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博士學位論文

Synthesis and Antiviral Evaluation of Novel Branched Nucleosides

朝鮮大學校 大學院

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李 花

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측쇄를 가진 신규 뉴크레오사이드의 합성 및 약효검색

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ABBREVIATION

DNA: Deoxyribonucleic acid
RNA: Ribonucleic acid
AIDS: Acquired immunodeficiency syndrome
FDA: Food and Drug Administration
AZT: 3′−Azido−2′,3′−dideoxythymidine
ddI: 2′,3′−Dideoxyinosine
ddC: 2′,3′−Dideoxycytidine
d4T: 2′,3′−Didehydro−2′,3′−dideoxythymidine
3TC: 2′,3′−Dideoxy−3′−thiacytidine
ABC: (1*S*,4*R*)−4−[2−Amino−6−(cyclopropylamino)−9*H*−purin−9−yl]−2−cyclopentene−1−methanol
FTC: β−L−3′−Thia−2′,3′−dideoxy−5−fluorocytidine
PMPA: (*R*)−9−(2−Phosphonylmethoxypropyl)adenine
RT: Reverse transcriptase
RCM: Ring−closing metathesis
d4AP: [5−(6−Aminopurin−9−yl)−2,5−dihydrofuran−2−yl−oxymethyl]−phosphonic acid
SATE: *S*−acyl−2−thioethyl
DIAD: Diisopropylazodicarboxylate
PPh_3: Triphenylphospine
DIBALH: Diisobutylaluminum hydride
TBAF: Tetrabutylammonium fluoride
THF: Tetrahydrofuran
NaOMe: Sodium methoxide
TEA: Triethylamine
DMF: *N*,*N*−Dimethylformamide
DMSO: Dimethyl sulfoxide
DMS: Dimethylsulfide
PCC: Pyridinium chlorochromate

4Å MS: 4Å Molecular sieves
PMBCl: *p*-Methoxybenzyl chloride
$(COCl)_2$: Oxalyl chloride
DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
OsO_4: Osmium tetroxide
NMO: 4-Methylmorpholine *N*-oxide
BnBr: Benzylbromide
m-CPBA: m-Chloroperoxybenzoic acid
CH_3CN: Acetonitrile
LiO*t*-Bu: Lithium *tert*-butoxide
TMSBr: Trimethylsilylbromide
TBDMSCl: *tert*-Butyldimethylsilyl chloride
TMSOTf: Trimethylsilyl trifluoromethansulfonate
DCC: *N*,*N*′-Dicyclohexylcarbodiimide
DMAP: 4-(Dimethylamino)pyridine
MnO_2: Manganese dioxide
NaOMe: Sodium methoxide
DCE: 1,2-dichloroethane
HPLC: High-pressure liquid chromatography
NOE: Nuclear overhauser effect
NMR: Nuclear magnetic resonance
TLC: Thin layer chromatography

국문초록

측쇄를 가진 신규 뉴크레오사이드의 합성 및 약효검색

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뉴크레오사이드는 구조적으로 당과 염기로 이루어져 있으므로 생물학적 및 화학적으로 개선된 새로운 유도체의 합성연구도 당부위 또는 염기부위의 분자수식으로 이루어진다. 고전적인 뉴크레오사이드의 당부분의 산소원자를 탄소원자로 치환된 카보사이클릭 뉴크레오사이와 당부분의 산소원자와 C2′의 메틸렌기의 위치가 바뀐 apio 다이데옥시뉴크레오사이드를 개발함으로서 효소에 의한 가수분해를 방지할 수 있었다. 그리고 phosphate 작용기를 가지고있는 뉴크레오사이드 phophonic acid 유도체는 counterpart에 비하여 안정적인데, 그 원인은 phosphorus-carbon 결합의 존재로 인해 쉽게 가수분해되어 분열되는 것을 방지할 수 있기 때문이다. 본 연구에서는 항 바이러스 활성이 기대되는 새로운 뉴크레오사이드 유도체를 설계하고, 합성하여 그 활성을 측정함으로써 항 바이러스활성에 요구되는 구조적 요건 등을 검토하고 궁극적으로는 보다 우수한 약효를 나타내는 항 바이러스제를 개발하고자 하였다.

측쇄를 가진 신규 카보사이클릭 뉴크레오사이드, 5′-norcarbocyclic 뉴크레오사이드, apio 다이데옥시뉴크레오사이드는 상업적으로 쉽게 구입할 수 있는 1,3-다이하이드록시아세톤, 아세톨, 에틸글리콜레이트 등 시약을 출발물질로 하여 합성하였다. 주요 중간물질인 알코올 유도체는 [3,3]-Sigmatropic rearrangement, Grignard addition, Eschenmoser's salt, Ring-closing metathesis 등 반응을 통하여 합성하였다. 합성한 중간체를 Mitsunobu reaction, Pd(0) catalyzed alkylation, Vorbrüggen reaction 등 반응을 이용하여 nucleosidic base와 축합하여 최종 화합물을 얻었다.

합성한 화합물들을 HIV-1, HSV-1, HSV-2, HCMV에 대하여 항바이러스 활성을 측정한 결과 화합물 **17**, **59**, **77**, **88**은 항 HIV-1활성을 나타내었지만 독성을 나타내었고 화합물 **25**, **31**, **45**, **144**은 항 HIV-1활성을 나타내면서 독성은 나타내지 않았다. 또한 합성한 화합물 **102**, **103**, **112**, **131~134**은 Huh-7 cell line에 있는 HCV RNA 복제를 억제하는 능력에 대해서 분석한 결과, 활성을 나타내지 않았다.

Ⅰ. INTRODUCTION

Viral infections are significant causes of human mortality and morbidity. Although there are a number of antiviral therapeutic agents available for the treatment of viral infections, the majority of viral infections are not currently curable by chemotherapy and many are still of serious health concerns. Therefore, the discovery and development of safe and effective antiviral therapies have been among the major scientific endeavours.

Natural nucleosides are constituted by the association of a purine (adenine and guanine) or a pyrimidine (cytosine, uracil and thymine) base with a pentose residue (β-D-ribofuranose or β-D-deoxyribofuranose). Esterification of their 5′-OH group with phosphoric acid leads to nucleotides. The synthetic nucleoside analogs, which resemble the natural nucleosides, but have a modified deoxyribose or ribose moiety, have played a major role in the treatment of human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus (HSV), human cytomegalovirus (HCMV), varicella zoster virus (VZV) and respiratory syncytial virus (RSV). The nucleoside analogues are phosphorylated to the triphosphate form within the infected cell, which compete with natural nucleotides for incorporation into viral DNA or RNA. Incorporation into the growing nucleic acid chain results in irreversible association with the viral polymerase and chain termination.

Viruses are microscopic organisms that can infect all living cells. Viruses consist of a nucleic acid core that contains either DNA or RNA, which is surrounded by a protein coat known as a capsid. The entire structure is called the nucleocapsid. They are parasitic and multiply at the expense of the host's metabolic system. Viruses have long been recognized as the cause of a wide variety of infections in animals and humans. Therefore, many diseases are produced by viruses. Respiratory, eye, skin, encephalitis and genital diseases of virus infection were included. Viruses are also linked with various other diseases, such as rheumatoid arthritis, multiple sclerosis, diabetes mellitus, cancer of the cervix, certain heart diseases, hepatitis and AIDS. The prime candidate involved in AIDS is the human immunodeficiency virus type-1 (HIV-1). AIDS has drawn

much public attention because of its fatal nature and lack of a cure. A growing incidence of this disease has been reported in the worldwide.[1, 2]

After an initially slow start, the development of new antiviral agents has recently entered an accelerated growth phase. And a lot of attention has been focused on nucleosides as reverse transcriptase inhibitors in search of more active and less toxic compounds. The HIV has now been established as the causative agent of the AIDS for over 20 years.[3, 4] During this time an unprece-dented success has been achieved in discovering anti-HIV drugs as reflected by the fact that there are now more drugs approved for the treatment of HIV than for all other viral infections taken together. The currently FDA approved anti-HIV drugs can be divided into seven nucleoside reverse transcriptase inhibitors (NRTIs: zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and emtricitabine) and one nucleotide reverse transcriptase inhibitor (NtRTI: tenofovir disoproxil). (Figure 1, Figure 2)[5]

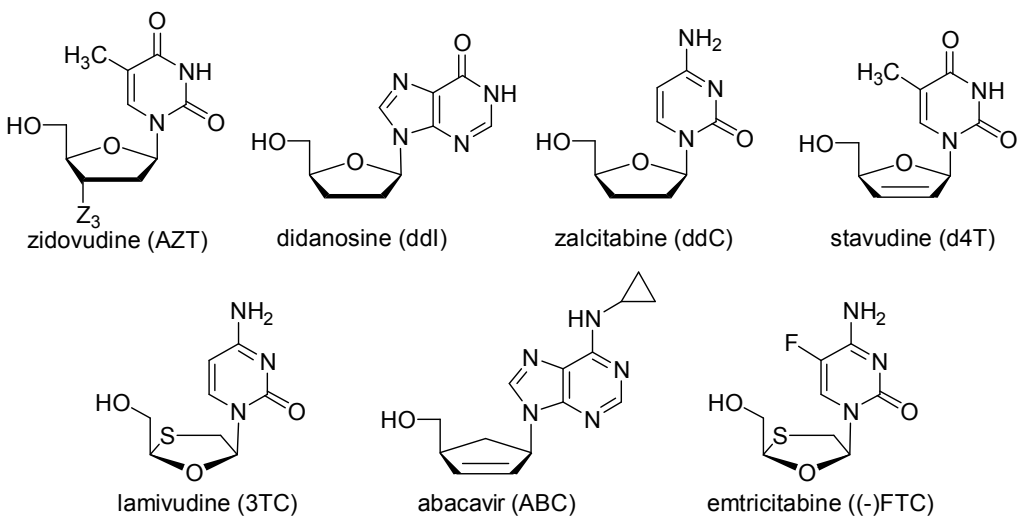


Figure 1. Structures of the currently FDA-approved anti-HIV NRTIs.

This arsenal of drugs, which is used in combinations, has moved the prognosis of HIV patients from that of high morbidity and mortality to, for many at least, a chronic, manageable but still complex disease.[6~8] However, the use of these drugs has been relatively limited by their toxicity,[9] drug resistance develop-

ment,[10] and more worryingly, the fact that some newly HIV-infected patients carry viruses that are already resistant to the currently approved AIDS treatments.[11] These issues along with drug-related side effects as well as, in some cases, poor tolerability of these drugs make it apparent that new anti-HIV drugs with acceptable toxicity and resistance profiles and, more importantly, new anti-HIV agents with novel mechanisms of action are clearly needed.[12]

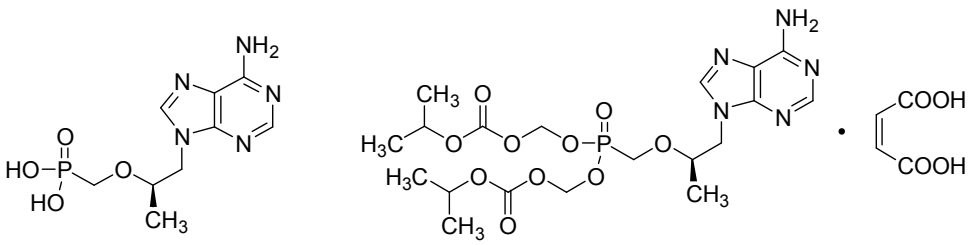


Figure 2. Structures formula of PMPA and bis(POC)PMPA.

NRTIs produce their anti-HIV effects by inhibiting the activity of the HIV reverse transcriptase. In order for these agents to produce such effects, they have to be phosphorylated consecutively by cellular kinases to their triphosphate derivatives.[13,14] As all NRTIs follow the same mechanism of inhibition of HIV reverse transcriptase, only the mechanism of action of ddC is included here as a representative for this class of drugs (Figure 3). The ddC is phosphorylated by deoxycytidine kinase, deoxycytidine monophosphate kinase, and nucleoside diphosphate kinase to form the monophosphate, diphosphate, and the active triphosphate derivative of ddC, respectively. This active moiety is then incorporated into the growing DNA by cellular DNA polymerases. The incorporation of ddC into the growing DNA results in terminating the elongation of the growing DNA double strand. This is mainly due to the fact that ddC and generally all NRTIs lack the 3′-hydroxyl group; therefore, they prevent the incorporation of the incoming nucleotide. One of the mechanisms by which resistance to chain-terminating NRTIs might arise is through removal of the chain-terminating residue, a kind of repair reaction involving pyrophosphorolysis, which can be regarded as the opposite of the reverse transcriptase reaction.[12]

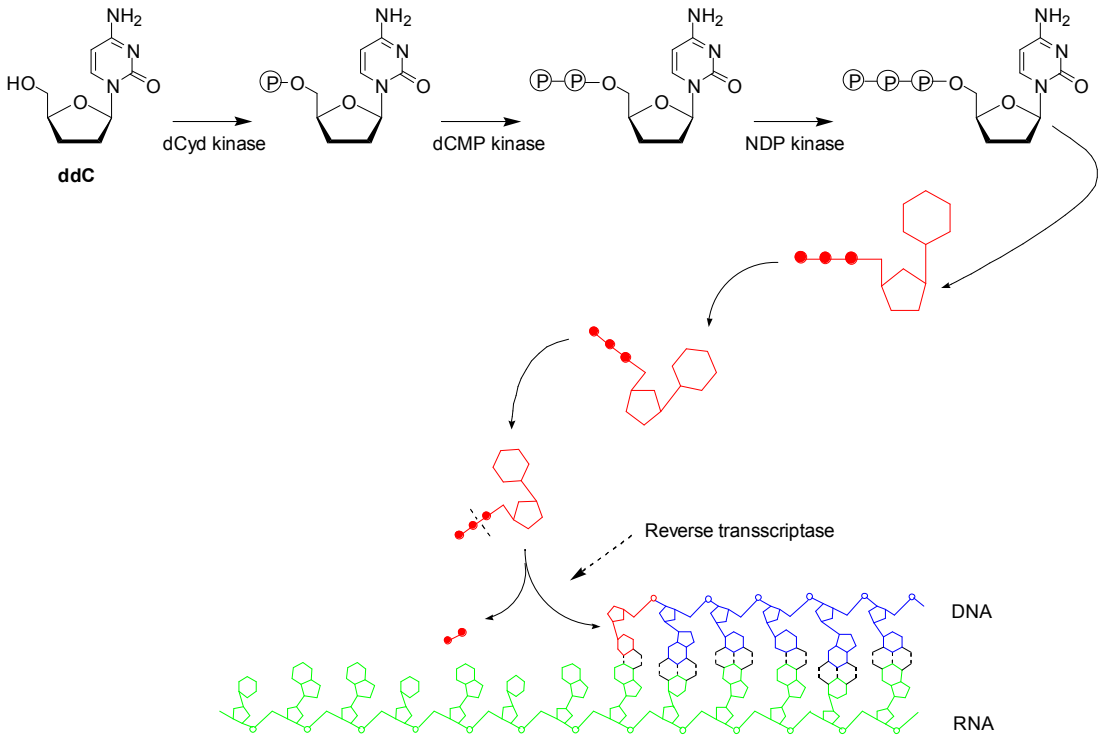


Figure 3. Mechanism of action of the NRTI ddC as a representative for the mechanism of action of NRTIs.

In addition to the presently approved seven NRTIs, there are currently four more undergoing either phase Ⅱ or phase Ⅲ clinical trials: apricitabine[15], racivir[16], amdoxovir[17] and elvucitabine[18]. (Figure 4)

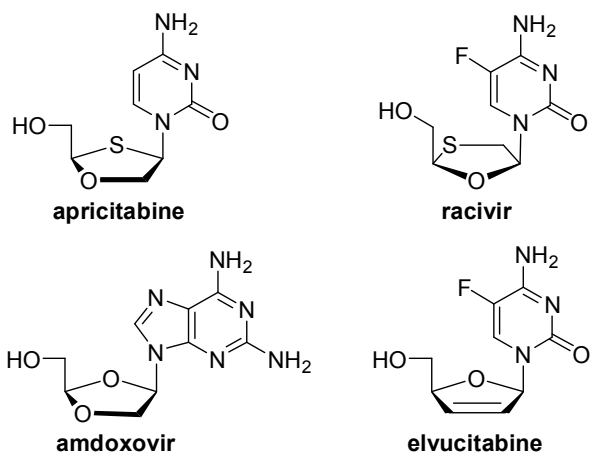


Figure 4. NRTIs currently undergoing either phase II or phase III of clinical trials.

In contrast to NRTIs, NtRTIs are already equipped with a phosphonate group that cannot be cleaved by hydrolyzes or esterases, making these compounds not easily cleaved off once incorporated at the 3′−terminal end compared with their regular nucleotide counterparts. As for the activation of phosphonates to produce their pharmacological activity, they only need two phosphorylation steps to be converted to their active diphosphate derivatives, which, akin to the triphosphate derivatives of NRTIs, serve as alternative substrates (with respect to the natural substrate 2′−deoxyadenosine triphosphate) in the reverse transcription reaction, and upon their incorporation they act as obligatory chain terminators (Figure 5).[19] Agents belonging to this class of drugs bear two negative charges that would limit their transport into cells; thus, monophosphate prodrugs are being extensively investigated to improve the cellular uptake of these agents and eventually the therapeutic effect.

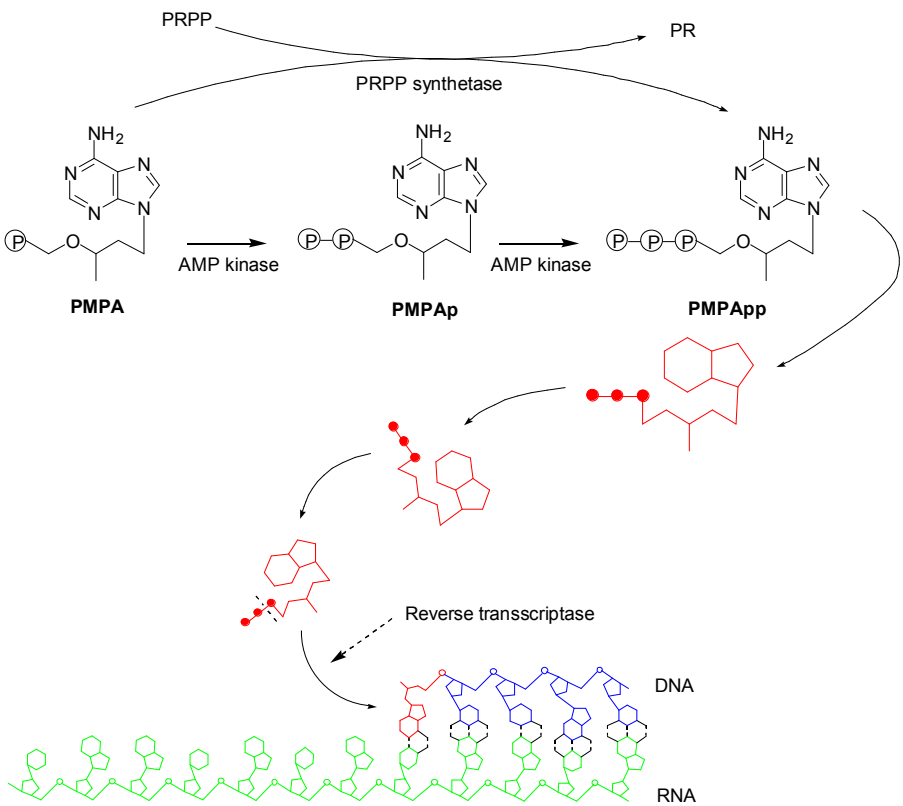


Figure 5. Activation and mechanism of action of TDF, a NtRTI.

For example, the phosphonate derivative of 2′−fluoro−2′,3′−didehydro−2′,3′−dideoxyadenosine (GS−9148, Figure 6) is being developed by Gilead Sciences as a potential treatment for HIV infections.[20] As well as possessing potent anti−HIV activity, retained activity against multiple NRTI−resistant HIV−1 strains and more importantly exhibited low renal and mitochondrial toxicities.[21] Gilead Sciences pursued the development of this compound in the phosphonamidate form (GS−9131, Figure 6) to improve oral bioavailability and cellular uptake.[22] The Gilead group has also studied the metabolism of this prodrug and identified cathepsin A as the major hydrolyzing enzyme. Hence, inside the cell GS−9131 is rapidly hydrolyzed to GS−9148, which is then intracellularly phosphorylated to the active diphosphate metabolite. Therefore, GS−9131 was a promising NtRTI drug candidate for the treatment of HIV−infected individuals.

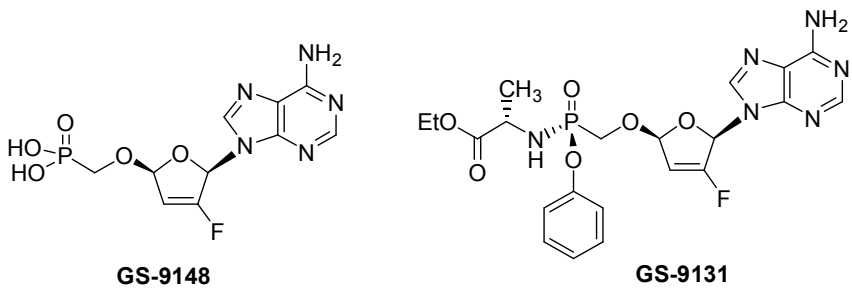


Figure 6. Structures of GS-9148 and GS-9131.

The only NtRTIs currently approved for use in patients suffering from HIV is tenofovir disoproxil fumarate (TDF) (Figure 2). TDF is a prodrug and orally bioavailable form of tenofovir and requires metabolic processing by esterase to its active metabolite. TDF is absorbed and then metabolized to tenofovir, which is, in turn, metabolized to the pharmacologically active metabolite, tenofovir diphosphate. Tenofovir is a phosphonate and its diphosphate is equivalent to the triphosphate of other NRTIs. Tenofovir diphosphate inhibits reverse transcriptase by competing with the natural substrate, deoxyadenosine 5′−triphosphate. Tenofovir diphosphate is also incorporated into HIV viral DNA, causing DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, γ and mitochondrial DNA polymerase. Tenofovir

disoproxil is active against HIV strains resistant to AZT, 3TC, ddI and ddC with EC_{50} values (0.04−0.001 μM).[23]

Carbocyclic nucleosides[24] are a group of compounds structurally analogous to natural and synthetic nucleosides in which the furanose oxygen has been replaced by a methylene group. This replacement changes the furanose ring into a cyclopentane. Due to the absence of a true glycosidic bond, carbocyclic nucleoside analogues are chemically more stable and not subject to the enzymatic degradation that occurs in conventional nucleosides.[25] The expected similarity in bond lengths and bond angles of the tetrahydrofuran and cyclopentane rings allows these analogues to behave as substrates or inhibitors of the enzymes in living cells. Therefore, the carbocyclic nucleosides possess a wide range of biological activities such as antiviral and antitumor effects. The recent discovery of olefinic carbocyclic nucleosides, such as carbovir[26], entecavir[27], 6′α−hydroxymethyl carbovir[28] and 6′α−methylcarbathymidine[29] as potential antiviral agents has attracted considerable attention in the search for novel nucleosides of this class. Recently, a number of 4′α−substituted nucleoside[30] analogues showed significant antitumor or antiviral activities. Among them, 4′α−*C*−ethenylthymidine[31], 4′α−*C*−ethynylthymidine[32], 4′−hydroxymethyl−thyiine[33] and 4′−fluoromethyl−2′−deoxycytidine[34] demosrated very potent biological activities. (Figure 7)

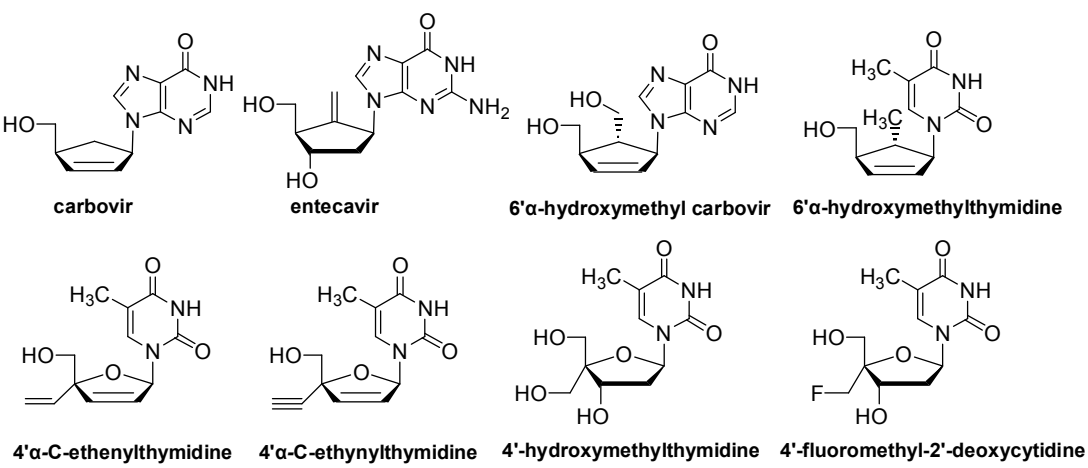


Figure 7. Structures of carbocyclic nucleosides and branched furanose nucleosides.

Based on these results and as part of our drug discovery program, we have designed novel 4′−branched carbocyclic nucleosides that mimic the properties of potent olefinic carbocyclic nucleosides, as well as biologically active 4′−branched furanose nucleosides. Herein, we disclose their de novo synthetic routes that employed a versatile three−step sequence ([3,3]−sigmatropic rearrangement, Eschenmoser's methylenation, RCM) from simple acyclic precursors.

5′−Nornucleoside phosphonic acid analogues such as d4AP[35] may be potential anti−HIV agents and have encouraged the search for novel nucleosides in this class of compounds.[36] The spatial location of the oxygen atom, namely the β−position from the phosphorus atom in the nucleoside analogue, plays a critical role for antiviral activity by increasing binding capacity of the phosphonate analogues to target enzymes.[37] The phosphonate has certain advantages over its phosphate counterpart as it is metabolically stable because its phosphorus−carbon bond is not susceptible to hydrolytic cleavage.[38] Moreover, a phosphonate nucleoside analogue can skip the requisite first phosphorylation, a rate−limiting crucial step for the activation of nucleosides that ultimately leads to tri−phosphates.[39] Steric and electronic parameters of 4′−substituents play significan roles in steering the whole conformation of nucleoside analogues. 4′−Branched nucleosides were first investigated by Maag *et al.*[40] in 1992, and 4′−azido−thymidine exerts potent activity against HIV−1. Extensive structure−activity studies found that other 4′−position lipophilic substituents, such as 4′−ethynyl−cpAP[41] and 4′−ethylthymidine[42], also exhibited high antiviral activity against HIV. Molecular modeling studies demonstrated the presence of a narrow, relatively hydrophobic 4′−pocket that can accommodate these substitutions, contributing to enhanced potency.[40] (Figure 8) Stimulated by these findings that 4′−branched nucleoside analogues and 5′−nornucleoside phosphate had excellent biological activities, we sought to synthesize a novel class of nucleosides comprising 4′−ethyl branched carbocyclic−5′−norcarbocyclic phosphonic acid analogues to search for more efficient therapeutic agents against HIV and to provide analogues used in probing the conformational preferences of enzymes associated with the metabolism of nucleosides and nucleotides.

Emerging drug−resistant viral strains and drug toxicity are major problems in

antiviral chemotherapy,[43] leading to research for structurally modified nucleosides. Although the pharmacophore of nucleoside antiviral activity is not completely defined, olefinic nucleosides such as stavudine,[28] d4AP[35] and 2′-Fd4AP (GS-9148)[36] as potential antiviral agents have encouraged the search for novel nucleosides in this class of compounds (Figure 8). Unlike nucleoside agents, a phosphonic acid nucleoside can skip the requisite initial phosphorylation, which is the crucial step for the activation of nucleosides.[44] However, the poor oral bioavailability of these nucleoside analogues are due to the phosphonate negative charges present in nucleoside phosphonic acid at physiological pH. One strategy has been to temporarily mask these charges with neutral groups to form more lipophilic derivatives capable of crossing the gastrointestinal wall and reverting back to the parent nucleoside phosphonic acid.[45] Because the ionic character of a phosphonic acid presents an obstacle for cellular permeability, an SATE prodrug was prepared. Esterification of a phosphonic acid with two SATE groups is a feasible strategy to deliver a phosphate or phosphonate drug into cells.[46] Usually, phosphonic acid nucleosides require an endocytosis-like process[47] or the ATP membrane receptor[48] to cross the cell membrane. We therefore applied the bis(SATE) approach to a novel nucleoside phosphonic acid. Herein, we synthesized a novel SATE prodrug of 2′-methyl-5′-norcarbocyclic nucleoside and 6′-fluoro-6′-methyl-5′-norcarcocyclic nucleoside to find new lead compounds with improved antiviral activity.

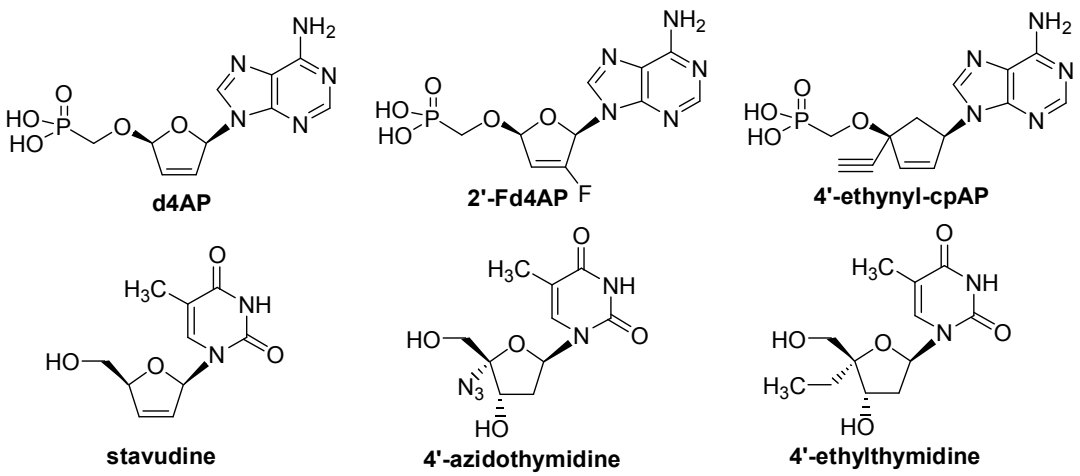


Figure 8. Some structures of nucleoside analogues as anti-HIV agents.

Hepatitis C virus (HCV) is a positive-strand RNA virus that was unambiguously identified in 1989.[49] The HCV RNA genome is approximately 10 kb in length and shares similarities with the genomes of flaviviruses and pestiviruses. HCV is the pathogen associated with the majority of sporadic and transfusion related non-A and non-B hepatitis infections. Approximately 270 million infected individuals are at risk of developing significant morbidity and mortality.[50] Although HCV is often asymptomatic, it is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals.[51] However, there is no effective chemotherapy for the treatment of HCV-infected people except immunotherapy using ribavirin in combination with interferon-α, which leads to a sustained virological response in only about half of the patients treated.[52]

The nonstructural protein NS5B has been characterized as an RNA-dependent RNA polymerase (RdRp) that is required for viral replication. This polymerase is considered to be an essential component in the HCV replication complex and therefore is an ideal target for drug discovery.[53] Since nucleoside analogues have been used as a drug of choice in curing viral infection including, a number of nucleoside analogues have been synthesized and evaluated for anti-HCV agent.[54] Generally, nucleosides are prodrugs, and their biological activity is exerted by their 5′-triphosphate derivatives. Intracellular phosphorylation is required to convert a nucleoside drug to its active 5′-triphosphate in order to be incorporated into a viral DNA. The sequential phosphorylation is normally executed by three viral or cellular kinases, including nucleoside kinase, nucleoside monophosphate kinase, and nucleoside diphosphate kinase.[55] Once incorporated into an elongating viral DNA chain, the nucleotide inhibitor functions as a terminator to abort viral DNA synthesis.

Nucleoside chain terminators comprise a major class of drugs that target a viral polymerase.[56] For example replacement of the 2′-hydrogen of natural ribonucleosides with a methyl group or hydroxymethyl group yields compounds with excellent chain-terminating properties. Among them, 2′-*C*-methyl-adenosine[57], 2′-*C*-methylcytidine[57], 2′-*C*-methyl-7-deazaadenosine[58] and 2′-*C*-hydroxymethyladenosine[59] (Figure 9) were found as the most potent inhi-

bitors of HCV RNA replication without significant toxicity. Natural as well as synthetic carbocyclic nucleosides[60] are well known for their interesting biological activities, including antitumor and antiviral activities against a wide variety of RNA and DNA viruses. Carbocyclic nucleosides are chemically more stable and are subject to the action of the enzymes that cleave the glycosyl linkage in conventional nucleosides.

On the basis of these findings that the methyl group of 2′−position could impose favorable steric as well as electronic effect on the interaction with HCV polymerase, we have determined to synthesize novel classes of nucleosides comprising 3′(β)−*C*−methylated carbodine analogues and 1′(α),2′(β)−*C*−dimethylated carbodine analogue, which transpose the methyl group from 2′− to 3′−position or additional methyl group in the 1′−position.

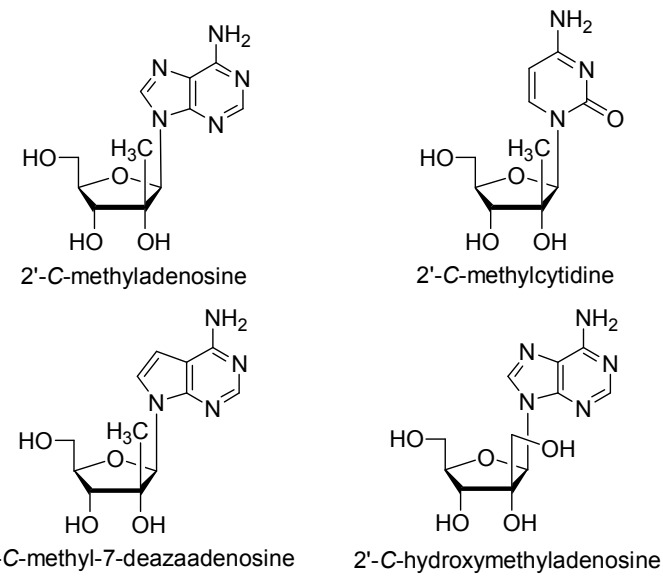


Figure 9. Structures of potent anti-HCV agents.

