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New Progresses in the Enantioselective Synthesis and Biological Properties of Carbocyclic Nucleosides

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Abstract: The recent advances in the chemistry of carbocyclic nucleosides focused on different synthetic approaches that lead to optically pure products as well as a comprehensive overview of their biological properties are discussed. In the latter aspect, molecular recognition of enzymes of pharmacological importance such as: reverse transcriptase, adenosine deaminase, thymidine kinase, DNA cytosine-C5 methyl transferase, *S*-adenosylhomocysteine hydrolase, etc are considered. The role of conformation and puckering of the glycon moiety in modulating the biological activity and also the use of carbanucleosides as building blocks to prepare oligonucleotides are carefully illustrated.

INTRODUCTION

The term carbanucleoside or carbocyclic nucleoside refers to a nucleoside analogue in which a methylene group has replaced the oxygen atom of the furanose ring. These analogues have potent metabolic stability because they are unaffected by phosphorylases and hydrolases that cleave the glycosidic bond of natural nucleosides. On the other hand, the pharmacological actions of conventional nucleosides have been extensively studied, especially as antiviral and antitumor agents. Interestingly, the same enzymes that recognize normal nucleosides displaying a wide range of biological properties, also recognize their *carba*-analogues. Enantioselective synthesis of these modified nucleosides has received much attention in the last years motivated by the urgent need of having effective antiviral agents especially against HIV. In effect, the lack of therapeutically valuable drugs against viral infections gave an enormous impetus to the search for new synthetic protocols that lead to optically pure nucleoside analogues. In addition, the methodology for the preparation of *carba*-C nucleosides is also included. In this case, a C-C bond instead of a N-C bond connects the heterocyclic base to the pseudosugar moiety. At the present time, several review articles have appeared covering not only the synthetic aspects of the chemistry of carbocyclic nucleosides [1–7] but also the important pharmacological properties they exhibit [8–9].

Different synthetic approaches have been developed for the synthesis of carbanucleosides, including the critical steps the preparation of the pseudosugar and the incorporation of the heterocyclic base onto the carbocyclic ring (linear or convergent approach). The linear strategy, that is step-by-step base construction, will not be covered in this article. It deserves to mention among the convergent methods those that are suitable for a specific transformation such as the base nucleophilic attack to an epoxide group; a nucleophilic attack of a suitable base on a sulfur or selenium-activated double bond; a palladium catalyzed alkylation; and base addition to a Michael receptor, and those in which a S_N2 attack on an activated hydroxyl group is involved. In this case the Mitsunobu-type reaction arises as the main protocol to introduce a nucleic base into a carbocyclic ring [10–12]. Nevertheless, this Mitsunobu type reaction presents some disadvantages regarding the competition between *N*-9 versus *N*-7 alkylation in the case of purines and *N*-alkylation versus *O*-alkylation when employed *N*-1-protected pyrimidines. In addition, the major drawback of this reaction is the elimination of associated products formed in the course of the reaction: triphenylphosphine oxide and the respective dialkyl hydrazinedicarboxylate. The use of basic phosphines to facilitate the removal of the corresponding oxidized product has not been widely accepted [13].

Solid Phase Synthesis of Carbocyclic Nucleosides

In order to overcome the problems associated to the Mitsunobu reaction, solid phase syntheses of different carbanucleosides have been attempted [14, 15]. Chu *et al.* have developed a solid phase strategy for synthesis of L-2'-deoxynucleosides of general structure **7** employing a Mitsunobu reaction to incorporate all the nucleic bases. The required synthetic intermediate **3** to achieve this approach was prepared from D-ribose (**1**) in 15 steps *via* the known carbocyclic ring **2**. Therefore, with the use of a *p*-nitrophenyl carbonate resin **4** [16], the purification problems associated to this reaction were overcome and also the reaction yields were significantly improved. In the case of pyrimidines, the regioselectivity of this reaction (N^1- vs O^2- alkylated pyrimidines) was enhanced with the exemption of the cytosine derivative where the O^2-alkylated cytosine was isolated as the major product. This effect is more noticeable in the preparation of purine derivatives where the undesired N^7-alkylated products were not detected [15] (Scheme **1**).

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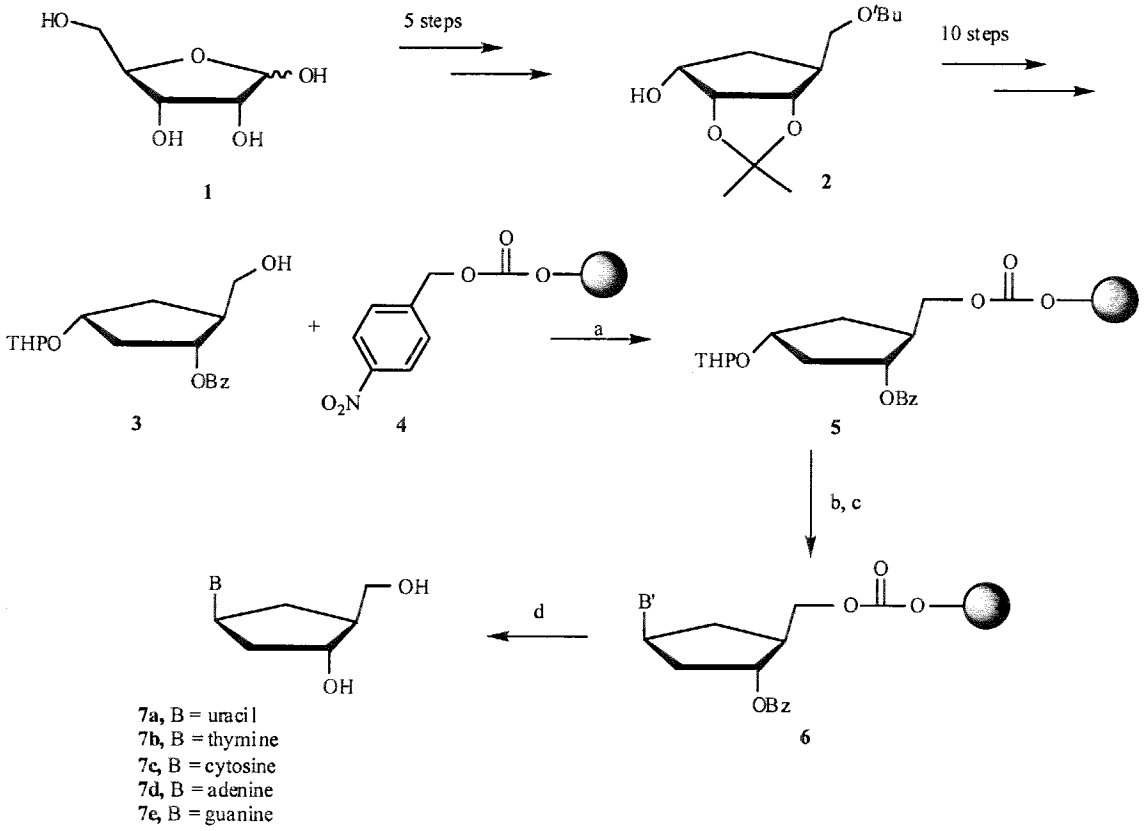
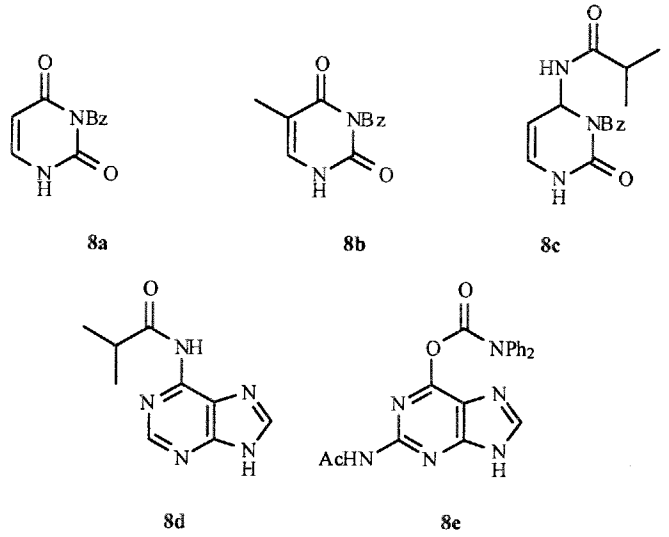


