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博士學位論文

A synthesis of novel nucleosides as potential antiviral agents

朝 鮮 大 學 校 大 學 院

藥 學 科

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항바이러스제로서 신규 뉴크레오사이드의 합성

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ABSTRACT

A synthesis of novel nucleosides as potential antiviral agents

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The synthesis of 4′−phenyl and 1′−methyl doubly branched, 1′,4′−dimethyl branched, 1′−methyl and 4′−hydroxy methyl doubly branched, 4′, 6′−methyl doubly branched carbocyclic nucleosides was accomplished from 2−hydroxy acetophenone, acetol and 1,3−dihydroxy acetone. The 4′−phenyl, methyl, hydr−oxymethyl group was installed *via* a [3,3]−sigmatropic rearrangement reaction and the carbonyl addition of methylmagnesium bromide was used to introduce the 1′−methyl group. The introduction of a methyl group in the 6′(*α*)−position was accomplished by Felkin−Ahn controlled alkylation. Cyclization of divinyls **5**, **15**, **26, 42**, **200** was performed using 2nd generation Grubbs catalyst. The coupling of cyclopeantenols **8*α***, **16*α***, **27**, **43**, **201** with bases by Mitsunobu reaction, Pd(0) catalyst and desilylation was used to synthesize the target nucleosides **11**, **21**, **22**, **34~37**, **49~51**, **206**.

The synthesis of apiosyl nucleosides was accomplished from material and 1,3−dihydroxy acetone. The key apiosyl intermediates of **58**, **177** were constructed by sequential ozonolysis, reductions and acetylation from the **52**, **174**. Condensation of the acetates of **59**, **180** with silylated pyrimidine bases and a purine base under Vorbrüggen conditions and deblocking afforded a series of apiosyl nucleosides of **66~69, 184~189**, **194**, **195**.

The synthesis of a novel carboacyclic version of 5′−norcarboacyclic nucleosides, acyclic nucleosides, phosphonic acid nucleosides, cyclopentene phosphonate nucleosides, acyclic phosphonate nucleoside, fluorocyclopropyl nucleosides, acyclic version 6′(*α*)−methylene and 6′(*α*)−methylated nucleosides was accomplished from 1,1−cyclobutane dicarboxylic acid, diethyl malonate, 2−

methylenepropane−1,3−diol, 2−butene−1,4−diol, 1,3−dihydroxy methyl. The introduction of a compound **209** methylene group to the requisite 6′−position was carried out employing a Mannich type reaction using Eshenmoser's salt. Carbonyl enolate alkylation was used to introduce a compound **215** methyl group to the 6′(α)−position. The condensation of the mesylates **73**, **87**, **98**, **109**, **120**, **127**, **141** and bromides **156**, **157**, **211**, **217** with the natural nucleosidic bases under standard nucleophilic substitution and deblocking conditions, afforded the target nucleosides **78~81**, **92~95**, **103~106**, **114~117**, **121~124**, **132~135**, **146~149**, **166~173**, **214**, **220**.

The synthesized compounds were evaluated for their antiviral activity against HIV−1, HSV−1, 2 and HCMV. Compounds **34**, **37**, **79**, **122**, **135**, **194**, **206**, **214**, **220** exhibit toxicity nonrelated to any anti−HIV−1 activity. Compounds **49**, **78**, **116**, **146**, **167** exhibited good antiviral activity against the HCMV.

Key words:

Antiviral agents; Branched nucleoside; Mitsunobu reaction; [3,3]−Sigmatropic rearrangement; Carbocyclic nucleoside; Felkin−Ahn model; Phosphonic acid nucleoside; Apiosyl nucleosides; 5′−Norcarboacyclic nucleoside; Cyclopropyl phosphonic acid nucleosides; Substituted apiosyl nucleoside; Acyclic nucleosides; Acyclic phosphonate nucleoside; Nucleoside; Ozonolysis; Quaternary carbon; Eschenmoser salt; Ring−closing metathesis; Alkylation;

ABBREVIATION

AZT: 3'−Azido thymidine
ACV: Acyclovir
AIDS: Acquired immunodeficiency syndrome
ADA: Adenosine deaminase
AZDU: 3'−Azido−2',3'−dideoxy uridine
AMP: Adenosine−5′−monophosphate
SAM: *S*−adenosyl methionine
AdoHcy: *S*−adenosyl−*L*−homocysteine
TBDMCl: *tert*−Butyldimethylsilyl chloride
NBS: *N*−Bromosuccinimide
CMV: Cytomegalo virus
18−*C*−6: 18−Crown−6
EC_{50}(μM):Concentration required to inhibit 50% of virus induced cytopathicity
CC_{50}(μM): Concentration required to reduce cell viability by 50%
DMAP: 4−(Dimethylamino)pyridine
DMSO: Dimethyl sulfoxide
DMF: *N*,*N*−Dimethyl formamide
ddNs: 2′,3′−Dideoxynucleosides
ddA: 2',3'−Dideoxy adenosine
FddC: 2',3'−Dideoxy−5'−fluoro cytidine
DIBAL−H: Diisobutylaluminum hydride
DIAD: Diisopropyl azodicarboxylate
DMS: Dimethyl sulfide
DCE: 1,2−Dichloroethane
ddC: 2',3'−Dideoxy cytidine
ddI: 2',3'−Dideoxy inosine
d4T: 2',3'−Didehydro−3'−deoxy thymidine
DNA: Deoxy ribose nucleo acid
FDA: Food and drug administration
GCV: Ganciclovir

HIV: Human immunodeficiency virus
HSV: Herpes simplex virus
HCMV: Human cytomegalovirus
HMDS: Hexamethyl disilazane
A 546: Human lung cancer
HBV: Hepatitis B virus
HMPA: [(*S*)-9(3-hydroxy-2-phophonylmethoxypropyl) adenine]
IC_{50}: 50% Inhibitory concentration
LiHMDS: Lithium *bis*-(trimethylsilyl) amide; Lithium hexamethyldisilazide
LAH: Lithium aluminum hydride
LiOt-Bu: Lithium *tert*-butoxide
MsCl: Methanesulfonyl Chloride
4Å-MS: 4Å Molecular sieves
ND: Not Determined
NOE: Nuclear overhauser effect (enhancement)
NMR: Nuclear Magnetic Resonance
PNP: Purine nucleoside phosphorylase
PMEA: [9-(2-(Phosphonylmethoxy)ethyl)adenine]
PCC: Pyridinium chlorochromate
RNA: Ribose nucleo acid
RT: Reverse transcriptase
RCM: Ring-closing metathesis
THF: Tetrahydrofuran
TBAF: Tetra butyl ammonium fluoride
TEA: Triethyl amine
TLC: Thin layer chromatography
TMS: Tetramethylsilane
PPh_3: Triphenyl phosphine
TMSOTf: Trimethylsilyl trifluoromethane sulfonate
$P(O-i-Pr)_3$: Triisopropyl phosphite
$Pd_2(dba)_3 \cdot CHCl_3$: Tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct

BACKGROUND

The concept of viruses as a natural phenomenon separated from other infectious organism is less than 100 years old, and their nature began to be understood 50 years ago. In more recent years, the appreciation that practically all living species may have viruses associated with them defines the widespread prevalence of theses agents and their potential importance in nature. Although not all viruses are pathogenic in their host, several have raised great concern in this century because of the serious epidemic threats in humans; occurrence of influenza in 1918, polimyelitis in the 1930s, herpes in the 1960s, and AIDS in the 1980s. These disease appear to be related to human societies and mutations of the viruses, have brought increased attention to this field of study.

Until the beginning of the 1960s, the problem of distinguishing viral functions from host ones was thought to be insurmontable, and the main strategy for controlling viral infections was the development of vaccines (and to a large extent it still is), which do not attack a virus directly but prevent infection by stimulating the immune system in advance. However, over the past two decades the knowledge of viral replication has been accumulated and made it possible to define specific targets which could be affected by antiviral agents.[1]

Among these antiviral agents known, nucleoside analogues are of great importance regarding to their unique role in living system. The term "nucleo-sides" introduced by Levene and Jacobs in 1909, is originally associated with nucleic acid, by hydrolysis of which they were isolated for the first time.

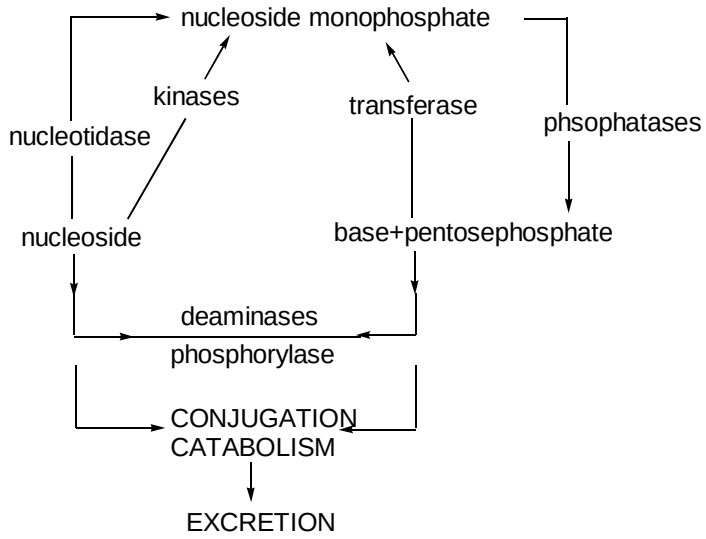
Natural nucleoside are constituted by the association of a purine (adenine and guanine) or a pyrimidine (cytosine, uracil and thymine) base with a pentose residue (β-D-ribofuranose or β-D-deoxyribofuranose). Esterification of their 5'-OH group with phosphoric acid leads to nucleotides. These nucleosides and nucleotides play a key role in many biosynthetic and regulatory process through molecular mechanisms of conservation, replication and transcription of the genetic information, and their extremely important function takes places at the level of the structure of ribo- and deoxyribonucleic acids.

The mechanism of replication (DNA → DNA) and of transcription (DNA →

RNA) involve the polymerization of nucleosides (in the form of their triphosphate precursors) by polymerases which catalyse the covalent binding of new triphosphate nucleoside units at the free 3'−OH end of the chain with elimination of pyrophosphate.

The biosynthesis of nucleoside triphosphate is a vital cellular process which occurs following two different mechanism: 1) de novo pathway from simple precursor metabolites such as CO_2, NH_3, formic acid etc. 2) salvage pathway from purine or pyrimidine bases and nucleosides arising from the degradation of nucleic acids or from nutrition. (Figure 1)

Figure 1. Nucleoside salvage cycle



purines are salvaged mainley as base and pyrimidines mainly as nuclosides

Owing to the fundamental place occupied by nucleotides in cellular life, the conception of analogues apt to interfere with process involved in the rapid proliferation of cancer cells or with the multiplication of pathogenic agents, seems to be an attractive approach in chemotherapy. Since the structure of chemically altered nucleoside analogues is believed to mimic that of natural nucleoside, a precursor of DNA or RNA.

Unfortunately, nucleotides are polyanionic compounds which cannot cross easily through cellular membranes. On the other hand, nucleosides and their

analogues are neutral molecules which can enter cells and therefore able to assume a therapeutic role. However, their biological activity usually depends on their subsequent intra cellular phosporylation by kinases.

Attempts to treat viral infections must take into account the variety of ways in which viruses interact with host cells. Since viruses do not multiply without living cells, they depend on the host cell to carry out their metabolic activities. All viruses infecting a cell has common replicative cycle:

1) adsorption of the virion to the cell membrane (generally on specific host cell receptors)
2) penetration and uncoating
3) replication of the viral genome and protein synthesis
4) assembly of macromolecules into a virion and
5) release of virions from the cells

Any drug interfering selectively with one of these events is a candidate for clinical use. In fact, the main targets of antiviral nucleosides are intra cellular biosynthetic events and their selectivity is generally due to the inhibition of virus-associated or induced enzymes involved in nucleoside and nucleotide metabolism.

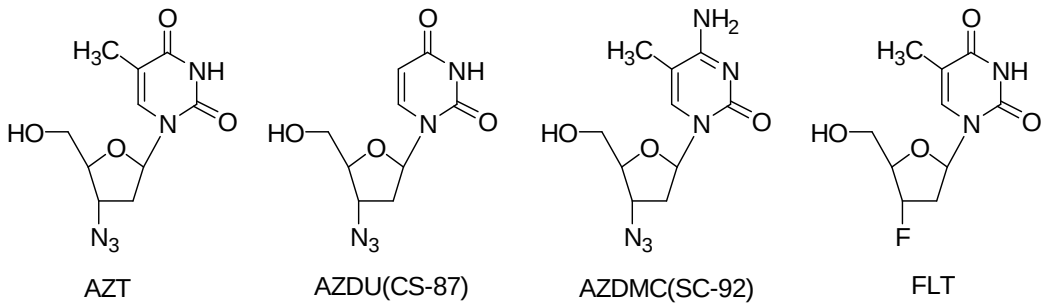
A number of nucleoside analogues have been found to possess activity against HIV-1 including AZT[2,3], DDC[4], DDI[3], D4T[5] approved for the treatment of AIDS and AIDS related complex. The nucleoside analogues with potent anti-HIV activity interact at the HIV RT, where the deoxynucleosede triphosphate normally bind, and act as competitive inhibitor and/or alternative substrate. Some analogues replaced 3'-OH with non esterificational group act also as chain terminators after incorporation into the growing DNA chain. However, these nucleoside analogues need to be phosphorylated successively to the 5'-mono, 5'-di, and 5'-triphosphate form beforebeing able to interact with their target enzyme.

The initial phosphorylation is a crucial first step in the intra cellular matabolism of nucleoside analogues.[6] This phophorylation rate may be influenced not only by the affinity of nucleoside analogue for the succesive kinase in the phosphory-lation step, but also by a number of feedback control mechanisms which may

either inhibit or stimulate the kinase activity.[7] Moreover, the nucleoside kinase activity of some resting cells such as monocytes/macrophages maybe insufficient to satisfactorily phosphorylate. To overcome this initial phosphorylation step, nucleoside phosphonate analogue [9-(2-(phosphonylmethoxy) ethyl) adenine] (PMEA) or alkyl phosphate derivatives are considered as a monophosphate precursor.[8,9,10] In addition, intra cellular delivery of the ddNMP form may be particulary advantageous for ddN analogues (i.e. 2',3'-dideoxy adenosine, ddA), because in their nucleoside form are more rapidly degraded. (i.e. by adenosine deaminase) than anabolized by cellular kinases (i.e. adenosine kinase) to their ddNMP form (i.e. ddAMP).[11]

a) 2' or 3'-substituted-2',3'-dideoxy nucleoside analogues **(Figure 2)**

Figure 2. Structure of 3'-substituted-2',3'-dideoxynucleosides



AZT[2,3] has remained the most potent and selective anti-HIV agent. AZT phosphorylated to AZTTP by host enzymes. AZTTP inhibits HIV RT competitively with respect to its natural nucleotide counterpart dTTP and thus benefits from the reduced leveles of the latter that result from the inhibition of thymidylate kinase.[12] AZTTP also serves as an alternative substrate for RT and incorporation of AZTMP into the growing DNA chain results in chain termination.[13,14]

AZT has oral bioavailability of 60%, but its serum half-life is only 1.1h and its major metabolite is the inactive 5'-glucuronide.[15] A particular advantage of AZT is its ability to penetrate the blood brain barrier, since HIV can infect cells in the

CNS and cause dementhia. Although, AZT has being used in clinically, its bone marrow supression presenting as anemia and neutropenia has been a serious problem of AZT therapy.[16] Another problem of AZT therapy is the emergence of AZT-resistant strains of HIV isolated from patients receiving AZT therapy.[17] Various prodrug of AZT to improve its bioavailivility and/or intra cellular metabolism has been synthesized.[18,19] Neoglycoproteins-AZT-MP conjugates which recognize lectin on blood cells have been shown to inhibit HIV-1 in MT-4 cells and decrease the toxicity of AZT.[20]

AZDU (CS-87, AzddU)[12,21]

The presence of a uracil moity imparts unique properties of this compound, especially low bone marrow toxicity and an unusual metabolism.[22] However, its lower anti-HIV activity copared to AZT and cross resistant with AZT-resistant virus has deterred further study. [23,24]

AZDMC (AzddMeC, CS-92)[25]

AZDMC has potent and selective activity against HIV-1 in human lymphocytes and low toxicity to human bone marrow cells. The major metabolite of AZDMC is AZT-MP without formation of AZDMC-MP and slowley converted intra cellulary to AZT.

FLT

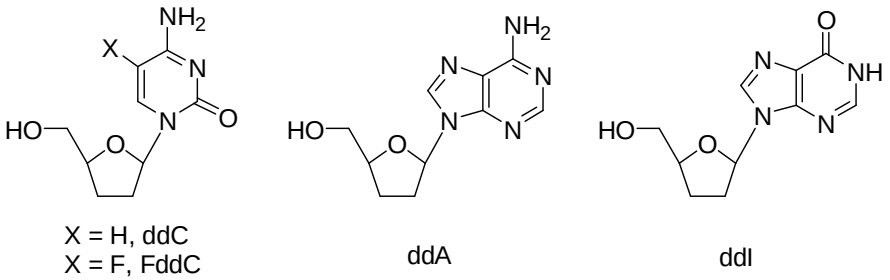
FLT is one of the most potent inhibitors of HIV-1 in various T-cells (EC_{50} = 1-10 μM). The major antiviral activity is a competitive inhibitor of HIV RT as its 5'-triphosphate form.[26] It didn't show cross resistance to AZT resistant virus. FLT penetrated into the cerebrospinal fluid of rhesus monkey test.[27,28] The main limiting toxicity is thrombocytopenia and anemia.

FDDC (FddC)

The 2'-fluoroarabinosyl derivative of DDC was found to have significant antiviral activity against HIV-1. However, its therapeutic index is inferior to that for AZT, and has considerable bone marrow toxicity in culture.

b) 2',3'−Dideoxynucleoside (Figure 3)

Figure 3. Structure of 2',3'-dideoxynucleosides



DDC (ddC)[4,29]

ddC was the first compound to be studied clinicly after AZT and now being used clinically for the treatment of AIDS and AIDS related complex in combination with AZT. ddC is phosphorylated to its triphosphate by cellular 2'−deoxycytidine kinase without reducing the levels of the natural nucleotide dCTP.[30] Unlike many cytidine analogues ddC is resistant to cytidine deaminase and have good bioavailability after oral administration. The major side effect of ddC linked to pripheral neuropathy which may be result of nucleoside interactions at other site in vivo outside of RT and DNA synthesis. ddC has been found to decrease the cellular content of mitochondrial DNA and increase the rate of glycosis. [ddC−TP is a potent inhibitor of DNA polymerase γ, mitochondrial polymerase, Ki = 0.016 μM].[31,32]

a: Deoxycytidine kinase (major), Adenosine kinase (minor)

b: Adenosine deaminase

c: Adenylate deaminase

d: Adenylosuccinate synthtase, Adenylosuccinatelyase

e: 5−Nucleotidase, Deoxyguanosine kinase

f: Purine nucleoside phosphorylase

DDA (ddA)

ddA is rapidly deaminated to ddI which is then bioconverted to ddA−MP via nucleotidase (or adenosine kinase) and adenylosuccinate synthetase. ddA−MP is further phosphorylated to ddA−TP which then inhibits HIV RT.[33] Some ddA analogues was synthesized to improve their bioavailability. N^6−Methyl−ddA would partially decrease the deamination by virtue of its eletronic as well as well as steric character of methyl group. N^6−Methyl−ddA was found to be most potent anti−HIV agent (EC_{50} = 0.26 μM in primary human lymphocytes infected with HIV−1) among the purine nucleosides and partially resistant to adenosine deaminase.[34] 6−Chloropurine derivative (EC_{50} = 0.66 μM) is interesting due to its high anti−HIV activity, increased lipophilicity, and its slow conversion to ddI in vitro and in vivo. The limiting toxicity of ddA is peripheral neuropathy and pancreatitis. It has also been shown to stimulate hepatic glycolysis leading to irreversible liver damage.[35,36]

DDI (ddI)[3]

ddI also approved by FDA for the treatment of HIV−1 infections who can not tolerate AZT chemotherapy. ddI has a complex metabolism and share a common active species ddA−TP. It is basically a prodrug of ddA.[37] ddI had a relatively high therapeutic index when compared with other dideoxynucleosides, relatively little toxicity for human bone marrow cells. ddI showed also peripheral neuro−pathy and pancreatitis as doselimiting toxicity.[38,39] ddI resistant strains was found to be cross resistant to ddC.[40]

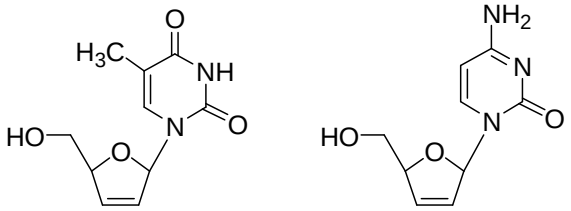
FddC[41~45]

2',3'−Dideoxy−5'−fluoro cytidine (FddC) is moderate inhibitor against HIV−1 (EC_{50} = 2 μM) and HBV. However, its enantiomer β−L−FddC has the most potent activity against HBV (EC_{50} = 0.01 μM) in dideoxy series in vitro. The IC_{50}

value of L-FddC against mitochondrial DNA synthesis is more than 100 μM (IC_{50} = 0.22 μM for ddC) So, L-FddC is one of the most promising compound to warrant further study of L-Nucleoside.

c) 2',3'-Didehydro-2',3'-dideoxynucleosides **(Figure 4)**

Figure 4. Structure of 2',3'-didehydro-2',3'-dideoxynucleosides

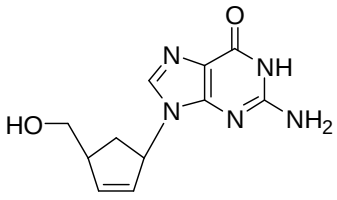


Of these class of compounds (commonly known as the d4 series), D4T[46~48] and D4C[46] exhibited good levels of potency.

D4T

D4T-TP is a potent inhibitor of HIV-1 RT. D4T is about 20 to 100 fold less toxic to human granulocyte macrophage progenitors than AZT. Unlike AZT, D4T has a poor affinity for the initial phosphorylation step leading to D4T-MP. The majority of the phosphorylated D4T is found as the 5'-triphosphate, the form that inhibit HIV-RT. D4T has no effect on the phosphorylation of thymidine and does not effect a reduction in dT-TP. Recently, D4T was found a good substrate for thymidine phosphorylase, which cleaves the glycosidic bond.

Figure 5. Structure of carbocyclic dideoxynucleosides



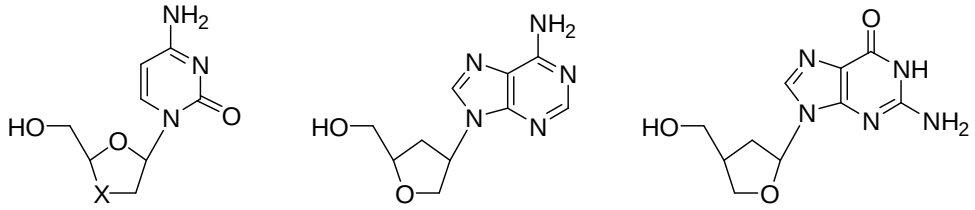
d) Carbocyclic nucleoside analogues **(Figure 5)**

Carbovir (carbocyclic−2',3'−didehydro−2',3'−dideoxyguanosine)[49]

Carbovir has been found potent inhibitor of HIV−RT as its triphosphate. Carbovir−TP inhibited HIV−1 RT to the same degree as AZT−TP, ddTTP and ddGTP, but was less inhibitory effect on DNA polymerase β and γ.[50] Due to its unique structure of carbocyclic nucleoside analogues, the glycosidic bond of carbovir is very stable even in acidic condition and also stable to enzymatic hydrolysis by purine nucleoside phosphorylase (PNP). The first synthesis of carvovir was done in racemic isomer, and as with many other carbocyclic nucleoside, the activity resides principally in the natural form, (−)−enantiomer.[51]

e) Isomeric and Isosteric 2',3'−dideoxynucleosides **(Figure 6)**

Figure 6. Structure of 3'-isomeric and isosteric-2',3'-dideoxynucleosides



Iso−DDA, Iso−DDG, Iso−DDI

These 3'−oxacarbocyclic nucleoside have unusual structure, which ring oxygen and 3'−carbon of 2',3'−dideoxyribose unit are interchanged. This structure exhibited the enhanced chemical and enzymatic stability to the isomeric dideoxynucleosides via elimination of the liable glycosidic bond.[52,53] Iso−ddA has potent anti−HIV activity (EC_{50} = 5~15 μM in ATH 8 cells), which is comparable to that of ddA. Iso−ddG also exhibited potent anti−HIV activity (EC_{50} = 10~50 μM in ATH 8 cells), but less potent than its counterpart ddG. Unlike ddA, Iso−ddA was not deaminated by adenosine deaminase and was stable to acid. Its half life is more than 14 days in pH 3 (1h for ddA). Iso−ddA was readily phospho−rylated in CEM cells to the triphosphate, which inhibited HIV RT but also DNA

polymerase α.[52] Other purine nucleoside analogues such as Iso-ddI were inactive.

The isosteric forms of 2',3'-dideoxynucloside, in which the 3'-methylene group is relaced by oxygen or sulfur, respectively, shows their unique character in anti-HIV activity.[54,55]

(±)Dioxolane T

(±)Dioxolane T has been reported to be moderate anti-HIV agent (EC_{50} = 0.09 μM in PBM cells).[54] Later, the β-D-(-)-dioxolane T was synthesized as optically pure isomer and found its potent anti-HIV activity (EC_{50} = 0.39 μM in PBM cells). Recently, (+)-dioxolane T was synthesized and its anti-HIV acti-vity was compared with that of racemic dioxolane T or (-)-dioxo-lane T.[56, 57] (+)-dioxolane T (EC_{50} > 100 μM) was found to be less active against HIV-1 than racemic dioxolane-T or (-)-dioxolane T. They have also reported structure activity relation ships of various enantiomerically pure D-dioxolanyl pyrimidine and purine nucleosides as potential anti-HIV agent. From this study, (+)-β-D-dioxolan C was found to exihibit the most potent activity (EC_{50} = 0.016 μM in PBM cells) against HIV-1 among the pyrimidine series tested. While (+)-β-D-dioxolan G was the most potent compound (EC_{50} = 0.03 μM in PBM cells) among purine derivatives tested.

(±)-BCH-189

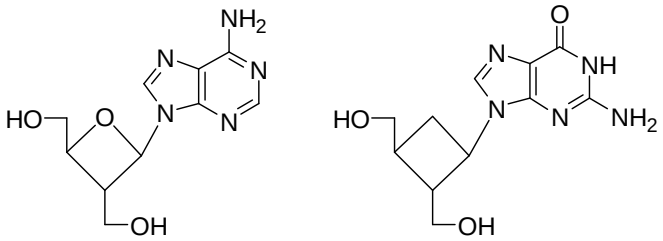
(±)-BCH-189 has potent activity against HIV-1 (EC_{50} = 0.02~0.06 μM), HIV-2 as racemates and their half life in rats is about 1 h similar to that of AZT.[58] Interestingly, the anti-HIV activity of (-)-enantiomer (3TC) (EC_{50} = 0.0018 μM), which is unnatural L-form, is more potent than (+)-D-enantiomer (EC50 = 0.21 μM) or racemates. In toxicity, (-)-L-enantiomer is better profile compare to its counterpart. This compound (3TC) is currently undergoing in clinical trials.[59,60]

f) Oxetanocine analogues **(Figure 7)**

Oxetanocine is characterized by the presence of the 4-membered oxetane ring. Of potential importance is that some of these analogues are inhibitors of CMV

(cytomegalo virus) in culture, although their therapeutic effect in rapidly dividing cells is modest.

Figure 7. Structure of oxetanocine analogues



OXT-A Cyclobut-G

OXT-A

Oxetanocine adenine is a natural product produced by Bacillus Megaterium NK 84-0218 and exhibited potent anti-HIV activity (EC_{50} = 1 μM in ATH 8 cells) without cytotoxxicity up to 100 μM.[61] However, in MT-4 cell system, oxetanocine was 6 time less potent than ddA. The pathway of metabolism and phosphorylation of oxetanocine-A and oxetanocine-H (hypoxanthine) are similar to those of dideoxypurine nucleosides. Of oxetanocine derivatives, oxetanocine-H showed the highest selectivity index.

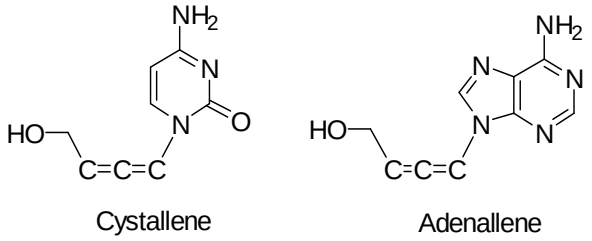
Also, transformation of the oxetanocine ring to a cyclobutyl ring, as in cyclobut-A, cyclobut-G, and cyclobut-DAP leads to products with marked anti-HIV selectivity.[62]

Cyclobut-G

The anti-HIV activity of cyclobut-G seemed to be comparable to that of AZT.[62,63] Cyclobut-G had similar potency to acyclovir against HSV-1 and HSV-2, and more potent than acyclovir against VZV and EBV. Both cyclobut-A and cyclobut-G displayed excellent activity against human and murine CMV. Meanwhile, cyclobut-A was potent than acyclovir against VZV, but less potent than HSV-1 and HSV-2.

g) Acyclic nucleosides **(Figure 8)**

Figure 8. Structure of acyclic nucleosides

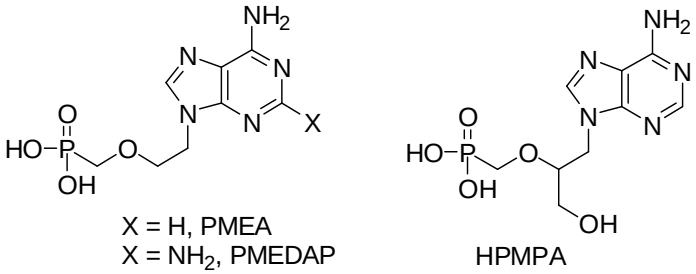


Cystallene and Adenallene

The 2',3'−dideoxynucleoside analogues loose their anti−HIV activity when the ring is opened at the 1',2'−bond[64] or 3',4'−bond.[65] However, when the sugar moiety is replaced by a 4−hydroxy−1,2−butadienyl group, significant anti−HIV activity is retained by certain cytosine and adenine derivatives containing such fourcarbon chain. These acyclic nucleosides analogues were found to inhibit replication and cytopathic effect of HIV in vitro.[66] The 4'−OH group of adenallene andcystallene is critical for their anti−HIV activity, which suggest that these compounds nust be phosphorylated to exert their antiviral effect.

h) Acyclic nucleoside phophonate and phosphate isoster (Figure 9)

Figure 9. Structure of acyclic nucleoside phosphonates



This class of compound was synthesized based on the following rational. Nucleoside analogues which posess antiviral activity must be phosphorylated intracellulary to their triphosphate to exhibit their inhibitory effects on viral replication. And phosphorylated nucleoside would seem to little, if any, use, unless their premature hydrolysis by phosphomonoesterase could be prevented.

So, nucleotide analogues in which the phosphorous atom was attached to the nucleoside via a P−C bond were designed and synthesized to confer adequate access to cells as well as stability to enzymatic hydrolysis.

PMEA, PMEDAP

PMEA, PMEDAP (EC_{50} = 1 μM and 2 μM in MT−4 cells) was markedly effective in inhibiting HIV replication.[61] PMEA is further phosphorylated in cells to the diphophate derivative, which inhibits HIV RT on both DNA and RNA primer template systems.[67] The activity spectrum extends to HSV, VZV, CMV, EBV and HBV.[68]

HMPA [(*S*)−9(3−hydroxy−2−phophonylmethoxypropyl) adenine]

The protype of this class of compounds is active against an even broader range of DNA viruses,[69] including HBV. However FPMPA, resulting from the 3−hydroxy function of HPMPA being replaced by a fluorine, showed anti−HIV activity but virtually inactive against DNA viruses.[70]

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is one of lethal disease currently threatening the public health throughout the world. First recognized as a distinct entity in 1981,[71] cases were noted as early as 1978 in New York and Port-Prince, Haiti. Studies subsequently conducted have indicated that AIDS first occurred in individuals returning in 1976 from central Africa, where the virus is thought to have emerged, perhaps as early as the 1950s.

The number of AIDS cases in the United States accumulated during the period of 1981~1993, is over 200,000 and many more, perhaps 1 million, have occurred in Africa. By the year 2000, epidemiologists predict that 30 million to 100 million people will be infected world wide. In the United states about 1 million people are currently believed to be infected by the AIDS retrovirus.

HIV is spread by blood and sexual contact as well as by transmission from mother to child, either before or during birth. There is no evidence for casual transmission. The most effective means of virus transfer is through virus-infected cells, which can pass HIVby cell-to-cell contact from lymphocytes to epithelial cells or by cell-to-cell fusion.

Two types of HIV are now recognized[72,73] HIV-1 and HIV-2, HIV-3 was first found associated with AIDS in West Africa and is spreading through Africa and parts of Europe. Like HIV-1, HIV-2 can be give rise to the same spectrume of disease caused by immune destruction, but infection course is believed to be more protracted and not to be transmitted so readily as HIV-1. Isolated infections have been found in the United States but are uncommon. Neverthless, because HIV-2, which differs in genome structure by 55% from the other HIV-1 subtype, primarily in its envelope genes, blood banks must now test for both subtype before using blood products.

Furthermore, hepatitis B virus (HBV), the causative agent of acute and chronic hepatitis, which affects nearly 350 million people world wide. There are several million chronic carriers need therapy for delaying or preventing the progression of disease. Chronic carriers of HBV are at an increased risk of liver damage that, in the worst case, can lead to cirrhosis of liver and/or to hepatocellular

carcinoma. In addition, since transplanted livers can be reinfected with HBV,[158] The need to develop effective and non toxic anti-HBV compounds for prevention of the destruction of liver tissue after transplantion is a urgent assignment.

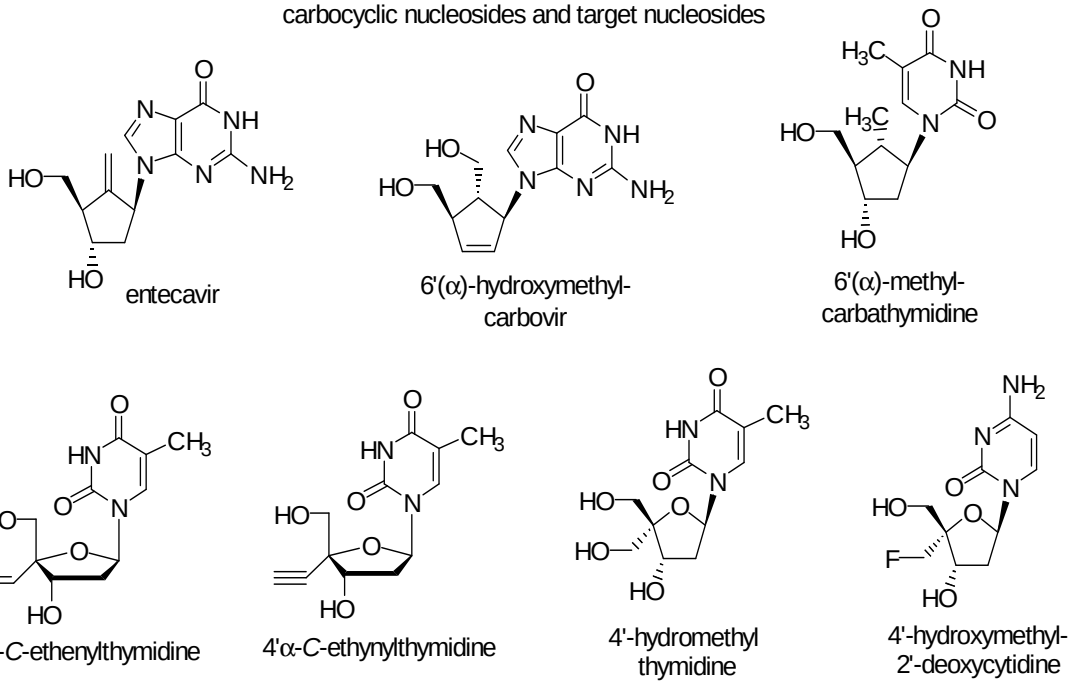
Interest in chemical entities capable of blocking or modifying cell metabolism ultimately goes back to the discovery of the structure of DNA in the 1950s. Several classes of drug have since been discoverered which depend for their effect on some kind of modification of the proper functioning of nucleic acids. Intercalators and alkylating agents were among the earliest therapeutic agents which were recognized as behaving and were widely used as treatments for bacterial infections and some forms of cancer. It was a small but significant step forward to arrive at the notion that analogues of the four natural nucleoside components of DNA might have similar effects.

Nucleoside analogues have been the cornerstone of antiviral chemotherapy over the past decades. Although structure-activity relationship studies have not let to a pharmacophore model for the antiviral activities of nucleosides, some structural features have been particularly successful. 3'-Azidothymidine (zidovudine, AZT) has been the cornerstone of HIV therapy since its introduc-tion, in spite of considerable problems with sideeffects and the emergence of drug-resistant strains of the virus. It possesses activity against both HIV-1 and HIV-2, as well as the murine and feline leukaemia viruses formerly used for primary testing in cell culture. But AZT is fairly lipophilic it is able to penetrate the bloodbrain barrier and may be effective at slowing the spread of the infection through the central nervous system. Nevertheless, AZT induces bone marrow suppression which results in neutropenia. Longerterm treatment with AZT has been shown to cause a destructive mitochondrial myopathy. Various attempts have been made to achieve higher concentrations of drug in the CNS by preparing lipophilic prodrugs or delivering it in liposomes but none of these approaches has demonstrated any benefit. 2'3'-Dideoxycytidine (zalcitabine, ddC) was tested clinically and is now approved for use as adjunct therapy with AZT. It is one of the most potent inhibitors of HIV-1 in vitro, but during use serious sideeffects have been seen in some patients as a result of peripheral neuropathy. The drug appears to reduce the cellular content of mitochondrial

DNA due to the triphosphate acting as an inhibitor of DNA polymerase γ in the mitochondria. 2',3'-Dideoxyinosine (didanosine, ddI) has a high therapeutic index when compared to other dideoxynucleosides, and relatively little toxicity towards human bone marrow cells, but caused some peripheral neuropathy and pancreasstitis in some cases. 2',3'-Dideoxy-2',3'-didehydrothymidine (d4T, stavudine) in the form of its triphosphate ester, is a potent inhibitor of HIV-RT and is about 20- to 100-fold less toxic to human granulocyte macrophage progenitor cells than AZT. The pharmacokinetic and therapeutic aspects of this compound have been reviewed by several groups. d4T is activated by cellular thymidine kinase and may be produced in higher concentration in some cells than in others due to the varying natural levels of this enzyme. In any case its monophosphorylation is the rate determining step, being subsequently rapidly converted through to the triphosplhate. d4T is cleaved by phosphorylases but neither the drug itself nor the unsaturated sugar appear to be toxic to bone marrow cells. Gross toxic effects seem to be limited to peripheral neuropathy. Nevertheless, the efficacy of these drugs is limited by their toxicity and side effects, as well as the emergence of many drug resistant viral strains. Therefore, there is a need for less toxic and more effective antiviral agents that do not have any crossresistance with existing drugs. In view of the stimulating results reported for acyclic nucleosides and as a part of our ongoing drug discovery efforts, the aim of this study was to synthesize novel nucleosides.

Recently, several branched nucleosides were synthesized and evaluated as potent antitumor or antiviral agents. Among them, 4′(α)-*C*-ethenylthymidine,[75] and 4′(α)-*C*-ethynylthymidine,[76] and 4′(α)-*C*-hydroxymethyl thymidine,[77] and 4′(α)-*C*-fluoromethyl-2′-deoxycytidine,[78] and 6′(α)-hydroxymethyl carbovir,[79] and 6′(α)-methylcarbathymidine,[80] which have additional branch at the 4′-position, were reported to exhibit potent antiviral activity, furthermore, carbocyclic nucleosides such as guanine derivative entecavir,[81] also showed significant antiviral and antitumor activity. **(Figure 10)**

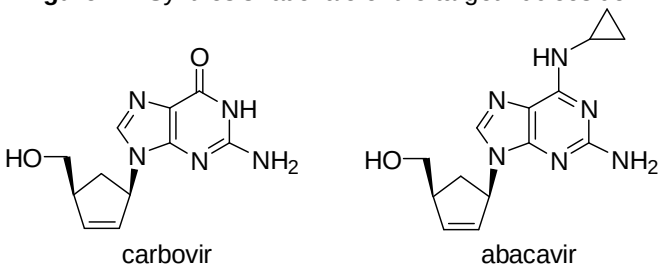
Figure 10. Structures of branched furanose nucleoside and carbocyclic nucleosides and target nucleosides



The replacement of the oxygen atom on the furanose ring by carbon is of particular interest because the resulting carbocyclic nucleosides[82] have a greater metabolic stability to phosphorylase,[83] which cleaves the glycosidic bond of nucleosides. Many carbocyclic nucleosides have interesting biological activities, particularly in the areas of antiviral and anticancer chemotherapy, because the cyclopentane ring of these compounds can imitate the furanose moiety.

The recent discovery of olefinic carbocyclic nucleosides, such as carbovir,[84] and abacavir,[85] which are potential anti-HIV agents, have increased interests in the search for novel nucleosides in this class of compounds. (Figure 11)

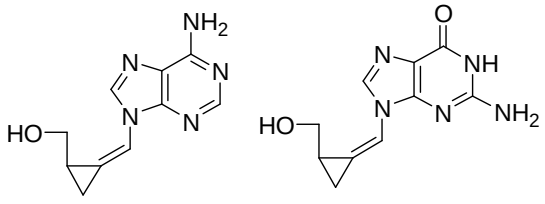
Figure 11. Synthesis rationale of the target nucleoside



Carbocyclic nucleosides are also believed to be potent inhibitors of the cellular enzyme, *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase, which is very important for regulating the *S*-adenosylmethionine (SAM) dependent methylation reactions, and has emerged as a specific target for the reversible hydrolysis of the AdoHcy linkage to adenosine and homocysteine.[86] Inhibition of the enzyme on intact cellular systems results in AdoHcy accumulation. A higher AdoHcy concentration suppresses the enzyme activity by acting as a product inhibitor of the AdoMet-dependent methylation reaction.[87] Methyltransferases are essential for the maturation of mRNA. Therefore, inhibiting the methyl transferases by blocking the AdoHcy metabolism can disrupt the viral mRNA maturation. AdoHcy inhibitors usually display a broad-spectrum of antiviral activities. Moreover, this mechanism might be used in a combination therapy in association with the nucleosides with a different mechanism of action.

