[UCI]I804:24011-200000276208

2014 年 8月

博士學位論文

# Synthesis and Conformational Study of Non−classical Nucleoside Phosphonic Acid Analogues as Antiviral Agents

朝鮮大學校 大學院

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항바이러스제로서 비전형적 뉴크레오사이드 포스폰산의
합성 및 구조에 대한 연구

2014年 8月 25日

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이 論文을 藥學 博士學位申請 論文으로 提出함.

2014 年 4月

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# ABBREVIATION

AIDS: Acquired immunodeficiency syndrome

HIV: Human immunodeficiency virus

HSV: Herpes simplex virus

HBV: Hepatitis B virus

HCV: Hepatitis C virus

VZV: Varicella zoster virus

FDA: Food and Drug Adiminaistration

EMA: European Medicines Agency

NRTIs: Nucleosides Reverse Transcriptase Inhibitors

NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors

PIs: Protease Inhibitors

CRIs: co-receptor inhibitors

INIs: Integrase Inhibitors

FIs: Fusion inhibitors

RT: Reverse transcriptase

DNA: Deoxyribonucleic acid

RNA: Ribonucleic acid

ATP: Adenosine triphosphate

AZT: 3′-azido-2′,3′-dideoxy thymidine

d4T: 2′,3′-didehydro-2′,3′-dideoxythymidine

3TC: 2′,3′-dideoxy-3′-thiacytidine

TK 1: Thymidine kinase 1

TMK: Thymidylate kinase

NDPK: Nucleoside Diphosphonate Kinase

DNKs: Deoxyribonucleoside kinases

Dck: Deoxycytidine kinase

TK 2: Thymidine kinase 2

dGK: Deoxyguanosine kinase

NMP: Nucleoside monophosphonate

NDP: Diphosphonate acceptor

dNPs: 2′-deoxynucleoside 5′-triphosphates

CMV: Cytomegalovirus

bis-SATE: bis-*S*-acyl thioethyl esters

TNA: Threose nucleic acids

GS-9148: [5-(6-Aminopurin-9-yl)-4-fluoro-2,5-dihydrofuran-2-yloxy-methyl] phosphonic acid

TAMs: Thymidine analogue mutations

$EC_{50}$; $EC_{50}$ values are for 50% inhibition of virus production as indicated by supernatant RT levels

$EC_{90}$; $EC_{90}$ values are for 90% inhibition of virus production as indicated by supernatant RT levels

$IC_{50}$: $IC_{50}$ values indicate 50% inhibition of cell growth

ddNs: 2′,3′-dideoxynucleosides

DIBALH: Diisobutyldimethylaluminim hydride

TMSOTf: *tert*-butyldimetylsilyl trifluoromethane sulfonate

DCE: Dichloroethane

NOE: Nuclear Overhauser effect

TMSBr: Bromotrimethylsilane

PBM: Peripheral blood mononuclear

MOI: Multiplicity of infection

DFT: Density functional theory

PMBCl: *p*-methoxy benzyl chloride

TBDMSCl: *t*-Butyldimethylsilyl chloride

DMS: Dimethylsulfide

DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

PCC: Pyridinium chlorochromate

RCM: Ring-closing metathesis

DIAD: Diisopropyl azodicarboxylate

TBAF: Tetrabutylammonium fluoride

PMEA: 9-[2-(Phosphonomethoxy)ethyl]adenine

DMF: *N,N*-Dimethylformamide

THF: Tetrahydronfuran

DEAD: Dithyl azodicarboxylate

NMO: *N*-methyl morpholine *N*-oxide

ND: Not determined

# 국문초록

## 항바이러스제로서 비전형적 뉴크레오사이드 포스폰산의 합성 및 구조에 대한 연구

신 광 환
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AIDS가 발견된 이후로, 선택적으로 HIV의 복제를 억제할 수 있는 화합물을 찾기위해 많은 노력을 해왔다. 새롭고 효능이 좋은 HIV 억제제를 발견하기 위한 하나의 논리적인 접근법은 phosphonate의 일부가 변환한 phosphonic acid 유사체의 모형을 포함한다. 효소의 인산화를 통한 뉴클레오사이드 monophosphonates을 모방한 화학적인 효소의 안정적인 phosphonate 유사체들은 HIV를 억제하는 더 효과적인 항바이러스 약품을 발견할 수 있게했다.

Kinases와 핵산의 결합에 의한 phosphonate는 (결론적으로 연쇄종결반응을 이끄는) 뉴클레오사이드의 근원적인 항바이러스활성의 결핍은 일반적으로 바이러스성 키나아제 세포들의 결핍된 기질의 특성에 따른 결과이다. 반면에, Phosphorylate된 알킬화 핵산 염기의 강한 항바이러스활성은 diphosphonates과 핵산의 변형된 뉴클레오사이드의 다루기 힘든 결합에서 세포내 인산화반응의 결과로 간주된다. 또한, 핵산에서 phosphonate 뉴클레오사이드의 효소결합은 일반적인 뉴클레오타이드에 대한 경우가 아니면 거의 돌이킬 수 없다.

phosphonate는 인-탄소 결합이 가수분해에 민감하지 않기 때문에 대사적으로 안정하여, phosphonate 대응물에 대해 특정한 이점을 가진다. 산소원자의 특정한 부분인 뉴클레오사이드 유사체의 인원자로부터 얻어지는 $\beta$-위치는 항바이러스 활성에 결정적인 역할을 한다. 이런 산소원자를 가진 활성화된 항바이러스성 활성은 목표효소로 가는 phosphonate 유사체들의 활성화된 결합능력에 따른 결과이다. 앞에서 언급된 $\beta$-위치가 탄소 원자일 경우에도 결정적인 역할을 한다고 증명되고 있다. 이런 항바이러스 활성을 위한 원자들은 목표효소로 가는 phosphonate 유사체들의 활성화된 결합능력에 따른 결과로 본다.

이 논문에서 우리는 더효과적인 HIV 억제 치료법을 찾기위한 뉴클레오사이드 phosphonate 유사체들의 새로운 물질을 합성하는 것과 뉴클레오사이드에서 뉴클레오사이드 kinases를 가진 효소결합에서 더 선호하는 배열을 탐색하기 위한 유사체를 합성하는 것을 목표로 하였다.

합성한 화학물들을 HIV-1에 대하여 항바이러스 활성을 측정 하였고 그중에서도 **23** ($EC_{50}$ = 10.2 $\mu$M), **81** ($EC_{50}$ = 7.9 $\mu$M), **120** ($EC_{50}$ = 2.2 $\mu$M), **157** ($EC_{50}$ = 10.8 $\mu$M)화합물이 가장 좋은 활성을 나타냈다.

**Keywords:** Anti-HIV agents; 5′-Deoxyphosphonic acid; 5′-Norcarbocyclic acid Threosyl nucleoside phosphonic acid; Sprionucleoside; Conformation analysis; Mistunobu reaction; Vorbruggen reaction.

# Ⅰ. INTRODUCTION

Since the beginning of the acquired immunodeficiency syndrome (AIDS) pandemic nearly 50 million people have been infected with human immunodeficiency virus (HIV) and over 16 million have died from AIDS. Combination anti-HIV chemotherapy has dramatically reduced mortality rates and increased life expectancy of infected individuals.[1,2] Acquired immunodeficiency syndrome (AIDS)[3,4] is a lethal disease caused by human immunodeficiency virus. The major modes of viral transmission have been through infected sexual partners and intravenous drug users. HIV can also be spread from mother to child, either before or during birth. The most effective-means of virus transfer is through virus-infected cells, which can pass HIV by cell-to-cell contact from lymphocytes to epithelial cells or cell-to-cell fusion.

There are two types of HIV: HIV-1 and HIV-2. The most is caused by HIV-1. HIV-2 is endemic to western Africa and it is not unusual in certain. Like HIV-1, HIV-2 can give rise to the same spectrum of disease caused by immune destruction, but infection course is believed to be more protracted and not be transmitted so readily as HIV-1, HIV-2 differs in genome structure by 55% from HIV-1, primarily in its envelope genes.

HIV Life Cycle and Anti-HIV Drugs

The HIV life cycle encompasses several crucial steps, starting from the attachment of the virus to the host cell membrane and finishing with the release of progeny virions from the cell, as summarized in (Figure 1). The HIV life cycle commences by a specific interaction

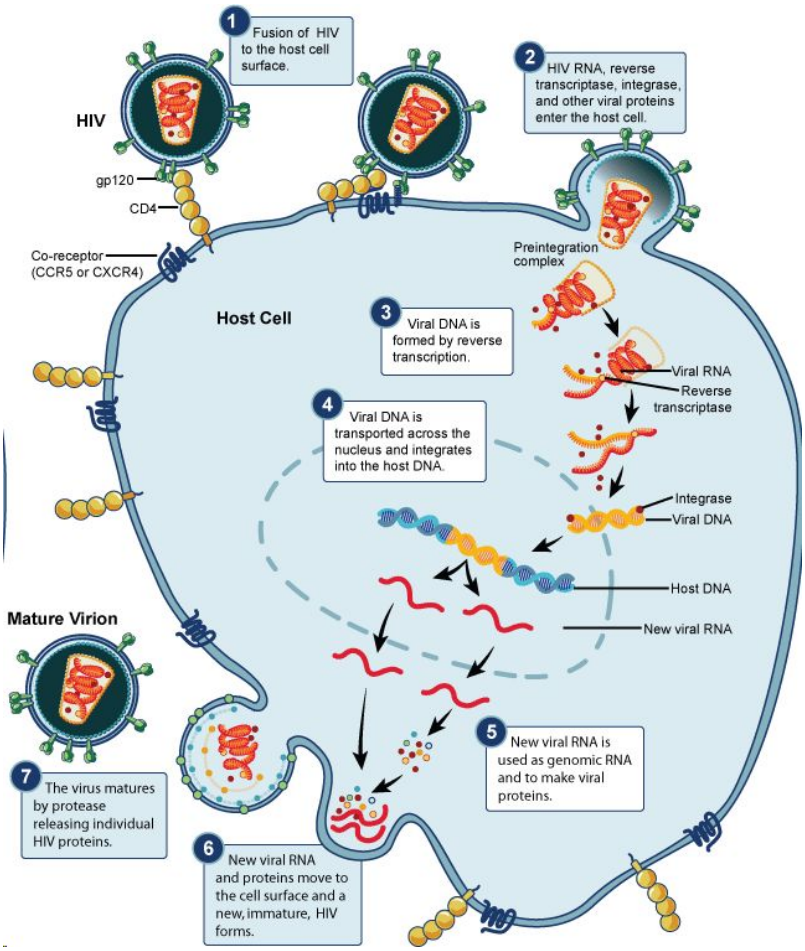



**Figure 1.** HIV Replication lifecycle. Reprimission from U.S. Department of Health and Human Services · National Institutes of Health (http://www.niaid.nih.gov/Pages/default.aspx)

between the virion glycoprotein gp120 on the outer membrane and the CD4 receptor on the host cell surface. This reaction results in a conformational change allowing the interaction of gp120 with the chemokine coreceptor CXCR4 or CCR5. This is then followed by further conformational changes that expose a fusogenic peptide, which anchors into the host cell membrane. Once the viral envelope and cell

membrane have fused, the virion is decapsidated releasing the viral RNA into the host cell's cytoplasm.

Through the reverse transcription, the viral RNA is transcribed to viral double-stranded DNA. This process is catalyzed by an RNA-dependent DNA polymerase, also known as reverse transcriptase, which is encoded by the viral genome. The viral DNA is then integrated into the host chromosome, and after transcription (facilitated by regulatory proteins Tat and Rev, which are themselves viral gene products) and translation into viral proteins using the cells' machinery, the assembly of the Gag and Gag-Pol polyproteins occurs near the cell membrane.[5,6] During viral assembly, two copies of single-stranded viral RNA are incorporated into the virion, which then buds off from the cell, taking with it part of the host cell membrane. Soon after budding, viral protease cleaves the Gag-Pol poly protein to generate a mature, functional virion.[6]

Nowadays around 60 antiviral drugs have been approved by US Food and Drug Administration (FDA) and the European Medicines Agency (EMA)[7]. Among them, compounds targeting proteases as well as viral nucleic acid replication and transcription are the largest group. Half of the approved drugs are against HIV[8,9,10]. The common categories used to classify the anti-HIV drugs are the following:[7,8]

- Nucleosides Reverse Transcriptase Inhibitors (NRTIs)
- Non-Nucleoside Reverse Transcriptase Inhibitors

(NNRTIs)

- Protease Inhibitors (PIs)
- co-receptor inhibitors (CRIs)
- Integrase Inhibitors (INIs)
- fusion inhibitors (FIs)

HIV therapy is based on a combination of these agents,[11,12,13] but the first used NRTI compound, Zidovudine (AZT)[14] is still a cornerstone of HIV treatment.[15] However, the use of these drugs has been relatively limited by their toxicity,[16] drug resistance development,[17] and more worryingly, the fact that some newly HIV-infected patients carry viruses that are already resistant to the currently approved AIDS treatments.[18] These issues along with drug-related side effects as well as, in some cases, poor tolerability of these drugs make it apparent that new anti-HIV drugs with acceptable toxicity and resistance profiles and, more importantly, new anti-HIV agents with novel mechanisms of action are clearly needed.

Nucleosides Reverse Transcriptase Inhibitors

Nucleotides are the structural units of nucleic acids. Each nucleotide consists of three subunits: one or more phosphate groups : a sugar moiety which can be either ribose (RNA) or deoxyribose (DNA); and a pyrimidine or purine base (Figure 2) Nucleosides differ from nucleotides in that they lack the phosphate group(s).

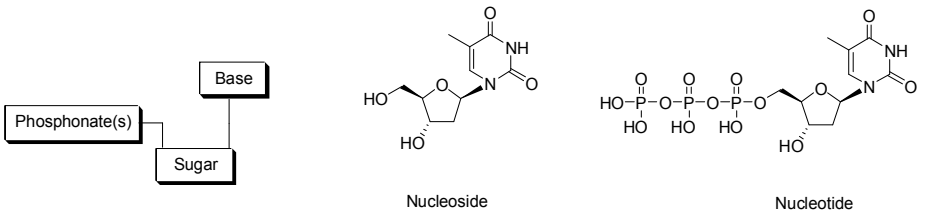



**Figure 2.** General structure of a nucleotide and structures of a natural pyrimidine nucleoside and nucleotide

Nucleosides are fundamental building blocks of biological systems that are widely used as therapeutic agents to treat cancer, fungal, bacterial, and viral infections.[19] Treatment of many other widespread diseases caused by viruses is mainly based on nucleoside analogues.[20,21] Indeed, nucleosides are the active ingredient of one third of the antiviral drugs approved by the FDA, becoming thus of great importance among the compounds with antiviral activity.[20,22-24] Additionally, a number of new nucleoside analogues are in various stages of clinical development to be approved as antiviral drugs.[8,25-27]

The first anti-HIV drug that was ever approved for the treatment of AIDS was the nucleoside reverse transcriptase inhibitor 3′-azido-2′,3′-dideoxy thymidine,[28] which is a nucleoside analogue that produces its activity by inhibiting the functioning of the HIV reverse transcriptase. Since then, there has been extensive research into identifying nucleoside-based compounds with good inhibitory activities of HIV reverse transcriptase. As a result, several nucleoside analogues, mainly 2′,3′-dideoxynucleosides, have been identified and

approved for treating HIV patients. Indeed, as well as AZT, there are currently seven more NRTIs approved for use in the clinics: d4T (2′,3′−didehydro−2′,3′−dideoxythymidine),[29] ddC (2′,3′−dide oxycyti dine),[29] ddI (2′,3′−dideoxyinosine),[30] ABC [(1S,4R)−4−[2−amino−6−(cyclopropylamino)−9H−purin−9−yl]−2−cyclopentene−1−methanol],[31] FTC [(−)−2′,3′−dideoxy−5−fluoro−3′−thiacytidine],[32] 3TC [(−)−2′,3′−dideoxy−3′−thiacytidine],[33] and TDF ({[(2*R*)−1−(6−amino−9*H*−purin−9−yl)propan−2−yl]oxy} methyl) phosphonic acid[34] (Figure 3). These agents are generally designed via three different ways:

- Modifications in the sugar moiety
- Modifications in the nucleic base moiety
- Modifications in both the sugar and base moieties

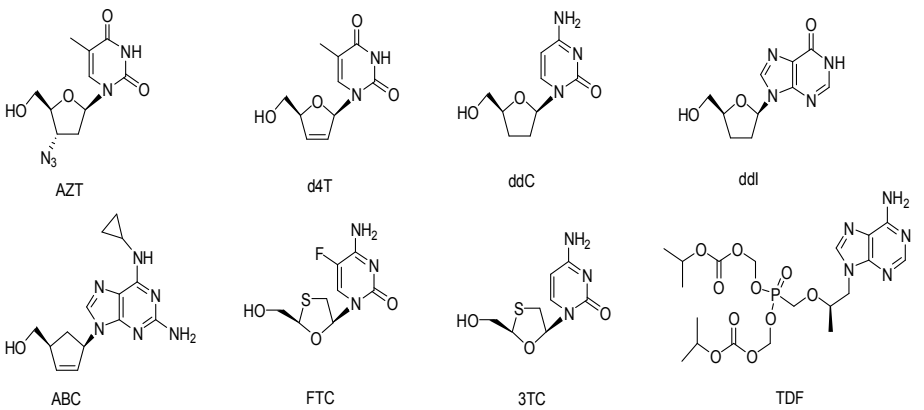



**Figure 3.** Structures of the currently FDA-approved anti-HIV drugs

NRTIs produce their anti-HIV effects by inhibiting the activity of the HIV reverse transcriptase.[35] In order for these agents to produce such effects, they have to be phosphorylated consecutively by cellular kinases to their triphosphate derivatives.[35,36] As all NRTIs follow the same mechanism of inhibition of HIV reverse transcriptase, only the mechanism of action of ddC is included here as a representative for this class of drugs.[37] Compound ddC is phosphorylated by deoxycytidine kinase, deoxycytidine monophosphate kinase, and nucleoside diphosphate kinase to form the monophosphate, diphosphate, and the active triphosphate derivative of ddC, respectively. This active moiety is then incorporated into the growing DNA by cellular DNA polymerases. The incorporation of ddC into the growing DNA results in terminating the elongation of the growing DNA double strand. This is mainly due to the fact that ddC and generally all NRTIs lack the 3′-hydroxyl group; therefore, they prevent the incorporation of the incoming nucleotide.

In addition, there are other nucleoside RT inhibitors at different stages of drug development. These drugs have been designed and developed to improve safety and efficacy profiles and to minimize drug resistance. Among them, three cytidine analogues have entered phase I and II clinical trials (Figure 4). Apricitabine [(−)-2′-deoxy-3′-oxa-4′-thiocytidine; AVX754; SPD754; (−)-dOTC] is active against HIV resistant to AZT, 3TC and other nucleoside RT

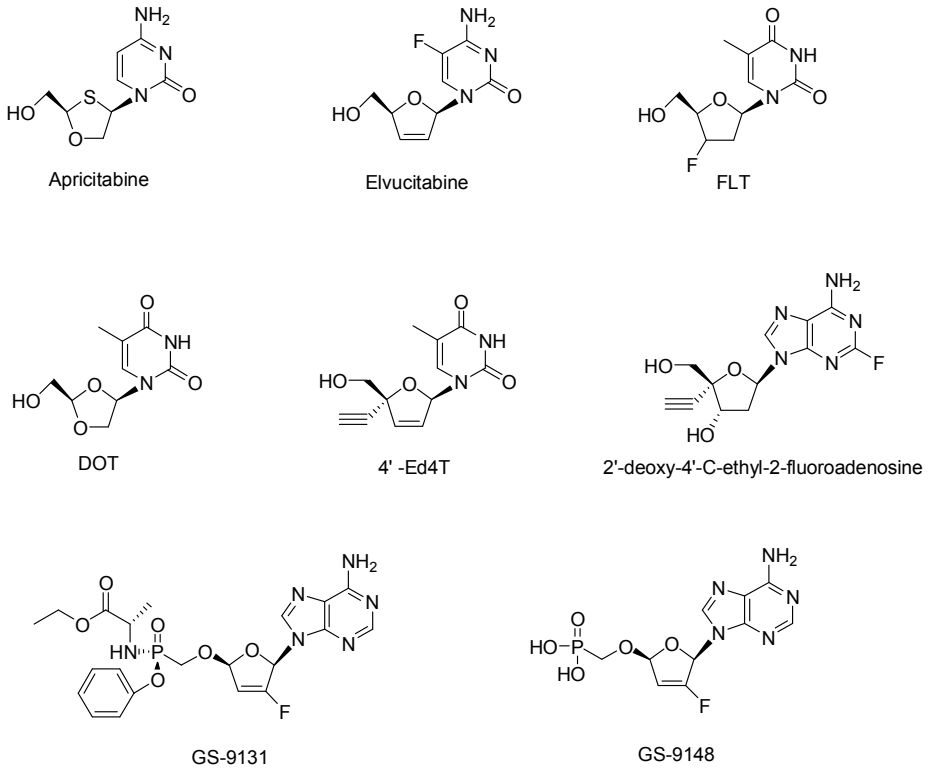



**Figure 4.** Novel nucleoside and nucleotide analogue RT inhibitors

inhibitors[38-42] but pharmacokinetic studies have shown that its intracellular levels are significantly reduced when combined with 3TC. Elvucitabine (β-L-2′,3′-didehydro-2′,3′-dideoxy-5-fluoro-cytidine; β-L-Fd4C; ACH-126,443)[43] and racivir [(±)-β-2',3'-dideoxy-5-fluoro-3′-thiacytidine; (±)-FTC][39] show good pharmacokinetic profiles, although bone marrow suppression has been observed at doses above 100 mg/day. Alovudine (β-D-3′-deoxy-3′-fluorothymidine; MIV-310; FLT) is a pyrimidine nucleoside analogue related to AZT and d4T, with potent activity against

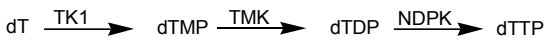
nucleoside RT inhibitor-resistant strains of HIV-1, including AZT-resistant isolates[45]. Thymidine analogues such as 1-( β -D-dioxolane)thymidine (DOT)[46,47], or the 2′,3′-didehydro-3′-deoxy-4′-ethynylthymidine (4′-Ed4T)[48-50] and 2′- or 3′-fluorocarbocyclic nucleosides[51] are also novel inhibitors in preclinical development. One of the most promising derivatives (2′-deoxy-4′-C-ethynyl-2-fluoroadenosine) has shown high potency against drug-resistant HIV-1 variants in cell culture assays, and low toxicity in mice.[52,53] In comparison with the approved nucleoside RT inhibitors, novel drugs should be more resilient to mutations that are commonly found in viruses derived from subjects failing multi nucleoside therapy. Among the nucleoside phosphonate analogues, GS-9148 ([5-(6-aminopurin-9-yl)-4-fluoro-2,5-dihydrofuran-2-yloxy-methyl] phosphonic acid) appears as the most promising candidate, showing high potency on multiple subtypes of HIV-1 clinical isolates, as well as against HIV-1 variants containing drug-resistance mutations such as K65R, L74V or M184V.[54]

**Mechanism of Action of Nucleoside Analogues in HIV Infected Cells**

In cells infected by HIV, the three successive phosphoryl transfers on antiviral agents such as AZT or d4T are carried out by human kinases,[55,56] More specifically, the activation process of dT analogues is performed by following enzymes: thymidine kinase 1 (TK 1), Thymidylate kinase (TMK), and nucleoside diphosphonate kinase

(NDPK), which mediate the formation of the mono-, di-, and triphosphorylated anabolites, respectively. (Scheme 1)[56]

**Scheme 1.** Kinases involved in the activation of pyrimidine analogues in HIV infected cells




TK1 is a cytosolic enzyme, key in human nucleotide metabolism since it catalyses the first phosphorylation step of deoxyribo-nucleosides in the salvage pathway. Three other deoxyri-bonucleoside kinases (dNKs), namely deoxycytidine kinase (dCK, sytosolic), thymidine kinase 2 (TK2, mitochondrial) and deoxy-guanosine kinase (dGK, mitochondrial) are also responsible for catalyzing this first phosphoryl transfer. In particular, pyrimidine compounds such as dT and dU are phosphorylated by TK1 and TK2, although some studies pointed out that TK2 contributes little to the cellular metabolism.[57] TK1 is well known to activate antiviral prodrugs like AZT and d4T,[55,58] despite it has a narrow substrate acceptance.

TMK belongs to the nucleoside monophosphonate (NMP) kinase family and it is responsible for catalyzing the reversible phosphoryl transfer to dTMP, using ATP as its preferred phosphoryl donor. Moreover, it is also known to participate in the activation of some anti-HIV prodrug (e.g. AZT and d4T).[56] The NMP kinase family is

completed by three other enzymes, which named according to their preferred natural substrate: adenylate kinase, guanylate kinase and uridylatecytidylate kinase. All these enzymes share a similar fold despite having a low primary structure identity.

NDPK catalyses the third phosphoryl transfer from a nucleoside triphosphonate to a diphosphonate acceptor (NDP) via an unusual mechanism. While in most kinase the donor and acceptor bind at two distinct sites and normally in a non-ordered manner, in NDPK both donor and acceptor share the same bingding site. Therefore, whereas normally the phosphoryl transfer is directly done from the donor from the donor to the acceptor, NDPK is known to catalyze the reaction via ping-pong mechanism, that is, the first product is released from the enzyme before the second substrate combines (Scheme 2).[59,60]

**Scheme 2.** Successive ping-pong steps for the activation of dipho-sphorylated derivatives by NDPK using ATP as the phosphoryl donor


NDPK binds first the donor, then phosphorylates a catalytic histidine residue and finally transfer the phosphoryl group from the His to the dephosphorylated substrate, so that the transfer takes place through two successive steps that imply the formation of

covalent enzyme−phosphate (E−P) intermediate. This mechanism is assumed to be the same for all pyrimidine and purine NDPK substrates.[61] Remarkably, NDPK is abundant in most living organisms and it is assumed to be the main source of the four triphosphorylated deoxynucleosides substrates of DNA polymerase. This enzyme is known to present large substrate promiscuity. Indeed, the nature of the base hardly affects the catalytic efficiency and the binding site can also accommodate non−natural bases. The activity of NDPK drops dramatically on analogues that lack the 3′−OH as a result of the catalytic mechanism itself.[62] The 3′−OH group of the sugar is responsible for donating a hydrogen bond to the oxygen atom bridging the $\beta-$ and $\gamma-$ phosphonates.[61,63,64] This oxygen acquires a negative charge when the $\gamma-$phosphonate is transferred to the catalytic His that is stabilized by the newly formed hydrogen bond, which accelerates the transfer by at least four orders of magnitude.[62,64] Since the catalysis is assisted by the substrate, and more precisely by the 3′−OH of the furanose, substrates lacking this moiety such as AZT or d4T are phosphorylated less efficiently by NDPK, despite they being in the same way as dT does.[65] Once the nucleosides have been activated, they must interact with HIV−1 RT to interfere in the replication of the viral nucleic acid. HIV−1 RT is known to have two enzymatic roles, DNA polymerase and ribonuclease (RNase H) activities, but antiviral agents are only aimed at the first one.

Moreover, it can employ either RNA or DNA template: primer, and then the dNTP that has to be bound to the 3′-primer terminus. A nucleophilic attack of the 3′-OH of the primer terminus to the $\alpha$-phosphorus of the incoming dNTP leads to its incorporation into the DNA growing chain, accompanied by a prrophosphate release. Anti-HIV agents are insert into the viral DNA via this mechanism, interrupting then the replication process.

Phosphonated Nucleoside Strategy for Antiviral

One of the mechanisms by which resistance to chain-terminating NRTIs might arise is through removal of the chain-terminating residue, a kind of repair reaction involving pyrophosphorolysis, which can be regarded as the opposite of the reverse transcriptase reaction.[66] It is worth noting that the three consecutive intracellular phosphorylation reactions required for the activation of NRTIs represent a problematic step for many nucleoside analogues. Nucleoside analogues, where extensive modifications have been made to a heterocyclic base and/or sugar moiety to avoid the disadvantages due primarily to enzymatic degradation, constitute a highly successful group of anticancer[67] and antiviral drugs.[68] Several classes of nucleoside analogues have been designed and synthesized to increase the resistance to enzymatic degradation and/or to reduce toxicity and the cross-resistance problems.[69] Some nucleoside analogues are incorporated with unconventional nucleobases (e.g., ribavirin, where a

triazole carboxyamide base mimics either adenine or guanine).[70] Other analogues, known as *C*-nucleosides (i.e., pyrazo-, tiazo-, selenazo-, and oxazofurin) are characterized by the replacement of the acid-labile C-N glycosidic bond by a stable C-C bond.[71-76] Moreover, different types of modifications have been carried out through the insertion of heteroatoms or replacement of the furanose oxygen with other atoms (heterocyclic nucleosides).[75,76] To be active, once they have entered the cell, nucleoside analogues have to be phosphorylated by a combination of human intracellular enzymes, through three consecutive phosphorylation steps, before they can interact in their active triphosphate form with their target enzyme, the viral DNA polymerase.[77] The therapeutic effect depends on the rate of intracellular phosphorylation. In their triphosphate form, the compounds compete with the normal substrates [2′-deoxynucleoside 5′-triphosphates (dNTPs)] for binding sites on reverse transcriptase. When incorporated into nascent viral DNA, they may act as chain terminators, thus preventing further chain elongation. Of crucial importance in the phosphorylation process is the monophosphorylation step, which is mediated by a specific virus-encoded thymidine kinase (TK) (for HSV and VZV) or a specific virus-encoded (UL97) protein kinase (PK) (for CMV).[78] Once the compounds have been monophosphorylated, the cellular kinases (i.e., guanosine monopho sphate kinase GMP and nucleoside diphosphate kinase NDP) will

afford further phosphorylation to the di- and triphosphate stages, respectively.[78-80]

In particular, the first phosphorylation step, which results in the formation of the nucleoside analogue monophosphate, is considered to be the most difficult. To overcome this problem, a series of prodrug strategies aimed at the delivery of nucleoside analogues monophosphates have been developed.[81] To improve the cellular permeability and enhance the anti-HIV activity of nucleoside analogues, two main synthetic strategies have been exploited. The first is based on the mononucleotide prodrug approach, where the polar monophosphate unit of the nucleoside, masked by different groups, such as phosphoramidate, bis-*S*-acyl thioethyl esters (bis-SATE), bis-pivaloxymethyl (bis-POM), cyclo-Saligenyl, *S*-pivaloyl-2-thioethyl (*t*-BuSATE) and phenyl, *S*-acylthioethyl mixed phosphate esters (mix-SATE), undergoes transient esterase-labile phosphate protection.[82] The drug-design rationale on which this approach is based is that these lipophilic nucleoside phosphotriesters are able to bypass the first monophosphorylation step catalyzed by dCK or TK1 and to deliver, by hydrolysis and/or enzymatic cleavage, the corresponding 5′-mononucleotide inside the cells.[81] The prodrug approach has been shown to be effective for both antiviral and anticancer applications.

The second strategy involves the design of monophosphate analogues where the phosphate moiety is changed to an isosteric and isoelectronic phosphonate unit.[83] A phosphonated nucleoside, where the phosphonate group is attached to the acyclic nucleoside moiety through a stable P-C bond, shows an advantage, over its phosphate counterpart in being more stable metabolically and chemically. These 5′-mononucleotide mimics are able to overcome the instability of mononucleotides toward phosphodiesterases and to enhance cellular uptake by bypassing the initial enzymatic phosphorylation step.[84] Furthermore, within cells, they must be phosphorylated by cellular nucleotide kinases to the corresponding diphosphates and then triphosphates to exert biological activity.

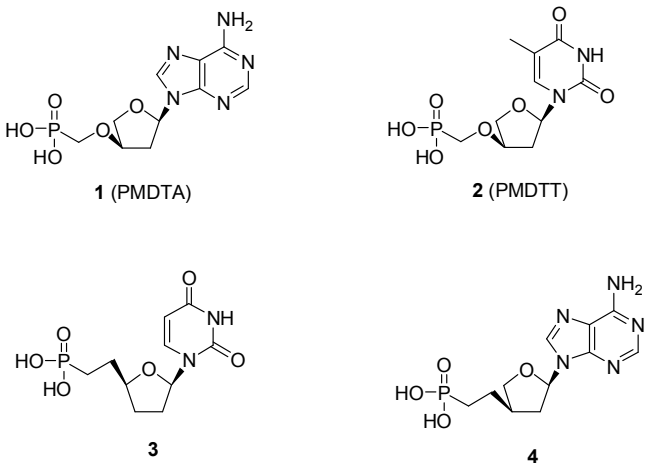
### Threosyl Phosphonic Acid Nucleosides

Phosphorus-modified nucleoside analogues, bearing a phosphonate group in their sugar moiety, have shown potent antiviral activity.[85] Since antiviral activity is often associated with nucleoside analogues bearing a phosphonomethoxy group in the sugar moiety, comparatively little attention have been paid to the properties and scopes of other phosphonate functions in relationship to biological activity. On the other hand, considerable attention has been paid to unusual nucleosides since modified nucleosides were reported to be promising anti-human immunodeficiency virus (HIV) and anti-hepatitis B virus (HBV) agents. Of these compounds, threose

nucleosides,[86] such as, PMDTA **1** and PMDTT **2**, have been previously synthesized (Figure 5) because they can be assembled from natural precursors.[87] Furthermore, it has been demonstrated that threose nucleic acids (TNA) form duplexes with DNA and RNA that are thermally stable, in an analogous manner to natural nucleic acid association. The triphosphates of threose nucleosides are substrates of several polymerases, and can be enzymatically incorporated into DNA.[88] Actually, these nucleosides are accepted as substitutes for ribonucleosides in the catalytic site of hammerhead ribozyme, although subsequently, the catalytic efficiency of the ribozyme is significantly reduced.[89] The phosphonoalkoxy group of the proposed threose nucleoside phosphonates is bound at the 3′-position, which brings the phosphorus atom and the nucleobase closer together than in previously synthesized nucleoside phosphonates, where the phosphonate group is bound to the primary hydroxyl group of the nucleoside. In the literature, nucleoside phosphonates have been prepared from several 5′-phosphate isosteres. As shown in Figure 5, compound **3**[90] is a simple 5′-deoxynucleoside phosphonate, in which the 5′-oxygen of a nucleoside phosphate is replaced by a methylene (Figure 5). More recently, we synthesized the novel threosyl 5′-deoxynucleoside adenine phosphonate **4**.[91] All phosphonates mimic the overall shape and geometry of nucleoside monophosphates. Phosphorylation by kinases and the incorporation into nucleic acid

(eventually leading to chain termination) is considered as important mechanism underlying the antiviral activities of nucleosides.

**Figure 5.** Structures of some threosyl phosphonic acid nucleosides as potent anviral agents




In fact, lack of antiviral activity by a nucleoside phosphonate is generally attributed to poor substrate properties for cellular and viral kinases. On the other hand, the potent antiviral activities of phosphonylated alkylated nucleobases are ascribed to their intracellular phosphorylation to diphosphates and to refractory incorporation of the modified nucleosides in nucleic acids.[92] Furthermore, the enzymatic incorporation of phosphonate nucleosides into nucleic acids is almost irreversible, which is not the case for regular nucleotides. Phosphonates have certain advantages over their phosphate counterparts because they are metabolically stable due to the lack of susceptibility of the phosphorus–carbon bond to hydrolytic cleavage.[93]

## Fluorinated Nucleoside Phosphonic Acid

Fluorinated nucleosides, containing fluorine atom or fluorine containing groups in the sugar moiety, have drawn increasing attention due to the introduction of the fluorine into some nucleosides resulting in a great improvement in the bioactivity and stability of the corresponding compounds.[94] GS-9148 **5** has a promising antiviral resistance profile, retaining potency toward HIV RT-resistant virus containing M184V, multiple thymidine analogue mutations (TAMs), and K65R resistance mutations.[95] GS-9131 **6**, an ethylalaninyl phosphonoamidate prodrug of GS-9148, demonstrated excellent potency toward multiple subtype of HIV-1 clinical isolates (mean $EC_{50}$ = 37 $\mu$M), several fold better than 3′-azido-2′,3′-dideoxythymidine (AZT).[96] Especially noteworthy is gemcitabine[97] (2′-deoxy-2′,2′-difluorocytidine) **7**, which has been approved by the FDA for the treatment of inoperable pancreatic cancer and of 5-fluorouracilresistant pancreatic cancer Figure 6.[98] Recently, 6'-fluorocarbocyclic nucleoside **8** exhibited moderate activities against herpes simplex virus type (HSV-1) and type (HSV-2) *in vitro*.[99]

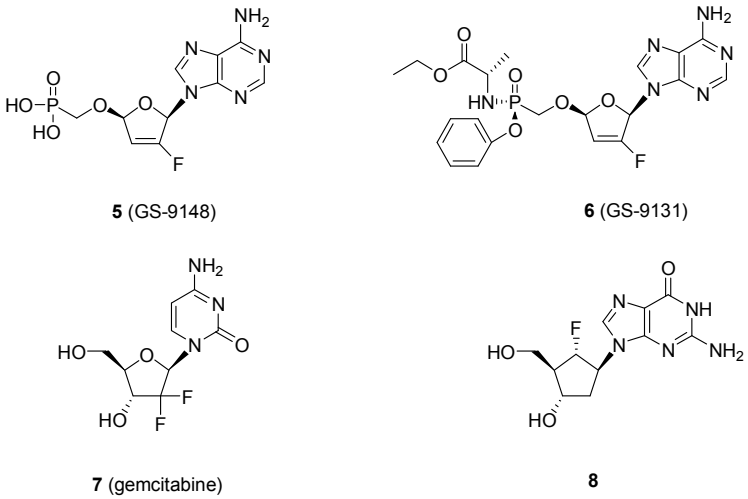



**Figure 6**. Structures of some fluorinated nucleoside as potent antiviral agents

The 2′,3′−dideoxynucleosides (ddNs) have been proved to the most effective therapeutic agents against human immunodeficiency virus (HIV) and hepatitis B virus (HBV).[100] 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.[101] Moreover, the spacial location of the oxygen atom, namely the $\beta$−position from the phosphorus atom in the nucleoside analogue, has been demonstrated to play a critical role for antiviral activity.[102] These atoms for antiviral activity may be attributed to the increased binding capacity of the phosphonate analogues to target enzymes. Phosphorylation by kinases and incorporation into nucleic acid (eventually leading to chain termination) is considered as an important mechanism to explain the antiviral activity of

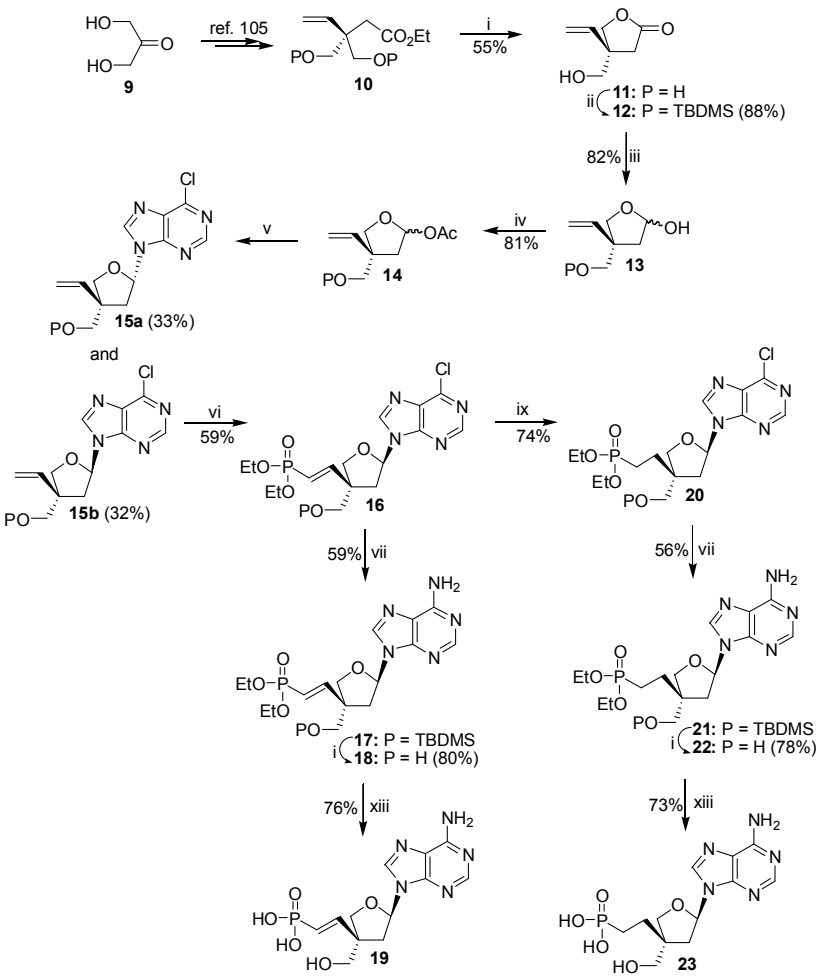
nucleosides.[103] The potent antiviral activity of phosphonylated nucleobases is ascribed to their intracellular phosphorylation to their diphosphates and to refractory incorporation of the modified nucleosides in nucleic acids.[104]

# Ⅱ. RESULTS AND DISCUSSION

As shown in Scheme 3, the target compounds were prepared from 1,3-dihydroxyacetone through an acyclic synthesis route.[105] The lactone functional group of **12** was prepared via desilylation, cyclization, and resilylation from **10**. The lactone **12** was reduced using DIBALH in toluene at −78℃ to give lactol **13**, which was acetylated in pyridine to furnish the key intermediate **14** as a glycosyl donor (Scheme 3). The synthesis of adenine nucleoside was carried out by condensation of compound **14** with silylated 6-chloropurine using TMSOTf as a catalyst in DCE to give protected 6-chloropurine derivative **15a** and **15b**, respectively. A complete NOE study allowed an unambiguous determination of their relative stereochemistry (Figure 7). For compound **15b**, strong NOE (1.1%) of H-1′ ↔CH-3′, which showed 1′,3′-*cis* relationships, was observed. According to this result, 3′-vinyl and 1′-purine base of **15b** were located on the $\beta$ face. On the other hand, for **15a** compound, weak NOE (0.7%), such as H-1′ ↔CH-3′, were assigned to the 1′,3′-*trans* relationships. Cross-metathesis[106] of **15b** with diethylphosphonate using second generation Grubbs catalyst[107] gave vinylidene phosphonate nucleoside analogue **16**. The chlorine group of purine analogue **16** was then converted to amine with methanolic ammonia at 65℃ to give a corresponding adenosine phosphonate derivative **17**, which was desilylated to

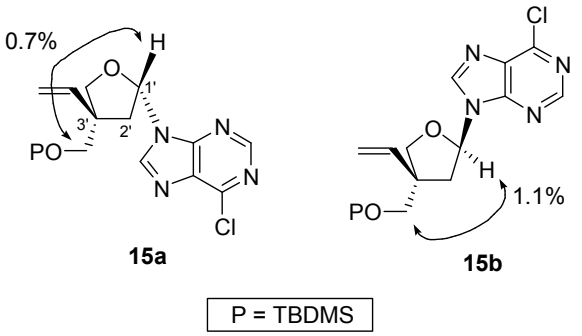
provide 18. Hydrolysis of diethyl phosphonate functional groups of 18 by treatment with bromotrimethylsilane in $CH_3CN$ in the presence of 2,6−lutidine gave an adenosine phosphonic acid derivative 19.[108]

**Scheme 3.** Synthesis of 4'-hydroxymethyl-5'-deoxythreosyl phosphonic acid adenine analogues




Reagents: i) TBAF, $CH_3CN$; ii) TBDMSCl, imidazole, DMF; iii) DIBALH, toluene; iv) $Ac_2O$, pyridine; v) silylated 6-chloropurine, TMSOTf, DCE; vi) Vinyldiethylphosphonate, Grubbs cat.(II) $CH_2Cl_2$; vii) $NH_3$, MeOH, 65 $^oC$; viii) TMSBr, 2,6-lutidine, $CH_3CN$; ix) Pd/C, cyclohexene, MeOH.

**Figure 7.** NOE differences between the proximal hydrogens of **15a** and **15b**



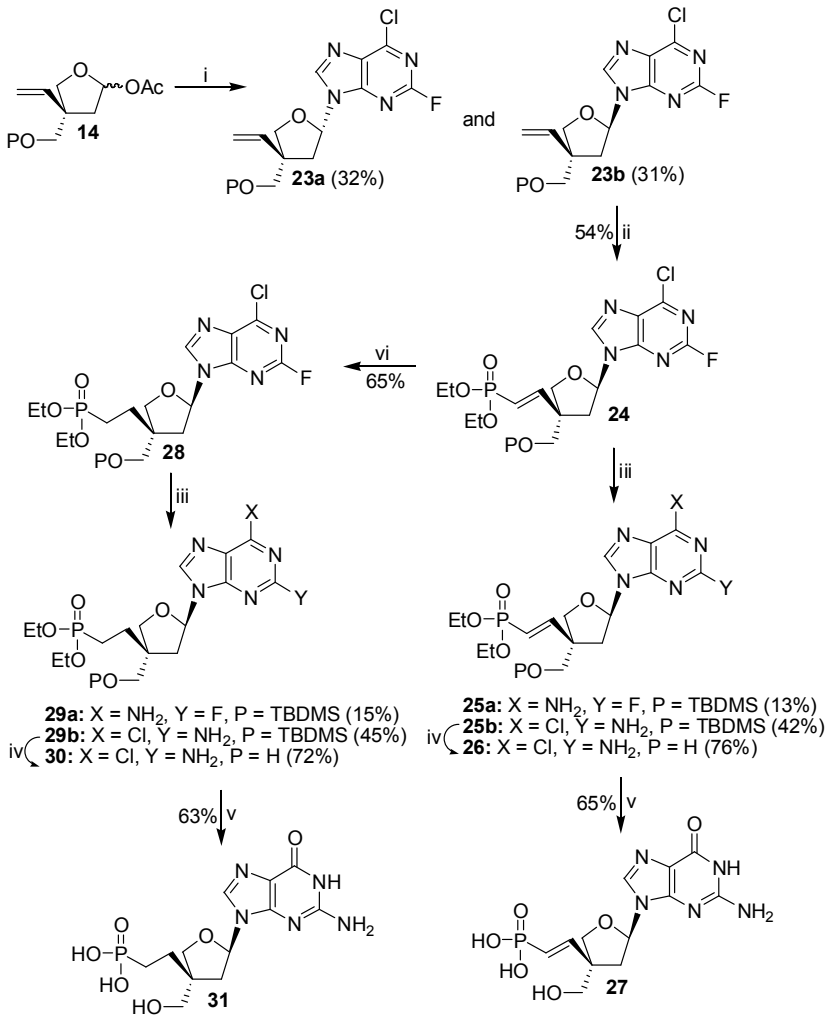

The vinylidene phosphonate was saturated in transfer catalytic hydrogenation conditions to give ethyl phosphonate nucleoside analogue **20** in a 74% yield. Adenine phosphonic acid analogue **23** was prepared through the similar reaction conditions such as ammonolysis, desilylation, and hydrolysis described for the preparation of **19**.

For the synthesis of guanine analogues, 2-fluoro-6-chloropurine[109] was condensed with glycosyl donor in the similar conditions used for the condensation of 6-chloropurine. Vorbruggen coupling[110] of the acetate **14** with 2-fluoro-6-chloropurine gives analogue **23a** (32%) and **23b** (31%), respectively. Cross-metathesis of **23b** and diethylvinylphosphonate gave **24** in a 54% yield.

Bubbling ammonia into the compound **21** gave separable 2-fluoro-6-aminopurine analogue[111] **25a** (13%) and 2-amino-6-chloropurine analogue**25b** (42%), respectively. Fluorine acts as a better leaving group than chlorine in nucleophilic aromatic substitution. 2-Amino-6-chloropurine derivative **25b**, which was desilylated to give **26** in

76% yields.

**Scheme 4.** thesis of 4'-hydroxymethyl-5'-deoxythreosyl phosphonic acid guanine analogues




Reagents: i) silylated 2-fluoro-6-chloropurine, TMSOTf, DCE; ii) vinyldiethylphosphonate, Grubbs cat.(II) $CH_2Cl_2$; iii) $NH_3$, DME, rt; iv) TBAF, $CH_3CN$; v) (a) TMSBr, 2,6-lutidine, $CH_3CN$; (b) NaOMe, $HSCH_2CH_2OH$, MeOH; vi) Pd/C, cyclohexene, MeOH.

Phosphonate 26 was treated with TMSBr to provide phosphonic acid and sequentially treated sodium methoxide and 2-mercaptoethanol inmethanol to give desired guanine vinylidene

phosphonic acid **27**, (Scheme 4).[112] The guanine phosphonate **31** was synthesized from **24** via transfer catalytic hydrogenation, ammonolysis, desilylation and hydrolysis using the similar conditions as described for the synthesis of **27**.

The antiviral activity of phosphonate nucleoside is mostly explained by their intracellular metabolism to their diphosphates followed by incorporation into the viral genome and chain termination.[113] The synthesized compounds **19**, **23**, **27**, and **31** were tested against HIV-1. Especially, the adenine analogue **23** did show moderate antiviral activity against HIV-1 (Table 1), indicating that this virus might allow the sugar moiety for diphosphorylation or some affinity of its diphosphate toward viral polymerases.

Anti-HIV activity was determined in human peripheral blood mononuclear (PBM) cells infected with HIV-1 strain LAI. PBM cells (1 × 105 cell/mL) were infected with HIV-1 at a multiplicity of infection (MOI) of 0.02 and cultured in the presence of various concentrations of the test compounds. After 4 days of incubation at 37 °C, numbers of viable cells were determined using the 3-(4,5-di-methylthiazole-2-yl)-2,5-diphenyltetrazolium bromide method. The cytotoxicities of the compounds were evaluated in parallel with their antiviral activities, which were assessed based on the viabilities of mock-infected cells.[114]

**Table 1.** The antiviral activities of the synthesized compounds **19**,

23, 27 and 31

| Compound | HIV-1 | | cytotoxicity $IC_{50(\mu M)}$ | | |
|---|---|---|---|---|---|
| | $EC_{50(\mu M)}$ | $EC_{90(\mu M)}$ | PBM | CEM | Vero |
| 19 | 44.6 | 95 | >100 | >100 | >100 |
| 23 | 10.2 | 80 | 45.5 | 32.0 | >100 |
| 27 | 65 | 95 | >100 | >100 | >100 |
| 31 | 80 | 95 | >100 | >100 | >100 |
| PMEA | 5.2 | ND | >100 | 40.5 | >100 |
| AZT | 0.123 | ND | >100 | 13.5 | 50.5 |

Based on the potent anti-HIV activity of 4′-branched nucleosides as well as threosyl phosphonic acid nucleoside analogues, we have designed and successfully synthesized novel 3′-hydroxymethyl 5′-deoxyphosphonic acid nucleoside analogues starting from 1,3-dihydroxyacetone. The 3′-modified adenine phosphonic acid 23 exhibits moderate antiviral activity ($EC_{50}$ = 10.2 $\mu$M). As shown in Figure 8, superimposed modeling of PMDTA 1 and 23 shows close similarity with slightly two different parts such as adenine base and phosphonic acid moiety. Energy minimization was optimized with the framework of the density functional theory (DFT), with Spartan modeling software. The B3LYP functional with 6-31G* basis set was employed.

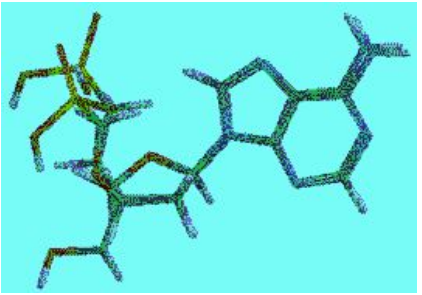
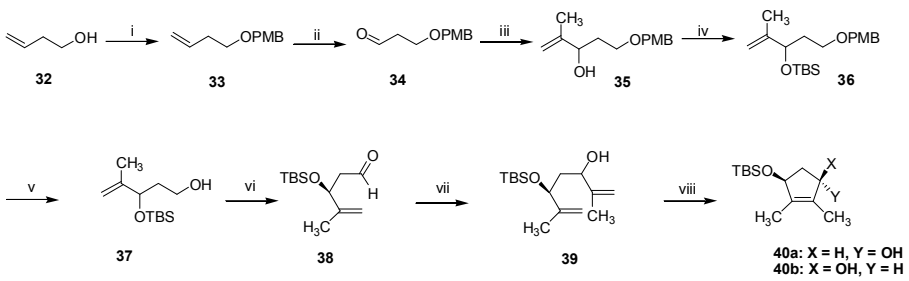


**Figure 8.** Superimposition of PMDTA **1** and **23**.

For the synthesis of phosphonate adenine nucleoside, the commercially available but-3-en-1-ol **32** was selected as a starting material. As shown in Scheme 1, the synthetic route is very simple and straightforward. The primary hydroxyl group of **32** was protected as temporary *p*-methoxy benzyl ether (PMB) by reaction[115] with PMBCl and NaH in DMF to afford the protected olefin **33** in a yield of 97%. The olefin of **33** was treated with ozone in methylene chloride at 78℃, followed by the decomposition of the ozonide by dimethylsulfide (DMS) to give the aldehyde **34**. Compound **34** was subjected to carbonyl addition with isopropenyl magnesium bromide to provide the secondary alcohol derivative **35**, which was protected with *t*-butyldimethylsilyl chloride (TBDMSCl) to give compound **36**. Oxidative deprotection of the PMB ether moiety of **36** was effected with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[116] in methylene chloride with a small amount of water to give the alcohol **37**, which was then oxidized to the aldehyde **38** using pyridinium

chlorochromate (PCC), which again underwent an addition reaction with isopropenyl magnesium bromide to provide a divinyl **39**. The divinyl **39** was subjected to standard ring-closing metathesis (RCM) conditions using a 2nd generation Grubbs catalyst to provide cyclopentenol **40a** (43%) and **40b** (42%), which were readily separated by silica gel column chromatography (Scheme 5).

