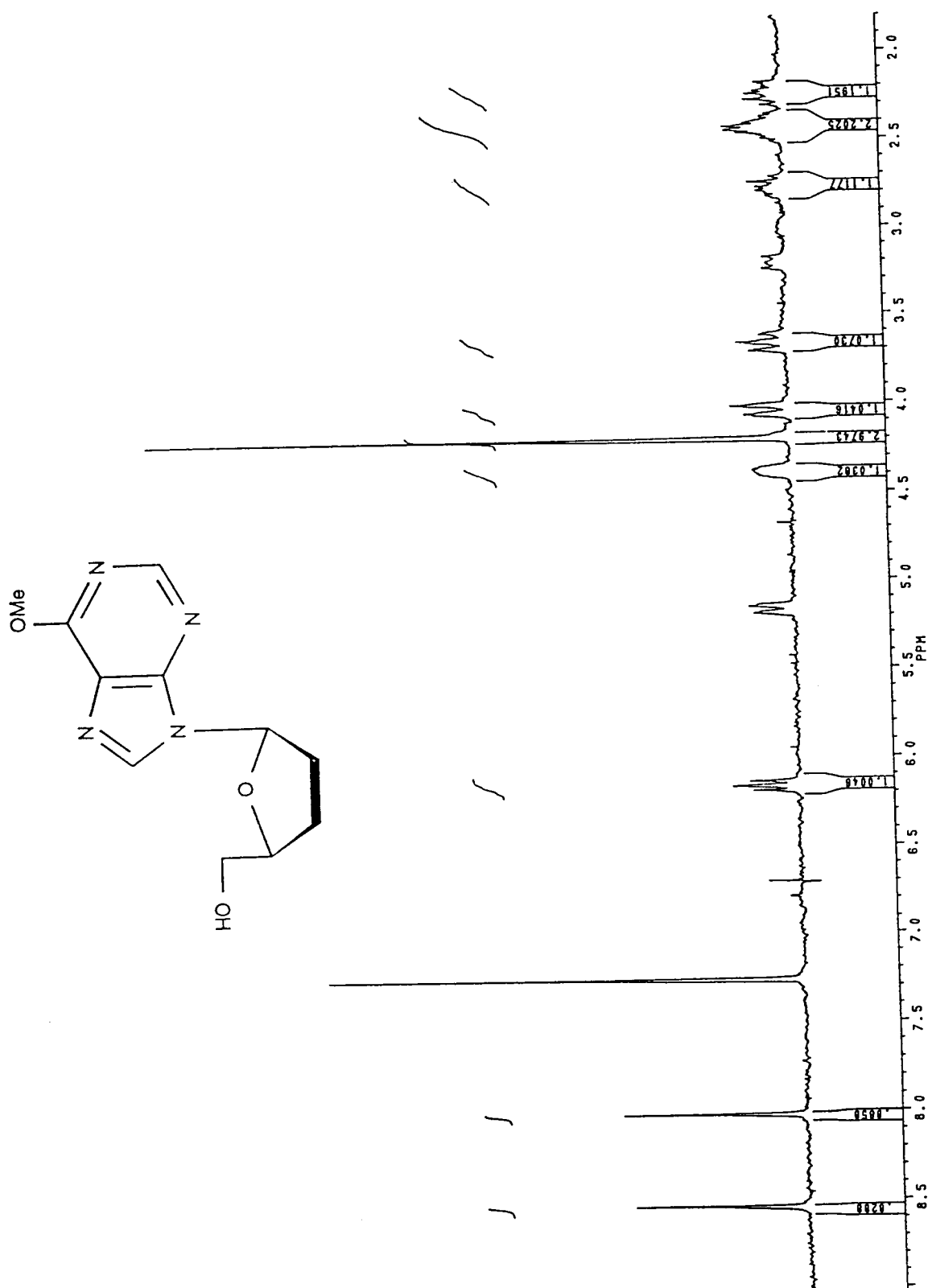
Spectra of Selected Compounds



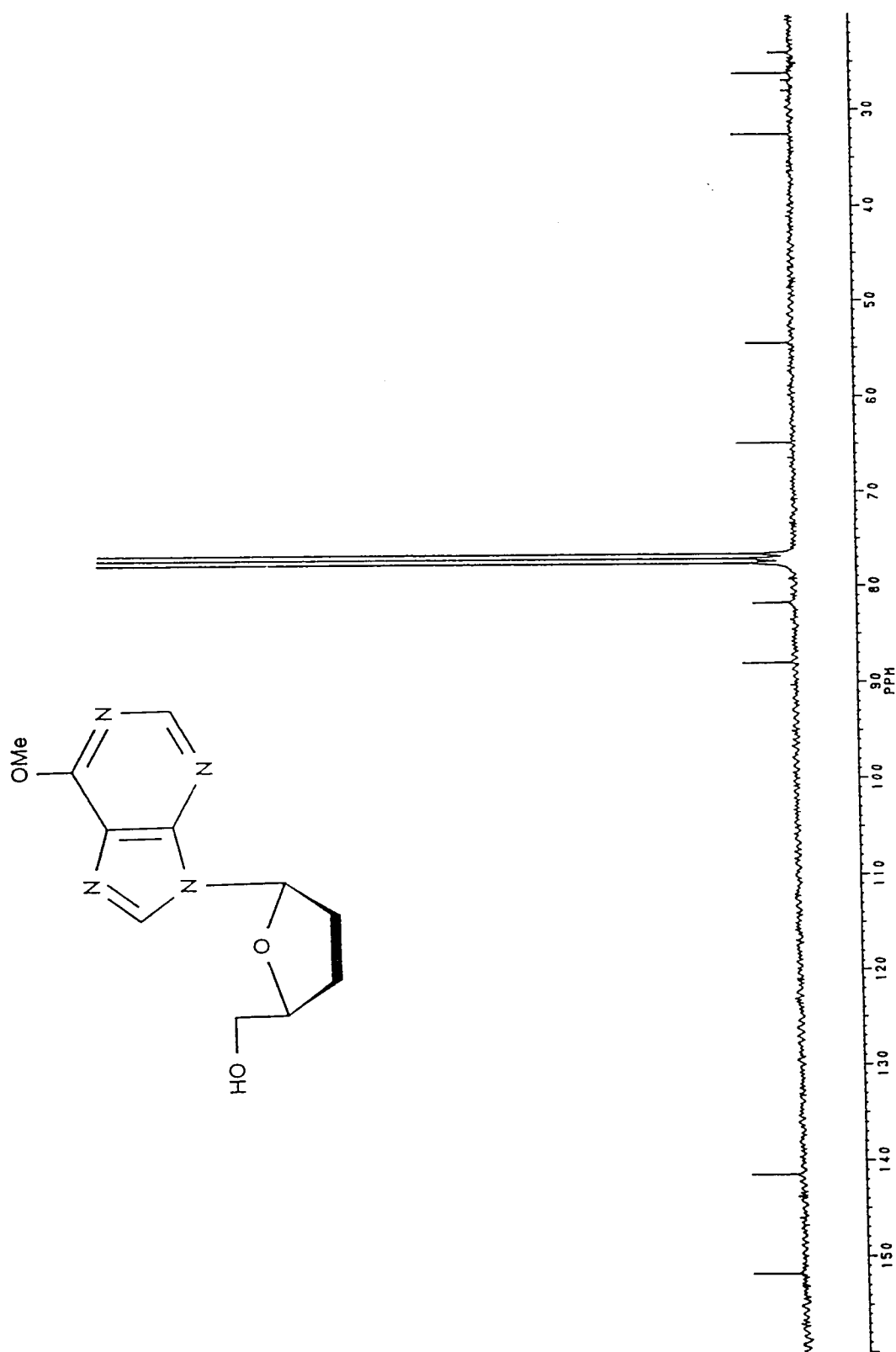
^1H NMR (CDCl_3 , 250 MHz) Spectrum of 9-(2-Deoxy-3,5-di-O-*p*-toluoyl- β -D-erythro-pentofuranosyl)-6-methoxy-9H-purine (6)



