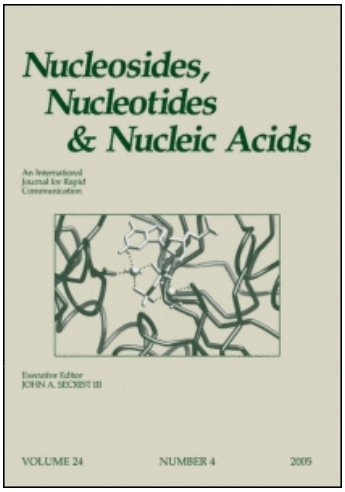


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

The Latest Progress in the Synthesis of Carbocyclic Nucleosides

Xue-Feng Zhu[a]
[a] Department of Chemistry, Texas A & M University, College Station, TX, USA

To cite this Article Zhu, Xue-Feng(2000) 'The Latest Progress in the Synthesis of Carbocyclic Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 19: 3, 651 — 690
To link to this Article: DOI: 10.1080/15257770008035015
URL: http://dx.doi.org/10.1080/15257770008035015

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(3), 651–690 (2000)

The Latest Progress in the Synthesis of Carbocyclic Nucleosides

Xue-Feng Zhu
Department of Chemistry, Texas A & M University, College Station,
TX 77842-3012, USA

ABSTRACT This review presents the latest developments in the field of *carba*-nucleosides (1994-1998). Special attention is paid to the synthesis of key precursors to those *carba*-nucleosides that possess significant biological activities or have novel structures.

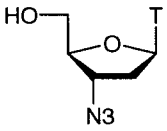
Contents

1. Introduction
2. Three-membered *Carba*-nucleosides
3. Four-membered *Carba*-nucleosides
4. Five-membered *Carba*-nucleosides
   - 4.1 Carbovir and related *Carba*-nucleosides
   - 4.2 Aristeromycin, neplanocin A and related *Carba*-nucleosides
   - 4.3 *Carba*-2′-deoxyguanosine, caclaradine, *Carba*-xylo-nucleosides and their related *Carba*-nucleosides
   - 4.4 Other five-membered *Carba*-nucleosides
5. Six- membered *Carba*-nucleosides
6. Bicyclic *Carba*-nucleosides

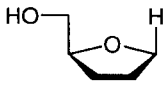
1. INTRODUCTION

Besides having been used as building units for the preparation of antisense oligonucleotides, nucleosides and their analogs have been widely studied as potential antitumor, antiinflammatory and antiviral agents. In the early 1980's, the acquired immunodeficiency syndrome (AIDS) epidemic was described and its causative agent, the

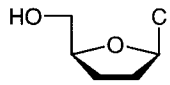
human immunodeficiency virus (HIV), was discovered. Since then, explosive fundamental research work has been carried out to identify substances effective against HIV and other viruses, in particular herpes simplex virus (HSV-1 and HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), which have been proven to be fatal to AIDS patients and other immune-compromised individuals.[1] As a result, quite a few nucleosides were found to show significant antiviral activity. Among them, AZT (3′-azido-3′-deoxythymidine) (**1**), ddI (2′, 3′-dideoxyinosine) (**2**), ddC (2′, 3′-dideoxycytidine) (**3**) and d4T (2′, 3′-didehydro-3′-deoxythymidine) (**4**) are four nucleosides approved by the FDA for the treatment of HIV infection as reverse transcriptase inhibitors.



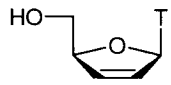
1 (AZT)



2 (ddI)

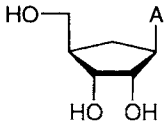


3 (ddC)

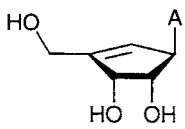


4 (d4T)

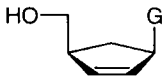
The clinical application of these nucleosides is greatly limited due to their inherent disadvantages such as toxicity, side effects and drug resistance; more seriously, some of them, such as ddI and ddC are substrates for enzymatic degradation.[2] Therefore, it is necessary to search for more stable and less toxic anti-HIV agents which are not cross-resistant with the existing drugs.



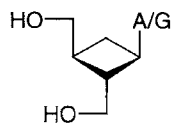
5



6



7



8/9

Carbocyclic nucleosides (*Carba*-nucleosides), where the furanose oxygen atom of the normal nucleosides is replaced by a methylene group, have received extraordinary attention over the last two decades. For example, the natural occuring *carba*-nucleosides aristeromycin (**5**) and neplanocin A (**6**) have been isolated from *Streptomyces citricolor* and *Actinoplanacea ampullariella*, respectively. Both **5** and **6** possess pronounced

activity. The synthetic *carba*-nucleosides carbovir (**7**), *carba*-oxetanocin A (**8**) and *carba*-oxetanocin G (**9**) are active against HIV. The direct result of this kind of replacement is that *carba*-nucleosides possess greater metabolic stability toward the phosphorylase enzymes which cleave glycosidic linkage of normal nucleosides. Furthermore, the comparatively higher lipophilicity of *carba*-nucleosides is potentially beneficial for increasing oral efficiency and cell wall penetration.[3]

The preparation of *carba*-nucleosides is composed of the following two crucial points: (i) the synthesis of the required *carba*-sugar moiety bearing the suitable functional groups; and (ii) the construction or introduction of the base moiety with high regio- and stereoselectivity. The first problem is the main point of a large body of synthetic work. The second problem is more easily resolved through the so called linear and convergent approaches, which have been extensively summarized in several excellent reviews.[4]

In this report, the latest developments in the field of *carba*-nucleosides, which have been reported in the literature from 1994 to 1998, are summarized. Special attention is paid to the synthesis of key precursors to those *carba*-nucleosides that possess significant biological activities or have novel structures. This review has been organized on the basis of size of the carbocyclic ring.

2. THREE-MEMBERED CARBA-NUCLEOSIDES

Three-membered *carba*-nucleosides can be generally divided into two types.[5] The first type are the cyclopropylmethyl analogs, which were synthesized as conformationally rigid rotamers of the *carba*-analogs of acyclovir **10** or ganciclovir **11**. They possess a methylene spacer between the base and the carbocyclic ring (Figure 1). Unfortunately, only few of them have very good activity.[5]

In 1998, Tsuji et al. reported that *carba*-nucleosides **12** exhibited strong antiviral activity. The 1′*S*,2′*R*-enantiomer **13**, when the base is guanine, has extraordinarily activity against HSV-1 and is nearly 20 times as potent as acyclovir **10** with better selectivity, and its anti-VZV potency is more than 10 times that of acyclovir.[6]

The synthesis of **13** is started from the optically active cyclopropane lactone **14** (>97% ee), which was prepared by condensation of diethyl malonate and *R*-(-)-

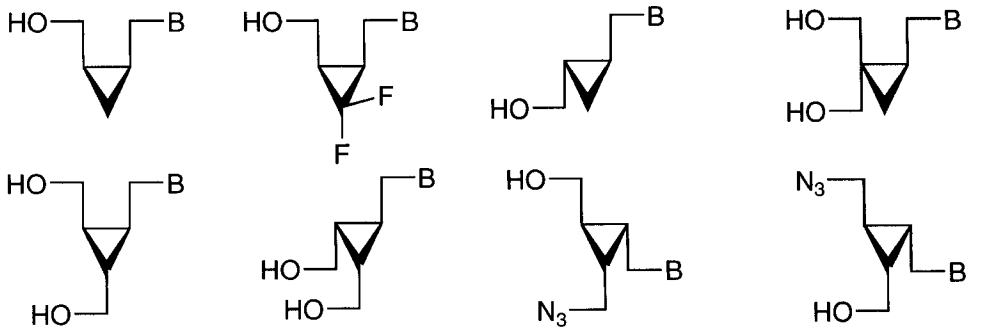
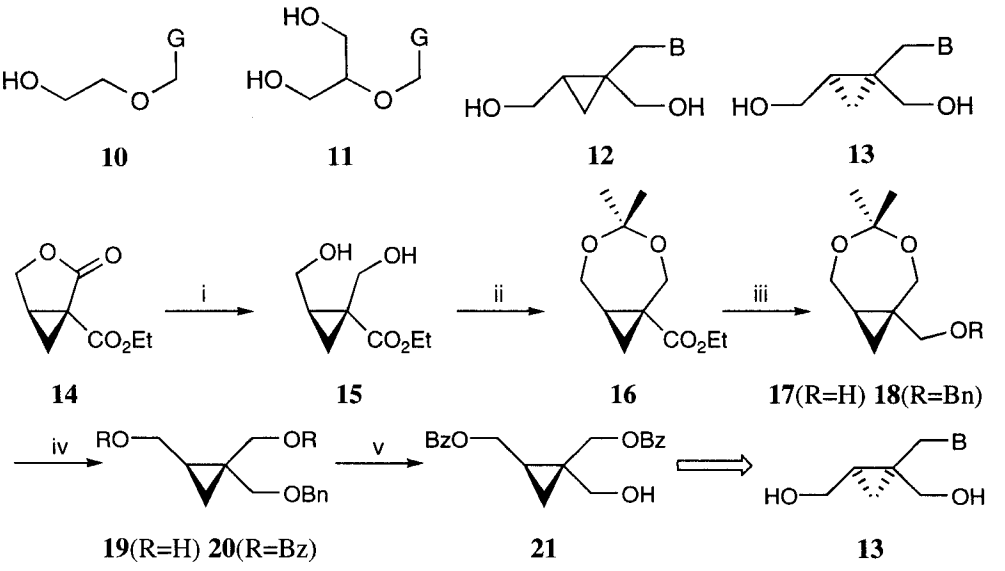


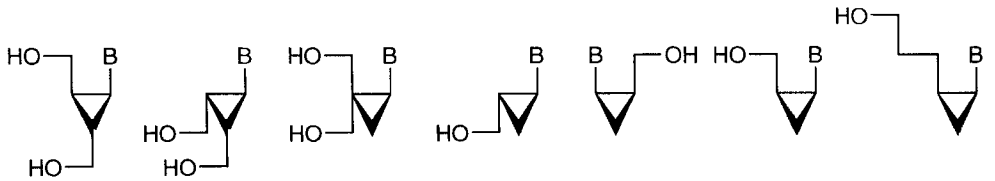
Figure 1. Some examples of synthetic three-membered *carba*-nucleosides



Scheme 1. (i) $NaBH_4$; (ii) 2,2-dimethoxypropane, cat. TsOH; (iii) $LiBH_4$; benzyl bromide, NaH; (iv) aq HCl; BzCl, pyridine; (v) H_2, Pd/C.

epichlorohydrin in ethanol under reflux in 65% yield. Treatment of **14** with $NaBH_4$ selectively reduced the lactone moiety to diol **15**, which was further transformed into an acetonide and then reduced to alcohol **17** by $LiBH_4$. After its hydroxy group was protected by benzylation, the resulting benzyl ether **18** was subsequently hydrolyzed to diol **19**. Benzoylation of **19**, followed by palladium catalyzed hydrogenation, afforded **21** as a key precursor to **13** (Scheme 1).[6]

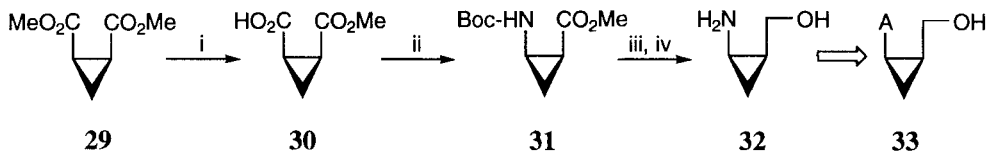
The second type of cyclopropyl *carba*-nucleosides, **22-25**, whose bases directly link to the ring, can be considered as ring contracted analogs of *carba*-oxetanocin. Although some derivatives of this type have been prepared in recent years, most of them do not display significant biological activity *in vitro* or *in vivo*; furthermore, none of the above mentioned cyclopropyl *carba*-nucleosides were synthesized *via* asymmetric procedures or from optically active intermediates. As a result, only racemic mixtures were obtained. More recently, the enantioselective synthesis of novel cyclopropyl *carba*-nucleoside such as **26-28** has received attention.



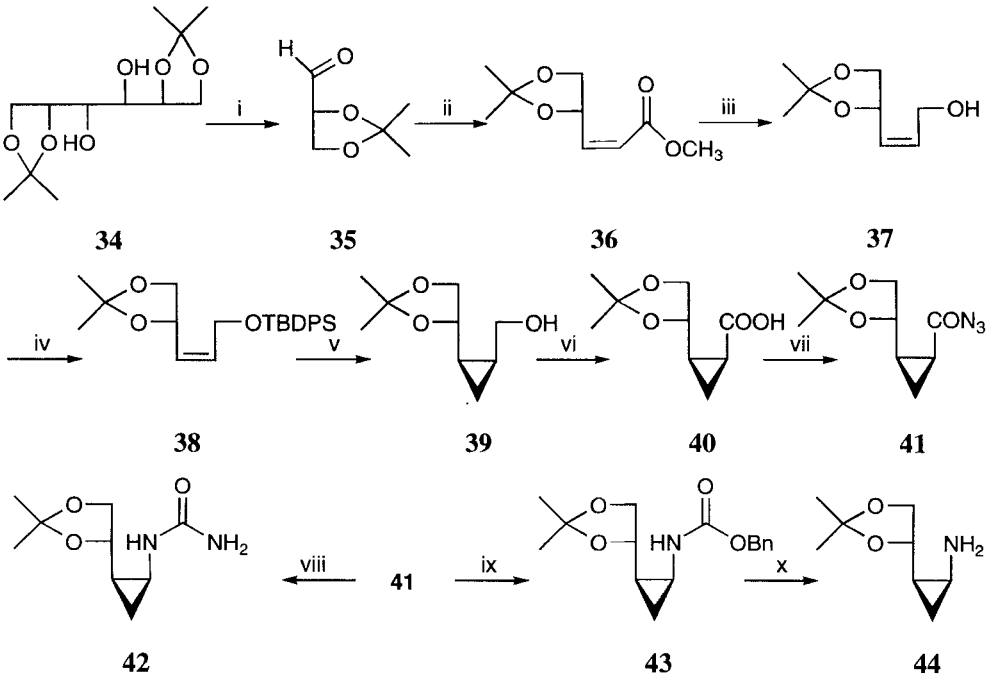
22 **23** **24** **25** **26** **27** **28**

Csuk and von Scholz[7] chose *meso*-diester **29**, which can be easily obtained in 39% yield from the reaction of methyl acrylate with methyl chloroacetate in the presence of sodium hydride. Treatment of **29** with pig liver esterase (PLE) at pH = 7.2 afforded (-)-**30** (ee ≥ 99.5%). Curtius degradation of the carboxylate moiety resulted in the formation of the N-Boc protected (-)-**31**, which was reduced with diisobutylaluminium hydride (DIBAH) at -78°C and subjected to acidic hydrolysis of the amide to give (-)-*cis*-**32** as a key precursor. Finally, adenine was built by the linear approach to provide the *L*-like *carba*-nucleoside (-)-**33** (Scheme 2).

