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2011 年 8 月

碩士學位論文

Synthesis and Antiviral Evaluation of Novel Carbocyclic Nucleosides

朝 鮮 大 學 校 大 學 院

藥 學 科

申 光 煥

Synthesis and Antiviral Evaluation of Novel Carbocyclic Nucleosides

신규 카보사이클릭 뉴크레오사이드의 합성 및 약효검색

2011 年 8 月 25 日

朝 鮮 大 學 校 大 學 院

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Synthesis and Antiviral Evaluation of Novel Carbocyclic Nucleosides

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이 論文을 藥學 碩士學位申請 論文으로 提出함.

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국문초록

신규 카보사이클릭 뉴크레오사이드의 합성 및 약효검색

신 광 환

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합성된 뉴크레오사이드는 당부위 또는 염기부위의 구조변형을 거친 천연 뉴크레오사이드와 비슷한 구조를 가진 유도체로서 anti-HIV의 중요한 역할을 가지고 있다. 또한 카보사이클릭 뉴크레오사이드는 당부분의 산소가 탄소로 치환된 구조를 가지고 있어 화학적으로 안정할 뿐만 아니라 생물학적으로 뛰어난 항암효과와 항바이러스 효과를 가진 유도체가 발견될 수 있는 확률이 매우 높다.

본 연구에서 신규 4′-cyclopropyl-5′-norcarbocyclic 아데노신 뉴크레오사이드 및 4′-하이드록시 카보사이클릭 뉴크레사이드의 합성은 propionaldehyde **5** 및 D-lactose로부터 완성되었다. 우선 중간물질 **13**, **28**을 Grignard reaction, ring-closing metathesis 등 일련의 반응을 통하여 합성하였고 얻은 화합물 **13**, **18**을 Mistunobu 반응을 거쳐서 base와 축합하여 최종 화합물질 **17**, **18**, **19**, **21**, **31**을 합성하였다. 이들 화합물에 대한 anti-HIV 작용을 검토한 결과 화합물 **18** (EC_{50} = 18.6 μM)이 좋은 결과를 나타내었다. 세포투과성을 높이고, 더 좋은 anti-HIV 활성을 기대하여 화합물 **18**의 SATE phosphonodiester nucleoside prodrug **23**을 합성하였으며, 화합물 **23**에 대하여 anti-HIV 작용을 검토한 결과, EC_{50} = 9.8 μM으로 prodrug 이전보다 2배 정도 상승한 결과를 보여주었다. 합성한 화합물 **31**은 약효를 나타내지 않았다.

List of Abbreviation

AIDS: Acquired immunodeficiency syndrome

HIV: Human immunodeficiency virus

FDA: Food and drug administration

AZT: 3′-Azido thymidine

RT: Reverse transcritase

ddC: 2′,3′-Dideoxy cytidine

ddI: 2′,3′-Dideoxy inosine

d4T: 2′,3′-Didehydro-3'-deoxy thymidine

DMAP: 4-(Dimetylamino)pyridine

DMF: N,N-Dimethyl formamide

DMSO: Dimethyl sulfoxide

DIAD: Diisopropylazodicaboxylate

PMBCl: *p*-Methoxybenzyl chloride

DEAD: Diethylazodicarboxylate

DDQ: 2,3-Dichloro-5,6-dicyano-*p*-benzenoquinone

NOE: Nuclear overhauser (enhancement)

PCC: Pyridinium chlorochromate

RCM: Ring-closing metathesis

THF: Tetrahydrofuran

TBAF: Tetra butyl ammonium fluoride

TBDMSCl: *tert*-Butyldimethylsilyl chloride

TEA: Triethylamine

EC_{50}: Concentration required to inhibit to inhibit the replication of virus by 50%

CC_{50}: Concentration required to reduce the viability of unaffected by 50%

DNA: Deoxyribonucleic acid

RNA: Ribonucleic acid

4Å-MS: 4Å Molecular sieves

LAH: Lithium aluminum hydride

NMR: Nuclear Magnetic Resonance

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

Introduction

The frist cases of acquired AIDS in the United States were described in 1981. It is estimated that human immudodeficiency virus, the etiologic cause of AIDS. Currently, In 2009, there are approximately 33.3 million people living with HIV. 2.6 million people were newly infected and 1.8 million people died of AIDS-related illnesses[1].

Viruses are intracellular pathogens sharing many of the nutritional requirements and synthetic pathways of the host cells they infect. Therefore, an ideal antiviral agent would be one that effectively interdicts viral infection as a consequence of interaction with a target that is unique to the virus, and hence of little or no concern to the uninfected host tissues. In principle, such selective antiviral activity can be achieved by targeting virusspecific enzymes such as viral polymerases. Retroviruses such as HIV are RNA viruses that through a double-strand DNA intermediate. This novel viral replication cycle requires that retroviruses carry a specific enzyme, reverse transcriptase (RT), since there are no cellular enzymes that can convert single-strand RNA into double-strand DNA. As a result of the key role of HIV-1 RT in viral repication, it has been a major target for the development of a series of anti-HIV drugs. The synthetic nucleoside analogues, which resemble the natural nucleosides, but have an modified deoxyribose or ribose moiety, have played a major role in the treatment of human immunodeficiency virus (HIV).

There are now many drugs in the NRTI class that are approved by the FDA for the treatment of HIV (Figure 1). Stavudine or d4T[2] is the only other thymidine analogues approved for clinical use 3TC[3] (lamivudine) and FTC (emtricitabine) are both cytidine analogs, and abacavir[4] is the only guanosine analog. Tenofovir[5] and ddl[6] (didanosine) round out the NRTI class as adenine analogs. All of the nucleoside analogs act in the same way as AZT[7] by competing with the cellular deoxynucleotides for incorporation into the DNA chain during reverse transcription. A number of nucleoside analogues were also

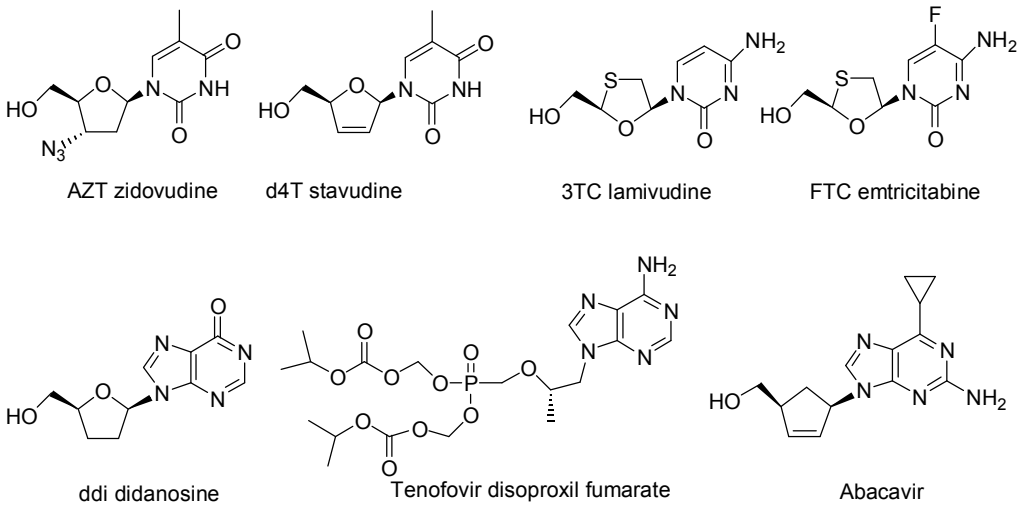


FIGURE 1 Chemical stuctures of the nucleoside analogue RT inhibitors

under development, which not only have potent antiviral activity against the wild-type as well as the drug-resistant mutant enzyme However, these nucleosides have their own limitations and problems in the treatment of diseases such as toxicity and emergence of resistant viral strains, which prompted extensive investigation to discover safer and more effective nucleoside analogues. In view of reason, we needed to develop the more novel nucleoside analogues with improved properties.

