EXPLORING SINEFUNGIN ANALOGS AS POTENTIAL ANTIVIRAL AGENTS

Tetyana S. Shulyak

A Dissertation

Submitted to

the Graduate Faculty of

Auburn University

in Partial Fulfillment of the

Requirements for the

Degree of

Doctor of Philosophy

Auburn, Alabama

August 8, 2005

VITA

Tetyana S. Shulyak, daughter of Stepan and Ludmila Shulyak, was born in Poninka, Ukraine, on March 03, 1973. After graduating from High School in June 1994, she began her studies at Kiev National T. Shevchenko University and received a Bachelor of Science degree in June 1998. A year later, she received a Master of Science degree in Chemistry from the same University. She began her Ph.D. studies at Auburn University in August 2001. She is married to Andriy S. Korchev, son of Sergiy and Irina Korchev.

DISSERTATION ABSTRACT

EXPLORING SINEFUNGIN ANALOGS AS POTENTIAL ANTIVIRAL AGENTS

Tetyana S. Shulyak

Doctor of Philosophy, 2005
(M.S., Kiev National T. Shevchenko University, 1999)

159 pages
directed by Dr. S. Schneller

Sinefungin bears a strong structural resemblance to S-adenosylmethionine and S-adenosylhomocysteine and, therefore is one of the most potent inhibitors of viral mRNA methyl transferase. Besides antiviral activity, sinefungin was found to have a variety of other biological effects including antifungal, amoebicidal and antiparasitical activities. However, clinical use of natural sinefungin is restricted because of its severe toxicity and very serious side effects.

To develop new antiviral agents retaining sinefungin-based antiviral activity while eliminating possible instability related to phosphorolysis of furanosyl nucleosides, carbocyclic sinefungin analogs are compounds of great scientific interest. In considering approaches to carbocyclic sinefungin, it was recognized that construction of the cyclopentane ring system with a sinefungin side-chain would be a challenging task. For

this purpose compounds **I** and **II** became targets to develop a method for the construction of 5'-C chain on the carbocyclic ring.

After we discovered a way of introducing the 5' chain on the cyclopentane ring, compounds of more complicated structure were designed. The carbocyclic analogs of sinefungin with the amino group replaced by a hydroxyl substituent and a shortened 5'-C side chain became target compounds **III** and **IV**. Compound **III** was successfully synthesized as an epimeric mixture at the 9' carbon and results of its antiviral testing are forthcoming. Compound **IV** was difficult to make due to instability of intermediate aldehyde resulting in undesired mixture of stereoisomers at the 4' carbon.

Furanosyl derivatives of sinefungin with side chain modifications were also designed as target compounds **V** and **VI**. Research toward those analogues provided an entry to a variety of carbocyclic nucleoside derivatives with a C-5' modified side chain.

ACKNOWLEDGMENTS

This dissertation would not have been possible without the help of many people. First and foremost, I would like to kindly thank my research adviser Dr. Stewart W. Schneller for providing me with valuable knowledge both professionally and personally, for guidance and support. Thanks are extended to members of Committee including Drs. Holly Ellis, J. Howard Hargis, Edward J. Parish and Dr. Randall Clark for their intellectual assistance and constructive suggestions. The great discussions and help from my group members, especially from Dr. Minmin Yang, are also sincerely acknowledged. Additionally, I extend my gratitude to Department of Chemistry and Biochemistry and National Institutes of Health for their financial support.

And finally, I am deeply indebted to my husband, Andriy Korchev for his patience, support, and never-ending encouragement.

Style manual or journal used:

American Chemical Society style

Computer software used:

Microsoft Word 2000, ISIS Draw 2.0

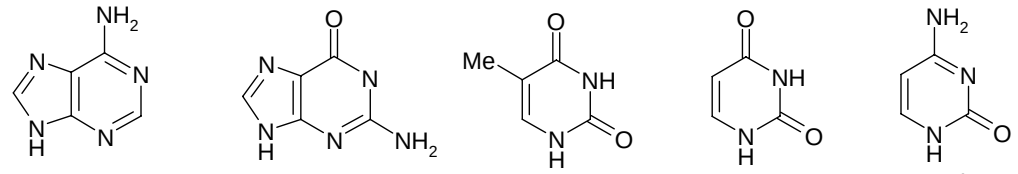
TABLE OF CONTENTS

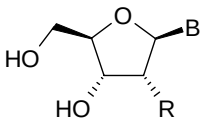
LIST OF SCHEMES

LIST OF FIGURES

Introduction.

Nucleosides are naturally occurring molecules that are the building blocks of DNA and RNA. [1] It's known that nucleic acids DNA and RNA are the genetic material that cells and viruses use to produce copies of themselves.[2] The monomeric units of DNA and RNA are nucleotides - phosphate esters of nucleosides. Nucleosides consist of a nitrogenous base linked to the 1'-C of a sugar residue (Figure 1). In ribonucleotides, the pentose is the D-ribose residue and the base can be adenine, guanine, uracil or cytosine. In deoxyribonucleosides, the sugar residue is 2'-deoxy-D-ribose and base can be adenine, guanine, uracil or thymine.





Building blocks of RNA: R=OH, B=A, G, U, C.

Building blocks of DNA: R=H, B=A, G, U, T

Figure 1. Nucleosides as monomeric units of DNA and RNA.

Nucleosides play important roles in biological metabolism. For example, adenine is a major component of ATP, coenzyme A and nicotinamide adenosine dinucleotide (NAD^+), which are central for a variety of biological effects.[3, 4]

Because of the increased possibility of bioterrorist attack nowadays, scientists are in an extensive search for new drugs against viral infections.[5] Particular attention has been paid to the orthopox family of viruses, especially to variola, the causative agent of smallpox. Although a vaccine is available for this disease, it is only effective in the first few days post-infection and there are complications associated with its use.[6] Thus, considering that variola virus is highly transmissible and smallpox has high mortality (30%), vaccine may not be effective enough to prevent the epidemic spread. This points to the need to develop drugs effective against smallpox.

Antiviral drugs are also needed to treat some diseases for which vaccines are not available (for example most respiratory-tract virus infections, herpes virus, hepatitis C virus (HCV), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV) [7]) or have some undesirable side-effects, such as hepatitis B vaccine.[8]

Because viral genetic material is composed of nucleic acids, modified nucleosides and nucleotides have high therapeutic potential against viral infections either in their native form or upon viral activation.

Since the discovery of the anti-herpes activity of 5-iodo-2'-deoxyuridine in 1959,[9] a great number of nucleosides has been synthesized in search of new antiviral agents.[10] Among those which were clinically approved, acyclovir,[11] gancyclovir[12] (both acyclic nucleoside analogues), and 5-iodo-2'-deoxyuridine[9] require viral processing to their

triphosphates for treatment of herpesviruses via inhibition of viral DNA polymerase (Figure 2).

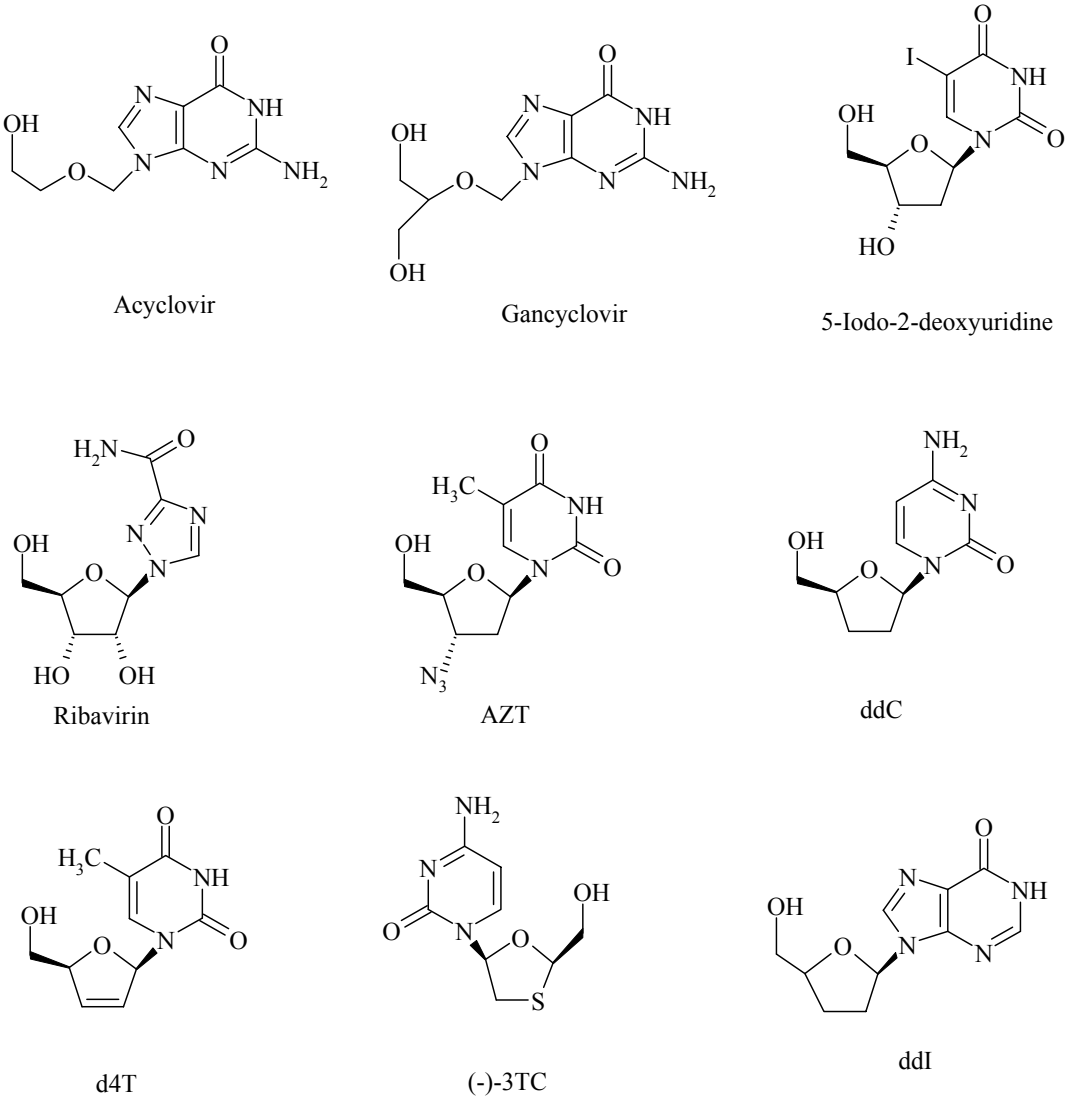
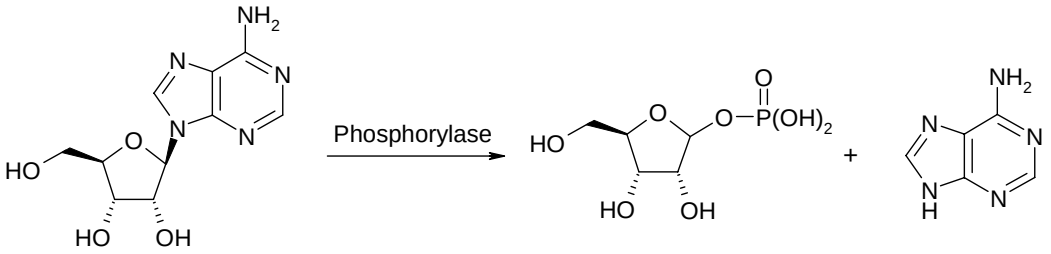


Figure 2. Nucleosides with antiviral activity.

Ribavirin represents a base-modified nucleoside analogue and it is used in combination with interferon-α for treatment of hepatitis C virus (HCV) and respiratory syncytial virus (RSV).[13] It also has been found to inhibit vaccinia virus replication *in*

vitro and have activity against several ortho- and paramyxoviral strains.[14] 3'-azido-3'-deoxythymidine (AZT)[15], 2',3'-dideoxycytidine (ddC),[16] 2',3'-dideoxyinosine (ddI),[16] 2',3'-didehydro-3'-deoxythymidine (d4T),[17] and (-)-2',3'-dideoxy-3'-thiacytidine ((-)-3TC)[18] as other modified nucleosides, have been approved as drugs against AIDS.

Unfortunately, clinical applications of these nucleosides have been limited by many accompanying side-effects such as toxicity and drug-resistance.[19] Also, there is a problem related to instability of the N-glycosidic bond between the heterocycle and the sugar moiety.[20] This bond can readily undergo phosphorolysis to give 1'- phosphoribose and base (Scheme 1), which makes it very difficult, if not impossible, for many active compounds to be delivered to their target intact for therapeutic action.



Scheme 1. Phosphorolysis of nucleosides.

To find a way of avoiding this undesirable reaction, investigations shifted to the synthesis of carbocyclic nucleosides, where a more stable C-N bond exists as a result of replacing the furanose oxygen of traditional nucleosides with a methylene group.[21] In addition to greater stability of carbocyclic nucleosides against phosphorylases, their higher lipophilicity is a potential benefit for oral uptake and cellular penetration. At the same time, the similarity between the cyclopentane ring of carbocyclic nucleosides and

the tetrahydrofuran ring of natural nucleosides renders carbocyclic nucleosides recognizable as substrates for the nucleoside processing enzyme in living cells.

Aristeromycin (Ari) and neplanocin A (NpcA) are two of the first important carbocyclic nucleosides found in nature that show significant antiviral activity. As shown on Figure 3, both of them are carbocyclic analogues of adenine and differ from each other only by the presence of a double bond between C-4' and C-6' of the carbocyclic ring of neplanocin.

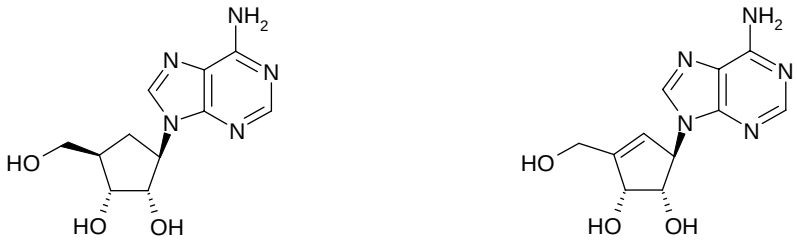


Figure 3. Structures of aristeromycin and neplanocin.

Aristeromycin was isolated form *Streptomyces citricolor* in 1969[22] while neplanocin A was isolated form the culture broth of *Ampullariella regularis* in 1979.[23] Both of these compounds were subjected to various biological testing assays and showed a characteristic antiviral activity spectrum, being effective against poxviruses, reoviruses and others.[24] The mode of action for aristeromycin and neplanocin A is inhibition of S-adenosyl-methionine (AdoMet) mediated biomethylations, which is a critical step in viral replication and, thus, a potential target for antiviral agents.[25]

Among other carbocyclic nucleosides showing great therapeutic potential are carbovir and abacavir (potent anti-HIV activity as triphosphates),[26] carbocyclic 2'-*ara*-2'-fluoroguanosine (anti-HSV activity),[27] and entecavir (anti-HBV activity)[28] (Figure 4).

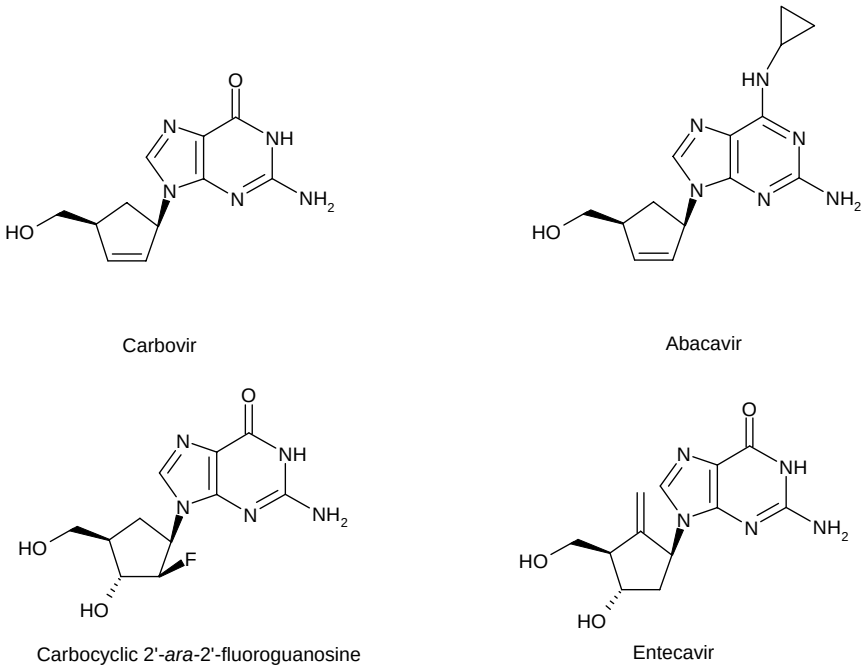


Figure 4. Carbocyclic nucleosides with antiviral activity.

Such broad antiviral activities of these compounds (Figures 3 and 4) sparked an enthusiastic explosion of interest in carbocyclic nucleosides.[29] In spite of a great variety of existing antiviral candidates, many of them are not well tolerated and with time face viral resistance. Search for new and better nucleoside drugs continues inspired.[30]

Potential agents against poxvirus infections.

History.

Orthopoxviruses (poxviruses) are the largest animal viruses visible with a light microscope and are larger than some bacteria. The family of poxviruses includes such

viruses as smallpox, vaccinia, cowpox, camelpox, monkeypox, parapoxvirus, tanapox, and molluscum contagiosum.

Poxviruses have been known for centuries -- their name coming from characteristic "pocks" produced by variola virus (smallpox). The origin of smallpox is uncertain, but it is believed to have originated in Africa and then spread to India and China thousands of years ago - spots on mummified remains of the face of the Pharaoh Ramses V, who died in 1157 B.C., are believed to be from smallpox. The disease reached Europe in 710 A.D. and was transferred to America by Hernando Cortez in 1520, leading to smallpox decimation of the native population, who never had been exposed to variola. In the cities of 17th and 18th century Europe, smallpox was the most serious infectious disease and accounted for a substantial proportion of deaths.[31]

The retreat of smallpox began with the realization that those who survived the disease were immune for the rest of their lives. This led to the development of variolation (that is, when a healthy person is exposed to infected material from a person with smallpox in order to produce a mild disease, immunity from further infection resulted). The first written record of variolation describes a Buddhist nun practicing around 1022 to 1063 AD, who would grind up scabs taken from a smallpox infected person into a powder, and then blow it into the nostrils of a non-immune person. By the 1700's, this method was common practice in India, China, and Turkey. European physicians started using this variolation method in the late 1700's, but reported discouraging results in some cases. Overall, 2% to 3% of people who were variolated died of smallpox, but this practice decreased the total number of smallpox fatalities by 10-fold.[32]

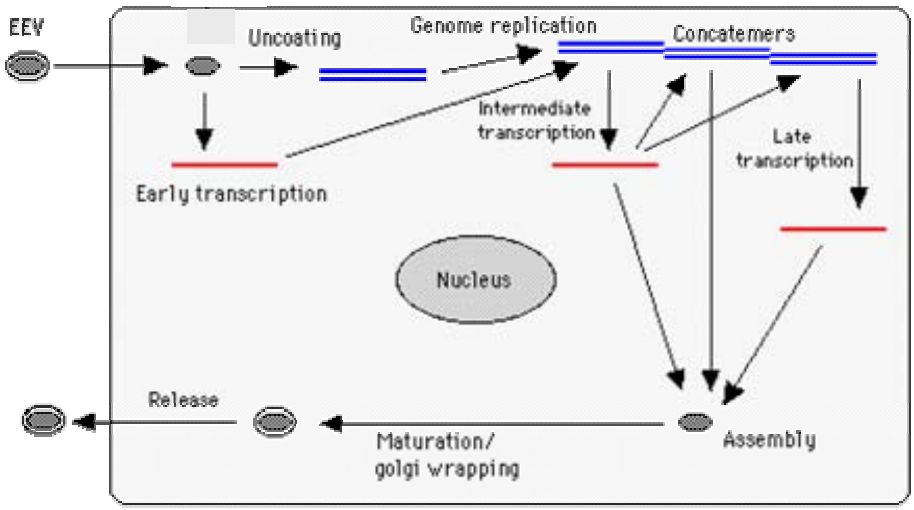
The next step towards the fall of smallpox occurred when a vaccine was developed by Jenner in 1796 by subcutaneously inoculating patients with the milder cowpox virus. Jenner coined the term "vaccinia" from the word "vaca" which means "cow" in Latin. His work was initially criticized, but was soon rapidly accepted and adopted.[32, 33] In 1967 the World Health Organization (WHO) started a worldwide campaign to eradicate smallpox using the Jenner results. This goal was accomplished in a large part due to massive worldwide vaccination efforts. The last case of smallpox occurred in Somalia in 1977. On May 8, 1980, the World Health Assembly declared the world free of smallpox.[34] The variola virus no longer exists outside of two laboratories, one in the United Stetes and one in Russia.

Structure and replication of poxviruses.

An intact virus particle is referred as virion and consists of nucleic acid molecules encased by a protein capsid. Poxviruses have the largest genome, comprised of 200 kilobase double-stranded DNA enclosed in a double membrane layer. Quite remarkably, they are the only viruses that replicate in cell cytoplasm without involvement of the host cell nucleus (that is, the virus is sufficiently complex to have acquired all the functions necessary for genome replication[35]).

The viral life cycle consists of several crucial steps, that can be represented by a general Scheme 2. The process begins when virus particles land on the cell surface and are taken into the cell by receptor-mediated endocytosis or fusion. A cellular trypsin-like enzyme cleaves surface glycoprotein into products which promote fusion of the virus envelope and the endosome membranes. A minor virus envelope protein acts as an ion

channel thereby making the inside of the virion more acidic. As a result, the major envelope protein dissociates from the nucleocapsid and the genetic information (DNA) of the virus is released into the cell via interaction between nucleoproteins and cellular transport machinery. [36]



Scheme 2. Pox virus replication.

After the initial phase of uncoating has occurred, the virus can make a limited number of mRNAs (the immediate early mRNAs) using a viral DNA-dependent RNA polymerase. Following modifications of capping, methylation and polyadenylation of the poxvirus mRNAs occur in the cytoplasm and are carried out by virally-coded enzymes. An uncoating enzyme is one of the immediate early mRNA translation products which allows further uncoating of the vaccinia DNA and more genes can now be transcribed with early genes being expressed. The early proteins are involved in DNA replication,

RNA transcription, RNA modification and uncoating. They also include a few structural proteins.[37]

Late transcription and translation is a complex process. After penetration, the genome of most viruses is transported to specific cytosolic membranes (or nucleus), where the viral polymerase complexes transcribe and replicate the vDNAs. Newly synthesized mRNAs migrate to the cytoplasm where they are translated. Posttranslational processing of surface glycoproteins includes transportation via the Golgi apparatus to the cell membrane. Nonstructural regulatory protein and nuclear export protein, a minor virion component, bind to freshly synthesized copies of vDNAs.

The newly formed nucleocapsids interact via matrix protein with a region of the cell membrane where surface glycoprotein have been inserted. The virus is usually released by host cell disintegration, but some may get out by budding through membranes (in which case they have an extra membrane).[38]

Importance of 5'-capped structures as a potential target for antiviral agents.

An ideal antiviral drug is expected to be active orally for ease of administration and have a long intracellular half-life for infrequent dosing. It also should be stable for long periods under adverse storage conditions, so that large amounts can be kept for prolonged time, and inexpensive. A tolerable safety profile is necessary for such a drug, so it can be used by select groups, such as children and immunocompromised individuals, as well as the general population.[39]

Two approaches can be used for design of antiviral drugs: (1) drug targeting viral proteins, yielding more specific, less toxic compounds that have a narrow spectrum of

antiviral activity but are apt to virus drug-resistance development: (2) targeting cellular proteins, which results in compounds with a broad activity spectrum, higher toxicity, but less chance of resistance development.[6]

A relevant approach for this dissertation research is antiviral drug design focused on the capping of mRNA. This occurs at the 5'-end of mRNA and consists of a 7-methylguanosine linked to the 5' end of the transcript by an unusual 5'-5' triphosphate bridge and methyl groups on the 2'-hydroxyl group of the penultimate adenine nucleotide (Figure 5). This structure is apparently conserved during processing of cytoplasmic messengers.[40]

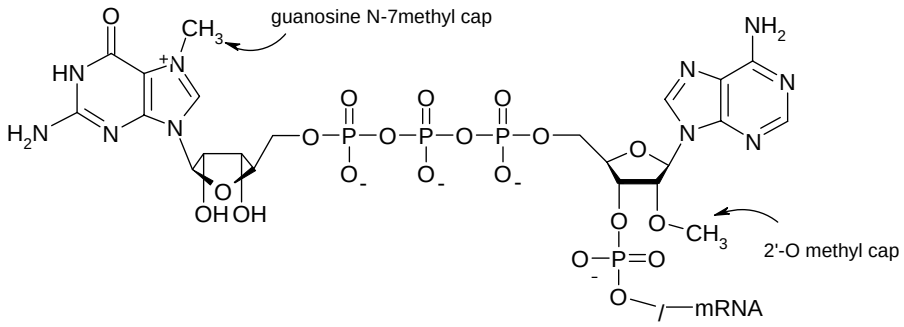


Figure 5. 5'-capped structure.

These structures play an important role in RNA structure and function by facilitating post-transcriptional processing, nucleocytoplasmatic transport and recognition of mature mRNA by the translation machinery.[41] They are necessary for stability of mRNA against phosphotases and ribonucleases,[42] efficient binding of the mRNA to ribosomes, subsequent polysome formation and the translation of the mRNA into proteins.[43] Since uncapped mRNA is much less likely to be translated into its protein, interference with formation of these 5'-caps could lead to inhibition of viral replication.

The capping process occurs by a series of three enzymatic reactions in which the initial 5'-triphosphate terminus is first cleaved by RNA triphosphatase to a diphosphate-terminated RNA followed by capping with GMP promoted by RNA guanyltransferase. This product is then methylated at the N7 position of guanine by RNA (guanine-7) methyltransferase.[41c]

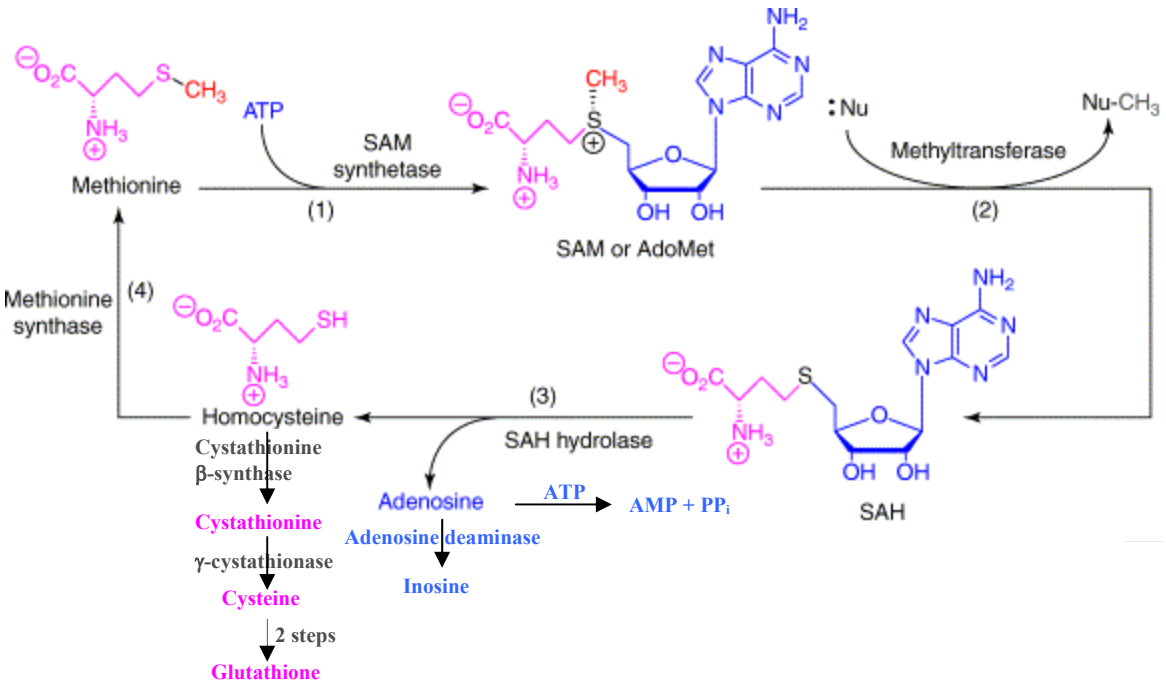
(i) $pppN(pN)_n \rightarrow ppN(pN)_n + P_i$

(ii) $ppN(pN)_n + pppG \rightleftharpoons G(5')pppN(pN)_n + PP_i$

(iii) $G(5')pppN(pN)_n + AdoMet \rightarrow m^7G(5')pppN(pN)_n + AdoHcy$

Both the sugar and base methylations at the 5'-terminus of mRNA are catalyzed by specific methyltransferases, which require S-adenosyl-L-methionine as the methyl donor.[41b, 44] S-adenosyl-L-methionine, also known as SAM or AdoMet, is an important biological sulfonium compound and is the second most widely used enzyme substrate after ATP.[45]

The biosynthesis of AdoMet occurs by a stereospecific reaction of methionine with ATP, which is catalyzed by SAM synthetase or methionine adenosyltransferase (Scheme 2(1)).[46] A nucleophilic displacement catalyzed by methyltransferase takes place when the S-methyl group from AdoMet is transferred to the 5'-guanine nucleoside of the cap (Nu:) and adenosyl-homocysteine (SAH or AdoHcy) is released as one of the products as illustrated by scheme 3 (2).[47]



Scheme 3. AdoMet metabolic cycle.

The AdoHcy is a strong feed-back inhibitor of methyl transferase and must therefore be metabolized rapidly. This is achieved by reversible hydrolysis catalyzed by AdoHcy hydrolase, which splits AdoHcy into adenosine and homocysteine (Scheme 3(3)).[48] Adenosine, then, can be catabolyzed to inosine (a process catalyzed by adenosine deaminase) or it can be transformed to ATP through series of phosphorylations.[49] Homocysteine can be metabolized by two ways: remethylation and transsulfuration.[50] In the remethylation pathway, methionine is formed via a methionine synthase catalyzed reaction (scheme 3(4)) acquiring methyl group from N^5-methyltetrahydrofolate (THF). In the transsulfuration pathway, homocysteine combines with serine to yield cystathionine, the reaction catalyzed by cystathionine β-synthase. Then cystathionine is hydrolyzed by γ-cystathionase to form cysteine and α-ketobutyrate. Cysteine reacts with glutamate and

with glycine in two consecutive reactions to form glutathione, a major cellular antioxidant.[51]

Inhibitors of SAM-mediated enzyme methylations.

There are two ways to block the mRNA methylation process: by direct or indirect inhibition of S-adenosylmethionine dependent methyl transferase enzymes.

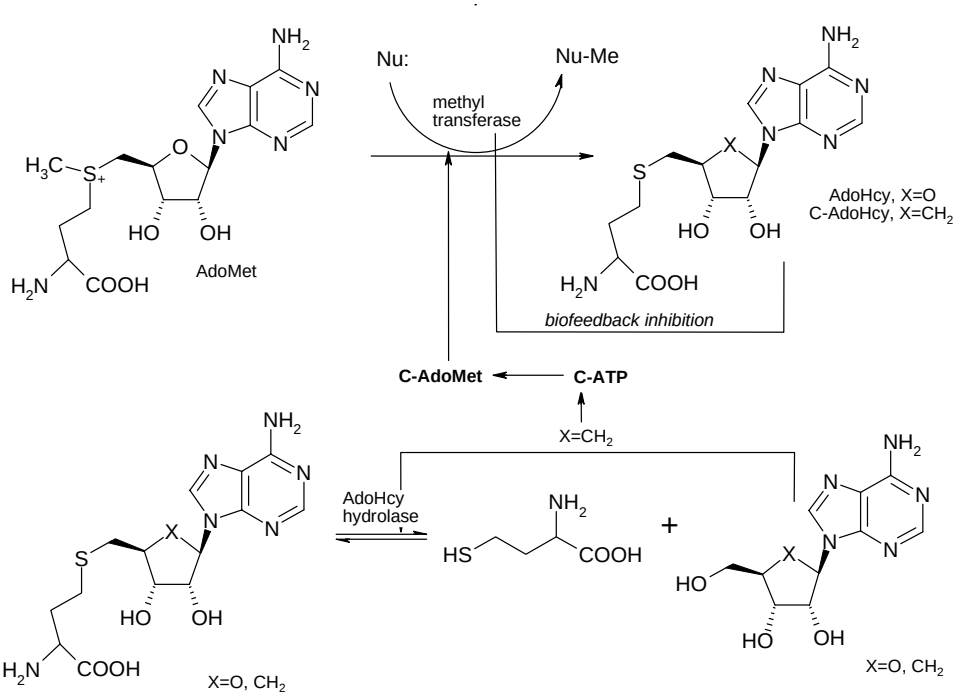
Indirect inhibition.

The indirect approach to inhibit AdoMet mediated methylation focuses on blocking S-adenosyl-homocysteine hydrolase,[25a] which allows build up of the intracellular concentration of AdoHcy, which then acts as a feedback inhibitor of methyl transferase. Fortunately, the intracellular ratio of AdoHcy to AdoMet required for antiviral activity is well below cytotoxic levels, suggesting that viral methyl transferases may be more sensitive to this ratio than cellular enzymes, and this selectivity is essential for this kind of antiviral agents.

The antiviral activity spectrum of AdoHcy hydrolase inhibitors is unique.[52] Besides vaccinia virus,[53] antiviral effects include other DNA viruses, such as human cytomegalovirus[54] and African Swine fever virus.[55] In addition, inhibitors of AdoHcy hydrolase were found effective against RNA viruses (parainfluenza virus, measles,[53b] mumps,[14b] respiratory syncytial virus (RSV),[56] Ebola virus,[52] and others), double-stranded RNA viruses (reovirus and rotavirus[53b, 57]) and retroviruses (HIV, under specific test conditions[58]).

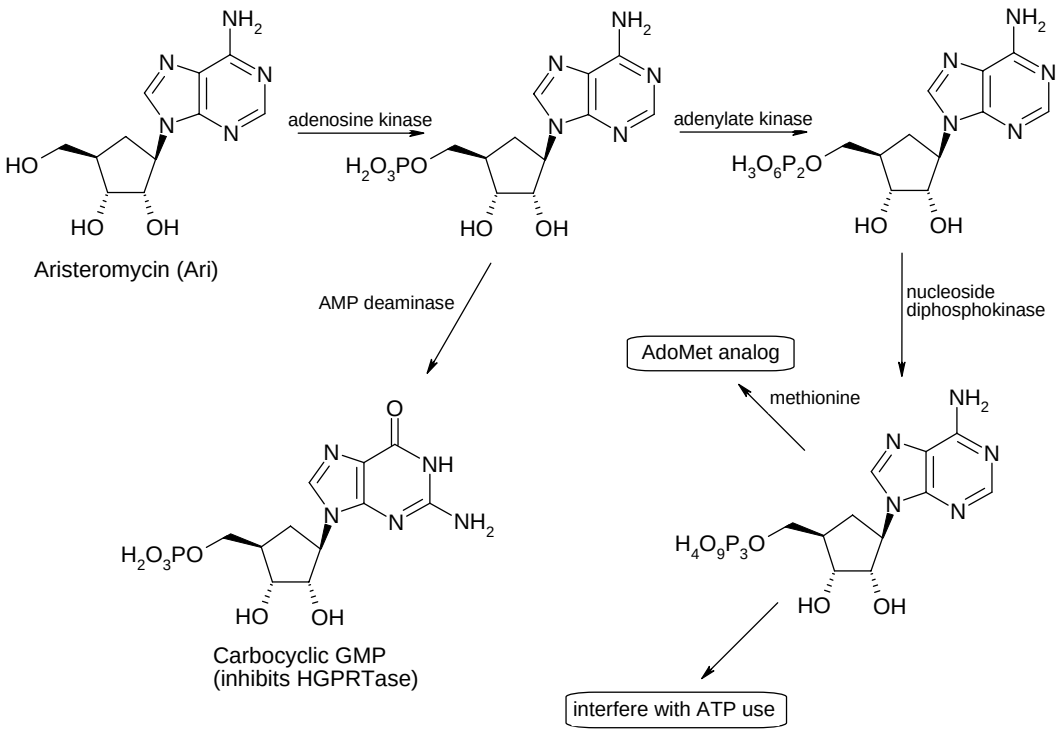
These inhibitors usually are structural analogs of adenosine, whereby the AdoHcy hydrolase recognizes them as substrates.[59] The well-studied example of such compounds

is aristeromycin (Figure 4), which is structurally very similar to adenosine (carbocyclic adenosine) and has been reported to be a reversible, competitive inhibitor of AdoHcy hydrolase[60] and show promising antiviral acivity.[24]



Scheme 4. Aristeromycin as an inhibitor of AdoHcy hydrolase.

As shown on a scheme 4, aristeromycin ($X=CH_2$) can shift the equilibrium of the reaction catalyzed by AdoHcy hydrolase to the left, which gives the enhanced concentration of the carbocyclic AdoHcy, and in turn, causes feedback inhibition of the methyl transferase.[61] On the other hand, aristeromycin may be phosphorylated to carbocyclic ATP, which later forms carbocyclic adenosylmethionine, this latter product can bind to the active site of the methyltransferase and block the enzyme. Besides inhibiting methylation of the virion 5'capped mRNA, this effect also is responsible for the undesirable toxicity of aristeromycin (Scheme 5).[25a, 62]



HGPRTase: Hypoxanthine(guanine)phosphoribosyltransferase

Scheme 5. Toxicity of aristeromycin.

Nucleotide formation of aristeromycin begins with adenosine kinase promoted aristeromycin as a substrate and metabolizing it to the 5'-phosphate derivative carbocyclic AMP.[63] Carbocyclic AMP, through series of phosphorylations by adenylate kinase and nucleoside diphosphokinase, yields aristeromycin triphosphate.[63, 64] Because of its resemblance to structure of ATP and the ubiquity of ATP in biological processes carbocyclic ATP interferes with metabolic processes involving ATP use. This results in deleterious side effects of aristeromycin.[65]

Toxicity can also result from transformation of carbocyclic ATP to the inosine monophosphate analog (carbaIMP) by AMP-deaminase enzyme.[66] This is then converted to carbocyclic GMP. Carbocyclic GMP, being the structural analog of natural guanosine

monophosphate, inhibits hypoxanthine(guanine)-phosphoribosyltransferase (HGPRTase),[67] an enzyme critical to the salvage pathway in nucleotide metabolism. This can lead to a complete blockade of the utilization of hypoxantine and guanine by cells upon treatment with aristeromycin.[65, 67]

Thus, to circumvent the undesirable phosphorylation yet retain the promising antiviral activity of aristeromycin, some analogs have been designed over the years. These structural modifications have taken two different approaches. One approach was based on the fact that 3-deazaadenosine is not phosphorylated, nor is it a substrate of adenosine deaminase.[68] In 1982, Montgomery and coworkers reported the synthesis of 3-deazaaristeromycin (Figure 6)[69a], which later was found to be a reversible and competitive inhibitor of AdoHcy hydrolase, and possesses a potent activity against vaccinia virus and moderate activity agains herpes simplex virus type I.[57a, 69] Similarly to 3-deazaadenosine, 3-deazaaristeromycin is not deaminated by calf intestinal deaminase and is not phosphorylated by L1210 leukemia cells.[69a]

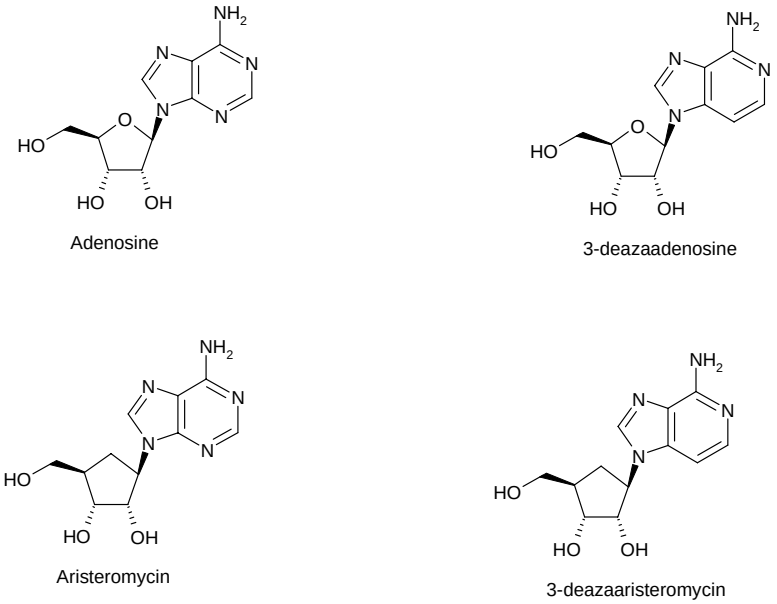


Figure 6. Aristeromycin analogs with antiviral activity.