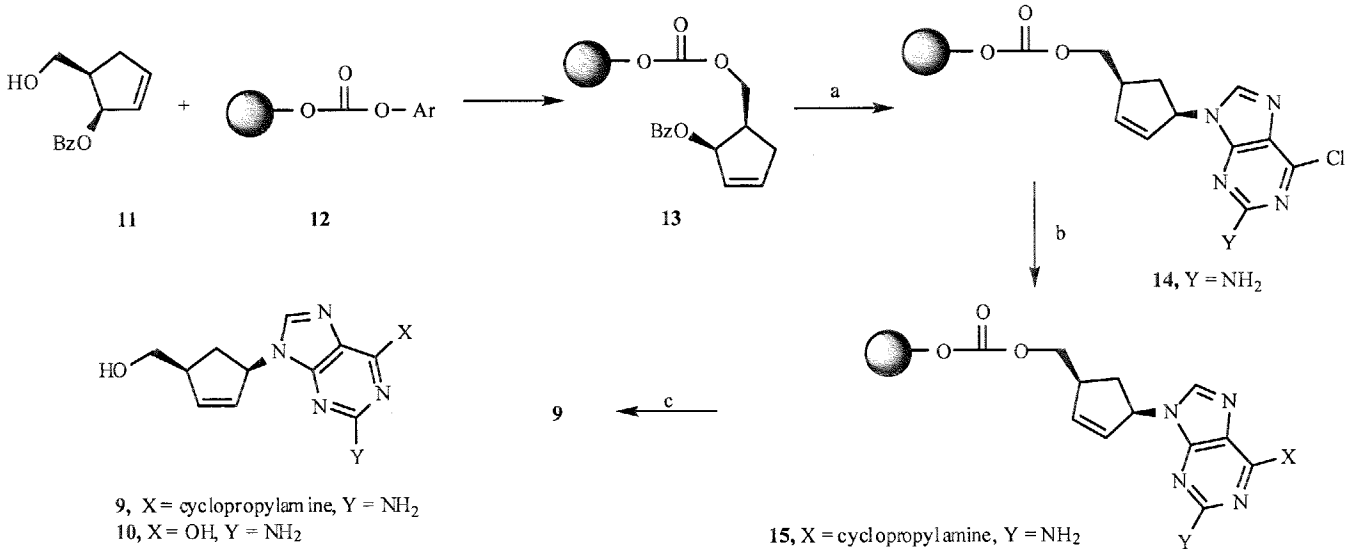
Solid phase synthesis of "unnatural" carbanucleosides



Structures of the corresponding heterocyclic bases (B'H):

Scheme 1. Reagents and Conditions: (a) **3** (3 eq.), DMAP (1 eq.), DIPEA (10 eq.), CH_2Cl_2, 40 °C, 2 days; (b) PPTs, *n*-BuOH/1,2-dichloroethane, 60 °C; (c) B'H (**8a-e**), DEAD, Ph_3P, DMF/1,4-dioxane or DMF, rt; (d) K_2CO_3, THF/MeOH, rt 50% for **7a**, 100% for **7b**, 97% for **7c**, 55% for **7d**, 62% for **7d** (all yields correspond to four steps from **3**).

Palladium-catalyzed allylic substitution of an allylic ester with either a purine or pyrimidine base is another useful coupling method for the direct introduction of a heterocyclic base onto the corresponding pseudosugar [17–19]. In this reaction, the yield of the reaction can be drastically impaired by formation of the N^7-alkylated product. By the use of this approach, Crimmins *et al.* have recently reported the solid phase synthesis of abacavir (**9**) and other closely related compounds to **9** and to carbovir ((–)-**10**), in which the N^9-alkylated product was obtained as a single compound in all cases. This particular behavior can be rationalized taking into account that the presence of the resin provokes an