Recently, Several branched nucleosides[8] have been synthesized and evaluated as potent antiviral agents. Among them, 4-vinyl-d4T (**1**)[9] and 4-ethynyl-d4T (**2**),[9] which have an additional double or triple bond at the 4′-position, were reported to have potent anti-HIV activities (Figure 2). Molecular modeling studies demonstrated the presence of a hydrophobic 4-pocket that could accommodate these substitutions and contribute to the observed enhancement in potency in anti-HIV activity.[10] Recently, 4′-branched-5′-norcarbocyclic phosphonic acid analogues, such as 4-vinyl-cpAP (**3**) and 4-ethynyl-cpAP (**4**),[10] have encouraged the search for novel nucleosides as potential anti-HIV agents among this class of compounds.[11] The phosphonate has certain

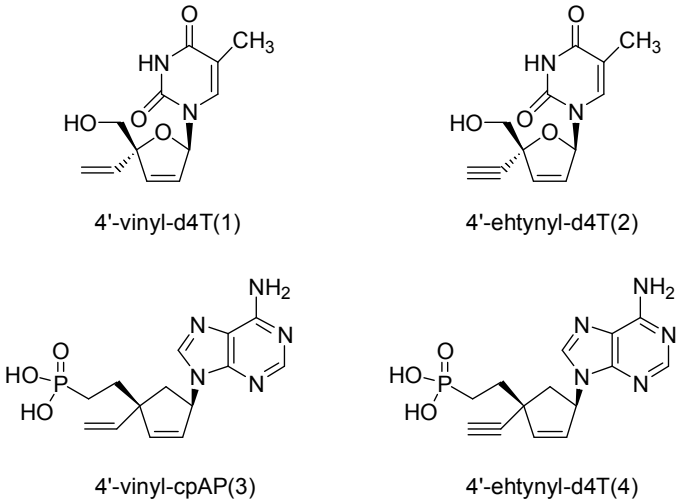


FIGURE 2 Synthesis 4'-branched nucleoside analogues anti-HIV agents

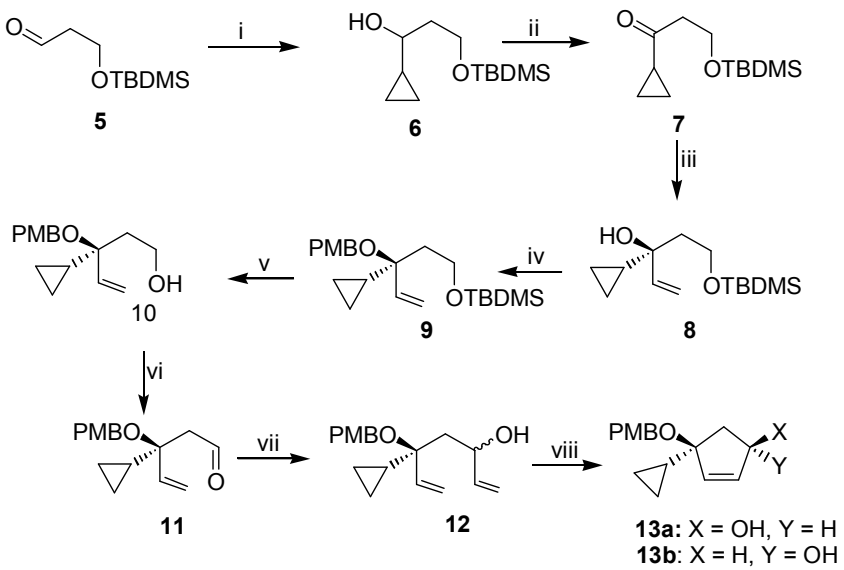
advantages over its phosphate counterpart as it is metabolically stable because its phosphorus-carbon bond is not susceptible to hydrolytic cleavage.[12] The spatial location of the oxygen atom, namely the β-position from the phosphorus atom in the nucleoside analogue, plays a critical role in the antiviral activity. This increased antiviral activity with this oxygen atom may be attributed to the increased binding capacity of the phosphonate analogues to target enzymes.[13] Moreover, a phosphonate nucleoside analogue can skip the requisite first phosphorylation, which is a crucial step for the activation of nucleosides. This is frequently a limiting step in the phosphorylation sequence, which ultimately leads to triphosphates.[14]

Stimulated by these findings that 4-branched nucleoside analogues and 5-norcarbocyclic nucleoside phosphonate have excellent biological activities, we sought to synthesize a novel class of nucleosides comprising 4-cyclopropane branched carbocyclic-5-norcarbocyclic phosphonic acid analogues in order to search for more effective therapeutics against HIV and to provide analogues for probing the conformational preferences of enzymes associated with the nucleoside kinases of nucleosides and nucleotides.

RESULTS AND DISCUSSION

As depicted in Scheme 1, the target compounds were prepared from protected to

SCHEME 1 synthesis of cyclopropentenol intermediate



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

propionaldehyde 5.[15] The aldehyde functional group of 5 was to functional group of 5 was subjected to carbonyl addition reaction by cyclopropylmagensium bromide to furnish the secondary alcohol 6, which was subjected to oxidation using PCC[16] to provide ketone derivative 7. The corresponding ketone group of 7 was again subjected to an addition reaction with vinylmagnesiun bromide to give the tertiary hydroxyl ad to an 8, which was successfully protected using PMBCl[17] to provide compound 9. Removal of silyl protecting group of 9 using TBAF gave primary alcohol 10, which was oxidized to the aldehyde 11 using Swern oxidation conditions[18] (DMSO, oxalyl chloride, TEA). The aldehyde 11 was subjected to nucleophilic Grignard conditions[19] with vinylmagnesium bromide to give divinyl 12, which was subjected to ring-closing metathesis (RCM) conditions using second

generation Grubbs′ catalyst ($C_{46}H_{65}Cl_2N_2PRu$)[20] to provide cyclopropane-substituted cyclopentenol **13a** (36%) and **13b** (37%), which were readily separated by silica gel column chromatography. The nuclear NOE experiments with cyclopentenols **13a** and **13b** confirmed these assignments. As expected, NOE enhancements were found between the cis-oriented hydrogens. Upon irradiation of C_1-*H*, weak NOE patterns were observed at the proximal hydrogens of compound **13b** [C_4-C*H*-(0.78%)] versus those of compound **13a** [C_4-C*H*-(1.21%)] (Figure 3).

