SEEKING mRNA METHYLATION INHIBITORS AS ANTIVIRAL AGENTS

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SEEKING mRNA METHYLATION INHIBITORS AS ANTIVIRAL AGENTS

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A Dissertation

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SEEKING mRNA METHYLATION INHIBITORS AS ANTIVIRAL AGENTS

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VITA

Weikuan Li, son of Chengmao Li and Enzhen Zhang, was born in Longchuan County, Yunnan Province, China, on June 16, 1979. In September 1997, he began his study in Lanzhou University, and received a Bachelor degree in chemistry in July 2001. He attended Nanjing University in September 2001 for three years and obtained a Master degree in analytical chemistry. He entered Graduate School, Auburn University, in August, 2004, under the direction of Dr. Stewart W. Schneller.

DISSERTATION ABSTRACT

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Aristeromycin and neplanocin A are two examples of potent S-adenosylhomocysteine hydrolase inhibitors. As a consequence, they show significant broad-spectrum antiviral activity, however, their clinical potential is limited by toxicity, which is associated with phosphorylation at their 5′-hydroxyl groups. 5′-Noraristeromycin has been found to exhibit wide-spectrum antiviral activity with reduced toxicity due to its inability to form the corresponding nucleotide. To explore new antiviral agents retaining aristeromycin-based activity while reducing undesired toxicity, 5′-fluoro-5′-deoxyaristeromycin (1), 4′-fluoro-4′-deoxynoraristeromycin (2), 3,7-dideazaaristeromycin (3) and 3,7-dideazanoraristeromycin (4) were synthesized. Compounds 1 and 2 showed moderate activity against measles but were inactive in other antiviral assays. Compounds 3 and 4 exhibited no significant activity against all viruses tested.

Another member of the adenosine (Ado) set is sinefungin (5), which is a naturally occurring analog of S-adenosyl-L-homocysteine (AdoHcy) or S-adenosylmethionine (AdoMet). The wide-spectrum biological activities (anti-fungal, anti-virus, anti-bacteria and anti-malarial) are associated with its inhibition of AdoMet dependent methyltransferases. The application of sinefungin is limited by its toxicity. A convenient synthesis of sinefungin and related compounds (6, 7 and 8) was developed.

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INTRODUCTION

Viruses are small, infectious particles whose growth, reproduction and propagation depend on hosts. The components of a viral particle, or virion, include genetic material (DNA or RNA) and a protective shell called a capsid. Many viral sizes and shapes have evolved. The shapes vary from simple helical to more complex structures with tails or envelopes.[1]

Life Cycle of a Virus

The life cycle of a virus can be separated into several basic stages, i.e. attachment, entry, replication, assembly, and release, although the details may differ significantly between species. The attachment of viruses to host cells is achieved by a specific binding between viral capsid proteins and specific receptors on the host cellular surface, which determines the site and infectious scope of a virus.[2-5] The attached virus then enters the host cell by receptor mediated endocytosis or membrane fusion. The viral capsid is removed and degraded by viral enzymes or host enzymes to release the viral genomic nucleic acid.[6-9] Replication follows with the synthesis of viral messenger RNA (mRNA, except for positive sense RNA viruses, where the viral nucleic acid core serves as an

mRNA) leading to viral protein synthesis and viral genome replication.[1, 10-11] The necessary viral building blocks synthesized in the host cell, including protein shells,structure units, capsids, segmented genomes are assembled into a progeny virions. Maturation of the viral proteins often occurs after the assembly of the virus particles. In some viruses, this maturation occurs after release of virions.[12-14]

Viral Disease and Bioterrorism

Virus-induced common human diseases (these diseases are usually self-limiting, but antiviral therapy is necessary for immune suppressed patients) include the common cold,[15] the flu,[16] and chickenpox.[17] Very serious diseases, like Ebola,[18] acquired immune deficiency syndrome (AIDS),[19] avian influenza[20] and severe acute respiratory syndrome (SARS)[21] are also caused by viruses. In addition, viruses can induce life-long or chronic infections where the viruses continue replicating at a certain rate in the body despite the adaptive or innate immune response. This is usually seen with people who are infected with hepatitis B virus (HBV)[22] and hepatitis C virus (HCV)[23] viruses. These types of viruses can be transmitted through high-risk intimate interaction between infected and healthy people such as unprotected body contact and blood transfusion.

An important point to be considered is the lethal threat that might arise from utilizing viruses as biological weapons.[24-28] The necessity for anti-biological terrorism plans was evidenced by the anthrax attacks in 2001 in the United States. Although some viruses, such as smallpox, were eradicated, the possible use of “eradicated” viruses in bioterrorism must be taken into account.[29] Other viruses, such as those that cause

hemorrhagic fevers, which can be generated in large amounts in cell culture, and then made transmissible in aerosol form, may become weapons of terrorism.[30-33] This threat is compounded by the fact that currently there are no vaccines or antivirals available for such viruses.[30]

Prevention and Antivirus Strategies

Vaccination is a tactic towards combating illness or the spread of virus by intentional introduction of antigenic material (antigen) to develop immunity to a disease. The antigen administered can be either live, or weakened forms of viruses, killed or inactivated forms of viruses, or purified material such as proteins.[1] Once a proper vaccine is developed and administered, it is a very good means to prevent viral diseases, however, for people already infected, the benefit of vaccination is limited. Developing a vaccine for fast mutating viruses, such as human immunodeficiency virus (HIV) and influeanza, poses major challenges, due to the high genetic variable nature of these viruses.[34-38]

Therapeutics agents directly towards viral infections can be broadly categorized as agents that assist and fortify host immune defenses, or that attack the virus and its replicative cycle directly.[30] Stimulation or protection of the immune system is a strategy to render host immunity as the viral defense, instead of attacking the viruses directly. Usually, these sorts of agents stimulate the immune system to fight against a range of pathogens. Interferon is one example of this class. The well-known "interferon alpha" is established as a treatment for hepatitis B and C,[22, 23] and other interferons are also being investigated as treatments for various diseases.[39] Some viruses, like vaccinia, influenza

virus, Ebola, and Marburg viruses produce interferon antagonists,[40-47] which allow them to evade the assault of host immune system. Modifying the innate immune response to fight against specific virus infections is calling forth a need for a deeper understanding of the interaction between virus and immune response.[30]

In principle, any stage of viral replication cycle can be selected for antiviral target success. To enter the host cell, a virus must go through a sequence of steps. The initial step is binding to a specific "receptor" on the surface of the host cells. In this regard, the cell receptors can be selected as antiviral targets that would block that site.[48-54] Other strategies include inhibiting uncoating and envelope fusion.[53]

During viral replication in a host cell, a number of viral or cellular functional proteins can be targeted.[55-59] For example, HIV reverse transcriptase has been a widely investigated viral specific enzyme. Inhibition of this enzyme suppresses the transition of single-stranded viral RNA into double-stranded proviral DNA (to be integrated into host chromosome), which, in turn, reduces the HIV replication and the human immunity is preserved.[60] Another example is blocking the RNA dependent RNA polymerase of HCV.[61]

The last step of the virus life cycle is release of progeny virion from the host cell. Preventing their release is a strategy that has attracted many researchers. One example of an antiviral agent of this type is oseltamivir (Tamiflu), which has been successfully introduced to treat influenza. The antiviral mechanism of Tamiflu is through the inhibition of neuraminidase, which prevents the release of virus from host cell.[56]

Nucleoside Analogs as Antiviral Agents

Nucleosides (Figure 1) are naturally occurring biomolecules, which serve as fundamental building blocks for DNA and RNA.

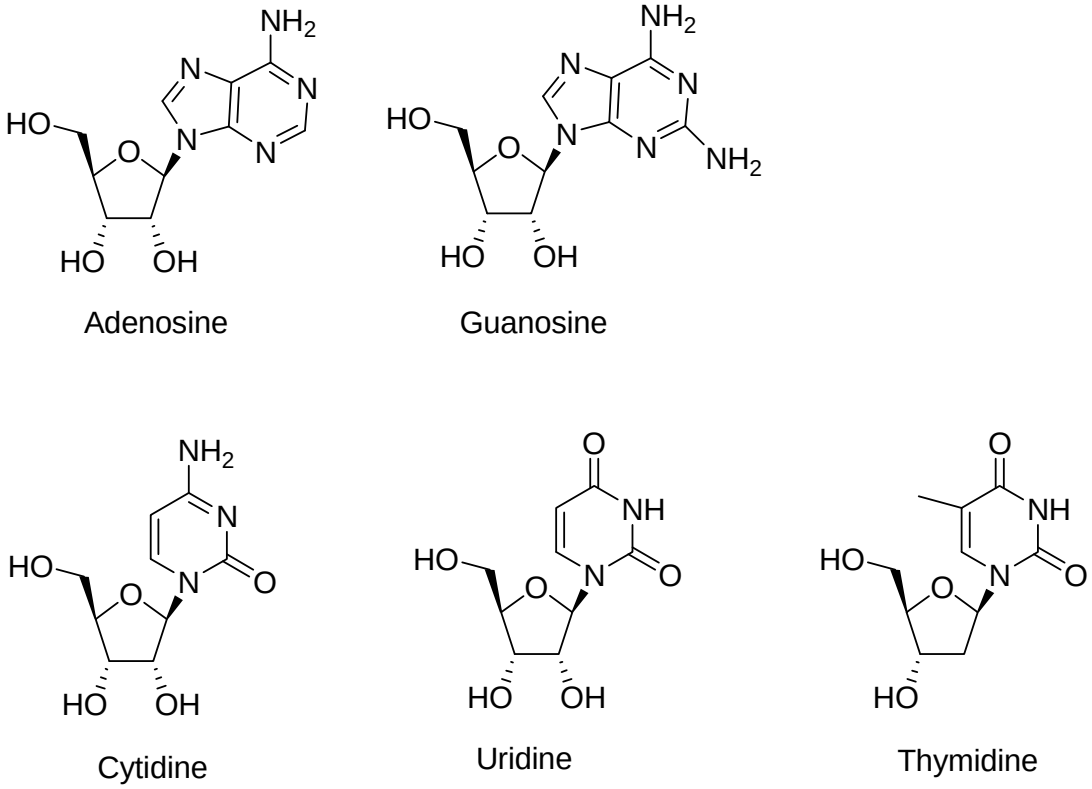

Figure 1. Naturally Occurring Nucleosides

The distinguishing structural characteristic of natural nucleosides shows a heterocyclic base moiety bonded to a ribofuranose in the beta configuration. The major purine base components in these nucleosides are adenine and guanine. The major pyrimidine base residues are cytosine, uracil (in RNA), and thymine (in DNA). Nucleosides are involved in a number of important biological metabolisms.[62] As a consequence, nucleoside analogs show a variety of biological activities, including medicinal effects of anti-viral,[63] anti-cancer,[64-67] anti-fungal[68, 69] and anti-malarial.[70, 71] Particularly relevant to this research are the antiviral activities of nucleoside and

nuleotide analogs with great clinical potential.[72-81] Among more than thirty FDA approved antiviral agents (not including interferons and immunoglobulins), many are nucleoside/nucleotide analogs. For example, FDA-approved HIV reverse transcriptase inhibitors zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine, and tenofovir disoproxil (Figure 2) are among them.[56]

These nucleosides are inhibitors of reverse transcriptase after conversion into the corresponding 5′ triphosphates by cellular or viral kinases. Subsequently, they are incorporated into the viral DNA chain, leading to viral DNA chain termination by their lacking a 3′-hydroxyl and inhibition of reverse transcriptase.[56]

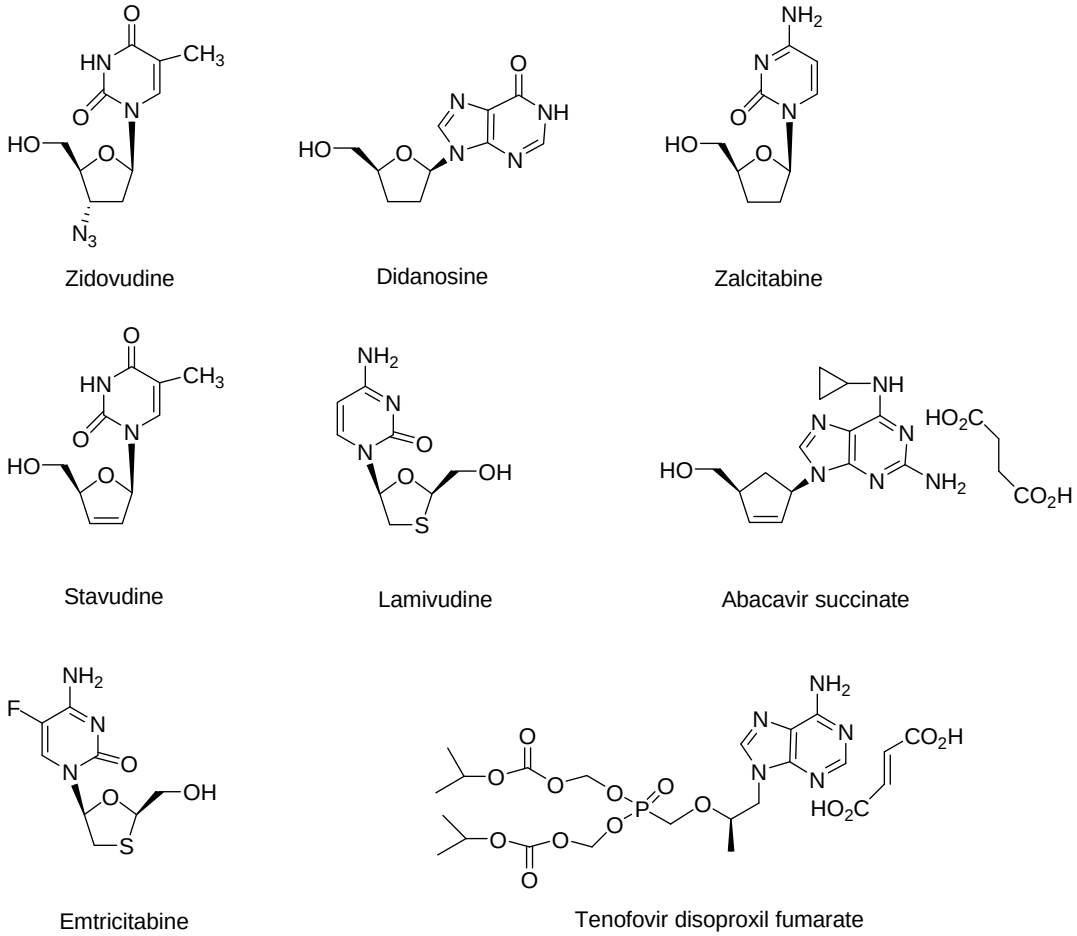

Figure 2. FDA-approved NRTI′s and NtRTI

AdoHcy Hydrolase as an Antiviral Therapy Target

The symbiotic relationships between viral pathogens and hosts have led to viral adaptation to host cellular mechanisms for entry, replication, assembly and progeny releasing. In addition to the viral specifically encoded components, the host cell also persents possible synthetic targets for developing of antiviral agents. The advantage of targeting a host process opens the door to development of broad spectrum antiviral agents. Once a common host pathway is blocked, all pathogens that rely on this pathway will be inhibited. This is especially useful for fighting against emerging or gene-engineered bio-pathogens, since valid vaccines or specific antivirals are not already available. A further advantage of this approach is less likelihood of drug resistance, since there are a limited number of alternative cellular pathways.[30]

S-Adenosyl-L-homocysteine (AdoHcy) hydrolase (EC 3.3.1.1), which is a cellular enzyme, fits this promise and has been regarded as a target for wide spectrum antiviral agent development.[57, 82-93] AdoHcy hydrolase catalyzes the reversible hydrolysis of AdoHcy to adenosine (Ado) and homocysteine (Hcy). The reaction is favored in the synthetic (reverse) direction. However, the fast removal of Ado and Hcy by metabolism (Ado is removed by Ado deaminase and Ado kinase, and Hcy follows to the cysteine synthesis and methionine regeneration) moves the reaction forward. The intracellular AdoHcy level will increase if AdoHcy hydrolase is inhibited. The accumulation of AdoHcy, in turn, inhibits essential S-adenosylmethionine (AdoMet)-dependent methylation reactions, where the AdoHcy is both the product and a potent feedback inhibitor (Figure 3). AdoMet dependent methylation is required for final maturation of the capped mRNA (Figure 4) from cellular and viral sources. Therefore, by inhibition of

AdoHcy hydrolase, the processing and maturation of viral mRNAs may be inhibited. As a consequence, requisite proteins and enzymes for progeny virion assembly are not generated.

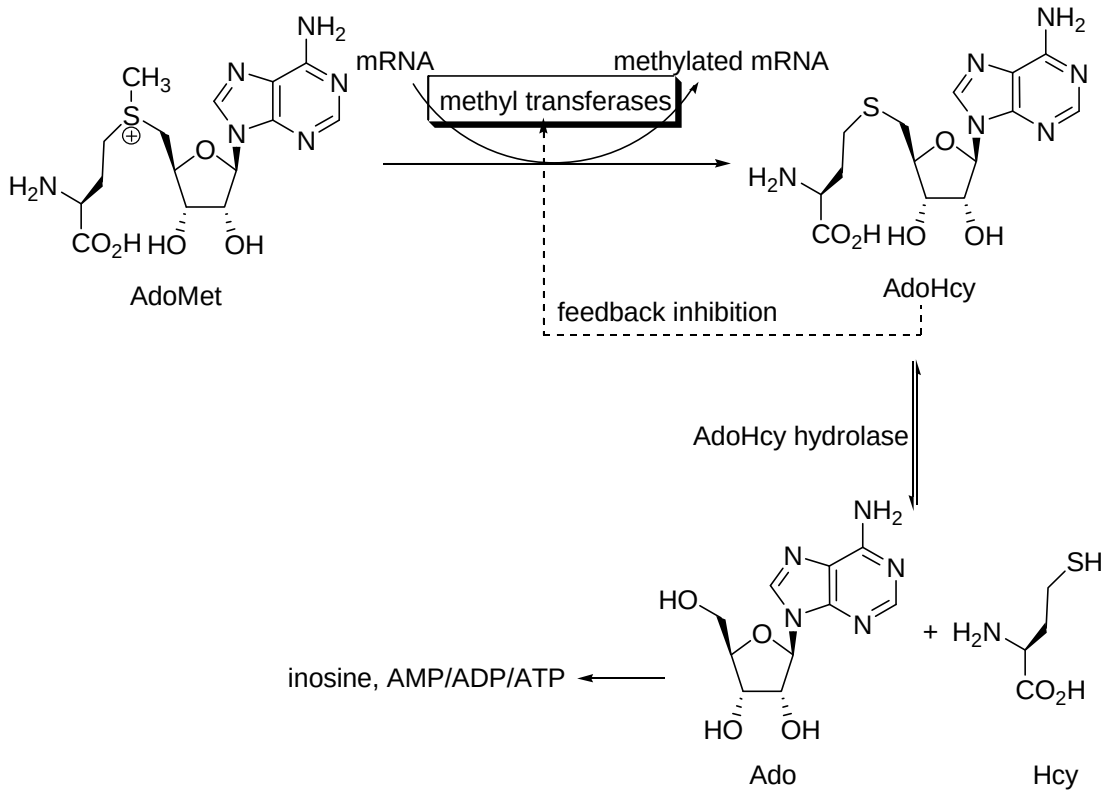

Figure 3. Feedback Inhibition of Methyltransferases by AdoHcy

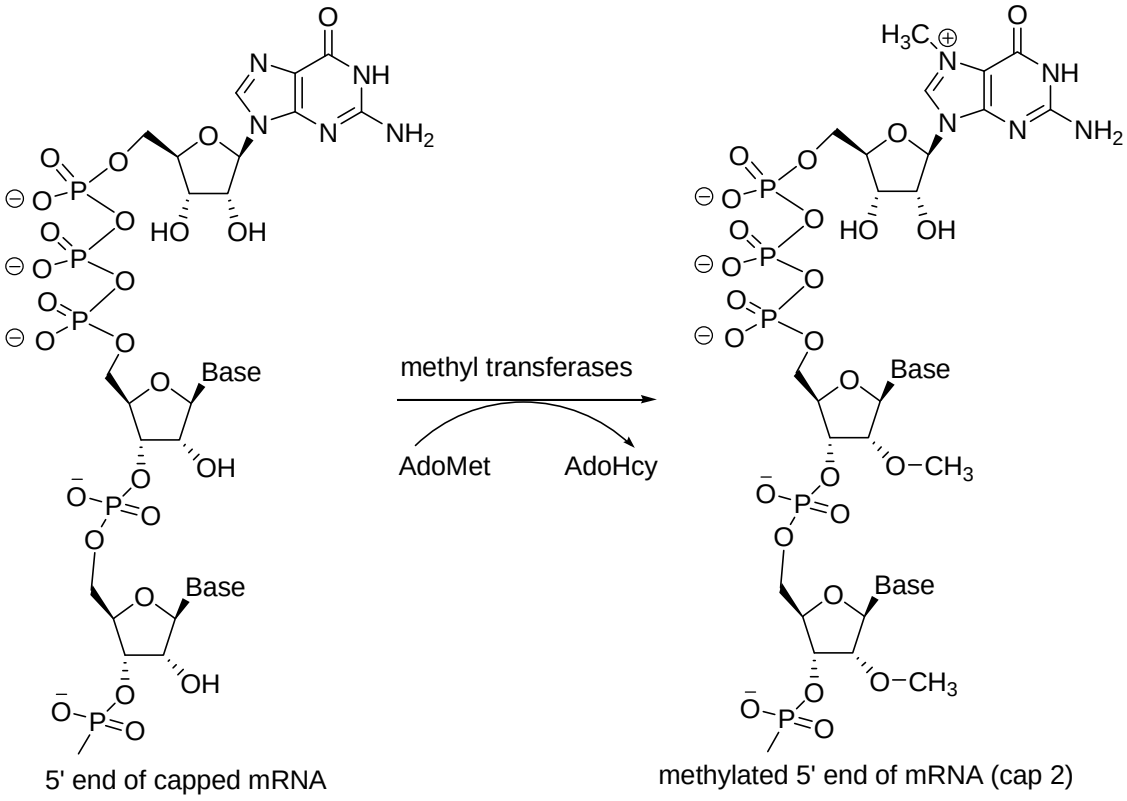

Figure 4. Methylation of Capped mRNA

Since the AdoHcy hydrolase inhibitors exert their antiviral activities through suppressing the methylation of mRNA, it is not surprising that some viruses, like poliovirus, have polypeptide capped 5′ end of mRNA, which was not methylated,[94-96] are intrinsically insensitive to this type of compounds.[90] On the other hand, because AdoHcy hydrolase is a cellular enzyme, it might be expected that its inhibition would lead to general suppression of cellular protein synthesis and subsequent host toxicity. However, examples exist where this is not a major drawback. For example, the successful treatment of filovirus by an AdoHcy hydrolase inhibitor without significant toxicity is noteworthy, and this may be the result of two mechanisms.[97] First, the fast replicative nature of the virus leads to increased demand for protein synthesis in the virally infected cells compared to uninfected cells. This would result in a greater demand for viral mRNA

methylation, which would render the methyltransferase more sensitive to inhibition by the bio-feedback partner, AdoHcy. Therefore, the elevated AdoHcy levels would significantly inhibit the activity of methyltransferases. Second, the virally encoded methyltransferase may have a different binding constant with AdoHcy compared to cellular methyl transferase. As a consequence, the preferential inhibition of viral methyltransferase would occur, producing significant antiviral activity with tolerable, or no toxicity. Undoubtedly, long term inhibition of AdoHcy hydrolase will suppress general cellular protein synthesis, leading to severe toxicity; Wolfe and Borchardt have suggested that "a temporary and partial inhibition, while not seriously altering cell function, may allow phosphatases and ribonucleases to destroy the foreign (that is, viral) mRNAs. After removal of the AdoHcy hydrolase inhibitor, favorable cellular mRNA cap methylation could resume and full protein synthesis would ensue".[82]

Mechanism of AdoHcy Hydrolase

The mechanism by which AdoHcy hydrolase acts is shown in Figure 5.[99-108] The 3′ hydroxyl group of AdoHcy (I, forward direction) or Ado (VII, reverse or synthetic direction) are first converted to 3′-keto derivatives (II or VI) *via* the oxidation by enzyme-bound NAD^+. This increases the acidity of 4′-proton and causes it to be abstracted by an enzyme base. The resulting carbanion species (III or V) facilitates an elimination of the 5′-substituents, Hcy (forward) or water (reverse), to give the central intermediate 3′-keto-4′,5′-dehydroadenosine (IV). A Michael type addition of water (forward) or Hcy (reverse) to this central intermediate, followed by reduction of

corresponding 3′-keto intermediates (II, VI) by the NADH, completes the AdoHcy hydrolase catalyzed "hydrolysis" (forward) or synthesis (reverse) of AdoHcy, resulting in the formation of the final product, Ado (VII) or AdoHcy (I).

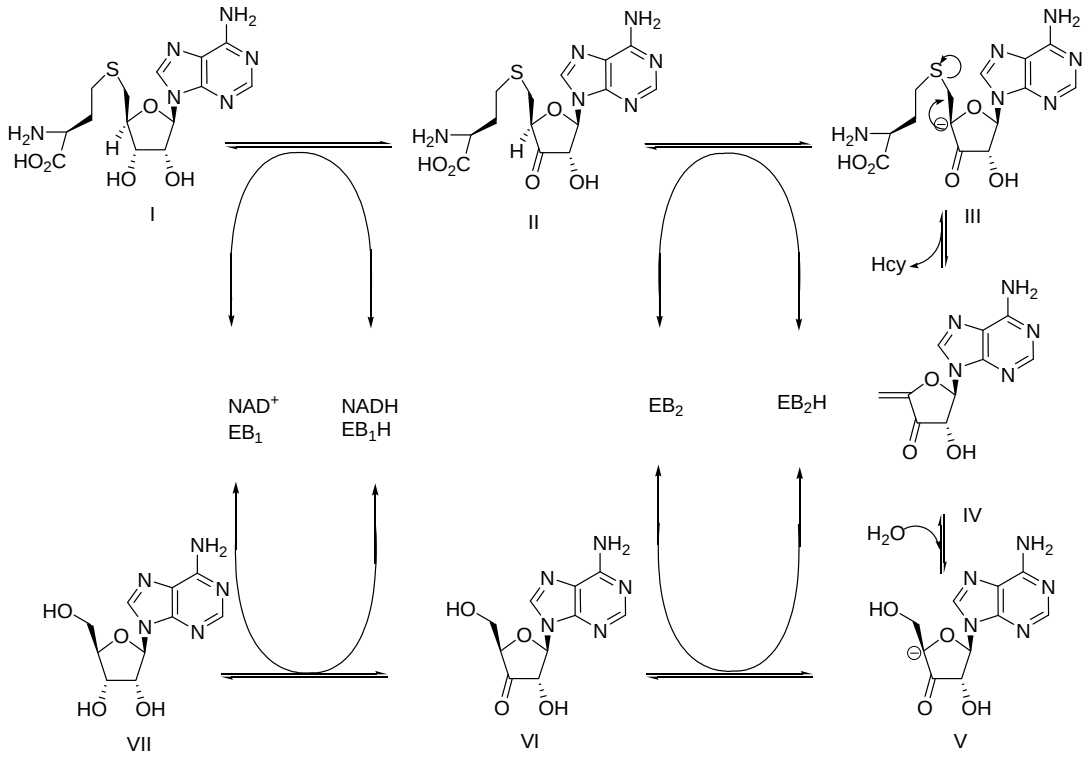

Figure 5. Mechanism of AdoHcy Hydrolase

AdoHcy hydrolase contains four identical subunits (denoted as A, B, C, and D).[106, 107, 109-121] In each subunit, there exists three domains: a large N-terminal domain for substrate-binding, a large cofactor binding domain, and a smaller C-terminal domain. The small C-terminal domain of A extends to the adjacent subunit B and forms part of the cofactor-binding site in that subunit. Also, the small C-terminal of B subunit inserts into A in the same manner and serves as part of cofactor binding domain. The same reciprocal penetration between A and B subunits also appears in C and D. However, the similar

linkage is not present between AB and CD. Therefore, the AdoHcy hydrolase can be regarded as dimer of dimers. A typical crystal structure of AdoHcy hydrolase is shown in Figure 6, where the substrate binding domain is bound to neplanocin A in its 3′-keto form (PDB code: 1LI4).[107]

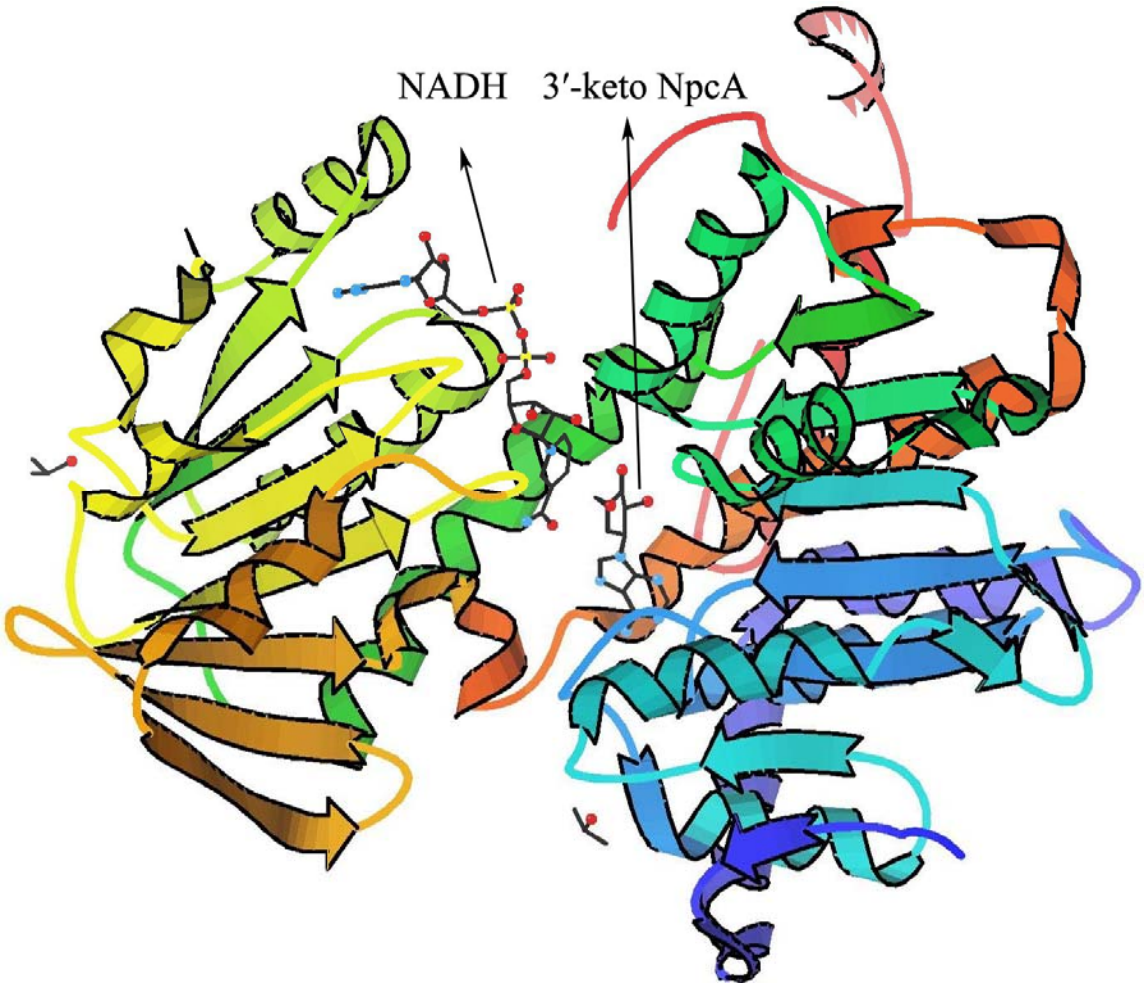

Figure 6. Ribbon Structure of AdoHcy Hydrolase

Up to now, ten three dimensional structures of AdoHcy hydrolase from different sources are available.[106, 107, 113, 114, 116, 118-121] The protein data bank codes are: 1LI4, 1B3R, 1A7A, 1D4F, 1KY4, 1KY5, 1V8B, 1XWF, 1K0U, and 2H5L. The crystal structures show that in the absence of substrate, the NAD^+ binding domain and substrate binding domain

are quite far from each other. The enzyme is in an "open" state.[114] Upon binding of substrate, the enzyme shifts to a "closed" state, where the cofactor binding domain and substrate binding form come close.[107] Based on the crystal structure, a detailed catalytic mechanism is proposed for this enzyme from rat liver, which bears 431 amino acid residues in each identical subunit.[114, 119] In this case, Glu155 abstracts the $O_{3'}$-H proton, while the $C_{3'}$-H proton is removed by NAD^+. General acid-base catalysis is performed by His54 or Asp130. The oxidation state of the bound NAD^+ is regulated by Cys194.

Inhibitors of AdoHcy hydrolase

Since inhibition of AdoHcy hydrolase has been targeted for antiviral drugs design, a number of potent inhibitors have been synthesized and evaluated.[84] Several examples of this class are shown in Figure 7, i.e., aristeromycin (Ari), noraristeromycin (Norari), neplanocin A (NpcA), 3-deazaaristeromycin, 3-deazaneplanocin A, and 2-fluoro and 6′-methyl derivatives of neplanocin A. Poxviruses (i.e., vaccinia virus), and rhabdoviruses (i.e., vesicular stomatitis virus) are very sensitive to these compounds.[84]

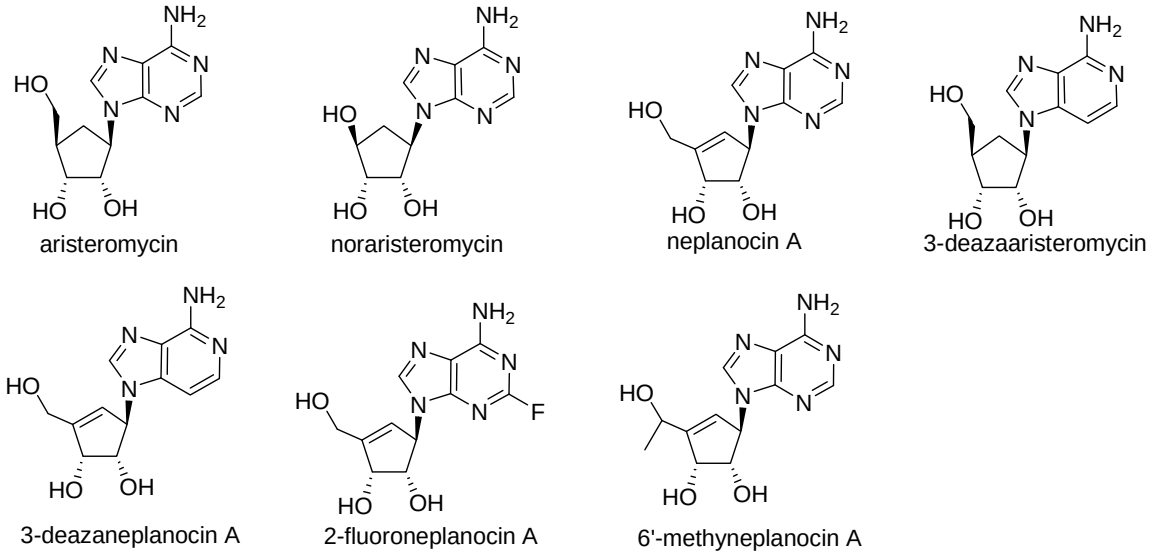

Figure 7. Examples of Potent AdoHcy Hydrolase Inhibitors

Ari and NpcA were two naturally occurring nucleosides. Ari was separated from the metabolites of *Steptomyces citricolor* in 1968,[122] and NpcA was isolated from *Ampullariella regularis* in 1981.[123, 124] Ari showed antiviral activity by inhibition of AdoHcy hydrolase.[82] Two mechanisms of NpcA′s antiviral activity have been proposed[125, 126]: (1) inhibition of AdoHcy hydrolase and (2) transformation into S-neplanocylmethionine, which is an AdoMet analog and acts by inhibiting the methyltransferase directly. In the first case, NpcA anchors to the active site of AdoHcy hydrolase with a high affinity and is oxidized by enzyme bound NAD^+ into its 3′-keto form. This causes the enzyme to enter the closed state and lose catalytic capability.[107]

The cytotoxicity, which was believed to be a result of cellular C5′ phosphorylation, has limited the further application of Ari and NpcA as broad spectrum antiviral agents. This phosphorylation by the sequence of adenosine kinase, adenylate kinase and nucleotide diphosphate kinase convert Ari or NpcA into the 5′-mono/di/triphosphates respectively (Figure 8).[127-131] The monophosphate of Ari can also be converted into the

inosine analog by adenosine monophosphate deaminase, and further to the carbocyclic guanosine monophosphate derivative. Instead of deamination of the monophosphate, NpcA is directly converted to the inactive inosine form by adenosine deaminase. The triphosphates of Ari and NpcA, resemble ATP in structure, leading to deleterious effects.[132-134]

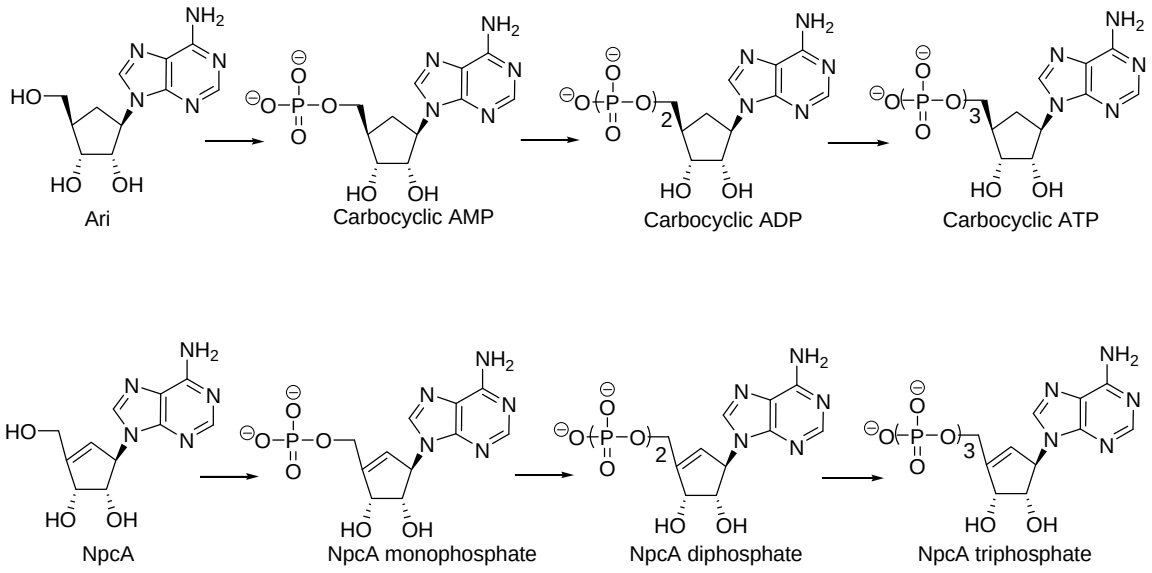

Figure 8. Phosphorylation of Ari and NpcA by Cellular Kinases

The further design of Ari and NpcA analogs, with the expectation of retaining their high activities while decreasing toxicity, focused on introducing structure modifications, which prevent or decrease the tendency of C5′ phosphorylation.

