SYNTHETIC EXPLORATIONS TO SINEFUNGIN ANALOGS

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# SYNTHETIC EXPLORATIONS TO SINEFUNGIN ANALOGS

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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
May 9, 2009

SYNTHETIC EXPLORATIONS TO SINEFUNGIN ANALOGS

Guoxia Zhao



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Date of Graduation

# VITA

Guoxia Zhao, daughter of Yijun Zhao and Hailian Zhang, was born in Shenxian County, Liaocheng City, Shandong Province, China, on April 6, 1978. After graduating from high school, she began her college studies first at Liaocheng University in September 1997 and then entered to Qufu Normal University at September 1999 as the fifth in Shandong Province University Entrance Examination (SPUEE) and received a Bachelor Degree in Chemistry in July 2001. Then, she attended national graduate-student entrance examination (NGEE) in December 2000. She entered the University of Science and Technology of China (USTC) to begin her graduate study at September 2001 and obtained a Master Degree in Organic Chemistry in July 2004 under the Professors Guan-wu Wang and Li-feng Yan. After she graduated from USTC in 2004, she got a research position (Assistant Professor) in a famous Institute of Chinese Academy in Beijing. However, she chose to study abroad to Auburn University. She began her Ph.D studies in Organic Chemistry under the direction of Prof. S. W. Schneller at Auburn University in August 2004. She is married to Hai, Li, son of Zhiheng Li and Yiqing Liu.

DISSERTATION ABSTRACT

SYNTHETIC EXPLORATIONS TO SINEFUNGIN ANALOGS

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Doctor of Philosophy, May 9, 2009
(M. S., University of Science and Technology of China, USTC, July 3, 2004)
(B. S., Qufu Normal University, July 4, 2001)

173 Typed Pages

Directed by Stewart W. Schneller

Sinefungin, a natural complex nucleoside, has been isolated from the cultures of *Streptomyces griseolous*, and from that of *Streptomyces incarnatus*. It is a structural analog of *S*-adenosylmethionine (AdoMet) and since its discovery, its biological activities have been thoroughly studied, including antifungal, antitumor, antiparasitic, antiviral and amoebicidal activities. The nature of these biological activities results from its inhibition of a variety of AdoMet-dependent methyltranferase enzymes. These methylation reactions are crucial in many biochemical processes, including virus-encoded mRNA cap methyltransferases, of which sinefungin is a selective inhibitor. As a

consequence of the latter observation, sinefungin and related compounds have attracted the attention of synthetic chemists in the design of antiviral chemotherapeutic agents.

However, the clinical usefulness of sinefungin has been precluded by its toxicity in *in vivo* assays. To seek a novel approach to toxic-free sinefungin-based compounds, the main body of this dissertation research considers the design and possible synthetic routes to the analog of carbocyclic sinefungin (target I) and related intermediates (47, 53, 55 and 79, 81, 86) for other sinefungin-based compounds.

In this research, the key synthetic steps that have been investigated are the installment of the C-6' and C-9' stereocenters by efficient asymmetric synthetic methods. In the C-6' case, a highly diastereoselective allylborating agent, (+) and/or (-)-B-allydi*iso*pinocampheylborane ($Ipc_2BCH_2CH{=}CH_2$) has been called forth. The requisite C-9' amino acid stereochemistry has been established by alkylation reactions with the Schöllkopf reagent. Finally, coupling of cyclopentyl or ribosyl units with the heterocyclic base (adenine) has been evaluated by standard $S_N2$ substituted reactions. These synthetic approaches are adaptable to a number of structural investigations relevant to analogs of carbocyclic sinefungin and the parent sinefungin.

# ACKNOWLEDGMENTS

Many people have contributed to this dissertation and have given me endless support. I am extremely grateful to each of them.

First and foremost, I would like to express my sincere gratitude to my research advisor, Professor Stewart W. Schneller, for his continuous support and encouragement during my graduate career. Without his dedication much of the research discussed in this dissertation would not have been possible. My gratitude is extended to the distinguished members of Committee including Drs. Peter Livant, Edward J. Parish, Susanne Striegler and Jack DeRuiter as my outside reader for their intellectual assistance and constructive suggestions.

I am grateful to all Schneller group members for their kind help, useful discussions, and friendship. In particular, I would like to thank these lab mates, Drs. Xue-qiang Yin, Weikuan Li, Mingming Yang, Atanu Roy, Yan Zhang, Wei Ye, and Mingzhu He. Additionally, I extend my gratitude to Department of Chemistry and Biochemistry and National Institutes of Health for their financial support.

Finally, I wish to thank my family and friends in China for their infinite love and support which made this dissertation possible. Especially, I am deeply indebted to my husband, Hai Li for his patience, support, and never-ending encouragement.

Style manual or jounal used:

American Chemical Society Style-*The Journal Organic Chemistry*

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Computer software used:

Microsoft Word 2003, ISIS Draw 2.0, EndNote X1

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# CHAPTER 1

# INTRODUCTION

Nucleosides are glycosylated nitrogen heterocyclic molecules and function biologically in their monomeric state or as units in the large molecules of nucleic acids: DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). In their latter role, DNA is a polymer of three components: phosphate, heterocyclic base, and 2-deoxy-D-ribose. The four bases in DNA are adenine (A), cytosine (C), guanine (G) and thymine (T). The structurally similar RNA is also composed of three components: phosphate, heterocyclic base, and D-ribose. In ribonucleosides, the bases are adenine (A), guanine (G), uracil (U) and cytosine (C). The structural difference between the deoxy-ribose of DNA and ribose of RNA is the presence of a hydroxyl group at the 2' position of the later ribose sugar. In both DNA and RNA, the ribose is in its furanose form. The nitrogen heterocyclic bases of nucleosides attach themselves to the C-1' sugar unit (Figure 1).

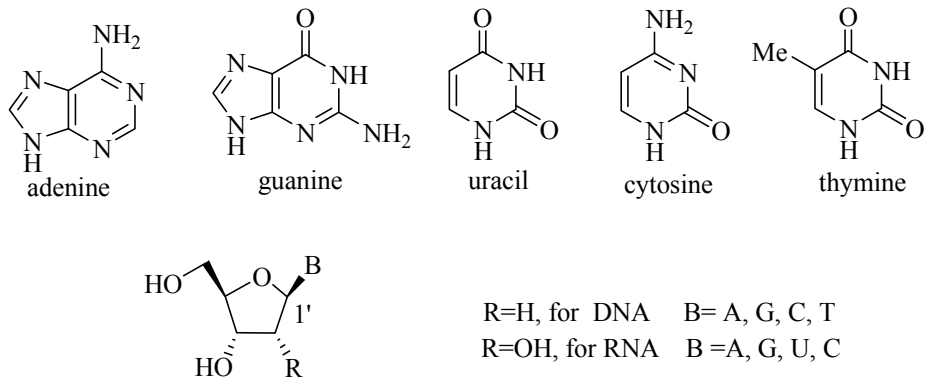



**Figure 1. Monomeric components of DNA and RNA-nucleosides.**

The nucleic acid DNA carries the inherited genetic code that cells use to direct their replication and behavior. DNA is transcribed into mRNA, which is then translated into protein sequence at the ribosomes. Monomeric nucleosides play important roles in the fundamental biological processes. For example, *S*-adenosylmethionine (AdoMet) serves directly as the methyl donor for numerous methyltransferases,[1a-b] such as small molecular weight neurotransmitters (histamine, norepinephrine) and macromolecules (proteins, lipids, nucleic acid) and as an important substrate for enzymatically catalyzed group transfer reactions [AdoMet is also decarboxylated by AdoMet decarboxylase to dcAdoMet. dcAdoMet serves as an aminopropyl donor toward the synthesis of polyamines and in the process is converted to 5'-methylthioadenosine (MTA)],[1c-d] and as substrate for the enzyme 1-aminocyclopropanecarboxylic acid synthase.[1e-f]

Because of their biological pervasiveness nucleosides have found a prominent place in drug discovery (for example, Severe Acute Respiratory Syndrome or SARS; Human Immunodeficiency Virus or HIV; and, Epstein-Barr virus).[2] It is reported that of

the thirty compounds currently marketed in the United States for treatment of viral infections, fifteen are nucleosides analogs.[3] This demonstrates the wide uses of the nucleosides as a source of antiviral drugs.

To discover new therapeutic nucleosides, two approaches exist: (1) molecular modification of the sugar moiety and (2) variation of the heterocyclic base.[3] In the former case, Figure 2 presents nucleosides clinically used for treating herpes simplex virus, HSV (acyclovir[4] and ganciclovir[5]) and HIV (AZT[6], ddC[7], ddI[8], d4T[9], (-)-3TC[10], avacavir[11]). Variation of the heterocyclic base has also led to effective anti-HSV drugs (5-iodo-2'-deoxyuridine, IDU, Idoxudine; and, 5-trifluoromethyl-2'-deoxyuridine, Trifluridine).[12]

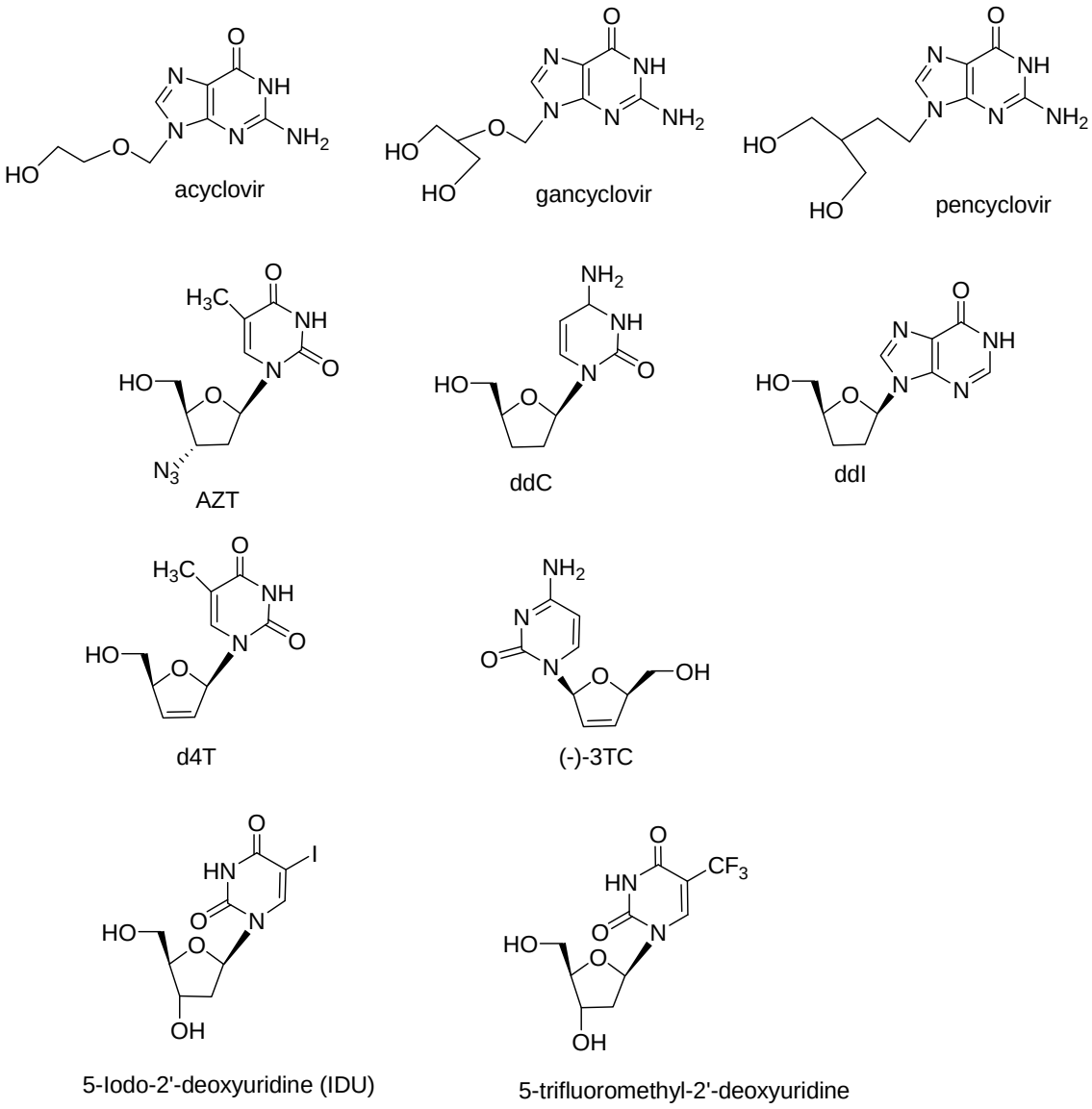



**Figure 2. Structures of approved nucleoside drugs.**

However, the clinical application for these nucleoside drugs has been restricted by their inherent undesirable properties, such as toxicity, drug resistance and stability.[13] Among them, IDU and 5-trifluromethyl-2'-deoxyuridine show very little selectivity against virus-infected cells and are highly toxic to host cells and mutagenic.[14] Another major problem with 5-substituted 2'-deoxyuridine derivatives is that they are easily

cleaved by pyrimidine phosphorylases at the glycosidic bond to their respective uracil bases (Figure 3).[15] Because of these limitations, the search for nucleoside derived antiviral agents continues in many laboratories.

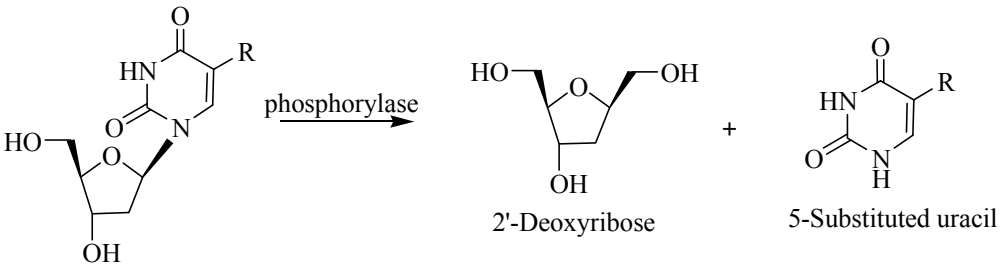



**Figure 3.** ***In vivo*** **metabolic deactivation.**

In that regard, among the sugar moiety modified nucleosides, the carbocyclic nucleoside or carbanucleoside is an important type of nucleoside. In this series of compounds, a methylene group replaces the oxygen atom of the furanose ring of the traditional nucleosides. Carbanucleosides have important biological properties, including: (i) metabolic stability and (ii) recognition by the enzymes and acceptors common to the standard nucleosides.[16] In the first case, their half-life *in vivo* is prolonged since they are not affected by the phosphorylases and hydrolases, which cleave the glycosidic bonds of natural nucleosides.[17] Their second relevant property arises from the similarity between the cyclopentane ring of carbocyclic nucleosides and the tetrahydrofuran ring of natural nucleosides. This renders carbocyclic nucleosides recognizable as substrates for numerous cellular enzymes. Moreover, the higher lipophilicity of carbocyclic nucleosides is beneficial for increasing their oral availability and cellular membrane penetration.[18]

Two of the most important carbocyclic nucleosides, aristeromycin[17d,19] (Ari) and neplanocin A[20] (NpcA), are naturally occurring nucleosides and have been enantioselectively synthesized and found to exhibit various antiviral activities. As shown in Figure 4, both Ari and NpcA are carbocyclic analogs of adenosine with the only difference being the presence of a double bond between C-4' and C-6' of the carbocyclic ring of NpcA.

Aristeromycin was first isolated from *Streptomyces citricolor* by Kusaka *et al.*[19a] and synthesized by Shealy and Clayton in 1966 in racemic form.[17d] Its adenosine-like biological properties and the chemical stability have made it a lead compound in the development of new drugs. Neplanocin A, the olefinic analog of Ari, first isolated from the culture of *Ampullariella regularis* A11079[20f] and then synthesized by some groups,[20g-i] possesses apparent *in vivo* antileukemic activity.[20a]

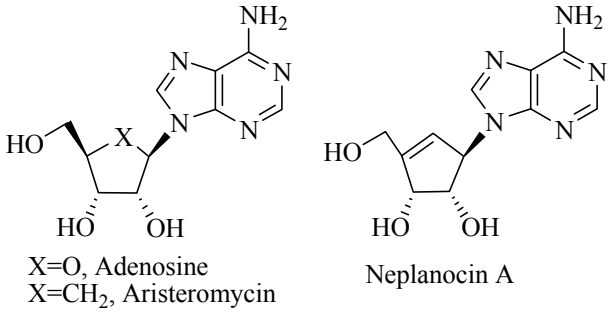



**Figure 4. Carbocyclic nucleosides, Ari and Npc A.**

Ari and NpcA have been subjected to various biological assays and both exhibit broad-spectrum antiviral activities. The antiviral activity of Ari has been correlated with its inhibition of the enzyme *S*-adenosyl-L-homocysteine hydrolase (AdoHcy hydrolase or

SAH hydrolase) and, subsequently, to inhibit viral mRNA methylation. Furthermore, only its (-) enantiomer shows biological activity in inhibiting tumor cell growth and viral replication.[21]

Neplanocin A has activity against a broad spectrum of viruses,[22] such as DNA viruses (vaccinia virus), (-) RNA viruses (such as parainfluenza, measles, and vesicular stomatitis), and double-stranded RNA viruses (such as reo) *in vitro* in cell culture. Its *in vivo* activity has been established against the vaccinia virus in mouse L-929 cells with little or no toxicity to the host cells.[22b] Neplanocin A also possesses significant antitumor activity *in vivo* against murine leukemias.[23] Based on its structural similarity to adenosine and aristeromycin, the pharmacological activity of NpcA has been investigated. This compound is a potent inhibitor of AdoHcy hydrolase both *in vitro* and *in vivo* as mentioned.

Because of the common inhibitory mechanism of antiviral effect of Ari and Npc A, AdoHcy hydrolase has been recognized as an important target for broad-spectrum antiviral agents.[24] It is known that *S*-adenosyl-L-homocysteine hydrolase plays an important role in regulating biological methylation reactions, for example, small molecules (triptamine and histamine) and macromolecules (nucleic acids, proteins and phospholipids).[25] The latter methylation reactions are catalyzed by specific AdoMet-dependent methyltransferases, which themselves are attracting the attention of medicinal chemists as potential targets for the design and synthesis of antitumor and antiviral agents.

It has been found that eukaryotic mRNA, but not prokaryotic mRNA, possesses a methylated 5'-capped structure linked to the 5' end of the transcript by a 5'-5' triphosphate bridge (Figure 5). This is essential to stabilize the mRNA against phosphatase and

ribonuclease and is crucial for the proper binding of the mRNA to the ribosome for translation to proteins.[25b,26,27] Shuman and co-workers[30] found that the 5'-end of eukaryotic mRNAs is capped with a 7'-methyl-GTP (guanosine triphosphate) residue, which protects the RNA from digestion by the aforementioned enzymes, and is linked to a polyadenylated tail of the code mRNA transcript (Figure 5).[31] Those adenosines also carry a 2' – methyl group. The capping is essential for successful translation into protein at the ribosomes.

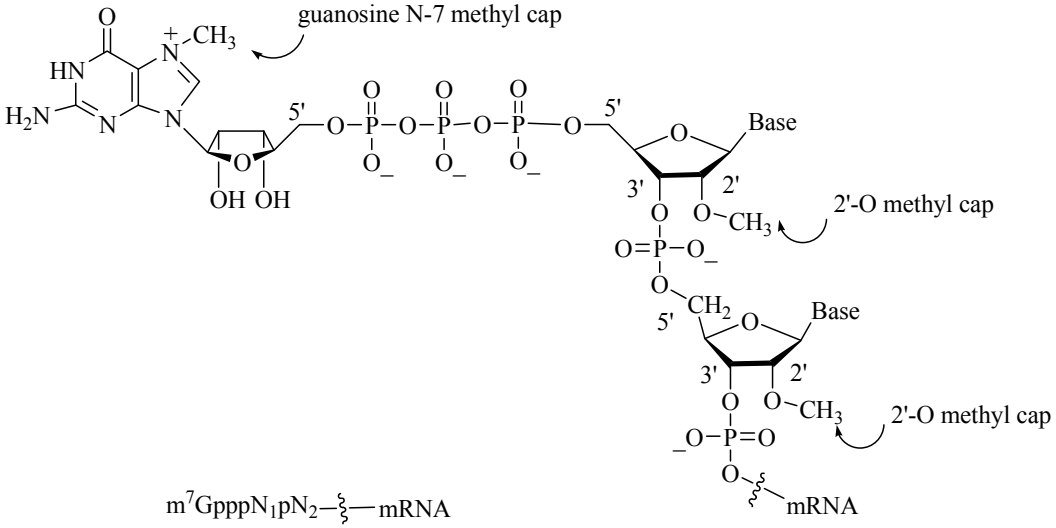
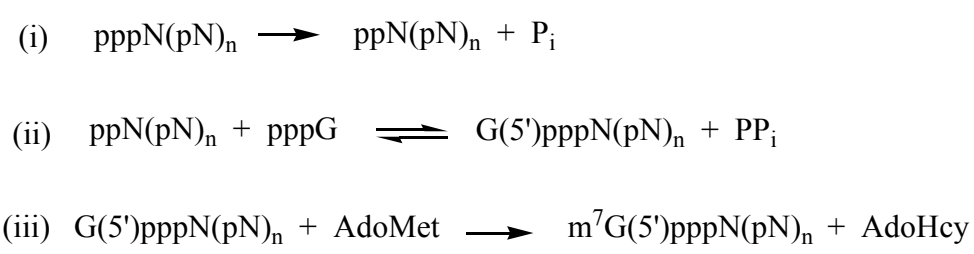



**Figure 5. 5'-methylated and capped structure of eukaryotic mRNA.**

The relevant capping process of mRNA involves three enzymatic reactions.[28] The first is the hydrolysis of the 5'-triphosphate end of the pre-mRNA to a diphosphate by RNA 5'-triphosphatase. The second reaction involves a RNA guanylyltransferase, which adds guanosine monophosphate (GMP) to the just formed diphosphate RNA end. The final step is the methylation of the guanyl capped mRNA by an RNA (guanine N-7)

methyltransferase, with a methyl group from *S*-adenosylmethionine (AdoMet) serving as the methyl source. This occurs at the N-7 position of the GpppN of the mRNA to produce a $m^7$GpppN RNA and *S*-adenosylhomocysteine (AdoHcy). This important biochemical process is conserved in all eukaryotic organisms and many eukaryotic viruses.[29] The latter observation produces the basis for drug development of inhibition of the cap methylation reaction as an anti-infective drug strategy, including antiviral agent design.



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

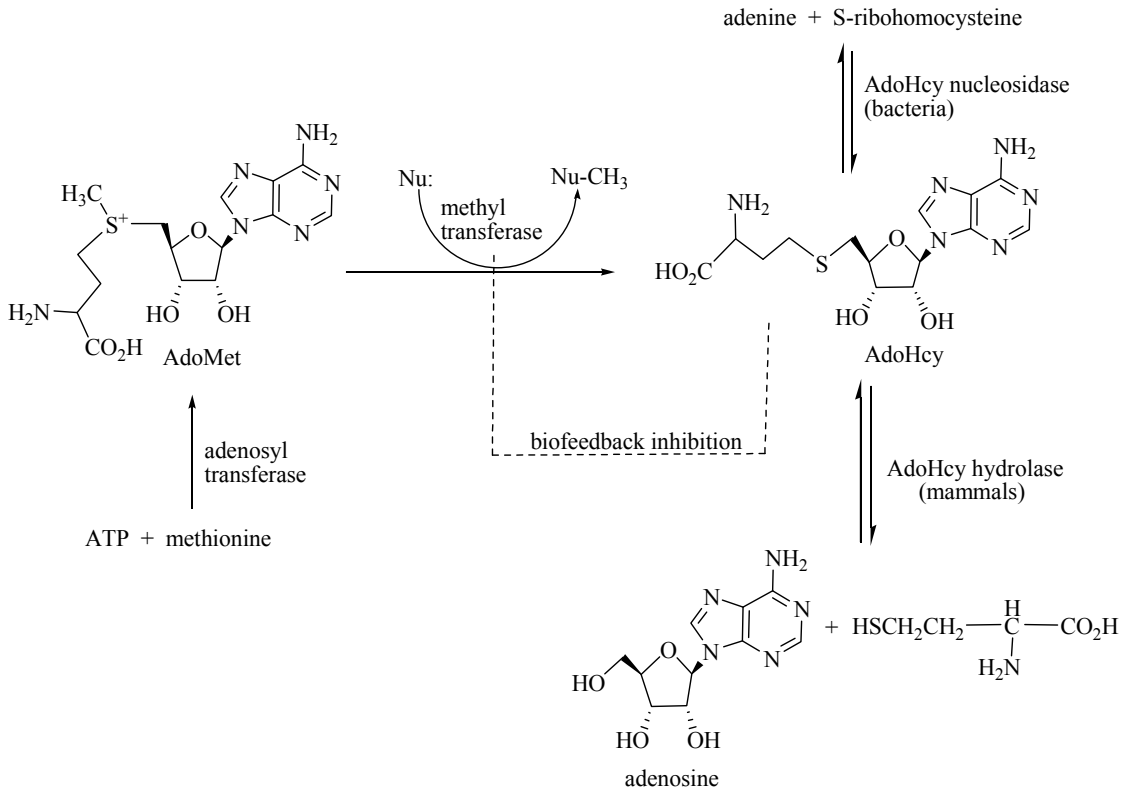
(ii) $ppN(pN)_n + pppG \rightleftharpoons G(5')pppN(pN)_n + PP_i$

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

## Inhibition of AdoMet methylation as a mechanism for antiviral drug design and discovery

Since the first discovery of *S*-adenosyl-L-methionine (AdoMet),[32] a large number of AdoMet-dependent methyltransferases have been extensively studied.[33] In the early 1980s, Borchardt[1] investigated AdoMet-dependent methyltransferases and found they were inhibited by AdoHcy, the AdoMet product (Scheme 1). Attention then turned to the AdoHcy catabolic enzyme, AdoHcy hydrolase. As seen in Scheme 1, AdoHcy hydrolase catalyzes the reversible hydrolysis of AdoHcy to adenosine and homocysteine in mammals, and thus controls the intracellular levels of the essential metabolites AdoHcy, adenosine and homocysteine. Cellular inhibition of the hydrolase leads to increased levels

of AdoHcy. This increased level of AdoHcy causes bio-feedback inhibition (product inhibition) of the essential AdoMet bio-methylation reactions.[35,42] Therefore, increasing the cellular concentration of AdoHcy by inhibition of AdoHcy hydrolase, results in limiting metabolic processes requiring methylations (for example, mRNA maturation) and blocking the chain of the viral replication.[22a] As a consequence, inhibitors of AdoHcy hydrolase can function indirectly on the viral mRNA methylation reactions by focusing on the steps of the mechanism by which AdoHcy hydrolase proceeds. Several approaches have lent themselves to inhibitor design as a means to potential antiviral chemtherapeutic agents.[43,44]




**Scheme 1. AdoMet-dependent methyltransferases and AdoHcy metabolism.**

In that direction, and referring to Scheme 1, inhibitor categories have been designated: direct and indirect.[1] Direct inhibitors, such as analogs of AdoMet and AdoHcy, function on a particular methyltransferase. They exert their effects by binding to the active site (AdoMet analogs) of the methyltransferase[34] or the AdoHcy inhibitory binding locale site of the transferases. The indirect inhibitors block the biosynthesis of AdoMet (that is via adenosyltransferase) or AdoHcy metabolism (that is, AdoHcy hydrolase, AdoHcy nucleosidase).

In the first category, Borchardt and co-workers[36,37] have made many important contributions with AdoHcy analogs and their effects in viral (Newcastle and vaccinia)

AdoMet-dependent mRNA (guanine-7)-methyltransferase. Their analogs focused on modifications in the amino acid, base and sugar moiety areas of AdoHcy.

Among of the amino acid modified analogs (Figure 6), it was found that there are important requirements for manifesting into inhibitors of virion mRNA (guanine-7)-methyltransferase: (i) with modifications of the sulfur atom (AdoHcy sulfone and AdoHcy sulfoxide) showed reduction (but less) of AdoHcy inhibitory properties; (ii) the *S* chirality of the amino acid (that is C-9') is necessary for inhibition;[38] (iii) the amino acid amine and carboxyl groups are necessary for binding to the methyltransferase; and, (iv) the two carbon atom distance between the sulfur atom and α-carbon of the amino acid is crucial for successful interaction with the methyltransferase. From these results, it is noteworthy that the virion mRNA (guanine-7)-methyltransferase appears capable of accommodating changes at the sulfur atom of AdoHcy.[36a]

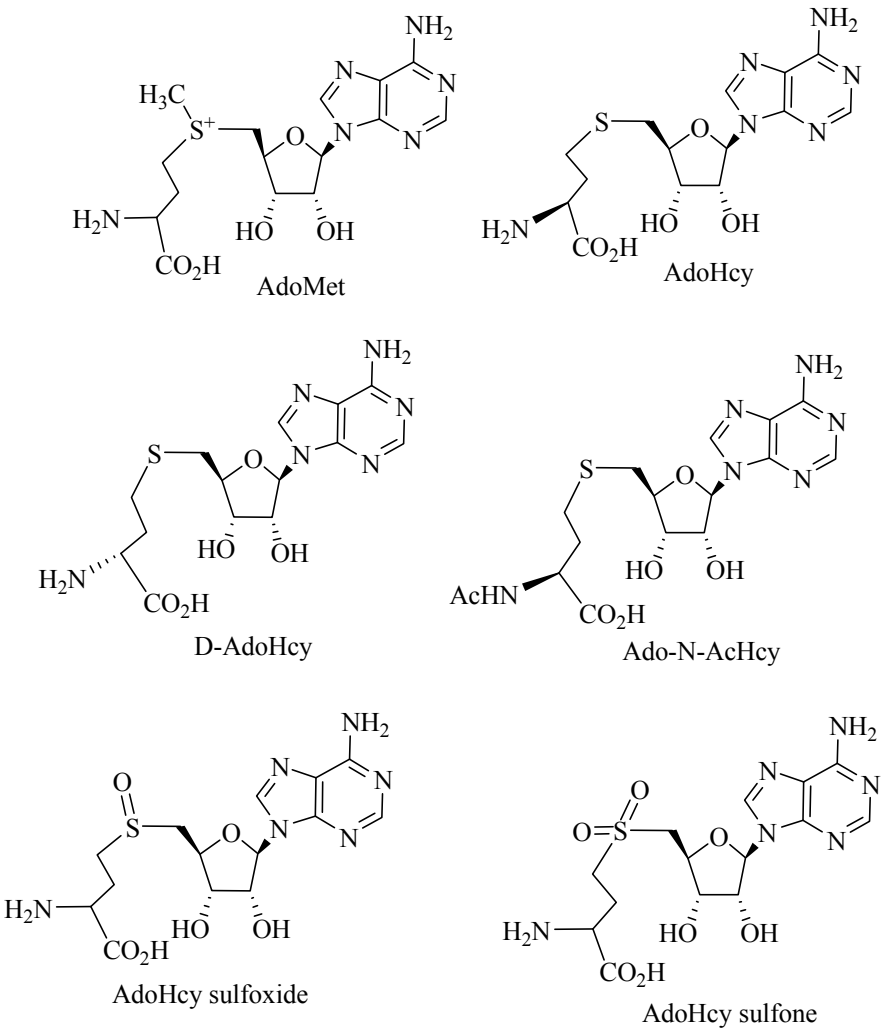



**Figure 6. Structural analogs of AdoHcy based on amino acid modifications.**

The base-modified analogs (Figure 7) of AdoHcy indicated that only $N^6$-methyl-AdoHcy and 3-deaza-AdoHcy show significant inhibitory activity toward the vaccinia (guanine-7)-methyltransferase. The other base-modified analogs displayed little or no inhibitory activity toward this enzyme.[36b] For the Newcastle disease viral transferase, 7-deaza-AdoHcy (TubHcy), $N^6$-methyl-AdoHcy, and 8-aza-AdoHcy were potent inhibitors. It was also found that replacement of the heterocyclic base (adenine) of AdoHcy with a

pyrimidine unit (cytosine or uracil) or a guanine base, resulted in complete loss of inhibitory activities towards the mRNA (guanine-7) methyltransferase.[36a]

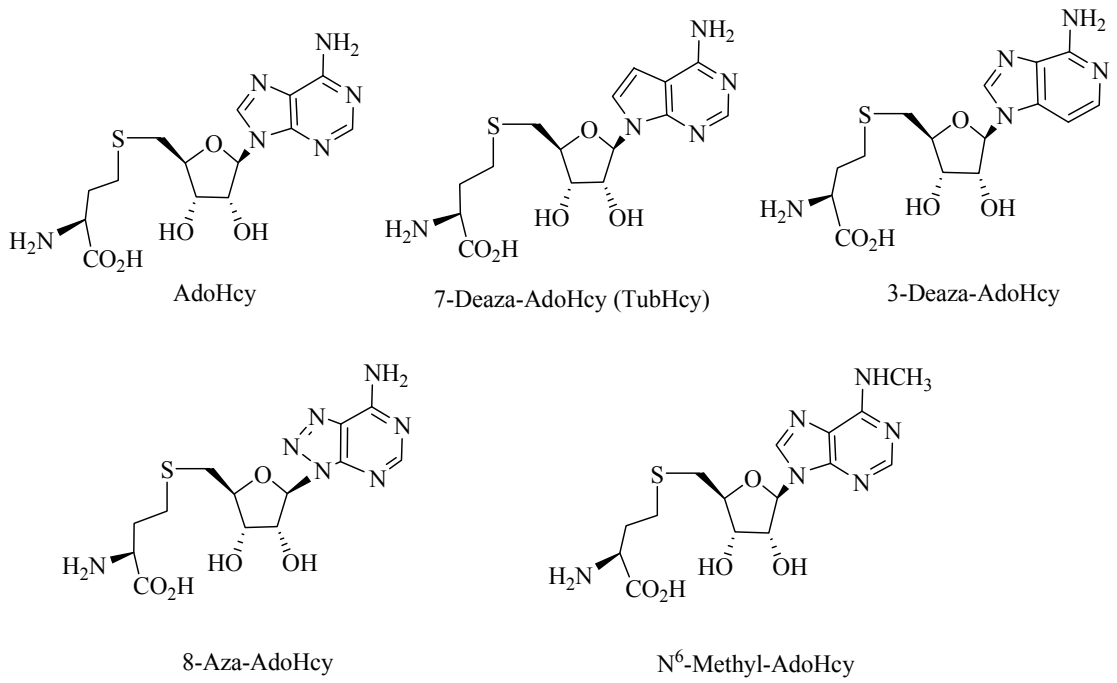



**Figure 7. Base-modified AdoHcy analogs.**

In the sugar-modified analog group (Figure 8), only the carbocylic AdoHcy (AriHcy) had significant inhibitory ability on the vaccinia (guanine-7)-methyltransferase.[36b] Other sugar-modified AdoHcy analogs (for example, 2'-deoxy-AdoHcy or 3'-deoxy-AdoHcy) are substantially less active or lose their inhibitory activity toward the vaccinia (guanine-7)-methyltransferase.[36b,37b] Thus, the roles of the 2'- and 3'-hydroxyl groups of the AdoHcy are very significant for the binding AdoHcy derivatives to the active site of the vaccinia methyltransferase.

On the other hand, for the Newcastle disease (guanine-7)-methyltransferase,[38a] both 2'-deoxy-AdoHcy and 3'-deoxy-AdoHcy exhibit some inhibitory activity ($K_i$ = 26 ±8 pM and $K_i$ = 78±3 pM, respectively, where $K_i$ represents the inhibition constants for the methyltransferase). This observation shows that the roles of these AdoHcy functional groups are not stringent in the NDV methyltransferase as they are with the vaccinia system. Johnson and co-workers[39] later reported the synthesis of 4'-methyl-AdoHcy. However, its biological activity remains unreported.

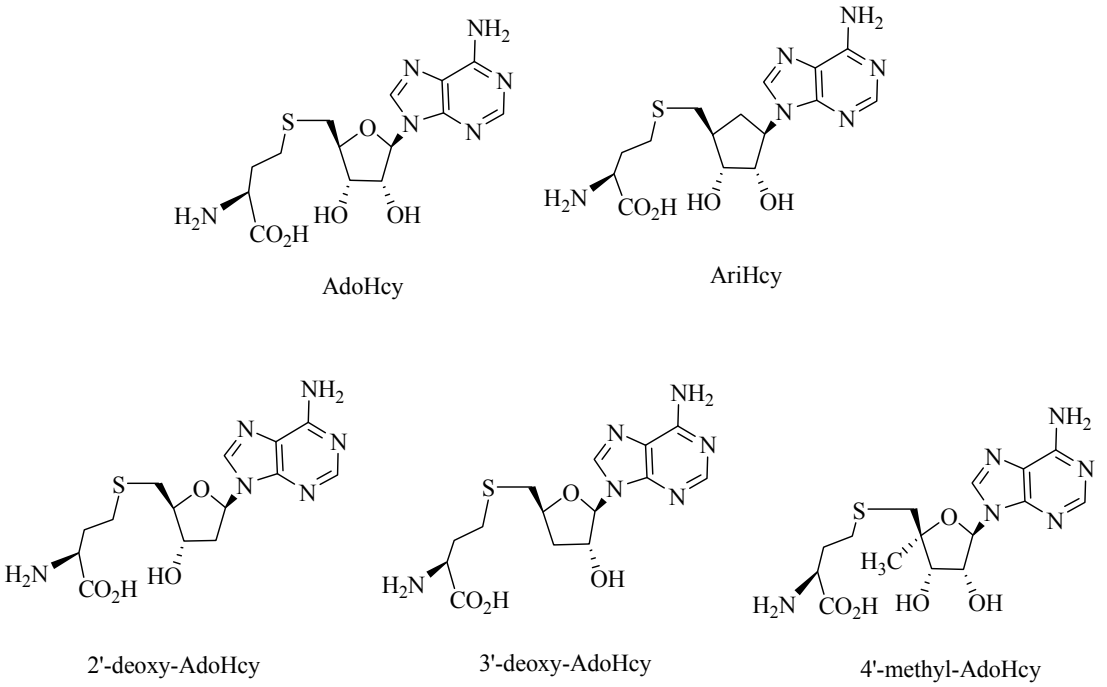


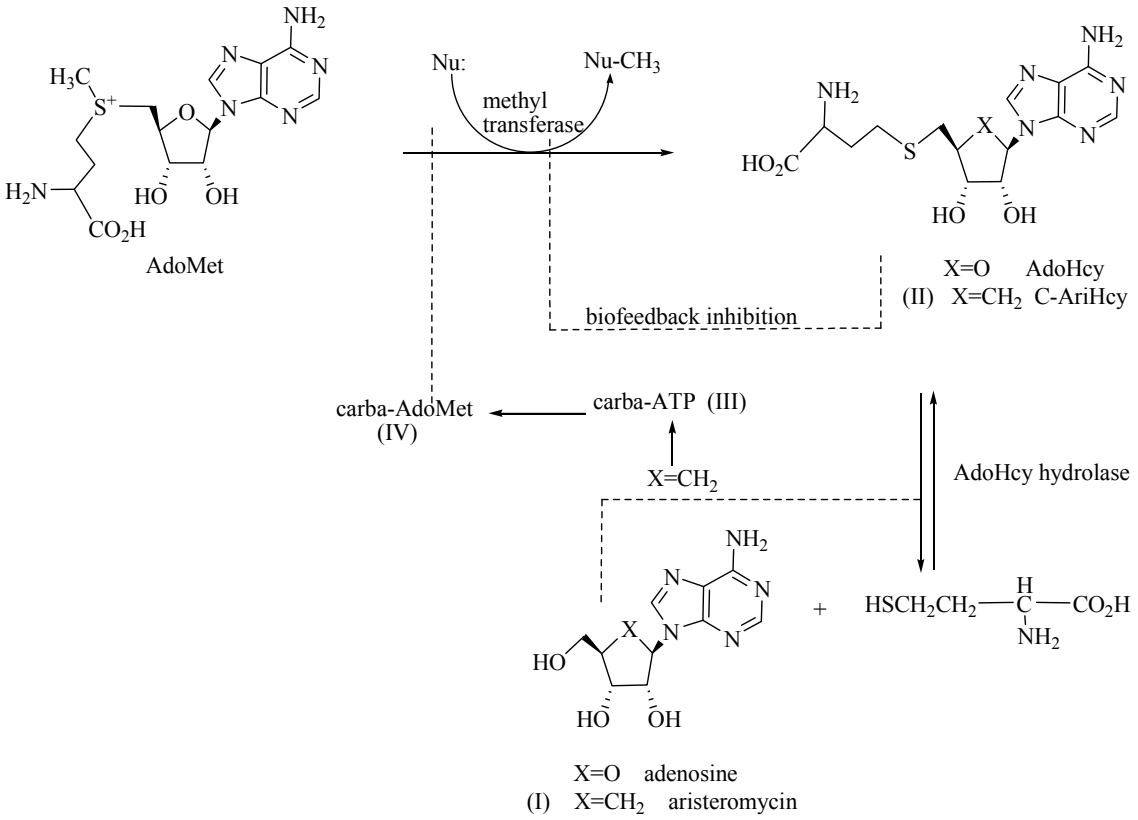

**Figure 8. Sugar modification analogs of AdoHcy.**

Among the indirect inhibitors (Scheme 1), two major designs exist: (i) blocking the biosynthesis of AdoMet by inhibiting the adenosyltranferase; and, (ii) preventing the catabolism of AdoHcy by inhibiting AdoHcy hydrolase or AdoHcy nucleosidase. Of

these, most research has concentrated on designing and synthesizing inhibitors of the catabolism of AdoHcy. To be sure, the pervasiveness of AdoHcy hydrolase in yeasts, plants, birds, and mammals,[40] has stimulated studies in this regard. On the other hand, the enzyme AdoHcy nucleosidase, has only been found in bacteria.[40b, 41]

From these investigations, De Clercq and co-workers[45] have shown that a close correlation exists between the antiviral potency of Ado-derived analogs and their inhibitory effects on AdoHcy hydrolase. Logically, Borchardt and co-workers[46] also have found that a close correlation exists between the antiviral potency of the nucleosides and their ability to increase the cellular levels of AdoHcy. As a result, inhibitors of AdoHcy hydrolase have exhibited broad-spectrum antiviral activities,[45a,47] by disrupting the essential viral mRNA methylation processes.[42e-f.]