The second general synthetic strategy was developed by Chu's group.[8] They started the synthesis from 1,2:5,6-di-*O*-isopropylidene-*D*-mannitol **34** as a chiral source. Optically pure cyclopropylmethyl alcohol **39** is the first key intermediate, which was prepared by a six-step procedure from **34** in high overall yield (62%) (Scheme 3). **39** was oxidized with $NaIO_4$ / RuO_2 to obtain acid **40**, which was treated with Et_3N and chloroethyl formate followed by the treatment with sodium azide to give acyl azide **41**. The Curtius rearrangement of **41** was carried out in toluene at 100°C followed by the introduction of anhydrous ammonia gas or benzyl alcohol to yield urea derivative **42** and

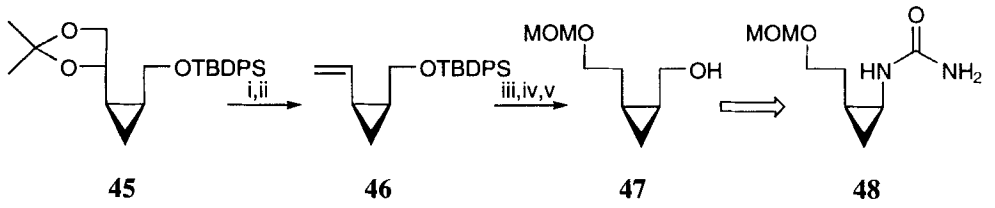


Scheme 2. (i) PLE, pH 7.2, 26°C, 7d, 90%. (ii) t-BuOH, Et_3N, DPPA, 50-55°C, 16h, argon, 47%. (iii) DIBAH, toluene, -78°C, argon, 54%. (iv) 6N HCl, 40-45°C, 3h, 57%.



Scheme 3. (i) $Pd(OAc)_4$, ethyl acetate, 5-10°C, 3h; Na_2CO_3, 30 min, 99%. (ii) $Ph_3P{=}CHCO_2Me$, MeOH, rt, overnight, 81%. (iii) DIBAH, CH_2Cl_2, -78°C, 30 min, argon, 84%. (iv) TBDPSCl, imidazole, DMF, rt, 2h, 96.5%. (v) $ZnEt_2$, ClCHI, CH_2Cl_2, 0°C, 20 min, 95.5%. (vi) $NaIO_4/RuO_2$, $CH_3CN/CHCl_3/H_2O$, 16h. (vii) Et_3N, ethyl chloroformate, acetone, 0°C, 1h; NaN_3. (viii) NH_3, toluene, 90-100°C, 5h. (ix)BnOH, toluene, 100°C, 87%. (x) H_2, Pd-C, 95%.

benzyl carbamate **43**, respectively. Catalytic hydrogenolysis of **43** provided cyclopropylamine **44**. Afterwards, **42** and **44** were used as key precursors for the preparation *D*-like *carba*-nucleosides **27** (B = C, U, T, A, H, G) by a linear approach. It is noteworthy that the *L*-cyclopropyl *carba*-nucleosides can also be synthesized by this approach if the 1,2:5,6-di-*O*-isopropylidene-*L*-mannitol is used as the starting material.[8d]

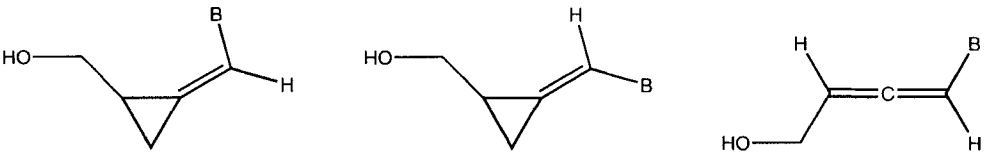


45 46 47 48

Scheme 4. (i) 80% AcOH; $NaIO_4$, MeOH or $Pd(OAc)_4$, EtOAc. (ii) $Ph_3P{=}CH_2$, THF, 68% for two steps. (iii) BH_3, THF; 30% H_2O_2, 1N NaOH. (iv)MOMCl, iPr_2NEt. (v) n-Bu_4NF, THF, 42% for three steps.

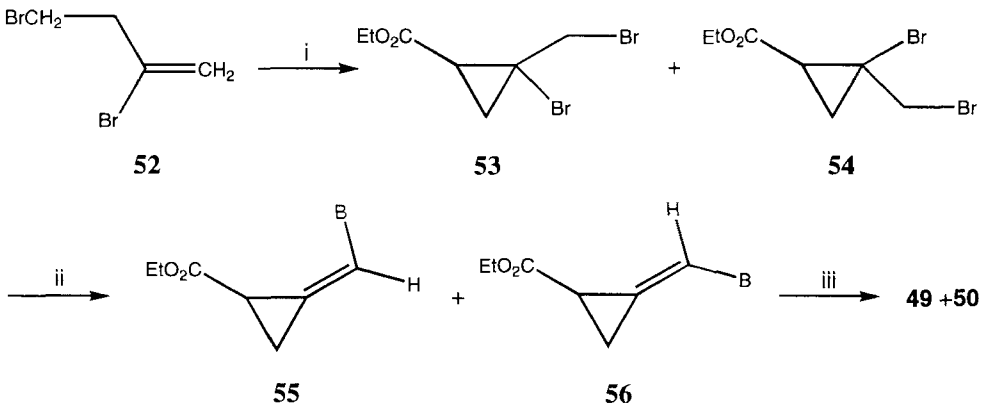
D-cyclopropyl *carba*-nucleosides **28** (B =U, T) were prepared by a similar strategy, which is outlined in Scheme 4.[8e]

A new kind of three-membered *carba*-nucleoside (**49**, **50**) with broad-spectrum antiviral activity was reported by Zemlicka et al in 1998.[9a] The design of these compounds was based on the popular viewpoint that introduction of a rigid structural element into nucleosides or *carba*-nucleosides can lead to effective antiviral analogs. They introduced a double bond as a linker between the heterocyclic base and cyclopropyl moiety. Because of the similarity of a double bond and cyclopropane ring, both **49** and **50** can also be regarded as analogs of adenallene and cytallene **51** (B=A,C), which can effctively inhibit the replication of HIV.[9b] Both **49** and **50** are very effective agents against human cytomegalovirus (HCMV), murine cytomegalovirus(MCMV) and EBV.



49 **50** **51**

The synthetic route to **49** and **50** is shown in Scheme 5. Addition of ethyl diazoacetate to 2,3-dibromopropene **52** proceeded smoothly to give a mixture of *E*- and *Z*-isomers **53** and **54** in 91% yield. The *E*/*Z* ratio is 1.5:1. Then, reaction of dibromo esters **53** and **54** with base using K_2CO_3 in DMF at 100°C for 22h gave a mixture of **55**

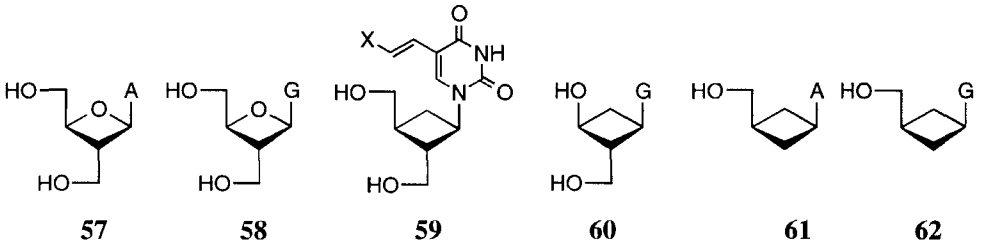


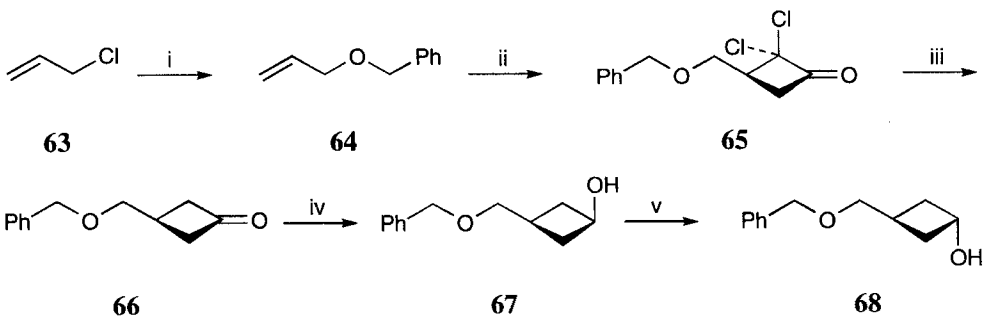
Scheme 5. (i) N_2CHCO_2Et, $Rh_2(OAc)_4$, CH_2Cl_2. (ii) K_2CO_3, DMF. 100°C. (iii) DIBALH, THF

and **56** in 39% yield and with an improved *Z*/*E* ratio (2:1). Reduction of esters **55** and **56** using DIBALH afforded a mixture of **49** and **50** in 75%. The main problem with this method is that **49** and **50** are poorly separable by column chromatography.

3. FOUR-MEMBERED CARBA-NUCLEOSIDES

The synthesis of cyclobutane *carba*-nucleosides was inspired by the unique structure and biological activity of oxetanocin A (**57**).[5a] Oxetanocin A is the first and only known example of a naturally occurring four-membered ring nucleoside. Both **57** and its synthetic analog oxetanocin G (**58**) display good antiviral activity, especially against HIV. In order to overcome the instability of the oxetanosyl-N-glycosyl linkage, *carba*-oxetanocin A (**8**) and *carba*-oxetanocin G (**9**) were synthesized and have shown excellent antiviral activity.





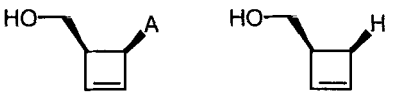
Scheme 6. (i) $PhCH_2OH$, $PhCH_2NEt_3Cl$, conc. aq.NaOH, rt, 96%. (ii) Cl_3CCOCl, $POCl_3$, Zn-Cu couple, ether, reflux, 50%. (iii) Zn dust, AcOH, reflux, 68%. (iv) L-Selectride, THF, -78°C, 90%. (v) 4-$(O_2N)C_6H_4CO_2H$, Ph_3P, DEAD, THF, rt; NaOH, aq. 1,4-dioxane, rt, 66%.

Encouraged by these exciting achievements, many chemists endeavoured to synthesize related *carba*-nucleosides, and a number of analogs of oxetanocin were consequently obtained.[5a,10] Some of them displayed potent antiviral activity, for instance, racemic *carba*-oxetanosyl 5-(halovinyl)uracil (**59**) (X = Cl, Br, I) had excellent activity against VZV (about ten fold more potent than acyclovir), and 2′-*nor*-*carba*-oxetanocin G (**60**) showed antiviral activity comparable to that of acyclovir against HSV-1, HSV-2, VZV, and was about ten fold more potent than acyclovir against human cytomegalovirus (HCMV).

More recently, Kaiwar et al. developed a novel and more efficient approach to make modified *carba*-oxetanocins **61** and **62**, which protected cells against the cytopathogenic effects of HIV in MT2 and ATH8 cells (Scheme 6).[11] Allyl benzyl ether **64** was prepared in 96% yield, followed by addition with dichloroketene to give the dichlorocyclobutanone **65**. The latter was converted to **66** on heating with zinc dust in glacial acetic acid. Asymmetric reduction of the ketone with *L*-Selectride afforded a ~20:1 mixture of the diastereoisomeric alcohols **67** and **68**. **67** can be transformed into **68** by Mitsunobu reaction, followed by the saponification of the resulting ester. With **68** in hand, the target *carba*-nucleosides **61** and **62** can be prepared by a convergent approach.

A short and efficient approach for the preparation of cyclobutene nucleosides **69** and **70**, considered to be norcarbovir analogs, was demonstrated by Huet.[12] However, both **69**

and **70** were found to be inactive against HIV-1, HIV-2 *in vitro* (CEM4 cells) as well as antitumor tests (KB cells).

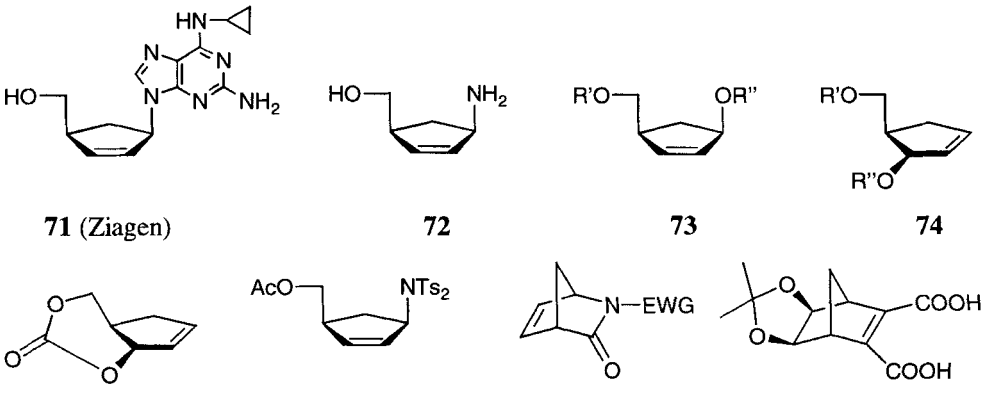


69 **70**

4. FIVE-MEMBERED CARBA-NUCLEOSIDES

4.1 Carbovir and related *carba*-nucleosides

(-)-Carbovir (**7**) was prepared for the first time by Vince's group in 1988 and was shown to have similar potency to AZT (**1**) in selectively inhibiting HIV reverse transcriptase.[13] However, (-)-carbovir was removed from clinical trial test due to its pharmacokinetic and toxicological deficiencies. More recently, a new reverse transcriptase inhibitor Abacavir (1592U89) (**71**),[14] which has a higher oral bioavailability and can penetrate the central nervous system (CNS) as well as AZT, has been approved as a drug in the US under the trade name of Ziagen.