Encouraged by these interesting structures and the biological activities of branched furanose and carbocyclic nucleosides, novel class of nucleosides comprising branched carbocyclic nucleosides with additional branches at 1′,4′-dually branched, and 4′(α),6′(α)-dually branched carbocyclic nucleoside, and nucleosides comprising 4′(α)-quaternary carbocyclic nucleosides with an additional methyl group at the 6′-position, hybrid guanine analogues that contain both a potent acyclic nucleoside moiety and the aforementioned olefinic carbocyclic nucleoside were synthesized.

Figure 12. Synthesis rationale of target compounds



Synadenol Synguanol

Spaced cyclopropyl nucleosides and D-apio-nucleosides avoiding high rigidity appear to be favorable either for the interaction with phosphorylating enzymes or for the interaction with viral DNA polymerase.[88] Among them, methylene-

spacered cyclopropane analogues of purine nucleosides[89] such as synadenol, synguanol **(Figure 12),** AZT,[90] ddC,[91] ddI,[92] d4T,[93] 3TC,[94] and abacavir[85] have shown potent antiviral activity, particularly against the human cytomegalovirus (HCMV) and anti-HIV.

The introduction of a fluorine atom to the carbohydrate moiety was found to confer interesting biological activities, as shown in FLT,[159] FIAU,[96] L-FMAU,[97] and L-2′-F-d4N.[98] The electronegativity of fluorine (4 *vs* 3.5 for oxygen) can have pronounced effects on the electron distribution in the molecule, effecting either the alkalinity or acidity of the neighboring groups, the dipole moments within the molecule and the overall reactivity and stability of the neighboring functional groups.[99] While there has been considerable interest in modifications at the 2′- and 3′-position of nucleosides, much less is known about 4′-modified compounds.[100]

Recently, Ahn et al. reported the synthesis of fluoroapiosyl pyrimidine nucleosides as a racemate.[101] We have also published preliminary accounts of the asymmetric synthesis of the 3′-fluoro-L-apionucleosides, of which the configuration was analogous to the natural D-nucleosides. **(Figure 13)**[102]

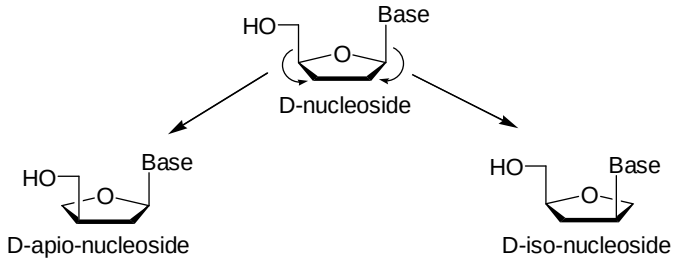


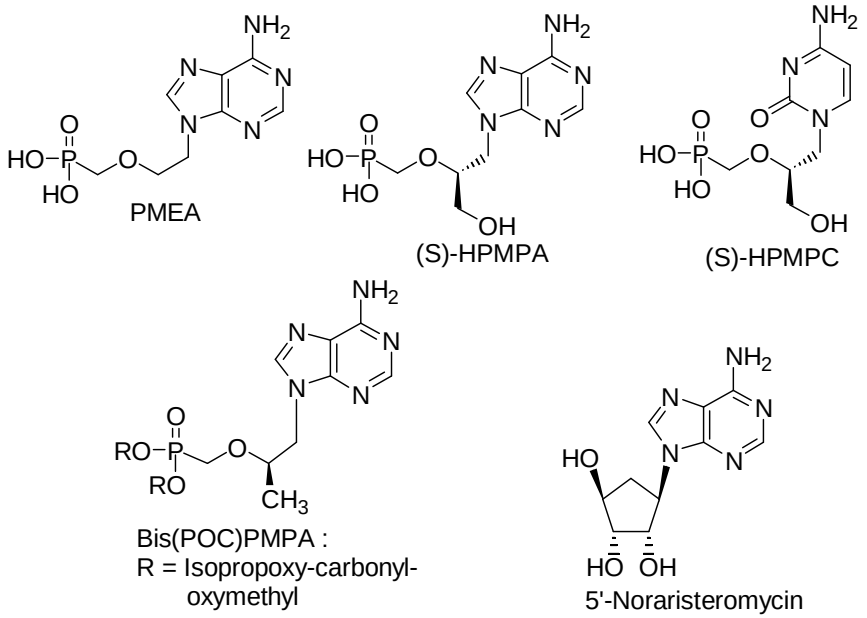
Figure 13. natural D-nucleoside

Therefore, as a part of an ongoing study searching for novel antiviral agents, novel classes of nucleosides comprising cyclopropyl backbone and trisubstituted cyclopropyl nucleosides with an additional fluorine group at 1′-position and fluorinated apionucleosides in a D-series with the modified strategies were synthesized.

Acyclic nucleosides[103] in which the 5′-hydroxy group has been replaced by a phosphonate or phosphonate ester can act as stable mimics of nucleoside

monophosphates and under go further phosphorylation in cells to afford species which are analogous to nucleoside triphosphates and are capable of inhibiting polymerases. The advantage of these compounds is to circumvent the need for primary phosphorylation of the parent nucleoside, which is often the stumbling block in attaining active compounds. During the past 20 years, many new synthetic schemes for various acyclic nucleoside phosphonic acid analogues[104] have been reported, and many of these molecules have exhibited promising antiviral activity.[160] Among them, PMEA,[106] (*S*)−HPMPA,[107] (*S*)−HPMPC,[108] penciclovir,[109] famciclovir,[110] cidofovir[108] exhibit potent antiviral activity against the HIV, HBV and HSV. Furthermore, the recent approval of *bis*(POC)PMPA[111] by the FDA as an anti−HIV agent warrants further study for acyclic nucleotide analogues as chemotherapeutic agents. **(Figure 14)**

Figure 14. Synthesis rationale of target nucleotide analogues

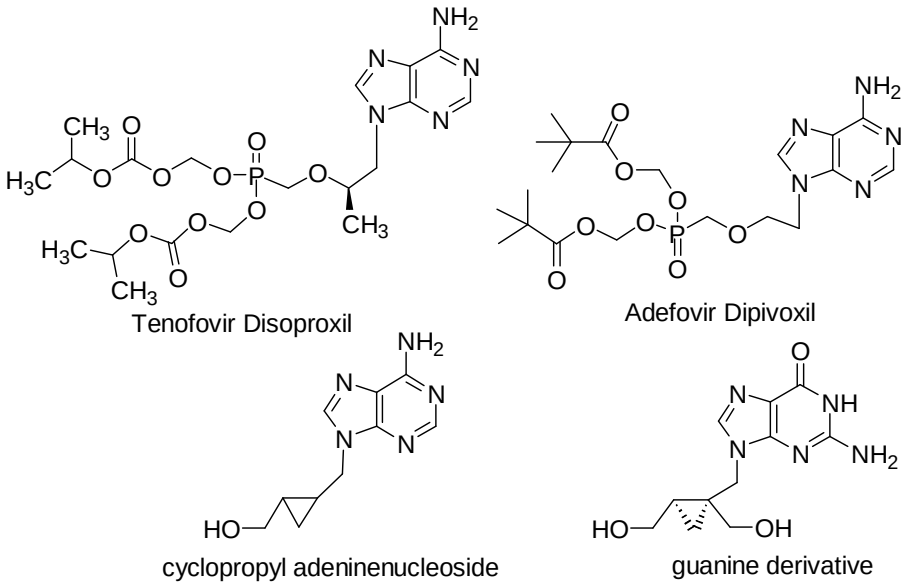


5′−Norcarbocyclic nucleosides have been found to have a variety of meaningful biological properties. Among them, 5′−noraristeromycin[112] was reported to be more potent against the HCMV than the licensed anti−HCMV agent, ganciclovir.[113] Nevertheless, the efficacy of these drugs is limited by their toxicity and side

effects, as well as the emergence of many drug resistant viral strains.[114] Therefore, there is a need for less toxic and more effective antiviral agents that do not have any crossresistance with existing drugs. In view of the stimulating results reported for acyclic nucleosides and as a part of our ongoing drug discovery efforts, novel 5′−norcarboacyclic nucleosides were synthesized.

One of acyclic phosphonic acid nucleosides, PMEA,[106,115] tenofovir disoproxil,[111,116] adefovir dipivoxil,[117,118] cyclopropyl adenine nucleoside,[157] guanine derivative (A−5021),[120] synadenol,[121] synguanol[89] shows a broad spectrum of antiviral activity and is effecttive against HBV,[111] human immunodeficiency virus (HIV),[122] and also the herpes simplex virus (HSV).[123] **(Figure 15)** Unlike nucleoside analogues, a phosphonic acid nucleoside has the advantage of skipping the requisite first phosphorylation which is crucial step for the activation of nucleosides.[124]

Figure 15. Rationale to the design of target nucleosides

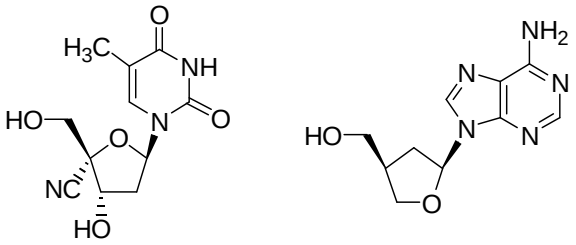


Recently, D− and L−carbocyclic nucleosides with exocyclic methylene in place of furanose oxygen were synthesized and evaluated for antiviral activities, among which D−guanine derivative (Entecavir) was very active HBV and was 100 times more potent than clinically available drug, lamivudine.[125] Unlike

nucleoside agents, a phosphonate nucleoside has the advantage of skipping the requisite first phosphorylation which is crucial step for the activation of nucleosides.[124] Encouraged by these interesting structures and antiviral activities of acyclic phosphonate nucleosides, cyclopeantene phosphonate nucleosides were synthesized.

4′(α)−*C*−cyanothymidine,[126] which has an additional branch at the 4′−position, was reported to show potent antiviral activity. More fundamental modifycations of the pentofuranose moiety, such as isonucleosides and apio−nucleosides, were reported to be compatible with the antiviral activities. The apiosyl nucleosides[127] are a group of compounds that are structurally similar to natural nucleosides where the 4′−hydroxymethyl group of the classical nucleosides is moved to the C3′ position. Among this type of nucleoside, the adenine analogue (apio−ddA) was reported to show comparable anti−HIV activity to the parent 2′,3′−didieoxy adenosine.[128] (Figure 16)

Figure 16. Synthesis rationale of target apio-nucleosides



4'(α)-C-cyanothymidine apio-ddA

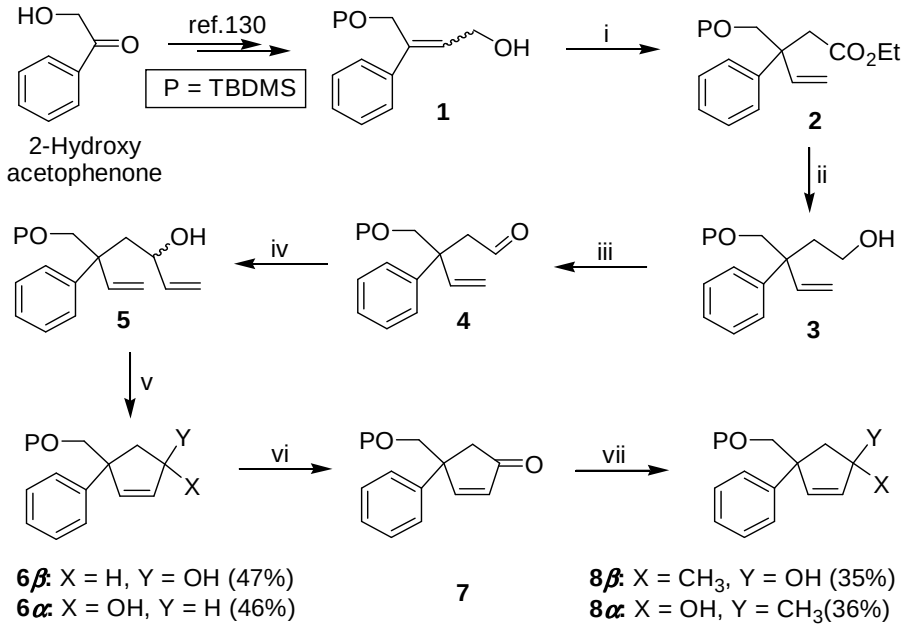
Apio−ddA appears to possess the intrinsic metabolic advantages such as resistance to ADA (adenosine deaminase) and enhanced stability of glycosidic bond under acidic and enzymatic conditions compared to natural ddNs (2′,3′−dideoxynucleosides) nucleosides.[129] Usually, ddNs have several drawbacks such as easy cleavage of their glycosidic bond under acidic conditions similar to a gastric environment and catabolism by ADA, AMP (adenosine−5′−monophos−phate) PNP (deaminase and purine nucleoside phosphorylase). Nevertheless, the systematic structure activity relationship of apiodideoxy nucleosides is not completely understood. Therefore, more effort is needed to search this class of

nucleosides for new antiviral agents. Herein, we studied the synthetic procedure of novel substituted apiosyl nucleosides in an atempt to find new lead compounds with improved biological activity.

RESULTS AND DISCUSSION

Allylic alcohol **1**, which is readily synthesized from 2-hydroxy acetophenone using previously reported method,[130] was subjected to the [3,3]-sigmatropic rearrangement reaction to give compound **2**. The ester derivative **2** was sequentially reduced and oxidized to provide aldehyde **4**, which was subjected to Grignard addition using vinylmagnesium bromide to give a divinyl **5** as an inseparable diastereomeric mixture. The divinyl **5** was cyclized under ring-closing metathesis conditions using a 2nd generation Grubbs' catalyst [(Im) $Cl_2Pcy_3RuCHPh$][131] to afford the cyclopentenols **6*α*** and **6*β***, respectively. The stereochemical assignments were accomplished based on the NOE experiments. Without separation, mixture of **6*α*** and **6*β*** was oxidized to ketone derivative **7**, which was also subjected to addition reaction of methyl magnesium bromide to yield **8*α*** and **8*β***, respectively. (Scheme 1)

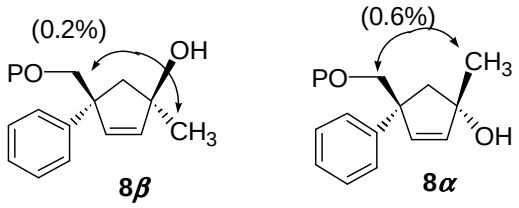
Scheme 1. Synthesis of cyclopentenols **8*α*** and **8*β***



Reagents: i) Triethylorthoacetate, Propionic acid; ii) DIBAL-H, CH_2Cl_2; iii) PCC, 4A-MS, CH_2Cl_2; iv) CH_2=CHMgBr, THF; v) Grubbs' catalyst II, CH_2Cl_2, reflux, overnight; vi) PCC, 4A-MS, CH_2Cl_2; vii) CH_3MgBr, THF;

Upon the irradiation of C_1-CH_3, a relatively strong NOE (0.6%) was observed at the methylene protons of compound **8*α***, but weak NOE (0.2%) was observed at the methylene protons of **8*β***. **(Figure 17)**

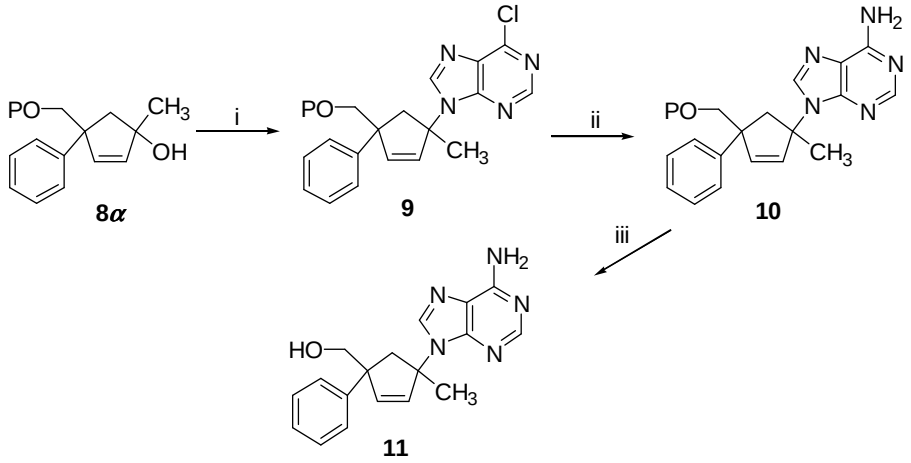
Figure 17. NOE comparisons of compounds **8*α*** and **8*β***



The Mitsunobu reactions were used tocouple the cyclopentenol with the nucleosidic base.[132] This methodology has been successfully used to synthesize the target nucleosides with the desired β-configuration. The required β-configurations of nucleoside **9** was successfully controlled from the β-configuration of compound **8*α***. The success of the Mitsunobu reactions in the synthesis of the nucleoside analogue depends on the conditions. The appropriate choice of solvent system, temperature and procedure are essential for the regioselectivity as well as for the yield. In purine synthesis, a 2:1 mixture of dioxane and DMF were used as the solvent for the coupling of the cyclopentenol **8*α*** with 6-chloropurine instead of THF. The heterocyclic bases had a better solubility in the dioxane and DMF mixture resulting in better yields. The slow addition of DIAD (diisopropylazodicarboxylate) to a mixture of cyclopentenol **8*α***, triphenylphosphine and the corresponding purine base in an anhydrous solvent gave a yellow solution, which was then stirred for 2 h at –20 ℃ to give the protected 6-chloropurine analogue **9**. The 6-chloropurine **9** was converted to a protected adenosine analogue **10** by treating it with a saturated solution of metahnolic ammonia in a steel bomb at 90~95 ℃ overnight. The final nucleoside **11** was obtained from the corresponding protected nucleoside by treating them withtetrabutylammonium fluoride (TBAF).

(Scheme 2)

Scheme 2. Synthesis of target nucleosides

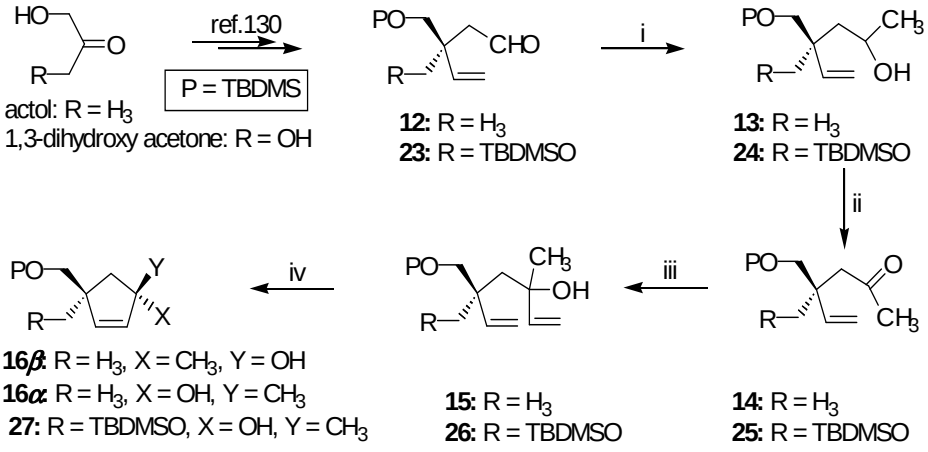


Reagents: i) 6-chloropurine, DIAD, PPh_3, dioxane/DMF; ii) NH_3/MeOH, steel bomb; iii) TBAF, THF.

In summary, the first synthetic method for 4′−phenyl and 1′−methyl doubly branched carbocyclic nucleoside from a α−hydroxy acetophenone was developed. The synthesized compound **11** were tested against several viruses such as HIV−1 (MT−4 cells), HSV−1,2 (CCL18 cells) and HCMV (AD−169). However, none of these compounds had any significant activity up to 100 μM. The lack of antiviral activity of these compounds is presumably associated with their unfavorable conformations for the phosphorylation occurring during the nucleotide activation process. However, the information obtained in the present study will be useful for the development of novel nucleoside antiviral agents.

Aldehydes **12** and **23**, which is readily synthesized from acetol and 1,3−dihydroxy acetone Claisen rearrangement using a previously reported method,[130] was subjected to the carbonyl addition of CH_3MgBr to give compounds **13** and **24** as a diastereomeric mixture. Without separation, the alcohol derivatives **13** and **24** was oxidized using PCC to give a single compounds **14** and **25**. The ketones **14** and **25** was subjected to Grignard addition using vinylmagnesium bromide to give a divinyls **15** and **26** as an inseparable diastereomeric mixture. The bisolefin **15** and **26** was cyclized under ring−closing metathesis conditions using a second−generation Grubbs' catalyst to afford the cyclopentenols **16α**, **16β** and **27** respectively. **(Scheme 3)**

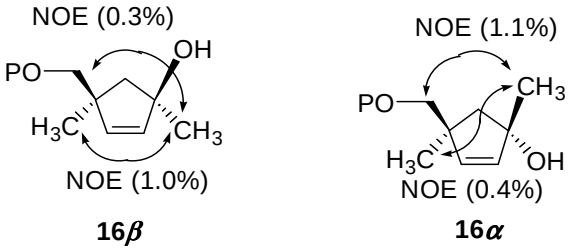
Scheme 3. Synthesis of cyclopentenols **16α**, **16β** and **27**



Reagents: i) CH_3MgBr, THF; ii) PCC, 4A-MS, CH_2Cl_2; iii) CH_2=CHMgBr, THF; iv) Grubbs' catalyst (II), CH_2Cl_2;

The cyclopentenols **16α**, **16β** of stereochemical assignments were based on the NOE experiments. Upon the irradiation of C_1-CH_3, a strong NOE was observed at the methylene protons of the hydroxymethyl group of compound **16α**, but not at the methylene protons of **16β**. The Mitsunobu reactions were used to couple the cyclopentenol with the nucleosidic bases.[132] This methodology has been successfully used to synthesize the target nucleosides with the desired β-configuration. The required β-configurations of nucleosides **17** and **19** were successfully controlled from the β-configuration of compound **16β**. (Figure 18)

Figure 18. NOE results of compound **16α** and **16β**



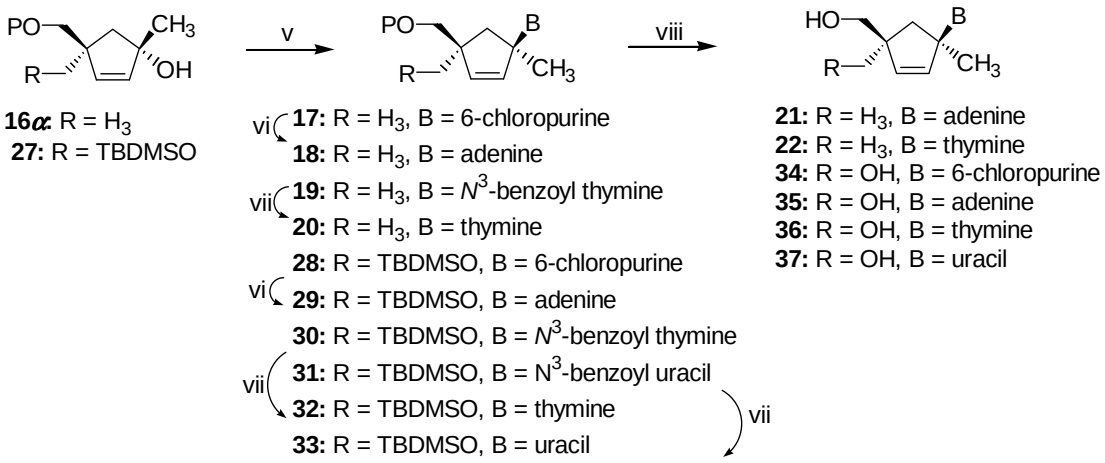
The success of the Mitsunobu reactions in the synthesis of the nucleoside analogues depends on the conditions. The appropriate choice of solvent system,

temperature and procedure are essentialfor the regioselectivity as well as for the yield. In purine synthesis, a 2:1 mixture of dioxane and DMF were used as the solvent for the coupling of the cyclopentenol **16*α*** with 6-chloropurine instead of THF. The heterocyclic bases had a better solubility in the dioxane-DMF mixture resulting in better yields. The slow addition of diisopropylazodicarboxylate (DIAD) to a mixture of cyclopentenol **16*α*** triphenylphosphine and the corres-ponding purine base in an anhydrous solvent gave a yellow solution, which was then stirred for 2 h at –20 ℃ to give the protected 6-chloropurine analogue **17**. And the cyclopentenol **27** with the bases using convenient S_N2 reaction. The allylic alcohol **27** was subjected to a mesylation condition (MsCl, TEA, CH_2Cl_2). Unexpectedly, the reaction was very complicated and was ireproducible. Therefore, our attention was turned to a Mitsunobu reaction to synthesize desired nucleoside **28**. The 6-chloropurine **17**, **28** was converted to a protected adenosine analogue **18**, **29** by treating it with a saturated solution of metahnolic ammonia in a steel bomb at 90~95 ℃ overnight.

On the other hand, the synthesis of the pyrimidine nucleosides was more complex than in the case of purine due to the formation of O^2-alkylated by-products. The formation of these compounds was inevitable under the conditions used. However, the ratio of N- to O-alkylation was improved by changing the solvent to a 2:1 mixture of dioxane-DMF. The regioisomer of the O^2-alkylated compounds were easily confirmed by acomparison of the publicccshed UV spectra.[133] The condensation of compound **16*α*** and **27** with N^3-benzoyl thymine and N^3-benzoyl uracil under the similar Mitsunobu conditions gave the protected thymine analogue **19**, **30** and uracil analogue **31** which was debenzoylated with sodium methoxide to afford the corresponding nucleosides **20**, **32**, **33**. The final nucleosides **21**, **22** and **34~37** were obtained from the corresponding protected nucleosides by treating them with tetrabutylammonium fluoride (TBAF).

(Scheme 4)

Scheme 4. Synthesis of 1',4'-doubly branched nucleosides



Reagents: v) DIAD, nucleosidic bases, PPh_3, dioxane/DMF; vi) NH_3/MeOH, steel bomb; vii) NaOMe, MeOH; viii) TBAF, THF.

Based on an extensive literature search, compounds **21**, **22** and **34~37** appear to be novel nucleosides. Antiviral activity assays were performed using the synthesized nucleosides against HIV-1, HSV-1, 2 and HCMV, EMCV. However, these compounds **21** and **22** showed no significant activity or cytotoxicity at concentrations up to 100 μM. And **34~37** and their results are shown in **(Table 1)**. Compounds **34** and **37** exhibited potent anti-HIV-1 activities, but these inhibitory effects were associated with the nonspecific cytotoxicity to MT-4 cells.

Table 1. The antiviral activities of the synthesized compounds.

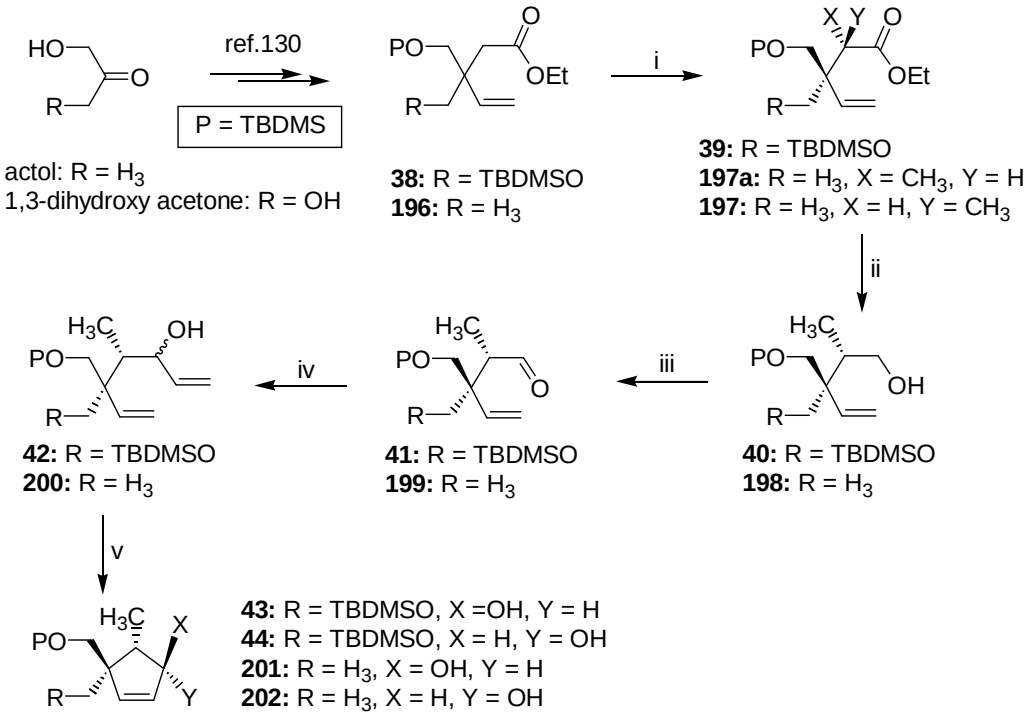
	HIV-1 EC_{50}(μM)	HSV-1 EC_{50}(μM)	HSV-2 EC_{50}(μM)	EMCV EC_{50}(μM)	cytotoxicity CC_{50}(μM)
34	48.58	>100	>100	>100	48.58
35	>100	>100	>100	>100	>100
36	>100	>100	>100	>100	>100
37	23.21	>100	>100	>100	23.21
AZT	0.0005	ND	ND	ND	5.41

ACV	ND	1.81	1.81	ND	>10
Ribavirin	ND	ND	ND	20.12	300.00

ND: Not Determined; $EC_{50}(\mu M)$: Concentration required to inhibit 50% of virus induced cytopathicity; $CC_{50}(\mu M)$: Concentration required to reduce cell viability by 50%

In conclusion, a simple synthetic method for synthesizing 1′,4′−dually branched carbocyclic nucleosides from an α−hydroxy ketone was developed. Compounds **34** and **37** exhibited toxicity nonrelated to any anti−HIV−1 activity. Based on this strategy, the enantiomeric synthesis of a doubly branched nucleoside with different bases and substituents is currently underway.

Scheme 5. Synthesis of divinyl intermediates **42** and **200**



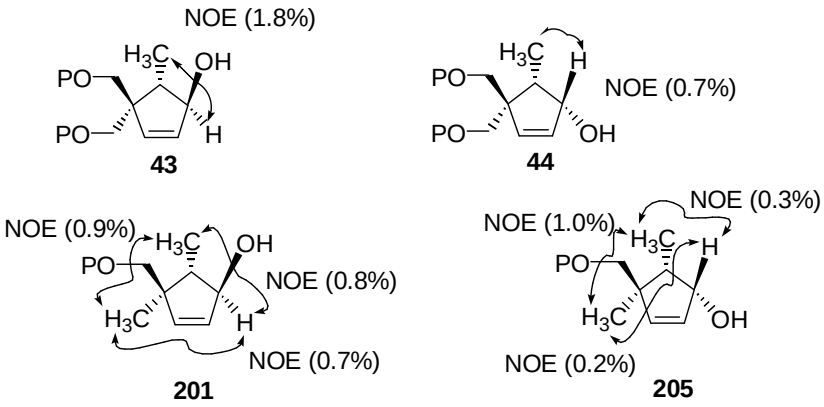
Reagents: i) LiHMDS, CH_3I, THF, -78 ^oC; ii) DIBALH, CH_2Cl_2, 0 ^oC; iv) PCC, 4A MS, CH_2Cl_2, 4 h, rt; iv) CH_2=CHMgBr, THF.

As shown in (Scheme 5), the quaternary carbon of γ,δ−unsaturated esters **38**,

196 was constructed successfully using a previously reported procedure. [130] The stereocontrolled introduction of a methyl group in **38**, **196** using an ester enolate alkylations (LiHMDS/ CH_3I) provided compounds **39**, **197a**, **197b** as diastereomeric mixtures. Each diastereomers **197a**, **197b** was separated by column chromatography and assigned its stereochemistry by various NMR technique. The addition of DIBAL-H to a solution of the ester **39**, **197a** in CH_2Cl_2 at 0 ℃ gave the alcohol derivatives **40**, **198**, which was subjected to oxidation conditions using PCC. The resulting aldehyde **41**, **199** was subjectted to Grignard reactions by vinyl magnesium bromide to yield a 10:1 bisolefin **42**, **200** as a diastereommeric mixture, which was not readily separable by conventional column chromatography.

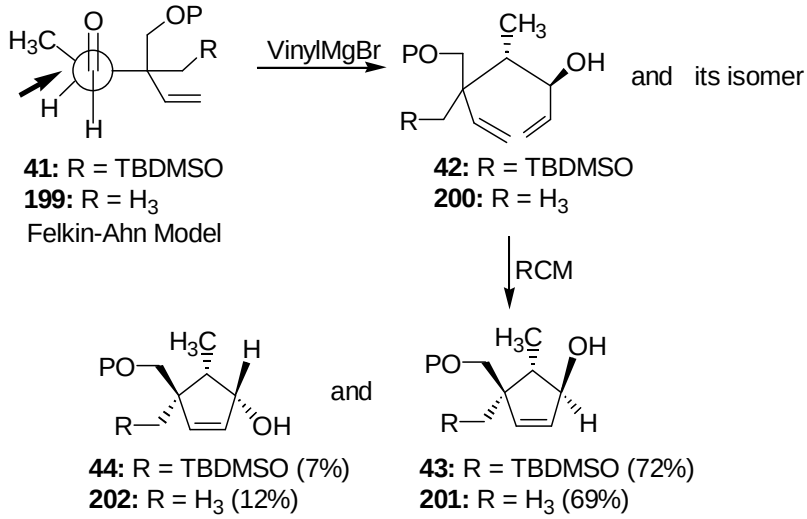
The diastereomeric mixture of **42** and **200** was not separated but instead subjected to standard ring-closing metathesis conditions using a second-generation Grubbs' catalyst [(Im) $Cl_2Pcy_3RuCHPh$] [131,134] to predominantly provide the required cyclopeantenols **43**, **44**, **201**, **202** as a minor isomer. The stereochemistry of the cyclized products (**43** and **44**, **201** and **202**) was determined by employing the NOE experiment between the corresponding hydrogen atoms. Upon the irradiation of C_1-H, a relatively strong NOE was observed at the methyl protons of **43** (1.8%, NOE), **202** [C_4-H (0.7%) & C_6-H (0.8)], but not at the methyl protons those of **44** (0.7%, NOE), **201** [C_4-H (0.2%) & C_6-H (0.3)]. **(Figure 19)**

Figure 19. Relative stereochemistry determination based on NOE comparisons of compounds **43**, **44** and **201**, **202**



The major stereochemical outcome of compounds **43**, **44** and **201**, **202** was reasonably explained by a mechanistic rational of the favored π-facial selection based on the Felkin-Ahn rule[135] depicted in **(Figure 20)**, which shows that the stereochemical assignment of the cyclopentenols **43**, **44** and **201**, **202** was correct. This rule states that the bulkiest of the α ligand (L) is placed in a perpendicular relationship to the plane of the carbonyl group anti to the incoming nucleophile, and the sterically next most bulky α substituent (M) is placed gauche to the carbonyl function. The correct configuration of compounds **41**, **199** could be assigned based on spectroscopic comparisons observed in compounds **43**, **44** and **201**, **202**. **(Figure 20)**

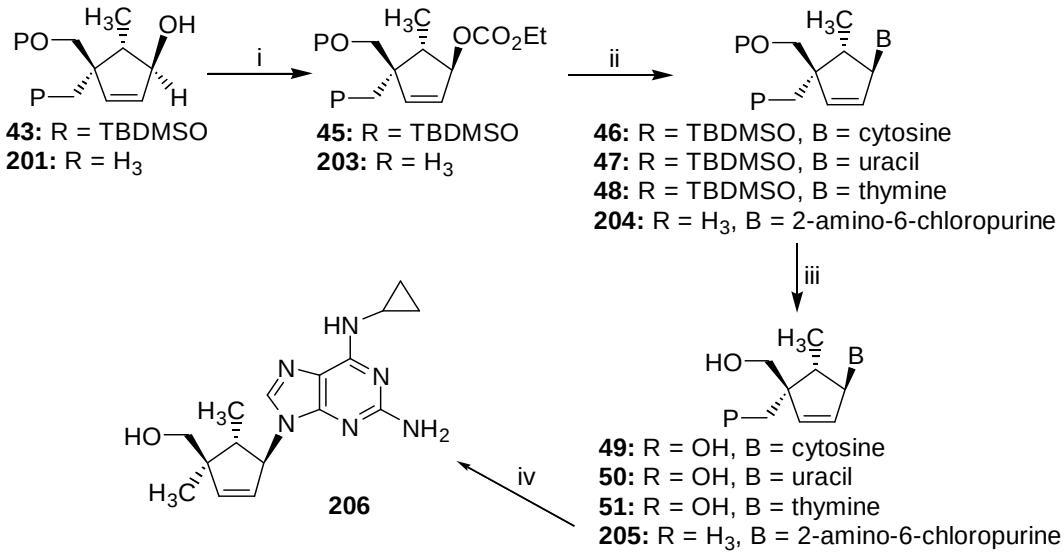
Figure 20. Addition of nucleophile to aldehyde **41**, **199** using Felkin-Ahn rule



The abacavir analogue was synthesized by activating the cyclopentenols **43**, **201** to the ethoxycarbonyl derivatives **45**, **204** using ethyl chloroformate. Compounds **45**, **204** was coupled with the 2-amino-6-chloropurine, cytosine, uracil, thymine anions generated by NaH/ DMSO with the [*tris*-(dibenzylodene-acetone)-dipalladium(0)-chloroform][136] adduct to give the compounds **46~48**, **204**. The required β-stereochemistry of the nucleosides **46~48**, **204** was controlled successfully from the β-configuration of compounds **43**, **201** *via* a Pd(0) catalyzed π-allyl complex mechanism. Compounds **46~48**, **204** were

desilylated by treating them with tetrabutylammonium fluoride (TBAF) to give the nucleoside **49~51**, **205**. Therefore, the exposure of compound **205** to cyclopropylamine in EtOH under reflux provided the desired nucleoside **206**. (Scheme 6)

Scheme 6. Synthesis of carbocyclic nucleosides



Reagents: i) $ClCO_2Et$, DMAP, pyridine, rt, overnight; ii) Bases (cytosine, uracil, thymine, 2-amino-6-chloropurine), $Pd_2(dba)_3.CHCl_3$, P(O-*i*-Pr)$_3$, NaH, THF/DMSO, reflux, overnight; iii) TBAF, THF, rt; v) cyclopropylamine, EtOH, reflux.

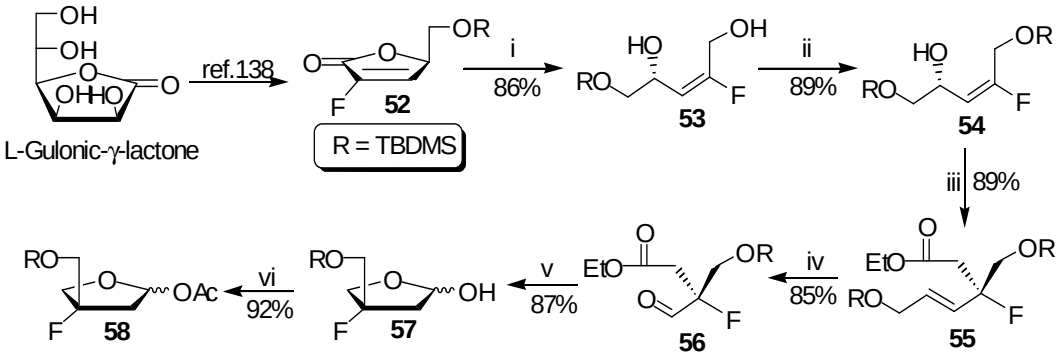
Compounds **49~51** and **206** were tested against several viruses such as the HIV-1 (MT-4 cells), HSV-1,2 (CCL81 cells), HCMV (AD-169, Davis cells). It is interesting to note that the cytosine analogue **49** exhibited good antiviral activity against the HCMV (10.7 μg/mL), and compound **206** showed moderate anti-HIV activity (EC_{50} = 10.67 μM, MT-4 cellslines)[137] without any cytoto-xicity up to 100 μM.

In summary, a simple synthetic method for 4′(α),6′(α)-dually branched carbocyclic nucleosides from simple 1,3-dihyroxy acetone and acetol. This procedure focuses on the simplicity of installing a quaternary carbon and the stereoselectivity in the methylation at cyclopentene ring systems.

The key strategy for the synthesis of the target compounds was based on the

implementation of a [3,3]-sigmatropic rearrangement to generate an optically active fluoroester **55**, which provides two useful functionalities, such as alkene and carbonyl groups, to obtain the fluorinated apiosyl moiety **56**. However, due to the difficulties in preparing the (*E*) or (*Z*)-fluorinated olefin in a large scale, the planning for the preparation of the intermediate for the Claisen rearrangement, was guided using the difference in the geometry between the (*E*)- and (*Z*)-isomers. Therefore, this study attempted to synthesize the (*E*)-isomer **53** *via a* 2-fluorobutenolide formation **52**, which could be readily prepared from L-Gulonic γ-Lactone in a large scale by the known procedure.[138] **(Scheme 7)**

Scheme 7. Synthesis of apiosyl acetate

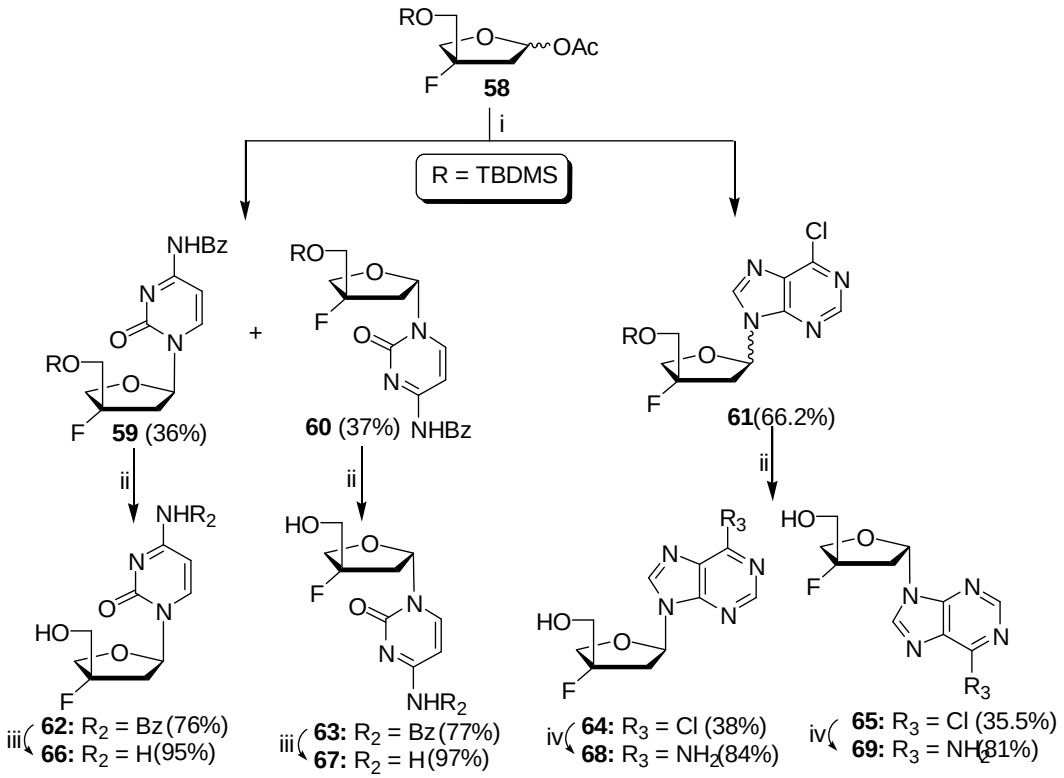


Reagents: i) (a) Dibal-H, -78 ^{o}C, (b) $CeCl_3.7H_2O$, $NaBH_4$, 0 ^{o}C; ii) TBDMSCl, imidazole, CH_2Cl_2; iii) Triethylorthoacetate, propionic acid, 140 ^{o}C; iv) O_3/DMS; v) Dibal-H, toluene, -78 ^{o}C; vi) Ac_2O, pyridine.