Apiosyl nucleosides[61,62] such as 3TC that belong to a novel class of nucleosides, which have the oxygen of the furanose and C2−methylene transposed, show anti−HIV activity and resistance to enzymatic deamination. Similarly, adenine analogues such as apio−ddA **(1)**[63] and aminoapio−ddA **(2)**[64] (Figure 10) show comparable anti−HIV and anti−HBV activity to the parent 2′,3′−dideoxy

adenosine. Apio-ddA is more resistant to adenosine deaminase (ADA) and shows enhanced stability of the glycosidic bond under acidic and enzymatic conditions compared to natural 2′,3′-dideoxynucleosides (ddNs) nucleosides.[65] Apio nucleoside phosphonates can be assembled from natural precursor molecules and form duplexes with DNA and RNA with thermal stability, similar to that of the natural nucleic acid association.[66] Diphosphoryl phosphonate of apio nucleoside (3), a substrate of several polymerases, can be enzymatically incurporated into DNA.[67, 68] These nucleosides can substitute for ribonucleosides in the catalytic site of a hammerhead ribozyme, although the catalytic efficiency of the ribozyme is significantly reduced.[69]

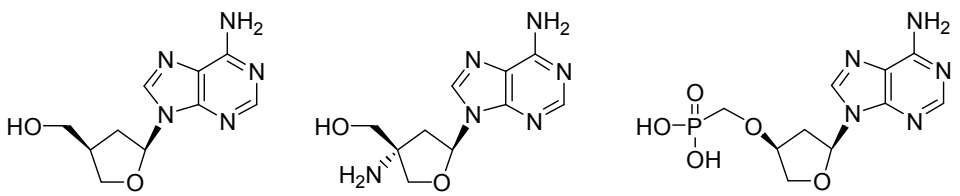


Figure 10. Examples of apiosyl nucleoside ananolgues as potent antiviral agents.

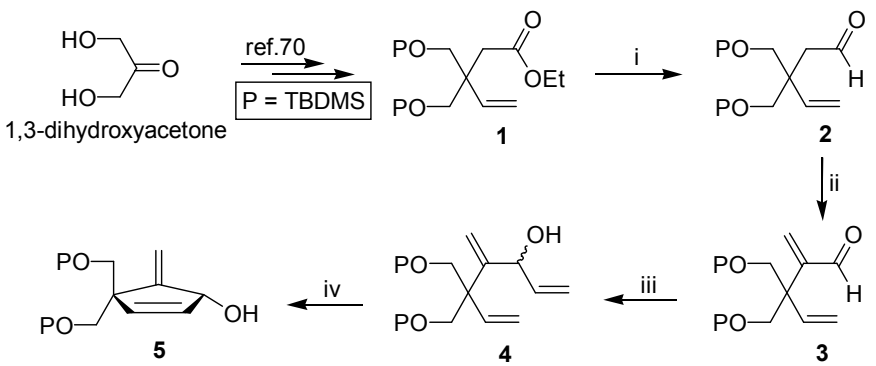
Because branched nucleoside derivatives are a drug of choice in curing viral infections, including HCV, a number of nucleoside derivatives have been synthesized and evaluated for anti-HCV activity. For example, 2′-*C*-methylcytidine, 2′-*C*-methyladenosine and 2′-*C*-hydroxymethyladenosine are potent and selective anti-HCV agents. These nucleosides are converted into their triphosphates and incorporated into proviral RNA, resulting in viral RNA chain termination, because subsequent incorporation of the substrate, nucleoside triphosphate, is sterically hindered by the 2′-methyl group. On the basis of potent anti-HCV activity of furanosyl nucleosides, it is known that the hydroxyl functional group of 3′-position and 2′(β)-methyl group were essential for nucleosides to show anti-HCV activity. Therefore, we applied similar structural environments to the design of novel doubly branched apiosyl nucleosides. We introduced not only hydroxylmethy funtional group at 4′-position but also methyl group at 5′-position for the purpose of causing the favorable interaction of 4′-

C-hydroxymethyl with NS5b RNA dependent RNA polymerase and the steric repulsion like the 5′-methyl group.

Ⅱ. RESULTS AND DISCUSSION

The synthetic route for the key intermediate **5** in the synthesis of the target nucleosides is illustrated in Scheme 1. The quaternary carbon of γ,δ-unsaturated ester **1** was constructed successfully from the 1,3-dihydroxy-acetone using a previously reported procedure.[70] The addition of one equivalent of DIBALH to a solution of the ester **1** in anhydrous toluene at −78 °C produced the aldehyde **2**. The treatment of carbonyl **2** with Eschenmoser's salt (methylene-*N,N*-dimethylammonium iodide)[71] gave exomethylene acyclic divinyl derivative **3**. We next turned our attention to the construction of a triene system for the metathesis cyclization reaction. Thus, the addition of vinylMgBr to the divinyl aldehyde **3** furnished the desired acyclic triene **4**, which was subjected to standard RCM conditions using a Grubbs' Ⅱ catalyst [(Im)$Cl_2PCy_3RuCHPh$][72] to provide the required exomethylene cyclopentenol **5**.

SCHEME 1 Synthesis of exomethylene cyclopentene intermediate **5**

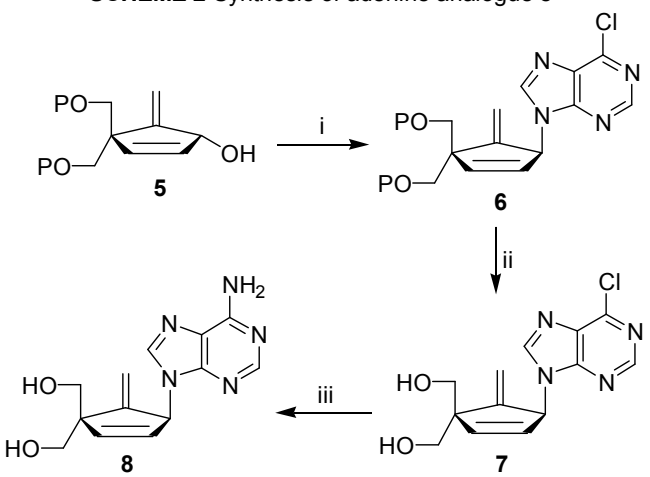


Reagents: i) DIBALH, toluene, -78°C; ii) methylene-*N,N*-dimethylamineammonium iodide, TEA, CH_2Cl_2; iii) vinylMgBr, THF; iv) Grubbs' catalyst II.

We initially hypothesized that palladium (0)-catalyzed reactions[73] could introduce functional groups into allylic positions of synthetic organic compounds, including the exomethylene cyclopentene derivative **5**, through an ethyl formate analogue. To our surprise, we could not find any nucleoside analogues and therefore needed an alternative coupling method. The Mitsunobu reactions can couple a cyclopentenol with nucleosidic bases, allowing us to synthesize our

target nucleosides with the desired regio- and stereochemistry.[74]

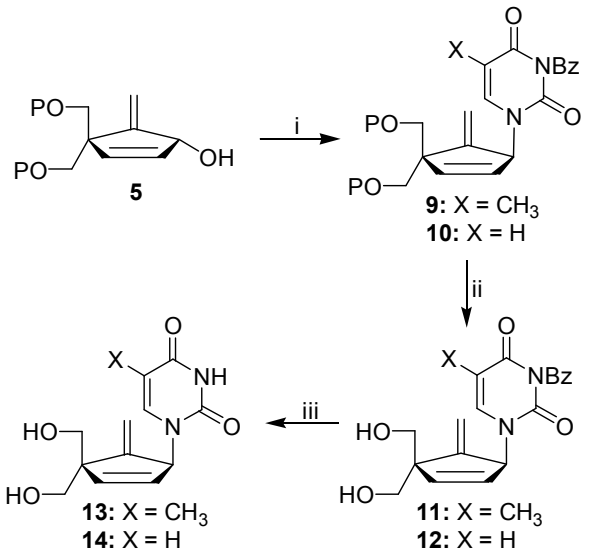
SCHEME 2 Synthesis of adenine analogue **8**



Reagents: i) 6-chloropurin, DIAD, PPh_3, dioxane/DMF;
ii) TBAF, THF/CH_3CN; iii) NH_3/MeOH, steel bomb.

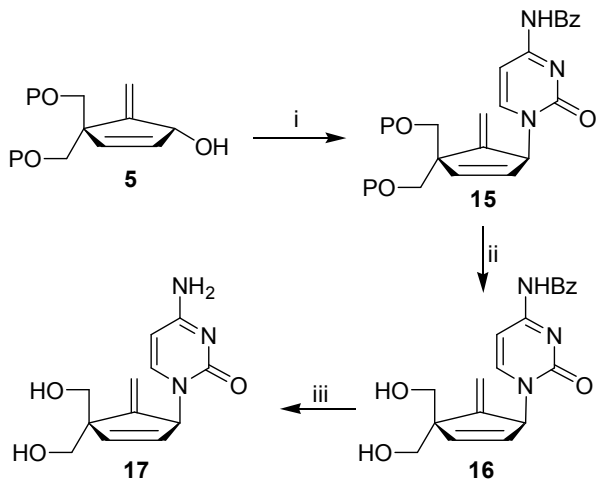
The success of a Mitsunobu reaction in the synthesis of nucleoside analogues depends on the reaction conditions, such as the solvent system, temperature, and addition procedure, to control the regiochemistry of the desired nucleosides. Instead of THF only, a 2:1 cosolvent mixture of dioxane/DMF was used for the coupling of the cyclopentenol **5** with the nucleobases; the heterocyclic bases had better solubility in the dioxane/DMF mixture, resulting in better yields.[75] The slow addition of DIAD to a mixture of cyclopentenol **5**, PPh_3, and the corresponding purine base in an anhydrous solvent produced a yellow solution, which was then stirred for 2 hours at −20 °C to yield the 6-chloropurine analogue **6** without the formation of *N*-7 isomers. The *N*-9 isomer of the coupling was confirmed by UV spectra data [λ_{max} (MeOH) 264 nm].[76] The desilylated nucleoside **7** was obtained from the corresponding nucleoside **6** by treatment with TBAF in a THF/CH_3CN (1/1) co-solvent system. The target adenosine analogue **8** was synthesized from the corresponding nucleoside analogue **7** by treatment with a saturated solution of methanolic ammonia in a steel bomb at 90-95 °C overnight (Scheme 2).

SCHEME 3 Synthesis of thymine & uracil analogues **13** and **14**



Reagents: i) N^3-benzoylated pyrimidine bases, DIAD, PPh_3, dioxane/DMF; ii) TBAF, THF/CH_3CN; iii) NaOMe, MeOH.

SCHEME 4 Synthesis of cytosine nucleoside analogue **17**



Reagents: i) N^4-benzoylcytosine, DIAD, PPh_3, dioxane/DMF; ii) TBAF, THF/CH_3CN; iii) NaOMe, MeOH.

To synthesize the pyrimidine nucleoside analogues, that is, the N^3 or N^4-benzoyl bases, we used a similar Mitsunobu procedure on the thymine, uracil and

cytosine bases to give the protected nucleoside analogues **9**, **10** and **15**. The regioisomers were easily confirmed by comparison of the UV literature data.[76] The desilylations of the nucleoside intermediates were performed similarly to that for adenine nucleoside **7** to produce pyrimidine the nucleosides **11**, **12** and **16**, which were debenzoylated by treatment with NaOMe in methanol to produce nucleosides **13**, **14** and **17** (Scheme 3, Scheme 4).

The antiviral activity against HIV-1, HSV-1, HSV-2 and HCMV was measured. The synthesized cytosine analogue **17** showed moderate anti-HIV activity (EC_{50} = 10.67 μM, MT-4 cell lines) without any cytotoxicity up to 100 μM (Table 1). The rigid arrangement in the exomethylene carbocyclic cytosine nucleoside analogue **17** may be conformationally similar to carbovir and entecavir. Hence, this arrangement will enhance the level of phosphorylation by kinase to produce the active monophosphate form.[77]

Table 1: Antiviral activity of the synthesized compounds

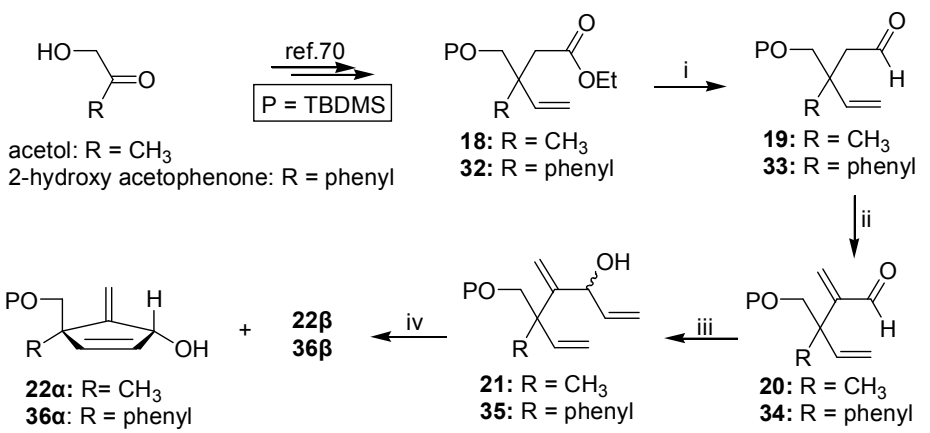
	HIV-1 EC_{50}(μM)	HSV-1 EC_{50}(μM)	HSV-2 EC_{50}(μM)	HCMV EC_{50}(μM)	Cytotoxicity CC_{50}(μM)
8	55.5	70.4	99	99	99
13	66	99	99	95	99
14	58	84	49	99	99
17	10.67	50.5	95	41.5	95
AZT	0.009	ND	ND	ND	1.17
GCV	ND	ND	ND	0.6	>10
ACV	ND	0.2	ND	ND	>100

AZT: Azidothymidine; GCV: Ganciclovir; ACV: Acyclovir. ND: Not Determined. EC_{50}(μM): Concentration required to inhibit 50% of virus-induced cytopathicity. CC_{50}(μM): Concentration required to reduce cell viability by 50%.

In summary, we developed a convenient method for synthesizing exomethylene carbocyclic nucleoside analogues via the triene intermediate **4**. Based on this strategy, the syntheses of other nucleosides such as branched carbocyclic nucleosides with different nucleobases are currently underway.

The synthetic route for the key intermediate **22α** and **36α** in the synthesis of the target nucleosides is illustrated in Scheme 5. The quaternary carbon of γ, δ−unsaturated ester **18** and **32** was constructed successfully from the acetol and 2−hydroxy acetophenone using a previously reported procedure. The addition of one equivalent of DIBALH to a solution of the ester **18** and **32** in anhydrous toluene at −78 ℃ produced the aldehyde **19** and **33**. The treatment of carbonyl **19** and **33** with Eschenmoser's salt (methylene−*N,N*−dimethylammonium iodide) gave exomethylene acyclic divinyl derivative **20** and **34**. We next turned our attention to the construction of a triene system for the metathesis cyclization reaction. Thus, the addition of vinylMgBr to the divinyl aldehyde **20** and **34** furnished the desired acyclic triene **21** and **35**, which was subjected to standard RCM conditions using a Grubbs' Ⅱ catalyst [(Im)$Cl_2PCy_3RuCHPh$] to provide the required exomethylene cyclopentenol **22** and **36**.

SCHEME 5 Synthesis of exomethylene cyclopentene intermediates **22** and **36**

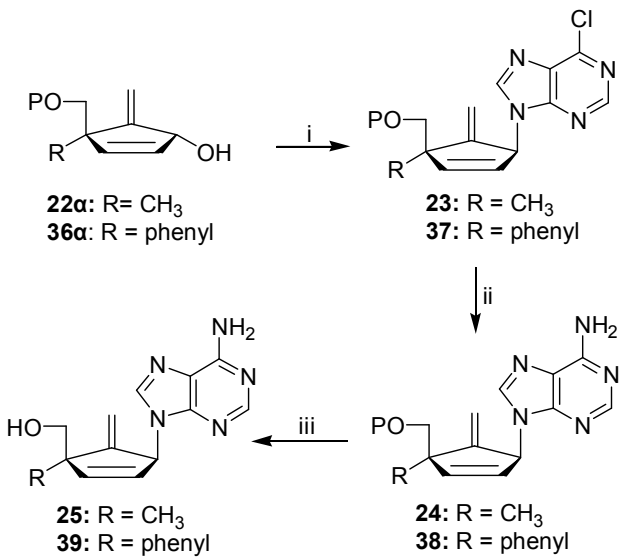


Reagents: i) DIBALH, toluene, -78°C; ii) methylene-*N,N*-dimethylamineammonium iodide, TEA, CH_2Cl_2; iii) vinylMgBr, THF; iv) Grubbs' catalyst (II).

We initially hypothesized that palladium (0)−catalyzed reactions could introduce functional groups into allylic positions of synthetic organic compounds, including the exomethylene cyclopentene derivative **22** and **36**, through an ethyl formate analogue. To our surprise, we could not find any nucleoside analogues and therefore needed an alternative coupling method. The Mitsunobu reactions

can couple a cyclopentenol with nucleosidic bases, allowing us to synthesize our target nucleosides with the desired regio- and stereochemistry.

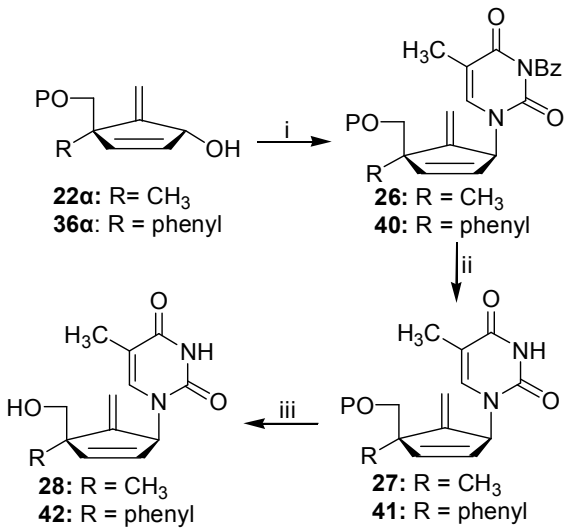
SCHEME 6 Synthesis of adenine analogues **25** and **39**



Reagents: i) 6-chloropurin, DIAD, PPh_3, THF; ii) NH_3/MeOH, steel bomb; iii) TBAF, THF.

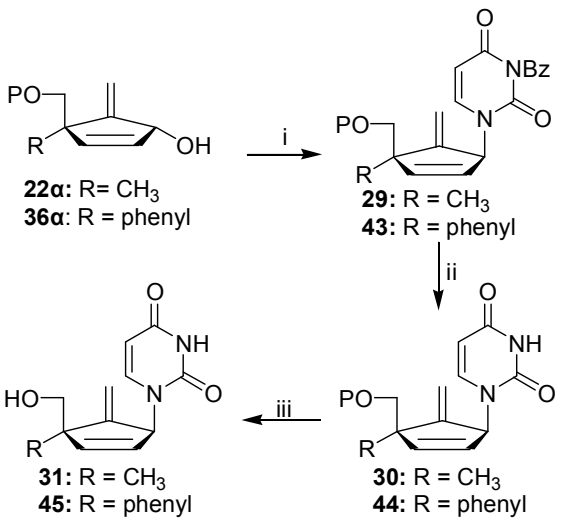
The success of a Mitsunobu reaction in the synthesis of nucleoside analogues depends on the reaction conditions, such as the solvent system, temperature, and addition procedure, to control the regiochemistry of the desired nucleosides. The cyclopentenol **22** and **36** with the nucleobases; the heterocyclic bases had better solubility in the THF. The slow addition of DIAD to a mixture of cyclopeantenol **22** and **36**, PPh_3, and the corresponding purine base in an anhydrous solvent produced a yellow solution, which was then stirred for 2 hours at −20 ℃ to yield the 6-chloropurine analogue **23** and **37** without the formation of *N*-7 isomers. The *N*-9 isomer of the coupling was confirmed by UV spectra data [λ_{max} (MeOH) 264 nm]. The adenosine analogue **24** and **38** was synthesized from the corresponding nucleoside analogue **23** and **37** by treatment with a saturated solution of methanolic ammonia in a steel bomb at 90-95 ℃ overnight. The target nucleosides **25** and **39** were obtained from the corresponding nucleosides **24** and **38** by treatment with TBAF in THF (Scheme 6).

SCHEME 7 Synthesis of thymine analogues **28** and **42**



Reagents: i) N^3-benzoylthymine, DIAD, PPh_3, THF; ii) NaOMe, MeOH; iii) TBAF, THF.

SCHEME 8 Synthesis of urasil analogues **31** and **45**



Reagents: i) N^3-benzoylurasil, DIAD, PPh_3, THF; ii) NaOMe, MeOH; iii) TBAF, THF.

To synthesize the pyrimidine nucleoside analogues, that is, the N^3-benzoyl bases, we used a similar Mitsunobu procedure on the thymine and uracil bases to give the protected nucleoside analogues **26**, **29**, **40** and **43**. The regioisomers

were easily confirmed by comparison of the UV literature data. The debenzo-ylated by treatment with NaOMe in methanol to produce nucleosides **27**, **30**, **41** and **44**, which were desilylations of the nucleoside intermediates were performed similarly to that for adenine nucleosides **24** and **38** to produce pyrimidine the nucleosides **28**, **31**, **42** and **45** (Scheme 7, Scheme 8). Synthesized compounds **25**, **31**, **45** showed significant anti-HIV activities without cytotoxicity up to 100 μM. (Table 2)

Table 2: Antiviral activity of the synthesized compounds

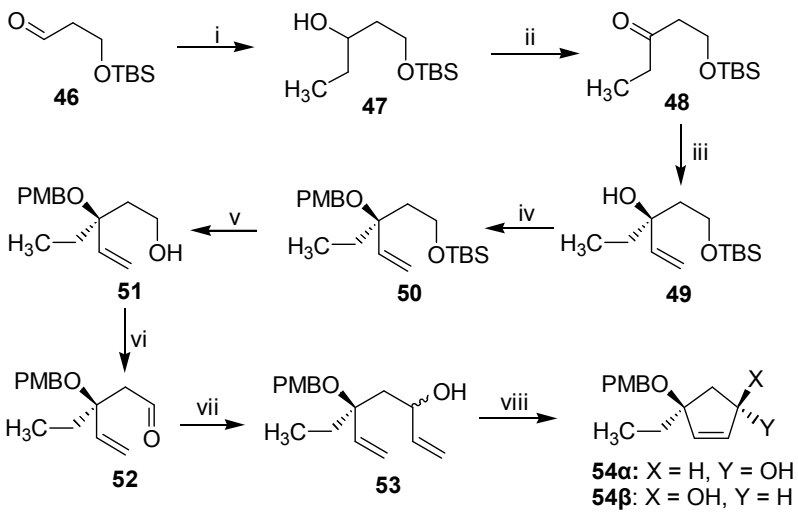
	HIV-1 EC_{50}(μM)	HCMV EC_{50}(μM)	Cytotoxicity CC_{50}(μM)
25	9.9	80.2	>100
28	>100	>100	>100
31	12.1	74.5	>100
39	>100	>100	>100
42	>100	>100	>100
45	8.4	77.4	>100
AZT	0.009	ND	1.17
GCV	ND	0.6	>10
ACV	ND	ND	>100

AZT: Azidothymidine; GCV: Ganciclovir; ACV: Acyclovir. ND: Not Determined. EC_{50}(μM): Concentration required to inhibit 50% of virus-induced cytopathicity. CC_{50}(μM): Concentration required to reduce cell viability by 50%.

As depicted in Scheme 9, the target compounds were prepared from protected propionaldehyde **46**.[78] The aldehyde functional group of **46** was subjected to a carbonyl addition reaction by ethylMgBr to furnish the secondary alcohol **47**, which was subjected to oxidation using PCC to provide ketone derivative **48**. The corresponding ketone functional group of **48** was again subjected to an addition reaction by vinylMgBr to give the tertiary hydroxyl analogue (±)-**49**, which was successfully protected using PMBCl to give the fully protected compound (±)-**50**. Removal of the silyl protecting group of (±)-**50** using TBAF provided the

primary alcohol (±)−**51**, which was oxidized to the aldehyde (±)−**52** using Swern oxidation conditions [DMSO, $(COCl)_2$, TEA]. The aldehyde (±)−**52** was subject−ted to nucleophilic Grignard conditions with vinylMgBr to give divinyl (±)−**53**, which was subjected to RCM conditions using a Grubbs' II catalyst[79] to provide ethyl ated cyclopentenol **54α** (40%) and **54β** (39%), which were readily separated by silica gel column chromatography.

SCHEME 9 Synthesis of key cyclopentenol intermediate **54**



Reagents: i) ethylMgBr, THF; ii) PCC, CH_2Cl_2; iii) VinylMgBr, THF; iv) PMBCl, NaH, DMF; v) TBAF, THF; vi) $(COCl)_2$, DMSO, TEA; vii) vinylMgBr, THF; viii) Grubbs (II), CH_2Cl_2.

The NOE experiments with cyclpopentenols **54α** and **54β** confirmed these assignments. As expected, NOE enhancements were found between the *cis*−oriented hydrogens. Upon irradiation of C_1−H, weak NOE patterns were observed at the proximal hydrogens of compound **54α** [C_4−CH_2 (0.24%)] *versus* those of compound **54β** [C_4−CH_2 (0.82%)]. (Figure 11)

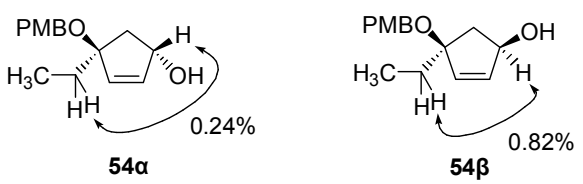
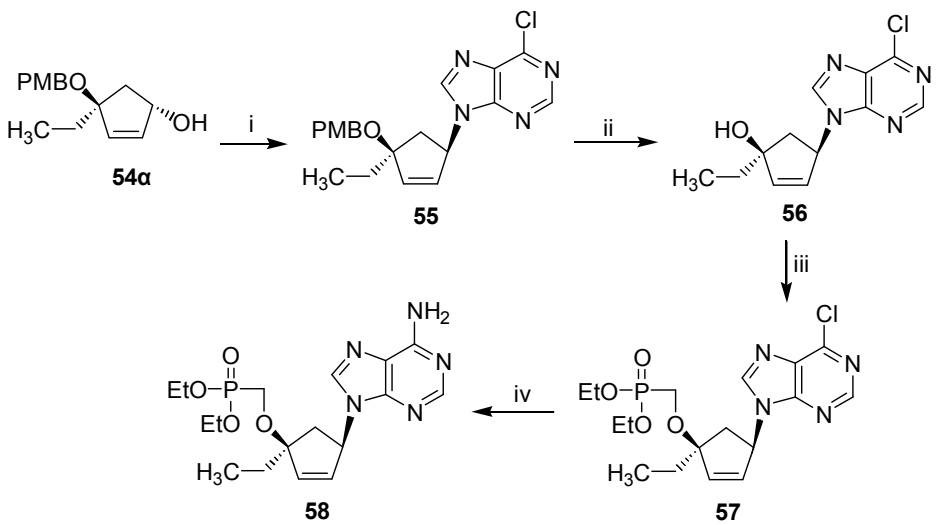


Figure 11. NOE difference between the proximal hydrogens of **54α** and **54β.**

To synthesize the desired 5′−norcarbocyclic adenine nucleoside analogue, the protected cyclopentenol **54*α*** was treated with 6−chloropurine under Mitsunobu conditions (DIAD and PPh_3). Slow addition of DIAD to a mixture of cyclopentenol **54*α***, PPh_3, and the 6−chloropurine in anhydrous tetrahydrofuran gave a yellow solution that was stirred for 3 hours at −20 °C to give a protected 6−chloropurine analogue **55** (Scheme 10).[80] The PMB protection group was removed with DDQ[81] to the 5′−nornucleoside analogue **56**, which was treated with diethylphosphonomethyl triflate[82] using LiO*t*−Bu to yield the nucleoside phosphonate **57**. The chlorine group of **57** was then converted to amine with methanolic ammonia at 70 °C to give a corresponding adenine phosphonate derivative **58**.

SCHEME 10 Synthesis of 5'-norcarbocyclic adenosine phosphonate **58**

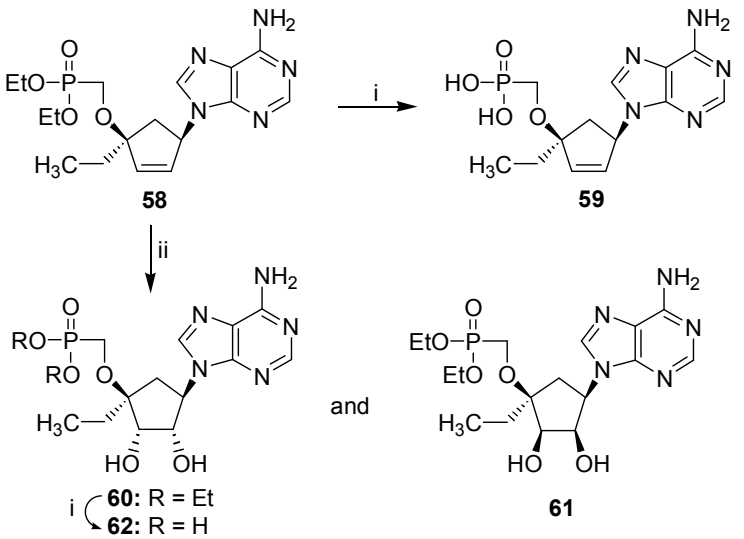


Reagents: i) PPh_3, DIAD, 6-chloropurine, THF; ii) DDQ, CH_2Cl_2/H_2O, rt; iii) $(EtO)_2POCH_2OTf$, LiO-*t*-Bu, THF; iv) NH_3/MeOH, 70 °C.

The nucleoside phosphonate mimics the overall shape and geometry of a nucleoside monophosphate. Hydrolysis of **58** by treatment with TMSBr in CH_3CN in the presence of 2,6−lutidine gave an adenine phosphonic acid derivative **59**.[83] Bishydroxylation[84] of the double bond in **58** was accomplished with a catalytic amount of OsO_4 and NMO as the oxidant to give the dihydroxylated isomer **60**

(34%) and **61** (29%), with a relatively low stereoselectivity (Scheme 11).[85] Their stereochemistries were also readily determined by NOE experiments. These stereochemical outcomes suggest that the steric environments of α and β-faces on the cyclopentene ring might be equivalent. Hydrolysis of the diethyl phosphonate functional groups of **60** by a similar procedure described for **59** gave an adenine phosphonic acid derivative **62**.

SCHEME 11 Synthesis of desired 5'-norcarbocyclic adenosine phosphonic acid analogues



Reagents: i) TMSBr, 2,6-lutidine, CH_3CN; ii) OsO_4, NMO, acetone/*t*-BuOH/H_2O.

The synthesized nucleoside phosphonate and phosphonic acid analogues **58**, **59**, **60** and **62** were evaluated for antiviral activity against HIV-1.[86] As shown in Table 3, nucleoside phosphonic acid **59** exhibited greater toxicity-dependent anti-HIV activity than its parent nucleoside phosphonate **58**. However, nucleotide analogs **60** and **62** did not show anti-HIV activity nor cytotoxicity up to 100 μM. In summary, on the basis of potent anti-HIV activity of 4′-alkyl branched nucleoside and 5′-norcarbocyclic nucleoside analogues, we have designed and successfully synthesized novel 4′-ethyl-5′-norcarbocyclic nucleotide analogues starting from propionaldehyde. In this series, adenosine phosphonic acid derivative **59** showed moderate toxicity-dependent anti-HIV-1 activity.

Table 3: Anti-HIV activity of synthesized compounds

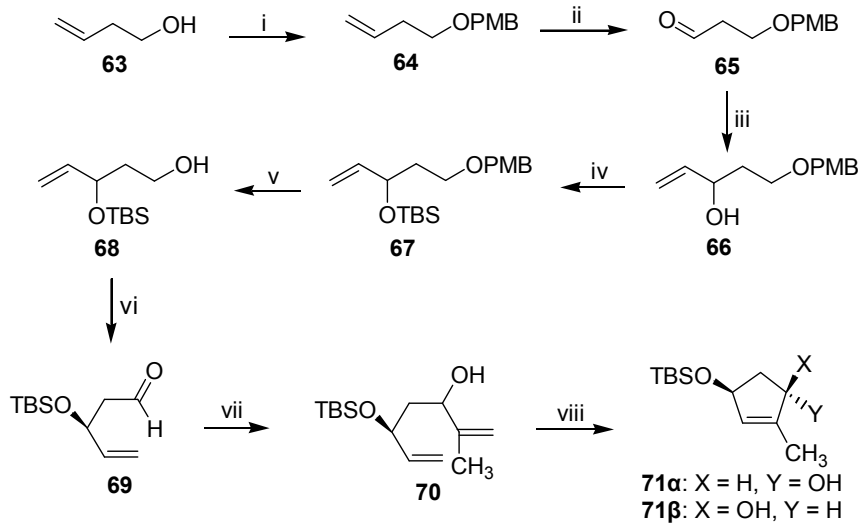
Compd	Anti-HIV-1 EC_{50}(μM)	Cytotoxicity CC_{50}(μM)
58	55	95
59	21	58
60	>100	>100
62	>100	>100
PMPA	3.6	>100

PMPA: 9-[2-(phosphonylmethoxypropyl)adenine. EC_{50}: Concentration (μM) required to inhibit the replication of HIV-1 by 50%. CC_{50}: Concentration (μM) required to reduce the viability of unaffected cells by 50%.

For the synthesis of phosphonate adenine nucleoside, the commercially available but-3-en-1-ol **63** was selected as a starting material. As shown in Scheme 12, the synthetic route is very simple and straightforward. The primary hydroxyl group of **63** was protected as temporary PMB ether by reaction[87] with PMBCl and NaH in DMF to afford the protected olefin **64** in a yield of 97%. The olefin of **64** was treated with ozone in methylene chloride at -78 °C, followed by the decomposition of the ozonide by DMS to give the aldehyde **65**. Compound **65** was subjected to carbonyl addition with vinylMgBr to provide the secondary alcohol derivative **66** was protected with TBDMSCl to give compound **67**. Oxidative deprotection of the PMB ether moiety of **67** was effected with DDQ[88] in methylene chloride with a small amount of water to give the alcohol **68**, which was then oxidized to the aldehyde **69** using PCC, which again underwent an addition reaction with isopropenylMgBr to provide a divinyl **70**. The divinyl **70** was subjected to standard RCM conditions using a Grubbs' II catalyst to provide cyclopentenol **71α** (43%) and **71β** (42%), which were readily separated by silica gel column chromatography.

As shown in Figure 12, the stereochemistry of **71α** and **71β** were unambiguously on the basis of the NOE correlations. On irradiation of C_4-H, relatively weak NOE was observed at C_1-H of **71α** (0.6%), but not at C_1-H of **71β** (1.1%).

SCHEME 12 Synthesis of cyclopentene intermediate **71**



Reagents: i) PMBCl, NaH, DMF, 0°C; ii) O_3, DMS, -78°C; iii) VinylMgBr, THF, -78°C; iv) TBDMSCl, imidazole, CH_2Cl_2, 0°C; v) DDQ, CH_2Cl_2/H_2O, rt; vi) PCC, 4MS, CH_2Cl_2; vii) isopropenylMgBr, THF, -78°C; viii) Grubbs II, CH_2Cl_2, 60°C, reflux, overnight.

