[UCI]I804:24011-200000263304

2012年 8月

博士學位論文

Design and Synthesis of Novel Branched Nucleoside Analogues as Antiviral Agents

朝鮮大學校 大學院

藥 學 科

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Design and Synthesis of Novel Branched Nucleoside Analogues as Antiviral Agents

항바이러스제로서 측쇄를 가진 신규 뉴클레오시드 유도체의 설계 및 합성

2012年 8月 24日

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Design and Synthesis of Novel Branched Nucleoside Analogues as Antiviral Agents

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이 論文을 藥學 博士學位申請 論文으로 提出함.

2012年 4月

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국문초록

Design and Synthesis of Novel Branched Nucleoside Analogues as Antiviral Agents

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뉴클레오시드 유도체는 바이러스 생활주기에서 DNA/RNA의 합성을 억제하기 위하여 디자인된 항바이러스제이다. 이러한 약물들은 천연적인 뉴클레오티드와 아주 비슷한 구조를 나타내고 있다. 뉴클레오시드는 항바이러스계중에서 최다 사용빈도를 나타내는 효과적인 약물로서 현재 20여종의 약물들이 바이러스에 의한 병을 치료하는데 사용되거나 몇몇의 임상실험 후보물질로 등극되고 있다. 뉴클레오시드 유도체는 대체로 푸린 유도체이거나 피리미딘 유도체이다. 이러한 약물의 구조는 천연적으로 존재하는 뉴클레오시드와 밀접한 공통점이 있다. 예를 들어 지도부딘, 스타부딘, 아시클로비어, 디다노신, 잘시타빈, 타미부딘 등을 포함하고 있다.

카보사이클릭 뉴클레오시드는 항바이러스, 항종양 작용과 같은 광범위한 생물학적 활성을 가지고 있을 뿐 만 아니라 카보사이클릭 뉴클레오시드는 약물이나 효소의 가수분해에 대한 대사과정에서의 높은 안정성도 가지고 있다. 새로운 약물-내성을 가지는 바이러스와 약물의 세포독성은 항 바이러스 화학치료요법에 있어서

핵심문제인데 이러한 문제를 해결하려면 구조적으로 변화된 뉴클레오시드의 연구가 필요하다.

2'-위치의 Geminal 치환은 바이러스 폴리미라아제와의 상호작용에서 입체적뿐만 아니라 전자작용을 더욱 유리하게 할 수 있다. 이러한 정보를 토대로 2'(β)-C-카보딘 뉴클레오시드에서 2'-위치의 변경에 초점을 두고 저는 카보사이크릭 뉴크레오시드 28, 31, 40, 42, 44, 45을 디자인하고 합성하였다. 흥미 있는 SAR (구조활성 관계)를 토대로 저는 새로운 뉴크레오시드 유도체 즉 4'-에티닐 카보사이크릭 뉴클레오시드 61, 62, 63, 66와 4'-사이클로프로필 카보사이클릭 뉴클레오시드 77, 78을 합성하였다. 여러 가지 바이러스에 더욱 유효한 치료제와 뉴클레오시드, 뉴크레오티드의 대사에 관여하는 효소의 구상을 검사하기 위한 유사체를 제공하기 위하여 저는 4'-branched-5'-nor카보사이클릭포스폰산 유도체 96, 97, 112, 113, 114와 116을 디자인하고 합성하였다. 6'-음전하 뉴클레오시드 유도체와 5'-nor카보사이클릭 뉴클레오시드 포스폰산은 좋은 생물학적 활성을 가지고 있다. 이러한 정보를 기초로하여 더욱 유력한 HIV치료제를 찾기 위하여 6'-메틸렌과 6'-sipro사이클로프로필 5'-nor카보사이클릭 포스폰산 유도체를 포함한 새로운 종류의 뉴크레오시드 유도체 (±)-129, (±)-130, (±)-134, (±)-135, (±)-136, 150, 151, 152α, 153, 155를 합성하였다.

합성한 뉴클레오시드 유도체들에 대하여 항바이러스 활성을 분석하였다. 시토신 유도체 28은 유력한 항-HCV 활성을 나타내었고 시토신 유도체 44는 레플리콘의 복제를 약하게 억제하였다. 구아닌 유도체 66은 HIV-1에 대하여 약한 항 바이러스 활성을 나타냈고 티민 유도체 62는 HCMV에 대하여 약한 항 바이러스 활성을 나타냈다. 합성물 77과 78은 Davis 세포에서 100μmol보다 높은 농도에서도 어떠한 독성도 나타내지 않았으며 HCMV에 대해 약한 항바이러스 활성을 나타냈다.

뉴클레오티드 포스폰산 97은 100 μM까지의 농도에서 본체 뉴클레오시드 데실 포스폰산염 96보다 더욱 강한 항-HIV 활성을 나타냈다. 아데노신 포스폰산 113은 IC_{50}=28.3에서 항-HIV활성을 나타냈다. 하지만 뉴클레오티드 유사체 112, 114와 116은 100 μM까지의 농도에서도 항-HIV활성이나 세포독성을 나타내지 않았다. 구아닌 뉴클레오시드 포스폰산 (±)-136은 유력한 항-HIV 활성을 나타냈다. 그러나 뉴클레오시드 유도체 (±)-129, (±)-130, (±)-134와 (±)-135는 100 μM까지의 농도에서도 낮은 항-HIV 활성 혹은 세포독성을 나타냈다. 뉴클레오시드 포스폰산 155은 본체 뉴클레오시드 린산 151과 비교했을 때 항-HIV 활성은 증가한 것으로 나타냈다. 하지만 뉴클레오시드 유도체 150, 152α와 153은 100 μM까지의 농도에서도 항-HIV 활성 혹은 세포독성을 나타나지 않았다.

ABBREVIATION

AIDS: Acquired immunodeficiency syndrome

HIV: Human immunodeficiency virus

DNA: Deoxyribonucleic acid

RNA: Ribonucleic acid

PR: Protease

HCV: Hepatitis C virus

RdPp: RNA-dependent RNA-polymerase

AZT: 3'-Azido-2',3'-dideoxythymine

D4T: Stavudine

GCV: Ganciclovir

ACV: Acyclovir

ND: Not determined

FDA: Food and Drug Administration

SAM: *S*-adenosylmethionine

SAR: Structure Activity Relationship

RT: Reverse transcriptase

HBV: Hepatitis B virus

SATE: *S*-acyl-2-thioethyl

R-MuLV: Rauchermurine Leukemia virus

d4AP: [5-(6-aminopurin-9-yl-)2,5-dihydrofuran-2-yl-oxymethyl]-phosphonic acid

BnBr: Benzylbromide

NaH: Sodium hydride

DMF: *N,N*−Dimethylformamide

DIAD: Diisopropylazodicarboxylate

PPh_3: Triphenylphospine

NaOMe: Sodium methoxide

TFA: Trifluoric acetic acid

TEA: Triethylamine

DCE: Dichloroethane

NOE: Nuclear magnetic resonance

RCM: Ring−closing metathesis

THF: Tetrahydrofuran

TBAF: Tetrabutylammonium fluoride

DMAP: 4−(Dimethylamino)pyridine

DMSO: Dimethyl sulfoxide

OsO_4: Osmium tetroxide

NMO: 4−Methylmorpholine *N*−oxide

TBDMSCl: *tert*−Butyldimethylsilyl chloride

DCC: *N,N'*−Dicyclohexylcarbodiimide

DIBALH: Diisobutylaluminum hydride

TBDMSOTf: *tert*−Butyldimethylsilyl trifluoromethanesulfonate

Li−*t*−Bu: Lithium *tert*−butyl

CH_3CN: Acetonitrile

DMS: Dimethylsulfide

BzCl: Benzylchloride

t−BuOLi: Lithium *tert*−butoxide

PMBCl: p−Methoxybenzyl chloride

MnO_2: Manganese dioxide

DEAD: Diethyl azodicarboxylate

DDQ: 2,3−Dichloro−5,6−dicyano−*p*−benzoquinone

TMSBr: Trimethylsilylbromide

NMR: Nuclear magnetic resonance

TLC: Thin layer chromatography

INTRODUCTION

Viral diseases are still one of the biggest challenges to medical science. Thanks to thousands of years of co-evolution with humans, their ability to harness the biology of their human hosts to survive and thrive makes them very difficult to target with medical treatment. During the last two decades, treatment of viral infections has advanced remarkably, driven particularly by the search for effective agents for the treatment of AIDS and viral hepatitis. In recent years, new and emerging viruses, such as new strains of hepatitis and herpes viruses, Ebola, West Nile, and SARS, have shown their lethal potential. Furthermore, the threat that viruses and other microorganisms could be used as biological weapons in warfare or bioterrorism has brought antiviral research to the forefront. Although vaccination is a valuable preventative tool for certain viral infections, new and effective antiviral agents are needed to prevent acute and chronic viral infections.

Human immunodeficiency virus (HIV) is a lentivirus that causes acquired immunodeficiency syndrome (AIDS),[1,2] a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate, or breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells.

HIV is a member of the genus Lentivirus,http://en.wikipedia.org/wiki/HIV - cite_note-ICTV61.0.6-15 part of the family of Retroviridae. Lentiviruses have many

morphologies and biological properties in common. Many species are infected by lentiviruses, which are characteristically responsible for long–duration illnesses with a long incubation period.[3] Lentiviruses are transmitted as single–stranded, positive–sense, enveloped RNA viruses. Upon entry into the target cell, the viral RNA genome is converted (reverse transcribed) into double–stranded DNA by a virally encoded reverse transcriptase that is transported along with the viral genome in the virus particle. The resulting viral DNA is then imported into the cell nucleus and integrated into the cellular DNA by a virally encoded integrase and host co–factors.[4]http://en.wikipedia.org/wiki/HIV - cite_note-JASmith-18 Once integrated, the virus may become latent, allowing the virus and its host cell to avoid detection by the immune system. Alternatively, the virus may be transcribed, producing new RNA genomes and viral proteins that are packaged and released from the cell as new virus particles that begin the replication cycle anew.

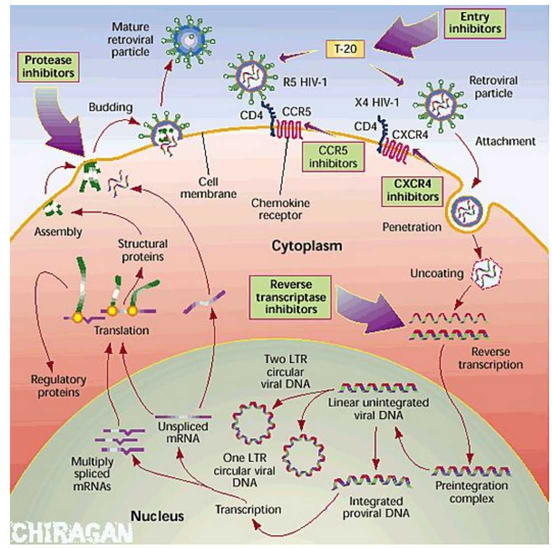


Figure 1. The diagram of HIV life cycle

HIV protease (HIV PR) is a retroviral aspartyl protease (retropepsin) that is essential for the life-cycle of HIV(**Figure 1**), the retrovirus that causes AIDS. [5,6] HIV PR cleaves newly synthesized polyproteins at the appropriate places to create the mature protein components of an infectious HIV virion. Without effective HIV PR, HIV virions remain uninfectious.[7,8] Thus, mutation of HIV PR's active site or inhibition of its activity disrupts HIV's ability to replicate and infect additional cells,[9] making HIV PR inhibition the subject of much pharmaceutical research.[10]

Hepatitis C virus (HCV) is spread by blood-to-blood contact with an infected person's blood. No vaccine against hepatitis C is available. The symptoms of infection can be medically managed, and a proportion of patients can be cleared of the virus by a long course of anti-viral medicines. Although early medical intervention is helpful, people with HCV infection often experience mild symptoms, and consequently do not seek treatment. An estimated 150-200 million people worldwide are infected with hepatitis C. Hepatitis C virus (HCV) is the major causative agent for non-A, non-B virally induced hepatitis.[11] Hepatitis C virus (HCV) infection[12] is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals. Once infected, about 20% of people clear the virus, but the rest can harbor HCV the rest of their life. About 10-20% of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. Current therapy based on pegylated interferon and ribavirin is often poorly

tolerated and effective in only 50% of patients.[13] Moreover, this limited efficacy is often associated with significant side effects, leading to discontinuation of treatment.[14] There is no established vaccine for HCV. Therefore, there is a need for the development of more effective therapeutic agents for the treatment of HCV infection.[15]

The hepatitis C virus particle consists of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and further encased in a lipid (fatty) envelope of cellular origin. Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope.[16] For the development of antiviral drugs against HCV entry, enveloped proteins have been extensively utilized, especially targeting the carbohydrate moieties on E1 and E2 proteins. The first step of HCV life cycle involves the attachment of viral particles to the cell surface which is followed by internalization. So, various entry inhibitors are reported to prevent the entry of virions.

HCV replication is instigated by the formation of replicase complex which is allied with intracellular membrane containing cellular proteins. Replicase complex consists of cleavage products of HCV polyprotein precursor especially NS3-5B which play an important role in replication (**Figure 2**). Along with these proteins and cis acting RNA elements, various host factors are also involved in HCV RNA replication[17-19]. NS5B is the RNA-dependent RNA polymerase (RdRp) which can start RNA synthesis do novo. RdRp activity is shown to be enhanced by interacting with cyclophilin B and viral factors such as NS3 and NS5A. A

negative−strand copy of viral genome is primarily produced by NS5B RdRp. In−vitro this enzyme has a preference for primer−dependent RNA synthesis, either

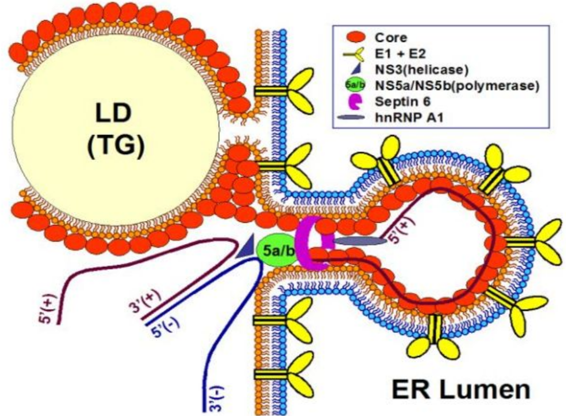


Figure 2. Hypothetical medel of HCV replication complex

by elongation of a primer hybridized to an RNA homopolymer or through a copy−back mechanism while exploiting heteropolymeric templates [20,21]. NS3 protein possesses helicase, protease and RNA triphosphatase activity. Even though NS3 exhibits innate proteolytic activity, NS4A cofactor is required for the cleavage of polyprotein. Due to vague understanding of helicase enzymology, NS3 helicase is a hard−hitting target for drug designing [22.]

Nucleoside analogs are a class of antiviral drugs designed to inhibit DNA/RNA synthesis in the viral life cycle. These drugs possess very similar structures to the natural nucleotides they are competing with. The drugs included in this class inhibit viral DNA/RNA synthesis due to the absence of a 3'−hyroxyl group. A great deal of the research spent on developing these types of drugs is a result of our fight against viruses such as HIV, HCV. Nucleosides are the most frequently used effective class of antiviral agents, with over 20

drugs currently approved for the treatment of viral diseases and a number of candidates in the clinical trials.[23] Nucleoside analogs may be either purine analogs or pyrimidine analogs(**Figure 3**). In either case, the structures of the drugs closely resemble their natural nucleotide counterparts. Examples of these include zidovudine(AZT), stavudine, acyclovir, didanosine, zalcitabine, and lamivudine.

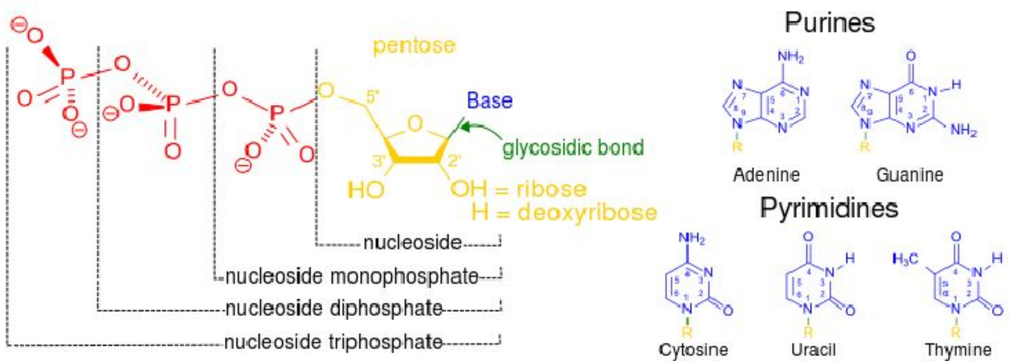


Figure 3. The structure elements of the nucleosides and the Phosphate group bearing nucleotides.

The general mode of action of nucleoside analogs is to compete with natural nucleotides for the active site of either reverse transcriptase or viral polymerases. Nucleoside analogs tend to have a higher affinity for these enzymes than do the natural nucleotides. Once attached to the growing chain of DNA, the lack of the 3'-hydroxyl group on the nucleoside analog results in chain termination (**Figure 4**). However, it is important to note that nucleoside analogs have no intrinsic activity against the target virus. The analogs must first be metabolized by the host cell to their respective 5'-triphosphate derivatives by

kinases, nucleotidases or other cellular enzymes in order to display antiviral activity.

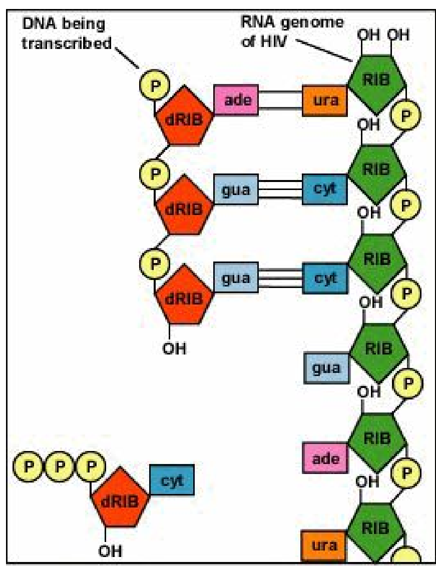


Figure 4. action of mechanism of anti viral nucleoside

Carbocyclic analogues of dideoxyadenosine were investigated for their anti-HIV activity. Minimal activity was first observed. Many nucleoside analogues were prepared and examined but only one had significant activity and satisfied the requirements for clinical use. That was 2',3'-didehydro analogue of dideoxyadenosine. Insertion of a cyclopropyl group on its 6-amino nitrogen of the adenine ring increased lipophilicity and thus enhanced brain penetration. The resulting compound is known as abacavir (Table 1).[24] Abacavir was approved by the FDA for use in therapy of HIV-1 infections in December 1998.[25] This drug is the only approved antiretroviral that is active as a guanosine analogue in vivo. First it is monophosphorylated by adenosine phosphotransferase and then the monophosphate is converted to carbovir 3'-monophosphate. Subsequently it is

fully phosphorylated and the carbovir is incorporated by the RT into the DNA chain and acts as a chain terminator. Carbovir is a related guanosine analogue that had poor oral bioavailability and thus was withdrawn from clinical development.[26]

Table 1. Comparison of chemical structures: Dideoxyadenosine, didanosine and abacavir

	Dideoxyadenosine	Didanosine	Abacavir
Chemical structure			

Nucleosides exert their activity against the hepatitis C virus by mimicking cellular nucleotides (the building blocks of RNA) and inhibiting RNA synthesis. Through this disruption of RNA production, incomplete and therefore incompetent copies of the hepatitis C viral genome are produced. Nucleoside analogs that have entered development for the treatment of chronic hepatitis C have demonstrated a high barrier to the development of resistance. While nucleoside analogs show great promise for the treatment of chronic hepatitis C, there are a limited number of compounds in development and none have progressed beyond phase II studies.

Nucleoside analogues are the drugs of choice in curing viral infection, and were synthesized and evaluated for anti-HCV activity.[27] These nucleosides are

incorporated into proviral RNA and act as chain terminators.[28] The nonstructural protein NS5B is an RNA-dependent RNA polymerase that is required for viral replication. This polymerase is an essential component in the HCV replication complex and therefore is an ideal target for drug discovery.[29] The molecular virology of HCV has led to the identification of a number of antiviral molecular targets, including the NS5B RNA-dependent RNA polymerase. Inhibition of this enzyme inhibits HCV replication, making this enzyme a crucial target for new anti-HCV agents. Recently, several 2'-modified nucleoside analogues with potent inhibitory activity against the HCV NS5B polymerase have been identified.[30] Modification in the vicinity of the 2'-hydroxy of the ribose in natural ribonucleosides can produce effective RNA chain terminators.[31] For example replacement of the 2'-hydrogen of natural ribonucleosides with a methyl group yields compounds with excellent chain-terminating properties. Among them, 2'-*C*-methylcytidine[32]1 and 2'-*C*-methyladenosine[33]2 are potent anti-HCV agents in clinical trials (Figure 5). Recently, Jeong et al. reported a synthetic procedure

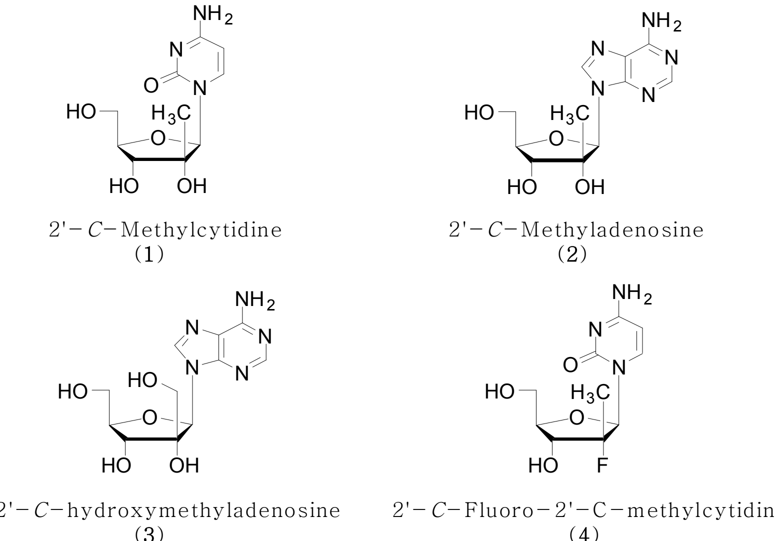


Figure 5. Structure of potent nucleoside anti-HCV agents.

and potent anti-HCV activity of 2'-*C*-hydroxy-methyl adenosine 3.[34] More recently, 2'-*C*-fluoro-2'-*C*-methylcytidine 4 was designed as a hepatitis C virus RNA-dependant RNA polymerase (HCV RdRp) inhibitor and showed better inhibitory activity in the HCV replicon assay than 2'-*C*-methylcytidine, with low cellular toxicity.

Carbocyclic nucleosides[35] are a group of compounds structurally analogous to natural and synthetic nucleosides in which the furanose oxygen has been replace by a methylene group. This replacement changes the furanose ring into a cyclopentane. 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. Although these two classes of rings are far from being identical, the cyclopentene or cyclopentane ring allows carbocyclic nucleosides to be recognized as substrates or inhibitors of various enzymes.[36] Therefore, the carbocyclic nucleosides possess a wide

range of biological activities such as antiviral and antitumor effects.

Based on this information, I designed fluorinated analogues of carbocyclic nucleosides as anti-HCV agents, focusing on the modification of the 2'-position of the potent 2'(β)-*C*-methyl carbodine nucleosides and 2' -*C*-hydroxyethylated carbodine analogues as potent anti-HCV agents. Geminal substitution at the 2'-position might impose favorable steric as well as electronic effect on the interaction with HCV polymerase.

The development of new effective antiviral agent is essential for overcoming viral diseases, such as acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV). Replacement of the furanose ring oxygen atom with carbon is of particular interest because the resulting carbocyclic nucleosides[37] have greater metabolic stability against chemical or enzymatic hydrolysis,[38] which cleaves the glycosidic bond of nucleosides. Many carbocyclic nucleosides have antiviral and anticancer activity because the cyclopentane ring of these compounds can emulate a furanose moiety. Carbocyclic nucleosides are also potent inhibitors of the cellular enzyme, *S*-adenosyl-*L*-homocysteine (AdoHcy) hydrolase, which regulates *S*-adenosylmethionine (SAM)-dependent methylation reactions, and are specific targets for the reversible hydrolysis of the AdoHcy linkage to adenosine and homocysteine.[39] The recent discovery of olefinic carbocyclic nucleosides, such as carbovir[40] and abacavir,[41] which are potential anti-HIV agents, has increased interest in the search for novel carbocyclic nucleosides, whereas their side effects[42] and the emergence of drug-resistant mutants are lasting concerns to be solved.[43]

The finding that thymidine analogues with 4'−azido 5[44] and 4'−cyano groups 6[45] show significant inhibitory activity against HIV proliferation have stimulated the synthesis of 4'−substituted nucleoside analogues to lead to the discovery of 4'−ethynylated stavudine 7[46] and thiostavudine 8[47] analogues which turned out to be efficient antiviral and antitumor agents (**Figure 6**).

(5): R = N_3
(6): R = CN

(7)

(8)

Figure 6. Stuctures and rationale of target 4'−ethynylated nucleosides.

Stimulated by these interesting SAR (structure activity relationship), me describe herein the synthesis of a novel class of nucleosides containing 4−ethynyl carbocyclic nucleosides and 4'−alkylated carbocyclic nucleoside with an additional cyclopropyl group which has a similar electron density as those of double or triple bond.

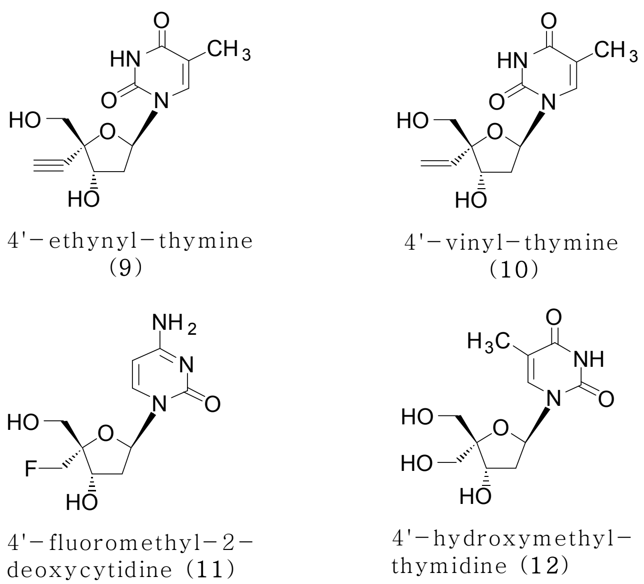


Figure 7. Structures of 4'−branched nucleoside analogues as potent anti−HIV agents.

Several branched nucleosides[48] have been synthesized and evaluated as potent antiviral agents. Among them, 4'−ethynylthymi−dine (9)[49] and 4'−vinylthymidine (10)[50] which have an additional triple or double bond at the 4'−position, were reported to have potent anti−HIV activities (**Figure 7**). Then 4'−homologated nucleosides such as 4'−fluoromethyl−2'−deoxycytidine (11)[51] and 4'−hydroxymethylthymidine(12)[52] analogues are molecules of considerable interest(**Figure 7**). One of reasons for this prominence arises from the notable biological activities as anti−HIV agents. Molecular modeling studies demonstrated the presence of a relatively hydrophobic 4'−pocket that can accommodate these substitutions, contributes to the observed enhancement in potency.[53]

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.[54] Moreover, a phosphonate nucleoside analogue can skip the requisite first phosphorylation, which is a crucial step for the activation of nucleosides. This is frequently a limiting event in the phosphorylation sequence, which ultimately leads to triphosphates.[55] The spacial location of the oxygen atom, namely the β−position from the phosphorus atom in the nucleoside analogue, has been demonstrated to play a critical role for antiviral activity. This oxygen atom for antiviral activity may be attributed to the increased binding capacity of the phosphonate analogues to target enzymes.[56]

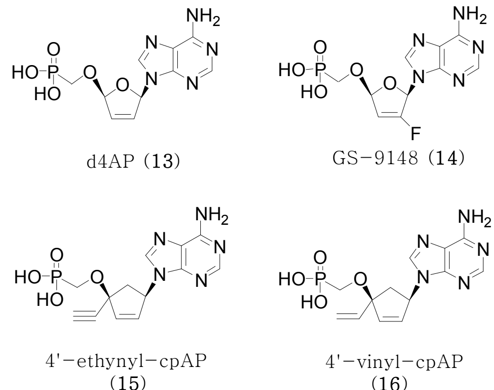


Figure 8. Structures of 5'−nornucleoside analogues as potent anti−HIV agents.

Emerging drug−resistant viral strains and drug toxicity are major problems in antiviral chemotherapy,[57] which has lead to research for structurally modified nucleosides. Although the pharmacophore of nucleoside antiviral activity is not completely defined, 5'−nornucleoside phosphonic acid analogues such as d4AP (13),[58] GS−9148 (14)[59] and 4'−Brnched−5'−Norcarbocyclic nucleoside phosphonic acid analogues such as 4'−ethynyl−cpAP (15), 4'−vinyl−cpAP (15)

as potential anti-HIV agents have encouraged the search for novel nucleosides in this class of compounds (Figure 8).

The target of nucleoside analogs in the war on HIV is reverse transcriptase. Reverse transcriptase makes a good target because it is unique to the virus. It was likely chosen with the hope of developing antiviral agents that would possess a high viral selective toxicity with little or no effect on the host cells. Unfortunately, due to the nature of nucleoside analogs, host cells have also suffered from the toxic effects of these antiviral agents. Actually, the exact role of substituent in 4'-position in nucleoside analogues in inhibiting reverse transcriptase (RT) has not been explored clearly. In continuation of our effort to find detailed structure activity relationship of branched nucleoside as RT inhibitor. More efficient therapeutic agents against HIV and to provide analogues for probing the conformational preferences of enzymes associated with the metabolism of nucleosides and nucleotides, I have designed and prepared a novel class of nucleosides comprising 4'-branched-5'-norcarbocyclic phosphonic acid analogues.

Much attention has been paid to unusual nucleosides since 6'-modified nucleosides were reported to be promising anti-human immunodeficiency virus (anti-HIV) and anti-hepatitis B virus (anti-HBV) agents. As mimics of nucleoside monophosphates, these nucleotide analogues exert their antiviral effect following sequential activation by cellular kinases to their diphosphate derivatives (nucleoside triphosphate analogues) which act as potent inhibitors of viral DNA polymerases.[60] A selective inhibition for these enzymes as opposed to

host cell DNA polymerases is critical for the potential use of such compounds as drugs. Various attempts to improve the selectivity index have led to rigid nucleoside analogues modified in their cyclopentane ring system by introduction of unsaturations, sometimes with an exomethylene moiety in 6'-position. Among these compounds, entecavir[61] 17 is being clinically used as anti-HBV drugs (Figure 9). Recently, an isonucleoside with an exomethylene[62] 18 or with a spirocyclopane[63] 19 moiety in place of a carbon atom of a furanose ring was reported to show antiviral activity, especially anti-HIV activity. The phosphonate analogue 20 was successfully prepared and evaluated for its inhibitory effect on the replication of retroviruses, including Rauchermurine Leukemia virus (R-MuLV) and HIV-1. Furthermore, compound 20 was superior to d4T in inhibiting R-MuLV at three orders magnitude low concentration, indicating that the murine model might be useful to evaluate 20 for its in vivo efficacy against the retrovirus.[64] Molecular modeling studies demonstrated the presence of an electronegative moiety at the 6'-position that could accommodate these substitutions and contribute to the observed enhancement in potency in anti-HIV activity.[63] Furthermore, 4'-bis-SATE (bis-*S*-acyl-2-thioethyl) prodrug of adenine analogue[65] (21) showed excellent antiviral activity in the genotype 1b subgenomic replicon system (Figure 9).

