Design and Synthesis of 3-Deazaaristeromycin Derivatives

by

Chun Chen

A dissertation submitted to the Graduate Faculty of
Auburn University
in partial fulfillment of the
requirements for the Degree of
Doctor of Philosophy

Auburn, Alabama
December 13, 2010

Copyright 2010 by Chun Chen

Approved by

Stewart W. Schneller, Chair, Professor of Chemistry and Biochemistry
Edward J. Parish, Professor of Chemistry and Biochemistry
Susanne Striegler, Associate Professor of Chemistry and Biochemistry
Evert C. Duin, Associate Professor of Chemistry and Biochemistry

Abstract

Analogs of naturally occurring nucleosides have served as structural models for the design of antitumor, antiviral, and antibacterial agents. The carbocyclic nucleosides aristeromycin and neplanocin A are two examples that show significant broad-spectrum antiviral activity. The significant antiviral properties of these two nucleosides have been attributed to inhibition of AdoHcy hydrolase, which in turn affects viral mRNA capping methylation. However, their clinical potential is limited by toxicity, which is associated with phosphorylation of the primary hydroxyl group at 5′ position. 3-Deazapurine carbocyclic nucleosides (3-deazaneplanocin A and 3-deazaaristeromycin) have been shown to retain antiviral activity with significant reduction of toxicity as a result of their incapability of undergoing phosphorylation. In the search for effective antiviral agents, fluorinated nucleosides and nucleotides, where the fluorine has been introduced into both the base and the sugar moiety, have found use in the treatment of viral infections. The placement of a fluorine atom can have significant effects on a biological molecule due to imparting increased lipophilicity, powerful electronic effects and altered metabolic properties. To further explore new antiviral agents retaining 3-deazaaristeromycin-based activity while reducing undesired toxicity, modification at the C-3′ and C-2′ position have been recognized as important means to promising compounds. The synthesis and biological properties of the 3′-fluoro-3′-deoxy- and 2′-fluoro-2′-deoxy-3-deazaaristeromycin derivatives **1**, **2**, **4** and **5** have been investigated. As a logical

extension of the 3′-deoxy- and 2′-deoxy-3-deazaaristeromycin derivatives **3** and **6** has been identified as important target.

4′-Substituted nucleosides were found to exert potent activity against HIV. In this dissertation, the 4′-methyl-3-deazaaristeromycin (**7**) was sought as an anti-HIV agent and an efficient route into the heretofore unknown 4′-alkylated-3-deazaaristeromycin framework was developed. The bioassays for all compounds will be forthcoming and under study.

Acknowledgments

Table of Contents

List of Tables

List of Figures

List of Schemes

Introduction

Introduction of viruses

A virus is a small infectious agent that can replicate only inside the living cells of organisms. The average virus is about one one-hundredth the size of the average bacterium. Virus particles consist of two or three parts: genes made from either DNA or RNA, long molecules that carry genetic information; a protein coat that protects these genes; and, in some cases, an envelope of lipids that surrounds the protein coat when they are outside a cell. A vast number of viruses cause infectious diseases.[1]

Viral populations do not grow through cell division, because they are acellular; instead, they use the machinery and metabolism of a host cell to produce multiple copies of themselves, and they assemble in the cell.[2] The genetic material within viruses, and the method, by which the materials is replicated, vary between different types of viruses.

Most DNA viruses create copies of their genomes in the cell's nucleus. If the cell has the appropriate receptor on its surface, these viruses enter the cell by fusion with the cell membrane or by endocytosis, by which cells absorb a virus from outside the cell by engulfing them with their cell membranes. Most DNA viruses are entirely dependent on the host cell's DNA and RNA synthesising machinery, and RNA processing machinery. The viral genome must cross the cell's nuclear membrane to access this machinery.

RNA viruses are unique because their genetic information is encoded in RNA. Replication usually takes place in the cytoplasm. RNA viruses can be classified into

about four different groups according to their modes of replication. The polarity of the RNA is the key point to determine the replicative mechanism whether the genetic material is single-stranded or double stranded. RNA viruses use their own RNA replicase enzymes to create copies of their genomes.

A reverse transcribing virus (retrovirus) is an RNA virus that is replicated in a host cell via the enzyme reverse transcriptase to produce DNA from its RNA genome. The order of steps from a retroviral gene to a retroviral protein is: RNA → DNA → RNA → protein. Retrovirus containing RNA genomes use a DNA intermediate to replicate. They use the reverse transcriptase enzyme to carry out the nucleic acid conversion. Retroviruses often integrate the DNA produced by reverse transcription into the host genome. They are susceptible to antiviral drugs that inhibit the reverse transcriptase enzyme, e.g. zidovudine[3] and lamivudine.[4] An example of a retrovirus is the human immunodeficiency virus (HIV).[5,6]

Viruses and human diseases

Most viral infections eventually result in the death of the host cell, which is caused by cessation of its normal activities because of suppression by virus specific proteins. [5,7] Some viruses cause no apparent changes to the infected cell, in which the virus is latent and inactive. However, some of such viruses are the established causes of cancer or other diseases.[8]

Examples of common human diseases caused by viruses include the common cold,[9] influenza,[10] chickenpox[11] and cold sores.[12] Some serious diseases, which caused epidemics and pandemics in history, such as Ebola,[13] acquired immune deficiency

2

syndrome (AIDS),[14] avian influenza[15] and severe acute respiratory syndrome (SARS)[16] are also caused by viruses. In addition, some viruses can result in life-long or chronic infections, where the viruses keep on replicating in the body despite the host's immune system defense. For example, hepatitis B virus (HBV) and hepatitis C virus (HCV) are common infections. People chronically infected serve as reservoirs of infectious virus. These viruses can transmitted through high-risk intimate interaction between infected and healthy people.

The ability of viruses to cause devastating epidemics has led to the concern that viruses could be utilized as biological weapons.[17-19] Thus, an anti-biological terrorism plan is very important and necessary to protect society from bioterrorism.

Prevention and treatment

There are two most effective medical approaches to defend against viral infections: (1) vaccination is an effective and comparably inexpensive way of combating infections by viruses and (2) antiviral drugs that interfere with the viral replication.

Vaccines are limited by some disadvantages. First, some vaccines towards certain viruses are not available but are urgently needed, for example, for HIV, the hepatitis C virus (HCV),[20] and the Epstein-Barr virus (EBV).[21] Antiviral drugs are currently the only way to treat those viral infections. Secondly, some vaccines have some undesirable side-effects, such as the hepatitis B virus (HBV) vaccine.[22] Thirdly, a vaccine may not be effective enough to prevent an epidemic viral spread because of rapid virus mutability, such as the avian flu in 1997s.[23] Finally, a vaccine is of little use for people post-infection.[24-28]

With these limitations in mind, more effective antiviral drugs are urgently needed because the threat of a viral epidemic or even a pandemic will confront society without warning.

Nucleoside analogs as antiviral agents

Antiviral agents are often nucleoside analogs, which interfere with viral replication. Nucleosides are glycosylamines consisting of a heterocyclic nucleobase to a ribose or deoxyribose ring. Examples of natural nucleosides include the pyrimidine, cytidine, uridine, thymidine, and, purine, guanosine, adenosine and inosine (Figure 1).

Purine   Pyrimidine

Cytidine (C)   Uridine (U)   Thymidine (T)

Guanosine (G)   Adenosine (A)   Inosine (I)
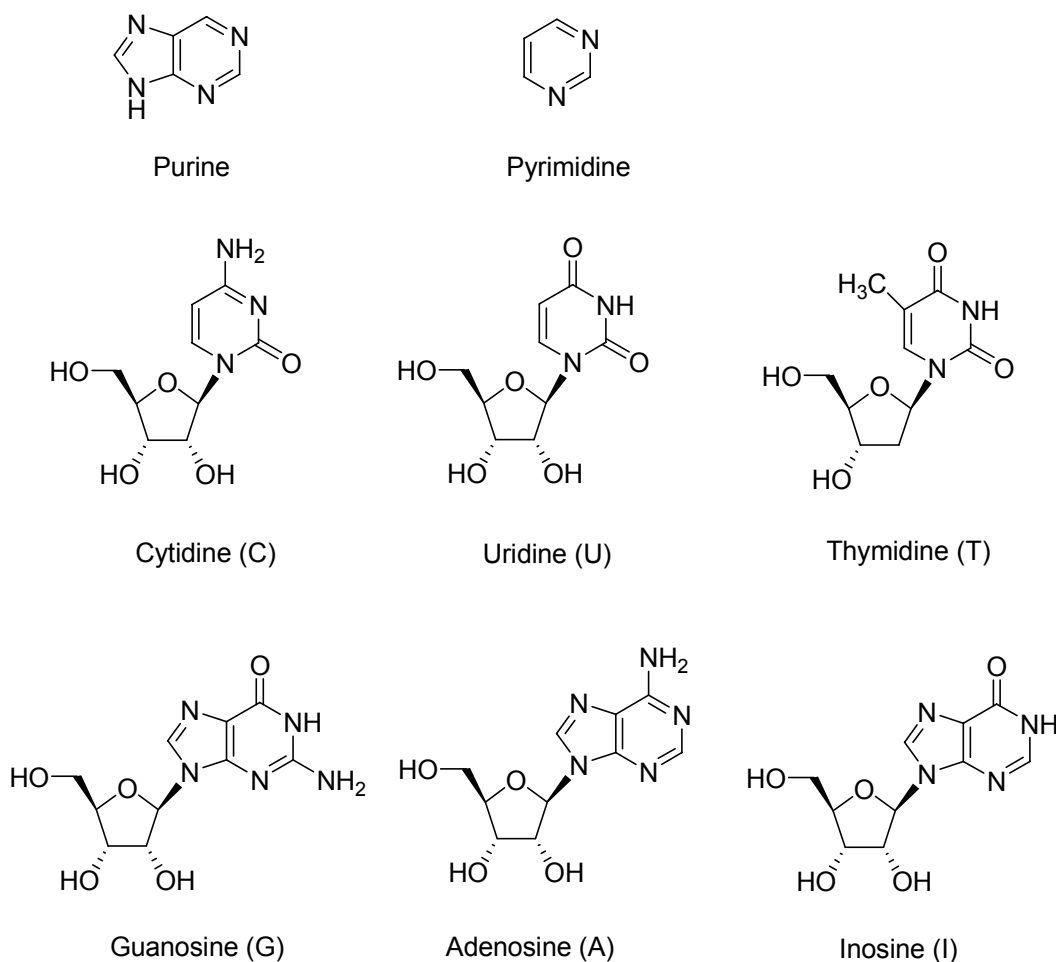
Figure 1. Naturally occurring nucleosides

The naturally occurring nucleosides are the basic building blocks of nucleic acids. Nucleosides can be phosphorylated by specific kinases to generate nucleotides that are the molecular building-blocks of DNA and RNA. Nucleic acids are polymeric macromolecules made from nucleotide monomers. In deoxyribonucleic acid (DNA), the purine bases are adenine and guanine and the pyrimidines are thymine and cytosine. Ribonucleic acid (RNA) uses uracil in place of thymine.[29,30] It is well known that DNA contains the genetic instructions used in the development and functioning of all organisms and some viruses. RNA is transcribed from DNA and is central to protein synthesis, which is very important to replicate genomes of most viruses. Natural nucleosides are not only serving as building blocks of nucleic acids, but have important roles in metabolism. For instance, adenosine is necessary for essential biological processes as a key component of ATP, [31] coenzyme A, nicotinamide adenine dinucleotide phosphate ($NADP^+$), flavin adenine dinucleotide (FAD) and nicotinamide dinucleotide (NAD^+) (Figure 2). Consequently, structural modifications within either the heterocyclic nucleobase part or sugar part will lead to diverse biological outcomes.[32-35]
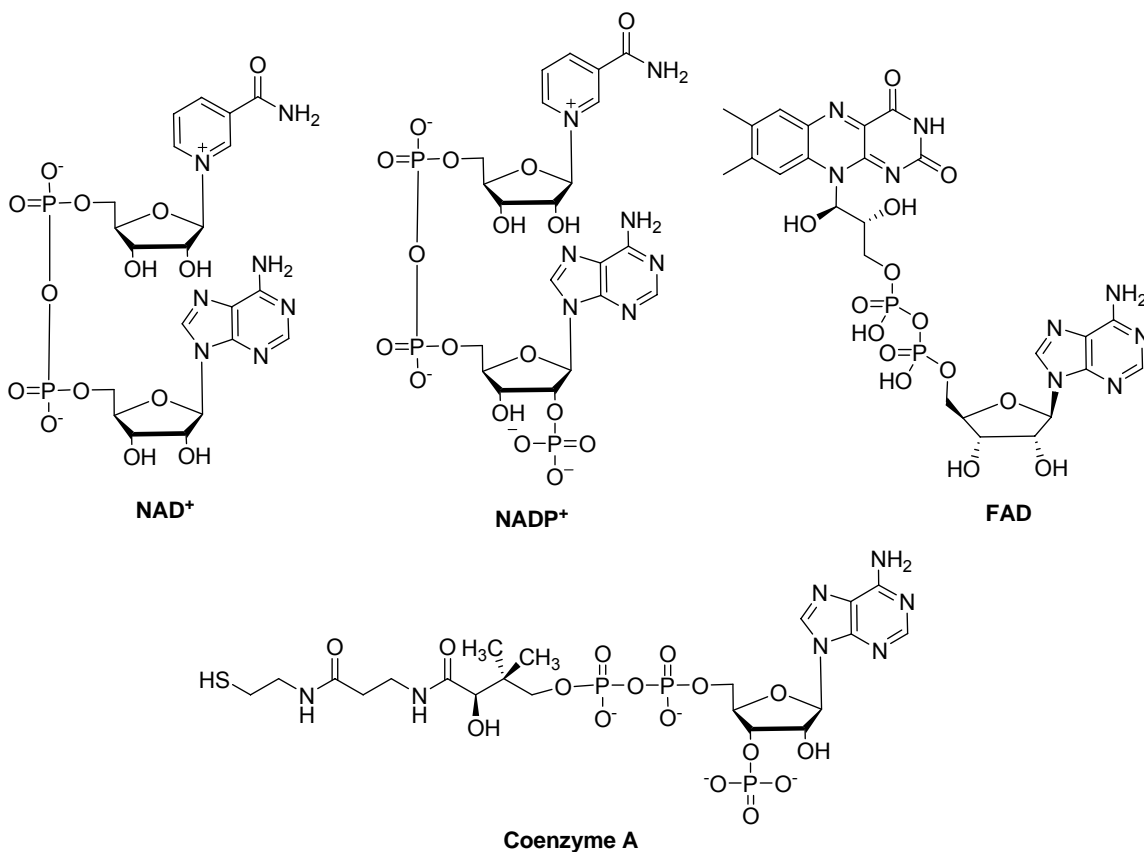
Figure 2. Examples of coenzymes

Traditional nucleoside derivatives

Nucleoside analogs have antiviral activities because they are fake DNA building blocks, which viruses mistakenly incorporate into their genomes during replication. The life-cycle of the virus is halted because the newly synthesised DNA is inactive.

Natural nucleosides all contain D-ribose or 2′-deoxy-D-ribose as their sugar moiety and either adenine, guanine, cytosine, uracil or thymine as their heterocyclic base. Two major strategies exist to discover new therapeutic nucleosides based on naturally occurring nucleosides that have potential antiviral activities. One strategy is modification of the sugar moiety and the second is to alter the heterocyclic base.[36,37]

Nucleosides have been prominent analogs in antiviral drug discovery. It is reported that of the thirty compounds currently marketed in the United States for treatment of viral infections, fifteen are nucleosides analogs.[38] Since the 5-iodo-2′-deoxyuridine (Figure 3) was found to have anti-herpetic activity in 1950s,[39] additional analogs of the natural nucleosides have served as structure models in the design of antiviral agents. Many nucleoside derivatives have been synthesized and found to have antiviral activities; some have been approved by the FDA as antiviral drugs. In this regard, there are clinically used antiviral drugs for treating HCV, varicella zoster virus (VZV), herpes simplex virus (HSV, acyclovir[40] and ganciclovir[41]) and HIV (Figure 3).[42]

5-Iodo-2'-deoxyuridine
(against HSV)

Didanosine
(against HIV)

Emtricitabine
(against HIV)

Trifluridine
(against HSV)

Vidarabine
(against HSV and VZV)

Ribavirin
(against HCV)
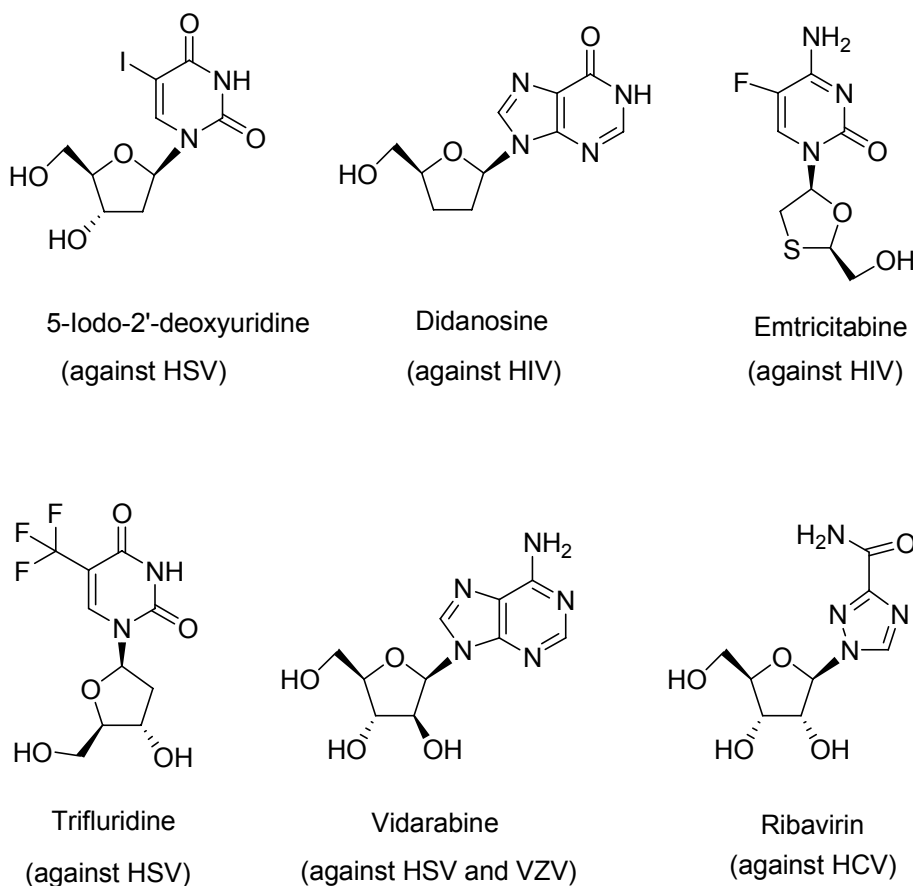
Figure 3. Examples of antiviral nucleosides

7

Didanosine and Emtricitabine are both nucleoside analog reverse transcriptase inhibitor (RTIs) and are effective against HIV infection in adult and children. Emtricitabine is also marketed in a fixed-dose combination with tenofovir. Trifluridine is an anti-herpesvirus antiviral drug, which is used primarily for the eye. Vidarabine is effective against the HSV and varicella zoster viruses (VZV). Ribavirin is an antiviral drug indicated for severe human respiratory syncytial virus (RSV)[43] infection, hepatitis C, and orthopox viruses[42,44].

The other approved nucleosides analogs as antiviral agents against HIV include: 3′-azido-2′,3′-dideoxythemidine (AZT); 2′,3′-dideoxycytidine (ddC); 2′,3′-didehydro-thymidine (d4T); (-)-β-L-3′-thia-2′,3′-dideoxycytidine (3TC); 2-amino-6-cyclopropyl-aminopurin-9-yl-2-cyclopentene (ABC).[42]

Antiviral activity via inhibition of *S*-adenosylhomocysteine hydrolase

A common characteristic of antiviral nucleosides derivatives is that they are potent product inhibitors of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase. The replication of viruses involves the synthesis of viral messenger RNA (mRNA) for the translational production of viral proteins that are required for the assembly of the new virions. Maturation of mRNA requires methylation of its 5′-terminus to provide a "cap" structure. This is necessary for viral protein translation and replication.

The starting point is the unaltered 5′ end of an RNA molecule. This features a final nucleotide followed by three phosphate groups attached to the primary hydroxyl group of 5′ carbon as following: (1) one of the terminal phosphate groups is removed (by a phosphatase), leaving two terminal phosphates; (2) GTP is added to the terminal

phosphates (by a guanylyl transferase), losing two phosphate groups (from the GTP) in the process. This process produces the 5′ to 5′ triphosphate linkage; (3) the 7-Nitrogen of guanine is methylated by a methyl transferase. The methylation leading to a fully functional mRNA is catalyzed by N-7 methyltransferases and nucleoside 2′-methyltransferases, which use AdoMet as the cofactor.[45]

1) $pppN(pN)_n \rightarrow ppN(pN)_n + Pi$

2) $ppN(pN)_n + pppG \rightarrow G(5')pppN(pN)_n + PPi$

3) $G(5')pppN(pN)_n + Adomet \rightarrow \mathbf{m}^7 G(5')pppN(pN)_n + AdoHcy$

The mRNA methylated 5′-cap has 4 main functions for its successful translation: (1) regulation of nuclear export; (2) prevention of degradation by ribonucleases and phosphatases; (3) mRNA splicing to ribosome; and (4) the initiation of translation of the viral mRNA.[46,47] Therefore, preventing the 5′-capping process will definitely stop the viruses from reproducing.

The 5′-capped viral mRNA (Figure 4) consists of a N^7-methylguanosine residue linked at its 5′-hydroxy group to the 5′-end of the mRNA strand by an unusual 5′-5′ triphosphate bridge. Further modification includes methylation of the 2′-hydroxyl group of penultimate adenine nucleosides.
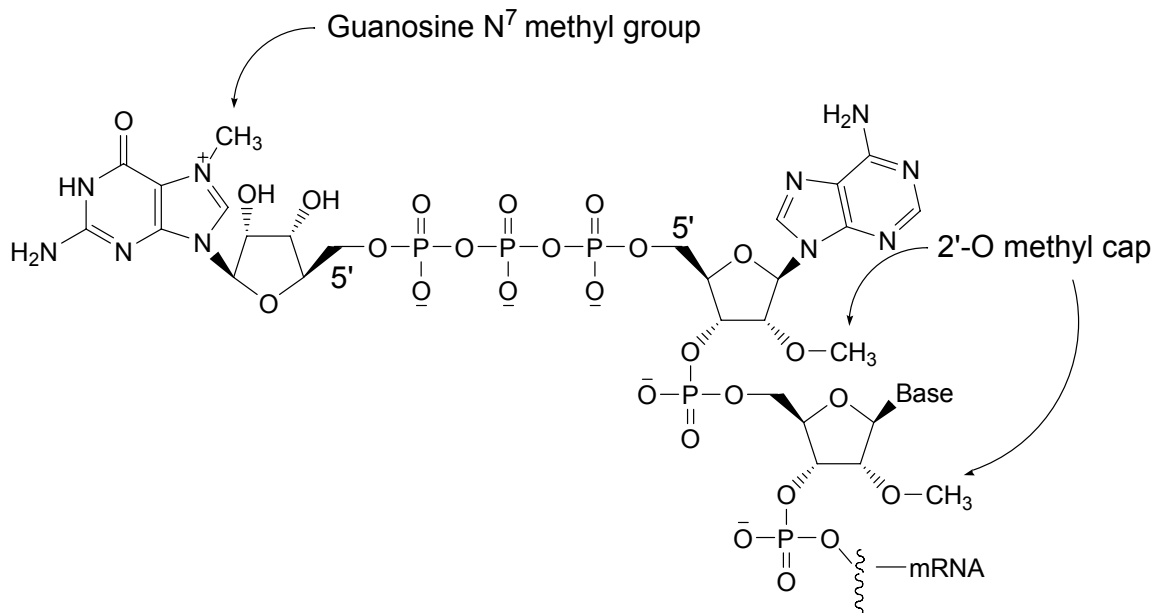
Figure 4. Structure of mRNA 5′-terminal cap

S-adenosylmethionine (AdoMet) is required as the methyl donor for both the sugar and base methylations in the capping of mRNA.[48,49] *S*-adenosylmethionine (AdoMet) is one of the most versatile co-factors in bio-methyl transfer. The positive sulfur center in AdoMet renders the attached methyl as a susceptible donor to bio-nucleophiles, for example, -OH, -NH, -SH, and doubles bonds. More than 40 metabolic reactions involve the transfer of a methyl group from AdoMet to various substrates. Acceptors include nucleic acids, proteins, and lipids. In this instance, the AdoMet *S*-methyl group is transferred in the capping process. In Scheme1, AdoMet is converted to *S*-adenosyl-homocysteine (AdoHcy).
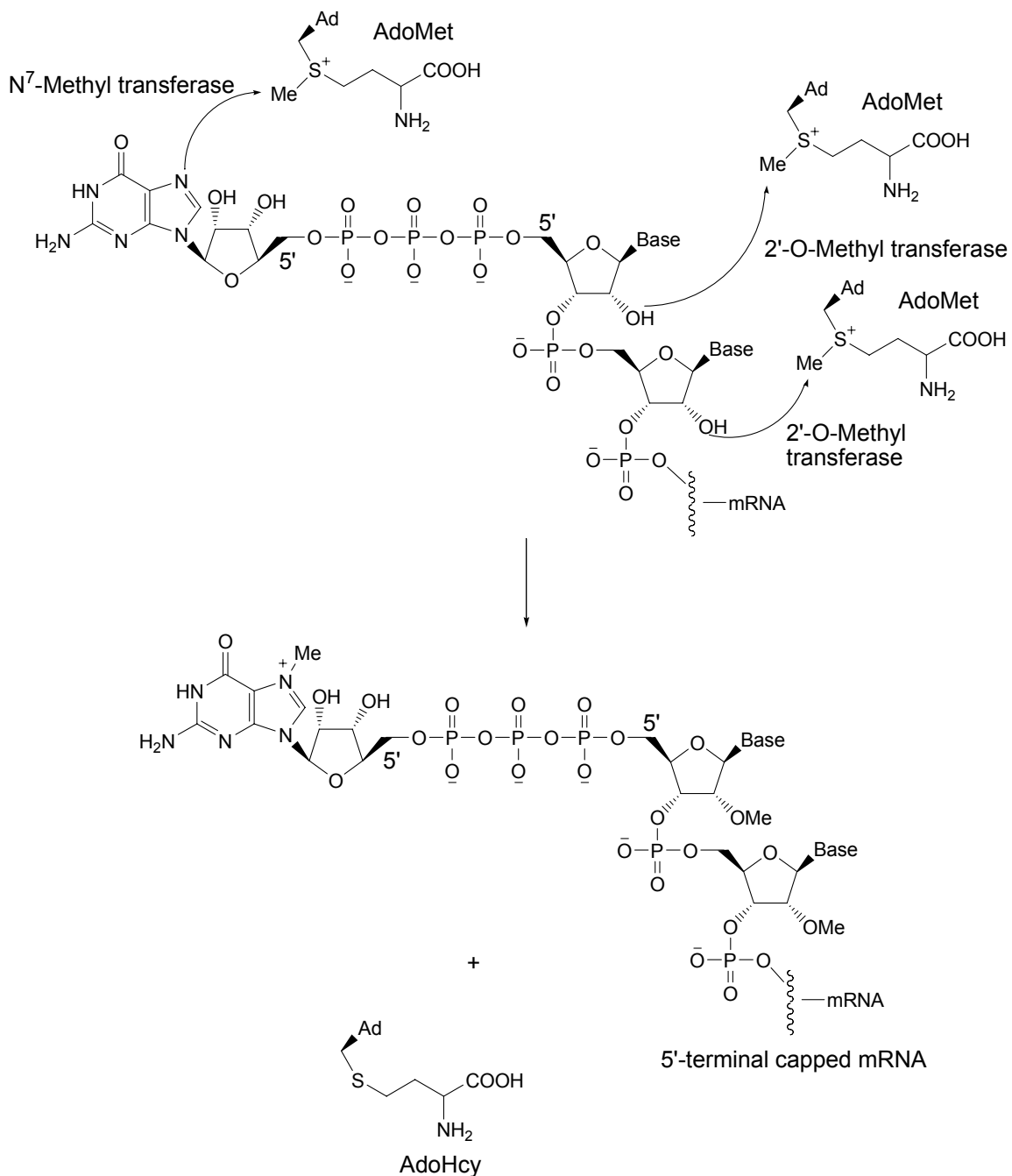
Scheme 1. The formation of 5′-terminal capped mRNA

The reactions that consume and generate/regenerate AdoMet comprise the AdoMet cycle. This cycle consists of four basic steps (Scheme 2). In the first step, the AdoMet dependent methylases use AdoMet as a substrate produce AdoHcy and a bio-methylated

product that is the 5′-capped methylated mRNA.[50] AdoHcy is a strong feedback inhibitor of methyl transferase and must be metabolized rapidly.[51,52] This follows with its hydrolysis to homocysteine and adenosine by *S*-adenosylhomocysteine hydrolase. Adenosine is further transformed to inosine by adenosine deaminase or it is converted to ATP through a series of phosphorylations.[53] The homocysteine is recycled back to methionine catalyzed by methionine synthase through transfer of a methyl group from 5-methyltetrahydrofolate (THF) or metabolized to cystathionine.[54] Finally, methionine reacts with ATP to give AdoMet under the influence of adenosyltransferase catalyst, completing the cycle.[55,56]
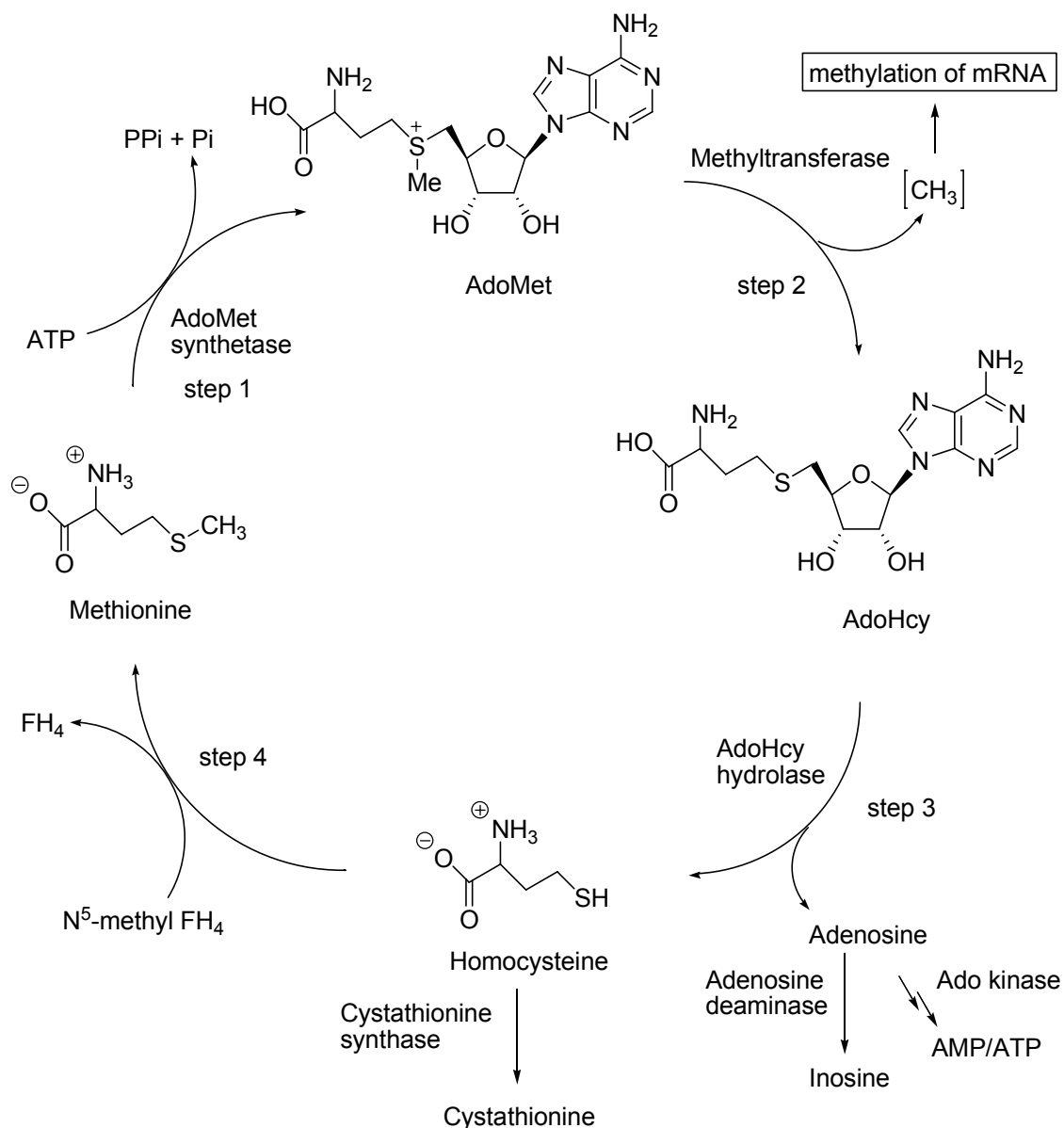
Scheme 2. The AdoMet cycle

Inhibition of AdoHcy hydrolase results in accumulation of AdoHcy, which is both the product and feedback inhibitor of the aforementioned essential 5′-capped methylation reaction (Scheme 1). With this in mind, inhibition of AdoHcy hydrolase has been recognized as a potential target for antiviral drug design for a long time. The mechanism of AdoHcy hydrolase was studied thoroughly over the last few decades. Scheme 3 shows

the mechanism that is widely accepted.[57-61] This process begins with crucial selective

NAD^+ oxidation of the hydroxyl group at the 3′ position to form 3′-ketoAdoHcy and

NADH. The acidity of C-4′ and α-hydrogen of 3′-ketoAdoHcy results in its enzymatic

removal. Then the homocysteine group at the 5′ position is eliminated and water is added

to the resultant enone in a Michael addition. Finally, adenosine is obtained via NADH

reduction of the 3′-keto to a hydroxyl group.

Ade = Adenine
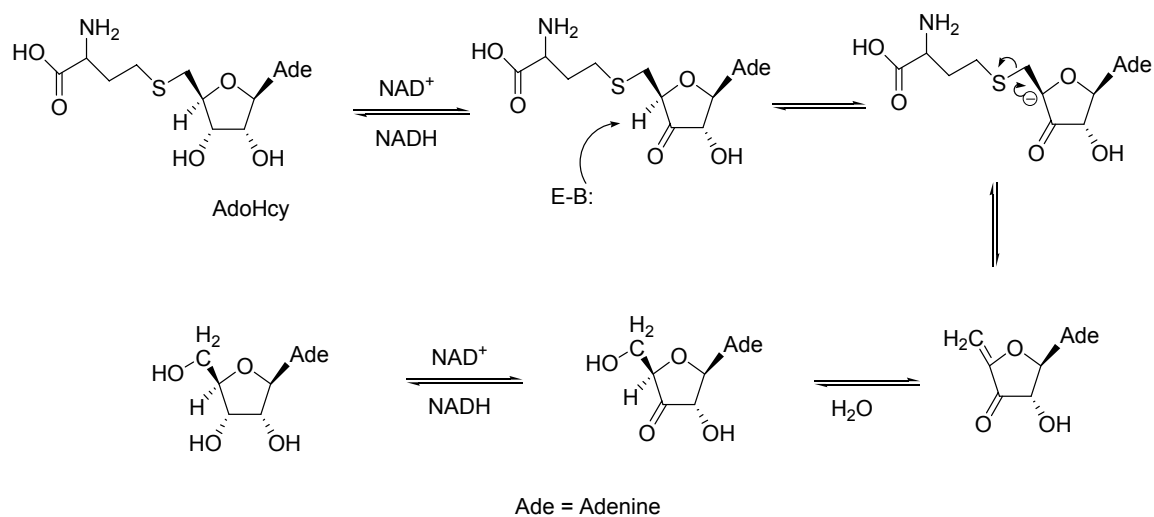
Scheme 3. Mechanism of AdoHcy hydrolase

By blocking AdoHcy hydrolase, the concentration of AdoHcy builds up and the

AdoMet methylation reaction, whose rate is regulated by intracellular ratio of

AdoMet/AdoHcy, is suppressed (Scheme 4).[48,54,62] The higher concentration of AdoHcy

lowers the ratio of AdoMet/AdoHcy and subsequently inhibits AdoMet transferases. This

will lead to the inhibition of the transmethylation and, in turn, the formation of 5′-capping

mRNA, reducing viral protein formation for its replication.[63-65]

14

X=$\overset{+}{S}$Me, AdoMet

X=S, AdoHcy

Adenosine + Homocysteine
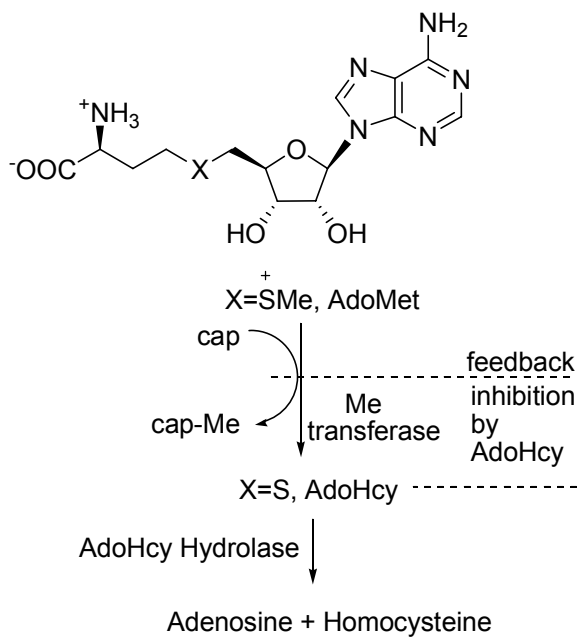
Scheme 4. AdoMet/AdoHcy metabolism

Carbocyclic nucleoside derivatives

Nucleoside analogs as inhibitors of AdoHcy hydrolase are effective for several medicinally important therapies, including antiviral treatment. However, prolonged inhibition of the hydrolase will overtake general cellular protein synthesis, leading to severe side effects such as toxicity and drug resistance. Thus, clinical application in this approach to drug therapy is limited by these inherent and unacceptable side effects.