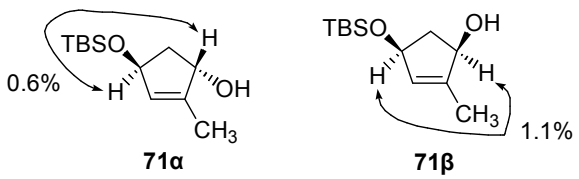
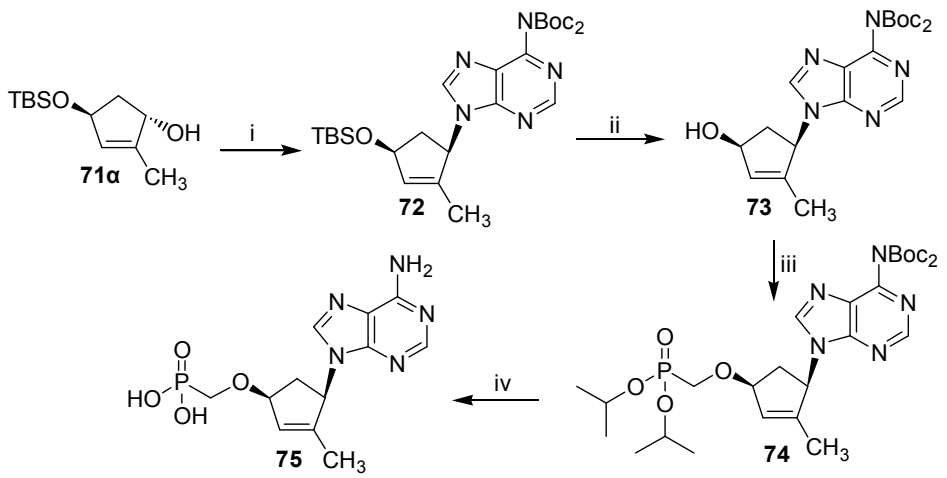


Figure 12. NOE difference of isomers **71α** and **71β.**

For coupling with a nucleobase, the hydroxyl group can activate mesylate for nucleophilic substitution. However, the yield of mesylation was very low and its product was unstable during work-up for storage. Alternatively, the alkylation of adenine was attempted under Mitsunobu conditions using DIAD and PPh_3 under a THF solvent. Unfortunately, the direct coupling of adenine with alcohol **71*α*** failed. A nucleobase precursor such as N^6-bis-Boc-adenine[89] was coupled with alcohol **71*α*** under Mitsunobu conditions[90] to give compound **72** with a chirality inversion. The silicon protection group of compound **72** was readily removed by treating it with TBAF in THF to give compound **73**. For the synthesis of phosphonate nucleoside, the hydroxyl group of **73** was phosphonated by treating them with diisopropyl bromomethylphosphonate[91] in anhydrous DMF to give the

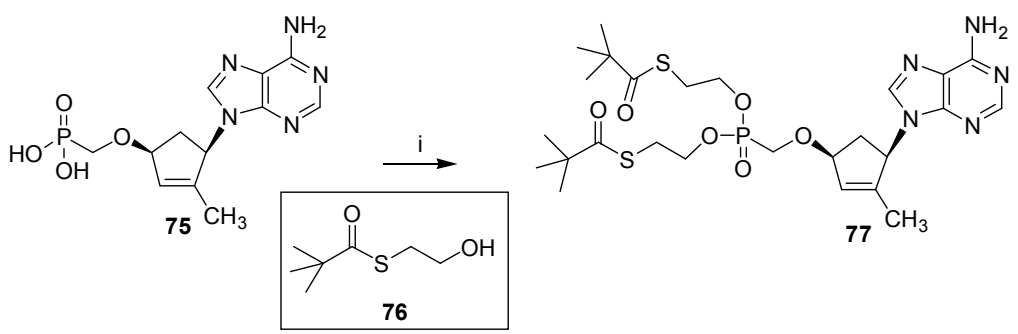
phosphonate nucleoside intermediate **74** (Scheme 13). Both protecting groups (N^6-bis-Boc & di-*O*-isopropyl) of the phosphonate nucleoside were simultaneously removed using TMSBr[92] to give nucleoside phosphonic acids **75**. To synthesize the thioester-protected analogues, phosphonic acid nucleoside was reacted with thioester[93] **76** in the presence of 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT)[94] to provide the final *t*-bu-SATE prodrug **77** (Scheme 14). The newly synthesized phosphonic nucleoside analogues **75** and **77** were assayed against HIV-1 virus. *In vitro* anti-HIV-1 drug testing involved the killing of T4-lymphocytes by HIV-1.

SCHEME 13 Synthesis of carbocycic adenine nucleoside **75**



Reagents: i) PPh_3, DIAD, N^6-bis-Boc-adenine, THF, -20 °C; ii) TBAF, THF, rt; iii) Diisopropyl bromomethylphosphonate, LiO^t-Bu, LiI, DMF, 60 °C; iv) TMSBr, CH_3CN.

SCHEME 14 Synthesis of final SATE prodrug of adenine analogue **77**



Reagents: i) **76**, 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole, pyridine.

T4-lymphocytes (MT-4 cell line) were exposed to HIV at a virusto-cell ratio of approximately 0.05 and treated with the compounds, dissolved in DMF, at doses ranging from 10^{-8} to 10^{-4}. A complete cycle of virus reproduction is necessary to obtain the required cell killing (incubation at 37 °C in a 5% carbon dioxide atmosphere for 6 days). Uninfected cells with the compounds served as a toxicity control, whereas the infected and uninfected cells without the compound served as basic control. After incubation, the tetrazolium salt XTT was added to all wells, and cultures were incubated to allow formazan color development by viable cells. Formazan production was measured spectrophotopmetically and possible protective activity was confirmed by microscopical detection of viable cells. The effect of each compound on cell growth of HIV infected and uninfected cells were compared to that of untreated uninfected cells.

The tested prodrug **77** enhanced the *in vitro* anti-HIV activity of the parent phosphonic acid **75** (Table 4). The increased anti-HIV activity for the neutral phosphodiester derivative could result from increased cellular uptake followed by intracellular release of the parent phosphonic acid.

Table 4: Enhanced antiviral activity of the synthesized compounds

Compd	HIV-1 EC_{50}(μM)	Cytotoxicity CC_{50}(μM)
75	85	90
77	20	24
PMEA	10.6	14.7

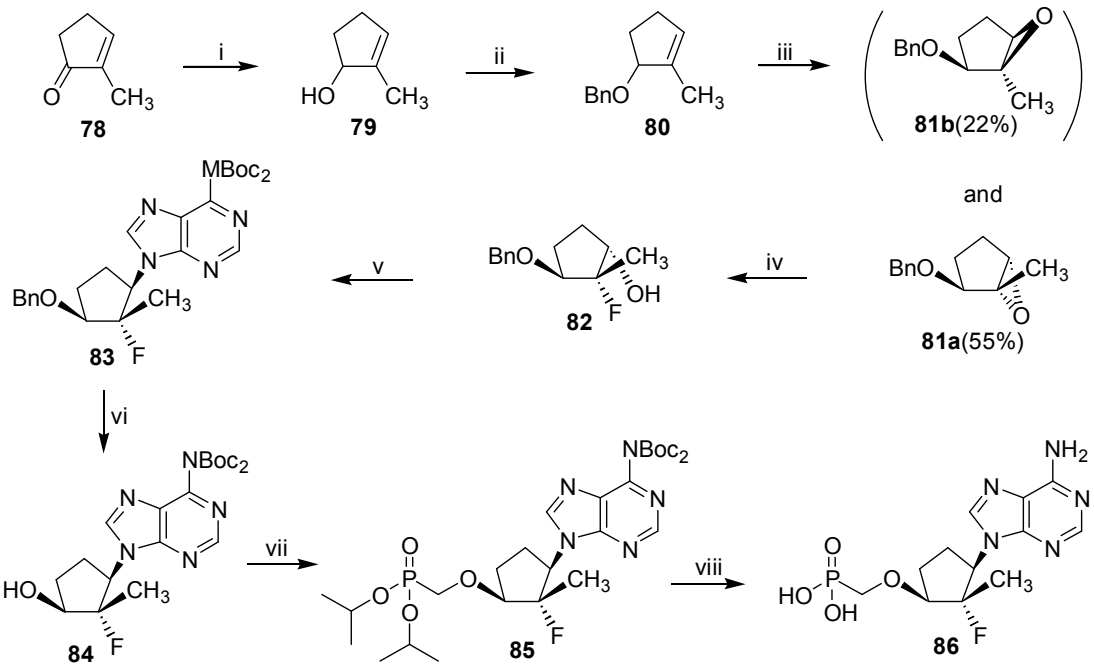
PMEA: 9-[2-(phosphonomethoxy)ethyl]adenine. EC_{50}: Concentration (μM) required to inhibit the replication of HIV-1 by 50%. CC_{50}: Concentration (μM) required to reduce the viability of unaffected cells by 50%.

In order to measure the relative chemical stability of the SATE prodrug using Gosselin's method,[46] we measured the percent of decomposition after 36 hours for **77** at 37 °C: (i) in Milli-Q water (pH 5.5), 2.3% decomposition was observed, and (ii) in pH 7.2 (ammonium buffer, 0.02 M), 4.1% decomposition was observed.

In conclusion, it is interesting to note that the SATE analogue **77** exhibited 4-

fold higher anti-HIV activity compared to its parent nucleoside **75**, indicating that this virus might allow the sugar moiety can serve as a template for DNA polymerase. The synthesis of other nucleoside analogues (uracil, thymine and cytosine) and enzymatic stability data will be reported elsewhere.

SCHEME 15 Synthesis of adenine phosphonic acid nucleoside **86**



Reagents: i)$NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 ^oC; ii) BnBr, NaH, DMF; iii) m-CPBA, CH_2Cl_2; iv) 47% HF, $(NH_4)_2SiF_6$, CsF; v) PPh_3, DIAD, N^6-bis-BOC-adenine; vi) $Pa(OH)_2$, cyclohexene, MeOH, reflux; vii) Diisopropyl bromomethylphosphonate, LiO^t-Bu, LiI, DMF, 60 ^oC; viii) TMSBr, CH_3CN.

As depicted in Scheme 15, we used the cyclopentenone intermediate **78** as commercially available starting material. When **78** was subjected to Luche's reduction conditions ($NaBH_4/CeCl_3 \cdot 7H_2O$),[95] the allylic alcohol derivative **79** was obtained. The hydroxyl functional group was protected with a benzyl group under the usual benzylation conditions (BnBr, NaH, DMF) to provide an inter-mediate **80**, which was epoxidized with m-CPBA to give **81a** (55%) as the major isomer compared to minor isomer **81b** (22%). As shown in Figure 13, the relative stereochemistry of **81a** and **81b** were unambiguously determined on the

basis of the NOE correlations. On irradiation of C_2–H, NOE was observed at C_5–H (0.72%) and C_1–CH_3 (0.82%) of **81a**, but also at C_5–H (1.14%) and C_1–CH_3 (1.34%) of **81b**. This stereochemical outcome suggests that a non–polar group such as benzyloxy reinforces the steric hindrance to the approach of the peroxyacid. The epoxide **81a** was subjected to a region and stereoselective ring–opening fluorination reaction with hydrofluoric acid in the presence of silicon fluorides and additives to provide *cis*–fluorohydrin **82** in good yield. The formation of the *cis*–isomer may be due to the hydrogen bonding and/or silyl ether formation as shown in Figure 14.[96]

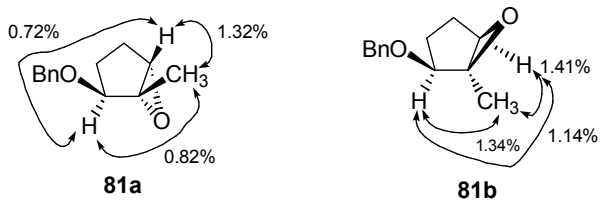


Figure 13. NOE percentage differences of isomers **81a** and **81b.**

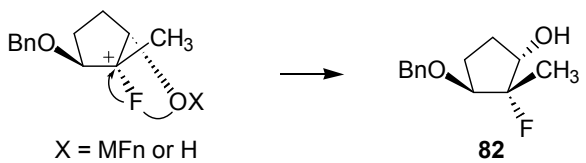
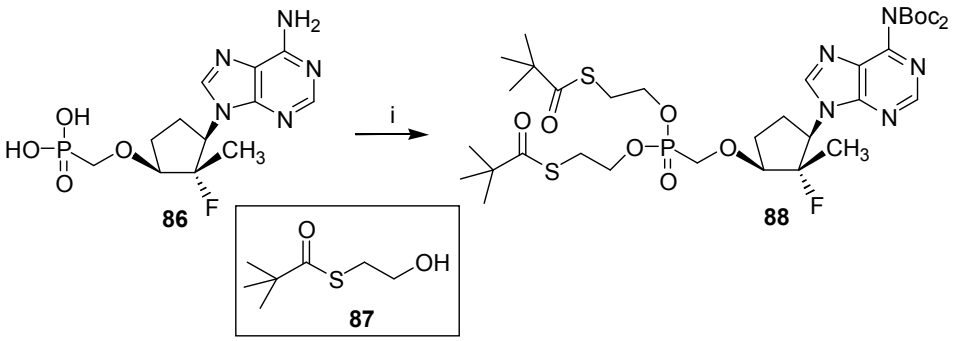


Figure 14. Possible mechanism for the formation of **82.**

To synthesize the desired carbocyclic nucleoside analogues, the alcohol derivative **82** was subjected to a Mitsunobu coupling condition, which is the most useful and common method for the direct substitution of the hydroxyl group with an inverted configuration.[97] First, N^6–bis–Boc–adenine[89] was treated with the protected fluorohydrin **82** in the presence of DIAD and PPh_3 to give **83** in 65% yield. Hydrogenolysis of the benzyl protecting group of **83** with palladium hydroxide and cyclohexene gave the adenine derivative **84**. For the synthesis of phosphonate nucleoside, the hydroxyl group of **84** was phosphonated with diisopropyl bromomethylphosphonate[91] in anhydrous DMF to give the phosphor–nate nucleoside intermediate **85**. Both protecting groups (N^6–bis–Boc & di–*O*–isopropyl) of the phosphonate nucleoside were simultaneously removed using

TMSBr[98] to give nucleoside phosphonic acids **86**. To synthesize the thioester-protected analogues, phosphonic acid nucleoside was reacted with thioester **87**[93] in the presence of 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT)[94] to provide the final *t*-Bu-SATE prodrug **88** (Scheme 16).

SCHEME 16 Synthesis of target SATE prodrug **88**



Reagents: i) **87**, 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole, pyridine.

The newly synthesized phosphonic nucleoside analogues **86** and its prodrug **88** were assayed in MT-4 cells for anti-HIV activity. The SATE prodrug analogue **88** showed enhanced cytotoxicity-dependent anti-HIV activity compared to the parent phosphonic acid **86** (Table 5).

Table 5: Antiviral activity of the SATE derivative **88** and its parent nucleotide **86**

Compd	HIV-1 EC_{50} (μM)	Cytotoxicity CC_{50} (μM)
86	62	70
88	16.7	31.4
PMEA	7.8	12.3
Bis(SATE)PMEA	0.69	1.9
AZT	0.004	6.3

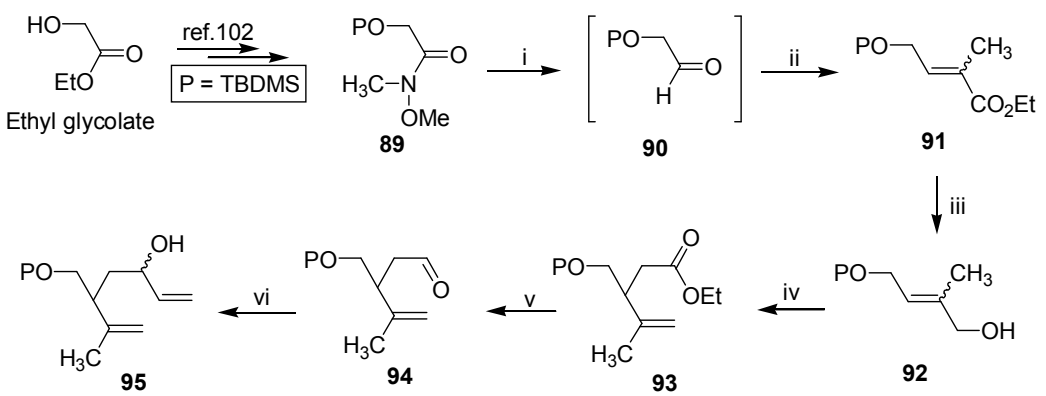
bis(SATE)PMEA: bis(*t*-Bu-SATE)-9-[2-(phosphonomethoxy)ethyl]adenine.[46] AZT: Azidothymidine. EC_{50} (μM): Concentration (μM) required to inhibit the replication of HIV-1 by 50%. CC_{50} (μM): Concentration (μM) required to reduce the viability of unaffected cells by 50%.

The increased anti-HIV activity for the neutral phosphodiester derivative could result from increased cellular uptake followed by intracellular release of the parent phosphonic acid. The procedures for measuring the anti-HIV activity toward HIV-1 and cytotoxicity have been reported previously.[86]

To measure the relative chemical stability of the SATE prodrug using an on-line HPLC cleaning method,[99] we measured the percentage of decomposition after 48 hours for **88** at 37 °C: (i) in Milli-Q water (pH 5.5), 5.1% decomposition was observed; (ii) in pH 7.2 (ammonium buffer, 0.02 M), 5.8% decomposition was observed.

We successfully synthesized novel 6′-fluoro-6′-methyl-5′-noradeonosine carbocyclic nucleoside phosphonic acid and its SATE prodrug from commercially available 2-methylcyclopentenone. The anti-HIV activity of the bis(*t*-Bu-SATE) prodrug **88** was higher than the parent nucleoside **86**. These molecules putatively have different (potentially better) *in vivo* bioavailability and biodistribution than the parent nucleosides. The synthesis of other nucleoside analogues (uracil, thymine and cytosine) and enzymatic stability data will be reported elsewhere.

SCHEME 17 Synthesis of diene intermediate **95**



Reagents: i) DIBALH, THF; ii) triethyl 2-phosphonopropionate, NaH, THF, 0 °C; iii) DIBAL-H, CH_2Cl_2, 0 °C; iv) triethylorthoacetate, propionic acid, 140 °C; v) DIBAL-H, toluene, -78 °C; vi) vinylMgBr, THF.

We describe a very convenient and general synthetic procedure for carbocyclic nucleosides using reiterative three step sequences ([3,3]-sigmatropic rearran-

gement[100], RCM[88] and vicinal dihydroxylation[101]). As shown in Scheme 17, we used the Weinreb amide **89** as starting material, which could be readily synthesized *via* silyl protection of the alcohol could be readily synthesized *via* silyl protection of the alcohol of commercially available starting material Ethyl glycolate followed by hydrolysis and amidation using DCC and DMAP coupling reagent as described in previous report.[102] Conversion of the amide **89** to aldehyde derivative **90** turned out to be successful under the usual carbonyl reduction condition (DIBALH, THF, 0 °C). Subjection of **90** to Horner-Wadsworth-Emmons (HWE) reaction condition[103] provided α,β-unsaturated ethyl ester **91** as *cis*/*trans* isomeric mixtures. It is unnecessary to separate the isomers, because they will be merged into one isomer in next reaction. Ester **91** was reduced to allylic alcohol **92** by using DIBALH, which underwent regular [3,3]-sigmatropic rearrangement using triethyl orthoacetate to give γ,δ-unsaturated ester **93**. Direct conversion of the ester **93** to the aldehyde **94** was possible by slow addition of DIBALH in the toluene solvent system at −78 °C. The aldehyde **94** was subjected to carbonyl addition by vinylMgBr to yield divinyl **95** as inseparable diastereomeric mixtures.

Without separation, divinyl **95** was subjected to standard RCM condition[104] using Grubbs' II catalyst [(Im)$Cl_2PCy_3RuCHPh$] to provide cyclopentenol **96α** and **96β**, respectively. As shown in Figure 15, the stereochemistry was unambiguously assigned on the basis of the NOE correlations between the proximal hydrogens. On irradiation of C_4-H, relatively weak NOE was observed at C_1-H of **96α** (0.1% NOE), but not at C_1-H of **96β** (0.4% NOE).

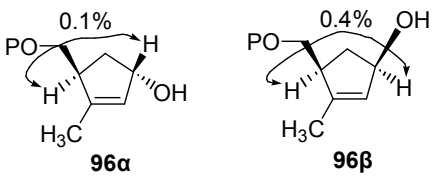


Figure 15. NOE results of compounds **96α** and **96β**.

Cyclopentenol **96β** was transformed to **97** using ethyl chloroformate, which was coupled with cytosine or adenine anions generated by NaH/DMSO with use

of catalyst [tris-(dibenzylideneacetone)-dipalladium(0)-chloroform] adduct to provide nucleoside analogues **98** and **99**. In order to synthesize the 2′,3′-dihydroxy nucleoside analogues **102** and **103**, the protected nucleosides **98** and **99** were subjected to a catalytic amount of OsO_4 and NMO to give the dihydroxylated **100** and **101** as the only reaction products. As shown in Figure 16, the stereochemistry was readily determined by NOE experiment. It is noteworthy that an unexpected higher stereoselectivity was observed in this study than what was reported in previously.[105] These stereochemical outcomes suggest that the bulky groups such as silylated hydroxymethyl group and nucleosidic base of **98** and **99** reinforce the steric hindrance of the β-faces.

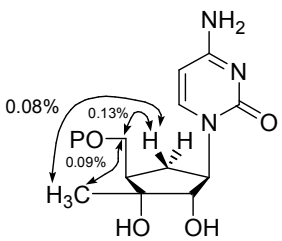


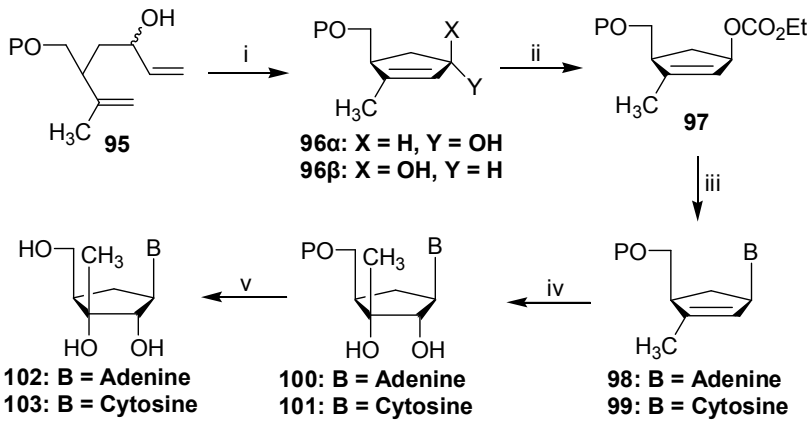
Figure 16. NOE result of compound **101**.

Removals of silyl protection group of **100** and **101** were preformed by the treatment of TBAF to give target nucleosides **102** and **103** (Scheme 18). The synthesized nucleoside analogues mentioned above were assayed for their ability to inhibit HCV RNA replication in a subgenomic replicon Huh7 cell line (LucNeo#2). These cells contain an HCV subgenomic replicon RNA encoding a luciferase reporter gene as a marker. The antiviral potency of the analogues against the HCV replicon is expressed as EC_{50}, which was quantified by a luciferase assay after two days incubation period with the corresponding compound. In addition, the associated cytotoxicity was evaluated in a tetrazolium (XTT)-based assay according to the manufacturer's protocol.[106] However, the synthesized nucleosides neither showed any significant antiviral activity nor toxicity up to 100 μM.

In summary, an efficient synthetic method of 3′(β)-*C*-metylated carbodine analogues from ethyl glycolate was developed. We can conclude that the methyl

group at 3′−position is responsible for the inability of the nucleoside kinase to catalyze the initial phosphorylation of the nucleosides to their monophosphates.

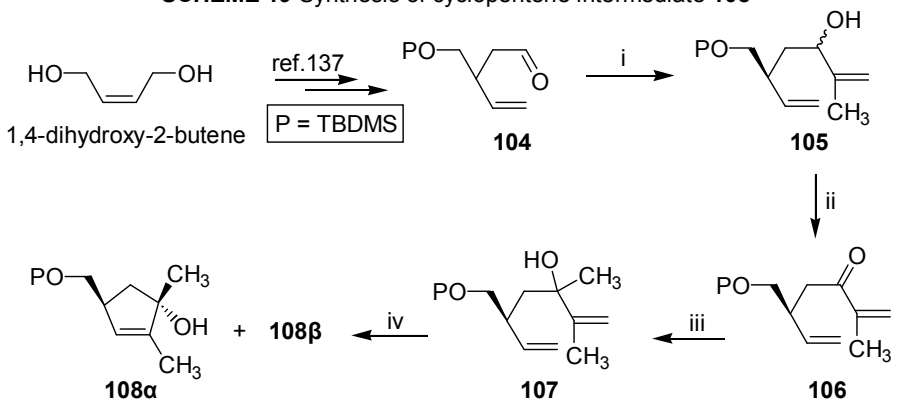
SCHEME 18 Synthesis of 3'-*C*-methyl carbocyclic nucleosides **102** and **103**



Reagents: i) Grubbs' catalyst (II), CH_2Cl_2; ii) ethylchloroformate, DMAP, pyridine; iii) nucleobases, $Pd_2(dba)_3$, $P(O\text{-}i\text{-}Pr)_3$, NaH, THF/DMSO, reflux, overnight; iv) TBAF, THF,rt.

To reach the target molecule, we used an aldehyde **104** as starting material, which could be readily synthesized from 1,4−dihydroxy−2−butene as described in previous report.[137] The aldehyde **104** was subjected to carbonyl addition reaction by CH_2=C(CH_3)MgBr to yield an allylic alcohol derivative **105** as inseparable diastereomeric mixtures. Alcohol derivative **105** was oxidized using MnO_2 to give ketone derivative **106**, which again underwent Grignard addition by methylMgBr to provide a divinyl **107**. The divinyl **107** was subjected to standard RCM condition using Grubbs' II catalyst[88] to provide cyclopentenols **108α** and **108β** with no stereoselectivity. As shown in Figure 17, the stereochemistries of **108α** and **108β** were unambiguously determined on the basis of the NOE correlations. On irradiation of C_4−H, relatively weak NOE was observed at C_1−H of **108α** (0.08%), but not at C_1−H of **108β** (0.27%). (Scheme 19)

SCHEME 19 Synthesis of cyclopentene intermediate **108**



Reagents: i) isopropenylMgBr, THF; ii) MnO_2, CCl_4, 60 °C, overnight; iii) methylMgBr, THF; iv) Grubbs' catalyst (II), benzene, reflux.

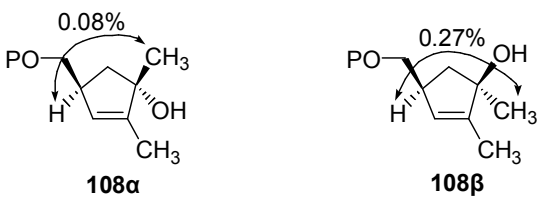
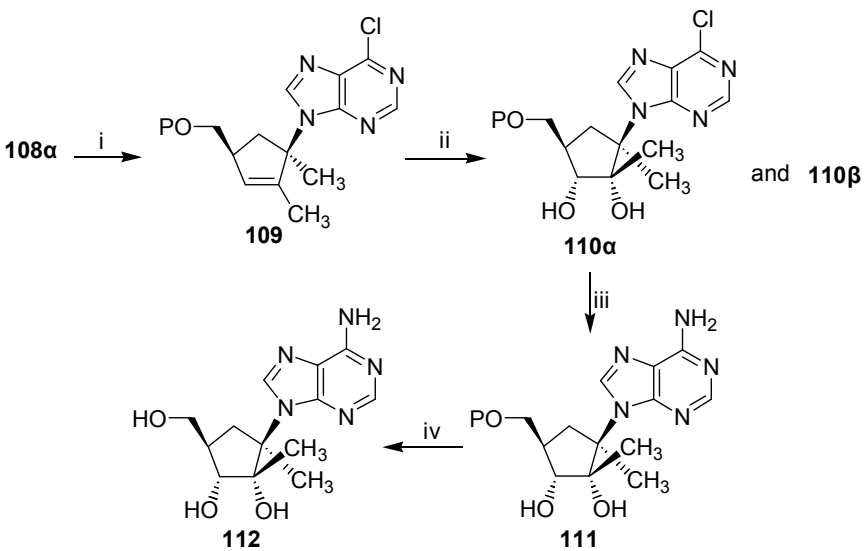


Figure 17. NOE data of compounds **108α** and **108β.**

First, attempt was made to couple the cyclopentenol **108*α*** with the base using convenient bimolecular nucleophilic substitution type (S_N2) reaction. The allylic alcohol **108*α*** was subjected to a mesylation condition (MsCl, TEA, CH_2Cl_2). Unexpectedly, the reaction was very complicated and was irreproducible. Therefore, our attention was turned to a Mitsunobu reaction to synthesize desired nucleoside. The success of Mitsunobu reactions in the synthesis of nucleoside analogues is known to depend on the condition employed. Appropriate choice of solvent system, temperature and procedure are critical for the regioselectivity as well as the yield. In purine synthesis, a 1:1 mixture of dioxane and DMF was used as solvent instead of only THF solvent for the coupling of the cyclopentenol **108*α*** with 6-chloropurine, because the use of a dioxane/DMF mixture allowed better solubility of the heterocyclic base and better yield. Slow addition of DIAD to a mixture of cyclopentenol **108*α***, triphenylphosphine and the 6-chloropurine in anhydrous solvent gave a yellow solution which was stirred

for 2 hours at 20 °C to give protected purine analogue **109** (λ_{max} 264.0 nm). In order to synthesize the 2′,3′−dihydroxy nucleoside analogue **110**, the protected nucleoside **109** was subjected to a catalytic amount of OsO_4 in the presence of stoichiometric amount of NMO to give the dihydroxylated **110α** (49%) as a major reaction product compared to **110β** (12%).[101] This stereochemical outcome suggested that the bulky groups such as silyloxymethyl group and purine base of **109** reinforce the steric hindrance of the β−face.[105]

SCHEME 20 Synthesis of 1',2'-C-dimethyl carbocyclic adenine analogue **112**



Reagents: i) 6-chloropurin, DIAD, PPh_3, dioxane/DMF(1/1); ii) OsO_4, NMO; vi) NH_3/MeOH, 90-95 °C, stee bomb; iv) TBAF, THF/CH_3CN, rt.

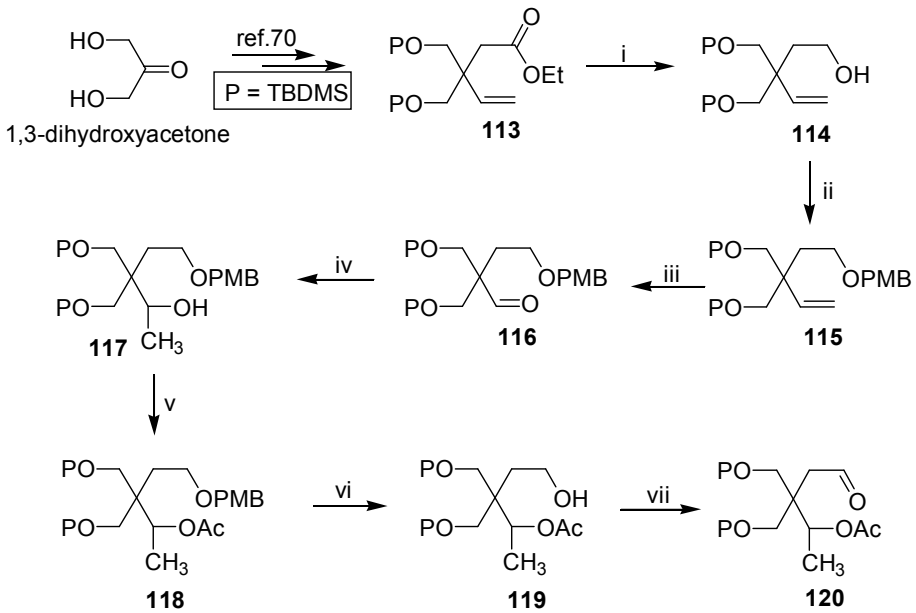
The 6−chloropurine derivative **110α** was transformed to a protected adenosine analogue **111** by treatment with a saturated solution of ammonia in methanol in a steel bomb at 90−95 °C for overnight. Removal of silyl protection group of **111** was performed by the treatment of TBAF in cosolvent system (THF/CH_3CN) to give target nucleoside **112** (Scheme 20). The synthesized nucleoside analogue mentioned above was assayed for its ability to inhibit HCV RNA replication in a subgenomic replicon cell line (Huh−7 cell line).[108] However, the nucleoside failed to inhibit HCV RNA replication in the cell−based replicon assay. In summary, structually related carbocyclic analogue of the active

adenosine based inhibitor was synthesized in order to assess the effect of changes in stereo- and regiochemistry of the sugar moiety. The corresponding 1′(α),2′(β)-*C*-dimethylated carbocyclic adenine analogue **112** was found to be inactive against HCV NS5B (EC_{50} > 50 μM), indicating that the lack of cell based activity is at least in part due to the enzyme's inability to accept this modification. The importance of substitutions in the molecular structure was studied by the synthesis of 1′(α),2′(β)-*C*-dimethyladenosine analogue.

To synthesize the target branched apiosyl nucleosides, we utilized the unsaturated ester intermediate **113** as a starting material, which was readily prepared by previously reported procedure from 1,3-dihydroxyacetone.[70] Ester **113** was subjected to DIBALH reduction to give the alcohol **114** in high yield. The primary hydroxyl group of **114** was protected as a temporary PMB by reaction[109] with PMBCl and NaH in DMF to afford the protected olefin **115** in a yield of 95%. The olefin of **115** was treated with ozone in methylene chloride at -78 °C, followed by the decomposition of the ozonide by DMS to give the aldehyde **116**. Compound **116** was subjected to carbonyl addition with methylMgBr to provide the secondary alcohol derivative **117**, which was acetylated with acetic anhydride in pyridine to give the ester **118**. Oxidative deprotection of the PMB ether of **118** was effected with DDQ[87] in CH_2Cl_2 with a small amount of water to give the alcohol **119**, which was subjected to Swern oxidation [DMSO, $(COCl)_2$, TEA][89] to provide aldehyde **120** in a quantitative yield. Deacetylation of **120** using NaOMe/MeOH provided the lactol derivative **121**, and subsequent acetylation with acetic anhydride in pyridine yielded a glycosyl donor **122**, which is ready for the condensation with bases Scheme 21.

Synthesis of the desired nucleosides is depicted in Scheme 22. The glycosyl donor **122** was condensed with silylated 6-chloropurine in the presence of TMSOTf and separated by silica gel column chromatography to provide the protected nucleosides **123** and **124**. As shown in Figure 18, the stereo-chemistries of **123** and **124** were unambiguously determined on the basis of the NOE correlations. On irradiation of C_2-H, a relatively weak NOE was observed at C_5-H of **123** (0.3%), but not at C_5-H of **124** (0.8%).