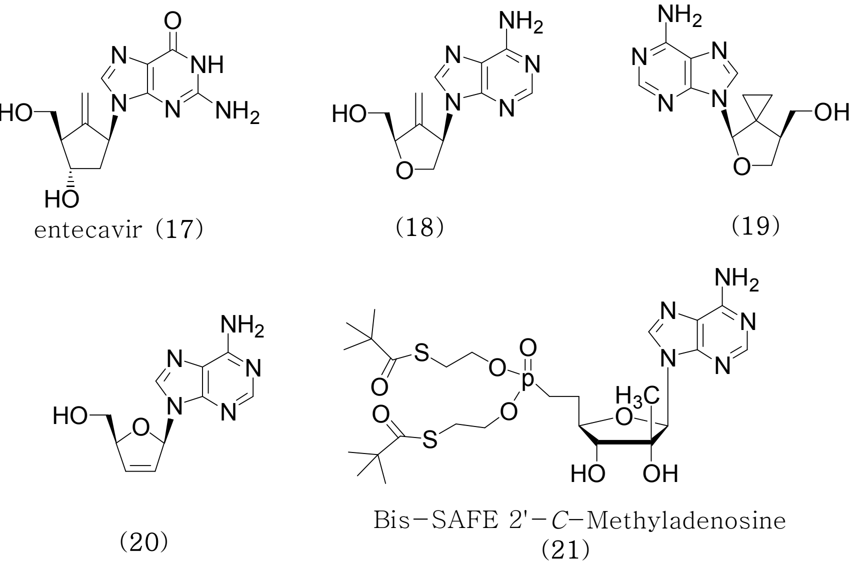


Figure 9. Structure of nucleoside analogures as potent antiviral agents.

Stimulated by these findings that 6'-electronegative nucleoside analogues and 5'-norcarbocyclic nucleoside phosphonates have excellent biological activities, I sought to synthesize a novel class of nucleosides comprising 6'-methylen and 6'-spirocyclopropyl 5'-norcarbocyclic phosphonic acid analogues in order to search for more effective therapeutics against HIV and to provide analogues for probing the conformational preferences of enzymes associated with the nucleoside kinases of nucleosides and nucleotides. And I sought to synthesize novel classes of nucleotides cyclic SATE phosphonodiester prodrug rather than its bis-SATE counterpart which has a bigger molecular size.

RESULTS AND DISCUSSION

As depicted in **Scheme 1**, I used the epoxide intermediate **23** as starting material, which could be readily synthesized via commercially available

methylcyclopentenone 22 as described in a previous report.[66] First, the hydroxy functional group was masked with a benzyl group under the usual benzylation conditions (BnBr, NaH, DMF) to provide a fully protected intermediate **24**, which underwent a ring−opening fluorination reaction with hydrofluoric acid in the presence of silicon fluorides and additives to provide cis−fluorohydrin in good yield (**Scheme 1**).[67] The formation of the cis−isomer may be due to the hydrogen

Reagents: i) BnBr, NaH, DMF; ii) 47% HF, $(NH_4)_2SiF_6$, CsF.

Scheme 1. Synthesis of fluorinated key intermediate **25**.

X = MF_n or H

Figure 10. Possible intermediate for the formation of **25**.

bonding and/or silyl ether formation as shown in **Figure 10**.

To synthesize the desired carbocyclic nucleoside analogues, the alcohol derivative 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 inversion of the configuration.[68] First, N^4−benzoyl cytosine was treated with the protected fluorohydrin **25** in the presence of diisopropylazodicarboxylate (DIAD) and PPh_3 to give **26** in 68% yield (**Scheme 2**). The removal of N^4−benzoyl group of nucleoside analogue **26** was performed by sodium methoxide. Hydrogenolysis of the benzyl protecting group of **27** with a palladium hydroxide gave the target cytosine derivative **28**. For the synthesis of the adenine nucleoside analogue, similar reactions for the synthesis of the cytosine analogue were attempted. N^6−Bis−Bocadenine[69] was similarly subjected to Mitsunobu co−

Reagents: i) N^4−Bz−cytosine, PPh_3, DIAD; ii) NaOMe/MeOH; iii) $Pa(OH)_2$, cyclohexene, MeOH, reflux.

Scheme 2. Synthesis of target 2'−fluoro−cytidine analogue.

upling conditions (DIAD, PPh_3) to give adenine analogue **29** in a high yield, 93%. Two boc−protection groups of **29** were removed in trifluoric acetic acid (TFA) conditions to give **30**, which was finally transformed to target compound **31** through the debenzylation conditions as used for **28** (**Scheme 3**).

Reagents: i) N^4−bis−Boc−adenine,PPh_3, DIAD, 0℃; ii) TFA, DCE/MeOH, rt; iii) $Pa(OH)_2$, cyclohexene, MeOH, reflux

Scheme 3. Synthesis of target 2'−fluoro−adenosine analogue.

Figure 11. Possible intermediate for the formation of 28.

As shown in **Figure 11**, the relative stereochemistry was unambiguously confirmed on the basis of the NOE results between the proximal hydrogens. On irradiation of $C_2(CH_3)$−H, relatively weak NOE was observed at C_1−H (0.21%), compared to that of C_3−H (0.86%).

The synthesized compounds were tested for anti−HCV activity using an *in vitro* assay. This system is composed of a human hepatocarcinoma cell line (Huh−7) supporting multiplication of an HCV replicon named NK−R2AN.[70] Cytosine analogue **28** weakly inhibited the replication of the replicon, NK−R2AN, in Huh−7 cells by 50% at 18.2 μM (**Table 2**).

Table 2. Anti−HCV activity of the newly synthesized compounds **28** and **31**

Compound no.	Anti−HCV EC_{50} (μg/mL)	Cytotoxicity CC_{50} (μg/mL)
28	18.2	32.1
31	>50	>50
2'−*C*−Me−Cyt	3.7	>50

2'−*C*−Me−Cyt: 2'−*C*−Methylcytidine. **EC_{50}** (μg/mL): Concentration required to inhibit 50% of the virus induced cytopathicity. **CC_{50}** (μg/mL): Concentration required to reduce cell viability by 50%.

In summary, the present ring−opening fluorination of epoxide using hydrofluoric acid offers a convenient procedure for the synthesis of cis−fluorhydrins. On the basis of potent anti−HCV activity of 2'−modified nucleosides, I have designed and synthesized 2'(α)−*C*−fluoro−2'(β)−*C*−methyl carbodine derivatives from 2−methyl cyclopentenone. The cytosine analogue **28** exhibited potent anti−HCV activity.

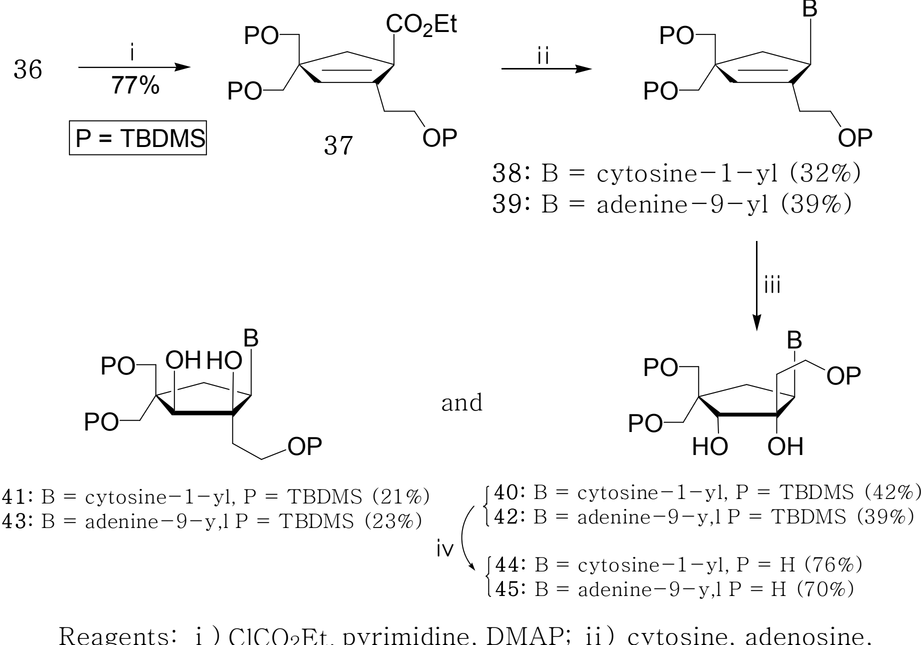
For the synthesis of target carbocyclic nucleoside analogues, cyclopentene derivative **37** was chosen as the key intermediate prepared from aldehyde **33** as starting material.[71] The aldehyde was condensed with the lithium reagent prepared from three equivalents of 3−bromo−but−3−enyloxy−*t*−butyldimeth−

ylsilane 34 and 2.5 equivalents of butyl lithium in THF at −110 ℃ to yield the diene analogue 35.[72] The diene analogue 35 was subjected to ring−closing metathesis (RCM) conditions[73] using secondsgeneration Grubbs catalysis to provide cyclopentenol 36 as a racemic mixture (Scheme 4).

Reagents: i) 34,(3−Bromo−but−3−enyloxy)−*t* −butyldimethylsilane, butylithium, −100℃, THF; ii) second Grubbs catalysis, benzene.

Scheme 4. Synthesis of cyclopentenol intermediate 36.

Cyclopentenol 36 was transformed to the ethyl formate analogue 37 using ethyl chloroformate in pyridine solvent, and readily coupled with cytosine and adenine by allylic functionalization using a palladium catalyst adduct to generate nucleoside analogues 38 and 39. Vicinal oxidations of olefin of the nucleoside analogues 38 and 39 gave carbodine−like nucleoside analogues 40 and 42 as m−



Reagents: i) $ClCO_2Et$, pyrimidine, DMAP; ii) cytosine, adenosine, $Pd_2(dba)_3 \cdot CHCl_3$, P(O−*i*−pr)$_3$, NaH, vTHF/DMSO; iii) OsO_4, NMO; iv) TBAF, THF/CH_3CN, room temperature.

Scheme 5. Synthesis of 2'−hydroxyethylated target compounds.

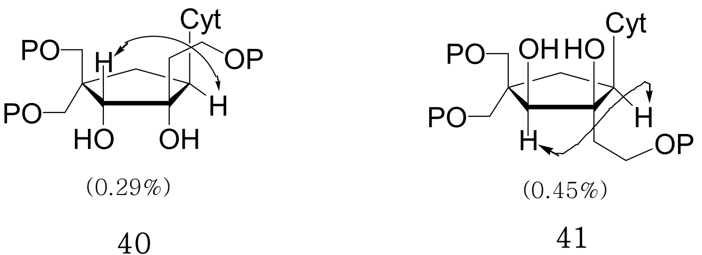


Figure 12. NOE comparisons of cytosine analogues **40** and **41**.

ajor reaction products, with **41** and **43** as minor isomers. These stereochemical outcomes suggest that bulky groups such as silylated hydroxymethyl group and nucleosidic bases (cytosine and adenine) reinforce the steric hindrance of the β−faces. Furthermore, I hypothesize that the cyclopentene ring causes one of

the protecting groups on the 4'−position to be in equatorial positions, which causes the other protecting group on 4'−substituent to be in the axial down position, making the dihydroxylation from the β−face more hindered. Their stereochemistries were readily determined by NOE experiments. For example, irradiation of 1'−*H* of compound **40** produced different NOE patterns at the proximal hydrogens such as 3'−*H* (0.29%), compared to 3'−*H* (0.45%) of compound **41** (**Figure 12**). Removal of the silyl protection groups of **40** and **42** was performed by tetrabutylammonium fluoride (TBAF) treatment to yield the desired carbodine analogues **44** and **45** (**Scheme 5**).

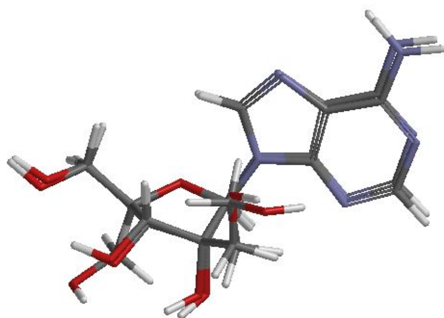


Figure 13. Superimposed conformations of nucleoside analogue **3**, as anti−HCV agent and an adenosine phosphonic acid derivative **45**. The lowest energy conformation for each molecules was calculated with the modeling package Spartan 02 and energy minimization with semi−empirical force field (PM3).

The synthesized nucleoside analogues were assayed for anti−HCV activity using an in vitro assay system. This system is composed of a human hepatocarcinoma cell line (Huh−7) supporting HCV replication. These cells contain an HCV subgenomic replicon RNA encoding a luciferase reporter gene as a marker. The antiviral potency of these analogues against the HCV replicon is

expressed as EC_{50}, which was quantified by a luciferase assay after a two-day incubation period with the compounds. To confirm the anti-HCV potency of compounds, subgenomic replicon RNA levels were quantified by real-time polymerase chain reaction (RT-PCR) analysis. In addition, the associated cytotoxicity was evaluated in a tetrazolium (XTT)-based assay. Cytosine analogue 44 weakly inhibited the replication of the replicon in Hua-7 cells by 50% at 21.1 μM.

In summary, on the basis of potent anti-HCV activity of 2'-modified nucleosides, I have designed and synthesized 2'-hydroxyethylated carbodine derivatives from 1,3-dihydroxy acetone. Synthesized cytosine analogue 44 exhibited weak anti-HCV activity.

As depicted in Scheme 6, I hypothesized that ringclosing metathesis (RCM) of proper divinyls 55, which could be readily synthesized via sequential reactions, such as Claisen rearrangement and Grignard addition starting from ethyl glycolate 46, would produce ethynylated cyclopentene 56β.

Silyl protection of the alcohol of the commercially available starting material 46 followed by hydrolysis gave carboxylic acid derivative 48, which was transformed to the Weinreb amide 49 by the treatment of DCC and DMAP coupling reagents.[74] Conversion of the amide to the propargyl ketone derivative 50 was successful under the usual carbonyl addition conditions (propargylMgBr, THF, 0 ℃). Treatment of 50 with triethylphosphonoacetate[75] provided α,β-unsaturated ethyl ester 51 as a cis/trans isomeric mixture. These isomers do not

Reagents: i) TBDMSCl, CH_2Cl_2, imidazole; ii) KOH, EtOH; iii) *N*−methylhydroxylamine hydrochloride, DCC, DMAP, TEA; iv) propargylmagnesium bromide, THF; v) Triethylphosphonoacetate, NaH, THF; vi) DIBALH, CH_2Cl_2, vii) Triethylorthoacetate, propionic acid, overnight, 135−140℃; viii) DIBALH, toluene, −78℃.

Scheme 6. Synthesis route of aldehyde intermediate **54**.

need separating because they merge into one isomer **53** after Claisen rearrangement. Addition of the diisobutylaluminum hydride (DIBALH) to **51** provided the allylic alcohol **52**, which was subjected to a regular Johnson's orthoester Claisen rearrangement[76] with triethyl orthoacetate to yield the γ,δ−unsaturated ester **53**. Direct reduction of the ester **53** to the aldehyde **54** was successfully accomplished by slow addition of DIBALH in the toluene solvent system at 78 ℃. The aldehyde **54** was subjected to carbonyl addition by CH_2=CHMgBr to give divinyl **55**.

Divinyl **55** was subjected to standard RCM[77] conditions using a second−

generation Grubbs catalyst to provide the diene metathesis product 56α/56β as well as enyne metathesis product, which were readily separated by simple silica gel column chromatography. The correct configurations of 56α and 56β were assigned based on NOE comparisons. Upon the irradiation of C_5−H, different NOE pattern was observed at the protons of compound 56 [C_1−H (0.03%) & C_6−Hβ (0.31%)], from those of compound 56 [C_1−H (0.08%) & C_6−Hα (0.29%)] (Figure 14).

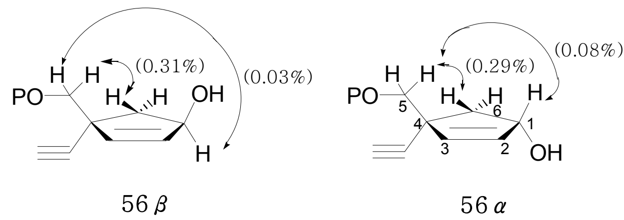


Figure 14. NOE comparisons of compound 56α and 56β.

PO CHO 54 → i 75% → PO OH 55 → ii → PO X Y

56α : X = H, Y = OH (22%)
56β : X = OH, Y = H (21%)

→ 75% iii → PO OCO$_2$Et 57 → iv → PO B → v → HO B

61: B = cytosine (74%)
62: B = thymine (69%)
63: B = uracil (75%)

58: B = cytosine (39%)
59: B = thymine (30%)
60: B = uracil (28%)

Reagents: i) vinylMgBr, THF; ii) Grubbs catalyst (II), CH_2Cl_2; iii) $ClCO_2Et$, pyridine, DMAP; iv) pyrimidine nucleosidic bases, $Pd_2(dba)_3 \cdot CHCl_3$, $P(O-i-Pr)_3$, NaH, THF/DMSO; v) TBAF, THF.

Scheme 7. Synthesis route of target pyrimidine nucleosides.

PO OCO$_2$Et 57 →(i, 28%) PO Cl N N N N NH$_2$ 64 →(iii, 62%) HO Cl N N N N NH$_2$ 65 →(iii, 60%) HO O N NH N N NH$_2$ 66

Reagents: i) 2-amino-6-chloropurine, $Pd_2(dba)_3 \cdot CHCl_3$, $P(O-i-Pr)_3$, NaH, THF/DMSO; ii) TBAF, THF; iii) (a) 2-mecaptoethanol, NaOMe, MeOH, (b) CH_3COOH.

Scheme 8. Synthesis route of target purine nucleosides.

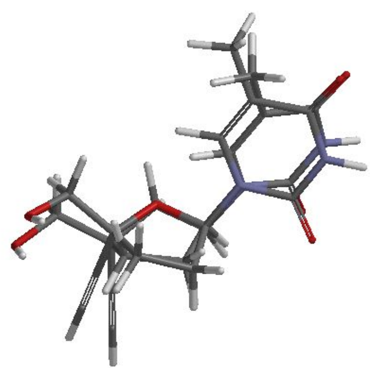


Figure 15. Superimposed conformations of nucleoside analogue **7**, as antiviral or antitumor agent and an thymine derivative **62**. The lowest energy conformation for each molecules was calculated with the modeling package Spartan 02 and energy minimization with semi-empirical force field (PM3).

First, I attempted the mesylation of 56α because mesylate is an excellent reactive intermediate for the replacement of free hydroxyl groups with nucleoside bases. To our surprise, the mesylate that appeared in the reaction mixture disappeared during the work-up, resulting in decomposition into an unidentifiable

byproduct and requiring an alternative coupling method. Alternatively, I turned out attention to Palladium(0)−catalyzed reactions of allylic carbonate.[78] To this end, cyclopentenol 56β was transformed to 57 using ethyl chloroformate, which was coupled with pyrimidine nucleosidic base (cytosine, thymine, uracil) anions generated by NaH/DMSO with use of catalyst [tris(dibenzylideneacetone)−dipalladium(0)−chloroform] adduct to provide nucleoside analogues 58−60. Removing the silyl protection groups of 58−60 was performed by the treatment of tetrabutylammonium fluoride (TBAF) to yield final nucleosides 61−63 (Scheme 7). Similarly, the guanine derivative was synthesized by coupling the same intermediate 57 as used in the preparation of pyrimidine analogues. The silicon protection group of compound 64 was removed by treatment with TBAF to produce compound 65. Treatment of compound 65 with 2−mercaptoethanol and sodium methoxide in methanol, followed by hydrolysis with acetic acid, gave the desired nucleoside 66 (Scheme 8).

Compounds, 61, 62, 63, and 66 were tested against HIV−1 (MT−4 cells), HSV−1 (CCL81 cells), HSV−2 (CCL−81 cells), and HCMV (AD−169, Davis cells). Among them, only guanine analogue 66 exhibited moderate antiviral activity against HIV−1 (Table 3); and the thymine analogue 62 showed weak antiviral activity against HCMV. The assay involved the killing of T4−lymphocytes by HIV−1. T4 lymphocytes (MT−4 cell line) were exposed to HIV at a virus−to−cell ratio of approximately 0.05 and treated with the compounds, dissolved in dimethylformamide, 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 ℃ 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.[79]

Table 3. Antiviral activity of the synthesized compounds

Compound no.	HIV−1 EC_{50} (μmol)	HSV−1 EC_{50} (μmol)	HSV−2 EC_{50} (μmol)	HCMV EC_{50} (μmol)	cytotoxicity EC_{50} (μmol)
61	90	>100	>100	>100	90
62	45.7	98	>100	**19.3**	98
63	99	>100	>100	99	>100
66	**11.91**	88	>100	36.4	99
D4T	0.05	ND	ND	ND	20
GCV	ND	ND	ND	0.8	>10
ACV	ND	0.2	ND	ND	>100

D4T: Stavudine. GCV: Ganciclovir. ACV: Acyclovir. ND: Not Determined. EC_{50} (μM): Concentration require to inhibit 50% of the virus-induced cytopathicity. CC_{50} (μM): Concentration required to reduce cell viability by 50%.

Compared to 7 and 8, it is surprising that their corresponding carbacyclic analog 62 did not show any noticeable activity. Investigation on the cause of this unexpected SAR would be an interesting topic as a guidance for further development of carbacyclic derivatives. In summary, we developed an efficient synthetic method to yield 4'−ethynyl carbocyclic nucleosides starting from ethyl glycolate. Based on this strategy, the syntheses of other nucleosides with different nucleobases are in progress in our laboratory.

For the synthesis 76, similar reactions for the synthesis of the 66 starting from ethyl glycolate. The allylic functionalization using palladium(0)−catalyzed reactions have been the central role in synthetic organic chemistry. I have succ−

Reagents: i) TBDMSCl, CH_2Cl_2, imidazole; ii) KOH, EtOH; iii) *N,O*-dimethylhydroxylamine hydrochloride, DCC, DMAP, TEA: iv) cyclopropylmagnesium bromide, NH_4Cl, THF; v) Triethylphosphonoacetate, NaH, THF; vi) DIBALH, CH_2Cl_2, vii) Triethyl orthoacetate, propionic acid, overnight, 135−140℃; viii) DIBALH, toluene, −78℃.

Scheme 9. Synthesis route of aldehyde intermediate 71.

essfully applied this methodology to the synthesis of desired nucleoside. Cyclopentenol 73β was transformed to 74 using ethyl chloroformate, which was coupled with 2−amino−6−chloropurine anions generated by NaH/DMSO with use of catalyst [tris(dibenzylidene−acetone)−dipalladium (0)−chloroform] adduct to provide nucleoside analogue 75. Based on ^{1}H NMR integration study, the product mixtures indicated no N7 isomer (less than 5%) formed in the reaction of 74. The analysis of the N7 and N9 coupling products is readily accomplished by ^{1}H NMR. Since the proton at the 8−position of the purine is well separated and readily distinguished in the two region−isomers. The C−8 isomers proton of the N9 isomer is typically upfield of the the N7 isomer.[80] Removal of silyl protection group of 75 was preformed by the treatment of tetrabutylammonium fluoride (T−

73α : X = H, Y = OH (41%)
73β : X = OH, Y = H (42%)

77: R = −NH−◁ (59%)
78: R = −OH (69%)

Reagents: i) vinylMgBr, THF, −78℃; ii) Grubbs catalyst (II), CH_2Cl_2; iii) $ClCO_2Et$, pyridine, DMAP; iv) NaH, 2−amino−6−chloropurine, $P(O-i-Pr)_3$, $Pd_2(dba)_3 \cdot CHCl_3$, NaH, THF/DMSO; v) TBAF, THF; vi) Cyclopropyl amine, EtOH; vii) 2−Mercaptoethanol, NaOMe, MeOH, AcOH.

Scheme 10. Synthesis route of target nucleosides.

BAF) to give nucleoside 76, which was treated with cyclopropylamine in EtOH under reflux to provide the desired 4'−cyclopropylated abacavir analogue 77. Treatment of compound 76 with 2−mercaptoethanol and sodium methoxide in methanol, followed by hydrolysis with acetic acid gave the desired acyclic nucleoside 78 (Scheme 9 and Scheme 10).

The antiviral assay against several viruses such as the human immunodeficiency virus 1 (HIV−1), herpes simplex virus−1,2 (HSV−1,2) and human cytomegalovirus (HCMV) was performed. As shown in Table 4, compound

77 and 78 exhibited moderate antiviral activity against HCMV in the Davis cell without any cytotoxicity up to 100 μmol.[81] It is believed that the arrangement between the 4'-branched carbocyclic nucleoside analogues may be conformationally similar to natural nucleosides containing ribose. Hence, the presence of cyclopropyl group at the 4'-position of nucleosides could be supposed to enhance the level of phosphorylation by kinase to produce the active monophosphate form.

Table 4. The antiviral activity of the synthesized compounds

Compound no.	HIV-1 EC_{50} (μmol)	HSV-1 EC_{50} (μmol)	HSV-2 EC_{50} (μmol)	HCMV EC_{50} (μmol)	cytotoxicity CC_{50} (μmol)
77	56.2	77.3	99	12.7	99
78	44.7	99	99	20.1	99
AZT	0.008	ND	ND	ND	2.25
GCV	ND	ND	ND	0.55	>10
ACV	ND	0.3	ND	ND	>100

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

In summary, an efficient synthetic method of 4'-cyclopropylated carbocyclic nucleoside from ethyl glycolate was developed. On the basis of this strategy, the syntheses of other nucleosides such as vinylated or acetylated carbocyclic nucleosides with different nucleobases are in progress.

As depicted in Scheme 11, the target compounds were prepared from commercially available 2,2-dimethyl-1,3-dioxolane-4-ethanol 79. The hydroxyl functional group of 79 was subjected to protection reaction by benzyl

89α : X = OH, Y = H (35%)
89β : X = H, Y = OH (36%)

Reagents: i) BnBr, NaH, THF; ii) HCl, MeOH; iii) TBDMSCl, imidazole, CH_2Cl_2; iv) NCS, DMS, toluene; v) vinylMgBr, THF; vi) TBDMSOTf, 2,6−lutidine, CH_2Cl_2; vii) Li, NH_3/THF; viii) $(COCl)_2$, DMSO, TEA, CH_2Cl_2; ix) Grubbs (II), CH_2Cl_2; x) $ClCO_2Et$, DMAP, pyridine.

Scheme 11. Synthesis of key cyclopentene ethylformate intermediate 90

bromide (BnBr, NaH, DMF) to furnish the acetonide 80, which was subjected to hydrolysis to provide diol derivative 81. The selective protection of primary hydroxyl group of 81 was successfully accomplished under mild silylation conditions (TBDMSCl, imidazole) to give the secondary alcohol 82.[82] The secondary hydroxyl group of 82 was oxidized to the ketone 83 using Corey and Kim's oxidation conditions (NCS, DMS).[83] The corresponding ketone functional group of 83 was subjected to an addition reaction by vinylmagnesium bromide to give the tertiary hydroxyl analogue 84, which was again silylated (TBDMSOTf, 2.6−lutidine)[84] to give the protected compound 85.

Removal of the benzyl protecting group of **85** under dissolving metal reduction[85] for a prolonged time (*ca* 25 min) furnished the desired alcohol **86**, which was oxidized to the aldehyde **87** using Swern oxidation conditions[86] (DMSO, oxalyl chloride, TEA). The aldehyde **87** was again subjected to nucleophilic Grignard conditions[87] by vinylmagnesium bromide to yield divinyl **88**, which was subjected to ring-closing metathesis (RCM) conditions using 2nd generation Grubbs catalyst ($C_{46}H_{65}Cl_2N_2PRu$)[88] to provide cyclopentenol **89α** (35%) and **89β** (36%), which were readily separated by silica gel column chromatography. The nuclear Overhauser enhancement (NOE) experiments with cyclopentenols **89α** and **89β** 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 **89β** [C_4-CH-(0.78%)] compared with those of compound **89α** [C_4-CH-(1.21%)] (**Figure 16**).

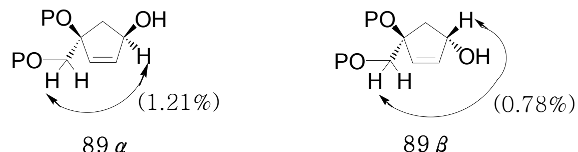


Figure 16. NOE difference between the proximal hydrogens of 89α and 89β.

Initially, to synthesize the desired 5'-norcarbocyclic adenosine nucleoside analogues, the protected cyclopentenol **89β** was treated with 6-chloropurine under Mitsunobu coupling conditions[89] (DIAD and PPh_3). However, the reaction produced a very low yield and was not reproducible. Alternatively, to couple the

Reagents: i) 6−chloropurine, $Pd_2(dba)_3$, $CHCl_3$, $P(O-i-Pr)_3$, NaH, THF/DMSO; ii) TBAF, CH_3CN; iii) TBDMSCl, imidazole, CH_2Cl_2, iv) $(EtO)_2POCH_2OTf$, Li−*t*−Bu, THF; v) NH_3/MeOH, 70 ℃; vi) TMSBr, lutidine, CH_3CN.

Scheme 12. Synthesis of target 4'−hydroxymethyl−5'−norcarbocyclic adenosine phosphonic acid.

6−chloropurine to cyclopentenol derivative **89α** using well known palladium(0)−catalysis,[90] hydroxyl group of **89α** was transformed to the allylic formate analogue **90** using ethyl chloroformate. Compound **90** was coupled with the nucleosidic base anions generated by NaH/DMSO using a catalyst [tris(dibenzylidene−acetone)−dipalladium(0)−chloroform] adduct to provide the 5'−norcarbocyclic nucleoside analogues **91** (**Scheme 12**). Sequential double desilylation of **91** and selective monosilylation of corresponding diol **92** produced the 5'−norcarbocyclic nucleoside analogue **93**, which was treated with diethylphosphonomethyl triflate[91] using lithium *t*−butoxide to yield the

nucleoside phosphonate analogue 94. The chlorine group of 94 was then converted to amine with methanolic ammonia at 70 ℃ to give the corresponding adenine phosphonate derivative 95. Desilylation of silicon protection group followed by hydrolysis of diethyl phosphonate functional groups of 96 gave the adenosine phosphonic acid derivative 97.

The synthesized nucleoside phosphonate and phosphonic acid analogues 96 and 97 were then evaluated for antiviral activity against human immunodeficiency virus. The procedures for measuring the antiviral activity toward wild-type HIV and cytotoxicity have been reported previously.[92] As shown in Table 5, nucleoside phosphonic acid 97 exhibited significantly more anti-HIV activity than its parent nucleoside diethyl phosphonate 96 at concentrations up to 100 μM. Further development toward optimal prodrugs will likely allow efficient delivery of the phosphonate to the lymphatic system and provide a novel nucleotide RT inhibitor for the treatment of HIV.

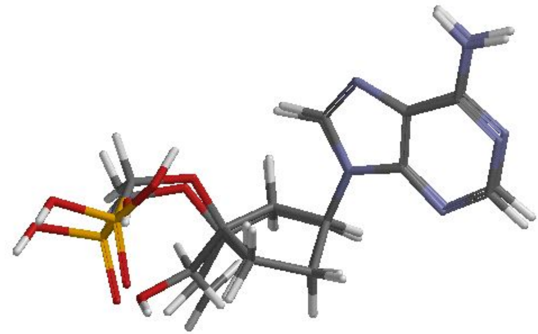


Figure 17. Superimposed conformations of 4'-branched-5'-norcarbocyclic phosphonic acid 16, as anti-HIV agent and an adenosine phosphonic acid derivative 97. The lowest energy conformation for each molecules was calculated with the modeling package Spartan 02 and energy minimization with semi-empirical force field (PM3).

