Synthesis and anti-HIV activity of novel phenyl branched cyclopropyl nucleosides and Neplanocin A derivatives

페닐측쇄를 가진 뉴크레오사이드 유도체와 네프라노신 A 유도체의 합성 및 항 HIV 약효검색

2006 年 8 月

朝鮮大學校 大學院

藥 學 科

武 營

Synthesis and anti-HIV activity of novel phenyl branched cyclopropyl nucleosides and Neplanocin A derivatives

指導敎授　洪　俊　憙

이 論文을 藥學 碩士學位申請 論文으로 提出함.

2006 年　4 月

朝鮮大學校 大學院

藥　學　科

武　　營

武營의 碩士學位論文을 認准함

委員長　朝鮮大學校 敎　授　高 玉 鉉　印

委　員　朝鮮大學校 敎　授　李 元 宰　印

委　員　朝鮮大學校 敎　授　洪 俊 憙　印

2006 年　5 月

朝鮮大學校 大學院

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

A 546 : Human lung cancer

AFU : Absolute fluorescent units

AIDS : Acquired immunodeficiency syndrome

AZT : 3'-Azido thymidine

AZDU : 3'-Azido uridine

18-C-6 : 18-Crown-6

Co12 : human colon cancer

ddC : 2',3'-Dideoxy cytidine

ddI : 2',3'-Dideoxy inosine

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

DMF : Dimethyl formamide

DMSO : Dimethyl sulfoxide

DIBAL-H : Diisobutylaluminum hydride

FDA : Food and drug administration

HIV : Human immunodeficiency virus

HSV : Herpes simplex virus

HCMV : Human cytomegalovirus

HBV : Hepatitis B virus

EC_{50} : 50% effect concentration

CC_{50} : 50% cycotoxic concentration

MOI : Multiplicity of infection

NBS : N-Bromosuccinimide

PBS : Phosphate-buffered saline

RCM : Ring-closing metathesis

RT : Reverse transcriptase

TBAF : Tetrabutyl ammonium fluoride

TBDMS-Cl : *tert*-Butyldimethylsilyl chloride

TEA: Triethyl amine

TLC : Thin layer chromatography

THF : Tetrahydrofuran

WHO : World health organization

국 문 초 록

본 논문에서는 페닐측쇄를 가진 뉴크레오사이드 유도체와 네프라노신 A 유도체를 합성하고 이들의 항HIV-1 약효를 검색하고자 하였다. $Zn(Et)_2$, CH_2I_2 시약으로 Simmons-Smith 반응을 수행하여 높은 수율로 우니가 얻자고 하는 물질을 합성하였으며 **11 와 12**에 K_2CO_3, 18-Crown-6, DMF를 사용하여 natural bases을 붙여서 페닐측쇄를 가진 최종 뉴크레오사이드 (**21-28)**를 합성하였다. 그리고 NBS, PPh_3, CH_2Cl_2 시약으로 SN_2반응을 수행하여 allylic bromide **34** 합성하였다. 여기에 base (T, U, 5-FU, 5-IU, C, A)을 붙여서 네프라노신 A derivatives를 합성하였다. 이어서 이 화합물들의 HIV-1, HSV-1, HSV-2, 및 HCMV 등 여러 가지 바이러스에 대한약효를 검색하였다. 그 결과 (**22, 25, 42 와 43)** 화합물이 HIV-1에 현저한 항바이러스효과를 나타내었다.

ABSTRACT

Synthesis and anti-HIV activity of novel phenyl branched cyclopropyl nucleosides and Neplanocin A derivatives

Ying Wu

Advisor: Prof. Joon Hee Hong, Ph.D.

Department of Pharmacy

Graduate School of Chosun University

Nucleoside analogues play a major role in antiviral chemotherapy. Although interest in the design of these analogues has relatively decreased during the past few years, the emergence of resistance to drugs has generated new interest for search of new active nucleoside analogues.

In view of these results, the novel phenyl branched cyclopropyl nucleoside analogues and acyclic Neplanocin A analogues were designed and synthesized as potential antiviral agents.

Firstly, cyclopropanation was performed via classical Simmons-Smith reaction using $Zn(Et)_2$ and CH_2I_2. Condensation of the mesylate **11** and **12** with natural base (A. C. T. U) under nucleophilic substitution reaction condition (K_2CO_3, 18-Crown-6, DMF) afforded a series of novel cyclopropyl nucleosides **(21-28)**. Secondly, the coupling of the alkyl bromide **34** with nucleoside base (T. U. 5-FU. 5-IU. C. A) and desilylation afforded a series of novel acyclic nucleosides. The synthesized compounds were evaluated for their antiviral and antitumor activity against various viruses such as HIV, HSV-1, HSV-2 and HCMV.

INTRODUCTION

Back Ground of Anti-HIV Chemotherapy

It was only a few decades ago that the number of virus carriers have reached more than 1 million with about 10,000 new infections occur annually, which ranks third in the reported illness behind venereal disease and chicken pox. AIDS is a major cause of morbidity and mortality recently. With more than 3.6 billion people worldwide are estimated as the carriers of chronic AIDS and the number of new infections continues to increase. It is listed by the World Health Organization (WHO) as the fifth leading cause of death. Not only that, Hepatitis B Virus (HBV) Infection is prevalent worldwide and has caused serious health problem, too.

All living species are dependent for survival on the efficient transmission of genetic information from the parental DNA strand to the offspring. The responsible replication machinery consists of the catalysis DNA synthesis by DNA polymerases. The template directed means by which these enzymes function, so as to achieve high fidelity are becoming increasingly known. Viral core is comprised two kinds of viral particulates: DNA virus and RNA virus. We found DNA virus can bring on some diseases (upper respiratory infections, chicken pox and small pox ……). RNA virus can cause infectious disease (encephalitis, gastroenteritis, influenza, measles, meningitis, mumps, pericarditis, pleurodynia, poliomyelitis, rabies……) which have arbo viruses, myxo viruses, picorna viruses, rhino viruses.

Nucleosides and nucleoside analogues known to be DNA and RNA subunits, have achieved considerable success against viral infection. Our own search for antiviral therapeutic agents has involved the synthesis of various classes of nucleosides. 2',3'-dideoxynucleosides represent the most fruitful class of compounds as anti-HIV agents. FDA has approved several analogues, including AZT[16], ddC[17], ddI[18] , d4T[19] and AZDU for the treatment of HIV infections. **Figure 1**. But since treatment of AIDS patients with these nucleosides has been associated with various clinical toxicities, long-term using of 2',3'-dideoxy compounds as therapeutic anti-HIV drugs is prohibited. In view of this reason, we needed to develop the more novel nucleoside analogues with improved properties.

Rational background to the synthesis of target

The search for antiviral agents was widely thought to be an exercise in futility and some high biological nucleoside and nucleoside analogues have been synthesized, studied and used. For example, AZT, ddC, ddI, d4T, 3TC and Abacavir have also been approved for the treatment of AIDS. In addition, several nucleosides used as anti-HBV agents including L-F-ddC and L-FMAV have been synthesized. However, since some nucleosides[1,2] have shown limited stability, high toxicity and lower bioactivity, the development of new antiviral and anticancer nucleoside analogues is intensively demanded despite great improvements against virus and cancer.