SCHEME 21 Synthesis of aldehyde intermediate **120**



Reagents: i) DIBALH, CH_2Cl_2; ii) PMBCl, NaH, THF; iii) O_3/DMS, CH_2Cl_2; iv) CH_3MgBr, THF; v) Ac_2O, pyridine; vi) DDQ, CH_2Cl_2-H_2O; vii) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C.

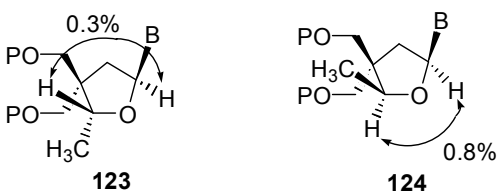
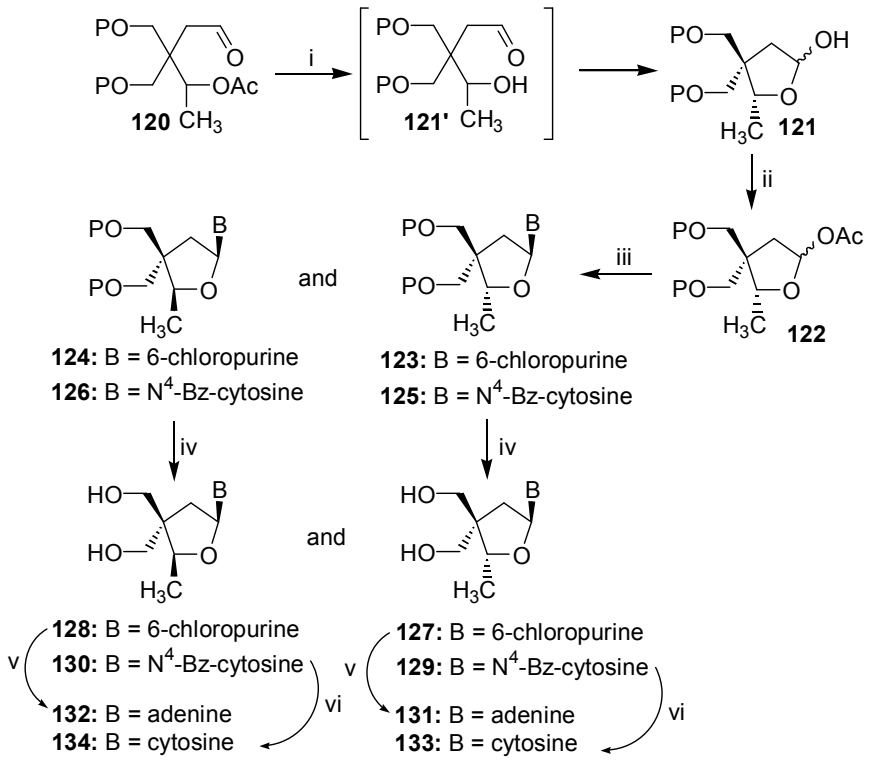


Figure 18. NOE comparisons of compounds **123** and **124.**

Desilylation of 123 and 124 with TBAF afforded the nucleoside analogues 127 and 128, respectively. Chloropurine derivatives 127 and 128 were individually transformed to 131 and 132 by treating with methanolic ammonia in a steel bomb at 90 °C. For the synthesis of cytosine analogues, the glycosyl donor 122 was condensed with silylated N^4-benzoyl cytosine in the presence of TMSOTf and separated by silica gel column chromatography to give the protected nucleosides 125 and 126. The stereochemistries of 125 and 126 were as described for 123 and 124 on the basis of the NOE correlations. Desilylation of each anomer was performed by TBAF in the THF/CH_3CN co-solvent system followed by

debenzolyation with methanolic ammonia to afford the final cytosine nucleosides **133** and **134**, respectively.

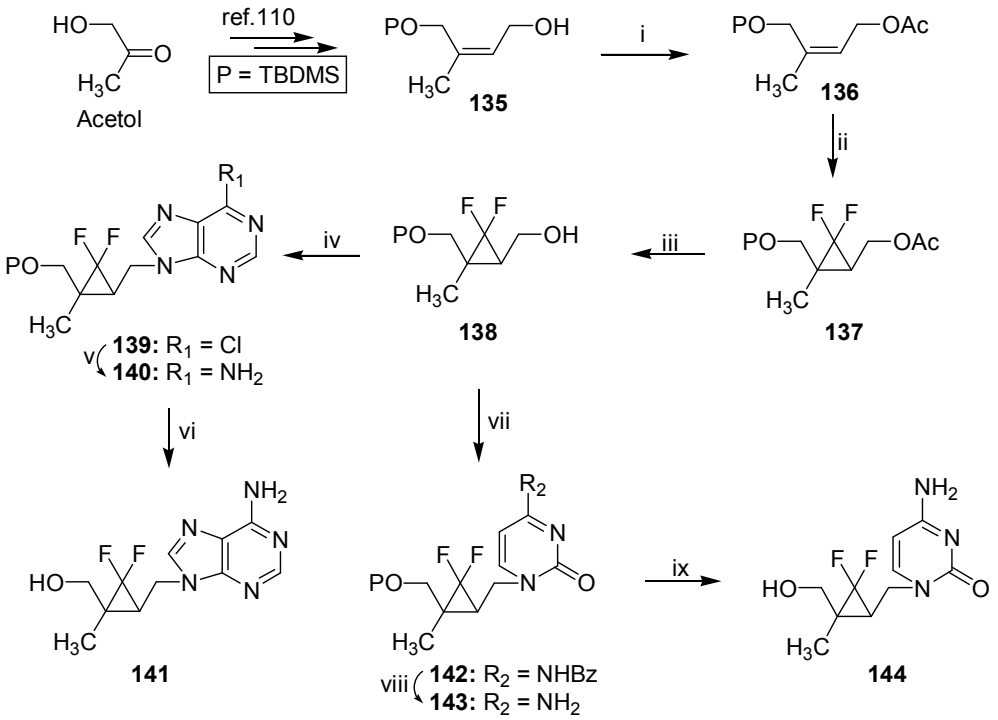
SCHEME 22 Synthesis of target nucleosides



Reagents: i) NaOMe, MeOH; ii) Ac_2O, DMAP, pyridine; iii) persilylated bases, TMSOTf, $ClCH_2CH_2Cl$; iv) TBAF, THF/CH_3CN; v) NH_3/MeOH, steel bomb, 90 ^oC; vi) NH_3/MeOH, room temperature.

All the synthesized compounds were tested for anti-HCV activity using an in vitro assay that is suitable for monitoring anti-HCV activities of compounds. This system is composed of a human hepatocarcinoma cell line (Huh-7) supporting multiplication of an HCV replicon named NK-R2AN. Compound **132** significantly inhibited the replication of the replicon NKR2AN in Huh-7 cells by 50% at 19 μM. Therefore, two branches at the 4′,5′-position make the apiosyl ring conformation favorable for phosphorylation at the 4′-hydroxyl group and subsequent incorporation into the growing RNA chain by the polymerase.

SCHEME 23 Synthesis of difluorocyclopropane nucleosides **141** and **144**



Reagents: i) Ac_2O, DMAP, pyridine, rt; ii) $ClCF_2CO_2Na$, diglyme, 190 °C, reflux; iii) NaOMe, MeOH, 0 °C; iv) 6-chloropurine, DIAD, PPh_3, THF, -20 °C; v) NH_3/MeOH, 100 °C; vi) TBAF, THF, 0 °C; vii) N^4-Bz-cytosine, DIAD, PPh_3, THF, -20 °C; viii) NaOMe, MeOH, 0 °C; ix) TBAF, THF, 0 °C.

To synthesize the target difluorocyclopropane nucleosides, we utilized the unsaturated alcohol intermediate **135** as a starting material, which was readily prepared by previously reported procedure from acetol.[70, 110] The alcohol **135** was acetylated with acetic anhydride in pyridine to give compound **136**, and the **136** was subjected to a difluorocyclopropanation reaction using sodium chloro-difluoroacetae in diglyme at 190 °C to afford the cyclopropane **137**.[111] Treatment of **137** with catalytic amounts of NaOMe in methanol gave very smoothly 91% of the key intermediate **138**. First, attempt was made to couple the alcohol **138** with the base using convenient bimolecular nucleophilic substitution type (S_N2) reaction. The alcohol **138** was subjected to a mesylation condition (MsCl, TEA, CH_2Cl_2).

Unexpectedly, the reaction was very complicated and was irreproducible.

Therefore, our attention was turned to a Mitsunobu reaction[29] to synthesize desired nucleoside. The success of Mitsunobu reactions in the synthesis of nucleoside analogues is known to depend on the condition employed. Appropriate choice of solvent system, temperature and procedure are critical for the regioselectivity as well as the yield. Slow addition of DIAD to alcohol **138**, triphenylphosphine and the 6-chloropurine in anhydrous THF gave a yellow solution which was stirred for 2 h at –20 °C to give protected purine analogue **139**. The 6-chloropurine derivative **139** was transformed to a protected adenosine analogue **140** by treatment with a saturated solution of ammonia in methanol in a steel bomb at 100 °C for overnight. Removal of silyl protection group of **140** was performed by the treatment of TBAF in THF to give target nucleoside **141**. To synthesize the pyrimidine nucleoside analogue N^4-benzoyl base, we used a similar Mitsunobu procedure on the cytosine base to give the protected nucleoside analogue **142**. The isomer was easily confirmed by comparison of the UV literature data.[76] The debenzoylated by treatment with sodium metoxide in methanol to produce nucleoside **143**, the desilylation of the nucleoside intermediate was performed similarly to that for adenine nucleoside **141** to produce pyramiding the nucleoside **144** (Scheme 23). The compounds **144** showed significant anti-HIV activities without cytotoxicity up to 100 μM. (Table 6)

Table 6: Antiviral activity of the synthesized compounds

Compd	HIV-1 EC_{50}(μM)	HCMV EC_{50}(μM)	Cytotoxicity CC_{50}(μM)
141	>100	>100	>100
144	10.4	68.4	31.4
AZT	0.009	ND	6.3

AZT: Azidothymidine. EC_{50} (μM): Concentration (μM) required to inhibit the replication of HIV-1 by 50%. CC_{50} (μM): Concentration (μM) required to reduce the viability of unaffected cells by 50%.

Ⅲ. CONCLUSION

Nucleoside analogues play a major role in antiviral chemotherapy. Although interest in the design these analogues have relatively decreased during the past few years, the emergence of resistance to currently FDA approved drugs has generated new interest for the search of new active nucleoside analogues. In recent years, attention has been increasingly focused on structural modifications of carbocyclic nucleosides. So branched carbocyclic nucleosides **8**, **13**, **14**, **17**, **25**, **28**, **31**, **39**, **42**, **45**, **102**, **103**, **112**; 5′-norcarbocyclic nucleosides **58**, **59**, **60**, **62**, **75**, **77**, **86**, **88**; apiosyl nucleosides **131~134** and difluorocyclopropane nucleosides **141**, **144** were synthesized. The synthesized compounds were evaluated for their antiviral activity against HIV-1, HSV-1, HSV-2, HCMV and HCV. Compounds **25**, **31**, **45**, **144** exhibited potent anti-HIV activities, compounds **17**, **59**, **77**, **88** were evaluated for toxicity (up to 100 μM) and related anti-HIV activity. Furthermore, these synthesized nucleoside analogues such as **102**, **103**, **112**, **131, 132, 133, 134** were evaluated for their potential to inhibit HCV RNA replication in a subgenomic replicon cell line (Huh-7 cell line). However, these nucleosides showed no significant inhibit HCV RNA replication in the cell-based replicon assay.

Ⅳ. EXPERIMENTAL SECTION

Melting points were determined on a Mel-temp Ⅱ laboratory device and are uncorrected. MR spectra were recorded on a JEOL 300 Fourier transform spe-ctrometer (JEOL, Tokyo, Japan); chemical shifts are reported in parts per million (δ) and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). UV spectra were obtained on a Beckman DU-7 spectrophotometer (Beckman, South Pasadena, CA, USA). The elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). Mass spectra were measured with FAB-MS modified Finninggan MAT 312 spectrometer (Arcade, NY 14009, USA). All reactions were carried out under an atmosphere of nitrogen unless specified. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

(±)-3,3-Bis-(*tert*-butyldimethylsilanyloxymethyl)-pent-4-enal (2): To a solution of **1** (3.5 g, 8.39 mmol) in toluene (100 mL), DIBALH (6.16 mL, 1.5 M in toluene) was added slowly at −78 °C, and stirred for 10 min at the same temperature. Methanol (10 mL) was then added to the mixture. The mixture was stirred at room temperature for 2 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **2** (4.4 g, 69%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 5.67 (dd, J = 17.7, 11.1 Hz, 1H), 5.21 (d, J = 11.1 Hz, 1H), 5.14 (d, J = 17.7 Hz, 1H), 3.58 (dd, J = 17.7, 10.2 Hz, 2H), 2.45 (s, 1H), 0.87 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.68, 139.65, 115.45, 65.74, 46.79, 46.61, 25.81, 18.22, −5.62; MS (FAB+) m/z 273 (M+H)+.

(±)-3,3-Bis-(*tert*-butyldimethylsilanyloxymethyl)-2-methylene-pent-4-enal (3): Eschenmoser's salt, methylene-*N*,*N*-dimethylammonium iodide, (2.18 g, 11.82 mmol) was added to a solution of aldehyde **2** (2.2 g, 5.91 mmol) and TEA (2.46 mL, 17.73 mmol) in CH_2Cl_2 at room temperature. The mixture was stirred overnight at room temperature. After adding saturated aq. $NaHCO_3$

solution, the mixture was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **3** (1.25 g, 55%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.12 (s, 1H), 6.09 (d, J = 0.6 Hz, 1H), 5.80 (d, J = 0.8 Hz, 1H), 5.60−5.52 (m, 1H), 5.06−4.98 (m, 2H), 3.61 (d, J = 10.8 Hz, 1H), 3.52 (d, J = 10.8 Hz, 1H), 0.89 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.86, 154.42, 136.78, 133.72, 109.71, 66.32, 52.43, 25.43, 18.39, −5.54; MS (FAB+) m/z 385 (M+H)+; Anal. calcd. for $C_{20}H_{40}O_3Si_2$: C, 62.44; H, 10.48. Found: C, 62.58; H, 10.39.

(±)−5,5−Bis−(*tert*−butyldimethylsilanyloxymethyl)−4−methylene−hepta−1, 6−dien−3−ol (4): VinylMgBr (7.8 mL, 1.0 M solution in THF) was added slowly to a solution of compound **3** (2.5 g, 6.5 mmol) in dry THF (100 mL) at −78 °C. After 2 h, saturated NH_4Cl solution (8 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc (2 × 200 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give a triene **4** (2.12 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85−5.37 (m, 3H), 5.37−5.30 (m, 2H), 5.14−4.93 (m, 3H), 4.65 (d, J = 2.4 Hz, 1H), 3.88 (d, J = 9.9 Hz, 1H), 3.75 (d, J = 9.9 Hz, 1H), 0.86 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.35, 140.35, 139.30, 116.56, 115.21, 113.93, 113.31, 70.98, 65.91, 64.18, 52.59, 25.88, 18.29, −5.43; Anal. calcd. for $C_{22}H_{44}O_3Si_2 \cdot 0.5$ EtOAc: C, 63.10; H, 10.59. Found: C, 63.19; H, 10.44.

(±)−4,4−Bis−(*tert*−butyldimethylsilanyloxymethyl)−5−methylenecyclopent−2−enol (5): A Grubbs' II catalyst (80 mg, 0.11 mmol) was added to a solution of compound **4** (3.92 g, 9.5 mmol) in dry CH_2Cl_2 (40 mL). The reaction mixture was refluxed overnight and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **5** (2.7 g, 74%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98 (dd, J = 6.0, 2.4 Hz, 1H), 5.68 (d, J = 6.0 Hz, 1H), 5.32 (s, 1H), 5.11 (s, 1H), 4.79 (dd, J = 10.8, 1.5 Hz, 1H), 3.74 (d, J = 9.3 Hz, 1H), 3.60 (d, J = 9.6 Hz, 1H), 3.50 (d, J = 9.3 Hz, 1H),

3.43 (d, J = 9.6 Hz, 1H), 0.87 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.77, 137.14, 134.04, 110.04, 77.96, 67.01, 66.76, 57.72, 25.55, 18.39, −5.54; MS (FAB+) m/z 385 (M+H)+, 407 (M+Na)+; Anal. Calcd. for $C_{20}H_{40}O_3Si_2$: C, 62.44; H, 10.48. Found: C, 62.53; H, 10.54.

(±)−9−[4,4−Bis−(*tert*−butyldimethylsilanyloxymethyl)−5−methylenecyclopent−2−enyl]−6−chloropurine (6): To a solution containing compound **5** (173 mg, 0.45 mmol), PPh_3 (0.705 g, 1.35 mmol) and 6−chloropurine (173 mg, 1.12 mmol) in anhydrous 1,4−dioxane (4 mL) and DMF (2 mL), DIAD (0.25 mL) was added dropwise at −20 °C for 30 min under nitrogen. The reaction mixture was stirred for 2 h at −20 °C under nitrogen. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give compound **6** (75 mg, 32%) as a white solid: m.p. 158−160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.71 (s, 1H), 8.17 (s, 1H), 6.22 (m, 2H), 5.90 (dd, J = 5.7, 2.1 Hz, 1H), 5.26 (d, J = 2.4 Hz, 1H), 5.08 (d, J = 1.5 Hz, 1H), 3.85 (d, J = 9.3 Hz, 1H), 3.72 (d, J = 9.3 Hz, 1H), 3.60 (d, J = 9.6 Hz, 1H), 3.54 (d, J = 9.6 Hz, 1H), 0.84 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.34, 154.47, 152.45, 148.28, 147.20, 137.71, 134.51, 130.04, 111.77, 68.00, 63.35, 57.28, 25.51, 18.32, −5.60; MS (FAB+) m/z 521 (M+H)+, 543 (M+Na)+; Anal. Calcd. for $C_{25}H_{41}ClN_4O_2Si_2$: C, 57.61; H, 7.93; N, 10.75. Found: C, 57.67; H, 8.05; N, 10.82.

(±)−9−[4,4−Bis−(hydroxymethyl)−5−methylenecyclopent−2−enyl]−6−chloropurine (7): TBAF (0.76 mL, 1.0 M solution in THF) at 0 °C was added to a solution of compound **6** (100 mg, 0.191 mmol) in THF/CH_3CN (2/2 mL). The mixture was stirred overnight at room temperature and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:8) to give compound **7** (79.25 mg, 72%) as a white solid: m.p. 163−165 °C; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.78 (s, 1H), 8.22 (s, 1H), 6.18 (d, J = 5.9 Hz, 1H), 6.02 (s, 1H), 5.93 (d, J = 6.0 Hz, 1H), 5.27 (br s, 1H), 5.13 (s, 1H), 4.94 (t, J = 5.0 Hz, 1H), 4,77 (t, J = 5.2 Hz, 1H), 3.88 (d, J = 9.9 Hz, 1H), 3.74 (d, J = 9.9 Hz, 1H), 3.64 (d, J = 9.6 Hz, 1H), 3.58 (d, J = 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.88, 154.54, 151.57, 148.66, 146.37, 138.98, 133.99, 130.02, 111.21, 78.09, 66.49, 56.32; MS (FAB+) m/z 293 (M+H)+, 315 (M+Na)+; Anal.

Calcd. for $C_{13}H_{13}ClN_4O_2$: C, 53.34; H, 4.48; N, 19.14. Found: C, 53.28; H, 4.52; N, 19.06.

(±)-9-[4,4-Bis-(hydroxymethyl)-5-methylenecyclopent-2-enyl]adenine (8): Compound **7** (79 mg, 0.27 mmol) was dissolved in saturated methanolic ammonia (5 mL) and the resulting solution was stirred overnight at 90-95 °C in a steel bomb. After removing the reaction solvent, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 4:1) to give compound **8** (72.8 mg, 70%) as a white solid: m.p. 177-179 °C; UV (H_2O) λ_{max} 261.5.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.10 (s, 1H), 8.01 (s, 1H), 6.12 (dd, J = 6.0, 1.5 Hz, 1H), 6.00 (t, J = 2.4 Hz, 1H), 5.94 (dd, J = 6.0, 2.1 Hz, 1H), 5.19 (d, J = 2.4 Hz, 1H), 4.96 (br s, 1H), 4.93 (t, J = 5.2 Hz, 1H), 4,76 (t, J = 5.2 Hz, 1H), 3.75 (d, J = 9.8 Hz, 1H), 3.65 (d, J = 9.8 Hz, 1H), 3.60 (d, J = 9.6 Hz, 1H), 3.55 (d, J = 9.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155, 69, 154.77, 152.76, 150.34, 141.72, 137.14, 134.04, 119.64, 110.24, 67.01, 66.44, 62.43, 58.72; MS (FAB+) m/z 274 (M+H)+, 296 (M+Na)+; Anal. Calcd. for $C_{13}H_{15}N_5O_2 \cdot 1.0\ H_2O$: C, 53.59; H, 5.88; N, 24.04. Found: C, 53.48; H, 5.80; N, 23.86.

(±)-1-[4,4-Bis-(*tert*-butyldimethylsilanyloxymethyl)-5-methylenecyclopent-2-enyl]-N^3-benzoylthymine (9): The benzoylthymine analogue was synthesized using a similar reaction procedure as that described for compound **6** as a white solid: m.p. 160-163 °C; yield 43%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89-7.85 (m, 2H), 7.61-7.55 (m, 1H), 7.45-7.40 (m, 2H), 7.15 (s, 1H), 6.31 (dd, J = 5.4, 1.8 Hz, 1H), 6.24 (dd, J = 5.4, 1.5 Hz, 1H), 5.98 (t, J = 1.8 Hz, 1H), 4.70 (d, J = 2.0 Hz, 2H), 3.67-3.57 (m, 4H), 1.88 (s, 3H), 0.86 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.05, 163.30, 149.70, 142.05, 140.58, 134.56, 131,70, 130.39, 129.03, 123.35, 110.64, 66.02, 64.59, 57.51, 25.89, 18.28, 12.38, -5.45; MS (FAB+) m/z 619 (M+Na)+; Anal. Calcd. for $C_{32}H_{48}N_2O_5Si_2$: C, 64.39; H, 8.11; N, 4.69. Found: C, 64.51; H, 7.98; N, 4.58.

(±)-1-[4,4-Bis-(*tert*-butyldimethylsilanyloxymethyl)-5-methylenecyclopent-2-enyl]-N^3-benzoyluracil (10): The benzoyluracil derivative was synthesized by a procedure similar to that used to prepare **6** as a white solid: m.p. 157-159 °C; yield 39%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92-7.88 (m, 2H), 7.63-7.56 (m, 1H), 7.48-7.42 (m, 2H), 7.27 (d, J = 8.1 Hz, 1H), 6.32 (dd, J = 5.4, 1.8 Hz,

1H), 6.27 (dd, J = 5.1, 1.5 Hz, 1H), 6.03 (t, J = 1.8 Hz, 1H), 5.76 (d, J = 8.1 Hz, 1H), 4.64 (d, J = 1.5 Hz, 2H), 3.68 (d, J = 9.0 Hz, 2H), 3.60 (d, J = 9.0 Hz, 2H), 0.85 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.56, 162.57, 149.65, 147.46, 144.65, 140.76, 134.52, 132.65, 130.21, 129.14, 129.07, 128.54, 102.21, 70.08, 64.68, 62.43, 57.64, 25.76, 18.32, −5.49; MS (FAB+) m/z 583 (M+H)+, 605 (M+Na)+; Anal. Calcd. for $C_{31}H_{46}N_2O_5Si_2$: C, 63.88; H, 7.95; N, 4.81. Found: C, 63.95; H, 8.06; N, 4.75.

(±)−1−[4,4−Bis−(*tert*−butyldimethylsilanyloxymethyl)−5−methylenecyclopent−2−enyl]−N^4−benzoylcytosine (15): The benzoylcytosine derivative was synthesized by a procedure similar to that used to prepare **6** as a white solid: m.p. 167−169 °C; yield 38%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90−7.83 (m, 2H), 7.78−7.73 (m, 2H), 7.48−7.41 (m, 2H), 7.29(d, J = 7.8 Hz, 1H), 6.35 (dd, J = 5.4, 1.8 Hz, 1H), 6.28 (dd, J = 5.1, 1.6 Hz, 1H), 6.00 (d, J = 1.9 Hz, 1H), 5.54 (d, J = 7.8 Hz, 1H), 4.71 (d, J = 1.6 Hz, 2H), 3.67–59 (m, 4H), 0.87 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.92, 165.88, 164.48, 160.66, 159.28, 154.75, 140.45, 139.28, 137.14, 132.88, 131,84, 129.02, 127.26, 110.23, 93.80, 67.02, 65.83, 64.87, 59.32, 25.90, 18.27, −5.59; MS (FAB+) m/z 583 (M+H)+; Anal. Calcd. for $C_{31}H_{47}N_3O_4Si_2$: C, 63.99; H, 8.14; N, 7.22. Found: C, 64.16; H, 8.23; N, 7.32.

(±)−1−[4,4−Bis−(hydroxymethyl)−5−methylenecyclopent−2−enyl]−N^3−benzoylthymine (11): For the desilylation of benzoylthymine analogue **9**, the reaction procedure was similar to that described for compound **7** as a white solid: m.p. 155−157 °C; yield 73%; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 7.88−7.84 (m, 2H), 7.60 (m, 1H), 7.46−7.41 (m, 2H), 7.09 (s, 1H), 6.30−6.25 (m, 2H), 5.99 (m, 1H), 4.89 (t, J = 5.4 Hz, 1H), 4.80 (t, J = 5.4 Hz, 1H), 4.65 (d, J = 1.8 Hz, 2H), 3.69−3.60 (m, 4H), 1.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.78, 163.03, 149.43, 147.80, 142.2, 139.90, 134,54, 131.43, 130.40, 129.32, 128.32, 120.35, 109.64, 66.32, 64.43, 58.32,12.22; MS (FAB+) m/z 369 (M+H)+, 391 (M+Na)+; Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.35; H, 5.30; N, 7.53.

(±)−1−[4,4−Bis−(hydroxymethyl)−5−methylenecyclopent−2−enyl]−N^3−benzoyluracil (12): For the desilylation of benzoyluracil derivative **10**, the reac−

tion procedure was similar to that used in the preparation of **7** as a white solid: m.p. 169−171 °C; yield 80%; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 7.88 (m, 2H), 7.59 (d, J = 6.2 Hz, 1H), 7.48−7.42 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 6.33−6.28 (m, 2H), 6.04 (d, J = 1.9 Hz, 1H), 5.73 (d, J = 8.0 Hz, 1H), 4.90 (t, J = 5.4 Hz, 1H), 4.80 (t, J = 5.4 Hz, 1H), 4.67 (d, J = 1.6 Hz, 2H), 3.67 (d, J = 9.1 Hz, 2H), 3.58 (d, J = 9.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.20, 163.11, 148.32, 146.67, 143.71, 141.77, 137.30, 133.81, 131.99, 130.71, 129.54, 129.02, 127.34, 101.76, 68.65, 63.21, 63.03, 58.65; MS (FAB+) m/z 355 (M+H)+, 377 (M+Na)+; Anal. Calcd. for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.57; H, 5.05; N, 7.89.

(±)−1−[4,4−Bis−(hydroxymethyl)−5−methylenecyclopent−2−enyl]−N^4−benzoylcytosine (16): For the desilylation of benzoylcytosine derivative **15,** the reaction procedure was similar to that used to prepare **7** as a white solid: m.p. 167−169 °C; yield 71%; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 7.89−7.84 (dd, J = 5.4, 1.8 Hz, 2H), 7.75−7.71 (m, 2H), 7.45 (m, 2H), 7.25 (d, J = 7.9 Hz, 1H), 6.32 (dd, J = 5.4, 1.9 Hz, 1H), 6.26 (dd, J = 5.2, 1.7 Hz, 1H), 6.01 (t, J = 2.0 Hz, 1H), 5.57 (d, J = 7.8 Hz, 1H), 4.86 (t, J = 5.3 Hz, 1H), 4.76 (br s, 1H), 4.68 (d, J = 1.7 Hz, 2H), 3.69 (d, J = 9.6 Hz, 2H), 3.56 (d, J = 9.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.43, 165.32, 163.67, 161.70, 158.21, 153.40, 142.21, 140.23, 136.90, 133.16, 131.22, 130.54, 128.52, 109.32, 94.01, 68.27, 64.67, 64.02, 57.30; MS (FAB+) m/z 254 (M+H)+, 376 (M+Na)+; Anal. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.65; H, 5.38; N, 11.82.

(±)−1−[4,4−Bis−(hydroxymethyl)−5−methylenecyclopent−2−enyl]thymine (13): To the solution of benzoylthymine derivative **11** (79 mg, 0.214 mmol) in MeOH (5 mL), NaOMe (0.5 mL, 1.0 M solution in MeOH) was added and the mixture was stirred overnight at room temperature. Glacial acetic acid (0.1 mL) was added to the mixture for neutralization. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 4:1) to give compound **13** (39 mg, 70%) as a white solid: yield 79%; m.p. 169−171 °C; UV (H_2O) λ_{max} 268.5.0 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 11.21 (br s, 1H), 7.11 (s, 1H), 6.29−6.24 (m, 2H), 6.01 (t, J = 1.9 Hz, 1H), 4.87 (t, J = 5.3 Hz, 1H), 4.79 (t, J = 5.4 Hz, 1H), 4.68

(s, 2H), 3.66 (d, J = 10.0 Hz, 2H), 3.53 (d, J = 9.9 Hz, 2H), 1.89 (s, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 164.58, 154.43, 151.39, 142.50, 137.29, 133.98, 109.28, 110.79, 66.99, 66.32, 61.47, 59.32, 12.43; MS (FAB+) m/z 265 (M+H)+, 287 (M+Na)+; Anal. Calcd. for $C_{13}H_{16}N_2O_4 \cdot 0.5$ MeOH: C, 57.84; H, 6.47; N, 9.99. Found: C, 57.74; H, 6.56; N, 10.09.

(±)−1−[4,4−Bis−(hydroxymethyl)−5−methylenecyclopent−2−enyl]uracil (14): The uracil derivative was synthesized from **12** using a procedure similar to that described for the preparation of **13**: yield 72%; m.p. 163−165 °C; UV (H_2O) λ_{max} 262.5.0 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 11.23 (br s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 6.02 (m, 2H), 6.01 (s, 1H), 5.69 (d, J = 8.0 Hz, 1H), 4.91 (t, J = 5.2 Hz, 1H), 4.82 (t, J = 5.3 Hz, 1H), 4.69 (s, 2H), 3.68 (d, J = 10.1 Hz, 2H), 3.55 (d, J = 10.0 Hz, 2H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 163, 87, 154.21, 151.98, 145.87, 136.93, 134.21, 101.22, 111.01, 67.31, 66.94, 62.44, 58.99; MS (FAB+) m/z 251 (M+H)+, 273 (M+Na)+; Anal. Calcd. for $C_{12}H_{14}N_2O_4 \cdot 1.0$ H_2O: C, 53.66; H, 6.01; N, 10.44. Found: C, 53.70; H, 5.94; N, 10.34.

(±)−1−[4,4−Bis−(hydroxymethyl)−5−methylenecyclopent−2−enyl]cytosine (17): The cytosine derivative **17** was synthesized from **16** by a procedure similar to that used in the preparation of **13**: yield 70%; m.p. 166−168 °C; UV (H_2O) λ_{max} 272.5.0 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 7.30 (d, J = 7.8 Hz, 1H), 7.07 (br d, 2H), 6.36 (dd, J = 5.4, 1.8 Hz, 1H), 6.27 (dd, J = 5.3, 1.6 Hz, 1H), 6.02 (br s, 1H), 5.56 (d, J = 7.8 Hz, 1H), 4.89 (t, J = 5.2 Hz, 1H), 4.79 (t, J = 5.3 Hz, 1H), 4.65 (d, J = 1.9 Hz, 2H), 3.65 (d, J = 9.9 Hz, 2H), 3.54 (d, J = 9.8 Hz, 2H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 165, 21, 156.44, 153.97, 145.36, 134.51, 133.86, 93.58, 110.75, 67.76, 66.54, 63.02, 58.31; MS (FAB+) m/z 250 (M+H)+, 272 (M+Na)+; Anal. Calcd. for $C_{12}H_{15}N_3O_3 \cdot 1.0$ H_2O: C, 53.92; H, 6.41; N, 15.72. Found: C, 54.12; H, 6.29; N, 15.70.

(±)−3−(*tert*−Butyldimethylsilanyloxymethyl)−3−methylpent−4−enal (19): The aldehyde analogue **19** was synthesized from **18** using a similar reaction procedure as that described for compound **2** as a colorless oil: yield 69%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.75 (t, J = 3.3 Hz, 1H), 5.96 (d, J = 11.1 Hz, 1H), 5.90 (d, J = 10.8 Hz, 1H), 5.14 (d, J = 8.4 Hz, 1H), 5.11 (d, J = 16.2 Hz, 1H), 3.49 (d, J = 9.6 Hz, 1H), 3.40 (d, J = 9.3 Hz, 1H), 2.41 (t, J = 3.0 Hz, 2H), 1.12

(s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.08, 142.61, 113.93, 70.53, 50.70, 41.60, 25.80, 21.30, −5.61; Anal. Calcd. for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81.

(±)−3−(*tert*−Butyldimethylsilanyloxymethyl)−3−methyl−2−methylenepent−4−enal (20): The compound **20** was synthesized from **19** using a procedure similar to that described for the preparation of **3** as a colorless oil: yield 56%; Without further purification, compound **20** was subject to next reaction.

(±)−5−(*tert*−Butyldimethylsilanyloxymethyl)−5−methyl−4−methylene−hepta−1,6−dien−3−ol (21): The compound **21** was synthesized from **20** using a procedure similar to that described for the preparation of **4** as a colorless oil: yield 77%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.97−5.78 (m, 2H), 5.33−5.21 (m, 2H), 5.14−4.93 (m, 4H), 4.67 (s, 1H), 3.65 (d, J = 9.3 Hz, 1H), 3.49 (d, J = 9.9 Hz, 1H), 1.11 (s, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.45, 143.39, 139.89, 115.37, 114.04, 113.01, 70.84, 70.19, 47.42, 25.82, 22.27, 18.28, −5.52; Anal. Calcd. for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.70.