**Scheme 5.** Synthesis of cyclopentene intermediate **40**

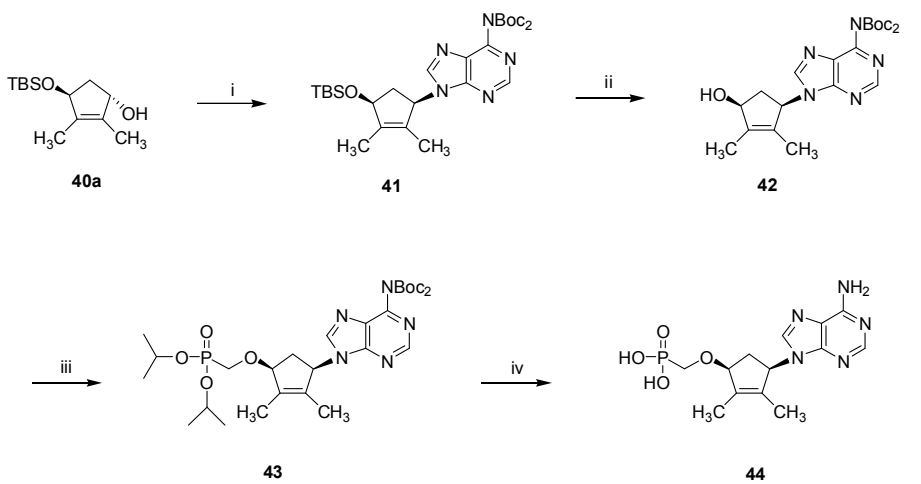



Reagents: i) PMBCl, NaH, DMF, 0°C; ii) $O_3$, DMS, -78°C; iii) isopropenylMgBr, THF, -78°C; iv) TBDMSCl, imidazol, $CH_2Cl_2$, 0°C; v) DDQ, $CH_2Cl_2/H_2O$, rt; vi) PCC, 4MS, $CH_2Cl_2$; vii) isopropenylMgBr, THF, -78°C; viii) Grubbs II, benzene, 60°C, reflux overnight.

For coupling with a nucleobase, the hydroxyl group was converted to mesylate for nucleophilic substitution. However, the yield of mesylation was very low and the mesylate was unstable during work-up for storage. Alternatively, the alkylation of adenine was attempted under Mitsunobu conditions using diisopropyl azodicarboxylate (DIAD) and $PPh_3$ under a THF solvent. Unfortunately, the direct coupling of adenine with alcohol **40a** failed. A nucleobase precursor such as $N^6$-bis-Boc-adenine[117] was coupled with alcohol **40a** under Mitsunobu conditions[118] to give compound **41** with a chirality inversion.

The silicon protection group of compound 41 was readily removed by treating it with tetrabutylammonium fluoride (TBAF) in THF to give compound 42. For the synthesis of phosphonate nucleoside, the hydroxyl group of 42 was phosphonated by treating it with diisopropyl bromomethyl phosphonate[119] in anhydrous in the presence of LiOt-Bu to give the phosphonate nucleoside intermediate 43 (Scheme 6). Both protecting groups ($N^6$-bis-BOC & di-O-isopropyl) of the phosphonate nucleoside were simultaneously removed using trimethylsilylbromide[120] to give nucleoside phosphonic acid 44.

**Scheme 6.** Synthesis of carbocyclic adenine nucleoside **44**




Reagents: i) PPh3, DIAD, $N^6$-bis-Boc-adenine, THF, -20°C; ii) TBAF, THF, rt; iii) Diisopropyl bromomethylphosphonate, LiO-*t*-Bu, LiI, DMF, 60°C; iv) TMSBr, $CH_3CN$.

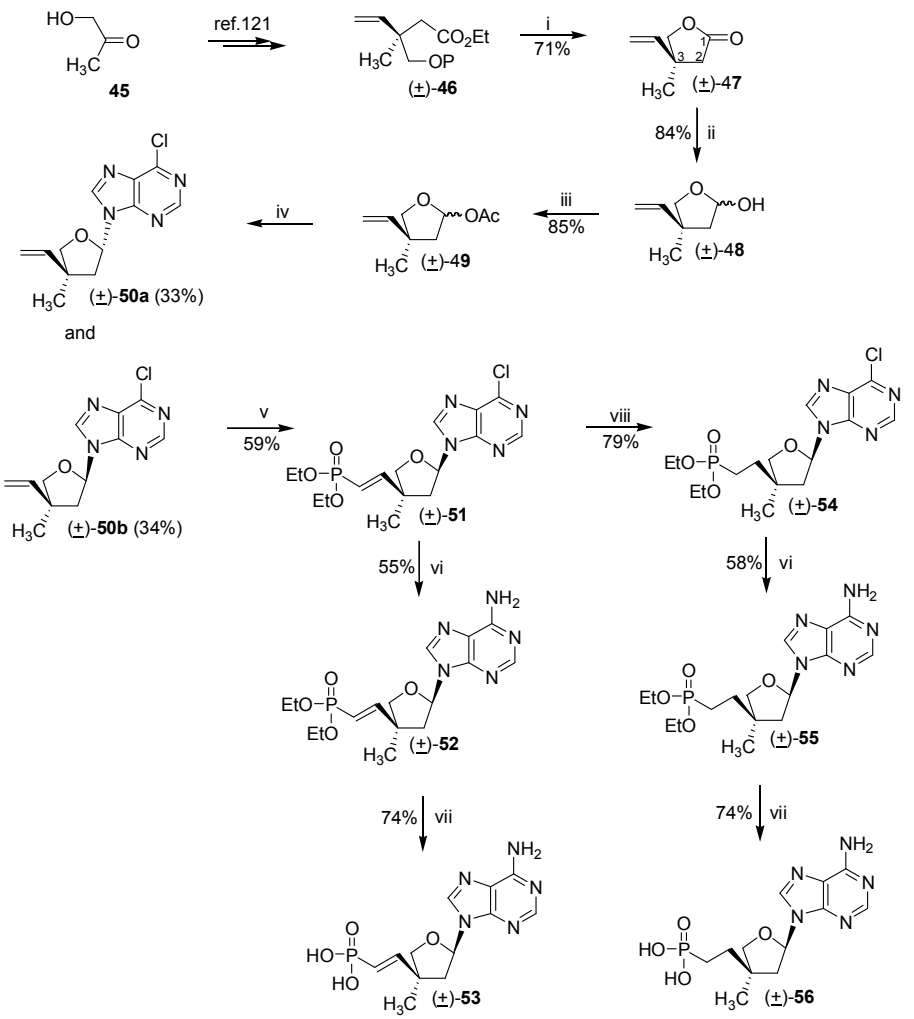
Antiviral assay against HIV-1 was performed for the adenine analogues 44. Unfortunately, it did not show any anti-HIV activity in

MT-4 cells.

As shown in Scheme 7, target compounds were prepared from acetol via an acyclic synthesis route.[121] The lactone functional group of **47** was prepared via desilylation and cyclization from **46**, and **47** was subsequently reduced using DIBALH in toluene at 78℃ to give lactol **48**, which was acetylated in pyridine to furnish the key intermediate **49** (a glycosyl donor) (Scheme 7). The synthesis of adenine nucleoside was carried out by condensation between **49** and silylated 6-chloropurine using TMSOTf as a catalyst in DCE to give the protected 6-chloropurine derivatives **50a** and **50b**, respectively. A complete NOE study allowed the unambiguous determination of their respective stereochemistries (Figure 9). For compound **50b**, strong NOE (0.7%) of H-1′ ↔ CH-3′, showing 1′,3′-cis relationships, was observed. According to this result, the 3′-vinyl group and the 1′-purine base of **50b** were located on the $\beta$ face. On the other hand, for **50a**, weak NOE (0.2%), such as, H-1′ ↔ CH-3′, were assigned to the 1′,3′-*trans* relationship. Cross-metathesis[106] of **50b** with diethyl phosphonate using 2nd generation Grubbs catalyst[107] gave the vinylidene phosphonate nucleoside analogue **51**, the chlorine group of which was then converted to amine using methanolic ammonia at 60℃ to give the corresponding adenosine phosphonate derivative **52**. Hydrolysis of the diethyl phosphonate functional groups of **52** with bromotrimethylsilane in $CH_3CN$ in the presence of 2,6-lutidine then

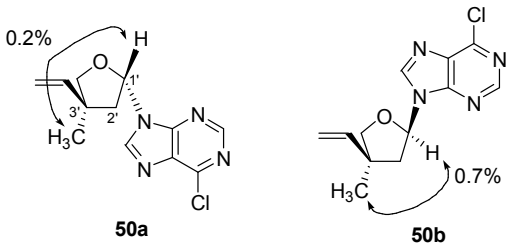
gave the adenosine phosphonic acid derivative 53.[108]

**Scheme 7.** Synthesis of threosyl-4'-methyl-5'-deoxyphosphonate adenine analogue




Reagents: i) TBAF, THF; ii) DIBALH, toluene; iii) $Ac_2O$, pyridine; iv) silyated 6-chloropurine TMSOTf, DCE; v) Vinyldiethylphosphonate, Grubbs cat.(II), $CH_2Cl_2$; vi) $NH_3$, MeOH, 60 °C; vii) TMSBr, 2,6-lutidine, $CH_3CN$; viii) Pd/C, cyclohehene, MeOH.

**Figure 9**. NOE differences between the proximal hydrogens of **50a** and **50b**



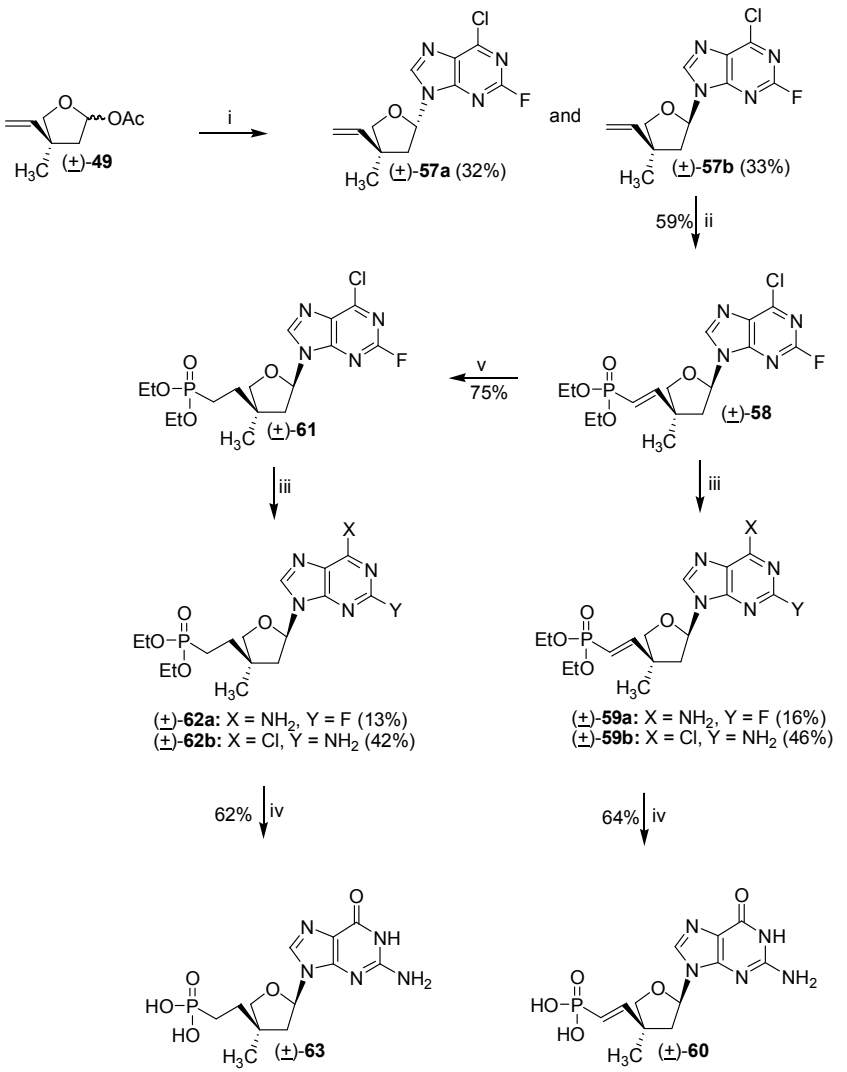

The vinylidene phosphonate of 51 was then saturated under transfer catalytic hydrogenation conditions to give the ethyl phosphonate nucleoside analogue 54. Adenine analogue 56 was prepared using reaction conditions (ammonolysis and hydrolysis) similar to those described to prepare 53.

To synthesize guanine analogues, 2-fluoro-6-chloropurine[109] was condensed with glycosyl donor using conditions similar to those used for the condensation of 6-chloropurine. Vorbruggen coupling[110] of the acetate 49 with 2-fluoro-6-chloropurine provided the analogues 57a (32%) and 17b (33%). Cross-metathesis of 57b and diethylvinylphosphonate then produced 58 at a yield of 59%.

Bubbling ammonia into compound 58 provided the two separable analogues 2-fluoro-6-aminopurine[111] 59a (16%) and 2-amino-6-chloropurine 59b (46%). Fluorine atom acts as a good leaving group than chlorine atom in nucleophilic aromatic substitution. The 2-amino-6-chloropurine derivative 59b was treated with TMSBr to provide phosphonic acid, and then treated with sodium methoxide and

2−mercaptoethanol in methanol to give the desired guanine vinylidene phosphonic acid 60 (Scheme 8).[112]

**Scheme 8.** Synthesis of threosyl-4'-methyl-5'-deoxyphosphonate guanine analogue




Reagents: i) silylated 2-fluoro-6-chloropurine, TMSOTf, DCE; ii) vinyldiethylphosphonate, Grubbs cat.(II) $CH_2Cl_2$; iii) $NH_3$, DME, rt; iv) (a) TMSBr, 2,6-lutidine, $CH_3CN$; (b) NaOMe, $HSCH_2CH_2OH$, MeOH; v) Pd/C, cyclohexene, MeOH.

The guanine phosphonate 63 was synthesized from 58 by transfer

catalytic hydrogenation and by ammonolysis and hydrolysis using conditions similar to those described for the synthesis of **60**.

The antiviral activity of phosphonate nucleosides is largely due to their intracellular conversions to diphosphates, their subsequent incorporation into the viral genome, and chain termination.[113] The synthesized compounds **53**, **56**, **60**, and **63** were tested against HIV-1 and for cytotoxicity using AZT and PMEA as positive controls; results are summarized in Table 2.

**Table 2.** The antiviral activities of the synthesized compounds **53**, **56**, **60** and **63**

| Compound | HIV-1 | | cytotoxicity $IC_{50(\mu M)}$ | | |
|---|---|---|---|---|---|
| | $EC_{50(\mu M)}$ | $EC_{90(\mu M)}$ | PBM | CEM | Vero |
| **53** | 50.6 | 90 | >100 | >100 | >100 |
| **56** | 22.2 | 80 | 42.4 | 30.4 | >100 |
| **60** | 70 | 95 | >100 | >100 | >100 |
| **63** | 85 | 95 | >100 | >100 | >100 |
| PMEA | 5.4 | ND | >100 | 50.3 | >100 |
| PMDTA | 2.6 | ND | >100 | >100 | >100 |
| AZT | 0.16 | ND | >100 | 14.7 | 51.2 |

Anti-HIV activity was determined in human peripheral blood mononuclear (PBM) cells infected with HIV-1 strain LAI. In

particular, the adenine analogue **56** show moderate antiviral activity against HIV-1, indicating that this virus might allow the sugar moiety for diphosphorylation or some affinity of its diphosphate toward viral polymerases. PBM cells (1 × 105 cell/mL) were infected with HIV-1 at a multiplicity of infection (MOI) of 0.02 and cultured in the presence of various concentrations of the test compounds. After 4 days of incubation at 37℃, numbers of viable cells were determined using the 3-(4,5-di-methylthiazole-2-yl)-2,5-diphenyltetrazolium bromide method. The cytotoxicities of the compounds were evaluated in parallel with their antiviral activities, which were assessed based on the viabilities of mock-infected cells.[114]

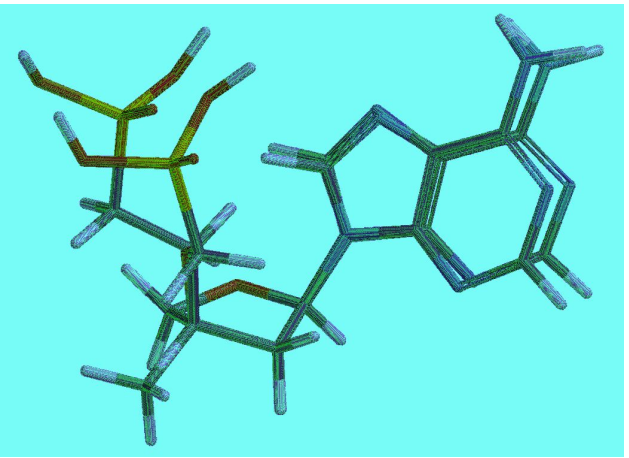


**Figure 10.** Superimpose model of PMDTA and **56**.

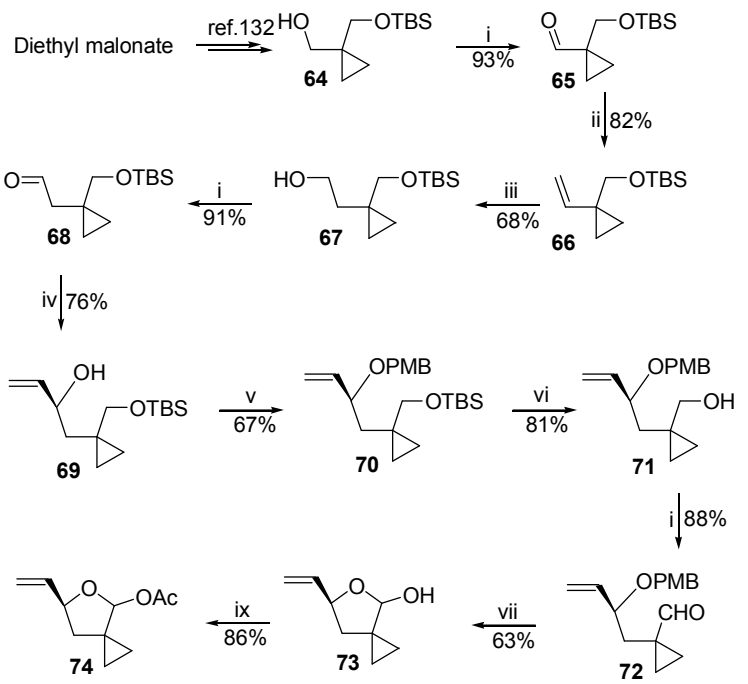
In summary, based on the known potent anti-HIV activities of threosyl 5′-norcarbocyclic nucleoside analogues, we designed and successfully synthesized novel 5′-deoxyphosphonate nucleoside

analogues starting from acetol. The previously synthesized adenine **4** exhibited better cell-based activity than 4′-methyl branched adenine phosphonic acid **56**, which suggests that the methyl substituent at the 4′-position is possibly responsible for the apparent lack of activity of **56**. Superimposed modeling of PMDTA and **56** highlighted differences in adenine bases and phosphonic acid moieties (Figure 10).[122]

As depicted in Scheme 9, the target compounds were prepared from monosilyl-cyclopropanoid **65**, which was readily prepared from diethyl malonate by the previously reported procedure.[123] For the homologation, Swern oxidation[124] of alcohol **64** gave an aldehyde **65**, which was subjected to the Wittig reaction[125] to give compound **66**. Hydroboration[126] and oxidation of corresponding olefin **66** provided alcohol derivative **67**, which was oxidized using the similar Swern conditions described for compound **65** in 91% yields. Carbonyl addition reaction by vinylmagensium bromide furnished the allylic alcohol **69**, which was successfully protected using *p*-methoxybenzyl chloride (PMBCl)[127] to provide compound **70**. Removal of the silyl protecting group of compound **70** using tetra *n*-butylammonium fluoride (TBAF) gave the primary alcohol **71**, which was oxidized to the aldehyde **72** using the same oxidation conditions as described for compound **68** in 71% two-step yields. The *p*-methoxybenzyl (PMB) protection group was removed with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)[128] to produce a lactol analogue **73** in 63% yields.

The lactol **73** was acetylated in pyridine to furnish the keyintermediate **74** in 86% yields as a glycosyl donor (Scheme 9).

**Scheme 9.** Synthesis of 2-spirocyclopropyl furanose glycosyl donor

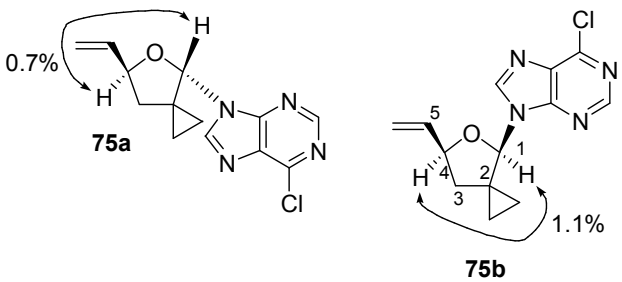



Reagents: i) $(COCl)_2$, DMSO, TEA, $CH_2Cl_2$; ii) *n*-BuLi, $Ph_3PCH_3I$, $PPh_3$, THF; iii) (a) $BH_3$/THF; (b) NaOH, $H_2O_2$, $H_2O$; iv) VinylMgBr, THF; v) PMBCl, DMF, NaH; vi) TBAF, THF; vii) DDQ, $CH_2Cl_2$, $H_2O$; ix) $Ac_2O$, pyridine.

The synthesis of adenine nucleoside was carried out by condensation of compound **74** with silylated 6-chloropurine using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst in dichloroethene (DCE) to give protected 6-chloropurine derivative **75a** (32%) and **75b** (33%), respectively. A complete nuclear Overhauser effect (NOE) study allowed an unambiguous determination of their respective stereochemistry (Figure 11). For

compound 75b, strong NOE (1.1%) of H−1′ ↔ H−4′, which showed 1′,4′−*cis* relationships, was observed. According to this result, the 4′−vinyl and 2′−purine base of compound 75b were located on the $\beta$ face. On the other hand, for 75a compound, weak NOE (0.7%), such as H−1′↔H−4′, was assigned to the 1′,4′−*trans* relationships.

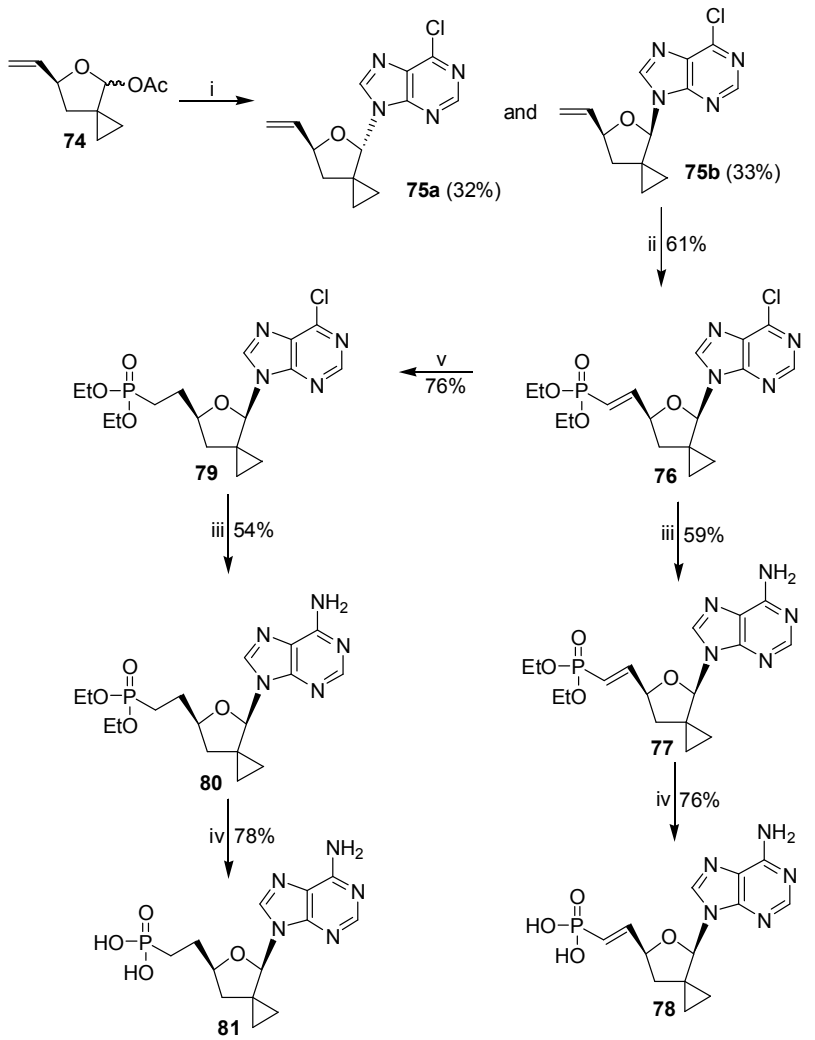
**Figure 11.** NOE differences between the proximal hydrogens of **75a** and **75b.**




Cross−metathesis[106] of compound 75b with diethylphosphonate using the 2nd generation Grubbs catalyst[107] gave vinylidene phosphonate nucleoside analogue 76 in a 61% yield. The chlorine group of purine analogue 76 was then converted to amine with methanolic ammonia at 64 ℃ to give acorresponding adenosine phosphonate derivative 77. Hydrolysis of diethyl phosphonate functional groups of compound 77 by treatment with bromo−trimethylsilane (TMSBr) in acetonitrile ($CH_3CN$) in the presence of 2,6−lutidine gave an adenosine phosphonic acid derivative 78.[108] The vinylidene phosphonate was saturated in transfer catalytic hydrogenation conditions to give ethyl phosphonate nucleoside

analogue 79. The adenine phosphonic acid analogue 81 was prepared through similar reaction conditions such as ammonolysis and hydrolysis described for the preparation of compound 78 (Scheme 10).

**Scheme 10.** Synthesis of 2'-spirocyclopropyl-5'-deoxyphosphonic acid adenine analogues.




Reagents: i) silylated 6-chloropurine, TMSOTf, DCE; ii) Vinyldiethylphosphonate, Grubbs cat.(II) $CH_2Cl_2$; iii) $NH_3$/MeOH; iv) TMSBr, 2,6-lutidine, $CH_3CN$. v) Pd/C, cyclohexene, MeOH.

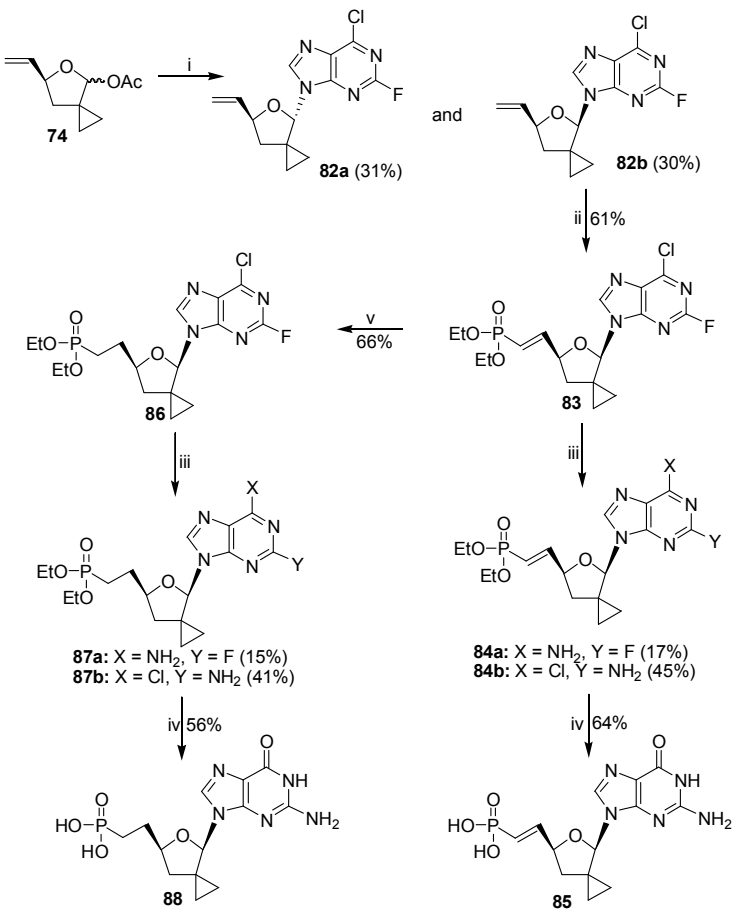
For the synthesis of guanine analogues, 2-fluoro-6-chloropurine[109] was condensed with glycosyl donor in similar conditions used for the condensation of 6-chloropurine. The Vorbruggen coupling[110] of acetate **74** with 2-fluoro-6-chloropurine gives analogue **82a** (31%) and **82b** (30%), respectively. Cross-metathesis of compound **82b** with diethylvinylphosphonate provided compound **83** in a 61% yield.

Bubbling ammonia into the compound **83** gave separable 2-fluoro-6-aminopurine analogue[111] **84a** (17%) and 2-amino-6-chloropurine analogue **84b** (45%), respectively. 2-Amino-6-chloropurine derivative **84b** was treated with TMSBr to provide phosphonic acid and sequentially treated sodium methoxide and 2-mercaptoethanol in methanol to give desired guanine vinylidene phosphonic acid **85** (Scheme 11).[112] The guanine phosphonic acid analogue **88** was synthesized from compound **83** via transfer catalytic hydrogenation, ammonolysis, and hydrolysis using similar conditions as described for the synthesis of adenine derivative **85**, respectively.

The antiviral activity of phosphonate nucleosides is mostly explained by their intracellular metabolism to their diphosphates followed by incorporation into the viral genome and chain termination.[113] MT-4 cells (1 × 105 cell/mL) were infected with HIV-1 (HTLV-$III_B$ strain) at a multiplicity of infection (MOI) of 0.02 and were cultured in the presence of various concentrations of the

test compounds. After a four-day incubation at 37℃, the number of viable cells was monitored by the 3-(4,5-di-methylthiazole-2-yl)-2,5-diphenyltetrazolium bromide method. The cytotoxicity of the compounds was evaluated in parallel with their antiviral activity, based on the viability of mock-infected cells.[114]

**Scheme 11.** Synthesis of 2'-spirocyclopropyl-5'-deoxyphosphonic acid guanine analogues




Reagents: i) Silylated 2-fluoro-6-chloropurine, TMSOTf, DCE; ii) vinyldiethylphosphonate, Grubbs cat.(II) $CH_2Cl_2$; iii) $NH_3$, DME, rt; iv) (a) TMSBr, 2,6-lutidine, $CH_3CN$; (b) NaOMe, $HSCH_2CH_2OH$, MeOH; v) Pd/C, cyclohexene, MeOH.

The synthesized compounds 78, 81, 85, and 88 were tested

against HIV-1. Especially, the adenine analogue **81** did show moderate antiviral activity against HIV-1 (Table 3), indicating that this virus might allow the sugar moiety for diphosphorylation or some affinity of its diphosphate toward viral polymerases. However, other 5′-deoxyphosphonicacid nucleoside analogues showed weak or lack of anti-HIV activity at concentrations up to 100 μM.

**Table 3.** Median effective ($EC_{50}$) and inhitory ($IC_{50}$) concentration of synthesized compounds **78**, **81**, **85** and **88**

| Compound No. | Anti-HIV-1 $EC_{50}$(μM) | Cytotoxicity $IC_{50}$(μM) |
|---|---|---|
| **78** | 21 | 90 |
| **81** | 7.9 | 80 |
| **85** | 54 | 98 |
| **88** | 43 | 98 |
| AZT | 0.002 | >100 |
| PMEA | 0.39 | >100 |

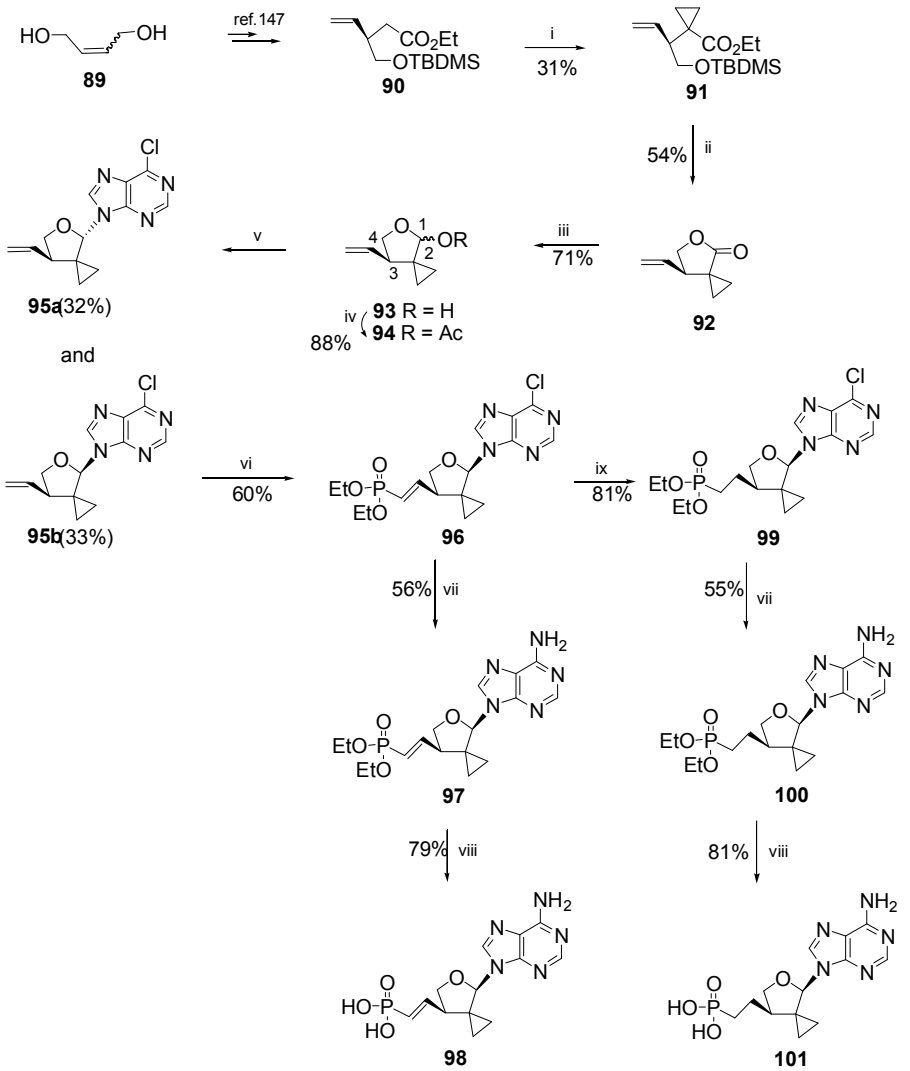
In summary, based on the potent anti-HIV activity of 2′-electropositive nucleosides and 5′-deoxyphosphonic acid nucleoside analogues, we have designed and successfully synthesized novel 2′-spirocyclopropyl-5′-deoxyphosphonic acid nucleoside analogues starting from diethylmalonate. The synthesized adenine analogue **81**

exhibited improvement in cell-based activity compared with 2′-modified guanine phosphonic acid analogues **85** and **88**. Since spirocyclopropanations of guanine nucleoside derivatives 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. As potent anti-hepatitis C virus (anti-HCV) agents, syntheses of (bis)S-acyl-2-thioethyl ((bis)SATE)-prodrug of compounds **78** and **81** are in progress in our laboratory.

As shown in Scheme 12, the target compounds were prepared from 1,4-dihydroxy-2-butene **89** through an acyclic synthesis route.[121] Cyclopropylation of ester **90** was effected through a enolate intermediate followed by alpha-alkylation using (2-chloroethyl)-dimethylsulfonium iodide and potassium tert-butoxide[129] to give a cyclopropanoid **91**. The lactone derivative **92** was prepared from **91** via desilylation and cyclization in a 54% yield. The lactone **92** was reduced using DIBALH in toluene at –78℃ to give lactol **93**, which was acetylated in pyridine to furnish the key intermediate **94** as a glycosyl donor. The synthesis of adenine nucleoside was carried out by condensation of compound **94** with silylated 6-chloropurine using TMSOTf as a catalyst in DCE to give protected 6-chloropurine derivative **95a** and **95b**, respectively. A complete NOE study allowed an unambiguous determination of their relative stereochemistry

(Figure 12).

**Scheme 12.** Synthesis of 2'-modified threosyl-4'-deoxyphosphonic acid adenine analogues.

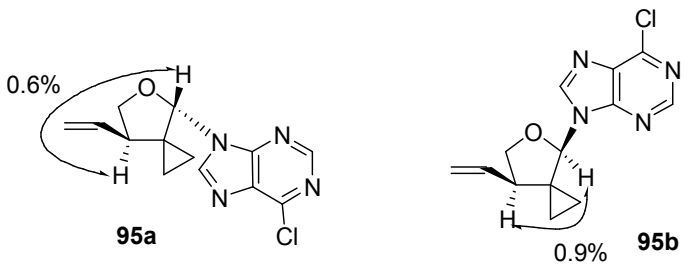



Reagents: i) $ClCH_2CH_2SMe_2I$, KI, *t*-BuOK, *t*-BuOH; ii) TBAF, THF; iii) DIBALH, toluene, -78 °C; iv) $Ac_2O$, pyridine; v) silylated 6-chloropurine, TMSOTf, DCE; vi) diethyl vinylphosphonate, Grubbs, cat. (II), $CH_2Cl_2$ vii) $NH_3$/MeOH; viii) TMSBr, 2,6-lutidine, $CH_3CN$; ix) Pd/C, cyclohexene, MeOH.

For compound **95b**, strong NOE (0.9%) of H−1′ ↔ CH−3′, which

showed 1′,3′−cis relationships, was observed. According to this result, 3′−vinyl and 1′−purine base of **95b** were located on the b face. On the other hand, for **95a** compound, weak NOE (0.6%), such as H−1′ ↔ CH−3′, were assigned to the 1′,3′−trans relationships.

**Figure 12.** NOE differences between the proximal hydrogens of **95a** and **95b**



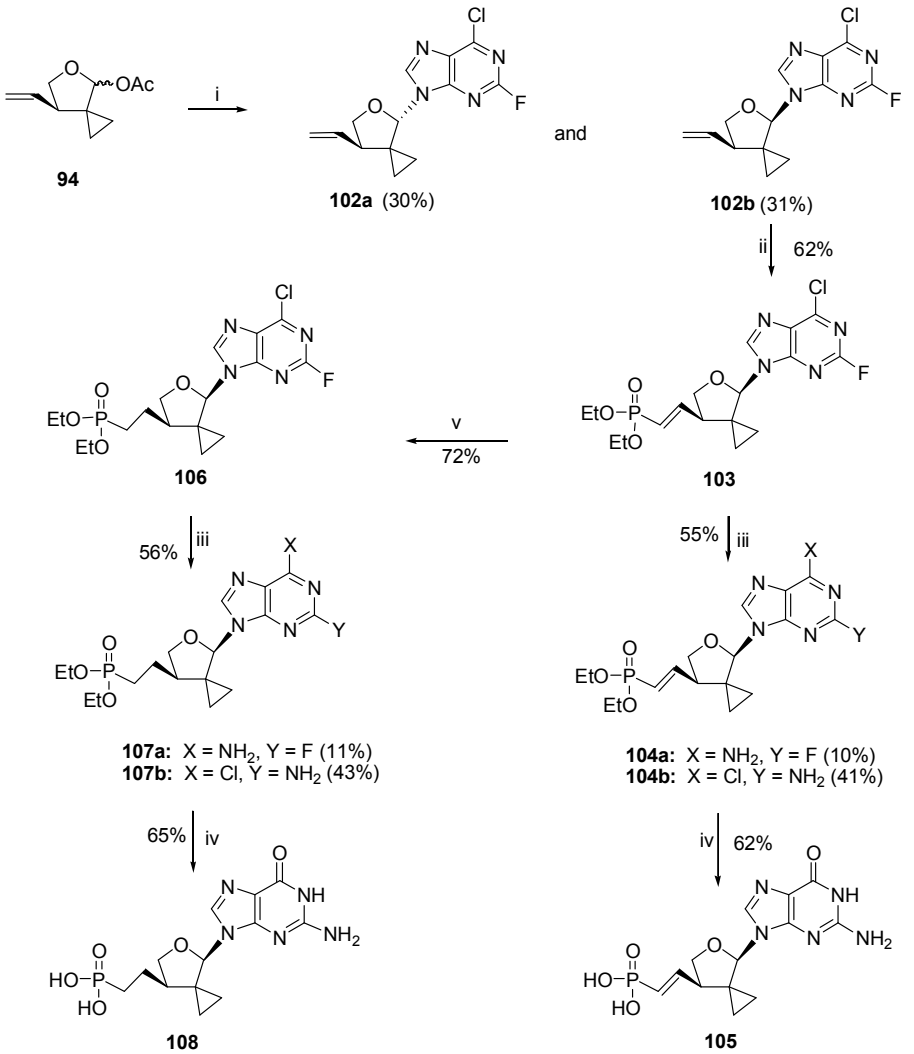

Cross−metathesis[106] of **95b** with diethyl vinylphosphonate using 2nd generation Grubbs catalyst[107] gave (E)−vinylidene phosphonate nucleoside analogue **96** in a 60% yield. The stereochemistry of the olefin was confirmed $^{1}$H NMR and $^{31}$P NMR spectroscopy. The coupling constants of the E and Z olefinic protons ($J_{\mathrm{Htrans-P}}$ = 22.5 Hz vs $J_{\mathrm{Hcis-P}}$ = 41.5 Hz) were readily characterized. The chlorine group of purine analogue **96** was then converted to amine with methanolic ammonia at 63 ℃ to give a corresponding adenosine phosphonate derivative **97**, which was hydrolyzed by treatment with bromo−trimethylsilane in $CH_3CN$ in the presence of 2,6−lutidine to give an adenosine phosphonic acid derivative **98**.[108] The vinylidene phosphonate **96** was saturated in transfer catalytic hydrogenation conditions to give ethyl phosphonate nucleoside analogue **99** in a 81%

yield. Adenine phosphonic acid analogue **101** was prepared through the similar reaction conditions such as ammonolysis and hydrolysis described for the preparation of **98**.

For the synthesis of guanine analogues, 2-fluoro-6-chloropurine[109] was condensed with glycosyl donor in the similar conditions used for the condensation of 6-chloropurine. Vorbruggen coupling[110] of the acetate **94** with 2-fluoro-6-chloropurine gave analogue **102a** (30%) and **102b** (31%), respectively. Cross-metathesis of **102b** and diethylvinylphosphonate gave **103** in a 62% yield. A complete NOE study allowed an unambiguous determination of their relative stereochemistry as described for **95a** and **95b**.

Bubbling ammonia into the compound **103** gave separable 2-fluoro-6-aminopurine **104a** (10%) and 2-amino-6-chloropurine **104b** (41%), respectively.[111] They are readily identified by UV spectral data. Fluorine acts as better leaving group than chlorine in nucleophilic aromatic substituteion. 2-Amino-6-chloropurine derivative **104b** was treated with TMSBr and 2,6-lutidine to provide phosphonic acid and sequentially which was treated with sodium methoxide and 2-mercaptoethanol in methanol to give desired guanine vinylidene phosphonic acid **105** in a 62% yield (Scheme 13).[112] The guanine phosphonate **108** was synthesized from **103** via transfer catalytic hydrogenation, ammonolysis and hydrolysis using the similar conditions as described for the synthesis of **105**.

**Scheme 13.** Synthesis of 2'-modified threosyl-4'-deoxyphosphonic acid guanine analogues.




Reagents: i) silylated 2-fluoro-6-chloropurine, TMSOTf, DCE; ii) diehtyl vinyl phosphonate, Grubbs cat. (II), CH2Cl2; iii) NH3, DME, rt; iv) (a) TMSBr, 2,6-lutidine, CH3CN (b) NaOMe, HSCH2CH2OH, MeOH; v) Pd/C, cyclohexene, MeOH.

The antiviral activity of phosphonate nucleoside is mostly explained by their intracellular metabolism to their diphosphates followed by incorporation into the viral genome and chain termination.[113] The synthesized compounds 98, 101, 105 and 108

were tested against HIV-1. However, none of them showed antiviral activity and cytotoxicity up to 100 $\mu$M (Table 4).

Table 4. The antiviral activities of synthesized compounds **98**, **101**, **105** and **108**

| Compound | HIV-1 | | cytotoxicity $IC_{50(\mu M)}$ | | |
|---|---|---|---|---|---|
| | $EC_{50(\mu M)}$ | $EC_{90(\mu M)}$ | PBM | CEM | Vero |
| **98** | 62.8 | 95 | >100 | >100 | >100 |
| **101** | 49.2 | 80 | >100 | >100 | >100 |
| **105** | 66 | 95 | >100 | >100 | >100 |
| **108** | 80 | 95 | >100 | >100 | >100 |
| PMEA | 5.0 | ND | >100 | 40.0 | >100 |
| AZT | 0.128 | ND | >100 | 12.6 | 50.0 |

This result indicates that the virus might not allow the sugar moiety for diphosphorylation or any affinity of its diphosphate toward viral polymerases. Anti-HIV activity was determined in human peripheral blood mononuclear (PBM) cells. Briefly, uninfected phytohemagglutinin-stimulated human PBMCs were infected with HIV-1 (strain LAV-1) (about 63,000 disintegrations of RT activity per minute per $10^7$ cells per 10 mL of medium) the drugs were then added to duplicate or triplicate cultures. Uninfected and untreated PBMCs were grown in parallel at equivalent cell concentrations as

controls. The cultures were maintained in a humidified 5% $CO_2$-95% air incubator at 37℃ for 6 days after infection, at which point all cultures were sampled for supernatant RT activity. The supernatant was clarified, and the viral particles were then pelleted at 40,000 rpm for 30 min by using a rotor (70.1 Ti; Bechman Instruments, Inc., Fullerton, Calif.) and suspended in virus-disrupting buffer. The RT assay was performed by a modification of the method of Spira et al.[130] in 96-well microdilution plates by using $(rA)_n \cdot (dT)_{12-18}$ as the template primer. The RT results were expressed in disintegrations per minute per milliliter of originally clarified supernatant.[131] The compounds were evaluated for their potential toxic effects on uninfected phytohemagglutinin-stimulated human PBMCs and also in CEM and Vero cells. PBMCs were obtained from whole blood of healthy HIV-1 and hepatitis B virus-seronegative volunteers and collected by single-step Ficoll-Hypaque discontinuous gradient centrifugation. The CEM cells were maintained in RPMI 1640 medium supplemented with 20% heat-inactivated fetal bovine serum, penicillin (100 U/mL), and streptomycin (100 μg/mL). The PBMCs and CEM cells were cultured with and without drug for 6 days, at which time portion were counted for cell proliferation and viability by the trypan blue exclusion method.[132] Only the effects on cell growth are reported, since these correlated well with cell viability. The toxicity of the compounds in Vero cells was assessed after 3 days of treatment with

a hemacytometer.[133]

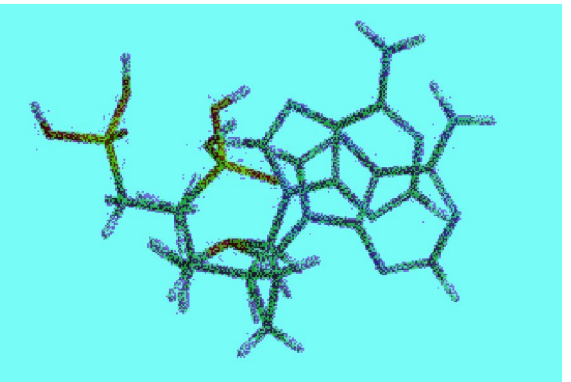
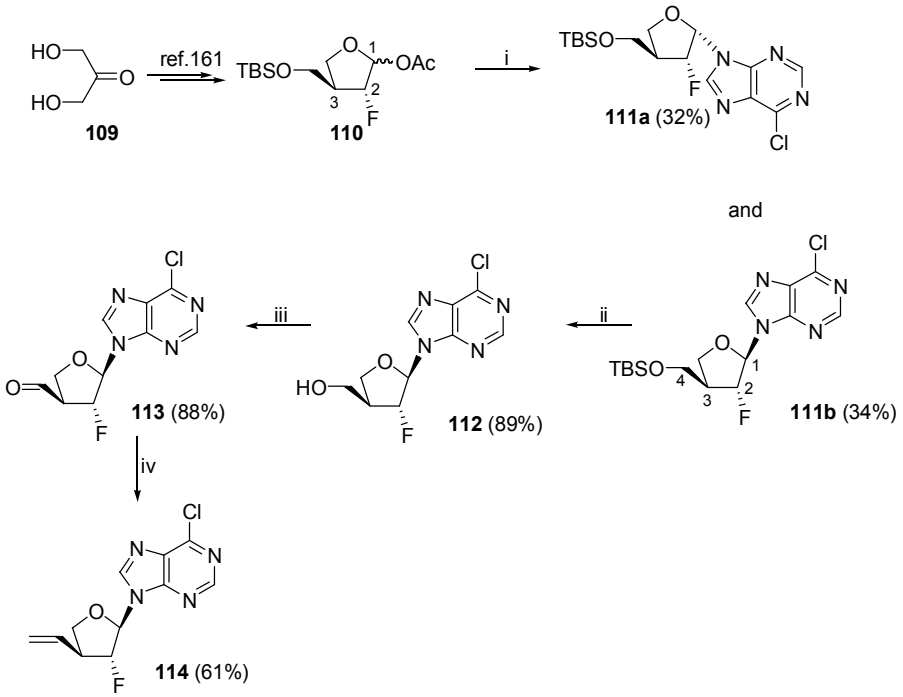


**Figure 13.** Superimpose of PMDTA **1** and **101**

Based on the potent anti-HIV activity of 6′-electropositive nucleosides as well as threosyl phosphonic acid nucleoside analogues, we have designed and successfully synthesized novel 2′-spirocyclopropanoid 4′-deoxyphosphonic acid nucleoside analogues starting from 1,4-dihydroxy-2-butene. None of the synthesized nucleosides exhibits significant antiviral activity up to 100 $\mu$M. As shown in Figure 13, superimposed modeling of PMDTA **1** and **101** do not shows any similarity with two parts such as adenine base and phosphonic acid moiety. Furthermore, the sugar puckering of compound **101** is not positioned closer to that of adenine analogue PMDTA **1**. Energy minimization was optimized with the framework of the density functional theory (DFT), with Spartan modeling software. The B3LYP functional with 6-31G* basis set was employed.

**Scheme 14.** Synthesis of threosyl-2'-fluoro-3'-vinylidene 6-chloropurine analogue

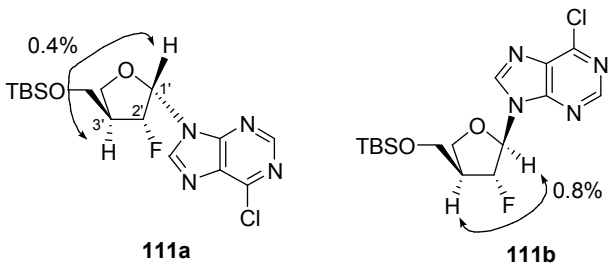



Reagents: i) Silylated 6-chloropurine, TMSOTf, DCE; ii) TBAF, THF; iii) Dess-Martin, $CH_2Cl_2$; iv) *n*-BuLi, $Ph_3PCH_3I$, $PPh_3$, THF.

As depicted in Scheme 14, target compounds were prepared from the fluorinated glycosyl donor **110**, which was readily prepared from 1,3-dihydroxyacetone **109**, as previously described.[134] The synthesis of adenine nucleoside was carried out by Vorbrüggen condensation[110] of compound **110** with silylated 6-chloropurine using TMSOTf as a catalyst in DCE to give the protected 6-chloropurine derivatives **111a** and **111b**, respectively. Strong NOE (0.8%) of H-1′ ↔ CH-3′, which showed a 1′,3′-cis relationship, was observed. According to this result, the 3′-hydroxymethyl group and the 1′-purine base of **111b** were located

on the $\beta$ face. On the other hand, for **111a** compound, weak NOE (0.4%) of H−1′ ↔ CH−3′, demonstrated a 1′,3′−trans relationship (Figure 14).

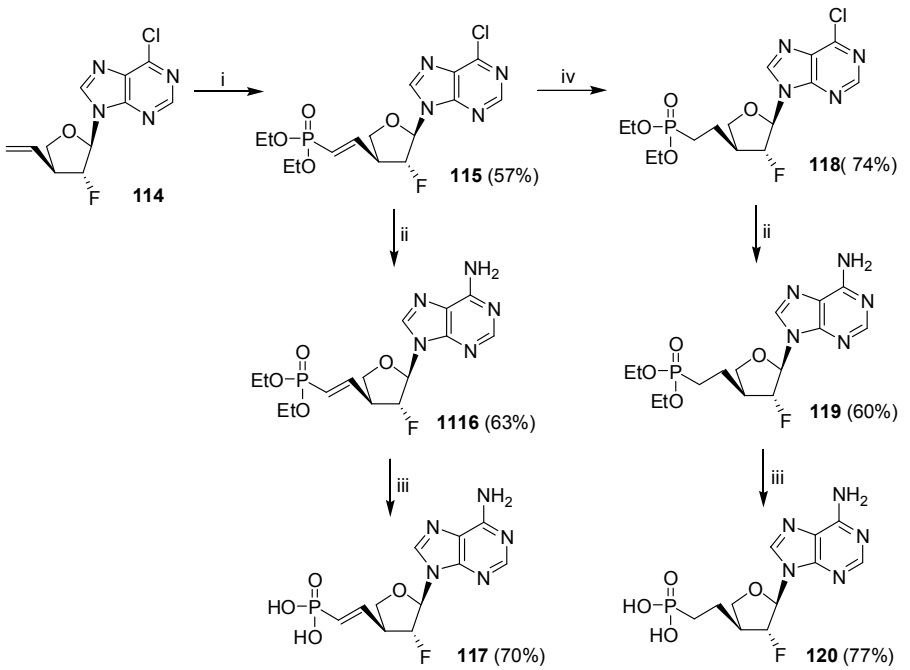
**Figure 14.** NOE differences between the proximal hydrogens of **111a** and **111b**




For the homologation, removal of the silyl protecting group of **111b** using tetra n−butylammonium fluoride (TBAF) gave the primary alcohol **112**. Dess−Martin oxidation[135] of the alcohol of **112** gave the aldehyde **113**, which was subjected to Wittig olefination[125] to give compound **114** without loss of the 3′−stereochemistry. Cross−metathesis[106] of **114** with vinyl diethylphosphonate using a 2nd generation Grubbs catalyst[107] gave the vinylidene phosphonate nucleoside analogue **115** in 57% yield. The chlorine group of the purine analogue **115** was then converted to amine with methanolic ammonia at 62℃ to give the corresponding adenosine phosphonate derivative **116** at in 63% yield. Hydrolysis of the diethyl phosphonate functional groups of **116** by treatment with bromotrimethylsilane in $CH_3CN$ in the presence of 2,6−lutidine then gave the adenosine phosphonic acid derivative **117**.[108] When the vinylidene phosphonate

was saturated under transfer catalytic hydrogenation conditions[106] it produced the ethyl phosphonate nucleoside analogue **118** in 74% yield.