Another approach involved modifications of the cyclopentane moiety of known carbocyclic nucleosides with antiviral activity. They include changing the chain length at the 5' carbon center or removing/replacing the 4'-hydroxymethyl group (Figure 7), which might prevent 5'-phosphorylation by Ado kinase and deamination by Ado deaminase.[70] Among the AdoHcy inhibitors developed by this method, (-)-5'-noraristeromycin (5'-NorAri) represents an exo chain-shortened compound lacking the methylene unit at 4'-position (Figure 7). 5'-NorAri was synthesized in Schneller group[71] and has shown a potent antiviral activity against vaccinia virus, hepatitis B virus, human cytomegalovirus, measles and influenza, along with the considerably low toxicity due to shortened C-5' chain length and a secondary alcohol being less reactive than the 5'-primary hydroxyl-group of aristeromycin.[71, 72]

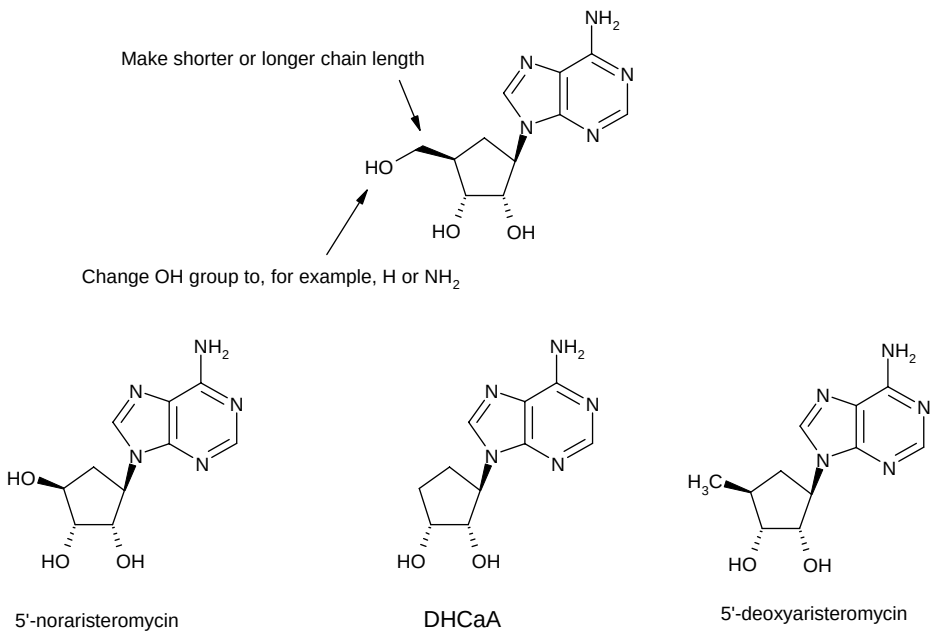


Figure 7. Modifications of aristeromycin side-chain.

Removal of the 4'-hydroxymethyl group led to a truncated analog of aristeromycin (DHCaA), which was synthesized by the Borchardt group and has shown potent antiviral activity with low associated toxicity.[57b, 73]

The 5'-deoxy analog of aristeromycin, synthesized in the Schneller group, cannot be phosphorylated because of the absence of 5'-hydroxyl group. This compound displayed moderate activity toward vaccinia virus and VSV with low toxicity.[72a]

Direct inhibition.

The focus of this research is toward blocking the methylation process by concentrating on direct inhibition of the methyltransferase enzyme itself. The ultimate goal is to design structural analogs of AdoMet and AdoHcy (Figure 8) which are able to bind to the active site of the methyl tranferase[74] and, thus, block the viral replication.

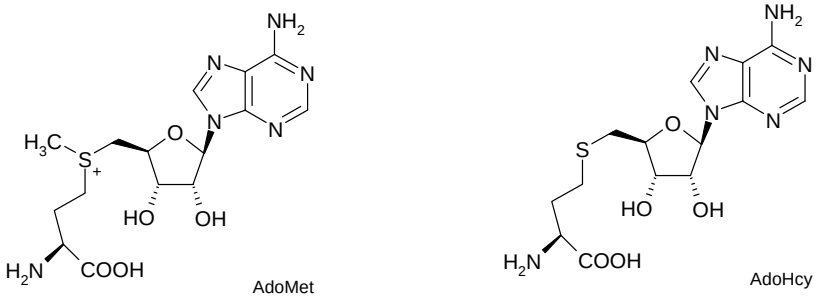


Figure 8. Structures of adenosyl-methionine and adenosyl-homocysteine.

Significant research in this area was performed by Borchardt[75] who studied different structural analogs of AdoHcy with modifications in the amino acid, base and sugar portion of the molecule, for their ability to inhibit the S-Adenosyl-L-methionine dependent transmethylations using the vaccinia virion mRNA methyltransferase assay.

Most of the base modified AdoHcy analogs (where adenine was replaced with different pyrimidine bases) showed little or no activity toward the vaccinia virus. Only 3-deaza-AdoHcy and N^6-methylAdoHcy showed significant inhibitory activity toward the vaccinia (guanine-7)methyltransferase (Figure 9).[76] Such results suggest that all of the general features of the adenine portion of AdoHcy are necessary for maximal effects on the methyltransferase enzyme of the vaccinia virion.

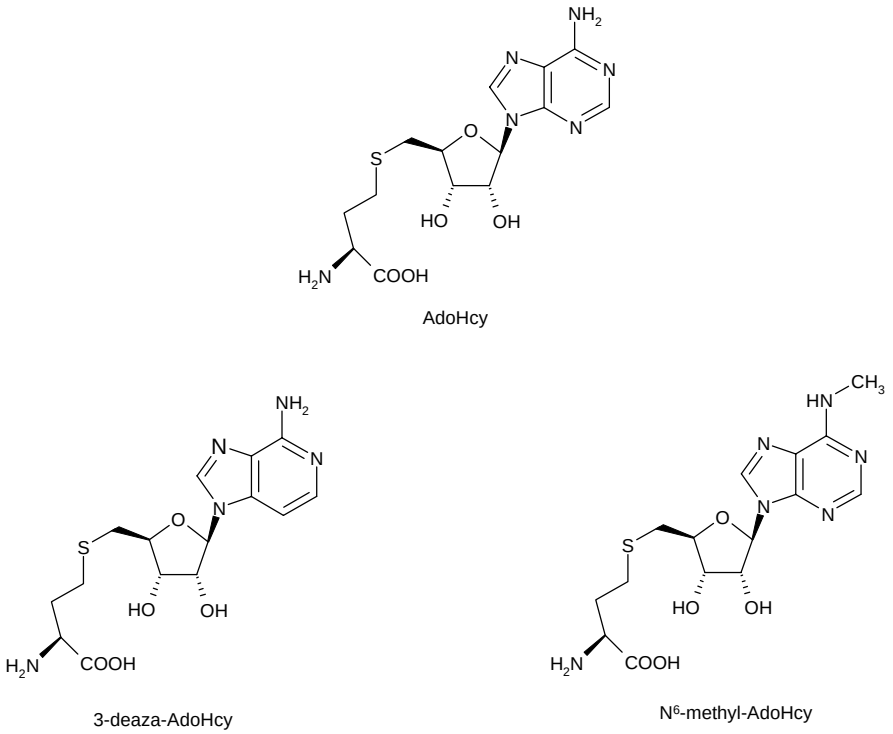


Figure 9. Base-modified AdoHcy analogs.

Of the sugar modified analogs (Figure 10), only carbocyclic adenosinehomocysteine (AriHcy)[77a] showed significant inhibition of the vaccinia methyltransferase. Removal of the 2' or 3' hydroxy groups, leading to other sugar-modified analogs,[77b] resulted in loss of activity. These results indicate that the 2'and 3' hydroxyl groups play crucial role in the enzymatic binding of AdoHcy.

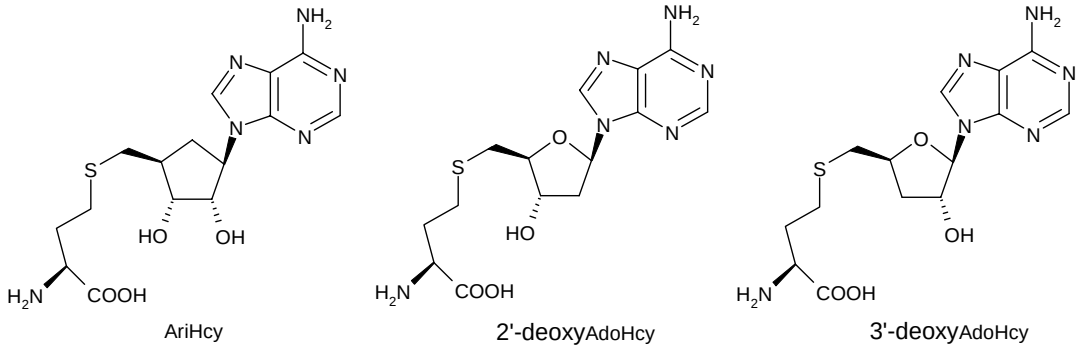


Figure 10. Sugar-modified AdoHcy analogs.

The AdoHcy analogs, that contained modifications at the sulfur atom (AdoHcy sulfoxide and AdoHcy sulfone) or had sulfur replaced (AdoDab), showed appreciable inhibitory activity toward the methyltransferase (Figure 11).[75, 78]

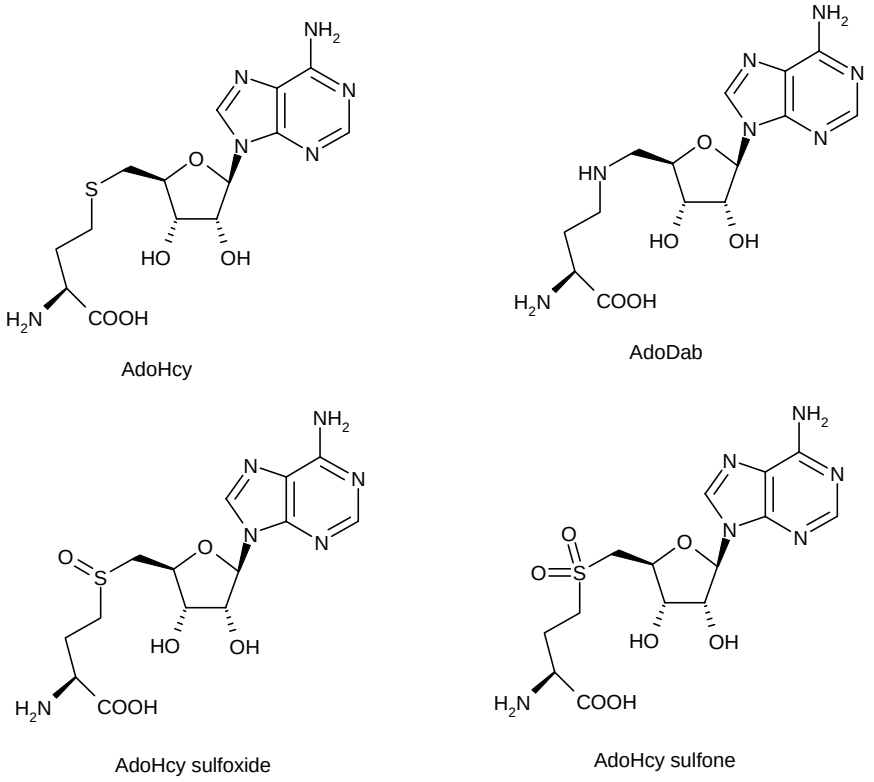


Figure 11. Sulfur-modified AdoHcy analogs.

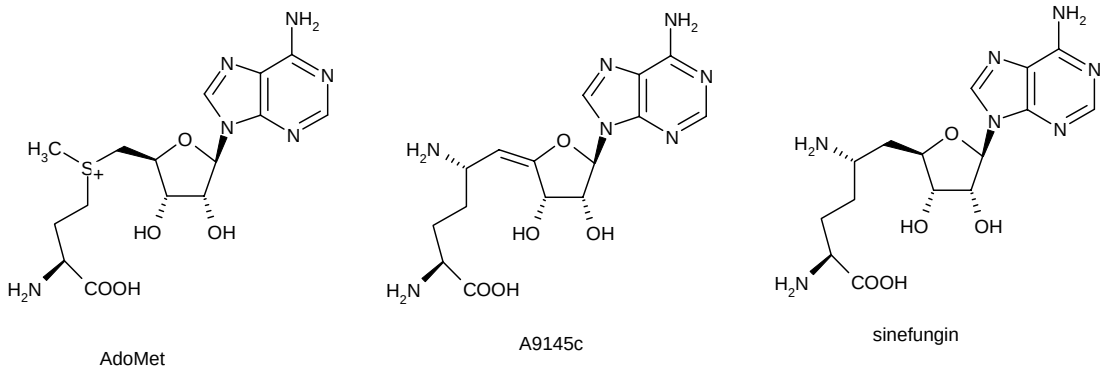


Figure 12. Side-chain modified AdoMet analogs.

Among amino acid modified analogs of AdoMet, naturally occurring sinefungin and A9145c were reported to be very potent inhibitors of the vaccinia mRNA methyltransferase (Figure 12).[79]

Sinefungin was isolated in 1973 from *Streptomyces griseolus*,[80] and later it was obtained from *Streptomyces incarnates*.[81] Its structure was assigned in 1978,[82] and absolute stereochemistry determined in 1990.[83] Sinefungin bears a strong structural resemblance to S-adenosylmethionine and S-adenosylhomocysteine (Figure 13).

Its structure is composed of an adenosine unit to which an ornithine residue has been attached at the C'-5 position. The C-6' chiral center has an S configuration, and the $CH(NH_2)$ unit at this position corresponds to methylated sulfur in AdoMet. The C'-9 chiral center of both AdoMet and sinefungin has the same S configuration.

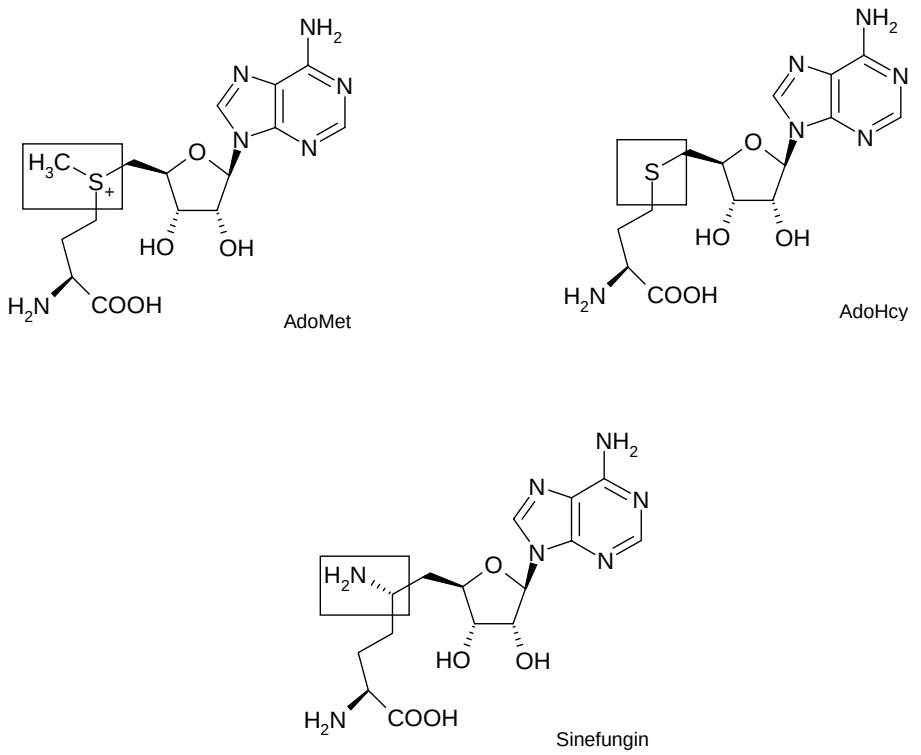


Figure 13. Sinefungin as AdoMet and AdoHcy analog.

Due to these structural similarities sinefungin can bind to the vaccinia mRNA methyl transferase instead of AdoMet, but it lacks the requisite methyl group, becoming a potent inhibitor of the capping process. Besides antiviral activity,[75, 79, 84] sinefungin was found to have a variety of other biological effects including antifungal,[81, 85] amoebicidal[86] and antiparasitical[87] activities.

However, clinical use of natural sinefungin is restricted because *in vivo* testing showed that it has severe toxicity and causes very serious side effects (nephrotoxicity in dogs and toxicity in bone marrow cells).[88]

Studying the affects of different amino acid modifications of the AdoHcy, Borchardt found the following structural features of importance in the binding of the amino acid portion to the vaccinia methyltransferase:[75]

- the chirality of the amino acid asymmetric carbon;

-the terminal amino group;

-the terminal carboxyl group;

-the three carbon distance between the sulfur atom and the terminal amino and terminal carboxyl groups;

-methyltransferases are capable of accommodating changes in and around the sulfur atom of AdoHcy.

This research is focused on developing and synthesis of sinefungin analogs with potentially improved therapeutic index.

Sinefungin based target design.

Based on previous discussion, sinefungin represents an important target for structural modifications in order to find new antiviral agents. Many researchers have been working on this molecule and many sinefungin analogs have already been synthesized and tested for biological activity.[89-94]

Replacing the adenine base of sinefungin with uracil[89] and thymidine[90] led to analogs **1** and **2** (Figure 14) with significantly lower antiviral and antiparasitic activity compared to natural sinefungin.

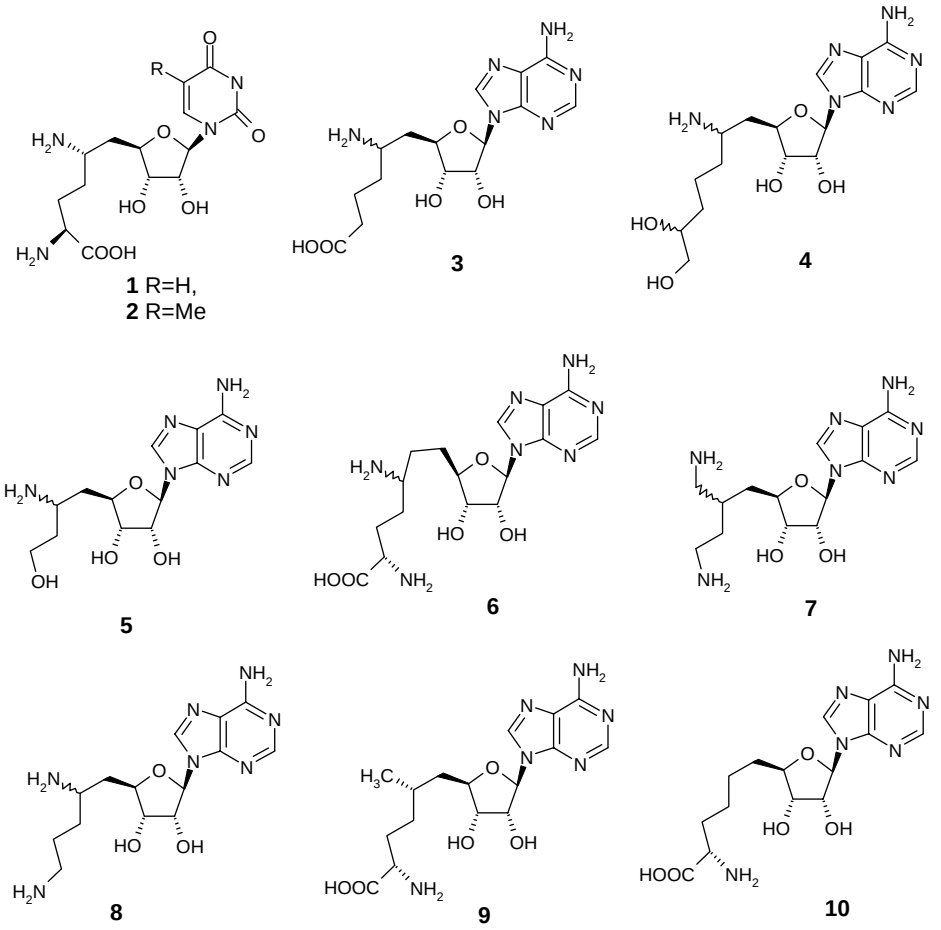


Figure 14. Examples of the known sinefungin analogs.

Thorough investigations on side chain modifications of sinefungin resulted in a number of analogs with altered amino acid moiety (compounds **3**, **4** and **5**)[91] (exhibiting loss of inhibitory activity toward methyltransferase and low toxicity), one carbon extension between 4'-C and 6' -C(NH_2) (compounds **6** and **7**)[92] and 6'-C-chain-extended derivatives (for example, compound **8**)[93] (showing no antiviral activity), and 6'-C functionalized sinefungin analogs **9** and **10** (not tested)[94] (Figure 14).

Based on historical data, this project has focused on sinefungin analogs with altered functionality of 6'-C atom while keeping the base and amino acid portions of the molecule intact. Although the source of the toxicity of natural sinefungin is unknown, the amino group at the 6' position of its side-chain may be responsible for this undesired effect since this functionality is the only structural difference between sinefungin and AdoMet (Figure 12). Only two sinefungin analogs lacking the amino group have been synthesized[94] (Figure 14) but results of their biological testing have not been reported. Thus, the effect of this group on the antiviral activity and toxicity of sinefungin is awaiting further scrutiny.

The importance and useful biological properties of the carbocyclic analogs of natural nucleosides was described earlier in this dissertation. Carbocyclic sinefungin (Figure 15) is a compound of great scientific interest but it has proved to be very difficult to make. Although several synthetic strategies toward carbocyclic sinefungin have been reported,[95] none of them were successful so far and this compound remains unknown. This structure was considered as one of the target systems for this research.

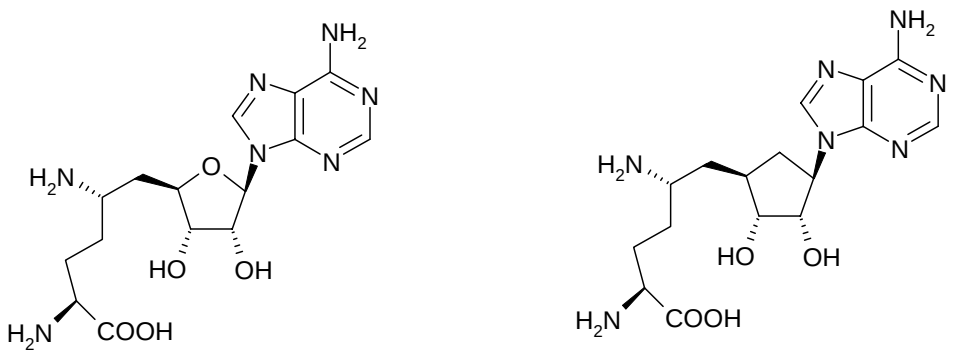


Figure 15. Carbocyclic sinefungin.

In considering approaches to carbocyclic sinefungin, it was recognized that construction of the cyclopentane ring system with a sinefungin side-chain would be a challenging task. For this purpose compounds **I** and **II** became targets (Figure 16) to develop a method for the construction of 5'-C chain on the carbocyclic ring. Also, as structural analogs of aristeromycin, **I** and **II** may be AdoHcy hydrolase inhibitors and possess antiviral activity.

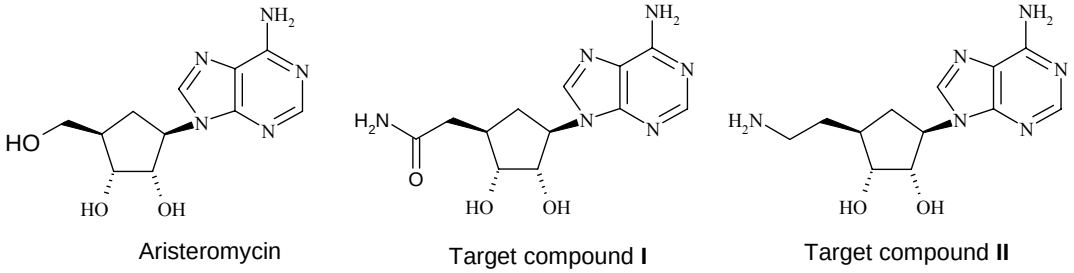


Figure 16. Target compounds **I** and **II**.

Once we discovered a way of introducing the 5' chain on the cyclopentane ring, compounds of more complicated structure were designed. The carbocyclic analogs of

sinefungin with the amino group replaced by a hydroxyl substituent and a shortened 5'-C side chain became target compounds **III** and **IV** (Figure 17).

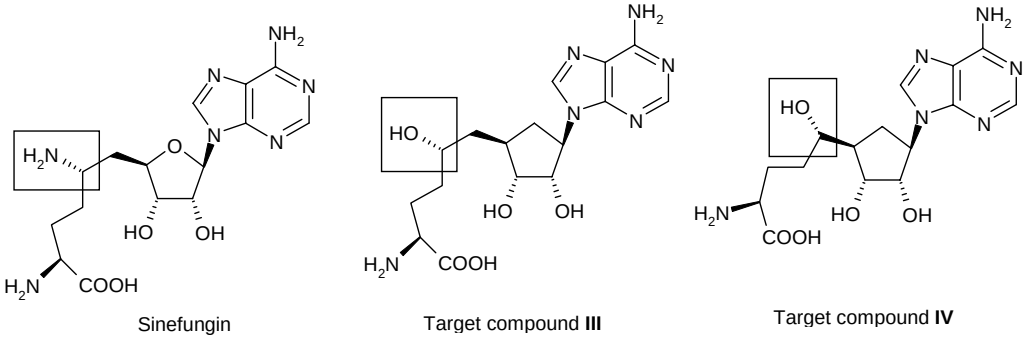


Figure 17. Target compounds **III** and **IV**.

Replacing the amino group at the 6' position with the less basic, yet of similar polarity, hydroxyl group may lead to the development of new antiviral agents with decreased toxicity. Retaining the same S-configuration of the 6' stereocenter in the target compounds is important for the binding to and inhibition of AdoMet transferase and AdoMet hydrolase.[74 b]

We were also interested in furanosyl derivatives of sinefungin with the aforementioned side chain modifications, which resulted in the design of target compound **V** (Figure 18).

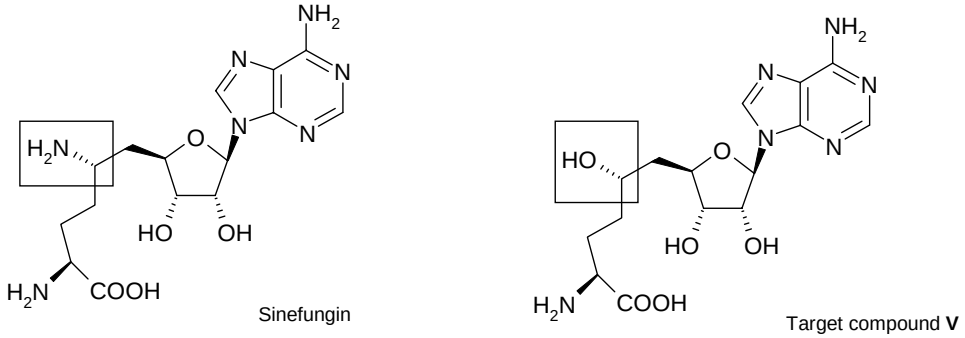


Figure 18. Target compound **V**.

Another modification of the side chain of the natural sinefungin, which has not been studied, is decreasing the distance between the 4' and 6' carbon atoms. So, 5'-nor-6'-deamino-6'-hydroxysinefungin was designed as another target compound **VI** (Figure 19).

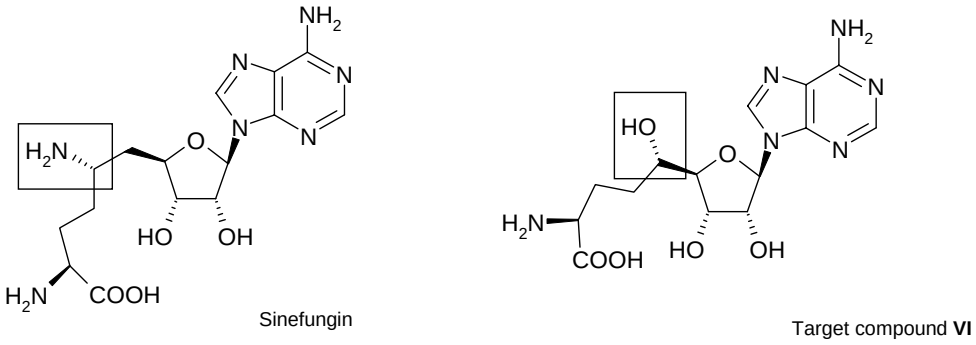
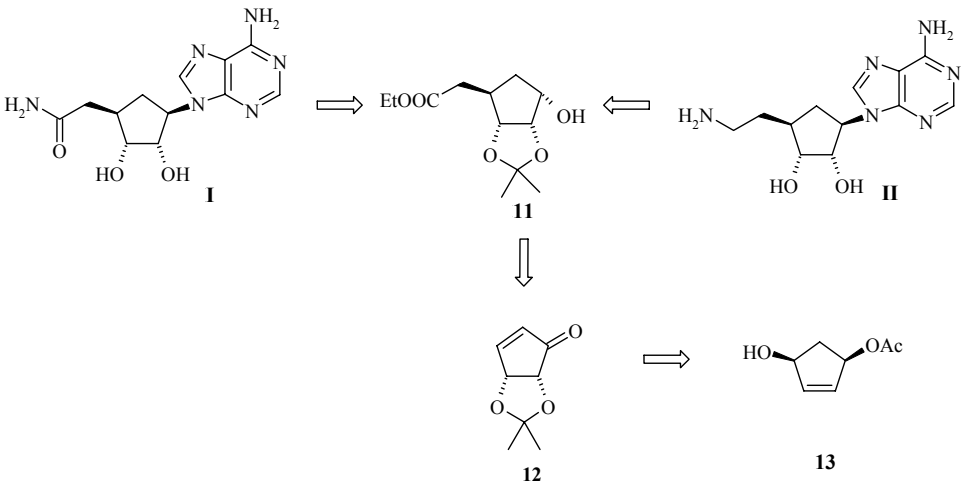


Figure 19. Target compound **VI**.

Chapter 1. Synthesis of the target compound I and II.

Retrosynthetic approach toward target compound I and II.

To develop a synthetic route toward carbocyclic nucleosides **I** and **II**, hydroxyester **11** was considered as a common intermediate. We expected to convert **11** into compound **I** by a Mitsunobu reaction with 6-chloropurine and further ammonolysis and deprotection. Reduction of amide **I** was envisioned to give an entry to target **IV**. To obtain hydroxyester **11**, an important intermediate **12** was designed with defined stereochemistry at the 2' and 3' carbons of future targets **I** and **II** (Scheme 6). Enone (-)-**12** is widely used in the carbocyclic nucleosides research and several synthetic routes exist toward this compound.[97] One of them was developed in the Schneller group starting from **(+)-**(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**13**).[98]

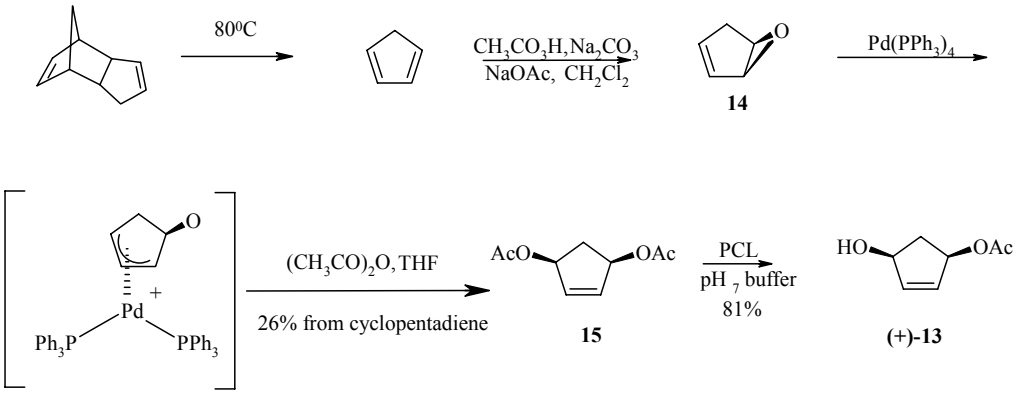


Scheme 6. Retrosynthetic analysis of target compounds **I** and **II**.

(+)-(1*R*,4*S*)-4-Hydroxy-2-cyclopenten-1-yl acetate (**13**) and (-)-(4*R*,5*R*)-4,5-(*iso*propylidenedioxy)-2-cyclopentenone (**12**) are the two most important enantiopure precursors for entry into the D-like configuration of the target carbocyclic nucleosides. Thus, these two compounds were sought in large quantities.

Synthesis of important precursors 12 and 13.

Synthesis of **(+)-**(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**13**) started with epoxidation of freshly cracked cyclopentadiene affording compound **14** (Scheme 7). Following a literature procedure, [99] the palladium catalyst *tetrakis*(triphenylphosphine)palladium (0) was used to open the epoxide ring. Then, the presumed palladium intermediate was treated with acetic anhydride to yield the *meso*-diacetate **15**.

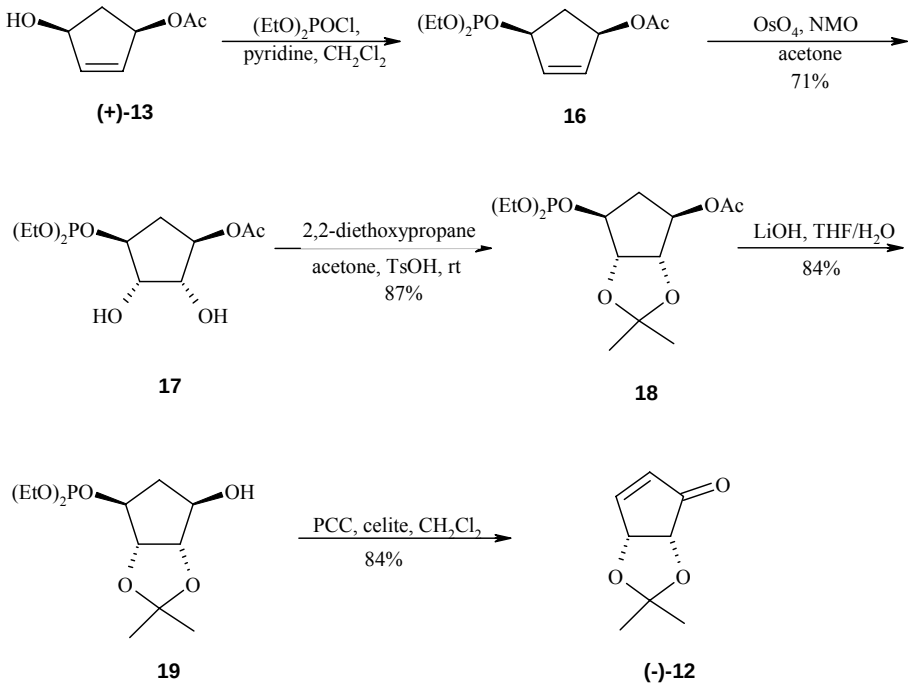


Scheme 7. Synthesis of **(+)-**(1R,4S)-4-hydroxy-2-cyclopenten-1-yl acetate **13**.

To transform **15** into the desired **13**, an enzymatic-catalyzed reaction was considered as a powerful and convenient method for synthesis of enantiopure compounds. [100] The enzymatic hydrolysis of prochiral diacetate **15** reported by Laumen

and Schneider [101] was considered as a route to (+)-monoacetate **13**. Using an optimized procedure developed in the Schneller laboratory, [102] *meso*-diacetate **15** was treated with *Pseudomonas cepacia* lipase (PCL) affording the allylic monoacetate **13**. Although PCL normally displays pro-*R* hydrolytic preference, [103] in this case *S*-hydrolysis was preferred.

Compound **13** was now ready to use for preparing the important chiral cyclopentenone **12**. This was to be accomplished by functional group manipulations in 5 steps (Scheme 8) using the method developed in the Schneller group. [98]



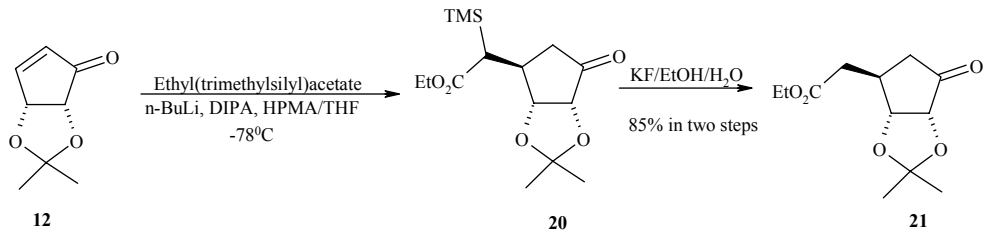
Scheme 8. Synthesis of (-)-(4R,5R)-4,5-(*iso*propylidenedioxy)-2-cyclopentenone **12**.

The synthesis began with treatment of (+)-**13** with diethyl chlorophosphate resulting in monophosphate **16**. Glycolization of **16** to diol **17** was achieved using N-methylmorpholine N-oxide and a catalytic amount of osmium tetroxide. Protection of **17**

with 2,2-dimethoxypropane followed by removal of the acetate group with lithium hydroxide afforded compound **19**. Conversion of **19** to (-)-**12** was accomplished by oxidative elimination with pyridinium chlorochromate.

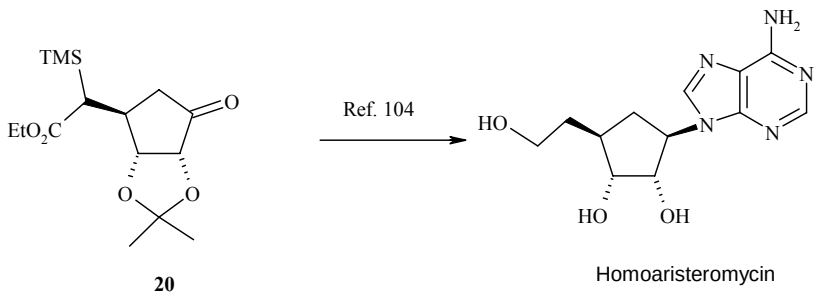
Synthesis of target compound I.

Seeking target compounds **I** and **II** (Figure 16) necessitated developing a way for the stereoselective introduction of the versatile substituent to the 4' carbon of the cyclopentane ring of the eventual carbocyclic nucleosides. For this purpose, a Michael addition reaction of the *in situ* generated carbanion of ethyl (trimethylsilyl)acetate to the enone **12** was considered (Scheme 9).[104]



Scheme 9. Synthesis of important intermediate **21**.

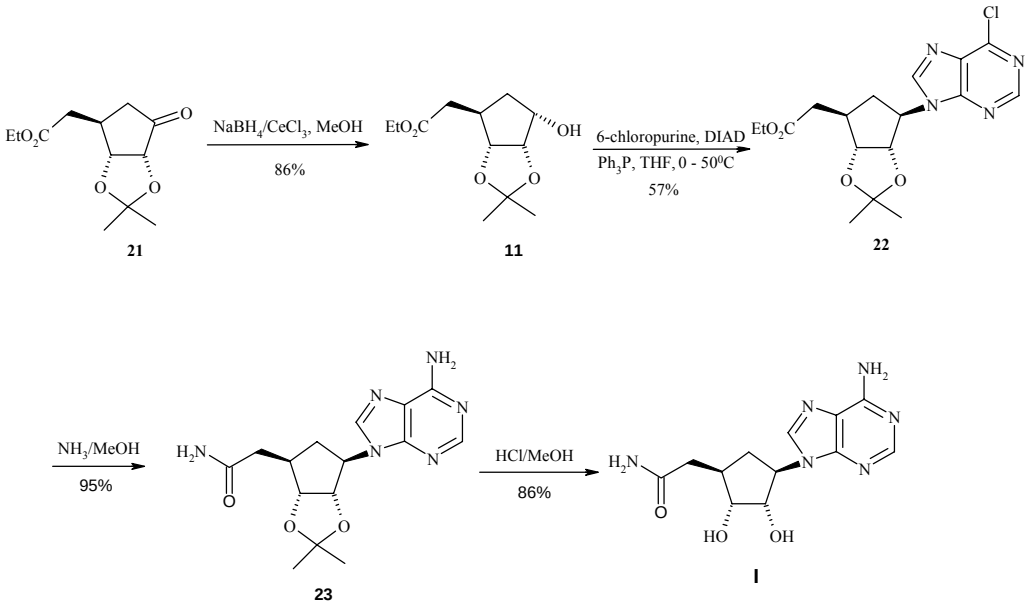
The β stereochemistry of the Michael adduct **20** was derived because the α (down) face of the enone **12** was sterically hindered, causing the nucleophile attack from the β (up) face yielding single stereoisomer **20**. The stereochemical outcome of this reaction was proved by the Schneller group by converting compound **20** to the known homoaristeromycin (Scheme 10).[104]



Scheme 10. Homoaristeromycin derived from **20**.

In-situ cleavage of the trimethylsilyl group of **20** was furnished by potassium fluoride in aqueous ethanol to afford compound **21** in 85% overall yield (Scheme 9). Thus, the important intermediate **21** containing a synthetically versatile ester side chain was accomplished.

To selectively reduce the keto carbonyl group of **21**, the Luche procedure was applied.[105] This method involves cerium (III) chloride along with sodium borohydride and led to α alcohol **11** as a single product in an excellent yield (Scheme 11).

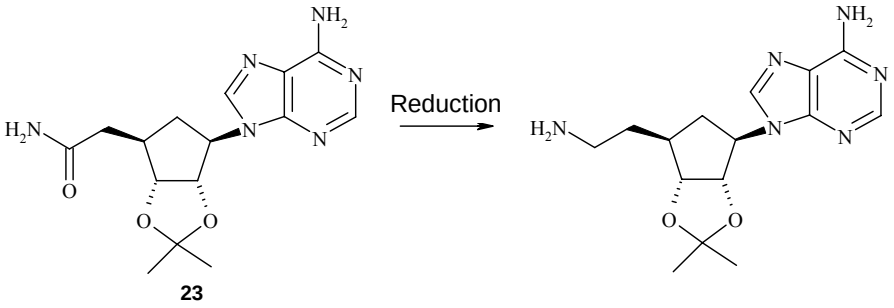


Scheme 11. Synthesis of the target compound **I**.