Usually, the lactones are rapidly reduced to the diol by various reducing agents such as LAH, $LiAlH(OMe)_3$, DIBAL-H, and $NaBH_4$. However, to our knowledge, there are only a few examples of the direct reduction of butenolide to the diol.[139] In order to identify the optimal conditions of **52** for the conversion into the allylic diol **53**, several reducing conditions were screened at various temperatures. Among the investigated conditions, the LAH and DIBAL-H reduction did not give satisfactory yields in several conditions. The use of DIBAL-H followed by a combination of $CeCl_3 \cdot 7H_2O$[140] and $NaBH_4$, gave the best yield (86%). The selective monosilylation of the allylic diol **53** and the subsequent Claisen rearrangement generated the α,β-unsaturated fluoroester **55** *via* the orthoester

intermediate in an 89% yield. Ozonolysis of compound **55**, followed by a DIBAL-H reduction furnished the lactol **57**, which was further converted into the key intermediate **58** in a 68% threestep yield.

Scheme 8. Synthesis of apio-nucleosides



Reagents: i) silylated N^4-Bz-cytosine, or 6-Cl-purine, TMSOTf, DCE;
ii) TBAF, CH_3CN; iii) sat. NH_3/MeOH, rt; iv) sat. NH_3/MeOH, 90-100 ^oC.

Condensation of compound **58** with silylated N^4-benzoyl cytosine gave compounds **59**, **60**, which were readily separated using normal column chromatography. (Scheme 8) The separate treatment of compounds **59**, **60** with TBAF in CH_3CN afforded the cytosine derivatives **62**, **63**. Debenzoylation was performed under the condition of saturated ammonia in MeOH to give the compounds **66**, **67**. The 6-chloropurine derivatives were obtained by conden-sation with compound **58** under the same conditions to give the anomeric mixture **61**, which were separated after desilylation with TBAF to give compounds **64**, **65**.

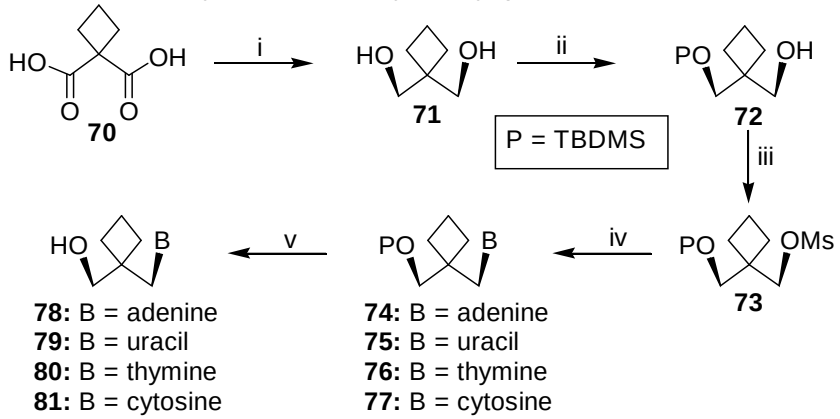
Compounds **64**, **65** were treated separately with NH_3/ MeOH in a steel bomb at 90~100 ℃ to give the adenine derivatives **68**, **69** in an 84% and 81% yield, respectively. The stereochemical assignments of the synthesized compounds were easily determined based on the spectroscopic data (^{1}H NMR and ^{13}C NMR). In addition, the specific rotations of the synthesized nucleoside **66** $[\alpha]^{24}_{D}$ = +41.1° (*c* 0.48, MeOH) was in good agreement with those of the reported antipode $[\alpha]^{27}_{D}$ = −40.7° (*c* 0.70, MeOH).[102]

The antiviral activities of the synthesized compounds **66~69** were evaluated against HIV−1, HSV−1,2 and polio virus, respectively. However, none of them showed significant antiviral activity or cytotoxicity at concentrations up to 100 μM.

In conclusion, this report described the synthesis of 3′−fluoro apionucleosides of the D−series, using a Claisen rearrangement of the allylic alcohol **54**, which was readily prepared from 2−fluorobutenolide **52** by a reduction with a combination of DIBAL−H and the Luche procedure.

For the synthesis of 6,6′−cyclobutyl geminated acyclic nucleosides **78~81** the commercially available cyclobutyl dicarboxylic acid **70** was selected as a starting material. **(Scheme 9)**

Scheme 9. Synthesis of 2,2-cyclobutyl geminated nucleosides



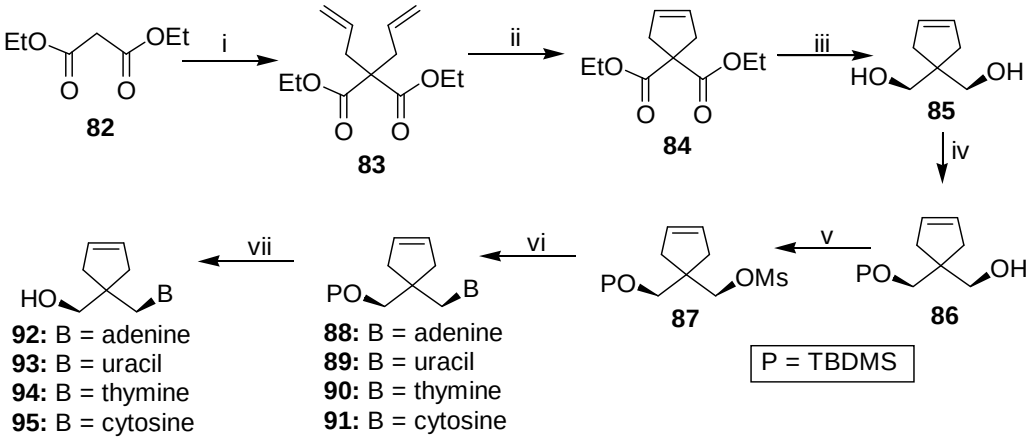
Reagents: i) $LiAlH_4$, THF; ii) TBDMSCl, imidazole, CH_2Cl_2; iii) MsCl, TEA, CH_2Cl_2; iv) Bases, K_2CO_3, 18-*C*-6, DMF; v) TBAF, THF.

The synthetic route is quite simple and straightforward. A reduction of the

carboxylic functional group of the starting material **70**, followed by a mono-silylation of the diol **71** afforded the alcohol derivative **73**. The hydroxyl group of compound **72** was mesylated by treating it with methanesulfonyl chloride (MsCl) in an anhydrous CH_2Cl_2 to give the key intermediate **73**, which was coupled with the natural nucleobases, adenine (A), thymine (T), uracil (U), cytosine (C), under well-known standard nucleophilic substitution conditions (K_2CO_3, 18-C-6, DMF)[141] to give the acyclic nucleoside derivatives **74~77**, respectively. Although a small quantity of the N^7-isomer[142] (less than 8%) of the adenine base was present, they could be readily differentiated [UV (MeOH) λ_{max} 279 nm]. The removal of the *tert*-butyldimethylsilyl (TBDMS) group of compounds **74~77** was accomplished using *tetr*-abutylammonium fluoride (TBAF) to give the final nucleosides **78~81**.

For the synthesis of the 6,6′-cyclopentenyl geminated carboacyclic nucleosides **92~95**, a similar reaction procedure described for synthesizing the nucleosides **78~81** was used. **(Scheme 10)**

Scheme 10. Synthesis of 2,2-cyclopentene geminated nucleosides



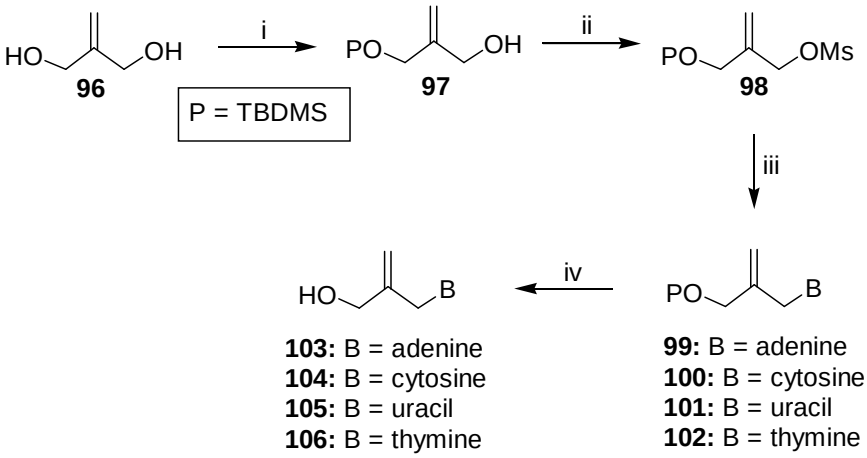
Reagents: i) NaH, allylic bromide, THF; ii) $Cl_2(Cy_3P)_2RuCHC_6H_5$, CH_2Cl_2; iii) $LiAlH_4$, THF; iv) TBDMSCl, imidazole, CH_2Cl_2; v) MsCl, TEA, CH_2Cl_2; vi) Bases, K_2CO_3, 18-*C*-6, DMF; vii) TBAF, THF.

Commercially available diethylmalonate **82** was selected as the starting material. Double allylation of the active methylene group of compound **82** and

ring-closing metathesis (RCM) of the corresponding divinyl **83** provided the cyclic compound **84** in a high yield. The ester functional group of compound **84** was reduced with lithium aluminum hydride (LAH) to give the diol **85**, which was monoprotected using *tert*-butyldimethylchlorosilane to give compound **86**. Compound **86** was subjected to similar reaction conditions as described above (mesylation, base condensation and deprotection) to provide the target nucleosides **92~95**.

For the synthesis of acyclic nucleosides **103~106** a similar reaction procedure described for synthesizing the compounds **78~81** was used. **(Scheme 11)**

Scheme 11. Synthesis of methylene acyclic nucleosides

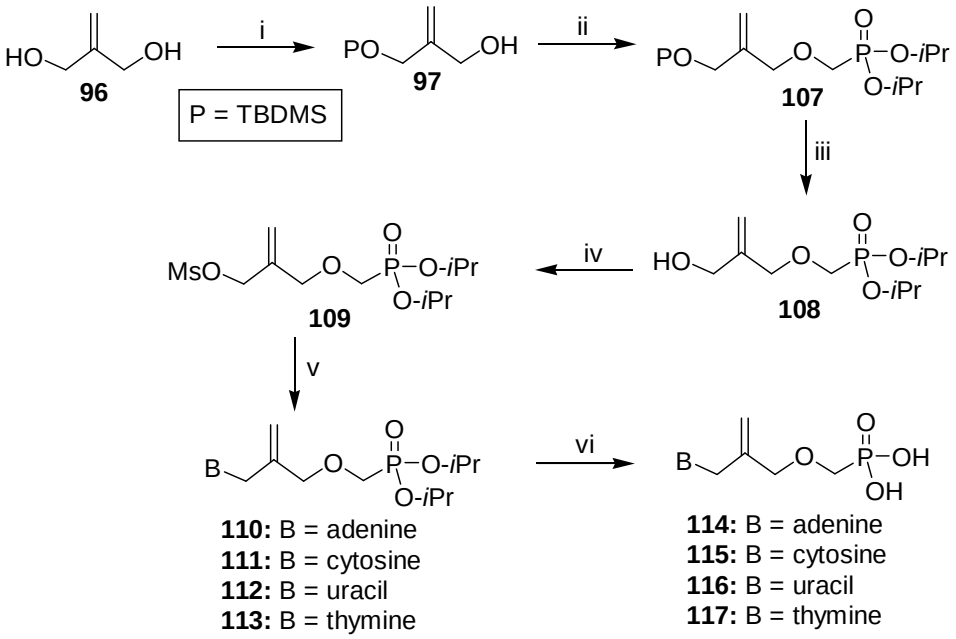


Reagents: i) TBDMSCl, imidazole, CH_2Cl_2; ii) MsCl, TEA, CH_2Cl_2; iii) nucleosidic bases (A,C,U, T), 18-Crown-6, K_2CO_3, DMF; iv) TBAF, THF.

For the synthesis of phosphonic acid nucleosides, the hydroxyl group of **97** was phosphonated by treating them with diisopropyl bromomethylphosphonate in anhydrous DMF to give the phosphonate intermediate **107**. Desilylation and sequential mesylation of corresponding hydroxyl group of **108** gave key intermediate **109**, which was also coupled with nucleosidic base under similar S_N2 substitution conditions to give the acyclic phosphonate nucleoside derivatives **110~113**, respectively. Although a small quantity of the N^7-isomer of **110** (less than 12%) of the adenine base was present, they could be readily

differentiated [UV (MeOH) λ_{max} 279 nm] and also readily separated by column chromatography. Isopropyl groups of phosphonates **110~113** were readily hydrolyzed using trimethylsilyl bromide (CH_3SiBr) to give target nucleoside phosphonic acids **114~117**. **(Scheme 12)**

Scheme 12. Synthesis of methylene acyclic phosphonic acid nucleosides

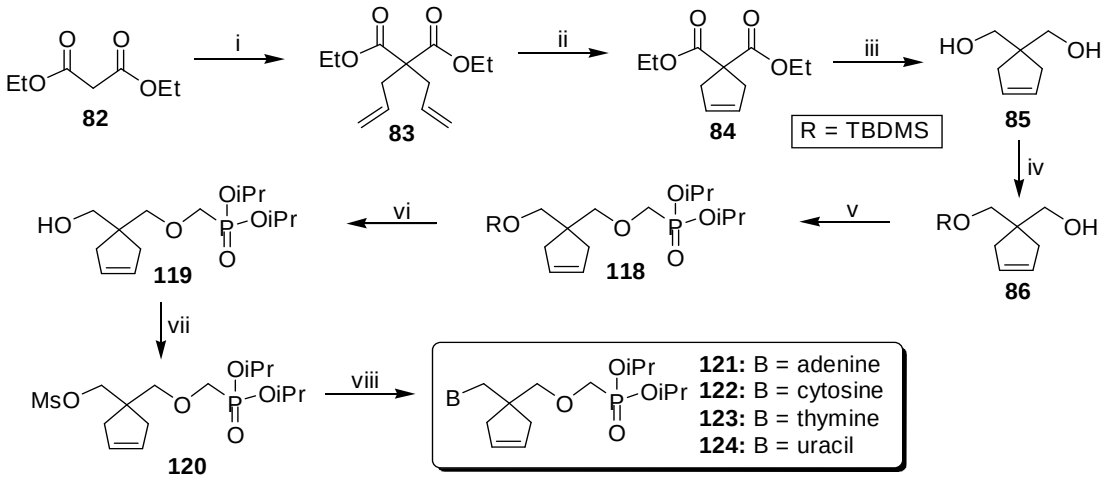


Reagents: i) TBDMSCl, imidazole, CH_2Cl_2; ii) Diisopropyl bromomethylphosphonate, LiO*t*-Bu, LiI, DMF; iii) TBAF, THF; iv) MsCl, TEA, CH_2Cl_2; v) Bases, K_2CO_3, 18-Crown-6, DMF; vi) $(CH_3)_3SiBr$, CH_2Cl_2.

For the synthesis of 1,1-cyclopentenyl geminated acyclic nucleosides **121~124**, Diethyl malonate **82** was selected as starting material. The synthetic route is very simple and straightforward. Double allylation of active methyllene group of **82** and ring-closing metathesis (RCM) of corresponding divinyl **83** provided cyclopentene derivative **84** in a high yield.[143,144] Material of aim nucleosides **121~124** was from cyclopentene **84** using the method described for synthesizing the nucleosides **114~ 117**.

(Scheme 13)

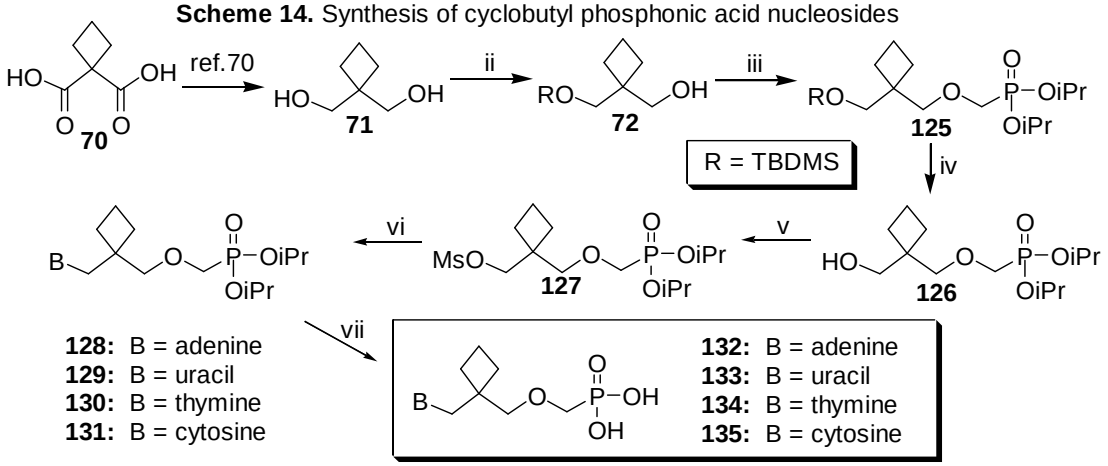
Scheme 13. Synthesis of acyclic phosphonate nucleosides



Reagents: i) NaH, allylic bromide, THF; ii) $Cl_2(Cy_3P)_2RuCHC_6H_5$, CH_2Cl_2; iii) $LiAlH_4$, THF; iv) TBDMSCl, imidazole, CH_2Cl_2; v) Diisopropyl bromomethylphosphonate, LiO*t*-Bu, LiI, DMF; vi) TBAF, THF; vii) MsCl, TEA, CH_2Cl_2; viii) Bases, K_2CO_3, 18-*C*-6, DMF.

For the synthesis of 5′−norcyclobutyl carboacyclic nucleoside phosphonic acids 128~131, a similar reaction procedure described for synthesizing the nucleosides 114~117 was used. The nucleosides 128~131 was accomplished using trimethylsilyl bromide[145] to provide desired nucleoside phosphonic acids 132~135. (Scheme 14)

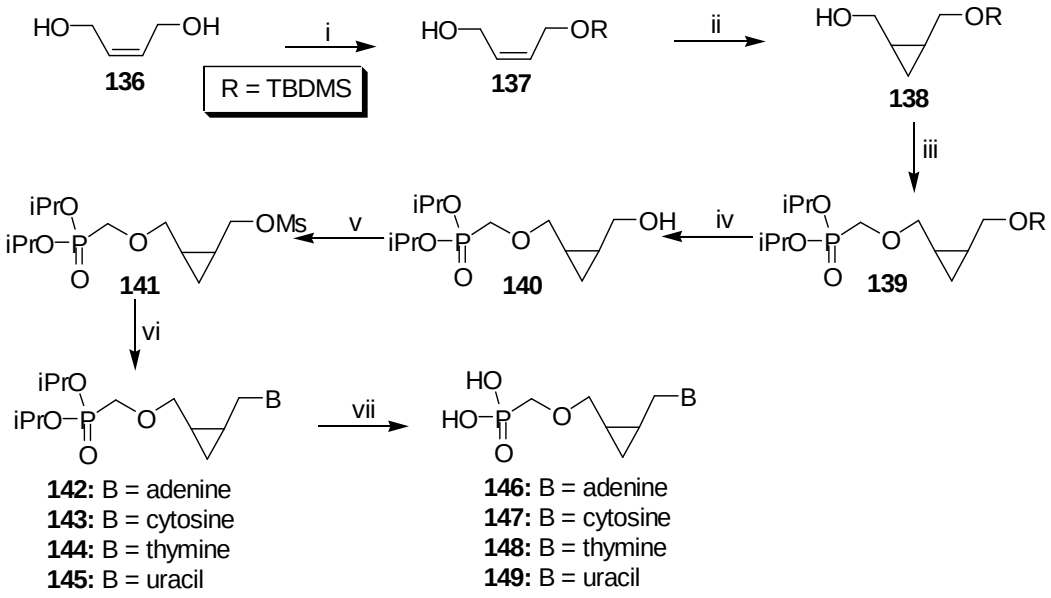
Scheme 14. Synthesis of cyclobutyl phosphonic acid nucleosides



Reagents:i) $LiAlH_4$, THF; ii) TBDMSCl, imidazole, CH_2Cl_2; iii) Diisopropyl bromomethylphosphonate, LiO*t*-Bu, LiI, DMF; iv) TBAF, THF; v) MsCl, TEA, CH_2Cl_2; vi) Bases, K_2CO_3, 18-*C*-6, DMF; vii) $(CH_3)_3SiBr$, CH_2Cl_2.

For the synthesis of target cyclopropyl nucleoside phosphonic acid **146~149**, a similar reaction procedure described for synthesizing the nucleosides **132~135** was used. Among the rest synthesis of cyclopropyl alcohol **138** was from provided the alcohol **137**, which was subjected to the Simmons-Smith carbene cycloaddition condition[146] using $Zn(Et)_2$ and CH_2I_2. **(Scheme 15)**

Scheme 15. Synthesis of cyclopropyl phosphonic acid nucleosides



Reagents: i) TBDMSCl, imidazole, CH_2Cl_2; ii) CH_2I_2, $Zn(Et)_2$, CH_2Cl_2; iii) Diisopropyl bromomethylphosphonate, Li*Ot*-Bu, LiI, DMF; iv) TBAF, THF; v) MsCl, TEA, CH_2Cl_2; vi) Bases, K_2CO_3, 18-*C*-6, DMF; vii) $(CH_3)_3SiBr$, CH_2Cl_2.

Antiviral activity assays were performed using the synthesized nucleosides **78~81**, **92~95**, **103~106**, **114~117**, **121~124**, **132~135**, **146~149** against HIV-1, HSV-1, 2 and HCMV.

The result, the nucleosides **78~81**, **92~95** appears shown in **(Table 2)**, none of the tested compounds showed excellent antiviral activity except for the uracil compound **79**, which exhibited weak anti-HIV activity in the MT-4 cell (EC_{50} = 32.5 μmol). However, the adenine analogue **78** was found to show significant anti-HCMV activity (EC_{50} = 11.2 μmol) without any cytotoxicity up to 100 μmol.

Table 2. The antiviral activities of the synthesized compounds.

	HIV-1 EC_{50}(μM)	HSV-1 EC_{50}(μM)	HSV-2 EC_{50}(μM)	HCMV EC_{50}(μM)	cytotoxicity CC_{50}(μM)
78	>100	>100	>100	11.2 ± 0.8	>100
79	32.5	>100	>100	>100	80 ± 4
80	>100	>100	>100	>100	>100
81	>100	>100	>100	>100	>100
92	>100	>100	>100	78.1 ± 5.2	>100
93	>100	>100	>100	>100	>100
94	>100	>100	>100	>100	>100
95	56.4 ± 4.3	>100	>100	>100	>100
AZT	0.0011±0.0003	ND	ND	ND	1.12±0.04
Ganciclovir	ND	ND	ND	0.76±0.05	>10
acyclovir	ND	0.16±0.02	ND	ND	>100

ND: Not Determined; EC_{50}(μM): Concentration required to inhibit 50% of virus induced cytopathicity; CC_{50}(μM): Concentration required to reduce cell viability by 50%.

And the nucleosides **103~106**, **114~117** appears shown in **(Table 3)**, none of the tested compounds showed excellent antiviral activity except for the uracil nucleotide **116**, which exhibited significant anti-HCMV activity in (EC_{50} = 10.24 μmol) without any cytotoxicity up to 100 μM.

Table 3. The antiviral activities of the synthesized compounds.

	HIV-1 EC_{50}(μM)	HSV-1 EC_{50}(μM)	HSV-2 EC_{50}(μM)	HCMV EC_{50}(μM)	cytotoxicity CC_{50}(μM)
103	>100	>100	>100	68.76	>100
104	>100	>100	>100	>100	>100
105	47.8	>100	>100	>100	>100
106	>100	>100	>100	>100	>100
114	>100	>100	>100	>100	>100

115	>100	>100	>100	>100	>100
116	>100	43.27	>100	10.24	>100
117	>100	>100	>100	54.71	>100
AZT	0.0005	ND	ND	ND	1.10
GCV	ND	ND	ND	0.85	>10
ACV	ND	0.15	ND	ND	>100

ND: Not Determined; EC_{50} (μM): Concentration required to inhibit 50% of virus induced cytopathicity; CC_{50} (μM): Concentration required to reduce cell viability by 50%.

And the nucleosides **121~124** appears shown in **(Table 4)**, any tested compounds did not display antiviral activity except cytosine nucleoside **122** which exhibited moderate anti-HIV activity in MT-4 cell (EC_{50} = 20.5 μmol).

Table 4. The antiviral activities of the synthesized compounds.

	HIV-1 EC_{50}(μg/mL)	HSV-1 EC_{50}(μg/mL)	HSV-2 EC_{50}(μg/mL)	cytotoxicity IC_{50}(μg/mL)
121	>100	>100	>100	>100
122	20.5	>100	>100	>100
123	>100	>100	>100	>100
124	60.0	>100	>100	>100
AZT	0.0009	ND	ND	1.02
ACV	ND	0.98	5.21	250

ND: Not Determined.

And the nucleosides **132~135** appears shown in **(Table 5)**, none of the tested compounds showed antiviral activity except for the cytosine nucleotide **135**, which exhibited moderate anti-HIV activity in the MT-4 cell (EC_{50} = 16.5 μmol).

Table 5. The antiviral activities of the synthesized compounds.

	HIV-1	HSV-1	HSV-2	HCMV	cytotoxicity

	EC_{50}(μM)	EC_{50}(μM)	EC_{50}(μM)	EC_{50}(μM)	CC_{50}(μM)
132	52.7	45.9	>100	>100	>100
133	>100	>100	>100	>100	>100
134	>100	>100	>100	>100	>100
135	16.5	>100	>100	72.1	>100
AZT	0.008	ND	ND	ND	1.15
GCV	ND	ND	ND	0.6	>10
ACV	ND	0.15	ND	ND	>100

ND: Not Determined; EC_{50}(μM): Concentration required to inhibit 50% of virus induced cytopathicity; CC_{50}(μM): Concentration required to reduce cell viability by 50%.

And the nucleosides **146~149** appears shown in **(Table 6)**, only the adenine analogue **146** was found to show moderate activities against HCMV, without significant toxicities to the host cell.

Table 6. The antiviral activities of the synthesized compounds.

	HIV-1 EC_{50} (μg/mL)	HSV-1 EC_{50} (μg/mL)	HCMV EC_{50} (μg/mL)	CoxB3 EC_{50} (μg/mL)	cytotoxicity IC_{50} (μg/mL)
146	>100	>100	22.80	>100	>100
147	>100	>100	>100	>100	>100
148	>100	>100	>100	>100	>100
149	>100	>100	>100	>100	>100
AZT	0.0008	ND	ND	ND	1.0
Ganciclovir	ND	1.34	0.77	ND	>10
Ribavirin	ND	ND	ND	25.43	>300

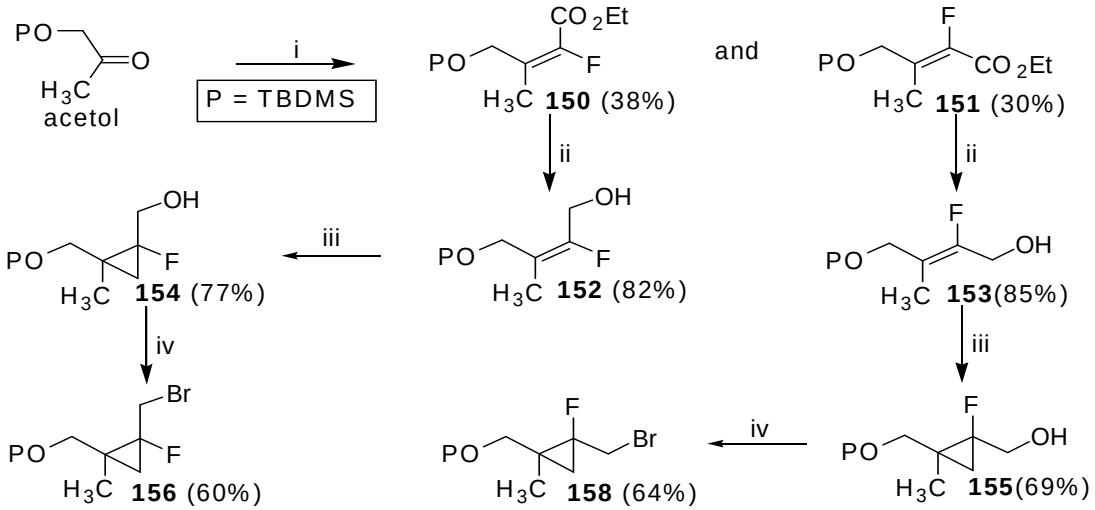
ND: Not Determined

In conclusion, this study performed the synthesis and biological evaluation of novel **78~81**, **92~95**, **103~106**, **114~117**, **121~124**, **132~135**, **146~149** starting

from cyclobutane dicarboxylic acid, 2-methylene-propane-1,3-diol, diethyl malonate and *cis*-2-butene-1,4-diol, respectively. None of the synthesized compounds exhibited significant antiviral activity except for the adenine derivatives **78**, **116**, **146**, which showed reasonable anti-HCMV activity. And cytosine derivative **122**, uracil derivative **79** showed moderate anti-HIV activity.

However, although no excellent antiviral agents could be found in this series, the findings of some antiviral suggest that this class of nucleosides may represent valuable new lead for the development of antiviral agents.

Scheme 16. Synthesis of fluorocyclopropyl bromides



Reagents: i) $(EtO)_2POCHFCO_2Et$, *n*-BuLi, THF; ii) DIBAL-H, CH_2Cl_2; iii) CH_2I_2, $Zn(Et)_2$, CH_2Cl_2; iv) PPh_3, NBS, CH_2Cl_2, rt.

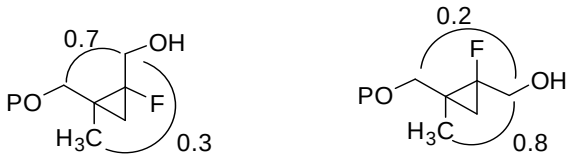
Scheme 16 shows the synthesis of the cyclopropyl compound, which is the key intermediate for the preparation of fluorinated cyclopropyl nucleosides. The fluoroesters **150** and **151** were prepared using similar procedure described elsewhere.[147] The structural determination of the synthesized isomers **150** and **151** was postponed to a latter stage. The reason for the higher reaction product of compound **150** compared with compound **151** is unclear at this stage. Compounds **150** and **151** were subjected to reduction conditions using diisobutyl aluminum hydride (DIBAL-H) to afford the fluoroallylic alcohols, which then underwent a Simmons-Smith reaction[148] with Et_2Zn/ CH_2I_2 to give compounds

154 and **155,** respectively.

A systemic NOE study on the cyclopropane derivatives was performed. On the irradiation of the methyl protons, a relatively strong NOE was observed at the hydroxymethylene protons of compound **155** (0.8%). However, a weak NOE was observed at the hydroxymethylene protons those of compound **154** (0.3%).

(Figure 21)

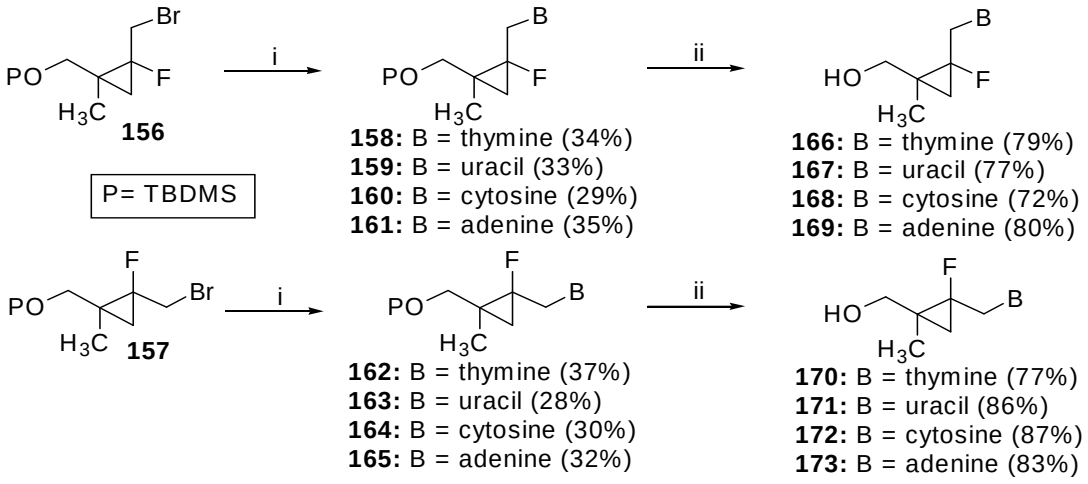
Figure 21. NOE comparisons of *cis*- and *trans*-fluorocyclopropanes



154 (trans) **155** (cis)

The structural determinations of compounds **150** and **151** were readily determined from the results of cyclopropane structures (compounds **154** and **155**). The sugar moiety was alkylated via a nucleophilic substitution reaction (S_N2) by converting the allylic alcohols **154** and **155** to the allylic bromides **156** and **157** in high yield by the sequential addition of NBS to a solution of the alcohols and triphenylphosphine in CH_2Cl_2.[149]

Scheme 17. Synthesis of fluorocyclopropyl nucleosides



Reagents: i) nucleosidic bases, $CsCO_3$, DMF, rt; ii) TBAF, THF, rt.

The condensation of the allylic bromide **156** with the bases (thymine, uracil, cytosine, adenine) in DMF with cesium carbonate as a basic catalyst ($CsCO_3$) afforded the nucleoside derivatives **158~165**. The deprotection of the *tert*-butyldimethylsilyl group using tetrabutylammonium fluoride in THF gave the desired fluorocyclopropyl nucleosides **166~173**. **(Scheme 17)**

Compounds **166~173** were tested against several viruses such as the HIV (MT-4 cells), HSV-1 (Herpes Simplex Virus type 1; CCL81), HSV-2 (Herpes Simplex Virus type 2; CCL-81) cells), and HCMV (Human Cytomegalovirus; AD-169). **(Table 7)** None of the tested compounds showed excellent antiviral activity except against HCMV. Among the compounds tested, the uracil derivative **167** showed the most potent (EC_{50} = 10.61 μg/mL) anti-HCMV activity up to 100 μg/mL without showing any significant toxicity to the host cells when compared with positive control, Ganciclovir (EC_{50} = 1.01 μg/mL, in AD-169).

Table 7. The antiviral activities of the synthesized compounds.

	HIV-1 $EC_{50}(\mu M)$	HSV-1 $EC_{50}(\mu M)$	HSV-2 $EC_{50}(\mu M)$	HCMV $EC_{50}(\mu M)$	cytotoxicity $CC_{50}(\mu M)$
166	89	>100	>100	51.43	>90
167	19.43	>100	>100	10.61	>98
168	>100	>100	>100	>100	>100
169	>100	67	>100	71	>90
170	35	>100	>100	>100	>100
171	>100	>100	>100	43	>100
172	65	>100	>100	>100	>100
173	>100	87	>100	>100	>100
AZT	0.0008	ND	ND	ND	1.2
GCV	ND	1.5	1.5	1.01	>10

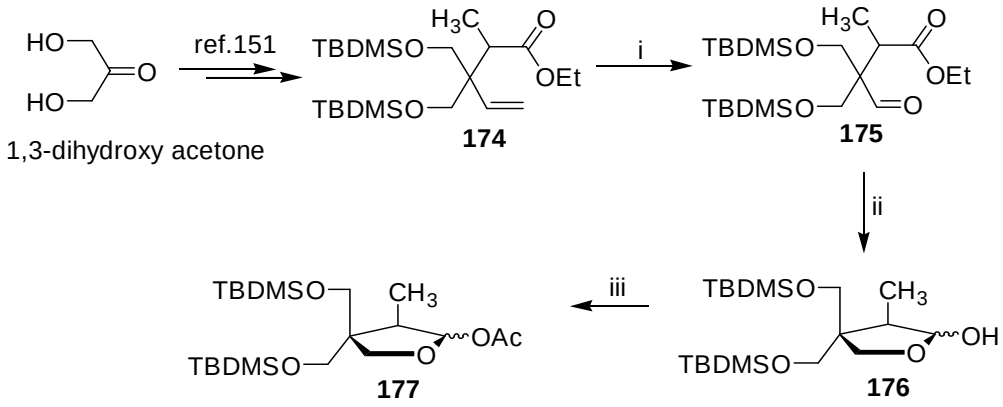
ND: Not Determined; $EC_{50}(\mu M)$: Concentration required inhibiting 50% of virus-induced cytopathicity; CC_{50} (μM): Concentration required to reduce cell viability by 50%.

In conclusion, novel fluorinated cyclopropyl nucleosides **166~173** were successfully synthesized starting from acetol using the Simmons-Smith reaction as a key step. It is interesting to note that the *cis*-like uracil analogue **167** showed higher anti-HCMV activity compared with the *trans*-like derivative **168**, indicating this virus might allow the sugar moiety to serve as a template for phosphorylation as well as for DNA polymerase, which is unlike other viruses.

These compounds were evaluated for their activity against various viruses because the fluorine group might act as a hydrogen bonding acceptor at the active site of their target enzyme. The information obtained in this study will be useful for the development of novel cyclopropyl nucleosides. Studies toward this end as well as to clarify the mechanism are underway. The anti-HCMV activity and cytotoxicity were determined as descryibed elsewhere.[150]

The γ,δ-unsaturated ester derivative **174**, which was readily synthesized from 1,3-dihydroxy acetone using a previously reported method,[151] was selected as the starting compound for the synthesis of the target nucleosides. Ester **174** was treated with ozone in methylene chloride at –78 ℃, followed by the decomposition of the ozonide by dimethylsulfide (DMS) to give the aldehyde **175**. Compound **175** was subsequently reduced using DIBAL-H in toluene at –78 ℃ to give the lactol **176** in 71% yield. The apiose lactol **176** was acetylated in pyridine to furnish the key intermediate **177** as the glycosyl donor. **(Scheme 18)**

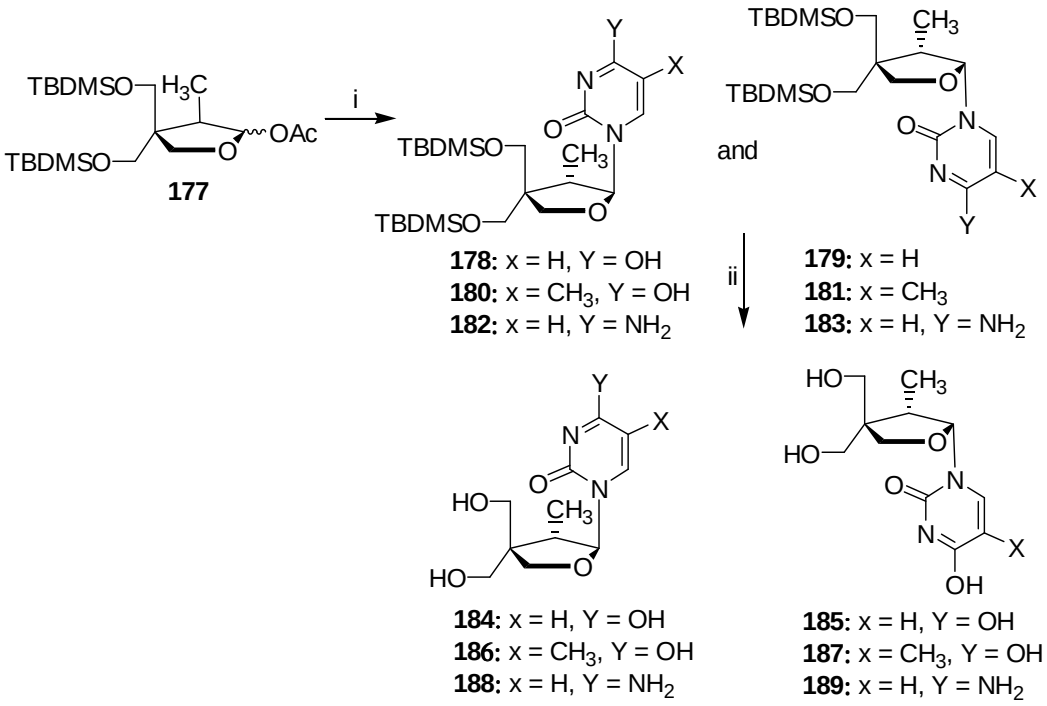
Scheme 18. Synthesis of apiosyl acetate



Reagents: i) O_3/DMS; ii) DIBALH, toluene, -78 ^{o}C; TBAF, THF; iii) Ac_2O, pyridine, rt.

The pyrimidine nucleosides were prepared by condensing compound **177** with the per-*O*-silylated bases of uracil, thymine and cytosine using trimethylsilyl trifluoromethanesulfonates (TMSOTf) as a catalyst in 1,2-dichloroethane (DCE) to give the protected nucleoside **178~183**. The stereochemical assignments of the synthesized compounds were carried out using ^{1}H NMR spectroscopy. The deprotected pyrimidine nucleosides were synthesized from the corresponding nucleoside by a treatment with tetrabutylammonium fluoride. (**Scheme 19**)

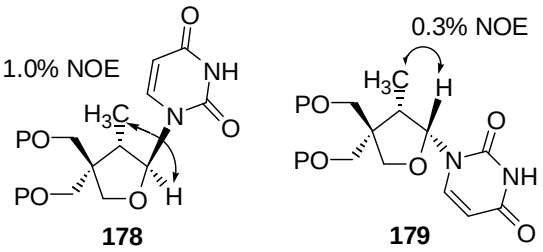
Scheme 19. Synthesis of dually branched pyrimidine nucleosides



Reagents: i) (a) Bases (uracil, thynine, cytosine), HMDS, $(NH_4)_2SO_4$, reflux, overnight; (b) silylated bases, TMSOTf, DCE; ii) TBAF, THF, rt.