Not surprisingly, much effort has been devoted in this undertaking. Since the 5′-hydroxyl group is the site at which phosphorylation occurs, a number of Ari analogs with a modified 5′ position were designed and synthesized. This strategy includes (but is not limited to) (1) removal of the 5′ hydroxyl group; (2) increasing the steric hindrance at the 5′ position; and (3) a change in chain length at the 5′ position (Figure 9).

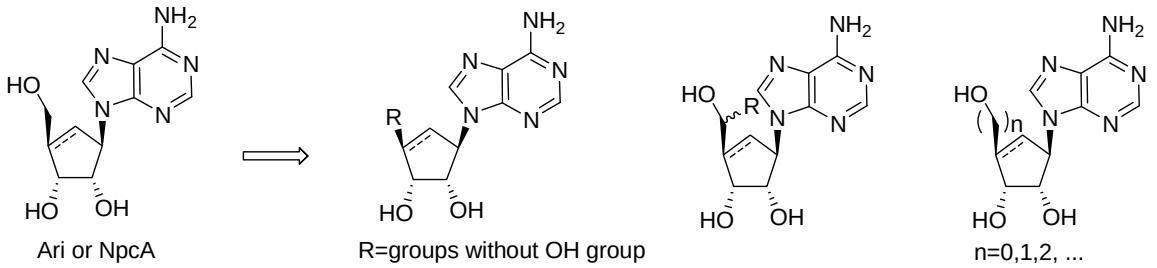

Figure 9. Design of Ari or NpcA Analogs by 5′ Position Modifications

For example, Borchardt′s group synthesized truncated analogs of Ari and NpcA, as well as their 3-deaza counterparts (Figure 10).[135-138] These compounds showed potent antiviral activity, while the associated toxicity was greatly decreased.

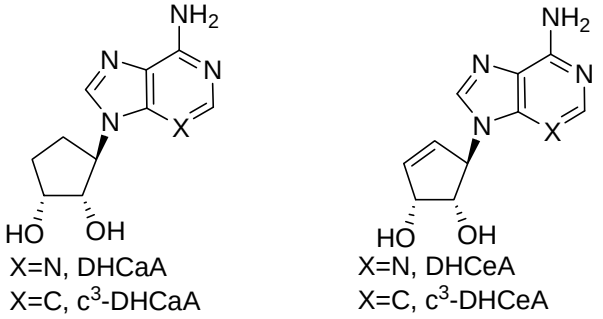

Figure 10. Truncated Analog of Ari and NpcA

The Schneller group developed chain-length modified analogs of Ari, as well as a sterically encumbered analog of Ari (Figure 11).[139-142] 5′-Noraristeromycin (Norari) showed significant antiviral activity against human cytomegalovirus (HCMV), hepatitis B virus (HBV), measles, influenza, and vaccinia virus. This compound is much less toxic than Ari.[139-140] Homoaristeromycin showed potent activity towards vaccinia, cowpox, and monkeypox viruses, with little associated toxicity.[141] Subsequently, targets **1** and **2** (Figure 12), the derivatives of Ari and Norari, where the 5′ and 4′ hydroxyl groups were replaced by fluoride, were designed and synthesized for this dissertation project, since the fluoride is incapable of phosphorylation.

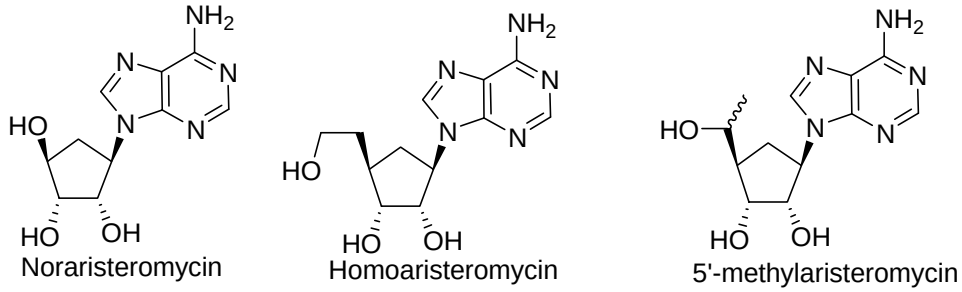

Figure 11. Chain-length Modified and Sterically Encumbered Analogs of Ari

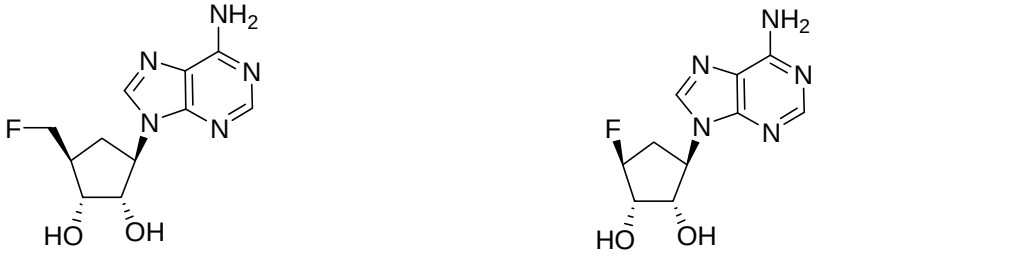

Figure 12. Targets 1 and 2

A second method to reduce the possibility of phosphorylation was to modify the base moiety, since it was well known the 3-deazaadenosine is not phosphorylated. The 3-deaza version of Ari and NpcA were synthesized (Figure 7). As expected, these analogs show potent antiviral activities and decreased toxicity.[143, 144]

Examples of other modified base analogs include 2-halopurine, 8-methylpurine, 1-deazapurine, and 7-deazapurine. 7-Deazapurine nucleosides, either naturally occurring or synthesized, exhibit antibacterial, antifungal, antiviral and anticancer activity (Figure 13).[145] While, of course, replacement of a nitrogen atom in the purine ring with a CH does not change the shape of the base, other properties, such as basicity of the 6-amino group and hydrogen bonding formation capability in various positions (that is 1, 3, 7),

will be different from the purine base. Furthermore, deazapurines make it possible to attach substituents at the 1, 3 and 7 positions, which is not possible for the parent purine ring. With this in mind, it is interesting to consider pursuing 3,7-dideazapurine nucleoside analogs. Therefore, targets **3** and **4** (Figure 14) for this dissertation research (the dideaza counterparts of Ari and Norari analogs) were sought.

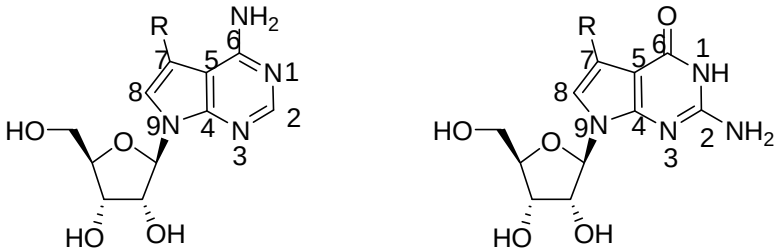

Figure 13. Natural and Synthesized 7-Deazapurine Nucleosides

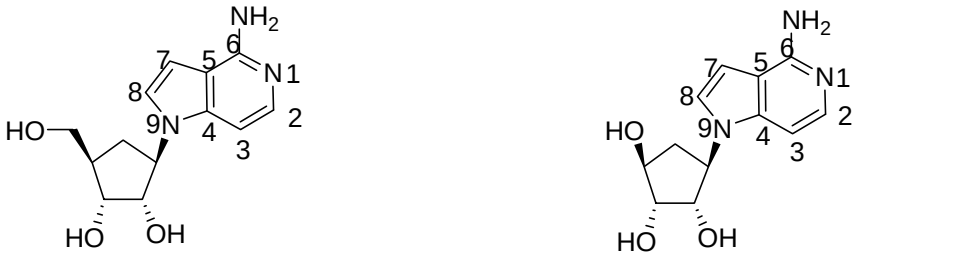

Figure 14. Targets 3 and 4

Methyl Transferase Inhibitors: Sinefungin and Its Analogs

As mentioned above, the Ado derivatives exert their antiviral activity by inhibition of AdoHcy hydrolase. Meanwhile, some Ado analogs (like NpcA) are metabolized into AdoHcy analogs,[125, 126] which may inhibit cellular methyltransferases as a result of their effects on AdoHcy hydrolase, or selectively inhibit virally coded methyltransferases. Another member of the Ado set is sinefungin (SF, or A9145), which is a naturally occurring analog of AdoHcy or AdoMet (Figure 15). It was isolated from *Streptomyces griseolus* (NRRL 3739)[146, 147] and showed potent antimalarial,[148-152] antibacterial,[153] antifungal[154-156] and antiviral[157-160] activities. The bioactivity of sinefungin is associated with its inhibition of AdoMet dependent methyltransferases.[154, 161-174] However, sinefungin was limited in application by its toxicity.[146-148] Thus, the synthesis of sinefungin,[175-185] sinefungin analogs with modification on the side chain or the base, [186-194] AdoHcy analogs,[195-198] carbocyclic sinefungin (analogs),[199, 200] and biosynthesis (effect) of sinefungin[201,202], have attracted a lot of researchers. An efficient, practical and diverse synthesis of sinefungin and related compounds has been developed in the Schneller group. This method has been successfully applied to the total synthesis of carbocyclic sinefungin.[199] For this dissertation research, an enantioselective, efficient and high yielding route to sinefungin that is adaptable to various modified compounds including modification at C6′ position (Figure 16) was sought.

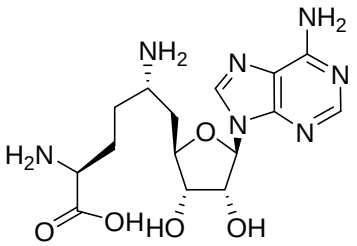

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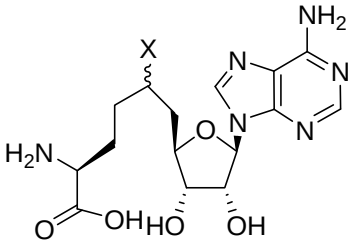
Figure 15. Sinefungin



X = H, OH, NH_2, N_3, F and OMe (R or S)

Figure 16. Target 5: Sinefungin and Related Compounds

Since AdoHcy is a potent feedback inhibitor of AdoMet-dependent methyltransferases, it is interesting to design and synthesize analogs of AdoHcy itself that highly resemble AdoHcy and can serve as a competing inhibitor of methyltransferases. The AdoHcy analog may also acts as an alternative substrate for AdoHcy hydrolase, leading to elevated levels of parent AdoHcy and inhibition of methylation. With these guidelines, oxa-AdoHcy, an AdoHcy analog, where the side chain sulfur was replaced by an oxygen, was designed and synthesized (Figure 17) in this project. Simultaneously, the Ari and NpcA version of oxa-AdoHcy analogs were also investigated (Figure 18).

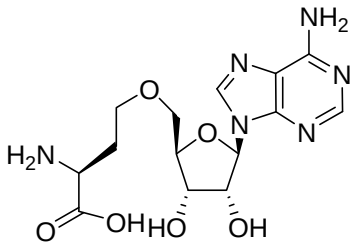


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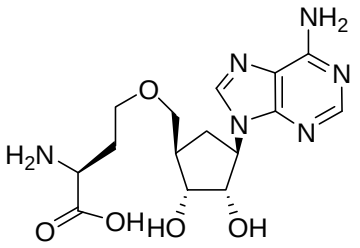
Figure 17. Target 6: Oxa-AdoHcy



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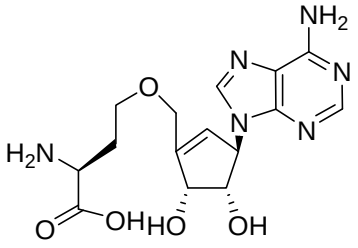

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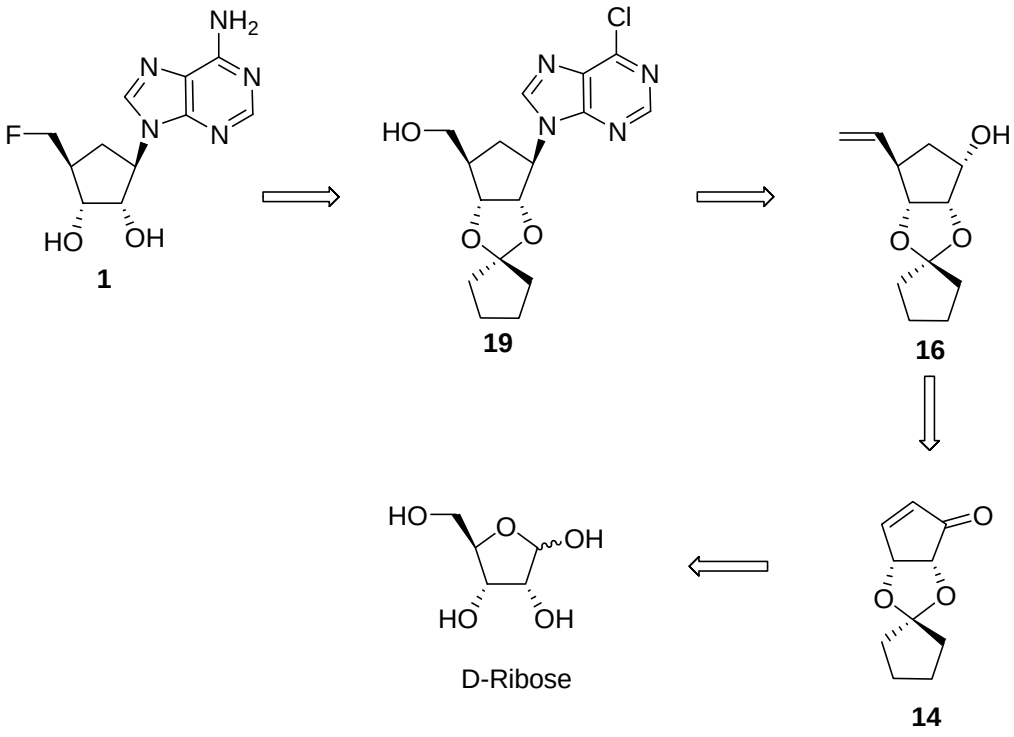
Figure 18. Targets 7 and 8: Ari and NpcA Version of Oxa-AdoHcy

5′-DEOXY-5′-FLUORO ARISTEROMYCIN

Experimental Design and Synthesis

Adenosine, the natural product of AdoHcy "hydrolysis", is in the D-configuration. The naturally occurring Ado analogs, Ari and NpcA are D-like analogs. It is not surprising that most of the high ranking AdoHcy hydrolase inhibitors are of D-like configuration.[84] For example, D-like Noari is much more potent than its L-like counterpart.[139] As a consequence, in the search for new hydrolase inhibitors, the D-like Ado analogs are designed and synthesized as a priority.

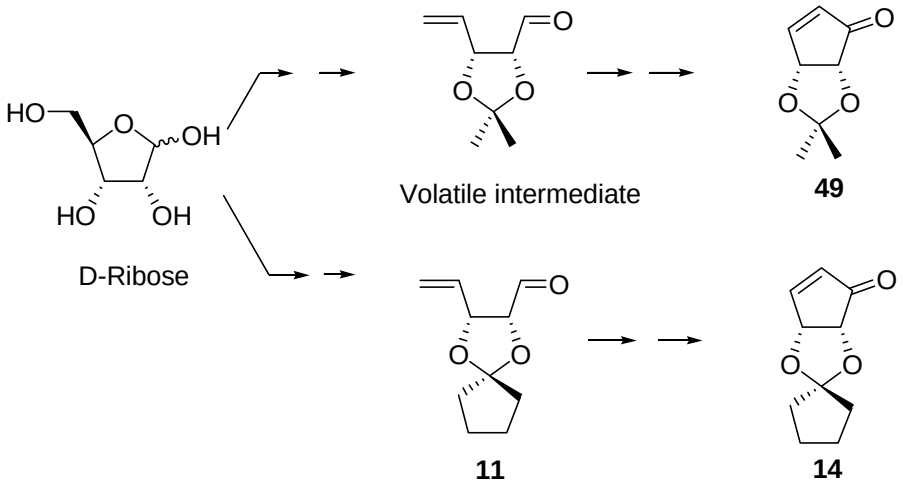
As mentioned previously, the toxicity of Ari is associated with the 5′-phosphorylation. Thus, Ado analogs incapable of C-5′ phosphorylation (or with less tendency to do so), are worthy targets. In that direction, the D-like 5′-fluoro-5′-deoxyaristeromycin (**1**) was selected as a synthetic target for this dissertation research. The initial retrosynthetic plan for this goal is shown in Scheme 1.



Scheme 1. Initial Retrosynthetic Analysis to 1

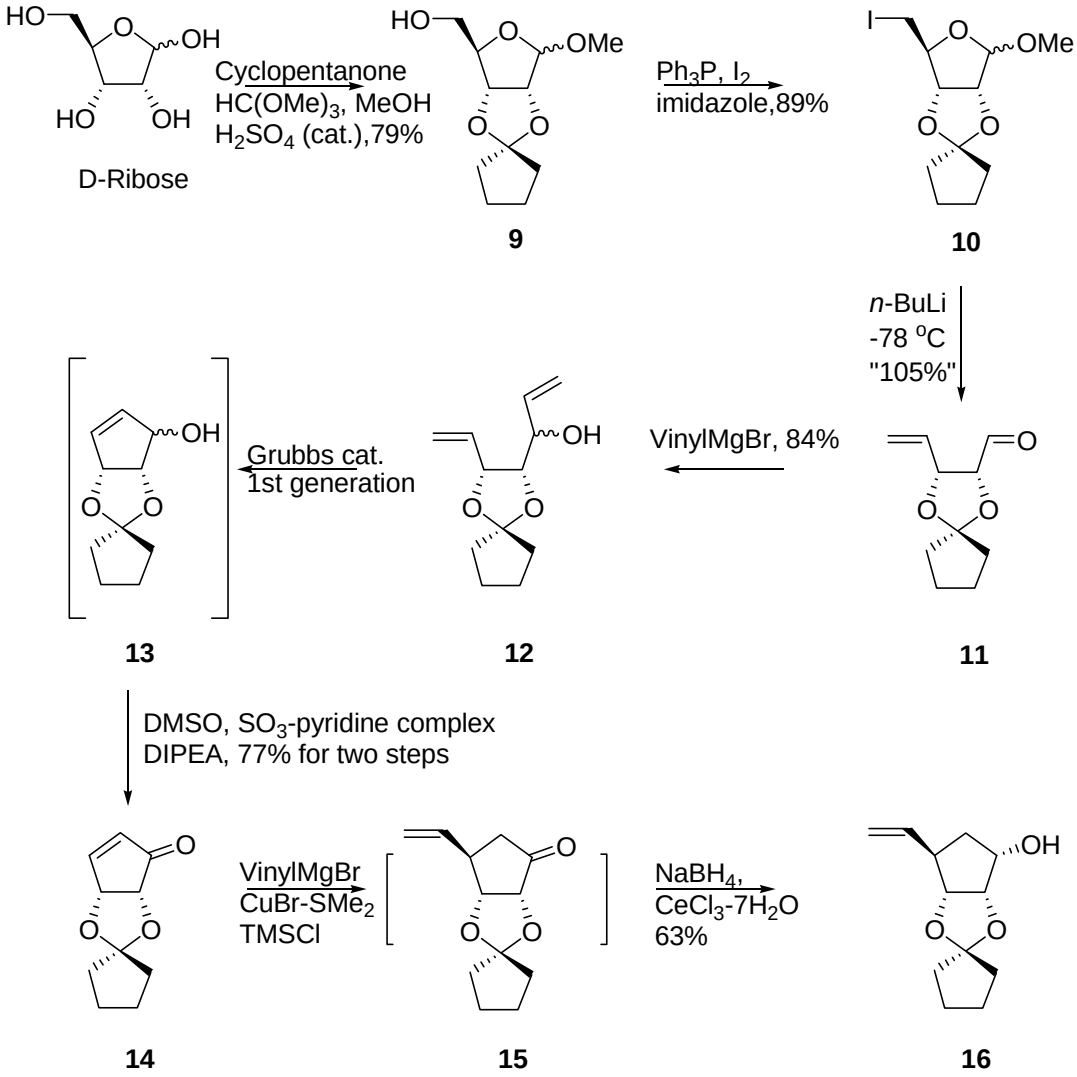
To ensure the D-like configuration, the synthesis was envisioned as starting from commercially available D-ribose, which has the predefined requisite stereochemistry. The key intermediate, the D-like cyclopentenone **14,** is a common beginning point for various carbocyclic adenosine analogs. Thus, the large scale synthesis of **14** was sought. In the Schneller group, a facile synthesis of (4*R*, 5*R*)-4,5-*O*-*iso*propylidene-2-cyclopentenone has been developed.[203] Optimization of this pathway to avoid the volatility of the intermediate aldehyde (2*R*, 3*R*)-2,3-*O*-*iso*propylidene-pent-4-enal has been achieved in this dissertation research by shifting the glycol protecting group from *iso*propylidene to cyclopentylidene (Scheme 2).

Scheme 2. Optimization of Enone Synthesis



As shown in Scheme 3, protection of D-ribose with cyclopentanone and methanol in the presence of trimethyl orthoformate and a catalytic amount of sulfuric acid gave **9**. The primary alcohol moiety of **9** was substituted with iodine using the combination of triphenylphosphine (TPP), imidazole, and iodine chips to give derivative **10**.[204] Reductive elimination of **10** with activated zinc powder in hot methanol yielded aldehyde **11**.[205] Treatment of **11** with vinyl magnesium bromide gave diene **12** as mixture of two diastereoisomers. Ring closure metathesis of olefin in the presence of Grubbs catalyst (1st generation) gave **13**,[206] which was not isolated. Instead, compound **13** was further oxidized with a modified Swern protocol[207] to provide the key intermediate **14**. With **14** in hand, a Michael addition of vinyl magnesium bromide under the catalysis of copper (I) salt and chlorotrimethylsilane (TMSCl) afforded **15**,[208] which was not isolated but transformed into **16** by a Luche reduction.[209]

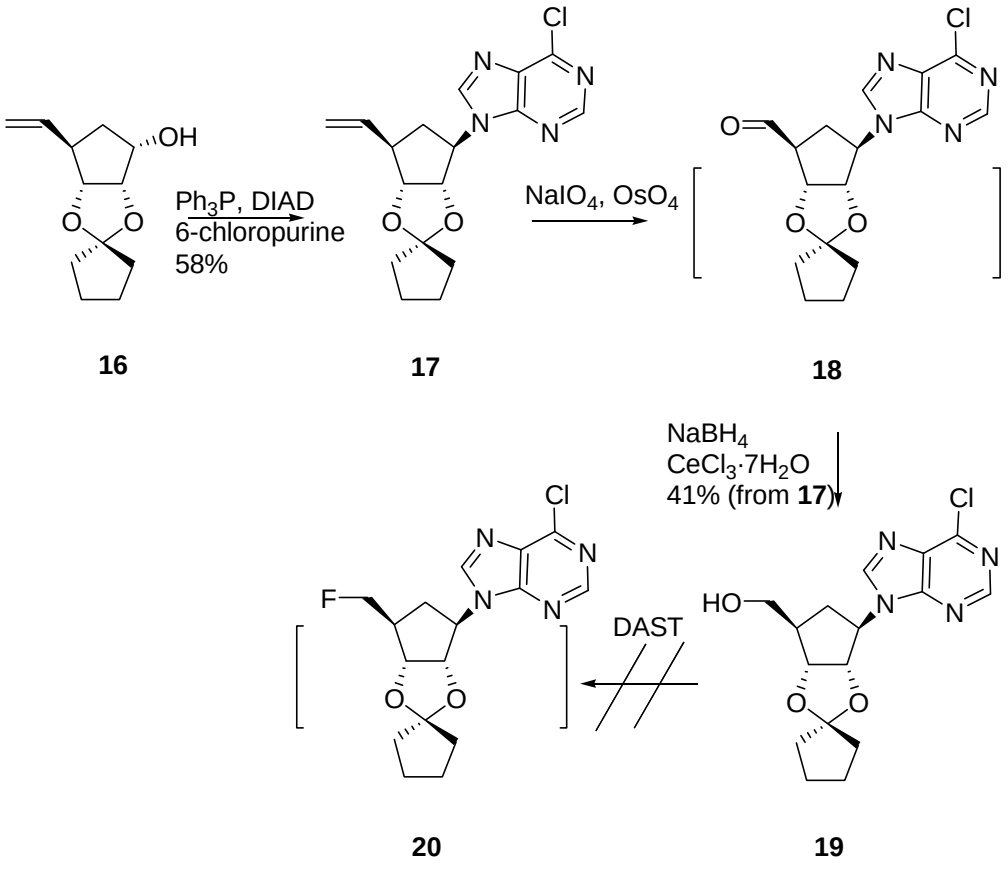
Scheme 3. Synthesis of Key Intermediate 16



Introduction of the base moiety was next considered (Scheme 4). The 6-chloropurine was used as adenine building block. Thus, 6-chloropurine was installed by a Mitsunobu coupling[210, 211] with **16** to give **17** as a mixture with di*iso*propyl hydrazine-1,2-dicarboxylate, which was used for next step withouth further purification. Oxidative cleavage of the double bond of **17** using sodium metaperiodate with a catalytic amount of osmium tetroxide[212, 213] resulted in **18.** This was not isolated, but reduced with sodium borohydride to yield **19**. The desired fluoro compound **20** could not be achieved

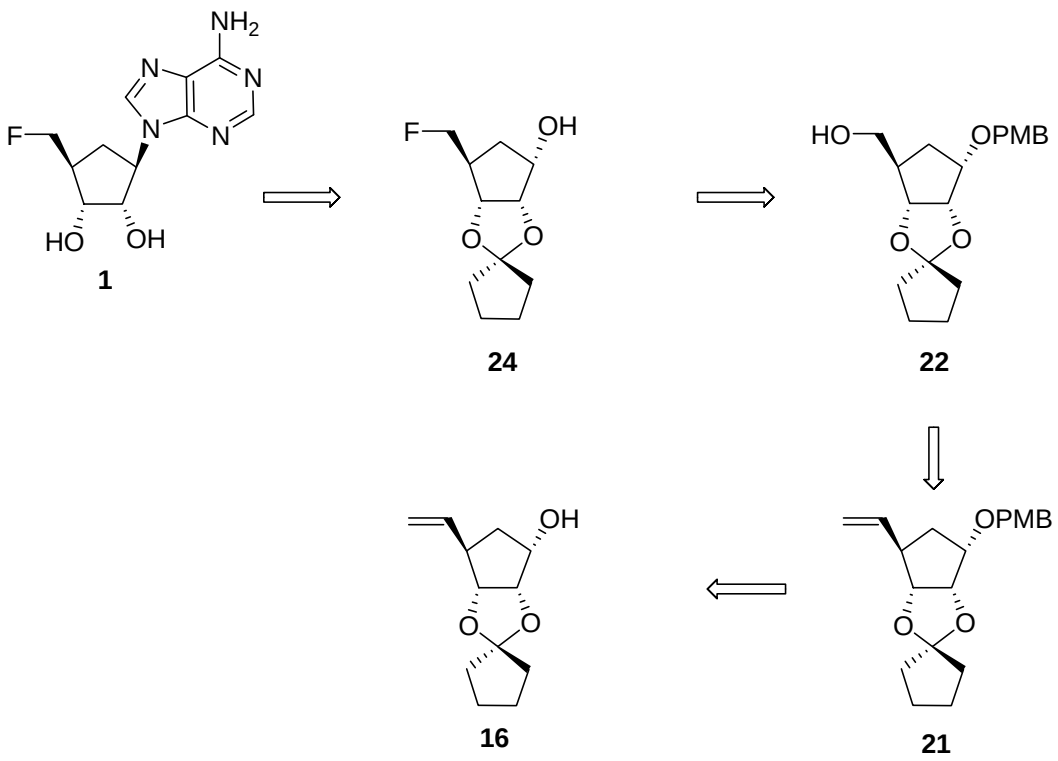
by various methods of fluorination (for example, combination of *N*,*N*-diethylaminosulfur trifluoride (DAST) and pyridine; conversion of **19** into corresponding "mesylate/tosylate" and treatment with sodium fluoride). Careful examination of NMR spectrum of the fluorination products mixture indicated that the 6-chloropurine moiety may interfere with the transformation of the hydroxyl group into fluoride, since the hydroxyl group was missing, while the expected fluoromethyl group was not present.

Scheme 4. Initial Attempt to 1



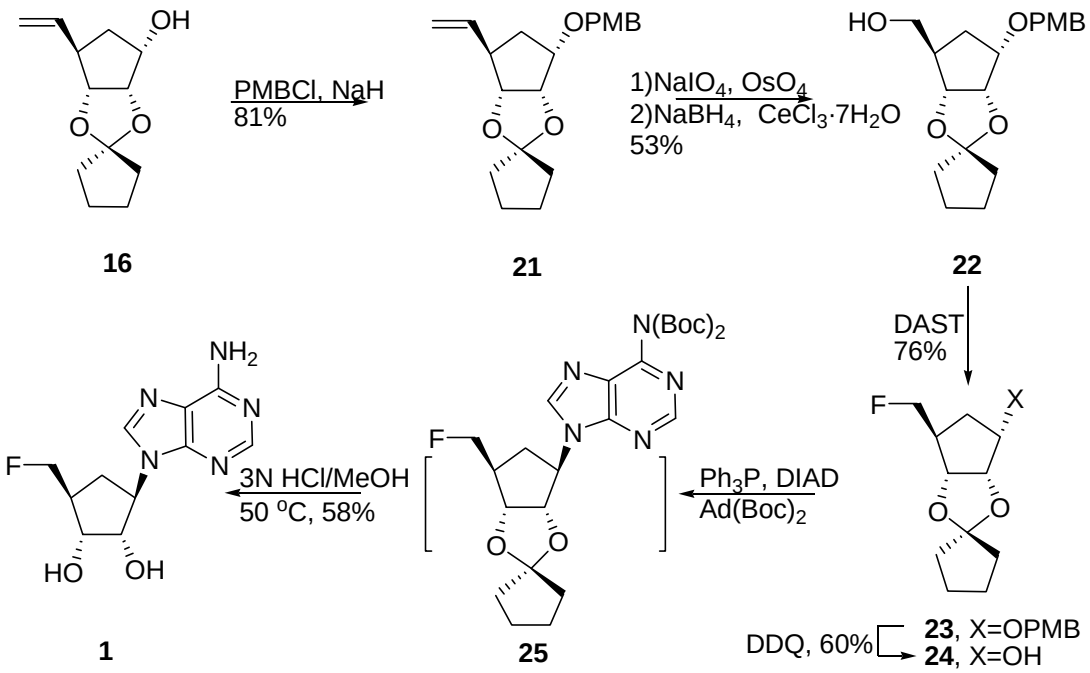
Realizing the difficulty of introducing fluoride in the presence of 6-chloropurine moiety, it was decided to introduce the purine base at a later stage, while introducing the fluorine at an earlier stage. A revised retrosynthetic plan is shown in Scheme 5.

Scheme 5. Revised Retrosynthetic Analysis towards Synthesis of 1



The execution of this plan is shown in Scheme 6. Protection of the secondary hydroxyl group of **16** with the *para*-methoxybenzyl (PMB) group gave **21**. Oxidative cleavage of the double bond of **21** followed by Luche reduction produced **22**. Fluorination of **22** with DAST[214] successfully yielded the desired **23**. Removal of the PMB protecting group of **23** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) formed **24** in good yield. Subjecting **24** to a Mitsunobu coupling with 9*H*-6-di(butoxylcarbonyl)aminopurine (Ad(Boc)$_2$) provided **25**. Acid deprotection of **25** successfully gave **1**.

Scheme 6. Synthesis of Target 1



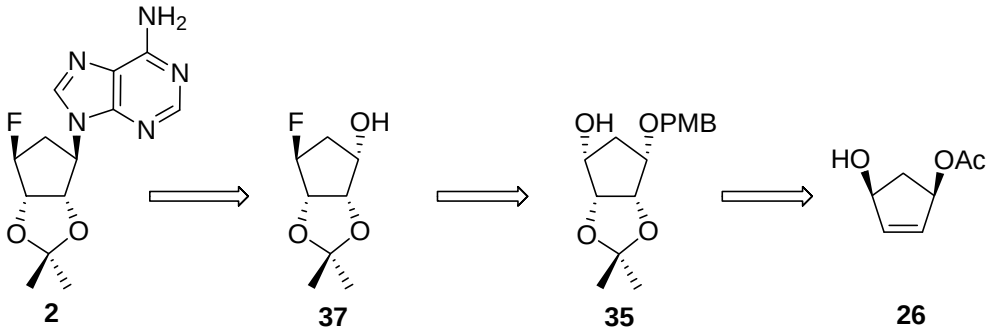
4′-DEOXY-4′-FLUORONORARISTEROMYCIN

Experimental Design and Synthesis

D-Noraristeromycin, designed and synthesized by the Schneller group, shows potent antiviral activity with little associated toxicity.[139] Encouraged by this result, similar compounds were sought. Out of this, 4′-fluoro-4′-deoxynoraristeromycin (**2**) was sought, since replacing the 4′-hydroxyl group with fluoride would abolish the potential capability of undesired 5′-noraristeromycin phosphorylation by a cellular kinase.

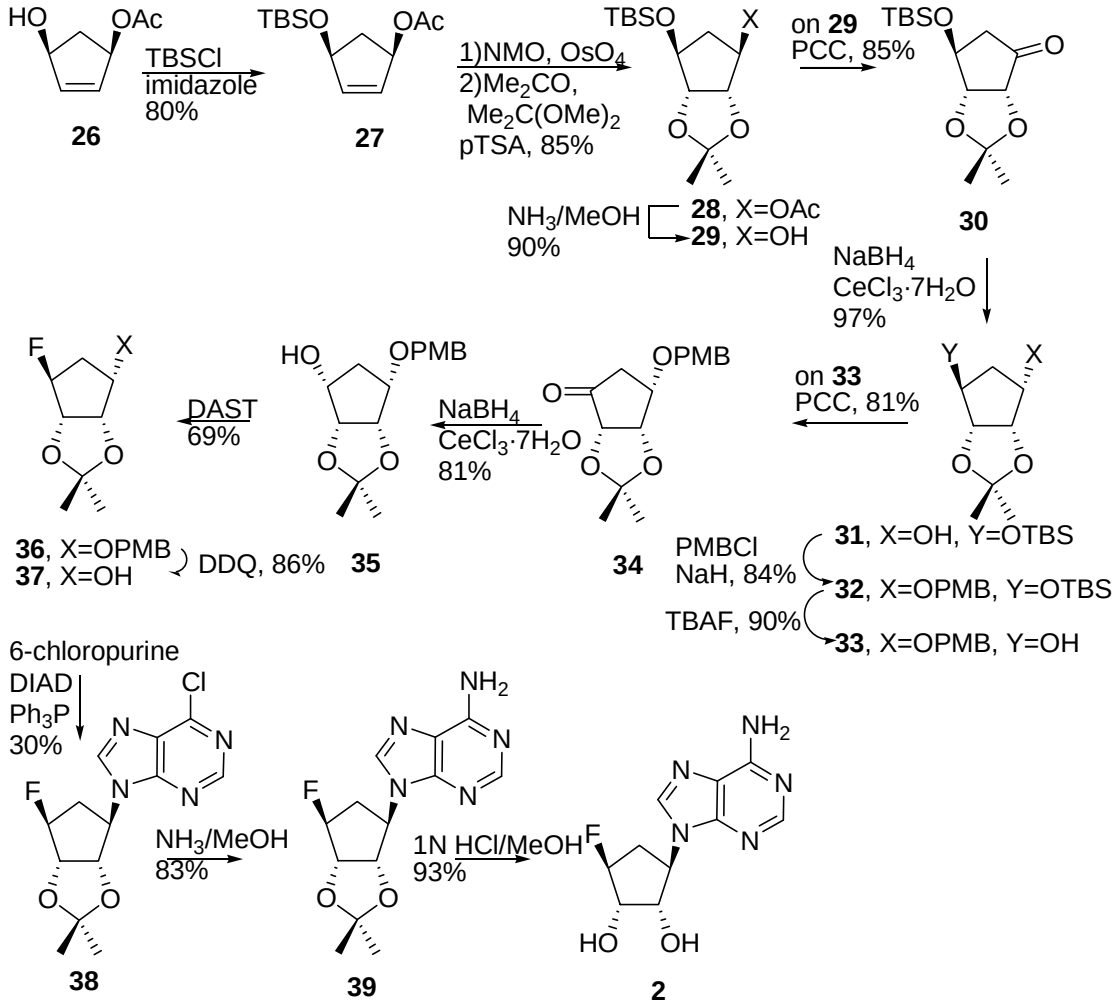
A convergent synthetic strategy was planned. The chosen retrosynthetic analysis is shown in Scheme 7. The basic idea was to build the desired carbocyclic moiety **37**, then couple it with a purine base under Mitsunobu conditions to give desired compound.