Among the AdoHcy hydrolase inhibitors, the adenosine analogs, (-)-Ari[17d,19] and (-)-NpcA[20] have exhibited broad and significant antiviral activities,[44] that correlate with their inhibitory effects of AdoHcy hydrolase.[45a,48] Reviewing Scheme 2 clarifies the inhibiting mechanism of Ari (I). A similar mechanism exits for NpcA and other analogs of adenosine.[42c] Aristeromycin's effect results from its conversion to carbocyclic AriHcy (C-AriHcy, II), which functions as a product inhibitor (just like AdoHcy) of AdoMet-dependent methylations and is responsible for its antiviral characteristics.



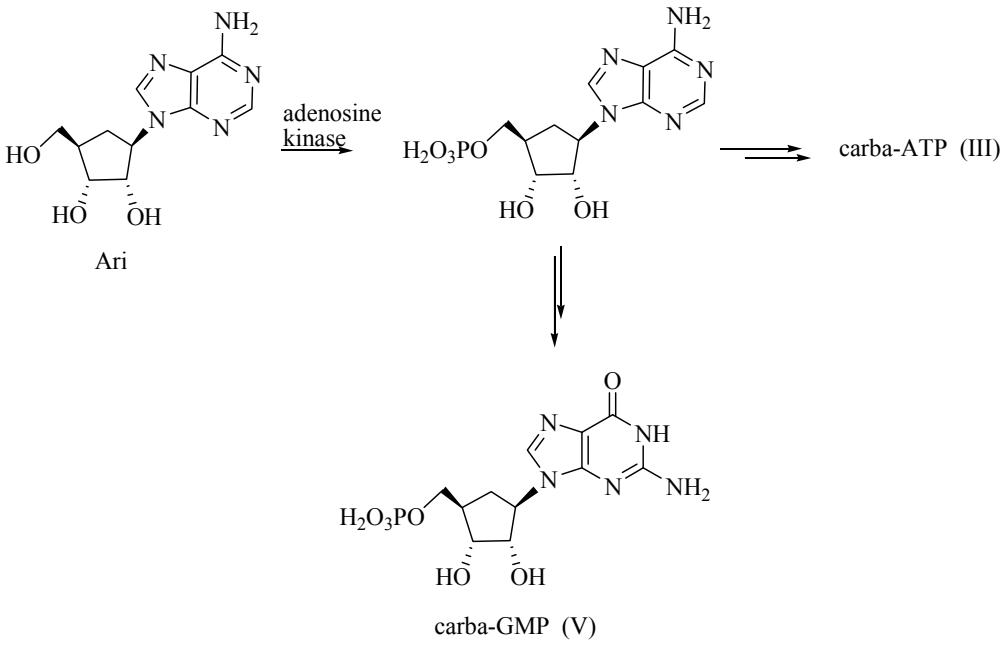

**Scheme 2. The principle of aristeromycin as inhibitor in AdoMet methylation reaction.**

Scheme 2 demonstates another relevant metabolic pathway for Ari: that is, it can be phosphorylated to carbocyclic ATP (III) by adenosine kinase. Subsequently, the latter compound is converted to carbocyclic AriMet (IV) under the catalysis of AdoMet synthetase.[42c,49] Then, carbocyclic AriMet (IV), the counterpart of AdoMet, can bind to the active site of the methyltransferase and inhibit the enzyme.

At the same time, these metabolites possess undesirable side effects for drug discovery, such as toxicity, both *in vitro* and *in vivo* testing, which preclude their clinical applications. Consequently, studies concerning the source of toxicity of carbocyclic

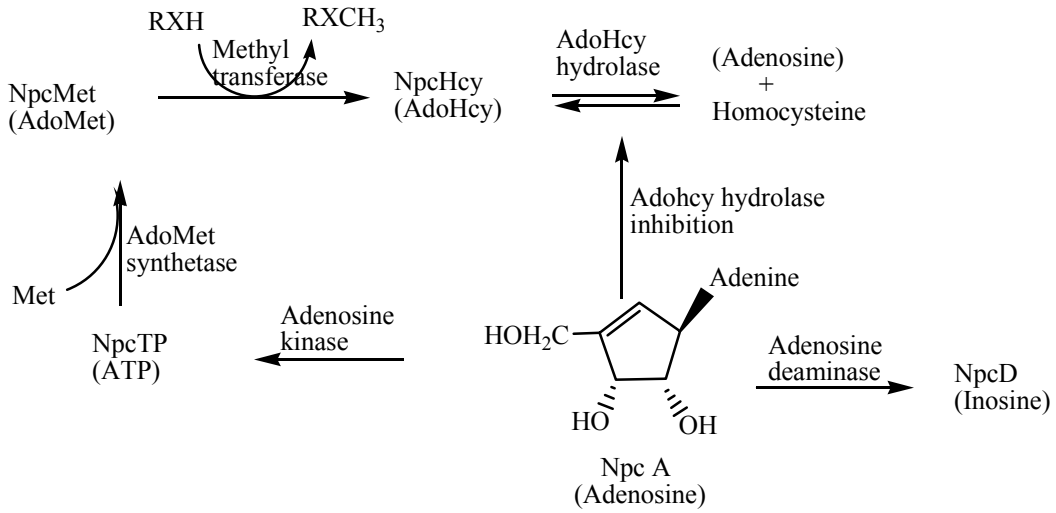
analogs of adenosine become important to the development of this series as antiviral agents.

The possible cause for this toxicity may exist in its metabolites: carba-ATP (III) (Scheme 2) and/or carba-GMP (V) (Scheme 3).[50] Carba-ATP (III), may replace ATP in uninfected cellular processes requiring the latter nucleotide for growth and/or it may be incorporated into the host DNA cells, leading to mutations. In the case of carba-GMP (V),[42c,51] that is formed from the monophosphate of Ari catalyed by AMP deaminase and other enzymes, inhibition of cellular hypoxanthine-(guanine) phosphoribosyltransferase can occur.[52] This enzyme is part of the purine salvage pathway and its inhibition can lead to complete blockade of the availability of hypoxanthine and guanine essential for disease free cellular metabolism.[52,53]




**Scheme 3. Metabolic pathway of Ari.**

For NpcA, Marquez and co-workers[54] and, Glazer and co-workers[55] found that NpcMet, the AdoMet-like metabolite of NpcA, inhibits cellular mRNA methylation (HT-29 cells), producing toxic effects (Scheme 4). Until now, there is no direct evidence for the effect of NpcMet on virus mRNA methyltransferase. On the other hand, there are no studies for NpcTP, as a source of NpcA toxicity. Glazer's laboratory[55] also found that NpcTP, the counterpart of ATP, forms NpcMet under the catalysis of AdoMet synthetase and is minimally incorporated into mRNA.




**Scheme 4. The metabolism of Npc A.**

From the metabolic studies above, adenosine kinase plays a major role in the toxicity of Ari and NpcA by promoting formation of the 5'-nucleotides. Thus, in order to develop potencial inhibitors of AdoHcy hydrolase based on Ari and NpcA, their susceptibility to adenosine kinase must be eliminated/reduced.

Guided by the conclusion that elimination/reduction of the effects by adenosine kinase (due to the toxicity caused by this adenosine kinase), inhibitor design has fallen into three categories: (i) analogs of AdoMet/AdoHcy; (ii) variation of the heterocyclic base[56] of Ari and NpcA; and, (iii) various cyclopentyl modifications (cyclic and acyclic).[57] Many research groups have made important contributions to this area (Figure 9). For example, Montgomery and co-workers[58] synthesized the 3-deaza Ari. Marquez and his colleagues[59] designed and synthesized 3-deaza NpcA. Borchardt's laboratory[60] synthesized DHCeA (dihydroxycyclopentenyladenine) and its saturated counterpart, DHCaA. The Schneller group designed and synthesized 5'-noraristeromycin and related

coumpounds.[61] Finally, acyclic nucleosides, such as Acycliovir[57g] and Penciclovir,[57h-i] were synthesized and reported as potent antiviral agents. In all of these examples, the aim is to increase the selectivities toward AdoHcy hydrolase (it means that these modified compounds lack substrate activity toward these two enzymes: adenosine kinase and adenosine deaminase) and reduce the nucleotide-related toxcities. This goal was accomplished by the secondary generation AdoHcy hydrolase inhibitors (compared with their corresponding parent compounds).

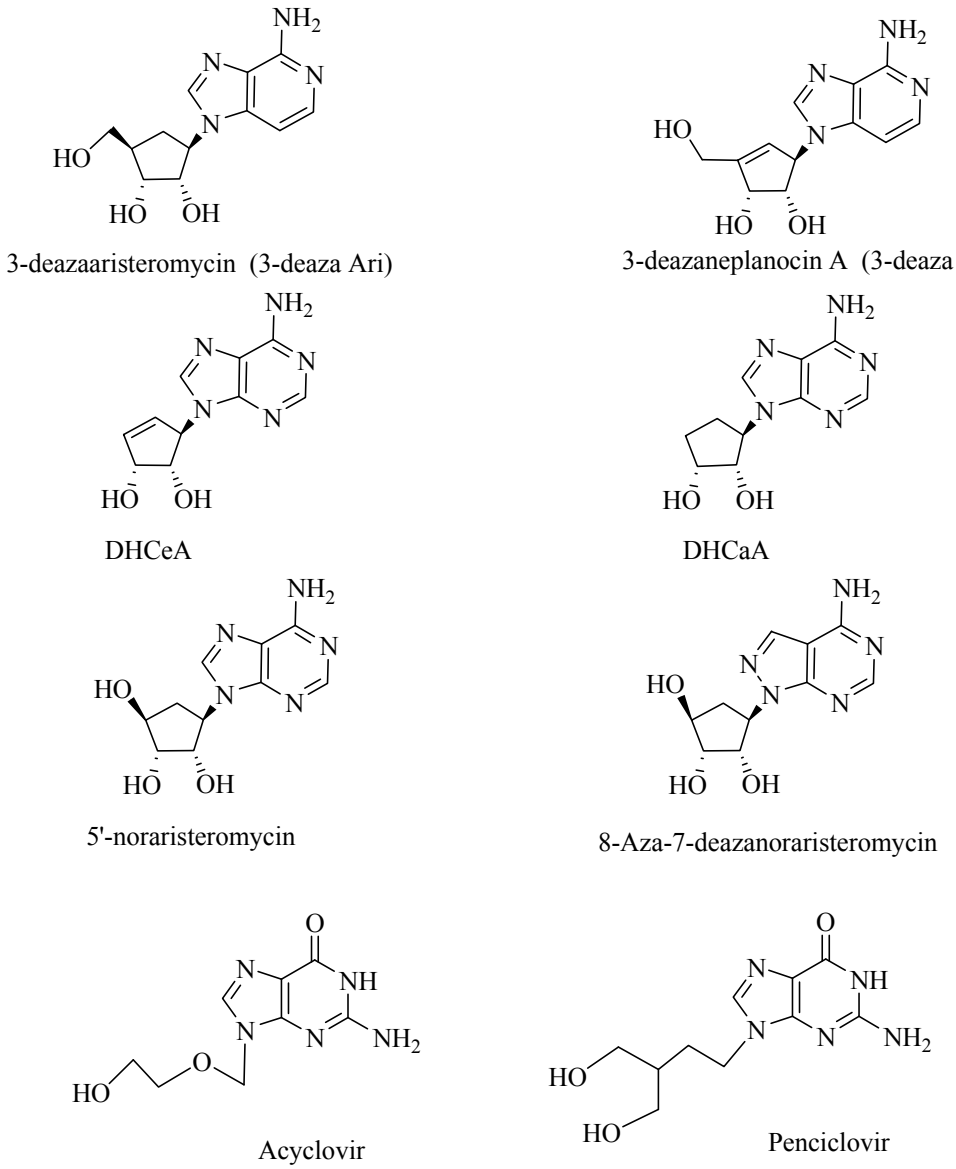



**Figure 9. The lead inhibitors of AdoHcy hydrolase.**

Very little effort has been devoted to the aforementioned category i, analogs of AdoMet/AdoHcy. This dissertation research addresses this situation by the design and synthesis of analogs of AdoMet/AdoHcy.

**Direct inhibitors targets: analogs of sinefungin**

It is known that inhibition of cap methylation of virus mRNA is the basis for two anti-infective strategies: (i) designing and developing inhibitors of AdoHcy hydrolase, which indirectly block the virus replication by the intracellular accumulation of AdoHcy; and, (ii) direct AdoMet methyltransferase inhibition by analogs of AdoMet/AdoHcy. This latter category can be addressed by screening structural analogues of AdoMet, such as sinefungin, AdoazaMet, MeAzaAdoMet, and carbocyclic AdoazaMet (Figure 10). Within this group, the neutral AdoazaMet derivative was first designed and synthesized by Minnick and co-workers.[62] Latter, Blackburn's group accomplished the total synthesis of AdoazaMet and MeAzaAdoMet.[63] It was found that AdoazaMet can act as a substrate of the AdeMet-dependent methylation reactions and can serve as a competitive inhibitor for the methyltransferases.[64] Recently, the Schneller research group described the total synthesis of the carbocyclic AdoazaMet.[65] The biological activities of these compounds have been studied by Shuman and co-workers.[28c] They found that, based on the cellular cap-methylating enzyme (Ecm1, the smallest known cap methyltransferase), the inhibitory effects of sinefungin were the $IC_{50}$ = 1.5μM ($IC_{50}$ is the half maximal inhibitory concentration of a substrate), while AdoazaMet and carbocyclic AdoAzaMet were relatively weak inhibitors of this Ecm1 (100 and 35μM, respectively).

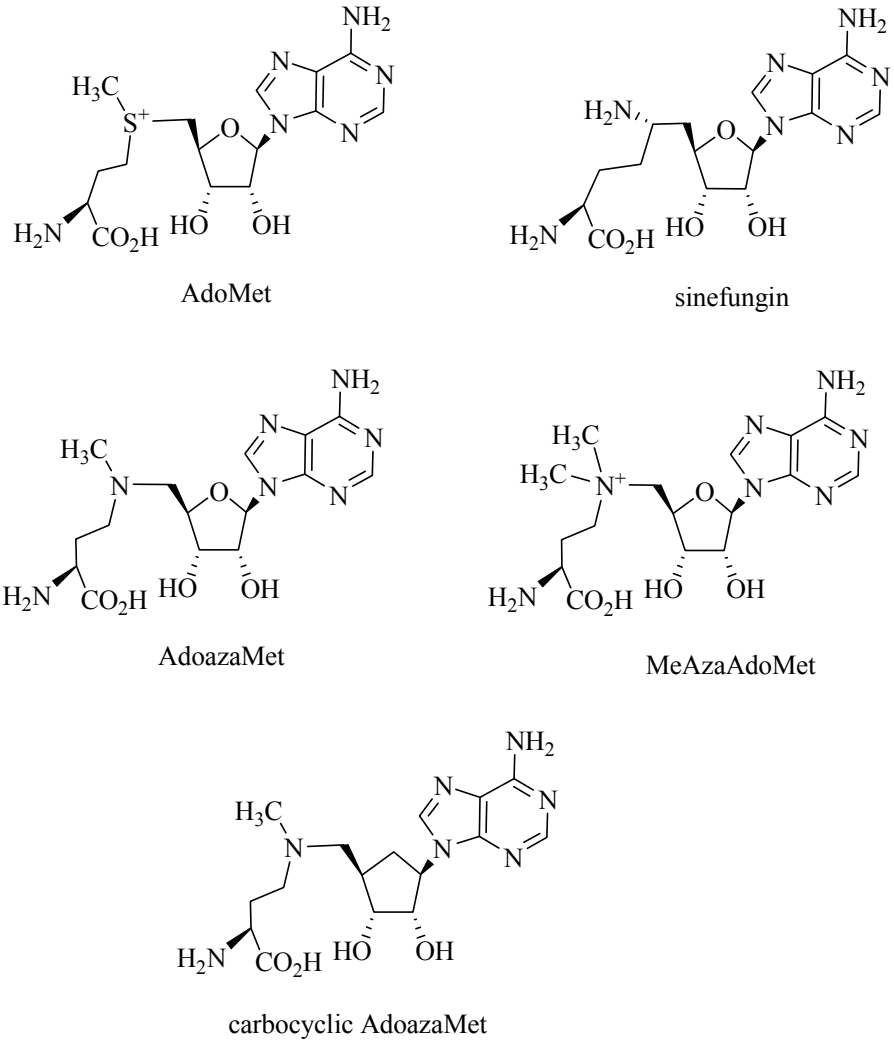



**Figure 10. Structural analogs of AdoMet.**

Among these related derivatives, sinefungin has attracted the most interest in the past few decades. It is known that sinefungin is an efficient inhibitor of cap methylation *in vitro* and can inhibit the growth of diverse viruses, fungi and protozoa.[66] Furthermore, recently, sinefungin was found to exhibit selectivity in inhibiting the yeast cap methyltransferase *versus* that of the human enzyme *in vivo*.[67]

Sinefungin, a natural complex nucleoside,[68] was first isolated from the cultures of *Streptomyces griseolus*,[69] and from that of *Streptomyces incarnatus*.[70] The structure of this nucleoside is very close to that of AdoMet (Figure 10).

Since the discovery of sinefungin, its biological activities have been thoroughly studied, including antifungal,[71,72] antitumor, antiparasitic and antiviral activities.[36b,73] The nature of these biological activities results from the inhibition of a variety of AdoMet-dependent methyltransferase enzymes.[74] Moreover, it was reported that sinefungin is a selective inhibitor of virus-encoded cap methyltransferases.[74c] Unfortunately, the clinical use of sinefungin has been severely precluded by its toxicity in *in vivo* assays.[75] To seek ways to eliminate the undesired side effects, the past decade has seen the total synthesis of sinefungin[76] and the preparation of structurally modified derivatives (side chain, sugar and base unit)[77] conducted for in-depth toxicity mechanistic studies. To pursue sinefungin, Moffatt and co-workers were the first to complete a total synthesis, but they could not separate the C-6' epimers (Figure 11).[76a] In 1991, Barton and co-workers published a convenient synthesis of natural sinefungin and its C-6' epimer by radical coupling reactions.[76f] Later, Fourrey's group succeeded in synthesizing sinefungin and separating its C-6' epimer by a practical method different from that of Moffatt's attempts.[76b] Rapoport and co-workers adopted another stereoselective appoach for synthesizing sinefungin and confirmed its C-6' chiral center as the *S* configuration by X-ray crystallographic analysis method.[76e]

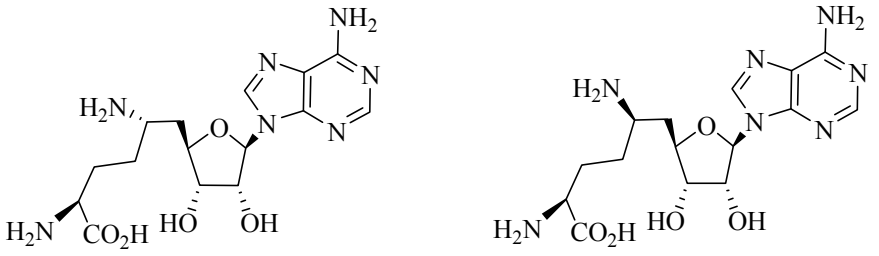



**Figure 11. Sinefungin and its C-6' epimers.**

Later, Rapoport's group reported the total synthesis of two analogs of sinefungin: (*S*)-6'-methyl-6'-deaminosinefungin and 6'-deaminosinefungin (Figure 12).[77f] Almost concurrently, Secrist and co-workers reported the synthesis of a series of analogs of sinefungin,[77b] for example, C-5' chain-extended adenosine derivatives related to sinefungin. Robert-Gero and colleagues synthesized a series of side-chain analogues of sinefungin and found that all completely lost activities.[77d] These studies indicated that the terminal amino and carboxyl groups, connecting at C-9' in (*S*) configuration, are necessary for maintaining the biological activities of the parent compound.

In 1990, Fourrey's group[77c] succeeded in preparing three analogues of sinefungin, and recently reported the total synthesis of higher homologs of sinefungin by a radical-based strategy.[77j] These latter studies lack any biological data.

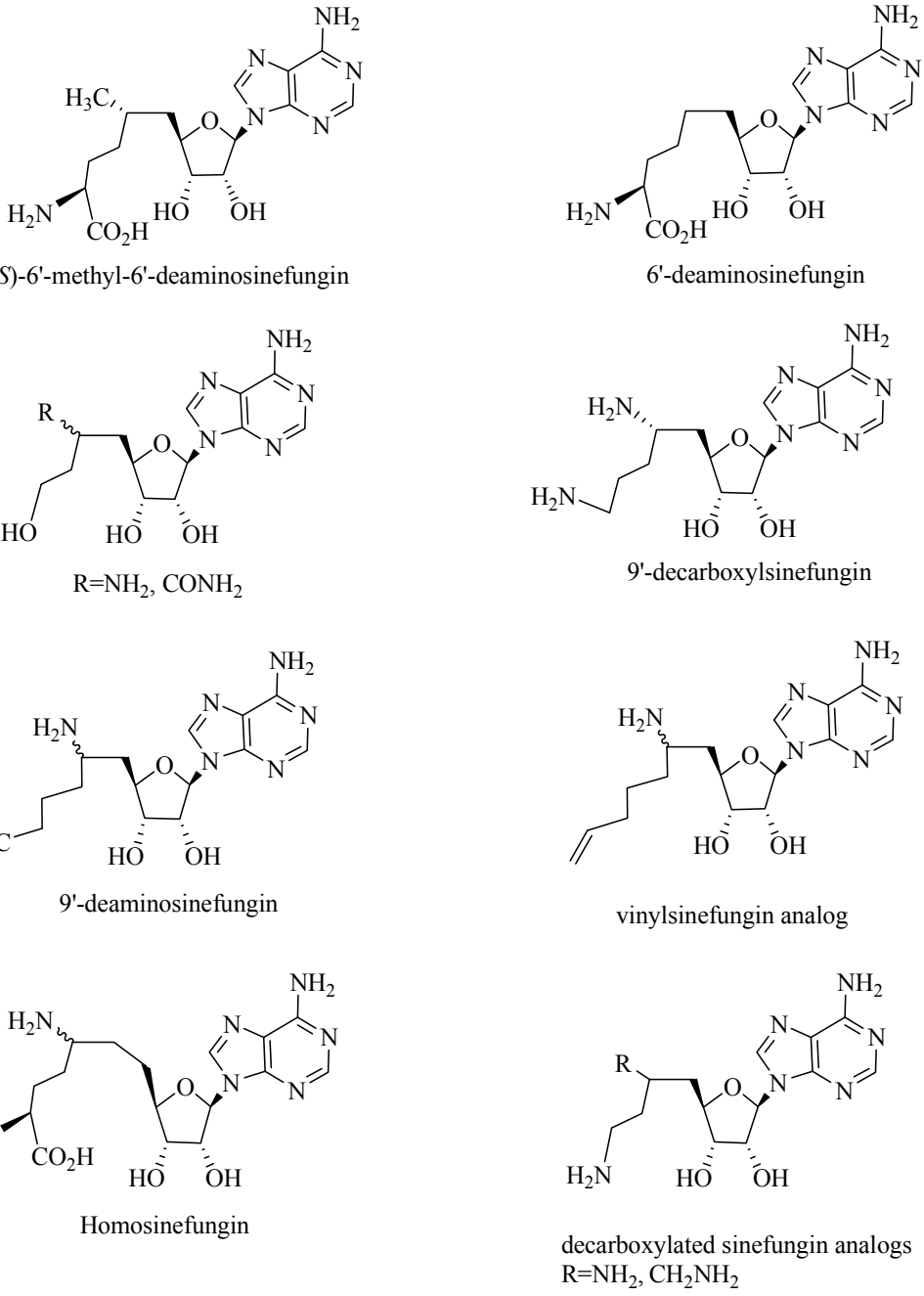
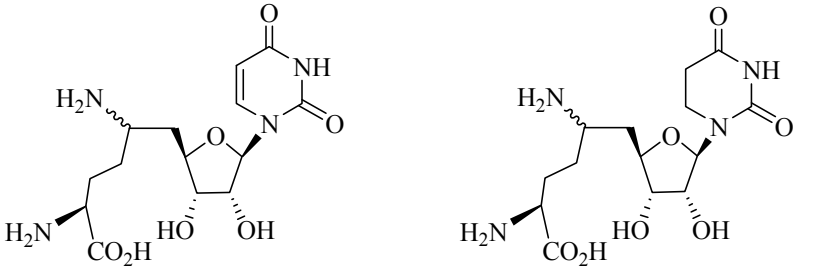



**Figure 12. Some nucleoside dervatives of sinefungin: modification on the side-chain.**

The Ghosh laboratories were the first to use efficient asymmetric synthetic methods to construct the two stereogenic centers (C-6' and C-9') of sinefungin.[76f-g]

Almost concurrently, the Fourrey group reported the first sugar modified analog of sinefungin: carbocyclic sinefungin.[77i] This grew out of the known bio-properties of carbocyclic nucleosides, whether naturally occurring or chemically synthesized.[78]

In addition to seeking the side-chain modified derivatives of sinefungin, changing the heterocyclic base is relevant to guiding this dissertation project. In that regard, Barton and co-workers reported the total synthesis of uracil derivatives of sinefungin (Figure 13).[77e] When compared to sinefungin, biological activities of these derivatives were dramatically reduced, as were their affinities for the methyltransferases. These observations point to the significance of the adenine portion of sinefungin for its biological properties.




uracil analog of sinefungin

dihydrouracil analog of sinefungin

**Figure 13. Base modified derivatives of sinefungin.**

Based on the various biological activities of sinefungin and its undesirable side effects (*in vitro* and *in vivo*), and its unique mechanism of action at viral mRNA methyltransferase level, the structurally related derivative target **I** (Figure 14), where the 6'-amino of carbocyclic sinefungin is replaced by the *iso*electronic hydroxyl group,

become a focus for this dissertation. Also, preliminary work on a new method towards carbocyclic sinefungin is decribed.

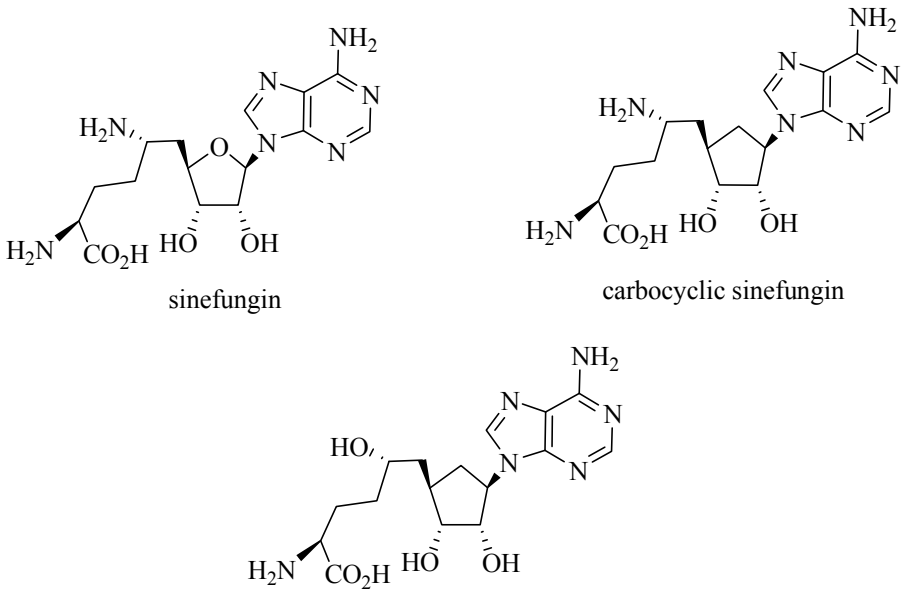
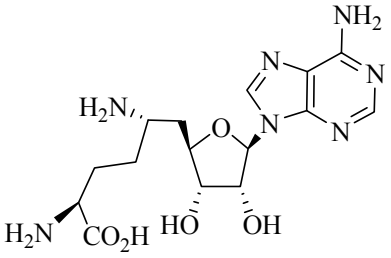
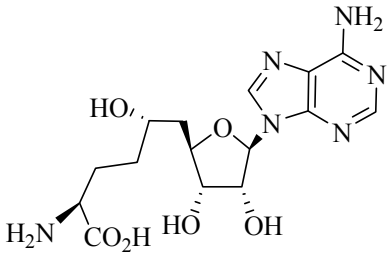



**Figure 14 Initial targets of dissertation research.**

For comparative purposes, target **II** (Figure 15) was seen as a possible goal. For this purpose, the synthesis of its sugar segment became a feature of this dissertation research.



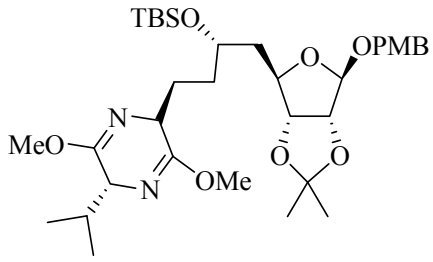
sinefungin



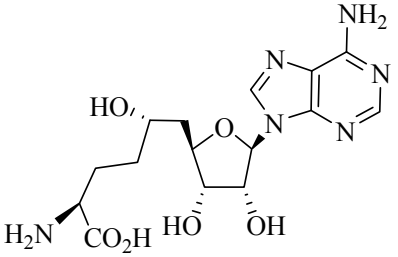
**target II**

**Figure 15. Initial target of dissertation research.**

In the meantime, due to the difference methods for coupling the heterocyclic base with the carbocyclic pseudo sugar and natural sugar, there was a challenge for target **II** to couple the heterocyclic base. Therefore, in the second project of this dissertation, the important precursor **2** toward target **II** was finished here (Figure 16).



**2**



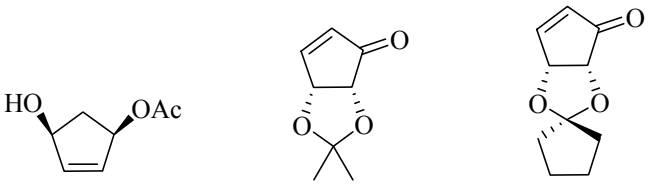
**target II**

**Figure 16. Important precursor 2 for target II.**

## CHAPTER 2

## SYNTHESIS OF THE IMPORTANT INTERMEDIATES FOR TARGET I AND CARBOCYCLIC SINEFUNGIN

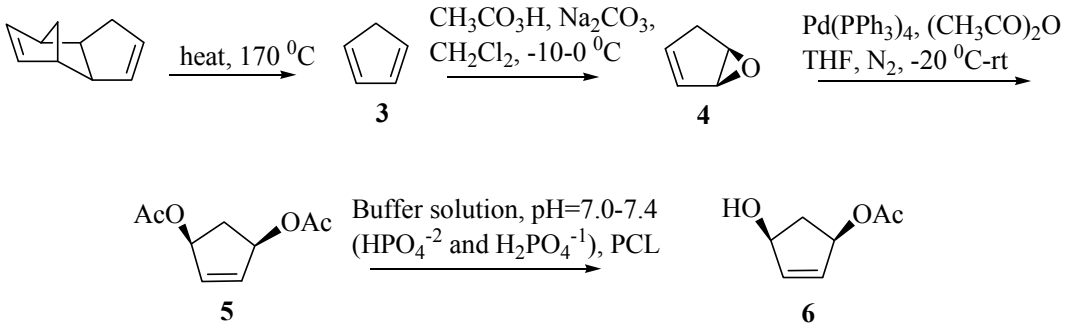
In order to pursue target **I** and carbocyclic sinefungin, three important intermediates (Figure 17) were needed in large scale.




**6** **11** **21**

**Figure 17. Important intermediates for the targets.**

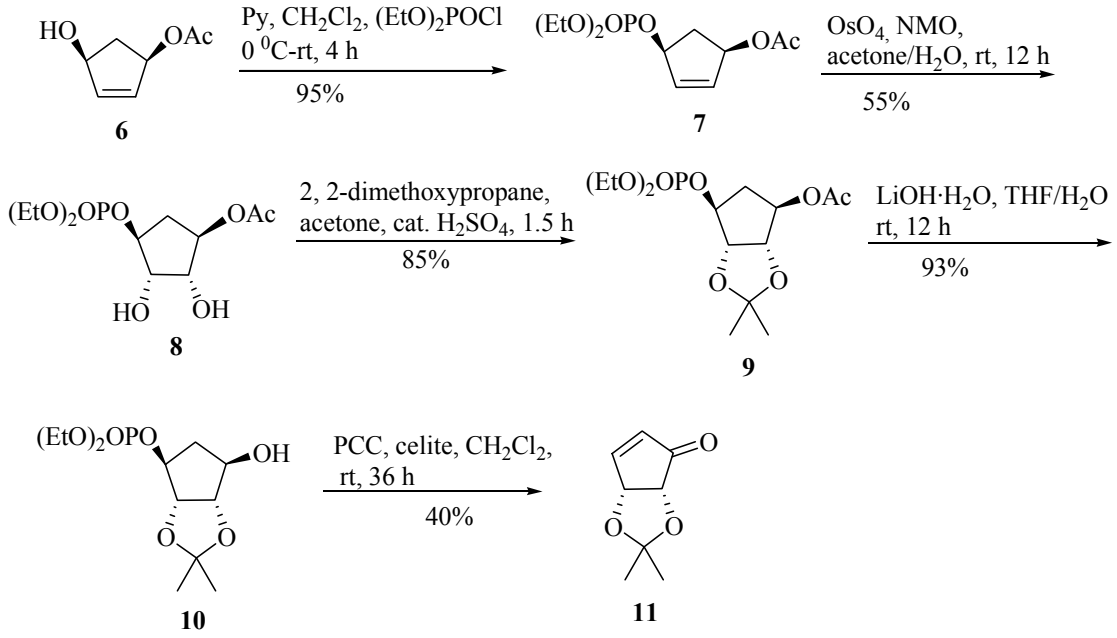
Compound **6**, (+)-(*1R,4S*)-4-hydroxy-2-cyclopentyl acetate, has served as a general building block for the synthesis of carbocyclic nucleosides in our laboratories and other groups.[61b,79] It can be obtained from the enzymatic-catalyzed chemical reaction of diacetate **5** (Scheme 5) with PCL (*Pseudomonas cepacia lipase*). The use of various enzymes in chemical reactions is now a common technique for the enantioselective synthesis of nucleosides.[80] This procedure has been developed more extensively in the Schneller laborotary.[61a,82]




**Scheme 5. Synthesis the important precursor 6.**

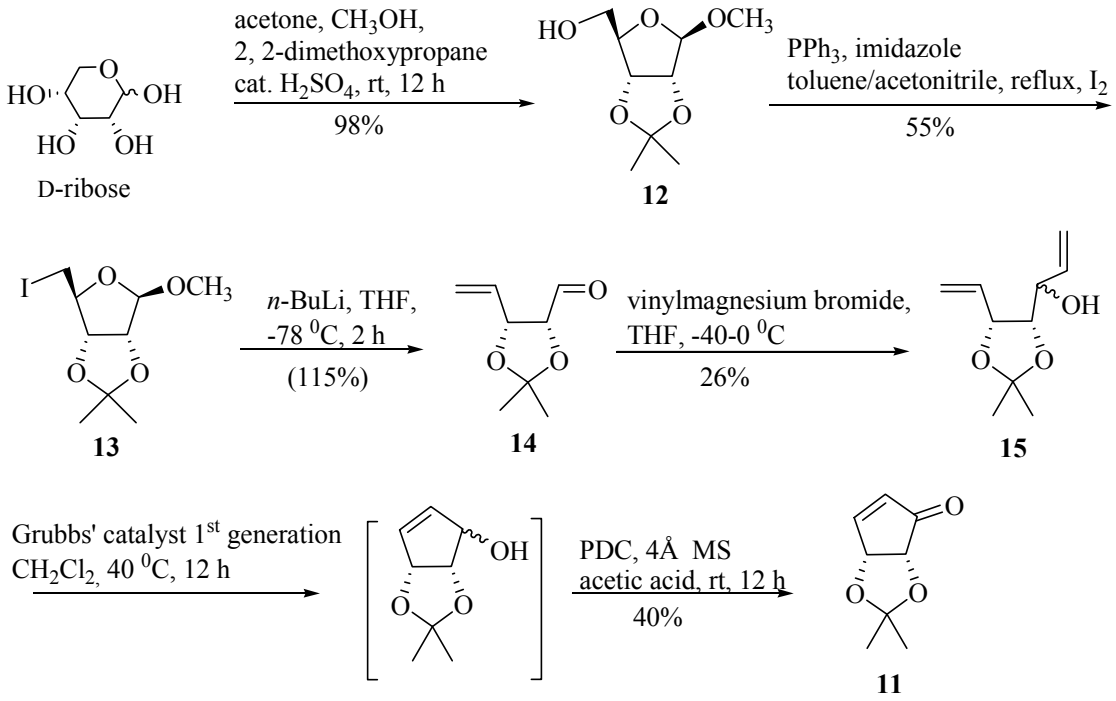
The requisite diacetate **5** was synthesized following reported procedures[81]: epoxidation of freshly prepared cyclopentadiene **3** gave epoxide **4**, that was, in turn, treated with *tetrakis*(triphenylphosphine)palladium(0) followed by subjecting the resultant palladio zwitterion to acetic anhydride.

Compound **6** permitted access to precursor **11** again using a procedure developed in our group and other groups (Scheme 6).[83] Thus, treatment of monoacetate **6** with diethylchlorophosphate provided **7**, whose the double bond was oxidized to the diol **8** under catalytic osmium tetraoxide and N-methylmorpholine N-oxide (NMO) conditions. After protecting the diol **8** with an *iso*propylidene group to compound **9**, lithium hydroxide hydrolysis formed **10**. Finally, oxidative-elimination by pyridinium chlorochromate (PCC) on **10** afforded compound **11**.[83b-c] The advantage of this method is that **11** can be obtained in large scale (more than 20 grams).




**Scheme 6. Synthesis of 11 from monoacetate 6.**

In addition to the above method, other groups developed alternative approaches to compound **11**.[84] However, some of these methods use extreme reaction conditions and the yields are not reproducible. Based on the previous procedures for the synthesis of **11**, the Schneller group developed another more efficient and practical method to **11** (Scheme 7).[65]

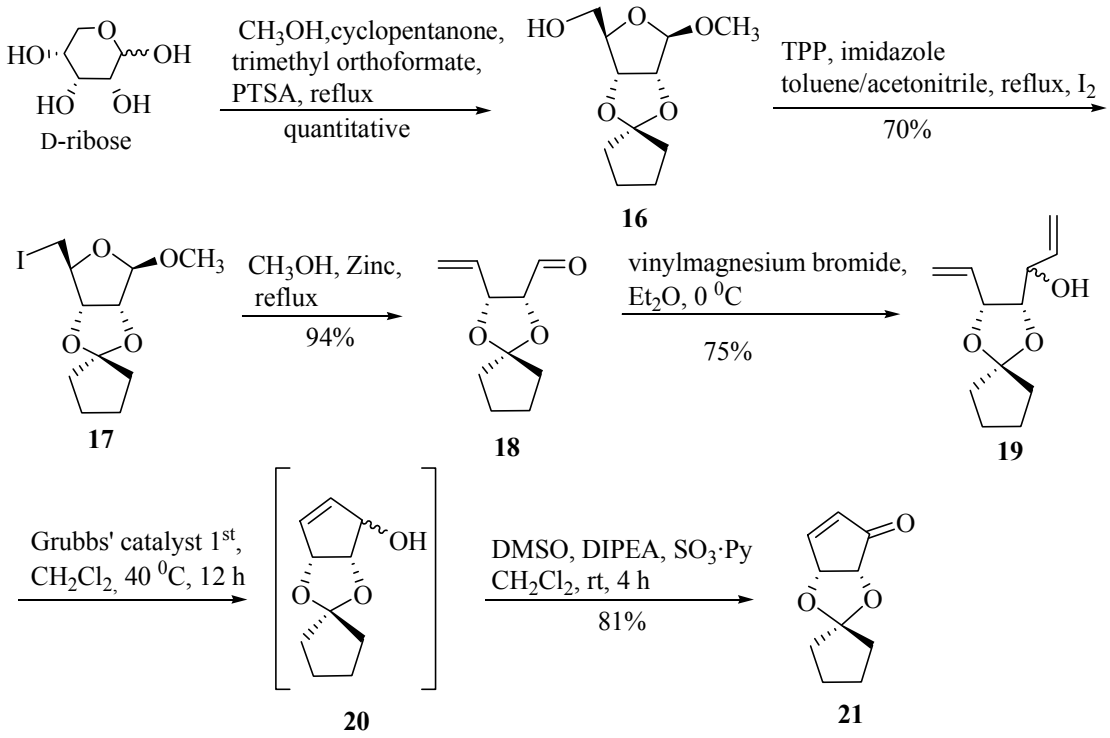



**Scheme 7. Another approach to form 11.**

This optimized method began with the commercially available D-ribose. Its protection using 2, 2-dimethoxypropane and methanol catalyzed by sulfuric acid afforded **12**, which was converted into the iodide **13**.[85] To secure the desired compound **14**, reductive elimination (Boord elimination) of **13** was used with *n*-butyllithium at low temperature.[86] Exposure of **14** to vinylmagnesium bromide yielded **15**. Ring-closing metathesis (RCM) of **15** catalyzed by Grubbs' 1st generation catalyst,[87] followed by oxidation of the intermediate allylic alcohol, provided **11**. The overall yield of **11** from D-ribose was very low, possibly due to instability and volatility of **14**.

In order to overcome this disadvantage in the synthesis of **11**, the cyclopentylidiene protected derivative (**21**) was proposed (Scheme 8).[88] In contrast to Scheme **7**, the first step in Scheme 8 replaced 2, 2-dimethoxypropane with

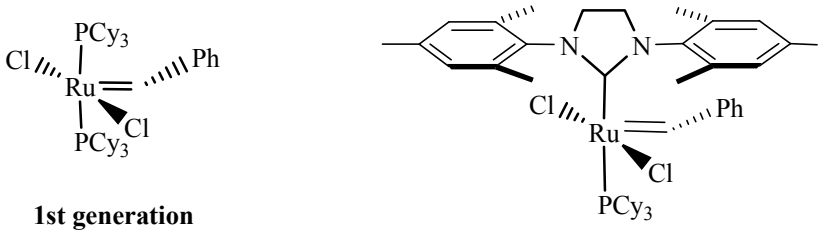
cyclopentanone. In addition, aldehyde **18,** which was more stable than **14**, was obtained by reductively cleaving **17** with activated zinc in hot methanol.[89] This eliminated the difficulty of scale-up associated with the *n*-butyl lithium step of Scheme 7. In this synthetic methodology, all the reaction conditions are mild and give good yields of **21,** up to 15 grams. The overall yield of this method was 40% for 5 steps.