Among the most promising antiviral agents based on inhibition of AdoHcy hydrolase to overcome these undesirable consequences are the carbocyclic nucleosides[35,66-68] that are nucleosides wherein the more common ribofuranose moiety is replaced by a cyclopentane ring. This structure alteration improves the stability of the N-glycosidic bond of the ribo-nucleosides against phosphorylases that cause nucleoside breakdown at the heterocyclic base and the sugar moiety interface. The consequence of this lysis is a 1′-

phosphoribose and a heterocyclic base resulting in failure of an intact active nucleosides being delivered to the bio-target. The hetero-base to cyclopentyl ring in carbocyclic nucleosides leads to nucleoside analogs more resistant to phosphorylsis (Scheme 5).

a ribo-nucleosoide

a carbocyclic nucleoside
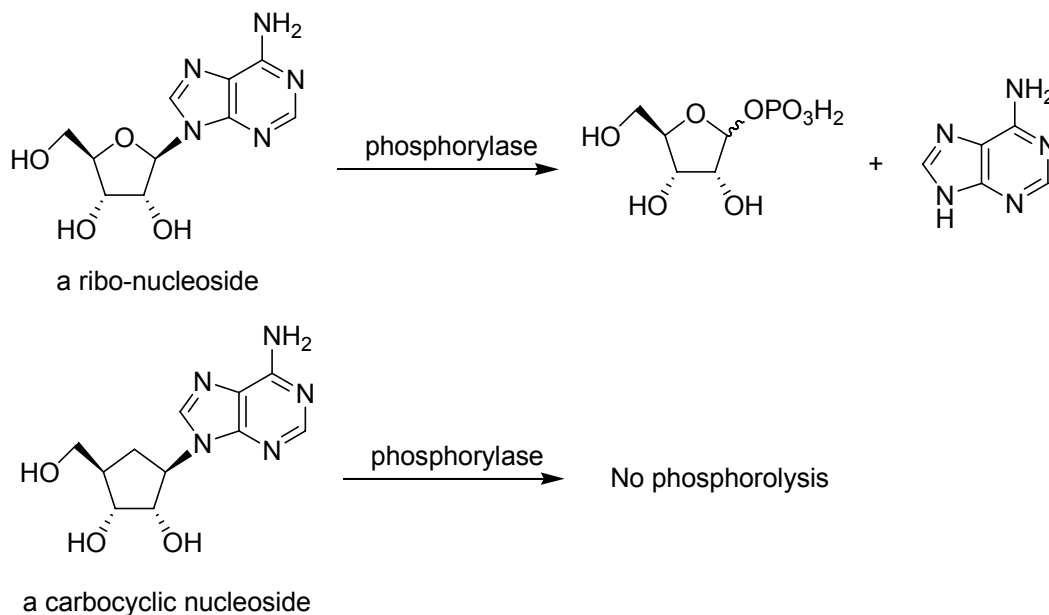
Scheme 5. Comparison of the response of ribo-nucleosides and carbocyclic nucleosides towards phosphorylase

In addition to their greater stability, there are other advantages of carbocyclic nucleosides, such as a higher lipophilicity for oral uptake and cellular penetration.[69,70] The similar structure of the cyclopentyl of carbocyclic nucleosides to the tetrahydrofuran ring of ribo-nucleosides renders carbocyclic nucleosides recognizable by the same enzymes involved with natural nucleosides as substrates (Scheme 6).[71]
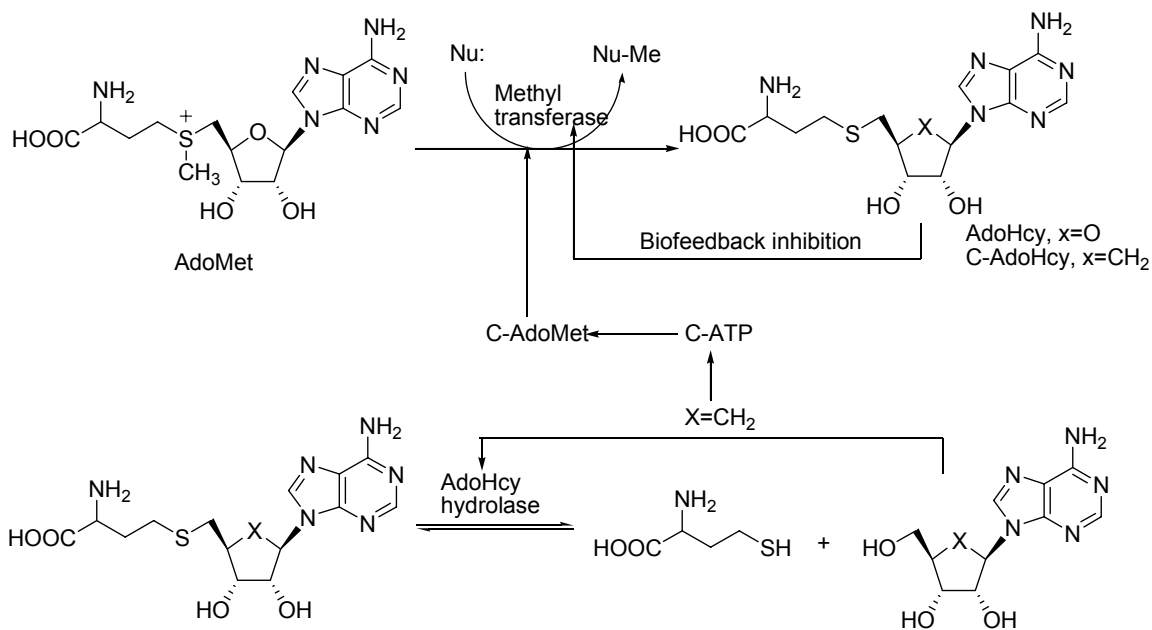
Scheme 6. Inhibition mechanism of nucleosides and carbocyclic nucleosides on AdoHcy hydrolase

In addition to their antiviral properties, carbocyclic nucleosides can serve as substrates for standard nucleoside processing enzymes (e.g., kinases that convert them to nucleotides), leading to anti-tumor and anti-viral candidates.[66-68,72]

With the promise of carbocyclic nucleosides, numerous related analogs have been discovered through isolation from nature or laboratory synthesis in the last few decades. Many of these compounds displayed broad-spectrum or specific antiviral activity. Some examples (Figure 5) in this category have been found therapeutic potential, such as abacavir and carbovir (anti-HIV),[73,74] entecavir (anti-HBV),[75,76] carboxentanocin G (anti-HIV),[77] aristeromycin and neplanocin A (broad-spectrum).[66-68,72]

Abacavir

Carbovir

Entecavir

Carboxentanocin G

Aristeromycin (Ari)
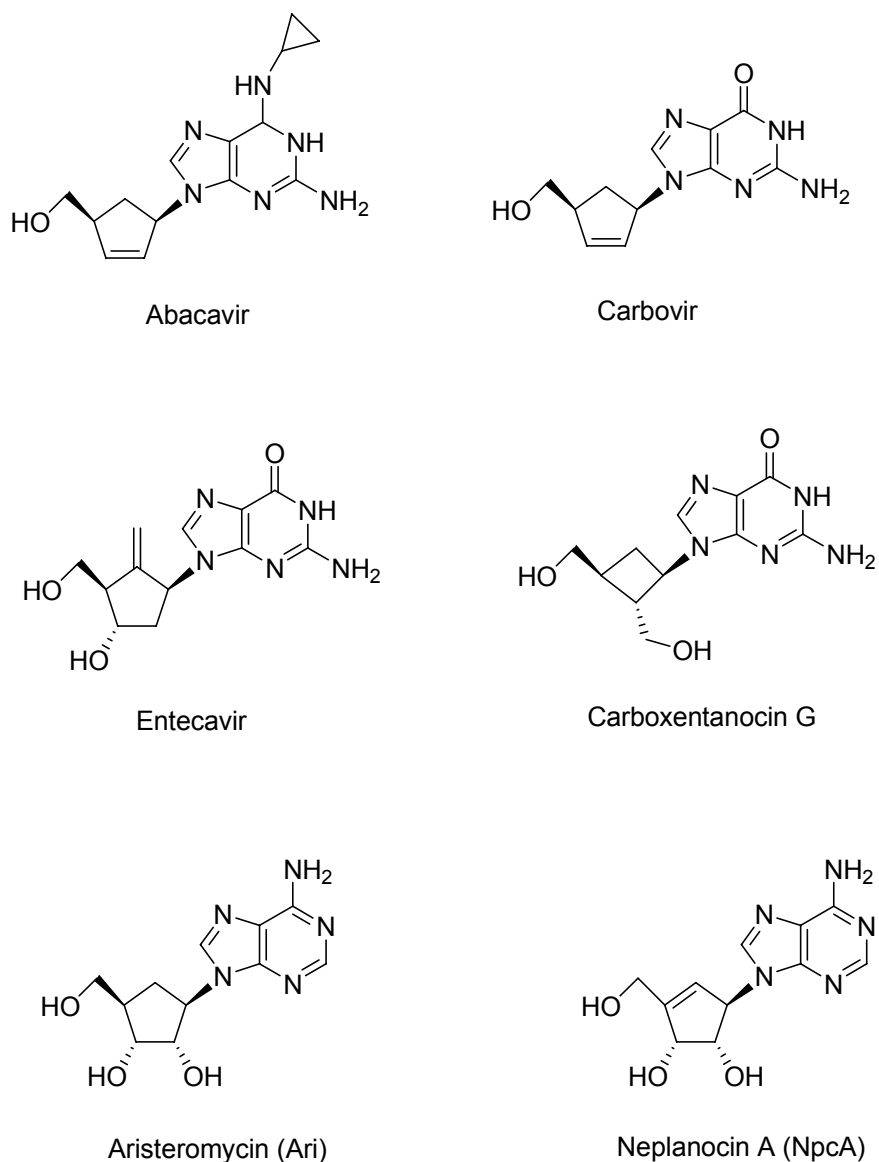
Neplanocin A (NpcA)

Figure 5. Carbocyclic nucleosides with antiviral activity

Aristeromycin (Ari) and neplanocin A (NpcA) are both natural occurring carbocyclic analogs of adenosine. Their structures differ by the presence of a double bond between C-4′ and C-6′ in NpcA. Neplanocin A was first isolated from the culture broth of *Ampullariella regularis* in 1979[78,79] while aristeromycin was synthesized[80-85] before it was isolated from a metabolite of *Steptomyces citricolor* in 1968.[86] Both aristeromycin

and neplanocin A have antiviral potential based on inhibition of AdoHcy hydrolase.[62,87] Both Ari and NpcA are phosphorylated by cellular kinases to their 5′-monophosphate-adenosine, 5′-diphosphate-adenosine and 5′-triphosphate nucleoside derivatives that may be the source of their undesirable side effect toxicity.[63,88] Ari-triphosphate can interfere with the metabolic processes involving ATP because of its structural resemblance to ATP. Meanwhile, Ari-MP serves as a substrate for AMP deaminase leading to the inosine monophosphate (IMP) analog of aristeromycin. In turn, this is converted to carbocyclic guanosine monophosphate (GMP), which inhibits the crucial cellular enzyme hypoxanthine (guanine)-phosphoribosyltransferase (HGPRTase).[88,89] This pathway may also account for the toxicity and decreased potency of Ari (Scheme 7).[90]
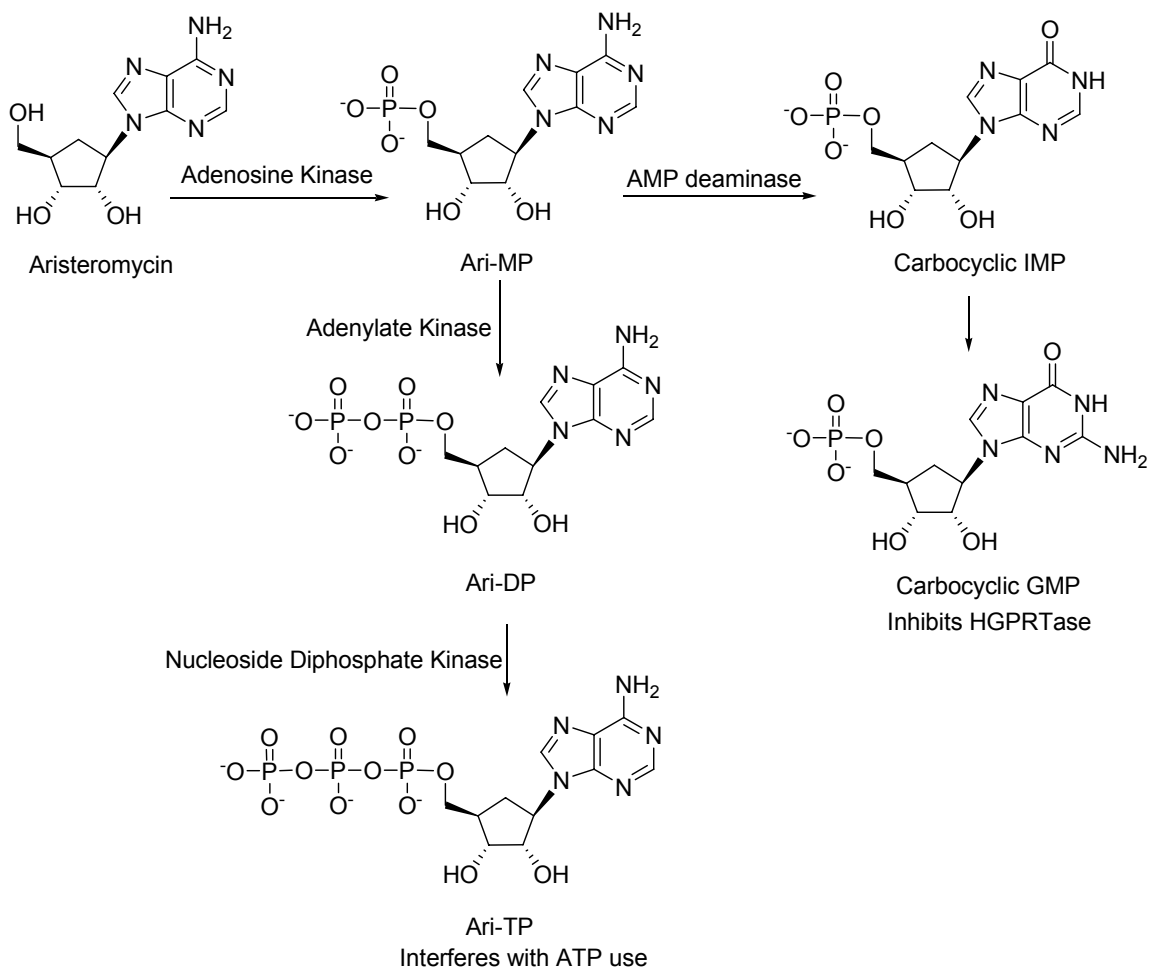
Scheme 7. Two metabolism pathways of Ari

The metabolism of NpcA follows a similar metabolic pathway.[63,90-92] In that regard, the toxicity of NpcA may also be attributed to the fact that the compound is readily phosphorylated to its 5′-triphosphate (Scheme 8), which then interferes with host-cell RNA synthesis.[89,90,93]
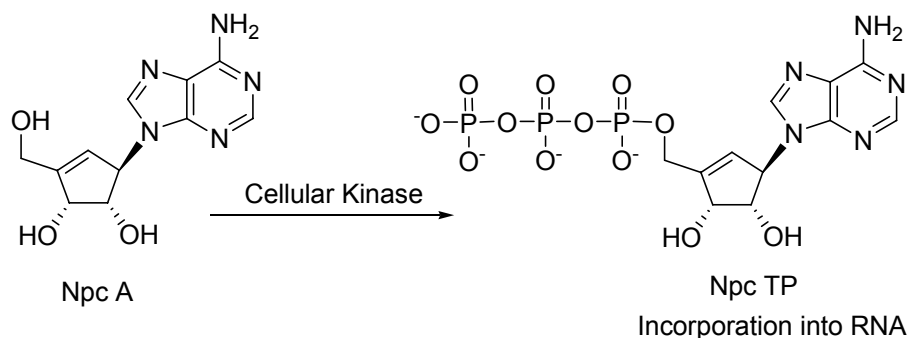
Scheme 8. Triphosphate of NpcA

With the antiviral activities of Ari and NpcA attributed to their inhibitory effect on AdoHcy hydrolase, their toxicity arising from nucleotide formation must be overcome if these compounds are to have a potential to provide a structural framework for agent design. Thus it became necessary to design similar analogs that are endowed with antiviral properties but lacking toxicity.

The naturally occurring nucleosides most are D-nucleosides analogs, such as adenosine, which is the natural product of AdoHcy hydrolysis. Ari and NpcA are both D-like analogs. Most of the D-like configuration analogs showed higher antiviral activity than their L-like counterpart. (-)-5′-norAri (the D-like configuration) is much more potent towards cytomegalovirus than (+)-5′-norAri (the L-like configuration).[94,95] Therefore, the D-like 3-deazaoaristeromycin analogs are designed and synthesized as a priority in the search for new hydrolase inhibitions of *S*-AdoHcy hydrolase.

In this regard, 3-deazaneplanocin A and the "decapitated" analogs of neplanocin A and 3-deazaneplanocin A, referred to as DHCA and DHCDA (Figure 6), were synthesized.[96-98] Both DHCA and DHCDA were indeed more selective in their activity against vaccinia virus than neplanocin A was.[99]
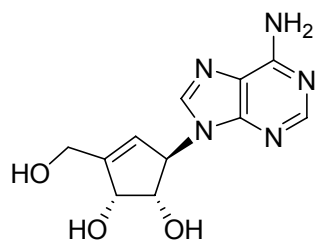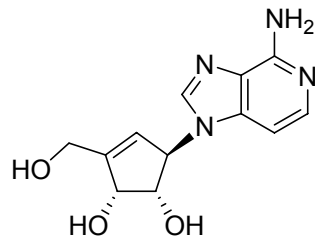
Figure 6. Structures of neplanocin A, 3-deazaneplanocin A and their decapitated analogs DHCA and DHCDA

The analogs of 3-deazaaristeromycin,[100] the "decapitated" aristeromycin (DHCaA) and 3-deaza-DHCaA (Figure 7) were synthesized and maintained the potent antiviral activity against vesicular stomatities virus, vaccinia virus, parainfluenza virus, reovirus, and rotavirus etc. with less toxicity.[101,102]
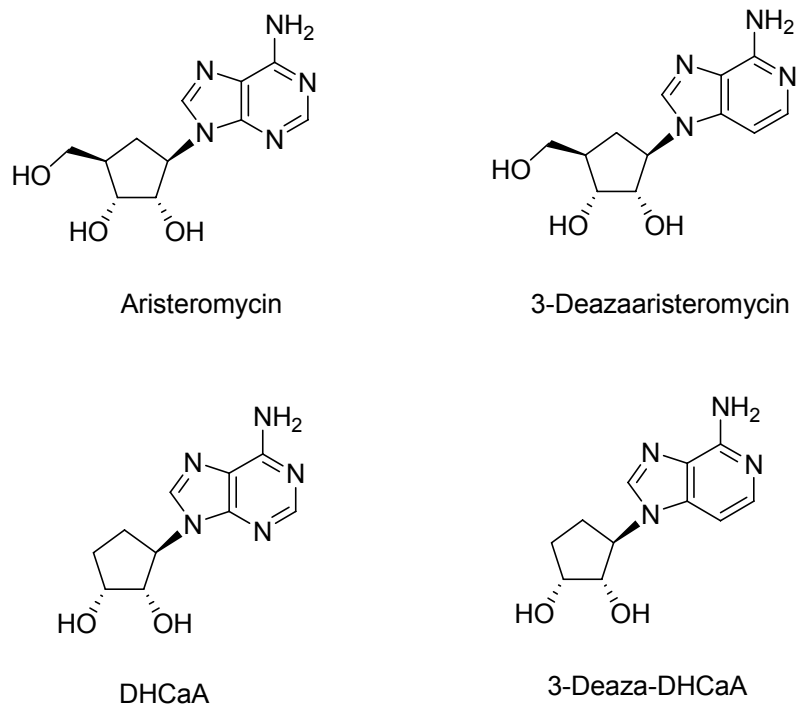
Figure 7. Structures of aristeromycin, 3-deazaaristeromycin and their decapitated analogs DHCaA and 3-deaza-DHCaA

The Schneller group also has developed many valuable analogs of aristeromycin and neplanocin A derivatives that show greater therapeutic potential without toxicity than aristeromycin and neplanocin A. The 5′-deoxy analog of Ari (Figure 8) showed moderate antiviral activity against vaccinia virus, vesicular stomatitis virus (VSV)[103] with little toxicity in the assays.[104] The reason for the reduced toxicity is believed to be due to lack of a C-5′ hydroxyl and hence no phosphorylation. The Schneller group has also reported efficient and stereoselective routes to synthesize (-)-3-deazaaristeromycin,[105] 5′-homoanaologues of Ari, 5′-homoanaologues of NpcA, and 6-*iso* analogs of Neplanocin A (Figure 8).[104,106,107] In that series, antiviral activity was shown against a wide variety of DNA and RNA viruses, such as the orthopox viruses, vaccinia, cowpox, and

monkeypox.[104] 5′-Homoneplanocin A showed noteworthy activity against both HBV and HCV.[107] 3-Halo-3-deaza-5′-noraristeromycin analogs possessing a halo atom at the C-3 position have been synthesized and evaluated in the Schneller laboratory. 3-chloro-3-deaza-5′-noraristeromycin (**a**) exhibits activity against HCV. 3-Bromo-3-deaza-5′-noraristeromycin (**b**) and 3-iodo-3-deaza-5′-noraristeromycin (**c**) display marked activity against HBV. Compounds **a**, **b** and **c** were also found to have a wide variety of other biological properties. 3-Methyl-3-deaza-5′-noraristeromycin (**d**) showed good activity against VSV and VV.
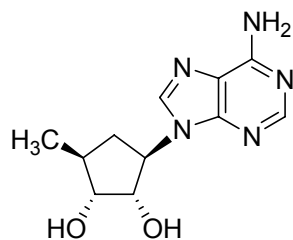
5′-Deoxyaristeromycin
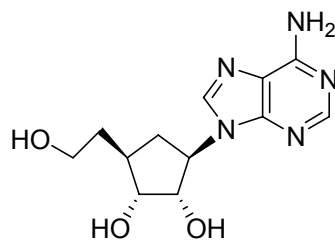
5′-Homoaristeromycin
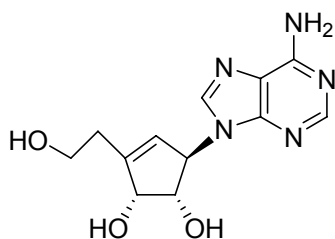
5'-Homoneplanocin
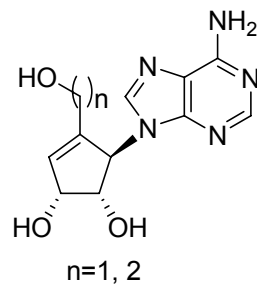
6-*iso*neplanocin A analogues

n=1, 2
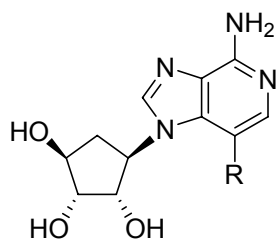
a: R=Cl, 3-chloro-3-deaza-5′-noraristeromycin
b: R=Br, 3-bromo-3-deaza-5′-noraristeromycin
c: R=I, 3-iodo-3-deaza-5′-noraristeromycin
d: R=Me, 3-Methyl-3-deaza-5′-noraristeromycin

Figure 8. Structures of aristeromycin and neplanocin A derivatives

Fluorine-containing nucleoside derivatives

In the search for effective antiviral agents, the presence of the small, electronegative fluorine substituent has provided promising structural entities with significant antiviral properties.[108-112] As a consequence, fluorinated nucleosides and nucleotides, where the

fluorine has been introduced into both the base and the sugar moiety (Figure 9), have found use in the treatment of viral infections.[113,114]

Alovudine

Lodenosine

2-Fluoro-8-azaadenosine

2'-deoxy-2'-Fluoro-adenosine
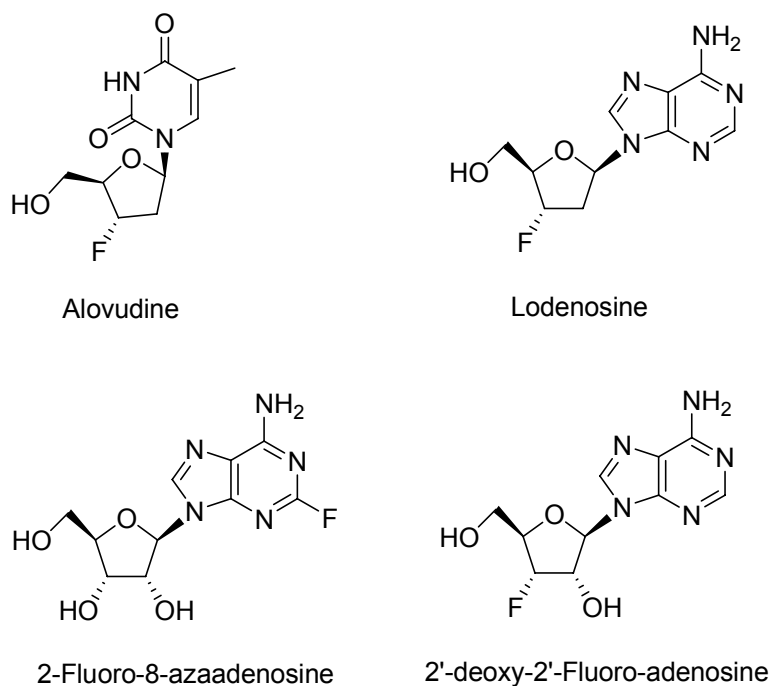
Figure 9. Structures of fluorine-containing nucleosides

Fluorine imparts desirable characteristics to drugs by modulating both the pharmacokinetics and pharmacodynamics properties of the drug candidate.[115,116] This is the consequence of:

1) Increased lipophilicity leads to an increase in fat solubility, which improves transportation through membranes and increases its bioavailability.

2) Aid hydrophobic interactions between the drug and binding sites on receptors or enzymes.

3) The electronic effect provided by fluorine's high electronegativity and small atomic radius gives unique properties to its structural framework as expressed by, for example, altering both the dipole moment and the pK_a of the molecule.

4) Altering the drug's metabolic properties due to the very strong C-F bond leading to higher oxidative and thermal stability than present in a carbon-hydrogen bond.

In summary, these properties affect a drug's metabolism and prolong its half-life. Therefore, incorporation of fluorine into a drug can increase lipophilicity, enhance absorption into biological membranes, and facilitate docking with drug receptors, all leading to a dramatic effect on biological activity.

In this direction, efficient and stereoselective synthesis of fluorine nucleosides was reported by the Schneller group (Figure 10).[110,117] 5′-fluoro-5′-deoxyaristeromycin and 4′-fluoro-4′-deoxyaristeromycin were evaluated and showed moderate activity against measles without toxicity.[117] This indicated that the replacement of the 5′-hydroxy of aristeromycin and 4′-hydroxyl of 5′-noraristeromycin with fluoride can remain potent and avoid the undesired phosphorylation and reduced toxicity successfully because the fluorine is incapable of phosphorylation. Fluorine-containing nucleosides are consideration because the fluorine is incapable of phosphorylation, oxidation, but with unique desirable drug characteristics.

5'-fluoro-5'-deoxyaristeromycin

4'-fluoro-4'-deoxyaristeromycin

(3'*R*)-3'-fluoro-3'-deoxy-5'-noraristeromycin

(3'*S*)-3'-fluoro-3'-deoxy-5'-noraristeromycin

3',3'-difluoro-3'-deoxy-5'-noraristeromycin
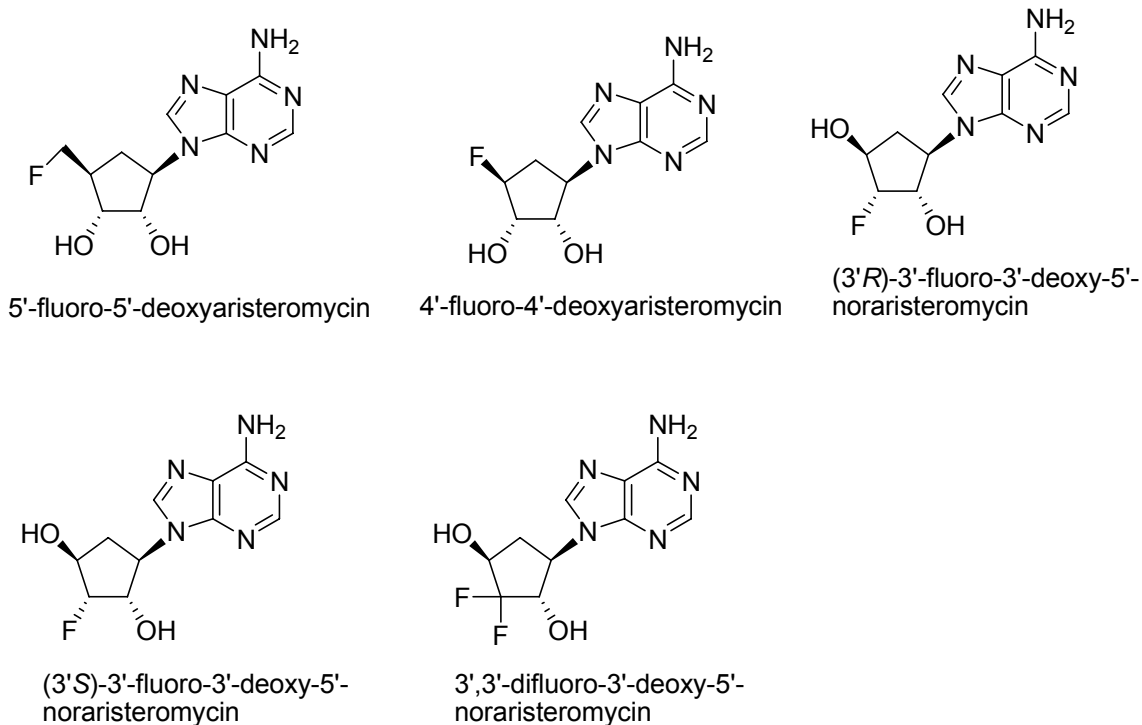
Figure 10. Fluorine-containing nucleosides synthesized in the Schneller Laboratory

Target design based on the SAH hydrolase inhibition

Seeking analogs that build on this framework, this dissertation research sought to structurally unite the biological potential of 3-deazaaristeromycin with fluorine's advantages to create new compounds as antiviral drug candidates.

As mentioned before, 3-deazaaristeromycin (Figure 11) has significant antiviral activity by its inhibition of S-adenosylhomocysteine hydrolase. The mechanism of AdoHcy hydrolase (Scheme 9) showed that the hydroxyl group at the C-3′ position is very important because it is selectively oxidized to form 3′ ketoAdoHcy in the first step. The inhibition of AdoHcy hydrolase results in the accumulation of AdoHcy and the methylation reaction starting from AdoMet to AdoHcy will be suppressed. Consequently,

formation of the 5′-capped structure of mRNA is interrupted and the replications of viruses are terminated.
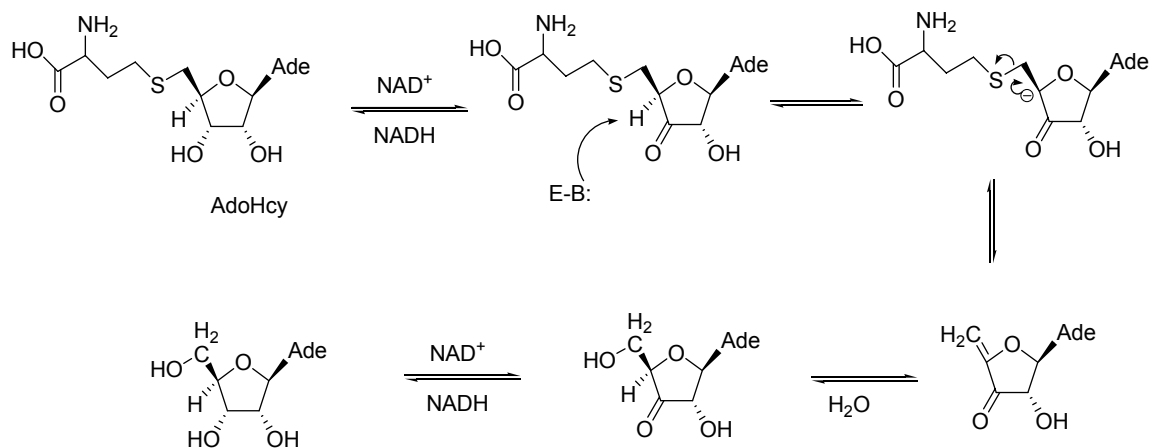
Replacement of the 3'-OH with F or H that is incapable of oxidation inhibits the AdoHcy hydrolase in the first step

a: R₁ = F, R₂ = H
b: R₁ = H, R₂ = F
c: R₁ = H, R₂ = H

Ade = Adenine
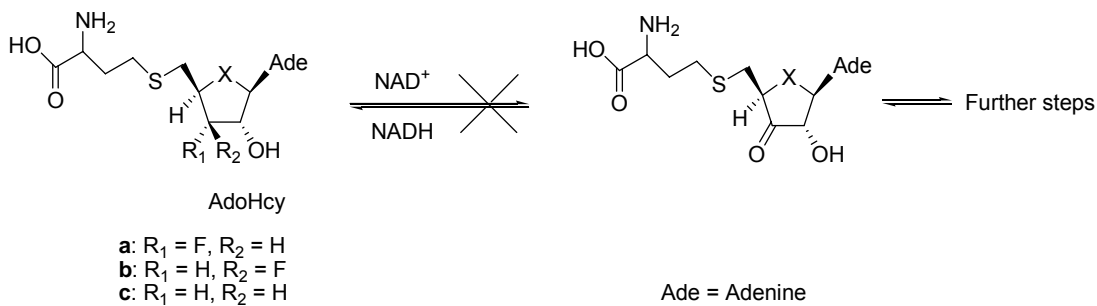
Scheme 9. Mechanism of AdoHcy hydrolase

Therefore, it is rational design to change the hydroxyl group at C-3′ position to fluorine or hydrogen that is incapable of oxidation in the first step and inhibit the AdoHcy hydrolase. The 3′-fluoro-3′-deoxy- and 3′-deoxy-3-deazaaristeromycin[118,119] derivatives **1**, **2**, **3** were sought as target compounds (Figure 11).
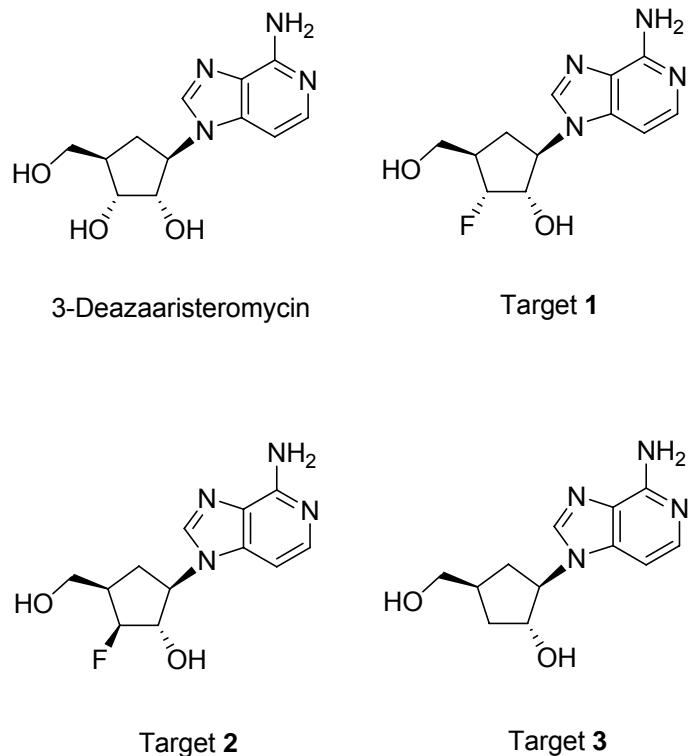
Figure 11. Structures of target 1, 2, and 3

A class of 2′-deoxy nucleosides found to be active against DNA viruses, such as HIV, was discovered in the late 1970s by Watanabe and Fox.[120] These compounds are (2′-fluoro-2′-deoxy-β-D-arabinofuranosyl) pyrimidines substituted in the 5′-position (Figure 12). With further investigations, the 1′, 2′ arrangement between the nucleobase attached at the anomeric center and the heteroatom at C-2′ is found in numerous biologically relevant nucleoside analogues, which are provided as antiviral drugs.[113,121-124]

R = H, CH$_3$, CH$_2$CH$_3$, I

(Anti-HIV)
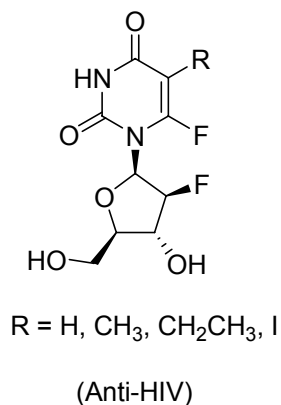
Figure 12. Analog of 2′-deoxy nucleosides against HIV

The design of target compounds is to change the hydroxyl group at C-2′ position to fluorine or hydrogen. The 2′-fluoro-2′-deoxy- and 2′-deoxy-3-deazaaristeromycin[118,119] derivatives **4**, **5**, **6** were sought as target compounds (Figure 13).

Target **4**   Target **5**   Target **6**
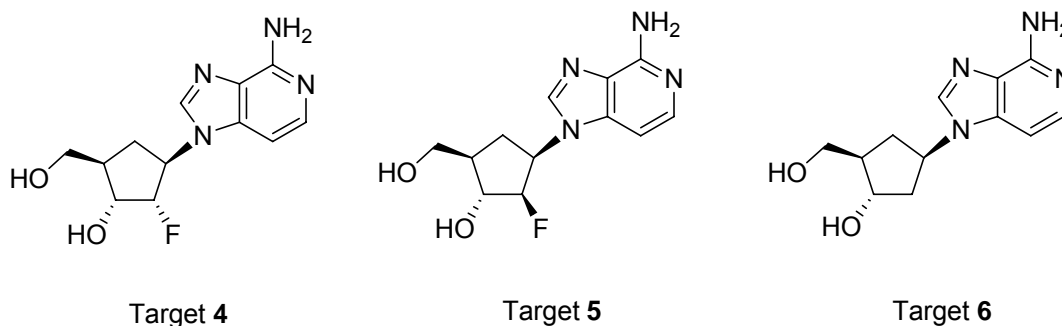
Figure 13. Structures of target 2′-deoxy-3-deazaaristeromycin derivatives

4′-Substituted nucleosides were first investigated by Maag et al. in 1992.[125] 4′-Azido-2′-deoxynucleosides (Figure 14) were found to exert potent activity against HIV. An extensive investigation found that other 4′-position substituent nucleosides also exhibited high antiviral activity against HIV.[126-130]

4'-azido-2'-deoxynucleosides 4'-methyl-2'-deoxynucleosides 4'-fluoromethyl-2'-deoxynucleosides

4'-cyano-2'-deoxynucleosides 4'-ethynyl-2'-deoxynucleosides 4'-ethynyl-nucleosides

Base = Adenine, Inosine, Guanine, Thymine, Uracil, Cytosine
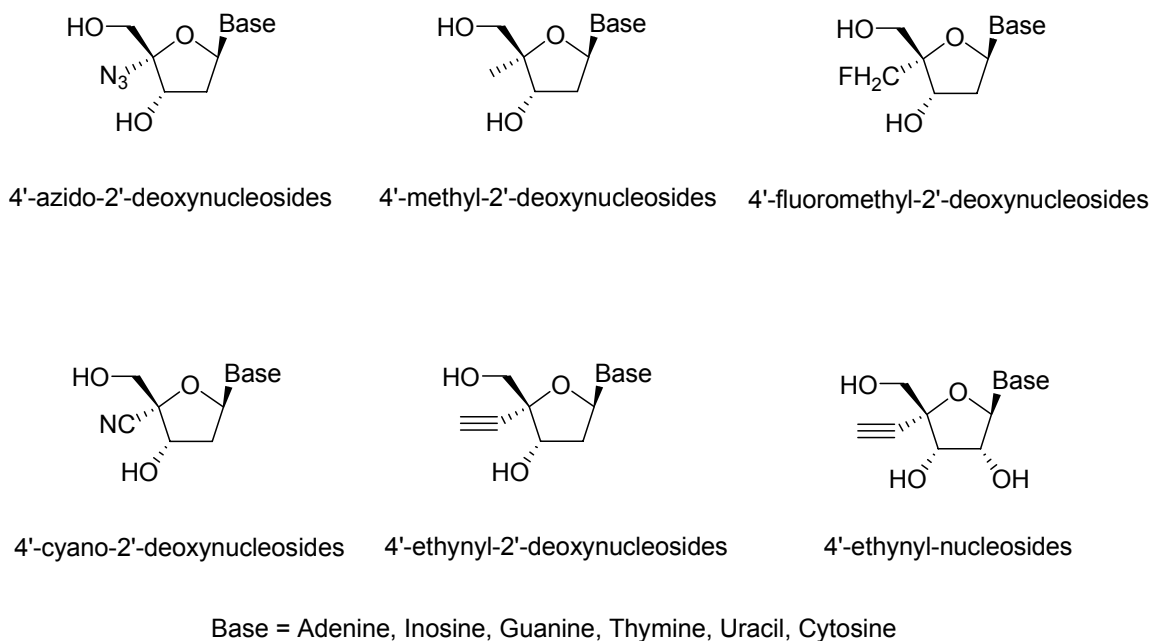
Figure 14. Structures of 4′-position substituted nucleosides against HIV

Finally, the 4′-methyl-3-deazaaristeromycin (**7**) was sought as anti-HIV agent and an efficient route into the heretofore unknown 4′-alkylated-3-deazaaristeromycin framework was developed (Figure 15).
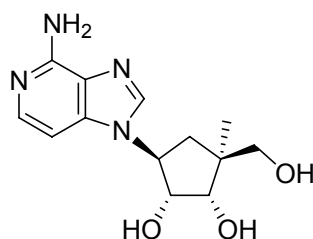
4'-methyl-3-deazaaristeromycin **7**

Figure 15. Structure of 4′-methyl-3-deazaaristeromycin

Results and Discussion

Synthesis of (3′*R*)-3′-deoxy-3′-fluoro-3-deazaaristeromycin (1)

Experimental Design and Synthesis.