Scheme 7. Retrosynthetic Analysis of 2



The synthesis began with (1*R*,4*S*)-4-hydroxycyclopent-2-enyl acetate **26**, which was prepared in large scale by a routine method used in the Schneller group.[203] Protection of the secondary hydroxyl group with the *tert*-butyldimethylsilyl (TBS) group gave **27**. Dihydroxylation[215] of **27**, followed by glycol protection, yielded **28**. Removal of the acetyl group of **28** with ammonia in methanol gave **29**. Pyridinium chlorochromate (PCC) oxidation of **29** yielded **30**. Luche reduction of **30** afforded **31**. The secondary hydroxyl group of **31** was protected as a PMB ether furnishing **32**. Removal of the silyl group of **32** with tetra-*n*-butylammonium fluoride (TBAF) formed **33**, which was subjected to a PCC oxidation and the Luche reduction to avail **35**. Fluorination of **35** with DAST yielded **36**. The PMB protecting group of **36** was removed by DDQ, producing the key intermediate **37**. Mitsunobu coupling of **37** with 6-chloropurine afforded **38**. Subsequent amination of **38** led to **39**, which was deprotected to give **2**.

Scheme 8. Synthesis of 2



To elucidate the relative configuration of **2**, ge-NOESY, ge-COSY and ge-HMBC were conducted on Bruker 400 NMR spectrometer. The following correlations were observed (Figure 19):

NOESY:

H1′—H5′ beta (weak), H5′ alpha (strong), H2′, H4′, 2′OH, 3′OH

H2′—H5′ beta (strong), H5′ alpha (very weak), H3′ (strong), 2′OH, 3′OH

H3′—H5′ beta (moderate), H2′, H4′, 3′OH, 2′OH

H4′—H1′, H5′ alpha (strong), H5′ beta (moderate), H3′ (moderate), H2′ (very weak), 2′OH (moderate), 3′OH (moderate)

H8—H1′ (strong), H2′ strong), H3′ (very weak), H5′ beta (strong), 2′OH (very weak), 3′OH (very weak)

HMBC:

H1′—C4 (150.2), C8 (140.2), C2′ (73.7), C5′ (33.3)

H2—C4 (150.2), C6 (156.0)

H8—C4 (150.2), C5 (119.4)

The dependence of NOE on the inverse of the distance to the sixth power allows for an estimation of the internuclear distance. According to this principle, a NOE between H1′ and H4′ indicates that they are in *syn* configuration, since the distance between H1′ and H4′ is shorter when they are in *syn* configuration, compared to *anti* configuration. Similarly, the NOE correlations of H8—H2′ and H8—H5′ (beta) supports the conclusion that adenine is connected to cyclopentane ring in the desired beta configuration. Normal N^{9-} product was confirmed by three-bond coupling between H1′ and C4 (150.2), C8 (140.2).

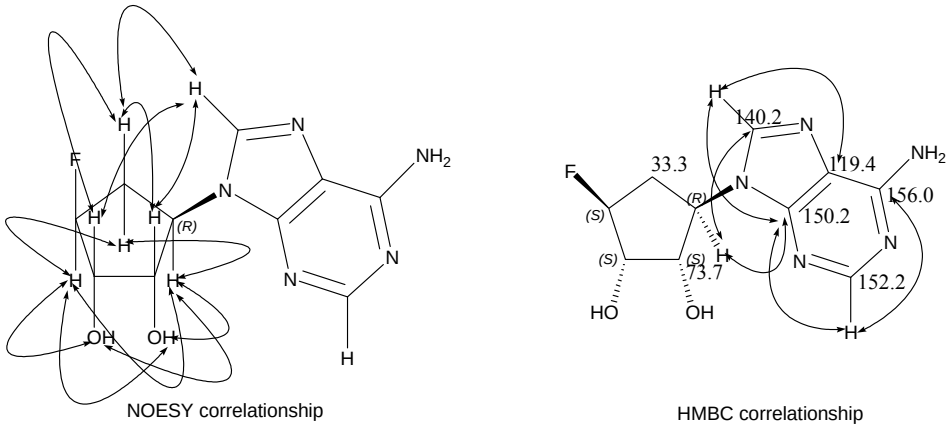


Figure 19. NOESY and HMBC Correlationship in DMSO-d_6

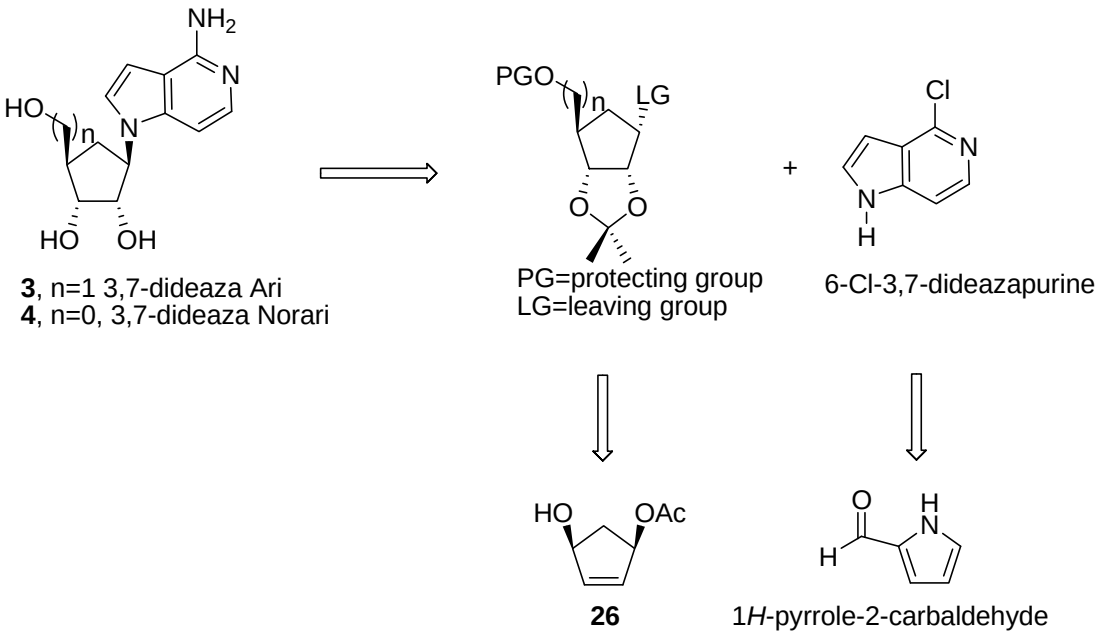
3,7-DIDEAZA ARISTEROMYCIN AND NORARISTEROMYCIN

Experimental Design and Synthesis

3-Deaza purine nucleosides show potent antiviral activity. For example, 3-deaza Ari and 3-deaza NpcA display significant activity, while their associated toxicity (relative to Ari and NpcA) was greatly reduced.[84] Similarly, 7-deazapurine nucleosides demonstrate a wide range of biological effects.[145] Combining these two structural features to create new modified base analogs of Ari or NpcA with decrease in related toxicity, leads to investigating 3,7-dideaza adenine as a novel modified purine base.

The synthesis was planned in a convergent strategy (Scheme 9), where the proper carbocyclic sugar moiety was seen as coupling with 3,7-dideaza-6-chloropurine to give the desired compounds. The carbocyclic sugar was to be derived from the common intermediate **26**. The modified purine base was foreseen from commercially available pyrrole-2-carboxaldehyde, by modifying a literature process. [216]

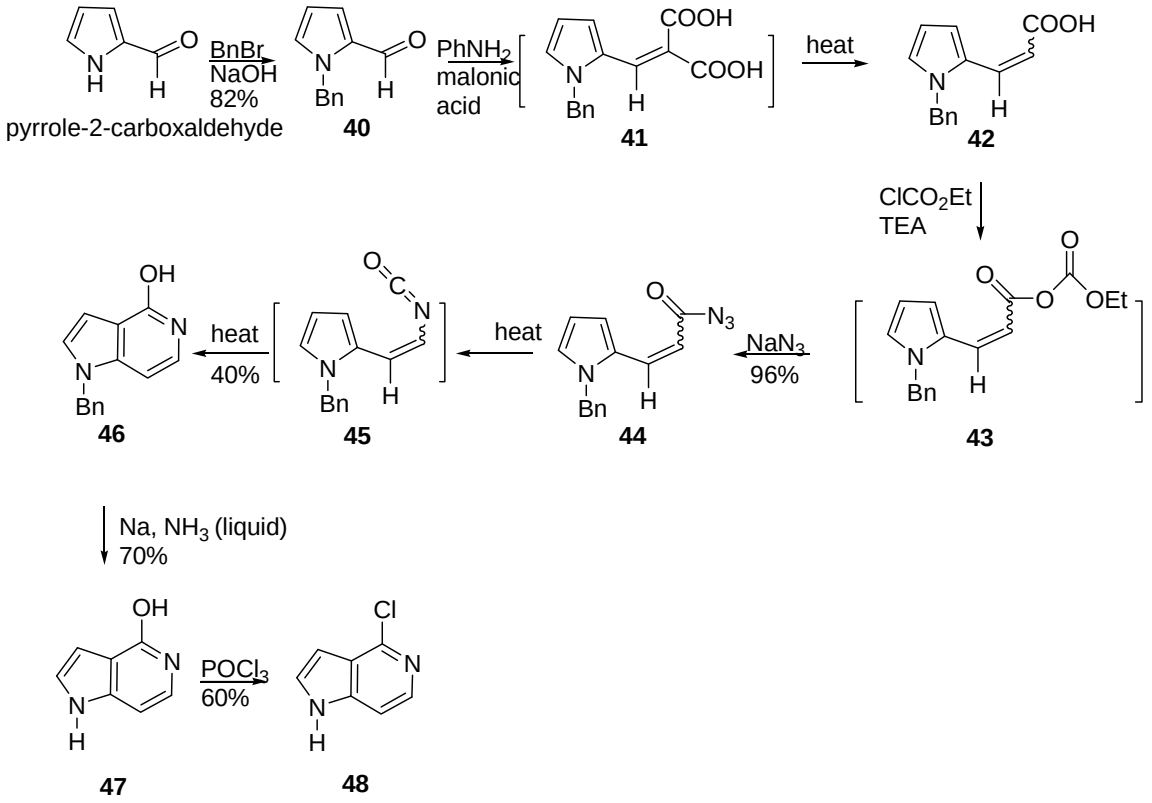
Scheme 9. Retrosynthetic Analysis of 3 and 4



Synthesis of 6-Chloro-3,7-dideazapurine

Synthesis of 6-chloro-3,7-deazapurine started from pyrrole-2-carboxaldehyde (Scheme 10). Protecting the ring nitrogen of pyrrole-2-carboxaldehyde gave **40**. Aldol condensation of **40** with malonic acid resulted in **41**, which spontaneously decarboxylated to **42**. Transformation of the carboxylic acid of **42** into mixed anhydride afforded **43**, which was further treated with sodium azide to provide **44**. A thermally induced Curtius rearrangement[217]of **44**, followed by a subsequent Friedel-Crafts like 'acylation' provided **46**. Removal of the benzyl protecting group of **46** with sodium metal in liquid ammonia furnished **47**. Chlorination of **47** gave **48**.

Scheme 10. Synthesis of 6-Chloro-3,7-dideazapurine

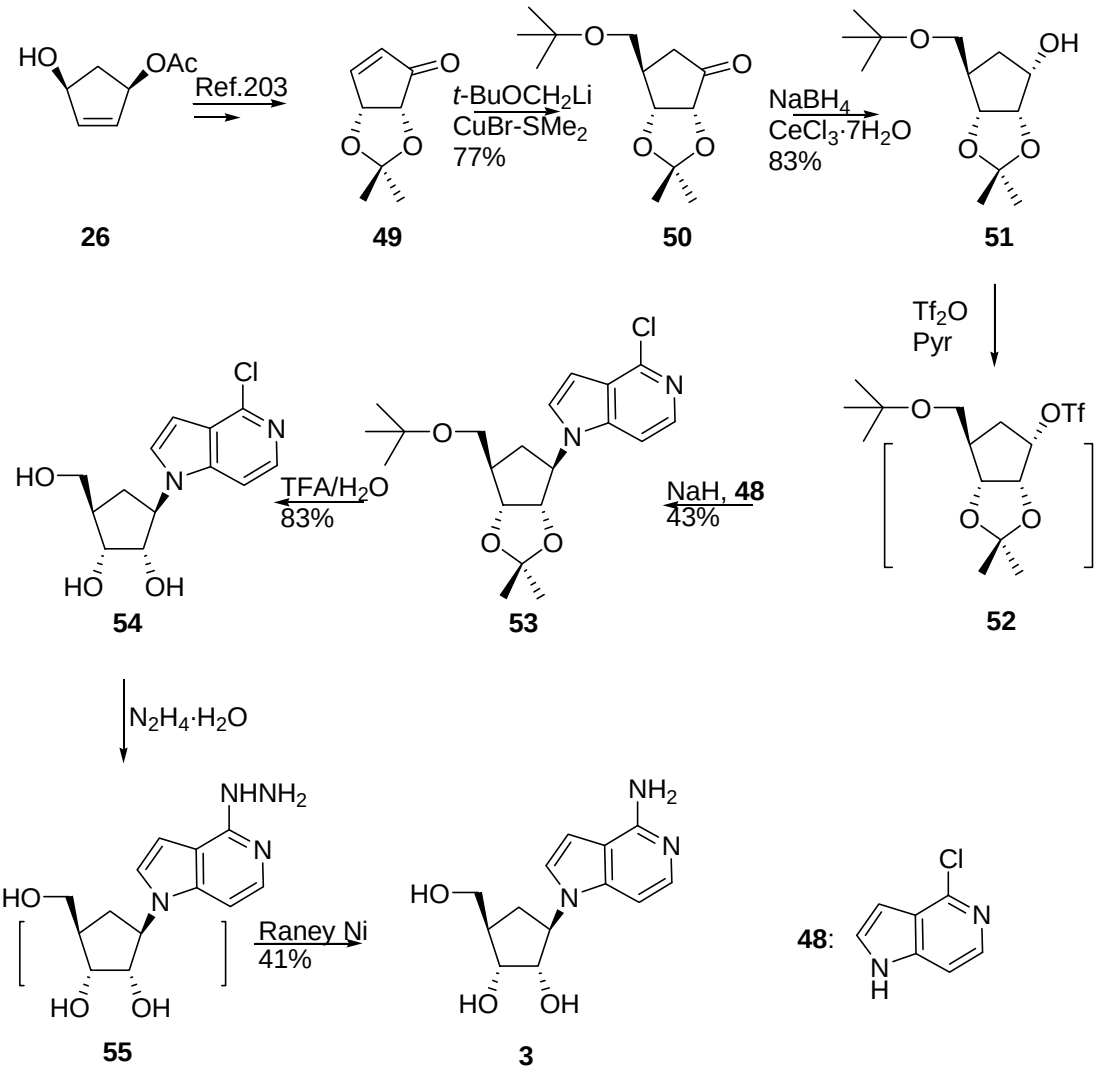


Synthesis of 3,7-Dideaza Aristeromycin

The synthesis of 3,7-dideaza Ari began with **26** (Scheme11), which was transformed into **49** in moderate scale (up to 20 g) using a methodology developed in Schneller group.[203] A Michael type 1,4-addition of the lithium salt of *tert*-butyl methyl ether catalyzed by copper (I) provided **50**. Luche reduction of **50** gave **51**. Since Mitsunobu coupling of **48** with various carbocyclic pseudosugars failed to yield desired compounds, a classical S_N2 reaction approach was taken into account. To minimize the possible accompanying elimination, triflate was selected as the S_N leaving group. Thus, treatment

of **51** with trifluoromethanesulfonic anhydride in the presence of pyridine in dichloromethane yielded **52**. It must be mentioned that the triflate **52** was not stable for long storage at room temperature (it became black). Coupling of triflate **52** with the sodium salt of dideaza base **48** gave **53** in moderate yield. Removal of the *iso*propylidene protecting group and *tert*-butyl group of **53** in strong acid conditions afforded **54**. Direct amination of **54** with ammonia in methanol failed to yield desired product. Therefore, a two-step, one pot procedure was applied. The chloride in **54** was replaced by hydrazine at high temperature to produce **55**. Reduction of **55** with Raney nickel gave **3** as its hydrochloride salt.

Scheme 11. Synthesis of 3,7-Dideaza Ari

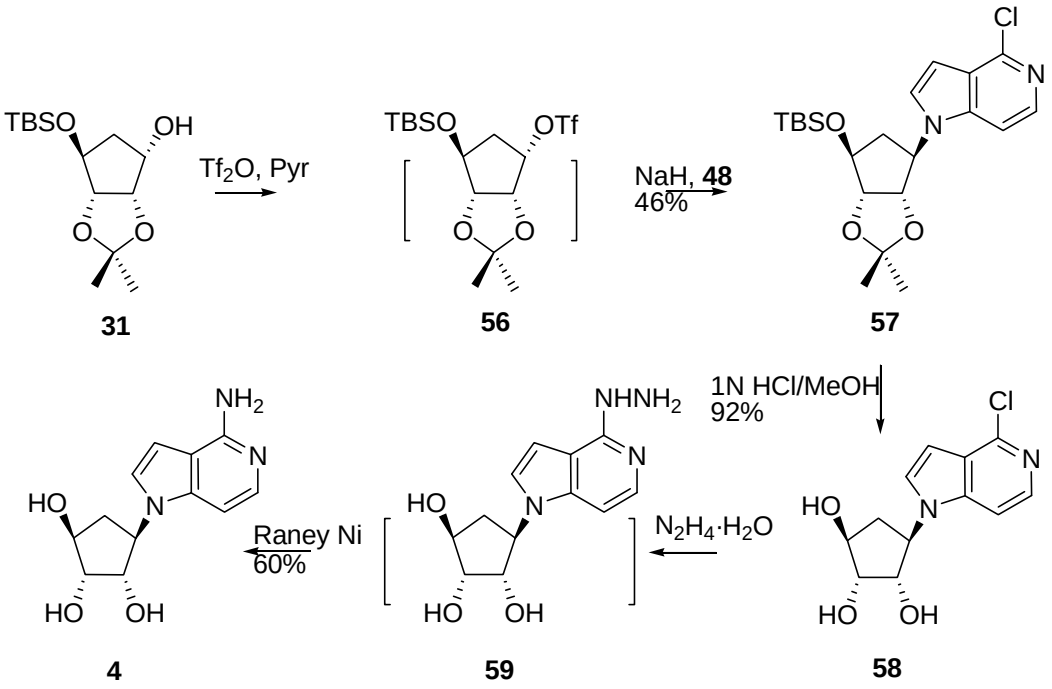


Synthesis of 3,7-Dideaza Noraristeromycin

The synthesis of **4** started from **31**, as shown in Scheme 12. Transformation of **31** into the corresponding triflate gave **56**, which was coupled with the sodium salt of 6-chloro-3,7-dideazapurine to produce **57**. Compound **58** was obtained by removal of the

protecting groups of **57.** Using the aforementioned two-step, one pot procedure, **58** was converted to the hydrazine derivative **59**, which was, in turn, reduced with Raney nickel to produce **4** as its hydrochloride salt.

Scheme 12. Synthesis of 3,7-Dideaza Norari



DEVELOPING AN ALTERNATIVE SYNTHESIS OF SINEFUNGIN AND RELATED COMPOUNDS

Experimental Design and Synthesis

Despite of a number of total syntheses of sinefungin (Figure 15) and related compounds,[175-200] a high yielding and versatile synthetic method remains to be decribed. To explore the preparation and activities of sinefungin and its derivatives, a high-efficiency synthetic pathway was sought in this dissertation research. For this purpose, the structure of sinefungin was separated into several building blocks: the terminal amino acid residue, the 6′-amino moiety, the furanose sugar and the adenine base. A practical and versatile synthesis of sinefungin will require bringing together these building blocks in the proper order.

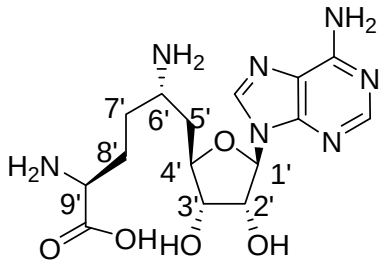


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Figure 15. Sinefungin

A detailed screening of the literature showed that the amino acid residue can be introduced by means of a Schöllkopf chiral auxiliary (Figure 20),[218-220] which is an

O-alkyl ether of a cyclic dipeptide. The stereoselectivity in using this auxiliary comes from the directing effect of the *iso*propyl group *via* masking one surface of the intermediate (that is the Schöllkopf carbanion).

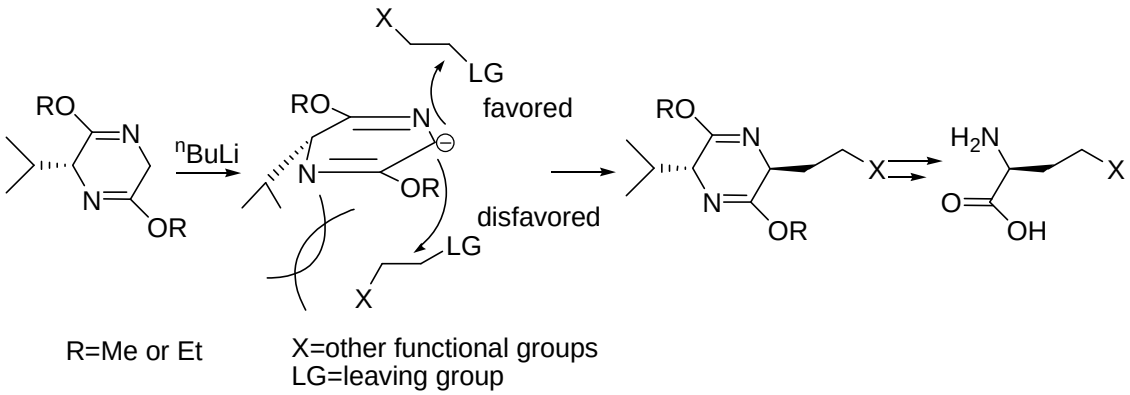


Figure 20. Stereoselectivity of Schöllkopf Auxiliary

Since azide is a good synthon for an amino group,[221] it was designed to be the source of the 6′-amino group, which, in turn, can be derived from an alcohol substituent. To build the correct stereochemistry for the 6′ position, a stereoselective addition of carbanionic species to an aldehyde was considered. Previous reports from the literature indicated that a Brown asymmetric allylation of an aldehyde would meet this criterion.[222-225] The stereoselectivity of the Brown allylation is achieved by a cyclic six-membered ring transition state mechanism, in which one face of aldehyde is shielded by chiral auxiliary (Figure 21).[225] The sugar moiety of sinefungin can be derived from D-ribose, since it has the desired stereochemistry. The adenine base segment follows from 6-chloropurine.

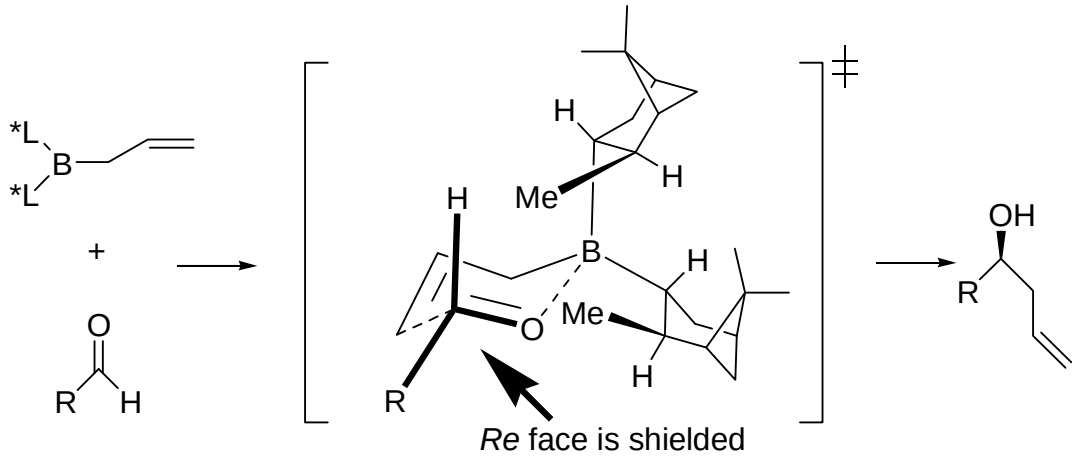
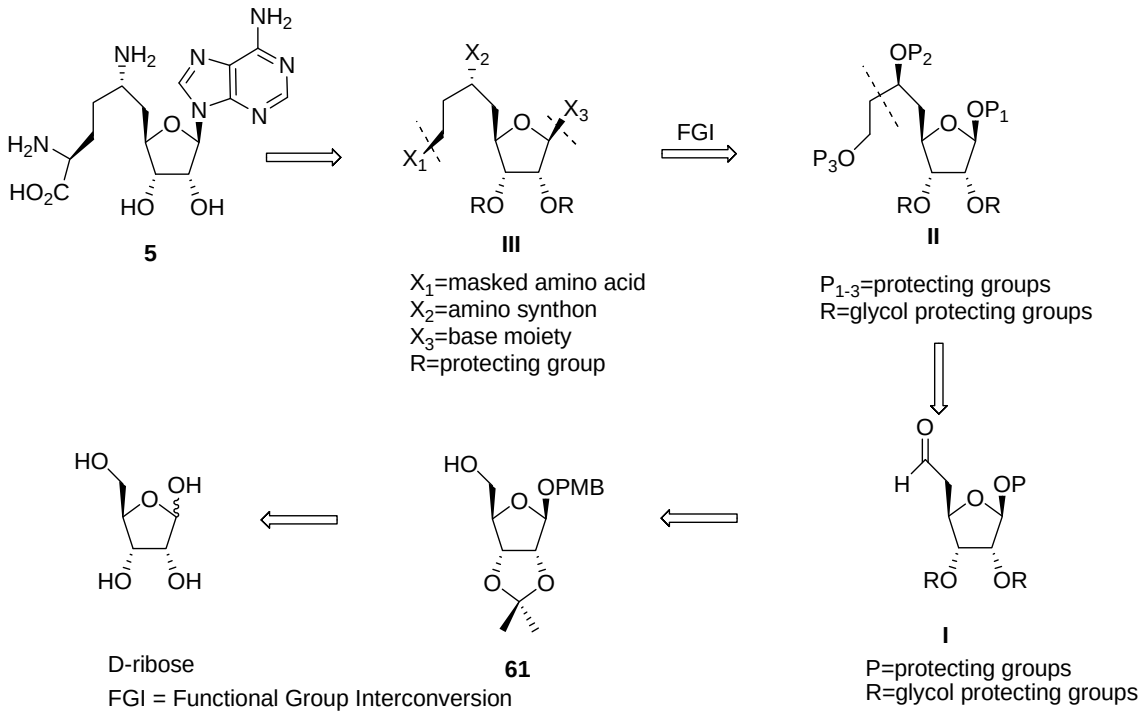


Figure 21. Stereoselectivity of Brown Allylation

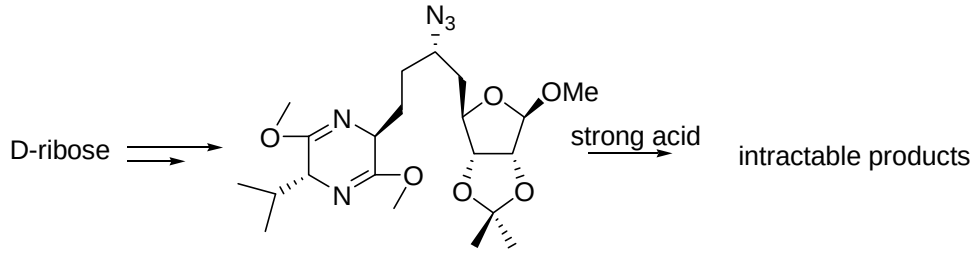
With these ideas in mind, a retrosynthetic analysis arose (Scheme 13). In this plan, the furanose sugar segment serves as the scaffold upon which to build the structure. All of the desired functional groups, i.e., the 6′-amino group, the amino acid residue and the purine are connected to this scaffold by the methods just described.

Scheme 13. Retrosynthetic Analysis of Sinefungin



In previous investigations in the Schneller group (Scheme 14), a methyl ether was selected as the anomeric hydroxyl protecting group, due to its ease of introduction. However, eventual cleavage of the methyl ether under strong acid conditions gave intractable products (Scheme 14). Thus, the anomeric hydroxyl group must be protected by a group that can be removed under mild conditions. To meet this criterion, PMB ether was considered as a protecting group, since its removal could be achieved conveniently by DDQ.

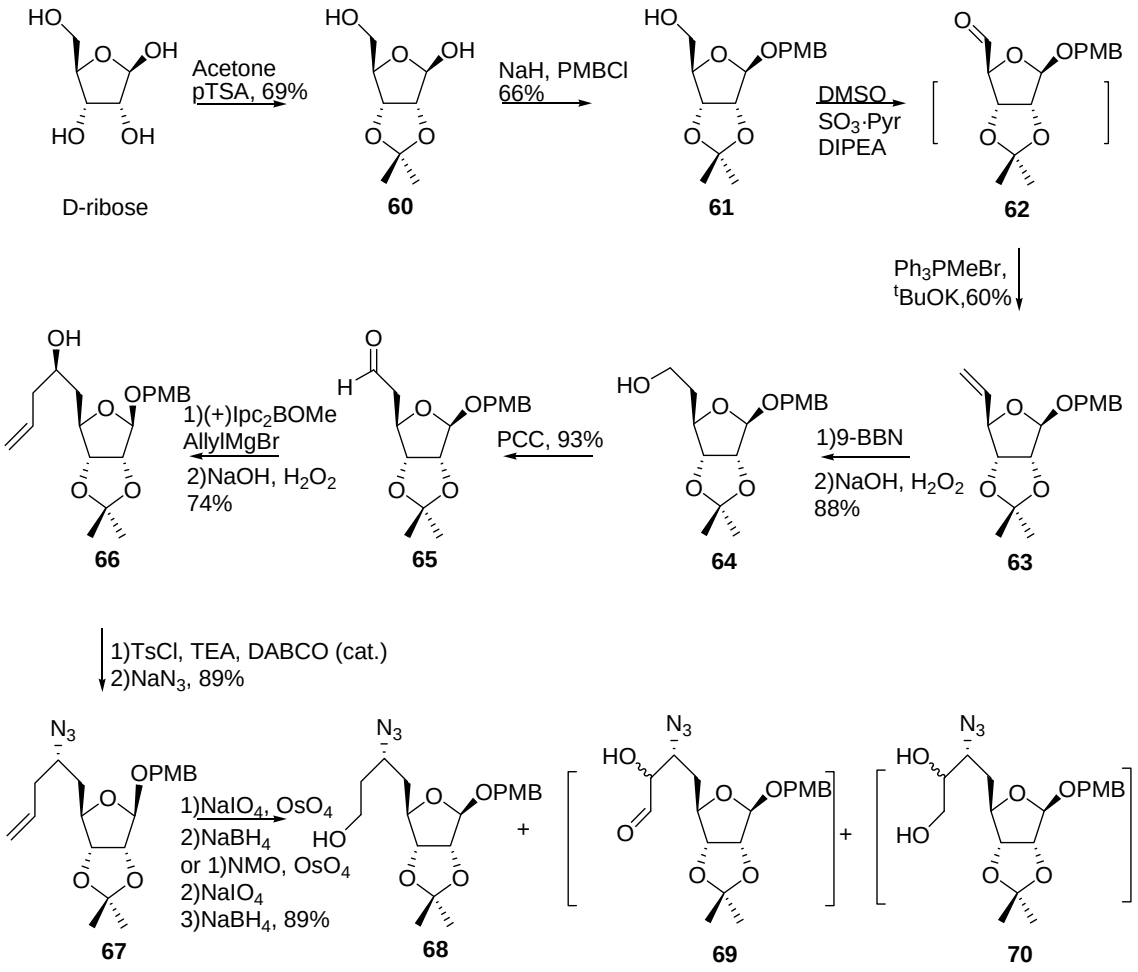
Scheme 14. Protection of Anomeric Hydroxyl as Methyl Ether



The synthetic pathway towards sinefungin started from D-ribose (Scheme 15). The *vicinal* hydroxyl groups were protected in the *iso*propylidene framework to give **60**. The anomeric hydroxyl of **60** was protected with PMB group to produce **61**. Dimethyl sulfoxide (DMSO) oxidation of **61** formed **62**, which was converted to **63** *via* a Wittig reaction. Hydroboration and oxidation of **63** led to **64**, which was further treated with PCC to yield **65**. Brown allylation of **65** gave **66**. The stereochemistry of **66** was tentatively assigned according to methodology established in the literature:[222-225] when (+)-*B*-methoxydi*iso*pinocamphenylborane ((+)-Ipc_2BOMe) is used as chiral auxiliary, the *Re* face of the aldehyde is masked (the nucleophile attacks the aldehyde from the *Si* face). Mesylation of **66**, followed by treatment with sodium azide, provided **67**. Double bond cleavage of **67** was performed by a combination of osmium tetroxide and sodium

metaperiodate. However, this method resulted in a low yield of the desired compound **68**, together with **69**, **70** and intractable materials.

Scheme 15. Synthesis of Compound 68

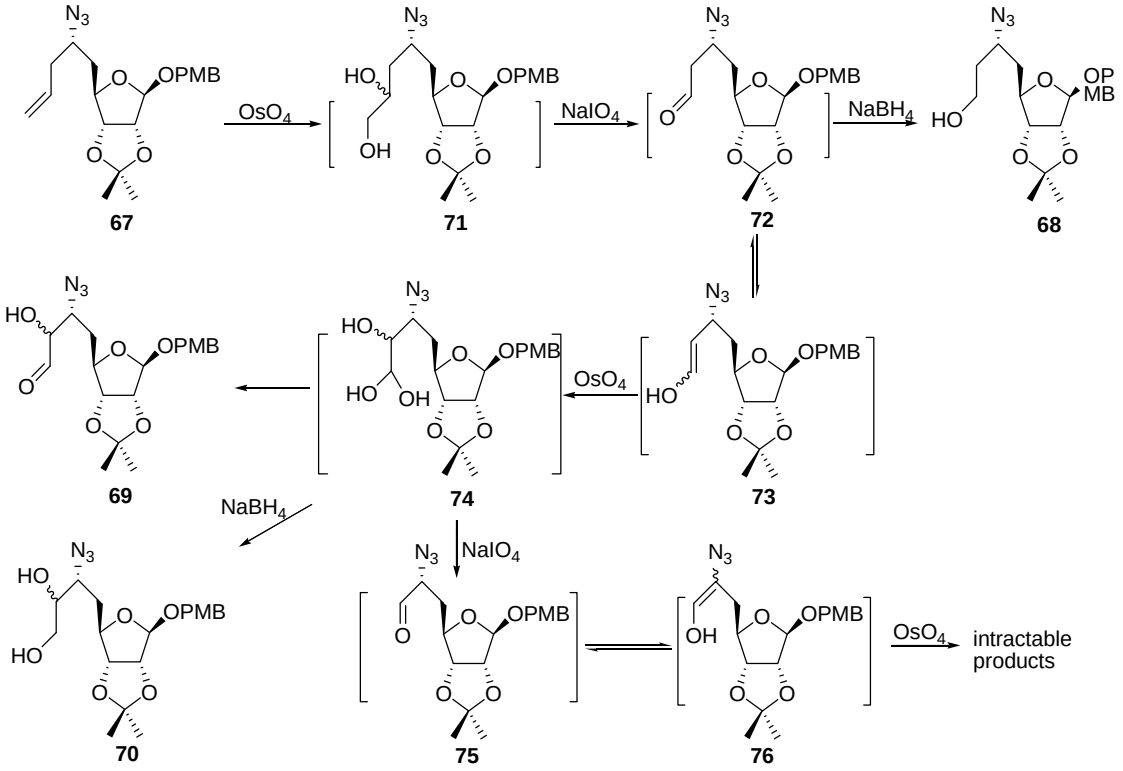


A possible pathway to this complication was analyzed *via* Scheme 16. Compound **67** was converted to **71** by osmium tetroxide. Cleavage of the *vicinal* hydroxyls of **71** with sodium metaperiodate gave intermediate **72**, which was reduced by $NaBH_4$ to produce desired compound **68**. The intermediate **72** also tautomerizes to **73**. Since **73** bears a double bond, this can be oxidized to give **74**. Compound **74** underwent a dehydration

reaction to yield **69**. Also, **74** can be cleaved by sodium metaperiodate to give **75**, which can tautomerize to **76** and undergo further reactions, leading to intractable products, making the isolation of **68** difficult. Similar results have been reported in the literature.[226]

To circumvent this complication, a three step procedure was used to prepare the desired **68**. Hence, compound **67** was converted to **71** by a combination of osmium tetroxide and 4-methylmorpholine *N*-oxide (NMO). The application of the Sharpless dihydroxylation protocol (AD-mix-alpha or AD-mix-beta) also gave **71**. Treatment of **71** with sodium metaperiodate gave **72**, which was reduced with sodium borohydride to provide **68**.