**Scheme 15.** Synthesis of threosyl-2'-fluoro-5'-deoxyphosphonic acid adenine analogues

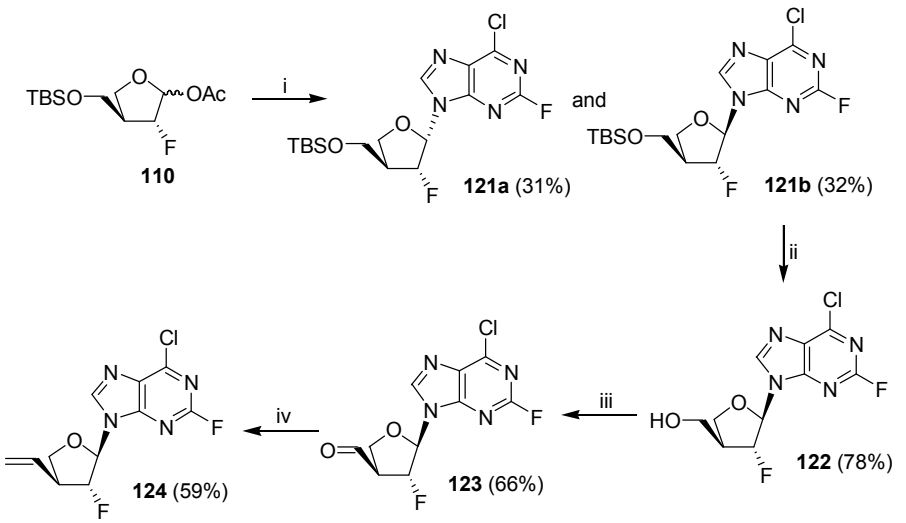



Reagents: i) Vinyldiethylphosphonate, Grubbs cat.(II) $CH_2Cl_2$; vi) $NH_3$, MeOH, 62 °C; iii) TMSBr, 2,6-lutidine, $CH_3CN$; iv) Pd/C, cyclohexene, MeOH.

The adenine phosphonic acid analogue **120** was prepared using conditions similar to the ammonolysis and hydrolysis described to produce **117** (Scheme 15). The guanine analogues, 2-fluoro-6-chloropurine[109] was condensed with the glycosyl donor **110** using conditions similar to those used for the preparation of **111a** and **111b** to give the analogues **121a** (31%) and **121b** (32%) from 6-chloropurine (Scheme 16). A complete NOE study allowed the unambiguous determination of the relative stereochemistries of

purine analogues as described for **111a** and **111b**. Homologation was performed using reactions similar to those used to produce **114**, such as desilylation, Dess−Martin oxidation and Wittig olefination. Cross−metathesis of **124** with diethylvinylphosphonate provided **125** in 60% yield.

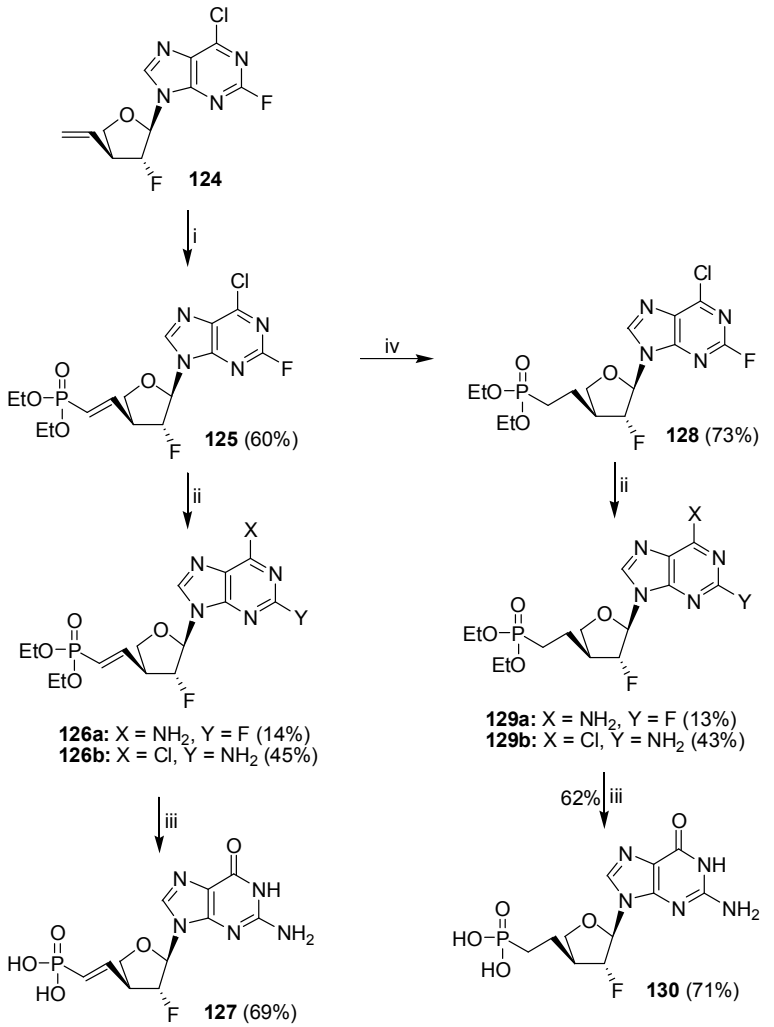
**Scheme 16.** Synthesis of threosyl-2'-fluoro-3'-vinylidene 2-fluoro-6-chloropurine analogue




Reagents: i) Silylated 2-fluoro-6-chloropurine, TMSOTf, DCE; ii) TBAF, THF; iii) Dess-Martin, $CH_2Cl_2$; iv) *n*-BuLi, $Ph_3PCH_3I$, $PPh_3$, THF.

Bubbling ammonia into the compound **125** gave separable 2−fluoro−6−aminopurine[111] **126a** (14%) and 2−amino−6−chloropurine **126b** (45%) analogues, respectively. The 2−amino−6−chloropurine derivative **126b** was treated with TMSBr to provide phosphonic acid and sequentially treated with sodium methoxide and 2−mercaptoethanol in methanol to give the desired guanine phosphonic acid **127** (Scheme 17).[112]

**Scheme 17.** Synthesis of threosyl-2'-fluoro-5'-deoxyphosphonic acid guanine analogues

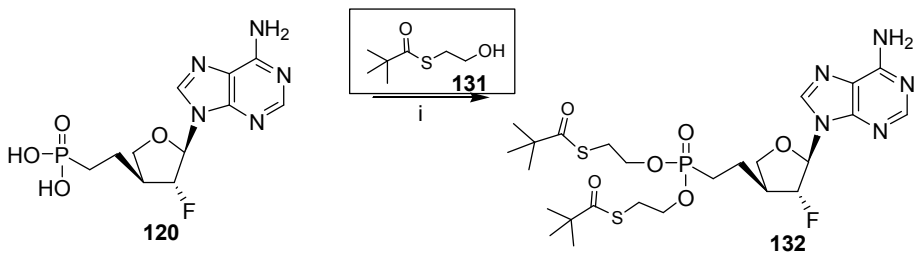



Reagents: i) vinyldiethylphosphonate, Grubbs cat.(II) $CH_2Cl_2$; ii) $NH_3$, DME, rt; iii) (a) TMSBr, 2,6-lutidine, $CH_3CN$; (b) NaOMe, $HSCH_2CH_2OH$, MeOH; iv) Pd/C, cyclohexene, MeOH.

Furthermore, the guanine phosphonic acid analogue 130 was synthesized from 125 via transfer catalytic hydrogenation, ammonolysis, and hydrolysis using conditions similar to those described for the synthesis of the adenine 130, line derivative 120. To synthesize the thioester-protected analogue, compound 120 was

reacted with thioester **131**[136] in the presence of 1-(2-mesitylenesulfonyl)-3-nitro-1H-1,2,4-triazole (MSNT)[137] to provide the bis(SATE) derivative as a target compound **132** (Scheme 18).

**Scheme 18.** Synthesis of target bis(SATE) prodrug of adenine analogue **132**




Reagents: i) thioester, **131**, 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole, pyridine.

**Antiviral Activity.** The antiviral activities of phosphonate nucleosides are explained by their intracellular metabolism to diphosphates, subsequent incorporation into the viral genome, and chain termination.[113] MT-4 cells (1 × 105 cell/ mL) were infected with HIV-1 (HTLV-$III_B$ strain) at a multiplicity of infection (MOI) of 0.02, and then cultured in the presence of various concentrations of the test compounds. After a 4-day incubation at 37℃, numbers of viable cells were determined using the 3-(4,5-di-methylthiazole-2-yl)-2,5-diphenyltetrazolium bromide method. The cytotoxicities of the compounds were evaluated in parallel with their antiviral

activities, by determining the viabilities of mockinfected cells.[114] Compounds **117**, **120**, **127**, **130** and **132** were tested against HIV-1, and the adenine analogue **120** showed moderate antiviral activity (Table 5). However, other three 5′-deoxyphosphonic acid nucleoside analogues showed weak or no anti-HIV activity at concentrations up to 100 μM.

**Table 5.** Median effective ($EC_{50}$) and inhitory ($IC_{50}$) concentration of synthesized nucleoside analogues **117**, **120**, **127**, **130** and **132**

| Compound No. | Anti-HIV-1 $EC_{50}$ (μM) | Cytotoxicity $CC_{50}$ (μM) |
|---|---|---|
| **117** | 34.2 | 95 |
| **120** | 8.8 | 80 |
| **127** | 66.8 | 98 |
| **130** | 47.1 | 98 |
| **132** | 2.2 | 80 |
| AZT | 0.003 | >100 |
| PMEA | >10 | >10 |
| Bis(SATE)PMEA | 0.81 | >10 |

In summary, based on the potent anti-HIV activities of 2′-electropositive nucleosides and 5′-deoxyphosphonic acid nucleoside analogues, we designed and successfully synthesized novel 2′-

fluoro-5′-deoxyphosphonic acid nucleoside analogues starting from 1,3-dihydroxy acetone. The synthesized bis(SATE) adenine analogue 132 showed significant activity in a cell-based assay than the 2′-modified guanine phosphonic acid analogues 117, 127 and 130. Since 2′-fluorinated guanine nucleoside derivatives are not perfect mimics of the ribofuranose moiety, mechanisms of virus inhibition, that is, phosphorylation or the inhibition of RNA synthesis, might be impaired for these compounds. For the discovery of improved antiviral nucleoside derivatives, bis(SATE) analogue 132 was synthesized and assayed for anti-HIV activity using an in vitro assay system, It showed much improved anti-HIV activity than adenine nucleoside phosphonic acid 120 (Table 5).

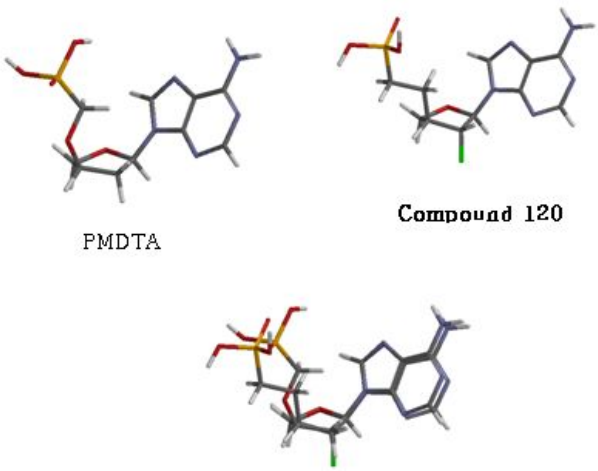
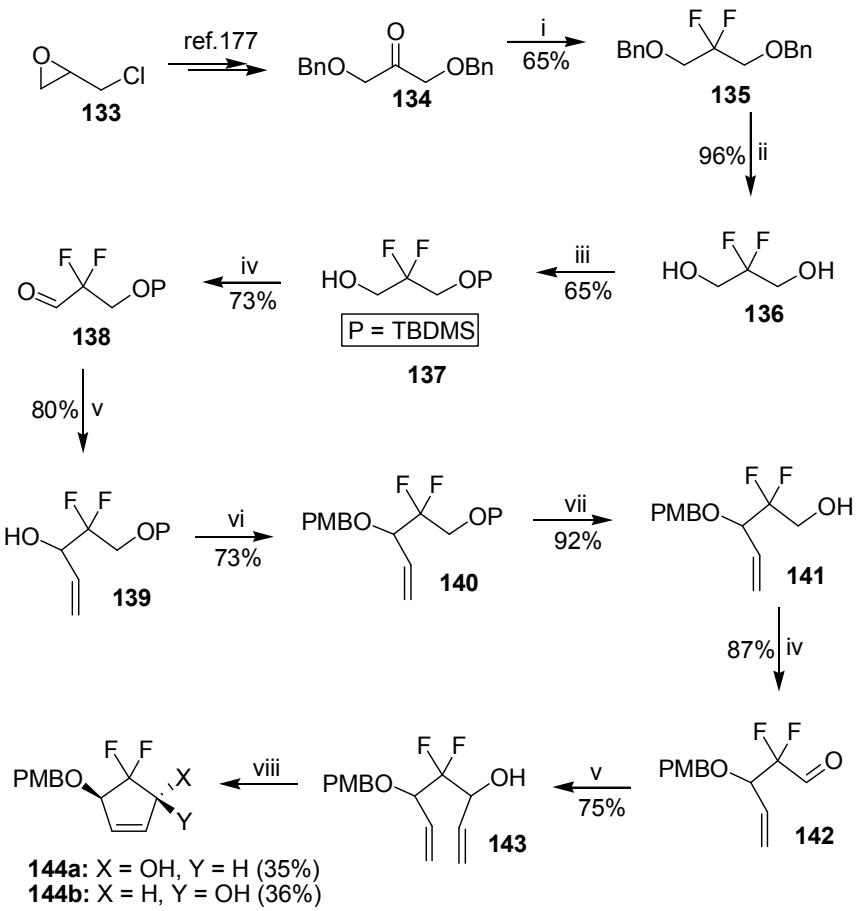



**Figure 15.** Superimpose of PMDTA and 120

As shown in the superimposition model of PMDTA 1 and the corresponding analogue 120 (Figure 15), discrepancies of phosphonic

acid regions are more pronounced than those of the base moiety. Note the furanose puckering of PMDTA 1 is closer to that of the adenine analogue 120.[122]

**Scheme 19.** Synthesis of difluoro cyclopentene ntermediate



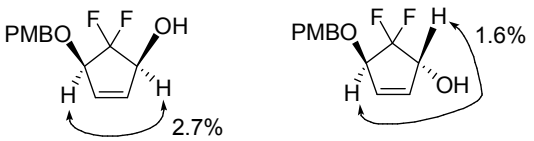

Reagents: i) DAST, $CH_2Cl_2$; ii) $H_2$, Pd/C, MeOH; iii) TBDMSCl, imidazole, DMF; iv) $(COCl)_2$, DMSO, TEA; v) vinylMgBr, THF; vi) PMBCl, NaH, DMF; vii) TBAF, THF; viii) Grubbs (II), $CH_2Cl_2$.

As depicted in Scheme 19, the target compounds were prepared from ketone derivative 134, which was synthesized from the

commercially available epichlorohydrin **133** *via* known procedure.[138] The reaction of **134** with DAST led to the key *gem*-difluoro compound **135** in 65% yield. Catalytic hydrogenolysis and selective monosilylation of corresponding diol **136** gave alcohol derivative **137**. Swern oxidation[124] of **137** provided an aldehyde **138**, which was subjected to the carbonyl addition reaction by vinylmagensium bromide[105] to furnish the alcohol **139**, which was successfully protected using *p*-methoxybenzyl chloride (PMBCl)[139] to provide compound **140**. Removal of the silyl protecting group of **140** using *t*-butylammonium fluoride (TBAF) gave the primary alcohol **141**, which was oxidized to the aldehyde **142** using same oxidation conditions as described for **138**. The aldehyde **142** was subjected to the second nucleophilic Grignard conditions with vinyl magnesium bromide to give divinyl **143**, which was subjected to ring-closing metathesis (RCM) conditions using 2$^{nd}$ generation Grubbs catalyst ($C_{46}H_{65}Cl_2N_2PRu$)[140] to provide 5′,5′-difluorocyclopentenol **144a** (35%) and **144b** (36%), which were readily separated by silica gel column chromatography.

The nuclear Overhauser enhancement (NOE) experiments with cyclopentenols **144a** and **144b** 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 **144b** [$C_4$-C$H$-(1.6%)] versus that of compound **144a** [$C_4$-C$H$-(2.7%)] (Figure 16).

**Figure 16.** NOE differences between the proximal hydrogens of **144a** and **144b**

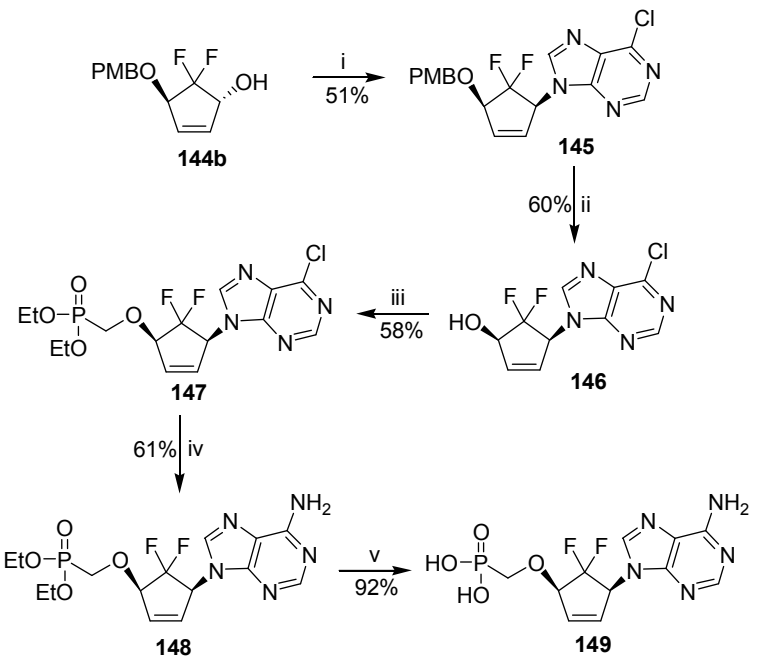



**144a** **144b**

To synthesize the desired 5′-norcarbocyclic adenosine nucleoside analogues, the protected cyclopentenol **144b** was treated with 6-chloropurine under Mitsunobu conditions[141] (DEAD and $PPh_3$). The appropriate choice of solvent system, temperature and procedure are essential for the regioselectivity and for the yield. In purine synthesis, a mixture of dioxane and DMF instead of THF were used as the solvent for the coupling of the cyclopentenol **144b** with 6-chloropurine. 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 **144b**, triphenylphosphine and the 6-chloropurine in anhydrous cosolvent (dioxane-DMF) gave a yellow solution, which was stirred for 2.0 h at −30℃ and further stirred overnight at rt to give the protected 6-chloropurine analogue **145** as an only $N^6$-regioisomer [UV (MeOH) $\lambda_{max}$ 263.5 nm].[142] The PMB protection group was removed with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)[143] to produce the 5′-nornucleoside analogue **146**, which was treated with diethyl phosphonomethyl triflate[144] using lithium *t*-butoxide to yield the

nucleoside phosphonate analogue **147** (Scheme 20). The chlorine group of **147** was then converted to amine with methanolic ammonia at 65℃ to give the corresponding adenine phosphonate derivative **148**. Hydrolysis of **148** by treatment with bromotrimethylsilane in $CH_3CN$ in the presence of 2,6-lutidine gave an adenine phosphonic acid derivative **149** (Scheme 20).[108]

**Scheme 20.** Synthesis of 6',6'-difluoro cyclopentenyl adenine phosphonic acid **149**

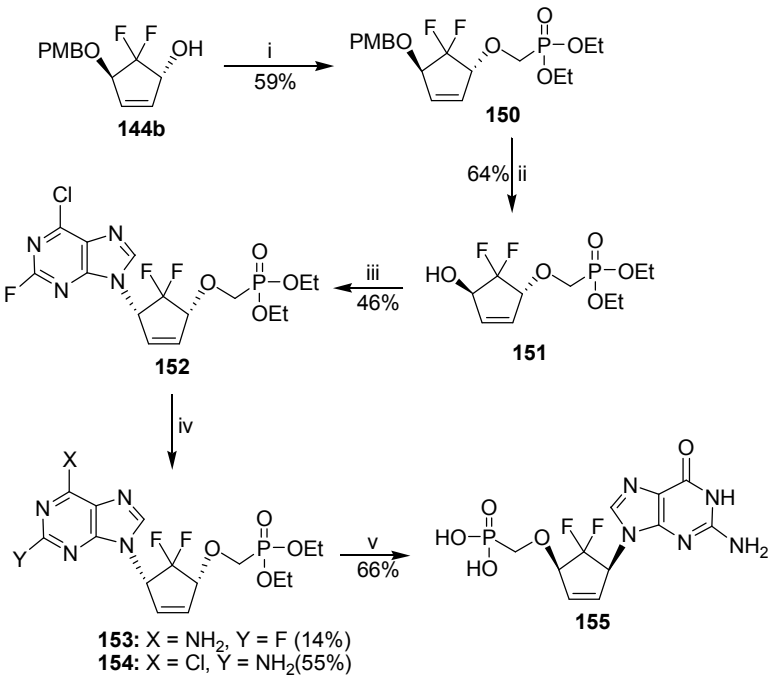



Reagents: i) 6-chloropurine, DEAD, $PPh_3$, 1,4-dioxane/DMF (v:v); ii) DDQ, $CH_2Cl_2/H_2O$ (10:1); iii) $(EtO)_2POCH_2OTf$, LiO-*t*-Bu, THF; iv) $NH_3$/MeOH, 65 $^oC$, 12 h; v) TMSBr, 2,6-lutidine, $CH_3CN$, 12 h.

The cyclopentenol intermediate **144b** was also used for the synthesis of 2,6-disubstituted purine analogues such as guanine derivative **155**. Regioselective coupling of the enol **144b** with 2-

fluoro-6-chloropurine[109] under the similar conditions for 6-chloropurine gives analogue **152**. Bubbling ammonia into the compound **152** gave separable 2-fluoro-6-aminopurine[110] analogue **153** (14%) and 2-amino-6-chloropurine analogue **154** (55%).

**Scheme 21.** Synthesis of 6',6'-difluoro cyclopentenyl guanine phosphonic acid **155**

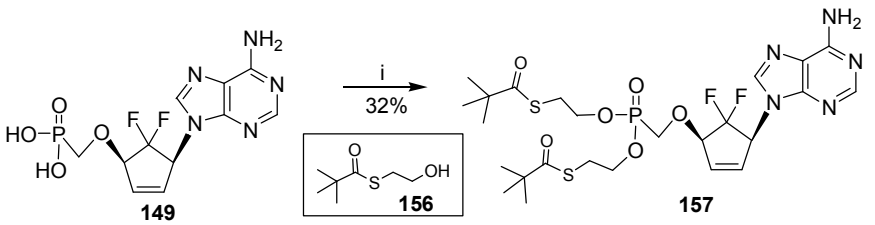



Reagents: i) $(EtO)_2POCH_2OTf$, LiO-*t*-Bu, THF; ii) DDQ, $CH_2Cl_2/H_2O$ (10:1); iii) 2-fluoro-6-chloropurine, DEAD, $PPh_3$, 1,4-dioxane/DMF (v:v); iv) $NH_3$/DME, rt; v) (a) TMSBr, 2,6-lutidine, $CH_3CN$; (b) NaOMe, $HSCH_2CH_2OH$, MeOH.

2-Amino-6-chloropurine derivative **154** was treated with TMSBr to give phosphonic acid and sequentially treated with sodium methoxide and 2-mercaptoethanol in methanol to give desired guanine phosphonic acid **155** (Scheme 21).[112] To synthesize the thioester prodrug of adenine analogue, derivative **149** was reacted

with thioester 156[136] in the presence of 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT)[137] to provide the bis(SATE) derivative as a target compound 157 (Scheme 22).

**Scheme 22.** Synthesis of target bis(SATE) prodrug of adenine analogue **157**




Reagents: i) thioester, **156**, 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole, pyridine.

The synthesized nucleoside phosphonate, phosphonic acid and thioester 148, 149, 154, 155 and 157 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.[145] As shown in Table 6, adenine nucleoside phosphonic ester 157 exhibits significant anti-HIV activity. However, nucleoside analogues 148, 149, 154, and 155 showed weak anti-HIV activity or cytotoxicity at concentrations up to 100 $\mu$M.

Table 6. Median effective ($EC_{50}$) and inhibitory ($CC_{50}$) concentration of synthesized nucleoside analogues in MT-4 cells

| Compound No. | Anti-HIV-1 $EC_{50}$ ($\mu$M) | Cytotoxicity $CC_{50}$ ($\mu$M) |
|---|---|---|
| 148 | 87.8 | 98 |

| | | |
|---|---|---|
| **149** | 19 | 90 |
| **154** | 90 | >100 |
| **155** | 32 | 90 |
| **157** | 10.8 | 90 |
| **d4T** | 1.3 | 98 |

In summary, based on the potent anti-HIV activity of 6′-electropositive nucleosides and 5′-norcarbocyclic nucleoside analogues, we have designed and successfully synthesized novel 6′,6′-difluoro-5′-norcarbocyclic nucleoside analogues starting from epichlorohydrin **133**. Although the adenine 5′-nornucleoside analogue **158** inhibits in vitro anti-HIV activity comparable to that of d4T, the synthesized carbocyclic version **149** shows weak anti-HIV activity. 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. Difluorination of 6′-position is another possible reason for the apparent lack of activity. Figure 17 shows the superposition of the calculated low energy conformers of **158** and **149**, highlighting the two difference parts such as purine bases and phosphonic acid functional moieties.

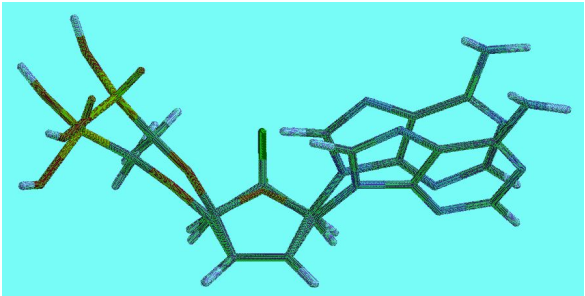


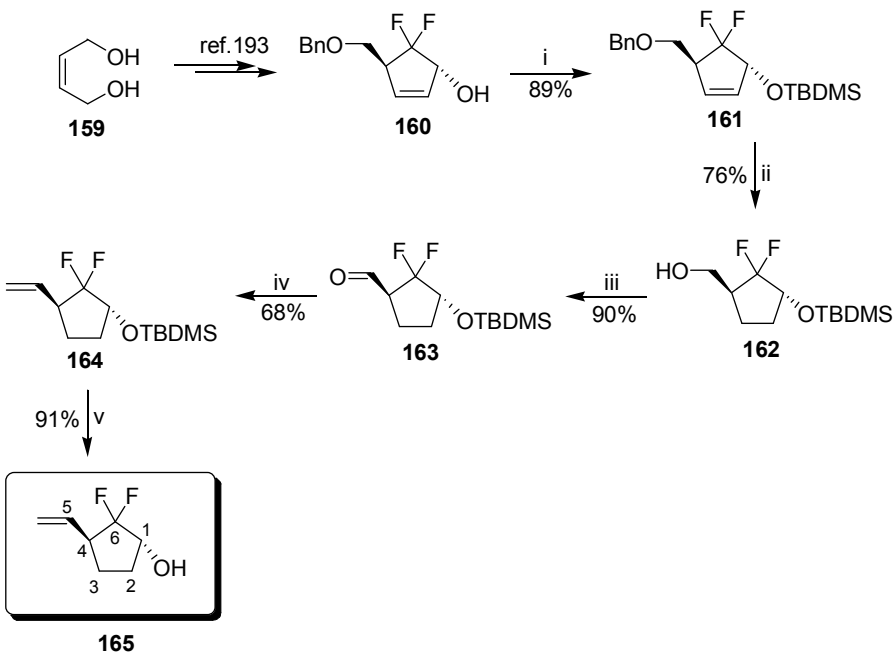
**Figure 17.** Superimposed **158** and **149**. The lowest energy conformation for each molecules was calculated with the modeling package Spartan 02' and energy minimization with semi-empirical force field (PM3).

The synthesized nucleoside prodrug 157 exhibited encouraging improvement in cell-based activity compared with phosphonic acid 149. A significant step forward in terms of activity could then be made with the introduction of SATE protecting group as a prodrug scaffold.

As shown in Scheme 23, the target compounds were prepared from 1,4-dihydroxy-2-butene through a cyclopentenol intermediate 160.[146] The cyclopentanol 162 was prepared *via* simultaneous catalytic hydrogenation of olefin and hydrogenolysis of benzyl protecting group after silylation of allylic alcohol from 160. Swern oxidation[124] of alcohol 162 gave an aldehyde 163, which was subjected to Wittig reaction[125] to give compound 164. Removal of the silyl protecting group of 164 using tetra *n*-butylammonium fluoride (TBAF) gave the secondary alcohol 165. To synthesize the desired 6′-difluorinated carbocyclic adenosine nucleoside analogues, the

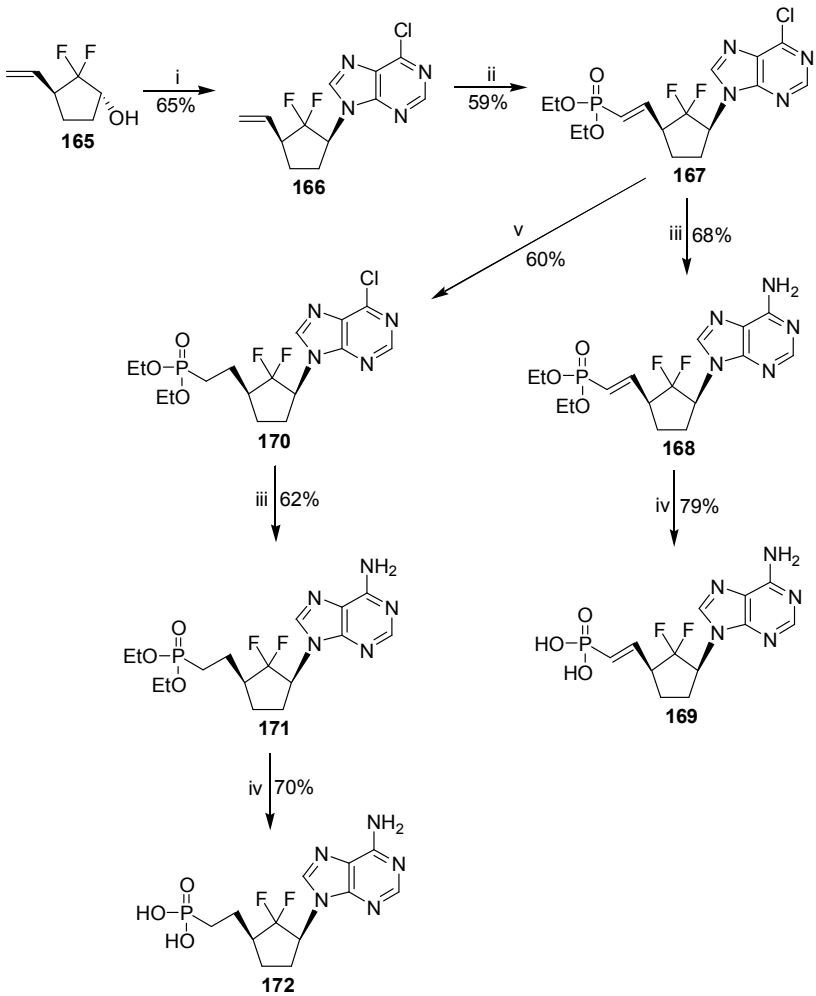
protected cyclopentanol 165 was treated with 6-chloropurine under Mitsunobu conditions[147] (DIAD and $PPh_3$). Slow addition of diisopropyl azodicarboxylate (DIAD) to a mixture of cyclopentanol 165, triphenylphosphine and the 6-chloropurine in anhydrous solvent (THF) gave a yellow solution, which was stirred for 30 min at 0℃ and further stirred overnight at rt to give the protected 6-chloropurine analogue 166 as an only $N^9$-regioisomer [UV (MeOH) $\lambda_{max}$ 264.0 nm].[142]

**Scheme 23.** Synthesis of difluorinated cyclopentanol intermediate **165**




Reagents: i) TBDMSCl, imidazole, $CH_2Cl_2$; ii) Pd/C, $H_2$, hexane; iii) DMSO, $(COCl)_2$, TEA, $CH_2Cl_2$; iv) *n*-BuLi, $Ph_3PCH_3I$, $PPh_3$, THF; v) TBAF, THF.

**Scheme 24.** Synthesis of 6',6'-difluorinated carbocyclic-5'-deoxyphosphonic acid adenine analogues




Reagents: i) DIAD, $PPh_3$, 6-chloropurine, THF; ii) vinyldiethylphosphonate, Grubbs cat.(II) $CH_2Cl_2$; iii) $NH_3$/MeOH; iv) TMSBr, 2,6-lutidine, $CH_3CN$; v) Pd/C, cyclohexene, MeOH.

Cross-metathesis[106] of 166 with diethyl vinylphosphonate using the 2nd generation Grubbs catalyst[107] gave vinylidene phosphonate nucleoside analogue 13. The chlorine group of purine analogue 167 was then converted to amine with methanolic ammonia at 62℃ to give a corresponding adenosine phosphonate derivative 168. Hydrolysis of

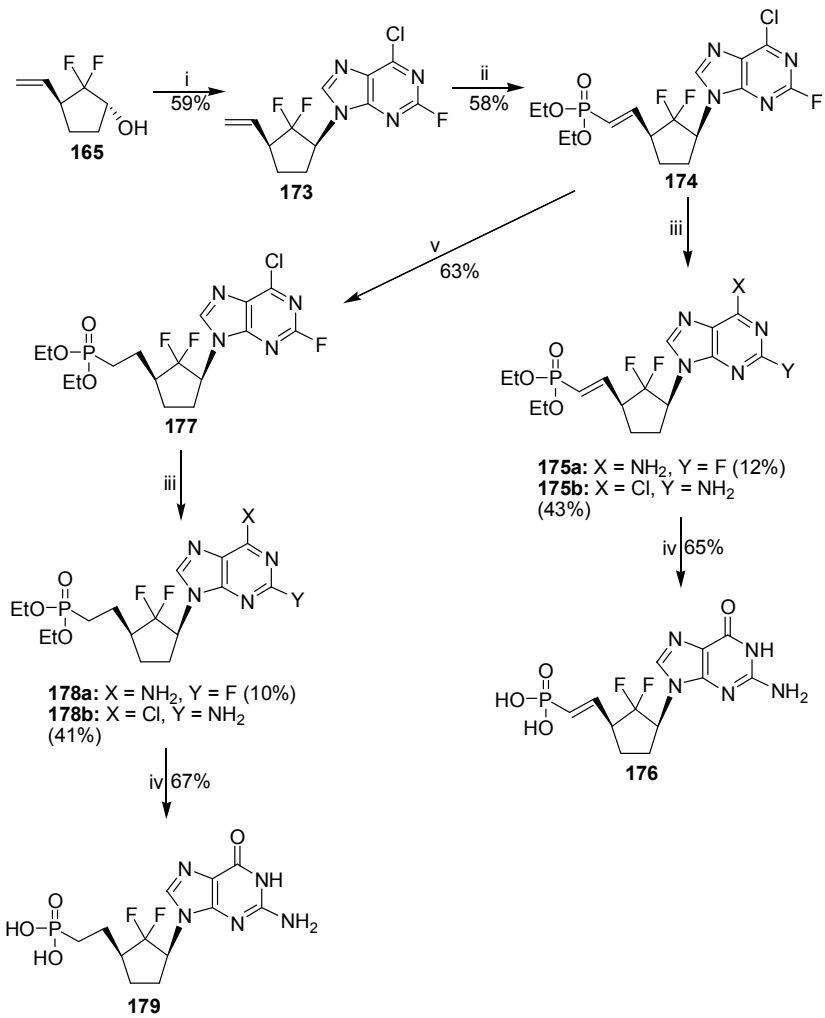
the diethyl phosphonate functional groups of **168** by treatment with bromotrimethylsilane in $CH_3CN$ in the presence of 2,6-lutidine gave a desired adenosine phosphonic acid derivative **169**.[108] The vinylidene phosphonate of **169** was then saturated under transfer catalytic hydrogenation conditions to give ethyl phosphonate nucleoside analogue **170** in a 60% yield. The adenine phosphonic acid analogue **172** was prepared using similar conditions, that is, with respect to ammonolysis and hydrolysis, as those described for the preparation of **169**. (Scheme 24)

For the synthesis of guanine analogues, 2-fluoro-6-chloropurine[109] was condensed with glycosyl donor using conditions similar to those used for the condensation of 6-chloropurine. Mitsunobu coupling of the alcohol **165** with 2-fluoro-6-chloropurine gives analogue **173**, and cross-metathesis of **173** and diethylvinyl phosphonate gave **174** at a yield of 58%.

Bubbling ammonia into the solution of **174** gave separable 2-fluoro-6-aminopurine[111] analogue **175a** (12%) and 2-amino-6-chloropurine analogue **175b** (43%), confirming and fluorine acts as a better leaving group than chlorine during nucleophilic aromatic substitution. Phosphonate **175b** was treated with TMSBr to provide phosphonic acid and this was treated with sodium methoxide and 2-mercaptoethanol in methanol to give the desired guanine vinylidene phosphonic acid **176**, (Scheme 25).[112] Guanine ethyl phosphonate **179**

was synthesized from 174 *via* transfer catalytic hydrogenation, ammonolysis and hydrolysis using conditions similar to those described for the synthesis of 172.

**Scheme 25.** Synthesis of 6',6'-difluorinated carbocyclic-5'-deoxyphosphonic acid guanine analogues




Reagents: i) DIAD, $PPh_3$, 2-fluoro-6-chloropurine, THF; ii) vinyldiethylphosphonate, Grubbs cat.(II) $CH_2Cl_2$; iii) $NH_3$, DME, rt; iv) (a) TMSBr, 2,6-lutidine, $CH_3CN$; (b) NaOMe, $HSCH_2CH_2OH$, MeOH; v) Pd/C, cyclohexene, MeOH.

Table 7. The antiviral activities of synthesized compounds **169**, **172**, **176** and **179**

| Compound | HIV-1 | | cytotoxicity $IC_{50(\mu M)}$ | | |
|---|---|---|---|---|---|
| | $EC_{50(\mu M)}$ | $EC_{90(\mu M)}$ | PBM | CEM | Vero |
| **169** | 55.6 | 95 | >100 | >100 | >100 |
| **172** | 46.2 | 90 | >100 | >100 | >100 |
| **176** | 62 | 95 | >100 | >100 | >100 |
| **179** | 68 | 95 | >100 | >100 | >100 |
| PMEA | 4.8 | ND | >100 | 35.8 | >100 |
| AZT | 0.115 | ND | >100 | 12.3 | 45.5 |

The antiviral activity of phosphonate nucleoside are substantially explained by their intracellular metabolism to diphosphates and subsequent incorporation into the viral genome and chain termination.[113] The synthesized compounds **169**, **172**, **176** and **179** were tested against HIV-1. However, none of them showed any significant antiviral activity against HIV-1 nor cytotoxicity up to 100 μM (Table 7), suggesting that might not allow the sugar-like moiety for diphosphorylation or some affinity of its diphosphate toward viral polymerases. Anti-HIV activity was investigated in human peripheral blood mononuclear (PBM) cells infected with HIV-1 strain LAI. PBM cells ($1x10^5$ cell/mL) were infected with HIV-1 at a multiplicity of

infection (MOI) of 0.02 and cultured in the presence of various concentrations of the test compounds. After 4 days of incubation at 37℃, numbers of viable cells were determined using an MTT (3-(4,5-di-methylthiazole-2-yl)-2,5-diphenyltetrazolium bromide) assay. Compound cytotoxicities were evaluated in parallel with their antiviral activities, which were assessed by examine the viabilities of mock-infected cells.[114]

Based on the potent anti-HIV activity of 6′-fluorinated carbocyclic nucleoside and those of phosphonic acid nucleoside analogues, we designed and successfully synthesized novel 6′,6′-difluorinated 5′-deoxycarbocyclic phosphonic acid nucleosides from 1,4-dihydroxy-2-butene. However, none of the compounds synthesized showed any significant antiviral activity against HIV-1. It is hoped that information obtained during the present study will be found useful by those involved in the development of novel nucleoside analogues. To increase the cellular uptake of phosphonic acid analogues, the developments of bis-SATE phosphonodiester prodrugs are underway. As shown in Figure 18, superimposing the monophosphates of **8** and **179** does not show any significance overlap and alter the guanine base or the phosphonic acid moiety. Furthermore, the sugar (cyclopentane) puckering is not positioned closer to that of the guanine analogue. Energy minimization was optimized using density functional theory (DFT) and Spartan modeling software, B3LYP functional with the 6-

31G* basis set.

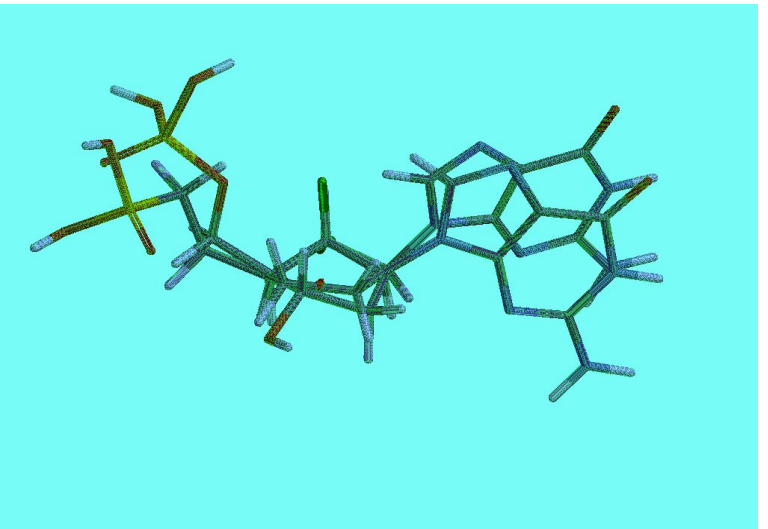
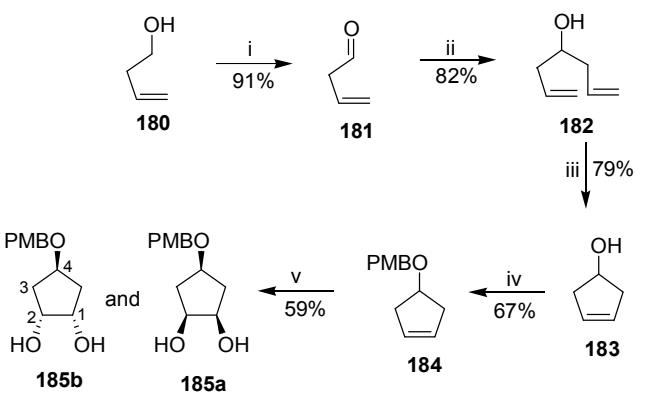


**Figure 18.** Superimpose of monophosphonate of **8** and **179.**

As shown in Scheme 26, the target compounds were prepared from but-3-en-1-ol **180** through a cyclopentenol intermediate **183**. The cyclopentandiol **185b** was prepared *via* catalytic osmium tetroxide and *N*-methyl morpholine *N*-oxide (NMO) of olefin **184**.

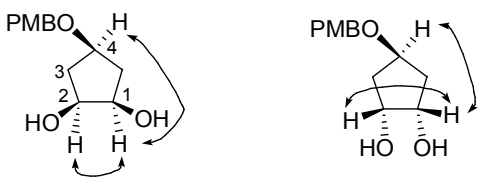
**Scheme 26.** Synthesis of cyclopentandiol intermediate **185**




Reagents: i) DMSO, $(COCl)_2$, TEA, $CH_2Cl_2$; ii) allylMgBr, THF; iii) Grubbs cat.(II) $CH_2Cl_2$; iv) PMBCl, NaH, DMF; v) $OsO_4$, NMO, acetone/*t*-BuOH/$H_2O$ (6:1:1).

As shown in Figure 19, the stereochemistry was readily determined by NOE experiment. On irradiation of $C_4-H$, relatively strong NOE was observed at $C_1-H$ and $C_2-H$ of **185a**, which showed 1,2,4-*cis* relationships. But relatively weak NOE was observed at $C_1-H$ and $C_2-H$ of **185b**, which means the 1,4- and 2,4-*trans* relationships. Selective benzoylation of **185b** gave cyclopentanol derivative **186** as racemic mixture. PCC oxidation[124] of alcohol **186** gave a ketone **187**, which was subjected to DAST fluorination[125] to give compound **188.**

**Figure 19.** NOE relationships between the proximal hydrogens of **185a** and **185b**

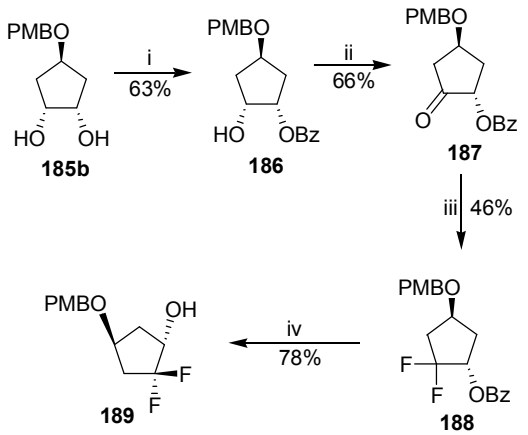



**185a** **185b**

Removal of the benzoyl protecting group of **188** in the condition of methanolic ammonia gave the secondary alcohol **189** (Scheme 27). To synthesize the 2′-difluorinated carbocyclic adenosine nucleoside analogues, the protected cyclopentanol **189** was treated with 6-chloropurine under Mitsunobu conditions[147] (DIAD and $PPh_3$). Slow addition of diisopropylazodicarboxylate (DIAD) to a mixture of cyclopentanol **189**, triphenylphosphine and the 6-chloropurine in anhydrous solvent (THF) gave a yellow solution, which was stirred for 30 min at 0℃ and further stirred overnight at rt to give the

protected 6-chloropurine analogue **190** as an only $N^9$-regioisomer [UV (MeOH) $\lambda_{max}$ 263.0 nm].[142]

**Scheme 27.** Synthesis of difluorinated cyclopentanol intermediate **189**

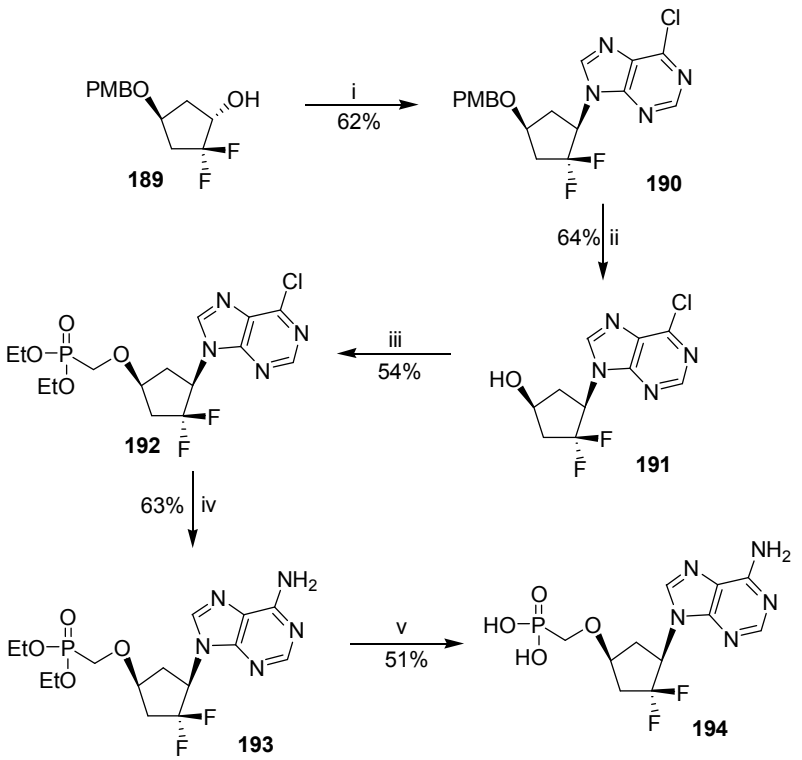



Reagents: i) BzCl, DMAP, Pyridine; ii) PCC, $CH_2Cl_2$; iii) DAST, $CH_2Cl_2$; iv) $NH_3$, MeOH.

The PMB protection group was removed with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)[143] to produce the 5′-nornucleoside analogue **191**, which was treated with diethylphosphonomethyl triflate[144] using lithium *t*-butoxide to yield the nucleoside phosphonate analogue **192** (Scheme 28).

The chlorine group of purine analogue **192** was then converted to amine with methanolic ammonia at 65 ℃ to give a corresponding adenosine phosphonate derivative **193**. Hydrolysis of diethyl phosphonate functional groups of **193** by treatment with bromo-trimethylsilane in $CH_3CN$ in the presence of 2,6-lutidine gave a desired adenosine phosphonic acid derivative **194**.[108]

**Scheme 28.** Synthesis of 2',2'-difluoro cyclopentanyl adenine phosphonic acid **194**



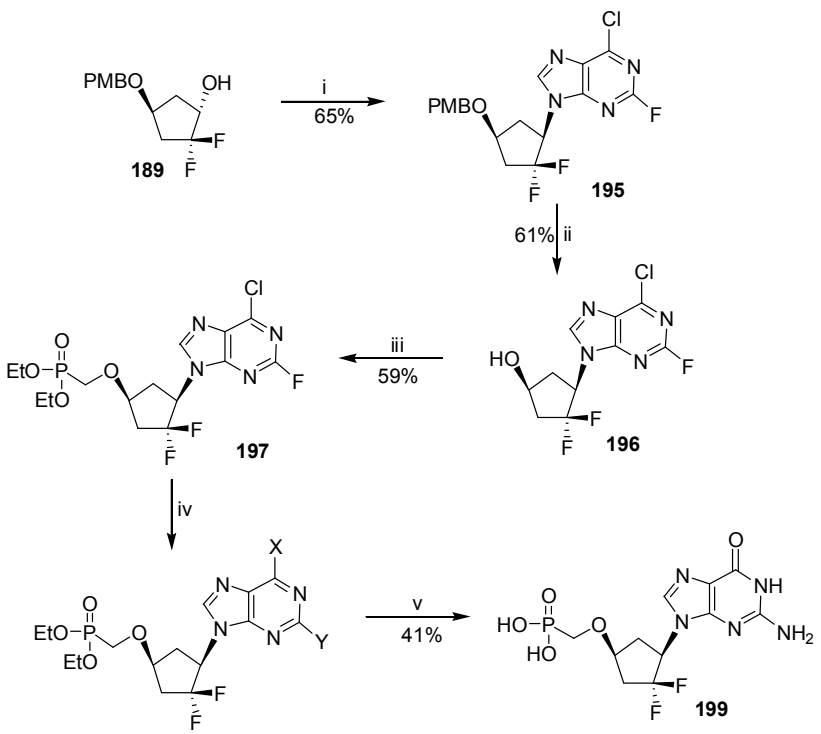

Reagents: i) 6-chloropurine, DEAD, $PPh_3$, 1,4-dioxane/DMF; ii) DDQ, $CH_2Cl_2/H_2O$ (10:1); iii) $(EtO)_2POCH_2OTf$, LiO-*t*-Bu, THF; iv) $NH_3$/MeOH, 63 °C; v) TMSBr, 2,6-lutidine, $CH_3CN$;

For the synthesis of guanine analogues, 2-fluoro-6-chloropurine[109] was condensed with glycosyl donor in the similar conditions used for the condensation of 6-chloropurine. Mitsunobu coupling of the alcohol 189 with 2-fluoro-6-chloropurine gives analogue 195, which was sequentially subjected to DDQ hydrolysis and phosphonate alkylation reactions in the similar procedure described for 192 to provide 197.

Bubbling ammonia into the compound 197 gave separable 2-fluoro-

6-aminopurine analogue[110] analogue **198a** (13%) and 2-amino-6-chloropurine analogue **198b** (51%), respectively. Fluorine acts as a better leaving group than chlorine in nucleophilic aromatic substitution. Phosphonate **198b** was treated with TMSBr to provide phosphonic acid and sequentially treated sodium methoxide and 2-mercaptoethanol in methanol to give a desired 5′-norcarbocyclic guanine phosphonic acid **199**, (Scheme 29). [112]

**Scheme 29.** Synthesis of 2',2'-difluoro cyclopentanyl guanine phosphonic acid **199**




Reagents: i) $(EtO)_2POCH_2OTf$, LiO-*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.