A wide variety of branched nucleosides analogues[3-6] including 4'α-ethenyl **1**[7] and 4'α-ethynyl **2**[8] which have an additional double or triple bond at the 4'-position, were tested for exhibition of antiviral and antitumor activities. Recently, novel nucleosides containing a cyclopropane moiety, a feature that replaces the sugar ring, were also synthesized as conformationaly constrained analogue of acyclic nucleosides. Among them, trans-configuration of the cyclopropyl adenine nucleoside[9] **3** showed moderate antiviral activity. The purine derivatives such as synadenol[10] **4** and synguanol[11] **5** of which the ribofuranoside moiety is replaced with a methylene cyclopropane ring were found to have potent antiviral activity, particularly against human cytomegalovirus (HCMV). Also, the guanine derivative (A-5021) **6**[12], which was one of trisubstituted cyclopropane nucleosides with an additional hydroxymethyl

group at 1'-position, showed more potent antiviral activity against HSV-1 than acyclovir. **Figure 2.**

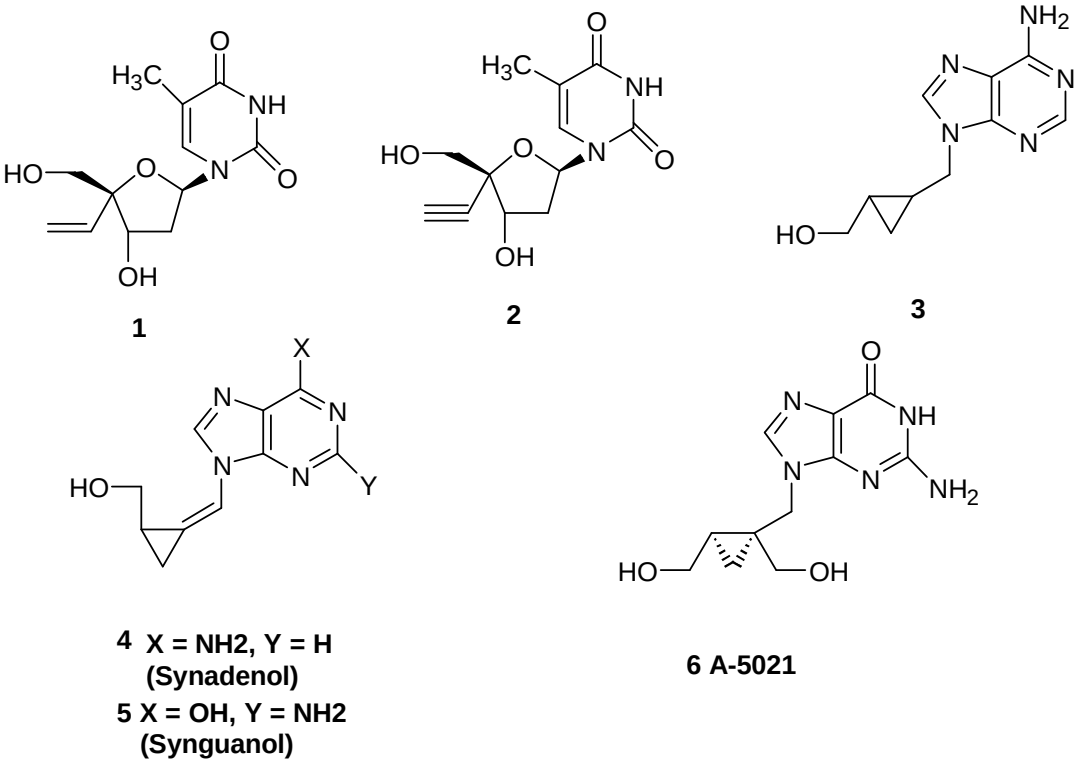


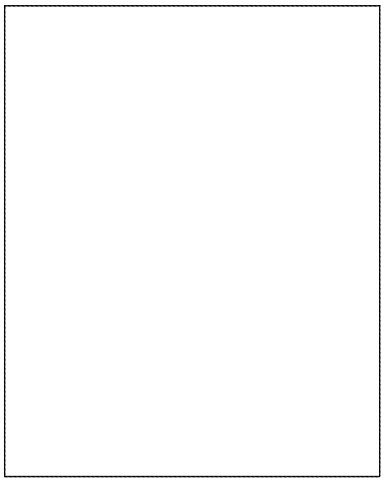
Figure 2: Rationale to the design of target nucleosides

With regards to these interesting mechanisms, as well as the antiviral

activity of branched cyclopropyl nucleosides, in this study, we synthesized and assayed novel cyclopropyl nucleosides with an additional phenyl group. It is well known that the cyclopropanation using Simmons-Smith reaction has been employed widely in synthetic organic chemistry. A very convenient and general synthetic procedure for nucleosides using these procedures is described in this paper.

The discovery of the potent and selective antiherpes agents, Acyclovir[27] and Ganciclovir[28] , have led to an extensive search for more novel nucleoside analogues with improved properties. More recently, the fermentation product Neplanocin A[29], which is a novel cyclic carba-analogue of adenosine with a cyclopentene ring, has generated considerable attention, both synthetically and biologically, due to the effect of the double bond on the compound activity and potency[30].

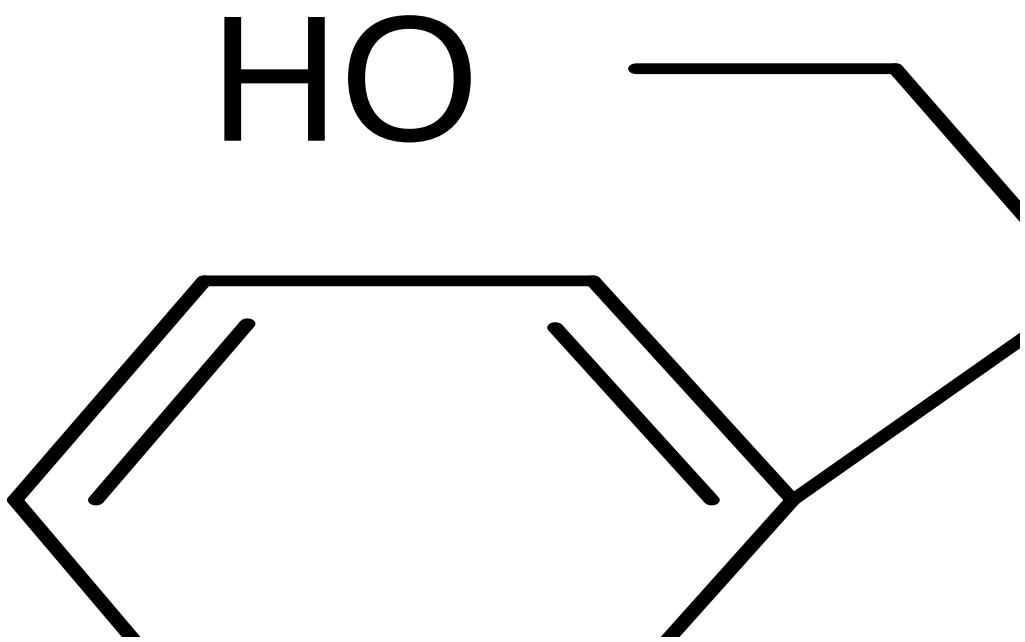
Because of the unusual presence of a double bond in Neplanocin A and the acyclic nature of Acyclovir, these two compounds have stimulated extensive research in the synthesis of new cyclic and acyclic carba-nucleoside analogues[31] that mimic the sugar portion of naturally occuring nucleosides[32]. However, with relatively few exceptions, the activities of most conventional carbocyclic nucleosides have been poorer than those of the corresponding ribosides. The loss of the furan oxygen in the carba-nucleosides is believed to have a critical effect on their antiviral activity[33]. The incorporation of halogen atoms into organic molecules has often been associated with profound changes in the biological profiles of the halogenated analogues compared to their hydrocarbon counterparts[34]. **Figure 3**.



In view of the stimulating results of carboacyclic nucleosides[27,28,29] and as part of our onging drug discovery efforts to search for less toxic and more effective antiviral agents, the bromovinyl nuclesides as acyclic analogues of Neplanocin A was synthesized.

RESULTS AND DISCUSSION

For the synthesis of target cyclopropyl nucleoside, 2-hydroxy aceto-phenone was selected as starting material.