Mitsunobu coupling of **11** with 6-chloropurine furnished compound **22** in 57% yield. [106] Ammonolysis of **22** went smoothly resulting in amide **23** with 95% yield. The synthesis was completed with hydrolytic deprotection of the isopropylidene group to afford **I**.

Synthesis of target compound II.

The initial synthetic approach toward target **II** focused on reduction of the amide group of **23** to the corresponding amine (Scheme 12). Attempts to reduce **23** with lithium aluminum hydride failed, mostly due to the poor solubility of **23** in ether and tetrahydrofuran. [107]



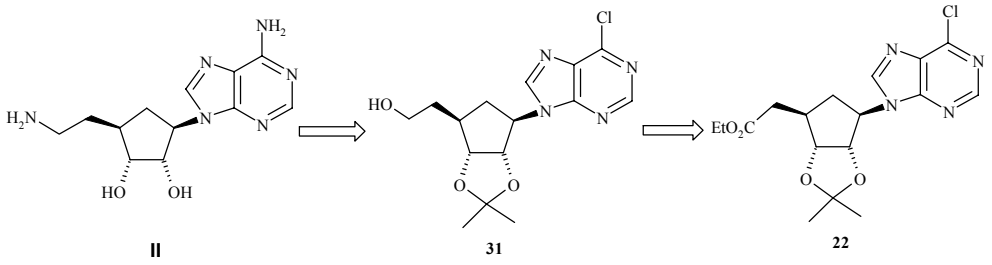
23

Scheme 12. Attempts to reduce the amide group.

Sodium borohydride has been reported as an excellent reducing agent for amides when used as a component of transition metal salt systems. [108] Unfortunately, when compound **23** was treated with sodium borohydride-cobalt dichloride system in methanol, the reduction reaction did not take place. Other methods using sodium borohydride in a

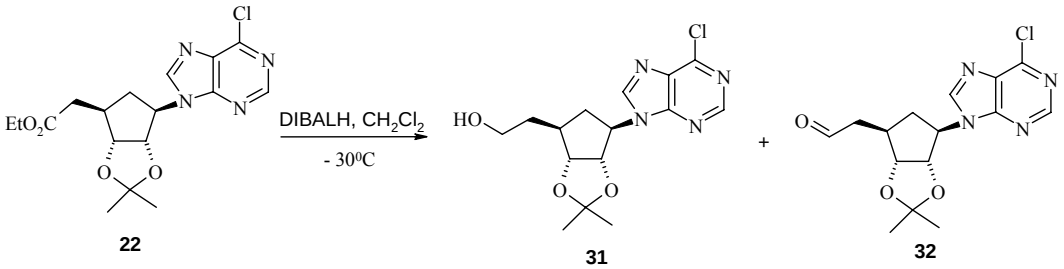
combination with dimethyl sulfoxide or with iodine were also unsuccessful. [109] So, after many failed attempts, this approach was abandoned.

To synthesize target **II**, an alternative route was designed (Scheme 13) which involved reduction of the ester **22** to the corresponding alcohol and replacing the hydroxyl group with an azide group to be followed by ammonolysis and reduction.



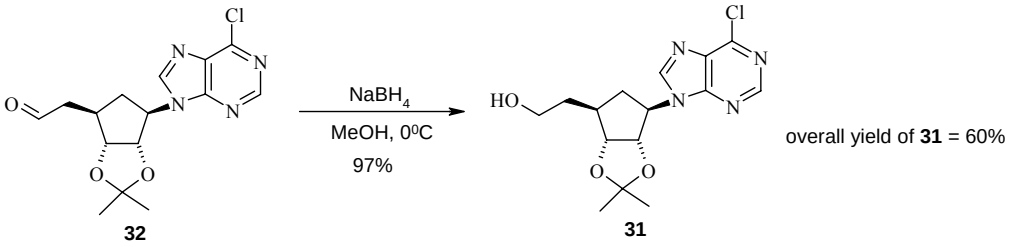
Scheme 13. Revised retrosynthetic analysis of the target compound **II**.

Reduction of **22** was performed using di*iso*butyl lithium aluminum hydride (DIBALH) in anhydrous methylene chloride at - 30 ^{0}C (Scheme 14). This reaction resulted in the 4:1 mixture of alcohol **31** and aldehyde **32** which could be easily separated by column chromatography.



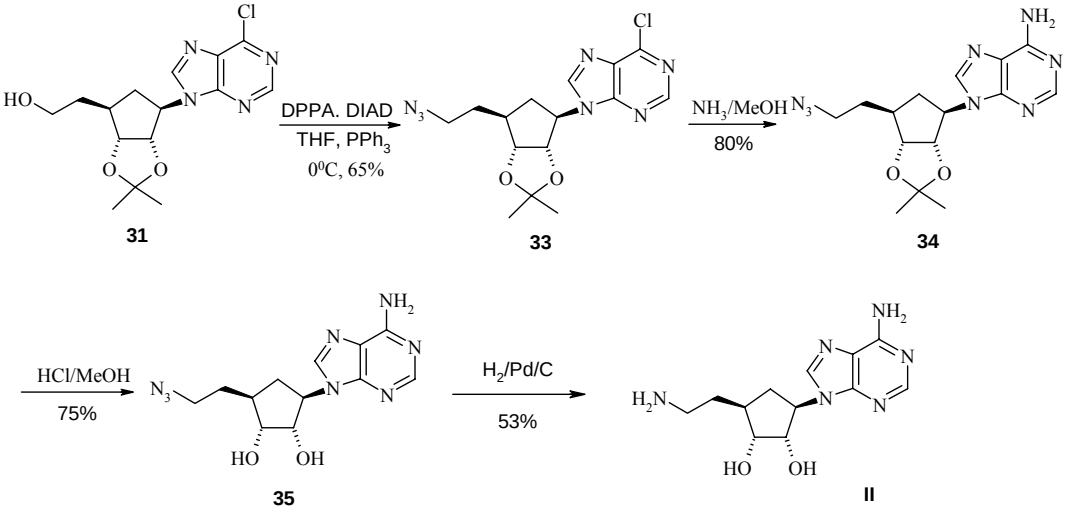
Scheme 14. Reduction of the ester **22**.

The aldehyde **32** was then converted to the alcohol using sodium borohydride in methanol with 97% yield (60% overall yield of **31** starting from **22**) (Scheme 15).



Scheme 15. Conversion of **31** to **32**.

Collected alcohol **31** was further transformed into the corresponding azide **33** upon treatment with diphenyl(phosphoryl)azide under Mitsunobu conditions (Scheme 16). Ammonolysis of **33** resulted in 80% yield of compound **34**.



Scheme 16. Synthesis of the target compound **II**.

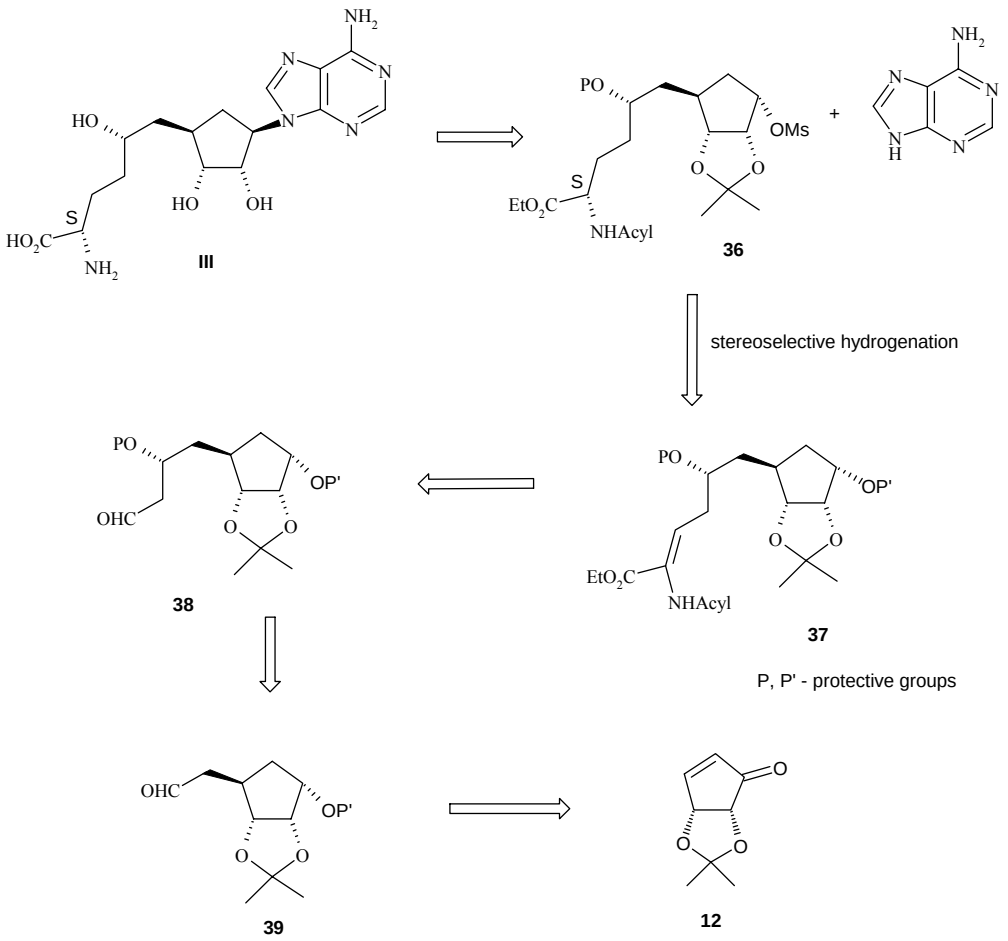
After careful consideration, hydrolytic deprotection step was carried out before reduction of the azide group to the amine, since an amino group tends to form salts with hydrochloric acid, which complicate hydrolysis. Thus, treatment of the azide **34** with 2N hydrochloric acid in methanol gave deprotected 9-[(1'R,2'S,3'R,4'S)-4'-(azidoethan-2'-yl)-2',3'-dihydroxycyclopentan-1'-yl]adenine (**35**) in 75% yield. Hydrogenation of 35 in Parr apparatus with palladium on charcoal resulted in the desired target **II** in 53% yield.

Chapter 2. Synthesis of the carbocyclic sinefungin derivatives III and IV.

Retrosynthetic approach toward target compound III.

Having developed a convenient route for the prolongation of the 5' carbon chain on the cyclopentane ring of the carbocyclic nucleosides, synthesis of more complicated structures was considered.

The key steps for this synthesis were stereoselective introduction of a 6' hydroxyl substituent and asymmetric hydrogenation of the α,β-unsaturated amino acid to construct a 9' stereocenter. Based on the previous studies, the only precedence for the successful asymmetric hydrogenation in our laboratory was with an abasic (*vide infra*) derivative, and because the literature suggested [110a, 111] that purine bases may affect the rhodium catalysts, we planned to generate the eventual asymmetric C-9' center from the corresponding α,β-unsaturated amino acid prior the attachment of the adenine base. Thus, the initial approach toward the target compound **III** first sought construction of the fully functionalized cyclopentane ring containing the amino acid moiety **36** with intentions to then couple this with the base either by an SN2 reaction or a Mitsunobu reaction (Scheme 17).

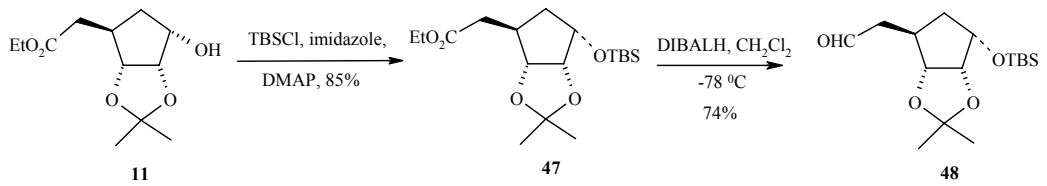


Scheme 17. Retrosynthetic analysis of the target **III**.

The phosphorylglycine method [112] was to be used for the introduction of the amino acid moiety via an aldehyde precursor **38**. To develop the C-6 asymmetric center, plans focused on using chiral organoborane reagents to reduce the aldehyde **39**. [113] With four stereocenters and the versatile aldehyde functionality on the 5 carbon atom, compound **39** is important to this effort and can be obtained from the enone (-)-**12**.

Synthesis of the intermediate compound 39 with different protective groups.

The important part of this project was finding suitable protective groups for secondary alcohols, which can subsequently be selectively and easily removed. Moving in that direction, *tert*-butyldimethylsilyl (TBS) was chosen as a protecting group for the eventual 1'-C. This group can be selectively removed upon treatment with tetrabutyl-ammonium fluoride (TBAF). [114] Thus, reaction of alcohol **11** with *tert*-butyldimethylsilyl chloride, imidazole and catalytic amount of 4-N,N-dimethylaminopyridine (DMAP) resulted in an 85% yield of **47** (Scheme 18).



11 **47** **48**

Scheme 18. Synthesis of the intermediate compound **48**.

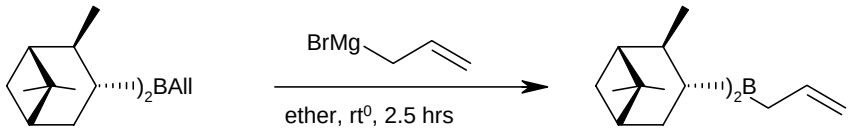
In this plan, the allyl group was to serve as the chain extension and source of the aldehyde. For its introduction, the ester was selectively reduced to aldehyde **48** using di*iso*butylaluminum hydride (DIBALH) at -78 ^{0}C (Scheme 18).

Stereoselective introduction of the 6' hydroxyl group is a very important step for the synthesis of the compound **III**. Among the available methods for C-C bond construction and simultaneous secondary alcohol formation, the addition reaction of allylborane reagents to aldehydes was chosen to be used for this project.

In 1961, Brown introduced asymmetric hydroboration for achieving chiral synthesis approaching 100% ee by a nonenzymatic process. [115] Since then, this method

has been improved and refined making many functional groups readily accessible in essentially enantiomerically pure form.

The standard method for the asymmetric allylboration of aldehydes involves reaction of the aldehyde with B-allyldi*iso*pinocampheylborane at low temperature in diethyl ether. [113] In order to achieve higher enantioselectivity, the reaction needs to be carried out at very low temperatures (-78 ^{0}C to -100 ^{0}C). [116] The B-allyldi*iso*pinocampheylborane can be prepared *in situ* from corresponding B-methoxydi*iso*pinocampheylborane and allylmagnesium bromide in ether (Scheme 19).



Scheme 19. Synthesis of (-)-B-allyldi*iso*pinocampheylborane.

Although enantioselectivity of allylboration reactions increases with lower temperature, only absolutely magnesium salt free reagent can be used at -78 ^{0}C to -100 ^{0}C because the reactive borane is sequestered by complex formation with methoxymagnesium bromide at this temperature. [117] In addition, Brown has found that the allylboration reaction rate is sufficiently higher in the absence of magnesium salts. [116] Considering reported results, we removed the magnesium by-product by evaporating the solvent and extracting the residue with pentane maintaining very dry conditions through the course of reaction.

Asymmetric allylboration proceeds via the initial complexation of the carbonyl oxygen with boron, followed by transfer of the allyl group from boron to the carbonyl

carbon involving a six-membered transition state. [118] The orientation of the ligands with respect to the transition structure core is very important for determining the face selectivity (Figure 20). [119]

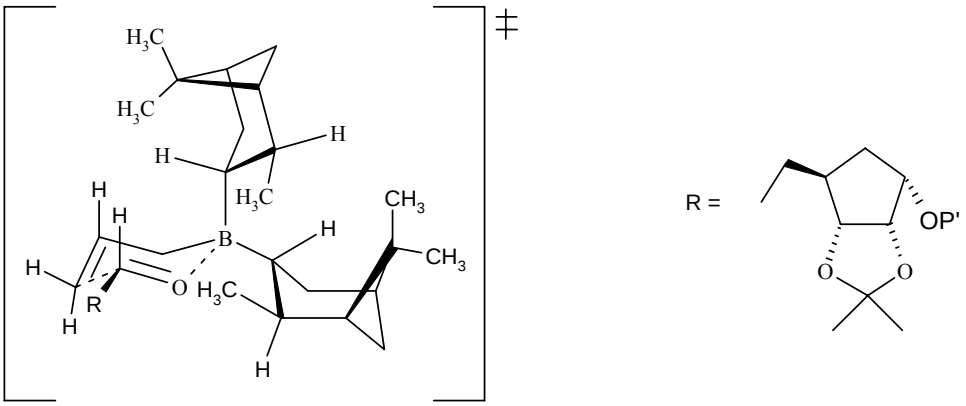
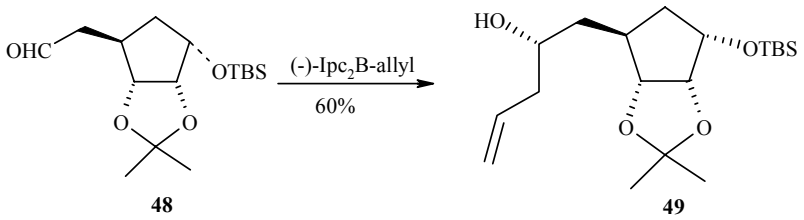


Figure 20. Transition state of allylboration reaction.

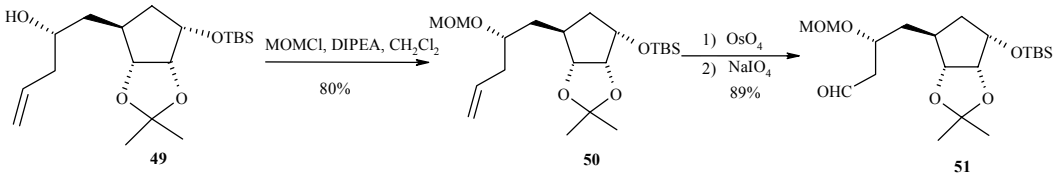
Allylation of aldehydes proceeds through a chair-like transition state where R occupies an equatorial position and the aldehyde facial selectivity derives from minimization of steric interactions between the axial *iso*pinocampheyl ligand and the allyl group.

Reaction of **48** with allyl (-)-*iso*campheylborane, generated *in situ*, resulted in 60% yield of (4*S*)-4-hydroxy-5-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-butyldimethylsilyloxy -cyclopentan-1'-yl]-1-penten (**49**) (Scheme 20).



Scheme 20. Stereoselective allylation of **48**.

The secondary hydroxyl of **49** was protected with a methyloxymethyl group (to **50**), which is stable against tetrabutylammonium fluoride and can be removed later together with the *iso*propylidene group upon acid hydrolysis (Scheme 21). [120]

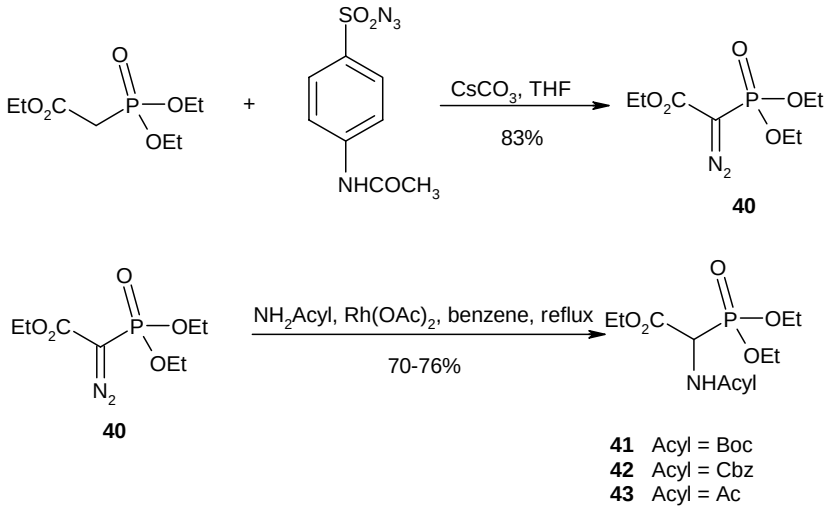


Scheme 21. Synthesis of the intermediate compound **51**.

In order to introduce the amino acid moiety to the molecule, aldehyde functionality was determined to be the most versatile. Thus, aldehyde **51** was obtained upon treatment of **50** with sodium periodate and osmium tetroxide in a mixture of methanol and water 3:1 in 89% yield (Scheme 21).

To construct the α,β-didehydroamino acid **37**, the phosphorylglycine method was employed, which involves condensation reaction of ketones and phosphorylglycine esters under basic conditions. [121] By using this method, all protecting group can be incorporated *a priori* to the starting materials.

N-Acylaminophosphonates were synthesized by a two step procedure starting from commercially available triethyl phosphonoacetate (Scheme 22). For the first step of the synthesis, a diazo transfer reaction was used. [122] Ethyl 2-diazo-2-diethylphosphoryl acetate **40** was obtained by reaction between *p*-acetamidobenzenesulfonyl azide as the diazo transfer reagent and triethyl phosphonoacetate as the methylene acid. Cesium carbonate was used to promote this reaction resulting in a high reaction rate, mild conditions, no need for basic aqueous work-up, and high yield. [122b]



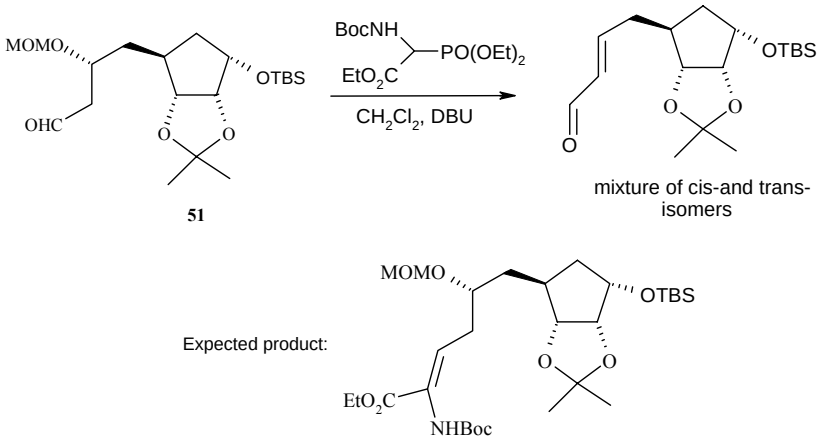
Scheme 22. Synthesis of N-acylaminophosphonates.

The second step of the N-acylaminophosphonate synthesis was furnished by a N-H insertion reaction of rhodium carbenoinds.[123] The rhodium (II) acetate catalyzed reaction of **40** with carbamate was carried out in boiling benzene for 18 hours resulting in high yields of racemic phosphorylglycine esters.

For the purpose of further investigation of the asymmetric hydrogenation, three different N-acylaminophosphonates 41-43 (Scheme 22) were synthesized with different amino protecting groups.

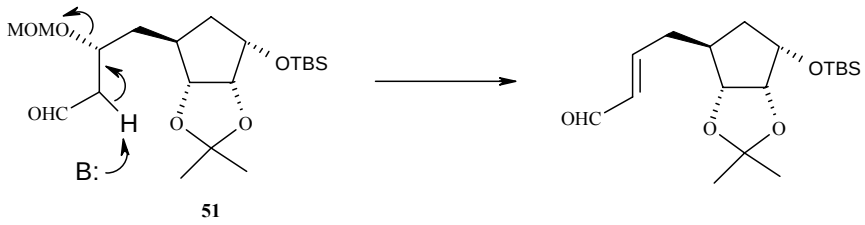
Originally, sodium hydride, potassium *tert*-butoxide or lithium di*iso*propylamide were used as a base for the phosphorylglycine method [124] resulting in a mixture of *Z* and *E* isomers, which were very difficult to separate, and contained sufficient amounts of by-products. Later, Masamune, Roush and Rathke have found that a mixture of lithium chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or triethylamine is superior to alkali bases in these types of reactions. [125] And, in 1992, Schmidt and coworkers [121] discovered that the use of lithium chloride is completely superfluous and often disadvantageous, and that the use of DBU in dichloromethane gives in predominantly *Z* product (>97%) in nearly quantitative yields.

Thus, condensation of **51** with phosphorylglycine ester, was expected to yield α,β-unsaturated amino acid derivative. Unfortunately, the outcome of this reaction was the elimination product (Scheme 23).



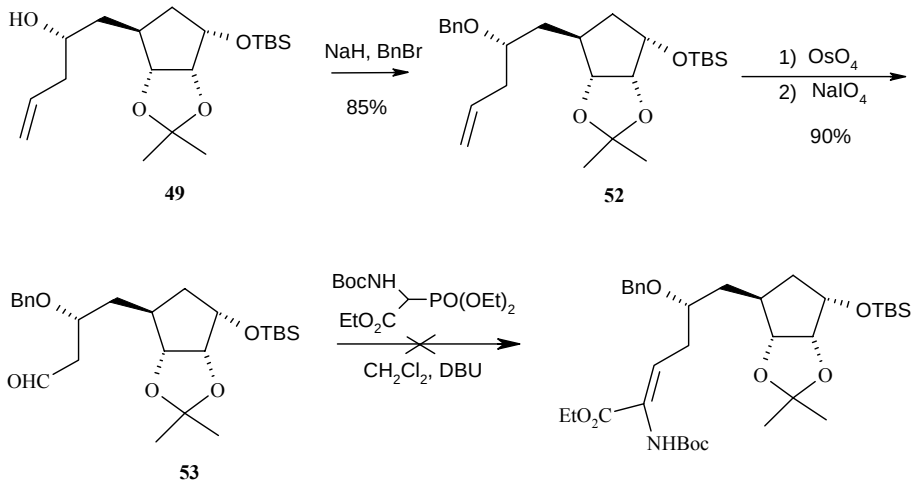
Scheme 23. Reaction of **51** with phosphorylglycine ester.

The possible reason for the formation of such products can be the abstraction of the acidic proton by the base (DBU), and subsequent β-elimination with cleavage of the MOM group and formation of the stable α,β-unsaturated aldehyde (Scheme 24).[126]



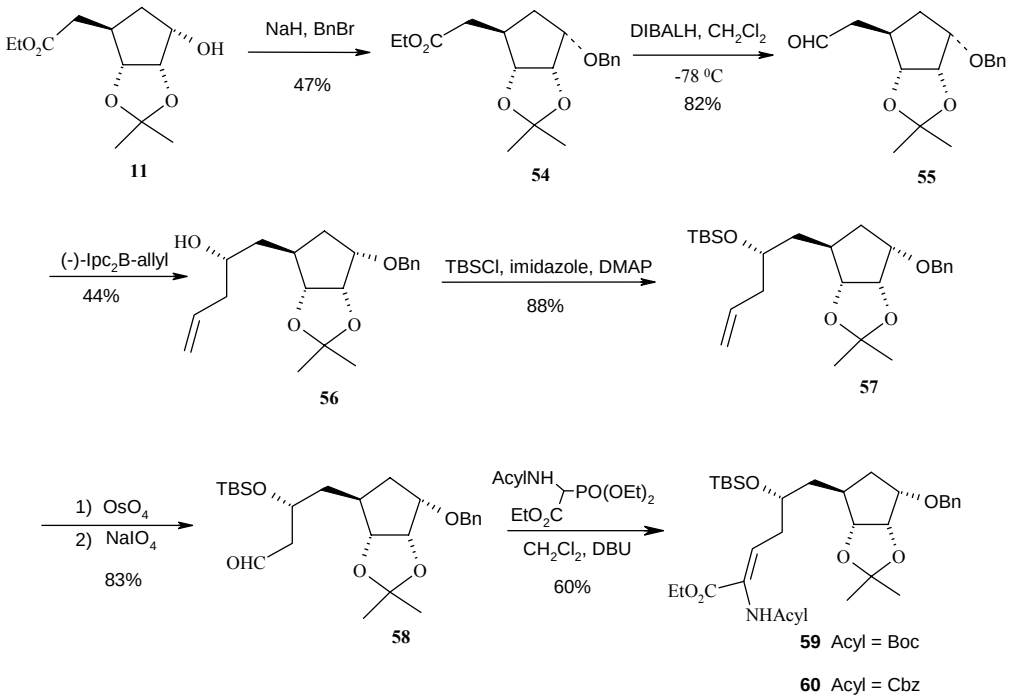
Scheme 24. Formation of the α,β-unsaturated aldehyde.

When attempts to perform this condensation reaction failed, the benzyl group was considered as a protective group for the 6' hydroxyl. Reaction of the alcohol **49** with benzyl bromide in the presence of sodium hydride went smoothly affording an 85% yield of compound **52** (Scheme 25). [127] Upon oxidative cleavage with osmium tetroxide and sodium periodate, the double bond of **52** was transformed into the aldehyde **53** in 90% yield. Treatment of the **53** with the phosphorylglycine ester and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in a complicated mixture with no apparent presence of desired α,β-unsaturated amino acid derivative. The same disappointing results were observed when 6' hydroxyl group was protected with an acetyl or trityl group.



Scheme 25. Attempt to synthesize α,β-unsaturated amino acid derivative.

With these difficulties in mind, a new C-6 protective strategy was undertaken by emplacing the *tert*-butyldimethyl group and protecting the C-1 hydroxyl with a benzyl moiety. The benzyl group can be removed by hydrogenation without affecting the *iso*propylidene group, *tert*-butyldimethyl or ester group. Thus, compound **11** was reacted with benzyl bromide and sodium hydride to afford a 47% yield of the protected alcohol **54** (Scheme 26). The yield is considerably lower than in case of the protection of the 6' hydroxy group (**49** to **52**) due to the significant steric hindrance of the C-1 hydroxyl.



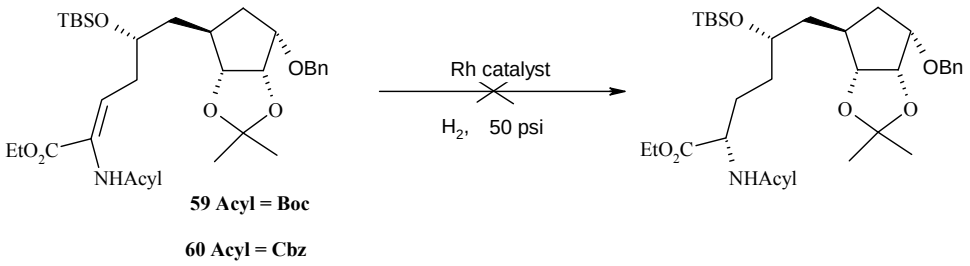
Scheme 26. Synthesis of the α,β-unsaturated amino acid derivatives **59** and **60**.

Reduction of the ester **54** with di*iso*butylaluminum hydride at -78 ^{0}C gave aldehyde **55** in 82% yield. Reaction of **55** with allyl (-)-*iso*campheylborane followed by

protection of the allylic alcohol **56** with a *tert*-butyldimethylsilyl group resulted in the compound **57**. Oxidative cleavage of the double bond went smoothly affording aldehyde **58** in 83% yield.

Construction of the α,β-didehydroamino acid esters **59** and **60** was successfully accomplished using the phosphorylglycine method. [121] In further studies of the furanose derivatives of sinefungin, it was shown that the requisite amino acid condensation reaction occurs poorly when the phosphoroglycine possessed an N-acetyl protective group and subsequent asymmetric hydrogenation was not possible. For these reasons, for the synthesis of the cyclopentane derivatives of sinefungin, only Cbz and Boc-substituted α,β-unsaturated amino acid esters **59** and **60** were constructed (Scheme 26). Since the major product of the phosphorylglycine method using DBU as a base was reported to be in *Z* configuration, [125] the geometry of the double bond in all the products was designated to be *Z*, no formation of *E* isomers as the minor products was observed in this reaction.

The next step of the synthesis was stereoselective hydrogenation of compounds **59** and **60** affording *S* stereochemistry at 9 carbon atom (Scheme 27).



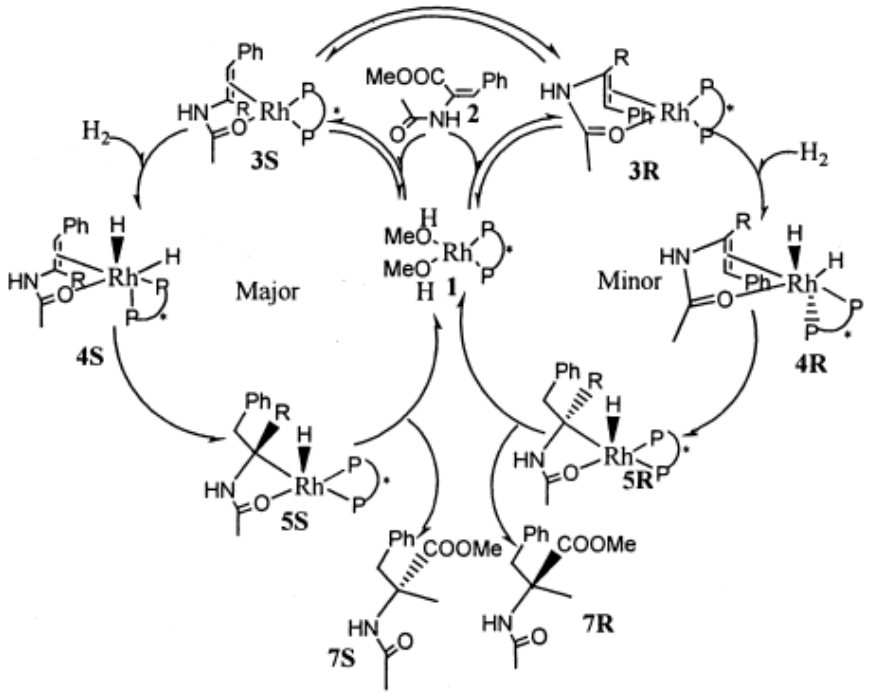
59 Acyl = Boc

60 Acyl = Cbz

Scheme 27. Asymmetric hydrogenation.

Up to date, no single asymmetric hydrogenation catalyst has been developed to directly provide a wide range of α-amino acid derivatives with very high enantioselectivity. Among the most successful candidates, asymmetric rhodium phosphine catalysts have been tested for a range of enamides and showed high efficiency and selectivity. [128] Remarkably, the 1,2-bis(phospholano)benzene (DuPHOS) rhodium catalysts display indifference toward olefin geometry, and high enantioselectivities have been achieved in the hydrogenation of *E*/*Z* mixtures. [128]

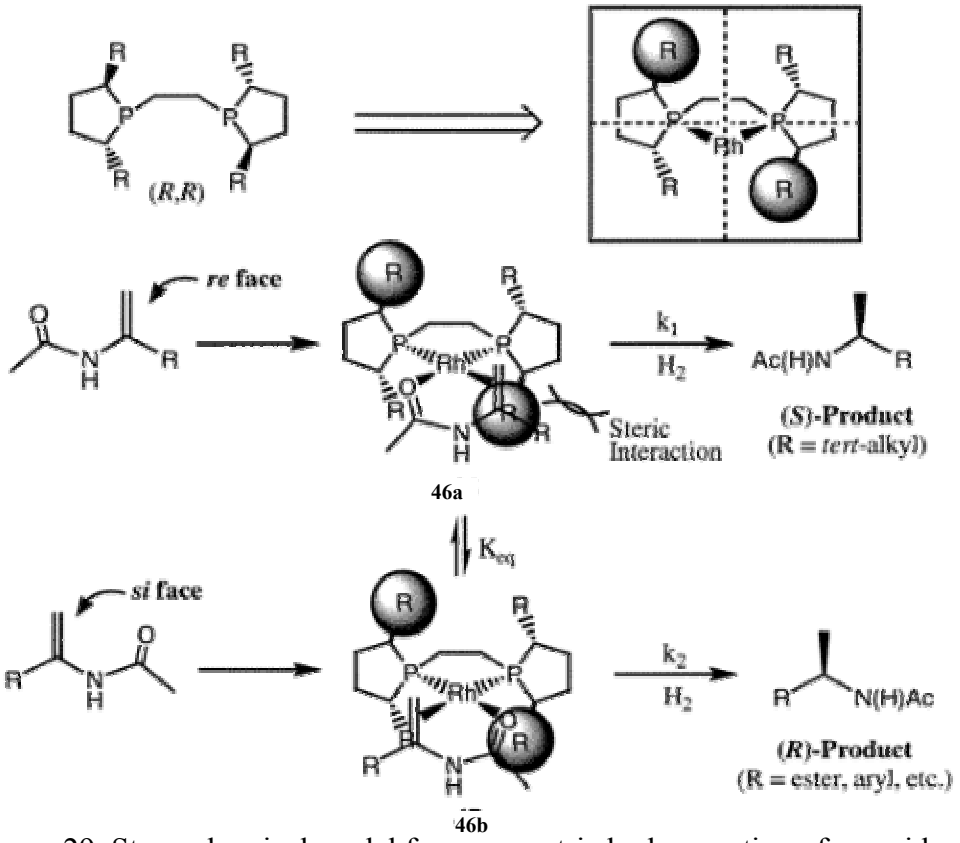
The mechanism of the rhodium catalyzed hydrogenation has not been fully comprehended yet, although recent mechanistic studies have unveiled some aspects of this process. A number of experimental investigations of the mechanism of the [Rh(chiraldiphosphine)]$^+$-catalyzed hydrogenation revealed the underlying sequence of steps by which the catalyst transforms enamides into chiral amino acids (Scheme 28). [128]



Scheme 28. Catalytic cycle for the [Rh(chiraldiphosphine)]$^{+}$-catalyzed hydrogenation of acetamidocimiamates (R=COOMe).[129]

The proposed sequence of reaction steps starts from binding of the alkene to the catalyst, followed by oxidative addition of hydrogen. Then the intermediate complex proceeds to product via migratory insertion and reductive elimination. These studies revealed a surprising "anti-lock-and-key" motif. Whereas most of the catalyst binds to one particular alkene enantioface, hydrogenation of the opposite enantioface leads to the hydrogenated product.

To facilitate the current understanding of these results of these studies, a simplistic stereochemical model was developed that incorporates all up-to-date information (Scheme 29). [130]



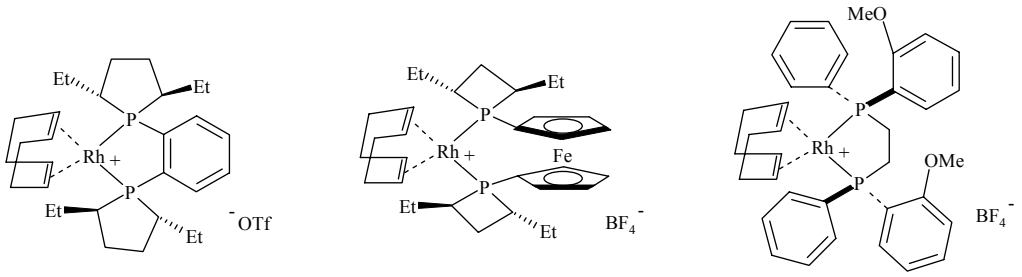
Scheme 29. Stereochemical model for asymmetric hydrogenation of enamides. [130]

A crucial assumption made for this model is that all enamide substrates chelate to rhodium in expected fashion through the alkene unit and N-acetyl carbonyl oxygen atom. The model also presumes that the rate- and stereochemistry-determining steps are the same and lead to oxidative addition of hydrogen to the rhodium center of intermediate diastereomeric enamide complexes.

Under these limits, binding of the *re* face of a prototypical enamide to the (*R*, *R*)-DuPHOS-Rh catalyst was envisioned to afford intermediate complex **46a**, whereas

coordination of the *si* face of the same enamide should lead to the diastereomeric intermediate of structure **46b**. Intermediate **46a** would experience a severe steric interaction between the α-substituent of the enamide and the phospolane *R*-substituent, while intermediate **46b** appears devoid of such unfavorable van der Waals repulsions. The hydrogen addition to each of the proposed intermediates **46a** and **46b** will occur with rate constants k_1 and k_2, respectively, which can be very different, since **46a** and **46b** are diastereomers. This situation can lead to a substantial enantiomeric enrichment through the predominance of one pathway. In the case of *R* being an ester, the literature data suggest that $k_2 >> k_1$ resulting in the (*R*) product with high enantioselectivity. [128] The actual mechanism, however, is an intricate interplay of numerous factors that are substrate dependent, giving sometimes unpredictable and unsatisfying results. [110]

In order to stereoselectively reduce the double bond of compounds **59** and **60**, three different catalysts that were reported to give the best results were considered for the double bond hydrogenation (Figure 21).



[Rh(I)(COD)-(S,S)-Et-DuPHOS]OTf

Catalyst 1

[Rh(COD)-(S,S)-[Et-($C_7H_{14}P$)]$_2$Fe]BF_4

Catalyst 2

[Rh(COD)-((S,S)-DIPAMP)$_2$]BF_4

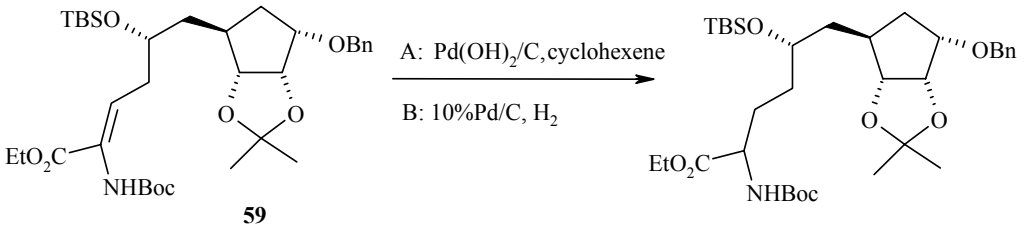
Catalyst 3

Figure 21. Rhodium catalysts that were used.