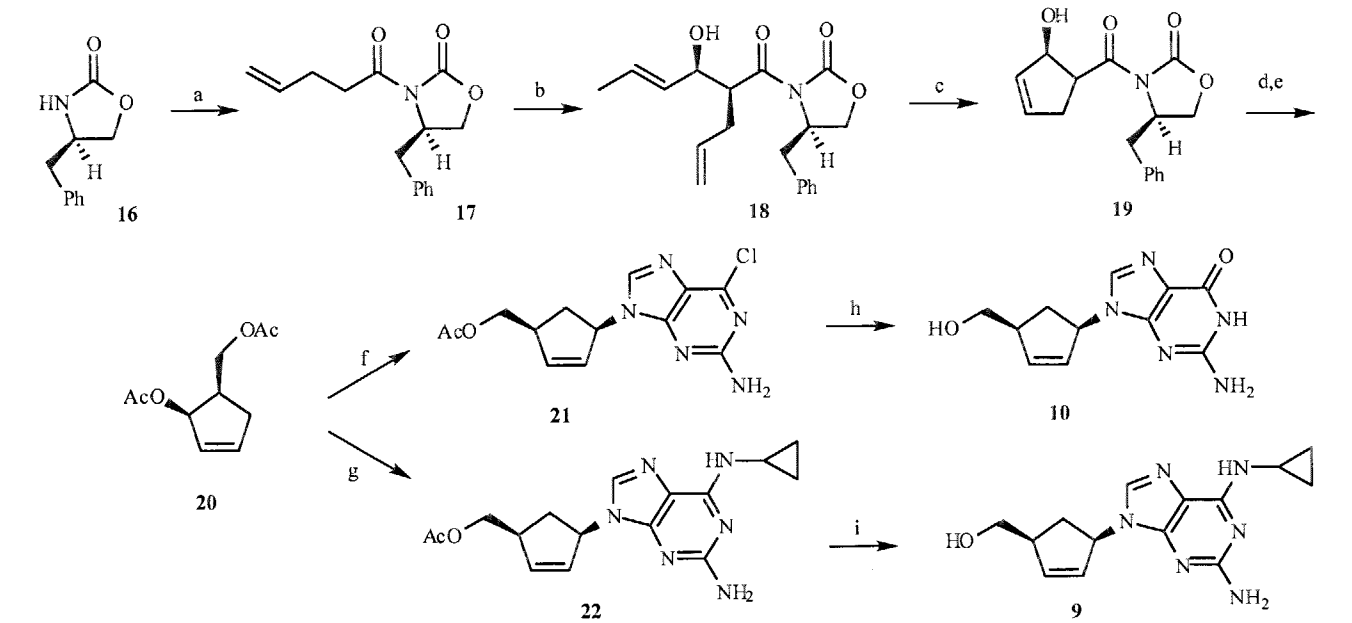


Scheme 2. Reagents and Conditions: (a) 10 mol % $Pd_2(dba)_3$, 0.4 equiv. PPh_3, 6.0 equiv. 1,2,2,6,6-pentamethylpiperidine, 1.5 equiv. 2-amino-6-chloropurine, THF-DMSO (1:1), 45 °C, 16 h; (b) cyclopropylamine, Et^iPr_2N, BuOH, 80 °C, 4 h; (c) 5% TFA, CH_2Cl_2.

enhancement of the steric effect in the trajectory of the base in its nucleophilic attack (Scheme **2**).

Asymmetric Synthesis of Carbocyclic Nucleosides via Aldol/ring-closing Metathesis Reaction

Abacavir (**9**) [20] and carbovir ((**–**)-**10**) [21] are synthetic carbanucleosides, which exhibit similar inhibitory activity than AZT against viral reverse transcriptase of the Human Immunodeficiency Virus (HIV). It deserves to point out that abacavir is a recently FDA-approved anti-HIV drug with less toxic effects than any other nucleoside analogues. These drugs and additional structurally related carbocyclic nucleosides have been enantioselectively prepared *via* an asymmetric aldol/ring-closing metathesis [22]. Thus, employing three powerful reactions, from the synthetic point of view, these carbanucleosides were synthesized in an elegant and efficient way. The reactions involved in this strategy are: (a) an asymmetric aldol addition employing Evans chiral auxiliaries to define the relative and the absolute stereochemistry [23, 24]; (b) a ruthenium-catalyzed ring-closing metathesis (RCM) to form the carbocyclic pseudosugar [25]; (c) palladium-catalyzed allylation reaction to incorporate the nucleic base onto the ring [17–19]. The last reaction is the key step in this commonly used



Scheme 3. Reagents and Conditions: (a) *n*-BuLi, THF, -78 °C, pivaloyl 4-pentenoate, 99%; (b) $TiCl_4$, (–)-sparteine, CH_2Cl_2, acrolein, 82%; (c) CH_2Cl_2, $Cl_2(Cy_3P)_2Ru$=CHPh, 25 °C, 97%; (d) $LiBH_4$, THF, MeOH, 78%; (e) Ac_2O, CH_2Cl_2, DMAP, Et_3N, 90%; (f) 2-amino-6-chloropurine, $Pd(PPh_3)_4$, NaH, THF-DMSO (1:1), 45 °C (g) 2-amino-6-cyclopropyl-aminopurine, $Pd(PPh_3)_4$, NaH, THF-DMSO (1:1), 40 °C, 62%; (h) NaOH, H_2O, 68%; (i) NaOH, H_2O.

convergent method for the preparation of carbocyclic nucleosides [1]. Therefore, the oxazolidinone **16** was used as chiral auxiliary. Compound **16** was acylated by treatment with 4-pentenoic pivalic mixed anhydride to give **17**, which on reaction with crotonaldehyde afforded the *syn* aldol product **18**. This compound was the substrate for the RCM reaction to give rise to carbocyclic **19**. Finally the third critical step was the coupling of the base employing a π-allylic palladium rearrangement as it is outlined in Scheme 3.

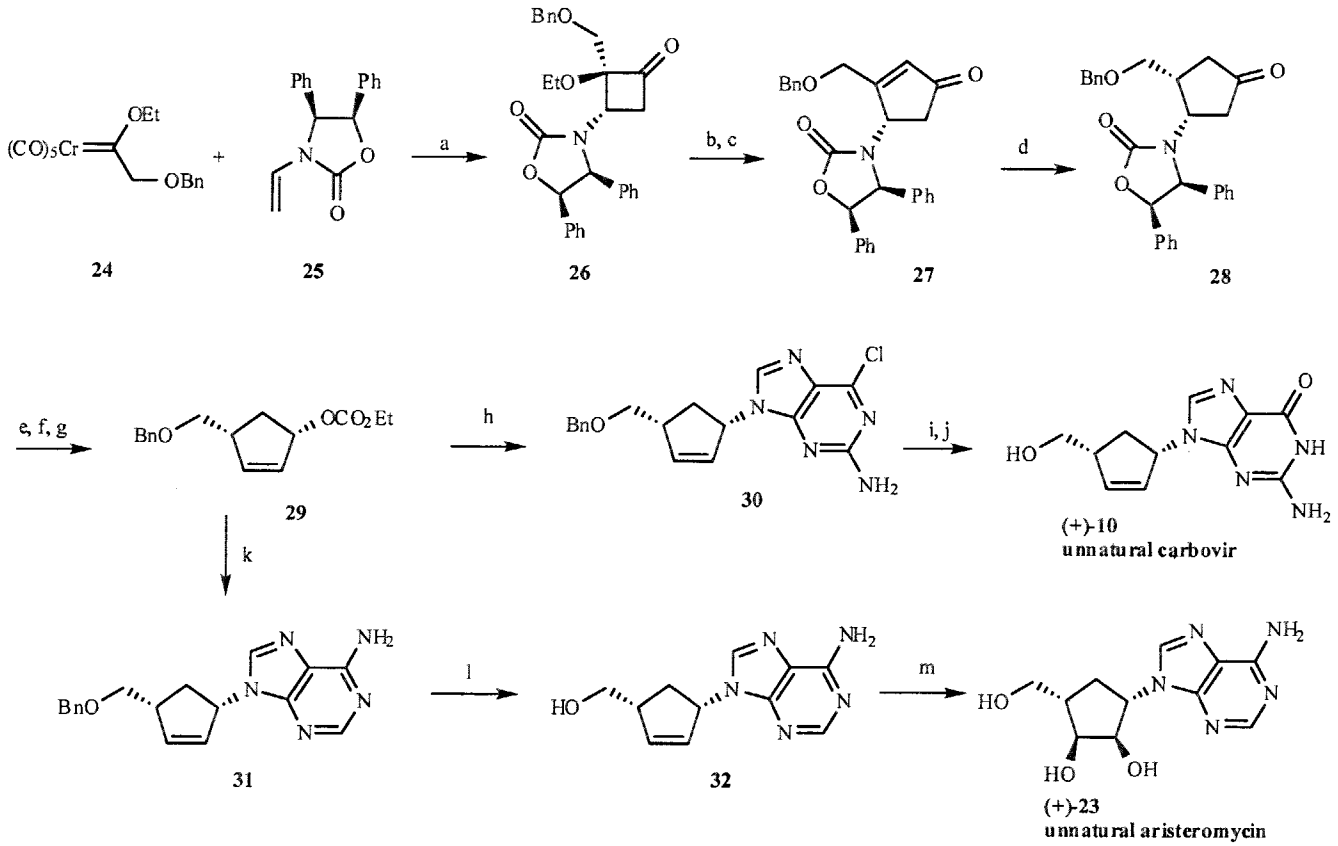
Synthesis of Carbovir via Ring-expansion Reaction of Cyclobutanones