71 (Ziagen) **72** **73** **74**

75 **76** **77** **78**

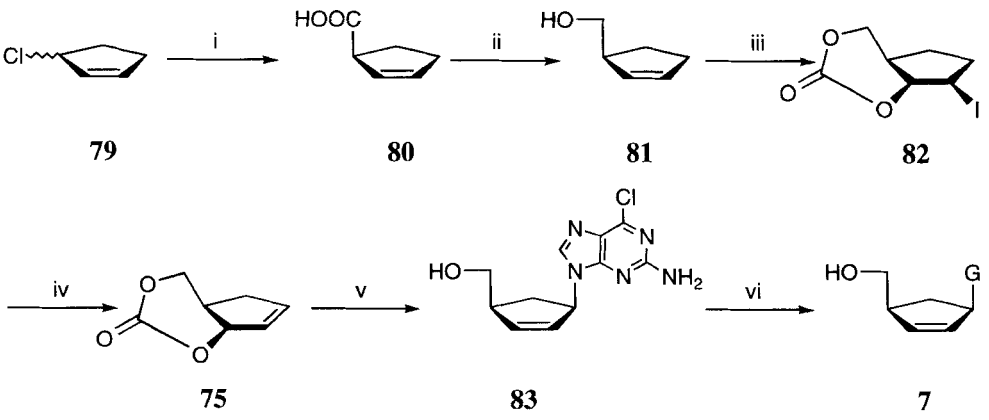
The fascinating antiviral potency of (-)-carbovir and Ziagen triggered an explosive synthetic effort of preparation of carbovir derivatives. Strategies employed were: (i)

synthesis from natural (-)-aristermomycin A (**5**);[15] (ii) linear approaches with stepwise construction of the guanine moiety from precursor (1*R*, 4*S*)-1-amino-4-(hydroxymethyl)-2-cyclopentene (**72**);[16] (iii) Another attractive and powerful convergent approach for the enantioselective synthesis of (-)-carbovir involves Trost's palladium-catalyzed nucleophilic coupling of purine bases with allylic carbonates or acetates, such as **73**,[17] **74**,[17d,18] **75**,[19] and even acetoxy tosylamide (**76**),[20] 2-substituted 2-azabicyclo[2.2.1]hept-5-ene-3-one (**77**),[19] hemiester (**78**).[22]

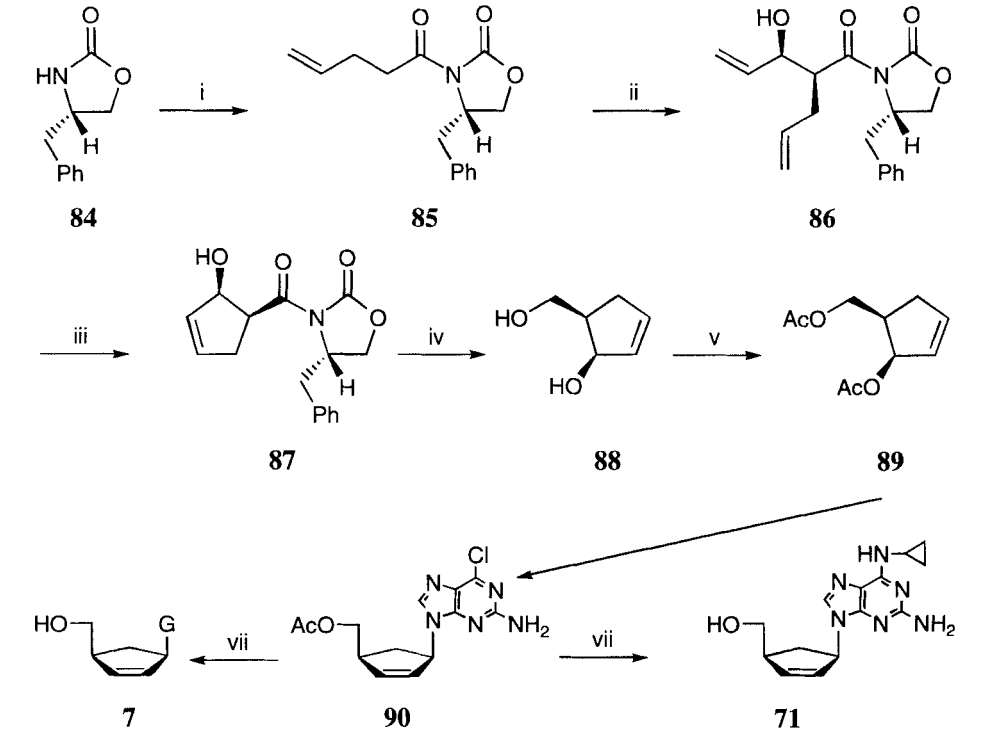
Herein we only briefly introduce Scheffold's and Crimmins' synthetic routes to (-)-carbovir. Scheffold et al. chose (*S*)-(cyclopent-2-enyl) methanol (**81**) as the starting material. Homoallylic alcohol **81** was easily prepared from racemic 3-chlorocyclopentene (**79**) by a two-step procedure in 54% overall yield (ee 98%). Sequential treatment of the homoallylic alcohol (-)-**81** at rt with BuLi, CO_2 and I_2 in THF led to the crystalline cyclic iodocarbonate **82**. Elimination of HI from **82** was effected with DBU under a vigorous stream of CO_2 to give the key precursor **75**. Reaction of **75** with 2-amino-6-chloropurine in THF / DMSO with 10% Pd(0) catalyst yielded (-)-carbovir precursor **83** in 59% yield. Hydrolysis of **83** with 0.33 M NaOH gave (-)-carbovir in 71% yield (Scheme 7).[19a]

An efficient alternative approach was developed by Crimmins and King recently.[17d] Their artful approach to (-)-carbovir and Ziagen relied on the realization that the combination of an asymmetric aldol condensation with a ring closure metathesis reaction can provide rapid entry into functionalized, enantiomerically pure carbocycles (Scheme 8).

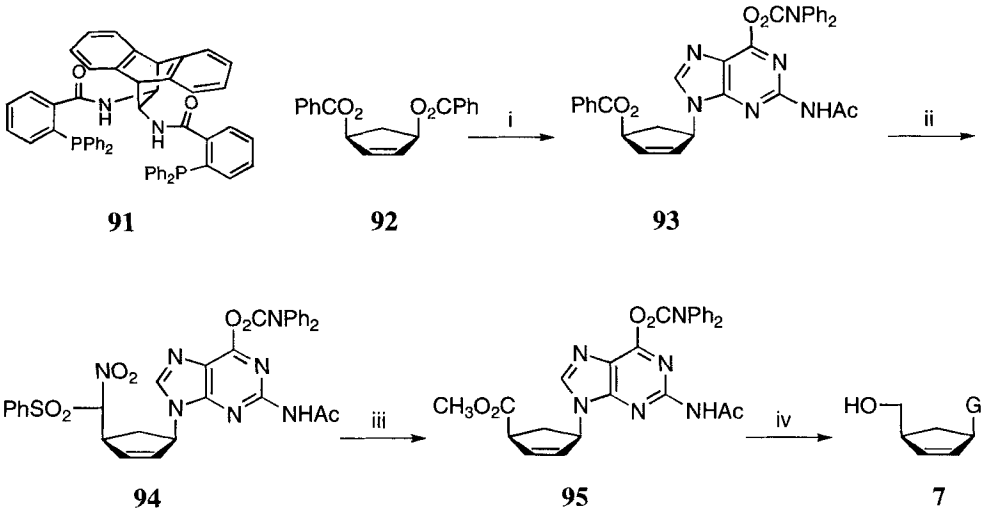
Condensation of lithiated (*S*)-4-benzyl-2-oxazolidinone (**84**) with pentenoic pivalic mixed anhydride provided **85**. Use of the Evans' dialkyl boron triflate protocol for diastereoselective *syn* aldol condensation with acrolein produced product **86** (de > 99%). The ring closure was accomplished by exposure of a CH_2Cl_2 solution of diene **86** to 10% of the Grubbs catalyst to form the cyclopentenol **87**, which was reduced to diol **88** with lithium borohydride. Diol **88** was then converted to diacetate **89**, followed by reaction of **89** with 2-amino-6-chloropurine in the presence of Pd(0) catalyst and sodium hydride to give an 86:14 mixture of the *carba*-nucleoside **90** (65% yield after chromatography) and the corresponding N7 coupling product (not shown). Treatment of the chloropurine **90** with cyclopropylamine in ethanol followed by hydrolysis of the acetate produced **71** in 81% overall yield. Alternatively, direct hydrolysis of **90** with sodium hydroxide produced (-)-carbovir.



Scheme 7. (i) Mg(0), THF, then CO_2; recrystallization as (-)-(α-phenylethyl)amine salt. (ii) $LiAlH_4$, ether, 54% overall yield. (iii) BuLi, then CO_2, I_2, THF, 53%. (iv) DBU, CO_2, toluene, 90°C, 63%. (v) 2-amino-6-chloropurine, allylpalladium chloride dimer, PPh_3, THF/DMSO, 59%. (vi) 0.33 M NaOH, 71%.



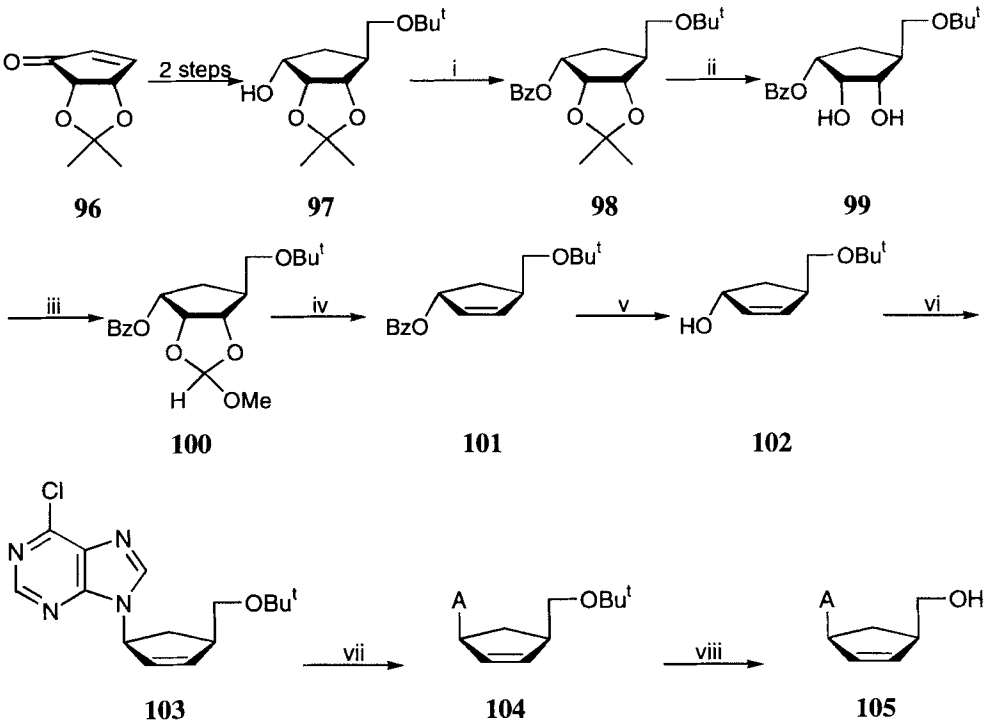
Scheme 8. (i) n-BuLi, THF, pentenoic pivalic mixed anhydride, -78°C, 99%. (ii) Bu_2BOTf, Et_3N, CH_2Cl_2, CH_2=CHCHO, -78°C, 82%. (iii)PhCH=Ru[$P(C_6H_{11})_3$]$_2Cl_2$, CH_2Cl_2, 97%. (iv) $LiBH_4$, THF, MeOH, 78%. (v)Ac_2O, CH_2Cl_2, Et_3N, DMAP, 90%. (vi) 2-amino-6-chloropurine, THF/DMSO(1:1),, NaH, $Pd(PPh_3)_4$, 65%. (vii) cyclopropylamine, EtOH; aq. NaOH, 81%. (viii) aq. NaOH, 68%.



Scheme 9. (i) $(\eta^3\text{-}C_3H_5PdCl)_2$, ligand, base, THF/DMSO, 0°C, 8h, 59%. (ii) phenylsulfonylnitromethane, Et_3N, THF, 1.5mol % of Pd(0) cat., PPh_3, rt, 99%. (iii) tetrabutylammonium-oxone, $MeOH/CH_2Cl_2$, 71%. (iv) a. calcium borohydride in THF; b. aq ammonia, 61%.

All of the above described approaches to (-)-carbovir involved optically pure precursors that were prepared before *carba*-sugar coupling with the base. More recently, Trost developed an outstanding approach that included a so-called enantiodiscriminating step in the palladium-catalyzed desymmetrization of a *meso*-diester with nucleophilic base.[23] This efficient approach allowed them to achieve (-)-carbovir in four steps. Thus, the *meso*-dibenzoate **92** reacted with base in the presence of $(\eta^3\text{-}C_3H_5PdCl)_2$ and ligand **91** at 0°C to afford the desired product **93** (ee > 98%). Treatment of **93** with phenylsulfonylnitromethane under Pd(0)-catalyzed conditions gave **94**. Chemoselective oxidative cleavage gave the ester **95**. Subsequent reduction with calcium borohydride followed by an aqueous ammonia work-up yielded (-)-carbovir in 61% yield (Scheme 9).

(+)-Carbovir and its analogs also can be prepared similarly by the approaches described above. Another synthetic route to (+)-carbovir analog **105**, which involved Mitsunobu nucleophilic coupling, was demonstrated by Chu et al in 1998.[24] This strategy started from the optical active alcohol **97**, which can be prepared by regioselective addition to the known enone **96** followed by DIBALH reduction. Benzoylation of the



96 97 98 99

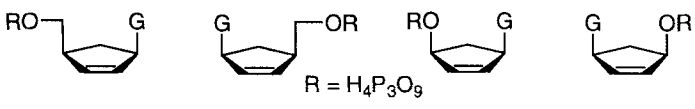
100 101 102

103 104 105

Scheme 10. (i) BzCl, pyridine, rt 12h, 93%. (ii) concd HCl:MeOH (1:70, v/v), rt, 2.5h, 93%. (iii) $CH(OMe)_3$, pyridinium toluene-p-sulphonate, rt, 2h. (iv) Ac_2O, 120-130°C, 3h, 68% from **99**. (v) 2N NaOH/MeOH, rt, 1.5h, 93%. (vi) 6-chloropurine, Ph_3P, diethyl azodicarboxylate, dioxane, rt, 10h, 35%. (vii) NH_3/MeOH, 80-90°C, 20h, 83%. (viii) CF_3CO_2H/H_2O (2:1), 50°C, 3h, 93%.

hydroxy group of **97** gave **98**, from which the acetal group was selectively removed to form the diol **99**. Treatment of **99** with trimethyl orthoformate afforded the cyclic orthoester, which was subsequently subjected to a thermal elimination reaction with acetic anhydride to form the cyclopentane **101**. Finally, the heterocyclic base was introduced by a Mitsunobu reaction as shown in Scheme 10.

(+)-Carbovir was found to be less active as an anti-HIV agent than (-)-carbovir *in vitro* tests.[5] However, it has been shown that the triphosphates **106** and **107** are approximately equipotent as HIV-RT inhibitors.[18a,25]



106 107 108 109

(-)-5′-Norcarbovir, (+)-5′-norcarbovir and their corresponding triphosphate analogs **108** and **109** have also been reported.[26] Interestingly, **108** showed good activity as an inhibitor of HIV-RT, being approximately equipotent to the triphosphate of (-)-carbovir. The enantiomer **109**, surprisingly, showed even greater activity as an inhibitor of HIV-RT. Some novel 5′-norcarbovir analogs and corresponding triphosphates have been reported recently.[27]

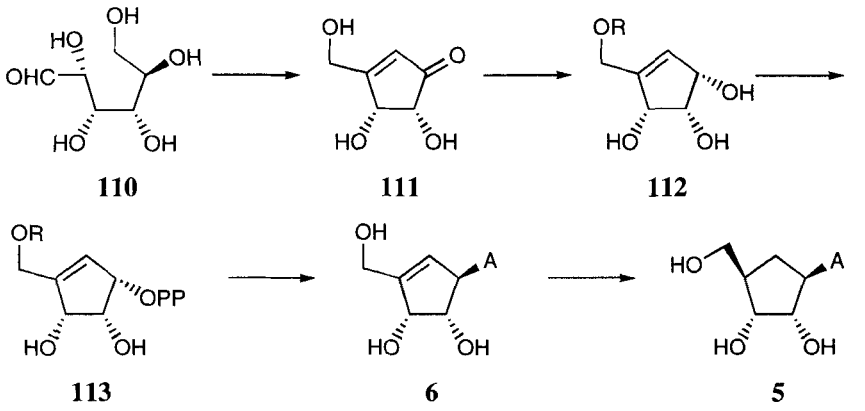
Additional carbovir analogs such as *trans*-carbovir,[28] 4′-hydroxyethyl substituted carbovir,[29] 2′-fluoro carbovir[30] and *C*-nucleoside analogs[31] have been synthesized. However, their biological activity has not yet been described.

