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Synthesis Of Carbocyclic L-Nucleosides
(Under the Direction of Dr C.K.Chu)

Nucleosides have been studied as potential anti-viral and anti-cancer agents. A number of nucleosides have been discovered with significant antiviral activity. However, toxicities and side effects as well as the emergence of drug resistant viral strains limit the usefulness of the currently available nucleosides as anti-viral agents. Furthermore, the disadvantage of normal nucleosides and their analogs is that the glycosidic bond is subjected to enzymatic hydrolysis by phosphorylase. To overcome these problems, we need to synthesize new agents, among which are carbocyclic nucleoside analogs. In this thesis, the new carbocyclic L-Nucleoside with 5'-methylene group was synthesized and the new scheme was designed to synthesize the similar analogs.

INDEX WORDS: Carbocyclic L-Nucleosides, Enzymatic Hydrolysis, Antiviral Agents, 5'-Methylene Group.

SYNTHESIS OF CARBOCYCLIC L-NUCLEOSIDES

by

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DEDICATION

To my parents, who have endowed intelligence in me;

To my brother, who has instilled in me courage; and

To my lovely son, Xi-Kai Isaac Wu, who has given great joys to us.

ACKNOWLEDGEMENTS

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Nucleoside analogs have been widely studied as potential anti-viral and anti-cancer agents. In the early 1980's, the acquired immunodeficiency syndrome (AIDS) appeared and the human immunodeficiency virus (HIV) was discovered. Since then, intensive research on nucleosides has been carried out in order to find effective agents against HIV and other viruses, such as herpes simplex virus (HSV-1 and HSV-2), cytomegalovirus (CMV), Epstein-Barr virus (EBV), of which infections are prevalent in AIDS patients.[1] From these efforts, a number of nucleosides have been discovered with significant antiviral activity (Figure 1.1). Among them, 3'-azido-3'-deoxythymidine (AZT, **1.1**),[2] 2', 3'-dideoxycytidine (ddC, **1.2**),[3] 2', 3'-didehydro-3'-deoxythymidine (d4T, **1.3**),[4] (-)-(2'R,5'S)-1-(2-hydroxymethyl-oxathiolan-5-yl)cytosine (3TC, **1.4**),[5] Abacavir (**1.5**),[6] 2',3'-dideoxyinosine (ddI, **1.6**)[7] exhibited potent anti-HIV activity and were approved by the FDA. On the other hand, 2'-fluoro-5-methyl-uridine (FMAU, **1.7**) and 2'-fluoro-5-iodo-uridine (FIAU, **1.8**) exhibited anti HSV properties.[8,9,10,11] However, toxicities and side effects as well as the emergence of drug resistant viral strains limit the usefulness of the currently available nucleosides as anti-HIV agents. Furthermore, the disadvantage of normal nucleosides and their analogs is that the glycosidic bond is subjected to enzymatic hydrolysis by phosphorylase. To overcome these problems, we need to synthesize new agents, among which are carbocyclic nucleoside analogs.

Carbocyclic nucleosides (*Carba*-nucleosides), where the furanose oxygen of normal nucleosides is replaced by a methylene group which is resistant to nucleoside phosphorylase, have received attention due to the unique structure features in the last two decades.[12,13,14] A number of carbocyclic nucleosides have been identified and
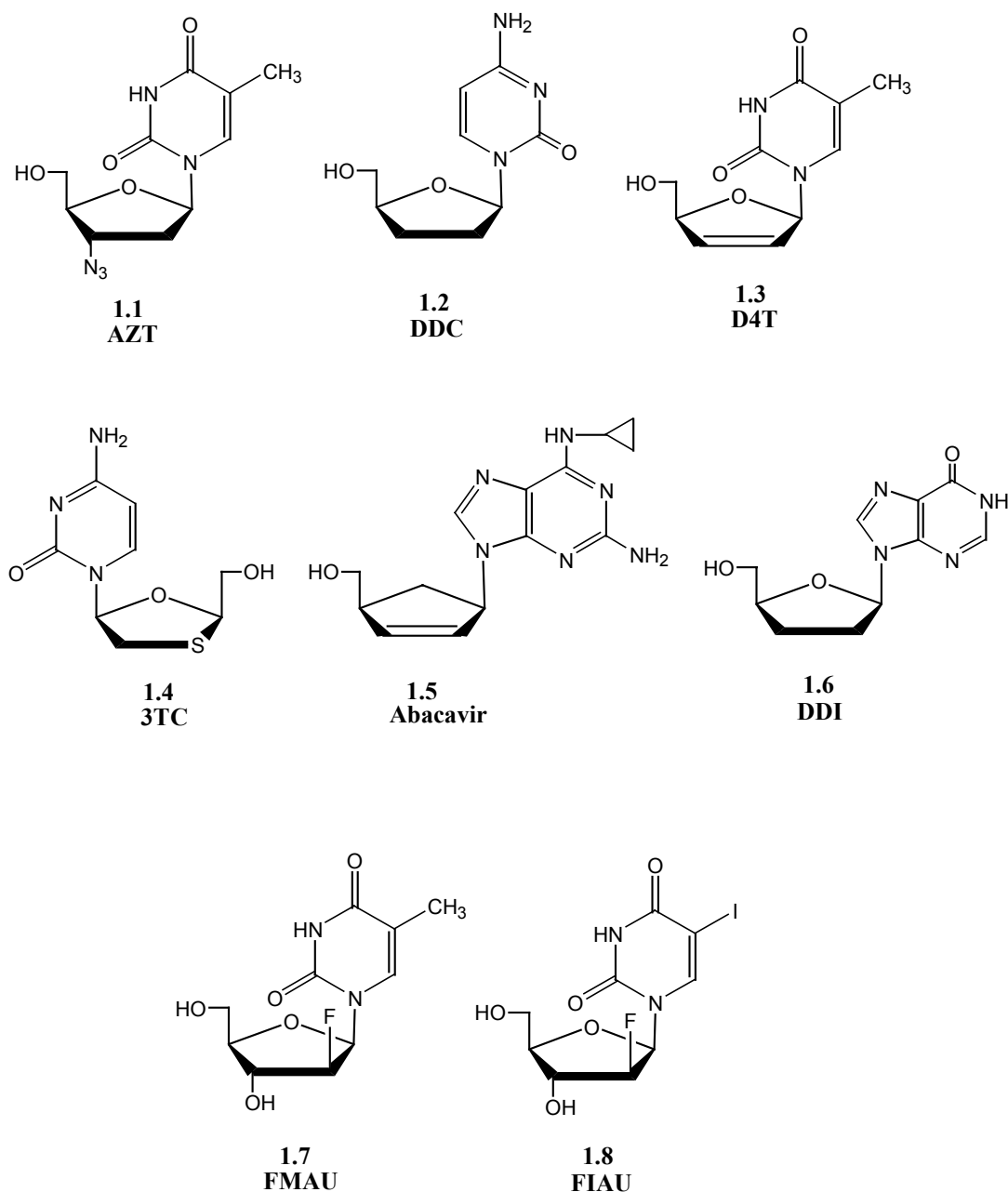
1

Figure 1.1

synthesized, and some of them exhibit interesting biological activity.[15] Carbocyclic

nucleosides, aristeromycin (**1.9**)[16] and neplanocin (**1.10**)[17], were isolated from

Streptomyces citricolor and *Actinoplanacea ampullariella,* respectively. Both

compounds exhibit interesting biological activity.[18] Synthetic carbocyclic nucleosides
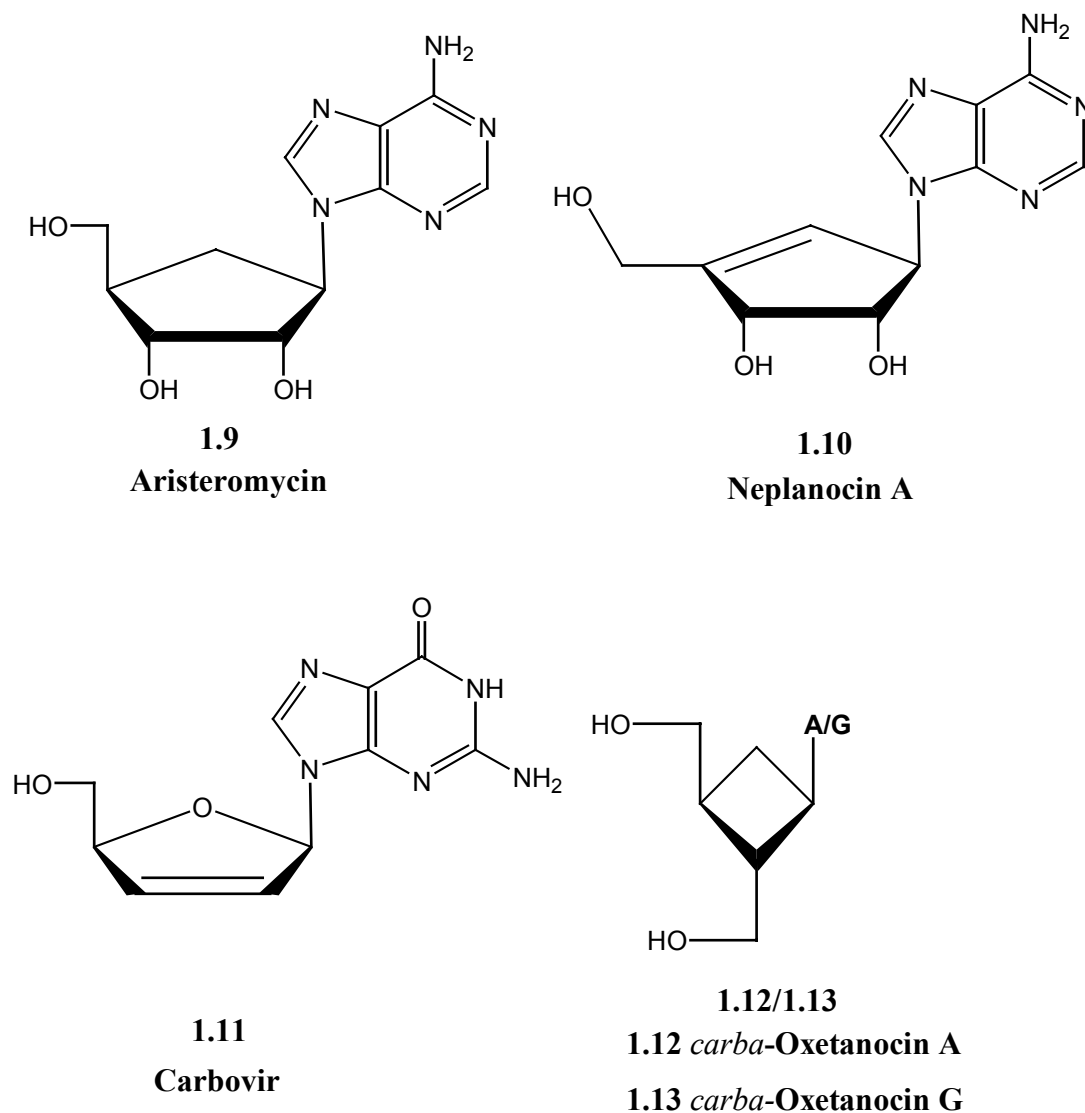
1.9
Aristeromycin

1.10
Neplanocin A

1.11
Carbovir

1.12/1.13
1.12 *carba*-**Oxetanocin A**
1.13 *carba*-**Oxetanocin G**

Figure 1. 2

such as carbovir (**1.11**), *carba*-oxetanocin A (**1.12**) and *carba*-oxetanocin G (**1.13**) exhibit anti-HIV activities.[19] Oral bioavailabilities of these compounds are increased since greater metabolic stability toward the phosphorylase enzymes, and higher lipophilicity is achieved due to the replacement of oxygen by methylene group.[15]

In general, two steps are involved in the synthesis of carbocyclic nucleosides: a) the synthesis of the required carbocyclic moiety bearing suitable functional groups; and b) the construction or introduction of the base moiety with high regio- and stereo-selectivity. The first step is the main problem while the second step is much more

easily resolved through the so-called linear and convergent approaches. Most of the carbocyclic nucleosides can be classified according their carba ring size.