An interesting new approach for the synthesis of carbanucleosides is the preparation of the unnatural isomers of carbovir ((+)-**10**) and aristeromycin ((+)-**23**) described by Hegedus [26]. For this purpose, a ring-expansion reaction of cyclobutanones was employed for the synthesis of the carbocyclic ring. The required chiral α-alkyl-α-alkoxycyclobutanone **26** is prepared via a photolytic reaction of the chromium carbene complex **24** with the Evans-type chiral enecarbamate **25** [27, 28]. Once the cyclobutanone is at hand, ring expansion is achieved by treatment with lanthanide triflates used as selective and mild Lewis acids [26]. The ring expansion proceeds with high regioselectivity favoring the desired β-substituted cyclopentanone **27** as indicated in Scheme 4. In this example the base is also coupled by the palladium–catalyzed coupling reaction to produce the corresponding carbocyclic nucleosides precursors **30** and **31**, respectively.

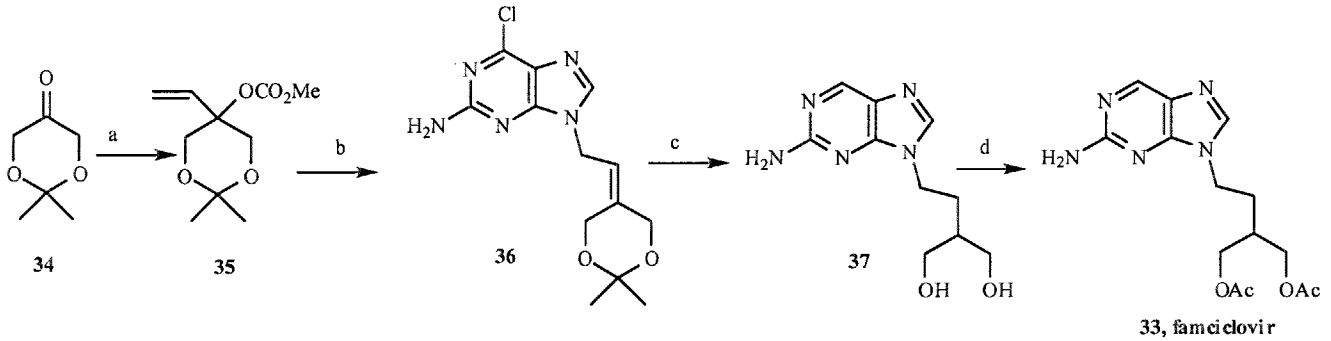
This π-allyl coupling method mediated with Pd (0) has been recently used by Smith *et al.* to prepare famciclovir (**33**) [29]. As illustrated in Scheme 5, the isopropyliden keto derivative (**34**) is reacted with vinyl magnesium bromide and the resulting alkoxy intermediate was trapped with methyl chloroformate to afford **35**, which is coupled with 2-amino-6-chloropurine to give the advanced carbanucleoside precursor **36**. Employing 1,2-bis(diphenylphosphino) ethane as a ligand and tris(dibenzylideneacetone) dipalladium(0) as palladium source, the ratio of N^9/N^7 alkylation product is 35:1. Cleavage of the protecting isopropylidene group afforded **37** that is further transformed into the desired drug **33** by treatment with acetic anhydride.

Preparation of Carbovir Analogues

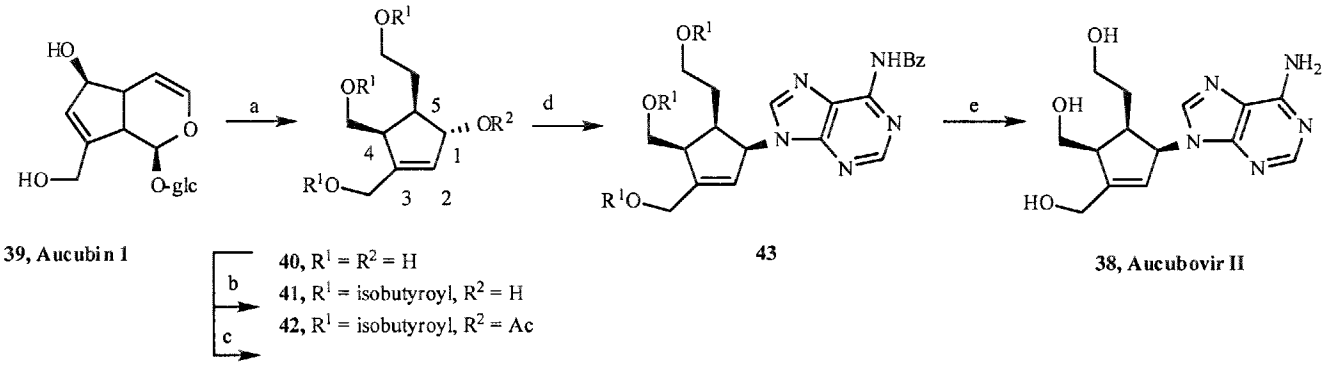
Bearing in mind the potential usefulness of carbovir as antiviral drug, several closely related compounds has been



Scheme 4. Reagents and Conditions: (a) hν, CH_2Cl_2, 76%; (b) $Me_3S(O)I$, NaH, $Sc(OTf_3)$, DMF; (c) Li_2CO_3, 74%; (d) H_2 (80 psi), $[Rh(COD)dppb]BF_4$, DMF, 77%; (e) LDA, THF, 0 °C; (f) DIBAL, THF, -78 °C, 50%; (g) $ClCO_2Et$, py, CH_2Cl_2, 87%; (h) $Pd(PPh_3)_4$, 2-amino-6-chloropurine, DMF, -40 °C → 10 °C, 63%; (i) BCl_3, CH_2Cl_2, -78 °C → 0 °C, then MeOH, 83%; (j) 0.5% aq. NaOH, 100 °C, 3.5 h, 72%; (k) $Pd(PPh_3)_4$, adenine, DMF, rt, 90 min, 65%; (l) BCl_3, CH_2Cl_2, -78 °C → 0 °C, then MeOH, 64%; (m) OsO_4, DMF, -15 °C, 36 h, 43%.