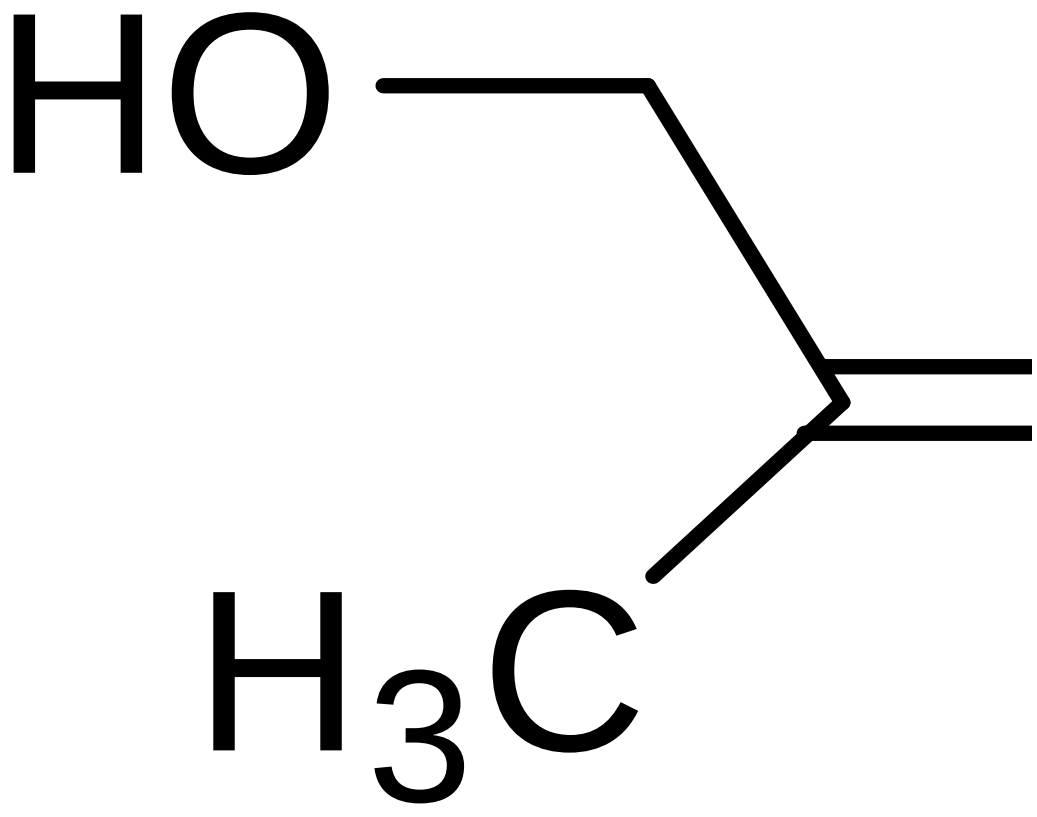
Scheme 1. Synthesis of phenyl branched cyclopropyl nucleosides
Reagents: (i) $Zn(Et)_2$, CH_2I_2, CH_2Cl_2; (ii) MsCl, TEA, CH_2Cl_2; (iii) bases K_2CO_3, 18-C-6, DMF; (iv) TBAF, THF.

As show in **Scheme 1**, the synthetic route is very simple and straightforward. Allylic alcohols **7** and **8** were readily synthesized using the previously reported procedure[13], which were subjected to Simmons-

Smith carbene cycloaddition condition[14] using $Zn(Et)_2$ and CH_2I_2 to give phenyl branched cyclopropyl alcohols **9** and **10**. The hydroxyl groups were methanesulfonylated in the condition of MsCl and TEA in anhydrous CH_2Cl_2 to give mesylates **11** and **12**, which were coupled with natural bases (adenine, cytosine, thymine, uracil) under well-known classical nucleophilic SN_2 substitution conditions[15] to give the cyclopropyl nucleosides **(13-20)**, respectively. Silyl protection groups were readily removed using tetrabutylammonium fluoride to give final branched cyclopropyl nucleosides **(21-28)**. Based on extensive literature search, the compounds **(21-28)** appear to be novel nucleosides.

In order to couple the allylic alcohol derivative with the adenine base using a nucleophilic substitution type reaction, the **33** was subjected to a mesylation reaction (MsCl, TEA, CH_2Cl_2). Unexpectedly, the reaction had a low yield (20%-30%) and was irreproducible. Therefore, our attention was turned to allylic bromide **34**, which was readily synthesized from hydroxy ketone derivatives, such as acetol **29** using a previously reported similar procedure[13] too. Conversion of allylic alcohol **33** to the bromo derivative **34** was accomplished by the sequential addition of NBS to a solution of the alcohol and triphenylphosphine in CH_2Cl_2, in high yield [35]. Direct coupling of the allylic bromide **34** with base (T, U, 5-FU, 5-IU, C, A) in DMF with cesium carbonate as a basic catalyst provided the desired alkylated pyrimidine derivatives **(35-40)**, and the alkylated purine derivative **40** in the case of adenine[36]. The UV data were in good agreement with those of the appropriate model compounds[37] . Deprotection of the *t*-butyldimethylsilyl group (TBDMS)

using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) gave the desired nucleosides **(41-46)** as shown in **Scheme 2**.



Scheme 2: Synthesis of unsaturated acyclic nucleosides

Reagents: (i) TBDMSCl, Imidazole, CH_2Cl_2; (ii) triethyl phosphonoacetate, NaH, THF; (iii) Br_2, pyridine, CCl_4; (iv) Dibal-H, CH_2Cl_2; (v) PPh_3, NBS, CH_2Cl_2; (vi) bases, $CsCO_3$, DMF, rt; (vii) TBAF, THF, rt.

Antiviral activity assays against HIV-1 were performed for all the final nucleosides and their results are shown in **Table 1.**

Table 1: The anti-HIV activities of the synthesized compounds

	EC_{50} (ug/ml)[a]	CC_{50} (ug/ml)[b]
21	> 100	> 100
22	3.12	< 3.12
23	> 100	> 100
24	> 100	> 100
25	2.29	< 2.29
26	46.7	< 46.7
27	> 100	> 100
28	> 100	> 100
AZT	0.001	1.0
41	> 100	> 100
42	3.36	< 3.46
43	1.81	< 1.81
44	> 100	> 100
45	> 100	> 100
46	> 100	> 100
AZT	0.0005	1.0

[a] Indicative of 50% effect concentration in virus-infected MT-4 cells

[b] Indicative of 50% cytotoxic concentration in virus-uninfected MT-4 cells

Unfortunately, none of them showed any anti-HIV-1 activity in MT-4 cells. Compounds **(22, 25, 42 and 43)** exhibited potent anti-HIV-1 activities, but these inhibitory effects were associated with a nonspecific cytotoxicity to MT-4 cells.

Because of the outstanding cytotoxic effects of compounds **(22, 25, 42 and 43)** to the MT-4 cell line, we further studied the cytotoxic effects of both compounds on several cancer cell lines. Therefore, based on the cytotoxicity of **(22, 25, 42 and 43)** their cytotoxic potentials were evaluated in cultured human lung cells **Table 2.** Relative cell viability compared with untreated cells of lines A 549 (human lung cancer) or Co12 (human colon cancer) was decreased to (60.3%, 51.5%) and (62.2%, 55.5%), respectively, after treatment of cells with compounds **22** (50 ug/ml) and **42** (50 ug/ml). Compounds **25** and **43** also showed similar cytotoxicity to lung cells; 61.8% and 58.3% survival of control in lung cancer cells; 45.2% and 49.5% in colon cancer cells, respectively.

Table 2. Cytotoxic potential of **(22, 25, 42 and 43)** in cultured human cancer cells.

Compounds	A549[a]	Co12[b]
22	62.2[c]	55.5[c]
25	61.8[c]	45.2[c]
42	60.3[c]	51.5[c]
43	58.3[c]	49.5[c]

[a] Human lung carcinoma cells.

[b] Human colon carcinoma cells.

[c] Percentage (%) of survival compared to control cultures at a test concentration of 50 ug/ml.

EXPERIMENTALS

All the chemicals were of reagent grade and were used as purchased. All the moisture-sensitive reactions were performed in an inert atmosphere with either N_2 or Ar using distilled dry solvents. The melting points were determined using a Mel-temp II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer; the chemical shifts are reported in parts per million (δ) and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). The UV spectra were obtained using a Beckman DU-7 spectrophotometer. The elemental analysis was performed using an Elemental Analyzer System (EA1112). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

Synthesis of novel phenyl branched cyclopropyl nucleosides

(±)-*trans*-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropyl]-methanol (9)

To a mixture of **7** (2.5 g, 8.97 mmol) in 35 ml of CH_2Cl_2 at 0℃ was added $Zn(Et)_2$ (17.94 ml, 1 M in hexane) and CH_2I_2 (9.61 g, 35.88 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/*n*-hexane, 1:5) to give 9 (2.1 g, 80%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.44-7.28 (m, 5H), 3.74 (s, 2H), 3.45-3.30 (m, 2H), 1.56 (m, 1H), 1.13 (m, 1H), 0.91 (m, 10H), 0.12 (d, J = 7.5 Hz, 6H); ^{13}C-NMR ($CDCl_3$): δ 139.83, 130.41, 128.18, 126.77, 69.61, 63.94, 33.12, 25.85, 23.07, 18.23, 12.25, -5.62.