(±)−4−(*tert*−Butyldimethylsilanyloxymethyl)−4−methyl−5−methylenecyclo−pent−2−enol (22): The compound **22** was synthesized from **21** using a procedure similar to that described for the preparation of **5** as a colorless oil: yield **22*α*** (37%) and **22*β*** (36%) as a colorless oils, respectively. Cyclopentenol **22*β*:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98 (dd, J = 6.0 Hz, 2.7 Hz, 1H), 5.67 (d, J = 5.7 Hz, 1H), 5.36 (s, 1H), 5.07 (s, 1H), 4.76 (d, J = 10.5 Hz, 1H), 3.47 (d, J = 9.3 Hz, 1H), 3.42 (d, J = 9.0 Hz, 1H), 1.09 (s, 3H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}H NMR ($CDCl_3$, 75 MHz) δ 140.39, 132.74, 109.39, 70.57, 52.03, 26.02, 21.45, −5.42. Cyclopentenol **22*α*:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.89−5.83 (m, 2H), 5.37 (s, 1H), 5.11 (s, 1H), 5.05 (d, J = 7.2 Hz, 1H), 3.40 (d, J = 9.6 Hz, 1H), 3.36 (d, J = 9.0 Hz, 1H), 1.17 (s, 3H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}H NMR ($CDCl_3$, 75 MHz) δ 159.42, 140.76, 132.23, 108.65, 78.15, 70.94, 52.79, 25.85, 18.27, −5.47; Anal. Calcd. for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30.

(±)−9−[4−(*tert*−Butyldimethylsilanyloxymethyl)−4−methyl−5−methylene−cyclopent−2−enyl]−6−chloropurine (23): The compound **23** was synthesized from **22*α*** using a procedure similar to that described for the preparation of **6** as a colorless oil: yield 36%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 7.99 (s,

1H), 6.17 (s, 2H), 5.75 (s, 1H), 5.23 (d, J = 15.9 Hz, 1H), 5.08 (d, J = 17.4 Hz, 1H), 3.57 (d, J = 9.6 Hz, 1H), 3.33 (d, J = 9.6 Hz, 1H), 1.18 (s, 3H), 0.80 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.06, 149.37, 145.63, 144.84, 143.53, 130.88, 129.27, 128.37, 107.76, 67.36, 58.67, 42.40, 25.87, 18.30, 16.50, −5.57; Anal. Calcd. for $C_{19}H_{27}ClN_4OSi$: C, 58.37; H, 6.96; N, 14.33.

(±)-9-[4-(*tert*-Butyldimethylsilanyloxymethyl)-4-methyl-5-methylene-cyclopent-2-enyl]adenine (24): The compound **24** was synthesized from **23** using a procedure similar to that described for the preparation of **8** as a white solid: yield 60%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (s, 1H), 7.94 (s, 1H), 6.25−6.19 (m, 2H), 5.78 (s, 1H), 5.21 (d, J = 16.8, 1H), 5.08 (d, J = 17.1 Hz, 1H), 3.57 (d, J = 9.6 Hz, 1H), 3.41 (d, J = 9.6 Hz, 1H), 1.22 (s, 3H), 0.89 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.17, 149.92, 143.44, 142.64, 129.21, 127.95, 67.36, 54.18, 42.02, 25.87, 18.29, 16.52, −5.52; Anal. Calcd. for $C_{19}H_{29}N_5OSi$: C, 61.42; H, 7.87; N, 18.85.

(±)-9-[4-(hydroxymethyl)-4-methyl-5-methylenecyclopent-2-enyl] adenine (25): For the desilylation of adenine analogue **25**, the reaction procedure was similar to that described for compound **7** as a white solid: yield 60%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.55 (s, 1H), 7.94 (s, 1H), 6.25−6.19 (m, 2H), 5.78 (s, 1H), 5.21 (d, J = 16.8, 1H), 5.08 (d, J = 17.1 Hz, 1H), 3.57 (d, J = 9.6 Hz, 1H), 3.41 (d, J = 9.6 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.17, 149.92, 143.44, 142.64, 129.21, 127.95, 67.36, 54.18, 42.02, 25.87; Anal. Calcd. for $C_{13}H_{15}N_5O$: C, 60.69; H, 5.88; N, 27.22.

(±)-1-[4-(*tert*-butyldimethylsilanyloxymethyl)-4-methyl-5-methylene-cyclopent-2-enyl]-N^3-benzoylthymine (26): The benzoylthymine analogue **26** was synthesized from **22*a*** using a similar reaction procedure as that described for compound **6** as a colorless oil: yield 43%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (d, J = 7.2 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.09 (s, 1H), 6.30−6.25 (m, 2H), 6.06 (s, 1H), 4.64 (s, 2H), 3.57 (d, J = 9.3 Hz, 1H), 3.43 (d, J = 9.6 Hz, 1H), 1.96 (s, 3H), 1.20 (s, 3H), 0.89 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.63, 140.88, 134.84, 130.37, 129.08, 120.04, 25.62, 23.20, 21.67, 10.38; Anal. Calcd. for $C_{26}H_{34}N_2O_4Si$: C, 66.92; H, 7.34; N, 6.00.

(±)-1-[4-(*tert*-Butyldimethylsilanyloxymethyl)-4-methyl-5-methylene-cyclopent-2-enyl]thymine (27): The thymine derivative **27** was synthesized from **26** using a procedure similar to that described for the preparation of **13** as a white solid: yield 70%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (s, 1H), 6.31-6.24 (m, 2H), 5.97 (s, 1H), 4.66 (d, J = 17.1 Hz, 1H), 4.54 (d, J = 17.4 Hz, 1H), 3.57 (d, J = 9.6 Hz, 1H), 3.42 (d, J = 9.6 Hz, 1H), 1.92 (s, 3H), 1.20 (s, 3H), 0.89 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.50, 142.89, 140.43, 134.47, 129.15, 127.61, 70.09, 67.27, 59.12, 25.84, 21.91, 16.53; Anal. Calcd. for $C_{19}H_{30}N_2O_3Si$: C, 62.95; H, 8.34; N, 7.73.

(±)-1-(4-Hydroxymethyl-4-methyl-5-methylenecyclopent-2-enyl) thymine (28): For the desilylation of thymine analogue **28**, the reaction procedure was similar to that described for compound **7** as a white solid: yield 73%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.97 (s, 1H), 6.31-6.24 (m, 2H), 5.97 (s, 1H), 4.66 (d, J = 17.1 Hz, 1H), 4.54 (d, J = 17.4 Hz, 1H), 3.57 (d, J = 9.6 Hz, 1H), 3.42 (d, J = 9.6 Hz, 1H), 1.92 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.50, 142.89, 140.43, 134.47, 129.15, 127.61, 70.09, 67.27, 59.12, 25.84; Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28.

(±)-1-[4-(*tert*-butyldimethylsilanyloxymethyl)-4-methyl-5-methylene-cyclopent-2-enyl]- N^3-benzoyluracil (29): The benzoyluracil derivative **29** was synthesized from **22*α*** by a procedure similar to that used to prepare **6** as a colorless oil: yield 39%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, J = 6.9 Hz, 2H), 7.68-7.62 (m, 1H), 7.50 (t, J = 6.9 Hz, 2H), 7.29 (d, J = 7.8 Hz, 1H), 6.30 (d, J = 5.1, 1H), 6.25 (d, J = 5.4, 1H), 6.08 (s, 1H), 5.82 (d, J = 8.1 Hz, 1H), 4.66 (s, 2H), 3.58 (d, J = 9.6 Hz, 1H), 3.42 (d, J = 9.3 Hz, 1H), 1.19 (s, 3H), 0.89 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.19, 144.22, 143.77, 135.01, 130.42, 129.19, 128.37, 102.01, 67.24, 58.67, 46.43, 25.93, 18.29, 16.51, -5.49; Anal. Calcd. for $C_{25}H_{32}N_2O_4Si$: C, 66.34; H, 7.13; N, 6.19.

(±)-1-[4-(*tert*-Butyldimethylsilanyloxymethyl)-4-methyl-5-methylene-cyclopent-2-enyl]uracil (30): The uracil derivative **30** was synthesized from **29** using a procedure similar to that described for the preparation of **13** as a white solid: yield 72%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.69 (br s, 1H), 7.13 (d, J = 7.5 Hz, 1H), 6.23-6.18 (m, 2H), 5.96 (s, 1H), 5.66 (dd, J = 8.1 Hz, 2.4 Hz, 1H),

4.65 (d, J = 16.8 Hz, 1H), 4.54 (d, J = 17.1 Hz, 1H), 3.53 (d, J = 9.3 Hz, 1H), 3.37 (d, J = 9.6 Hz, 1H), 1.15 (s, 3H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.55, 150.65, 149.56, 144.51, 143.62, 142.92, 139.41, 129.16, 128.05, 102.02, 67.26, 58.59, 46.04, 25.85, 18.28, 16.51, −5.52; Anal. Calcd. for $C_{18}H_{28}N_2O_3Si$: C, 62.03; H, 8.01; N, 8.04.

(±)−1−(4−Hydroxymethyl−4−methyl−5−methylenecyclopent−2−enyl)uracil (31): The uracil derivative **31** was synthesized from **30** by a procedure similar to that used in the preparation of **7** as a white solid: yield 70%; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 7.08 (d, J = 8.0 Hz, 1H), 5.97 (s, 1H), 5.58 (d, J = 8.1, 1H), 5.44 (d, J = 7.5 Hz, 1H), 5.27 (s, 1H), 4.81−4.73 (m, 2H), 1.13 (s, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 171.61, 157.55, 153.75, 150.35, 140.75, 131.33, 113.46, 99.38, 57.42, 55.35, 48.95, 9.80; Anal. Calcd. for $C_{12}H_{14}N_2O_3$, C, 61.53; H, 6.02; N, 11.96.

(±)−3−(*tert*−Butyldimethylsilanyloxymethyl)−3−phenylpent−4−enal (33): The aldehyde analogue **33** was synthesized from **32** using a similar reaction procedure as that described for compound **19** as a colorless oil; yield 71%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.63 (s, 1H), 7.34−7.26 (m, 5H), 6.09 (dd, J = 17.7 Hz, 11.1 Hz, 1H), 5.34 (d, J = 11.1 Hz, 1H), 5.16 (d, J = 17.4 Hz, 1H), 3.86 (s, 2H), 2.97 (dq, J = 16.2 Hz, 3.0 Hz, 1H), 0.88 (s, 9H), −0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.86, 142.38, 141.49, 128.38, 127.33, 126.83, 115.70, 69.28, 49.01, 25.76, 18.19, −5.74; Anal. Calcd. for $C_{18}H_{28}O_2Si$: C, 71.00; H, 9.27.

(±)−3−(*tert*−Butyldimethylsilanyloxymethyl)−2−methylene−3−phenylpent−4−enal (34): The compound **34** was synthesized from **33** using a procedure similar to that described for the preparation of **20** as a colorless oil; yield 58%; Without further purification, compound **34** was subject to next reaction.

(±)−5−(*tert*−Butyldimethylsilanyloxymethyl)−4−methylene−5−phenyl−hepta−1,6−dien−3−ol (35): The compound **35** was synthesized from **34** using a procedure similar to that described for the preparation of **21** as a colorless oil: yield 77%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23−7.05 (m, 5H), 6.25−6.16 (m, 1H), 5.82−5.73 (m, 1H), 5.50 (s, 1H), 5.23 (s, 2H), 5.05−4.99 (m, 2H), 4.43 (dd, J = 17.7 Hz, 1.2 Hz, 1H), 4.31 (d, J = 4.5 Hz, 1H), 4.20 (d, J = 9.9 Hz, 1H), 4.06 (d, J = 9.9 Hz, 1H), 0.79 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 Mz) δ

152.66, 142.61, 140.66, 139.24, 128.29, 127.31, 126.78, 118.52, 115.94, 113.88, 70.98, 67.93, 25.79, 18.22, −5.52; Anal. Calcd. for $C_{21}H_{32}O_2Si$: C, 73.20; H, 9.36.

(±)−4−(*tert*−Butyldimethylsilanyloxymethyl)−5−methylene−4−phenylcyclo−pent−2−enol (36): The compound **36** was synthesized from **35** using a procedure similar to that described for the preparation of **22** as a colorless oil: yield **36α** (36%) and **36β** (35%) as a colorless oils, respectively. Cyclopentenol **36β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26−7.12 (m, 5H), 6.08 (dd, J = 5.7 Hz, 1.8 Hz, 1H), 5.86 (d, J = 5.7 Hz, 1H), 5.41 (s, 1H), 4.95 (s, 1H), 4.87 (dd, J = 11.1 Hz, 1.5 Hz, 1H), 3.98 (d, J = 9.0 Hz, 1H), 3.89 (d, J = 9.0 Hz, 1H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}H NMR ($CDCl_3$, 75 MHz) δ 157.20, 142.93, 138.74, 133.94, 128.29, 126.62, 112.28, 68.63, 60.04, 25.97, 18.51, −5.40. Cyclopentenol **36α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.18 (m, 5H), 6.09 (t, J = 7.5 Hz, 2H), 5.48 (d, J = 1.2 Hz, 1H), 5.10 (s, 1H), 5.02 (d, J = 2.1 Hz, 1H), 4.01 (d, J = 9.3 Hz, 1H), 3.85 (d, J = 9.6 Hz, 1H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}H NMR ($CDCl_3$, 75 MHz) δ 158.13, 144.00, 139.45, 133.17, 128.16, 126.98, 126.33, 112.08, 68.94, 60.45, 25.75, 18.19, −5.52; Anal. Calcd. for $C_{19}H_{28}O_2Si$: C, 72.10; H, 8.92.

(±)−9−[4−(*tert*−Butyldimethylsilanyloxymethyl)−5−methylene−4−phenyl−cyclopent−2−enyl]−6−chloropurine (37): The compound **37** was synthesized from **36α** using a procedure similar to that described for the preparation of **23** as a colorless oil: yield 37%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.76 (s, 1H), 8.31 (s, 1H), 7.39−7.29 (m, 5H), 6.45 (d, J = 5.7 Hz, 1H), 6.36 (s, 1H), 6.04 (dd, J = 5.7 Hz, 1.5 Hz, 1H), 5.33 (s, 1H), 5.16 (s, 1H), 4.13 (d, J = 9.9 Hz, 1H), 4.07 (d, J = 9.6 Hz, 1H), 0.87 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.11, 151.98, 144.70, 142.38, 139.32, 128.71, 128.65, 127.69, 127.12, 126.58, 126.40, 96.96, 69.40, 61.88, 31.60, 26.01, 14.04, −5.32; Anal. Calcd. for $C_{24}H_{29}ClN_4OSi$: C, 63.63; H, 6.45; N, 12.37.

(±)−9−[4−(*tert*−Butyldimethylsilanyloxymethyl)−5−methylene−4−phenyl−cyclopent−2−enyl]adenine (38): The compound **38** was synthesized from **37** using a procedure similar to that described for the preparation of **24** as a white solid: yield 58%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.50 (s, 1H), 8.30 (s, 1H), 7.34−7.17 (m, 5H), 6.36 (d, J = 5.7 Hz, 1H), 6.26 (t, J = 2.1 Hz, 1H), 5.97 (dd, J = 6.0 Hz, 2.1 Hz, 1H), 5.23 (d, J = 2.4 Hz, 1H), 5.09 (s, 1H), 0.81 (s, 9H), −

0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.09, 152.52, 152.08, 142.31, 141.54, 140.84, 128.54, 128.16, 126.72, 121.50, 114.25, 113.10, 69.49, 62.64, 54.18, 25.81, 18.56, −5.37; Anal. Calcd. for $C_{24}H_{31}5_5OSi$: C, 66.48; H, 7.21; N, 16.15.

(±)−9−[4−(hydroxymethyl)−5−methylene−4−phenylcyclopent−2−enyl] adenine (39): For the desilylation of adenine analogue **39**, the reaction procedure was similar to that described for compound **25** as a white solid: yield 62%; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.48 (s, 1H), 8.06 (s, 1H), 7.38−7.27 (m, 5H), 6.51 (d, J = 3.6 Hz, 1H), 6.12 (t, J = 2.1 Hz, 1H), 6.04 (d, J = 5.7 Hz, 1H), 5.50 (s, 1H), 5.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.20, 151.52, 150.22, 142.05, 141.34, 140.55, 129.09, 128.66, 127.41, 126.44, 125.97, 113.74, 69.59, 61.54, 54.35; Anal. Calcd. for $C_{18}H_{17}N_5O$: C, 67.70; H, 5.37; N, 21.93.

(±)−1−[4−(*tert*−butyldimethylsilanyloxymethyl)−5−methylene−4−phenyl−cyclopent−2−enyl]−N^3−benzoylthymine (40): The benzoylthymine analogue **40** was synthesized from **36*α*** using a similar reaction procedure as that described for compound **23** as a colorless oil: yield 42%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, J = 6.9 Hz, 2H), 7.65 (t, J = 7.5 Hz, 1H), 7.53−7.48 (m, 2H), 7.40 (s, 1H), 7.31−7.22 (m, 5H), 6.43 (dd, J = 5.4 Hz, 2.1 Hz, 1H), 6.20 (s, 1H), 5.88 (dd, J = 6.0 Hz, 1.8 Hz, 1H), 5.40 (d, J = 10.5 Hz, 1H), 5.33 (d, J = 10.5 Hz, 1H), 4.04 (d, J = 10.2 Hz, 1H), 4.48 (d, J = 10.2 Hz, 1H), 1.94 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.11, 162.96, 150.99, 150.55, 142.51, 141.88, 141.80, 137.31, 134.90, 130.42, 129.11, 128.55, 127.04, 126.65, 112.29, 111.12, 69.12, 62.77, 60.89, 25.96, 12.50, −5.38; Anal. Calcd. for $C_{31}H_{36}N_2O_4Si$: C, 70.42; H, 6.86; N, 5.30.

(±)−1−[4−(*tert*−Butyldimethylsilanyloxymethyl)−5−methylene−4−phenyl−cyclopent−2−enyl]thymine (41): The thymine derivative **41** was synthesized from **40** using a procedure similar to that described for the preparation of **27** as a white solid: yield 70%; NMR ($CDCl_3$, 300 MHz) δ 8.39 (br s, 1H), 7.32 (d, J = 4.5 Hz, 1H), 7.27 (d, J = 4.5 Hz, 2H), 7.25−7.16 (m, 2H), 7.02 (d, J = 1.2 Hz, 1H), 6.35 (dd, J = 6.0 Hz, 1.5 Hz, 1H), 6.18−6.14 (m, 1H), 5.80 (dd, J = 5.7 Hz, 1.5 Hz, 1H), 5.30 (d, J = 3.0 Hz, 1H), 5.20 (d, J = 2.1 Hz, 1H), 3.97 (d, J = 9.9 Hz, 1H), 3.92 (d, J = 10.5 Hz, 1H), 1.86 (s, 3H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C

NMR ($CDCl_3$, 75 MHz) δ 163.71, 151.19, 141.96, 141.54, 137.76, 128.52, 127.00, 126.69, 126.39, 114.37, 111.95, 111.08, 69.07, 62.57, 60.63, 25.93, 18.53, 12.41, −5.41; Anal. Calcd. for $C_{24}H_{32}N_2O_3Si$: C, 67.89; H, 7.60; N, 6.60.

(±)-1-(4-Hydroxymethyl-5-methylene-4-phenylcyclopent-2-enyl) thymine (42): For the desilylation of thymine analogue **42**, the reaction procedure was similar to that described for compound **25** as a white solid: yield 69%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.46-7.26 (m, 5H), 6.41 (dd, J = 5.7 Hz, 1.8 Hz, 1H), 6.05 (dt, J = 11.4 Hz, 2.1 Hz, 1H), 5.97 (dd, J = 5.7 Hz, 2.1 Hz, 1H), 5.38 (d, J = 2.4 Hz, 1H), 5.20 (d, J = 1.5 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.28, 154.09, 152.83, 151.75, 143.29, 141.79, 138.59, 137.40, 128.65, 126.44, 112.25, 109.54, 67.36, 62.06, 60.82; Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03.

(±)-1-[4-(*tert*-butyldimethylsilanyloxymethyl)-5-methylene-4-phenyl-cyclopent-2-enyl]-N^3-benzoyluracil (43): The benzoyluracil derivative **43** was synthesized from **36*α*** by a procedure similar to that used to prepare **23** as a colorless oil: yield 40%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97-7.94 (m, 2H), 7.70-7.64 (m, 1H), 7.52 (t, J = 8.1 Hz, 2H), 7.40-7.31 (m, 4H), 7.27 (s, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.43 (dd, J = 6.0 Hz, 1.5 Hz, 1H), 6.25 (t, J = 2.1, 1H), 6.00 (dd, J = 6.0, 2.4 Hz, 1H), 5.68 (d, J = 8.1 Hz, 1H), 5.42 (s, 1H), 5.29 (d, J = 2.1 Hz, 1H), 4.02 (d, J = 9.6 Hz, 1H), 3.94 (d, J = 9.6 Hz, 1H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.88, 162.10, 152.24, 150.41, 142.82, 142.14, 141.25, 135.05, 131.49, 130.46, 129.16, 128.71, 128.36, 127.08, 126.54, 114.62, 102.49, 69.63, 63.51, 61.03, 25.97, 18.16, −5.57; Anal. Calcd. for $C_{30}H_{34}N_2O_4Si$: C, 70.01; H, 6.66; N, 5.44.

(±)-1-[4-(*tert*-Butyldimethylsilanyloxymethyl)-5-methylene-4-phenyl-cyclopent-2-enyl]uracil (44): The uracil derivative **44** was synthesized from **43** using a procedure similar to that described for the preparation of **27** as a white solid: yield 68%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.84 (br s, 1H), 7.36-7.25 (m, 5H), 6.84 (d, J = 8.1 Hz, 1H), 6.37 (dd, J = 6.3 Hz, 1.5 Hz, 1H), 6.26 (t, J = 2.1 Hz, 1H), 5.93 (dd, J = 5.7 Hz, 1.8 Hz, 1H), 5.56 (dd, J = 8.1 Hz, 2.4 Hz, 1H), 5.32 (s, 1H), 5.19 (s, 1H), 4.01 (d, J = 9.6 Hz, 1H), 3.90 (d, J = 9.6 Hz, 1H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.04, 152.46, 151.27,

142.47, 142.24, 141.57, 128.62, 126.96, 126.60, 114.34, 102.57, 69.64, 63.14, 60.95, 25.94, 18.19, −5.56; Anal. Calcd. for $C_{23}H_{30}N_2O_3Si$: C, 67.28; H, 7.36; N, 6.82.

(±)−1−(4−Hydroxymethyl−5−methylene−4−phenylcyclopent−2−enyl)uracil (45): The uracil derivative **45** was synthesized from **44** by a procedure similar to that used in the preparation of **25**: yield 69%; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 11.34 (br s, 1H), 7.37−7.29 (m, 4H), 7.24−7.19 (m, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.30 (dd, J = 6.0 Hz, 2.1 Hz, 1H), 6.05−5.97 (m, 2H), 5.53 (d, J = 8.1 Hz, 1H), 5.00−4.95 (m, 2H), 3.92−3.86 (m, 1H), 3.77−3.71 (m, 1H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 163.53, 154.55, 151.58, 143.20, 141.80, 129.30, 128.78, 126.98, 126.68, 126.42, 112.73, 102.26, 67.81, 62.62, 61.04; Anal. Calcd. for $C_{17}H_{16}N_2O_3$, C, 68.91; H, 5.44; N, 9.45.

(±)−1−(*tert*−Butyldimethylsilanyloxy)−pentan−3−ol (47): To a solution of **46** (2.5 g, 13.27 mmol) in dry THF (25 mL) was slowly added ethylMgBr (15.9 mL, 1.0 M solution in THF) at −20 °C and stirred 5 h at 0 °C. Saturated NH_4Cl solution (16 mL) was added to the mixture, which was slowly warmed to room temperature. The mixture was further diluted with water (80 mL) and extracted with EtOAc (2 × 80 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:6) to give **47** (2.58 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.71 (t, J = 6.8 Hz, 2H), 3.32 (m, 2H), 1.45 (m, 2H), 0.97 (t, J = 6.9 Hz, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.7, 58.8, 42.5, 32.1, 25.5, 18.5, 9.8, -5.4.

1−(*tert*−Butyldimethylsilanyloxy)−pentan−3−one (48): To a solution of compound **47** (1.39 g, 6.4 mmol) in CH_2Cl_2 (50 mL), 4Å molecular sieves (3.75 g) and PCC (3.45 g, 16.05 mmol) were added slowly at 0 °C, and stirred overnight at room temperature. To the mixture, excess diethyl ether (400 mL) was then added. The mixture was stirred vigorously for 3 h at the same temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **48** (1.08 g, 78%) as a

colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.09 (t, J = 7.0 Hz, 2H), 2.68 (t, J = 7.0 Hz, 2H), 2.52 (q, J = 7.2 Hz, 2H), 1.09 (t, J = 7.2 Hz, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.7, 60.4, 34.3, 25.6, 18.3, 10.5, -5.5.

(±)-5-(*tert*-Butyldimethylsilanyloxy)-3-ethyl-pent-1-en-3-ol (49): To a solution of **48** (2.5 g, 11.55 mmol) in dry THF (25 mL) was slowly added vinylMgBr (12.7 mL, 1.0 M solution in THF) at -20 °C and stirred 4 h at 0 °C. Saturated NH_4Cl solution (17 mL) was added to the mixture, which was slowly warmed to room temperature. The mixture was further diluted with water (80 mL) and extracted with EtOAc (2 × 80 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give **49** (2.25 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.89 (m, 1H), 5.21-5.12 (m, 2H), 3.82 (t, J = 6.2 Hz, 2H), 1.70 (t, J = 6.3 Hz, 2H), 1.45 (q, J = 6.9 Hz, 2H), 0.97 (t, J = 6.8 Hz, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.1, 112.7, 71.5, 58.9, 46.2, 34.6, 25.5, 18.5, 11.8, -5.6; Anal. Calc. for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.55; Found: C, 63.92; H, 11.52.

(±)-*tert*-Butyl-[3-ethyl-3-(4-methoxybenzyloxy)-pent-4-enyloxy]-dimethylsilane (50): NaH (60% in mineral oil, 207 mg, 83.21 mmol) was added portion-wise to a solution of alcohol **49** (3.5 g, 14.31 mmol) and PMBCl (2.46 g, 15.74 mmol) in DMF (20 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. The solvent was concentrated under reduced pressure and the residue was quenched with H_2O followed by extraction with diethyl ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **50** (4.33 g, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (m, 2H), 6.88 (m, 2H), 5.95-5.86 (m, 1H), 5.15-5.03 (m, 2H), 4.49 (s, 2H), 3.81 (s, 3H), 3.73 (t, J = 6.8 Hz, 2H), 1.65 (t, J = 6.7 Hz, 2H), 1.46 (m, 2H), 0.95 (t, J = 6.9 Hz, 3H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.3, 143.7, 136.2, 131.5, 128.7, 117.6, 112.9, 72.4, 71.2, 69.2, 58.3, 55.6, 43.1, 32.6, 25.3, 18.4, 10.6, -

5.6; Anal. Calc. for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.95; Found: C, 69.23; H, 9.89.

(±)-3-Ethyl-3-(4-methoxybenzyloxy)-pent-4-en-1-ol (51): To a solution of **50** (300 mg, 0.823 mmol) in THF (8.0 mL), TBAF (1.0 mL, 1.0 M solution in THF) was added at 0 °C. The mixture was stirred for 6 h at room temperature and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:5) to give **51** (183 mg, 89%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (m, 2H), 6.89 (m, 2H), 5.94-5.85 (m, 1H), 5.20-5.09 (m, 2H), 4.50 (s, 2H), 3.83 (s, 3H), 3.75 (t, J = 6.7 Hz, 2H), 1.66 (t, J = 6.8 Hz, 2H), 1.45 (q, J = 6.8 Hz, 2H), 0.97 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 143.8, 138.5, 132.1, 129.0, 119.2, 115.1, 71.9, 71.0, 68.3, 58.8, 54.8, 44.7, 33.1; Anal. Calc. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; Found: C, 71.94; H, 8.91.

3-Ethyl-3-(4-methoxybenzyloxy)-pent-4-enal (52): To a stirred solution of oxalyl chloride (212 mg, 1.67 mmol) in CH_2Cl_2 (10 mL) was added a solution of DMSO (195 mg, 2.5 mmol) in CH_2Cl_2 (5.0 mL) dropwise at −78 °C. The resulting solution was stirred at -78 °C for 10 min, and a solution of alcohol **51** (210 mg, 0.839 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was stirred at −78 °C for 30 min and TEA (507 mg, 5.01 mmol) was added. The resulting mixture was warmed to 0 °C and stirred for 30 min. H_2O (15 mL) was added, and the solution was stirred at room temperature for 30 min. The mixture was diluted with water (120 mL) and then extracted with EtOAc (2 × 120 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give aldehyde compound **52** (189 mg, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.82 (s, 1H), 7.30 (m, 2H), 6.91 (m, 2H), 5.93-5.85 (m, 1H), 5.20-5.11 (m, 2H), 4.49 (s, 2H), 3.78 (s, 3H), 2.55 (dd, J = 10.0. 8.2 Hz, 2H), 1.47 (q, J = 6.9 Hz, 2H), 0.98 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205, 160.0, 144.1, 138.3, 133.6, 128.9, 121.6, 114.1, 71.9, 69.1, 55.1, 32.6, 9.8.

***(rel)*-(3*R* and 3*S*,5*S*)-5-Ethyl-5-(4-methoxybenzyloxy)-hepta-1,6-dien-3-ol (53):** Divinyl analogue **53** was prepared from aldehyde **52** using the similar procedure as described for **49** as a diastereomeric mixture: yield 87%; ^{1}H NMR

($CDCl_3$, 300 MHz) δ 7.29−7.27 (m, 2H), 6.89 (m, 2H), 5.96−5.83 (m, 2H), 5.16−4.99 (m, 4H), 4.59 (s, 2H), 3.89 (m, 1H), 3.78 (s, 3H), 1.65−1.58 (m, 2H), 1.48 (m, 2H), 0.97 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.6, 143.7, 141.2, 137.5, 134.0, 127.5, 121.9, 113.1, 112.4, 71.5, 69.6, 68.2, 57.5, 47.0, 33.3, 9.6.

(*rel*)−(1*R*,4*S*)−4−ethyl−4−(4−methoxybenzyloxy)cyclopent−2−enol (54α) and (*rel*)−(1*S*,4*S*)−4−Ethyl−4−(4−methoxybenzyloxy)cyclopent−2−enol (54β): To a solution of **53** (205 mg, 0.74 mmol) in dry methylene chloride (6 mL) was added Grubbs' II catalyst (38.0 mg 0.0452 mmol). The reaction mixture was refluxed overnight and cooled to room temperature. The mixture was concentrated in *vacuo*, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give cyclopentenol **54β** (71.6 mg, 39%) and **54α** (73.5 mg, 40%). **Data for 54β:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (m, 2H), 6.88 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.36 (m, 1H), 4.68 (s, 2H), 4.08 (m, 1H), 3.79 (s, 3H), 2.16 (dd, J = 13.4. 8.8 Hz, 1H), 2.02 (dd, J = 13.4, 6.8 Hz, 1H), 1.52 (m, 2H), 0.97 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 139.3, 136.6, 134.4, 130.5, 129.6, 118.4, 78.9, 71.8, 68.6, 57.0, 42.8, 32.6, 9.4; Anal. Calc. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; Found: C, 72.58; H, 8.15. **Data for 54α:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (m, 2H), 6.91 (m, 2H), 5.58 (d, J = 5.4 Hz, 1H), 5.36 (dd, J = 5.3, 4.2 Hz, 1H), 4.69 (s, 2H), 4.03 (dd, J = 6.0, 4.8 Hz, 1H), 3.81 (s, 3H), 2.19 (dd, J = 13.6. 8.2 Hz, 1H), 2.06 (dd, J = 13.5, 7.6 Hz, 1H), 1.49 (m, 2H), 0.98 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 138.8, 135.7, 130.4, 130.5, 129.6, 117.4, 79.1, 72.3, 69.3, 56.7, 43.2, 33.4, 9.6; Anal. Calc. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; Found: C, 72.49; H, 8.08.

(*rel*)−(1'*R*,4'*S*)−9−[4−Ethyl−(4−methoxybenzyloxy)−cyclopent−2−enyl]−6−chloropurine (55): To a solution containing compound **54α** (112 mg, 0.45 mmol), PPh_3 (415 mg, 1.584 mmol), and 6−chloropurine (139 mg, 0.90 mmol) in anhydrous THF (7.0 mL), DIAD (182 mg, 0.90 mmol) was added dropwise at −20 °C for 30 min under nitrogen. The reaction mixture was stirred for 3 h at −20 °C under nitrogen and further stirred overnight at rt. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give compound **55** (74 mg,

43%): m.p. 156−158 °C; UV (MeOH) λ_{max} 264.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.72 (s, 1H), 8.44 (s, 1H), 7.30 (m, 2H), 6.90−6.87 (m, 2H), 5.64 (d, J = 5.3 Hz, 1H), 5.35 (dd, J = 5.2, 4.2 Hz, 1H), 4.64 (s, 2H), 4.43 (m, 1H), 3.80 (s, 3H), 2.21 (dd, J = 13.5. 8.4 Hz, 1H), 2.04 (dd, J = 13.6, 7.2 Hz, 1H), 1.53 (m, 2H), 0.96 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.6, 152.6, 151.3, 147.9, 141.5, 137.5, 135.3, 133.4, 117.7, 81.3, 70.9, 57.1, 54.6, 38.7, 32.6, 9.7; Anal. Calc. for $C_{20}H_{21}ClN_4O_2$ (+ 0.5 EtOAc): C, 61.60; H, 5.87; N, 13.06; Found: C, 61.56; H, 5.90; N, 13.11.

(*rel*)−(1'*R*,4'*S*)−9−(4−Ethyl−4−hydroxycyclopent−2−enyl)−6−chloropurine (56): To a solution of compound **55** (435 mg, 1.13 mmol) in CH_2Cl_2/H_2O mixture (10 mL, 10:1 v/v) was added DDQ (280 mg, 1.24 mmol) and the mixture was stirred for 4 h at room temperature. Saturated $NaHCO_3$ (1.5 mL) was added to quench the reaction and further diluted with water (80 mL). The mixture was extracted with CH_2Cl_2 (3 × 80 mL) and the combined organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 4:1:0.04) to give compound **56** (200 mg, 67%): m.p. 169−171 °C; UV (MeOH) λ_{max} 264.0 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.75 (s, 1H), 8.46 (s, 1H), 5.59 (d, J = 5.2 Hz, 1H), 5.36 (m, 1H), 5.09 (s, 1H), 4.50 (m, 1H), 2.25 (dd, J = 13.6. 8.5 Hz, 1H), 2.06 (dd, J = 13.5, 7.4 Hz, 1H), 1.51 (m, 2H), 0.98 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 152.3, 151.6, 150.5, 148.2, 138.5, 136.6, 132.4, 76.8, 52.9, 40.3, 34.3, 9.3; Anal. Calc. for $C_{12}H_{13}ClN_4O$: C, 54.45; H, 4.95; N, 21.17; Found: C, 54.51; H, 4.91; N, 21.21.