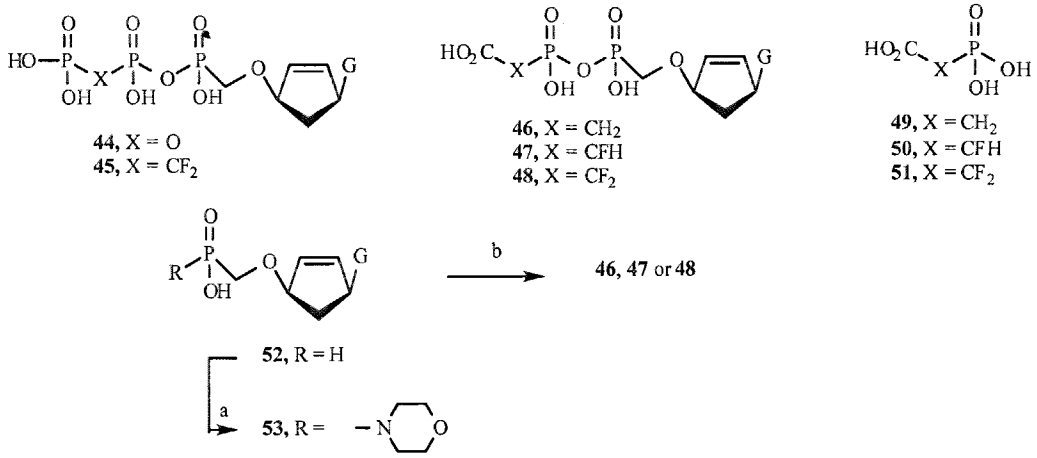
Scheme 5. Reagents and Conditions: (a) CH_2=CHMgBr, THF, then $ClCO_2Me$, 73%; (b) $Pd_2(dba)_3$, dppe, Cs_2CO_3, DMF, 80 °C, 7.5 h, 72%; (c) i. H_2, Pd/C, Et_3N, THF, ii. MeOH/HCl, 93%; (d) Ac_2O, DMAP, Et_3N, MDC, 80%.



Scheme 6. Reagents and Conditions: (a) i. $Hg(OAc)_2$, $NaBH_4$, or ii. β-glucosidase, $NaBH_4$, 90%; (b) isobutyric anhydride, py, 0 °C → 25 °C, 90 min, 90%; (c) Ac_2O, py, 1 h, 99%; (d) i. N_6-benzoyl-adenine, MeCN, TMSCl, HMDS, ii. $CF_3(CF_2)_3Si(CH_3)_3$, CH_2Cl_2, reflux, 8 h, 20%; (e) DIBAL, CH_2Cl_2, -78 °C, 95%.

designed and prepared. In fact, Bianco *et al.* have recently depicted the enantioselective synthesis of aucubovir II (**38**) [30] employing the Vorbrüggen methodology for introducing the base onto the carbocyclic ring as key step [31, 32]. In this case, aucubin 1 (**39**) was employed as chiral starting material (Scheme 6). There is no information about the antiviral activity of aucubovir II.

Roberts *et al.* have described a very interesting example in the preparation of di- and tri-phosphorylated fluor-containing derivatives of carbovir [33] keeping the base as guanine based on the modified triphosphorylated drugs **44** and **45**, which proved to be potent inhibitors of HIV-reverse transcriptase [34]. These kinds of nucleotides are able to liberate phosphonoacetic acids. In this case, carbanucleotides (**46-48**) act as prodrugs [33] releasing compounds **49-51**. These drugs have been designed not only to evaluate the nucleotides per se but also on the basis that phosphonoacetic acids are non-competitive inhibitors of viral DNA polymerases (herpes simplex virus, cytomegalovirus, HIV)

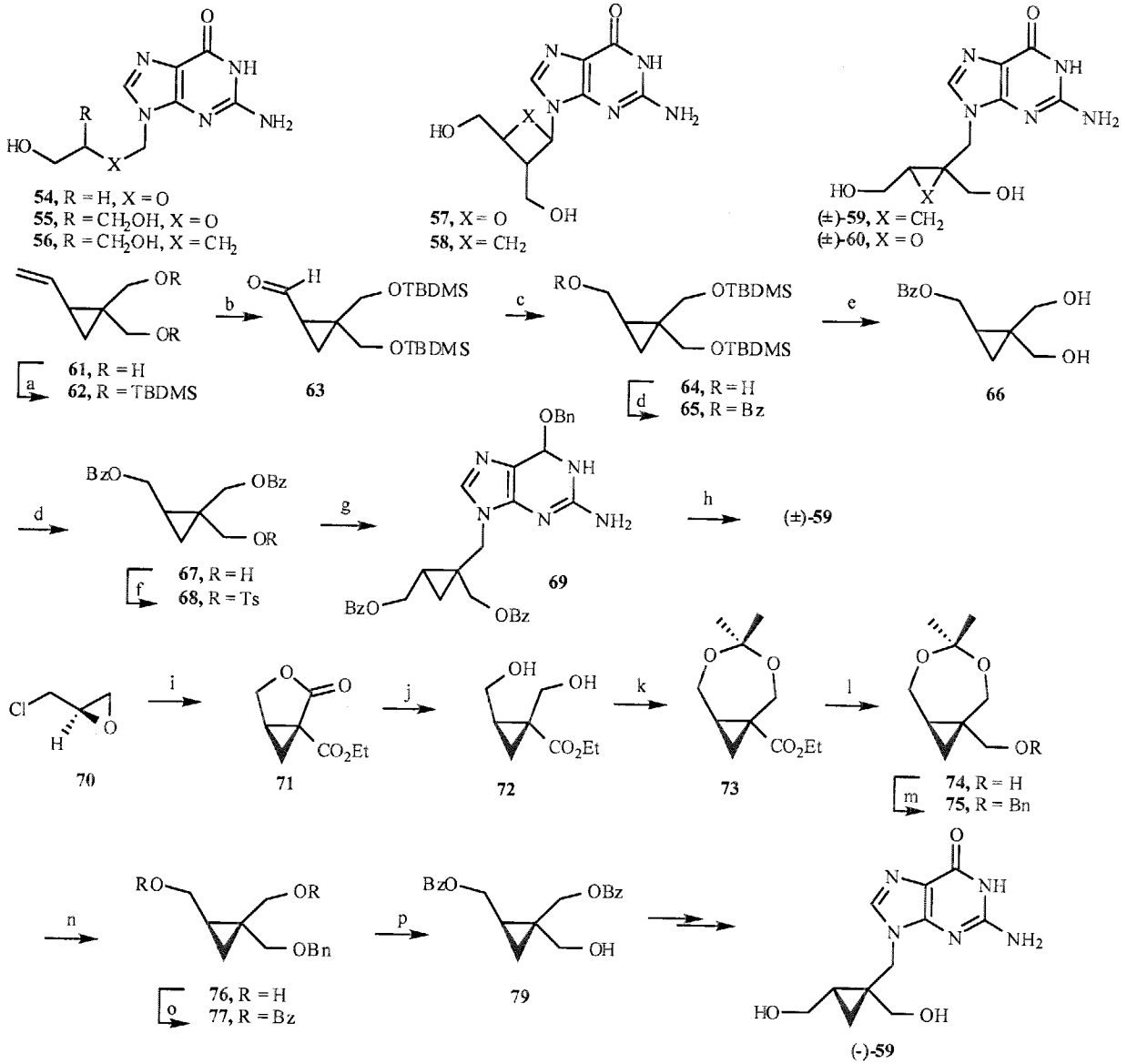


Scheme 7. Reagents and Conditions: (a) morpholine, DCC, ^{t}BuOH–H_2O, reflux, 4 h; (b) **46**, **47** or **48** (NBu_3, salt), DMSO, 14–39 h, rt, 50% for **49**, 32% for **50**, 13% for **51**.