(±)-*cis*-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropyl]-methanol (10)

Compound **10** was prepared from **8** as described for **9**. Yield 77%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.67-7.46 (m, 5H), 4.41-4.32 (s, 2H), 3.88 (dd, J = 11.7, 5.4 Hz, 2H), 2.00(m, 1H), 1.30 (dd, J = 8.1, 5.1 Hz, 1H), 1.14 (s, 9H), 1.01 (t, J = 5.1 Hz, 1H); ^{13}C-NMR ($CDCl_3$): δ 144.13, 130.06, 128.02, 126.63, 68.75, 63.66, 32.48, 25.81, 25.73, 18.11, 16.07, -5.93.

(±)-*trans*-[Methanesulfonic-acid-2-(tert-butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropylmethyl]-ester (11)

To a solution of the alcohol **9** (2.74 g, 9.36 mmol) in anhydrous CH_2Cl_2 (30 ml), anhydrous triethylamine (3.0 ml) and MsCl (1.28 g, 11.22 mmol) was added at 0℃. The mixture was stirred at the same temperature for 5 h, and quenched by a cold saturated $NaHCO_3$ solution (4.0 ml). The mixture was extracted with CH_2Cl_2 (250 ml)/water (250 ml) two times. 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/*n*-hexane , 1:6) to give **11** (2.36 g, 68%) as a colorless syrup. ^{1}H-NMR

($CDCl_3$, 300 MHz): δ 7.50-7.30 (m, 5H), 3.82 (s, 2H), 3.40 (m, 2H), 3.04 (s, 3H), 1.96 (m, 1H), 1.33 (m, 10H), 1.28(t, J = 5.2 Hz, 1H), 0.90 (s, 9H), 0.11 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 140.54, 132.21, 127.78, 125.23, 70.42, 64.12, 36.29, 33.56, 25.76, 24.34, 18.45, 12.87, -5.35.

(±)-*cis*-[Methanesulfonic-acid-2-(tert-butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropymethyl]-ester (12)

Compound **12** was prepared from **10** as described for **11**. Yield 57%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.60-7.42 (m, 5H), 4.63 (dd, J = 14.1, 5.7Hz, 1H), 4.28 (d, J = 10.5 Hz, 1H), 3.82 (dd, J = 14.1, 9.3 Hz, 2H), 3.07 (s, 3H), 1.80 (m, 1H), 1.21 (dd, J = 8.7, 4.8 Hz, 1H), 0.95 (s, 10H), 0.17 (s, 6 H); ^{13}C-NMR ($CDCl_3$): δ 143.43, 129.56, 126.11, 69.42, 65.67, 36.12, 33.87, 25.78, 25.73, 23.76, 18.34, 15.55, -5.86.

(±)-*trans*-9-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropylmethyl]-adenine (13)

A solution of the mesylate **11** (154.9 mg, 0.418 mmol), K_2CO_3 (115 mg, 0.875 mmol), 18-crown-6 (110 mg, 0.418 mmol) and adenine (68 mg, 0.5 mmol) in dry DMF (4.0 ml) was stirred overnight at 90-100℃. The mixture was cooled to room temperature and concentrated in high vacuo. The residue was diluted with brine (20 ml) and extracted with CH_2Cl_2 (30 ml x 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:10) to give compound **13** (68 mg, 40%) as a white solid: ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.45 (s, 1H), 7.78(s, 1H), 7.45-7.38 (m, 5H), 5.79 (br s, 2H), 4.25 (dd, J = 15.9, 7.5 Hz, 1H), 3.88-3.64 (m, 3H), 1.96 (m, H), 1.31

(dd, J = 8.4, 5.1 Hz, 1H), 1.14 (t, J = 5.0 Hz, 1 H), 0.92 (s, 9 H), 0.39 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 155.32, 152.79, 150.17, 140.30, 138.59, 130.36, 128.48, 127.32, 119.68, 69.14, 45.51, 33.49, 25.81, 19.95, 18.25, 13.93, -5.53.

(±)-*trans*-1-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropylmethyl]-cytosine (14)

Compound **14** was prepared from **11** as described for **13**. Yield 35%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.31-7.26 (m, 5H), 7.14 (d, J = 6.9, 5.7Hz, 1H), 5.59 (d, J = 6.9 Hz, 1H), 3.85 (dd, J = 14.1, 5.7 Hz, 1H), 3.65 (s, 2H), 3.04 (dd, J = 13.8, 8.1 Hz, 1H), 1.69 (m, 1H),1.10 (dd, J = 8.4, 4.8 Hz, 1H), 0.91 (t, J = 5.4 Hz, 1H), 0.81 (s, 9H), 0.12 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 165.80, 155.98, 145.92, 141.67, 133.51, 130.37, 124.21, 100.35, 70.11, 51.27, 33.67, 25.45, 20.15, 18.23, 13.59, -5.70.

(±)-*trans*-1-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropylmethyl]-thymine (15)

Compound **15** was prepared from **11** as described for **13**. Yield 30%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.40 (br s, 1H), 7.46-7.34 (m, 5H), 6.69 (s, 1H), 3.84-3.72 (m, 3H), 3.16 (dd, J = 14.4, 8.4 Hz, 1H), 2.14 (s, 3H), 1.75 (m, 1H), 1.36 (m, 1H), 1.14 (m, 1H), 0.88 (s, 9H), 0.21 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 163.97, 150.71, 140.70, 138.78, 130.32, 128.39, 127.21, 109.81, 69.23, 50.11, 32.81, 25.81, 25.82, 19.67, 18.27, 13.60, 12.28, -5.50.

(±)-*trans*-1-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropylmethyl]-uracil (16)

Compound **16** was prepared from **11** as described for **13**. Yield 37%;

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.66 (br s, 1H), 7.42-7.36 (m, 5H), 7.09 (d, J = 8.1 Hz, 1H), 5.68 (d, J = 8.1 Hz, 1H), 3.85-3.68 (m, 3H), 3.14 (dd, J = 13.8, 8.4 Hz, 1H), 1.71 (m, 1H), 1.26 (m, 1H), 1.05 (m, 1H), 0.92 (s, 9H), 0.20 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 163.54, 150.78, 144.34, 138.62, 130.23, 128.47, 127.31, 101.54, 69.27, 50.19, 32.96, 25.84, 19.39, 18.27, 13.65, -5.51.

(±)-*cis*-9-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropylmethyl]-adenine (17)

Compound **17** was prepared from **12** as described for **13**. Yield 43%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.57 (s, 1H), 8.23 (s, 1H), 7.40-7.31 (m, 5H), 5.04 (dd, J = 14.4, 6.3 Hz, 1H), 4.69 (dd, J = 14.4, 8.7 Hz, 1H), 4.33 (d, J = 11.4 Hz, 1H), 3.92 (d, J = 11.4 Hz, 1H), 2.13-2.03 (m, 1H), 1.30 (dd, J = 9.0, 5.1 Hz, 1H), 1.16 (t, J = 5.7 Hz, 1H), 0.92 (s, 9H), 0.14 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 154.92, 152.79, 149.52, 142.53, 137.43, 129.47, 128.24, 126.91, 113.50, 67.05, 41.19, 33.74, 25.86, 22.79, 18.76, 14.90, -5.69.

(±)-*cis*-1-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropylmethyl]-cytosine (18)

Compound **18** was prepared from **12** as described for **13**. Yield 43%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.01 (d, J = 9.2 Hz, 1H), 7.44-7.32 (m, 5H), 5.89 (d, J = 7.2 Hz, 1H), 4.63 (dd, J = 14.1, 5.7 Hz, 1H), 4.28 (d, J = 11.4 Hz, 1H), 3.82 (dd, J = 14.1, 9.3 Hz, 2H), 1.77-1.69 (m, 1H), 1.20 (dd, J = 8.7, 4.8 Hz, 1H), 0.93 (m, 10H), 16 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 165.75, 156.75, 146.27, 143.42, 129.64, 128.03, 126.62, 93.68, 66.82, 48.07, 33.05, 25.79, 23.37, 18.20, 14.25, -5.78.

(±)-*cis*-1-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropylmethyl]-thymine (19)

Compound **19** was prepared from **12** as described for **13**. Yield 33%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.33 (br s, 1H), 7.56 (s, 1H), 7.40-7.33 (m, 5H), 4.34 (dd, J = 14.4, 6.6 Hz, 1H), 4.21 (d, J = 10.8 Hz, 1H), 3.95 (dd, J = 13.8, 7.2 Hz, 1H), 3.79 (d, J = 11.1 Hz, 1H), 2.08 (s, 3H), 1.60 (t, J = 6.9 Hz, 1H), 1.22 (dd, J = 9.3, 5.7 Hz, 1H), 1.00 (m, 10H), 0.91 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 163.88, 143.29, 140.22, 129.46, 128.20, 126.64, 113.64, 110.27, 66.96, 47.30, 33.01, 25.85, 22.99, 18.28, 14.56, 12.32, -5.52.