4.2 Aristeromycin, neplanocin A and related *carba*-nucleosides

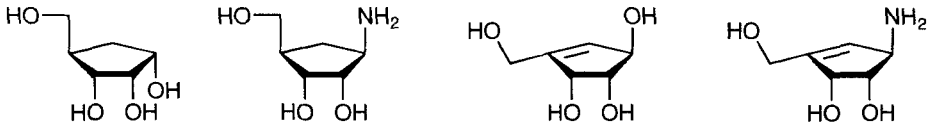
Aristeromycin (**5**) and neplanocin A (**6**) are two naturally occurring *carba*-nucleosides produced by certain prokaryotic organisms. Structurally, **5** and **6** are closely related, differing only in the presence in **6** of a double bond between at C4′ and C1a′; both contain a carbocyclic ribose ring to which is attached an adenine ring at C1′. Studies on the biosynthesis of aristeromycin and neplanocin A suggested that **6** is the direct precursor of aristeromycin and the carbocyclic ring is derived from *D*-glucose **110** *via* tetrol **112** as a key intermediate (Scheme 11).[32]

Aristeromycin and neplanocin A have been shown to possess potent biological activity. For example, aristeromycin can inhibit cell division and elongation in rice plants and prohibit AMP synthesis in mammalian cells; neplanocin A exhibits broad-spectrum antiviral and antitumor activity; both aristeromycin and neplanocin A are good inhibitors of *S*-adenosylhomocysteine hydrolase (*S*-AdoHcy-ase). Owing to their potential use as therapeutic agents, efficient synthetic approaches to aristeromycin and neplanocin A have consequently been the subject over the past decades.[32]

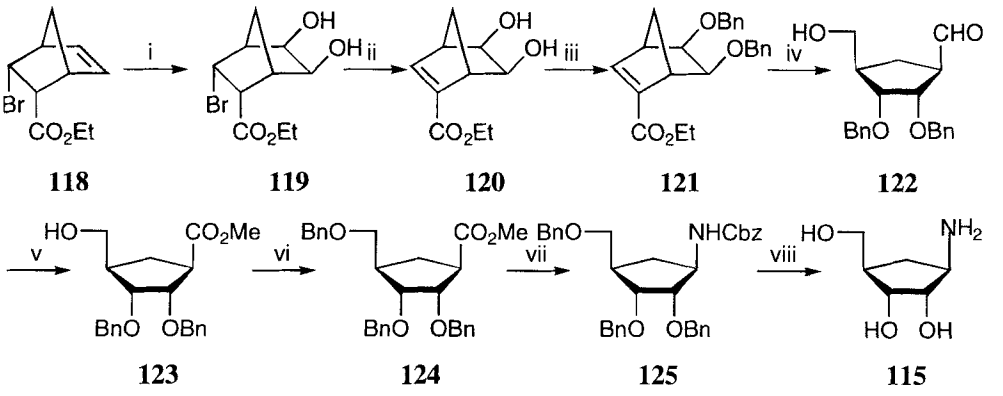
Aristeromycin and neplanocin A can be prepared, at least in principle, *via* the following precursors: the saturated tetrol **114**, aminotriol **115**, the unsaturated tetrol **112**, its corresponding C1-epi-tetrol **116**, and the unsaturated aminotriol **117**. Surprisingly, most of the recently reported approaches have only employed aminotriol **115** as precursor for aristeromycin[33] or the unsaturated tetrol **112** as precursor for neplanocin A.[34]



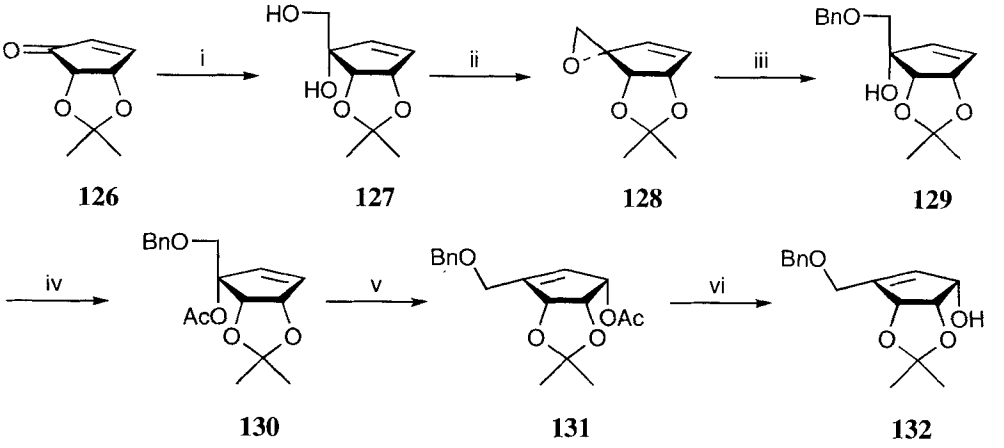
Scheme 11. A proposed pathway for the biosynthesis of aristeromycin and neplanocin A.



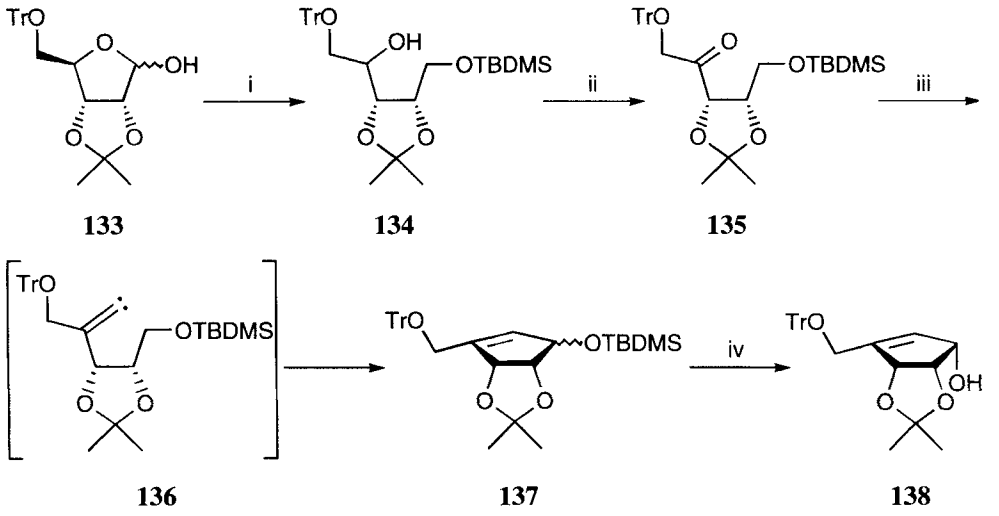
Leahy's approach to **115** started from (-)-**118**, which was easily prepared by Hawkins' asymmetric Diels-Alder reaction in excellent yield (94%) and with high enantioselectivity (ee = 95.4%).[35] Dihydroxylation of **118** with OsO_4 / NMO from the least hindered face of the bicyclic system afforded diol **119**, which underwent elimination of the bromide with DBU to give **120**. The bisbenzyl ether **121** was formed by treating **120** with benzyl bromide in the presence of silver oxide and 3Å molecular sieves. Ozonolytic cleavage of **121** followed by reductive workup and periodate oxidation generated labile aldehyde **122**, which was immediately oxidized to ester **123** with bromine in methanol. The primary alcohol of **123** was protected under the same condition previously described for **121**. Ester **124** was then converted into the corresponding acyl azide *via* standard protocol, and Curtius rearrangement in the presence of benzyl alcohol yielded fully protected cyclopentane **125**. Complete deprotection with sodium in ammonia provided the known aminotriol **115**. With 11 steps and 13% overall yield, it represented one of the most efficient approaches reported to date (Scheme 12).[33c]



Scheme 12. (i) N-methylmorpholine N-oxide, OsO_4, acetone/H_2O(4:1), 40°C, 13h, 74%. (ii) DBU, ether, rt, 24h, 97%. (iii) BnBr, benzene, 3Å sieves, Ag_2O, 0°C-rt, 23h, argon, 80%. (iv) O_3, CH_2Cl_2/CH_3OH (38:1), -78°C; $LiBH_4$, THF, 0°C-rt, 20h; $NaIO_4$, THF/H_2O (3:1), pH 5 rt, 2h. (v) Br_2, CH_3OH/H_2O(9:1), rt, 1h, 66%. (vi) same as (iii). (vii) hydrazine, EtOH, reflux, 46h; N_2O_4, CCl_4, -78°C, 2h; BnOH, benzene, reflux, 36h, 67%. (viii) NH_3/Na, THF/CH_3OH(20:1), -78°C, 2h, 61%.



Scheme 13. (i) $ClCH_2I$, BuLi, THF, -78°C, 15min, 99%. (ii) KOH, MeOH, rt, 20min, 98%. (iii) BnONa, THF, rt-40°C, 1d, 94%. (iv) Ac_2O, Et_3N, DMAP(cat.), CH_2Cl_2, rt, 1d, 99%. (v) $PdCl_2(MeCN)_2$(cat.), pBQ, THF, 55°C, 3.5h, 92%. (vi) aq. KCO_3, MeOH, rt, 20 min, 94%.



Scheme 14. (i) $LiAlH_4$, ether, 85%; TBDMSCl, imidazole, DMF, 97%. (ii) $(COCl)_2$, DMSO then, Et_3N, CH_2Cl_2, 89%. (iii) TMSC(Li)N_2, THF, 0°C, 1h, 55-65%. (iv) Bu_4NF, THF, 69%; PDC, CH_2Cl_2, 80%; $LiAlH_4$, THF, 87%.

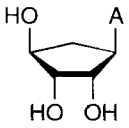
Nokami and co-workers developed a short and efficient approach to the unsaturated alcohol **132**.[34b] Starting from the known synthon **126**, **132** can be obtained, as shown in Scheme 13, in six steps and 78% overall yield.

Ohira et al. reported a novel approach for preparation of protected alcohol **138** starting from *D*-ribose, using a C-H insertion reaction of a methylidene carbene as a key step (Scheme 14).[34c] Protected *D*-ribose **133** was reduced with $LiAlH_4$ to give a diol whose primary hydroxyl group was subsequently protected as silyl ether **134**. Swern oxidation of the secondary alcohol provided the ketone **135**. Treatment of **135** with 3 eq. of lithium (trimethylsilyl)diazomethane at 0°C generated the alkylene carbene **136**, which was inserted to the C-H bond adjacent to the protected hydroxyl group, and the cyclopentene derivative **137** was obtained in 55-65% yield as 2.7:1 epimeric mixture. The major product has the undesired stereochemistry. Without separation, the TBDMS-group was removed, and oxidation of the epimers with PDC followed by the reduction with $LiAlH_4$ yielded the desired alcohol **138** as a single stereoisomer.

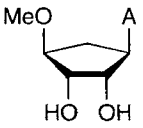
More recently, Matsuda employed this methodology for synthesizing (-)-neplanocin A from adenosine in seven steps. The significance of this approach is that the (-)-neplanocin A was obtained from its furanose counterpart for the first time. However, further studies are needed to improve the yield and selectivity of the C-H insertion reaction.[36]

The (+)-aristeromycin and its thymidine analog were devoid of antiviral activity.[37] In contrast, 3-deazaaristeromycin, 8-azaaristeromycin and N6-methylaristeromycin were all good inhibitors of *S*-AdoHcy-ase, and this activity correlated well with their antiviral effects against vaccinia virus (VV). 5′-Deoxyaristeromycin, isolated from *Streptomyces citricolor*, displayed excellent activity against VV and vesicular stomatitis virus (VSV).

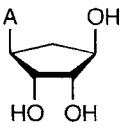
Another promising analog of aristeromycin is (-)-5′-noraristeromycin **139**, which is found to have a broad-spectrum of antiviral activity similar to that of other adenosine analogs that target S-AdoHcy-ase showing good activity against VV and VSV, parainfluenza type 3, measles, respiratory syncytial virus (RSV) and HCMV. In addition, the lack of reactive 5′-OH group prevents enzymatic phosphorylation and avoids the formation of toxic 5′-phosphate. Therefore **139** was much less cytotoxic than aristeromycin.[38] (+)-5′-Noraristeromycin **141** shows good activity against hepatitis B virus (HBV)[39] and (+)-7-deaza-5′-noraristeromycin has been found to be a good anti-trypanosomal agent.[40] Meanwhile, C-4′-*O*-methylated analogs **140** and **142** were found to be much less effective, revealing that a free hydroxyl hydrogen at C-4′ was essential for the biological properties of 5′-noraristeromycin.[41]



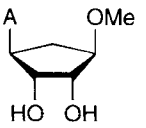
139



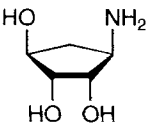
140



141

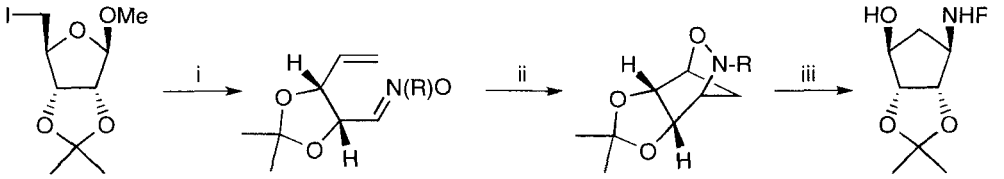


142



143

Amine **143**, a key intermediate in the preparation of (-)-5′-noraristeromycin **139**, could be easily synthesized from *D*-ribose *via* an intramolecular nitrone cycloaddition reaction (Scheme 15).[42] Another approach was illustrated by Ranganathan starting from



144 **145** **146** **147**

Scheme 15. (i) Zn, EtOH, reflux, 1h; RNHOH, EtOH, 15min. (ii) chlorobenzene, reflux, 30min, 33-70% overall yield. (iii) Zn, acetic acid, ether, rt, 48h, 78-99%.

the easily accessible 2-aza-3-oxabicyclo[2.2.1]heptene hydrochloride. However, only racemic **143** can be prepared at present.[43]

A great number of analogs of neplanocin A also have been synthesized. Some analogs, such as the cytidine analog of neplanocin A, 3-deazaneplanocin A, (6′R)-6′-C-methylneplanocin A (RMNPA), (6′R)-6′-C-ethynylneplanocin A (RENPA), 6′-homoneplanocin A (HNPA),[36] and 2-Fluoro neplanocin A,[44] displayed significant antiviral activity.