[35]. Therefore, a synergistic effect would be anticipated because these metabolites acting as DNA polymerase inhibitors would combine their action with the original reverse transcriptase blocking effect of the nucleosides. Unfortunately these derivatives are almost devoid of activity against HIV reverse transcriptase [33]. The corresponding tributylammonium salts of these phosphonoacetic acids (**46-48**) are coupled with morpholidate **53**, which in turn was prepared from the known phosphonate **52** [36] (Scheme 7).

Cyclopropane Derivatives

Tsuji *et al.* have designed and prepared several carbocyclic nucleosides structurally related to acyclovir (**54**), ganciclovir (**55**) and penciclovir (**56**), as well as the carbanucleoside analogues of oxetanocin G (**57**), and cyclobut-G (**58**) [37]. For the design of these drugs, the relative position and special alignment of both 3' and 5' hydroxyl groups of 2'-deoxyribose ring were considered [37]. A cyclopropane group, an epoxide ring, or a double bond were employed to impart a certain degree of rigidity required to orientate the hydroxyl groups for molecular recognition. The designed compounds are presented in Scheme 8. At the beginning, only racemic syntheses were carried out, but once the biological evaluation was at hand, the enantioselective preparation of the more prospective compounds was developed. From the synthesized carbanucleosides, **(±)-59** resulted to be very effective against HSV-1 (IC_{50} 0.046 μg/mL) and 20 times more potent than acyclovir (IC_{50} 0.81 μg/mL) under the same assays

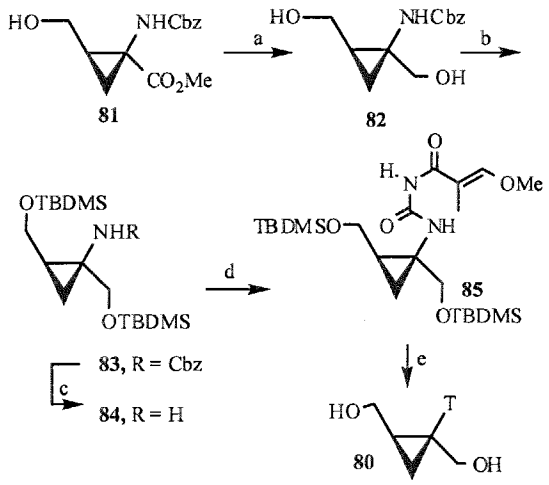


Scheme 8. Reagents and Conditions: (a) TBDMSCl, Im, DMF, 0 °C, 56%; (b) i. OsO_4, NMO, THF–H_2O, rt, 84 h, ii. $NaIO_4$, rt, 16 h, 81%; (c) $NaBH_4$, MeOH, 0 °C, 30 min, 87%; (d) BzCl, py, 0 °C, 30 min, 97% for **65**, 30% for **67**; (e) aq. HCl, MeOH, rt, 40 min, 100%; (f) ClTs, 4-DMAP, CH_2Cl_2, 0 °C, 1 h, 84%; (g) 2-amino-6-(benzyloxy)purine, K_2CO_3, 18-crown-6, DMF, 60 °C, 2 h, 61%; (h) i. MeONa/MeOH, 40 °C, 30 min, ii. 1 N HCl, 50 °C, 30 min, 81%; (i) EtONa/EtOH, diethyl malonate, 75 °C, 20 h, 70%; (j) $NaBH_4$, EtOH, rt, 2 h, 69%; (k) 2,2-dimethoxypropane, *p*-TsOH, DMF, rt, 12 h, 49%; (l) $LiBH_4$, THF, reflux, 12 h, 64%; (m) NaH, DMF, BnBr, rt, 14 h, 90%; (n) HCl, THF, 0 °C, 30 min, 86%; (o) BzCl, py, $CHCl_3$, 0 °C, 12 h, 68%; (p) H_2, 10% Pd/C, EtOH–EtOAc, 1 atm, 3 days, 99%.

conditions, while the pure enantiomer **(–)-59** presented an IC_{50} value of 0.020 μg/mL, that is, 2-fold more potent than the racemic mixture [37]. The enantioselective synthesis of **(–)-59** was achieved starting from the available cyclopropane lactone **71**, which in turn, is obtained by condensation of diethyl malonate and (*R*)-(–)-epichlorhydrin (**70**) according to Pirrung *et al.* [38] (Scheme 8).**(+)-59**, is prepared in the same way from (*S*)-(+)-epichlorhydrin. This unusual activity can be explained by the introduction of a conformational restriction modulated by the cyclopropane ring, which force the hydroxyl groups to adapt a somewhat defined spatial orientation that is required for a better interaction with the involved enzymes. All of these cyclopropyl-containing nucleosides are not completely rigid, they have preferential hydroxyl groups orientation, in other words, they have such a flexibility that can interact either with thymidine kinases or viral DNA polymerases in an efficient way leading to potent antiviral agents [37]. Epoxides derivative like **(±)-60** is moderately active against HSV-1. This low activity may be attributed to ring-opening under the assays conditions.

Among these cyclopropyl-containing carbanucleosides, Ortuño *et al.* have reported an enantioselective synthesis of a new series of this family of compounds, in which the base, in the case of thymine, is bonded to the cyclopropyl group instead of to the methylene group as Tsuji's nucleosides to produce **80** [39]. These compounds were prepared according to Scheme 9 employing (–)-(*Z*)-2,3-methanohomoserine (**81**) as a chiral starting material [39]. This linear approach is very efficient and occurs with high stereoselectivity with 16% overall yield for the thymidine derivative.

It deserves to mention another synthetic methodology to prepare *cis,cis*-trisubstituted cyclopropyl carbocyclic nucleosides with the base also linked to the cyclopropyl ring [40]. These compounds were designed taking into account that the base closeness to the carbocyclic ring would favour the interactions with the different involved enzymes.

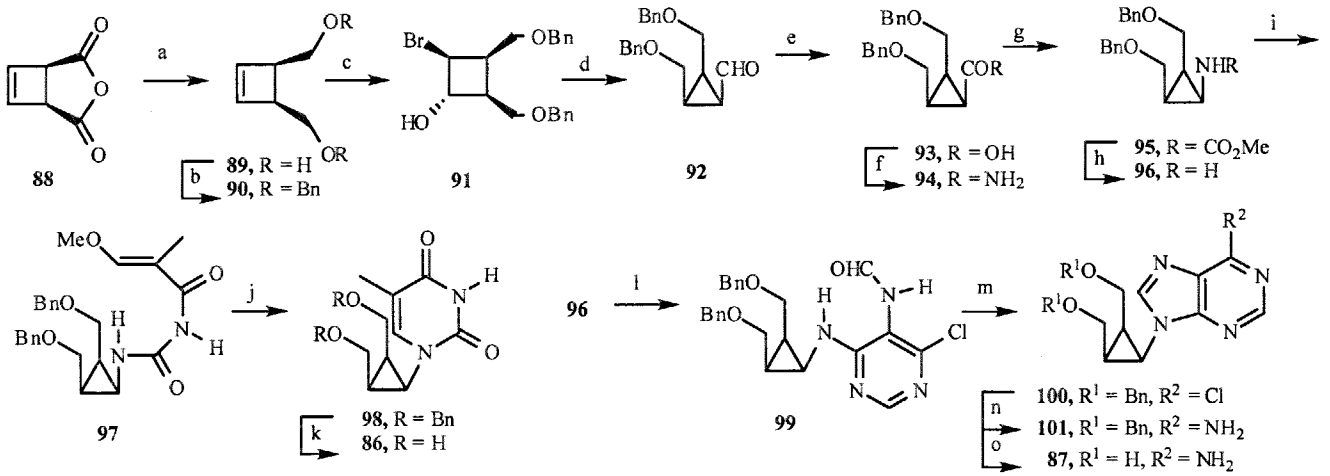


Scheme 9. Reagents and Conditions: (a) $LiBH_4$, 94%; (b) TBDMSCl; (c) H_2, $Pd(OH)_2$, 83% two steps; (d) 3-methoxy-2-methylacrylic acid, $(COCl)_2$, AgOCN, 30%; (e) 0.2 M HCl, 68%.