(±)-*cis*-1-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-2-phenyl-cyclopropylmethyl]-uracil (20)

Compound **20** was prepared from **12** as described for **13**. Yield 29%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.73 (br s, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.54-7.42 (m, 5H), 5.95 (dd, J = 8.1, 2.4 Hz, 1H), 4.65 (dd, J = 14.4, 5.1 Hz, 1H), 4.35 (d, J = 11.1 Hz, 1H), 3.98-3.80 (m, 2H), 1.71 (m, 1H), 1.32 (m, 1H), 1.12 (m, 1H), 0.89 (s, 9H), 0.20 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 163.46, 150.88, 145.06, 142.95, 130.20, 129.63, 128.45, 126.91, 101.95, 66.74, 46.88, 33.26, 25.75, 22.97, 19.36, 18.25, 13.99, -5.62.

(±)-*trans*-9-[2-(Hydroxymethyl)-2-phenyl-cyclopropylmethyl]-adenine (21)

To a solution of **13** (200 mg, 0.49 mmol) in tetrahydrofuran (5 ml) was added tetrabutylammonium fluoride (0.73 ml, 1.0 M solution in THF) at 0℃ and stirred for 6 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel

column chromatography (MeOH/CH_2Cl_2, 1:5) to give **21** (112 mg, 78%) as a white solid. m.p. 182-183℃; UV (H_2O) λ_{max} 260.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 8.06 (s, 1H), 8.01(s, 1H), 7.36-7.15 (m, 5H), 4.76 (t, J = 6.0 Hz, 1H), 4.15 (dd, J = 13.8, 5.1 Hz, 1H), 3.55-3.41 (m, 2H), 3.22 (dd, J = 14.1, 9.6 Hz, 1H), 1.70 (m, 1H), 1.05 (t, J = 4.8 Hz, 1H), 0.96 (dd, J = 8.4, 4.5 Hz, 1H); ^{13}C-NMR (DMSO-d_6): δ 155.88, 152.28, 149.46, 140.37, 139.51, 130.18, 128.19, 126.65, 118.64, 68.08, 44.70, 33.41, 20.36, 13.83, 128.19, 126.65, 118.64, 68.08, 44.70, 33.41, 20.36, 13.83; Anal calc. for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 64.82; H, 5.91; N, 23.58.

(±)-*trans*-1-[2-(Hydroxymethyl)-2-phenyl-cyclopropylmethyl]-cytosine (22)

Compound **22** was synthesized from compound **14** using the method described for synthesizing compound **21.** Yield 81%; m.p. 160-163℃; UV (H_2O) λ_{max} 271.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 7.25 (d, J = 7.2 Hz, 1H), 7.26 (m, 5H), 6.98 (br d, 2H), 5.57 (d, J = 7.2 Hz, 1H), 4.73 (t, J = 5.4 Hz, 1H), 3.71 (dd, J = 13.5, 3.9 Hz, 1H), 3.55-3.40 (m, 2H), 2.64 (dd, J = 12.6, 9.9 Hz, 1H), 1.48 (m, 1H), 0.98 (m, 1H), 0.90 (m, 1H); ^{13}C-NMR (DMSO-d_6): δ 165.83, 157.79, 145.63, 139.81, 130.17, 128.15,126.54, 93.05, 68.25, 49.92, 32.76, 20.03, 13.38; Anal calc. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.32; H, 6.21; N, 15.6.

(±)-*trans*-1-[2-(Hydroxymethyl)-2-phenyl-cyclopropylmethyl]-thymine (22)

Compound **23** was prepared from compound **15** using the method

described for synthesizing compound **21.** Yield 70%; m.p. 161-163℃; UV (H_2O) λ_{max} 267.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 7.32 (m, 5H), 7.24 (s, 1H), 4.73 (t, J = 5,8 Hz, 1H), 3.69 (dd, J = 13.5, 3,6 Hz, 1H), 3.54 (dd, J = 9.9, 5.1 Hz, 1H), 2.71 (dd, J = 12.6, 9.9 Hz, 1H), 1.69 (s, 3H), 1.47 (m, 1H), 1.038 (m, 1H), 0.94 (m, 1H); ^{13}C-NMR (DMSO-d_6): δ 164.27, 150.91, 141.34, 139.56, 130.13, 128.13, 126.57, 108.16, 68.07, 48.81, 32.63, 19.71, 13.37, 11.93; Anal calc. for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 66.98; H, 6.30; N, 9.69.

(±)-*trans*-1-[2-(Hydroxymethyl)-2-phenyl-cyclopropylmethyl]-uracil (24)

Compound **24** was synthesized from compound **16** using the method described for synthesizing compound **21.** Yield 81%; m.p. 164-165℃; UV (H_2O) λ_{max} 261.0 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 7.48 (d, J = 8.1 Hz, 1H), 7.32-7.22 (m, 5H), 5.48 (d, J = 8.1 Hz, 1H), 4.75 (t, J = 5.8 Hz, 1H), 3.74 (dd, J = 13.8, 3.3 Hz, 1H), 3.52 (dd, J = 11.1, 6.0 Hz, 1H), 2.71 (dd, J = 12.0, 9.9 Hz, 1H), 1.46 (m, 1H), 1.02-0.94 (m, 2H); ^{13}C-NMR (DMSO-d_6): δ 163.74, 151.02, 145.45, 139.54, 130.16, 128.20, 126.65, 100.66, 68.06, 48.99, 32.75, 19.58, 13.42; Anal calc. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.33; H, 6.03; N, 10.39.

(±)-*cis*-9-[2-(Hydroxymethyl)-2-phenyl-cyclopropylmethyl]-adenine (25)

Compound **25** was synthesized from compound **17** using the method described for synthesizing compound **21.** Yield 84%; m.p. 188-190℃; UV (H_2O) λ_{max} 260.0 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 8.48 (s, 1H), 7.96 (br d, 2H), 7.76 (s, 1H), 7.23-7.11 (m, 5H), 5.55 (t, J = 5.6 Hz,

1H), 4.63 (dd, J = 14,1, 7.5 Hz, 1H), 4.49 (dd, J = 13.8, 6.3 Hz, 1H), 3.99 (dd, J = 12.0, 6.0 Hz, 1H), 3.70 (dd, J = 11.7, 2.1 Hz, 1H), 1.76 (quint, J = 7.2 Hz, 1H), 0.99-0.89 (m, 2H); ^{13}C-NMR (DMSO-d_6): δ 155.12, 152.09, 149.51, 144.24, 143.73, 128.51, 127.91, 126.02, 120.49, 64.37, 49.12, 32.70, 24.13, 15.69; Anal calc. for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 64.82; H, 5.61; N, 23.60.

(±)-*cis*-1-[2-(Hydroxymethyl)-2-phenyl-cyclopropylmethyl]-cytosine (26)

Compound **26** was synthesized from compound **18** using the method described for synthesizing compound **21.** Yield 77%; m.p. 157-160℃; UV (H_2O) λ_{max} 272.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 7.41 (d, J = 7.6 Hz, 1H), 7.33-7.11 (m, 5H), 6.97 (br d, 2H), 5.68 (d, J = 7.6 Hz, 1H), 4.87 (t, J = 4.6 Hz, 1H), 3.99 (dd, J = 13.2, 6.9 Hz, 1H), 3.86-3.75 (m, 2H), 3.60 (dd, J = 11.1, 7.8 Hz, 1H), 1.40 (m, 1H), 0.82-0.76 (m, 2H); ^{13}C-NMR (DMSO-d_6): δ 166.08, 156.01, 145.93, 144.61, 128.37, 127.91, 125.91, 93.33, 64.51, 48.21, 31.99, 20.27, 13.54; Anal calc. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.52; H, 6.30; N, 15.37.