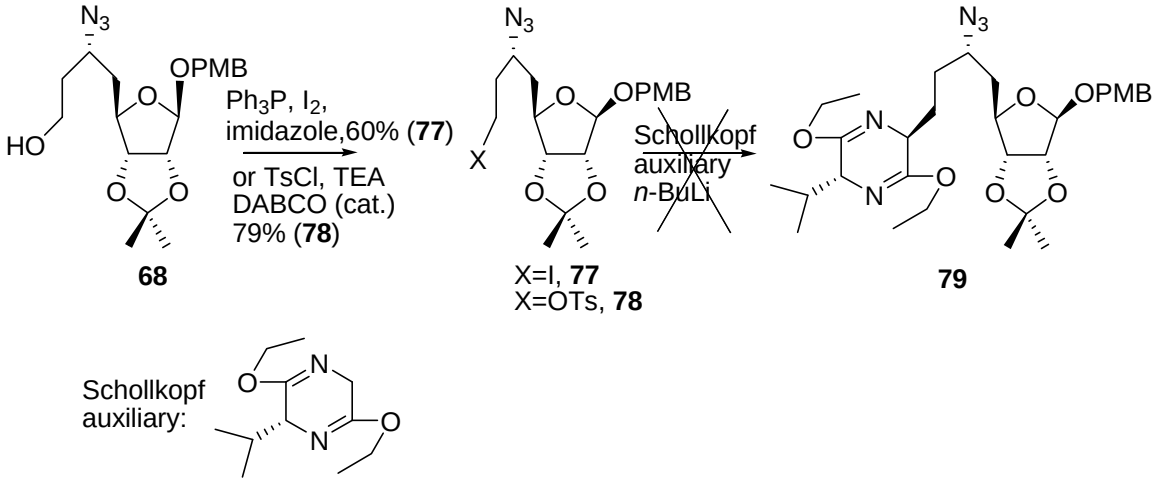
Scheme 16. Proposed Side Reactions in Double Bond Cleavage by OsO_4/$NaIO_4$



To install the Schöllkopf chiral auxiliary, the hydroxyl group of **68** was transformed into a good leaving group (Scheme 17). Thus, treatment of **68** with imidazole, iodine and

triphenylphosphine (TPP) gave **77** in moderate yield (30%-60%). The low yield may be due to involvement of the azido group in an undesired side mechanism, since it is well known that azido group can be reduced to an amino group by a phosphine species at room temperature.[221] Consequently, another leaving group was sought. Previous reports[220] indicated that the tosylate would serve this purpose. Converting the hydroxyl of **68** into the tosylate gave **78** in high yield (80%-95%). Compound **77** and **78** were subjected to coupling with the Schöllkopf chiral auxiliary. However, the desired compound **79** was not obtained. Careful NMR analysis of the products showed that the azido group and the leaving groups (iodo, tosyl) disappeared, while the desired dihydropyrazine moiety was not present. The starting materials were not recovered. This observation indicated that azido group was not compatible with organolithium species in this case.

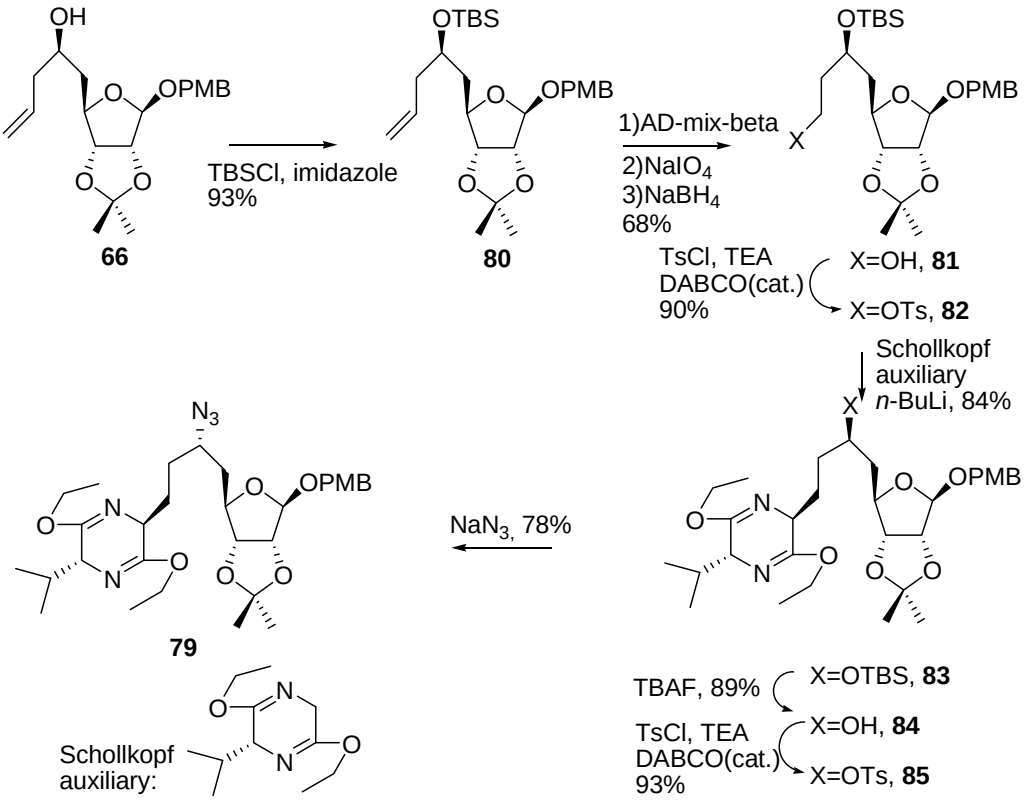
Scheme 17. Attempted Synthesis of Compound 79



To avoid this, introduction of the azido functionality was considered after installation of the Schöllkopf auxiliary (Scheme 18). For this reason, the secondary hydroxyl in **66**

was protected as a silyl ether to provide **80**. Conversion of the double bond of **80** into a hydroxyl yielded **81**. Compound **81** was transformed into tosylate **82**, which was coupled with the Schöllkopf auxiliary to give **83**. Removal of the silyl group of **83** by TBAF led to **84**, which was further converted to **85** by another tosylation. Introduction of the azido group by sodium azide gave **79** in high yield.

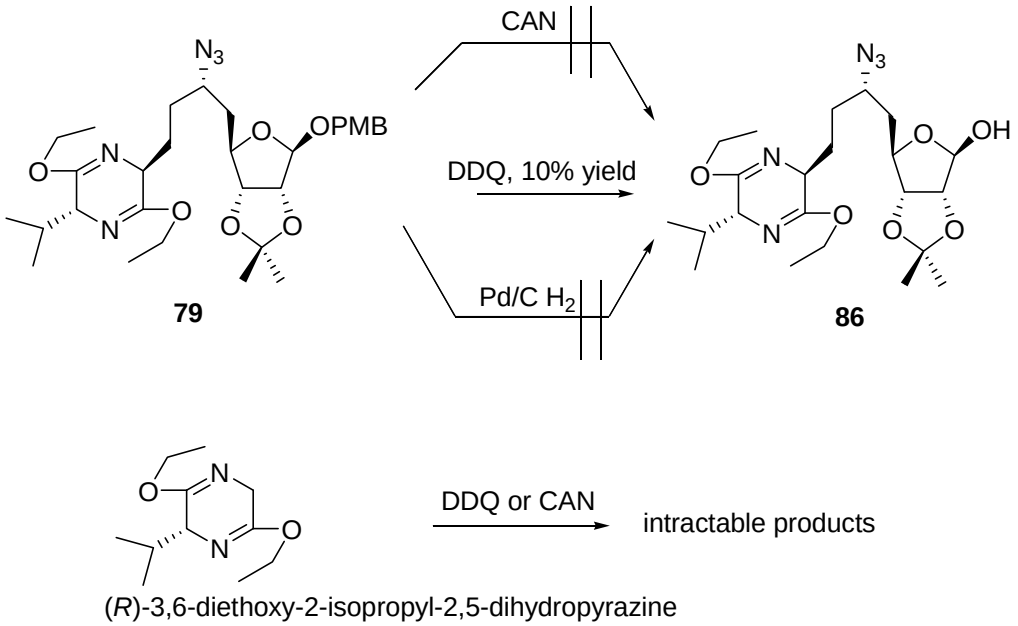
Scheme 18. Synthesis of Compound 79



Upon initial effort, removal of PMB ether was performed using DDQ oxidation (Scheme 19), however, the desired compound **86** was obtained only in low yield (usually 10-20%). In addition, purification of **86** was complicated with unknown side products. Other methods, such as oxidation with cerium ammonium nitrate (CAN), catalytic hydrogenation or strong acid hydrolysis did not give the expected results. Subjecting the

Schöllkopf auxiliary to DDQ or CAN also gave intractable products. These facts pointed to the necessity of removal of the PMB group prior to introduction of the Schöllkopf auxiliary.

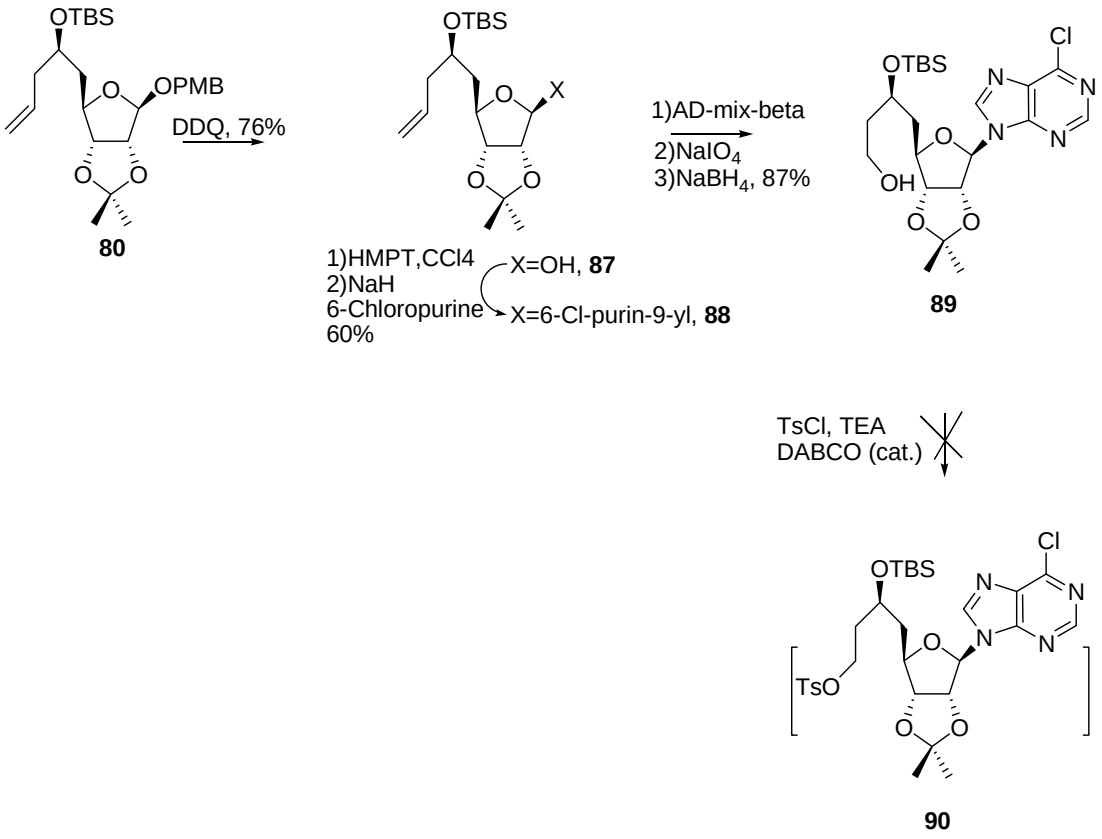
Scheme 19. Unexpected Result of PMB Ether Cleavage



A new synthetic pathway, in which the PMB was removed before the Schöllkopf auxiliary installation, was sought (Scheme 20). In this scheme, the base moiety was added at an earlier stage. Thus, the removal of PMB from **80** produced **87**. 6-Chloropurine was introduced by a two-step one-pot procedure (converting the anomeric hydroxyl of **87** into corresponding chloride followed by an S_N2 reaction with sodium salt of 6-chloropurine) to provide **88**. Double bond cleavage followed by Luche reduction converted **88** into **89**, however, transformation of **89** into **90** was not successful. Instead of giving the desired compound **90**, the reaction formed water soluble products. An attempt to couple this with the Schöllkopf auxiliary failed to form expected compound.

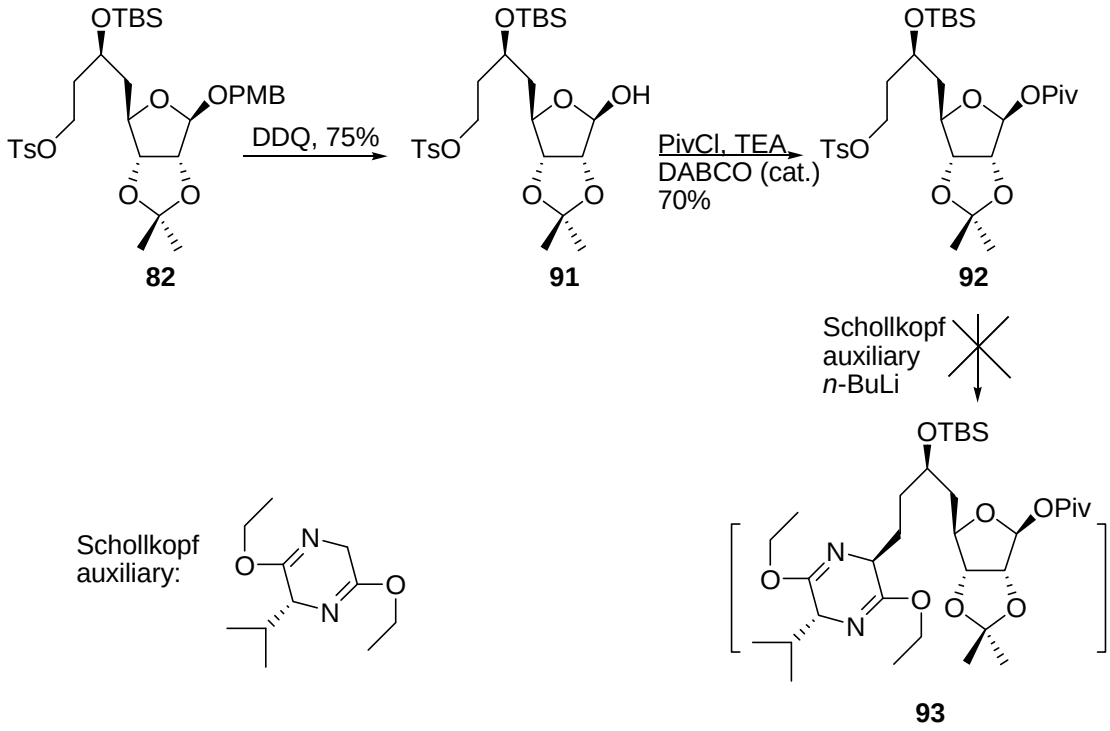
This indicated that 6-chloropurine moiety is incompatible with a good leaving group within the same molecule. Accordingly, introducing of 6-chloropurine as base moiety must be conducted after installation of Schöllkopf auxiliary.

Scheme 20. Attempted Introduction of Base at Early Stage



Based on the results described above, the best order of introducing functional groups incorporation was concluded to be (1) the Schöllkopf auxiliary, (2) the azido group and (3) the purine base moiety. For this reason, a new synthetic cascade was designed (Scheme 21).

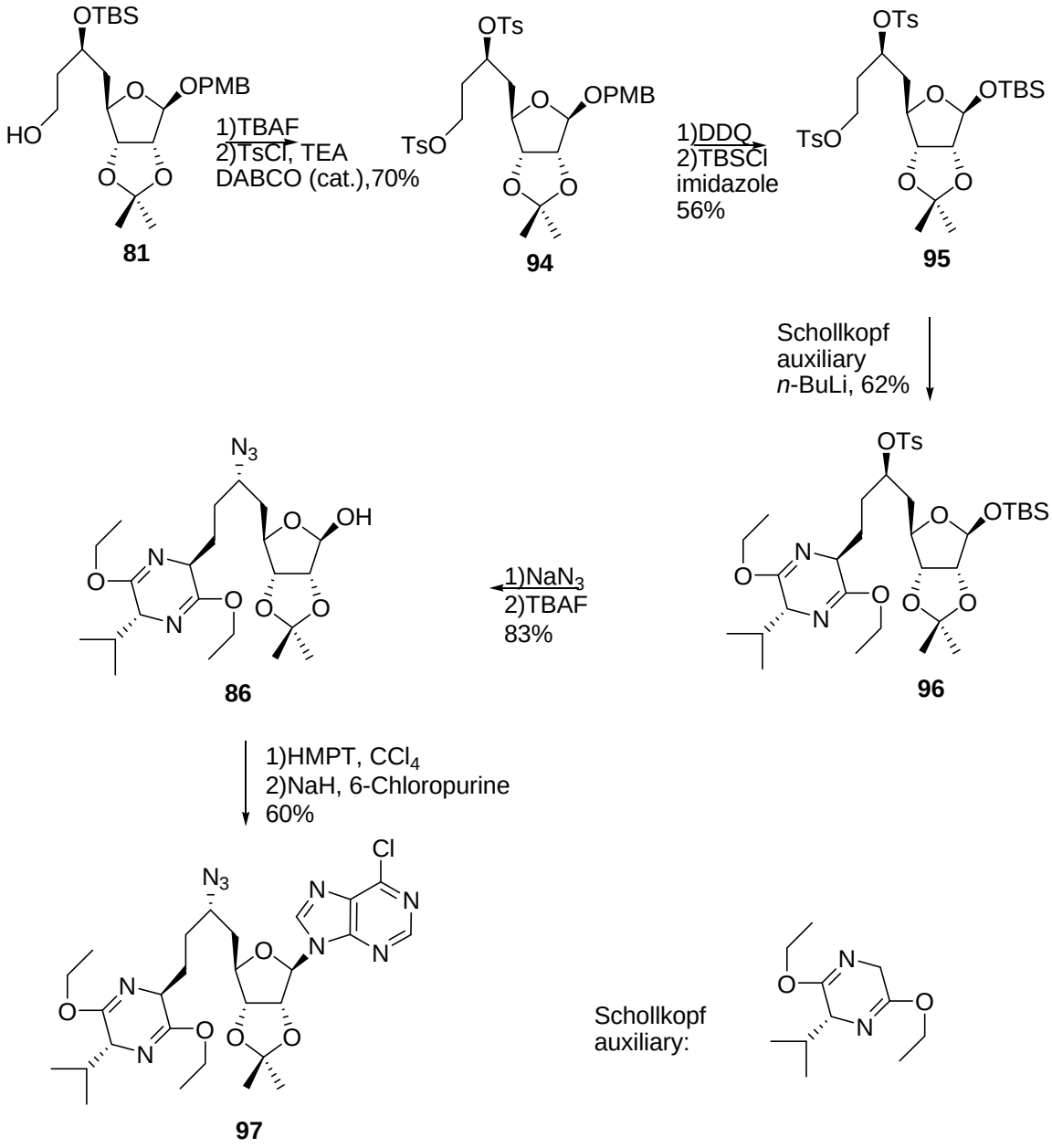
Scheme 21 Attempted Synthesis of Compound 93



Removal of the PMB group of **82** produced **91**. The anomeric hydroxyl group was protected as its pivalate ester to give **92**. Installation of the Schöllkopf auxiliary on **92** failed to provide **93**, indicating that the pivalate is not a suitable protective group for this purpose.

An alternative pathway to circumvent this complication was planned (Scheme 22). Compound **81** was converted into **94** by desilylation and tosylation. The PMB ether of **94** was removed and the anomeric hydroxyl was reprotected with *tert*-butyldimethylsilyl (TBS) group to afford **95**. Introduction of the Schöllkopf auxiliary onto **95** gave **96**, which was further transformed into **86** by installation of azido group and desilylation. Compound **86** was converted to **97** by installation of base moiety.

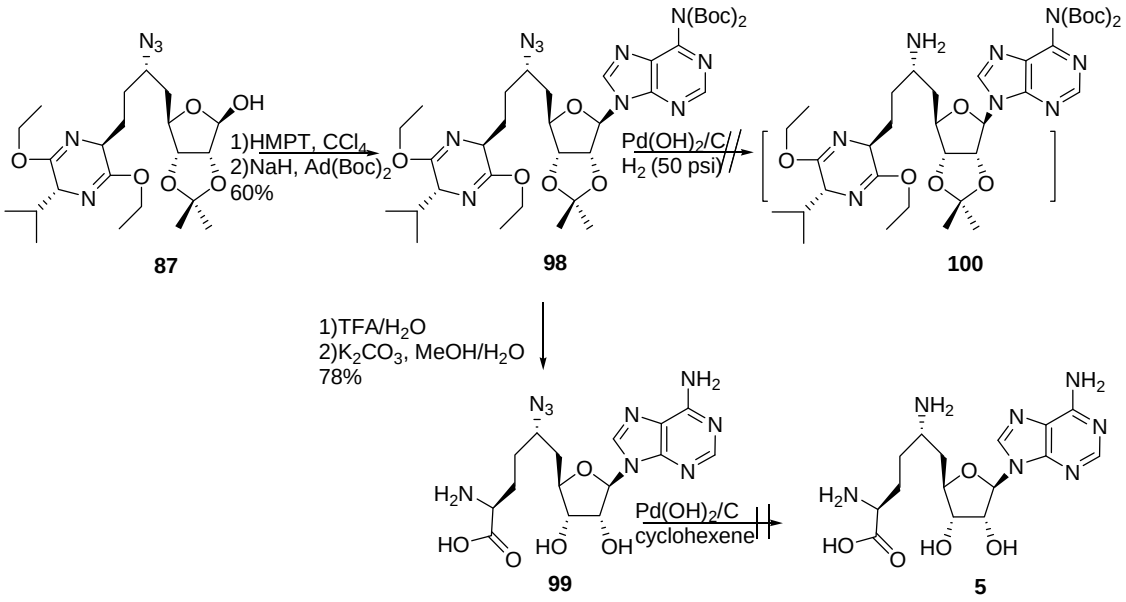
Scheme 22. Synthesis of Compound 97



Transformation of the 6-chloropurine moiety of **97** into the adenine moiety failed to give desired product. Thus, $Ad(Boc)_2$ was introduced as base building block on **87** (Scheme 23) to provide **98**. An attempt to convert the azido group of **98** under catalytic

hydrogenation conditions failed to give desired compound **100**. Consequently, removal of protecting groups at earlier stage was considered. Liberation of the amino acid residue and removal of the *iso*propylidene of **98** gave **99**. However, hydrogenation of **99** did not afford desired compound.

Scheme 23. Synthesis of Azidosinefungin

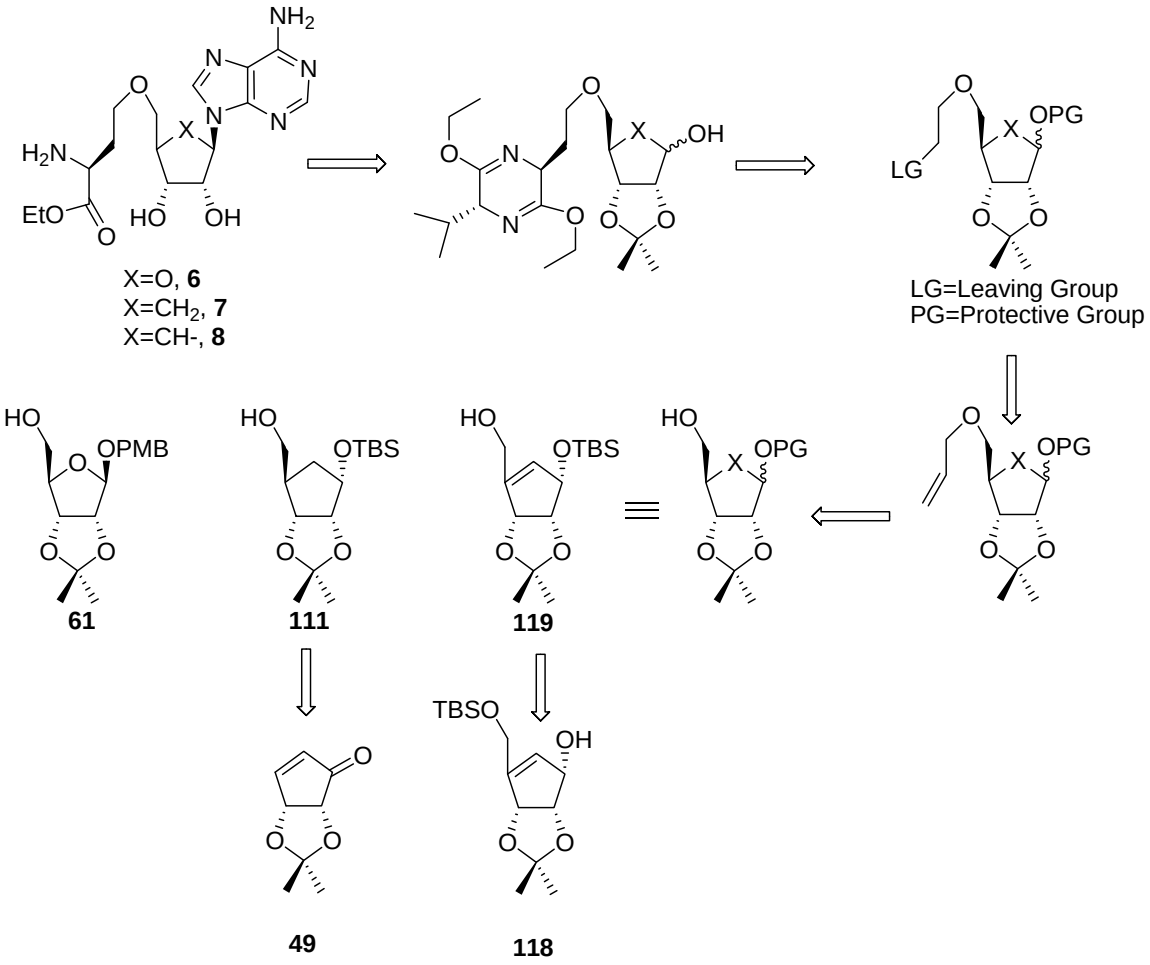


SYNTHESIS OF OXA-ADOHCY AND RELATED COMPOUNDS

Experimental Design and Synthesis

Since AdoHcy is a potent bio-feedback inhibitor of AdoMet dependent methyltransferases, it is interesting to synthesize compounds resembling AdoHcy to mimic AdoHcy, which may serve as methyltranferases inhibitors. For this purpose, oxa-AdoHcy in which the side chain sulfur was replaced by an oxygen was investigated. Two closely related compounds, the Ari and NpcA versions of oxa-AdoHcy (Ari-oxa-AdoHcy and NpcA-oxa-AdoHcy) were also in the scope of study. Based on chemistry developed in synthesis of sinefungin, a retrosynthetic analysis was established (Scheme 24).

Scheme 24. Retrosynthetic Analysis of Compounds 6, 7 and 8

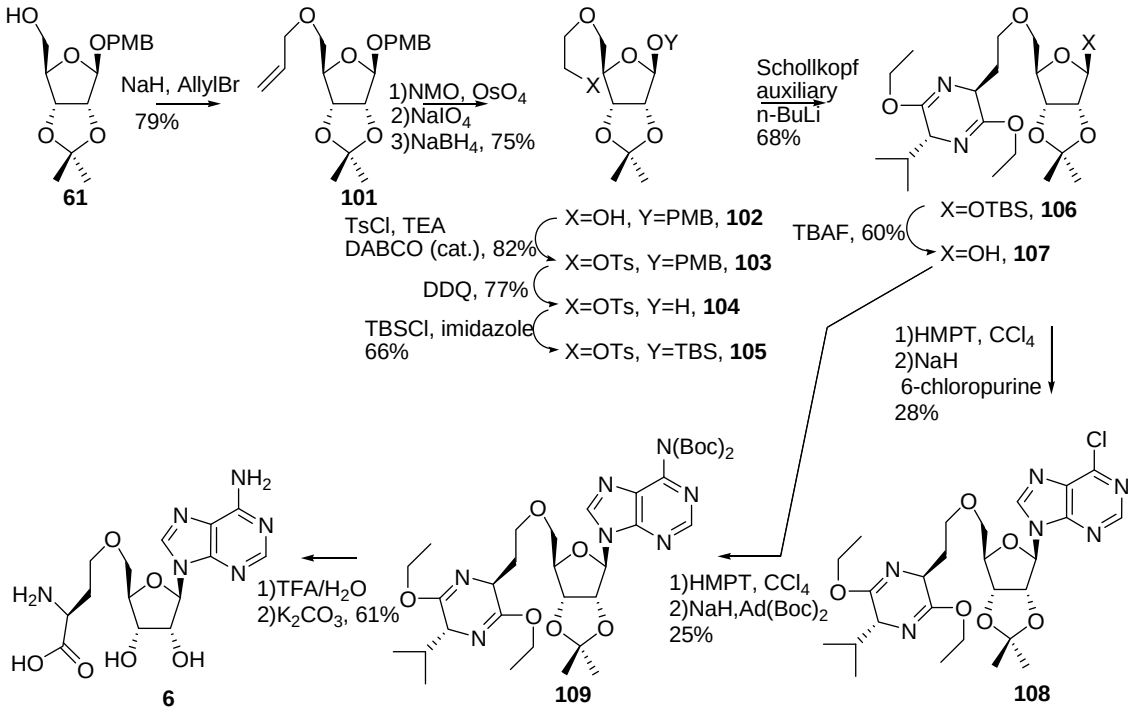


Synthesis of Oxa-AdoHcy

The synthesis of oxa-AdoHcy started from compound **61** (Scheme 25). Allylation of primary hydroxyl group of **61** afforded **101**. Double bond cleavage followed by reduction converted **101** into **102**. Compound **102** was tosylated to give **103**. Removal of the PMB group of **103** led to **104**. The anomeric hydroxyl of **104** was protected as a silyl ether to yield **105**, which was coupled with the Schöllkopf auxiliary to provide **106**. Desilylation of **106** afforded **107**. Installation of the 6-chloropurine was achieved by a

two-step one pot procedure which converted **107** into **108**. However, amination of **108** at elevated temperature gave intractable products. Thus, $Ad(Boc)_2$ was introduced as base moiety on **107** to give **109**. Global deprotection of **109** finished the synthesis of oxa-AdoHcy **6**.

Scheme 25. Synthesis of Compound 6

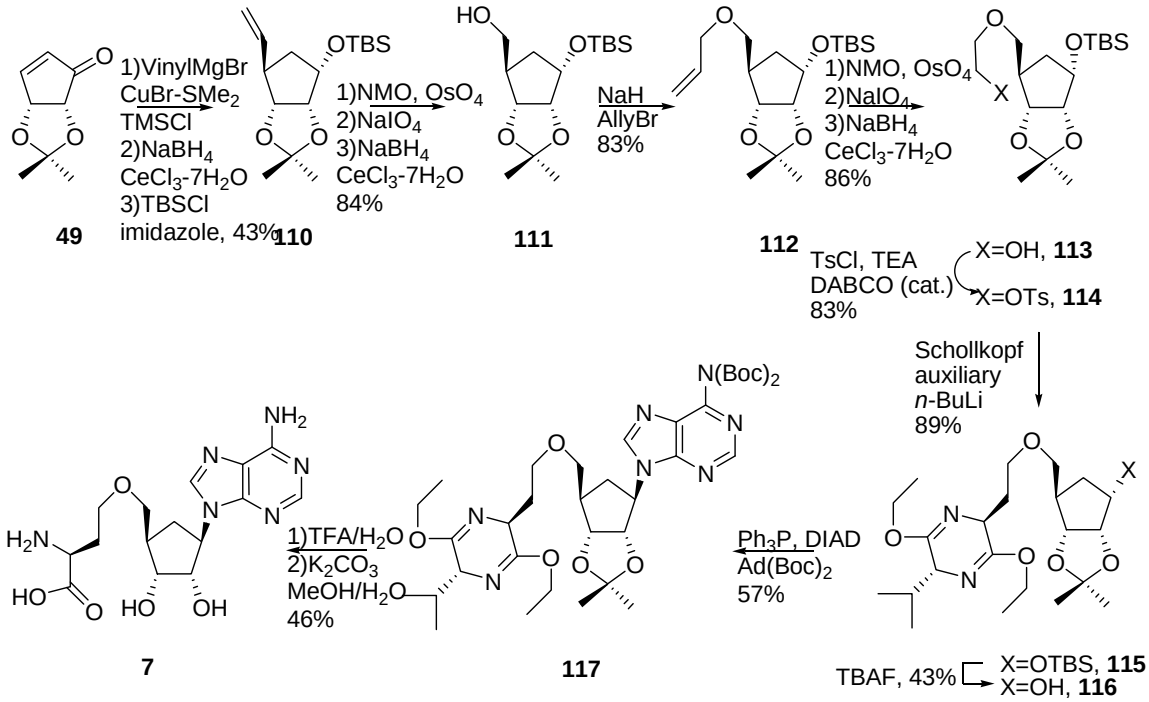


Synthesis of Ari-oxa-AdoHcy

The synthesis begins with **49**. After a Michael addition, a subsequent Luche reduction followed by protecting the hydroxyl as a silyl ether gave **110**. Oxidative cleavage of the double bond of **110** followed by reduction afforded **111**, which was allylated at the primary hydroxyl to provide **112**. Compound **112** was converted into **113**, which was transformed into tosylate **114**. Coupling of **114** with the Schöllkopf auxiliary gave **115**. Removal of the silyl protecting group of **115** afforded **116**. Installation of the base moiety

was achieved by a Mitsunobu reaction on **116** to yield **117**. Global deprotection of **117** gave **7**.

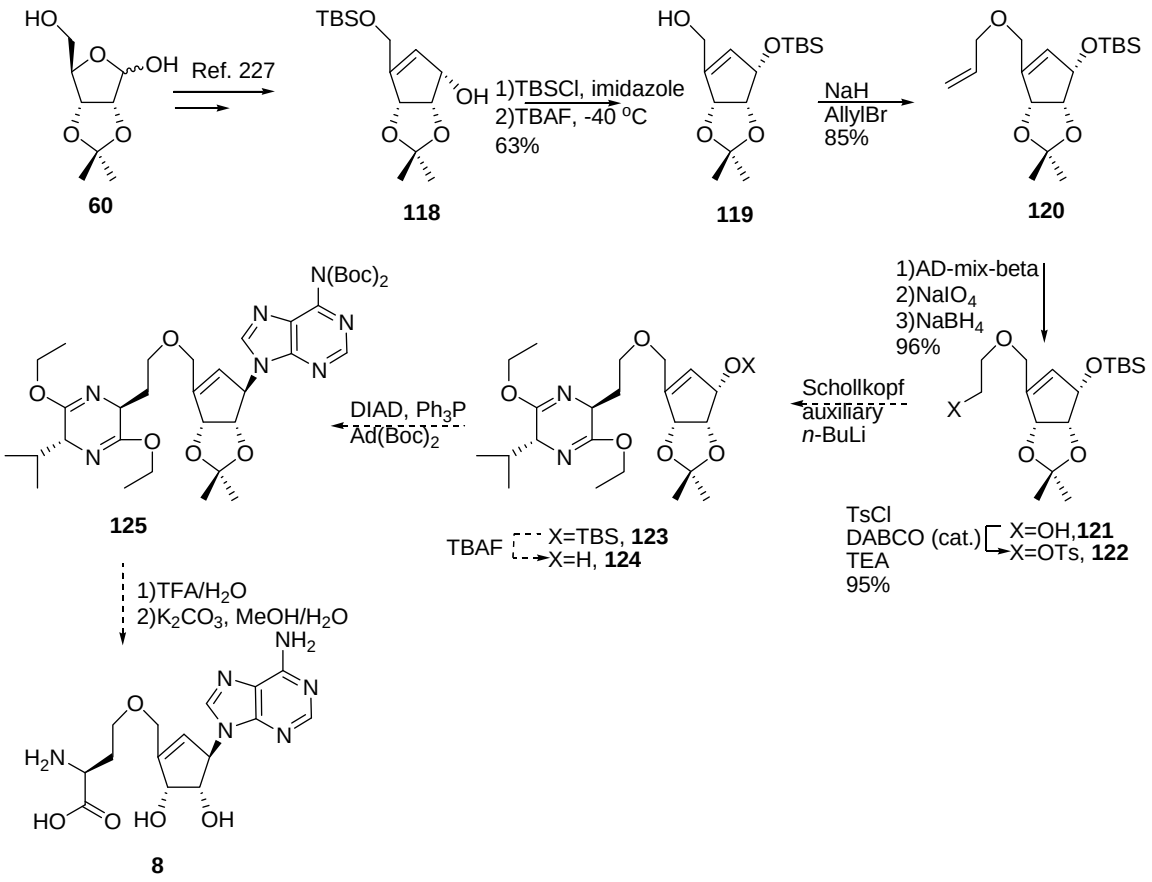
Scheme 26. Synthesis of Ari-oxa-AdoHcy



Attempted Synthesis of NpcA-oxa-AdoHcy

Starting from **60**, compound **118** was prepared according to the literature (Scheme 27).[227] Protection of the secondary hydroxyl as a TBS ether and selectively removal of the primary silyl protecting group afforded **119**. Allylation of **119** provided **120**, which was converted to a primary alcohol **121**. Tosylation of **121** gave **122**.