In the introduction part, it was pointed out that the inhibition of AdoHcy hydrolase results in the accumulation of AdoHcy and the methylation reaction starting from AdoMet to AdoHcy will be suppressed because the AdoHcy will inhibit the methylation reaction of viral mRNA. Consequently, formation of 5′-capped mRNA is interrupted and viral replication terminated. The mechanism of AdoHcy hydrolase (Scheme 9) has shown that the hydroxyl group at the C-3′ position is selectively oxidized to form 3′ ketoAdoHcy in the first step. Therefore, a rational inhibitor design arises by replacing the hydroxyl group at the C-3′ position of 3-deazaaristeromycin with a fluorine rendering this site incapable of oxidation while at the same time adding other advantages as illustrated previously in this dissertation. Thus, (3′*R*)-3′-deoxy-3′-fluoro-3-deazaaristeromycin (**1**) was selected as target compound. The retrosynthetic analysis to **1** is shown in Scheme 10.[109,131]
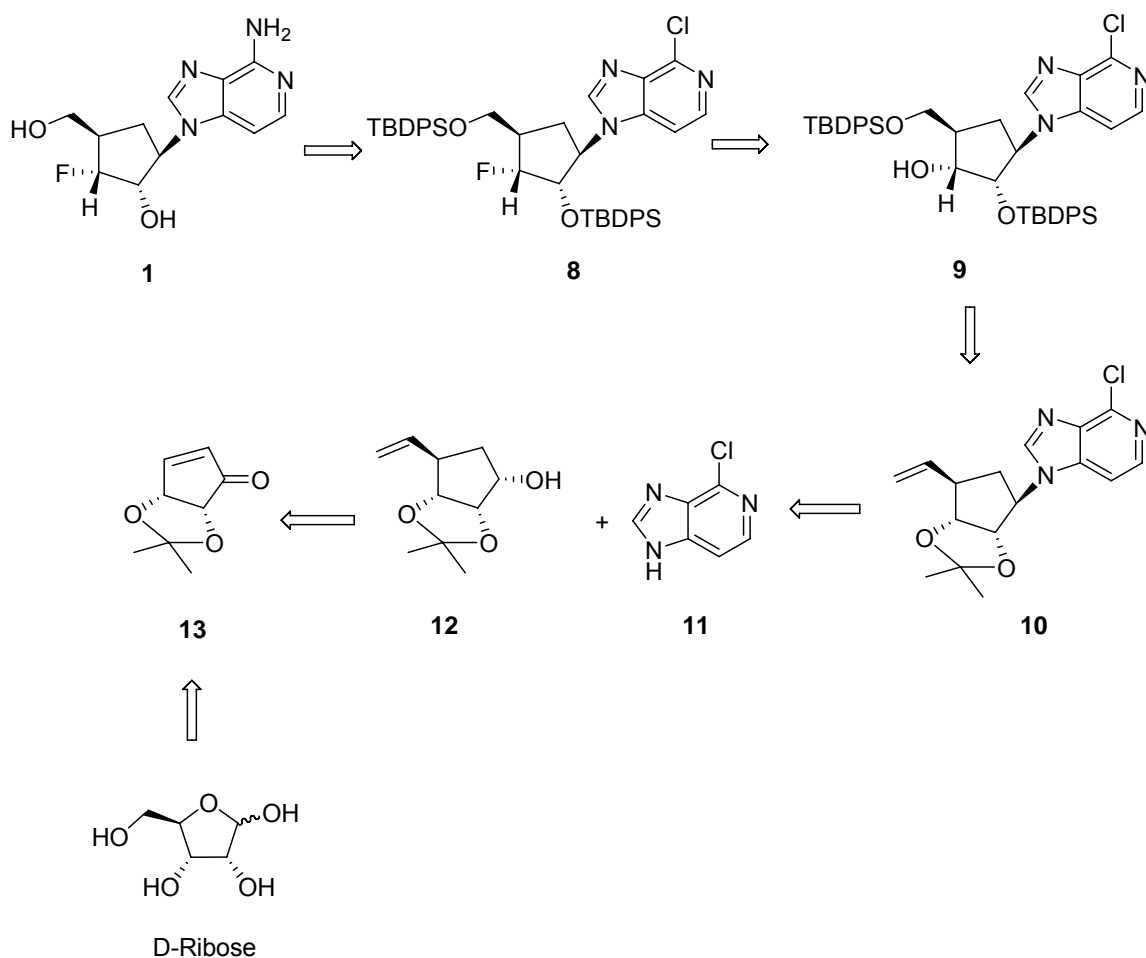
Scheme 10. Retrosynthetic analysis of (3′R)-3′-deoxy-3′-fluoro-3-deazaaristeromycin 1

The preparation of **1** started from D-ribose and 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (6-chloro-3-deazapurine, **11**). D-ribose is commercially available and its stereochemistry is predefined for the purposes here. On the other hand, heterocyclic base **11** is not commercially available, but can be synthesized in four steps from the commercially available 3-nitropyridine-4-ol (**14**) (Scheme 11). In that direction, chlorination of alcohol **14** with phosphorus pentachloride afforded a chloride intermediate that was reacted with ethanol to afford **15** in 95% yield. Compound **15** was treated with ammonium acetate

under reflux to give amine **16** in 82% yield. The nitro group of **16** was reduced by tin(II) chloride (SnCl$_2$) in concentrated hydrochloric acid, and followed by a chlorination reaction to introduce a chlorine at the 2 position of **16** in one pot leading to 2-chloro-3,4-diaminopyridine **17** in 70% yield. Finally, **17** was reacted with triethyl orthoformate to construct the fused heterocyclic ring product **11** was obtained in 74% yield. Purification of crude 6-chloro-3-deazapurine **11** involved filtering and washing by ether, and the solid residue was recrystallized twice in methanol/ethyl acetate to give pure **11**.
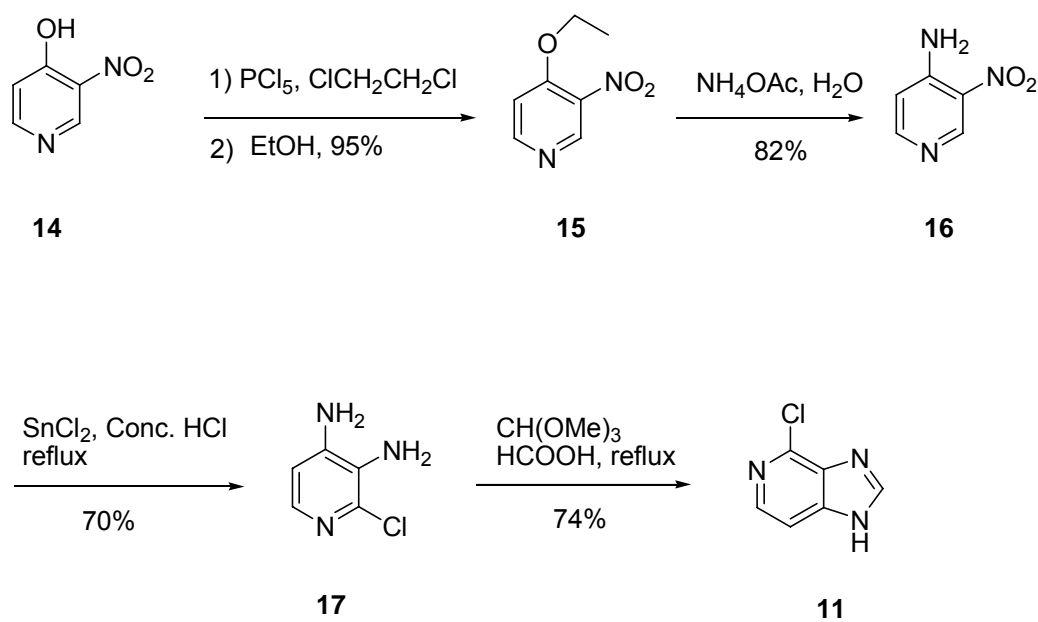
Scheme 11. Synthesis of 6-chloro-3-deazapurine 11

The requisite D-like cyclopentenone **13** is a very versatile intermediate, which is used as multipurpose synthon for the synthesis of carbocyclic nucleosides, and a central synthon for the target compounds in this dissertation. Therefore, an efficient, large scale, and economic synthesis of cyclopentenone **13** was highly demanded. In this direction, the synthesis of **13** was investigated.[132-137] There are two major synthetic routes that start

with D-ribose. Route A[135] (Scheme 12) and Route B[132,136,138,139] (Scheme 13). They both used for achieving **13**.

In route A (Scheme 12), D-ribose was reacted with acetone in the presence of sulfuric acid to give protected **18**. A Grignard reaction of **18** with vinyl magnesium bromide afforded the triol **19**. Oxidation of **19** with sodium periodate gave **20**. Subjecting aldehyde **20** to a Wittig reaction with methyl triphenylphosphonium bromide and sodium hydride afforded the diene **21**. With **21** in hand, it was subjected to ring-closing metathesis (RCM) reaction conditions with 1 mol% of Grubbs' 1st generation catalyst and followed oxidation with pyridinium chlorochromate (PCC) to afford cyclopentenone **13**. However, it was not an economic and safe scale-up route. When **18** was converted to diol **19** under Grignard reaction conditions, this reaction need 3.5 equivalents vinylmagnesium bromide to give **19**. At least 2 equivalents of Grignard reagents were consumed and quenched by 2 hydroxyl groups of **18** before the Grignard reagent really reacted with aldehyde group of **18**. A large scale Wittig reaction of **20** needed a considerable amount of sodium hydride (NaH), which could ignite in air (especially upon contact with water to release hydrogen) and also is flammable. It was dangerous to handle so much NaH in this synthesis, particularly when the reaction was scaled up in the lab. So attention changed to route B.
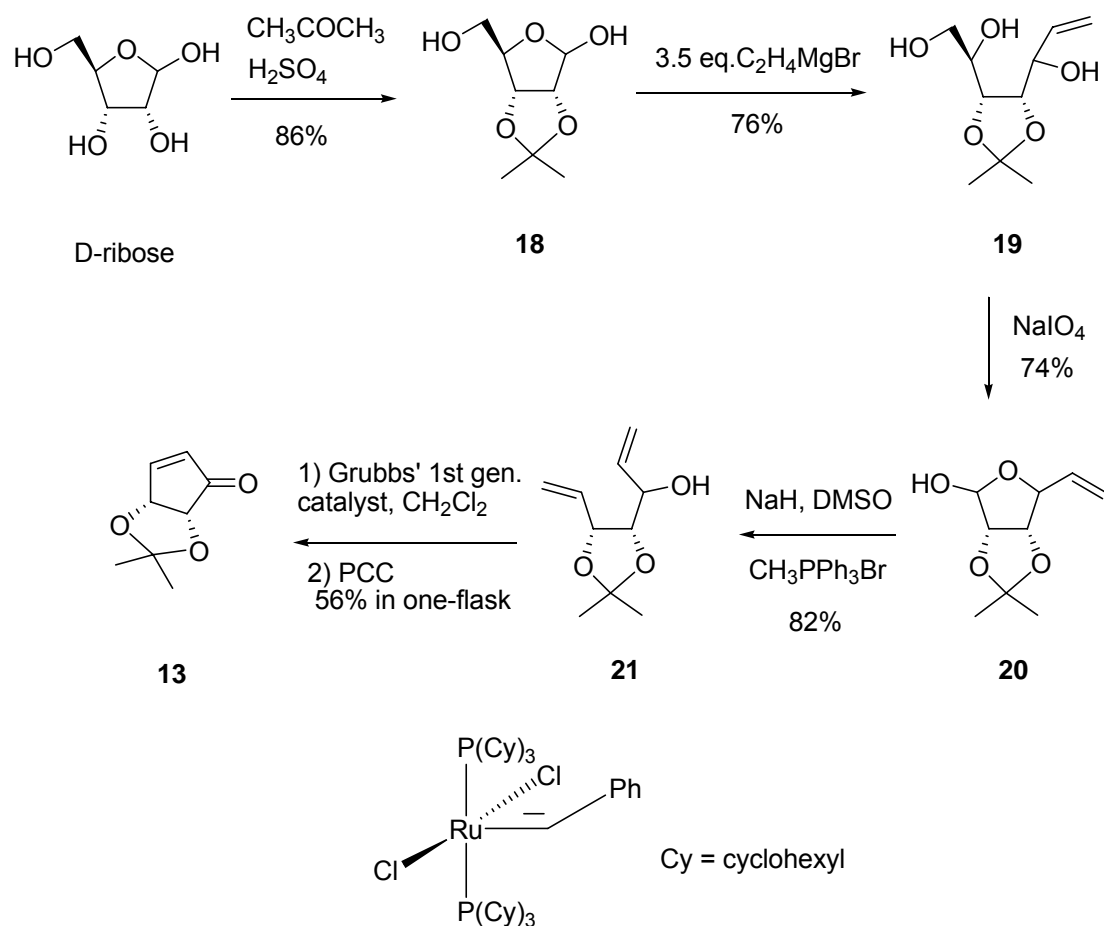
Grubbs' 1st generation catalyst

Scheme 12. Route A for synthesis of cyclopentenone 13

Route B (Scheme 13) presented itself as a facile synthesis route for **13**. Treatment of D-ribose with 2,2-dimethoxypropane and hydrochloric acid in methanol gave primary alcohol **22** with diol protection as the *iso*propylidene unit and methylation at the anomeric hydroxyl center. The compound **22** was treated with triphenylphosphine (Ph₃P) and iodine to give iodide **23**. Reductive cleavage of **23** with active zinc powder in refluxing methanol afforded aldehyde **24**, which was quite volatile and unstable. A Grignard 1, 2- addition of **24** with vinylmagnesium bromide afforded diene **21**.

Subjecting **21** to ring-closing metathesis (RCM) conditions with 1 mol% of Grubbs' 1st

generation catalyst and followed by oxidation with pyridinium chlorochromate (PCC)

provided the desired cyclopentenone **13**.
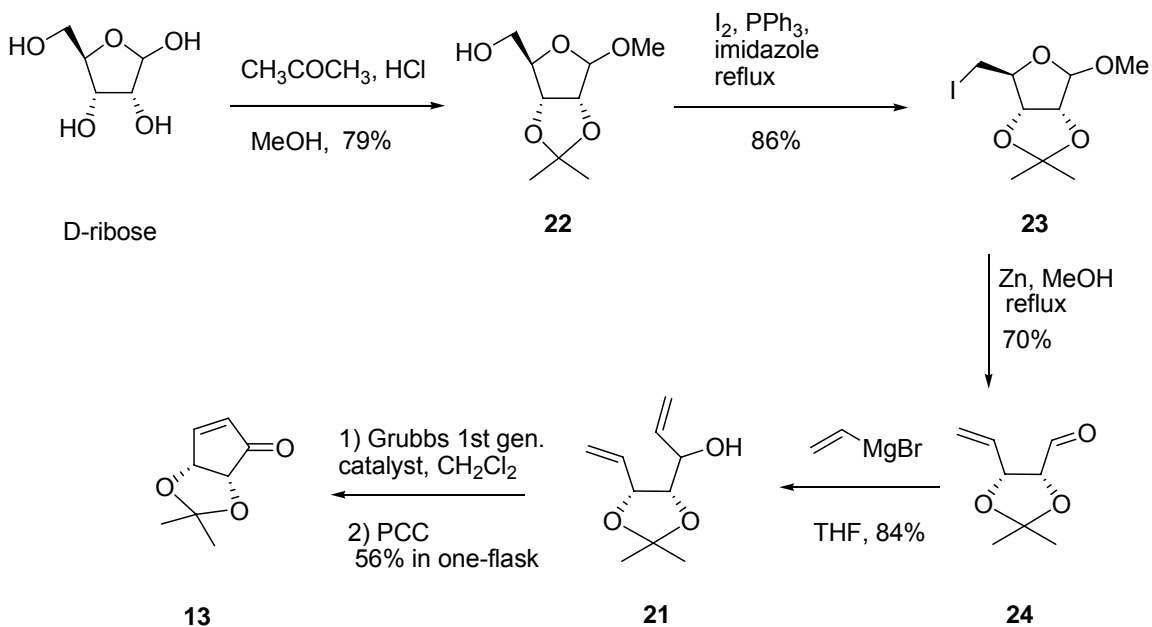
Scheme 13. Route B for synthesis of cyclopentenone 13

Compound **24** was very volatile that caused problems when removing the methanol in

the **23** to **24** step, a necessary procedure to avoid complications in the subsequent

Grignard process. Also, aldehyde **24** was susceptible to zinc promoted reduction to

alcohol **25** (Scheme 14) during the reductive cleavage of iodine **23** if the temperature and

the reaction time was not carefully monitored. Finally, some oxidization of **24** to **26** was

observed as a consequence of the tedious work-up required.
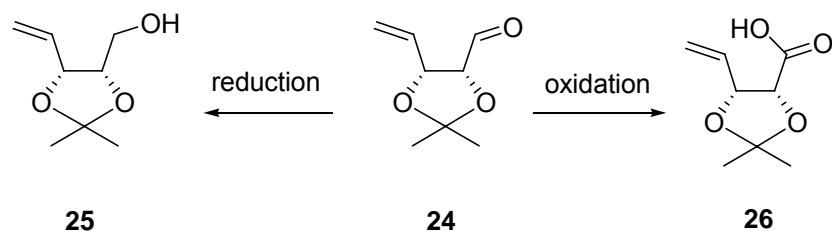
Scheme 14. Reduction and oxidation of unstable aldehyde 24

Because of these problems with **24** affected the overall yield, alternatives were considered. This led to changing the ribose protecting group from *iso*propylidene to cyclopentylidene to decrease the volatiles of the desired aldehyde.[117] Thus, a revised route C (Scheme 15) arose. Following a procedure similar to that used for synthesizing **24**, **28** was obtained by replacing acetone with cyclopentenone to **27**, followed by iodination reduction of **28** with active zinc powder afforded aldehyde **29** under a mild reduction conditions at 40 ℃ rather than reflux of Scheme 13. The reaction was traced by TLC in order to stop as soon as iodide **28** disappeared. Conversion of **29** into **30** was carried out under Grignard conditions with vinyl magnesium bromide. As a mixture of diastereomers, diene **30** was subjected to a RCM reaction with 1 mol% of Grubbs' 1st generation catalyst. This reaction produced an intermediate **31** that was followed by an oxidation with active manganese dioxide (MnO_2) powder at room temperature for overnight to give desired cyclopentenone **32**. In this latter step, the PCC used in the oxidation of Scheme 13 was changed to MnO_2 because this oxidant provided easier work-up than PCC, which generated a muddy pyridine chromate salt containing celite.
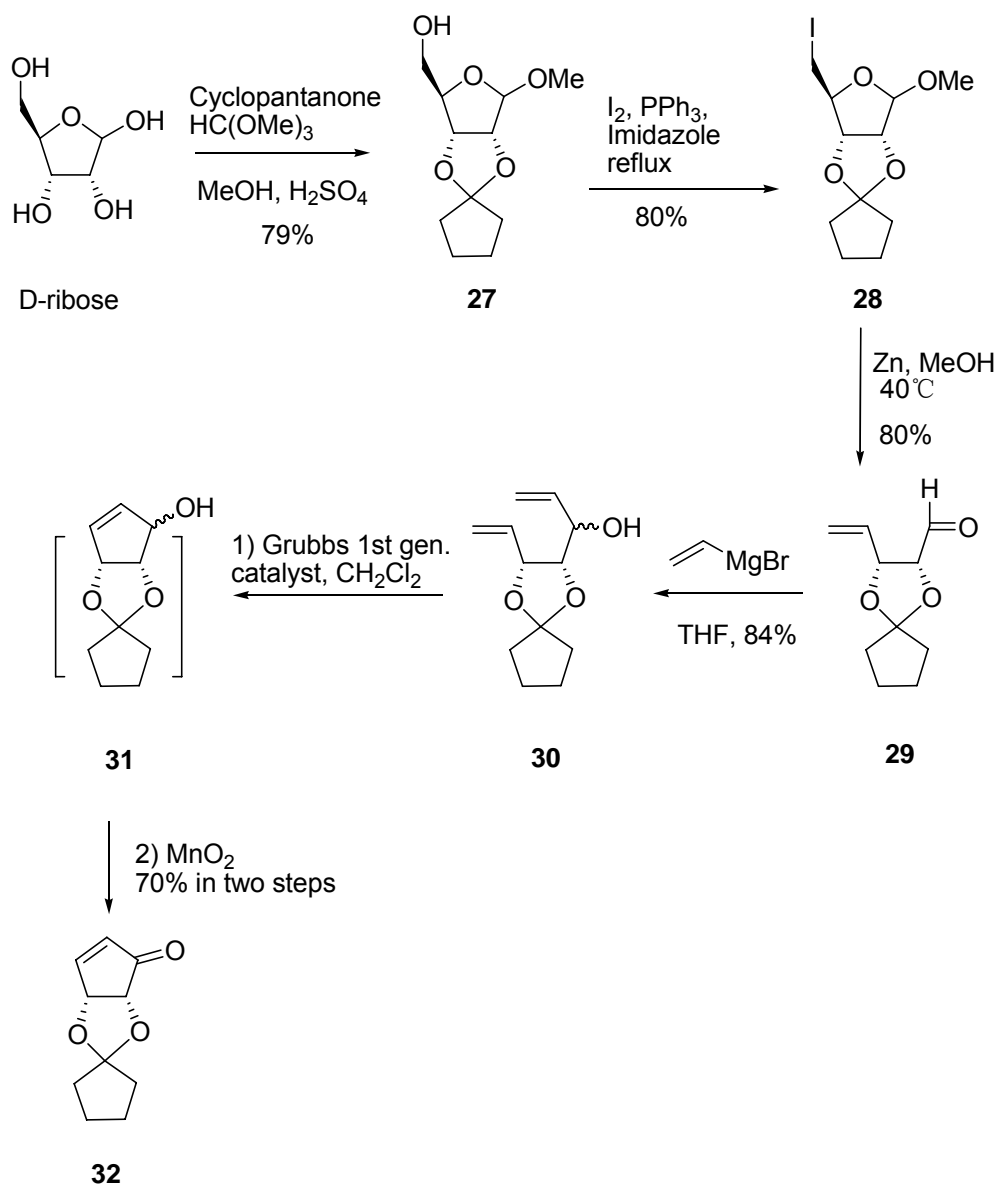
Scheme 15. Route C for synthesis of cyclopentenone 32

With cyclopentenone **32** in hand, the *iso*propylidene cyclopentenone **13** was replaced by cyclopentylidene cyclopentenone **32** in the retrosynthetic analysis of **1** (Scheme 10). Attention then turned to compound **34** that was synthesized from **32** by two steps (Scheme 16). Michael addition of **32** with vinyl magnesium bromide in the presence of

copper(I) bromide · dimethyl sulfide complex (CuBr·Me$_2$S), and chlorotrimethylsilane (TMSCl) generated ketone **33**. Following a literature procedure,[140-142] Luche reduction of **33** with NaBH$_4$ and cerium(Ш) chloride heptahydrate (CeCl$_3$·7H$_2$O) gave alcohol **34** The Luche conditions gave a highly diastereoselective 1,2-reduction.[141,142] That is, the secondary alcohol of **34** exists in *S*-configuration.
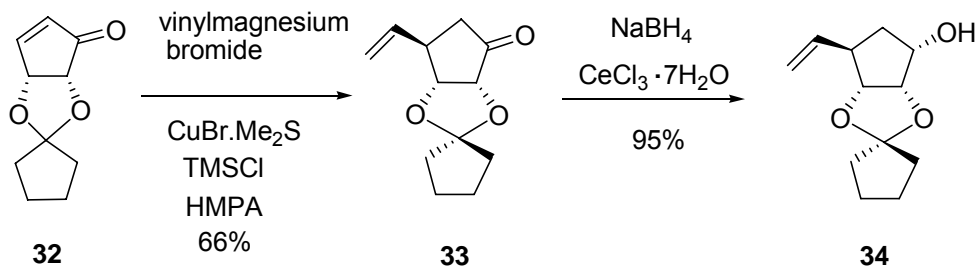
Scheme 16. Synthesis of 2, 3-(cyclopentylidenedioxy)-4-vinyl-cyclopentanol 34

With the synthesis of the two key intermediates 2, 3-(cyclopentylidenedioxy)-4-vinyl-cyclopentanol (**34**) and 6-chloro-3-deazapurine (**11**), a Mitsunobu coupling reaction involving this pair of compounds afforded the desired compound **35** (Scheme 17) along with di*iso*propyl hydrazine-1, 2-dicarboxylate.[131,143-145] Crude **35** was used directly in the next step without further purification. Hydrolysis of **35** with hydrochloric acid in methanol gave diol **36**. Subjecting **36** to a regioselectively protection of C-2′ hydroxyl group with 4-methoxybenzyl chloride (PMBCl) resulted in C-2′ (**37**) and C-3′ (**38**). Due to their structural similar, these two products were difficult to separate by silica gel column chromatography.
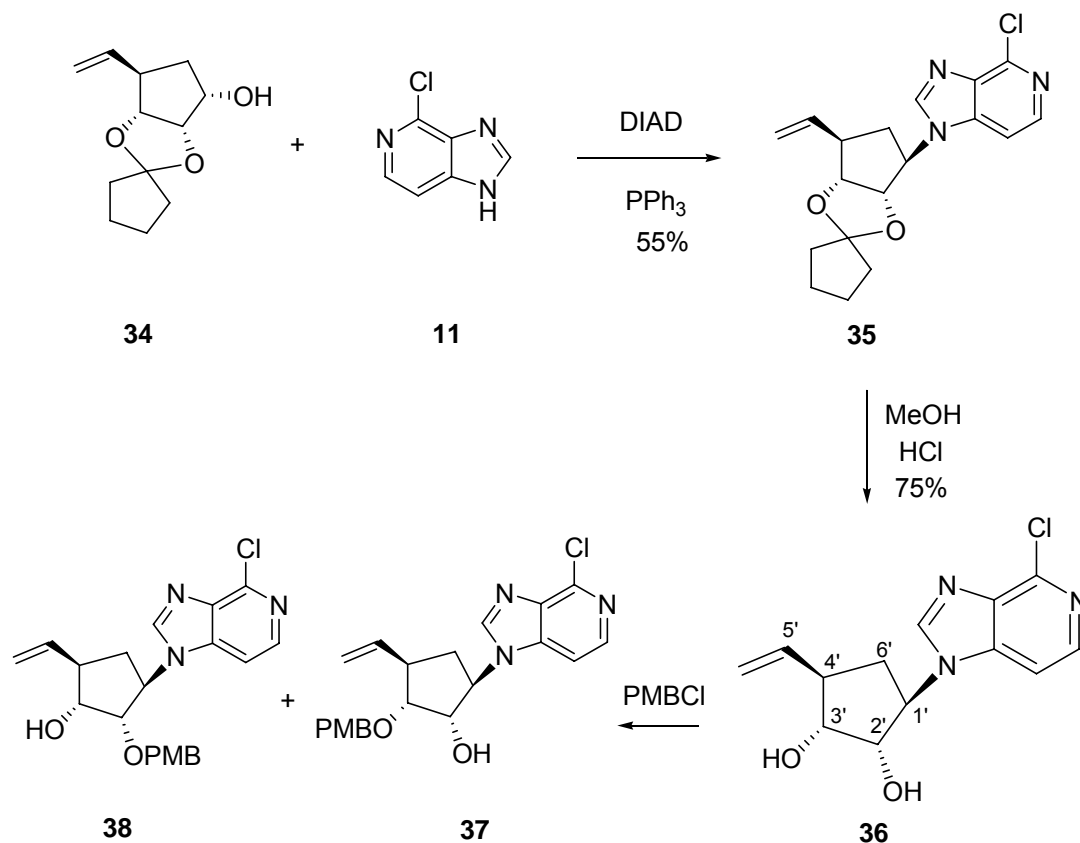
Scheme 17. Synthesis of mono-protected alcohol 38

For the purposes of this project, a means to protected C-2′ and C- 3′ derivatives that could be separated was required. Because the hydroxyl groups on C-2′ and C- 3′ position existed in different chemical environments, a few different reaction conditions were carried out to regioselectively protect the hydroxyl group at the C-2′ position (Table 1). However none of the reactions under these conditions could regioselectively protect only the hydroxyl group on C-2′ position with the consequences being mixtures of products, as **37** and **38** (Scheme 17) and **39** and **40** (Scheme 18) that were difficult to separate by silica gel column chromatography.

No.	Bases	Protection group	Solvents	Reaction conditions	products	yield
1	NaH	PMBCl	THF	0 ℃ to RT., 3 h	**37** and **38**	low
2	NaH	PMBCl	THF	-78 to - 40℃, 5 h	**37**, **38**, and **36**	low
3	Dibutyltin oxide, Tetrabutylammonium bromide,	PMBCl	Benzene	Reflux, 3 h	**37**, **38**	low
4	Et3N	PMBCl	THF	0 ℃ to RT., 5 h	**37**, **38**	80%
5	Imidazole	TBSCl	THF	0 ℃ to RT., 5 h	**39**, **40** (Scheme 18)	77%

Table 1. Different conditions for regioselective protection of C-2 hydroxyl group
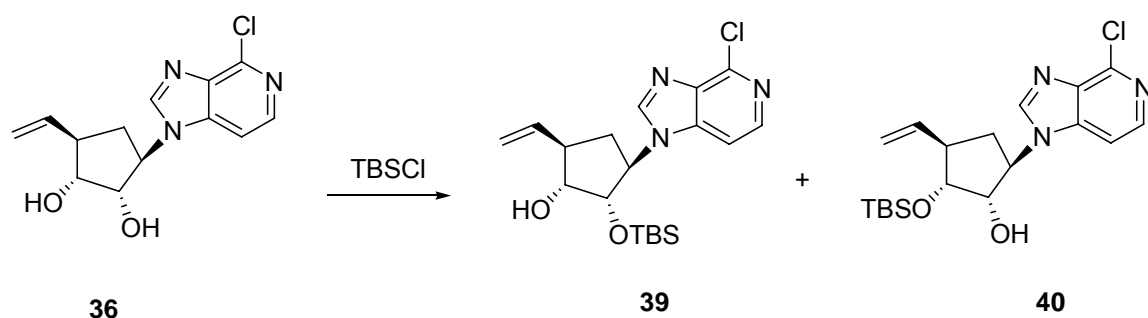
Scheme 18. Synthesis of mono-protected alcohol 39 from 36 with TBSCl

Further investigations into the regioselective protection of the hydroxyl groups on the C-2′ and C-3′ positions were conducted.[110,146-149] Scheme 19 shows a new route for this purpose. The dihydroxylation of the double bond of **35** with osmium tetraoxide (OsO$_4$) and N-methylmorpholine-N-oxide (NMO) afforded diol intermediate, which was subjected to oxidative cleavage with sodium periodate (NaIO$_4$) in one reaction vessel to produce an aldehyde. This aldehyde was subjected to reduction with sodium borohydride (NaBH$_4$) to give primary alcohol **41**. Protection of the C-5′ hydroxyl of **41** with *tert-*

butylchlorodiphenylsilane (TBDPSCl) yielded **42** that was deprotected with hydrochloric

acid in methanol to selectively remove the cyclopentylidene group to yield **43**.
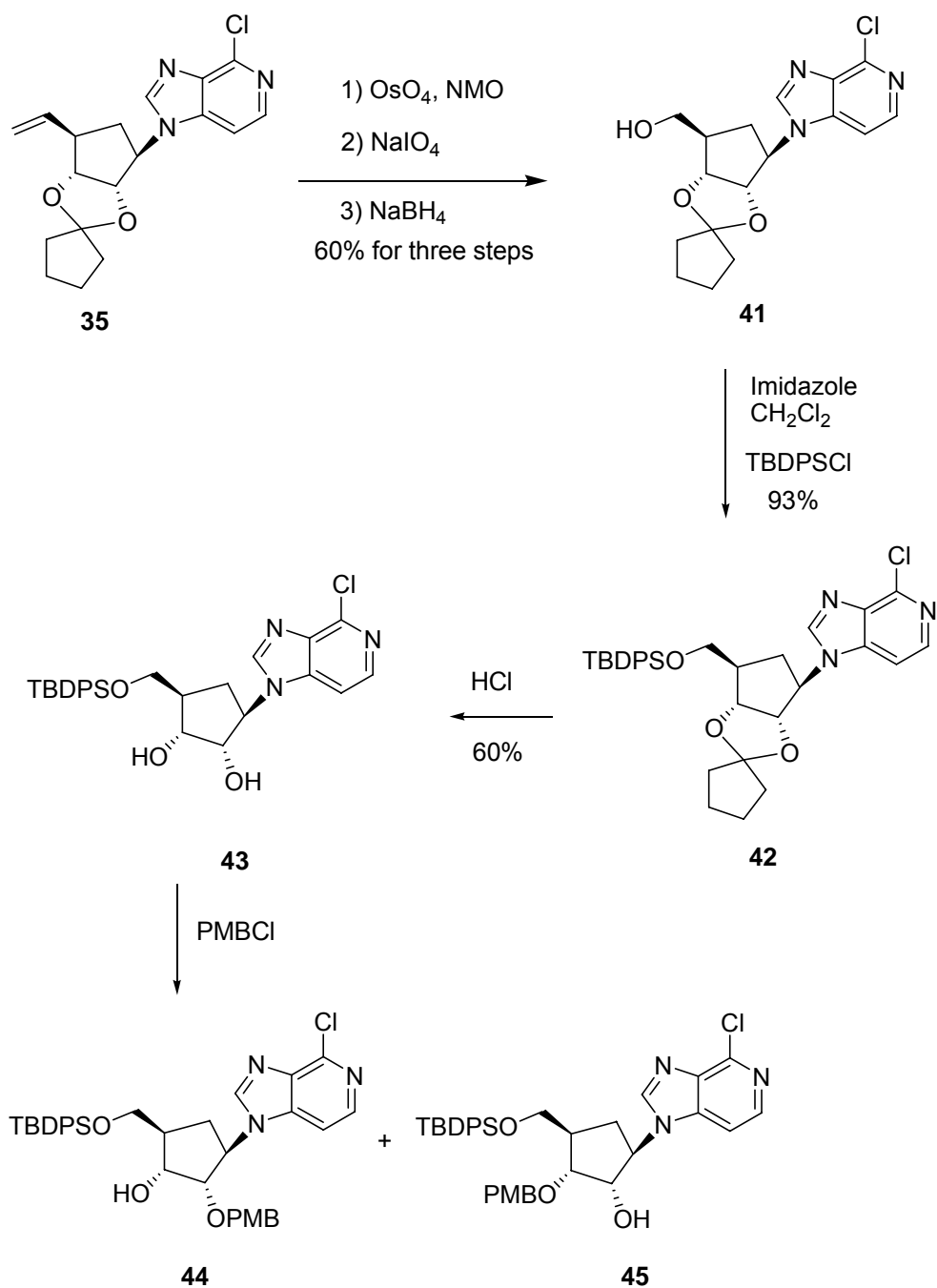
Scheme 19. Synthesis of mono-protected alcohol 44

The desired pure diol **43** was obtained in low yield, being accompanied by triol **46** as a consequence of the TBDPS protection group being sensitive to hydrochloric acid leading to its removal under the reaction conditions (Scheme 20).
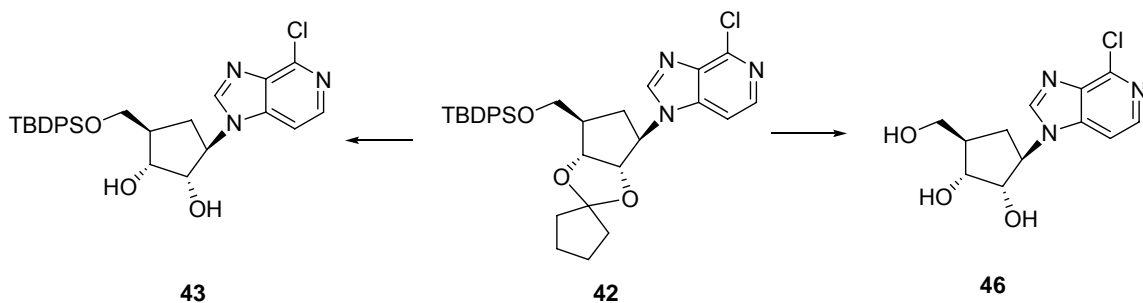
Scheme 20. Selective deprotection of 42

Optimized reaction conditions were sought to selectively remove the cyclopentylidene unit leaving the TBDPS protection group in tact (Table 2). With reaction condition 5, treating **42** with a catalytic amount of 0.6 M hydrochloric acid in methanol afforded **43** as the major product, which was along with minimum amounts of **42** and **46**.

No.	Acid	Reaction conditions	Product	Yield
1	HCl (2 M) , pH <1	0 ℃ to RT., 5 h	**46**	88%
2	HCl (0.6 M), pH <1	0 ℃ to RT., 5 h	**42**, **43**, and **46**	low
3	Acetic acid	0 ℃ to RT., 5 h	No reaction	
4	Phosphoric acid	0 ℃ to RT., 5 h	**42**, **43**, and **46**	low
5	HCl (0.6 M) catalyst amount, pH 4-5	0 ℃ to RT., Overnight	**43** was major product **42**, **46** were minority	60%

Table 2. Different conditions for selective deprotection of 42

An alternative route (Scheme 21) was considered to diol **43** since the hydrolysis of **42** was difficult to control (Table 2) and monitor by TLC. The new route began with deprotection of **41** with hydrochloric acid to provide triol **46** in 88% yield. Triol **46** was then treated with 1.1 equivalent of TBDPSCl, imidazole and 4-dimethylaminopyridine (DMAP) to selectively protect the C-5′ primary alcohol in 86% yield. This route was higher yield and more efficiency for synthesis of diol **43** than the route reported in Scheme 19.
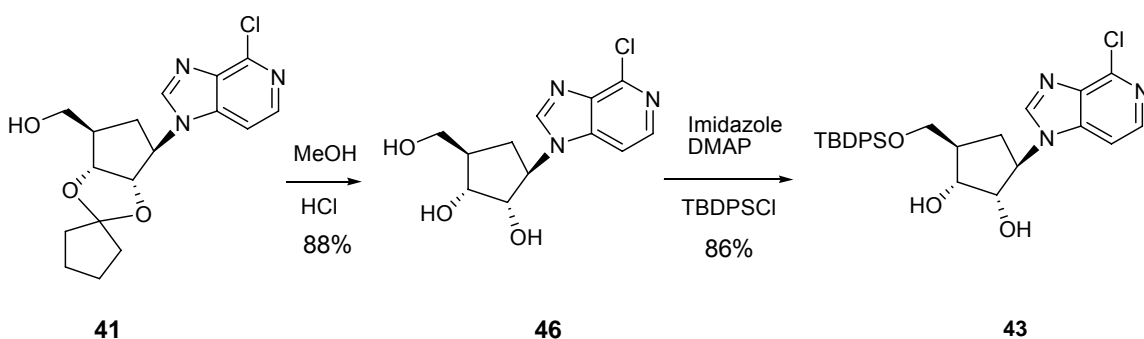
Scheme 21. Synthesis of 43

With diol **43** available, a renewed effort of regioselective protection of hydroxyl group at the C-2′ and C-3′ was followed (Scheme 22, where PG = protecting group).
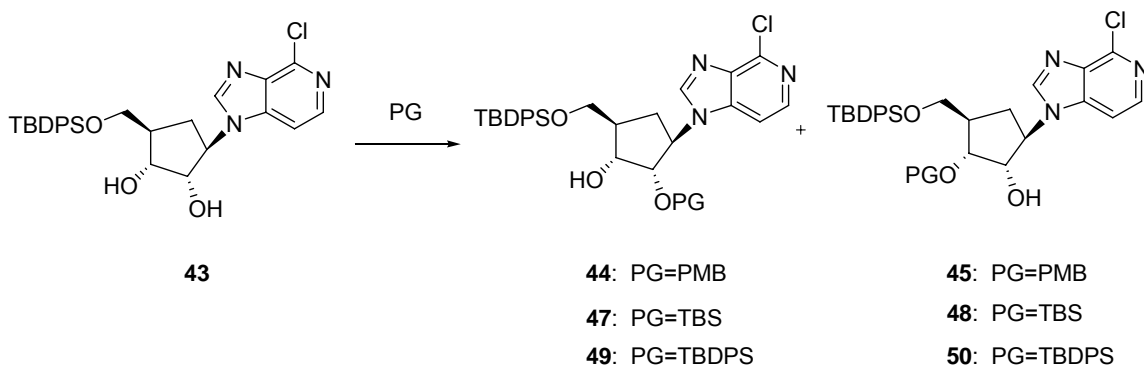
Scheme 22. Regioselective protection of diol 43

The reaction conditions of Table 3 were carried out. However, in all cases (PMBCl, TBSCl, and TBDPSCl) reactions with **43** in the presence of different bases produced mixtures of products, in which either hydroxyl group was protected. Fortunately, the mixture of **49** and **50** from reaction of **43** with TBDPSCl in CH_2Cl_2 at -40 to 0 ℃ for 6 hours could be separated by silica gel column chromatography. This was apparently due to a change in product polarity with introduction of the TBDPS groups.