Unfortunately, attempts at stereoselective reduction of the double bond in **59** and **60** using different rhodium catalysts (Figure 21) and various solvents have been unsuccessful (Scheme 27). The reason for the difficulties we encountered in the asymmetric hydrogenation process may be extreme sensitivity of the rhodium catalysts. There was a precedence reported [121] of unsuccessful hydrogenation using these catalysts due to unremovable by-products from the previous phosphorylglycine condensation step, which can poison the catalyst. Even though compounds **59** and **60** were purified, passed elemental analysis and there were no impurities seen on NMR, there might be some undetectable micro quantity of by-product just enough to poison the catalyst.

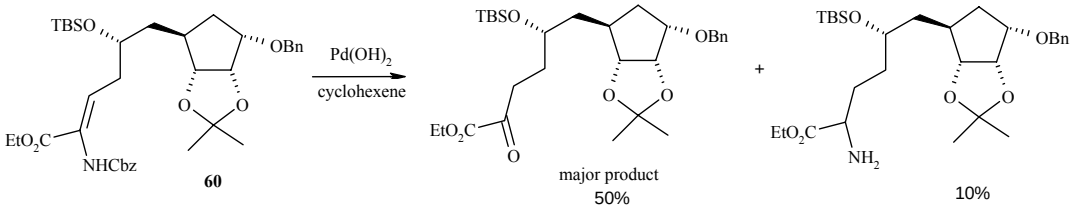
Attention then turned to the target compound **III** as an epimeric mixture at 9' carbon that would permit a non-stereoselective hydrogenation of compounds **59** and **60**. Along with the reduction of the double bond, this reaction was expected to cleave the benzyl protective group, affording, thus, C-1 hydroxyl in the correct α orientation for introducing the purine base using the Mitsunobu reaction or a SN2 coupling.

After compound **59** was refluxed with palladium hydroxide on charcoal and cyclohexene in ethanol, a compound with the reduced double bond but an intact benzyl protecting group was produced (Scheme 30). [131] The same product was obtained as a result of hydrogenation of the compound **59** in Parr apparatus with palladium on charcoal as a catalyst. [132]



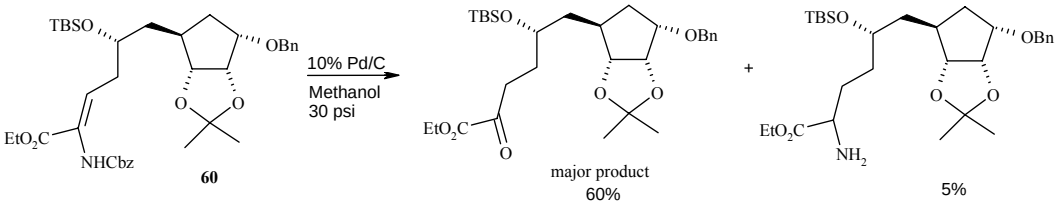
Scheme 30. Hydrogenation of compound **59**.

When benzyloxycarbonyl protected α,β-unsaturated amino acid **60** was treated with palladium hydroxide on charcoal and cyclohexene, two products were obtained (Scheme 31). The structures of these products were determined using ^{1}H and ^{13}C NMR spectroscopy and confirmed by elemental analysis. The major product was an α-keto ester that was formed as a result of cleavage of the Cbz protective group prior to the double bond hydrogenation under the reaction conditions. Hydrolysis of the vinyl amine (a primary enamine) led to the α-keto functionality. The minor product was an amino acid ester resulting from the deprotection of the amino group following the hydrogenation of the double bond. Both products retained the C-1 benzyl protective group.



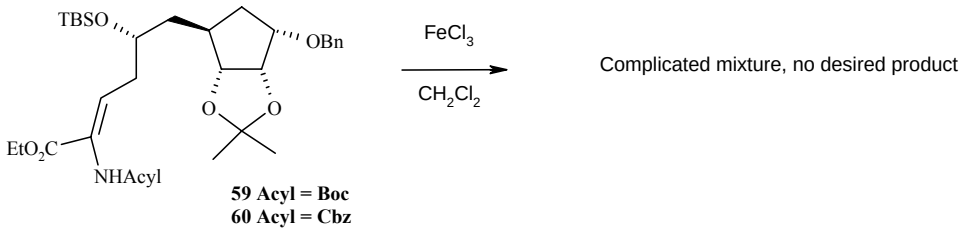
Scheme 31. Hydrogenation of compound **60** with palladium hydroxide.

A similar outcome was observed for the hydrogenation of the compound **60** in Parr apparatus (Scheme 32), even though less amino acid ester product was formed.



Scheme 32. Hydrogenation of the compound **60** in Parr apparatus.

Since conventional methods for removal of the benzyl protecting group failed, and an unprotected C-1 hydroxyl was needed for the coupling of the cyclopentane moiety with purine base, an alternative approach was considered. In this regard the method of deprotecting a secondary benzyl group, reported by Rodebaugh and coworkers, [133] using ferric chloride was evaluated. Unfortunately, when this method was applied for the cleavage of the benzyl group in the compounds **59** and **60**, a complicated mixture with no desired product was formed (Scheme 33).



Scheme 33. Using ferric chloride to cleave the benzyl group.

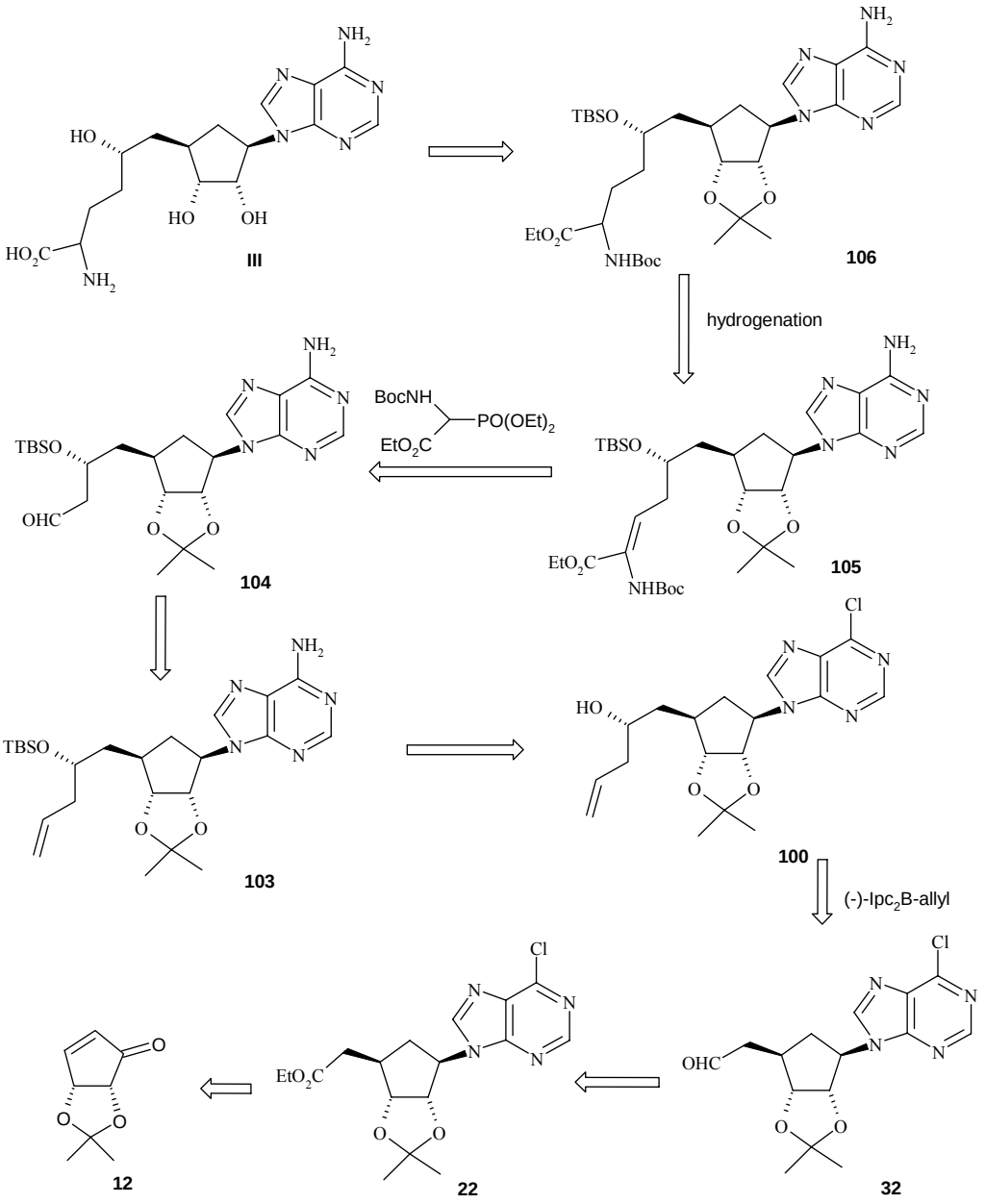
At this stage, the synthetic plan had to be revised to avoid the difficulties of deprotection of the C-1 hydroxy group.

Retrosynthetic analysis of the target compound III (revised).

Since the asymmetric hydrogenation approach did not work for the cyclopentane derivative precursors of sinefungin and plans to consider a C-9 epimeric mixture as a target failed, attention returned to studying the possibility that success could be achieved on a derivative bearing a purine moiety. This would preclude the aforementioned difficulties of removing the C-1 benzyl group.

Thus, the new synthetic route toward the carbocyclic sinefungin derivative **III** was designed (Scheme 34). Taking advantage of the developed method for the synthesis of targets **I** and **II**, the aldehyde **32**, which can be obtained by the reduction of the ester **22**, was considered as an important intermediate. As described elsewhere, compound **22** was readily available from (-)-(4*R*,5*R*)-4,5-(*iso*propylidenedioxy)-2-cyclopentenone (**12**). The reaction sequence developed in the abasic cyclopentane approach can be used to construct the C-5' chain of the target sinefungin derivative including the stereoselective allylboration and introduction of the amino acid moiety by the phosphorylglycine method.

Since use of the Cbz protected amino group led to the α-keto ester as the predominant product upon standard hydrogenation procedures, the Boc protected amino group derivative **105** was sought as the fully functionalized intermediate for the synthesis of the target **III**.

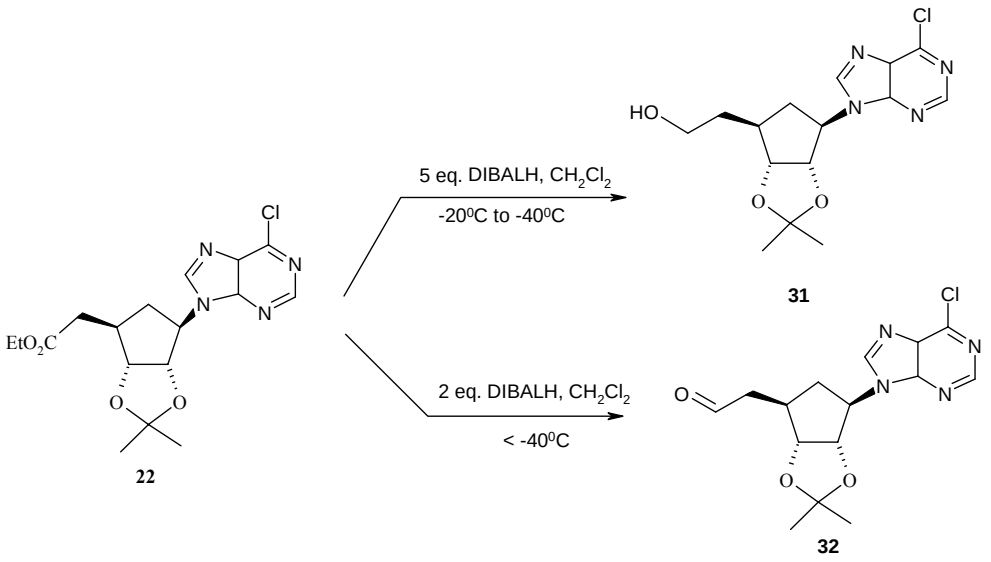


Scheme 34. Retrosynthetic analysis of the target compound **III** (revised).

Synthesis of the carbocyclic sinefungin derivative III.

The synthesis started with compound **22**, which was synthesized in large amount starting from the enone **12** (Schemes 9 and 11). By controlling the reaction conditions,

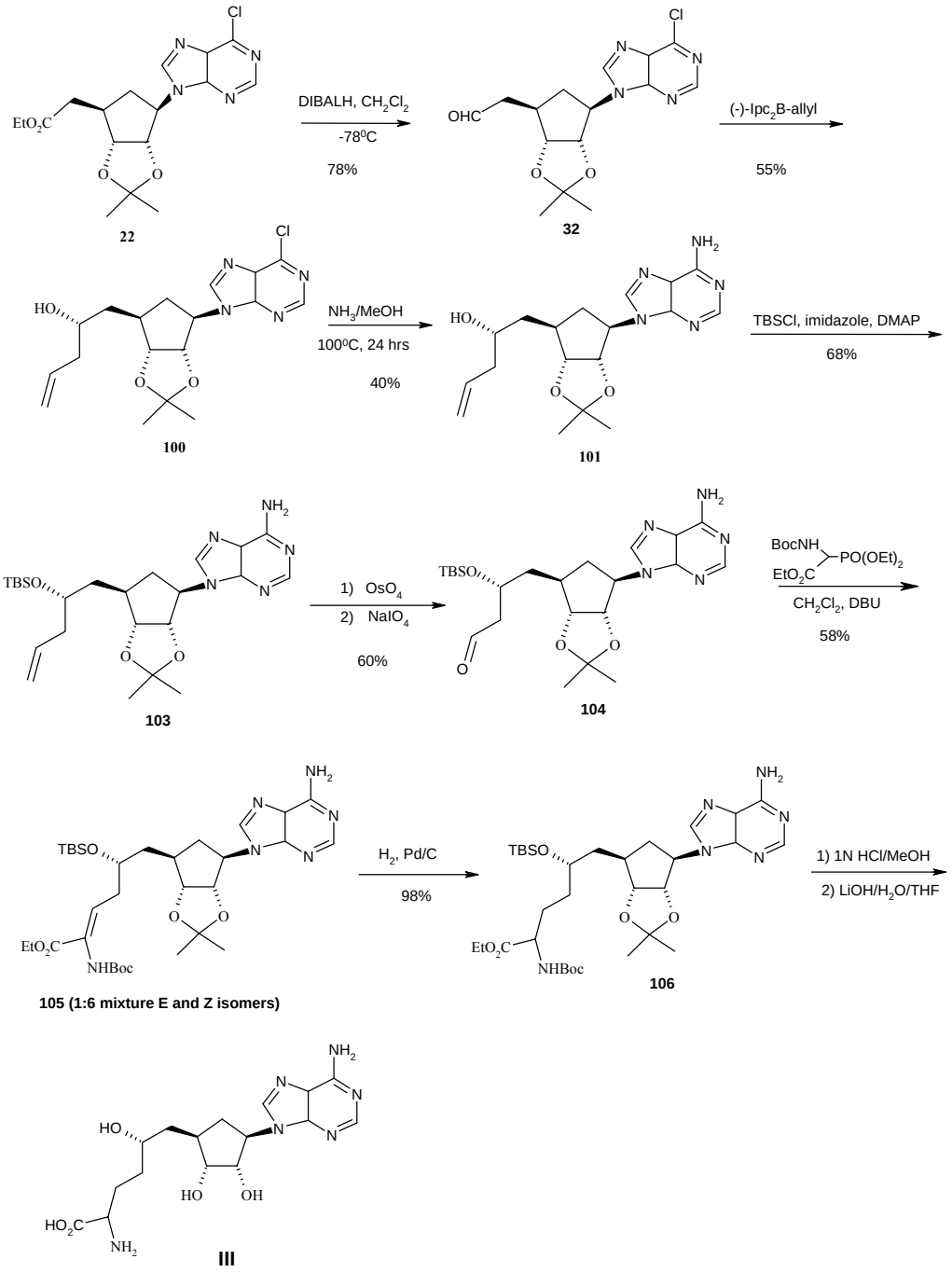
di*iso*butylaluminum hydride proved to be a very useful reducing reagent for this research. To evaluate the conditions, reaction conducted with five equivalents of di*iso*butylaluminum hydride at temperatures higher than -40 ^{0}C resulted in a mixture of alcohol and aldehyde (Scheme 35), with alcohol **31** being the major product. Increasing the reaction temperature led to more alcohol being formed. At temperatures higher than -20 ^{0}C, no aldehyde was produced and the yield of alcohol was considerably lower and necessitated careful purification to remove it from side-products. The best result for achieving the alcohol occurred at a temperature around -30 ^{0}C. These were the conditions that guided this plan to the target compound **II**.



Scheme 35. DIBALH as a reducing agent.

At temperatures lower than -40 ^{0}C, aldehyde was the major product of the di*iso*butylaluminum hydride promoted reduction reaction. To avoid alcohol formation, a lower amount of di*iso*butylaluminum hydride was required. Thus, when ester **22** was treated with two equivalents of di*iso*butylaluminum hydride at -78 ^{0}C, the aldehyde **32**

was obtained as a single product in 78% yield (Scheme 36). The reaction was very clean, and the product was used in the next step after easy purification by fast column chromatography.



Scheme 36. Synthesis of the target compound **III**.

The allyl (-)-*iso*campheylborane reagent was synthesized as described previously herein and was immediately added to a solution of aldehyde **32** in the freshly distilled methylene chloride/anhydrous ether (1:3 mixture) under nitrogen atmosphere affording allylic alcohol **100** in 55% yield.

Compounds with the attached purine base have considerably lower solubility than the corresponding abasic compounds. This was the reason for using a solvent mixture in the previous reaction instead of just diethyl ether. The low solubility of the intermediate compounds also caused difficulties with isolation and purification of the reaction products during the course of the synthesis of the target compounds **III** and **IV**, and was responsible for lower reaction yields compared to the sequence described above for the construction of the C-5 side chain of the abasic cyclopentane derivatives.

Ammonolysis was performed prior to protection of the C-6' hydroxy group, since the *tert*-butyldimethylsilyl group is sensitive to ammonium salts [133] and can be cleaved by the formation of ammonium chloride in subsequent ammonolysis reactions. Heating of the compound **100** with ammonia saturated methanol solution in a steel bomb for 24 hours gave a 40% yield of adenine derivative **101** (Scheme 36). Protecting the allylic alcohol with *tert*-butyldimethylsilyl group under standard conditions afforded compound **103** with 68% yield. The oxidative cleavage of the double bond was achieved upon treatment of the **103** with osmium tetroxide and sodium periodate to yield aldehyde **104**.

When the phosphorylglycine method was applied to introduce the amino acid moiety to the 5' side chain of the carbocyclic sinefungin analog, a 1:6 mixture of the *E* and *Z* isomers of the α,β-didehydroamino acid **105** was obtained. These isomers can not be distinguished using TLC method because of the similar R_f and, thus, can not be

separated. The ratio of *E* and *Z* isomers was determined using ^{1}H NMR spectroscopy. The protons of allylic carbon are more strongly deshielded when the latter is *cis* to the carboxy group (*E* geometry of the double bond) than when they are *trans*. [121]

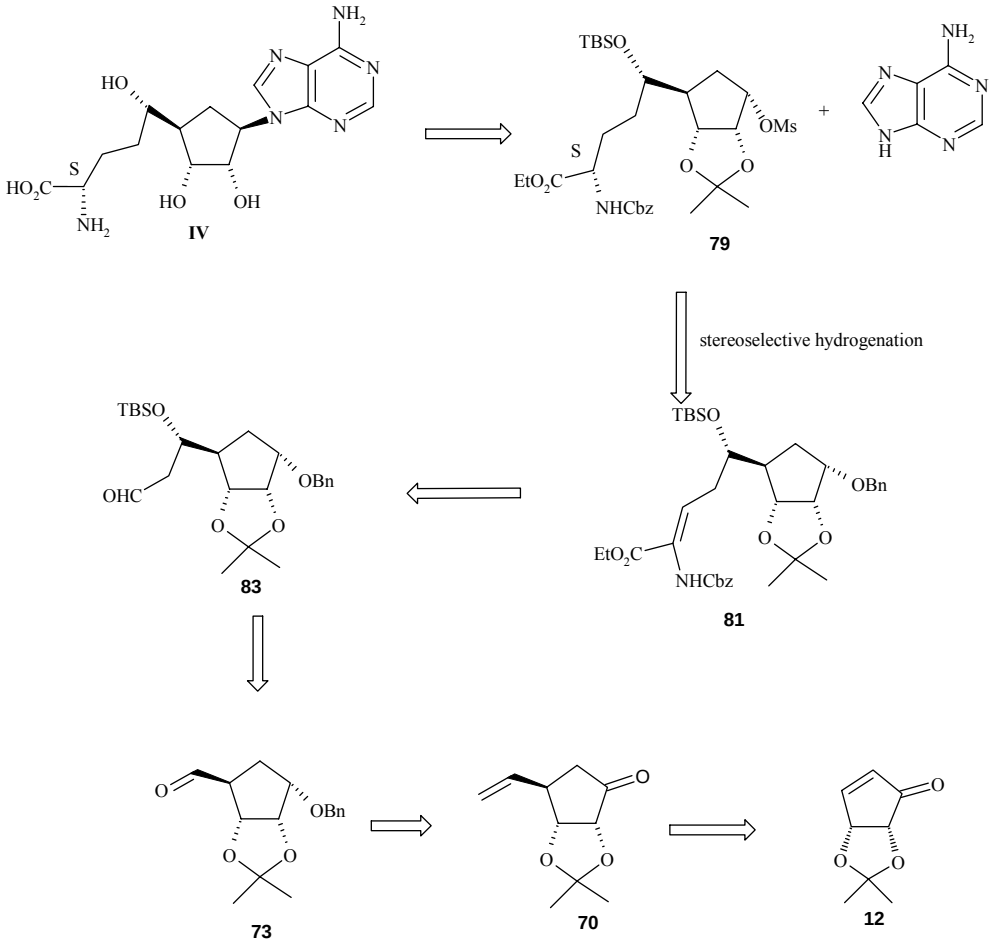
Since the geometry of the double bond does not influence both asymmetric and nonstereospecific hydrogenation, [128] the mixture of isomers was used for the further transformations. After numerous attempts of the asymmetric hydrogenation using different rhodium catalysts and reaction conditions failed, the double bond of the α,β-unsaturated amino acid **105** was reduced with palladium on charcoal at 30 psi pressure in the Parr apparatus affording compound **106** in 98% yield (Scheme 36).

Compound **106** represents a fully functionalized skeleton of the target carbocyclic sinefungin derivative **III** with a constructed amino acid side chain, cyclopentane ring and adenine base. This compound has five defined stereocenters at 1', 2', 3', 4' and 6' carbon atoms, which had been selectively constructed in the course of synthesis, and epimeric 9' carbon. The last transformations needed for the production of the target compound **III** included cleavage of all the protective groups.

The *iso*propylidene and *tert*-butyldimethylsilyl protective groups were removed upon acidic hydrolysis using 1N hydrochloric acid in methanol. Following treatment of the product from this reaction with lithium hydroxide solution in aqueous tetrahydrofuran cleaved the Boc protective group with concurrent hydrolysis of the ethyl ester to provide the target compound **III**, which was purified using column chromatography (5% ammonia solution in methanol).

Retrosynthetic approach toward target compound IV.

Research toward target **IV** was pursued concurrently with effort seeking **III**. Thus, benefits of the problems in removing the C-1 benzyl group were not available. As a consequence, the retrosynthetic plan of Scheme 37 was the blueprint for achieving **IV**.



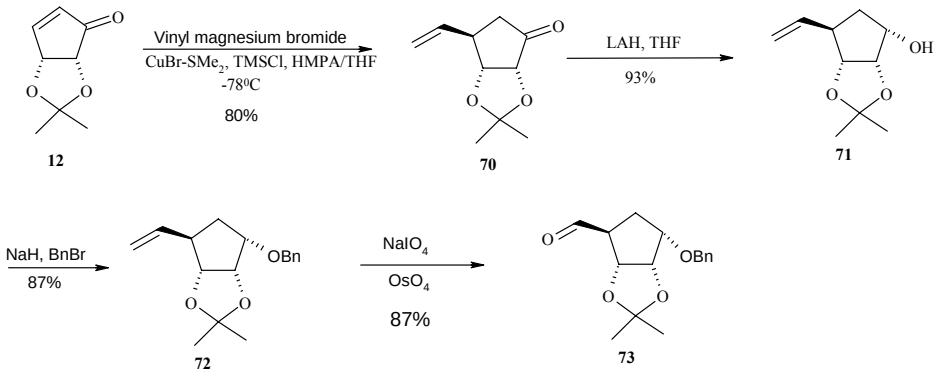
Scheme 37. Retrosynthetic analysis of target **IV**.

As before, a key step in this approach was that the abasic α,β-unsaturated amino acid ester **81** could be stereoselectively hydrogenated using rhodium catalysts 1-3 (Figure 21). Introduction of the glycine moiety was envisioned to follow from aldehyde **83,** which, in turn, could be obtained from compound **73**. Aldehyde **73** was recognized as a

potential source of some difficulty related to possible C-4 tautomerization under basic conditions resulting in a mixture of products with α and β orientation of the aldehydic substituent. Careful analysis of **73** suggested that since the three C-1, C-2 and C-3 substituents of the cyclopentane ring existed in an α orientation, it is reasonable to expect that β orientation of the C-4 substituent will prevail. Even with this in mind, a synthetic sequence that allowed for immediate reaction of the aldehyde **73** to avoid C-4 epimerization was sought. The vinyl moiety of compound **70** was chosen as a source of C-4 aldehyde functionality of **73**. The vinyl group of **70** would be available via the known high-yielding 1,4-addition to enone **12**. [134]

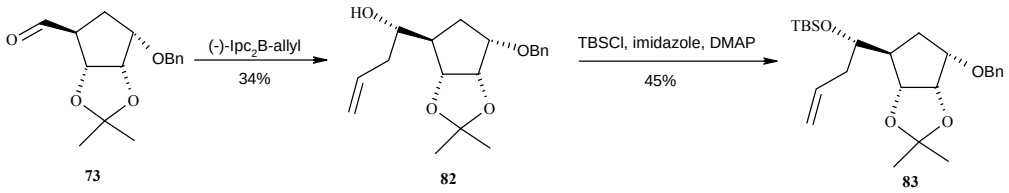
Synthesis of the intermediate compound 73.

Compound **70** was obtained in 80% yield employing a reported procedure for 1,4-addition of vinylmagnesium bromide to enone **12**. [136] Since the α face of the cyclopentane ring of **12** is sterically hindered with a 2,3-*iso*-propylidenedioxy group, addition of the vinyl unit occured from the β face yielding compound **70** as a single product (Scheme 38). Reduction of **70** with lithium aluminum hydride resulted in alcohol **71** as the only isomer in 93% yield. Exclusive formation of an α oriented hydroxy group can be explained as a result of aluminum coordination with the carbonyl group and two oxygen atoms of the 2,3-*iso*-propylidenedioxy group from the α face of the ring, thus allowing the hydride attack only from β face of the molecule.



Scheme 38. Synthesis of intermediate **73**.

Protection of the C-1 hydroxyl with a benzyl group yielded compound **72**, which was converted to an aldehyde **73** in 87% yield upon treatment with sodium periodate and catalytic amount of osmium tetroxide.



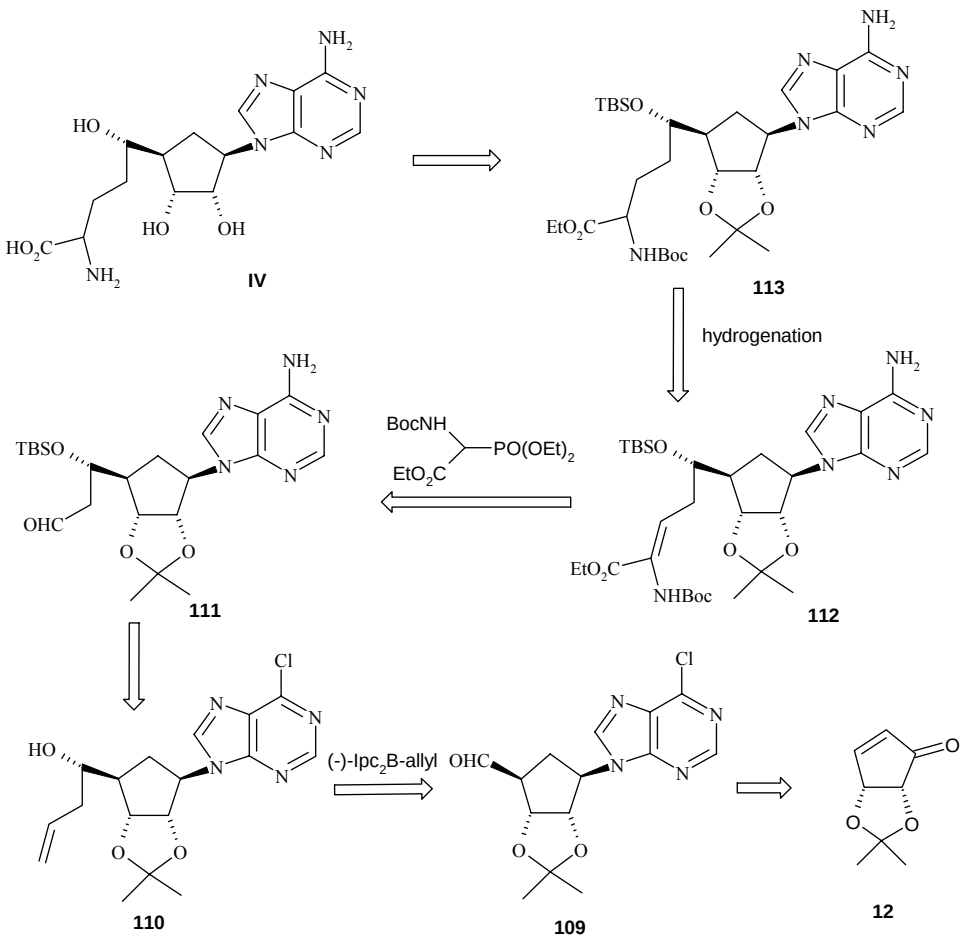
Scheme 39. Synthesis of intermediate **83**.

Aldehyde **73** was immediately reacted with freshly obtained (-)-allyldi*iso*pinocampheylborane affording (4*S*)-4-hydroxy-4-[(1'S,2'R,3'S,4'S)-2',3'-(*iso*propylidendioxy)-4'-benzyloxycyclopentan-1'-yl]-1-buten (**82**) in low (34%) yield. NMR data suggested that only one isomer as shown by structure of **82** was formed in this reaction. Protection of the C-5 hydroxy group with *tert*-butyldimethylsilyl group resulted in 45% yield of **83** (Scheme 39).

At this time, we encountered difficulties in the stereoselective hydrogenation of the double bond of the α,β-unsaturated amino acid and removal of the benzyl protective group from compounds **59** and **60** (Schemes 30-32) while working on the previously described project. Since the same problem could exist for the benzyl group in this study to a one carbon shorter homologue of **59** and **60**, it was decided to check if the benzyl group could be removed from **83** prior to conducting further transformations. Unfortunately, all attempts to deprotect 1-C hydroxyl group of **83** have failed.

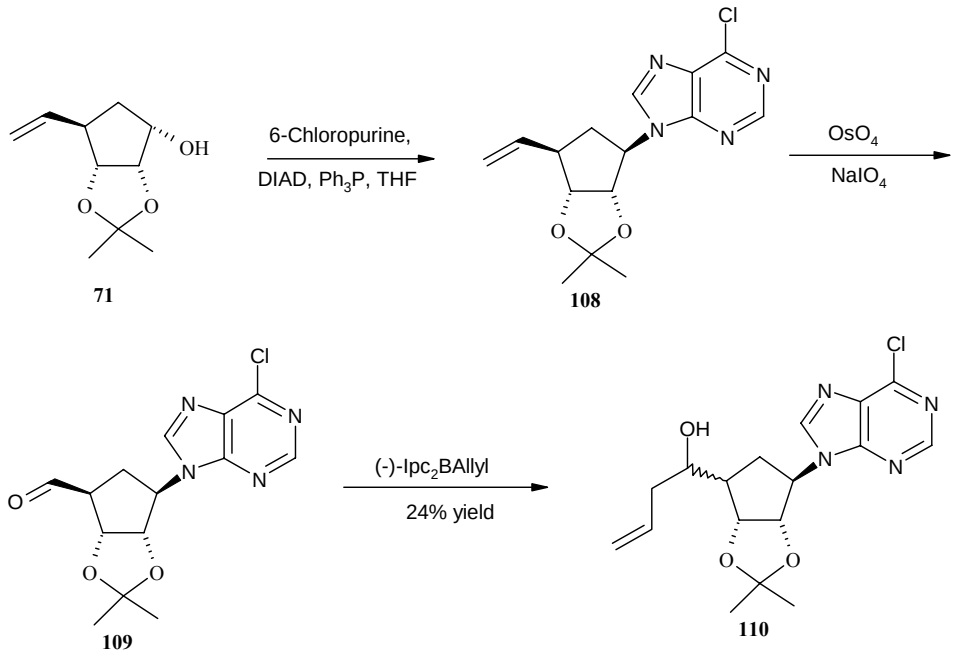
New synthetic approach toward target compound IV.

Thus, considering aforementioned problems and taking advantage of successful synthesis of target **III,** the new synthetic route toward the carbocyclic sinefungin derivative **IV** was designed (Scheme 40). This approach included synthesis of the nucleoside core **109** and, then, modifying its side chain through a developed sequence of chemical transformations. This method would avoid problems with deprotection of C-1 hydroxyl group.



Scheme 40. Revised retrosynthetic analysis of **IV**.

Compound **71** was coupled with 6-chloropurine by a Mitsunobu reaction giving a product **108**, which was inseparable from an azadicarboxylate by-product and, consequently, was used as a mixture in the next step (Scheme 41).[136]



Scheme 41. Synthesis of the intermediate **110**.

The double bond of **108** was transformed into the aldehyde **109** upon an oxidative cleavage using osmium tetroxide and sodium periodate. Compound **109** was immediately carried into the reaction with (-)-allyldi*iso*pinocampheylborane resulting in the formation of product **110** in low (24%) yield, NMR spectra of which revealed a 1:1 mixture of epimers at the C-4' atom. Since epimerization at this center was not observed for the aldehyde group of the abasic compound **73** (Scheme 39), it was concluded that this effect may be the result of increased steric hindrance from the β face of the molecule by the C-1' purine base. This can be seen in Figure 22 wherein for **73**, the C-4 aldehyde in the only β orientation (**73β**) is much more stable than the sterically hindered α aldehyde (**73α**). Compound **109** has the relatively large purine base in a β orientation, thus, reducing the difference between the stabilities of the aldehydes **109α** and **109β**. In fact, the 1:1 ratio of α and β products **110** suggests that stabilities of **109α** and **109β** are very close.

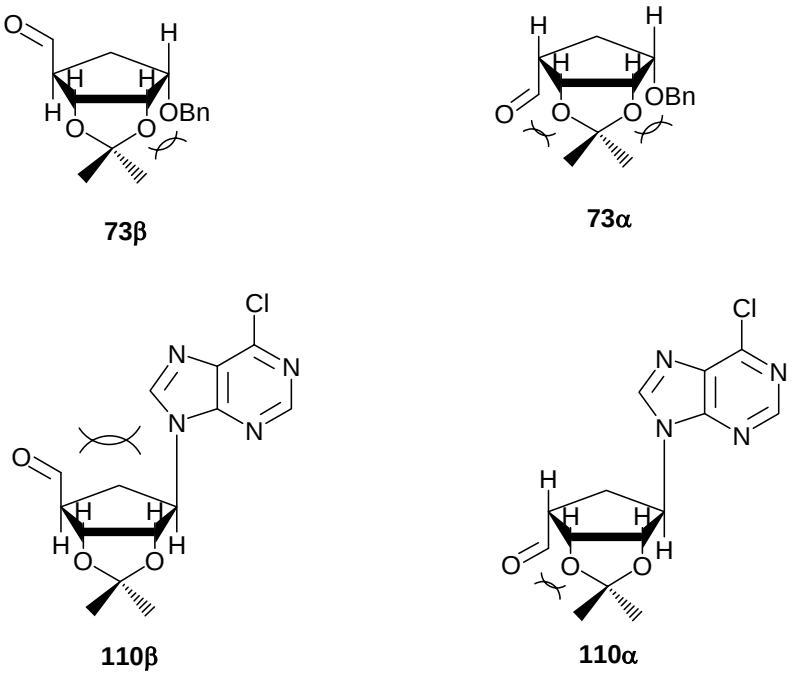


Figure 22. Steric interactions.

For studying the antiviral activity of the sinefungin analogs and other carbocyclic nucleosides, β orientation of the C-4' substituent is crucial.[10, 21] Because of the very low yield of the inseparable epimeric mixture of **110**, this compound was not practical for further chain of transformations. Because our synthetic efforts toward the target **IV** were disappointing, the project was not considered further.

Chapter 3. Studies toward the synthesis of the sinefungin derivatives V and VI.

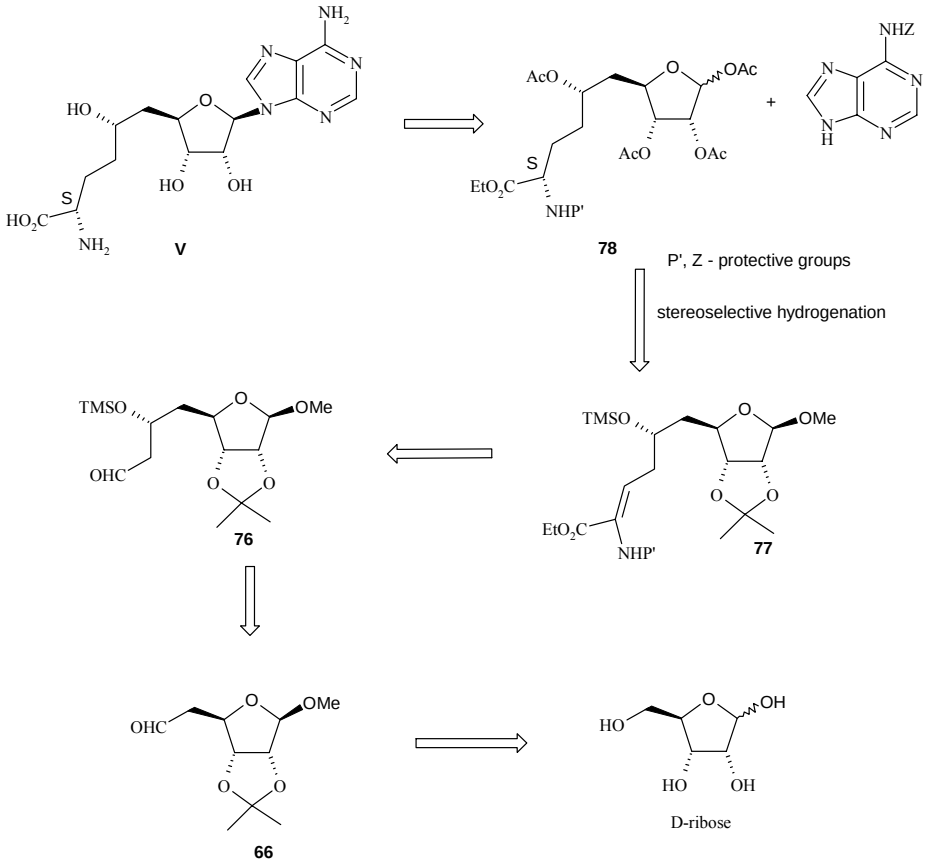
Retrosynthetic approach toward target compound V.

There are several publications describing total synthesis of sinefungin.[83, 96] Although they offer some valuable insights toward construction of the sinefungin side-chain, most of the reported synthetic strategies include a Curtius rearrangement as a key step for incorporation of the C-6' amino functionality.[96] Reduction of the corresponding nitro group was another way to introduce amino group at the 6' position.[83] Since the target compound **V** lacks this functionality, a new synthetic strategy had to be developed in order to make these compounds.

Our retrosynthetic analysis of the target compound **V** is outlined in Scheme 42.