However, these compounds are devoid of antitumor activity. The preparation of the adenosine and thymidine derivatives, compounds **86** and **87**, respectively, is illustrated in Scheme 10. The critical step in this approach is the ring contraction of a cyclobutane ring in compound **91** to give rise to the desired cyclopropyl intermediate **92** in excellent yield [41].

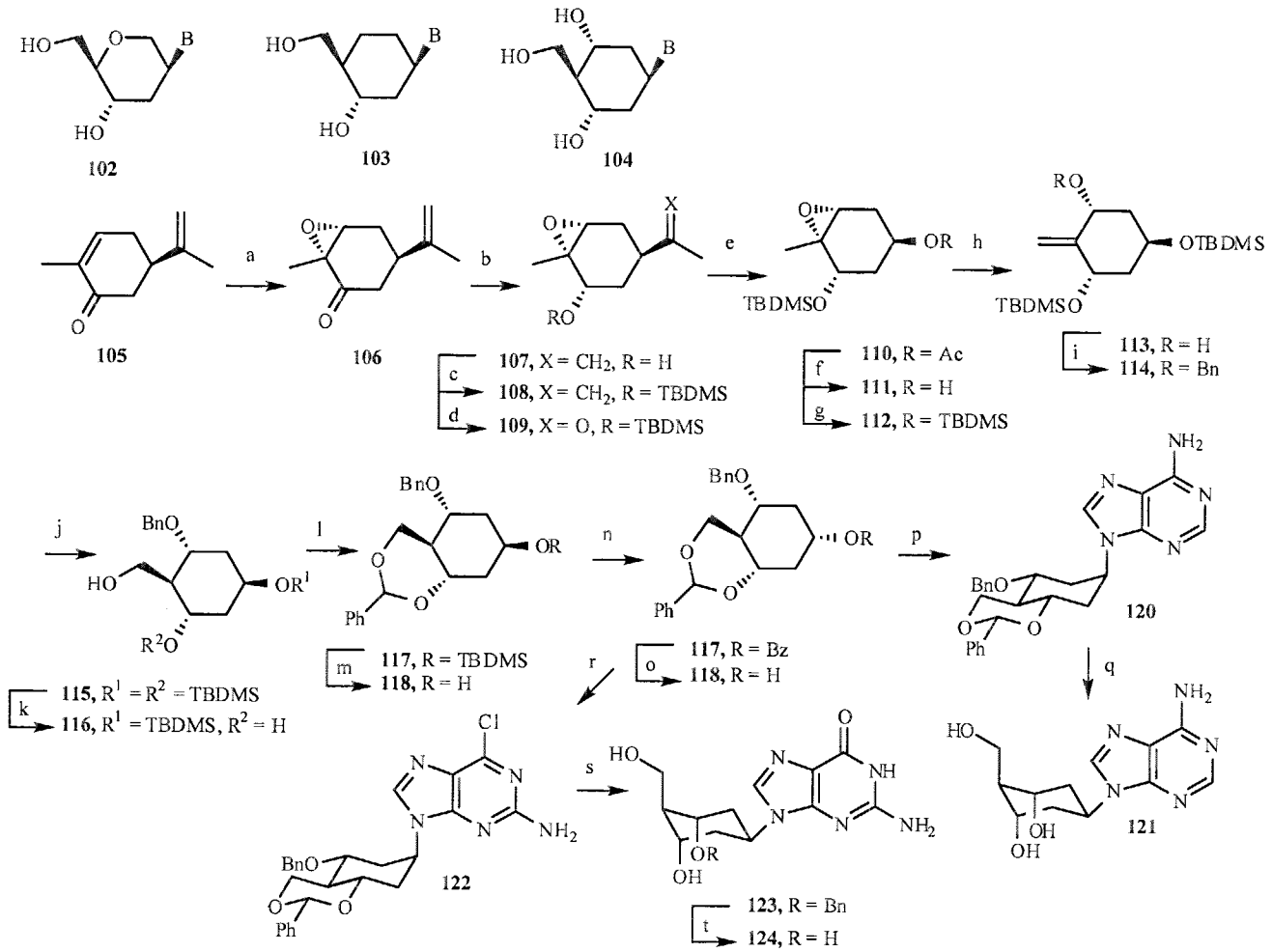
Cyclohexane Derivatives

Analogues of anhydrohexitol nucleosides **102** represent very good examples of the potential utility of nucleosides analogues (Scheme 11). These drugs, developed by Herdewijn *et al.*, exhibit potent antiviral activity [42, 43], while the carbocyclic analogues of general formula **103** are devoid of antiviral activity [44]. This lack of antiviral action may be attributable to the fact that, in anhydronucleosides,