(*rel*)−(1'*R*,4'*S*)−Diethyl−[9−(4−hydroxy−4−ethylcyclopent−2−en−1−yl)−6−chloropurine]methylphosphonate (57): Both LiO*t*−Bu (2.084 mL of 0.5 M solution in THF, 1.042 mmol) and a solution of diethyl phosphonomethyltriflate (313 mg, 1.042 mmol) in 10.0 mL of THF were slowly added to a solution of the 6−chloropurine analogue **56** (138 mg, 0.521 mmol) in 5.0 mL of THF at 0 °C and stirred overnight at rt under anhydrous conditions. The mixture was quenched by adding saturated NH_4Cl solution (3 mL) and further diluted with additional H_2O (80 mL). The aqueous layer was extracted with EtOAc (3 × 80 mL). The

combined organic layer was dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (MeOH/Hexane/EtOAc, 0.05:4:1) to give **57** (153 mg, 71%): m.p. 142−144 °C; UV (MeOH) λ_{max} 265.0 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.74 (s, 1H), 8.48 (s, 1H), 5.62 (d, J = 5.4 Hz, 1H), 5.35 (m, 1H), 4.51 (m, 1H), 4.18 (m, 4H), 4.09 (d, J = 8.0 Hz, 2H), 2.28 (dd, J = 13.6. 8.7 Hz, 1H), 2.04 (dd, J = 13.6, 7.5 Hz, 1H), 1.52 (m, 2H), 1.36 (m 6H), 0.98 (m, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 152.3, 151.9, 149.3, 146.6, 145.7, 136.5, 132.6, 81.8, 66.5, 65.2, 63.6, 54.1, 38.2, 32.5, 16.8, 9.6; Anal. Calc. for $C_{17}H_{24}ClN_4O_4P$ (+ 1.0 MeOH): C, 48.38; H, 6.31; N, 12.54; Found: C, 48.44; H, 6.27; N, 12.49.

(*rel*)−(1'*R*,4'*S*)−Diethyl−[9−(4−hydroxy−1,4−dimethylcyclopent−2−en−1−yl) adenine]methylphosphonate (58): A solution of **57** (132 mg, 0.318 mmol) in saturated methanolic ammonia (8 mL) was stirred at 70 °C in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:10) to give **58** (74 mg, 59%): m.p. 171−173 °C; UV (MeOH) λ_{max} 260.5 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.32 (s, 1H), 8.12 (s, 1H), 7.17 (br s, 2H), 5.67 (d, J = 5.2 Hz, 1H), 5.31 (dd, J = 5.3, 4.2 Hz, 1H), 4.52 (m, 1H), 4.17 (m, 4H), 4.05 (d, J = 8.2 Hz, 2H), 2.26 (dd, J = 13.5. 8.8 Hz, 1H), 2.05 (m, 1H), 1.51 (m, 2H), 1.34 (m 6H), 0.98 (t, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 155.0, 153.3, 144.2, 137.7, 134.2, 131.8, 119.2, 82.4, 67.1, 66.0, 64.2, 54.5, 39.1, 33.7, 17.2, 9.9; Anal. Calc. for $C_{17}H_{26}N_5O_4P$ (+ 0.5 MeOH): C, 51.09; H, 6.86; N, 17.02; Found: C, 51.15; H, 6.92; N, 16.98.

(*rel*)−(1'*R*,4'*S*)−[9−(4−Ethylcyclopenten−1−yl)−adenine]−4−methylphosphonic acid (59): To a solution of the phosphonate **58** (125 mg, 0.316 mmol) in anhydrous CH_3CN (10 mL) and 2,6−lutidine (0.8 mL) was added trimethylsilyl bromide (483 mg, 3.16 mmol). The mixture was heated overnight at 60 °C and then concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 (70 mL) and distilled clean water (60 mL). The aqueous layer was washed out with CH_2Cl_2 two times and then freeze−dried to give phosphonic acid **59** (73 mg, 68%) in a yellowish form: UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.29 (s, 1H), 8.11 (s, 1H), 7.16 (br s, 2H), 5.64 (d, J

= 5.3 Hz, 1H), 5.32 (dd, *J* = 5.4, 4.2 Hz, 1H), 4.50 (m, 1H), 4.11 (d, *J* = 8.0 Hz, 2H), 2.29 (m, 1H), 2.02 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.52 (m, 2H), 0.96 (m, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.7, 152.9, 142.7, 136.8, 135.5, 132.7, 120.1, 81.9, 65.2, 56.3, 38.7, 34.1, 9.6; Anal. Calc. for $C_{13}H_{18}N_5O_4P$ (+ 2.0 H_2O): C, 41.60; H, 5.91; N, 18.66; Found: C, 41.56; H, 5.92; N, 18.59.

(*rel*)−(1'*R*,2'*S*,3'*S*,4'*S*)−Diethyl−[9−(2,3−dihydroxy−4−ethylcyclopent−1−yl) adenine]−4−methylphosphonate (60) and (*rel*)−(1'*R*,2'*R*,3'*R*,4'*S*)−Diethyl−[9−(2,3−dihydroxy−4−ethyl−cyclopent−1−yl)adenine]−4−methylphosphonate (61): Compound **58** (158 mg, 0.4 mmol) was dissolved in a cosolvent system (10 mL) (acetone/*t*−BuOH/H_2O = 6:1:1) along with NMO (82 mg, 0.8 mmol). Subsequently, OsO_4 (0.19 mL, 0.03 mmol, 4% wt % in H_2O) was added. The mixture was stirred overnight at rt and quenched with saturated Na_2SO_3 solution (3 mL). The resulting solid was removed by filtration through a pad of Celite, and filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:6) to give **60** (58 mg, 34%) and **61** (49 mg, 29%): **Spectroscopical data for 60:** ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.30 (s, 1H), 8.13 (s, 1H), 7.15 (br s, 2H), 4.25 (m, 4H), 4.14 (d, *J* = 8.2 Hz, 2H), 3.75−3.68 (m, 2H), 3.32 (m, 1H), 2.13 (dd, *J* = 13.6, 8.7 Hz, 1H), 1.94 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.48 (m, 2H), 1.31 (m 6H), 0.98 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.6, 153.2, 147.7, 138.4, 119.3, 78.4, 77.6, 69.1, 66.2, 65.1, 63.7, 48.6, 28.8, 26.4, 17.1, 9.9; Anal. Calc. for $C_{17}H_{28}N_5O_6P$ (+ 1.0 MeOH): C, 46.85; H, 6.99; N, 15.17; Found: C, 46.91; H, 7.05; N, 15.13. **Spectroscopical data for 61:** ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.34 (s, 1H), 8.15 (s, 1H), 7.17 (br s, 2H), 4.27(m, 4H), 4.12 (d, *J* = 8.1 Hz, 2H), 3.76 (dd, *J* = 6.4, 5.2 Hz, 1H), 3.66 (d, *J* = 6.0 Hz, 1H), 3.25 (m, 1H), 2.15 (dd, *J* = 13.7, 8.8 Hz, 1H), 1.96 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.50 (m, 2H), 1.32 (m 6H), 0.97 (m, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.5, 151.7, 146.8, 134.6, 120.7, 79.3, 76.2, 68.5, 65.8, 64.2, 63.0, 47.3, 30.6, 27.5, 16.8, 9.5; Anal. Calc. for $C_{17}H_{28}N_5O_6P$ (+ 1.0 MeOH): C, 46.85; H, 6.99; N, 15.17; Found: C, 46.79; H, 6.95; N, 15.20.

(*rel*)−(1'*R*,2'*S*,3'*S*,4'*S*)−[9−(2,3−Dihydroxy−4−ethylcyclopent−1−yl)adenine] 4−methylphosphonic acid (62): The final adenosine phosphonic acid **62** was synthesized from **60** using a similar procedure described for **59** as a formy solid:

yield 60%; UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.29 (s, 1H), 8.14 (s, 1H), 3.98 (d, J = 8.0 Hz, 2H), 3.78 (m, 1H), 3.68 (d, J = 6.1 Hz, 1H), 3.22 (m, 1H), 2.13 (dd, J = 13.8, 8.7 Hz, 1H), 1.95 (dd, J = 13.8, 7.6 Hz, 1H), 1.51 (m, 2H), 0.95 (m, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.9, 152.5, 147.4, 132.8, 119.6, 78.6, 77.3, 67.8, 64.9, 63.1, 48.1, 31.4, 28.8, 10.0; Anal. Calc. for $C_{13}H_{20}N_5O_6P$ (+ 3.0 H_2O): C, 36.54; H, 6.13; N, 16.39; Found: C, 36.49; H, 6.08; N, 16.44.

1−But−3−enyloxymethyl−4−methoxybenzene (64): NaH (60% in mineral oil, 3.33 g, 83.21 mmol) was added portion wise to a cooled (0 °C) solution of but−3−en−1−ol **63** (5.0 g, 69.34 mmol) and PMBCl (10.34 mL, 76.27 mmol) in DMF (100 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was quenched with H_2O followed by extraction with EtOAc two times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **64** (12.93 g, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (m, 2H), 6.87 (m, 2H), 5.87−5.97 (m, 1H), 5.13−5.01 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.49 (t, J = 6.7 Hz, 2H), 2.36 (q, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.12, 135.29, 130.52, 129.24, 116.28, 113.74, 72.53, 69.28, 55.25, 34.21.

3−(4−Methoxybenzyloxy)−propionaldehyde (65): A solution of compound **64** (3.7 g, 19.25 mmol) in anhydrous CH_2Cl_2 (50 mL) was cooled down to −78 °C, and ozone gas was then bubbled into the reaction mixture until a blue color persisted for an additional 5 min. The reaction mixture was degassed with nitrogen, and dimethyl sulfide (5.94 mL, 80.83 mmol) was slowly added at −78 °C. The mixture was stirred for 1 h at −78 °C under argon gas and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give compound **65** (2.99 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.78 (s, 1H), 7.26 (m, 2H), 6.88 (m, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.59 (t, J = 6.1 Hz, 2H), 2.02 (q, J = 6.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.26, 159.20, 130.09, 129.34, 113.79, 72.78, 64.90, 55.25, 32.15.

(±)-5-(4-Methoxybenzyloxy)-pent-1-en-3-ol (66): To a solution of **65** (2.4 g, 12.36 mmol) in dry THF (35 mL) was slowly added vinylMgBr (18.53 mL, 1.0 M solution in THF) at −78 °C. After 5 h, saturated NH_4Cl solution (20 mL) was added, and the reaction mixture was slowly warmed to room temperature. The mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL) two times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give **66** (2.09 g, 76%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, J = 6.7 Hz, 2H), 6.88 (d, J = 6.6 Hz, 2H), 5.92−5.81 (m, 1H), 5.26 (d, J = 13.8 Hz, 1H), 5.10 (d, J = 7.2 Hz, 1H), 4.44 (s, 2H), 3.80 (s, 3H), 3.69−3.57 (m, 2H), 2.90 (s, 1H), 1.86−1.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.27, 140.52, 130.00, 129.33, 114.31, 113.83, 72.95, 71.97, 68.07, 55.27, 36.25; Anal. Calc. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.26; H, 8.20.

(±)-*tert*-Butyl-{1-[2-(4-methoxybenzyloxy) ethyl] allyloxy} dimethylsilane (67): TBDMSCl (0.97 g, 6.43 mmol) was added slowly to a solution of **66** (1.3 g, 5.85 mmol) and imidazole (0.60 g, 8.77 mmol) in CH_2Cl_2 (20 mL) at 0 °C, and stirred for 5 h at the same temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in water 100 mL) and extracted with diethyl ether (100 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **67** (1.71 g, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, J = 6.9 Hz, 2H), 6.84 (d, J = 6.6 Hz, 2H), 5.79−5.71 (m, 1H), 5.11 (d, J = 17.1 Hz, 1H), 4.98 (d, J = 10.5 Hz, 1H), 4.45−4.32 (m, 2H), 4.25 (q, J = 6.2 Hz, 1H), 3.77 (s, 3H), 3.55−3.41 (m, 2H), 1.73 (q, J = 13.2 Hz, 2H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.09, 141.59, 130.62, 129.29, 113.71, 113.65, 72.62, 70.75, 66.39, 55.24, 38.08, 25.85, 18.18, -4.67; Anal. Calc. for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.58. Found: C, 67.88; H, 9.54.

(±)-3-(*tert*-Butyldimethylsilanyloxy)-pent-4-en-1-ol (68): To a solution of compound **67** (0.76 g, 2.26 mmol) in CH_2Cl_2/H_2O mixture (10 mL, 20:1 v/v) was added DDQ (0.56 g, 2.48 mmol) and the mixture was stirred for 2 h at room

temperature. Saturated $NaHCO_3$ (2 mL) was added to quench the reaction and further diluted with water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give compound **68** (0.43 g, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.91–5.79 (m, 1H), 5.22 (d, J = 17.4 Hz, 1H), 5.07 (d, J = 10.2 Hz, 1H), 4.42 (q, J = 4.5 Hz, 1H), 3.82–3.69 (m, 2H), 2.44 (br s, 1H), 1.89–1.66 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.60, 114.39, 73.20, 60.10, 39.10, 25.80, 18.09, -5.07; Anal. Calc. for $C_{11}H_{24}O_2Si$: C, 61.05; H, 11.18. Found: C, 60.98; H, 11.21.

(±)-3-(*tert*-Butyldimethylsilanyloxy)-pent-4-enal (69): 4Å MS (3.0 g) and PCC (2.99 g, 13.86 mmol) were added slowly to a solution of compound **68** (1.2 g, 5.55 mmol) in CH_2Cl_2 (15 mL) at 0 °C, and stirred overnight at room temperature. An excess of diethyl ether (20 mL) was then added to the mixture. The mixture was stirred vigorously for 2 h at the same temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **69** (0.95 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.77 (s, 1H), 5.93–5.82 (m, 1H), 5.26 (d, J = 17.4 Hz, 1H), 5.12 (d, J = 10.2 Hz, 1H), 4.65 (q, J = 5.4 Hz, 1H), 2.65–2.48 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.59, 139.82, 114.85, 69.38, 51.19, 25.68, 18.05, -5.07; Anal. Calc. for $C_{11}H_{22}O_2Si$: C, 61.63; H, 10.34. Found: C, 61.66; H, 10.29.

(*rel*)-5-(*tert*-Butyldimethylsilanyloxy)-2-methyl-hepta-1,6-dien-3-ol (70): To a solution of compound **69** (0.25 g, 1.17 mmol) in dry THF (4 mL), isopropenylMgBr (3.50 mL, 1.0 M solution in THF) was added slowly at -78 °C. After 3 h, a saturated NH_4Cl solution (4 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc/water two times. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **70** (0.24 g, 80%) as a diastereomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81–5.71 (m, 1H), 5.20–4.98 (m,

4H), 4.42−4.15 (m, 2H), 1.67 (m, 5H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.28, 140.75, 114.61, 110.28, 74.65, 72.19, 43.28, 25.82, 18.37, 18.06, -4.84; Anal. Calc. for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 66.61; H, 10.97.

(*rel*)−(1*S*,4*S*)−4−(*tert*−Butyldimethylsilanyloxy)−2−methylcyclopent−2−enol (71α) and (*rel*)−(1*R*,4*S*)−4−(*tert*−Butyldimethylsilanyloxy)−2−methylcyclopent−2−enol (71β): To a solution of **70** (254 mg, 0.99 mmol) in dry benzene (3 mL) was added Grubbs' II catalyst (10 mg). The reaction mixture was refluxed overnight at 100 °C, and cooled to room temperature. The mixture was concentrated in vacuum, and residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give cyclopentenol **71α** (97 mg, 43%) and **71β** (95 mg, 42%) as colorless oils. Cyclopentenol **71α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.43 (s, 1H), 4.51 (m, 1H), 4.23 (m, 1H), 1.93 (s, 3H), 1.82−1.70 (m, 2H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.96, 130.92, 73.94, 45.13, 29.68, 25.92, 18.20, 13.52, −4.64; Anal. Calc. for $C_{12}H_{24}O_2Si$: C, 63.10; H, 10.59. Found: C, 63.02; H, 10.52. Cyclopentenol **71β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.40 (s, 1H), 4.53 (m, 1H), 4.23 (m, 1H), 1.99 (s, 3H), 1.88−1.72 (m, 2H), 0.83 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.02, 130.98, 74.00, 45.43, 28.54, 25.72, 18.65, 13.81, -5.31; Anal. Calc. for $C_{12}H_{24}O_2Si$: C, 63.10; H, 10.59. Found: C, 63.14; H, 10.63.

(*rel*)−(1*R*,4*S*)−9−[4−(*tert*−Butyldimethylsilanyloxy)−2−methylcyclopent−2−enyl]−N^6,N^6−bis−(*tert*−butoxycarbonyl)adenine (72): To a stirred solution of PPh_3 (518 mg, 1.98 mmol) in THF (4 mL) at 0 °C was added dropwise the DIAD (0.38 mL, 1.98 mmol) and the yellow reaction mixture was stirred at this temperature for 30 min. After that, a solution of compound **71α** (347 mg, 1.52 mmol) in THF (3.0 mL), was added and the reaction mixture was stirred at 0 °C for 10 min. Then, the cold bath was removed and the yellow solution was stirred for 30 min at room temperature. Bis−Boc adenine (662 mg, 1.98 mmol) was added and the solution became clear after 2 min. The reaction mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give **72** (522 mg, 63%) as a yellow

solid: m.p. 134–136 °C; UV (MeOH) λ_{max} 264.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.86 (s, 1H), 7.92 (s, 1H), 5.88 (s, 1H), 5.71 (s, 1H), 5.18 (s, 1H), 2.44 (t, J = 5.5 Hz, 2H), 1.63 (s, 3H), 1.46 (s, 18H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.28, 152.05, 150.53, 143.00, 139.65, 135.50, 83.72, 75.84, 62.38, 42.85, 27.79, 25.87, 13.94, -4.64; Anal. Calc. for $C_{27}H_{43}N_5O_5Si$: C, 59.42; H, 7.94; N, 12.83. Found: C, 59.39; H, 8.01; N, 12.85.

(*rel*)-(1*R*,4*S*)-[N^6,N^6-Bis-(*tert*-butoxycarbonyl)-adenine]-3-methylcyclo-pent-2-enol (73): To a solution of **72** (132 mg, 0.24 mmol) in THF (3 mL) was added TBAF (0.51 mL, 1.0 M solution in THF) at 0 °C. The mixture was stirred overnight at room temperature and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give **73** (87 mg, 83%) as a white solid: m.p. 152–154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.81 (s, 1H), 8.55 (s, 1H), 5.82 (s, 1H), 5.72 (s, 1H), 5.05 (s, 1H), 2.30–2.21 (m, 2H), 1.42 (s, 3H), 1.34 (s, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.93, 145.83, 134.89, 128.13, 83.35, 73.69, 41.00, 27.23, 21.91, 13.21; Anal. Calc. for $C_{21}H_{29}N_5O_5$: C, 58.45; H, 6.77; N, 16.23. Found: C, 58.47; H, 6.74; N, 16.27.

(*rel*)-(1*R*,4*S*)-{4-[N^6,N^6-Bis-(*tert*-butoxycarbonyl)-adenine]-3-methyl-cyclopent-2-enyloxymethyl} phosphonic acid diisopropyl ester (74): To a solution of **73** (85 g, 0.20 mmol) in DMF 2 mL), LiI (1.98 mg, 0.015 mmol) was added at 25 °C. LiO*t*-Bu (0.32 mL, 1.0 M solution in THF) and a solution of diisopropyl bromomethylphosphonate (0.06 mL, 0.24 mmol) in DMF (2 mL) were slowly and simultaneously added to the reaction mixture for 5 h at 60 °C under anhydrous conditions. The mixture was quenched by adding water (10 mL), and the organic solvents (THF) were removed in *vacuo*. The aqueous layer was extracted with EtOAc two times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give **74** (77 mg, 64%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1H), 7.81 (s, 1H), 6.00 (s, 1H), 5.82 (s, 1H), 5.73 (s, 1H), 4.83–4.73 (m, 2H), 3.24 (d, J = 9.9 Hz, 2H), 2.72–2.53 (m, 2H), 1.56 (s, 18H), 1.50 (s, 3H), 1.36 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.02, 144.93, 140.55, 129.74, 82.55, 80.21, 75.55, 72.23, 61.71, 39.11, 28.12, 27.77, 23.89, 19.89, 17.78; Anal. Calc. for $C_{28}H_{44}N_5O_8P$ (+ 0.5

MeOH): C, 54.71; H, 7.41; N, 11.19. Found: C, 54.68; H, 7.43; N, 11.21.

(*rel*)-(1*R*,4*S*)-[4-(6-Aminopurin-9-yl)-3-methylcyclopent-2-enyloxy-methyl] phosphonic acid (75): To a solution of the phosphonate **74** (67 mg, 0.11 mmol) in CH_3CN (8 mL) was added TMSBr (168 mg, 1.11 mmol). The mixture was heated overnight at 60 °C and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 (10 mL) and distilled H_2O (10 mL). The aqueous layer was washed with CH_2Cl_2 and then freezedried to give target compound **75** (23 mg, 64%) as a yellowish foamy solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.74 (s, 1H), 7.81 (s, 1H), 6.00 (s, 1H), 5.82 (m, 1H), 5.73 (m, 1H), 3.73 (d, J = 9.2 Hz, 2H), 2.72-2.53 (m, 2H), 1.50 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.24, 149.51, 145.57, 138.54, 129.74, 79.59, 69.36, 60.65, 31.61, 17.78; Anal. Calc. for $C_{12}H_{16}N_5O_4P$ (+ 2.0 H_2O): C, 39.89; H, 5.58; N, 19.38. Found: C, 39.91; H, 5.60; N, 19.41.

(*rel*)-(1*R*,4*S*)-*t*-Butyl SATE phosphoester of 9-[1-(3,4-dimethylcyclopent-3-enylmethoxymethyl)]adenine (77): A solution of adenine phosphonic acid derivative **75** (69 mg, 0.212 mmol) and tributylamine (360 μL, 1.44 mmol) in water (2.4 mL) was mixed for 40 min and concentrated under reduced pressure. The residue was thoroughly dried with anhydrous ethanol and toluene. The resulting foamy solid was dissolved in anhydrous pyridine (15 mL) to which thioester **76** (324 mg, 1.98 mmol) and 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (266 mg, 0.9 mmol) were added. The mixture was stirred for 15 h at room temperature and quenched with tetrabutylammonium bicarbonate buffer (9.0 mL, 1 M solution, pH 8.0). The mixture was concentrated under reduced pressure and the residue was diluted with water (80 mL) and extracted twice with CH_2Cl_2 (60 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (MeOH/hexane/EtOAc, 0.03:4:1) to give **77** (42 mg, 33%) as a solid: m.p. 121-123 °C; UV (H_2O) λ_{max} 262.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.24 (s, 1H), 8.12 (s, 1H), 5.89 (s, 1H), 5.76 (m, 1H), 5.32 (dd, J = 6.2, 2.4 Hz, 1H), 4.02 (m, 4H), 3.55 (d, J = 9.0 Hz, 2H), 3.16 (t, J = 6.3 Hz, 4H), 2.62-2.50 (m, 2H), 1.51 (s, 3H), 1.20 (s, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.32, 154.64, 146.32, 143.51, 139.54, 128.43, 78.81, 70.21, 62.54, 59.43,

45.12, 33.45, 30.61, 18.21; Anal. Calc. for $C_{26}H_{40}N_5O_6PS_2$ (+ 1.0 MeOH): C, 50.22; H, 6.87; N, 10.84. Found: C, 50.19; H, 6.85; N, 10.88.

(±)-2-Methylcyclopent-2-enol (79): $CeCl_3 \cdot 7H_2O$ (3.13 g, 8.4 mmol) was added to a solution of **78** (530 mg, 5.52 mmol) in MeOH (25 mL) at 0 °C and stirred for 30 min. Then, $NaBH_4$ (416 mg, 11.0 mmol) was carefully added to the mixture and stirred for 3 h at room temperature. The reaction mixture was quenched by addition of acetic acid (1.0 mL) and concentrated under reduced pressure. The resulting residue was diluted with H_2O (100 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was sequentially washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, concentrated in *vacuo*, and purified by column chromatography (EtOAc/hexane, 1:5) to give compound **79** (487 mg, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.39 (dd, J = 5.8, 2.6 Hz, 1H), 4.07 (dd, J = 6.0, 2.8 Hz, 1H), 2.34-2.22 (m, 2H), 1.94 (m, 2H), 1.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.6, 123.2, 83.9, 29.6, 26.2, 16.9.

(±)-(2-Methylcyclopent-2-enyloxymethyl)benzene (80): To a solution of enol derivative **79** (439 mg, 4.48 mmol) in dry DMF (10 mL) was slowly added NaH (129 mg, 5.37 mmol) at 0 °C. After 30 min, benzyl bromide (840 mg, 4.92 mmol) was added, and the reaction mixture was stirred for 5 h at room temperature. The mixture was quenched by adding of saturated ammonium chloride (2 mL) and concentrated in a high vacuum. The residue was diluted with water (50 mL) and with EtOAc (2 × 30 mL). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered, and evaporated. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give **80** (733 mg, 87%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.25 (m, 5H), 5.21 (m, 1H), 4.59 (s, 2H), 3.52 (dd, J = 8.4, 5.2 Hz, 1H), 2.35 (m, 2H), 2.05 (m, 2H), 1.66 (s, 3H); ^{13}C NMR($CDCl_3$) δ 138.3, 128.7, 127.5, 127.0, 126.3, 123.4, 84.2, 74.1, 27.8, 25.6, 15.9.

***(rel)*-(1*R*,2*S*,5*S*)-2-Benzyloxy-1-methyl-6-oxa-bicyclo[3.1.0]hexane (81a) and *(rel)*-(1*S*,2*S*,5*R*)-2-benzyloxy-1-methyl-6-oxa-bicyclo[3.1.0]hexane (81b):** m-Chloroperbenzoic acid (1.82 g, 7.8 mmol, 77%

purity) was added to a solution of **80** (1.12 g, 5.98 mmol) in anhydrous CH_2Cl_2 (40 mL) at 0 °C. The solution was stirred at 0 °C for 2 h and stirred for an additional 2 h at room temperature. A saturated $NaHCO_3$ solution (80 mL) was added to the reaction mixture and extracted with EtOAc (2 × 80 mL). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, concentrated in *vacuo*, and purified by column chromatography (EtOAc/hexane, 1:8) to give compound **81a** (672 mg, 55%) and **81b** (269 mg, 22%) as syrup, respectively: Compound **81a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31−7.25 (m, 5H), 4.58 (s, 2H), 3.21 (dd, J = 6.2, 4.8 Hz, 1H), 2.58 (m, 1H), 1.71−1.62 (m, 4H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.9, 128.4, 127.6, 126.2, 82.9, 75.6, 70.4, 64.4, 21.1, 16.5, 14.3; Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.41; H, 7.89; Compound **81b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.29 (m, 5H), 4.60 (s, 2H), 3.27 (dd, J = 6.4, 4.8 Hz, 1H), 2.62 (dd, J = 6.8, 5.2 Hz, 1H), 1.69−1.58 (m, 4H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.4, 128.1, 127.7, 126.4, 83.5, 76.3, 71.7, 65.7, 23.5, 17.7, 14.9; Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.48; H, 7.93.

(*rel*)−(1*S*,2*S*,3*S*)−3−Benzyloxy−2−fluoro−2−methylcyclopentanol (82): To a mixture of $(NH_4)_2SiF_6$ (1.068 g, 6.0 mmol), CsF (182.3 mg, 1.2 mmol) and epoxide **81a** (245 mg, 1.2 mmol) in 1,2−dichloroethane (15 mL) was added 47% hydrofluoric acid (0.152 mL, 3.6 mmol) and i−Pr_2NEt (0.21 mL, 1.2 mmol) at 0 °C, and the mixture was stirred for 5 h at 0 °C. A saturated $NaHCO_3$ solution (15 mL) was slowly added and the mixture was extracted with diethyl ether (2 × 80 mL). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered, and evaporated. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give alcohol **82** (129 mg, 48%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.25 (m, 5H), 4.60 (s, 2H), 3.73 (ddd, J = 2.8, 6.4, 19.8 Hz, 1H), 3.21 (dd, J = 5.4, 14.2 Hz, 1H), 1.70 (m, 2H), 1.62 (m, 2H), 1.30 (d, J = 21.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 137.8, 128.3, 127.8, 126.7, 104.2 (d, J = 180.8 Hz), 81.3 (d, J = 44.0 Hz), 76.4 (d, J = 19.2 Hz), 73.8, 20.3, 17.4, 13.4 (d, J = 22.2 Hz); Anal. Calcd. for $C_{13}H_{17}FO_2$: C, 69.62; H, 7.64. Found: C, 69.59; H, 7.61.

(*rel*)-(1*R*,2*S*,3*S*)-9-(3-Benzyloxy-2-fluoro-2-methylcyclopentan-1-yl) N^6-bis-Boc-adenine (83): To a stirred solution of PPh_3 (673 mg, 2.57 mmol) in dry THF (15 mL) at 0 °C was added dropwise the DIAD (518 mg, 2.57 mmol), and the reaction mixture was stirred at this temperature for 30 min. After that, a solution of the fluorinated alcohol **82** (287 mg, 1.28 mmol) in THF (15 mL) was added and the reaction mixture was stirred at 0 °C for 30 min. Then the cold bath was removed and the yellow solution was stirred for 30 min at room temperature. N^6-bis-Boc adenine (861 mg, 2.57 mmol) was then added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give compound **83** (450 mg, 65%) as a white solid; m.p. 167-169 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.86 (s, 1H), 7.85 (s, 1H), 7.31-7.24 (m, 5H), 4.69 (s, 2H), 4.01 (dd, J = 5.6, 17.6 Hz, 1H), 3.18 (ddd, J = 2.2, 6.0, 15.4 Hz, 1H), 2.01 (m, 2H), 1.75 (m, 2H), 1.41 (d, J = 21.8 Hz, 3H), 1.35 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 155.0, 152.3, 150.5, 147.7, 143.5, 138.3, 128.7, 128.0, 127.3, 101.3 (d, J = 179.8 Hz), 82.9, 80.2 (d, J = 40.8 Hz), 74.0, 58.6 (d, J = 18.2 Hz), 27.7, 17.2, 15.5, 14.2 (d, J = 24.4 Hz); Anal. Calcd. for $C_{28}H_{36}FN_5O_5$: C, 62.09; H, 6.70; N, 12.93. Found: C, 62.12; H, 6.68; N, 12.89.

(*rel*)-(1*R*,2*S*,3*S*)-9-(3-Hydroxy-2-fluoro-2-methylcyclopentan-1-yl) N^6-bis-Boc-adenine (84): A solution of **83** (230 mg, 0.425 mmol) in MeOH (10 mL) was treated with palladium hydroxide (80 mg, 20% in activated charcoal) at 0 °C. Cyclohexene (5 mL) was added and the reaction mixture was refluxed overnight. The suspension was cooled to room temperature, filtered over Celite, and the filtrates were concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 4:1:0.05) to give compound **84** (119 mg, 62%) as a white solid: m.p. 175-177 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.81 (s, 1H), 7.83 (s, 1H), 4.70 (s, 2H), 4.00 (dd, J = 5.7, 18.0 Hz, 1H), 3.18 (ddd, J = 2.2, 6.0, 15.4 Hz, 1H), 2.04 (m, 2H), 1.77 (m, 2H), 1.39 (d, J = 21.8 Hz, 3H), 1.34 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 153.7, 152.6, 150.6, 147.3, 142.4, 127.5, 102.6 (d, J = 176.6 Hz), 82.4, 79.9 (d, J = 42.4 Hz), 73.6, 57.8 (d, J = 17.8 Hz), 28.0, 17.7, 15.6, 14.1 (d, J = 22.0 Hz); Anal. Calcd. for $C_{21}H_{30}FN_5O_5$: C,

55.86; H, 6.70; N, 15.51. Found: C, 55.83; H, 6.72; N, 15.49.

(*rel*)-(1*R*,2*S*,3*S*)-[3-(N^6-Bis-Boc-adenine-9-yl)-2-fluoro-2-methylcyclopentyloxymethyl]phosphonic acid diisopropyl ester (85): To a solution of the cyclopentenol **84** (1.92 g, 4.25 mmol) in 15 mL of DMF was added LiI (42.68 mg, 0.32 mmol) at room temperature. Both Li*O*t-Bu (6.8 mL of 1.0 M solution in THF, 6.8 mmol) and a solution of diisopropyl bromomethylphosphonate (1.38 mL, 5.76 mmol) in 10 mL of DMF were slowly added to the reaction mixture and stirred for 3 h at 60 °C under anhydrous conditions. The mixture was quenched by adding water (10 mL) and the organic solvents were removed in *vacuo*. The residue was diluted with water (80 mL) and was extracted with EtOAc (3 × 80 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to give **85** (1.42 g, 53%) as a solid: m.p. 162-164 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 (s, 1H), 7.86 (s, 1H), 4.71 (m, 2H), 4.03 (ddd, J = 1.8, 6.0, 18.8 Hz, 1H), 3.62 (d, J = 8.8 Hz, 2H), 3.18 (ddd, J = 1.8, 6.2, 14.6 Hz, 1H), 2.01 (m, 2H), 1.69 (m, 2H), 1.38 (d, J = 20.6 Hz, 3H), 1.36 (s, 12H), 1.34 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 153.8, 152.3, 150.9, 150.3, 142.7, 130.4, 101.4 (d, J = 173.2 Hz), 83.6, 82.0 (d, J = 43.4 Hz), 70.4, 65.4, 59.5 (d, J = 16.8 Hz), 28.1, 23.6, 17.2, 15.1, 14.2 (d, J = 20.8 Hz); Anal. Calcd. for $C_{28}H_{45}FN_5O_8P \cdot 0.5$ MeOH: C, 53.01; H, 7.33; N, 10.85. Found: C, 52.97; H, 7.35; N, 10.81.

(*rel*)-(1*R*,2*S*,3*S*)-[3-(6-Aminopurin-9-yl)-2-fluoro-2-methylcyclopentyloxymethyl]phosphonic acid (86): To a solution of the phosphonate **85** (104 mg, 0.165 mmol) in CH_3CN (11 mL) was added TMSBr (252 mg, 1.665 mmol). The mixture was heated overnight at 60 °C and concentrated under reduced pressure. The residue was partitioned between pure CH_2Cl_2 (16 mL) and distilled H_2O (16 mL). The aqueous layer was washed out with CH_2Cl_2 and then freezedried to give target compound **86** (33.6 mg, 59%) as a yellowish foamy solid. UV (H_2O) λ_{max} 262.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.86 (s, 1H), 7.85 (s, 1H), 4.01 (dd, J = 6.2, 20.4 Hz, 1H), 3.60 (d, J = 8.6 Hz, 2H), 3.17 (dd, J = 6.1, 16.2 Hz, 1H), 2.08 (m, 2H), 1.71 (m, 2H), 1.37 (d, J = 20.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 155.4, 152.7, 150.5, 142.3, 120.4, 101.1 (d, J = 172.4 Hz), 82.6

(d, J = 40.8 Hz), 64.6, 58.9 (d, J = 18.3 Hz), 17.3, 15.1, 14.2 (d, J = 22.8 Hz); Anal. Calcd. for $C_{12}H_{17}FN_5O_4P \cdot 2.0\ H_2O$: C, 37.80; H, 5.55; N, 18.37. Found: C, 37.83; H, 5.52; N, 18.35.