Table 8. The antiviral activities of the synthesized compounds **193**, **194**, **198a**, **198b** and **199**

| Compound | HIV-1 | | cytotoxicity $IC_{50(\mu M)}$ | | |
|---|---|---|---|---|---|
| | $EC_{50(\mu M)}$ | $EC_{90(\mu M)}$ | PBM | CEM | Vero |
| **193** | 42 | 90 | >100 | >100 | >100 |
| **194** | 13 | 90 | >100 | >100 | >100 |
| **198a** | 81 | 95 | >100 | >100 | >100 |
| **198b** | 68 | 95 | >100 | >100 | >100 |
| **199** | 43 | 95 | >100 | >100 | >100 |
| PMEA | 4.4 | ND | >100 | 35.8 | >100 |
| AZT | 0.112 | ND | >100 | 11.6 | 42.8 |

The antiviral activity of phosphonate nucleoside is mostly explained by their intracellular metabolism to their diphosphates followed by incorporation into the viral genome and chain termination.[113] As shown in Table 8, adenine nucleoside phosphonic ester **194** exhibits significant anti-HIV activity. However, nucleoside analogues **193**, **198a**, **198b** and **199** showed weak anti-HIV activity or cytotoxicity at concentrations up to 100 $\mu$M.

Anti-HIV activity was determined in human peripheral blood mononuclear (PBM) cells infected with HIV-1 strain LAI. PBM cells

($1x10^5$ cell/mL) were infected with HIV-1 at a multiplicity of infection (MOI) of 0.02 and cultured in the presence of various concentrations of the test compounds. After 4 days of incubation at 37℃, numbers of viable cells were determined using the 3-(4,5-di-methylthiazole-2-yl)-2,5-diphenyltetrazolium bromide method. The cytotoxicities of the compounds were evaluated in parallel with their antiviral activities, which were assessed based on the viabilities of mock-infected cells.[114]

Based on the potent anti-HIV activity of 2′-fluorinated nucleoside as well as phosphonic acid nucleoside analogues, we have designed and successfully synthesized novel 2′,2′-difluorinated 5′-norcarbocyclic phosphonic acid nucleosides starting from but-3-en-1-ol. Interestingly, adenine analogue **194** shows significant antiviral activity against HIV-1. As shown in Figure 20, superimposed modeling of monophosphate of **5** and **194** shows significant overlap between two parts such as phosphonic acid and the sugar (cyclopentane) moiety. However, adenine base moiety is not positioned closer to that of the adenine analogue **1**. Energy minimization was optimized with the framework of the density functional theory (DFT), with Spartan modeling software. The B3LYP functional with 6-31G* basis set was employed. The information obtained in the present study will be useful for the development of a novel nucleoside analogue. To increase the cellular uptake of

phosphonic acid analogues, developments of bis-SATE phosphono-diester prodrugs are underway.

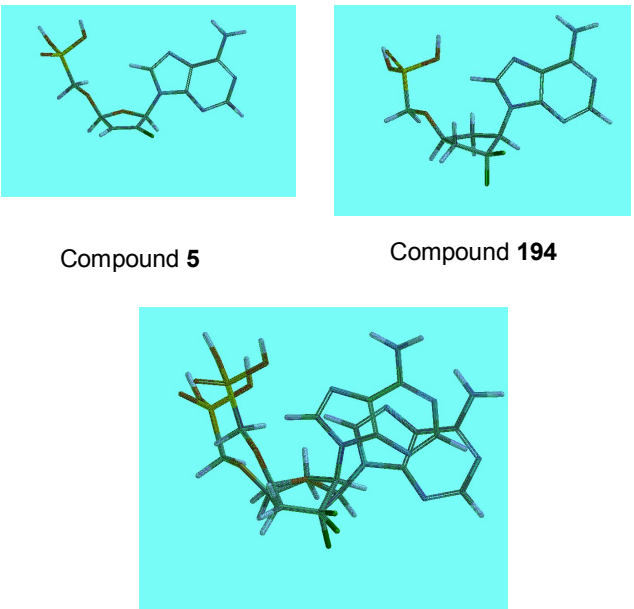



**Figure 20.** Superimpose of monophosphate of **5** and **194**

# Ⅲ. CONCLUSION

The antiviral activity of phosphonate nucleoside is mostly explained by their intracellular metabolism to their diphosphates followed by incorporation into the viral genome and chain termination. In summary, based on the potent anti-HIV activity of nucleoside phosphonic acid analogues, we have designed and successfully synthesized a class of novel nucleoside phosphonic acid analogues. The synthesized target compounds were tested against HIV-1. Especially, adenine analogues **23** ($EC_{50}$ = 10.2 μM), **81** ($EC_{50}$ = 7.9 μM), **120** ($EC_{50}$ = 8.8 μM) and **132** ($EC_{50}$ = 2.2 μM), **157** ($EC_{50}$ = 10.8 μM) exhibits significant anti-HIV activity, the compounds **194** ($EC_{50}$ = 13 μM), **56** ($EC_{50}$ = 22.2 μM), did show moderate antiviral activity against HIV-1, indicating that this virus might allow the sugar moiety for diphosphorylation or some affinity of its diphosphate toward viral polymerases. However, other nucleoside phosphonic acid analogues showed weak or no anti-HIV activity at concentrations up to 100 μM.

# Ⅳ. EXPERIMENTAL SECTION

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 s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). UV spectra were obtained on a Beckman DU-7 spectrophotometer (Beckman, South Pasadena, CA, USA). MS spectra were collected in electrospray ionization (ESI) mode. The elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). 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 otherwise 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.

**(±)-4-Hydroxymethyl-4-vinyl-dihydro-furan-2-one (11).** To a solution of **10** (1.4 g, 3.36 mmol) in THF (6 mL), TBAF (7.4 mL, 1.0 M solution in THF) was added at 0℃. The mixture was stirred overnight at room temperature and concentrated in vacuum. The residue was purified by silica gel column chromatography (Hexane/

EtOAc, 1:1) to give **11** (262 mg, 55%): $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.75−5.70 (m, 1H), 5.06-4.99 (m, 2H), 4.29 (dd, $J$ = 10.4, 6.2 Hz, 2H), 3.51 (dd, $J$ = 8.2, 4.8 Hz, 2H), 2.32 (d, $J$ = 6.2 Hz, 1H), 2.23 (d, $J$ = 6.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 172.2, 149.1, 108.6, 78.8, 73.5, 45.7, 37.6.

**(±)−4−(t−Butyldimethylsilanyloxymethyl)−4−vinyl−dihydrofuran−2−one (12).** To a stirred solution of compound **11** (2.82 g, 19.86 mmol) and imidazole (2.025 g, 29.79 mmol) in $CH_2Cl_2$ (70 mL), *t*−butyldimethylsilyl chloride (3.14 g, 20.85 mmol) was added at 0℃. The mixture was stirred for 4 h at room temperature, and quenched by adding a $NaHCO_3$ aqueous solution (5 mL). The mixture was stirred for 30 min, diluted with water (100 mL) and extracted using EtOAc (2 × 100 mL). The combine organic layer was dried over anhydrous $MgSO_4$, filtered and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:7) to give **12** (4.48 g, 88%) as a colorless syrup: $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.72−5.68 (m, 1H), 5.05−4.98 (m, 2H), 4.29 (d, $J$ = 7.2 Hz, 1H), 4.17 (d, $J$ = 7.1 Hz, 1H), 3.76 (dd, $J$ = 8.0, 4.0 Hz, 2H), 2.28 (d, $J$ = 7.8 Hz, 1H), 2.19 (d, $J$ = 7.9 Hz, 1H), 0.82 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 173.2, 148.8, 110.2, 78.7, 76.3, 46.1, 38.8, 25.5, 18.4, 5.4.

**(±)−4−(t−Butyldimethylsilanyloxymethyl)−4−vinyl−tetrahydrofuran−2−ol (13).** To a cooled (78℃), stirred solution of lactone **12** (323

mg, 1.26 mmol) in dry toluene (6 mL) was added dropwise a 1.0 M solution of diisobutylaluminium hydride (DIBALH) (1.38 mL, 1.38 mmol). The reaction was stirred for 15 min. at −78℃ followed by dropwise addition of methanol (1.38 mL) and diluted with ethyl acetate. The reaction mixture was warmed to room temperature and stirred for 1 h, and the precipitate was removed by filtration through a pad of Celite, washed with ethyl acetate. The filtrate and washings were concentrated in vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give **13** (267 mg, 82%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.71−5.64 (m, 1H), 5.49 (m, 1H), 5.05−4.96 (m, 2H), 3.75−3.65 (m, 4H), 2.01 (m, 2H), 1.25 (s, 3H): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.72−5.68 (m, 1H), 5.05−4.98 (m, 2H), 4.29 (d, $J$ = 7.2 Hz, 1H), 4.17 (d, $J$ = 7.1 Hz, 1H), 3.77−3.72 (m, 2H), 2.01−1.92 (m, 2H), 0.83 (s, 9H), 0.01 (s, 6H).

**(±)−Acetic Acid 4−(t−butyldimethylsilanyloxymethyl)−4−vinyl−tetrahydrofuran2−yl Ester (14).** To a solution of compound **13** (457 mg, 1.77 mmol) in anhydrous pyridine (10 mL), $Ac_2O$ (0.265 g, 2.62 mmol) was slowly added, and the mixture was stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure and co−evaporated with toluene. The residue was diluted with $H_2O$ (100 mL), extracted with EtOAc (2 × 100 mL). The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by

silica gel column chromatography (EtOAc/hexane, 1:22) to give compound **14** (430 mg, 81%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.24 (m, 1H), 5.74−5.69 (m, 1H), 5.05−4.97 (m, 2H), 3.74−3.69 (m, 2H), 2.08−2.00 (m, 2H), 0.82 (s, 0H), 0.02 (s, 6H).

**(*rel*)−(1′*R*,3′*S*)−9−(3−t−Butyldimethylsilanyloxymethyl−3′−vinyl−tetrahydrofuran−1′−yl) 6−Chloropurine (15a) and (*rel*)−(1′*R*,3′*R*)−9−(3′−t−ButyldimethylSilanyloxymethyl−3′−vinyl−tetrahydrofuran−1′−yl) 6−Chloropurine (15b).** 6−Chloropurine (189 mg, 1.23 mmol), anhydrous HMDS (10 mL), and a catalytic amount of ammonium sulfate (14 mg) were refluxed to a clear solution, and the solvent was distilled under anhydrous conditions. The residue was dissolved in anhydrous 1,2−dichloroethane (10 mL). To this mixture, a solution of **10** (216 mg, 0.72 mmol) in dry DCE (10 mL) and TMSOTf (273 mg, 1.23 mmol) was added, and the resulting mixture was stirred for 5 h at room temperature. The reaction mixture was quenched with 2.0 mL of saturated $NaHCO_3$ and stirred for 1.5 h. The resulting solid was filtered through a Celite pad, and the filtrate was diluted with water (60 mL) and extracted with $CH_2Cl_2$ (2 × 60 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 3:1) to give compound **15a** (93 mg, 33%) and **15b** (91 mg, 32%): data for **15a**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.69 (s, 1H), 8.21 (s, 1H), 5.96 (dd, $J$ =

6.2, 1.8 Hz, 1H), 5.73 (m, 1H), 5.05−4.96 (m, 2H), 3.76−3.71 (m, 4H), 2.27 (d, $J$ = 6.8 Hz, 1H), 2.19 (d, $J$ = 6.7 Hz, 1H), 0.83 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 151.6, 151.3, 150.8, 144.5, 142.3, 131.8, 108.6, 85.7, 69.7, 68.4, 42.6, 38.5, 25.7, 18.3, 5.3. data for **15b**: $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.76 (s, 1H), 8.25 (s, 1H), 6.01 (dd, $J$ = 6.2, 1.8 Hz, 1H), 5.77−5.72 (m, 1H), 5.08−5.01 (m, 2H), 3.78−3.74 (m, 3H), 3.64 (d, $J$ = 6.6 Hz, 1H), 2.29 (d, $J$ = 7.2 Hz, 1H), 2.21 (d, $J$ = 7.3 Hz, 1H), 0.82 (s, 9H), 0.03 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 151.8, 151.5, 151.0, 146.1, 141.4, 132.5, 109.9, 84.8, 68.8, 68.1, 41.9, 37.6, 25.4, 18.7, 5.6.

**(*rel*)−(1′*R*,3′*S*)−Diethyl {9−(3′−t−Butyldimethylsilanyloxymethyl−3′−vinyltetrahydrofuran−1′−yl) 6−Chloropurine} Phosphonate (16).** To a $CH_2Cl_2$ (10 mL) solution of 6−chloropurine derivative **15b** (109 mg, 0.412 mmol) and diethyl vinylphosphonate (338 mg, 2.06 mmol), second−generation Grubbs catalyst (17.49 mg, 0.0206 mmol) was added. The reaction mixture was refluxed for 36 h under dry argon gas and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/*n*−Hexane/MeOH, 4:1:0.02) to give **16** (129 mg, 59%) as a form: $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.72 (s, 1H), 8.27 (s, 1H), 6.61 (dd, $J$ = 17.1, 20.4 Hz, 1H), 6.09 (dd, $J$ = 17.2, 19.4. Hz, 1H), 5.95 (dd, $J$ = 5.4, 1.4 Hz, 1H), 4.17−4.13 (m, 4H), 3.76−3.68 (m, 4H), 2.27 (d, $J$ = 7.6 Hz, 1H), 2.20 (d, $J$ = 7.7 Hz, 1H), 1.33-1.30 (m, 9H), 0.83 (m, 9H), 0.03 (s,

6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 151.7, 151.3 153.5, 151.6, 143.3, 132.5, 114.9, 84.7, 71.6, 69.4, 63.5, 62.8, 42.7, 36.7, 25.4, 18.7, 15.2, 4.6.

**(*rel*)-(1′*R*,3′*S*)-Diethyl{9-(3′-t-Butyldimethylsilanyloxymethy-3′-vinyl-tetrahydrofuran-1′-yl)Adenine}Phosphonate (17).** A solution of **16** (160 mg, 0.313 mmol) in saturatedmethanolic ammonia (5mL) was stirred overnight at 65℃ in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/$CH_2Cl_2$, 1:10) to give **17** (94.5 mg, 59%) as a white solid: mp 177-179℃; UV (MeOH) $\lambda_{max}$ 260.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.35 (s, 1H), 8.14 (s, 1H), 6.65 (dd, $J$ = 21.0, 17.6 Hz, 1H), 6.19 (dd, $J$ = 19.9, 17.6 Hz, 1H), 5.94 (dd, $J$ = 6.0, 1.8 Hz, 1H), 4.19-4.14 (m, 4H), 3.74-3.69 (m, 3H), 3.60 (d, $J$ = 6.6 Hz, 1H), 2.27 (d, $J$ = 6.4 Hz, 1H), 2.13 (d, $J$ = 6.5 Hz, 1H), 1.22-1.18 (m, 9H), 0.81 (m, 9H), 0.02 (s, 6H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 154.8, 153.2, 149.4, 147.5, 140.7, 119.4, 115.1, 85.2, 71.5, 68.6, 62.9, 62.2, 43.8, 37.7, 25.5, 18.7, 15.2, 5.5.

**(*rel*)-(1′*R*,3′*S*)-Diethyl {9-(3′-Hydroxymethy-3′-vinyl-tetrahydrofuran-1′-yl) Adenine} Phosphonate (18).** To a solution of **17** (250 mg, 0.488 mmol) in $CH_3CN$ (7 mL), TBAF (0.732 mL, 1.0 M solution in THF) was added at 0℃. The mixture was stirred overnight at room temperature and concentrated in vacuum. The residue was purified by silica gel column chromatography (MeOH/$CH_2Cl_2$, 1:8) to give **18** (155

mg, 80%): $^{1}$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.37 (s, 1H), 8.15 (s, 1H), 6.67 (dd, $J$ = 21.2, 17.4 Hz, 1H), 6.19 (dd, $J$ = 19.4, 17.5 Hz, 1H), 5.97 (dd, $J$ = 6.2, 2.0 Hz, 1H), 5.01 (t, $J$ = 1.9 Hz, 1H), 4.19 4.15 (m, 4H), 3.75−3.68 (m, 4H), 2.28 (d, $J$ = 6.2 Hz, 1H), 2.18 (d, $J$ = 6.2 Hz, 1H), 1.26−1.21 (m, 9H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 155.2, 152.5, 150.4, 149.3, 141.7, 119.4, 114.8, 84.5, 71.3, 69.5, 62.6, 62.0, 44.5, 38.3, 14.9.

**(*rel*)−(1′*R*,3′*S*)−9−(3′−Hydroxymethy−3′−vinyl−tetrahydrofuran−1′−yl)Adenine}Phosphonic acid (19).** To a solution of the phosphonate **18** (192 mg, 0.483 mmol) in anhydrous $CH_3CN$ (10 mL) and 2,6−lutidine (1.125 mL, 9.67 mmol) was added trimethylsilyl bromide (0.739 mg, 4.83 mmol). The mixture was heated overnight at 75℃ under nitrogen gas and then concentrated in vacuum. The residue was partitioned between $CH_2Cl_2$ (100 mL) and purified water (100 mL). The aqueous layer was washed with $CH_2Cl_2$ (2 × 80 mL) and then freeze−dried to give phosphonic acid **19** (125 mg, 76%) as a yellowish foam: UV ($H_2O$) $\lambda_{max}$ 261.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.32 (s, 1H, H−8), 8.16 (s, 1H, H−2), 6.64 (dd, $J$ = 20.7, 17.2 Hz, 1H, H−2′), 6.20 (dd, $J$ = 19.4, 17.2 Hz, 1H, H−5′), 5.93 (dd, $J$ = 6.2, 2.0 Hz, 1H, PCH), 3.73−3.67 (m, 3H, H−6′a, H−6′b, H−4″a), 3.60 (d, $J$ = 6.2 Hz, 1H, H−4″b), 2.26 (d, $J$ = 6.8 Hz, 1H, H−3′a), 2.17 (d, $J$ = 6.8 Hz, 1H, H−3′b); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 155.1, 152.7, 150.4, 149.1, 140.9, 119.3, 115.0, 84.2, 72.2, 69.5, 42.2,

36.8; MS *m/z* 342 $(M+H)^+$.

**(*rel*)-(1′*R*,3′*S*)-Diethyl{9-(3′-*t*-Butyldimethylsilanyloxymethy-3′-ethyltetrahydrofuran-1′-yl) 6-Chloropurine} Phosphonate (20).** A solution of vinyl phosphonate nucleoside analogue **16** (508 mg, 0.957 mmol) in methanol (15 mL) was added 10% Pd/C (12 mg) and cyclohexene (6 mL) under Ar. The reaction mixture was refluxed for 36 h. The reaction mixture was filtered through a pad of Celite, evaporated, and purified by silica gel column chromatography using methanol and methylene chloride (12:1) to give ethyl phosphonate analogue **20** (377 mg, 74%) as a white solid: mp 168-170℃; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.73 (s, 1H), 8.29 (s, 1H), 5.97 (dd, $J$ = 5.8, 2.0 Hz, 1H), 4.19-4.14 (m, 4H), 3.73-3.66 (m, 3H), 3.58 (d, $J$ = 6.2 Hz, 1H), 2.22-2.15 (m, 6H), 1.70-1.64 (m, 6H), 0.83 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 151.6, 151.3, 150.3, 143.4, 135.5, 84.2, 70.3, 69.6, 63.3, 62.6, 40.6, 37.2, 28.4, 25.5, 19.1, 18.3, 14.6, 5.5.

**(*rel*)-(1′*R*,3′*S*)-Diethyl{9-(3′-*t*-Butyldimethylsilanyloxymethy-3′-ethyltetrahydrofuran-1′-yl) adenine} Phosphonate (21).** Adenine derivative **21** was prepared from 6-chloropurine analogue **20** by the similar ammonolysis procedure as described for **17**: yield 56%; mp 167-169℃; UV (MeOH) $\lambda_{max}$ 260.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.35 (s, 1H), 8.18 (s, 1H), 5.94 (dd, $J$ = 6.0, 1.9 Hz, 1H), 4.20-4.16 (m, 4H), 3.75-3.69 (m, 3H), 3.63 (d, $J$ = 6.0 Hz, 1H),

2.25−2.19 (m, 6H), 1.69−1.63 (m, 6H), 0.81 (s, 9H), 0.01 (s, 6H); $^{1}$3C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 155.0, 152.8, 150.3, 142.1, 120.3, 83.8, 69.5, 68.9, 62.8, 62.3, 39.5, 36.7, 29.1, 25.3, 19.7, 18.4, 14.1, 5.2.

**(*rel*)−(1′*R*,3′*S*)−Diethyl{9−(3′−Hydroxymethy−3′−ethyltetrahydrofuran−1′−yl)adenine}Phosphonate (22).** Desilylation of purine phosphonate analogue **21** was performed by the similar condition used for **18** to give **22**: yield 78%; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.38 (s, 1H), 8.19 (s, 1H), 5.99 (dd, $J$ = 6.0, 2.0 Hz, 1H), 4.21-4.15 (m, 4H), 3.72−3.63 (m, 4H), 2.23−2.16 (m, 6H), 1.67−1.61 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75MHz) $\delta$ 154.7, 152.2, 150.1, 143.6, 119.5, 84.2, 70.7, 68.2, 63.3, 62.7, 40.6, 37.5, 28.8, 18.4, 14.3.

**(*rel*)−(1′*R*,3′*S*)−{9−(3′−Hydroxymethyl−3′−Ethyltetrahydrofuran−1′−yl) adenine}Phosphonic acid (23).** Adenine phosphonic acid **23** was synthesized from **22** using the similar hydrolysis procedure as described for **19**: yield 73%, UV ($H_2O$) $\lambda_{max}$ 261.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.38 (s, 1H, H−8), 8.18 (s, 1H, H−2), 6.00 (dd, $J$ = 6.1, 2.0 Hz, 1H, H−2′), 3.77−3.69 (m, 3H, H−6′a, H−6′b, H−4″a), 3.60 (d, $J$ = 6.3 Hz, 1H, H−4″b), 2.25−2.19 (m, 6H, H−3′a, H−3′b, H−5′a, H−5′b, $PCH_2$); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 155.5, 152.2, 149.1, 138.5, 119.8, 83.7, 74.6, 42.7, 32.2, 28.4, 20.7, 18.8.

**(*rel*)−(1′*R*,3′*S*)−(3′−*t*−Butyldimethylsilanyloxymethy−3′−vinyl−tetrahydrofuran−1′−yl) 2−fluoro−6−chloropurine (23a) and (*rel*)−**

**(1′*R*,3′*S*)−(3′−*t*−Butyldimethylsilanyloxymethy−3′−vinyl−tetrahydrofuran−1′−yl) 2−Fluoro−6−chloropurine (23b).** Coupling of **14** with 2−fluoro−6−chloropurine under the similar condensation conditions as described for **15** to give **23a** and **23b**, respectively: data for **23a**: yield 32%; UV (MeOH) $\lambda_{max}$ 268.5 nm; $^{1}$H NMR ($CDCl_3$ ,300 MHz) $\delta$ 8.44 (s, 1H), 5.94 (dd, $J$ = 5.8, 1.8 Hz, 1H), 5.73−5.70 (m, 1H), 5.04−4.95 (m, 2H), 3.75−3.68 (m, 4H), 2.27 (d, $J$ = 9.2 Hz, 1H), 2.19 (d, $J$ = 9.2 Hz, 1H), 0.83 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 154.8, 152.2, 149.7, 147.6, 143.9, 128.2, 109.8, 84.6, 71.2, 69.9, 42.0, 37.5, 25.6, 18.3, 4.8. data for **23b**: yield 31%; UV (MeOH) $\lambda_{max}$ 269.5 nm; $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.43 (s, 1H), 5.96 (dd, $J$ = 6.0, 2.0 Hz, 1H), 5.74 (m, 1H), 5.07−4.99 (m, 2H), 3.74−3.69 (m, 2H), 3.64 (dd, $J$ = 9.8, 6.8 Hz, 1H), 2.28 (d, $J$ = 9.6 Hz, 1H), 2.20 (d, $J$ = 9.5 Hz, 1H), 0.82 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 154.7, 152.4, 150.1, 147.9, 144.2, 127.1, 109.4, 83.9, 70.8, 69.4, 41.6, 38.6, 25.3, 18.5, −5.3.

**(*rel*)−(1′*R*,3′*S*)−Diethyl{9−(3′−*t*−Butyldimethylsilanyloxymethy−3′−vinyltetrahydrofuran−1′−yl)2−Fluoro−6−chloropurine}Phosphonate (24).** Phosphonate nucleoside analogue **24** was prepared from **23b** using the same crossmetathesis procedure as described for **16**: yield 54%; $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.46 (s, 1H), 6.58 (dd, $J$ = 17.3, 20.8 Hz, 1H), 6.14 (dd, $J$ = 17.2, 20.7 Hz, 1H), 6.01 (dd, $J$ = 6.0, 1.8 Hz, 1H), 4.18−4.12 (m, 4H), 3.71−3.65 (m, 4H), 2.25 (d, $J$ = 8.8 Hz,

1H), 2.18 (d, $J$ = 8.8 Hz, 1H), 1.34−1.31 (m, 6H), 0.82 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 154.7, 152.6, 150.3, 149.2, 147.2, 128.3, 115.4, 83.9, 71.4, 69.6, 63.8, 63.2, 43.2, 37.7, 25.5, 18.3, 5.6.

**(*rel*)−(1′*R*,3′*S*)−Diethyl {9−(3′−*t*−Butyldimethylsilanyloxymethy−3′−vinyltetrahydrofuran−1′−yl) 2−Fluoro−6−aminopurine} Phosphonate (25a) and (*rel*)−(1′*R*,3′*S*)−diethyl{9−(3′−*t*−Butyldimethylsilanyloxy methy−3′−vinyl−tetrahydrofuran−1′−yl)2−Amino−6−chloropurine} Phosphonate (25b).** Dry ammonia gas was bubbled into a stirred solution of **24** (250 mg, 0.455 mmol) in DME (10 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 **25a** (31 mg, 13%) and **25b** (104 mg, 42%), respectively: Data for **25a**; UV (MeOH) $\lambda_{max}$ 260.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.22 (s, 1H), 7.74 (br s, $NH_2$, 2H), 6.66 (dd, $J$ = 20.8, 17.2 Hz, 1H), 6.15 (dd, $J$ = 20.2, 17.2 Hz, 1H), 5.96 (dd, $J$ = 6.0, 1.8 Hz, 1H), 4.16−4.09 (m, 4H), 3.74-3.69 (m, 3H), 3.63 (d, $J$ = 8.9 Hz, 1H), 2.29 (d, $J$ = 8.4 Hz, 1H), 2.20 (d, $J$ = 8.4, 1H), 1.24−1.20 (m, 6H), 0.83 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 155.1, 152.5, 149.5, 147.8, 144.5, 128.3, 115.4, 84.7, 71.4, 69.4, 63.5, 62.8, 42.5, 37.5, 25.6, 18.4, 15.1, 4.7. Data for **22b**; UV (MeOH) $\lambda_{max}$ 308.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.18 (s, 1H), 7.71 (br s, $NH_2$, 2H),

6.64 (dd, $J$ = 20.4, 17.2 Hz, 1H), 6.12 (dd, $J$ = 21.1, 17.2 Hz, 1H), 5.99 (dd, $J$ = 6.2, 1.8 Hz, 1H), 4.18-4.12 (m, 4H), 3.73−3.65 (m, 4H), 2.28 (d, $J$ = 8.4 Hz, 1H), 2.19 (d, $J$ = 8.3 Hz, 1H), 1.20 (m, 6H), 0.83 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 158.5, 154.3, 151.1, 149.4, 143.3, 124.7, 115.3, 84.7, 70.8, 68.9, 63.3, 62.6, 42.7, 37.2, 25.5, 18.3, 14.6, 4.7.

**(*rel*)−(1′*R*,3′*S*)−Diethyl{9−(3′−Hydroxymethy−3′−vinyl−tetrahydrofuran−1′−yl)2−Amino−6−chloropurine}Phosphonate (26).** Desily−lation of phosphonate **25b** was performed by the same conditions for **16**: yield 76%; UV (MeOH) $\lambda_{max}$ 309.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.20 (s, 1H), 7.71 (br s, $NH_2$, 2H), 6.62 (dd, $J$ = 20.5, 16.8 Hz, 1H), 6.19 (dd, $J$ = 20.5, 16.8 Hz, 1H), 5.98 (dd, $J$ = 6.1, 1.8 Hz, 1H), 5.98 (t, $J$ = 2.1 Hz, 1H), 4.21−4.17 (m, 4H), 3.69−3.61 (m, 4H), 2.28 (d, $J$ = 8.2 Hz, 1H), 2.19 (d, $J$ = 8.2 Hz, 1H), 1.21−1.18 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 158.4, 153.9, 150.8, 149.1, 143.3, 124.7, 114.2, 83.3, 70.7, 69.8, 62.4, 61.7, 42.4, 37.2, 14.5.

**(*rel*)−(1′*R*,3′*S*)−9−{(3′−Hydromethyl−3′−vinyl−tetrahydrofuran−1′−yl) Guanine}Phosphonic acid (27).** To a solution of **26** (136.4 mg, 0.316 mmol) dry $CH_3CN$ (15 mL) was added trimethylsilyl bromide (0.0728 mL, 5.52 mmol) at room temperature. After this mixture was stirred for 28 h, the solvent was removed, evaporating three times with methanol. The residue was dissolved in MeOH (12.0 mL) and 2−mercaptoethanol (86.4 $\mu$L, 1.266 mmol) and NaOMe (67.2 mg, 1.266

mmol) was added to the mixture. The mixture was refluxed for 12 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 **27** (73.3 mg, 65%) as a yellowish form. UV ($H_2O$) $\lambda_{max}$ 252.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 10.10 (br s, NH, 1H), 8.18 (s, 1H, H-8), 7.07 (br s, $NH_2$, 2H), 6.68 (dd, $J$ = 20.6, 17.2 Hz, 1H, H-2′), 6.17 (dd, $J$ = 19.1, 17.3 Hz, 1H, H-5′), 5.96 (dd, $J$ = 6.0, 2.0 Hz, 1H, PCH), 3.75-3.67 (m, 4H, H-4″a, H-4″b, H-6′a, H-6′b), 2.29 (d, $J$ = 10.4 Hz, 1H, H-3′a, H-3′b), 2.18 (d, $J$ = 10.5 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 157.4, 154.3, 152.5, 149.2, 136.4, 115.7, 74.7, 70.3, 62.6, 61.8, 42.3, 37.2, 34.6; MS *m/z* 358 $(M+H)^+$.

**(*rel*)-(1′*R*,3′*S*)-Diethyl{9-(3′-*t*-butyldimethylsilanyloxymethy-3′-ethyltetrahydrofuran-1′-yl)2-Fluoro-6-chloropurine} Phosphonate (28).** Compound **28** was synthesized from **24** by the similar catalytic hydrogenation procedure as described for **20**: yield 65%; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.52 (s, 1H), 5.98 (dd, $J$ = 6.0, 2.0 Hz, 1H), 4.21-4.15 (m, 4H), 3.69-3.64 (m, 3H), 3.57 (d, $J$ = 8.2 Hz, 1H), 2.28-2.19 (m, 6H), 1.33-1.30 (m, 6H), 0.81 (s, 9H), 0.03 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 154.8, 152.6, 148.2, 143.5, 125.6, 84.8, 72.3, 70.8, 63.4, 62.8, 41.2, 37.8, 28.4, 25.5, 19.6, 18.6, 5.2.

**(*rel*)-(1′*R*,3′*S*)-Diethyl{9-(3′-*t*-Butyldimethylsilanyloxymethy-3′-ethyltetrahydrofuran-1′-yl)2-Fluoro-6-aminopurine} Phosphonate**

(29a) and (*rel*)−(1′*R*,3′*S*)−diethyl{9−(3′−*t*−Butyldimethyl silanyloxy methy−3′−ethyl−tetrahydrofuran−1′−yl)2−amino−6−chloropurine} Phosphonate (29b). Ammonolysis of 28 was performed using the similar procedure as described for 21: Data for 29a; yield 15%; UV (MeOH) $\lambda_{max}$ 260.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.21 (s, 1H), 7.66 (br s, $NH_2$, 2H), 5.98 (dd, $J$ = 6.0, 1.8 Hz, 1H), 4.24−4.20 (m, 4H), 3.74−3.70 (m, 3H), 3.62 (d, $J$ = 8.2 Hz, 1H), 2.29−2.19 (m, 6H), 1.25−1.18 (m, 6H), 0.83 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 155.1, 153.6, 148.4, 142.3, 124.7, 83.5, 70.4, 69.1, 63.0, 62.5, 40.8, 37.0, 28.6, 25.6, 18.9, 18.2, 14.3, −4.3; Data for 29b; yield 45%; UV (MeOH) $\lambda_{max}$ 309.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.18 (s, 1H), 7.69 (br s, $NH_2$, 2H), 5.97 (dd, $J$ = 5.9, 2.0, Hz, 1H), 4.21−4.19 (m, 4H), 3.69−3.64 (m, 3H), 3.54 (d, $J$ = 8.8 Hz, 1H), 2.23−2.15 (m, 6H), 1.22−1.16 (m, 4H), 0.81 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 157.4, 153.2, 151.0, 142.9, 124.4, 84.6, 71.2, 69.6, 63.3, 62.7, 41.5, 37.6, 28.8, 25.6, 19.4, 18.3, 15.2, 5.4.

(*rel*)−(1′*R*,3′*S*)−Diethyl{9−(3′−Hydroxymethy−3′−ethyl−tetrahydrofuran−1′−yl)−2−amino−6−chloropurine}Phosphonate(30). Deprotection of 29b was performed by the same desilylation conditions for 22: yield 72%; UV (MeOH) $\lambda_{max}$ 308.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.22 (s, 1H), 7.72 (br s, $NH_2$, 2H), 6.02 (dd, $J$ = 6.2, 1.8, Hz, 1H), 4.23−4.18 (m, 4H), 3.72−3.68 (m, 3H), 3.58 (d,

$J$ = 8.6 Hz, 1H), 2.21−2.15 (m, 6H), 1.20−1.15 (m, 4H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 157.3, 154.2, 152.6, 143.4, 124.7, 83.4, 70.7, 68.9, 62.8, 62.1, 40.7, 36.8, 29.0, 18.7, 14.7.

**(*rel*)−(1′*R*,3′*S*)−9−{(3′−Hydromethyl−3′−ethyl−tetrahydrofuran−1′−yl) Guanine}Phosphonic acid (31).** Guanine nucleoside phosphonic acid **31** was prepared from **30** by the same hydrolysis conditions used for **27**: yield 63%; UV ($H_2O$) $\lambda_{max}$ 254.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 10.8 (br s, NH, 1H), 8.05 (s, 1H, H−8), 7.01 (br s, $NH_2$, 2H), 5.98 (dd, $J$ = 6.1, 2.0 Hz, 1H, H−2′), 3.73−3.66 (m, 4H, H−4″a, H−4″b, H−6′a, H−6′b), 2.25−2.19 (m, 6H, H−3′a, H−3′b, H−5′a, H−5′b, $PCH_2$); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 157.5, 154.2, 152.1, 136.3, 117.6, 74.2, 70.7, 40.7, 37.4, 28.6, 19.4.

**1−But−3−enyloxymethyl−4−methoxy−benzene (33).** NaH (60% in mineral oil, 3.33 g, 83.21 mmol) was added portion wise to a cooled (0℃) solution of but−3−en−1−ol **32** (5.0 g, 69.34 mmol) and *p*−methoxy benzyl chloride (10.34 mL, 76.27 mmol) in DMF (100 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was quenched with $H_2O$ followed by extraction with EtOAc two times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **33** (12.93 g, 97%) as a colorless oil. $^1$H NMR ($CDCl_3$, 300 MHz)

δ 7.25 (m, 2H), 6.87 (m, 2H), 5.87−5.97 (m, 1H), 5.13−5.01 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.49 (t, $J$ = 6.7 Hz, 2H), 2.36 (q, $J$ = 6.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.12, 135.29, 130.52, 129.24, 116.28, 113.74, 72.53, 69.28, 55.25, 34.21.

**3−(4−Methoxy−benzyloxy)−propionaldehyde (34).** A solution of compound **33** (3.7 g, 19.25 mmol) in anhydrous $CH_2Cl_2$ (50 mL) was cooled down to 78℃, and ozone gas was then bubbled into the reaction mixture until a blue color persisted for an additional 5 minutes. The reaction mixture was degassed with nitrogen, and dimethyl sulfide (5.94 mL, 80.83 mmol) was slowly added at −78℃. The mixture was stirred for 1 h at −78℃ under argon gas and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give compound **34** (2.99 g, 80%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 9.78 (s, 1H), 7.26 (m, 2H), 6.88 (m, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.59 (t, $J$ = 6.1 Hz, 2H), 2.02 (q, $J$ = 6.1 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 201.26, 159.20, 130.09, 129.34, 113.79, 72.78, 64.90, 55.25, 32.15.

**5−(4−methoxybenzyloxy)−2−methylpent−1−en−3−ol (35).** To a solution of **34** (2.4 g, 12.36 mmol) in dry THF (35 mL) was slowly added isopropenyl magnesium bromide (18.53 mL, 1.0 M solution in THF) at 78℃. After 5 h, saturated $NH_4Cl$ solution (20 mL) was added, and the reaction mixture was slowly warmed to room temperature.

The mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL) two times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give **35** (2.09 g, 76%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.24 (d, $J$ = 6.7 Hz, 2H), 6.76 (d, $J$ = 6.6 Hz, 2H), 5.26 (d, $J$ = 13.8 Hz, 1H), 5.10 (d, $J$ = 7.2 Hz, 1H), 4.42 (s, 2H), 3.96 (s, 3H), 3.54−3.47 (m, 2H), 3.01 (s, 1H), 1.94 (s, 9H), 1.86−1.78 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 159.68, 140.26, 129.36, 128.96, 115.35, 110.65, 73.16, 71.59, 67.26, 55.66, 35.20, 18.54.

**(5−(4−methoxybenzyloxy)−2−methylpent−1−en−3−yloxy)(tert−butyl)dimethylsilane (36).** TBDMSCl (0.97 g, 6.43 mmol) was added slowly to a solution of **35** (1.3 g, 5.85 mmol) and imidazole (0.60 g, 8.77 mmol) in $CH_2Cl_2$ (20 mL) at 0℃, and stirred for 5 h at the same temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in water (100 mL) and extracted with diethyl ether (100 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **36** (1.71 g, 87%) as a colorless oil. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.22 (d, $J$ = 6.8 Hz, 2H), 6.78 (d, $J$ = 6.5 Hz, 2H), 5.26 (d, $J$ = 13.8 Hz, 1H), 5.16 (d,

$J$ = 7.4 Hz, 1H), 4.45−4.32 (m, 2H), 4.18 (q, $J$ = 5.9 Hz, 1H), 3.74 (s, 3H), 3.46−3.88 (m, 2H), 1.92 (s, 3H), 0.94 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 159.60, 141.53, 130.28, 129.00, 114.86, 112.10, 74.28, 72.15, 67.34, 54.38, 36.43, 24.68, 18.65, 4.67.

**3−(tert−Butyldimethylsilanyloxy)−4−methylpent−4−en−1−ol (37).** To a solution of compound **36** (0.76 g, 2.26 mmol) in $CH_2Cl_2/H_2O$ mixture (10 mL, 20:1 v/v) was added DDQ (0.56 g, 2.48 mmol) and the mixture was stirred for 2 h at room temperature. Saturated $NaHCO_3$ (2 mL) was added to quench the reaction and further diluted with water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give compound **37** (0.43 g, 87%) as a colorless oil. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.16 (d, $J$ = 16.8 Hz, 1H), 5.02 (d, $J$ = 10.2 Hz, 1H), 4.38 (q, $J$ = 4.2 Hz, 1H), 3.86−3.71 (m, 2H), 2.42 (brs, 1H), 1.88−1.67 (m, 2H), 1.68 (s, 3H), 0.94 (s, 9H), 0.08 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 148.65, 114.68, 80.26, 73.20, 61.08, 36.94, 24.88, 17.56, 3.96.

**3−(tert−Butyldimethylsilanyloxy)−4−methyl−pent−4−enal (38).** 4 Å Molecular sieves (3.0 g) and PCC (2.99 g, 13.86 mmol) were added slowly to a solution of compound **37** (1.2 g, 5.55 mmol) in $CH_2Cl_2$ (15 mL) at 0℃, and stirred overnight at room temperature. An excess of

diethyl ether (20 mL) was then added to the mixture. The mixture was stirred vigorously for 2 h at the same temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **38** (0.95 g, 80%) as a colorless oil. $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 9.78 (s, 1H), 5.24 (d, $J$ = 16.8 Hz, 1H), 5.12 (d, $J$ = 10.2 Hz, 1H), 4.52 (q, $J$ = 5.3 Hz, 1H), 2.85−2.54 (m, 2H), 1.92 (s, 3H), 0.87 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 201.86, 154.47, 114.45, 76.07, 50.12, 23.45, 18.12, 3.45.

**5−(tert−Butyldimethylsilanyloxy)−2,6−dimethyl−hepta−1,6−dien−3−ol (39).** To a solution of compound **38** (0.25 g, 1.17 mmol) in dry THF (4 mL), isopropenyl magnesium bromide (3.50 mL, 1.0 M solution in THF) was added slowly at −78℃. After 3 h, a saturated $NH_4Cl$ solution (4 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc/water two times. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **39** (0.24 g, 80%) as a diastereomeric mixture. $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.19−4.97 (m, 4H), 4.43−4.16 (m, 2H), 1.66 (m, 8H), 0.88 (s, 9H), 0.03 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 148.25, 113.42, 110.28, 74.34, 71.05, 45.36, 25.86, 18.64, 16.37, 4.84.

**(1*S*,4*S*)-4-(tert-Butyldimethylsilanyloxy)-2,3-dimethylcyclopent-2-enol (40a) and (1*R*,4*S*)-4-(tert-Butyldimethylsilanyloxy)-2,3-di methyl-cyclopent-2-enol (40b).** To a solution of **39** (254 mg, 0.99 mmol) in dry benzene (3 mL) was added 2nd generation Grubbs catalyst (10 mg). The reaction mixture was refluxed overnight at 60℃, and cooled to room temperature. The mixture was concentrated in vacuum, and residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give cyclopentenol **40a** (97 mg, 43%) and **40b** (95 mg, 42%) as colorless oils. Cyclopentenol **40a**: $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 4.46 (m, 1H), 4.25 (m, 1H), 1.94 (s, 6H), 1.87-1.76 (m, 2H), 0.92 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 145.01, 76.94, 74.50 45.12, 25.76, 18.38, 11.36, -4.64; Cyclopentenol **40b**: $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 4.38 (m, 1H), 4.16 (m, 1H), 1.95 (s, 6H), 1.88-1.75 (m, 2H), 0.93 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 146.32, 75.46, 73.38, 46.10, 24.44, 17.86, 10.87, 4.90.

**(1*R*,4*S*)-9-[4-(tert-Butyldimethylsilanyloxy)-2,3-Dimethylcyclopent-2-enyl]-$N^6$,$N^6$-bis-(tert-butoxy-carbonyl)adenine (41).** To a stirred solution of triphenylphosphine (518 mg, 1.98 mmol) in THF (4 mL) at 0℃ was added dropwise the diisopropyl azodicarboxylate (DIAD, 0.38 mL, 1.98 mmol) and the yellow reaction mixture was stirred at this temperature for 30min. After that, a solution of compound **40a** (347 mg, 1.52 mmol) in THF (3.0 mL), was added and

the reaction mixture was stirred at 0℃ for 10 min. Then, the cold bath was removed and the yellow solution was stirred for 30 min at room temperature. Bis-BOC adenine (662 mg, 1.98 mmol) was added and the solution became clear after 2 min. The reaction mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give **41** (522 mg, 63%) as a yellow solid. $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.92 (s, 1H), 8.34 (s, 1H), 4.78 (s, 1H), 3.96 (s, 1H), 2.44-2.37 (m, 2H), 1.84 (s, 18H), 1.02 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 154.23, 152.12, 148.72, 145.58, 141.66, 133.47, 120.00, 74.60, 51.24, 39.14, 30.86, 24.90, 13.15, 11.12, 9.43, -5.12.

**(1*R*,4*S*)-($N^6$,$N^6$-Bis-(tert-butoxycarbonyl)adenine)-2,3-dimethyl-cyclopent-2-enol (42).** To a solution of **41** (132 mg, 0.24 mmol) in THF (3 mL) was added TBAF (0.51 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 (EtOAc/hexane, 2:1) to give **42** (87 mg, 83%) as a white solid. $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.54 (s, 1H), 8.29 (s, 1H), 5.05 (s, 1H), 4.38 (s, 1H), 2.43 (q, $J$ = 5.4 Hz, 2H), 1.42 (s, 6H), 1.28 (s, 18H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 148.27, 146.44, 143.36, 138.32, 136.64, 129.65, 78.46, 57.28, 42.43, 31.54, 23.00, 12.14, 9.36.

**(1*R*,4*S*)−{4−[$N^6$,$N^6$−Bis−(tert−butoxycarbonyl)adenine]−2,3−dimethyl−cyclopent−2−enyloxymethyl}−phosphonic acid diisopropyl ester (43).** To a solution of **42** (85 g, 0.20 mmol) in DMF (2 mL), LiI (1.98 mg, 0.015 mmol) was added at 25℃. LiO−*t*−Bu (0.32 Ml, 1.0 M solution in THF) and a solution of diisopropyl bromomethyl phosphonate (0.06 mL, 0.24 mmol) in DMF(2 mL) were slowly and simultaneously added to the reaction mixture for 5 h at 60℃ under anhydrous conditions. The mixture was quenched by adding water (10 mL), and the organic solvents (THF) were removed in vacuo. The aqueous layer was extracted with EtOAc two times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give **43** (77 mg, 64%) as a colorless syrup: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.83 (s, 1H), 8.01 (s, 1H), 6.21 (s, 1H), 5.20 (s, 1H), 4.57 (s, 1H), 4.12−4.01 (m, 2H), 3.46 (d, $J$ = 9.8 Hz, 2H), 2.46−2.37 (m, 2H), 1.58 (s, 18H), 1.48 (s, 6H), 1.32 (s, 12H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 153.02, 144.93, 140.55, 129.74, 82.55, 80.21, 75.46, 72.23, 61.71, 39.24, 27.63, 25.46, 22.60, 19.43, 12.36, 9.87.

**(1*R*,4*S*)−[4−(6−Amino−purin−9−yl)−2,3−dimethyl−cyclopent−2−enyloxymethyl] phosphonic acid (44).** To a solution of the phosphonate **43** (67 mg, 0.11 mmol) in $CH_3CN$ (8 mL) was added trimethylsilyl bromide (168 mg, 1.11 mmol). The mixture was heated overnight at

60℃ and concentrated under reduced pressure. The residue was partitioned between $CH_2Cl_2$ (10 mL) and distilled $H_2O$ (10 mL). The aqueous layer was washed with $CH_2Cl_2$ and then freeze-dried to give target compound **44** (23 mg, 64%) as a yellowish foamy solid. $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.92 (s, 1H, H-8), 7.84 (s, 1H, H-2), 5.32 (s, 1H, H-1′), 3.72 (d, $J$ = 9.3 Hz, 2H, H-6′a, H-6′b), 2.46-2.37 (m, 2H, $PCH_2$), 1.48 (s, 6H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 153.28, 151.23, 145.46, 138.54, 129.74, 80.23, 68.35, 59.67, 31.60, 12.18, 10.96.

**(±)-3-Methyl-3-vinyl-dihydrofuran-1-one (47):** To a solution of **46** (1.2 g, 4.19 mmol) in THF (10 mL), TBAF (5.03 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, 10:1) to give **47** (375 mg, 71%): $^1$H NMR ($CDCl_3$, 300 MHz) δ 5.73-5.67 (m, 1H), 5.05-4.98 (m, 2H), 4.30 (d, $J$ = 6.4 Hz, 1H), 4.21 (d, $J$ = 6.5 Hz, 1H), 2.31 (d, $J$ = 7.0 Hz, 1H), 2.23 (d, $J$ = 7.0 Hz, 1H), 1.25 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 172.6, 148.8, 109.1, 84.2, 50.2, 31.7, 27.1.

**(±)-3-Methyl-3-vinyl-tetrahydrofuran-1-ol (48):** To a cooled (-78℃), stirred solution of lactone **47** (320 mg, 2.53 mmol) in dry toluene (12 mL) was added dropwise a 1.0 M solution of diisobutylaluminium hydride (DIBALH) (3.0 mL, 3.0 mmol). The reaction was stirred for 20 min. at -78℃, followed by dropwise

addition of methanol (3.0 mL) and diluted with ethyl acetate. The reaction mixture was warmed to room temperature and stirred for 2 h, and the precipitate was removed by filtration through a pad of Celite, washed with ethyl acetate. The filtrate and washings were concentrated *in vacuo* and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **48** (272 mg, 84%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 5.76−5.65 (m, 1H), 5.50−5.43 (m, 2H), 5.02−4.99 (m, 2H), 3.73−3.68 (m, 2H), 2.01 (m, 2H), 1.25 (s, 3H).

**(±)−Acetic acid 3−methyl−3−vinyl−tetrahydrofuran−1−yl ester (49):** To a solution of compound **48** (151 mg, 1.18 mmol) in anhydrous pyridine (8 mL), $Ac_2O$ (0.177 g, 1.75 mmol) was slowly added, and the mixture was stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure and co−evaporated with toluene. The residue was diluted with $H_2O$ (50 mL), extracted with EtOAc (60 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **49** (170 mg, 85%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.25−6.20 (m, 1H), 5.71−5.67 (m, 1H), 5.04−4.95 (m, 2H), 3.73−3.70 (m, 2H), 2.06−2.00 (m, 2H), 2.03 (s, 3H), 1.24 (s, 3H).

**(*rel*)−(1′*R*,3′*R*)−9−(3′−Methyl−3′−vinyl−tetrahydrofuran−1′−yl) 6−chloropurine (50a) and (*rel*)−(1′*S*,3′*R*)−9−(3′−methyl−3′−vinyl−**

**tetrahydrofuran-1′-yl) 6-chloropurine (50b)**: 6-Chloropurine (158 mg, 1.027 mmol), anhydrous HMDS (8 mL), and a catalytic amount of ammonium sulfate (12 mg) were refluxed to a clear solution, and the solvent was distilled under anhydrous conditions. The residue was dissolved in anhydrous 1,2-dichloroethane (8 mL). To this mixture, a solution of **49** (102 mg, 0.6 mmol) in dry DCE (10 mL) and TMSOTf (228 mg, 1.027 mmol) was added, and the resulting mixture was stirred for 8 h at rt. The reaction mixture was quenched with 2.5 mL of saturated $NaHCO_3$ and stirred for 1 h. The resulting solid was filtered through a Celite pad, and the filtrate was extracted with $CH_2Cl_2$ two times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/hexane, 4:1) to give compound **50a** (52 mg, 33%) and **50b** (54 mg, 34%): data for **50a**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1H), 8.31 (s, 1H), 5.96 (t, $J$ = 5.2 Hz, 1H), 5.72 (m, 1H), 5.04-4.95 (m, 2H), 3.72 (d, $J$ = 5.8 Hz, 1H), 3.61 (d, $J$ = 5.9 Hz, 1H), 2.28 (d, $J$ = 6.2 Hz, 1H), 2.21 (d, $J$ = 6.2 Hz, 1H), 1.24 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.7, 151.4, 151.1, 144.7, 142.4, 132.6, 109.7, 84.4, 76.2, 43.5, 34.3, 21.7. data for **50b**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 8.27 (s, 1H), 5.94 (dd, $J$ = 5.8, 2.0 Hz, 1H), 5.73-5.70 (m, 1H), 5.02-4.96 (m, 2H), 3.71 (d, J = 6.0 Hz, 1H), 3.64 (d, $J$ = 6.0 Hz, 1H), 2.29 (d, $J$ = 6.2 Hz, 1H), 2.22 (d, $J$ = 6.1 Hz, 1H), 1.23 (s, 3H); $^{13}$C NMR

($CDCl_3$, 75 MHz) δ 151.5, 151.3, 151.0, 144.3, 142.9, 132.3, 108.7, 83.6, 74.8, 43.5, 34.8, 21.7.

**(*rel*)-(1′*R*,3′*R*)-Diethyl{9-(3′-Methyl-3′-vinyl-tetrahydrofuran-1′-yl) 6-chloropurine} phosphonate (51):** To a $CH_2Cl_2$ (10 mL) solution of 6-chloropurine derivative **50b** (218 mg, 0.824 mmol) and diethyl vinylphosphonate (676 mg, 4.12 mmol), $2^{nd}$-generation Grubbs catalyst (34.98 mg, 0.0412 mmol) was added. The reaction mixture was refluxed for 20 h under dry argon gas and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/*n*-Hexane/MeOH, 3:1:0.03) to give **51** (194 mg, 59%) as a form: $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1H), 8.31 (s, 1H), 6.57 (dd, *J* = 16.4, 20.5 Hz, 1H), 6.06 (dd, *J* = 16.5, 19.8. Hz, 1H), 5.97 (dd, *J* = 5.8, 1.8 Hz, 1H), 4.15-4.10 (m, 4H), 3.73 (d, *J* = 6.4 Hz, 1H), 3.66 (d, *J* = 6.5 Hz, 1H), 2.28 (d, *J* = 7.2 Hz, 1H), 2.22 (d, *J* = 7.2 Hz, 1H), 1.21-1.31 (m, 9H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.7, 151.4, 153.2, 149.9, 144.6, 133.1, 115.3, 84.2, 76.1, 63.6, 63.1, 43.6, 35.5, 21.3, 14.4.

**(*rel*)-(1′*R*,3′*R*)-Diethyl {9-(3′-methyl-3′-vinyl-tetrahydrofuran-1′-yl) adenine}phosphonate (52):** A solution of **51** (213 mg, 0.533 mmol) in saturated methanolic ammonia (10 mL) was stirred overnight at 60℃ 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 **52** (112 mg, 55%) as a white solid: mp

174−176℃; UV (MeOH) $\lambda_{max}$ 261.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.31 (s, 1H), 8.10 (s, 1H), 6.61 (dd, $J$ = 20.4, 17.0 Hz, 1H), 6.15 (dd, $J$ = 18.9, 17.1 Hz, 1H), 5.96 (dd, $J$ = 6.4, 1.8 Hz, 1H), 4.15−4.07 (m, 4H), 3.73 (d, $J$ = 6.4 Hz, 1H), 3.65 (d, $J$ = 6.3 Hz, 1H), 2.26−2.14 (m, 6H), 1.24−1.19 (m, 9H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.4, 152.5, 149.4, 148.3, 140.5, 119.5, 116.2, 84.6, 75.4, 62.4, 61.6, 42.7, 35.2, 21.5, 14.5.