**Scheme 8. Synthesis of the important precursor 21 from D-ribose.**

The key step for achieving the important intermediates (**11** and **21**) was the ring closing metathesis using the Grubbs' catalysts (Figure 18). In the past two decades, olefin metathesis has become the most important method for the formation of carbon-carbon single bonds.[90] The Grubbs' catalysts are the most prominent for this purpose.[91] Some of the ruthenium-based catalysts are commercially available, such as those designated as

Grubbs' 1st and 2nd generation. These agents are highly efficient catalysts, can tolerate various functional groups, and are stable to air, water, and acids.[92] These advantages make this class of catalysts attractive for practical applications in organic chemistry and related areas.




**1st generation**

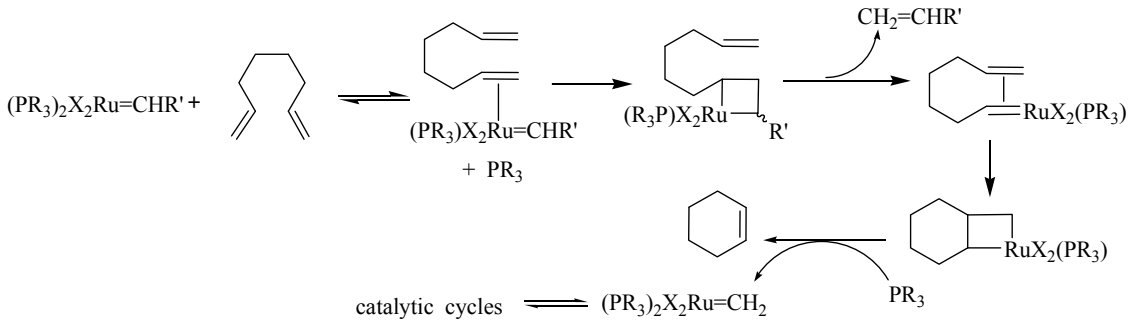
**2nd generation**

Cy=Cyclohexyl

**Figure 18. Grubbs' catalysts.**

The mechanism of olefin metathesis catalysis has been proposed via two routes: associative and dissociative.[87b] The latter one is considered the dominant mechanism (Scheme 9). During the catalytic cycle, one ligand (the phosphine) first dissociates from the ruthenium center. Then, ruthenium binds the olefin, forming a 16, 18, or 14-electron coordinate complex (Scheme 9, a 14-electron coordinate complex). This complex undergoes the metathesis to form the four-member ring at the ruthenium center, which follows with disconnection of one olefin from the system. The newly formed ruthenium center coordinates another part of the olefin and forms a new 16, 18, or 14-electron coordinate complex. Finally, after the metathesis (forming the four-member ring product),

the desired olefin is obtained and the catalyst can be regenerated by recombining the first phosphine ligand, and enters the next catalytic cycle.



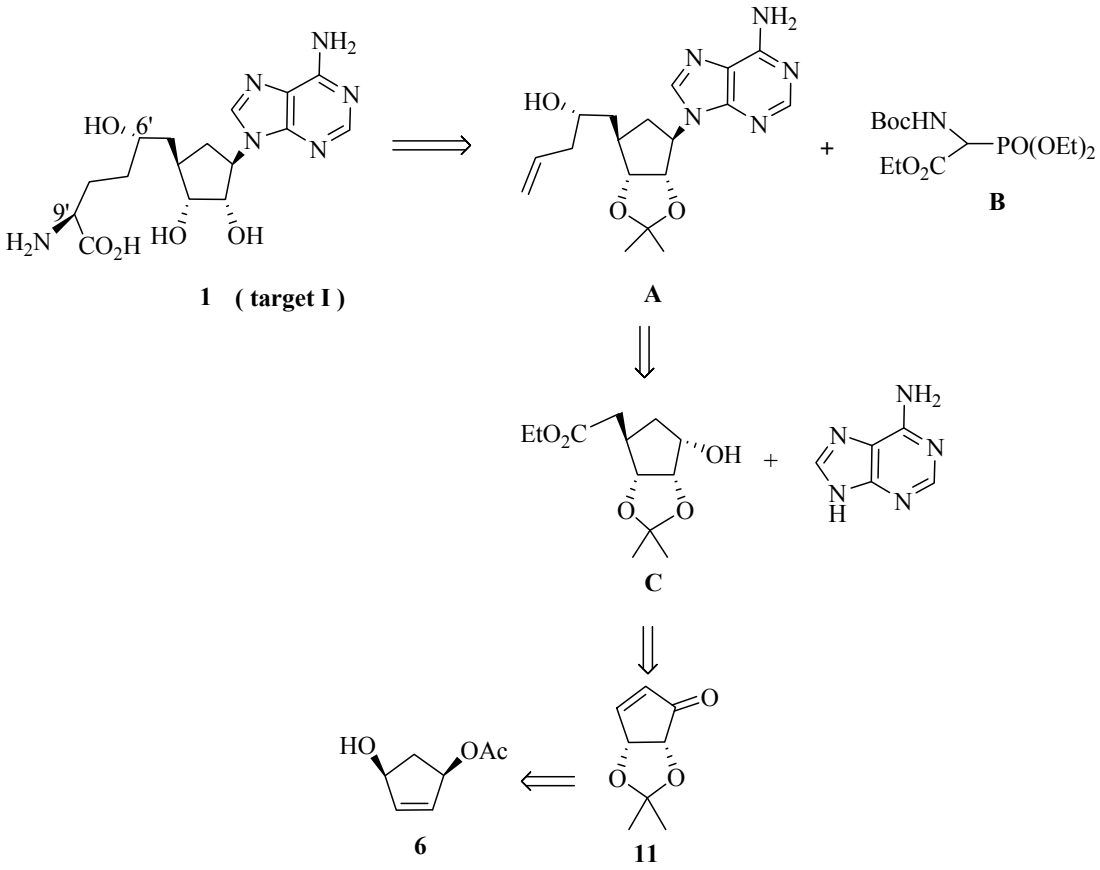

**Scheme 9. Dissociative mechanism of olefin metathesis.**

# CHAPTER 3

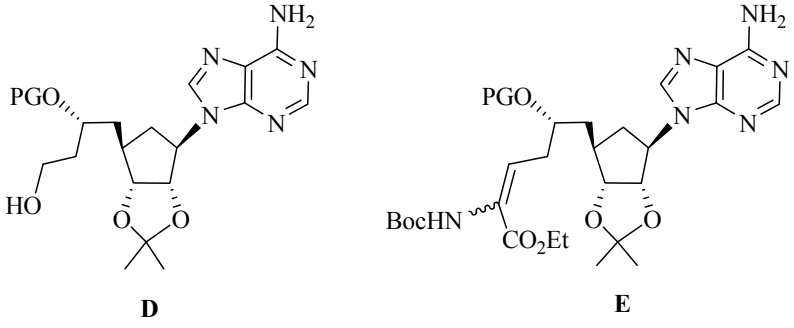
# SYNTHESIS OF TARGET I

Experiment Design and Approaches

In order to design the synthesis of target **I**, a retrosynthetic analysis was considered (Scheme 10). The key steps in this approach are installation of the C-6' and C-9' stereo centers by efficient asymmetric synthetic methods. The C-6' hydroxyl chiral center arises from building block **A** that can be constructed by calling on a highly diastereoselective allylborating agent.[93] The amino acid at C-9' was seen available in three steps: (i) cleaving the double bond of the allylic alcohol of **A** and oxidizing the resultant primary alcohol (**D**) (Figure 19) to the corresponding aldehyde; (ii) using a Wittig-Horner reaction,[94] with the phosphonate **B,** which can be generated from Boc-glycine ethyl ester,[95] to deliver the amino acid moiety (**E**), while extending the side chain needed for target **I**; and, (iii) asymmetric hydrogenation of the newly formed double bond of **E** to give the desired configuration at C-9', (*S*).



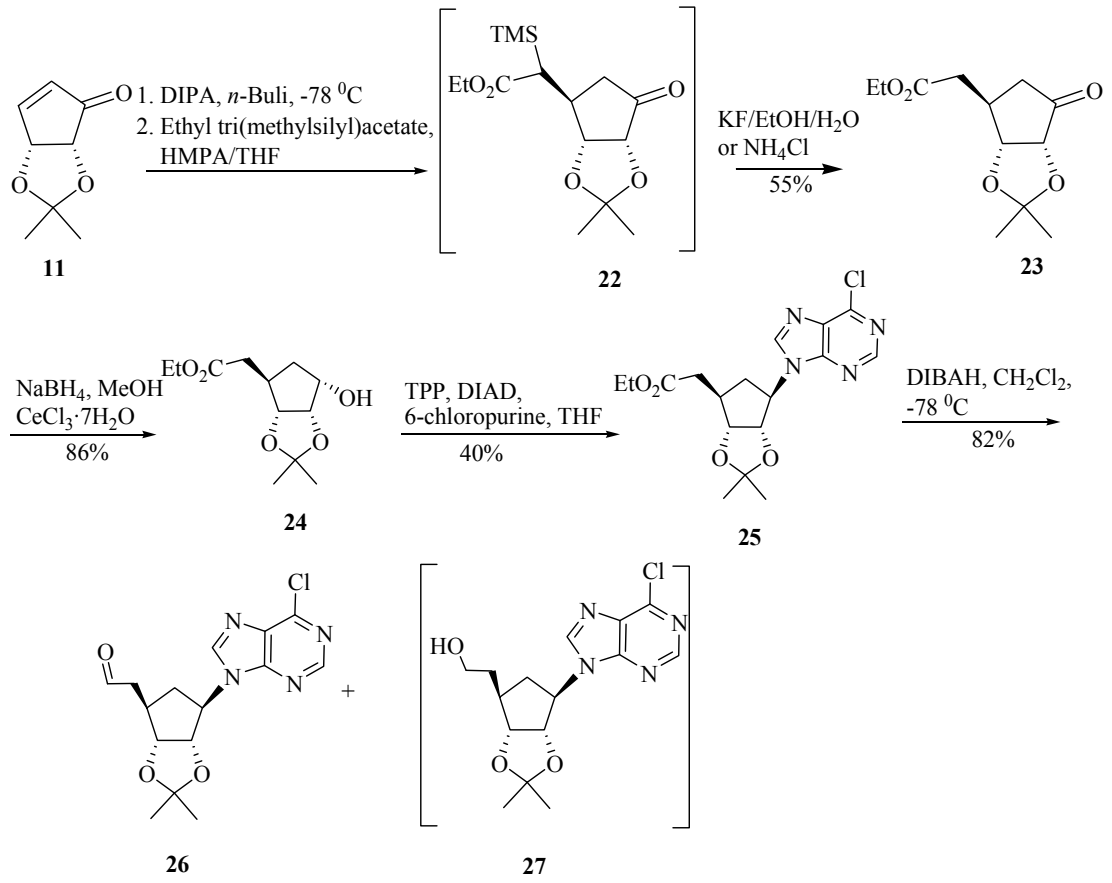

**Scheme 10. Retrosynthetic analysis of target I.**




PG = protecting group

**Figure 19. Proposed intermediates for target I.**

It was seen from Scheme 11 that building block **C** (**24**) was achieved by two steps: (i) a regioselective and stereoselective 1,4 Michael addition with ethyl tri(methylsilyl) acetate to **11** followed by hydrolysis to remove the TMS group to furnish **23** (Scheme 11), in 55% yield for two steps[96]; and, (ii) reduction of **23** with sodium borohydride/cerium chloride heptahydrate (Luche reduction) stereoselectively to afford **24** (also **C** of Scheme 11).[97] Then, compound **24** was subjected to standard Mitsunobu conditions (di*iso*propyl azodicarboxylate and triphenylphosphine, TPP) to provide **25** in 40% yield.[98] Finally, reduction the ester of **25** with di*iso*butylaluminum hydride (DIBAH) at low temperature yielded a mixture of **26** and **27** (**27** is a byproduct confirmed by TLC and $^{1}$H NMR).[99] The mixture was difficult to separate by standard silica gel column chromatography.

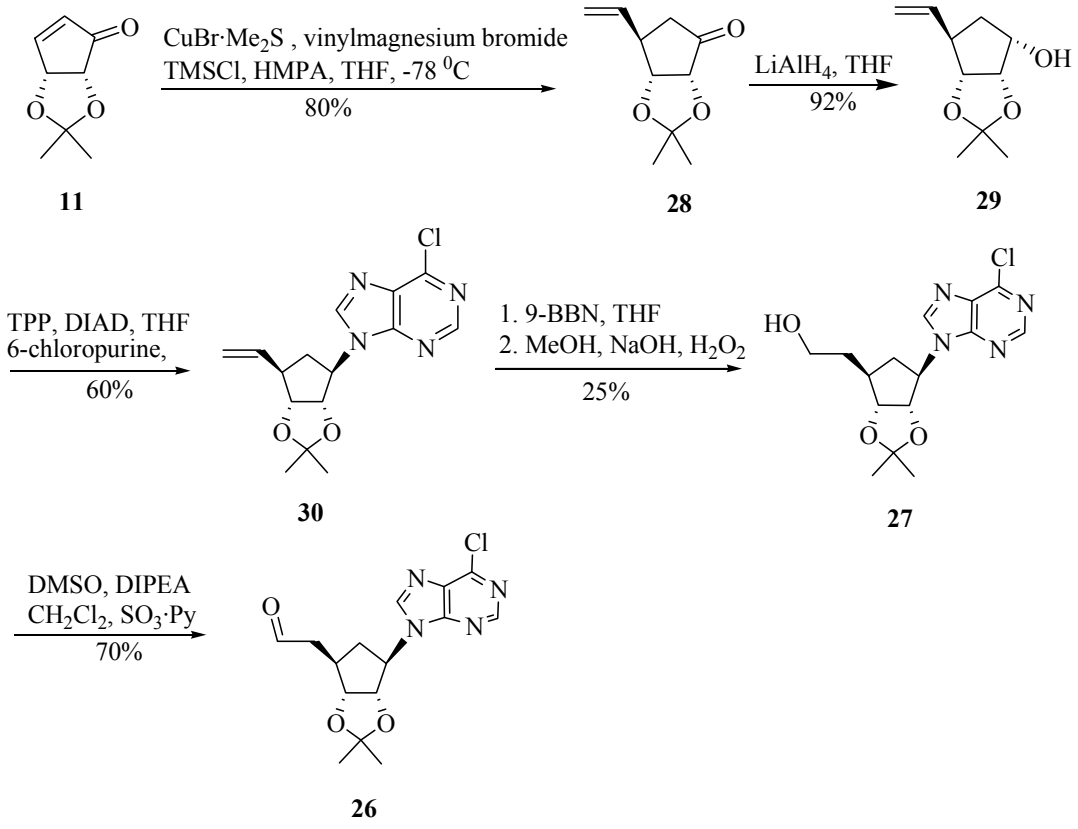



**Scheme 11. First approach to building block A.**

To resolve this problem, an alternative approach (Scheme 12) was explored. In this method, introduction of a vinyl group to **11** by a cuprate-catalyzed Michael addition selectively afforded **28** in 80% yield. Adding trimethylsilyl chloride (TMSCl) and hexamethylphosphoramide (HMPA) accelerates the selectivity for the 1,4-addition.[65] Reduction of **28** using lithium aluminum hydride selectively provided **29** in high yield, 92%. Employing Mitsunobu reaction conditions, compound **30** was successfully obtained. Hydroboration-oxidation was conducted with **30** to produce **27**. Unfortunately, the yield in this step was very low, 25%. A possible explanation may be the steric hindrance of the heterocyclic base, affecting the attack of the bulky hydroborating agent on the double

bond from the desirable *syn* face. To move forward with this project, subjecting compound **27** to a modified Swern oxidation reaction[100] produced aldehyde **26**.

Having authentic compound **27** was used to confirm its presence in the mixture with **26** in Scheme 11.




**Scheme 12. The second approach for 26.**

The aldehyde **26** was then employed to set up the C-6' stereocenter and to extend the side-chain by two carbon atoms. Asymmetric allylation was pursued for this purpose.[101] In this direction, there are many asymmetric allylation methods and related chiral auxiliaries developed for this purpose.[93,102,103] The most common are boron-based

agents as shown in Figure 20: (i) the tartrate-based allylboron compound (Roush's reagent); (ii) Corey's allylating reagent; and, (iii) Brown's reagents. From the view of the target preparation, focus was on the highly efficient and easy synthesized chiral allylborane auxiliary: (+) and (-)-B-allyldi*iso*pinocampheylborane ($Ipc_2BCH_2CH{=}CH_2$), which can be achieved *in situ* from the commercially available precursor (B-methoxydi*iso*pinocampheylborane) upon reaction with allylmagnesium bromide.[93a]

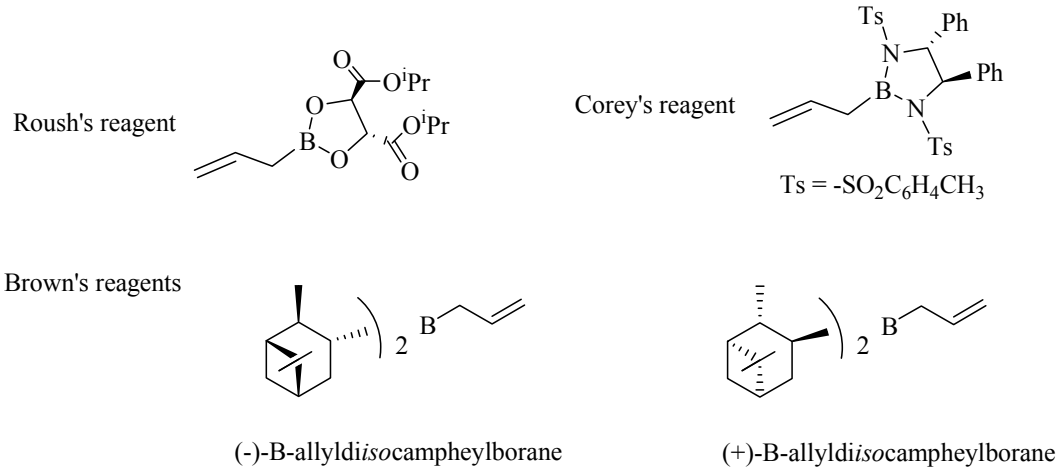
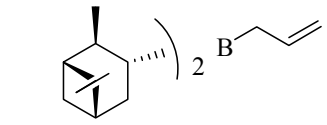


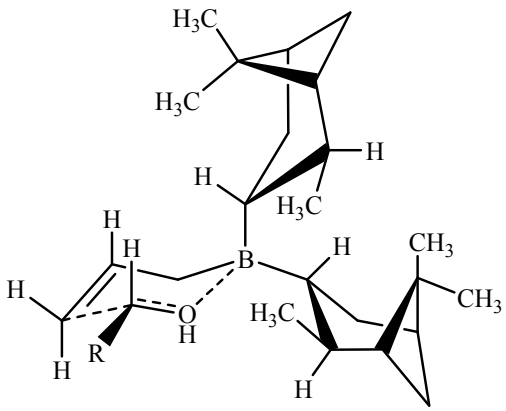

**Figure 20. Boron-based allylating reagents.**

A comment about the mechanism of allylation of aldehydes with Brown's reagent ($Ipc_2BAll$) is appropriate at this point (Figure 21).[93f] It has been shown that the allylboration reagent ($Ipc_2BAll$) can form a chair-like six-membered ring transition state with the aldehyde. Due to the face selectivity of the aldehyde, there are two possible transition states: *Si* face and *Re* face (the allylborane attacking the aldehyde from two different sides). The nature of face selectivity results from the minimization of the steric

interactions in space between the bulky axial Ipc ligand and the aldehyde group. In this allylation reaction, the chirality of the boron ligands induces the chirality of the new asymmetric center (asymmetric allylic alcohol).[101a]



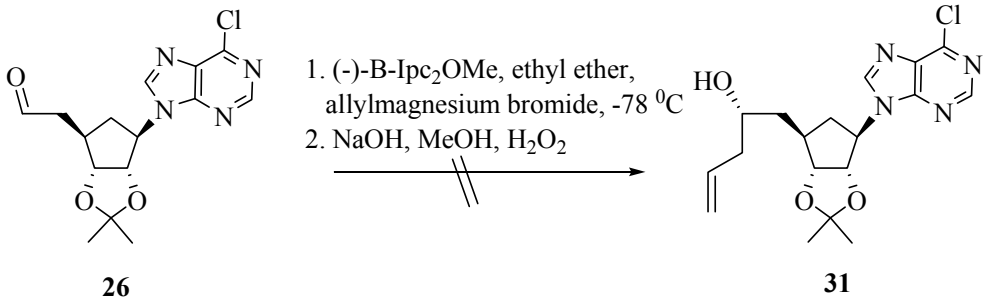

(-)-B-allyldi*iso*campheylborane




*Si* Face

**Figure 21. Proposed mechanism of allylation of aldehydes with Brown's reagent.**

Unfortunately, allylation reaction of **26** with $Ipc_2BAll$ (synthesized *in situ* following the literature[93a]) led to a complex mixture (by TLC; not the desired **31**) (Scheme 13). It was concluded that this observation was due to the instability of the newly formed $Ipc_2BAll$ to air or moisture, even though the filtration was handled under dry nitrogen. Finally, a one-pot synthetic method (without removal the magnesium salt) was developed to successfully carry out this allylation reaction to give the desired enantiomeric pure product.




**26** **31**

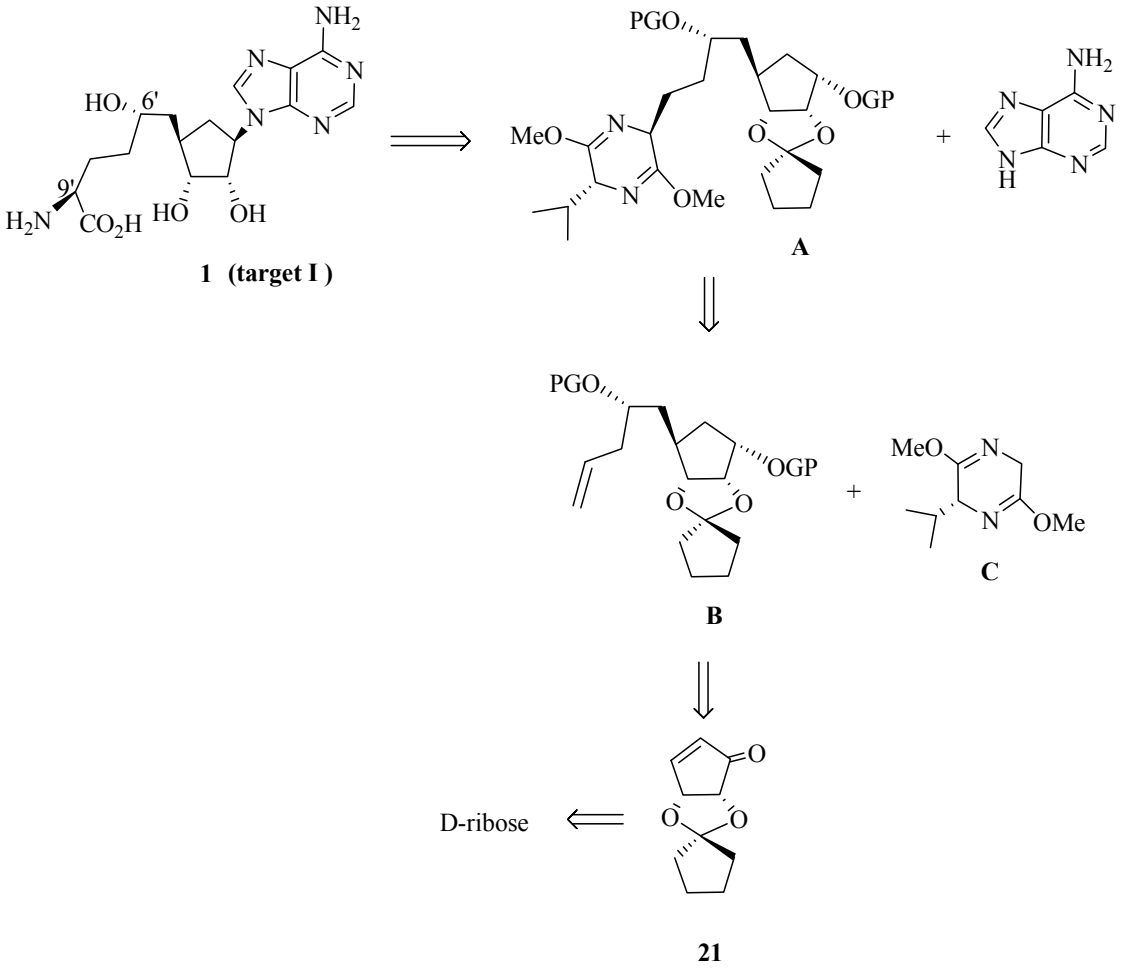
**Scheme 13. Allylation reaction of 26.**

At this point attention returned to the limitations to the routes being pursued. In that regard, while Scheme 12 represents a successful process to **26**, it is limited by several disadvantages. First, the yield in the hydroboration-oxidation step (i.e., **30** to **27**) is low. Also, the pathway from compound **11** to **27** is very time consuming and the yield of coupling the 6-chloropurine with **29** to **30** was poor. Additionally, there was some uncertainty whether the 6-chloropurine of **26** could withstand further requisite side chain conversions.

Based on the previous studies in our group, another concern was whether the asymmetric hydrogenation of the Wittig-Horner product **E** (Figure 19) would be straightforward. Other difficulties were foreseen (such as low yields and numerous protection/deprotection steps) for installing the side chain of target **I**, from **26**. Therefore, a more suitable strategy to target **I** was sought.

The alternative approach (Scheme 14) was to replace 6-chloropurine with adenine as the coupling heterocyclic base with the building block **A** near the end of the synthesis and to replace the *iso*propylidene protected **11** with the cyclopentanone as protected product **21** (see earlier in dissertation). The amino acid unit in this approach was to be

introduced via Schöllkopf's *bis*-lactim ether chiral auxiliary (building block **C**, Scheme 14).[104] Building block **A** was to be achieved from precursor **B**, and **B** to be obtained from the allylation reaction under Brown's reagent from the corresponding aldehyde, which was expected from **21**.



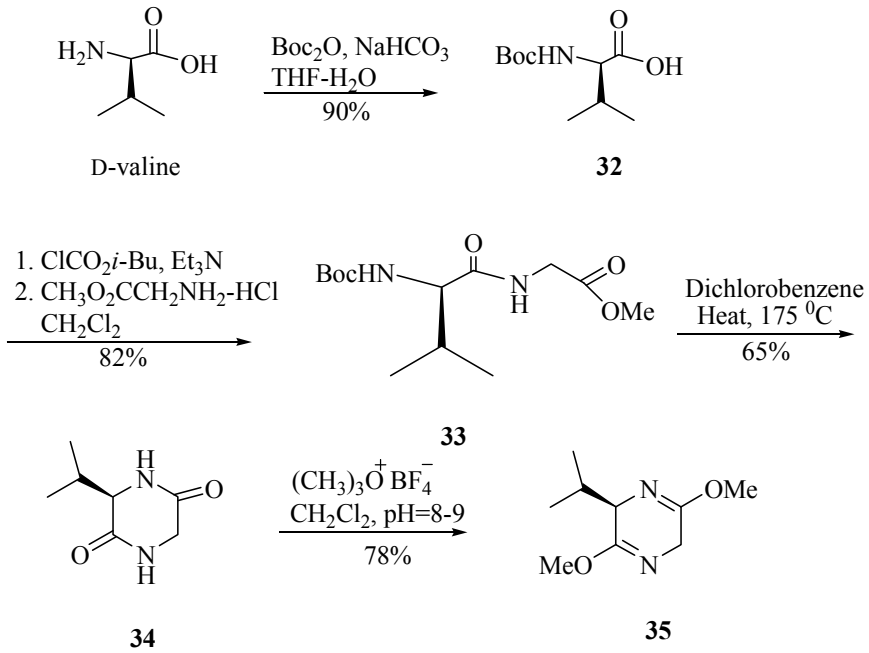

**Scheme 14. Optimized approach for target I.**

The selection of Schollkopf's *bis*-lactim ether chiral auxiliary for the purpose of this project arose from the following consideration: it is known that α-amino acids exist

in either the D or L form (Figure 22), with the majority of naturally occurring amino acids being L-amino acids. For target **I**, the terminal amino acid is L (by the Cahn-Ingold-Prelog designation, it is *S* configuration). Often in the laborotary, L-amino acids are obtained by biological methods, such as enzymatic syntheses and resolution techniques.[105] Alternatively, asymmetric synthesis methodology using chiral reagents or auxiliaries or synthons, is a powerful tool for preparing the optically active α-amino acid derivatives.[106] Among the synthetic methods, various asymmetric derivatives of glycine or corresponding glycine equivalents, provide convenient precursors for direct formation of the new stereogenic amino acid center.[107] The first efficient derivative of a glycine equivalent was developed by Schöllkopf and co-workers,[104d] which later was called Schöllkopf reagent (building block **C**, Scheme 14), and was proved to be a highly efficient enantioselective reagent for preparing α-amino acids.[108] Although building block **C** is commercially available, it is very expensive. Therefore, a modified literature procedure[109] was designed for **C** as shown in Scheme 15.


(*S*)-L-amino acid (*R*)-D-amino acid

**Figure 22. Configurations of amino acids.**

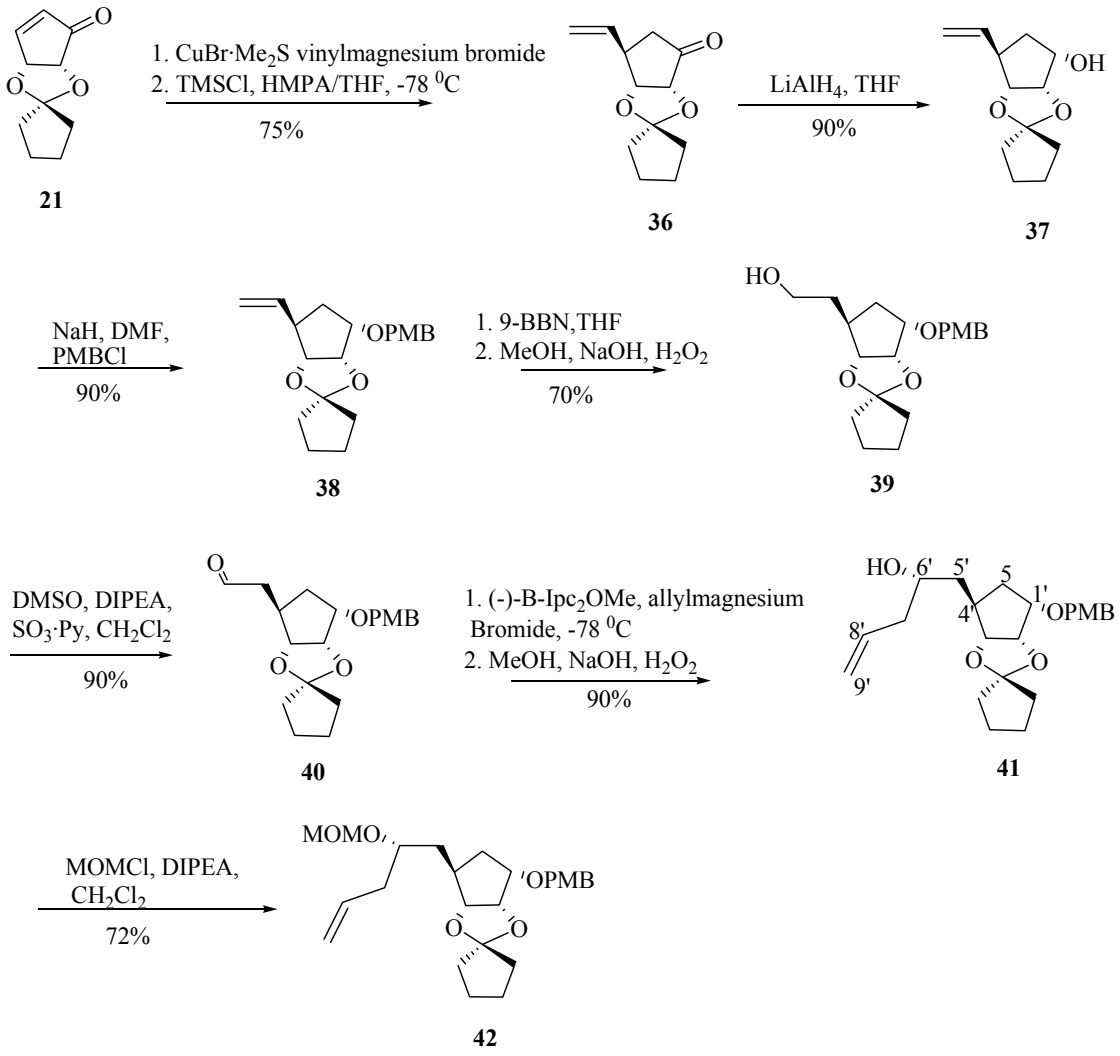



**Scheme 15. Synthesis of the Schöllkopf reagent (35, building block C).**

Protection of commercially available D-valine with di-*tert*-butyl dicarbonate led to **32** in quantitative yield. Treatment of **32** with *iso*butyl chloroformate under basic conditions followed by glycine methyl ester hydrochloride, provided the Boc-protected dipeptide **33**. Then, cyclization of **33** in 1, 2-dichlorobenzene gave **34** in excellent yield. Finally, methylation of **34** with the commercially available trimethyloxonium tetrafluoroborate in dichloromethane at room temperature resulted in (2*R*)-2, 5-dihydro-3, 6-dimethoxy-2-*iso*propylpyrazine, **35** (also **C** in Scheme 14) in good yield**,** after the high vacuum distillation. The NMR ($^{1}$H and $^{13}$C) data of **35** was in agreement with the literature.[109c]

After building block **C** (compound **35**) was in hand, attention was shifted to constructing additional components of Scheme 14**,** shown in Scheme 16. With compound

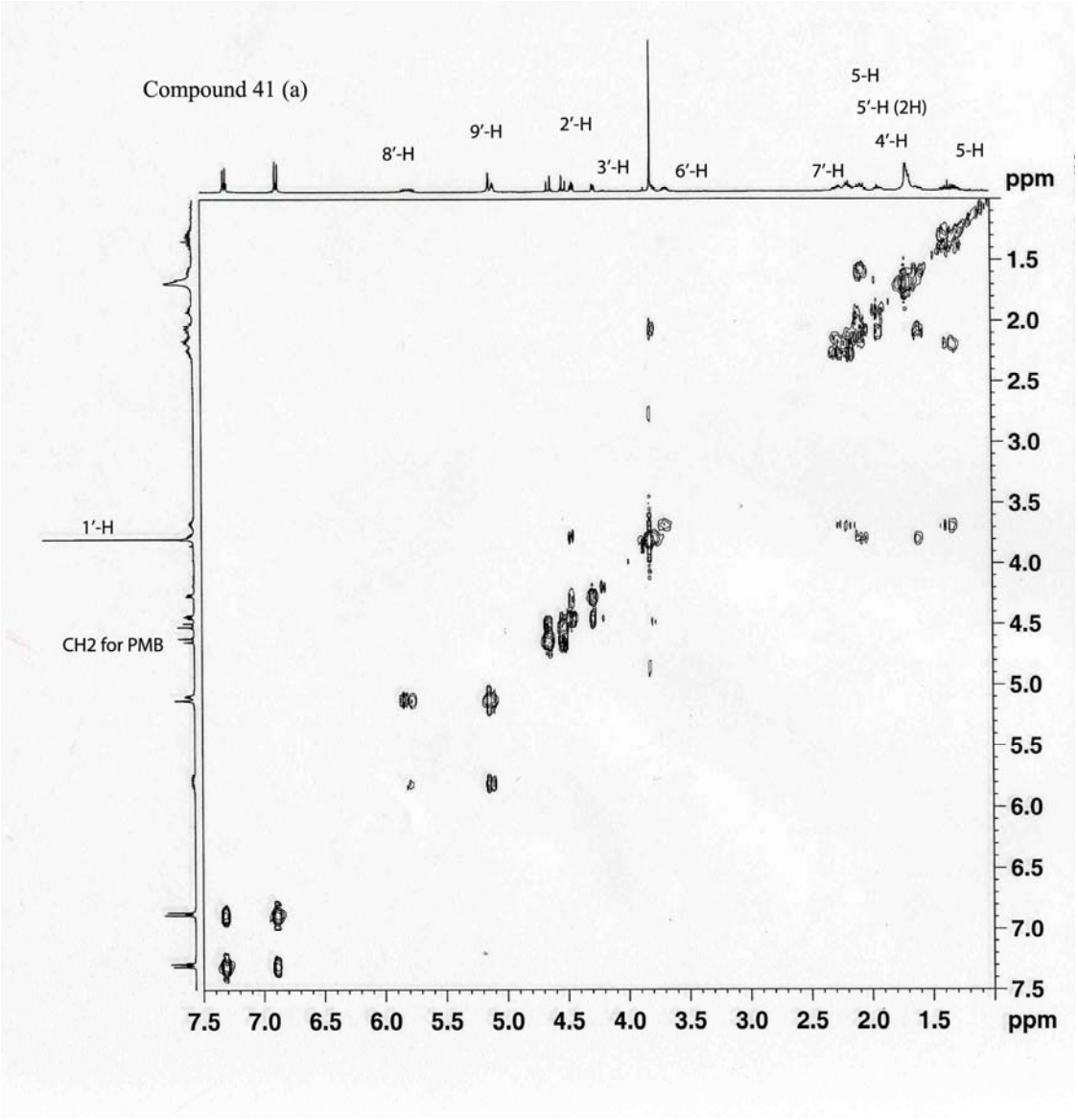
**21** as the starting material, the first two steps were adopted from Scheme 12. Thus, a Michael addition reaction employing vinylmagnesium bromide and the enone **21** provided compound **36** as the single isomer. Reduction of **36** using lithium aluminum hydride selectively afforded the secondary alcohol **37** in 90% yield. Scheme 14 shows that a modification of the side chain of **37** was necessary for coupling of the heterocyclic base (adenine). Therefore, protection of **37** with *p*-methoxybenzyl chloride under strongly basic conditions, provided **38**. The hydroboration-oxidation reaction was then conducted on **38**, resulting in the primary alcohol **39** in good yield. The oxidation of **39** using modified Swern oxidation conditions, yielded aldehyde **40**.




**Scheme 16. Synthesis of the important intermediate 42 (building block B).**

The aforementioned Brown stereospecific hydroboration was next performed on the aldehyde **40**, using freshly prepared (-)-B-allyldi*iso*pinocampheylborane (*in situ*), to afford the desired enantiomerically pure homoallylic alcohol **41** in 90% yield for two steps. This product was confirmed by two-dimensional NMR Spectroscopy ($^1$H, $^1$H-COSY) illustrated in Figure 23. The ($^1$H, $^1$H-COSY) 2D spectrum of compound **41** in $CDCl_3$ (Scheme 16) shows that. the diagonal peak labeled 8'-H on the left-hand corner

has the symmetric cross-peaks with 9'-H (2H) around the diagonal. When proceeding along the diagonal line, the symmetric cross-peaks are the $CH_2$ in PMB group. Then further moving along the diagonal line, 2'-H has a symmetric cross-peak with 3'-H and it has another upper cross-peak in the vertical line, which is deduced for 1'-H. From the diagonal peak of 1'-H, the cross-peaks of 5-H (2H) are confirmed. Besides the symmetric cross-peaks of 5-H (2H) around the diagonal line, both of them has another symmetric cross-peaks, which is deduced as 4'-H. Continuing moving along the diagonal line, the diagonal peak of 6'-H has a weaker cross-peak, which is identified as 7'-H (2H) and also has two cross-peaks. The much stronger intensity is identified as 5'-H (*trans* with the H atom of C-6') and the other is considered as the *cis* 5'-H. The remaining diagonal peaks are not accompanied by any cross-peak.