Three-Membered Carbocyclic Nucleosides

There are three types of three-membered carbocyclic nucleosides.[20] The first type of three-membered carbocyclic nucleosides has its own characteristics as compared to other two types since its base is directly connected to the sugar moiety by a N-glycosidic bond.[20] Many of this kind of *carba*-nucleoside were synthesized in recent years,[21] however, both *in vitro* or *in vivo* experiments failed to show any significant biological activity.
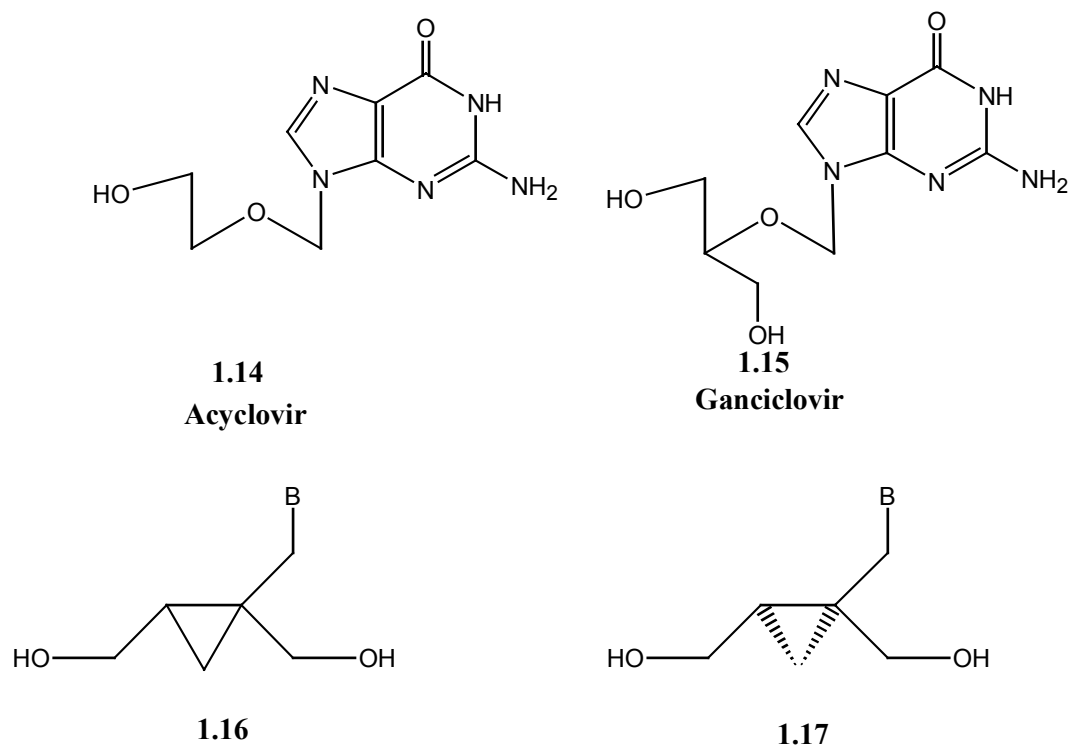

1.14
Acyclovir

1.15
Ganciclovir

1.16

1.17

Figure 1. 3

The second type of three-membered carbocyclic nucleosides[20] is the cyclopropylmethyl analogs, which were synthesized as conformationally rigid

rotamers of the carbocyclic analogs of acyclovir (**1.14**) of ganciclovir (**1.15**). They have a methylene spacer between the base and the carbocyclic ring. However, only a few of them have pronounced biological activity. In 1998, carbocyclic nucleoside analog **1.16** was found to exhibit strong antiviral activity.[22] When comparing antiviral activity against HSV-1, 1'S,2'R-enantiomer (**1.17**) has twenty times higher activity than **1.16**. In addition, it also shows 10 times greater anti-VZV potency than acyclovir.[23]

The third type of three-membered *carba*-nucleoside (**1.18** and **1.19**) with broad-spectrum antiviral activity was reported by Zemlicka et al in 1998.[24] Both of them are very effective against human cytomegalovirus (HCMV), murine cytomegalovirus (MCMV) and EBV.
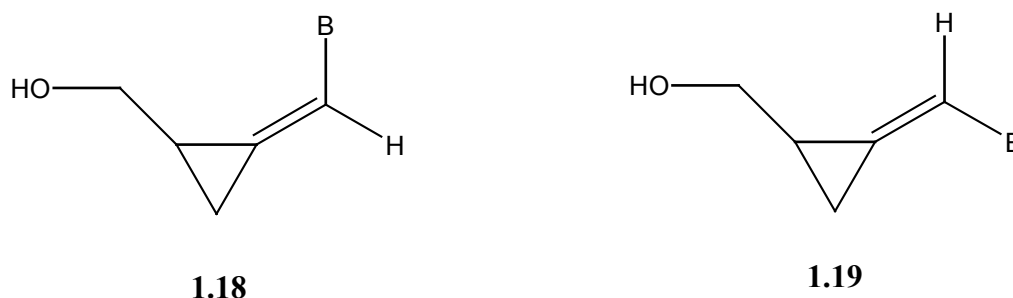

1.18   **1.19**

Figure 1. 4

Four-membered carbocyclic nucleosides

Oxetanocin A (**1.20**)[25] is the first and only known example of a naturally occurring four-membered ring nucleoside. Further studies showed both oxetanocin A and its synthetic analog oxetanocin G (**1.21**) exhibited good antiviral activity against HIV. However, the oxetanosyl-N-glycosyl bond of these two compounds was unstable. Later, other investigators successfully synthesized *carba*-oxetanocin A (**1.12**) and G (**1.13**) which showed excellent antiviral activity.[26] Additional synthetic work has been conducted to prepare related carbocyclic nucleosides analogs of oxetanocin, and some of the analogs show potent antiviral activity.[25,27] Racemic

carba-oxetanosyl 5-(halovinyl)uracil (**1.22**) had excellent activity against VZV. 2'-
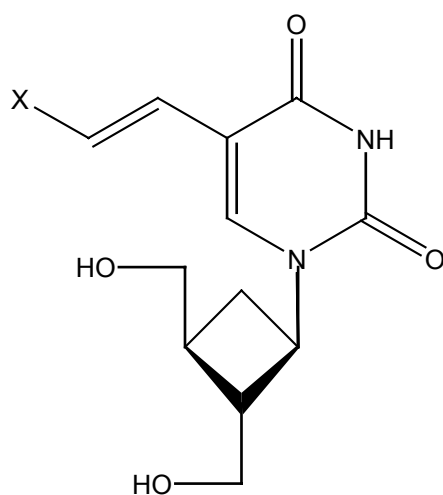*Nor-carba*-oxetanocin G (**1.23**) showed antiviral activity comparable to that of
acyclovir against HSV-1, HSV-2 and VZV, and was about ten fold more potent than
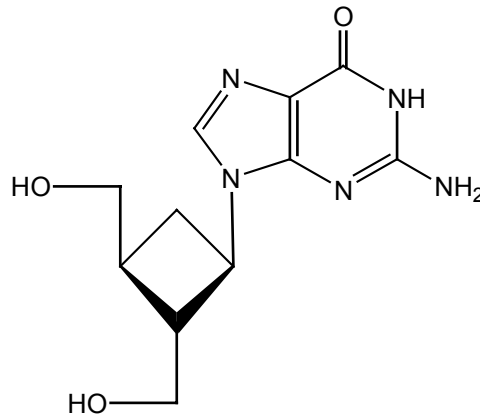acyclovir against human cytomegalovirus (HCMV).
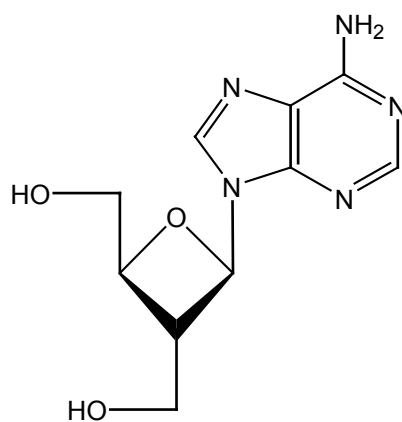
1.20
Oxetanocin A
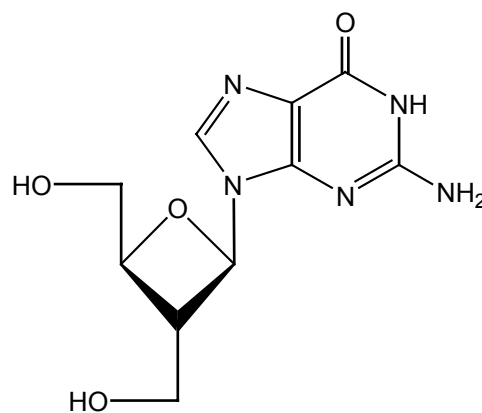
1.21
Oxetanocin G

1.22

1.23

Figure 1. 5

Five-membered carba-nucleosides

Carbovir and related carba-nucleosides

(-)-Carbovir (**1.11**) was reported to exhibit similar potency to AZT in selectively inhibiting HIV reverse transcriptase (RT).[22] However, clinical trial of (-)-carbovir was stopped because of its pharmacokinetic and toxicological problems. As a prodrug of carbovir, abacavir (**1.5**)[28] was synthesized with higher oral bioavailability. Moreover, it can penetrate the central nervous system (CNS) as high as AZT, which has been approved by FDA as Ziagen[®].

Following Abacavir's success, many chemists began to synthesize carbovir derivatives. Several strategies were developed to synthesize carbovir and its analogs as below:

 (i) synthesis from natural (-)-aristermomycin A (**1.9**);[29]

 (ii) linear approaches with stepwise construction of the guanine moiety from precursor, (1R, 4S)-1-amino-4-(hydroxymethyl)-2-cyclopentene (**1.24**);[30]

 (iii) enantioselective aynthesis of (-)-carbovir involves Trost's palladium-catalyzed nucleophilic coupling of purine bases with allylic carbonates or acetates, such as compound **1.25**,[31] **1.26**,[32,33] **1.27**,[34] acetoxy tosylamide (**1.28**),[35] 2-substituted 2-azabicyclo[2.2.1]hept-5-ene-3-one (**1.29**),[36] and hemiester (**1.30**).[37]

In this review, Scheffold's and Crimmins' synthetic routes to (-)-carbovir is briefly described below. (S)-(cyclopent-2-enyl) methanol (**1.1.3**) was chosen as the starting material. Homoallylic alcohol was readily prepared from racemic 3-chlorocyclopentene (**1.1.1**) by two-step procedure in 54% overall yield. Sequential treatment of the homoallylic alcohol at room temperature with BuLi, CO_2 and I_2 in THF led to the crystalline cyclic iodocaronate. Elimination of HI from **1.1.4** was effected with DBU under a vigorous stream of CO_2 to give the key precursor (**1.1.5**). Reaction of **1.1.5** with 2-amino-6-chloropurine in THF/DMSO with 10% Pd catalyst

1.24

1.25

1.26

1.27

1.28

1.29

1.30
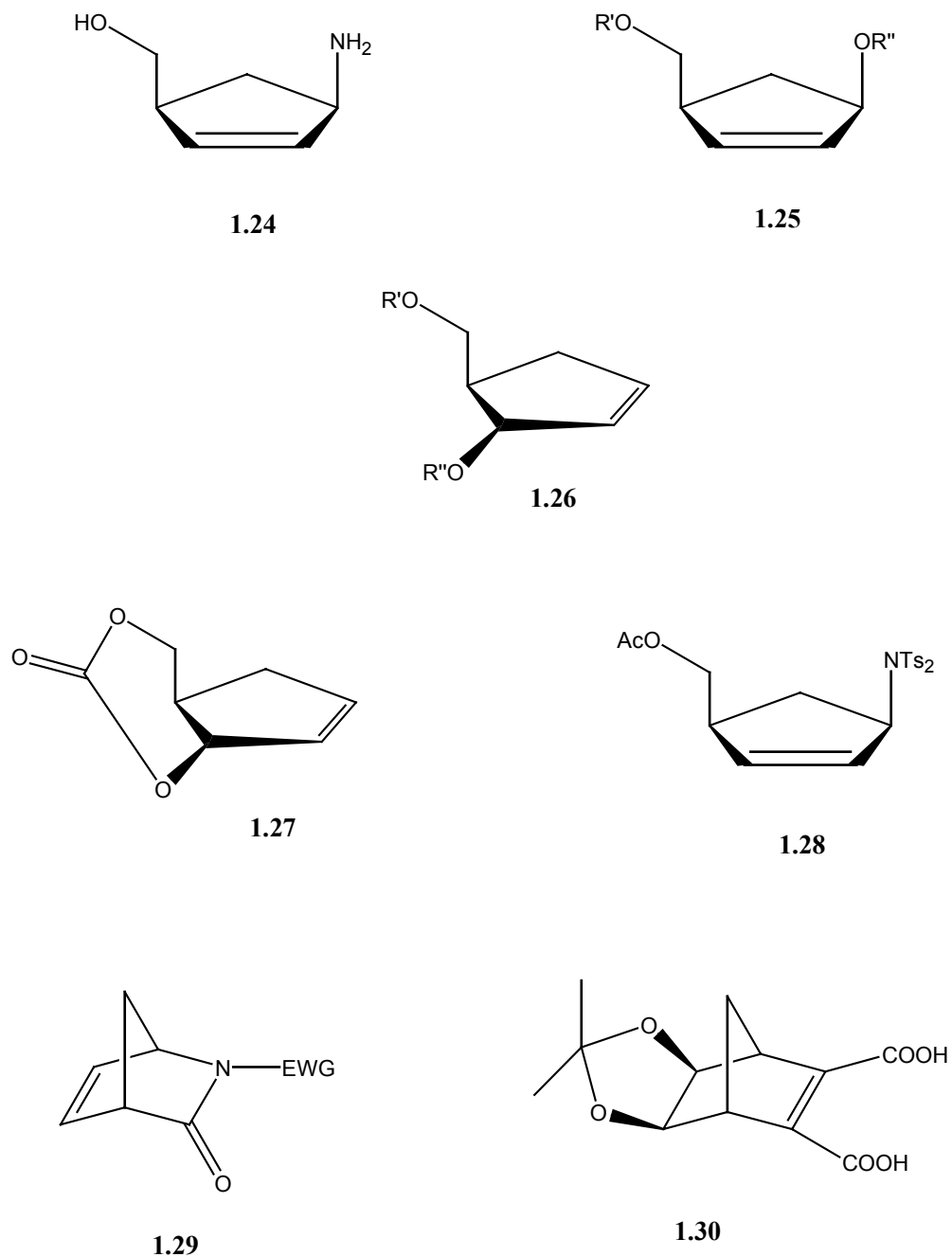
Figure 1.6

yielded (-)-carbovir precursor (**1.1.6**) in 59% yield. Hydrolysis of **1.1.6** with 0.33 N

NaOH gave (-)-carbovir in 71% yield as shown in Scheme 1.1.[34]

Crimmins and King reported an efficient alternative approach recently.