Scheme 27. Attempted Synthesis of Compound 8



BIOLOGICAL RESULTS

The synthesized compounds **1-4** were evaluated against a wide variety of viruses (Table 1) to determine their antiviral activity. The detailed results were shown in Tables 2-19.

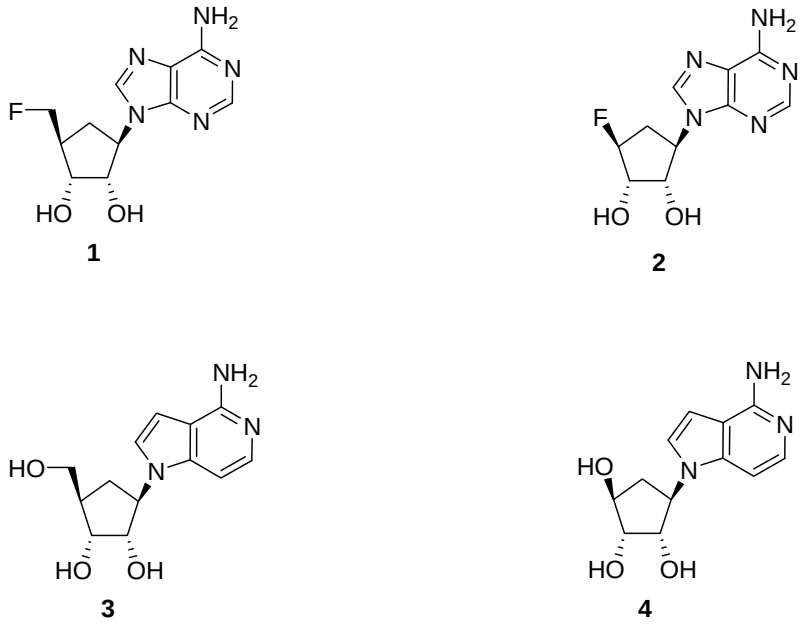


Figure 22. Compounds for Antiviral Evaluation

Table 1. Viruses Used for Bioassay

Virus Family	Individual Virus
Adenoviridae	Adenovirus
Arenaviridae	Pichinde Virus
Bunyaviridae	Punta Toro Virus
Coronaviridae	Human Coronavirus, Severe Acute Respiratory Syndrome (SARS) virus
Filoviridae	Ebola Virus
Flaviviridae	Hepatitis C Virus (HCV), West Nile Virus, Yellow Fever Virus
Hepadnaviridae	Hepatitis B Virus (HBV)
Herpesviridae	Epstein-Barr Virus (EBV), Human Cytomegalovirus (HCMV), Varicella-Zoster Virus (VZV), Herpes Simplex Virus (HSV)
Orthomyxoviridae	Influenza A Virus, Influenza B Virus
Paramyxoviridae	Parainfluenza Virus, Measles Virus, Respiratory Syncytial Virus (RSV)
Piconoviridae	Rhinovirus
Poxviridae	Cowpox Virus, Vaccinia Virus
Reoviridae	Reovirus
Rhabdoviridae	Vesicular Stomatitis Virus
Togaviridae	Venezuelan Equine Encephalitis Virus (VEE), Sindbis Virus

Table 2. Antiviral Activity Towards HCV [a]

Compound	Activity (% Inh Virus Control)	Cytotoxicity (% Cell Control)	SI
1	0.0	104.3	<1
2	0.0	109.8	<1
3	N.D.	N.D.	
4	N.D.	N.D.	

[a] Assay: HCV RNA replicon; Cell type: Huh7ET; Assay type: Single dose (primary); High test concentration: 20 μM.

N.D.: not determined

Table 3. Antiviral Activity Towards Influenza in MDCK Cell Cultures

Compound	Minimum cytotoxic concentration[a]	EC_{50}[b]					
		Influenza A H1N1 subtype		Influenza A H3N2 subtype		Influenza B	
		Visual CPE score	MTS	Visual CPE score	MTS	Visual CPE score	MTS
1	100 μM.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
2	100 μM.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
3	N.D.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
4	N.D.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.

[a] Minimum compound concentration that causes a microscopically detectable alteration of cell morphology

[b] 50% Effective concentration, or concentration producing 50% inhibition of virus-induced cytopathic effect, as determined by visual scoring of the CPE, or by measuring the cell viability with the colorimetric formazan-based MTS assay.

MDCK cells: Madin Darby canine kidney cells

N.A.: not active at the highest concentration tested, or at subtoxic concentrations.

Table 4. Anti-Feline Corona Virus (FIPV) Activity and Cytotoxicity in CRFK Cell Cultures

Compound	CC_{50}[a] (μM.)	EC_{50}[b] (μM.)
1	>100	>100
2	>100	>100
3	>100	>100
4	>100	>100

[a] 50% Cytotoxic concentration, as determined by measuring the cell viability with the colorimetric formazan-based MTS assay

[b] 50% Effective concentration, or concentration producing 50% inhibition of virus-induced cytopathic effect, as determined by visual scoring of the CPE, or by

measuring the cell viability with the colorimetric formazan-based MTS assay.

CRFK cells: Crandell-Rees Feline Kidney cells

Table 5. Activity and Cytotoxicity Towards Vesicular Stomatitis Virus, Coxsackie Virus B4 and Respiratory Syncytial Virus in HeLa Cell Cultures

Compound	Minimum cytotoxic concentration (μM)	EC_{50}(μM)		
		Vesicular stomatitis virus	Coxsackie virus B4	Respiratory syncytial virus
1	>100	100	>100	N.D.
2	>100	>100	>100	N.D.
3	>200	200	>200	>200
4	>200	>200	120	>200

Table 6. Activity and Cytotoxicity Towards Para-influenza 3 Virus, Reovirus-1, Sindbis Virus, Coxsackie Virus B4 and Punta Toro Virus in Vero Cell Cultures

Compound	Minimum cytotoxic concentration (μM)	EC_{50}(μM)				
		Para-influenza 3 Virus	Reovirus -1	Sindbis virus	Coxsackie virus B4	Punta toro virus
1	>100	>100	>100	>100	>100	>100
2	>100	>100	>100	>100	>100	>100
3	>200	>200	>200	>200	>200	>200
4	>200	>200	>200	>200	>200	>200

Table 7. Activity and Cytotoxicity Towards Herpes Simplex Virus-1 (KOS), Herpes Simplex Virus-2 (G), Vaccina Virus, Vesicular Stomatitis Virus, Herpes Simplex Virus-1 TK^-KOS ACV^+ in IL Cell Cultures

compound	Minimum cytotoxic concentration (μM)	EC_{50}(μM)				
		Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Vaccina virus	Vesicular stomatitis virus	Herpes simplex virus-1 TK^-KOS ACV^+
1	>100	>100	>100	>100	>100	>100
2	>100	>100	>100	>100	>100	>100
3	>200	>200	>200	>200	>200	>200
4	>200	>200	>200	>200	>200	>200

Table 8. Activity and Cytotoxicity Towards Cowpox and Vaccinia Viruses[a]

compound	virus	EC_{50}	EC_{90}	CC_{50}	SI	CDV EC_{50}	CDV EC_{90}
1	Cowpox	>300	>300	>300	0	7.3	58
	Vaccinia	>300	>300	>300	0	7.6	12
2	Cowpox	>300	>300	>300	0	7.3	58
	Vaccinia	>300	>300	>300	0	7.6	12.1
3	Cowpox	>300	>300	>300	0	N.D.	N.D.
	Vaccinia	>300	>300	>300	0	N.D.	N.D.
4	Cowpox	>300	>300	>300	0	N.D.	N.D.
	Vaccinia	>300	>300	>300	0	N.D.	N.D.

[a] Assay: CPE; Cell Line: HFF Cells; Drug Unit: μM

Table 9. Activity and Cytotoxicity Towards EBV[a]

Compound	EC_{50}	EC_{90}	CC_{50}	SI	ACV EC_{50}
1	3.3	14.4	24.1	6.5	2.4
2	17.5	>20	51.8	3	2.4
3	N.D.	N.D.	N.D.		
4	N.D.	N.D.	N.D.		

[a] Assay: DNA Hybridation; Cell Line: Akata Cells; Drug Unit: μM

Table 10. Activity and Cytotoxicity Towards West Nile Virus[a]

Compound	Assay	EC_{50}	IC_{50}	SI
1	Neutral Red	>100	>100	0
	Visual	>100	>100	0
2	Neutral Red	>100	>100	0
	Visual	>100	>100	0
3	Neutral Red	N.D.	N.D.	
	Visual	N.D.	N.D.	
4	Neutral Red	N.D.	N.D.	
	Visual	N.D.	N.D.	

[a] Vehicle: DMSO; Cell Line: Vero 76; Drug Unit: µg/mL; Virus Strain: New York Isolate

Table 11. Activity and Cytotoxicity Towards Parainfluenza Virus[a]

Compound	Assay	EC_{50}	IC_{50}	SI
1	Neutral Red	>100	>100	0
	Visual	>81	81	0
2	Neutral Red	>100	>100	0
	Visual	>100	>100	0
3	Neutral Red	>100	>100	0
	Visual	>100	>100	0
4	Neutral Red	>100	>100	0
	Visual	>100	>100	0

[a] Vehicle: DMSO; Cell Line: MA-104; Drug Unit: µg/mL; Virus Strain: 14702

Table 12. Activity and Cytotoxicity Towards Adenovirus[a]

Compound	Assay	EC_{50}	IC_{50}	SI
1	Neutral Red	>58	58	0
	Visual	>100	>100	0
2	Neutral Red	>100	>100	0
	Visual	>100	>100	0
3	Neutral Red	N.D.	N.D.	
	Visual	N.D.	N.D.	
4	Neutral Red	N.D.	N.D.	
	Visual	N.D.	N.D.	

[a] Vehicle: DMSO; Cell Line: A-549; Drug Unit: µg/mL; Virus Strain: 65089/Chicago

Table 13. Activity and Cytotoxicity Towards Measles[a]

Compound	Assay	EC_{50}	IC_{50}	SI
1	Neutral Red	2.8	>100	>35
	Visual	13	>100	>7.8
2	Neutral Red	1.2	21	18
	Visual	14	36	2.5
3	Neutral Red	N.D.	N.D.	
	Visual	N.D.	N.D.	
4	Neutral Red	N.D.	N.D.	
	Visual	N.D.	N.D.	

[a] Vehicle: DMSO; Cell Line: CV-1; Drug Unit: µg/mL; Virus Strain: MO6

Table 14. Activity and Cytotoxicity Towards Respiratory Syncytial A Virus[a]

Compound	Assay	EC_{50}	IC_{50}	SI
1	Neutral Red	>100	>100	0
	Visual	>100	>100	0
2	Neutral Red	>100	>100	0
	Visual	>100	>100	0
3	Neutral Red	>100	>100	0
	Visual	>100	>100	0
4	Neutral Red	>100	>100	0
	Visual	>100	>100	0

[a] Vehicle: DMSO; Cell Line: MA-104; Drug Unit: µg/mL; Virus Strain: A2

Table 15. Activity and Cytotoxicity Towards Rhinovirus[a]

Compound	Assay	EC_{50}	IC_{50}	SI
1	Neutral Red	>100	>100	0
	Visual	>100	>100	0
2	Neutral Red	>100	>100	0
	Visual	>100	>100	0
3	Neutral Red	N.D.	N.D.	
	Visual	N.D.	N.D.	
4	Neutral Red	N.D.	N.D.	
	Visual	N.D.	N.D.	

[a] Vehicle: DMSO; Cell Line: Hela Ohio-1; Drug Unit: µg/mL; Virus Strain: HGP

Table 16. Activity and Cytotoxicity Towards VZV[a]

Compound	EC_{50}	EC_{90}	CC_{50}	SI
1	N.D.	N.D.	N.D.	
2	N.D.	N.D.	N.D.	
3	>60	>60	214	<3.6
4	>300	>300	>300	0

[a] Assay: CPE; Cell Line: HFF Cells; Drug Unit: μM

Table 17. Activity and Cytotoxicity Towards HCMV[a]

Compound	EC_{50}	EC_{90}	CC_{50}	SI
1	N.D.	N.D.	N.D.	
2	N.D.	N.D.	N.D.	
3	>60	>60	202	<3.4
4	>60	>60	269	<4.5

[a] Assay: CPE; Cell Line: HFF Cells; Drug Unit: μM

Table 18. Activity and Cytotoxicity Towards HSV-1 and HSV-2 in HFF Cells[a]

Compound	EC_{50}		EC_{90}		CC_{50}		SI	
	HSV-1	HSV-2	HSV-1	HSV-2	HSV-1	HSV-2	HSV-1	HSV-2
1	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
2	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
3	>60	>60	>60	>60	227	227	<3.8	<3.8
4	>300	>300	>300	>300	>300	>300	0	0

[a] Assay: CPE; Cell Line: HFF Cells; Drug Unit: μM

Table 19. Activity and Cytotoxicity Towards Human Corona (SARS) Virus

Compound	EC_{50} (μM)	CC_{50} (μM)
1	N.D.	N.D.
2	N.D.	N.D.
3	>100	>100
4	>100	>100

Table 20. Activity and Cytotoxicity Towards HBV[a]

Compound	EC_{50}	EC_{90}	CC_{50}
1	N.D.	N.D.	N.D.
2	N.D.	N.D.	N.D.
3	>10	>10	>300
4	>10	>10	>300

[a] Assay: VIR; Drug Unit: μM

Compound **1** and **2** show moderate activity against measles virus. Against most of tested viruses, compounds **1**-**4** did not show any activity. The bioassay data for **5**, **6**, **7** and **8** will be forthcoming as part of future study in the Schneller group.

CONCLUSIONS

S-Adenosylmethionine (AdoMet)-dependent methylation reactions are essential for maturation of mRNA (including host and viral mRNA). These reactions are regulated by S-adenosylhomocysteine (AdoHcy), the product of AdoMet-dependent methylation, *via* a biofeedback inhibition mechanism. AdoHcy is "hydrolyzed" by AdoHcy hydrolase into adenosine and homocysteine. By inhibiting the AdoHcy hydrolase, the cellular AdoHcy level is elevated, which, in turn, inhibits the biomethylation, including 5′-capping of mRNA. Aristeromycin is a naturally occurring potent AdoHcy hydrolase inhibitor and shows significant antiviral activity. However, its clinical potential is limited by its toxicity, which is associated with phosphorylation at its 5′-hydroxyl.

To avoid or decrease the tendency of phosphorylation at the 5′-hydroxyl center while retaining the aristeromycin-based antiviral activity, two strategies were sought: (1) replacing the 5′-hydroxyl of aristreomycin (and the 4′-hydroxyl of noraristeromycin) with a substituent incapable of phosphorylation and (2) using a modified purine (3,7-dideazapurine) as the base moiety since some deazapurine nucleosides are not phosphorylated by the cellular kinases. Compounds **1** and **2** were designed according to the first strategy. Their synthesis was achieved by a convergent approach in which the desired carbocyclic pseudo-sugar moieties containing fluoride were coupled with the

purine precursors (6-chloropurine and 6-di-(*tert*-butoxylcarbonyl)aminopurine) under the Mitsunobu conditions. The synthetic design for compounds **3** and **4** occurred by the second strategy. The key steps in these synthesis were S_N2 reactions between the sodium salt of 3,7-dideaza-6-chloropurine in *N,N*-dimethylformamide (DMF) and the triflates (prepared *in situ*) of corresponding carbocyclic units.

Compounds **1** and **2** were evaluated against a variety of viruses. They showed moderate activity against measles, but lacked antiviral activity against the other viruses tested. No cytotoxicity was observed. This indicated that the replacement of the 5′-hydroxyl of aristeromycin and 4′-hydroxyl of 5'-noraristeromycin with fluoride abolish the undesired phosphorylation (reduced cytotoxicity) at the expense of losing antiviral activity. Thus, 5′-hydroxyl of aristeromycin and the 4′-hydroxyl of 5'-noraristeromycin are necessary for activity and, likely, the inhibition of AdoHcy hydrolase.

Compounds **3** and **4** exhibited no significant activity against all viruses tested. They also showed no cytotoxicty to host cells. This suggested that the 3,7-dideazapurine carbocyclic nucleosides were not inhibiting AdoHcy hydrolase.

An alternative strategy to aristeromycin analogs for the inhibition of biomethylations is to design AdoHcy analogs, since AdoHcy is a natural methyltransferases inhibitor. Sinefungin is a naturally occurring AdoHcy/AdoMet analog that shows significant biological activity, including antiviral, antimalarial, antifungal, antibacterial, and antitumor effects. However, the potential of sinefungin is limited by its toxicity. To explore structural variations and corresponding activity of AdoHcy/AdoMet analogs based on sinefungin, chemistry towards compounds **5**, **6**, **7** and **8** was investigated. A convenient, diverse and high yield strategy to these analogs was explored. In this

direction, (1) the stereochemistry at the 6′ position of sinefungin (**5**) was built by a Brown allylation procedure, (2) the terminal amino acid moieties of **5**-**8** were introduced through the Schöllkopf auxiliary and (3) the 6-di-(*tert*-butoxylcarbonyl)aminopurine served as the purine precursor for the synthesis of theses analogs.

EXPERIMENTAL

Materials and Methods

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR were performed on Bruker Avance 250 MHz or 400 MHz spectrometers. Two dimensional NMR experiments were conducted on the Bruker Avance 400 MHz spectrometer. NMR spectra were reported in δ relative to internal standard (TMS, 0.00) or solvent (DMSO-d_6, 2.50; D_2O, 4.87). The spin multiplicities are shown 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, GA. Reactions were monitored by silica thin layer chromatography (TLC, Whatman® TLC K6F plates). Flash columns were performed on silica (Silicycle® Siliaflash® F60) columns.

1-Methoxy-2,3-(cyclopentylidenedioxy)-4-hydroxymethyl Tetrahydrofuran (9). D-ribose (100g, 0.667 mol), cyclopentanone (200 mL), MeOH (300 mL) and trimethylorthoformate (200 mL) were added to a 1 L flask. H_2SO_4 (3.0 mL) was also added. 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 **9** as yellow oil (122 g, 79.7%). ^{1}H NMR (250 MHz, $CDCl_3$), δ 4.98 (s, 1H), 4.77 (d, J=6.0 Hz, 1H), 4.53 (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, J1=9.7 Hz, J2=3.5 Hz, 1H), 1.93 (m, 2H), 1.66 (m, 6H). ^{13}C NMR (62 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, 57.17; H, 7.99.

1-Methoxy-2,3-(cyclopentylidenedioxy)-4-iodomethyl Tetrahydrofuran (10). 9 (122 g, 0.529 mol) was dissolved in MeCN/toluene (1/1, 500 mL). Imidazole (60.0 g, 0.999 mol), triphenylphosphine (TPP) (188 g, 0.701 mol) was added. I_2 was added in portions until the solution turned black. The solution was stirred at room temperature for 2 hours. H_2O (300 mL), sodium thiosulfate (10 g) were added. The organic layer was separated, dried over sodium sulfate, concentrated, and purified with column chromatography (Hex/EtOAc=5/1). The product **10** was isolated as colorless oil (161 g, 89.6%). ^{1}H NMR (250 MHz, $CDCl_3$), δ 5.06 (s, 1H), 4.72 (d, J=0.7Hz, 1H), 4.69 (d, J=0.7 Hz, 1H), 4.44 (m, 1H), 3.37 (s, 3H), 3.28 (m, 1H), 3.16 (m, 1H), 1.90 (m, 2H), 1.67 (m, 6H). ^{13}C NMR (62 MHz, $CDCl_3$), δ 122.1, 109.4, 87.0, 85.1, 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, 39.07; H, 5.05.

2,3-(Cyclopentylidenedioxy)-pent-4-enal (11). 10 (24.8 g, 72.9 mmol) was dissolved in ether. *n*-BuLi (38.0 mL, 2.5M in hexanes, 95.0 mmol) was added in portions over 15 minutes at –78 ^{o}C. The solution was stirred at this temperature for 2 hours. NH_4Cl (10 g) was added after the reaction mixture was warmed to –40 ^{o}C. H_2O (100 mL) was added. The mixture was extracted with ether (3×100 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure to give crude **11** with solvent (14.0 g, "105%"), which was used immediately without further purification. ^{1}H NMR (250 MHz, $CDCl_3$), δ 9.54 (d, J=3.2 Hz, 1H), 5.7 (m, 1H), 5.3-5.5 (m, 2H), 4.75 (m, 1H),

4.34 (m, 1H), 2.09 (m, 2H), 1.75 (m, 6H). ^{13}C NMR (62 MHz, $CDCl_3$), δ 200.9, 131.3, 121.2, 120.0, 81.9, 79.4, 36.9, 36.8, 24.1, 23.3.

2,3-(Cyclopentylidenedioxy)-hepta-1,6-dien-3-ol (12). 11 (14.0 g, crude product) was dissolved in DCM. At –78 ^{o}C, vinylmagnesium bromide (120 mL, 1M in THF, 120 mmol) was added. The mixture was warmed to 0 ^{o}C. Saturated NH_4Cl (40 mL) was added. The organic layer was separated, dried over sodium sulfate, and concentrated using a rotavapor (bath temperature 10 ^{o}C). The residue was purified with silica gel column (Hex/EtOAc=5/1) to give **12** as colorless oil (mixture of two diastereomers, 12.9 g, 84.8% from **10**). ^{1}H NMR (250 MHz, $CDCl_3$), δ 6.13 (m, 1H), 5.79 (m, 1H), 5.20-5.59 (m, 4H), 4.48-4.62 (m, 1H), 4.2 (m, 1H), 4.02 (m, 1H), 2.01 (m, 2H), 1.65 (m, 6H). ^{13}C NMR (62 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.

2,3-(Cyclopentylidenedioxy)-cyclopent-2-enone (14). 12 (1.4 g, 6.6 mmol) was dissolved in dry DCM (100 mL). N_2 was bubbled to remove O_2 for 10 minutes. Grubbs catalyst (5.3 mg, 0.0060 mmol) was added. The solution was stirred at room temperature for 12 hours. Dimethyl sulfoxide (DMSO) (5.0 mL) was added. Di*iso*propylethylamine (DIPEA) (2.3 mL, 13.3 mmol) was added. The solution was cooled to 0 ^{o}C. SO_3-pyrridine complex (2.2 g, 13 mmol) was added portionwise. The mixture was warmed to room temperature, stirred 2h. Water (20.0 mL) was added. The organic layer was separated, dried over Na_2SO_4, concentrated, and purified with column chromatography (Hexanes/EtOAc=2/1) to give **14** as white needle-like solid (0.92 g, 77%), m.p.: 54-55 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.63 (dd, J1= 4.8 Hz, J2= 2.4 Hz, 1H), 6.28 (d, J= 6.0 Hz, 1H), 5.23 (dd, J1= 5.2 Hz, J2= 2.0 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, 66.99; H, 7.08.

2,3-(Cyclopentylidenedioxy)-4-vinyl-cyclopentanol (16). To a suspension of $CuBr{\cdot}SMe_2$ (1.59 g, 7.73 mmol) in THF was added vinylmagnium bromide (155.0 mL, 0.155 mol) at –78 ^{o}C. A solution of **14** (14.23 g, 78.97 mmol), trimethylsilyl chloride (TMSCl) (19.6 mL, 0.155 mol), hexamethylphosphoramide (HMPA) (13.0 mL, 77.7 mmol) in THF was added dropwise at –78 ^{o}C. The mixture was stirred at –78 ^{o}C for 2 hours, and then warmed slowly to room temperature. The reaction was quenched with saturated NH_4Cl solution (100 mL). After the removal of solvent, the mixture was extracted with EtOAc (3×200 mL). The combined organic layer was dried over sodium sulfate, concentrated to give brown oil. THF (100 mL) was added. At 0 ^{o}C, $LiAlH_4$ (4.60 g, 121 mmol) was added slowly. The mixture was stirred at room temperature overnight. The reaction was quenched with water. The mixture was filtered through celite, and then extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated, and purified by silica column chromatography (Hexanes:EtOAc=10:1 to 2:1) to isolate **16** as a colorless oil (10.60 g, 63.84%). ^{1}H NMR (400 MHz, CDCl3), δ 5.72 (m, 1H), 5.04-5.10 (m, 2H), 4.39 (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, $CDCl_3$), δ138.2, 121.6, 115.4, 84.4, 79.0, 71.3, 44.3, 36.3, 35.7, 35.5, 24.2, 23.0. Calcd HRMS for $C_{12}H_{18}O_3$: 210.1253; Found: 210.1256.

6-Chloro-9-(2′,3′-(cyclopentylidenedioxy)-4′-vinyl-cyclopentyl)-purine (17). 16 (10.9 g, 51.8 mmol) was dissolved in THF (100 mL). 6-Chloropurine (10.0 g, 64.7 mmol),

(Ph_3)P (17.0g, 64.8 mmol) was added. The solution was cooled to –40 ^oC. Di*iso*propyl azodicarboxylate (DIAD) (12.5 mL, 64.5 mmol) was added dropwise. The mixture was warmed to room temperature, then heated to 60 ^oC for 24 hours. The solvent was removed under reduced pressure. The residue was purified by silica column (Hex:EtOAc=5:1 to 2:1) to give **17** as organce oil**,** contaminated with diisopropyl hydrazine-1,2-dicarboxylate (10.4 g, 57.9%). The mixture was used in next step without further purification.

6-Chloro-9-(2′,3′-(cyclopentylidenedioxy)-4′-hydroxymethyl-cyclopentyl)-purine (19). 17 (0.73 g, 2.1 mmol) was dissolved in MeOH (50 mL). Water (0.5 mL) was added. $NaIO_4$ (0.99 g, 4.6 mmol) was added. The mixture was cooled to 0 ^oC. OsO_4 (10 mg, 0.040 mmol, 2% mol) was added. The mixture was stirred at 0 ^oC for 2 hours. The mixture was filtered. MeOH was removed by reduced pressure. The residue was extracted with DCM (3×50 mL). The organic layer was washed with brine, dried over sodium sulfate, concentrated. The residue was dissolved in methanol (20 mL). $NaBH_4$ (0.10 g, 2.6 mmol) was added portionwise at 0 ^oC. The mixture as stirred at 0 ^oC 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, concentrated. The residue was purified by silica column (Hex:EtOAc=1:1 to 1:10) to provide **19** as a colorless oil (0.30 g, 41%).^1H NMR (400 MHz, $CDCl_3$), δ 8.74 (s, 1H), 8.28 (s, 1H), 4.99 (m, 1H), 4.91 (m, 1H), 4.66 (m, 1H), 3.87 (m, 2H), 2.93 (t, J=4.8 Hz, 1H), 2.44-2.64 (m, 3H), 2.03 (m, 2H), 1.70 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 151.8, 151.7, 151.4, 144.9, 132.4, 123.4, 83.8, 82.0, 63.6, 62.7, 45.0, 36.8, 36.6, 33.3,

23.8, 23.2. Calcd HRMS for $C_{16}H_{19}ClN_4O_3$ (-cyclopentanone):284.0677, Foud: 284.0667.

2′,3′-(Cyclopentylidenedioxy)-4′-vinylcyclopentyl 4-Methoxybenzyl Ether (21). **16** (0.70 g, 3.32 mmol) was dissolved in dry DMF (50 mL). The solution was cooled to 0 ^oC. NaH (147 mg, 60% in mineral oil, 3.67 mmol) was added in one portion. The solution was stirred for 30 minutes. *para*-Methoxybenzyl chloride (PMBCl) (0.54 mL, 4.0 mmol) was added at 0 ^oC in one portion. The solution was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure. Saturated NH_4Cl 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 (Hex:EtOAc=20:1) to provide **21** as a colorless oil (0.90g, 81%). ^1H NMR (400 MHz, $CDCl_3$), δ 7.30 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 5.63-5.72 (m, 1H), 4.97-5.01 (m, 2H), 4.51-4.63 (m, 2H), 4.43-4.46 (m, 2H), 4.31 (d, J=5.6 Hz, 1H), 3.80 (s, 3H), 3.76-3.79 (m, 1H) 2.66 (m, 1H), 2.07-2.10 (m, 3H), 1.90-1.93 (m, 1H), 1.78-1.81 (m, 1H), 1.70 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 159.2, 138.6, 130.5, 129.5, 120.7, 114.8, 113.7, 83.7, 78.2, 77.6, 71.4, 55.2, 43.9, 35.5, 35.3, 31.8, 24.0, 23.0. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93; Found: C, 72.37; H, 7.87.

2′,3′-(Cyclopentylidenedioxy)-4′-hydroxymethylcyclopentyl 4-Methoxybenzyl Ether (22). **21** (0.90 g, 2.7 mmol) was dissolved in MeOH (50 mL), and cooled to 0 ^oC. Water (5 mL) was added. $NaIO_4$ (1.45 g, 6.81 mmol) was added. OsO_4 (20 mg) was added. The solution was stirred at 0 ^oC for 2 hours. The mixture was filtered through Celite. The solvent was removed under reduced pressure. The residue was extracted with DCM (3×50 mL). The combined organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was dissolved in MeOH (50 mL), cooled to 0 ^oC.

$NaBH_4$ (0.20 g, 5.4 mmol) was added in portionwise. The mixture was stirred for 2 hours. Saturated NH_4Cl solution (30 mL) was added. MeOH was removed under reduced pressure. The residue was extracted with EtOAc (3×50 mL). The combined organic layer was dried over sodium sulfate, concentrated and purified by silica gel column (Hex:EtOAc=3:1) to give **22** as colorless oil (0.49 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.30 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 4.52-4.63 (m, 2H), 4.43-4.45 (m, 1H), 4.36 (m, 1H), 3.86 (m, 1H), 3.80 (s, 3H), 3.49-3.52 (m, 1H), 3.41-3.45 (m, 1H), 2.17 (m, 1H), 2.10 (m, 2H), 2.04 (m, 1H), 1.70 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 159.2, 130.5, 129.4, 120.9, 113.7, 81.6, 79.0, 77.9, 71.4, 64.3, 55.2, 44.2, 35.7, 35.5, 30.7, 24.01, 23.0. Calcd HRMS for $C_{19}H_{26}O_5$: 334.1780, Found: 334.1777.

2′,3′-(Cyclopentylidenedioxy)-4′-fluoromethyl-cyclopentyl 4-Methoxybenzyl Ether (23). 22 (0.35 g, 1.0 mmol) was dissolved in dry DCM (20 mL), and cooled to –78 ^{o}C. Pyridine (0.17 mL, 2.1 mmol), (Diethylamino)sulfur trifluoride (DAST) (0.20 mL, 1.5 mmol) was added. The solution was warmed to room temperature, and then refluxed under protection of N_2 for 12 h. the reaction was quenched with saturated Na_2CO_3 solution (20 mL). The organic layer was separated, washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel column (Hex:EtOAc=10:1) to provide **23** as a colorless oil (0.27 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.30 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 4.51-4.63 (m, 2H), 4.42-4.46 (m, 1.5H), 4.39 (m, 1H), 4.30-4.34 (m, 1H), 4.19-4.22 (m, 0.5H), 3.80-3.86 (m, 1H), 3.80 (s, 3H), 2.15 (dm, J=10 Hz, 1H), 2.05-2.20 (m, 2H), 1.93 (m, 1H), 1.74-1.76 (m, 1H), 1.70 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 159.2, 130.4, 129.5, 121.1, 113.7, 85.5 (d, J=168Hz), 81.2 (d, J=6Hz), 79.1, 78.0, 79.0, 71.5, 55.2, 42.6 (d, J=19 Hz), 35.6 (d, J=15 Hz), 30.8, 24.0, 23.0. Calcd

HRMS for $C_{19}H_{25}FO_4$: 336.1744; Found: 336.1737.

2,3-(Cyclopentylidenedioxy)-4-fluoromethyl-cyclopentanol (24). 23 (0.78 g, 2.3 mmol) was dissolved in 19:1 DCM/H_2O (50 mL). DDQ (0.63 g, 2.8 mmol) was added in one portion. The mixture was stirred at room temperature for 2 hours. Saturated Na_2CO_3 solution (30 mL) was added. The organic layer was separated, washed with saturated Na_2CO_3 solution (30 mL), brine (30 mL), dried over sodium sulfate, concentrated and purified by silica gel column (Hex:EtOAc=5:1) to provide **24** as a colorless oil (0.31 g, 60%). ^{1}H NMR (250 MHz, $CDCl_3$), δ 4.11-4.69 (m, 5H), 2.43-2.46 (m, 2H), 2.30-2.40 (m, 1H), 1.85-2.02 (m, 3H), 1.65-1.75 (m, 6H). ^{13}C NMR (62 MHz, $CDCl_3$) δ 121.9, 84.9 (d, J=160 Hz), 81.9 (d, J=4.8 Hz), 79.6, 71.3 (d, J=1.8 Hz), 42.6 (d, J=17.4 Hz), 35.5 (d, J=10.8 Hz), 34.8, 34.7, 23.9, 22.8. Anal. Calcd for $C_{11}H_{17}FO_3$: C, 61.10; H, 7.92; Found: C, 60.94; H, 8.00.

5′-Fluoro-5′-deoxy aristeromycin (1). **24** (0.14 g, 0.65 mmol) was dissolved in dry THF (50 mL), TPP (0.34 g, 1.3 mmol), 6-di(*tert*-butoxylcarbonyl)aminopurine ($Ad(Boc)_2$)(0.26 g, 0.78 mmol) was added. The solution was cooled to 0 ^{o}C, DIAD (0.20 mL, 0.98 mmol) was added in one portion. The solution was warmed to room temperature and stirred 5 hours. The solvent was removed under reduced pressure, the residue was purified by silica gel column (Hex:EtOAc=2:1) to give intermediate **25** as an orange oil, contaminated with diisopropyl hydrazine-1,2-dicarboxylate (from DIAD). Without further purification, **25** was dissolved in 3N HCl MeOH solution, stirred at 50 ^{o}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 (EtOAc:MeOH:$NH_3 \cdot H_2O$=4:1:0.3) to provide **1** as a

white solid (0.10 g, 58%), mp=168-169 ^{o}C. ^{1}H NMR (400 MHz, DMSO), δ 8.19 (s, 1H), 8.12 (s, 1H), 7.20 (s, 2H), 5.06 (d, J=6.0 Hz, 1H), 4.91 (d, J=4.0 Hz, 1H), 4.70 (m, 1H), 4.58 (m, 1H), 4.45 (m, 1H),4.35 (m, 1H), 3.89 (m, 1H), 2.27 (m, 2H), 1.80 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 156.0, 152.1, 149.6, 140.1, 119.3, 84.55(d, J=165 Hz), 74.2, 70.7 (d, J=5.0 Hz), 59.1, 43.4 (d, J=18.0 Hz), 27.8 (d, J=6.0 Hz). Anal. Calcd for $C_{11}H_{14}FN_5O_2$ (+0.2H_2O): C, 48.77; H, 5.35; N, 25.85; Found: C, 48.71; H, 5.47; N, 25.96. Calcd mass for $C_{11}H_{14}FN_5O_2$: 267.1132; Found: 267.1131

(1*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)cyclopent-2-enyl Acetate (27). **26** (5.0 g, 0.035 mol) was dissolved in dry DCM (60 mL). 4-(Dimethylamino)pyridine (DMAP) (20 mg) was added. The solution was treated with imidazole (5.9 g, 0.087 mol), and *tert*-butyldimethylsilyl chloride (TBSCl) (6.4 g, 0.042 mol) at 0 ^{o}C. The solution was then warmed to room temperature and stirred for 2 hours. Water (20 mL) was added to quench the reaction. The organic layer was separated, washed with brine, dried over sodium sulfate, concentrated under reduced pressure. The residue was purified by silica column (Hexanes/EtOAc=15:1) to give **27** as a colorless oil (7.3 g, 80%). The NMR spectra are consistent with the literature.[228]

(3*aS*,4*R*,6*S*,6*aS*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl Acetate (28). 27 (7.0 g, 27 mmol) was dissolved in THF (50 mL). 4-Methylmorpholine *N*-oxide (NMO) (8.8 mL, 50% water solution, 42 mmol) was added. The solution was cooled to 0 ^{o}C. OsO_4 (20 mg, 0.078 mmol, 0.28% moles) was added. The mixture was warmed to room temperature and stirred overnight. Sodium thiosulfate (2.2 g, 14 mmol) was added and stirred 30 minutes. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc, dried over sodium sulfate,

and filtered through a short silica column (5 cm). The filtrate was concentrated. The resulting oil was dissolved in dry acetone (100 mL). 2,2-dimethoxypropane (30 mL) was added. *p*-Toluenesulfonic acid monohydrate (100 mg) was added. The solution was stirred at room temperature overnight. Ammonium hydroxide (29.6%, 1 mL) was added. The solution was dried over sodium sulfate and concentrated. The residue was purified by silica column (hexanes/EtOAc=10:1) to provide **28** as a colorless oil (8.3 g, 85%). The NMR spectra are consistent with literature.[229]

(3*aS*,4*R*,6*S*,6*aS*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-ol (29). 28 (8.3 g, 25 mmol) was dissolved in methanol (200 mL) in a high pressure reaction vessel. The solution was cooled to 0 ^{o}C and saturated with ammonia. The reaction vessel was sealed and warmed to room temperature overnight. The solvent was removed under reduced pressure. The residue was purified by silica column (hexanes/EtOAc=5:1) to give **29** as a colorless oil (5.0 g, 90%). The NMR spectra were consistent with literature.[229]

(3*aR*,6*S*,6*aS*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4(5H)-one (30). 29 (1.0 g, 3.5mmol) was dissolved in dry DCM (20 mL). PCC (1.6 g, 6.9 mmol) was added. The solution was stirred at room temperature for 3 hours. The solution was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica column (hexanes/EtOAc=7:1) to give **30** as a colorless oil (0.85 g, 85%). The NMR spectra were consistent with literature.[229]

(1*S*,2*S*,3*S*,4*S*)-4-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-*iso*propylidenecyclopentane-1,2,3,4-tetrol (31). To a solution of **30** (0.35 g, 1.2 mmol) in MeOH (10 mL) was added $CeCl_3 \cdot 7H_2O$ (0.45 g,

1.2 mmol). The mixture was cooled to 0 ^{o}C. $NaBH_4$ (60.0 mg, 1.58 mmol) was added portion-wise. The mixture was stirred for 30 minutes at 0 ^{o}C, then warmed to room temperature, stirred for 1 hour. The reaction was quenched with saturated NH_4Cl solution (5 mL). The solvent was removed under reduced pressure. The residue was poured to water and extracted with EtOAc (3×10 mL). The combined organic layer was dried over sodium sulfate, and concentrated. The residue was purified by silica gel column (EtOAc/Hexanes=3:1) to produce **31** as a colorless oil (0.34 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ4 .56 (t, J= 5.4 Hz,1H), 4.34-4.26 (m, 2H), 4.01 (dd, J1=3.5 Hz, J2=0.4 Hz, 1H), 2.25 (d, J=10.4 Hz, 1H), 1.89-1.93 (m, 1H), 1.68-1.75(m, 1H), 1.46 (s, 3H), 1.34 (s, 3H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ111.3, 85.8, 78.6, 73.4, 72.0, 39.3, 26.1, 25.9, 24.4, 18.1, -4.6, -4.7. Anal. Calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78; Found: C, 58.34; H, 9.85.

tert*-Butyl((3*aS*,4*S*,6*S*,6*aS*)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydro-3*a ***H*-cyclopenta[*d*][1,3]dioxol-4-yloxy)dimethylsilane (32). 31** (7.56 g, 26.2 mmol) was dissolved in dry DMF (100 mL). The solution was cooled to 0 ^{o}C, NaH (1.26 g, 60.0% in mineral oil, 31.4 mmol) was added portionwise. The solution was stirred at 0 ^{o}C for 30 minutes. PMBCl (4.30 mL, 31.4 mmol) was added in one portion. The solution was warmed to room temperature, stirred for 3 hours. The solvent was removed under reduced pressure. The residue was quenched with water, and extracted by EtOAc. The organic layer was dried over sodium sulfate, concentrated, and purified with a silica column (Hex: EtOAc=10:1) to provide **32** as a colorless oil (9.00 g, 84.1%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.29 (d, J=8.4 Hz, 2H), 6.87 (d, J=8.4 Hz, 2H), 4.61 (m, 1H), 4.45-4.58 (m, 2H), 4.25 (dd, J1=5.6 Hz, J2=1.6 Hz, 1H), 4.02-4.05 (m, 1H), 3.94 (d, J=4.0 Hz, 1H),

3.79 (s, 3H), 1.90-1.94 (m, 1H), 1.75-1.76 (m, 1H), 1.48 (s, 3H), 1.30 (s, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 159.2, 130.4, 129.7, 113.7, 110.9, 85.7, 77.7, 77.5, 73.4, 71.5, 55.2, 35.7, 26.1, 25.7, 24.0, 17.9, -4.8. Anal. Calcd for $C_{22}H_{36}O_5Si$: C, 64.67; H, 8.88; Found: C, 64.99; H, 8.64.