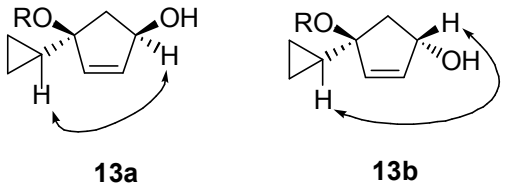
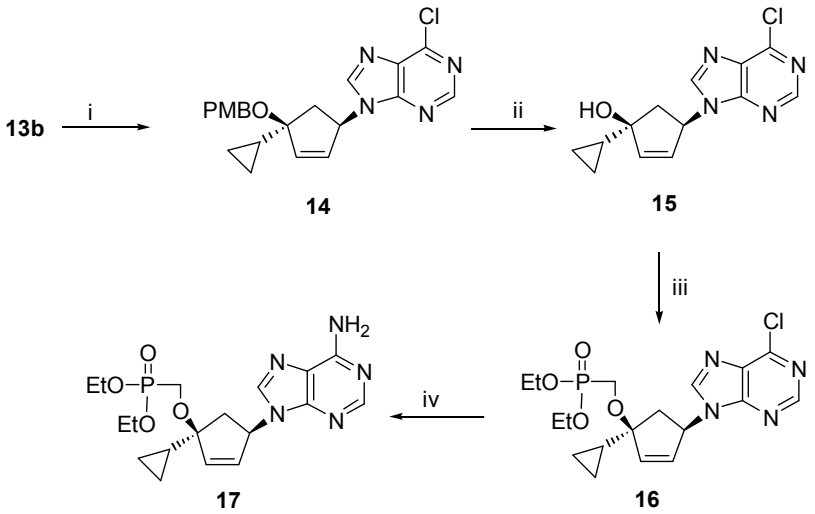


FIGURE 3 NOE diferences between the proximal hydrogens of **13a** and **13b**

To synthesize the desired 5′-norcarbocyclic adenosine nucleoside analogues, the protected cyclopentenol **13b** was treated with 6-chloropurine under Mitsunobu conditions[21] (DEAD and PPh_3). Slow addition of diethylazodicarboxylate (DEAD) to a mixture of cyclopentenol **13b**, triphenylphosphine and the 6-chloropurine in THF solvent gave a yellow solution, which was stirred for 2 hours at -40°C and further stirred overnight at room, temperature to give the projected 6-chloropurine analogue **14** as an only N^9-regioisomer [UV (MeOH) λ_{max} 264.0 nm][22]. The PMB protection group was removed with DDQ[23] to produce the 5′-nornucleoside analogue **15**, which was treat with diethylphosphonomethyl triflate[24] using lithium *t*-butoxide to yield the nucleoside phosphonate analogue **16** (Scheme 2). The chlorine group of **16** was then converted to amine with methanolic ammonia at 70°C to give the corresponding adenine phosphonate derivative **17**. Hydrolysis of **17** by treatment with bromotrimethylsilane in CH_3CN in the presence of 2,6-lutidine gave an adenine phosphonic acid derivative **18** (Scheme 3).[25]

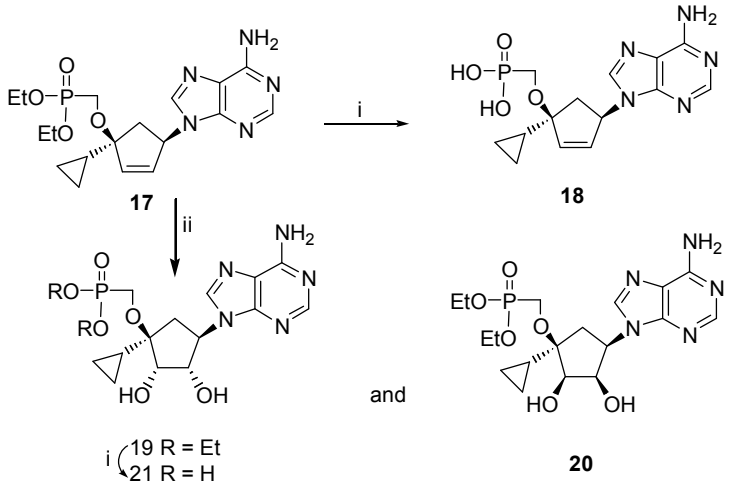
SCHEME 2 Synthesis of 5'-norcarbocyclic adenosine phosphonate



Reagents: i) 6-chloropurine, DEAD, PPh_3, THF; ii) DDQ, CH_2Cl_2 (10:1); iii) $(EtO)_2POCH_2OTf$, LiO-*t*-Bu, THF; iv) NH_3/MeOH, 70°C

In order to synthesize the 2′,3′-dihydroxy nucleoside analogues, the protected

SCHEME 3 Synthesis of 5'-norcarbocyclic adenosine phosphonate and phosphonic acid



Reagents: i) 6-chloropurine, DEAD, PPh_3, THF; ii) DDQ, CH_2Cl_2 (10:1); iii) $(EtO)_2POCH_2OTf$, LiO-*t*-Bu, THF; iv) NH_3/MeOH, 70°C

nucleosides 17 was subjected to vicinal hydroxylation conditions[26] using catalytic amount of OsO_4 and NMO to give the 19 (27%) and 20 (26%), respectively[27]. As shown in (Figure 3), the stereochemistry was readily determined by NOE experiment. On irradiation of C_1-*H*, relatively strong NOE was observed at C_2-*H* and C_3-*H* of 20, which showed 1′,2′.3′-cis relationships, But relatively weak NOE was observed at C_2-H and C_3H of 19, which means the 1′,2′- and 1′,3′-trans relationships. The adenosine phosphonic acid 21 was synthesized from 19 by the similar procedures described for 18 (Figure 4).

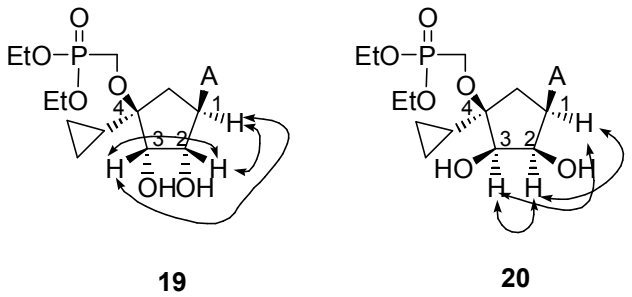
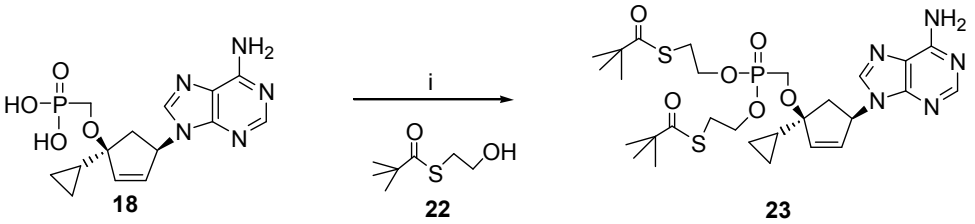


FIGURE 4 NOE relationships between proximal hydrogens of **19** and **20**

To synthesize the thioester prodrug analogue, compound 18 was reated with thioester 22[28] in the presence of 1-(2-mesitylenesulfonyl)-3-nitro-1H-1,2,4-triazole (MSNT)[29] to provide the bis (SATE) derivative as a target compound 23 (Scheme 4).



SCHEME 4 Synthesis of target (bis) SATE prodrug of adenine analogue **23**. Reagents: i) thioester, **22**, 1-(2-mestiylenesulfonyl-nitro-1*H*-1,2,4-triazole,pyridine.

The synthesized nucleoside phosphonate and phosphonic acid analogues 17, 18,

19, 21, and 23 were then evaluated for antiviral activity against human immunodeficiency virus. The procedures for measuring the antiviral activity toward wild-type HIV and cytotoxicity has been reported previously[30]. As shown in Table 1. the synthesized nucleoside 23 exhibited in cell-based activity compared with phosphonic acid 18. Although SATE protecting group as a prodrug scaffold was introduced, the antiviral activity was slightly increased. However, nucleoside analogues 17, 19 and 21 did not show anti-HIV activity or cytotoxicity at concentrations up to 100 μM.

TABLE 1 Anti-HIV activity of synthesized compounds.