Condensation of lithiated (*S*)-4-benzyl-2-oxazolidinone (**1.2.1**) with pentenoic pivalic
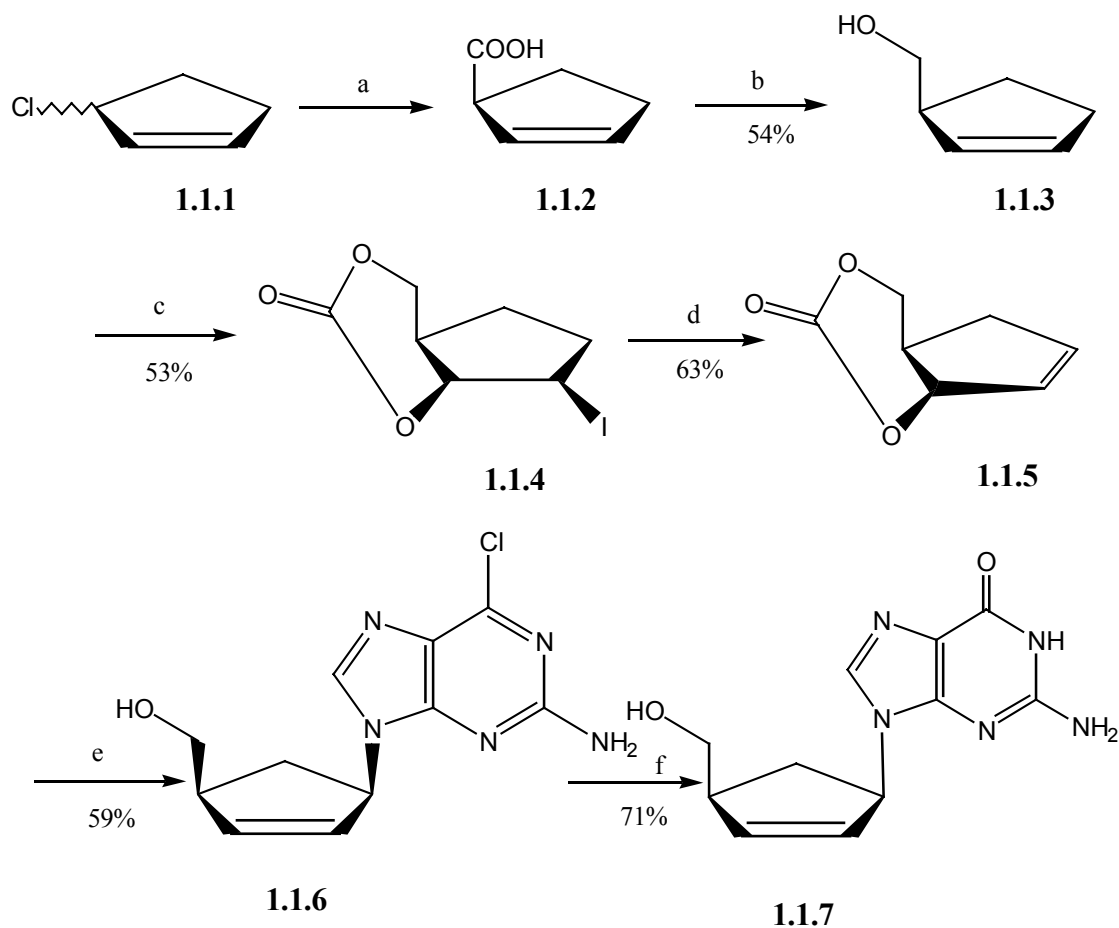
Scheme 1.1

mixed anhydride provided **1.2.2**. Use of the Evans' dialkyl boron triflate protocol for

diastereoselevtive *syn* aldol condensation with acrolein produced product **1.2.3**

(de>99%). The ring closure was accomplished by exposure of a CH_2Cl_2 solution of

diene **1.2.3** to 10% of the Grubbs catalyst to form the cyclopentenol **1.2.4**, which was

reduced to diol **1.2.5** with lithium borohydride. Diol **1.2.5** was then converted to

diacetate **1.2.6**, followed by reaction of **1.2.6** with 2-amino-6-chloropurine in the

presence of Pd(0) catalyst and sodium hydride to give an 86:14 mixture of the carbocyclic nucleoside **1.2.7** (65% yield after chromatography) and the corresponding N7 coupling product (not shown). Treatment of the chloropurine **1.2.7** with cyclopropylamine in ethanol followed by hydrolysis of the acetate produced **1.2.8** in 81% overall yield. Alternatively, direct hydrolysis of with sodium hydroxide produced (-)-carbovir.
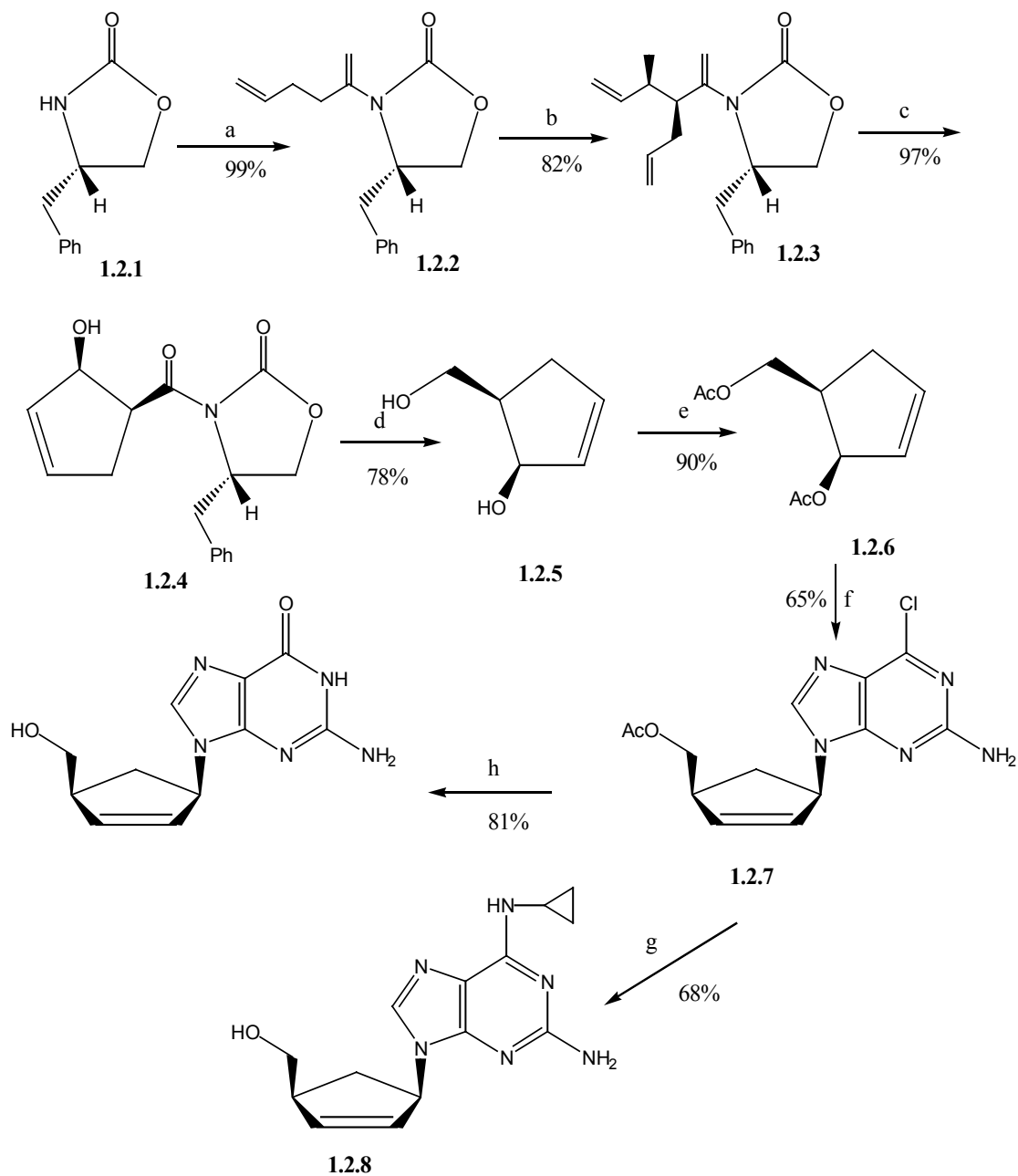
(+)-L-Carbovir and its analogs also were prepared with similar approaches described above. Chu's group reported the synthesis of (+)-L-carbovir and its analog **1.3.10** in 1998 (Scheme 1.3).[38] They started from the optical active enone (**1.3.1**), followed by 1, 4-addition, DIBAL reduction, benzoyl protection and deprotection of acetal group to obtain compound **1.3.4**. Treatment of **1.3.4** with trimethyl orthoformate afforded the cyclic orthoester (**1.3.5**), which was subsequently subjected to a thermal elimination reaction with acetic anhydride to form the cyclopentane (**1.3.6**). Finally, the heterocyclic base was introduced by a Mitsunobu reaction.

(-)-5'-Norcarbovir (**1.31**), (+)-5'-norcarbovir (**1.32**) and their corresponding triphosphate analogs have also been reported.[39] Both of them and some of their analogs have been reported to be good HIV RT inhibitors.

Aristeromycin, neplanocin A and related carbocyclic

Aristeromycin and neplanocin A are naturally occurring carbocyclic nucleosides. Aristeromycin inhibits cell division and elongation in rice plants and prohibits AMP synthesis in mammalian cells.[40] Aristeromycin was synthesized from the saturated tetrol (**1.33**) or aminotriol (**1.34**). Aminotriol was prepared as shown in Scheme 1.4.[41]

Neplanocin A (**1.10**) shows a wide range of biological activities. It is an antitumor antibiotic, and active against vaccinia virus, parainfluenza, measles and VSV *in vitro*.[14] It is also good inhibitor of S-adenosylhomocysteine hydrolase.[40] The synthesis of neplanocin usually uses unsaturated tetrol (**1.35**) and the unsaturated

a: n-BuLi, THF, pentenoic pivalic mixed anhydride, -78°C. b: Bu$_2$BOTf, Et$_3$N, CH$_2$Cl$_2$, CH$_2$=CHCHO, -78°C. c: PhCH=Ru[P(C$_6$H$_{11}$)$_3$]$_2$Cl$_2$, CH$_2$Cl$_2$. d: LiBH$_4$, THF, MeOH. e: Ac$_2$O, CH$_2$Cl$_2$, Et$_3$N, DMAP. f: 2-amino-6-chloropurine, THF/DMSO(1:1), NaH, Pd(PPh$_3$)$_4$. g: cyclopropylamine, EtOH; aq. NaOH. h: aq. NaOH.

Scheme 1.2

1.3.1 → 2steps → **1.3.2** → a → **1.3.3**

b → **1.3.4** → c → **1.3.5** → d → **1.3.6**

e → **1.3.7** → f → **1.3.8**

g → **1.3.9** → h → **1.3.10**
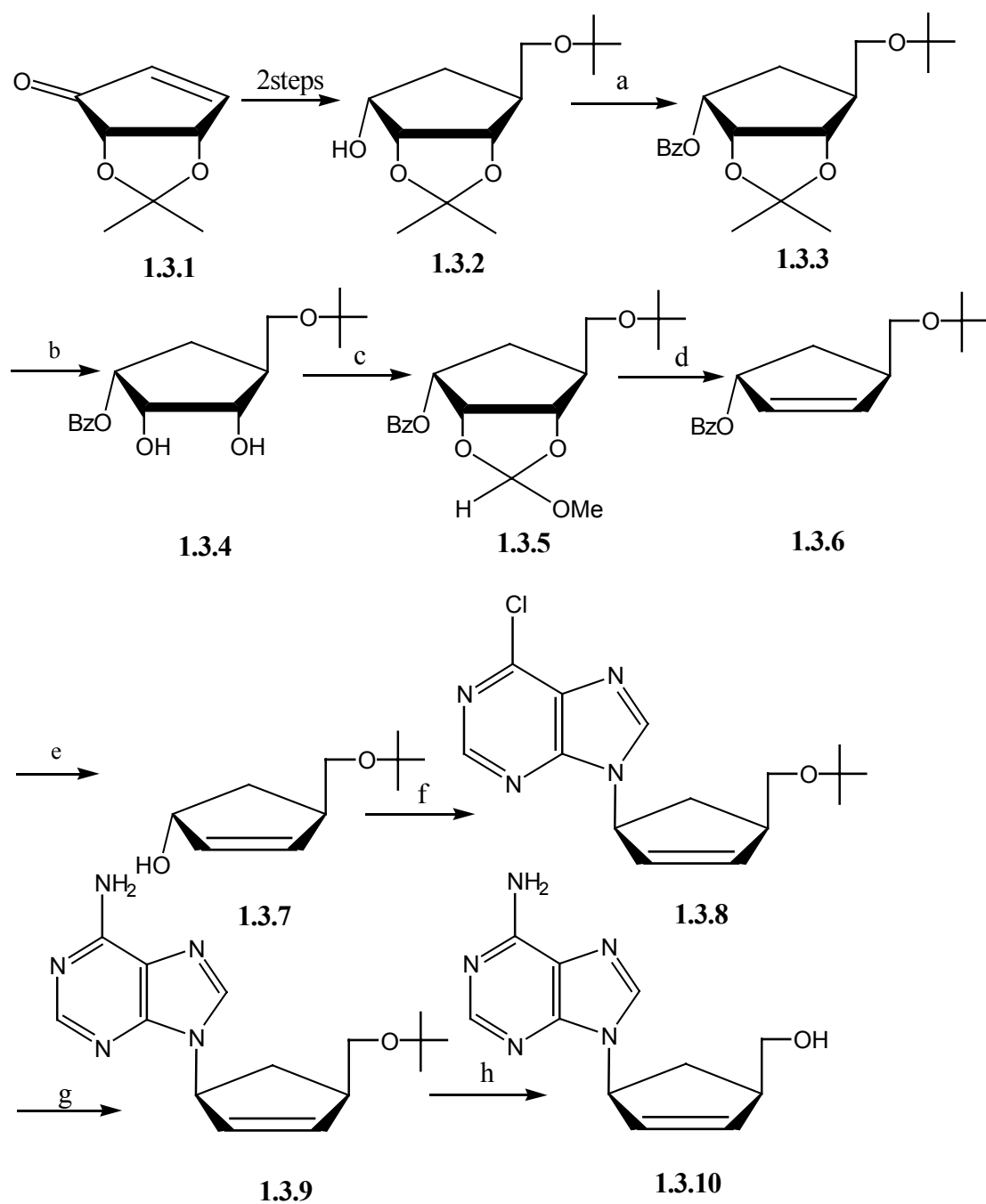
a: BzCl, pyridine, rt 12 h. b: concd HCl:MeOH (1:70,v/v), rt, 2.5 h. c: CH(OMe)$_3$, pyridinium p-sulphonate-toluene, rt 2 h. d: Ac$_2$O, 120-130 °C, 3 h. e: 2 N NaOH/MeOH, rt, 1.5 h. f: 6-chloropurine, Ph$_3$P, diethyl azodicarboxylate, dioxane, rt, 10 h. g: NH$_3$/MeOH, 80-90 °C, 20 h. h: CF$_3$CO$_2$H/H$_2$O (2:1), 50 °C, 3 h.