Target compound **V** can be obtained by anomeric adenosylation of compound **78**, which has a fully constructed side-chain and furanose ring with desired stereochemistry, and appropriate deprotection. We anticipated that the amino acid derivative **78** could be made by asymmetric hydrogenation of compound **77** in order to set the stereochemistry at the C-9 position. To afford enamine **77**, aldehyde **76** was envisioned to undergo diastereoselective condensation by the phosphoroglycine method. [124] For establishing 6-C asymmetric center on the desired intermediate **76**, the plan considered use of chiral

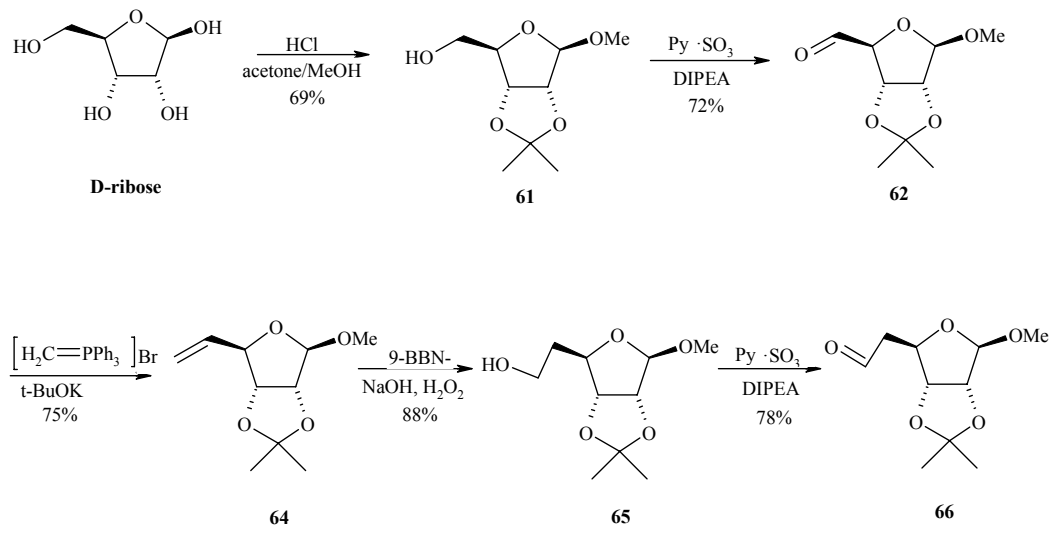
organoborane reagents and aldehyde **66**, which is an important precursor with four stereocenters and is readily available from D-ribose. [137]



Scheme 42. Retrosynthetic analysis of target compound **V**.

Synthesis of the precursor 66.

Although methyl 5-deoxy-2,3-O-*iso*propylidene-D-ribohexodialdo-1.4-furanoside **66** is a known compound, reported procedures for its synthesis offered complicated work-ups and low yields. [137] Since large quantities of the compound **66** were needed for this research, a new and improved synthetic protocol had to be developed for making this compound.



Scheme 43. Synthesis of precursor **66**.

The synthesis started with D-ribose, which was dissolved in a 1:1 mixture of methanol and acetone and treated with hydrochloric acid with refluxing for 3 hours to afford 2, 3-O-*iso*propylidene-D-ribofuranoside (**61**) in 69% yield (Scheme 43). [138]

To oxidize primary alcohol **61** to aldehyde **62**, the Parikh-Doering method, [139] which involves activation of DMSO by sulfur trioxide pyridine, was used. Low temperature -5 ^{0}C was easily maintained by a sodium chloride/ice bath and the reaction was completed in one hour in 72% yield. Mild conditions, short reaction time and ease of work-up make this method very convenient for large scale synthesis of important precursors.

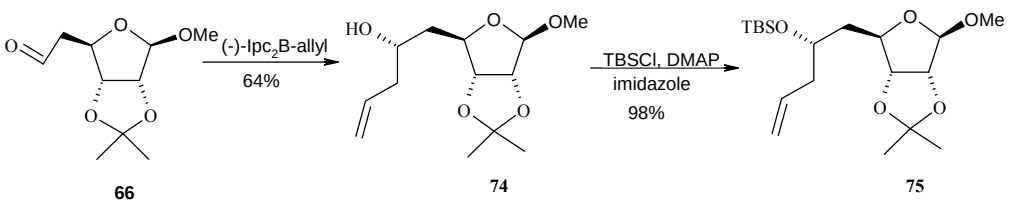
Aldehyde **62** was treated with methyltriphenylphosphonium bromide and potassium t-butoxide in anhydrous ether to yield compound **64**. [140] Hydroboration reaction of alkene **64** with 9-borobicyclo[3.3.1]nonane, hydrogen peroxide and sodium hydroxide regiospecifically led to anti-Markovnikov product **65** in 88% yield. Parikh-

Doering oxidation of alcohol **65** yielded 5-deoxy-2,3-O-*iso*propylidene-D-ribo-hexodialdo-1,4-furanoside (**66**) in 78% yield.

With this method, the synthesis of the precursor **66** was successfully accomplished in 5 steps and 25.6% overall yield starting from D-ribose.

Synthesis of target compound V.

In order to stereoselectively introduce the C-6 hydroxyl group, compound **66** was reacted with freshly synthesized (-)-B-allyldi*iso*pinocampheylborane in ether at -85 ^{0}C resulting in methyl (6*S*)-6-allyl-5-deoxy-2,3-O-*iso*propylidene-D-ribohexo-1,4-furanoside (**74**) with 64% yield (Scheme 44).

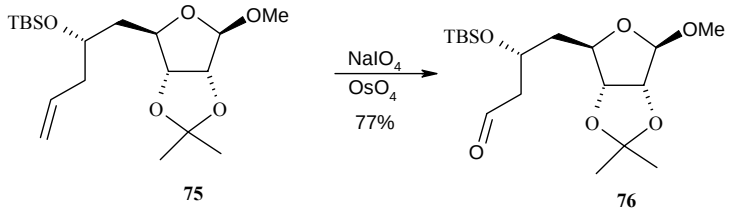


66 74 75

Scheme 44. Synthesis of intermediate **75**.

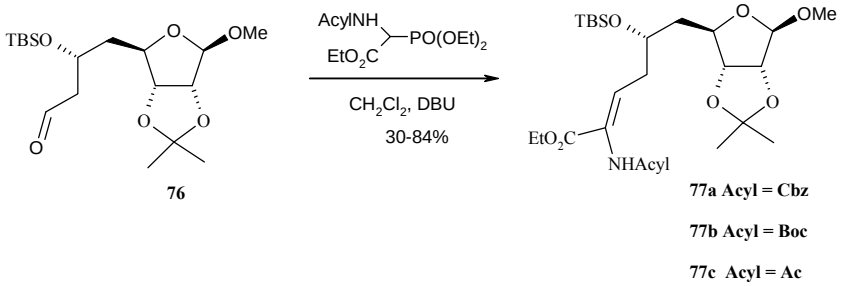
Protection of the secondary alcohol with *tert*-butyldimethylsilyl chloride, imidazole and N,N-dimethyl-4-aminopyridine in methylene chloride went smoothly at room temperature affording compound **75** in 98% yield.

In order to introduce the amino acid moiety to the molecule, aldehyde functionality was determined to be the most versatile. Reaction of the compound **75** with osmium tetroxide and sodium periodate furnished aldehyde **76** in 89% yield (Scheme 45).



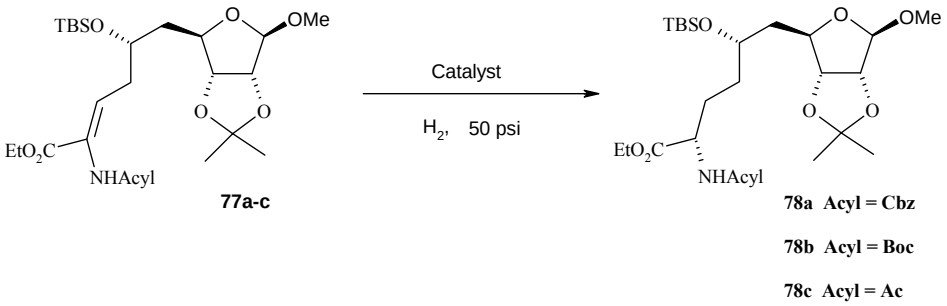
Scheme 45. Synthesis of intermediate **76**.

To construct the α,β-didehydroamino acid **77**, the phosphorylglycine method was used. The aldehyde **76** was reacted with ethyl N-acyl-phosphorylglycine ester in methylene chloride in the presence of DBU (Scheme 46) affording α,β-dideoxyamino acid esters **77a-c**. The best yield (84%) was achieved with the N-benzyloxycarbonyl-phosphorylglycine ester (**77a**). A good yield (75%) was also obtained in the case of **77b**, while the N-acetyl protected derivative **77c** was synthesized in very low yield (30%).



Scheme 46. Phosphorylglycine method to make intermediates **77**.

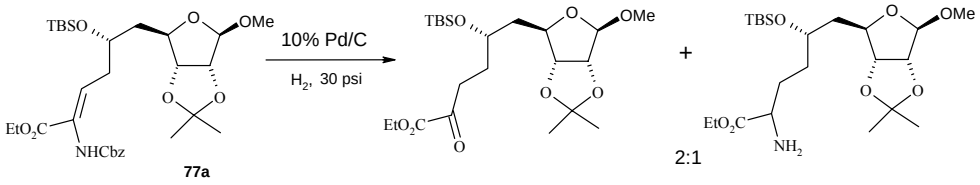
The next step of the synthesis was stereoselective hydrogenation of compounds **77** affording *S* stereochemistry at 9 carbon atom using catalysts shown on the Figure 21 (Scheme 47).



Scheme 47. Asymmetric hydrogenation.

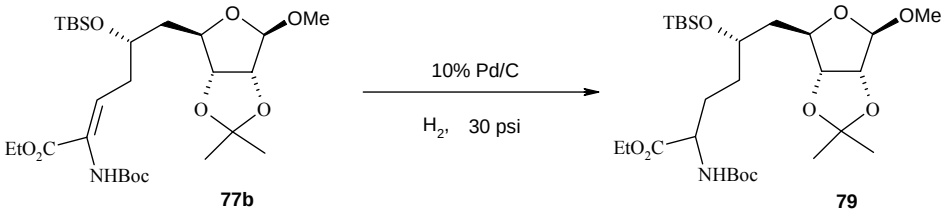
When catalyst 1 (Figure 21) was applied to the compound **77a** in methanol at 50 psi hydrogen pressure, hydrogenation went stereoselectively affording the amino acid **78a** in 98% yield (Scheme 47). Unfortunately, this result has proven to be non-reproducible, and we were unsuccessful in further attempts to repeat this reaction. The same catalyst was exploited to reduce compounds **77b** and **77c**, since different substituents on the amine group were reported to influence binding of the substrates to the rhodium catalyst giving the desired product. [111] But the reactions did not take place despite the different conditions that we tried. When compounds **77a-c** were treated with catalysts 2 and 3, hydrogenation also did not proceed with starting material being recovered.

Since asymmetric hydrogenation was not working, an epimeric mixture at C-9' of compound **V** was considered as a new target. When non-selective hydrogenation of the compound **77a** was performed using Pd/C catalyst and 30 psi hydrogen pressure, two products were formed in a 2:1 ratio (Scheme 48). Their structures were determined using NMR spectroscopy and confirmed by an elemental analysis. The major product formed as a result of cleavage of the Cbz protective group, prior the double bond hydrogenation, followed by hydrolysis of the resultant enamine.



Scheme 48. Hydrogenation of the compound **77a**.

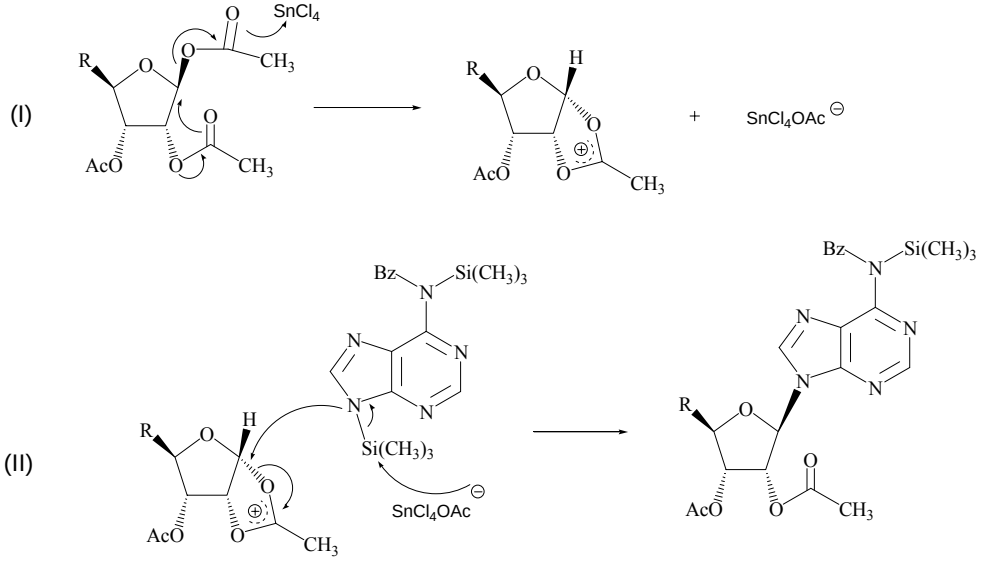
The same hydrogenation procedure was applied to **77b** resulting in a 90% yield of the desired product **79** as an inseparable mixture of epimers at 9 carbon (Scheme 49).



Scheme 49. Hydrogenation of the compound **77b**.

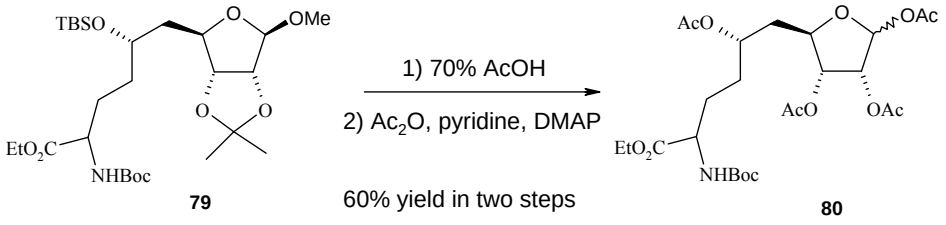
Condensation of a sugar and a heterocycle, which corresponds to a nucleoside base, is called glycosylation and this is a typical method used for the chemical synthesis of nucleosides. Among many glycosylation methods, the Vorbrüggen modification [141] of the Hilbert-Johnson reaction [142] has been widely employed for the preparation of different modified nucleosides by reacting silylated nucleoside bases and sugar derivatives with suitable leaving groups at the anomeric center. This reaction is catalyzed by Friedel-Crafts catalysts, such as tin tetrachloride or trimethylsilyl methylsulfonate, which convert acylated sugar into the 1,2-acyloxonium salt (Scheme 50 (I)). The nucleophilic silylated

base can only attack the stable sugar cation from the top affording β-nucleoside as an exclusive product (Scheme 50 (II)). [141c]



Scheme 50. Mechanism of nucleoside synthesis.

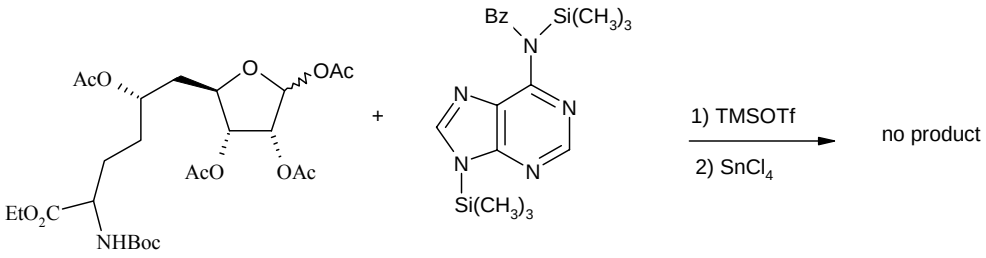
Thus, in order to follow this process to incorporate a nucleoside base on the compound **79**, the latter was transformed into anomeric acetate **80** by a two-step procedure (Scheme 51): first, **79** was kept in 70% acetic acid at 70 ^{0}C for 12 hours, and, then, the resulting alcohol was acetylated using acetic anhydride and pyridine in the presence of 4-N,N-dimethylaminopyridine.



79 **80**

Scheme 51. Acetylation of **79**.

N^6-Benzoyladenine was silylated by refluxing with trimethylchlorosilane in 1,1,1,3,3,3-hexamethyldisilazane for 7 hours. A solution of the silylated base in dry 1,2-dichloroethane was reacted with a solution of anomeric acetates **80** in 1,2-dichloroethane in the presence of different reagents (Scheme 52) but no desired product was produced.



80

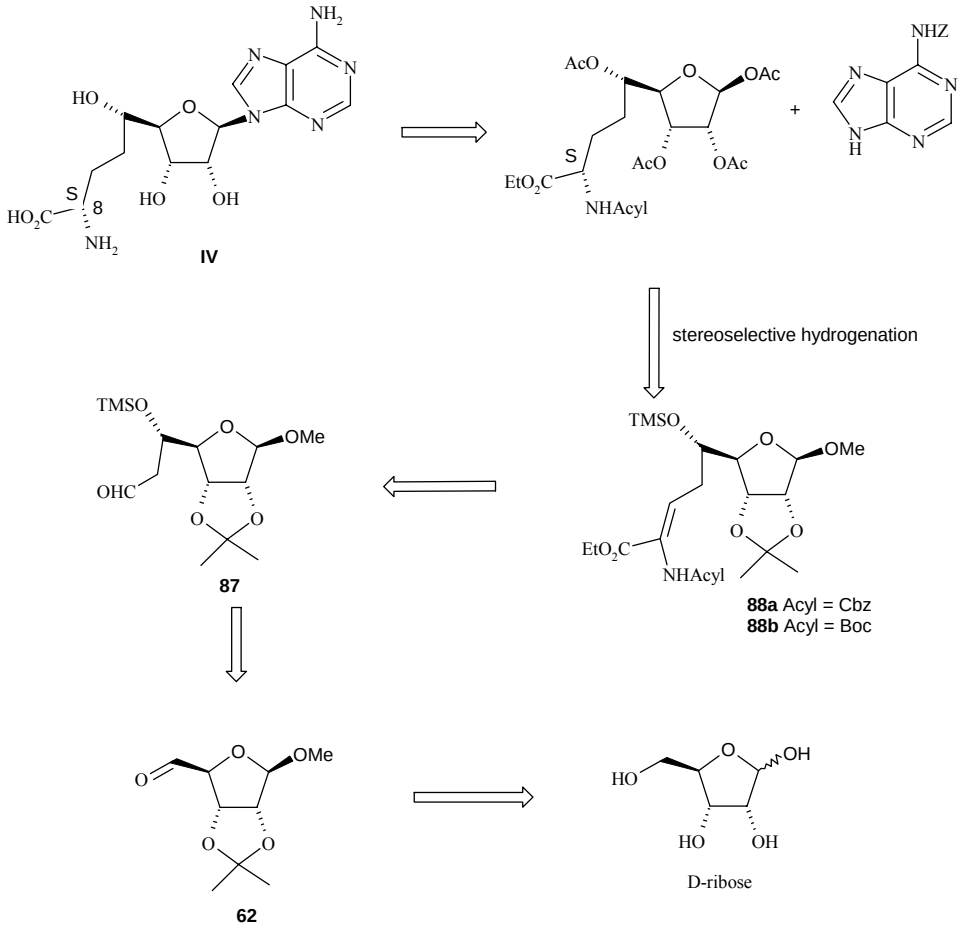
Scheme 52. Attempts of glycosylation of **80**.

A possible reason for such an unfortunate outcome may be interference of 6-acetoxy group of compound **80**. Attempts to selectively deprotect and acetylate C-1, C-2, and C-3 hydroxyl groups of **79** without removing the TBS protective group from the C-6 hydroxyl group and, thus, avoid the difficulties with glycosylation, have failed.

Even though we were unsuccessful in the preparation of the target compound **V**, this research provided insight into synthetic avenues for other sinefungin analogs and gave an entry to a variety of carbocyclic nucleoside derivatives with a C-5' modified side chain.

Retrosynthetic approach toward target compound VI.

Another furanosyl derivative of sinefungin considered as a target was compound **IV** with a shortened side chain (Figure 19 and Scheme 53). A retrosynthetic analysis of target **VI** was similar to that of target **V** (Scheme 53).



Scheme 53. Retrosynthetic analysis of the target compound **VI**.

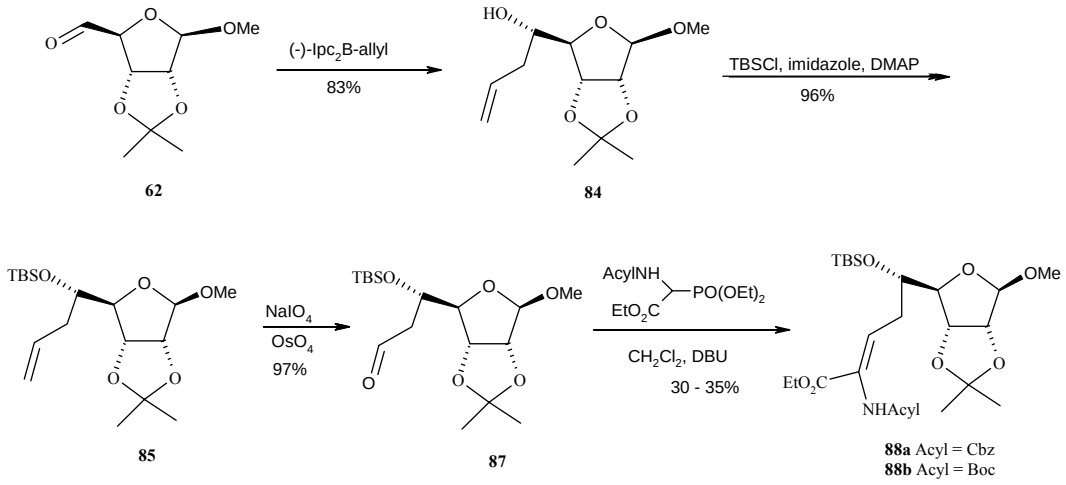
In this regard anomeric adenosylation of a compound with a fully constructed furanosyl side-chain can lead to the target **VI**. The protected amino acid derivative was envisioned to be made by asymmetric hydrogenation of compound **88a,b** in order to set the stereochemistry at the C-8 position. The phosphoroglycine method [112] was planned to be used for the transformation of the aldehyde **87** to the compound **88a,b**. Aldehyde **87** is an important intermediate compound with four stereocenters and was expected to be available by a series of reactions from compound **62**. Thus, methyl 2,3-O-*iso*propylidene-

D-ribopentodialdo-1,4-furanoside (**62**) became an important precursor for the synthesis of **VI**. Its synthesis was possible from D-ribose by the procedure described above (Scheme 53).

Synthesis of the target compound VI.

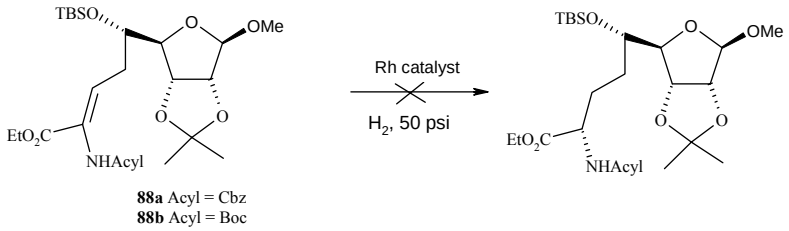
The synthesis started with the asymmetric allylation of the aldehyde **62** with allyl (-)-*iso*campheylborane generated in situ resulting in a 83% yield of methyl (5*S*)-5-allyl-2,3-O-*iso*propylidene-D-ribopenta-1,4-furanoside (**84**) (Scheme 54). [116] The secondary hydroxy group was protected with *tert*-butyldimethylsilyl chloride and imidazole in the presence of 4-N,N-dimethylaminopyridine (DMAP) yielding compound **85**. Oxidative cleavage of the double bound was achieved using osmium tetroxide and sodium periodate to afford aldehyde **87** in 97% yield.

The α,β-didehydroamino acid esters **88a** and **88b** were obtained upon treatment of **87** with N-benzyloxycarbonyl and N-*tert*-butoxycarbonyl phosphorylglycine esters respectively. [121] The reaction yields were significantly lower compared to the same reaction with furanose **76**.



Scheme 54. Synthesis of intermediate compound **88**.

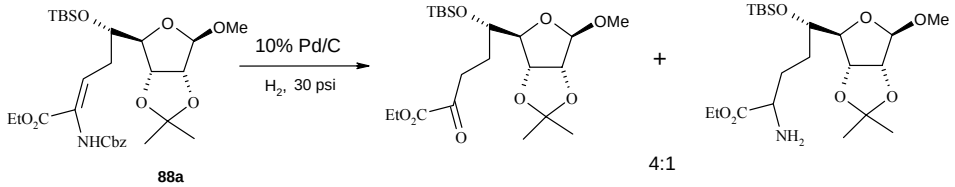
The next step of the synthesis was asymmetric hydrogenation of **88a-b** in order to introduce the *S* configuration at the C-8 center. Unfortunately, attempts of stereoselective reduction of the double bond using different rhodium catalysts (Figure 21) and various solvents have been unsuccessful (Scheme 55).



88a Acyl = Cbz
88b Acyl = Boc

Scheme 55. Attempts of asymmetric hydrogenation.

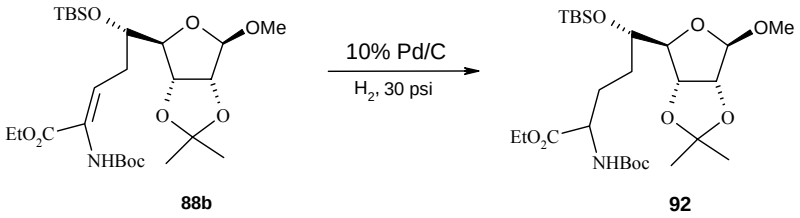
So, a new target containing an epimeric mixture at the C-8' center was considered. For this purpose, a non-stereoselective reduction of the double bond of **88a-b** was carried out using 10% palladium on a charcoal catalyst and hydrogen pressure 30 psi. In the case of the Cbz-protected amino acid ester, cleavage of the protecting group went faster than the double bond reduction resulting in the keto-ester as a major product and deprotected amino acid ester as a minor product (Scheme 56).



88a

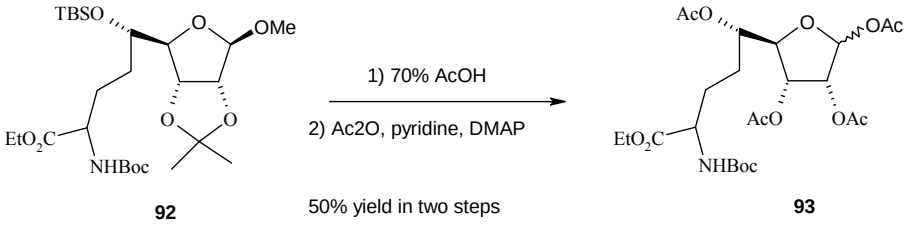
Scheme 56. Hydrogenation of **88a**.

Hydrogenation of **88b** went smoothly affording the desired product **92** in 93% yield (Scheme 57).



Scheme 57. Hydrogenation of **88b**.

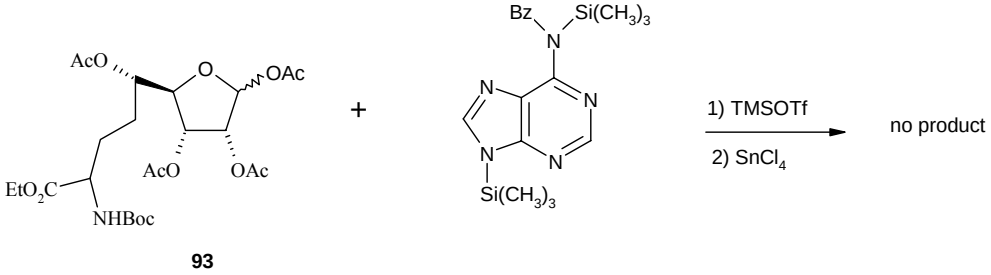
In order to introduce an adenine base, transformation of methyl furanoside **92** to anomeric acetate **93** was accomplished in a two step reaction sequence including treatment of **92** with 70% acetic acid at 80 ^{0}C followed by treatment with acetic anhydride and pyridine in the presence of 4-N,N-dimethylamino pyridine (Scheme **58**).



Scheme 58. Acetylation of **92**.

Knowing about potential interference of the side chain acetoxy group with the glycosylation reaction observed when working on the synthesis of target **V**, we used different reaction conditions in order to keep 5' *tert*-butyldimethylsylioxy group intact while deprotecting and acetylating the rest of hydroxyl groups but were unsuccessful. So,

compound **93** was carried into the next step and reacted with silylated N^6-benzoyladenine in the presence of different reagents (Scheme 59).



Scheme 59. Attempts of glycosylation of **93**.

Unfortunately, no desired product was formed and only N^6-benzoyladenine was isolated in the end of reaction. Compound **93** was completely decomposed, possibly due to the formation of the six member ring (Figure 24).

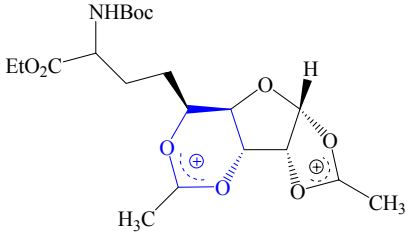


Figure 24. Possible intermediate of glycosylation of **93**.

So, considering aforementioned difficulties with the important glycosylation step, this project was abandoned.

Conclusion

S-Adenosylmethionine (AdoMet) methyl transferase is an important target for antiviral agent development. Structural analogs of AdoMet and AdoHcy are able to bind to the active site of the methyl transferase and, thus, block viral replication. Sinefungin can bind to the vaccinia mRNA methyl transferase instead of AdoMet, but it lacks the requisite methyl group, becoming a potent inhibitor of the capping process essential for virus replication. Besides antiviral activity, sinefungin was found to have a variety of other biological effects including antifungal, amoebicidal and antiparasitical activities. However, its potential use as an antiviral agent sinefungin is restricted because of its severe toxicity.

This project has focused on developing new antiviral agents retaining sinefungin-based antiviral activity while eliminating its toxicity. Although the source of the toxicity of natural sinefungin is unknown, the amino group at the 6' position of its side-chain may be responsible for this undesired effect since this functionality is the only structural difference between sinefungin and AdoMet. Sinefungin analogs with altered functionality of 6'-C atom while keeping the base and amino acid portions of the molecule intact were designed as target compounds.

Carbocyclic sinefungin is a compound of great scientific interest but it has proved to be very difficult to make. Although several synthetic strategies toward carbocyclic

sinefungin have been reported, none of them were successful so far and this compound remains unknown. In order to develop a method for the construction of 5'-C chain on the carbocyclic ring, compounds **I** and **II** were synthesized.

Replacing the amino group at the 6' position of sinefungin with the less basic, yet of similar polarity, hydroxyl group led to the design of a new potential antiviral agent **III**. Compound **III** was synthesized in a 21 step reaction sequence with stereoselective introduction of six stereocenters and as an epimeric mixture at 9' carbon. Retaining the same S-configuration of the 6' stereocenter in the target compounds is important for the binding to and inhibition of AdoMet transferase and AdoMet hydrolase while configuration of 9' stereocenter is not essential. The bioassay data for compound **III** will be forthcoming as part of future studies in the Schneller lab.

Progress toward furanosyl derivatives of sinefungin with side chain modifications **V** and **VI** was made, providing insight into synthetic avenues for other sinefungin analogs.

In closing, methods for construction of the modified side chain of both natural and carbocyclic sinefungin were developed in this dissertation, giving an entry to a variety of carbocyclic nucleoside derivatives with a C-5' modified side chain.

Experimental section.

Materials and methods:

Melting points were recorded on a Meltemp II point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 Spectrometer (operated at 250 or 62.9 MHz, respectively) or AC 400 Spectrometer (operated at 400 or 100 MHz, respectively). All ^{1}H chemical shifts are reported in δ relative to the internal standart tetramethylsilane (TMS, δ 0.00). ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.23) or relative to DMSO-d_6 (center of septet, δ 39.51). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Elemental analyses were performed by the Atlantic Microlabs, Atlanta, Georgia. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E. Merk silica gel 60-F_{254} percoated silica gel plates with visualization by the irradiation with Mineralight UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 2-25 μm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

Tetrakis(triphenylphosphine)palladium (0): Palladium (II) chloride (5.00 g, 28.2 mmol) and triphenylphosphine (36.96 g, 141 mmol) were dissolved in DMSO (200 mL) under nitrogen, and solution was brought to 200 ^{0}C, at which temperature it was stirred

for 15 min. Hydrazine hydrate (5.64 g, 112.8 mmol) was carefully added, and the resulting mixture was allowed to cool to room temperature. Precipitate was filtered under nitrogen, washed with absolute ethanol (2 x 50 mL) and dry diethyl ether (2 x 50 mL) to afford compound **1** as yellow green crystals (32 g, 98 %), whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values. [99]

(Z)-cyclopentene-3,5-diol diacetate (15): Freshly distilled cyclopentadiene (260 g, 3.94 mol) was dissolved in methylene chloride (2.2 L) and sodium carbonate (1000 g, 9.43 mol) was added. Suspension was cooled to –5 ^{0}C, and solution of sodium acetate (20 g, 0.24 mol) in 40% peracetic acid (500 mL) was added dropwise, maintaining the temperature of reaction mixture around –5 ^{0}C to +5 ^{0}C. After addition was complete, resulting suspension was stirred at room temperature for 15 h. White precipitate was filtered off, washed with methylene chloride (3x600 mL), solvent was evaporated under reduced pressure to yield crude epoxide **14**.

Acetic anhydride (450 g, 4.41 mol) was slowly added to a solution of tetrakis(triphenylphosphine)palladium (0) (7g, 6.06 mmol) in dry THF (600 mL) under constant nitrogen flow, maintaining temperature at 0 ^{0}- -5 ^{0}C. Epoxide **14** was dissolved in dry THF (200 mL) and added dropwise to the catalyst solution at 2 ^{0}C. After stirring at room temperature for 12 h, THF was evaporated under reduced pressure at 25 ^{0}C, resulting solution was filtered through a pad of silica gel and magnesium sulfate, which was washed with ether (3 x 200 mL). After ether was evaporated under reduced pressure at room temperature, acetic anhydride was removed under high vacuum at 50 ^{0}C. Distillation of remaining brown oil under vacuum gave compound **15 (**186 g, 26% yield

from cyclopentadiene), whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values. [102]

(+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (13): Compound **15** (186 g, 1.01 mol) was added to a solution of KH_2PO_4 (11.9 g, 87.0 mmol) in water (820 mL), and pH value was adjusted to 7.00 by adding 6N NaOH solution. Then *Pseudomonas cepasia lipase* (6.10 g) was carefully added, and 1N solution of NaOH (1.00 L) was added dropwise, maintaining pH value around 6.9 to 7.2. After addition was completed, reaction mixture was filtered through celite, and filtrate was extracted with EtOAc (3 x 2.0 L). The combined organic layer was dried over anhydrous sodium sulfate and evaporated. The resulting residue was purified by distillation to give product **13** as pale yellow solid (115 g, 81%), whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values.[102]

(+)-(1*S*,4*R*)-4-acetoxycyclopent-2-en-1-yl diethyl phosphate (16): Compound **13** (20.60 g, 145 mmol) was dissolved in dry methylene chloride (150 mL) and pyridine (21.4 mL, 265 mmol). Solution was cooled to 0 ^{0}C, and diethyl chlorophosphate (27.9 mL, 195 mmol) was added dropwise. Reaction was then stirred at room temperature for 6 h.

For workup, 5% aqueous HCl (120 mL, ice-cold) was added to the reaction mixture. Organic layer was washed with 5% aqueous HCl (2 x 120 mL), saturated sodium bicarbonate solution (100 mL) and Brine (100 mL), dried over anhydrous sodium

sulfate. Solvent was evaporated to afford compound **16** as yellow liquid (44.13 g, 110%), whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values. [98]

(+)-(1*S*,2*S*,3*S*,4*R*)-4-Acetoxy-2,3-dihydroxycyclopentan-1-yl diethyl phosphate (17): Compound **16** (44.13 g, 158 mmol) was dissolved in acetone (350 mL) and N-methylmorpholine N-oxide monohydrate (73.7 mL, 356 mmol). Water was added till mixture turns clear (75 mL). Then osmium tetraoxide (307 mg, 1.2 mmol) was carefully added to iced-cooled solution. Resulting mixture was stirred at room temperature for 20 h. Solvent was removed under reduced pressure. Brown residue was purified by column chromatography (EtOAc) to give product **17** as pale yellow liquid (32.32 g, 71%), whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values. [98]

(+)-(1*S*,2*S*,3*S*,4*R*)-4-acetoxy-2,3-(*iso*propylidendioxy)cyclopentan-1-yl diethyl phosphate (18): Compound **17** (32.32 g, 103.6 mmol) was dissolved in acetone (300 mL) and 2, 2-dimethoxypropane (75 mL, 616.7 mmol). To this, *p*-toluenesulfonic acid monohydrate (0.989 g, 5.21 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. Acetone and 2, 2-dimethoxypropane were removed under reduced pressure at 35 ^{0}C. Residue was dissolved in EtOAc (100 mL), washed with saturated sodium carbonate solution (2 x 30 mL). Aqueous layer was extracted with EtOAc (2 x 70 mL). Combined organic layers were dried over sodium sulfate and evaporated to afford compound **18** as yellow liquid (32.71 g, 87%), whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values. [98]

(+)-**(1*S*,2*S*,3*S*,4*R*)-4-hydroxy-2,3-(*iso*propylidendioxy)cyclopentan-1-yl diethyl phosphate (19):** a solution of compound **18** (32.71 g, 92.9 mmol) in THF (60 mL) was added to a solution of lithium hydroxide monohydrate (4.92 g, 117 mmol) in water (80 mL). After the reaction mixture was stirred at room temperature for 12 h, it was extracted with EtOAc (3 x 200 mL). Combined organic layers were dried over sodium sulfate and evaporated to yield compound **19** as pale yellow oil (24.08 g, 84%), whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values. [98]

(-)-(4*R*,5*R*)-4,5-(*iso*propylidenedioxy)-2-cyclopentenone (12): To a solution of compound 1**9** (8.32 g, 26.8 mmol) in methylene chloride (100 mL) were added pyridinium chlorochromate (14.35 g, 66.57 mmol) and celite (21 g). This mixture was stirred at room temperature for 36 h and filtered. Solvent was removed under reduced pressure, and residue was purified by column chromatography (EtOAc-hexanes 1:1), yielding compound **12** as white crystals (3.20 g, 77%), whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values. [98]

[(1'*R*,2'*R*,3'*R*)-2',3'-(*iso*propylidendioxy)-4'-cyclopentanone-1'-yl]acetic acid, ethyl ester (21): A solution of diisopropylamine (1 mL, 7.15 mmol) in dry THF (20 mL) was cooled to – 10 ^{0}C, and n-BuLi (3.00 mL, 7.5 mmol, 2.5M solution in hexanes) was added dropwise. Above solution was cooled to – 40 ^{0}C, and ethyl trimethylsilylacetate (1.00 mL, 5.47 mmol) was added dropwise. After the reaction mixture was stirred at this temperature for 40 min, hexamethylphosphoramide/THF (6 mL, 1:1 mixture) was added dropwise.

The above mixture was further cooled to –72 ^{0}C, and solution of compound **12** (0.77 g, 5.00 mmol) in dry THF (5mL) was added dropwise. The reaction mixture was stirred at this temperature for 2 h, and then gradually warmed up to –40 ^{0}C.

At this point saturated solution of ammonia chloride (10 mL) was added. The reaction mixture was extracted with methylene chloride (4 x 30 mL). Combined organic layers were washed with Brine (150 mL), dried over sodium sulfate and evaporated to afford compound **20** as yellow oil, which was used directly in the next reaction without purification.

A solution of compound **20** in aqueous ethanol (70 mL) was stirred with potassium fluoride (0.66 g) for 16 h at room temperature. Then solid was filtered off, filtrate was extracted with methylene chloride (3 x 100 mL). Combined organic layers were washed with Brine (150 mL), dried over sodium sulfate and evaporated. Residue was purified by column chromatography (EtOAc-hexanes 1:3) to afford compound **21** (1.03 g, 85%). ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, *J* = 7.2 Hz), 1.28 (s, 3H), 1.40 (s, 3H), 2.08 (m, 1H), 2.49 (dd, 2H, *J* = 5.5 Hz, 2.5 Hz), 2.8 (m, 2H), 4.12 (q, 2H, *J* = 7.1 Hz), 4.37 (d, 1H, *J* = 6.0 Hz), 4.59 (d, 1H, *J* = 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.36, 24.93, 29.66, 34.07, 37.87, 39.81, 61.21, 81.06, 82.17, 112.38, 171.73, 213.07. Anal. calc. for $C_{12}H_{18}O_5$: C (59.50), H (7.44). Found: C (59.34), H (7.53).

[(1'*R*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-hydroxy-cyclopentan-1'-yl]acetic acid, ethyl ester (11): Compound **21** (1.03 g, 4.26 mmol) was dissolved in dry methanol (30 mL) and the solution was cooled to 0 ^{0}C. Cerium chloride heptahydrate (1.35 g, 3.63 mmol) was added. Sodium borohydride (0.241 g, 6.36 mmol) was added by portions. The

reaction mixture was stirred at 0 ^{0}C for 1.5 h, quenched with saturated solution of ammonia chloride (8 mL) and extracted with methylene chloride (3 x 40 mL). Combined organic layers were washed with Brine (60 mL), dried over sodium sulfate and evaporated to give pure compound **11** as pale yellow oil (0.89 g, 86%). ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, *J* = 7.2 Hz), 1.28 (s, 3H), 1.40 (s, 3H), 1.73 (m, 1H), 1.94 (m, 1H), 2.27 (dd, 1H, *J* = 5.6 Hz, 2.6 Hz), 2.40 (d, 2H, *J* = 5.7 Hz), 4.05 (m, 1H), 4.12 (q, 2H, *J* = 7.1 Hz), 4.40 (d, 1H, *J* = 2.7 Hz), 4.51 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.46, 24.62, 26.34, 36.96, 37.13, 38.32, 60.87, 71.36, 79.43, 84.50, 116.00, 172.14.[104]

6-Chloro-1-[(1'*R*,2'*S*,3'*R*,4'*R*)-4'-ethoxyacetyl-2',3'-(*iso*propylidenedioxy)-cyclopentan-1'-yl]purine (22): A solution of compound **11** (2.31 g, 9.4 mmol) in dry THF (100 mL) was cooled to –5 ^{0}C. Then triphenylphosphine (2.59 g, 9.81 mmol) and 6-chloropurine (1.59 g, 10.28 mmol) were added. The reaction mixture was stirred at this temperature for 30 min.