No.	Base	Protection group	Solvent	Reaction conditions	Product	Yield
1	Dibutyltin oxide, Tetrabutylammonium bromide	PMBCl	Benzene	Reflux	**44**, **45**	low
2	NaH, Bu$_4$NI	PMBCl	THF	0 ℃ to RT	No product	0
3	NaH	PMBCl	DMF	0 ℃ to RT	**44** and **45**	low
4	NaOC(CH$_3$)$_3$	PMBCl	DMF	0 ℃ to RT	**44** and **45**	low
5	Et$_3$N	TBSCl	THF	0 ℃ to RT	**44** and **45**	80%
6	Imidazole	TBSCl	THF	0 ℃ to RT	**47** and **48**	75%
7	Imidazole, DMAP	TBDPSCl	CH$_2$Cl$_2$	-40 to 0℃	**49** and **50**	82%

Table 3. Different conditions for regioselective protection of 43

When hydroxyl group on C-2′ position was protected alcohol to get **49**, a Mitsunobu reaction of 49 with chloroacetic acid caused C-3′ stereo-reversion to ester **51** in 55% yield (Scheme 23). Hydrolysis of ester **51** with lithium hydroxide gave alcohol **52**, in which the C-3′ was successfully changed to *S*-configuration from the *R*-configuration in alcohol **49**. Fluorination of 52 with (diethylamino)sulfur trifluoride (DAST) gave **53** in 50% yield.[108,150-153] Hydrolysis of **53** with hydrochloric acid removed the TBDPS protection groups to yield diol **54**. Unfortunately, subsequent amination of 6-chlorine of

54 with hydrazine and followed reduction with Raney Nickel did not lead to the desired

target **1**.
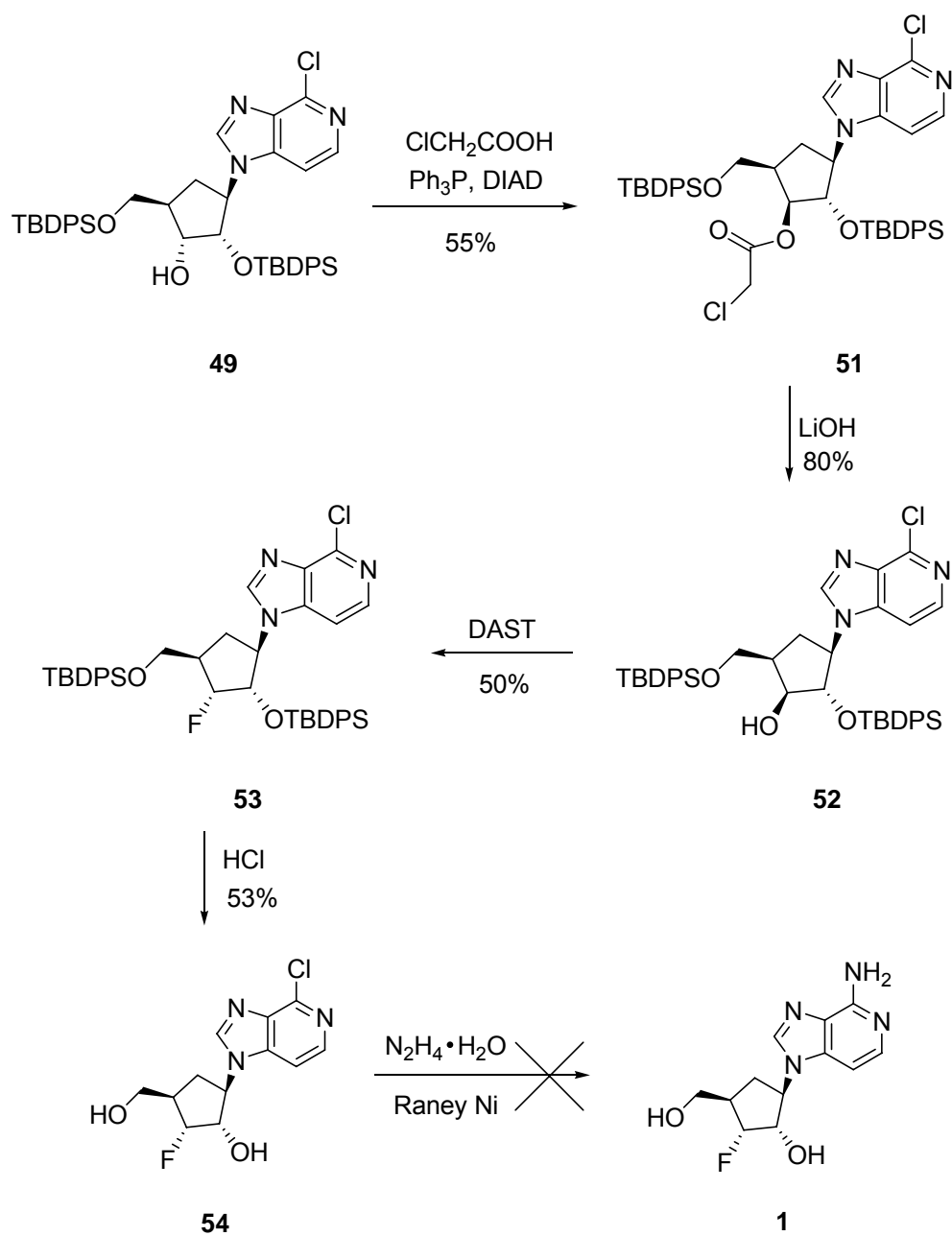
Scheme 23. Synthesis of 1

Although several attempts were carried out and tried to find out the reasons for failure to convert **54** to **1**, it was concluded that decomposition of **1** might have occurred under the harsh conditions of the amination with hydrazine and reduction with Raney Nickel under reflux in water for an extended period. Realizing the difficulty to convert the 6-chlorine of **54** to an amino group at the final stage, a revised retrosynthetic analysis of target **1** was developed (Scheme 24). In this regard, a synthetic strategy was foreseen with the basic idea being to convert the 6-chloro of 3-deazapurine **11** into an amino substituent first. This strategy could avoid the failed amination and reduction reactions at the final stage of the previous synthetic route.
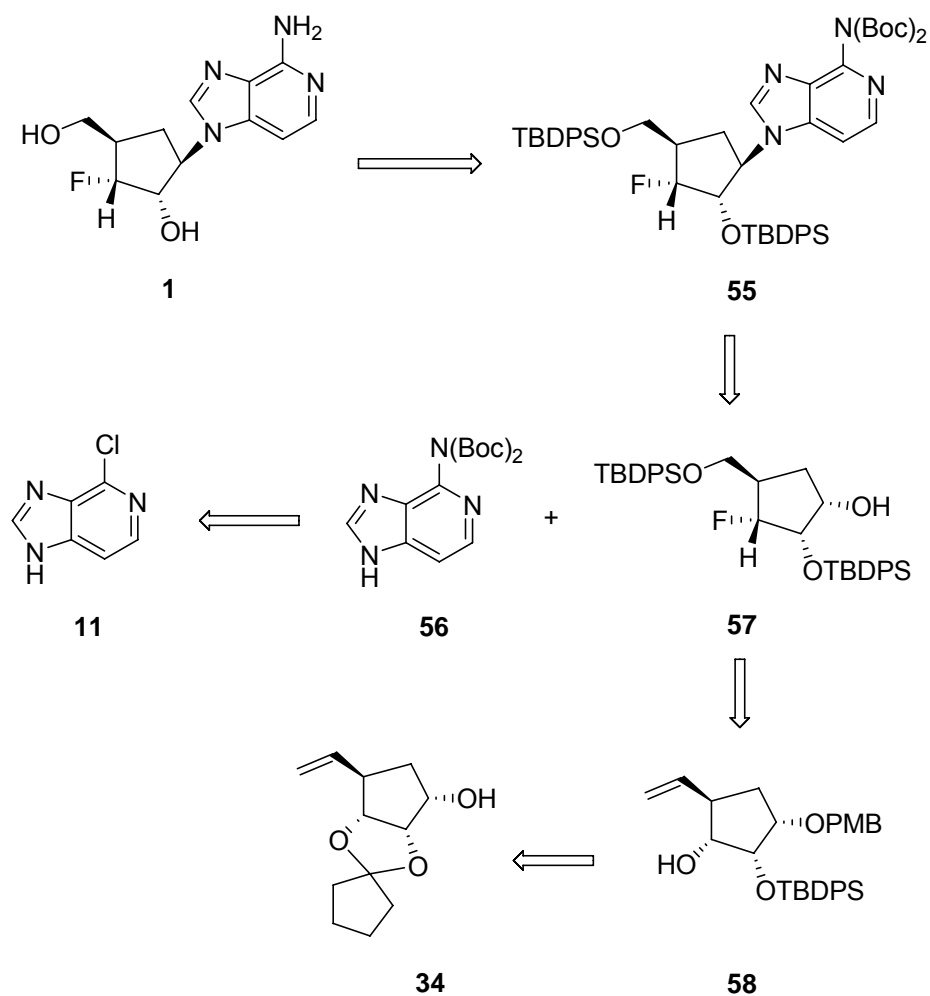
Scheme 24. Revised retrosynthetic analysis of (3′R)-3′-deoxy-3′-fluoro-3-deazaaristeromycin 1

The previous key intermediate **34** (Scheme 25) was treated with NaH and PMBCl to afford protected **59**. Hydrolysis of **59** with hydrochloric acid resulted in diol **60**. Subjecting **60** to regioselective protection of the C-2 and C-3 hydroxyl groups with TBDPSCl gave **58** and **61**, which were separated by silica gel column chromatography. The ratio of **58** and **61** was 55 : 45 in 75% yield.
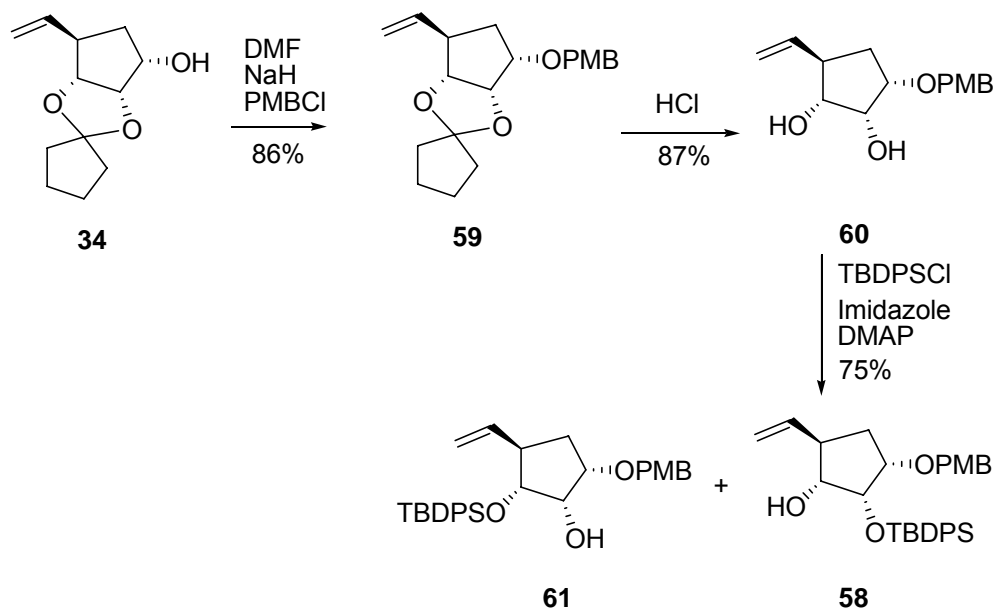
Scheme 25. Synthesis of mono-protected alcohol 58 and 61

In Scheme 26, the key intermediate **57** was obtained from alcohol **58** by beginning with a Mitsunobu reaction using chloroacetic acid to produce the chloroacetate **62** that was hydrolyzed to alcohol **63**, in which the configuration at the C-3 was inverted in relation to alcohol **58**. Introduction of the requisite fluorine atom was accomplished by exposure of alcohol **63** to DAST[154] in CH_2Cl_2 to afford fluoro **64**. In this fluorination step,

the reaction conditions were very careful controlled because the TBDPS group in known to be unstable in the presence of fluoride anions.[151-153,155] When the reaction was carried out at -78 ℃ to -20 ℃, the fluorination occurred slowly and in low yield due to a long reaction time and the TBDPS group was removed during reaction because of the fluoride anions that generated during the decomposition of DAST. Higher reaction temperatures also resulted in a rapid removal of the TBDPS group. Finally, an optimized condition was found in which the reaction was carried out at 20 ℃ for about 30 minutes, tracing by TLC until the alcohol **63** disappeared, in 65% yield. This step was followed by dihydroxylation with osmium tetraoxide and N-methylmorpholine N-oxide, and subsequent NaBH$_4$ reduction to alcohol **65**. The primary alcohol of **65** was protected with TBDPS to **66** and removal of the PMB group of **66** with 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (DDQ) gave the desired **57**.
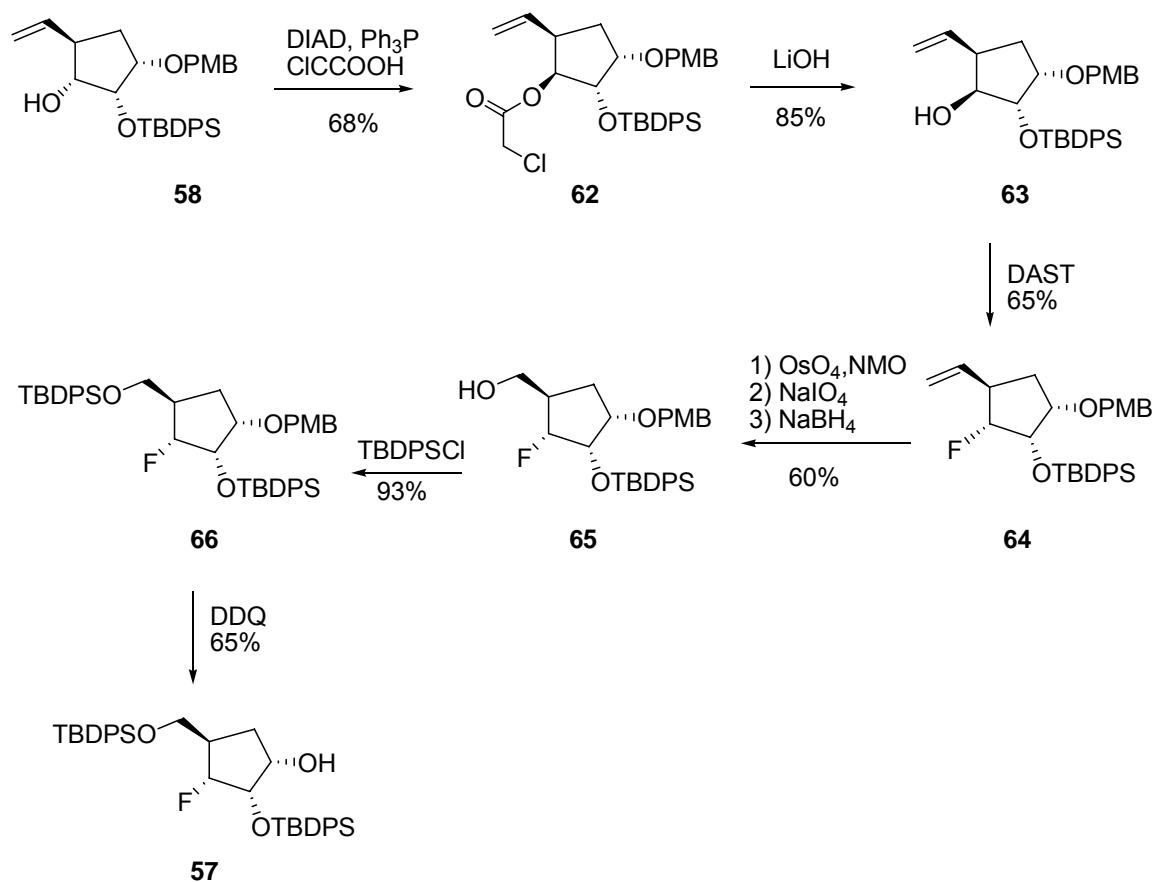
Scheme 26. Synthesis of 3′-fluoro-cyclopentanol derivative 57

To follow Scheme 24, the di-Boc protected derivative of 3-deazaadenine **56** was needed and it was prepared through an optimized route developed in the Schneller laboratory (Scheme 27). Amination of 6-chloro-3-deazapurine (**11**) with hydrazine in 1-propanol under reflux followed reduction with Raney Nickel afforded 3-deazaadenine **67**. Initial protection of **67** with di-*tert*-butyldicarbonate [(Boc)₂O] and DMAP yielded the tri-Boc derivative **68**,[156] which could be mono-deprotected to **56** in the presence of *tetra*-n-butylammonium fluorine (TBAF) overnight in 63% yield.
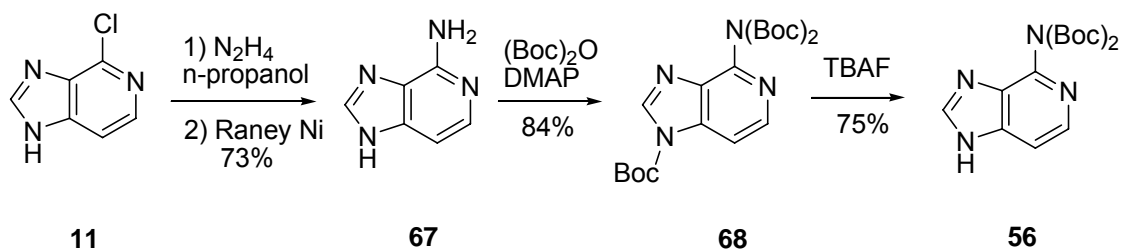
Scheme 27. Synthesis of 3-deazaadenine derivative 56

Finally, the synthesis of (3′R)-3′-deoxy-3′-fluoro-3-deazaaristeromycin (**1**) (Scheme 28) was accomplished via **56** and **57** by calling on a Mitsunobu reaction to **69**, which was contaminated with reduced DIAD species, and followed by removal of all the protecting groups of **69**. The reason of overall low yield was that alcohol **57** and 3-deazaadenine **56** under the Mitsunobu conditions did not react well, which was along with byproduct.
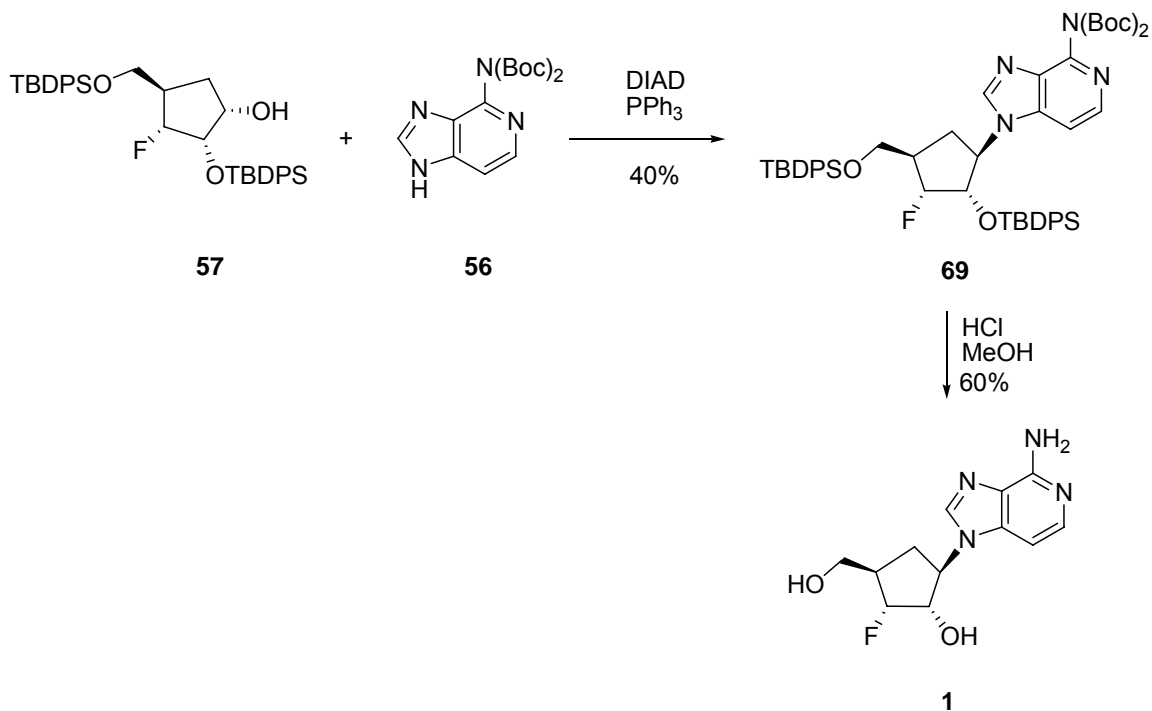
Scheme 28. Synthesis of (3′R)-3′-deoxy-3′-fluoro-3-deazaaristeromycin 1

Synthesis of (3′*S*)-3′-deoxy-3′-fluoro-3-deazaaristeromycin (2)

Experimental Design and Synthesis.

As mentioned before, the mechanism of AdoHcy hydrolase (Scheme 9) showed that hydroxyl group at C-3′ position is very important because it is selectively oxidized to form 3′ ketoAdoHcy in the first step. Therefore, in continuing to consider the possibilities of a fluoro atom at that center would bring antiviral properties, the diastereomer of **1**, (3′*S*)-3′-deoxy-3′-fluoro-3-deazaaristeromycin (**2**) was another target compound. Based on the results leading to **1**, the retrosynthetic analysis towards **2** is shown (Scheme 29). The mono-protected alcohol **58** and di-Boc-3-deazaadenine **56** were seen as start materials.
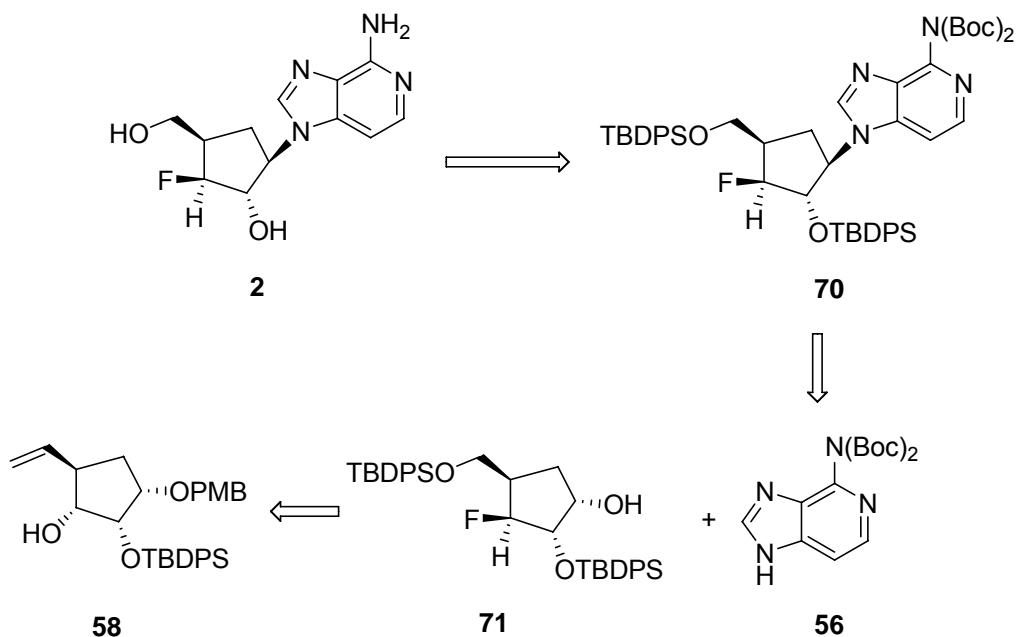
Scheme 29. Retrosynthetic analysis of 2

The intermediate **71** was synthesized from **58** (Scheme 30). Introduction of the fluorine atom was accomplished by exposure of **58** to DAST to afford **72**. The dihydroxylation of the exocyclic double bond of **72** with OsO_4 and NMO afforded a diol intermediate, which was subjected to oxidative cleavage with $NaIO_4$ in the reaction vessel to produce an aldehyde intermediate. The aldehyde intermediate, without further purification, was reduced with $NaBH_4$ to give primary alcohol **73**. Product **73** was protected with TBDPSCl to afford **74**. Removal of the PMB group of **74** with DDQ gave **71**.
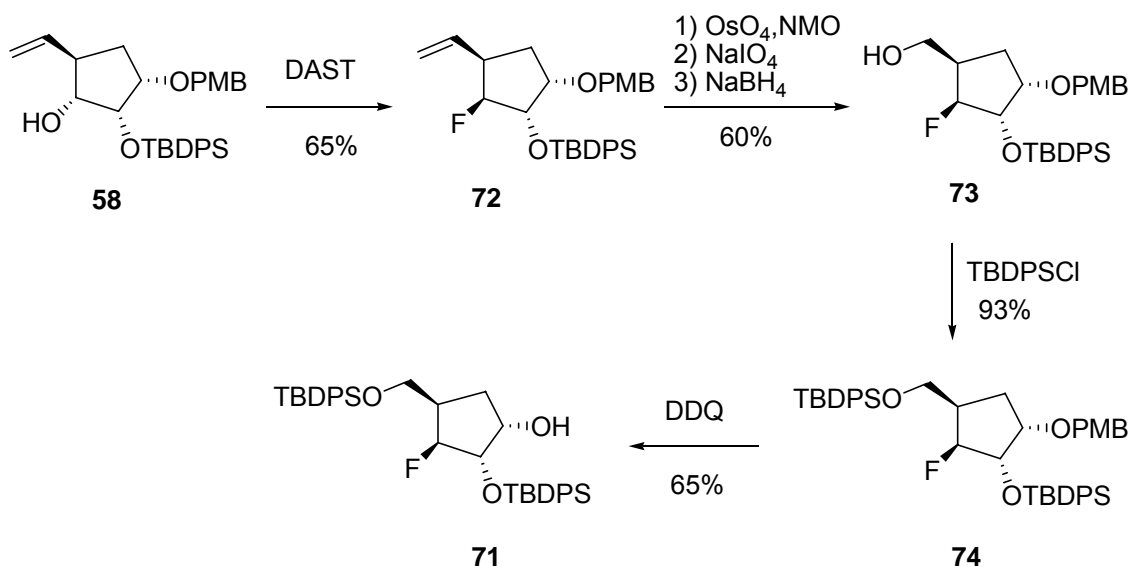
Scheme 30. Synthesis of 71

By Scheme 31, (3′*S*)-3′-deoxy-3′-fluoro-3-deazaaristeromycin (**2**) was achieved accomplished via **71** and **56** through a Mitsunobu reaction and followed by removal of all the protecting groups of **75** with hydrochloric acid.
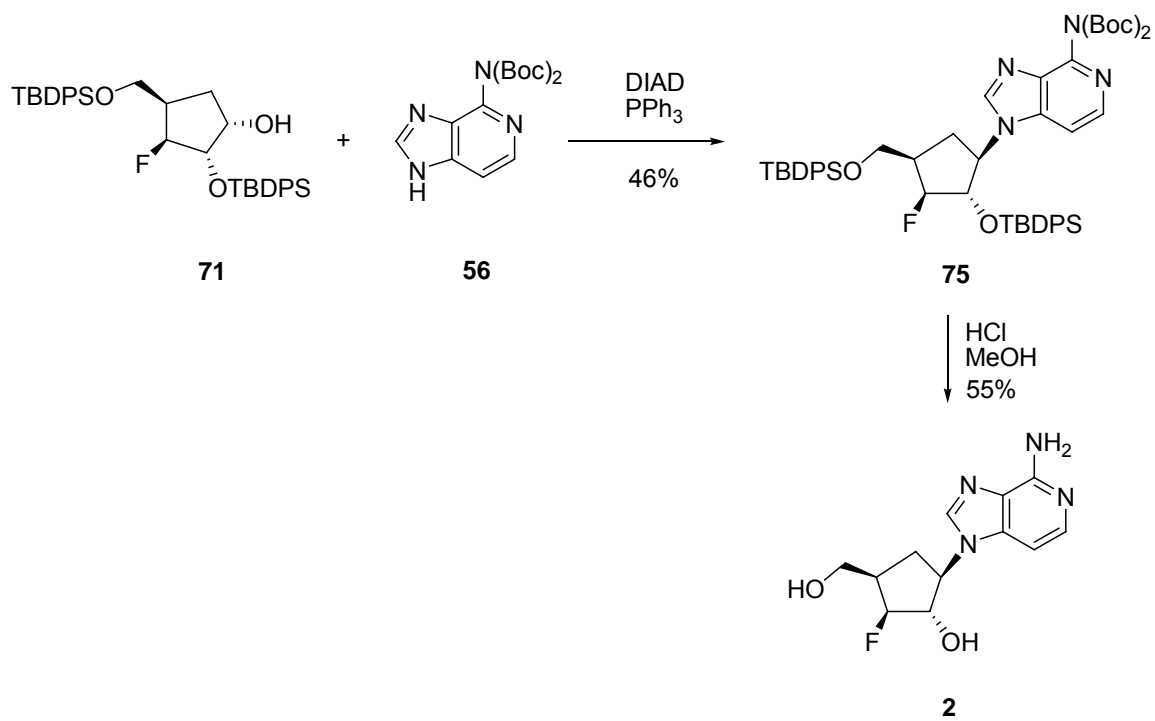
Scheme 31. Synthesis of (3′*S*)-3′-deoxy-3′-fluoro-3-deazaaristeromycin 2

Synthesis of 3′-deoxy-3-deazaaristeromycin (3)

Experimental Design and Synthesis.

Because of the role C-3′ hydroxyl center of substrates plays in the metabolic processes of AdoHcy hydrolase, deleting the C-3′ hydroxyl (hence, removing the possibility for oxidation at this site) became a target in this research. Thus, 3′-deoxy-3-deazaaristeromycin (**3**) was sought and its retrosynthetic analysis is shown (Scheme 32). In this case, mono-protected alcohol **58** and di-Boc-3-deazaadenine derivative **56** were projected as start materials.

Scheme 32. Retrosynthetic analysis of 3′-deoxy-3-deazaaristeromycin 3

The intermediate **77** was synthesized from **58** (Scheme 33). Beginning with a Barton deoxygenation of **58** to the thiocarbonyl derivative **78**, compound **78** was reacted with tributyltin hydride (Bu$_3$SnH) in the presence of a catalytic amount of azobis*iso*butyronitrile (AIBN) in refluxing toluene. Although the desired deoxygenated **79** was obtained, the yield was low, varying between 30-50%. As described elsewhere herein oxidative cleavage of **79** by OsO$_4$-NaIO$_4$ produced an aldehyde intermediate that was subjected to reduction with NaBH$_4$ to primary alcohol **80**. This product **80** was protected with TBDPSCl to result in **81.** Removal of the PMB group of **81** with DDQ provided **77**.
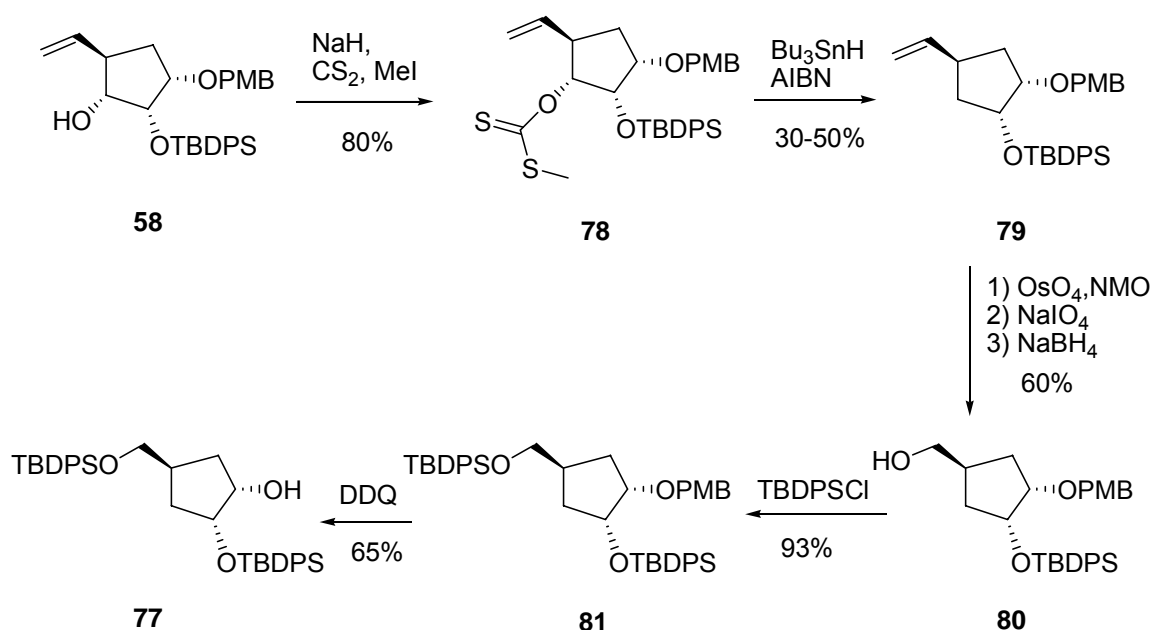
Scheme 33. Synthesis of 77

The Barton deoxygenation reaction was further investigated to improve deoxygenation of alcohol **58**.[157-163] The mechanism of the Barton deoxygenation (Scheme 34) shows that it is a free radical reaction and the low concentration of Bu$_3$Sn· effects the

reaction. A higher concentration of Bu$_3$Sn· is helpful to improve the yield. However, the radicals also attack double bonds suggesting that the vinyl group in **78** may be susceptible to Bu$_3$Sn· in a radical chain reaction, which would make it difficult to optimize the Barton deoxygenation reaction conditions for the purposes of this project for higher yield.

Initiation:

$$Bu_3Sn-H \xrightarrow{\text{AIBN}} Bu_3Sn\cdot \; + \; \cdot H$$
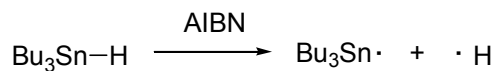
The catalytic cycle, in which low concentration of the ·SnBu$_3$ effects the reaction:
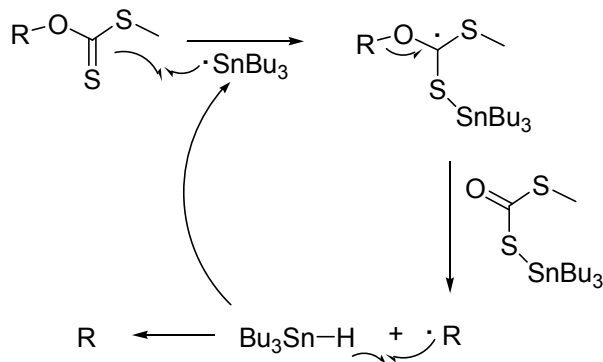
Scheme 34. The mechanism of the Barton deoxygenation

Realizing the difficulty to use Barton deoxygenation, an alternative route was chosen to synthesize **79** (Scheme 35).[163] Alcohol **58** was treated with methanesulfonyl chloride (MsCl) to avail **82**, which was followed by a reduction with lithium aluminium hydride (LiAlH$_4$) to give **79** in 45% yield for two steps.
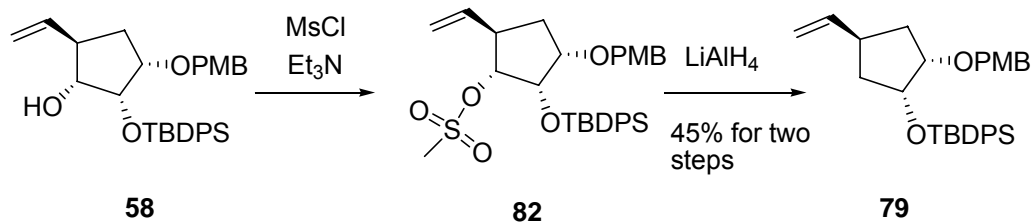
Scheme 35. Synthesis of 79

In turn, 3′-deoxy-3-deazaaristeromycin (**3**) (Scheme 36) was achieved via **77** and **56** under Mitsunobu conditions followed by removal of all the protecting groups of **83** with hydrochloric acid.
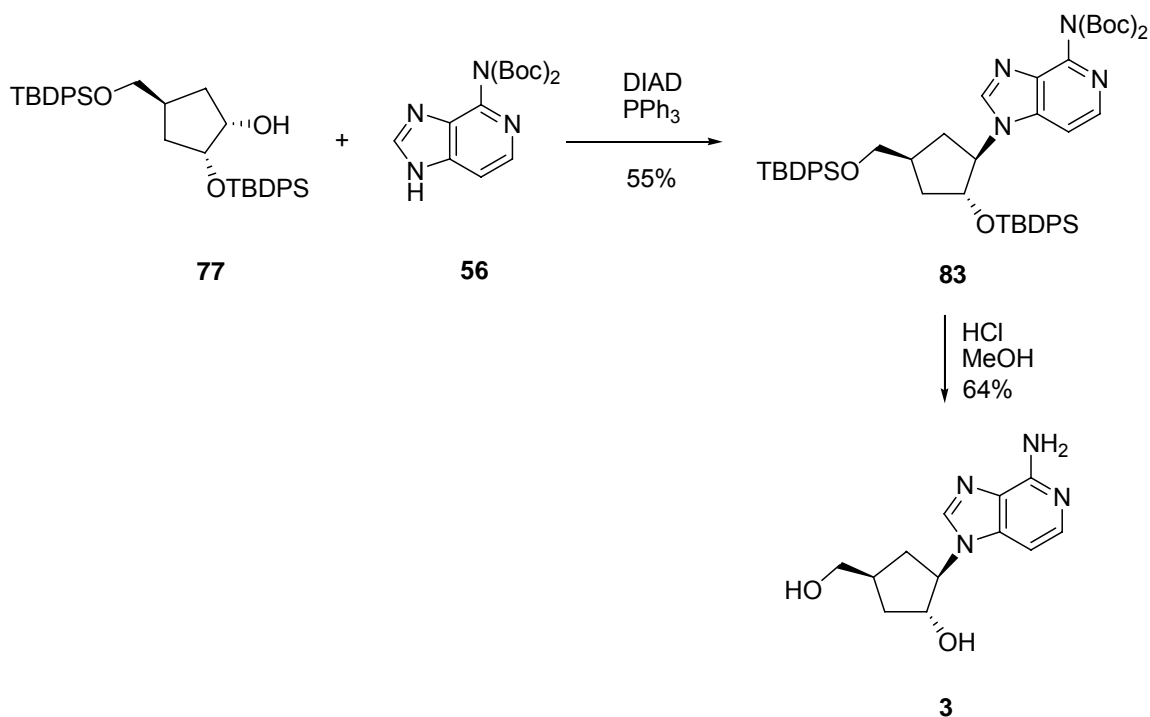
Scheme 36. Synthesis of 3′-deoxy-3-deazaaristeromycin 3

Synthesis of (2′*S*)-2′-deoxy-2′-fluoro-3-deazaaristeromycin (4)

Experimental Design and Synthesis.

As mentioned earlier, the 1′, 2′ arrangement between the nucleobase attached at the anomeric center and the heteroatom at C-2′ was found in numerous biologically relevant nucleoside analogues.[121-123] In that regard, (2′*S*)-2′-deoxy-2′-fluoro-3-deazaaristeromycin (**4**) became a goal and retrosynthetic analysis for this purpose is shown in Scheme 37. The mono-protected alcohol **61** and di-Boc-3-deazaadenine **56** were to be starting materials.
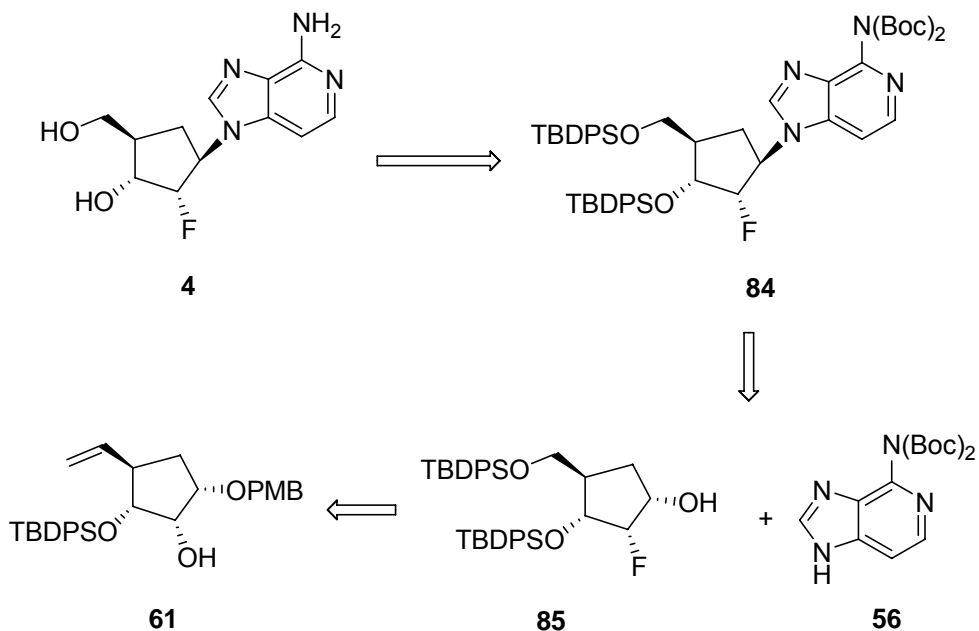
Scheme 37. Retrosynthetic analysis of (2′*S*)-2′-deoxy-2′-fluoro-3-deazaaristeromycin 4

The 2-fluoro cyclopentanol derivative **85** was synthesized from **61** (Scheme 38). Again calling on the Mitsunobu reaction, **61** was treated with chloroacetic acid to produce the chloroacetate **86**, which was hydrolyzed to alcohol **87**. Introduction of the fluorine atom was accomplished by exposure of alcohol **87** to DAST in CH_2Cl_2 to lead to **88**. This was followed by dihydroxylation with osmium tetraoxide and N-methylmorpholine N-oxide, and subsequent $NaBH_4$ reduction to get alcohol **89**. The primary alcohol of **89** was protected with TBDPS to **90** followed removal of the PMB group of **90** with DDQ gave **85**.
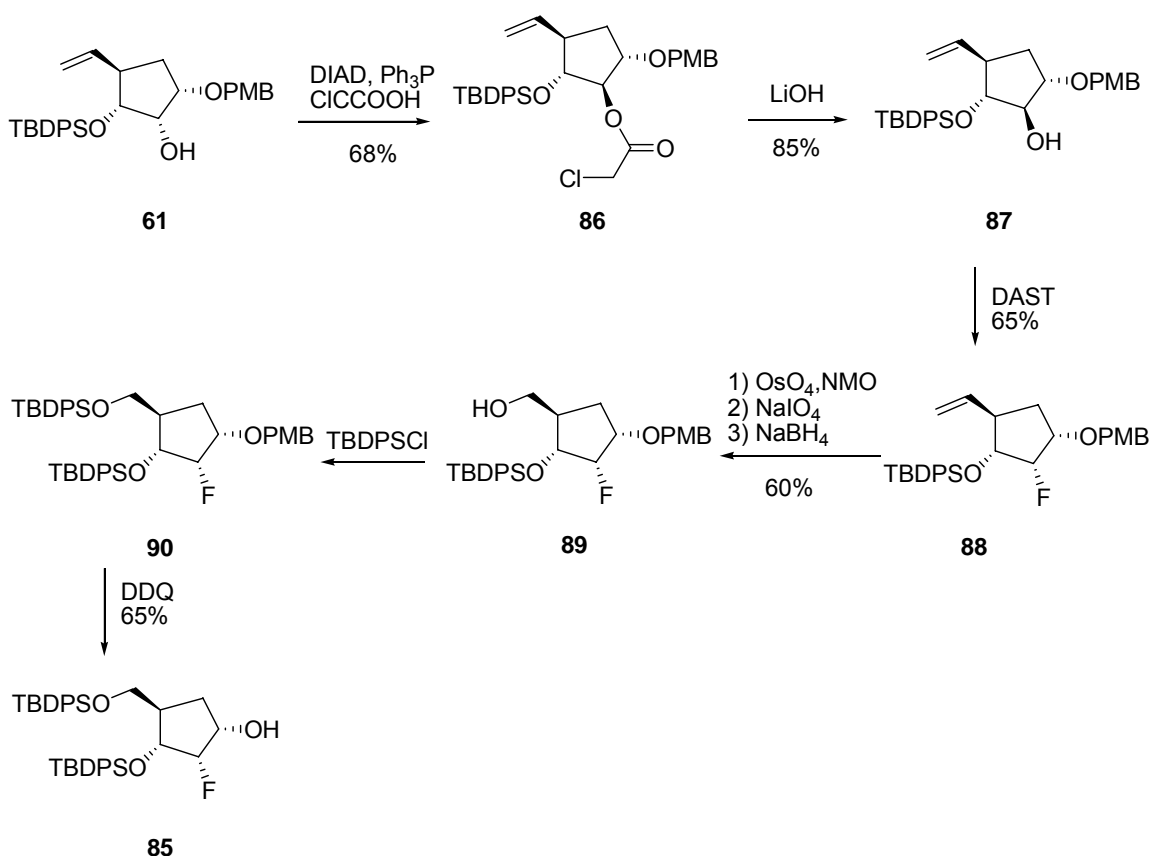
Scheme 38. Synthesis of 2-fluoro cyclopentanol derivative 85

Calling on the Mitsunobu reaction, (2′*S*)-2′-deoxy-2′-fluoro-3-deazaaristeromycin (**4**) (Scheme 39) was accomplished via **56** and **85** to **91**. This was followed by removal of all the protecting groups of **91**.
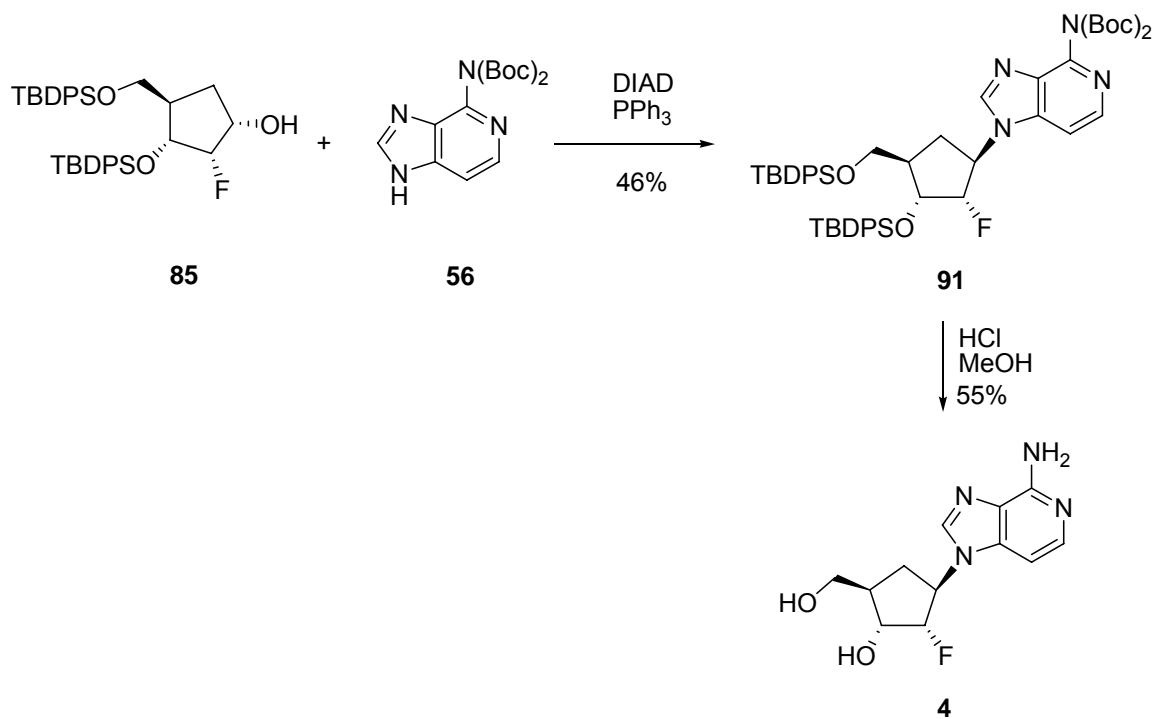
Scheme 39. Synthesis of (2′*S*)-2′-deoxy-2′-fluoro-3-deazaaristeromycin 4

Synthesis of (2′*R*)-2′-deoxy-2′-fluoro-3-deazaaristeromycin (5)

Experimental Design and Synthesis.