Scheme 1.3
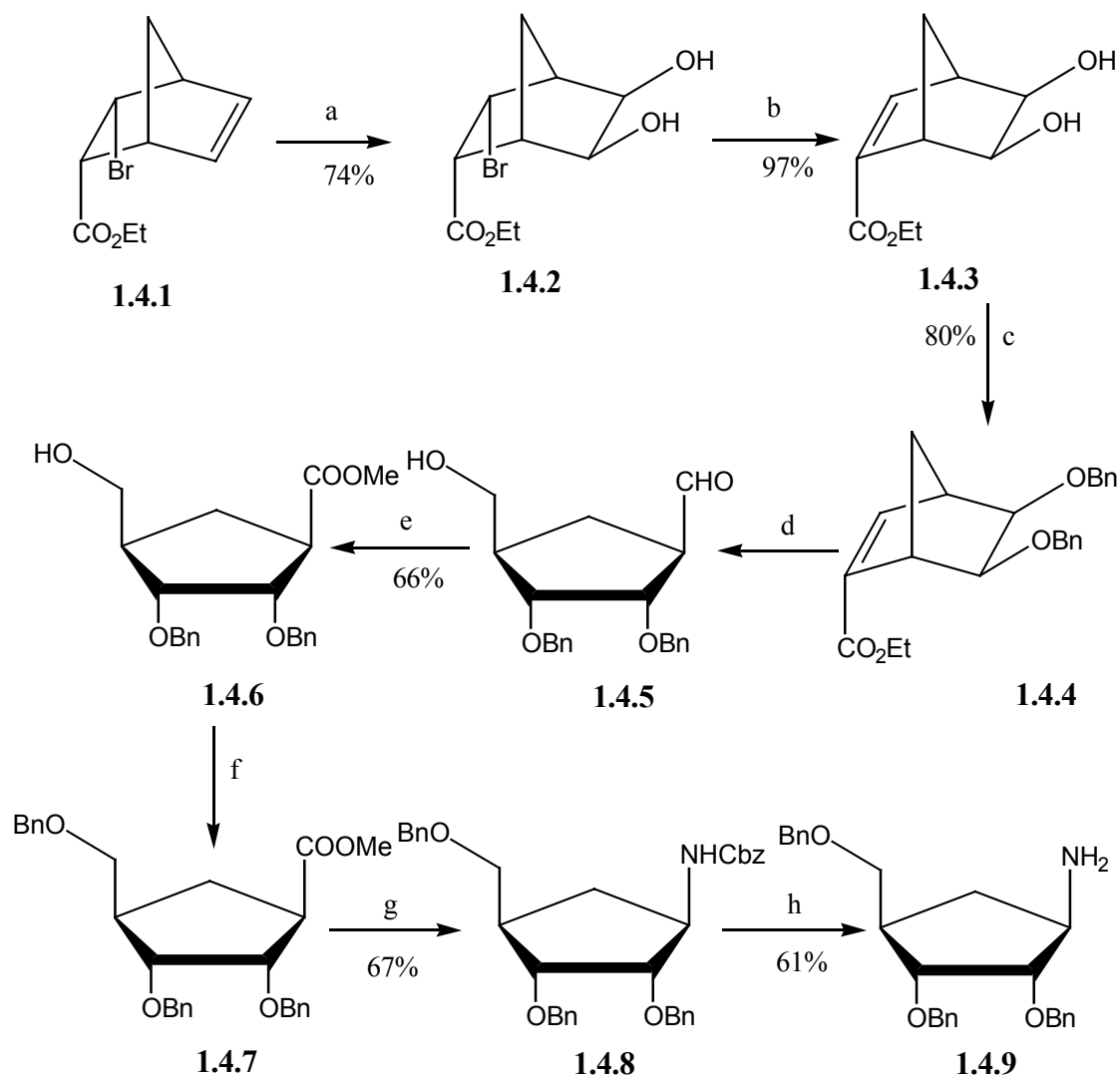
a: N-methylmorpholine N-oxide, OsO$_4$, acetone/H$_2$O(4:1), 40 °C, 13 h. b: DBU, ether, rt, 24 h. c: BnBr, benzene, molecular sieves, Ag$_2$O, 0 °C-rt, 23 h, argon. d: O$_3$, CH$_2$Cl$_2$/CH$_3$OH (38:1), -78 °C; LiBH$_4$, THF, 0 °C-rt, 20 h; NaIO$_4$, THF/H$_2$O (3:1), pH=5, rt, 2 h. e: Br$_2$,CH$_3$OH/H$_2$O(9:1), rt, 1 h. f: same as c: g: hydrazine, EtOH, reflux, 46 h; N$_2$O$_4$, CCl$_4$, -78 °C, 2 h; BnOH, benzene, reflux, 36 h. h: NH$_3$/Na, THF/CH$_3$OH (20:1), -78 °C, 2 h.

Scheme 1.4

aminotriol (**1.36**) as the key intermediates. The unsaturated tetrol was prepared as shown in Scheme 1.5.[42]

| 1.31 | 1.32 |

$R=H_4P_3O_9$
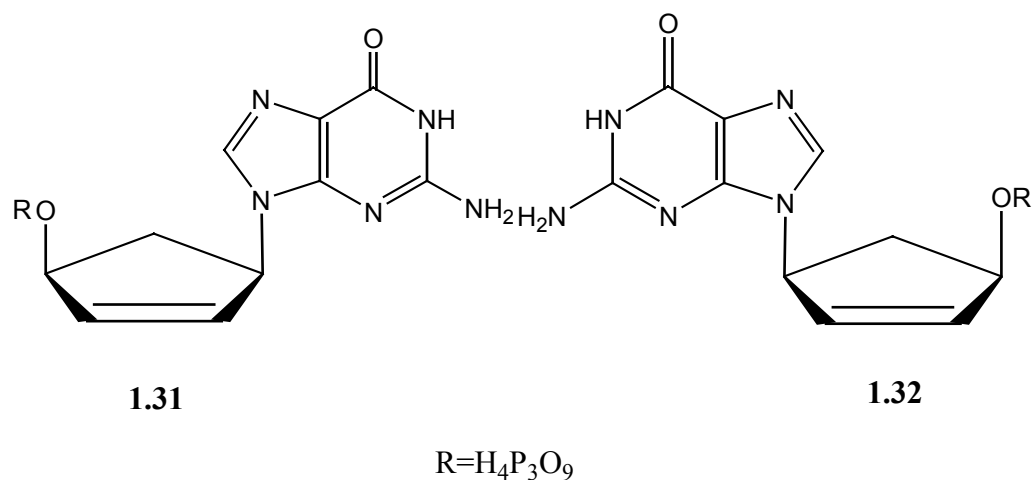
Figure 1.7

(-)-5'-Noraristeromycin (**1.37**) is found to have broad-spectrum antiviral activity. It is active against vaccinia virus (VV) and vesicular stomatitis virus (VSV), measles, respiratory syncytial virus (RSV) and human cytomegalo virus (HCMV). The toxicity is also decreased in comparison with other carbocyclic nucleosides because it can avoid the formation of toxic 5'-phosphate since it doesn't have 5'-hydroxy group.[43] (+)-5'-Noraristeromycin (**1.39**) shows good activity against hepatitis

| 1.33 | 1.34 |
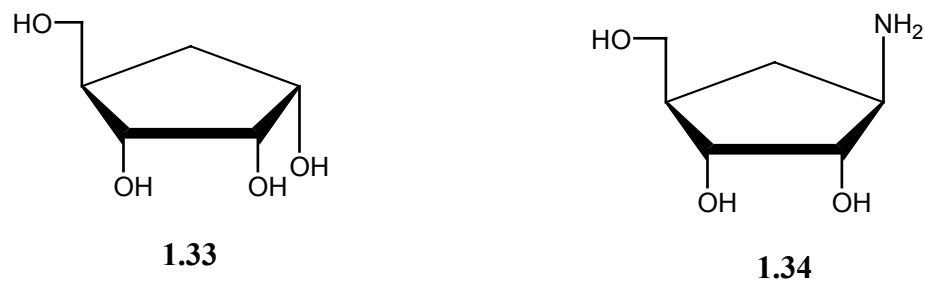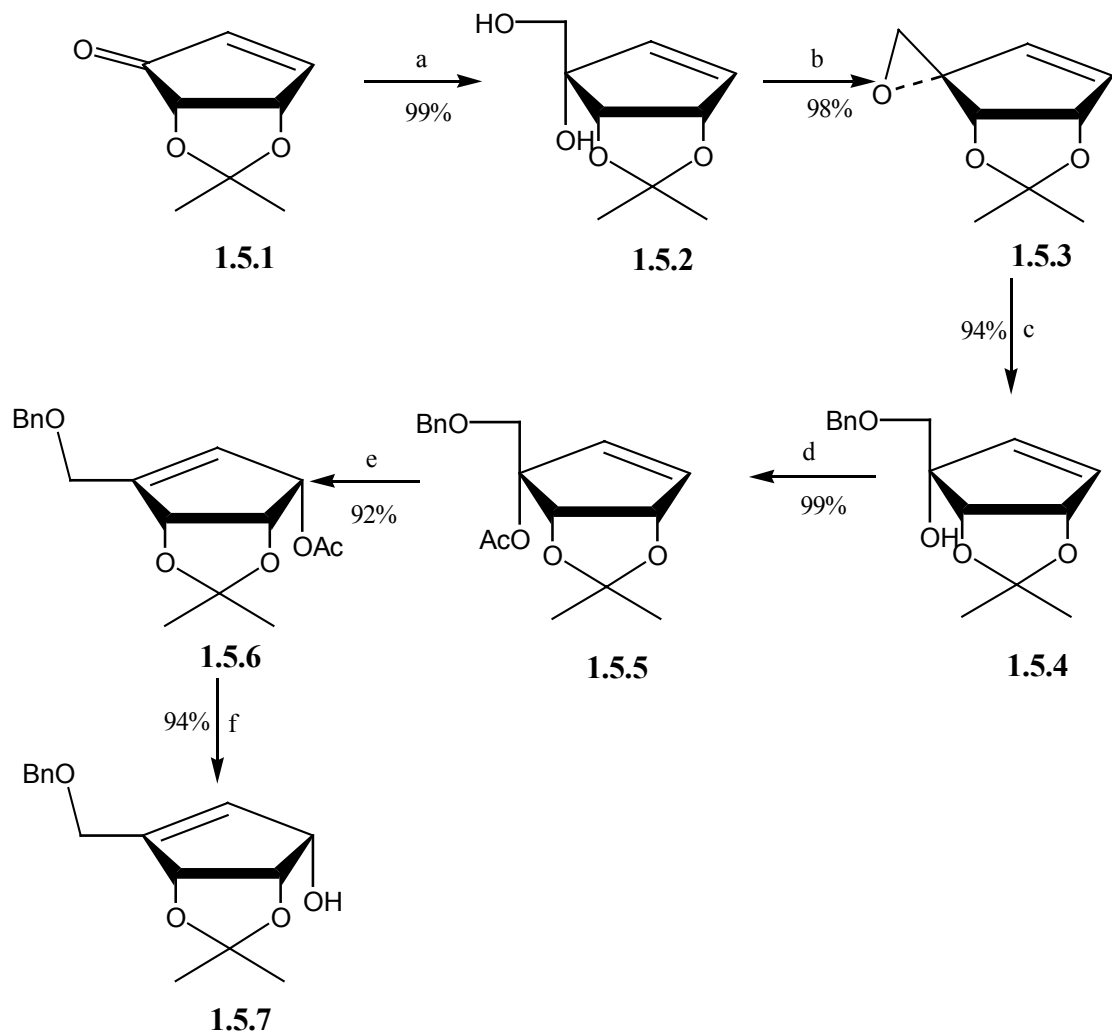
Figure 1.8

a: ClCH$_2$I, BuLi, THF, -78 $^{\circ}$C, 15 min. b: KOH, MeOH, rt, 20 min. c: BnONa, THF, rt-40 $^{\circ}$C, 1 day. d: Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt, 1 day. e: PdCl$_2$(MeCN)$_2$, pBQ, THF, 55 $^{\circ}$C, 3.5 h. f: aq. KCO$_3$, MeOH, rt, 20 min.