Table 5. Anti−HIV activity of synthesized compounds 96 and 97

Compound no.	Anti−HIV−1 EC_{50} (μM)	Cytotoxicity IC_{50}(μM)
96	47.5	98
97	8.61	90
AZT	0.01	100
PMEA	0.51	10

AZT: azidothymidine. PMEA: 9−[2−(phosphonomethoxy)ethyl]adenine. 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%.

In summary, based on the potent anti−HIV activity of 4'−branched nucleoside and 5'−norcarbocyclic nucleoside analogues, I have designed and successfully synthesized novel 4'−hydroxymethyl−5'−norcarbocyclic nucleoside analogues starting from 2,2−dimethyl−1,3−dioxolane−4−ethanol. 4'−Vinyl analogue (16) and ethynyl analogue (15) were found to inhibit RT with an IC_{50} = 0.67 μM, and 0.15 μM, respectively.[53] Taking these data into account, the proposed 4'−pocket in the active site of RT is sensitive to steric and electronic changes in the 4'−substituent, especially when this involves increasing the van der Waals radius or possibly changes in the projection angle of the 4'−substituent into the pocket. Compounds 96 and 97 exhibited weak anti−HIV activity, indicating that the hydrophilic pocket such as hydroxymethyl group at 4'−position of 5'−norcarbocyclic nucleosides system makes the conformation to be unfavorable for interaction with enzymes associated with the kinases of nucleosides and nucleotides.

As shown in Scheme 13, the target compounds were prepared from propion−

Reagents: i) phenylMgBr, THF; ii) NCS, DMS, toluene; iii) vinylMgBr, THF; iv) TBAF, THF/CH_3CN; v) BzCl, DMAP, pyridine; vi) TBDMSOTf, 2,6−lutidine, CH_2Cl_2; vii) NH_3/MeOH; viii) $(COCl)_2$, DMSO, TEA, CH_2Cl_2; ix) vinylMgBr, THF.

Scheme 13. Synthesis of divinyl intermediate **107**.

aldehyde **98**, which was readily synthesized from 1,3−propan−ediol using known procedure.[93] The aldehyde functional group of **78** was subjected to carbonyl addition reaction by phenylmagnesium bromide to give the secondary alcohol **99**, which was subjected to oxidation condition using Corey−Kim's oxidation procedure[83] to provide corresponding ketone derivative **100**. The ketone functional group of **100** was again subjected to addition reaction by vinylmagnesium bromide to give tertiary hydroxyl analogue **101**.

In order to differentiate the two hydroxyl groups, the silicon protection group of the primary hydroxyl was replaced with a benzoyl group by sequential desilylation and benzoylation to provide **103**. Silylation of the tertiary hydroxyl

group of **103** was successfully accomplished using *t*−butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf, 2,6−lutidine)[84] to give the fully protected compound **104**. Removal of the benzoyl protecting group of **104** under methanolic ammonium condition (NH_3/MeOH) provided the primary alcohol **105**, which was oxidized to the aldehyde **106** using Swern oxidation conditions (Oxalyl chloride, DMSO, TEA).[94] The aldehyde **106** was subjected to nucleophilic Grignard conditions with vinylmagnesium bromide to give divinyl **107** which was subjected to ring−closing metathesis (RCM) conditions using 2nd generation Grubbs catalyst to provide phenyl substituted cyclopentenol **108α** (34%) and **108β** (35%), which were readily separated by silica gel column chromatography. The NOE experiments with cyclopentenols **108α** and **108β** confirmed these assignments. Also, the exact structural determinations were performed in the latter stage of compounds **115** and **116** (**Figure. 18**).

Reagens: i) Grubbs (II), CH_2Cl_2; ii) 6−Chloropurine, DIAD, PPh_3, THF; iii) TBAF, THF/CH_3CN, iv) $(EtO)_2POCH_2OTf$, *t*−BuOLi, THF: v) NH_3/MeOH, 65 ℃.

Scheme 14. Synthesis of 5'−norcarbocyclic adenosine phosphonate.

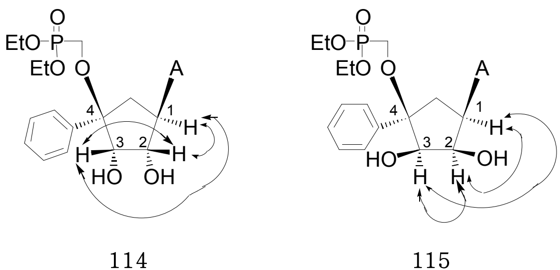


Figure 18. NOE differences between the proximal hydrogens of **114** and **115**

To synthesize the desired 5'-norcarbocyclic adenosine nucleoside analogues, the protected cyclopentenol **108β** was treated with 6-chloropurine under Mitsunobu conditions[89] (DIAD and PPh_3). Slow addition of diisopropyl azodicarboxylate (DIAD) to a mixture of cyclopentenol **108β**, triphenylphosphine and the 6-chloropurine in anhydrous tetrahydrofuran (THF) gave a yellow solution which was stirred for 3 h at −10 ℃ to give the 6-chloropurine analogue **109** (**Scheme 14**).[95] The silicon protection group was removed with tetrabutylammonium fluoride (TBAF) to provide 5'-norcarbocyclic nucleoside analogue **110**. The hydroxyl group was phosphonated with diethylphosphonomethyl triflate[91] using lithium *t*-butoxide to give the nucleoside phosphonate **111**. The chlorine group of purine analogue **111** was then converted to amine with methanolic ammonia at 65 ℃ to give a corresponding adenosine phosphonate derivative **112**. Hydrolysis of diethyl phosphonate functional groups of **112** by treatment with bromotrimethylsilane in CH_3CN in the presence of 2,6-lutidine gave an adenosine phosphonic acid derivative **113**.[96]

Bishydroxylation of the double bond in **112** was accomplished with a catalytic amount of osmium tetraoxide (OsO_4) and 4-methyl-morpholine *N*-oxide (NMO)

Reagents: i) TMSBr, 2,6−lutidine, CH_3CN, ii) OsO_4, NMO, acetone/*t*−BuOH/H_2O: 8/ 1/ 1/.

Scheme 15. Synthesis of 5'−norcarbocyclic adenosine phosphonates and phosphonic acids.

as an oxidant to give the dihydroxylated isomer **114** (32%) and **115** (30%) with almost equal amount (**Scheme 15**).[97] A complete NOE study allowed an unambiguous determination of their respective stereochemistry (**Figure. 18**). For compound **115**, strong NOE of H−1' ↔ H−2' as well as H−1' ↔ H−3', which showed 1',2',3'−*cis* relationships, was observed. According to this result, 2'− and 3'−hydroxyl groups of **115** were located on the b face. On the other hand, for **114** compound, weak NOE, such as H−1' ↔ H−2' and H−1' ↔ H−3', were assigned to the 1',2'− and 1',3'−trans relationships and a face stereochemicals of 2'− and 3'−hydroxyl groups. Hydrolysis of diethyl phosphonate functional groups of **114** by the similar procedure described for **113** gave an adenosine phosphonic acid derivative **116**.

The synthesized nucleoside phosphonate and phosphonic acid analogues **112**, **113**, **114** and **116** were then evaluated for antiviral activity against human

immunodeficiency virus. The procedures for measuring the antiviral activity toward wild-type HIV and cytotoxicity have been reported previously.[92]

As shown in **Table 6**, adenosine phosphonic acid **113** exhibited moderate anti-HIV activity with IC_{50} = 28.3 μM. Also, nucleotide analogues **112**, **114** and **116** did not show anti-HIV activity nor cytotoxicity up to 100 μM.

Table 6. Anti-HIV activity of synthesized compounds

Compound no.	Anti-HIV IC_{50} (μM)	Cytotoxicity CC_{50} (μM)
112	>100	>100
113	28.3	90
114	>100	>100
116	80	>100
ABC	0.13	>10

ABC: Abacavir. **IC_{50}** (μM): Concentration (μM) of the inhibitor required to reduce the activity of the enzyme by 50%. **CC_{50}** (μM): Concentration (μM) required to reduce the viability of unaffected cells by 50%.

After demonstrating that adenine nucleoside analogue **113** slightly inhibits HIV-1 polymerase, I decide to study its properties computationally. **Figure 19** shows the superposition of the calculated low energy conformers of **15**, **16** and **113**, underscoring the overall similarity of the three analogues and also highlighting the difference at purine base. Furthermore, the position of sterically bulky group such as phenyl group at 4'-position leads to the predicted difference in location of the phosphonic acid group. **Figure 20** shows a pronounced difference in the 4'-cavity of the synthesized compound **113** compared to the selected nucleoside **15** bounds to the active site. The location of the wider cavity below 4'-substituents is formed by residue M184 and Y115 in the synthesized

analogue **113** than the 4'-ethynyl-cpAP **16**.

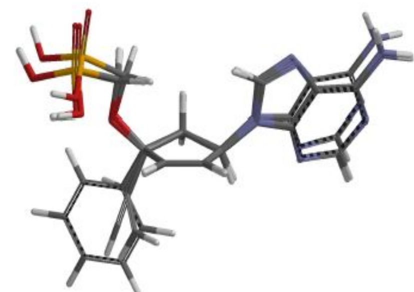
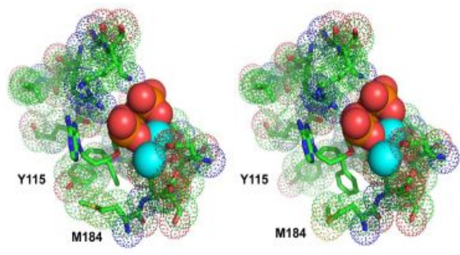


Figure 19. Superimposed low energy conformations of 4'-branched nucleoside **15**,**16** as anti-HIV-1 agents and an adenosine phosphonic acid derivative **113**. The lowest energy conformation for each of all three molecules was calculated with the modeling package Spartan using B3LYP/6-31G**.



(a) 4'-ethynyl-cpAP (**15**) (b) Adenosine phosphonic acid derivative **113**

Figure 20. Model of the active site of HIV-1 RT crystal structure. (a) 4'-ethynyl-cpAP (**15**) and (b) the synthesized nucleoside phosphonic acid analogue **113** are in stick representation; Protein is a dot rendering and a stick model; Mg ions are cyan spheres and the diphosphophosphonates are red spheres. The lowest energy conformations are calculated by the modeling package Spartan using MMFF force field. The labels represent amino acids so called "primer grip".

In summary, on the basis of potent anti-HIV activity of 4'-olefin branched nucleoside and 5'-norcarbocyclic nucleoside analogues, I have designed and successfully synthesized novel 4'-phenyl-5'-norcarbocyclic nucleoside analogues starting from propionaldehyde **98**. Ethynyl analogue (**15**) and 4'-vinyl analogue (**16**) were found to inhibit RT with IC_{50} = 0.14 μM and 0.65 μM,

respectively. Taking these data into account, the proposed 4'−pocket in the active site of RT is sensitive to changes in the 4'−substituent, especially when this involes increasing the van der Waals radius or possibly changes in the bulkiness. Compounds **113** and **116** exhibited weak anti−HIV activity, indicating that the bulky hydrophobic pocket such as phenyl group at 4'−position of 5'−no−rcarbocyclic nucleosides system are not perfect mimics for nucleoside analogues with small 4'−substituent. Therefore, the mechanisms of virus inhibition, that is, either phosphorylation or inhibition of RNA synthesis, might be impaired in these compounds.

As depicted in **Scheme 16**, the target compounds were prepared from 2−methylene−propane−1,3−diol (**117**). Monosilylation of diol **117** and subsequent

Reagents: i) TBDMSCl, imidazole, DMF; ii) MnO_2, CCl_4; iii) vinylMgBr, THF; iv) PMBCl, NaH, DMF; v) TBAF, THF; vi) Grubbs (II), CH_2Cl_2

Scheme 16. Synthesis of 6'−methylene cyclopentene intermediate (±)− 125 β:

oxidation of corresponding allylic alcohol **118** gave *α*,*β*−unsaturated aldehyde **119**. The aldehyde functional group of **119** was subjected to carbonyl addition reaction by vinylmagensium bromide to furnish the secondary alcohol **(±)−120**, which was successfully protected using *p*−methoxybenzyl chloride (PMBCl)[98] to provide compound **(±)−121**. Removal of the silyl protecting group of **(±)−121** using tetra *n*−butylammonium fluoride (TBAF) gave the primary alcohol **(±)−122**, which was oxidized to the aldehyde **(±)−123** using same oxidation conditions as described for **119**. The aldehyde **(±)−123** was subjected to nucleophilic Grignard conditions with vinylmagnesium bromide to give divinyl **(±)−124**, which was subjected to ring−closing metathesis (RCM) conditions u−

Reagents: i) 6−chloropurine, DEAD, PPh_3, 1,4−dioxane /DMF; ii) DDQ, CH_2Cl_2/H_2O (10:1); iii) $(EtO)_2POCH_2OTf$, Li−*t*−Bu, THF; iv) NH_3/MeOH, 65 ℃; v) TMSBr, 2,6−lutidine, CH_3CN.

Scheme 17. Synthesis of 6'−methylene cyclopentenyl adenine phosphonic acid **(±)−130**

sing 2nd generation Grubbs catalyst ($C_{46}H_{65}Cl_2N_2PRu$) to provide 6'-cyclopentntenol (±)-125α (38%) and (±)-125β (39%), which were readily separated by silica gel column chromatography. The Nuclear Overhauser Enhancement (NOE) experiments with cyclopentenols (±)-125α and (±)-125β 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 (±)-125β [C_4-C*H*-(1.9%)] versus those of compound (±)-125α [C_4-C*H*-(3.0%)] (Figure 21).

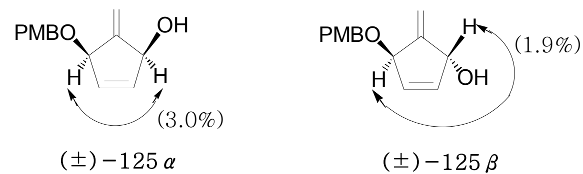


Figure 21. NOE differences between the proximal hydrogens of (±)-125α and (±)-125β.

To synthesize the desired 5'-norcarbocyclic adenosine nucleoside analogues, the protected cyclopentenol (±)-125β was treated with 6-chloropurine under Mitsunobu conditions (DEAD and PPh_3). The appropriate choice of solvent system, temperature and procedure are essential for the regioselectivity as well as for the yield. In purine synthesis, a mixture of dioxane and DMF were used as the solvent for the coupling of the cyclopentenol (±)-125β with 6-chloropurine instead of THF. The heterocyclic bases had a better solubility in the dioxane-DMF mixture resulting in better yields. Slow addition of diethyl azodicarboxylate (DEAD) to a mixture of cyclopentenol (±)-125β,

triphenylphosphine and the 6−chloropurine in anhydrous cosolvent (dioxane−DMF) gave a yellow solution, which was stirred for 2.0 h at −40 ℃ and further stirred overnight at rt to give the protected 6−chloropurine analogue (±)−126 as an only N^9−regioisomer [UV (MeOH) λ_{max} 264.5 nm].[99] The PMB protection group was removed with 2,3−dichloro−5,6−dicyano−*p*−benzoquinone (DDQ)[100] to produce the 5'−nornucleoside analogue (±)−127, which was treated with diethylphosphonomethyl triflate[91] using lithium *t*−butoxide to yield the nucleoside phosphonate analogue (±)−128 (Scheme 17). The chlorine group of (±)−128 was then converted to amine with methanolic ammonia at 65 ℃ to give the corresponding adenine phosphonate derivative (±)−129. Hydrolysis of (±)−129 by treatment with bromotrimethylsilane in CH_3CN in the presence of 2,6−lutidine gave an adenine phosphonic acid derivative (±)−130 (Scheme 17).

The cyclopentenol intermediate (±)−132 was also used for the synthesis of 2,6−disubstituted purine analogues such as guanine derivative (±)−136. Regioselective coupling of the enol (±)−132 with 2−fluoro−6−chloropurine[101] under the similar conditions for 6−chloropurine gives analogue (±)−133. Bubbling ammonia into the compound (±)−133 gave separable 2−fluoro−6−aminopurine[102] analogue (±)−134 (11%) and 2−amino−6−chloropurine analogue (±)−135 (57%), respectively. 2−Amino−6−chloropurine derivative (±)−135 was treated with TMSBr to provide phosphonic acid and sequentially treated sodium methoxide and 2−mercaptoethanol in methanol to give desired guanine phosphonic acid (±)−135 (Scheme 18).[103]

The synthesized nucleoside phosphonate and phosphonic acid analogues

(±)-125β → (±)-131 (i, 57%) → (±)-132 (ii, 67%) → (±)-133 (iii, 41%) → (±)-134 / (±)-135 (iv) → (±)-136 (v, 61%)

(±)-134: X = NH_2, Y = F (11%)
(±)-135: X = Cl, Y = NH_2 (57%)

Reagents: i) $(EtO)_2POCH_2OTf$, Li-*t*-Bu, THF; ii) DDQ, CH_2Cl_2/H_2O (10:1); iii) 2-fluoro-6-chloropurine, DEAD, PPh_3, 1,4-dioxane/DMF; iv) NH_3/DME, rt; v) (a) TMSBr, 2,6-lutidine, CH_3CN; (b) NaOMe, $HSCH_2CH_2OH$, MeOH.

Scheme 18. Synthesis of 6'-methylene cyclopentenyl guanie phosphonic acid (±)-136

Table 7. Median effective (EC_{50}) and inhibitory (IC_{50}) Concentration of synthesized nucleoside analogues in PBM and Vero cells

Compound no.	Anti-HIV-1 in PBM cells EC_{50} (μM)	Cytotoxicity in PMB cells IC_{50} (μM)	Cytotoxicity in Vero cells IC_{50} (μM)
129	56.4	>100	98
130	26	>100	95
134	80	>100	>100
135	60	>100	98
136	8.1	>100	80
AZT	0.004	>100	>100
PMEA	0.51	>100	>100

AZT: azidothymidine. **PMEA:** 9-[2-(phosphonomethoxy)ethyl]adenine. **EC_{50}** (μM): EC_{50} values are for 50% inhibition of virus production as indicated by supernatant RT levels. **IC_{50}** (μM): IC_{50} values indicates 50% inhibition of cell growth.

(±)-129, (±)-130, (±)-134, (±)-135 and (±)-136 were then evaluated for antiviral activity against human immunodeficiency virus. The procedures for

measuring the antiviral activity toward wild-type HIV and cytotoxicity have been reported previously. As shown in **Table 7**, guanine nucleoside phosphonic acid **(±)-136** exhibits significant anti-HIV activity. However, nucleoside analogues **(±)-129**, **(±)-130**, **(±)-134**, and **(±)-135** showed weak anti-HIV activity or cytotoxicity at concentrations up to 100 μM.

In summary, based on the potent anti-HIV activity of 6'-electronegative nucleosides and 5'-norcarbocyclic nucleoside analogues, I have designed and successfully synthesized novel 6'-methylene-5'-norcarbocyclic nucleoside analogues starting from 2-methylene-propane-1,3-diol (**117**). The synthesized nucleotide guanine **(±)-136** exhibited improvement in cell-based activity compared with adenine phosphonic acid **(±)-130**. Although the nucleotide analogue **13** inhibits in vitro anti-HIV activity, the carbocyclic versions shows weak anti-HIV activity except guanine analogue **(±)-136**. Since rigid cyclopentene carbocycles are not perfect mimics for ribofuranose moiety, the mechanisms of virus inhibition, that is, either phosphorylation or inhibition of RNA synthesis, might be impaired in these compounds. Homologation of 6'-pos-

Figure 22. Superimposed conformations of nucleoside analogue **13**, as *anti*-HIV agent and an adenosine phosphonic acid derivative **130**. The lowest energy conformation for each molecules was calculated with the modeling package Spartan 02 and energy minimization with semi-empirical force field (PM3).

ition is another possible reason for the apparent lack of activity. Figure 22 shows the superposition of the calculated low energy conformers of 13 and 130, highlighting the two difference parts such as purine bases and phosphonic acid functional moieties.

As depicted in Scheme 19, the target compounds were prepared from diethylmalonate 137[104]. For the synthesis 151, similar reactions for the synthesis of the 130 starting 117 (Scheme 19 and Scheme 20).

Reagents: i) TBDMSCl, imidazole, DMF; ii) $(COCl)_2$, DMSO, TEA; iii) vinylMgBr, THF; iv) PMBCl, NaH, DMF; v) TBAF, THF

Scheme 19. Synthesis of cyclopropyl divinyl intermediate 145.

In order to synthesize the 2',3'-dihydroxy nucleoside analogues, the protected nucleoside 150 was subjected to vicinal hydroxylation conditions using a catalytic amount of OsO_4 and NMO to give 152α (33%) and 152β (31%), respectively.[97] As shown in Figure 23, the stereochemistry was readily determined by the NOE experiment. Upon irradiation of C_4-H, a relatively strong

Reagents: i) Grubbs (II), CH_2Cl_2; ii) 6-chloropurine, DEAD,PPh_3, 1,4-dioxane/DMF; iii) DDQ, CH_2Cl_2/H_2O,(10:1); iv) $(EtO)_2POCH_2OTf$, Li-*t*-Bu, THF; v)NH_3/MeOH, 70 ℃; vi) TMSBr, 2,6-lutidine,CH_3CN.

Scheme 20. Synthesis of 6'-spirocyclopropyl cyclopentenyl adenine phosphonic aicd.

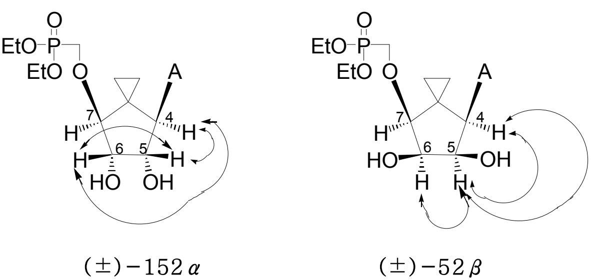


Figure 23. NOE relationships between the proximal hydrogens.

NOE was observed at C_5-*H* and C_6-*H* of **152β**, which showed 1',2',3'-*cis* relationships. But a relatively weak NOE was observed at C_5-*H* and C_6-*H* of **152α**, which indicates 1',2'- and 1',3'-*trans* relationships. The adenosine phosphonic acid **153** was synthesized from **152α** by similar procedures described for **151** (**Scheme 21**).

To synthesize the thioester prodrug analogue, compound **151** was reacted with thioester **154**[105] in the presence of 1−(2−mesitylenesulfonyl)−3−nitro−1−*H*−1,2,4−triazole (MSNT)[106] to provide the bis (SATE) derivative as a target compound **155** (**Scheme 22**).

Reagents: i) OsO_4, NMO, acetone/*t*−BuOH/H_2O (6:1:1);
ii) TMSBr, 2,6−lutidine, CH_3CN.

Scheme 21. Synthesis of 6'−cyclopropyl−2',3'−dihydroxyoxy−cyclo−pentanyl adenine phosphonic acid.

Reagents: i) thioester, **154**, 1−(2−mesitylenesulfonyl)−3−nitro−1*H* −1,2,4−triazole, pyridine.

Scheme 22. Synthesis of the target bis(SATE) prodrug of adenine analogue **155**.

The synthesized nucleoside phosphonate and phosphonic acid analogues **150−153** and **155** were then evaluated for antiviral activity against HIV. The procedures for measuring the antiviral activity toward wild−type HIV and cytotoxicity have been reported previously. As shown in **Table 8**, nucleoside phosphonic acid **155** exhibited increased anti−HIV activity compared with its parent nucleoside phosphonic acid **151**. However, nucleoside analogues **150**, **152**, and **153** did not show anti−HIV activity or cytotoxicity at concentrations up to 100 μM.

Table 8. Anti−HIV activity of Synthesized compounds

Compound no.	Anti−HIV EC_{50} (μM)	Cytotoxicity CC_{50} (μM)
150	80.0	98
151	19.1	80
152	88.9	100
153	90	100
155	12.3	50
AZT	0.01	100
PMEA	0.51	10

AZT: azidothymidine. PMEA: 9−[2−(phosphonomethoxy)ethyl]adenine. 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%.

In summary, on the basis of the potent anti−HIV activity of 6'−electroposit−ive nucleosides and 5'−norcarbocyclic nucleoside analogues, I have designed and successfully synthesized novel 6'−spirocyclopropyl−5'−norcarbocyclic nucleoside analogues starting from the commercially available diethylmalonate **137**.

The synthesized nucleoside prodrug **155** exhibited slight improvement in cell−based activity compared with phosphonic acid **151**. Although the SATE

protecting group as a prodrug scaffold was introduced, the antiviral activity was slightly increased.

CONCLUSION

Nucleosides are glycosylamines consisting of a nucleobase (often referred to as simply base) bound to a ribose or deoxyribose sugar via a beta-glycosidic linkage. Examples of nucleosides include cytidine, uridine, adenosine, guanosine, thymidine and inosine.

The synthesized nucleoside analogues 28, 31, 40, 42, 44 and 45 were assayed for anti-HCV activity using an in vitro assay. The cytosine analogue 28 exhibited potent anti-HCV activity, cytosine analogue 44 weakly inhibited the replication of the replicon.

And compounds, 61, 62, 63, 66, 77 and 78 were tested against HIV-1, HSV-2, and HCMV virus. Among them, only guanine analogue 66 exhibited moderate antiviral activity against HIV-1; and the thymine analogue 62 showed weak antiviral activity against HCMV. Compound 77 and 78 exhibited moderate antiviral activity against HCMV in the Davis cell without any cytotoxicity up to 100 μmol.

The synthesized nucleoside phosphonate and phosphonic acid analogues 96, 97, 112, 113, 114, 116, (±)-129, (±)-130, (±)-134, (±)-135, (±)-136, 150, 151, 152α, 153 and 155 were then evaluated for antiviral activity against human immunodeficiency virus. Nucleoside phosphonic acid 97 exhibited significantly more anti-HIV activity than its parent nucleoside diethyl phosphonate 96 at concentrations up to 100 μM. Adenosine phosphonic acid 113 exhibited moderate anti-HIV activity with IC_{50} = 28.3 μM. Also, nucleotide analogues 112, 114 and 116 did not show anti-HIV activity nor cytotoxicity up to 100 μM.

Guanine nucleoside phosphonic acid (±)-136 exhibits significant anti-HIV activity. However, nucleoside analogues (±)-129, (±)-130, (±)-134, and (±)-135 showed weak anti-HIV activity or cytotoxicity at concentrations up to 100 μM. Nucleoside phosphonic acid 155 exhibited increased anti-HIV activity compared with its parent nucleoside phosphonic acid 151. However, nucleoside analogues 150, 152α, and 153 did not show anti-HIV activity or cytotoxicity at concentrations up to 100 μM. The synthesized nucleoside prodrug 155 exhibited slight improvement in cell-based activity compared with phosphonic acid 151.

EXPERIMENTAL

Melting points were determined on a Mel−temp Ⅱ laboratory device and are uncorrected. NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer (JEOL, Tokyo, Japan); chemical shifts are reported in parts per million (δ) and signals are reported as a (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. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. (7558, Newark, DE, 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.

Molecular Modeling. The low energy conformations are calculated by quantum mechanics method using B3LYP/6−31G**. For modeling of the complex form, the structure of the ternary complex of HIV−1 RT (PDB code 1RTD) was used as the starting point. The dTTP of the active site was modified into our anti−HIV−1 RT agent analogues. All template positions of the enzyme are fixed except M184 and Y115 so called 'primer grip' in the minimization of the complex. For maintaining the bind site, Mg ions and diphosphophosphonates group are also fixed. Therefore, the agents and primer grip region are flexible.

All modeling studies and the calculations are performed by the modeling package Spartan software. For minimization of the complex, molecular mechanics force field such as MMFF was used.

(*rel*)-(1*S*,2*R*,3*S*,5*S*)-2-Benzyloxy-3-benzyloxymethyl-1-methyl-6-oxa-biocyclo[3.1.0]hexane (24): To a solution of epoxide derivative **23** (2.1 g, 8.96 mmol) in dry DMF (20 mL) was slowly added NaH (258 mg, 10.75 mmol) at 0 ℃. After 30 min, benzyl bromide (1.68 g, 9.85 mmol) was added, and the reaction mixture was stirred for 3 h at rt. The mixture was quenched by adding of saturated ammonium chloride (2 mL) and poured into water (30 mL). The mixture was extracted with ethyl acetate (30 mL) two times. 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, 1:20) to give **24** (2.29 g, 79%) as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.29 (m, 10H), 4.59 (s, 2H), 4.53 (s, 2H), 3.98 (d, J = 7.0 Hz, 1H), 3.50 (dd, J = 5.4, 9.2 Hz, 1H), 3.34 (dd, J = 6.2, 9.2 Hz, 1H), 2.31 (m, 1H), 2.13 (m, 1H), 1.79 (dd, J = 6.3, 10.6 Hz, 1H), 1.64 (dd, J = 8.2, 10.5 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.2, 138.1, 128.3, 127.9, 127.1, 126.4, 79.4, 77.2, 74.2, 72.6, 68.8, 60.7, 41.3, 26.4, 14.3; MS (FAB+) m/z 325 $(M+H)^+$.

(*rel*)-(1*S*,2*S*,3*R*,4*S*)-3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2-methyl-cyclopentanol (25): To a mixture of $(NH4)_2SiF_6$ (890 mg, 5.0 mmol), CsF (151.9 mg, 1.0 mmol) and epoxide (324 mg, 1.0 mmol) in 1,2-dichloroethane (10 mL) in polyethylene bottle was added 47% hydrofluoric acid (0.127 mL, 3.0

mmol) at 0 ℃, and the mixture was stirred for 7 h at 0 ℃. A saturated $NaHCO_3$ solution (10 mL) was slowly added and the whole mixture was extracted with diethyl ether (10 mL) two times. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered, and evaporated. The filtrate was concentrated under vacuum and residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:10) to give alcohol **25** (175 mg, 51%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.27 (m, 10H), 4.61 (s, 2H), 4.57 (s, 2H), 3.86 (ddd, J = 2.8, 6.2, 18.4 Hz, 1H), 3.57 (dd, J = 5.8, 9.0 Hz, 1H), 3.24 (dd, J = 5.8, 13.8 Hz, 1H), 2.29 (m, 1H), 1.76 (dd, J = 6.2, 10.4 Hz, 1H), 1.59 (dd, J = 8.4, 10.4 Hz, 1H), 1.28 (d, J = 21.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.8, 138.2, 130.1, 128.4, 127.6, 127.0, 126.1, 102.8 (d, J = 181.2 Hz), 80.2 (d, J = 42.6 Hz), 76.1, 75.5, 73.2 (d, J = 18.8 Hz), 69.2, 38.8, 28.4, 14.1 (d, J = 24.5 Hz); Anal. calc. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.82; H, 7.38; MS (FAB+) m/z 345 $(M+H)^+$; Anal. calc. for $C_{21}H_{25}FO_3$: C, 73.23; H, 7.32. Found: C, 73.29; H, 7.27.

(*rel*)-(1*R*,2*S*,3*R*,4*S*)-1-(3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2-methyl-cyclopentan-1-yl) *N*^{4}-benzoyl cytosine (26): To a stirred solution of triphenylphosphoine (561 mg, 2.14 mmol) in dry THF (8 mL) at 0 ℃ was added dropwise the diisopropyl azodicarboxylate (DIAD) (432 mg, 2.14 mmol) and the reaction mixture was stirred at this temperature for 30 min. After that, a solution of the alcohol **25** (368 mg, 1.07 mmol) in THF (8 mL) was added and the reaction mixture was stirred at 0 ℃ for 15 min. Then the cold bath was removed and the yellow solution was stirred for 30 min at room temperature.