(±)-*cis*-1-[2-(Hydroxymethyl)-2-phenyl-cyclopropylmethyl]-thymine (27)

Compound **27** was synthesized from compound **19** using the method described for synthesizing compound **21.** Yield 78%; m.p. 163-165℃; UV (H_2O) λ_{max} 266.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 7.40-7.30 (m, 5H), 7.22 (s, 1H), 4.75 (t, J = 5.0 Hz, 1H), 3.99 (dd, J = 13.6, 6.6 Hz, 1H), 3.87-3.72 (m, 2H), 2.60 (dd, J = 12.2, 5.8 Hz, 1H), 1.87 (s, 3H), 1.42 (quint, J = 6.8 Hz, 1H), 1.00 (dd, J = 9.1, 4.6 Hz, 1H), 0.84 (m,

1H); ^{13}C-NMR (DMSO-d_6): δ 163.96, 151.45, 141.20, 138.54, 130.33, 128.56, 126.67, 109.51, 67.56, 47.23, 33.03, 20.12, 13.34, 12.01; Anal calc. for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.28; H, 6.19; N, 9.98.

(±)-cis-1-[2-(Hydroxymethyl)-2-phenyl-cyclopropylmethyl]-uracil (28)

Compound **28** was synthesized from compound **20** using the method described for synthesizing compound **21.** Yield 79%; m.p. 160-162℃; UV (H_2O) λ_{max} 261.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.27 (br s, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.26-7.14 (m, 5H), 5.58 (d, J = 8.1 Hz, 1H), 4.74 (t, J = 4.8 Hz, 1H), 4.02 (dd, J = 13.8, 6.6 Hz, 1H), 3.92-3.78 (m, 2H), 2.59 (dd, J = 12.0, 4.8 Hz, 1H), 1.43 (quint, J = 6.9 Hz, 1H), 0.96 (dd, J = 9.0, 4.8 Hz, 1H), 0.89-0.81 (m, 1H); ^{13}C-NMR (DMSO-d_6): δ 163.85, 151.23, 145.88, 144.44, 128.41, 128.00, 125.96, 100.86, 64.35, 47.11, 31.91, 23.90, 15.87; Anal calc. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.93; H, 5.84; N, 10.08.

Synthesis of Acyclic Version of Neplanocin A

2- (tert-Butyldimethylsilyloxy)-acetone (30)

To a stirred solution of compound acetol (20 g, 0.27 mmol) and imidazole (27 g, 0.405 mmol) in CH_2Cl_2 (300 ml), *t*-butyldimethylsilyl chloride (44 g, 0.297 mmol) was added at 0℃. The mixture was stirred at the same temperature for 5 h and concentrated under reduced pressure. The residue was extracted using EtOAc, dried over anhydrous $MgSO_4$, filtered and then concentrated. The residue was purified by

silica gel column chromatography (EtOAc/*n*-hexane, 1:10) to give **30** (39.6 g, 78%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.05 (s, 2H), 2.07 (s, 3H), 0.84 (s, 9H), -0.01 (s, 6H); ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 208.96, 69.47, 25.67, 18.19, -5.61; Anal calc. for $C_9H_{20}O_2Si$: C, 57.39; H, 10.70; Found: C, 57.21; H, 10.50.

(E)-4-(tert-Butyldimethylsilyloxy)-3-methyl-but-2-enoic acid ethyl ester (31)

Sodium hydride (60% in mineral oil, 1.11 g, 27.75 mmol) was suspended in anhydrous THF. To the mixture was slowly added triethyl phosphonoacetate (4.21 g, 27.75 mmol) at 0℃ and stirred for 1 h at room temperature. Compound **30** (5.18 g, 27.5 mmol) was added to the reaction mixture at 0℃, stirred for 1 h at room temperature and extracted with EtOAc. 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 silica gel column chromatography (EtOAc/*n*-hexane, 1:15) to give **31** (4.26 g, 60%) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.99 (s, 1H), 4.19 (q, J = 6.9 Hz, 2H), 4.13 (s, 2H), 1.96 (s, 3H), 1.96 (s, 3H), 1.22 (t, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 167.02, 157.06, 113.35, 66.21, 59.51, 25.83, 18.09, -5.36; Anal calc. for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14; Found: C, 60.37; H, 9.97.

(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enoic acid ethyl ester (32)

To a stirred solution of compound **31** (300 mg, 1.16 mmol) in CCl_4

under nitrogen was added bromine (203 mg, 1.27 mmol) followed by slow addition of triethylamine (0.242 ml, 1.74 mmol) in an ice bath. The reaction mixture was stirred for 5 h at 0℃, filtered and washed with CCl_4. The filtrate was washed with 2 N HCl and then with sodium bicarbonate solution, dried with anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (EtOAc /*n*-hexan, 1:20) to give **32** (200 mg, 51%). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.45 (s, 2H), 4.19 (q, J = 7.2 Hz, 2H), 2.01 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 0.83 (s, 9H), 0.06 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 163.72, 151.55, 109.31, 100.52, 64.01, 62.08, 25.71, 21.09, 18.24, 13.98, -5.55; Anal calc. for $C_{13}H_{25}BrO_3Si$: C, 46.29; H, 7.47; Found: C, 46.01; H, 7.51.

(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-en-1-ol (33)

To a solution of compound **32** (5.0 g, 14.82 mmol) in CH_2Cl_2 (200 ml), DIBALH (31.12ml, 1.0 M solution in hexane) was added slowly at 0℃, and stirred for 1 h at the same temperature. To the mixture, methanol (30 ml) was added. The mixture was then stirred at room temperature for 3 h, and the resulting solid was filtered though a celite pad. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography (EtOAc/*n*-hexane, 1:20) to give **33** (4.07 g, 93%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.42 (s, 2H), 4.24 (s, 2H), 1.94 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 136.45, 112.38, 68.11, 65.21, 25.83, 18.56, 13.56, -5.48; Anal calc. for $C_{11}H_{23}BrO_2Si$: C, 44.74; H, 7.85; Found: C, 4.50; H, 7.74.

(E)-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl bromide (34)

To a solution of compound **33** (2.04 g, 6.93 mmol) and triphenylphosphine (3.63 g, 13.86 mmol) was added slowly at 0℃, stirred for 5 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/*n*-hexane, 1:30) to give the allylic bromide **34** (2.16 g, 87%) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.61 (s, 2H), 3.94 (s, 2H), 1.87 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 142.21, 110.38, 67.78, 38.89, 25.67, 18.33, 13.91, -5.48; Anal calc. for $C_{11}H_{22}Br_2OSi$: C, 36.89; H, 6.19; Found: C, 37.08; H, 5.93.

1-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl]-thymine (35)

A solution of the allylic bromide **34** (318 mg, 0.89 mmol), thymine (169 mg, 1.34 mmol) and cesium carbonate (436 mg, 1.34mmol) in anhydrous DMF (5 ml) was stirred overnight at room temperature. The mixture was quenched by the addition of water and 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/*n*-hexane/MeOH, 4:1:0.2) to give compound **35** (244 mg, 68%) as a solid. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.42 (br s, 1H), 7.14 (s, 1H), 4.65

(s, 2H), 4.25 (s, 2H), 1.86 (s, 3H), 1.82(s, 3H), 0.96 (s, 9H), 0.13 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 163.91, 159.67, 141.50, 139.74, 118.29, 10.52, 63.27, 50.99, 25.81, 22.18, 18.33, 12.38, -5.38; Anal calc. for $C_{16}H_{27}BrN_2O_3Si$: C, 47.64; H, 6.75; N, 6.94. Found: C, 47.87; H, 6.66; N, 6.90.

1-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl]-uracil (36)

Compound **36** was prepared from **34** as described for **35**. Yield 64%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.75 (br s, 1H), 7.32 (d, J = 7.8 Hz, 1H), 5.59 (d, J = 7.8 Hz, 1H), 4.72 (s, 2H), 4.30 (s, 2H), 1.90 (s, 3H), 0.88 (s, 18H), 0.15 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 163.46, 150.67, 144.05, 141.98, 117.86, 102.04, 63.29, 51.46, 25.82, 22.20, 18.27, -5.37; Anal calcd. for $C_{15}H_{25}BrN_2O_3Si$: C, 46.27; H, 6.47; N, 7.19. Found: C, 46.49; H, 6.31; N, 7.28.

1-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl]-5-fluorouracil (37)

Compound **37** was prepared from **34** as described for **35.** Yield 60%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 9.00 (br s, 1H), 7.51 (d, J = 5.6 Hz, 1H), 4.77 (s, 2H), 4.41 (s, 2H), 1.92 (s, 3H), 0.89 (s, 18H) ,0.23 (s, 6 H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 165.23, 153.67, 143.21, 10.98, 127.81, 101.32, 64.26, 52.32, 25.67, 22.32, 18.43, -5.47; Anal calc. for $C_{15}H_{24}BrFN_2O_3Si$: C, 44.23; H, 5.94; N, 6.88. Found: C, 44.06; H, 6.01; N, 7.08.