A relatively strong cross peak (1.0%) between the proximal hydrogen atoms (anomeric H and CH_3) was found in the NOE spectrum for compound **178**. However, there were weak cross peaks (0.3%) in the spectrum of compound **179**. The stereochemistry of the other nucleoside analogues was determined in a similar manner based on the NOE data. **(Figure 22)**

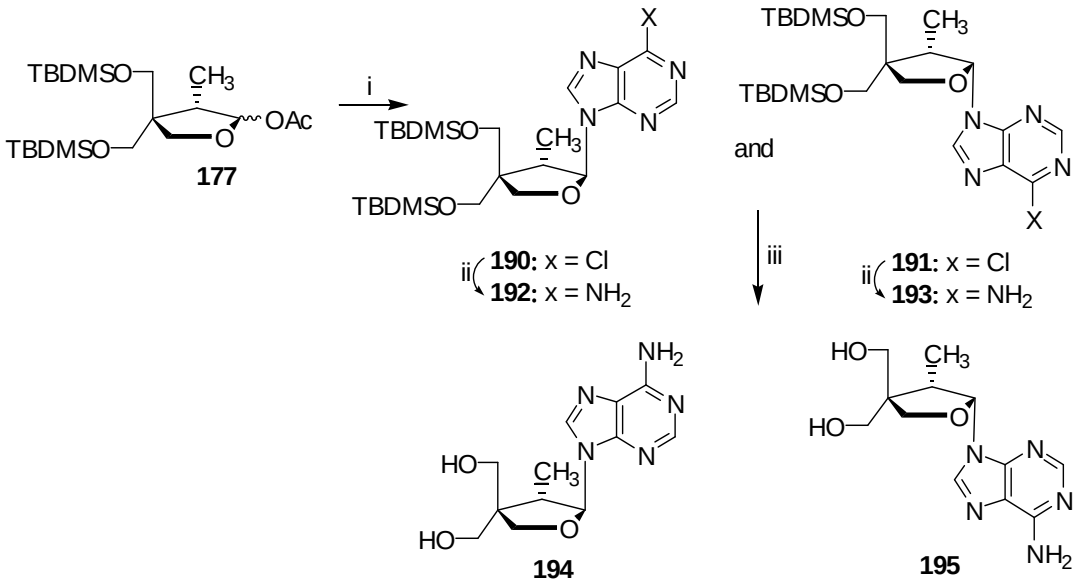
Figure 22. NOE result of uracil derivatives **178**, **179**



Actually, high stereoselectivity was not observed in any glycosidation reactions, which could be anticipated from the planar structures of oxonium ion. The synthesis of the purine nucleoside was carried out by the condensation of compound **177** with silylated 6-chloropurine using TMSOTf as a catalyst in DCE to give the protected 6-chloropurine derivatives **190** and **191**, respectively. These were then treated with ammonia in methanol in a steel bomb at 95~100 ℃ followed by desilylation to give the final adenine nucleosides **194** and **195**.

(Scheme 20)

Scheme 20. Synthesis of dually branched purine nucleosides



Reagents: i) (a) 6-chloropurine, HMDS, $(NH_4)_2SO_4$, reflux, overnight; (b) silylated 6-chloropurine, TMSOTf, DCE; ii) NH_3/MeOH, 95 ^oC-100^o C, overnight; iii) TBAF, THF.

The antiviral evaluation of the synthesized compounds **184~189**, **194**, **195** was performed against several viruses, HIV-1 (MT-4 cells), HSV-1, 2 (CCL-81 cells), and HCMV (AD-169). **(Table 8)** However, the adenine derivative **194** showed weak antiviral activity against HIV-1 (EC_{50} = 10.1 μg/mL) without having any cytotoxicity up to a concentration of 100 μg/mL.

Table 8. Antiviral activity of the synthesized compounds.

	HIV-1 EC_{50}(μg/ml)	HSV-1 EC_{50}(μg/ml)	HSV-2 EC_{50}(μg/ml)	HCMV EC_{50}(μg/ml)	cytotoxicity CC_{50}(μg/ml)
184	>100	66.3	>100	56.7	>100
185	>100	88.9	>100	>100	>100
186	37.1	>100	87.4	67.8	>90
187	>100	56.3	>100	>100	>100
188	76.9	>100	90.2	34.7	>100
189	27.2	>100	>100	>100	>100
194	10.1	32.6	>100	41.6	>100
195	37.5	78.4	>100	78.9	>100
AZT	0.008	ND	ND	ND	1.36
GCV	ND	ND	ND	1.3	>10
ACV	ND	0.25	ND	ND	>100

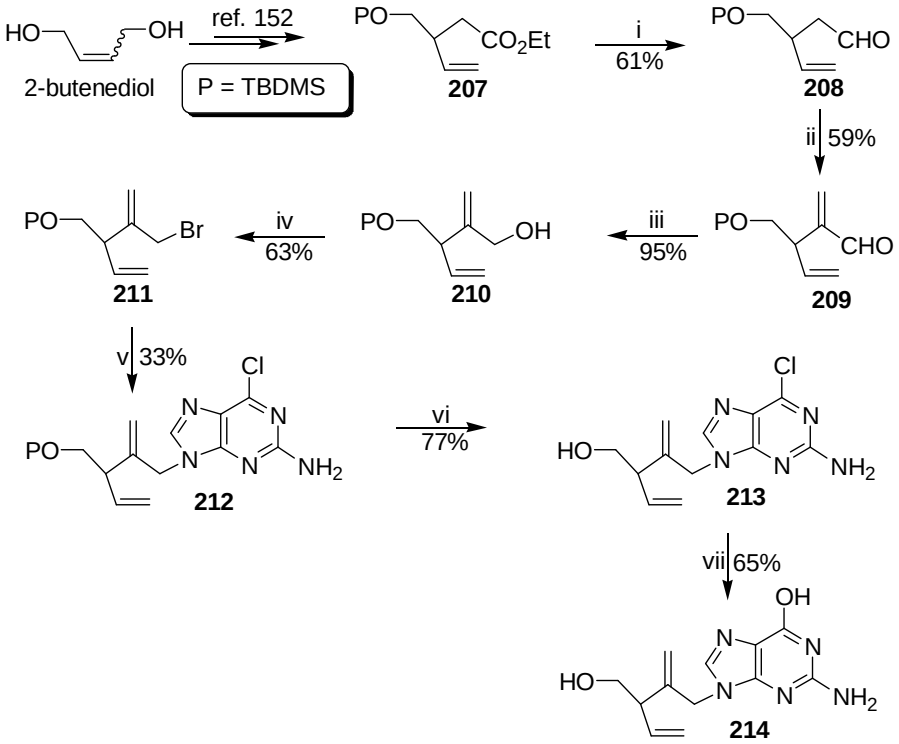
AZT: Azidothymidine; GCV: Ganciclovir; ACV: Acyclovir

ND: Not Determined; EC_{50}(μg/ml): Concentration required to inhibit 50% of the virus induced cytopathicity; CC_{50}(μg/ml): Concentration required to reduce cell viability by 50%; HCMV: Human cytomegalovirus.

In summary, a novel method was developed for synthesizing substituted apiosyl analogues from 1,3-dihydroxyacetone. None of the synthesized compo-unds exhibited significant antiviral activity except for the adenine derivative **194**, which showed reasonable anti- HIV activity. Although we did not find excellent analogue of this class, the information obtained in the present study will be useful for the development of novel nucleoside antiviral agents.

As shown in (Scheme 21), the γ,δ−unsaturated ester 207 was readily synthesized from the commercially available 2−butene−1,4−diol using the reported procedure.[152] The addition of one equivalent of DIBAL−H to a solution of the ester 207 in anhydrous toluene at −78 ℃ gave the reduced aldehyde derivative 208. The treatment of carbonyl 208 with the Eschenmoser salt (methylene−*N*,*N*−dimethylammonium iodide)[153,154] gave α−methylenated aldehyde derivative 209, which was subjected to the Luche reduction procedure ($NaBH_4$/ $CeCl_3 \cdot 7H_2O$)[155,156] using sodium borohydride in the presence of cerium chloride to provide the allylic alcohol 210. Material of aim nucleosides 214 was from allylic alcohol 210 using the method described for synthesizing the nucleosides 166~173.

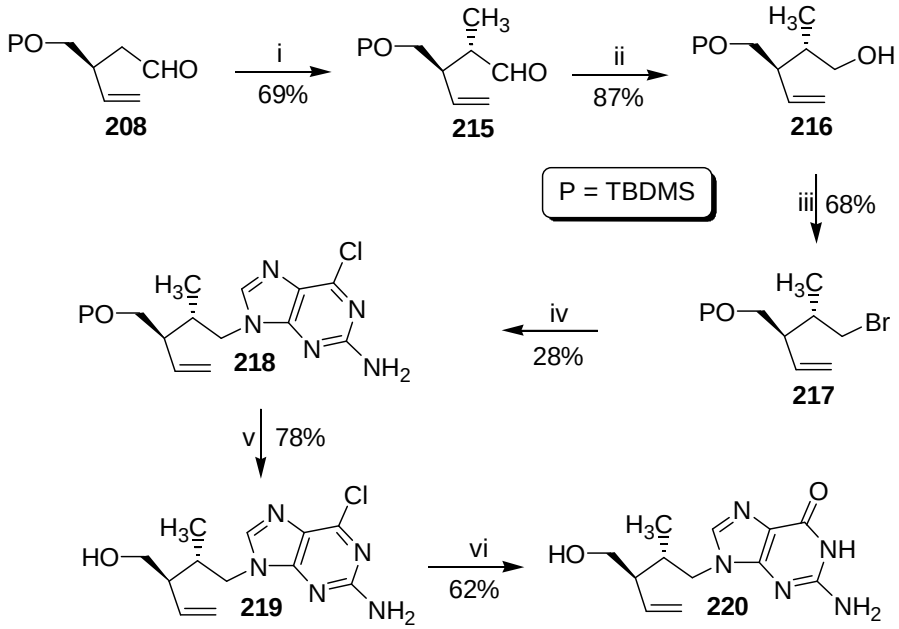
Scheme 21. Synthesis of acyclic entecavir analogue **214**



Reagents: i) DIBAL, toluene, -78 ^{o}C; ii) methylene-*N*,*N*-dimethylammonium iodide, Et_3N, CH_2Cl_2, rt; iii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH; iv) NBS, PPh_3, CH_2Cl_2; v) 2-amino-6-chloropurine, NaH, DMF; vi) TBAF, THF; vii) (a) 2-mercaptoethanol, NaOMe, MeOH; (b) CH_3COOH.

The methylated acyclic guanine derivative **220** was synthesized using a similar reaction procedure described for synthesizing the exo-methylene guanine nucleoside **214**. First, an attempt was made to methylate the carbonyl derivative **208** using the well-known alkylation procedure (LiHMDS/ CH_3I), which was previously developed in our laboratory obtaining **215**.[152] The carbonyl functional group of compound **215** was reduced using the Luche procedure to give the alcohol **216**. Compound **216** was subjected to similar reaction conditions as described above for compound **214** to provide the target nucleoside **220**.
(Scheme 22)

Scheme 22. Synthesis of acyclic abacavir analogue **220**



Reagents: i) LiHMDS, CH_3I, THF, -78 ^oC; ii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH; iii) NBS, PPh_3, CH_2Cl_2; iv) 2-amino-6-chloropurine, NaH, DMF; v) TBAF, THF; vi) (a) 2-mecaptoethanol, NaOMe, MeOH, (b) CH_3COOH.

The anti-HIV activity of the guanine analogues was evaluated in the human T-lymphoid cell lines MT-4. As shown in (Table 9), compounds **214** and **220** exhibited potent anti-HIV-1 activities, but these inhibitory effects were associated with their nonspecific cytotoxicity to MT-4 cells.

Table 9. The anti-HIV activity of the synthesized compounds.

compound	EC_{50}(μg/mL)[a]	CC_{50}(μg/mL)[b]
214	3.57	<3.57
220	5.02	<5.02
AZT	0.004	110

[a] Concentration required to inhibit HIV-1 induced cytopathic effect by 50% in MT-4 cells; [b] Concentration required to reduce the viability of MT-4 cells by 50%.

In view of the outstanding cytotoxic effects of compounds **214** and **220** to the MT-4 cell line, the cytotoxic effects of both compounds were further examined in cancer cell lines. Therefore, based on the cytotoxicity of compounds **214** and **220** (50 μg/mL), their cytotoxic potential was evaluated in cultured human cells. **(Table 10)**

Table 10. The cytotoxicity of compounds **214** and **220** in cultured human cancer cells.

Compounds	Col2[a]	A549[b]
214	51.6[c]	56.1[c]
220	68.8[c]	56.3[c]

[a] human colon carcinoma cells; [b] human lung carcinoma cells; [C] % survival compared with the control cultures at the test concentration of 50 μg/mL

In summary, this study developed a novel method for synthesizing acyclic guanine analogues from simple 2,4-dihydroxy-2-butene. When the synthesized compounds were tested against HIV-1, they showed toxicity that was not related to any anti-HIV activity. Although no good anti-HIV agents were identified in this study, the finding of some anticancer activity in this series means that these compounds and their derivatives have potential as new anti-cancer agents.

CONCLUSION

Currently, over 500 million people worldwide are estimated as the chronic carriers of Virus (HIV, HBV, AIDS) infection person, which comprise about 5% of the world population, most of whom live in Asia and Africa. In the USA, the number of this virus carriers has reached more than one million with about ranks 10,000 new infection occurring annually, which ranks the third in the reported illness behind venereal disease and chickenpox. So recently, several branched nucleosides, acyclic nucleosides, phohonic acid nucleosides were synthesized and evaluated as potent antitumor or antiviral agents. But emerging drug-resistant virus in addition to the toxicity of various drugs was the issue important. Therefore, there is becoming a great deal of the research into the synthesis of a number of structurally modified nucleosides. Does so, From this research the synthesized 1′,4′-doubly branched nucleosides **11**, **21**, **22**, **34~37**, **49~51**, **206** and apiosyl nucleosides **66~69**, **184~189**, **194**, **195** and 5′-norcarboacyclic nucleosides, acyclic nucleosides, phosphonic acid nucleosides, cyclopentene phosphonate nucleosides, acyclic phosphonate nucleoside, fluorocyclopropyl nucleosides, 6′(α)-methylene and 6′(α)-methylated nucleosides **78~81**, **92~95**, **103~106**, **114~117**, **121~124**, **132~135**, **146~ 149**, **166~173**, **214**, **220**. And antivirus medicinal effect of the compounds in order to search accomplished the reaction of chain.

EXPERIMENTAL

The melting points were determined on a Mel-tem II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL JNM-LA 300 spectrometer. The chemical shifts are reported as parts per million (δ), and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet) and dq (doublet of quartet). The UV spectra were obtained using a Beckman DU-7 spectrophotometer. The elemental analyses were performed using an Elemental Analyzer System (EA 1112). TLC was performed on Uniplates (silica gel) that were purchased from Analtech Co. Unless otherwise specified, all the reactions were carried out in a N_2 atmosphere. Dry dichloro methane, benzene and pyridine were obtained by distillation from CaH_2. The dry THF was obtained by distillation from Na and benzophenone immediately before use.

(±)-3-(*t*-Butyldimethylsilyloxymethyl)-3-phenyl-pent-4-enoic acid ethyl ester (2): A solution of allylic alcohol **1** (19.30 g, 69.32 mmol) in triethyl orthoacetate (300 mL) and (0.90 mL) of propionic acid was heated at 130~135 ℃ overnight with stirring to allow for the removal of ethanol. The excess of triethyl orthoacetate was removed by distillation and the residue was purified by silica gel column chromatography (EtOAc/ hexane, 1:15) to give **2** (19.60 g, 81%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.36-7.25 (m, 5H), 6.26 (dd, J = 18.0, 11.1 Hz, 1H), 5.31 (dd, J = 11.4, 1.2 Hz, 1H), 5.16 (dd, J = 17.7, 0.6 Hz, 1H), 4.10-3.99 (m, 4H), 3.00 (s, 2H), 1.18 (t, J = 6.9 Hz, 3H), 0.99 (s, 9H), 0.02 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.51, 143.17, 142.33, 127.82, 127.34, 126.30, 114.34, 67.73, 59.94, 48.70, 39.74, 25.76, 18.19, 14.07, -5.71.

(±)-3-(*t*-Butyldimethylsilanyloxymethyl)-3-phenyl-pent-4-en-1-ol (3): To a solution of **2** (4.50 g, 12.90 mmol) in CH_2Cl_2 (100 mL), DIBAL-H (28.40 mL, 1 M solution in hexane) was added slowly at -78 ℃, and stirred for 1 h at the same temperature. To the mixture, methanol (30 mL) was added. The mixture was stirred at room temperature for 3 h, and the resulting solid was filtered through a celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/ hexane, 1:12)

to give **3** (3.48 g, 88%) as colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.35−7.25 (m, 5H), 6.12 (dd, J = 17.2, 10.3 Hz, 1H), 5.21 (d, J = 17.2 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 4.12 (t, J = 6.2 Hz, 2H), 3.96 (s, 2H), 1.82 (t, J = 6.2 Hz, 2H), 0.89 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 142.45, 140.75, 128.55, 127.30, 113.21, 69.45, 57.64, 45.32, 38.76, 25.89, 18.27, −5.74.

(±)−3−(*t*−Butyldimethylsilyloxymethyl)−3−phenyl−pent−4−enal (4): To a solution of compound **3** (3.58 g, 11.68 mmol) in CH_2Cl_2 (50 mL), 4Å molecure sieves (8.25 g) and PCC (6.75 g, 31.50 mmol) were added slowly at 0 ℃, and stirred overnight at room temperature. To the mixture, excess diethyl ether (400 mL) was then added. The mixture was stirred vigorously for 3 h at the same temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/ hexane, 1:30) to give compound **4** (3.09 g, 87%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.63 (s, 1H), 7.34−7.26 (m, 5H), 6.09 (dd, J = 17.7, 11.1 Hz, 1H), 5.34 (d, J = 11.1 Hz, 1H), 5.16, (d, J = 17.4 Hz, 1H), 3.86 (s, 2H), 2.97 (dq, J = 16.2, 3.0 Hz, 2H), 0.88 (s, 9H), −0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 202.86, 142.38, 141.49, 128.38, 127.33, 126.83, 115.70, 69.28, 49.01, 25.76, 18.19, −5.74.

(*rel*)−(3*R* and 3*S*,5*S*)−5−(*t*−Butyldimethylsilyloxymethyl)−5−phenyl−hepta−1,6−dien−3−ol (5): To cooled (−78 ℃) solution of **4** (7.00 g, 23.10 mmol) in dry THF (120 mL) vinylmagnesium bromide (27.70 mL, 1 M solution in THF) was added slowly. After 2h, a saturated NH_4Cl solution (23 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc (2×150 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/ hexane, 1:10) to give **5** (6.4 g. 84%) as a diastereomeric mixture; ^{1}H NMR ($CDCl_3$) δ 7.36−7.21 (m, 5H), 6.02−5.96 (m, 2H), 5.21−4.96 (m, 4H), 4.11−3.89 (m, 2H), 2.21− 2.07 (m, 2H), 0.88 (m, 9H), 0.04 (m, 6H).

(*rel*)−(1*R*,4*S*)−4−(*t*−Butyldimethylsilyloxymethyl)−4−phenyl−cyclopent−2−enol (6*β*) and (*rel*)−(1*S*,4*S*)−4−(*t*−Butyldimethylsilyloxymethyl)−4−phenyl−cyclopent−2−enol (6*α*): To a solution of **5** (3.10 g, 9.24 mmol) in dry (20 mL)

CH_2Cl_2, second generation Grubbs' catalyst (0.78 mg, 0.92 mmol) in dry CH_2Cl_2 (20 mL) was added under a N_2 atmosphere. The reaction mixture was refluxed overnight, and cooled to room temperature. The mixture was concentrated under vacuum, and the residue was purified by silica gel column chromatography (EtOAc/ hexane, 1:5) to give the cyclopentenol **6*β*** (1.32 g, 47%) and **6*α*** (1.30 g, 46%), as colorless oils, respectively. Only for the characterizations, separation by column chromatography was accomplished; Compound **6*β***: ^{1}H NMR ($CDCl_3$) δ 7.28−7.12 (m, 5H), 6.03−5.97 (m, 2H), 4.60−4.53 (m, 1H), 3.65 (d, J = 9.6 Hz, 1H), 3.50 (d, J = 9.6 Hz, 1H), 2.33 (dd, J = 13.8, 6.9 Hz, 1H), 2.12 (dd, J = 8.1, 6.9 Hz, 1H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.04, 136.44, 135.53, 128.46, 126.61, 75.62, 69.77, 58.70, 45.73, 26.00, 18.62, −5.41. Anal. Calcd for $C_{18}H_{28}O_2Si$: C, 71.00; H, 9.27. Found: C, 70.73; H, 9.08; Compound **6*α***: ^{1}H NMR ($CDCl_3$) δ 7.24−7.19 (m, 5H), 6.12 (d, J = 4.8 Hz, 1H), 5.93 (dd, J = 6.0, 2.1 Hz, 1H), 4.87 (s, 1H), 3.55 (s, 2H), 2.70 (dd, J = 13.2, 7.2 Hz, 1H), 1.83 (dd, J = 18.0, 4.8 Hz, 1H), 0.75 (s, 9H), −0.13, 0.15 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 144.98, 135.74, 135.03, 127.86, 125.51, 75.02, 68.12, 57.65, 43.23, 25.78, 18.14, −5.43; Anal. Calcd for $C_{18}H_{28}O_2Si$: C, 71.00; H, 9.27. Found: C, 71.19; H, 9.11.

(±)−4−(*t*−Butyldimethylsilanyloxymethyl)−4−phenyl−cyclopent−2−enone (7): Compound **7** was synthesized from compound **6*β*** and **6*α*** using the method described for synthesizing compound **4**: yield (80%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 6.0 Hz, 1H), 7.43−7.29 (m, 5H), 6.36 (d, J = 6.0 Hz, 1H), 3.87 (dd, J = 11.1, 9.6 Hz, 2H), 2.85 (d, J = 18.0 Hz, 1H), 2.57 (d, J = 18.0 Hz, 1H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 208.55, 166.68, 142.51, 134.09, 128.59, 126.99, 126.59, 54.83, 46.07, 25.64, 18.07, −5.69.

(*rel*)−(1*R*,4*S*)−4−(*t*−Butyldimethylsilanyloxymethyl)−1−methyl−4−phenyl−cyclopent−2−enol (8*β*) and (*rel*)−(1*S*,4*S*)−4−(*t*−Butyldimethylsilanyloxymethy−l)−1−methyl−4−phenyl−cyclopent−2−enol (8*α*): To a solution of compound **7** (1.60 g, 5.30 mmol) in dry THF (20 mL), methylmagnesium bromide (6.36 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 (200 mL). The organic

layer was washed with brine, dried over $MgSO_4$, filtered, and then evaporated. The residue was purified by silica gel column chromatography (EtOAc/ hexane, 1:15) to give compound **8*β*** (0.59 g, 35%) and **8*α*** (0.61 mg, 37%) as a syrup, respectively; Compound **8*β***: ^{1}H NMR ($CDCl_3$) δ 7.38−7.25 (m, 5H), 5.85 (s, 2H), 3.67 (d, J = 9.6 Hz, 1H), 3.49 (d, J = 9.6 Hz, 1H), 2.31 (d, J = 14.1 Hz, 1H), 2.12 (d, J = 14.1 Hz, 1H), 1.55 (s, 3H), 0.87 (s, 9H), 0.15 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.30, 140.11, 133.80, 128.48, 126.61, 126.38, 81.00, 70.46, 59.00, 51.81, 26.16, 25.69, 18.64, −5.45; Compound **8*α***: ^{1}H NMR ($CDCl_3$) δ 7.42−7.30 (m, 5H), 6.25 (d, J = 5.4 Hz, 1H), 6.01 (d, J = 6.0 Hz, 1H), 3.82 (d, J = 9.6 Hz, 1H), 3.73 (d, J = 9.6 Hz, 1H), 2.55 (d, J = 13.8 Hz, 1H), 2.35 (d, J = 13.8 Hz, 1H), 1.57 (s, 3H), 0.89 (s, 9H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 146.01, 140.72, 134.26, 128.01, 127.83, 126.14, 83.15, 70.60, 58.57, 50.29, 27.70, 25.77, 18.22, −5.65.

(*rel*)−(1'*R*,4'*S*)−9−[4−(*t*−Butyldimethylsilanyloxymethyl)−1−methyl−4−phenyl−cyclopent−2−enyl]−6−chloropyrine (9): To a solution containing **8*α*** (0.34 g, 1.08 mmol), triphenylphosphine (1.69 g, 3.24 mmol) and 6−chloropurine (0.42 mg, 2.68 mmol) in anhydrous dioxane (10 mL) and DMF (7 mL), diisopropyl azodicarboxylate (0.59 mL) was added dropwise at –20 ℃ for 30 min. under nitrogen. The reaction mixture was stirred for 2.5 h at –20 ℃ under nitrogen. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/ hexane, 1:15) to give compound **9** (0.14 mg, 28%): UV (MeOH) λ_{max} 266.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1H), 7.89 (s, 1H), 7.34−7.26 (m, 5H), 6.53 (d, J = 5.4 Hz, 1H), 6.30 (d, J = 5.4 Hz, 1H), 3.75 (d, J = 6.9 Hz, 2H), 2.04 (dd, J = 12.6, 8.6 Hz, 2H), 1.57 (s, 3H), 0.90 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 152.56, 151.32, 150.93, 146.54, 141.97, 136.45, 132.88, 128.31, 126.61, 125.97, 71.51, 70.14, 59.23, 47.23, 27.16, 25.80, 18.45, −5.58; Anal. Calcd for $C_{24}H_{31}ClN_4OSi$: C, 63.34; H, 6.87; N, 12.31. Found: C, 63.12; H, 6.90; N, 12.45.

(*rel*)−(1'*R*,4'*S*)−9−[4−(*t*−Butyldimethylsilanyloxymethyl)−1−methyl−4−phenyl−cyclopent−2−enyl] adenine (10): Compound **9** (111.50 mg, 0.35 mmol) was dissolved in saturated methanolic ammonia (10 mL) and the resulting solution was stirred overnight at 95~100 ℃ in a steel bomb. After removing the reaction

solvent, the residue was purified by silica gel column chromatography (EtOAc/ hexane/ MeOH, 1:3:0.4) to give compound **10** (106.70 mg, 70%): UV (MeOH) λ_{max} 260.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1H), 8.11 (s, 1H), 7.30−7.22 (m, 5H), 6.21 (d, J = 5.4 Hz, 1H), 5.90 (d, J = 5.4 Hz, 1H), 3.66 (d, J = 10.6 Hz, 2H), 2.01 (d, J = 10.2 Hz, 1H), 1.75 (dd, J = 11.8, 8.6 Hz, 1H), 1.48 (s, 3H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.65, 152.56, 150.71, 146.67, 141.97, 137.66, 132.66, 128.31, 127.65, 126.34, 118.34, 71.67, 69.23, 58.34, 46.89, 26.76, 25.76, 18.67, −5.71; Anal. Calcd for $C_{24}H_{33}N_5OSi$: C, 66.17; H, 7.64; N, 16.08. Found: C, 66.04; H, 7.48; N, 15.77.

(*rel*)−(1'*R*,4'*S*)−9−[4−(Hydroxymethyl)−1−methyl−4−phenyl−cyclopent−2−enyl] adenine (11): To a solution of compound **10** (152.40 mg, 0.35 mmol) in THF (10 mL) at 0℃, TBAF (0.70 mL, 1 M solution in THF) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was purified by silica gel column chromatography (MeOH/ CH_2Cl_2, 1:5) to give compound **11** (78.70 mg, 70%) as a white solid: mp 170−173 ℃; UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.42 (s, 1H), 8.07 (s, 1H), 7.32−7.21 (m, 5H), 6.25 (d, J = 5.6 Hz, 1H), 5.99 (d, J = 5.4 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 3.87 (d, J = 10.6 Hz, 1H), 3.65 (d, J = 10.6 Hz, 1H), 2.04 (d, J = 9.8 Hz, 1H), 1.80 (d, J = 9.8 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (DMSO−d_6, 75 MHz) δ 154.97, 152.23, 149.65, 147.89, 142.54, 138.40, 133.45, 128.67, 127.78, 127.12, 126.11, 119.20, 70.56, 68.91, 59.67, 46.72, 27.82; Anal. Calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.36; H, 6.10; N, 21.87.

(±)−4−(*t*−Butyldimethylsilanyloxymethyl)−4−methyl−hex−5−en−2−ol (13): Compound **13** was synthesized from compound **12** using the method described for synthesizing compound **8**: yield (80%) as a diasteromeric mixture; ^{1}H NMR ($CDCl_3$) δ 5.98−5.58 (m, 1H), 5.72−5.61 (m, 1H), 5.04−4.90 (m, 4H), 3.90 (m, 1H), 3.88 (m, 3H), 3.46−3.31 (m, 5H), 1.58−1.38 (m, 4H), 1.08 (s, 3H), 0.97 (s, 3H), 0.83 (s, 18H), 0.23 (s, 6H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.63, 144.05, 113.32, 112.13, 71.03, 70.56, 64.40, 63.81, 48.74, 41.33, 41.14, 25.81, 24.51, 22.74, 20.61, 18.29, −5.54.

(±)−4−(*t*−Butyldimethylsilanyloxymethyl)−4−methyl−hex−5−en−2−one(14): Compound **14** was synthesized from compound **13** using the method described

for synthesizing compound **4**: yield (89%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.95 (dd, J = 17.7, 11.1 Hz, 1H), 5.04 (d, J = 10.5 Hz, 1H), 4.95 (d, J = 16.2 Hz, 1H), 3.46 (d, J = 8.8 Hz, 1H), 3.37 (d, J = 8.8 Hz, 1H), 2.51 (d, J = 14.7 Hz, 1H), 2.43 (d, 8.7 Hz, 1H), 2.09 (s, 3H), 1.05 (s, 3H), 0.86 (s, 9H), 0.21 (s, 6H); ^{13}C ($CDCl_3$) δ 208.43, 143.57, 112.95, 69.90, 49.75, 41.58, 32.11, 25.84, 20.79, 18.26, −5.56; Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.71; H, 11.12.

(±)−5−(*t*−Butyldimethylsilanyloxymethyl)−3,5−dimethyl−hepta−1,6−dien−3−ol (15): Compound **15** was synthesized from compound **14** using the method described for synthesizing compound **5**: yield (72%) as a diasteromeric mixture; ^{1}H NMR ($CDCl_3$) δ 6.02−5.84 (m, 2H), 4.96−4.22 (m, 4H), 3.51−3.28 (m, 2H), 1.80−1.61 (m, 2H), 1.16 (s, 3H), 0.97 (s, 3H), 0.81 (s, 9H), 0.21 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 146.83, 146.10, 145.12, 112.50, 111.91, 110.27, 73.20, 72.87, 71.09, 70.21, 51.38, 50.81, 42.11, 31.57, 31.32, 25.87, 23.56, 23.19, 18.35, −5.52.

(*rel*)−(1*S*,4*S*)−4−(*t*−Butyldimethylsilyloxymethyl)−1,4−diethylcyclopent−2−enol (16*α*); and (*rel*)−(1*R*,4*S*)−4−(*t*−Butyldimethylsilyloxymethyl)−1,4−dimethylcyclopent−2−enol (16*β*): Compounds **16*α*** and **16*β*** was synthesized from compound **15** using the method described for synthesizing compound **6**: yield **16*α*** (41%), **16*β*** (28%); Compound **16*α***: ^{1}H NMR ($CDCl_3$) δ 5.66 (d, J = 5.1 Hz, 1H), 5.29 (d, J = 5.4 Hz, 1H), 3.33 (dd, J = 11.7, 9.6 Hz, 2H), 1.87 (d, J = 14.1 Hz, 1H), 1.63 (d, J = 14.2 Hz, 1H), 1.31 (s, 3H), 0.93 (s, 3H), 0.81 (s, 9H), 0.31 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.61, 137.84, 81.55, 69.95, 51.37, 50.53, 26.37, 26.04, 23.71, 18.61, −5.52; Compound **16*β***: ^{1}H NMR ($CDCl_3$) δ 5.60 (s, 2H), 3.34 (dd, J = 15.6, 9.3 Hz, 2H), 1.99 (d, J = 18.8 Hz, 1H), 1.64 (d, J = 14.1 Hz, 1H), 1.37 (s, 3H), 1.11 (s, 3H), 0.86 (s, 9H), 0.22 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 140.09, 136.50, 83.55, 70.70, 51.37, 51.06, 49.78, 28.75, 25.89, 25.17, 18.31, −5.46.

(*rel*)−(1'*R*,4'*S*)−9−[4−(*t*−Butyldimethylsilanyloxymethyl)−1,4−dimethylcyclopent−2−enyl]−6−chloropurine (17): Compound **17** was synthesized from compound **16*α*** using the method described for synthesizing compound **9**: yield (17%): UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 1H), 8.11 (s, 1H),

5.74 (d, J = 5.2 Hz, 1H), 5.41 (d, J = 5.4 Hz, 1H), 3.56 (dd, J = 12.0, 9.2 Hz, 2H), 1.82 (d, J = 13.6 Hz, 1H), 1.61 (d, J = 12.8 Hz, 1H), 1.34 (s, 3H), 0.99 (s, 3H), 0.87 (s, 9H), 0.1 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 152.45, 151.12, 149.45, 141.81, 137.45, 136.42, 69.23, 62.76, 52.81, 49.71, 26.76, 25.82, 23.66, 18.43, −5.57.

(*rel*)−(1'*R*,4'*S*)−9−[4−(*t*−Butyldimethylsilanyloxymethyl)−1,4−dimethylcyclopent−2−enyl] adenine (18): Compound **18** was synthesized from compound **17** using the method described for synthesizing compound **10**: yield (75%): UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 7.94 (s, 1H), 5.79 (d, J = 5.4 Hz, 1H), 5.44 (d, J = 5.2 Hz, 1H), 3.66 (d, J = 11.2 Hz, 1H), 3.42 (d, J = 11.0 Hz, 1H), 1.87 (d, J = 12.2 Hz, 1H), 1.71 (d, J = 11.8 Hz, 1H), 1.36 (s, 3H), 0.98 (s, 3H), 0.88 (s, 9H), 0.2 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.34, 152.77, 150.56, 141.72, 137.56, 136.23, 119.31, 68.56, 60.92, 52.72, 50.76, 26.56, 25.76, 23.71, 18.56, −5.56.

(*rel*)−(1'*R*,4'*S*)−1−[4−(*t*−Butyldimethylsilanyloxymethyl)−1,4−dimethylcyclopent−2−enyl]−N^3−benzoyl thymine (19): Compound **19** was synthesized from compound **16*α*** and N^3−benzoyl thymine using the method described for synthesizing compound **9**: yield (35%): UV (MeOH) λ_{max} 254.5 nm; ^{1}H NMR ($CDCl_3$) δ 7.88−7.41 (m, 6H), 5.89 (d, J = 5.2 Hz, 1H), 5.56 (d, J = 5.4 Hz, 1H), 3.50 (dd, J = 11.8, 8.8 Hz, 2H), 1.90 (d, J = 12.2 Hz, 1H), 1.73 (d, J = 12.4 Hz, 1H), 1.40 (s, 3H), 1.26 (s, 3H), 0.98 (s, 3H), 0.85 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.76, 163.31, 151.23, 138.84, 137.74, 134.65, 130.33, 107.34, 69.67, 62.23, 53.65, 48.32, 26.54, 25.61, 23.81, 18.59, 12.14, −5.43.

(*rel*)−(1'*R*,4'*S*)−1−[4−(*t*−Butyldimethylsilanyloxymethyl)−1,4−dimethylcyclopent−2−enyl] thymine (20): To a stirred solution of compound **19** (194 mg, 02 mmol) in MeOH (5 mL), NaOMe (0.30 mL, 1 M solution in MeOH) was added at 0 ℃ under nitrogen and stirred overnight. The reaction mixture was neutralized with acetic acid and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/ hexane/ MeOH, 2:1:0.3) to give compound **20** (151 mg, 70%): UV (MeOH) λ_{max} 268.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.20 (br s, 1H), 7.31 (s, 1H), 5.90 (d, J = 5.8 Hz, 1H), 5.61 (d, J = 6.0 Hz, 1H), 3.56 (d, J = 9.6 Hz, 1H), 3.42 (d, J = 9.8 Hz, 2H), 1.92 (d, J = 9.2 Hz, 1H),

1.74 (d, J = 10.4 Hz, 1H), 1.78 (s, 3H), 1.45 (s, 3H), 1.02 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.07, 151.72, 142.56, 108.55, 67.54, 60.32, 51.87, 47.32, 26.71, 25.34, 23.77, 18.43, 11.89, −5.71.

(*rel*)−(1'*R*,4'*S*)−9−[4−(Hydroxymethyl)−1,4−dimethylcyclopent−2−enyl] adenine (21): Compound **21** was synthesized from compound **18** using the method described for synthesizing compound **11**: yield (69%) as a solid: mp 178~180 ℃; UV (H_2O) λ_{max} 262.5 nm; ^{1}H NMR (DMSO−d_6) δ 8.52 (s, 1H), 8.20 (s, 1H), 5.58 (d, J = 5.2 Hz, 1H), 5.38 (d, J = 5.4 Hz, 1H), 4.82 (t, J = 5.0 Hz, 1H), 3.42−3.31 (dd, J = 12.0, 9.2 Hz, 2H), 2.46 (d, J = 12.2 Hz, 1H), 2.32 (d, J = 12.6 Hz, 1H), 1.76 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (DMSO−d_6) δ 155.66, 151.98, 150.12, 142.45, 138.35, 136.54, 119.61, 68.87, 61.72, 52.78, 47.77, 26.27, 23.67; Anal. Calcd for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 21.01. Found: C, 60.35; H, 6.10; N, 26.82.

(*rel*)−(1'*R*,4'*S*)−9−[4−(Hydroxymethyl)−1,4−dimethylcyclopent−2−enyl] thymine (22): Compound **22** was synthesized from compound **20** using the method described for synthesizing compound **11**: yield (65%) as a solid: mp 168~170 ℃; UV (H_2O) λ_{max} 267.5 nm; ^{1}H NMR (DMSO−d_6) δ 11.55 (br s, 1H), 7.46 (s, 1H), 5.89 (d, J = 5.4 Hz, 1H), 5.64 (d, J = 5.2 Hz, 1H), 4.81 (t, J = 5.2 Hz, 1H), 3.45 (dd, J = 11.8, 8.9 Hz, 2H), 2.50 (d, J = 12.4 Hz, 1H), 2.13 (d, J = 11.8 Hz, 1H), 1.41 (s, 3H), 1.24 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (DMSO−d_6) δ 152, 151.78, 139.12, 138.22, 136.24, 105.92, 68.23, 62.65, 52.76, 47.76, 26.73, 23.41, 11.88; Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.47; H, 7.11; N, 11.02.

(±)−4,4−*Bis*−(*t*−butyldimethylsilanyloxymethyl)−hex−5−en−2−ol(24): Compound **24** was synthesized from compound **23** using the method descrybed for synthesizing compound **8**: yield (84%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.71 (dd, J = 18.0, 11.1 Hz, 1H), 5.07 (d, J = 11.4 Hz, 1H), 4.96 (d, J = 17.7 Hz, 1H), 3.90 (m, 1H), 3.60 (dd, J = 12.6, 9.9 Hz, 2H), 3.40 (s, 2H), 1.56−1.45 (m, 2H), 1.10 (d, J = 6.3 Hz, 3H), 0.82 (s, 18H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 141.62, 114.44, 66.98, 65.51, 63.59, 64.07, 43.72, 25.85, 24.46, 18.25, −5.58.

(±)-4,4-*Bis*-(*t*-butyldimethylsilanyloxymethyl)-hex-5-en-2-one (25): Compound **25** was synthesized from compound **24** using the method descrybed for synthesizing compound **4**: yield (80%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.82 (dd, J = 18.0, 11.4 Hz, 1H), 5.09 (d, J = 8.7 Hz, 1H), 5.01 (d, J = 18.0 Hz, 1H), 3.56 (dd, J = 12.4, 9.6 Hz, 4H), 2.52 (s, 2H), 2.09 (s, 3H), 0.84 (s, 18H), 0.03 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 207.97, 140.38, 114.17, 64.79, 45.15, 32.02, 25.64, 18.22, −5.65.

(±)-5,5-*Bis*-(*t*-butyldimethylsilanyloxymethyl)-3-methyl-hepta-1,6-dien-3-ol (26): Compound **26** was synthesized from compound **25** using the method described for synthesizing compound **5**: yield (78%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.95 (dd, J = 17.4, 10.8 Hz, 1H), 5.72 (dd, J = 18.0, 10.5 Hz, 1H), 5.25 (d, J = 17.1 Hz, 1H), 5.04 (d, J = 11.4 Hz, 1H), 4.89 (t, J = 9.6 Hz, 2H), 3.50−3.40 (m, 4H), 1.78 (d, J = 14.7 Hz, 1H), 1.69 (d, J = 14.7 Hz, 1H), 1.18 (s, 3H), 0.84 (s, 18H), 0.04 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 146.82, 142.69, 113.91, 110.16, 74.79, 66.36, 65.99, 65.74, 46.58, 45.89, 31.35, 25.72, 21.96, 20.71, 18.35, −5.50.

(±)-4,4-*Bis*-(*t*-butyldimethylsilanyloxymethyl)-1-methylcyclopent-2-enol (27): Compound **27** was synthesized from compound **26** using the method described for synthesizing compound **6**: yield (90%); ^{1}H NMR ($CDCl_3$) δ 5.73 (d, J = 5.7 Hz, 1H), 5.49 (d, J = 5.4 Hz, 1H), 3.60 (d, J = 9.3 Hz, 1H), 3.51 (d, J = 9.3 Hz, 1H), 3.39 (t, J = 9.3 Hz, 1H), 3.34 (d, J = 9.3 Hz, 1H), 1.75 (d, J = 13.8 Hz, 1H), 1.61 (d, J = 14.1 Hz, 1H), 0.86 (s, 18H), 0.03 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 139.82, 134.37, 80.97, 68.17, 67.11, 56.93, 46.77, 25.77, 18.57, 18.14, −5.57.

(±)-9-[4,4-*Bis*-(*t*-butyldimethylsilanyloxymethyl)-1-methylcyclopent-2-enyl]-6-chloropurine (28): Compound **28** was synthesized from compound **27** using the method described for synthesizing compound **9**: yield (27%) as a yellow oil: UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.86 (s, 1H), 8.22 (s, 1H), 5.83 (s, 1H), 5.45 (s, 1H), 3.85 (d, J = 11.4 Hz, 1H), 3.69 (d, J = 11.2 Hz, 1H), 3.43 (d, J = 9.3 Hz, 1H), 3.18 (d, J = 9.4 Hz, 1H), 2.44 (d, J = 18.0 Hz, 1H), 2.23 (d, J = 18.0 Hz, 1H), 1.92 (s, 3H), 0.87 (s, 18H), 0.04 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 152.23, 151.72, 150.93, 144.21, 141.48, 133.35, 72.15, 65.93,

65.70, 58.90, 45.07, 27.62, 25.65, 18.57, −5.61.