(*rel*)-(1*R*,2*S*,3*S*)-*tert*-Butyl SATE phosphoester of 9-(2-fluoro-2-methyl-cyclopentyloxymethan-1-yl)adenine (88): A solution of adenine phosphonic acid derivative **86** (81.6 mg, 0.254 mmol) and tributylamine (432 μL, 1.728 mmol) in methanol (8.6 mL) was mixed for 30 min and concentrated under reduced pressure. The residue was thoroughly dried with anhydrous ethanol and toluene. The resulting foamy solid was dissolved in anhydrous pyridine (16 mL) to which thioester **87** (389 mg, 2.37 mmol) and 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (319 mg, 1.08 mmol) were added. The mixture was stirred for 16 h at room temperature and quenched with tetrabutylammonium bicarbonate buffer (12 mL, 1 M solution, pH 8.0). The mixture was concentrated under reduced pressure and the residue was diluted with water (100 mL) and extracted twice with CH_2Cl_2 (100 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (Hexane/EtOAc/MeOH, 4:1:0.01) to give **88** (59 mg, 37%) as a solid: m.p. 125-127 °C; UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.79 (s, 1H), 7.80 (s, 1H), 4.05-4.00 (m, 5H), 3.61 (d, J = 8.8 Hz, 2H), 3.17-3.14 (m, 5H), 2.05 (m, 2H), 1.75 (m, 2H), 1.38 (d, J = 21.2 Hz, 3H), 1.20 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 205.1, 154.7, 151.9, 149.4, 143.6, 119.6, 103.2 (d, J = 170.8 Hz), 81.7 (d, J = 38.2 Hz), 64.4, 62.2, 57.8 (d, J = 20.4 Hz), 46.2, 30.5, 26.2, 18.1, 16.0, 14.5 (d, J = 20.2 Hz); Anal. Calcd. for $C_{26}H_{41}FN_5O_6PS_2 \cdot 1.0$ MeOH: C, 48.71; H, 6.81; N, 10.52. Found: C, 48.68; H, 6.83; N, 10.49.

(*tert*-Butyldimethylsilanyloxy)acetaldehyde (90): To a solution of Weinreb amide **89** (3.0 g, 12.85 mmol) in dry THF (60 mL) was slowly added DIBALH (15.42 mL, 1.0 M solution in Hexane) at 0 °C. After 2 h, methanol (15 mL) was added, and the reaction mixture was slowly warmed to room temperature. The mixture was stirred at room temperature for 2 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20)

to give crude aldehyde **90** (1.77 g, 79%) as colorless oil. Without further purification, compound **90** was subject to next reaction.

(*E*) and (*Z*)-4-(*tert*-Butyldimethylsilanyloxy)-2-methyl-but-2-enoic acid ethyl ester (91): To a suspension of sodium hydride (0.4 g, 9.98 mmol, 60% in dispersion of oil) in distilled THF (50 mL) was added drop wise triethyl 2-phosphonopropionate (2.38 g, 9.98 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h. The aldehyde **90** (1.74 g, 9.98 mmol) was added to this mixture and the mixture was for 2 h. The solution was neutralized with AcOH (2.0 mL) and poured into H_2O (100 mL) and extracted with EtOAc (150 × 2). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **91** (1.8 g, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.20 (dd, J = 4.2, 1.8 Hz, 1H), 4.49 (m, 2H), 4.14 (q, J = 7.0 Hz, 2H), 1.95 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H), 0.83 (m, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.4, 137.9, 127.3, 67.3, 60.2, 25.5, 18.4, 17.2, 12.9, −5.5.

(*E*) and (*Z*)-3-(*tert*-Butyldimethylsilyloxymethyl)-2-methyl-but-2-en-1-ol (92): To a solution of **91** (2.7 g, 10.5 mmol) in CH_2Cl_2 (70 mL), DIBALH (23.1 mL, 1.0 M solution in hexane) was added slowly at −20 °C, and stirred for 1 h at the same temperature. To the mixture, methanol (23 mL) was added. The mixture was stirred at room temperature for 1 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give alcohol **92** (2.04 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.62 (dd, J = 4.0, 1.6 Hz, 1H), 4.41−4.30 (m, 4H), 1.72 (s, 3H), 0.83 (m, 9H), 0.01 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 139.4, 122.2, 71.3, 65.3, 25.5, 18.4, 13.8, −5.6.

(±)-3-(*tert*-Butyldimethylsilyloxymethyl)-2-methylpent-4-enoic acid ethyl ester (93): A solution of allylic alcohol **92** (3.4 g, 15.8 mmol) in triethyl orthoacetate (60 mL) and 0.05 mL of propionic acid was heated at 140 °C overnight with stirring under condition for distillative removal of ethanol. The excess of triethyl orthoacetate was distilled off and the residue was purified by

silica gel column chromatography (EtOAc/hexane, 1:20) to give **93** (3.62 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.63−5.55 (m, 2H), 4.09 (q, J = 7.0 Hz, 2H), 3.53 (d, J = 9.6 Hz, 1H), 3.42 (d, J = 9.6 Hz, 1H), 2.60 (dd, J = 14.0, 5.2 Hz, 1H), 2.36 (dd, J = 14.0, 8.6 Hz, 1H), 2.27 (m, 1H), 1.79 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.4, 139.4, 118.2, 66.4, 61.8, 45.9, 40.3, 25.7, 18.6, 17.4, 13.6, −5.6.

(±)−3−(*tert*−Butyldimethylsilyloxymethyl)−2−methylpent−4−enal (94): To a solution of **93** (3.0 g, 10.5 mmol) in toluene (50 mL), DIBALH (7.7 mL, 1.5 M solution in toluene) was added slowly at −78 °C, and stirred for 10 min at the same temperature. To the mixture, methanol (8 mL) was added. The mixture was stirred at room temperature for 1 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **94** (2.54 g, 63%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.71 (s, 1H), 5.60−5.53 (m, 2H), 3.62 (dd, J = 9.8, 5.0 Hz, 1H), 3.45 (d, J = 9.6, 5.6 Hz, 1H), 2.70 (m, 1H), 2.61 (dd, J = 13.6, 5.4 Hz, 1H), 2.39 (dd, J = 13.6, 5.6 Hz, 1H), 1.76 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 202.1, 140.7, 119.7, 69.5, 61.8, 46.1, 41.6, 25.7, 18.7, 17.9, −5.5.

(*rel*)−(3*R* and *3S*,5*S*)−5−(*tert*−Butyldimethylsilanyloxymethyl)−6−methyl−hepta−1,6−dien−3−ol (95): To a solution of **94** (1.86 g, 7.7 mmol) in dry THF (30 mL) was slowly added vinylMgBr (8.47 mL, 1.0 M solution in THF) at −78 °C. After 5 h, saturated NH_4Cl solution (9 mL) was added, and the reaction mixture was slowly warmed to room temperature. The mixture was extracted with EtOAc/water two times. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **95** (1.58 g, 76%) as a diastereomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.71−5.63 (m, 2H), 5.30−5.18 (m, 4H), 4.11 (m, 1H), 3.56−3.40 (m, 2H), 2.37 (m, 1H), 2.22−1.78 (m, 1H), 1.66 (s, 3H), 1.58−1.49 (m, 1H), 0.82 (s, 9H), 0.01 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 147.1, 139.2, 139.1, 115.7, 115.6, 111.4, 73.8, 73.7, 66.5, 43.0, 27.3, 27.2, 25.8, 18.3, 17.3, −5.5.

(*rel*)−(1*R*,4*S*)−4−(*tert*−Butyldimethylsilyloxymethyl)−3−methylcyclopent−2−

enol (96β); and (rel)-(1*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-3-methylcyclopent-2-enol (96α): To a solution of **95** (2.78 g, 10.3 mmol) in dry CH_2Cl_2 (20 mL) was added Grubbs' II catalyst (152 mg, 0.18 mmol). The reaction mixture was refluxed overnight, and cooled to room temperature. The mixture was concentrated in vacuum, and residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give cyclopentenol **96β** (1.07 g, 43%) and **96α** (1.09 g, 44%) as colorless oils, respectively. Cyclopentenol **96β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.67 (dd, J = 5.4, 2.4 Hz, 1H), 4.52 (d, J = 4.8 Hz, 1H), 3.45 (dd, J = 13.8, 8.4 Hz, 2H), 2.88 (m, 1H), 1.98 (dd, J = 13.4, 6.8 Hz, 1H), 1.77 (dd, J = 13.4, 8.2 Hz, 1H), 1.40 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.7, 131.4, 77.1, 67.2, 47.4, 38.6, 25.3, 18.4, 14.5, -5.7. Cyclopentenol **96α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.60 (d, J = 5.2 Hz, 1H), 4.48 (m, 1H), 3.47 (d, J = 13.6 Hz, 1H), 3.33 (d, J = 13.6 Hz, 1H), 2.82 (m, 1H), 1.92 (dd, J = 13.6, 8.4 Hz, 1H), 1.71 (dd, J = 13.6, 7.2 Hz, 1H), 1.49 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 143.6, 130.2, 76.3, 66.3, 47.2, 38.8, 25.5, 18.4, 14.2, -5.6.

(*rel*)-(1*R*,4*S*)-1-Ethoxycarbonyloxy-4-(*tert*-butyldimethylsilyloxymethyl)-3-methylcyclopent-2-ene (97): To a solution of **96β** (2.51 g, 10.38 mmol) in anhydrous pyridine (20 mL) was added ethyl chloroformate (2.25 g, 20.7 mmol) and DMAP (122 mg, 1.0 mmol). The reaction mixture was stirred overnight at 50 °C. The reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL), stirred for 10 min and concentrated in reduced pressure. The residue was extracted with EtOAc/H_2O two times, and combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **97** (2.55 g, 78%) as colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92 (dd, J = 5.4 Hz, 1H), 5.72 (dd, J = 4.8, 1.4 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.40 (d, J = 13.2 Hz, 2H), 2.98 (m, 1H), 2.10-1.90 (m, 2H), 1,71 (s, 3H), 1.26 (t. J = 7.2 Hz, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.3, 138.5, 133.2, 85.7, 66.7, 63.5, 46.5, 35.3, 25.8, 18.3, 14.3, 12.8, -5.5.

(*rel*)-(1'*R*,4'*S*)-9-[4-(*tert*-Butyldimethylsilyloxymethyl)-3-methylcyclopent-2-en-1-yl]adenine (98): In order to generate nucleosidic base anion,

adenine (162 mg, 0.94 mmol) was added to a pure NaH (25.2 mg, 1.05 mmol) in anhydrous DMSO (6.0 mL). The reaction mixture was stirred for 30 min at 50–55 °C and cooled to room temperature. Simultaneously, P(O–*i*–Pr)$_3$ (87 mg, 0.42 mmol) was added to a solution of $Pd_2(dba)_3 \cdot CHCl_3$ (55.6 mg, 5.37 μmol) in anhydrous THF (5.0 mL), which was stirred for 30 min. To the adenine solution of DMSO was sequentially added catalyst solution of THF and **97** (277 mg, 0.88 mmol) dissolved in anhydrous THF (5.0 mL). The reaction mixture was stirred overnight at refluxing temperature and quenched with water (3.0 mL). The reaction solvent was removed in vacuum. The residue was purified by silica gel column chromatography (MeOH/hexane/EtOAc, 0.1:4:1) to give **98** (123.4 mg, 39%) as a white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 7.75 (s, 1H), 6.01 (s, 1H), 5.95 (br s, 2H), 5.60 (d, J = 5.2 Hz, 1H), 3.58 (d, J = 10.0 Hz, 2H), 3.15 (m, 1H), 2.39 (dd, J = 13.6, 8.2 Hz, 1H), 2.12–2.05 (m, 1H), 1.67 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.3, 152.7, 150.7, 142.4, 140.1, 131.1, 119.5, 68.5, 63.2, 47.5, 34.5, 25.6, 18.4, 14.0, −5.5; Anal. Calcd. for $C_{18}H_{29}N_5OSi$: C, 60.13; H, 8.13; N, 19.48. Found: C, 60.32; H, 8.20; N, 19.50.

(*rel*)–(1'*R*,4'*S*)–1–[4–(*tert*–Butyldimethylsilyloxymethyl)–3–methylcyclopent–2–en–1–yl]cytosine (99): Cytosine nucleoside analogue **99** was synthesized from **97** by the similar procedure as described for **98**: yield 39%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14 (d, J = 7.2 Hz, 1H), 5.79 (s, 1H), 5.70 (d, J = 7.2 Hz, 1H), 3.46 (dd, J = 9.8, 7.8 Hz, 2H), 2.94 (m, 1H), 2.24–2.15 (m, 1H), 1.79 (dd, J = 10.2, 7.8 Hz, 1H), 1.62 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.2, 156.3, 140.1, 138.7, 131.1, 95.1, 67.9, 61.9, 47.1, 35.7, 25.7, 18.6, 13.8, −5.6; Anal. Calcd. for $C_{17}H_{29}N_3O_2Si$: C, 60.86; H, 8.71; N, 12.52. Found: C, 60.77; H, 8.80; N, 12.48.

(*rel*)–(1'*R*,2'*S*,3'*S*,4'*R*)–9–[4–(*tert*–Butyldimethylsilyloxymethyl)–3–methyl–2,3–dihydroxycyclopentan–1–yl]adenine (100): To a stirred solution of **98** (604 mg, 1.68 mmol) in cosolvent (6.0 mL, acetone:water/5:1) was added NMO (393 mg, 3.36 mmol), and OsO_4 (0.1 mL, 4% in water). The mixture was stirred overnight at 50 °C, and quenched with saturated Na_2SO_3 solution (6 mL). Resulting solid was removed by filtration through a pad of Celite, and filtrate was concentrated in reduced pressure. The residue was purified by silica gel column

chromatography (MeOH/CH_2Cl_2, 1:6) to give **100** (522 mg, 79%) as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.15 (s, 1H), 8.10 (s, 1H), 7.20 (br d, 2H, D_2O exchangeable), 5.18 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 5.11 (s, 1H, D_2O exchangeable), 5.03 (m, 1H), 3.97 (d, J = 4.8 Hz, 1H), 3.46 (dd, J = 12.6, 7.2 Hz, 1H), 3.30 (dd, J = 12.6, 8.4 Hz, 1H), 2.44 (dd, J = 10.6, 3.8 Hz, 1H), 2.31 (dd, J = 10.6, 8.8 Hz, 1H), 1.60 (s, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 155.7, 152.0, 149.7, 140.5, 119.4, 79.3, 69.7, 53.7, 41.5, 25.6, 18.4, 14.2, -5.8; Anal calc for $C_{18}H_{31}N_5O_3Si$: C, 54.93; H, 7.94; N, 17.80. Found: C, 54.85; H, 7.90; N, 17.74.

(*rel*)-(1'*R*,2'*S*,3'*S*,4'*R*)-1-[4-(*tert*-Butyldimethylsilyloxymethyl)-3-methyl-2,3-dihydroxycyclopentan-1-yl]cytosine (101): Cytosine nucleoside analogue **101** was synthesized from **99** by the similar procedure as described for **100**: yield 76%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.60 (d, J = 7.2 Hz, 1H), 7.06 (br d, 2H, D_2O exchangeable), 5.60 (d, J = 7.2 Hz, 1H), 5.12 (d, J = 4.6 Hz, 1H, D_2O exchangeable), 5.05 (s, 1H, D_2O exchangeable), 5.01 (m, 1H), 3.88 (d, J = 4.8 Hz, 1H), 3.49 (dd, J = 12.8, 6.8 Hz, 1H), 3.31 (dd, J = 12.8, 8.6 Hz, 1H), 3.02 (m, 1H), 2.21-1.97 (m, 2H), 1.59 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 165.0, 156.1, 145.2, 95.1, 76.5, 71.2, 52.1, 40.4, 25.3, 18.7, 13.9, -5.5; Anal. Calcd. for $C_{17}H_{31}N_3O_4Si$: C, 55.25; H, 8.64; N, 11.37. Found: C, 55.17; H, 8.76; N, 11.28.

(*rel*)-(1'*R*,2'*S*,3'*S*,4'*R*)-9-[4-(Hydroxymethyl)-3-methyl-2,3-dihydroxy-cyclopentan-1-yl]adenine (102): To a solution of **100** (138 mg, 0.35 mmol) in THF (5 mL) was TBAF (0.53 mL, 1.0 M solution in THF) at 0 °C. The mixture was stirred overnight at room temperature, and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:5) to give **102** (76 mg, 78%) as a white solid: m.p. 195-197 °C; UV (H_2O) λ_{max} 259.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.17 (s, 1H), 8.09 (s, H1), 7.19 (br d, 2H, D_2O exchangeable), 5.21 (d, J = 4.6 Hz, 1H, D_2O exchangeable), 5.10 (s, 1H, D_2O exchangeable), 5.04 (m, 1H), 4.78 (t, J = 4.8 Hz, 1H, D_2O exchangeable), 3.91 (m, 1H), 3.48 (dd, J = 12.8, 7.4 Hz, 1H), 3.33 (dd, J = 12.8, 8.4 Hz, 1H), 2.44 (dd, J = 10.8, 4.0 Hz, 1H), 2.31 (dd, J = 10.8, 8.6 Hz, 1H), 1.61 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 155.7, 151.8, 148.5, 141.4, 118.3, 78.4, 68.6, 54.6, 42.6,

13.9; Anal calc for $C_{12}H_{17}N_5O_3 \cdot 1.0$ MeOH: C, 50.15; H, 6.79; N, 22.49. Found: C, 50.22; H, 6.81; N, 22.45.

(*rel*)-(1'*R*,2'*S*,3'*S*,4'*R*)-1-[4-(Hydroxymethyl)-3-methylcyclopent-2-en-1-yl]cytosine (103): Cytosine nucleoside analogue **103** was synthesized from **101** by the similar condition as described for **102** as a white solid: yield 73%; m.p. 163-165 °C; UV (H_2O) λ_{max} 273.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.62 (d, J = 7.2 Hz, 1H), 7.07 (br d, 2H, D_2O exchangeable), 5.59 (d, J = 7.2 Hz, 1H), 5.12 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 5.05 (s, 1H, D_2O exchangeable), 5.03 (m, 1H), 4.81 (t, J = 5.0 Hz, 1H), 3.91 (dd, J = 8.6, 4.4 Hz, 1H), 3.48 (dd, J = 12.4, 7.0 Hz, 1H), 3.32 (dd, J = 12.4, 8.2 Hz, 1H), 3.07 (m, 1H), 2.23-2.10 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.4, 156.3, 145.5, 96.6, 77.4, 69.2, 54.1, 42.3, 13.2; Anal. Calcd. for $C_{11}H_{17}N_3O_4 \cdot 1.0$ H_2O: C, 48.34; H, 7.00; N, 15.38. Found: C, 48.27; H, 6.95; N, 15.42.

(*rel*)-(3*R* and 3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxymethyl)-2-methyl-hepta-1,6-dien-3-ol (105): To a solution of compound **104** (4.0 g, 16.49 mmol) in dry THF (150 mL), isopropenylMgBr (19.78 mL, 1.0 M solution in THF) was added slowly at -78 °C. After 3 h, a saturated NH_4Cl solution (22 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc (2 × 300 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **105** (3.56 g, 80%) as a diastereomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72-5.60 (m, 1H), 5.03 (d, J = 8.4 Hz, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.78 (s, 1H), 4.11 (m, 1H), 3.56 (dd, J = 9.9, 4.8 Hz, 1H), 3.41 (dd, J = 9.9, 7.5 Hz, 1H), 2.40 (m, 1H), 1.81-1.73 (m, 1H), 1.66 (s, 3H), 1.58-1.49 (m, 1H), 0.84 (s, 12H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.03, 139.80, 115.79, 111.43, 73.87, 66.64, 43.05, 36.93, 25.89, 18.30, 17.50, -5.47.

(±)-5-(*tert*-Butyldimethylsilanyloxymethyl)-2-methyl-hepta-1,6-dien-3-one (106): A mixture of allylic alohol **105** (1.2 g, 4.45 mmol), manganese (IV) dioxide (1.08 g, 12.4 mmol) in CCl_4 (15 mL) was stirred at 60 °C. Additional manganese (IV) dioxide (180 mg, 2.06 mmol) was added per hour and the progress of the reaction was monitored by TLC (EtOAc/hexane, 1:25). The

resultant mixture was filtered through a plug of celite, washed with ethyl acetate. The filtrate and washings were concentrated in *vacuo* to give a residue, which was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give α,β-unsaturated ketone derivative **106** (848 mg, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98-5.81 (m, 2H), 5.27-5.16 (m, 1H), 4.93 (s, 1H), 3.62 (dd, J = 12.2, 5.2 Hz, 1H), 3.43 (dd, J = 12.2, 7.6 Hz, 1H), 2.89-2.79 (m, 2H), 2.42 (m, 1H), 1.87 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.9, 147.4, 142.4, 122.6, 113.17, 68.7, 38.2, 36.2, 25.5, 18.3, 17.1, -5.4.

(*rel*)-(3*R* and *3S*,5*S*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-2,3-dimethyl-hepta-1,6-dien-3-ol (107): To a solution of **106** (1.77 g, 6.6 mmol) in dry THF (40 mL) was slowly added methylMgBr (7.92 mL, 1.0 M solution in THF) at -20 °C. After 4 h, saturated NH_4Cl solution (8 mL) was added, the reaction mixture was slowly warmed to room temperature and to the mixture water (150 mL) was poured. The mixture was extracted with EtOAc (150 mL) two times. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **107** (1.16 g, 62%) as a diastereomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76-5.66 (m, 2H), 5.12-5.01 (m, 2H), 3.56-3.48 (m, 2H), 2.27 (m, 1H), 1.52-1.46 (m, 2H), 1.38 (s, 3H), 0.81 (s, 9H), 0.01 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 148.2, 141.4, 118.6, 110.4, 78.1, 76.5, 43.6, 33.5, 26.2, 25.1, 18.2, 14.1, -5.5.

(*rel*)-(1*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-1,2-dimethylcyclopent-2-enol (108β) and (*rel*)-(1*S*,4*S*)-4-(*tert*-butyldimethylsilyloxymethyl)-1,2-dimethylcyclopent-2-enol (108α): To a solution of **107** (1.76 g, 6.18 mmol) in dry benzene (8 mL) was added Grubbs' II catalyst (136 mg 0.16 mmol). The reaction mixture was refluxed overnight at 100 °C, and cooled to room temperature. The mixture was concentrated in vacuum, and residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give cyclopentenol **108β** (539 mg, 34%) and **108α** (555 mg, 35%) as colorless oils, respectively. Cyclopentenol **108β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.27 (dd, J = 8.2, 6.2 Hz, 1H), 3.70 (d, J = 12.2 Hz, 1H), 3.58 (d, J = 12.2 Hz, 1H), 2.83 (m,

1H), 2.42 (dd, J = 12.6, 4.8 Hz, 1H), 2.21 (dd, J = 12.6, 7.6 Hz, 1H), 1.73 (s, 3H), 1.32 (s, 3H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 143.2, 126.3, 82.1, 71.0, 39.4, 37.8, 25.9, 25.3, 18.5, 13.9, −5.5; Cyclopentenol **108α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.31 (m, 1H), 3.63 (dd, J = 14.2, 8.8 Hz, 2H), 2.87 (m, 1H), 2.38 (dd, J = 12.8, 6.8 Hz, 1H), 2.27 (dd, J = 12.7, 8.8 Hz, 1H), 1.82 (s, 3H), 1.39 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 142.9, 125.5, 81.8, 72.4, 40.1, 37.2, 26.1, 25.4, 18.6, 14.6, −5.7.

(*rel*)−(1'*R*,4'*S*)−9−[4−(*tert*−Butyldimethylsilyloxymethyl)−1,2−dimethylcyclopent−2−en−1−yl]−6−chloropurine (109): To a solution of compound **108α** (372 mg, 1.45 mmol), PPh_3 (1.13 g, 4.32 mmol) and 6−chloropurine (553 g, 3.58 mmol) in anhydrous dioxane (7 mL) and DMF (7 mL) was added DIAD (808 mg, 4.0 mmol) dropwise at −20 °C for 30 min under nitrogen. The reaction mixture was stirred for 2 h at −20 °C under nitrogen. The solvent was concentrated under reduced pressure and the residue was directly purified by silica gel column chromatography (EtOAc/hexane, 1:4) to give the compound **109** (382 mg, 62%) as a yellow solid; UV (MeOH) λ_{max} 264.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.71 (s, 1H), 8.18 (s, 1H), 5.41 (d, J = 5.2 Hz, 1H), 3.63 (d, J = 10.2 Hz, 1H), 3.40 (d, J = 10.3 Hz, 1H), 2.78 (m, 1H), 2.43 (dd, J = 12.4, 6.2 Hz, 1H), 2.19 (dd, J = 12.4, 8.4 Hz, 1H), 1.82 (s, 3H), 1.70 (s, 3H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 165.7, 154.9, 144.2, 125.5, 120.35, 71.4, 66.4, 40.3, 33.5, 25.6, 22.4, 18.5, 14.3, −5.6; Anal calc for $C_{19}H_{29}ClN_4OSi$: C, 58.07; H, 7.44; N, 14.26. Found: C, 57.96; H, 7.41; N, 14.32.

(*rel*)−(1'*R*,2'*S*,3'*R*,4'*R*)−9−[4−(*tert*−Butyldimethylsilyloxymethyl)−1,2−dimethyl−2,3−dihydroxycyclopentan−1−yl]−6−chloropurine (110α) and (*rel*)−(1'*R*,2'*R*,3'*S*,4'*R*)−9−[4−(*tert*−butyldimethylsilyloxymethyl)−1,2−dimethyl−2,3−dihydroxycyclopentan−1−yl]−6−chloropurine (110β): To a stirred solution of **109** (393 mg, 1.0 mmol) in cosolvent (8.0 mL, acetone/water, 5/1) was added NMO (351 mg, 3.0 mmol), and OsO_4 (0.07 mL, 4% in water). The mixture was stirred overnight at 50 °C, and quenched with saturated Na_2SO_3 solution (8 mL). Resulting solid was removed by filtration through a pad of Celite, and filtrate was concentrated in reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:6) to give **110α** (209 mg, 49%) and **110β**

(51 mg, 12%) as a white solid; **110α**: m.p. 196−198 °C; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.71 (s, 1H), 8.51 (s, 1H), 5.10 (s, 1H, D_2O exchangeable), 5.01 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 3.81 (d, J = 10.8 Hz, 1H), 3.61−3.50 (m, 2H), 2.09−1.99 (m, 2H), 1.72−1.65 (m, 4H), 1.34 (s, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO−d_6) δ 169.8, 165.4, 157.7, 137.5, 121.4, 87.3, 74.5, 67.7, 63.4, 30.4, 25.6, 23.7, 18.4, 15.3, 14.2, −5.4; Anal calc for $C_{19}H_{31}ClN_4O_3Si$ (+0.5 MeOH): C, 52.86; H, 7.50; N, 12.64. Found: C, 52.74; H, 7.42; N, 12.51; **110β**: m.p. 203−205 °C; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.67 (s, 1H), 8.48 (s, 1H), 5.08 (s, 1H, D_2O exchangeable), 5.00 (d, J = 4.7 Hz, 1H, D_2O exchangeable), 3.79−3.70 (m, 2H), 3.42 (d, J = 7.2 Hz, 1H), 2.08 (dd, J = 8.6, 6.2 Hz, 1H), 1.75−1.67 (m, 2H), 1.53 (s, 3H), 1.32 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO−d_6) δ 169.1, 164.8, 157.2, 136.8, 122.5, 88.9, 73.6, 66.2, 62.6, 31.3, 25.5, 22.9, 18.7, 14.6, 13.7, −5.6; Anal calc for $C_{19}H_{31}ClN_4O_3Si$: C, 53.44; H, 7.32; N, 13.12. Found: C, 53.53; H, 7.40; N, 13.07.

(*rel*)−(1'*R*,2'*S*,3'*R*,4'*R*)−9−[4−(*tert*−Butyldimethylsilyloxymethyl)−1,2−dimethyl−2,3−dihydroxycyclopentan−1−yl]adenine (111). Compound **110α** (119 mg, 0.28 mmol) was dissolved in saturated methanolic ammonia (10 mL) and the resulting solution was stirred overnight at 90−95 °C in a steel bomb. After removal of reaction solvent, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to give the compound **111** (84 mg, 74%) as a white solid: m.p. 200−202 °C; UV (MeOH) λ_{max} 259.5 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.16 (s, 1H), 8.10 (s, 1H), 7.19 (br s, 1H, D_2O exchangeable), 5.17 (s, 1H, D_2O exchangeable), 5.05 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 3.78 (d, J = 10.7 Hz, 1H), 3.50 (d, J = 10.6 Hz, 1H), 3.41 (dd, J = 8.4, 6.4 Hz, 1H), 2.02−1.93 (m, 2H), 1.80 (s, 3H), 1.67 (m, 1H), 1.32 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO−d_6) δ 155.2, 152.5, 149.4, 138.7, 119.4, 85.3, 73.5, 67.3, 62.1, 32.5, 25.7, 24.2, 18.4, 14.8, 13.9, −5.5; Anal calc for $C_{19}H_{33}N_5O_3Si$ (+1.0 MeOH): C, 54.64; H, 8.48; N, 15.93. Found: C, 54.72; H, 8.41; N, 16.02.

(*rel*)−(1'*R*,2'*S*,3'*R*,4'*R*)−9−[4−(Hydroxymethyl)−1,2−dimethyl−2,3−dihydroxycyclopentan−1−yl]adenine (112). To a solution of **111** (159 mg, 0.39 mmol) in cosolvent (5.0 mL, THF:CH_3CN/1:1), TBAF (0.58 mL, 1.0 M solution in THF)

was added at 0 °C. The mixture was stirred overnight at room temperature, and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:4) to give **112** (78 mg, 68%) as a white solid: m.p. 209−212 °C; UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.21 (s, 1H), 8.13 (s, 1), 7.21 (br s, 2H, D_2O exchangeable), 5.18 (s, 1H, D_2O exchangeable), 5.10 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 4.81 (t, J = 4.6 Hz, 1H, D_2O exchan−geable), 3.79 (d, J = 10.8 Hz, 1H), 3.49−3.38 (m, 2H), 2.02−1.93 (m, 2H), 1.78 (s, 3H), 1.63 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (DMSO−d_6) δ 155.6, 152.3, 148.2, 135.3, 118.8, 86.2, 72.9, 67.7, 61.9, 33.2, 24.7, 14.2, 13.4; Anal calc for $C_{13}H_{19}N_5O_3$(+1.0 H_2O): C, 51.65; H, 7.00; N, 23.16. Found: C, 51.54; H, 6.95; N, 23.22.

3,3−Bis−(*tert*−butyldimethylsilanyloxymethyl)−pent−4−en−1−ol (114): To a solution of **113** (5.5 g, 13.19 mmol) in CH_2Cl_2 (100 mL), DIBALH (27.71 mL, 1.0 M solution in hexane) was added slowly at −20 °C, and the mixture was stirred for 2 h at the same temperature. To the mixture, methanol (28 mL) was added. The mixture was stirred at room temperature for 2 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:7) to give alcohol **114** (4.55 g, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70−5.63 (m, 1H), 4.91−4.98 (m, 2H), 3.71−3.64 (m, 4H), 3.52 (m, 2H), 1.45−1.39 (m, 2H), 0.81 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.6, 107.9, 70.5, 59.1, 38.7, 34.1, 25.3, 18.7, −5.4; Anal. Calc. for $C_{19}H_{42}O_3Si_2$: C, 60.90; H, 11.30. Found: C, 60.94; H, 11.26.

1−[3,3−Bis−(*tert*−butyldimethylsilanyloxymethyl)−pent−4−enyloxymethyl]−4−methoxybenzene (115): Compound **114** (5.2 g, 13.87 mmol) was dissolved in dry DMF (50 mL). After cooling the solution to 0 °C, NaH (0.4 g, 60% in mineral oil, 16.6 mmol) was added. The solution was stirred at 0 °C for 30 min and then 4−methoxybenzyl chloride (2.6 g, 16.6 mmol) was slowly added. After warming the solution to room temperature, it was stirred for 3 h. The solvent was removed under reduced pressure and the residue was quenched with H_2O followed by extraction with EtOAc (2 × 60 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, and concentrated under

reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **115** (5.83 g, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 8.2 Hz, 2H), 5.82–5.05 (m, 2H), 4.65 (s, 2H), 3.73–3.63 (m, 7H), 3.38 (t, J = 6.8 Hz, 2H), 1.43–1.36 (m, 2H), 0.82 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 148.5, 130.4, 129.7, 113.6, 109.3, 76.2, 70.6, 65.6, 57.4, 39.8, 31.8, 25.5, 18.4, −5.5; Anal. Calc. for $C_{27}H_{50}O_4Si_2$: C, 65.53; H, 10.18. Found: C, 65.59; H, 10.21.

2,2-Bis-(*tert*-butyldimethylsilanyloxymethyl)-4-(4-methoxybenzyloxy)-butyraldehyde (116): A solution of compound **115** (4.5 g, 9.1 mmol) in anhydrous CH_2Cl_2 (60 mL) was cooled down to −78 °C, and ozone gas was then bubbled into the reaction mixture until a blue color persisted for an additional 5 min. The reaction mixture was degassed with nitrogen, and dimethyl sulfide (2.79 mL, 38 mmol) was slowly added at −78 °C. The mixture was stirred for 1 h at room temperature under argon gas and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **116** (1.79 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.78 (s, 1H), 7.26 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 8.2 Hz, 2H), 4.62 (s, 2H), 4.02–3.94 (m, 4H), 3.75 (s, 3H), 3.36 (dd, J = 7.0, 1.2 Hz, 2H), 1.75–1.68 (m, 2H), 0.81 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.2, 160.2, 130.1, 129.2, 114.1, 75.7, 65.3, 62.3, 56.8, 55.8, 25.6, 24.5, 18.3, −5.6.

3,3-Bis-(*tert*-butyldimethylsilanyloxymethyl)-5-(4-methoxybenzyloxy)-pentan-2-ol (117): To a solution of **116** (2.1 g, 4.22 mmol) in dry THF (30 mL) was slowly added CH_3MgBr (5.0 mL, 1.0 M solution in THF) at −78 °C. After 5 h, saturated NH_4Cl solution (5 mL) and water (50 mL) were sequentially added, and the reaction mixture was slowly warmed to room temperature. The mixture was extracted with EtOAc (60 mL) two times. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **117** (1.86 g, 86%) as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 4.65 (s, 2H), 3.72–3.63 (m, 7H), 3.36–3.30 (m, 3H), 1.37–1.29

(m, 2H), 1.20 (d, J = 6.8 Hz, 3H), 0.82 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.1, 131.2, 128.4, 112.9, 75.8, 68.5, 65.6, 62.8, 56.5, 45.5, 25.7, 24.8, 18.4, 17.2, −5.4; Anal. Calc. for $C_{27}H_{52}O_5Si_2$: C, 63.23; H, 10.22. Found: C, 63.26; H, 10.19.