1-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl]-5-iodouracil (38)

Compound **38** was prepared from **34** as described for **35**. Yield 68%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 9.21 (br s, 1H), 7.72 (s, 1H), 4.83 (s, 2H), 4.27 (s, 2H), 1.93 (s, 3H), 0.90 (s, 18H), 0.32 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 161.46, 151.10, 146.85, 141.33, 116.37, 68.94, 62.35, 50.89, 25.80, 22.54, 18.57, -5.67; Anal calc. for $C_{15}H_{24}BrIN_2O_3Si$: C, 34.97; H, 4.69; N, 5.44. Found: C, 34.40; H, 4.58; N, 5.61.

1-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl]-cytosine (39)

Compound **39** was prepared from **34** as described for **35**. Yield 68%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.38 (d, J = 7.5 Hz, 1H), 5.78 (d, J = 7.5 Hz, 1H), 4.72 (s, 1H), 4.35 (s, 1H), 4.11 (s, 2H), 1.89 (s, 3H), 0.89 (s, 18H), 0.15 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.06, 154.90, 141.30, 118.82, 115.16, 98.97, 64.63, 52.76, 25.80, 21.91, 18.22, -5.47; Anal calc. for $C_{15}H_{26}BrN_3O_2Si$: C, 46.39; H, 6.75; N, 10.82. Found: C, 46.21; H, 6.67; N, 10.89.

9-[(E)-2-Bromo-4-(tert-butyldimethylsilyloxy)-3-methyl-but-2-enyl]-adenine (40)

Compound **40** was prepared from **34** as described for **35**. Yield 68%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.26 (s, 1H), 7.75 (s, 1H), 4.72 (s, 1H), 6.09 (br s, 2H), 4.70 (s, 2H), 4.21 (s, 2H), 1.91 (s, 3H), 0.86 (s, 18H), 0.25 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 155.67, 152.78, 150.43, 141.98, 141.02, 119.49, 118.12, 63.72, 51.22, 15.81, 22.04, 18.20, -5.32; Anal calc. for $C_{16}H_{26}BrN_5OSi$: C, 46.60; H, 6.35; N, 16.98. Found: C, 46.88; H, 6.21; N, 17.19.

1-[(E)-2-Bromo-4-hydroxy-3-methyl-but-2-enyl]-thymine (41)

To a solution of compound **35** (181 mg, 0.45 mmol) in THF (5 ml), TBAF (0.675 ml, 1.0 M solution in THF) at 0℃ was added. The mixture ws stirred at room temperature for 6 h, and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:5) to give compound **41** (105 mg, 81%) as a white solid. m.p. 174-176 0℃; UV (H_2O) λ_{max} 268.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.47 (br s, 1H), 7.33 (s, 1H), 5.10 (t, J = 6.0 Hz, 1H), 4.68 (s, 2H), 3.95 (s, 2H), 1.90 (s, 3H), 1.81 (s, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 163.66, 149.13, 136.09, 116.68, 110.44, 96.60, 65.67, 43.33, 16.38, 12.07; Anal calc. for $C_{10}H_{13}BrIN_2O_3$: C, 41.54; H, 4.53; N, 9.69. Found: C, 41.30; H, 4.62; N, 9.81.

1-[(E)-2-Bromo-4-hydroxy-3-methyl-but-2-enyl]-uracil (42)

Compound **42** was prepared from **36** as described for **41**. Yield 77%; m.p. 161-163 0℃; UV (H_2O) λ_{max} 263.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.57 (br s, 1H), 7.30 (d, J = 7.9 Hz, 1H), 5.48 (d, J = 7.8 Hz, 1H), 5.03 (t, J = 5.4 Hz, 1H), 4.62 (s, 2H), 4.10 (s, 2H), 1.91 (s, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 163.65, 151.21, 145.45, 140.31, 117.34, 103.78, 64.56, 44.34, 16.20; Anal calc. for $C_9H_{11}BrN_2O_3$: C, 39.29; H, 4.03; N, 10.18. Found: C, 30.37; H, 3.87; N, 10.30.

1-[(E)-2-Bromo-4-hydroxy-3-methyl-but-2-enyl]-5-fluorouracil (43)

Compound **43** was prepared from **37** as described for **41**. Yield 87%; m.p. 160-163 0℃; UV (H_2O) λ_{max} 270.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.87 (br s, 1H), 7.76 (d, J = 6.0 Hz, 1H), 5.05 (t, J = 5.2 Hz, 1H), 4.80 (s, 2H), 4.32 (s, 2H), 1.90 (s, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 165.76, 154.78, 144.66, 139.26, 126.91, 109.78, 63.92, 43.82,

16.67; Anal calc. for $C_9H_{10}BrFN_2O_3$: C, 36.88; H, 3.44; N, 9.56. Found: C, 36.68; H, 3.47; N, 9.77.

1-[(E)-2-Bromo-4-hydroxy-3-methyl-but-2-enyl]-5-iodouracil (44)

Compound **44** was prepared from **38** as described for **41**. Yield 83%; m.p. 178-180 0℃; UV (H_2O) λ_{max} 286.0 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.70 (br s, 1H), 7.96 (s, 1H), 5.00 (br s, 1H), 4.61 (s, 2H), 4.14 (s, 2H), 1.97 (s, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 161.78, 151.21, 146.71, 140.34, 115.67, 170.78, 63.67, 44.28, 16.75; Anal calc. for $C_9H_{10}BrIN_2O_3$: C, 26.96; H, 2.51; N, 6.99. Found: C, 27.17; H, 2.36; N, 7.29.

1-[(E)-2-Bromo-4-hydroxy-3-methyl-but-2-enyl]-cytosine (45)

Compound **45** was prepared from **39** as described for **41.** Yield 75%; m.p. 157-160 0℃; UV (H_2O) λ_{max} 273.0 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 7.41 (d, J = 7.6 Hz, 1H), 5.80 (d, J = 7.6 Hz, 1H), 4.92 (t, J = 5.6 Hz, 1H), 4.62 (s, 2H), 4.09 (s, 2H), 1.88 (s, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 166.62, 153.31, 140.87, 117.21, 114.87, 99.62, 65.21, 44.76, 16.65; Anal calc. for $C_9H_{12}BrN_3O_2$: C, 39.43; H, 4.41; N, 15.33. Found: C, 39.65; H, 4.61; N, 15.21.

9-[(E)-2-Bromo-4-hydroxy-3-methyl-but-2-enyl]-adenine (46)

Compound **46** was prepared from **40** as described for **41**. Yield 80%; m.p. 181-183 0℃; UV (H_2O) λ_{max} 261.0 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 8.16 (s, 1H), 8.05 (s, 1H), 7.21 (br s, 2H), 5.07 (t, J = 5.4 Hz, 1H), 4.72 (s, 2H), 4.27 (s, 2H), 1.87 (s, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 155.97, 152.36, 150.04, 141.42, 140.87, 119.25, 117.67, 66.02,

45.28, 17.20; Anal calc. for $C_{10}H_{12}BrN_5O$: C, 40.29; H, 4.06; N, 23.49. Found: C, 40.05; H, 4.18; N, 23.3.

CONCLUSION

The simple synthetic method for synthesis of phenyl branched cyclopropyl nucleosides from an α-hydroxy ketone derivative and novel acyclic Neplanocin A analogues from a ketone derivative were developed in this study. When the synthesized compounds were tested against HIV-1, compounds **(22, 25, 42 and 43)** exhibited toxicity non-related to any anti-HIV-1 activity. Although we could not find good anti-HIV agents in this study, it is expected that the results of some anticancer activity in this series will allow this class of nucleosides to be a new template for the development of new anti-cancer agents.