(±)−9−[4,4−*Bis*−(*t*−butyldimethylsilanyloxymethyl)−1−methylcyclopent−2−enyl] adenine (29): Compound **29** was synthesized from compound **28** using the method described for synthesizing compound **10**: yield (78%): UV (MeOH) λ_{max} 267.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 7.96 (s, 1H), 5.50 (s, 1H), 5.40 (s, 1H), 3.34 (d, J = 10.5 Hz, 1H), 3.19 (d, J = 10.2 Hz, 1H), 2.39 (d, J = 17.7 Hz, 1H), 2.23 (d, J = 17.7 Hz, 1H), 1.88 (s, 3H), 0.89 (s, 18H), 0.05 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 156.34, 152.41, 147.01, 145.05, 122.33, 66.93, 62.91, 53.74, 52.86, 41.87, 27.43, 25.42, 18.60, −5.51.

(±)−1−[4,4−*Bis*−(*t*−butyldimethylsilanyloxymethyl)−1−methylcyclopent−2−enyl]−N^3−benzoyl thymine (30): Compound **30** was synthesized from compound **27** and N^3−benzoyl thymine using the method described for synthesizing compound **9**: yield (31%): UV (MeOH) λ_{max} 254.5 nm; ^{1}H NMR ($CDCl_3$) δ 7.90−7.43 (m, 6H), 5.99 (d, J = 5.4 Hz, 1H), 5.84 (d, J = 5.4 Hz, 1H), 3.55−3.36 (m, 4H), 2.21 (d, J = 17.2 Hz, 1H), 2.13 (d, J = 17.4 Hz, 1H), 1.92 (s, 3H), 1.27 (s, 3H), 0.87 (s, 18H), 0.06 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 169.51, 163.09, 150.73, 137.84, 134.74, 133.17, 130.33, 129.08, 108.76, 74.78, 62.43, 61.78, 57.86, 27.83, 25.84, 12.69, −5.54.

(±)−1−[4,4−*Bis*−(*t*−butyldimethylsilanyloxymethyl)−1−methylcyclopent−2−enyl]−N^3−benzoyl uracil (31): Compound **31** was synthesized from compound **27** and N^3−benzoyl uracil using the method described for synthesizing compound **9**: yield (21%): UV (MeOH) λ_{max} 253.0 nm; ^{1}H NMR ($CDCl_3$) δ 7.85−7.40 (m, 6H), 5.97 (d, J = 5.4 Hz, 1H), 5.82 (d, J = 5.4 Hz, 1H), 5.72 (d, J = 8.0 Hz, 2H), 3.62−3.41 (m, 4H), 2.22 (d, J = 17.6 Hz, 1H), 2.11 (d, J = 17.4 Hz, 1H), 1.90 (s, 3H), 0.86 (s, 18H), 0.04 (s, 12H), ^{13}C NMR ($CDCl_3$) δ 168.17, 162.09, 150.12, 134.23, 133.17, 131.78, 128.61, 107.62, 74.78, 64.26, 62.91, 55.21, 26.99, 25.45, 18.72, −5.40.

(±)−1−[4,4−*Bis*−(*t*−butyldimethylsilanyloxymethyl)−1−methylcyclopent−2−enyl] thymine (32): Compound **32** was synthesized from compound **30** using the method described for synthesizing compound **20**: yield (60%): UV (MeOH) λ_{max} 270.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.14 (br, s, 1H), 7.25 (s, 1H), 5.96 (d, J = 6.0 Hz, 1H), 5.78 (d, J = 6.0 Hz, 1H), 3.54 (d, J = 9.3 Hz, 1H), 3.45 (d, J = 10.5 Hz,

2H), 3.35 (d, J = 9.6 Hz, 1H), 2.28 (d, J = 14.4 Hz, 1H), 2.09 (d, J = 14.4 Hz, 1H), 1.90 (s, 3H), 1.55 (s, 3H), 0.91 (s, 18H), 0.03 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 166.87, 153.65, 140.54, 138.21, 133.48, 108.55, 74.06, 66.21, 65.93, 57.73, 27.22, 25.84, 18.28, 12.57, −5.60.

(±)−1−[4,4−*Bis*−(*t*−butyldimethylsilanyloxymethyl)−1−methylcyclopent−2−enyl] uracil (33): Compound **33** was synthesized from compound **31** using the method described for synthesizing compound **20**: yield (66%): UV (MeOH) λ_{max} 267.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.21 (br, s, 1H), 7.49 (d, J = 6.6 Hz, 1H), 5.98 (d, J = 5.8 Hz, 1H), 5.86 (d, J = 6.6 Hz, 1H), 5.78 (d, J = 5.8 Hz, 1H), 3.57−3.36 (m, 4H), 2.27 (d, J = 15.4 Hz, 1H), 2.01 (d, J = 15.2 Hz, 1H), 1.94 (s, 3H), 0.88 (s, 18H), 0.04 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 166.87, 157.29, 143.72, 137.22, 131.67, 108.89, 75.16, 65.78, 65.81, 57.23, 27.02, 25.45, 18.81, −5.63.

(±)−9−[4,4−*Bis*−(hydroxymethyl)−1−methylcyclopent−2−enyl]−6−chloropurine (34): Compound **34** was synthesized from compound **28** using the method described for synthesizing compound **11**: yield (66%) as a white solid: mp 170~172 ℃; UV (H_2O) λ_{max} 266.5 nm; ^{1}H NMR (DMSO−d_6) δ 8.72 (s, 1H), 8.12 (s, 1H), 5.81 (d, J = 3.4 Hz, 1H), 5.42 (d, J = 3.4 Hz, 1H), 5.01−4.90 (dr, s, 2H), 3.55−3.28 (m, 4H), 2.47 (d, J = 16.5 Hz, 1H), 2.15 (d, J = 16.0 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (DMSO−d_6) δ 152.17, 151.68, 151.26, 144.30, 143.63, 140.98, 133.45, 73.25, 66.68, 64.31, 55.21, 46.37, 27.25.

(±)−9−[4,4−*Bis*−(hydroxymethyl)−1−methylcyclopent−2−enyl]adenine (35): Compound **35** was synthesized from compound **29** using the method described for synthesizing compound **11**: yield (78%) as a solid: mp 174~176 ℃; UV (H_2O) λ_{max} 253.0 nm; ^{1}H NMR (DMSO−d_6) δ 8.47 (s, 1H), 8.19 (s, 1H), 5.52 (s, 1H), 5.42 (s, 1H), 4.80 (d, J = 5.1 Hz, 1H), 4.17 (d, J = 5.1 Hz, 1H), 3.50−3.29 (m, 4H), 2.37 (d, J = 17.1 Hz, 1H), 2.19 (d, J = 17.1 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR (DMSO−d_6) δ 156.87, 150.84, 147.31, 146.01, 133.87, 121.54, 113.54, 66.74, 64.22, 55.21, 53.67, 41.37, 25.25.

(±)−1−[4,4−*Bis*−(hydroxymethyl)−1−methylcyclopent−2−enyl]thymine (36): Compound **36** was synthesized from compound **32** using the method described for synthesizing compound **11**: yield (60%) as a solid: mp 164~166 ℃; UV (H_2O) λ_{max} 269.0 nm; ^{1}H NMR (DMSO−d_6) δ 11.08 (br, s, 1H), 7.42 (s, 1H), 6.02 (d, J

= 5.6 Hz, 1H), 5.86 (d, *J* = 5.6 Hz, 1H), 4.68−4.50 (br, s, 1H), 3.45−3.33 (m, 4H), 2.27 (d, *J* = 16.4 Hz, 1H), 2.98 (d, *J* = 16.4 Hz, 1H), 1.80 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (DMSO−d_6) δ 164.87, 150.65, 139.38, 138.78, 133.84, 106.87, 73.14, 64.66, 57.50, 57.24, 26.94, 12.19.

(±)−1−[4,4−*Bis*−(hydroxymethyl)−1−methylcyclopent−2−enyl] uracil (37): Compound **37** was synthesized from compound **33** using the method described for synthesizing compound **11**: yield (62%) as a solid: mp 167~169℃; UV (H_2O) λ_{max} 267.0 nm; ^{1}H NMR (DMSO−d_6) δ 11.12 (br, s, 1H), 7.70 (d, *J* = 6.4 Hz, 1H), 6.01 (d, *J* = 6.4 Hz, 1H), 5.91 (d, *J* = 5.0 Hz, 1H), 5.85 (d, *J* = 5.0 Hz, 1H), 4.60−4.33 (br, d, 2H), 3.42−3.30 (m, 4H), 2.31 (d, *J* = 16.8 Hz, 1H), 2.07 (d, *J* = 16.8 Hz, 1H), 1.89 (s, 3H); ^{13}C NMR (DMSO−d_6) δ 165.99, 152.81, 144.45, 139.24, 134.12, 106.18, 72.23, 63.60, 58.77, 55.82, 27.02.

(±)−3,3'−*Bis*−(*t*−butyldimethylsilyloxymethyl)−2−methyl−pent−4−enoic acid ethyl ester (39): To a stirred solution of LiHMDS (12.70 mL, 1 M solution in THF) in tetrahydrofuran (50 mL), compound **38** (2.60 g, 6.30 mmol) dissolved in tetrahydrofuran (10 mL) was added using a syringe at –78 ℃. After stirring for 4 h at the same temperature, the reaction mixture was warmed to −20~−25 ℃ and stirred for an additional 2 h at the same temperature. The reaction was quenched by the addition of a saturated ammonium chloride solution (10 mL). The resulting mixture was warmed to room temperature and partitioned between water (200 mL) and ethyl acetate (200 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (EtOAc/ hexane, 1:50) to give **39** (2.2 g, 80%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.79 (dd, *J* = 11.7, 18.3 Hz, 1H), 5.12 (d, *J* = 11.4 Hz, 1H), 4.96 (d, *J* = 18.3 Hz, 1H), 4.06 (q, *J* = 6.9 Hz, 2H), 3.71 (d, *J* = 9.6 Hz, 1H), 3.65 (d, *J* = 9.6 Hz, 1H), 3.56 (d, *J* = 9.6 Hz, 1H), 3.49 (d, *J* = 9.6 Hz, 1H), 2.71 (d, *J* = 7.5 Hz, 1H), 1.05 (d, *J* = 7.5 Hz, 3H), 0.83 (s, 18H), 0.03 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 175.43, 142.54, 138.20, 115.43, 63.74, 61.71, 59.89, 47.94, 40.76, 25.83, 18.21, 14.27, 12.32, −5.63; Anal. Calcd for $C_{22}H_{46}O_4Si_2$: C, 61.34; H, 10.76. Found: C, 61.19; H, 9.67.

(±)−3,3'−*Bis*−(*t*−butyldimethylsilyloxymethyl)−2−methyl−pent−4−enol (40): Compound **40** was synthesized from compound **39** using the method described

for synthesizing compound **3**: yield (91%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.67 (dd, J = 18.3, 11.4 Hz, 1H), 5.06 (d, J = 11.4 Hz, 1H), 4.86 (d, J = 18.3 Hz, 1H), 3.61−3.48 (m, 6H), 1.80 (m, 1H), 0.90 (d, J = 7.2 Hz, 3H), 0.82 (s, 18H), 0.04 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 140.67, 114.32, 64.44, 64.17, 63.90, 48.14, 38.68, 25.84, 18.23, 12.38, −5.62; Anal. Calcd for $C_{20}H_{44}O_3Si_2$: C, 61.79; H, 11.41. Found: C, 61.87; H, 11.50.

(±)−3,3'−*Bis*−(*t*−butyldimethylsilyloxymethyl)−2−methyl−pent−4−enal (41): Compound **41** was synthesized from compound **40** using the method described for synthesizing compound **4**: yield (86%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.74 (s, 1H), 5.82 (dd, J = 17.7, 11.1 Hz, 1H), 5.14 (d, J = 11.1 Hz, 1H), 5.00 (d, J = 17.7 Hz, 1H), 3.65 (d, J = 9.9 Hz, 2H), 3.59 (d, J = 9.9 Hz, 2H), 2.48 (q, J = 6.9 Hz, 1H), 1.02 (d, J = 6.9 Hz, 3H), 0.84 (s, 18H), 0.02 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 204.77, 139.27, 115.47, 63.88, 49.54, 47.98, 25.81, 18.23, 17.74, 8.71, −5.69; Anal. Calcd for $C_{20}H_{42}O_3Si_2$: C, 62.12; H, 10.95. Found: C, 61.90; H, 10.86.

(*rel*)−(3*R* and 3*S*,4*S*)−5,5'−*Bis*−(*t*−butyldimethylsilyloxymethyl)−4−methyl−hepta−1,6−dien−3−ol (42): Compound **42** was synthesized from compound **41** using the method described for synthesizing compound **5**: yield (85%) as a colorless oil; as a diastereomeric mixture for ^{1}H NMR ($CDCl_3$) δ 5.73−5.63 (m, 2H), 5.21−4.84 (m, 4H), 3.69−3.48 (m, 5H), 1.77 (m, 1H), 0.82−0.78 (m, 21H), 0.02 (2s, 12H); ^{13}C NMR ($CDCl_3$) δ 141.82, 140.96, 113.97, 113.68, 69.96, 64.51, 63.86, 48.67, 41.86, 25.85, 18.29, 6.94, −5.62; Anal. Calcd for $C_{22}H_{46}O_3Si_2$: C, 63.71; H, 11.18. Found: C, 63.51; H, 10.97.

(*rel*)−(1*R*,5*S*)−4,4'−*Bis*−(*t*−butyldimethylsilyloxymethyl)−5−methylcyclopent−2−enol (43) and (*rel*)−(1*S*,5*S*)−4,4'−*Bis*−(*t*−butyldimethylsilyloxymethyl)−5−methylcyclopent−2−enol (44): Compounds **43** and **44** was synthesized from compound **42** using the method described for synthesizing compound **6**: yield **43** (72%), **44** (7%) as colorless oil; Compound **43**: ^{1}H NMR ($CDCl_3$) δ 5.80 (dd, J = 5.4, 1.8 Hz, 1H), 5.58 (d, J = 6.0 Hz, 1H), 4.26 (m, 1H), 3.57−3.43 (m, 4H), 1.75 (m, 1H), 1.05 (d, J = 7.5 Hz, 3H), 0.84 (s, 9H), 0.82 (s, 9H), 0.03 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 136.19, 134.67, 84.37, 67.51, 63.78, 57.04, 47.95, 25.81, 18.41, 18.13, 13.16, −5.60; Anal. Calcd for $C_{20}H_{42}O_3Si_2$: C, 62.12;

H, 10.95. Found: C, 62.07; H, 10.81; Compound **44**: ^{1}H NMR ($CDCl_3$) δ 6.04 (dd, J = 5.4, 2.1 Hz, 1H), 5.73 (d, J = 6.0 Hz, 1H), 4.29−4.22 (m, 1H), 3.61 (d, J = 9.9 Hz, 1H), 3.50 (d, J = 10.2 Hz, 2H), 3.36 (d, J = 9.6 Hz, 1H), 1.80 (m, 1H), 1.01 (d, J = 7.5 Hz, 3H), 0.86 (s, 18H), 0.03 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 137.39, 135.32, 77.24, 67.94, 63.05, 57.14, 42.70, 25.95, 25.80, 18.51, 18.17, 9.40, −5.57; Anal. Calcd for $C_{20}H_{42}O_3Si_2$: C, 62.12; H, 10.95. Found: C, 62.36; H, 11.09.

(*rel*)−(1'*R*,5'*S*)−1−Ethoxycarbonyloxy−4,4'−(*t*−butyldimethylsilyloxymethyl)−5−methylcyclopent−2−ene (45): To a solution of compound **43** (2.00 g, 5.20 mmol) in anhydrous pyridine (10 mL) ethyl chloroformate (0.80 mL, 5.60 mmol) and DMAP (55 mg, 0.40 mmol) were added. The reaction mixture was stirred overnight at room temperature. The reaction mixture was then quenched using a saturated $NaHCO_3$ solution (0.5 mL) and concentrated under vacuum. The residue was extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/ hexane, 1:25) to give compound **45** (2.10 mg, 88%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 5.87 (dd, J = 5.7, 1.5 Hz, 1H), 5.80 (dd, J = 6.0, 1.2 Hz, 1H), 5.31 (dt, J = 6.9, 1.5 Hz, 1H), 4.18 (q, J = 6.9 Hz, 2H), 3.62−3.43 (m, 4H), 2.04 (m, 1H), 1.30 (t, J = 6.9 Hz, 3H), 1.15 (d, J = 7.5 Hz, 3H), 0.88 (s, 18H), 0.02 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 155.26, 139.25, 130.55, 90.07, 67.07, 63.70, 63.30, 56.90, 44.48, 25.88, 25.83, 18.25, 18.16, 14.29, 12.42, −5.59; Anal. Calcd for $C_{23}H_{45}O_5Si_2$: C, 60.21; H, 10.11. Found: C, 60.49; H, 10.05.

(*rel*)−(1'*R*,5'*S*)−1−[4,4'−*Bis*−(*t*−butyldimethylsilyloxymethyl)−5−methycyclopent−2−en−1−yl] cytosine (46): To pure NaH (26.60 mg, 1.11 mmol) in anhydrous DMSO (6 mL), cytosine (123 mg, 1.11 mmol) was added. The reaction mixture was stirred for 30 min at 50~55 ℃ and then cooled to room temperature. Simultaneously, $P(O-i-Pr)_3$ (0.28 mL, 0.70 mmol) was added to a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (14 mg, 7.50 μmol) in anhydrous THF (5 mL), which was then stirred for 30 min. To the adenine solution in DMSO, a catalyst solution of THF and compound **45** (481 mg, 1.05 mmol) dissolved in anhydrous THF (3 mL) was added slowly. The reaction mixture was stirred overnight under reflux and then reaction mixture was stirred overnight under reflux and the quenched

with water (4 mL). The reaction solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/ CH_2Cl_2, 1:10) to give compound **46** (146 mg, 29%) as a white solid: mp 170~172 ℃; UV (MeOH) λ_{max} 271.0 nm; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 7.2 Hz, 1H), 5.70 (d, J = 5.2 Hz, 1H), 5.61 (t, J = 7.2 Hz, 1H), 3.65−3.52 (m, 4H), 2.21 (m, 1H), 1.09 (d, J = 7.0 Hz, 3H), 0.84 (s, 18H), 0.03 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 165.40, 156.21 145.34, 142.09, 137.81, 132.50, 84.12, 68.21, 64.55, 58.34, 48.78, 25.42, 18.12, 13.09, −5.51; Anal. Calcd for $C_{24}H_{45}N_3O_3Si_2$: C, 60.08; H, 9.45; N, 8.76. Found: C, 59.88; H, 9.38; N, 8.80.

(*rel*)−(1'*R*,5'*S*)−1−[4,4'−*Bis*−(*t*−butyldimethylsilyloxymethyl)−5−methycyclopent−2−en−1−yl] uracil (47): Compound **47** was synthesized from compound **45** and uracil using the method described for synthesizing compound **46**: yield (22%) as a white solid: mp 168~170 ℃; UV (MeOH) λ_{max} 261.0 nm; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 7.4 Hz, 1H), 5.72 (dd, J = 5.4, 1.8 Hz, 1H), 5.58 (t, J = 6.0 Hz, 1H), 5.51 (t, J = 7.4 Hz, 1H), 4.30 (m, 1H), 3.52−3.45 (m, 4H), 1.83 (m, 1H), 1.05 (d, J = 7.5 Hz, 3H), 0.84 (s, 18H), 0.04 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 165.10, 152.33, 142.92, 137.21, 134.87, 101.05, 85.45, 67.61, 63.88, 52.24, 48.32, 25.81, 18.42, 18.02, 13.28, −5.55.

(*rel*)−(1'*R*,5'*S*)−1−[4,4'−*Bis*−(*t*−butyldimethylsilyloxymethyl)−5−methylcyclopent−2−en−1−yl] thymine (48): Compound **48** was synthesized from compound **45** and thymine using the method described for synthesizing compound **46**: yield (26%) as a white solid: mp 164~167 ℃; UV (MeOH) λ_{max} 266.5 nm; ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 1H), 5.74 (d, J = 6.8 Hz, 1H), 5.61 (d, J = 6.2 Hz, 1H), 4.26 (m, 1H), 3.78−3.61 (m, 4H), 1.77−1.75 (m, 4H), 1.11 (d, J = 7.6 Hz, 3H), 0.86 (s, 9H), 0.82 (s, 9H), 0.04 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.93, 151.56, 137.71, 136.19, 134.67, 107.87, 84.37, 67.51, 63.78, 57.04, 47.95, 25.84, 18.43, 18.23, 13.23, 11.73, −5.55.

(*rel*)−(1'*R*,5'*S*)−1−[4,4'−*Bis*−(hydroxymethyl)−5−methyl−cyclopent−2−en−1−yl] cytosine (49): Compound **49** was synthesized from compound **46** using the method described for synthesizing compound **11**: yield (72%) as a white solid: mp 170~172 ℃; UV (H_2O) λ_{max} 271.0 nm; ^{1}H NMR (DMSO−d_6) δ 7.74 (d, J = 7.2 Hz, 1H), 7.20 (br d, D_2O exchangeable, $-NH_2$), 5.78 (d, J = 5.6 Hz, 1H),

5.59 (d, J = 7.2 Hz, 1H), 5.29−5.20 (br d, D_2O exchangeable, 2×OH), 3.66−3.55 (m, 4H), 2.23 (m, 1H), 1.08 (d, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO−d_6) δ 165.56, 156.31, 145.90, 142.11, 138.02, 131.56, 84.21, 68.01, 64.82, 58.34, 49.92, 13.19.

(*rel*)−(1'*R*,5'*S*)−1−[4,4'−*Bis*−(Hydroxymethyl)−5−methyl−cyclopent−2−en−1−yl] uracil (50): Compound **50** was synthesized from compound **47** using the method described for synthesizing compound **11**: yield (70%) as a white solid: mp 170~173 ℃; UV (H_2O) λ_{max} 262.0 nm; ^1H NMR (DMSO−d_6) δ 11.34 (br s, D_2O exchangeable, −NH), 7.49 (d, J = 7.2 Hz, 1H), 5.70 (d, J = 5.8 Hz, 1H), 5.58 (dd, J = 6.0, 1.8 Hz, 1H), 5.56 (d, J = 7.2 Hz, 1H), 5.27 (br s, D_2O exchangeable, OH), 5.21 (br s, D_2O exchangeable, OH), 4.30 (m, 1H), 3.52−3.45 (m, 4H), 1.83 (m, 1H), 1.8 (d, J = 7.6 Hz, 3H); ^{13}C NMR (DMSO−d_6) δ 165.14, 152.81, 143.02, 137.21, 134.87, 102.11, 85.45, 67.45, 63.80, 57.25, 48.24, 13.21.

(*rel*)−(1'*R*,5'*S*)−1−[4,4'−*Bis*−(hydroxymethyl)−5−methyl−cyclopent−2−en−1−yl] thymine (51): Compound **51** was synthesized from compound **48** using the method described for synthesizing compound **11**: yield (71%) as a white solid: mp 170~173 ℃; UV (H_2O) λ_{max} 266.0 nm; ^1H NMR (DMSO−d_6) δ 11.34 (br s, D_2O exchangeable, −NH), 7.31 (s, 1H), 5.75 (d, J = 7.0 Hz, 1H), 5.56 (d, J = 6.4 Hz, 1H), 5.30−5.25 (br d, D_2O exchangeable, 2×OH), 4.26 (m, 1H), 3.82−3.75 (m, 4H), 1.77 (s, 3H), 1.72−1.67 (m, 1H), 1.06 (d, J = 7.6 Hz, 3H); ^{13}C NMR (DMSO−d_6) δ 164.97, 151.62, 137.78, 136.20, 134.34, 107.72, 84.32, 67.61, 62.12, 58.78, 48.07, 13.28, 11.22.

(*E*)(*R*)−5−(*t*−Butyldimethylsiloxy)−2−fluoropent−2−en−1,4−diol (53): To a solution of **52** (10 g, 40.60 mmol) in CH_2C_{l2} (150 mL), DIBAL−H (60.88 mL, 60.88 mmol, 1 M solution in toluene) was added dropwise at –78 ℃ and the mixture was then stirred at –78 ℃ for 2 h. The reaction was treated with dilute nitrc acid. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered and evaporated to a pale yellow oil, which was used for the next step without further purification.

To a solution of the crude lactol in MeOH, $NaBH_4$ (1.51 g, 40 mmol) and $CeCl_3 \cdot 7H_2O$ (14.90 g, 40 mmol) was added with saturated NH_4Cl and extracted using

ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by a column chromatography (hexane/ EtOAc, 3:1) to give compound **53** (8.74 g, 86%) as a colorless oil: $[\alpha]^{25}_D$ = +3.31° (*c* 1.56, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.24 (dd, *J* = 8.4, 20.0 Hz, 1H), 4.11−4.42 (m, 2H), 3.51−3.65 (m, 2H), 3.14, 3.33 (2s, 2H), 0.92 (s, 9H), 0.09 (s, 6H); Anal. Calcd for $C_{11}H_{23}FO_3Si$: H, 9.26; C, 52.77. Found: C, 52.52; H, 9.48.

(*E*)(*R*)−1,5−*Bis*−(*t*−butyldimethylsiloxy)−2−fluoropent−2−en−4−ol (54): To a mixture of the diol **53** (8 g, 31.95 mmol) and imidazole (4.35 g, 61.90 mmol) in CH_2Cl_2 (200 mL), a solution of TBDMSCl (5.29 g, 35.14 mmol) in anhydrous CH_2Cl_2 (100 mL) was added drop wise at 0 ℃. The mixture was stirred at 0 ℃ for 3 h and then washed with water (2×50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified on a silica gel column (hexane/ EtOAc, 2:1) to give compound **54** (10.36 g, 89%) as a colorless oil: $[\alpha]^{24}_D$ = +2.7° (*c* 2.5, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.21 (dd, *J* = 8.8, 20.0 Hz, 1H), 4.24−4.43 (m, 2H), 3.63 (dd, *J* = 4.0, 10.0 Hz, 1H), 3.48 (dd, *J* = 7.6, 9.6 Hz, 1H), 2.64 (d, *J* = 2.8 Hz, 1H), 0.91 (s, 18H), 0.08, 0.11 (2s, 12H); Anal. Calcd for $C_{17}H_{23}FO_3Si$: C, 55.99; H, 10.23. Found: C, 56.25; H, 10.10.

(*E*)−6−*O*−(*t*−Butyldimethylsiloxy)−*S*−(*t*−Butyldimethylsiloxymethyl)−3−fluoro−hex−4−enoic acid ethyl ester (55): Compound **55** was synthesized from compound **54** using the method described for synthesizing compound **2**: yield (89%) as a colorless oil: $[\alpha]^{24}_D$ = −40.25° (*c* 1.45, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.83−5.95 (m, 2H), 4.21 (s, 2H, H−6), 4.12 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 1H), 3.78 (dd, *J* = 10.8, 18.4 Hz, 1H), 2.73−2.93 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.89, 0.91 (s, 9H), 0.05, 0.06 (s, 12H); Anal. Calcd for $C_{21}H_{43}FO_4Si_2$: C, 58.02; H, 9.97. Found: C, 57.82; H, 9.78.

(*R*)−3−(*t*−Butyldimethylsiloxymethyl)−3−fluoro−4−oxo−butyric acid ethyl ester (56): A solution of compound **55** (3.50 g, 8.05 mmol) in methanol (30 mL) was treated with O_3 at –78 ℃ until a slight blue color persisted. The solution was degassed with N_2 and brought to 0 ℃, whereupon methyl sulfide (2 mL, 22.70 mmol) was added. The mixture was stirred at 0 ℃ for 1 h. The mixture was concentrated and taken up into water. The combined organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by a

column chromatography (hexane/ EtOAc, 8:1) to give compound **56** (2 g, 85%) as a colorless oil: $[\alpha]^{24}_{D}$ = −42.1° (*c* 1.3, MeOH); ^{1}H NMR ($CDCl_3$) δ 9.90 (d, *J* = 4.4 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.74−3.93 (m, 2H), 2.90−3.04 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.06, 0.07 (2s, 6H); Anal. Calcd for $C_{13}H_{25}FO_4Si$: C, 53.40; H, 8.62. Found: C, 53.54; H, 8.68.

1−*O*−Acetyl−3−*C*−(*t*−butyldimethylsiloxy)−3−deoxy−3−fluoro−D−erythro−tetrafuranose (58): A solution of compound **56** (4.50 g, 15.38 mmol) in toluene (50 mL), a 1 M solution of DIBAL−H in hexane (32.30 mL, 32.30 mmol) was added dropwise at –78 ℃ and the mixture was stirred at the same temperature for 0.5 h. The reaction was quenched with methanol (30 mL) and then allowed warm to room temperature. The resulting white solid was filtered and the filtrate was concentrated to a pale yellowish oil, which was used for the next step without further purification.

To a solution of the crude lactol **57** (3.35 g, 13.37 mmol, 87%) in anhydrous pyridine (30 mL), acetic anhydride (2 mL, 19.76 mmol) was added at 0 ℃ and then the mixture was stirred overnight at rt. The mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate, which was washed with saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concecntrated. The residue was purified by a column chromatography (hexane/ EtOAc, 15:1) to give compound **58** as an anomeric mixture in pale yellow oil (3.59 g, 92%); ^{1}H NMR ($CDCl_3$) δ 6.45 (dd, *J* = 2.0, 6.0 Hz, 1H), 6.33 (d, *J* = 5.2 Hz, 1H), 3.70−4.25 (m, 2H), 2.22−2.59 (m, 1H), 2.04, 2.09 (2s, 3H), 0.89, 0.91 (s, 9H), 0.08, 0.09 (2s, 6H); Anal. Calcd for $C_{13}H_{25}FO_4Si$: C, 53.40; H, 8.62. Found: C, 53.26; H, 8.59.

***N*^{4}−Benzoyl−1−[3−*C*−(*t*−butyldimethylsiloxymethyl)−2,3−deoxy−3−fluoro−*β*−D−erythro−tetrafuranosyl] cytosine (59) and *N*^{4}−Benzoyl−1−[3−*C*−(*t*−butyldimethylsiloxymethyl)−2,3−deoxy−3−fluoro−*α*−D−erythro−tetrafuranosyl] cytosine (60):** A suspension of *N*^{4}−benzoyl cytosine (420 mg, 1.95 mmol), HMDS (20 mL) and ammonium sulfate (catalytic amount) was refluxed overnight under a nitrogen atmosphere, and excess HMDS was removed under a high vacuum. To the residue, dry 1,2−dichloroethane (DCE) (10 mL), a solution of the acetates **58** (456.54 mg, 1.56 mmol) in dry DCE (10 mL), and trimethylsilyl

trifluoromethane sulfonate (TMSOTf) (0.40 ml, 1.92 mmol) was added at rt and the resulting reaction mixture was stirred for 1 h at rt. Sat. $NaHCO_3$ (5 mL) was added to the reaction mixture and stirred another 30 min, which was extracted with methylene chloride (30 mL×2). The combined organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue of the anomeric mixture was separated by silica gel column chromatography (hexane/ EtOAc, 2:1) to give compound **59** (313.93 mg, 36%) and **60** (322.90 mg, 37%) as a foam, respectively; Compound **59**: ^{1}H NMR ($CDCl_3$) δ 8.78 (br s, 1H, D_2O exchangeable), 7.64−7.26 (m, 7H), 6.20 (t, J = 6.4 Hz, 1H), 4.53−4.22 (m, 2H), 3.76−3.61 (m, 2H), 3.10 (m, 1H), 2.36 (m, 1H), 0.9 (s, 9H), 0.08 (s, 6H); Anal. Calcd for $C_{22}H_{30}FN_3O_4Si$: C, 59.04; H, 6.76; N, 9.39. Found: C, 58.77; H, 6.69; N, 9.22. compound **60**: ^{1}H NMR ($CDCl_3$) δ 8.70 (br s, 1H, D_2O exchangeable), 8.00−7.30 (m, 7H), 6.23 (t, J = 7.1 Hz, 1H), 4.49−4.21 (m, 2H), 3.77−3.56 (m, 2H), 2.79−2.49 (m, 2H), 0.91 (s, 9H), 0.09 (s, 6H); Anal. Calcd for $C_{22}H_{30}FN_3O_4Si$: C, 59.04; H, 6.76; N, 9.39. Found: C, 58.91; H, 6.79; N, 9.43.

6−Chloro−9−[3−*C*−(*t*−butyldimethylsilyloxymethyl)−2,3−deoxy−3−fluoro−D−erythro−tetrafuranosyl] purine (61): The suspension of 6−chloropurine (1.59 g, 10.30 mmol) in HMDS (50 mL), and ammonium sulfate (catalytic amount) was refluxed under a nitrogen atmosphere for 4 h and excess HMDS was removed under a high vacuum under anhydrous conditions to yield a yellow solid, which was dissolved in dry CH_2Cl_2 (10 mL). To the solution, the acetates **58** (1.60 g, 4.14 mmol) in dry CH_2Cl_2 (20 mL) and TMSOTf (2 mL, 10.30 mmol) were added at 0 ℃ and the resulting reaction mixture was stirred for 2 h at rt. Sat. $NaHCO_3$ (20 mL) was then added to the reaction mixture, which was extracted with methylene chloride (20 mL×2). The combined organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue of the anomeric mixture was separated by silica gel column chromatography (hexane/ EtOAc, 4:1) to give an inseparable anomeric mixture **61** (1.06 g, 62%): UV (H_2O) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.44 (s, 1H), 8.27 (s, 1H), 6.60 (d, J = 7.6 Hz, 1H), 6.53 (t, J = 6.8 Hz, 1H), 4.16−4.49 (m, 1H), 3.83−3.99 (m, 1H), 2.56−3.17 (m, 1H), 0.9, 0.92 (2s, 18H), 0.1, 0.11 (2s, 12H); Anal. Calcd for $C_{16}H_{24}ClFN_4O_2Si$: C, 49.67; H, 6.25; N, 14.48. Found: C,

49.45; H, 6.12; N, 14.56.

N^4-Benzoyl-1-[3-*C*-(hydroxymethyl)-2,3-deoxy-3-fluoro-*β*-D-erythro-o-tetrafuranosyl] cytosine (62): A solution of compound **59** (250 mg, 0.56 mmol) in CH_3CN (7 mL) was treated with TBAF (1 M solution THF, 0.67 mL) and then residue was purified by silica gel column chromatography (hexane/ EtOAc, 1:3) to give compound **62** (141 mg, 76%): as a white solid: mp 156~158 ℃; $[\alpha]^{24}_D$ = 44.9° (*c* 1.3, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.67-7.26 (m, 6H), 7.29 (br d, 2H, D_2O exchangeable), 6.18 (t, *J* = 6.9 Hz, 1H), 5.80 (d, *J* = 7.4 Hz, 1H), 5.33 (t, *J* = 5.7 Hz, 1H, D_2O exchangeable), 4.32 (dd, *J* =10.4, 35.1 Hz, 1H), 4.06 (dd, *J* =10.4, 21.7 Hz, 1H), 3.78-3.70 (m, 2H), 2.53-2.21 (m, 2H); Anal. Calcd for $C_{16}H_{16}FN_3O_4$: C, 57.65; H, 4.84; N, 12.61. Found: C, 57.42; H, 4.71; N, 12.67.

N^4-Benzoyl-1-[3-*C*-(hydroxymethyl)-2,3-deoxy-3-fluoro-*α*-D-erythr-o-tetrafuranosyl] cytosine (63): Compound **63** was prepared from comound **60** using the method for the preparation of compound **62**: yield (77%): mp 160~163 ℃; $[\alpha]^{24}_D$ = -72° (*c* 0.77, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.17- 7.29 (m, 6H), 6.03 (dd, *J* = 1.6, 7.4 Hz, 1H), 4.37-3.94 (m, 2H), 3.71 (m, 2H), 2.87-2.77 (m, 1H), 2.30-2.17 (m, 1H); Anal. Calcd for $C_{16}H_{16}FN_3O_4$: C, 57.65; H, 4.84; N, 12.61. Found: C, 57.44; H, 4.90; N, 12.72.

6-Chloro-9-[3-*C*-(hydroxymethyl)-2,3-deoxy-3-fluoro-*β*-D-erythro-tetrafuranosyl] purine (64) and 6-Chloro-9-[3-*C*-(hydroxymethyl)-2,3-deoxy-3-fluoro-*α*-D-erythro-tetrafuranosyl] purine (65): Compounds **64** and **65** was prepared from comound **61** using the method for the preparation of compound **62**: yield **64** (38%), **65** (35.5%) as a white solid, respectively; compound **64**: mp 102~104 ℃; $[\alpha]^{24}_D$ = -36.5° (*c* 1.12, MeOH); UV (MeOH) λ_{max} 263.0 nm; ^{1}H NMR (DMSO-d_6) δ 8.88 (s, 1H), 8.82 (s, 1H), 6.62 (t, *J* = 6.8 Hz, 1H), 5.40 (t, *J* = 5.6 Hz, 1H, D_2O exchangeable), 4.34 (dd, *J* = 10.9, 35.6 Hz, 1H), 4.12 (dd, *J* = 10.8, 20.4 Hz, 1H), 3.81-3.88 (m, 2H), 2.92-3.04 (m, 1H), 2.73-2.84 (m, 1H); Anal. Calcd for $C_{10}H_{10}FClN_4O_2$: C, 44.05; H, 3.70; N, 20.55. Found: C, 43.80; H, 3.56; N, 20.36; compound **65**: mp 121~123 ℃; $[\alpha]^{24}_D$ = +22.2° (*c* 1.40, MeOH); UV (MeOH) λmax 264.5 nm; ^{1}H NMR (DMSO-d_6) δ 8.16 (s, 1H), 8.15 (s, 1H), 7.30 (br s, 2H, D_2O exchangeable), 6.39 (dd, *J* = 3.0,

7.3 Hz, 1H), 5.39 (t, J = 5.3 Hz, 1H, D_2O exchangeable), 4.33 (dd, J = 10.7, 20.9 Hz, 1H), 4.11 (dd, J = 10.8, 30.8 Hz, 1H), 3.74−3.67 (m, 2H), 2.88−2.72 (m, 2H); Anal. Calcd for $C_{10}H_{10}FClN_4O_2$: C, 44.05; H, 3.70; N, 20.55. Found: C, 43.80; H, 3.67; N, 20.52.

1−[3−*C*−(Hydroxymethyl)−2,3−deoxy−3−fluoro−*β*−D−erythro−tetrafurano−syl] cytosine (66): Compound **66** was prepared from comound **62** using the method for the preparation of compound **20**: yield (95%): $[\alpha]^{24}_D$ = +41.1° (*c* 0.48, MeOH); UV (H_2O) λ_{max} 271 nm; ^{1}H NMR (DMSO−d_6) δ 7.62 (d, J = 7.4 Hz, 1H), 7.15, 7.24 (2 br s, 2H, D_2O exchangeable), 6.12 (t, J = 6.9 Hz, 1H), 5.73 (d, J = 7.4 Hz, 1H), 5.12 (t, J = 5.7 Hz, 1H, D_2O exchangeable), 4.20 (dd, J =10.4, 35.1 Hz, 1H), 3.96 (dd, J =10.4, 21.7 Hz, 1H), 3.59−3.72 (m, 2H), 2.15−2.47 (m, 2H); Anal. Calcd for $C_9H_{12}FN_3O_3$: H, 5.28; C, 47.16; N, 18.33. Found: C, 47.35; H, 5.52; N, 18.25.

1−[3−*C*−(Hydroxymethyl)−2,3−deoxy−3−fluoro−*α*−D−erythro−tetrafurano−syl] cytosine (67): Compound **67** was prepared from compound **63** using the method for the preparation of compound **20**: yield (97%): mp 181~183 ℃; $[\alpha]^{24}_D$ = −75.8° (*c* 0.50, MeOH); UV (H_2O) λ_{max} 271 nm; ^{1}H NMR (DMSO−d_6) δ 7.55 (d, J = 7.4 Hz, 1H), 7.07, 7.16 (2 br d, 2H, D_2O exchangeable), 6.04 (dd, J = 2.3, 7.5 Hz, 1H), 5.72 (d, J = 7.4 Hz, 1H), 5.28 (s, 1H, D_2O exchangeable), 4.00 (dd, J = 3.5, 5.6 Hz, 1H), 3.92 (dd, J = 5.2, 5.6 Hz, 1H), 3.56−3.66 (m, 2H), 2.53−2.64 (m, 1H), 2.10 (dd, J = 2.4, 5.6 Hz, 1H); Anal. Calcd for $C_9H_{12}FN_3O_3$: C, 47.16; H, 5.28; N, 18.33. Found: C, 47.35; H, 5.30; N, 18.27.

9−[3−*C*−(Hydroxymethyl)−3−deoxy−3−fluoro−*β*−D−erythro−tetrafuranos−yl] adenine (68): Compound **68** was prepared from compound **64** using the method for the preparation of compound **10**: yield (84%): mp 195~197 ℃; $[\alpha]^{24}_D$ = −85.5° (*c* 0.78, MeOH); UV (H_2O) λ_{max} 259.0 nm; ^{1}H NMR (DMSO−d_6) δ 8.34 (s, 1H), 8.16 (s, 1H), 7.32 (br s, 2H, D_2O exchangeable), 6.47 (t, J = 7.0 Hz, 1H), 5.37 (t, J = 5.7 Hz, 1H, D_2O exchangeable), 4.37−4.25 (dd, J = 10.5, 35.4 Hz, 1H), 4.09−4.02 (dd, J = 10.4, 20.1 Hz, 1H), 3.88 (dd, J = 5.5, 20.5 Hz, 2H), 3.05−2.91 (ddd, J = 6.9, 14.9, 34.6 Hz, 1H), 2.76−2.65 (m, 1H); Anal. Calcd for $C_{10}H_{12}FClN_5O_2$: C, 47.43; H, 4.78; N, 27.66. Found: C, 47.26; H, 4.76; N, 27.62.

9-[3-*C*-(Hydroxymethyl)-3-deoxy-3-fluoro-α-D-erythro-tetrafuranosyl] adenine (69): Compound **69** was prepared from compound **65** using the method for the preparation of compound **10**: yield (81%): mp 198~200 ℃; $[\alpha]^{24}_{D}$ = +56.2° (*c* 1.04, MeOH); UV (H_2O) λ_{max} 260 nm; ^{1}H NMR (DMSO-d_6) δ 8.16 (s, 1H), 8.15 (s, 1H), 7.30 (br s, 2H, D_2O exchangeable), 6.39 (dd, *J* = 3.0, 7.3 Hz, 1H), 5.39 (t, *J* = 5.3 Hz, 1H, D_2O exchangeable), 4.33 (dd, *J* = 10.7, 20.9 Hz, 1H), 4.11 (dd, *J* = 10.8, 30.8 Hz, 1H), 3.74-3.67 (m, 2H), 2.88 -2.72 (m, 2H); Anal. Calcd for $C_{10}H_{12}FClN_5O_2$: C, 47.43; H, 4.78; N, 27.66. Found: C, 47.67; H, 4.57; N, 27.48.