Compound 41 (a)
8′-H
9′-H
2′-H
3′-H
6′-H
7′-H
5-H
5′-H (2H)
4′-H
5-H
ppm
1′-H
CH2 for PMB
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
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7.5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm

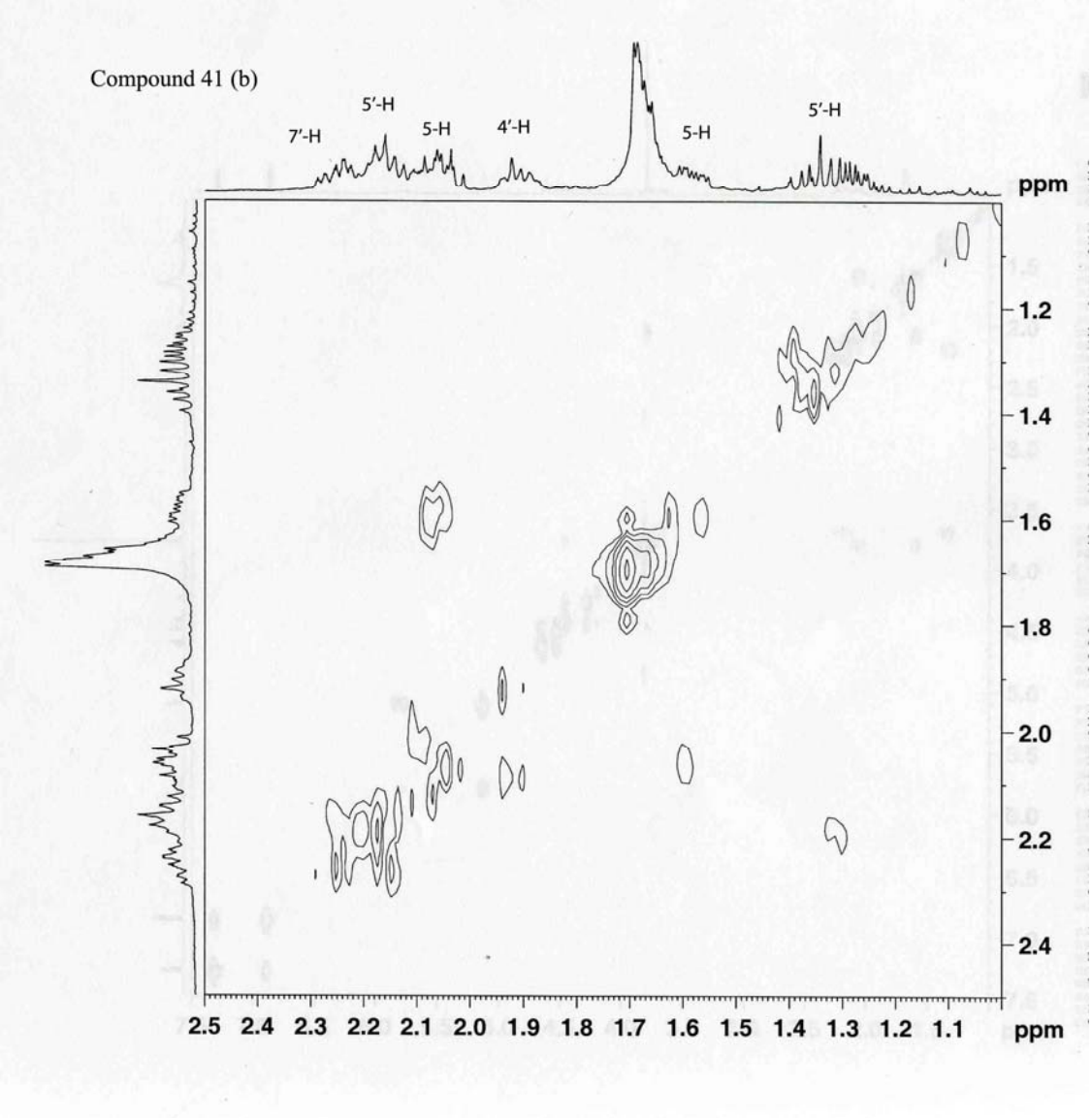
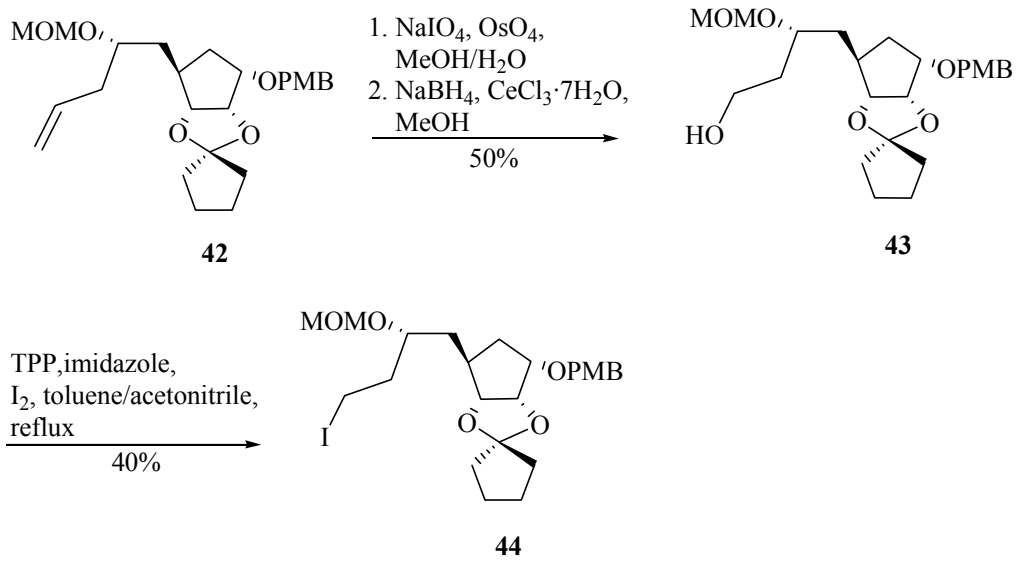



**Figure 23. COSY spectrum of compound 41 in deuteriochloroform: (a) the small one chemical shift δ (1.0-7.5) and (b) the magnified one δ (1.0-2.5).**

With **41** available, its C-6' hydroxyl group was protected as the methoxymethyl ether to provide **42** (also building block **B** in Scheme 14).[110]

Combining **42** and **35** was next addressed. Based on the literature,[104,108] the use of the Schöllkopf's auxiliary, **35** (building block **C**), is best conducted using its lithiated

(2*R*)-2,5-dihydro-3,6-dimethoxy-2-*iso*propylpyrazine derivative together with haloderivatives as co-reactant. The most common halo derivative is the bromo species. However, in this case, the iodo derivative **44** was chosen for its ease of preparation and efficiency as a good leaving group (Scheme 17).

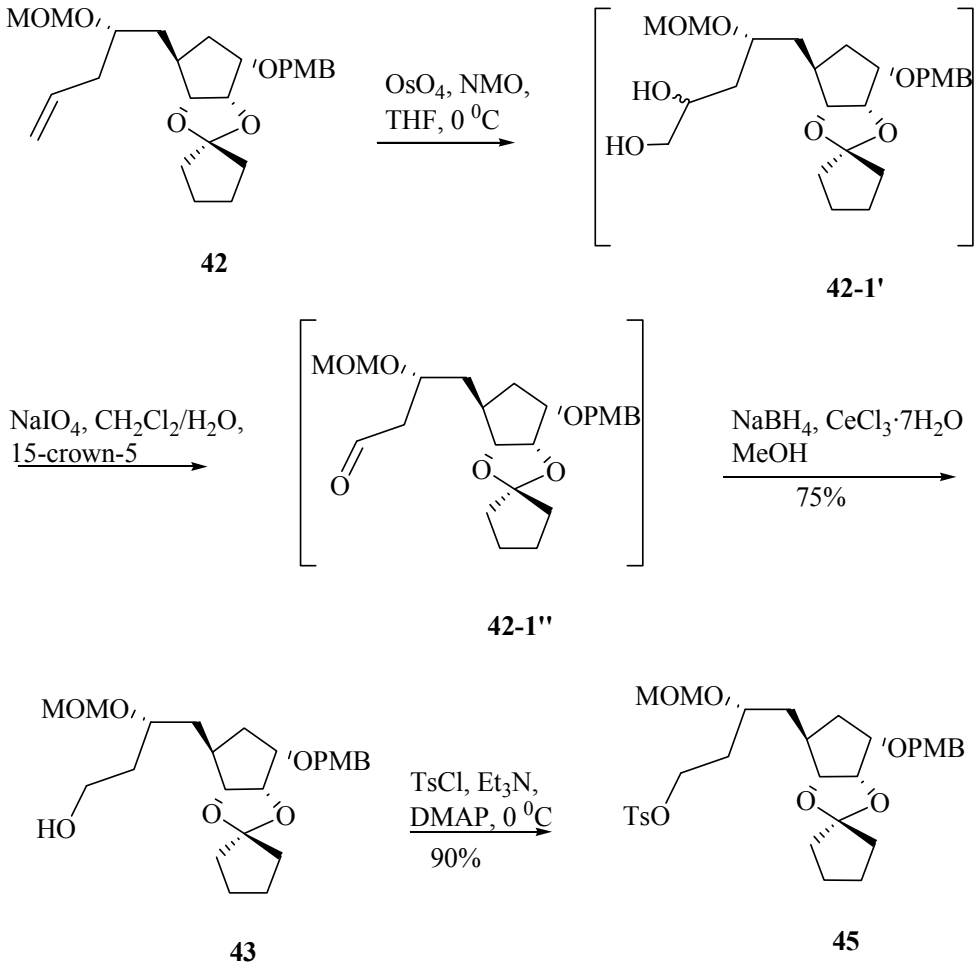



**42** **43** **44**

**Scheme 17. Synthesis of iodide 44.**

To achieve **44**, compound **42** was subjected to oxidative-cleavage conditions using sodium (meta) periodate (under osmium tetroxide catalysis). This was followed by reduction of the resulting aldehyde to afford **43** in moderate yield. Then, compound **43** was converted to iodide **44** according to standard iodination conditions (triphenylphosphine, imidazole, iodine), but resulted in very low yield.[85b] This low yield was believed to be due to the formation of unwanted intermediates in the conversion of **42** to **43**.

To move past this problem, Scheme 18 shows an optimized approach to afford the tosylate **45,** which we hope to use in place of the iodide **44**. In this method, oxidation of the double bond of **42** under osmium tetraoxide/N-methylmorpholine N-oxide (NMO) conditions provided the diol **42-1'**. This was followed by cleaving **42-1'** under sodium periodate standard conditions to **42-1''** in quantitative yield.[111] Compound **42-1'** and **42-1''** were proved by $^{1}$H NMR Spectroscopy data (also TLC analysis). In turn, Luche reduction of aldehyde **42-1''** gave **43** in excellent yield (three steps, 75%). Treatment of **43** with *p*-toluenesulfonyl chloride under basic conditions using triethylamine and catalytic amount of 4-dimethylaminopyridine (DMAP) afforded the tosylate **45** in good yield.[112]




**Scheme 18. Optimized approach for the synthesis of tosylate 45.**

Compound **45** was then used in the next stage of the synthesis (Scheme 19), that is, to construct the terminal amino acid unit. Thus, treating the tosylate **45** with the lithio derivative of **35** (building block **C,** Scheme 14) in anhydrous THF at low temperature gave compound **46**. The stereospecificity of the transformation from tosylate **45** to **46** was attributed to steric interaction imposed by the bulky moiety of **45** with the chiral dihydropyrazine to the less hindered face of lithio (2*R*)-2,5-dihydro-3,6-dimethoxy-2-*iso*propylpyrazine masked amino acid (Figure 24) to afford diastereoselectively the *trans*

product **46** in 70% yield. Then compound **46** was subjected to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to provide the product **47**.[119] From compound **47** to **49** (target **I**), these two steps could not be finished in the time available.

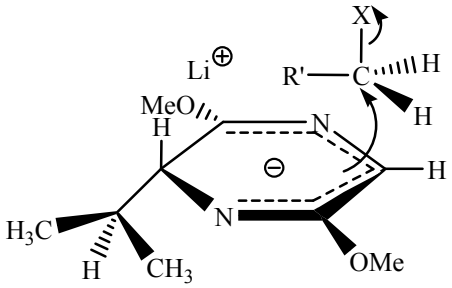
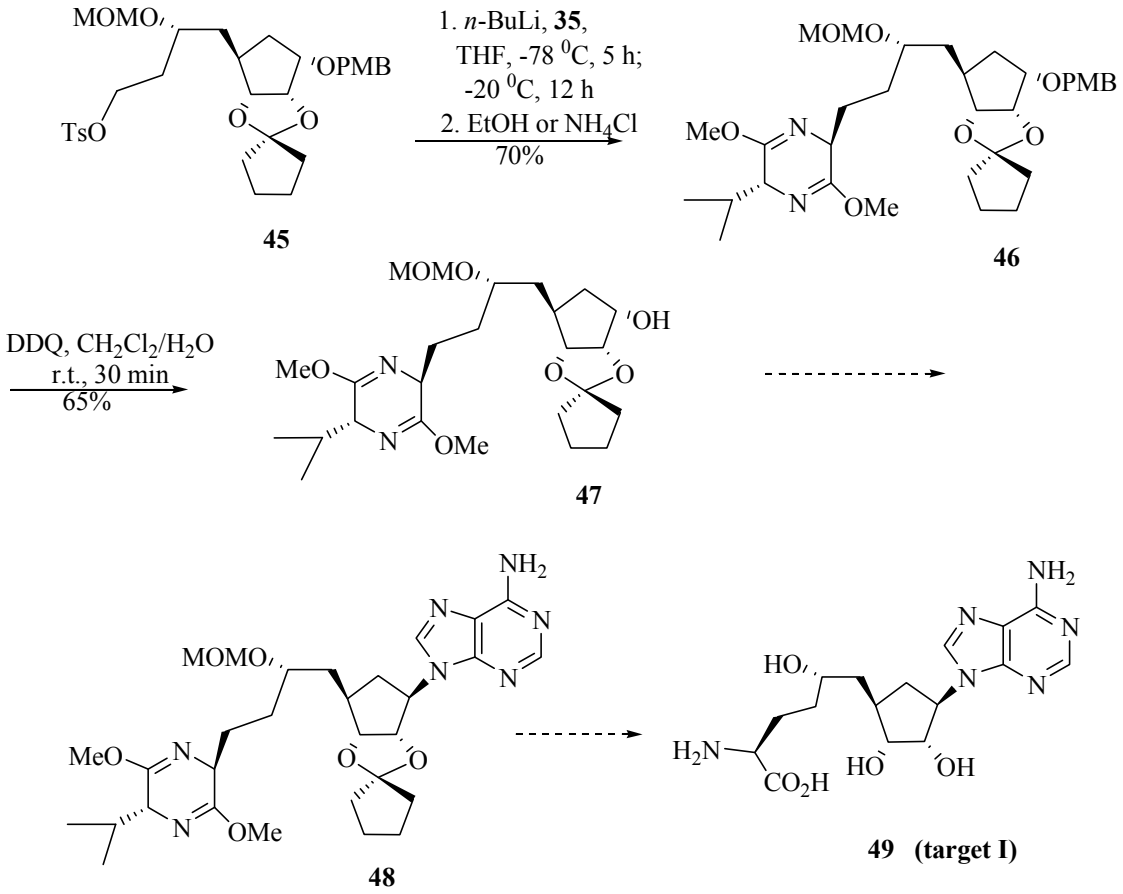



**Figure 24. Transition state for the alkylation reaction.**



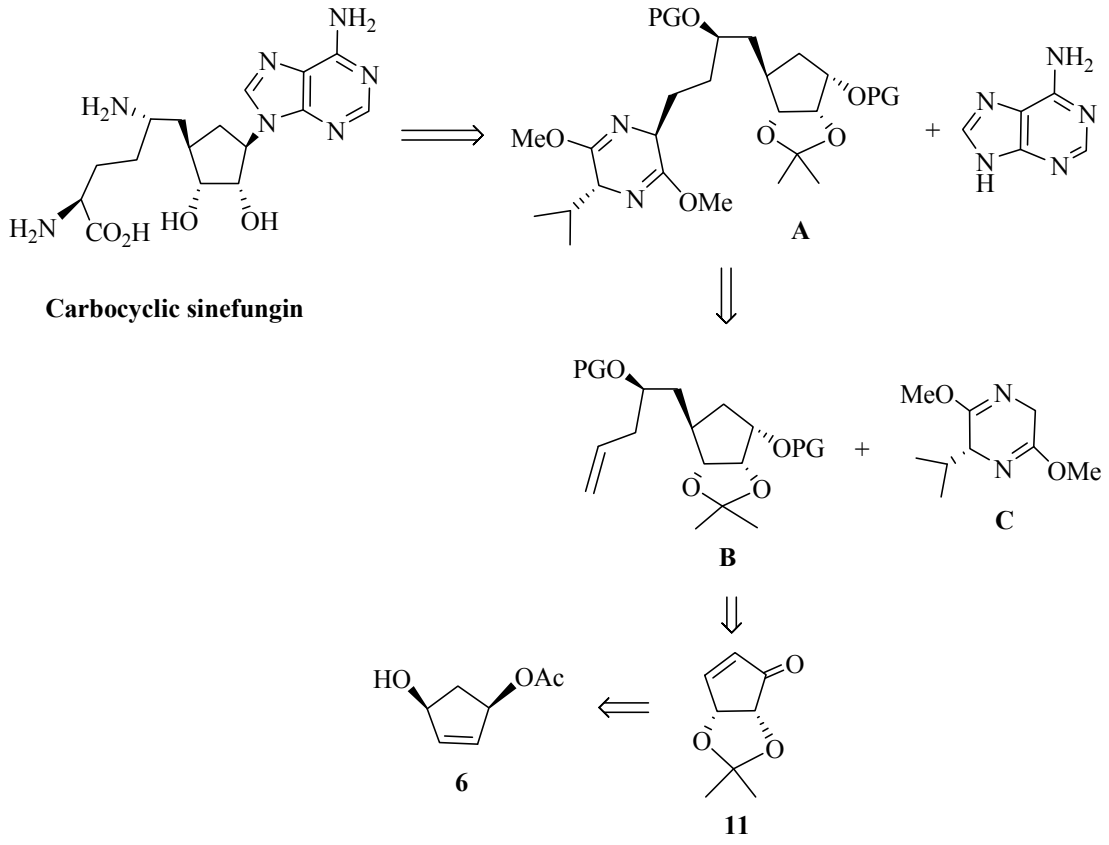

**Scheme 19. Synthesis of 47, a close precursor to target I.**

# CHAPTER 4

# SYNTHESIS OF CARBOCYCLIC SINEFUNGIN BUILDING BLOCKS (53 and 55)

## Experimental Design and Approaches

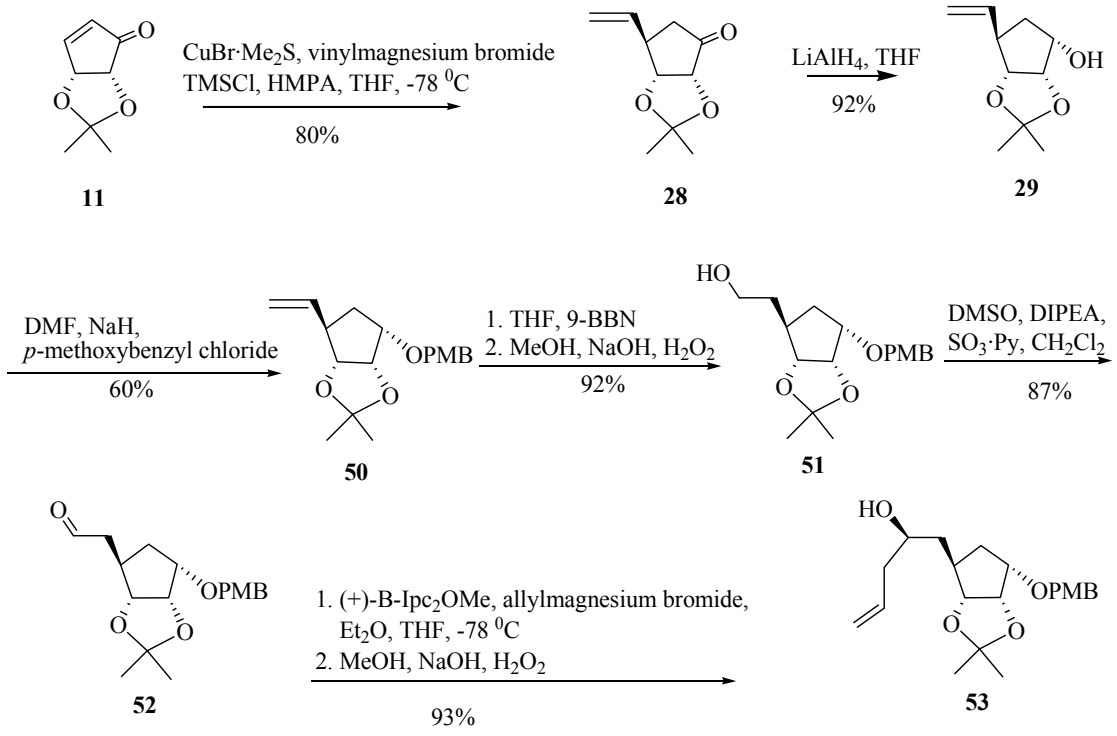
Carbocylic sinefungin is a target of this dissertation research. Scheme 20 represents a retrosynthetic analysis to this compound. Installation of the C-6' and C-9' stereocenters was seen by adapting the efficient asymmetric synthetic methods of Scheme 14. In that direction, the C-6' (*S*) amine group of building block **A** was foreseen to be constructed in three steps: (i) employing a highly diastereoselective allylborating agent to introduce a C-6' (*R*) hydroxyl group; (ii) a $S_N2$ substitution reaction by sodium azide under the basic conditions; and, (iii) hydrogenation of the azide species to the desired primary amine. The amino acid at C-9' was to be achieved using Schöllkopf's auxiliary alkylation reaction whereby the absolute configuration of the newly introduced C-9' stereo center (as *S*) was to be set based on the findings in Schöllkopf's asymmetric amino acid synthesis.[104e]




**Scheme 20. Retrosynthetic analysis of carbocyclic sinefungin.**

Working collaboratively with Dr. Xue-Qiang, Yin (a postdoctor fellow in our group) on this investigation, building block **B** was established for this dissertation project. Thus, beginning with enone, compound **11** (see chapter 2), a conjugate addition (Michael reaction) was conducted with vinylmagnesium bromide in the presence of a copper bromide dimethylsulfide complex to afford **28** in 80% yield (Scheme 21). Reduction of **28** with lithium aluminum hydride selectively provided **29** in 92% yield. At this stage, modification of the side chain of **29** was necessary. Thus, protection of the secondary alcohol of **29** was carried out with *p*-methoxybenzyl chloride under strong basic

conditions to yield **50**. Hydroboration of compound **50** with 9-borabicyclo[3.3.1]nonane (9-BBN) was followed by oxidation under hydrogen peroxide conditions to achieve the primary alcohol **51** in good yield. Finally, oxidation of **51** by modified Swern oxidation conditions provided intermediate **52**.



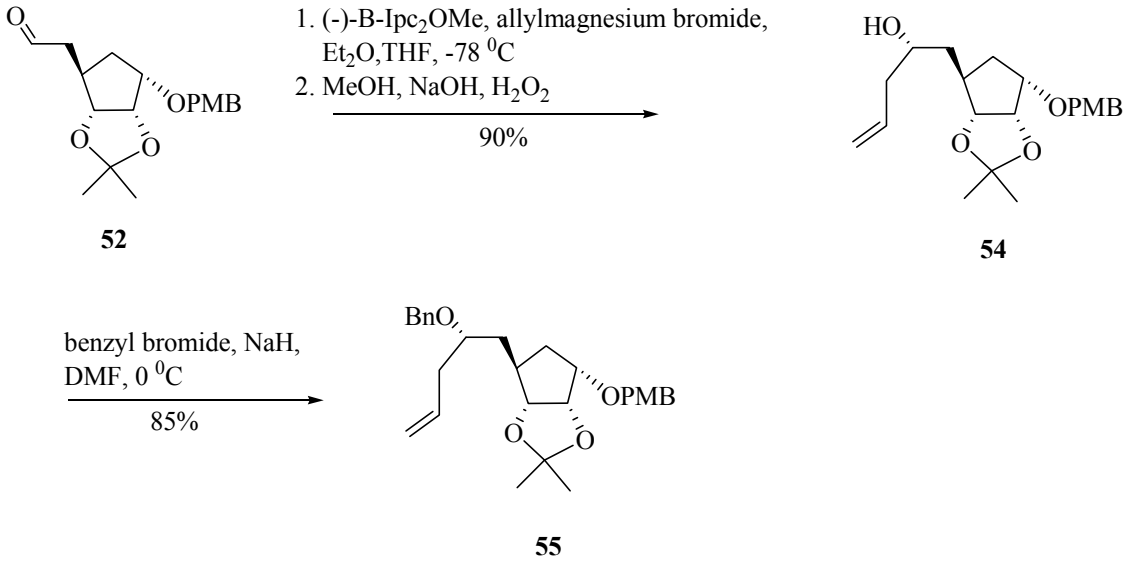

**Scheme 21. Synthesis of 53.**

At this point, attention was drawn to establishing the C-6' (*S*) chiral center by an allylation reaction with the aldehyde **52**. For this purpose, the aforementioned Brown's stereospecific hydroborating reagent, freshly prepared (+)-B-allydi*iso*pinocampheylborane *in situ* was used to accomplish the allylation reaction with

aldehyde **52**. This afforded the desired enantiomerically pure homoallylic alcohol **53** in two steps (93%).[93]

Compound **53** was provided to Dr. Yin to finish the latter total synthesis of carbocyclic sinefungin, which has subsequently been published.[113]

To investigate the allylation procedure more extensively, in this instance the aldehyde **52** was subjected to the freshly prepared (-)-B-allydi*iso*pinocampheylborane (*in situ*) to provide the enantiomerically pure homoallylic alcohol **54** in two steps in excellent yield (Scheme 22). Then, protection of the homoallylic alcohol with benzyl bromide under the basic conditions afforded compound **55** in good yield (85%).[117]

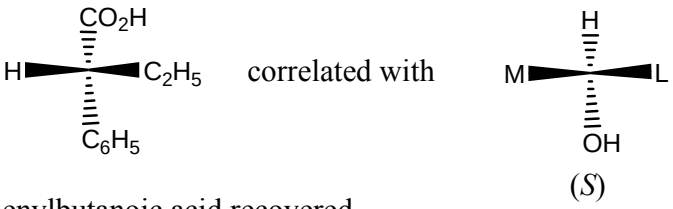



**Scheme 22. Synthesis of 55.**

Compound **55** was initially considered as an important intermediate for accomplishing of target **I** (Chapter 3, Scheme 14). But later, based on that fact that

compound **21** was developed in our group as a good building block for carbocyclic nucleoside derivatives,[88] replacing **11** with **21** (Chapter 2, Figure 17) became acceptable for target **I** (Scheme 14).

The stereochemistry of the homoallylic alcohol center was established by the Horeau method. There are several methods available to determine the absolute configuration of secondary alcohols in chiral molecules, such as X-ray diffraction method,[114a] chemical interrelation method,[114b] Horeau's method[115] and Nuclear Magnetic Resonance method.[114c-d] Among the methods, Horeau's method was chosen here as an empirically correlative approach (based on the kinetic resolution of 2-phenylbutyric anhydride), and its determination of the absolute configuration of secondary alcohols has been successfully applied to natural products.[116] In the method, the excess anhydride is hydrolyzed and the net rotation of the resulting acid is measured. It has been found experimentally that there is a relationship between the sign of optical rotation of the recovered 2-phenylbutyric acid and the absolute configuration of the stereo-alcohol involved.[115] Thus, if the resulting rotation of 2-phenylbutyric acid recovered is levorotatory, the secondary alcohol will be configured in the (*S*) form that is shown in Figure 25 (L and M refer to the large and medium substituents.). On the contrary, if the rotation of 2-phenylbutyric acid recovered is dextrorotatory, the secondary alcohol will be in the (*R*) configuration.




(*R*)-(-)-2-phenylbutanoic acid recovered

**Figure 25. Horeau's method.**

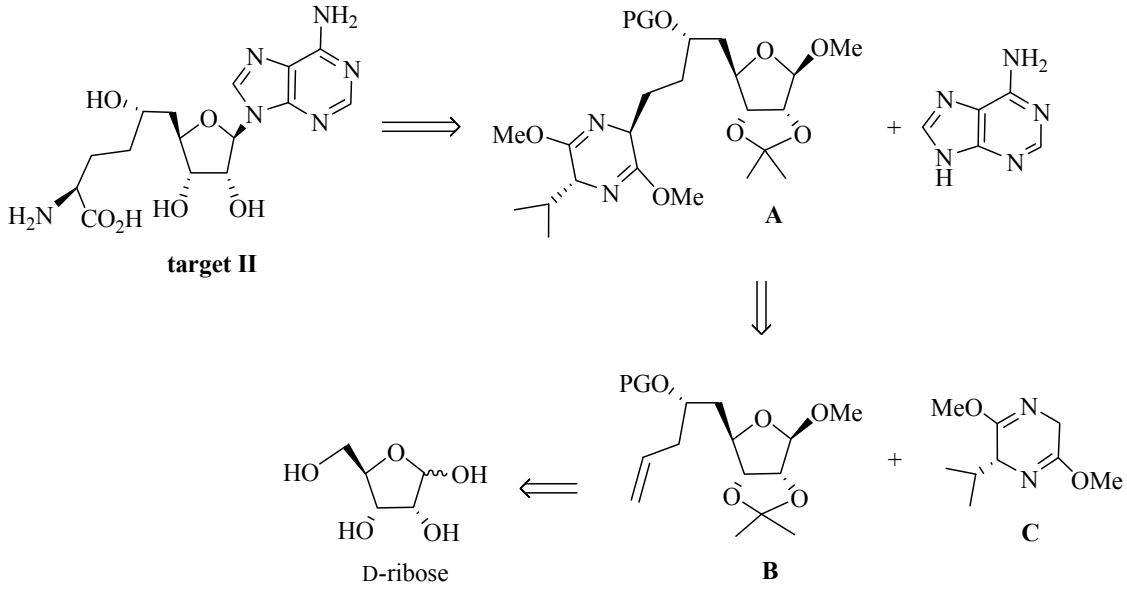
Based on Horeau's method, a modified approach using racemic 2-phenylbutyryl chloride to replace the anhydride as the resolving reagent has been shown to be more effective for the secondary alcohols with bulky groups.[114d] Therefore, experimentally, the excess racemic 2-phenylbutyryl chloride reacted with compound **53** (Scheme 21) under the basic conditions, followed by the hydrolysis, the rotation of the resulting 2-phenylbutyric acid was measured as *levorotatory*. So, the secondary alcohol of **53** was deduced to be in (*S*) configuration. At the same time, this result is consistent with the *Si* face selectivity with the Brown allyboration conditions employed in Figure 21.[93f]

# CHAPTER 5

# SYNTHESIS OF TARGET II

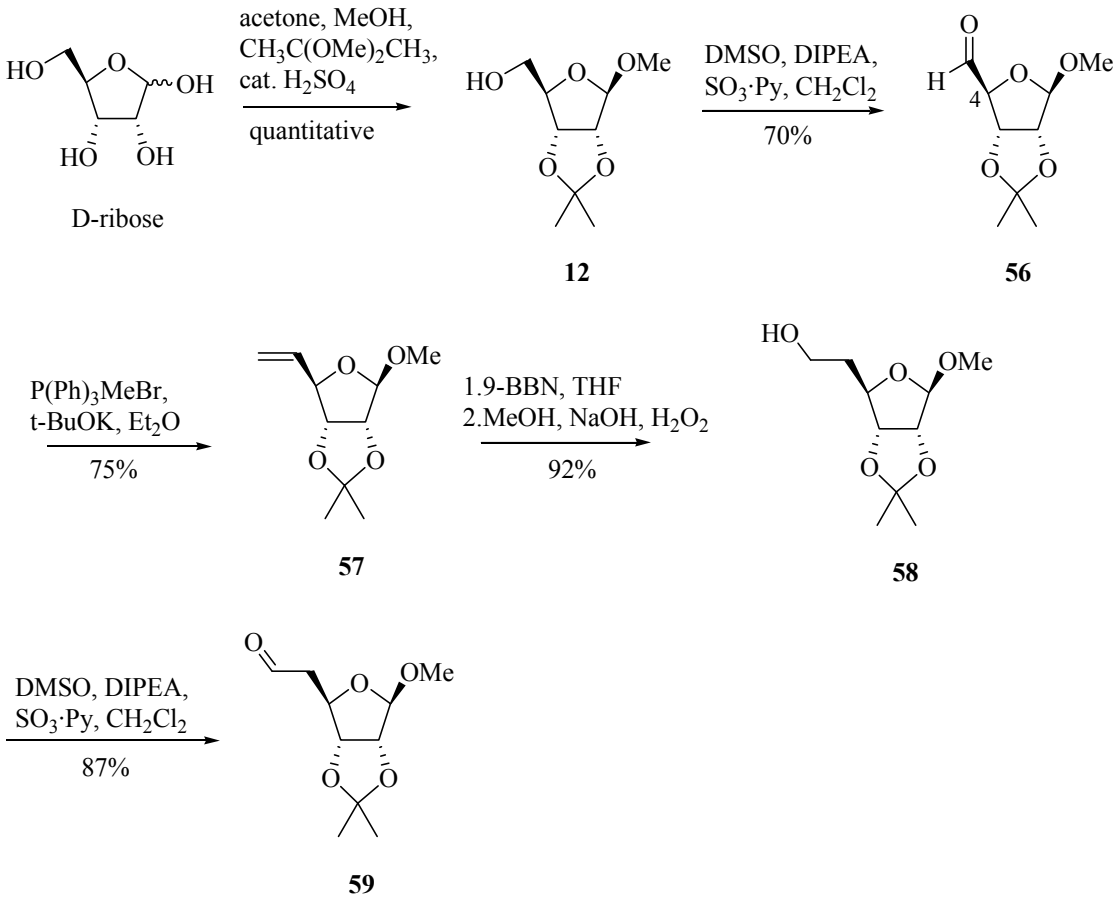
Experiment Design and Approaches

A retrosynthetic design to the 6'-hydroxyl analog of sinefungin (target **II**) is shown in Scheme 23. As before the key steps in this synthesis are establishment of the C-6' and C-9' stereo centers by efficient asymmetric synthetic methods, as employed to target **I**. The C-6' hydroxyl chiral center of building block **A** (Scheme 23) should be available by the highly diastereoselective allylborating conditions.[93] Likewise, the C-9' amino acid was to be introduced via now well established Schollkopf's *bis*-lactim ether chiral auxiliary, (building block **C**) of Scheme 14.[104] Building block **A** was envisioned from **B**, and **B**, in turn, was obtainable from commercially available D-ribose in several steps.



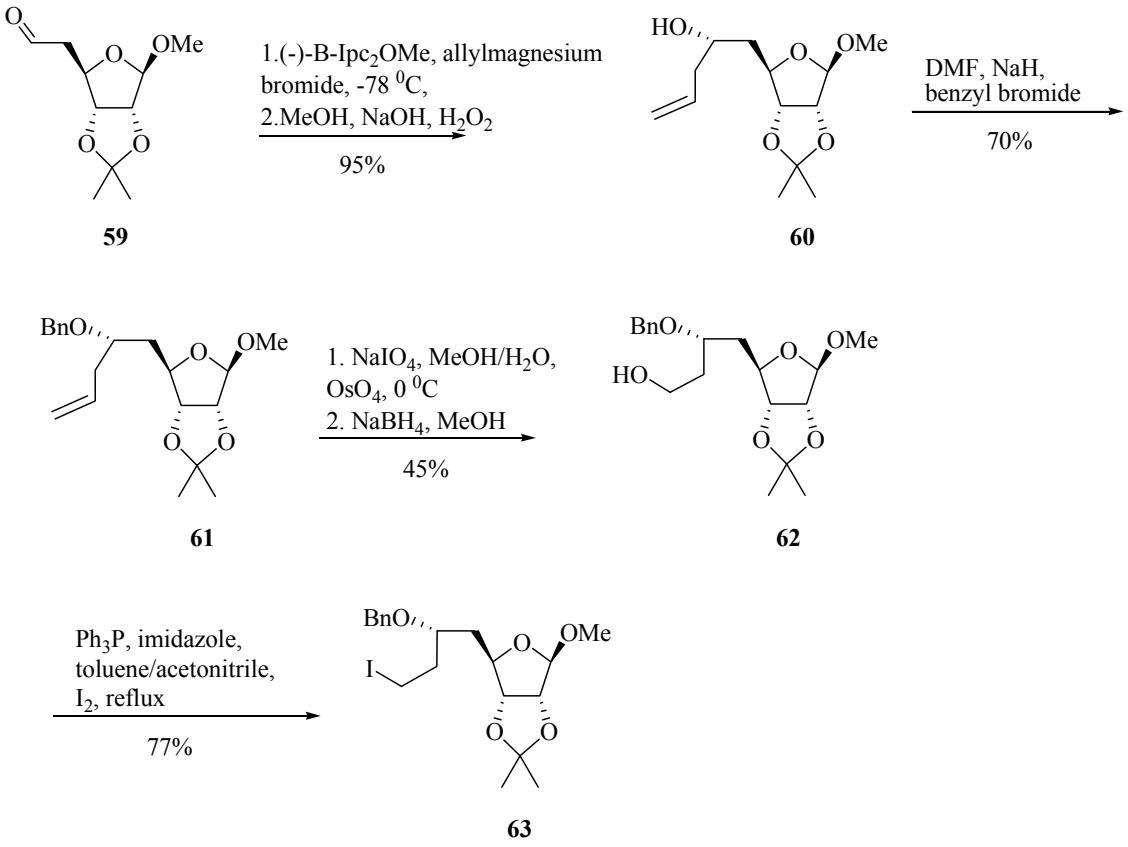

**Scheme 23. Retrosynthetic analysis of target II.**

Realization of precursor **B** began with commercially available D-ribose (Scheme 24). Its protection using 2, 2-dimethoxypropane and methanol catalyzed by surfuric acid afforded **12**, which was then subjected to oxidation under modified Swern oxidation conditions to provide **56** in moderate yield. Compound **56** underwent a Wittig reaction with methyl triphenylphosphonium bromide under the strong basic conditions to furnish **57**.[84a] It was noted that the transformation from **56** to **57** was accompanied epimerization at C-4, due to the strong basic conditions, so the yield for the desired product **57** was moderate. Hydroboration-oxidation conducted on **57**, resulted in the primary alcohol **58** in good yield. Oxidation of **58** using a modified Swern oxidation afforded aldehyde **59**.




**Scheme 24. Synthesis of important intermediate 59.**

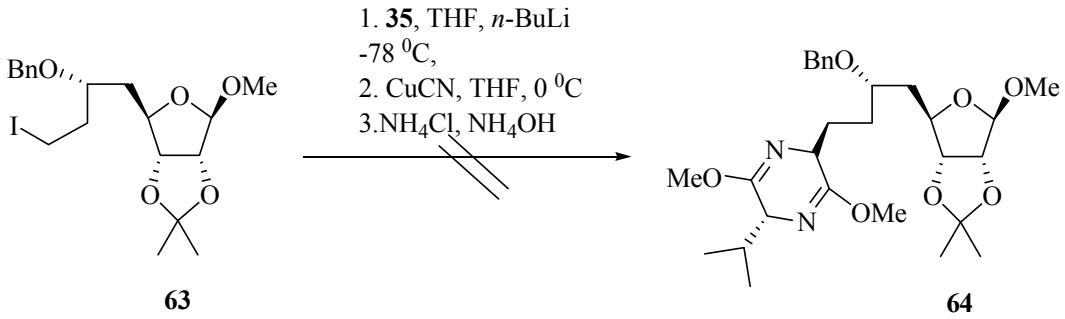
With aldehyde **59** available, focus turned to the allylation reaction with the aforementioned Brown's reagent to be followed by side chain modification (Scheme 25).[93] Thus, freshly prepared (-)-B-allyldi*iso*pinocampheylborane (*in situ*) was reacted with the aldehyde **59** at low temperature to provide the desired enantiomerically pure **60** in a yield of 95% in two steps. The C-6' hydroxyl group of compound **60** was protected by benzyl bromide under the strong basic conditions to furnish **61** in 70% yield.[117]




**Scheme 25. Synthesis of 63.**

With compound building block **B** (**61**) and building block **C** (**35**) obtained, the alkylation coupling reaction to the requisite amino acid was considered. As mentioned in Chapter 3, the asymmetric synthesis of terminal α-amino acids via Schöllkopf's chiral auxiliary is best conducted using lithiated (2*R*)-2,5-dihydro-3,6-dimethoxy-2-*iso*propylpyrazine and halogen derivatives of the co-reactant.[104] The most common haloderivative is the bromospecies. However, iododerivative **63** was chosen for its ease of preparation and efficiency as a good leaving group. Therefore, compound **61** was subjected to a two-step process: (i) the oxidative-cleavage with osmium tetroxide and sodium periodate followed by (ii) reduction with sodium borohydride to yield the primary

alcohol in the side chain of **62** with the moderate yield in two steps. Then, the primary alcohol in **62** was converted to iodide **63** in moderate yield, according to standard iodination conditions.[85b] Finally, the alkylation reaction (Scheme 26) of iodide **63** with lithiated (2*R*)-2, 5-dihydro-3, 6-dimethoxy-2-*iso*propylpyrazine (*in situ*) was performed at low temperature with copper cyanide catalysis. Unfortunately, this alkylation reaction did not provide the desired product **64**, giving only recovered reactant **63** and a very strong UV absorbing material (TLC). The explanation for this failure may lie in two areas: (i) the pyrazine unit may decompose with *n*-butyl lithium at the reaction temperature (> -78$^0$C) to give the UV product, and/or (ii) the reaction intermediate was extremely susceptible to moisture.

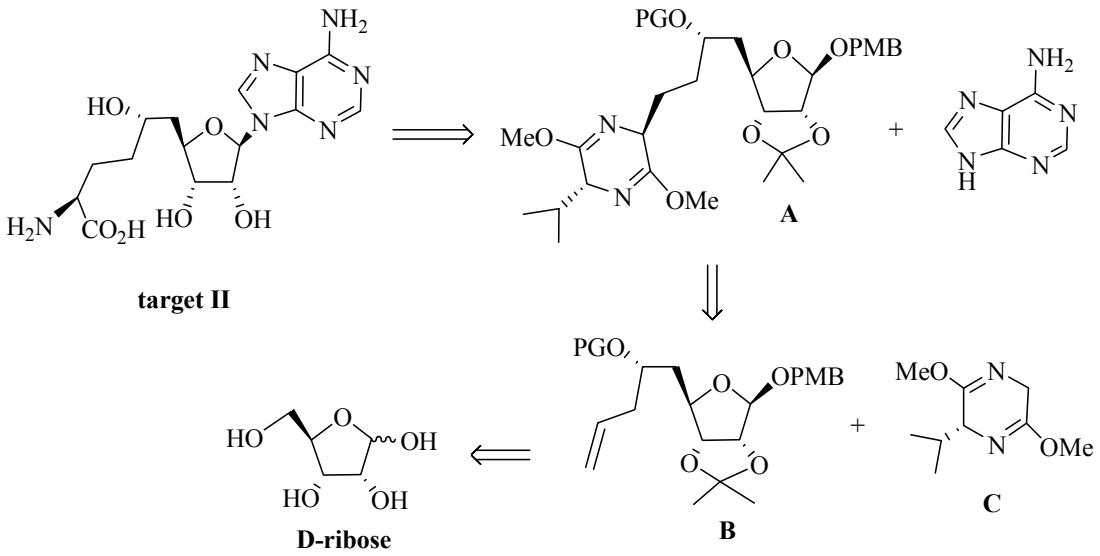



**63** **64**

**Scheme 26. Synthesis of 64.**

Another possible concern arose when thinking further about using Schöllkopf's chiral auxiliary: that is, after installation of the pyrazine part on iodide **63**, in the removal of the C-1 methoxyl group step under the usual strong acid conditions for coupling with the heterocyclic base may affect the pyrazine center. Thus, removal of the methoxyl group before setting in place the pyrazine unit was reviewed as a more suitable approach

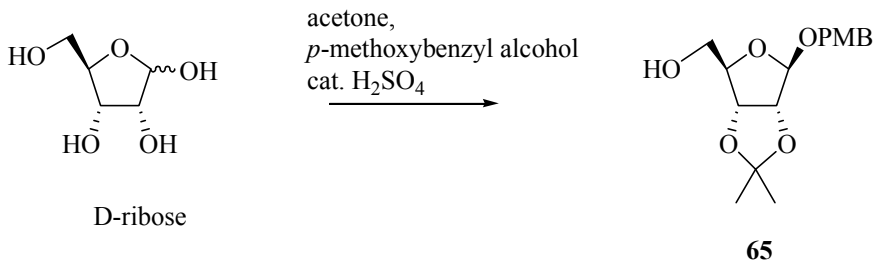
for target **II**, where *p*-methoxybenzyl protecting seemed viable, building block **B** of Scheme 27.