N^4-Benzoyl cytosine (460 mg, 2.14 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, 3:1) to give compound **26** (401 mg, 68%); mp 178−180 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (d, *J* = 7.2 Hz, 1H), 7.92 (dd, *J* = 5.6, 8.6 Hz, 2H), 7.62 (d, *J* = 5.0 Hz, 2H), 7.38−7.26 (m, 11H), 5.60 (d, *J* = 7.2 Hz, 1H), 4.63 (s, 2H), 4.56 (s, 2H), 4.02 (dd, *J* = 5.8, 16.8 Hz, 1H), 3.54 (dd, *J* = 8.2, 12.0 Hz, 1H), 3.22 (ddd, *J* = 1.8, 6.2, 14.6 Hz, 1H), 2.30 (m, 1H), 1.85 (dd, *J* = 8.6, 10.8 Hz, 1H), 1.49 (dd, *J* = 6.2, 10.7 Hz, 1H), 1.32 (d, *J* = 22.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.38, 165.9, 157.8, 138.2, 136.2, 133.5, 132.9, 129.6, 128.1, 127.7, 127.1, 126.3, 101.9 (d, *J* = 181.8 Hz), 94.3, 81.5 (d, *J* = 44.1 Hz), 78.2, 76.2, 68.7, 55.5 (d, *J* = 16.8 Hz), 36.2, 25.2, 14.5 (d, *J* = 28.6 Hz); MS (FAB+) m/z 564 $(M+Na)^+$.

(*rel*)−(1*R*,2*S*,3*R*,4*S*)−1−(3−Benzyloxy−4−benzyloxymethyl−2−fluoro−2−methyl−cyclopentan−1−yl) cytosine (27): To a stirred solution of compound **26** (324 mg, 0.6 mmol) in MeOH (8 mL), NaOMe (0.3 mL, 1 M solution in MeOH) was added at 0 ℃ under nitrogen and stirred overnight. The reaction mixture was neutralized with acetic acid and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexane/MeOH, 3:1:0.2) to give compound **27** (233 mg, 89%) as a white solid: mp 169−171 ℃; UV (MeOH) λ_{max} 271.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, *J* = 7.2 Hz, 1H), 7.31−7.25 (m, 10H), 5.57 (d, *J* = 7.2 Hz, 1H), 4.64 (s, 2H), 4.57 (s, 2H), 4.06 (ddd, *J* = 2.8, 6.4, 18.8 Hz, 1H), 3.59 (dd, *J* = 8.2, 12.2 Hz, 1H), 3.27 (dd, *J*

= 6.4, 14.4 Hz, 1H), 2.34 (m, 1H), 1.81 (dd, J = 8.4, 10.6 Hz, 1H), 1.39 (dd, J = 6.2, 10.6 Hz, 1H), 1.37 (d, J = 20.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.7, 156.5, 142.5, 137.8, 136.8, 134.2, 133.2, 129.4, 128.6, 127.9, 127.2, 126.9, 103.1 (d, J = 181.2 Hz, 2H), 94.9, 83.5 (d, J = 42.1 Hz), 79.0. 77.1, 68.4, 56.7 (d, J = 17.2 Hz), 35.8, 26.7, 14.2 (d, J = 27.8 Hz); MS (FAB+) m/z 438 $(M+H)^+$.

(*rel*)-(1*R*,2*S*,3*R*,4*S*)-1-(3-Hydroxy-4-hydoxymethyl-2-fluoro-2-methyl-cyclopentan-1-yl) cytosine (28): A solution of **27** (371 mg, 0.85 mmol) in MeOH (25 mL) was treated with palladium hydroxide (170 mg, 20% in acetivated charcoal) at 0 ℃. Cyclohexane (10 mL) was added and the reaction mixture was refluxed overnight. The suspension was cooled down to room temperature, filtered over Celite, and the filtrates were concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 5:1) to give compound **28** (188 mg, 86%) as a white solid: mp 202-204 ℃; UV (H_2O) λ_{max} 271.5 nm; ^1H NMR (300 MHz, DMSO-d_6, D_2O exchanged) δ 7.87 (d, J = 7.2 Hz, 1H), 5.67 (d, J = 7.2 Hz, 1H), 4.97 (d, J = 5.2 Hz, 1H), 4.98 (t, J = 5.4 Hz, 1H), 4.65 (s, 2H), 4.57 (s, 2H), 4.03 (dd, J = 6.6, 18.6 Hz, 1H), 3.52 (dd, J = 8.0, 10.8 Hz, 1H), 3.31 (dd, J = 6.6, 14.8 Hz, 1H), 2.36 (m, 1H), 1.83 (dd, J = 8.6, 11.2 Hz, 1H), 1.39 (dd, J = 6.4, 11.2 Hz, 1H), 1.39 (d, J = 21.6 Hz, 3H); ^{13}C NMR (300 MHz, DMSO-d_6, D_2O exchanged) δ 165.8, 156.3, 143.6, 101.9 (d, J = 182.0 Hz), 94.5, 84.1 (d, J = 40.8 Hz), 78.9, 76.3, 68.8, 55.8 (d, J = 16.8 Hz), 36.5, 25.3, 13.8 (d, J = 26.6 Hz); MS (FAB+) m/z 280 $(M+Na)^+$; Anal. calc. for $C_{11}H_{16}FN_3O_3$ (+0.5 MeOH): C, 50.54; H, 6.64; N, 16.38. Found: C, 5046; H, 6.59; N, 16.32.

(*rel*)-(1*R*,2*S*,3*R*,4*S*)-9-(3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2-methyl-cyclopentan-1-yl) N^6-bis-Boc-adenine (29): Nucleoside analogue **29** was synthesized from N^6-bis-Boc-protected adenine by the same procedure as described for the preparation of **26**: yield 93%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.82 (s, 1H), 7.97 (s, 1H), 7.32-7.24 (m, 10H), 4.66 (s, 2H), 4.58 (s, 2H), 4.07 (ddd, J = 2.0, 6.8, 15.6 Hz, 1H), 3.58 (dd, J = 8.4, 12.2 Hz, 1H), 3.38 (dd, J = 6.8, 15.2 Hz, 1H), 2.34 (m, 1H), 1.82 (dd, J = 8.8, 12.2 Hz, 1H), 1.54 (dd, J = 6.6, 12.2 Hz, 1H), 1.43 (s, 18H), 1.33 (d, J = 20.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 153.1, 152.8, 152.1, 150.4, 142.4, 138.5, 137.5, 134.2, 133.6, 129.1, 128.2, 127.8, 127.2, 119.4, 104.9 (d, J = 182.2 Hz), 83.6, 79.5 (d, J = 40.8 Hz), 77.8, 76.1, 67.9, 54.3 (d, J = 17.6 Hz), 37.4, 27.5, 26.7, 14.1 (d, J = 26.4 Hz); MS (FAB+) m/z 684 $(M+Na)^+$.

(*rel*)-(1*R*,2*S*,3*R*,4*S*)-9-(3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2-methyl-cyclopentan-1-yl) adenine (30): To a stirred solution of **29** (410 mg, 0.62) in $ClCH_2CH_2Cl$/MeOH = 1:1 (5 mL) was added dropwise trifluoric acid (2.6 g, 23.1 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/Hexane/ MeOH, 3:1:0.1) to give compound **30** (263 mg, 92%) as a white solid: mp 200-202 ℃; UV (MeOH) λ_{max} 259.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.63 (s, 1H), 8.28 (s, 1H), 7.36-7.28 (m, 10H), 4.61 (s, 2H), 4.52 (s, 2H), 4.01 (dd, J = 6.4, 15.8 Hz, 1H), 3.52 (dd, J = 8.6, 12.0 Hz, 1H), 3.40 (dd, J = 7.0, 15.8 Hz, 1H), 2.37 (m, 1H), 1.79 (dd, J = 8.6, 12.0 Hz, 1H), 1.56 (dd, J = 6.4, 12.1 Hz, 1H),

1.35 (d, J = 21.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.6, 152.2, 150.1, 149.4, 137.8, 136.4, 134.5, 132.2, 129.4, 128.1, 127.2, 119.6, 101.5 (d, J = 180.8 Hz), 80.1 (d, J = 44.3 Hz), 78.2, 76.5, 68.5, 56.7 (d, J = 18.8 Hz), 38.3, 27.1, 14.7 (d, J = 25.8 Hz); MS (FAB+) m/z 484 $(M+Na)^+$.

(*rel*)-(1*R*,2*S*,3*R*,4*S*)-9-(3-Hydroxy-4-hydroxymethyl-2-fluoro-2-methyl-cyclopentan-1-yl) adenine (31): Adenine analogue **31** was obtained by a similar procedure as described for the preparation of **28**: yield 84%; mp 216-219 ℃; UV (H_2O) λ_{max} 260 nm; ^{1}H NMR (300 MHz, DMSO-d_6, D_2O exchanged) δ 8.32 (s, 1H), 8.24 (s, 1H), 4.62 (s, 2H), 4.55 (s, 2H), 4.00 (dd, J = 6.2, 15.4 Hz, 1H), 3.51 (dd, J = 8.8, 12.2 Hz, 1H), 3.39 (dd, J = 7.2, 15.6 Hz, 1H), 2.35 (m, 1H), 1.80 (dd, J = 8.8, 12.0 Hz, 1H), 1.58 (dd, J = 6.6, 12.0 Hz, 1H), 1.37 (d, J = 21.0 Hz, 3H); ^{13}C NMR (300 MHz, DMSO-d_6, D_2O exchanged) δ 155.7, 153.2, 150.2, 148.3, 120.0, 130.6 (d, J = 182.2 Hz), 81.2 (d, J = 44.6 Hz), 79.1, 75.2, 68.8, 55.3 (d, J = 20.2 Hz), 37.1, 26.7, 14.1 (d, J = 24.6 Hz); MS (FAB+) m/z 304 $(M+Na)^+$; Anal. calcd. for $C_{12}H_{16}FN_5O_2$ (+1.0 H_2O): C, 48.15; H, 6.06; N, 23.40. Found: C, 48.19; H, 5.97; N, 23.36.

(3-Bromo-but-3-enyloxy)-*t*-butyldimenthylsilane (34): To a stirred solution of 3-bromo-but-3-en-1-ol (6.6 g, 43.8 mmol) and imidazole (4.62 g, 67.88 mmol) in CH_2Cl_2 (150 mL), *t*-butyldimethylsilyl chloride (7.26 g, 48.18 mmol) at 0 ℃ was added. The mixture was stirred at room temperature for 6 hours and concentrated under vacuum. The residue was extracted using EtOAc (200 mL) and water (200 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography

(EtOAc/ Hexane, 1:35) to give compound **34** (11 g, 95%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.59 (d, *J* = 5.8 Hz, 1H), 5.40 (d, *J* = 5.8 Hz, 1H), 3.79 (t, *J* = 7.2 Hz, 2H), 2.11 (t, *J* = 7.2 Hz, 2H), 0.81 (s, 9H), 0.1 (s, 6H).

(±)-2-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-5,5-bis-(*tert*-butyl-dimethyl-silanyloxymethyl)-hepta-1,6-dien-3-ol (35): To a solution of compound **34** (581 mg, 2.19 mmol) in dry THF (8 mL) cooled at −110 ℃ (ether and liquid nitrogen), 1.6 M butyllithium in hexane (1.36 mL, 2.19 mmol) was slowly added for 5 minutes under an argon atomsphere. After stirred for 15 minutes at the same temperature, a solution of **33** (326 mg, 0.877 mmol) in dry THF (2 mL) was slowly added to the mixture over 5 minutes and stirred for 15 minutes at the same temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (3 mL) and warmed slowly to room temperature. The mixture was extracted with diethyl ether (50 mL) two times and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/Hexnae, 1:30) to give a diastereomeric mixture of **35** (309 mg, 63%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72 (dd, *J* = 5.6, 2.4 Hz, 1H), 5.08-4.97 (m, 4H), 3.92 (m, 1H), 3.81-3.72 (m, 4H), 3.61 (t, *J* = 7.0 Hz, 2H), 2.24 (t, *J* = 7.0 Hz, 1H), 1.45-1.39 (dd, *J* = 6.8, 2.8 Hz, 2H), 0.81 (m, 27H), 0.01 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.7, 148.3, 110.1, 108.7, 74.1, 70.7, 70.6, 65.1, 36.6, 35.2, 35.1, 25.4, 18.5, −5.6.

(±)-2-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-4,4-bis-(*tert*-butyl-dimethyl-silanyloxymethyl)-cyclopent-2-enol (36): To a solution of

compound **35** (1.74 g, 3.12 mmol) in dry benzene (10 mL), a second-generation Grubbs' catalyst (21 mg, 0.0236 mmol) was added. The reaction mixture was refluxed overnight and concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:25) to give the cyclopentenol **36** (1.32 mg, 80%) as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.47 (s, 1H), 4.10 (dd, J = 5.4, 1.2 Hz, 1H), 3.86 (t, J = 7.2 Hz, 2H), 3.77–3.69 (m, 4H), 2.12 (t, J = 7.1 Hz, 2H), 2.03 (dd, J = 12.8, 6.8 Hz, 1H), 1.89 (dd, J = 12.8, 5.4 Hz, 1H), 0.82 (m, 27H), 0.01 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.5, 133.2, 75.3, 70.7, 70.0, 64.2, 46.2, 36.1, 30.7, 25.5, 18.7, −5.4.

(±)-2-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-4,4-bis-(*tert*-butyl-dimethyl-silanyloxymethyl)-cyclopent-2-enyl ethyl carbonate (37): To a solution of compound **36** (2.98 g, 5.61 mmol) in anhydrous pyridine (15 mL), ethyl chloroformate (656 mg, 6.05 mmol) and DMAP (60 mg, 0.49 mmol) were added. The reaction mixture was stirred overnight at 65 ℃. The raction mixture was then quenched using a saturated $NaHCO_3$ solution (1.0 mL) and vacuum-concentrated. Water (150 mL) was poured into the residue and extracted with EtOAc (150 mL) two times. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:30) to give compound **37** (2.6 g, 77%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.42 (s, 1H), 4.78 (t, J = 6.2, 4.8 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.85 (t, J = 7.0 Hz, 2H), 3.76–3.68 (m, 4H), 2.14 (t, J = 7.0 Hz, 2H), 2.08 (dd, J = 12.8, 7.0 Hz, 1H), 1.89 (dd, J = 12.8, 8.8 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 0.82 (m, 27H), 0.01 (m, 18H); ^{13}C

NMR ($CDCl_3$, 75 MHz) δ 153.2, 140.7, 132.9, 83.5, 70.7, 70.1, 64.2, 63.2, 46.1, 36.3, 28.1, 25.4, 18.7, 13.7, −5.7.

(±)−1−[2−[2−(*tert*−Butyl−dimethyl−silanyloxy)−ethyl]−4,4−bis−(*tert*−butyl−diemthyl−silanyloxymethyl)−cyclopent−2−enyl] cytosine (38): To generate a nucleosidic base anion, cytosine (124 mg, 1.12 mmol) was added to hexane−washend NaH (26.8 mg, 1.12 mmol) in anhydrous DMSO (7.0 mL). The reaction mixture was stirred for 30 minutes at 50−55 ℃ and cooled to room temperature. Simultaneously, $P(O\text{−}i\text{−}Pr)_3$ (93 mg, 0.448 mmol) was added to a solution of $Pd_2(dba)_3$ and $CHCl_3$ (60 mg, 5.76 μmol) in anhydrous THF (5.0 mL), which was stirred for 30 minutes. A catalyst solution of THF and **37** (603 mg, 1.0 mmol) dissolved in anhydrous THF (7.0 mL) was sequentially added to the cytosine solution of DMSO. The reaction mixture was stirred overnight at refluxing temperature and quenched with water (3.0 mL). The reaction solvent was removed under vacuum. The residue was purified by silica gel column chromatography (MeOH/Hexane/EtOAc, 0.1:4:1) to yield **38** (200 mg, 32%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (d, J = 7.0 Hz, 1H), 5.38 (d, J = 7.0 Hz, 1H), 4.42 (dd, J = 6.6, 2.4 Hz, 1H), 3.84 (t, J = 6.8 Hz, 2H), 3.73−3.65 (m, 4H), 2.17 (t, J = 6.9 Hz, 1H), 2.16 (dd, J = 13.2, 6.8 Hz, 1H), 1.91 (dd, J = 13.2, 8.8 Hz, 1H), 0.82 (m, 27H), 0.02 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.3, 156.2, 146.6, 139.6, 132.8, 94.1, 69.8, 69.3, 64.0, 55.8, 46.7, 37.2, 27.5, 25.7, 18.5, −5.6.

(±)−9−[2−[2−(*tert*−Butyl−dimethyl−silanyloxy)−ethyl]−4,4−bis−(*tert*−butyl−diemthyl−silanyloxymethyl)−cyclopent−2−enyl] adenine (39): Adenine

nucleoside analogue **39** (147 mg, 0.227 mmol) was synthesized from **37** (351 mg, 0.582 mmol) by a similar procedure as described for **38**: yield 39%: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (s, 1H), 8.19 (s, 1H), 5.40 (s, 1H), 4.72 (t, J = 6.0 Hz, 1H), 3.82 (t, J = 7.0 Hz, 2H), 3.74–3.65 (m, 4H), 2.27 (dd, J = 12.8, 7.0 Hz, 1H), 2.14 (t, J = 7.0 Hz, 2H), 1.89 (dd, J = 12.9, 8.9 Hz, 1H), 0.81 (m, 2H), 0.01 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 154.9, 153.2, 146.9, 143.2, 138.9, 132.5, 127.4, 70.5, 70.2, 63.6, 58.9, 47.3, 37.5, 26.5, 25.6, 18.4, −5.7.

(*rel*)−(1'*R*,2'*R*,3'*R*)−1−[2−[2−(*tert*−Butyl−dimethyl−silanyloxy)−ethyl]−4,4−bis−(*tert*−butyl−dimethyl−silanyloxymethyl)−2,3−dihydroxy−cyclopentyl] cytosine (40); (*rel*)−(1'*R*,2'*S*,3'*S*)−1−[2−[2−(*tert*−Butyl−dimethyl−silanyloxy) −ethyl]−4,4−bis−(*tert*−butyl−dimethyl−silanyloxymethyl)−2,3−dihydroxy−cy−clopentyl] cytosine (41): To a stirred solution of **38** (377 mg, 0.605 mmol) in cosolvent (7.0 mL, acetone/water = 5:1) was added *N*−methylmorpholine−*N*−oxide (NMO) (283 mg, 1.21 mmol) and OsO_4 (0.51 mL, 4% in water). The mixture was stirred overnight at room temperature and quenched with saturated Na_2SO_3 solution (5 mL). The resulting solid was removed by filtration through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:6) to give **40** (167 mg, 42% yield) and **41** (83 mg, 21% yield) as a white solid, respectively.

Compound for **40**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J = 7.1 Hz, 1H), 5.32 (d, J = 7.0 Hz, 1H), 3.80 (t, J = 6.9 Hz, 2H), 3.72−3.64 (m, 5H), 3.28 (d, J = 6.0 Hz, 1H), 1.66−1.56 (m, 3H), 1.32 (dd, J = 13.0, 8.4 Hz, 1H), 0.81 (m,

27H), 0.02 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 164.9, 156.4, 145.7, 93.0, 76.8, 76.2, 64.7, 64.5, 58.4, 40.1, 34.3, 25.3, 18.7, 17.1, −5.7; Anal. calc. for $C_{13}H_{63}N_3O_6Si_3$: C, 56.58; H, 9.65; N, 6.39. Found: C, 56.62; H, 9.58; N, 6.29.

Compound for **41**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, *J* = 7.0 Hz, 1H), 5.35 (d, *J* = 7.2 Hz, 1H), 3.85 (t, *J* = 7.0 Hz, 2H), 3.76−3.67 (m, 4H), 3.52 (dd, *J* = 6.8, 1.8 Hz, 1H), 3.31 (d, *J* = 5.9 Hz, 1H), 1.63−1.55 (m, 3H), 1.30 (dd, *J* = 12.8, 8.2 Hz, 1H), 0.82 (m, 27H), 0.01 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 164.6, 156.6, 146.0, 92.5, 76.2, 75.9, 64.3, 64.0, 59.1, 41.2, 33.9, 25.7, 18.6, 16.6, −5.6; Anal. calc. for $C_{13}H_{63}N_3O_6Si_3$: C, 56.58; H, 9.65; N, 6.39. Found: C, 56.50; H, 9.71; N, 6.37.

(*rel*)−(1'*R*,2'*R*,3'*R*)−9−[2−[2−(*tert*−Butyl−dimethyl−silanyloxy)−ethyl]−4,4−bis−(*tert*−butyl−dimethyl−silanyloxymethyl)−2,3−dihydroxy−cyclopentyl] adenie (42); (*rel*)−(1'*R*,2'*S*,3'*S*)−9−[2−[2−(*tert*−butyl−dimethyl−silanyloxy)−ethyl]−4,4−bis−(*tert*−butyl−dimethyl−silanyloxymethyl)−2,3−dihydroxy−cycl−opentyl] adenie (43): The adenine nucleoside analogues **42** (113 mg, 0.166 mmol) and **43** (67 mg, 0.09 mmol) were synthesized from **39** (276 mg, 0.426 mmol) by a similar procedure as described for **40** and **41** as a white solid, respectively. Data for **42**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 8.18 (s, 1H), 3.79−3.70 (m, 3H), 3.70−3.62 (m, 4H), 3.28 (s, 1H), 1.60 (t, *J* = 7.0 Hz, 2H), 1.89−1.80 (m, 2H), 0.81 (m, 27H), 0.01 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 154.9, 152.8, 147.6, 143.2, 127.8, 76.7, 76.4, 65.3, 65.1, 57.8, 56.9, 40.1, 34.7, 25.6, 18.7, 17.1, −5.5; Anal. calc. for $C_{32}H_{63}N_5O_5Si_3$: C, 56.34; H, 9.31; N, 10.27. Found: C, 56.29; H, 9.33; N, 10.25. Data for **43**: yield 23%; ^{1}H NMR ($CDCl_3$, 300

MHz) δ 8.32 (s, 1H), 8.21 (s, 1H), 3.78 (dd, J = 5.2, 1.2 Hz, 1H), 3.71−3.63 (m, 6H), 3.26 (s, 1H), 1.62 (t, J = 7.1 Hz, 2H), 1.87−1.79 (m, 2H), 0.82 (m, 27H), 0.01 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 155.1, 153.1, 147.9, 143.6, 128.1, 76.9, 76.2, 65.8, 65.4, 57.2, 56.7, 41.2, 34.2, 25.7, 18.6, 16.9, −5.6; Anal. calc. for $C_{32}H_{63}N_5O_5Si_3$: C, 56.34; H, 9.31; N, 10.27. Found: C, 56.46; H, 9.28; N, 10.31.

(*rel*)−(1'*R*,2'*R*,3'*R*)−1−[2−[2−(Hydroxy)−ethyl]−4,4−bis−(hydroxymethyl)−2,3−dihydroxy−cyclopentyl] cytosine (44): To a solution of **40** (178 mg, 0.27 mmol) in cosolvent (4.0 mL, THF/CH_3CN = 1:1) was added TBAF (1.35 mL, 1.0 M solution in THF) at 0 ℃. 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 **44** (64 mg, 76%) as a white solid: m.p. 202−204 ℃; UV (H_2O) λ_{max} 271.0 nm (ε 16.370, pH 7); ^{1}H NMR (DMSO−d_6, 300 MHz) δ 7.47 (d, J = 7.0 Hz, 1H), 7.04 (br d, 2H), 5.37 (d, J = 7.1 Hz, 1H), 3.69 (d, J = 6.2 Hz, 1H), 3.54−3.35 (m, 6H), 1.66−1.57 (m, 3H), 1.35 (dd, J = 12.8, 6.8 Hz, 1H); ^{13}C NMR (DMSO−d_6) δ 165.2, 156.1, 145.5, 94.7, 75.9, 75.6, 62.5, 62.1, 55.4, 37.4, 34.1, 17.1; Anal. calc. for $C_{13}H_{21}N_3O_6$ (+ 1.0 H_2O): C, 46.84; H, 6.95; N, 12.60. Found: C, 46.77; H, 7.02; N, 12.65.

(*rel*)−(1'*R*,2'*R*,3'*R*)−9−[2−[2−(Hydroxy)−ethyl]−4,4−bis−(hydroxymethyl)−2,3−dihydroxy−cyclopentyl] adenine (45): Adenine derivative **45** (68 mg, 0.2 mmol) was prepared from **42** (196 mg, 0.287 mmol) by the same procedure as described for **44**: yield 70%; m.p. 210−213 ℃; UV (H_2O) λ_{max} 265.5 nm (ε 16.370, pH 7); ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.50 (s, 1H), 8.21 (s, 1H),

6.23 (br s, 2H), 3.77 (d, J = 6.2 Hz, 1H), 3.52 (t, J = 7.1 Hz, 2H), 3.46−3.37 (m, 4H), 3.27 (s, 1H), 1.88−1.79 (dd, J = 13.0, 6.8 Hz, 1H), 1.60 (t, J = 7.1 Hz, 2H); ^{13}C NMR (DMSO−d_6) δ 154.9, 152.7, 147.3, 145.4, 128.5, 77.0, 76.8, 61.5, 61.2, 56.5, 54.7, 37.4, 34.5, 16.8; Anal. calc. for $C_{14}H_{21}N_5O_5$ (+ 1.0 H_2O): C, 47.05; H, 6.49; N, 19.59. Found: C, 46.94; H, 6.52; N, 19.49.

(*tert*−Butyldimethylsilyloxy)−acetic acid ethyl ester (47): To a solution of ethyl glycolate **46** (10.0 g, 0.09 mmol) and imidazole (8.80 g, 0.14 mmol) in CH_2Cl_2 (200 mL), TBDMSCl (15.9 g, 0.10 mol) was added slowly at 0 ℃, and stirred for 5 h at the same temperature. The reaction solvent was evaporated under reduced pressure. The residue was extracted twice with diethyl ether and water. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure, The residue was purified by silica gel column chromatography (EtOAc/Hexnane, 1:20) to give compound **47** (19.9 g, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.12 (s, 2H), 4.08 (q, J = 6.9 Hz, 2H), 1.17 (t, J = 6.9 Hz, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 171.54, 61.80, 60.66, 25.69, 18.35, 14.12, −5.50.

(*tert*−Butyldimethylsilyloxy) acetic acid (48): A solution of KOH (2.57 g, 59.5 mmol) in EtOH (20 mL) was slowly added to a solution of **47** (10.0 g, 45.7 mmol) in EtOH (200 mL) at 0 ℃. The mixture was stirred overnight at rt and concentrated under reduced pressure. The residue was dissolved in water (200 mL) and carefully neutralized with *c*−HCl solution to Ph 3−4. The solution was extracted with EtOAc two times. The 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, 1:3) to give **48** (7.84 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.12 (s, 2H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 171.02, 61.90, 25.55, 18.71, −5.57.

2-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-methyl-acetamide (49): To a solution of acid derivative **48** (5.00 g, 26.2 mmol) in a anhydrous CH_2Cl_2 (150 mL), *N,O*-dimethylhydroxylamine hydrochloride (3.06 g, 31.4 mmol), DCC (6.48 g, 31.4 mmol), DMAP (317 mg, 2.60 mmol) and triethylamine (3.18 g, 31.4 mmol) were sequentially added to the reaction mixture. The solution was stirred overnight at rt. After addition of methanol (5 mL) and acetic acid (5 mL), the mixture was stirred for 1 h and neutralized with saturated aqueous $NaHCO_3$ solution. The resulting solid was filtered off through a short pad of Celite and the filtrate was concentrated in vacuum. The resulting residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:1.5) to give Weinreb amide **49** (5.21 g, 85%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.48 (s, 2H), 3.57 (s, 3H), 3.05 (s, 3H), 0.08 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 171.63, 61.00, 52.63, 31.67, 25.54, 18.49, −5.61.

1-(*tert*-Butyldimethylsilyloxy)-but -3-yn-2-one (50): Ethynylmagnesium bromide (32.8 mL, 0.5 M solution in THF) was slowly added to a solution of Weinred amide **49** (3.20 g, 13.7 mmol) in dry THF (70 mL) at 0 ℃ and stirred for 5 h at the same temperature. The mixture was quenched with saturated NH_4Cl (16 mL), and the reaction mixture was slowly warmed to room temperature. The mixture was extracted with EtOAc (2 × 100 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The

residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:10) to give **50** (1.87 g, 69%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.34 (s, 2H), 2.98 (s, 1H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 196.31, 82.87, 79.43, 73.43, 25.76, 18.34, −5.58; Anal. calcd. for $C_{10}H_{18}O_2Si$: C, 60.56; H, 9.15. Found: C, 60.45; H, 9.07.

(*E*) and (*Z*)-3-(*tert*-Butyldimethylsilyloxymethyl)-pent-2-en-4-ynoic acid ethyl ester (51): To a suspension of sodium hydride (0.40 g, 16.7 mmol) in distilled THF (100 mL) was added drop wise triethyl phosphonoacetate (3.74 g, 16.7 mmol) at 0 ℃ and the mixture was stirred at room temperature for 2 h. The ketone **50** (3.31 g, 16.7 mmol) was added to this mixture and stirred for 2 h. The solution was neutralized with AcOH (3 mL) and poured into H_2O (150 mL) and extracted with EtOAc. The 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, 1:2) to give **51** (3.22 g, 72%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (s, 1H), 4.50 (s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 3.09 (s, 1H), 1.31 (t, J = 7.2 Hz, 2H), 0.84 (s, 9H), 0.02 (s, 6H).

(*E*) and (*Z*)-3-(*tert*-Butyldimethylsilyloxymethyl)-pent-2-en-4-yn-1-ol (52): DIBALH (35.2 mL, 1.0 M solution in hexane) was slowly added to a solution of **51** (4.50 g, 16.7 mmol) in CH_2Cl_2 (150 mL) at −20 ℃, and stirred for 1.5 h at the same temperature. Methanol (35 mL) was 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, 1:7) to give alcohol **52** (3.41 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.17 (t, *J* = 1.8 Hz, 1H), 4.31 (d, *J* = 6.6 Hz, 2H), 4.08 (s, 2H), 3.10 (s, 1H), 0.86 (m, 9H), 0.01 (m, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 139.74, 135.52, 123.81, 83.65, 79.05, 64.79, 60.90, 25.78, 18.56, −5.50.

(±)-3-(*tert*-Butyldimethylsilyloxymethyl)-3-ethynyl-pent-4-enoic acid ethyl ester (53): A solution of allylic alcohol **52** (5.50 g, 24.3 mmol) in triethyl orthoacetate (150 mL) and 0.2 mL of propionic acid was heated at 135-140 ℃ overnight with stirred for the distillation of ethanol. The excess triethyl orthoacetate was distilled off and residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:25) to give **53** (6.05 g, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92 (d, *J* = 9.8 Hz, 1H), 5.80 (d, *J* = 10.4 Hz, 1H), 5.31 (d, *J* = 1.4 Hz, 1H), 4.02 (q, *J* = 6.9 Hz, 2H), 3.64 (d, *J* = 9.6 Hz, 1H), 3.51 (d, *J* = 9.6 Hz, 1H), 2.30 (d, *J* = 7.8 Hz, 1H), 2.24 (d, *J* = 7.8 Hz, 1H), 1.98 (s, 1H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 171.75, 143.54, 114.50, 80.76, 77.65, 69.34, 61.32, 49.35, 25.76, 18.76, 13.76, −5.76; Anal. calcd. for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.52. Found: C, 65.03; H, 9.67.