(1-Hydroxymethyl-cyclobutyl) methanol (71): To a suspension of lithium aluminum hydride (0.80 g, 21.10 mmol) in dry tetrahydrofuran (THF) (20 mL), a solution of 1,1-cyclobutane dicarboxylic acid **70** (1.08 g, 7.49 mmol) in dry THF (20 mL) was added dropwise at 0 ℃. The resulting suspension was stirred overnight, followed by cooling to 0 ℃. The suspension was quenched with water (0.83 mL), 15% sodium hydroxide (0.83 mL) and water (2.48 mL) at the same temperature. The mixture was stirred at room temperature for another hour. The white gel suspension was filtered through a celite pad and was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 4:1) to give the diol **71** (575 mg, 87%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 4H), 3.11 (s, 2H), 1.96-1.70 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 69.47, 43.14, 25.80, 15.39; Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 62.29; H, 10.37.

[1-(*t*-Butyldimethylsilanyloxymethyl)-cyclobutyl] methanol (72): Compound **72** was prepared from compound **71** using the method for the preparation of compound **54**: yield (98%): as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 2H), 3.60 (s, 2H), 1.86-1.59 (m, 6H), 0.81 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 71.16, 70.24, 43.07, 25.80, 18.20, 15.45, -5.56; Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.72; H, 11.45.

Methanesulfonic acid 1-(*t*-butyldimethylsilanyloxymethyl)-cyclobutylmethyl ester (73): To a stirred solution of the alcohol **72** (320 mg, 1.39 mmol) in anhydrous CH_2Cl_2, anhydrous triethylanmine (0.36 mL) and MsCl (195 mg, 1.68 mmol) was added at 0 ℃. The mixture was stirred at the same temperature for 3

h and quenched by adding a cold saturated $NaHCO_3$ solution (10 mL). The mixture was extractedwith CH_2Cl_2 (100 mL) and water (100 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under vacuum and the residue was purified by flash silica gel column chromatography (EtOAc/ hexane, 1:5) to give compound **73** (343 mg, 80%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 4.15 (s, 2H), 3.53 (s, 2H), 2.91 (s, 3H), 1.88−1.72 (m, 6H), 0.83 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 76, 65.37, 42.60, 36.79, 25.77, 25.28, 18.19, 15.07; Anal. Calcd for $C_{13}H_{28}O_4SSi$: C, 50.61; H, 9.15. Found: C, 50.79; H, 9.16.

9−[1−(*t*−Butyldimethylsilanyloxymethyl)−cyclobutylmethyl] adenine (74): A solution of the mesylate **73** (382 mg, 1.24 mmol), and adenine (170 mg, 1.26 mmol) in dry DMF (15 mL) was stirred overnight at 80~90 ℃. The mixture was cooled to room temperature and concentrated under high wacuum. The residue was diluted with brine (30 mL) and extracted three times with CH_2Cl_2 (50 mL each). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/ MeOH, 10:1) to give compound **74** (258 mg, 60%): ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 1H), 7.75 (s, 1H), 6.07 (s, 2H), 4.22 (9s, 2H), 3.59 (s, 3H), 3.40 (s, 2H), 2.00−1.58 (m, 6H), 1.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.60, 152.82, 150.65, 141.49, 119.16, 70.49, 66.13, 47.90, 66.13, 47.90, 44.00, 26.83, 18.20, 14.97, −5.46. Anal. Calcd for $C_{17}H_{29}N_5OSi$: C, 58.75; H, 8.41; N, 20.15. Found: C, 58.60; H, 8.36; N, 20.26.

1−[1−(*t*−Butyldimethylsilanyloxymethyl)−cyclobutylmethyl] uracil (75): Co−mpound **75** was prepared from compound **73** using the method descrilbed for synthesizing compound **74**: yield (48%); ^{1}H NMR ($CDCl_3$) δ 9.33 (br s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 5.54 (d, J = 8.4 Hz, 1H), 3.78 (s, 2H), 3.47 (s, 2H), 1.96−1.57 (m, 6H), 0.82 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 163.91, 151.72, 148.04, 101.19, 65.88, 52.34, 44.11, 27.06, 25.85, 18.28, 15.38, −5.40; Anal. Calcd for $C_{16}H_{28}N_2O_3Si$: C, 59.22; H, 8.70; N, 8.63. Found: C, 59.49; H, 8.76; N, 8.50.

1−[1−(*t*−Butyldimethylsilanyloxymethyl)−cyclobutylmethyl] thymine (76): C−ompound **76** was synthesized from compound **73** using the method descrybed for

synthesizing compound **74**: yield (42%); ^{1}H NMR ($CDCl_3$) δ 8.64 (br s, 1H), 7.15 (s, 1H), 3.73 (s, 2H), 3.45 (s, 2H), 1.91−1.56 (m, 9H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.03, 151.56, 142.14, 109.47, 65.84, 52.02, 44.12, 27.08, 25.88, 18.28, 15.35, 12.23, −5.40; Anal. Calcd for $C_{17}H_{30}N_2O_3Si$: C, 60.32; H, 8.93; N, 8.28. Found: C, 60.48; H, 8.70; N, 8.37.

1−[1−(*t*−Butyldimethylsilanyloxymethyl)−cyclobutylmethyl]cytosine (77): C−ompound **77** was synthesized from compound **73** using the method described for synthesizing compound **74**: yield (56%); ^{1}H NMR ($CDCl_3$) δ 7.31 (d, J = 6.9 Hz, 1H), 5.52 (d, J = 6.9 Hz, 1H), 3.85 (s, 2H), 3.44 (s, 2H), 2.02−1.55 (m, 6H), 0.84 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.20, 156.55, 145.71, 92.57, 65.59, 51.90, 43.72, 25.77, 25.27, 17.50, 14.54, −6.02; Anal. Calcd for $C_{16}H_{29}N_3O_2Si$: C, 59.40; H, 9.04; N, 12.99. Found: C, 59.53; H, 8.89; N, 13.12.

9−[1−(Hydroxymethyl)−cyclobutylmethyl] adenine (78): Compound **78** was prepared from compound **74** using the method for the preparation of compound **11**: yield (79%) as a white solid: mp 180~181 ℃; UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO−d_6) δ 8.13 (s, 1H), 8.06 (s, 1H), 7.23 (br s, 2H), 5.01 (t, J = 5.4 Hz, 1H), 3.49 (s, 2H), 3.25 (s, 2H), 1.93−1.63 (m, 6H); ^{13}C NMR (DMSO−d_6) δ 155.98, 152.35, 150.01, 141.47, 118.27, 64.63, 47.39, 25.93, 14.40; Anal. Calcd for $C_{11}H_{15}N_5O$: C, 56.64; H, 6.48; N, 30.02. Found: C, 56.82; H, 6.41; N, 29.88.

1−[1−(Hydroxymethyl)−cyclobutylmethyl] uracil (79): Compound **79** was prepared from compound **75** using the method descrilbed for synthesizing compound **11**: yield (80%) as a solid: mp 167~168 ℃; UV (H_2O) λ_{max} 262.0 nm; ^{1}H NMR (DMSO−d_6) δ 11.23 (br s, 1H), 7.53 (d, J = 6.3 Hz, 1H), 5.54 (d, J = 6.4 Hz, 1H), 4.79 (t, J = 5.4 Hz, 1H), 3.73 (s, 2H), 3.35 (s, 2H), 1.84−1.64 (m, 6H); ^{13}C NMR (DMSO−d_6) δ 163.67, 151.83, 146.60, 100.48, 64.43, 51.49, 43.96, 30.71, 26.08, 14.86; Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.28; H, 6.61; N, 13.38.

1−[1−(Hydroxymethyl)−cyclobutylmethyl] thymine (80): Compound **80** was prepared from compound **76** using the method descrilbed for synthesizing compound **11**: yield (77%) as a solid: mp 164~166 ℃; UV (H_2O) λ_{max} 267.0 nm; ^{1}H NMR (DMSO−d_6) δ 11.23 (br s, 1H), 7.41 (s, 1H), 4.77 (t, J = 5.5 Hz, 1H),

3.70 (s, 2H), 3.31 (s, 2H), 1.78 (s, 3H), 1.83−1.63 (m, 6H); ^{13}C NMR (DMSO−d_6) δ 164.21, 151.81, 142.36, 108.05, 64.45, 51.29, 44.00, 26.00, 14.85, 11.99; Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 59.08; H, 7.33; N, 12.31.

1−[1−(Hydroxymethyl)−cyclobutylmethyl] cytosine (81): Compound **81** was prepared from compound **77** using the method descrilbed for synthesizing compound **11**: yield (71%) as a solid: mp 165~167 ℃; UV (H_2O) λ_{max} 271.5 nm; ^{1}H NMR (DMSO−d_6) δ 7.55 (d, J = 7.2 Hz, 1H), 7.09 (br s, 2H), 5.66 (d, J = 7.2 Hz, 1H), 4.87 (d, J = 5.4 Hz, 1H), 3.73 (s, 2H), 3.24 (d, J = 6.0 Hz, 2H), 1.88−1.73 (m, 2H), 1.62−1.58 (m, 2H); ^{13}C NMR (DMSO−d_6) δ 165.83, 157.12, 146.73, 93.36, 64.36, 52.15, 44.06, 26.15, 14.82; Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.62; H, 7.11; N, 19.91.

2,2−Diallylmalonic acid diethyl ester (83): To a stirred suspension of sodium hydride (3.74 g, 0.16 mol) in tetrahydrofuran (250 mL), diethyl malonate **82** (10 g, 62.40 mmol) was added slowly at 0 ℃ and stirred for 2 h at room temperature. The resulting mixture was cooled to 0 ℃ and allyl bromide (15.80 g, 0.13 mol) was added slowly. The mixture was stirred for 4 h at room temperature. and quenched with asaturated ammonium chloride solution (10 mL). The mixture was extracted using EtOAc (300 mL)/ water (300 mL), dried over $MgSO_4$, filtered and then concentrated. The residue was purified by silica gel column chromato−graphy (EtOAc/ hexane, 1:20) to give compound **83** (14.7 g, 97%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.58 (m, 2H), 5.06 (m, 2H), 4.21 (q, J = 6.9 Hz, 4H), 2.54 (m, 4H), 1.28 (t, J = 6.9 Hz, 6H).

Cyclopent−3−ene−1,1−dicarboxylic acid diethyl ester (84): Compound **84** was prepared from compound **83** using the method for the preparation of compound **6**: yield (97%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.50 (s, 2H), 4.10 (q, J = 6.9 Hz, 4H), 2.81 (s, 4H), 1.21 (t, J = 6.9 Hz, 6H).

(1−Hydroxymethyl−cyclopent−3−enyl) methanol (85): Compound **85** was synthesized from compound **84** using a similar procedure described for synthesizing compound **71**: yield (82%); ^{1}H NMR ($CDCl_3$) δ 5.64 (s, 2H), 3.67 (s, 4H), 2.20 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 128.74, 69.83, 47.54, 38.63; Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.38; H, 9.30.

[1-(*t*-Butyldimethylsilanyloxymethyl)cyclopent-3-enyl] methanol(86): Compound **86** was synthesized from compound **85** using the method described for synthesizing compound **54**: yield (95%); ^{1}H NMR ($CDCl_3$) δ 5.53 (s, 2H), 3.57 (d, J = 5.7 Hz, 4H), 2.20-2.01 (m, 4H), 0.83 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 128.74, 47.51, 38.51, 25.63, 18.06, -5.70; Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.22; H, 10.91.

Methanesulfonic acid 1-(*t*-butyldimethylsilanyloxymethyl)cyclopent-3-enyl-methyl ester (87): Compound **87** was synthesized from compound **86** using a similar procedure described for synthesizing compound **73**: yield (82%); ^{1}H NMR ($CDCl_3$) δ 5.54 (s, 2H), 4.12 (s, 2H), 3.45 (s, 2H), 2.94 (s, 3H), 2.15 (s, 4H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 128.52, 72.52, 65.26, 47.09, 38.39, 36.75, 25.76, 18.15, -5.58; Anal. Calcd for $C_{14}H_{28}O_4SSi$: C, 52.46; H, 8.81. Found: C, 52.65; H, 8.72.

9-[1-(*t*-Butyldimethylsilanyloxymethyl)cyclopent-3-enyl-methyl] adenine (88): Compound **88** was synthesized from compound **87** using a similar procedure described for synthesizing compound **74**: yield (52%); ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.82 (s, 1H), 5.83 (s, 2H), 5.51 (s, 2H), 4.21 (s, 2H), 3.30 (s, 2H), 2.34 (d, J = 14.7 Hz, 2H), 2.00 (d, J = 14.7 Hz 2H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.44, 152.89, 150.81, 141.91, 128.72, 119.16, 66.20, 48.69, 47.79, 39.71, 25.87, 18.21, -5.44; Anal. Calcd for $C_{18}H_{29}N_5OSi$: C, 60.13; H, 8.13; N, 19.48. Found: C, 60.31; H, 8.26; N, 19.50.

1-[1-(*t*-Butyldimethylsilanyloxymethyl)cyclopent-3-enylmethyl] uracil (89): Compound **89** was prepared from compound **87** using the method described for synthesizing compound **74**: yield (40%); ^{1}H NMR ($CDCl_3$) δ 8.87 (br s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 6.67 (s, 2H), 5.50 (d, J = 7.6 Hz, 1H), 4.19 (s, 2H), 3.61 (s, 2H), 2.31 (s, 4H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 163.66, 151.81, 147.94, 128.71, 100.65, 68.78, 66.31, 48.91, 38.38, 25.67, 18.28, -5.40;Anal. Calcd for $C_{17}H_{28}N_2O_3Si$: C, 60.68; H, 8.39; N, 8.32. Found: C, 60.89; H, 8.41; N, 8.20.

1-[1-(*t*-Butyldimethylsilanyloxymethyl)cyclopent-3-enyl-methyl] thymine (90): Compound **90** was synthesized from compound **87** using the method described for synthesizing compound **74**: yield (41%); ^{1}H NMR ($CDCl_3$) δ 8.38

(br s, 1H), 7.34 (s, 1H), 5.60 (s, 2H), 4.21 (s, 2H), 3.55 (s, 2H), 2.22 (s, 4H), 1.76 (s, 3H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.12, 152.03, 142.45, 128.51, 102.81, 67.85, 65.65, 47.66, 38.89, 25.67, 18.72, 12.21, −5.53; Anal. Calcd for $C_{18}H_{30}N_2O_3Si$: C, 61.68; H, 8.63; N, 7.99. Found: C, 61.78; H, 8.77; N, 8.09.

1−[1−(*t*−Butyldimethylsilanyloxymethyl)cyclopent−3−enyl−methyl] cytosine (91): Compound **91** was synthesized from compound **87** using the method described for synthesizing compound **74**: yield (48%); ^{1}H NMR ($CDCl_3$) δ 8.02 (d, J = 5.7 Hz, 1H), 6.10 (d, J = 5.7 Hz, 1H), 5.61 (s, 2H), 5.11 (s, 2H), 4.3 (s, 2H), 3.62 (s, 2H), 2.29 (s, 4H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.61, 164.65, 157.32, 128.85, 99.19, 69.76, 65.81, 47.10, 38.68, 25.80, 18.16, −5.57; Anal. Calcd for $C_{17}H_{29}N_3O_2Si$: C, 60.86; H, 8.71; N, 12.52. Found: C, 60.99; H, 8.84; N, 12.40.

9−[1−(Hydroxymethyl)cyclopent−3−enyl−methyl] adenine (92): Compound **92** was synthesized from compound **88** using a similar procedure described forsynthesizing compound **11**: yield (72%): mp 184~186 ℃; UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO−d_6) δ 8.13 (s, 1H), 8.09 (s, 1H), 7.24 (br s, 2H), 5.54 (s, 2H), 5.26 (t, J = 5.7 Hz, 1H), 4.08 (s, 2H), 3.17 (d, J = 5.1 Hz, 2H), 2.34 (d, J = 15.0 Hz, 2H), 2.09 (d, J = 15.0 Hz, 2H); ^{13}C NMR (DMSO−d_6) δ 156.03, 152.35, 150.08, 141.67, 128.72, 118.22, 64.86, 48.14, 47.63, 39.08; Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.58; H, 6.01; N, 28.38.

1−[1−(Hydroxymethyl)cyclopent−3−enyl−methyl] uracil (93): Compound **93** was synthesized from compound **89** using the method described for synthesizing compound **11**: yield (63%): mp 169~171 ℃; UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO−d_6) δ 11.21 (br s, 1H), 7.57 (d, J = 5.7 Hz, 1H), 5.67 (s, 2H), 5.51 (d, J = 5.7 Hz, 1H), 4.86 (t, J = 5.6 Hz, 1H), 4.09 (s, 2H), 3.62 (s, 2H), 2.38 (s, 4H); ^{13}C NMR (DMSO−d_6) δ 163.54, 152.21, 146.87, 128.51, 101.21, 65.33, 49.91, 47.62, 38.31; Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.20; H, 6.19; N, 12.88.

1−[1−(Hydroxymethyl)cyclopent−3−enyl−methyl] thymine (94): Compound **95** was prepared from compound **90** using the procedure described for synthe−sizing compound **11**: yield (79%): mp 168~170 ℃; UV (H_2O) λ_{max} 267.1 nm; ^{1}H

NMR (DMSO−d_6) δ 11.21 (br s, 1H), 7.40 (s, 1H), 5.77 (s, 2H), 4.95 (t, J = 5.7 Hz, 1H), 4.01 (s, 2H), 3.53 (s, 2H), 2.34 (s, 4H), 1.70 (s, 3H); ^{13}C NMR (DMSO−d_6) δ 164.38, 152.11, 143.09, 128.61, 107.15, 70.02, 66.71, 47.87, 39.21, 12.02; Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.88; H, 6.75; N, 12.01.

1−[1−(Hydroxymethyl)cyclopent−3−enyl−methyl] cytosine (95): Compound **95** was synthesized from compound **91** using the method described for synthe−sizing compound **11**: yield (77%): mp 162~164 ℃; UV (H_2O) λ_{max} 271.0 nm; ^{1}H NMR (DMSO−d_6) δ 7.80 (d, J = 5.4 Hz, 1H), 7.06 (br d, 2H), 5.75 (d, J = 5.4 Hz, 1H), 5.55 (s, 2H), 4.89 (t, J = 5.5 Hz, 1H), 4.14 (s, 2H), 3.52 (s, 4H), 3.32 (s, 2H), 2.23 (s, 4H); ^{13}C NMR (DMSO−d_6) δ 165.54, 158.21, 146.67, 128.81, 98.21, 67.12, 65.32, 46.01, 39.12; Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.48; H, 6.73; N, 18.90.

2−(*t*−Butyldimethylsilanyloxymethyl)−prop−2−en−1−ol (97): Compound **97** was prepared from compound **96** using the method for the preparation of compound **54**: yield (78%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 4.99 (m, 2H), 4.15 (s, 2H), 4.07 (s, 2H), 0.83 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 147.43, 111.04, 65.05, 64.59, 25.83, 18.26, −5.46.

Methanesulfonic acid 2−(*t*−butyldimethylsilanyloxymethyl) allyl ester (98): Compound **98** was prepared from compound **97** using the method for the preparation of compound **73**: yield (76%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 5.26 (s, 1H), 5.19 (s, 1H), 4.65 (s, 2H), 4.12 (s, 2H), 2.96(s, 3H), 0.82 (s, 9H), 0.03 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 142.23, 116.76, 69.91, 63.02, 37.45, 25.78, 18.81, −5.76.

9−[2−(*t*−Butyldimethylsilanyloxymethyl) allyl ester] adenine (99): Compound **99** was prepared from compound **98** using the method for the preparation of compound **74**: yield (30%); ^{1}H NMR ($CDCl_3$) δ 8.35 (s, 1H), 7.80 (s, 1H), 5.62 (s, 1H), 5.22 (s, 1H), 4.78 (s, 2H), 4.11 (s, 2H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.45, 153.24, 143.92, 141.01, 113.51, 64.11, 45.65, 25.45, 18.43, −5.54.

1−[2−(*t*−Butyldimethylsilanyloxymethyl) allyl ester] cytosine (100): Cytosine derivative **100** was synthesized from **98** by the similar procedure as described

for **74**: yield (37%); ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 6.6 Hz, 1H), 5.74 (d, J = 6.6 Hz, 1H), 5.27 (s, 1H), 4.95 (s, 1H), 4.41 (s, 2H), 4.15 (s, 2H), 0.91 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.31, 155.80, 147.61, 146.80, 109.54, 64.21, 49.72, 25.67, 18.82, −5.23.

1−[2−(*t*−Butyldimethylsilanyloxymethyl) allyl ester] uracil (101): Uracil derivative **101** was synthesized from **98** by the similar procedure as described for **74**: yield (30%); ^{1}H NMR ($CDCl_3$) δ 8.43 (br s, 1H), 7.21 (d, J = 7.6 Hz, 1H), 5.75 (d, J = 7.6 Hz, 1H), 5.35 (s, 1H), 5.20 (s, 1H), 4.54 (s, 2H), 4.32 (s, 2H), 0.88 (s, 8H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.56, 153.82, 145.78, 141.21, 119.55, 103.27, 64.38, 49.25, 25.34, 18.82, −5.53.

1−[2−(*t*−Butyldimethylsilanyloxymethyl) allyl ester] thymine (102): Thymine derivative **102** was synthesized from **98** by the similar procedure as described for **74**: yield (27%); ^{1}H NMR ($CDCl_3$) δ 8.74 (br s, 1H), 7.05 (s, 1H), 5.41 (s, 1H), 5.10 (s, 1H), 4.56 (s, 2H), 4.21 (s, 2H), 1.56 (s, 3H), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.23, 152.76, 143.33, 141.90, 119.72, 106.45, 64.78, 48.99, 25.61, 18.58, 13.12, −5.34.

9−[2−(Hydroxymethyl) allyl ester] adenine (103): Adenine nucleoside **103** was prepared from compound **99** using the method for the preparation of compound **11**: yield (81%) as a white solid: mp 179~181 ℃; UV (H_2O) λ_{max} 262.0 nm; ^{1}H NMR (DMSO−d_6) δ 8.15 (s, 1H), 8.05 (s, 1H), 7.08 (br s, 2H), 5.52 (s, 1H), 5.17 (s, 1H), 4.99 (s, 1H), 4.65 (s, 2H), 4.13 (s, 2H); ^{13}C NMR (DMSO−d_6) δ 154.98, 153.24, 149.60, 145.92, 141.01, 118.51, 110.76, 64.11, 45.65; Anal. Calcd for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.90; H, 5.52; N, 34.10.

1−[2−(Hydroxymethyl) allyl ester] cytosine (104): Cytosine nucleoside **104** was synthesized from **100** by the similar procedure as described for **11**: yield (70%) as a white solid: mp 168~170 ℃; UV (H_2O) λ_{max} 272.0 nm; ^{1}H NMR (DMSO−d_6) δ 7.44 (d, J = 6.9 Hz, 1H), 6.98 (br d, 2H), 5.04 (s, 1H), 4.95 (t, J = 5.4 Hz, 1H), 4.68 (s, 1H), 4.22 (s, 2H), 3.84 (d, J = 5.1 Hz, 2H); ^{13}C NMR (DMSO−d_6) δ 165.87, 155.81, 146.20, 145.84, 113.78, 109.53, 62.67, 49.52; Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.91; H, 6.22; N, 23.11.

1-[2-(Hydroxymethyl) allyl ester] uracil (105): Uracil nucleoside **105** was synthesized from **101** by the similar procedure as described for **11**: yield (74%) as a white solid: mp 166~169 ℃; UV (H_2O) λ_{max} 262.0 nm; ^{1}H NMR (DMSO-d_6) δ 11.25 (br s, 1H), 7.47 (d, J = 7.4 Hz, 1H), 5.73 (d, J = 7.4 Hz, 1H), 5.45 (s, 1H), 5.18 (s, 1H), 4.50 (s, 2H), 4.22 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 165.68, 152.24, 145.61, 143.83, 118.24, 102.90, 63.76, 49.28; Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.90; H, 5.68; N, 15.46.

1-[2-(Hydroxymethyl) allyl ester] thymine (106): Thymine nucleoside **106** was synthesized from **102** by the similar procedure as described for **11**: yield (79%) as a white solid: mp 164~165 ℃; UV (H_2O) λ_{max} 266.0 nm; ^{1}H NMR (DMSO-d_6) δ 8.69 (br s, 1H), 7.12 (s, 1H), 5.38 (s, 1H), 5.09 (s, 1H), 4.50 (s, 2H), 4.18 (s, 2H), 1.55 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.62, 153.87, 144.38, 141.45, 118.72, 103.26, 64.78, 49.12, 13.21; Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.91; H, 5.97; N, 14.11.

[2-(*t*-Butyldimethylsilanyloxymethyl)-allyloxymethyl] phosphonic acid diiso-propyl ester (107): To a solution of **97** (2.14 g, 10.60 mmol) in (11 mL) of DMF was added LiI (108 mg, 0.79 mmol) at 25 ℃. Li*O*t-Bu (17.10 mL of 1 M solution in THF, 17.10 mmol) and a solution of diisopropyl bromomethylphosphonate (3.75 g, 14.40 mmol) in 10 mL of DMF were slowly and simultaneously added to the reaction mixture for 5 h at 60 ℃ under anhydrous condition. The mixture was quenched by adding water (80 mL), and the organic solvents (THF) were removed in *vacuo*. The aqueous layer was extracted with EtOAc (3x150 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concen-trated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/ hexane, 1:2) to give **107** (2.58 g, 64%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 5.11 (m, 2H), 4.71 (m, 2H), 4.53 (s, 2H), 4.19 (s, 2H), 3.73 (d, J = 7.8 Hz, 2H), 1.36 (m, 12H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.21, 112.35, 70.23, 66.32, 65.34, 64.50, 25.82, 23.45, 18.21, -5.56.

(2-Hydroxymethylallyloxymethyl) phosphonic acid diisopropyl ester (108): Compound **108** was prepared from **107** by the procedure as described for **11**: yield (80%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 5.09 (m, 2H), 4.75 (m, 2H), 4.44 (s, 2H), 4.21 (s, 2H), 3.70 (d, J = 8.0 Hz, 2H), 1.35 (m, 12H); ^{13}C NMR

($CDCl_3$) δ 146.45, 115.43, 69.23, 66.72, 65.56, 63.23, 23.67.

Methanesulfonic acid 2-(diisopropoxyphosphorylmethoxymethyl) allyl ester (109): Mesylate **109** was prepared from **108** by the procedure as descrybed for **73**: yield (78%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 5.12 (m, 2H), 4.77 (m, 2H), 4.61 (s, 2H), 4.33 (s, 2H), 3.73 (d, J = 8.2 Hz, 2H), 3.03 (s, 3H), 1.37 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 149.21, 118.21, 71.02, 67.56, 65.45, 63.89, 36.45, 23.81.

9-[2-(Diisopropoxyphosphorylmethoxymethyl) allyl] adenine (110): Adenine derivative **110** was synthesized from **109** using the reaction condition as described for **74**: yield (35%) as a yellow syrup; ^{1}H NMR ($CDCl_3$) δ 8.33 (s, 1H), 7.78 (s, 1H), 5.60 (s, 1H), 5.19 (s, 1H), 4.79 (s, 2H), 4.75 (m, 2H), 4.08 (s, 2H), 3.74 (d, J = 8.0 Hz, 2H), 1.36 (m, 12H);^{13}C NMR ($CDCl_3$) δ 155.38, 153.17, 143.16, 140.91, 70.57, 65.56, 64.11, 45.21, 23.81; Anal. Calcd for $C_{16}H_{26}N_5O_4P$: C, 50.13; H, 6.84; N, 18.27. Found: C, 49.97; H, 6.72; N, 18.11.

1-[2-(Diisopropoxyphosphorylmethoxymethyl) allyl] cytosine (111): Cytosine derivative **111** was prepared from compound **109** using the method described for synthesizing compound **74**: yield (30%) as a yellow syrup; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J = 6.9 Hz, 1H), 5.71 (d, J = 6.9 Hz, 1H), 5.25 (s, 1H), 4.98 (s, 1H), 4.70 (m, 2H), 4.43 (s, 2H), 4.12 (s, 2H), 3.74 (d, J = 7.9 Hz, 2H), 1.35 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 165.78, 155.89, 147.32, 146.81, 108.43, 95.45, 70.25, 65.87, 64.15, 50.64, 23.66; Anal. Calcd for $C_{15}H_{26}N_3O_5P$: C, 50.13 H, 7.29; N, 11.69. Found: C, 49.90; H, 7.12; N, 11.81.

1-[2-(Diisopropoxyphosphorylmethoxymethyl) allyl] uracil (112): Uracil derivative **112** was prepared from compound **109** using the method described for synthesizing compound **74**: yield (28%) as a yellow syrup; ^{1}H NMR ($CDCl_3$) δ 8.40 (br s, 1H), 7.17 (d, J = 7.8 Hz, 1H), 5.73 (d, J = 7.8 Hz, 1H), 5.36 (s, 1H), 5.18 (s, 1H), 4.72 (m, 2H), 4.57 (s, 2H), 4.40 (s, 2H), 3.71 (d, J = 7.8 Hz, 2H), 1.36 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 163.23, 151.70, 143.34, 141.25, 118.56, 102.56, 70.56, 66.21, 64.71, 49.71, 23.56; Anal. Calcd for $C_{15}H_{25}N_2O_6P$: C, 50.00; H, 6.99; N, 7.77. Found: C, 49.80; H, 7.13; N, 7.89.

1-[2-(Diisopropoxyphosphorylmethoxymethyl) allyl] thymine (113): Thymine derivative **113** was prepared from compound **109** using the method desribed for

synthesizing compound **74**: yield (25%) as a yellow syrup; ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1H), 6.96 (s, 1H), 5.34 (s, 1H), 5.17 (s, 1H), 4.71 (m, 2H), 4.57 (s, 2H), 4.19 (s, 2H), 3.72 (d, J = 7.8 Hz, 2H), 1.78 (s, 3H), 1.35 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 164.20, 151.81, 144.21, 142.67, 118.87, 108.12, 70.78, 65.28, 64.49, 49.44, 23.61, 12.98; Anal. Calcd for $C_{16}H_{27}N_2O_6P$: C, 51.33; H, 7.27; N, 7.48. Found: C, 51.41; H, 7.17; N, 7.61.

9-[2-(Hydroxymethyl)-allyloxymethylphosphonic acid] denine (114): To a solution of the phosphonate **110** (150 mg, 0.39 mmol) in 10 mL of anhydrous methylene chloride was added $(CH_3)_3SiBr$ (0.57 g, 3.74 mmol). The mixture was refluxed for overnight and concentrated *in vacuo*. The residue was partitioned between distilled water and washed out by CH_2Cl_2. The aqueous layer was dried by freezer dryer to give **114** (92 mg, 79%): UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6) δ 8.11 (s, 1H), 8.07 (s, 1H), 5.07 (s, 1H), 5.02 (t, J = 5.4 Hz, 1H), 4.75 (s, 2H), 3.91 (d, J = 5.7 Hz, 2H), 3.74 (d, J = 8.2 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 155.97, 152.52, 149.58, 145.54, 141.03, 118.49, 110.63, 65.27, 61.97, 44.50.

1-[2-(Hydroxymethyl)-allyloxymethylphosphonic acid] cytosine (115): Cytosine nucleotide **115** was prepared from **111** using the method as descrybed for **114**: yield (69%): UV (H_2O) λ_{max} 271.0 nm; ^{1}H NMR (DMSO-d_6) δ 7.46 (d, J = 6.9 Hz, 1H), 7.06 (br d, 2H), 5.64 (d, J = 6.9 Hz, 1H), 5.47 (s, 1H), 4.95 (t, J = 5.4 Hz, 1H), 4.68 (s, 1H), 4.22 (s, 2H), 3.86 (d, J = 5.1 Hz, 2H), 3.72 (d, J = 7.8 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 165.88, 155.80, 146.28, 145.84, 109.71, 93.48, 65.61, 62.05, 49.51.

1-[2-(Hydroxymethyl)-allyloxymethylphosphonic acid] uracil (116): Uracil nucleotide **116** was prepared from compound **112** using the method described for synthesizing compound **114**: yield (65%): UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6) δ 8.40 (br s, 1H), 7.15 (d, J = 7.6 Hz, 1H), 5.70 (d, J = 7.6 Hz, 1H), 5.21 (s, 1H), 5.11 (s, 1H), 4.97 (t, J = 5.6 Hz, 1H), 4.21 (s, 2H), 3.85 (s, 2H), 3.71 (d, J = 8.0 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 163.65, 152.45, 142.89, 141.23, 110.43, 101.34, 65.48, 63.56, 49.78.

1-[2-(Hydroxymethyl)-allyloxymethylphosphonic acid] thymine (117): Thymine nucleotide **117** was prepared from compound **113** using the method

described for synthesizing compound **114**: yield (76%): UV (H_2O) λ_{max} 267.5 nm; ^{1}H NMR (DMSO−d_6) δ 7.12 (s, 1H), 5.24 (s, 1H), 5.12 (s, 1H), 4.99 (t, J = 5.4 Hz, 1H), 4.27 (s, 2H), 3.87 (s, 2H), 3.73 (d, J = 7.8 Hz, 2H), 2.02 (s, 3H); ^{13}C NMR (DMSO−d_6) δ 164.67, 152.34, 144.56, 142.81, 113.57, 105.62, 65.27, 64.12, 49.67, 13.11.

Diisopropyl {[1−(*t*−butyldimethylsilanyloxymethyl) cyclopent−3−enyl]−oxy} methyl phosphonate (118): Compound **118** was prepared from compound **86** using the method for the preparation of compound **107**: yield (64%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 5.53 (s, 2H), 4.72 (m, 2H), 3.72 (d, J = 8.1 Hz, 2H), 3.45 (d, J = 3.6 Hz, 4H), 2.13 (s, 4H), 1.30 (m, 12H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 128.79, 76.90, 76.76, 70.72, 67.31, 65.86, 65.09, 47.82, 31.74, 25.53, 23.92, 18.15, −5.57. Anal. Calcd for $C_{20}H_{41}O_5PSi$: C, 57.11; H, 9.83. Found: C, 57.02; H, 10.01.

Diisopropyl {[1−(hydroxymethyl)−cyclopent−3−enyl]−oxy} methyl phosphonate (119): Compound **119** was prepared from compound **118** using the method for the preparation of compound **11**: yield (87%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 5.59 (s, 2H), 4.76 (m, 2H), 3.74 (dd, J = 6.6, 0.9 Hz, 2H), 3.62 (s, 2H), 3.52 (s, 2H), 2.25 (d, J = 15.3 Hz, 2H), 2.16 (d, J = 15.2 Hz, 2H), 1.35 (d, J = 6.3 Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 128.68, 78.35, 78.27, 71.17, 67.16, 66.79, 64.59, 47.52, 38.84, 23.96. Anal. Calcd for $C_{14}H_{27}O_5P$: C, 54.89; H, 8.88. Found: C, 54.67; H, 8.73.

Methanesulfonic acid 1−[diisopropyl {[1−(hydroxymethyl)−cyclopent−3−enyl]−oxy} methyl phosphonate] ester (120): Compound **120** was prepared from compound **119** using the method for the preparation of compound **73**: yield (75%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 5.60 (s, 2H), 4.72 (m, 2H), 4.16 (s, 2H), 3.75 (d, J = 9.3 Hz, 2H), 3.52 (s, 3H), 2.26 (s, 4H), 1.34 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 128.42, 75.88, 75.73, 72.38, 70.97, 67.23, 65.00, 46.02, 38.79, 36.88, 23.99. Anal. Calcd for $C_{15}H_{29}O_7PS$: C, 46.86; H, 7.60. Found: C, 46.78; H, 7.72.

9−[1−[Diisopropyl {[1−(hydroxymethyl)−cyclopent−3−enyl]−oxy} methyl−phosphonate]] adenine (121): Compound **121** was prepared from compound **120** using the method for the preparation of compound **74**: yield (52%): UV (MeOH)

λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1H), 8.11 (s, 1H), 6.83 (br s, 2H), 5.62 (s, 2H), 4.84 (m, 2H), 4.33 (s, 2H), 3.80 (d, J = 8.4 Hz, 2H), 3.37 (s, 2H), 2.52 (d, J = 14.7 Hz, 2H), 2.20 (d, J = 14.7 Hz, 2H), 1.38 (dd, J = 6.3, 2.7 Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 155.72, 152.78, 150.56, 142.00, 128.49, 119.05, 70.98, 67.03, 64.80, 47.83, 47.56, 40.05, 24.00, 22.56. Anal. Calcd for $C_{19}H_{30}N_5O_4P$: C, 53.89; H, 7.14; N, 16.54. Found: C, 54.11; H, 6.97; N, 16.36.

1-[1-[Diisopropyl {[1-(hydroxymethyl)-cyclopent-3-enyl]-oxy} methyl-phosphonate]] cytosine (122): Compound **122** was prepared from **120** using the method as described for **74**: yield (42%): UV (MeOH) λ_{max} 271.0 nm; ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 6.0 Hz, 1H), 6.11 (d, J = 6.0 Hz, 1H), 5.60 (s, 2H), 4.72 (m, 2H), 4.20 (s, 2H), 3.76 (d, J = 7.8 Hz, 2H), 3.63 (s, 2H), 2.32 (s, 2H), 1.28 (t, J = 6.0 Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 164.96, 156.42, 145.60, 128.76, 99.50, 71.08, 69.65, 67.24, 65.04, 46.05, 39.15, 23.98. Anal. Calcd for $C_{18}H_{30}N_3O_5P$: C, 54.13; H, 7.57; N, 10.52. Found: C, 54.33; H, 7.42; N, 10.59.

1-[1-[Diisopropyl {[1-(hydroxymethyl)-cyclopent-3-enyl]-oxy} methyl-phosphonate]] thymine (123): Compound **123** was prepared from **120** using the method as described for **74**: yield (38%): UV (MeOH) λ_{max} 266.5 nm; ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 1H), 5.60 (s, 1H), 5.55 (s, 1H), 4.72 (m, 2H), 4.15 (s, 1H), 3.88 (s, 1H), 3.70 (t, J = 7.5 Hz, 2H), 3.48 (s, 1H), 3.85 (s, 1H), 2.30 (d, J = 14.4 Hz, 2H), 1.95 (d, J = 14.4 Hz, 2H), 1.34 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 165.34, 153.34, 139.93, 128.83, 109.16, 79.08, 70.80, 67.13, 64.90, 52.41, 48.56, 48.06, 46.28, 39.68, 39.19, 24.04, 13.06. Anal. Calcd for $C_{19}H_{31}N_2O_6P$: C, 55.06; H, 7.54; N, 6.76. Found: C, 54.87; H, 7.40; N, 6.89.

1-[1-[Diisopropyl {[1-(hydroxymethyl)-cyclopent-3-enyl]-oxy} methyl-phosphonate]] uracil (124): Compound **124** was prepared from **120** using the method as described for **74**: yield (40%): UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$) δ 9.41 (br s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 5.65 (s, 2H), 5.52 (d, J = 7.8 Hz, 1H), 4.77 (m, 2H), 4.23 (s, 2H), 3.81 (d, J = 7.8 Hz, 2H), 3.63 (s, 2H), 2.12 (s, 2H), 1.30 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 164.76, 150.45, 147.23, 128.65, 100.25, 71.45, 69.62, 66.90, 65.12, 45.87, 39.81, 23.99. Anal. Calcd for $C_{18}H_{29}N_2O_6P$: C, 53.99; H, 7.30; N, 7.00. Found: C, 54.23; H, 7.40; N, 6.81.

[1-(*t*-Butyldimethylsilanyloxymethyl) cyclobutyl] methyl phosphonic acid diisopropyl ester (125): Compound **125** was prepared from compound **72** using the method for the preparation of compound **107**: yield (62%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 4.76 (m, 2H), 3.74 (d, J = 8.0 Hz, 2H), 3.65 (s, 2H), 3.60 (s, 2H), 1.82-1.60 (m, 6H), 1.37 (m 12H), 0.87 (s, 9H), 0.16 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 72.75, 70.67, 70.02, 65.31, 43.34, 25.56, 23.78, 18.58, 15.45, -5.45; Anal. Calcd for $C_{19}H_{41}O_5PSi$: C, 55.85; H, 10.11. Found: C, 55.71; H, 10.03.

[1-(Hydroxymethyl) cyclobutyl] methyl phosphonic acid diisopropyl ester (126): Compound **126** was prepared from compound **125** using the method for the preparation of compound **11**: yield (77%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 4.78 (m, 2H), 3.70 (d, J = 8.2 Hz, 2H), 3.66 (s, 2H), 3.61 (s, 2H), 1.80-1.61 (m, 6H), 1.36 (m 12H); ^{13}C NMR ($CDCl_3$) δ 71.89, 71.13, 70.23, 65.63, 44.12, 23.69, 15.38.

Methanesulfonate-1-(*t*-butyldimethylsilanyloxymethyl) cyclobutyl-methyl phosphonic acid diisopropyl ester (127): Compound **127** was prepared from compound **126** using the method for the preparation of compound **73**: yield (70%) as colorless oil; ^{1}H NMR ($CDCl_3$) δ 4.76 (m, 2H), 4.16 (s, 2H), 3.72 (d, J = 7.8 Hz, 2H), 3.58 (s, 2H), 3.01 (s, 3H), 1.90-1.70 (m, 6H), 1.35 (m 12H); ^{13}C NMR ($CDCl_3$) δ 72.87, 71.67, 66.65, 65.63, 43.12, 36.72, 23.77, 15.71.

9-[1-(Diisopropoxyphosphorylmethoxymethyl) cyclobutyl-methyl] adenine (128): Compound **128** was prepared from compound **127** using the method for the preparation of compound **74**: yield (52%); ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H), 8.03 (s, 1H), 4.74 (m, 2H), 4.18 (s, 2H), 3.70 (d, J = 7.6 Hz, 2H), 3.61 (s, 2H), 1.88-1.68 (m, 6H), 1.34 (m 12H); ^{13}C NMR ($CDCl_3$) δ 154.72, 153.03, 142.65, 118.67, 71.83, 71.21, 67.92, 64.39, 44.28, 27.63, 23.61, 15.75.

1-[1-(Diisopropoxyphosphorylmethoxymethyl) cyclobutyl-methyl] uracil (129): Compound **129** was prepared from compound **127** using the method described for synthesizing compound **74**: yield (23%); ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 7.8 Hz, 1H), 5.64 (d, J= 7.8 Hz, 1H), 4.80 (m, 2H), 3.97 (s, 2H), 3.70 (d, J = 7.6 Hz, 2H), 3.60 (s, 2H), 1.90-1.71 (m, 6H), 1.36 (m 12H); ^{13}C NMR ($CDCl_3$) δ 164.65, 152.59, 143.63, 103.88, 72.48, 71.72, 66.35, 63.85, 43.65, 26.74, 23.21, 15.23.