PG = Protecting Group

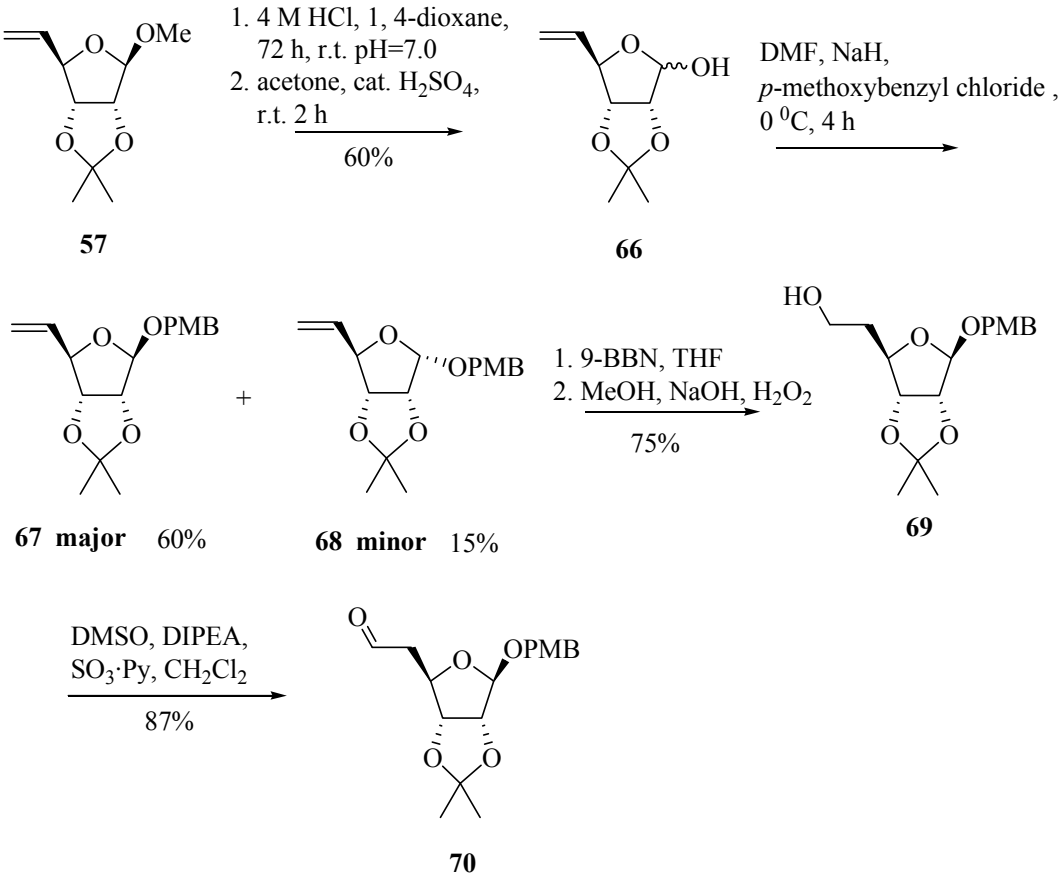
**Scheme 27. Optimized approach for target II.**

To explore conditions to **B**, a simple method was investigated (Scheme 28). Thus, protection of D-ribose using anhydrous acetone in the presence of excess of *p*-methoxybenzyl alcohol afforded the desired **65**. However, **65** and unreacted *p*-methoxybenzyl alcohol showed the same polarity (TLC), and could not be separated by routine silica gel column chromatography.



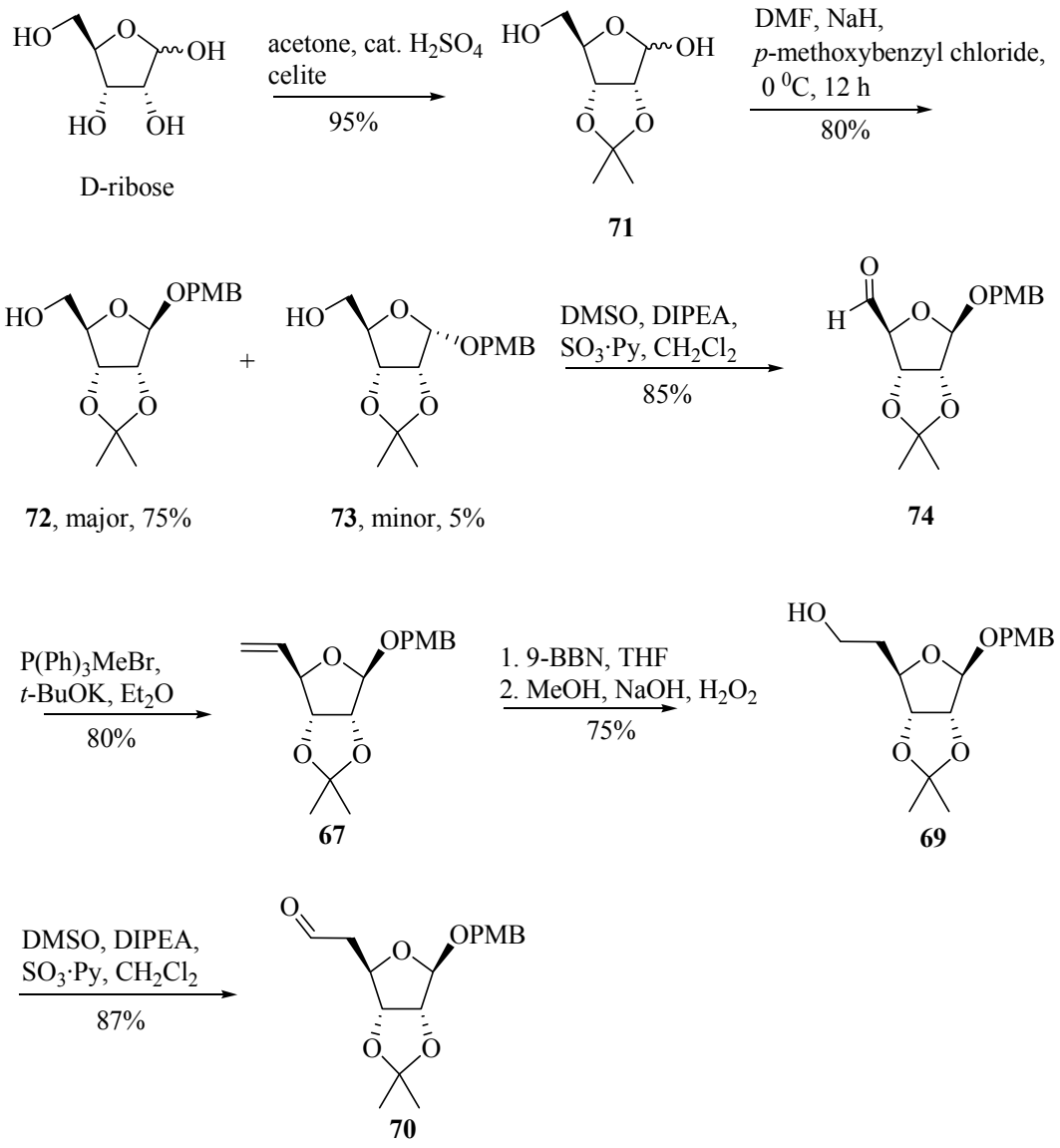

**Scheme 28. Synthesis of 65.**

Thus, another strategy was evaluated (Scheme 29) to construct the building block **B**. In that regard, compound **57** (Scheme 29) was treated with 4 M hydrochloric acid in dioxane to afford the intermediate-1,2,3-triols. That was followed by 2,3-diol protection with anhydrous acetone and sulfuric acid catalysis to give **66** in 60% yield in two steps. Protection of **66** with *p*-methoxybenzyl chloride under strongly basic conditions furnished the desired **67** as a major product and **68**, as a minor product. At this stage, compound **67** and **68** could be distinguished by $^{1}$H NMR. After separation by silica gel column chromatography, **67** was subjected to hydroboration-oxidation to result in the primary alcohol **69** in moderate yield. Oxidation of **69** using modified Swern oxidation conditions afforded the aldehyde **70** in 87% yield.




**Scheme 29. Synthesis of 70.**

Although the important intermediate **70** could be obtained by the approach shown in Scheme 29, the transformation from **57** to **66** was time-consuming and led to only a moderate yield. Furthermore, this route encountered the by-product **68** when producing **67**. To overcome these disadvantages, a more efficient approach for constructing **70** was envisioned and shown in Scheme 30.

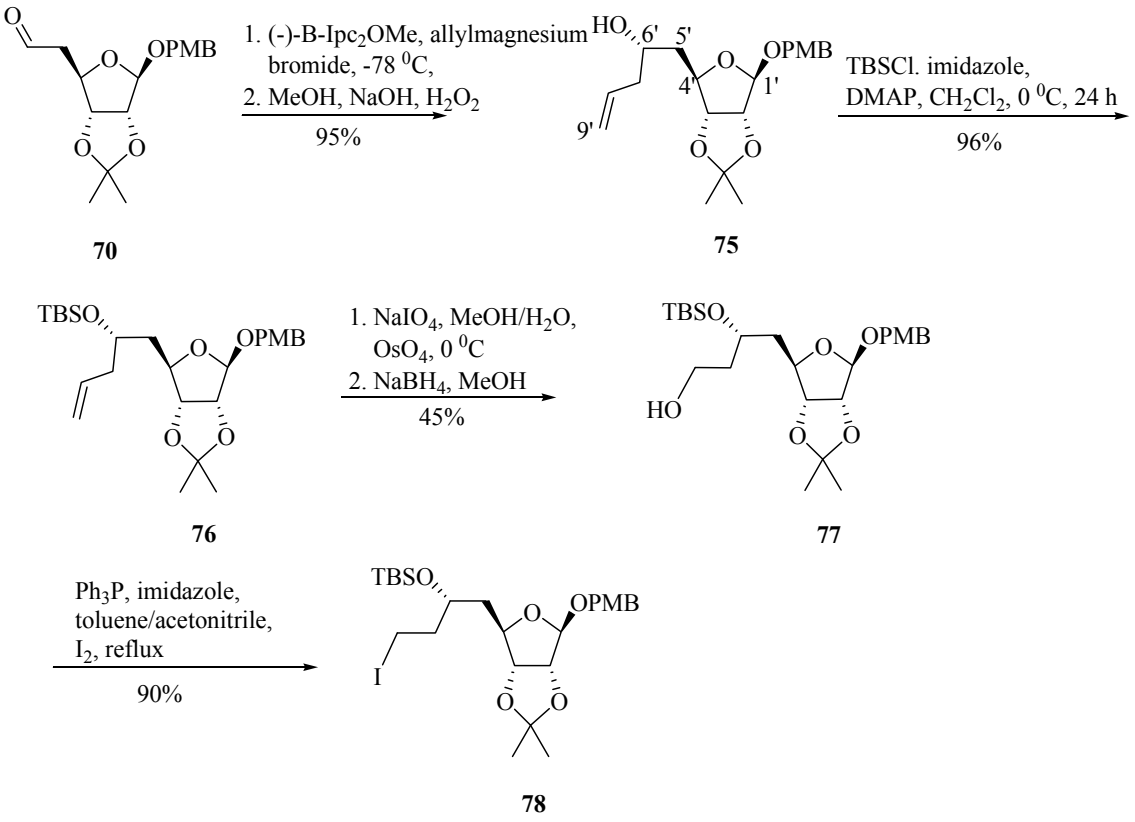



**Scheme 30. Another approach for 70.**

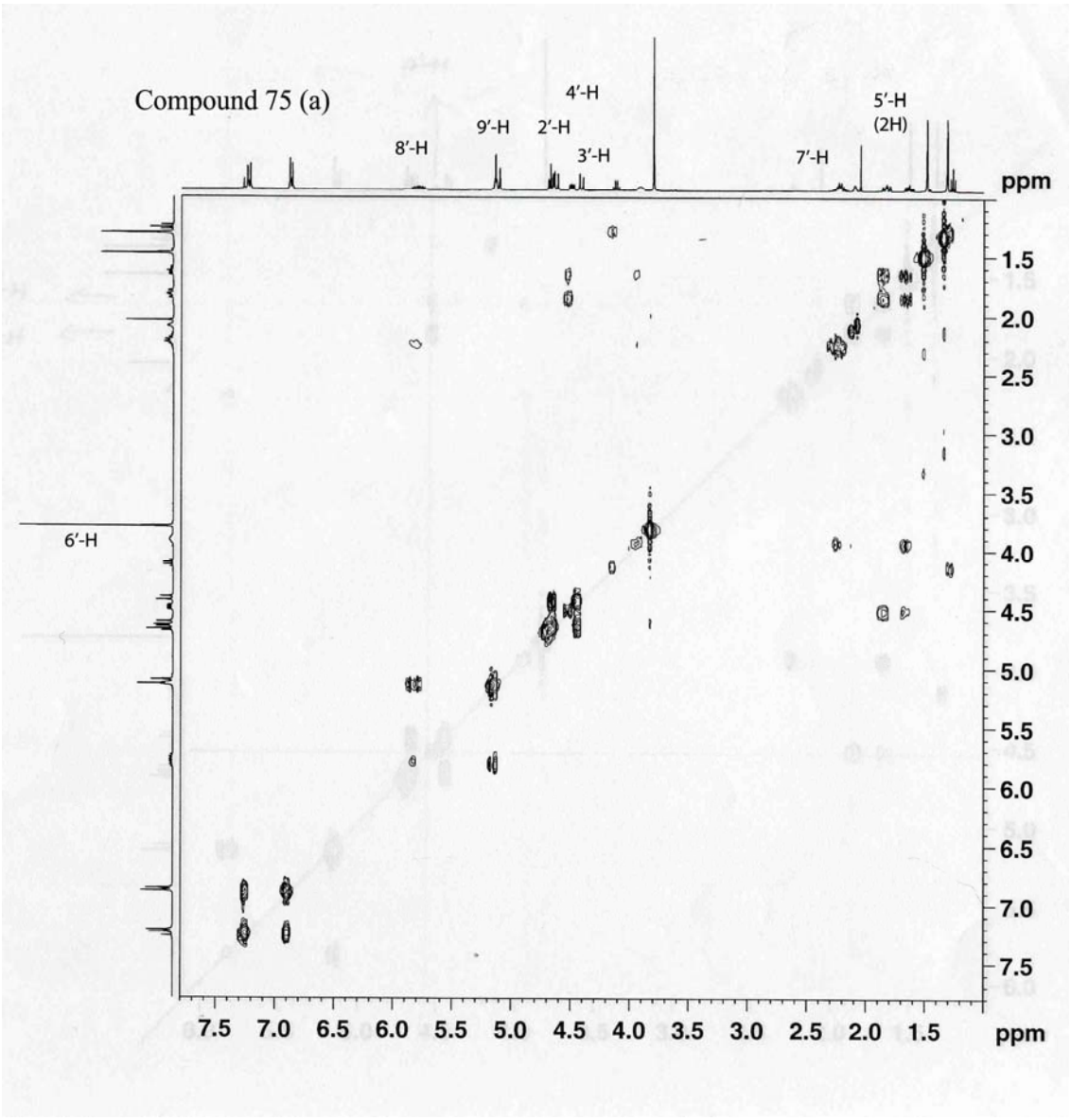
In this method, protection of D-ribose by acetone under anhydrous conditions provided **71**. Then, compound **71** was placed in the vacuum drying oven for 12 h before it was subjected to the next modification. Using *p*-methoxybenzyl chloride to protect the primary alcohol of **71** under the basic conditions afforded **72** as the major product in 75% yield and, disappointingly, **73** as a by-product in 5% yield. Following separation of these

two products by silica gel column chromatography, oxidation of **72** using modified Swern oxidation conditions furnished aldehyde **74** in 85% yield. Subjecting **74** to a Wittig reaction with methyl triphenylphosphonium bromide under the strong basic conditions formed **67** in good yield.[84a] The transformation of **67** to **70** was the same that in Scheme 29.

With aldehyde **70** in hand, further modifications toward building block **B** as outlined were pursued in Scheme 31. Subjecting aldehyde **70** to the Brown stereospecific hydroboration reagent of freshly prepared (-)-B-allyldi*iso*pinocampheylborane (*in situ*), furnished the desired enantiomerically pure **75** in 95% yield in two steps, whose structure was confirmed by two-dimensional NMR spectroscopy ($^1$H, $^1$H-COSY) shown in Figure 26. The ($^1$H, $^1$H-COSY) 2D NMR spectrum of compound **75** in $CDCl_3$ (Scheme 31) was explained here. The diagonal peak labeled 8'-H has two cross-peaks: one is the coupled with 9'-H (2H) and is placed symmetrically around the diagonal line; and, the other is coupled with 7'-H (2H). From the latter cross-peak, the position of 6'-H is deduced. The diagonal peak of 6'-H has two cross-peaks: one results from the protons of the neighboring 7'-H (2H) group and the other belongs to the proton of a *trans* 5'-H. Beginning with the diagonal peak of *trans* 5'-H, a symmetrical cross-peaks of *cis* 5'-H is confirmed. From the cross-peaks of *trans* 5'-H and *cis* 5'-H, the diagonal peak of 4'-H is identified. When moving from the diagonal line, the diagonal peaks (2'-H and 3'-H) and their symmetric cross-peaks are proved. The remaining diagonal peaks are not accompanied by any cross-peak.




**Scheme 31. Synthesis of iodide 78.**


Compound 75 (a)
8′-H
9′-H
2′-H
4′-H
3′-H
7′-H
5′-H
(2H)
6′-H
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
ppm

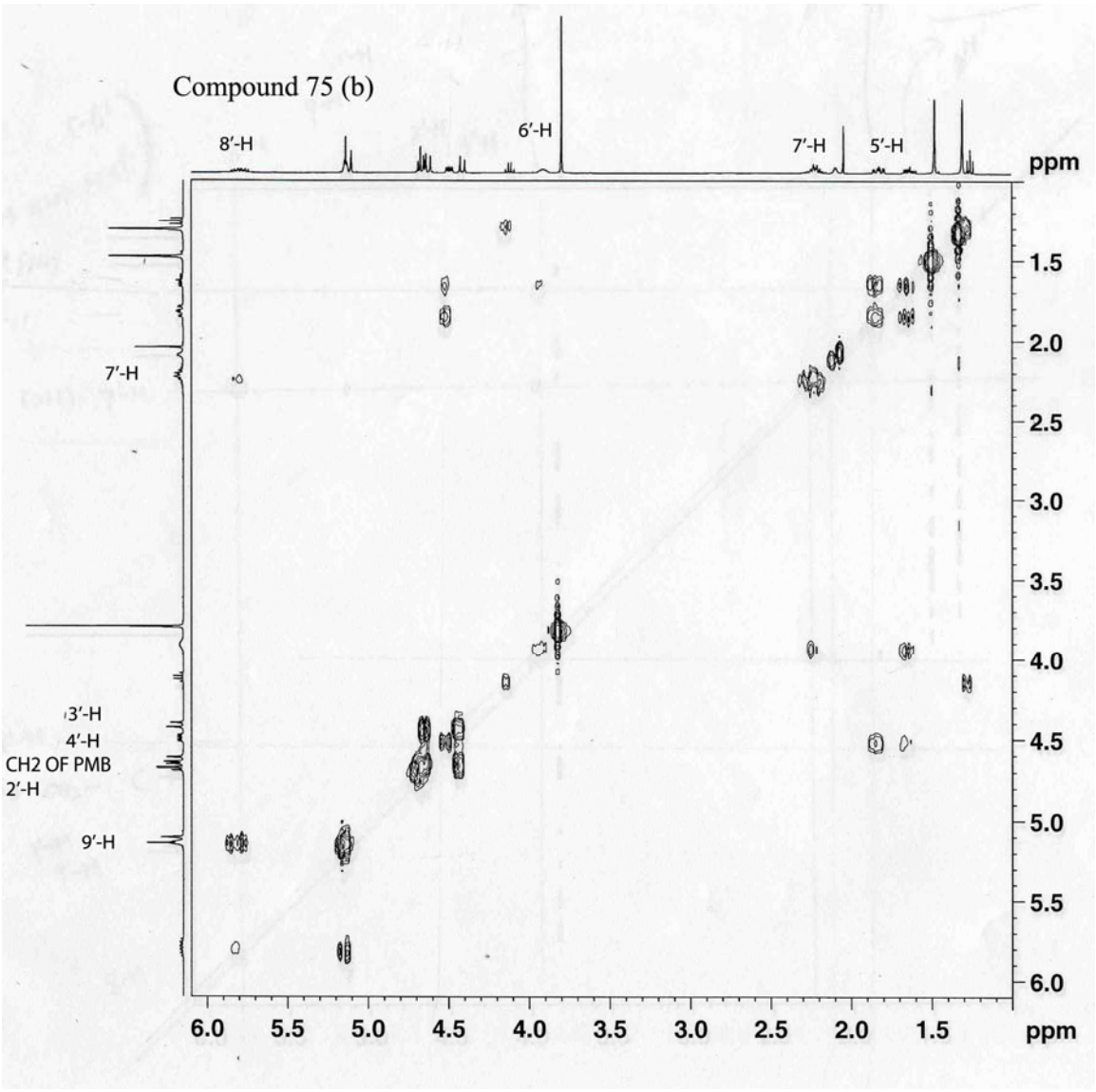
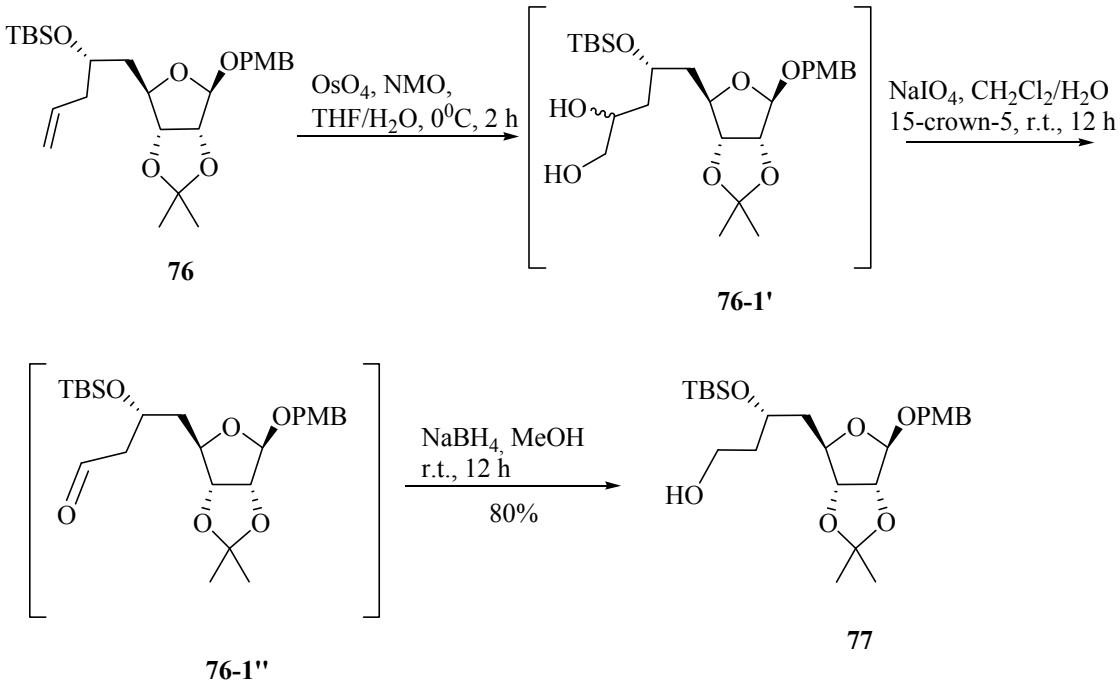



**Figure 26. COSY spectrum of compound 75 in deuteriochloroform: (a) the small one chemical shift δ (1.0-7.8) and (b).the magnified one δ (1.0-6.1).**

Protection of the newly formed secondary alcohol of **75** as a *tert*-butyldimethylsilyl ether with *tert*-butyldimethylsilyl chloride and imidazole catalyzed by DMAP provided **76** in 96% yield.[118] Under oxidative-cleavage and reduction conditions with osmium tetraoxide/sodium periodate, followed by sodium borohydride, the C-8

primary alcohol of **77** was achieved in moderate yield. Finally, iodination of **77** under the standard reaction conditions afforded iodide **78** in 90% yield.

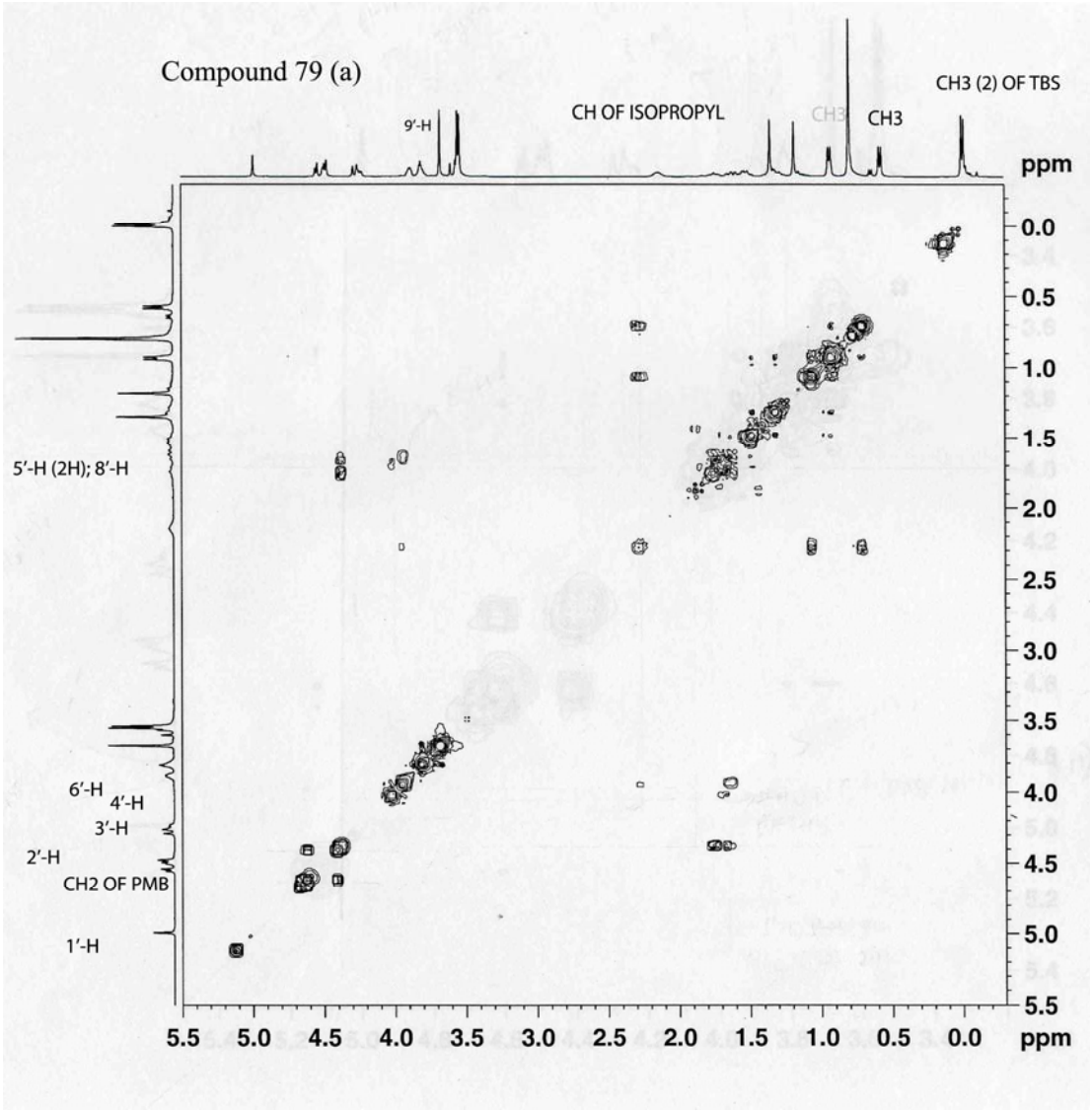
Considering the poor yield in the oxidative-cleavage/reduction series (from **76** to **77**), an optimization method was sought (Scheme 32) that was based on the approach in Scheme 18. Thus, double bond of **76** was oxidized under osmium tetraoxide/N-methylmorpholine N-oxide (NMO) conditions to provide the diol **76-1'**. After isolating **76-1',** it was subjected to cleavage with sodium periodate to furnish aldehyde **76-1''**. The intermediates **76-1'** and **76-1''** could be identified by $^1$H NMR spectroscopy and TLC. Luche reduction of the aldehyde **76-1''** achieved **77** in excellent yield (three steps, 80%).




**76** **76-1'** **76-1''** **77**

**Scheme 32. Optimization approach for 77.**

Compound **78** was then used for the Schöllkopf coupling reaction (Scheme 33), for the purpose of constructing the terminal amino acid unit. Thus, **78** was alkylated with the lithio derivative of **35** (Scheme 15) in anhydrous THF at low temperature to afford compound **79**, whose structure was proved by spectral data: NMRs ($^{1}$H and $^{13}$C) and two-dimentional NMR ($^{1}$H, $^{1}$H, COSY) shown in Figure 27. The ($^{1}$H, $^{1}$H-COSY) 2D NMR spectrum of compound **79** in $CDCl_3$ (Scheme 33) was addressed here. The diagonal peak of 2'-H has one symmetric cross-peak, belonging to the proton of 3'-H. When proceeding on the diagonal peak of 4'-H, two cross-peaks are confirmed: a *trans* 5'-H and a *cis* 5'-H. From the diagonal peak of 6'-H, the *trans* 5'-H is identified by their cross-peak. When proceeding along the diagonal line, the diagonal peak of pyrazine (2H) has two cross-peaks, one is the the proton of CH group of *iso*propyl in pyrazine; and the other belongs to the proton of 9'-H (1H). From the cross-peak of the latter, 8'-H (2H) are proved. Finally, the remaining diagonal peaks are not accompanied by any cross-peak.


Compound 79 (a)
9′-H
CH OF ISOPROPYL
CH3
CH3
CH3 (2) OF TBS
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5′-H (2H); 8′-H
6′-H
4′-H
3′-H
2′-H
CH2 OF PMB
1′-H
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

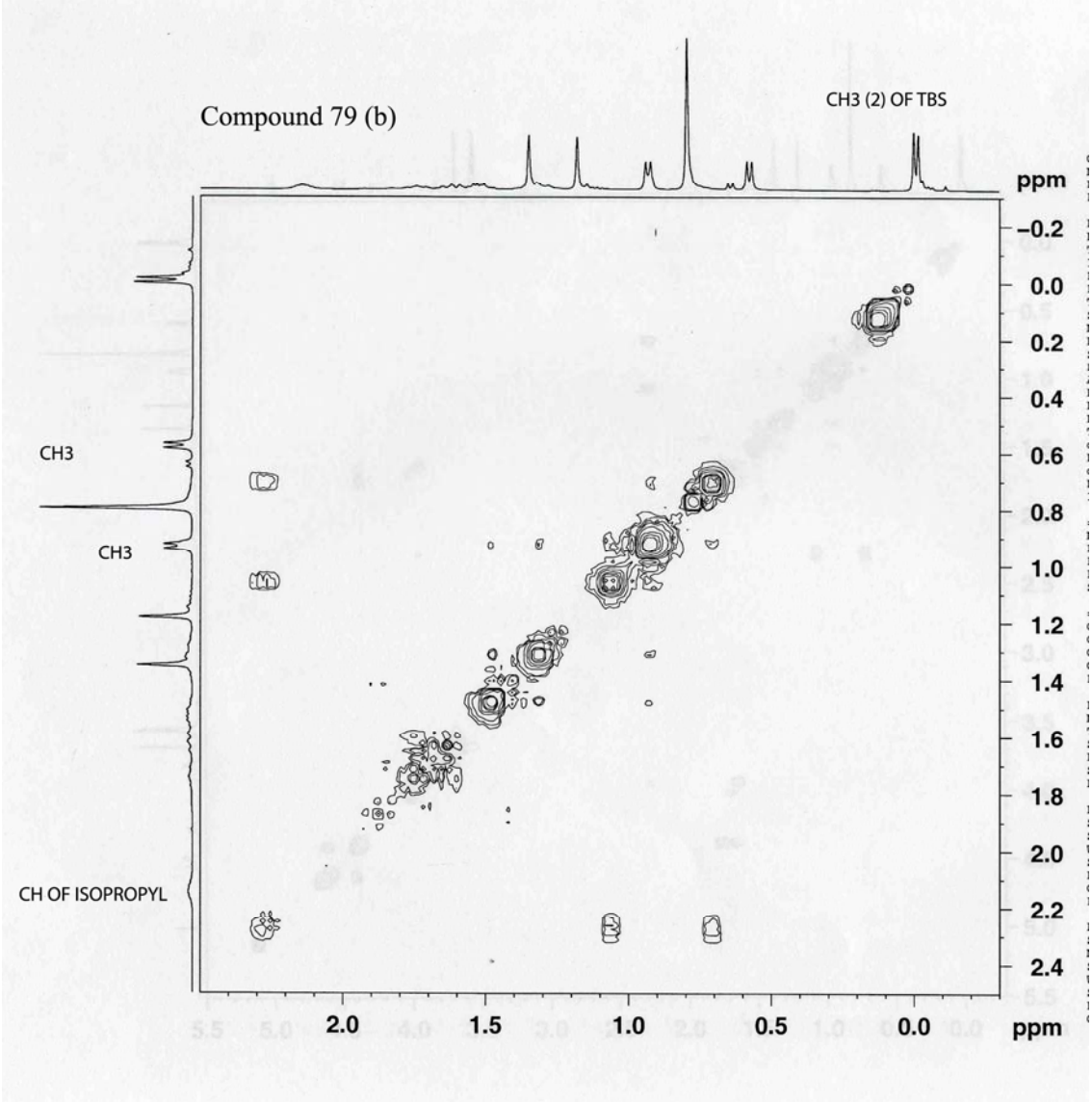
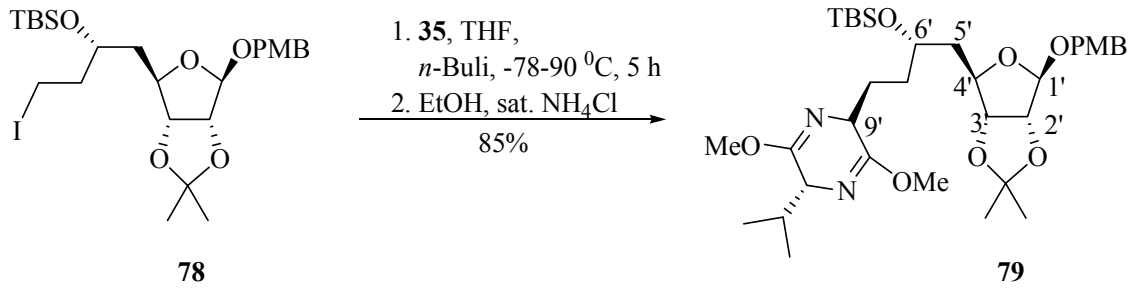



**Figure 27. COSY spectrum of compound 79 in deuteriochloroform: (a), the small one chemical shift δ (-0.30-5.5) and (b).the magnified one δ (-0.30-2.5).**

As before, the stereospecificity transformation (**78** to **79)** arises from the steric interactions imposed by bulky moiety of **78** with chiral dihydropyrazine anion (lithio (2*R*)-2, 5-dihydro-3, 6-dimethoxy-2-*iso*propylpyrazine) to the less hindered face of the masked amino acid to afford diastereoselectively the *trans* product **79** in 85% yield.[104,108]

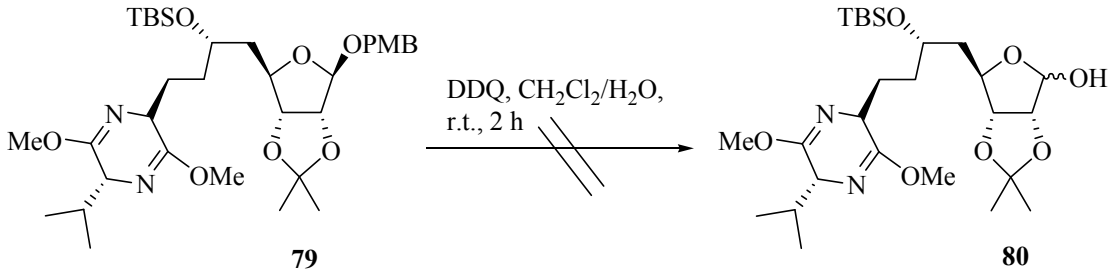



**78** **79**

**Scheme 33. Synthesis of 79.**

To this point, compound **79** (building block **A**) was successfully obtained from D-ribose in 13 steps. Attention then shifted to coupling the heterocyclic base (adenine) with building block **A** (**79**). Therefore, deprotection of the PMB group became very important.

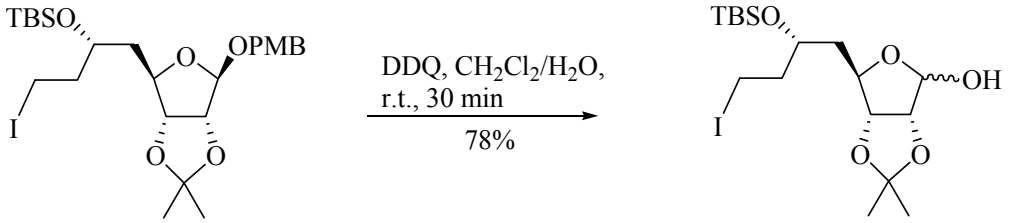
In this direction, treatment of **79** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was expected to follow oxidative cleavage to compound **80** (Scheme 34).[119] However, this transformation (**79** to **80**) resulted in a complex mixture (from $^{1}$H NMR analysis). Possible reasons for this result are: (i) decomposition (by $^{1}$H NMR spectra and TLC analysis) of the masked amino acid unit (pyrazine) during the oxidation-reduction process of removal of the PMB group; and/or, (ii) the anomeric center of **79** could not withstand the oxidative-reduction cleavage conditions.




**79** **80**

**Scheme 34. Synthesis of 80.**

Because of the failure of the **79** to **80** transformation (Scheme 34), another strategy was explored (Scheme 35) with compound **78** that lacked the pyrazine unit. This proved successful by producing the desired compound **81**.

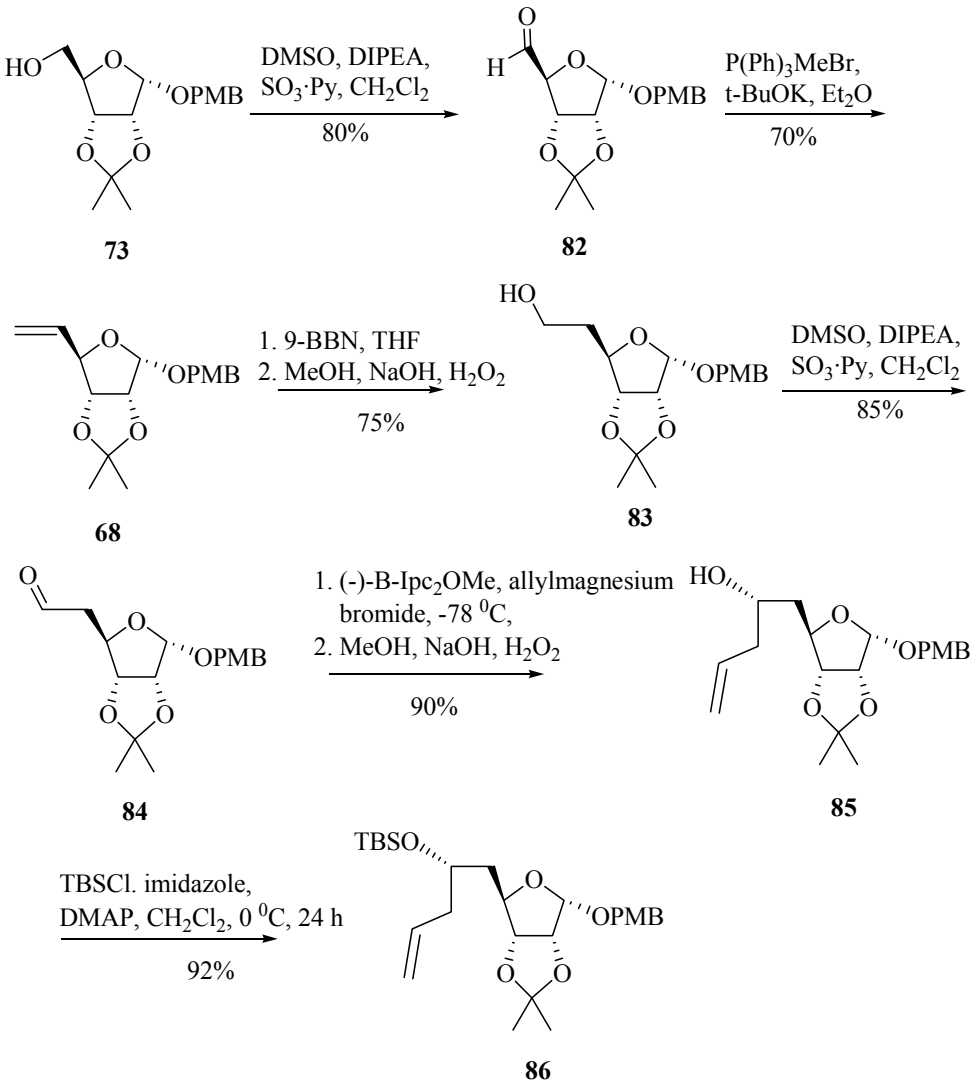



**78** **81**

**Scheme 35. Synthesis of 81.**

During these explorations, the minor product **73** was accumulated for the modifications in Scheme 36. Oxidation of compound **73** under standard Swern oxidation conditions provided **82** in 80% yield. Compound **82** was subjected to Wittig reaction conditions to give **68** in moderate yield (compare to **68** in Scheme 29). Hydroboration-oxidation of compound **68** was carried out to afford the primary alcohol **83** in 75% yield. Oxidation of **83** again using modified Swern oxidation conditions afforded aldehyde **84**

in good yield (85%). Calling again the Brown stereospecific hydroboration reagent freshly prepared (-)-B-allyldi*iso*pinocampheylborane (*in situ*) on aldehyde **84**, furnished the desired enantiomerically pure **85** in 90% yield for two steps. Finally, protection of the newly formed side chain secondary alcohol of **85** as a *tert*-butyldimethylsilyl ether with *tert*-butyldimethylsilyl chloride and imidazole catalyzed by DMAP provided **86** in 92% yield.