Di*iso*propyl diazodicarboxylate (2.44 mL, 12.35 mmol) was added to the above mixture. After stirring at room temperature for 1 h, the reaction mixture was brought to 50 ^{0}C and was stirred at this temperature for 36 h.

Solvent was evaporated and the residue was purified by column chromatography (EtOAc-hexanes 1:1) to afford a compound 22 as pale yellow liquid (2.92 g, 82%). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H *J* = 7.2 Hz), 1.28 (s, 3H), 1.40 (s, 3H), 1.26 (t, EtOAc), 1.30 (s, 6H), 2.05 (s, EtOAc) 2.60 (m, 3H), 4.10 (q, EtOAc), 4.14 (m, 4H), 4.61 (dd, 1H, *J* = 6.2 Hz, 3.6 Hz), 4.83 (m, 1H), 5.09 (dd, 1H, *J* = 7.5 Hz, 4.0 Hz), 8.18 (s, 1H), 8.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.40, 21.04 (EtOAc), 21.25, 25.40, 27.74, 36.54, 37.35, 40.54,

60.50 (EtOAc), 60.59,60.95, 62.46, 83.57, 83.69, 114.50, 144.76, 151.95, 171.36, 200.44. Anal. calc. for $C_{17}H_{21}Cl\ N_4O_4 \bullet 1.2EtOAc$: C (53.84), H (6.29), N (11.50), Cl (7.30). Found: C (54.35), H (6.18), N (11.43), Cl (7.13).

α-[(1'*R*,2'*R*,3'*S*,4'*R*)-2',3'-(*iso*propylidendioxy)-4'-(aden-9"-yl)-cyclopentan-1'-yl] acetamide (23): Ammonia (gas) was bubbled through ice-cold solution of compound **22** (0.95 g, 2.5 mmol) in methanol (50 mL) for 15 min. Then the reaction mixture was kept at 120 ^{0}C for 36 h in a Parr stainless steel sealed reaction vessel. Volatiles were removed under reduced pressure, residue was purified by column chromatography (EtOAc-methanol 1:3) to afford compound **23** (came together with SiO_2) as pale beige solid (0.88 g, 107%), m.p. 195 ^{0}C. ^{1}H NMR (MeOH-d_4) δ 1.15 (s, 3H), 1.41 (s, 3H), 2.10 (m, 3H), 2.30 (m, 2H), 4.13 (dd, 1H, *J* = 6.0 Hz, 3.3 Hz), 4.72 (m, 1H), 4.97 (dd, 1H, *J* = 7.3 Hz, 3.9 Hz), 6.00 (dd, 2NH), 6.40 (dd, 2NH), 7.32 (s, 1H), 7.44 (s, 1H). ^{13}C NMR (MeOH-d_4) δ 25.19, 27.44, 36.69, 36.87, 60.07, 83.01, 83.30, 97.65, 112.80, 140.03, 149.10, 150.34, 152.08, 155.87, 172.69. Anal. calc. for $C_{15}H_{20}N_6O_3 \bullet 0.9\ SiO_2$.: C (46.75), H (5.20), N (21.81). Found: C (46.70), H (5.59), N (21.67).

α-[(1'*R*,2'*R*,3'*S*,4'*R*)-2',3'-dihydroxy-4'-(aden-9N-yl)-cyclopentan-1'-yl]acetamide (I): Compound **23** (0.40 g, 1.2 mmol) was treated with 3N HCl-methanol solution (10 mL) at room temperature for 4 h. After solvent was removed under reduced pressure, the residue was dissolved in aqueous methanol (20 mL) and stirred with resin Amberlite IR400 for 1 h. The reaction mixture was filtered and concentrated to give a compound (**I**) as yellow solid (0.30 g, 86%), m.p. 203 ^{0}C. ^{1}H NMR (MeOH-d_4) δ 1.50 (m, 3H), 1.78 (m, 2H), 3.53

(m, 2H), 4.00 (m, 1H), 6.15 (dd, 2NH), 6.64 (dd, 2NH), 7.76 (s, 1H), 7.91 (s, 1H), 8.18 (br, 1H), 8.87 (br, 1H). ^{13}C NMR (MeOH-d_4) δ 32.53, 60.43, 74.95, 74.80, 77.47, 118.32, 143.34, 144.24, 148.51, 150.13, 173.39. Anal. calc. for $C_{12}H_{16}N_6O_3 \bullet 2HCl \bullet 1.7H_2O$: C (36.40), H (5.40), N (21.23), Cl (17.94). Found: C (36.32), H (5.29), N (21.14), Cl (17.77).

6-Chloro-1-[(1'*R*,2'*S*,3'*R*,4'*S*)-4'-(hydroxyethan-2''-yl)-2',3'-(*iso*propylidenedioxy)-cyclopentan-1'-yl]purine (31): A solution of compound **22** (1.67 g, 4.4 mmol) in dry Methylene chloride (50 mL) was cooled to –30 ^{0}C. Di*iso*butyl aluminum hydride (22.13 mL, 22.13 mmol, 1M solution in hexanes) was added dropwise. The reaction mixture was stirred at this temperature for 4 h, then it was quenched with methanol (10 mL) and water (5 mL). Then saturated solution of potassium sodium tartrate (20 mL) was added and the resulting mixture was allowed to warm up to room temperature. Organic layer was separated and aqueous layer was extracted with methylene chloride (3 x 60 mL). Combined organic layers were dried over sodium sulfate and evaporated. The residue was purified by column chromatography (EtOAc) to give alcohol **31** (0.55 g) and aldehyde **32** (0.30 g).

Compound **32** (0.30 g, 0.89 mmol) was dissolved in dry methanol (20 mL) and cooled to 0 ^{0}C. Then sodium borohydride (0.05 g, 1.33 mmol) was slowly added. The resulting mixture was stirred at this temperature for 1 h, quenched with saturated ammonia chloride solution (5 mL) and extracted with methylene chloride. Combined organic layers were dried over Sodium sulfate and concentrated to give compound **31** (0.29 g, 97%, overall yield from compound **22** 60%). ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3H), 1.54 (s, 3H), 1.77 (m, 2H), 2.04 (m, 3H), 3.75 (m, 2H), 4.07 (m, 1H), 4.37 (t, 1H, J = 5.2 Hz), 4.82 (dt, 1H, J

= 5.1 Hz, 2.7 Hz), 5.22 (dd, 1H, *J* = 3.0 Hz, 1.6 Hz), 7.26 (s, 1H), 7.84 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.37, 27.67, 36.00, 37.38, 42.12, 61.72, 66.59, 83.80, 84.50, 114.10, 130.35, 144.85, 151.56, 151.78, 151.87. Anal. calc. for $C_{15}H_{19}ClN_4O_3$: C (53.17), H (5.61), N (16.54), Cl (10.49). Found: C (53.22), H (5.77), N (16.48), Cl (10.36).

α-[(1'*R*,2'*R*,3'*S*,4'*R*)-2',3'-(*iso*propylidendioxy)-4'-(6''-chloropurin-1''-yl)-cyclopentan-1'-yl]acetaldehyde (32): A solution of compound **22** (0.82 g, 2.16 mmol) in dry methylene chloride (150 mL) was cooled to –78 ^{0}C. Di*iso*butyl aluminum hydride (4.32 mL, 4.32 mmol, 1M solution in hexanes) was added dropwise. The reaction mixture was stirred at this temperature for 3 h, then it was quenched with methanol (10 mL) and water (10 mL). The reaction mixture was warmed up to –40 ^{0}C and saturated solution of potassium sodium tartrate (50 mL) was added. The resulting mixture was allowed to warm up to room temperature. Organic layer was separated and aqueous layer was extracted with methylene chloride (3 x 60 mL). Combined organic layers were dried over Sodium sulfate and evaporated. The residue was purified by column chromatography (EtOAc) to give aldehyde **32** as pale yellow foam (0.54 g, 75%). ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3H), 1.53 (s, 3H), 2.37 (m, 3H), 2.64 (m, 1H), 2.78 (m, 1H), 4.36 (dd, 1H, *J* = 5.3 Hz, 2.6 Hz), 4.87 (dd, 1H, *J* = 5.5 Hz, 2.8 Hz), 5.17 (m, 1H), 7.27 (s, 1H), 7.83 (s, 1H), 9.79 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 18.23, 20.01, 24.31, 27.71, 52.21, 55.57, 62.49, 84.86, 106.32, 128.66, 132.39, 144.83, 150.01, 152.89, 200.14. Anal. calc. for $C_{15}H_{17}ClN_4O_3$: C (53.62), H (5.05), N (16.64), Cl (10.55). Found: C (53.73), H (4.97), N (16.39), Cl (10.42).

6-Chloro-1-[(1'*R*,2'*S*,3'*R*,4'*S*)-4'-(azidoethan-2''-yl)-2',3'-(*iso*propylidenedioxy)-cyclopentan-1'-yl]purine (33): PPh_3 (1.34 g, 5.1 mmol) was added to an ice-cooled solution of compound **31** (0.60 g, 1.7 mmol) in dry THF (50 mL). Then DPPA (1.1 mL, 5.1 mmol) and DIAD (0.96 mL, 5.1 mmol) were added. After the reaction mixture was stirred at 0 ^{0}C for 2 h, solvent was evaporated. The residue was purified by column chromatography (EtOAc-hexanes 1:3) to afford compound **33** (0.40 g, 65%), m.p. 123 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 1.26 (t, EtOAc), 1.28 (s, 3H), 1.55 (s, 3H), 1.89 (m, 2H), 2.05 (s, EtOAc), 2.40 (m, 3H), 3.43 (t, 2H, *J* = 7.8 Hz), 4.12 (q, EtOAc), 4.52 (dd, 1H, *J* = 6.0 Hz, 3.1 Hz), 4.78 (dt, 1H, *J* = 5.8 Hz, 2.6 Hz), 5.06 (dd, 1H, *J* = 5.8 Hz, 2.8 Hz), 8.15 (s, 1H), 8.71 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.19 (EtOAc), 21.04 (EtOAc), 21.21, 27.61, 32.74, 36.82, 41.92, 49.92, 60.49 (EtOAc), 83.50, 84.47, 114.64, 132.60, 144.86, 151.55, 151.74, 151.87. Anal. calc. for $C_{15}H_{18}ClN_7O_2$•0.3 EtOAc: C (49.86), H (5.23), N (25.13), Cl (9.77). Found: C (50.13), H (5.27), N (25.01), Cl (9.57).

9-**[(1'*R*,2'*S*,3'*R*,4'*S*)-4'-(azidoethan-2''-yl)-2',3'-(*iso*propylidenedioxy)-cyclopentan-1'-yl] adenine (34):** Ammonia (gas) was bubbled through ice-cold solution of compound **33** (0.50 g, 1.37 mmol) in methanol (50 mL) for 15 min. Then the reaction mixture was kept at 100 ^{0}C for 20 h in a Parr stainless steel sealed reaction vessel. Volatiles were removed under reduced pressure, residue was purified by column chromatography (EtOAc) to afford compound **33** as white solid (0.61 g, 80%), m.p. 142 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 1.26 (t, EtOAc), 1.29 (s, 3H), 1.56 (s, 3H), 2.02 (m, 3H), 2.05 (s, EtOAc), 2.40 (m, 2H), 3.43 (t, 2H, *J* = 7.6 Hz), 4.12 (q, EtOAc), 4.53 (dd, 1H, *J* = 6.1 Hz, 3.0 Hz), 4.72 (dt, 1H, *J* = 5.9 Hz, 2.7 Hz), 5.10 (dd, 1H, *J* = 6.0 Hz, 2.9 Hz), 5.73 (s, 2NH), 7.81 (s,

1H), 8.32 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.19 (EtOAc), 21.04 (EtOAc), 25.37, 27.67, 32.77, 37.04, 42.05, 50.02, 60.49 (EtOAc), 62.01, 83.65, 84.47, 114.40, 140.36, 146.76, 152.65, 155.49, 163.56. Anal. calc. for $C_{15}H_{20}N_8O_2$•0.4 EtOAc: C (52.81), H (6.15), N (29.69). Found: C (52.83), H (5.81), N (29.73).

9-**[(1'*R*,2'*S*,3'*R*,4'*S*)-4'-(azidoethan-2''-yl)-2',3'-dihydroxy-cyclopentan-1'-yl]adenine (35):** Compound **34** (0.63 g, 1.8 mmol) was treated with 2N HCl-methanol solution (50 mL) at room temperature for 4 h. After solvent was removed under reduced pressure, the residue was dissolved in aqueous methanol (20 mL) and stirred with resin Amberlite IR400 for 10 h. The reaction mixture was filtered and concentrated to give a compound **35** as yellow solid (0.42 g, 75%), which was directly used in the next step without purification.

7'-aminohomoarysteromycin (II): Compound **35** (0.50 g, 1.65 mmol) was dissolved in methanol (150 mL), and nitrogen was bubbled through the solution for 20 min. Then Pd-C (10%, 367 mg) was added, and the reaction mixture was hydrogenated at 30 psi for 3 days. Then reaction mixture was filtered through a pad of Celite and solvent was evaporated. The residue was purified by column chromatography (EtOAc-methanol 1:1 with 2% NH_4OH) to afford compound (**36**) (0.26 g, 53%), m.p. 191 ^{0}C. ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 3H), 2.43 (m, 2H), 3.05 (t, 2H, *J* = 7.1 Hz), 3.16 (s, MeOH), 3.40 (br, 2H), 3.72 (t, 1H, *J* = 7.8 Hz), 4.48 (t, 1H, *J* = 7.9 Hz), 4.75 (dt, 1H, *J* = 8.0 Hz, 4.2 Hz), 8.15 (s, 1H), 8.17 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 32.08, 33.28, 42.03, 44.2, 64.5, 75.3, 76.4, 120.01, 140.3, 149.1, 152.1, 156.3. Anal. calc. for

$C_{12}H_{18}N_6O_2$•0.7MeOH•0.58SiO_2: C (45.46), H (6.20), N (25.06). Found: C (45.58), H (6.04), N (25.17).

2-Diazo-2-(diethylphosphinyl)acetic acid, ethyl ester (40): 4-(acetylamino)-benzenesulfonyl azide (0.995 g, 5.00 mmol) was dissolved in THF (75 mL). Triethylphosphonoacetate (1.01 mL, 5.05 mmol) and cesium carbonate (0.965 g, 5.00 mmol) were added to the above solution. The reaction mixture was stirred at room temperature for 24 h. Solvent was evaporated and the residue was purified by column chromatography (EtOAc-hexanes 1:2) to afford compound **40** (1.04 g, 83%), whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values. [122]

2-(Diethoxyphosphinyl)-2-([*tert*-butoxycarbonyl]amino)acetic acid, ethyl ester (41): To the solution of compound **40** (1.04 g, 4.16 mmol) in dry benzene (150 mL), t-butylcarbamate (0.49 g, 4.16 mmol) and rhodium (II) acetate dimer (0.02 g, 0.04 mmol) were added. The reaction mixture was refluxed for 20 h, then solvent was evaporated and residue was purified by flash column chromatography (EtOAc-hexanes 1:1) to afford compound **41** as yellow solid (1.06 g, 76%), whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values.[123]

2-(Diethoxyphosphinyl)-2-([benzyloxycarbonyl]amino)acetic acid, ethyl ester (42): To the solution of compound **40** (3.06 g, 12.24 mmol) in dry benzene (200 mL), benzylcarbamate (1.84 g, 12.24 mmol) and rhodium (II) acetate dimer (0.05 g, 0.10 mmol) were added. The reaction mixture was refluxed for 20 h, then solvent was

evaporated and residue was purified by flash column chromatography (EtOAc-hexanes 1:1) to afford compound **42** as pale yellow solid (4.14 g, 91%), whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values.[123]

[(1'*R*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-*tert*-butyldimethylsilyloxy-cyclopentan-1'-yl]acetic acid, ethyl ester (47): Imidazole (1.30 g, 19.1 mmol) was added to a solution of compound **11** (1.87 g, 7.66 mmol) in methylene chloride (100 mL) at room temperature. *t*-Butyldimethylsilyl chloride (1.44 g, 9.6 mmol) and DMAP (0.10 g, 0.77 mmol) were added. The reaction mixture was stirred at room temperature for 2 days. White precipitate was filtered and washed with methylene chloride (2 x 100 mL). Filtrate was evaporated, residue was purified be column chromatography (EtOAc-hexanes 1:4) to yield compound **47** (2.33 g, 85%). ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.91 (s, 9H), 1.23 (t, 3H, J = 7.2 Hz), 1.30 (s, 3H), 1.57 (s, 3H), 2.19 (m, 5H), 4.04 (m, 1H), 4.12 (q, 2H, J = 7.1 Hz), 4.28 (d, 1H, J = 3.9 Hz), 4.40 (dd, 1H, J = 4.1 Hz, 2.7 Hz). ^{13}C NMR ($CDCl_3$) δ -4.50, 0.20, 14.10, 18.56, 24.12, 26.21, 36.05, 36.93, 46.89, 61.40, 72.61, 80.98, 84.54, 111.86, 173.14. Anal. calc. for $C_{18}H_{34}O_5$: C (60.33), H (9.49). Found: C (60.22), H (9.31).

[(1'*R*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-*tert*-butyldimethylsilyloxy-cyclopentan-1'-yl]acetaldehyde (48): A solution of compound **47** (2.33 g, 6.51 mmol) in dry methylene chloride (250 mL) was cooled to -78 ^{0}C. Di*iso*butyl aluminum hydride (13.1 mL, 13.1 mmol, 1M solution in hexanes) was added dropwise. The reaction mixture

was stirred at this temperature for 2.5 h, then it was quenched with methanol (10 mL) and water (5 mL). The reaction mixture was warmed up to -40 ^{0}C and saturated solution of potassium sodium tartrate (20 mL) was added. The resulting mixture was allowed to warm up to room temperature. Organic layer was separated and aqueous layer was extracted with methylene chloride (4 x 50 mL). Combined organic layers were dried over Sodium sulfate and evaporated. The residue was purified by column chromatography (EtOAc-hexanes 1:4) to give aldehyde **48** as pale liquid (1.51 g, 74%). ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.28 (s, 3H), 1.53 (s, 3H), 2.07 (m, 2H), 2.38 (m, 3H), 4.05 (m, 1H), 4.22 (d, 1H, *J* = 7.1 Hz), 4.40 (dd, 1H, *J* = 7.3 Hz, 3.0 Hz), 9.74 (t, 1H, *J* = 3.5 Hz). ^{13}C NMR ($CDCl_3$) δ -4.22, 0.20, 18.64, 26.19, 35.95, 36.89, 47.05, 72.56, 80.62, 84.38, 112.19, 201.14.

(4*S*)-4-hydroxy-5-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-*tert*-butyldimethylsilyloxy-cyclopentan-1'-yl]-1-penten (49): To an ice-cooled solution of (-)-di*iso*pinocampheylmethoxyborane (2.72 g, 8.60 mmol) in dry diethyl ether (50 mL), allylmagnesium bromide (8.6 mL, 8.6 mmol, 1M solution in diethyl ether) was added dropwise under nitrogen. Above solution was stirred at room temperature for 3 h. After ether was evaporated under reduced pressure, white residue was extracted with pentane (100 mL) and filtered under nitrogen to afford the solution of (-)-allyldi*iso*pinocampheylborane in pentane.

The resulting solution (100 mL) was added dropwise to a solution of compound **48** (1.80 g, 5.73 mmol) in dry diethyl ether (90 mL), previously cooled to -80 ^{0}C. The

reaction mixture was stirred at this temperature for 2.5 h, quenched with methanol (5 mL) and stirred for 1 h at room temperature.

Saturated solution of sodium bicarbonate (10 mL) and hydrogen peroxide (8 mL, 30% solution in water) were carefully added. The resulting mixture was stirred at room temperature for 14 h and extracted with EtOAc (2 x 50 mL). Combined organic layers were dried over sodium sulfate and evaporated. The residue was purified by column chromatography (eluent EtOAc-hexanes 1:10 to 1:4) to afford compound **49** as pale liquid (1.0 g, 49%). ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.22 (s, 3H), 1.40 (s, 3H), 2.00 (m, 3H), 2.27 (m, 4H), 3.74 (m, 1H), 4.07 (dd, 1H, *J* = 7.5 Hz, 3.7 Hz), 4.37 (m, 2H), 5.10 (dd, 2H, *J* = 12.6 Hz, 6.2 Hz), 5.81(m, 1H). ^{13}C NMR ($CDCl_3$) δ -4.19, 0.2, 14.39, 21.24, 26.22, 26.67, 38.26, 39.74, 40.17, 60.61, 70.44, 72.17, 80.96, 85.48, 112.53, 118.26, 134.97. Anal. calc. for $C_{19}H_{36}O_4Si$: C (64.04), H (10.11). Found: C (63.92), H (10.19).

(4*S*)-4-Methoxymethyloxy-5-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-*tert*-butyldimethylsilyloxy -cyclopentan-1'-yl]-1-penten (50): Compound **49** (0.67 g, 1.88 mmol) was dissolved in dry methylene chloride (100 mL) and cooled to 0 ^{0}C. Methoxymethylchloride (0.17 mL, 2.07 mmol, 90%) and N,N-diisopropylethylamine (0.30 mL, 2.26 mmol) were added. The reaction mixture was stirred at 0 ^{0}C for 1 hr and at room temperature for 12 h.

Then, it was washed with water (100 mL). Organic solvent was evaporated, residue was purified by column chromatography (eluent EtOAc-hexanes 1:10 to 1:5) to yield compound **50** (0.61 g, 80%). ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.91 (s, 9H), 1.22 (s,

3H), 1.47 (s, 3H), 2.01 (m, 5H), 2.32 (dd, 2H, *J* = 6.2 Hz, 2.8 Hz), 3.38 (s, 3H), 3.67 (m, 1H), 4.07 (dd, 1H, *J* = 7.6 Hz, 3.8 Hz), 4.30 (m, 2H), 4.74 (m, 2H), 5.10 (dd, 2H, *J* = 12.6 Hz, 6.2 Hz), 5.79 (m, 1H). ^{13}C NMR ($CDCl_3$) δ -4.19, 0.2, 14.39, 25.01, 26.22, 26.61, 36.68, 38.05, 39.21, 55.91, 72.68, 75.95, 80.62, 85.18, 96.02, 111.89, 117.68, 134.58. Anal. calc. for $C_{21}H_{40}O_5Si$: C (63.00, H (10.00). Found: C (63.30), H (10.11).

(3*R*)-3-methoxymethyloxy-4-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-*tert*-butyldimethylsilyloxy-cyclopentan-1'-yl]-butanal (51): Compound **50** (0.93 g, 2.32 mmol) was dissolved in mixture of methanol (90 mL) and water (30 mL), and the resulting solution was cooled to 0 ^{0}C. Osmium tetroxide (0.10 g, 0.4 mmol) and sodium periodate (0.99 g, 4.64 mmol) were added. The reaction mixture was stirred for 1 h at 0 ^{0}C and 1 h at room temperature. Solid was filtered off, solvent was evaporated, and the residue was purified by column chromatography (EtOAc-hexanes 1:2) to afford compound **51** as pale yellow liquid (0.83 g, 89%). ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.22 (s, 3H), 1.45 (s, 3H), 1.56 (m, 2H), 2.03 (m, 3H), 2.66 (m, 2H), 3.35 (s, 3H), 4.06 (m, 2H), 4.22 (dd, 1H, *J* = 7.8 Hz, 4.9 Hz), 4.35 (dd, 1H, *J* = 8.2 Hz, 3.9 Hz), 4.72 (dd, 2H, *J* = 10.1 Hz, 5.2 Hz), 9.80 (t, 1H, *J* = 3.5 Hz). ^{13}C NMR ($CDCl_3$) δ -4.19, 0.2, 18.67, 25.12, 26.22, 26.61, 37.92, 38.35, 39.10, 55.96, 72.34, 72.65, 80.77, 85.20, 96.36, 112.25, 201.26. Anal. calc. for $C_{20}H_{38}O_6Si$ x $0.8H_2O$: C (57.63), H (9.51). Found: C (57.45), H (9.23).

(4*S*)-4-benzyloxy-5-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-*tert*-butyldimethylsilyloxy -cyclopentan-1'-yl]-1-penten (52): To an iced-cooled solution of

compound **49** (0.63 g, 1.77 mmol) in dry THF (75 mL), sodium hydride (0.52 g, 1.80 mmol, 95% suspension in oil) was carefully added. Above mixture was stirred at room temperature for 1.5 h.

Then tetrabutylammonium iodide (0.063 g, 0.177 mmol) and benzylbromide (0.22 g, 1.77 mmol) were added. The resulting mixture was stirred at room temperature for 24 h. Solvent was evaporated. The residue was purified by column chromatography (EtOAc-hexanes 1:4) to afford compound **52** (0.70 g, 89%). ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.88 (s, 9H), 1.22 (s, 3H), 1.47 (s, 3H), 2.01 (m, 5H), 2.32 (m, 2H), 3.52 (m, 1H), 4.01 (dd, 1H, *J* = 7.5 Hz, 3.7 Hz), 4.35 (m, 2H), 4.57 (d, 2H, *J* = 13.8 Hz, 4.5 Hz), 5.13 (dd, 2H, *J* = 12.6 Hz, 6.2 Hz), 5.82 (m, 1H), 7.34 (m, 5H).

(3*R*)-3-*tert*-benzyloxy-4-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-*tert*-butyldimethylsilyloxy-cyclopentan-1'-yl]-butanal (53): Compound **52** (0.70 g, 1.56 mmol) was dissolved in mixture of methanol (90 mL) and water (30 mL), and the resulting solution was cooled to 0 ^{0}C. Osmium tetroxide (0.10 g, 0.4 mmol) and sodium periodate (0.67 g, 3.11 mmol) were added. The reaction mixture was stirred for 1 h at 0 ^{0}C and 1 h at room temperature. Solid was filtered off, solvent was evaporated, and the residue was purified by column chromatography (EtOAc-hexanes 1:2) to afford compound **53** (0.26 g, 38%). ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 1.30 (s, 3H), 1.50 (s, 3H), 2.02 (m, 5H), 2.67 (m, 2H), 4.03 (m, 2H), 4.25 (dd, 1H, *J* = 7.7 Hz, 4.7 Hz), 4.35 (dd, 1H, *J* = 8.2 Hz, 3.9 Hz), 4.56 (s, 2H), 7.34 (m, 5H), 9.82 (t, 1H, *J* = 3.5 Hz). ^{13}C NMR ($CDCl_3$) δ -4.19, -4.59, 12.01, 14.08, 18.67, 26.22, 26.35, 38.38, 38.44, 48.51, 71.06, 73.00, 74.78, 79.80, 85.14, 111.23, 128.05, 128.15, 128.66, 145.67, 201.44.

[(1'*R*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-benzyloxy-cyclopentan-1'-yl]acetic acid, ethyl ester (54): To an iced-cooled solution of compound **11** (3.92 g, 16.00 mmol) in dry THF (160 mL), sodium hydride (0.40 g, 16.00 mmol, 95% suspension in oil) was carefully added. Above mixture was stirred at room temperature for 1.5 h.

Then tetrabutylammonium iodide (0.86 g, 1.60 mmol) and benzylbromide (1.91 g, 16.00 mmol) were added. The resulting mixture was stirred at room temperature for 21 h. Solvent was evaporated. Residue was purified by column chromatography (eluent EtOAc-hexanes 1:10 / EtOAc-hexanes 1:4) to afford compound **54** as pale yellow liquid (2.52 g, 47%). ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H, *J* = 7.2 Hz), 1.31 (s, 3H), 1.59 (s, 3H), 2.15 (m, 4H), 2.45 (m, 1H), 3.79 (m, 1H), 4.12 (q, 2H, *J* = 7.1 Hz), 4.29 (d, 1H, *J* = 2.7 Hz), 4.57 (dd, 2H, *J* = 12.9 Hz, 4.8 Hz), 4.69 (m, 1H), 7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 14.42, 24.61, 26.53, 32.85, 37.59, 38.20, 60.79, 71.96, 77.98, 78.68, 84.14, 111.70, 128.08, 128.58, 138.48, 172.12. Anal. calc. for $C_{19}H_{26}O_5 \bullet 0.1C_6H_{14}$: C (68.65), H (7.98). Found: C (68.72), H (7.86).

[(1'*R*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-benzyloxy-cyclopentan-1'-yl]acetaldehyde (55): A solution of compound **54** (2.52 g, 7.55 mmol) in dry methylene chloride (150 mL) was cooled to -78 ^{0}C. Di*isi*butyl aluminum hydride (10.1 mL, 15.1 mmol, 1.5M solution in toluene) was added dropwise. The reaction mixture was stirred at this temperature for 2 h, then it was quenched with methanol (9 mL) and water (5 mL). The reaction mixture was warmed up to -40 ^{0}C and saturated solution of potassium sodium tartrate (20 mL) was added. The resulting mixture was allowed to warm up to

room temperature. Organic layer was separated and aqueous layer was extracted with methylene chloride (3 x 70 mL). Combined organic layers were dried over sodium sulfate and evaporated. The residue was purified by column chromatography (EtOAc-hexanes 1:2) to give aldehyde **55** as pale liquid (1.80 g, 82%). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.63 (s, 3H), 2.20 (m, 4H), 2.54 (m, 1H), 3.79 (m, 1H), 4.24 (d, 1H, *J* = 7.3 Hz), 4.57 (d, 1H, *J* = 7.0 Hz), 4.71 (dd, 2H, *J* = 10.6 Hz, 6.0 Hz), 7.40 (m, 5H), 9.70 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 24.59, 26.47, 33.02, 35.63, 46.76, 71.98, 78.71, 84.23, 111.70, 127.90, 128.02, 128.57, 138.36, 200.75. Anal. calc. for $C_{17}H_{22}O_4$: C (70.34), H (7.57). Found: C (70.52), H (7.45).

(4*S*)-4-hydroxy-5-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-benzyloxy-cyclopentan-1'-yl]-1-penten (56): To an ice-cooled solution of (-)-di*iso*pinocampheylmethoxyborane (1.99 g, 6.30 mmol) in dry diethyl ether (70 mL), allylmagnesium bromide (6.4 mL, 6.4 mmol, 1M solution in diethyl ether) was added dropwise under N_2. Above solution was stirred at room temperature for 2.5 h. After ether was evaporated under reduced pressure, white residue was extracted with pentane (2 x 60 mL) and filtered under nitrogen to afford the solution of (-)-allyldiisopinocampheyl-borane in pentane.

The resulting solution (120 mL) was added dropwise to a solution of compound **55** (1.23 g, 4.2 mmol) in dry diethyl ether (50 mL), previously cooled to -80 ^{0}C. The reaction mixture was stirred at this temperature for 3.5 h, quenched with methanol (6 mL) and stirred 1 h at room temperature.

Saturated solution of sodium bicarbonate (9 mL) and hydrogen peroxide (7 mL, 30% solution in water) was carefully added. The resulting mixture was stirred at room temperature for 14 h and extracted with EtOAc (2 x 200 mL). Combined organic layers were dried over Sodium sulfate and evaporated. The residue was purified by column chromatography (EtOAc-hexanes 1:4) to afford compound **56** as pale liquid (0.61 g, 44%). ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.60 (s, 3H), 1.76 (m, 3H), 2.24 (m, 4H), 3.79 (m, 1H), 3.92 (m, 1H), 4.36 (m, 1H), 4.58 (m, 1H), 4.69 (dd, 2H, *J* = 10.6 Hz, 6.1 Hz), 5.05 (dd, 2H, *J* = 12.6 Hz, 6.2 Hz), 5.89 (m, 1H), 7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 24.79, 26.58, 33.86, 39.14, 39.76, 42.36, 69.89, 72.03, 79.09, 85.24, 111.74, 118.60, 127.81, 128.56, 129.99, 134.68, 140.65. Anal. calc. for $C_{20}H_{28}O_4$: C (72.29), H (8.43). Found: C (72.00), H (8.33).

(4*S*)-4-*tert*-butyldimethylsilyloxy-5-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-benzyloxy-cyclopentan-1'-yl]-1-penten (57): Imidazole (0.312 g, 4.58 mmol) was added to a solution of compound **56** (0.61 g, 1.84 mmol) in methylene chloride (50 mL) at room temperature. *t*-Butyldimethylsilyl chloride (0.35 g, 2.3 mmol) and DMAP (0.05 g, 0.02 mmol) were added. The reaction mixture was stirred at room temperature for 3 days. White precipitate was filtered and washed with methylene chloride (2 x 50 mL). Filtrate was evaporated, residue was purified be column chromatography (EtOAc-hexanes 1:3) to yield compound **57** (0.72 g, 88%). ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.88 (s, 9H), 1.21 (s, 3H), 1.26 (t, EtOAc), 1.47 (s, 3H), 2.05 (m, 5H), 2.19 (m, 2H), 3.72 (m, 1H), 4.12 (q, EtOAc), 4.15 (d, 1H, *J* = 7.2 Hz), 4.30 (m, 1H), 4.53 (d, 1H, *J* = 7.6 Hz), 4.70 (dd, 2H, *J* = 10.6 Hz, 6.8 Hz), 5.03 (dd, 2H, *J* = 12.6 Hz, 6.2 Hz), 5.77 (m, 1H), 7.34 (m, 5H). ^{13}C NMR ($CDCl_3$)

δ 18.24, 24.62, 25.86, 26.50, 33.19, 37.87, 39.36, 42.57, 70.64, 74.03, 78.27, 85.48, 111.05, 117.38, 127.81, 128.11, 128.53, 129.99, 134.85. Anal. calc. for $C_{26}H_{42}O_4Si$•0.5 EtOAc: C (68.57), H (9.39), Found: C (68.51), H (9.41).

(3*R*)-3-*tert*-butyldimethylsilyloxy-4-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-benzyloxy-cyclopentan-1'-yl]-butanal (58): Compound **57** (0.96 g, 2.15 mmol) was dissolved in mixture of methanol (90 mL) and water (30 mL), and the resulting solution was cooled to 0 ^{0}C. Osmium tetroxide (0.10 g, 0.4 mmol) and sodium periodate (0.92 g, 4.30 mmol) were added. The reaction mixture was stirred for 1 h at 0 ^{0}C and 1 h at room temperature. Solid was filtered off, solvent was evaporated, and the residue was purified by column chromatography (EtOAc-hexanes 1:2) to afford compound **58** as pale yellow liquid (0.80 g, 83%). ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 6H), 0.95 (s, 9H), 1.41 (s, 3H), 1.61 (s, 3H), 2.16 (m, 3H), 2.64 (m, 2H), 3.85 (m, 2H), 4.26 (m, 3H), 4.67 (m, 1H), 4.80 (dd, 2H, *J* = 10.8 Hz, 6.0 Hz), 7.43 (m, 5H), 9.87 (t, 1H, *J* = 3.4 Hz). ^{13}C NMR ($CDCl_3$) δ -4. 26, 14.21, 18.12, 24.72, 24.95, 26.55, 33.91, 38.03, 51.98, 68.54, 78.62, 82.00, 86.03, 111.44, 127.96, 128.11, 128.57, 136.75, 201.34. Anal. calc. for $C_{25}H_{40}O_5Si$: C (66.96), H (8.93). Found: C (67.00), H (8.88).

(Z)-(5*S*)-2-[*tert*-butoxycarbonyl]amino-6-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-benzyloxy-cyclopentan-1'-yl]-5-*tert*-butyldimethylsilyloxy-hex-2-enoic acid, ethyl ester (59): To a solution of ethyl ester of 2-(diethoxyphosphinyl)-2-([t-butoxycarbonyl]amino)acetic acid (**41**) (0.61 g, 1.84 mmol) in dry methylene chloride (30 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.18 mL, 1.74

mmol) was added. The resulting mixture was stirred at room temperature for 30 min. Then solution of compound **58** (0.75 g, 1.67 mmol) in dry methylene chloride (50 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 20 h. Solvent was removed under reduced pressure. The residue was purified by column chromatography to give compound **59** (0.60 g, 60%). ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.27 (t, 3H, *J* = 7.2 Hz), 1.45 (s, 9H), 1.51 (s, 3H), 1.61 (s, 3H), 2.04 (m, 3H), 2.35 (m, 2H), 3.80 (m, 2H), 4.13 (q, 2H, *J* = 7.2 Hz), 4.24 (m, 3H), 4.55 (m, 3H), 4.70 (d, 1H, *J* = 12.3 Hz), 6.16 (br, 1NH), 6.54 (t, 1H, *J* = 7.0 Hz), 7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ -4.33, 14.40, 18.20, 21.24, 24.74, 26.06, 26.57, 28.41, 37.93, 40.57, 60.52, 61.54, 67.50, 70.15, 72.03, 78.32, 78.63, 85.30, 99.77, 111.40, 127.81, 128.08, 128.54, 128.73, 136.18, 138.65, 171.34. Anal. calc. for $C_{34}H_{55}NO_8Si$: C (64.35), H (8.69), N (2.21). Found: C (64.05), H (8.73), N (2.18).

(Z)-(5*S*)-2-[benzyloxycarbonyl]amino-6-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-benzyloxy-cyclopentan-1'-yl]-5-*tert*-butyldimethylsilyloxy-hex-2-enoic acid, ethyl ester (60): To a solution of ethyl ester of 2-(diethoxyphosphinyl)-2-([benzyloxycarbonyl]amino)acetic acid (**42**) (0.73 g, 1.96 mmol) in dry methylene chloride (30 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.19 mL, 1.87 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. Then solution of compound **58** (0.77 g, 1.72 mmol) in dry methylene chloride (50 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 20 h. Solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc-hexanes 1:4) to give compound **60** (0.72 g, 64%). ^{1}H NMR ($CDCl_3$) δ 0.04 (s,

6H), 0.87 (s, 9H), 1.27 (t, 3H, *J* = 7.3 Hz), 1.31 (s, 3H), 1.51 (s, 3H), 2.05 (m, 3H), 2.32 (m, 2H), 3.81 (m, 2H), 4.14 (q, 2H, *J* = 7.4 Hz), 4.24 (m, 3H), 4.56 (m, 3H), 4.71 (d, 1H, *J* = 7.5 Hz), 5.14 (s, 2H), 6.40 (br., 1H), 6.66 (t, 1H, *J* = 6.9 Hz), 7.37 (m, 10H). ^{13}C NMR ($CDCl_3$) δ -4.30, 14.36, 18.16, 21.24, 24.74, 26.02, 26.55, 37.92, 40.61, 60.58, 61.66, 67.53, 69.93, 72.01, 78.29, 78.64, 85.30, 99.77, 111.40, 127.79, 127.96, 128.04, 128.33, 128.45, 128.53, 128.57, 128.73, 136.18, 138.65, 171.34. Anal. calc. for $C_{37}H_{53}NO_8Si$: C (66.56), H (7.94), N (2.10). Found: C (66.48), H (8.00), N (2.22).

Methyl 2,3-O-*iso*propylidene-D-ribofuranoside (61): D-ribose (35.00 g, 233 mmol) was dissolved in mixture of acetone (140 mL) and methanol (140 mL). Then concentrated HCl (3.00 mL) was added at room temperature. After the resulting mixture was refluxed for 2.5 h, it was cooled to room temperature and pyridine (4 mL) was added. The reaction mixture was partinioned between EtOAc and water, and aqueous layer was extracted with EtOAc (3 x 100 mL). Combined organic layers were dried over sodium sulfate and solvent was evaporated. Residue was purified through distillation under vacuum to afford compound **61** as pale liquid (33.08 g, 69%). ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.49 (s, 3H), 3.24 (dd, 1H, *J* = 9.7 Hz, 2.6 Hz), 3.44 (s, 3H), 3.63 (td, 1H, *J* = 9.6 Hz, 2.8 Hz), 3.68 (dt, 1H, *J* = 10.2 Hz, 2.4 Hz), 4.43 (t, 1H, *J* = 2.4 Hz), 4.59 (d, 1H, *J* = 7.2 Hz), 4.84 (d, 1H, *J* = 7.2 Hz), 4.97 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 24.89, 26.55, 55.74, 64.22, 81.68, 86.03, 88.58, 110.19, 112.31. [137]

Methyl 2,3-O-*iso*propylidene-D-ribo-pentodialdo-1,4-furanoside (62): Compound (**61**) (10.95 g, 53 mmol) was dissolved in mixture of dry methylene chloride (160 mL)

and DMSO (20 mL) and cooled to -5 ^{0}C. Then DIPEA (23 mL, 129 mmol) was added, followed by slow addition of the solution of pyridinium sulfotrioxide (17.45 g, 105 mmol) in DMSO (40 mL). The reaction mixture was stirred for 1 h at –5 ^{0}C, then it was diluted with diethyl ether (500 mL) and rinsed with water (2 x 150 mL), 5% sodium bicarbonate solution (100 mL), 10% copper sulfate solution (2 x 80 mL) and brine (100 mL). The organic phase was dried with magnesium sulfate. Solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc-hexanes 1:4) to afford compound **62** as needle crystals (10.84 g, 72%). ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.51 (s, 3H), 3.44 (s, 3H), 3.88 (m, 2H), 4.59 (m, 1H), 4.84 (m, 1H), 9.37 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.06, 26.41, 55.95, 80.98, 84.19, 89.71, 109.36, 112.67(112.90), 200.98.[140]

6N-benzyloxycarbonyladenine (63): Sodium hydride (1.54 g, 60.8 mmol, 95% suspension in oil) was added to anhydrous DMF (60 mL), cooled to 0 ^{0}C. Then adenine (2.00 g, 14.8 mmol) was added in small portions. Reaction mixture was stirred at room temperature for 15 min. Then it was cooled to 0 ^{0}C and benzyl chlorophormate (4.6 mL, 32.6 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 4.5 h. Then it was poured into ice water, pH value was adjusted to 7 using 1N HCl solution. The formed precipitate was filtered, washed with water (2 x 100 mL) and diethyl ether (50 mL) and purified by recrystallyzation from methanol to afford compound **63** as pale yellow solid (0.70 g, 18%). ^{1}H NMR ($CDCl_3$) δ 5.35(s, 2H), 7.46(m, 5H), 8.33(s, 1H), 8.77(s, 1H). Physical data of the **63** was in agreement with those for commercially available compound.