1-[1-(Diisopropoxyphosphorylmethoxymethyl) cyclobutyl-methyl] thymine (130): Compound **130** was obtained from compound **127** using the similar method described for **74**: yield (22%); ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H), 4.82 (m, 2H), 3.90 (s, 2H), 3.73 (d, J = 7.8 Hz, 2H), 3.67 (s, 2H), 1.76 (s, 3H), 1.89-1.68 (m, 6H), 1.40 (m 12H); ^{13}C NMR ($CDCl_3$) δ 164.92, 154.25, 139.63, 107.61, 71.66, 70.32, 67.72, 64.76, 44.28, 26.11, 23.83, 14.97, 11.59.

1-[1-(Diisopropoxyphosphorylmethoxymethyl) cyclobutyl-methyl] cytosine (131): Compound **131** was synthesized from compound **127** using the similar procedure described for **74**: yield (43%); ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 7.6 Hz, 1H), 6.84 (br d, 2H), 5.67 (d, J = 7.6 Hz, 1H), 4.79 (m, 2H), 4.02 (s, 2H), 3.75 (d, J = 8.0 Hz, 2H), 3.65 (s, 2H), 1.88-1.67 (m, 6H), 1.39 (m 12H); ^{13}C NMR ($CDCl_3$) δ 165.67, 155.84, 146.26, 93.38, 72.76, 70.94, 67.45, 65.36, 43.31, 27.25, 22.99, 15.03.

9-[1-(Hydromethyl) cyclobutylmethylphosphonic acid] adenine (132): Compound **132** was prepared from compound **128** using the method for the preparation of compound **114**: yield (78%) as a solid: mp 136~138 ℃; UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO-d_6) δ 8.08 (s, 1H), 7.71 (s, 1H), 4.05 (s, 2H), 3.73 (d, J = 8.0 Hz, 2H), 3.67 (s, 2H), 1.90-1.68 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 154.95, 151.23, 143.12, 114.87, 65.56, 64.40, 58.34, 43.76, 26.76, 14.82; Anal. Calcd for $C_{12}H_{18}N_5O_4P \cdot 1.5H_2O$: C, 40.68; H, 5.97; N, 19.77. Found: C, 40.77; H, 6.11; N, 19.64.

1-[1-(Hydroxymethyl) cyclobutylmethylphosphonic acid] uracil (133): Compound **133** was obtained from compound **129** using the method described for synthesizing compound **114**: yield (76%): mp 142~144 ℃; UV (H_2O) λ_{max} 262.5 nm; ^{1}H NMR (DMSO-d_6) δ 11.23 (br s, 1H), 7.67 (d, J = 6.8 Hz, 1H), 5.57 (d, J = 6.8 Hz, 1H), 4.12 (s, 2H), 3.70 (d, J = 8.2 Hz, 2H), 3.62 (s, 2H), 1.86-1.66 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 163.78, 153.23, 144.29, 102.65, 66.34, 64.73, 57.65, 44.59, 26.12, 14.66; Anal. Calcd for $C_{11}H_{17}N_2O_6P \cdot 0.2MeOH$: C, 43.30; H, 5.78; N, 9.02. Found: C, 43.11; H, 5.65; N, 8.87.

1-[1-(Hydroxymethyl) cyclobutylmethylphosphonic acid] thymine (134): Compound **134** was synthesized from compound **130** using the similar method described for **114**: yield (72%): mp 128~130 ℃; UV (H_2O) λ_{max} 267.0 nm; ^{1}H

NMR (DMSO-d_6) δ 11.38 (br s, 1H), 7.42 (s, 1H), 3.99 (s, 2H), 3.72 (d, J = 8.2 Hz, 2H), 3.52 (s, 2H), 1.79 (s, 3H), 1.80-1.61 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 164.76, 152.21, 141.74, 107.43, 65.39, 64.63, 52.76, 43.37, 27.25, 14.85, 12.19; Anal. Calcd for $C_{12}H_{19}N_2O_6P$: C, 45.29; H, 6.02; N, 8.80. Found: C, 45.41; H, 5.92; N, 8.98.

1-[1-(Hydroxymethyl) cyclobutylmethylphosphonic acid] cytosine (135): Compound **135** was synthesized from compound **131** usingthe similar procedure described for compound **114**: yield (75%): mp 133~136 ℃; UV (H_2O) λ_{max} 272.5 nm; ^{1}H NMR (DMSO-d_6) δ 7.76 (d, J = 7.0 Hz, 1H), 7.09 (br d, 2H), 5.69 (d, J = 7.0 Hz, 1H), 3.93 (s, 2H), 3.69 (d, J = 7.8 Hz, 2H), 3.58 (s, 2H), 1.86-1.62 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 165.81, 156.48, 145.51, 94.65, 65.87, 63.34, 53.76, 43.76, 26.43, 14.81; Anal. Calcd for $C_{11}H_{18}N_3O_5P \cdot 2H_2O$: C, 38.94; H, 6.54; N, 12.38. Found: C, 39.12; H, 6.47; N, 12.10.

***cis*-4-(*t*-Butyldimethylsilanyloxy)-but-2-en-1-ol (137)**: Compound **137** was prepared from compound **136** using the method for the preparation of compound **54**: yield (61%) as acolorless syrup; ^{1}H NMR ($CDCl_3$) δ 5.60 (d, J = 4.8 Hz, 2H), 4.17 (d, J = 4.5 Hz, 2H), 4.11 (d, J = 4.5 Hz, 2H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 131.31, 130.08, 59.58, 58.83, 25.90, 18.32, -5.24.

(±)-*cis*-[2-(*t*-Butyldimethylsilanyloxymethyl)-cyclopropyl-methanol (138): To a mixture of **137** (3.50 g, 17.29 mmol) in (50 mL) of CH_2Cl_2 at 0 ℃ was added $Zn(Et)_2$ (34.58 mL, 1 M in hexane) and CH_2I_2 (69.16 mmol). The mixture was stirred at 0 ℃ for 3 h and quenched with a saturated NH_4Cl. After the mixture was concentrated to 1/3 of the original volume, the aqueous layer was extracted with EtOAc. The organic layer was 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 **138** (2.95 g, 79%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 4.07 (dd, J = 11.1, 5.4 Hz, 1H), 3.84 (m, 1H), 3.10 (m, 2H), 1.25 (m, 1H), 1.13 (m, 1H), 0.97 (s, 9H), 0.78 (m, 1H), 0.32 (m, 1H), 0.21 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 63.85, 63.09, 25.81, 18.45, 18.15, 15.36, 8.35, -5.56.

(±)-*cis*-[2-(*t*-Butyldimethylsilanyloxymethyl)-cyclopropyl-methoxymethyl-phosphonic acid diisopropyl ester (139): Compound **139** was prepared from compound **138** using the method for the preparation of compound **107**: yield (66%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 4.67 (m, 2H), 3.72 (d, J = 8.0 Hz, 2H), 3.50 (m, 4H), 1.35 (m, 13H), 1.18 (m, 1H), 0.91 (s, 9H), 0.72 (m, 1H), 0.35 (m, 1H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 69.81, 66.87, 64.34, 63.77, 25.80, 23.81, 18.78, 18.21, 17.35, 7.64, -5.41; Anal. Calcd for $C_{18}H_{39}O_5PSi$: C, 54.79; H, 9.96. Found: C, 54.99; H, 9.70.

(±)-*cis*-[2-(Hydroxymethyl)-cyclopropyl-methoxymethyl-phosphonic acid diisopropyl ester (140): Compound **140** was prepared from compound **139** using the method for the preparation of compound **11**: yield (81%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 4.71 (m, 2H), 3.82 (d, J = 8.2 Hz, 2H), 3.67 (m, 4H), 1.41 (m, 12H), 1.29 (m, 2H), 0.86 (m, 1H), 0.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 71.21, 66.72, 65.98, 64.12, 23.85, 18.23, 14.65, 7.98.

(±)-*cis*-Methanesulfonic acid-2-(diisopropoxyphosphorylmethoxymethyl)-cyclopropyl methyl ester (141): Compound **141** was prepared from compound **140** using the method for the preparation of compound **73**: yield (62%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 4.80 (m, 2H), 3.73 (d, J = 8.2 Hz, 2H), 3.64-4.55 (m, 4H), 3.05 (s, 3H), 1.37 (m, 12H), 1.21 (m, 2H), 0.83 (m, 1H), 0.34 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 71.45, 65.43, 63.45, 65.67, 36.43, 23.93, 20.34, 18.55, 14.32, 7.12.

(±)-*cis*-9-[2-(Diisopropoxyphosphorylmethoxymethyl)-cyclopropyl-methyl ester] adenine (142): Compound **142** was prepared from compound **141** using the method for the preparation of compound **74**: yield (41%); ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1H), 8.05 (s, 1H), 5.61 (br s, 2H), 4.85 (m, 2H), 4.33 (dd, J = 14.4, 6.3 Hz, 1H), 4.11-3.96 (m, 2H), 3.71 (d, J = 8.4, Hz, 2H), 3.50 (dd, J = 11.7, 8.7 Hz, 1H), 1.38-1.23 (m, 14H), 0.87 (m, 1H), 0.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 155.96, 152.30, 140.84, 118.62, 71.23, 66.45, 62.21, 42.96, 23.56, 18.21, 15.83, 7.56.

(±)-*cis*-1-[2-(Diisopropoxyphosphorylmethoxymethyl)-cyclopropyl-methyl ester] cytosine (143): Compound **143** was prepared from **141** using the method as described for **74**: yield (41%); ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 7.5 Hz, 1H),

5.60 (d, J = 7.5 Hz, 1H), 4.81 (m, 2H), 4.10 (dd, J = 14.4, 5.7 Hz, 1H), 3.90 (dd, J = 12.3 Hz, 1H), 3.72 (d, J = 8.1 Hz, 2H), 3.49−3.33 (m, 2H), 1.30−1.23 (m, 14H), 0.80 (m, 1H), 0.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 165.63, 156.79, 145.96, 93.52, 69.87, 65.98, 62.35, 47.78, 23.59, 18.27, 15.23, 6.89.

(±)−*cis*−1−[2−(Diisopropoxyphosphorylmethoxymethyl)−cyclopropyl−methyl ester] thymine (144): Compound **144** was prepared from **141** using the method as described for **74**: yield (40%); ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1H), 4.87 (m, 2H), 3.96−3.88 (m, 2H), 3.70 (d, J = 8.3 Hz, 2H), 3.52 (dd, J = 14.7, 7.2 Hz, 1H), 3.37 (dd, J = 11.4, 8.1 Hz, 1H), 1.84 (s, 3H), 1.36−1.20 (m, 14H), 0.79 (m, 1H), 0.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 155.65, 153.63, 138.76, 109.21, 71.05, 65.65, 63.23, 45.56, 24.09, 18.12, 15.87, 13.02, 7.34.

(±)−*cis*−1−[2−(Diisopropoxyphosphorylmethoxymethyl)−cyclopropyl−methyl ester] uracil (145): Compound **145** was prepared from **141** using the method as described for **74**: yield (44%); ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 6.8 Hz, 1H), 5.62 (d, J = 6.8 Hz, 1H), 4.80 (m, 2H), 4.09 (dd, J = 14.1, 5.1 Hz, 1H), 3.99 (dd, J = 11.7, 4.8 Hz, 1H), 3.66 (s, 2H), 3.33−3.29 (m, 2H), 1.30 (m, 12H), 1.21 (m, 2H), 0.82 (m, 1H), 0.29 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.75, 151.09, 144.91, 101.79, 70.99, 65.21, 62.18, 46.18, 23.67, 18.30, 15.01, 6.70.

(±)−*cis*−9−[2−(Methoxymethyl)−cyclopropyl−methyl phosphonic acid] adenine (146): Compound **146** was prepared from compound **142** using the method for the preparation of compound **114**: yield (74%): UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO−d_6) δ 8.19 (s, 1H), 8.01 (s, 1H), 5.61 (br s, 2H), 7.07 (br s 2H), 4.68 (t, J = 5.6 Hz, 1H), 4.12 (dd, J = 13.5, 6.6 Hz, 1H), 3.97 (dd, J = 14.4, 7.2 Hz, 1H), 3.71 (d, J = 8.0 Hz, 2H), 3.62−3.52 (m, 1H), 3.28−3.24 (m, 2H), 1.29−0.96 (m 2H), 0.57 (m, 1H), 0.20 (m,1H); ^{13}C NMR (DMSO−d_6) δ 155.89, 152.21, 149.76, 140.78, 112.41, 71.46, 60.17, 42.42, 18.71, 15.81, 7.74.

(±)−*cis*−1−[2−(Methoxymethyl)−cyclopropyl−methyl phosphonic acid] cytosine (147): Compound **147** was prepared from **143** using the method as described for **114**: yield (79%): UV (H_2O) λ_{max} 271.5 nm; ^{1}H NMR (DMSO−d_6) δ 7.48 (d, J = 7.2 Hz, 1H), 6.77 (br d, 2H), 5.45 (d, J = 7.5 Hz, 1H), 4.67 (t, J = 5.1 Hz, 1H), 3.81 (dd, J = 13.8, 6.6 Hz, 1H), 3.68− 3.52 (m, 4H), 3.26 (m, 1H), 1.16−1.05 (m, 2H), 0.60 (m, 1H), 0.21 (m, 1H); ^{13}C NMR (DMSO−d_6) δ 165.90,

156.12, 145.99, 93.13, 69.87, 60.39, 47.56, 23.59, 18.51, 15.27, 7.20.

(±)-*cis*-1-[2-(Methoxymethyl)-cyclopropyl-methyl phosphonic acid] thymine (148): Compound **148** was prepared from **144** using the method as described for **114**: yield (84%): UV (H_2O) λ_{max} 267.5 nm; ^{1}H NMR (DMSO-d_6) δ 7.45 (s, 1H), 4.67 (t, J = 6.0 Hz, 1H), 3.82-3.94 (m, 2H), 3.73 (d, J = 8.4 Hz, 2H), 3.41 (dd, J = 13.7, 7.0 Hz, 1H), 3.27 (dd, J = 12.4, 7.8 Hz, 1H), 1.80 (s, 3H), 1.31-1.21 (m, 2H), 0.81 (m, 1H), 0.27 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 155.56, 154.76, 137.12, 104.98, 69.78, 61.76, 44.87, 23.88, 18.43, 14.98, 13.43, 7.23.

(±)-*cis*-1-[2-(Methoxymethyl)-cyclopropyl-methyl phosphonic acid] uracil (149): Compound **149** was prepared from**145** using the method as described for **114**: yield (74%): UV (H_2O) λ_{max} 262.5 nm; ^{1}H NMR (DMSO-d_6) δ 7.89 (d, J = 6.6 Hz, 1H), 5.70 (d, J = 6.7 Hz, 1H), 4.78 (t, J = 5.8 Hz, 1H), 3.98 (dd, J = 14.4, 6.2 Hz, 1H), 3.76 (dd, J = 12.7, 5.0 Hz, 1H), 3.68 (d, J = 7.9 Hz, 2H), 3.43-3.30 (m, 2H), 1.25 (m, 2H), 0.80 (m, 1H), 0.31 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 163.79, 152.65, 145.90, 100.81, 71.23, 61.99, 45.31, 18.34, 14.87, 7.12.

(*E*)-4-(*t*-Butyldimethylsilanyloxy)-2-fluoro-3-methyl-but-2-enoic acid ethyl ester (150) and (*Z*)-4-(*t*-Butyldimethylsilanyloxy)-2-fluoro-3-methyl-but-2-enoic acid ethyl ester (151): n-Butyllithium (6.75 Ml, 10.80 mmol of 1.60 M solution in hexane) was added slowly to a stirred solution of triethyl 2-fluoro-2-phosphonoacetate (10 mmol) in tetrahydrofuran (20 mL) at -78 ℃. The reaction mixture was then stirred at the same temperature for a further 30 min. A solution of acetol (1.79 g, 9.50 mmol) in THF (5 mL) was added to the above reaction mixture, stirred at -78 ℃ for 1 h and allowed to warm slowly to room temperature. The mixture was quenched with water (3 mL), and the reaction mixture was extracted with ethyl acetate. The combined extract was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column chromatography (EtOAc/ hexane, 1:50) to give compounds **150** (945 mg, 36%) and **151** (788 mg, 30%) as colorless oils; Compound **150**: ^{1}H NMR ($CDCl_3$) δ 4.35 (d, J = 3.3 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 2.11 (d, J = 3.3 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 0.88 (m, 9H), 0.02 (m, 6H); MS (EI) for $C_{13}H_{25}FO_3Si$: m/z 276 (M^+); Compound **151**: ^{1}H

NMR ($CDCl_3$) δ 4.65 (d, J = 2.1 Hz, 2H), 4.31 (q, J = 7.2 Hz, 2H), 1.89 (d, J = 4.5 Hz, 3H), 1.33 (t, J = 7. 2Hz, 3H), 0.86 (s, 9H), 0.02 (m, 12H); MS (EI) for $C_{13}H_{25}FO_3Si$: m/z 276 (M^+).

(*E*)-4-(*t*-Butyldimethylsilanyloxy)-2-fluoro-3-methyl-bu-2-ten-1-ol (152): Compound **152** was prepared from compound **150** using the method for the preparation of compound **3**: yield (82%) as a colorless oil; ^1H NMR ($CDCl_3$) δ 4.19 (d, J = 3.0 Hz, 2H), 4.17 (d, J = 21.9 Hz, 2H), 1.65 (d, J = 3.0 Hz, 3H), 0.87 (m, 9H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 153.99, 150.73, 116.00, 115.83, 59.44, 58.24, 57.83, 25.60, 18.29, 12.64, 12.59, −5.41; MS (EI) for $C_{11}H_{23}FO_2Si$: m/z 234 (M^+).

(*Z*)-4-(*t*-Butyldimethylsilanyloxy)-2-fluoro-3-methyl-but-2-en-1-ol (153): Compound **153** was synthesized from compound **151** using a similar procedure to that described for synthesizing compound **3**: yield (85%); ^1H NMR ($CDCl_3$) δ 4.20 (d, J = 3.3 Hz, 2H), 4.15 (d, J = 19.8 Hz, 2H), 1.70 (d, J = 2.4 Hz, 3H), 0.88 (m, 9H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 154.12, 150.98, 116.21, 115.99, 59.51, 59.41, 58.31, 57.94, 25.74, 18.65, 12.87, 12.95, −5.54; MS (EI) for $C_{11}H_{23}FO_2Si$: m/z 234 (M^+).

(±)-(1*R*,2*R*)-[2-(*t*-Butyldimethylsilanyloxymethyl)-2-methyl-1-fluoro-cyclopropyl]-methanol (154): Compound **154** was prepared from compound **152** using the method for the preparation of compound **138**: yield (77%) as a colorless oil; ^1H NMR ($CDCl_3$) δ 4.18 (d, J = 2.8 Hz, 2H), 4.13 (dd, J = 12.2, 0.9 Hz, 2H), 1.35 (d, J = 3.2 Hz, 3H), 1.00 (dd, J = 18.8, 7.0 Hz, 1H), 0.89 (m, 9H), 0.74 (t, J = 8.0 Hz, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 85.67, 83.21, 63.76, 63.51, 60.59, 60.43, 32.76, 32.65, 25.87, 19.42, 18.71, 11.61, −5.70; MS (EI) for $C_{12}H_{25}FO_2Si$: m/z 248 (M^+).

(±)-(1*S*,2*R*)-[2-(*t*-Butyldimethylsilanyloxymethyl)-2-methyl-1-fluoro-cyclopropyl]-methanol (155): Compound **155** was obtained from compound **153** using a similar procedure to that described for synthesizing compound **138**: Yield (69%); ^1H NMR ($CDCl_3$) δ 4.26−4.19 (m, 4H), 1.30 (d, J = 3.0 Hz, 3H), 1.05 (dd, J = 18.2, 4.2 Hz, 1H), 0.88 (m, 9H), 0.77 (m, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 84.98, 83.03, 62.45, 59.71, 59.62, 33.81, 33.73, 25.65, 19.76, 18.62, 11.43, 11.36, −5.51; MS (EI) for $C_{12}H_{25}FO_2Si$: m/z 248 (M^+).

(±)-(1*R*,2*R*)-1-Bromomethyl-2-(*t*-butyldimethylsilanyloxymethyl)-2-methyl-1-fluoro-cyclopropane (156): *N*-Bromosuccinimide (0.90 g, 2.60 mmol) was added slowly to a solution of compound **154** (320 mg, 1.29 mmol) and triphenylphosphine (675 mg, 2.60 mmol) in CH_2Cl_2 (15 mL) at 0 ℃. The resulting mixture was stirred for 4 h at room temperature, and diluted with CH_2Cl_2. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and filtered through a celite pad. The filtrate was concentrated under vacuum and the residue was purified by quick flash silica gel column chromatography (EtOAc/ hexane, 1:30) to give the bromide derivative **156** (241 mg, 60%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 4.24 (d, J = 3.2 Hz, 2H), 4.17 (d, J = 16.4 Hz, 2H), 1.32 (d, J = 2.8 Hz, 3H), 0.99 (m, 1H), 0.87 (m, 9H), 0.72 (t, J = 7.6 Hz, 1H), 0.01 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 83.98, 81.02, 61.43, 61.35, 38.57, 33.54, 33.43, 25.72, 19.12, 18.58, 11.87, −5.45; MS (EI) for $C_{12}H_{24}BrFOSi$: m/z 311 (M^+).

(±)-(1*S*,2*R*)-1-Bromomethyl-2-(*t*-butyldimethylsilanyloxymethyl)-2-methyl-1-fluoro-cyclopropane (157): Compound **157** was synthesized from compound **155** using a similar procedure to that described for synthesizing **156**: yield (64%); ^{1}H NMR ($CDCl_3$) δ 4.21 (m, 2H), 4.11 (d, J = 10.2 Hz, 2H), 1.37 (d, J = 2.8 Hz, 3H), 1.04 (m, 1H), 0.89 (m, 9H), 0.73 (t, J = 7.2 Hz, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 84.54, 82.1, 61.43, 61.31, 37.92, 32.65, 32.73, 25.39, 19.43, 18.54, 11.76, 11.68, −5.50; MS (EI) for $C_{12}H_{24}BrFOSi$: m/z 311 (M^+).

(±)-(1′*R*,2′*R*)-1-[2′-[(*t*-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] thymine (158): A solution of the fluorocyclopropyl derivative **156** (165 mg, 0.53 mmol), thymine (103 mg, 0.81 mmol) and cesium carbonate (262 mg, 0.81 mmol) in anhydrous DMF (7 mL) was stirred overnight at room temperature. Water was added to quench the mixture, which was then diluted with ethyl acetate. The organic layer was separated and washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (EtOAc/ hexane, 4:1) to give compound **158** (64 mg, 34%); ^{1}H NMR ($CDCl_3$) δ 8.40 (br s, 1H), 7.24 (s, 1H), 4.19 (d, J = 3.2 Hz, 2H), 3.24 (dd, J = 8.2, 2.8 Hz, 2H), 1.43 (d, J = 2.8 Hz, 3H), 1.21 (s, 3H), 1.02 (dd, J = 8.0, 2.8 Hz, 1H), 0.87 (s, 9H), 0.73 (dd, J =

10.8, 2.8 Hz, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 164.74, 150.98, 143.54, 109.00, 84.32, 82.19, 62.76, 62.65, 48.54, 48.47, 32.34, 32.27, 25.65, 19.45, 18.54, 12.81, 11.43, −5.61; MS (EI) for $C_{17}H_{29}FN_2O_3Si$: m/z 358 ($M+1^+$).

The fluorocyclopropyl nucleoside derivatives **159~165** were synthesized using a similar procedure to that described for synthesizing compound **160**:

(±)−(1′*R*,2′*R*)−1−[2′−[(*t*−Butyldimethylsilanyloxymethyl)−2′−methyl−1′−fluoro]−cycloprop−1′−yl] uracil (159): yield (33%); ^{1}H NMR ($CDCl_3$) δ 8.39 (br s, 1H), 7.22 (d, J = 7.4 Hz, 1H), 5.43 (d, J = 7.2 Hz, 1H), 4.20 (d, J = 2.8 Hz, 2H), 3.19 (dd, J = 10.6, 2.8 Hz, 2H), 1.37 (d, J = 2.8 Hz, 3H), 0.98 (m, 1H), 0.88 (s, 9H), 0.72 (m, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 164.54, 152.76, 145.65, 101.87, 83.41, 81.76, 62.87, 62.77, 47.54, 32.43, 32.31, 25.54, 19.32, 18.65, 11.45, −5.50; MS (EI) for $C_{16}H_{27}FN_2O_3Si$: m/z 343 ($M+1^+$).

(±)−(1′*R*,2′*R*)−1−[2′−[(*t*−Butyldimethylsilanyloxymethyl)−2′−methyl−1′−fluoro]−cycloprop−1′−yl] cytosine (160): yield (29%); ^{1}H NMR ($CDCl_3$) δ 7.44 (d, J = 7.8 Hz, 1H), 5.80 (d, J = 7.6 Hz, 1H), 4.22 (d, J = 3.0 Hz, 2H), 3.25 (dd, J = 10.2 Hz, 2.8 Hz, 2H), 1.47 (d, J = 2.8 Hz, 3H), 1.09 (m, 1H), 0.89 (s, 9H), 0.75 (dd, J = 10.8, 2.8 Hz, 1H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 166.00, 156.32, 145.61, 94.91, 84.82, 82.56, 62.45, 62.36, 48.51, 33.51, 33.42, 25.52, 19.73, 18.56, 11.27, −5.40; MS (EI) for $C_{16}H_{28}FN_3O_2Si$: m/z 343 ($M+1^+$).

(±)−(1′*R*,2′*R*)−9−[2′−[(*t*−Butyldimethylsilanyloxymethyl)−2′−methyl−1′−fluoro]−cycloprop−1′−yl] adenine (161): yield (35%); ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 1H), 7.90 (s, 1H), 6.10 (br d, 2H), 4.24 (d, J = 2.8 Hz, 2H), 3.19 (dd, J = 12.4, 3.0 Hz, 2H), 1.40 (s, 3H), 1.02 (d, J = 2.8 Hz, 1H), 0.88 (s, 9H), 0.78 (t, J = 7.8 Hz, 1H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 156.32, 151.56, 149.97, 143.32, 118.43, 85.54, 83.61, 62.65, 47.71, 33.54, 33.43, 25.78, 19.32, 18.49, 11.98, −5.54; MS (EI) for $C_{17}H_{28}FN_5OSi$: m/z 367 ($M+1^+$).

(±)−(1′*S*,2′*R*)−1−[2′−[(*t*−Butyldimethylsilanyloxymethyl)−2′−methyl−1′−fluoro]−cycloprop−1′−yl] thymine (162): yield (37%); ^{1}H NMR ($CDCl_3$) δ 8.32 (br s, 1H), 7.21 (s, 1H), 4.21 (d, J = 3.0 Hz, 2H), 3.18 (m, 2H), 1.38 (d, J = 2.8 Hz, 3H), 1.18 (s, 3H), 1.00 (m, 1H), 0.88 (s, 9H), 0.74 (t, J = 7.6 Hz, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 165.11, 151.65, 142.32, 108.89, 85.71, 83.69, 63.61, 63.65, 49.12, 33.54, 33.46, 25.32, 19.10, 18.59, 12.48, 11.54, 11.47, −5.39; MS

(EI) for $C_{17}H_{29}FN_2O_3Si$: m/z 358 ($M+1^+$).

(±)-(1′*S*,2′*R*)-1-[2′-[(*t*-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] uracil (163): yield (28%); ^{1}H NMR ($CDCl_3$) δ 8.27 (br s, 1H), 7.20 (d, J = 7.2 Hz, 1H), 5.39 (d, J = 7.2 Hz, 1H), 4.21 (d, J = 2.8 Hz, 2H), 3.20 (m, 2H), 1.39 (d, J = 2.6 Hz, 3H), 1.03 (d, J = 2.8 Hz, 1H), 0.87 (s, 9H), 0.75 (t, J = 8.8 Hz, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 165.21, 153.72, 144.33, 102.59, 84.82, 82.78, 61.79, 61.68, 48.41, 48.32, 32.76, 32.68, 25.49, 19.82, 19.74, 18.45, 11.92, 11.85, −5.63; MS (EI) for $C_{16}H_{27}FN_2O_3Si$: m/z 343 ($M+1^+$).

(±)-(1′*S*,2′*R*)-1-[2′-[(*t*-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] cytosine (164): yield (30%); ^{1}H NMR ($CDCl_3$) δ 7.42 (d, J = 7.6 Hz, 1H), 5.79 (d, J = 7.4 Hz, 1H), 4.18 (d, J = 3.0 Hz, 2H), 3.89 (m, 2H), 1.40 (d, J = 3.0 Hz, 3H), 1.01 (m, 1H), 0.87 (s, 9H), 0.72 (m, J = 1H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 165.85, 155.21, 144.76, 94.39, 83.67, 81.70, 62.76, 47.97, 32.31, 32.24, 25.49, 19.65, 18.42, 11.90, −5.71; MS (EI) for $C_{16}H_{28}FN_3O_2Si$: m/z 343 ($M+1^+$).

(±)-(1′*S*,2′*R*)-9-[2′-[(*t*-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] adenine (165): yield (32%); ^{1}H NMR ($CDCl_3$) δ 8.29 (s, 1H), 7.94 (s, 1H), 6.12 (br d, 2H), 4.20 (d, J = 2.8 Hz, 2H), 3.33 (m, 2H), 1.38 (d, J = 2.6 Hz, 3H), 1.02 (m, 1H), 0.87 (s, 9H), 0.73 (dd, J = 10.2, 2.6 Hz, 1H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 155.71, 152.54, 148.91, 143.32, 119.43, 83.43, 81.70, 62.65, 62.55, 48.54, 32.40, 32.32, 25.52, 19.39, 18.49, 11.69, −5.61; MS (EI) for $C_{17}H_{28}FN_5OSi$: m/z 367 ($M+1^+$).

(±)-(1′*R*,2′*R*)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] thymine (166): Compound **166** was prepared from compound **158** using the method for the preparation of compound **11**: yield (79%) as a white solid: mp 154~156 ℃; UV (H_2O) λ_{max} 267.0 nm; ^{1}H NMR (DMSO-d_6) δ 11.36 (br s, 1H), 7.31 (s, 1H), 4.89 (t, J = 5.2 Hz, 1H), 4.21 (d, J = 3.0 Hz, 2H), 3.19 (dd, J = 10.8, 2.8 Hz, 2H), 1.38 (d, J = 2.8 Hz, 3H), 1.17 (s, 3H), 0.91 (m, 1H), 0.74 (t, J = 7.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.45, 152.65, 142.54, 108.66, 84.32, 82.45, 62.76, 62.68, 48.89, 33.32, 33.24, 19.32, 12.65, 11.78; Anal. Calcd for $C_{11}H_{15}FN_2O_3$ (+0.5H_2O): C, 52.58; H, 6.42; N, 11.15. Found: C, 52.31; H, 6.67, N,

11.33.

The target nucleosides **167~173** were synthesized using a similar procedure to that described for synthesizing compound **11**:

(±)-(1′*R*,2′*R*)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] uracil (167): yield (77%): mp 161~163 ℃; UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6) δ 11.54 (br s, 1H), 7.40 (d, J = 7.2 Hz, 1H), 5.48 (d, J = 7.0 Hz, 1H), 4.98 (t, J = 5.2 Hz, 1H), 4.21 (m, 2H), 3.27 (dd, J = 10.2, 2.8 Hz, 2H), 1.34 (s, 3H), 1.02 (m, 1H), 0.74 (dd, J = 10.4, 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.71, 152.35, 144.19, 104.21, 83.32, 81.40, 62.54, 47.88, 33.61, 19.56, 19.48, 11.76; Anal. Calcd for $C_{10}H_{13}FN_2O_3$: C, 52.63; H, 5.74; N, 12.27. Found: C, 52.78; H, 5.65, N, 12.31.

(±)-(1′*R*,2′*R*)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] cytosine (168): yield (72%): mp 155~158 ℃; UV (H_2O) λ_{max} 272.5 nm; ^{1}H NMR (DMSO-d_6) δ 7.40 (d, J = 7.6 Hz, 1H), 5.60 (d, J = 7.4 Hz, 1H), 4.95 (t, J = 5.2 Hz, 1H), 4.20 (m, 2H), 3.21 (m, 2H), 1.42 (s, 3H), 0.99 (m, 1H), 0.78 (t, J = 8.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 166.54, 155.43, 143.81, 93.38, 83.78, 81.44, 62.54, 62.46, 48.77, 32.71, 19.71, 11.45, 11.38; Anal. Calcd for $C_{10}H_{14}FN_3O_2$: C, 52.86; H, 6.21; N, 18.49. Found: C, 52.99; H, 6.17, N, 18.54.

(±)-(1′*R*,2′*R*)-9-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] adenine (169): yield (80%): mp 183 ~185 ℃; UV (H_2O) λ_{max} 264.0 nm; ^{1}H NMR (DMSO-d_6) δ 8.21 (s, 1H), 8.01 (s, 1H), 7.27 (br s, 2H), 4.90 (t, J = 5.4 Hz, 1H), 4.22 (m, 2H), 3.13 (dd, J = 10.6, 2.8 Hz, 2H), 1.40 (s, 3H), 1.00 (m, 1H), 0.73 (dd, J = 10.6, 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 154.43, 151.76, 147.67, 142.60, 118.12, 84.76, 62.54, 62.47, 48.43, 34.02, 19.65, 11.21; Anal. Calcd for $C_{11}H_{14}FN_5O$ (+0.5MeOH): C, 51.68; H, 6.03; N, 26.20. Found: C, 51.42; H, 5.88, N, 26.04.

(±)-(1′*S*,2′*R*)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] thymine (170): yield (77%): mp 158~160 ℃; UV (H_2O) λ_{max} 267.5 nm; ^{1}H NMR (DMSO-d_6) δ 11.47 (br s, 1H), 7.26 (s, 1H), 4.91 (t, J = 5.4 Hz, 1H), 4.18 (s, 2H), 3.19 (m,, 2H), 1.40 (s, 3H), 1.15 (s, 3H), 0.98 (dd, J = 6.8, 2.8 Hz, 1H), 0.71 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 166.04, 153.71, 142.34, 109.18, 85.39, 83.45, 63.23, 49.65, 49.58, 33.43, 18.99, 12.21, 11.45, 11.35; Anal. Calcd

for $C_{11}H_{15}FN_2O_3$: C, 54.54; H, 6.24; N, 11.56. Found: C, 54.68; H, 6.12, N, 11.62.

(±)-(1′*S*,2′*R*)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] uracil (171): yield (86%): mp 160~162 ℃; UV (H_2O) λ_{max} 263.5 nm; ^{1}H NMR (DMSO-d_6) δ 11.42 (br s, 1H), 7.35 (d, J = 7.4 Hz, 1H), 5.40 (d, J = 7.2 Hz, 1H), 4.91 (t, J = 5.2 Hz, 1H), 4.16 (d, J = 3.0 Hz, 2H), 3.19 (d, J = 10.4, 2H), 1.36 (d, J = 2.6 Hz, 3H), 1.02 (m, 1H), 0.78 (d, J = 10.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.54, 153.77, 142.71, 103.69, 84.54, 82.49, 62.50, 62.41, 48.43, 34.12, 33.04, 19.02, 11.58, 11.49; Anal. Calcd for $C_{10}H_{13}FN_2O_3$: C, 52.63; H, 5.74; N, 12.27. Found: C, 52.78; H, 5.65, N, 12.31.

(±)-(1′*S*,2′*R*)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] cytosine (172): yield (87%): mp 158~160 ℃; UV (H_2O) λ_{max} 272.0 nm; ^{1}H NMR (DMSO-d_6) δ 7.38 (d, J = 7.8 Hz, 1H), 5.46 (d, J = 7.6 Hz, 1H), 4.90 (t, J = 5.2 Hz, 1H), 4.14 (dd, J = 6.2, 2.8 Hz, 2H), 3.21 (m, 2H), 1.42 (d, J = 3.0 Hz, 3H), 0.96 (m, 1H), 0.70 (dd, J = 8.8, 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.21, 154.53, 141.27, 94.67, 85.48, 83.21, 62.21, 47.33, 33.32, 33.24, 19.32, 19.22, 11.67; Anal. Calcd for $C_{10}H_{14}FN_3O_2$ (+0.7H2O): C, 50.07; H, 6.47; N, 17.52. Found: C, 49.96; H, 6.37, N, 17.54.

(±)-(1′*S*,2′*R*)-9-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]-cycloprop-1′-yl] adenine (173): yield (83%): mp 187~189 ℃; UV (H_2O) λ_{max} 263.0 nm; ^{1}H NMR (DMSO-d_6) δ 8.20 (s, 1H), 7.99 (s, 1H), 7.21 (br s, 2H), 4.89 (t, J = 5.2 Hz, 1H), 4.17 (d, J = 3.0 Hz, 2H), 3.13 (dd, J = 10.2, 3.0 Hz, 2H), 1.38 (d, J = 2.8 Hz, 3H), 0.97 (m, 1H), 0.73 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 155.21, 152.43, 146.76, 141.54, 119.61, 83.97, 63.87, 63.79, 47.41, 33.82, 33.74, 19.21, 11.21, 11.14; Anal. Calcd for $C_{11}H_{14}FN_5O$: C, 52.58; H, 5.62; N, 27.87. Found: C, 52.69; H, 5.48, N, 27.74.

(±)-Ethyl-3,3′-*bis*-(*t*-butyldimethylsilyloxymethyl)-2-methyl-4-oxo-butyrate (175): Compound **175** was prepared from compound **174** using the method for the preparation of compound **56**: yield (80%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.88-3.69 (m, 4H), 2.72 (q, J = 7.4 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 7.4 Hz, 3H), 0.86 (s, 18H), 0.02 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 204.36, 175.33, 64.54, 61.36, 55.32, 41.11, 25.81, 18.67, 14.10, 12.30, -5.65.

(*rel*)-(2*R* and 2*S*,3*S*)-4,4-*Bis*-(*t*-butyldimethylsilanyloxymethyl)-tetrahydrofuran-3-methyl-2-ol (176): Compound **176** was prepared from compound **175** using the method for the preparation of compound **57**: yield (66%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.26 (m, 1H), 3.74-3.38 (m, 6H), 1.82 (m, 1H), 1.15 (dd, J = 12.8, 6.8 Hz, 3H), 0.87 (s, 9H), 0.82 (s, 9H), 0.02 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 102.63, 73.29, 65.22, 63.04, 61.54, 52.42, 37.95, 34.10 25.74, 18.21, 12.88, 11.12, -5.68; Anal. Calcd for $C_{19}H_{42}O_4Si_2$: C, 58.41; H, 10.84. Found: C, 58.20; H, 10.82.

(*rel*)-(2*R* and 2*S*,3*S*)-Acetic acid-[4,4-*bis*-(*t*-butyldimethylsilanyloxymethyl)-tetrahydrofuran-3-methyl-2-yl] ester (177): Compound **177** was prepared from compound **176** using the method for the preparation of compound **58**: yield (83%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.13, 6.02 (s, s, 1H), 3.81 (d, J = 9.6 Hz, 1H), 3.77 (d. J = 9.6 Hz, 1H), 3.60 (d, J = 9.4 Hz, 1H), 3.50 (d, J = 9.4 Hz, 1H), 2.05, 2.00 (s, s, 3H), 1.11 (m, 1H), 1.01 (d, J = 6.9 Hz, 1H), 0.88 (s, 9H), 0.82 (s, 9H), 0.03 (s, 6), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 102.64, 95.45, 73.30, 73.09, 65.21, 63.06, 62.68, 52.45, 37.43, 25.81, 18.15, 12.91, 11.14, -5.65; Anal. Calcd for $C_{21}H_{44}O_5Si_2$: C, 58.29; H, 10.25. Found: C, 58.51; H, 10.01.

(*rel*)-(2′*R*,3′*S*)-1-[4,4-*Bis*-(*t*-butyldimethylsilanyloxymethyl)-tetrahydrofuran-3-methyl-2-yl] uracil (178) and (*rel*)-(2′*S*,3′*S*)-1-[4,4-*Bis*-(*t*-butyldimethylsilanyloxymethyl)-tetrahydrofuran-3-methyl-2-yl] uracil (179): Uracil (150 mg, 1.33 mmol), anhydrous HMDS (15 mL), and a catalytic amount of ammonium sulfate were heated under reflux until a clear solution had formed, and the solvent was distilled under anhydrous conditions. The residue was dissolved in anhydrous 1,2-dichloroethane (DCE). A solution of compound **177** (290 mg, 0.67 mmol) in dry DCE (7 mL) and TMSOTf (0.24 mL, 1.33 mmol) was added to this mixture. The resulting mixture was stirred at rt for 2 h. The reaction was quenched with 3 mL of saturated $NaHCO_3$ and stirred for 20 min. The resulting solid was filtered through a celite pad, and the filtrate was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/ hexane, 3:1) to give compounds **178** (101 mg, 31%) and **179** (107 mg, 33%), respectively;

Compound **178**: ^{1}H NMR ($CDCl_3$) δ 8.24 (br s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 6.17 (s, 1H), 5.65 (dd, J = 8.1, 2.4 Hz, 1H), 4.28 (t, J = 8.4 Hz, 1H), 3.79−3.61 (m, 3H), 3.52 (d, J = 10.8 Hz, 1H), 3.42 (d, J = 10.8 Hz, 1H), 2.45−2.36 (m, 1H), 1.05 (d, J = 8.7 Hz, 3H), 0.87 (s, 9H), 0.80 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.14, 150.31, 141.44, 100.71, 75.48, 63.40, 62.24, 54.07, 36.46, 25.81, 18.28, 10.29, −5.69; Compound **179**: ^{1}H NMR ($CDCl_3$) δ 8.26 (br s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 6.11 (d, J = 4.8 Hz, 1H), 5.69 (d, J = 7.8 Hz, 1H), 4.21 (t, J = 8.4 Hz, 1H), 3.81 (d, J = 10.2 Hz, 1H), 3.75 (d, J = 10.2 Hz, 3.63 (d, J = 10.4 Hz, 1H), 3.48−3.32 (m, 2H), 2.42 (m, 1H), 1.03 (d, J = 8.6 Hz, 3H), 0.89 (s, 9H), 0.83 (s, 9H), 0.06 (s, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.32, 150.54, 140.76, 101.65, 74.22, 63.87, 62.06, 54.47, 37.61, 25.38, 18.58, 11.32, −5.49.