(3*aR*,4*S*,6*S*,6*aS*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-ol (33). 32 (9.00 g, 22.0 mmol) was dissolve in THF (100mL). Tetrabutylammonium fluoride (TBAF) (33.0 mL, 1.0M in THF, 33.0 mmol) was added. The mixture was stirred at room temperature for one hour. The mixture was quenched with water, extracted with EtOAc (3×300 mL). Combined organic layer was dried over sodium sulfate, concentrated, and purified with a silica column (Hex:EtOAc=5:1 to 1:1) to give **33** as a colorless oil (5.80 g, 89.6%).^{1}H NMR (400 MHz, $CDCl_3$), δ 7.31 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 4.52-4.66 (m, 3H), 4.32 (dd, J1=5.6 Hz, J2=1.2 Hz, 1H), 4.04-4.09 (m, 2H), 3.80 (s, 3H), 2.00-2.07(m, 1H), 1.83-1.88 (m, 1H), 1.58 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 171.4, 159.4, 130.5, 129.7, 113.9, 111.3, 85.5, 77.9, 73.4, 71.7, 55.4, 35.8, 26.3, 24.2. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53; Found: C, 65.03; H, 7.62.

(3*aS*,6*S*,6*aS*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4(5*H*)-one (34). 33 (5.80 g, 19.7 mmol) was dissolved in dry DCM (200 mL). DMSO (10 mL), *N*,*N*-Di*iso*propylethylamine (DIPEA) (6.95 mL, 39.4 mmol) was added. The solution was cooled to 0 ^{o}C. SO_3·Py complex (6.25 g, 39.4 mmol) was added portionwise. The solution was stirred at 0 ^{o}C for 1 hour. The mixture was quenched with ice cold water (200 mL). The organic layer was separated, washed with saturated $NaHCO_3$ and brine, and concentrated. the residue was purified by silica gel column (Hex:

EtOAc=5:1 to 1:1) to give **34** as a colorless oil (4.71 g, 81.8%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.31 (d, J=8.8 Hz, 2H), 6.89 (d, J=8.8 Hz, 2H), 4.80 (t, J=4.2 Hz, 1H), 4.60-4.68 (m, 2H), 4.18 (dt, J1=4.8 Hz, J2=1.2 Hz, 1H), 4.05-4.11 (m, 1H), 3.81(s, 3H), 2.68-2.76 (m, 1H), 2.47-2.53 (m, 1H), 1.48 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 211.0, 159.6, 129.7, 129.2, 113.9, 113.5, 80.5, 77.6, 71.4, 70.0, 55.3, 39.8, 26.9, 25.2. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.60; H, 6.91.

(3*aR*,4*R*,6*S*,6*aS*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydro-3*aH*-cyclope nta[*d*][1,3]dioxol-4-ol (35). 34 (0.27 g, 0.92 mmol) was dissolved in dry THF (20 mL). $LiAlH_4$ (52.3 mg, 1.38 mmol) was added portionwise at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 3 hours. The mixture was quenched with water, and filtered through celite. The filtrate was extracted with EtOAc (3×50 mL). The combined organic layer was dried over sodium sulfate and concentrated to give **35** as colorless oil (0.22 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.28 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 4.52-4.59 (m, 3H), 4.40 (t, J=5.6 Hz, 1H), 3.80 (s, 3H), 3.69-3.78 (m, 1H), 3.45-3.51 (m, 1H), 2.41 (d, J=10.8 Hz, 1H), 2.10-2.15(m, 1H), 1.72-1.80 (m, 1H), 1.56 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 159.5, 130.1, 129.7, 114.0, 111.5, 78.4, 78.0, 73.7, 71.3, 68.5, 55.4, 34.7, 25.9, 24.4. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53; Found: C, 65.13; H, 7.53.

(3*aS*,4*S*,6*S*,6*aS*)-4-Fluoro-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydro-3*aH* -cyclopenta[*d*][1,3]dioxole (36). **35** (4.70 g, 15.9 mmol) was dissolved in dry DCM (100 mL). Pyridine (2.5 mL, 31 mmol) was added at 0 ^{o}C. DAST (4.1 mL, 31 mmol) was added through a syringe at 0 ^{o}C. The mixture was warmed to room temperature, then refluxed 2 days under protection of nitrogen. The mixture was quenched with saturated $NaHCO_3$ solution (100 mL). The organic layer was separated, dried over sodium sulfate,

concentrated, and purified with a silica column (Hex: EtOAc=5:1) to give **36** as a colorless oil (3.27 g, 69.4%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.3 (d, J=8.8 Hz, 2H), 6.88 (d, J=8.8 Hz, 2H), 4.47-4.81 (m, 5H), 4.00-4.05 (m, 1H), 3.81 (s, 3H), 2.04-2.14 (m, 2H), 1.48 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 159.6, 130.2, 129.8, 114.1, 111.8, 94.4 (d, J=174.5 Hz), 82.82(d, J=33.4 Hz), 77.8, 77.1, 71.9, 55.5, 33.7 (d, J=20.1 Hz), 26.3, 24.2. Anal. Calcd for $C_{16}H_{21}FO_4$: C, 64.85; H, 7.14. Found: C, 64.72; H, 7.19.

(3*aS*,4*S*,6*S*,6*aS*)-6-Fluoro-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-ol (37). 36 (0.98 g, 3.3 mmol) was dissolved in DCM/H_2O mixture (100 mL DCM, 5 mL H_2O). DDQ (0.90 g, 4.0 mmol) was added. The mixture was stirred at room temperature for 1 hour. Saturated $NaHCO_3$ (20 mL) was added to quench the reaction. The organic layer was separated, washed with brine, dried over sodium sulfate, concentrated, and purified by silica chromatography (Hex:EtOAc=5:1) to give **37** as white solid (0.49 g, 86%). Mp=51~52^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$/D_2O), δ 4.68 (dd, J1=46.0 Hz, J2=3.6 Hz, 1H), 4.56-4.60 (m, 2H), 4.26-4.32 (m, 1H), 2.26-2.32 (td, J1=15.2 Hz, J2= 5.6Hz, 1H), 1.83 (dddd, J1=44.4 Hz, J2=14.4 Hz, J3=10.8 Hz, J4=3.6 Hz, 1H), 1.47 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 111.7, 93.8 (d, J=172.3 Hz), 82.4 (d, J=33.2 Hz), 78.2, 71.4, 36.8 (d, J=20.8 Hz), 25.9, 24.1.

6-Chloro-9-((3*aS*,4*R*,6*S*,6*aS*)-6-fluoro-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*]-[1,3]dioxol-4-yl)-9*H*-purine (38). 37 (0.73 g, 4.1 mmol) was dissolved in dry THF (50 mL). TPP (1.30 g, 4.96 mmol), 6-chloropurine (0.76 g, 4.9 mmol) were added. The mixture was cooled to 0 ^{o}C. DIAD (0.95 mL, 4.9 mmol) was added. The mixture was warmed to room temperature, then heated and stirred at 50 ^{o}C overnight. The solvent was removed under reduced pressure. The residue was purified by silica column to give **38**

with di*iso*propyl hydrazine-1,2-dicarboxylate (0.40 g, 30%). This product was used directly without further purification.

9-((3*aS*,4*R*,6*S*,6*aS*)-6-Fluoro-2,2-dimethyl-tetrahydro-3aH-cyclopenta[*d*][1,3]dioxol-4-yl)-9*H*-purin-6-amine (39). In a higher pressure reaction vessel, **38** (0.50 g, 1.6 mmol) was dissolved in dry MeOH (100 mL). The solution was cooled to 0 ^{o}C, and saturated with NH_3. The solution was sealed, and heated to 120 ^{o}C overnight. The solvent was removed under reduced pressure, and the residue was purified by silica column to give **39** as white solid (0.37 g, 83%).mp=158-160 ^{o}C. ^{1}H NMR (250 MHz, DMSO), δ 8.16 (s, 1H), 8.10 (s, 1H), 7.25(br, 2H), 4.8-5.2 (m, 4H), 2.55-2.80 (m, 2H), 1.45 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (62.8 MHz, DMSO), δ 156.0, 152.4, 149.4, 139.1 (d, J=6.5 Hz), 118.8, 111.4, 96.9 (d, J=177.6 Hz), 83.5 (d, J=23.1 Hz), 83.2, 58.6, 35.1(d, J=20.3 Hz), 26.2, 24.1. Anal. Calcd for $C_{13}H_{16}N_5FO_2$: C, 53.24; H, 5.50; N, 23.88; Found: C, 53.05; H, 5.47; N, 23.74.

(1*S*,2*S*,3*R*,5*S*)-3-(6-Amino-9H-purin-9-yl)-5-fluorocyclopentane-1,2-diol (2). **39** (0.40 g, 1.4 mmol) was dissolved in 0.5 M HCl MeOH solution (100 mL). The mixture was stirred at room temperature overnight. The mixture was neutralized with Amberlite® IRA-67 (commercially available from Aldrich) ion exchange resin. The mixture was filtered, concentrated and purified by silica chromatography (EtOAc:MeOH:NH_4OH (29.6%)=3:1:0.2) to give **2** as a white solid (0.32 g, 93%). Mp=218-220 ^{o}C （sample recrystalized from MeOH/H_2O）. ^{1}H NMR (250 MHz, DMSO), δ 8.16 (s, 1H), 8.12 (s, 1H), 7.22 (s, 2H), 5.36 (d, J=4.2 Hz, 1H), 5.25 (d, J=6.5 Hz, 1H), 4.59-4.97 (m, 2H), 4.58-4.63 (m, 1H), 4.04 (dm, J=12.0 Hz, 1H), 2.68-2.76 (m, 1H), 2.20-2.34 (m, 1H). ^{13}C NMR (62 MHz, DMSO), δ 156.0, 152.2, 149.6, 140.2, 119.4, 95.1 (d, J=177.7 Hz), 73.7

(d, J=10.5 Hz), 73.4, 57.8 (d, J=3.1 Hz), 33.3 (d, J=22.6 Hz). Anal. Calcd for $C_{10}H_{12}FN_5O_2$: C, 47.43; H, 4.78; N, 27.66; Found: C, 47.28; H, 4.86; N, 27.36.

1-Benzyl-1*H*-pyrrole-2-carbaldehyde (40). Pyrrole-2-carboxaldehyde (25 g, 0.27 mol), benzene (125 mL), NaOH solution (50%, 125 mL), tetrabutylammonium iodide (TBAI) (1.0 g) were mixed and refluxed over 24 hours. The mixture was cooled to room temperature. The organic layer was separated, washed with water (3×100mL), dried over sodium sulfate, and concentrated to give crude **40** as a yellow oil (43 g, 82%), which was used without further purification.

3-(1-Benzyl-1*H*-pyrrol-2-yl)acrylic Acid (42). **40** (43 g, 0.23 mol) was dissolved in dry ethanol (200 mL). Malonic acid (26 g, 0.25 mol), aniline (23 g, 0.25 mol) were added. The mixture was refluxed until white solid formed. The flask was cooled with ice-water. The precipitate was filtered, and washed with benzene. The solid was dried under vacuum to give **42** as white solid (37 g, 72%). The NMR spectra are consistent with literature.[216]

3-(1-Benzyl-1*H*-pyrrol-2-yl)acryloyl Azide (44). 42 (10.0 g, 44.0 mmol) was dissolved in dry acetone (200 mL). Triethylamine (TEA) (5.8 g, 57 mmol) was added. Chloroethyl formate (6.2 mL, 66 mmol) was added dropwise *via* a syringe at 0 ^{o}C. The solution was stirred at the same temperature for 1 hour. Sodiam azide (4.4 g, 66 mmol) in minimum water was added dropwise. The mixture was warmed to room temperature and stirred 1 hour. The solvent was removed under reduced pressure. Water was added. The mixture was extracted with EtOAc (200 mL). The organic layer was separated, washed with brine, dried over sodium sulfate, and concentrated to give **44** as yellow oil (11 g, 96%). The NMR spectra were consistent with literature.[216]

1-Benzyl-1*H*-pyrrolo[3,2-*c*]pyridin-4-ol (46). 44 (10.6 g, 42.0 mmol) in diphenyl ether (20 mL, 60 ^{o}C) was added dropwise to a solution of *n*-Bu_3N (2.0 mL) in diphenyl ether (30 mL) at 220 ^{o}C (maintaining this temperature during addition of **44**). The solution was stirred at same temperature for 15 minutes. The solvent was removed under reduced pressure. The residue was purified with silica column (EtOAc/MeOH=5:1) to give **46** as a yellow solid (3.80 g, 40.4%). The NMR spectra are consistent with literature.[216]

1*H*-Pyrrolo[3,2-*c*]pyridin-4-ol (47). 46 (7.6 g, 34 mmol) was dissolved in liquid ammonia at -78 ^{o}C (about 100 mL). Sodium metal (in small pieces) was added until the solution remained blue for 5 minutes. Ammonium chloride (15 g) was added to quench the reaction. The mixture was warmed to room temperature. The mixture was purified by silica column (EtOAc/MeOH=3:1) to give **47** as white solid (3.1 g, 70%). The NMR spectra are consistent with literature.[216]

4-Chloro-1*H*-pyrrolo[3,2-*c*]pyridine (48). 47 (3.1 g, 25 mmol) was dissolved in $POCl_3$ (20 mL) in high pressure reaction vessel. The mixture was heated to 170 ^{o}C overnight. The $POCl_3$ was removed under reduced pressure. The residue was poured to ice-water. The resulting mixture was extracted with EtOAc (4×100 mL). The combined organic layer was washed with brine (3×20 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (EtOAc) to give **48** as white solid (2.3 g, 60%). The NMR spectra are consistent with literature.[216]

(3*aR*,6*R*,6*aR*)-6-(*tert*-Butoxymethyl)-2,2-dimethyl-dihydro-3*aH*-cyclopenta[*d*]-[1, 3]dioxol-4(5H)-one (50). *tert*-BuOMe (10 mL), *tert*-BuOK (2.0 g, 17 mmol) was dissolved in dry THF (30 mL) and cooled to -78 ^{o}C. *sec*-BuLi (16 mL, 1.4 M in hexane,

22 mmol) was added dropwise. The mixture was stirred at -78 ^{o}C for 2 hours. LiBr (2.9 g, 34 mmol) in THF (10 mL) was added over 10 min at -70 ^{o}C. The mixture was warmed to -30 ^{o}C, stirred 30 minutes. The mixture was recooled to -78 ^{o}C. $CuBr{\cdot}SMe_2$ (1.8 g, 8.7 mmol), SMe_2 (10 mL) in THF (10 mL) was added dropwise over 5 minutes. **49** (0.70 g, 4.5 mmol) in THF (5 mL) was added dropwise at the same temperature. The mixture was warmed to -30 ^{o}C and stirred 30 minutes. MeOH (15 mL), saturated NH_4Cl solution (15 mL) were added. The mixture was extracted with diethyl ether (3×100 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, and concentrated. The residue was purified by silica column (hexanes/EtOAc=10:1) to give **50** as a colorless oil (0.84 g, 77%). The NMR spectra were consistent with literature.[230]

(3*aS*,4*S*,6*R*,6*aR*)-6-(*tert*-Butoxymethyl)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta [*d*]-[1,3]dioxol-4-ol (51). 50 (0.30 g, 1.2 mmol) was dissolved in MeOH (10mL) at 0 ^{o}C. $CeCl_3{\cdot}7H_2O$ (0.46 g, 1.2 mmol) was added. $NaBH_4$ (0.12 g, 2.4 mmol) was added portionwise, and stirred 30 minutes. Saturated NH_4Cl solution (3 mL) was added. The solvent was removed under reduced pressure. The residue was extracted with EtOAc (3×30 mL). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate and concentrated. The residue was purified with silica column (hexanes/EtOAc=5:1) to give **51** as colorless oil (0.25 g, 83%). The NMR spectra were consistent with the literature.[230]

1-((3*aS*,4*R*,6*R*,6*aR*)-6-(*tert*-Butoxymethyl)-2,2-dimethyl-tetrahydro-3*aH*-cyclope nta[*d*]-[1,3]dioxol-4-yl)-4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine (53). To a chilled (-20 ^{o}C) solution of **51** (0.9 0g, 3.7 mmol) and pyridine (0.59 mL, 7.4 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise trifluoromethansulfonic anhydride (0.93 mL, 5.5 mmol). The

mixture was placed in an ice/water bath, and stirred for 1 hour. Ice cold water was added to quench the reaction. The organic layer was washed with ice cold water (3×10 mL). The organic layer was separated and dried by Na_2SO_4. The solvent was removed at reduced pressure to give an orange oil (1.2 g, 84%). The resulting oil was dissolved in anhydrous DMF (20 mL) and cooled to –20 ^oC. The resulting solution was added to pre-prepared sodium salt of **48** in DMF (by addting NaH (0.22 g, 60% in mineral oil, 5.5 mmol) to a solution of **48** (0.84 g, 5.5 mmol) in DMF at romm temperature) at –40 ^oC. The mixture was stirred at room temperature for 2 days. The solvent was removed under reduced pressure. The residue was dissolved in water, extract with EtOAc (3×10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column (Hexanes/EtOAc=5:1) to give **53** as a colorless oil (0.60 g, 43%).^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J=9.4 Hz, 1H), 7.46 (d, J=9.6 Hz, 1H), 7.31 (d, J=5.6 Hz, 1H), 6.68 (d, J=5.4 Hz, 1H), δ4.74 (m, 1H), 4.60 (m, 2H), 3.54 (m, 2H), 2.51 (m, 2H), 2.33 (m, 1H), 1.64 (s, 3H), 1.33 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 141.1, 139.9, 126.1, 123.9, 113.3, 105.6, 101.5, 85.5, 81.3, 77.2, 72.9, 63.2, 61.6, 43.9, 33.2, 27.6, 27.5, 27.0, 25.1. Anal. Calcd for $C_{20}H_{27}ClN_2O_3$: C, 63.40; H, 7.18; Cl, 9.36; N, 7.39; Found: C, 63.63; H, 7.27; Cl, 9.06; N, 7.14.

3-(4-Chloro-pyrrolo[3,2-*c*]pyridin-1-yl)-5-hydroxymethyl-cyclopentane-1,2-diol (54). **53** (0.40 g, 1.06 mmol) was dissolved in CF_3COOH/H_2O=2:1 (30 mL). The mixture was refluxed under N_2 overnight. The solvent was removed at reduced pressure, and the residue was neutralized with saturated $NaHCO_3$ solution. The solvent was removed under reduced pressure. The residue was purified with a silica gel column (CH_2Cl_2/MeOH=8:1) to give **54** as a yellow solid (0.25 g, 83%), mp=194-196 ^oC. ^1H NMR (400 MHz, MeOD)

δ 7.96 (d, J=6.0 Hz, 1H), 7.66 (d, J=3.6 Hz, 1H), 7.60 (d, J=6.0 Hz, 1H), 6.71 (d, J=3.6 Hz, 1H), 4.8 (m, 1H), 4.21 (m, 1H), 3.98 (m, 1H), 3.68 (m, 2H), 2.40 (m, 1H), 2.24 (m, 1H), 1.80 (m, 1H). ^{13}C NMR (100 MHz, MeOD) δ 144.1, 143.3, 139.6, 128.7, 124.9, 107.2, 102.5, 77.9, 73.8, 64.3, 62.6, 46.7, 30.2. Anal. Calcd for $C_{13}H_{15}ClN_2O_3 \cdot 0.5H_2O$: C, 53.52; H, 5.52; Cl, 12.15; N, 9.60; Found: C, 53.75; H, 5.44; Cl, 12.26; N, 9.39.

3-(4-Amino-pyrrolo[3,2-*c*]pyridin-1-yl)-5-hydroxymethyl-cyclopentane-1,2-diol Hydrochloride Salt Monohydrate (3). 54 (1.0 g, 3.7 mmol) was dissolved in 2-methoxy ethanol (30 mL). The solution was degassed with N_2 for 10 minutes. Hydrazine monohydrate (20 mL) was added in one portion. The mixture was heated to reflux under N_2 overnight. The solvent was removed under reduced pressure, co-evaporated with ethanol three times (20 mL each). Water (30 mL) was added. The solution was degassed with N_2 for 10 minutes. Raney® 2800 Nickel (3.0 g in water suspension) was added. The mixture was refluxed under N_2 overnight. The mixture was filtered, concentrated. The residue was purified by silica gel column (EtOAc/MeOH/NH_4OH (29.6%)=3:1:0.1) to give **3** as gel. Recrystallization from MeOH/EtOAc give **3** as white solid (as hydrochloric acid salt, 0.40 g, 41%). m.p.: decomposed above 200 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, J=3.2 Hz, 1H), 7.46 (d, J=7.2 Hz, 1H), 7.22 (d, J= 7.2 Hz, 1H), δ7.00 (d, J=3.2 Hz, 1H), 4.81 (m, 1H), 4.18 (m, 1H), 3.98 (m, 1H), 3.68 (m, 2H), 2.38 (m, 1H), 2.24 (m, 1H), 1.80 (m, 1H). ^{13}C NMR (100 MHz, MeOD) δ151.1, 142.1, 127.4, 127.1, 111.1, 104.5, 100.8, 78.1, 73.8, 64.3, 62.6, 46.7, 30.4. Anal. Calcd for $C_{13}H_{18}ClN_3O_3$ (+H_2O): C, 49.14; H, 6.34; Cl, 11.16; N, 13.22; Found: C, 49.26; H, 6.28; Cl, 11.17; N, 13.09.

1-[6-(*tert*-Butyl-dimethyl-silanyloxy)-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxol-4-yl]-4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine (57). To a chilled (-20 ^{o}C) solution of **31**

(2.6 g, 9.0 mmol) and pyridine (0.76 mL, 9.1 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise trifluoromethansulfonic anhydride (1.5 mL, 9.1 mmol). The mixture was placed in an ice/water bath, and stirred for 1 hour. Ice chilled water (5 mL) was added to quench the reaction. The organic layer was washed with ice cold water (3×10 mL). The organic layer was separated and dried by Na_2SO_4. The solvent was removed at reduced pressure to give **56** as orange oil. The resulting **56** was dissolved in anhydrous DMF (20 mL) and cooled to –20 ^oC. The resulting solution was added to sodium salt of **48** in DMF solution (prepared by addition of NaH (0.54 g, 60% dispersion in mineral oil, 13 mmol) to a solution of **48** (2.1 g, 13 mmol) in DMF) at –40 ^oC. The mixture was stirred at room temperature for 2 days. The solvent was removed under reduced pressure. The residue was dissolved in water, extracted with EtOAc (3×50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column (Hexanes/EtOAc=2:1) to give **57** as yellow oil (1.4 g, 46%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J=10.6 Hz, 1H), 7.55 (d, J=3.3 Hz, 1H), 7.32 (d, J=5.8 Hz, 1H), 6.60 (d, J=3.3 Hz, 1H), 4.81 (d, J=8.3 Hz, 1H), 4.71(d, J=5.7 Hz, 1H), 4.55 (d, J=5.8 Hz, 1H), 4.43 (m, 1H), 2.75 (m, 1H), 2.18 (d, J=2.5 Hz, 1H), 1.54 (s, 3H), 1.26 (s, 3H), 0.91 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.1, 140.0, 128.1, 111.84, 105.2, 101.0, 87.6, 86.6, 63.1, 37.9, 32.4, 27.0, 26.0, 24.5, 23.0, 18.2, 14.5, -4.6, -4.7. Anal. Calcd for $C_{21}H_{31}ClN_2O_3Si$: C, 59.62; H, 7.39; Cl, 8.38; N, 6.62; Found: C, 59.69; H, 7.38; Cl, 8.08; N, 6.33.

4-(4-Chloro-pyrrolo[3,2-*c*]pyridin-1-yl)-cyclopentane-1,2,3-triol (58). **57** (1.2 g, 2.8 mmol) was dissolved in 0.5 N HCl methanol solution (20 mL). The mixture was stirred at room temperature for 24 hours. The mixture was neutralized with ammonium

hydroxide (29.6%). The solvent was removed under reduced pressure. The residue was purified by silica gel column (EtOAc/MeOH=10:1) to give **58** as white solid (0.70 g, 92%). m.p.: 173-175 ^{o}C. ^{1}H NMR (400 MHz, DMSO) δ 7.97 (d, J=5.8 Hz, 1H), 7.68-7.66 (m, 2H), 6.62 (d, J=3.1 Hz, 1H), 5.27 (s, 1H), 4.98 (s, 2H), 4.78-4.72 (m, 1H), 4.32-4.29 (m, 1H), 3.96 (d, J=5.9 Hz, 1H), 3.75 (d, J=3.6 Hz, 1H), 2.72-2.64 (m, 1H), 1.75-1.69(m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 142.3, 140.7, 139.0, 128.9, 122.9, 106.3, 100.2, 76.8, 76.7, 73.5, 60.7, 36.5. Anal. Calcd for $C_{12}H_{13}ClN_2O_3$: C, 53.64; H, 4.88; Cl, 13.19; N, 10.43; Found: C, 53.58; H, 4.79; Cl, 13.39; N, 10.21.

4-(4-Amino-pyrrolo[3,2-*c*]pyridin-1-yl)-cyclopentane-1,2,3-triol Hydrochloride Salt (4). **58** (0.40g, 1.5 mmol) was dissolved in 2-methoxyethanol (20 mL). The solution was degassed by N_2 for 10 minutes. Hydrazine monohydrate (20 mL) was added in one portion. The mixture was heated to reflux under N_2 overnight. The solvent was removed under reduced pressure, co-evaporated with ethanol three times (30 mL each). Water (30 mL) was added. The solution was degassed with N_2 for 10 minutes. Raney 2800 Nickel (2.0 g in water suspension) was added. The mixture was refluxed under N_2 overnight. The mixture was filtered, and concentrated. The residue was purified by silica gel column (EtOAc/MeOH/NH_4OH (29.6%)=3:1:0.1) to give **4** as gel. Recrystallization from MeOH/EtOAc give **4** as white solid (as hydrochloride salt, 0.20 g, 53%). Mp=218-219 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.60 (d, J=3.4 Hz, 1H), 7.46 (d, J=7.2 Hz, 1H), 7.26 (d, J=6.7 Hz, 1H), 7.01 (d, J=3.6 Hz, 1H), 4.84 (m, 1H), 4.44 (m, 1H), 4.13 (m, 1H), 3.93 (m, 1H), 2.81-2.87 (m, 1H), 1.84-1.87 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 149.4, 139.5, 126.9, 126.6, 109.3, 103.5, 99.2, 77.3, 76.6, 73.5, 60.7, 36.7; Anal. Calcd for $C_{12}H_{16}ClN_3O_3$: C, 50.44; H, 5.64; Cl, 12.41; N, 14.71; Found: C, 50.35; H, 5.67; Cl,

12.44; N, 14.44.

(3*aR*,4*R*,6*R*,6*aR*)-6-(Hydroxymethyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (60). D-Ribose (123 g, 0.823 mol), dry acetone (500 mL) and sulfuric acid (1 mL) were mixed and stirred at room temperature overnight. Ammonium hydroxide (29.6% water solution) was added to neutralize the solution. The solution was dried over Na_2SO_4 and directly filtered through a silica column. The column was rinsed with acetone/THF mixture. The combined filtrate was concentrated, and coevaporated with dry THF (3×50 mL) to give **60** as gel-like foam (103 g, 69.3%). The NMR spectra are consistent with literature.[231]

((3*aR*,4*R*,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)methanol (61). 60 (2.98 g, 16.6mmol) was dissolved in DMF. The solution was cooled to 0 ^oC. NaH (0.68 g, 60% in mineral oil, 17 mmol) was added in portionwise. The mixture was stirred at same temperature for 1 hour. PMBCl (2.76 mL, 20.4 mmol) was added. The solution was warmed to room temperature, stirred overnight. The solvent was removed under reduced pressure. The residue was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc (3×30 mL). The combined organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanse/EtOAc=2:1) to give **61** as colorless oil contaminated with *para*-methoxybenzyl alcohol (PMBOH) (3.38 g, 65.6%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.89 (m, 2H), 5.16 (s, 1H), 4.83 (d, J=6.0 Hz, 1H), 4.69 (d, J=11.2 Hz, 1H), 4.62 (m, 2H), 4.50 (d, J=11.2 Hz, 1H), 4.43 (m, 1H), 3.80 (s, 3H), 3.68 (m, 2H), 1.47 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 130.0, 128.6, 114.1, 112.1, 107.7, 88.4, 86.0, 81.5, 69.9, 55.3, 26.4, 24.7. Calcd

HRMS for $C_{16}H_{22}O_6$: 310.1416; Found: 310.1409.

(3*aR*,4*R*,6*R*,6*aR*)-4-(4-Methoxybenzyloxy)-2,2-dimethyl-6-vinyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxole (63). 61 (50 g, 0.16 mol) was dissolved in DCM (300 mL). DIPEA (33 mL, 0.19 mol), SO_3·Py (31 g, 0.19 mol) were added in portion. The mixture was stirred at the same temperature for 2 hours. Ice chilled water (50 mL) was added. The organic layer was separated, washed with ice water (3×50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated. The residue was filtered through a short silica column. The filtrate was concentrated to give intermediate **62**, which was directly used in next step. $(Ph)_3PMeBr$ (70 g, 0.20 mol) was suspended in THF (300 mL). *tert*-BuOK (23 g, 0.20 mol) was added portionwise at 0 ^oC. The mixture was warmed to room temperature and stirred 3 hours. The solution was recooled to -78 ^oC. **62** in THF (100 mL) was added dropwise. The mixture was warmed to room temperature and stirred overnight. Water (50 mL) was added to quech the reaction. The solvent was removed under reduced pressure. The residue was extracted with EtOAc (3×200 mL). The combined organic layer was washed with water (100 mL), brine (100 mL), dried over sodium sulfate, and concentrated. The residue was purified by silica column (hexanse/EtOAc=10:1) to give **63** as a colorless oil (30 g, 60%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, J=8.8 Hz, 2H), 6.93 (d, J=1.8 Hz, 2H), 6.03 (m, 1H), 5.36 (d, J=17.6 Hz, 1H), 5.23 (d, J=17.6 Hz, 1H), 5.20 (s, 1H), 4.18 (m, 2H), 4.50 (s, 2H), 4.46 (d, J=12.0 Hz, 1H), 3.84 (s, 3H), 1.53 (3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 137.2, 129.8, 129.3, 117.5, 130.4, 112.3, 106.9, 88.7, 85.7, 84.6, 68.5, 55.3, 26.5, 24.9.

2-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)ethanol (64). To a solution of **63** (4.6 g, 15 mmol) in dry THF (20 mL)

at 0 °C was added 9-borabicyclo[3.3.1]nonane (9-BBN) (36 mL, 0.5M in THF, 18 mmol) dropwise. The reaction mixture was stirred at room temperature for overnight and MeOH (10 mL), NaOH (3N aq, 20 mL) and H_2O_2 (20 mL, 30% aq. solution) were added dropwise sequentially. The resulting mixture was evaporated after 4 hours at room temperature and extracted with EtOAc (3×50 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography. Elution with hexane-EtOAc (1:l) gave **64** (4.3 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, J=8.8 Hz, 2H), 6.86 (d, J=8.8 Hz, 2H), 5.17 (s, 1H), 4.72-4.64 (m, 3H), 4.54 (t, J=7.6 Hz, 2H), 3.85 (m, 2H), 3.83 (s, 3H), 2.07 (br, 1H), 1.98 (m, 1H), 1.87 (m, 1H), 1.53 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 129.7, 129.3, 113.9, 112.4, 107.5, 85.6, 85.4, 84.5, 69.2, 60.4, 55.3, 37.4, 26.5, 25.0; Anal. Cald for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46; Found: C, 63.13; H, 7.52.

2-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*] -[1,3]dioxol-4-yl)acetaldehyde (65). To a solution of **64** (3.8 g, 12 mmol), DMSO (20 mL) and DIPEA (5 mL) in CH_2Cl_2 (100 mL) was added dropwise a solution of SO_3·Py (3.7 g, 23 mmol) in DMSO (20 mL) at 0 °C. The reaction was then warmed to room temperature and stirred for 2 hours. The reaction mixture was then diluted with CH_2Cl_2 (200 mL), washed with water (20 mL), saturated $NaHCO_3$ (30 mL) and brine (30 mL). The mixture was dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography. Elution with hexane-EtOAc (5:l) gave **65** (3.4 g, 93%) as a white solid. MP=87-88 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.83 (dd, J=2.4, 1.2 Hz, 1H), 7.29 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.8 Hz, 2H), 5.17 (s, 1H), 4.80 (dd. J=8.8, 6.4 Hz, 1H), 4.74 (d, J=6.0 Hz, 1H), 4.64 (dd, J=8.0, 6.0 Hz, 2H), 4.41 (d, J=11.2 Hz, 1H), 3.83 (s, 3H), 2.94

(ddd, J=16.8, 8.8, 2.4 Hz, 1H), 2.76 (ddd, 16.8, 6.4, 1.2 Hz, 1H), 1.51 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.9, 159.4, 129.9, 128.9, 113.9, 112.7, 107.5, 85.6, 84.1, 81.7, 69.1, 55.3, 48.9, 26.5, 25.0; Anal. Cald for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88; Found: C, 63.55; H, 7.01.

(*R*)-1-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)pent-4-en-2-ol (66). Allyl magnesiumbromide (18 mL, 1M in diethyl ether, 18 mmol) was added dropwise to solution of (+)-*B*-methoxy di*iso*pinocampheylborane ((+)-Ipc$_2$BOMe) (5.7 g, 18 mmol) in diethyl ether (100 mL) at 0 °C. The reaction mixture stirred at room temperature for 1 hour to give a white suspension. This suspension was cooled to -78 °C and **65** (3.4 g, 11 mmol) in THF (30 mL) was then added dropwise. The new reaction mixture was then stirred at the same temperature for 3 hours and allowed to warm to room temperature in 2 hours. MeOH (10 mL), followed by NaOH aqueous solution (3M, 25 mL) and H_2O_2 (25 mL) was added into reaction mixture. The suspension was then stirred at room temperature for another 4 hours and concentrated. The residue was diluted with EtOAc (200 mL), washed with water (50 mL) and brine (50 ml), dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by column chromatography. Elution with hexane-EtOAc (10:1 to 5:1) gave **66** (3.2 g, 74 %) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, J=8.8 Hz, 2H), 6.91 (d, J=8.8 Hz, 2H), 5.87 (m, 1H), 5.17 (m, 3H), 4.74 (d, J=10.8, 1H), 4.69 (d, J=6.0 Hz, 1H), 4.62 (d, J=6.0 Hz, 1H), 4.46 (m, 2H), 3.93 (s, 1H), 3.83 (s, 3H), 2.76 (s, 1H), 2.33 (m, 2H), 1.91-1.76 (m, 2H), 1.51 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 134.5, 129.9, 129.2, 118.1, 113.9, 112.5, 107.6, 86.6, 85.5, 84.4, 69.7, 69.4, 55.3, 41.8, 41.1, 26.5, 25.0; Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74; Found: C, 65.48; H,

7.72.