Scheme 1.5
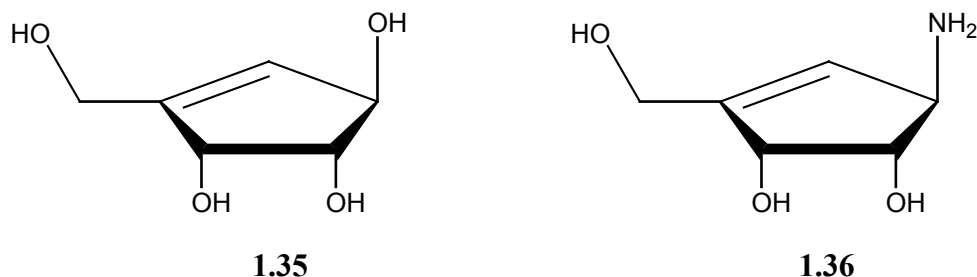
Figure 1.9

B virus (HBV).[44] However, *C*-4'-*O*-methylated analogs (**1.38**, **1.40**) were found to be much less effective, which indicates that a free hydroxyl hydrogen at *C*-4' was essential for the biological properties of 5'-noraristeromycin.[45]

BMS-200457 and other cyclopentyl carbocyclic

In 1997, Bisacchi et. al. reported a practical 10-step asymmetric synthesis of BMS-200475 (**1.6.7**), which is a remarkably potent inhibitor of HBV *in vitro* with low cytotoxicity.[46] He used chiral cyclopentyl epoxide (**1.6.3**) as a key intermediate, which can be prepared from commercially available sodium cyclopentadienide (**1.6.1**) with 63% overall yield in three steps. The epoxide ring (**1.6.3**) was opened by 6-benzyloxy-2-aminopurine with presence of LiH at 125°C. Then the purine amino group was protected by monomethoxytrityl (MMT) group. Dess-Martin oxidation of compound **1.6.5** followed by Nysted methylenation afforded compound **1.6.6** followed by deprotection of compound **1.6.6** to give BMS-200457.

Earlier in 1987, Ernest J. Prisbe reported synthesis of compound **1.7.5** as a racemic mixture. The compound showed good activity against HSV-1, HSV-2 and vaccinia virus. [47]

BMS-200457 and compound **1.7.5** have similar structure. Both of them are D-carbocyclic nucleoside with 5'-methylene group and show good antiviral activities.
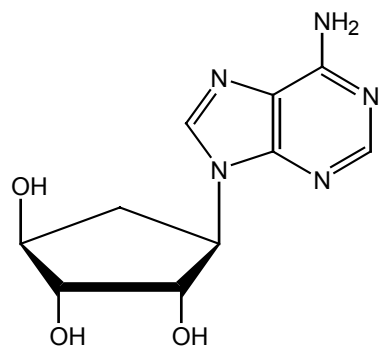
1.37
D-5'-noraristeromycin
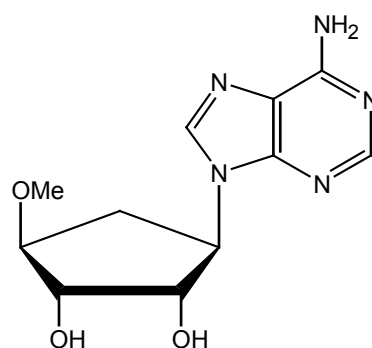
1.38
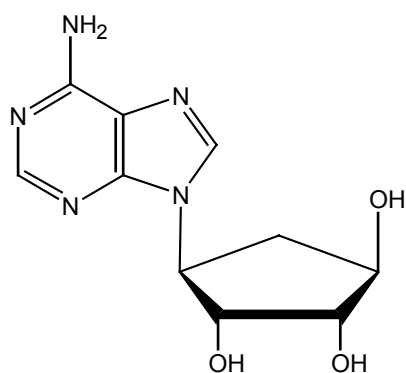
1.39
L-5'-noraristeromycin
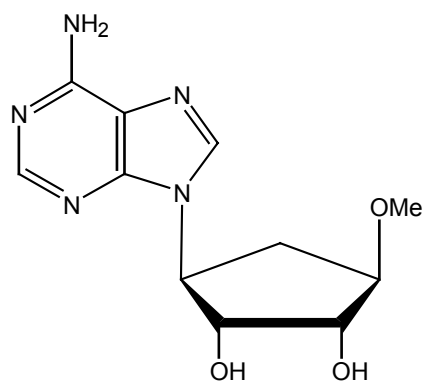
1.40

Figure 1.10

Therefore, it is of interest to synthesize the corresponding L-carbocyclic nucleosides with 5'-methylene group as potent antiviral agents.
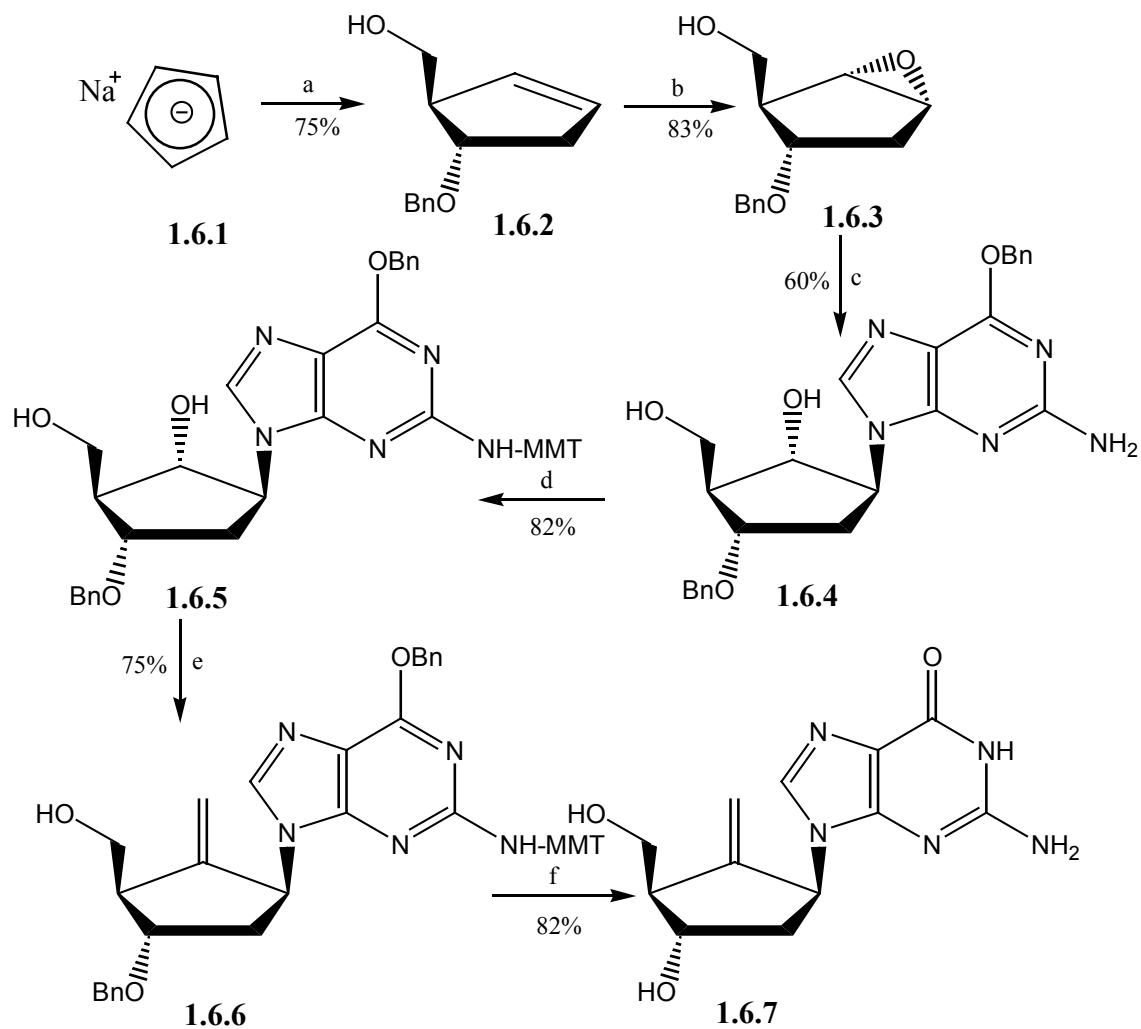
a: BnOCH$_2$Cl, THF, -65 ^{o}C to -78 ^{o}C; diisopenylcampheyllborane, THF, -65 ^{o}C to -78 ^{o}C; aq NaOH, H$_2$O$_2$. b:VO(acac)$_2$, t-BuOOH, CH$_2$Cl$_2$; BnBr, NaH, Bu$_4$NI, DMF. c: 6-benzyloxy-2-aminopurine, LiH, DMF, 125 ^{o}C. d: 4-monomethoxytrityl chloride, TEA, DMAP, CH$_2$Cl$_2$. e: Dess-Martin reagent, t-BuOH, CH$_2$Cl$_2$; Nysted reagent, TiCl$_4$, THF. f: aq. HCl, THF, MeOH, 55 ^{o}C; BCl$_3$, CH$_2$Cl$_2$, -78 ^{o}C.

Scheme 1.6
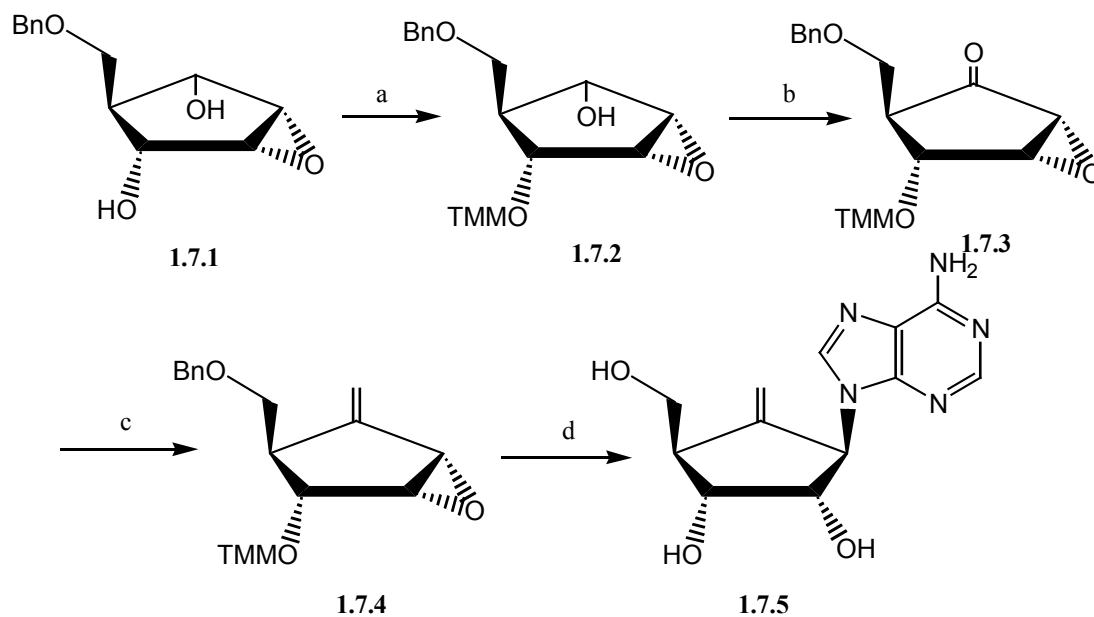
a: p-chlorodiphenylmethane, pyridine, rt, 2 days. b: Methylphosphonic acid,
1,3-dicyclohexylcarbodiimide, Me$_2$SO$_4$, rt, 16 h; oxalic acid/ H$_2$O. c:
Methyltriphenylphosphonium bromide, n-butyllithium, THF, -78 $^{\circ}$C; added
1.6.3/THF. d: adenine, NaH, DMF, 120 $^{\circ}$C, 15 min; added epoxide, reflux 2 h;
80% AcOH, rt 4.5 h; palladium hydroxide on carbon, cyclohexene, EtOH, reflux
1.5 h.

Scheme 1.7

CHAPTER 2

RESULTS AND DISCUSSION

Our strategy for 5'-methylene carbocyclic L-nucleosides is similar to that for the regular carbocyclic nucleosides. Some of the 5'-methylene carbocyclic nucleosides have been synthesized by a similar method as BMS-200457 (Scheme 1.6).[46] This approach is similar to Scheme 1.7 which involved the opening of epoxide ring, which gave a racemic mixture.[47] However, Scheme 1.6 is only proper for the 2'-deoxy derivatives and hard to use directly for the synthesis of ribose derivatives. Scheme 1.7 used a racemic mixture as key intermediate and is not proper for the development of a regio- and stereo-selective synthesis. Therefore, we devised our own synthetic approach (Scheme 2.1), in which cyclopentenone (**G**) can serve as a chiral intermediate to obtain the alcohol **D**.   In addition, it also can be converted to the triflate (**B**) or the cyclopentylamine (**C**). The compound **B** and **C** can serve as the common intermediates for the synthesis of pyrimidine and purine carbocyclic nucleosides by coupling **B** with the corresponding heterocycles or construction of heterocycles by linear approaches from the intermediate **C**.

For the synthesis of L-cyclopentyl nucleosides, (+)-cyclopentenone (**2.2.1**) was selected as a chiral starting material, which was prepared from D-ribose in 3 steps using the procedure of Ali *et al*.[48] Compound **2.2.1** was converted to the cyclopentanone (**2.2.2**) by a modified procedure reported by Wolfe *et al*.[49] Treatment of **2.2.1** with a solution of lithium bis(*tert*-butoxymethyl)cuprate at −30 °C gave the optically pure cyclopentanone (**2.2.2**) as a single isomer in 87% yield.