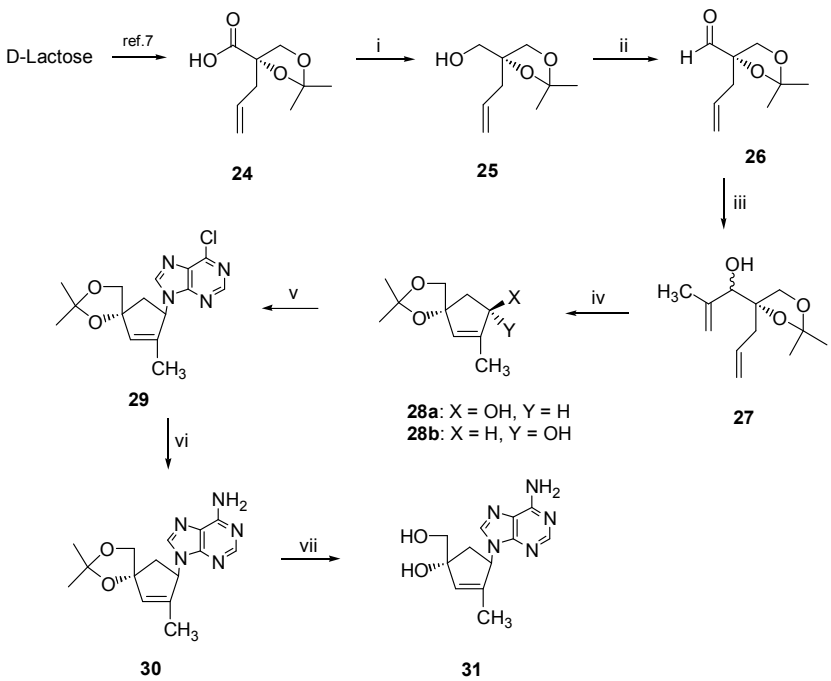
Compound No.	anti-HIV EC_{50} (μM)	Cytotoxity CC_{50} (μM)
17	62.5	98
18	18.6	90
19	> 100	> 100
21	> 100	> 100
23	9.8	65
AZT	0.01	100
PMEA	0.51	10

In summary, based on the potent anti-HIV activity of 4′-branched nucleoside and 5′-norcarbocyclic nucleoside analogues, we have designed and successfully synthesized novel 4′-cyclopropyl-5′-norcarbocyclic nucleoside analogues starting from propionaldehyde.

As shown in Scheme 5, it is envisaged that a ring-closing metathesis (RCM) of a derivative 27 could provide a desired key intermediate 29, which is a direct precursor of the targeted nucleosides. The acid derivative 24 was readily synthesized from D-lactose in five steps by a well-known procedure.[31] Acid 24 with equimolar amount of $LiAlH_4$ (1.0 M, in THF solution) at 80°C reflux overnight to give pentenol 25 which was oxidized to the aldehyde 26 using Swern oxidation conditions (DMSO, oxalyl chloride, TEA). The aldehyde 26 was subjected to nucleophilic Grignard conditions[32] with isopropenylmagnesium bromide to give 27 as an inseparable 1:1 diastereomeric mixture. Without separation, a direct of 27

was subjected to ring-closing metathesis[33] conditions using second generation Gruubs′ catalyst ($C_{46}H_{65}C_{12}N_2PRu$) to provide cyclopentenols **28a** (46%) and **28b** (47%).

Scheme 5 Synthesis of 4'-hydroxy carbocyclic adenosine



Reagents: i) $LiAlH_4$ (1.0 M in THF), THF; ii) $(COCl)_2$, DMSO, TEA; iii) isopropenylMgBr, THF; iv) Grubbs(II), CH_2Cl_2; v) 6-chloropurine, DEAD, PPh_3; vi) NH_3/MEOH; vii) 80% AcOH

To synthesized the protected cyclopentenol **28b** was treated with 6-chloro-purine, under Mitsunobu conditions[34] (DEAD and PPh_3). Slow addition of DEAD to a mixture of cyclopentenol **28b**, PPh_3 and the 6-chloropurine in hydrous THF solvent gave a yellow solution, which was stirred for 2 hours at -40°C and further stirred overnight at room temperature to give the protected 6-chloropurine analogue **29**. The chlorine group of **29** was then converted to amine with methanolic amonia at 70°C to give derivative **30**. The 2′-methyl-4′-hydroxy-carbocyclic nucleoside **31** were synthesized by an acidic hydrolysis (80% AcOH, 80°C) of **30**.

In summary, a short and concise synthetic route was developed for various

types of novel 4′-hydroxy-carbocyclic nucleosides starting from a carboxyl derivative **24**. The required stereochemistry of the desired nucleosides was successfully controlled by Grubbs' cyclization and Mitsnobu reaction, it should be noted that all the final nucleosides are novel.[35]

CONCLUSION

Some of the synthesized carbocyclic nucleosides display significant antiviral activity a perpetual structure-activity relationship study should be undertaken to find novel antiviral agents. For this research, target compound **17**, **18**, **19**, **21**, **23** and **31** were synthesized, which were subjected to antiviral screening against HIV-1. Among them, the compound **18** (EC_{50} = 18.6 μM) has well activity. The synthesized nucleoside prodrug **23** (EC_{50} = 9.8 μM) exhibited slight improvement in cell-based activity compared with phosphonic acid **18**. Although SATE protecting group as a prodrug scaffold was introduced, the antiviral activity was slightly increased. The target compound **31** didn't show antiviral activity.

EXPERIMENTAL

Melting points were determined on a Mel-temp Ⅱ laboratory device and are uncorrected. NMR spectra were recorded on a JEOL 300 Fourier in parts per million (δ) and signals are reported as a (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublet), violet (UV) spectra were obtained on a Beckman DU-7 spectrophotometer(Beckman, south Pasadena, CA, USA). MS spectra were clollected in electrospray ionization (ESI) mode, The elemental analyses were perform using a Perkin-Elmer 2400 analyzer (perkin-Elmer, Norwalk, CT, USA). Thin layer chromatography (TLC) was performed on Uniplates (silica gel) purchased from Analtech Co. (7558, Newark, DE, USA). All reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

(±)-3-(t-Butyldimethylsilanyloxy)-1-cyclopropyl-propan-1-ol (6): To a solution of **5** (2.0 g, 10.62mmol) in dry THF (20mL) was slowly added cyclopropyl-magnesium bromide (25.49 mL, 0.5 M solution in THF) at -25°C; the mixture was stirred 4 hours at 0°C. Saturated NH_4Cl to room temperature (room temperature). The mixture was diluted with water (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **6** (1.93 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.82 (t, J = 5.2 Hz, 2H), 3.21 (m, 1H), 0.81 (s, 9H), 0.39-0.18 (m, 4H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 73.6, 60.2, 41.5, 25.3, 19.5, 18.5, 3.1, 2.3, -5.3.

3-(t-Butyldimethylsilanyloxy)-1-cyclopropyl-propan-1-one (7): 4Å molecular sieves (3.8 g) and PCC (3.91 g, 18.13 mmol) were added slowly to a solution of compound **6** (1.66 g, 7.2 mmol) in CH_2Cl_2 (60 mL) at 0°C, and the mixture was stirred overnight at room temperature. An excess of diethylether (150 mL) was then added to the mixture. The mixture was stirred vigorously for 3 hours at room

temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **7** (1.26 g, 77%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.09 (t, J = 6.4 Hz, 2H), 2.65 (6.4 Hz, 1H), 2.99 (m, 1H), 1.23 (m, 2H), 1.03 (m, 2H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.6, 60.8, 43.2, 25.5, 18.9, 18.3, 11.4, -5.6.