**(*rel*)−(1′*R*,3′*R*)−9−(3′−Methyl−3′−vinyl−tetrahydrofuran−1′−yl) adenine}phosphonic acid (53):** To a solution of the phosphonate **52** (153 mg, 0.403 mmol) in anhydrous $CH_3CN$ (10 mL) and 2,6−lutidine (0.938 mL, 8.06 mmol) was added trimethylsilyl bromide (0.616 mg, 4.03 mmol). The mixture was heated overnight at 70℃ under nitrogen gas and then concentrated *in vacuo*. The residue was partitioned between $CH_2Cl_2$ (100 mL) and purified water (100 mL). The aqueous layer was washed with $CH_2Cl_2$ (2 × 70 mL) and then freeze−dried to give phosphonic acid **53** (97 mg, 74%) as a yellowish foam: UV ($H_2O$) $\lambda_{max}$ 261.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.34 (s, 1H, H−8), 8.14 (s, 1H, H−2), 6.61 (dd, $J$ = 20.4, 17.0 Hz, 1H, H−2′), 6.15 (dd, $J$ = 18.9, 17.1 Hz, 1H, H−5′), 5.95 (dd, $J$ = 6.4, 1.8 Hz, 1H, PCH), 3.75 (d, $J$ = 6.2 Hz, 1H, H−6′a), 3.67 (d, $J$ = 6.3 Hz, 1H, H−6′b), 2.24−2.12 (m, 2H, H−3′a, H−3′b), 1.25 (m, 3H, $CH_3$); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 155.3, 152.3, 149.4, 148.7, 139.3, 118.9, 115.2, 84.6, 75.7, 43.5, 35.3, 19.8.

**(*rel*)-(1′*R*,3′*R*)-Diethyl{9-(3′-methyl-3′-ethyltetrahydrofuran-1′-yl)6-chloropurine}phosphonate (54):** A solution of vinyl phosphonate nucleoside analogue **51** (320 mg, 0.798 mmol) in methanol (15 mL) was added 10% Pd/C (10 mg) and cyclohexene (5 mL) under Ar. The reaction mixture was refluxed for 25 h. The reaction mixture was filtered through a pad of Celite, evaporated, and purified by silica gel column chromatography using methanol and methylene chloride (10:1) to give ethyl phosphonate analogue **54** (254 mg, 79%) as a white solid: mp 162-164℃; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 8.35 (s, 1H), 5.96 (dd, $J$ = 5.6, 1.8 Hz, 1H), 4.18-4.12 (m, 4H), 3.71 (d, $J$ = 6.4 Hz, 1H), 3.62 (d, $J$ = 6.3 Hz, 1H), 2.28-2.12 (m, 6H), 1.72-1.63 (m, 9H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.8, 151.5, 150.4, 143.8, 135.2, 85.6, 76.1, 63.3, 62.3, 43.5, 32.1, 27.7, 21.2, 19.4, 14.0.

**(*rel*)-(1′*R*,3′*R*)-Diethyl {9-(3′-methyl-3′-ethyltetrahydrofuran-1′-yl) adenine} phosphonate (55):** Adenine derivative **55** was prepared from 6-chloropurine analogue **54** by the similar ammonolysis procedure as described for **52**: yield 58%; mp 167-169℃; UV (MeOH) $\lambda_{max}$ 262.5 nm; $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 8.28 (s, 1H), 8.07 (s, 1H), 5.94 (dd, $J$ = 6.2, 1.8 Hz, 1H), 4.12-4.06 (m, 4H), 3.72 (d, $J$ = 6.4 Hz, 1H), 3.63 (d, $J$ = 6.3 Hz, 1H), 2.26-2.14 (m, 6H), 1.24-1.19 (m, 9H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.3, 152.4, 149.3, 140.6, 120.1, 84.4, 75.3, 62.5, 61.5, 42.6, 32.3, 28.6,

21.5, 18.4, 14.5.

**(*rel*)−(1′*R*,3′*R*)−{9−(3′−Methyl−3′−ethyl−tetrahydrofuran−1′−yl) adenine} phosphonic acid (56):** Phosphonic acid **56** was synthesized from **55** using the similar hydrolysis condition as described for **53**: yield 74%, UV ($H_2O$) $\lambda_{max}$ 262.0 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.33 (s, 1H, H−8), 8.14 (s, 1H, H−2), 5.93 (dd, $J$ = 6.3, 1.8 Hz, 1H, H−2′), 3.72 (d, $J$ = 6.2 Hz, 1H, H−6′a), 3.66 (d, $J$ = 6.2 Hz, 1H, H−6′b), 2.23−2.12 (m, 6H, H−3′a, H−3′b, H−5′a, H−5′b, $PCH_2$), 1.26 (m, 3H, $CH_3$); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 155.5, 152.2, 149.1, 138.5, 119.8, 83.7, 74.6, 42.7, 32.2, 28.4, 20.7, 18.8; Anal. Calc. for $C_{12}H_{18}N_5O_4P$ (+ 1.0 $H_2O$): C, 41.74; H, 5.84; N, 20.28; Found: C, 41.71; H, 5.82; N, 20.30; MS *m/z* 328 $(M+H)^+$.

**(*rel*)−(1′*R*,3′*S*)−3′−Methyl−3′−vinyl−tetrahydrofuran−1′−yl) 2−fluoro−6−chloropurine (57a) and (*rel*)−(1′*R*,3′*R*)−3′−methyl−3′−vinyl−tetrahydrofuran−1′−yl)2−fluoro−6−chloropurine(57b):**Coupling of **49** with 2−fluoro−6−chloropurine under the similar condensation conditions as described for **50** to give **57a** and **57b**, respectively: data for **57a**: yield 32%; UV (MeOH) $\lambda_{max}$ 269.0 nm; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 1H), 5.98 (t, $J$ = 5.5 Hz, 1H), 5.73 (m, 1H), 5.06−4.94 (m, 2H), 3.74 (d, $J$ = 6.8 Hz, 1H), 3.53 (d, $J$ = 6.7 Hz, 1H), 2.28 (dd, $J$ = 10.2, 8.2 Hz, 1H), 2.20 (dd, $J$ = 10.2, 6.8 Hz, 1H), 1.24 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 154.9, 152.4, 149.3, 147.9, 144.5, 128.6, 110.1, 84.2, 75.7, 43.3, 34.2, 20.7. data for **57b**: yield 33%; UV

(MeOH) $\lambda_{max}$ 268.5 nm; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 5.97−5.90 (dd, *J* = 6.2, 2.8 Hz, 1H), 5.74−5.69 (m, 1H), 3.73 (d, *J* = 6.6 Hz, 1H), 3.68 (d, *J* = 6.7 Hz, 1H), 1H), 2.31 (dd, *J* = 6.8, 10.4 Hz, 1H), 2.23 (dd, *J* = 8.8, 10.3 Hz, 1H), 1.25 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 150.0, 152.7, 149.6, 143.7, 136.5, 129.1, 109.8, 84.4, 76.2, 42.9, 33.8, 20.3.

**(*rel*)−(1′*R*,3′*R*)−Diethyl {9−(3′−methyl−3′−vinyltetrahydrofuran−1′−yl) 2−fluoro−6−chloropurine} phosphonate (58):** Phosphonate nucleoside analogue **58** was prepared from **57b** using the similar cross metathesis procedure as described for **51**: yield 59%; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.50 (s, 1H), 6.63 (dd, *J* = 16.9, 19.7 Hz, 1H), 6.16 (dd, *J* = 17.1, 19.7 Hz, 1H), 5.99 (dd, *J* = 1.6, 6.0 Hz, 1H), 4.16−4.08 (m, 4H), 3.74 (d, *J* = 7.0 Hz, 1H), 3.63 (d, *J* = 6.9 Hz, 1H), 2.29 (d, *J* = 6.8, 10.4 Hz, 1H), 2.20 (dd, *J* = 8.4, 10.4 Hz, 1H), 1.32 (m, 6H), 1.24 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.1, 153.5, 150.5, 145.7, 129.1, 115.7, 110.2, 84.6, 76.3, 63.2, 62.4, 43.5, 35.3, 21.6, 20.1, 14.3.

**(*rel*)−(1′*R*,3′*R*)−Diethyl {9−(3′−methyl−3′−vinyl−tetrahydrofuran−1′−yl) 2−fluoro−6−aminopurine} phosphonate (59a) and (*rel*)−(1′*R*,3′*R*)−diethyl {9−(3′−methyl−3′−vinyl−tetrahydrofuran−1′−yl) 2−amino−6−chloropurine} phosphonate (59b):** Dry ammonia gas was bubbled into a stirred solution of **58** (390 mg, 0.96 mmol) in DME (18.4 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/$CH_2Cl_2$, 1:8) to give **59a** (41 mg, 16%) and **59b** (170 mg, 46%), respectively: Data for **59a**; UV (MeOH) $\lambda_{max}$ 261.0 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.22 (s, 1H), 7.74 (br s, $NH_2$, 2H), 6.66 (dd, $J$ = 21.1, 17.2 Hz, 1H), 6.13 (dd, $J$ = 20.5, 17.2 Hz, 1H), 5.94 (dd, $J$ = 2.0, 6.0. Hz, 1H), 4.15−4.05 (m, 4H), 3.73 (d, $J$ = 6.8 Hz, 1H), 3.64 (d, $J$ = 6.7 Hz, 1H), 2.32 (dd, $J$ = 8.0, 10.6 Hz, 1H), 2.23 (dd, $J$ = 6.4, 10.6 Hz, 1H), 1.26−1.20 (m, 9H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.3, 152.5, 149.3, 147.6, 143.3, 125.3, 116.7, 84.7, 75.6, 63.1, 62.8, 62.1, 43.8, 35.4, 21.1, 14.5, 13.9; Data for **59b**; UV (MeOH) $\lambda_{max}$ 309.0 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.15 (s, 1H), 7.69 (br s, $NH_2$, 2H), 6.60 (dd, $J$ = 20.9, 17.3 Hz, 1H), 6.12 (dd, $J$ = 21.2, 17.2 Hz, 1H), 5.92 (dd, $J$ = 1.8, 6.5. Hz, 1H), 4.15−4.06 (m, 4H), 3.75 (d, $J$ = 6.9 Hz, 1H), 3.62 (d, $J$ = 6.8 Hz, 1H), 2.31 (dd, $J$ = 6.4, 10.6 Hz, 1H), 2.20 (dd, $J$ = 8.2, 10.6 Hz, 1H), 1.27−1.20 (m, 9H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 158.7, 154.6, 151.5, 149.3, 143.5, 125.8, 116.2, 84.5, 75.4, 63.0, 62.3, 61.7, 43.4, 35.7, 21.5, 15.6.

**(*rel*)−(1′*R*,3′*R*)−9−{(3′−Methyl−3′−vinyl−tetrahydrofuran−1′−yl) guanine} phosphonic acid (60)**: To a solution of **59b** (65.7 mg, 0.158 mmol) dry $CH_3CN$ (12 mL) was added trimethylsilyl bromide (0.0364 mL, 2.76 mmol) at room temperature. After this mixture was stirred for 36 h, the solvent was removed, coevaporating three times with

methanol. The residue was dissolved in MeOH (6.0 mL) and 2-mercaptoethanol (43.2 μL, 0.633 mmol) and NaOMe (33.6 mg, 0.633 mmol) was added to the mixture. The mixture was refluxed for 12 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 **60** (34.5 mg, 64%) as a yellowish form. UV ($H_2O$) $\lambda_{max}$ 254.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.7 (br s, NH, 1H), 8.11 (s, 1H, H-8), 7.02 (br s, $NH_2$, 2H), 6.65 (dd, $J$ = 20.4, 17.6 Hz, 1H, H-2′), 6.14 (dd, $J$ = 19.3, 17.6 Hz, 1H, H-5′), 5.92 (dd, $J$ = 2.4, 6.6. Hz, 1H, PCH), 3.75 (d, $J$ = 6.8 Hz, 1H, H-6′a), 3.59 (d, $J$ = 6.7 Hz, 1H, H-6′b), 2.33 (dd, $J$ = 6.8, 10.8 Hz, 1H, H-3′a), 2.22 (dd, $J$ = 8.4, 10.8 Hz, 1H, H-3′b), 1.27 (s, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.7, 154.1, 152.6, 148.9, 137.2, 120.5, 112.7, 86.3, 76.4, 62.5, 61.9, 43.6, 36.0, 34.6, 20.5, 15.1; 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, 38.23; H, 5.32; N, 18.55; MS *m/z* 342 $(M+H)^+$.

**(*rel*)-(1′*R*,3′*R*)-Diethyl {9-(3′-methyl-3′-ethyl tetrahydrofuran-1′-yl) 2-fluoro-6-chloropurine} phosphonate (61):** Compound **61** was synthesized from **58** by the similar catalytic hydrogenation procedure as described for **56**: yield 75%; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.64 (s, 1H), 5.94 (dd, $J$ = 1.8, 6.6 Hz, 1H), 4.15-4.03 (m, 4H), 3.73 (d, $J$ = 6.8 Hz, 1H), 3.60 (d, $J$ = 6.7 Hz, 1H), 2.31 (dd, $J$ = 6.4,

10.7 Hz, 1H), 2.13 (m, 3H), 1.73 (m, 2H), 1.28 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.3, 152.5, 147.7, 142.8, 124.5, 83.6, 75.5, 63.4, 62.8, 61.7, 44.1, 32.7, 28.4, 20.5, 18.6, 14.3.

**(*rel*)−(1′*R*,3′*R*)−Diethyl{9−(3′−methyl−3′−ethyl−tetrahydrofuran−1′−yl) 2−fluoro−6−aminopurine} phosphonate (62a) and (*rel*)−(1′*R*,3′*R*)−diethyl{9−(3′−methyl−3′−ethyl−tetrahydrofuran−1′−yl) 2−amino−6−chloropurine} phosphonate (62b)**: Ammonolysis of **61** was performed using the similar procedure as described for **55**: Data for **62a**; yield 13%; UV (MeOH) $\lambda_{max}$ 261.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.19 (s, 1H), 7.76 (br s, $NH_2$, 2H), 5.94 (dd, $J$ = 2.2, 6.2. Hz, 1H), 4.14−4.10 (m, 4H), 3.74 (d, $J$ = 6.8 Hz, 1H), 3.62 (d, $J$ = 6.8 Hz, 1H), 2.30 (dd, $J$ = 6.6, 10.4 Hz, 1H), 2.14−2.09 (m, 3H), 1.69 (m, 2H), 1.25 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.0, 152.5, 147.2, 143.8, 125.6, 84.2, 75.7, 62.4, 61.7, 43.8, 33.0, 27.6, 20.6, 18.9, 14.3; Data for **62b**; yield 42%; UV (MeOH) $\lambda_{max}$ 309.0 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.15 (s, 1H), 7.68 (br s, $NH_2$, 2H), 5.96 (dd, $J$ = 2.4, 6.4, Hz, 1H), 4.14−4.09 (m, 4H), 3.73 (d, $J$ = 6.8 Hz, 1H), 3.59 (d, $J$ = 6.8 Hz, 1H), 2.18−2.10 (m, 4H), 1.72 (m, 2H), 1.28 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.8, 153.8, 151.5, 143.7, 125.7, 85.0, 74.6, 62.7, 62.0, 61.5, 44.1, 33.2, 27.5, 21.2, 18.9, 16.2, 15.1.

**(*rel*)−(1′*R*,3′*R*)−9−{(3′−Methyl−3′−ethyl−tetrahydrofuran−1′−yl) guanine} phosphonic acid (63)**: Nucleoside phosphonic acid **23** was

prepared from **62b** by the similar hydrolysis conditions used for **60**: yield 62%; UV ($H_2O$) $\lambda_{max}$ 253.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 10.9 (br s, NH, 1H), 8.07 (s, 1H, H−8), 6.98 (br s, $NH_2$, 2H), 5.95 (dd, $J$ = 2.3, 6.6. Hz, 1H, H−2′), 3.72 (d, $J$ = 6.7 Hz, 1H, H−6′a), 3.62 (d, $J$ = 6.8 Hz, 1H, H−6′b), 2.34 (dd, $J$ = 6.4, 10.2 Hz, 1H, H−3′a), 2.18−2.10 (m, 3H, H−3′b, $PCH_2$), 1.72 (m, 2H, H−5′a, H−5′b), 1.27 (s, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.7, 154.8, 152.4, 136.2, 118.5, 75.8, 73.1, 45.3, 33.1, 28.5, 22.4, 20.3; MS *m/z* 344 $(M+H)^+$.

**1−(*t*−Butyldimethylsilanyloxymethyl)cyclopropanecarbaldehyde(65):** To a stirred solution of oxalyl chloride (254 mg, 2.0 mmol) in $CH_2Cl_2$ (12 mL) was added a solution of DMSO (234 mg, 3.0 mmol) in $CH_2Cl_2$ (8.0 mL) dropwise at –78℃. The resulting solution was stirred at −78℃ for 10 min, and a solution of alcohol **64** (216 mg, 1.0 mmol) in $CH_2Cl_2$ (12 mL) was added dropwise. The mixture was stirred at −78℃ for 20 min and TEA (608 mg, 6.01 mmol) was added. The resulting mixture was warmed to 0℃ and stirred for 30 min. $H_2O$ (30 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 150 mL two times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane,

1:20) to give aldehyde compound **65** (199 mg, 93%) as a colorless oil: $^{1}$H NMR ($CDCl_3$, 300MHz) δ 9.79 (s, 1H), 3.99 (s, 2H), 0.75−0.63 (m, 4H), 0.83 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 204.2, 73.5, 25.4, 18.42, 8.7, −5.5.

***t*−Butyldimethyl−(1−vinyl−cyclopropylmethoxy)silane (66)**: To ylide solution [methyltriphenylphosphonium iodide (376 mg, 0.925 mmol), triphenylphosphine (28.5 mg, 0.11 mmol), 1.6 M *n*−butyllithium solution (0.578 mL, 0.925 mmol) in dry tetrahydrofuran (7.0 mL) at −78℃, was dropwise added to a solution of olefin **65** (198 mg, 0.925 mmol) in dry THF (7 mL). The reaction mixture was warmed to room temperature and stirred for 5 h, quenched by saturated sodium bicarbonate solution. The reaction mixture was partitioned between saturated sodium bicarbonate solution and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in* vacuum and chromatographed (hexane−EtOAc, 20:1) to afford **66** (161 mg, 82%) as a colorless oil. $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 5.34 (m, 1H), 5.05−4.96 (m, 2H), 3.75 (m, 2H), 1.02−0.94 (m, 2H), 0.82 (s, 9H), 0.35−0.31 (m, 2H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 148.8, 109.3, 77.6, 25.5, 24.8, 18.4, 6.4, −5.3.

**2−[1−(*t*−Butyldimethylsilanyloxymethyl) cyclopropyl] ethanol (67)**: Anhydrous tetrahydrofuran (THF) solution of 1 M borane/THF

complex (11.1 mL, 11.1 mmol) was stirred at 0℃ under a nitrogen atmosphere and was treated dropwise with compound **66** (1.0 g, 4.715 mmol) in THF (10 mL). The solution was stirred at room temperature for 2.5 h. After cooling, the mixture was subsequently treated with THF/$H_2O$ (8.5 mL, 1:1, v/v), 2N NaOH (8.85 mL), and 30% $H_2O_2$ (7.35 mL). The turbid mixture was stirred at room temperature for 2 h. Diethylether (50 mL) was added to the reaction mixture, which was then washed twice with ice/water (15 mL) and saturated NaCl solution (15 mL). After drying over anhydrous $MgSO_4$, the solvents were evaporated and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give compounds **67** (738 mg, 68%) as colorless oils. $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.72 (m, 2H), 3.49 (t, $J$ = 7.0 Hz, 2H), 1.48 (t, $J$ = 7.0 Hz, 2H), 0.94−0.90 (m, 2H), 0.81 (s, 9H), 0.37−0.32 (m, 2H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 77.5, 59.1, 41.3, 25.6, 18.7, 17.3, 6.1, −5.5.

**[1−(*t*−Butyldimethylsilanyloxymethyl) cyclopropyl] acetaldehyde (68):** Aldehyde **68** was synthesized from **67** using the similar Swern oxidation conditions described for **65**. Yield 91%; $^1$H NMR ($CDCl_3$, 300 MHz) δ 9.81 (s, 1H), 3.73 (m, 2H), 2.36 (s, 2H), 1.01−0.94 (m, 2H), 0.82 (s, 9H), 0.35−0.30 (m, 2H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 199.7, 78.2, 53.4, 25.3, 18.2, 15.8, 7.2, −5.3.

**(±)−1−[1−(*t*−Butyldimethylsilanyloxymethyl)cyclopropyl]but−3−en−2−ol (69):** To a solution of **68** (1.1 g, 4.8 mmol) in dry THF (10

mL), vinyl magnesium bromide (5.28 mL, 1.0 M solution in THF) was slowly added at –30℃ and stirred 5 h at 0℃. Saturated $NH_4Cl$ solution (6 mL) was added to the mixture, which was slowly warmed to rt. The mixture was diluted with water (80 mL) and extracted with EtOAc (80 mL) two times. 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, 1:13) to give **69** (935 mg, 76%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 5.91–5.89 (m, 1H), 5.25–5.22 (m, 2H), 3.92 (m, 1H), 3.73 (s, 2H), 1.43 (m, 1H), 1.11–1.05 (m, 2H), 0.82–0.79 (s, 11H), 0.36–0.32 (m, 1H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 141.3, 114.6, 80.1, 71.5, 45.7, 25.3, 18.6, 16.1, 6.9, –5.6.

**(±)–*t*–Butyl–{1–[2–(4–methoxybenzyloxy)–but–3–enyl] cyclo propylmethoxy} dimethylsilane (70):** NaH (60% in mineral oil, 78.6 mg, 1.99 mmol) was added portion–wise to a cooled (0℃) solution of alcohol **69** (426 mg, 1.662 mmol) and *p*–methoxybenzyl chloride (0.246 mL, 1.82 mmol) in anhydrous DMF (10 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was diluted with $H_2O$ (80 mL) followed by extraction with diethyl ether (80 mL) two times. 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 **70**

(419 mg, 67%) as a colorless oil. $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.22 (m, 2H), 6.91–6.85 (m, 2H), 5.91 (m, 1H), 5.25–5.21 (m, 2H), 4.64 (s, 2H), 3.73 (s, 3H), 3.70–3.66 (m, 2H), 3.54 (m, 1H), 1.40 (m, 2H), 1.15–1.10 (m, 1H), 0.82 (s, 9H), 0.67–0.63 (m, 2H), 0.35–0.31 (m, 1H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.7, 141.5, 133.3, 127.6, 121.4, 115.8, 114.5, 80.4, 73.5, 46.2, 25.5, 18.5, 16.2, 7.3, −5.4.

**(±)−{1−[2−(4−Methoxybenzyloxy)−but−3−enyl] cyclopropyl} methanol (71):** To a solution of **70** (1.63 g, 4.33 mmol) in THF (15 mL), TBAF (5.11 mL, 1.0 M solution in THF) was added at 0℃. The mixture was stirred overnight at rt and concentrated *in vacuum*. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 4:1) to give **71** (920 mg, 81%): $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.24 (m, 2H), 6.94–6.86 (m, 2H), 5.91–5.86 (m, 1H), 5.25–5.20 (m, 2H), 4.63 (s, 2H), 3.74 (s, 3H), 3.58–3.51 (m, 3H), 1.40 (m, 2H), 1.07–1.02 (m, 1H), 0.43–0.38 (m, 2H), 0.19–0.15 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.4, 141.7, 132.4, 127.9, 118.1, 115.0, 77.2, 74.1, 73.4, 56.0, 45.3, 13.5, 6.5.

**(±)−1−[2−(4−Methoxy−benzyloxy)−but−3−enyl] cyclopropane carbaldehyde (72):** Aldehyde derivative **72** was synthesized from **71** by the similar Swern oxidation procedure as described for **65** or **68**: yield 88%; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 9.87 (s, 1H), 7.31–7.24 (m, 2H), 6.91–6.85 (m, 2H), 5.90–5.88 (m, 1H), 5.24–5.19 (m, 2H),

4.65 (s, 2H), 3.74 (s, 3H), 3.54 (m, 1H), 1.73−1.70 (m, 2H), 1.11−1.05 (m, 1H), 0.69−0.63 (m, 2H), 0.32−0.27 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 200.7, 159.3, 141.1, 130.7, 129.3, 117.0, 114.2, 74.2, 73.3, 55.4, 41.3, 29.1, 13.6, 7.1.

**(*rel*)−(1*R*,4*S*) and (1*S*,4*S*)−4−Vinyl−2−spirocyclopropyl−tetrahydrofuran−1−ol (73):** To a solution of compound **72** (80.9 mg, 0.311 mmol) in $CH_2Cl_2/H_2O$ (6 mL, 10:1 v/v) was added DDQ (70.6 mg, 0.311 mmol), and the mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ (0.4 mL) was added to quench the reaction, which was then stirred for 3 h at room temperature. The mixture was diluted with water (60 mL) and extracted with $CH_2Cl_2$ (3 × 60 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuum* and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give compound **73** (27 mg, 63%): $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 5.92−5.88 (m, 1H), 5.47 (m, 1H), 5.25−5.22 (m, 2H), 4.45−4.41 (m, 1H), 1.78−1.75 (m, 2H), 1.09−1.02 (m, 1H), 0.70−0.63 (m, 2H), 0.33−0.26 (m, 1H).

**(±)−Acetic acid (4−vinyl−2−spirocyclopropyl−tetrahydrofuran−1−yl) ester (74):** To a solution of compound **73** (450 mg, 3.21 mmol) and DMAP (20 mg) in anhydrous pyridine (8 mL), $Ac_2O$ (491 mg, 4.81 mmol) was slowly added, and the mixture was stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure

and co-evaporated with toluene. The residue was diluted with $H_2O$ (100 mL), extracted with EtOAc (100 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **74** (503 mg, 86%) as a colorless oil: $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 18 (d, $J$ = 4.2 Hz, 1H), 5.91-5.86 (m, 1H), 5.26-5.22 (m, 2H), 4.46-4.42 (m, 1H), 2.02 (s, 3H), 1.79-1.74 (m, 2H), 1.10-1.02 (m, 1H), 0.69-0.62 (m, 2H), 0.35-0.28 (m, 1H).

**(*rel*)-(1′*S*,4′*S*)-9-(4′-Vinyl-2′-spirocyclopropyl-tetrahydrofuran-1′-yl) 6-chloropurine (75a) and (*rel*)-(1′*R*,4′*S*)-9-(4′-vinyl-2′-spirocyclopropyl-tetrahydrofuran-1′-yl) 6-chloropurine (75b):** 6-Chloropurine (216 mg, 1.4 mmol), anhydrous HMDS (10 mL), and a catalytic amount of ammonium sulfate (14 mg) were refluxed to a clear solution, and the solvent was distilled under anhydrous conditions. The residue was dissolved in anhydrous 1,2-dichloro ethane (8 mL). To this mixture, a solution of **74** (255 mg, 0.6 mmol) in dry DCE (10 mL) and TMSOTf (311 mg, 1.4 mmol) was added, and the resulting mixture was stirred for 12 h at rt. The reaction mixture was quenched with 5.0 mL of saturated $NaHCO_3$ and stirred for 1 h. The resulting solid was filtered through a Celite pad, and the filtrate was extracted with $CH_2Cl_2$ (80 mL) two times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated

under vacuum. The residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 4:1:0.01) to give compound **75a** (52 mg, 32%) and **75b** (54 mg, 33%): data for **75a**: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.71 (s, 1H), 8.37 (s, 1H), 5.95 (d, $J$ = 1.8 Hz, 1H), 5.88 (m, 1H), 5.26−5.23 (m, 2H), 4.46 (m, 1H), 1.82 (dd, $J$ = 10.8, 6.8 Hz, 1H), 1.70 (dd, $J$ = 10.9, 8.2 Hz, 1H), 1.08−1.02 (m, 1H), 0.71−0.65 (m, 2H), 0.38−0.32 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.7, 151.4, 151.0, 144.4, 141.4, 131.7, 114.5, 98.5, 73.5, 41.2, 26.4, 14.3, 7.1; data for **75b**: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 8.38 (s, 1H), 5.95 (d, $J$ = 1.9 Hz, 1H), 5.88 (m, 1H), 5.25−5.21 (m, 2H), 4.45 (m, 1H), 1.84 (dd, $J$ = 10.6, 7.6 Hz, 1H), 1.70 (dd, $J$ = 10.7, 8.0 Hz, 1H), 1.10−1.04 (m, 1H), 0.69−0.62 (m, 2H), 0.36−0.31 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.5, 151.0, 150.7, 144.1, 141.2, 131.3, 114.1, 97.1, 74.2, 43.5, 27.8, 13.8, 6.5.

**(*rel*)−(1′*R*,4′*S*)−Diethyl {9−(4′−vinyl−2′−spirocyclopropyl−tetrahydrofuran−1′−yl) 6−chloropurine} phosphonate (76):** To a $CH_2Cl_2$ (4.0 mL) solution of 6−chloropurine derivative **75b** (150 mg, 0.542 mmol) and diethyl vinylphosphonate (355 mg, 2.168 mmol), 2$^{nd}$−generation Grubbs catalyst (18.42 mg, 0.0217 mmol) was added. The reaction mixture was refluxed for 24 h under dry argon gas and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/*n*−Hexane/MeOH, 4:1:0.02) to give **76** (136 mg, 61%) as a form: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1H), 8.34

(s, 1H), 6.68 (dd, $J$ = 17.0, 22.4 Hz, 1H), 6.12 (dd, $J$ = 17.1, 19.4. Hz, 1H), 5.98 (d, $J$ = 2.0 Hz, 1H), 4.49 (m, 1H), 4.12−4.06 (m, 4H), 1.85 (dd, $J$ = 10.6, 6.8 Hz, 1H), 1.72 (d, $J$ = 10.6, 8.2 Hz, 1H), 1.32 (m, 6H), 1.09−1.04 (m, 1H), 0.71−0.65 (m, 2H), 0.31−0.24 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.6, 151.4, 151.1, 149.6, 145.6, 132.3, 116.7, 97.2, 74.6, 63.8, 63.3, 41.7, 24.7, 15.2, 13.2, 7.2.

**(*rel*)−(1′*R*,4′*S*)−Diethyl {9−(4′−vinyl−2′−spirocyclopropyl−tetrahydrofuran−1′−yl) adenine} phosphonate (77):** A solution of **76** (166 mg, 0.4 mmol) in saturated methanolic ammonia (7 mL) was stirred overnight at 64℃ in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH /$CH_2Cl_2$, 1:10) to give **77** (92 mg, 59%) as a white solid: mp 179−181℃; UV (MeOH) $\lambda_{max}$ 260.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.38 (s, 1H), 8.16 (s, 1H), 6.65 (dd, $J$ = 17.0, 21.8 Hz, 1H), 6.15 (dd, $J$ = 17.0, 19.0. Hz, 1H), 5.94 (d, $J$ = 2.1 Hz, 1H), 4.40 (m, 1H), 4.13−4.05 (m, 4H), 1.82 (dd, $J$ = 10.8, 6.8 Hz, 1H), 1.70 (d, $J$ = 10.7, 8.6 Hz, 1H), 1.37 (m, 6H), 1.11−1.07 (m, 1H), 0.64−0.60 (m, 2H), 0.27−0.22 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.3, 152.6, 150.4, 148.8, 141.7, 119.2, 116.8, 96.9, 73.8, 62.8, 62.4, 42.4, 25.8, 16.7, 12.9, 6.6.

**(*rel*)−(1′*R*,4′*S*)−9−(4′−Vinyl−2′−spirocyclopropyl−tetrahydrofuran−1′−yl)adenine}phosphonic acid (78):** To a solution of the phosphonate **77** (165 mg, 0.419 mmol) in anhydrous $CH_3CN$ (10 mL)

and 2,6-lutidine (0.898 mL, 8.38 mmol) was added trimethylsilyl bromide (641 mg, 4.19 mmol). The mixture was heated overnight at 75 ℃ under nitrogen gas and then concentrated *in vacuo*. The residue was partitioned between $CH_2Cl_2$ (100 mL) and purified water (100 mL). The aqueous layer was washed with $CH_2Cl_2$ (2 × 70 mL) and then freeze-dried to give phosphonic acid **78** (107 mg, 76%) as a yellowish foam: UV ($H_2O$) $\lambda_{max}$ 261.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.33 (s, 1H, H-8), 8.16 (s, 1H, H-2), 6.64 (dd, $J$ = 17.0, 21.8 Hz, 1H, H-1′), 6.17 (dd, $J$ = 17.2, 18.6 Hz, 1H, H-5′), 5.97 (dd, $J$ = 2.0 Hz, 1H, PCH), 4.47 (m, 1H, H-4′), 1.85 (dd, J = 10.6, 6.8 Hz, 1H, H-3′a), 1.67 (dd, 10.6, 8.2 Hz, 1H, H-3′b), 1.13-1.08 (m, 1H, H-1″a), 0.66-0.61 (m, 2H, H-1″b, H-2″a), 0.31-0.27 (m, 1H, H-2″b); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 155.5, 152.4, 150.5, 149.5, 141.6, 120.1, 116.3, 98.6, 74.5, 41.3, 25.7, 13.2, 7.1.

**(*rel*)-(1′*R*,4′*S*)-Diethyl {9-(4′-ethyl-2′-spirocyclopropyl-tetrahydrofuran-1′-yl) 6-chloropurine} phosphonate (79):** A solution of vinyl phosphonate nucleoside analogue **76** (225 mg, 0.546 mmol) in methanol (6 mL) was added 10% Pd/C (8 mg) and cyclohexene (3 mL) under Ar. The reaction mixture was refluxed for 20 h. The reaction mixture was filtered through a pad of Celite, evaporated, and purified by silica gel column chromatography using methanol and methylene chloride (10:1) to give ethyl phosphonate analogue **79** (172 mg, 76%) as a white solid: mp 174-176℃; $^1$H NMR ($CDCl_3$, 300

MHz) δ 8.74 (s, 1H), 8.33 (s, 1H), 5.92 (d, $J$ = 1.9 Hz, 1H), 4.16–4.11 (m, 4H), 3.74 (m, 1H), 2.21–2.12 (m, 4H), 1.63 (m, 6H), 1.09–1.04 (m, 1H), 0.62–0.57 (m, 2H), 0.29–0.23 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.7, 151.5, 151.1, 145.1, 132.4, 98.4, 71.5, 62.9, 62.4, 42.0, 25.3, 19.4, 14.2, 13.1, 7.3.

**(*rel*)–(1′*R*,4′*S*)–Diethyl {9–(4′–ethyl–2′–spirocyclopropyl–tetrahydrofuran–1′–yl) adenine} phosphonate (80):** Adenine derivative **80** was prepared from 6–chloropurine analogue **79** by the similar ammonolysis procedure as described for **77**: yield 54%; mp 172–174℃; UV (MeOH) $\lambda_{max}$ 261.5 nm; $^{1}$H NMR (DMSO–$d_6$, 300 MHz) δ 8.34 (s, 1H), 8.13 (s, 1H), 5.91 (d, $J$ = 2.1 Hz, 1H), 4.12–4.07 (m, 4H), 3.76 (m, 1H), 2.18–2.12 (m, 4H), 1.60–1.55 (m, 6H), 1.11–1.07 (m, 1H), 0.65–0.59 (m, 2H), 0.34–0.27 (m, 1H); $^{13}$C NMR (DMSO–$d_6$, 75 MHz) δ 155.6, 152.5, 151.4, 141.5, 120.1, 99.1, 72.6, 63.2, 62.8, 41.7, 24.8, 19.1, 15.4, 14.3, 6.8.

**(*rel*)–(1′*R*,4′*S*)–{9–(4′–Ethyl–2′–spirocyclopropyl–tetrahydrofuran–1′–yl) adenine} phosphonic acid (81):** Phosphonic acid **81** was synthesized from **80** using the similar hydrolysis condition as described for **78**: yield 78%, UV ($H_2O$) $\lambda_{max}$ 261.0 nm; $^{1}$H NMR (DMSO–$d_6$, 300 MHz) δ 8.34 (s, 1H, H–8), 8.15 (s, 1H, H–2), 5.92 (s, 1H, H–1′), 3.75 (m, 1H, H–4′), 2.12–2.07 (m, 4H, H–3′a, H–3′b, H–5′a, H–5′b, $PCH_2$), 1.12–1.08 (m, 1H, H–1″a), 0.67–0.59 (m, 2H, H–1″b, H–2″a), 0.36–0.31 (m, 1H, H–2″b); $^{13}$C NMR (DMSO–$d_6$, 75

MHz) δ 155.3, 152.5, 150.6, 141.7, 119.4, 97.8, 72.5, 41.5, 28.4, 25.3, 19.1, 13.7, 7.2.

**(*rel*)−(1′*S*,4′*S*)−(4′−Vinyl−2′−spirocyclopropyl−tetrahydrofuran−1′−yl) 2−fluoro−6−chloropurine (82a) and (*rel*)−(1′*R*,4′*S*)−( 4′−vinyl−2′−spirocyclopropyl−tetrahydrofuran−1′−yl) 2−fluoro−6−chloropurine (82b):** Condensation of **74** with 2−fluoro−6−chloropurine under the similar Vorbruggen condensation conditions as described for **75a** and **75b** to give **82a** and **82b**, respectively: data for **82a**: yield 31%; UV (MeOH) $\lambda_{max}$ 268.0 nm; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 5.96 (s, 1H), 5.88 (m, 1H), 5.25−5.22 (m, 2H), 4.45 (m, 1H), 1.85 (dd, *J* = 10.6, 8.6 Hz, 1H), 1.71 (dd, *J* = 10.5, 6.4 Hz, 1H), 1.14−1.09 (m, 1H), 0.69−0.64 (m, 2H), 0.32−0.21 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 154.7, 152.1, 149.3, 147.7, 144.6, 141.2, 128.4, 115.2, 98.5, 72.5, 41.2, 25.3, 13.6, 7.8. data for **82b**: yield 30%; UV (MeOH) $\lambda_{max}$ 269.5 nm; $^{1}$H NMR ($CDCl_3$, 300 MHz) 8.45 (s, 1H), 5.95 (d, *J* = 2.2 Hz, 1H), 5.84 (m, 1H), 5.26−5.21 (m, 2H), 4.47 (m, 1H), 1.86 (dd, *J* = 10.5, 6.2 Hz, 1H), 1.78 (dd, *J* = 10.6, 8.8 Hz, 1H), 1.09−1.02 (m, 1H), 0.66−0.60 (m, 2H), 0.29−0.22; $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 154.4, 151.8, 148.9, 147.2, 143.8, 140.7, 128.5, 114.8, 99.2, 73.3, 40.9, 24.8, 14.2, 6.9.

**(*rel*)−(1′*R*,4′*S*)−Diethyl {9−(4′−vinyl−2′−spirocyclopropyl−tetrahydrofuran−1′−yl)2−fluoro−6−chloropurine} phosphonate (83):** Phosphonate nucleoside analogue **83** was prepared from **82b** using the

similar cross metathesis procedure as described for **76**: yield 61%; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.46 (s, 1H), 6.69 (dd, $J$ = 21.4, 17.0 Hz, 1H), 6.22 (dd, $J$ = 19.2, 17.1 Hz, 1H), 5.98 (d, $J$ = 2.1 Hz, 1H), 4.14−4.09 (m, 4H), 1.84 (dd, $J$ = 10.6, 8.4 Hz, 1H), 1.71 (dd, $J$ = 10.7, 6.6 Hz, 1H), 1.34 (m, 6H), 1.08−0.99 (m, 1H), 0.59−0.52 (m, 2H), 0.28−0.23 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 154.8, 152.4, 149.2, 144.7, 130.4, 115.8, 98.2, 74.7, 62.9, 62.5, 41.2, 21.8, 13.7, 7.5.

**(*rel*)−(1′*R*,4′*S*)−Diethyl {9−(4′−vinyl−2′−spirocyclopropyl−tetrahydrofuran−1′−yl) 2−fluoro−6−aminopurine} phosphonate (84a) and (*rel*)−(1′*R*,4′*S*)−diethyl {9−(4′−vinyl−2′−spirocyclopropyl−tetrahydrofuran−1′−yl) 2−amino−6−chloropurine} phosphonate (84b)**: Dry ammonia gas was bubbled into a stirred solution of **83** (210 mg, 0.487 mmol) in DME (8.5 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 **84a** (34 mg, 17%) and **84b** (93 mg, 45%), respectively: Data for **84a**; UV (MeOH) $\lambda_{max}$ 260.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.19 (s, 1H), 7.75 (br s, $NH_2$, 2H), 6.67 (dd, $J$ = 20.8, 17.2 Hz, 1H), 6.24 (dd, $J$ = 20.8, 17.1 Hz, 1H), 5.92 (d, $J$ = 2.0 Hz, 1H), 4.14−4.08 (m, 4H), 1.69 (s, 6H), 1.06−0.95 (m, 1H), 0.62−0.54 (m, 2H), 0.30−0.23 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.5, 152.2, 148.8, 147.2, 142.5, 124.7, 117.5,

97.6, 74.2, 63.5, 62.9, 62.4, 40.9, 25.3, 13.9, 8.0; Data for **84b**; UV (MeOH) $\lambda_{max}$ 308.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.12 (s, 1H), 7.67 (br s, $NH_2$, 2H), 6.70 (dd, $J$ = 21.6, 16.9 Hz, 1H), 6.22 (dd, $J$ = 17.0, 21.5 Hz, 1H), 5.96 (d, $J$ = 1.8 Hz, 1H), 4.15−4.06 (m, 4H), 3.75 (d, $J$ = 6.9 Hz, 1H), 3.62 (d, $J$ = 6.8 Hz, 1H), 2.31 (dd, $J$ = 6.4, 10.6 Hz, 1H), 2.19−2.11 (m, 1H), 1.71 (m, 6H), 1.11−1.06 (m, 1H), 0.67−0.59 (m, 2H), 0.34−0.29 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 158.5, 154.3, 151.2, 149.5, 141.6, 124.5, 117.5, 97.7, 73.6, 63.2, 62.8, 41.6, 24.7, 14.2, 7.6.

**(*rel*)−(1′*R*,4′*S*)−9−{(4′−vinyl−2′−spirocyclopropyl−tetrahydrofuran−1′−yl) guanine} phosphonic acid (85):** To a solution of **84b** (135 mg, 0.316 mmol) dry $CH_3CN$ (13 mL) was added trimethylsilyl bromide (0.0728 mL, 5.52 mmol) at room temperature. After this mixture was stirred for 24 h, the solvent was removed, co evaporating three times with methanol. The residue was dissolved in MeOH (13.0 mL) and 2−mercaptoethanol (86.4 μL, 1.266 mmol) and NaOMe (67.2 mg, 1.266 mmol) was added to the mixture. The mixture was refluxed for 12 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 preparative reversed−phase C18 silica gel eluting water to give **85** (34.5 mg, 64%) as a yellowish form. UV ($H_2O$) $\lambda_{max}$ 254.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 10.6 (br s, NH, 1H), 8.12 (s, 1H, H−8), 7.05 (br s, $NH_2$, 2H), 6.65 (dd, $J$ = 20.4, 17.6 Hz, 1H,

H−1′), 6.14 (dd, $J$ = 19.3, 17.6 Hz, 1H, H−5′), 5.94 (d, $J$ = 2.2 Hz, 1H, PCH), 4.38 (m, 1H, H−4′), 1.82 (dd, $J$ = 6.8, 10.4 Hz, 1H, H−3′a), 1.74 (dd, $J$ = 8.6, 10.4 Hz, 1H, H−3′b), 1.12−1.05 (s, 1H, H−1″a), 0.67−0.61 (m, 2H, H−1″b, H−2″a), 0.32−0.27 (m, 1H, H−2″b); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.6, 154.5, 152.5, 148.9, 136.5, 117.5, 114.7, 98.5, 75.4, 63.4, 62.8, 41.7, 25.3, 13.1, 7.9; Anal. Calc. for $C_{13}H_{16}N_5O_5P$ (+ 1.0 $H_2O$): C, 42.05; H, 4.88; N, 18.86; Found: C, 42.08; H, 4.90; N, 18.85; MS *m/z* 354 $(M+H)^+$.

**(*rel*)−(1′*R*,4′*S*)−Diethyl {9−(4−ethyl−tetrahydrofuran−1−yl) 2−fluoro−6−chloropurine} phosphonate (86):** Compound **86** was synthesized from **83** by the similar transfer catalytic hydrogenation procedure as described for **79**: yield 66%; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.41 (s, 1H), 5.95 (d, $J$ = 2.0 Hz, 1H), 4.15−4.11 (m, 4H), 3.77 (s, 1H), 2.24−2.17 (m, 4H), 1.11−1.05 (m, 1H), 0.61−0.55 (m, 2H), 0.31−0.27 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 154.7, 152.1, 147.5, 144.6, 127.9, 98.3, 70.4, 63.6, 62.1, 41.7, 28.7, 25.5, 19.1, 13.9, 6.6.

**(*rel*)−(1′*R*,4′*S*)−Diethyl {9−(4−ethyl−tetrahydrofuran−1−yl) 2−fluoro−6−aminopurine} phosphonate (87a) and (*rel*)−(1′*R*,4′*S*)−diethyl{9−(4−ethyl−tetrahydrofuran−1−yl) 2−amino−6−chloropurine} phosphonate (87b):** Ammonolysis of **86** using the same procedure described for **84a** and **84b** to gave **87a** and **87b**, respectively: Data for **87a**; yield 15%; UV (MeOH) $\lambda_{max}$ 261.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.18 (s, 1H), 7.76 (br s, $NH_2$, 2H, $D_2O$

exchangeable), 5.98 (d, $J$ = 2.2 Hz, 1H), 3.75 (m, 1H), 2.54−2.44 (m, 4H), 1.63 (dd, $J$ = 8.0, 10.6 Hz, 1H), 1.52 (dd, $J$ = 6.0, 10.7 Hz, 1H), 1.42 (m, 6H), 0.99−0.92 (m, 1H), 0.54−0.47 (m, 2H), 0.21−0.16 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 154.8, 152.0, 147.1, 142.8, 124.3, 97.5, 72.1, 63.2, 62.5, 61.9, 43.0, 29.5, 24.6, 18.5, 13.5, 8.1. Data for **87b**; yield 41%; UV (MeOH) $\lambda_{max}$ 307.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.15 (s, 1H), 7.68 (br s, $NH_2$, 2H, $D_2O$ exchangeable), 5.96 (d, $J$ = 2.1 Hz, 1H), 3.77 (m, 1H), 2.36−2.30 (m, 4H), 1.70 (dd, $J$ = 8.5, 10.7 Hz, 1H), 1.54 (dd, $J$ = 6.2 Hz, 10.6 Hz, 1H), 1.35 (m, 6H), 1.02−0.91 (m, 1H), 0.56−0.48 (m, 2H), 0.22−0.18 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.8, 153.2, 150.6, 143.5, 124.8, 98.5, 77.7, 63.2, 62.6, 42.1, 29.4, 24.7, 18.8, 13.1, 7.4.

**(*rel*)−(1′*R*,4′*S*)−9−{(4−Ethyl−tetrahydrofuran−1−yl)guanine} phosphonic acid (88):** Nucleoside phosphonic acid **88** was synthesized by the hydrolysis conditions used for **85**. Yield 56%; UV ($H_2O$) $\lambda_{max}$ 253.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 10.5 (br s, NH, 1H, $D_2O$ exchangeable), 8.07 (s, 1H, H−8), 7.01 (br s, $NH_2$, 2H, $D_2O$ exchangeable), 5.95 (d, $J$ = 2.4 Hz, 1H, H−1′), 3.76 (m, 1H, H−4′), 2.30−2.23 (m, 4H, H−5′a, H−5′b, $PCH_2$), 1.67 (dd, $J$ = 8.2, 10.6 Hz, 1H, H−3′a), 1.52 (dd, $J$ = 6.6, 10.5 Hz, 1H, H−3′b), 0.98−0.90 (m, 1H, H−1″a), 0.48−0.41 (m, 2H, H−1″b, H−2″a), 0.24−0.19 (m, 1H, H−2″b); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.5, 154.3, 152.1, 136.7, 118.0, 96.2, 74.3, 63.4, 62.9, 42.5, 28.7, 25.2, 19.0, 14.3, 7.6; Anal.

Calc. for $C_{13}H_{18}N_5O_5P$ (+2.0 $H_2O$): C, 39.90; H, 5.66; N, 17.89; Found: C, 39.88; H, 5.68; N, 17.91; MS *m/z* 356 $(M+H)^+$.

**(±)-1-[1-(t-Butyldimethylsilanyloxymethyl)Allyl]CycloPropane carboxylic Acid Ethyl Ester (91).** A solution of ester derivative **90** (444 mg, 1.63 mmol) in *t*-butyl alcohol (5.0 mL) was added to a stirred mixture of potassium tbutoxide (738 mg, 6.60 mmol) in *t*-butyl alcohol (5.0 mL). After the mixture was stirred at room temperature for 20 min, potassium iodide (546 mg, 3.3 mmol) and (2-chloroethyl)dimethylsulfonium iodide (768 mg, 3.06 mmol) were added in portions under a stream of nitrogen. The mixture was stirred at room temperature for 2.0 h, diluted with saturated $NH_4Cl$ solution (50 mL), and extracted with ether (2 × 120 mL). The combined organic layer was washed with brine, dried under anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (EtOAc/hexane, 1:20) on silica gel to give cyclopropanoid **91** (150 mg, 31%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.72-5.68 (m, 1H), 5.04-4.96 (m, 2H), 4.15 (q, $J$ = 6.8 Hz, 2H), 3.81 (m, 2H), 2.89 (m, 1H), 1.32 (m, $J$ = 6.8 Hz, 3H), 1.01-0.96 (m, 2H), 0.82 (s, 9H), 0.27-0.21 (m, 2H), 0.02 (m, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 184.3, 143.2, 115.1, 65.3, 61.3, 51.4, 25.5, 24.1, 18.4, 10.2, -5.3.

**(±)-3-Vinyl-2-spiropropyl-dihydrofuran-1-one (92).** To a solution of **91** (1.1 g, 3.68 mmol) in THF (6 mL), TBAF (4.4 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, 8:1) to give **92** (274 mg, 54%): $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.71−5.67 (m, 1H), 5.04−4.98 (m, 2H), 4.34 (dd, $J$ = 6.6, 10.2 Hz, 1H), 4.24 (dd, $J$ = 8.2, 10.2 Hz, 1H), 2.78 (m, 1H), 1.02 (m, 2H), 0.55 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 184.8, 143.6, 115.3, 71.4, 44.3, 33.8, 15.7, 10.4.

**(±)−3−Vinyl−2−spiropropyl−dihydrofuran−1−ol (93).** To a cooled (−78℃), stirred solution of lactone **92** (450 mg, 3.25 mmol) in dry toluene (10 mL) was added dropwise a 1.0 M solution of diisobutylaluminium hydride (DIBALH) (3.58 mL, 3.58 mmol). The reaction was stirred for 20 min. at −78℃, followed by dropwise addition of methanol (3.5 mL) and diluted with ethyl acetate (50 mL). The reaction mixture was warmed to room temperature and stirred for 1 h, and the precipitate was removed by filtration through a pad of Celite, washed with ethyl acetate. The filtrate and washings were concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give **93** (323 mg, 71%) as a colorless oil: $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.74−5.68 (m, 1H), 5.47 (m, 1H), 5.03−4.95 (m, 2H), 3.77−3.68 (m, 2H), 2.53−2.49 (m, 1H), 0.98−0.95 (m, 2H), 0.35−0.30 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 141.5, 140.9, 115.4, 110.2, 109.7, 62.2, 61.8, 45.3, 40.2, 39.8, 16.3, 15.9, 10.7.

**( ± )−Acetic Acid 3−Vinyl−2−spiropropyl−dihydrofuran−1−yl Ester (94)**. To a solution of compound **93** (124 mg, 0.88 mmol) in anhydrous pyridine (6 mL), $Ac_2O$ (132 mg, 1.31 mmol) was slowly added, and the mixture was stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure and co−evaporated with toluene. The residue was diluted with $H_2O$ (60 mL), extracted with EtOAc (2 × 60 mL). The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromate−graphy (EtOAc/hexane, 1:20) to give compound **94** (142 mg, 88%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.22−6.19 (m, 1H), 5.75−5.70 (m, 1H), 5.04−4.96 (m, 2H), 3.76−3.70 (m, 2H), 2.52−2.48 (m, 1H), 0.94−0.90 (m, 2H), 0.34−0.29 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 171.4, 171.1, 140.8, 114.6, 114.3, 112.2, 111.9, 61.5, 61.2, 44.7, 44.2, 32.8, 32.5, 18.7, 18.4, 16.0, 15.7, 11.2, 10.8.

**(*rel*)−(1′*R*,3′*S*)−9−(3′−Vinyl−2′−spiropropyl−dihydrofuran−1′−yl) 6−chloropurine (95a) and (*rel*)−(1′*S*,3′*S*)−9−(3′−vinyl−2′−spiropropyl−dihydrofuran−1′−yl)6−chloropurine (95b)**. 6−Chloropurine (226 mg, 1.48 mmol), anhydrous HMDS (15 mL), and a catalytic amount of ammonium sulfate (20 mg) were refluxed to a clear solution, and the solvent was distilled under anhydrous conditions. The residue was dissolved in anhydrous 1,2−dichloroethane (15 mL). To this mixture, a solution of **94** (157 mg,

0.86 mmol) in dry DCE (15 mL) and TMSOTf (327 mg, 1.48 mmol) was added, and the resulting mixture was stirred for 4 h at rt. The reaction mixture was quenched with 3.0 mL of saturated $NaHCO_3$ and stirred for 1 h. The resulting solid was filtered through a Celite pad, andthe filtrate was diluted with water (120 mL) and extracted with $CH_2Cl_2$ (2 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 2:1:0.03) to give compound **95a** (76 mg, 32%) and **95b** (78 mg, 33%): data for **95a**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.72 (s, 1H), 8.25 (s, 1H), 5.95 (dd, $J$ = 5.8, 2.0 Hz, 1H), 5.71−5.68 (m, 1H), 5.03−4.95 (m, 2H), 3.76 (dd, $J$ = 10.6, 6.2 Hz, 1H), 3.65 (dd, $J$ = 10.5, 8.2 Hz, 1H), 2.53 (m, 1H), 0.94 (m, 1H), 0.45 (m, 2H), 0.12 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 151.8, 151.5, 150.9, 144.7, 141.7, 132.5, 114.5, 97.3, 64.4, 48.3, 32.1, 13.5, 7.5; data for **95b**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.70 (s, 1H), 8.23 (s, 1H), 5.94 (m, 1H), 5.74−5.69 (m, 1H), 5.06−5.01 (m, 2H), 3.77 (dd, $J$ = 10.8, 7.8 Hz, 1H), 3.65 (dd, $J$ = 10.8, 8.8 Hz, 1H), 2.54−2.51 (m, 1H), 1.01 (m, 1H), 0.43−0.38 (m, 2H), 0.11 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 151.7, 151.4, 150.8, 143.9, 141.5, 133.7, 115.0, 94.8, 65.7, 47.8, 33.5, 16.4, 8.0.