4.3 *Carba*-2′-deoxyguanosine, Cyclaradine, *carba-xylo*-nucleosides and their related *carba*-nucleosides

Many *carba*-2′-deoxynucleosides have potent and selective activity as antiviral agents. In particular, *carba*-2′-deoxyguanosine (*carba*-2′ dG) and *carba*-2′-deoxy-5[(E)-2-bromovinyl]uridine (C-BVDU) have emerged as two of the most impressive analogs of this group over the past years. *Carba*-2′ dG has broad-spectrum antiviral activity against HSV-2,[45a] HCMV[45b] and hepatitis B virus (HBV),[45c] while C-BVDU possesses a complementary activity against HSV-1[45d] and VZV.[45e]

Recently, Lang and Moser developed an efficient method for the preparation of enantiomerically pure *carba*-2′-deoxynucleosides in 12 steps and 9-12% overall yield.[46] They started their synthesis from the known cyclopentene diol **148**. Thus, **148** was first converted to the silanediyl derivatives **149** by using the bis(triflate) reagent. Hydroformylation of **149** was carried out under pressurized H_2 / CO atmosphere in the

presence of a Rh-catalyst to give a single diastereoisomer, (+/-)-**150**. Reduction of **150** with $NaBH_4$, tritylation with (chloro)triphenylmethane and removal of the silanediyl group by the treatment with Bu_4NF gave (+/-)-**153**. Diol **153** was then resolved by enzymatic transesterification using *Pseudomonas fluorescens* lipase (PFL) in vinyl acetate to give (-)-**154** (ee > 98%) and (-)-**155** (ee> 99%). Selective deprotection was performed by treatment of (-)-**154** with ethylenediamine to give the trityloxy-diol (+)-**156**. The diol (+)-**156** was treated with a slight excess of $SOCl_2$ in CH_2Cl_2 /Et_3N and the resulting cyclic sulfite was subsequently oxidized with $RuCl_3$ / $NaIO_4$ to give cyclic sulfate (+)-**157**. The bases or base precursors were then introduced specifically at C1′ position, and following the proper hydrolysis or ammonolysis work-ups, *carba*-2′-deoxynucleosides **158** were obtained in good yields (Scheme 16).

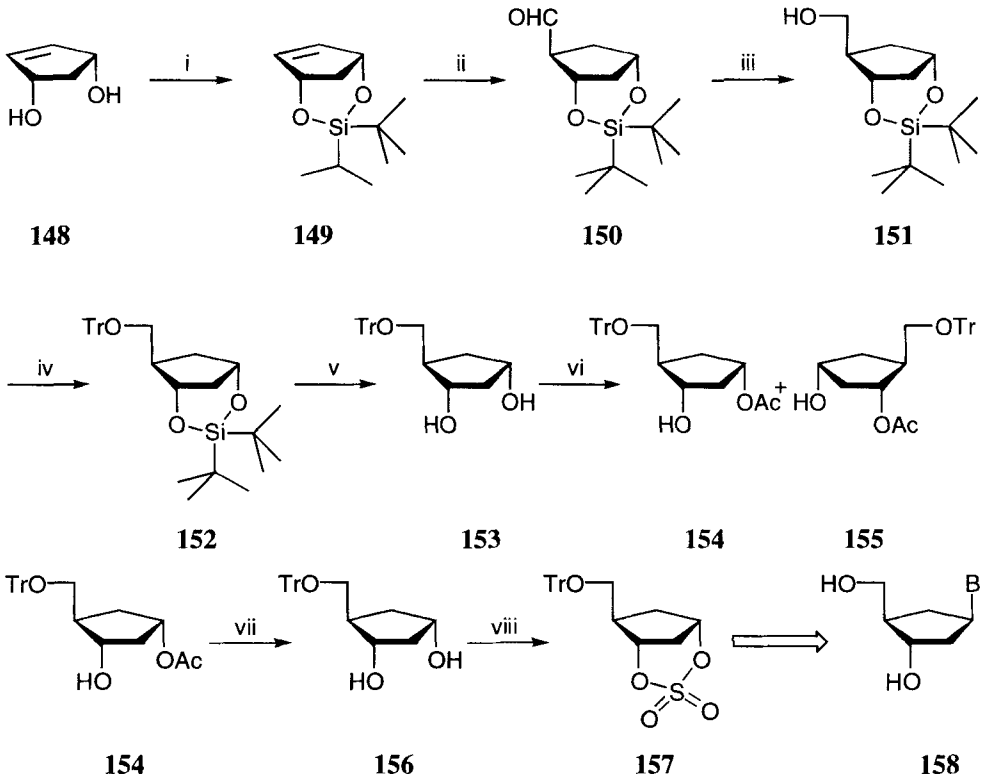
Soon after, Borthwick et al. reported their efficient strategy for the preparation of a chiral precursor of 2′-dG which involved an asymmetric cyclopentone reduction to the corresponding alcohol (de > 98%) using *Mucor circinelloides*.[45f,47]

Unlike the general *carba*-2′-deoxynucleosides, which are normally synthesized from corresponding triol precursor, the preparation of C-BVDU **164** started from its amino diol precusor **159** because of its unnatural heterocyclic base. Scheme 17 shows the synthetic route to C-BVDU developed by Wyatt et al.[48] The stereospecific preparation of aminodiol **159** was demonstrated by Brayl et al.[49]

In 1998, Roberts et al. reported another synthetic strategy for 2′-deoxy carbocyclic nucleosides utilizing the relatively readily available carbovir analogs (Scheme 18).[50] Treatment of carbovir analog **165** with NBS or bromoacetate afforded **166** as the sole product in 68% yield. Debromination of **166** was accomplished by using radical reaction and 2′-deoxy carbocyclic nucleoside **168** can be obtained in high yield.

Ara-A **169** has a broad-spectrum activity against viruses, however, it is very easily deaminated by adenosine deaminase to form Ara-H **170**, which is much less active than Ara-A. This situation greatly limits the clinical utility of Ara-A. For example, Ara-A is used in the treatment of HSV infection only as a drug for external use.[51,52]

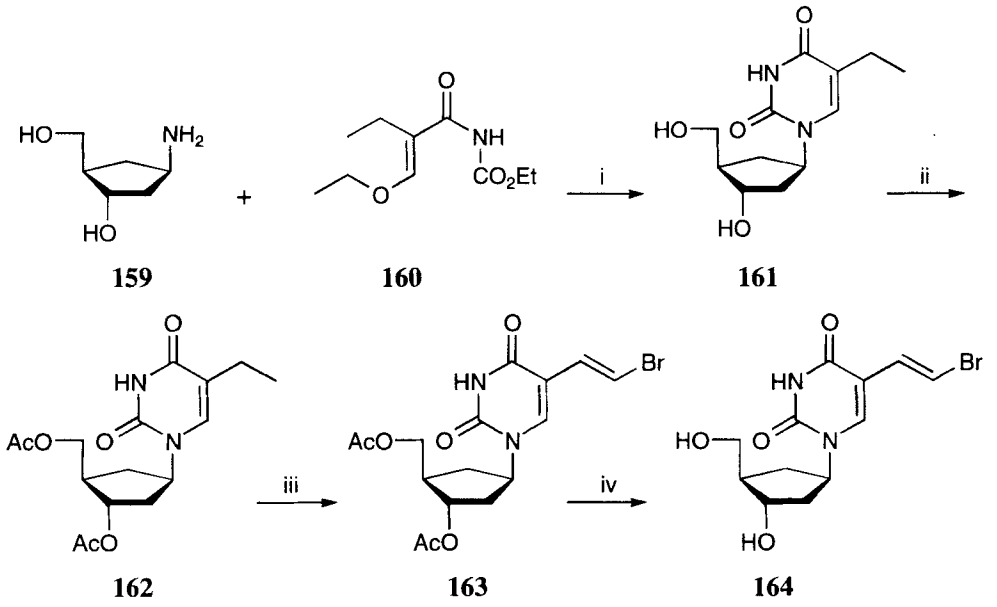
To overcome the deamination problem, cyclaradine (*carba*-Ara-A) **171** became an obvious synthetic target as an adenosine deaminase-resistant Ara-A derivative. (-)-*L*-enantiomer of **171** was found to be completely ineffective for inhibition of virus



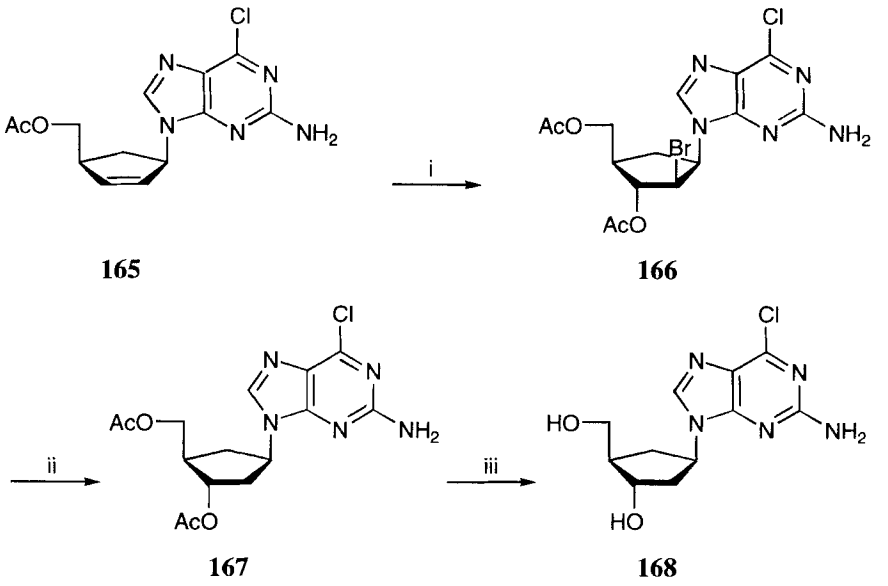
Scheme 16. (i) $(t\text{-}Bu)_2Si(SO_3CF_3)$, 2,3-lutidine, CH_2Cl_2, 0°C, 30 min, 80%. (ii) 0.4 mol % $[RhCl(PPh_3)_3]$, THF, H_2/CO at 80 bar, 80°C, 5h, 95%. (iii) $NaBH_4$, THF/H_2O (9:1), rt, 10 min, 98%. (iv) TrCl, DMAP, Et_3N, CH_2Cl_2, rt, 18h, 88%. (v) Bu_4NF/H_2O, THF, rt, 5h, 100%. (vi) 20 weight % of PFL, vinyl acetate, rt, 50h, 89%. (vii) ethylenediamine, MeOH, 50°C, 15h, 95%. (viii) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 19 min; MeCN/CCl_4, H_2O, 1.5mol % of $RuCl_3$, $NaIO_4$, 0°C, 1h, 100%.

replication, therefore, much effort has been made to synthesize the (+)-*D*-cyclaradine **171**. Unfortunately, clinical evaluation of **171** never started due to its toxicity in animals.

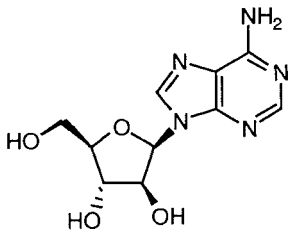
Yoshikawa et al. reported their approach to (+)-**171** starting from *D*-arabinose as a chiral source (Scheme 19).[51] This approach involved a stereoselective nitromethane addition reaction to form a branched nitropyranose as a key step, but this route is of little practical value because of the lengthy procedure (20 steps) and low overall yield (~ 3.6%). More recently, Katagiri et al. demonstrated a highly efficient synthesis of (+)-**171** from (-)-2-azabicyclo[2.2.1]hept-5-en-3-one (**172**), which is commercially available.[52] This method



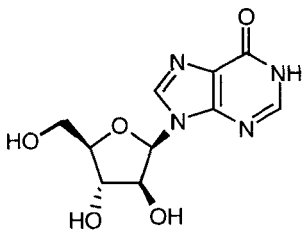
Scheme 17. (i) NEt_3, dioxane; 2% 2N HCl in dioxane. (ii) Ac_2O, DMAP, dioxane. (iii) NBS/dioxane or $Br_2/CHCl_3$. (v) NaOH, EtOH or H_2O.



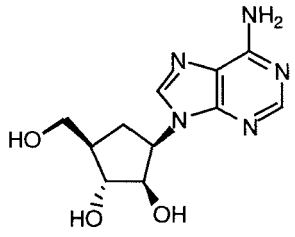
Scheme 18. (i) NBS or *N*-bromoacetamide, AgOAc, AcOH, 18h, rt, 47-69%. (ii) Bu_3SnH, AIBN, THF, heat, 3-7h, 68-92%. (iii) K_2CO_3, MeOH, 2h, 96%.



169



170



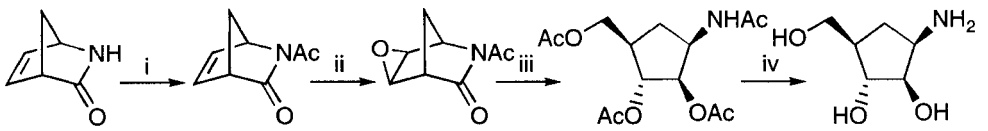
171

included the following key steps: (i) the stereo-controlled epoxidation of bicyclic amide **173**, (ii) the reductive amide bond cleavage reaction (RAC reaction) by $NaBH_4$ and (iii) the regioselective cleavage of the epoxide by neighboring participation. Thus, (-)-**172** was acetylated with acetic anhydride to give N-acetyl bicyclic amide (-)-**173**. The acetyl group served as an electron-withdrawing group to faciliate the RAC reaction and induce neighboring participation. Epoxidation of (-)-**173** with *m*-CPBA afforded *exo*-epoxide (-)-**174** as the sole product. The epoxide (-)-**174** was then subjected to the RAC reaction using $NaBH_4$, followed by acetylation to give the carbocyclic arabinofuranosylamine tetraacetate (+)-**175**. Acidic hydrolysis of (+)-**175** with 2N HCl followed by treatment with ion-exchange resin yielded the amine (+)-**176** as precursor for 2′-dG. The base (guanine) can be built up using a conventional linear approach.

A series of *carba*-nucleosides with *xylo*-configuration have been reported by Griengl's group recently (Scheme 20).[53] The heterocyclic bases were introduced regiospecifically using ring opening of the key epoxide **181** by bases in alkaline medium. This synthetic work began with racemic norbornenone **177**, which was first transformed into lactone **178** by Baeyer-Villiger oxidation. The lactone ring was then opened using KOH in dioxane, the secondary hydroxy group of the resulting diol was selectively protected by benzylation to give carboxylic acid **179**. After the carboxy group was converted into isocyanate by Curtius degradation, it was further transformed into ester **180**. Treatment of **180** with *m*-CPBA afforded epoxide **181** as a key precursor to *carba-xylo*-nucleosides **183**.