REFERENCES

1. C. Tantillo, J. Ding, A. Jacobo-Molina, R.G. Nanni, P.L. Boyer, S.H. Hughs, R. Pauwels, K. Andries, P.A. Janssen, E. Arnold, Locations of anti-AIDS drug binding sites and resistance mutations in the three-dimensional structure of HIV-1 reverse transcriptase; implications for mechanism of drug inhibition and resistance, *J. Mol. Biol. 243* (1994) 369-387.
2. D.D. Richman, Resistance, drug failure and disease progression, *AIDS Res. Hum. Retroviruses 7* (1994) 647-654.
3. O.H. Ko, J.H. Hong, Efficient synthesis of novel carbocyclic nucleosides via sequential Claisen rearrangement and ring-closing metathesis *Tetrahedron Lett. 43* (2002) 6399-6402.
4. J.H. Hong, C.H. Oh, J.H. Cho, Stereocontrolled synthesis of novel 6' (α)-hydroxy carbovir analogues, *Tetrahedron 59* (2003) 6103-6108.
5. M.S. Chen, R.T. Suttmann, E. Papp, P.D. Cannon, M.J. McRobert, C. Bach W.C. Copeland, T.S. Wang, Selective action of 4'-azidothymidine triphosphate on reverse transcriptase of human immunodeficiency virus type 1 and human DNA polymerase alpha and beta, *Biochemistry 32* (1993) 6002-6010.
6. H. Maag, J.T. Nelson, J.L. Rios-Steiner, E.J. Prisbe, Solid-state and solution conformations of the potent HIV inhibitor, 4'-azidothymidine, *J. Med. Chem. 37* (1994) 431-438.
7. I. Sugimoto, S. Shuto, S. Mori, S. Shigeta, A. Matuda, Synthesis of 4'-alpha-branched thymidines as a new type of antiviral agent, *Bioorg. Med. Chem. Lett. 9* (1999) 385-388.

8. M. Nomura, S. Shuto, M. Tanaka, T. Sasaki, S. Mori, S. Shigeta, A. Matuda, Synthesis and biological activities of 4'α-C-branched-chain sugar pyrimidine nucleosides, *J. Med. Chem. 42* (1999) 2901-2908.
9. A.T. Ashton, L.C Meurer, C.L. Cantone, A.K. Field, J. Hannah, J.D. Karkas R. Liou, G.F Patel, H.C. Perry, A.F.Wagner, E. Walton, R.L. Tolman, Synthesis and antiherpetic activity of (±)-9-[{(Z)-2-(hydroxymethyl)cyclopropyl}methyl] guanine and related compounds, *J. Med Chem. 31* (1998) 2304-2315.
10. Y.L. Qiu, A. Hempel, N. Camerman, A. Camerman, F. Geiser, R.G. Ptak, J.M. Brietenbach, T. Kira, L. Li, E. Gullen, Y.C. Cheng, J.C. Drach, J. Zemlicka, (R)-(-)-and (S)-(+)-Synadenol: synthesis, absolute configuration, and enantioselectivity of antiviral effect, *J. Med. Chem. 41* (1998) 5275-5264.
11. Y.L. Qiu, M.B. Ksebati, R.G. Ptak, B.Y. Fan, J.M.Breitenbach, J.S. Lin, Y.C. Cheng, E.R. Kern, J.C. Drach, J. Zemlicka, (Z)- and (E)-2-((Hydroxymethyl)-cyclopropylidene) methyladenine and guanine: new nucleoside analogues with a broad-spectrum antiviral activity, *J. Med. Chem. 41* (1998) 10-23.
12. T. Sekiyama, S. Hatsuya. Y. Tanaka, M. Uchiyama, N. Ono, S. Iwayama, M. Oikawa, K. Suzuki, M. Okunishi, T.Tsuji, Synthesis and antiviral activity of novel acyclic nucleosides: discovery of a cyclopropyl nucleoside with potent inhibitory activity against herpes viruses, *J. Med. Chem. 41* (1998) 1284-1298.
13. J.H. Hong, O.H. Ko, Synthesis and antiviral evaluation of novel acyclic nucleoside, *Bull. Korean Chem. Soc. 24* (2003) 1284-1288.
14. Y. Zhao, T. Yang, M.G. Lee, D.W. Lee, M. Gary Newton, C.K. Chu,

Asymmetric synthesis of (1'S,2'S)-cyclopropyl carbocyclic nucleosids, *J. Org. Chem. 60* (1995) 5236-5242.

15. N. Hossain, J. Rozenski, E. De Clercq, P. Herdewijn, Synthesis and antiviral activity of acyclic analogues of 1,5-anhydrohexitol nucleosides using Mitsunobu reaction, *Tetrahedron. 52* (1996) 13655-13670.
16. P.A. Furman, J.A. Fyfe, M.H. St.Clair, K. Weinhold, J.L. Rideout, G.A. Freeman, S.N. Lehrman *et al., Proc. Natl. Acad. Sci, USA 83* (1986) 8333-8337.
17. R. Yarchoan, C.F. Perno, R.V. Thomas, R.W. Klecker, J.P. Allain, R.J. Wills, N. McAtee *et al., Lancet 1* (1988) 76-81.
18. R. Yarchoan, H. Mitsuya, R.V. Thomas, J.M. Pluda, N.R. Hartman, C.F. Perno, K.S.Marczyk *et al., Science 245* (1989) 412-415.
19. T.S. Lin, R.F. Schinazi, W.H. Prusoff, *Biochem. Pharmacol. 36* (1987) 2713-2718.
20. R.F. Schinazi, C.K. Chu, A. Peck, A. McMillan, R. Mathis, D. Cannon, L.S. Jeong *et al., Antimicrob. Agents Chemother. 36* (1992) 672-676.
21. S.M. Daluge, S.S. Good, M.B. Faletto, W.H. Miller, M.H. StClair, L.R. Boone, M. Tisdale *et al., Antimicrob. Agents Chemother. 41* 1997) 1082-1093.
22. T.S. Lin, M.Z. Luo, M.C. Liu, S.B. Pai, G.E. Dutschman, Y.C. Cheng, *J. Med. Chem. 37* (1994) 798-8031.
23. C.K. Chu, T.W. Ma, K. Shanmuganathan, C.G. Wang, Y.J. Xiang, S.B. Pai, G.Q. Yao, J.P. Sommadossi, Y.C. Cheng, *Antimicrob, Agents Chemother. 39* (1995) 979-981.
24. M.N. Arimilli, C.U. Kim, J. Dougherty, A. Mulato, R. Oliyai, J.P. Shaw,

K.C. Cundy, N. Bischofberger, *Antiviral Chem. Chemother. 8* (1997) 557-564.

25. W.B. Parker, Y.C. Cheng, *J. NIH Res. 6* (1994) 57-61.
26. P.A. Chatis, C.S. Crumpacker, *Antimicrob. Agents Chemother. 36* (1992) 1589-1595.
27. H.J. Schaeffer, L. Beauchamp, P. DeMiranda, G.B. Elion, D.J. Bauer, P. Collins, *Nature. 272* (1978) 583-585.
28. F.M. Hamzeh, P.S. Lietman, *Antimicrob. Agents Chemother. 35*(1991) 1818-1823.
29. R. Borchardt, B. Keller, U. Patel-Thrombre, *J. Biol. Chem. 259*(1984) 4353-4358.
30. V.E. Marquez in *Advances in Antiviral Drug Design,* Vol. 2, JAJ Press, (1996) 89-146, and references therein.
31. L.A. Agrofoglio, S.R. Challang, *Acyclic, Carbocyclic and L-Nucleosides*, Kluwer Academic Publisher. (1998) 18-173.
32. M.N. Arimilli, C.U. Kim, J. Dougherty, A. Mulato, R. Oliyai, J.P. Shaw, K.C. Cundy, N. Bischofberger, *Antiviral Chem. Chemother. 8* (1997) 557-564.
33. D.L. Earnshaw, T.H. Bacon, S.J. Darlison, K. Edmonds, R.M. Perkins, R.A. Vere Hodge, *Antimicrob. Agents Chemother. 36* (1992) 2747-2757.
34. L.S. Jeong, S.J. Yoo, K.M. Lee, M.J. Koo, W.J. Choi, H.O. Kim, H.R. Moon *et al., J. Med. Chem. 46* (2003) 201-203.
35. D.R. Borcherding, S. Narayanan, M. Hasobe, J.G. McKee, B.T. Keller, R.T. Borchardt, *J. Med. Chem. 31* (1988) 1729-1738.
36. J.J. Bronson, I. Ghazzouli, M.J.M. Hichcock, R.R. Webb, J.C. Martin, *J.*

Med. Chem. 32 (1989) 1457-1463.

37. A.F. Cook, M.J. Holman, *J. Med. Chem. 23* (1980) 852-857.