(±)-3-(*t*-Butyldimethylsilyloxymethyl)-3-ethynyl-pent-4-enal (54): To a solution of **53** (2.50 g, 8.43 mmol) in toluene (40 mL), DIBALH (6.18 mL, 1.5 M solution in toluene) was added slowly at −78 ℃, and stirred for 15 minutes at the same temperature. To the mixture, methanol (7 mL) was added. The mixture was stirred at room temperature for 1.5 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 **54** (1.29 g, 61%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.80 (m, 1H), 5.85 (d, J = 10.0 Hz, 1H), 5.70 (d, J = 9.4 Hz, 1H), 5.33 (d, J = 8.0 Hz, 1H), 3.79 (s, 2H), 2.93 (m, 2H), 2.01 (s, 1H), 0.83 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 202.78, 143.32, 113.76, 81.36, 78.61, 69.55, 48.43, 25.78, 18.72, −5.76; Anal. calcd. for $C_{14}H_{24}O_2Si \cdot 0.5$ Hx: C, 69.33; H, 10.26. Found: C, 69.49; H, 10.40.

(*rel*)−(3*R* and 3*S*,5*S*)−5−(*t*−Butyldimethylsilyloxymethyl)−5−ethynyl−hepta−1,6−dien−3−ol (55): To a solution of **54** (4.20 g, 16.6 mmol) in dry THF (100 mL) was slowly added vinyl magnesiumbromide (19.9 mL, 1.0 M solution in THF) at −78 ℃. After 4 h, saturated NH_4Cl solution (20 mL) and water (100 mL) was sequentially added, and the reaction mixture was slowly warmed to rt. The mixture was extracted with EtOAc (2 × 120 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:18) to give **55** (3.50 g, 75%) as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.08−5.70 (m, 2H), 5.41−5.17 (m, 4H), 4.27 (m, 1H), 3.52 (m, 2H), 2.02 (m, 1H), 1.69−1.57 (m, 2H), 0.82 (m, 9H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 142.91, 140.54, 114.76, 114.64, 112.12, 111.99, 88.32, 73.45, 68.57, 68.43, 67.09, 41.12, 41.35, 30.06, 25.43 (m), 18.70, −5.71 (m); Anal. calcd. for $C_{16}H_{28}O_2Si \cdot 0.5$ EtOAc: C, 66.62; H, 9.94. Found: C, 66.68; H, 9.96.

(*rel*)−(1*R*,4*S*)−4−(*t*−Butyldimethylsilyloxymethyl)−4−ethynyl−cyclopent−2−enol (56*β*); and (*rel*)−(1*S*,4*S*)−4−(*t*−Butyldimethylsilyloxymethyl)−4−

ethynyl-cyclopent-2-enol (55α): A second-generation Grubbs catalyst (153 mg, 0.18 mmol) was added to a solution of **55** (1.55 g, 5.54 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was refluxed overnight and cooled to room temperature. The mixture was concentrated in a vacuum, and the residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:10) to give cyclopentenol **56β** (293 mg, 21%) and **56α** (307 mg, 22%) as colorless oils. Cyclopentenol **55β**: ^{1}H NMR ($CDCl_3$, 300 MHz) d 6.00−5.92 (m, 5H), 4.54 (m, 1H), 3.68 (d, *J* = 9.4 Hz, 1H), 3.51 (d, *J* = 9.4 Hz, 1H), 2.30 (dd, *J* = 13.2, 6.8 Hz, 1H), 1.99 (s, 1H), 1.59 (dd, *J* = 8.4, 6.8 Hz, 1H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 141.10, 134.65, 80.76, 78.49, 73.35, 68.99, 52.34, 45.38, 25.56, 18.57, −5.62; Anal. Calcd. for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.70; H, 9.68. Cyclopentenol **56α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.79−5.68 (m, 2H), 4.82 (dd, *J* = 6.6, 1.4 Hz, 1H), 3.37 (s, 2H), 2.28 (dd, *J* = 13.4, 7.2 Hz, 1H), 2.01 (s, 1H), 1.48 (dd, *J* = 13.4, 7.2 Hz, 1H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 140.97, 132.82, 89.57, 75.54, 71.69, 69.12, 52.43, 44.28, 25.76, 18.72, −5.78; Anal. calcd. for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.48; H, 9.51.

(*rel*)−(1*R*,4*S*)−1−Ethoxy carbonyloxy−4−(*t*−butyldimethylsilyloxymethyl)−4−ethynyl−cyclopent−2−ene (57): Ethyl chloroformate (1.65 mL, 17.3 mmol) and DMAP (102 mg, 0.84 mmol) were added to a solution of **56β** (2.18 g, 8.65 mmol) in anhydrous pyridine (15 mL). The reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (1.5 mL) and concentrated in vacuum. The residue

was extracted with $EtOAc/H_2O$ and the organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:12) to give **57** (2.1 g, 75%) as a colorless syrup: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.41−6.36 (m, 2H), 5.50 (dd, *J* = 6.4, 1.4 Hz, 1H), 4.29 (q, *J* = 7.4 Hz, 2H), 3.86 (d, *J* = 9.6 Hz, 1H), 3.79 (d, *J* = 9.6 Hz, 1H), 2.43 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.17 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.09 (s, 1H), 1.31 (t, *J* = 7.4 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 154.95, 143.99, 128.51, 88.72, 84.03, 73.58, 71.12, 64.52, 50.78, 41.49, 25.59, 18.67, 14.62, −5.57; Anal. calcd. for $C_{17}H_{28}O_4Si \cdot 1.0$ EtOAc: C, 61.13; H, 8.79. Found: C, 61.11; H, 8.64.

(*rel*)−(1'*R*,4'*S*)−9−[4−(*t*−Butyldimethylsilyloxymethyl)−4−ethynyl−cyclo−pent−2−en−l−yl] cytosine (58): Cytosine (109 mg, 0.98 mmol) was added to pure NaH (23.5 mg, 0.98 mmol) in anhydrous DMSO (6.00 mL). The reaction mixture was stirred for 30 min at 50−55 ℃ and cooled to room temperature. Simultaneously, $P(O-i-Pr)_3$ (0.07 mL, 0.22 mmol) was added to a solution of $Pd_2(dba)_3 \cdot CHCl_3$ (4.60 mg, 2.50 mmol) in anhydrous THF (5.0 mL), which was stirred for 30 min. To the nucleosidic base solution of DMSO was sequentially added catalyst solution of THF and **57** (286 mg, 0.88 mmol) dissolved in anhydrous THF (5 mL). The reaction mixture was stirred overnight at refluxing temperature and quenched with water (3 mL). The reaction solvent was removed in a vacuum. The residue was purified by silica gel column chromatography (MeOH/Hexane/EtOAc, 0.1:1:1.5) to give **58** (118 mg, 39%) as a white soli: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, *J* = 7.0 Hz, 1H), 6.06 (d, *J* = 5.4 Hz, 1H),

5.96 (m, 1H), 5.54 (d, *J* = 7.0 Hz, 1H), 5.39 (dd, *J* = 6.4, 1.4 Hz, 1H), 3.81 (d, *J* = 9.2 Hz, 1H), 3.75 (d, *J* = 9.0 Hz, 1H), 2.67 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.22 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.05 (s, 1H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 165.72, 156.67, 145.39, 144.21, 127.88, 93.71, 89.56, 71.42, 69.54, 55.62, 42.32, 25.67, 18.66, −5.61; Anal. calcd. for $C_{18}H_{27}N_3O_2Si$ · 1.0 MeOH: C, 57.62; H, 7.89; N, 10.61. Found: C, 57.42; H, 7.79; N, 10.73.

(*rel*)−(1'*R*,4'*S*)−9−[4−(*t*−Butyldimethylsilyloxymethyl)−4−ethynyl−cyclo−pent−2−en−1−yl] thymine (59): The thymine nucleoside analogue **59** was synthesized from **57** as described for **58**: yield 30%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.29 (br s, 1H), 7.15 (s, 1H), 6.11 (d, *J* = 5.2 Hz, 1H), 6.00−5.93 (m, 2H), 5.35 (m, 1H), 3.76 (d, *J* = 9.0 Hz, 1H), 3.60 (d, *J* = 9.0 Hz, 1H) 2.59 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.18 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.03 (s, 1H), 1.55 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 164.21, 151.70, 143.59, 142.29, 128.21, 109.39, 88.43, 73.39, 69.43, 56.19, 41.54, 25.60, 18.59, 12.30, −5.62; Anal. calcd. for $C_{19}H_{28}N_2O_3Si$: C, 63.30; H, 7.83; N, 7.77. Found: C, 63.43; H, 7.70; N, 7.62.

(*rel*)−(1'*R*,4'*S*)−9−[4−(*t*−Butyldimethylsilyloxymethyl)−4−ethynyl−cyclo−pent−2−en−1−yl] uracil (60): The uracil nucleoside analogue **60** was obtained from **57** as described for **58**: yield 28%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.35 (br s, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 6.05 (dd, *J* = 5.4, 1.8 Hz, 1H), 5.93−5.88 (m, 2H), 5.68−5.59 (m, 2H), 3.69 (d, *J* = 9.2 Hz, 1H), 3.51 (d, *J* = 9.2 Hz, 1H), 2.40 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.09−2.00 (m, 2H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 163.86, 151.21, 147.30, 143.50, 127.39, 101.47,

89.38, 74.32, 70.55, 57.78, 43.19, 25.67, 18.59, −5.73; Anal. calcd. for $C_{18}H_{26}N_2O_3Si$ · 0.5 EtOAc: C, 61.50; H, 7.74; N, 7.17. Found: C, 61.44; H, 7.61; N, 7.16.

(*rel*)−(1'*R*,4'*R*)−9−[4−(Hydroxymethyl)−4−ethynyl−cyclopent−2−en−1−yl] cytosine (61): TBAF (0.43 mL, 1.0 M solution in THF) was added to a solution of **58** (99.0 mg, 0.27 mmol) in THF (5 mL) at 0 ℃. 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 **61** (50.0 mg, 74%) as a white solid: mp 164−167 ℃; ^1H NMR (DMSO−d_6, 300 MHz) δ 7.39 (d, J = 7.2 Hz, 1H), 6.99 (br d, 2H), 6.08 (dd, J = 5.6, 1.2 Hz, 1H), 5.97 (d, J = 5.6 Hz, 1H), 5.56−5.49 (m, 2H), 4.97 (t, J = 5.4 Hz, 1H), 3.68 (d, J = 9.2 Hz, 1H), 3.59 (d, J = 9.2 Hz, 1H), 2.51 (dd, J = 14.0, 8.2 Hz, 1H), 2.06 (m, 2H); ^{13}C NMR (DMSO−d_6, 300 MHz) δ 165.42, 155.78, 146.49, 143.93, 128.37, 92.37, 88.54, 73.43, 68.99, 54.32, 43.41; Anal. calcd. for. $C_{12}H_{13}N_3O_2$ · 1.0 H_2O: C, 57.82; H, 6.06; N, 16.85. Found: C, 57.99; H, 5.97; N, 16.80.

(*rel*)−(1'*R*,4'*R*)−9−[4−(Hydroxymethyl)−4−ethynyl−cyclopent−2−en−1−yl] thymine (62): The thymine carbocyclic nucleoside analogue **62** was synthesized from **59** by the procedure described for **61**: yield 69%; mp 160−163 ℃; ^1H NMR (DMSO−d_6, 300 MHz) δ 11.19 (br s, 1H), 7.18 (s, 1H), 6.13 (d, J = 5.4 Hz, 1H), 6.98−5.91 (m, 2H), 5.38 (m, 1H), 4.90 (t, J = 5.4 Hz, 1H), 3.65 (d, J = 9.2 Hz, 1H), 3.52 (d, J = 9.2 Hz, 1H), 2.42 (dd, J = 14.2, 7.6 Hz, 1H), 2.01−1.95 (m, 2H), 1.52 (s, 3H); ^{13}C NMR (DMSO−d_6, 300 MHz) δ

164.56, 151.49, 144.50, 143.79, 128.51, 108.90, 89.31, 72.49, 69.77, 54.54, 43.48, 12.28; Anal. calcd. for. $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.53; H, 5.92; N, 11.43.

(*rel*)-(1'*R*,4'*R*)-9-[4-(Hydroxymethyl)-4-ethynyl-cyclopent-2-en-1-yl] uracil (63): The uracil nucleoside analogue **63** was synthesized form **60** using the deprotection procedure described for **61**: yield 75%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.21 (br s, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 6.08 (d, *J* = 5.6 Hz, 1H), 6.01-5.93 (m, 2H), 5.59-5.50 (m, 2H), 3.64 (d, *J* = 9.2 Hz, 1H), 3.55 (d, *J* = 9.2 Hz, 1H), 2.38 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.02 (s, 1H), 1.90 (dd, *J* = 14.0, 6.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 164.10, 152.54, 147.88, 144.21, 128.02, 102.08, 89.54, 73.45, 69.29, 57.47, 44.38; Anal. calcd. for. $C_{12}H_{12}N_2O_3 \cdot$ 0.5 MeOH: C, 60.47; H, 5.68; N, 11.28. Found: C, 60.55; H, 5.72; N, 11.09.

(*rel*)-(1'*R*,4'*S*)-9-[4-(*t*-Butyldimethylsilyloxymethyl)-4-ethynyl-cyclopent-2-en-1-yl] 2-amino-6-chloropurine (64): The purine nucleoside analogue **64** was synthesized with the condensation reaction method described for **58**: yield 28%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.95 (s, 1H), 6.08 (d, *J* = 5.6 Hz, 1H), 5.98 (dd, *J* = 4.8, 1.4 Hz, 1H), 5.47 (dd, *J* = 5.2, 1.8 Hz, 1H), 3.62 (d, *J* = 9.2 Hz, 1H), 3.54 (d, *J* = 9.2 Hz, 1H), 2.47 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.04-1.92 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 159.20, 154.31, 151.10, 143.89, 143.11, 126.54, 125.23, 90.02, 74.42, 69.54, 58.21. 43.58, 25.72, 18.58, -5.62; Anal. calcd. for. $C_{19}H_{26}ClN_5OSi$: C, 56.49; H, 6.49; N, 17.34. Found: C, 56.58; H, 4.35; N, 17.27.

(*rel*)-(1'*R*,4'*S*)-9-[4-(Hydroxymethyl)-4-ethynyl-cyclopent-2-en-1-

yl] 2-amino-6-chloropurine (65): The nucleoside analogue **65** was abtained from **64** as described for **61**; yield 62%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.89 (s, 1H), 6.10 (dd, J = 5.4, 1.4 Hz, 1H), 6.02 (dd, J = 5.2, 1.6 Hz, 1H), 5.50 (m, 1H), 4.91 (t, J = 5.2 Hz, 1H), 3.58 (d, J = 9.2 Hz, 1H), 3.49 (d, J = 9.2 Hz, 1H), 2.50 (dd, J = 14.2, 7.8 Hz, 1H), 2.07-1.99 (m, 2H), 0.86 (s, 9H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 159.65, 153.98, 150.87, 143.21, 142.79, 125.42, 124.21, 89.64, 73.43, 69.11, 57.42, 42.28; Anal. calcd. for. $C_{13}H_{12}ClN_5O \cdot 0.5$ MeOH: C, 53.03; H, 4.61; N, 22.91. Found: C, 52.90; H, 4.56; N, 22.80.

(*rel*)-(1'*R*,4'*S*)-9-[4-(Hydroxymethyl)-4-ethynyl-cyclopent-2-en-1-yl] guanine (66): 2-Mercaptoethanol (0.14 mL, 1.90 mmol) and NaOMe (1.76 mL, 1.76 mmol, 1.0 M solution in MeOH) was added to a solution of compound **65** (95.6 mg, 0.33 mmol) in MeOH (10 mL), and heated overnight under reflux. After cooling, the reaction mixture was neutralized with a few drops of glacial AcOH and concentrated under reduced pressure. The residue was purified by silica gel chromatography (MeOH/CH_2Cl_2, 1:4) to give compound **66** (53.0 mg, 60%) as a solid: mp 180-183 ℃; UV (H_2O) λ_{max} 253.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.80 (br s, 1H), 7.95 (s, 1H), 6.56 (br s, 2H), 6.87 (d, J = 6.2 Hz, 1H), 6.14 (d, J = 5.6 Hz, 1H), 6.07 (dd, J = 5.0, 1.4 Hz, 1H), 5.48 (m, 1H), 4.93 (t, J = 5.4 Hz, 1H), 3.42 (d, J = 9.0 Hz, 1H), 3.31 (d, J = 9.0 Hz, 1H), 2.45 (dd, J =14.0, 8.4 Hz, 1H), 2.05-1.98 (m, 2H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 157.58, 154.32, 152.57, 143.56, 136.36, 124.98, 117.39, 88.98, 72.87, 69.32, 58.43, 43.65; Anal. calcd. for. $C_{13}H_{13}N_5O_2 \cdot 1.0\ H_2O$: C, 53.97; H, 5.23; N, 24.21. Found: C, 54.11; H, 5.30; N, 24.17.

2-(*tert*-Butyldimethylsilyloxy)-1-cyclopropyl-ethanone (67): To a solution of Weinreb amide **49** (2.5 g, 10.71 mmol) in dry THF (60 mL) was slowly added cyclopropylmagnesium bromide (25.70 mL, 0.5 M solution in THF) at 0 ℃. After 4 hours, saturated NH_4Cl solution (16 mL) was added, and the reaction mixture was slowly warmed to room temperature. The mixture was extracted with EtOAc (2 × 60 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:10) to give **67** (1.65 g, 72%) as colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.21 (s, 2H), 2.18-2.10 (m, 1H), 1.17 (m, 2H), 0.97 (m, 2H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 210.41, 69.61, 25.76, 18.34, 16.11, 11.27, -5.46; Anal. calcd. for $C_{11}H_{22}O_2Si \cdot 0.5$ EtOAc: C, 60.41; H, 10.14. Found: C, 60.49; H, 10.01.

(*E*) and (*Z*)-4-(*tert*-Butyldimethylsilyloxy)-3-cyclopropyl-but-2-enoic acid ethyl ester (68): To a suspension of sodium hydride (0.5 g, 20.8 mmol) in distilled THF (100 mL) was added drop wise triethyl phosphonoacetate (4.66 g, 20.8 mmol) at 0 ℃ and the mixture was stirred at room temperature for 1 hour. The ketone **67** (4.46 g, 20.8 mmol) was added to this mixture and the mixture was for 2 hours. The solution was neutralized with AcOH (5 mL) and poured into H_2O (100 mL) and extracted with EtOAc. The 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 **68** (4.73 g, 80%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.96 (s, 1H), 4.15 (m, 4H), 2.21 (m, 1H), 1.19-1.09 (m, 2H), 0.97 (m, 2H), 0.83 (s, 9H),

0.02.

(*E*) and (*Z*)−4−(*tert*−Butyldimethylsilyloxy)−3−cyclopropyl−but−2−en−1−ol (69): To a solution of **68** (5.0 g, 17.57 mmol) in CH_2Cl_2 (100 mL), DIBALH (36.9 mL, 1.0 M solution in hexane) was added slowly at −20 ℃, and stirred for 1 hour at the same temperature. To the mixture, methanol (35 mL) was added. The mixture was stirred at room temperature for 2 hours, 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, 1:5) to give alcohol **69** (3.87 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.69 (s, 1H), 4.19 (d, J = 6.8 Hz, 2H), 4.04 (s, 2H), 2.23 (m, 1H), 1.17−1.07 (m, 2H), 0.95 (m, 2H), 0.81 (m, 9H), 0.01 (m, 6H).

(±)−3−(*t*−Butyldimethylsilyloxymethyl)−3−cyclopropyl−pent−4−enoic acid ethyl ester (70): A solution of allylic alcohol **69** (8.4 g, 34.66 mmol) in triethyl orthoacetate (150 mL) and 0.3 mL of propionic acid was heated at 135−140 ℃ 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 **70** (8.66 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.90 (d, J = 10.6 Hz, 1H), 5.87 (d, J = 11.2 Hz, 1H), 5.03 (d, J = 1.2 Hz, 1H), 5.03 (d, J = 7.6 Hz, 1H), 4.03 (q, J = 7.2 Hz, 2H), 3.44 (d, J = 9.4 Hz, 1H), 3.42 (d, J = 9.4 Hz, 1H), 2.42 (d, J = 3.2 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H), 0.82 (s, 9H), 0.46 (m, 1H), 0.28−0.21 (m, 4H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 171.96, 143.18, 114.04, 69.82, 60.07, 41.30, 25.82, 18.23, 14.56, 11.26, 8.46, −5.50; Anal. calcd.

for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32. Found: C, 65.42; H, 10.27.

(±)-3-(*t*-Butyldimethylsilyloxymethyl)-3-cyclopropyl-pent-4-enal (71): To a solution of **70** (3.0 g, 9.6 mmol) in toluene (40 mL), DIBALH (7.1 mL, 1.5 M solution in toluene) was added slowly at −78 ℃, and stirred for 20 minutes at the same temperature. To the mixture, methanol (10 mL) was added. The mixture was stirred at room temperature for 1 hour, 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 **71** (1.72 g, 67%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.78 (s, 1H), 5.92 (dd, J = 17.7, 11.1 Hz, 1H), 5.21 (d, J = 11.1 Hz, 1H), 5.14 (d, J = 17.7 Hz, 1H), 3.50 (d, J = 9.4 Hz, 1H), 3.32 (d, J = 9.4 Hz, 1H), 2.43-2.37 (m, 2H), 0.82 (s, 9H), 0.52 (m, 1H), 0.29 (m, 4H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 203.11, 143.32, 112.21, 69.86, 51.32, 42.54, 25.82, 18.45, 10.98, 6.72, −5.61; Anal. calcd. for $C_{15}H_{28}O_2Si \cdot 1.0$ EtOAc: C, 63.99; H, 10.17. Found: C, 64.12; H, 9.98.

(*rel*)-(3*R* and 3*S*,5*S*)-5-(*t*-Butyldimethylsilyloxymethyl)-5-cyclopropyl-hepta-1,6-dien-3-ol (72): To a solution of **71** (3.1 g, 11.55 mmol) in dry THF (50 mL) was slowly added vinyl magnesiumbromide (13.86 mL, 1.0 M solution in THF) at −78 ℃. After 3 hours, saturated NH_4Cl solution (10 mL) and water (50 mL) was sequentially added, and the reaction mixture was slowly warmed to room temperature. The mixture was extracted with EtOAc (2 × 50 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/Hexane. 1:5)

to give **72** (2.7g, 79%) as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.05−5.77 (m, 2H), 5.25−4.97 (m, 4H), 4.22 (m, 1H), 3.47 (m, 2H), 1.68−1.55 (m, 2H), 0.81 (s, 9H), 0.05 (m, 1H), 0.37−0.30 (m, 4H), 0.02 (m, 6H).

(*rel*)−(1*R*,4*S*)−4−(*t*−Butyldimethylsilyloxymethyl)−4−cyclopropyl−cyclopent−2−enol (73β); and (*rel*)−(1*S*,4*S*)−4−(*t*−Butyldimethylsilyloxymethyl)−4−cyclopropyl−cyclopent−2−enol (73α): To a solution of **72** (1.37 g, 4.62 mmol) in dry CH_2Cl_2 (10 mL) was added 2nd generation Grubbs catalyst (127 mg, 0.15 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 **73β** (521 mg, 42%) and **73α** (508 mg, 41%) as colorless oils, respectively. Cyclopentenol **73β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.86 (d, J = 5.4 Hz, 1H), 5.47 (d, J = 5.6 Hz, 1H), 4.52 (dd, J = 7.6, 1.2 Hz, 1H), 3.35 (s, 2H), 1.85 (dd, J = 14.2, 6.8 Hz, 1H), 1.68 (dd, J = 14.2, 2.4 Hz, 1H), 0.83 (s, 9H), 0.55 (m, 1H), 0.37−0.29 (m, 4H), 0.01 (s, 6H): ^{13}C NMR ($CDCl_3$, 300 MHz) δ 140.49, 133.98, 76.35, 68.99, 49.91, 44.78, 25.54, 18.48, 12.54, 7.90, −5.57; Anal. calcd. for $C_{18}H_{32}O_4Si$: C, 63.49; H, 9.47. Found: C, 63.36; H, 9.58.

Cyclopentenol **73α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78−5.69 (m, 2H), 4.80 (dd, J = 6.4, 1.2 Hz, 1H), 3.33 (s, 2H), 2.19 (dd, J = 13.6, 7.4 Hz, 1H), 1.32 (dd, J = 13.6, 4.4 Hz, 1H), 0.84 (s, 9H), 0.56 (m, 1H), 0.28−0.22 (m, 4H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 140.95, 132.65, 76.78, 69.97, 51.21, 43.54, 25.58, 18.48, 10.58, 7.34, −5.48; Anal. calcd. for $C_{18}H_{32}O_4Si$ · 0.5 EtOAc: C, 65.33; H, 10.32. Found: C, 65.36; H, 10.41.

(*rel*)-(1*R*,4*S*)-1-Ethoxy carbonyloxy-4-(t-butyldimethylsilyloxymethyl)-4-cyclopropyl-cyclopent-2-ene (74): To a solution of **73β** (1.94 g, 7.21 mmol) in anhydrous pyridine (8 mL) was added ethyl chloroformate (1.38 mL, 14.43 mmol) and DMAP (85 mL, 0.7 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (1 mL) and concentrated in vacuum. The residue was extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:10) to give **74** (1.77 g, 72%) as colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.88 (dd, *J* = 5.6 Hz, 1H), 5.72 (dd, *J* = 5.6, 2.4 Hz, 1H), 5.52 (m, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.31 (s, 2H), 1.89 (dd, *J* = 14.2, 7.2 Hz, 1H), 1.69 (dd, *J* = 14.2, 4.0 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.82 (s, 9H), 0.58 (m, 1H), 0.30-0.23 (m, 4H), 0.01 (s, 6H): ^{13}C NMR ($CDCl_3$, 300 MHz) δ 154.89, 144.90, 127.67, 83.41, 70.11, 63.21, 52.21, 40.56, 25.71, 18.48, 14.71, 11.98, 6.45, -5.58; Anal. calcd. for $C_{18}H_{32}O_4Si$: C, 63.49; H, 9.47. Found: C, 63.36; H, 9.58.

(*rel*)-(1'*R*,4'*S*)-9-[4-(*t*-Butyldimethylsilyloxymethyl)-4-cyclopropyl-c-yclopent-2-en-1-yl] 2-amino-6-chloropurine (75): To a pure NaH (12 mg, 0.49 mmol) in anhydrous DMSO (3.0 mL) was added 2-amino-6-chloropurine (83 mg, 0.49 mmol). The reaction mixture was stirred for 30 minutes at 50-55 ℃ and cooled to room temperature. Simultaneously, $P(O\text{-}i\text{-}Pr)_3$ (0.048 mL, 0.11 mmol) was added to a solution of $Pd_2(dba)_3 \cdot CHCl_3$ (2.3 mg, 1.25 μmol) in anhydrous THF (20 mL), which was stirred for 30 minutes. To the nucleosidic base solution of DMSO was sequentially added catalyst solution of THF and **74**

(150 mg, 0.44) dissolved in anhydrous THF (2 mL). The reaction mixture was stirred overnight at refluxing temperature and quenched with water (1 mL). The reaction solvent was removed in vacuum. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:15) to give **75** (78 mg, 42%) as a white solid. mp 168-171℃; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.91 (s, 1H), 6.02 (d, J = 5.4 Hz, 1H), 5.80-5.71 (m, 2H), 5.30 (br s, 2H), 3.60 (d, J = 9.4 Hz, 1H), 3.49 (d, J = 9.4 Hz, 1H), 2.32 (dd, J = 14.2, 8.8 Hz, 1H), 2.00 (dd, J = 14.2, 5.6 Hz, 1H), 0.84 (s, 9H), 0.58 (m, 1H), 0.31-0.22 (m, 4H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 159.32, 154.34, 151.79, 144.36, 140.76, 133.73, 124.32, 70.42, 60.42, 52.54, 41.87, 25.45, 18.54, 13.01, 6.98, -5.65; Anal. calcd. for $C_{20}H_{30}ClN_5OSi$ · 0.8 MeOH: C, 56.06; H, 7.51; N, 15.71. Found: C, 55.89; H, 7.64; N, 15.79.

(*rel*)-(1'*R*,4'*R*)-9-[4-(Hydroxymethyl)-4-cyclopropyl-cyclopent-2-en-1-yl] 2-amino-6-chloropurine (76): To a solution of **75** (88 mg, 0.21 mmol) in THF (5 mL) was TBAF (0.31 mL, 1.0 M solution in THF) at 0 ℃. The mixture was stirred at room temperature for 5 hours, and concentrated. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:5) to give **76** (46 mg, 71%) as a white solid: mp 172-174 ℃; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.88 (s, 1H), 5.96 (d, J = 6.2 Hz, 1H), 5.71-5.60 (m, 2H), 4.97 (t, J = 5.4 Hz, 1H), 3.54 (d, J = 9.4 Hz, 1H), 3.42 (d, J = 9.4 Hz, 1H), 2.27 (dd, J = 14.0, 8.8 Hz, 1H), 1.98 (dd, J = 14.0, 5.4 Hz, 1H), 0.56 (m, 1H), 0.30 (m, 4H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 159.42, 154.55, 150.48, 143.89, 141.76, 133.56, 124.78, 68.56, 61.42, 53.76, 42.28, 12.76, 6.39; Anal. calcd. for $C_{14}H_{16}ClN_5O$ ·

0.5 MeOH: C, 54.12; H, 5.64; N, 21.76. Found: C, 53.98; H, 5.52; N, 21.82.

(*rel*)−(1'*R*,4'*R*)−9−[4−(Hydroxymethyl)−4−cyclopropyl−cyclopent−2−en−1−yl] 2−amino−6−cyclopropylpurine (77): Cyclopropyl amine (0.173 mL, 1.98 mmol) was added to a solution of compound **76** (121 mg, 0.396 mmol) in EtOH (15 mL) and refluxed for 6 hours. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:5) to give compound **77** (76 mg, 59%) as a solid: mp 186−188 ℃; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 7.90 (s, 1H), 5.87 (d, J = 6.2 Hz, 1H), 5.68 (d, J = 6.2 Hz, 1H), 5.30 (dd, J = 8.0, 2.0 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 3.32 (d, J = 9.0 Hz, 1H), 3.21 (d, J = 9.2 Hz, 1H), 2.31 (dd, J = 14.2, 8.6 Hz, 1H), 2.04 (dd, J = 14.2, 5.2 Hz, 1H), 0.71−0.59 (m, 2H), 0.32−0.17 (m, 8H); ^{13}C NMR (DMSO−d_6, 300 MHz) δ 159.21, 154.11, 150.40, 144.10, 141.45, 132.54, 125.02, 67.32, 62.54, 52.21, 42.22, 13.21, 12.79, 7.02, 6.32; Anal. calcd. for $C_{17}H_{22}N_6O$ · 1.0 H_2O: C, 59.28; H, 7.02; N, 24.40. Found: C, 59.40; H, 6.90; N, 24.38.

(*rel*)−(1'*R*,4'*R*)−9−[4−(Hydroxymethyl)−4−cyclopropyl−cyclopent−2−en−1−yl] 2−amino−6−hydroxypurine (78): 2−Mercaptoethanol (0.135 mL, 1.935 mmol) and NaOMe (1.755 mL, 1.755 mmol, 1.0 M solution in MeOH) was added to a solution of compound **76** (101 mg, 0.33 mmol) in MeOH (13 mL), and heated overnight under reflux. After cooling, the reaction mixture was neutralized with a few drops of glacial AcOH and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:6) to give compound **78** (65 mg, 69%) as a solid: mp 178−180; ^{1}H NMR (DMSO−d_6,

300 MHz) δ 7.96 (s, 1H), 5.80 (d, J = 6.2 Hz, 1H), 5.39 (m, 2H), 4.94 (t, J = 5.4 Hz, 1H), 3.56 (d, J = 9.2 Hz, 1H), 3.45 (d, J = 9.2 Hz, 1H), 2.35 (dd, J = 14.0, 8.6 Hz, 1H), 1.96 (dd, J = 14.0, 5.6 Hz, 1H), 0.53–0.57 (m, 1H), 0.29–0.33 (m, 4H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 160.19, 155.87, 150.91, 144.42, 142.28, 134.56, 125.11, 68.79, 62.08, 52.88, 44.00, 13.14, 6.97; Anal. calcd. for $C_{14}H_{17}N_5O_2$ · 1.0 MeOH: C, 56.41; H, 6.62; N, 21.93. Found: C, 56.32; H, 6.72; N, 22.07.