(±)-5-(t-Butyldimethylsilanyloxy)-3-cyclopropyl-pent-1-en-ol (8): To a solution of **7** (3.5 g, 15.32 mmol) in dry THF (50 mL) was slowly added at -10°C and stirred 5 hours at 0°C. Saturated NH_4Cl solution (18 mL) was added to the mixture, which was slowly warmed to room temperature. The mixture was diluted with water (100 mL) and extracted with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **8** (2.55 g, 65%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.91 (m, 1H), 5.26-5.19 (m, cuo. Th80 (t, J = 5.8 Hz, 2H), 1.65 (dd, J = 5.7, 2.6 Hz, 2H), 0.95 (m, 1H), 0.82 (s, 9H), 0.46-0.23 (m, 4H) 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.5, 114.2, 79.2, 59.1, 43.5, 25.5, 20.1, 18.2, 3.5, 2.9, -5.2; Anal. Calc. for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00; C, 65.54; H, 10.98.

(±)-t-Butyl-[4-methoxybenzyloxy)-3-cyclopropyl-pent-4-enyloxy]-dimethylsilane (9): NaH (60% in mineral oil, 330 mg, 8.3 mmol) was added portion wise to cooled (0°C) solution of tertiary alcohol **8** (1.77 g, 6.93 mmol) and *p*-methoxybenzyl chloride (1.03 mL, 7.62 mmol) in DMF (30 mL), The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was diluted with water (110 mL) followed by extraction with diethyl ether (2 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **9** (1.98 g, 76%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29-7.24 (m, 2H), 6.91-6.85 (m, 2H), 5.89 (m, 1H), 5.28-5.22 (m, 2H), 4.49 (s, 2H), 3.81 (s, 3H), 3.76 (t, J = 6.2 Hz, 2H), 1.62 (m, 2H), 0.98 (m, 1H), 0.81 (s, 9H), 0.44-0.23 (m, 4H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.4, 143.7, 130.6, 129.3, 116.3, 114.1, 80.1, 73.0, 58.7, 56.2, 41.8, 25.3, 19.9, 18.4, 4.1, 3.6, -5.5; Anal. Calc. for $C_{22}H_{36}O_3Si$ (+0.5 EtOAc): C, 68.52; H,

9.58; Found: C, 68.48; H, 9.60.

(±)-3-(4-Methoxybenzyloxy)-3-cyclopropyl-pent-4-en-1-ol (10): To a solution of **9** (1.05 g, 2.78 mmol) in THF (20 mL), TBAF (3.33 mL, 1.0 M solution in THF) was added 0°C. The mixture was stirred overnight at room temperature and concentrated in vacuo, The residue was purified by silica gel column chromatography (Hexane/EtOAc, 5:1) to give **10** (649 mg, 89%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.27 (m, 2H), 6.91-6.85 (m, 2H), 5.89 (m, 1H), 6.95-6.87 (m, 2H), 5.90 (m, 1H), 5.25-5.19 (m, 2H), 4.51 (s, 2H), 3.79 (s, 3H), 3.57 (t, J = 6.2 Hz, 2H), 1.60 (m, 2H), 0.93 (m, 1H), 0.41 (m, 2H), 0.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 144.0, 131.2, 129.7, 117.1, 114.8, 79.8, 72.6, 57.8, 54.8, 40.2, 18.9 3.6, 3.2; Anal. Calc. for $C_{16}H_{22}O_3$: C,73.28; H, 8.45; Found: C, 73.28; H, 8.42.

(±)-3-(4-Methoxybenzyloxy)-3-cyclopropyl-pent-4-enal (11): To a stirred solution of oxalyl chloride (215 mg, 1.7 mmol) in CH_2Cl_2 (14 mL) was added a solution of DMSO (265 mg, 3.4 mmol) in CH_2Cl_2 (5 mL) dropwise at -78°C. The resulting solution was stirred at -78°C for 10 minutes and TEA (0.94 mL, 6.8 mmol) was added. The resulting mixture was warmed to 0°C and stirred for 30 minutes. Water (15 mL) was added, and the solution was stirred at room temperature for 30 minutes. The mixture was diluted with water (130 mL) and then extracted with EtOAc (2 × 130 mL). The combined organic layer was washed with brine, dried over anhydrous $MgS0_4$ and filtered. The filtrate was concentrated in vacuo and residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give aldehyde compound **11** (208 mg, 94%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.25 (m, 2H), 6.94-6.88 (m, 2H), 5.91 (m, 1H), 5.27-5.21 (m, 2H), 4.66 (s, 2H), 3.74 (s, 3H), 2.58-2.49 (dd, J = 8.6, 4.0 Hz, 2H), 0.89 (m, 1H), 0.93 (m, 1H), 0.39 (m, 2H), 0.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.7, 159.3, 142.9, 130.8, 129.1, 116.7, 114.2, 76.1, 71.2, 57.3, 51.9, 19.7, 4.8, 4.2.

(*rel*)-(3R and 3S, 5S)-5-(4-Methoxybenzyloxy)-5-cyclopropyl-hepta-1,6-dien-3-ol (12): Divinyl analogue **12** was synthesized as a diastereomeric mixture from aldehyde **11** by a procedure similar to that described for **8** yield 79%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.26 (m, 2H), 6.91-6.85 (m, 2H), 5.96-5.87 (m, 2H),

5.17-4.99 (m, 4H), 4.64 (s, 2H), 3.91 (m, 1H), 3.76 (s, 3H), 1.67-1.58 (m, 2H), 0.93-0.84 (m, 1H) 0.40-0.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.4, 159.7, 141.5, 140.7, 131.8, 129.8, 128.4, 117.8, 116.7, 115.5, 114.7, 78.2, 72.0, 68.1, 56.9, 44.3, 20.2, 5.1, 4.6, 3.8.

(*rel*)-(1S,4S)-4-(4-Methoxy-benzyloxy)-4-cyclopropylcyclopent-2-enol (13a) and (*rel*)-(1R,4S)-4-(4-methoxy-benzyloxy)-4-cyclopropylcyclopent -2-enol (13b): To a solution of **12** (260 mg, 0.901 mmol) in dry methylene chloride (7 mL) was added second generation Grubbs′ catalyst (40.0 mg, 0.0471 mmol). The mixture was refluxed overnight and cooled to room temperature. The mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give cyclopentenol **13a** (84 mg, 36%) and **13b** (86 mg, 37%). Data for **13a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (m, 2H), 6.88-6.79 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.34 (m, 1H), 4.69 (s, 2H), 4.08 (m, 1H), 3.78 (s, 3H), 2.20 (dd, J = 13.6, 8.2 Hz, 1H), 2.06 (dd, J = 13.5, 6.6 Hz, 1H) 0.93 (m, 1H), 0.41-0.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.8, 138.8, 136.9, 131.4, 128.5, 117.1, 88.7, 73.1, 67.9, 57.3, 39.2, 18.2, 5.9; Anal. Calc. for $C_{16}H_{20}O_3$ (+0.5 EtOAc): C, 71.02; H, 7.94; Found: C, 70.95; H, 7.97.

Data for **13b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.28 (m, 2H), 6.87 (m, 2H), 5.68 (d, J = 5.5 Hz, 1H), 5.38-5.34 (m, 1H), 4.71 (s, 2H), 4.01 (m, 1H), 3.75 (s, 3H), 2.28 (dd, J = 13.8, 8.6 Hz, 1 H), 2.10-2.05 (dd, J = 13.7, 6.8 Hz, 1H), 0.97 (m, 1H), 0.43 1H), 2.10-31 (m, 2H), 0.97 (m, 1H), 0.43 (m, 2H), 0.31(m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.2, 139.1, 135.6, 131.8, 129.3, 118.0, 87.4, 72.2, 67.9, 56.9, 38.8, 17.9, 6.2, 5.7; Anal. Calc. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74; Found: C, 73.79; H, 7.72.