Methyl 5,6-dideoxy-2,3-O-*iso*propylidene-D-ribohex-5-eno-1,4-furanoside (64): Methyl triphenylphosphonium bromide (12.84 g, 35.2 mmol) was added in portions to a suspension of potassium *tert*-butoxide (4.45 g, 37.7 mmol) in anhydrous diethyl ether (100 mL) at 0 ^{0}C. After the resulting suspension was stirred at 0 ^{0}C for 1 h and at room temperature for 1.5 h, it was cooled to 0 ^{0}C and treated dropwise with a solution of compound **62** (6.00 g, 29.5 mmol) in anhydrous diethyl ether (100 mL). The reaction mixture was then stirred at room temperature for 12 h, filtered to remove solid. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc-hexanes 1:6) to give compound **64** as colorless oil (4.44 g, 75%). ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.51 (s, 3H), 3.40 (s, 3H), 4.62 (m, 3H), 4.98 (s, 1H), 5.16 (m, 1H), 5.28 (m, 1H), 5.91 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 25.24, 26.71, 54.85, 84.79, 85.78, 88.71, 109.55, 112.58, 117.56, 137.88. [140]

Methyl 5-Deoxy-2,3-O-*iso*propylidene-D-ribo-hexo-1,4-furanoside (65): To a solution of compound **64** (4.49 g, 22.2 mmol) in dry THF (150 mL) at 0 ^{0}C under nitrogen was added 9-borabicyclo[3.3.1]nonane (51.2 mL, 25.6 mmol, 0.5M solution in THF), and the mixture was stirred at room temperature for 3 h. NaOH (34 mL, 1M solution in water) and hydrogen peroxide (17 mL, 50% solution in water) were added, and stirring was continued for further 30 min. The reaction mixture was diluted with EtOAc (400 mL) and washed with saturated solution of sodium bicarbonate (100 mL). The organic layer was dried over magnesium sulfate, concentrated to give the crude product as a colorless oil, which was purified by flash column chromatography (EtOAc-hexanes 1:2) to afford

alcohol **65** as a colorless liquid (4.23 g, 88%). ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.51 (s, 3H), 1.89 (m, 4H), 3.38 (s, 3H), 3.83 (t, 1H, *J* = 6.1 Hz), 4.38 (m, 1H), 4.64 (s, 2H), 4.99 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.25, 26.74, 37.54, 55.42, 60.62, 84.59, 85.56, 85.59, 110.05, 112.61.[137]

Methyl 5-Deoxy-2,3-O-*iso*propylidene-D-ribo-hexodialdo-1.4-furanoside (66): Compound **65** (3.56 g, 16.2 mmol) was dissolved in mixture of dry methylene chloride (80 mL) and DMSO (20 mL) and cooled to –5 ^{0}C. Then DIPEA (6.96 mL, 39.5 mmol) was added, followed by slow addition of the solution of pyridinium sulfotrioxide (5.32 g, 32.3 mmol) in DMSO (20 mL). The reaction mixture was stirred for 1 h at –5 ^{0}C, then it was diluted with diethyl ether (250 mL) and rinsed with water (2 x 70 mL), 5% sodium bicarbonate solution (50 mL), 10% copper sulfate solution (2 x 40 mL) and brine (40 mL). The organic phase was dried with magnesium sulfate. Solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc-hexanes 1:4) to afford compound **66** (2.73 g, 78%). ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.53 (s, 3H), 2.55 (m, 1H), 2.68 (m, 1H), 3.30 (s, 3H), 4.58 (m, 2H), 4.70 (dd, 1H, *J* = 6.5 Hz, 4.7 Hz), 5.04 (s, 1H), 9.75 (t, 1H, *J* = 3.5 Hz). ^{13}C NMR ($CDCl_3$) δ 25.15, 26.62, 49.05, 55.13, 81.74, 84.15, 85.52, 109.98, 113.61, 200.08. [137]

(2*R*,3*R*,4*R*)-2, 3-(*iso*propylidenedioxy)-4-vinyl-cyclopentanone (70): To a suspension of copper (I) bromide dimethysulfide (0.34 g, 1.64 mmol) in dry THF (80 mL) at –78 ^{0}C was added dropwise vinylmagnesium bromide (24 mL, 24 mmol, 1M solution in diethyl ether). The mixture was stirred for 10 min at this temperature, after which a solution of

enone **12** (2.97 g, 19.3 mmol), trimethylsilyl chloride (5.38 mL, 28.98 mmol) and hexamethylphosphoramide (8.64 mL, 49.34 mmol) in dry THF (20 mL) was added dropwise. After the reaction was stirred at –78 ^{0}C for 3 h, it was warmed to 0 ^{0}C, quenched with saturated solution of ammonia chloride (20 mL) and stirred at this temperature for 30 min. The reaction mixture was diluted with EtOAc (300 mL). Organic phase was separated, washed with water (2 x 30 mL) and brine (40 mL), dried over magnesium sulfate. Solvent was removed under reduced pressure, the residue was purified by column chromatography (EtOAc-hexanes 1:3) to afford compound **70** (3.10 g, 88%). ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.46 (s, 3H), 2.30 (dm, 1H, *J* = 19.4 Hz), 2.85 (dd, 1H, *J* = 19.4 Hz, 8.6 Hz), 3.10 (m, 1H), 4.21 (d, 1H, *J* = 5.3 Hz), 4.65 (d, 1H, *J* = 5.3 Hz), 5.16 (m, 2H), 5.80 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 25.13, 27.07, 38.75, 39.96, 78.07, 81.60, 116.65, 137.36, 150.16, 213.45. Anal. calc. for $C_{10}H_{14}O_3$: C (65.90), H (7.69). Found: C (65.33), H (7.67).

(1*R*,2*R*,3*R*,4*R*)-2,3-(*iso*propylidenedioxy)-4-vinyl-cyclopentanol (71): A solution of compound **70** (3.10 g, 17.00 mmol) in dry THF (15 mL) was added dropwise to a suspension of lithium aluminum hydride (1.15 g, 29.4 mmol) in dry THF (50 mL) at 0 ^{0}C. Reaction mixture was stirred at room temperature for 3 h and quenched with water (1mL), 15% solution of NaOH (1 mL) and water again (3 mL). Solid was removed by filtration. The filtrate was evaporated to afford compound **71** (2.86 g, 91%). ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.51 (s, 3H), 1.90 (m, 1H), 2.42 (br, 1H), 2.76 (m, 1H), 4.14 (m, 1H), 4.47 (m, 1H), 5.08 (m, 2H), 5.77 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 24.52, 26.28, 36.20,

44.53, 71.31, 79.17, 84.50, 111.83, 115.50, 138.36. Anal. calc. for $C_{10}H_{16}O_3$: C (65.19), H (8.75). Found: C (64.96), H (8.77).

(1*R*,2*R*,3*R*,4*R*)-1-benzyloxy-2,3-(*iso*propylidenedioxy)-4-vinyl-cyclopentane (72): Sodium hydride (0.39 g, 15.5 mmol, 95% suspension in oil) was added to an iced-cooled solution of compound **71** (2.86 g, 15.5 mmol) in dry THF (100mL). Resulting mixture was stirred at room temperature for 1.5 h. Tetrabutylammonium iodide (0.83 g, 1.55 mmol) and benzyl bromide (1.84 mL, 1.55 mmol) were added, and reaction mixture was stirred at room temperature for 2 days. Solvent was removed under reduced pressure, and resifue was purified by column chromatography to give compound **72** (4.46 g, 97%). ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.60 (s, 3H), 1.90 (dd, 1H, *J* = 9.2 Hz, 6.7 Hz), 2.22 (m, 1H), 2.73 (t, 1H, *J* = 7.0 Hz), 3.84 (m, 1H), 4.48 (m, 1H), 4.53 (m, 1H), 4.57 (d, 1H, *J* = 12.3 Hz), 4.70 (d, 1H, *J* = 12.2 Hz), 5.08 (dd, 1H, *J* = 14.5 Hz, 4.6 Hz), 5.77 (m, 1H), 7.4 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 24.48, 26.32, 35.87, 46.03, 62.01, 71.35, 79.21, 84.61, 112.10, 115.46, 127.49, 127.89, 128.72, 137.88, 138.29. Anal. calc. for $C_{17}H_{22}O_3 \bullet 0.7$ SiO_2: C (64.56), H (6.96). Found: C (64.67), H (6.94).

(1*R*,2*R*,3*R*,4*R*)-1-benzyloxy-2,3-(*iso*propylidenedioxy)-4-formyl-cyclopentane (73): Compound **72** (4.46 g, 15.5 mmol) was dissolved in mixture of methanol (35 mL) and water (18 mL), and the resulting solution was cooled to 0 ^{0}C. Osmium tetroxide (0.30 g, 1.2 mmol) and sodium periodate (4.93 g, 23.0 mmol) were added. The reaction mixture was stirred for 1 h at 0 ^{0}C and 2 h at room temperature. Solid was filtered off and solvent was evaporated. The residue was diluted with methylene chloride (200 mL) and washed

with water (50 mL) and brine (30 mL). The organic phase was dried over Sodium sulfate and solvent was removed under reduced pressure at room temperature to afford compound **73** as pale yellow liquid (3.73 g, 87%). ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.60 (s, 3H), 2.22 (m, 2H), 2.97 (d, 1H, *J* = 9.3 Hz), 3.67 (m, 1H), 4.65 (m, 3H), 4.90 (d, 1H, *J* = 6.6 Hz), 7.41 (m, 5H), 9.72 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 24.52, 26.53, 27.22, 54.63, 72.25, 77.93, 78.32, 11.68, 128.05, 128.16, 128.63, 138.09, 201.02. Anal. calc. for $C_{16}H_{20}O_4$: C (69.56), H (7.24). Found: C (69.47), H (7.15).

Methyl (6*S*)-6-allyl-5-deoxy-2,3-O-*iso*propylidene-D-ribohexo-1,4-furanoside (74): To an ice-cooled solution of (-)-di*iso*pinocampheylmethoxyborane (4.17 g, 13.2 mmol) in dry diethyl ether (100 mL), allylmagnesium bromide (13.0 mL, 13.0 mmol, 1M solution in diethyl ether) was added dropwise under nitrogen. Above solution was stirred at room temperature for 2 h. After ether was evaporated under reduced pressure, white residue was extracted with pentane (2 x 60 mL) and filtered under nitrogen to afford the solution of (-)-allyldi*iso*pinocampheylborane in pentane.

The resulting solution (120 mL) was added dropwise to a solution of compound **66** (2.57 g, 11.8 mmol) in dry diethyl ether (100 mL), previously cooled to –80 ^{0}C. The reaction mixture was stirred at this temperature for 3 h, quenched with methanol (10 mL) and stirred 1 h at room temperature.

Saturated solution of sodium bicarbonate (8 mL) and hydrogen peroxide (5.5 mL, 30% solution in water) was carefully added. The resulting mixture was stirred at room temperature for 14 h and extracted with EtOAc (2 x 200 mL). Combined organic layers were dried over Sodium sulfate and concentrated. The residue was purified by column

chromatography (EtOAc-hexanes 1:4) to afford compound **74** as pale liquid (1.97 g, 64%). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.48 (s, 3H), 1.75 (m, 2H), 2.26 (m,2H), 3.33 (s, 3H), 3.37 (m, 1H), 3.88 (m, 1H), 4.13 (m, 1H), 4.43 (m, 1H), 4.92 (m, 1H), 5.16 (d, 2H, *J* = 12.3 Hz), 5.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.39, 21.25, 25.26, 26.73, 41.69, 42.65, 55.33, 60.61, 68.22, 84.59, 84.75, 85.68, 110.01, 112.49, 118.60, 134.57. Anal. calc. for $C_{13}H_{22}O_5$: C (60.52), H (8.53). Found: C (60.65), H (8.72).

Methyl (6*S*)-6-allyl-5-deoxy-2,3-O-*iso*propylidene-6-O-*tert*-butyldimethylsilyl-D-ribohexofuranoside (75): Imidazole (1.29 g, 18.9 mmol) was added to a solution of compound **74** (1.97 g, 7.60 mmol) in methylene chloride (100 mL) at room temperature. *t*-Butyldimethylsilyl chloride (1.44 g, 9.46 mmol) and DMAP (0.10 g, 0.04 mmol) were added. The reaction mixture was stirred at room temperature for 3 days. White precipitate was filtered and washed with methylene chloride (2 x 50 mL). Filtrate was evaporated, residue was purified be column chromatography (EtOAc-hexanes 1:4) to yield compound **75** (2.76 g, 98%). ^{1}H NMR ($CDCl_3$) δ 0.098 (s, 3H), 0.17 (s, 3H), 0.91 (s, 9H), 1.31 (s, 3H), 1.47 (s, 3H), 1.70 (m, 2H), 2.24 (m, 2H), 3.31 (s, 3H), 3.35 (m, 1H), 3.91 (m, 1H), 4.31 (dd, 1H, *J* = 9.7 Hz, 7.1 Hz), 4.53 (m, 1H), 4.92 (m, 1H), 5.03 (d, 2H, *J* = 12.5 Hz), 5.76 (m, 1H). ^{13}C NMR ($CDCl_3$) δ -4.5, -4.14, 15.19, 18.28, 25.40, 26.12, 26.73, 36.75, 42.11,43.5, 55.15, 60.01, 69.19, 84.10, 84.96, 85.81, 109.85, 112.60, 117.45, 134.77. Anal. calc. for $C_{19}H_{36}O_5Si$: C (61.29), H (9.68). Found: C (61.30), H (9.71).

Methyl (6*R*)-5,7-dideoxy-2,3-O-*iso*propylidene-6-O-*tert*-butyldimethylsilyl-D-ribo-octadialdo-1,4-furanoside (76): Compound **75** (2.32 g, 6.20 mmol) was dissolved in

mixture of methanol (90 mL) and water (30 mL), and the resulting solution was cooled to 0 ^{0}C. Osmium tetroxide (0.20 g, 0.8 mmol) and sodium periodate (2.68 g, 12.4 mmol) were added. The reaction mixture was stirred for 1 h at 0 ^{0}C and 1 h at room temperature. Solid was filtered off, solvent was evaporated, and the residue was purified by column chromatography (EtOAc-hexanes 1:2) to afford compound **76** as pale yellow liquid (1.73 g, 77%). ^{1}H NMR ($CDCl_3$) δ 0.067 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 1.34 (s, 3H), 1.50 (s, 3H), 1.76 (m, 2H), 2.63 (m, 2H), 3.37 (s, 3H), 4.37 (m, 2H), 4.58 (m, 2H), 4.96 (m, 1H), 9.83 (t, 1H, J = 3.2 Hz). ^{13}C NMR ($CDCl_3$) δ -4.5, 14.98, 18.19, 25.40, 26.01, 26.74, 43.32, 55.06, 55.37, 65.87, 83.68, 84.82, 85.68, 110.12, 112.54, 201.66. Anal. calc. for $C_{18}H_{34}O_6Si\bullet 0.3\ H_2O$: C (56.93), H (9.12). Found: C (56.95), H (9.11).

Methyl Z-(6*S*)-9-[(benzyloxycarbonyl)amino]-9-ethoxycarbonyl-5,7,8,9-tetradeoxy-2,3-O-*iso*propylidene-6-O-*tert*-butyldimethylsilyl-D-ribonon-8-eno-1,4-furanoside (77a): To a solution of ethyl ester of 2-(diethoxyphosphinyl)-2-([benzyloxycarbonyl]amino)acetic acid **42** (1.87 g, 5.02 mmol) in dry methylene chloride (50 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.50 mL, 4.92 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. Then solution of compound **76** (1.73 g, 4.60 mmol) in dry methylene chloride (30 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 20 h. Solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc-hexanes 1:3) to give compound **77a** (1.75 g, 64%). ^{1}H NMR ($CDCl_3$) δ 0.095 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 1.27 (t, 3H, J = 7.3 Hz), 1.31 (s, 3H), 1.48 (s, 3H), 1.61 (m, 2H), 2.41 (dd, 2H, J = 10.1 Hz, 5.7 Hz), 3.32 (s, 3H), 4.03 (q, 2H, J = 7.2 Hz), 4.20 (m, 3H), 4.53

(d, 1H), 4.58 (d, 1H), 5.15 (s, 2H), 6.32 (br, 1NH), 6.69 (t, 1H, *J* = 7.1 Hz), 7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ -4.5, -4.29, 14.38, 18.24, 25.40, 26.07, 26.74, 37.25, 42.96, 55.16, 60.61, 61.73, 67.56, 68.47, 83.86, 84.84, 85.71, 109.88, 112.46, 128.35, 128.48, 128.77, 132.79, 136.18, 154.12, 164.63. Anal. calc. for $C_{30}H_{47}NO_9Si$: C (60.71), H (7.92), N(2.36). Found: C (60.82), H (8.02), N (2.41).

Methyl Z-(6*S*)-9-[(*tert*-butoxycarbonyl)amino]-9-ethoxycarbonyl-5,7,8,9-tetradeoxy-2,3-O-*iso*propylidene-6-O-*tert*-butyldimethylsilyl-D-ribonon-8-eno-1,4-furanoside (77b): To a solution of ethyl ester of 2-(diethoxyphosphinyl)-2-([*tert*-butoxycarbonyl]amino)acetic acid **41** (2.78 g, 8.30 mmol) in dry methylene chloride (50 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.85 mL, 8.30 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. Then solution of compound **76** (3.02 g, 8.07 mmol) in dry methylene chloride (50 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 20 h. Solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc-hexanes 1:4) to give compound **77b** (3.52 g, 78%). ^{1}H NMR ($CDCl_3$) δ 0.068 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.26 (t, 3H, *J* = 7.3 Hz), 1.28 (s, 3H), 1.46 (s, 3H), 1.47 (s, 9H), 1.66 (m, 2H), 2.39 (dd, 2H, *J* = 9.8 Hz, 5.1 Hz), 3.34 (s, 3H), 4.05 (m, 1H), 4.22 (q, 2H, *J* = 7.2 Hz), 4.31 (dd, 1H, *J* = 8.4 Hz, 4.5 Hz), 4.53 (d, 1H, *J* = 5.7 Hz), 4.58 (d, 1H, *J* = 5.6 Hz), 4.94 (s, 1H), 6.14 (br, 1H), 6.57 (t, 1H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ -4.51, -4.27, 14.40, 18.23, 21.29, 25.35, 25.98, 26.07, 26.71, 28.37, 42.85, 55.16, 60.62, 61.58, 68.63, 77.44, 83.86, 84.83, 85.68, 109.82, 112.41, 131.45, 164.93. Anal. calc. for $C_{27}H_{49}NO_9Si$: C (58.01), H (8.84), N (2.50). Found: C (58.14), H (9.04), N (2.41).

Methyl (6*S*,9*S*)-9-[(benzyloxycarbonyl)amino]-9-ethoxycarbonyl-5,7,8,9-tetradeoxy-2,3-O-*iso*propylidene-6-O-*tert*-butyldimethylsilyl-D-ribonon-1,4-furanoside (78a): Compound **77a** (0.195 g, 0.32 mmol) was dissolved in methanol (10 mL), and nitrogen was bubbled through the solution for 30 min. (+)-1, 2-*Bis*((2S, 5S)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium (I) trifluoromethanesulfonate (8 mg, 0.01 mmol) was quickly added under nitrogen, and the reaction mixture was hydrogenated at 50 psi for 24 h. Then solvent was removed under reduced pressure and residue was purified by column chromatography (EtOAc-hexanes 1:3) to afford compound **78a** (0.19 g, 97%). ^{1}H NMR (CDCl3) δ 0.063 (s, 3H), 0.094 (s, 3H), 0.89 (s, 9H), 1.27 (t, 3H, *J* = 7.2 Hz), 1.29 (s, 3H), 1.47 (s, 3H), 1.60 (m, 4H), 1.82 (m, 2H), 3.30 (s, 3H), 3.90 (m, 1H), 4.14 (q, 2H, *J* = 7.1 Hz), 4.20 - 4.31 (m, 2H), 4.53 (d, 1H, *J* = 6.1 Hz), 4.58 (d, 1H, *J* = 6.0 Hz), 4.92 (m, 1H), 5.11 (s, 2H), 5.34 (d, 1NH, *J* = 6.7 Hz), 7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ -4.45, -4.23, 14.38, 18.25, 25.40, 26.10, 26.74, 27.91, 33.49, 42.22, 54.11, 55.20, 60.62, 61.69, 67.18, 68.75, 84.05, 84.9, 85.75, 109.94, 112.43, 127.96, 128.34, 128.76, 129.29, 156.01, 172.51. Anal. calc. for $C_{30}H_{49}NO_9Si \bullet 0.2C_6H_{14}$: C (61.15), H (8.46), N (2.29). Found: C (61.11), H (8.38), N (2.37).

Methyl (6*S*)-9-[(*tert*-butoxycarbonyl)amino]-9-ethoxycarbonyl-5,7,8,9-tetradeoxy-2,3-O-*iso*propylidene-6-O-t-butyldimethylsilyl-D-ribonon-1,4-furanoside (79): Compound **77b** (3.52 g, 6.29 mmol) was dissolved in methanol (30 mL), and nitrogen

was bubbled through the solution for 30 min. Palladium on charcoal (10%, 50 mg) was quickly added under nitrogen, and the reaction mixture was hydrogenated at 30 psi for 24 h. Then solution was filtered through pad of celite, washed with ethanol. Solvent was removed under reduced pressure and residue was purified by column chromatography (EtOAc) to afford compound **79** (3.24 g, 92%). ^{1}H NMR ($CDCl_3$) δ 0.067 (s, 3H), 0.094 (s, 3H), 0.88 (s, 9H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.30 (s, 3H), 1.44 (s, 3H), 1.49 (s, 9H), 1.69 (m, 4H), 1.86 (m, 2H), 3.32 (s, 3H), 3.94 (m, 1H), 4.17 (q, 2H, *J* = 7.2 Hz), 4.20 (m, 1H), 4.29 (m, 1H), 4.53 (m, 1H), 4.58 (m, 1H), 4.92 (m, 1H), 5.10 (dm, 1NH, *J* = 10.4 Hz). ^{13}C NMR ($CDCl_3$) δ -4.47, -4.19, 14.40, 18.25, 25.38, 26.12, 26.73, 28.00, 28.52, 33.65, 42.20, 53.66, 55.19, 61.53, 68.74, 68.82, 77.43, 79.99, 84.05, 84.81, 85.75, 109.92, 112.41, 155.53, 172.93. Anal. calc. for $C_{27}H_{51}NO_9Si$: C (57.81), H (9.09), N (2.49). Found: C (58.13), H (9.12), N (2.21).

Tetraacetyl (6*S*,9*S*)-9-[(*tert*-butoxycarbonyl)amino]-9-ethoxycarbonyl-5,7,8,9-tetradeoxy-D-ribonon-1,4-furanoside (80): A solution of compound **79** (3.15 g, 5.60 mmol) in 70% acetic acid (100mL) was brought to 80 ^{0}C and kept at this temperature for 14 h. Solvent was removed under reduced pressure, residue was dissolved in a mixture of pyridine (20 mL) and acetic anhydride (16 mL). Then DMAP (80 mg) was added and the resulting mixture was stirred at room temperature for 6 h. Solvent was co-evaporated with toluene, the residue was purified by column chromatography (EtOAc-hexanes 5:1) to give compound **80** (1.40 g, 44%). ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H, *J* = 7.2 Hz), 1.50 (s, 9H), 1.82 (m, 4H), 2.07 (m, 2H), 2.09 (s, 3H), 2.10 (s, 3H), 2.13 (s, 3H), 2.14 (s, 3H),

4.14 (q, 2H, *J* = 7.3 Hz), 4.50 (m, 3H), 4.83 (m, 1H), 5.05 (m, 1H), 5.23(m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.39, 20.85, 21.39, 21.68, 28.51, 40.85, 53.38, 61.67, 75.14, 80.44, 84.38, 85.66, 110.10, 156.09, 169.99, 170.78. Anal. calc. for $C_{25}H_{39}NO_{13}$: C (53.47), H (6.95), N (2.49). Found: C (53.58), H (6.90), N (2.60).

(4*S*)-4-hydroxy-4-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-benzyloxy-cyclopentan-1'-yl]-1-buten (82): To an ice-cooled solution of (-)-di*iso*pinocampheylmethoxyborane (4.27 g, 13.55 mmol) in dry diethyl ether (100 mL), allylmagnesium bromide (13.55 mL, 13.55 mmol, 1M solution in diethyl ether) was added dropwise under nitrogen. Above solution was stirred at room temperature for 3 h. After ether was evaporated under reduced pressure, white residue was extracted with pentane (100 mL) and filtered under nitrogen to afford the solution of (-)-allyldi*iso*pinocampheylborane in pentane.

The resulting solution (100 mL) was added dropwise to a solution of compound **73** (3.37 g, 15.55 mmol) in dry diethyl ether (100 mL), previously cooled to -80 ^{0}C. The reaction mixture was stirred at this temperature for 3 h, quenched with methanol (10 mL) and stirred 1 h at room temperature.

Saturated solution of sodium bicarbonate (7 mL) and hydrogen peroxide (5 mL, 30% solution in water) was carefully added. The resulting mixture was stirred at room temperature for 14 h and extracted with EtOAc (2 x 100 mL). Combined organic layers were dried over sodium sulfate and evaporated. The residue was purified by column chromatography (EtOAc-hexanes 1:3) to afford compound **82** as pale liquid (1.46 g,

34%). ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.53 (s, 3H), 2.13 (m, 5H), 3.60 (m, 1H), 3.98 (m, 1H), 4.44 (d, 1H, *J* = 7.1 Hz), 4.56 (d, 1H, *J* = 6.8 Hz), 4.59 (m, 2H), 4.72 (d, 1H, *J* = 6.7 Hz), 5.14 (dd, 2H, *J* = 14.2 Hz, 7.3 Hz), 5.77 (m, 1H), 7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 25.03, 26.83, 29.26, 40.77, 47.72, 71.55, 72.08, 78.83, 79.90, 83.74, 111.75, 119.18, 127.69, 128.02, 128.51, 134.61, 138.95. Anal. calc. for $C_{19}H_{26}O_4 \bullet 0.43SiO_2$: Calc.: C(66.32), H(7.56). Found: C (66.31), H (7.67).

(4*S*)-4-t-butyldimethylsilyloxy-4-[(1'*S*,2'*R*,3'*S*,4'*S*)-2',3'-(*iso*propylidendioxy)-4'-benzyloxy-cyclopentan-1'-yl]-1-buten (83): Imidazole (0.78 g, 11.4 mmol) was added to a solution of compound **82** (1.46 g, 4.59 mmol) in methylene chloride (100 mL) at room temperature. *t*-Butyldimethylsilyl chloride (0.87 g, 5.74 mmol) and DMAP (0.1 g) were added. The reaction mixture was stirred at room temperature for 4 days. White precipitate was filtered and washed with methylene chloride (2 x 50 mL). Filtrate was evaporated, residue was purified be column chromatography (EtOAc-hexanes 1:3) to yield compound **83** (0.90 g, 45%). ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.80 (s, 9H), 1.26 (t, EtOAc), 1.37 (s, 3H), 1.55 (s, 3H), 2.05 (s, EtOAc), 2.15 (m, 5H), 3.60 (m, 1H), 3.80 (m, 1H), 4.12 (q, EtOAc), 4.38 (d, 1H, *J* = 7.0 Hz), 4.58 (d, 1H, *J* = 6.7 Hz), 4.62 (m, 2H), 4.78 (m, 1H), 5.07 (dd, 2H, *J* = 14.2 Hz, 7.2 Hz), 5.80 (m, 1H), 7.40 (m, 5H). Anal. calc. for $C_{25}H_{40}O_4Si \bullet 1.5$ EtOAc: C (65.95), H (9.21), Found: C (65.81), H (9.13).

Methyl (5*S*)-5-allyl-2,3-O-*iso*propylidene-D-ribopenta-1,4-furanoside (84): To an ice-cooled solution of (-)-di*iso*pinocampheylmethoxyborane (5.42 g, 17.00 mmol) in dry

diethyl ether (100 mL), allylmagnesium bromide (17.0 mL, 17.0 mmol, 1M solution in diethyl ether) was added dropwise under nitrogen. Above solution was stirred at room temperature for 2.5 h. After ether was evaporated under reduced pressure, white residue was extracted with pentane (100 mL) and filtered under nitrogen to afford the solution of (-)-allyldi*iso*pinocampheylborane in pentane.

The resulting solution (100 mL) was added dropwise to a solution of compound **62** (3.14 g, 15.46 mmol) in dry diethyl ether (100 mL), previously cooled to –80 ^{0}C. The reaction mixture was stirred at this temperature for 3 h, quenched with methanol (12 mL) and stirred 1 h at room temperature.

Saturated solution of sodium bicarbonate (9 mL) and hydrogen peroxide (7 mL, 30% solution in water) were carefully added. The resulting mixture was stirred at room temperature for 14 h and extracted with EtOAc (2 x 100 mL). Combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (EtOAc-hexanes 1:4) to afford compound **84** as pale liquid (4.00 g, 96%). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.48 (s, 3H), 2.40 (m, 2H), 3.40 (s, 3H), 3.63 (d, 1H, *J* = 6.1 Hz), 3.75 (m, 1H), 4.05 (m, 1H), 4.35 (d, 1H, *J* = 6.2 Hz), 4.58 (d, 1H, *J* = 8.1 Hz), 4.89 (d, 1H, *J* = 8.0 Hz), 5.16 (dd, 2H, *J* = 14.6 Hz, 9.3 Hz), 5.85 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 20.96, 24.90, 41.99, 48.00, 55.79, 71.93, 80.13, 86.05, 91.08, 110.18, 112.34, 118.14, 134.39. Anal. calc. for $C_{12}H_{20}O_5$: C (59.01), H (8.19). Found: C (59.00), H (8.38).

Methyl (5*S*)-5-allyl-2,3-O-*iso*propylidene-6-O-*tert*-butyldimethylsilyl-D-ribo-pento-furanoside (85): Imidazole (3.33 g, 49.0 mmol) was added to a solution of compound **84** (4.00 g, 16.39 mmol) in methylene chloride (100 mL) at room temperature. *t*-Butyldimethylsilyl chloride (6.24 g, 41.0 mmol) and DMAP (0.10 g, 0.04 mmol) were added. The reaction mixture was stirred at room temperature for 3 days. White precipitate was filtered and washed with methylene chloride (2 x 50 mL). Filtrate was evaporated, residue was purified be column chromatography (EtOAc-hexanes 1:4) to yield compound **85** (5.64 g, 96%). ^{1}H NMR ($CDCl_3$) δ 0.084 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.31 (s, 3H), 1.48 (s, 3H), 2.39 (m, 2H), 3.36 (s, 3H), 3.63 (m, 1H), 4.00 (d, 1H, *J* = 11.0 Hz), 4.50 (d, 1H, *J* = 8.7 Hz), 4.74 (d, 1H, *J* = 8.6 Hz), 5.12 (dd, 2H, *J* = 14.0 Hz, 7.8 Hz), 5.87 (m, 1H). ^{13}C NMR ($CDCl_3$) δ -3.67, -3.10, 18.28, 21.28, 25.01, 31.80, 38.47, 55.75, 71.76, 81.89, 85.25, 88.07, 110.14, 112.30, 118.16, 133.84. Anal. calc. for $C_{18}H_{34}O_5Si$: C (60.33), H (9.49). Found: C (60.31), H (9.67).

Methyl (5*R*)-7-deoxy-2,3-O-*iso*propylidene-5-O-*tert*-butyldimethylsilyl-D-ribo-heptadialdo-1,4-furanoside (87): Compound **85** (2.00 g, 5.50 mmol) was dissolved in mixture of methanol (90 mL) and water (30 mL), and the resulting solution was cooled to 0 ^{0}C. Osmium tetroxide (0.20 g, 0.8 mmol) and sodium periodate (2.50 g, 11.0 mmol) were added. The reaction mixture was stirred for 1 h at 0 ^{0}C and 1 h at room temperature. Solid was filtered off, solvent was evaporated, and the residue was purified by column chromatography (EtOAc-hexanes 1:3) to afford compound **87** (1.95 g, 97%). ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 1.32 (s, 3H), 1.48 (s, 3H), 2.45 (m,

2H), 3.35 (s, 3H), 4.38 (m, 2H), 4.55 (d, 1H, *J* = 8.0 Hz), 4.74 (d, 1H, *J* = 7.9 Hz), 4.96 (s, 1H), 9.86 (t, 1H, *J* = 3.7 Hz). ^{13}C NMR ($CDCl_3$) δ -4.5, 18.18, 25.10, 26.13, 26.70, 42.13, 55.97, 72.24, 81.84, 85.19, 89.05, 110.26, 112.66, 202.66. Anal. calc. for $C_{17}H_{32}O_6Si \bullet 0.7\ H_2O$: Calc.: C (55.04), H (9.01). Found: C (55.16), H (8.90).

Methyl Z-(5*S*)-8-[(benzyloxycarbonyl)amino]-8-ethoxycarbonyl-6,7,8-trideoxy-2,3-O-*iso*propylidene-5-O-*tert*-butyldimethylsilyl-D-riboocta-7-eno-1,4-furanoside (88a): To a solution of ethyl ester of 2-(diethoxyphosphinyl)-2-([benzyloxycarbonyl]amino)acetic acid **42** (1.14 g, 3.08 mmol) in dry methylene chloride (40 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 mL, 2.31 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. Then solution of compound **87** (1.00 g, 2.78 mmol) in dry methylene chloride (40 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 20 h. Solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc-hexanes 1:3) to give compound **88a** (0.41 g, 26%). ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 6H), 0.93 (s, 9H), 1.27 (t, 3H, *J* = 7.4 Hz), 1.29 (s, 3H), 1.51 (s, 3H), 2.61 (m, 2H), 3.33 (s, 3H), 3.81 (m, 1H), 3.88 (d, 1H, *J* = 9.5 Hz), 4.24 (q, 2H, *J* = 7.4 Hz), 4.54 (d, 1H, *J* = 8.0 Hz), 4.71 (d, 1H, *J* = 8.0 Hz), 4.95 (s, 1H), 5.18 (d, 1H, *J* = 18.2 Hz), 5.22 (d, 1H, *J* = 18.2 Hz), 6.67 (t, 1H, *J* = 6.7 Hz), 6.88 (br, 1NH), 7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ -4.5, -3.84, 14.33, 18.24, 24.90, 25.95, 26.59, 56.13, 61.61, 67.36, 71.22, 81.81, 85.11, 88.32, 110.41, 112.63, 120.05, 128.30, 128.69, 130.57, 141.21, 154.12, 165.03. Anal. calc. for $C_{29}H_{45}NO_9Si$: C (60.10), H (7.77), N (2.42). Found: C (60.19), H (7.92), N (2.38).

Methyl Z-(5*S*)-8-[(*tert*-butoxycarbonyl)amino]-8-ethoxycarbonyl-6,7,8-trideoxy-2,3-O-*iso*propylidene-5-O-*tert*-butyldimethylsilyl-D-riboocta-7-eno-1,4-furanoside (88b): To a solution of ethyl ester of 2-(diethocxyphosphinyl)-2-([*tert*-butoxycarbonyl]amino)acetic acid **41** (2.39 g, 7.12 mmol) in dry methylene chloride (60 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.73 mL, 7.12 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. Then solution of compound **87** (2.50 g, 6.92 mmol) in dry methylene chloride (50 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 16 h. Solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc-hexanes 1:5) to give compound **88b** (1.25 g, 36%). ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.91 (s, 9H), 1.23 (t, 3H, *J* = 7.3 Hz), 1.30 (s, 3H), 1.44 (s, 9H), 1.48 (s, 3H), 2.55 (m, 2H), 3.39 (s, 3H), 3.77 (m, 1H), 3.88 (d, 1H, *J* = 8.7 Hz), 4.24 (q, 2H, *J* = 7.4 Hz), 4.52 (d, 1H, *J* = 6.8 Hz), 4.70 (d, 1H, *J* = 6.7 Hz), 4.94 (s, 1H), 6.53 (br, 1NH), 6.65 (t, 1H, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ -4.55, -3.82, 14.39, 18.25, 24.87, 25.95, 26.57, 28.40, 32.96, 56.13, 61.47, 71.28, 81.78, 85.13, 88.27, 110.41, 112.59, 129.18, 153.62, 164.89. Anal. calc. for $C_{26}H_{47}NO_9Si$: C (57.35), H (8.45), N (2.57). Found: C (57.60), H (8.77), N (2.56).

Methyl (5*S*)-8-[(*tert*-butoxycarbonyl)amino]-8-ethoxycarbonyl-6,7,8-trideoxy-2,3-O-*iso*propylidene-5-O-*tert*-butyldimethylsilyl-D-riboocta-1,4-furanoside (92): Compound **88b** (1.25 g, 2.29 mmol) was dissolved in methanol (30 mL), and nitrogen

was bubbled through the solution for 30 min. Palladium on charcoal (10%, 30 mg) was quickly added under nitrogen, and the reaction mixture was hydrogenated at 30 psi for 24 h. Then solution was filtered through pad of celite, washed with ethanol. Solvent was removed under reduced pressure and residue was purified by column chromatography (EtOAc) to afford compound **92** (1.17 g, 94%). ^{1}H NMR (CDCl3) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.23 (t, 3H, *J* = 7.4 Hz), 1.31 (s, 3H), 1.43 (s, 9H), 1.48 (s, 3H), 1.70 (m, 3H), 1.95 (m, 1H), 3.37 (s, 3H), 3.72 (m, 1H), 3.93 (d, 1H, *J* = 8.9 Hz), 4.19 (q, 2H, *J* = 7.4 Hz), 4.21 (m, 1H), 4.51 (d, 1H, *J* = 7.0 Hz), 4.70 (d, 1H, *J* = 6.9 Hz), 4.91 (s, 1H), 5.12 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR (CDCl3) δ -4.49, -3.71, 14.37, 18.67, 25.04, 26.02, 26.67, 28.52, 53.05, 56.12, 61.50, 71.35, 82.78, 85.23, 87.74, 110.18, 112.37, 153.37, 164.89. Anal. calc. for $C_{26}H_{49}NO_9Si$: C (57.04), H (8.96), N (2.56) Found: C (57.06), H (9.16), N (2.56).

Acetyl (5*S*)-8-[(*tert*-butoxycarbonyl)amino]-8-ethoxycarbonyl-6,7,8-trideoxy-2,3,5-O-triacetyl-D-ribo-octa1,4-furanoside (93): A solution of compound **92** (1.15 g, 2.10 mmol) in 70% acetic acid (40mL) was brought to 80 ^{0}C and kept at this temperature for 12 h. Solvent was removed under reduced pressure, residue was dissolved in a mixture of pyridine (8 mL) and acetic anhydride (5 mL). Then DMAP (30 mg) was added and the resulting mixture was stirred at room temperature for 4 h. Solvent was co-evaporated with toluene, the residue was purified by column chromatography (EtOAc-hexanes 2:1) to give compound **93** (0.61 g, 53%). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.4 Hz), 1.50 (s, 9H), 1.75 (m, 4H), 2.01 (s, 3H), 2.05 (s, 3H), 2.10 (s, 3H), 2.11 (s, 3H),

4.17 (q, 2H, *J* = 7.3 Hz), 4.29 (m, 2H), 4.89 (d, 1H, *J* = 9.0 Hz), 5.03 (m, 1H), 5.42 (m, 1H), 6.05 (t, 1H, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 14.29, 18.14, 20.72, 21.57, 23.30, 24.91, 25.89, 26.58, 28.41, 29.00, 52.35, 55.72, 60.54, 61.60, 71.18, 75.10, 82.18, 85.10, 87.14, 106.45, 110.10, 112.30, 152.57, 164.76. Anal. calc. for $C_{24}H_{37}NO_{13}$: C (52.65), H (6.76), N (2.56) Found: C (52.86), H (6.90), N (2.54).

6-Chloro-1-[(1'*R*,2'*S*,3'*R*,4'*S*)-4'-[(2''*S*)-2''-hydroxypent-4''-en-1''-yl]-2',3'-(*iso*propylidenedioxy)-cyclopentan-1'-yl]purine (100): To an ice-cooled solution of (-)-di*iso*pinocampheylmethoxyborane (1.63 g, 5.01 mmol) in dry diethyl ether (100 mL), allylmagnesium bromide (5.01 mL, 5.01 mmol, 1M solution in diethyl ether) was added dropwise under nitrogen. Above solution was stirred at room temperature for 3 h. After ether was evaporated under reduced pressure, white residue was extracted with pentane (100 mL) and filtered under nitrogen to afford the solution of (-)-allyldi*iso*pinocampheylborane in pentane.