(±)-4-(2-Benzyloxyethyl)-2,2-dimethyl-1,3-dioxolane (80): To a suspen-sion of NaH (60% in mineral oil, 495 mg, 12.45 mmol) in THF (50 mL) was slowly added a solution of alcohol **79** (1.52 g, 10.39 mmol) in THF (50 mL). Benzyl bromide (1.95 g, 11.43 mmol) in THF (50 mL) was added to the mixture at 0 ℃ and stirred overnight at rt. The reaction was quenched by water (10 mL) and further diluted with water (150 mL). The mixture was extracted with EtOAc (2 × 150 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:20) to give **80** (2.23 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25–7.20 (m, 5H), 4.59 (s, 2H), 3.92–3.85 (m, 3H), 3.41 (t, J = 6.8 Hz, 2H), 1.61 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H).

(±)-4-Benzyloxy-butane-1,2-diol (81): To a solution of **80** (120 mg, 0.508 mmol) dissolved in MeOH (10 mL), con. HCl (1 mL) was added. The mixture was stirred at rt for 12 h and neutralized with TEA. The mixture was concentrated in vacuo and the residue was dissolved in H_2O (50 mL). The

mixture was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 2:1) to give **81** (80 mg, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24−7.19 (m, 5H), 4.61 (s, 2H), 3.78 (dd, *J* = 6.8, 4.8 Hz, 2H), 3.39 (t, *J* = 6.9 Hz, 2H), 3.31 (m, 1H), 1.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.8, 128.5, 127.8, 127.2, 76.4, 72.2, 71.1, 63.8, 35.7.

(±)−4−Benzyloxy−1−(*t*−butyldimethylsilanyloxy)−butan−2−ol (82). To a stirred solution of diol **81** (2.2 g, 11.25 mmol) and imidazole (1.14 g, 16.87 mmol) in CH_2Cl_2 (80 mL), *t*−butyldimethylsilyl chloride (1.86 g, 12.37 mmol) was slowly added at −10 ℃. The mixture was stirred at 0 ℃ for 2 h, and further stirred for 3 h at rt. The mixture was quenched by adding a $NaHCO_3$ solution (5 mL) and further diluted with water (100 mL). The mixture was extracted using CH_2Cl_2 (150 mL), dried over $MgSO_4$, filtered and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:10) to give compound **82** (2.72 g, 78%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24−7.20 (m, 5H), 4.65 (s, 2H), 3.91 (dd, *J* = 7.0, 5.0 Hz, 2H), 3.38 (t, *J* = 6.8 Hz, 2H), 3.32 (m, 1H), 1.63−1.60 (m, 2H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.9, 128.6, 127.7, 127.1, 75.8, 74.5, 72.6, 64.2, 36.0, 25.7, 18.4, −5.2.

(±)−4−Benzyloxy−1−(*t*−butyldimethylsilanyloxy)−butan−2−one (83). *N*−Ch−lorosuccinimide (NCS, 1.57 g, 11.75 mmol) was suspended in toluene (40 mL) and the mixture was cooled in an ice bath. Methyl sulfide (1.47 mL, 19.75

mmol) was added and a white precipitate formed immediately. The solution was attired for 30 min at 0 ℃ and then cooled to −20℃. A solution of alcohol **82** (2.48 g, 8 mmol) in toluene (15 mL) was slowly added to the mixture. The mixture was kept under nitrogen for 4 h, whereupon TEA (1.65 mL, 11.75 mmol) was added, and the solution was allowed to warm to room temperature and was then stirred for 2 h. The mixture was extracted with ethyl acetate, washed with 1 N−HCl, water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:15) to give **83** (1.85 g, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25−7.21 (m, 5H), 4.98 (s, 2H), 4.62 (s, 2H), 3.66 (t, J = 6.8 Hz, 2H), 2.64 (t, J = 6.9 Hz, 2H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.2, 139.6, 128.9, 128.0, 127.3, 76.8, 75.5, 64.6, 38.5, 25.5, 18.6, −5.4

(±)−5−Benzyloxy−3−(*t*−butyldimethylsilanyloxymethyl)−pent−1−en−3−ol (84): To a solution of **83** (1.5 g, 4.86 mmol) in dry THF (20 mL) was slowly added vinylmagnesium bromide (5.8 mL, 1.0 M solution in THF) at −20 ℃ and the mixture was stirred 4 h at 0 ℃. Saturated NH_4Cl solution (5 mL) was added to the mixture, which was slowly warmed to room temperature. The mixture was diluted with water (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:12) to give **84** (1.32 g, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24−7.20 (m, 5H), 5.72 (dd, J = 16.8, 10.5

Hz, 1H), 5.33 (dd, J = 17.0, 3.6 Hz, 1H), 5.17 (dd, J = 10.5, 2.1 Hz, 1H), 4.65 (s, 2H), 3.98 (dd, J = 6.9, 5.0 Hz, 2H), 3.40 (m, 2H), 1.63 (m, 2H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.2, 140.3, 128.7, 127.6, 127.0, 112.5, 77.4, 74.6, 62.2, 39.3, 25.6, 18.5, −5.6; Anal. calc. for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.58; Found: C, 67.77; H, 9.61.

(±)−[3−(*t*−Butyldimethylsilanyloxy)−3−(*t*−butyldimethylsilanyloxymethyl) −pent−4−enyloxymethyl]−benzene (85): To a cooled, stirred solution of tertiary alcohol **84** (242 mg, 0.72 mmol) and 2,6−lutidine (0.6 mL, 6.14 mmol) in dry methylene chloride (12 mL) was added *t*−butyldimethylsilyl trifluoromethane sulfonate (TBDMSOTf, 0.9 mL, 3.07 mmol). The reaction mixture was warmed to room temperature, and stirred for 3 h at the same temperature. The mixture was quenched by saturated sodium bicarbonate (5 mL) and water (80 mL) was added. The mixture was extracted with ethyl acetate (80 mL), washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:25) to give **85** (282 mg, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25−7.21 (m, 5H), 5.74−5.72 (dd, J = 16.9, 10.4 Hz, 1H), 5.34 (dd, J = 17.0, 3.8 Hz, 1H), 5.18 (d, J = 10.4 Hz, 1H), 4.64 (s, 2H), 4.01 (dd, J = 6.8, 5.0 Hz, 2H), 3.39 (t, J = 6.8 Hz, 2H), 1.65 (m, 2H), 0.82 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.7, 139.6, 128.5, 127.7, 113.6, 76.7, 73.5, 64.1, 38.9, 25.3, 18.6, −5.4; Anal. calc. for $C_{25}H_{46}O_3Si_2 \cdot 0.5$ EtOAc: C, 65.53; H, 10.18; Found: C, 65.49; H, 10.12.

(±)−3−(*t*−Butyldimethylsilanyloxy)−3−(*t*−butyldimethylsilanyloxymethyl)

−pent−4−en−1−ol (86): Anhydrous ammonia (approximately 12 mL) was condensed into a flask containing a solution of benzyl ether **85** (246 mg, 0.546 mmol) in dry tetrahydrofuran (4 mL) at −78 ℃. To this mixture was added a piece of metallic lithium sufficient to maintain a blue color, and the resulting deep blue solution was stirred at −78 ℃ for 3 min. Methanol was added dropwise at the same temperature until the blue color disappeared. The colorless solution was stirred for 30 min at −78 ℃, and then solid ammonium chloride (*ca.* 3.5 g) was added. After stirring for 1 h at −78 ℃, the ammonia was allowed to evaporate. Diethyl ether (40 mL) was added, and the mixture was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:10) to give **86** (163 mg, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.79−5.74 (dd, J = 17.0, 10.2 Hz, 1H), 5.34 (dd, J = 17.1, 3.6 Hz, 1H), 5.18 (dd, J = 10.2, 2.6 Hz, 1H), 3.98 (dd, J = 6.8, 4.8 Hz, 2H), 3.54 (t, J = 6.8, 2H), 1.66 (m, 2H), 0.81 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8, 112.2, 78.5, 70.2, 56.2, 42.4, 25.5, 18.4, −5.5; Anal. Calc. for $C_{18}H_{40}O_3Si_2$: C, 59.94; H, 11.18; Found: C, 59.97; H, 11.15.

(±)−3−(*t*−Butyldimethylsilanyloxy)−3−(*t*−butyldimethylsilanyloxymethyl)−pent−4−enal (87): To a stirred solution of oxalyl chloride (264 mg, 2.08 mmol) in CH_2Cl_2 (15 mL) was added a solution of DMSO (244 mg, 3.12 mmol) in CH_2Cl_2 (4.5 mL) dropwise at −78 ℃ The resulting solution was stirred at −78 ℃ for 10 min, and a solution of alcohol **86** (375 mg, 1.04 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was stirred at −78 ℃ for 20 min and TEA (632

mg, 6.24 mmol) was added. The resulting mixture was warmed to 0 ℃ 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 (150 mL) and then extracted with EtOAc (2 × 150 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:20) to give aldehyde compound **87** (332 mg, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.73 (s, 1H), 5.81–5.76 (dd, J = 17.0, 10.0 Hz, 1H), 5.35 (dd, J = 17.0, 3.5 Hz, 1H), 5.19 (d, J = 10.0 Hz, 1H), 3.96 (dd, J = 6.9, 5.0 Hz, 2H), 2.57 (dd, J = 6.6, 4.8 Hz, 2H), 0.82 (m, 18H), 0.03 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.5, 143.6, 111.9, 77.8, 67.1, 52.6, 25.7, 18.5, −5.3.

(*rel*)−(3*R* and 3*S*,5*S*)−5−(*t*−Butyldimethylsilanyloxy)−5−(*t*−butyldimethy−lsil−anyloxymethyl)−hepta−1,6−dien−3−ol (88): Divinyl analogue **88** was synthesi−zed as a diastereomeric mixture from aldehyde **87** by a procedure similar to that described for **84**: yield 74%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.82−5.74 (m, 2H), 5.35−31 (m, 2H), 5.18−5.13 (m, 2H), 3.97−3.90 (m, 2H), 1.65−1.60 (m, 2H), 0.81 (m, 18H), 0.02 (m, 12H).

(*rel*)−(1*R*,4*S*)−4−(*t*−Butyldimethylsilanyloxy)−4−(*t*−butyldimethylsilanyl−ox−ymethyl)−cyclopent−2−enol (89α) and (*rel*)−(1*S*,4*S*)−4−(*t*−butyldimethy−lsilanyloxy)−4−(*t*−butyldimethylsilanyloxy−methyl)−cyclopent−2−enol (89β): To a solution of **88** (417 mg, 1.08 mmol) in dry methylene chloride (10 mL) was added 2nd generation Grubbs catalyst (48.0 mg, 0.0565 mmol). The reaction

mixture was refluxed overnight and cooled to rt. The mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:10) to give cyclopentenol **89α** (135 mg, 35%) and **89β** (139 mg, 36%).

Data of 89α: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.62 (d, J = 5.6 Hz, 1H), 5.38 (dd, J = 5.5, 2.8 Hz, 1H), 4.04 (m, 1H), 3.98 (dd, J = 6.2, 4.6 Hz, 2H), 2.22 (dd, J = 13.8. 8.8 Hz, 1H), 2.08 (dd, J = 13.7, 6.8 Hz, 1H), 0.82 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.2, 128.8, 78.3, 77.5, 69.1, 41.3, 25.6, 18.7, −5.4; Anal. calc. for $C_{18}H_{38}O_3Si_2$ · 0.5 EtOAc: C, 59.65; H, 10.51; Found: C, 59.69; H, 10.46.

Data of 89β: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.60 (d, J = 5.6 Hz, 1H), 5.36 (dd, J = 5.6, 2.4 Hz, 1H), 4.06 (m, 1H), 3.93 (dd, J = 6.4, 5.0 Hz, 2H), 2.20 (dd, J = 13.7. 8.6 Hz, 1H), 2.04 (dd, J = 13.6, 6.6 Hz, 1H), 0.81 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.0, 129.1, 78.7, 76.7, 68.4, 42.0, 25.4, 18.3, −5.6; Anal. calc. for $C_{18}H_{38}O_3Si_2$: C, 60.28; H, 10.68; Found: C, 60.33; H, 10.72.

(*rel*)−(1'*R*,4'*S*)−1−Ethoxycarbonyloxy−4−(*t*−butyldimethylsilanyloxy)−4−(*t*−butyldimethyl silanyloxymethyl) cyclopent−2−ene (90). To a solution of compound **89α** (839 mg, 2.34 mmol) in anhydrous pyridine (15 mL), ethyl chloroformate (273 mg, 2.52 mmol) and DMAP (49 mg, 0.4 mmol) were added. The reaction mixture was stirred overnight at 65 ℃. The reaction mixture was then quenched using a saturated $NaHCO_3$ solution (0.5 mL) and evaporated under reduced pressure. The residue was partitioned between water and ethyl acetate

and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer extracts were washed with brine, dried over $MgSO_4$ and filtered. The organic solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:13) to give **90** (695 mg, 69%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.63 (d, *J* = 5.5 Hz, 1H), 5.43 (dd, *J* = 5.6, 3.2 Hz, 1H), 4.76 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.97 (dd, *J* = 6.6, 5.2 Hz, 2H), 2.31 (dd, *J* = 13.5. 8.8 Hz, 1H), 2.09 (dd, *J* = 13.6, 6.7 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.82 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.2, 137.8, 127.8, 78.2, 77.5, 76.2, 64.6, 38.5, 25.6, 18.5, 13.8, −5.6; Anal. calc. for $C_{21}H_{42}O_5Si_2$: C, 58.56; H, 9.83; Found: C, 58.61; H, 9.79.

(*rel*)-(1'*R*,4'*S*)-9-[4-(*t*-Butyldimethylsilanyloxy)-4-(*t*-butyldimethylsil-anyloxymethyl)cyclopent-2-enyl]-6-chloropurine (91): 6-Chloropurine (145 mg, 0.94 mmol) was added to a solution of NaH (22.5 mg, 0.94 mmol) in anhydrous DMSO (5.0 mL). The reaction mixture was stirred for 30 min at 50-55 ℃ and cooled to room temperature. Simultaneously, P(O-*i*-Pr)$_3$ (78 mg, 0.374 mmol) was added to a solution of $Pd_2(dba)_3 \cdot CHCl_3$ (50 mg, 4.8 μmol) in anhydrous THF (4.5 mL), which was stirred for 30 min. The catalyst solution in THF and **90** (357 mg, 0.83 mmol) dissolved in anhydrous THF (6.0 mL) was sequentially added to the purine base solution in DMSO. The reaction mixture was refluxed overnight, and then cooled and quenched with water (2.5 mL). The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (Hexane/EtOAc, 1:2.5) to give compound **91**

(238 mg, 58%) as a white solid. mp 167−169 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.77 (s, 1H), 8.39 (s, 1H), 5.62 (d, *J* = 5.6 Hz, 1H), 5.41 (dd, *J* = 5.6, 3.3 Hz, 1H), 4.51 (m, 1H), 3.97 (dd, *J* = 6.6, 5.2 Hz, 2H), 2.42 (dd, *J* = 13.6. 8.2 Hz, 1H), 2.07 (dd, *J* = 13.7, 5.3 Hz, 1H), 0.82 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.7, 151.4, 151.2, 145.2, 135.3, 132.4, 128.5, 79.3, 77.7, 54.7, 37.6, 25.5, 18.4, −5.4; Anal. Calc. for $C_{23}H_{39}ClN_4O_2Si_2$ · 0.5 MeOH: C, 55.21; H, 8.08; N, 10.96; Found: C, 55.15; H, 8.12; N, 10.91.

(*rel*)−(1'*R*,4'*S*)−9−[4−(Hydroxy)−4−(hydroxymethyl) cyclopent−2−enyl]−6−chloropurine (92): To a solution of **91** (160 mg, 0.323 mmol) in acetonitrile (6.0 mL), TBAF (0.807 mL, 1.0 M solution in THF) was added at 0 ℃. The mixture was stirred overnight at room temperature and concentrated in vacuo. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:10) to give **92** (60 mg, 70%) as a white solid: mp 171−173 ℃; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.78 (s, 1H), 8.43 (s, 1H), 5.60 (d, *J* = 5.6 Hz, 1H), 5.39 (m, 1H), 5.13 (s, 1H, D_2O exchangeable), 4.91 (t, 1H, D_2O exchangeable), 4.54 (m, 1H), 3.67 (dd, *J* = 6.7, 5.4 Hz, 2H), 2.48 (dd, *J* = 13.8. 8.0 Hz, 1H), 2.11 (dd, *J* = 13.7, 5.5 Hz, 1H); 13C NMR (DMSO−d_6, 75 MHz) δ 151.9, 151.3, 146.4, 135.7, 133.2, 128.5, 78.4, 74.2, 55.2, 36.4; Anal. calc. for $C_{11}H_{11}ClN_4O_2$ · 1.5 MeOH: C, 47.70; H, 5.44; N, 17.80; Found: C, 47.76; H, 5.39; N, 17.77.

(*rel*)−(1'*R*,4'*S*)−9−[4−(Hydroxy)−4−(*t*−butyldimethylsilanyloxymethyl) c−yclopent−2−enyl]−6−chloropurine (93): Nucleoside analogue **93** was prepared from **92** using the similar selective silylation procedure as described for **92**: yield

61%: mp 169−171 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.79 (s, 1H), 8.42 (s, 1H), 5.63 (d, J = 5.6 Hz, 1H), 5.42 (dd, J = 5.5, 4.2 Hz, 1H), 4.52 (m, 1H), 3.89 (dd, J = 6.8, 5.2 Hz, 2H), 2.51 (dd, J = 13.7. 8.2 Hz, 1H), 2.13 (dd, J = 13.7, 5.3 Hz, 1H), 0.82 (m, 9H), 0.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.6, 151.1, 150.8, 145.7, 135.8, 132.6, 127.5, 79.5, 77.6, 54.7, 37.2, 25.6, 18.5, −5.6; Anal. calc. for $C_{17}H_{25}ClN_4O_2Si$: C, 53.60; H, 6.61; N, 14.71; Found: C, 53.64; H, 6.56; N, 14.67.

(*rel*)−(1'*R*,4'*S*)−Diethyl {9−[(4−Hydroxy)−4−(*t*−butyldimethylsilanyloxy−methyl) cyclopent−2−en−1−yl]−6−chloropurine} 4−methylphosphonate (94): Both LiO*t*−Bu (2.976 mL of 0.5 M solution in THF, 1.488 mmol) and a solution of diethyl phosphonomethyltriflate (417 mg, 1.392mmol) in 8.0 mL of THF were slowly added to a solution of the 6−chloropurine analogue **93** (265 mg, 0.696 mmol) in 10 mL of THF at −20 ℃ and stirred overnight at rt under nitrogen. The mixture was quenched by adding saturated NH_4Cl solution (8 mL) and further diluted with additional H_2O (120 mL). The aqueous layer was extracted with EtOAc (3 × 120 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, 0.02:4:1) to give **94** (192 mg, 52%) as a foam: ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.78 (s, 1H), 8.48 (s, 1H), 5.68 (d, J = 5.4 Hz, 1H), 5.41 (dd, J = 5.5, 2.8 Hz, 1H), 4.50 (m, 1H), 4.28 (m, 4H), 3.95 (d, J = 8.1 Hz, 2H), 3.81 (dd, J = 6.7, 4.2 Hz, 2H), 2.41−2.35 (dd, J = 13.8. 8.7 Hz, 1H), 2.08 (dd, J = 13.8, 6.8 Hz, 1H), 1.37 (m 6H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (DMSO−d6, 75 MHz) δ 152.0, 151.6, 150.9, 147.3,

138.2, 133.8, 130.2, 85.8, 75.1, 67.8, 65.6, 64.8, 54.8, 35.8, 25.4, 18.6, 15.9, −5.4; Anal. Calc. for $C_{22}H_{36}ClN_4O_5PSi$: C, 49.76; H, 6.83; N, 10.55; Found: C, 49.70; H, 6.88; N, 10.49.

(*rel*)−(1'*R*,4'*S*)−Diethyl {9−[(4−Hydroxy)−4−(*t*−butyldimethylsilanyloxy−methyl) cyclopent−2−en−1−yl] adenine} 4−methylphosphonate (95): A solution of **94** (224 mg, 0.423 mmol) in saturated methanolic ammonia (10 mL) was stirred overnight at 70 ℃ in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:7) to give **95** (116 mg, 54%) as a white solid: mp 162−164 ℃; UV (MeOH) λ_{max} 261.5 nm; ^1H NMR (DMSO−d_6, 300 MHz) δ 8.28 (s, 1H), 8.10 (s, 1H), 6.08 (br s, 2H, D_2O exchangeable), 5.66 (d, J = 5.5 Hz, 1H), 5.38 (m, 1H), 4.49 (m, 1H), 4.30 (m, 4H), 3.96−3.88 (m, 4H), 2.43 (dd, J = 13.8. 8.8 Hz, 1H), 2.10 (m, 1H), 1.39−1.36 (m 6H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.7, 151.6, 148.4, 142.5, 137.9, 132.9, 120.1, 84.6, 76.3, 68.1, 65.2, 64.4, 55.0, 36.4, 25.5, 18.4, 16.3, −5.3; Anal. calc. for $C_{22}H_{38}N_5O_5PSi \cdot 1.0$ MeOH: C, 50.81; H, 7.78; N, 12.88; Found: C, 50.75; H, 7.84; N, 12.91.

(*rel*)−(1'*R*,4'*S*)−Diethyl {9−[(4−Hydroxy)−4−(hydroxymethyl) cyclopent−2−en−1−yl] adenine} 4−methylphosphonate (96): Nucleoside analogue **96** was synthesized from **95** using thsimilar desilyation procedure describe for **92**: yield 76%; mp 145−147 ℃; UV (H_2O) λ_{max} 261.0 nm; ^1H NMR (DMSO−d_6, 300 MHz) δ 8.30 (s, 1H), 8.14 (s, 1H), 6.11 (br s, 2H, D_2O exchangeable), 5.68 (d, J = 5.6 Hz, 1H), 5.42 (dd, J = 5.7, 2.4 Hz, 1H), 4.93 (t, J = 4.8 Hz, 1H, D_2O exchangeable), 4.52 (m, 1H), 4.32 (m, 4H), 3.95−3.86 (m, 4H), 2.45 (m, 1H),

2.11 (dd, J = 13.7, 6.4 Hz, 1H), 1.38−1.35 (m 6H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.8, 151.7, 147.8, 143.4, 138.3, 134.1, 119.7, 86.5, 75.4, 67.8, 66.0, 65.6, 54.5, 37.1, 16.3; Anal. calc. for $C_{16}H_{24}N_5O_5P$ · 1.0 MeOH: C, 47.54; H, 6.57; N, 16.31; Found: C, 47.49; H, 6.60; N, 16.26.

(*rel*)−(1'*R*,4'*S*)−{9−[(4−Hydroxy)−4−(hydroxymethyl) cyclopent−2−en−1−yl] adenine} 4−methylphosphonic acid (97): To a solution of the phosphonate **96** (167 mg, 0.42 mmol) in anhydrous CH_3CN (10 mL) and 2,6−lutidine (0.978 mL, 8.4 mmol) was added trimethylsilyl bromide (0.642 mg, 4.2 mmol). The mixture was heated overnight at 60 ℃ under nitrogen gas and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (80 mL) and distilled purified water (80 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 60 mL) and then freezedried to give phosphonic acid **97** (112 mg, 78%) as a yellowish foam: UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.29 (s, 1H), 8.12 (s, 1H), 6.07 (br s, 2H, D_2O exchangeable), 5.66 (d, J = 5.7 Hz, 1H), 5.43 (dd, J = 5.6, 2.4 Hz, 1H), 4.89 (br s, 1H, D_2O exchangeable), 4.54 (m, 1H), 3.81 (dd, J = 6.7, 4.8 Hz, 2H), 2.48−2.38 (dd, J = 13.7, 8.7 Hz, 1H), 2.15 (dd, J = 13.6, 6.7 Hz, 1H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.6, 151.4, 148.3, 141.9, 137.8, 132.8, 119.8, 85.2, 74.6, 65.2, 64.8, 55.8, 36.8; Anal. calc. for $C_{12}H_{16}N_5O_5P$ · 2.0 H_2O: C, 38.20; H, 5.34; N, 18.56; Found: C, 38.14; H, 5.39; N, 18.49.

(±)−3−(*t*−Butyldimethylsilanyloxy)−1−phenylpropan−1−ol (99): To a solution of **98** (4.01 g, 21.31 mmol) in dry THF (60 mL) was slowly added phenylmagnesium bromide (25.6 mL, 1.0 M solution in THF) at −10 ℃ and

stirred 5 h at 0 ℃ under nitrogen. Saturated NH_4Cl solution (25 mL) was added to the mixture, which was slowly warmed to rt. The mixture was further diluted with water (150 mL) and extracted with EtOAc (2 × 150 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:8) to give **99** (4.37 g, 77%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25−7.20 (m, 5H), 4.52 (dd, *J* = 5.4, 2.8 Hz, 1H), 3.81 (m, 2H), 1.97 (m, 2H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.8, 128.7, 127.7, 127.1, 72.1, 60.3, 44.6, 25.6, 18.4, −5.4.

3−(*t*−Butyldimethylsilanyloxy)−1−phenylpropan−1−one (100): N−Chlorosuccinimide (NCS, 3.15 g, 23.5 mmol) was suspended in toluene (80 mL) and the mixture was cooled in an ice bath. Methyl sulfide (2.95 mL, 39.5 mmol) was added and a white precipitate formed immediately. The solution was attired for 30 min at 0 ℃ and then cooled to −20 ℃. A solution of alcohol **99** (4.26 g, 16 mmol) in toluene (25 mL) was slowly added to the mixture. The mixture was kept under nitrogen for 3 h, whereupon TEA (3.3 mL, 23.5 mmol) was added, and the solution was allowed to warm to room temperature and was then stirred for 2 h. The mixture was extracted with ethyl acetate, washed with 1 N HCl, water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:12) to give **100** (3.3 g, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 (d, *J* = 5.4 Hz, 2H), 7.43−7.38 (m, 3H), 3.99 (t, *J* = 6.8 Hz, 2H), 2.86 (t, *J* = 6.9 Hz, 2H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.6,

139.1, 133.4, 128.7, 128.0, 60.3, 44.6, 25.7, 18.3, −5.5.

(±)−5−(*t*−Butyldimethylsilanyloxy)−3−phenylpent−1−en−3−ol (101). To a solution of **100** (4.95 g, 18.72 mmol) in dry THF (80 mL) was slowly added vinylmagnesium bromide (22.46 mL, 1.0 M solution in THF) at −20 ℃ and stirred 6 h at 0 ℃ under nitrogen. Saturated NH_4Cl solution (22 mL) was added to the mixture, which was slowly warmed to rt. The mixture was further diluted with water (120 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:14) to give **101** (3.28 g, 60%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26−7.21 (m, 5H), 5.99 (m, 1H), 5.14−5.05 (m, 2H), 3.81 (t, J = 6.8 Hz, 2H), 1.98 (m, 2H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.6, 139.7, 129.5, 128.3, 127.3, 125.6, 115.7, 74.2, 58.5, 47.6, 25.6, 18.4, −5.6; Anal. calc. for $C_{17}H_{28}O_2Si \cdot 0.5$ EtOAc: C, 67.80; H, 9.58; Found: C, 67.76; H, 9.56.

(±)−3−Phenylpent−4−ene−1,3−diol (102). TBAF (9.22 mL, 1.0 M solution in THF) was added to a solution of **101** (1.8 g, 6.15 mmol) in cosolvent (12 mL, THF/CH_3CN 1:1 v/v) at 0 ℃. 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 **102** (898 mg, 82%): ^{1}H NMR (DMSO−d_6, 300 MHz) δ 7.26−7.22 (m, 5H), 5.90 (dd, J = 17.4, 11.1 Hz, 1H), 5.34 (dd, J = 17.3, 3.2 Hz, 1H), 5.14 (dd, J = 11.2, 2.4 Hz, 1H), 5.12 (s, 1H), 4.88 (t, J = 4.8 Hz, 1H), 3.67 (m, 2H), 1.95 (m, 2H); ^{13}C NMR (DMSO−d_6) δ

144.3, 138.7, 128.5, 124.2, 112.3, 74.4, 56.1, 47.1; Anal. calc. for $C_{11}H_{14}O_2 \cdot 0.5$ MeOH: C, 71.10; H, 8.30; Found: C, 71.13; H, 8.28.

(±)-Benzoic Acid 3-Hydroxy-3-phenylpent-4-enyl Ester (103). To a solution of **102** (1.25 g, 7.01 mmol) in anhydrous pyridine (12 mL) was added benzoyl chloride (1.08 g, 7.71mmol) and DMAP (43 mg, 0.355 mmol) at 0 ℃. The reaction mixture was stirred overnight at rt. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL), stirred for 20 minutes and concentrated under reduced pressure. The residue was poured into water (100 mL) and extracted with EtOAc (100 mL) twice. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:5) to give **103** (1.44 g, 73%) as a colorless syrup: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03 (m, 2H), 7.57 (m, 1H), 7.45 (m, 2H), 7.25-7.21 (m, 5H), 5.89 (dd, J = 17.4, 10.8 Hz, 1H), 5.25 (d, J = 17.4 Hz, 1H), 5.07 (d, J = 10.8 Hz, 1H), 4.50-4.40 (m, 2H), 2.10-1.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 166.5, 144.2, 137.5, 132.9, 130.1, 129.5, 128.9, 128.3, 124.7, 112.3, 76.3, 58.6, 44.3; Anal. calc. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; Found: C, 76.50; H, 6.38.

(±)-Benzoic Acid 3-(*t*-Butyldimethylsilanyloxy)-3-phenyl-pent-4-enyl Ester (104): To a solution of **103** (1.6 g, 5.66 mmol) in anhydrous CH_2Cl_2 (12 mL) was added 2,6-lutidine (2.42 g, 22.6 mmol) at 0 ℃. t-Butyldimethylsilyl trifluomethanesulfonate (TBDMSOTf) (2.24 g, 8.49 mmol) was added to this mixture and the reaction mixture was stirred overnight at rt and quenched with cold H_2O (10 mL). The mixture was diluted with water (80 mL) and extracted

with EtOAc (2 × 80 mL). Combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:25) to give **104** (1.82 g, 81%) as colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (m, 2H), 7.45 (m, 1H), 7.31−7.23 (m, 7H), 5.87 (dd, J = 17.3, 10.8 Hz, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.13 (d, J = 10.8 Hz, 1H), 4.36−4.30 (m, 2H), 1.95−1.87 (m, 2H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.5, 144.8, 139.2, 132.7, 130.4, 129.5, 128.2, 123.9, 112.2, 74.4, 63.8, 45.1, 25.8, 18.2, −5.56; Anal. Calc. for $C_{24}H_{32}O_3Si \cdot 0.5$ EtOAc: C, 70.87; H, 8.23; Found: C, 70.92; H, 8.24.

(±)−3−(*t*−Butyldimethylsilanyloxy)−3−phenylpent−4−en−1−ol (105): A solution of **104** (670 mg, 1.69 mmol) in methanolic ammonia (10 mL) was stirred overnight at room temperature and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 5:1) to give **105** (420 mg, 85%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25−7.21 (m, 5H), 5.98−5.91 (m, 1H), 5.14−5.05 (m, 2H), 3.64 (m, 2H), 1.99 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.7, 138.3, 128.7, 127.4, 125.7, 115.3, 75.7, 58.3, 46.1, 25.4, 18.6, −5.3; Anal. calc. for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65; Found: C, 69.77; H, 9.59.