Compounds **180~183, 190** and **191** were prepared from the corresponding bases using a similar procedure as that described for synthesizing compounds **178** and **179**:

(*rel*)−(2′*R*,3′*S*)−1−[4,4−*Bis*−(*t*−butyldimethylsilanyloxymethyl)−tetrahydrofuran−3−methyl−2−yl] thymine (180) and (*rel*)−(2′*S*,3′*S*)−1−[4,4−*Bis*−(*t*−butyldimethylsilanyloxymethyl)−tetrahydrofuran−3−methyl−2−yl] thymine (181): Compound **180**: yield (29%); ^{1}H NMR ($CDCl_3$) δ 8.24 (br s, 1H), 7.36 (s, 1H), 6.07 (s, 1H), 4.32 (t, J = 8.2 Hz, 1H), 3.98 (d, J = 12.2 Hz, 1H), 3.77 (d, J = 12.4 Hz, 1H), 3.65 (d, J = 11.4 Hz, 1H), 3.54 (m, 2H), 2.10 (m, 1H), 1.98 (s, 3H), 1.10 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.76, 151.54, 134.54, 107.76, 75.81, 64.29, 63.76, 55.65, 36.68, 25.54, 18.54, 12.21, 11.32, −5.65; Compound **181**: yield (28%); ^{1}H NMR ($CDCl_3$) δ 8.27 (br s, 1H), 7.31 (s, 1H), 6.05 (d, J = 5.4 Hz, 1H), 4.33 (t, J = 8.4 Hz, 1H), 3.98 (d, J = 12.2 Hz, 1H), 3.77 (d, J = 12.4 Hz, 1H), 3.65 (d, J = 11.4 Hz, 1H), 3.54 (m, 1H), 3.38 (d, J = 11.7 Hz, 1H), 2.10 (m, 1H), 1.98 (s, 3H), 1.10 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.76, 151.54, 134.54, 107.76, 75.81, 64.29, 63.76, 55.65, 36.68, 25.54, 18.54, 12.21, 11.32, −5.65.

(*rel*)-(2′*R*,3′*S*)-1-[4,4-*Bis*-(*t*-butyldimethylsilanyloxymethyl)-tetrahydrofuran-3-methyl-2-yl] cytosine (182) and (*rel*)-(2′*S*,3′*S*)-1-[4,4-*Bis*-(*t*-butyldimethylsilanyloxymethyl)-tetrahydrofuran-3-methyl-2-yl] cytosine (183): Compound **182**: yield (19%); ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 7.5 Hz, 1H), 6.13 (s, 1H), 5.61 (d, J = 7.6 Hz, 1H), 4.28 (t, J = 7.5 Hz, 1H), 3.83-3.69 (m, 3H), 3.46 (dd, J = 14.4, 10.8 Hz, 1H), 2.54 (m, 1H), 1.12 (d, J = 7.4 Hz, 3H), 0.88 (s, 9H), 0.82 (s, 9H), 0.04 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.32, 156.43, 145.87, 93.44, 74.76, 63.69, 62.21, 54.55, 36.76, 25.61, 18.39, 11.02, -5.51; Compound **183**: yield (15%); ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 7.6 Hz, 1H), 6.12 (d, J = 5.8 Hz, 1H), 5.58 (d, J = 7.6 Hz, 1H), 4.30 (t, J = 7.6 Hz, 1H), 3.87 (d, J = 10.2 Hz, 1H), 3.65 (m, 2H), 3.54 (d, J = 12.8 Hz, 1H), 3.45 (d, J = 12.7 Hz, 1H), 2.47 (m, 1H), 1.09 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.21, 156.67, 144.76, 94.65, 75.76, 64.71, 62.93, 54.50, 36.61, 25.54, 18.29, 11.32, -5.58.

(*rel*)-(2′*R*,3′*S*)-1-[4,4-*Bis*-(hydroxymethyl)-tetrahydrofuran-3-methyl-2-yl] uracil (184): Compound **184** was prepared from compound **178** using the method for the preparation of compound **11**: yield (76%): mp 157~159 ℃; UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6) δ 11.21 (br s, 1H), 7.29 (d, J = 7.6 Hz, 1H), 6.08 (s, 1H), 5.57 (d, J = 7.6 Hz, 1H), 4.99 (t, J = 5.2 Hz, 1H), 4.80 (t, J = 5.2 Hz, 1H), 4.26 (t, J = 8.2 Hz, 1H), 3.82 (d, J = 10.0 Hz, 2H), 3.67-59 (m, 2H), 2.46 (m, 1H), 1.01 (d, J = 8.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 165.76, 151.43, 142.80, 102.49, 74.37, 64.10, 62.42, 53.42, 37.59, 10.95; Anal. Calcd for $C_{11}H_{16}N_2O_5$ (+0.7H2O): C, 49.13; H, 6.52; N, 10.42. Found: C, 48.98; H, 6.41; N, 10.56.

Compounds **185~189**, **194** and **195** were prepared from thymine using a similar procedure to that described for synthesizing compounds **11**.

(*rel*)-(2′*S*,3′*S*)-1-[4,4-*Bis*-(hydroxymethyl)-tetrahydrofuran-3-methyl-2-yl] uracil (185): yield (70%); mp 162~164 ℃; UV (H_2O) λ_{max} 263.0 nm; ^{1}H NMR (DMSO-d_6) δ 11.31 (br s, 1H), 7.27 (d, J = 7.4 Hz, 1H), 6.10 (d, J = 5.8 Hz, 1H), 5.55 (d, J = 7.6 Hz, 1H), 4.95 (t, J = 5.4 Hz, 1H), 4.82 (t, J = 5.2 Hz, 1H), 4.23 (t, J = 8.4 Hz, 1H), 3.80-3.71 (m, 2H), 3.63-51 (m, 3H), 2.44 (m, 1H), 1.00 (d, J = 8.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 166.21, 152.67, 143.51,

105.77, 75.71, 64.89, 61.62, 54.72, 36.70, 11.02; Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.72; H, 6.36; N, 10.78.

(*rel*)-(2′*R*,3′*S*)-1-[4,4-*Bis*-(hydroxymethyl)-tetrahydrofuran-3-methyl-2-yl] thymine (186): yield (80%); mp 161~163 ℃; UV (H_2O) λ_{max} 267.0 nm; ^{1}H NMR (DMSO-d_6) δ 11.50 (br s, 1H), 7.25 (s, 1H), 6.03 (s, 1H), 4.26 (d, J = 7.6 Hz, 1H), 3.80 (d, J = 6.8, 1H), 3.68-3.57 (m, 3H), 3.57 (d, J = 10.6 Hz, 1H), 2.43 (m, 1H), 1.31 (s, 3H), 1.04 (d, J = 9.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 165.62, 151.57, 138.61, 102.69, 73.32, 65.81, 63.38, 56.00, 36.62, 11.85, 10.76; Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.21; H, 6.83; N, 10.48.

(*rel*)-(2′*S*,3′*S*)-1-[4,4-*Bis*-(hydroxymethyl)-tetrahydrofuran-3-methyl-2-yl] thymine (187): yield (76%); mp 154~156 ℃; UV (H_2O) λ_{max} 267.6 nm; ^{1}H NMR (DMSO-d_6) δ 11.57 (br s, 1H), 7.24 (s, 1H), 6.11 (d, J = 5.4 Hz, 1H), 4.94 (br s, 1H), 4.85 (t, J = 5.4 Hz, 1H), 4.24 (t, J = 7.6 Hz, 1H), 3.89-3.78 (m, 3H), 3.59 (d, J = 10.2 Hz, 1H), 3.57 (d, J = 10.2 Hz, 1H), 2.48 (m, 1H), 1.34 (s, 3H), 1.01 (d, J =10.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 164.69, 152.41, 137.69, 101.74, 74.69, 64.37, 62.18, 57.37, 37.72, 11.90, 10.97; Anal. Calcd for $C_{12}H_{18}N_2O_5$ (+0.5MeOH): C, 52.44; H, 7.04; N, 9.78. Found: C, 52.28; H, 6.92; N, 9.67.

(*rel*)-(2′*R*,3′*S*)-1-[4,4-*Bis*-(hydroxymethyl)-tetrahydrofuran-3-methyl-2-yl] cytosine (188): yield (82%); mp 159~161 ℃; UV (H_2O) λ_{max} 271.5 nm; ^{1}H NMR (DMSO-d_6) δ 7.52 (d, J = 7.6 Hz, 1H), 5.99 (s, 1H), 5.71 (d, J = 7.6 Hz, 1H), 4.27 (t, J = 8.4 Hz, 1H), 3.87 (dd, J = 12.6, 6.8 Hz, 2H), 3.70 (d, J = 10.2 Hz, 1H), 3.62 (d, J = 10.0 Hz, 1H), 3.56 (d, J = 10.2 Hz, 1H), 2.38 (m, 1H), 0.98 (d, J = 9.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 166.26, 154.71, 143.82, 91.49, 74.32, 64.43, 62.29, 56.91, 36.30; Anal. Calcd for $C_{11}H_{17}N_3O_4$ (+1.0H_2O): C, 48.34; H, 7.00; N, 15.37. Found: C, 48.52; H, 6.86; N, 15.47.

(*rel*)-(2′*S*,3′*S*)-1-[4,4-*Bis*-(hydroxymethyl)-tetrahydrofuran-3-methyl-2-yl] cytosine (189): yield (76%); mp 162~164 ℃; UV (H_2O) λ_{max} 272.0 nm; ^{1}H NMR (DMSO-d_6) δ 7.49 (d, J = 7.6 Hz, 1H), 6.05 (d, J = 5.2 Hz, 1H), 5.70 (d, J = 7.6 Hz, 1H), 5.02 (t, J = 5.4 Hz, 1H), 4.89 (t, J = 5.4 Hz, 1H), 4.20 (t, J = 8.4 Hz, 1H), 3.89 (dd, J = 12.6, 6.8 Hz, 2H), 3.71 (d, J = 10.2 Hz, 1H), 3.60 (dd, J

= 13.4, 6.8 Hz, 2H), 2.45 (m, 1H), 1.13 (d, *J* = 10.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 165.62, 153.45, 142.21, 93.78, 75.63, 65.67, 63.79, 57.23, 37.02; Anal. Calcd for $C_{11}H_{17}N_3O_4$ (+0.6MeOH): C, 50.75; H, 7.12; N, 15.31. Found: C, 50.60; H, 7.37; N, 15.46.

(*rel*)-(2′*R*,3′*S*)-6-Chloro-9-[4,4-*bis*-(*t*-butyldimethylsilanyloxymethyl)-tetrahydrofuran-3-methyl-2-yl] purine (190) and (*rel*)-(2′*S*,3′*S*)-6-Chloro-9-[4,4-*bis*-(*t*-butyldimethylsilanyloxymethyl)-tetrahydrofuran-3-methyl-2-yl] purine (191): Compound **190**: yield (28%); ^{1}H NMR ($CDCl_3$) δ 8.92 (s, 1H), 8.36 (s, 1H), 5.96 (s, 1H), 4.29 (t, *J* = 7.8 Hz, 1H), 3.80 (m, 3H), 3.63 (d, *J* = 10.0 Hz, 1H), 3.46 (d, *J* = 10.2 Hz, 1H), 2.50 (m, 1H), 1.12 (d, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.82 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.98, 151.87, 147.31, 145.65, 131.65, 74.28, 65.43, 63.10, 55.74, 36.32, 25.64, 18.82, 11.06, −5.60; Compound **191**: yield (25%); ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H), 8.20 (s, 1H), 5.99 (d, *J* = 5.8 Hz, 1H), 4.33 (t, *J* = 7.6 Hz, 1H), 3.89-3.78 (m, 3H), 3.58 (dd, *J* = 14.8, 6.8 Hz, 2H), 2.42 (m, 1H), 1.09 (d, *J* = 7.6 Hz, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.21, 152.54, 146.39, 144.78, 129.38, 73.44, 64.21, 62.78, 54.51, 36.82, 25.48, 18.56, 11.32, −5.66.

(*rel*)-(2′*R*,3′*S*)-9-[4,4-*Bis*-(*t*-butyldimethylsilanyloxymethyl)-tetrahydrofuran-3-methyl-2-yl] adenine (192): Compound **192** was prepared from compound **190** using the method for the preparation of compound **10**: yield (77%); ^{1}H NMR ($CDCl_3$) δ 8.29 (s, 1H), 8.00 (s, 1H), 6.05 (s, 1H), 4.21 (t, *J* = 8.8 Hz, 1H), 3.82-3.74 (m, 3H), 3.63 (dd, *J* = 13.6, 9.6 Hz, 2H), 2.46 (m, 1H), 1.07 (d, *J* = 9.8 Hz, 3H), 0.88 (s, 9H), 0.82 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.65, 152.89, 150.61, 141.45, 119.62, 75.62, 64.61, 62.39, 56.42, 36.63, 25.53, 18.21, 11.07, −5.39.

(*rel*)-(2′*S*,3′*S*)-9-[4,4-*Bis*-(*t*-butyldimethylsilanyloxymethyl)-tetrahydrofuran-3-methyl-2-yl] adenine (193): Adenine derivative **193** was synthesized from compound **191** by the similar method to that described for synthesizing compound **10**: yield (75%); ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H), 8.05 (s, 1H), 6.01 (d, *J* = 5.8 Hz, 1H), 4.15 (t, *J* = 9.6 Hz, 1H), 3.79 (dd, *J* = 12.4, 8.6 Hz, 2H), 3.67-3.57 (m, 3H), 2.32 (m, 1H), 0.98 (d, *J* = 9.6 Hz, 3H), 0.86 (s, 9H), 0.80 (s,

9H), 0.04 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.43, 151.32, 149.48, 140.32, 118.31, 74.70, 65.31, 62.39, 55.42, 35.79, 25.41, 18.20, 10.82, −5.52.

(*rel*)−(2′*R*,3′*S*)−9−[4,4−*Bis*−(hydroxymethyl)−tetrahydrofuran−3−methyl−2−yl] adenine (194): yield (73%): mp 172~175 ℃; UV (H_2O) λ_{max} 263.0 nm; ^{1}H NMR (DMSO−d_6) δ 8.15 (s, 1H), 8.02 (s, 1H), 5.97 (s, 1H), 5.01 (t, J = 5.4 Hz, 1H), 4.92 (t, J = 5.4 Hz, 1H), 4.16 (t, *J* = 8.8 Hz, 1H), 3.79 (dd, *J* = 12.8, 8.6 Hz, 2H), 3.63 (d, *J* = 9.2 Hz, 1H), 3.52 (dd, *J* = 12.8, 9.4 Hz, 2H), 2.40 (m, 1H), 1.04 (d, *J* = 9.6 Hz, 3H); ^{13}C NMR (DMSO−d_6) δ 154.98, 151.37, 149.47, 141.21, 118.57, 74.17, 64.21, 61.89, 56.65, 36.32, 10.87; Anal. Calcd for $C_{12}H_{17}N_5O_3$ (+0.8 MeOH): C, 50.42; H, 6.67; N, 22.97. Found: C, 50.56; H, 6.81; N, 22.96.

(*rel*)−(2′*S*,3′*S*)−9−[4,4−*Bis*−(hydroxymethyl)−tetrahydrofuran−3−methyl−2−yl] adenine (195): yield (78%): mp 175~177 ℃; UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO−d_6) δ 8.18 (s, 1H), 8.03 (s, 1H), 5.94 (dd, *J* =5.6 Hz, 1H), 4.96 (t, *J* = 5.2 Hz, 1H), 4.89 (br s, 1H), 4.12 (t, *J* = 8.6 Hz, 1H), 3.84 (dd, *J* = 13.4, 8.2 Hz, 2H), 3.75−3.66 (m, 2H), 3.55 (d, *J* = 10.4 Hz, 1H), 2.44 (m, 1H), 1.01 (d, *J* = 9.6 Hz, 3H); ^{13}C NMR (DMSO−d_6) δ 155.43, 151.65, 147.41, 140.61, 118.50, 74.67, 65.52, 62.71, 57.44, 35.90, 10.88; Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.83; H, 6.82; N, 16.59.

(*rel*)−(2*S*,3*S*)−3−(*t*−Butyldimethylsilyloxymethyl)−3−methyl−2−methyl−pent−4−enoic acid ethyl ester (197a) and (197b): Compounds **197a** and **197b** was prepared from compound **196** using the method for the preparation of compound **39**: yield **197a** (57%), **197b** (21%); Compound **197a**: ^{1}H NMR ($CDCl_3$) δ 6.02 (dd, *J* = 18.6, 10.8 Hz, 1H), 5.08 (dd, *J* = 10.8, 1.0 Hz, 1H), 5.00 (d, *J* = 18.6 Hz, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.39 (dd, *J* = 8.7, 5.1 Hz, 2H), 2.71 (q, *J* = 7.4 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.99 (s, 3H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 175.57, 142.28, 113.51, 68.99, 59.86, 43.74, 25.85, 18.26, 14.30, 12.62, −5.56; Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 64.16; H, 10.60; Compound **197b**: ^{1}H NMR ($CDCl_3$) δ 5.82 (dd, *J* = 18.4, 10.2 Hz, 1H), 5.09 (dd, *J* = 10.2, 0.9 Hz, 1H), 5.98 (d, *J* = 18.4 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.37 (d, *J* = 8.4 Hz, 2H), 2.68 (q, *J* = 7.5 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.97 (s, 3H), 0.87 (s, 9H),

0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 175.54, 142.10, 113.74, 68.84, 59.78, 43.64, 25.81, 18.27, 14.27, 12.34, −5.60; Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 63.84; H, 10.80.

(*rel*)−(2*S*,3*S*)−3−(*t*−Butyldimethylsilyloxymethyl)−3−methyl−2−methyl−pe−nt−4−enol (198): Compound **198** was prepared from compound **197a** using the method for the preparation of compound **3**: yield (92%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.81 (dd, J = 18.8, 10.4 Hz, 1H), 5.01 (d, J = 18.8 Hz, 1H), 4.89 (d, J = 18.2 Hz, 1H), 3.42 (dd, J = 13.5, 2.4 Hz, 1H), 3.32 (dd, J = 9.9, 5.4 Hz, 1H), 1.72 (q, J = 6.8 Hz, 1H), 0.90 (s, 3H), 0.88 (d, J = 3.3 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 143.61, 113.00, 68.86, 64.72, 43.46, 41.14, 25.64, 18.20, 17.18, 12.29, −5.62; Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70. Found: C, 64.89; H, 11.58.

(*rel*)−(2*S*,3*S*)−3−(*t*−Butyldimethylsilyloxymethyl)−3−methyl−2−methyl−pe−nt−4−enal (199): Compound **199** was prepared from compound **198** using the method for the preparation of compound **4**: yield (86%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.72 (s, 1H), 5.95 (dd, J = 17.7, 11.1 Hz, 1H), 5.13 (d, J = 11.2 Hz, 1H), 5.08 (d, J = 17.7 Hz, 1H), 3.48 (dd, J = 9.9, 4.8 Hz, 2H), 2.48 (q, J = 6.8 Hz, 1H), 1.00 (d, J = 7.5 Hz, 3H), 0.98 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 205.04, 141.85, 114.25, 68.58, 50.75, 44.18, 25.77, 18.49, 18.20, 8.59, −5.68.

(*rel*)−(3*R* and 3*S*,4*S*,5*S*)−5−(*t*−Butyldimethylsilyloxymethyl)−5−methyl−4−methyl−hepta−1,6−dien−3−ol (200): Compound **200** was prepared from compo−und **199** using the method for the preparation of compound **5**: yield (85%) as a diastereomeric mixture; ^{1}H NMR ($CDCl_3$) δ 5.92 (dd, J = 18.1, 10.8 Hz, 1H), 5.75−5.69 (m, 1H), 5.04−4.83 (m, 2H), 3.59−3.27 (m, 3H), 1.54(m, 1H), 1.02 (s, 3H), 0.91 (s, 3H), 0.82−0.79 (m, 12H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 144.82, 143.94, 141.32, 141.18, 113.53, 112.44, 71.31, 70.80, 67.84, 67.28, 45.84, 45.11, 44.12, 21.33, 20.64, 18.34, 7.13, −5.61; Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34. Found: C, 67.42; H, 11.25.

(*rel*)−(1*R*,4*S*,6*S*)−4−(*t*−Butyldimethylsilyloxymethyl)−4−methyl−5−methyl−cyclopent−2−enol (201) and (*rel*)−(1*S*,4*S*,6*S*)−4−(*t*−Butyldimethylsilyloxyme−thyl)−4−methyl−5−methyl−cyclopent−2−enol (202): Compounds **201** and **202**

was prepared from compound **200** using the method for the preparation of compound **6**: yield **201** (69%), **202** (12%) as colorless oils; Compound **201**: ^{1}H NMR ($CDCl_3$) δ 5.82 (d, J = 5.8 Hz, 1H), 5.56 (d, J = 5.9 Hz, 1H), 4.49 (d, J = 6.5 Hz, 1H), 3.48 (d, J = 9.9 Hz, 1H), 3.28 (d, J = 9.9 Hz, 1H), 1.57 (q, J = 7.5 Hz, 1H), 1.14 (d, J = 7.2 Hz, 3H), 0.98 (s, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 139.84, 134.18, 84.10, 67.05, 53.46, 51.56, 25.95, 22.72, 18.11, 10.63, −5.57; Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.47; H, 10.83; Compound **202**: ^{1}H NMR ($CDCl_3$) δ 5.80 (d, J = 6.0 Hz, 1H), 5.59 (d, J = 6.0 Hz, 1H), 4.50 (d, J = 6.6 Hz, 1H), 3.45 (d, J = 9.8 Hz, 1H), 3.26 (d, J = 9.8 Hz, 1H), 1.55 (q, J = 7.4 Hz, 1H), 1.16 (d, J = 7.3 Hz, 3H), 0.97 (s, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 140.12, 134.32, 83.98, 66.94, 53.32, 51.12, 25.62, 22.67, 18.49, 10.28, −5.53; Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.68; H, 11.17.

(*rel*)−(1*R*,4*S*,6*S*)−1−Ethoxycarbonyloxy−4−(*t*−Butyldimethylsilyloxymethyl)−4−methyl−5−methyl−cyclopent−2−ene (203): Compound **203** was prepared from compound **201** using the method for the preparation of compound **45**: yield (79%) as a colorless syrup; ^{1}H NMR ($CDCl_3$) δ 5.83 (dd, J = 5.4, 1.4 Hz, 1H), 5.72 (dd, J = 5.4, 1.8 Hz, 1H), 5.21 (dt, J = 6.6, 1.5 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.37 (s, 2H), 2.06 (quint, J = 7.5 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 7.2 Hz, 3H), 0.90 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.30, 143.39, 127.96, 89.87, 89.46, 70.44, 63.76, 51.28, 43.88, 25.86, 18.15, 14.26, 13.01, 10.76, −5.54; Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 62.05; H, 9.95.

(*rel*)−(1′*R*,4′*S*,6′*S*)−9−[4−(*t*−Butyldimethylsilyloxymethyl)−4−methyl−6−methyl−cyclopent−2−en−1−yl] 2−amino−6−chloropurine (204): Compound **204** was prepared from compound **203** using the method for the preparation of compound **46**: yield (32%); ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 5.82 (dd, J = 5.8, 1.8 Hz, 1H), 5.69 (dd, J = 6.0, 1.8 Hz, 1H), 5.39 (dd, J = 11.4, 2.0 Hz, 1H), 3.38 (dd, J = 9.9, 2.1 Hz, 2H), 2.29 (q, J = 7.8 Hz, 1H), 1.01 (d, J = 7.6 Hz, 3H), 0.90 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 159.20, 154.27, 151.21, 143.11, 140.54, 134.67, 125.31, 68.81, 65.79, 52.91, 47.31, 25.71, 21.57, 18.22, 12.23, 10.93, −5.57; Anal. Calcd for $C_{19}H_{30}ClN_5OSi$: C, 55.93; H,

7.41; N, 17.16. Found: C, 56.13; H, 7.55; N, 17.01.

(*rel*)-(1′*R*,4′*S*,6′*S*)-9-[4-(Hydroxymethyl)-4-methyl-6-methyl-cyclopent-2-en-1-yl] 2-amino-6-chloropurine (205): Compound **205** was prepared from compound **204** using the method for the preparation of compound **11**: yield (71%) as a white solid: mp 178~180 ℃; ^{1}H NMR (DMSO-d_6) δ 7.95 (s, 1H), 5.81 (dd, J = 5.4, 2.1 Hz, 1H), 5.57 (dd, J = 6.0, 1.5 Hz, 1H), 5.07 (dt, J = 8.4, 1.8 Hz, 1H), 4.87 (t, J = 5.4 Hz, 1H), 3.29 (d, J = 10.5 Hz, 1H), 3.12 (d, J = 10.5 Hz, 1H), 1.98 (quint, J = 8.1 Hz, 1H), 0.98 (d, J = 7.2 Hz, 3H), 0.89 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 159.76, 154.81, 150.99, 142.84, 140.85, 135.01, 125.67.65, 65.42, 51.53, 40.33, 17.52, 12.47; Anal. Calcd for $C_{13}H_{16}ClN_5O$: C, 53.15; H, 5.49; N, 23.84. Found: C, 53.27; H, 5.55; N, 23.73.

(*rel*)-(1′*R*,4′*S*,6′*S*)-9-[4-(Hydroxymethyl)-4-methyl-6-methyl-cyclopent-2-en-1-yl] 2-amino-6-cyclopropylpurine (206): Cyclopropyl amine (0.11 mL, 1.65 mmol) was added to a solution of compound **205** (96.90 mg, 0.33 mmol) in EtOH (12 mL) and refluxed for 5 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/ CH_2Cl_2, 1:5) to give compound **206** (62 mg, 68%) as a solid: mp 181~183 ℃; ^{1}H NMR (DMSO-d_6) δ 7.97 (s, 1H), 5.80 (dd, J = 5.6, 2.0 Hz, 1H), 5.65 (dd, J = 6.2, 2.0 Hz, 1H), 5.24 (dt, J = 8.2, 1.8 Hz, 1H), 4.89 (t, J = 5.2 Hz, 1H), 3.02 (m, 1H), 2.37 (d, J = 10.2 Hz, 1H), 2.29 (d, J = 10.5 Hz, 1H), 2.04 (q, J = 8.0 Hz, 1H), 0.99 (d, J = 7.6 Hz, 3H), 0.92 (s, 3H), 0.57-0.71 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 158.98, 153.79, 150.21, 142.23, 141.47, 134.87, 125.14, 67.66, 64.18, 50.39, 41.32, 23.79, 16.99, 12.71, 6.43; Anal. Calcd for $C_{16}H_{22}N_6O$: C, 61.13; H, 7.05; N, 26.73. Found: C, 60.90; H, 6.92; N, 26.68; MS (EI) m/z 315 $(M+1)^+$.

(±)-3-(*t*-Butyldimethylsilanyloxymethyl)-pent-4-enal(208): Compound **208** was prepared from compound **207** using the method for the preparation of compound **57**: yield (61%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.59 (s, 1H), 5.65-5.57 (m, 1H), 5.06-5.01 (m, 2H), 3.68-3.51 (m, 2H), 2.60 (m, 1H), 2.42 (dd, J = 13.8, 5.6 Hz, 1H), 2.19 (dd, J = 13.8, 8.6 Hz, 1H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 203.96, 134.87, 116.43, 63.51, 46.67, 37.40, 25.65, 18.27, -5.53.

(±)-3-(*t*-Butyldimethylsilanyloxymethyl)-2-methylene-pent-4-enal (209): (4.36 g, 23.64 mmol) Eschenmoser's salt, methylene-*N*,*N*-dimethylammonium iodide, was added to a solution of aldehyde **208** (2.70 g, 11.82 mmol) and triethylamine (4.92 mL, 35.46 mmol) in CH_2Cl_2 at room temperature. The mixture was stirred overnight at room temperature. After adding a saturated aq. $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/ hexane, 1:35) to give compound **209** (1.67 g, 59%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.54 (s, 1H), 6.11 (d, J = 0.8 Hz, 1H), 5.82 (d, J = 0.7 Hz, 1H), 5.61-5.52 (m, 1H), 5.04-4.96 (m, 2H), 3.69 (d, J = 10.2 Hz, 1H), 3.50 (d, J = 10.2 Hz, 1H), 2.87 (m, 1H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 203.32, 150.21, 134.45, 130.72, 115.40, 64.53, 38.32, 25.56, 18.41, -5.57.

(±)-3-(*t*-Butyldimethylsilanyloxymethyl)-2-methylene-pent-4-enol (210): Compound **210** was prepared from compound **209** using the method for the preparation of compound **53**: yield (95%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.63-5.54 (m, 1H), 5.01-4.92 (m, 3H), 4.81 (dd, J = 1.5, 2.0 Hz, 1H), 4.12 (d, J = 6.2 Hz, 2H), 3.74-3.66 (m, 2H), 2.92 (m, 1H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.21, 134.71, 114.21, 108.40, 65.82, 63.51, 36.46, 25.50, 18.64, -5.59; MS (EI) for $C_{13}H_{26}O_2Si$: m/z 242 $(M)^+$.

(±)-3-(*t*-Butyldimethylsilanyloxymethyl)-2-methylene-pent-4-en-1-bromide (211): Compound **211** was prepared from compound **210** using the method for the preparation of compound **156**: yield (63%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 5.60-5.41 (m, 1H), 5.00-4.89 (m, 4H), 3.78-3.69 (dd, J = 12.0, 8.8 Hz, 2H), 3.41 (d, J = 5.2 Hz, 2H), 2.88 (m, 1H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.47, 133.21, 115.81, 109.45, 66.51, 37.90, 34.11, 25.28, 18.60, -5.64; MS (EI) for $C_{13}H_{25}BrOSi$: m/z 306 $(M+1)^+$.

(±)-9-[3-(*t*-Butyldimethylsilanyloxymethyl)-2-methylene-pent-4-en-1-yl] 2-amino-6-chloropurine (212): Compound **212** was prepared from compound **211** using the method for the preparation of compound **158**: yield (33%) as a solid; ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1H), 5.69-5.51 (m, 2H), 5.05-4.90 (m, 3H), 4.17 (d, J = 6.4 Hz, 2H), 3.61 (d, J = 10.4 Hz, 1H), 3.48 (d, J = 10.2 Hz, 1H),

3.11 (m, 1H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 159.21, 154.71, 151.44, 149.47, 143.88, 133.21, 124.67, 115.81, 109.45, 67.78, 47.90, 34.11, 25.47, 18.52, −5.39; Anal. Calcd for $C_{18}H_{28}ClN_5OSi$: C, 54.87; H, 7.16; N, 17.78. Found: C, 54.69; H, 7.02; N, 17.87; MS (EI): m/z 395 $(M+1)^+$.

(±)−9−[3−(Hydroxymethyl)−2−methylene−pent−4−en−1−yl] 2−amino−6−chloropurine (213): Compound **213** was prepared from compound **212** using the method for the preparation of compound **11**: yield (77%) as a colorless syrup: ^{1}H NMR (DMSO−d_6) δ 7.93 (s, 1H), 5.56−5.42 (m, 2H), 5.11−4.93 (m, 4H), 4.02 (d, J = 6.8 Hz, 2H), 3.72−3.64 (m, 2H), 2.95 (m, 1H); ^{13}C NMR (DMSO−d_6) δ 159.78, 154.32, 151.07, 148.23, 142.36, 134.71, 125.77, 117.89, 108.19, 66.41, 48.32, 36.82; Anal. Calcd for $C_{12}H_{14}ClN_5O$: C, 51.52; H, 5.04; N, 25.04. Found: C, 51.77; H, 4.92; N, 24.88; MS (EI): m/z 281 $(M+1)^+$.

(±)−9−[3−(Hydroxymethyl)−2−methylene−pent−4−en−1−yl] 2−amino−6−hydroxypurine (214): 2−Mercaptoethanol (0.09 mL, 1.29 mmol) and NaOMe (1.17 mL, 1.17 mmol, 1 M solution in MeOH) was added to a solution of compound **213** (61 mg, 0.22 mmol) in MeOH (8 mL), and heated overnight under reflux. After cooling, the reaction mixture was neutralized with a few drops of glacial AcOH and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/ CH_2Cl_2, 1:6) to give compound **214** (37 mg, 65%) as a solid: mp 188~190 ℃; UV (H_2O) λ_{max} 253.5 nm; ^{1}H NMR (DMSO−d_6) δ 7.88 (s, 1H), 5.50−5.39 (m, 2H), 5.15−5.14 (m, 2H), 4. 92 (t, J = 5.2 Hz, 1H), 4.13 (d, J = 6.6 Hz, 2H), 3.65 (d, J = 10.2 Hz, 1H), 3.32 (d, J = 10.2 Hz, 1H), 2.95 (m, 1H); ^{13}C NMR (DMSO−d_6) δ 159.31, 154.59, 150.37, 147.43, 141.55, 134.19, 126.32, 115.32, 109.16, 67.27, 47.29, 37.25; Anal. Calcd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.80. Found: C, 54.90; H, 5.72; N, 26.98; MS (EI): m/z 261 $(M)^+$.

***(rel)*−(2*S*,3*R*)−3−(*t*−Butyldimethylsilanyloxymethyl)−2−methyl−pent−4−enal (215):** Compound **215** was prepared from compound **208** using the method for the preparation of compound **39**: yield (69%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.57 (s, 1H), 5.59−5.52 (m, 1H), 5.07−5.01 (m, 2H), 3.51 (m, 2H), 2.51 (m, 1H), 2.01 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 203.96, 135.18, 116.83, 64.01, 47.27, 38.51, 25.36, 18.55, 13.84, −

5.57.

(*rel*)-(2*S*,3*R*)-3-(*t*-Butyldimethylsilanyloxymethyl)-2-methyl-pent-4-en-1-ol (216): The alcohol **216** was obtained from compound **215** using similar conditions for synthesizing compound **53**: yield (89%); ^{1}H NMR ($CDCl_3$) δ 5.66-5.54 (m, 1H), 5.02-4.96 (m, 2H), 3.63-3.42 (m, 4H), 2.16 (m, 1H), 1.75 (m, 1H), 0.84 (s, 9H), 0.81 (d, J = 5.1 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.93, 116.71, 66.44, 65.19, 49.18, 37.18, 25.86, 18.25, 14.15, -5.52; MS (EI) for $C_{13}H_{28}O_2Si$: m/z 244 (M^+).

(*rel*)-(2*S*,3*R*)-3-(*t*-Butyldimethylsilanyloxymethyl)-2-methyl-pent-4-en-1-bromide (217): Compound **217** was synthesized from compound **216** using a similar procedure for synthesizing compound **156**: yield (68%); ^{1}H NMR ($CDCl_3$) δ 5.62-5.58 (m, 1H), 5.00 (s, 1H), 4.98-4.90 (m, 1H), 3.89 (m, 2H), 3.54 (dd, J = 10.2, 8.6 Hz, 2H), 2.23 (m, 1H), 1.89 (m, 1H), 0.85 (s, 9H), 0.80 (d, J = 5.2 Hz, 3H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.54, 117.13, 67.56, 48.32, 36.71, 33.46, 25.32, 18.67, 14.42, -5.57; MS (EI) for $C_{13}H_{27}BrOSi$: m/z 308 $(M+1)^+$.

(*rel*)-(2′*S*,3′*R*)-9-[3-(*t*-Butyl dimethyl silanyloxymethyl)-2-methyl-pent-4-en-1-yl] 2-amino-6-chloropurine (218): The purine derivative **218** was synthesized from compound **217** using a similar procedure for synthesizing compound **158**: yield (28%);^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 5.74-5.62 (m, 1H), 5.58 (s, 1H), 5.24-5.10 (m, 1H), 4.18-4.10 (m, 2H), 3.57 (d, J = 7.0 Hz, 2H), 2.67 (m, 1H), 2.19 (m, 1H), 0.86 (s, 9H), 0.82 (d, J = 6.2 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 159.19, 154.22, 151.04, 143.20, 137.51, 124.39, 116.34, 63.81, 49.04, 48.03, 32.81, 25.74, 18.11, 12.58, -5.57; Anal. Calcd for $C_{18}H_{30}ClN_5OSi$: C, 54.59; H, 7.64; N, 17.69. Found: C, 54.38; H, 7.73; N, 17.56; MS (EI): m/z 397 $(M+1)^+$.

(*rel*)-(2′*S*,3′*R*)-9-[3-(Hydroxymethyl)-2-methyl-pent-4-en-1-yl]2-amino-6-chloropurine (219): Compound **219** was prepared from compound **218** using the method for the preparation of compound **11**: yield (78%); ^{1}H NMR (DMSO-d_6) δ 7.89 (s, 1H), 6.02 (br s, 2H), 5.70-5.57 (m, 2H), 5.12 (m, 1H), 5.01 (t, J = 5.2 Hz, 1H), 4.22 (dd, J = 13.4, 6.8 Hz, 1H), 4.02 (dd, J = 13.4, 7.8 Hz, 1H), 3.63 (m, 2H), 2.59 (m, 1H), 2.18 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 159.63, 154.65, 151.27, 143.66, 134.90, 124.39, 118.92,

63.98, 48.71, 47.99, 32.97, 12.42; Anal. Calcd for $C_{12}H_{16}ClN_5O$: C, 51.16; H, 5.72; N, 24.86. Found: C, 51.09; H, 5.68; N, 24.99; MS (EI): m/z 283 $(M+1)^+$.

(*rel*)-(2′*S*,3′*R*)-9-[3-(Hydroxymethyl)-2-methyl-pent-4-en-1-yl]2-amino-6-hydroxypurine (220): The guanine derivative **220** was synthesized from compound **219** using a similar procedure for synthesizing described for compound **214**: yield (62%): mp 180~182 ℃; UV (H_2O) λ_{max} 255.0 nm; ^{1}H NMR (DMSO-d_6) δ 7.86 (s, 1H), 6.02 (br s, 2H), 5.78-5.66 (m, 1H), 5.30-5.15 (m, 2H), 4.99 (t, J = 5.4 Hz, 1H), 4.21 (dd, J = 13.8, 6.6 Hz, 1H), 4.05 (dd, J = 13.8, 7.8 Hz, 1H), 3.76-3.62 (m, 2H), 2.45 (m, 1H), 2.22 (m, 1H), 0.89 (d, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 159.45, 153.78, 150.23, 141.32, 134.32, 123.27, 117.78, 64.03, 48.69, 48.61, 33.67, 13.69; Anal. Calcd for $C_{12}H_{17}N_5O_2$: C, 54.74; H, 6.51; N, 26.60. Found: C, 54.84; H, 6.45; N, 26.36; MS (EI): m/z 264 $(M+1)^+$.

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국문초록

A synthesis of novel nucleosides as potential antiviral agents

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4′-페닐과 1′-메틸 더블 측쇄, 1′,4′-다이메틸 측쇄, 4′-하이드록시 메틸과 1′-메틸 더블 측쇄, 4′, 6′-메틸 더블 측쇄를 가진 카보사이클릭 뉴크레오사이드의 합성은 간단한 2-하이드록시 아세토페논, 아세톨, 1,3-다이하이드록시 아세톤에서 완성되었다. 4′-페닐, 메틸, 하이드록시 메틸 그룹은 [3,3]-sigmatropic rearrangement 반응을 경유하여 설치되었고 1′-메틸 그룹을 도입하기 위하여 methylmagnesium bromide 의 카보닐 추가를 이용하였으며 6′(α)-위치의 메틸 그룹의 소개는 Felkin-Ahn 에 의하여 통제된 알킬화에 의해 완성되었다. Divinyls **5**, **15**, **26, 43**, **200** 의 cyclization 은 Grubbs catalyst 2nd 를 사용하여 실행되었다. Cyclopentenols **8α**, **16α**, **27**, **43**, **205** 과 Bases 의 연결에 Mitsunobu 반응, Pd(0) catalyst, desilylation 을 이용하여 목표의 뉴크레오사이드 **11**, **21**, **22**, **34~37**, **49~51**, **206** 을 합성하였다.

또한 apiosyl 뉴크레오사이드의 합성은 간단한 material 과 1,3-다이하이드록시 아세톤에서 완성되었다. 중간물질 **58**, **177** 을 ozonolysis, reductions, acetylation 을 이용하여 **52** 과 **174** 에서 얻어 피리미딘, 퓨린 Bases 와 연결하여 apiosyl 뉴크레오사이드 **66~69, 184~189**, **194**, **195** 을 얻었다.

또한 새로운 5′-norcarboacyclic 뉴크레오사이드, acyclic 뉴크레오사이드, phosphonic acid 뉴크레오사이드, cyclopentene phosphonate 뉴크레오사이드, acyclic phosphonate 뉴크레오사이드, fluorocyclopropyl 뉴크레오사이드, acyclic version 6′-methylene and 6′(α)-methylated 뉴크레오사이드를 얻기 위하여 간단한 1,1-사이클로뷰탄 다이칼복실릭산, 다이에틸 말론네트, 2-메틸렌프로판-1,3-다이올, 2-뷰텐-1,4-다이올, 1,3-다이하이드록시 메틸에서 완성되었다.화합물 **209** 의 6′-위치의 메틸렌 그룹은 Mannich 반응 Eshenmoser's salt 을 이용하여 설계하고 화합물 **215** 의 6′(α)-위치의 메틸 그룹은 알킬화반응을 이용하여 설계하였다. 중간물질인 mesylates **73**, **87**, **98**, **109**, **120**, **127**, **141**; bromides **156**, **157**, **211**, **217** 와 Bases 는 친핵성 치환반응과 deblocking condition 을 통하여 뉴크레오사이드 **78~81**, **92~95**,

103~106, **114~117**, **121~124**, **132~135**, **146~ 149**, **166~173**, **214**, **220**을 합성하였다.

그리고 합성한 화합물들을 HIV-1, HSV1, 2, HMCV 에 대한 항바이러스를 검색한 결과 화합물 **34**, **37**, **79**, **122**, **135**, **194**, **206**, **214**, **220**는 항 HIV-1 약효를 나타내고 화합물 **49**, **78**, **116**, **146**, **167**는 항 HMCV 약효를 나타내었다.

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감사드립니다. 또한 김경옥, 김명길, 박영길, 류경학 선배님들, 옥란이, 무영이, 은화, 진우, 우항, 송단, 해도, 향숙이, 영화, 영란이, 이화, 청파, 련금이, 복선이… 등 모든 친구와 후배들에게도 감사드리며, 저를 관심해주시고 항상 힘이 되어 주신 외삼촌, 외숙모, 고모부, 고모, 형부, 언니, 오빠, 등 모든 친지분들에게도 감사드리며 옆에 없었지만 항상 나를 지켜봐주고 힘이 되어 주고 내 편이 되어 준 성매, 귀영이, 홍매, 리화, 정복이… 등 많은 친구들에게도 감사하다는 말을 전하고 싶습니다.

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2008 년 06 월 30 일
김 애 홍 (올림)

저작물 이용 허락서

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	영문: A synthesis of novel nucleosides as potential antiviral agents				

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건 아래 조선대학교가 저작물을 이용할 수 있도록 허락하고 동의합니다.

- 다 음 -

1. 저작물의 DB 구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함.
2. 위의 목적을 위하여 필요한 범위 내에서의 편집과 형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함.
3. 배포·전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5 년으로 하고, 기간종료 3 개월 이내에 별도의 의사 표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 출판을 허락을 하였을 경우에는 1 개월 이내에 대학에 이를 통보함.
6. 조선대학교는 저작물 이용의 허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음.
7. 소속 대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송·출력을 허락함.

동의여부: 동의(√) 반대( )

2008 년 6 월 30 일

저 작 자: 김 애 홍 (인)

조선대학교 총장 귀하