Several different reactions were conducted in order to introduce the 5'-methylene group as illustrated in Scheme 2.3. First, we tried a modified Mannich reaction, in which the cyclopentanone was treated with trioxane and *N*-
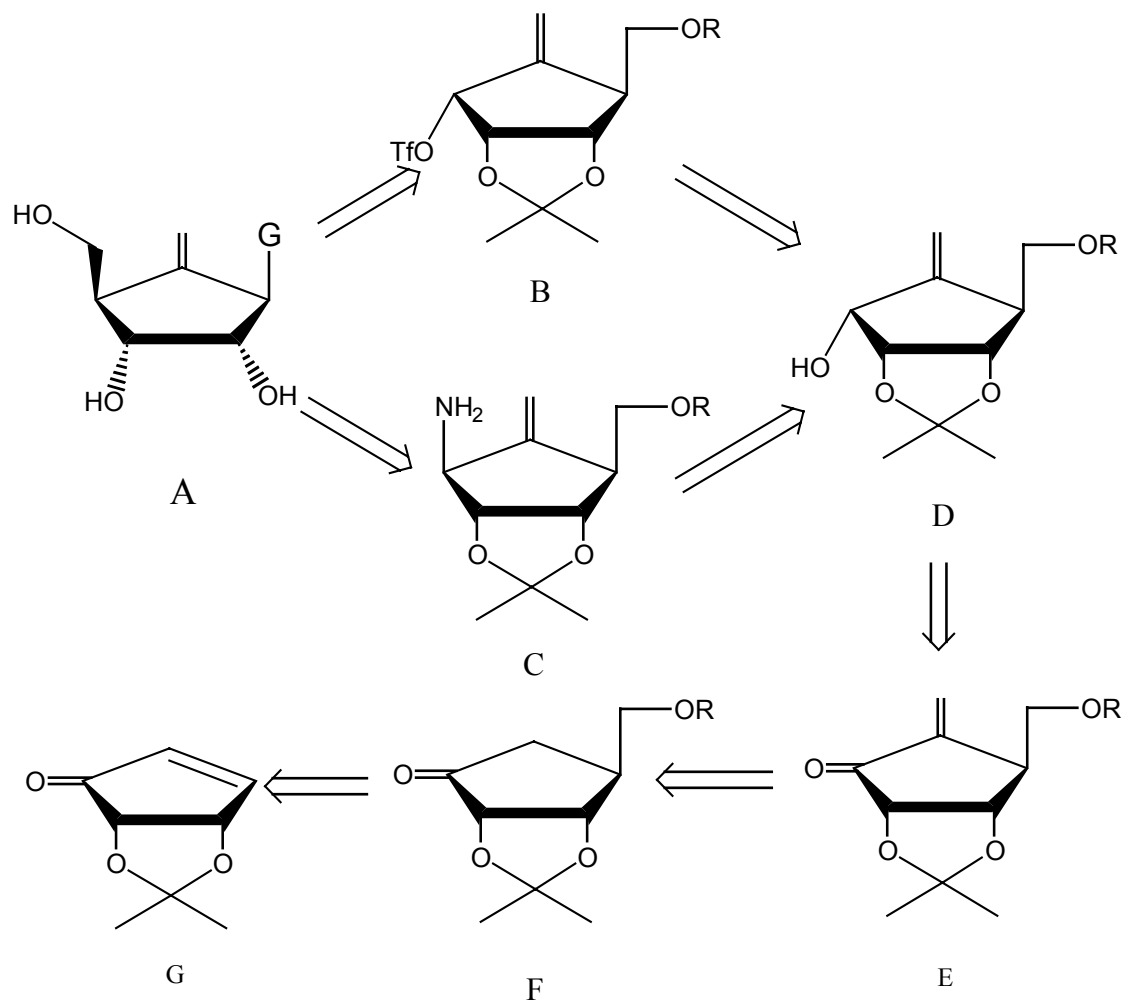
Scheme 2.1 Retrosynthetic Analysis of L-5'-methylene-Carbocyclic Nucleosides
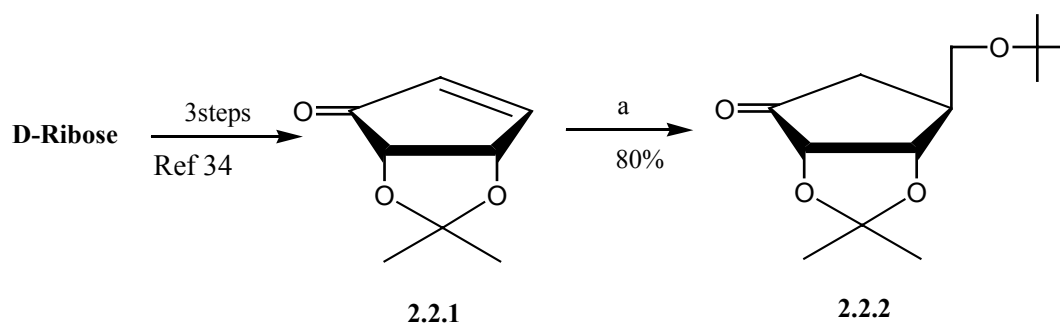
a: (t-BuOCH$_2$)$_2$CuLi, t-BuOMe/THF, -30 °C, 30 min.

Scheme 2.2

Methylanilinium trifluoroacetate (TAMA) in anhydrous THF under reflux for 3 days, during which most of the starting material was decomposed and no desired product was observed.[50] The reaction did not go because of the mild acidity of TAMA, which caused decomposition of the cyclopentanone. Then, we tried to treat the cyclopentanone with LDA in anhydrous THF at −78 °C for 2 h followed by the addition of formaldehyde.[51] The reaction mixture was continuously stirred at −78 °C for 3 h, then temperature was increased to −10 °C, however, no reaction was observed. Further increasing the temperature caused the starting material to decompose. The reaction did not go because of the poor reactivity of the formaldehyde. Finally, we tried to use Eschenmoser's salt.[52] Cyclopentanone was treated with LDA in anhydrous THF at −78 °C for 2 h followed by the addition of the Eschenmoser's salt. The reaction mixture was continuously stirred at −78 °C for 4 h and room temperature for 10 h, iodomethane added and kept stirred for 5 h, followed by washing with water solution of sodium bicarbonate, and purification by silica gel column to give the 5'-methylene cyclopentanone (**2.3.3**) in 90% total yield from **2.2.2.**

(1) TAMA, trioxane THF

(2) LDA, formaldehyde, THF

2.2.2

2.3.3

a

90% c

2.3.1

b

2.3.2
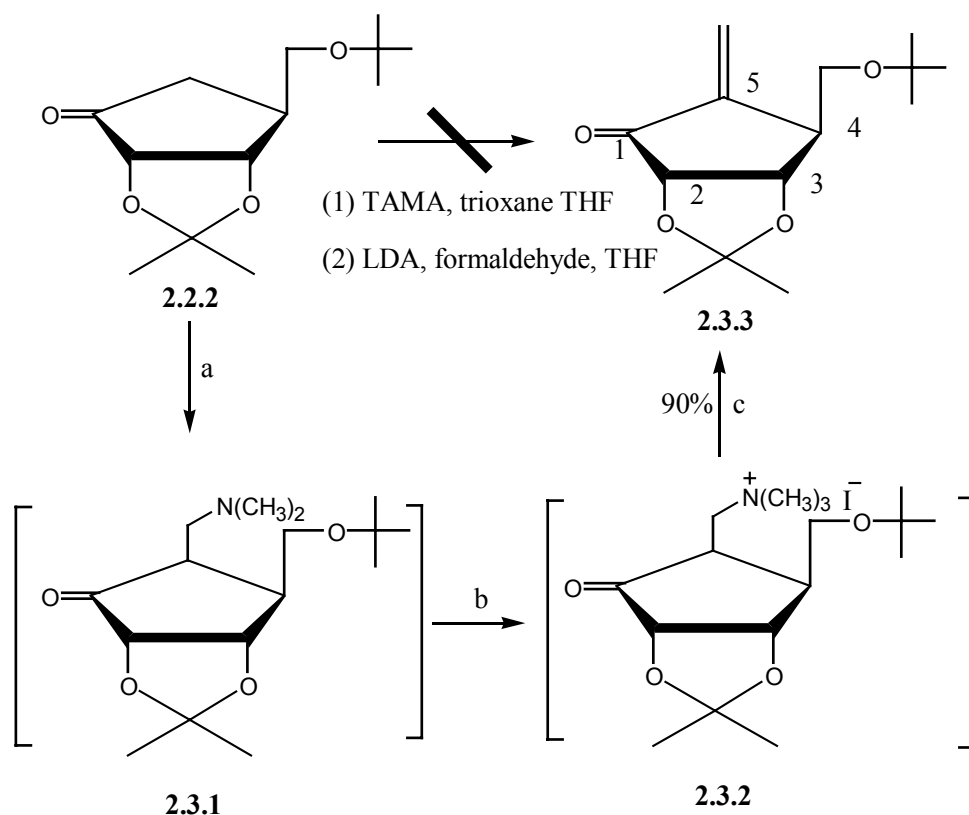
a: LDA, Eschenmoser's salt, THF, -78 °C. b: CH$_3$I, rt. c: NaHCO$_3$

Scheme 2.3

Reduction of 5-methylene cyclopentanone with sodium borohydride gave regioselectively the α-alcohol (**2.4.1**) in 92% yield. Another key intermediate 5'-methylene cyclopentylamine (**2.4.3**) was prepared from alcohol (**2.4.1**): treatment of **2.4.1** with methanesulfonyl chloride afforded the mesyl derivative in quantitative yield. The treatment of mesyl derivative with lithium azide in hot DMF for 4 h gave the azide (**2.4.2**) in 88% yield. Reduction of **2.4.2** by lithium aluminum hydride in hot THF afforded the amino derivative **2.4.3**.

Usually, the bases can be introduced to the sugar moiety by direct introduction of the heterocycle or construction via precursors. There are four different strategies to

2.3.3   **2.4.1**   **2.4.2**

2.4.3
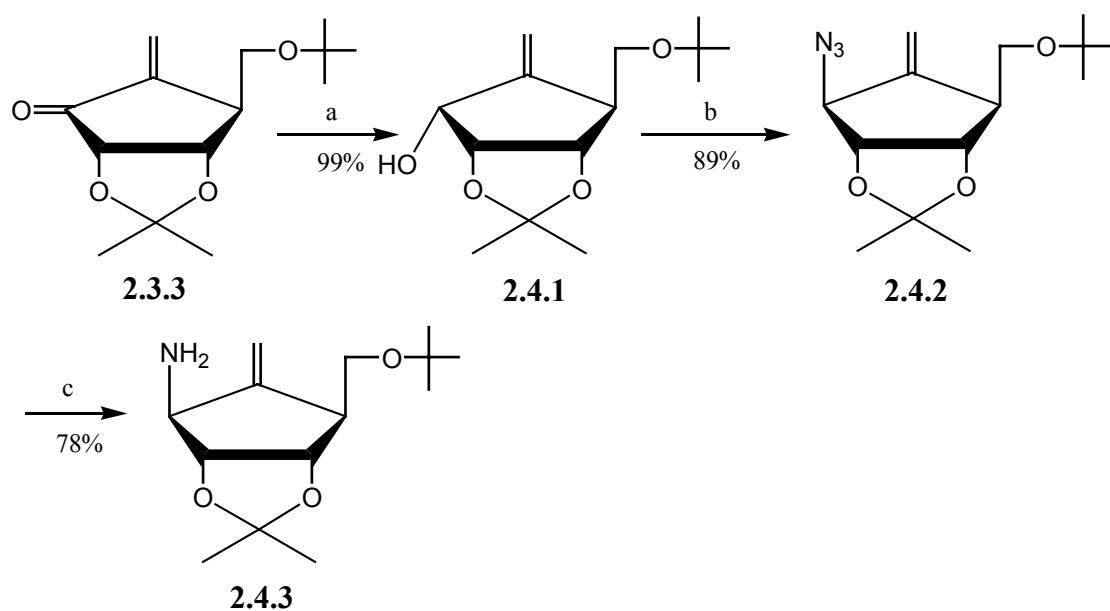
a: NaBH$_4$, Cerium(III) chloride heptahydrate, MeOH, 0 ^{o}C, 10 min. b: (1) Methanesulfonyl chloride, TEA, CH$_2$Cl$_2$, 0 ^{o}C, 1 h; (2) NaN$_3$, DMF, reflux, 6 h. c: Lithium alumium hydride, THF, reflux, 2 h.

Scheme 2.4

introduce a base to a functionalized cyclopentane.

1. by nucleophilic displacement of an activated α hydroxyl group (MsO-, TsO-, see Figure 2.1)[53,54]

R=Ms, Ts; X,Y=H, OH, F...
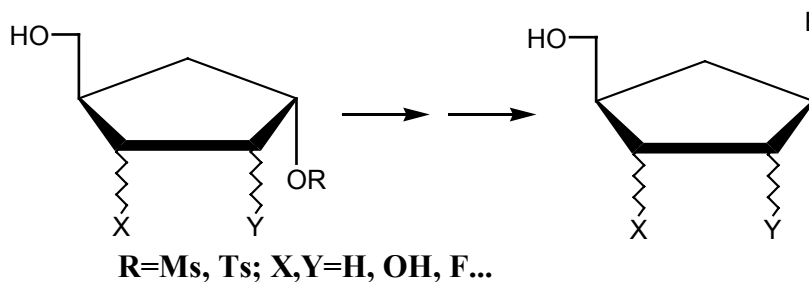
Figure 2.1

2 by ring opening of an epoxide (Figure 2.2)[55,56,57,58]

X,Y=H, OH, F,...
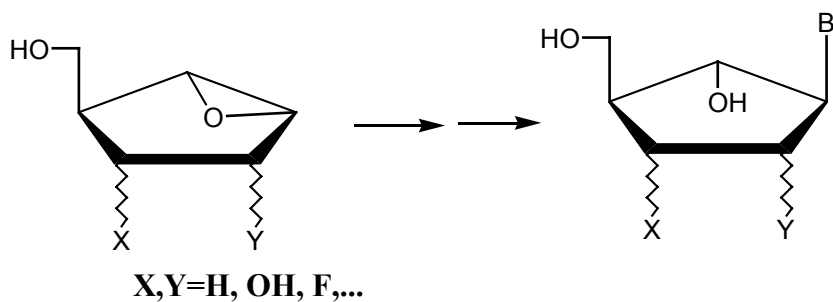
Figure 2.2

3   by a Mitsunobu reaction (Figure 2.3)[59]