2,2−Bis−(*tert*−butyldimethylsilanyloxymethyl)−4−(4−methoxybenzyloxy)−1−methylbutyl acetate (118): To a solution of compound **117** (2.5 g, 4.87 mmol) in anhydrous pyridine (30 mL), Ac_2O (497 mg, 1.53 mmol) was slowly added, and the mixture was stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure and co−evaporated with toluene. The residue was poured into water (50 mL) and extracted with EtOAc (50 mL) two times. The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give compound **118** (2.46 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 8.1 Hz, 2H), 4.65 (s, 2H), 4.13 (q, J = 6.8 Hz, 1H), 3.75−3.67 (m, 7H), 3.34 (dd, J = 6.2, 1.2 Hz, 2H), 2.03 (s, 3H), 1.39−1.31 (m, 5H), 0.83 (s, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 159.9, 130.7, 129.1, 113.6, 76.5, 72.5, 66.3, 64.2, 56.8, 43.1, 25.7, 24.9, 18.4, 17.4, 14.3, −5.6; Anal. Calc. for $C_{29}H_{54}O_6Si_2$: C, 62.77; H, 9.81. Found: C, 62.81; H, 9.78.

2,2−Bis−(*tert*−butyldimethylsilanyloxymethyl)−4−hydroxy−1−methylbutyl acetate (119): To a solution of compound **118** (2.2 g, 3.96 mmol) in CH_2Cl_2/H_2O mixture (119 mol CH_2Cl_2, 5.94 mol H_2O) was added DDQ (1.08 g, 4.75 mmol) and the mixture was stirred for 2 h at room temperature. Saturated $NaHCO_3$ (20 mL) was added to quench the reaction. The organic layer was separated, washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **119** (2.46 g, 83%) as a colorlessoil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.13 (m, 1H), 3.73−3.65 (m, 4H), 3.51 (t, J = 6.6 Hz, 2H), 2.02 (s, 3H), 1.42−1.36 (m, 5H), 0.81 (m, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 71.6, 64.2, 58.7, 41.8, 27.9, 25.4, 18.4, 17.5, 15.6, −5.5; Anal. Calc. for $C_{21}H_{46}O_5Si_2$: C, 58.01; H, 10.66. Found: C, 58.09; H, 10.70.

2,2-Bis-(*tert*-butyldimethylsilanyloxymethyl)-1-methyl-4-oxobutylacetate (120): To a stirred solution of oxalyl chloride (0.06 mL, 0.68 mmol) in CH_2Cl_2 (6 mL) was added a solution of DMSO (0.06 mL, 0.9 mmol) in CH_2Cl_2 (0.34 mL) dropwise at −78 °C. The resulting solution was stirred at −78 °C for 5 min, and a solution of alcohol **119** (197 mg, 0.454 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was stirred at −78 °C for 20 min and triethylamine (0.32 mL, 2.26 mmol) was added. The resulting mixture was warmed to 0 °C and stirred for 30 min. H_2O (6 mL) was added, and the solution was stirred at room temperature for 20 min. The mixture was poured into water (40 mL), extracted with EtOAc (40 mL) two times. The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **120** (193 mg, 99%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.75 (s, 1H), 4.12 (m, 1H), 3.74−3.67 (m, 4H), 2.34 (dd, J = 8.4, 6.2 Hz, 1H), 2.03 (s, 3H), 0.81 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.5, 171.5, 71.8, 65.0, 58.7, 38.4, 37.3, 25.5, 18.6, 15.7, −5.4.

(*rel*)-(2*S*,5*R* and 5*S*)-4,4-Bis-(*tert*-butyldimethylsilanyloxymethyl)-5-methyltetrahydrofuran-2-ol (121): To a solution of **120** (2.3 g, 5.31 mmol) in methanol (10 mL) was added NaOMe (1.0 mmol, 1.0 M in MeOH). The mixture was stirred for 4 h at room temperture and neutralized with acetic acid (0.1 mL). The mixture was concentrated under reduced pressure. The residue was poured into water (60 mL) and extracted with EtOAc (60 mL) two times. The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give compound **121** (1.74 g, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.67 (m, 1H), 3.91 (m, 1H), 3.72−3.63 (m, 4H), 1.94−1.89 (m, 1H), 1.82 (m, 1H), 1.22 (d, J = 6.2 Hz, 3H), 0.81 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 93.1, 92.9, 68.0, 67.8, 63.8, 63.7, 47.3, 38.4, 34.3, 34.2, 25.5, 25.4, 18.6, −5.7, −5.6.

(*rel*)-(2*S*,5*R* and 5*S*)-Acetic acid 4,4-bis-(*tert*-butyldimethylsilanyloxymethyl)-5-methyltetrahydrofuran-2-yl ester (122): To a solution of compound **121** (3.1 g, 7.93 mmol) in anhydrous pyridine (30 mL), Ac_2O (1.21 g, 11.9

mmol) and DMAP (36 mg, 0.3 mmol) were slowly added, and the mixture was stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure and co-evaporated with toluene. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give diastereomeric compound **122** (2.95 g, 86%) as a syrup: ^{1}H NMR($CDCl_3$, 300 MHz) δ 6.13 (dd, J = 5.4, 1.2 Hz, 1H), 3.93 (m, 1H), 3.74-3.65 (m, 4H), 2.09-2.01 (m, 4H), 1.83-1.76 (m, 1H), 1.22 (dd, J = 6.6, 4.2 Hz, 3H), 0.81 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 170.8, 97.3, 68.1, 64.2, 64.1, 47.0, 46.9, 31.3, 25.5, 18.4, 17.5, 15.2, -5.7.

(*rel*)-(2*S*,5*R*)-6-Chloro-9-[4,4-Bis-(*tert*-butyldimethylsilanyloxymethyl)-5-methyltetrahydrofuran-2-yl]purine (123) and (*rel*)-(2*S*,5*S*)-6-chloro-9-[4,4-bis-(*tert*-butyldimethylsilanyloxymethyl)-5-methyltetrahydrofuran-2-yl] purine (124): 6-Chloropurine (541 mg, 3.5 mmol), anhydrous HMDS (20 mL), and a catalytic amount of ammonium sulfate (20 mg) were refluxed to a clear solution (overnight), and the solvent was distilled under anhydrous conditions. The residue was dissolved in anhydrous DCE (10 mL). To this mixture, a solution of **122** (757 mg, 1.75 mmol) in dry DCE (10 mL) and TMSOTf (778 mg, 3.5 mmol) was added, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with 20 mL of saturated $NaHCO_3$ and stirred for 20 min. The resulting solid was filtered through a Celite pad, and the filtrate was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give compound **123** (286 mg, 31%) and **124** (304 mg, 33%) as white solids, respectively: compound for **123**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.43 (s, 1H), 8.11 (s, 1H), 6.14 (br s, 2H), 6.01 (dd, J = 5.4, 1.4 Hz, 1H), 3.92 (m, 1H), 3.72-3.64 (m, 4H), 2.25 (dd, J = 12.6, 6.6 Hz, 1H), 1.87 (dd, J = 12.6, 8.6 Hz, 1H), 1.19 (d, J = 6.8 Hz, 3H), 0.82 (m, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.7, 152.6, 148.4, 147.8, 129.5, 82.5, 68.4, 64.2, 48.1, 31.9, 25.6, 18.7, 14.7, -5.5; Anal. Calc. for $C_{24}H_{43}ClN_4O_3Si_2$: C, 54.67; H, 8.22; N, 10.63. Found: C, 54.71; H, 8.19; N, 10.69; compound for **124**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (s, 1H), 8.29 (s, 1H),

6.11 (br s, 2H), 6.00 (d, J = 5.8 Hz, 1H), 3.87 (q, J = 6.2 Hz, 1H), 3.78−3.69 (m, 4H), 2.31 (dd, J = 12.8, 7.2 Hz, 1H), 1.90 (dd, J = 12.7, 6.8 Hz, 1H), 1.16 (d, J = 6.6 Hz, 3H), 0.81 (m, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.2, 151.7, 147.4, 145.8, 128.1, 83.3, 67.9, 63.6, 49.7, 32.2, 25.4, 18.3, 14.9, −5.6; Anal. Calc. for $C_{24}H_{43}ClN_4O_3Si_2$: C, 54.67; H, 8.22; N, 10.63. Found: C, 54.65; H, 8.25; N, 10.59.

(*rel*)−(2*S*,5*R*)−1−[4,4−Bis−(*tert*−butyldimethylsilanyloxymethyl)−5−methyltetrahydrofuran−2−yl]−N^4−benzoylcytosine (125) and (*rel*)−(2*S*,5*S*)−1−[4,4−bis−(*tert*−butyldimethylsilanyloxymethyl)−5−methyltetrahydrofuran−2−yl]−N^4−benzoylcytosine (126): The glycosyl donor **122** (389 mg, 0.9 mmol) was condensed with N^4−benzoylcytosine (387 mg, 1.8 mmol) by the same procedure as described for the preparation of **123** and **124** to give **125** (148mg, 28%) and **126** (142 mg, 27%) as white solids, respectively: compound for **125**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96−7.91 (m, 2H), 7.51−7.42 (m, 4H), 5.89 (d, J = 5.6, 1.8 Hz, 1H), 5.77 (d, J = 6.8 Hz, 1H), 3.89 (q, J = 6.8 Hz, 1H), 3.70−3.62 (m, 4H), 2.21 (dd, J = 12.8, 6.8 Hz, 1H), 1.88 (dd, J = 12.7, 8.4 Hz, 1H), 1.18 (d, J = 6.8 Hz, 3H), 0.81 (m, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 164.9, 159.7, 134.7, 133.4, 131.2, 129.5, 127.4, 99.3, 79.2, 68.9, 63.6, 63.1, 49.3, 30.5, 25.5, 18.7, 15.1, −5.6; Anal. Calc. for $C_{30}H_{49}N_3O_5Si_2$: C, 61.29; H, 8.40; N, 7.15. Found: C, 61.34; H, 8.37; N, 7.19; compound for **126**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, J = 6.2 Hz, 7.90 (m, 1H), 7.49−7.40 (m, 4H), 5.93 (t, J = 5.4, Hz, 1H), 5.71 (d, J = 7.0 Hz, 1H), 3.91 (q, J = 6.7 Hz, 1H), 3.73−3.61 (m, 4H), 2.19 (dd, J = 13.0, 8.2 Hz, 1H), 1.91 (dd, J = 12.9, 6.2 Hz, 1H), 1.16 (d, J = 6.4 Hz, 3H), 0.83 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 164.5, 158.2, 133.8, 132.6, 131.4, 128.1, 127.4, 124.5, 98.6,80.1, 67.4, 63.7, 63.3, 48.8, 30.7, 25.6, 18.4, 14.9, −5.7; Anal. Calc. for $C_{30}H_{49}N_3O_5Si_2$: C, 61.29; H, 8.40; N, 7.15. Found: C, 61.26; H, 8.44; N, 7.11.

(*rel*)−(2*S*,5*R*)−6−Chloro−9−[4,4−Bis−(hydroxymethyl)−5−methyltetrahydrofuran−2−yl]purine (127): To a solution of **123** (322 mg, 0.61 mmol) in THF/CH_3CN (1/1 co−mixture) (12 mL), TBAF (1.83 mL, 1.0 M solution in THF) was added at 0 °C. The mixture was stirred overnight at room temperature, and concentrated under reduced pressure. The residue was purified by silica gel

column chromatography (MeOH/CH_2Cl_2, 1:7) to give compound **127** (144 mg, 79%) as a white solid: UV (MeOH) λ_{max} 264.5 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.96 (s, 1H), 8.67 (s, 1H), 5.96 (dd, J = 5.6, 1.8 Hz, 1H), 3.92 (m, 1H), 3.46−3.35 (m 4H), 2.21 (dd, J = 12.8, 6.8 Hz, 1H), 1.89 (dd, J = 12.8, 9.2 Hz, 1H), 1.20 (d, J = 6.7 Hz, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.9, 152.1, 147.2, 127.6, 81.4, 69.1, 61.7, 61.3, 47.1, 31.5, 14.5; Anal. Calc. for $C_{12}H_{15}ClN_4O_3$: C, 48.25; H, 5.06; N, 18.76. Found: C, 48.32; H, 5.12; N, 18.69.

(*rel*)−(2*S*,5*S*)−6−Chloro−9−[4,4−Bis−(hydroxymethyl)−5−methyltetrahydrofuran−2−yl]purine (128): Purine derivative **128** was synthesized from **124** by the same procedure described for **127**: yield 75%; UV (MeOH) λ_{max} 264.0 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.85 (s, 1H), 8.36 (s, 1H), 5.99 (d, J = 5.4 Hz, 1H), 3.92 (m, 1H), 3.45–3.33 (m 4H), 2.24 (dd, J = 12.6, 8.2 Hz, 1H), 1.91 (dd, J = 12.6, 6.2 Hz, 1H), 1.19 (d, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 155.3, 153.2, 146.4, 128.1, 81.8, 68.9, 61.2, 60.8, 47.5, 30.8, 14.6; Anal. Calc. for $C_{12}H_{15}ClN_4O_3$: C, 48.25; H, 5.06; N, 18.76. Found: C, 48.18; H, 4.96; N, 18.82.

(*rel*)−(2*S*,5*R*)−1−[4,4−Bis−(hydroxymethyl)−5−methyltetrahydrofuran−2−yl] N^4−benzoylcytosine (129): Compound **129** was synthesized from **125** by the same procedure described for **127**: yield 79%; UV (MeOH) λ_{max} 259.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.24 (d, J = 6.7 Hz, 1H), 7.87 (m, 2H), 7.49−7.41 (m, 3H), 5.85 (m, 1H), 5.62 (d, J = 7.0 Hz, 1H), 3.86 (q, J = 6.7 Hz, 1H), 3.51−3.43 (m, 4H), 2.19 (dd, J = 13.2, 8.8 Hz, 1H), 1.84 (dd, J = 13.1, 7.4 Hz, 1H), 1.16 (d, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 164.3, 158.5, 135.2, 132.4, 130.3, 127.5, 124.4, 100.4, 78.7, 67.3, 61.7, 61.3, 46.1, 30.1, 14.3; Anal. Calc. for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.09; H, 5.78; N, 11.77.

(*rel*)−(2*S*,5*S*)−1−[4,4−Bis−(hydroxymethyl)−5−methyltetrahydrofuran−2−yl] N^4−benzoylcytosine (130): Compound **130** was synthesized from **126** by the same procedure described for **127**: yield 79%; UV (MeOH) λ_{max} 259.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (d, J = 6.6 Hz, 1H), 7.89 (d, J = 5.2 Hz, 1H), 7.47–7.42 (m, 4H), 5.93 (dd, J = 5.2, 1.2 Hz, 1H), 5.48 (d, J = 6.8 Hz, 1H), 3.86 (q, J = 6.8 Hz, 1H), 3.46−3.40 (m, 4H), 2.24 (dd, J = 12.8, 8.2 Hz, 1H), 1.89 (m,

1H), 1.14 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1, 165.1, 157.7, 134.5, 131.4, 129.1, 126.9, 123.4, 98.9, 79.1, 68.2, 63.3, 63.0, 47.2, 30.6, 15.7. Anal. Calc. for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.22; H, 5.91; N, 11.65.

(*rel*)-(2*S*,5*R*)-9-[4,4-Bis-(hydroxymethyl)-5-methyltetrahydrofuran-2-yl] adenine (131): A solution of **127** (180 mg, 0.6 mmol) in saturated methanolic ammonia (15 mL) was stirred in a steel bomb at 90-95 °C overnight and the mixture was concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:4) to give compound **131** (144 mg, 86%) as a white solid: m.p. 199-201 °C; UV (MeOH) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29 (s, 1H), 8.15 (s, 1H), 5.99 (d, J = 6.2 Hz, 1H), 4.93 (t, J = 5.2 Hz, 1H, D_2O exchangeable), 4.87 (t, J = 5.4 Hz, 1H, D_2O exchangeable), 3.93 (q, J = 6.8 Hz, 1H), 3.48-3.39 (m 4H), 2.18 (dd, J = 12.6, 6.6 Hz, 1H), 1.86 (dd, J = 12.7, 8.8 Hz, 1H), 1.19 (d, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.7, 152.5, 149.8, 141.3, 119.4, 80.8, 68.3, 61.2, 60.9, 46.3, 30.1, 15.0; Anal. Calc. for $C_{11}H_{17}N_3O_4$ (+0.5 MeOH): C, 50.83; H, 6.48; N, 23.71. Found: C, 50.91; H, 6.36; N, 23.77.

(*rel*)-(2*S*,5*S*)-9-[4,4-Bis-(hydroxymethyl)-5-methyltetrahydrofuran-2-yl] adenine (132): Compound **132** was synthesized from **128** by the same procedure described for **131**: yield 82%: m.p. 199-201 °C; UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.31 (s, 1H), 8.22 (s, 1H), 5.96 (t, J = 5.8 Hz, 1H), 4.91 (t, J = 5.3 Hz, 1H, D_2O exchangeable), 4.85 (t, J = 5.4 Hz, 1H, D_2O exchangeable), 3.89 (m, 1H), 3.46-3.33 (m 4H), 2.15 (m, 1H), 1.85 (dd, J = 12.8, 8.2 Hz, 1H), 1.21 (d, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.6, 152.8, 148.4, 142.0, 118.5, 79.2, 68.6, 60.9, 60.4, 46.5, 30.6, 14.6; Anal. Calc. for $C_{12}H_{17}N_5O_3$ (+1.0 H_2O): C, 48.47; H, 6.44; N, 23.55. Found: C, 48.53; H, 6.50; N, 23.51.

(*rel*)-(2*S*,5*R*)-1-[4,4-Bis-(hydroxymethyl)-5-methyltetrahydrofuran-2-yl] cytosine (133): A solution of **129** (123 mg, 0.34 mmol) in saturated methanolic ammonia (10 mL) was stirred overnight at room temperature and the mixture was concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:4) to give compound **133** (73 mg, 84%) as a

white solid: m.p. 202–204 °C; UV (MeOH) λ_{max} 271.0 nm; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 7.86 (d, J = 7.4 Hz, 1H), 5.87 (dd, J = 5.8, 1.8 Hz, 1H), 5.68 (d, J = 7.5 Hz, 1H), 4.89 (t, J = 5.4 Hz, 1H, D_2O exchangeable), 4.79 (t, J = 5.2 Hz, 1H, D_2O exchangeable), 3.89 (m, 1H), 3.47–3.38 (m, 4H), 2.20 (dd, J = 13.0, 6.2 Hz, 1H), 1.89 (dd, J = 12.9, 8.7 Hz, 1H), 1.24 (d, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO–d_6, 75 MHz) δ 165.2, 156.3, 142.3, 95.5, 79.0, 68.2, 60.7, 60.3, 47.2, 30.1; Anal. Calc. for $C_{11}H_{17}N_3O_4$ (+1.0 MeOH): C, 50.16; H, 7.37; N, 14.62. Found: C, 50.09; H, 7.33; N, 14.71.

(*rel*)–(2*S*,5*S*)–1–[4,4–Bis–(hydroxymethyl)–5–methyl–tetrahydrofuran–2–yl]cytosine (134): Compound **134** was synthesized from **130** by the same procedure described for **133**: yield 87%: m.p. 198–201 °C; UV (MeOH) λ_{max} 271.5 nm; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 7.84 (d, J = 7.6 Hz, 1H), 5.92 (d, J = 6.0 Hz, 1H), 5.62 (d, J = 7.7 Hz, 1H), 4.87 (t, J = 5.2 Hz, 1H, D_2O exchangeable), 4.77 (t, J = 5.2 Hz, 1H, D_2O exchangeable), 3.92 (q, J = 7.0 Hz, 1H), 3.49–3.39 (m, 4H), 2.18 (dd, J = 12.6, 7.2 Hz, 1H), 1.86 (dd, J = 12.7, 8.8 Hz, 1H), 1.22 (d, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO–d_6, 75 MHz) δ 165.4, 156.5, 143.0, 96.1, 79.6, 69.6, 61.8, 61.5, 47.8, 29.9; Anal. Calc. for $C_{11}H_{17}N_3O_4$ (+1.0 H_2O): C, 48.34; H, 7.00; N, 15.37. Found: C, 48.26; H, 7.03; N, 15.42.

Acetic acid 4–(*tert*–butyldimethylsilanyloxy)–3–methyl–but–2–enyl ester (136): To a solution of compound **135** (2.560 g, 11.83 mmol) in anhydrous pyridine (12 mL), DMAP (0.145 g, 1.18 mmol) and Ac_2O (1.34 mL, 14.20 mmol) was added, and the reaction mixture was stirred overnight at room temperature. The pyridine was evaporated under reduced pressure and co–evaporated with toluene. The residue was poured into water (50 mL) and extracted with EtOAc (50 mL) two times. The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **136** (2.782 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.53 (t, J = 7.1 Hz, 1H), 4.57 (d, J = 6.9 Hz, 2H), 4.12 (s, 2H), 1.98 (s, 3H), 1.60 (s, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.09, 140.71, 117.35, 67.40, 60.93, 25.89, 21.01, 18.37, 13.57, −5.38; Anal. Calc. for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14; O, 18.57; Si, 10.87.

Acetic acid 2-(*tert*-butyldimethylsilanyloxymethyl)-3,3-difluoro-2-methyl-cyclopropyl methyl ester (137): A solution of **136** (1.427 g, 5.52 mmol) in dry diglyme (3 mL) was heated to 190 °C. A solution of sodium chlorodifluoroacetate (9.260 g, 60.74 mmol) in dry diglyme (20 mL) was added at this temperature over a period of 60 min. After keeping the reaction at 190 °C for an additional 15 min, and cooling to room temperature, the reaction mixture was poured into ice water, the aqueous solution was extracted with hexane (50 mL) two times, and the combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **137** (1.277 g, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.19-4.00 (m, 2H), 3.60-3.40 (m, 2H), 1.99 (s, 3H), 1.66-1.56 (m, 1H), 1.49 (s, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.94, 58.47, 29.67, 25.73, 20.84, 18.17, 14.10, 9.46, 0.98, -5.50; Anal. Calc. for $C_{14}H_{26}F_2O_3Si$: C, 54.52; H, 8.50; F, 12.32; O, 15.56; Si, 9.11.

[2-(*tert*-Butyldimethylsilanyloxymethyl)-3,3-difluoro-2-methylcyclopropyl] methanol (138): A solution of **137** (1.712 g, 5.55 mmol) in MeOH (15 mL) was treated with catalytic mounts of NaOMe. After 30 min the reaction was complete and the reaction mixture was neutralized by the addition of 10 % aqueous hydrochloric acid. The mixture was extracted with ethyl acetate (30 mL) two times. The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvents were evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **138** (1.346 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.79-3.47 (m, 4H), 1.61-1.51 (m, 1H), 1.17 (s, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 65.16, 56.75, 31.13, 30.37, 25.77, 18.20, 9.30, -5.48; Anal. Calc. for $C_{12}H_{24}F_2O_2Si$: C, 54.10; H, 9.08; O, 12.01; Si, 10.54.

9-[2-(*tert*-Butyldimethylsilanyloxymethyl)-3,3-difluoro-2-methylcyclopropylmethyl]-6-chloropurine (139): To a stirred solution of PPh_3 (389 mg, 1.48 mmol) in THF (5 mL) at -20 °C was added dropwise the DIAD (0.29 mL, 1.48 mmol) and the yellow reaction mixture was stirred at this temperature for 30 min. After that, a solution of the compound **138** (304 mg, 1.14 mmol) in THF (3

mL), was added and the reaction mixture was stirred at −20 °C for 10 min. Then, the cold bath was removed and the yellow solution was stirred for 30 min at room temperature. 6−Chloropurine (212 mg, 1.37 mmol) was added finally and the solution became clear after 5 min. The reaction mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give **139** (289 mg, 63%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1H), 8.26 (s, 1H), 4.40 (d, J = 7.8 Hz, 2H), 3.61 (q, J = 8.7 Hz, 2H), 2.08−1.98 (m, 1H), 1.35 (s, 3H), 0.82 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.70, 144.50, 131.65, 118.19, 114.27, 110.50, 64.67, 38.58, 31.67, 27.01, 25.64, 18.14, 9.54, −5.59; Anal. Calc. for $C_{17}H_{25}ClF_2N_4OSi$: C, 50.67; H, 6.25; Cl, 8.80; F, 9.43; N, 13.90; O, 3.97; Si, 6.97.

9−[2−(*tert*−Butyldimethylsilanyloxymethyl)−3,3−difluoro−2−methylcyclopr−opylmethyl]adenine (140): Compound **139** (284 mg, 0.70 mmol) was dissolved in saturated methanolic ammonia (20 mL) and the resulting solution was stirred overnight at 100 °C in a steel bomb. After removal of reaction solvent, the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give the compound **140** (200 mg, 74%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (s, 1H), 8.04 (s, 1H), 4.32 (d, J = 7.5 Hz, 2H), 3.57 (t, J = 2.1 Hz, 2H), 2.02−1.92 (m, 1H), 1.24 (s, 3H), 0.81 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.09, 141.44, 64.86, 54.21, 25.73, −5.59; Anal. Calc. for $C_{17}H_{27}F_2N_5OSi$: C, 53.24; H, 7.10; F, 9.91; N, 18.26; O, 4.17; Si, 7.32.

9−[2−(Hydroxymethyl)−3,3−difluoro−2−methylcyclopropylmethyl]adenine (141): To a solution of **140** (76 mg, 0.20 mmol) in THF (3 mL) was added TBAF (0.79 mL, 1.0 M solution in THF) at 0 °C. The mixture was stirred overnight at room temperature and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to give **141** (44 mg, 83%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54 (s, 1H), 8.03 (s, 1H), 4.46−4.30 (m, 2H), 3.69 (s, 2H), 2.11 (q, J = 7.5 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.09, 141.68, 64.90, 54.31, 38.36, 27.43, 9.46; Anal. Calc. for $C_{11}H_{13}F_2N_5O$: C, 49.07; H, 4.87; F, 14.11; N, 26.01; O, 5.94.

9−[2−(*tert*−Butyldimethylsilanyloxymethyl)−3,3−difluoro−2−methylcyclopr−

opylmethyl]−N^4−benzoylcytosine (142): To a stirred solution of PPh_3 (531 mg, 2.03 mmol) in THF (5 mL) at −20 °C was added dropwise the DIAD (0.39 mL, 2.03 mmol) and the yellow reaction mixture was stirred at this temperature for 30 min. After that, a solution of the compound **138** (415 mg, 1.56 mmol) in THF (3 mL), was added and the reaction mixture was stirred at −20 °C for 10 min. Then, the cold bath was removed and the yellow solution was stirred for 30 min at room temperature. N^4−benzoylcytosine (402 mg, 1.87 mmol) was added finally and the solution became clear after 5 min. The reaction mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give **142** (441 mg, 61%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 1.8 Hz, 2H), 7.48 (t, J = 4.6 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.03 (d, J = 7.8 Hz, 1H), 6.49 (d, J = 7.9 Hz, 1H), 3.60−3.44 (m, 4H), 1.72 (t, J = 6.6 Hz, 1H), 1.24 (s, 3H), 0.79 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.17, 155.91, 150.43, 139.74, 136.01, 132.46, 129.69, 128.23, 98.68, 64.79, 43.92, 37.21, 31.13, 26.50, 25.74, 18.18, 9.56, −5.50; Anal. Calc. for $C_{23}H_{31}ClF_2N_3O_3Si$: C, 59.59; H, 6.74; F, 8.20; N, 9.06; O, 10.35; Si, 6.06.

9−[2−(*tert*−Butyldimethylsilanyloxymethyl)−3,3−difluoro−2−methylcyclopr−opylmethyl]cytosine (143): To a solution of **142** (304 mg, 0.66 mmol) in MeOH (5 mL) was added NaOMe (2 mL, 1.0 M in MeOH). The mixture was stirred for 4 h at room temperature and neutralized with acetic acid. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 4:1) to give compound **143** (170 mg, 72%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (s, 1H), 5.79 (s, 1H), 4.22−4.08 (m, 1H), 1.95−1.83 (m, 4H), 1.30 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.51, 126.21, 100.86, 63.87, 35.99, 33.57, 31.79, 25.54, 8.36, 7.83; Anal. Calc. for $C_{16}H_{27}F_2N_3O_2Si$: C, 53.46; H, 7.57; F, 10.57; N, 11.69; O, 8.90; Si, 7.81.

9−[2−(Hydroxymethyl)−3,3−difluoro−2−methylcyclopropylmethyl]cytosine (144): To a solution of **143** (87 mg, 0.24 mmol) in THF (3 mL) was added TBAF (0.97 mL, 1.0 M solution in THF) at 0 °C. The mixture was stirred overnight at

room temperature and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to give **144** (47 mg, 79%) as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.62 (s, 1H), 5.71 (s, 1H), 4.98 (t, J = 5.7 Hz, 2H), 3.90 (d, J = 6.6 Hz, 2H), 1.89 (t, J = 6.9 Hz, 1H), 1.15 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 162.18, 150.80, 143.73, 100.48, 63.04, 42.75, 34.05, 30.64, 26.24, 9.17; Anal. Calc. for $C_{10}H_{13}F_2N_3O_2$: C, 48.98; H, 5.34; F, 15.49; N, 17.14; O, 13.05.

In Vitro Anti-HIV-1 Activity Assay

The assay involved the killing of T4-lymphocytes by HIV-1. T4 lymphocytes were exposed to HIV at a virus-to-cell ratio of approximately 0.05 μM and treated with the compounds, dissolved in dimethylformamide, at doses ranging from 10^{-8} to 10^{-4} M. A complete cycle of virus reproduction is necessary to obtain the required cell killing (incubation at 37 °C in a 5% carbon dioxide atmosphere for 6 days). Uninfected cells with the compounds served as a toxicity control, whereas the infected and uninfected cells without the compound served as basic controls. After incubation, the tetrazolium salt XTT was added to all wells, and cultures were incubated to allow formazan color development by viable cells. Formazan production was measured spectrophotometrically and protective activity was confirmed by microscopy. The effect of each compound on cell growth of HIV-infected and uninfected cells was compared to that of untreated uninfected cells. All tests were compared with AZT as a positive control performed under identical conditions.

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ABSTRACT

Synthesis and antiviral evaluation of novel branched nucleosides

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Virus afflicts a tremendous crowd worldwide, and the development of direct acting antivirals may offer substantial benefit compared to the current standard of care. Nucleoside analogues play a major role in antiviral chemotherapy. Extensive modifications have been made to both the heterocyclic bases and the sugar moieties. Among several approaches to modify the structure of nucleosides, carbocyclic nucleosides have attracted great interest, because the former replacement of the furanose ring oxygen and C2′-methylene are transposed, which were reported to offers greater metabolic stability to the endogenous phosphorylase. The phosphonate functional group in nucleoside phosphonic acid analogues has certain advantages over its phosphate counterpart, which is metabolically stable because its phosphorus-carbon bond is not susceptible to hydrolytic cleavage.

Accordingly, novel branched carbocyclic nucleosides, 5′-norcarbocyclic nucleosides and apio dideoxynucleosides were designed and synthesized from the key intermediate and evaluated for their anti-virus efficacy. The key intermediate alcohol derivatives were successfully prepared by sequential [3,3]-sigmatropic rearrangement, Grignard addition, Eschenmoser's salt and ring-closing metathesis (RCM). Coupling of alcohol derivatives with nucleosidic bases *via* Mitsunobu reaction, Pd(0) catalyzed alkylation and Vorbrüggen condition afforded the target compounds. Among the synthesized nucleosides,

compounds **25**, **31**, **45**, **144** exhibited potent anti-HIV activities and compounds **17**, **59**, **77**, **88** were evaluated for toxicity (up to 100 μM) and related anti-HIV activity. Furthermore, these synthesized nucleoside analogues such as **102**, **103**, **112**, **131, 132, 133, 134** were evaluated for their potential to inhibit HCV RNA replication in a subgenomic replicon cell line (Huh-7 cell line). However, these nucleosides showed no significant inhibit HCV RNA replication in the cell-based replicon assay.

Key words:

Antiviral agents; Branched nucleoside; Carbocyclic nucleoside; Phosphonic acid nucleoside; SATE prodrug; Apiosyl nucleosides; Carbodine; [3,3]-Sigmatropic rearrangement; Ozonolysis; Grignard reaction; Eschenmoser's salt; Ring-closing metathesis; Mitsunobu reaction; Vicinal dihydroxylation.

감사의 글

열심히 해보겠다는 열정 하나만으로 한국에 와서 시작한 대학원 생활, 어느덧 세월이 흘러 그 마지막 시간을 맞이하게 되었습니다. 처음 실험을 시작하면서 실수도 수없이 하고 적지 않은 실패도 거듭하였지만, 반응을 한 step씩 진행하면서 좋은 실험결과가 나오기를 간절히 바라는 마음과 그 결과를 보면서 느끼는 희열감은 실험실 생활을 하는데 큰 힘이 되었고 그 한순간 한순간의 교훈들이 앞으로의 삶에 있어서 커다란 가르침이 될거라 믿습니다.

지난 5년간, 소정의 과정을 마치고 무사히 졸업하기까지 주위에 많은 고마운 분들이 있었기 때문입니다. 제게 이 분야에 대한 꿈을 가지게 해주셨고, 항상 세심한 관심과 배려로 부족한 저를 지도해주신 홍준희 지도교수님께 마음 깊이 감사드립니다. 바쁘신 와중에도 논문심사에 참여하시어 꼼꼼하게 검토를 해주시고 많은 조언을 해주신 우은란 교수님, 유진철 교수님, 이원재 교수님, 김은애 교수님께도 깊은 감사를 드리며 항상 따뜻한 웃음으로 반겨주셨던 고옥현 교수님께도 감사를 드립니다. 그외 열정적인 강의와 세미나 등을 통하여 저에게 많은 지식을 가르쳐 주신 약대에 계신 모든 교수님들께도 감사를 드립니다.

한국에 처음 왔을 때, 연구와 생활면에서 모두 많은 도움과 조언을 해주었던 애홍언니에게도 너무 감사하다는 말을 전하고싶습니다. 또한 한국에서 좋은 추억을 같이 만들었던 여러 선배님들과 후배들께도 감사드리며, 같은 공간에서 많은 일들을 공유하면서 소중한 시간을 보낸 실험실 식구들께도 감사드립니다. 그리고 어려울 때에는 같이 고민하고 기쁠 때는 같이 그 기쁨을 나누면서 저에게 큰 힘이 되어준 성춘, 관림이를 비롯한 많은 친구들에게도 너무너무 감사하다는 말을 전하고 싶습니다.

끝으로 한창 대학생활을 즐기면서 자기 꿈을 키워가고있는 사랑하는 동생과 지금까지 커다란 사랑으로 언제나 묵묵히 지켜봐 주시며 끝없이 저를 지지해주시는 사랑하는 부모님께 감사하는 마음으로 이 논문을 바칩니다.