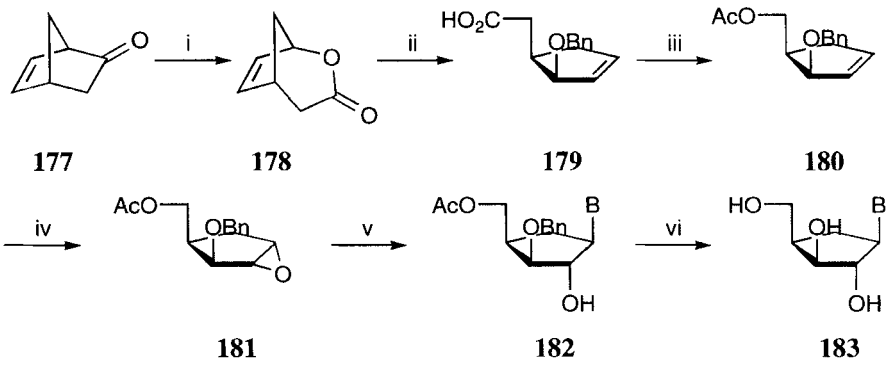
4.4 Other cyclopentyl *carba*-nucleosides

The synthesis of five-membered *carba*-nucleosides is still one of the most active and fasinating fields of nucleoside chemistry. Besides the *carba*-nucleosides described above,



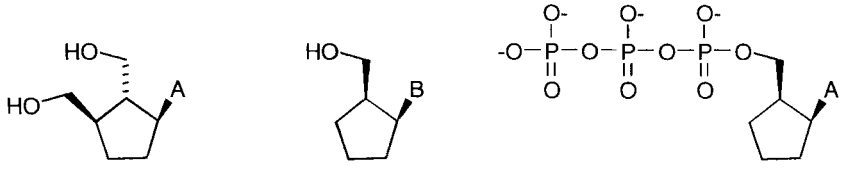
172 173 174 175 176

Scheme 19. (i) Ac_2O, Et_3N, DMAP, $CHCl_3$, rt, 4h, 78%. (ii) *m*-CPBA, $CHCl_3$, rt 72h, 68%. (iii) $NaBH_4$, MeOH, 30 min; Ac_2O, pyridine, 1h, 63%. (iv) 2N HCl, 70°C, 1h, 100%.

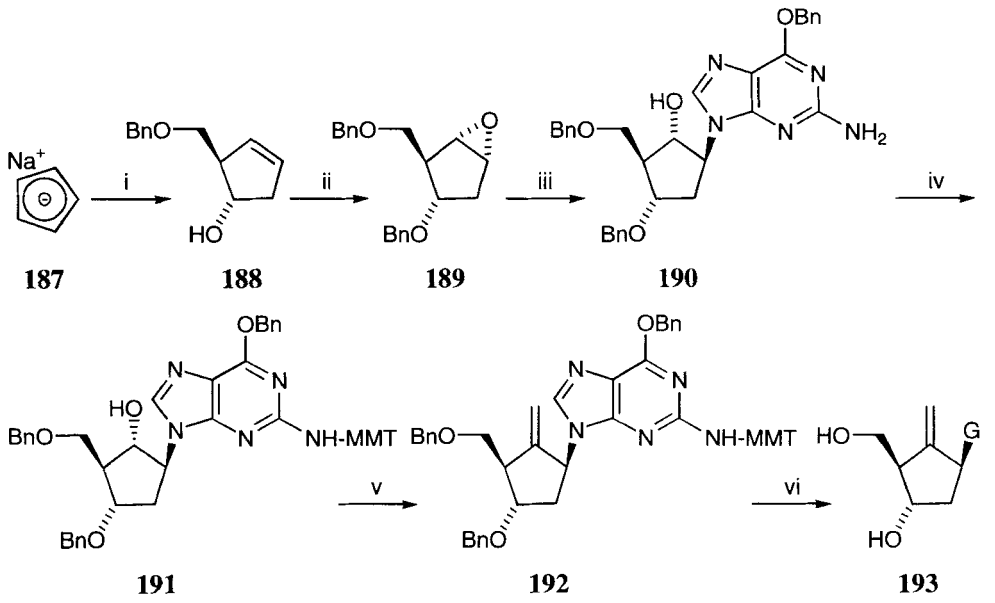


Scheme 20. (i) diethyl ether/H2O/H_2SO_4/H_2O_2. (ii) KOH/1,4-dioxane, reflux; benzyl bromide, reflux. (iii) ethyl chloroformate/Et_3N/acetone, NaN/H_2O, toluene/reflux; $NaNO_2$/acetic acid/CH_2Cl_2. (iv) *m*-CPBA/toluene, reflux. (v) Et_3Al/base/THF, rt. (vi) CH_3ONa/CH_3OH; H_2/Pd-C(10%)/CH_3OH.

many cyclopentyl *carba*-nucleosides with novel structures have been synthesized and their biological activities have been screened. For example, (-)-BCA **184** has been shown to be a good inhibitor of HIV,[54] 1,2-disubstitued *carba*-nucleosides **185** were synthesized as potential antiviral agents,[55] the corresponding triphosphate analogs **186** emerged as strong inhibitors of terminal deoxynucleotidyl transferase (TdT).[56]



184 185 186



Scheme 21. (i) $BnOCH_2Cl$, THF, -65 to -78°C; diisopinylcampheyllborane, THF, -65 to -78°C; aq NaOH, H_2O_2, 75%. (ii) $VO(acac)_2$, t-BuOOH, CH_2Cl_2; BnBr, NaH, Bu_4NI, DMF, 83%. (iii) 6-benzyloxy-2-aminopurine, LiH, DMF, 125°C, 60%. (iv) 4-monomethoxytrityl chloride, TEA, DMAP, CH_2Cl_2, 82%. (v) Dess-Martin reagent, t-BuOH, CH_2Cl_2; Nysted reagent, $TiCl_4$, THF, 75%. (vi) aq. HCl, THF, MeOH, 55°C; BCl_3, CH_2Cl_2, -78°C,82%.

In 1997, Bisacchi et al. reported a practical 10-step asymmetric synthesis of BMS-200475 (**193**), which is a remarkably potent inhibitor of HBV *in vitro* with relatively low cytotoxicity.[57] The known chiral cyclopentyl epoxide **189** (96.6-98.8% ee) is a useful synthon for the preparation of **193** and can be obtained from commercially available sodium cyclopentadienide in 63% overall yield in three steps. Treatment of **189** with 6-benzyloxy-2-aminopurine and LiH in DMF at 125°C gave the N-9 adduct **190**, the purine amino group of which was then protected by monomethoxytrityl (MMT) group. Dess-Martin oxidation of **191** followed by Nysted methylenation afforded **192** in 75% overall yield. After deprotection of purine and debenzylation of the hydroxy group **193** was obtained in 82% overall yield (>99% ee) (Scheme 21).

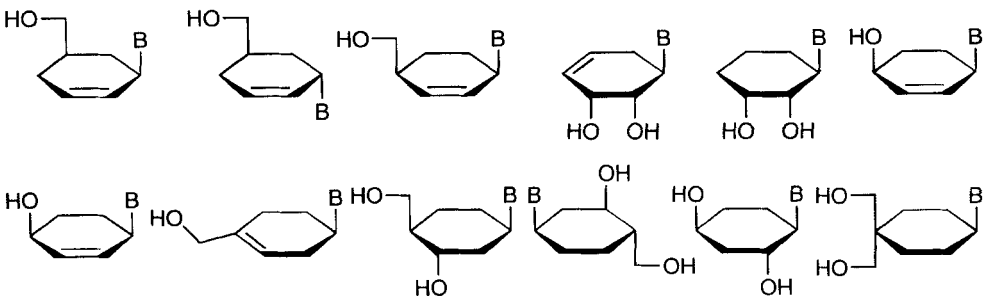
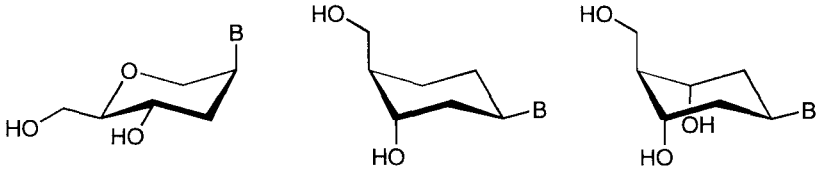


Figure 2. Some examples of synthetic six-membered *carba*-nucleosides

5. SIX-MEMBERED CARBA-NUCLEOSIDES

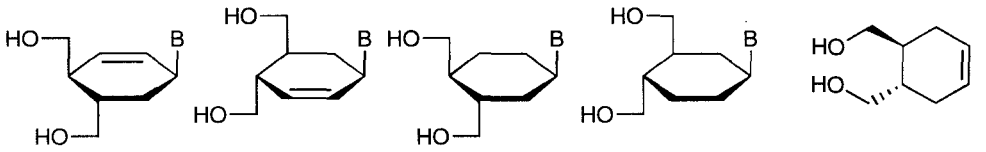
Despite the fact that quite a few six-membered *carba*-nucleosides have been synthesized and evaluated in the past several years (Figure 2), none of them has shown significant activity.[58]

Herdewijn et al. considered that conformation is a decisive factor which is responsible for the inactivity of six-membered *carba*-nucleosides against viruses.[59] They compared the antiviral activity of anhydrohexitol nucleosides **194** with their carbocyclic congeners **195**, and found that nearly all activity disappeared when the oxygen atom was replaced by a methylene group. The loss in antiviral activity also paralleled a change in conformation. The structure of the anhydrohexitol nucleosides **194** with their axially positioned base moiety resembles the structure of a furanose nucleoside in its Northern (2′ *exo* / 3′ *endo*) puckered conformation, whereas the carbocyclic analogs **195** mimic Southern conformation. In other words, the high structural similarity between anhydrohexitol nucleosides **194** and C3′-*endo* puckered furanose nucleosides, and the lack of this similarity in the case of carbocyclic congeners **195**, might explain their differences in activity against HSV-1 and HSV-2. This explanation was further supported by their recent work of 2-(hydroxymethyl)-cyclohexane-1,3-diol *carba*-nucleosides **196**, which are also inactive. Despite the fact that **196** has three axial substituents, the base moieties are still equatorially oriented.[60]



194 **195** **196**

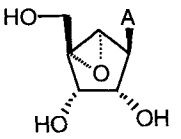
Another disappointing fact is that almost all of the six-membered nucleosides were only synthesized in racemic form. More recently, **197**, **198** and their corresponding saturated analogs **199** and **200** have been prepared in enantiomerically pure form by Samuelsson and co-workers. This approach was based on the successful resolution of the racemic starting diol **201**, *via* a lipase-catalyzed transesterification process. Once again, unfortunately, **197-200** were found to be inactive against HIV. Further screening against other viruses is under way.[61]



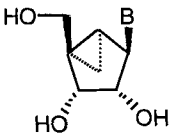
197 **198** **199** **200** **201**

6. BICYCLIC CARBA-NUCLEOSIDES

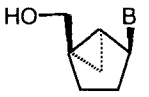
As we have seen, the conformation of nucleosides plays a very important role in modulating their biological activity. Inspired by the crystal structure of neplanocin C (**202**), a naturally occurring carbocyclic nucleoside, a series of conformationally equivalent bicyclo[3.1.0]hexane systems were chosen to generate rigid nucleosides with a conformation typical of a Northern geometry (2′-*exo* / 3′-*endo*). Both **203** and **204** were synthesized and evaluated for their inhibitory effect on *S*-AdoHcy-ase or for anti-HIV activity as rigid Northern conformers. Unfortunately, only the adenine analog of **203** showed considerable activity.[5]



202



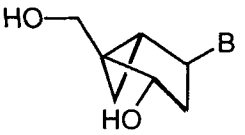
203



204

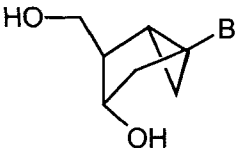
4′, 1′a-Methanocarbocyclic nucleosides **205-209** and 1′, 1′a-methanocarbocyclic nucleosides **210-214** are two types of bicyclic *carba*-nucleosides that were studied amply and systematically (Figure 3). 4′, 1′a-Methanocarbocyclic thymidine **205** and 1′, 1′a-methanocarbocyclic thymidine **210** were primarily synthesized and incorporated into oligonucleotides to evaluate their potential usefulness in antisense applications by Swiss chemists.[62] Altmann and co-workers found that the modified oligonucleotides containing **205** exhibited increased binding affinity (ΔT_m/mod. = 0.8 ~ 2.1°C) for complementary RNA as compared with their unmodified counterparts. On the contrary, the modified oligonucleotides containing **210** displayed a decreased binding affinity for complementary RNA (ΔT_m/mod. = -1.1 ~ -1.9°C) or DNA (ΔT_m/mod. = -2.5 ~ -4.4°C).[62]

Marquez et al. subsequently found that the antiviral activity of these two types of bicyclic *carba*-nucleosides had a very similar phenomena. Among 4′, 1′a-methanocarbocyclic nucleosides, **205**, **207**, and **208** have shown significant antiviral activity. In contrast, all compounds with a Southern conformation were devoid of antiviral activity, except for **213**, the anti-HCMV potency of which is slightly better than that of its Northern pseudorotational antipode. Marquez deemed that the distinct biological activity could be attributed to their distinct conformations.[63] In the cases of 4′, 1′a-methanocarbocyclic nucleosides, the conformation of the pseudosugar mimics that of a 2′-deoxysugar locked in the Northern hemisphere of the pseudorotational cycle, whereas in 1′, 1′a-methanocarbocyclic nucleosides, the pseudosugar mimics a 2′-deoxysugar locked in the Southern hemisphere. These two assumed conformations were supported by the crystal structures of **205** and **210**.[62] Other 4′, 1′a-methanocarbocyclic nucleosides, where a hydroxymethyl was introduced to replace hydroxy group in the 3′-position, were synthesized by Jeong and Marquez.[64] Very surprisingly, these compounds were inactive against HIV. This fact indicated that not only the conformation but also the 3′-substituent were responsible for the biological activity.



$_2$E (C2'-*exo*, North)

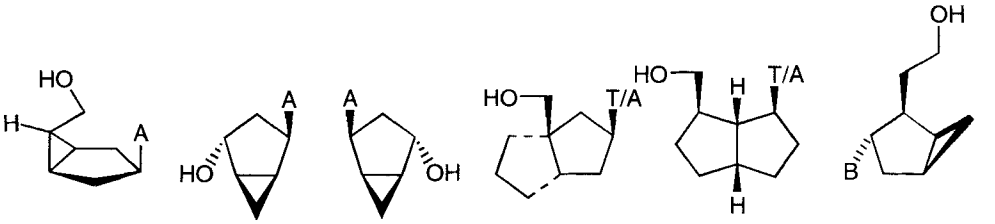
205	B=thymine	[(N)-*methanocarba*-T]
206	B=uracil	[(N)-2'd-*methanocarba*-U]
207	B=cytosine	[(N)-2'd-*methanocarba*-C]
208	B=adenine	[(N)-2'd-*methanocarba*-A]
209	B=guanine	[(N)-2'd-*methanocarba*-G]



$_3$E (C3'-*exo*, South)

210	B=thymine	[(S)-*methanocarba*-T]
211	B=uracil	[(S)-2'd-*methanocarba*-U]
212	B=cytosine	[(S)-2'd-*methanocarba*-C]
213	B=adenine	[(S)-2'd-*methanocarba*-A]
214	B=guanine	[(S)-2'd-*methanocarba*-G]

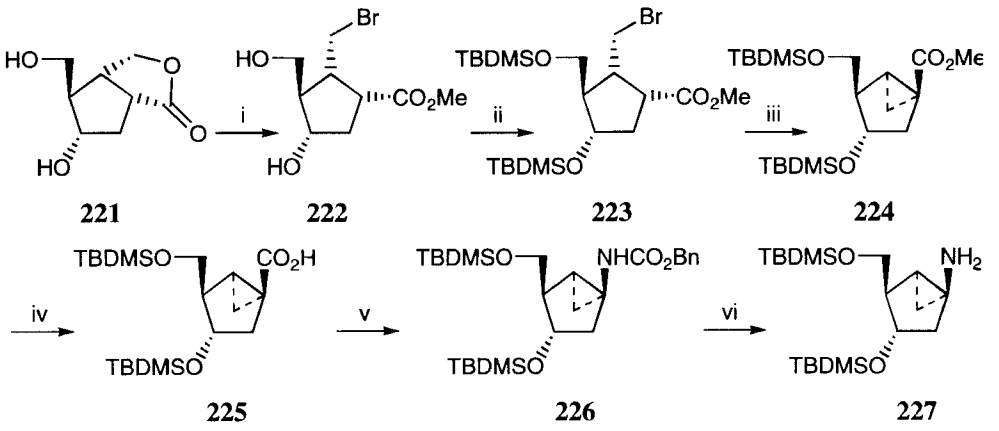
Figure 3. The conformations of 4', 1'a-*methanocarba*-nucleosides and 1', 1'a-*methanocarba*-nucleosides



215 **216** **217** **218** **219** **220**

Over the past few years, some novel *carba*-nucleosides built on varied bicyclic systems, such as **215-220**, have been reported, but data about their biological activity has not been published.[65] Therefore, only the preparation of 4', 1'a-methanocarbocyclic nucleosides and 1', 1'a-methanocarbocyclic nucleosides will be presented here.