X,Y=H, OH, F,...
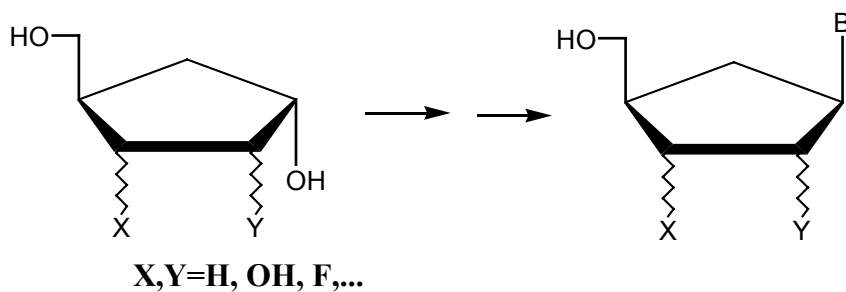
Figure 2.3

4   by a Michael 1,2-addition (Figure 2.4)[60,61]

X, Y=H, OH, F,...; Z=NO$_2$
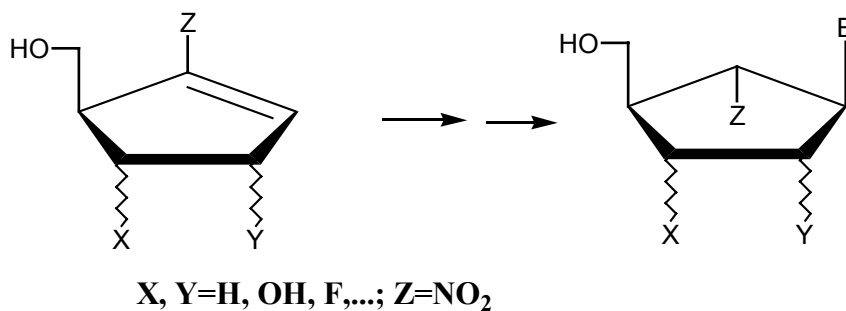
Figure 2.4

Among all these methods, 1 and 3 were apparently best for our key precursor. First, we prepared both the methylated and tosylated precursor to try to introduce the base by method 1, however, we failed to get any product with this method. Then, we

tried the Mitsunobu reaction without success. A possible explanation may be the stereo-hindrance of the *tert*-butoxyl group at 5 position.

After failure of the direct introduction of the base moiety, we started to construct the guanine moiety (Scheme 2.5).

We followed the procedure described by Shealy *et al.*[62,63] The coupling reaction of cyclopentylamine (**2.4.3**) with 2-amino-4,6-dichloropyrimidine in the presence of triethylamine afford **2.5.1** in 87% yield. The isopropylidene group was selectively removed by a mixture of concentrated HCl and MeOH(1:75, v/v) to obtain a diol, which was directly used for diazotization with (*p*-chlorophenyl) diazonium chloride. The diazo derivative was reacted with zinc dust to give di-amino derivative (**2.5.2**). The treatment of **2.5.2** with triethyl orthoformate in the presence of concentrated HCl gave the 2-amino-6-chloropurine analog, which was then hydrolyzed by 2 N HCl to afford the desired guanine derivative (**2.5.3**).

In summary, we developed a new strategy to synthesis compound **2.5.3**. The complete scheme is shown in Scheme **2.6**.
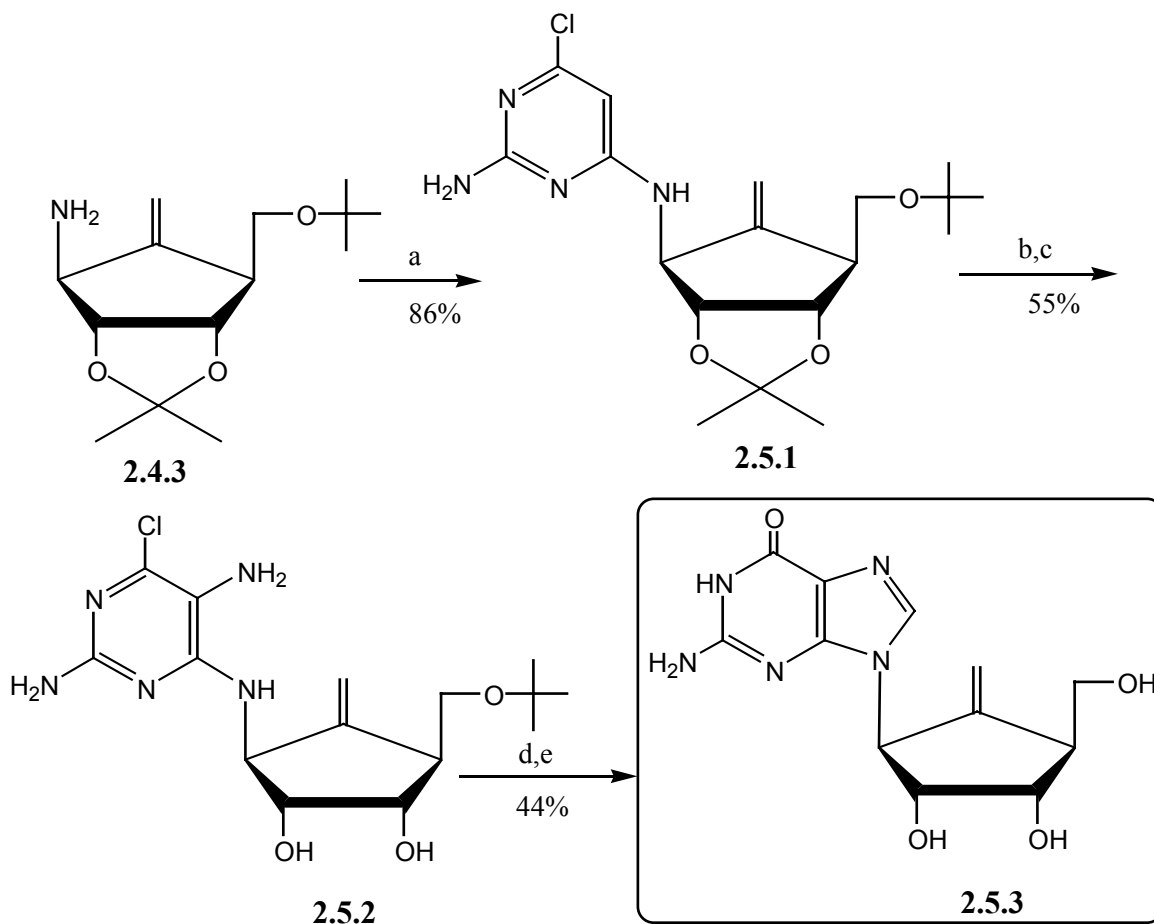
a: 2-amino-4,6-dichloropyrimidine, Et$_3$N, EtOH, reflux, 48 h. b: (1) HCl/MeOH, rt, 2 h, (2) *p*-ClC$_6$H$_4$N$_2$Cl. rt, 18 h. c: Zn/AcOH, H$_2$O/EtOH, 70 $^{\circ}$C, 20 min. d: CH(OEt)$_3$, HCl; 50% AcOH; sat NH$_4$OH. e: 2 N HCl, reflux, 5 h.

Scheme 2.5

Scheme 2.6

D-Ribose →(3steps, Ref 34)→ **2.2.1** →(a, 80%)→ **2.2.2** →(b)→ **2.3.3** →(c, 99%)→ **2.4.1** →(d, 89%)→ **2.4.2** →(e, 78%)→ **2.4.3** →(f, 86%)→ **2.5.1** →(g, h, 55%)→ **2.5.2** →(i)→ →(j, 44%)→ **2.5.3**
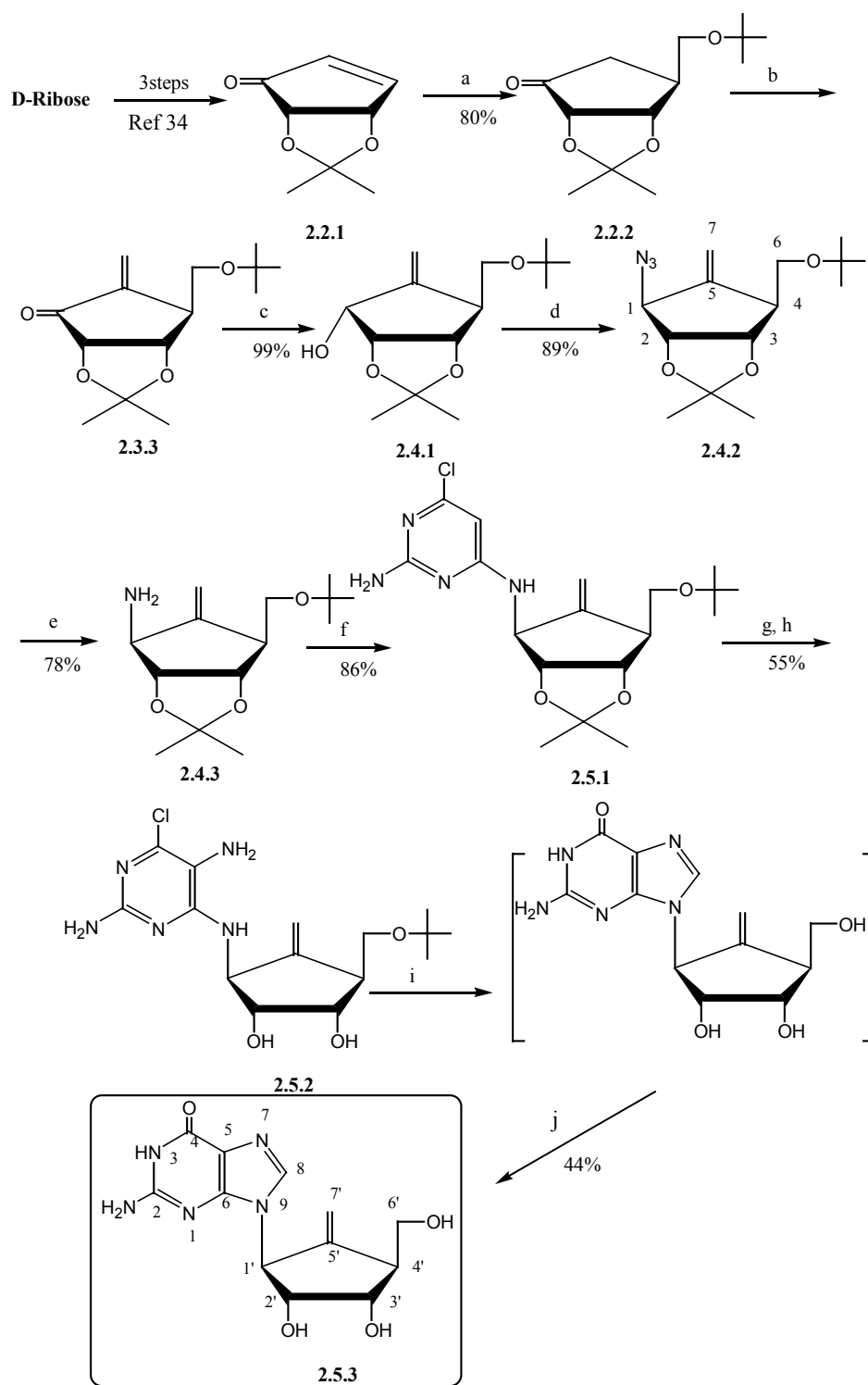
a: (*t*-BuOCH$_2$)$_2$CuLi, *t*-BuOMe/THF, -30 °C, 30 min. b: LDA, Eschenmoser's salt, THF, -78 °C. CH$_3$I, rt. NaHCO$_3$. c: NaBH$_4$, Cerium(III) chloride heptahydrate, MeOH, 0 °C, 10 min. d: Methanesulfonyl chloride, TEA, CH$_2$Cl$_2$, 0 °C, 1 h; NaN$_3$, DMF, reflux, 6 h. e: Lithium alumium hydride, THF, reflux, 2 h. :f: 2-amino-4,6-dichloropyrimidine, Et$_3$N, EtOH, reflux, 48 h. g: (1) HCl/MeOH, rt, 2 h, (2) *p*-ClC$_6$H$_4$N$_2$Cl. rt, 18 h. h: Zn/AcOH, H$_2$O/EtOH,70 °C, 20 min. i: CH(OEt)$_3$, HCl; 50% AcOH; sat NH$_4$OH/MeOH. j: 2 N HCl, reflux, 5 h.

Scheme 2.6

CHAPTER 3

EXPERIMENT

Melting points were determined on a Mel-temp II apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker 400 AMX spectrometer at 400 MHz for 1H NMR with tetramethylsilane as the internal standard. Chemical shifts(δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d(doublet), t(triplet), q(quartet), m(multiplet), or br s(broad singlet). UV spectra were recorded on a Beckman DU-650 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Mass spectra were recorded on a Micromass Autospec high-resolution mass spectrometer. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using silica gel G (TLC grade, >440 mesh) for vacuum flash column chromatography. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

(2S,3S,4S)-4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)-1-cyclopentanone (2.2.2). To a suspension of potassium *tert*-butoxide (16.43 g, 146.4 mmol) and anhydrous *tert*-butylmethyl ether (525 mL) cooled to –78 °C, *sec*-butyllithium (1.3 M in cyclohexane, 112.7 mL, 146.4 mmol) was added dropwise over 10 min under nitrogen. After stirring 2.5 h at –78 °C, a solution of LiBr (2 M, 25.44 g of LiBr in 145 mL of THF) was added dropwise to the resulting mixture over 10 min at –78 °C and then allowed to warm to –15 °C (ice-salt bath) and stirred for 30 min at –15 °C. Upon recooling to –78 °C a solution of CuBr.SMe$_2$ (15.05 g, 71.75 mmol) in diisopropylsulfide (75 mL) was added dropwise over 10 min and the viscous dark solution stirred for 1 h. A solution of the enone **2.2.1** (7.4 g, 48 mmol) in THF (67 mL) was added dropwise over 5 min. The reaction mixture was allowed to warm to

29

–30 °C over 15 min, stirred at this temperature for an additional 30 min, then quenched with 168 mL of AcOH/MeOH (1:1), which was poured into 1680 mL of NH_4Cl/ NH_4OH (pH = 9). After removing the aqueous layer, the organic layer was washed with 1:1 mixture of saturated NH_4Cl and 3% NH_4OH solutions (3 X 400 mL) and brine (400 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography with 10-20% EtOAc in hexanes to give **2.2.2** (10.13g, 87.1%) as a solid: mp. 64-65 °C; $[\alpha]^{26}_D$ 185.36° (c 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.62 (d, J=5.3Hz, 1H, 2-H), 4.23 (d, J=5.3Hz, 1H, 3-H), 3.50(dd, J=2.3,8.5Hz, 1H, 6-H), 3.35 (dd, J=2.6,8.5Hz, 1H, 6-H) 2.71 (dd, J=8.9,17.9Hz, 1H, 5-H), 2.54 (d, J=8.9Hz, 1H, 4-H), 2.05 (d, J=17.9Hz, 1H, 5-H), 1.43 (s, 3H, CH_3), 1.11 (s, 9H, *tert*-Butyl). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.18; H, 9.13. HR-FAB MS Obsd: m/z 243.1596. Calcd for $C_{13}H_{22}O_4$: m/z 243.1596 $(M+H)^+$.