The resulting solution (100 mL) was added dropwise to a solution of compound **32** (1.56 g, 4.64 mmol) in a mixture of dry diethyl ether (100 mL) and dry methylene chloride (20 mL), previously cooled to -80 ^{0}C. The reaction mixture was stirred at this temperature for 3 h, quenched with methanol (5 mL) and stirred 1 h at room temperature. Saturated solution of sodium bicarbonate (3 mL) and hydrogen peroxide (3 mL, 30% solution in water) were carefully added. The resulting mixture was stirred at room temperature for 14 h and extracted with EtOAc (2 x 100 mL). Combined organic layers were dried over sodium sulfate and evaporated. The residue was purified by column chromatography (eluent EtOAc-hexanes 2:1 to EtOAc-methanol 3:1) affording

compound **100** (0.96 g, 55%), m.p. 109 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.76 (s, 3H), 1.79 (m, 2H), 2.28 - 2.54 (m, 6H), 3.49 (s, MeOH), 3.81 (m, 1H), 4.66 (t, 1H, *J* = 8.7 Hz), 4.86 (m, 1H), 5.09 (dd, 1H, *J* = 8.5 Hz, 6.5 Hz), 5.16 (dd, 2H, *J* = 14.9 Hz, 7.8 Hz), 5.95 (m, 1H), 8.18 (s, 1H), 8.77 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.33, 27.66, 37.44, 40.35, 42.35, 42.75, 50.41 (MeOH), 62.04, 70.33, 83.86, 84.77, 114.55, 118.36, 126.15, 131.34, 134.79, 144.80, 151.90, 151.98. Anal. calc. for $C_{18}H_{23}ClN_4O_3$•0.8 CH_3OH: C (55.82), H (6.46), N (13.85), Cl (8.78). Found: C (55.83), H (6.19), N (13.75), Cl (8.57).

1-[(1'*R*,2'*S*,3'*R*,4'*S*)-4'-[(2''*S*)-2''-hydroxypent-4''-en-1''-yl]-2',3'-(*iso*propylidenedioxy)-cyclopentan-1'-yl]adenine (101): Ammonia (gas) was bubbled through the ice-cold solution of compound **100** (0.96 g, 2.53 mmol) in methanol (30 mL) for 45 min. Then the reaction mixture was kept at 100 ^{0}C for 24 h in a Parr stainless steel sealed reaction vessel. Volatiles were removed under reduced pressure, residue was purified by column chromatography (EtOAc) to afford compound **101** (0.38 g, 42%). ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.61 (s, 3H), 2.53 (m, 7H), 3.51 (m, 1H), 4.66 (m, 1H), 4.78 (m, 1H), 5.15 (dd, 2H, *J* = 14.8 Hz, 8.0 Hz), 5.80 (m, 1H), 5.91 (m, 1H), 6.35 (d, 2NH), 7.93 (s, 1H), 8.30 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 21.22, 25.28, 27.62, 37.05, 42.29, 60.58, 70.05, 84.08, 86.00, 104.12, 114.17, 118.00, 134.94, 140.08, 150.65, 152.43, 155.83.

1-[(1'*R*,2'*S*,3'*R*,4'*S*)-4'-[(2''*S*)-2''-*tert*-butyldimethylsilyloxypent-4''-en-1''-yl]-2',3'-(*iso*propylidenedioxy)-cyclopentan-1'-yl]adenine (103): Imidazole (0.23 g, 3.34 mmol)

was added to a solution of compound **101** (0.48 g, 1.33 mmol) in methylene chloride (20 mL) at room temperature. *t*-Butyldimethylsilyl chloride (0.25 g, 1.67 mmol) and DMAP (0.05 g, 0.02 mmol) were added. The reaction mixture was stirred at room temperature for 4 days. White precipitate was filtered and washed with methylene chloride (2 x 50 mL). Filtrate was evaporated, residue was purified be column chromatography (EtOAc-hexanes 1:1) to yield compound **103** (0.41 g, 65%), m.p. 116 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.26 (t, EtOAc), 1.30 (s, 3H), 1.56 (s, 3H), 1.82 (m, 3H), 2.05 (s, EtOAc), 2.28 (m, 2H), 2.49 (m, 2H), 3.78 (m, 1H), 4.12 (q, EtOAc), 4.46 (m, 1H), 4.70 (m, 1H), 5.04 (m, 1H), 5.08 (dd, 2H, *J* = 14.5 Hz, 7.8 Hz), 5.61 (s, 2NH), 5.90 (m, 1H), 8.03 (s, 1H), 8.39 (s, 1H). ^{13}C NMR ($CDCl_3$) δ -5.40, -4.73, 14.19 (EtOAc), 18.01, 21.04 (EtOAc), 25.84, 26.10, 27.82, 36.43, 37.44, 40.62, 43.56, 60.49 (EtOAc), 61.76, 70.43, 83.74, 85.84, 114.15, 120.05, 120.42, 137.71, 140.07, 149.94, 152.59, 155.91. Anal. calc. for $C_{24}H_{39}N_5O_3Si$•0.6 EtOAc: C (60.25), H (8.33), N (13.31). Found: C (60.37), H (8.09), N (13.11).

1-[(1'*R*,2'*S*,3'*R*,4'*S*)-4'-[(2''*S*)-2''-*tert*-butyldimethylsilyloxy-4''-oxobut-1''-yl]-2',3'-(*iso*propylidenedioxy)-cyclopentan-1'-yl]adenine (104): Compound **103** (0.35 g, 0.74 mmol) was dissolved in mixture of methanol (15 mL) and water (5 mL), and the resulting solution was cooled to 0 ^{0}C. Osmium tetroxide (0.05 g, 0.2 mmol) and sodium periodate (0.32 g, 1.48 mmol) were added. The reaction mixture was stirred for 1 h at 0 ^{0}C and 1 h at room temperature. Solid was filtered off, solvent was evaporated, and the residue was purified by column chromatography (EtOAc) to afford compound **104** (0.21 g, 60%). ^{1}H

NMR ($CDCl_3$) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.23 (s, 3H), 1.55 (s, 3H), 1.76 (m, 3H), 2.41 (m, 3H), 2.63 (m, 1H), 4.11 (m, 1H), 4.50 (m, 1H), 4.70 (m, 1H), 5.06 (m, 1H), 5.72 (s, 2H), 7.83 (s, 1H), 8.33 (s, 1H), 9.83 (t, 1H, *J* = 3.8 Hz). ^{13}C NMR ($CDCl_3$) δ -4.40, -4.23, 18.07, 25.32, 25.86, 27.64, 37.44, 40.63, 41.56, 50.70, 61.76, 66.73, 83.74, 84.84, 114.10, 120.42, 140.07, 149.94, 152.59, 155.91, 202.08. Anal. calc. for $C_{23}H_{37}N_5O_4Si$: C (58.10), H (7.79, N (14.74). Found: C (57.95), H (8.56), N (14.45).

Ethyl ester of (5*S*)-2-*tert*-butoxycarbonylamino-5-*tert*-butyldimethylsilyloxy-5-[(5'-deoxy-2',3'- O-*iso*propylidene)aristeromycin-5'-yl]pent-2-enoic acid (105): To a solution of ethyl ester of 2-(diethoxyphosphinyl)-2-([*tert*-butoxycarbonyl]amino)acetic acid **41** (0.15 g, 0.46 mmol) in dry methylene chloride (10 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.05 mL, 0.44 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. Then solution of compound **104** (0.20 g, 0.42 mmol) in dry methylene chloride (10 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 20 h. Solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc-methanol 3:1) to give compound **105** (0.16 g, 58%). ^1H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.84 (s, 9H), 1.19 (t, 3H, *J* = 7.4 Hz), 1.21 (s, 9H), 1.23 (s, 3H), 1.40 (s, 3H), 1.69 (m, 1H), 1.80(m, 1H), 2.40 (m, 5H), 3.49 (s, MeOH), 3.87 (t, 1H, *J* = 7.8 Hz), 4.18 (q, 2H, *J* = 7.3 Hz), 4.43 (t, 1H, *J* = 6.7 Hz), 4.66 (t, 1H, *J* = 7.0 Hz), 5.03 (t, 1H, *J* = 6.7 Hz), 6.32 (s, 2NH), 6.55 (t, 1H, *J* = 6.5 Hz), 7.79 (s, 1H), 8.27 (s, 1H). ^{13}C NMR ($CDCl_3$) δ -4.41, -4.34, 13.80, 18.13, 21.14, 25.29, 25.94, 27.58, 28.24, 37.56, 40.65, 50.41 (MeOH), 60.48,

61.38, 69.95, 80.46, 83.74, 84.93, 120.47, 130.12, 130.98, 140.06, 149.98, 152.78, 155.88, 164.97, 171.24. Anal. calc. for $C_{32}H_{52}O_7N_6Si \bullet 1.0$ MeOH: C (57.22), H (8.09), N (12.11). Found: C (57.20), H (7.98), N (11.71).

Ethyl ester of (5*S*)-2-*tert*-butoxycarbonylamino-5-*tert*-butyldimethylsilyloxy-5-[(5'-deoxy-2',3'- O-*iso*propylidene)aristeromycin-5'-yl]pentanoic acid (106): Compound **105** (0.16 g, 0.24 mmol) was dissolved in methanol (20 mL), and nitrogen was bubbled through the solution for 30 min. Palladium on charcoal (10%, 30 mg) was quickly added under nitrogen, and the reaction mixture was hydrogenated at 30 psi for 24 h. Then solution was filtered through pad of celite, washed with ethanol. Solvent was removed under reduced pressure and product **106** (0.16 g, 99%) was carried into the next step without purification. ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.27 (t, 3H, *J* = 7.3 Hz), 1.33 (s, 3H), 1.46 (s, 9H), 1.57 (s, 3H), 1.64 (m, 4H), 2.46 (m, 5H), 3.49 (t, 1H, *J* = 6.0 Hz), 3.90 (t, 1H, *J* = 6.3 Hz), 4.22 (q, 2H, *J* = 7.3 Hz), 4.49 (m, 1H), 4.70 (m, 1H), 5.07 (m, 1H), 6.02 (s, 2NH), 6.56 (d, 1NH), 7.84 (s, 1H), 8.34 (s, 1H). ^{13}C NMR ($CDCl_3$) δ -4.33, -4.25, 14.37, 18.19, 25.27, 25.37, 26.08, 27.70, 28.38, 28.50, 37.60, 40.72, 44.01, 61.49, 61.87, 62.03, 70.03, 80.02, 83.79, 84.99, 114.16, 120.59, 140.05, 140.16, 150.09, 152.93, 155.82, 165.03, 171.16**.**

Carba-6'-deamino-6'-hydroxy-sinefungin (III): Compound **106** (0.16 g, 0.24 mmol) was dissolved in 1N HCl (10 mL) and was stirred at room temperature for 4 h. Solvent was coevaporated with ethanol, the residue was dissolved in tetrahydrofuran (5 mL) and

added to a solution of lithium hydroxide monohydrate (0.07 g, 1.67 mmol) in water (6 mL). After stirring at room temperature for 18 h, the resulting solution was extracted with EtOAc (3 x 10 mL), dried over sodium sulfate and evaporated. Column chromatography (5% NH_4OH in methanol) gave target compound **III** (30 mg, 33% yield), m.p. 231 ^{0}C. ^{1}H NMR (DMSO-d_6) δ 1.19 (m, 5H), 1.59 (m, 4H), 2.06 (m, 3H), 3.96 (m, 1H), 4.24 (m, 1H), 4.61 (dd, 1H, *J* = 9.6 Hz, 7.7 Hz), 4.75 (dd, 1H, *J* = 10.0 Hz, 7.0 Hz), 5.03 (t, 1H, *J* = 6.8 Hz), 6.60 (d, 2NH, *J* = 14.7 Hz), 7.16 (s, 2NH), 8.09 (s, 1H), 8.21 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 28.89, 30.04, 35.52, 36.60, 40.41, 45.76, 62.70, 77.83, 78.10, 81.77, 83.89, 121.60, 143.69, 152.02, 155.04, 158.19, 186.80, 186.55. Anal. calc. for $C_{16}H_{24}O_5N_6$•1.2 MeOH: C (49.33), H (6.88), N (20.07). Found: C (49.20), H (6.71), N (19.91).

6-Chloro-1-[(1'*R*,2'*S*,3'*R*,4'*S*)-2',3'-(*iso*propylidenedioxy)- 4'-vinyl-cyclopentan-1'-yl]purine (108): **A** solution of compound **71** (2.44 g, 13.26 mmol) in dry THF (100 mL) was cooled to -5 ^{0}C. Then triphenylphosphine (6.97 g, 26.64 mmol) and 6-chloropurine (2.93 g, 18.74 mmol) were added. The reaction mixture was stirred at this temperature for 30 min.

Diisopropyl diazodicarboxylate (5.51 mL, 26.64 mmol) was added to the above mixture. After stirring at 0 ^{0}C for 1 h, the reaction mixture was stirred at room temperature for 24 h, then it was brought to 50 ^{0}C and was stirred at this temperature for another 24 h.

The solvent was evaporated and the residue was purified by column chromatography (EtOAc-hexanes 1:3) to afford a compound **108** contaminated with the azadicarboxylate byproduct.[136]

6-Chloro-1-[(1'*R*,2'*S*,3'*R*,4'*R*)-2',3'-(*Iso*propylidenedioxy)-4'-formyl-cyclopentan-1'-yl]purine (109): The above mixture was dissolved in methanol (35 mL) and water (18 mL), and sodium periodate (4.33 g, 20.2 mmol) was added. After the mixture was cooled to 0 ^{0}C, osmium tetroxide (30 mg) was added. The reaction was stirred at the same temperature for 1 h and then at room temperature for 2 h. The white solid was removed by filtration and the filtrate was removed under reduced pressure at room temperature. The residue was dissolved in methylene chloride (200 mL), washed with water (30 mL), brine (30 mL) and dried over magnesium sulfate. The methylene chloride was removed under reduced pressure at room temperature to afford compound **109** as a yellow liquid (1.75 g, 41% yield from **71**) which was immediately used in the next step. ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.60 (s, 3H), 2.73 (m, 2H), 3.19 (m, 1H), 3.76 (m, 1H), 4.94 (m, 1H), 5.12 (m, 1H), 5.26 (m, 1H), 5.48 (t, 1H, *J* = 6.9 Hz), 8.09 (s, 0.5H), 8.14 (s, 0.5H), 8.72 (s, 0.5H), 8.75 (s, 0.5H), 9.88 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ 14.41, 21.28, 24.28, 25.01, 26.38, 27.41, 30.40, 30.74, 55.42, 56.81, 60.62, 62.46, 62.64, 79.60, 80.93, 83.75, 85.47, 114.04, 131.60, 140.49, 144.64, 144.95, 151.97, 199.39.

6-Chloro-1-[(1'*R*,2'*S*,3'*R*,4'*R*)-4'-[(1''*S*)-1''-hydroxypent-4''-en-1''-yl]-2',3'-(*iso*propylidenedioxy)-cyclopentan-1'-yl]purine (110): To an ice-cooled solution of (-)-

di*iso*pinocampheylmethoxyborane (1.90 g, 5.96 mmol) in dry diethyl ether (100 mL), allylmagnesium bromide (5.96 mL, 5.96 mmol, 1M solution in diethyl ether) was added dropwise under nitrogen. Above solution was stirred at room temperature for 3 h. After ether was evaporated under reduced pressure, white residue was extracted with pentane (100 mL) and filtered under nitrogen to afford the solution of (-)-allyldi*iso*pinocampheylborane in pentane.

The resulting solution (100 mL) was added dropwise to a solution of compound **109** (1.75 g, 5.42 mmol) in a mixture of dry diethyl ether (30 mL) and dry methylene chloride (10 mL), previously cooled to –80 ^{0}C. The reaction mixture was stirred at this temperature for 3 h, quenched with methanol (6 mL) and stirred 1 h at room temperature. Saturated solution of sodium bicarbonate (4 mL) and hydrogen peroxide (3 mL, 30% solution in water) were carefully added. The resulting mixture was stirred at room temperature for 14 h and extracted with EtOAc (2 x 100 mL). Combined organic layers were dried over sodium sulfate and evaporated. The residue was purified by column chromatography (EtOAc-hexanes 1:1) affording compound **110** (0.49 g, 24%) as a mixture of epimers at 4' carbon atom. ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.57 (s, 3H), 2.43 (m, 5H), 3.92 (m, 1H), 4.74-5.24 (m, 6H), 5.86 (m, 1H), 8.21 (s, 0.5H), 8.24 (s, 0.5H), 8.76 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.41, 25.32, 27.76, 31.47, 40.72, 48.51, 62.76, 71.07, 81.78, 83.84, 84.24, 114.04, 119.47, 131.60, 134.17, 140.49, 144.60, 144.95, 151.98.

References.

1. Voet, D.; Voet, J. G. in *Biochemistry*, chapter V, **1990**, pp. 771-837.

2. Orgel, L. *Science* **2000**, *290*, 1306.

3. Porkka-Heiskanen, T.; Strecker, R. E.; Thakkar, M.; Bjorkum, A. A.; Greene, R. W.; McCarley, R. W. *Science* **1997**, *276*, 1265.

4. a) Robins, R. K. *Chem. Eng. News* **1986**, *64*, 28; b) Isono, K. *Pharmacol. Ther.* **1991**, *52*, 269; c) De Clerck, E. *Nucleosides Nucleotides* **1994**, *13*, 1271; d) Isono, K. *J. Antibiot.* **1988**, *41*, 1711.

5. Polgreen, P.; Helms, C. *Primary Care Clinics in Office Practice* **2001**, *28(4)*, 807.

6. De Clerck, E.; Neyts, J. *Rev. Med. Virol.*, **2004**, *14*, 289.

7. De Clercq, E. *Nature Reviews Drug Discovery* **2002**, *1*, 13.

8. Rebora, A.; Rongioletti, F.; Drago, F. *Dermatology* **1999**, *198*, 1.

9. Prusoff, W. H. *Biochim. Biophys. Acta* **1959**, *32*, 295.

10. a) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319; b) Ichikawa, E.; Kato, K. *Current Med. Chem.* **2001**, *8*, 385.

11. a) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; De Miranda, P.; Beauchamp, L.; Schaeffer H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716; b) Schaeffer H. J.; Beauchamp, L.; De Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature*, **1978**, *272*, 583.

12. Faulds, D. H.; Rennie, C. *Drugs*, **1990**, *39*, 597.

13. Hall, C. B.; McBride, J. T.; Walsh, E. E.; Bell, D. M.; Gala, C. L.; Hildreth, S.; Ten Eyck, L. G.; Hall, W. J. *Engl. J. Med.* **1983**, *308*, 1443.

14. a) Pugh, C. S. G.; Borchardt, R. T. *Biochemistry* **1982**, *21*, 1535; b) Shigeta, S.; Mori, S.; Baba, M.; Ito, M.; Honzumi, K.; Nakamura, K.; Oshitani, H.; Numazaki, Y.; Matsuda, A.; Obara, T.; Shoto, S.; De Clercq, E. *Antimicrob. Agents Chemother.* **1992**, *36*, 435.

15. Gaertner, H.; Janta-Lipinski, M.; Langen, P.; Lehman, C.; Mathes, E.; Rosenthal, H.; Scholz, D. *Biochim. Biophys. Res. Commun.* **1987**, *148*, 78.

16. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911.

17. a) Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; John, P. G. *Mol. Pharmacol.* **1987**, *32*, 162; b) Hamamoto, Y.; Nakashima, H.; Matsui, T.; Matsuda, A.; Ueda, T.; Yamamoto, N. *Antimicrob. Agents Chemother.* **1987**, *31*, 1907.

18. a) Coates, J. A.; Cammack, N.; Jenkinson, H. J.; Jowett, A. J.; Jowett, M. A.; Pearson, B. A.; Penn, C. R.; Rouse, P. L.; Viner, K. C.; Cameron, J. M. *Antimicrob. Agents Chemother.* **1992**, *36*, 733; b) Hart, G. J.; Orr, D. C.; Penn, C. R.; Figueiredo, H. T.; Gray, N. M.; Boehme, R. E.; Cameron, J. M. *Antimicrob. Agents Chemother.* **1992**, *36*, 1688.

19. Dayan, A. D.; Anderson, D. in *Antiviral Agents: The Development and Assessment of Antiviral Chemotherapy*, Chapt. 5-6; **1988**, Vol. I, pp. 111-150.

20. Desgranges, C.; Razaka, G.; Drouillet, F.; Bricaud, H.; Herdewijn, P.; De Clercq, E. *Nucleic Acids Res.* **1984**, *12*, 2081.

21. a) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 3075; b) Caperelli, C. A.; Price, M. F. *Arch. Biochem. Biophys.* **1988**, *264*, 340; c)Lui, D.; Caperelli, C. A. *J. Biol. Chem.* **1991**, *266*, 16699; d) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571; e) Marquez, V. *Advances in Antiviral Drug Design* **1996**, *2*, 89.

22. Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255.

23. a) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, *24*, 359; b) Hayashi, M.; Yaginuma, S. *J. Antibiot.* **1981**, *24*, 675.

24. a) Robins, R. K. *C & E news* **1986**, *64*, 28; b) Mansuri, M M.; Martin, J. C. *Ann. Rep. Med. Chem.* **1987**, *22*, 147.

25. a) Yuan, C.-S.; Liu, S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T. *Advances in Antiviral Drug Design* **1996**, *2*, 41; b) Wolfe, M. S.; Borchardt, R. T. *J. Med. Chem.* **1991**, *34*, 1521.

26. a) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17; b) Coates, J. A.; Ingall, H.; Pearson, B. A.; Penn, C. R.; Storer, R.; Williamson, C.; Cameron, J. M. *Antiviral Res.* **1991**, 161.

27. Borthwick, A. D.; Kirk, B. E.; Biggadike, K.; Exall, A. M.; Butt, S.; Roberts, S. M.; Knight, D. J.; Coates, J. A. V.; Ryan, D. M. *J. Md. Chem.* **1991**, *34*, 907.

28. a) Innaimo, S. F.; Seifer, M.; Bisacchi, G. S.; Standring, D. M.; Zahler, R.; Colonno, R. J. *Antimicrob. Agents Chemother.* **1997**, *41*, 1444; b) Genovesi, E. V.; Lamb, L.; Medina, I.; Taylor, D.; Seifer, M.; Innaimo, S.; Colonno, R. J.; Standring, D. M.; Clark, J. M. *Antimicrob. Agents Chemother.* **1998**, *42*, 3209; c) Bisacchi, G. S.; Chao,

S. T.; Bachard, C.; Daris, J. P.; Innaimo, S.; Jacobs, J. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127.

29. a) Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T. *J. Antibiot.* **1968**, *21*, 255; b) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, 34, 359.
30. Dalton, L. W. *C & E News* **2004**, 45.
31. Web address: http://www-micro.msb.le.ac.uk/3035/Poxviruses.html.
32. Silvers, M.; Steptoe, M. *Primary Care Clinics in Office Practice* **2001**, *28(4)*, 685.
33. Polgreen, P.; Helms, C. *Primary Care Clinics in Office Practice* **2001**, *28(4)*, 807.
34. World Health Organization. The global eradication of smallpox: final report of the Global Commission for the Certification of Smallpox Eradication. Geneva: World Health Organization; **1980**.
35. Diven, D. *Journal of the American Academy of Dermatology* **2001**, *44(1)*, 1.
36. Smith, A. E.; Helenius, A. *Science* **2004**, *304*, 237.
37. Murray et al., *Medical Microbiology* 3rd Ed., Chapter 6.
38. Baron, S. *Ed. Medical Microbiology* 4th Edition. 1996.
39. Kern, E. R. *Antiviral Res.* **2003**, *57*, 35.
40. a) Banerjee, A. K. *Microbiol. Rev.* **1980**, *44*, 175; b) Green, M. R.; Maniatis, T.; Melton, D. A. *Cell* **1983**, *32*, 681; c) Konarska, M. M.; Padgett, R. A.; Sharp, P. A. *Cell* **1984**, *38*, 731.
41. a) Banerjee, A. K; Abraham, G.; Colonno, R. J. *J. Gen. Virol* **1977**, *34(Pt.1)*, 1; b) Krug, R. M.; Broni, B. A.; Bouloy, M. *Cell* **1979**, *18*, 329; c) Shuman, S. *Prog.*

Nucleic Acid Res. Mol. Biol. **1995**, *50*, 101; d) Jones, P. A.; Takai, D. *Science* **2001**, *293*, 1068.

42. Furuichi, Y.; LaFiandra, A.; Shatkin, A. J. *Nature* **1977**, *266*, 235.
43. Both, G.; Furuichi, Y.; Muthukrishnan, S.; Shatkin, A. J. *Cell* **1975**, *6*, 185.
44. a) Borchardt, R. T. *J. Med. Chem.* **1980**, *23*, 347; b) Usdin, E.; Borchardt, R. T. Editors of *Biochemistry of S-Adenosylmethionine and related compounds*; Macmillan Press, London, **1982**.
45. Cantoni, G. L. *Annu. Rev. Biochem.* **1975**, *44*, 435.
46. Fontecave, M.; Atta, M.; Mulli, E. *Trends in Biochemical Sciences* **2004**, *29(5)*, 243.
47. a) Salvatore, F.; Borek, E.; Zappia, V.; Williams-Ashman, H. G.; Schlenk, F.; Eds.; *The Biochemistry of S-Adenosylmethionine*; Columbia University Press, New York, **1977**; b) Borchardt, R. T.; Creveling, C. R.; Ueland, P. M.; Eds.; *Biological Methylation and Drug Design*; Humana Press, Clifton, NJ, **1986**.
48. a) Liu, S.; Wolfe, M. S.; Borchardt, R. T. *Antiviral Res.* **1992**, *19*, 247; b) Turner, M. A.; Yang, X.; Yin, D.; Kuczera, K.; Borchardt, R. T.; Howell, P. L. *Cell Biochem. Biophys.* **2000**, *33*, 101.
49. Henderson, J. F. *Methods in Pharmacology* **1985**, *6*, 67-82.
50. Lieber, C. S.; Packer, L. *Am. J. Clin. Nutr.* **2002**, *76*, 1148S.
51. Selhub, J. *Ann. Rev. Nutr.* **1999**, *19*, 217.
52. De Clercq, E. *Nucleosides Nucleotides*, **1998**, *17*, 625.
53. a) Borchardt, R. T.; Keller, B. T.; Patel-Thombre, U. *J. Biol. Chem.* **1984**, *259*, 4353; b) De Clercq, E. *Antimicrob. Agents Chemother.* **1985**, *28*, 84.

54. Snoeck, R.; Andrei, G.; Neyts, J, Schols, D.; Cools, M.; Balzarini, J.; De Clercq, E. *Antiviral Res.* **1993**, *21*, 197.

55. Villalon, M. D. G.; Gil-Fernandez, C.; De Clercq, E. *Antiviral Res.* **1993**, *20*, 131.

56. De Clercq, E. *Int. J. Antimicrob. Agents* **1996**, *31*, 1225.

57. a) De Clercq, E.; Montgomery, J. A. *Antiviral Res.* **1983**, *3*, 17; b) De Clercq, E.; Cools, M.; Balzarini, J.; Marquez, V. E.; Borchering, D. R.; Borchardt, R. T.; Drach, J. C.; Kitaoka, S.; Konno, T. *Antimicrob. Agents Chemother.* **1989**, *33*, 1291; c) Kitaoka, S.; Konno, T.; De Clercq, E. *Antiviral Res.* **1986**, *6*, 57.

58. Mayers, D. L.; Mikovits, J. A.; Joshi, B.; Hewlett, I. K.; Estrada, J. S.; Wolfe, A. D.; Garcia, G. E.; Doctor, B. P.; Burke, D. S.; Gordon, R. K.; Lane, J. L.; Chiang, P. K. *Proc. Natl. Acad. Sci. USA*, **1995**, *92*, 215.

59. Hu, Y.; Yang, X.; Yin, D. H.; Mahadevan, J.; Kuczera, K.; Schowen, R. L.; Borchardt, R. T. *Biochemistry* **2001**, *40*, 15143.

60. Guranowski, A.; Montgomery, J. A.; Cantoni, G. L.; Chiang, P. K. *Biochemistry* **1981**, *20*, 110.

61. Borchardt, R. T.; Wu, Y.-S. *J. Med. Chem.* **1976**, *19(1)*, 197.

62. Keller, B. T.; Borchardt, R. T. In *Antiviral Drugs Development – A Multidisciplinary Approach*, Plenum Press, New York, **1988**, 123.

63. a) Bennett, L. L. Jr.; Allan, P. W.; Hill, D. L. *J. Mol. Pharmacol*. **1968**, *4*, 208; b) Ault-Riche, D. B.; Lee, Y.; Yuan, C. S.; Hasobe, M.; Wolfe, M. S.; Borcherding, D. R.; Borchardt, R. T.; *J. Mol. Pharmacol*. **1993**, *43*, 989.

64. a) Saunders, P. P.; Tan, M. T.; Robins, R. K. *Biochem. Pharmacol*. **1985**, *34*, 2749; b) Glazer, R. I.; Knode, M. C. *J. Biol. Chem.* **1984**, *259*, 12964; c) Whaun, J. M.; Miura,

G. A.; Brown, N. D.; Gordon, R. K.; Chiang, P. K. *J. Pharmacol. Exp. Ther.* **1986**, *236*, 277.

65. Hill, D. L.; Straight, S.; Allan, P. W.; Bennett, L. L. *J. Mol. Pharmacol*. **1971**, *7*, 375.
66. Bennett, L. L. Jr.; Allan, P. W.; Rose, L. M.; Comber, R. N.; Secrist, J. A. III *Mol. Pharmacol*. **1986**, *29*, 383.
67. Bennett, L. L. Jr.; Brockman, R. W.; Rose, L. M.; Allan, P. W.; Shaddix, S. C.; Shealy, Y. F.; Clayton, J. D. *Mol. Pharmacol*. **1985**, *27*, 666.
68. Hasobe, M.; Liang, H.; Ault-Riche, D. B.; Borcherding, D. R.; Wolfe, M. S.; Borchardt, R. T.; *Antiviral Chem. Chemoth.* **1993**, *4*, 245.
69. a) Montgomery, J. A.; Clayton, S. J.; Thomas, H. J.; Shannon, W. M.; Arnett, G.; Bodner, A. J.; Kion, I.-K.; Cantoni, G. L.; Chiang, P. K. *J. Med. Chem.* **1982**, *25*, 626; b) Glazer, R. I.; Hartman, K. D.;Knode, M. C.; Richard, M. M.; Chiang, P. K.; Tseng, C. K.; Marquez, V. E. *Biochem. Biophys. Res. Commun.* **1989**, *135*, 688.
70. Bloch, A.; Robins, M. J.; McCarthy, J. R. , Jr. *J. Med. Chem.* **1967**, *10*, 908.
71. Patil, S. D.; Schneller, S. W.; Hosoya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1992**, *35*, 3372.
72. a) Siddiqi, S. M.; Schneller, S. W. *Nucleosides Nucleotides* **1993**, *12*, 185; b) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 551; c) Seley, K. L.; Schneller, S. W.; Kobra, B. *Nucleosides Nucleotides* **1997**, *16*, 2095.
73. a) Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem.* **1987**, *52*, 5457; b) Hasobe, M.; McKee, J. G.; Borcherding, D. R.; Keller, B. T.; Borchardt, R. T. *Mol.*

Pharmacol. **1988**, *33*, 713; c) Wolfe, M. S.; Lee, Y.; Bartlett, W. J.; Borcherding, D. R.; Borchardt, R. T. *J. Med. Chem.* **1992**, *35*, 1782.

74. a) Lin, Q.; Jiang, F.; Schultz, P. G.; Gray, N. S. *J. Am. Chem. Soc.* **2001**, *123*, 11608; b) Thomas, C. B.; Scavetta, R. D.; Gumport, R. I.; Churchill, W. E. A. *J. Biol. Chem.* **2003**, *278(28)*, 26054.
75. Pugh, C. S.; Borchardt, R. T. *Biochemistry* **1982**, *21*, 1535.
76. Borchardt, R. T.; Huber, J. A.; Wu, Y. S. *J. Med. Chem.* **1974**, *17(8)*, 868-73.
77. a) Borchardt, R. T.; Wu, Y. S. *J. Med. Chem.* **1976**, *19*, 197; b) Borchardt, R. T.; Wu, Y. S. *J. Med. Chem.* **1975**, *18*, 300.
78. Borchardt, R. T.; Wu, Y. S. *J. Med. Chem.* **1974**, *17*, 862.
79. Pugh, C. S.; Borchardt, R. T.; Stone, H. O. *J. Biol. Chem.* **1978**, *253(12)*, 4075.
80. Hamill, R. L.; Hoehn, M. M. *J. Antibiot.* **1973**, *26*, 463.
81. Florent, J.; Lunel, J.; Mancy, D. *US Patent* 4 189 349, **1980**.
82. Fuller, R. W.; Nagarajan, R. *Biochem. Pharmacol.* **1978**, *27*, 981.
83. Maguire, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 948.
84. Vedel, M.; Lawrence, F.; Robert-Gero, M.; Ledere, E. *Biochem. Biophys. Res. Commun.* **1978**, *85*, 371.
85. Hamill, R. L.; Nagarajan, R. *US Patent*4 087 603, **1976**.
86. Ferrante, A.; Ljungstroem, L.; Huldt, G.; Lederer, E. *Trans. R. Soc. Trop. Med. Hyg.* **1984**, *78*, 837.
87. Trager, W.; Tershacovac, M.; Chiang, P. K.; Cantoni, G. L. *Exp. Parasitol.* **1980**, *50*, 83.

88. Zweygerth, E.; Schillinger, D.; Kaufmann, W.; Roettcher, D *Trop. Med. Parasitol.* **1986**, *37*, 255.

89. Barton, D. H. R.; Gero, S. D.; Lawrence, F.; Robert-Gero, M.; Quislet-Sire, B.; Samadi, M. *J. Med. Chem.* **1992**, *35*, 63.

90. Barton, D. H. R.; Gero, S. D.; Negron, G.; Quislet-Sire, B.; Samadi, M.; Vincent, C. *Nuclesides Nucleotides* **1995**, *14(8)*, 1619.

91. a) Blanchard, P.; Dodic, N.; Fourrey, J.-L.; Lawrence, F.; Mouna, A. M.; Robert-Gero, M. *J. Med. Chem.* **1991**, *34*, 2798; b) Marasco, C. J. Jr.; Kramer, D. L.; Miller, J.; Porter, C. W.; Bacchi, C. J.; Rattendi, D.; Kucera, L.; Iyer, N.; Bernacki, R.; Pera, P., Sufrin, J. R. *J. Med. Chem.* **2002**, *45*, 5112.

92. Maria, E. J.; Da Silva, A. D.; Fourrey, J.-L. *Eur. J. Org. Chem.* **2000**, 627.

93. Secrist III, J. A.; Talekar, R. R. *Nuclesides Nucleotides* **1990**, *9(4)*, 619.

94. a) Lyga, J. W.; Secrist III, J. A. *J. Org. Chem.* **1983**, *48*, 1982; b) Peterli-Roth, P.; Maguire, M. P.; Leon, E.; Rapoport, H. *J. Org. Chem.***1994**, *59*, 4186.

95. a) Gage, J. L.; Priour, A. A.; Savela, G. C.; Miller, M. J. *Book of Abstracts, 216th ACS National Meeting*, Boston, August 23-27 (**1998**), ORGN-314; b) Da Silva, A. D.; Maria, E. J.; Blanchatd, P.; Fourrey, J.-L.; Robert-Gero, M. *Nucleosides Nucleotides* **1998**, *17*, 2175; c) Miller, M. J.; Jin, B.; Warshakoon, N. C.; Gage, J. L. *Abstracts of Papers, 226th ACS National Meeting,* New York, NY, United States, September 7-11, **2003**, ORGN-589.

96. See, for example a) Barton, D. H. R.; Gero, S. D.; Quincet-Sire, B.; Samadi, M. *J. Chem. Soc. Perkin Trans.1* **1991**, 981; b) Ghosh, A. K.; Liu, W. *J. Org. Chem.* **1996**, *61*, 6175; c) Ghosh, A. K.; Wang, Y. *J. Chem. Soc. Perkin Trans.1*, **1999**, 3597.

97. See, for example, Choi, W. J.; Park, J. G.; Yoo, S. J.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jung, Y. H.; Jeong, L. S. *J. Org. Chem.* **2001**, *66*, 6490 and references cited herein.

98. Yin, X.-Q.; Rajappan, V. P.; Roy, A.; Schneller, S. W. *Synth. Commun.* **2003**, *33(9)*, 1477.

99. Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett.* **1985**, *26*, 5615.

100. Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319.

101. Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875.

102. Siddiqi, S. M.; Chen, X.; Schneller, S. W. *Nucleosides Nucleotides* **1993**, *12*, 267.

103. Nishizava, K.; Ohgami, Y.; Matsuo, N.; Kishida, H.; Hirohara, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1293.

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

105. Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

106. Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751.

107. DeBernarddis, J. F.; Zalle, R. I. *US Patent* 4 963 563, **1990**.

108. Satoh, T.; Suzuki, S. *Tetrahedron Lett.* **1969**, *52*, 4555.

109. a) Wann, S. R.; Thorsen, P. T.; Kreevoy, M. M. *J. Org. Chem.* **1981**, *46*, 2579; b) Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1992**, *48*, 4623.

110. a) Wills, M'; Palmer, M.; Smith, A.; Kenny, J.; Walsgrove, T. *Molecules* **2000**, *5*, 4; b) Genet, J. P. *Pure Appl. Chem.* **2002**, *74*, 77.

111. McCarrity, J. F.; Brieden, W.; Fuchs, R.; Mettler, H.-P.; Schmidt, B.; Werbitzky, O. *Asymmetric catalysis on industrial scale* Wiley-VCH Verlag GmbH & Co. **2004**, pp. 238-308.

112. Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 33.

113. a) Brown, H. C.; Jadhav, P.K. *J. Am. Chem. Soc.* **1983**, *105*, 2092; b) Jadhav, P.K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

114. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

115. Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486.

116. Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.

117. Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

118. Brown, H. C.; Jadhav, P.K. *J. Org. Chem.* **1984**, *49*, 4091.

119. Vulpetti, A.; Gardner, M.; Gennari, C.; Bernardi, A.; Goodman, G. M.; Paterson, I. *J. Org. Chem.* **1993**, *58*, 1711.

120. AuerBach, J.; Weinreb, S. M. *J. Chem. Soc., Chem. Commun.* **1974**, 298.

121. Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487.

122. a) Alloum, A. B.; Villemin, D. *Synthetic Commun.* **1989**, *19*, 2567; b) Lee, J. C.; Yuk, J. Y. *Synthetic Commun.* **1995**, *25*, 1511.

123. Ferris, L.; Haigh, D.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2885.

124. Schmidt, U.; Lieberknecht, A.; Wild, J *Synthesis* **1984**, 51.

125. a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A.; Masamune, S.; Roush, W. R.; Sasaki, T *Tetrahedron Lett.* **1984,** *25*, 2183; b) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2625.

126. Schelhaas, M.; Waldmann, H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2056.

127. Fukuzawa, A.; Sato, H.; Masamune, T. *Tetrahedron Lett.* 1987, *28*, 4303.

128. Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

129. Li, M.; Tang, D.; Luo, X.; Shen, W. *Int. J. Quant. Chem.* **2005**, *102*, 53 and references herein.

130. Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.

131. Matteson, D. S.; Man, H. W.; Ho, O. C. *J. Am. Chem. Soc.* **1996**, *118*, 4560.

132. ElAmin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1978**, *43*, 4194.

133. Rodebauhj, R.; Debenham, J. S.; Frase-Reid, B. *Tetrahedron Lett.* **1996**, *37*, 5477.

134. a) White, J. D.; Amedio, J. C.; Gut, S.; Jayasinghe, L. *J. Org. Chem.* **1989**, *54*, 4268; b) Zgang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177.

135. Johnson, C. R.; Chen, Y. F. *J. Org. Chem.* **1991**, *56*, 3344.

136. Yang, M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, *69*, 3993.

137. a) Sepulchre, A. M.; Vass, G.; Gero, S. D. *Tetrahedron Letters* **1973**, *14*, 3619; b) Hampton, A.; Perini, F.; Harper, P. J. *Carbohydrate Research* **1974**, *37(2)*, 359; c) Paulsen, H.; Stubbe, M.; Heiker, F. R. *Liebigs Annalen der Chemie* **1980**, 825.

138. Barrett, A. G. M.; Lebold, S. A. J. Org. Chem. **1990**, *55(12)*, 3853.

139. a) Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.,* **1999**, *121 (29)*, 6816; b) Parikh, J.P.; Doering, W.E. *J. Am. Chem. Soc.,* **1967**, *89*, 5505.

140. Ugarkar, B. G.; DaRe, J. M.; Kopcho, J. J.; Browne, C. E. ,III; Schanzer, J. M.; Wiesner, J. B.; Erion, M. D. *J. Med. Chem.* **2000**, 43*(15)*, 2883.

141. a) Vorbrüggen, H.; Krolikievicz, K. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 421; b) Vorbrüggen, H.; Krolikievicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234; c) Vorbrüggen, H.; Höfle, G. *Chem. Ber.* **1981**, *114*, 1256; d) Vorbrüggen, H.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1279.

142. Hilbert, G. E.; Johnson, T. B. *J. Am. Chem. Soc.* **1930**, *52*, 4489.