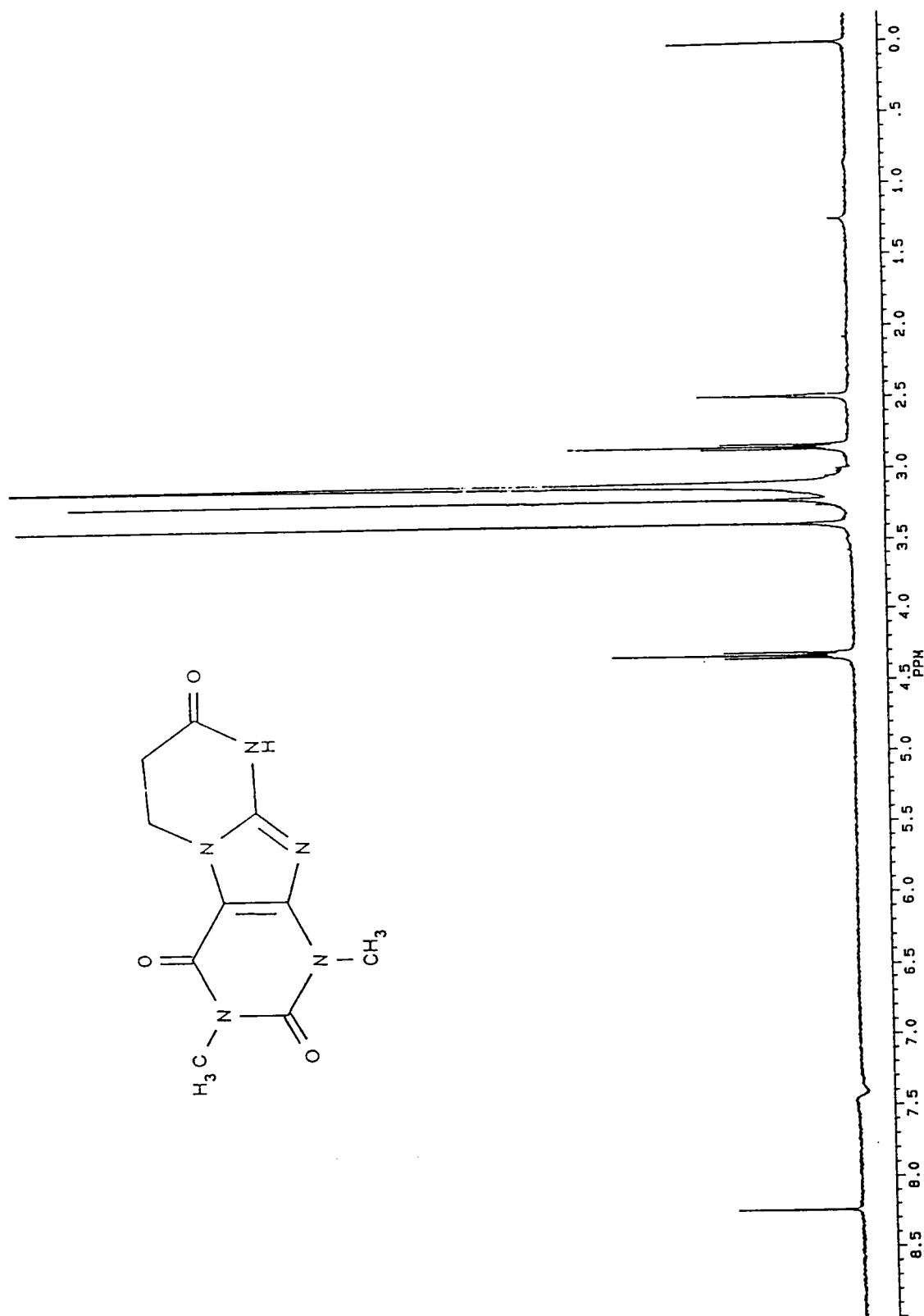
^{13}C NMR (CDCl_3 , 62.5 MHz) Spectrum of 9-(2-Deoxy-3,5-di-O-*p*-toluoxy- β -D-erythro-pentofuranosyl)-6-methoxy-9H-purine (6)