**Scheme 36. Synthesis of 86.**

Compound **86**, just like intermediate compound **76**, was also an important building block with further modifications to synthesize target **II**.

Due to difficulties in dealing with deprotection of the PMB group and possible challenge in the installation of the heterocyclic base (adenine) on the 5-member ring, this dissertation research finished the important intermediates: **79**, **81** and **86**. Compound **79**

was the most direct precursor of target **II** and it needs more research process to target **II** from here.

# CONCLUSION

Sinefungin, a naturally occurring complex nucleoside, has many important biological activities, including antifungal, antitumor, antiparasitic, antiviral and amoebicidal activities. The nature of these biological activities results from its inhibition of a variety of AdoMet-dependent methyltranferase enzymes. In one instance, the resulting inhibition of AdoMet methyltransferase leads to the disruption of important biomethylations, such as the viral mRNA 5'-capping process, which leads to blocking viral replication. However, the clinical usefulness of sinefungin has been precluded by its toxicity in *in vivo* assays.

To circumvent the detrimental side-effects of sinefungin, structural analogs became the focus of this dissertation. The synthesis of a carbocyclic analog of sinefungin (target **I**) in a stereocontrolled fashion from D-ribose and important intermediates (**47** for target **I** and **53, 55** for carbocyclic sinefungin) has been investigated. Variation on this approach to sinefungin-based analog using **79, 81** and **86 (**to target **II)** is described.

The key strategies for the construction of C-6' and C-9' stereocenters of targets **I** and **II** brought forth efficient catalytic asymmetric syntheses. The C-6' hydroxyl chiral center was found accessible by the highly diastereoselective allylborating agent: (+)

and/or (-)-B-allydi*iso*pinocampheylborane ($Ipc_2BCH_2CH=CH_2$). This asymmetric homoallylic alcohol reagent provided access to either diastereomeric possibility at C-6'. The C-9' amino acid stereochemistry of targets **I** and **II** was established by a diastereoselective alkylation reaction with the Schöllkopf reagent. Finally, coupling of the heterocyclic base (adenine) with these 5-membered rings employed standard $S_N2$ substitution reactions.

The synthetic processes analyzed provide adaptable possibilities to a number of structural sinefungin analogs for biological evaluation.

## EXPERIMENTAL SECTION

### Materials and Methods:

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker AV 250 Spectrometer (operated at 250 or 62.9 MHz, respectively) or AV 400 Spectrometer (operated at 400 or 100 MHz, respectively). The assignments of various NMR spectra were assisted by homonuclear ($^{1}H/^{1}H$) correlation spectroscopy (COSY) on the AV 400 Spectrometer. All $^{1}H$ chemical shifts are reported in δ relative to the internal standard tetramethylsilane (TMS, δ 0.00). $^{13}C$ chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.23) or relative to DMSO-$d_6$ (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. Merck silica gel 60-F254 precoated silica gel plates with visualization by the irradiation with Mineralight UVGL-25 lamp, or exposure to iodine vapor, or exposure to the basic solution of $KMnO_4$. 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.

**(1*R*,3*S*)-Cyclopent-4-ene-1,3-diyldiacetate (5).** The freshly synthesized cyclopentadiene (189 g, 2.85 mol) was immediately dissolved in a 5 L three-neck round bottom flask containing 2.2 L methylene chloride, and sodium carbonate (724 g, 6.83 mol) was added to the above reaction mixture. The mixture of sodium acetate (14.5 g, 0.177 mol), peracetic acid (363 mL, 5.45 mol) and methylene chloride (150 mL) were added dropwise to the stirring cyclopentadiene solution, which was pre-cooled to -20 $^0$C. During the adding process, the temperature between -10 $^0$C and 0 $^0$C, was maintained until all the mixture was completely added. The whole reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered and the filtrate was evaporated to give pale yellow liquid product, which was crude monoepoxide **4** and could be directly used to the next step.

The monoepoxide **4** dissolved in anhydrous THF (145 mL) was added dropwise to a stirred solution of *tetrakis*(triphenylphosphine)palladium(0) (4.98 g, 1.72 mmol) and acetic anhydride (255 mL, 2.70 mol) in THF (350 mL). The reaction mixture was maintained from

-5 $^0$C to 0 $^0$C and under nitrogen condition stirred at room temperature overnight. After evaporation of THF at room temperature under reduced pressure, the resulting solution was passed through a pad of silica gel and anhydrous magnesium sulfate using ether as eluant. The solvent was removed and the residue was distilled using high vacuum at the temperature 90-95 $^0$C to afford a pale yellow liquid (139 g, 36 % for two steps), which was diacetate **5** in agreement with the literatures.[61b,79]

**(1*R*,4*S*)-4-Hydroxycyclopent-2-enyl acetate (6).** Diacetate **5** (139 g, 752 mmol) was added to a three-neck 5 L round flask, which contained the 0.1 M phosphate buffer (1.00

L) and the pH was maintained at 7.00-7.40 by the addition of 6 M NaOH. The enzyme, *pseudomonas cepacia lipase* (5.18 g), was added to the above flask and the pH of the reaction mixture was kept constant (7.00-7.40) during the whole hydrolysis process by adding dropwise the 1 M NaOH solution (753 mL). After the reaction was finished (it was seen from the pH meter that the pH was constant within 30 min), the solution was filtered through celite and extracted with EtOAc. The combined organic layer was dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the crude yellow liquid. Finally, the yellow liquid was distilled at the reduced pressure (at the temperature 88-93 $^0$C) to get the pure monoacetate **6** (86.7 g, 82 %) as a light yellow solid. The $^1$H NMR data agreed with the literature.[83a]

**(1*R*,4*S*)-4-(Diethoxyphosphoryloxy)cyclopent-2-enyl acetate (7).** Diethyl chlorophosphate (9.32 g, 52.7 mmol) was added dropwise to the solution of monoacetate **6** (5.75 g, 40.5 mmol) dissolved in $CH_2Cl_2$ and pyridine (6.00 mL, 72.9 mmol), which was cooled to 0-5 $^0$C. The reaction mixture was stirred at room temperature for 5 h and 5% aqueous HCl (30.0 mL, cooled with ice-water) was added to the above reaction mixture. After dilution of the reaction mixture with $CH_2Cl_2$ (50.0 mL) and washing with saturated equeous $NaHCO_3$ and brine, the organic phase was obtained. After drying over anhydrous $MgSO_4$ and removing the solvent under reduced pressure, **7** (11.0 g, 98 %) was obtained as a pale yellow liquid and could be used in the further steps without purification.

**(1*R*, 2*R*, 3*S*, 4*S*)-4-(Diethoxyphosphoryloxy)-2,3-dihydroxycyclopentyl acetate (8).** 50 % aqueous NMO (N-methylmorpholine N-oxide, 27.0 mL, 54.0 mmol) was added to a solution of **7** (16.8 g, 60.3 mmol) in 120 mL acetone at 0 $^0$C. $H_2O$ (50.0 mL) was added

until the solution became clear. The oxidant, $OsO_4$ (119 mg, 0.468 mmol) was slowly added to the above clear solution. The whole reaction mixture was stirred at room temperature overnight. After evaporating the solvents under reduced pressure, the residue was purified by silica gel column chromatography with EtOAc as eluent to afford the colorless liquid **8** (9.24 g, 50 %).

**(1*R*,2*R*,3*S*,4*S*)-4-(Diethoxyphosphoryloxy)-2,3-(*iso*propylidenedioxy)-cyclopentyl acetate (9).** A solution of **8** (9.24 g, 29.6 mmol) in anhydrous acetone (85.0 mL, 1.16 mol) and 2,2-dimethoxypropane (22.0 mL, 178 mmol) was treated with *p*-toluenesulfonic acid monohydrate (288 mg, 5.0 % mmol). The reaction was stirred at r.t. overnight. Solvents were evaporated under vacuum, the residue was dissolved in EtOAc and washed with $Na_2CO_3$ (20.0 mL) and brine. The organic layer was dried over $MgSO_4$, filtered and solvents removed under reduced pressure to provide **9** (9.90 g, 95 %) as pale yellow liquid, which could be used in the next step without further purification.

**(1*R*,2*R*,3*S*,4*S*)-4-Hydroxy-2,3-(*iso*propylidenedioxy)cyclopentyl-1-yl diethyl phosphate (10).** Compound **9** (9.90 g, 28.1 mmol) was dissolved in THF (25.0 mL) and added to a solution of $LiOH{\cdot}H_2O$ (1.83 g, 43.6 mmol) in $H_2O$ (40.0 mL). The reaction was stirred at room temperature overnight. After removal of THF and most of $H_2O$ under vacuum, the residue was extracted by $CH_2Cl_2$ (3×50 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated the solvent to give **10** (8.72 g, 82 %). The $^1H$ NMR data was agreed with the literature.[83a]

**(-)-(4*R*,5*R*)-4,5-*O*-*iso*propylidene-2-cyclopentenone (11)-based on the monoacetate 6.** Pyridinium chlorochromate (15.1 g, 70.1 mmol) and celite (10.0 g) were added to a solution of compound **10** (8.72 g, 28.1 mmol) in anhydrous $CH_2Cl_2$ (105 mL). The

reaction mixture was stirred at room temperature for 36 h. The reaction mixture was diluted with $CH_2Cl_2$ and filtrated to remove the celite. The filtrate was evaporated under reduced pressure to give the residue, which was purified by column chromatography (1/1, Hexane/EtOAc) to afford pure **11** (1.95 g, 50 %) as the yellow liquid: $^1$H NMR (250 MHz, $CDCl_3$) δ 7.62 (dd, J=2.25, 6.0, 1H), 6.23 (d, J=6.0, 1H), 5.28 (dd, J= 2.25, 5.50, 1H), 4.48 (d, J=5.50, 1H), 1.42 (s, 6H). The NMR spectral data agreed with the literature.[84a]

**Methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (12).** 2,2-dimethoxypropane (76.0 mL, 1.06 mol) was added to a solution of D-ribose (32.0 g, 213 mmol) in acetone (300 mL) and methanol (100 mL). Sulfuric acid (4.00 mL, 5 % mmol) was added to the above solution and the reaction mixture was stirred at room temperature overnight. After neutralized with ammonium hydroxide, $H_2O$ (50.0 mL) and EtOAc (200 mL) were added to the reaction mixture. The aqueous layer was extracted with EtOAc, and the combined organic phase was concentrated under reduced pressure to afford **12** (58.4 g, 98 %) as colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.0 (s, 1H), 4.87 (d, J=5.90, 1H), 4.62 (d, J=5.90, 1H), 4.46 (t, J=2.80, 1H), 3.75-3.60 (m, 2H), 3.46 (s, 3H), 3.28 (dd, J=10.50, 2.50, 1H), 1.51 (s, 3H), 1.34 (s, 3H).

**Methyl 5-deoxy-5-iodo-2,3-*O*-*iso*propylidene-β-D-ribofuranoside (13).** The furanoside **12** (58.4 g, 286 mmol) was dissolved in toluene (600 mL) and acetonitrile (150 mL). After the addition of imidazole (29.2 g, 429 mmol) and triphenylphosphine (90.0 g, 343 mmol), the iodine was introduced in approximately 100 mg portions to the above reaction mixture until the reaction mixture remained dark-brown in color. The dark-brown solution was heated to reflux for 30 min and cooled to room temperature.

Diethyl ether (200 mL) was added to dilute the solution and then the solution was washed with 10% sodium thiosulfate solution and brine. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to obtain a residue, which was purified through a short plug of silica gel (elution with 20:1 Hexanes/EtOAc) to provide **13** (47.1 g, 60 %) as a colorless oil. The $^1$H NMR data was in agreement with the literature.[85]

**4,5-Dideoxy-2,3-*O*-*iso*propylidene-D-*erythro*-4-pentenose (14).** The iodide **13** (47.1 g, 150 mmol) was dissolved in anhydrous THF (300 mL) in a flame-dried flask under a nitrogen atmosphere. The above solution was cooled to -78 $^0$C and *n*-BuLi (89.7 mL, 224 mmol, 10. 0 M solution in THF) was added dropwise over a period of 30 min by syringe. The reaction mixture was stirred at -78 $^0$C for 2 h and quenched with solid $NH_4Cl$ (15.0 g). The mixture was allowed to warm to -40 °C and $H_2O$ (50.0 mL) was slowly added and the aqueous phase was extracted with diethyl ether (3 × 50.0 mL). The combined organic solution was dried with anhydrous $MgSO_4$ and concentrated in vacuo (since the aldehyde **4** is somewhat volatile, the temperature of the rotorvapor was kept below 30 $^0$C). The aldehyde **14** (36.2 g, 115 %) was obtained as a colorless oil, which was used in the next reaction without further purification.

**(4*S*,5*R*)-4,5-*O*-*iso*propylidenehepta-1,6-diene-3,4,5-triols (15).** The aldehyde **14** (36.2 g, 232 mmol) was dissolved in anhydrous $CH_2Cl_2$ (100 mL) under a nitrogen atmosphere and the above solution was cooled to -40 $^0$C. Vinylmagnesium bromide (350 mL, 1.0 M in THF) was added dropwise via a cannula to the above stirred solution over 1 h. The reaction mixture was kept at the same temperature for 2 h and allowed to warm to room temperature. Saturated $NH_4Cl$ (30.0 mL) was added to quench the reaction and EtOAc (3×150 mL) was used to extracted the organic phase. The organic phase was

washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified on silica gel column chromatography (7/1, Hexane/EtOAc) to afford the diene **15** (15.6 g, 30 %): $^1$H NMR (400 MHz, $CDCl_3$) δ 6.10 (m, 1H), 5.55 (m, 1H), 5.23 (m, 4H), 4.54 (t, J=6.0, 1H), 4.16 (dd, J=6.40, 2H), 3.23 (dd, J=6.50, 1H), 1.54 (s, 3H), 1.39 (s, 3H).

**(-)-(4*R*,5*R*)-4,5-*O*-*iso*propylidene-2-cyclopentenone (11)-based on D-ribose.** The diene **15** (15.6 g, 84.2 mmol) was dissolved in anhydrous $CH_2Cl_2$ (300 mL) and the above solution was flushed with $N_2$ for 30 min at room temperature. Grubbs' catalyst 1$^{st}$ generation (1 % mmol, 693 mg) was added to the diene solution. After stirred at 40 $^0$C for 48 h, pyridinium dichromate(63.4 g, 168 mmol), 4 Å molecular sieves (15.0 g) and acetic acid (0.24 mL, 5 mmol %) were added to the above reaction mixture. The reaction mixture was stirred at room temperature for 12 h and filtrated over celite pad with EtOAc. After removal of the solvent, the residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **11** (2.90 g, 22 %): $^1$H NMR (250 MHz, $CDCl_3$) δ 7.62 (dd, J=2.25, 6.0, 1H), 6.23 (d, J=6.0, 1H), 5.28 (dd, J= 2.25, 5.50, 1H), 4.48 (d, J=5.50, 1H), 1.42 (s, 6H).

**Methyl-2,3-*O*-cyclopentanyl-β-D-ribofuranoside (16).** To a solution of D-ribose (20.0 g, 133 mmol) in anhydrous methanol (200 mL) under a nitrogen atmosphere at room temperature, were added cyclopentanone (23.7 mL, 267 mmol), trimethyl orthoformate (66.5 mL, 400 mmol) and catalyzed amount *p*-toluenesulfonic acid monohydrate (1.27 g, 6.66 mmol, 5 % mmol). The reaction mixture was refluxed for 30 min. After removed the excess cyclopentanone at high vacuum pump, the residue was diluted with EtOAc and brine. The organic phase was extracted with EtOAc, dried with

anhydrous $MgSO_4$ and evaporated. The residue was purified on silica gel column chromatography (1/1, Hexane/EtOAc, confirmed by preparative TLC) to afford pale yellow liquid **16** (35.9 g, quantitative)**,** which was the major epimer.

**Methyl 5-deoxy-5-iodo-2,3-*O*-cyclopentanyl-β-D-ribofuranoside (17).** The furanoside **16** (35.9 g, 156 mmol) was dissolved in toluene (400 mL) and acetonitrile (100 mL). After the addition of imidazole (21.2 g, 311 mmol) and triphenylphosphane (49.0 g, 187 mmol), the iodine was introduced in approximately 100 mg portions to the above reaction mixture until the mixture remained dark-brown in color. The dark-brown solution was heated to reflux for 55 minutes and cooled to room temperature. The solution was diluted with diethyl ether (400 mL) and washed with 10 % sodium thiosulfate solution and brine. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to obtain a residue, which was purified through a short plug of silica gel column chromatography (5/1, Hexanes/EtOAc) to provide **17** (37.2 g, 70 %) as a colorless oil: $^1$H NMR (250 MHz, $CDCl_3$) δ 5.06 (s, 1H, 1'-H), 4.72 (d, J=6.0, 1H, 2'-H), 4.59 (d, J=6.00, 1H, 3'-H), 4.45 (m, 1H, 4'-H), 3.38 (s, 3H, $OCH_3$), 3.35-3.13 (m, 2H, 5'-Ha, 5'-Hb), 1.95-1.65 (br, 8H); $^{13}$C NMR (62.90 MHz, $CDCl_3$) δ 122.4, 109.7, 87.3, 85.4, 83.0, 55.5, 36.1, 36.0, 23.8, 23.4, 6.9.

**4,5-Dideoxy-2,3-*O*-cyclopentanyl-D-*erythro*-4-pentenose (18).** To a solution of the iodide **17** (37.2 g, 111 mmol) in anhydrous methanol (300 mL) in a flame-dried flask under a nitrogen atmosphere, was added zinc power (7.86 g, 120 mmol) activated with acetic acid. The above solution was refluxed for 1 h and cooed to room temperature. After filtrating the precipitate with a celite pad, the filtrate was concentrated in vacuum at 35 $^0$C and the residue was loaded to a short silica gel column chromatography (4/1,

Hexane/EtOAc) to yield the colorless oil **18** (18.4 g, 94%): $^1$H NMR (250 MHz, $CDCl_3$) δ 9.55 (d, J=3.0, 1H, 1'-H), 5.83-5.70 (m, 1H), 5.51 (d, J=17.3, 1H), 5.36 (d, J=10.3, 1H), 4.75 (t, J=7.50, 1H, 3'-H), 4.36 (dd, J=3.0, J=7.50, 1H, 2'-H), 2.06 (m, 2H), 1.76 (br, 6H).

**(4*S*,5*R*)-4,5-*O*-cyclopentanyl-1,-6-diene-3,4,5-triols (19).** The aldehyde **18** (18.4 g, 102 mmol) was dissolved in anhydrous diethyl ether (100 mL) under a nitrogen atmosphere and the above solution was cooled to -20-0 $^0$C. Vinylmagnesium bromide (113 mL, 113 mmol, 1.0 M in THF) was added dropwise to the above stirred solution over 1 h via a cannula. The reaction mixture was kept at the same temperature for 2 h and allowed to warm to room temperature. Saturated $NH_4Cl$ (30.0 mL) was added to quench the reaction and diethyl ether (3×150 mL) was used to extracted the organic phase. The combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford the diene **19** (12.2 g, 60 %) as clear yellow oil: $^1$H NMR (250.1 MHz, $CDCl_3$) δ 6.05 (m, 4H), 5.35 (m, 8H), 4.59 (t, J=4.0, 1H), 4.51 (d, J=4.0, 1H), 4.18-4.11 (m, 2H), 4.00-3.93 (m, 2H), 2.04-1.91 (m, 4H), 1.78-1.66 (m, 14H).

**(-)-(4*R*,5*R*)-4,5-*O*-cyclopentanylidene-2-cyclopentenone (21).** The diene **19** (12.2 g, 58.6 mmol) was dissolved in anhydrous $CH_2Cl_2$ (300 mL) and the above solution was flushed with dry nitrogen for 45 min at room temperature. Grubbs' catalyst 1$^{st}$ generation (1 % mmol, 482 mg) was slowly added to the diene solution. After stirred at 40 $^0$C for 48 h, the formed **20** intermediate was oxidized by a modified Swern oxidation method. Dimethyl sulphoxide (62.4 mL, 879 mmol), di*iso*propylethylamine (30.6 mL, 176 mmol) and $SO_3$·Py complex (14.0 g, 87.9 mmol) were added to the above solution of **20** at -10-0

$^0$C. The reaction mixture was kept 0 $^0$C for 2 h and continued stirring for 4 h at room temperature. After the reaction completed, the solution was diluted with $CH_2Cl_2$ (200 mL) and $H_2O$ (20.0 mL). The organic phase was extracted with $CH_2Cl_2$, washed with $H_2O$, saturated $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **21** (8.45 g, 81 %) as yellow liquid: $^1$H NMR (250 MHz, $CDCl_3$) δ 7.67 (dd, J=2.50, J=6.0, 1H), 6.29 (d, J=6.0, 1H), 5.26 (dd, J=5.5, J=2.50, 1H), 4.42 (d, J=5.50, 1H), 1.92-1.83 (m, 2H), 1.73-1.60 (br, 6H).

**Ethyl 2-((3*aR*,4*R*,6*aR*)-2,2-dimethyl-6-oxotetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)acetate (23).** *n*-BuLi (3.0 mL, 7.50 mmol, 2.50 M in hexane) was added dropwise to a three-neck flask at -10-0 $^0$C by syringe, which contained anhydrous THF (20.0 mL) and DIPA (di*iso*propylamine, 1.00 mL). The above solution was cooled further to -40 $^0$C. Ethyl (trimethylsilyl) acetate (1.00 mL, 5.47 mmol) was added dropwise over 10 min to the above solution by syringe and the reaction mixture was stirred at the same temperature for 40 min. HMPA (hexamethylphosphoramide) / THF(v/v, 1/1, 6.0 mL) was added to the above mixture and the above solution was further cooled to -78 $^0$C. Compound **11** (0.770 g, 5.00 mmol) in anhydrous THF (3.0 mL) was added dropwise via a cannula to the above reaction mixture at -78 $^0$C and the mixture was kept stirring at the same temperature for 1.5 h to provide the intermediate **22**. After the temperature of the reaction mixture warmed to -40 $^0$C, saturated $NH_4Cl$ (10.0 mL) was used to quench the reaction. When the amount of **11** was increased, the mixture of KF/EtOH/$H_2O$ (20/1/1, v/v/v, saturated KF solution) was introduced to quench the above reaction mixture. The aqueous phase was extracted with

$CH_2Cl_2$ (3×50.0 mL) and the organic layer was dried over anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was separated on silica gel column chromatography (5/1, Hexane/EtOAc) to afford **23** (0.490 g, 55 % for two steps): $^1$H NMR (250.1 MHz, $CDCl_3$) δ 4.61 (d, J=5.50, 1H), 4.39 (d, J=5.50, 1H), 4.18 (q, 2H), 2.88 (m, 1H), 2.81 (m, 2H), 2.50 (m, 1H), 2.16 (m, 1H), 1.44 (s, 3H), 1.34 (s, 3H), 1.29 (t, 3H).

**Ethyl 2-((3*aR*,4*R*,6*S*,6*aS*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)acetate (24).** Sodium borohydride (115 mg, 3.04 mmol) and cerium chloride heptahydrate, $CeCl_3 \cdot 7H_2O$ (0.640 g, 1.72 mmol) were added to the solution of **23** (0.490 g, 2.03 mmol) in methanol (12.0 mL) at -10-0$^0$C. The reaction mixture was kept 0 $^0$C for 1.5 h and continuing stirring at room temperature for 2 h. Saturated $NH_4Cl$ (4.00 mL) was used to quench the above reaction. Extracted with $CH_2Cl_2$ (3×20.0 mL) and evaporated the solvents under reduced pressure, the residue was purified on silica gel column chromatography (1/1, Hexane/EtOAc) to yield **24** (0.420 g, 86%): $^1$H NMR (250 MHz, $CDCl_3$) δ 4.53 (d, J=5.50, 1H), 4.42 (d, J=5.50, 1H), 4.19 (q, 2H), 2.55 (br, 1H), 2.43 (d, J=7.85, 1H), 2.29 (m, 2H), 1.98 (m, 1H), 1.76 (m, 1H), 1.51 (s, 3H), 1.34 (s, 3H), 1.29 (t, 3H).

**Ethyl 2-((3*aR*,4*R*,6*R*,6*aS*)-6-(6-chloro-9*H*-purin-9-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)acetate (25).** DIAD (di*iso*propyl azodicarboxylate, 0.450 mL, 2.32 mmol) was added by syringe to a solution of TPP (triphenyl phosphine, 0.480 g, 1.83 mmol) in anhydrous THF (10.0 mL) at -10 $^0$C under a nitrogen atmosphere. The above solution was stirred at the same temperature for 20 min. 6-chloropurine (292 mg, 1.89 mmol) and a solution of **24** (0.420 g, 1.72 mmol) in anhydrous THF (5.00 mL)

were added to the above reaction mixture at room temperature. The whole reaction mixture was stirred at room temperature for 1 h and then was heated to 50 $^0$C for 36 h. After the reaction completed, the solvent was removed under reduced pressure. The residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **25** (0.250 g, 40 %): $^1$H NMR (250 MHz, $CDCl_3$) δ 8.74(s, 1H), 8.17(s, 1H), 5.12(t, J=5.80, 1H), 4.84(m, 1H), 4.64(m, 1H), 4.21(q, 2H), 2.78-2.40(m, 5H), 1.58(s, 3H), 1.31(s, 3H), 1.27(t, 3H).

**2-((3*aR*,4*R*,6*R*,6*aS*)-6-(6-Chloro-9*H*-purin-9-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)acetaldehyde (26).** Di*iso*butylaluminum (DIBAH, 0.220 mL, 1.32 mmol, 1.5 M in toluene) was added dropwise by syringe to a solution of **25** (0.250 g, 0.660 mmol) in $CH_2Cl_2$ (10.0 mL) at -78 $^0$C. The reaction mixture was stirred at the same temperature for 3 h and quenched by methanol (2.0 mL) and $H_2O$ (10.0 mL) at -78 $^0$C. The reaction mixture was warmed to room temperature and extracted with $CH_2Cl_2$ (3×20.0 mL). After the solvent was removed under reduced pressure, the residue was purified on silica gel column chromatography (1/1, Hexane/EtOAc) to afford **26** (800 mg, 82 %): $^1$H NMR (400 MHz, $CDCl_3$) δ 9.84 (t, J=1.04, 1H), 8.84 (s, 1H), 8.17 (s, 1H), 5,12 (q, 1H), 4.85 (m, 1H), 4.62 (q, 1H), 2.92 (m, 1H), 2.74-2.64 (m, 3H), 2.41 (m, 1H), 1.58 (s, 6H).

It was noted that if the above reduction reaction was quenched at -50 $^0$C or room temperature, from TLC analysis, two products (**26** and **27**) were obtained, which are inseparated by standard silica gel column chromatography method.

**(2*R*,3*R*,4*R*)-4-Vinyl-2,3-*O*-*iso*propylidene-1-cyclopentenone (28).** Vinylmagnesium bromide (16.5 mL, 16.5 mmol, 1.0 M in THF) was added dropwise by syringe to a

suspension of $CuBr{\cdot}Me_2S$ (0.230 g, 1.12 mmol) in anhydrous THF (40.0 mL) at -90-78 $^0$C. The reaction mixture was stirred at the same temperature for 30 min before a solution of **11** (2.00 g, 13.0 mmol) and TMSCl (3.40 mL, 26.5 mmol) and HMPA (5.80 mL, 33.1 mmol) in THF (20.0 mL) were added dropwise via a cannula to the above reaction mixture. The reaction mixture was kept stirring at -78 $^0$C for 5 h and warmed to room temperature. Saturated $NH_4Cl$ (15.0 mL) and *tert-n*-butylammonium fluoride (TBAF, 3.0 mL) were added to quench the reaction and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc (100 mL) and extracted with EtOAc (3×50.0 mL). The combined organic phases were washed with brine, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **28** (1.89 g, 80 %): $^1$H NMR (250 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.19-5.07 (m, 2H), 4.66 (d, J=5.50, 1H), 4.22 (d, J=5.50, 1H), 3.11 (m, 1H), 2.90 (m, 1H), 2.33 (d, 18.0, 1H), 1.45 (s, 3H), 1.36 (s, 3H).

**(1*S*,2*S*,3*R*,4*R*)-4-Vinyl-2,3-*O*-*iso*propylidenecyclopentan-1-ol (29).** Sodium borohydride (405 mg, 10.7 mmol) and cerium chloride heptahydride, $CeCl_3{\cdot}7H_2O$ (2.22 g, 5.95 mmol) were added to a solution of **28** (1.30 g, 7.14 mmol) in anhydrous methanol (50.0 mL) at -10-0 $^0$C. The reaction mixture was kept at 0 $^0$C for 1.5 h and continued stirring at room temperature for 2 h. Saturated $NH_4Cl$ (9.00 mL) was used to quench the reaction. The reaction mixture was diluted with EtOAc (50.0 mL) and extracted with EtOAc (3×30.0 mL). The combined organic phases were washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (3/1, Hexane/EtOAc) to provide **29** (1.21 g, 92 %) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.59 (m, 1H), 5.11 (m, 2H), 4.49 (d, J=3.30,

2H), 4.10 (br s, 1H), 2.76 (m, 1H), 2.44 (d, J=8.0, 1H), 1.92-1.86 (m, 2H), 1.52 (s, 3H), 1.36 (s, 3H).

**6-Chloro-9-((3*aS*,4*R*,6*R*,6*aR*)-2,2-dimethyl-6-vinyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-9*H*-purine (30).** A solution of DIAD (di*iso*propyl azodicarboxylate, 2.13 mL, 11.0 mmol) was added by a syringe to a solution of TPP (triphenyl phosphine, 2.88 g, 11.0 mmol) in anhydrous THF (50.0 mL) at -10 $^0$C under a nitrogen atmosphere. The above solution was stirred at the same temperature for 30 min. 6-chloropurine (1.27 g, 8.24 mmol) and a solution of **29** (1.01 g, 5.49 mmol) in THF (10.0 mL) were slowly added to the above reaction mixture. The whole reaction mixture was stirred at room temperature for 12 h and then was heated to 50 $^0$C for 8 h. The solvent was removed under reduced pressure, and the residue was purified on silica gel column chromatography (3/1, Hexane/EtOAc) to afford **30** (0.990 g, 60 %) contaminated with the azadicarboxylate byproduct.

**2-((3*aR*,4*R*,6*R*,6*aS*)-6-(6-Chloro-9*H*-purin-9-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)acetaldehyde (26)–the Second Method.** Dimethyl sulphoxide (1.15 mL, 12.2 mmol), diisopropyl ethylamine (0.420 mL, 2.43 mmol) and $SO_3$·Py complex (0.260 g, 1.62 mmol) were added to the solution of compound **27** (0.260 g, 0.81 mmol) in $CH_2Cl_2$ (10.0 mL) at 0$^0$C. The reaction mixture was kept at the same temperature for 2 h and continued stirring for 4 h at room temperature. After the reaction completed, the solution was diluted with $CH_2Cl_2$ (50.0 mL) and $H_2O$ (10.0 mL). Extracted with $CH_2Cl_2$, the organic phase was washed with $H_2O$, $NaHCO_3$ and brine and dried over $MgSO_4$. After removing the solvent under the reduced pressure, the residue

was purified by column chromatography (3/1, Hexane/EtOAc) to afford **26** (0.170 g, 66 %). The $^1$H NMR data was the same as that of the first method.

**(*S*)-1-((3*aR*,4*R*,6*R*,6*aS*)-6-(6-Chloro-9*H*-purin-9-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopental[d][1,3]dioxol-4-yl)pent-4-en-2-ol (31).** Allylmagnesium bromide (1.10 mL, 1.10 mmol, 1.0 M in diethyl ether) was added dropwise to a solution of (-)-B-methoxydi*iso*campheylboron (348 mg, 1.10 mmol) in anhydrous diethyl ether (22.0 mL) at 0 $^0$C at room temperature under a nitrogen atmosphere. The above solution was well stirred at -78 $^0$C for 15 min and allowed to warm to room temperature for 3 h. The formation of $Ipc_2BAll$ was indicated by precipitation of the magnesium salts. The reaction mixture was filtered under nitrogen to remove the solid residue (magnesium salts) and washed the solid residue with pentane.

Evaporation the solvents at reduced pressure, the resulting solution was added dropwise to a solution of **26** (0.380 g, 1.00 mmol), previously cooled to at -78 $^0$C, in a mixture of anhydrous diethyl ether (20.0 mL) and methylene chloride (5.00 mL). The reaction mixture was stirred at -78 $^0$C for 3 h, quenched with methanol (1.50 mL) and stirred at room temperature for 1 h. Saturated sodium bicarbonate (3.00 mL) and $H_2O_2$ (3.00 mL, 32 wt % in $H_2O$) were carefully added. The resulting mixture was stirred at room temperature for 14 h. The solvent was removed under reduced pressure and the residue was extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. TLC analysis showed that it formed a complex and no desired product (**31**) was found from NMR. The reactant **26** was recovered.

It was noted that the allylation reaction with Brown's reagent using this procedure failed. Later, with the help of Dr. Yin, the one-pot allylation approach was developed and succeeded in getting the desired product, such as **41**, **53**.

**N-(*tert*-butoxycarbonyl)-D-valine (32).** Solid $NaHCO_3$ (21.5 g, 256 mmol) was added to a solution of D-valine (15.0 g, 128 mmol) in $H_2O$ (100 mL) and then a solution of di-*tert*-butyl dicarbonate (28.0 g, 128 mmol) in THF (100 mL) was added to the above reaction mixture. The reaction mixture was stirred and heated under reflux for 16 h and then concentrated under vacuum to remove THF. EtOAc (150 mL) was added to the above residue and the mixture was cooled to 10 °C and then adjusted the solution to pH=3.0 with 1.0 M sulfuric acid solution. The aqueous layer was extracted with EtOAc (3×200 mL) and the combined organic layers were washed with water (200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum to give **32** (24.3 g, 87 %) as colorless oil, or a whiteless foam: $^1$H NMR (400 MHz, $CDCl_3$) δ 10.89 (br s, 1H), 6.50 (d, J=7.60, 1H), 5.24 (d, J=9.20, 1H), 2.20 (m, 1H), 1.45 (s, 9H), 1.00 (d, J=6.80, 3H), 0.94 (d, J=7.20, 3H).

**Methyl N-(*tert*-butoxycarbonyl)-D-valyl glycinate (33).** *Iso*butyl chloroformate (14.6 mL, 112 mmol) was added to a stirred mixture of **32** (24.3 g, 112 mmol) and triethylamine (15.6 mL, 112 mmol) in $CH_2Cl_2$ (200 mL) at 0-5°C. When the addition was complete, the mixture was stirred at 0-5 °C for 30 min. In a separate flask, a mixture of glycine methyl ester hydrochloride (14.0 g, 112 mmol), triethylamine (15.6 mL, 112 mmol) and $CH_2Cl_2$ (200 mL) was stirred for 30 min and this mixture was then added to the first flask containing **32** over 1 h. After the addition was complete, the mixture was stirred at room temperature for 16 h and then washed with water (3×50.0 mL) and brine

(100 mL), dried with anhydrous $MgSO_4$ and concentrated under vacuum to give **33** (27.2 g, 89 %) as yellow solid: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.52 (br s, 1H), 5.06 (br s, 1H), 3.98-4.02 (m, 1H), 3.76 (s, 3H), 2.20 (m, 1H), 1.45 (s, 9H), 0.99 (d, J=6.80, 3H), 0.94 (dd, J=7.20, 4.00, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ 172.1, 170.3, 52.6, 46.0, 41.3, 31.1, 31.0, 28.5 (3C), 19.5, 19.1, 8.9.

**(2*R*)-*Iso*propylpiperazine-3,6-dione (34)** A solution of **33.** (27.2 g, 99.1 mmol) dissolved in 1,2-dichlorobenzene (150 mL) was heated at 175-180 °C for 18 h and during this process, formed methanol was removed by distillation. After removing 1,2-dichlorobenzene with high-vacuum pump, the residue was cooled to 50 °C. *Tert*- butyl methyl ether (200 mL) was slowly added to the above residue. The reaction mixture was further cooled to room temperature and filtered. The resulting solid was washed with *tert*-butyl methyl ether (200 mL) and ethyl ether (100 mL), dried under vacuum at 100 °C to give **34** (8.83 g, 60 %) as white needle solid: $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.19 (br s, 1H), 8.01 (br s, 1H), 3.84 (AB, 1H), 3.64 and 3.60 (AB, 1H), 3.52 (t, J= 3.20, 1H), 2.11 (m, 1H), 0.93 (d, J=6.80, 3H), 0.86 (d, J=6.80, 3H).

**(2*R*)-2,5-Dihydro-3,6-dimethoxy-2-*iso*propylpyrazine (35).** Trimethyloxonium tetrafluoroborate (10.0 g, 67.6 mmol) was slowly added to a suspension of **34** (3.52 g, 22.5 mmol) in anhydrous $CH_2Cl_2$ (50.0 mL) at room temperature. The mixture was stirred at room temperature for 84 h. The resulting solid was added in portions under a nitrogen atmosphere to a vigorously stirred mixture of saturated aqueous $NaHCO_3$ (150 mL) and $CH_2Cl_2$ (100 mL) at 0-4 °C, while maintaining the pH between 8.0 and 9.0 by the simultaneous addition of 3 M aqueous NaOH as required. The mixture was separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3×200 mL). The combined organic

phases were washed with brine (50.0 mL), dried with anhydrous $MgSO_4$ and concentrated under vacuum. The pale yellow residual oil was purified by reduced-pressure distillation to give **35** (2.91 g, 70 %, > 95 % ee from $^1$H NMR) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 3.98-4.02 (m, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 2.26 (m, 1H), 1.04 (d, J=6.80, 3H), 0.76 (d, J=6.8, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ 165.1, 162.5, 61.3, 52.7, 52.9, 46.8, 32.7, 19.2, 17.2.

**(2*R*,3*R*,4*R*)-4-Vinyl-2,3-*O*-cyclopentanyl-1-cyclopentenone (36).** Vinylmagnesium bromide (89.2 mL, 89.2 mmol, 1.0 M in THF) was added dropwise to a suspension of CuBr·$Me_2S$ (0.780 g, 3.79 mmol) in THF (100.0 mL) at -90-78 $^0$C. The reaction mixture was stirred at the same temperature for 30 min before a solution of **21** (8.04 g, 44.6 mmol) and TMSCl (12.6 mL, 98.1 mmol) and HMPA (19.6 mL, 112 mmol) in anhydrous THF (30.0 mL) were added dropwise via a cannula to the above reaction mixture over 50 min. The reaction mixture was kept stirring at the same temperature for 5 h and warmed to room temperature. Saturated $NH_4Cl$ (15.0 mL) and *tetra*-butylammonium fluoride (3.00 mL) were added to quench the reaction and the reaction mixture was stirred for 30 min. EtOAc (200 mL) was added to dilute the reaction mixture and the organic phase was extracted with EtOAc (3×100 mL). The combined organic layer was washed with brine and dried with anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **36** (6.78 g, 73 %) as a clear yellow oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.17-5.08 (m, 2H), 4.56 (d, J=5.60, 1H), 4.18 (d, J= 5.20, 1H), 3,12 (m, 1H), 2.85 (dd, J=8.40, 1H), 2.30 (dm, J=18.0, 1H), 1.94-1.65 (m, 8H); $^{13}$C NMR (62.9 MHz, $CDCl_3$)

δ 213.2, 137.3, 122.3, 116.5, 81.6, 77.7, 40.0, 38.8, 36.3, 36.2, 23.9, 23.1. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 67.36; H, 7.79.

**(1*S*,2*S*,3*R*,4*R*)-4-Vinyl-2,3-*O*-cyclopentanyl-cyclopentan-1-ol (37).** A solution of **36** (6.87 g, 32.6 mmol) in anhydrous THF (30.0 mL) was added dropwise to a suspension of lithium aluminum hydride (3.18 g, 81.4 mmol) in anhydrous THF (50.0 mL) at -10-0 °C. The reaction mixture was stirred at room temperature overnight. $H_2O$ (2.0 mL) and NaOH (5.0 mL, 6 M in $H_2O$) were added to quench the above reaction. The resulting solid was removed by filtration and the solvent was evaporated under vacuum to afford **37** (6.06 g, 89 %) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.75 (m, 1H), 5.11-5.04 (m, 2H), 4.39 (m, 2H), 4.08 (m, 1H), 2.78 (m, 1H), 2.45 (d, J=8.0, 1H), 1.99-1.84 (m, 2H), 1.71 (m, 8H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ 138.3, 121.7, 115.5, 84.5, 79.1, 71.4, 44.4, 36.4, 35.8, 35.6, 24.2, 23.1. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 67.31; H, 8.64.