(3*aR*,4*R*,6*R*,6*aR*)-4-((*S*)-2-Azidopent-4-enyl)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxole (67). To a solution of **66** (2.7 g, 7.4 mmol) and triethylamine (3 mL) in anhydrous CH_2Cl_2 (20 mL) was added MsCl (0.84 mL, 15 mmol) at 0°C. The reaction mixture became a yellow solution after stirring for 1 hour at room temperature. It was then diluted with CH_2Cl_2 (20 mL) and washed with icy water (20 mL), dried (Na_2SO_4) and filtered. Evaporation of filtrate provided a sticky yellow oil which was directly used for the next step. A suspension of above oil in dry DMF (20 mL) was added NaN_3 (2.0 g, 30.8 mmol). The mixture was stirred at 100 °C overnight. The solvents was evaporated, quenched with water (10 mL), extracted with EtOAc (3×20 mL) and dried (Na_2SO_4). The organic layers was filtered and concentrated to give yellow oil. The residue was purified by column chromatography with hexances-EtOAc (5:1) to give **67** (2.0 g, 89 %) as colorless oil%), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.8 Hz, 2H), 5.82 (m, 1H), 5.18 (m, 3H), 4.70 (d, J=6.4 Hz, 1H) 4.66 (d, J=11.6 Hz, 1H), 4.61 (d, J=6.0 Hz, 1H), 4.49 (m, 2H), 3.83 (s, 3H), 3.67 (m, 1H), 2.38 (m, 2H), 1.87(m, 1H),1.61 (m, 1H), 1.51 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 133.4, 129.4, 129.2, 118.7, 113.9, 112.4, 107.9, 85.7, 84.4, 84.0, 69.5, 69.4, 59.4, 55.3, 39.4, 26.5, 25.0; Anal. Calcd for $C_{20}H_{27}N_3O_5$: C, 61.68; H, 6.99; N, 10.79; Found: C, 61.91; 7.02; N, 10.65.

(*S*)-3-Azido-4-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butan-1-ol (68). Method A: **67** (2.3 g, 6.0 mmol) was dissolved in MeOH/H_2O (2:1) (50 mL) at 0 ^{o}C. $NaIO_4$ (3.2 g, 15 mmol) was added. OsO_4 (20 mg, 0.078 mmol) was added. The mixture was stirred at 0 ^{o}C for 2 hours. The mixture

was filtered. The filtrate was concentrated under reduced pressure and extracted with DCM (3×100 mL). The combined organic layer was washed with water (50 mL), brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was dissolved in MeOH (30 mL) at 0 ^oC. $NaBH_4$ (0.45 g, 12 mmol) was added portionwise. The mixture was stirred at same temperature for 30 minutes. Saturated NH_4Cl solution (30 mL) was added. The mixture was filtered through a celite pad. The solvent was removed under reduced pressure. The residue was purified by silica column (hexanes/EtOAc=3:1 to 1:1) to give **68** (oil, 0.50 g, 20%), **69** (oil, 0.20 g, 10%), **70** (oil, 0.10 g, 5%) and a lot of intractable products. **68:** ^1H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, J=8.8 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 5.18 (s, 1H), 4.72 (d, J=6.0 Hz, 1H), 4.67 (d, J=11.6Hz, 1H), 4.61 (d, J=6.0Hz, 1H), 4.48 (m, 2H), 3.84 (m, 1H), 3.83 (s, 3H), 3.76 (q, J=6.0 Hz, 2H), 2.02 (s, 1H), 1.88(ddd, J=14.0, 11.2, 3.2 Hz, 1H), 1.77 (m, 2H), 1.68 (ddd, J=14.0, 11.2, 3.6 Hz, 1H), 1.61 (m, 1H), 1.51 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 129.5, 129.3, 113.9, 112.4, 107.9, 85.6, 84.4, 84.0, 69.5, 59.2, 57.2, 55.3, 40.0, 37.5, 26.5, 25.0; Anal. Calcd for $C_{19}H_{27}N_3O_6$: C, 58.00; H, 6.92; N, 10.68; Found: C, 58.27; H, 7.14; N, 10.45; **69:** ^1H NMR ($CDCl_3$, 400 MHz) δ 9.55 (d, J=8.0 Hz, 1H), 7.23 (m, 2H), 6.89 (m, 2H), 6.23 (m, 1H), 5.12 (s, 1H), 4.72 (d, J=6.0 Hz, 1H), 4.60-4.65 (m, 2H), 4.38-4.46 (m, 2H), 3.82 (s, 3H), 2.76 (m, 1H), 2.65 (m, 1H), 1.50 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.7, 159.5, 153.6, 134.8, 129.6, 128.9, 113.9, 112.6, 107.5, 85.5, 85.4, 83.7, 69.3, 55.3, 38.4, 26.4, 24.9; **70:** ^1H NMR ($CDCl_3$, 400 MHz) δ 7.23 (m, 2H), 6.89 (m, 2H), 5.72-5.74 (m, 2H), 5.13 (s, 1H), 4.64-4.69 (m, 2H), 4.58 (m, 1H), 4.40 (m, 1H), 4.25 (m, 1H), 4.12 (m, 2H), 3.80 (s, 3H), 2.50 (m, 1H), 2.35 (m, 1H). 1.47 (s, 3H), 1.30 (s, 3H). ^{13}C NMR δ159.4, 132.2, 129.7, 129.3, 128.2, 113.9, 112.3, 86.8, 85.7, 83.5, 68.9, 63.6,

55.3, 37.9, 26.5, 24.9.

Method B: **67** (1.9 g, 5.2 mmol) was dissolved in THF (50 mL). NMO (2.4 mL, 50% in water, 10 mmol) was added. OsO_4 (5 mg, 0.020 mmol) was added. The mixture was stirred at room temperature overnight. Sodium thiosulfate (5 g) was added to quench the reaction. The mixture was stirred for another 2 hours. The mixture was filtered through a short silica column (5 cm). The column was rinsed with EtOAc. The combined organic liquid was concentrated. The residue was dissolved in DCM/H_2O (1:1, 30 mL). $NaIO_4$ (3.2 g, 15 mmol) was added at room temperature. The mixture was stirred 3 hours. The organic layer was diluted with DCM (100 mL), separated, washed with water (20 mL), dried over sodium sulfate and concentrated. The residue was dissolved in MeOH (30 mL) at 0 ^oC. $NaBH_4$ (450 mg, 12 mmol) was added portionwise. The mixture was stirred at same temperature for 30 minutes. Saturated NH_4Cl solution (30 mL) was added. The mixture was filtered through a celite pad. The solvent was removed under reduced pressure. The residue was purified by silica column (hexanes/EtOAc=3:1 to 1:1) to give **68** exclusively as colorless oil (1.7 g, 89%)

Method C: **67** (1.0 g, 2.6 mmol) was dissolved in *tert*-BuOH/H_2O (1:1 30 mL). AD-mix-beta (3.6 g) was added at room temperature. The mixture was stirred at room temperature overnight. Sodium thiosulfate (5 g) was added. The mixture was stirred for another 2 hours. The mixture was filtered through celite pad. The pad was rinsed with *tert*-BuOH. The organic layer was sperated. $NaIO_4$ (0.80 g, 7.6 mmol) in water (10 mL) was added at room temperature. The mixture was stirred 3 hours. The mixture was filtered to remove precipitate. $NaBH_4$ (0.10 mg, 2.7 mmol) was added portionwise. The mixture was stirred at same temperature for 30 minutes. Saturated NH_4Cl solution (30

mL) was added. The mixture was filtered through a celite pad. The solvent was removed under reduced pressure. The residue was extracted with EtOAc (3×50 mL). The combined organic layer was washed with water (10 mL), brine (50 mL), dried over sodium sulfate. The residue was purified by silica column (hexanes/EtOAc=3:1 to 1:1) to give **68** exclusively as a colorless oil (0.72 g, 72%)

(3*aR*,4*R*,6*R*,6*aR*)-4-((*R*)-2-Azido-4-iodobutyl)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxole (77). 68 (1.4 g, 3.5 mmol) was dissolved in PhMe/MeCN (1:1, 50 mL). Ph_3P (1.0 g, 3.8 mmol), imidazole (1.2 g, 18 mmol) were added. I_2 chip was added until the solution turned purple. The mixture was stirred at room temperature for 2 hours. Water (10 mL), sodium thiosulfate (1 g) was added. The organic layer was separated. The aqueous phase was extracted with EtOAc (50 mL). The combined organic layer was dried over sodium sulfate and concentrated. The residue was purified with silica column (hexanes/EtOAc=10:1) to give **77** as white solid (1.1 g, 60%). MP= 99-100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, J=8.4 Hz, 2H), 6.93 (d, J=8.4 Hz, 2H), 5.20 (s, 1H), 4.74 (m, 2H), 4.69 (d, J=6.0 Hz, 1H), 4.61 (d, J=11.2 Hz, 1H), 4.48 (dd, J=11.2, 2.8 Hz, 1H), 3.84 (s, 3H), 3.73 (m, 1H), 3.28 (m, 2H), 1.97 (m, 2H), 1.87(dt, J=14.0, 2.7Hz, 1H), 1.70 (m, 1H), 1.51 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 129.5, 129.2, 114.0, 112.5, 107.9, 85.6, 84.4, 83.8, 69.6, 60.4, 55.3, 39.9, 39.0, 26.5, 25.0, 1.63; Anal. Cald for $C_{19}H_{26}IN_3O_5$·0.6EtOAc: C, 46.17; H, 5.41; N, 7.55; Found: C, 46.12; H, 5.19; N, 7.42.

(*S*)-3-Azido-4-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butyl 4-Methylbenzenesulfonate (78). 68 (0.25 g, 0.64 mmol) was dissolved in DCM (10 mL). Triethylamine (TEA) (0.5 mL), *p*-toluenesulfonyl

chloride (TsCl) (0.24 g, 1.2 mmol), and 1,4-diazabicyclo[2.2.2]octane (DABCO) (20 mg) were added at room temperature. The mixture was stirred at room temperature for 30 minutes. Water (10 mL) was added. The mixture was stirred for 30 minutes. The organic layer was separated, washed with brine (5 mL), dried over sodium sulfate and concentrated. The residue was purified by silica column (hexanse/EtOAc=5:1) to give **78** as yellow oil (0.28 g, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (m, 2H), 7.32 (m, 2H), 7.21 (m, 2H), 6.89 (m, 2H), 5.15 (s, 1H), 4.67 (d, J=6.0 Hz, 1H), 4.57 (d, J=11.6 Hz, 1H), 4.53 (d, J=6.0 Hz, 1H), 4.38 (d, J=11.6 Hz, 1H), 4.37 (dd, J=11.2, 3.6 Hz, 1H), 4.12 (m, 2H), 3.80 (s, 3H), 3.71 (m, 1H), 2.43 (s, 3H), 1.65-1.84 (m, 4H), 1.48 (s, 3H), 1.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.6, 145.3, 132.9, 130.2, 129.7, 128.1, 114.2, 112.7, 108.1, 85.8, 84.6, 83.9, 69.8, 66.8, 56.6, 55.5, 52.3, 40.5, 34.6, 26.6, 25.1, 21.8.

***tert*-Butyl((*R*)-1-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)pent-4-en-2-yloxy)dimethylsilane (80). 66** (2.9 g, 8.1 mmol) was dissolved in DCM (50 mL). The solution was treated with imidazole (1.0 g, 15 mmol), TBSCl (1.8 g, 12 mmol) and DMAP (20 mg). The mixture was stirred at room temperature overnight. Water (10 mL) was added. The organic layer was separated, washed with brine (20 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanes/EtOAc=20:1) to give **80** as colorless oil contaminated with *tert*-butyldimethylsilanol (TBSOH) (3.6 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (m, 2H), 6.82 (m, 2H), 5.78 (m, 1H), 5.04 (m, 3H), 4.6 (m, 2H), 4.56 (m, 1H), 4.35 (m, 2H), 3.85 (m, 1H), 3.76 (s, 3H), 2.27 (m, 2H), 1.82 (m, 1H), 1.73 (m, 1H), 1.42 (s, 3H), 1.25 (s, 3H), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5, 134.8, 129.9, 117.5, 114.0, 112.3, 107.2, 85.9, 84.5, 69.4, 68.9, 66.1, 55.5, 41.9,

41.7, 26.7, 26.2, , 25.8, 25.2, 18.2, 18.1, 15.5, -3.4, -3.5.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butan-1-ol (81). 80 (1.1 g, 2.3 mmol) was dissolved in THF (50 mL). NMO (2.4 mL, 50% in water, 10.4 mmol) was added. OsO_4 (5 mg) was added. The mixture was stirred at room temperature overnight. Sodium thiosulfate (5 g) was added. The mixture was stirred for another 2 hours. The mixture was filtered through a short silica column (5 cm). The column was rinsed with EtOAc. The combined organic liquid was concentrated. The residue was dissolved in DCM/H_2O (1:1, 30 mL). $NaIO_4$ (1.0 g, 4.7 mmol) was added at room temperature. The mixture was stirred vigorously 3 hours. The organic layer was diluted with DCM (100 mL), separated, washed with water (20 mL), dried over sodium sulfate, and concentrated. The residue was dissolved in MeOH (30 mL) at 0 ^oC. $NaBH_4$ (0.24 mg, 6.5 mmol) was added portionwise. The mixture was stirred at same temperature for 30 minutes. Saturated NH_4Cl solution (30 mL) was added. The mixture was filtered through celite. The solvent was removed under reduced pressure. The residue was purified by silica column (hexanes/EtOAc=3:1 to 1:1) to give **81** exclusively as a colorless oil (0.75 g, 68%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25 (m, 2H), 6.87 (m, 2H), 5.09 (s, 1H), 4.64-4.67 (m, 2H), 4.58-4.60 (m, 1H), 4.42 (d, J=11.6 Hz, 1H), 4.3 (m, 1H), 4.12 (m, 2H), 3.80 (s, 3H), 3.75 (m, 1H), 2.22 (m, 1H), 1.83-1.95 (m, 2H), 1.45-1.79 (m, 2H), 1.45 (s, 3H), 1.29 (s, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 129.5, 129.3, 113.9, 112.3, 107.3, 85.7, 84.5, 84.2, 69.1, 68.9, 59.9, 55.3, 41.9, 37.7, 26.5, 25.8, 25.0, 17.9, -4.4, -4.6.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2

,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butyl 4-Methylbenzenesulfonate (82). 81 (2.0 g, 4.2 mmol) was dissolved in DCM (50 mL). TEA (2 mL), TsCl (1.2 g, 6.3 mmol), DABCO (20 mg) were added. The mixture was stirred at room temperature 30 minutes. Water (10 mL) was added. The mixture was stirred at room temperature 1 hour. The organic layer was separated, washed with brine (10 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanes/EtOAc=5:1) to give **82** as orange oil (2.4 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (m, 2H), 7.33 (m, 2H), 7.21 (m, 2H), 6.88 (m, 2H), 5.07 (s, 1H), 4.53-4.63 (m, 3H), 4.39 (d, J=11.6 Hz, 1H), 4.29 (m, 1H), 4.13 (m, 2H), 3.95 (m, 1H), 3.80 (s, 3H), 2.43 (s, 3H), 1.81-1.91 (m, 3H), 1.66-1.71 (m, 1H), 1.44 (s, 3H), 1.28 (s, 3H), 0.81 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 144.7, 133.1, 129.8, 129.6, 129.3, 127.9, 113.9, 112.3, 107.2, 85.6, 84.5, 83.7, 69.0, 67.4, 66.1, 65.8, 55.3, 42.1, 35.6, 26.5, 25.7, 25.0, 21.6, 17.9, 15.3, -4.3, -4.8.

(2*S*,5*R*)-2-((*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-((3*aR*,4*R*,6*R*,6a*R*)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butyl)-3,6-diethoxy-5-*isopropyl*-2,5-dihydropyrazine (83). (*R*)-3,6-Diethoxy-2-*iso*propyl-2,5-dihydropyrazine (1.2 mL, 5.7 mmol) was dissolved in THF (2 mL). The solution was cooled to -78 ^{o}C. *n*-BuLi (2.4 mL, 2.5 M in hexanes, 6.0 mmol) was added dropwise. The mixture was stirred at -78 ^{o}C 1 hour. **82** (2.4 g, 3.8 mmol) was dissolved in THF (5 mL) was added dropwise *via* syringe. The mixture was slowly warmed up to -30 ^{o}C and kept 2 hours, and then warmed to room temperature, stirred overnight. Water (10 mL) was added to quench the reaction. The mixture was extracted with ethyl ether (3×50 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, and

concentrated. The residue was purified with silica column (hexanes/EtOAc=10:1) to give **83** as colorless oil (2.2 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (m, 2H), 6.86 (m, 2H), 5.08 (m, 1H), 4.60-4.66 (m, 3H), 4.38-4.40 (m, 2H), 4.09-4.13 (m, 6H), 3.98 (m, 1H), 3.89 (m, 1H), 3.82 (m, 1H), 3.79 (s, 3H), 2.25 (m, 1H), 1.83-1.88 (m, 2H), 1.72-1.78 (m, 2H), 1.45 (s, 3H), 1.23-1.28 (m, 9H), 1.04 (d, J=6.8 Hz, 3H), 0.88 (s, 9H), 0.71 (d, J=6.8 Hz, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.16, 163.14, 159.32, 141.6, 129.7, 129.4, 113.9, 112.1, 106.9, 85.8, 84.4, 84.3, 69.6, 68.7, 60.53, 60.49, 60.40, 55.3, 55.2, 41.8, 31.9, 31.5, 29.6, 26.5, 26.0, 25.9, 25.0, 19.1, 18.1, 16.6, 14.4, 14.2, -4.4, -4.5.

(*R*)-4-((2*S*,5*R*)-3,6-Diethoxy-5-*iso*propyl-2,5-dihydropyrazin-2-yl)-1-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)butan-2-ol (84). 83 (1.5 g, 2.2 mmol) was dissolved in THF (5 mL). TBAF (5 mL, 1.0M in THF, 5% water content) was added. The mixture was heated to 60 ^{o}C for 1 hour. The solvent was removed under reduced pressure. The residue was purified by silica column (hexanes/EtOAc=5:1) to give **84** as colorless oil (1.1 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (m, 2H), 6.86 (m, 2H), 5.14 (s, 1H), 4.66-4.70 (m, 2H), 4.58-4.61 (m, 1H), 4.37-4.40 (m, 2H), 4.05-4.20 (m, 5H), 3.88-3.97 (m, 4H), 3.79 (s, 3H), 2.26 (m, 1H), 2.08 (m, 1H), 1.89 (m, 1H), 1.71 (m, 2H), 1.47 (s, 3H), 1.28 (m, 9H), 1.03 (d, J=6.8 Hz, 3H), 0.73 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8, 163.0, 159.4, 129.0, 129.3, 113.9, 112.4, 107.4, 86.2, 85.6, 84.4, 69.4, 69.2, 65.9, 61.0, 60.98, 55.3, 55.2, 41.8, 33.1, 32.1, 29.9, 26.5, 24.9, 19.1, 16.8, 14.4, 14.3;

(*R*)-4-((2*S*,5*R*)-3,6-Diethoxy-5-*iso*propyl-2,5-dihydropyrazin-2-yl)-1-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)b

utan-2-yl 4-Methylbenzenesulfonate (85). 84 (0.19 g, 0.36 mmol) was dissolved in DCM (50 mL). TEA (2.0 mL), TsCl (0.12 g, 0.63 mmol), DABCO (20 mg) were added. The mixture was stirred at room temperature 30 minutes. Water (10 mL) was added to quench the reaction. The mixture was stirred at room temperature 1 hour. The organic layer was separated, washed with brine (10 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanes/EtOAc=5:1) to give **85** as orange oil (0.24 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (m, 2H), 7.24-7.28 (m, 4H), 6.85 (m, 2H), 5.06 (s, 1H), 4.83 (m, 1H), 4.58-4.62 (m, 2H), 4.51 (m, 1H), 4.35 (d, J=11.6 Hz, 1H), 4.05-4.20 (m, 7H), 3.90 (m, 1H), 3.86 (m, 1H), 3.79 (s, 3H), 2.40 (s, 3H), 2.23 (m, 1H), 2.13 (m, 1H), 1.95 (m, 1H), 1.72-1.85 (m, 2H), 1.42 (s, 3H), 1.27 (m, 9H), 0.88 (d, J=6.8 Hz, 3H), 0.69 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 162.7, 159.4, 144.4, 134.5, 129.8, 129.7, 129.3, 127.7, 113.9, 112.3, 107.2, 85.5, 84.4, 83.6, 81.4, 69.0, 65.9, 60.9, 60.5, 55.3, 54.9, 39.3, 31.9, 28.9, 28.7, 26.4, 24.9, 21.62, 19.1, 16.7, 15.3, 14.4;

(2*S*,5*R*)-2-((*S*)-3-Azido-4-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butyl)-3,6-diethoxy-5-*iso*propyl-2,5-dihydropyrazine (79). 85 (6.0 g, 8.4 mmol) was dissolved in DMF. NaN_3 (1.3 g, 20 mmol) was added. The mixture was heated to 80 ^{o}C overnight. The solvent was removed under reduced pressure. Water (20 mL) was added to the residue. The mixture was extracted with EtOAc (3×100 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanes/EtOAc=10:1) to give **79** as white solid (3.9 g, 78%). MP=65-67 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (m, 2H), 6.87 (m, 2H), 5.13 (m, 1H),

4.67 (d, J=6.0 Hz, 1H), 4.55-4.57 (m, 2H), 4.43-4.47 (m, 2H), 4.05-4.21 (m, 4H), 3.92-3.97 (m, 1H), 3.88-3.91 (m, 1H), 3.79 (s, 3H), 3.51-3.58 (m, 1H), 2.23-2.28 (m, 1H), 1.76-1.95 (m, 3H), 1.52-1.65 (m, 3H), 1.47 (s, 3H), 1.25 (m, 9H), 1.03 (d, J=6.8 Hz, 3H), 0.71 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 162.7, 159.4, 129.5, 129.2, 113.9, 112.4, 107.7, 85.6, 84.4, 84.2, 69.4, 60.9, 60.7, 60.6, 59.9, 55.2, 54.9, 39.9, 32.0, 30.5, 30.0, 26.5, 24.9, 19.1, 16.7, 14.4, 14.3;

(3*aR*,4*R*,6*R*,6*aR*)-6-((*R*)-2-(*tert*-Butyldimethylsilyloxy)pent-4-enyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (87). 80 (1.2 g, 2.5 mmol) was dissolved in DCM/H_2O (20:1, 30 mL). 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (0.63 g, 2.7 mmol) was added. The mixture was stirred vigorously at room temperature 3 hours. The precipitate was removed by filtration. The filtrate was diluted with DCM (100 mL) and washed with saturated $NaHCO_3$ solution (3×30 mL). The organic layer was dried over sodium sulfate and concentrated. The residue was purified by a very careful silica column (hexanes/EtOAc=20:1) to give **87** as colorless oil (mixture of β and α isomers, β:α=6:1, 0.68 g, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.81 (m, 1H), 5.41 (d, J=2.4 Hz, 1H), 5.08 (d, J=6.0 Hz, 1H), 5.04 (m, 1H), 4.61 (m, 2H), 4.33 (t, J=8.4 Hz, 1H), 3.90 (m, 1H), 2.76 (d, J=2.4 Hz, 1H), 2.31-2.34 (m, 1H), 2.25-2.26 (m, 1H), 1.85 (m, 1H), 1.75 (m, 1H), 1.47 (s, 3H), 1.31 (s, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.7, 117.3, 112.3, 130.2, 86.2, 84.8, 84.4, 69.3, 42.0, 41.2, 26.5, 25.8, 24.9, 18.0, -4.4, -4.5.

9-((3*aR*,4*R*,6*R*,6*aR*)-6-((*R*)-2-(*tert*-Butyldimethylsilyloxy)pent-4-enyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-6-chloro-9*H*-purine (88). 87 (0.20 g, 0.56 mmol) was dissolve in THF (10 mL). CCl_4 (0.06 mL, 0.7 mmol) was added. At -78 ^{o}C,

hexamethylphosphorous triamide (HMPT) (0.1 mL, 0.7 mmol) was added dropwise. The mixture was stirred at same temperature for 1 hour then warmed to 0 ^{o}C, stirred 1 hour. The solution was recooled to -78 ^{o}C. Sodium salt of 6-chloropurine in DMF (10 mL) (prepared by addition of 40 mg 60% NaH in mineral oil to 0.15 g 6-chloropurine in 10 mL DMF) was added dropwise. The mixture was warmed to room temperature. Water (20 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanes/EtOAc=10:1) to give **88** as yellow oil (0.16 g, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.80 (s, 1H), 8.26 (s, 1H), 6.14 (d, J=2.4 Hz, 1H), 5.72-8.85 (m, 1H), 5.50 (m, 1H), 5.03-5.15 (m, 2H), 4.94 (m, 1H), 4.45 (m, 1H), 3.82 (m, 1H), 2.28 (m, 2H), 1.86 (m, 2H), 1.65 (s, 3H), 1.42 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.1, 151.6, 150.9, 144.5, 134.3, 117.5, 114.8, 112.2, 103.3, 90.7, 84.7, 84.4, 68.91, 41.2, 40.4, 27.1, 25.9, 25.8, 25.4, 24.9, 18.1, -4.4, -4.8.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-((3*aR*,4*R*,6*R*,6*aR*)-6-(6-chloro-9*H*-purin-9-yl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butan-1-ol (89). 88 (0.90 g, 1.9 mmol) was dissolved in *tert*-BuOH/H_2O (1:1, 20 mL). AD-mix-beta (2.8 g) was added. The mixture was stirred at room temperature overnight. Sodium thiosulfate (2 g) was added and stirred 1 hour. The mixture was extracted with EtOAc (3×30 mL). The organic layer was passed through a short silica pad (5 cm), concentrated, and dissolved in MeOH/H_2O (1:1, 50 mL). $NaIO_4$ (089 g, 4.2 mmol) was added. The mixture was stirred vigorously at room temperature for 1 hour. The precipitate was removed by filtration. The solvent was removed at reduce pressure. The residue was extracted with EtOAc (3×30

mL). The combined organic layer was concentrated, and dissolved in MeOH. $NaBH_4$ (0.15 g, 4.1 mmol) was added portionwise at 0 ^oC. The mixture was stirred at same temperature for 30 minutes. Saturated NH_4Cl solution (10 mL) was added. The mixture was filtered through celite. The solvent was removed at reduced pressure. The residue as extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanes/EtOAc=10:1) to give **89** as yellow oil (0.78 g, 87%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.88 (s, 1H), 8.31 (s, 1H), 6.18 (d, J=2.4 Hz, 1H), 5.54 (dd, J=6.4 Hz, 2.4 Hz, 1H), 5.02 (dd, J=6.4 Hz, 2.4 Hz, 1H), 4.42 (m, 1H), 4.07 (m, 1H), 3.82 (m, 2H), 2.03-2.14 (m, 3H), 1.90 (m, 1H), 1.80 (m, 1H), 1.71 (s, 3H), 1.48 (s, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.2, 151.6, 150.9, 144.5, 132.5, 115.0, 90.7, 84.6, 84.4, 83.9, 68.3, 59.8, 40.9, 37.7, 27.2, 25.7, 25.4, 17.9, -4.8, -4.9.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-((3*aR*,4*R*,6*R*,6*aR*)-6-hydroxy-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butyl 4-Methylbenzenesulfonate (91). 82 (0.20 g, 0.31 mmol) was dissolved in DCM/H_2O (20:1, 30 mL). DDQ (0.11 g, 0.48 mmol) was added. The mixture was stirred vigorously at room temperature 3 hour. The precipitate was removed by filtration. The filtrate was diluted with DCM (100 mL) and washed with saturated $NaHCO_3$ solution (3×30 mL). The organic layer was dried over sodium sulfate and concentrated. The residue was purified by a silica column (hexanes/EtOAc=3:1) to give **91** as organge oil (mixture of β and α isomers, β:α=5:1, 0.12 g, 75%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80 (m, 2H), 7.35 (m, 2H), 5.42 (s, 1H), 4.53-4.63 (m, 2H), 4.25 (m, 1H), 4.15 (m, 2H), 3.95 (m, 1H), 2.68 (d, J=2.8 Hz, 1H),

2.45 (s, 3H), 1.85-1.95 (m, 2H), 1.75-1.82 (m, 1H), 1.62-1.67 (m, 1H), 1.46 (s, 3H), 1.30 (s, 3H), 0.82 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.7, 133.1, 129.8, 127.9, 112.4, 103.2, 86.1, 84.9, 83.7, 67.6, 66.1, 42.4, 35.3, 26.5, 25.7, 24.9, 21.6, 17.9, -4.4, -4.8.

(3*aR*,4*S*,6*R*,6*aR*)-6-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-(tosyloxy)butyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl Pivalate (92). 91 (1.5 g, 2.9 mmol) was dissolved in DCM (50 mL). Pivaloyl chloride (PivCl) (0.54 mL, 4.4 mmol), DABCO (0.50 g, 4.5 mmol) were added. The mixture was stirred at room temperature overnight. Water (20 mL) was added and stirred 1 hour to quench the reaction. The organic layer was separated, washed with brine (20 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanes/EtOAc=10:1) to give **92** as orange oil (1.2 g, 69%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.80 (m, 2H), 7.35 (m, 2H), 6.07 (d, J=4.8 Hz, 1H), 4.80 (m, 1H), 4.40 (m, 2H), 4.21 (m, 1H), 4.10 (m, 1H), 3.95 (m, 1H), 2.45 (s, 3H), 1.85 (m, 2H), 1.73 (m, 2H), 1.53 (s, 3H), 1.34 (s, 3H), 1.25 (s, 9H), 0.82 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 177.3, 144.7, 133.0, 129.8, 127.9, 116.6, 95.6, 83.8, 80.3, 79.8, 67.4, 65.7, 40.2, 38.9, 35.8, 27.1, 26.4, 25.7, 25.3, 21.6, 17.9, -4.4, -4.5;

(*R*)-4-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butane-1,3-diyl *bis*(4-Methylbenzenesulfonate) (94). A solution of **81** (5.0 g, 10 mmmol) was treated with TBAF (13 mL, 1M in THF, 5% water content, 13 mmol) at room temperature, stirred 1 hour. Water (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine (2×20 mL), dried over sodium sulfate and concentrated. The

residue was filtered through a short silica column (10 cm, elute with hexanes/EtOAc=2:1). The fluorescent fraction was collected, concentrated and dissolved in DCM (50 mL). TEA (10 mL), TsCl (6.0 g, 32 mmol), DABCO (50 mg) were added. The mixture was stirred at room temperature 1 hour and quenched with water (10 mL). The organic layer was separated, washed with brine (10 mL), dried over sodium sulfate and concentrated. The residue was purified by silica column (hexanse/EtOAc=5:1) to give **94** as orange gel (4.7 g, 70%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (m, 4H), 7.33 (m, 6H), 6.88 (m, 2H), 5.05 (s, 1H), 4.86 (m, 1H), 4.61 (m, 2H), 4.46 (m, 1H), 4.37 (m, 1H), 4.12 (m, 2H), 3.95 (m, 1H), 3.80 (s, 3H), 2.44 (s, 3H), 2.42 (s, 3H), 2.05 (m, 3H), 1.86 (m, 1H), 1.42 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 159.4, 144.9, 133.7, 132.9, 130.0, 129.9, 129.7, 129.2, 127.9, 127.8, 113.9, 112.4, 107.4, 85.4, 84.3, 83.1, 69.2, 65.9, 55.3, 52.2, 45.9, 39.5, 33.1, 26.5, 24.9, 21.7.

(*R*)-4-((3*aR*,4*R*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)butane-1,3-diyl *bis*(4-Methylbenzenesulfonate) (95). 94 (2.0 g, 3.2 mmol) was dissolved in DCM/H_2O (20:1, 30 mL). DDQ (1.1 g, 4.8 mmol) was added. The mixture was stirred vigorously at room temperature 3 hour. The precipitate was removed by filtration. The filtrate was diluted with DCM (100 mL) and washed with saturated $NaHCO_3$ solution (3×30 mL). The organic layer was dried over sodium sulfate and concentrated. The residue was purified by a silica column (hexanes/EtOAc=3:1) to give the intermediate as orange oil. This intermediate was dissolved in dry DCM (50 mL) and treated with imidazole (0.42 g, 6.4 mmol), DMAP (20 mg) and TBSCl (0.72 g, 4.8 mmol) at room temperature. The mixture was stirred overnight. Water (10 mL) was added to quench the reaction. The organic layer was

separated, washed with brine (20 mL), dried over sodium sulfate, and concentrated. The residue was purified by silica column (hexanes/EtOAc=10:1) to give **95** as an orange oil (1.2 g, 56%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (m, 4H), 7.33 (m, 4H), 5.29 (s, 1H), 4.81 (m, 1H), 4.47 (m, 2H), 4.10 (m, 1H), 4.05 (m, 1H), 3.94 (m, 1H), 2.45 (s, 3H), 2.44 (s, 3H), 1.97-2.04 (m, 4H), 1.43 (s, 3H), 1.29 (s, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.1, 145.0, 133.8, 132.9, 130.1, 130.0, 128.0, 127.9, 112.6, 103.6, 87.5, 84.5, 82.7, 77.1, 66.2, 39.6, 33.6, 26.7, 25.8, 25.2, 21.8, 18.1, -4.2, -5.3.

(*R*)-1-((3*aR*,4*R*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydrofuro-[3,4-*d*][1,3]-dioxol-4-yl)-4-((2*S*,5*R*)-3,6-diethoxy-5-*iso*propyl-2,5-dihydropyrazin-2-yl)-butan-2-yl 4-Methylbenzenesulfonate (96). (*R*)-3,6-diethoxy-2-*iso*propyl-2,5-dihydropyrazine (0.96 mL, 4.5 mmol) was dissolved in THF (2 mL). The solution was cooled to -78 ^{o}C. *n*-BuLi (2.0 mL, 2.5 M in hexanes, 6.0 mmol) was added in dropwise. The mixture was stirred at -78 ^{o}C 1 hour. **95** (2.4 g, 3.8 mmol) was dissolved in THF (5 mL) was added dropwise *via* syringe. The mixture was slowly warmed up to -30 ^{o}C and kept 2 hours, and then warmed to room temperature, stirred overnight. Water (10 mL) was added. The mixture was extracted with ethyl ether (3×50 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanes/EtOAc=10:1) to give **96** as orange oil (2.0 g, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (m, 2H), 7.30 (m, 2H), 5.30 (s, 1H), 4.75 (m, 1H), 4.55 (m, 1H), 4.45 (m, 1H), 4.05-4.18 (m, 5H), 3.85-3.95 (m, 2H), 2.42 (s, 3H), 2.24 (m, 1H), 1.95-2.05 (m, 2H), 1.65-1.72 (m, 4H), 1.45 (s, 3H), 1.25 (m, 9H), 1.03 (d, J=6.8 Hz, 3H), 0.88 (s, 9H), 0.68

(d, J=6.8 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 162.7, 144.3, 134.5, 129.7, 127.7, 112.3, 103.4, 87.5, 84.3, 83.1, 81.2, 60.8, 60.6, 60.5, 60.3, 54.7, 69.5, 31.9, 26.5, 25.7, 25.0, 21.6, 21.0, 19.0, 17.9, 16.7, 14.4, 14.3, -4.25, -5.3.

(3*aR*,4*R*,6*R*,6*aR*)-6-((*S*)-2-Azido-4-((2*S*,5*R*)-3,6-diethoxy-5-*iso*propyl-2,5-dihydro pyrazin-2-yl)butyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (86). 96 (1.2 g, 1.7 mmol) was dissolved in DMF (10 mL). NaN_3 (0.50 g, 7.7 mmol) was added. The mixture was stirred at 80 ^{o}C overnight. The solvent was removed at reduced pressure. TBAF (5.0 mL, 1.0M in THF, 5% water content, 5.0 mmol) was added. The mixture was heated to 60 ^{o}C for 2 hour. The solvent was removed under reduced pressure. The residue was purified with silica column (hexanes/EtOAc=5:1) to give **86** as colorless oil (mixture of two isomers, beta:alpha=3:1, 0.66 g, 83%). ^{1}H NMR (mixture of two isomers, $CDCl_3$, 250 MHz) δ 5.44 (m, 1H), 4.57-4.65 (m, 2H), 4.33-4.38 (m, 2H), 4.05-4.20 (m, 5H), 3.92 (m, 2H), 2.45 (m, 1H), 2.25 (m, 1H), 1.87 (m, 2H), 1.6 (m, 3H), 1.48 (s, 3H), 1.3 (m, 9H), 1.02 (d, J=6.8 Hz, 3H), 0.70 (d, J=6.8 Hz, 3H); ^{13}C NMR (mixture of two isomers, $CDCl_3$, 62 MHz) δ 163.7, 163.5, 162.9, 162.8, 114.9, 112.4, 103.3, 95.6, 86.1, 85.0, 84.7, 84.5, 84.3, 84.0, 79.3, 77.2, 68.5, 67.7, 60.9, 60.8, 60.76, 60.70, 60.4, 59.4, 54.8, 54.6, 53.7, 39.8, 37.6, 32.0, 31.9, 30.4, 30.2, 30.0, 27.8, 26.5, 25.0, 24.9, 23.9, 22.2, 20.8, 19.1, 16.8.