(*rel*)-(1′R′,4′S)-9-[4-Cyclopropyl-(4-methoxybenzyloxy)-cyclopent-2-enyl]-6 chloropurine (14): To a solution containing compound **13b** (161 mg, 0.62 mmol), triphenylphosphine (440 mg, 1.68 mmol) and 6-chloropurine (191 mg, 1.24 mmol) in anhydrous THF (12.0 mL), diethyl azodicarboxylate (DEAD) (0.226 mL, 1.24 mmol) was added dropwise at -40°C for 10 minutes under nitrogen. The reaction mixture was stirred for 2 hours at the same temperature under nitrogen and further stirred overnight at room temperature. The solvent was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/hexane, 3:1) to

give compound **14** (96 mg, 39%): m.p 165-167°C; UV (MEOH) λ_{max} 264.0 nm: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.76 (s, 1H), 8.38 (s, 1H), 7.30-7.25 (m, 2H), 6.92-6.87 (m, 2H), 5.66 (d, J = 5.6 Hz, 1H), 5.36 (m, 1H), 4.69 (s, 2H), 4.44 (m, 1H), 3.72 (s, 3H), 2.31 (dd, J = 13.7, 8.8 Hz, 1H), 2.11-2.07 (dd, J = 13.8, 7.0 Hz, 1H) 0.92 (m, 1H), 0.41 (m, 2H), 0.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 151.8, 150.8, 145.7, 138.6, 134.9, 132.5, 131.5, 129.1, 117.6, 86.8, 73.5, 57.6, 54.7, 36.2, 19.3, 6.8; Anal. Calc. for $C_{21}H_{21}ClN_4O_2$ (+1.0 MeOH): C, 61.60; H, 5.87; N, 13.06; Found: C, 6.56; H, 5.90; N, 13.10.

(*rel*)-(1′R,4′S)-9-(4-Cyclopropyl-4-hydroxycyclopent-2-enyl)-6-chloropurine (15): To a solution of compound **14** (420 mg, 1.058 mmol) in CH_2Cl_2/H_2O (12 mL, 10:1 v/v) was added DDQ (358 mg, 1.58 mmol), and the mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ (2.0 mL) was added to quench the reaction, which was then stirred for 1 hours at room temperature. The mixture was diluted with water (160 mL) and extracted with CH_2Cl_2 (2 × 160 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 4:1:0.03) to give compound **15** (199 mg, 68%): m.p 176-178°C; UV (MEOH) λ_{max} 264.5 nm: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.74 (s, 1H), 8.39 (s, 1H), 5.64 (d, J = 5.5, 4.0 Hz, 1H), 5.32 (dd, J = 5.5, 4.0 Hz, 1H), 4.51 (m, 1H), 2.28 (dd, J = 13.8, 8.7 Hz, 1H), 2.10-2.04 (m, 1H), 0.96 (m, 1H), 0.42 (m, 2H), 0.33 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.9, 150.3, 149.2, 137.2, 134.8, 132.4, 86.5, 56.7, 39.6, 18.6, 7.1, 6.7; Anal. Calc. for $C_{13}H_{13}ClN_4O$ (+1.5 MeOH): C, 62.55; H, 5.89; N, 17.25; Found: C, 62.59; H, 5.92; N, 17.20.

(*rel*)-(1′R′,4′S)-Diethyl [9-(4-Hydroxy-4-cyclopropylcyclopent-2-en-1-yl)-6-chloropurine] methylphosphonate (16): Both LiO*t*-Bu (2.32 mL of 0.5 M solution in THF, 1.24 mmol) and a solution of diethyl phosphonomethyltriflate (348 mg, 1.16 mmol) in 8.0 mL of THF were slowly added to a solution of the 6-chloropurine analogue **15** (160 mg, 0.58 mmol) in 7.0 mL of THF at -30°C and stirred overnight at room temperature under nitrogen. The mixture was quenched by adding saturated NH_4Cl solution (5 mL) and further diluted with additional water (100 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The

combined organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH/Hexane/EtOAc, 0.03:4:1) to give **16** (143 mg, 58%) as a foamy solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.76 (s, 1H), 8.50 (s, 1H), 5.65 (d, J = 5.3 Hz, 1H), 5.39 (dd, J = 5.5, 4.4 Hz, 1H), 4.51 (m, 1H), 4.31 (m, 4H), 3.98 (d, J = 8.0 Hz, 2H), 2.31-2.23 (dd, J = 13.8, 8.8 Hz, 1H), 2.09 (dd, J = 13.7, 6.8 Hz, 1H), 1.39 (m, 6H), 0.97 (m, 1H), 0.43-0.35 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.9, 151.2, 150.5, 146.0, 137.7, 133.3, 132.5, 88.7, 66.3, 65.8, 64.5, 55.3, 36.7, 19.3, 17.2, 7.6, 6.6; Anal. Calc. for $C_{18}H_{24}ClN_4O_4P$ (+1.0 MeOH): C, 49.73; H, 6.15; N, 12.21; Found: C, 49.69; H, 6.18; N, 12.16.

(*rel*)-(1′R′,4′S)-Diethyl[9-(4-Hydroxy-4-cyclopropylcyclopent-2-en-1-yl)-adenine] methylphosphonate (17): A solution of **16** (202 mg, 0.473 mmol) in saturated methanolic ammonia (12 mL) was stirred overnight at 70°C in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:7) to give **17** (111 mg, 58%) as a white solid: m.p 149-151°C; UV (MeOH) λ_{max} 260.5 nm: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29 (s, 1H), 8.12 (s, 1H), 5.68 (d, J = 5.5, Hz, 1H), 5.39 (m, 1H), 4.50 (m, 1H), 4.35-4.41 (m, 4H), 4.02 (d, J = 8.1 Hz, 2H), 2.30-2.24 (dd, J = 13.7, 8.8 Hz, 1H), 2.12-2.06 (m, 1H), 1.41 -1.35 (m, 6H), 0.90 (m, 1H), 0.44 (m, 2H), 0.34 (m ,2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.2, 152.6, 150.7, 141.7, 138.1, 134.7, 120.2, 89.3, 65.7, 64.1, 63.2, 54.9, 37.1, 20.2, 16.8, 7.5, 6.3; Anal. Calc. for $C_{18}H_{26}N_5O_4P$: C, 53.07; H, 6.43; N, 17.19; Found: C, 53.01; H, 6.38; N, 17.25.

(*rel*)-(1′R′,4′S)-[9-(4-Cyclopropylcyclopent-1-yl)-adenine]-4-methylphosphonic acid (18): To a solution of the phosphonate **17** (149 mg, 0.35 mmol) in anhydrous CH_3CN (10 mL) and 2,6-lutidine (0.815 mL, 7.0 mmol) was added trimethylsilyl bromide (0.535 mg, 3.5 mmol). The mixture was heated overnight at 70°C under nitrogen gas and then concentrated in vacuo, The residue was partitioned between CH_2Cl_2 (70 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 50 mL) and then freeze-dried to give phosphonic acid **18** (88 mg, 72%) as a yellowish foam: UV (H_2O) λ_{max} 260.0 nm: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.28 (s, 1H), 8.09 (s, 1H), 5.69 (d, J = 5.4, Hz, 1H), 5.37 (dd, J = 5.5, 4.2, Hz, 1H), 4.52

(m, 1H), 4.17 (d, J = 8.0 Hz, 2H), 2.31 (dd, J = 13.7, 8.8 Hz, 1H), 2.13-2.08 (dd, J = 13.8, 6.9, Hz, 1H), 0.88 (m, 1H), 0.37-0.31 (m ,4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.8, 151.8, 149.5, 140.3, 138.6, 133.8, 119.6, 88.6, 64.7, 55.2, 36.7, 17.9, 6.7; Anal. Calc. for $C_{14}H_{18}N_5O_4P$ (+2.0 H_2O): C, 50.64; H, 5.72; N, 18.08; Found: C, 50.59; H, 5.68; N, 18.12.