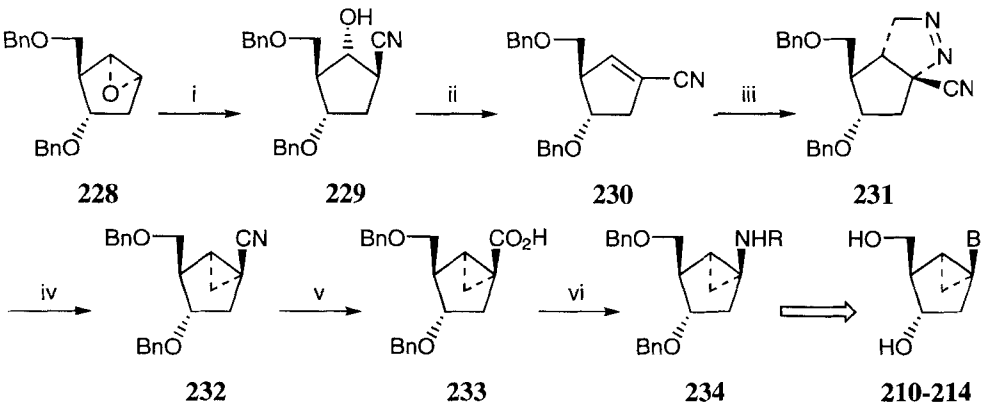
Because of the instability of the bicyclo[3.1.0]hexane system, all of the heterocyclic bases were recommended to be constructed from a suitably OH-protected bicyclic amine by a linear approach. The first synthesis of 1', 1'a-methanocarbocyclic nucleoside was reported by Altmann et al. (Scheme 22).[62b] They employed the known chiral bicyclic lactone **221** as the starting material. Opening of the lactone ring with TMS-Br / MeOH gave γ-bromoester **222**, which was immediately converted to its bis-TBDMS ether **223**. Treatment of **223** with KOBu^t in t-BuOH at 0°C yielded **224**, followed by saponification of **224** with KOH / EtOH at 80°C gave bicyclic acid **225**. The latter was converted to the



Scheme 22. (i) TMSBr (10 equiv.), MeOH, ZnBr (cat.), 0°C, 18h, 70%. (ii) N-TBDMS, N-methyl acetamide (3 equiv.), DMF, 0°C-rt, 2.5h, 64%. (iii) KOBu^t, t-BuOH, rt, 30 min, 76%. (iv) KOH/EtOH, 80°C, 5h, 78%. (v) a. DPPA, Et_3N, toluene, 0°C, 1h, rt, 1h; b. 80°C, 2h; c. BnOH, 0°C, 2h, 100°C, 15 min, 85%. (vi) H_2, Pd-C, toluene, 84%.

benzyloxycarbonyl protected amine **226** by a 3-step one-pot procedure, including formation of the carboxylic acid azide, *in situ* Curtius rearrangement, and finally quenching of the ensuing isocyanate with benzyl alcohol. Removal of the amino protecting group *via* catalytic hydrogenation gave the bicyclic amine **227**. After the construction of the heterocyclic base as well as the deprotection of TBDMS-group, the target molecule **210** was obtained in 13% overall yield. Despite the good overall yield, this approach was still limited by the lengthy process and the requirement of the initial separation of diastereoisomeric (-)-ephedrine salts of the starting tetrahydrophthalic acid monomethyl ester.

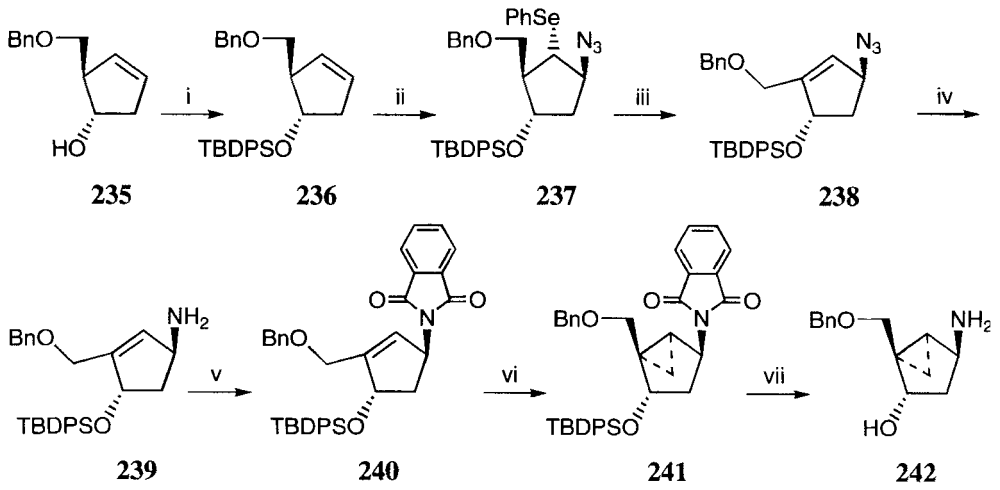
Marquez et al. developed another simpler approach starting from the known epoxide **228**, which can be obtained in optically pure form (ee>98%) (Scheme 23).[63c,66] Nucleophilic opening of the epoxide ring occurred with excellent regioselectivity to give the cyano intermediate **229**, from which the desired α,β-unsaturated nitrile **230** was obtained following the *syn*-β-elimination of the transitional thiocarbonyl imidazolide. The 1,3-dipolar cycloaddition of diazomethane to **230** to give the *cis*-fused pyrazoline intermediate **231** occurred with the expected regioselectivity The desired



Scheme 23. (i) KCN, $LiClO_4$, MeCN, 70°C, 24h, argon, 75%. (ii) 1, 1′-thiocarbonyldiimidazole, DMAP, DMF, rt, 3h, 70°C, 30 min, argon, 84%. (iii) CH_2N_2, ether, 0°C, 3d, 94%. (iv) *hv*, 2h, benzene-MeCN (1:1), 79%. (v) NaOH/MeOH, reflux, 24h, acidified to pH 5 at 0°C, 62%. (vi) a. DPPA, Et_3N, toluene, 0°C-rt 2h, 80°C, 2h argon; b. 2-trimethylsilylethanol, 80°C, 2h; c. tetrabutylammonium fluoride, CH_3CN-THF, rt-70°C, 4h, argon.

bicyclo[3.1.0]hexane intermediate nitrile **232** was obtained after nitrogen extrusion from **231** by photolysis. Following the standard protocol, the nitrile functional group was converted to the protected carbocyclic amine derivative **234**, from which all the targets **210-214** were obtained using a linear approach.

The first 4′, 1′a-*methanocarba*-nucleoside **205** was also first demonstrated by Altmann.[62a] More recently, Marquez developed another efficient strategy to 4′, 1′a-*methanocarba*-nucleosides by utilizing the same starting material **235** as used for the preparation of 1′, 1′a-*methanocarba*-nucleoside (**228** was prepared from **235**).[67] Thus, azido-phenylselenylation of protected olefin **236** proceeded with complete stereochemical control to give the desired **237**. Subsequently, the *in situ* oxidation of the phenylselenide group yielded almost exclusively the allylic azide **238**, which was efficiently reduced, and the resulting carbocyclic amine **239** was protected as the phthalimide derivative **240**. After deprotection of the TBDPS-group, the bicyclo[3.1.0]hexane derivative **241** was obtained as the sole product of the Simmons-Smith reaction because of the bulky phthalimido group. Hydrazinolysis of the phthalimido group afforded the desired amine **242** (Scheme 24).



Scheme 24. (i) TBDPSCl, imidazole, DMF, rt 14h, 76%. (ii) Phenylselenium chloride, DMSO rt; NaN_3, rt overnight, argon, 87%. (iii) $NaIO_4$, MeOH-H2O (9:1), rt, 36h, 76%. (iv) PPh_3, THF, reflux, 4h, 90%. (v) phthalic anhydride, pyridine, 90°C, 2h, argon; acetic anhydride, 90°C, 2h, 77%. (vi)triethylamine trihydrofluoride, CH_3CN, reflux, overnight, argon; Et_2Zn, CH_2Cl_2, 0°C, CH_2I_2, 0°C, 10h, rt, overnight, 86%. (vii)methanolic hydrazine rt, 30 min, 50°C, 3.5h, 100%.

Concluding remarks. Although many *carba*-nucleosides have been synthesized and evaluated as antiviral agents over the past two decades, only a few of them have been found to possess any useful activity and a few of these are in clinical trial at present. More research work is still needed to identify the more potent *carba*-nucleosides with better selectivity. More efforts will be made to develop novel, simple, efficient, practical and economic procedures for those highly active agents and corresponding key intermediates. The future work will continue to focus mainly on the cyclopentyl carbocyclic nucleosides. Meanwhile, other nucleosides with different *carba*-sugar ring size, such as three-membered *carba*-nucleosides and bicyclic *carba*-nucleosides will play more and more important roles in the field of *carba*-nucleosides chemistry.

Acknowledgment The author is grateful to Prof. Dr. Albert Gossauer for reading this manuscript and helpful comments.

References

1. (a) Johnston, M. I.; Hoth, D. F. *Science* **1993**, *260*, 1286. (b) Norbeck, D. W.; Kern, E.; Hiyashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erickson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. J. *J. Med. Chem.* **1990**, *33*, 1281-1285.
2. (a) Larder, B. A.; Darby, G.; Richman, D. D. *Science* **1989**, *243*, 1731-1734. (b) Larder, B. A.; Sharon, D. K. *Science* **1989**, *246*, 1155.
3. (a) Wachtmeister, J.; Classon, B.; Samuelsson, B.; Kvarnström, I. *Tetrahedron* **1995**, *51*, 2029-2038. (b) Wachtmeister, J.; Classon, B.; Samuelsson, B.; Kvarnström, I. *Tetrahedron* **1997**, *53*, 1861-1872.
4. (a) Marquez, V. E.; Lim, M-I. *Med. Res. Rev.* **1986**, *6*, 1-40. (b) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571-623. (c) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611-10670. (d) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229-9272.
5. (a) Marquez, V. E. In *Advances in Antiviral Drug design*, Vol. 2 (De Clercq, E. ed.), **1996**, pp 89-146. (b) Cluet, F.; Haudrechy, A.; Le Ber, P.; Sinay, P.; Wick, A. *Synlett* **1994**, 913.
6. Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem.* **1998**, *41*, 1284-1298.
7. Csuk, R.; von Scholz, Y. *Tetrahedron* **1994**, *50*, 10431-10442.
8. (a) Zhao, Y.; Yang, T.-F.; Lee M.; Chun, B. K.; Du, J.; Schinazi, R. F.; Lee, D., Newton, M. G.; Chu, C. K. *Tetrahedron Lett.* **1994**, *35*, 5405-5408. (b) Zhao, Y.; Yang, T.-F.; Lee M.; Lee, D., Newton, M. G.; Chu, C. K. *J. Org. Chem.* **1995**, *60*, 5236-5242. (c) Zhao, Y.; Lee M.; Yang, T.-F.; Chun, B. K.; Du, J.; Schinazi, R. F.; Chu, C. K. *Nucleosides Nucleotides,* **1995**, *14*, 303-305. (d) Lee, M.; Lee, D.; Zhao, Y.; Newton, M. G.; Chun, M. W.; Chu, C. K. *Tetrahedron Lett.* **1995**, *36*, 3499-3502. (e) Yang, T.-F.; Kim, H.; Kotra, L. P.; Chu, C. K. *Tetrahedron Lett.* **1996**, *37*, 8849-8852.
9. (a) Qiu, Y. L.; Ksebati, M. B.; Ptak, R. G.; Fan, B. Y.; Breitenbach, J. M.; Lin, J. S.; Cheng, Y. c.; Kern, E. R.; Drach, J. C.; Zemlicka, J. *J. Med. Chem.* **1998**, *41*,

10-23. (b) Winter, H.; Maeda, Y,; Mitsuya, H.; Zemlicka, J. . *J. Med. Chem.* **1996**, *39*, 3300-3306

10. (a) Gharbaoui, T.; Legraverend, M.; Ludwig, O.; Bisagni, E.; Aubertin, A.-M.; Chertanova, L. *Tetrahedron* **1995**, *51*, 1641-1652. (b) Ishigami, S.; Togo, H.; Yokoyama, M. *J. Chem. Soc. Perkin Trans 1* **1994**, 2407-2412. (c) Mévellec, L.; Huet, F. *Tetrahedron* **1994**, *50*, 13145-13154. (d) Mévellec, L.; Huet, F. *Tetrahedron* **1997**, *53*, 5797-5812. (e) Wu, J.; Schneller, S. W.; Seley, K. L. *J. Med. Chem.* **1997**, *40*, 1401-1406.

11. Kaiwar, V.; Reese, C. B.; Gray, E. J.; Neidle, S. *J. Chem. Soc. Perkin Trans 1* **1995**, 2281-2287.

12. Gourdel-Martin, M.-E.; Huet, F. *J. Org. Chem.* **1997**, *62*, 2166-2172.

13. (a) Vince, R.; Hua, M.; Brownell, J.; Daluge, S.; Lee, F.; Shannon, W. M.; Lavelle, G. C.; Qualls, J.; Weislow, O. S.; Kiser, R.; Canonico, P. G.; Schultz, R. H.; Narayanan, V. L.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Biochem. Biophys. Res. Commun.* **1988**, 156, 1046-1053. (b) Vince, R.; Brownell, J. *Biochem. Biophys. Res. Commun.* **1990**, 168, 912-916. (c) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, 33, 17-21.