As mentioned before, (2′*R*)-2′-deoxy-2′-fluoro-3-deazaaristeromycin (**5**) was selected as a target compound because its 1′, 2′-*cis* arrangement is related to numerous biologically relevant nucleoside analogues. A retrosynthetic analysis for this purpose is shown in Scheme 40 and calls for the mono-protected alcohol **61** and di-Boc-3-deazaadenine **56** as starting materials.
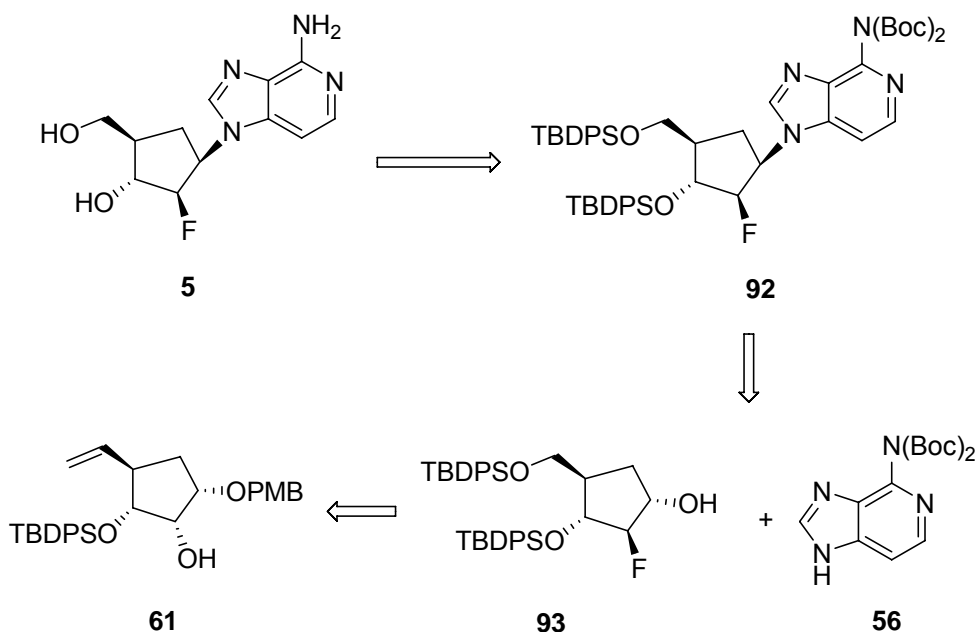
Scheme 40. Retrosynthetic analysis of 5

The 2-fluorocyclopentanol derivative **93** was synthesized from **61** (Scheme 41). The introduction of the fluorine atom was accomplished by exposure of **61** to DAST to

produce **94**. Dihydroxylation of the double bond of **94** with OsO$_4$ and NMO afforded a diol intermediate, which was subjected to oxidative cleavage with NaIO$_4$ in the same reaction vessel to produce an aldehyde intermediate. This intermediate, without further purification, was subjected to reduction with NaBH$_4$ to give **95**. Protection of **95** with TBDPSCl to **96** and followed removal of the PMB group with DDQ gave **93**.
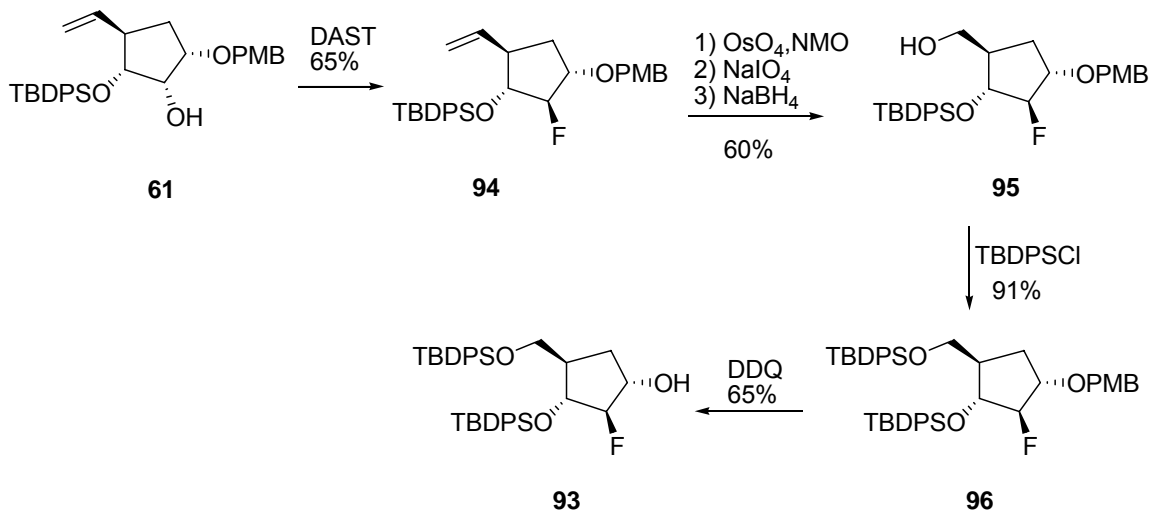
Scheme 41. Synthesis of 2-fluoro-cyclopentanol derivative 93

Finally, (2$'$*R*)-2$'$-deoxy-2$'$-fluoro-3-deazaaristeromycin (**5**) (Scheme 42) was accomplished via **93** and **56** through a Mitsunobu reaction. This was followed by removal of all the protecting groups of **97** with hydrochloric acid to give **5**.
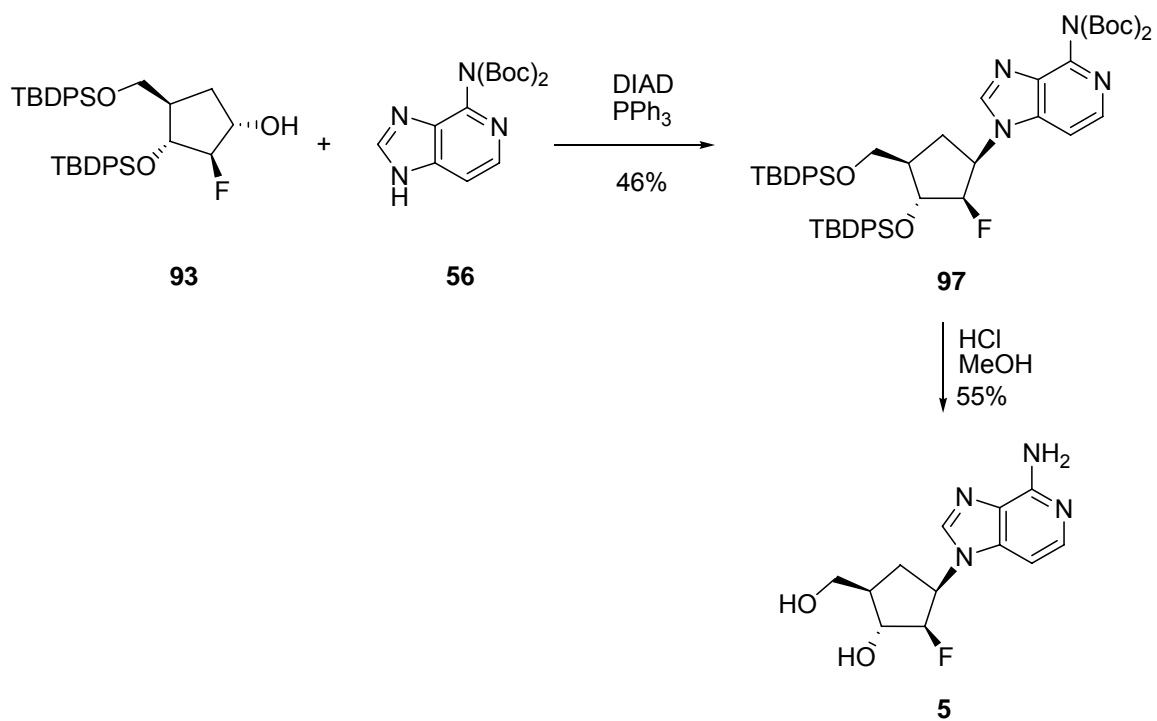
Scheme 42. Synthesis of (2′*R*)-2′-deoxy-2′-fluoro-3-deazaaristeromycin 5

Synthesis of 2′-deoxy-3-deazaaristeromycin (6)

Experimental Design and Synthesis.

To complete the analog series of this project, 2′-deoxy-3-deazaaristeromycin (**6**) was target compound. Its retrosynthetic analysis was foreseen as Scheme 43 and follows other approaches by calling on alcohol **61** and base **56**.
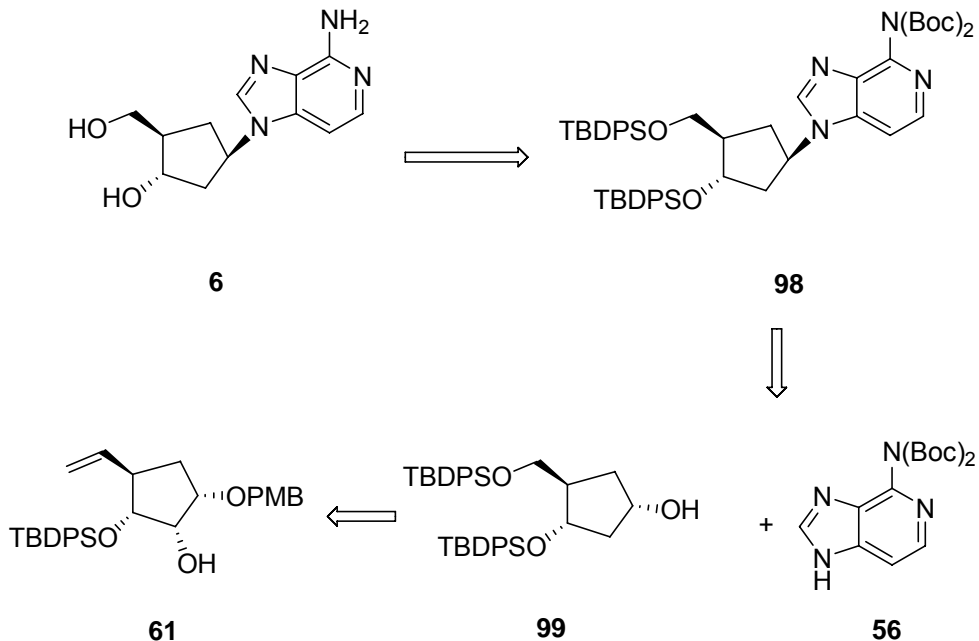
Scheme 43. Retrosynthetic analysis of 2′-deoxy-3-deazaaristeromycin 6

The 2-deoxycyclopentanol derivative **99** was synthesized from **61** (Scheme 44). Barton deoxygenation of **61** began with conversion to the thiocarbonyl derivative **100**, which was then reacted with Bu₃SnH in the presence of catalytic amount of AIBN in refluxing toluene to the deoxygenated **101.** Oxidative cleavage of **101** by OsO₄-NaIO₄ to

an aldehyde intermediate that was subjected to reduction with NaBH$_4$ resulted in alcohol **102**. Protection of **102** with TBDPSCl to **103** was followed by removal of the PMB group with DDQ to provide **99**.
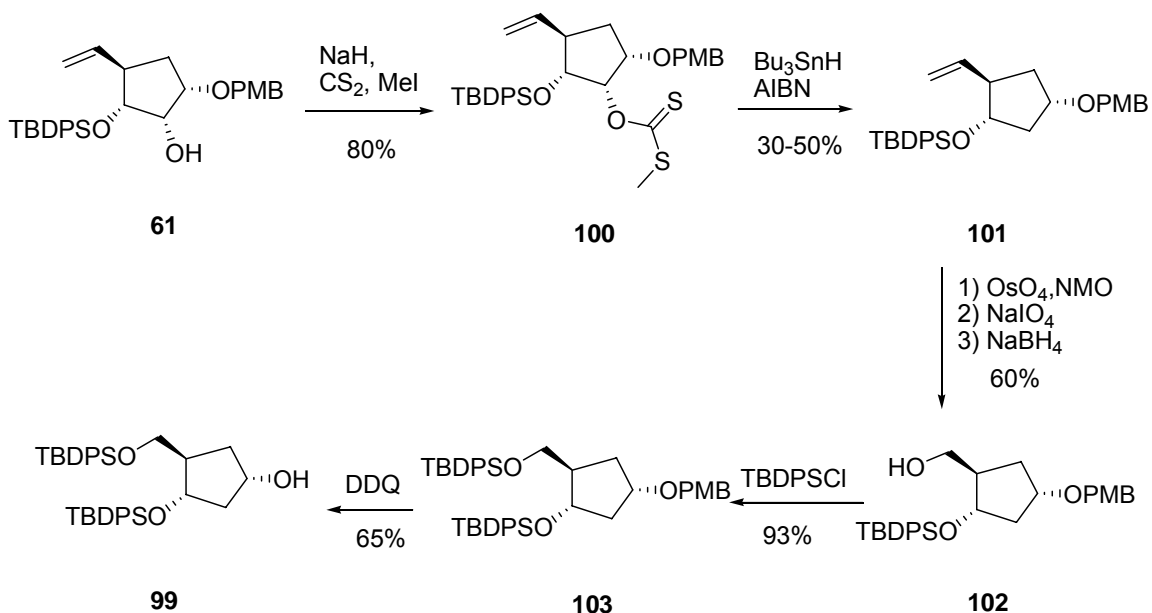
Scheme 44. Synthesis of 2-deoxy-cyclopentanol derivative 99

Finally, 2′-deoxy-3-deazaaristeromycin (**6**) (Scheme 45) was accomplished via **99** and **56** through a Mitsunobu reaction. This was followed by removal of all the protecting groups of **104** with hydrochloric acid to give **6**.
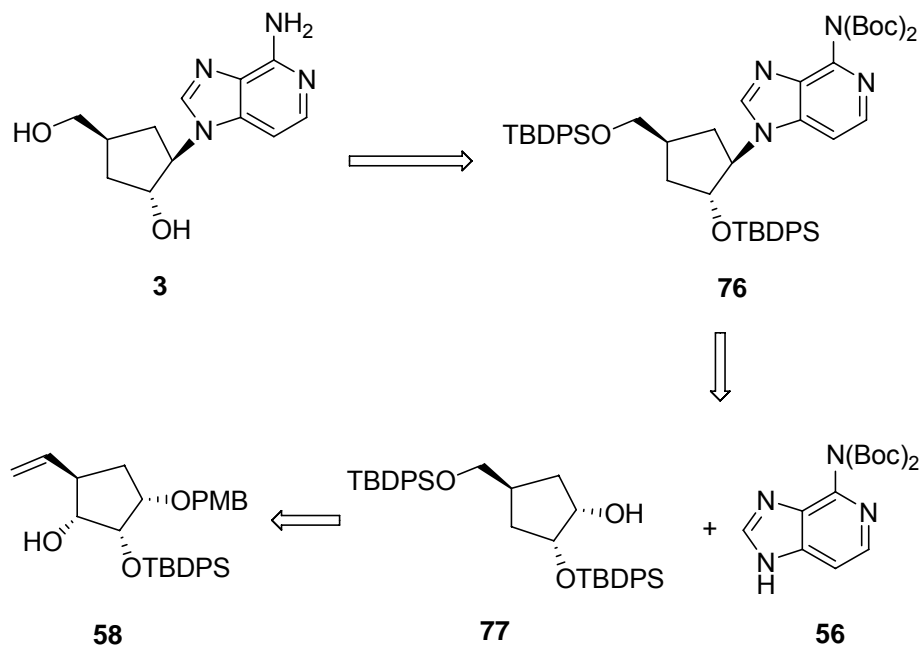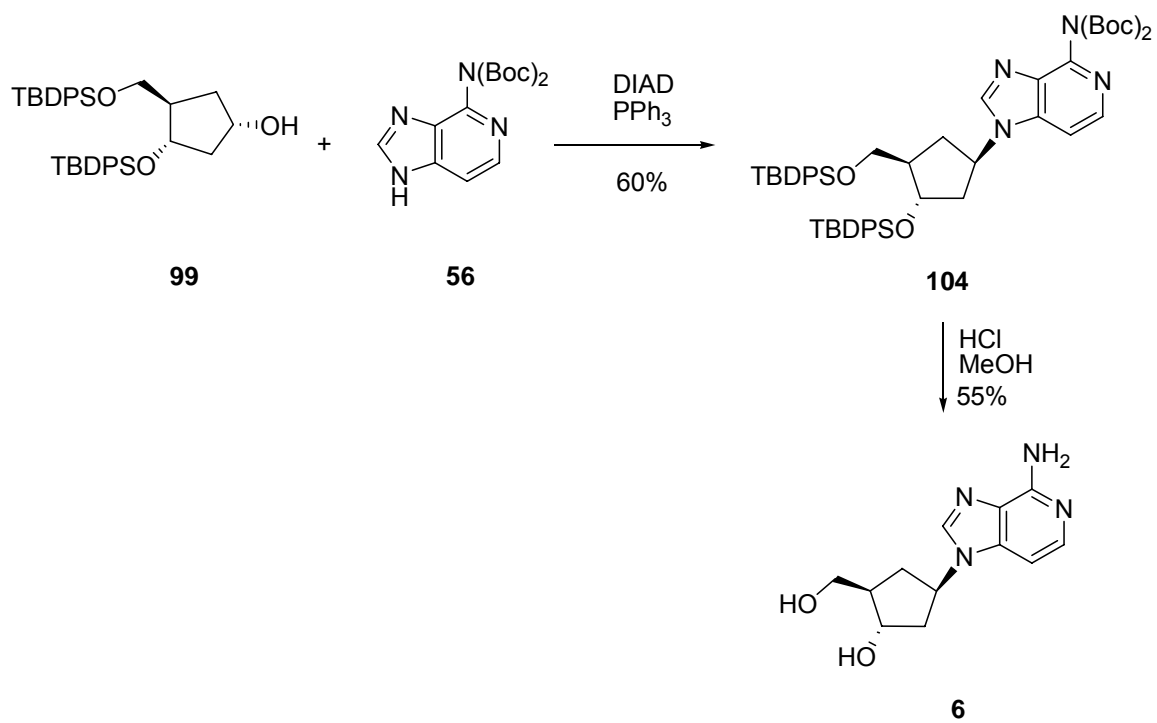
Scheme 45. Synthesis of 2′-deoxy-3-deazaaristeromycin 6

Synthesis of 4′-methyl-3-deazaaristeromycin (7)

Experimental Design and Synthesis.

As a potential antiviral agent against HIV mentioned in the introduction, 4′-methyl-3-deazaaristeromycin (**7**) was selected as target compound via the retrosynthetic analysis of Scheme 46. The intermediate cyclopentylidene cyclopentenone **32** and 6-chloro-3-deazapurine **11** were set as start points.
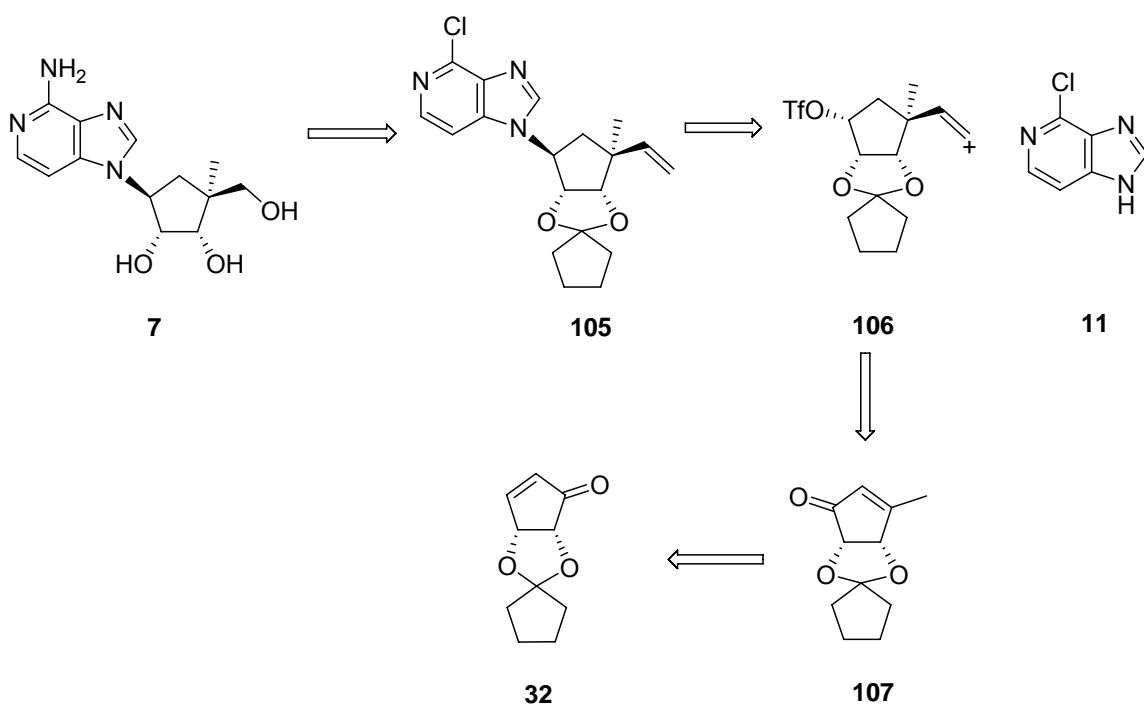
Scheme 46. Retrosynthetic analysis of 4′-methyl-3-deazaaristeromycin 7

The execution of this route is shown in Scheme 47. Treatment of the cyclopentenone **32** with methyllithium (MeLi) in THF at -78 ℃ yielded the tertiary allylic alcohol **108** in

85% yield. Subjecting **108** to the known oxidative rearrangement of tertiary allylic alcohols by pyridinium dichromate (PDC) afforded **109**.[164] However, the transformation of **108** to 4-methylcyclopentenone **109** with PDC proved to be problematic possibly due to the steric hindrances of the 2,3-cyclopentylidene group that made it difficult to generate the necessary intermediate **116** with PDC (Scheme 48). This steric hindrance might have prevented the subsequent 3, 3-sigmatropic rearrangement as well as subsequent 4-methylcylcopentenone **109**. Upon further analysis of the oxidative rearrangement of tertiary allylic alcohols,[165,166] addition of acetic anhydride led to successful PDC oxidation of **108** to **109**. This was followed by the conjugate 1, 2-addition reaction of vinylmagnesium bromide to **109** in the presence of CuBr·Me$_2$S as the catalyst to obtain the ketone **110**. Following a literature procedure,[140-142] this was accelerated by TMSCl and hexamethylphosphoramide (HMPA). Luche reduction of **110** with NaBH$_4$ and cerium(III) chloride heptahydrate (CeCl$_3$·7H$_2$O) gave alcohol **111**.

The Luche conditions gave a highly diastereoselective 1,2-reduction.[141,142] X-ray crystallography of the eventual target **7** (Figure 16) confirmed the relative configuration of the C-4- quaternary stereocenter of **111**. Alcohol **111** was converted to its triflate **106** with trifluoromethanesulfonic anhydride (Tf$_2$O) and a subsequent S$_N$2 substitution reaction of the triflate **106** with a sodium salt of 6-chloro-3-deazapurine **11** in the presence of catalytic amount of 18-crown-6 in DMF afforded nucleoside **112**. Transformation of the vinyl group of **112** to a hydroxyl group followed the usual two step sequenced to obtain **113** in 66% yield. Deprotection of **113** with hydrochloric acid afforded triol **114**. Amination of **114** with hydrazine and subsequent reduction of **115**

with Raney nickel to produced the desired 4′-methyl-3-deazaaristeromycin (**7**) (30% yield, two steps).
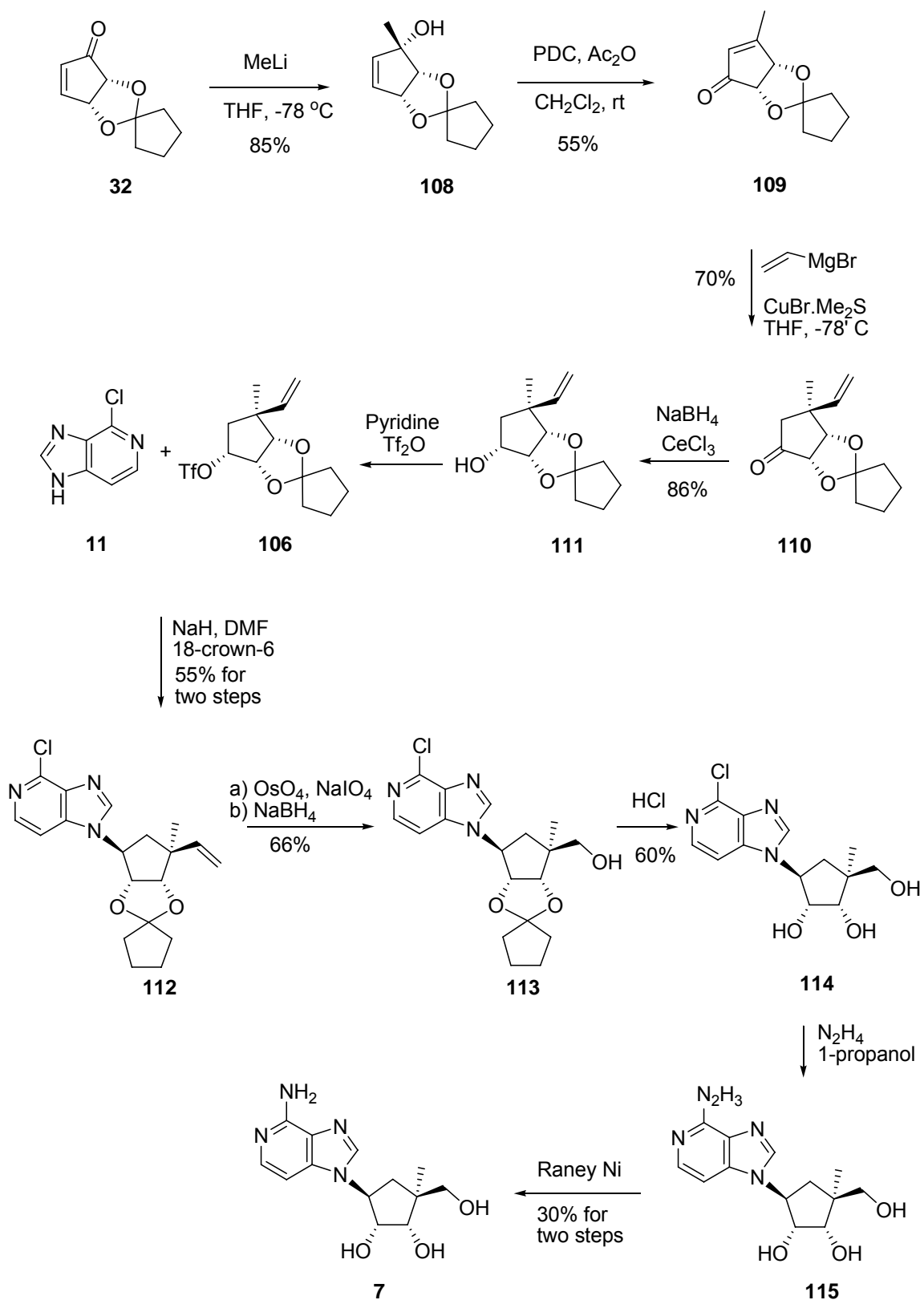
Scheme 47. Synthesis of 4′-methyl-3-deazaaristeromycin 7
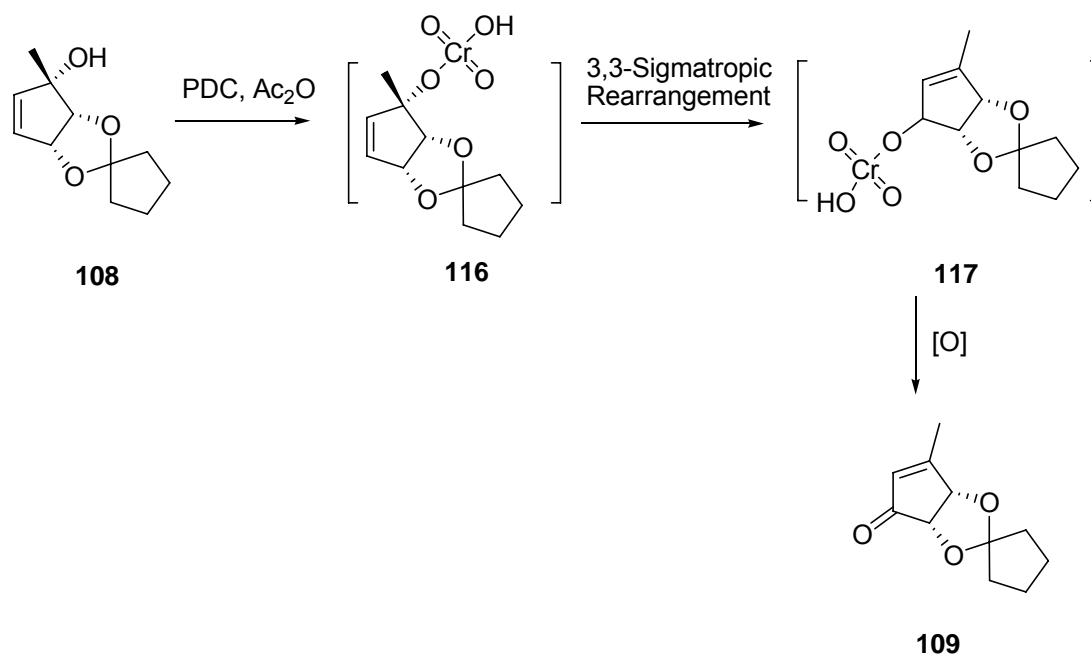
Scheme 48. Oxidative rearrangement of 108 towards 109

In addition to NMR data, the structure of 4′-methyl-3-deazaaristeromycin (**7**) was confirmed by X-ray crystallography (Figure 16).
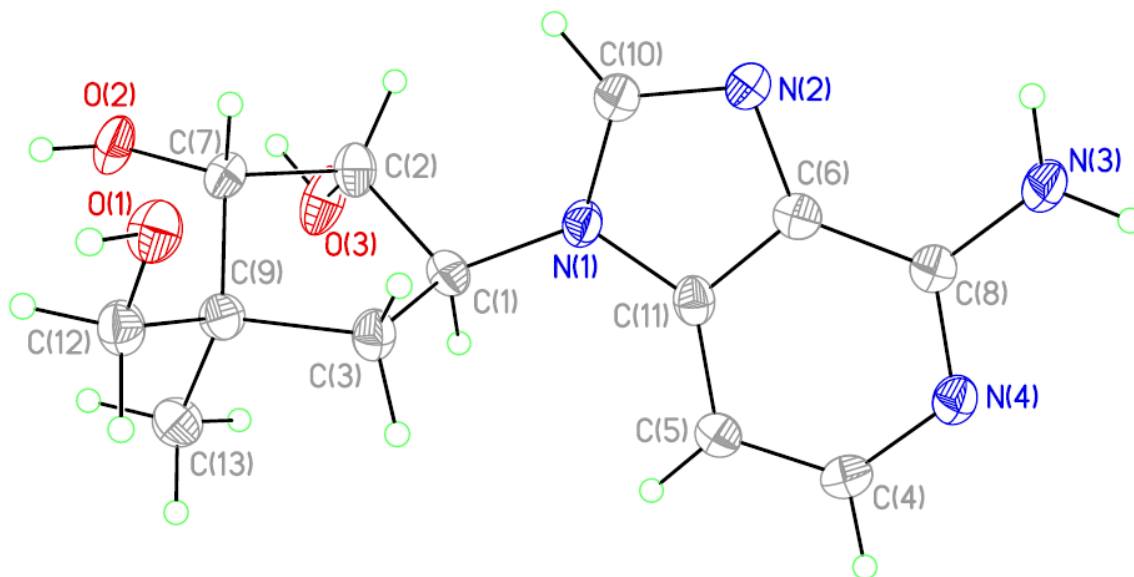
Figure 16. X-ray crystallography of 4′-methyl-3-deazaaristeromycin 7

The C-1 was shown as *S*-configuration that was the reversed *R*-configuration in alcohol **111** obtained from the Luche reduction from **110**. The methyl group on C-9 was shown as *S*-configuration.

Conclusion

A common characteristic of antiviral carbocyclic nucleosides derivatives is that they are potent inhibitors of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase. The replication of viruses involves the synthesis of viral mRNA that is dependent on *S*-adenosylmethionine (AdoMet)-dependent methylation reaction. By blocking AdoHcy hydrolase, the concentration of AdoHcy builds up and the AdoMet methylation reaction, whose rate is regulated by intracellular ratio of AdoMet/AdoHcy, is suppressed. This will lead to the inhibition of the transmethylation and, in turn, the formation of 5′-capping mRNA reducing viral protein formation for its replication. Aristeromycin is a potent AdoHcy hydrolase inhibitor and shows significant antiviral activity. However, its clinical potential is limited by a toxicity arising from 5′-phosphate formation. In order to retain its antiviral activity and avoid the undesired phosphorylation that may cause toxicity, further structural modifications of 3-deazaaristeromycin were investigated.

The biofeedback inhibition mechanism of AdoHcy showed that hydroxyl group at C-3′ position is selectively oxidized to form 3′ ketoAdoHcy. Replacement of this hydroxyl group with hydrogen or fluorine that contains unique desirable drug characteristics might inhibit AdoHcy hydrolase efficiently. In this direction, compounds **1**, **2**, and **3** were sought as promising targets. As a logical extension, compounds **4**, **5**, and **6** were identified as important targets since analogs of 2′-deoxy nucleosides were found to provide antiviral agents.[113,121-124] Their synthesis were achieved by a convergent approach, in which the desired C-2′ or C-3′ selective protected sugar moieties were coupled with the

3-deazaadenine under the Mitsunobu conditions. The key steps in the synthesis were how to selectively protect hydroxyl at C-2′ and C-3′ with proper protection groups.

4′-Azido-2′-deoxynucleosides derivatives were found to exert potent activity against HIV in 1992. Extensive investigation found that other 4′-position substituent nucleosides also exhibited high antiviral activity against HIV. The 4′-methyl-3-deazaaristeromycin (**7**) was sought as anti-HIV agent and an efficient route into the heretofore unknown 4′-alkylated-3-deazaaristeromycin framework was developed. This synthetic process provides a convenient method for synthesis of 4′-position substituent analogs.

Experimental

Materials and methods

Melting points were recorded on a Meltemp II point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 250 Spectrometer (operated at 250 or 62.9 MHz, respectively) or AV 400 Spectrometer (operated at 400 or 100 MHz, respectively). All ^{1}H chemical shifts are reported in δ relative to the internal standard tetramethylsilane (TMS, δ 0.00). [13]C chemical shifts are reported in δ relative to CDCl$_3$ (center of triplet, δ 77.23) or relative to DMSO-d (center of septet, δ 39.51). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Elemental analyses were performed by the Atlantic Microlabs, Atlanta, Georgia. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E. Merck silica gel 60-F$_{254}$ coated silica gel plates with visualization by the irradiation with a Mineralight UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 2-25 μm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

4-Ethoxy-3-nitropyridine (15). Compound **14** (15 g, 107 mmol) and PCl$_5$ (25.8 g, 95%, 118 mmol) were added to ClCH$_2$CH$_2$Cl (200 mL) sequentially. The resulting suspension was heated to reflux for about 3.5 h until the slurry turned into clear solution.

The temperature was lowered to 15 °C by ice-water hath. Absolute ethanol (100 mL) was added to the reaction dropwise below 50 °C. After the addition, the mixture was brought to reflux for 1h. Heating was removed and the reaction was cooled to 10 °C by an ice-water bath. The mixture stood for 1 h to form precipitate. The solid was collected by filtration and washed with ethanol (2 × 50 mL). Compound **15** (17.1 g, 95%) was obtained as white solid after drying in oven at 35 °C under vacuum. mp 46-48 °C (lit. [167,168] mp 46.5-48 °C).

4-Amino-3-nitropyridine (16). Nitro **15** (17.71 g, 105 mmol) and ammonium acetate (24.36 g, 318 mmol) was added to water (200 mL). The resulting slurry was heated to reflux for about 6 hours. TLC was used to trace reaction. After TLC showed the disappearance of the starting material **15**, the heating was removed and the reaction was cooled to room temperature. By an ice-water bath, addition of 30% aq. ammonium hydroxide (80 mL) to the solution adjusted the pH to 8. The slurry stood in an ice-water bath for 1 h to form precipitate. The solid was collected by filtration and was washed with cold water (2 × 50 mL). Compound **16** (12.01 g, 82.0%) was obtained as a yellow solid after drying in oven at 100 °C under vacuum. mp 195-198 °C. The NMR spectra are consistent with literature.[169]

2-Chloro-3,4-diaminepyridine (17). $SnCl_2$ (60 g, 431 mmol) was added to conc. HCl (200 mL) and the resulting suspension was heated to 60-70 °C. The reaction mixture became clear solution. Nitro **16** (60 g, 0.43 mol) was then added portion wise slowly at this temperature. After the addition, the reaction mixture was brought to reflux and allowed to react for another 5 h. After TLC showed the disappearance of the starting material **16**, the heating was removed and the reaction was cooled to room temperature

with an ice-water bath. The cooled mixture was poured over crushed ice (200 g). 3 M NaOH and then saturated ammonium hydroxide solution were added to adjust the acidic solution to pH 8. The neutralized solution was extracted with ethyl acetate (3×100 mL). The combined organic layers were dried (Na_2SO_4). Evaporation of the solvent afforded **17** (43.3 g, 70%) as a yellow solid. mp 185-188 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 7.36 (d, J=5.13 Hz, 1H), 6.31 (d, J=5.2 Hz, 1H), 5.29 (br, 2H), 4.46 (br, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 143.6, 137.1, 134.8, 125.9, 107.94.

4-Chloro-1*H*-imidazo[4,5-*c*]pyridine (11). Under a nitrogen atmosphere, compound **17** (20.0 g, 139 mmol) was added to anhydrous trimethyl orthoformate (200 mL). The solution was heated to reflux at about 100 °C to afford a clear solution. The solution was allowed to cool to 90 °C. Then 8 mL of formic acid was added dropwise at 90 °C. The reaction was brought to reflux again and a solid began to appear in the solution. Reflux was allowed for another 2 h. After TLC showed the disappearance of the starting material **17**, the heat was removed and the reaction was cooled to 10 °C with an ice-water bath. The mixture stood for another 1 h in the bath to form a precipitate completely. The mixture was filtered and the precipitate was washed with cold ether (2 × 50 mL). Compound **11** (15.83 g, 74%) was obtained as a light yellow solid after drying in oven at 100 °C under vacuum. mp 234-237 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.39 (s, 1H), 8.05 (d, J=5.2 Hz, 1H), 7.51 (d, J=5.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 144.7, 141.1, 140.7, 139.5, 135.4, 108.8.

2,3-*O*-Isopropylidene-D-ribose (18). To a stirred suspension of D-ribose (15 g, 100 mmol) in acetone (100 mL) was added dropwise conc. H_2SO_4 (2 mL) at room temperature and the reaction mixture was stirred at room temperature for 2.5 h. The

mixture was neutralized with solid NaHCO₃, filtered and evaporated under reduced pressure to give colorless oil. The residue was purified by silica gel column chromatography (hexane : EtOAc = 1:1) to afford **18** as colorless oil (16.34 g, 86%). The NMR spectra are consistent with literature.[135]

1-[(4R,5S)-5-((1S)-1-Hydroxyallyl)-2,2-dimethyl-   [1,3]dioxolan-4-yl]ethane-1,2-diol (19). To a stirred solution of **18** (16.34 g, 86 mmol) in THF (250 mL) was added dropwise vinylmagnesium bromide (400 mL, 400 mmol, 1.0 M solution in THF) at −78°C and the reaction mixture was stirred at 0°C for 3 h. After adding water (150 mL) at 0°C, the resulting precipitate was removed through a pad of celite. The filtrate was extracted with ethyl acetate (3 × 150 mL), dried, filtered, and evaporated under reduced pressure to give an oil, which was purified by silica gel column chromatography (hexane : EtOAc = 1:2) to afford **19** as a white solid (14.25 g, 76%). The NMR spectra are consistent with literature.[135]

(3aS,4R,6S,6aS)- and (3aS,4S,6S,6aS)-2,2-Dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (20). To a stirred solution of **19** (14.25 g, 65.3 mmol) in methylene chloride (130 mL) was added dropwise an aqueous solution of NaIO₄ (121 mL, 78 mmol, 0.65 M solution) at 0°C and the reaction mixture was stirred at room temperature for 40 min. After water (130 mL) was added, the mixture was extracted with methylene chloride (3 × 100 mL), dried, filtered, and evaporated under reduced pressure to give an oil, which was purified by silica gel column chromatography (hexane : EtOAc = 2:1) to give **20** as a colorless oil (9 g, 74%). The NMR spectra are consistent with literature.[133,170]

(4R,5S)-1-(2,2-Dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-prop- 2-en-1-ol (21).