**(3*aS*,4*S*,6*R*,6*aR*)-4-(4-Methoxybenzyloxy)-6-vinyltetrahydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1'-cyclopentane] (38).** Sodium hydride (1.15 g, 28.8 mmol) was added in portions to a solution of **37** (6.06 g, 28.8 mmol) in anhydrous N, N-dimethylformamide (DMF, 30.0 mL) at -10-0 °C. The reaction mixture was stirred at the same temperature for 30 min and then *p*-methoxybenzyl chloride (4.70 mL, 34.6 mmol) was added dropwise by a syringe to the above reaction mixture. The reaction was kept at $0^0$C for 1 h and at room temperature for 4 h. After removed DMF by high pressure vacuum, the residue was quenched by $H_2O$ (3.0 mL) and extracted with EtOAc (3×100 mL). The combined organic layer was washed with brine and dried with anhydrous $MgSO_4$. After removal of the solvents under vacuum, the residue was purified on silica

gel column chromatography (4/1, Hexane/EtOAc) to afford **38** (8.63 g, 90 %) as a shallow yellow oil: $^{1}$H NMR (250 MHz, $CDCl_3$) δ 7.32 (dd, J=8.50, 2.00, 2H), 6.89 (dd, J=8.75, 2.00, 2H), 5.68 (m, 1H), 5.03 (m, 1H), 4.97 (m, 1H), 4.65 (d, J=11.76, 1H), 4.55 (d, J=11.51, 1H), 4.43 (t, J=6.50, 5.25, 1H), 4.30 (d, J=5.75, 1H), 3.81 (m, 4H), 2.66 (t, J= 7.25, 6.75, 1H), 2.16-2.03 (m, 2H), 1.94-1.70 (m, 8H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 159.5, 138.9, 130.8, 129.7, 121.0, 115.0, 114.0, 84.0, 78.5, 77.9, 71.7, 55.5, 44.1, 35.8, 35.6, 32.1, 24.3, 23.3. Anal. Calcd for $C_{20}H_{36}O_4$: C, 72.70; H, 7.93. Found: C, 72.55; H, 8.06.

**2-((3*a*S,4*S*,6*S*,6*a*R)-4-(4-Methoxybenzyloxy)tetrahydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1'-cyclopentane]-6-yl)ethanol (39).** 9-Borabycyclo [3.3.1] nonane (9-BBN, 78.4 mL, 39.2 mmol, 0.5 M in THF) was added dropwise by syringe to a solution of **38** (8.63 g, 26.1 mmol) in anhydrous THF (50.0 mL) at -10-0 °C. The reaction mixture was stirred at room temperature overnight. Methanol (10.0 mL), NaOH (6 M, 12.0 mL) and $H_2O_2$ (15.0 mL, 32 wt % in $H_2O$) were added dropwise to the above solution at 0 $^{0}$C, respectively. The reaction was stirred for 4 h at room temperature. After diluted the reaction with EtOAc (50.0 mL), the organic phase was washed with saturated $NaHCO_3$ and brine and dried with anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified on silica gel column chromatography (1/1, Hexane/EtOAc) to afford **39** (6.70 g, 66 %) as a colorless oil: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J=8.80, 2.00, 2H), 6.89 (dd, J=8.80, 2.00, 2H), 4.65 (d, J=11.61, 1H), 4.54 (d, J=12.01, 1H), 4.45 (t, J=5.20, 5.60, 1H), 4.21 (d, J= 6.00, 1H), 3.83-3.78 (m, 4H), 3.72-3.62 (m, 2H), 2.11-2.04 (m, 2H), 1.92 (m, 1H), 1.71-1.56 (m, 9H), 1.49-1.41 (m, 2H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 159.5, 130.8, 129. 7, 121.5,

114.0, 84.8, 79.0, 77.8, 71.7, 61.7, 55.5, 38.4, 36.0, 35. 8, 33.7, 24.1, 23.3, 14.4. Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.05; H, 8.18.

**2-((3*aS*,4*S*,6*S*,6*aR*)-4-(4-Methoxybenzyloxy)tetrahydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1'-cyclopentane]-6-yl)acetaldehyde (40).** Dimethyl sulphoxide (20.4 mL, 287 mmol) and di*iso*propyl ethylamine (8.33 mL, 47.8 mmol) were added to the solution of **39** in $CH_2Cl_2$ (50.0 mL) at -10-0 °C. After the reaction was stirred at 0 $^0$C for 30 min, $SO_3$·Py complex (4.56 g, 28.7 mmol) was added to the above solution. The reaction mixture was kept at the same temperature for 2 h and continued stirring for 4 h at room temperature. The reaction mixture was diluted with $CH_2Cl_2$ (100 mL) and $H_2O$ (10.0 mL) and extracted with $CH_2Cl_2$ (3×100 mL). The combined organic phases were washed with saturated $NaHCO_3$, $H_2O$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (1/1, Hexane/EtOAc) to afford the aldehyde **40** (6.41 g, 97 %) as the colorless oil: $^1$H NMR (250 MHz, $CDCl_3$) δ 9.70 (t, J=2.00, 1.75, 1H), 7.31 (dd, J= 8.50, 2.00, 2H), 6.89 (dd, J=8.75, 2.25, 2H), 4.64 (d, J=11.76, 1H), 4.55 (d, J=11.76, 1H), 4.44 (t, J=5.25, 5.00, 1H), 4.16 (d, J=5.75, 1H), 3.82-3.74 (m, 4H), 2.54 (m, 1H), 2.36-2.04 (m, 3H), 1.95 (m, 1H), 1.68-1.54 (m, 8H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 200.9, 159.5, 130.5, 129.7, 121.5, 114.0, 84.0, 78.7, 77. 6, 71.7, 55.5, 46.9, 35.8, 35.6, 35.4, 33.0, 24.3, 23.3. Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.00; H, 7.50.

**(*S*)-1-((3*aS*,4*S*,6*S*,6*aR*)-4-(4-Methoxybenzyloxy)tetrahydro-3a*H*-spiro-[cyclopenta[*d*][1,3]dioxole-2-1'-cyclopentane]-6-yl)pent-4-en-2-ol (41).** Allylmagnesium bromide (34.2 mL, 34.2 mmol, 1.0 M in diethyl ether) was added dropwise to a solution of (-)-B-methoxydi*iso*campheylboron (10.8 g, 34.2 mmol) in

anhydrous diethyl ether (80.0 mL) at -10-0 °C under a nitrogen atmosphere. The reaction was stirred at room temperature for 2 h to give a white suspension. Then, the reaction flask was cooled to -90-78 °C and the aldehyde **40** (6.41 g, 18.5 mmol) dissolved in anhydrous THF (25.0 mL) was added dropwise via a cannula over 50 min to the above reaction mixture. The newly reaction mixture was kept at -78 °C for 6 h and allowed to warm to room temperature for another 4 h. Finally, methanol (10.0 mL), NaOH (6 M, 13.0 mL) and $H_2O_2$ (25.0 mL, 32 wt % in $H_2O$) were added dropwise to the above solution at 0 °C, respectively. The reaction was stirred for 4 h at room temperature. After diluted the reaction with EtOAc (150 mL) and extracted with EtOAc (3×150 mL), the combined organic phase was washed with $H_2O$ and brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **41** (6.43 g, 90 %) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J=8.80, 2.00, 2H), 6.89 (dd, J=8.80, 2.00, 2H), 5.85 (m, 1H), 5.14-5.10 (m, 2H), 4.64 (d, J=11.61, 1H), 4.53 (d, J=12.01, 1H), 4.45 (t, J=5.60, 5.20, 1H), 4.28 (d, J=7.60, 1H), 3.81 (m, 4H), 3.72-3.64 (m, 1H), 2.26 (m, 1H), 2.18-2.05 (m, 4H), 1.91 (m, 1H), 1.70-1.56 (m, 8H), 1.39-1.29 (m, 2H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 159.4, 134.8, 130.8, 129.7, 121.5, 118.5, 114.0, 85.1, 79.1, 77.6, 71.7, 69.9, 55.5, 42.4, 39.9, 38.9, 36.1,35.8, 34.0, 24.2, 23.3. Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 71.26; H. 8.43.

**(3*aS*,4*S*,6*S*,6*aR*)-4-(4-Methoxybenzyloxy)-6-((*S*)-2-(methoxymethoxy)pent-4-enyl)tetrahydro-3a*H*-spiro-[cyclopenta[*d*][1,3]dioxole-2-1'-cyclopentane] (42).** To a solution of **41** (6.43 g, 16.6 mmol) in anhydrous $CH_2Cl_2$ (25.0 mL) was added di*iso*propyethylamine (DIPEA, 10.1 mL, 57.9 mmol) at -10-0 °C under a nitrogen

atmosphere. After the mixture was stirred for 30 min and kept at -10 °C, chloromethyl methyl ether (2.52 mL, 16.6 mmol) was slowly added by a syringe. The whole reaction mixture was then stirred for 1 h, warmed to room temperature and transferred to stir for 24 h at 40 °C in oil bath. After the reaction mixture was diluted with EtOAc and saturated $NaHCO_3$ at -10-0 °C. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×150 mL). The combined organic phases were washed with water and brine, dried with $MgSO_4$, and then evaporated in vacuo to afford the crude product, which was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to furnish **42** (5.07 g, 72%) as a yellow oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J=8.75, 2.00, 2H), 6.86 (dd, J=8.50, 2.00, 2H), 5.75 (m, 1H), 5.08-5.03 (m, 9'-H, *cis* and *trans*, 2H), 4.68 (d, mom-H, J=7.20, 1H), 4.62 (d, pmb-H, J=12.0, 1H), 4.59 (d, mom-H, J=7.20, 1H), 4.54 (d, pmb-H,J=12.0, 1H), 4.42 (t, J=5.25, 2'-H, 1H), 4.21 (d, 3'-H, J=5.60, 1H), 3.80 (s, PMB, -$OCH_3$, 3H), 3.77-3.72 (m, multi, 5, 6'-H, 1H), 3.65-3.59 (m, 1'-H, 1H), 3.35 (s, MOM, -$OCH_3$, 3H), 2.30-2.26 (m, 7'-H, 2H), 2.16-2.01 (m, 5'-H, 2H; 5-H, 1H), 1.92-1.83 (m, 4'-H, 1H; 5-H, 1H), 1.68-1.61 (m, cyclopentanone, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.4, 134.5 (8'-C), 130.6, 129.6 (2C), 120.9 (2C), 117.6 (cyclopentanone, 1-C), 113.9 (9'-C), 95.6 (MOM, $CH_2$), 85.0 (2'-C), 78.4 (3'-C), 77.6 (1'-C), 75.4 (6'-C), 71.5 (PMB, -$OCH_2$), 55.8 (PMB, $OCH_3$), 55.4 (MOM, $OCH_3$), 39.1, 37.7 (CYCLO), 37.2 (7'-C), 35.7 (5'-C), 35.5 (5-C), 32.6 (4'-C), 24.2, 23.2 (CYCLO). Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.48; H, 8.49.

**(*R*)-4-((3*aS*,4*S*,6*S*,6*aR*)-4-(4-Methoxybenzyloxy)tetrahydro-3a*H*-spiro-[cyclopenta[*d*][1,3]dioxole-2-1'-cyclopentane]-6yl)-3-(methoxymethoxy)butan-1-ol (43).** Sodium periodate (4.95 g, 23.4 mmol) was added to a solution of **42** (5.07 g, 11.7

mmol) in MeOH /$H_2O$ (160 mL, v/v=3/1) at -10-0 °C. Catalytic amount of osmium tetroxide (488 mg) was slowly added to the above reaction mixture. The reaction mixture was stirred at 0 °C for 1 h and kept for 2 h at room temperature. The mixture was filtrated with a little pad of celite, diluted with $CH_2Cl_2$ and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic phases was dried over anhydrous $MgSO_4$ and then evaporated under reduced pressure to give a yellow syrup, which was used to the next reaction without further purification.

To a stirred solution of the yellow synrup in anhydrous MeOH (50.0 mL) at -10-0 °C was added sodium borohydride (532 mg, 14.1 mmol) and the reaction mixture was stirred at 0 °C for 1 h and kept for 2 h at room temperature. Saturated $NH_4Cl$ solution (5.0 mL) was added to quench the reaction mixture. The residue was diluted with EtOAc (120 mL), dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (3/1, Hexane/EtOAc) to furnish **43** (2.54 g, 50 %) as a colorless oil: $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J=8.50, 2.00, PMB, 2H), 6.88 (dd, J=8.50, 2.00, PMB, 2H), 4.65-4.60 (m, 3H, PMB, 2H; MOM, 1H),4.53 (d, 1H, J=12.00, MOM, 1H), 4.43 (t, 2'-H, J=5.25 1H), 4.19 (d, 3'-H, J= 5.75, 1H), 3.80 (s, PMB, $OCH_3$, 3H), 3.78-3.74 (m, 3H; 6'-H, 1H; 8'-H, 2H), 3.69-3.62 (m, 1H; 1'-1H), 3.38 (s, 3H, MOM),2.52 (br, 1H, OH), 2.12-2.02 (m, 3H; 4'-H, 1H; 7'-H, 2H), 1.91-1.88 (m, 1H; 5'-H, 1H), 1.83-1.77 (m, 1H; cyclopentane), 1.71-1.64 (m, 7H; cyclopentane), 1.63-1.60 (m, 1H; 5'-H), 1.56-1.49 (m, 1H; 5-H, 1H), 1.29-1.22 (m, 1H; 5-H, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 159.4, 130.6, 129.6 (2C), 121.1 (1C, cyclopentane), 113.9 (2C), , 96.3 (1C, MOM, $CH_2$), 84.9 (2'-C), 78.6 (3'-C), 77.7 (1'-C), 75.0 (6'-C), 71.5 (1C, PMB, $CH_2$), 59.5 (1C, 8'-C,OH), 56.0 (PMB, $OCH_3$), 55.4 (MOM,

$OCH_3$), 38.0, 37.7, (2C, cyclopentane, 2 & 5 position), 37.1 (7'-C), 35.8 (5'-C), 35.5 (5-C), 33.3 (4'-C), 24.1, 23.2 (2C, cyclopentane, 3 & 4 position). Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 65.58; H, 8.33.

**(*R*)-4-((3*aS*,4*S*,6*S*,6*aR*)-4-(4-Methoxybenzyloxy)tetrahydro-3a*H*-spiro-[cyclopenta[*d*][1,3]dioxole-2-1'-cyclopentane]-6yl)-3-(methoxymethoxy)butan-1-ol (43)-the Optimized Method.** To a solution of **42** (7.22 g, 16.7 mmol) in THF (80.0 mL) was added a catalytic amount of osmium tetroxide (100 mg) and 50 % aqueous N-methylmorpholine N-oxide (NMO, 20.0 mL) at -10-0 °C. The reaction mixture was stirred at the same temperature for 2 h and warmed to room temperature and kept stirring for 12 h. After evaporated the solvent (THF) under reduced pressure, the residue was diluted and extracted with EtOAc. The organic phase was concentrated again to give a yellow liquid, which was purified on silica gel column chromatography (EtOAc) to furnish the diol **42-1'** (6.33 g, 83 %). **42-1'** was not necessary to be conducted with NMR and further used to the next reaction after separation.

To a stirred solution of **42-1'** in a mixture of $CH_2Cl_2/H_2O$ (200 mL, 3/1, v/v) at -10-0 °C was slowly added sodium periodate (7.44 g, 34.0 mmol). A catalytic amount of 15-crown-5 (1.00 mL) was added to the above reaction mixture. The reaction mixture was stirred at the same temperature for 2 h and warmed to room temperature and kept stirring for 12 h. The solution was diluted with $CH_2Cl_2$ (150 mL), and the aqueous layer was extracted with $CH_2Cl_2$ (3×150 mL). The combined organic phases were washed with $H_2O$ and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (1/1, Hexane/EtOAc) to

afford the aldehyde **42-1''** (5.59 g, 95 %) as a colorless oil and the aldehyde **42-1''** was used to the next reaction without NMR data.

The aldehyde **42-1''** (5.59 g, 12.9 mmol) thus obtained was dissolved in anhydrous MeOH (80.0 mL) at -10-0 °C. To this solution were added sodium borohydride (771 mg, 32.2 mmol) and $CeCl_3 \cdot 7H_2O$ (5.75 g, 15.4 mmol). The reaction mixture was stirred at -10-0 °C for 1 h and kept for 2 h at room temperature. Saturated $NH_4Cl$ solution (5.0 mL) was added to quench the reaction mixture. The residue was diluted with EtOAc (2×60.0 mL), dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (2/1, Hexane/EtOAc) to furnish **43** (4.32 g, 77%) as a colorless oil in 80% yield in three steps from **43**. The NMRs ($^1H$, $^{13}C$) of **43** were the same as that of **43**, which was achieved from the first oxidative-cleavage method.

**(3*aR*,4*S*,6*S*,6*aS*)-4-((*R*)-4-Iodo-2-(methoxymethoxy)butyl)-6-(4 methyoxybenzyloxy)tetrahydro-3a*H*-spiro-[cyclopenta[*d*][1,3]dioxole-2-1'-cyclopentane] (44).** A solution of **43** (6.42 g, 14.7 mmol) in toluene (50.0 mL) and acetonitrile (10.0 mL) was treated with imidazole (2.51 g, 36.8 mmol) and triphenylphosphane (9.65 g, 36.8 mmol). Then, iodine was introduced in approximately 10.0 mg portions to the above reaction mixture until the reaction mixture remained dark-brown in color. The dark-brown solution was heated to reflux for 10 minutes and cooled to room temperature. The reaction mixture was diluted with $Et_2O$ (50.0 mL) and washed with 10 % sodium thiosulfate solution and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified through a short plug of silica gel column chromatography (1/1, Hexanes/EtOAc) to provide **44** (3.22 g, 40%) as a

yellow oil: $^{1}$H NMR (400 MHz, $CDCl_3$) 7.31 (dd, J=8.40, 2.00), 6.88 (dd, J=8.80, 2.00), 4.65-4.59 (m, 3H), 4.55 (d, J=12.00, 1H), 4.43 (t, J=5.60, 5.20, 1H), 4.18 (d, J=5.60, 1H), 3.79 (s, 3H), 3.77-3.74 (m, 1H), 3.68-3.59 (m, 1H), 3.36 (s, 3H), 3.24-3.13 (m, 2H), 2.15-1.88 (m, 5H), 1.68-1.62 (m, 8H), 1.47 (m, 1H), 1.22 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) 159.3, 130.5, 129.5, 121.0, 113.8, 96.0, 84.8, 78.4, 77.4, 76.6, 71.4, 55.8, 55.3, 38.8, 37.5, 37.1, 35.7, 35.4, 32.9, 24.1, 23.1, 1.8.

**(*R*)-4-((3*aS*,4*S*,6*S*,6*aR*)-4-(4-Methoxybenzyloxy)tetrahydro--3a*H*-spiro-[cyclopenta[*d*][1,3]dioxole-2-1'-cyclopentane]-6-yl)-3-(methoxymethoxy)butyl 4-methylbenzenesulfonate (45).** To a solution of **43** (2.79 g, 6.39 mmol) in anhydrous $CH_2Cl_2$ (30.0 mL) were added triethylamine (22.3 mL, 160 mmol) and a catalytic amount of DMAP (500 mg) at room temperature under a nitrogen atmosphere. After the reaction mixture was stirred for 30 min and then cooled to -10-0 °C, *p*-toluenesulfonyl chloride (3.05 g, 16.0 mmol) was slowly added. The whole reaction mixture was stirred at the same temperature for 2 h, warmed to room temperature and stirred overnight. After the reaction mixture was diluted with ice-water (10.0 mL), the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×80.0 mL). The combined organic phases were washed with 1 % HCl and brine, dried with anhydrous $MgSO_4$ and concentrated in vacuuo to give the crude product, which was purified on silica gel column chromatography (3/1, Hexane/EtOAc) to furnish **45** (3.40 g, 90%) as a colorless oil: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J=8.40, 1.60, 2H, Tos 2H), 7.35 (dd, J=9.20, 2.00, Tos 2H), 7.31 (dd, J=8.40, 2.00, PMB, 2H), 6.89 (dd, J=8.40, 2.00, PMB 2H), 4.63 (d, J=12.00, PMB, $CH_2$, 1H), 4.55-4.49 (m, PMB, $CH_2$, 1H; MOM, $CH_2$, 2H), 4.42 (t, J=5.20, 2'-H, 1H), 4.14 (m, 3'-H, 1H; 8'-H, 2H), 3.80 (s, PMB, $OCH_3$, 3H), 3.77-3.72 (m,

1'-H, 1H), 3.66-3.58 (m, 6'-H, 1H), 3.27 (s, MOM, $OCH_3$, 3H), 2.44 (s, TOS, $CH_3$, 3H), 2.08-2.00 (m, 5-H, 1H; cyclopentane, 2H), 1.92-1.77 (m, 7'-H, 2H; 4'-H, 1H), 1.72-1.63 (m, cyclopentane, 6H), 1.59-1.55 (m, 5-H, 1H), 1.46-1.38 (m, 5'-H, 1H), 1.23-1.18 (m, 5'-H, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.4, 145.0 (Tos, 1C), 133.3 (Tos, 1C), 130.7 (Tos, 1C), 130.0 (Tos, 2C), 129.7 (Tos, 2C), 128.1 (2C), 121.1 (cyclopentane, *tert*-C), 113.9 (PMB, 2C), 96.3 (MOM, $CH_2$, 1C), 84.9 (2'-C), 78.6 (3'-C), 77.7 (1'-C), 73.4 (6'-C), 71.6 (Tos, $CH_2$, 1C), 67.3 (8'-C), 55.9 (PMB, $OCH_3$), 55.5 (MOM, $OCH_3$), 37.9 and 37.6 (cyclopentane, 2 and 5 position), 35.8 (7'-C), 35.6 (5'-C), 34.2 (5-C), 33.2 (4'-C), 24.2 and 21.8 (cyclopentane, 3 and 4 position), 23.2 (tosyl, $CH_3$).

**(2*R*,5*S*)-2-*Iso*propyl-3,6-dimethoxy-5-((*S*)-4-((3*aS*,4*S*,6*S*,6*aR*)-4-(4-methoxybenzyloxy)tetrahydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2-1'-cyclopentane]-6-yl)-3-(methoxymethoxy)butyl)-2,5-dihydropyrazine (46).** To a solution of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-*iso*propylpyrazine **35** (0.450 mL, 2.71 mmol) in anhydrous THF (10.0 mL) under a nitrogen atmosphere was added *n*-BuLi (1.1 mL, 2.71 mmol, 2.5 M in THF) dropwise at -90-78 °C by a syringe. This solution was stirred at -90-78 °C for 30 min. Then, to this solution was slowly added a solution of **45** (0.800 g, 1.35 mmol) in anhydrous THF (10.0 mL) via a cannula over 40 min at -90-78 °C. The reaction mixture was stirred at -90-78 °C for 5 h, kept at -20 °C for 12 h and allowed to slowly warm to room temperature. The solution was then quenched with the addition of saturated $NH_4Cl$ (3.0 mL) and ammonium hydroxide (3.0 mL) and ethanol (3.0 mL). The THF was removed under reduced pressure, and the residue was diluted with EtOAc. The organic phase was separated and the aqueous layer was extracted with EtOAc (3×50.0 mL). The combined organic phases were washed with brine and dried

over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **46** (1.96 g, 85 %) as the yellow oil, the only diastereoisomer: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J=8.80, 2H), 6.89 (d, J=8.80, 2H), 4.64-4.49 (m, PMB, $CH_2$; MOM, $CH_2$, 4H), 4.43 (t, J=5.60, 2'-H, 1H), 4.13 (t, J=6.0, 3'-H, 1H), 4.05-3.91 (AB, pyrazine, 2H), 3.80 (s, 3H), 3.78-3.73 (br s, 6'-H, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.65-3.60 (m, 1'-H, 1H), 3.27 (s, MOM, OCH3, 3H), 2.28-2.22 (m, pyrazine, 1H), 2.08-2.01 (m, 5-H, cyclopentane, 3H), 1.90-1.81(m, 4'-H, 7'-H, 3H), 1.70-1.65(m, cyclopentane, 6H), 1.62-1.58 (m, 5-H, 1H), 1.48-1.43 (m, 5'-H, 8'-H, 3H), 1.27-1.24 (m, 5'-H, 1H), 1.05 (d, J=6.80, 3H), 0.70 (d, J=6.80, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.1 (pyrazine), 159.1, 155.3 (pyrazine), 138.1, 130.7 (2C), 121.0, 113.9 (2C), 93.8 (PMB, $CH_3O\underline{C}H_2$-), 84.9 (2'-C), 78.4 (3'-C), 77.8 (1'-C), 76.1 (6'-C), 71.6 (8'-C), 56.2, 55.8 (PMB, $OCH_3$), 55.5 (MOM, $OCH_3$), 54.0 (pyrazine, $OCH_3$), 53.9 (pyrazine, $OCH_3$), 38.6 and 37.5 (cyclopentane, 2, 5 positions), 38.51(pyrazine, 9'-C), 35.8 (7'-C), 35.6 (5'-C), 32.8 (5-C), 28.5 (pyrazine, $\underline{C}H(CH_3)_2$), 28.3 (4'-C), 24.2 and 21.3 (cyclopentane, 3, 4 positions), 21.2 and 20.7 (pyrazine, $CH(\underline{C}H_3)_2$).

**((3*aS*,4*S*,6*R*,6*aR*)-6-((*S*)-4-((2*S*,5*R*)-*Iso*propyl-3,6-diemethoxy-2,5-dihydropyrazin-2-yl)-2-(methoxymethoxy)butyl)tetrahydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2-1'-cyclopentan]-4-ol (47).** To a solution of **46** (70.0 mg, 0.12 mmol) in $CH_2Cl_2$ (10.0 mL) at -10-0 °C were added $H_2O$ (0.50 mL) and 2,3-dichloro-5,6-dicyano-p-benzoquinone (39.6 mg, 1.17 mmol). The reaction mixture was stirred at -10-0 °C for 30 min and allowed to slowly warm to room temperature. After removal of solvent, the residue was purified by column chromatography (3/1, Hexane/EtOAc) to afford the desired product

**47** (32.0 mg) as a yellow oil: $^1$H NMR (250 MHz, $CDCl_3$) δ 4.64 (m, MOM, $CH_2$, 2H), 4.49 (t, J=5.75, 1H), 4.35(dd, J=2.0, 6.25, 1H), 4.09 (AB, pyrazine, 2H), 3.95 (t, J=3.25, 1H), 3.70 (s, 3H), 3.69 (s, 3H),3.62 (m, C-6', 1H) 3.39 (s, $OCH_3$, 3H), 2.43 (br s, C-1, 1H), 2.31 (br s, C<u>H</u>$(CH_3)_2$, 1H), 1.97-1.86 (m, 2H), 1.73-1.66 (m, 4H), 1.63-1.50 (m, cylcopentanone, 8H), 1.42-1.40 (m, 3H), 1.07 (d, J=7.0, 3H), 0.72 (d, J=7.0, 3H).

**(3*aS*,4*S*,6*R*,6*aR*)-4-(4-Methoxybenzyloxy)-2,2-dimethyl-6-vinyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxle (50).** Sodium hydride (1.83 g, 49.2 mmol) was added in portions to a solution of **29** (7.53 g, 41.0 mmol) in anhydrous N, N-dimethylformamide (DMF, 70.0 mL) at -10-0 °C. The reaction mixture was stirred at the same temperature for 30 min and then *p*-methoxybenzyl chloride (6.52 mL, 49.2 mmol) was added dropwise by syringe to the above reaction mixture. The reaction was kept at 0 °C for 1 h and at room temperature for 4 h. After removed DMF by high pressure vacuum, the residue was quenched by $H_2O$ (5.0 mL) and extracted with EtOAc (3×150 mL). The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. After removal the solvents under reduced pressure, the residue was purified on silica gel column chromatography (10/1, Hexane/EtOAc) to afford **50** (6.90 g, 60 %) as a yellow oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J=8.50, 2H), 6.89 (d, J=8.50, 2H), 5.72 (m, 1H), 5.02-4.97 (m, 2H), 4.63 (t, J=4.0, 8.0, 2H), 4.57-4.46 (m, 2H), 4.41 (d, J=6.0, 1H), 3.82 (s, 3H), 3.81-3.76 (m, 3H), 1.52 (s, 3H), 1.28 (s, 3H).

**2-((3*aR*,4*S*,6*S*,6*aS*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxl-4-yl)ethanol (51).** 9-Borabycyclo [3.3.1] nonane (9-BBN, 68.1 mL, 34.0 mmol, 0.5 M in THF) was added dropwise to a solution of **50** (6.90 g, 22.7 mmol) in anhydrous THF (50.0 mL) at -10-0 °C. The reaction mixture was stirred at

room temperature overnight. Methanol (15.0 mL), NaOH (6 M, 15.0 mL) and $H_2O_2$ (20.0 mL, 32 wt % in $H_2O$) were added dropwise to the above solution at 0 °C, respectively. The reaction was stirred for 4 h at room temperature. After diluted the reaction with EtOAc (100 mL), the organic phase was washed with saturated $NaHCO_3$ and brine and dried with anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified on silica gel column chromatography (1/1, Hexane/EtOAc) to afford **51** (6.73 g, 92 %) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, J=9.60, 2.00, 2H), 6.89 (dd, J=9.60, 2.00, 2H), 4.65-4.62 (d, J=12.0, 2H), 4.57-4.50 (m, 3H), 4.30 (d, J=5.60, 2H), 3.81 (s, 3H), 3.80-3.77 (m, 1H), 3.70-3.65 (m, 3H), 2.10-2.08 (m, 2H), 1.52 (s, 3H), 1.33 (s, 3H).

**2-((3*aR*,4*R*,6*S*,6*aS*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxl-4-yl)acetaldehyde (52).** Dimethyl sulphoxide (65.0 mL, 914 mmol) and di*iso*propyl ethylamine (14.7 mL, 84.4 mmol) were added to the solution of **51** (6.73 g, 20.9 mmol) in anhydrous $CH_2Cl_2$ (50.0 mL) at -10-0 °C. After the reaction was stirred at 0 °C for 30 min, $SO_3$·Py complex (6.80 g, 33.6 mmol) was added to the above solution. The reaction mixture was kept at the same temperature for 2 h and continued stirring for 4 h at room temperature. The reaction mixture was diluted with $CH_2Cl_2$ (150 mL) and $H_2O$ (10.0 mL) and extracted with $CH_2Cl_2$ (3×100 mL). The combined organic phases were washed with saturated $NaHCO_3$, $H_2O$ and brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (1/1, Hexane/EtOAc) to afford the aldehyde **52** (5.82 g, 87 %) as the colorless oil: $^1$H NMR (250 MHz, $CDCl_3$) δ 9.71 (t, J=1.75, 1H), 7.31 (d, J=8.50, 2H), 6.90 (d, J=8.50, 2H), 4.64-4.50 (m, 3H), 4.25 (d, J=5.50, 1H), 3.81

(s, 3H), 3.79-3.75 (m, 1H), 2.56-2.13 (m, 5H), 1.53 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 200.6, 157.6, 130.2, 129.5 (2C), 113.8 (2C), 111.5, 84.0, 78.5, 77.3, 71.4, 55.3, 46.6, 35.5, 32.7, 26.3, 24.4.

**(*R*)-1-((3*aR*,4*S*,6*S*,6*aS*)-6-(4-Methoxybenzyloxy)-2,2-diemthyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)pent-4-en-2-ol (53).** Allylmagnesium bromide (17.6 mL, 17.6 mmol, 1.0 M in diethyl ether) was added dropwise to a solution of (+)-B-methoxydi*iso*campheylboron (5.60 g, 17.6 mmol) in anhydrous diethyl ether (30.0 mL) at -10-0 °C under dry nitrogen. The reaction was stirred at room temperature for 2 h to give a white suspension. Then, the reaction flask was cooled to -90-78 °C and the aldehyde **52** (3.75 g, 11.7 mmol) dissolved in THF (15.0 mL) was added dropwise for 50 min to the above reaction mixture by a cannula. The newly reaction mixture was kept at -78 °C for 5 h and allowed to warm to room temperature for another 4 h. Finally, methanol (9.00 mL), NaOH (6 M, 7.50 mL) and $H_2O_2$ (15.0 mL, 32 wt % in $H_2O$) were added dropwise to the above solution at 0 °C, respectively. The reaction was stirred for 4 h at room temperature. After diluted the reaction with EtOAc (150 mL), the organic phase was washed with $H_2O$ and brine and dried with anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **51** (3.95 g, 93%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J=8.40, 2H), 6.88 (d, J=8.40, 2H), 5.80-5.73 (m, 1H), 5.12-5.04 (m, 2H), 4.64-4.48 (m, 3H), 4.27 (d, J=5.60, 1H), 3.83-3.80 (m, 1H), 3.78 (s, 3H), 3.68-3.60 (br, s, 1H), 2.29-1.88 (m, 6H), 1.73-1.57 (m, 2H), 1.52 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.1, 134.6, 130.5, 129.4 (2C), 118.0, 113.7 (2C), 111.2, 84.3, 78.7, 77.8, 71.3, 68.8, 55.2, 42.0, 39.7, 37.9, 33.9, 26.4, 24.5.

**(*S*)-1-((3*aR*,4*S*,6*S*,6*aS*)-6-(4-Methoxybenzyloxy)-2,2-diemthyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)pent-4-en-2-ol (54).** Allylmagnesium bromide (20.8 mL, 20.8 mmol, 1.0 M in diethyl ether) was added dropwise to a solution of (-)-B-methoxydi*iso*campheylboron (6.60 g, 20.8 mmol) in anhydrous diethyl ether (30.0 mL) at -10-0 °C under a nitrogen atmosphere. The reaction was stirred at room temperature for 2 h to give a white suspension. Then, the reaction flask was cooled to -90-78 °C and the aldehyde **52** (4.43 g, 13.8 mmol) in THF (10.0 mL) was added dropwise via a cannula over 50 min to the above reaction mixture. The reaction mixture was kept at -78 °C for 6 h and allowed to warm to room temperature for another 4 h. Finally, methanol (8.0 mL), NaOH (3.0 M, 15.0 mL) and $H_2O_2$ (15.0 mL, 32 wt % in $H_2O$) were added dropwise to the above solution at 0 °C, respectively. After being stirred at room temperature for 4 h, the reaction mixture was diluted with EtOAc (100 mL) and washed with $H_2O$ and brine, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **54** (4.51 g, 90%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J=8.40, 2H), 6.89 (d, J=8.40, 2H), 5.83 (m, 1H), 5.15 (m, 2H), 4.65-4.49 (m, 3H), 4.36 (dd, J=5.20, 3'-H, 1H), 3.80 (s, 3H), 3.79-3.75 (m, 1'-H, 1H), 3.70 (br s, 6'-H, 1H), 2.30-2.03 (m, 6H), 1.87-1.77 (m, 1H), 1.52 (s, 3H), 1.31 (s, 3H).

**(3*aR*,4*S*,6*S*,6*aS*)-4-((*S*)-2-(Benzyloxy)pent-4-enyl)-6-(4-methoxybenzyloxy)-2,2-diemthyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxole (55).** To a solution of **54** (3.96 g, 10.9 mmol) in anhydrous N, N-dimethylformamide (DMF, 50.0 mL) at -10-0 °C, was added sodium hydride (524 mg, 13.1 mmol). The reaction mixture was stirred at 0 °C for 30 min before benzyl chloride (1.55 mL, 13.1 mmol) was added dropwise by syringe.

The reaction mixture was kept at 0 °C for 2 h and continued stirring for 6 h at room temperature. After removal of DMF by high pressure vacuum, the residue was quenched by $H_2O$ (5.0 mL) and extracted with EtOAc (3×80.0 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification of the residue on silica gel column chromatography (4/1, Hexane/EtOAc) afforded **55** (4.20 g, 85 %): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33-2.27 (m, 7H), 6.87 (d, J=8.0, 2H), 5.83 (m, 1H), 5.09-5.05 (m, 2H), 4.60-4.33 (m, benzyl, $CH_2$; PMB, $CH_2$; 2'-H; 3'-H; 6H), 3.79 (s, 3H), 3.72 (m, 1'-H, 1H), 3.45 (br s, 6'-H, 1H), 2.33-1.90 (m, 7'-H, 2H; 4'-H; 5-H, 2H; 5H), 1.52 (s, 3H), 1.42-1.38 (m, 5'-H, 1H), 1.30 (s, 3H), 1.23 (m, 5'-H, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.2, 138.6, 134.4 (8'-C), 130.6, 129.5 (2C, PMB), 128.4 (2C, benzyl), 128.0 (2C, benzyl), 127.6, 117.5 (9'-C), 113.8 (2C, PMB), 111.1 ($C(CH_3)_2$), 84.9 (2'-C), 78.6 (3'-C),78.2 (1'-C), 77.6 (6'-C), 71.3 ($CH_2$, PMB), 71.2 ($CH_2$, benzyl), 55.3 ($OCH_3$), 38.2 (7'-C), 37.4 (5'-C), 37.0 (5-C), 32.7 (4'-C), 26.4, 24.5.

**(3*aR*,4*S*,6*R*,6*aR*)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4-caraldehyde (56).** Dimethyl sulphoxide (53.0 mL, 560 mmol), di*iso*propyl ethylamine (27.0 mL, 155 mmol) and $SO_3$·Py complex (25.5 g, 155 mmol) were added to a solution of **55** (12.7 g, 61.8 mmol) in $CH_2Cl_2$ (100 mL) at 0 °C. The reaction mixture was kept at 0 °C for 2 h and continued stirring for 4 h at room temperature. After the reaction completed, the solution was diluted with $CH_2Cl_2$ (100 mL) and $H_2O$ (10.0 mL). Extracted with $CH_2Cl_2$ (3×100 mL), the organic phase was washed with $H_2O$, saturated $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified on silica gel column chromatography (4/1,

Hexane/EtOAc) to afford the aldehyde **56** (8.82 g, 70 %). $^1$H NMR (400 MHz, $CDCl_3$) δ 9.58 (t, J=9.25, 4.50, 1H), 5.10 (s, 1H), 5.03-4.96 (m, 1H), 4.52-4.48 (m, 2H), 3.44 (s, 3H), 1.52 (s, 3H), 1.36 (s, 3H).

**(3*aR*,4*R*,6*R*,6*aR*)-4-Methoxy-2,2-dimethyl-6-vinyltetrahydrofuro[3,4-*d*][1,3]dioxole (57).** To a suspension of methyl triphenylphosphonium bromide (6.57 g, 18.4 mmol) in anhydrous diethyl ether (100 mL) at -10-0 °C was added potassium *tert*-butoxide (2.10 g, 18.4 mmol) portionwise. The yellow mixture was stirred at 0 °C for 1 h and kept at room temperature for 1.5 h. The reaction mixture was re-cooled to -10-0 °C, and a solution of the aldehyde **56** (2.50 g, 12.3 mmol) in $Et_2O$ (10.0 mL) was added dropwise. The mixture was stirred at room temperature overnight. $H_2O$ (10.0 mL) was used to quench the reaction. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (3×30.0 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (10/1, Hexane/EtOAc) to afford **57** (1.75 g, 75 %). $^1$H NMR (400 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.31-5.13 (m, 2H), 4.99 (s, 1H), 4.63 (m, 3H), 3.34 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H).

**2-((3*aR*,4*R*,6*R*,6*aR*)-6-Methoxy-2,2-dimethyltetrahydro[3,4-*d*][1,3]dioxol-4-yl)ethanol (58).** 9-Borabycyclo [3.3.1] nonane (9-BBN, 119 mL, 59.3 mmol, 0.5 M in THF) was added dropwise to a solution of **57** (7.99 g, 39.6 mmol) in anhydrous THF (50.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. Methanol (15.0 mL), NaOH (6 M, 11.0 mL) and $H_2O_2$ (20.0 mL, 32 wt % in $H_2O$) were added dropwise to the above solution at 0 °C, respectively. The reaction was stirred for 4 h at room temperature. After diluted the reaction with EtOAc (100 mL), the organic

phase was washed with saturated $NaHCO_3$ and brine and dried with $MgSO_4$. After removal of the solvents, the residue was purified by column chromatography (1/1, Hexane/EtOAc) to afford **58** (8.00g, 92%). Compound **58** was then directly used to the next step without NMR data.

**2-((3*aR*,4*R*,6*R*,6*aR*)-6-Methoxy-2,2-dimethyltetrahydro[3,4-*d*][1,3]dioxol-4-yl)acetaldehyde (59).** Dimethyl sulphoxide (79.5 mL, 840 mmol), di*iso*propyl ethylamine (36.0 mL, 207 mmol) and $SO_3$·Py complex (15.8 g, 99.4 mmol) were added to a solution of **58** (18.2 g, 82.8 mmol) in anhydrous $CH_2Cl_2$ (150 mL) at 0 °C. The reaction mixture was kept at the same temperature for 2 h and continued stirring for 6 h at room temperature. After the reaction completed, the solution was diluted with $CH_2Cl_2$ (150 mL) and $H_2O$ (15.0 mL). Extracted with $CH_2Cl_2$ (3×150 mL), the organic phase was washed with $H_2O$, saturated $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified on silica gel column chromatography (5/1, Hexane/EtOAc) to afford the aldehyde **59** (15.7 g, 87%). $^1$H NMR (400 MHz, $CDCl_3$) δ 9.81 (t, 1H), 4.98 (s, 1H), 4.75-4.71 (m, 1H), 4.65-4.58 (m, 2H), 3.33 (s, 3H), 2.86-2.79 (qd, J=2.30, 1H), 2.72-2.66 (qd, J=1.20, 1H), 1.50 (s, 3H), 1.33 (s, 3H).

**(*S*)-1-((3*aR*,4*R*,6*R*,6*aR*)-6-Methoxy-2,2-dimethyltetrahydro[3,4-*d*][1,3]dioxol-4-yl)pent-4-en-2-ol (60).** Allylmagnesium bromide (37.3 mL, 37.3 mmol, 1.0 M in diethyl ether) was added dropwise to a solution of (-)-B-methoxydi*iso*campheylboron (11.8 g, 37.3 mmol) in anhydrous diethyl ether (50.0 mL) at -10-0 °C under a nitrogen atmosphere. The reaction was stirred at room temperature for 2 h to give a white suspension. Then, the reaction flask was cooled to -90-78 °C and the aldehyde **59** (5.37 g,

24.8 mmol) dissolved in anhydrous THF (25.0 mL) was added dropwise over 50 min to the above reaction mixture by a cannula. The newly reaction mixture was kept at -78 °C for 6 h and allowed to warm to room temperature for another 4 h. Finally, methanol (10.0 mL), NaOH (6 M, 12.0 mL) and $H_2O_2$ (22.0 mL, 32 wt % in $H_2O$) were added dropwise to the above solution at -10-0 °C, respectively. The reaction was stirred for 4 h at room temperature. The reaction mixture was diluted with EtOAc (150 mL) and extracted with EtOAc (3×150 mL). The combined organic phases were washed with $H_2O$ and brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **60** (6.09 g, 95 %) as a colorless oil: $^1$H NMR (250 MHz, $CDCl_3$) δ 5.91-5.75 (m, 1H), 5.18-5.09 (m, 2H), 4.98 (s, 1'-H, 1H), 4.61-4.56 (m, 2H), 4.41 (t, J=7.75, 1H), 3.89 (br s, 6'-H, 1H), 3.36 (s, 3H), 2.66 (d, J=2.50, 1H), 2.33-2.22 (m, 2H), 1.76-1.70 (m, 2H), 1.49 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 134.5, 117.5, 112.2, 109.7, 85.6, 85.3, 84.1, 68.9, 54.9, 41.6, 41.1, 26.4, 24.9.