14. (a) Daluge, S. M.; Good, S. S.; Faletto, M. B.; Miller, W. H.; St. Clair, M. H.; Boone, L. R.; Tisdale, M.; Parry, N. R.; Reardon, J.; Dornsife, R. E.; Averett, D. R.; Krenitsky, T. A. *Antimicrob. Agents Chemother.* **1997**, 41(5), 1082-1093. (b) Tisdale, M.; Alnadaf, T.; Cousens, D. *Antimicrob. Agents Chemother.* **1997**, 41(5), 1094-1098. (c) Faletto, M. B.; Miller, W. H.; Garvey, E. P.; St. Clair, M. H.; Daluge, S. M.; Good, S. S. *Antimicrob. Agents Chemother.* **1997**, 41(5), 1099-1107. (d) kumar, P. N.; Sweet, D. E.; McDowell, J. A.; Symonds, W.; Lou, Y.; Hetherington, S.; Lafon, S. *Antimicrob. Agents Chemother.* **1999**, 43(3), 603-608. (e) Hughes, W.; McDowell, J. A.; Shenep, J.; Flynn, P.; Kline, M. W.; Yogey, R.; Symonds, W.; Lou, Y.; Hetherington, S. *Antimicrob. Agents Chemother.* **1999**, 43(3), 609- 615.

15. Exall, A. M.; Jones, M. F.; Mo, C.-L.; Myers, P. L.; Paternoster, I. L.; Singh, H.; Storer, R.; Weingarten, G. G.; Williamson, C.; Brodie, A. C.; Cook, J.; Lake, D. E.; Meerholz, C. A.; Turnbull, P. J.; Highcock, R. M. *J. Chem. Soc. Perkin Trans 1* **1991**, 2467-2477.

16. (a) Park, K. H.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 394-399. (b) Martinez, L. E.; Nugent, W. A.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 7963-7966. (c) Zhang, D.; Ghosh, A.; Süling, C.; Miller, M. J. *Tetrahedron Lett.* **1996**, *37*, 3799-3802. (d) Campbell, J. A.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 4602-4616. (e) Tanaka, M.; Norimine, Y.; Fujita, T.; Suemune, H.; *J. Org. Chem.* **1996**, *61*, 6952-6957.

17. (a) Nokami, J.; Matsuura, H.; Nakasima, K.; Shibata, S. *Chemistry Lett.* **1994**, 1071-1074. (b) Hodgson, D. M.; Witherington, J.; Moloney, B. A. *Tetrahedron: Asymmetry* **1994**, *5*, 337-338. (c) Hodgson, D. M.; Witherington, J.; Moloney, B. A. *J. Chem. Soc. Perkin Trans 1* **1994**, 3373-3378. (d) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192-4193. (e) Popescu, A.; Hörnfeldt, A. B.; Gronowitz, S. *Nucleosides Nucleotides* **1995**, *14*, 1233-1249.

18. (a) Berranger, T.; Langlois, Y. *Tetrahedron Lett.* **1995**, *36*, 5523-5526. (b) Burlina, F.; Favre, A.; Fourrey, J. L.; Thomas, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 247-250.

19. Hildbrand, S.; Troxler, T.; Scheffold, R. *Helv. Chim. Acta* **1994**, *77*, 1236-1240.

20. Jung, M. E.; Rhee, H. *J. Org. Chem.* **1994**, *59*, 4719-4720.

21. Katagiri, N.; Takebayashi, M.; Kokufuda, H.; Kaneko, C.; Kanehira, K.; Torihara, M. *J. Org.Chem.* **1997**, *62*, 1580-1581.

22. Diaz, M.; Ibarzo, J.; Jiménez, J. M.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 129-140.

23. Trost, B. M.; Madsen, R.; Guile, S. G.; Elia, A. E. H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1569-1572.

24. Wang, P.; Schinazi, R. F.; Chu, C. K. *Bioorg. Med. Chem. Lett*, **1998**, *8*, 1585-1588.

25. Miller, W. H.; Daluge, S. M.; Garvey, E. P.; Hopkins, S.; Reardon, J. E.; Boyd, F: L.; Miller, R. L. *J. Biol. Chem.* **1992**, *267*, 21220.

26. Merlo, V.; Roberts, S. M.; Storer, R.; Bethell, R. C. *J. Chem. Soc. Perkin Trans 1* **1994**, 1477-1481.

27. (a) Dyatkina, N.; Costisella, B.; Theil, F.; von Janta-Lipinski, M. *Tetrahedron Lett.* **1994**, *35*, 1961-1964. (b) Dyatkina, N.; Theil, F.; von Janta-Lipinski, M. *Tetrahedron* **1995**, *51*, 761-772. (c) Ghosh, A.; Miller, M. J. *Tetrahedron Lett.*

1995 *36*, 6399-6402. (d) Vogt, P. F.; Hansel, J.-G.; Miller, M. J. *Tetrahedron Lett.* **1997**, *38*, 2803-2804.

28. Grumann, A.; Marley, H.; Taylor, R. J. K. *Tetrahedron Lett.* **1995**, *36*, 7767-7768.
29. (a) Akella, L. B.; Vince, R. *Tetrahedron* **1996**, *52*, 2789-2794. (b) Olivo, H.; Yu, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3785-3788.
30. Toyota, A.; Nishimura, A.; Kaneko, C. *Tetrahedron Lett.* **1998**, *39*, 4687-4690.
31. Hildbrand, S.; Leumann, C.; Scheffold R. *Helv. Chim. Acta* **1996**, *79*, 702-709.
32. (a) Parry, R. J.; Jiang, Y. *Tetrahedron Lett.* **1994**, *35*, 9665-9668. (b) Hill, J. M.; Jenkins, G. N.; Rush, C. P.; Turner, N. J.; Willetts, A. J.; Buss, A. D.; Dawson, M. J.; Rudd, B. A. M. *J. Am. Chem. Soc.* **1995**, *117*, 5391-5392. (c) Jenkins G. N.; Turner, N. J. *Chem. Soc. Rev.* **1995**, 169-176.
33. (a) Csuk, R.; Dörr, P.; *Tetrahedron* **1995**, *51*, 5789-5798. (b) Deardorff, D. R.; Savin, K. A.; Justman, C. J.; Karanjawala, Z. E.; Sheppeck II, J. E.; Hager, D. C.; Aydin, N. *J. Org. Chem.* **1997**, *61*, 3616-3622. (c) Boyer, S. J.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 3976-3980.
34. (a) Hill, J. M.; Hutchinson, E. J.; Le Grand, D. M.; Roberts, S. M.; Thorpe, A. J.; Turner, N. J. *J. Chem. Soc. Perkin Trans 1* **1994**, 1483-1487. (b) Nokami, J.; Matsuura, H.; Takahashi, H.; Yamashita, M. *Synlett* **1994**, 491-493. (c) Ohira, S.; Sawamoto, T.; Yamato, M. *Tetrahedron Lett.* **1995**, *36*, 1537-1538.
35. Hawkins, J. M.; Loren, S.; Nambu, M. *J. Am. Chem. Soc.* **1994**, *116*, 1657-1660.
36. Niizuma, S.; Shuto, S.; Matsuda, A. *Tetrahedron* **1997**, *53*, 13621-13632.
37. Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K. *Tetrahedron Lett.* **1997**, *38*, 4207-4210.
38. Patil, S. D.; Schneller, S. W.; Hosoya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clerq, E. *J. Med. Chem.* **1992**, *35*, 3372.
39. Seley, K. L.; Schneller, S. W.; Korba, B. *Nucleosides Nucleotides* **1997**, *16*, 2095-2099.
40. (a) Seley, K. L.; Schneller, S. W.; Rattendi, D.; Bacchi, C. J. *J. Med. Chem.* **1997**, *40*, 622-624. (b) Seley, K. L.; Schneller, S. W.; Rattendi, D.; Lane, S.; Bacchi, C. J. *J. Med. Chem.* **1997**, *40*, 625-629.

41. (a) Seley, K. L.; Schneller, S. W. *J. Org. Chem.* **1997**, *62*, 5645. (b) Seley, K. L.; Schneller, S. W.; Clercq, D. E.; Rattendi, D.; Lane, S.; Bacchi, C.J.; Korba, B. *Bioorg. Med. Chem.* **1998**, *6*, 797-801.

42. Gallos, J. K.; Goga, E. G.; Koumbis, A. E. *J. Chem. Soc. Perkin Trans 1* **1994**, 613-614.

43. Ranganathan, S.; George, K. S. *Tetrahedron* **1997**, *53*, 3347-3362.

44. Kato, K.; Hayakawa, H.; Tanaka, H.; Kumamoto, H.; Shindoh, S.; Shuto, S.; Miyasaka, T. *J. Org. Chem.* **1997**, *62*, 6833-6841.

45. (a) Shealy, Y. F.; O'Dell, C. A.; Shannon, W. M.; Arnett, G. *J. Med. Chem.*, **1984**, *27*, 1416. (b) Shannon, W. M. In *Advances in Chemotherapy of AIDS*; Diasio, R. B. abd Sommadossi, J. P., Ed.; Pergammon Press, Inc., N. Y., 1990, p75-95. (c) Price, P. M.; Banerjee, R.; Acs, G. *Proc. Natl. Acad. Sci. USA*, **1989**, *86*, 8541. (d) Boehme, R. E.; Beresford, A.; Hart, G. J.; Angier, S. J.; Thompson, G.; Van Wely, C.; Huang, J-L.; Mack, P.; Soike, K. F. *Antiviral Research*, **1994**, *23*, S(1), 97. (e) Cameron, J. M. *Reviews in Medical Virology*, **1993**, *3*, 225. (f) Bothwick, A. D.; Crame, A. J.; Exall, A. M.; Weingarten, G. G.; Mahmoudian, M. *Tetrahedron Lett.* **1995**, *36*, 6929-6932.

46. Lang, H.; Moser, H. E. *Helv. Chim. Acta.* **1994**, *77*, 1527-1540.

47. Bothwick, A. D.; Crame, A. J.; Exall, A. M.; Weingarten, G. G. *Tetrahedron Lett.* **1994**, *35*, 7677-7680.

48. Wyatt, P. G.; Anslow, A. S.; Coomber, B. A.; Cousins, R. P. C.; Evans, D. N.; Gilbert, V. S.; Humber, D. C.; Paternoster, I. L.; Sollis, S. L.; Tapolczay, D. J.; Weingarten, G. G. *Nucleosides Nucleotides* **1995**, *14*, 2039-2049.

49. Brian, L. B.; Dolan, S. C.; Halter, B.; Lackey, J. W.; Schilling, M. B.; Tapolczay, D. J. *Tetrahedron Lett.* **1995**, *36*, 4483-4486.

50. Barkley, J. V.; Dhanda, A.; Knutsen, L. J. S.; Nielsen, M. B.; Roberts, S. M.; Varley, D. R. *Chem. Commun.* **1998,** 1117-1118.

51. Yoshikawa, M.; Yokokawa, Y.; Inoue, Y.; Yamaguchi, S.; Murakami, N.; Kitagawa, I. *Tetrahedron* **1994**, *50*, 9961-9974.

52. Katagiri, N.; Matsuhashi, Y.; Kokufuda, H.; Takebayashi, M.; Kaneko, C. *Tetrahedron Lett.* **1997**, *38*, 1961-1964.

53. Kapeller, H.; Baumgartner, H.; Marschner, C.; Pucher, R.; Griengl, H. *Monatsh. Chem.* **1997**, *128*, 953-960.

54. Katagiri, N.; Nomura, M.; Sato, H.; Kaneko, C.; Yusa, K.; Tsuruo, T. *J. Med.Chem.* **1992**, *35*, 1882-1886.

55. Santana, L.; Teijeira, M.; Uriarte, E.; Balzarini, J.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1349-1352.

56. Theil, F.; Ballschuh, S.; Flatau, S.; von Janta-Lipinski, M.; Matthes, E. *Bioorg. Med. Chem.* **1998**, *6*, 701-706.

57. Bisacchi, G. S.; Chao, S. T.; Bachard, C.; Daris, J. P.; Innaimo, S.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W. S.; Sundeen, J. E.; Yong, M. G.; Colonno, R.; Zahler, R. *Bioorg. Med. Chem. Lett.*, **1997**, *2*, 127-132.

58. (a) Ramesh, K.; Wolfe, M. S.; Lee, Y.; Velde, D. V.; Borchardt, R. T. *J. Org. Chem.* **1992**, *57*, 5861-5868. (b) Konkel, M. J.; Vince, R. *Nucleosides & Nucleotides* **1995**, *14*, 2061-2077. (c) Konkel, M. J.; Vince, R. *Tetrahedron* **1996-65**, *52*, 799-808. (d) Konkel, M. J.; Vince, R. *Tetrahedron* **1996**, *52*, 8969-8978. (e) Pérez-Pérez, M.-J.; Rozenski, J.; Busson, R.; Herdewijn, P. *J. Org. Chem.* **1995**, *60*, 1531-1537. (f) Calvani, F.; Macchia, M.; Rossello, A.; Gismondo, M. R.; Drago, L.; Fassina, M. C.; Cisternino, M.; Domiano, P. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2567-2572. (g) Mikhailov, S.; Blaton, N.; Rozenski, J.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *Nucleosides Nucleotides* **1996**, *15*, 867.

59. Maurinsh, Y.; Schraml, J.; De Winter, H.; Blaton, N.; Peeters, O.; Lescrinier, E.; Rozenski, J.; Van Aerschot, A.; De Clercq E.; Busson, R.; Herdewijn, P. *J. Org. Chem.* **1997**, *62*, 2861-2871.

60. Wang, J.; Busson, R.; Blaton, N.; Rozenski, J.; Herdewijn, P. *J. Org. Chem.* **1998**, *63*, 3051-3058.

61. Rosenquist, A.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1996**, *61*, 6282-6288.

62. (a) Altmann, K.-H.; Kesselring R.; Francotte, E.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 2331-2334. (b) Altmann, K.-H.; Imwinkelried, R.; Kesselring R.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 7625-7628.

63. (a) Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R. W.; Matteucci, M. D. *J. Med. Chem.* , **1996**, *39*, 3739-3747. (b) Siddiqui, M. A.; Ford, H.; George, C.; Marquez, V. E. *Nucleosides Nucleotides* **1996**, *15*, 235-250. (c) Ezzitouni, A.; Marquez, V. E. *J. Chem. Soc. Perkin Trans 1* **1997**, 1073-1078. (d) Marquez, V. E.; Ezzitouni, A.; Siddiqui, M. A.; Russ, P.; Ikeda, H.; George, C. *Nucleosides Nucleotides* **1997**, *16*, 1431-1434.

64. Jeong, , L. S.; Marquez, V. E. *Tetrahedron Lett.* **1996**, *37*, 2353-2356.

65. (a) Gooding, H.; Roberts, S. M.; Storer, R. *J. Chem. Soc. Perkin Trans 1* **1994**, 1891-1892. (b) Theil, F.; Ballschuh, S.; von Janta-Lipinski, M.; Johnson, R. A. *J. Chem. Soc. Perkin Trans 1* **1996**, 255. (c) Chao, Q.; Nair, V. *Tetrahedron Lett.* **1995**, *36*, 7375-7378. (d) Chao, Q.; Nair, V. *Tetrahedron* **1997**, *53*, 1957-1970. (e) Demaison, C.; Hourioux, C.; Roingeard, P.; Agrofoglio, L. A. *Tetrahedron Lett.* **1998**, *39*, 9175-9178.

66. Ezzitouni, A.; Barchi, J. J.; Marquez, V. E. *J. Chem. Soc., Chem. Commun.* **1995**, 1345-1346.

67. Ezzitouni, A.; Russ, P.; Marquez, V. E. *J. Org. Chem.* **1997**, *62*, 4870-4873.

Received 4/21/99
Accepted 10/25/99