Method 1: To a suspension of sodium hydride (4.06g, 102 mmol, 60% dispersion in mineral oil) in tetrahydrofuran (100 mL) in was added dimethyl sulfoxide (14.42 mL, 203 mmol) at 0 °C. After being stirred for 30 min at room temperature, the mixture was transferred to a suspension of methyltriphenylphosphonium bromide (51.8 g, 145 mmol) in tetrahydrofuran (300 mL) at 0 °C, and the mixture was stirred for 1 h at room temperature. To this reaction mixture was added a solution of aldehyde **20** (9 g, 48.3 mmol) in tetrahydrofuran (100 mL) at 0 °C, and the reaction mixture was stirred at room temperature overnight. Diethyl ether was added to the mixture, and a white solid precipitated out. The mixture was filtered through a short silica gel pad, washed with diethyl ether, and evaporated. The residue was purified by silica gel column chromatography (hexane : EtOAc = 8:1) to give diene **21** (7.3 g, 82%) as a colorless oil. The NMR spectra are consistent with literature.[133,138]

Method 2: To a solution of aldehyde **24** (7.92 g, 50.7 mmol) in anhydrous CH_2Cl_2 (100 mL) was added dropwise a solution of vinylmagnesium bromide (60.9 mL, 60.9 mmol, 1.0 M in THF) at -40 °C. The reaction was allowed to warm to 0 °C over 1 h and then stirred at this temperature for 2 h. Saturated NH_4Cl (50 mL) was added to quench the reaction. The organic layer was separated, washed with brine, and dried by anhydrous Na_2SO_4. The solvent was removed by evaporation under reduced pressure and the residue purified by silica gel column chromatography (hexane : EtOAc = 8:1) to afford diene **21** (7.87 g, 84.2%) as a colorless oil. The NMR spectral data agreed with literature.[133,138]

(3a*R*,6a*R*)-2,2-Dimethyl-3a,6a-dihydrocyclopenta[1,3]-dioxol-4-one ((4*R*,5*R*)-4,5-*O*-*iso*propylidene-2-cyclopentenone) (13) To a suspension of the Grubbs' 1st catalyst benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (223 mg, 0.27 mmol, flushed

with N_2 three times) in anhydrous CH_2Cl_2 (100 mL) was added a solution of the diene **21** (5 g, 27.1 mmol) in anhydrous CH_2Cl_2 (50 mL). After being stirred at 24 °C for 4h, 4 Å molecular sieve (20 g), pyridinium dichromate (20.42 g, 54.3 mmol), and acetic acid (0.078 mL, 1.36 mmol) were added to the resulting dark brown mixture. The reaction mixture was stirred at the same temperature for 12 h and filtered through a silica gel pad with EtOAc. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (hexane : EtOAc = 8:1), giving compound **13** (2.34 g, 56.0%) as a white solid. The NMR spectral data agreed with literature.[136]

Methyl-2,3-*O-iso*propylidene-β-D-ribofuranoside (22). Concentrated hydrochloric acid (2 mL) was added to a suspension of D-ribose (15 g, 100 mmol) in acetone (50 mL) and methanol (50 mL) at room temperature. The mixture was refluxed for 1 h. The reaction was cooled to room temperature, neutralized with pyridine, and partitioned between water (100 mL) and ether (50 mL). The separated aqueous phase was extracted with ether (2 x 50 mL) and ethyl acetate (3 x 50 mL), and the combined organic phases were washed with saturated copper sulfate solution, water, and brine prior to drying and solvent evaporation. The residue was distilled to give 17.80 g (79.5%) of **22** as a colorless oil as a mixture of anomers. The NMR spectral data agreed with literature.[139]

Methyl-5-deoxy-5-iodo-2,3-*O-iso*propylidene-β-D-ribofuranoside (23). A solution of these epimers **22** (17.8 g, 88 mmol), imidazole (9 g, 132 mmol), and triphenylphosphine (25.4 g, 97 mmol) in toluene (150 mL) and acetonitrile (100 mL) was treated portionwise with iodine (24.57.0 g, 97 mmol), refluxed for 5 min, and cooled to room temperature. Additional iodine was introduced in approximately 100 mg portions until the reaction mixture remained dark-brown in color. After dilution with ether and

repeated washing of the organic extracts sequentially with 10% sodium thiosulfate solution, water, and brine, the solution was dried over anhydrous $MgSO_4$ and concentrated in vacuo to leave a residue, which was filtered through a short plug of silica gel, which was eluted with (hexane : EtOAc = 10:1) to give **23** (23.7 g, 86.2%) as a colorless oil of the mixture of anomers. The NMR spectral data agreed with literature.[139]

(2*R*,4*R*)-2-Dimethyl-5-vinyl-1,3-dioxolane-4-carboxaldehyde (24). To a stirred solution of iodide **23** (23.7 g, 75 mmol) in MeOH (200 mL) at room temperature was added zinc powder (5.43 g, 83 mmol, Aldrich, dust, <10 micron) in one batch, followed by addition of acetic acid (0.23 mL, 7.54 mmol) in one portion via syringe. The reaction mixture was heated to reflux for 5 h. The reaction was cooled to room temperature, filtered through a short plug of celite, and washed with a 1:1 mixture of THF/pentane (100 mL). The filtrate was concentrated by evaporation under reduced pressure to provide a colorless oil, which was purified by silica gel column chromatography (hexane : EtOAc = 8:1) to afford the product **24** (7.92 g, 67.2%) as a colorless oil. The NMR spectral data agreed with literature.[139]

((3a′*R*,6′*R*,6a′*R*)-4′-Methoxytetrahydrospiro[cyclopentane-1,2′-furo[3,4-*d*] [1,3]dioxole]-6′-yl)methanol (27). D-ribose (15g, 100 mmol), cyclopentanone (88 mL, 1 mol), MeOH (100 mL) and trimethylorthoformate (55 mL, 500 mmol) were added to a 500 mL flask. H_2SO_4 (0.5 mL) was also added into flask carefully. The mixture was stirred at room temperature for 2 days. Ammonia hydroxide (29.6%) was added to neutralize the mixture. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give **27** as yellow oil (17.81 g, 78.0%). ^{1}H NMR (400 MHz, CDCl$_3$),

δ 4.98 (s, 1H), 4.79 (d, J=6.0 Hz, 1H), 4.55 (d, J=6.0 Hz, 1H), 4.44 (t, J=2.8 Hz, 1H), 3.67 (m, 2H), 3.44 (s, 3H), 3.29 (dd, J=3.6, 9.6 Hz, 1H), 1.95 (m, 2H), 1.68 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$), δ 121.8, 109.8, 88.2, 85.6, 81.5, 64.1, 55.6, 35.8, 35.7, 23.8, 23.3. Anal. Calcd for C$_{11}$H$_{18}$O$_5$: C, 57.38; H, 7.88; Found: C, 57.27; H, 7.96.

(3a′S,4′S,6a′R)-4′-(Iodomethyl)-6′-methoxytetrahydrospiro[cyclopentane-1,2′-furo[3,4-d][1,3]dioxole] (28). Compound **27** (17.81 g, 78 mmol) was dissolved in MeCN/toluene (1/1, 250 mL). Imidazole (7.97 g, 117 mmol), triphenylphosphine (TPP) (22.5 g, 86 mmol) was added. I$_2$ (21.8g, 86 mmol) was added in portions until the solution turned black. The solution was stirred at room temperature for 2 hours. Water (100 mL) and sodium thiosulfate (5 g) were added until the solution turned clear. The organic layer was separated, dried over sodium sulfate, concentrated, and purified with column chromatography (hexane : EtOAc = 5:1). The product **28** was isolated as colorless oil (21.13 g, 80.1%). ^{1}H NMR (400 MHz, CDCl$_3$), δ 5.06 (s, 1H), 4.71 (d, J=5.6Hz, 1H), 4.7 (d, J=5.6 Hz, 1H), 4.45 (m, 1H), 3.37 (s, 3H), 3.3 (m, 1H), 3.18 (m, 1H), 1.90 (m, 2H), 1.68 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$), δ 123.1, 109.9, 87.9, 85.8, 82.7, 55.2, 35.8, 35.7, 23.6, 23.2, 6.7. Anal. Calcd for C$_{11}$H$_{17}$IO$_4$: C, 38.84; H, 5.04; Found: C, 39.08; H, 5.09.

(2R,3R)-3-Vinyl-1,4-dioxaspiro[4.4]nonane-2-carbaldehyde (29). To a stirred solution of iodide **28** (21.13 g, 62 mmol) in MeOH (200 mL) at room temperature was added zinc powder (4.47 g, 68 mmol, Aldrich, dust, <10 micron,) in one batch, followed by addition of acetic acid (0.23 mL, 7.54 mmol) in one portion via syringe. The reaction mixture was heated to reflux for 5 h. The reaction was cooled to room temperature, filtered through a short plug of celite, and washed with a 1:1 mixture of THF/hexane (100

mL). The filtrate was concentrated by evaporation under reduced pressure to provide a colorless oil, which was purified by silica gel column chromatography (hexane : EtOAc = 2:1) to afford the product **29** (9.07 g, 80.1%) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$), δ 9.55 (d, *J*=3.2 Hz, 1H), 5.75 (m, 1H), 5.3-5.5 (m, 2H), 4.76 (m, 1H), 4.34 (m, 1H), 2.09 (m, 2H), 1.75 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$), δ 200.8, 131.2, 121.1, 120.0, 81.9, 79.4, 36.9, 36.8, 24.1, 23.3.

1-((2S,3R)-3-Vinyl-1,4-dioxaspiro[4.4]nonan-2-yl)prop-2-en-1-ol (30). Compound **29** (9.07 g, 49.8 mmol) was dissolved in dichloromethane (50 mL). Vinylmagnesium bromide (59.7 mL, 59.7 mmol, 1M in THF) was added at -78 °C. The mixture was warmed to 0 °C. Saturated NH$_4$Cl (40 mL) was added to quench the reaction. The organic layer was separated, dried over sodium sulfate, and concentrated using a rotavapor (bath temperature <10 °C). The residue was purified with silica gel column chromatography (hexane : EtOAc = 5:1) to give **30** as colorless oil (8.77 g, 83.8%, mixture of two diastereomers). ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.13 (m, 1H), 5.79 (m, 1H), 5.35 (m, 4H), 4.55 (m, 1H), 4.2 (m, 1H), 4.02 (m, 1H), 2.01 (m, 2H), 1.65 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$), δ 137.7, 136.9, 134.0, 133.9, 119.8, 119.0, 118.7, 117.2, 116.6, 80.7, 80.6, 79.0, 78.7, 71.3, 70.9, 37.1, 37.0, 36.9, 36.6, 24.2, 24.1, 23.4, 23.3.

(3aR,6aR)-3aH-Spiro[cyclopenta[*d*][1,3]dioxole-2,1′-cyclopentan]-4(6aH)-one (32). Compound **30** (8.77 g, 41.7 mmol) was dissolved in dry dichloromethane (100 mL). N$_2$ was bubbled to remove O2 for 30 minutes. Grubbs 1st generation catalyst (343 mg, 0.417 mmol) was added. The solution was stirred at room temperature for 12 hours. The solution was cooled to 0 °C and actived MnO$_2$ powder (10.88g, 125 mmol) was added. The mixture was warmed to room temperature, stirred overnight. Water (200 mL) was

86

added. The organic layer was separated, filtered, dried over Na_2SO_4, concentrated, and purified with column chromatography (hexane : EtOAc = 2:1) to give **32** as white solid (5.28 g, 70.2%), mp 53-55 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.63 (dd, *J*= 2.4, 4.8 Hz, 1H), 6.28 (d, *J*= 6.0 Hz, 1H), 5.23 (dd, *J*=2.0, 5.2 Hz, 1H), 4.40 (d, *J*= 5.2 Hz, 1H), 1.86 (m, 2H), 1.66 (m, 6H). ^{13}C NMR (100MHz, $CDCl_3$), δ 204.0, 159.9, 135.5, 124.3, 78.2, 76.2, 37.9, 37.4, 24.1, 23.3. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71; Found: C, 66.79; H, 7.02.

(3a*R*,6*R*,6a*R*)-6-Vinyldihydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1′-cyclopentan]-4(6a*H*)-one (33). Vinylmagnesium bromide (17.34 mL, 17.34 mmol, 1.0 M in THF) was added dropwise by syringe to a suspension of $CuBr·Me_2S$ (0.285 g, 1.39 mmol) in anhydrous THF (20 mL) at -78 °C. The reaction mixture was stirred at the same temperature for 30 min before a solution of **32** (2.5 g, 13.9 mmol) and TMSCl (3.68 mL, 29.1 mmol) and HMPA (6.28 mL, 36.1 mmol) in THF (20 mL) were added dropwise via a cannula to the above reaction mixture. The reaction mixture was kept stirring at -78 °C for 5 h and warmed to room temperature. Saturated NH_4Cl (15 mL) and *tert-n*-butylammonium fluoride (TBAF, 3.0 mL) were added to quench the reaction and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc (100 mL) and extracted with EtOAc (3×50 mL). The combined organic phases were washed with brine, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (hexane : EtOAc = 4:1) to afford **33** as a colorless oil (1.92 g, 66 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.17-5.08 (m, 2H), 4.56 (d, *J*=5.6 Hz, 1H), 4.18 (d, *J*= 5.2 Hz, 1H), 3,13 (m, 1H), 2.85 (dd, *J*=8.40 Hz, 1H), 2.32 (m, *J*=18.0 Hz, 1H), 1.94-1.65 (m, 8H); ^{13}C NMR

(100 MHz, CDCl$_3$) δ 213.2, 137.3, 122.3, 116.5, 81.6, 77.7, 40.0, 38.8, 36.3, 36.2, 23.9, 23.1. Anal. Calcd for C$_{12}$H$_{16}$O$_3$: C, 69.21; H, 7.74. Found: C, 67.34; H, 7.8.

2,3-(Cyclopentylidenedioxy)-4-vinyl-cyclopentanol (34). To a stirred solution of cyclopentenone **33** (1.92g, 9.2 mmol) and CeCl$_3$·7H$_2$O (2.93 g, 10.1 mmol) in MeOH (30 mL) at 0 °C was added NaBH$_4$ (0.698 g, 18.4 mmol) in small portions. After stirring at room temperature for 1 h the mixture was neutralized with conc. HCl, reduced to 2/3 volume, extracted with brine and ether, and the organic layers combined, dried (MgSO$_4$), and concentrated to give **34** as a colorless oil (1.84 g, 94.7%). ^{1}H NMR (400 MHz, CDCl$_3$), δ 5.72 (m, 1H), 5.06-5.10 (m, 2H), 4.4 (m, 2H), 4.07-4.13 (m, 1H), 2.76 (m, 1H), 2.41 (d, *J*=7.6 Hz, 1H), 1.89-1.96 (m, 4H), 1.7 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$), δ138.5, 121.6, 115.3, 84.4, 79.0, 71.3, 44.3, 36.3, 35.7, 35.5, 24.2, 23.1. Anal. Calcd for C$_{12}$H$_{18}$O$_3$: C, 68.54; H, 8.63. Found: C, 68.33; H, 8.60.

6-Chloro-9-(2′,3′-(cyclopentylidenedioxy)-4′-vinyl-cyclopentyl)-3-deazapurine (35). Compound **34** (5 g, 23.8 mmol) was dissolved in THF (50 mL). **11** (5.11 g, 33.3 mmol), Ph$_3$P (12.5g, 47.6 mmol) was added. The solution was cooled to -40 °C. D*iso*propyl azodicarboxylate (DIAD) (9.2 mL, 47.6 mmol) was added dropwise. The mixture was warmed to room temperature and then heated to 60 °C for 24 hours. The solvent was removed under reduced pressure. The residue was purified by silica column (hexane : EtOAc = 5:1 to 2:1) to give crude **35** as a yellow foam (4.53 g, 55.1%). The crude product, which contaminated with diisopropyl hydrazine-1,2-dicarboxylate, was used in next step without further purification.

6-Chloro-9-(2′,3′-diol-4′-vinyl-cyclopentyl)-3-deazapurine (36). Compound **35** (5g, 14.46 mmol) was dissolved in 3 N HCl (0.5 mL) in MeOH solution, stirred at 25 °C

overnight. NaHCO$_3$ was added to neutralize the solution until it stopped bubble. The mixture was filtered. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc) to provide **36** as a white solid (3.03 g, 58%), mp 87-89 ℃. ^{1}H NMR (400 MHz, DMSO-d_6), δ 8.69 (s, 1H), 8.17 (d, *J*=5.2 Hz, 1H), 7.81 (d, *J*=5.2 Hz, 1H), 5.97-6.05 (m, 2H), 5.09 (dd, *J*=10.4, 26.8 Hz, 1H), 4.71-4.76 (m, 1H), 4.16-4.2 (m, 1H), 3.85-3.9 (m, 1H), 2.52-2.62 (m, 1H), 2.36-2.42 (m, 1H), 1.86-1.91 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ146.5, 143.1, 142.7, 141.5, 138.5, 137.4, 115.3, 110.8, 84.4, 79.0, 59.4, 44.3, 36.3. Anal. Calcd for C$_{13}$H$_{14}$ClN$_3$O$_2$: C, 55.82; H, 5.04. Found: C, 55.51; H, 4.99.

6-Chloro-9-(2′-(4-methoxybenzyloxy)-3′-hydroxyl-4′-vinyl-cyclopentyl)- 3-deaza purine (38). Compound **36** (1.5 g, 5.36 mmol) was dissolved in dry DMF (10 mL). The solution was cooled to 0 °C. NaH (214 mg, 5.36 mmol, 60% in mineral oil) was added in one portion. The solution was stirred for 30 minutes. *para*-Methoxybenzyl chloride (PMBCl) (0.8 mL, 5.9 mmol) was added at 0 °C in one portion. The solution was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure. Saturated NH$_4$Cl solution (10 mL) was added. The mixture was extracted with EtOAc (3×50 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 1:1) to provide **38** as a white foam, which mixed with 6-chloro-9-(2′-hydroxyl-3′-(4-methoxybenzyloxy)-4′-vinyl-cyclopentyl)-purine **(37)**.

6-Chloro-9-(2′-(*tert*-butyldimethylsilyl)-3′-hydroxyl-4′-vinyl-cyclopentyl)-3-deazapurine (39). Compound **36** (1.5 g, 5.36 mmol) was dissolved in dry dichloromethane (10 mL). 4-(Dimethylamino)pyridine (DMAP) (33 mg, 0.27 mmol) was

added. The solution was treated with imidazole (438 mg, 6.43 mmol), and *tert*-butyldimethylsilyl chloride (TBSCl) (0.89 mL, 5.9 mol) at 0 °C. The solution was then warmed to room temperature and stirred for 2 hours. Water (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3 ×15 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 3:1) to provide **39** as a gum, which mixed with 6-chloro-9-(2′-hydroxyl-3′-(*tert*-butyldimethylsilyl)-4′-vinyl-cyclopentyl)-purine **(40)**.

6-Chloro-9-(2′,3′-(cyclopentylidenedioxy)-4′-hydroxymethyl-cyclopentyl)-3-deazapurine (41). Compound **35** (2.5 g, 7.23 mmol) was dissolved in MeOH (25 mL). Water (24 mL) was added. $NaIO_4$ (3.4 g, 15.9 mmol) was added. The mixture was cooled to 0 °C. OsO_4 (90 mg, 0.36 mmol, 5% mol) was added. The mixture was stirred at 0 °C for 2 hours. The mixture was filtered. MeOH was removed by reduced pressure. The residue was extracted with dichloromethane (3 ×50 mL). The organic layer was washed with brine, dried over sodium sulfate, concentrated. The residue was dissolved in methanol (20 mL). $NaBH_4$ (684 mg, 18.1 mmol) was added portionwise at 0 °C. The mixture as stirred at 0 °C for 1 hour. Saturated NH_4Cl solution (20 mL) was added. The mixture was filtered through celite. The solvent was removed with reduced pressure. The residue was extracted with EtOAc (3×20 mL). The combined organic layer was dried over sodium sulfate and concentrated. The residue was purified by silica column (hexane : EtOAc = 3:1) to provide **41** as a white solid (1.52 g, 60.2%), mp 66-69 ℃. ^{1}H NMR (400 MHz, CDCl$_3$), δ 8.20 (s, 1H), 8.18 (d, *J*=2.8 Hz, 1H), 7.63 (d, *J*=2.8 Hz, 1H), 4.69-4.73 (m, 1H), 4.59-4.62 (m, 2H), 3.90-3.91 (m, 2H), 2.63-2.68 (m, 1H), 2.53-2.56 (m, 1H), 2.45-2.5 (m, 1H), 2.06 (m, 4H), 1.73 (m, 4H). ^{13}C NMR (100 MHz, CDCl3), δ143.2,

143.1, 141.3, 139.2, 138.3, 107.8, 106.4, 84.0, 81.8, 63.5, 63.0, 45.4, 39.0, 37.9, 37.4, 25.2, 24.1, Anal. Calcd for $C_{17}H_{20}ClN_3O_3$: C, 58.37; H, 5.76. Found: C, 58.5; H, 5.75.

6-Chloro-9-(2′,3′-(cyclopentylidenedioxy)-4′-*O*-(*tert*-butyldiphenylsilyl)-cyclo pentyl)-3-deazapurine (42). Compound **41** (2.5 g, 8.81 mmol) was dissolved in dry dichloromethane (20 mL). 4-(Dimethylamino)pyridine (DMAP) (54 mg, 0.44 mmol) was added. The solution was treated with imidazole (720 mg, 10.6 mmol), and *tert*-butyldiphenylchlorosilane (TBDPSCl) (2.5 mL, 9.69 mol) at 0 °C. The solution was then warmed to room temperature and stirred for 2 hours. Water (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×20 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 2:1) to provide **42** as a white soild (4.3g, 93.4%). ^{1}H NMR (400 MHz, CDCl$_3$), δ 8.18 (d, *J*=8 Hz, 1H), 7.97 (s, 1H), 7.63-7.68 (m, 5), 7.54 (d, *J*=8 Hz, 1H), 7.26-7.46 (m, 5H), 4.93-5.03 (m, 1H), 4.54 (m, 2H), 4.08-4.16 (m, 2H), 2.65-2.7 (m, 1H), 2.50-2.53 (m, 1H), 2.4-2.45 (m, 1H), 2.01 (m, 4H), 1.83 (m, 4H), 1.08-1.11 (m, 9H). ^{13}C NMR (100 MHz, CDCl$_3$), δ 145.2, 143.5, 141.2, 139.1, 137.3, 132.0, 130.6, 128.4, 107.6, 107.4, 86.0, 88.7, 66.5, 62.0, 45.7, 38.0, 36.9, 36.7, 22.3, 23.0, 19.6. Anal. Calcd for $C_{33}H_{38}ClN_3O_3Si$: C, 67.38; H, 6.51 Found: C, 67.5; H, 6.73.

6-Chloro-9-(2′,3′-diol-4′-*O*-(*tert*-butyldiphenylsilyl)-cyclopentyl)-3-deazapurine (43).

Method 1: Compound **42** (3.0g, 5.1 mmol) was dissolved in 0.6 N HCl (1 mL) in MeOH at 0 ℃ and stirred at 25 °C overnight. NaHCO$_3$ was added to neutralize the solution until it no longer bubbled. The mixture was filtered. The solvent was removed under reduced pressure, and the residue was purified by silica gel column

chromatography (EtOAc:MeOH=2:1) to provide **43** as a white foam (1.6 g, 60.2%), which contaminated with **42** and **46**.

Method 2: Compound **46** (2.5 g, 8.81 mmol) was dissolved in dry dichloromethane (20 mL). 4-(Dimethylamino)pyridine (DMAP) (54 mg, 0.44 mmol) was added. The solution was treated with imidazole (720 mg, 10.6 mmol), and *tert*-butyldiphenylchlorosilane (TBDPSCl) (2.5 mL, 9.69 mol) at 0 °C. The solution was then warmed to room temperature and stirred for 2 hours. Water (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×20 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 2:1) to provide **43** as a white solid (1.84g, 86%), mp 55-57 ℃. ^{1}H NMR (400 MHz, CDCl$_3$): 8.20 (s, 1H), 7.95 (d, *J*=5.6 Hz, 1H), 7.73 (d, *J*=5.6 Hz, 1H), 7.63-7.68 (m, 5), 7.26-7.46 (m, 5H), 5.55 (s, 1H), 5.12 (s, 1H), 4.75 (m, 1H), 4.31 (d, *J*=5.6 Hz, 1H), 4.36 (d, *J*=3.6 Hz, 1H), 3.86 (d, *J*=5.6 Hz, 2H),1.99 (dd, *J*=5.6, 13.2 Hz, 1H), 1 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ144.7, 141.9, 141.2, 138.6, 137.4,132.7, 130.5, 128.3, 106.8, 78.4, 76.6, 74.7, 62.7, 61.5, 37.3, 26.0, 18.3. Anal. Calcd for C$_{28}$H$_{32}$ClN$_3$O$_3$Si: C, 64.41; H, 6.18; N, 8.05. Found: C, 64.01; H, 6.22; N, 8.08.

6-Chloro-9-(2′-(4-methoxybenzyloxy)-3′-hydroxyl-4′-*O*-(*tert*-butyldiphenylsilyl)-cyclopentyl)-3-deazapurine (44). Compound **43** (2.5 g, 4.79 mmol) was dissolved in dry DMF (15 mL). The solution was cooled to 0 °C. NaH (230 mg, 60% in mineral oil, 5.75 mmol) was added in one portion. The solution was stirred for 30 minutes. *para*-Methoxybenzyl chloride (PMBCl) (0.71 mL, 5.3 mmol) was added at 0 °C in one portion. The solution was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure. Saturated NH$_4$Cl solution (15 mL) was added. The mixture was

extracted with EtOAc (3×50 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 3:1) to provide **44** as a white solid, which mixed with 6-chloro-9-(2′- hydroxyl-3′-(4-methoxybenzyloxy)-4′-*O*-(*tert*-butyldiphenylsilyl)-cyclopentyl)-3-deaza-purine (**45**).

6-Chloro-9-(2′,3′-diol-4′-hydroxymethyl-cyclopentyl)-3-deazapurine (46).

Compound **41** (2.5g, 7.23 mmol) was dissolved in 3 N HCl (0.2 mL) in MeOH and stirred at 25 °C overnight. NaHCO$_3$ was added to neutralize the solution until it no longer bubbled. The mixture was filtered. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc : MeOH = 10:1) to provide **46** as a white solid (1.78 g, 88%), mp 182-184 ℃. ^{1}H NMR (400 MHz, CDCl$_3$): 8.11 (s, 1H), 7.92 (d, *J*=5.6 Hz, 1H), 7.89 (d, *J*=5.6 Hz, 1H), 5.22 (s, 1H), 5.17 (s, 1H), 4.78-4.82 (m, 1H), 4.72 (s, 1H), 4.37-4.4 (m, 1H), 4.31-4.34 (m, 1H), 3.83 (d, *J*=5.6 Hz, 2H), 2.35-2.42 (m, 2H),1.99-2.02 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ143.2, 142.1, 141.7, 139.1, 136.3, 106.2, 78.3, 75.2, 74.8, 63.4, 62.5, 37.3, 25.4. Anal. Calcd for C$_{12}$H$_{14}$ClN$_3$O$_3$: C, 50.80; H, 4.97; N, 14.81. Found: C, 50.22; H, 5.01; N, 14.12.

6-Chloro-9-(2′-(*tert*-butyldimethylsilyl)-3′-hydroxyl-4′-*O*-(*tert*-butyl diphenylsilyl)- cyclopentyl)-3-deazapurine (47). Compound **43** (1 g, 1.92 mmol) was dissolved in dry dichloromethane (10 mL). 4-(Dimethylamino)pyridine (DMAP) (12 mg, 0.1 mmol) was added. The solution was treated with imidazole (130 mg, 1.92 mmol), and *tert*-butyldimethylsilyl chloride (TBSCl) (0.32 mL, 2.1 mol) at 0 °C. The solution was then warmed to room temperature and stirred for 2 hours. Water (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3 ×10 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by

silica gel column chromatography (hexane : EtOAc = 2:1) to provide **47** as a white solid, which mixed with 6-chloro-9-(2′- hydroxyl-3′-(*tert*-butyldimethylsilyl)-4′-*O*-(*tert*-butyl diphenylsilyl)-cyclopentyl)-3-deazapurine (**48**).

6-Chloro-9-(2′-(*tert*-butyldiphenylsilyl)-3′-hydroxyl-4′-*O*-(*tert*-butyldiphenyl silyl)-cyclopentyl)-3-deazapurine (49). Compound **43** (1 g, 1.92 mmol) was dissolved in dry dichloromethane (10 mL). 4-(Dimethylamino)pyridine (DMAP) (12 mg, 0.1 mmol) was added. The solution was treated with imidazole (130 mg, 1.92 mmol), and TBDPSCl (0.54 mL, 2.1 mol) at 0 °C. The solution was then warmed to room temperature and stirred for 2 hours. Water (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×10 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 3:1) to provide **49** (0.7g, 48%) and 6-chloro-9-(2′- hydroxyl-3′-(*tert*-butyldiphenylsilyl)-4′-*O*-(*tert*-butyldiphenylsilyl)-cyclopentyl)-3-deazapurine (**50**) (0.49g, 33.6%) as white foam. **49:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.33 (s, 1H), 7.82 (d, *J*=5.6 Hz, 1H), 7.34-7.54 (m, 21H), 5.02-5.12 (m, 1H), 4.83 (d, *J*=5.6 Hz, 1H), 4.28 (m, 1H), 3.72 (m, 1H), 3.56-3.66 (m, 2H), 2.21-2.34 (m, 2H), 1.78-1.9 (m, 1H), 0.92 (s, 9H), 0.85 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ145.8, 141.9, 141.2, 138.6, 137.4, 132.8, 132.7, 130.5, 130.3, 128.6, 128.2, 106.8, 78.4, 77.2, 74.9, 62.7, 61.5, 37.3, 26.1, 25.8, 17.9. Anal. Calcd for C$_{44}$H$_{50}$ClN$_3$O$_3$Si$_2$: C, 69.49; H, 6.63; N, 5.53. Found: C, 69.01; H, 6.44; N, 5.21. **50:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.51 (s, 1H), 8.00 (d, *J*=5.6 Hz, 1H), 7.62-7.7 (m, 6H), 7.29-7.44 (m, 15H), 5.3 (d, *J*= 6.8 Hz, 1H), 4.93-4.96 (m, 1H), 4.27 (m, 1H), 4.12 (m, 1H), 3.29-3.31 (m, 1H), 3.17-3.19 (m, 1H), 2.4 (m, 1H), 2.21 (m, 1H), 1.68-1.78 (m, 1H), 1.16 (s, 9H), 0.84 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ143.7,

142.4, 141.5, 137.6, 137.1, 132.6, 132.4, 131.3, 130.8, 128.9, 127.2, 104.6, 78.6, 76.5, 74.8, 63.6, 62.4, 37.2, 27.2, 26.6, 18.8. Anal. Calcd for $C_{44}H_{50}ClN_3O_3Si_2$: C, 69.49; H, 6.63; N, 5.53. Found: C, 69.33; H, 6.12; N, 5.08

(1*S*,2*S*,3*R*,5*R*)-2-(*tert*-Butyldiphenylsilyloxy)-5-((*tert*-butyldiphenylsilyloxy) methyl)-3-(4-chloro-1H-imidazo[4,5-c]pyridin-1-yl)cyclopentyl-2-chloroacetate (51). Compound **49** (2 g, 2.63 mmol) was dissolved in THF (20 mL). Chloroacetic acid (323 mg, 3.42 mmol), Ph₃P (1.38g, 5.26 mmol) was added. The solution was cooled to -40 °C. Di*iso*propyl azodicarboxylate (DIAD) (0.76 mL, 3.94 mmol) was added dropwise. The mixture was warmed to room temperature, and then heated to 60 °C for 24 hours. The solvent was removed under reduced pressure. The residue was purified by silica column (hexane : EtOAc = 4:1) to give **51** as white foam (1.22 g, 55.2%). The crude product, which contaminated with diisopropyl hydrazine-1,2-dicarboxylate, was used in next step without further purification.

(1*S*,2*S*,3*S*,5*R*)-2-(*tert*-Butyldiphenylsilyloxy)-5-((*tert*-butyldiphenylsilyloxy) methyl)-3-(4-chloro-1H-imidazo[4,5-c]pyridin-1-yl)cyclopentanol (52). Compound **51** (1.22g, 1.46 mmol) was dissolved in 1 N LiOH (3 mL) in MeOH (10 mL) and stirred at 25 °C for 2 hours. 0.5 N HCl aqueous solution was added to neutralize the solution. Water (10 mL) was added and the mixture was extracted with EtOAc (3×10 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 3:1) to provide **52** as white foam (1.17g, 80.2%). ¹H NMR (400 MHz, CDCl₃): δ 8.33 (s, 1H), 7.82 (d, *J*=5.6 Hz, 1H), 7.34-7.54 (m, 21H), 5.02-5.12 (m, 1H), 4.83 (d, *J*=5.6, 1H), 4.32 (m, 1H), 3.91 (m, 1H), 3.45-3.56 (m, 2H), 2.21-2.34 (m, 2H), 1.78-1.9 (m, 1H), 0.92 (s, 9H), 0.85 (s, 9H). ¹³C

NMR (100 MHz, CDCl$_3$): δ145.4, 141.7, 141.1, 138.8, 137.2, 132.6, 132.2, 130.1, 129.7, 128.3, 128.1, 106.8, 80.3, 76.1, 74.9, 62.7, 61.5, 36.2, 26.1, 25.8, 18. Anal. Calcd for C$_{44}$H$_{50}$ClN$_3$O$_3$Si$_2$: C, 69.49; H, 6.63; N, 5.53. Found: C, 69.41; H, 6.52; N, 5.45.

1-((1*S*,2*S*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy) methyl)-3-fluorocyclopentyl)-4-chloro-1H-imidazo[4,5-*c*]pyridine (53). Compound **52** (1.17 g, 1.54 mmol) was dissolved in dry dichloromethane (10 mL), pyridine (0.24 mL, 3.08 mmol) and (diethylamino)sulfur trifluoride (DAST) (0.26 mL, 2.3 mmol) were added. The solution was warmed to room temperature under protection of N$_2$ for 12 h. The reaction was quenched with saturated Na$_2$CO$_3$ solution (15 mL). The organic layer was separated, washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 3:1) to provide **53** as a white foam (0.622 g, 53%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.29 (s, 1H), 7.78 (d, *J*=5.6 Hz, 1H), 7.34-7.54 (m, 21H), 4.56 (d, *J*=5.6, 1H), 4.28 (m, 1H), 3.45-3.56 (m, 2H), 3.40 (m, 1H), 2.18-2.22 (m, 2H), 1.8-1.9 (m, 1H), 0.93 (s, 9H), 0.88 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ146.3, 140.7, 139.9, 138.6, 137.4, 132.8, 132.6, 130.1, 129.9, 128.8, 128.2, 105.8, 92.3, 80.3, 73.1, 62.7, 61.5, 31.6, 24.3, 25.7, 19.4. Anal. Calcd for C$_{44}$H$_{49}$ClFN$_3$O$_2$Si$_2$: C, 69.31; H, 6.48; N, 5.51. Found: C, 69.42; H, 6.48; N, 5.36.

(1*S*,2*R*,3*R*,5*S*)-5-(4-Chloro-1H-imidazo[4,5-*c*]pyridin-1-yl)-2-fluoro-3-(hydroxyl methyl)cyclopentanol (54). Compound **53** (0.5g, 0.66 mmol) was dissolved in 1 N HCl (0.1 mL) in MeOH, stirred at 25 °C overnight. Amberlite IRA-400(Cl) ion exchange resin was added to neutralize the solution until pH was 7. The mixture was filtered. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc:MeOH=10:1) to provide **54** as a white solid (0.1 g,

53.3%), mp 172-174 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.88 (d, J=5.6 Hz, 1H), 7.67 (d, J=5.6 Hz, 1H), 5.46 (d, J=4.4 Hz, 1H), 4.85-4.95 (m, 2H), 4.80(d, J=4.4 Hz, 1H), 3.95-4.05 (m, 2H), 3.52-3.65 (m, 2H), 2.3-2.36 (m, 1H), 1.99-2.01 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ149.3, 143.6, 139.2, 137.8, 135.1, 108.7, 94.2, 79.4, 72.9, 63.9, 32.5, 25.3. Anal. Calcd for $C_{12}H_{13}ClFN_3O_2$: C, 50.45; H, 4.59; N, 14.71. Found: C, 50.33; H, 4.48; N, 14.82.

(3a*S*,4*S*,6*R*,6a*R*)-4-(4-Methoxybenzyloxy)-6-vinyltetrahydro-3a*H*-spiro [cyclopenta[*d*][1,3]dioxole-2,1′-cyclopentane] (59). Compound **34** (3 g, 14.3 mmol) was dissolved in dry DMF (15 mL). The solution was cooled to 0 °C. NaH (685 mg, 17.1 mmol, 60% in mineral oil) was added in one portion. The solution was stirred for 30 minutes. *p*-Methoxybenzyl chloride (PMBCl) (4.15 mL, 28.5 mmol) was added at 0 °C in one portion. The solution was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure. Saturated NH_4Cl solution (40 mL) was added. The mixture was extracted with EtOAc (3×50 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 8:1) to provide **59** as a colorless oil (4.06g, 86.2%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32 (d, J=8.80 Hz, 2H), 6.89 (d, J=8.8 Hz, 2H), 5.68 (m, 1H), 5.03 (m, 1H), 4.97 (m, 1H), 4.65 (d, J=10.4 Hz, 1H), 4.55 (d, J=10.4 Hz, 1H), 4.43 (t, J=6.4, 5.6 Hz, 1H), 4.30 (d, J=5.6 Hz, 1H), 3.81 (m, 4H), 2.66 (t, J= 7.2 Hz, 6.75, 1H), 2.03-2.16 (m, 2H), 1.70-1.94 (m, 8H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.5, 138.9, 130.8, 129.7, 121.0, 115.0, 114.0, 84.0, 78.5, 77.9, 71.7, 55.5, 44.1, 35.8, 35.6, 32.1, 24.3, 23.3. Anal. Calcd for $C_{20}H_{36}O_4$: C, 72.70; H, 7.93. Found: C, 72.35; H, 8.01.

(1*R*,2*R*,3*S*,5*R*)-3-(4-Methoxybenzyloxy)-5-vinylcyclopentane-1,2-diol (60).

Compound **59** (4.06g, 12.29 mmol) was dissolved in 3 N HCl (0.41 mL) in MeOH and stirred at 25 °C overnight. NaHCO$_3$ was added to neutralize the solution until it no longer bubbled. The mixture was filtered. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane : EtOAc = 3:1) to provide **60** as a colorless oil (2.82 g, 86.7%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.26 (d, *J*=8.8 Hz, 2H), 6.88 (d, *J*=8.8 Hz, 2H), 5.77 (m, 1H), 5.05 (m, 1H), 4.97 (m, 1H), 4.65 (d, *J*=11.6 Hz, 1H), 4.55 (d, *J*=11.6 Hz, 1H), 4.02 (t, *J*=6.4, 5.6 Hz, 1H), 3.99 (m, 1H), 3.81 (s, 3H), 3.66 (t, *J*= 6.4, 7.6, 1H), 2.63-2.7 (m, 1H), 2.05-2.09 (m, 1H), 1.59-1.67 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.7, 138.7, 131.1, 129.5, 121.1, 114.0, 84.0, 78.5, 77.9, 71.7, 55.5, 44.3, 32.2. Anal. Calcd for C$_{15}$H$_{20}$O$_4$: C, 68.16; H, 7.63 Found: C, 68.14; H, 7.52.

(1*R*,2*R*,3*S*,5*R*)-2-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)-5-vinyl cyclopentanol (58) and (1*S*,2*R*,3*R*,5*S*)-2-(*tert*-butyldiphenylsilyloxy)-5-(4-methoxy benzyloxy)-3-vinylcyclopentanol (61) . Compound **60** (2.82 g, 10.67 mmol) was dissolved in dry dichloromethane (20 mL). 4-(Dimethylamino)pyridine (DMAP) (65 mg, 0.53 mmol) was added. The solution was treated with imidazole (726 mg, 10.67 mmol), and TBDPSCl (3.0 mL, 11.74 mol) at 0 °C. The solution was then warmed to room temperature and stirred for 2 hours. Water (20 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×20 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 5:1) to provide **58** (2.2g, 41%) and **61** (1.82g, 34%) as colorless oil. **58:** ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68-7.71 (m, 4H), 7.27-7.42 (m, 6H), 7.25 (d, *J*=2 Hz, 2H), 6.86 (d, *J*=2 Hz, 2H), 5.32-5.42 (m,1H), 4.83 (m, 1H), 4.71-4.81

(m, 1H), 4.49 (d, J=11.6 Hz, 1H), 4.42 (d, J=11.6 Hz, 1H), 3.78 (m, 5H), 2.74-2.8 (m, 1H), 2.7 (s, 1H), 2.02-2.12 (m, 1H), 1.55-1.65 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.1, 138.4, 135.5, 133.5, 131.1, 130.1, 129.7, 127.6, 121.1, 114.0, 84.0, 78.5, 77.9, 71.7, 55.5, 44.3, 32.2, 25.3, 19.3. Anal. Calcd for C$_{31}$H$_{38}$O$_4$Si: C, 74.06; H, 7.62 Found: C, 75.01; H, 7.53. **61:** ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68-7.71 (m, 4H), 7.34-7.43 (m, 6H), 7.25 (d, J=4.8 Hz, 2H), 6.85 (d, J=4.8, 2H), 5.30-5.42 (m,1H), 4.8-4.92 (m, 2H), 4.41-4.49 (m, 2H), 3.79 (s, 3H), 3.71-3.79 (m, 2H), 2.81-2.9 (m, 1H), 2.49 (s, 1H), 2.02-2.12 (m, 1H), 1.55-1.65 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.7, 136.3, 134.1, 133.1, 131.2, 130.3, 129.2, 128.1, 120.9, 114.3, 85.2, 79.3, 77.9, 72.8, 55.5, 47.3, 33.3, 27.2, 19.4. Anal. Calcd for C$_{31}$H$_{38}$O$_4$Si: C, 74.06; H, 7.62 Found: C, 74.55; H, 7.59.