**(3*aR*,4*R*,6*R*,6*aR*)-4-((*S*)-2-(Benzyloxy)pent-4-enyl)-6-methoxy-2,2-dimethyltetrahydro[3,4-*d*][1,3]dioxole (61).** To a solution of **60** (2.09 g, 8.10 mmol) in anhydrous N, N-dimethylformamide (DMF, 20.0 mL) at -10-0 °C, was added sodium hydride (363 mg, 9.72 mmol). The reaction mixture was stirred at -10-0 °C for 20 min before benzyl chloride (1.15 mL, 9.72 mmol) was added by a syringe. The reaction mixture was kept at 0 °C for 2 h and continued stirring for 6 h at room temperature. After removal of DMF by high pressure vacuum, the residue was quenched by $H_2O$ (3.0 mL) and extracted with EtOAc (3×50.0 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification

of the residue on silica gel column chromatography (4/1, Hexane/EtOAc) afforded **61** (1.97 g, 70 %): $^{1}$H NMR (250 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 5.80 (m, 1H), 5.14 (m, 2H), 4.94 (s, 1H), 4.56-4.63 (m, Bn, $CH_2$, 4'-H, 2'-H, 4H), 4.44-4.51 (m, 3'-H, 1H), 3.65-3.76 (m, 6'-H, 1H), 3.32 ( s, 3H), 2.25-2.45 (m, 7'-H, 2H), 1.66-1.82 (m, 5'-H, 2H), 1.49 (s,3H), 1.30 (s, 3H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 138.2, 134.3, 128.3 (2C), 127.8, 127.5 (2C), 117.5, 112.1, 109.9, 85.6, 84.6, 84.3, 76.2, 71.8, 55.1, 40.1, 38.8, 26.5, 25.0.

**(*S*)-3-(Benzyloxy)-4-((3*aR*,4*R*,6*R*,6*aR*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butan-1-ol (62).** Sodium periodate (2.72 g, 12.7 mmol) was added to a solution of **60** (2.21 g, 6.34 mmol) in MeOH and $H_2O$ (80 mL, v/v=3/1) at 0 °C. Catalytic amount of osmium tetroxide (100 mg) was slowly added to the above reaction mixture. The reaction mixture was stirred at 0 °C for 1 h and kept for 2 h at room temperature. The mixture was filtrated with a little pad of celite, diluted with $CH_2Cl_2$ and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic phases were dried over anhydrous $MgSO_4$ and then evaporated under reduced pressure to give a yellow syrup, which was used to the next reaction without further purification.

To a stirred solution of the yellow synrup in anhydrous MeOH (40.0 mL) at -10-0 °C was added sodium borohydride (254 mg, 6.34 mmol) and the reaction mixture was stirred at 0 °C for 1 h and kept for 2 h at room temperature. Saturated $NH_4Cl$ solution (5.0 mL) was used to quench the reaction mixture. The residue was diluted with EtOAc (2×60.0 mL), dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (3/1, Hexane/EtOAc) to furnish **62** (0.940 g, 44 %): $^{1}$H NMR (250 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 4.95 (s, 1H), 4.580-4.610 (m, 4H), 4.41-4.47 (m, 1H), 3.88-3.3.86 (m, 6'-H, 1H), 3.78-3.67 (m, 8'-

H, 2H), 3.30 (s, 3H), 2.80-2.50 (br, OH, 1H), 1.88-1.71 (m, 7'-H, 5'-H, 4H), 1.49 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 138.2, 128.4 (2C), 127.9 (2C),127.8, 112.2, 109.9, 85.5, 84.6, 84.2, 75.3, 72.2, 59.8, 55.1, 40.3, 36.6, 26.5, 25.0.

**(3*aR*,4*R*,6*R*,6*aR*)-4-((*R*)-2-(Benzyloxy)-4-iodobutyl)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1, 3]dioxole (63).** A solution of **62** (940 mg, 2.67 mmol) in toluene (20.0 mL) and acetonitrile (10.0 mL) was treated with imidazole (273 mg, 4.0 mmol) and triphenylphosphane (841 mg, 3.20 mmol). Then, iodine was introduced in approximately 10.0 mg portions to the above reaction mixture until the reaction mixture remained dark-brown in color. The dark-brown solution was heated to reflux for 10 min and cooled to room temperature. Diethyl ether (20.0 mL) was added to dilute the solution and then the solution was washed with 10% sodium thiosulfate solution and brine. The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated in vacuo to obtain a residue, which was purified through a short plug of silica gel column chromatography (6/1, Hexanes/EtOAc) to provide **63** (0.940 g, 77 %): $^1$H NMR (250 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 4.98 (s, 1H), 4.65-4.56 (m, 4H), 4.49-4.42 (m, 1H), 3.82-3.72 (m, 6'-H, 1H), 3.39 (s, 3H), 3.31-3.18 (m, 8'-H, 2H), 2.13-2.02 (m, 7'-H, 2H), 1.79-1.70 (m, 5'-H, 2H),1.49 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 138.4, 128.5 (2C), 127.9 (2C), 127.8, 112.3, 110.1, 85.6, 84.6, 84.0, 76.5, 72.8, 55.5, 40.3, 39.5, 26.5, 25.0, 1.9 (-$CH_2$I).

**(2*R*,5*R*)-2-((*S*)-3-(Benzyloxy)-4-((3*aR*,4*R*,6*R*,6*aR*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butyl-5-*iso*propyl-3,6-dimethoxy-2,5-dihydropyrazine (64).** To a solution of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-*iso*propylpyrazine **35** (0.380 mL, 2.08 mmol) in anhydrous THF (5.0 mL) under a

nitrogen atmosphere was added *n*-BuLi (0.830 mL, 2.08 mmol) dropwise at -90-78 °C. This solution was stirred at -78 °C for 10 min. Then, this solution was transferred via a cannula over 10 min to a suspension of CuCN (93.6 mg, 1.04 mmol) in THF (10.0 mL) at -10-0$^0$C. The reaction mixture was stirred at -10-0 °C for 5 min then it was cooled to -90-78 °C. A solution of **63** (0.480 g, 1.04 mmol) in anhydrous THF (10.0 mL) was added dropwise via a cannula over 20 min to the above reaction mixture. The reaction mixture was stirred at -90-78 °C for 5 h and kept at -20 °C for 12 h. The solution was quenched with the addition of saturated $NH_4Cl$ (5.0 mL) and ammonium hydroxide (3.0 mL). From TLC analysis, it formed a complex, including a very strong UV activity point. Finally, THF was removed at reduced pressure, and the residue was separated to recover the reactant **63**. The desired product **64** was not obtained, due to the possible decomposition of the pyrazine unit.

**((3*aR*,4*R*,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-methanol (65).** To a solution of D-ribose (5.00 g, 33.3 mmol) in anhydrous acetone (100 mL), *p*-methoxybenzyl alcohol (6.20 mL, 50.0 mmol) and catalytic amount of sulfuric acid (0.5 mL) were added. The reaction mixture was stirred at room temperature overnight. After neutralized with ammonium hydroxide, $H_2O$ (10.0 mL) and EtOAc (100 mL) were added to the solution. The aqueous layer was extracted with EtOAc, and the combined organic phases were concentrated under reduced pressure to afford the crude product **65** and the excess unreacted *p*-methoxybenzyl alcohol, which were very difficult to be separated by the general silica gel column chromatography (the same polarity from TLC analysis after several developments in Hexane/EtOAc, 2/1).

**(3*aR*,6*R*,6*aR*)-2,2-Dimethyl-6-vinyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (66).** To a solution of **57** (7.68 g, 38.4 mmol) in 1,4-dioxane (60.0 mL), 4 M hydrochloric acid (30.0 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 72 h. 6 M NaOH was used to neutralize the excess acid until the solution was pH = 7.0. After removal of the solvents in vacuo, the residue (triols) was obtained, diluted with MeOH, and dried with anhydrous $MgSO_4$. Evaporating the solvent under reduced pressure, the residue was used in the next step without purification. Then, the residue was dissolved in anhydrous acetone (30.0 mL) and catalytic amount of sulfuric acid (1.0 mL) was added to the above solution. The reaction mixture was stirred at room temperature for 2 h. After removal of the solvent under reduced pressure, the residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to furnish **66** (3.16 g, 60 %): $^1$H NMR (250 MHz, $CDCl_3$) δ 6.05 (m, 1H), 5.48 (d, J=3.0, 1H), 5.32-5.13 (m, 2H), 4.69-4.59 (m, 3H), 4.21 (d, J=3.0, 1H), 1.50 (s, 3H), 1.32 (s, 3H).

**(3*aR*,4*R*,6*R*,6*aR*)-4-(4-Methoxybenzyloxy)-2,2-dimethyl-6-vinyltetrahydrofuro[3,4-*d*][1,3]dioxole (67 & 68).** Sodium hydride (489 mg, 20.4 mmol, 60 % in material oil) was added in portions to a solution of **66** (3.16 g, 17.0 mmol) in anhydrous N, N-dimethylformamide (DMF, 30.0 mL) at -10-0 °C. The reaction mixture was stirred at the same temperature for 30 min and then *p*-methoxybenzyl chloride (2.80 mL, 20.4 mmol) was added dropwise to the above reaction mixture. The reaction was kept at 0 °C for 2 h and at room temperature for 4 h. After removal of DMF by high pressure vacuum, the residue was quenched by $H_2O$ (3.0 mL) and extracted with EtOAc (3×50.0 mL). The combined organic layera were washed with $H_2O$ and brine, and dried with anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the

residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to privide **67** (3.16 g, 60 %) as a shallow yellow oil, a major product and a by-product **68** (0.620 g, 15 %). For **67**: $^{1}$H NMR (250 MHz, $CDCl_3$) δ 7.26 (dd, J=6.75, 2.25, 2H), 6.89 (dd, J=6.75, 2.25, 2H), 5.96 (m, 1H), 5.33-5.19 (m, 2H), 5.15 (s, 1H), 4.70-4.56 (m, 4H), 4.42-4.34 (m, 1H), 3.79 (s, 3H), 1.49 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 159.4, 132.6, 130.0, 129.6 (2C), 119.4, 114.3, 114.0 (2C), 105.2, 85.6, 81.5, 71.6, 68.8, 55.5, 26.2, 25.0.

For **68**: $^{1}$H NMR (250 MHz, $CDCl_3$) 7.34 (d, J=6.75, 2H), 6.91 (d, J=6.75, 2H), 5.84 (m, 1H), 5.80-5.20 (m, 2H), 5.06 (d, J=4.25, 1H), 4.84-4.45 (m, PMB, $CH_2$; 2'-H; 3'-H; 4'-H; 5H), 3.80 ($OCH_3$, 3H), 1.56 (s, 3H), 1.35 (s, 3H).

**2-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethanol (69).** 9-Borabycyclo [3.3.1] nonane (9-BBN, 29.5 mL, 14.8 mmol, 0.5 M in THF) was added dropwise to a solution of **67** (3.16 g, 9.83 mmol) in anhydrous THF (30.0 mL) at -10-0 °C. The reaction mixture was stirred at room temperature for 12 h. Methanol (13.0 mL), NaOH (6 M, 8.0 mL) and $H_2O_2$ (15.0 mL, 32 wt % in $H_2O$) were added dropwise to the above solution at -10-0 °C, respectively. The reaction was stirred for 4 h at room temperature. After diluted the reaction with EtOAc (50.0 mL), the organic phase was washed with saturated $NaHCO_3$ and brine, and dried with anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified on silica gel column chromatography (3/1, Hexane/EtOAc) to afford **69** (2.51 g, 75 %): $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J=8.80, 2.80, 2H), 6.89 (dd, J=8.80, 2.80, 2H), 5.14 (s, 1H), 4.69-4.61(m, 3H), 4.41-4.38 (m, 2H), 3.82-3.79 (m, 2H), 3.78 (s, 3H), 2.51 (br s, 1H), 1.97-1.85 (m, 1H), 1.83-1.77 (m, 1H), 1.47 (s, 3H), 1.30 (s,

3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.5, 129.8 (2C), 129.5, 114.0 (2C), 112.4, 107.5, 85.7, 85.1, 84.5, 69.2, 60.1, 55.4, 37.6, 26.6, 25.3.

**2-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)acetaldehyde (70).** Dimethyl sulphoxide (80.4 mL, 1.13 mol), di*iso*propyl ethylamine (28.2 mL, 162 mmol) and $SO_3$·Py complex (7.72 g, 48.5 mmol) were added to a solution of **69** (10.5 g, 32.3 mmol) in $CH_2Cl_2$ (80.0 mL) at -10-0 °C. The reaction mixture was kept at the same temperature for 2 h and continued stirring for 4 h at room temperature. The solution was diluted with $CH_2Cl_2$ (100 mL) and $H_2O$ (10.0 mL) and extracted with $CH_2Cl_2$ (3×100 mL). The combined organic phases were washed with saturated $NaHCO_3$, $H_2O$ and brine, dried over anhydrous $MgSO_4$ and evaporated at reduced pressure. The residue was purified on silica gel column chromatography (5/1, Hexane/EtOAc) to afford the aldehyde **70** (9.07 g, 87 %): $^1$H NMR (250 MHz, $CDCl_3$) δ 9.80 (dd, J=2.50, 1.25, 1H), 7.27 (dd, J=8.80, 2.80, 2H), 6.89 (dd, J=8.80, 2.80, 2H), 5.14 (s, 1H), 4.79-4.68 (m, PMB, $CH_2$, 2H), 4.62 (d, J=2.50, 2'-H, 1H), 4.58 (d, J=2.50, 3'-H, 1H), 4.38 (d, J=11.25, 4'-H, 1H), 3.79 (s, 3H), 2.93-2.83 (qd, J=2.50, 5'-H, 1H), 2.75-2.65 (qd, J=1.25, 5'-H, 1H), 1.49 (s, 3H), 1.30 (s, 3H).

**(3*aR*,6*R*,6*aR*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (71).** A catalytic amount sulfuric acid (1.0 mL) and celite (5.0 g) were slowly added to a suspension of D-ribose (22.3 g, 149 mmol) in anhydrous acetone (200 mL). The reaction mixture was stirred at the same temperature for 2 h. Solid $NaHCO_3$ was used to neutralize the reaction mixture to pH = 7.0. The solution was filtrated and the residue was washed with EtOAc. The filtrate was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give a viscous liquid, which was purified on silica gel column

chromatography (3/1, Hexane/EtOAc) to afford **71** (26.8 g, 95 %): $^1$H NMR (250 MHz, $CDCl_3$) δ 5.44 (d, J=6.25, 1H), 4.86 (d, J=5.75, 1H), 4.61 (d, J=6.00, 1H), 4.46-4.41 (m, 2H), 3.76-3.72 (m, 2H), 3.38 (br s, 1H), 1.49 (s, 3H), 1.33 (s, 3H).

**((3*aR*,4R,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol (72 & 73).** Sodium hydride (6.43 g, 161 mmol, 60 % in material oil) was added in portions to a solution of **71** (30.6 g, 161 mmol) in anhydrous N, N-dimethylformamide (DMF, 90.0 mL) at -10-0 °C. The reaction mixture was stirred at the same temperature for 50 min and then *p*-methoxybenzyl chloride (21.8 mL, 161 mmol) was added dropwise by a syringe over 40 min to the above solution. The reaction mixture was kept at -10-0 °C for 2 h and at room temperature for 12 h. After removal of DMF under high pressure vacuum, the residue was quenched by $H_2O$ (12.0 mL) and extracted with EtOAc (3×150 mL). The combined organic layers were washed with $H_2O$ and brine, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to privide a major product **72** (37.4 g, 75 %) as and a possible by-product **73** (< 10%). For **72**: $^1$H NMR (250 MHz, $CDCl_3$) δ 7.24 (d, J=8.40, 2H), 6,87 (d, J=8.40, 2H), 5.15 (s, 1H), 4.84 (d, J=6.0, 1H), 4.71-4.58 (m, 3H), 4.46 (d, J=15.2, 1H), 4.41 (t, J=4.0, 1H), 3.79 (s, 3H), 3.72-3.64 (m, 2H), 1.47(s, 3H), 1.30 (s, 3H).

**(*S*)-1-((3*aR*,4R,6*R*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)pent-4-en-2-ol (75).** Allylmagnesium bromide (40.2 mL, 40.2 mmol, 1.0 M in diethyl ether) was added dropwise to a solution of (-)-B-methoxydi*iso*campheylboron (12.7 g, 40.2 mmol) in anhydrous diethyl ether (50.0 mL) at -10-0 °C under a nitrogen atmosphere. The reaction was stirred at room temperature for 2

h to give a white suspension. Then, the reaction flask was cooled to -90-78 °C and the aldehyde **70** (8.64 g, 26.8 mmol) dissolved in anhydrous THF (25.0 mL) was added dropwise over 50 min to the above reaction mixture by a cannula. The newly reaction mixture was kept at -78 °C for 6 h and allowed to warm to room temperature for another 4 h. Finally, methanol (10.0 mL), NaOH (6 M, 10.0 mL) and $H_2O_2$ (25.0 mL, 32 wt % in $H_2O$) were added dropwise to the above solution at -10-0 °C, respectively. The reaction was stirred for 4 h at room temperature. The reaction mixture was diluted with EtOAc (150 mL) and extracted with EtOAc (3×150 mL). The combined organic phases were washed with $H_2O$ and brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **75** (9.28 g, 95 %) as a white solid: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd. J=8.50, 2.00, 2H), 6.89 (dd, J=8.75, 2.00, 2H), 5.74-5.85 (m, 8'-H, 1H), 5.13-5.15 (m, CH2=CH, $CH_2$, 2H), 5.10 (s, 1'-H, 1H), 4.66-4.69 (m, PMB, $CH_2$, 2H), 4.64 (d, J=11.25, 2'-H, 1H), 4.48-4.51 (dd, J=4.80, 4'-H, 1H), 4.43 (d, J=11.25, 1H), 3.91 (br s, 6'-H, 1H), 3.80 (s, 3H), 2.15-2.28 (m, 7'-H, 2H), 2.09 (br s, -OH, 1H), 1.79-1.86 (qd, J=2.80, 5'-H, *trans* with 6'-H, 1H), 1.59-1.67 (qd, J=4.8, 5'-H, *cis* with 6'-H, 1H), 1.48(s, 3H), 1.31(s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.5, 134.6, 129.7 (2C), 129.5, 118.5 ($\underline{C}H_2$=CH), 114.0 (2C), 112.4 (*iso*propyl C), 107.8 (C-1'), 85.8 (5'-H), 84.8 (C-2'), 84.7 (PMB, $\underline{C}H_2$), 69.3 (C-4'), 68.1 (C-6'), 55.4 (O$\underline{C}H_3$), 42.7 (C-7'), 41.8 (C-5'), 26.7, 25.2. HRMS: calcd for $C_{20}H_{28}O_6$ [(M - $CH_3$)$^+$] 349.1651; found 349.1653.

***Tert*-butyl((*S*)-1-((3*aR*,4R,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)pent-4-en-2-yloxy)dimethylsilane (76).** To a solution of **75** (1.08 g, 2.96 mmol) in anhydrous $CH_2Cl_2$ (25.0 mL) were added

imidazole (504 mg, 7.40 mmol) and a catalytic amount of DMAP (2 % mmol, 7.23 mg) at -10-0 °C under a nitrogen atmosphere. After the mixture was stirred for 30 min at room temperature and then re-cooled -10 °C, *tert*-butyldimethylsilyl chloride (670 mg, 4.45 mmol) was slowly added. The whole reaction mixture was then stirred at the same temperature for 1 h, warmed to room temperature and stirred for 24 h. After the reaction mixture was diluted with ice-water, the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×50.0 mL). The combined organic phases were washed with $H_2O$ and brine, dried with anhydrous $MgSO_4$, and then evaporated in vacuo to afford the crude product, which was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to furnish **76** (1.36 g, 96 %) as a colorless oil: $^1$H NMR (250 MHz, $CDCl_3$) δ 7.09 (d, J=8.00, 2H), 6.72 (d, J=8.00, 2H), 5.58 (m, 1H), 4.96 (s, 1H), 4.90 (irregular t, J=8.75, 9.25, 2H), 4.52 (m, 3H), 4.26 (d, J=11.50, 2H), 3.80 (br s, 1H), 3.61 (s, 3H), 2.08 (m, 2H), 1.57-1.66 (m, 1H), 1.39-1.47 (m, 1H), 1.32 (s, 3H), 1.14 (s, 3H), 0.78 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 159.4, 134.5, 129.5 (2C), 127.6, 117.4, 113.9, 112.1, 107.6, 85.9, 84.9, 84.3, 69.12, 69.0, 55.2, 43.1, 42.1, 26.6, 26.0 (3C), 25.8, 25.2, 18.2, -4.2, -4.6. Anal. Calcd for $C_{26}H_{42}O_6Si$: C, 65.24; H, 8.84; Found: C, 65.38; H, 8.91.

**(*S*)-3-(*Tert*-butyldimethylsilyloxy)-4-((3*aR*,4R,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butan-1-ol (77)-the First Method.** Sodium periodate (4.65 g, 21.7 mmol) was slowly added to a solution of **76** (5.20 g, 10.9 mmol) in a mixture of MeOH /$H_2O$ (120 mL, v/v=3/1) at -10-0 °C. Catalytic amount of osmium tetraoxide (200 mg) was slowly added to the above reaction mixture. The reaction mixture was stirred at 0 °C for 1 h and kept for 2 h at room temperature. The

mixture was filtrated with a little pad of celite, diluted with $CH_2Cl_2$ and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic phases were dried over anhydrous $MgSO_4$ and then evaporated under reduced pressure to give a yellow syrup, which was used to the next reaction without further purification.

To a stirred solution of the yellow synrup in anhydrous MeOH (50.0 mL) at -10-0 °C was added sodium borohydride (495 mg, 13.1 mmol). The reaction mixture was stirred at -10-0 °C for 1 h and kept for 2 h at room temperature. Saturated $NH_4Cl$ solution (5.0 mL) was used to quench the reaction mixture. The residue was diluted with EtOAc (2×60.0 mL), dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (3/1, Hexane/EtOAc) to furnish **77** (2.36 g, 45 %) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, J=8.50, J=2.0, 2H), 6.75 (dd, J=8.75, J=2.0, 2H), 4.98 (s, 1H), 4.54 (d, J=6.0, 1H), 4.44-4.48 (m, 2H), 4.29 (d, J=11.6, 1H), 4.20 (t, J=11.6, 1H), 3.99 (m, 1H), 3.65 (s, 3H), 3.51-3.66 (m, 2H), 2.13 (br s, 1H), 1.68-1.77 (m, 1H), 1.61-1.64 (m, 2H), 1.43-1.50 (m, 1H), 1.33 (s, 3H), 1.16 (s, 3H), 0.77 (s, 9H), -0.02 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.5, 129.6 (2C), 129.6, 114.1 (2C), 112.4, 107.7, 85.9, 84.9, 84.1, 69.2, 68.5, 59.8, 55.5, 42.1, 39.3, 26.7, 26.1 (3C), 25.3, 18.2, -4.3, -4.5. Anal. Calcd for $C_{25}H_{42}O_7Si$: C, 62.21; H, 8.77. Found: C, 61.99; H, 8.84.

**(*S*)-3-(*Tert*-butyldimethylsilyloxy)-4-((3*aR*,4R,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butan-1-ol (77)- the Optimized Method.** To a solution of **76** (10.3 g, 21.4 mmol) in THF (100 mL) was added a catalytic amount of osmium tetroxide (200 mg) and 50 % aqueous N-methylmorpholine N-oxide (NMO, 30.0 mL) at -10-0 °C. The reaction mixture was stirred at the same temperature

for 2 h and warmed to room temperature and kept stirring for 12 h. After evaporated the solvents under reduced pressure, the residue was diluted and extracted with EtOAc. The organic phase was concentrated again to give a yellow liquid, which was purified on silica gel column chromatography (1/1, Hexane/EtOAc) to furnish the diol **76-1'** (8.92 g, 85 %). **76-1'** was not necessary to be conducted with NMR and further used to the next reaction.

To a stirred solution of **76-1'** in a mixture of $CH_2Cl_2/H_2O$ (160 mL, 3/1, v/v) at -10-0 °C was slowly added sodium periodate (7.44 g, 34.8 mmol). A catalytic amount of 15-crown-5 (1.0 mL) was added to the above reaction mixture. The reaction mixture was stirred at the same temperature for 2 h and warmed to room temperature and kept stirring for 12 h. The solution was diluted with $CH_2Cl_2$ (150 mL), and the aqueous layer was extracted with $CH_2Cl_2$ (3×150 mL). The combined organic phases were washed with $H_2O$ and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (1/1, Hexane/EtOAc) to afford the aldehyde **76-1''** (7.74 g, 93 %) as a colorless oil and the aldehyde **76-1''** was used to the next reaction.

The aldehyde **76-1''** (7.74 g, 16.1 mmol) thus obtained was dissolved in anhydrous MeOH (80.0 mL) at -10-0 °C. To this solution were added sodium borohydride (772 mg, 32.2 mmol) and $CeCl_3 \cdot 7H_2O$ (6.00 g, 16.1 mmol). The reaction mixture was stirred at -10-0 °C for 1 h and kept for 2 h at room temperature. Saturated $NH_4Cl$ solution (5.0 mL) was used to quench the reaction mixture. The residue was diluted with EtOAc (2×60.0 mL), dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (2/1,

Hexane/EtOAc) to furnish **77** (6.27 g, 80 %) as a colorless oil in three steps from **76**. The NMRs ($^{1}H$, $^{13}C$) of **77** were the same as that of **77**, which was achieved from the first oxidative-cleavage method.

***Tert*-butyl(*R*)-4-iodo-1-((3*aR*,4R,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butan-2-yloxy)dimethylsilane (78).** A solution of **77** (5.17 mg, 483 mmol) in toluene (100 mL) and acetonitrile (20.0 mL) was treated with imidazole (1.10 g, 16.1 mmol) and triphenylphosphane (4.20 g, 16.1 mmol). Then, iodine was introduced in approximately 10.0 mg portions to the above reaction mixture until the reaction mixture remained dark-brown in color. The dark-brown solution was heated to reflux for 30 min and cooled to room temperature. The reaction mixture was diluted with $Et_2O$ (50.0 mL) and washed with a 10% sodium thiosulfate solution and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified through a short plug of silica gel column chromatography (6/1, Hexanes/EtOAc) to provide **78** (5.92 g, 90 %) as a yellow oil: $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J=8.40, 2.0, 2H), 6.89 (d, J=8.80, 2.0, 2H), 5.12 (s, 1H), 4.55-4.67 (m, 2H), 4.62-4.65 (d, J=11.60, 1H), 4.43-4.46 (d, J=11.60, 1H), 4.36 (dd, J=4.80, 1H), 3.91-3.94 (m, 1H), 3.81 (s, 3H), 3.07-3.17 (m, 2H), 1.98-2.05 (m, 2H), 1.64-1.76 (m, 2H), 1.47 (s, 3H), 1.30 (s, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 159.6, 129,7 (2C), 129.6, 114.1 (2C), 112.5, 107.6, 86.0, 85.0, 84.0, 69.9, 69.4, 55.5, 42.7, 42.4, 26.8, 26.1 (3C), 25.4, 18.3, -4.0. -4.3.

**(2*R*,5*R*)-2-((*S*)-3-(*Tert*-butyldimethylsilyloxy)-4-((3*aR*,4*R*,6*R*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butyl)-5-*iso*propyl-3,6-dimethoxy-2, 5-dihydropyrazine (79).** To a solution of (2*R*)-2,5-dihydro-

3,6-dimethoxy-2-*iso*propylpyrazine **35** (1.20 mL, 7.20 mmol) in anhydrous THF (20.0 mL) under a nitrogen atmosphere was added *n*-BuLi (2.90 mL, 7.20 mmol) dropwise at -90-78 °C by a syringe. This solution was stirred at -78 °C for 30 min. Then, to this solution was slowly added a solution of **78** (2.10 g, 3.60 mmol) in anhydrous THF (20.0 mL) via a cannula over 40 min at -90-78 °C. The reaction mixture was stirred at -90-78 °C for 5 h, kept at -20 °C for 12 h and allowed to slowly warm to room temperature. The solution was then quenched with the addition of saturated $NH_4Cl$ (5.0 mL) and ammonium hydroxide (3.0 mL). The THF was removed under the reduced pressure, and the residue was diluted with EtOAc. The organic phase was separated and the aqueous layer was extracted with EtOAc (3×100 mL). The combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the residue was purified on silica gel column chromatography (3/1, Hexane/EtOAc) to afford **79** (1.96 g, 85 %) as the yellow oil, the only diastereoisomer, which was confirmed by NMRs and ($^1$H, $^1$H, COSY). $^1$H NMR (400 MHz, $CDCl_3$) 7.12 (d, J=8.40, 2H), 6.76 (d, J=8.80, 2H), 4.99 (s, 1H), 4.55 (d, J=6.00, 2'-H, 1H), 4.50 (m, PMB, CH2, 2H), 4.29 (d, J=11.20,3-H', 1H), 4.24 (m, 4-H', 1H), 3.89 (m, 6-H', 1H), 3.82 (m, 2H), 3.68 (s, 3H), 3.55 (s, 3H), 3.54 (s, 3H), 2.15 (m, 1H), 1.77-1.71 (m,7-H', 1H),1.65-1.47 (m, 5-H' down, 5-H' up, 8-H', 4H), 1.35 (s, 3H), 1.28 (m, 7-H', 1H), 1.18 (s, 3H), 0.94 (d, J=6.80, 3H), 0.80 (s, 9H), 0.59 (d, J=6.80, 3H), 0.00 (s, 3H), -0.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 163.8, 163.8, 159.5, 129.8 (2C), 129.6, 114.0 (2C), 112.2, 107.6, 85.9, 84.9, 84.5, 69.5, 69.2, 60.9, 55.4, 52.5, 52.5, 42.3, 33.1 (7-C'), 31.9 (5-C'), 29.3, 26.7, 26.1 (3C), 26.1 (8-C'), 25.3, 19.3, 18.3, 16.8, -4.2, -4.5.

**((3*aR*,6*R*,6*aR*)-6-((*S*)-2-(*Tert*-butyldimethylsilyloxy)-4-((2*R*,5*R*)-5-*iso*propyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)butyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (80).** To an ice-cooled solution of **79** (220 mg, $3.39\times10^{-4}$ mmol) in $CH_2Cl_2$ (20.0 mL) were added $H_2O$ (2.0 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (115 mg, 0.510 mmol). The reaction mixture was stirred at -10-0 °C for 2 h and allowed to slowly warm to room temperature. The reaction mixture was diluted with $CH_2Cl_2$, filtered with a pad of celite, and washed with saturated $NaHCO_3$, $H_2O$, and brine, and dried with anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the residue was purified on silica gel column chromatography (6/1-1/1, Hexane/EtOAc). However, no the desired product **80** was obtained from the separated several points (from $^1$H NMR data).

**(3*aR*,6*R*,6*aR*)-6-((*R*)-2-(*Tert*-butyldimethylsilyloxy)-4-iodobutyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (81).** To a solution of **78** (850 mg, 1.43 mmol) in $CH_2Cl_2$ (20.0 mL) at -10-0 °C were added $H_2O$ (1.0 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (391 mg, 1.72 mmol). The reaction mixture was stirred at -10-0 °C for 2 h and allowed to slowly warm to room temperature. The reaction mixture was diluted with $CH_2Cl_2$, filtrated with a pad of celite, and washed with saturated $NaHCO_3$, $H_2O$, and brine, and dried with $MgSO_4$. After removal of solvent, the residue was purified by column chromatography (2/1, Hexane/EtOAc) to afford the desired product **81** (0.530 g, 78 %) as a yellow oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.13 (m, 1H), 4.64-4.61 (d, J=11.60, 2'-H, 1H), 4.47-4.42 (d, J=11.60, 3'-H, 1H), 4.32 (dd, J=4.80, 4'-H, 1H), 3.94-3.92 (br s, 6'-H, 1H), 3.17-3.00 (m, 2H), 2.08-1.98 (m, 2H), 1.78-1.64 (m, 2H), 1.49 (s,

3H), 1.31 (s, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 112.5, 107.6, 85.9, 85.1, 69.8, 69.3, 42.6, 42.3, 26.8, 26.2(3C), 25.4, 18.3, 1.7, -4.0. -4.3.

**(3*aR*,4*S*,6*S*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4-carbaldehyde (82).** Dimethyl sulphoxide (20.6 mL, 290 mmol), di*iso*propyl ethylamine (12.6 mL, 72.5 mmol) and $SO_3$·Py complex (3.46 g, 48.5 mmol) were added to a solution of **73** (4.50 g, 14.5 mmol) in $CH_2Cl_2$ (50.0 mL) at 0 °C. The reaction mixture was kept at the same temperature for 2 h and continued stirring for 4 h at room temperature. The solution was diluted with $CH_2Cl_2$ (50.0 mL) and $H_2O$ (8.0 mL) and extracted with $CH_2Cl_2$ (3×80.0 mL). The combined organic phases were washed with saturated $NaHCO_3$, $H_2O$ and brine, dried over anhydrous $MgSO_4$ and evaporated at reduced pressure. The residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford the aldehyde **82** (3.58 g, 80%). From TLC analysis, **82** was confirmed compared with the reactant **73** was further used to the next step.

**(3*aR*,4*S*,6*S*,6*aR*)-4-(4-Methoxybenzyloxy)-2,2-dimethyl-6-vinyltetrahydrofuro[3,4-*d*][1,3]dioxole (68)-the Second Approach from 73.** To a suspension of methyltriphenylphosphonium bromide (6.21 g, 17.4 mmol) in anhydrous diethyl ether (50.0 mL) at -10-0 °C was added potassium *tert*-butoxide (1.99 g, 17.4 mmol) portionwise. The yellow mixture was stirred at 0 °C for 1 h and kept at room temperature for 1.5 h. The reaction mixture was re-cooled to -10-0 °C, and a solution of the aldehyde **82** (3.58 g, 11.6 mmol) in $Et_2O$ (15.0 mL) was added dropwise. The mixture was stirred at room temperature overnight. $H_2O$ (5.0 mL) was used to quench the reaction. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (3×30.0 mL). The combined organic phase was dried with anhydrous $MgSO_4$ and evaporated under

reduced pressure. The residue was purified on silica gel column chromatography (5/1, Hexane/EtOAc) to afford **68** (2.49 g, 70 %). The NMR data of **68** was the same with that of the first method obtained.

**2-((3*aR*,4*R*,6*S*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethanol (83).** 9-Borabycyclo [3.3.1] nonane (9-BBN, 41.0 mL, 20.3 mmol, 0.5 M in THF) was added dropwise to a solution of **68** (4.35 g, 13.5 mmol) in anhydrous THF (30.0 mL) at -10-0 °C. The reaction mixture was stirred at room temperature for 12 h. Methanol (12.0 mL), NaOH (6 M, 8.0 mL) and $H_2O_2$ (12.0 mL, 32 wt % in $H_2O$) were added dropwise to the above solution at -10-0 °C, respectively. The reaction was stirred for 4 h at room temperature. After diluted the reaction with EtOAc (50.0 mL), the organic phase was washed with saturated $NaHCO_3$ and brine and dried with anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified on silica gel column chromatography (2/1, Hexane/EtOAc) to afford **83** (3.45 g, 75%). From TLC analysis, **83** was confirmed and used to the next step.

**2-((3*aR*,4*R*,6*S*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)acetaldehyde (84).** Dimethyl sulphoxide (10.3 mL, 145 mmol), di*iso*propyl ethylamine (6.30 mL, 36.3mmol) and $SO_3$·Py complex (776 mg, 10.9 mmol) were added to the solution of **83** (2.46 g, 7.25 mmol) in $CH_2Cl_2$ (30.0 mL) at -10-0 °C. The reaction mixture was kept at the same temperature for 2 h and continued stirring for 4 h at room temperature. The solution was diluted with $CH_2Cl_2$ (30.0 mL) and $H_2O$ (8.0 mL) and extracted with $CH_2Cl_2$ (3×80.0 mL). The combined organic phases were washed with saturated $NaHCO_3$, $H_2O$ and brine, dried over anhydrous $MgSO_4$ and evaporated at reduced pressure. The residue was purified on silica gel column chromatography (4/1,

Hexane/EtOAc) to afford the aldehyde **84** (2.08 g, 85 %): $^1$H NMR (400 MHz, $CDCl_3$) 9.74 (t, J=2.80, 1H), 7.31 (dd, J=8.40, 1.60, 2H), 6.91 (dd, J=8.40, 1.60, 2H), 5.03 (d, J=4.40, 1H), 4.77-4.45 (m, PMB, $CH_2$; 2'-H; 3'-H; 4'-H; 5H), 3.82 (s, 3H), 2.69-2.36 (m, 5'-H, 2H), 1,56 (s, 3H), 1.37 (s, 3H).

**(*S*)-1-((3*aR*,4*R*,6*S*,6*aR*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)pent-4-en-2-ol (85).** Allylmagnesium bromide (5.0 mL, 4.65 mmol, 1.0 M in diethyl ether) was added dropwise to a solution of (-)-B-methoxydi*iso*campheylboron (1.47 g, 4.65 mmol) in anhydrous diethyl ether (30.0 mL) at -10-0 °C under a nitrogen atmosphere. The reaction was stirred at room temperature for 2 h to give a white suspension. Then, the reaction flask was cooled to -90-78 °C and the aldehyde **84** (1.44 g, 3.10 mmol) dissolved in anhydrous THF (15.0 mL) was added dropwise over 30 min to the above reaction mixture by a cannula. The newly reaction mixture was kept at -78 °C for 6 h and allowed to warm to room temperature for another 4 h. Finally, methanol (8.0 mL), NaOH (6 M, 8.0 mL) and $H_2O_2$ (15.0 mL, 32 wt % in $H_2O$) were added dropwise to the above solution at -10-0 °C, respectively. The reaction was stirred for 4 h at room temperature. The reaction mixture was diluted with EtOAc (100 mL) and extracted with EtOAc (3×100 mL). The combined organic phases were washed with $H_2O$ and brine, dried with anhydrous $MgSO_4$ and evaporated at reduced pressure. The residue was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to afford **85** (1.47 g, 90 %): $^1$H NMR (250 MHz, $CDCl_3$) δ 7.33 (dd, J=8.75, 2.50, 2H), 6.91 (dd, J=8.75, 2.50, 2H), 5.91-5.76 (m, 1H), 5.74-5.5.72 (d, J=3.75, 1'-H, 1H), 5.16-5.01 (m, 2H), 4.77-4.43 (m, PMB, $CH_2$; 2'-H; OH; 4H), 4.32-4.12 (m, 3'-H; 4'-H; 2H), 3.81 (s, $OCH_3$), 3.52-3.47 (m, 6'-H, 1H), 2.28-2.20 (m, 7'-H, 2H), 1.80-1.71

(m, 5'-H, 2H), 1.60 (s, 3H), 1.36 (s, 3H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 159.5, 134.6, 129.6 (2C), 129.5, 118.4, 114.0 (2C), 112.4, 107.7, 85.8, 84.8, 84.6, 69.3, 68.1, 55.4, 42.6, 41.7, 26.6, 25.1.

***Tert*-butyl((*S*)-1-((3*aR*,4*R*,6*S*,6*aR*)-6-(4-methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)pent-4-en-2-yloxy)dimethylsilane (86).** To a solution of **85** (1.50 g, 4.10 mmol) in anhydrous $CH_2Cl_2$ (20.0 mL) were added imidazole (697 mg, 10.3 mmol) and a catalytic amount of DMAP (5 % mmol, 25 mg) at -10-0 °C under a nitrogen atmosphere. After the mixture was stirred for 30 min at the room temperature and then re-cooled -10 °C, *tert*-butyldimethylsilyl chloride (1.60 mg, 10.3 mmol) was slowly added. The whole reaction mixture was then stirred at the same temperature for 1 h, warmed to room temperature and stirred for 24 h. After the reaction mixture was diluted with ice-water, the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×50.0 mL). The combined organic phases was washed with water and brine, dried with anhydrous $MgSO_4$, and then evaporated in vacuo to afford the crude product, which was purified on silica gel column chromatography (4/1, Hexane/EtOAc) to furnish **86** (1.81 g, 92 %) as a colorless oil: $^1$H NMR (250 MHz, $CDCl_3$) δ 7.15 (dd, J=11.50, 2.50, 2H), 6.79 (dd, J=11.50, 2.50, 2H), 5.73-5.58 (m, 1H), 4.99-4.87 (m, 9'-H; 1'-H; 3H), 4.56-4.47 (m. PMB, CH2; 2'-H; 3H), 4.32-4.23 (m, 3'-H; 4'-H; 2H), 3.88-3.77 (br s, 6'-H, 1H), 3.69 (s, $OCH_3$, 3H), 2.21-2.09 (m, 7'-H, 2H), 1.80-1.47 (m, 5'-H, 2H), 1.36 (s, 3H), 1.19 (s, 3H), 0.80 (s, $C(CH_3)_3$, 9H), 0.02 (s, 3H), -0.01 (s, 3H); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 159.5, 134.7, 129.7 (2C), 129.7, 117.5, 114.1 (2C), 112.3, 107.7, 86.0, 85.0, 84.4, 69.2, 55.5, 43.1, 42.2, 29.9, 26.7, 26.1 (3C), 25.3, 18.3, -4.1, -4.5.

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