**(*rel*)−(1′*S*,3′*S*)−Diethyl{9−(3′−vinyl−2′−spiropropyl−dihydrofuran−1′−yl) 6−chloropurine}phosphonate (96).** To a $CH_2Cl_2$ (6 mL) solution

of 6-chloropurine derivative **95b** (57 mg, 0.21 mmol) and diethyl vinylphosphonate (169 mg, 1.03 mmol), $2^{nd}$-generation Grubbs catalyst (8.7 mg, 0.01 mmol) was added. The reaction mixture was refluxed for 36 h under dry argon gas and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/n-Hexane/MeOH, 4:1:0.05) to give **96** (51 mg, 60%) as a form: $_1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.75 (s, 1H), 8.28 (s, 1H), 6.64 (dd, $J$ = 16.8, 20.0 Hz, 1H), 6.11 (dd, $J$ = 16.8, 20.1 Hz, 1H), 5.97 (dd, $J$ = 5.8, 1.8 Hz, 1H), 4.10-4.05 (m, 4H), 3.77 (dd, $J$ = 10.0, 6.8 Hz, 1H), 3.61 (dd, $J$ = 10.1, 8.6 Hz, 1H), 2.53-2.49 (m, 1H), 1.31-1.28 (m, 6H), 0.95 (m, 1H), 0.39-0.36 (m, 2H), 0.11 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 151.6, 151.2, 150.5, 149.4, 144.5, 135.2, 116.1, 97.8, 65.4, 63.7, 63.2, 49.4, 32.4, 16.7, 13.5, 7.9.

**(*rel*)-(4′*S*,7′*S*)-Diethyl{9-(3′-vinyl-2′-spiropropyl-dihydrofuran-1′-yl) adenine} phosphonate (97).** A solution of **96** (115 mg, 0.28 mmol) in saturated methanolic ammonia (6 mL) was stirred overnight at 63℃ 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 **97** (61.7 mg, 56%) as a white solid: mp 173-175℃; UV (MeOH) $\lambda_{max}$ 260.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.38 (s, 1H), 8.17 (s, 1H), 6.65 (dd, $J$ = 17.0, 20.2 Hz, 1H), 6.12 (dd, $J$ = 16.9, 20.2 Hz, 1H), 5.95 (dd, $J$ = 5.8, 2.0 Hz, 1H), 4.09-4.05 (m, 4H), 3.73 (dd, $J$ = 10.1, 6.8 Hz, 1H), 3.60 (dd, $J$ = 10.2, 8.6 Hz, 1H),

2.53 (m, 1H), 1.29−1.25 (m, 6H), 0.97 (m, 1H), 0.40−0.37 (m, 2H), 0.12 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 154.7, 152.6, 150.4, 148.7, 141.6, 119.5, 115.5, 97.8, 66.3, 63.8, 63.2, 47.6, 32.7, 14.5, 13.7, 7.7.

**(*rel*)−(4′*S*,7′*S*)−9−(3′−Vinyl−2′−spiropropyl−dihydrofuran−1′−yl) adenine} phosphonic acid (98).** To a solution of the phosphonate **97** (95 mg, 0.24 mmol) in anhydrous $CH_3CN$ (6 mL) and 2,6−lutidine (0.562 mL, 4.80 mmol) was added trimethylsilyl bromide (0.269 mg, 2.41 mmol). The mixture was heated overnight at 80℃ under nitrogen gas and then concentrated in vacuo. The residue was partitioned between $CH_2Cl_2$ (60 mL) and purified water (60 mL). The aqueous layer was washed with $CH_2Cl_2$ (2 × 60 mL) and then freeze−dried to give phosphonic acid **98** (64 mg, 79%) as a yellowish foam: UV ($H_2O$) $\lambda_{max}$ 261.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.35 (s, 1H, H−8), 8.18 (s, 1H, H−2), 6.66 (dd, $J$ = 17.2, 20.2 Hz, 1H, H−1′), 6.18 (dd, $J$ = 17.3, 19.9 Hz, 1H, H−4′), 5.96 (dd, $J$ = 1.9, 6.0 Hz, 1H, PCH), 3.74 (dd, $J$ = 10.2, 6.6 Hz, 1H, H−5′a), 3.60 (dd, $J$ = 10.0, 8.6 Hz, 1H, H−5′b), 2.56−2.53 (m, 1H, H−3′), 1.01 (m, 1H, H−1″a), 0.42−0.38 (m, 2H, H−1″b, H−2″a), 0.11 (m, 1H, H−2″b); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 154.9, 152.8, 151.7, 149.2, 142.0, 119.6, 115.3, 99.1, 63.3, 49.5, 32.6, 14.6, 8.1.

**(*rel*)−(4′*S*,7′*S*)−Diethyl{9−(3′−ethyl−2′−spiropropyl−dihydrofuran−1′−yl) 6−chloropurine} phosphonate (99).** To a solution of vinyl

phosphonate nucleoside analogue **96** (197 mg, 0.48 mmol) in methanol (8 mL) was added 10% Pd/C (8 mg) and cyclohexene (3 mL) under argon gas. The reaction mixture was refluxed for 24 h. The reaction mixture was filtered through a pad of Celite, evaporated, and purified by silica gel column chromatography using methanol and methylene chloride (12:1) to give ethyl phosphonate analogue **99** (387 mg, 81%) as a white solid: mp 176−178℃; $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.76 (s, 1H), 8.26 (s, 1H), 5.99 (dd, $J$ = 5.8, 1.8 Hz, 1H), 4.14−4.08 (m, 4H), 3.73 (dd, $J$ = 10.4, 6.8 Hz, 1H), 3.62 (dd, $J$ = 10.3, 8.2 Hz, 1H), 2.16−2.11 (m, 4H), 1.86 (m, 1H), 0.96 (m, 1H), 0.40 (m, 2H), 0.13 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 151.8, 151.4, 151.1, 143.6, 134.7, 96.6, 65.7, 63.7, 63.2, 47.2, 31.6, 28.3, 18.3, 13.7, 6.9.

**(*rel*)−(4′*S*,7′*S*)−Diethyl{9−(3′−ethyl−2′−spiropropyl−dihydrofuran−1′−yl) adenine} phosphonate (100).** Transformation of 6−chloropurine to adenine derivative **100** was performed from **99** by the similar ammonolysis procedure as described for **98**: yield 55%; mp 177−179℃; UV (MeOH) $\lambda_{max}$ 261.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.35 (s, 1H), 8.16 (s, 1H), 5.96 (dd, $J$ = 5.9, 1.8 Hz, 1H), 4.16−4.10 (m, 4H), 3.75 (dd, $J$ = 10.2, 6.6 Hz, 1H), 3.63 (dd, $J$ = 10.2, 8.4 Hz, 1H), 2.22−2.17 (m, 4H), 1.83 (m, 1H), 0.96 (s, 1H), 0.42−0.38 (m, 2H), 0.12 (s, 1H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 154.9, 152.5, 151.4, 143.5, 119.6, 97.8, 64.2, 63.2, 62.8, 45.7, 32.3, 28.5, 18.4, 14.3, 7.2.

**(*rel*)−(4′S,7′S)−{9−(3′−Ethyl−2′−spiropropyl−dihydrofuran1′−yl) adenine} phosphonic acid (101).** Adenine phosphonic acid **101** was synthesized from **100** using the similar hydrolysis procedure as described for **98**: yield 81%, UV ($H_2O$) $\lambda$max 260.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.36 (s, 1H, H−8), 8.17 (s, 1H, H−2), 5.99 (dd, $J$ = 5.8, 2.0 Hz, 1H, H−1′), 3.74 (dd, J = 10.4, 6.6 Hz, 1H, H−5′a), 3.62 (dd, $J$ = 10.3, 8.4 Hz, 1H, H−5′b), 2.20−2.16 (m, 4H, H−4′a, H−4′b, $PCH_2$), 1.85 (m, 1H, H−3′), 1.02 (m, 1H, H−1″a), 0.42−0.38 (m, 2H, H−1″b, H−2″a), 0.13 (m, 1H, H−2″b); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 155.2, 152.1, 149.4, 137.8, 119.3, 97.6, 64.6, 46.8, 32.2, 27.2, 17.6, 13.8, 7.7; MS m/z 340 $(M+H)^+$.

**(*rel*)−(1′*R*,3′*S*)−9−(3′−Vinyl−2′−spiropropyl−dihydrofuran−1′−yl) 2−fluoro−6−chloropurine (102a) and (*rel*)−(1′*S*,3′*S*)−9−(3′−Vinyl−2′−spiropropyl−dihydrofuran−1′−yl) 2−fluoro−6−chloropurine (102b)** Coupling of **94** with 2−fluoro−6−chloropurine under the similar condensation conditions as described for **95** to give **102a** and **102b**, respectively: Data for **102a**: yield 30%; UV (MeOH) $\lambda_{max}$ 269.0 nm; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.42 (s, 1H), 5.91 (dd, $J$ = 5.8, 2.0 Hz, 1H), 5.71−5.67 (m, 1H), 5.05−4.97 (m, 2H), 3.75 (dd, $J$ = 10.4, 6.2 Hz, 1H), 3.60 (dd, $J$ = 10.3, 8.2 Hz, 1H), 2.48 (m, 1H), 1.03 (m, 1H), 0.40−0.35 (m, 2H), 0.10 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 158.2 (d, $J$ = 235.8 Hz), 153.0, 147.9, 145.8, 136.8, 120.4, 114.6, 97.5, 64.2, 48.5, 31.3, 13.8, 7.8. Data for **102b**: yield 31%; UV

(MeOH) $\lambda_{max}$ 269.5 nm; $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.45 (s, 1H), 5.94 (dd, $J$ = 6.0, 1.8 Hz, 1H), 5.71 (m, 1H), 5.05−4.96 (m, 2H), 3.75 (dd, $J$ = 10.2, 8.0 Hz, 1H), 3.65 (dd, J = 10.2, 6.6 Hz, 1H), 2.49 (m, 1H), 1.01− 0.98 (m, 1H), 0.39−0.35 (m, 2H), 0.12 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 157.7 (d, $J$ = 233.8 Hz), 155.4, 152.2, 144.9, 141.6, 118.5, 113.8, 98.2, 63.9, 47.2, 33.0, 15.1, 9.4, 8.2.

**(*rel*)−(1′*S*,3′*S*)−Diethyl{9−(3′−vinyl−2′−spiropropyl−dihydrofuran−1′−yl) 2−fluoro−6−chloropurine} phosphonate (103).** Phosphonate nucleoside analogue **103** was prepared from **102b** using the same cross−metathesis procedure as described for **96**: yield 62%; $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.45 (s, 1H), 6.61 (dd, $J$ = 16.8, 19.8 Hz, 1H), 6.18 (dd, $J$ = 16.8, 20.4 Hz, 1H), 5.97 (dd, $J$ = 6.0, 1.8 Hz, 1H), 4.12−4.08 (m, 4H), 3.73 (dd, $J$ = 10.2, 8.4 Hz, 1H), 3.62 (dd, $J$ = 10.3, 6.8 Hz, 1H), 2.47 (m, 1H), 0.99 (m, 1H), 0.37−0.31 (m, 2H), 0.09 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 157.7 (d, $J$ = 221.6 Hz), 153.6, 152.4, 147.8, 144.5, 128.1, 116.1, 96.8, 62.2, 49.6, 31.3, 14.8, 10.3, 7.8.

**(*rel*)−(1′*S*,3′*S*)−Diethyl{9−(3′−vinyl−2′−spiropropyl−dihydrofuran−1′−yl)−2−fluoro−6−aminopurine} phosphonate (104a) and (*rel*)−(1′*S*,3′*S*)−diethyl{9−(3′−vinyl−2′−spiropropyl−dihydrofuran−1′−yl) 2−amino−6−chloropurine} phosphonate (104b).** Dry ammonia gas was bubbled into a stirred solution of **103** (220 mg, 0.51 mmol) in DME (10 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 **104a** (21 mg, 10%) and **104b** (89 mg, 41%), respectively: Data for **104a**; UV (MeOH) $\lambda_{max}$ 261.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.19 (s, 1H), 7.70 (br s, $NH_2$, 2H), 6.63 (dd, $J$ = 20.2, 16.8 Hz, 1H), 6.19 (dd, $J$ = 20.0, 16.9 Hz, 1H), 5.98 (dd, $J$ = 5.8, 2.0 Hz, 1H), 4.13−4.09 (m, 4H), 3.77 (dd, $J$ = 10.2, 8.5 Hz, 1H), 3.64 (dd, $J$ = 10.2, 6.7 Hz, 1H), 2.49 (m, 1H), 1.26−1.22 (m, 6H), 0.98 (m, 1H), 0.38−0.34 (m, 2H), 0.10 (s, 1H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 159.9 (d, $J$ = 256.8 Hz), 155.7, 152.8, 144.1, 141.6, 118.6, 115.6, 96.6, 65.8, 63.2, 62.8, 48.3, 30.7, 15.2, 8.1. Data for **104b**; UV (MeOH) $\lambda_{max}$ 308.0 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.13 (s, 1H), 7.68 (br s, $NH_2$, 2H), 6.66 (dd, $J$ = 20.0, 17.1 Hz, 1H), 6.19 (dd, $J$ = 22.2, 17.0 Hz, 1H), 5.99 (dd, $J$ = 6.0, 1.8 Hz, 1H), 4.10 (m, 4H), 3.73−3.75 (dd, $J$ = 10.4, 8.8 Hz, 1H), 3.62 (dd, $J$ = 10.3, 6.8 Hz, 1H), 2.51 (m, 1H), 1.29−1.26 (m, 6H), 1.01 (m, 1H), 0.39−0.33 (m, 2H), 0.10−0.09 (s, 1H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 155.0, 151.8, 149.7, 147.9, 144.0, 127.8, 115.9, 98.2, 66.5, 63.5, 62.9, 47.7, 32.1, 15.7, 11.7, 8.7.

**(*rel*)−(1′*S*,3′*S*)−9−{(3′−Vinyl−2′−spiropropyl−dihydrofuran−1′−yl) guanine} phosphonic acid (105).** To a solution of **104b** (216 mg, 0.51 mmol) dry $CH_3CN$ (18 mL) and 2,6−lutidine (1.88 mL, 17.6 mmol) was added trimethylsilyl bromide (1.35 g, 8.83 mmol) at room

temperature. After this mixture was stirred for 24 h, the solvent was removed, coevaporating three times with methanol. The residue was dissolved in MeOH (17.0 mL) and 2-mercaptoethanol (158 mg, 2.03 mmol) and NaOMe (107.52 mg, 2.03 mmol) was added to the mixture. The mixture was refluxed for 16 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 **105** (110.6 mg, 62%) as a yellowish form. UV ($H_2O$) $\lambda_{max}$ 254.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 10.11 (br s, NH, 1H), 8.17 (s, 1H, H-8), 7.09 (br s, $NH_2$, 2H), 6.66 (dd, $J$ = 20.1, 17.2 Hz, 1H, H-1′), 6.16 (dd, $J$ = 20.2, 17.2 Hz, 1H, H-4′), 5.95 (dd, $J$ = 6.0, 1.9 Hz, 1H, PCH), 3.74 (dd, $J$ = 10.6, 8.4 Hz, 1H, H-5′a), 3.62 (dd, $J$ = 10.5, 6.4 Hz, 1H, H-5′b), 2.56-2.54 (m, 1H, H-3′), 0.98 (m, 1H, H-1″a), 0.39 (m, 2H, H-1″b, H-2″a), 0.09 (m, 1H, H-2″b); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 157.4, 154.3, 152.6, 149.7, 136.4, 118.4, 115.5, 88.3, 64.2, 49.2, 32.0, 16.0, 8.9, 7.8; Anal. Calc. for $C_{13}H_{16}N_5O_5P$ (+2.0 $H_2O$): C, 40.10; H, 5.18; N, 17.99; Found: C, 40.08; H, 5.17; N, 18.01; MS m/z 354 $(M+H)^+$.

**(*rel*)-(1′*S*,3′*S*)-Diethyl{9-(3′-ethyl-2′-spiropropyl-dihydrofuran-1′-yl) 2-fluoro-6-chloropurine} phosphonate (106).** Compound **106** was synthesized from **103** by the similar catalytic hydrogenation procedure as described for **99**: yield 72%; UV (MeOH) $\lambda_{max}$ 170.5 nm; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.56 (s, 1H), 5.94 (dd, $J$ = 6.0, 2.1

Hz, 1H), 4.16−4.11 (m, 4H), 3.74 (dd, $J$ = 10.4, 8.2 Hz, 1H), 3.60 (dd, $J$ = 10.3, 6.8 Hz, 1H), 2.20−2.16 (m, 4H), 1.99 (m, 1H), 1.00 (m, 1H), 0.34−0.30 (m, 2H), 0.10−0.08 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 158.1 (d, $J$ = 232.4 Hz), 153.7, 145.5, 136.3, 121.8, 97.8, 64.8, 63.6, 62.9, 47.1, 32.3, 28.4, 18.6, 14.7, 8.8.

**(*rel*)−(1′*S*,3′*S*)−Diethyl{9−(3′−ethyl−2′−spiropropyl−dihydrofuran−1′−yl) 2−fluoro−6−aminopurine} phosphonate (107a) and (rel)−(1′*S*,3′*S*)−diethyl {9−(3′−ethyl−2′−spiropropyl−dihydrofuran−1′−yl) 2−amino−6−chloropurine} phosphonate (107b).** Ammonolysis of **106** was performed using the similar procedure as described for **104a** and **104b**: Data for **107a**: yield 11%; UV (MeOH) $\lambda_{max}$ 262.0 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.28 (s, 1H), 7.71 (br s, $NH_2$, 2H), 5.98 (dd, $J$ = 5.9, 1.8 Hz, 1H), 4.18−4.14 (m, 4H), 3.74 (dd, $J$ = 10.2, 8.6 Hz, 1H), 3.63 (dd, $J$ = 10.2, 7.2 Hz, 1H), 2.30− 2.24 (m, 4H), 1.88 (m, 1H), 1.05−1.00 (m, 1H), 0.39−0.36 (m, 2H), 0.11−0.08 (m, 1H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 160.4 (d, J = 258.2 Hz), 156.2, 151.7, 142.8, 119.2, 99.5, 65.2, 63.8, 63.4, 46.2, 32.4, 28.9, 18.6, 14.3, 7.3; Data for **107b**: yield 43%; UV (MeOH) $\lambda_{max}$ 307.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.15 (s, 1H), 7.67 (br s, $NH_2$, 2H), 5.95 (dd, $J$ = 6.0, 1.6, Hz, 1H), 4.20−4.16 (m, 4H), 3.76 (dd, $J$ = 10.6, 8.0 Hz, 1H), 3.61 (dd, $J$ = 10.5, 6.6 Hz, 1H), 2.20−2.16 (m, 4H), 1.82 (m, 1H), 0.93 (m, 1H), 0.40−0.37 (m, 2H), 0.12 (s, 1H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 156.8, 152.9, 150.7, 143.2, 125.2, 95.6, 65.2,

63.0, 62.5, 46.2, 31.8, 28.3, 18.7, 16.2, 10.3, 8.4.

**(*rel*)−(1′*S*,3′*S*)−9−{(3′−Ethyl−2′−spiropropyl−dihydrofuran−1′−yl) guanine} phosphonic acid (108).** Guanine nucleoside phosphonic acid **108** was prepared from **107b** by the same hydrolysis conditions used for **105**: yield 65%; UV ($H_2O$) $\lambda_{max}$ 253.0 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 10.7 (br s, NH, 1H), 8.08 (s, 1H, H−8), 7.05 (br s, $NH_2$, 2H), 5.95 (dd, $J$ = 6.0, 1.9 Hz, 1H, H−1′), 3.75 (dd, $J$ = 10.2, 8.5 Hz, 1H, H−5′a), 3.62 (dd, $J$ = 10.3, 6.4 Hz, 1H, H−5′b), 2.22−2.17 (m, 4H, H−4′a, H−4′b, $PCH_2$), 1.89 (m, 1H, H−3′), 0.99 (m, 1H, H−1″a), 0.37−0.33 (m, 2H, H−1″b, H−2″a), 0.09−0.07 (m, 1H, H−2″b); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 157.2, 153.9, 152.2, 135.8, 116.9, 88.2, 65.3, 46.2, 31.8, 28.9, 19.0, 15.2, 10.2, 8.7.

**(*rel*)−(1′*S*,2′*R*,3′*S*)−9−(3′−*t*−Butyldimethylsilanyloxymethyl−2′−fluoro−tetrahydrofuran−1′−yl) 6−chloropurine (111a) and (*rel*)−(1′*R*,2′*R*,3′*S*)−9−(3′−*t*−butyldimethylsilanyloxymethyl−2′−fluoro−tetrahydrofuran−1′−yl) 6−chloropurine (111b):** 6−Chloropurine (216 mg, 1.4 mmol), anhydrous HMDS (10 mL), and a catalytic amount of ammonium sulfate (14 mg) were refluxed to a clear solution, and the solvent was then distilled off under anhydrous conditions. The residue obtained was dissolved in anhydrous 1,2−dichloroethane (8 mL), and to this mixture, a solution of **110** (175 mg, 0.6 mmol) in dry DCE (10 mL) and TMSOTf (311 mg, 1.4 mmol) was added, and stirred for 8 h at rt. The reaction mixture was quenched with 5.0 mL of saturated

$NaHCO_3$, stirred for 1 h, filtered through a Celite pad, and the filtrate obtained was then extracted twice with $CH_2Cl_2$ (80 mL). Combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 4:1:0.01) to give compounds **111a** (74 mg, 32%) and **111b** (79 mg, 34%). Data for **111a**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.72 (s, 1H), 8.34 (s, 1H), 6.23 (dd, $J$ = 18.6, 5.8 Hz, 1H), 3.77−3.67 (m, 5H), 2.39−2.28 (m, 1H), 0.87 (m, 9H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.7, 151.4, 151.1, 144.8, 132.5, 92.2 (d, $J$ = 172.0 Hz), 88.5 (d, $J$ = 23.2 Hz), 60.5, 57.4, 39.3 (d, $J$ = 22.2 Hz), 25.4, 18.3, −5.1. Data for **111b**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 8.31 (s, 1H), 6.19 (dd, $J$ = 18.2, 4.8 Hz, 1H), 3.77−3.63 (m, 5H), 2.38−2.27 (m, 1H), 0.83 (m, 9H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.6, 151.3, 151.0, 144.7, 132.3, 91.6 (d, $J$ = 170.8 Hz), 87.2 (d, $J$ = 21.2 Hz), 59.4, 56.2, 38.2 (d, $J$ = 21.4 Hz), 25.5, 18.4, −4.8.

**(*rel*)−(1′*R*,2′*R*,3′*S*)−9−(3′−Hydroxymethyl−2′−fluoro−tetrahydrofuran−1′−yl) 6−chloropurine (112):** To a solution of **111b** (2.54 g, 6.56 mmol) in THF (12 mL), TBAF (7.7 mL, 1.0 M solution in THF) was added at 0℃. The mixture was stirred overnight at RT and concentrated *in vacuum*. The residue was purified by silica gel column chromatography (Hexane/EtOAc/MeOH, 2:1:0.05) to give **112** (1.59 g, 89%): $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.69 (s, 1H), 8.29 (s, 1H), 6.15

(dd, $J$ = 16.8, 5.4 Hz, 1H), 3.79−3.64 (m, 5H), 2.36−2.24 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.8, 151.4, 151.1, 144.5, 132.6, 92.5 (d, $J$ = 166.8 Hz), 86.4 (d, $J$ = 20.4 Hz), 60.2, 56.2, 38.2 (d, $J$ = 21.4 Hz).

**(*rel*)−(1′*R*,2′*R*,3′*R*)−9−(3′−Carbaldehyde−2′−fluoro−tetrahydrofuran−1′−yl) 6−chloropurine (113):** Compound **112** (290 mg, 1.066 mmol) was dissolved in anhydrous $CH_2Cl_2$ (8 mL), and to this solution was added Dess−Martin reagent (588 mg, 1.38 mmol). The mixture was stirred for 3 h at ambient temperature, concentrated and the residue was purified by silica gel column chromatography using Hexane/EtOAc (1:4) as eluent. A second column, which was also eluted with EtOAc, was necessary to remove traces of Dess−Martin reagent−related impurities to give **113** (253 mg, 88%): $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 9.69 (s, 1H), 8.70 (s, 1H), 8.28 (s, 1H), 6.19 (dd, $J$ = 18.0, 5.6 Hz, 1H), 4.05−3.94 (m, 3H), 2.93−2.85 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 204.7, 151.5, 151.0, 150.7, 144.1, 133.4, 92.5 (d, $J$ = 18.4 Hz), 88.5 (d, $J$ = 164.4 Hz), 55.7, 51.1 (d, $J$ = 18.8 Hz).

**(*rel*)−(1′*R*,2′*R*,3′*S*)−9−(3′−Vinyl−2′−fluoro−tetrahydrofuran−1′−yl)6−chloropurine (114):** To ylide solution [methyltriphenyl phosphonium iodide (188 mg, 0.462 mmol), triphenylphosphine (14.25 mg, 0.055 mmol), 1.6 M *n*−butyllithium solution (0.289 mL, 0.462 mmol) in dry tetrahydrofuran (5.0 mL) at −78℃, was added dropwise to a solution of olefin **113** (125 mg, 0.462 mmol) in dry THF (7 mL).

The reaction mixture was warmed to room temperature, stirred for 4 h, quenched with saturated sodium bicarbonate solution, and then partitioned between saturated sodium bicarbonate solution and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. Combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuum*, and chromatographed (Hexane−EtOAc, 1:2) to afford **114** (76 mg, 61%) as a colorless oil. $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 8.31 (s, 1H), 6.21 (dd, $J$ = 19.2, 5.2 Hz, 1H), 5.76 (m, 1H), 5.05−4.96 (m, 2H), 3.74−3.68 (m, 3H), 2.85−2.81 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.7, 151.3, 150.9, 144.6, 143.6, 132.8, 112.3, 96.1 (d, $J$ = 168.4 Hz), 88.3 (d, $J$ = 16.8 Hz), 62.1, 39.4 (d, $J$ = 18.4 Hz).

**(*rel*)−(1′*R*,2′*R*,3′*S*)−Diethyl{9−(3′−vinyl−2′−fluoro−tetrahydrofuran−1′−yl) 6−chloropurine} phosphonate (115):** To a solution of the 6−chloropurine derivative **114** (174 mg, 0.650 mmol) and diethyl vinylphosphonate (426 mg, 2.60 mmol) in $CH_2Cl_2$ (8.0 mL), 2$^{nd}$−generation Grubbs catalyst (22.10 mg, 0.026 mmol) was added. The reaction mixture was refluxed for 26 h under dry argon and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/*n*−Hexane/MeOH, 2:1:0.05) to give **115** (150 mg, 57%) as a foam: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.72 (s, 1H), 8.32 (s, 1H), 6.67 (dd, $J$ = 17.2, 21.4 Hz, 1H), 6.20 (dd, $J$ = 19.2, 5.2 Hz, 1H), 6.11 (dd, $J$ = 17.2, 19.8. Hz, 1H), 4.12−4.06

(m, 4H), 3.73−3.66 (m, 3H), 2.82−2.78 (m, 1H), 1.33−1.30 (m, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.8, 151.4, 151.0, 149.5, 144.2, 132.6, 117.2, 95.6 (d, $J$ = 168.4 Hz), 87.6 (d, $J$ = 17.0 Hz), 62.4, 61.8, 60.6, 40.7 (d, $J$ = 16.4 Hz), 15.8.

**(*rel*)−(1′*R*,2′*R*,3′*S*)−Diethyl{9−(3′−vinyl−2′−fluoro−tetrahydrofuran−1′−yl) adenine} phosphonate (116):** A solution of **115** (188 mg, 0.464 mmol) in saturated methanolic ammonia (7 mL) was stirred overnight at 66℃ in a steel bomb, and volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/$CH_2Cl_2$, 1:10) to give **116** (112 mg, 63%) as a white solid: UV (MeOH) $\lambda_{max}$ 261.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.36 (s, 1H), 8.17 (s, 1H), 6.65 (dd, $J$ = 17.4, 20.8 Hz, 1H), 6.23 (dd, $J$ = 18.0, 5.4 Hz, 1H), 6.10 (dd, $J$ = 17.2, 19.8. Hz, 1H), 4.10−4.05 (m, 4H), 3.76−3.68 (m, 3H), 2.83−2.77 (m, 1H), 1.32 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 155.5, 152.7, 150.4, 148.8, 141.3, 119.0, 115.6, 94.8 (d, $J$ = 167.8 Hz), 88.4 (d, $J$ = 16.6 Hz), 63.3, 62.7, 61.5, 41.2 (d, $J$ = 16.6 Hz), 15.3.

**(*rel*)−(1′*R*,2′*R*,3′*S*)−9−[(3′−Vinyl−2′−fluoro−tetrahydrofuran−1′−yl) adenine]phosphonic acid (117):** To a solution of the phosphonate **116** (161 mg, 0.419 mmol) in anhydrous $CH_3CN$ (10 mL) and 2,6−lutidine (0.898 mL, 8.38 mmol) was added trimethylsilyl bromide (641 mg, 4.19 mmol). The mixture was heated overnight at 75℃ under nitrogen and then concentrated *in vacuo*. The residue obtained

was partitioned between $CH_2Cl_2$ (100 mL) and purified water (100 mL), and the aqueous layer was washed with $CH_2Cl_2$ (2 × 70 mL) and freeze-dried to give phosphonic acid **117** (96 mg, 70%) as a yellowish foam: UV ($H_2O$) $\lambda_{max}$ 261.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.34 (s, 1H, H-8), 8.16 (s, 1H, H-2), 6.66 (dd, $J$ = 17.6, 21.0 Hz, 1H, H-1′), 6.21 (dd, $J$ = 17.6, 5.2 Hz, 1H, H-5′), 6.12 (dd, $J$ = 17.4, 19.4. Hz, 1H, PCH), 3.72-3.65 (m, 3H, H-2′, H-4′a, H-4′b), 2.85-2.78 (m, 1H, H-3′); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 155.3, 152.4, 150.1, 148.5, 141.5, 118.8, 114.7, 93.6 (d, $J$ = 165.8 Hz), 89.6 (d, $J$ = 16.8 Hz), 61.6, 40.6 (d, $J$ = 16.8 Hz); Anal. Calc. for $C_{11}H_{13}FN_5O_4P$ (+2.0 $H_2O$): C, 36.17; H, 4.69; N, 19.17; Found: C, 36.21; H, 4.71; N, 19.19; MS *m/z* 330 $(M+H)^+$.

**(*rel*)-(1′*R*,2′*R*,3′*S*)-Diethyl{9-(3′-ethyl-2′-fluoro-tetrahydrofuran-1′-yl) 6-chloropurine} phosphonate (118):** A solution of vinyl phosphonate nucleoside analogue **117** (265 mg, 0.655 mmol) in methanol (8 mL) was added 10% Pd/C (10 mg) and cyclohexene (4 mL) under Ar. The reaction mixture was refluxed for 24 h. The reaction mixture was filtered through a pad of Celite, evaporated, and purified by silica gel column chromatography using methanol and methylene chloride (10:1) to give ethyl phosphonate analogue **118** (197 mg, 74%) as a white solid: $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.34 (s, 1H), 6.19 (dd, $J$ = 18.6, 5.4 Hz, 1H), 4.11-4.06 (m, 4H), 3.76-3.68 (m, 3H), 2.28-1.86 (m, 5H), 1.31-1.28 (m, 6H); $^{13}$C

NMR ($CDCl_3$, 75 MHz) δ 151.8, 151.4, 150.0, 142.9, 132.8, 94.8 (d, $J$ = 162.8 Hz), 89.1 (d, $J$ = 16.8 Hz), 61.4, 38.9 (d, $J$ = 16.8 Hz), 28.7, 18.8, 14.9.

**(*rel*)-(1′*R*,2′*R*,3′*S*)-Diethyl{9-(3′-ethyl-2′-fluoro-tetrahydrofuran-1′-yl) adenine} phosphonate (119):** The adenine derivative **119** was prepared from the 6-chloropurine analogue **118** using an ammonolysis procedure similar to that described for **116**: yield 60%; mp 172-174℃; UV (MeOH) $\lambda_{max}$ 260.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.38 (s, 1H), 8.19 (s, 1H), 6.16 (dd, $J$ = 18.8, 5.5 Hz, 1H), 4.15-4.09 (m, 4H), 3.73-3.65 (m, 3H), 2.27 (m, 2H), 2.01-1.88 (m, 3H), 1.30-1.26 (m, 6H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 154.9, 152.3, 150.2, 141.4, 118.7, 93.5 (d, $J$ = 162.4 Hz), 88.4 (d, $J$ = 16.3 Hz), 60.6, 37.6 (d, $J$ = 16.2 Hz), 28.3, 18.5, 15.1.

**(*rel*)-(1′*R*,2′*R*,3′*S*)-{9-(3′-Ethyl-2′-fluoro-tetrahydrofuran-1′-yl) adenine} phosphonic acid (120):** Phosphonic acid **120** was synthesized from **119** using hydrolysis conditions identical to that for **117**: yield 77%, UV ($H_2O$) $\lambda_{max}$ 262.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.36 (s, 1H, H-8), 8.17 (s, 1H, H-2), 6.14 (dd, $J$ = 17.6, 5.4 Hz, 1H, H-1′), 3.70-3.64 (m, 3H, H-2′, H-4′a, H-4′b), 2.25-2.21 (m, 2H, H-3′, H-5′a), 2.03-1.89 (m, 3H, H-5′b, $PCH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 155.2, 152.5, 150.6, 141.9, 119.4, 95.2 (d, $J$ = 160.8 Hz), 87.7 (d, $J$ = 16.4 Hz), 61.4, 38.2 (d, $J$ = 16.5 Hz), 29.1, 18.8; MS $m/z$ 332 $(M+H)^+$.

(*rel*)−(1′*S*,2′*R*,3′*S*)−9−(3′−*t*−Butyldimethylsilanyloxymethyl−2′−fluoro−tetrahydrofuran−1′−yl) 6−chloropurine (121a) and (*rel*)−(1′*R*,2′*R*,3′*S*)−9−(3′−*t*−Butyldimethylsilanyloxymethyl−2′−fluoro−tetrahydrofuran−1′−yl)2−fluoro−6−chloropurine (121b):Condensation of **110** with 2−fluoro−6−chloropurine under Vorbruggen condensation conditions similar to those described for **111a** and **111b** gave **121a** and **121b**, respectively. Data for **121a**: yield 31%; UV (MeOH) $\lambda_{max}$ 267.5 nm; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 1H), 6.21 (dd, *J* = 18.4, 5.4 Hz, 1H), 3.75−3.68 (m, 5H), 2.23−2.19 (m, 1H), 0.89 (m, 9H), 0.02 (m, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.1 (d, *J* = 219 Hz), 153.3, 145.6, 136.2, 120.6, 92.2 (d, *J* = 166.7 Hz), 89.1 (d, *J* = 16.4 Hz), 60.5, 57.6, 38.7 (d, *J* = 16.2 Hz), 25.5, 18.7, −4.6. Data for **121b**: yield 32%; UV (MeOH) $\lambda_{max}$ 268.5 nm; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 6.19 (dd, *J* = 18.5, 5.5 Hz, 1H), 3.74−3.67 (m, 5H), 2.22−2.18 (m, 1H), 0.87 (m, 9H), 0.01 (m, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.3 (d, *J* = 219.6 Hz), 153.5, 145.8, 135.8, 120.8, 91.6 (d, *J* = 167.8 Hz), 88.5 (d, *J* = 16.6 Hz), 59.6, 57.4, 38.4 (d, *J* = 16.4 Hz), 25.4, 18.4, −5.2.

(*rel*)−(1′*R*,2′*R*,3′*S*)−9−(3′−Hydroxymethyl−2′−fluoro−tetrahydrofuran−1′−yl) 2−fluoro−6−chloropurine (122): Desilylation of **121b** was performed using a procedure similar to that described for **112**: yield 78%; UV (MeOH) $\lambda_{max}$ 269.5 nm; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.46 (s, 1H), 6.21 (dd, *J* = 18.4, 5.5 Hz, 1H), 3.74−3.67 (m, 3H), 3.50 (m,

2H), 2.21−2.15 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 156.9 (d, $J$ = 217.8 Hz), 154.0, 144.6, 134.8, 121.6, 91.6 (d, $J$ = 169.4 Hz), 89.4 (d, $J$ = 16.8 Hz), 57.6, 56.2, 37.2 (d, $J$ = 16.6 Hz).

**(*rel*)−(1′*R*,2′*R*,3′*S*)−9−(3′−Carbaldehyde−2′−fluoro−tetrahydrofuran−1′−yl) 2−fluoro−6−chloropurine (123)**: Oxidation of **122** was performed using the Dess−Martin reaction conditions described for **113**: yield 66%; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 6.20 (dd, $J$ = 18.6, 5.6 Hz, 1H), 3.72−3.68 (m, 3H), 3.48−3.42 (m, 2H), 2.23−2.16 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 204.6, 157.4 (d, $J$ = 218.6 Hz), 154.2, 144.7, 133.9, 122.3, 91.3 (d, $J$ = 167.8 Hz), 88.5 (d, $J$ = 16.6 Hz), 58.4, 57.4, 38.4 (d, $J$ = 16.4 Hz).

**(*rel*)−(1′*R*,2′*R*,3′*S*)−9−(3′−Vinyl−2′−fluoro−tetrahydrofuran−1′−yl) 2−fluoro−6−chloropurine} phosphonate (124)**: Wittig olefination of the aldehyde **123** was performed using a procedure similar to that described for **114**: yield 59%; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.46 (s, 1H), 6.21 (dd, $J$ = 18.4, 5.4 Hz, 1H), 5.73 (m, 1H), 5.05−4.98 (m, 2H), 3.73−3.68 (m, 3H), 3.50 (m, 2H), 2.81−2.76 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.6 (d, $J$ = 219.4 Hz), 154.5, 144.3, 142.5, 134.6, 123.6, 112.3, 95.6 (d, $J$ = 167.8 Hz), 90.2 (d, $J$ = 16.8 Hz), 61.6, 39.1 (d, $J$ = 16.4 Hz).

**(*rel*)−(1′*R*,2′*R*,3′*S*)−Diethyl{9−(3′−vinyl−2′−fluoro−tetrahydrofuran−1′−yl) 2−fluoro−6−chloropurine} phosphonate (125)**: Phosphonate nucleoside analogue **125** was prepared from **124** using a cross

metathesis procedure similar to that described for **115**: yield 60%; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.44 (s, 1H), 6.67 (dd, $J$ = 20.2, 18.6 Hz, 1H), 6.21−6.15 (m, 2H), 4.15−4.10 (m, 4H), 3.72−3.66 (m, 3H), 2.80−2.75 (m, 1H), 1.35 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 157.3 (d, $J$ = 218.8 Hz), 154.7, 149.5, 143.1, 133.9, 124.3, 115.3, 95.7 (d, $J$ = 166.6 Hz), 89.4 (d, $J$ = 16.4 Hz), 62.2, 61.5, 60.9, 40.4 (d, $J$ = 16.2 Hz), 15.7.

**(*rel*)−(1′*R*,2′*R*,3′*S*)−Diethyl {9−(3′−vinyl−2′−fluoro−tetrahydrofuran−1′−yl) 2−fluoro−6−aminopurine} phosphonate (126a) and (*rel*)−(1′*R*,2′*R*,3′*S*)−diethyl {9−(3′−vinyl−2′−fluoro−tetrahydrofuran−1′−yl) 2−amino−6−chloropurine} phosphonate (126b)**: Dry ammonia gas was bubbled into a stirred solution of **125** (180 mg, 0.426 mmol) in DME (8.0 mL) at room temperature overnight. Salts were removed by filtration and the filtrate was concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography (MeOH/$CH_2Cl_2$, 1:10) to give **126a** (24 mg, 14%) and **126b** (80 mg, 45%). Data for **126a**; UV (MeOH) $\lambda_{max}$ 261.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.21 (s, 1H), 7.74 (br s, $NH_2$, 2H), 6.65 (dd, $J$ = 19.8, 16.4 Hz, 1H), 6.21 (dd, $J$ = 19.7, 18.2 Hz, 1H), 6.09 (dd, $J$ = 12.8, 5.2 Hz, 1H), 4.13−4.09 (m, 4H), 3.73−3.65 (m, 3H), 2.81−2.74 (m, 1H), 1.54−1.50 (s, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 160.7 (d, $J$ = 268.8 Hz), 155.2, 152.3, 148.8, 142.3, 119.4, 115.4, 94.8 (d, $J$ = 168.4 Hz), 87.2 (d, $J$ = 17.2 Hz), 63.4, 62.8, 61.5, 39.6

(d, $J$ = 16.6 Hz), 14.4. Data for **126b**; UV (MeOH) $\lambda_{max}$ 308.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.14 (s, 1H), 7.71 (br s, $NH_2$, 2H), 6.62 (dd, $J$ = 20.2, 17.8 Hz, 1H), 6.24 (dd, $J$ = 19.6, 17.7 Hz, 1H), 6.12 (dd, $J$ = 14.6, 5.0 Hz, 1H), 4.16−4.10 (m, 4H), 3.75−3.68 (m, 3H), 2.82−2.75 (m, 1H), 1.53−1.49 (s, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 158.5, 154.4, 151.7, 149.4, 144.0, 125.2, 114.6, 93.9 (d, $J$ = 166.8 Hz), 88.7 (d, $J$ = 16.8 Hz), 62.8, 62.2, 61.6, 41.2 (d, $J$ = 16.8 Hz), 14.7.

**(*rel*)−(1′*R*,2′*R*,3′*S*)−9−{(3′−vinyl−2′−fluoro−tetrahydrofuran−1′−yl) guanine} phosphonic acid (127)**: To a solution of **126b** (159 mg, 0.379 mmol) in dry $CH_3CN$ (15 mL) was added trimethylsilyl bromide (0.0873 mL, 6.62 mmol) at room temperature. The mixture was stirred for 24 h, and solvent was removed by co−evaporation with methanol three times. The residue was dissolved in MeOH (15.0 mL) and 2−mercaptoethanol (103.6 μL, 1.52 mmol), and then NaOMe (80.6 mg, 1.52 mmol) was added. The mixture was refluxed for 12 h under $N_2$, cooled, neutralized with glacial AcOH, and evaporated to dryness under vacuum. The residue was purified by preparative reversed−phase C18 silica gel column chromatography using water as eluent to give **127** (90.2 mg, 69%) as a yellowish foam. UV ($H_2O$) $\lambda_{max}$ 254.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 10.8 (br s, NH, 1H), 8.12 (s, 1H, H−8), 7.03 (br s, $NH_2$, 2H), 6.63 (dd, $J$ = 19.4, 17.2 Hz, 1H, H−1′), 6.17−6.08 (m, 2H, H−5′, PCH), 3.72−3.65 (m, 3H, H−2′,

H−4′a, H−4′b), 2.80−2.75 (m, 1H, H−3′); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 157.4, 154.6, 152.3, 149.4, 136.2, 119.1, 115.3, 96.0 (d, $J$ = 168.1 Hz), 86.9 (d, $J$ = 17.4 Hz), 63.0, 62.5, 61.8, 40.4 (d, $J$ = 17.2 Hz); MS *m/z* 346 $(M+H)^+$.

**(*rel*)−(1′*R*,2′*R*,3′*S*)−Diethyl{9−(3′−ethyl−2′−fluoro−tetrahydrofuran−1−yl) 2−fluoro−6−chloropurine} phosphonate (128)** Compound **128** was synthesized from **125** by transfer catalytic hydrogenation similar to that described for **118**: yield 73%; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.43 (s, 1H), 6.12 (dd, $J$ = 15.8, 5.0 Hz, 1H), 4.12−4.09 (m, 4H), 3.73−3.66 (m, 3H), 2.81−2.76 (m, 1H), 2.14−2.02 (m, 4H), 1.51 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 157.1 (d, $J$ = 218.8 Hz, 1H), 153.1, 145.3, 136.2, 121.2, 96.2 (d, $J$ = 166.8 Hz), 88.5 (d, $J$ = 16.7 Hz), 61.8, 41.1 (d, $J$ = 17.2 Hz), 28.5, 18.4, 14.7.

**(*rel*)−(1′*R*,2′*R*,3′*S*)−Diethyl{9−(3′−ethyl−2′−fluoro−tetrahydrofuran−1−yl) 2−fluoro−6−aminopurine} phosphonate (129a) and (*rel*)−(1′*R*,2′*R*,3′*S*)−diethyl {9−(3′−ethyl−2′−fluoro−tetrahydrofuran−1−yl) 2−amino−6−chloropurine} phosphonate (129b)**: Ammonolysis of **128** using the same procedure described for **126a** and **126b** to gave **128a** and **128b**. Data for **128a**; yield 13%; UV (MeOH) $\lambda_{max}$ 261.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.20 (s, 1H), 7.74 (br s, $NH_2$, 2H, $D_2O$ exchangeable), 6.08 (d, $J$ = 15.8, 5.2 Hz, 1H), 4.14−4.10 (m, 4H), 3.71−3.64 (m, 3H), 2.82−2.75 (m, 1H), 2.12−1.99 (m, 4H), 1.54 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 161.0 (d, $J$ = 267.8 Hz, 1H),

155.3, 152.3, 142.6, 123.4, 98.6 (d, $J$ = 168.4 Hz), 89.4 (d, $J$ = 16.8 Hz), 60.6, 40.4 (d, $J$ = 17.4 Hz), 29.4, 18.7, 15.4. Data for **128b**; yield 43%; UV (MeOH) $\lambda_{max}$ 307.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.22 (s, 1H), 7.75 (br s, $NH_2$, 2H, $D_2O$ exchangeable), 6.13 (d, $J$ = 16.0, 5.0 Hz, 1H), 4.15−4.11 (m, 4H), 3.72−3.67 (m, 3H), 2.81−2.74 (m, 1H), 2.14−2.02 (m, 4H), 1.53 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 158.6, 154.8, 151.0, 143.8, 125.7, 99.2 (d, $J$ = 167.8 Hz), 88.6 (d, $J$ = 16.4 Hz), 61.7, 41.2 (d, $J$ = 16.7 Hz), 28.7, 19.0, 14.8.

**(*rel*)−(1′*R*,2′*R*,3′*S*)−9−{(3′−Ethyl−2′−fluoro−tetrahydrofuran−1−yl) guanine} phosphonic acid (130):** Nucleoside phosphonic acid **130** was synthesized using the hydrolysis conditions used for **127**. Yield 56%; UV ($H_2O$) $\lambda_{max}$ 252.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 10.8 (br s, NH, H, $D_2O$ exchangeable), 8.11 (s, 1H, H−8), 7.10 (br s, $NH_2$, 2H, $D_2O$ exchangeable), 6.11 (d, $J$ = 16.2, 5.2 Hz, 1H, H−1′), 3.70−3.64 (m, 3H, H−2′, H−4′a, H−4′b), 2.77−2.71 (m, 1H, H−3′), 2.09−1.94 (m, 4H, H−5′a, H−5′b, $PCH_2$); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 157.8, 154.4, 152.3, 136.5, 119.2, 97.2 (d, $J$ = 168.0 Hz), 90.1 (d, $J$ = 16.4 Hz), 60.5, 40.4 (d, $J$ = 16.4 Hz), 28.5, 18.6, 15.3; MS *m/z* 348 $(M+H)^+$.

**(*rel*)−(1′*R*,2′*R*,3′*S*)−Bis(SATE) phosphoester of [9−(3′−ethyl phosphonate−2′−fluoro−tetrahydrofuran−1−yl)] adenine (132):** A solution of adenine phosphonic acid derivative **120** (70 mg, 0.212 mmol) and tri−*n*−butylamine (117 mg, 0.636 mmol) in methanol (4.5

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 (15 mL) to which thioester **131** (649 mg, 4.0 mmol) and 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (251 mg, 0.848 mmol) were added. The mixture was stirred overnight at room temperature and quenched with tetrabutylammonium bicarbonate buffer (12.0 mL, 1 M solution, pH 8.0). The mixture was concentrated under reduced pressure and the residue was diluted with water (70 mL) and extracted with $CHCl_3$ (80 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 **132** (48 mg, 37%) as a white solid: mp 131-133℃; UV (MeOH) $\lambda_{max}$ 262.0 nm; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H, H-8), 8.15 (s, 1H, H-2), 6.11 (d, *J* = 16.1, 5.0 Hz, 1H, H-1′), 4.02 (m, 4H, $OCH_2$), 3.56 (d, *J* = 9.6 Hz, 3H, H-2′, H-4′a, H-4′b), 3.16 (t, *J* = 6.4 Hz, 4H, $SCH_2$), 2.21-2.13 (m, 5H, H-3′, H-5′a, H-5′b, $PCH_2$), 1.22-1.16 (s, 18H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 204.2, 57.1, 154.7, 152.8, 148.2, 145.6, 124.6, 119.4, 96.6 (d, *J* = 168.2 Hz), 88.8 (d, *J* = 18.4 Hz), 83.6, 67.5, 67.3, 62.4, 61.6, 53.4, 38.4 (d, *J* = 16.4 Hz), 30.2, 28.7, 28.5, 23.7, 14.6; MS *m/z* 620 $(M+H)^+$.

**2,2-Difluoro-1,3-bis-benzyloxy-propane (135):** A solution of

compound **134** (129 mg, 0.48 mmol) in anhydrous $CH_2Cl_2$ (38 mL) was treated with DAST (0.496 mL, 3.76 mmol) under argon at room temperature. The reaction mixture was stirred for 6 h and was then quenched by adding a saturated solution of $NaHCO_3$ in water. The organic phase was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 80 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give the *gem*-difluorinated product **135** (91 mg, 65%) as a colorless syrup: $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.28 (m, 10H), 4.65 (s, 4H), 3.71 (t, $J$ = 9.8 Hz, 4H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 136.1, 128.5, 128.3, 128.0, 113.9 (t, $J$ = 213 Hz), 78.5 (t, $J$ = 20.8 Hz), 74.1.

**2,2-Difluoro-1,3-bis-hydroxy-propane (136):** To a solution of **135** (450 mg, 1.54 mmol) in *n*-propanol (10 mL), Pd/C (10%, 340 mg, 0.31 mmol) was added. The mixture was thoroughly, deoxygenated, then saturated with hydrogen gas (1.1 bar) and stirred at 50 °C for 24 h. The charcoal was, then, removed by filtration through a short Celite pad. The filtrate was concentrated to dryness to give crude **136** (165.7 mg, 96%), which was subjected to next reaction procedure without further purification.

**3-(t-Butyldimethylsilanyloxy)-2,2-difluoro-propan-1-ol (137):** To a stirred solution of previous compound **136** (165.7 mg, 1.478

mmol) and imidazole (201 mg, 2.956 mmol) in anhydrous DMF (8 mL), *t*−butyldimethylsilyl chloride (269 mg, 1.625 mmol) was slowly added at 0℃. The mixture was stirred at the same temperature for 4 h, and quenched by adding a $NaHCO_3$ aqueous solution (3 mL). The mixture was extracted using diethyl ether (80 mL × 2), dried over $MgSO_4$, filtered and then evaporated to dryness. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:7) to give **137** (217 mg, 65%) as a colorless syrup: $^1$H NMR ($CDCl_3$, 300 MHz) δ 4.20 (t, *J* = 8.1 Hz, 2H), 3.86 (t, *J* = 8.6 Hz, 2H), 0.83 (s, 9H), 0.02 (s, 6H) ; $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 119.5 (t, *J* = 210.2 Hz), 72.2 (t, *J* = 20.3 Hz), 68.5 (t, *J* = 19.8 Hz), 25.6, 18.4, −5.4.

**3−(t−Butyldimethylsilanyloxy)−2,2−difluoro−propenal (138):** To a mixture of allylic alcohol **137** (468 mg, 2.07 mmol), manganese (IV) dioxide (539 mg, 6.2 mmol) and $CCl_4$ (10 mL) was added and refluxed overnight. Additional manganese (IV) dioxide (90 mg, 1.03 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, 1:20) to give α,β−unsaturated aldehyde **138** (339 mg, 73%) as a colorless oil. $^1$H NMR ($CDCl_3$, 300 MHz) δ 9.73 (s, 1H), 4.48 (t, *J* = 9.4 Hz, 2H), 0.83 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 119.5 (t, *J* = 211.2

Hz), 72.2 (t, $J$ = 18.6 Hz), 68.9 (t, $J$ = 19.6 Hz), 25.6, 18.4, −5.4.

**(±)−5−(t−Butyldimethylsilanyloxy)−4,4−difluoro−pent−1−en−3−ol (139):** To a solution of **138** (1.05 g, 4.68 mmol) in dry THF (12 mL), vinylmagnesium bromide (5.14 mL, 1.0 M solution in THF) was slowly added at 0 °C and stirred 6 h at 0 °C. Saturated $NH_4Cl$ solution (5 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 to dryness. The residue was purified by silica gel column chromat−ography (EtOAc/hexane, 1:15) to give **139** (944 mg, 80%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 5.93 (m, 1H), 5.29−5.24 (m, 2H), 4.47 (m, 1H), 4.13 (m, 2H), 0.81 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 139.5, 122.2 (t, $J$ = 198.2 Hz), 81.5 (dd, $J$ = 20.8, 18.9 Hz), 70.6 (t, $J$ = 20.1 Hz), 25.2, 18.7, −5.6.