(2S,3S,4S)-4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)-5-(methylenyl)-cyclopentanone (2.3.3)   To a solution of compound **2.2.2** (1 g, 4.1 mmol) in anhydrous THF (50 mL) at –78 °C, LDA (1.5 M in cyclohexane, 2.7 mL) was added. The reaction mixture was stirred for 3 h at –78 °C, Eschenmosar's salt (2.8 g, 15.3 mmol) was added to with continual stirring at the same temperature for 3 more hours, warmed up to room temperature and stirred for another 8 h, Iodomethane (15 mL) added, the mixture was stirred at room temperature for another 4 h. The mixture was filtered and concentrated to dryness. The residue was purified by flash silica gel column with 10% ethyl acetate in hexanes to give **2.3.3** 0.94 g (90% yield) as a solid: mp. 30-31 °C, $[\alpha]^{26}_D$ 221.03° (c 0.11, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 6.23 (s, 1H, 7-H), 5.52 (s, 1H, 7-H) 4.59 (d, J=5.2Hz, 1H, 2-H), 4.48 (d, J=5.2Hz, 1H, 3-H), 3.64 (d, J=8 Hz, 1H, 6-H), 3.35 (d, J=8 Hz, 1H, 6-H), 3.08 (s,1H, 4-H), 1.37 (s, 3H, CH_3), 1.1 (s, 3H, CH_3), 1.07 (s, 9H, *tert*-Butyl). Anal. Calcd for $C_{14}H_{22}O_4 \cdot 0.1$Hexane: C, 66.12; H,

8.72. Found: C, 66.68; H, 8.79. HR-FAB MS Obsd: m/z 255.1557. Calcd for

$C_{14}H_{23}O_4$: m/z 255.1518 (M+H)$^+$.

(1R,2R,3S,4S)-4-(*tert*-Butoxylmethyl)-2,3-(isopropylidenedioxy)-5-(methylenyl)-cyclopentane-1-ol (2.4.1) To a solution of compound **2.3.3** (0.3 g, 1.2mmol) in methanol (50 mL), cerium chloride heptahydride (0.6 g) and sodium boron hydride (88.8 mg, 2.4 mmol) was added at 0 °C, stirred for 20 min and filtered with Celite pad. The filtrate was washed concentrated to dryness and purified by flash silica gel column with 10% EtOAc in hexane to give 0.27 g of compound **2.4.1** (89% yield) as a solid : mp. 34-35 °C. $[\alpha]^{26}_D$ 27.03° (c 0.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 5.25 (s, 1H, 7-H), 5.11 (s, 1H, 7-H), 4.51 (m, 1H, 1-H), 4.11 (m, 2H, 2-H, 3-H), 3.45 (dd, J=3.6, 8 Hz, 1H, 6-H), 3.26 (dd, J=3.6, 8 Hz, 1H, 6-H), 2.62 (s, 1H, 4-H), 2.26 (d, J=10 Hz, 1H, OH, D_2O exchangeable) 1.39 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.11 (s, 9H, *tert*-Butyl). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.61; H, 9.65. HR-FAB MS Obsd: m/z 257 . Calcd for $C_{14}H_{25}O_4$: m/z 257 (M+H)$^+$.

(1S,2R,3S,4S)-1-Azido-4-(*tert*-butoxylmethyl)-2,3-(isopropylidenedioxy)-5-(methylenyl)-cyclopentane (2.4.2)   To a solution of compound **2.4.1** (1.5 g, 5.86 mmol) in anhydrous methylene chloride (100 mL), methanesulfonyl chloride (1.5 g, 13.1 mmol) and triethyl amine (1.09 g, 10.8 mmol) was added at 0 °C, stirred for 30 min and quenched with water. The aqueous layer was extracted with CH_2Cl_2 (3 X 50 mL), combined, washed with brine (50 mL) and dried by magnesium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in 50 mL of anhydrous dimethyl formide (DMF) in the presence of sodium azide and was heated at 140 °C for 4 h with stirring. After the reaction was completed, the reaction mixture was concentrated to dryness and purified by flash silica gel column with 5% EtOAc in hexane to give compound **2.4.2** 1.45 g (88% yield) as a syrup. $[\alpha]^{26}_D$ 31.58° (c 0.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 5.28 (s, 1H, 7-H), 5.21 (s, 1H, 7-H), 4.69 (d, J=6.0 Hz, 1H, 2-H), 4.23 (d, J=6.0 Hz,1H, 3-H), 3.66 (s, 1H, 1-H), 3.46 (m, 1H, 6-H), 3.3

(m,1H, 6-H), 2.71 (s, 1H, 4-H), 1.40 (s, 3H, CH$_3$), 1.34 (s, 3H, CH$_3$), 1.16 (s, 9H, *tert*-Butyl). FAB MS Obsd: m/z 282 . Calcd for C$_{14}$H$_{24}$N$_3$O$_4$: m/z 282 (M+H)$^+$.

(1S,2R,3S,4S)-4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)-5-(methylenyl)-1-cyclopentanamine (2.4.3) To a solution of compound **2.4.2** (1g, 3.5 mmol) in anhydrous THF (60 mL), lithium aluminum hydride (168 mg, 4.2 mmol) was added at room temperature. The mixture was stirred under reflux for 2 h and quenched with methanol (10 mL) and filtered. The filtrate was concentrated to dryness and filtered by celite pad and washed the pad with 2% methanol in methylene chloride to give crude compound **2.4.3** 696 mg (78% yield) which was used for next step without further purification. ^{1}H NMR (CDCl$_3$) δ 5.77 (d, *J*=3.2Hz, 1H, 7-H), 5.66 (s, 1H, 7-H), 4.81 (s, 2H, 2-H, 1-H), 4.48 (d, *J*=5.2Hz, 1H, 3-H), 3.51 (m, 1H, 6-H), 3.38 (m, 1H, 6-H), 2.86 (s, 1H, 4-H), 1.41 (s, 3H, CH$_3$), 1.33 (s, 3H, CH$_3$), 1.18 (s, 9H, *tert*-Butyl). FAB MS Obsd: m/z 256. Calcd for C$_{14}$H$_{26}$NO$_3$: m/z 256 (M+H)$^+$.

(1S',2R',3S',4S')-2-Amino-4-[[4-(*tert*—butoxymethyl)-2,3-(isopropylidenedioxy)-5-(methylenyl)cyclopentan-1-yl]amino]-6-chloropyrimidine (2.5.1) To a solution of compound **2.4.3** (870 mg, 3.41 mmol) in ethanol (70 mL), 2-amino-4,6-dichloropyrimidine (890 mg, 5.43 mmol) and Et$_3$N (0.5 mL) was added at room temperature and refluxed for 48 h under nitrogen. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (0.2% methanol in chloroform) to give compound **2.5.1** 1.13 g (87%, yield) as a solid: mp 140-141 °C. [α]$^{26}_D$ –21.04 (c 0.25, CH$_2$Cl$_2$); UV (MeOH) λ$_{max}$ 286 nm, 237.5 nm; ^{1}H NMR (CDCl$_3$) δ 6.64 (s, 1H, NH, D$_2$O exchangeable) 5.71 (s, 1H, ArH), 5.6 (s, 1H, methylene-H), 5.27 (s, 1H, methylene-H), 4.98 (d, *J*= 6.4 Hz, 1H, 2'-H), 4.8 (s, 1H, 1'-H), 4.41 (d, *J*= 6.4 Hz, 1H, 3'-H), 3.43(m, 1H, 6'-H), 3.31 (m, 1H, 6'-H), 2.79 (s, 1H, 4'-H), 1.33 (s, 3H, CH$_3$), 1.25 (s, 3H, CH$_3$), 1.11 (s, 9H, *tert*-Butyl). FAB MS Obsd: m/z 383. Calcd for C$_{18}$H$_{28}$ClN$_4$O$_4$: m/z 383 (M+H)$^+$.

(1'S,2'R,3'S,4'S)-4-[[4-(*tert*-Butoxymethyl)-2,3-dihydroxy-5-(methylenyl)cyclopentan-1-yl]amino]-6-chloro-2,5-diaminopyrimidine (2.5.2)   A solution of compound **2.5.2** (191 mg, 5.02 mmol) in methanol (20 mL) containing concentrated HCl (0.27 mL) was stirred at room temperature for 2 h. The reaction mixture was neutralized with $NaHCO_3$ solid at 0 °C and the mixture was concentrated to dryness. The residue was washed with MeOH and filtered. The filtrate was concentrated to dryness and the residue was used in the next step without further purification. To a solution of *p*-chloroaniline (100 mg, 0.78 mmol) in concentrated HCl (0.45 mL) and water (0.9 mL), a solution of $NaNO_2$ (60 mg, 0.86 mmol) in water (0.8 mL) was added dropwise at 0 °C. The resulting cold solution was added to the solution of above residue in water (3.4 mL), acetic acid (3.4 mL) and sodium acetate trihydrate (1.45 g) at 0-5 °C. The reaction mixture was stirred at room temperature for 18 h and the yellow solid precipitated. The solid was collected by filtration and used for the next step without further purification. A mixture of yellow solid, THF (3.4 mL), ethanol (3.4 mL), water (3 mL), and acetic acid (0.3 mL) was heated and stirred at 70 °C. Zinc dust (0.26 g, 35 mmol) was added and the mixture was heated 65-70 °C for 20 min. The reaction mixture was filtered and the filtrate concentrated to dryness. The residue was purified by flash silica gel column chromatography with 1-3% methanol in CH_2Cl_2 to give crude compound **2.5.2** 82 mg (46%, yield) as a foam.; UV λ_{max} 203.5, 303.5nm (PH=7); ^{1}H NMR ($CDCl_3$ + D_2O) δ 5.3 (s, 1H, 7-H), 5.22 (s, 1H, 7-H), 4.7 (t, *J*= 5.6 Hz, 1H, 2'-H), 4.51 (d, *J*= 5.6Hz, 1H, 1'-H), 4.23 (d, *J*=5.6Hz, 1H, 3'-H), 3.50(dd, *J*=2.3,8.5Hz, 1H, 6-H), 3.49 (m, 1H, 6'-H), 3.32 (m, 1H, 6'-H) 2.73 (s, 1H, 4'-H), 1.15 (s, 9H, *tert*-Butyl). FAB MS Obsd: m/z 356. Calcd for $C_{15}H_{25}ClN_5O_4$: m/z 356 (M+H)$^+$.

(1'S,2'R,3'S,4'S)-9-[-2,3-Dihydroxy-4-(hydroxymethyl)-5-(methylenyl)cyclopentan-1-yl]guanine (2.5.3) To a mixture of compound **2.5.2** (65 mg, 0.18 mmol) triethyl orthoformate (1.5 mL), and DMF (1 mL) was added

concentrated HCl (38 μL). The mixture was stirred at 0-5 °C for 8 h, and then stirred

at room temperature for 8 h. After the solvent was removed under reduced pressure,

the residue was stirred in 50% acetic acid (2 mL) for 16 h at room temperature. The

mixture was concentrated and the residue was stirred in ammonia-saturated methanol

(5 mL) at room temperature for 4 h. The mixture was concentrated again to dryness to

give the crude protected nucleoside, which was dissolved in 2 N HCl (5 mL) and the

mixture was heated under reflux for 5 h. The mixture was then concentrated in

vacuum at 50 °C. The residue was purified by silica gel column with 15% MeOH in

CH_2Cl_2 to give 58 mg crude product which was further purified by HPLC (10-15% of

acetonitrile in water) to give compound **2.5.3** 23 mg (44%, yield). $[\alpha]^{26}_D$ −29.28° (c

0.1, DMF); UV λ_{max} 253.5 (ε=11954, PH=7), 255.5nm (PH=2), 269nm (PH=11); ^{1}H

NMR (DMSO-d_6+D_2O) δ 7.69 (s, 1H, 8-H) 5.17 (s, 1H, 7'-H), 5.04 (s, 1H, 7'-H),

4.66 (m, 2H, 2'-H, 3'-H), 4.25 (s, 1H, 1'-H), 3.64(m, , 1H, 6'-H), 3.52 (m, 1H, 6'-H),

2.38 (s, 1H, 4'-H) Anal. Calcd for $C_{12}H_{15}N_5O_4$·0.22Acetonitrile: C, 49.14; H, 5.16; N,

23.88. Found: C, 48.92; H, 5.10; N. 24.69. FAB MS Obsd: m/z 294. Calcd for

$C_{12}H_{16}N_5O_4$: m/z 294 $(M+H)^+$.

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