(1S,2S,3S,5R)-2-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)-5-vinyl cyclopentyl-2-chloroacetate (62). Compound **58** (2.2 g, 4.38 mmol) was dissolved in THF (20 mL). Chloroacetic acid (538 mg, 5.69 mmol) and Ph$_3$P (2.3g, 8.75 mmol) were added. The solution was cooled to -40 °C. Di*iso*propyl azodicarboxylate (DIAD) (1.27 mL, 6.56 mmol) was added dropwise. The mixture was warmed to room temperature, and then heated to 60 °C for 24 hours. The solvent was removed under reduced pressure. The residue was purified by silica column (hexane : EtOAc = 6:1) to give **62** as colorless oil (1.72 g, 67.7%). The crude product, which contaminated with diisopropyl hydrazine-1,2-dicarboxylate, was used in next step without further purification.

(1S,2R,3S,5R)-2-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)-5-vinyl cyclopentanol (63). Compound **62** (1.72g, 2.97 mmol) was dissolved in 1 N LiOH (5.9 mL) in MeOH (20 mL) and stirred at 25 °C for 2 hours. 0.5 N HCl aqueous solution was

added to neutralize the solution. Water (10 mL) was added and the mixture was extracted with EtOAc (3×20 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 6:1) to provide **63** as a colorless oil (1.27g, 84.8%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68-7.71 (m, 4H), 7.27-7.42 (m, 6H), 7.25 (d, J=2 Hz, 2H), 6.86 (d, J=2 Hz, 2H), 5.32-5.42 (m,1H), 4.83 (m, 1H), 4.71-4.81 (m, 1H), 4.49 (d, J=11.6 Hz, 1H), 4.42 (d, J=11.6 Hz, 1H), 3.76-3.78 (m, 5H), 2.74-2.8 (m, 1H), 2.7 (s, 1H), 2.02-2.12 (m, 1H), 1.55-1.65 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.1, 138.4, 135.5, 133.5, 131.1, 130.1, 129.7, 127.6, 121.1, 114.0, 84.0, 78.5, 77.9, 71.7, 55.5, 44.3, 32.2, 25.3, 19.3. Anal. Calcd for C$_{31}$H$_{38}$O$_4$Si: C, 74.06; H, 7.62 Found: C, 74.62; H, 7.49.

tert-Butyl((1_S_,2_R_,3_R_,5_S_)-2-fluoro-5-(4-methoxybenzyloxy)-3-vinylcyclo pentyloxy)diphenylsilane (64). Compound **63** (1.27 g, 2.53 mmol) was dissolved in dry dichloromethane (10 mL). Pyridine (0.4 mL, 5.05 mmol) and DAST (0.435 mL, 3.79 mmol) were added. The solution was warmed to room temperature under protection of N$_2$ for 12 h. The reaction was quenched with saturated Na$_2$CO$_3$ solution (15 mL). The mixture was extracted with EtOAc (3×20 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 6:1) to provide **64** as a colorless oil (0.83g, 65.1%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68-7.71 (m, 4H), 7.27-7.42 (m, 6H), 7.25 (d, J=2 Hz, 2H), 6.86 (d, J=2 Hz, 2H), 5.32-5.42 (m,1H), 4.83 (m, 1H), 4.71-4.81 (m, 1H), 4.49 (d, J=11.6, 1H), 4.42 (d, J=11.6 Hz, 1H), 3.81-3.92(m, 2H), 3.76 (s, 3H), 2.81-2.89 (m, 1H), 2.7 (s, 1H), 2.02-2.12 (m, 1H), 1.55-1.65 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.1, 138.4, 135.5, 133.5, 131.1, 130.1, 129.7, 127.6, 121.1, 114.0, 85.2, 79.2, 77.9, 71.7, 55.5,

44.3, 33.1, 25.3, 19.3. Anal. Calcd for $C_{31}H_{37}FO_3Si$: C, 73.77; H, 7.39 Found: C, 74.02; H, 7.38.

((1*R*,2*R*,3*S*,4*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-fluoro-4-(4-methoxybenzyloxy) cyclopentyl)methanol (65). Compound **64** (2 g, 3.96 mmol) was dissolved in MeOH (20 mL). Water (13 mL) and $NaIO_4$ (1.86 g, 8.72 mmol) were added. The mixture was cooled to 0 °C. OsO_4 (50 mg, 0.198 mmol, 5% mol) was added. The mixture was stirred at 0 °C for 2 hours. The mixture was filtered. MeOH was removed by reduced pressure. The residue was extracted with dichloromethane (3×50 mL). The organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was dissolved in methanol (20 mL). $NaBH_4$ (375 mg, 9.91 mmol) was added portionwise at 0 °C. The mixture as stirred at 0 °C for 1 hour. Saturated NH_4Cl solution (20 mL) was added. The mixture was filtered through celite. The solvent was removed with reduced pressure. The residue was extracted with EtOAc (3×15 mL). The combined organic layer was dried over sodium sulfate, concentrated. The residue was purified by silica column (hexane : EtOAc = 5:1) to provide **65** as a colorless oil (1.22 g, 60.3%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68-7.71 (m, 4H), 7.27-7.42 (m, 6H), 7.25 (d, *J*=8.4 Hz, 2H), 6.86 (d, *J*=8.4 Hz, 2H), 4.49 (d, *J*=11.6 Hz, 1H), 4.42 (d, *J*=11.6 Hz, 1H), 3.81-3.92(m, 2H), 3.76 (s, 3H), 3.31-3.40(m, 2H), 2.81-2.89 (m, 1H), 2.7 (s, 1H), 1.71-1.85 (m, 2H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.1, 138.4, 133.5, 131.1, 130.1, 129.7, 127.6, 121.1, 85.2, 79.2, 77.9, 71.7, 61.2, 55.5, 44.3, 33.1, 25.3, 19.3. Anal. Calcd for $C_{30}H_{37}FO_4Si$: C, 70.83; H, 7.33 Found: C, 70.23; H, 7.45.

tert-**Butyl((((1*R*,2*R*,3*S*,4*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-fluoro-4-(4-methoxy benzyloxy)cyclopentyl)methoxy)diphenylsilane (66)**. Compound **65** (1.22 g, 2.4 mmol)

was dissolved in dry dichloromethane (10 mL). 4-(Dimethylamino)pyridine (DMAP) (15 mg, 0.12 mmol) was added. The solution was treated with imidazole (163 mg, 2.4 mmol), and TBDPSCl (0.68 mL, 2.64 mol) at 0 °C. The solution was then warmed to room temperature and stirred for 2 hours. Water (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3 ×10 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 8:1) to provide **66** as a colorless oil (1.67g, 93.2%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.68-7.71 (m, 8H), 7.27-7.42 (m, 12H), 7.25 (d, J=8.4 Hz, 2H), 6.86 (d, J=8.4 Hz, 2H), 4.56 (d, J=5.6 Hz, 1H), 4.49 (d, J=11.6 Hz, 1H), 4.42 (d, J=11.6 Hz, 1H), 4.28 (m, 1H), 3.76 (s, 3H), 3.45-3.56 (m, 2H), 3.40 (m, 1H), 2.18-2.22 (m, 2H), 1.8-1.9 (m, 1H), 0.93 (s, 9H), 0.88 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.1,138.4, 134.1, 133.5, 132.3, 131.1, 130.1, 130.4, 129.7, 128.5, 127.6, 121.1, 85.2, 79.2, 77.9, 71.7, 61.2, 55.5, 44.3, 33.1, 25.3, 25.1, 19.3, 19.1. Anal. Calcd for C$_{46}$H$_{55}$FO$_4$Si$_2$: C, 73.95; H, 7.42 Found: C, 73.83; H, 7.24.

(1*S*,2*S*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy) methyl)-3-fluoro-cyclopentanol (57). Compound **66** (1.67 g, 2.24 mmol) was dissolved in 19:1 dichloromethane/H$_2$O (20 mL). DDQ (634 mg, 2.79 mmol) was added in one portion. The mixture was stirred at room temperature for 2 hours. Saturated Na$_2$CO$_3$ solution (20 mL) was added. The mixture was extracted with EtOAc (3 ×15 mL) and the organic layer was separated, washed with saturated Na$_2$CO$_3$ solution (20 mL), brine (20 mL), dried over sodium sulfate, concentrated and purified by silica gel column chromatography (hexane : EtOAc = 5:1) to provide **57** as a colorless oil (1.46 g, 65.1%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.68-7.71 (m, 8H), 7.27-7.42 (m, 12H), 4.56 (d, J=5.6 Hz,

1H), 4.28 (m, 1H), 3.46-3.56 (m, 2H), 3.40 (m, 1H), 2.28-2.32 (m, 2H), 1.8-1.9 (m, 1H), 0.91 (s, 9H), 0.87 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 138.3, 134.2, 133.6, 132.2, 131.1, 130.1, 130.6, 127.5, 85.1, 79.3, 77.9, 61.2, 44.2, 33.1, 25.3, 25.1, 19.3, 19.1. Anal. Calcd for C$_{38}$H$_{47}$FO$_3$Si$_2$: C, 72.80; H, 7.56 Found: C, 72.91; H, 7.53.

1*H*-Imidazo[4,5-*c*]pyridin-4-amine (67). Compound **11** (22.4 g, 146 mmol) was added to a mixture of anhydrous hydrazine (99%, 45.8 mL) and propan-1-ol (100 mL). The solution was brought to reflux for 8 h. The reaction was cooled to room temperature and the residual hydrazine and propan-1-ol was evaporated under reduced pressure. Water (100 mL) was added to dissolve the residue. Raney nickel (25.7 g) was added portionwise. The mixture was heated to reflux for 1 h. After the reaction had completed, the reaction mixture was filtered through a celite pad. The filtrate was evaporated under reduced pressure to afford **67** as a white solid (14.28 g, 73%). The NMR spectral data agreed with literature.[156]

***tert*-Butyl 4-(*bis*(*tert*-butoxycarbonyl) amino) -1*H* –imidazo [4,5-*c*] pyridine-1-carboxylate (68).** To **67** (6 g, 44.7 mmol) and 4-(dimethylamino)pyridine (DMAP) (546 mg, 4.47 mmol) was added 100 mL of dry THF. To the resulting suspension was added (Boc)$_2$O (39 g, 179 mmol). The reaction mixture was stirred for 2 days at room temperature under a nitrogen atmosphere. TLC analysis (hexane : EtOAc = 3:2) was used to monitor the reaction progress. Solvent was removed by evaporation under reduced pressure to give yellow oil. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 1:1) to give **68** (16.4 g, 84.2%) as a white foam. ^{1}H NMR (400 MHz, CDCl$_3$): 8.47 (s, 1H), 8.46 (d, *J*=5.6 Hz, 1H), 7.88 (d, *J*=5.6 Hz, 1H), 1.73 (s, 9H), 1.40 (s, 18H). ^{13}C NMR (100 MHz, CDCl$_3$): 150.9, 147.1, 144.7, 143.5,

142.7, 138.4, 136.7, 109.67, 91.0, 83.1, 28.0, 27.8. Anal. Calcd for $C_{21}H_{30}N_4O_6$: C, 58.05; H, 6.96; N, 12.89. Found: C, 58.15; H, 6.89; N, 12.77.

4-(*bis*(*tert*-Butoxycarbonyl)amino)-1*H*-imidazo[4,5-*c*]pyridine-1-carboxylate (56). Compound **68** (5 g, 11.5 mmol) was dissolved in 100 mL of dry THF under N_2. Bu$_4$NF (43.3 mL, 43.3 mmol, 1 M in THF) was added and the reaction mixture was stirred for 12 h. TLC analysis was used to monitor the reaction progress. Water (100 mL) was added. After extraction with EtOAc (3 × 100 mL), the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 1:3) to afford **56** (2.89 g, 75%) as a white foam. ^{1}H NMR (400 MHz, CDCl$_3$): 8.31 (d, *J*=5.6 Hz, 1H), 8.30 (s, 1H), 7.61 (d, *J*=5.6 Hz, 1H), 1.35 (s, 18H). ^{13}C NMR (100 MHz, CDCl$_3$): 149.8, 147.1, 144.7, 143.5, 142.7, 138.4, 136.7, 109.67, 89.6, 84.2, 27.7. Anal. Calcd for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.32; H, 6.54; N, 16.88.

1-((1*R*, 2*S*, 3*R*, 4*R*)-2-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyl diphenylsilyloxy) methyl)-3-fluorocyclopentyl)-4-(*N*,*N*-di-(*tert*-butyl-*O*-carbonyl)amino)-1H-imidazo [4,5-*c*]pyridine (69). Compound **57** (2 g, 3.19 mmol) was dissolved in THF (20 mL). **56** (1.6 g, 4.79mmol) and Ph$_3$P (1.67g, 6.38 mmol) were added. The solution was cooled to -40 °C. Di*iso*propyl azodicarboxylate (DIAD) (0.93 mL, 4.79 mmol) was added dropwise. The mixture was warmed to room temperature, and then heated to 60 °C for 24 hours. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 2:1) to give crude **69** as yellow oil (1.2 g,

39.8%). The crude product, which contaminated with diisopropyl hydrazine-1,2-dicarboxylate, was used in next step without further purification.

1-((1*R*,2*S*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy) methyl)-3-fluorocyclopentyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine (1). Compound **69** (1.2g, 1.27 mmol) was dissolved in 1 N HCl (0.127 mL) in MeOH and stirred at 25 °C overnight. Amberlite IRA-400(Cl) ion exchange resin was added to neutralize the solution until pH was 7. The mixture was filtered. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc : MeOH : $NH_3 \cdot H_2O$ = 20:2:1) to provide **1** as a white solid (0.2 g, 59.7%), mp 246-249 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.82 (d, *J*=6 Hz, 1H), 7.64 (d, *J*=6 Hz, 1H), 6.14 (br, 2H), 5.46 (d, *J*=2 Hz, 1H), 4.85-4.95 (m, 2H), 4.80(d, *J*=2 Hz, 1H), 3.95-4.01 (m, 2H), 3.51-3.63 (m, 2H), 2.31-2.36 (m, 1H), 1.97-2.00 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ152.3, 140.7, 140.6, 136.8, 135.2, 108.7, 94.2, 79.4, 72.9, 63.9, 32.5, 25.3. Anal. Calcd for $C_{12}H_{15}FN_4O_2$: C, 54.13; H, 5.68; N, 21.04. Found: C, 54.24; H, 5.62; N, 20.98.

***tert*-Butyl((1*S*,2*S*,3*R*,5*S*)-2-fluoro-5-(4-methoxybenzyloxy)-3-vinylcyclopentyloxy) diphenylsilane (72)**. Compound **72** was prepared from **58** by the same procedure as described for the synthesis of compound **64**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66-7.71 (m, 4H), 7.37-7.42 (m, 6H), 7.25 (d, *J*=2 Hz, 2H), 6.86 (d, *J*=2 Hz, 2H), 5.32-5.42 (m,1H), 4.83 (m, 1H), 4.69-4.72 (m, 1H), 4.49 (d, *J*=11.6 Hz, 1H), 4.42 (d, *J*=11.6 Hz, 1H), 3.81-3.92(m, 2H), 3.76 (s, 3H), 2.81-2.89 (m, 1H), 2.7 (s, 1H), 2.02-2.12 (m, 1H), 1.55-1.65 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.2, 138.5, 135.6, 133.8, 131.2,

130.2, 129.6, 127.5, 121.2, 114.1, 85.1, 79.1, 78.0, 71.8, 55.5, 44.5, 33.1, 25.3, 19.3. Anal. Calcd for $C_{31}H_{37}FO_3Si$: C, 73.77; H, 7.39 Found: C, 73.89; H, 7.42.

((1*R*,2*S*,3*S*,4*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-fluoro-4-(4-methoxybenzyloxy) cyclopentyl)methanol (73). Compound **73** was prepared from **72** by the same procedure as described for the synthesis of compound **65**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67-7.71 (m, 4H), 7.26-7.41 (m, 6H), 7.24 (d, *J*=8.4 Hz, 2H), 6.87 (d, *J*=8.4 Hz, 2H), 4.48 (d, *J*=11.6 Hz, 1H), 4.43 (d, *J*=11.6 Hz, 1H), 3.80-3.91(m, 2H), 3.75 (s, 3H), 3.32-3.41(m, 2H), 2.82-2.89 (m, 1H), 2.7 (s, 1H), 1.71-1.82 (m, 2H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.2, 138.3, 133.6, 131.2, 130.1, 129.6, 127.5, 121.2, 85.3, 79.1, 78.0, 71.6, 61.3, 55.4, 44.2, 33.2, 25.4, 19.2. Anal. Calcd for $C_{30}H_{37}FO_4Si$: C, 70.83; H, 7.33 Found: C, 70.64; H, 7.39.

tert-Butyl(((1*R*,2*S*,3*S*,4*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-fluoro-4-(4-methoxy benzyloxy)cyclopentyl)methoxy)diphenylsilane (74). Compound **74** was prepared from **73** by the same procedure as described for the synthesis of compound **66**. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.69-7.72 (m, 8H), 7.29-7.42 (m, 12H), 7.27 (d, *J*=8.4 Hz, 2H), 6.87 (d, *J*=8.4 Hz, 2H), 4.57 (d, *J*=5.6 Hz, 1H), 4.50 (d, *J*=11.6 Hz, 1H), 4.43 (d, *J*=11.6 Hz, 1H), 4.28-4.30 (m, 1H), 3.75 (s, 3H), 3.46-3.55 (m, 2H), 3.39-3.41 (m, 1H), 2.19-2.23 (m, 2H), 1.8-1.9 (m, 1H), 0.94 (s, 9H), 0.89 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.2, 138.5, 134.2, 133.4, 132.2, 131.2, 130.2, 130.4, 129.7, 128.6, 127.7, 121.2, 85.3, 79.3, 77.8, 71.7, 61.3, 55.4, 44.2, 33.2, 25.4, 25.2, 19.3, 19.0. Anal. Calcd for $C_{46}H_{55}FO_4Si_2$: C, 73.95; H, 7.42 Found: C, 73.91; H, 7.33.

(1*S*,2*S*,3*S*,4*R*)-2-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy) methyl)-3-fluorocyclopentanol (71). Compound **71** was prepared from **74** by the same

106

procedure as described for the synthesis of compound **57**. ^{1}H NMR (400 MHz, CDCl$_3$):

δ7.68-7.71 (m, 8H), 7.27-7.42 (m, 12H), 4.56 (d, *J*=5.6 Hz, 1H), 4.28 (m, 1H), 3.46-3.56

(m, 2H), 3.41 (m, 1H), 2.27-2.31 (m, 2H), 1.8-1.9 (m, 1H), 0.92 (s, 9H), 0.88 (s, 9H). [13]C

NMR (100 MHz, CDCl$_3$): δ 138.5, 134.3, 133.7, 132.4, 131.1, 130.2, 130.7, 127.6, 85.2,

79.4, 77.9, 61.3, 44.3, 33.2, 25.4, 25.3, 19.5, 19.2. Anal. Calcd for C$_{38}$H$_{47}$FO$_3$Si$_2$: C,

72.80; H, 7.56 Found: C, 72.89; H, 7.44.

**1-((1*R*,2*S*,3*S*,4*R*)-2-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy)
methyl)-3-fluorocyclopentyl)-4-(*N*,*N*-di-(*tert*-butyl-*O*-carbonyl)amino)-1H-
imidazo[4,5-*c*]pyridine (75)**. Compound **75** was prepared from **71** and **56** by the same
procedure as described for the synthesis of compound **69**, which was used in next step
without further purification.

**(1*S*,2*S*,3*R*,5*R*)-5-(4-amino-1H-imidazo[4,5-*c*]pyridin-1-yl)-2-fluoro-3-(hydroxyl
methyl)cyclopentanol (2)**. Compound **2** was prepared from **75** by the same procedure as
described for the synthesis of compound **1**. Mp 248-250 ℃. ^{1}H NMR (400 MHz, DMSO-
d$_6$) δ 8.15 (s, 1H), 7.81 (d, *J*=6 Hz, 1H), 7.63 (d, *J*=6 Hz, 1H), 6.13 (br, 2H), 5.45 (d, *J*=2
Hz, 1H), 4.84-4.94 (m, 2H), 4.79(d, *J*=2 Hz, 1H), 3.96-4.01 (m, 2H), 3.50-3.62 (m, 2H),
2.32-2.36 (m, 1H), 1.97-2.00 (m, 1H). ^{13}C NMR (100 MHz, DMSO-*d$_6$*): δ152.4, 140.9,
140.6, 136.9, 135.3, 108.8, 94.3, 79.5, 73.0, 63.9, 32.6, 25.4. Anal. Calcd for
C$_{12}$H$_{15}$FN$_4$O$_2$: C, 54.13; H, 5.68; N, 21.04. Found: C, 54.18; H, 5.62; N, 20.89.

O-(1*R*,2*S*,3*S*,5*R*)-2-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)-5-
vinylcyclopentyl S-methyl carbonodithioate (78). A solution of compound **58** (2 g,
3.98 mmol) and imidazole (27 mg, 0.4 mmol) in dry THF (20 mL) was added NaH (318
mg, 7.96 mmol, 60% in mineral oil). The reaction was stirred for 30 min, after which

time CS$_2$ (0.6 mL, 9.95 mmol) was added. MeI (1.0 mL, 15.91 mmol) was then added after another 40 min. The mixture was stirred for 40 min. It was quenched with CH$_2$Cl$_2$ (20 mL), poured into water (20 mL), and extracted with CH$_2$Cl$_2$ (3 × 20 mL). The organic phase was dried with anhydrous Na$_2$SO$_4$ and then evaporated to dryness. The residue was submitted to silica gel column chromatography (hexane : EtOAc = 6:1) to yield **78** as a yellow oil (1.89 g, 50.1%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68-7.71 (m, 4H), 7.34-7.37 (m, 6H), 7.28 (d, J=8.8 Hz, 2H), 6.89 (d, J=8.8 Hz, 2H), 5.32-5.42 (m,1H), 4.83 (m, 1H), 4.71-4.81 (m, 1H), 4.53 (d, J=11.6 Hz, 1H), 4.45 (d, J=11.6 Hz, 1H), 3.76-3.82 (m, 5H), 2.72-2.6 (m, 1H), 2.7 (s, 1H), 2.42 (s, 3H), 2.01-2.10 (m, 1H), 1.54-1.57 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 215.4, 157.9, 137.3, 135.3, 133.2, 131.2, 130.3, 129.6, 127.5, 121.2, 114.1, 83.8, 79.2, 77.8, 71.6, 55.4, 44.2, 33.8, 25.3, 19.9, 19.4. Anal. Calcd for C$_{33}$H$_{40}$O$_4$S$_2$Si: C, 66.85; H, 6.8 Found: C, 66.76; H, 6.64.

tert-Butyl-((1_R_,2_S_,4_S_)-2-(4-methoxybenzyloxy)-4-vinylcyclopentyloxy) diphenyl silane (79).

Method 1: To a refluxing solution of Bu$_3$SnH (4.2 mL, 15.94 mmol) in dry toluene (10 mL) was added dropwise a solution of compound **78** (1.89 g, 3.19 mmol) and AIBN (52 mg) in dry toluene (10 mL). The reaction was stirred for 30 min, and then the reaction mixture was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic phase was dried with anhydrous Na$_2$SO$_4$ and concentrated to dryness. The residue was submitted to silica gel column chromatography (hexane : EtOAc = 6:1) to provide **79** as a light yellow oil (725 mg, 46.7%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68-7.71 (m, 4H), 7.34-7.37 (m, 6H), 7.28 (d, J=8.8 Hz, 2H), 6.89 (d, J=8.8 Hz, 2H), 5.32-5.42 (m,1H), 4.81-4.82 (m, 1H), 4.71-4.80 (m, 1H), 4.53 (d, J=11.6 Hz, 1H), 4.45 (d, J=11.6 Hz, 1H), 4.11-4.16 (m, 1H),

3.84-3.91 (m, 1H), 3.82 (s, 3H), 3.40-3.51 (m, 2H), 1.75-1.82 (m, 1H), 1.65-1.72 (m, 1H), 1.52-1.58 (m, 1H), 0.88 (s, 9H) ^{13}C NMR (100 MHz, CDCl$_3$) δ157.8, 137.2, 135.2, 133.3, 131.2, 130.2, 129.5, 127.4, 121.1, 119.9, 79.4, 76.2, 70.3, 55.2, 44.1, 36.2, 33.7, 25.2, 19.5. Anal. Calcd for C$_{31}$H$_{38}$O$_3$Si: C, 76.5; H, 7.78 Found: C, 76.66; H, 7.70.

Method 2: MsCl (0.19 mL, 2.39 mmol) was added dropwise over 15 min to a cooled (0 °C) and stirred solution of **58** (1 g, 1.99 mmol) and Et$_3$N (0.33 mL, 2.39 mmol) in CH$_2$Cl$_2$ (10 mL). After the mixture had stirred for another 0.5 h at that temperature, H$_2$O (10 mL) was added, and the mixture was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The organic extract was washed with H$_2$O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal in vacuo afforded the residue containing the crude mesylate **82**. A solution of the above mesylate **82** in THF (10 mL) was added dropwise to a suspension of LiAlH$_4$ (0.159 g, 4.18 mmol) in THF (10 mL) at room temperature. After the mixture had heated at reflux for 4 h, it was cooled with ice water, and treated with sat. aq Na$_2$SO$_4$ (1.5-2.0 mL). The white gelatinous precipitate was filtered, the precipitate was washed with Et$_2$O, and the filtrate was concentrated in vacuo. This gave a residue, which was purified by silica gel column chromatography (hexane : EtOAc = 7:1) to afford **79** as a colorless oil (0.43g, 44.8%);

((1S,3R,4S)-3-(tert-Butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy) cyclopentyl) methanol (80). Compound **80** was prepared from **79** by the same procedure as described for the synthesis of compound **65**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66-7.70 (m, 4H), 7.32-7.36 (m, 6H), 7.24 (d, J=8.8 Hz, 2H), 6.95 (d, J=8.8 Hz, 2H), 4.55 (d, J=11.6 Hz, 1H), 4.47(d, J=11.6 Hz, 1H), 4.12-4.17 (m, 1H), 3.88-3.92 (m, 1H), 3.82 (s, 3H), 3.41-3.51 (m, 2H), 1.74-1.80 (m, 2H), 1.67-1.71 (m, 2H), 1.53-1.59 (m, 1H), 0.89 (s, 9H) ^{13}C

NMR (100 MHz, CDCl$_3$): δ156.7, 134.1, 133.5, 131.4, 130.3, 129.6, 127.7, 121.4, 79.3, 76.3, 70.7, 68.2, 54.9, 44.3, 36.1, 32.9, 25.1, 19.4. Anal. Calcd for C$_{30}$H$_{38}$O$_4$Si: C, 73.43; H, 7.81 Found: C, 73.33; H, 7.76.

tert-Butyl(((1S,3R,4S)-3-(tert-butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy) cyclopentyl) methoxy)diphenylsilane (81). Compound **81** was prepared from **80** by the same procedure as described for the synthesis of compound **66**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76-7.82 (m, 8H), 7.44-7.49 (m, 12H), 7.21 (d, *J*=8.8 Hz, 2H), 6.93 (d, *J*=8.8 Hz, 2H), 4.54 (d, *J*=11.6 Hz, 1H), 4.46(d, *J*=11.6 Hz, 1H), 4.11-4.15 (m, 1H), 3.87-3.90 (m, 1H), 3.83 (s, 3H), 3.40-3.49 (m, 2H), 1.74-1.79 (m, 2H), 1.62-1.66 (m, 2H), 1.52-1.58 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H) ^{13}C NMR (100 MHz, CDCl$_3$) δ156.8, 134.2, 134.0, 133.5, 132.5, 131.4, 130.2, 130.1, 129.5, 128.3, 127.6, 121.3, 79.3, 76.5, 70.8, 68.1, 54.8, 44.2, 36.1, 32.8, 25.3, 25.2, 19.6, 19.4. Anal. Calcd for C$_{46}$H$_{56}$O$_4$Si$_2$: C, 75.78; H, 7.74 Found: C, 75.66; H, 7.73.

(1S,2R,4S)-2-(tert-Butyldiphenylsilyloxy)-4-((tert-butyldiphenylsilyloxy)   methyl) cyclopentanol (77). Compound **77** was prepared from **81** by the same procedure as described for the synthesis of compound **57**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75-7.81 (m, 8H), 7.45-7.49 (m, 12H), 4.11-4.15 (m, 1H), 3.77-3.82 (m, 1H), 3.41-3.48 (m, 2H), 1.68-1.72 (m, 2H), 1.61-1.66 (m, 2H), 1.53-1.57 (m, 1H), 0.90 (s, 9H), 0.88 (s, 9H) ^{13}C NMR (100 MHz, CDCl$_3$) δ 134.3, 134.1, 133.7, 132.7, 131.4, 130.4, 130.1, 127.7, 79.4, 76.5, 68.2, 44.3, 36.2, 32.7, 25.3, 24.1, 19.6, 19.4. Anal. Calcd for C$_{38}$H$_{48}$O$_3$Si$_2$: C, 74.95; H, 7.94 Found: C, 74.88; H, 7.86.

1-((1R, 2R, 4S)-2-(tert-Butyldiphenylsilyloxy) -4-((tert-butyldiphenylsilyloxy) methyl) -cyclopentyl) -4- (N,N-di- (tert-butyl-O-carbonyl)amino)-1H-imidazo[4,5-c]

110

pyridine (83). Compound **83** was prepared from **77** and **56** by the same procedure as described for the synthesis of compound **69**, which was used in next step without further purification.

(1R,2R,4S)-2-(4-Amino-1H-imidazo[4,5-c]pyridin-1-yl)-4-(hydroxymethyl) cyclo pentanol (3). Compound **3** was prepared from **83** by the same procedure as described for the synthesis of compound **1**. Mp 221-224 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.77 (d, J=6 Hz, 1H), 7.63 (d, J=6 Hz, 1H), 6.15 (br, 2H), 4.11-4.15 (m, 1H), 3.77-3.82 (m, 1H), 3.41-3.48 (m, 2H), 1.68-1.72 (m, 2H), 1.61-1.66 (m, 2H), 1.53-1.57 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ155.2, 141.6, 141.7, 135.2, 135.0, 108.5, 79.3, 72.9, 63.8, 41.1, 32.6, 25.2. Anal. Calcd for $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.5; N, 22.57. Found: C, 58.14; H, 6.63; N, 22.21.

(1R,2R,3R,5S)-2-(tert-Butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)-3-vinyl cyclopentyl 2-chloroacetate (86). Compound **86** was prepared from **61** by the same procedure as described for the synthesis of compound **62**, which was used in next step without further purification.

(1R,2R,3R,5S)-2-(tert-Butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)-3-vinyl cyclopentanol (87). Compound **87** was prepared from **86** by the same procedure as described for the synthesis of compound **63**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65-7.72 (m, 4H), 7.35-7.42 (m, 6H), 7.24 (d, J=4.8 Hz, 2H), 6.84 (d, J=4.8 Hz, 2H), 5.35-5.44 (m,1H), 4.7-4.93 (m, 2H), 4.42-4.48 (m, 2H), 3.8 (s, 3H), 3.73-3.79 (m, 2H), 2.82-2.89 (m, 1H), 2.5 (s, 1H), 2.01-2.09 (m, 1H), 1.56-1.61 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.6, 136.2, 134.2, 133.2, 131.3, 130.2, 129.3, 128.1, 120.9, 114.2, 85.1,

79.2, 77.8, 72.7, 55.4, 47.2, 33.2, 27.1, 19.4. Anal. Calcd for $C_{31}H_{38}O_4Si$: C, 74.06; H, 7.62 Found: C, 74.03; H, 7.51.

tert-Butyl((1R,2S,3S,5R)-2-fluoro-3-(4-methoxybenzyloxy)-5-vinylcyclo pentyloxy)diphenylsilane (88). Compound **88** was prepared from **87** by the same procedure as described for the synthesis of compound **64**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69-7.72 (m, 4H), 7.27-7.42 (m, 6H), 7.25 (d, J=2 Hz, 2H), 6.86 (d, J=2 Hz, 2H), 5.32-5.42 (m,1H), 4.83-4.92 (m, 2H), 4.39-4.44 (m, 2H), 3.81-3.92(m, 2H), 3.76 (s, 3H), 2.80-2.86 (m, 1H), 2.5 (s, 1H), 2.02-2.12 (m, 1H), 1.55-1.65 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.2, 138.6, 135.4, 133.4, 130.9, 130.3, 129.5, 127.6, 121.2, 114.1, 85.3, 79.3, 78, 71.6, 55.4, 44.3, 33.1, 25.2, 19.5. Anal. Calcd for $C_{31}H_{37}FO_3Si$: C, 73.77; H, 7.39 Found: C, 73.82; H, 7.33.

((1R,2R,3S,4S)-2-(tert-Butyldiphenylsilyloxy)-3-fluoro-4-(4-methoxybenzyloxy) cyclopentyl)methanol (89). Compound **89** was prepared from **88** by the same procedure as described for the synthesis of compound **65**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67-7.70 (m, 4H), 7.28-7.41 (m, 6H), 7.25 (d, J=8.4 Hz, 2H), 6.86 (d, J=8.4 Hz, 2H), 4.41-4.48 (m, 2H), 3.80-3.88(m, 2H), 3.74 (s, 3H), 3.69-3.72(m, 2H), 2.81-2.89 (m, 1H), 2.5 (s, 1H), 1.71-1.85 (m, 2H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 157.9, 138.3, 133.4, 131.2, 129.8, 129.6, 127.5, 121.2, 85.3, 79.1, 77.8, 71.5, 61.4, 55.2, 44.2, 32.8, 25.4, 19.6. Anal. Calcd for $C_{30}H_{37}FO_4Si$: C, 70.83; H, 7.33 Found: C, 70.63; H, 7.44.

tert-Butyl(((1R,2R,3S,4S)-2-(tert-butyldiphenylsilyloxy)-3-fluoro-4-(4-methoxy benzyloxy)cyclopentyl)methoxy)diphenylsilane (90). Compound **90** was prepared from **89** by the same procedure as described for the synthesis of compound **66**. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.69-7.72 (m, 8H), 7.23-7.33 (m, 12H), 7.26 (d, J=8.4 Hz, 2H), 6.93 (d,

J=8.4 Hz, 2H), 4.57 (d, J=5.6 Hz, 1H), 4.47-4.51 (m, 2H), 4.26 (m, 1H), 3.75 (s, 3H), 3.66-3.72 (m, 2H), 3.41 (m, 1H), 2.19-2.23 (m, 2H), 1.81-1.89 (m, 1H), 0.94 (s, 9H), 0.89 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.5,138.3, 134.2, 133.4, 132.2, 131.2, 130.4, 130.1, 129.7, 128.6, 127.5, 121.2, 85.2, 79.2, 77.9, 71.8, 61.2, 55.6, 44.3, 33.2, 25.3, 25.1, 19.2, 19.0. Anal. Calcd for C$_{46}$H$_{55}$FO$_4$Si$_2$: C, 73.95; H, 7.42 Found: C, 73.78; H, 7.32.

(1*S*,2*S*,3*R*,4*R*)-3-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy) methyl)-2-fluorocyclopentanol (85). Compound **85** was prepared from **90** by the same procedure as described for the synthesis of compound **57**. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.69-7.73 (m, 8H), 7.32-7.42 (m, 12H), 4.66 (d, J=5.6 Hz, 1H), 4.28-4.31 (m, 1H), 3.71-3.79 (m, 2H), 3.23-3.26 (m, 1H), 2.29-2.32 (m, 2H), 1.82-1.92 (m, 1H), 0.91 (s, 9H), 0.87 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 138.2, 134.1, 133.5, 132.1, 131.3, 130.3, 130.7, 127.6, 85.2, 79.2, 77.2, 61.3, 44.3, 33.2, 25.3, 25.2, 19.3, 19.0. Anal. Calcd for C$_{38}$H$_{47}$FO$_3$Si$_2$: C, 72.80; H, 7.56 Found: C, 72.81; H, 7.44.

1-((1*R*,2*S*,3*R*,4*R*)-3-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy) methyl)-2-fluorocyclopentyl)-4-(*N*,*N*-di-(*tert*-butyl-*O*-carbonyl)amino)-1H-imidazo [4,5-*c*]pyridine (91). Compound **91** was prepared from **85** and **56** by the same procedure as described for the synthesis of compound **69,** which was used in next step without further purification.

(1*R*,2*S*,3*R*,5*R*)-3-(4-amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-2-fluoro-5-(hydroxyl methyl) cyclopentanol (4). Compound **4** was prepared from **91** by the same procedure as described for the synthesis of compound **1**. Mp 238-241 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.69 (d, J=6 Hz, 1H), 6.84 (d, J=6 Hz, 1H), 6.14 (br, 2H), 5.46 (d, J=2 Hz, 1H), 4.81-4.92 (m, 2H), 4.80(d, J=2 Hz, 1H), 3.92-4.00 (m, 2H), 3.71-3.79 (m, 2H),

2.32-2.37 (m, 1H), 1.98-2.02 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ151.8, 141.5, 141.3, 135.5, 135.1, 108.6, 94.1, 78.8, 72.8, 62.8, 32.4, 24.9. Anal. Calcd for $C_{12}H_{15}FN_4O_2$: C, 54.13; H, 5.68; N, 21.04. Found: C, 54.14; H, 5.61; N, 20.93.

tert-Butyl(((1R,2R,3S,5R)-2-fluoro-3-(4-methoxybenzyloxy)-5-vinylcyclopentyloxy) diphenylsilane (94). Compound **94** was prepared from **61** by the same procedure as described for the synthesis of compound **64**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.7-7.74 (m, 4H), 7.29-7.42 (m, 6H), 7.26 (d, J=2 Hz, 2H), 6.87 (d, J=2 Hz, 2H), 5.34-5.43 (m,1H), 4.83-4.92 (m, 2H), 4.4-4.45 (m, 2H), 3.81-3.90(m, 2H), 3.73 (s, 3H), 2.81-2.86 (m, 1H), 2.51 (s, 1H), 2.06-2.14 (m, 1H), 1.53-1.63 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 157.3, 137.5, 135.1, 133.3, 130.9, 130.3, 129.6, 127.6, 121.3, 114.2, 85.3, 79.3, 78, 71.5, 55.6, 44.3, 33.2, 25.1, 19.5. Anal. Calcd for $C_{31}H_{37}FO_3Si$: C, 73.77; H, 7.39 Found: C, 73.71; H, 7.29.

((1R,2R,3R,4S)-2-(tert-Butyldiphenylsilyloxy)-3-fluoro-4-(4-methoxybenzyloxy) cyclopentyl)methanol (95). Compound **95** was prepared from **94** by the same procedure as described for the synthesis of compound **65**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67-7.70 (m, 4H), 7.27-7.38 (m, 6H), 7.25 (d, J=8.4 Hz, 2H), 6.87 (d, J=8.4 Hz, 2H), 4.42-4.48 (m, 2H), 3.82-3.89(m, 2H), 3.73 (s, 3H), 3.69-3.72(m, 2H), 2.82-2.88 (m, 1H), 2.49 (s, 1H), 1.71-1.85 (m, 2H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 157.4, 138.3, 133.3, 131.2, 130.1, 129.5, 127.5, 121.3, 85.4, 79.1, 77.9, 71.5, 61.4, 55.3, 44.3, 32.7, 25.5, 19.7. Anal. Calcd for $C_{30}H_{37}FO_4Si$: C, 70.83; H, 7.33 Found: C, 70.71; H, 7.41.

tert-Butyl((((1R,2R,3R,4S)-2-(tert-butyldiphenylsilyloxy)-3-fluoro-4-(4-methoxy benzyloxy) cyclopentyl) methoxy) diphenylsilane (96). Compound **96** was prepared from **95** by the same procedure as described for the synthesis of compound **66**. ^{1}H NMR

(400 MHz, CDCl$_3$): δ 7.7-7.74 (m, 8H), 7.25-7.33 (m, 12H), 7.26 (d, *J*=8.4 Hz, 2H), 6.92 (d, *J*=8.4 Hz, 2H), 4.56 (d, *J*=5.6 Hz, 1H), 4.46-4.50 (m, 2H), 4.25 (m, 1H), 3.75 (s, 3H), 3.64-3.70 (m, 2H), 3.40 (m, 1H), 2.17-2.22 (m, 2H), 1.82-1.89 (m, 1H), 0.93 (s, 9H), 0.88 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.1, 138.3, 134.2, 133.3, 132.1, 131.1, 130.3, 130.1, 129.5, 128.4, 127.1, 121.1, 85.4, 79.5, 77.3, 71.8, 61.1, 55.4, 44.2, 33.2, 25.3, 25.1, 19.2, 19.0. Anal. Calcd for C$_{46}$H$_{55}$FO$_4$Si$_2$: C, 73.95; H, 7.42 Found: C, 73.87; H, 7.36.

(1*S*,2*R*,3*R*,4*R*)-3-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy) methyl)-2-fluorocyclopentanol (93). Compound **93** was prepared from **96** by the same procedure as described for the synthesis of compound **57**. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.66-7.70 (m, 8H), 7.28-7.37 (m, 12H), 4.62 (d, *J*=5.6 Hz, 1H), 4.24-4.27 (m, 1H), 3.71-3.76 (m, 2H), 3.21-3.25 (m, 1H), 2.29-2.3 (m, 2H), 1.81-1.88 (m, 1H), 0.91 (s, 9H), 0.87 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 137.6, 134.5, 133.4, 132.1, 131.4, 130.2, 130.8, 127.5, 85.3, 79.1, 77.1, 61.3, 44.1, 32.9, 25.4, 25.2, 19.3, 19.2. Anal. Calcd for C$_{38}$H$_{47}$FO$_3$Si$_2$: C, 72.80; H, 7.56 Found: C, 72.68; H, 7.53.

1-((1*R*,2*R*,3*R*,4*R*)-3-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyldiphenyl silyloxy) methyl)-2-fluorocyclopentyl)-4-(*N,N*-di-(*tert*-butyl-*O*-carbonyl)amino)-1*H*-imidazo[4,5-*c*]pyridine (97). Compound **97** was prepared from **93** and **56** by the same procedure as described for the synthesis of compound **69,** which was used in next step without further purification.