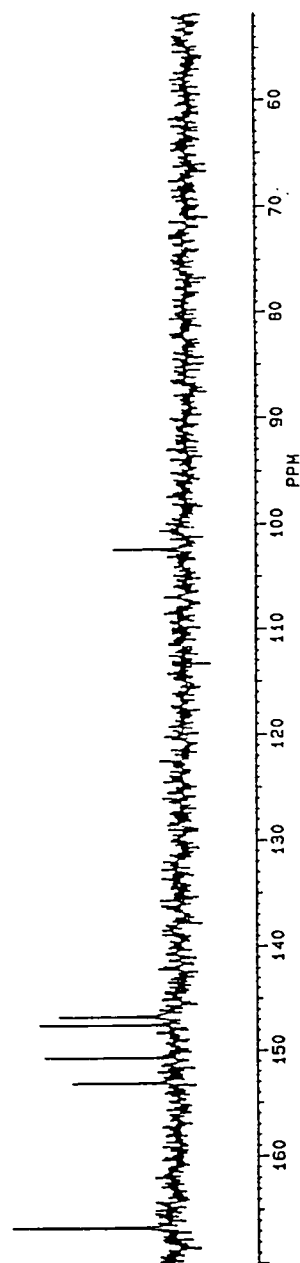
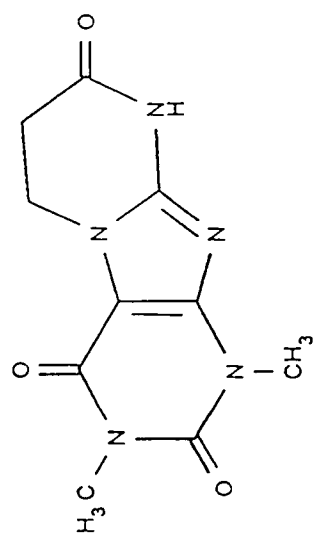
Partial ^1H NMR (CDCl_3 , 250 MHz) Spectrum of 9-(2,3-Dideoxy-β-D-erythro-pentofuranosyl)-6-methoxy-9H-purine (12)



^{13}C NMR (CDCl₃, 62.5 MHz) Spectrum of 9-(2,3-Dideoxy- β -D-erythro-pentofuranosyl)-6-methoxy-9H-purine (12)



¹H NMR (DMSO-*d*₆, 360 MHz) Spectrum of 1,2,3,4,6,7,8,9-Octahydro-1,3-dimethylpyrimido[2,1-f]purine-2,4,8-trione (1)



Partial ^{13}C NMR (DMSO- d_6 , 90MHz) Spectrum of 1,2,3,4,6,7,8,9-Octahydro-1,3-dimethylpyrimido[2,1-f]purine-2,4,8-trione
(1)

VITA

Vivekanand Kamath was born in Mangalore, India, on March 20, 1964. He did his schooling in St. John the Baptist High School, Thana. Thereafter, he received his Bachelor of Science degree from the University of Bombay in 1984 with a major in Chemistry. His keen interest in the applications of Chemistry made him pursue B.Sc (Tech), a three-year integrated course from the University of Bombay, Department of Chemical Technology. After graduating in 1987, he worked as a plant supervisor at Raymonds for a period of one year. In the fall of 1988 he joined the graduate school in the Department of Chemistry at The University of Alabama. In fall of 1989 he joined Dr. Baker's group and in the fall of 1990 he transferred to The University of Tennessee, Knoxville along with the whole group. He received the Doctor of Philosophy degree in December 1994.