**(±)−t−Butyl−[2,2−difluoro−3−(4−methoxybenzyloxy)−pent−4−enyloxy]−dimethylsilane (140):** NaH (60% in mineral oil, 66.4 mg, 1.66 mmol) was added portion−wise to a cooled (0℃) solution of secondary alcohol **139** (349 mg, 1.385 mmol) and $p$−methoxybenzyl chloride (0.206 mL, 1.52 mmol) in anhydrous DMF (6 mL). The reaction mixture was stirred overnight at RT. The solvent was removed *in vacuo* and the residue was diluted with $H_2O$ (60 mL) followed by extraction with diethyl ether (2 × 60 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, 1:16) to give **140** (376 mg, 73%) as a colorless oil. $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.31−7.25 (m, 2H), 6.94−6.88 (m, 2H), 5.90 (m, 1H), 5.29−5.24 (m, 2H), 4.63 (s, 2H), 4.49 (s, 2H), 4.11−4.08 (m, 2H), 3.74 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.3, 138.6, 130.5, 129.3, 122.0 (dd, $J$ = 201.2, 50.2 Hz), 115.5, 114.2, 84.1 (dd, $J$ = 19.8, 17.4 Hz), 73.6, 70.3 (t, $J$ = 19.4 Hz), 56.3, 25.7, 18.4, −5.5.

**(±)−2,2−Difluoro−3−(4−methoxybenzyloxy)−pent−4−en−1−ol (141):** To a solution of **140** (1.05 g, 2.82 mmol) in THF (20 mL), TBAF (4.2 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, 4:1) to give **141** (670 mg, 92%): $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.23 (m, 2H), 6.92−6.85 (m, 2H), 5.89 (m, 1H), 5.32−5.25 (m, 2H), 4.64 (s, 2H), 4.08 (m, 2H), 3.87 (m, 2H), 3.75 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.4, 138.2, 130.7, 128.2, 120.5 (dd, $J$ = 208.6, 32.8 Hz), 116.0, 114.1, 83.5 (dd, $J$ = 20.4, 14.7 Hz), 73.6, 67.2 (dd, $J$ = 18.8, 10.6 Hz), 56.3.

**(±)−2,2−Difluoro−3−(4−methoxybenzyloxy)−2−methylene−pent−4−enal (142):** Difluorinated aldehyde derivative **142** was synthesized from **141** by the similar procedure as described for **138**: yield 87%;

$^{1}$H NMR ($CDCl_3$, 300 MHz) δ 9.79 (m, 1H), 7.30−7.23 (m, 2H), 6.91−6.85 (m, 2H), 5.89 (m, 1H), 5.27−5.23 (m, 2H), 4.62 (s, 2H), 4.27−4.23 (m, 1H), 3.71 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.5, 137.8 (dd, $J$ = 220.4, 53.2 Hz), 136.3, 131.1, 129.6, 115.9, 115.2, 80.2 (dd, $J$ = 20.4, 14.6 Hz), 74.0, 56.1.

**(*rel*)−(3*R* and *3S*,5*S*)−4,4−Difluoro−5−(4−methoxy−benzyloxy)−hepta−1,6−dien−3−ol (143):** Divinyl analogue **143** was synthesized as a diastereomeric mixture from aldehyde derivative **142** by a procedure similar to that described for **139** as diastereomeric mixture: yield 75%; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.23 (m, 2H), 6.93−6.83 (m, 2H), 5.91−5.87 (m, 2H), 5.25−5.21 (m, 4H), 4.65 (m, 2H), 4.45 (m, 1H), 4.12−4.06 (m, 1H), 3.74 (s, 3H).

**(*rel*)−(1*S*,4*R*)−5,5−Difluoro−4−(4−methoxy−benzyloxy)−cyclopent−2−enol (144a) and (*rel*)−(1*R*,4*R*)−5,5−difluoro−4−(4−methoxy−benzyloxy)−cyclopent−2−enol (144b):** To a solution of **143** (160. mg, 0.562 mmol) in dry methylene chloride (6 mL) was added 2$^{nd}$ generation Grubbs catalyst (30.0 mg, 0.0352 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 **144a** (50 mg, 35%) and **144b** (52 mg, 36%). Data for **144a**: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.27 (m, 2H), 6.93−6.85 (m, 2H), 5.62−5.47 (m, 2H), 4.62−4.57 (m, 3H), 4.21 (m, 1H), 3.74 (s, 3H); $^{13}$C

NMR ($CDCl_3$, 75 MHz) δ 159.6, 131.2, 130.7, 129.2, 122.7 (dd, $J$ = 210.2, 60.5 Hz), 115.2, 84.6 (dd, $J$ = 20.2, 10.4 Hz), 80.3 (ddd, $J$ = 18.8, 10.8, 2.8 Hz), 74.2, 57.1; Data for **144b**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.24 (m, 2H), 6.90−6.82 (m, 2H), 5.61−5.45 (m, 2H), 4.61−4.55 (m, 3H), 4.21−4.18 (m, 1H), 3.74 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.4, 131.0, 130.1, 128.8, 123.1 (dd, $J$ = 208.2, 48.6 Hz), 114.4, 83.8 (dd, $J$ = 18.8, 12.6 Hz), 79.5 (dd, $J$ = 19.0, 10.2 Hz), 73.9, 56.5.

**(*rel*)−(1*S*,4*R*)−9−[5,5−Difluoro−4−(4−methoxybenzyloxy)−cyclopent−2−en−1−yl] 6−chloropurine (145):** To a solution containing compound **144b** (95 mg, 0.372 mmol), triphenylphosphine (264 mg, 1.008 mmol) and 6−chloropurine (115 mg, 0.744 mmol) in anhydrous cosolvent (1,4−dioxane, 4.0 mL and DMF, 3.0 mL), diethyl azodicarboxylate (DEAD) (0.135 mL, 0.744 mmol) was added dropwise at 30℃ for 15 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 evaporated to dryness and the residue was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give compound **145** (74 mg, 51%): mp 168−171℃; UV (MeOH) $\lambda_{max}$ 263.5 nm: $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1H), 8.29 (s, 1H), 7.27−7.20 (m, 2H), 6.90−6.85 (m, 2H), 5.63−5.57 (m, 2H), 5.05 (m, 1H), 4.65 (s, 2H), 4.18 (ddd, $J$ = 16.2, 10.0, 2.8 Hz, 1H), 3.74 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.5, 151.6,

151.0, 145.2, 132.4, 130.7, 129.8, 128.9, 119.0 (dd, $J$ = 198.4, 50.6 Hz), 115.8, 85.2 (dd, $J$ = 18.6, 12.4 Hz), 73.8, 65.2 (dd, $J$ = 20.2, 10.4 Hz), 57.5.

**(*rel*)-(1*S*,4*R*)-9-(5,5-Difluoro-4-hydroxy-cyclopent-2-en-1-yl) 6-chloropurine (146):** To a solution of compound **145** (199 mg, 0.507 mmol) in $CH_2Cl_2/H_2O$ (10 mL, 10:1 v/v) was added DDQ (170 mg, 0.747 mmol), and the mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ (1.2 mL) was added to quench the reaction, which was then stirred for 3 h at RT. The mixture was diluted with water (150 mL) and extracted with $CH_2Cl_2$ (3x150 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated to dryness and the residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 4:1:0.03) to give compound **146** (83 mg, 60%): mp 176-178 °C; UV (MeOH) $\lambda_{max}$ 265.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.67 (s, 1H), 8.28 (s, 1H), 5.63-5.59 (m, 2H), 5.04-5.00 (dd, $J$ = 16.8, 9.8 Hz, 1H), 4.56-4.52 (m, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 151.7, 151.3, 151.1, 145.2, 132.5, 130.2, 129.3, 121.1 (dd, $J$ = 192.2, 40.2 Hz), 81.5 (dd, $J$ = 18.4, 12.0 Hz), 64.6 (dd, $J$ = 19.4, 11.0 Hz).

**(*rel*)-(1*S*,4*R*)-Diethyl [9-(5,5-difluoro-4-hydroxy-cyclopent-2-en-1-yl) 6-chloropurine] phosphonate (147):** Both LiO*t*-Bu (1.488 mL of 0.5 M solution in THF, 0.744 mmol) and a solution of diethyl phosphonomethyltriflate (209 mg, 0.696 mmol) in 6.0 mL of

THF were slowly added to a solution of the nucleoside analogue **146** (95 mg, 0.348 mmol) in 6.0 mL of THF at 40℃ and stirred overnight at rt under nitrogen. The mixture was quenched by adding saturated $NH_4Cl$ solution (5 mL) and further diluted with additional $H_2O$ (100 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue was purified by silica gel column chromate graphy (MeOH/Hexane/EtOAc, 0.03:4:1) to give **147** (85 mg, 58%) as a foam: $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.69 (s, 1H), 8.28 (s, 1H), 5.62−5.56 (m, 2H), 5.03−4.97 (ddd, $J$ = 18.6, 10.3, 3.2 Hz, 1H), 4.35−4.31 (m, 4H), 4.13 (m, 1H), 4.01 (d, $J$ = 8.1 Hz, 2H), 1.37 (m 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 151.6, 151.0, 145.3, 132.6, 130.6, 128.7, 118.1 (dd, $J$ = 190.6, 52.4 Hz), 88.5 (dd, $J$ = 19.8, 10.2 Hz), 66.3 (dd, $J$ = 18.8, 9.8 Hz), 64.8, 63.2, 14.7.

**(*rel*)−(1*S*,4*R*)−Diethyl [9−(5,5−difluoro−4−hydroxy−cyclopent−2−en−1−yl) adenine] phosphonate (148):** A solution of **147** (120 mg, 0.283 mmol) in saturated methanolic ammonia (10 mL) was stirred for 12 h at 65℃ in a steel bomb, and the volatiles were evaporated to dryness. The residue was purified by silica gel column chromatography (MeOH/$CH_2Cl_2$, 1:10) to give **148** (69 mg, 61%) as a white solid: mp 158−161℃; UV (MeOH) $\lambda_{max}$ 262.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.29 (s, 1H), 8.18 (s, 1H), 5.63−5.58 (m, 2H), 5.04 (dd, $J$ = 19.2, 10.8 Hz, 1H), 4.34−4.30 (m, 4H), 4.18 (m,

1H), 3.99 (d, $J$ = 8.2 Hz, 2H), 1.36 (m 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 155.3, 152.6, 150.4, 130.4, 119.3, 117.2 (dd, $J$ = 196.7, 42.8 Hz), 87.1 (dd, $J$ = 19.2, 11.0 Hz), 65.3 (dd, $J$ = 19.0, 10.4 Hz), 64.2, 63.4, 15.1.

**(*rel*)−(1*S*,4*R*)−[9−(5,5−Difluoro−4−hydroxy−cyclopent−2−en−1−yl) adenine] 4−phosphonic acid (149):** To a solution of the nucleoside phosphonate **148** (84 mg, 0.21 mmol) in anhydrous $CH_3CN$ (8 mL) and 2,6−lutidine (0.489 mL, 4.2 mmol) was added trimethyl silyl bromide (0.277 mL, 2.1 mmol). The mixture was heated for 12 h at 50℃ under nitrogen gas and then concentrated *in vacuo*. The residue was partitioned between $CH_2Cl_2$ (60 mL) and distilled purified water (50 mL). The aqueous layer was washed with $CH_2Cl_2$ (2 × 60 mL) and then freeze−dried to give phosphonic acid **149** (67 mg, 92%) as a yellowish foam: UV ($H_2O$) $\lambda_{max}$ 265.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.26 (s, 1H, H−8), 8.12 (s, 1H, H−2), 5.62−5.57 (m, 2H, H−2′, H−3′), 5.01 (ddd, $J$ = 19.6, 11.0, 2.8 Hz, 1H, H−1′), 4.19 (ddd, $J$ = 18.8, 10.8, 3.4 Hz, 1H, H−4′), 3.98 (d, $J$ = 8.0 Hz, 2H, $PCH_2$); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 154.7, 152.5, 150.3, 130.7, 129.2, 119.3, 117.7 (dd, $J$ = 198.2, 52.8 Hz), 88.0 (dd, $J$ = 20.4, 9.8 Hz), 64.5 (dd, $J$ = 19.2, 10.2 Hz), 63.4, 62.8; Anal. Calc. for $C_{11}H_{12}F_2N_5O_4P$ (+$H_2O$): C, 36.17; H, 3.86; N, 19.18; Found: C, 36.15; H, 3.85; N, 19.20; MS *m/z* 348 $(M+H)^+$.

**(*rel*)−(1*R*,4*R*)−[5,5−Difluoro−4−(4−methoxybenzyloxy)−cyclopent**

**−2−enyloxymethyl]−phosphonic acid diethyl ester (150):** Diethyl phosphonate analogue **150** was synthesized from **144b** by the similar procedure used for **147**: yield 59%; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.28−7.23 (m, 2H), 6.90−6.85 (m, 2H), 5.61−5.58 (m, 2H), 4.46 (s, 2H), 4.34−4.30 (m, 4H), 4.18−4.14 (m, 2H), 4.02 (d, $J$ = 8.2 Hz, 2H), 3.74 (s, 3H), 1.36 (m 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.4, 130.6, 129.4, 119.4 (dd, $J$ = 194.6, 50.4 Hz), 116. 3, 86.5 (dd, $J$ = 19.4, 10.6 Hz), 73.2, 64.7, 63.3 (dd, $J$ = 18.4, 9.2 Hz), 62.6, 55.3, 14.3.

**(*rel*)−(1*R*,4*R*)−(5,5−Difluoro−4−hydroxy−cyclopent−2−enyloxy methyl)−phosphonic acid diethyl ester (151):** Deprotection of **150** was performed under the similar procedure as described for the preparation of **146**: yield 64%; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 5.62−5.58 (m, 2H), 4.58 (ddd, $J$ = 18.6, 10.2, 2.8 Hz, 1H), 4.32−4.28 (m, 4H), 4.18 (ddd, $J$ = 19.2, 12.6, 4.0 Hz, 1H), 4.01 (d, $J$ = 8.0 Hz, 2H), 1.37 (m 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 130.6, 129.7, 122.2 (dd, $J$ = 190.6, 44.8 Hz), 86.7 (dd, $J$ = 21.2, 10.6 Hz), 79.4 (dd, $J$ = 19.7, 10.5 Hz), 64.5, 63.8, 14.5.

**(*rel*)−(1*S*,4*R*)−Diethyl [9−(5,5−difluoro−4−hydroxy−cyclopent−2−en−1−yl)2−fluoro−6−chloropurine] phosphonate (152):** Mitsunobu coupling of **151** with 2−fluoro−6−chloropurine under the similar reaction condition as described for **145**: yield 46%; UV (MeOH) $\lambda_{max}$ 269.5 nm; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.41 (s, 1H), 5.61−5.54 (m, 2H), 5.08 (ddd, $J$ = 19.2, 11.4, 3.4 Hz, 1H), 4.27−4.20 (m, 5H), 4.00

(d, $J$ = 8.1 Hz, 2H), 1.37 (m 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.2, 152.7, 148.2, 144.5, 130.6, 129.2, 128.4, 118.3 (dd, $J$ = 194.2, 58.6 Hz), 87.3 (dd, $J$ = 20.4, 9.8 Hz), 66.4 (dd, $J$ = 18.9, 8.8 Hz), 64.5, 63.6, 62.4, 16.3.

**(*rel*)-(1*S*,4*R*)-Diethyl [9-(5,5-difluoro-4-hydroxy-cyclopent-2-en-1-yl) 2-fluoro-6-aminopurine] phosphonate (153) and (*rel*)-(1′*S*,4′*R*)-diethyl [9-(5,5-difluoro-4-hydroxy-cyclopent-2-en-1-yl) 2-amino-6-chloropurine] phosphonate (154):** Dry ammonia gas was bubbled into a stirred solution of **152** (560 mg, 1.27 mmol) in DME (20 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/$CH_2Cl_2$, 1:12) to give **153** (75 mg, 14%) and **154** (305 mg, 55%), respectively: Data for **153**; UV (MeOH) $\lambda_{max}$ 268.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.43 (s, 1H), 5.60-5.57 (m, 2H), 5.03 (dd, $J$ = 19.0, 10.2 Hz, 1H), 4.23-4.17 (m, 5H), 4.03 (d, $J$ = 8.0 Hz, 2H), 1.35-1.38 (m 6H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 154.6, 152.2, 147.3, 145.6, 130.8, 129.5, 128.6, 118.6 (dd, $J$ = 196.6, 52.8 Hz), 86.2 (dd, $J$ = 20.2, 9.4 Hz), 65.2 (dd, $J$ = 19.8, 9.4 Hz), 63.8, 62.9, 17.1; Data for **154**; UV (MeOH) $\lambda_{max}$ 310.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.43 (s, 1H), 5.62-5.58 (m, 2H), 5.04 (dd, $J$ = 19.3, 10.4 Hz, 1H), 4.21-4.16 (m, 5H), 4.01 (d, $J$ = 8.0 Hz, 2H), 1.36 (m 6H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 155.7, 153.1,

148.3, 144.9, 130.5, 129.2, 128.2, 118.6 (dd, $J$ = 198.1, 56.2 Hz), 88.1 (dd, $J$ = 20.7, 9.6 Hz), 64.6 (dd, $J$ = 19.4, 9.9 Hz), 63.4, 62.5, 16.5.

**(*rel*)-(1*S*,4*R*)-9-(5,5-difluoro-4-hydroxy-cyclopent-2-en-1-yl) guanine] phosphonic acid (155):** To a solution of **154** (20.8 mg, 0.0495 mmol) dry DMF (7 mL) was added trimethylsilyl bromide (114 μL, 0.862 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 (2.0 mL) and 2-mercaptoethanol (13.9 μL, 0.198 mmol) and NaOMe (10.7 mg, 0.198 mmol) was added to the mixture. The mixture was refluxed for 5 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 **155** (6.8 mg, 66%) as a solid. UV (MeOH) $\lambda_{max}$ 254.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 7.98 (s, 1H, H-8), 5.61-5.56 (m, 2H, H-2′, H-3′), 5.02 (ddd, $J$ = 20.4, 10.6, 3.2 Hz, 1H, H-1′), 4.16 (ddd, $J$ = 18.8, 9.6, 2.8 Hz, 1H, H-4′), 4.00 (d, $J$ = 8.1 Hz, 2H, $PCH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 157.2, 153.8, 149.1, 141.5, 131.1, 130.2, 119.5, 118.2 (dd, $J$ = 192.5, 46.6 Hz), 86.5 (dd, $J$ = 19.4, 10.2 Hz), 64.5, 54.4 (dd, $J$ = 19.6, 9.8 Hz).

**(*rel*)-(1*S*,4*R*)-Bis(SATE) phosphoester of [9-(5,5-difluoro-4-hydroxy-cyclopent-2-en-1-yl]adenine (157):** A solution of adenine

phosphonic acid derivative **149** (117 mg, 0.338 mmol) and tri-*n*-butylamine (189 mg, 1.02 mmol) in methanol (8 mL) was mixed for 30 min and evaporated to dryness under reduced pressure. The residue was thoroughly dried with anhydrous ethanol and toluene. The resulting foamy solid was dissolved in anhydrous pyridine (20 mL) to which thioester **156** (1.04 g, 6.4 mmol) and 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (402 mg, 1.356 mmol) were added. The mixture was stirred overnight at room temperature and quenched with tetrabutylammonium bicarbonate buffer (20.0 mL, 1 M solution, pH 8.0). The mixture was concentrated under reduced pressure and the residue was diluted with water (150 mL) and extracted with $CHCl_3$ (150 mL) two times. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and evaporated to dryness under vacuum. The residue was purified by silica gel column chromatography (MeOH/Hexane/EtOAc, 0.04:3:1) to give **157** (68 mg, 32%) as a white solid: mp 140-143℃; UV (MeOH) $\lambda_{max}$ 260.0 nm; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.28 (s, 1H, H-8), 8.11 (s, 1H, H-2), 5.59-5.54 (m, 2H, H-2′, H-3′), 5.02 (dd, $J$ = 18.8, 10.2 Hz, 1H, H-1′), 4.21-4.15 (m, 3H, H-4′, $PCH_2$), 3.94-3.94 (m, 4H, $OCH_2$), 3.18-3.15 (m, 4H, $SCH_2$), 1.23-1.19 (m, 18H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 202.9, 154.8, 152.2, 147.5, 144.6, 130.7, 129.0, 119.8, 118.2 (dd, $J$ = 190.3, 48.8 Hz), 87.7 (dd, $J$ = 19.8, 10.2 Hz), 65.8 (dd, $J$ = 20.0, 9.8 Hz), 64.3, 62.8, 58.5, 49.3, 34.8, 25.7;

MS *m/z* 636 $(M+H)^+$.

**(*rel*)-(1*R*,4*S*)-(4-Benzyloxymethyl-6,6-difluorocyclopent-2-enyloxy)*t*-butyldimethylsilane (161):** To a stirred solution of compound **160** (2.38 g, 9.93 mmol) and imidazole (1.012 g, 14.89 mmol) in $CH_2Cl_2$ (30 mL), *t*-butyldimethylsilyl chloride (1.57 g, 10.425 mmol) was added at 0℃. The mixture was stirred overnight at RT, and quenched by adding a $NaHCO_3$ aqueous solution (3 mL). The mixture was stirred for 30 min, diluted with water (60 mL) and extracted using EtOAc (2 × 60 mL). The combine organic layer was dried over anhydrous $MgSO_4$, filtered and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:7) to give **161** (3.13 g, 89%) as a colorless syrup: $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.29 (m, 5H), 6.01 (m, 1H), 5.94 (m, 1H), 4.67 (m, 1H), 4.55 (s, 2H), 3.69 (m, 1H), 3.57 (m, 1H), 3.31-3.24 (m, 1H), 0.82 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 138.0, 133.6, 130.6 (dd, *J* = 251.2, 256.6 Hz), 128.9, 128.3, 127.5, 127.2, 85.4 (dd, *J* = 20.5, 24.6 Hz), 64.3, 44.4 (dd, *J* = 19.4, 23.7 Hz), 25.4, 18.6, -5.3.

**(*rel*)-(1*R*,4*S*)-[1-(*t*-Butyldimethylsilanyloxy)6,6-difluorocyclopentyl] methanol (162):** A stirred solution of benzyl ether **161** (744 mg, 2.1 mmol) and Pd/C (10%, 25 mg) in methanol (15 mL) was hydrogenated for 24 h at room temperature under rubber balloon . The mixture was filtered and the solvent was evaporated under

reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **162** (425 mg, 76%) as a colorless syrup: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 3.80−3.76 (m, 1H), 3.63 (dd, $J$ = 8.6, 5.8 Hz, 1H), 3.50 (dd, $J$ = 8.6, 6.8 Hz, 1H), 2.27 (m, 1H), 2.01−1.74 (m, 4H), 0.83 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 128.2 (dd, $J$ = 250.4, 255.3 Hz), 78.5 (dd, $J$ = 21.2, 25.4 Hz), 57.3, 43.1 (dd, $J$ = 20.5, 23.6 Hz), 28.3, 25.5, 22.5, 18.4, −5.6.

**(*rel*)−(1*R*,4*S*)−1−(*t*−Butyldimethylsilanyloxy)−6,6−difluorocyclopentanecarbaldehyde (163):** To a stirred solution of oxalyl chloride (129 mg, 1.02 mmol) in $CH_2Cl_2$ (10 mL) was added a solution of DMSO (159 mg, 2.04 mmol) in $CH_2Cl_2$ (4.0 mL) dropwise at 78℃. The resulting solution was stirred at 78℃ for 30 min, and a solution of alcohol **162** (271 mg, 1.02 mmol) in $CH_2Cl_2$ (8 mL) was added drop wise. The mixture was stirred at 78℃ for 30 min and TEA (0.57 mL, 4.07 mmol) was added. The resulting mixture was warmed to 0℃ and stirred for 30 min. $H_2O$ (8 mL) was added, and the solution was stirred for 30 min at RT. The mixture was diluted with water (80 mL) and then extracted with EtOAc (2 × 80 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, 1:15) to give aldehyde compound **163** (242 mg, 90%) as a colorless oil: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 9.71 (s, 1H), 3.79−3.74 (m, 1H), 2.94 (m,

1H), 2.03−1.77 (m, 4H), 0.81 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 202.6, 129.5 (dd, $J$ = 251.1, 256.4 Hz), 79.3 (dd, $J$ = 20.5, 24.8 Hz), 56.5 (dd, $J$ = 21.3, 24.7 Hz), 28.7, 25.4, 22.3, 18.5, −5.2.

**(*rel*)−(1*R*,4*S*)−*t*−Butyl−(6,6−difluoro−4−vinyl−cyclopentyloxy) dimethylsilane (164):** To ylide solution [methyltriphenylphosphonium iodide (376 mg, 0.925 mmol), triphenylphosphine (28.5 mg, 0.11 mmol), 1.6 M *n*−butyllithium solution (0.578 mL, 0.925 mmol) in dry tetrahydrofuran (7.0 mL) at −78℃, was dropwise added to a solution of olefin aldehyde **163** (198 mg, 0.925 mmol) in dry THF (7 mL). The reaction mixture was warmed to room temperature and stirred for 6 h, quenched by saturated sodium bicarbonate solution. The reaction mixture was partitioned between saturated sodium bicarbonate solution and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuum* and chromatographed (hexane−EtOAc, 20:1) to afford **164** (161 mg, 82%) as a colorless oil. $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 5.74−5.70 (m, 1H), 5.04−4.98 (m, 2H), 3.77−3.73 (m, 1H), 2.88 (m, 1H), 1.99−1.75 (m, 4H), 0.82 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 141.3, 130.2 (dd, $J$ = 251.3, 256.8 Hz), 115.7, 78.5 (dd, $J$ = 19.8, 23.5 Hz), 45.2 (dd, $J$ = 20.6, 23.9 Hz), 29.1, 25.6, 22.7, 18.4, −5.5.

**(*rel*)−(1*R*,4*S*)−6,6−Difluoro−4−vinyl−cyclopentan−1−ol (165):**

To a solution of **164** (0.6 g, 2.286 mmol) in THF (10 mL), TBAF (2.74 mL, 1.0 M solution in THF) was added at 0℃. The mixture was stirred for 6 h at RT and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 8:1) to give **165** (308 mg, 91%): $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 5.73−5.69 (m, 1H), 5.02−4.97 (m, 2H), 3.79−3.75 (m, 1H), 2.78 (m, 1H), 2.00−1.78 (m, 4H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 140.7, 129.6 (dd, $J$ = 250.3, 255.5 Hz), 114.3, 76.9 (dd, $J$ = 19.6, 22.9 Hz), 44.7 (t, $J$ = 19.3 Hz), 27.8, 22.1.

**(*rel*)−(1′*S*,4′*S*)−9−(6′,6′−Difluoro−4′−vinyl−cyclopentan−1′−yl) 6−chloropurine (166):** To a stirred solution of triphenylphosphine (281 mg, 1.07 mmol) in dry THF (5 mL) at 0℃ was added dropwise the diisopropyl azodicarboxylate (DIAD) (216 mg, 1.07 mmol) and the reaction mixture was stirred at this temperature for 30 min. After that, a solution of the alcohol **165** (79 mg, 0.535 mmol) in THF (5 mL) was added and the reaction mixture was stirred at 0℃ for 30 min. Then the cold bath was removed and the yellow solution was stirred for 30 min at room temperature. 6−Chloropurine (230 mg, 1.07 mmol) was then added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 2.5:1) to give compound **166** (90 mg, 59%); UV (MeOH) $\lambda_{max}$ 264.0 nm: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.70

(s, 1H), 8.29 (s, 1H), 5.72−5.65 (m, 1H), 5.03−4.98 (m, 2H), 5.12−5.08 (m, 1H), 2.78−2.74 (m, 1H), 2.04−1.81 (m, 4H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.8, 151.4, 151.1, 145.7, 140.3, 128.8 (dd, $J$ = 250.5, 253.9 Hz), 132.5, 114.6, 67.4 (dd, $J$ = 14.3, 18.6 Hz), 45.8 (dd, $J$ = 17.3, 19.2 Hz), 28.5, 22.7.

**(*rel*)−(1′*S*,4′*S*)−Diethyl {9−(6′,6′−difluoro−4′−vinyl−cyclopentan−1′−yl) 6−chloropurine} phosphonate (167):** To a $CH_2Cl_2$ (10 mL) solution of 6−chloropurine derivative **166** (117 mg, 0.412 mmol) and diethyl vinylphosphonate (338 mg, 2.06 mmol), 2$^{nd}$−generation Grubbs catalyst (17.49 mg, 0.0206 mmol) was added. The reaction mixture was refluxed for 24 h under dry argon gas and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/*n*−Hexane/MeOH, 3:1:0.04) to give **167** (102 mg, 59%) as a form: $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.70 (s, 1H), 8.29 (s, 1H), 6.68 (dd, $J$ = 17.2, 21.4 Hz, 1H), 6.15 (dd, $J$ = 17.2, 19.7 Hz, 1H), 5.18−5.13 (m, 1H), 4.15−4.10 (m, 4H), 2.81−2.79 (m, 1H), 2.00−1.74 (m, 4H), 1.21−1.17 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 151.5, 151.0, 150.8, 148.7, 145.1, 128.5 (dd, $J$ = 249.9, 253.2 Hz), 131.8, 115.2, 65.7 (dd, $J$ = 15.7, 18.9 Hz), 63.2, 62.8, 46.8 (dd, $J$ = 18.1, 21.5 Hz), 29.2, 22.5, 15.4.

**(*rel*)−(1′*S*,4′*S*)−Diethyl {9−(6′,6′−difluoro−4′−vinyl−cyclopentan−1′−yl) adenine} phosphonate (168):** A solution of **167** (135 mg, 0.32 mmol) in saturated methanolic ammonia (5 mL) was stirred overnight

at 62℃ in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/ $CH_2Cl_2$, 1:10) to give **168** (87 mg, 68%) as a white solid: UV (MeOH) $\lambda_{max}$ 261.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.24 (s, 1H), 7.71 (s, 1H), 6.65 (dd, $J$ = 17.0, 21.6 Hz, 1H), 6.18 (dd, $J$ = 17.1, 20.3 Hz, 1H), 5.11−5.06 (m, 1H), 4.18−4.13 (m, 4H), 2.84−2.81 (m, 1H), 2.02−1.77 (m, 4H), 1.19−1.15 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 154.8, 152.5, 150.7, 149.2, 142.0, 127.9 (dd, $J$ = 250.3, 254.5 Hz), 119.4, 114.6, 66.3 (dd, $J$ = 17.4, 19.8 Hz), 63.5, 63.1, 46.8 (dd, $J$ = 18.3, 21.6 Hz), 30.1, 23.2, 15.8.

**(*rel*)−(1′*S*,4′*S*)−9−(6′,6′−Difluoro−4′−vinyl−cyclopentan−1′−yl) adenine} phosphonic acid (169)**: To a solution of the phosphonate **168** (194 mg, 0.483 mmol) in anhydrous $CH_3CN$ (10 mL) and 2,6−lutidine (1.125 mL, 9.67 mmol) was added trimethylsilyl bromide (0.740 mg, 4.83 mmol). The mixture was heated for 24 hour at 70℃ under nitrogen gas and then concentrated *in vacuum*. The residue was partitioned between $CH_2Cl_2$ (80 mL) and purified water (80 mL). The aqueous layer was washed with $CH_2Cl_2$ (2 × 70 mL) and then freeze−dried to give phosphonic acid **169** (125 mg, 79%) as a yellowish foam: UV ($H_2O$) $\lambda_{max}$ 262.5 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.22 (s, 1H, H−8), 7.73 (s, 1H, H−2), 6.68 (m, 1H, H−5′), 6.20 (dd, $J$ = 16.7, 19.5 Hz, 1H, PCH), 5.14−5.10 (m, 1H, H−1′), 2.84−2.79 (m, 1H, H−4′), 2.05−1.79 (m, 4H, H−2′a, H−2′b, H−3′a,

H−3′b); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 154.4, 152.1, 150.3, 148.3, 141.6, 128.6 (dd, $J$ = 251.5, 254.7 Hz), 120.3, 115.7, 67.4 (dd, $J$ = 16.7, 18.7 Hz), 44.6 (dd, $J$ = 17.7, 20.5 Hz), 28.7, 22.3; MS *m/z* 346 $(M+H)^+$.

**(*rel*)−(1′*S*,4′*S*)−Diethyl{9−(6′,6′−difluoro−4′−ethyl−cyclopentan−1′−yl) 6−chloropurine} phosphonate (170):** A solution of vinyl phosphonate nucleoside analogue **167** (200 mg, 0.478 mmol) in methanol (8 mL) was added Pd/C (10%, 8 mg) and cyclohexene (4 mL) under argon gas. The reaction mixture was refluxed for 36 h. The reaction mixture was filtered through a pad of Celite, evaporated, and purified by silica gel column chromatography using methanol and methylene chloride (1:10) to give ethyl phosphonate analogue **170** (121 mg, 60%) as a white solid: mp 171−173℃; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.74 (s, 1H), 8.27 (s, 1H), 6.68 (dd, $J$ = 17.2, 21.4 Hz, 1H), 6.15 (dd, $J$ = 17.2, 19.7 Hz, 1H), 5.18−5.13 (m, 1H), 4.15−4.10 (m, 4H), 2.81−2.79 (m, 1H), 2.00−1.74 (m, 4H), 1.21−1.17 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 151.5, 151.0, 150.8, 148.7, 145.1, 128.5 (dd, $J$ = 249.9, 253.2 Hz), 131.8, 115.2, 65.7 (dd, $J$ = 15.7, 18.9 Hz), 63.2, 62.8, 46.8 (dd, $J$ = 18.1, 21.5 Hz), 29.2, 22.5, 15.4.

**(*rel*)−(1′*S*,4′*S*)−Diethyl{9−(6′,6′−difluoro−4′−ethyl−cyclopentan−1′−yl) adenine} phosphonate (171):** Adenine derivative **171** was prepared from 6−chloropurine analogue **170** by the similar ammonolysis procedure as described for **168**: yield 62%; mp 170−

172℃; UV (MeOH) $\lambda_{max}$ 261.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.27 (s, 1H), 7.74 (s, 1H), 5.13−5.09 (m, 1H), 4.16−4.12 (m, 4H), 2.79−2.76 (m, 1H), 2.13−1.75 (m, 8H), 1.20−1.15 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 155.5, 152.6, 150.3, 141.3, 127.8 (dd, $J$ = 251.0, 254.8 Hz), 118.8, 66.4 (dd, $J$ = 17.2, 20.6 Hz), 62.8, 62.4, 44.5 (dd, $J$ = 17.6, 20.3 Hz), 29.5, 28.3, 22.3, 18.7, 14.8.

**(*rel*)−(1′*S*,4′*S*)−{9−(6′,6′−Difluoro−4′−ethyl−cyclopentan−1′−yl) adenine} phosphonic acid (172):** Adenine phosphonic acid **172** was synthesized from **171** using the similar hydrolysis procedure as described for **169**: yield 73%, UV ($H_2O$) $\lambda_{max}$ 261.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.26 (s, 1H, H−8), 7.79 (s, 1H, H−2), 5.09−5.05 (m, 1H, H−1′), 2.54−2.51 (m, 1H, H−4′), 2.15−1.81 (m, 8H, $CH_2$); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 154.8, 152.2, 151.0, 142.6, 129.1 (dd, $J$ = 250.4, 253.7 Hz), 119.5, 63.9 (dd, $J$ = 16.8, 19.2 Hz), 44.5 (dd, $J$ = 18.7, 21.4 Hz), 30.3, 28.7, 21.8, 18.2; MS *m/z* 348 $(M+H)^+$.

**(*rel*)−(1′*S*,4′*S*)−(6′,6′−Difluoro−4′−vinyl−cyclopentan−1′−yl) 2−fluoro−6−chloropurine (173):** Coupling of **165** with 2−fluoro−6−chloropurine under the similar condensation conditions as described for **166** to give **173**: yield 59%; UV (MeOH) $\lambda_{max}$ 265.5 nm; $^{1}$HNMR ($CDCl_3$, 300 MHz) δ 8.42 (s, 1H), 5.71–5.64 (m, 1H), 5.02−4.96 (m, 2H), 5.09−5.05 (m, 1H), 2.74−2.70 (m, 1H), 2.11−1.89 (m, 4H); $^{13}$CNMR ($CDCl_3$, 75MHz) δ 157.1 (d, $J$ = 219.8 Hz), 153.7, 145.7,

141.2, 136.6, 128.8 (dd, $J$ = 248.6, 251.2 Hz), 120.5, 114.8, 68.8 (dd, $J$ = 17.2, 20.7 Hz), 44.8 (dd, $J$ = 16.7, 19.8 Hz), 29.2, 22.3.

**(*rel*)-(1′*S*,4′*S*)-Diethyl{9-(6′,6′-difluoro-4′-vinyl-cyclopentan-1′-yl) 2-fluoro-6-chloropurine} phosphonate (174):** Phosphonate nucleoside analogue **174** was prepared from **173** using the similar cross-metathesis procedure as described for **167**: yield 58%; $^{1}$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.47 (s, 1H), 6.69 (dd, $J$ = 17.3, 21.8 Hz, 1H), 6.18 (dd, $J$ = 17.2, 20.6 Hz, 1H), 5.14-5.09 (m, 1H), 2.73 (m, 1H), 2.04-1.81 (m, 4H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 157.4 (d, $J$ = 220.1 Hz), 153.9, 145.8, 150.2, 136.3, 129.5 (dd, $J$ = 249.4, 254.5 Hz), 121.0, 116.1, 66.5 (dd, $J$ = 16.7, 19.8 Hz), 63.1, 62.7, 45.8 (dd, $J$ = 17.8, 21.2 Hz), 29.2, 22.3.

**(*rel*)-(1′*S*,4′*S*)-Diethyl{9-(6′,6′-difluoro-4′-vinyl-cyclopentan-1′-yl) 2-fluoro-6-aminopurine} phosphonate (175a) and (*rel*)-(1′*S*,4′*S*)-diethyl {9-(6′,6′-fluoro-4′-vinyl-cyclopentan-1′-yl) 2-amino-6-chloropurine} phosphonate(175b):** Dry ammonia gas was bubbled into a stirred solution of **174** (210 mg, 0.478 mmol) in DME (8 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/CH2Cl2, 1:10) to give **175a** (24 mg, 12%) and **175b** (89 mg, 43%), respectively: Data for **175a**; UV (MeOH) $\lambda_{max}$ 261.5 nm; $^{1}$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.19 (s, 1H), 6.71 (dd, $J$ = 16.8, 19.2

Hz, 1H), 6.21 (dd, $J$ = 16.8, 20.0 Hz, 1H), 5.06−5.01 (m, 1H), 2.76−2.71 (m, 1H), 2.12−1.80 (m, 4H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 160.7 (d, $J$ = 219.8 Hz), 155.5, 152.4, 151.2, 141.7, 130.1 (dd, $J$ = 248.7, 253.8 Hz), 118.8, 115.3, 68.6 (dd, $J$ = 17.2, 20.3 Hz), 63.6, 62.9, 47.2 (dd, $J$ = 16.7, 18.9 Hz), 29.6, 21.8. Data for **175b**; UV (MeOH) $\lambda_{max}$ 307.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.13 (s, 1H), 6.75 (dd, $J$ = 15.6, 18.4 Hz, 1H), 6.23 (dd, $J$ = 17.1, 19.4 Hz, 1H), 5.12–5.07 (m, 1H), 2.75−2.69 (m, 1H), 2.10–1.79 (m, 4H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 158.4, 154.7, 151.6, 149.7, 143.4, 128.4 (dd, $J$ = 250.2, 254.5 Hz), 124.2, 115.6, 66.7 (dd, $J$ = 15.7, 18.8 Hz), 63.2, 62.7, 62.1, 46.8 (dd, $J$ = 16.2, 18.4 Hz), 27.9, 21.7.

**(*rel*)−(1′*S*,4′*S*)−9−{(6′,6′−Difluoro−4′−vinyl−cyclopentan−1′−yl) guanine} phosphonic acid (176):** To a solution of **175b** (275 mg, 0.632 mmol) dry $CH_3CN$ (20 mL) was added trimethylsilyl bromide (0.146 mL, 11.04 mmol) at room temperature. After this mixture was stirred for 30 h, the solvent was removed, evaporating three times with methanol. The residue was dissolved in MeOH (24.0 mL) and 2−mercaptoethanol (172.8 $\mu$L, 2.532 mmol) and NaOMe (134.4 mg, 2.532 mmol) were added to the mixture. The mixture was refluxed for 18 h under $N_2$, cooled, neutralized with glacial AcOH, and evaporated to dryness under vacuum. The residue was purified by chromatography on a preparative column of reversed−phase C18 silica gel eluting by water to give **176** (148 mg, 65%) as a yellowish

form. UV (H2O) $\lambda_{max}$ 254.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 7.83 (s, 1H, H−8), 6.71 (dd, $J$ = 16.3, 18.7 Hz, 1H, H−5′), 6.19 (dd, $J$ = 17.4, 20.2 Hz, 1H, PCH), 5.13−5.08 (m, 1H, H−1′), 2.70−2.65 (m, 1H, H−4′), 2.09−1.76 (m, 4H, $CH_2$); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 157.7, 154.6, 152.5, 150.3, 136.5, 129.6 (dd, $J$ = 251.0, 254.6 Hz), 118.7, 114.8, 68.1 (dd, $J$ = 14.6, 17.3 Hz), 62.6, 62.0, 44.5 (dd, $J$ = 15.5, 17.6 Hz), 29.2, 22.4; MS *m/z* 362 $(M+H)^+$.

**(*rel*)−(1′*S*,4′*S*)−Diethyl{9−(6′,6′−difluoro−4′−ethyl−cyclopentan−1′−yl) 2−fluoro−6−chloropurine} phosphonate (177):** Compound **177** was synthesized from **174** by the similar catalytic hydrogenation procedure as described for **170**: yield 65%; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) $\delta$ 8.45 (s, 1H), 5.12−5.07 (m, 1H), 4.15−4.09 (m, 4H), 2.67−2.64 (m, 1H), 2.18−1.73 (m, 8H), 1.27−1.23 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) $\delta$ 157.3 (d, $J$ = 220.2 Hz), 153.7, 145.3, 136.5, 128.9 (dd, $J$ = 250.4, 253.2 Hz), 120.5, 66.8 (dd, $J$ = 15.4, 18.0 Hz), 63.1, 62.3, 61.8, 45.8 (dd, $J$ = 16.3, 18.7 Hz), 29.5, 28.7, 22.1, 18.8, 15.4.

**(*rel*)−(1′*S*,4′*S*)−Diethyl{9−(6′,6′−difluoro−4′−ethyl−cyclopentan−1′−yl) 2−fluoro−6−aminopurine} phosphonate (178a) and (*rel*)−(1′*S*,4′*S*)−diethyl {9−(6′,6′−difluoro−4′−ethyl−cyclopentan−1′−yl) 2−amino−6−chloropurine} phosphonate (178b):** Ammonolysis of **177** was performed using the similar procedure as described for **171**: Data for **178a**; yield 10%; UV (MeOH) $\lambda_{max}$ 261.0 nm; $^{1}$H NMR (DMSO−$d_6$,

300 MHz) δ 8.19 (s, 1H), 5.17−5.11 (m, 1H), 4.12−4.08(m, 4H), 2.58−2.54 (m, 1H), 2.17−1.76 (m, 8H), 1.20−1.15 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 161.2 (d, $J$ = 267.7 Hz), 155.2, 152.6, 141.3, 127.3 (dd, $J$ = 248.5, 252.7 Hz), 118.5, 67.5 (dd, $J$ = 15.8, 18.1 Hz), 63.1, 62.7, 46.2 (dd, $J$ = 15.4, 17.6 Hz), 30.2, 29.3, 23.2, 19.4, 15.8; Data for **178b**; yield 41%; UV (MeOH) $\lambda_{max}$ 308.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.12 (s, 1H), 5.09−5.03 (m, 1H), 4.16−4.11 (m, 4H), 2.62−2.58 (m, 1H), 2.19−1.81 (m, 8H), 1.18−1.12 (m, 6H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 158.5, 154.6, 151.1, 142.8, 129.1 (dd, $J$ = 246.8, 250.4 Hz), 125.0, 65.7 (dd, $J$ = 16.8, 18.5 Hz), 62.4, 61.9, 44.6 (dd, $J$ = 16.2, 18.7 Hz), 28.8, 27.5, 21.7, 18.6, 14.6.

**(*rel*)−(1′*R*,3′*S*)−9−{(6′,6′−Difluoro−4′−ethyl−cyclopentan−1′−yl) guanine} phosphonic acid (179):** Guanine nucleoside phosphonic acid **179** was prepared from **178b** by the similar hydrolysis conditions used for **176**: yield 67%; UV ($H_2O$) $\lambda_{max}$ 253.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 7.84 (s, 1H, H−8), 5.13−5.09 (m, 1H, H−1′), 2.70−2.66 (m, 1H, H−4′), 2.14−1.75 (m, 8H, $CH_2$); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 157.6, 153.9, 152.4, 136.3, 127.8 (dd, $J$ = 248.5, 253.7 Hz), 118.5, 65.7 (dd, = 16.8, 18.5 Hz), 44.6 (dd, $J$ = 16.2, 18.7 Hz), 29.6, 28.2, 22.5, 18.3; MS *m/z* 364 $(M+H)^+$.

**But−3−enal (181):** To a stirred solution of oxalyl chloride (155 mg, 1.224 mmol) in $CH_2Cl_2$ (12 mL) was added a solution of DMSO (191 mg, 2.448 mmol) in $CH_2Cl_2$ (5.0 mL) dropwise at 78℃. The resulting

solution was stirred at 78℃ for 30 min, and a solution of alcohol **180** (88 mg, 1.224 mmol) in $CH_2Cl_2$ (8 mL) was added dropwise. The mixture was stirred at 78℃ for 30 min and TEA (0.684 mL, 4.88 mmol) was added. The resulting mixture was warmed to 0℃ and stirred for 30 min. $H_2O$ (10 mL) was added, and the solution was stirred for 30 min at RT. The mixture was diluted with water (100 mL) and then extracted with EtOAc (2 × 100 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 subjected to next reaction without further purification: Crude yield 91%; $^1$H NMR ($CDCl_3$, 300 MHz) δ 9.73 (m, 1H), 6.03−5.94 (m, 1H), 5.18−5.14 (m, 2H), 3.10 (t, $J$ = 6.8 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 202.0, 135.5, 118.3, 48.4.

**Hepta−1,6−dien−4−ol (182)**: To a solution of **181** (2.3 g, 32.81 mmol) in dry THF (10 mL), vinylmagnesium bromide (39.37 mL, 1.0 M solution in THF) was slowly added at −10℃ and stirred 4 h at 0℃. Saturated $NH_4Cl$ solution (20 mL) was added to the mixture, which was slowly warmed to RT. The mixture was diluted with water (150 mL) and extracted with EtOAc (150 mL) two times. 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, 1:10) to give **182** (3.02 g, 82%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 5.73−5.69 (m,

2H), 5.05−4.98 (m, 4H), 3.31 (m, 1H), 2.13 (m, 4H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 140.4, 115.7, 74.7, 43.5.

**Cyclopent−3−enol (183):** To a solution of **182** (270. mg, 2.406 mmol) in dry methylene chloride (5 mL) was added 2$^{nd}$ generation Grubbs catalyst (15.0 mg, 0.0176 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, 1:8) to give cyclopentenol **183** (159.8 mg, 79%): $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 5.63 (m, 2H), 3.65 (quint, 1H), 2.55 (m, 2H), 2.36 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 134.5, 72.4, 43.5.

**1−[(Cyclopent−3−enyloxy)methyl]−4−methoxybenzene (184):** NaH (60% in mineral oil, 66.4 mg, 1.66 mmol) was added portion−wise to a cooled (0℃) solution of secondary alcohol **183** (116 mg, 1.385 mmol) and *p*−methoxybenzyl chloride (0.206 mL, 1.52 mmol) in anhydrous DMF (8 mL). The reaction mixture was stirred overnight at RT. The solvent was removed *in vacuo* and the residue was diluted with $H_2O$ (50 mL) followed by extraction with diethyl ether (60 mL) two times. 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, 1:20) to give **184** (189.6 mg, 67%) as a colorless oil: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.11 (d, $J$ = 7.8 Hz,

2H), 6.72 (d, $J$ = 7.9 Hz, 2H), 5.62 (m, 2H), 4.65 (s, 2H), 3.74 (s, 3H), 3.25 (quint, 1H), 2.57 (m, 2H), 2.38 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.7, 137.5, 134.5, 129.9, 115.7, 73.5, 72.6, 56.3, 42.5.

**4-(4-Methoxybenzyloxy)cyclopentane-1,2-diol (185a** and **185b)**: Compound **184** (118.5 mg, 0.58 mmol) was dissolved in a cosolvent system (10 mL) (acetone: $t$-BuOH: $H_2O$ = 6:1:1) along with 4-methylmorpholine $N$-oxide (135 mg, 1.16 mmol). Subsequently, $OsO_4$ (0.29 mL, 4% wt. % in $H_2O$) was added. 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 filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/$CH_2Cl_2$, 1:5) to give **185a** (40.08 mg, 29%) and **185b** (41.46 mg, 30%) as a colorless oils: spectroscopical data for **185a**; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 7.09 (d, $J$ = 7.7 Hz, 2H), 6.71 (d, $J$ = 7.8 Hz, 2H), 4.89 (d, $J$ = 5.0 Hz, 2H, $D_2O$ exchangeable), 4.64 (s, 2H), 3.72 (s, 3H), 3.38-3.32 (m, 2H), 2.87 (quint, 1H), 1.90 (m, 2H), 1.68 (m, 2H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 159.4, 131.8, 129.5, 114.8, 77.5, 73.4, 71.9, 55.7, 41.6. data for **185b**; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 7.11 (d, $J$ = 7.8 Hz, 2H), 6.71 (d, $J$ = 7.8 Hz, 2H), 4.92 (d, $J$ = 5.2 Hz, 2H, $D_2O$ exchangeable), 4.67 (s, 2H), 3.56 (s, 3H), 3.30-3.24 (m, 2H), 2.81-2.78 (m, 1H), 1.94-1.90 (m, 2H), 1.70-1.67 (m, 2H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 159.7, 131.3, 129.7, 115.1, 77.6, 73.6, 71.5,

54.8, 40.9.

**(*rel*)-(1*S*,2*R*,4*R*)-4-(4-Methoxybenzyloxy)-2-hydroxycyclopentyl benzoate (186):** To a solution of compound **185b** (557 mg, 2.34 mmol) in anhydrous pyridine (11 mL), benzoyl chloride (354 mg, 2.52 mmol) and DMAP (24.5 mg, 0.2 mmol) were added. The reaction mixture was stirred overnight at RT. The reaction mixture was then quenched using a saturated $NaHCO_3$ solution (0.4 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 under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexanes 1:12) to yield compound **186** (504 mg, 63%) as a colorless oils. $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.98 (m, 2H), 7.46-7.38 (m, 3H), 7.09 (d, $J$ = 6.8 Hz, 2H), 6.70 (d, $J$ = 6.8 Hz, 2H), 4.64 (s, 2H), 4.09 (m, 1H), 3.84 (m, 1H), 3.74 (s, 3H), 2.87-2.84 (m, 1H), 2.21 (m, 1H), 2.12 (br s, 1H), 1.94-1.90 (m, 2H), 1.67 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 169. 7, 159.6, 134.5, 130.3, 129.5, 128.6, 115.2, 77.1, 73.5, 72.9, 71.3, 55.5, 41.4, 38.4.

**(*rel*)-(1*S*,4*S*)-4-(4-Methoxybenzyloxy)-2-oxocyclopentyl benzoate (187):** To a solution of compound **186** (1.64 g, 4.8 mmol) in $CH_2Cl_2$ (50 mL), 4Å molecular sieves (2.8 g) and PCC (2.58 g, 12.03

mmol) were added slowly at 0℃, and stirred overnight at RT. To the mixture, excess diethyl ether (200 mL) was then added. The mixture was stirred vigorously for 3 h at the same temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give compound **187** (1.07 g, 66%) as a colorless oil: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, $J$ = 7.0 Hz, 2H), 7.45−7.37 (m, 3H), 7.08 (d, $J$ = 6.8 Hz, 2H), 6.71 (d, $J$ = 6.8 Hz, 2H), 4.65 (s, 2H), 4.55 (m, 1H), 3.74 (s, 3H), 3.38 (m, 1H), 2.71−2.64 (m, 3H), 2.18−2.14 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 211.2, 168. 9, 159.7, 134.4, 131.5, 129.7, 128.4, 114.7, 77.4, 72.8, 71.5, 54.8, 42.5, 28.1.

**(*rel*)−(1*S*,4*S*)−4−(4−Methoxybenzyloxy)−2,2−difluorocyclopentyl benzoate (13):** A solution of compound **187** (326 mg, 0.96 mmol) in anhydrous $CH_2Cl_2$ (40 mL) was treated with DAST (0.992 mL, 7.52 mmol) under argon at room temperature. The reaction mixture was stirred overnight and was then quenched by adding a saturated solution of $NaHCO_3$ in water (20 mL). The organic phase was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give the difluorinated product **188** (160 mg, 46%) as a colorless syrup. $^{1}$H

NMR ($CDCl_3$, 300 MHz) δ 8.01 (m, 2H), 7.48−7.37 (m, 3H), 7.08 (d, $J$ = 7.0 Hz, 2H), 6.73 (d, $J$ = 6.9 Hz, 2H), 4.64 (s, 2H), 4.51−4.45 (m, 1H), 3.74 (s, 3H), 2.89 (m, 1H), 2.19−1.94 (m, 4H); $^{19}$F NMR ($CDCl_3$, 282 MHz) δ −101.4 (dm, $J$ = 246.7 Hz, 1F), −119.6 (dm, $J$ = 247.9 Hz, 1F); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 167.8, 159.5, 133.7, 130.4, 129.8, 129.3, 128.2, 114.6, 110.2 (dd, $J$ = 234.6, 240.4 Hz), 78.1 (dd, $J$ = 20.2, 22.4 Hz), 72.9, 71.5, 67.0, 55.4, 37.5 (dd, $J$ = 19.5, 21.6 Hz), 31.5.