(1*R*,2*R*,3*R*,5*R*)-3-(4-Amino-1*H*-imidazo[4,5-c]pyridin-1-yl)-2-fluoro-5-(hydroxyl methyl)cyclopentanol (5). Compound **5** was prepared from **97** by the same procedure as described for the synthesis of compound **1**. Mp 239-242 ℃. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.14 (s, 1H), 7.67 (d, *J*=6 Hz, 1H), 6.82 (d, *J*=6 Hz, 1H), 6.15 (br, 2H), 5.44 (d, *J*=2

Hz, 1H), 4.79-4.89 (m, 2H), 4.75(d, J=2 Hz, 1H), 3.90-3.97 (m, 2H), 3.70-3.79 (m, 2H), 2.31-2.36 (m, 1H), 1.98-2.02 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ151.6, 141.3, 141.1, 135.1, 135.0, 107.9, 94.4, 78.6, 72.5, 62.6, 32.4, 24.8. Anal. Calcd for C$_{12}$H$_{15}$FN$_4$O$_2$: C, 54.13; H, 5.68; N, 21.04. Found: C, 54.05; H, 5.59; N, 20.94.

O-(1S,2R,3R,5S)-2-(*tert*-Butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)-3-vinyl cyclopentyl S-methyl carbonodithioate (100). Compound **100** was prepared from **61** by the same procedure as described for the synthesis of compound **78**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68-7.71 (m, 4H), 7.34-7.37 (m, 6H), 7.28 (d, J=8.8 Hz, 2H), 6.89 (d, J=8.8 Hz, 2H), 5.32-5.42 (m,1H), 4.81-4.92 (m, 2H),4.47-4.53 (m, 2H), 3.78 (s, 3H), 3.71-3.76 (m, 2H), 2.81-2.91 (m, 1H), 2.5 (s, 1H), 2.42 (s, 3H), 2.01-2.10 (m, 1H), 1.54-1.57 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 216.3, 157.1, 136.8, 135.3, 133.8, 131.3, 130.3, 129.7, 127.5, 121.3, 114.2, 83.8, 79.5, 77.6, 71.4, 55.3, 44.2, 33.6, 25.3, 19.7, 19.2. Anal. Calcd for C$_{33}$H$_{40}$O$_4$S$_2$Si: C, 66.85; H, 6.8 Found: C, 66.72; H, 6.71.

tert-Butyl((1S,2R,4S)-4-(4-methoxybenzyloxy)-2-vinyl cyclo pentyloxy) diphenyl silane (101). Compound **101** was prepared from **100** by the same procedure as described for the synthesis of compound **79**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68-7.71 (m, 4H), 7.34-7.37 (m, 6H), 7.28 (d, J=8.8 Hz, 2H), 6.89 (d, J=8.8 Hz, 2H), 5.32-5.42 (m,1H), 4.82-4.88 (m, 2H), 4.48-4.53 (m, 2H), 4.12-4.16 (m, 1H), 3.84-3.91 (m, 1H), 3.79 (s, 3H), 3.42-3.51 (m, 2H), 1.76-1.83 (m, 1H), 1.66-1.73 (m, 1H), 1.53-1.59 (m, 1H), 0.89 (s, 9H) ^{13}C NMR (100 MHz, CDCl$_3$) δ157.6, 137.3, 135.2, 133.4, 131.3, 130.3, 129.6, 127.6, 121.3, 119.7, 79.4, 76.4, 70.3, 55.3, 44.3, 36.2, 33.7, 25.3, 19.6. Anal. Calcd for C$_{31}$H$_{38}$O$_3$Si: C, 76.5; H, 7.78 Found: C, 76.56; H, 7.87.

((1*R*,2*S*,4*S*)-2-(*tert*-Butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy) cyclopentyl) methanol (102). Compound **102** was prepared from **101** by the same procedure as described for the synthesis of compound **65**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.64-7.71 (m, 4H), 7.30-7.35 (m, 6H), 7.26 (d, *J*=8.8 Hz, 2H), 6.97 (d, *J*=8.8 Hz, 2H), 4.42-4.48 (m, 2H), 4.12-4.17 (m, 1H), 3.88-3.92 (m, 1H), 3.78 (s, 3H), 3.66-3.69 (m, 2H), 1.68-1.74 (m, 2H), 1.64-1.67 (m, 2H), 1.54-1.60 (m, 1H), 0.89 (s, 9H) ^{13}C NMR (100 MHz, CDCl$_3$): δ156.3, 134.2, 133.5, 131.6, 130.3, 129.7, 127.7, 121.6, 79.3, 76.2, 70.7, 68.2, 54.8, 44.3, 36.1, 32.8, 25.2, 19.3. Anal. Calcd for C$_{30}$H$_{38}$O$_4$Si: C, 73.43; H, 7.81 Found: C, 73.37; H, 7.71.

tert-Butyl((((1*R*, 2*S*, 4*S*)-2-(*tert*-butyldiphenylsilyloxy)-4-(4-methoxy benzyloxy) cyclopentyl)methoxy)diphenylsilane (103). Compound **103** was prepared from **102** by the same procedure as described for the synthesis of compound **66**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78-7.84 (m, 8H), 7.41-7.51 (m, 12H), 7.22 (d, *J*=8.8 Hz, 2H), 6.94 (d, *J*=8.8 Hz, 2H), 4.41-4.51 (m, 2H), 4.13-4.16 (m, 1H), 3.87-3.90 (m, 1H), 3.7 (s, 3H), 3.66-3.69 (m, 2H), 1.73-1.78 (m, 2H), 1.64-1.68 (m, 2H), 1.51-1.57 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H) ^{13}C NMR (100 MHz, CDCl$_3$) δ156.6, 134.1, 134.0, 133.5, 132.6, 131.4, 130.1, 130.1, 129.5, 128.2, 127.4, 121.3, 79.3, 76.6, 70.8, 68.2, 54.8, 44.2, 36.2, 32.7, 25.3, 25.1, 19.5, 19.2. Anal. Calcd for C$_{46}$H$_{56}$O$_4$Si$_2$: C, 75.78; H, 7.74 Found: C, 75.71; H, 7.62.

(1*S*,3*S*,4*R*)-3-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyl diphenyl silyloxy) methyl) cyclopentanol (99). Compound **99** was prepared from **103** by the same procedure as described for the synthesis of compound **57**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73-7.79 (m, 8H), 7.42-7.48 (m, 12H), 4.12-4.16 (m, 1H), 3.71-3.79 (m, 1H), 3.42-3.47 (m, 2H), 1.68-1.72 (m, 2H), 1.61-1.65 (m, 2H), 1.52-1.58 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H) ^{13}C NMR

(100 MHz, CDCl$_3$) δ 135.4, 134.7, 133.2, 131.6, 132.4, 130.3, 130.2, 127.3, 78.8, 76.5, 68.3, 44.3, 36.9, 32.9, 25.3, 24.1, 19.6, 19.4. Anal. Calcd for C$_{38}$H$_{48}$O$_3$Si$_2$: C, 74.95; H, 7.94 Found: C, 75.03; H, 7.88.

1-((1R,3S,4R)-3-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy) methyl)-cyclopentyl)-4-(*N*,*N*-di-(*tert*-butyl-*O*-carbonyl)amino)-1H-imidazo[4,5-c] pyridine (104). Compound **104** was prepared from **99** and **56** by the same procedure as described for the synthesis of compound **69**, which was used in next step without further purification.

(1S,2R,4R)-4-(4-Amino-1H-imidazo[4,5-c]pyridin-1-yl)-2-(hydroxymethyl) cyclopentanol (6). Compound **6** was prepared from **104** by the same procedure as described for the synthesis of compound **1**. Mp 223-226 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.68 (d, J=6 Hz, 1H), 6.81 (d, J=6 Hz, 1H), 6.12 (br, 2H), 4.12-4.16 (m, 1H), 3.77-3.82 (m, 1H), 3.71-3.79 (m, 2H), 1.68-1.72 (m, 2H), 1.61-1.66 (m, 2H), 1.51-1.55 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ155.3, 141.5, 140.8, 135.3, 135.1, 108.3, 79.2, 72.8, 63.7, 41.3, 32.6, 25.3. Anal. Calcd for C$_{12}$H$_{16}$N$_4$O$_2$: C, 58.05; H, 6.5; N, 22.57. Found: C, 58.08; H, 6.48; N, 22.61.

(3aR,4S,6aR)-4-Methyl-4,6a-dihydro-3aH-spiro[cyclopenta[d][1,3]dioxole-2,1′-cyclopentan]-4-ol (108). MeLi (31.2 mL, 1.6 M, 49.9 mmol) was added to a solution of **32** (5.0 g, 27.7 mmol) in dry THF (50 mL) at -78 ℃ dropwise. After stirring at -78 ℃ for 30 min, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched by the addition of aqueous NH$_4$Cl (50 mL) at 0 ℃, the aqueous phase was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified

through silica gel column chromatography (hexane : EtOAc = 5:1) to give **108** (4.63 g, 85%) as a white solid: mp 43-44 ℃; ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.81 (d, *J*=9.2 Hz, 1H), 5.74 (d, *J*=9.2 Hz, 1H), 5.04-5.07 (m, 1H), 4.24 (d, *J*=9.2 Hz, 1H), 3.09 (s, 1H), 1.79-1.84 (m, 4H), 1.61-1.70 (m, 4H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ142.3, 131.7, 114.8, 84.9, 81.9, 80.3, 78.9, 39.3, 37.9, 20.3, 20.1; Anal. Calcd for C$_{11}$H$_{16}$O$_3$: C, 67.32; H, 8.22. Found: C, 67.18; H, 8.13.

(3a*S*,6a*S*)-6-Methyl-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1′-cyclopentan]-4(6aH) -one (109). A mixture of **108** (3.43 g, 17.6 mmol), PDC (13.26 g, 35.3 mmol), 4 Å molecular sieves (3.0 g), and Ac$_2$O (7.84 mL, 141 mmol) in dichloromethane (100 mL) was stirred at room temperature overnight. The solvent was removed in vacuo and the residue partitioned between saturated aqueous Na$_2$CO$_3$ (100 mL) and CH$_2$Cl$_2$ (100 mL). The aqueous layer was washed with CH$_2$Cl$_2$ (2 × 100 mL) and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The residuewas purified by silica gel column chromatography (hexane : EtOAc = 10:1) to afford **109** (1.87 g, 54.8%) as a white solid: mp 80-81 ℃. ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.99 (s, 1H), 4.96 (d, *J*=5.6 Hz, 1H), 4.41 (d, *J*=5.6 Hz, 1H), 2.2 (s, 3H), 1.68-1.86 (m, 4H), 1.62-1.67 (m, 4H); ^{13}C NMR (100 MHz, CDCl^3) δ 202.8, 184.3, 174.8, 130.0, 116.0, 80.7, 37.3, 35.9, 24.9, 20.5, 20.1; Anal. Calcd for C$_{11}$H$_{14}$O$_3$: C, 68.02; H, 7.27. Found: C, 68.18; H, 7.26.

(3a*S*,4*S*,6a*S*)-4-methyl-4-vinyldihydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1′-cyclopentan]-6(6aH)-one (110). Vinylmagnesium bromide (10.95 mL, 10.95 mmol, 1.0 M in THF) and HMPA (3.2 mL, 18.25 mmol) were added to a suspension of CuBr·Me2S (150 mg, 0.73 mmol) in dry THF (20 mL) at -78 ℃ over 10 min. After stirring at -78 ℃

for 15 min, a solution of **109** (1.42 g, 7.3 mmol) and TMSCl (1.94 mL, 15.33 mmol) in dry THF (20 mL) was added dropwise over 30 min. The reaction mixture was stirred at -78 ℃ for 2 h, and then quenched by the addition of saturated NH_4Cl (10 mL). The reaction mixture was extracted with EtOAc (3 × 40 mL), the combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane : EtOAc = 10:1) to give **110** (1.13 g, 69.8%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.66-5.73 (m, 1H), 4.99-5.04 (m, 2H), 4.4-4.43 (d, *J*=5.6 Hz, 1H), 4.11-4.22 (d, *J*=5.6 Hz, 1H), 1.94 (d, *J*=7 Hz, 2H), 1.68-1.86 (m, 4H), 1.62-1.67 (m, 4H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.6, 142.9, 114.4, 113.3, 82.8, 79.2, 44.5, 41.6, 36.7, 34.6, 25.0, 21.9, 21.7; Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.11; H, 8.09.

(3a*S*, 4*S*, 6*R*, 6a*R*)-4-Methyl-4-vinyltetrahydro-3a*H*-spiro[cyclopenta[*d*] [1,3] dioxole-2,1′-cyclopentan]-6-ol (111). $CeCl_3 \cdot 7H_2O$ (1.43 g, 4.95 mmol) was added to a solution of **110** (1 g, 4.5 mmol) in MeOH (10 mL) at -30 ℃. After stirring for 15 min at -30 ℃, $NaBH_4$ (340 mg, 9.0 mmol) was added carefully and the reaction mixture was warmed to room temperature for 30 min. The mixture was neutralized with conc. HCl, reduced to 2/3 volume, extracted with brine and ether. The organic layers combined, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane : EtOAc = 5:1) to give **111** (866 mg, 85.8%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.66-5.73 (m, 1H), 4.99-5.03 (m, 2H), 4.37 (t, *J*=6.0 Hz, 1H), 4.22 (d, *J*=5.5 Hz, 1H), 3.99-4.03 (m, 1H), 2.41 (d, *J*=10.0 Hz, 1H), 1.94-1.98 (m, 5H), 1.52-1.72 (m, 5H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 112.9, 111.2,

84.7, 78.5, 70.8, 44.2, 41.9, 35.9, 33.9, 25.2, 21.3, 20.99; Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.73; H, 8.82.

4-Chloro-1-((3aS,4S,6S,6aR)-4-methyl-4-vinyltetrahydro-3aH-spiro[cyclopenta [d][1,3]dioxole-2,1′-cyclopentane]-6-yl)-1H-imidazo[4,5-c]pyridine (112). Tf$_2$O (1.5 mL, 8.92 mmol) was added to a solution of **111** (1 g, 4.46 mmol) and pyridine (1.44 mL, 17.83 mmol) in dry dichloromethane (10 mL) at 0 ℃. After stirring for 50 min at 0 ℃, cold dichloromethane (10 mL) and ice-water (20 mL) were added. The aqueous layer was washed with cold dichloromethane (15 mL) and the combined organic phases were dried over MgSO$_4$, filtered, and concentrated to give the crude triflate **106**, which was dried in vacuo at 0 ℃ for 1 h. A solution of **11** (1.3 g, 8.47 mmol), NaH (357 mg, 8.92 mmol, 60% dispersion in mineral oil), and 18-crown-6 (2.36 g, 8.92 mmol) in DMF (15 mL) was heated at 70 ℃ for 4 h and then cooled to 0 ℃. To this mixture was added the solution of previously prepared triflate in DMF (5 mL), and the reaction mixture was allowed to stir at 0 ℃ for 12 h and then at room temperature for 2 days. DMF was removed in vacuo and the residue was purified by silica gel column chromatography (hexane : EtOAc = 5:1) to give **112** (882 mg, 55%) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.09 (s, 1H), 7.65 (d, J=5.6 Hz, 1H), 7.55 (d, J=5.6 Hz, 1H), 5.95-6.01 (m, 1H), 5.06-5.14 (m, 3H), 4.98-5.02 (m, 1H), 4.69 (d, J=6.5 Hz, 1H), 2.64-2.69 (m, 1H), 2.26-2.3 (m, 1H), 1.80-1.82 (m, 2H), 1.64-1.69 (m 2H), 1.48- 1.59 (m, 4H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ149.8, 139.7, 137.2, 136.7, 132.3, 122.6, 114.8, 113.0, 108.1, 84.9, 83.9, 61.5, 46.3, 42.8, 36.1, 34.2, 25.1, 21.9, 21.7; HRMS calcd for $C_{19}H_{22}ClN_3O_2$ 359.1488, found 359.1438.

((3a*R*, 4*S*, 6*S*, 6a*S*) -4- (4-Chloro-1*H*-imidazo [4,5-*c*] pyridin-1-yl)-6-methyl tetrahydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1′-cyclopentane]-6-yl)methanol (113). Compound **112** (882 mg, 2.45 mmol) was dissolved in MeOH (8 mL). Water (8.3 mL) was added. NaIO$_4$ (1.15 g, 5.39 mmol) was added. The mixture was cooled to 0 °C. OsO$_4$ (31 mg, 0.12 mmol, 5% mol) was added. The mixture was stirred at 0 °C for 2 hours. The mixture was filtered. MeOH was removed by reduced pressure. The residue was extracted with dichloromethane (3×10 mL). The organic layer was washed with brine, dried over sodium sulfate, concentrated. The residue was dissolved in methanol (10 mL). NaBH$_4$ (232 mg, 6.13 mmol) was added portionwise at 0 °C. The mixture as stirred at 0 °C for 1 hour. Saturated NH$_4$Cl solution (10 mL) was added. The mixture was filtered through celite. The solvent was removed with reduced pressure. The residue was extracted with EtOAc (3 ×10 mL). The combined organic layer was dried over sodium sulfate, concentrated. The residue was purified by silica gel column chromatography (hexane : EtOAc = 3:1) to provide **113** as a white foam (587 mg, 65.8%). ^{1}H NMR (400 MHz, CDCl$_3$), δ 8.27 (s, 1H), 8.22 (d, *J*=5.6 Hz, 1H), 7.57 (d, *J*=5.6 Hz, 1H), 4.74-4.78 (m, 1H), 4.63-4.65 (m, 1H), 4.46-4.48 (d, *J*= 6.4 Hz, 1H), 3.61 (d, *J*=5.6 Hz, 2H), 2.62-2.68 (m, 1H), 2.31-2.37 (m, 1H), 1.65-1.8 (m, 8H), 1.2 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ149.9, 139.6, 137.1, 132.2, 122.7, 113.2, 108.2, 84.7, 83.9, 67.5, 61.5, 46.2, 42.6, 36.2, 34.3, 25.2, 21.9, 21.7; Calcd HRMS for C$_{18}$H$_{22}$ClN$_3$O$_3$: 363.1377, Foud: 363.1367.

(1*R*,2*S*,3*S*,5*S*)-5-(4-Chloro-1H-imidazo[4,5-c]pyridin-1-yl)-3-(hydroxymethyl)-3-methylcyclopentane-1,2-diol (114). Compound **113** (587 mg, 1.61 mmol) was dissolved in 2 N HCl (1 mL) in MeOH at 0 °C and stirred at 25 °C overnight. NaHCO$_3$ was added to neutralize the solution until it no longer bubbled. The mixture was filtered. The solvent

was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc : MeOH = 2:1) to provide **114** as a white solid (287 mg, 59.7%), mp 184-186 ℃. ^{1}H NMR (400 MHz, DMSO-d_6), δ 8.56 (s, 1H), 8.13 (d, J=5.6 Hz, 1H), 7.82 (d, J=5.6 Hz, 1H), 4.82-4.92 (m, 1H), 4.53-4.57 (m, 1H), 3.9-3.93 (m, 1H), 3.51 (d, J=5.6 Hz, 1H), 3.44 (d, J=5.6 Hz, 1H), 3.29 (s, 1H), 2.09-2.18 (m, 1H), 2.01-2.07 (m, 1H), 1.12 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.3, 138.4, 136.8, 132.1, 119.2, 108.4, 75.7, 74.5, 69.4, 60.4, 44.4, 36.7, 18.4; Calcd HRMS for $C_{13}H_{16}ClN_3O_3$: 297.0965, Foud: 297.0961.

(1R,2S,3S,5S)-5-(4-Amino-1H-imidazo[4,5-c]pyridin-1-yl)-3-(hydroxymethyl)-3-methylcyclopentane-1,2-diol (7). To a mixture of anhydrous hydrazine (99%, 1 mL) and propan-1-ol (3 mL) was added **114** (287 mg, 1.87 mmol). The solution was brought to reflux for 8 h. The reaction was cooled to room temperature and the residual hydrazine and propan-1-ol was evaporated under reduced pressure. Water (5 mL) was added to dissolve the residue. Raney nickel (0.8 g) was added portionwise. The mixture was heated to reflux for 1 h. After the reaction had completed, the reaction mixture was filtered through a celite pad. The filtrate was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc : MeOH : $NH_3·H_2O$ = 20:2:1) to provide **7** as a white solid (76 mg, 30.3%), mp 208-209 ℃. ^{1}H NMR (400 MHz, MeOD), δ 8.21 (s, 1H), 7.64 (d, J=6 Hz, 1H), 7.0 (d, J=6 Hz, 1H), 4.56-4.78 (m, 1H), 4.53-4.57 (m, 1H), 3.94 (d, J=6 Hz, 1H), 3.51 (d, J=5.6 Hz, 1H), 3.48 (d, J=5.6 Hz, 1H), 2.08-2.13 (m, 1H), 1.98-2.05 (m, 1H), 1.13 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 176.5, 153.3, 142.3, 140.4, 128.2, 99.7, 77.5, ,76.0, 70.6, 62.7, 45.7, 37.7, 20.1. Calcd HRMS for $C_{13}H_{18}N_4O_3$: 279.1469, Foud: 279.1457.

References

(1)   Fisher, B.; Harvey, R. P.; Champe, P. C. Lippincott's Illustrated Reviews: Microbiology 2007, 354.

(2)   Boevink, P.; Oparka, K. J. Virus-host Interactions During Movement Processes 2005, 4, 1815.

(3)   Broder, S. Antivir. Res. 2009, 1, 1.

(4)   Fox, Z.; Dragsted, U. B. Antivir. Ther. 2006, 6, 761.

(5)   Collier, L.; Balows, A.; Sussman, M. Virology 1998, 1, 79.

(6)   Douek, D. C.; Roederer, M. Annu. Rev. Med. 2009, 60, 471.

(7)   Roulston, A.; Marcellus, R. C. Annu. Rev. Microbiol. 1999, 53, 577.

(8)   Subramanya, D.; Grivas, P. Postgrad. Med. 2008, 7.

(9)   Patick, A. K. Antivir. Res. 2006, 71, 391.

(10)   Hayden, F. G. Antivir. Res. 2006, 71, 372.

(11)   Quiinlivan, M.; Breuer, J. Rev. Med. Virol. 2006, 16, 225.

(12)   James, W. D.; Berger, T. G. Andrews's Diseases of the skin: clinical dermatology. 2006, 368.

(13)   Ute, S.; Heinz, F. Expert Opin. Inv. Drug. 2006, 15, 1523.

(14)   Butler, I. F.; Pandrea, I.; Marx, P. A.; Apetrei, C. Curr. HIV Res. 2007, 5, 23.

(15)   Oxford, J. S. Influ. Other Respir. Viruses 2007, 1, 27.

(16)   Haagmans, B. L.; Osterhaus, A. D. Antivir. Res. 2006, 71, 397.

(17)   Jahrling, P. B.; Frits, E. A.; Hensley, L. E. Curr. Mol. Med. 2005, 5, 817.

(18)   Bronze, M. S.; GreenField, R. A. Drug Discov. Today 2003, 8, 740.

(19)   Goff, A. J.; Paragas, J. Antivir. Chem. Chemother. 2005, 16, 283.

(20)   Zeisel, M.; Barth, H.; Schuster, C.; Baument, T. F. Frontiers in Bioscience: A Journal and Virtual Library 2009, 14, 3274.

(21)   Lockey, T. D.; Zhan, X.; Surman, S.; Sample, C. E.; Hurwitz, J. L. Front. Biosci. 2008, 13, 5916.

(22)   Rebora, A.; Rongioletti, F. Dermatology 1999, 198, 1.

(23)   Sinal, S. H.; Cabinum, F. E.; Socolar, R. South Med. J. 2008, 7, 703.

(24)   Mcmichael, A. J. Annu. Rev. Immunol. 2006, 24, 227.

(25)   Brander, C.; Frahm, N.; Walker, B. D. Curr. Opin. Immunol. 2006, 18, 430.

(26)   Singh, M. Virol. J. 2006, 3, 60.

(27)   Kim, W.; Liau, L. M. Neurosurg. Clin. N. Am. 2010, 1, 139.

(28)   Stern, A. M.; Markel, H. Health Aff. 2005, 3, 611.

(29)   Venter, J.; Adams, M. D.; Myers, E. W. Science 2001, 5507, 1304.

(30)   Berg, J. M.; Tymoczko, J. L.; Stryer, L. Biochemistry 2002, 118.

(31)   Porkka, H. T.; Stercker, R. E.; Thakkar, M.; Bjorkum, A. A.; Greene, R. W.; McCarley, R. W. Science 1997, 276, 1265.

(32)   Robins, R. K. Chem. Eng. News 1986, 64, 28.

(33)   Isono, K. Pharmacol. Ther. 1991, 52, 269.

(34)   Isono, K. J. Antibiot. 1988, 41, 1711.

(35)   De Clercq, E. Nucleosides Nucleotides 1994, 13, 1271.

(36)   Anastasi, C.; Quelever, G.; Burlet, S.; Garino, C.; Souard, F.; Kraus, J. L. Curr. Med. Chem. 2003, 10, 1825.

(37)   De Clercq, E. Nat. Rev. Drug Discovery 2002, 1, 13.

(38)   Carroll, S. S.; Olsen, D. B. Infectious Disorders-Drug Targets 2006, 6, 17.

(39)   Prusoff, W. H. Biochim. Biophys. Acta 1959, 32, 295.

(40)   Elion, G. B.; Furman, P. A.; Fyfe, J. A. Proc. Natl. Acad. Sci. 1977, 74, 5716.

(41)   Meier, C.; Habel, C.; Haller-Meier, F.; Lomp, A. Antivir. Chem. Chemother. 1998, 9, 389.

(42)   Erik, D. C. Nature Reviews Microbiology 2004, 2, 704.

(43)   Glezen, W. P.; Taber, L. H.; Frank, A. L.; Kasel, J. A. Am. J. Dis. Child. 1986, 6, 543.

(44)   Yang, G.; Pevear, D. C.; Davies, M. J. Virol. 2005, 20, 13139.

(45)   Shuman, S. Prog. Nucleic Acid Res. Mol. Biol. 1995, 50, 101.

(46)   Kapp, L. D.; Lorsch, J. R. Annu. Rev. Biochem 2004, 1, 657.

(47)   Parker, R.; Sheth, U. Molecular Cell 2007, 5, 635.

(48)   Borchardt, R. T. J. Med. Chem. 1980, 23, 347.

(49)   Konarska, M. M.; Padgett, R. A.; Sharp, P. A. Cell 1984, 38, 731.

(50)   Finkelstein, J.; Martin, J. Int. J. Biochem. Cell Biol 2000, 4, 385.

(51)   Henderson, J. F. Methods Pharmacol. 1985, 6, 67.

(52)   Lieber, C. S.; Packer, L. Am. J. Clin. Nutr. 2002, 76, 1148S.

(53)   Turner, M. A.; Yang, X.; Yin, D.; Kuczera, K.; Borchardt, R. T.; Howell, P. L. Cell Biochem. Biophys. 2000, 33, 101.

(54)   Saha, N.; Shuman, S.; Schwer, B. J. J. Virol. 2003, 77, 7300.

(55)   Barbosa, E.; Moss, B. J. J. Biol. Chem. 1978, 253, 7692.

(56)   Fodinger, M.; Horl, W.; Sunder-Plassmann, G. J. Nephrol 2000, 1, 20.

(57)   Fontecave, M.; Atta, M.; Mulliez, E. Trends Biochem. Sci. 2004, 29, 243.

(58)   yang, X.; Hu, Y.; Yin, D. H.; Turner, M. A.; Wang, M.; Borchardt, R. T.; Howell, P. L.; Kuczera, K.; Schowen, R. L. Biochemistry 2003, 42, 1900.

(59)   Duerre, J. A. J. Biol. Chem. 1962, 237, 3737.

(60)   Martin, S. A.; Moss, B. J. Biol. Chem. 1975, 250, 9330.

(61)   Gong, C.; Shuman, S. Virology 2003, 309, 125.

(62)   Wolfe, M. S.; Borchardt, R. T. J. Med. Chem. 1991, 34, 1521.

(63)   Bennett, L. L.; Allan, P. W.; Hill, D. L. Mol. Pharmacol. 1968, 4, 208.

(64)   De Clercq, E. Antiviral Res. 2005, 67, 56.

(65)   Cantoni, G. L. Annu. Rev. Biochem 1975, 44, 435.

(66)   Crimmins, M. T. Tetrahedron 1998, 54, 9229.

(67)   Borthwick, A. D.; Biggadike, K. Tetrahedron 1992, 48, 571.

(68)   Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R. Tetrahedron 1994, 50, 10611.

(69)   Wachtmeister, J.; Classon, B.; Samuelsson, B.; Kvarnstroem, I. Tetrahedron 1995, 51, 2029.

(70)   Wachtmeister, J.; Classon, B.; Samuelsson, B.; Kvarnstroem, I. Tetrahedron 1997, 53, 1861.

(71)   Marquez, V. E.; Lim, M. I. Med. Res. Rev. 1986, 6, 1.

(72)   Marquez, V. E. Adv. Antiviral Drug Design 1996, 2, 89.

(73)   Vince, R.; Hua, M. J. J. Med. Chem. 1990, 33, 17.

(74)   Mallal, S.; Philips, E.; Carosi, G. N. Engl. J. Med. 2008, 6, 568.

(75)   Sims, K. A.; Woodland, A. M. Pharmacotherapy 2006, 12, 1745.

(76)   Scott, L. J.; Keating, G. M. Drugs 2009, 69, 1003.

(77)   Izuta, S.; Shimada, N.; Kitagawa, M.; Suzuki, M.; Kojima, K.; Yoshida, S. J. J. Biochem 1992, 112, 81.

(78)   Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. J. Antibiot. 1981, 34, 359.

(79)   Hayashi, M.; Yaginuma, S.; Yoshioka, H.; Nakatsu, K. J. Antibiot. (Tokyo) 1981, 34, 675.

(80)   Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. J. Am. Chem. Soc. 1983, 105, 4049.

(81)   Herdewijn, P.; balzarini, J.; De Clercq, E.; Vanderhaeghe, H. J. Med. Chem. 1985, 28, 1385.

(82)   Lim, M. I.; Marquez, V. E. Tetrahedron Lett. 1983, 24, 5559.

(83)   Nokami, J.; Matsuura, H.; Takahashi, H.; Yamashita, M. Synlett 1994, 491.

(84)   Tseng, C. K. H.; Marquez, V. E. Tetrahedron Lett. 1985, 26, 3369.

(85)   Wolfe, M. S.; Anderson, B. L.; Borcherding, D. R.; Borchardt, R. T. J. Org. Chem. 1990, 55, 4712.

(86)   Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. J. Antibiot. 1968, 21, 255.

(87)   Yuan, C. S.; Liu, S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T. Advances in Antiviral Drug Design 1996, 2, 41.

(88)   Bennett, L. L.; Brockman, R. W.; Rose, L. M.; Allan, P. W.; Shaddix, S. C.; Shealy, Y. F.; Clayton, J. D. Mol. Pharmacol 1985, 27, 666.

(89)   Bennett, L. L.; Allan, P. W.; Rose, L. M.; Comber, R. N.; Secrist, J. A. Mol. Pharmacol. 1986, 29, 383.

(90)   De Clercq, E.; Cools, M.; Balzarini, J.; Marquez, V. E.; Borcherding, D. R. Antimicrob. Agents Chemother. 1989, 33, 1291.

(91)   Saunders, P. P.; Tan, M. T.; Robins, R. K. Biochem. Pharmacol. 1985, 34, 2749.

(92)   Hill, D. L.; Straight, S.; Allan, P. W.; Bennett, L. L. Mol. Pharmacol 1971, 7, 375.

(93)   Inaba, M. K.; Nagashima, S.; Tsukagoshi; Sakurai, Y. Caner Res. 1986, 46, 1063.

(94)   Siddiqi, S. M.; Chen, X.; Schenller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. J. Med. Chem. 1994, 37, 551.

(95)   Seley, K. L.; Schneller Stewart, W.; Korba, B. J. Med. Chem. 1997, 16, 2095.

(96)   Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. J. Org. Chem. 1987, 52, 5457.

(97)   Glazer, R. I.; Knode, M. C.; Tseng, C. K. H.; Haines, D. R.; Marquez, V. E. Biochem. Pharmacol. 1986, 35, 4523.

(98)   Narayanan, S. R.; Keller, B. T.; Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. J. Med. Chem. 1988, 31, 500.

(99)   Hasobe, M.; Mckee, D. R.; Borcherding, D. R.; Borchardt, R. T. Antimicrob. Agents Chemother. 1987, 31, 1849.

(100)   Hasobe, M.; Liang, H.; Ault-Riche, D. B.; Borcherding, D. R.; Wolfe, M. S.; Borchardt, R. T. Antiviral Chem. Chemother. 1993, 4, 245.

(101)   Greenberg, L. M.; Chaffee, S.; Hershfiled, S. M. The Journal of Biological Chemistry 1989, 15, 795.

(102)   Ault-Riche, D. B.; Lee, Y.; Yuan, C. S.; Hasobe, M.; Wolfe, M. S.; Borcherding, D. R.; Borchardt, R. T. Mol. Pharmacol. 1993, 43, 989.

(103)   Ozduman, K.; Wollman, G.; Piepmeier; Van, D. P. the Journal of Neuroscience 2008, 28, 1882.

(104)   Yang, M.; Schneller, S. W. Bioorg. Med. Chem. Lett. 2005, 15, 149.

(105)   Yang, M.; Zhou, J.; Schneller, S. W. Tetrahedron Lett. 2004, 45, 8981.

(106)   Ye, W.; He, M.; Schneller, S. W. Tetrahedron Lett. 2009, 50, 7156.

(107)   Yang, M.; Schenller, S. W.; Korba, B. J. J. Med. Chem. 2005, 48, 5043.

(108)   Biggadike, K.; Borthwick, A. D. J. Chem. Soc., Chem. Commun. 1990, 19, 1380.

(109)   Roy, A.; Schneller, S. W.; Keith, K. A.; Hartline, C. B.; Kern, E. R. Bioorg. Med. Chem. 2005, 13, 4443.

(110)   Roy, A.; Serbessa, T.; Schenller, S. W. Bioorg. Med. Chem. 2006, 14, 4980.

(111)   Li, W.; Yin, X.; Schneller, S. W. Bioorg. Med. Chem. Lett. 2008, 18, 220.

(112)   Liu, L. J.; Hoon, J. H. Nucleosides, Nucleotides and Nucleic Acids 2010, 29, 216.

(113)   Van Aerschot, A.; Herdewijn, P.; Janssen, G.; Cools, M.; De Clercq, E. Antiviral Res. 1989, 12, 133.

(114)   Mikhailopulo, I. A.; Poopeiko, N. E.; Pricota, T. I.; Sivets, G. G.; Kvasyuk, E. I.; Balzarini, J.; De Clercq, E. J. Med. Chem. 1991, 34, 2195.

(115)   Ismail Fraz, M. D. J. Fluorine Chem. 2002, 118, 27.

(116)   Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. Annu. Rev. Pharmacol. Toxicol. 2002, 41, 443.

(117)   Li, W. K.; Yin, X. Q.; Schenller, S. W. Bioorg. Med. Chem. Lett. 2008, 18, 220.

(118)   Haba, G.; Agostini, S.; Bozzi, A.; Merta, A.; Unson, C.; Cantoni, G. L. Biochemisty 1986, 25, 8337.

(119)   Abeles, R. H.; Fish, S.; Lapinskas, B. biochemistry 1982, 21, 5557.

(120) Su, T. L.; Watanabe, K. A.; Schinazi, R. F.; Fox, J. J. J. Med. Chem. 1986, 151.

(121) Sabini, E.; Ort, S.; Monnerjahn, C.; Konrad, M.; Lavie, A. Nat. Struct. Biol. 2003, 10, 513.

(122) Chuang, R. Y.; Chuang, L. F. Nature 1976, 260, 549.

(123) Bonate, P. L.; Arthaud, L.; Cantrell, W. R.; Stephenson, K.; Secrist, J. A.; Weitman, S. Nat. Rev. Drug Discovery 2006, 5, 855.

(124) He, J. L.; Mikhailopulo, I. A.; Seela, F. 2003, 68, 5519.

(125) Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawfordruth, D.; Verheyden, J. P. H. J. Med. Chem. 1992, 35.

(126) Kohgo, S.; Yamada, K.; Kitano, K.; Iwai, Y.; Sakata, S. Nucleosides Nucleotides Nucleic Acids 2004, 23, 671.

(127) Summerer, D.; Marx, A. Bioorg. Med. Chem. Lett. 2005, 15, 869.

(128) Kitano, K.; Miura, S.; Ohrui, H.; Meguro, H. Tetrahedron 1997, 53, 53315.

(129) Strerath, M.; Cramer, J.; Restle, T.; Marx, A. J. Am. Chem. Soc. 2002, 124, 11231.

(130) Sugimoto, I.; Shuto, S.; Mori, S. Bioorg. Med. Chem. Lett. 1999, 1, 385.

(131) Yang, M.; Zhou, J.; Schneller, S. W. Tetrahedron 2006, 62, 1295.

(132) Yin, X.; Rajappan, V. P.; Roy, A.; Schneller Stewart, W. Synth. Commun. 2003, 33, 1477.

(133) Choi, W. J.; Park, J. G.; Yoo, S. J.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jung, Y. H.; Jeong, L. S. J. Org. Chem. 2001, 66, 6490.

(134) Smith, A. B., III; Han, Q.; Breslin, P. A. S.; Beauchamp, G. K. Org. Lett. 2005, 7, 5075.

(135) Moon, H. R.; Choi, W. J.; Kim, H. O.; Jeong, L. S. Tetrahedron: Asymmetry 2002, 13, 1189.

(136) Jin, Y. H.; Wang, J.; Baker, R.; Huggins, J.; Chu, C. K. J. Org. Chem. 2003, 68, 9012.

(137) Liu, P.; Chu, C. K. Can. J. Chem. 2006, 84, 784.

(138) Yang, M.; Ye, W.; Schneller Stewart, W. J. O. Chem 2004, 69, 3993.

(139) Palmer, A. M.; Jager, V. Eur. J. Org. Chem. 2001, 1293.

(140) Gemal, A. L.; Luche, J. L. J. Am. Chem. Soc. 1981, 103, 5454.

(141) Luche, J. L.; Rodriguez-Hahn, L.; Crabbe, P. J. Chem. Soc., Chem. Commum 1978, 601.

(142) Seley, K. L.; Mosley, S. L.; Zeng, F. Org. Lett. 2003, 5, 4401.

(143) Jenny, T. F.; Previsani, N.; Benner, S. A. Tetrahedron Lett. 1991, 32, 7029.

(144) Peterson, M. L.; Vince, R. J. Med. Chem. 1991, 34, 2787.

(145) Michel, B. Y.; Strazewski, P. Tetrahedron 2007, 63, 9836.

(146) Kojima, H.; Kozaki, A.; Iwata, M.; Ando, T.; Kitade, Y. Biorg. Med. Chem. 2008, 16, 6575.

(147) Ramana, C. V.; Reddy, B. S.; Gurjar, K. M. Tetrahedron Lett. 2004, 45, 2817.

(148) Hu, G.; Zimmermann, M.; Ramana, C. V.; Vasella, A. Chem. Commun. 2003, 952.

(149) Moris, M. A.; Caron, A. Z.; Guillemette, G.; Schlewer, G. Biorg. Med. Chem. 2004, 12, 3995.

(150) Yin, X. Q.; Schenller, S. W. Tetrahedron Lett. 2005, 46, 7535.

(151) Schmidt, A. W.; Doert, T.; Goutal, S.; Gruner, M.; Mende, T. Eur. J. Org. Chem. 2006, 16, 3687.

(152) Kabat, M. M.; Garofalo, L. M.; Daniewski, A. R.; Hutchings, S. D.; Liu, W. J. Org. Chem. 2001, 18, 6141.

(153) Shiuey, S. J.; Kulesha, I.; Baggiolini, E. G.; Uskokovic, M. R. J. Org. Chem. 1990, 1, 243.

(154) Andrew, s.; Jonh, V. Chem. Commun. 1999, 17, 1739.

(155) Hanessian, S.; Lavallee, P. Can. J. Chem. 1975, 53, 2975.

(156) Crey-Desbiolles, C.; Kotera, M. Bioorg. Med. Chem. 2006, 14, 1935.

(157) Li, N. S.; Lu, J.; Piccirilli, J. A. J. Org. Chem. 2009, 74, 2227.

(158) Spiegel, D. A.; Wiberg, K. B.; Schacherer, N. L.; Wood, L. J. J. Am. Chem. Soc. 2005, 127, 12513.

(159) Barton, H. D.; McCombie, W. S. J. Chem. Soc., Perkin Trans. 1975, 1, 1574.

(160) Ren, Z.-X.; Yang, Q.; Price, K. N.; Chen, T.; Nygren, C.; Turner, J. F. C.; Baker, D. C. Carbohydrate Research 2007, 342, 1668.

(161) Iacono, S.; Rasmussen, R. J. Organic Synthesis 1990, 7, 139.

(162) Abad, A.; Agullo, C. Tetrahedron 2007, 63, 1664.

(163) Roy, S.; Sharma, A.; Dhotare, B.; Vichare, P.; Chattopadhyay, S. C. Synthesis 2007, 7, 1082.

(164) Trost, B. M.; Fleming, I.; Ley, S. V. Comprehensive Organic Synthesis 1991, 252.

(165) Anderson, F.; Samuelsson, B. Carbohydrate Research 1984, 129, C1.

(166) Choi, W. J.; Moon, H. R.; Kim, H. O.; Yoo, B. N.; Lee, J. A. J, Org. Chem. 2004, 69, 3985.

(167) Houston, D. M.; Dolence, E. K.; Keller, B. T.; Patel-Thombre, U.; Borchardt, R. T. J. Med. Chem. 1985, 28, 467.

(168) Bijlsma, U. G.; Den-Hertog, H. J.; Jouwersma, C.; Kolder, C. R.; Combe, W. P.; Krol, B.; Buurman, D. J. Recl. Trav. Chim. Pays-Bas Belg. 1956, 75, 1187.

(169) Bakke, J. M.; Riha, J. J. Heterocycl. Chem. 1999, 36, 1143.

(170) Van Boggelen, M. P.; Van Dommelen, B. F.; Jiang, S.; Singh, G. Tetrahedron 1997, 53, 16897.