9-((3*aR*,4*R*,6*R*,6*aR*)-6-((*S*)-2-Azido-4-((2*S*,5*R*)-3,6-diethoxy-5-*iso*propyl-2,5-dihy dropyrazin-2-yl)butyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-6-chloro-9*H*-purine (97). 86 (0.17 g, 0.36 mmol) was dissolve in THF (10 mL). CCl_4 (0.04 mL, 0.4 mmol) was added. At -78 ^{o}C, HMPT (0.08 mL, 0.4 mmol) was added dropwise. The mixture was stirred at same temperature for 1 hour then warmed to 0 ^{o}C, stirred 1 hour. The solution was recooled to -78 ^{o}C. Sodium salt of 6-chloropurine in DMF (10 mL)

(prepared by addition of 40 mg 60% NaH in mineral oil to 0.15 g 6-chloropurine in 10 mL DMF) was added dropwise. The mixture was warmed up to room temperature. Water (20 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate and concentrated. The residue was purified with silica column (hexanes/EtOAc=10:1) to give **97** as yellow oil (0.13 g, 60%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.89 (s, 1H), 8.63 (s, 1H), 6.61 (d, J=4.3 Hz, 1H), 5.05 (m, 1H), 4.73 (m, 2H), 4.05-4.25 (m, 4H), 3.92 (m, 1H), 3.62 (m, 1H), 2.26 (m, 2H), 1.91 (m, 2H), 1.64-1.73 (m, 4H), 1.26-1.33 (m, 12H), 1.03 (d, J=6.8 Hz, 3H), 0.72 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 62 MHz) δ 163.8, 163.8, 152.5, 147.9, 142.5, 121.9, 114.7, 87.4, 84.6, 81.1, 80.5, 61.1, 60.9, 60.8, 60.6, 59.2, 54.8, 37.2, 32.2, 30.5, 30.0, 25.7, 24.6, 19.2, 16.9, 14.5, 14.4.

9-((3*aR*,4*R*,6*R*,6*aR*)-6-((*S*)-2-Azido-4-((2*S*,5*R*)-3,6-diethoxy-5-*iso*propyl-2,5-dihydropyrazin-2-yl)butyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-*bis*(*tert*-butoxylcarbobyl)amine (98). 86 (0.80 g, 1.8 mmol) was dissolve in THF (10 mL). CCl_4 (0.21 mL, 2.2 mmol) was added. At -78 ^{o}C, HMPT (0.40 mL, 2.3 mmol) was added dropwise. The mixture was stirred at same temperature for 1 hour then warmed to 0 ^{o}C, stirred 1 hour. The solution was recooled to -78 ^{o}C. Sodium salt of $Ad(Boc)_2$ in DMF (10 mL) (prepared by addition of 200 mg 60% NaH in mineral oil to 1.5 g $Ad(Boc)_2$ in 10 mL DMF) was added dropwise. The mixture was warmed to room temperature. Water (20 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate and concentrated. The residue was purified with silica column (hexanes/EtOAc=10:1) to give **98** as yellow oil (1.3 g, 60%). ^{1}H NMR ($CDCl_3$,

250 MHz) δ 8.86 (s, 1H), 8.14 (s, 1H), 6.08 (d, J=2.5 Hz, 1H), 5.46 (m, 1H), 4.92 (m, 1H), 4.38-4.42 (m, 1H), 4.05-4.15 (m, 4H), 3.92 (m, 1H), 3.35 (m, 1H), 2.25 (m, 2H), 1.75-1.90 (m, 6H), 1.47 (s, 21H), 1.39 (s, 3H), 1.25 (m, 6H), 1.03 (d, J=6.8 Hz, 3H), 0.69 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 62 MHz) δ 163.6, 162.9, 152.5, 152.4, 150.9, 150.6, 144.3, 129.8, 115.2, 90.7, 84.4, 84.1, 84.0, 83.9, 60.8, 60.7, 60.6, 59.5, 54.9, 38.4, 32.2, 30.4, 30.1, 27.9, 27.4, 25.6, 19.2, 16.9, 14.5, 14.4.

(2*S*,5*S*)-2-Amino-6-((2*R*,3*S*,4*R*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)-5-azidohexanoic Acid (99). 98 (0.20 g, 0.34 mmol) was dissolved in TFA/H_2O (2:1, 2 mL) at -20 ^{o}C. The solution was stirred at 0 ^{o}C 6h. IRA-67 ion exchange resin was added until pH=7. The solvent was removed at reduce pressure. The residue was dissolved in MeOH/H_2O (2:1, 2 mL). K_2CO_3 (0.10 g, 0.72 mmol) was added. The mixture was stirred at room temperature for 5 hours. The solvent was removed at reduce pressure. The residue was purified with silica column (EtOAc/MeOH/NH_4OH (29.6%) =2:1:0.5) to give **99** as white solid (0.10 g, 78%). Mp>200 ^{o}C (decomposed). ^{1}H NMR (D_2O, 400 MHz) δ 8.32 (s, 1H), 8.27 (s, 1H), 6.07 (d, J=5.2 Hz, 1H), 4.85 (m, 1H), 4.33 (m, 1H), 4.15 (m, 1H), 3.80 (m, 1H), 3.65 (m, 1H), 2.00-2.10 (m, 6H). ^{13}C NMR (D_2O, 250 MHz) δ 174.4, 155.2, 152.2, 149.0, 140.8, 119.2, 88.2, 81.5, 73.7, 73.6, 69.8, 54.7, 37.5, 29.4, 27.3.

(3*aR*,4*R*,6*R*,6*aR*)-4-(Allyloxymethyl)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxole (101). 61 (10.02 g, 32.32 mmol) was dissolved in DMF (50 mL). NaH (1.54 g, 38.5 mmol, 60% in mineral oil) was added in portions. AllylBr (5.50 mL, 64.1 mmol) was added dropwise *via* a syringe. The mixture was stirred at room temperature 12 hours. Water (10 mL) was added to quench the reaction. The mixture was

extracted with ethyl ether (3×100 mL). The combined organic layer was washed with water (3×20 mL), brine (50 mL), dried over sodium sulfate, and concentrated. The residue was purified by silica column (hexanes/EtOAc=20:1) to give **101** as colorless oil (8.97 g, 79.5%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.22 (m, 2H), 6.89 (m, 2H), 5.85-5.92 (m, 1H), 5.13-5.31 (m, 3H), 4.61-4.68 (m, 3H), 4.37-4.46 (m, 2H), 4.02 (m, 2H), 3.82 (s, 3H), 3.50 (m, 2H), 1.48 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 62 MHz) δ 159.4, 134.6, 129.8, 129.2, 117.3, 113.8, 112.3, 106.9, 85.3, 85.2, 82.2, 72.2, 71.0, 68.8, 55.3, 26.4, 24.9; Calcd HRMS for $C_{19}H_{26}O_6$ (M-CH_3): 335.1499; Found: 335.1445.

2-(((3*aR*,4*R*,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)methoxy)ethanol (102). 101 (7.11 g, 20.31 mmol) was dissolved in THF (50 mL). NMO (7.20 mL, 50% in water, 31.2 mmol) was added. OsO_4 (20 mg, 0.078 mmol) was added. The mixture was stirred at room temperature overnight. Sodium thiosulfate (10 g) was added. The mixture was stirred for another 2 hours. The mixture was filtered through a short silica column (5 cm). The column was rinsed with EtOAc. The combined organic liquid was concentrated. The residue was dissolved in DCM/H_2O (1:1, 30 mL). $NaIO_4$ (6.40 g, 30.0 mmol) was added at room temperature. The mixture was stirred 3 hours. The organic layer was diluted with DCM (100 mL), separated, washed with water (20 mL), dried over sodium sulfate, and concentrated. The residue was dissolved in MeOH (30 mL) at 0 ^{o}C. $NaBH_4$ (1.80 g, 48.6 mmol) was added portionwise. The mixture was stirred at same temperature for 30 minutes. Saturated NH_4Cl solution (30 mL) was added. The mixture was filtered through celite. The solvent was removed under reduced pressure. The residue was purified by silica column (hexanes/EtOAc=3:1 to 1:1) to give **102** exclusively as a colorless oil (5.41 g, 75.2%). ^{1}H

NMR ($CDCl_3$, 400 MHz) δ 7.25 (m, 2H), 6.88 (m, 2H), 5.14 (s, 1H), 4.69 (d, J=6.0 Hz, 1H), 4.62-4.65 (m, 2H), 4.36-4.40 (m, 2H), 3.80 (s, 3H), 3.72 (m, 2H), 3.54-3.60 (m, 4H), 2.38 (m, 1H), 1.47 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.6, 129.9, 129.3, 114.1, 112.6, 107.5, 85.7, 85.5, 82.3, 72.6, 72.4, 69.2, 61.9, 55.5, 26.7, 25.2; Calcd HRMS for $C_{18}H_{26}O_7$ (M-CH_3): 339.1444; Found: 339.1444.

2-(((3*aR*,4*R*,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)methoxy)ethyl 4-Methylbenzenesulfonate (103). 102 (6.05 g, 17.0 mmol), TEA (20 mL), TsCl (3.90 g, 20.5 mmol), DABCO (50 mg) were mixed in DCM (100 mL) and stirred at room temperature 30 minutes. Water (10 mL) was added. The organic layer was separated, washed with brine (20 mL), dried over sodium sulfate and concentrated. The residue was purified by silica column (hexanse/EtOAc=5:1) to give **103** as organe oil (7.15 g, 82.3%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80 (m, 2H), 7.31 (m, 2H), 7.22 (m, 2H), 6.87 (m, 2H), 5.10 (s, 1H), 4.55-4.60 (m, 3H), 4.37 (d, J=11.6 Hz, 1H), 4.24 (m, 1H), 4.09-4.16 (m, 2H), 3.80 (s, 3H), 3.67 (m, 2H), 3.43 (m, 2H), 2.43 (s, 3H), 1.47 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.6, 145.0, 133.2, 130.0, 129.9, 129.4, 128.2, 114.1, 112.6, 107.2, 85.5, 85.1, 82.3, 72.4, 69.3, 69.0, 68.9, 55.5, 26.6, 25.1, 21.8; Calcd HRMS for $C_{25}H_{32}O_9S$: 508.1767; Found: 508.1774.

2-(((3*aR*,4*R*,6*R*,6*aR*)-6-Hydroxy-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)ethyl 4-Methylbenzenesulfonate (104). 103 (4.87 g, 9.59 mmol) was dissolved in DCM/H_2O (20:1, 30 mL). DDQ (1.10 g, 4.85 mmol) was added. The mixture was stirred vigorously at room temperature 3 hours. The precipitate was removed by filtration. The filtrate was diluted with DCM (100 mL) and washed with saturated $NaHCO_3$ solution (3×30 mL). The organic layer was dried over sodium sulfate and

concentrated. The residue was purified by a silica column (hexanes/EtOAc=3:1) to give **104** as orange oil (β:α=6:1, 2.88 g, 77.4%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (m, 2H), 7.37 (m, 2H), 5.27 (d, J=10.8 Hz, 1H), 4.71 (m, 1H), 4.45 (d, J=5.6 Hz, 1H), 4.32 (m, 1H), 4.11-4.20 (m, 3H), 3.72-3.78 (m, 2H), 3.55-3.65 (m, 2H), 2.45 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.2, 132.6, 129.9, 128.0, 112.1, 103.9, 87.2, 85.3, 81.8, 72.6, 69.1, 68.2, 26.4, 24.8, 21.7; Calcd HRMS for $C_{17}H_{24}O_8S$ ($M+NH_4$): 406.1537; Found: 406.1536.

2-(((3*aR*,4*R*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydrofuro-[3,4-*d*][1,3]dioxol-4-yl)methoxy)ethyl 4-Methylbenzenesulfonate (105). 104 (1.54 g, 3.97 mmol) was dissolved in dry DCM (60 mL). DMAP (20 mg) was added. The solution was treated with imidazole (0.68 g, 10.4 mmol), and TBSCl (1.21 g, 8.07 mmol) at 0 ^{o}C. The solution was then warmed to room temperature and stirred for 2 hours. Water (20 mL) was added to quench the reaction. The organic layer was separated, washed with brine, dried over sodium sulfate, concentrated under reduce pressure. The residue was purified by silica column (hexanes/EtOAc=5:1) to give **105** as a colorless oil (1.32 g, 66.2%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (m, 2H), 7.35 (m, 2H), 5.34 (s, 1H), 4.65 (dd, J=6.0, 0.4 Hz, 1H), 4.49 (d, J=6.0 Hz, 1H), 4.13 (m, 3H), 3.66 (m, 2H), 3.43 (m, 2H), 2.45 (s, 3H), 1.47 (s, 3H), 1.32 (s, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.8, 132.9, 129.9, 128.0, 112.3, 103.3, 87.2, 84.9, 82.5, 72.6, 69.1, 68.7, 26.5, 25.7, 25.1, 21.7, 17.9, -4.3, -5.4; Calcd HRMS for $C_{23}H_{38}O_8SSi$ ($M+NH_4$): 520.2406; Found: 520.2400.

(2*S*,5*R*)-2-(2-(((3*aR*,4*R*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetra hydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)ethyl)-3,6-diethoxy-5-*iso*propyl-2,5-dihydr

opyrazine (106). (*R*)-3,6-Diethoxy-2-*iso*propyl-2,5-dihydropyrazine (1.50 mL, 7.04 mmol) was dissolved in THF (3 mL). The solution was cooled to -78 ^{o}C. *n*-BuLi (3.00 mL, 2.5 M in hexanes, 7.50 mmol) was added in dropwise. The mixture was stirred at -78 ^{o}C for 1 hour. **105** (2.76 g, 5.49 mmol) was dissolved in THF (5 mL) was added dropwise *via* syringe. The mixture was slowly warmed up to -30 ^{o}C and kept 2 hours, and then warmed to room temperature, stirred overnight. Water (10 mL) was added to quench the reaction. The mixture was extracted with ethyl ether (3×50 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanes/EtOAc=10:1) to give **106** as orange oil, which contaminated with (*R*)-3,6-diethoxy-2-*iso*propyl-2,5-dihydropyrazine (2.03 g, "68.4%"). This product was used directly in next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.35 (s, 1H), 4.72 (m, 1H), 4.51 (m, 1H), 3.85-4.25 (m, 6H), 3.42-3.65 (m, 4H), 2.25 (m, 2H), 2.15 (m, 1H), 1.85 (m, 1H), 1.47 (s, 3H), 1.25 (m, 9H), 1.03 (d, J= 6.8 Hz, 3H), 0.89 (s, 9H), 0.77 (d, J= 6.8 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.2, 163.4, 163.1, 161.8, 112.1, 103.3, 87.3, 85.1, 82.7, 72.0, 67.7, 61.0, 60.7, 60.6, 60.5, 52.6, 46.7, 34.1, 32.6, 31.9, 26.5, 25.6, 25.0, 19.1, 19.0, 17.8, 17.0, 16.7, 14.3, -4.3, -5.5. Calcd HRMS for $C_{27}H_{50}N_2O_7Si$: 542.3387; Found: 542.3379.

(3*aR*,4*R*,6*R*,6*aR*)-6-((2-((2*S*,5*R*)-3,6-Diethoxy-5-*iso*propyl-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (107). 106 (1.72 g mixture, "3.17" mmol) was dissolved in THF (5 mL). TBAF (10.0 mL, 1M in THF) was added. The mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The residue was purified by silica column

(hexanes/EtOAc=3:1) to give **107** as colorless oil (0.81 g, 59.7%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.28 (d, J=11.0 Hz, 1H), 4.95 (d, J=11.0 Hz, 1H), 4.75 (d, J=6.0 Hz, 1H), 4.37 (m, 1H), 4.00-4.22 (m, 5H), 3.85-3.95 (m, 1H), 3.55-3.72 (m, 4H), 2.35-2.45 (m, 1H), 2.15-2.30 (m, 2H), 1.78-1.90 (m, 1H), 1.48 (s, 3H), 1.28 (m, 9H), 1.03 (d, J=6.8 Hz, 3H), 0.71 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 163.6, 162.9, 111.9, 103.8, 87.5, 85.6, 81.9, 71.9, 68.8, 60.8, 53.9, 52.3, 33.6, 29.2, 26.4, 24.8, 20.8, 19.1, 16.8, 14.4, 14.3; Calcd HRMS for $C_{21}H_{36}N_2O_7$: 428.2523; Found: 425.2518.

6-Chloro-9-((3*aR*,4*R*,6*R*,6*aR*)-6-((2-((2*S*,5*R*)-3,6-diethoxy-5-*iso*propyl-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purine (108). 107 (0.18 g, 0.42 mmol) was dissolve in THF (2 mL). CCl_4 (0.15 mL, 1.56 mmol) was added. At -78 ^{o}C, HMPT (0.09 mL, 0.50 mmol) was added dropwise. The mixture was stirred at same temperature for 1 hour then warmed to 0 ^{o}C, stirred 1 hour. The solution was recooled to -78 ^{o}C. Sodium salt of 6-chloropurine in DMF (10 mL) (prepared by addition of 260 mg 60% NaH in mineral oil to 1.00 g 6-chloropurine in 10 mL DMF) was added dropwise. The mixture was warmed to room temperature. Water (20 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine (3×30 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanes/EtOAc=3:1) to give **108** as yellow oil (0.07 g, 28%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.72 (s, 1H), 8.41 (s, 1H), 6.64 (m, 1H), 4.91 (m, 1H), 4.51 (m, 1H), 4.05-4.21 (m, 6H), 3.90 (m, 1H), 3.60-3.72 (m, 4H), 2.18-2.25 (m, 2H), 1.90 (m, 1H), 1.43 (s, 3H), 1.28 (m, 9H), 1.03 (d, J=7.2 Hz, 3H), 0.71 (d, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 163.0, 151.9, 151.1, 150.7, 145.1, 131.5, 113.4, 86.5, 82.5, 82.2, 79.8,

72.7, 68.8, 60.8, 52.7, 34.1, 31.9, 25.7, 24.0, 19.1, 16.7, 14.4, 14.3, 14.2, 14.1; Calcd HRMS for $C_{26}H_{37}ClN_6O_6$: 564.2463; Found: 564.2448.

9-((3*aR*,4*R*,6*R*,6*aR*)-6-((2-((2*S*,5*R*)-3,6-Diethoxy-5-*iso*propyl-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9H-6-*bis*(tert-butoxylcarboxyl)aminopurine (109). 107 (0.61 g, 1.43 mmol) was dissolve in THF (10 mL). CCl_4 (0.20 mL, 2.0 mmol) was added. At -78 ^oC, HMPT (0.35 mL, 2.0 mmol) was added dropwise. The mixture was stirred at same temperature for 1 hour then warmed to 0 ^oC, stirred 1 hour. The solution was recooled to -78 ^oC. Sodium salt of $Ad(Boc)_2$ in DMF (10 mL) (prepared by addition of 260 mg 60% NaH in mineral oil to 1.80 g $Ad(Boc)_2$ in 10 mL DMF) was added dropwise. The mixture was warmed to room temperature and stirred overnight. Water (20 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine (3×30 mL), dried over sodium sulfate and concentrated. The residue was purified with silica column (hexanes/EtOAc=3:1) to give **109** as yellow oil (0.23 g, 25%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.88 (s, 1H), 8.38 (s, 1H), 6.28 (d, J=2.8 Hz, 1H), 5.23 (m, 1H), 4.95 (m, 1H), 4.52 (m, 1H), 3.95-4.23 (m, 6H), 3.55-3.65 (m, 4H), 2.25 (m, 1H), 2.28 (m, 1H), 1.82 (m, 1H), 1.65 (s, 3H), 1.38-1.48 (m, 27H), 1.02 (d, J=7.2 Hz, 3H), 0.70 (d, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.3, 163.0, 152.9, 152.3, 150.4, 150.3, 143.4, 133.6, 137.0, 129.3, 114.2, 91.4, 85.8, 85.1, 83.7, 81.8, 70.9, 68.4, 60.75, 60.71, 60.62, 60.56, 52.6, 33.8, 31.9, 27.8, 27.3, 25.3, 19.1, 14.4, 14.3; Calcd HRMS for $C_{36}H_{55}N_7O_{10}$: 745.4010; Found: 740.3993.

(*S*)-2-Amino-4-(((2*R*,3*S*,4*R*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methoxy)butanoic Acid (6). 109 (0.10 g, 0.92 mmol) was dissolved in

TFA/H_2O (2:1, 2 mL) at -20 ^oC. The solution was stirred at 0 ^oC for 6 hours. IRA-67 ion exchange resin was added to neutralize the mixture. The resin was removed by filtration. The solvent was removed at reduce pressure. The residue was dissolved in MeOH/H_2O (2:1, 2 mL). K_2CO_3 (0.20 g, 1.4 mmol) was added. The mixture was stirred at room temperature for 5 hours. The solvent was removed under reduced pressure. The residue was purified with silica column (EtOAc/MeOH/NH_4OH (29.6%) =1:1:1) to give **6** as white foam (0.030 g, 61%). m.p.>210 ^oC (decomposed). ^1H NMR (D_2O, 250 MHz) δ 8.35 (s, 1H), 8.22 (s, 1H), 6.07 (d, J=5.0 Hz, 1H), 4.78 (m, 2H), 4.43 (m, 1H), 4.32 (m, 1H), 3.65-3.85 (m, 4H), 2.15-2.25 (m, 2H). ^{13}C NMR (D_2O, 62 MHz) δ 175.3, 155.8, 152.8, 140.7, 88.3, 83.7, 74.2, 71.0, 70.8, 68.8, 54.0, 30.6. Calcd HRMS for $C_{14}H_{20}N_6O_6$ (M+H): 369.1522; Found: 369.1525.

***tert*-Butyl((3*aR*,4*S*,6*R*,6*aR*)-2,2-dimethyl-6-vinyl-tetrahydro-3*aH*-cyclopenta-[*d*]-[1,3]dioxol-4-yloxy)dimethylsilane (110).** VinylMgBr (25 mL, 1.0 M in THF, 25 mmol) was added to a suspension of CuBr·SMe_2 (0.41 g, 2.0 mmol) in THF (30 mL) at -78 ^oC. The mixture was stirred at this temperature for 1 hour. Compound **49** (3.0 g, 19 mmol), HMPA (10 mL), TMSCl (3.2 mL, 25 mmol) in THF (30 mL) was added dropwise at -78 ^oC. The mixture was warmed to room temperature and stirred overnight. Saturated NH_4Cl solution (30 mL) was added to quench the reaction. The mixture was exctracted with ethyl ether (3×100 mL). The combined organic layer was washed with bine (100 mL), dried over sodium sulfate, and concentrated. The residue was dissolved in MeOH (100 mL). $CeCl_3·7H_2O$ (7.4 g, 20 mmol) was added at 0 ^oC. $NaBH_4$ (0.74 g, 20 mmol) was added portionwise. The mixture was stirred at this temperature for 1 hour. Saturated NH_4Cl solution (20 mL) was added to quench the reaction. The mixture was filtered

through celite. The filtrated was concentrated. The residue was extrated with ethyl ether (3×100 mL). The combined organic layer was dried over sodium sulfate, and filtered through a short silica column (10 cm). The filtrate was concentrated. The residue was dissolved in DCM (100 mL). TBSCl (3.0 g, 20 mmol), imidazole (2.0 g, 31 mmol) were added at room temperature. The mixture was stirred 3 hours. Water (10 mL) was added to quench the reaction. The organic layer was sperated, washed with water (20 mL), dried over sodium sulfate, and concentrated. The residu was purified by silica column (Hexanes/EtOAc=20:1) to give **110** as a colorless oil (2.5 g, 43%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76 (m, 1H), 5.02-5.08 (m, 2H), 4.37 (m, 2H), 4.07 (m, 1H), 2.66 (m, 1H), 2.03 (m, 1H), 1.73 (m, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.1, 114.7, 111.3, 84.1, 80.1, 72.5, 44.3, 35.6, 26.3, 25.7, 24.7 18.4, -4.4, -4.7. Cacld HRMS for $C_{16}H_{30}O_3Si$ (M+H): 299.2042; Found: 299.2043.

((3*aR*,4*R*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methanol (111). **110** (2.5 g, 8.4 mmol) was dissolved in THF (50 mL). NMO (3.6 mL, 50% in water, 16 mmol) was added. OsO_4 (20 mg, 0.078 mmol) was added. The mixture was stirred at room temperature overnight. Sodium thiosulfate (5 g) was added. The mixture was stirred for another 2 hours. The mixture was filtered through a short silica column (5 cm). The column was rinsed with EtOAc. The combined organic liquid was concentrated. The residue was dissolved in DCM/H_2O (1:1, 30 mL). $NaIO_4$ (2.1 g, 9.9 mmol) was added at room temperature. The mixture was stirred 3 hours. The organic layer was diluted with DCM (90 mL), separated, washed with water (20 mL), dried over sodium sulfate, and concentrated. The residue was dissolved in MeOH (30 mL) at 0 ^{o}C. $NaBH_4$ (0.30 g, 6.4 mmol) was added portionwise.

The mixture was stirred at same temperature for 30 minutes. Saturated NH_4Cl solution (30 mL) was added. The mixture was filtered through celite. The solvent was removed under reduced pressure. The residue was purified by silica column (hexanes/EtOAc=3:1 to 1:1) to give **111** exclusively as a colorless oil (2.1 g, 84%). The NMR spectra are consistent with the literature.[232]

((3*aR*,4*S*,6*R*,6*aR*)-6-(Allyloxymethyl)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta--[*d*][1,3]dioxol-4-yloxy)(*tert*-butyl)dimethylsilane (112). Compound **111** (1.6 g, 5.3 mmol) was dissolved in DMF (50 mL). NaH (0.25 g, 6.3 mmol, 60% in mineral oil) was added in portions. AllylBr (1.1 mL, 12 mmol) was added dropwise *via* a syringe. The mixture was stirred at room temperature 12 hours. Water (10 mL) was added to quench the reaction. The mixture was extracted with ethyl ether (3×100 mL). The combined organic layer was washed with water (3×20 mL), brine (50 mL), dried over sodium sulfate, and concentrated. The residue was purified by silica column (hexanes/EtOAc=20:1) to give **112** as a colorless oil (1.6 g, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (m, 1H), 5.14-5.26 (m, 2H), 4.38 (m, 2H), 4.19 (m, 1H), 3.94 (m, 2H), 3.37 (m, 1H), 3.30 (m, 1H), 2.24 (m, 1H), 2.05 (m, 1H), 1.68 (m, 1H), 1.48 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.8, 116.7, 111.3, 82.5, 80.9, 77.3, 72.9, 72.0, 42.3, 34.8, 26.6, 26.1, 24.9, 18.5, -4.4, -4.7. Calcd HRMS for $C_{18}H_{34}O_4Si$ (M+H): 343.2305; Found: 343.2312.

2-(((3*aR*,4*R*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methoxy)ethanol (**113**). Compound **113** was prepared from **112** by the same procedure used in synthesis of **111**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.38 (m, 2H), 4.14 (m, 1H), 3.72 (m, 2H), 3.55 (m, 2H), 3.42 (m, 1H), 3.35 (m, 1H), 2.29

(br, 1H), 2.03 (m, 2H), 1.62 (m, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.6, 82.3, 80.9, 73.0, 72.9, 72.2, 61.8, 42.4, 34.6, 26.5, 26.0, 24.9, 18.5, -4.4, -4.8. Calcd HRMS for $C_{17}H_{34}O_5Si$ (M+H): 347.2254; Found: 347.2249.

2-(((3*aR*,4*R*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methoxy)ethyl 4-Methylbenzenesulfonate (114). Compound **114** was prepared from **113** by the same procedure used in synthesis of **103**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (m, 2H), 7.33 (m, 2H), 4.31 (m, 2H), 4.13 (m, 3H), 3.62 (m, 2H), 3.37 (m, 1H), 3.28 (m, 1H), 2.45 (s, 3H), 2.18 (m, 1H), 2.05 (m, 1H), 1.53 (m, 1H), 1.47 (s, 3H), 1.30 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.9, 133.0, 129.9, 127.9, 111.4, 82.2, 80.9, 77.2, 73.2, 72.9, 69.1, 68.5, 68.0, 42.2, 34.6, 26.6, 25.6, 24.9, 21.7, 18.5, -4.4, -4.7. Calcd HRMS for $C_{24}H_{40}O_7SSi$ (M+H): 501.2342; Found: 501.2338.

(2*S*,5*R*)-2-(2-(((3*aR*,4*R*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methoxy)ethyl)-3,6-diethoxy-5-*iso*propyl-2,5-dihydropyrazine (115). Compound **115** was prepared from **114** by the same procedure used in synthesis of **106**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.28-4.38 (m, 3H), 4.15 (m, 2H), 4.10 (m, 2H), 4.05 (m, 1H), 3.87 (m, 1H), 3.55 (m, 1H), 3.45 (m, 1H), 3.25-3.35 (m, 2H), 2.25 (m, 1H), 2.17 (m, 2H), 2.05 (m, 1H), 1.77 (m, 1H), 1.62 (m, 1H), 1.48 (s, 3H), 1.25-1.32 (m, 9H), 1.03 (d, J=6.8 Hz, 3H), 0.91 (s, 9H), 0.72 (d, J=6.8 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 163.0, 111.1, 82.5, 81.1, 73.1, 72.7, 67.7, 61.9, 61.8, 60.6, 60.5, 52.6, 42.3, 31.9, 29.2, 26.6, 26.1, 24.8, 19.1, 18.5, 16.7, 14.7, 14.4, -4.4, -4.7. Calcd HRMS for $C_{28}H_{52}N_2O_6Si$: 540.3595; Found: 540.3584.

(3*aS*,4*S*,6*R*,6*aR*)-6-((2-((2*S*,5*R*)-3,6-Diethoxy-5-*iso*propyl-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-ol (116). Compound **116** was prepared from **115** by the same procedure used in synthesis of **107**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.49 (m, 1H), 4.45 (m, 1H), 4.08-4.21 (m, 5H), 3.96 (m, 1H), 3.87 (m, 1H), 3.53 (m, 1H), 3.45 (m, 1H), 3.35 (m, 1H), 3.25 (m, 1H), 2.40 (d, J=8.4 Hz, 1H), 2.25 (m, 2H), 2.12 (m, 1H), 1.82 (m, 3H), 1.49 (s, 3H), 1.34 (s, 3H), 1.25-1.28 (m, 6H), 1.03 (d, J=6.8 Hz, 3H), 0.72 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.2, 163.1, 111.2, 83.1, 79.6, 76.3, 72.2, 67.8, 60.69, 60.65, 60.57, 60.51, 52.7, 42.0, 35.5, 34.2, 31.9, 26.2, 26.1, 14.4, 14.3. Calcd HRMS for $C_{22}H_{38}N_2O_6$: 426.2730; Found: 426.2733.

9-((3*aS*,4*R*,6*R*,6*aR*)-6-((2-((2*S*,5*R*)-3,6-Diethoxy-5-*iso*propyl-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)-9*H*-purin-6-di(*tert*-butoxylcarbonyl)amine (117). Comound **116** (0.14 g, 0.33 mmol) was dissolved in THF. Ph_3P (0.17 g, 0.66 mmol), $Ad(Boc)_2$ (0.22 g, 0.66 mmol) were added. DIAD (0.13 mL, 0.66 mmol) was added portionwise *via* a syringe at 0 ^{o}C. The mixture was warmed to room temperature and stirred overnight. The solvent was removed under reduced pressure. The residu was purified with a silica column to give **117** as an organge oil (0.14 g, 57%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85 (s, 1H), 8.21 (s, 1H), 5.09 (m, 1H), 4.95 (m, 1H), 4.85 (m, 1H), 4.63 (m, 1H), 4.05-4.21 (m, 6H), 3.85 (m, 1H), 3.55 (m, 3H), 2.45 (m, 2H), 2.25 (m, 1H), 2.15 (m, 1H), 1.90 (m, 1H), 1.55 (s, 3H), 1.47 (s, 18H), 1.35 (s, 3H), 1.27 (m, 6H), 1.03 (d, J=6.8 Hz, 3H), 0.70 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 163.2, 153.5, 151.8, 150.6, 150.4, 143.9, 129.4, 113.7, 83.7, 71.8, 67.9, 61.9, 60.6, 60.5, 59.6, 52.7, 43.8, 33.9, 33.7, 31.9, 27.9, 27.8, 27.7, 25.1, 21.9, 21.8,

19.2, 16.8, 14.4, 14.2. Calcd HRMS for $C_{37}H_{57}N_7O_9$: 743.4218; Found: 743.4208.

(*S*)-2-Amino-4-(((1*R*,2*R*,3*S*,4*R*)-4-(6-amino-9*H*-purin-9-yl)-2,3-dihydroxycyclopentyl)methoxy)butanoic Acid (7). Compound **7** was prepared from **117** by the same procedure used in synthesis of **6**. ^{1}H NMR (D_2O/MeOD, 400 MHz) δ 8.24 (s, 1H), 8.17 (s, 1H), 4.75 (m, 1H), 4.50 (m, 1H), 4.09 (m, 2H), 3.85 (m, 1H), 3.65 (m, 2H), 3.55 (m, 2H), 2.40 (m, 2H), 2.25 (m, 1H), 2.15 (m, 1H); ^{13}C NMR (D_2O/MeOD, 100 MHz) δ 173.4, 155.4, 152.0, 149.1, 140.5, 118.7, 74.7, 72.5, 72.2, 67.9, 59.6, 53.7, 42.8, 29.9, 28.9. Calcd HRMS for $C_{15}H_{22}N_6O_5$ (M+H): 367.1730; Found: 367.1740.

((3*aR*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-6,6a-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methanol (119). Compound **118** (0.85 g, 2.8 mmol) was dissolve in DCM (30 mL). TBSCl (0.85 g, 5.6 mmol), imidazole (0.36 g, 5.6 mmol) were added at room temperature. The mixture was stirred at room temperature for 5 hours. Water (10 mL) was added to quench the reaction. The organic layer was separated, dried over sodium sulfate, and filtered through a short silica column. The filtrate was concentrated under reduce pressure (water bath temperature: 80 ^{o}C). The resulting colorless oil was dissolved in THF and cooled to -78 ^{o}C. TBAF (2.8 mL, 1.0 M in THF, 2.8 mmol) was added. The solution was slowly warmed to room temperature. Saturated NH_4Cl solution (10 mL) was added. The mixture was extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine (3×20 mL), dried over sodium sulfate, and concentrated. The residue was purified with silica column (hexanes/EtOAc=2:1) to give **119** as a colorless oil (0.54 g, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.67 (m, 1H), 4.89 (m, 1H), 4.64-4.67 (m, 2H), 4.30-4.38 (m, 2H), 2.05 (br, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.7, 130.5,

112.4, 83.2, 79.1, 74.5, 60.2, 27.4, 26.7, 25.9, 18.5, -4.4, -4.7.

((3*aR*,4*S*,6*aR*)-6-(Allyloxymethyl)-2,2-dimethyl-4,6*a*-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yloxy)(*tert*-butyl)dimethylsilane (120). Compound **120** was prepared from **119** by the same procedure used in synthesis of **101**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.85-5.95 (m, 1H), 5.70 (m, 1H), 5.26 (dm, J=17.2 Hz, 1H), 5.19 (dm, J= 10.4 Hz, 1H), 4.88 (d, J=4.8 Hz, 1H), 4.65 (m, 2H), 4.13 (m, 2H), 4.03 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.8, 134.6, 131.6, 117.2, 112.2, 82.8, 78.9, 74.6, 71.9, 66.5, 27.5, 26.8, 25.9, 18.5, -4.4, -4.7.

2-(((3*aR*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-6,6*a*-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methoxy)ethanol (121). Compound **120** (0.35 g, 1.0 mmol) was dissolved in *tert*-BuOH/H_2O (1:1, 10 mL). AD-mix-beta (1.4 g) was added. The mixture was stirred at room temperature for 24 hours. Sodium thiosulfate (2.0 g) was added to quench the reaction. The mixture was extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, and concentrated. The residue was dissolved in MeOH/H_2O (1:1, 10 mL). $NaIO_4$ (0.26 g, 1.2 mmol) was added. The mixture was stirred at room temperature for 3 hours. $NaBH_4$ (0.24 g, 5.1 mmol) was added portionwise. The mixture was stirred at room temperature for 30 minutes. Saturated NH_4Cl solution (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×100 mL). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, and concentrated. The residue was purified by a silica column (Hexanes/EtOAc=2:1) to produce **121** as colorless oil (0.34 g, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.69 (m, 1H), 4.89 (d, J=5.2 Hz, 1H), 4.65 (m, 2H), 4.19 (m, 2H), 3.75 (m, 2H), 3.59 (m, 2H), 1.41 (s, 3H), 1.37 (s, 3H), 0.92 (s, 9H), 0.14 (s,

3H), 0.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.6, 131.9, 112.3, 82.9, 78.9, 74.5, 71.9, 67.5, 61.8, 27.4, 26.7, 25.9, 18.5, -4.4, -4.7.

2-(((3*aR*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-6,6*a*-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methoxy)ethyl 4-Methylbenzenesulfonate (122). Compound **122** was prepared from **121** by the same procedure used in synthesis of **103**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (dm, J=8.4 Hz, 2H), 7.34 (dm, J=8.4 Hz, 2H), 5.64 (d, J=1.2 Hz, 1H), 4.80 (d, J=4.0 Hz, 1H), 4.63 (m, 2H), 4.08-4.18 (m, 4H), 3.64-3.67 (m, 2H), 2.44 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.8, 141.2, 133.0, 132.0, 129.9, 128.0, 112.2, 82.7, 78.9, 74.5, 69.1, 68.2, 67.6, 27.4, 26.8, 25.9, 21.7, 18.2, -4.4, -4.7.

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