(*rel*)-(1′R,2′S,3′S,4′S)-Diethyl[9-(2,3-dihydroxy-4-cyclopropylcylopent-1-yl) adenine]-4-methylphosphonate (19) and (*rel*)-(1′R,2′R,3′R,4′S)-diethyl-[9-(2,3-dihydroxy-4-cyclopropylcylopent-1-yl)-adenine]-4-methylphosphonate (20): Compound **17** (236 mg, 0.58 mmol) wsa dissolved in a co-solvent system (10 mL) (acetone:t-BuOH:H_2O = 6:1:1) along with 4-methylmorpholine N-oxide (135 mg, 1.16 mmol). Subsequently, OsO_4 (0.29 mL, 4% wt% in H_2O) was added. The mixture was stirred overnight at room temperature and quenched with saturated Na_2SO_3 solution (5 mL). The resulting solid was removed by filtration through a pad of Celite, and filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:5) to give **19** (69 mg, 27%) and **20** (66 mg, 26%) as a solid compound **19**: m.p. 151-153℃; UV (H_2O) λ_{max} 259.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.27 (s, 1H), 8.17 (s, 1H), 4.23 - 4.16 (m, 4H), 4.10 (d, J = 8.0 Hz, 2H), 3.81 (m, 1H), 3.69 (d, J = 5.6 Hz, 1H), 3.31 (m, 1H), 2.15 - 2.08 (dd, J = 13.6, 8.7 Hz, 1H), 1.95 - 1.90 (dd, J = 13.8, 6.8 Hz, 1H), 1.35 - 1.32 (m 6H), 0.92 (m, 1H), 0.38 (m, 2H), 0.30 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.4, 152.6, 150.1, 142.7, 119.8, 86.2, 76.8, 70.5, 66.4, 64.6, 63.5, 47.5, 29.2, 19.6, 17.8, 7.8, 6.9; Anal. Calc. for $C_{18}H_{28}N_5O_6P$ (+ 1.5 MeOH): C, 47.85; H, 7.00; N, 14.30; Found: C, 47.79; H, 7.03; N, 14.26 Compound **20**: m.p. 144-146°C; UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29 (s, 1H), 8.18 (s, 1H), 4.32 - 4.25 (m, 4H), 4.16 (d, J = 8.1 Hz, 2H), 3.82 (m, 1H), 3.62 (d, J = 5.5 Hz, 1H), 3.35 (dd, J = 5.6, 4.0 Hz, 1H), 2.17 (dd, J = 13.8, 8.6 Hz, 1H), 1.98 - 1.89 (dd, J = 13.7, 7.0 Hz, 1H), 1.36 (m 6H), 0.90 (m, 1H), 0.42 (m, 2H), 0.35 (m, 2H); ^{13}C NMR (DMSO-d_6, 75MHz) δ 154.9, 152.2, 149.7, 143.2, 120.7, 85.6, 75.2, 67.5, 65.2, 64.7, 48.0, 27.8, 18.9, 17.2, 6.4; Anal. Calc. for $C_{18}H_{28}N_5O_6P$ (+1.0 MeOH): C, 48.20; H, 6.81; N, 14.79; Found: C, 48.15; H, 6.77; N, 14.84.

(*rel*)-(1′R,2′S,3′S,4′S)-[9-(2,3-Dihydroxy-4-cyclopropylcylopent-1-yl)-adenin

e]-4-methylphosphonic acid (21): Final adenosine phosphonic acid **21** was synthesized from **19** using the similar procedure described for **18** as a light yellow foamy solid: yield 67%; UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.31 (s, 1H), 8.19 (s, 1H), 4.12 (d, J = 8.1 Hz, 2H), 3.67 (d, J = 5.4 Hz, 1H), 3.35 (m, 1H), 2.18-2.11 (dd, J = 13.8, 8.8 Hz, 1H), 1.93 (dd, J = 13.7, 6.9 Hz, 1H), 0.90 (m, 1H), 0.39 - 0.33 (m, 4H); ^{13}C NMR (DMSO-d_6, 75MHz) δ 154.6, 153.7, 151.3, 143.2, 119.3, 87.1, 77.4, 68.52, 65.7, 48.1, 27.4, 18.8, 6.2, 5.7; Anal. Calc. for $C_{14}H_{20}N_5O_6P$ (+3.0 H_2O): C, 38.27; H, 5.96; N, 15.94; Found: C, 38.34; H, 6.01; N, 15.89.

(*rel*)-(1′R,4′S)-(SATE) phosphoester of [9-(4-methyloxyphosphonate-4-cyclo propylcyclopentyl)] adenine (23): A solution of adenine phosphonic acid derivative **18** (59 mg, 0.169 mmol) and tri-*n*-butylamine (94 mg, 0.510 mmol) in methanol (3.8 mL) was mixed for 30 minutes and concentrated under reduced pressure. The residue was thoroughly dried with anhydrous ethanol and toluene. The resulting foamy solid was dissolved in anhydrous pyridine (10 mL) to which thioester **22** (519 mg, 3.2 mmol) and 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (201 mg, 0.678 mmol) were added. The mixture was stirred overnight at room temperature and quenched with tetrabutylammonium bicarbonate buffer (10.0 mL, 1 M solution, pH 8.0). The mixture was concentrated under reduced pressure and the residue was diluted with water (58 mL) and extracted with $CHCl_2$ (62 mL) two times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography (MeOH/Hexane/EtOAc, 0.06:3:1) to give **23** (42 mg, 39%) as a white solid: m.p. 124-125°C; UV (MeOH) λ_{max} 262.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (s, 1H), 8.15 (s,1H), 5.58 (d, J = 5.6 Hz, 1H), 5.33 (dd, J = 5.7 ,4.0 Hz, 1H), 4.51 (m, 1H), 4.20 (d, J = 8.1 Hz, 2H), 3.92 (m, 4H), 3.18-3.16 (m, 4H), 2.26 (dd, J = 13.6, 8.9 Hz, 1H), 2.12-2.08 (dd, J =,13.7, 6.7 Hz, 1H), 1.23-1.19 (m, 18), 0.89 (m, 1H), 0.38-0.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 204.4, 154.5, 152.5, 149.0, 144.2, 128.2,124.4, 118.2, 84.7, 65.3, 64.9, 62.3, 54.9, 48.3, 35.8, 31.4, 262.2, 17.3, 6.8; Anal. Calc. for $C_{28}H_{42}N_5O_6PS_2$ (+1.0 MeOH): C, 51.84; H, 6.90; N, 10.42; Found: C, 51.78; H, 6.87; N, 10.38.

(4-Allyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-mathanol (25): To the solution of **24** (20 g, 107.4 mmol) in dry THF (200 mL) was slowly added $LiAlH_4$ (1.0 M in THF) at 0°C. The mixture was refluxed overnight and cooled to room temperature. The reaction quenched with water and NaOH at 0°C, filtered through Celite pad and concentrated under vacuum, the residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:2) to give amide **25** (12.5g, 68%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.82 (m, 1H), 5.11 (d, J = 6.0 Hz, 1H), 4.50 (d, J = 8.7 Hz, 1H), 3.93 (d, J = 8.6 Hz, 1H), 3.75 (d, J = 8.7 Hz, 1H) 3.69 (d, J = 8.8 Hz, 1H), 3.50 (d, J = 8.9 Hz, 1H), 2.05 (d, J = 7 Hz, 2H), 1.44 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 114.93, 101.35, 84.64, 76.49, 68.77, 34.79, 28.57, 28.34;

4-Allyl-2,2-dimethyl-[1,3]dioxolane-4-carbaldehyde (26): To a stirred solution of oxalyl chloride (1.31 mL) in CH_2Cl_2 (3 mL) was added a solution of DMSO (0.28 mL) in CH_2Cl_2 (5 mL) dropwise at -78°C. The resulting solution was stirred at -78°C for 10 minutes and TEA (0.91 mL) was added. The resulting mixture was quenched with saturated $NaHCO_3$. The mixture was diluted with water (5 mL) and then extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with brine, dried over anhydrous $MgS0_4$ and filtered. The filtrate was concentrated in vacuo and residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give aldehyde **26** (3.04 g, 82%) as a colorless oil.