(±)−3−(*t*−Butyldimethylsilanyloxy)−3−phenylpent−4−enal (106): To a stirred solution of oxalyl chloride (190 mg, 1.5 mmol) in CH_2Cl_2 (11 mL) was added a solution of DMSO (234 mg, 3.0 mmol) in CH_2Cl_2 (5.0 mL) dropwise at 78 ℃. The resulting solution was stirred at 78 ℃ for 10 min under nitrogen, and a solution of alcohol **105** (219 mg, 0.75 mmol) in CH_2Cl_2 (12 mL) was added

dropwise. The mixture was stirred at 78 ℃ for 30 min and TEA (607 mg, 6.0 mmol) was added. The resulting mixture was warmed to 0 ℃ and stirred for 30 min under nitrogen. H_2O (17 mL) was added, and the solution was stirred at room temperature for 30 min. The mixture was further diluted with water (110 mL) and then extracted with EtOAc (2 × 110 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:12) to give aldehyde compound **106** (198 mg, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.82 (s, 1H), 7.26−7.23 (m, 5H), 6.01−5.93 (m, 1H), 5.11−4.99 (m, 2H), 2.89 (dd, J = 10.2, 6.8 Hz, 2H), 0.87 (s, H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.3, 142.6, 138.9, 129.3, 128.2, 127.2, 117.5, 115.3, 71.2, 58.5, 25.4, 18.6, −5.5.

(±)−3*R* and 3*S*,5*S*)−5−(*t*−Butyldimethylsilanyloxy)−5−phenyl−hepta−1,6−dien−3−ol (107): Divinyl analogue **107** was synthesized from aldehyde **106** by the similar procedure as described for **101** as a diastereomeric mixture: yield 74%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26−7.22 (m, 5H), 5.98−5.85 (m, 2H), 5.13−4.96 (m, 4H), 3.87 (m, 1H), 1.95−1.88 (m, 2H), 0.88 (m, 9H), 0.02 (m, 6H).

(±)−(1*S*,4*S*)−4−(*t*−Butyldimethylsilanyloxy)−4−phenylcyclopent−2−enol (108α) and (±)−(1*R*,4*S*)−4−(*t*−butyldimethylsilanyloxy)−4−phenyl−cyclop−ent−2−enol (108β). To a solution of **107** (259 mg, 0.814 mmol) in dry methylene chloride (8 mL) was added 2nd generation Grubbs catalyst (42.8 mg, 0.0497 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, 1:10) to give cyclopentenol **108α** (80 mg, 34%) and **108β** (82 mg, 35%). Data for **108α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.23 (m, 5H), 5.63 (d, *J* = 5.2 Hz, 1H), 5.39 (m, 1H), 4.01 (m, 1H), 3.79 (s, 3H), 2.18 (dd, *J* = 13.0. 8.8 Hz, 1H), 2.09 (dd, *J* = 13.0, 6.8 Hz, 1H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 137.7, 129.1, 128.3, 127.6, 124.9, 81.2, 67.8, 48.9, 25.4, 18.5, −5.3; Anal. calc. for $C_{17}H_{26}O_2Si$: C, 70.29; H, 9.02; Found: C, 70.33; H, 9.05.

Data for **108β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26–7.21 (m, 5H), 5.60 (d, *J* = 5.3 Hz, 1H), 5.42 (dd, *J* = 5.4, 4.2 Hz, 1H), 4.03 (m, 1H), 2.14 (dd, *J* = 12.8. 8.4 Hz, 1H), 2.05 (dd, *J* = 12.9, 6.6 Hz, 1H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 137.3, 133.8, 127.6, 125.6, 80.5, 68.2, 47.6, 25.6, 18.4, −5.5; Anal. calc. for $C_{17}H_{26}O_2Si$: C, 70.29; H, 9.02; Found: C, 70.25; H, 8.96.

(±)-(1'R,4'S)-9-[4-Phenyl-(*t*-butyldimethylsilanyloxy)-cyclopent-2-enyl]-6-chloropurine (109): To a solution containing compound **108β** (162 mg, 0.56 mmol), triphenylphosphine (440 mg, 1.68 mmol) and 6-chloropurine (173 mg, 1.12 mmol) in anhydrous THF (10.0 mL), diisopropyl azodicarboxylate (DIAD) (226 mg, 1.12 mmol) was added dropwise at 10 ℃ for 30 min under nitrogen. The reaction mixture was stirred for 4 h at 10 ℃ under nitrogen and further stirred overnight at rt. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (EtOAc/Hexane, 2.5:1) to give compound **109** (95 mg, 40%): mp 176–178 ℃; UV (MeOH) λ_{max} 263.5

nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 8.45 (s, 1H), 7.27–7.23 (m, 5H), 5.63 (d, J = 5.4 Hz, 1H), 5.37 (d, J = 5.4 Hz, 1H), 4.47 (m, 1H), 2.67 (dd, J = 13.1. 8.6 Hz, 1H), 2.26 (dd, J = 13.2, 6.8 Hz, 1H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.1, 148.2, 143.7, 140.7, 138.2, 137.2, 134.8, 132.3, 127.4, 126.9, 81.8, 53.5, 46.1, 25.4, 18.7, −5.4; Anal. calc. for $C_{22}H_{27}ClN_4OSi \cdot 0.5$ EtOAc: C, 61.19; H, 6.63; N, 11.89; Found: C, 61.23; H, 6.59; N, 11.92.

(±)–(1'R,4'S)–9–(4–Phenyl–4–hydroxycyclopent–2–enyl)–6–chloropurine (110): Desilylation of **109** was performed using the similar procedure as described for **102**: yield 72%; mp 160–163 ℃; UV (MeOH) λ_{max} 264.5 nm; ^{1}H NMR (DMSO–d_6, 300 MHz) δ 8.71 (s, 1H), 8.43 (s, 1H), 7.34–7.26 (m, 5H), 5.61 (d, J = 5.2 Hz, 1H), 5.39 (m, 1H), 5.10 (br s, 1H), 4.45 (m, 1H), 2.22 (dd, J = 13.2. 8.8 Hz, 1H), 2.03 (dd, J = 13.1, 6.8 Hz, 1H); ^{13}C NMR (DMSO–d_6, 75 MHz) δ 152.2, 151.7, 147.5, 138.7, 137.8, 135.4, 132.3, 129.6, 81.2, 54.2, 45.8; Anal. calc. for $C_{16}H_{13}ClN_4O \cdot 1.0$ MeOH: C, 59.22; H, 4.97; N, 16.25; Found: C, 59.18; H, 4.99; N, 16.27.

(±)–(1'R,4'S)–Diethyl [9–(4–hydroxy–4–phenylcyclopent–2–en–1–yl)–6–chloropurine] methylphosphonate (111): Both LiO*t*–Bu (2.48 mL of 0.5 M solution in THF, 1.24 mmol) and a solution of diethyl phosphonomethyltriflate (372 mg, 1.24 mmol) in 10.0 mL of THF were slowly added to a solution of the 6–chloropurine analogue **110** (194 mg, 0.62 mmol) in 7.0 mL of THF at 30 ℃ and stirred overnight at rt under nitrogen. The mixture was quenched by adding saturated NH_4Cl solution (5 mL) and further diluted with additional H_2O (120

mL). The aqueous layer was extracted with EtOAc (3 × 120 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, 0.02:5:1) to give **111** (183 mg, 64%) as a formy solid: UV (MeOH) λ_{max} 263.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.76 (s, 1H), 8.50 (s, 1H), 7.31-7.23 (m, 5H), 5.65 (d, *J* = 5.3 Hz, 1H), 5.39 (m, 1H), 4.49 (m, 1H), 4.23 (m, 4H), 4.04 (d, *J* = 8.2 Hz, 2H), 2.25-2.19 (dd, *J* = 13.2. 8.6 Hz, 1H), 2.06 (dd, *J* = 13.2, 6.8 Hz, 1H), 1.36-1.33 (m 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.4, 151.2, 149.3, 138.6, 137.3, 134.8, 130.2, 129.3, 128.7, 84.9, 65.2, 64.7, 63.2, 53.7, 40.4, 17.0; Anal. calc. for $C_{21}H_{24}ClN_4O_4P$: C, 54.49; H, 5.23; N, 12.10; Found: C, 54.55; H, 5.20; N, 12.12.

(±)-(1'*R*,4'*S*)-Diethyl [9-(4-hydroxy-4-phenylcyclopent-2-en-1-yl)-adenine] methylphosphonate (112): A solution of **111** (187 mg, 0.404 mmol) in saturated methanolic ammonia (10 mL) was stirred overnight at 65 ℃ in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:8) to give **112** (93 mg, 52%) as a solid: mp 156-158 ℃; UV (MeOH) λ_{max} 260.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.35 (s, 1H), 8.11 (s, 1H), 7.15 (br s, 2H), 7.30-7.24 (m, 5H), 5.68 (d, *J* = 5.2 Hz, 1H), 5.37 (dd, *J* = 5.4, 4.2 Hz, 1H), 4.56 (m, 1H), 4.19 (m, 4H), 4.03 (d, *J* = 8.2 Hz, 2H), 2.24 (dd, *J* = 13.2. 8.8 Hz, 1H), 2.07 (dd, *J* = 13.1, 6.6 Hz, 1H), 1.35-1.31 (m 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.6, 152.7, 146.7, 138.2, 133.2, 129.8, 128.6, 127.8, 126.2, 119.2, 87.0, 64.6, 63.3, 62.2, 54.1, 41.2, 17.2; Anal. calc. for $C_{21}H_{26}N_5O_4P \cdot 0.5$ MeOH: C, 56.20; H, 6.14; N, 15.24;

Found: C, 56.17; H, 6.11; N, 15.21.

(±)−(1'*R*,4'*S*)−[9−(4−Phenylcyclopenten−1−yl)−adenine]−4−methylphosphonic Acid (113): To a solution of the phosphonate **112** (142 mg, 0.32 mmol) in anhydrous CH_3CN (10 mL) and 2,6−lutidine (685 mg, 6.4 mmol) was added trimethylsilyl bromide (0.42 mL, 3.2 mmol). The mixture was heated overnight at 60 ℃ and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (80 mL) and distilled clean water (80 mL). The aqueous layer was washed out with CH_2Cl_2 two times and then freeze−dried to give phosphonic acid **113** (73 mg, 70%) as a yellowish form: UV (H_2O) λ_{max} 260.5 nm; ^1H NMR (DMSO−d_6, 300 MHz) δ 8.29 (s, 1H), 8.11 (s, 1H), 7.16 (br s, 2H), 7.32−7.26 (m, 5H), 5.66 (d, J = 5.2 Hz, 1H), 5.36 (m, 1H), 4.49 (m, 1H), 4.14 (d, J = 8.2 Hz, 2H), 2.27 (dd, J = 13.2, 8.6 Hz, 1H), 2.07 (dd, J = 13.3, 7.2 Hz, 1H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.4, 152.4, 143.6, 138.2, 135.5, 133.2, 130.4, 128.3, 127.6, 125.2, 120.2, 87.1, 63.8, 54.8, 39.2; Anal. calc. for $C_{17}H_{18}N_5O_4P \cdot 3.0\ H_2O$: C, 46.26; H, 5.48; N, 15.86; Found: C, 46.31; H, 4.52; N, 15.83.

(±)−(1'*R*,2'*S*,3'*S*,4'*S*)−Diethyl [9−(2,3−dihydroxy−4−phenylcyclopent−1−yl)−denine]−4−methylphosphonate (114) and (±)−(1'*R*,2'*R*,3'*R*,4'*S*)−diethyl [9−(2,3−dihydroxy−4−phenylcyclopent−1−yl)−adenine]−4−methylphosphonate (115): Compound **112** (244 mg, 0.55 mmol) was dissolved in in a cosolvent system (12 mL) (acetone:*t*−BuOH:H_2O = 8:1:1) along with 4−methylmorpholine *N*−oxide (128 mg, 1.1 mmol). Subsequently, OsO_4 (0.22 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 (5 mL). The resulting solid was removed by filtration through a pad of Celite, and filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:5) to give **114** (84 mg, 32%) and **115** (78 mg, 30%): compound **114** as formy solid: ^1H NMR (DMSO-d_6, 300 MHz) δ 8.28 (s, 1H), 8.16 (s, 1H), 7.16 (br s, 2H), 7.32-7.26 (m, 5H), 4.21-4.17 (m, 4H), 4.13 (d, J = 8.1 Hz, 2H), 4.04 (d, J = 5.6 Hz, 1H), 3.68 (m, 1H), 3.26 (dd, J = 5.6, 2.6 Hz, 1H), 2.16-2.09 (dd, J = 13.1, 8.8 Hz, 1H), 1.91 (dd, J = 13.2, 7.6 Hz, 1H), 1.33 (m 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.2, 152.7, 146.6, 138.5, 137.3, 128.7, 127.4, 125.9, 119.6, 82.5, 80.7, 69.3, 67.8, 64.7, 63.7, 62.5, 46.3, 31.5, 17.1; Anal. calc. for $C_{21}H_{28}N_5O_6P \cdot 2.0\ MeOH$: C, 51.01; H, 6.70; N, 12.93; Found: C, 50.96; H, 6.74; N, 12.88; Compound **115**: ^1H NMR (DMSO-d_6, 300 MHz) δ 8.31 (s, 1H), 8.18 (s, 1H), 7.19 (br s, 2H), 7.30-7.22 (m, 5H), 4.19 (m, 4H), 4.08 (d, J = 8.2 Hz, 2H), 3.99 (d, J = 5.8 Hz, 1H), 3.70 (m, 1H), 3.30 (m, 1H), 2.17 (dd, J = 13.0, 8.7 Hz, 1H), 1.94 (dd, J = 13.1, 7.8 Hz, 1H), 1.34 (m 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.6, 152.1, 147.4, 138.6, 136.9, 128.6, 127.4, 126.2, 120.1, 81.4, 78.2, 68.7, 66.2, 65.3, 64.8, 63.2, 47.3, 32.1, 17.6; Anal. calc. for $C_{21}H_{28}N_5O_6P \cdot 1.0\ MeOH$: C, 51.86; H, 6.33; N, 13.74; Found: C, 51.91; H, 6.28; N, 13.69.

(±)-(1'*R*,2'*S*,3'*S*,4'*S*)-[9-(2,3-Dihydroxy-4-phenylcyclopent-1-yl)] adenine]-4-methylphosphonic Acid (116). Final adenosine phosphonic acid **116** was synthesized from **114** using the similar procedure described for **113** as a light yellow formy solid: yield 63%; UV (H_2O) λ_{max} 261.5 nm; ^1H NMR (DMSO-

d$_6$, 300 MHz) δ 8.31 (s, 1H), 8.18 (s, 1H), 7.32–7.25 (m, 5H), 4.09 (d, *J* = 8.1 Hz, 2H), 3.97 (d, *J* = 6.0 Hz, 1H), 3.71 (m, 1H), 3.31 (m, 1H), 2.17 (dd, *J* = 13.3, 8.6 Hz, 1H), 1.92 (dd, *J* = 13.2, 7.8 Hz, 1H); ^{13}C NMR (DMSO–*d*$_6$, 75 MHz) δ 155.1, 153.4, 146.7, 133.5, 138.3, 128.4, 127.8, 126.2, 120.6, 81.7, 79.6, 68.3, 64.5, 63.6, 46.7, 32.1; Anal. Calc. for $C_{17}H_{20}N_5O_6P \cdot 2.0\ H_2O$: C, 44.64; H, 5.29; N, 15.31; Found: C, 44.59; H, 5.35; N, 15.26.

2–(*t*–Butyldimethylsilanyloxymethyl)prop–2–en–1–ol (118): To a stirred solution of compound **117** (3.5 g, 39.72 mmol) and imidazole (4.05 g, 59.58 mmol) in CH_2Cl_2 (150 mL), tbutyldimethylsilyl chloride (6.28 g, 41.7 mmol) was added

At 0 ℃. The mixture was stirred at the same temperature for 4 h, and quenched by adding a $NaHCO_3$ aqueous solution (10 mL). The mixture was extracted using EtOAc (200 mL), dried over $MgSO_4$, filtered and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:7) to give **118** (6.27 g, 78%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.99 (m, 2H), 4.15 (s, 2H), 4.07 (s, 2H), 0.83 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 147.43, 111.04, 65.05, 64.59, 25.83, 18.26, –5.46.

2–(*t*–Butyldimethylsilanyloxymethyl)propenal (119): To a mixture of allylic alcohol **118** (838 mg, 4.14 mmol), manganese (IV) dioxide (1.08 g, 12.4 mmol) and CCl_4 (12 mL) was added and refluxed overnight. Additional manganese (IV) dioxide (180 mg, 2.06 mmol) was added and refluxed for an additional 12 h. The progress of the reaction was monitored by TLC. The resulting mixture was filtered through a pad of celite, washed with ethyl acetate. The filtrate and

washings were condensed in vacuo and the residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:15) to give α,β-unsaturated aldehyde **119** (622 mg, 75%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.74 (s, 1H), 6.42-6.26 (m, 2H), 4.51 (m, 2H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.3, 154.9, 128.7, 65.5, 25.4, 18.6, -5.6.

(±)-2-(*t*-Butyldimethylsilanyloxymethyl)penta-1,4-dien-3-ol (120): To a solution of **119** (1.55 g, 7.73 mmol) in dry THF (20 mL), vinylmagnesium bromide (9.3 mL, 1.0 M solution in THF) was slowly added at -20 ℃ and stirred 5 h at 0 ℃. Saturated NH_4Cl solution (10 mL) was added to the mixture, which was slowly warmed to rt. The mixture was diluted with water (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:15) to give **120** (1.34 g, 76%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.91 (m, 1H), 5.31-5.22 (m, 4H), 4.61 (m, 2H), 4.42 (m, 2H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.2, 137.5, 115.8, 108.4, 76.6, 68.1, 25.5, -5.5; MS m/z 229 $(M+H)^+$.

(±)-*t*-Butyl-[3-(4-methoxybenzyloxy)-2-methylenepent-4-enyloxy] dimethylsilane (121): NaH (60% in mineral oil, 131 mg, 3.32 mmol) was added portion-wise to a cooled (0 ℃) solution of secondary alcohol **120** (632 mg, 2.77 mmol) and p-methoxybenzyl chloride (0.41 mL, 3.04 mmol) in anhydrous DMF (10 mL). The reaction mixture was stirred overnight at rt. The solvent was removed in vacuo and the residue was diluted with H_2O (70 mL) followed by

extraction with diethyl ether (2 × 70 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:15) to give **121** (675 mg, 70%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29−7.23 (m, 2H), 6.93−6.87 (m, 2H), 5.89 (m, 1H), 5.28−5.22 (m, 4H), 4.64 (s, 2H), 4.49 (s, 2H), 4.20 (m, 1H), 3.75 (s, 3H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 151.2, 143.4, 133.7, 128.7, 115.5, 108.5, 79.6, 74.1, 68.0, 56.3, 25.7, 18.4, −5.5; MS m/z 349 $(M+H)^+$.

(±)−3−(4−Methoxybenzyloxy)−2−methylenepent−4−en−1−ol (122). To a solution of **121** (1.35 g, 3.87 mmol) in THF (16 mL), TBAF (5.8 mL, 1.0 M solution in THF) was added at 0 ℃. The mixture was stirred overnight at rt and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 5:1) to give **122** (807 mg, 89%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.22 (m, 2H), 6.92−6.86 (m, 2H), 5.87 (m, 1H), 5.30−5.23 (m, 4H), 4.65 (s, 2H), 4.48 (s, 2H), 4.22 (m, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 152.0, 142.7, 132.5, 127.8, 116.3, 107.6, 78.7, 73.6, 67.6, 57.5; MS m/z 235 $(M+H)^+$.

(±)−3−(4−Methoxybenzyloxy)−2−methylenepent−4−enal (123). Aldehyde derivative **123** was synthesized from **122** by the similar procedure as described for **119**: yield 78%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.69 (s, 1H), 7.28−7.21 (m, 2H), 6.89−6.82 (m, 2H), 6.42 (d, J = 1.6 Hz, 1H), 6.19 (d, J = 1.5 Hz, 1H), 5.88 (m, 1H), 5.25−5.20 (m, 2H), 4.65 (s, 2H), 4.23 (m, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.5, 159.5, 154.7, 142.8, 132.0, 129.5, 116.1, 76.1, 73.5,

56.2; MS m/z 233 $(M+H)^+$.

(*rel*)−(3*R* and 3*S*,5*S*)−5−(4−Methoxybenzyloxy)−4−methylenehepta−1,6−dien−3−ol (124): Divinyl analogue **124** was synthesized as a diastereomeric mixture from aldehyde **123** by a procedure similar to that described for **122** as diastereomeric mixture: yield 77%; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31−7.23 (m, 2H), 6.91−6.83 (m, 2H), 5.91−5.86 (m, 2H), 5.25−5.18 (m, 6H), 4.63−4.58 (m, 3H), 4.21 (m, 1H), 3.75 (s, 3H).

(*rel*)−(1*R*,4*S*)−4−(4−Methoxybenzyloxy)−5−methylenecyclopent−2−enol (125α) and (rel)−(1*S*,4*S*)−4−(4−Methoxybenzyloxy)−5−methylenecyclopent−2−enol (125β): To a solution of **124** (140.5 mg, 0.54 mmol) in dry methylene chloride (5 mL) was added 2nd generation Grubbs catalyst (20.0 mg, 0.0235 mmol). The reaction mixture was refluxed overnight and cooled to rt. The mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:10) to give cyclopentenol **125α** (47 mg, 38%) and **125β** (49 mg, 39%). Data for 12a: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.24 (m, 2H), 6.90−6.84 (m, 2H), 5.64 (dd, J = 5.4, 2.4 Hz, 1H), 5.36 (dd, J = 5.5, 3.0 Hz, 1H), 5.21−5.18 (m, 2H), 4.64−4.58 (m, 3H), 4.19 (d, J = 3.1 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 151.6, 138.4, 137.1, 132.2, 129.3, 126.9, 108.5, 80.5, 77.0, 74.2, 56.4; MS m/z 233 $(M+H)^+$.

Data for **125β**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31−7.23 (m, 2H), 6.89−6.82 (m, 2H), 5.65 (dd, J = 5.5, 2.6 Hz, 1H), 5.40 (dd, J = 5.6, 3.2 Hz, 1H), 5.20 (m, 2H), 4.63−4.58 (m, 3H), 4.21 (d, J = 3.2 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 152.0, 138.7, 137.3, 133.7, 128.8, 127.5, 107.9, 81.1,

76.7, 73.5, 57.2; MS m/z 233 $(M+H)^+$.

(*rel*)-(1*R*,4*S*)-9-[4-(4-Methoxybenzyloxy)-5-methylenecyclopent-2-en-1-yl] 6-chloropurine (126): To a solution containing compound **125β** (183 mg, 0.744 mmol), triphenylphosphine (528 mg, 2.016 mmol) and 6-chloropurine (229 mg, 1.488 mmol) in anhydrous cosolvent (1,4-dioxane, 8.0 mL and DMF, 6.0 mL), diethyl azodicarboxylate (DEAD) (0.271 mL, 1.488 mmol) was added dropwise at 40 ℃ for 10 min under nitrogen. The reaction mixture was stirred for 2 h at the same temperature under nitrogen and further stirred overnight at rt. The solvent was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/Hexane, 3:1) to give compound **126** (102 mg, 36%): mp 162-164 ℃; UV (MeOH) λ_{max} 264.5 nm: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.71 (s, 1H), 8.37 (s, 1H), 7.25-7.19 (m, 2H), 6.91-6.84 (m, 2H), 5.62 (dd, J = 5.5, 2.8 Hz, 1H), 5.38 (dd, J = 5.6, 3.3 Hz, 1H), 5.18-5.15 (m, 2H), 5.08 (d, J = 2.9 Hz, 1H), 4.64 (s, 2H), 4.22 (d, J = 3.2 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 149.9, 147.4, 141.3, 136.6, 131.2, 124.7, 108.5, 81.8, 74.6, 62.3, 57.0; MS m/z 369 $(M+H)^+$.

(*rel*)-(1*R*,4*S*)-9-(4-Hydroxy-5-methylene-cyclopent-2-en-1-yl)-6-chloropurine (127): To a solution of compound **126** (156 mg, 0.423 mmol) in CH_2Cl_2/H_2O (8 mL, 10:1 v/v) was added DDQ (143 mg, 0.623 mmol), and the mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ (0.8 mL) was added to quench the reaction, which was then stirred for 2 h at rt. The mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered.

The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/Hexane/MeOH, 4:1:0.05) to give compound **127** (72 mg, 69%): mp 166–168 ℃; UV (MeOH) λ_{max} 264.5 nm; ^{1}H NMR (DMSO–d$_6$, 300 MHz) δ 8.68 (s, 1H), 8.28 (s, 1H), 5.74 (dd, *J* = 5.4, 2.8 Hz, 1H), 5.68 (dd, *J* = 5.5, 3.4 Hz, 1H), 5.15 (dd, *J* = 4.2, 1.4 Hz, 2H), 5.03 (d, *J* = 3.0 Hz, 1H), 4.94 (d, *J* = 4.0 Hz, 1H), 4.55 (d, *J* = 3.5 Hz, 1H); ^{13}C NMR (DMSO–d_6, 75 MHz) δ 152.4, 151.3, 147.1, 143.8, 138.6, 135.2, 125.7, 108.1, 78.2, 61.5; MS m/z 249 (M+H)$^+$.

(*rel*)–(1*R*,4*S*)–Diethyl [9–(4–hydroxy–5–methylene–cyclopent–2–en–1–yl)–6–chloropurine] phosphonate (128): Both LiO*t*–Bu (2.98 mL of 0.5 M solution in THF, 1.488 mmol) and a solution of diethyl phosphonomethyltriflate (417 mg, 1.392 mmol) in 11.0 mL of THF were slowly added to a solution of the 6–chloropurine nucleoside analogue **127** (173 mg, 0.696 mmol) in 10.0 mL of THF at 20 ℃ and stirred overnight at rt under nitrogen. The mixture was quenched by adding saturated NH_4Cl solution (7 mL) and further diluted with additional H_2O (150 mL). The aqueous layer was extracted with EtOAc (3 × 150 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 **128** (127 mg, 46%) as a foam: ^{1}H NMR (DMSO–d_6, 300 MHz) δ 8.77 (s, 1H), 8.46 (s, 1H), 5.77 (dd, *J* = 5.5, 2.8 Hz, 1H), 5.52 (dd, *J* = 5.6, 4.0 Hz, 1H), 5.17–5.15 (m, 2H), 5.01 (d, *J* = 3.2 Hz, 1H), 4.33–4.30 (m, 4H), 4.20 (d, *J* = 3.3 Hz, 1H), 3.96 (d, *J* = 8.0 Hz, 2H), 1.37 (m 6H); ^{13}C NMR (DMSO–d_6, 75 MHz) δ 151.8, 151.3, 150.4, 147.5,

145.2, 132.2, 130.2, 125.2, 108.2, 84.2, 65.5, 64.8, 62.3, 60.6, 14.5; Anal. calc. for $C_{16}H_{20}ClN_4O_4P$: C, 48.19; H, 5.06; N, 14.05; Found: C, 48.21; H, 5.09; N, 14.03; MS m/z 399 $(M+H)^+$.

(*rel*)-(1*R*,4*S*)-Diethyl [9-(4-hydroxy-5-methylene-cyclopent-2-en-1-yl)adenine] phosphonate (129): A solution of **128** (170 mg, 0.426 mmol) in saturated methanolic ammonia (10 mL) was stirred overnight at 65 ℃ in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:8) to give **129** (93 mg, 58%) as a white solid: mp 148-150 ℃; UV (MeOH) λ_{max} 261.5 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.27 (s, 1H), 8.12 (s, 1H), 7.81 (br s, NH_2, 2H, D_2O exchangeable), 5.75 (dd, J = 5.6, 2.8 Hz, 1H), 5.55 (dd, J = 5.7, 3.4 Hz, 1H), 5.16 (m, 2H), 5.04 (d, J = 3.3 Hz, 1H), 4.35-4.31 (m, 4H), 4.21 (d, J = 2.9 Hz, 1H), 3.98 (d, J = 8.1 Hz, 2H), 1.38-1.36 (m 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.7, 152.3, 150.3, 147.3, 145.3, 132.3, 130.6, 126.0, 107.6, 83.7, 64.2, 62.6, 61.2, 14.6; Anal. calc. for $C_{16}H_{22}N_5O_4P$ (+1.0 MeOH): C, 49.63; H, 6.37; N, 17.02; Found: C, 49.60; H, 6.39; N, 17.05; MS m/z 380 $(M+H)^+$.

(*rel*)-(1'*R*,4'*S*)-[9-(4-hydroxy-5-methylene-cyclopent-2-en-1-yl) adenine]-4-phosphonic Acid (130): To a solution of the phosphonate **129** (159 mg, 0.42 mmol) in anhydrous CH_3CN (13 mL) and 2,6-lutidine (0.978 mL, 8.4 mmol) was added trimethylsilyl bromide (0.642 mg, 4.2 mmol). The mixture was heated overnight at 65 ℃ under nitrogen gas and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (110 mL) and distilled water (110 mL). The aqueous layer was washed with CH2Cl2 (2 × 60 mL) and then

freeze-dried to give phosphonic acid **130** (108 mg, 80%) as a yellowish foam: UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29 (s, 1H), 8.12 (s, 1H), 5.78 (dd, J = 5.7, 2.9 Hz, 1H), 5.58 (dd, J = 5.6, 3.0 Hz, 1H), 5.17 (m, 2H), 5.04 (d, J = 3.0 Hz, 1H), 4.22-4.17 (m, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.4, 152.3, 150.5, 147.2, 141.5, 130.3, 124.3, 119.5, 108.1, 84.1, 67.3, 61.6; Anal. calc. for $C_{12}H_{14}N_5O_4P$ (+3.0 H_2O): C, 38.20; H, 5.34; N, 18.56; Found: C, 38.19; H, 5.36; N, 18.52; MS m/z 324 $(M+H)^+$.

(*rel*)-(1'*S*,4'*S*)-[4-(4-Methoxybenzyloxy)-5-methylenecyclopent-2-en-yloxymethyl]phosphonic Acid Diethyl Ester (131): Diethylphosphonate analogue **131** was synthesized from **125β** by the similar procedure used for **128**: yield 57%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27-7.21 (m, 2H), 6.90-6.82 (m, 2H), 5.75 (dd, J = 5.6, 3.2 Hz, 1H), 5.58 (dd, J = 5.6, 3.0 Hz, 1H), 5.21 (m, 2H), 4.63 (s, 2H), 4.29-4.17 (m, 6H), 4.02 (d, J = 8.0 Hz, 2H), 3.74 (s, 3H), 1.37 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2. 152.0, 130.6, 129.3, 128.7, 116.5, 107.2, 83.0, 81.2, 72.8, 66.2, 64.4, 56.3, 16.7; MS m/z 383 $(M+H)^+$.

(*rel*)-(1'S,4'S)-[4-(4-Hydroxy-5-methylene-cyclopent-2-enyloxymet-hyl)] phosphonic Acid Diethyl Ester (132): Deprotection of **131** was performed under the similar procedure as described for **127**: yield 67%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78 (dd, J = 5.7, 3.4 Hz, 1H), 5.58 (dd, J = 5.6, 3.1 Hz, 1H), 5.22-5.20 (m, 2H), 4.60 (d, J = 3.0 Hz, 1H), 4.23-4.18 (m, 5H), 4.05 (d, J = 8.2 Hz, 2H), 1.38 (m, 6H); ^{1}3C NMR ($CDCl_3$, 75 MHz) δ 151.7, 132.2, 129.3, 108.1, 83.2, 77.3, 65.2, 64.8, 17.1; MS m/z 263 $(M+H)^+$.