**(*rel*)−(1*S*,4*S*)−4−(4−Methoxybenzyloxy)−2,2−difluorocyclopentanol (189):** A solution of **188** (205 mg, 0.566 mmol) in saturated methanolic ammonia (10 mL) was stirred overnight at RT, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give **189** (114 mg, 78%): $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.11 (d, $J$ = 7.0 Hz, 2H), 6.72 (d, $J$ = 6.9 Hz, 2H), 4.65 (s, 2H), 3.79−3.69 (m, 4H), 2.87 (m, 1H), 2.11−1.94 (m, 5H); $^{19}$F NMR ($CDCl_3$, 282 MHz) δ −103.5 (dm, $J$ = 251.1 Hz, 1F), −122.1 (dm, $J$ = 251.9 Hz, 1F); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.8, 130.1, 128.4, 114.7, 114.7 (dd, $J$ = 238.6, 242.6 Hz), 74.2 (dd, $J$ = 19.8, 21.5 Hz), 72.3, 65.7, 56.1, 37.1 (dd, $J$ = 20.2, 22.4 Hz), 33.8.

**(*rel*)−(1′*S*,4′*S*)−9−[4−(4−Methoxybenzyloxy)−2′,2′−difluorocyclopentan−1′−yl] 6−chloropurine (190):** To a stirred solution of triphenyl phosphine (281 mg, 1.07 mmol) in dry THF (5 mL) at 0℃ was added

dropwise the diisopropyl azodicarboxylate (DIAD) (216 mg, 1.07 mmol) and the reaction mixture was stirred at this temperature for 30 min. After that, a solution of the alcohol **189** (138.2 mg, 0.535 mmol) in THF (5 mL) was added and the reaction mixture was stirred at 0℃ for 30 min. Then the cold bath was removed and the yellow solution was stirred for 30 min at room temperature. 6-Chloropurine (230 mg, 1.07 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/MeOH, 1:3:0.02) to give compound **190** (131 mg, 62%); UV (MeOH) $\lambda_{max}$ 263.0 nm; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.69 (s, 1H), 8.27 (s, 1H), 7.10 (d, $J$ = 7.0 Hz, 2H), 6.69 (d, $J$ = 7.0 Hz, 2H), 4.64 (s, 2H), 4.27 (m, 1H), 3.74 (s, 3H), 2.85 (m, 1H), 2.21-1.84 (m, 4H); $^{19}$F NMR ($CDCl_3$, 282 MHz) δ -106.3 (dm, $J$ = 236.4 Hz, 1F), -120.6 (dm, $J$ = 237.2 Hz, 1F); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.6, 154.3, 148.8, 141.7, 132.6, 130.5, 128.4, 114.7, 110.7 (dd, $J$ = 237.2, 244.4 Hz), 72.3, 67.8, 57.7 (dd, $J$ = 20.4, 22.4 Hz), 55.3, 37.7 (dd, $J$ = 20.3, 21.6 Hz), 30.2.

**(*rel*)-(1′*S*,4′*S*)-9-(4-Hydroxy-2′,2′-difluorocyclopentan-1′-yl) 6-chloropurine(191):** To a solution of compound **190** (167 mg, 0.423 mmol) in $CH_2Cl_2/H_2O$ (6 mL, 10:1 v/v) was added DDQ (143 mg, 0.632 mmol), and the mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ (0.9 mL) was added to quench the

reaction, which was then stirred for 3 h at room temperature. The mixture was diluted with water (75 mL) and extracted with $CH_2Cl_2$ (3 × 80 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, 4:1:0.02) to give compound **191** (74 mg, 64%) as a white solid: mp 167−169℃; UV (MeOH) $\lambda_{max}$ 263.0 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.69 (s, 1H), 8.26 (s, 1H), 4.89 (d, $J$ = 5.0 Hz, 1H, $D_2O$ exchangeable), 4.31−4.24 (m, 1H), 3.26 (m, 1H), 2.21−1.85 (m, 4H); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 151.9, 151.6, 150.9, 145.6, 132.5, 110.6 (dd, $J$ = 228, 232.6 Hz), 60.5, 57.5 (dd, $J$ = 20.2, 21.8 Hz), 41.6 (dd, $J$ = 18.8, 20.6 Hz), 31.7.

**(*rel*)−(1′*S*,4′*S*)− Diethyl [9−(4−hydroxymethyl−2′,2′−difluorocyclopentan−1′−yl) 6−chloropurine] phosphonate (192):** Both LiO*t*−Bu (1.49 mL of 0.5 M solution in THF, 0.744 mmol) and a solution of diethyl phosphonomethyltriflate (208 mg, 0.696 mmol) in 7.0 mL of THF were slowly added to a solution of the 6−chloropurine analogue **191** (96 mg, 0.348 mmol) in 6.0 mL of THF at 10℃ and stirred overnight at rt under nitrogen. The mixture was quenched by adding saturated $NH_4Cl$ solution (5 mL) and further diluted with additional $H_2O$ (100 mL). The aqueous layer was extracted with EtOAc (3x100 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, 0.02:3:1) to give **192** (79 mg, 54%) as a foam: $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.71 (s, 1H), 8.34 (s, 1H), 4.26 (m, 1H), 4.09−4.01 (m, 4H), 3.91 (d, $J$ = 8.2 Hz, 2H), 2.87 (m, 1H), 2.21−1.83 (m, 4H), 1.18 (m 6H); $^{19}$F NMR (DMSO−$d_6$, 282 MHz) δ −105.7 (dm, $J$ = 231.6 Hz, 1F), −121.3 (dm, $J$ = 232.9 Hz, 1F); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 151.7, 151.2, 150.4, 146.5, 136.8, 111.4 (dd, $J$ = 230.0, 238.4 Hz), 69.0, 63.2, 62.6, 62.1, 59.0 (dd, $J$ = 19.4, 21.2 Hz), 38.1 (dd, $J$ = 20.2, 21.8 Hz), 29.4, 14.2.

**(*rel*)−(1′*S*,4′*S*)− Diethyl [9−(4−hydroxymethyl−2′,2′−difluorocyclopentan−1′−yl) adenine] phosphonate (193):** A solution of **192** (168 mg, 0.395 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 **193** (101 mg, 63%) as a white solid: mp 156−158℃; UV (MeOH) $\lambda_{max}$ 261.5 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.30 (s, 1H), 8.12 (s, 1H), 6.12 (br s, 2H, $D_2O$ exchangeable), 4.23 (m, 1H), 4.08−4.02 (m, 4H), 3.89 (d, $J$ = 8.0 Hz, 2H), 2.86 (m, 1H), 2.22−1.88 (m, 4H), 1.14 (m 6H); $^{19}$F NMR (DMSO−$d_6$, 282 MHz) δ −101.4 (dm, $J$ = 229.7 Hz, 1F), −118.9 (dm, $J$ = 231.2 Hz, 1F); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 155.3, 152.7, 150.5, 141.5, 120.5, 110.8 (dd, $J$ = 228.4, 234.4 Hz), 68.9, 63.6, 62.7, 62.2, 57.9 (dd, $J$ = 20.4, 21.8 Hz), 38.1 (dd, $J$ = 21.7, 23.0 Hz), 29.6,

15.0.

**(*rel*)−(1′*S*,4′*S*)−9−[(4−Hydroxymethyl−2′,2′−difluorocyclopentan−1′−yl) adenine] phosphonic acid (194):** To a solution of the phosphonate **193** (234 mg, 0.579 mmol) in anhydrous $CH_3CN$ (12 mL) and 2,6−lutidine (1.35 mL, 11.6 mmol) was added trimethylsilyl bromide (0.888 mg, 5.79 mmol). The mixture was heated for 24 hour at 75 °C under nitrogen gas and then concentrated *in vacuum* to give a brown residue, and co−evaporated from conc aqueous $NH_4OH$ (2 × 30 mL). The resultant solid was triturated with acetone (2 × 10 mL) and the residue was purified by reverse−phase chromatography. Lyophilization of an appropriate fraction provided phosphonic acid salt **194** (108 mg, 51%) as a white salt (ammonium salt): UV ($H_2O$) $\lambda_{max}$ 262.0 nm; $^1$H NMR ($D_2O$, 300 MHz) δ 8.22 (s, 1H, H−8), 8.13 (s, 1H, H−2), 4.29−4.24 (m, 1H, H−1′), 3.78 (d, $J$ = 8.0 Hz, 1H), 2.85 (m, 1H, H−4′), 2.21−1.84 (m, 4H, $CH_2$); $^{19}$F NMR ($D_2O$, 282 MHz) δ −110.4 (dm, $J$ = 234.2 Hz, 1F), −126.4 (dm, $J$ = 235.4 Hz, 1F); $^{13}$C NMR ($D_2O$, 75 MHz) δ 154.5, 152.5, 150.3, 141.6, 119.7, 110.3 (dd, $J$ = 221.4, 234.8 Hz), 69.1, 67.6, 58.2 (dd, $J$ = 19.6, 20.4 Hz), 38.6 (dd, $J$ = 18.7, 20.4 Hz), 30.2.

**(*rel*)−(1′*S*,4′*S*)−9−[4−(4−Methoxybenzyloxy)−2′,2′−difluorocyclopentan−1′−yl] 2−fluoro−6−chloropurine (195):** Coupling of **189** with 2−fluoro−6−chloropurine under the similar condensation conditions as described for **190** to give **195** as a solid: yield 65%; UV (MeOH)

$\lambda_{max}$ 265.0 nm; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 8.43 (s, 1H), 7.10 (d, $J$ = 6.8 Hz, 2H), 6.72 (d, $J$ = 6.9 Hz, 2H), 4.65 (s, 2H), 4.27−4.23 (m, 1H), 3.74 (s, 3H), 2.87 (m, 1H), 2.19−1.83 (m, 4H); $^{19}$F NMR ($CDCl_3$, 282 MHz) δ −107.3 (dm, $J$ = 241.5 Hz, 1F), −123.6 (dm, $J$ = 242.7 Hz, 1F); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.6, 157.1 (d, $J$ = 218.6 Hz), 153.4, 136.4, 129.6, 128.5, 120.7, 114.9, 110.5 (dd, $J$ = 221.4, 234.8 Hz), 73.1, 67.5, 56.0 (dd, $J$ = 19.2, 21.7 Hz), 37.8 (dd, $J$ = 18.7, 19.3 Hz), 30.3.

**(*rel*)−(1′*S*,4′*S*)−9−(4−Hydroxy−2′,2′−difluorocyclopentan−1′−yl) 2−fluoro−6−chloropurine (196):** Deprotection of **196** was performed from **195** using the similar procedure as described for **191** as a solid: yield 61%; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.46 (s, 1H), 4.91 (d, $J$ = 5.2 Hz, 1H, $D_2O$ exchangeable), 4.27−4.23 (m, 1H), 3.35 (m, 1H), 2.23−1.87 (m, 4H); $^{19}$F NMR (DMSO−$d_6$, 282 MHz) δ −105.7 (dm, $J$ = 234.2 Hz, 1F), −123.8 (dm, $J$ = 235.7 Hz, 1F); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 157.2 (d, $J$ = 218.4 Hz), 153.2, 145.4, 136.1, 121.2, 110.2 (dd, $J$ = 219.2, 220.4 Hz), 60.6, 59.3 (dd, $J$ = 18.8, 21.6 Hz), 40.3 (dd, $J$ = 18.8, 20.2 Hz), 32.2.

**(*rel*)−(1′*S*,4′*S*)−Diethyl [9−(4−hydroxymethyl−2′,2′−difluorocyclo pentan−1′−yl) 2−fluoro−6−chloropurine] phosphonate (197):** Phosphonation of **196** was performed by the similar procedure as described for **192** as a form: yield 59%; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.45 (s, 1H), 4.25−4.22 (m, 1H), 4.10−4.07 (m, 4H), 3.86 (d,

$J$ = 8.0 Hz, 2H), 2.85 (m, 1H), 2.21−1.85 (m, 4H), 1.38−1.30 (m, 6H); $^{19}$F NMR (DMSO−$d_6$, 282 MHz) δ −111.2 (dm, $J$ = 239.3 Hz, 1F), −127.8 (dm, $J$ = 240.7 Hz, 1F); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 157.5 (d, $J$ = 219.2 Hz), 153.5, 144.9, 136.7, 122.0, 111.1 (dd, $J$ = 218.4, 220.4 Hz), 69.2, 63.4, 63.2, 60.6, 58.8 (dd, $J$ = 18.6, 21.4 Hz), 39.8 (dd, $J$ = 18.9, 20.8 H), 30.2, 15.1.

**(*rel*)−(1′*S*,4′*S*)−Diethyl [9−(4−hydroxymethyl−2′,2′−difluorocyclo pentan−1′−yl) 2−fluoro−6−aminopurine] phosphonate (198a) and (*rel*)−(1′*S*,4′*S*)−Diethyl [9−(4−hydroxymethyl−2′,2′−difluorocyclo pentan−1′−yl) 2−amino−6−chloropurine] phosphonate (198b):** Dry ammonia gas was bubbled into a stirred solution of **197** (250 mg, 0.564 mmol) in DME (10 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/$CH_2Cl_2$, 1:8) to give **198a** (31 mg, 13%) and **198b** (126 mg, 51%) as solids: Data for **198a**; UV (MeOH) $\lambda_{max}$ 261.0 nm; $^1$H NMR (DMSO−$d_6$, 300 MHz) δ 8.20 (s, 1H), 6.67 (br d, 2H), 4.26−4.22 (m, 1H), 4.08 (m, 4H), 3.89 (d, $J$ = 8.1 Hz, 2H), 2.88 (m, 1H), 2.19−1.85 (m, 4H), 1.35 (m, 6H); $^{19}$F NMR (DMSO−$d_6$, 282 MHz) δ −108.2 (dm, $J$ = 235.5 Hz, 1F), −129.6 (dm, $J$ = 237.0 Hz, 1F); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 160.3 (d, $J$ = 268.4 Hz), 155.3, 152.5, 141.5, 118.2, 110.7 (dd, $J$ = 208.4, 210.6 Hz), 69.0, 63.4, 62.2, 58.2 (dd, $J$ = 18.6, 20.4 Hz), 37.2 (dd, $J$ = 16.7, 18.9 Hz), 29.6, 15.1;

Data for **198b**; UV (MeOH) $\lambda_{max}$ 308.0 nm; $^{1}$H NMR (DMSO−$d_6$, 300 MHz) δ 8.13 (s, 1H), 6.77 (br d, 2H), 4.27−4.23 (m, 1H), 4.08−4.05 (m, 4H), 3.86 (d, $J$ = 8.0 Hz, 2H), 2.87−2.86 (m, 1H), 2.18−1.83 (m, 4H), 1.39−1.34 (m, 6H); $^{19}$F NMR (DMSO−$d_6$, 282 MHz) δ −106.8 (dm, $J$ = 231.5 Hz, 1F), −126.8 (dm, $J$ = 232.8 Hz, 1F); $^{13}$C NMR (DMSO−$d_6$, 75 MHz) δ 158.3, 154.2, 151.1, 143.2, 124.7, 111.2 (dd, $J$ = 210.4, 212.8 Hz), 69.1, 63.2, 62.4, 59.2 (dd, $J$ = 19.6, 21.6 Hz), 38.4 (dd, $J$ = 19.7, 10.8 Hz), 30.3, 14.8.

**(*rel*)−(1′*S*,4′*S*)−9−[(4−Hydroxymethyl−2′,2′−difluorocyclopentan−1′−yl) guanine] phosphonic acid (199):** To a solution of **198b** (278 mg, 0.632 mmol) dry $CH_3CN$ (20 mL) was added trimethylsilyl bromide (0.146 mL, 11.04 mmol) at room temperature. After this mixture was stirred for 30 h, the solvent was removed, evaporating three times with methanol. The residue was dissolved in MeOH (24.0 mL) and 2−mercaptoethanol (172.8 μL, 2.532 mmol) and NaOMe (134.4 mg, 2.532 mmol) was added to the mixture. The mixture was refluxed for 18 h under $N_2$, cooled, neutralized with glacial AcOH, and evaporated to dryness under vacuum. The residue was co−evaporated from conc $NH_4OH$ (2 × 32 mL) and the resultant solid was triturated with acetone (2 × 12 mL). The residue was purified by chromatography on a preparative column of reversed−phase C18 silica gel eluting water. Lyophilization of an appropriate fraction provided **199** (99 mg, 41%) as a yellowish salt (ammonium salt). UV ($H_2O$) $\lambda_{max}$ 253.5 nm;

$^{1}$H NMR ($D_2O$, 300 MHz) δ 7.81 (s, 1H, H−8), 4.25−4.21 (m, 1H, H−1′), 3.67−3.62 (d, $J$ = 8.0 Hz, 2H, $PCH_2$), 2.88 (m, 1H, H−4′), 2.18−1.81 (m, 4H, $CH_2$); $^{19}$F NMR ($D_2O$, 282 MHz) δ −109.5 (dm, $J$ = 234.2 Hz, 1F), −122.4 (dm, $J$ = 235.9 Hz, 1F); $^{13}$C NMR ($D_2O$, 75 MHz) δ 157.6, 154.3, 152.0, 136.2, 117.7, 109.9 (dd, $J$ = 210.4, 214.8 Hz), 70.1, 67.8, 48.2 (dd, $J$ = 18.6, 20.3 Hz), 37.6 (dd, $J$ = 18.6, 19.8 Hz), 30.2.

# V. REFERENCES


1. Mehellou, Y.; De Clercq, E. *J. Med. Chem.* 2010, *53*, 521−538.
2. De Clercq, E. *Curr. Opin. Pharmacol.* 2010, *10*, 507−515.
3. Barre−Sinossi, F.; Chermann, J. C.; Rey, F.; Nugeyre, M. T.; Charmaret, S. Gruest, J; Dauguet, C.; Axler−Blin, C.; Vezinet−Brum, F.; Rouzioux, C.; Rozedbaum, W.; Montagnier, L. Isolation of a T−lymphotrophic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS).
4. Levy, J. A.; Hoffman, A. D.; Kramer, S. M.; Landis, J. A.; Shimbukukuro, J. M. *Science* 1984, *225*, 840−842.
5. De Clercq, E. *Nat. Rev. Drug Discovery.* 2002, *1*, 13−25.
6. Meadows, D. C.; Gervay−Hague, J. *ChemBioChem.* 2006, *1*, 16−29.
7. De Clercq, E. *Futrue Virol.* 2008, *3*, 393−405.
8. Esté. J. A.; Cihlar, T. *Antiviral Res.* 2010, *85*, 25 −33.
9. Naeger, L. K.; Struble, K. A.; Murray, J. S.; Birmkrant, D. B. *Antiviral Res.* 2010, *85*, 232−240.
10. De Clercq, E. In Advances in Antiviral Drug Design; Elsevier Ltd, 2007, 5 1−58.
11. Zolopa, A. R. *Antiviral Res.* 2010, *85*, 241−244.
12. Arribas, J. R.; Pozniak, A. L.; Gallant, J. E.; Dejesus, E.; Gazzard,

B.; Campo, R. E.; Chen, S. S.; McColl, D.; Holmes, C. B.; Enejosa, J.; Toole, J. J.; Cheng, A. K. *Acquir. Immune. Defic. Syndr.* 2008, *47*, 74–78.

13. Mehellou, Y.; De Clercq, E. *J. Med. Chem.* 2010, *53*, 521–538.
14. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci.* U. S. A. 1985, *82*, 7096–7100.
15. Broder, S. *Antiviral Res.* 2010, *85*, 1–18.
16. Carr, A. *Nat. Rev. Drug Discovery*. 2003, *2*, 624–634.
17. Martinez–Picado, J.; De Pasquale, M. P.; Kartsonis, N.; Hanna, G. J.; Wong, J.; Finzi, D.; Rosenberg, E.; Gunthard, H. F.; Sutton, L.; Savara, A.; Petropoulos, C. J.; Hellmann, N.; Walker, B. D.; Richman, D. D.; Siliciano, R.; D' Aquila, R. T. *Proc. Natl. Acad. Sci. U.S.A.* 2000, *97*, 10948–10953.
18. Little, S. J.; Holte, S.; Routy, J. P.; Daar, E. S.; Markowitz, M.; Collier, A. C.; Koup, R. A.; Mellors, J. W.; Connick, E.; Conway, B.; Kilby, M.; Wang, L.; Whitcomb, J. M.; Hellmann, N. S.; Richman, D. D. *N. Engl. J. Med.* 2002, *347*, 385–394.
19. (a) De Clercq, E. *Curr. Opin. Microbiol.* 2005, *8*, 552–560. (b) *Frontiers in Nucleosides and Nucleic Acids*; Schinazi, R. F.; Liotta, D. C., Eds.; IHL Press: Tucker, GA, 2004. (c) Rachakonda, S.; Cartee, L. *Curr. Med. Chem.* 2004, *11*, 775–793. (d) De Clercq, E. *J. Clin. Vir.* 2004, *30*, 115–133. (e) *Recent Advances in*

*Nucleosides: Chemistry and Chemotherapy*; Chu, C. K., Ed.; Elsevier Science: New York, 2002.

20. De Clercq, E. *Antiviral Res.* 2010, *85*, 19–24.
21. Kulikowski, T. *Pharm. World Sci.* 1994, *16*, 127–138.
22. Périgaud, C.; Gosselin, G.; Imbach, J. L. *Nucleosides, Nucleotides & Nucleic Acids*. 1992, *11*, 903–945.
23. Martin, J. C.; Hitchcock, M. J. M.; De Clercq, E.; Prusoff, W. H. *Antiviral Res.* 2010, *85*, 34–38.
24. Razonable, R. R. *Mayo Clin. Proc.* 2011, *86*, 1009–1026.
25. Cihlar, T.; Ray, A. S. *Antiviral Res.* 2010, *85*, 39–58.
26. Asahchop, E. L.; Wainberg, M. A.; Sloan, R. D.; Tremblay, C. L. *Antimicrob. Agents Chemother.* 2012, *56*, 5000–5008.
27. Price, N. B.; Prichard, M. N. *Curr. Opin. Vorol.* 2011, *1*, 548–554.
28. Mitsuya, H.; Weinhold, K. J.; Furman, P. A., St; Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* 1985, *82*, 7096–7100.
29. Balzarini, J.; Kang, G. J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G. *Mol. Pharmacol.* 1987, *32*, 162–167.
30. Mitsuya, H.; Broder, S. Antiviral Compositions and Methods. U. S. Patent 4, 861, 759, 1989.
31. Daluge, S. M.; Good, S. S.; Faletto,M. B.; Miller, W.H., St; Clair, M. H.; Boone, L. R.; Tisdale, M.; Parry, N. R.; Reardon, J. E.; Dornsife, R. E.; Averett, D. R.; Krenitsky, T. A. *Antimicrob. Agents*

*Chemother*. 1997, *41*, 1082-1093.

32. Gosselin, G.; Schinazi, R. F.; Sommadossi, J. P.; Mathé, C.; Bergogne, M. C.; Aubertin, A. M.; Kirn, A.; Imbach, J. L. *Antimicrob. Agents Chemother.* 1994, *38*, 1292-1297.
33. Schinazi, R. F.; Chu, C. K.; Peck, A.; McMillan, A.; Mathis, R.; Cannon, D.; Jeong, L. S.; Beach, J. W.; Choi, W. B.; Yeola, S.; Liotta, S. C. *Antimicrob. Agents Chemother*. 1992, *36*, 672-676.
34. Balzarini, J.; Holy, A.; Jindrich, J; Naesens, L.; Snoeck, R.; Schols, D.; De Clercq, E. *Antimicrob Agents Chemother*. 1993, *37*, 332-338.
35. Balzarini, J. *Pharm. World Soc.* 1994, *16*, 113-126.
36. Hao, Z.; Cooney, D. A.; Farquhar, D.; Perno, C. F.; Zhang, K.; Masood, R.; Wilson, Y.; Hartman, N. R.; Balzarini, J.; Johns, D. G. *Mol. Pharmacol*. 1990, *37*, 157-163.
37. De Clercq, E. *Nat. Rev. Drug Discovery*. 2002, *1*, 13-25.
38. De Muys, J. M.; Gourdeau, H., Nguyen-Ba, N.; Taylor, D. L., Ahmed, P. S., Mansour, T.; Locas, C.; Richard, N.; Wainberg, M. A.; Rando, R. F. *Antimicrob. Agents Chemother.* 1999, *43*, 1835-1844.
39. Richard, N.; Salomon, H.; Rando, R.; Mansour, T.; Bowlin, T. L.; Wainberg, M. A. *Antimicrob. Agents Chemother.* 2000, *44*, 1127-1131.
40. Bethell, R. C.; Lie, Y. S.; Parkin, N. T. *Antivir. Chem. Chemother.*

2005, *16*, 295 –302.

41. Gu, Z.; Allard, B., de Muys, J. M.; Lippens, J., Rando, R. F.; Nguyen–Ba, N.; Ren, C.; McKenna, P.; Taylor, D. L.; Bethell, R. *Antimicrob. Agents Chemother*. 2006, *50*, 625–631.
42. Wainberg, M. A.; Cahn, P.; Bethell, R. C.; Sawyer, J.; Cox, S. *Antivir. Chem. Chemother*. 2007, *18*, 61–70.
43. Shi, J.; McAtee, J. J.; Schlueter Wirtz, S.; Tharnish, P.; Juodawlkis, A.; Liotta, D. C.; Schinazi, R. F. *J. Med. Chem.* 1999, *42*, 859–867.
44. Dutschman, G. E.; Grill, S. P.; Gullen, E. A.; Haraguchi, K.; Takeda, S.; Tanaka, H.; Baba, M.; Cheng, Y. C. *Antimicrob. Agents Chemother*. 2004, *48*, 1640–1646.
45. Kim, E. Y.; Vrang, L.; Öberg, B.; Merigan, T. C. *AIDS Res. Hum. Retroviruses*. 2001, *17*, 401–407.
46. Lennerstrand, J.; Chu, C. K.; Schinazi, R. F. *Antimicrob. Agents Chemother*. 2007, *51*, 2078–2084.
47. Murakami, E.; Bao, H.; Basavapathruni, A.; Bailey, C. M.; Du, J.; Steuer, H. M. M.; Niu, C.; Whitaker, T.; Anderson, K. S.; Otto, M. J.; Furman, P. A. *Antivir. Chem. Chemother*. 2007, *18*, 83–92.
48. Kodama, E. I.; Kohgo, S.; Kitano, K.; Machida, H.; Gatanaga, H.; Shigeta, S.; Matsuoka, M.; Ohrui, H.; Mitsuya, M. *Antimicrob. Agents Chemother*. 2001, *45*, 1539–1546.
49. Nikolenko, G. N.; Palmer, S.; Maldarelli, F.; Mellors, J. W.; Coffin, J. M.; Pathak, V. K., 2005. *Proc. Natl. Acad. Sci. U.S.A.* 2005, *102*,

2093-2098.

50. Yang, G.; Dutschman, G. E.; Wang, C. J.; Tanaka, H.; Baba, M.; Anderson, K. S.; Cheng, Y. C. *Antivir. Res.* 2007, *73*, 185-191.

51. (a) Wang, J.; Jin, Y.; Rapp, K. L.; Bennett, M.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* 2005, *48*, 3736-3748. (b) Wang, J.; Jin, Y.; Rapp, K. L.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* 2007, *50*, 1828-1839.

52. Ohrui, H. *Chem. Rec.* 2006, *6*, 133-143.

53. Nakata, H.; Amano, M.; Koh, Y.; Kodama, E.; Yang, G.; Bailey, C. M.; Kohgo, S.; Hayakawa, H.; Matsuoka, M.; Anderson, K. S.; Cheng, Y. C.; Mitsuya, H. *Antimicrob. Agents Chemother.* 2007, *51*, 2701-2708.

54. Cihlar, T.; Ray, A. S.; Boojamra, C. G.; Zhang, L.; Hui, H.; Laflamme, G.; Vela, J. E.; Grant, D.; Chen, J.; Myrick, F.; White, K. L.; Gao, Y.; Lin, K. Y.; Douglas, J. L.; Parkin, N. T.; Carey, A.; Pakdaman, R.; Mackman, R. L. *Antimicrob. Agents Chemother.* 2008, *52*, 655-665.

55. Furman, P. A.; Fyfe, J. A.; St.Clair, M. H.; Weinhold, K.; Rideout, J. L.; Freeman, G. A.; Lehrman, S. N.; Bolognesi, D. P.; Broder, S.; Mitsuya, H.; Barry, D. W. *Proc.Natl. Acad. Sci. U. S, A.* 1986, *83*, 8333-8337.

56. Deville-Bonne, D.; El Amri,C.; Meyer, P.; Chen, Y.; Agrofoglio, L. A.; Janin, J. *Antiviral Res.* 2010, *86*, 101-120.

57. Pontarin, G.; Gallinaro, L.; Ferraro, P.; Reichard, P.; Bianchi, V. *Proc. Natl. Acad. Sci. U. S. A.* 2003, *100*, 12159–12164.

58. Eriksson, S.; Munch–Petersen, B.; Johansson, K.; Eklund, H. *Cell. Mol. Life Sci.* 2002, *59*, 1327–1346.

59. Garces, E.; Cleland, W. W. *Biochemistry*. 1969, *8*, 633–640.

60. Lascu, I.; Gonin, P. J. *Bioenerg. Biomembr*. 2000, *32*, 237–246.

61. Cherfils, J.; Moréra, S.; Lascu, I.; Véron, M.; Janin, J. *Biochemistry*. 1994, *33*, 9062–9069.

62. Schaertl, S.; Konrad, M.; Geeves, M. A. *J. Biol. Chem*. 1998, *273*, 5662–5669.

63. Chen, Y.; Gallois–Montbrun, S.; Schneider, B.; Véron, M.; Moréra, S.; Deville– Bonne, D.; Janin, J. *J. Mol. Biol*. 2003, *332*, 915–926.

64. Schneider, B.; Xu, Y. W.; Sellan, O.; Sarfati, R.; Janin, J.; Véron, M.; Deville–Bonne, D. *J. Biol. Chem*. 1998, *273*, 11491–11497.

65. Xu, Y.; Sellam, O.; Moréra, S.; Sarfati, S.; Biondi, R.; Véron, M.; Janin, J. *Proc. Natl. Acad. Sci. U. S. A.* 1997, *94*, 7162–7165.

66. De Clercq, E. *Nat. Rev. Drug Discovery*. 2002, *1*, 13–25.

67. (a) Parker, W. B. *Chem. Rev.* 2009, *109*, 2880–2893; (b) Liu, G.; Pranssen, E.; Fitch, E. F.; Warnew, E. *J.Clin. Oncol.* 1997, *15*, 110–115; (c) Hishitsuka, H.; Shimma, N. In *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, Herdewijn, P., Ed., Wiley, Hoboken, NJ, 2008, pp. 587–600; (d) Takahashi, T.; Shimuzu, M.; Akinaga, S. *Cancer Chemother. Pharmacol.* 2002, *50*,

1930-1201; (e) Thottassery, J. V.; Westbrook, L.; Someya, H.; Parker, W. B. *Mol. Cancer Ther.* 2006, *5*, 400-410; (f) Miura, S.; Izuta, S. *Current Drug Targets*. 2004, *5*, 191-195; (g) Klopfer, A.; Hasenjager, A.; Belka, C.; Schulze-Osthoff, K.; Dorken, B.; Daniel, P. T. *Oncogene.* 2004, *23*, 9408-9418.

68. (a) De Clercq, E. *Rev. Med. Virol.* 2009, *19*, 287-299; (b) De Clercq, E. *Biochem. Pharmacol.* 2007, *73*, 911-922; (c) Cihlar, T.; LaFlamme, G.; Fisher, R.; Carey, A. C.; Vela, J. E.; Mackman, R.; Ray, A. S. *Antimicrob. Agents Chemother.* 2009, *53*, 150-156; (d) Choo, H.; Beadle, J. R.; Kern, E. R.; Prichard, M. N.; Keith, K. A.; Hartlina, C. B.; Trahan, J.; Aldern, K. A.; Korba, B. E.; Hostetler, K. Y. *Antimicrob. Agents Chemother.* 2007, *51*, 611-615; (e) Krcmerova, M.; Holý, A.; Piskala, A.; Masojidkova, M.; Andrei, G.; Naesens, L.; Neyts, J.; Balzarini, J.; De Clercq, E.; Snoeck, R. *J. Med. Chem.* 2007, *50*, 1069-1077; (f) Lebeau, I.; Andrei, G.; Krecmerova, M.; De Clercq, E.; Hol'y, A.; Snoeck, R. *Antimicrob. Agents Chemother.* 2007, *51*, 2268-2273.

69. (a) Vanek, V.; Budesinsky, M.; Rinnova, M.; Rosemberg, I. *Tetrahedron.* 2009, *65*, 862-876; (b) Kumamoto, H.; Topalis, D.; Broggi, J.; Pradere, U.; Roi, V.; Berteina-Raboin, S.; Nolan, S. P.; Deville-Bonne, D.; Andrei, G.; Snoeck, R.; Garin, D.; Grance, G. M.; Agrofoglio, L. A. *Tetrahedron.* 2008, *64*, 3517-3526; (c) Vrbkova, S.; Dracinsky, M.; Hol'y, A. *Tetrahedron.* 2007, *63*,

11391- 11398.

70. Wedemeyer, H.; Hardtke, S.; Cornberg, M. *Chemother. J.* 2012, *21*, 1-7.

71. Elgemeie, G. H.; Zaghary, W. A.; Amin, K. M.; Nasr, T. M. *Nucleosides, Nucleotides & Nucleic Acids.* 2005, *24*, 1227-1247.

72. (a) Mironiuk-Puchalska, E.; Koszytkowska-Stawinska, M.; Sas, W.; De Clercq, E.; Naesens, L. *Nucleosides, Nucleotides & Nucleic Acids.* 2012, *31*, 72-84; (b) Merino, P.; Tejero, T.; Unzurrunzaga, F. J.; Franco, S.; Chiacchio, U.; Saita, M. G.; Iannazzo, D.; Piperno, A.; Romeo, G. *Tetrahedron Asymmetry*. 2005, *16*, 3865-3876; (c) Chiacchio, U.; Rescifina, A.; Saita, M. G.; Iannazzo, D.; Romeo, G.; Mates, J. A.; Tejero, T.; Merino, P. *J.Org. Chem.* 2005, *70*, 8991-9001.

73. Franchetti, P.; Cappellacci, L.; Perlini, P.; Jayaram, H. N.; Butler, A.; Schneider, B. P.; Collart, F. R.; Huberman, E.; Grifantini, M. *J. Med. Chem.* 1998, *41*, 1702 -1707.

74. Franchetti, P.; Cappellacci, L.; Marchetti, S.; Martini, C.; Costa, B.; Varani, K.; Borea, P. A.; Grifantini, M. *Bioorg. Med. Chem.* 2000, *8*, 2367-2373.

75. Romeo, G.; Chiacchio, U.; Corsaro, A.; Merino, P. *Chem. Rev.* 2010, *110*, 3337-3370.

76. Merino, P. *Curr. Med. Chem.* 2006, *13*, 539-545.

77. (a) De Clercq, E.; Neyts, J.; Hand B. *Exp. Pharmacol.* 2009, *189*,

53-84; (b) Berdis, A. J. *Biochemistry*. 2008, *47*, 8253-8260.

78. Hutter M. C.; Helms V. *ChemBioChem.* 2002, *3*, 643-651.

79. (a) Schneider, B.; Sarfati, R.; Deville-Bonne, D.; Veron, M. *J.Bioenerg. Biomembr.* 2000, *32*, 317-324; (b) Stein, D. S.; Moore, K. H. P. *Pharmacotherapy*. 2001, 2137-2146; (c) Lascu, I.; Gonin, P. *J.Bioenerg. Biomembr.* 2000, *32*, 237-246.

80. Miller, W. H; Miller, R. L. *J. Biol. Chem*. 1980, *255*, 7204-7207; *Biochem. Pharmacol. 1982*, 31, 3879-3884.

81. (a) McGuigan, C.; Harris, S. A.; Daluge, S. M.; Gudmundsson, K. S.; McLean, E. W.; Burnette, T. C.; Marr, H.; Hazen, R. *J. Med. Chem.* 2005, *48*, 3504-3515; (b) Perrone, P.; Luoni, G. M.; Kelleher, M. R.; Daverio, F.; Angell; A.; Mulready, S.; Congiatu, C.; Rajyaguru, S.; Martin, J. A.; Leveque, V.; Le Pogam, S.; Najera, I.; Klumpp, K.; Smith, D. B.; McGuigan, C. *J. Med. Chem.* 2007, *50*, 1840-1849; (c) McGuigan, C.; Derudes, M.; Bugert, J. J.; Andrei, G.; Snoecke, R.; Balzarini, J. *Bioorg. Med. Chem. Lett.* 2008, *18*, 4364-4367.

82. (a) Hecker, S. J.; Erion, M. D. *J. Med.Chem.* 2008, *51*, 2328-2345; (b) Schultz, C. *Bioorg. Med. Chem.* 2003, *11*, 885-898; (c) Mackman, R. L., Cihlar, T. *Annu. Rep. Med. Chem.* 2004, *39*, 305-321; (d) He, G. X.; Krise, J. P.; Oliyai, R. In *Prodrugs: Challenges and Rewards*, Springer-Verlag, New York, 2007, pp. 223-264; (e) Ariza, M. E. *Drug Des. Rev.* 2005, *2*,

273–387; (f) Congiatu, C.; McGuigan, C.; Jiang, W. G.; Davies, G.; Mason, M. D. *Nucleosides, Nucleotides & Nucleic Acids*. 2005, *24*, 485–489.

83. (a) De Clercq, E.; Holý, A. *Nat. Res. Drug Discov.* 2005, *4*, 928–940; (b) Deville–Bonne, D.; El Amri, C.; Meyer, P.; Chen, Y. X.; Agrofoglio, L. A.; Janin, J. *Antiviral Res.* 2010, *86*, 101–120; (c) De Clercq, E. *Med. Res. Rev.* 2009, *29*, 571–610; (d) De Clercq, E. *Antiviral Res.* 2010, *85*, 19–24; (e) De Clercq, E. *Biochem. Pharmacol.* 2011, *82*, 99–109.

84. (a) Gallier, F.; Péyrottes, S.; Périgaud C. *Tetrahedron*. 2009, *65*, 6039–6046; (b) Meurillon, M.; Gallier, F.; Peyrottes, S.; Périgaud, C. *Eur. J. Org. Chem.* 2007, 925–933; (c) Gallier, F.; Alexandre, J. A. C.; El Amri, C.; Deville–Bonne, D.; Peyrotts, S.; Périgaud, C. *Chem. Med. Chem.* 2011, *6*, 1094–1106.

85. (a) Holy, A. *Curr. Pharm. Des*. 2003, *9*, 2567–2592. (b) De Clercq, E.; Holy, A. *Nat. Rev. Drug Discovery*. 2005, *4*, 928–940.

86. Vina, D.; Wu, T.; Renders, M.; Laflamme, G.; Herdewijn, P. *Tetrahedron.* 2007, *63*, 2634–2646.

87. Schöning, K.; Scholz, P.; Guntha, S.; Wu, X.; Krishnamurthy, R.; Eschenmoser, A. *Science.* 2000, *5495*, 1347–1351.

88. (a) Kempeneers, V.; Vastmans, K.; Rozenski, J.; Herdewijn, P. *Nucleic Acids Res*. 2003, *31*, 6221–6226. (b) Chaput, J. C.; Szostak, J. W. *J. Am. Chem. Soc*. 2003, *125*, 9274–9275.

89. Kempeneers, V.; Froeyen, M.; Vastmans, K.; Herdewijn, P. *Chem. Biodivers.* 2004, *1*, 112−123.

90. (a) Secrist, J. A. 3rd; Riggs, R. M.; Comber, R. N.; Montgomery, J. A. *Nucleosides, Nucleotides.* 1992, *11*, 947−956. (b) Montgomery, J. A.; Thomas, H. J.; Kisliuk, R. L.; Gaumont, Y. *J. Med. Chem.* 1979, *22*, 109−111.

91. Liu, J. L.; Kim, E. A.; Hong, J. H. *Nucleosides, Nucleotides & Nucleic Acids.* 2012, *31*, 411−422.

92. Wang, W.; Jin, H.; Fuselli, N.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* 1997, *7*, 2567−2572.

93. Wu, T.; Froeyen, M.; Kempeneers, V.; Pannecouque, C.; Wang, J.; Busson, R.; De Clercq, E.; Herdewijn, P. *J. Am. Chem. Soc.* 2005, *127*, 5056−5065.

94. Qiu, X. L.; Xu, X. H.; Qing, F. L. Recent advances in the synthesis of fluorinated nucleosides. *Tetrahedron.* 2010, 66, 789−843.

95. Boojamra, C. G.; Mackman, R. L.; Markevitch, D. Y.; Prasad, V.; Ray, A. S.; Douglas, J.; Grant, D.; Kim, C. U.; Cihlar, T. *Bioorg. Med. Chem. Lett.* 2008, *18*, 1120−1123.

96. (a)Mackman, R. L.; Ray, A. S.; Hui, H. C.; Zhang, L.; Birkus, G.; Boojamra, C. G.; Desai, M. C.; Douglas, J. L.; Gao, Y.; Grant, D.; Laflamme, G.; Lin, K. Y.; Markevitch, D. Y.; Mishra, R.; McDermott, M.; Pakdaman, R.; Petrakovsky, O. V.; Vela, J. E.; Cihlar, T. *Bioorg. Med. Chem.* 2010, *18*, 3606−3617. b) Cihlar, T.; Ray, A. S.;

Boojamra, C. G.; Zhang, L.; Hui, H.; Laflamme, G.; Vela, J. E.; Grant, D.; Chen, J.; Myrick, F.; White, K. L.; Gao, Y.; Lin, K. Y.; Douglas, J. L.; Parkin, N. T.; Carey, A.; Pakdaman, R.; Mackman, R. L. *Antimicrob Agents Chemother.* 2008, *52*, 655−665.

97. (a) Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. *J. Org. Chem.* 1988, *53*, 2406−2409. b) Hertel, L. W.; Boder, G. B.; Kroin, J. S., Rinzel, S. M.; Poore, G. A.; Todd, G. C.; Grindey, G. B. *Cancer Res.* 1990, *50*, 4417−4422.

98. Noble, S.; Goa, K. L. Gemcitabine. *Drugs*. 1997, *54*, 447−472.

99. Borthwick, A. D.; Kirk, B. E.; Biggadike, K.; Exall, A. M.; Butt, S.; Roberts, S. M.; Knight, D. J.; Coates, J. A.; Ryan, D. M. *J. Med. Chem.* 1991, *34*, 907–914.

100. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. USA.* 1986, *83*, 1911−1915.

101. Wu, T.; Froeyen, M.; Kempeneers, V.; Pannecouque, C.; Wang, J.; Busson, R.; De Clercq, E.; Herdewijn, P. *J. Am. Chem. Soc.* 2005, *127*, 5056–5065.

102. Kim, C. U.; Luh, B. Y.; Misco, P. F.; Bronson, J. J.; Hitchcock, M. J.; Ghazzouli, I.; Martin, J. C. *J. Med. Chem*. 1990, *33*, 1207−1213.

103. De Clercq, E.; Holý, A.; Rosenberg, I. *Antimicrob Agents Chemother*. 1989, *33*, 185−191.

104. Wang, W.; Jin, H.; Fuselli, N.; Mansour, T. S. *Bioorg. Med. Chem.*

*Lett.* 1997, *7*, 2567-2572.

105. Ko, O. H.; Hong, J. H. *Tetrahedron Lett.* 2002, *43*, 6399-6402.

106. (a) Kumamoto, H.; Topalis, D.; Broggi, J.; Pradere, U.; Roy, V.; Berteina-Raboin, S.; Nolan, S. P.; Deville-Bonne, D.; Andrei, G.; Snoeck, R.; Garin, D.; Crance, J. M.; Agrofoglio, L. A. *Tetrahedron* 2008, *64*, 3517-3526; (b) Montagu, A.; Pradere, U.; Roy, V.; Nolan, S. P.; Agrofoglio, L. A. *Tetrahedron.* 2011, *67*, 5317-5328; (c) Huang, Q.; Herdewijn, P. *J. Org. Chem.* 2011, *76*, 3742-3753.

107. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* 1999, *1*, 953-956.

108. Hocková, D.; Holý, A.; Masojídková, M.; Keough, D. T.; De Jersey, J.; Guddat, L. W. *Bioorg. Med. Chem.* 2009, *17*, 6218-6232.

109. Robins, M. J.; Uznanski, B. *Can. J. Chem.* 1981, *59*, 2608-2611.

110. Vorbruggen, H.; Ruh-Pohlenz, C. *Handbook of Nucleoside Synthesis*; Eds, John Wiley & Sons, Inc.: New York, 2001.

111. Montgomery, J.; Hewson, K. *J. Med. Chem.* 1969, *12*, 498-504.

112. Tong, G. L.; Ryan, K. J.; Lee, W. W.; Acton, E. M. Goodman, L. *J. Org. Chem.* 1967, *32*, 859-862.

113. Holy, A.; Votruba, I.; Merta, A.; Cerny, J.; Vesely, J.; Vlach, J.; Sediva, K.; Rosenberg, I.; Otmar, M.; Hrebabecky, H.; Travniekb, M.; Vonkac, V.; Snoeck, R.; De Clercq, E. *Antiviral Res.* 1990, *13*, 295-311.

114. Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. *J. Virol. Methods.* 1988, *20*, 309-321.

115. (a) Yin, X. Q.; Li, W. K.; Yang, M.; Schneller, S. W. *Bioorg. Med.Chem.* 2009, *17*, 3126-3219; (b) Sisu, E.; Sollogoub, M.; Mallet, J. M.;Sinay, P. *Tetrahedron* 2002, *58*, 10189-10196.

116. (a) Furstner, A. *Angew. Chem. Int. Ed.* 2000, *39*, 3012-3043; (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* 2005, *44*, 4442-4489; (c) Hansen, E. C.; Lee, D. *Acc. Chem. Res.* 2006, *39*, 509-519.

117. Michel, B. Y.; Strazewski, P. *Tetrahedron.* 2007, *63*, 9836-9841.

118. Tanaka, M.; Norimine, Y.; Fujita, T.; Suemune, H.; Sakai, K. *J. Org. Chem.* 1996, *61*, 6952-6957.

119. (a) Kim, A.; Oh, C. H.; Hong, J. H. *Nucleosides, Nucleotides Nucleic Acids* 2006, *25*, 1399-1406; (b) Kim, A.; Hong, J. H. *Nucleosides, Nucleotides & Nucleic Acids* 2006, *25*, 1-8.

120. El-Subbagh, H. I.; Racha, S.; Abushanab, E.; Panzica, R. P. *J. Org. Chem.* 1996, *61*, 890-894.

121. Hong, J. H. *Arch. Pharm. Res.* 2007, *30*, 131-137.

122. All geometries were optimized with the framework of the density functional theory (DFT), with Spartan modeling software. The B3LYP functional with 6-31G* basis set was employed.

123. (a) House, H.O.; Lord, R. C.; Rao, H. S. J. *J. Org. Chem.* 1956, *21*,

1487−1491; (b) Gosselck, J.; Schmidt, G. *Angew. Chem. Int. Ed.* **1968**, *7*, 456−457.

124. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.

125. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

126. Smith, K.; Pelter, A. For a review of organoboron chemistry. In. Trost, B. M.; Fleming, I. Eds., *Comprehensive Organic Synthesis*, vol. 8, Pergamon Press, Oxford, 1991, p. 703.

127. Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1989**, *30*, 7349−7352.

128. Kozikowski, A. P.; Wu, J. P. *Tetrahedron Lett.* **1987**, *28*, 5125−5128.

129. (a) Ruder, S. M.; Ronald, R. C. Tetrahedron Lett. **1984**, *25*, 5501−5504. (b) Kigoshi, H.; Imamura, Y.; Mizuta, K.; Niwa, H.; Yamada, K. J. Am. Chem. Soc. **1993**, *115*, 3056−3065.

130. Spira, T. J.; Bozeman, L. H.; Holman, R. C.; Warfield, D. T.; Phillips, S. K.; Feorino, P. M. *J. Clin. Microbiol.* **1987**, *25*, 97−99.

131. Schinazi, R. F.; Cannon, D. L.; Arnold, B. H.; Martino−Saltzman, D. *Antimicrob. Agents Chemother.* **1988**, *32*, 1784−1792.

132. Sommadossi, J. P.; Carlisle, R.; Schinazi, R. F.; Zhou, Z. *Antimicrob. Agents Chemother.* **1988**, *32*, 997−1001.

133. Schinazi, R. F.; Peters, J.; Williams, C. C.; Chance, D.; Nahmias, A. *J. Antimicrob Agents Chemother.* **1982**, *22*, 499−507.

134. Hong, J. H.; Kim, H. O.; Moon, H. R.; Jeong, L. S. *Arch. Pharm. Res.* 2001, 24, 95−99.

135. (a) Amey, R. L.; Martin. J. C. *J. Am. Chem. Soc.* 1978, *100*, 300−301; (b) Amey, R. L.; Martin, J. C. *J. Am. Chem. Soc.* 1979, *101*, 5294−5299.

136. Lefebvre, I.; Périgaud, C.; Pompon, A.; Aubertin, A. M.; Girardet, J. L.; Kirn, A.; Gosselin, G.; Imbach, J. L. *J. Med. Chem.* 1995, *38*, 3941−3950.

137. Périgaud, C.; Gosselin, G.; Lefebvre, I.; Girardet, J. L.; Benzaria, S.; Barber, I.; Imbach, J. L. *Bioorg. Med. Chem. Lett.* 1993, *3*, 2521−2526.

138. Choi, M. H.; Kim, H. D. *Arch. Pharm. Res.* 2003, *26*, 990−996.

139. Marco, J. L.; Hueso−Rodriquez, J. A. *Tetrahedron Lett.* 1988, *29*, 2459−2462.

140. (a) Jeong, L. S.; Lee, J. A. *Antiviral Chem. Chemother.* 2004, *15*, 235−250; (b) Amblard, F.; Nolan, S. P.; Agrofoglio, L. A. *Tetrahedron* 2005, *61*, 7067−7080.

141. (a) Wachmeister J.; Classon, B.; Samuelsson, B. *Tetrahedron.* 1995, *51*, 2029−2038; (b) Cadet, G.; Chan, C. S.; Daniel, R. Y.; Davis, C. P.; Guiadeen, D.; Rodriguez, G.; Thomas, T.; Walcott, S.; Scheiner, P. *J. Org. Chem.* 1998, *63*, 4574−4580; (c) Diaz, Y.; Bravo, F.; Castillon, S. *J. Org. Chem.* 1999, *64*, 6508−6511.

142. Chong, Y. H.; Gumina, G.; Chu, C. K. *Tetrahedron: Asymmetry.*

2000, *11*, 4853−4875.

143. Oh, H. S.; Kang H. Y. *Tetrahedron.* 2010, *66*, 4307−4317.

144. (a) Phillion, D. P.; Andrew, S. S. *Tetrahedron Lett.* 1986, *27*, 1477−1480; (b) Xu, Y.; Flavin, M. T.; Xu, Z. Q. *J. Org. Chem.* 1996, *61*, 7697−7701.

145. Lian, L. J.; Yoo, J. C.; Hong, J. H. *Nucleosides, Nucleotides & Nucleic Acids.* 2009, *28*, 150−164.

146. Yang, Y. Y.; Meng, W. D.; Qing, F. L. *Org. Lett.* 2004, *6*, 4257−4259.

147. (a) Tanaka, M.; Norimine, Y.; Fujita, T.; Suemune, H.; Sakai, K.; *J. Org. Chem.* 1996, *61*, 6952−6957; (b) Liu, L. J.; Kim, S. W.; Lee, W.; Hong, J. H. *Bull. Korean Chem. Soc.* 2009, *30*, 2989−2992.

# VI. ABSTRACT

## Synthesis and Conformational Study of Non-classical Nucleoside Phosphonic Acid Analogues as Antiviral Agents

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Since the discovery of human immunodeficiency syndrome (AIDS), there has been intense effort to find compounds that can selectively block the replication of HIV. One logical approach to discovery of new and potent HIV inhibitors involves the design of phosphonate analogues where the phosphonate moiety is changed to isosteric and isoelectronic phosphonates. These enzymatically and chemically stable phosphonate analogues, which mimic the nucleoside monophosphonates by passing the initial enzymatic phosphorylation could lead to more effective antiviral agents against HIV.

Phosphorylation by kinases and the incorporation into nucleic acid

(eventually leading to chain termination) is considered as important mechanism underlying the antiviral activities of nucleosides. In fact, lack of antiviral activity by a nucleoside phosphonate is generally attributed to poor substrate properties for cellular and viral kinases. On the other hand, the potent antiviral activities of phosphorylated alkylated nucleobases are ascribed to their intracellular phosphory-lation to diphosphates and to refractory incorporation of the modified nucleosides in nucleic acids. Furthermore, the enzymatic incorporation of phosphonate nucleosides into nucleic acids is almost irreversible, which is not the case for regular nucleotides.

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. The special location of the oxygen atom, namely the $\beta$-position from the phosphorus atom in the nucleoside analogue, plays a critical role in the antiviral activity. This increased antiviral activity with this oxygen atom may be attributed to the increased binding capacity of the phosphonate analogues to target enzymes. The special location of the carbon atom, namely the $\beta$-position from the phosphorus atom in the nucleoside analogue, has been demonstrated to play a critical role for antiviral activity. These atoms for antiviral activity may be attributed to the increased binding capacity of the phosphonate analogues to target enzymes.

In this thesis, we sought to synthesize a novel class of nucleoside phosphonate 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.

**Keywords**: Anti-HIV agents; 5′-deoxyphosphonic acid; 5′-norcarbocyclic acid; Threosyl nucleoside phosphonic acid; Conformation analysis; Spironucleoside; Mistunobu reaction; Vorbruggen reaction.

# ACKNOWLEDGMETS

I would like to express my sincere thanks to my research advisor, Professor Joon Hee Hong for his guidance, support and encouragement. His extensive knowledge of organic chemistry and his dedication to teaching have made my gradute career a truly rewarding experience.

I would like to thank Hua Li and Lian Jin Liu who have shared the same lab with me.

I would like to thank my friend Hu Huang for his help and encouragement.

Finally, my utmost thanks go to my parents and young sister Chun Lian Shen for their endless support.