1-(4-Allyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-2methyl-prop-2-en-1-ol (27): To a cooled (0°C) solution of aldehyde **26** (0.193 g, 1.13 mmol) in dry THF (3 mL) was slowly added isopropenylmagnesium bromide (3.4 mL, 1.0 M solution in THF). After 1hour, saturated NH_4Cl solution (3.4 mL) was added, and the reaction mixture was slowly warmed to room temperature. The mixture was extracted with EtOAc (3 × 5 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give **27** (65 mg, 67%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76 (m 1H), 5.02-5.12 (m, 2H), 5.0-5.04 (m, 4H), 4.30 (m, 1H), 3.90 (m, 2H), 1.76 (s 3H), 1.43 (s, 6H).

(rel)-(1S′,4S′)-2,2,8-Trimethyl-1,3-dioxa-spiro[4,4]non-8-en-7-ol (28a) and

(rel)-(1R′,4S′)-2,2,8-Trimethyl -1,3-dioxa-spiro[4,4]non-8-en-7-ol (28b): To a solution of **27** (260 mg, 0.901 mmol) in dry methylene chloride (7 mL) was added second generation Grubbs′ catalyst (40.0 mg, 0.0471 mmol). The mixture was refluxed overnight and cooled to room temperature. The mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give cyclopentenol **28a** (84 mg, 46%) and **28b** (86 mg, 47%). Data for **28b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.48 (s, 1H), 4.11 (d, J = 7.8 Hz, 1H), 4.07 (d, J = 8.7 Hz, 1H), 4.01 (d, J = 8.7 Hz, 1H), 1.78 (s, 3H), 1.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.42, 124.22, 110.08 87.42, 80.18 72.68 41.83, 26.66, 26.30, 14.25; Data for **28a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.94 (dd, J = 5.1, 2.4 Hz, 1H), 5.83 (m, 1H), 4.35 (d, J = 6.0 Hz, 1H), 4.09 (d, J = 8.7 Hz, 1H), 4.02 (d, J = 9.0 Hz, 1H), 2.77-2.41 (m, 2H), 1.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.96, 132.12, 118.66, 110.17, 86.89, 78.12, 72.81, 42.26, 26.53, 26.30. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29.

6-Chloro-9-(2,2,8-Trimethyl-1,3-dioxa-spiro[4,4]non-8-en-7-yl)-9*H*-purine (29): To a solution containing compound **28b** (161 mg, 0.62 mmol), triphenyl-phosphine (440 mg, 1.68 mmol) and 6-chloropurine (191 mg, 1.24 mmol) in anhydrous THF (12.0 mL), diethyl azodicarboxylate (DEAD) (0.226 mL, 1.24 mmol) was added dropwise at -40°C for 10 minutes under nitrogen. The reaction mixture was stirred for 2 hours at the same temperature under nitrogen and further stirred overnight at room temperature. The solvent was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/hexane, 3:1) to give compound **29** (96 mg, 39%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.0 (s, 1H), 5.88 (s, 1H), 5.71 (t, 1H), 4.15 (d, J = 9.0 Hz, 1H), 4.03 (d, J = 8.7 Hz, 1H), 2.41 (d, J = 4.8 Hz, 1H), 2.36 (d, J = 4.5 Hz, 1H), 1.63 (s, 3H), 1.42 (s, 6H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.99, 143.61, 141.23, 134.35, 109.60, 89.86, 73.09, 62.34, 44.52, 31.41, 30.32, 29.68. 26.80 13.87.

9-(2,2,8-Trimethyl-1,3-dioxa-spiro[4,4]non-8-en-7-yl)-9*H*-purin-6-ylamine (30): A solution of **29** (202 mg, 0.473 mmol) in saturated methanolic ammonia (12 mL) was stirred overnight at 70°C in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography

(MeOH/CH_2Cl_2, 1:7) to give **30** (111 mg, 58%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (s, 1H), 6.33 (s, 1H), 4.41 (s, 1H), 4.26 (t, 1H), 2.72 (d, J = 9 Hz, 1H), 2.60 (d, J = 9 Hz, 1H), 1.39-1.40 (m = 2H), 0.64 (s, 3H), 0.16-0.22 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.9, 152.0, 147.9, 144.8, 139.65, 138.21, 128.07, 125.7, 10.76, 80.4, 78.0, 58.72, 28.7 26.86, 17.24.

4-(6-Amino-purin-9-yl)-1-hydroxymethyl-3-methyl-cyclopent-2-enol (31): Compound **30** (100 mg, 0.35 mmol) was dissolved in 80% aqueous AcOH solution (5 mL) and stirred for 5 h at 70-80°C. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure and coevaporated three times with toluene. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:4) to give **31** (69.2 mg, 80%) as a white solid, yield 67%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.12 (s, 1H), 7.99 (s, 1H), 7.20 (br s, 2H, D_2O exchangeable), 5.99 (dd, J = 8.7, 6.9 Hz, 2H), 5.72 (m, 1H), 5.02 (s, 1H, D_2O exchangeable), 5.38 (s, 1H), 3.45 (d, J = 11.1 Hz, 1H), 3.35 (d, J = 11.1 Hz, 1H), 2.37 (dd, J = 13.8, 8.1 Hz, 1H), 2.09 (dd, J = 18.9, 4.8 Hz, 1H); ^{13}C NMR (DMSO-d_6,75 MHz) δ 156.00, 152.26, 149.09, 141.03, 138.73, 131.24, 122.03, 118.87, 84. 51, 67.05, 58.41, 42.58, 18.3.

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ABSTRACT

Synthesis and antiviral evaluation of novel carbocyclic nucleosides

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The synthetic nucleoside analogues, which resemble the natural nucleosides, but have an modified deoxyribose or ribose moiety, have played a major role in the treatment of human immunodeficiency virus (HIV).

Novel 4′-cyclopropyl-5′-norcarbocyclic adenosine phosphonic acid analogues and novel 4′-hydroxy-carbocyclic nucleoside were synthesized from propionaldehyde **5** and D-lactose. Synthesized intermidiate **13a**, **13b**, **28a**, **28b** were used Grignard reaction and ring-closing metathesis (RCM). The coupling of cyclopententols **13b** and **28b** with bases by Mitsunobu reaction, target compound **17**, **18**, **19**, **21**, **23** and **31** were synthesized, which were subjected to antiviral screening against HIV-1. Among them, the compound **18** (EC_{50} = 18.6 μM) has well activity. To improve cellular permeability and enhance the anti-HIV activity of this phosphonic acid, SATE phosphonodiester nucleoside prodrug **23** (EC_{50} = 9.8 μM) was prepared, which exhibited in cell-based activity compared with phosphonic acid **18**. The target compound **31** didn't show antiviral activity.

Key Words:

anti-HIV agents; 4-cyclopropane branched nucleoside; phosphonic acid nucleosides; Grignard reaction; Ring-closing metathesis; Mitsunobu reaction.