(*rel*)-(1'*S*,4'*R*)-Diethyl [9-(4-hydroxy-5-methylene-cyclopent-2-en-

1−yl)−2−fluoro−6−chloropurine] phosphonate (133): Mitsunobu coupling of **132** with 2−fluoro−6−chloropurine under the similar reaction condition as described for **126**: yield 41%; UV (MeOH) λ_{max} 269.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.43 (s, 1H), 5.76 (dd, J = 5.5, 3.3 Hz, 1H), 5.56 (dd, J = 5.6, 3.0 Hz, 1H), 5.18 (dd, J = 4.4, 1.2 Hz, 2H), 5.02 (d, J = 3.1 Hz, 1H), 4.21−4.18 (m, 5H), 4.01 (d, J = 8.1 Hz, 2H), 1.38 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.3, 152.3, 151.8, 148.1, 146.3, 144.6, 130.6, 128.5, 125.1, 108.1, 83.9, 64.5, 62.1, 60.7, 17.4; Anal. calc. for $C_{16}H_{19}ClFN_4O_4P$: C, 46.11; H, 4.60; N, 13.44; Found: C, 46.08; H, 4.63; N, 13.41; MS m/z 417 $(M+H)^+$.

(*rel*)−(1'*S*,4'*R*)−Diethyl [9−(4−hydroxy−5−methylene−cyclopent−2−en−1−yl)−2−fluoro−6−aminopurine]phosphonate (134) and (*rel*)−(1'*S*,4'*R*)−diethyl [9−(4−hydroxy−5−methylenecyclopent−2−en−1−yl)−2−amino−6−chloropuri−ne] phosphonate (135): Dry ammonia gas was bubbled into a stirred solution of **133** (850 mg, 2.40 mmol) in DME (45 mL) at room temperature overnight. The salts were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:10) to give **134** (104 mg, 11%) and **135** (566 mg, 57%), respectively: Data for **134**; UV (MeOH) λ_{max} 268.0 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.21 (s, 1H), 7.88 (br s, NH_2, 2H, D_2O exchangeable), 5.73 (dd, J = 5.6, 3.0 Hz, 1H), 5.58 (dd, J = 5.6, 3.2 Hz, 1H), 5.15−5.13 (m, 2H), 5.02 (d, J = 3.1 Hz, 1H), 4.21−4.17 (m, 5H), 4.01 (d, J = 8.0 Hz, 2H), 1.37 (m 6H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 155.0, 152.3, 151.8, 147.2, 146.6, 144.5, 130.2, 128.3, 125.2, 107.9, 84.4, 65.7, 64.8, 62.7, 17.8; Anal. calc. for $C_{16}H_{21}FN_5O_4P$

(+1.0 MeOH): C, 47.55; H, 5.87; N, 16.31; Found: C, 47.59; H, 5.85; N, 16.28; MS m/z 398 $(M+H)^+$.

Data for **135**; UV (MeOH) λ_{max} 309.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.11 (s, 1H), 7.97 (br s, NH_2, 2H, D_2O exchangeable), 5.72 (dd, J = 5.7, 3.2 Hz, 1H), 5.54 (dd, J = 5.6, 3.0 Hz, 1H), 5.16 (dd, J = 4.8, 2.0 Hz, 2H), 5.00 (d, J = 3.2 Hz, 1H), 4.26-4.20 (m, 5H), 4.06 (d, J = 8.0 Hz, 2H), 1.38-1.36 (m 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.7, 151.9, 151.2, 147.6, 145.8, 143.1, 129.7, 124.6, 108.4, 83.5, 64.5, 63.9, 62.2, 16.9; Anal. calc. for $C_{16}H_{21}ClN_5O_4P$ (+1.0 MeOH): C, 45.79; H, 5.65; N, 15.70; Found: C, 45.84; H, 5.63; N, 15.69; MS m/z 414 $(M+H)^+$.

(rel)-(1'*S*,4'*R*)-9-(4-Hydroxy-5-methylene-cyclopent-2-en-1-yl)guanine]phosphonic Acid (136): To a solution of **135** (13.6 mg, 0.033 mmol) dry DMF (4 mL) was added trimethylsilyl bromide (75.9 mL, 0.575 mmol) at room temperature. After this mixture was stirred for 2 days, the solvent was removed, coevaporating three times with methanol. The residue was dissolved in MeOH (1.0 mL) and 2-mercaptoethanol (9 mL, 0.132 mmol) and NaOMe (7 mg, 0.132 mmol) was added to the mixture. The mixture was refluxed for 4 h under N_2, cooled, neutralized with glacial AcOH, and evaporated to dryness under vacuum. The residue was purified by chromatography on a column of reversed-phase C18 silica gel eluting water to give **136** (6.8 mg, 61%) as a white solid. UV (H_2O) λ_{max} 253.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.5 (br s, NH, H, D_2O exchangeable), 8.03 (s, 1H), 6.98 (br s, NH_2, 2H, D_2O exchangeable), 5.77 (dd, J = 5.6, 3.3 Hz, 1H), 5.58 (dd, J = 5.5, 3.2 Hz, 1H), 5.14 (dd, J = 4.8, 2.2 Hz, 2H),

5.01 (d, J = 3.3 Hz, 1H), 4.20 (d, J = 3.0 Hz, 1H), 4.02 (d, J = 8.1 Hz, 2H); ^{13}C NMR (DMSO−d_6, 75MHz) δ 157.5, 154.2, 152.7, 147.2, 136.3, 125.0, 117.6, 108.9, 84.3, 64.7, 64.1; Anal. calc. for $C_{12}H_{14}N_5O_5P$ (+2.0 H_2O): C, 38.40; H, 4.83; N, 18.66; Found: C, 38.36; H, 4.80; N, 18.61; MS m/z 340 $(M+H)^+$.

[1−(*t*−Butyldimethylsilyloxymethyl) cyclopropyl]methanol (139). *t*−Butyld−imethylsilylchloride (743 mg, 4.93 mmol) was added to a stirred solution of compound **138** (480 mg, 4.7 mmol) and imidazole (477 mg, 7.02 mmol) in CH_2Cl_2 (40 mL) at 0 ℃. The mixture was stirred at rt for 3 hours, and quenched by adding a $NaHCO_3$ solution (5 mL). The mixture was extracted using an EtOAc/water system, dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:5) to give compound **139** (813 mg, 80%) as a colorless syrup: ^1HNMR ($CDCl_3$, 300 MHz) δ 3.54 (s, 2H), 3.49 (s, 2H), 0.84 (s, 9H), 0.44 (d, J = 3.9 Hz, 2H), 0.39 (d, J = 3.9 Hz, 2H), 0.02 (s, 6H); ^{13}C NMR (CDCl3) δ 76.6, 66.1, 25.8, 24.7, 18.2, 13.7, −5.5; MS m/z 217 $(M+H)^+$.

1−(*t*−Butyldimethylsilanyloxymethyl) cyclopropanecarbaldehyde (140). 4Å molecular sieves (1.9 g) and PCC (1.95 g, 9.06 mmol) were added slowly to a solution of compound **139** (779 mg, 3.6 mmol) in CH_2Cl_2 (40 mL) at 0 ℃, and the mixture was stirred at rt for 10 hours. An excess of diethyl ether (120 mL) was then added to the mixture. The mixture was stirred vigorously at rt for 2 hours, 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, 1:35) to give compound **140** (617 mg, 81%) as

a colorless oil: ^{1}H NMR (CDCl3, 300 MHz) δ 9.58 (s, 1H), 4.06 (s, 2H), 0.82 (s, 9H), 0.75 (d, J = 3.8 Hz, 2H), 0.58 (d, J = 3.8 Hz, 2H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.2, 71.5, 40.6, 25.3, 18.5, 13.5, −5.3; MS m/z 215 $(M+H)^+$.

(±)−1−[1−(*t*−Butyldimethylsilanyloxymethyl)cyclopropyl]prop−2−en−1−ol (141). To a solution of **140** (1.64 g, 7.66 mmol) in dry THF (40 mL), vinylmagnesium bromide (9.2 mL, 1.0 M solution in THF) was slowly added at −20℃ and stirred at 0 ℃ for 4 hours. A saturated NH_4Cl solution (10 mL) was added to the mixture, which was slowly warmed to rt. The mixture was diluted with water (80 mL) and extracted with EtOAc (2 × 80 mL). The combined organic layer was washed with brine, dried over anhydrous MgSO4, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:12) to give **141** (1.35 g, 73%) as a colorless oil: ^{1}HNMR ($CDCl_3$, 300 MHz) δ 5.90 (m, 1H), 5.27−5.18 (m, 2H), 3.89 (d, J = 4.2 Hz, 1H), 3.73 (m, 2H), 0.82 (s, 9H), 0.72−0.67 (m, 2H), 0.44−0.36 (m, 2H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.8, 114.5, 82.7, 73.4, 30.3, 25.4, 9.2, −5.5; MS m/z 243 $(M+H)^+$.

(±)−*t*−Butyl−{1−[1−(4−methoxybenzyloxy)allyl]cyclopropylmethoxy} di−methylsilane (142). NaH (60% in mineral oil, 264 mg, 6.64 mmol) was added portion−wise to a cooled (0 ℃) solution of secondary alcohol **141** (1.34 g, 5.54 mmol) and *p*−methoxybenzyl chloride (0.82 mL, 6.09 mmol) in anhydrous DMF (20 mL). The reaction mixture was stirred overnight at rt. The solvent was removed in vacuo and the residue was diluted with H_2O (100 mL), followed by

extraction with diethyl ether (2 × 80 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:15) to give **142** (1.47 g, 72%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29−7.23 (m, 2H), 6.92−6.86 (m, 2H), 5.88 (m, 1H), 5.29−5.23 (m, 2H), 4.50 (s, 2H), 3.79 (s, 3H), 3.64−3.52 (m, 3H), 0.83 (s, 9H), 0.74−0.69 (m, 2H), 0.48−0.40 (m, 2H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.6, 143.4, 131.7, 128.7, 117.5, 114.5, 86.7, 77.4, 75.2, 55.9, 25.6, 24.2, 18.5, 10.5, 9.9, −5.3; MS m/z 363 $(M+H)^+$.

(±)−1−[1−(4−Methoxybenzyloxy)allyl]cyclopropyl˝methanol (143). To a solution of **142** (1.2 g, 3.31 mmol) in THF (15 mL), TBAF (4.96 mL, 1.0 M solution in THF) was added at 0 ℃. The mixture was stirred overnight at rt and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 7:1) to give **143** (747.9 mg, 91%): ^1HNMR ($CDCl_3$, 300 MHz) δ 7.33−7.28 (m, 2H), 6.96−6.87 (m, 2H), 5.91 (m, 1H), 5.28−5.21 (m, 2H), 4.61 (s, 2H), 3.76 (s, 3H), 3.55−3.47 (m, 3H), 0.70−0.64 (m, 2H), 0.49−0.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 143.0, 131.5, 129.4, 118.6, 114.3, 87.1, 74.8, 70.8, 57.1, 25.5, 10.0, 9.4; MS m/z 249 $(M+H)^+$.

(±)−1−[1−(4−Methoxybenzyloxy)allyl]cyclopropanecarbaldehyde (144). To a stirred solution of oxalyl chloride (258 mg, 2.04 mmol) in CH_2Cl_2 (17 mL) was added a solution of DMSO (318 mg, 4.08 mmol) in CH_2Cl_2 (6.0 mL) dropwise at 78℃. The resulting solution was stirred at −78 ℃ for 30 minutes, and a solution of alcohol **143** (253 mg, 1.02 mmol) in CH_2Cl_2 (12 mL) was added

dropwise. The mixture was stirred at −78 ℃ for 30 min and TEA (1.14 mL, 8.16 mmol) was added. The resulting mixture was warmed to 0 ℃and stirred for 30 minutes. H_2O (15 mL) was added, and the solution was stirred for 30 min at rt. The mixture was diluted with water (150 mL) and then extracted with EtOAc (2 × 150 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:20) to give aldehyde compound **144** (226 mg, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.68 (s, 1H), 7.29−7.22 (m, 2H), 6.91−.86 (m, 2H), 5.89 (m, 1H), 5.26−5.19 (m, 2H), 4.69 (s, 2H), 3.75 (s, 3H), 3.71 (d, *J* = 4.0 Hz, 1H), 0.73−0.67 (m, 2H), 0.49−0.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.1, 159.6, 143.5, 132.0, 128.2, 117.8, 114.5, 83.2, 74.7, 56.9, 39.3, 10.7, 10.2; MS m/z 247 $(M+H)^+$.

(*rel*)−(3*R* and 3*S*,5*S*)−5−(4−Methoxybenzyloxy)−4−cyclopropyl−hepta−1,6−dien−3−ol (145). Divinyl analogue **1145** was synthesized as a diastereomeric mixture from aldehyde **144** by a procedure similar to that described for **140** as a diastereomeric mixture: yield 74%; ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.32−7.24 (m, 2H), 6.92−6.83 (m, 2H), 5.93−5.85 (m, 2H), 5.23−5.15 (m, 4H), 4.65 (s, 2H), 3.89 (d, *J* = 4.1 Hz, 1H), 3.76−3.68 (m, 4H), 0.75−0.65 (m, 2H), 0.48−0.37 (m, 2H).

(*rel*)−(4*S*,7*S*)−7−(4−Methoxybenzyloxy)−spiro[2.4]hept−5−en−4−ol (146β) and (*rel*)−(4*R*,7*S*)−7−(4−methoxybenzyloxy)−spiro[2.4]hept−5−en−4−ol (145α). To a solution of **145** (296 mg, 1.08 mmol) in dry methylene

chloride (7 mL) was added a 2nd generation Grubbs catalyst (40.0 mg, 0.0471 mmol). The reaction mixture was refluxed overnight and cooled to rt. The mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give cyclopentenol **145α** (106 mg, 40%) and **146β** (103 mg, 39%). Data for **145α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31−7.26 (m, 2H), 6.89−6.83 (m, 2H), 5.66 (dd, *J* = 2.8, 5.3 Hz, 1H), 5.38 (m, 1H), 4.65 (s, 2H), 4.02 (d, *J* = 2.9 Hz, 1H), 3.77 (s, 3H), 3.62 (d, *J* = 3.1 Hz, 1H), 2.20 (dd, *J* = 13.6. 8.2 Hz, 1H), 0.77−0.71 (m, 2H), 0.51−0.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.6, 138.1, 137.0, 132.2, 127.6, 118.4, 87.4, 82.6, 74.5, 57.7, 24.7, 11.5, 9.9; MS m/z 247 $(M+H)^+$.

Data for **146β**: ^{1}HNMR($CDCl_3$, 300 MHz) δ 7.29−7.21 (m, 2H), 6.88−6.83 (m, 2H), 5.66 (dd, *J* = 2.8, 5.4 Hz, 1H), 5.34 (m, 1H), 4.68 (s, 2H), 4.00 (dd, *J* = 4.2, 2.6 Hz, 1H), 3.73−3.65 (m, 4H), 0.78−0.73 (m, 2H), 0.49−0.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.8, 138.7, 136.1, 134.5, 129.8, 118.4, 88.2, 73.8, 27.5, 8.8, 7.7; MS m/z 247 $(M+H)^+$.

(*rel*)−(4'*R*,7'*S*)−9−[7−(4−Methoxybenzyloxy)−spiro[2.4]hept−5−en−4−yl] 6−chloropurine (147). To a solution containing compound **146β** (183 mg, 0.744 mmol), triphenylphosphine (528 mg, 2.016 mmol) and 6−chloropurine (229 mg, 1.488 mmol) in anhydrous cosolvent (1,4−dioxane, 8.0 mL and DMF, 6.0 mL), DEAD (0.271 mL, 1.488 mmol) was added dropwise at −40 ℃ for 10 minutes under nitrogen. The reaction mixture was stirred at the same temperature for 1.5 hours under nitrogen and further stirred overnight at rt. The solvent was concentrated in vacuo and the residue was purified by silica gel

column chromatography (EtOAc/Hexane, 3:1) to give compound **147** (102 mg, 36%): mp 162−164 ℃; UV (MeOH) λ_{max} 265.0 nm: ^{1}HNMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 8.36 (s, 1H), 7.20−7.24 (m, 2H), 6.93−6.86 (m, 2H), 5.67 (d, *J* = 5.4 Hz, 1H), 5.34 (dd, *J* = 3.2, 5.5 Hz, 1H), 4.66 (s, 2H), 4.45 (d, *J* = 3.3 Hz, 1H), 3.74 (s, 3H), 0.78−0.72 (m, 2H), 0.48−0.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 151.4, 149.9, 143.8, 137.5, 135.7, 132.3, 131.5, 128.5, 118.4, 89.5, 75.1, 67.7, 56.3, 21.5, 8.6, 8.0; MS m/z 383 $(M+H)^+$.

(*rel*)−(4'*R*,7'*S*)−[9−(7−Hydroxy)−spiro[2.4]hept−5−en−4−yl] 6−chloro−purine (148). To a solution of compound **147** (324 mg, 0.846 mmol) in CH_2Cl_2/H_2O (10 mL, 10:1 v/v) was added DDQ (286 mg, 1.264 mmol), and the mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ (1.7 mL) was added to quench the reaction, which was then stirred at rt for 2 hours. The mixture was diluted with water (150 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/Hexane/MeOH, 3:1:0.05) to give compound **148** (155 mg, 70%): mp 179−181 ℃; UV (MeOH) λ_{max} 264.0 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.67 (s, 1H), 8.29 (s, 1H), 5.62 (d, *J* = 5.5 Hz, 1H), 5.34 (dd, *J* = 5.6, 3.9 Hz, 1H), 4.50 (d, *J* = 5.4 Hz, 1H), 3.98 (d, *J* = 5.2 Hz, 1H), 0.39−0.29 (m, 4H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 152.0, 151.5, 149.9, 145.4, 137.5, 135.2, 132.4, 83.8, 67.4, 21.9, 8.5, 7.8; MS m/z 263 $(M+H)^+$.

(*rel*)−(4'*R*,7'*S*)−Diethyl [9−(7−hydroxymethyl)−spiro[2.4]hept−5−en−4−yl) 6−chloropurine] phosphonate (149). Both LiO*t*−Bu (2.98 mL of 0.5 M

solution in THF, 1.488 mmol) and a solution of diethyl phosphonomethyltriflate (417 mg, 1.392 mmol) in 11.0 mL of THF were slowly added to a solution of 6-chloropurine analogue **148** (183 mg, 0.696 mmol) in 9.0 mL of THF at 25 ℃ and stirred overnight at rt under nitrogen. The mixture was quenched by adding a saturated NH_4Cl solution (7 mL) and further diluted with additional H_2O (150 mL). The aqueous layer was extracted with EtOAc (3 × 150 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, 0.04:3:1) to give **149** (140 mg, 49%) as a foam: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.78 (s, 1H), 8.49 (s, 1H), 5.63 (d, *J* = 5.4 Hz, 1H), 5.38 (dd, *J* = 5.3, 4.2 Hz, 1H), 4.48 (d, *J* = 4.2 Hz, 1H), 4.32 (m, 4H), 3.94 (d, *J* = 8.1 Hz, 2H), 3.67 (d, *J* = 5.1 Hz, 1H), 1.38 (m 6H), 0.41-0.32 (m, 4H); ^{13}C NMR (DMSO-d_6, 75MHz) δ 151.7, 151.0, 150.2, 146.5, 137.8, 134.2, 132.2, 90.4, 69.1, 65.4, 64.6, 59.2, 22.1, 14.7, 9.1, 8.3; MS m/z 413 $(M+H)^+$.

(*rel*)-(4'*R*,7'*S*)-Diethyl [9-(7-hydroxymethyl)spiro[2.4]hept-5-en-4-yl)-adenine]-phosphonate (150). A solution of **149** (180 mg, 0.436 mmol) in saturated methanolic ammonia (10 mL) was stirred overnight at 65 ℃ in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:7) to give **150** (94 mg, 55%) as a white solid: mp 144-146 ℃; UV (MeOH) λ_{max} 261.0 nm; ^{1}HNMR (DMSO-d_6, 300 MHz) δ 8.28 (s, 1H), 8.13 (s, 1H), 5.66 (d, *J* = 5.4 Hz, 1H), 5.37 (m, 1H), 4.43 (d, *J* = 5.2 Hz, 1H), 4.35-4.30 (m, 4H), 4.00 (d, *J* = 8.2 Hz, 2H), 3.59 (d, *J* = 5.0 Hz, 1H), 1.41-1.37 (m 6H), 0.41-0.36 (m, 4H); ^{13}C NMR (DMSO-d_6, 75

MHz) δ 154.6, 152.7, 150.1, 142.2, 137.3, 132.9, 119.4, 90.5, 67.7, 64.6, 63.7, 57.7, 21.5, 15.2, 8.0, 7.2; Anal. calc. for $C_{17}H_{24}N_5O_4P$ (+0.5 MeOH): C, 51.39; H, 6.40; N, 17.11; Found: C, 51.44; H, 6.42; N, 17.09; MS m/z 394 $(M+H)^+$.

(*rel*)−(4'*R*,7'*S*)−[9−(7−Hydroxymethyl)−spiro[2.4]hept−5−en−4−yl)−ad−enine]−7−phosphonic acid (151). To a solution of the phosphonate **150** (82.5 mg, 0.21 mmol) in anhydrous CH_3CN (7 mL) and 2,6−lutidine (0.489 mL, 4.2 mmol) was added trimethylsilyl bromide (0.321 mg, 2.1 mmol). The mixture was heated overnight at 60 ℃ under nitrogen gas and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (50 mL) and distilled purified water (50 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 30 mL) and then freeze−dried to give phosphonic acid **151** (56 mg, 79%) as a yellowish foam: UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO−d_6, 300 MHz) δ 8.29 (s, 1H), 8.10 (s, 1H), 5.67 (d, *J* = 5.3 Hz, 1H), 5.35 (dd, *J* = 5.4, 4.3 Hz, 1H), 4.49 (d, *J* = 4.5 Hz, 1H), 4.15 (d, *J* = 8.2 Hz, 2H), 0.39−0.32 (m, 4H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.7, 152.1, 150.2, 141.7, 136.9, 133.6, 120.0, 90.2, 67.3, 57.8, 21.4, 8.7, 7.6; Anal. calc. for $C_{13}H_{16}N_5O_4P$ (+3.0 H_2O): C, 39.92; H, 5.67; N, 18.76; Found: C, 39.89; H, 5.66; N, 18.78; MS m/z 338 $(M+H)^+$.

(*rel*)−(4'*R*,5'*R*,6'*S*,7'*S*)−Diethyl [9−(7−hydroxymethyl)−5,6−dihydroxy−s−piro[2.4]hept−5−en−4−yl)−adenine] phosphonate (152α) and (*rel*)−(4'*R*,5'*S*, 6'*R*,7'*S*)−diethyl [9−(7−hydroxymethyl)−5,6−dihydroxy−spiro[2.4]hept−5−en−4−yl)−adenine] phosphonate (152β). Compound **150** (205 mg, 0.522 mmol) was dissolved in a cosolvent system (10 mL) (acetone: *t*−BuOH:H_2O = 6:1:1) along with 4−methylmorpholine *N*−oxide (121 mg, 1.044 mmol). Subsequently, OsO_4

(0.261 mL, 4% wt. % in H_2O) was added. The mixture was stirred overnight at rt and quenched with a saturated Na_2SO_3 solution (5 mL). The resulting solid was removed by filtration through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:4) to give **152α** (73 mg, 33%) and **152β** (66 mg, 31%) as a solid: compound **152α**: mp 147−149 ℃; UV (H_2O) λ_{max} 260.0 nm; ^1H NMR (DMSO−d_6, 300 MHz) δ 8.30 (s, 1H), 8.19 (s, 1H), 4.24−4.17 (m, 4H), 4.09 (d, J = 8.1 Hz, 2H), 3.79 (d, J = 5.0 Hz, 1H), 3.67 (m, 1H), 3.30 (dd, J = 6.8, 4.6 Hz, 1H), 2.96 (d, J = 6.1 Hz, 1H), 1.36−1.30 (m 6H), 0.38−0.31 (m, 4H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.8, 152.2, 149.5, 142.7, 119.8, 84.6, 67.6, 66.2, 64.2, 63.7, 59.3, 20.4, 9.2, 8.5; Anal. calc. for $C_{17}H_{26}N_5O_6P$ (+0.5 MeOH): C, 47.42; H, 6.37; N, 15.80; Found: C, 47.39; H, 6.39; N, 15.78; MS m/z 428 $(M+H)^+$.

Compound **152β**: mp 153−154 ℃; UV (H_2O) λ_{max} 260.5 nm; ^1H NMR (DMSO−d_6, 300 MHz) δ 8.29 (s, 1H), 8.15 (s, 1H), 4.35−4.28 (m, 4H), 4.15 (d, J = 8.0 Hz, 2H), 3.76 (br s, 1H), 3.59−3.46 (m, 2H), 1.38−1.34 (m 6H), 0.41−0.37 (m, 4H); ^{13}CNMR (DMSO−d_6, 75 MHz) δ 154.6, 152.5, 150.7, 143.2, 120.2, 85.2, 68.1, 65.3, 64.7, 60.8, 19.9, 8.0, 7.3; Anal. calc. for $C_{17}H_{26}N_5O_6P$ (+1.0 MeOH): C, 47.08; H, 6.58; N, 15.25; Found: C, 47.11; H, 6.60; N, 15.27; MS m/z 428 $(M+H)^+$.

(*rel*)−(4'*R*,5'*R*,6'*S*,7'*S*)−[9−(7−Hydroxymethyl)−5,6−dihydroxy−spiro[2.4] hept−5−en−4−yl)−adenine] phosphonic acid (153). The final adenosine phosphonic acid **153** was synthesized from **152α** using a similar procedure

described for **151** as a light yellow foamy solid: yield 64%; UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29 (s, 1H), 8.17 (s, 1H), 4.14 (d, J = 8.2 Hz, 2H), 3.80 (d, J = 5.5 Hz, 1H), 3.66 (dd, J = 5.8, 4.8 Hz, 1H), 3.39 (dd, J = 5.4, 4.7 Hz, 1H), 0.41-0.34 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.5, 152.6, 151.7, 142.5, 120.0, 84.2, 67.4, 64.4, 63.7, 59.8, 19.6, 8.4, 7.3; Anal. calc. for $C_{13}H_{18}N_5O_6P$ (+2.0 H_2O): C, 38.35; H, 5.44; N, 17.20; Found: C, 38.32; H, 5.46; N, 17.17; MS m/z 372 $(M+H)^+$.

(*rel*)-(4'*R*,7'*S*)-Bis(SATE) phosphoester of [9-(7-methyloxyphosphonate-spiro[2.4]hept-5-en-4-yl)]-adenine (155). A solution of adenine phosphonic acid derivative **151** (57 mg, 0.169 mmol) and tri-*n*-butylamine (94 mg, 0.510 mmol) in methanol (3.9 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 (10 mL) to which thioester **154** (519 mg, 3.2 mmol) and 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (201 mg, 0.678 mmol) were added. The mixture was stirred overnight at rt and quenched with tetrabutylammonium bicarbonate buffer (10.0 mL, 1 M solution, pH 8.0). The mixture was concentrated under reduced pressure and the residue was diluted with water (60 mL) and extracted with $CHCl_3$ (70 mL) two times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography (MeOH/Hexane/EtOAc, 0.05:4:1) to give **155** (38 mg, 36%) as a white solid: mp 130-133 ℃; UV (MeOH) λ_{max} 260.5 nm; ^{1}HNMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H), 8.12 (s, 1H), 5.54 (d, J = 5.7 Hz, 1H), 5.31

(dd, J = 5.6, 4.4 Hz, 1H), 4.49 (m, 1H), 4.22 (d, J = 8.0 Hz, 2H), 3.93−3.90 (m, 4H), 3.17−3.14 (m, 4H), 1.22−1.18 (m, 18), 0.88 (m, 1H), 0.39−0.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.8, 154.7, 152.3, 148.5, 143.8, 127.6, 123.7, 119.8, 84.7, 66.8, 64.5, 62.8, 58.5, 48.3, 35.8, 26.2, 19.7, 8.8, 7.5; Anal. calc. for $C_{27}H_{40}N_5O_6PS_2$ (+0.5 MeOH): C, 51.46; H, 6.59; N, 10.91; Found: C, 51.49; H, 6.61; N, 10.89; MS m/z 626 $(M+H)^+$.

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ABSTRACT

Design and Synthesis of Novel Branched Nucleoside Analogues as Antiviral Agents

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Nucleoside analogs are a class of antiviral drugs designed to inhibit DNA/RNA synthesis in the viral life cycle. These drugs possess very similar structures to the natural nucleotides. Nucleosides are the most frequently used effective class of antiviral agents, with over 20 drugs currently approved for the treatment of viral diseases and a number of candidates in the clinical trials.

Nucleoside analogs may be either purine analogs or pyrimidine analogs. In either case, the structures of the drugs closely resemble their natural nucleotide counterparts. Examples of these include zidovudine(AZT), stavudine, acyclovir, didanosine, zalcitabine, and lamivudine.

The carbocyclic nucleosides possess a wide range of biological activities such as antiviral and antitumor effects, as well as carbocyclic nucleosides have greater metabolic stability against chemical or enzymatic hydrolysis. Emerging drug−resistant viral strains and drug toxicity are major problems in antiviral chemotherapy, which has lead to research for structurally modified nucleosides.

Geminal substitution at the 2'−position might impose favorable steric as well as electronic effect on the interaction with virus polymerase. Based on information, focusing on the modification of the 2'−position of the potent 2'(β)−*C*−carbodine nucleosides, I designed and synthesized carbocyclic nucleosides **28**, **31**, **40**, **42**, **44**, **45**. Stimulated by interesting SAR (structure activity relationship), I synthesis of a novel class of nucleosides containing 4'−ethynyl carbocyclic nucleosides **61**, **62**, **63**, **66** and 4'−cyclopropyl carbocyclic nucleoside **77, 78**. More efficient therapeutic agents against several virus and to provide analogues for probing the conformational preferences of enzymes associated with the metabolism of nucleosides and nucleotides, I have designed and prepared a novel class of nucleosides comprising 4'−branched−5'−norcarbocyclic phosphonic acid analogues **96**, **97**, **112**, **113**, **114** and **116**. Stimulated by these findings that 6'−electronegative nucleoside analogues and 5'−norcarbocyclic nucleoside phosphonates have excellent biological activities, I sought to synthesize a novel

class of nucleosides comprising 6'-methylene and 6'-spirocyclopropyl 5'-norcarbocyclic phosphonic acid analogues (±)-129, (±)-130, (±)-134, (±)-135, (±)-136, 150, 151, 152α, 153 and 155 in order to search for more effective therapeutics against HIV.

The synthesized nucleoside analogues were assayed for antiviral activity. The cytosine analogue 28 exhibited potent anti-HCV activity, cytosine analogue 44 weakly inhibited the replication of the replicon. Guanine analogue 66 exhibited moderate antiviral activity against HIV-1; and the thymine analogue 62 showed weak antiviral activity against HCMV. Compound 77 and 78 exhibited moderate antiviral activity against HCMV in the Davis cell without any cytotoxicity up to 100 μmol. Nucleoside phosphonic acid 97 exhibited significantly more anti-HIV activity than its parent nucleoside diethyl phosphonate 96 at concentrations up to 100 μM. Adenosine phosphonic acid 113 exhibited moderate anti-HIV activity with IC_{50} = 28.3 μM. Also, nucleotide analogues 112, 114 and 116 did not show anti-HIV activity nor cytotoxicity up to 100 μM. Guanine nucleoside phosphonic acid (±)-136 exhibits significant anti-HIV activity. However, nucleoside analogues (±)-129, (±)-130, (±)-134, and (±)-135 showed weak anti-HIV activity or cytotoxicity at concentrations up to 100 μM. Nucleoside phosphonic acid 155 exhibited increased anti-HIV activity compared with its parent nucleoside phosphonic acid 151. However, nucleoside analogues 150, 152α, and 153 did not show anti-HIV activity or cytotoxicity at concentrations up to 100 μM.