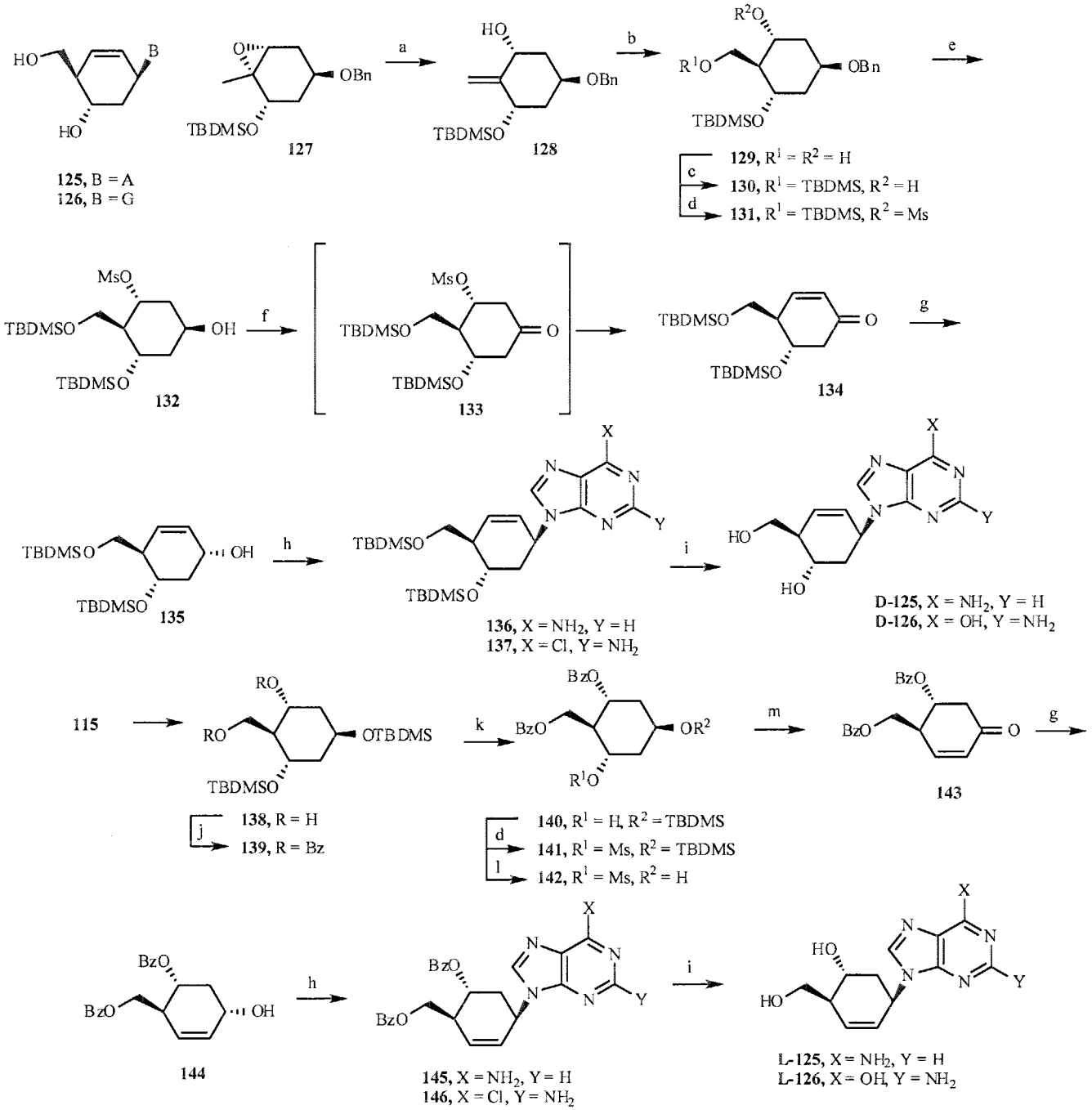
Scheme 10. Reagents and Conditions: (a) $LiAlH_4$, 96%; (b) NaH, BrBn, 94%; (c) NBS, H_2O, 76%; (d) NaOH, 100%; (e) Jones' reagent, -5 °C, 10 h, 71%; (f) i. $ClCO_2Et$, Et_3N, THF, -5 °C, 1 h, ii. NH_3/THF, 0 °C, 1 h, 82%; (g) $PhI(OAc)_2$, KOH, MeOH, rt, 2 h, 78%; (h) KOH, MeOH, reflux, 48 h, 83%; (i) 3-methoxy-2-methylacryloyl chloride, AgOCN, PhH, reflux, 20 h, 90%; (j) NH_4OH, MeOH, 85 °C, 24 h, 57%; (k) i. BCl_3, CH_2Cl_2, -78 °C, ii. MeOH, -78 °C, 60%; (l) 5-formamido-4,6-dichloropyrimidine, Et_3N, dioxane, reflux, 8 h, 50%; (m) i. diethoxymethylacetate, 120 °C, 22 h, ii. NH_4OH, MeOH, rt, 1 h, 58%; (n) NH_3/MeOH (saturated at –78 °C) 80 °C, 24 h, 73%; (o) BCl_3, CH_2Cl_2, -78 °C, ii. MeOH, -78 °C, 75%.

the base adapts an axial position (conformation $^1C_4$), while in the carbocyclic nucleosides the base is equatorial orientated (conformation $^4C_1$) [45]. Moreover, NMR conformational studies indicate that carbocyclic nucleosides do not mimic quite well the characteristic 3'-*endo* conformation of conventional nucleosides, while the conformation found in anhydrohexitol nucleosides is almost similar to that found in normal nucleosides [45]. In spite of these results, a new series of carbanucleosides bearing an additional hydroxyl group was investigated [46]. In this case, an α-oriented hydroxyl group at the C-5' position in carbanucleosides of general formula **104** was designed, synthesized and evaluated against different viruses due to the presence of this new substituent might favor the conformation $^1C_4$ similar to that found in anhydrohexitoles [45]. Neither of these drugs exhibited any inhibitory action against HSV-1, HSV-2, HIV-1, HIV-2, vaccinia virus, vesicular stomatitis virus, etc. According to the ^1H NMR analysis, the conformation $^4C_1$ with equatorial base is still preferred [45]. The enatioselective synthesis for this family of compounds employs (*R*)-(−)-carvone as chiral source. The key steps for this approach are the regio- and stereoselective hydroboration reaction of the double bond of a 2-methylencyclohexane-1,3-diol derivative (compound **114**) to give **115**, and the introduction of the base through a Mitsunobu-type reaction to afford the title compounds **121** and **124** (Scheme 11). Bearing in mind that the antiviral activity of nucleosides is attributed to complex interactions among a set of enzymes, Herdewijn *et al.* designed a somewhat flexible carbanucleoside analogue capable of interacting with all the enzymes involved. Employing this concept, and in order to have a low energetic barrier between both conformations, a double bond was introduced onto the carbocyclic ring of general formula **125** and **126**. Molecular modelling studies and careful analysis of the proton NMR spectra confirm that the pseudoaxial position of the base corresponds to the preferred conformer, probably, due to the existence of overlapping between the π orbital (C5'–C6') and the antiligand bond C1'–N that favors the conformation $^3H_2$ over the $^2H_3$. In addition, the values of the energy barrier result to be 1.6 kJ/mol less than the cyclohexanes derivatives [45]. The synthetic strategy to prepare



Scheme 11. Reagents and Conditions: (a) H_2O_2,/NaOH, MeOH, 83%; (b) L-selectride, THF, -65 °C; (c) TBDMSCl, Im, DMF, 93%; (d) 1% OsO_4/$NaIO_4$, THF-H_2O, rt, 83%; (e) *m*-CPBA, $CHCl_3$, pH = 8, rt, 73%; (f) K_2CO_3, MeOH-H_2O, 73%; (g) TBDMSCl, Imidazole, DMF, 80%; (h) LiTMP/Et_2AlCl, PhH, 0 °C, 100%; (i) NaH, BnBr, TBAI, THF, rt; (j) 9-BBN, THF, rt, 62%; (k) TBAF (1 equiv.), THF, rt, 93%; (l) $PhCH(OMe)_2$, PTSA, dioxane, 90%; (m) TBAF, THF, 93%; (n) $PhCO_2H$, DEAD, PPh_3, dioxane; (o) K_2CO_3, MeOH, 72%; (p) adenine, DEAD, PPh_3, dioxane, rt, 93%; (q) Pd(OH)$_2$/C, cyclohexene, MeOH, reflux, 73%; (r) 6-chloro-2-aminopurine, DEAD, PPh_3, dioxane, rt, 37%; (s) CF_3CO_2H/H_2O (3:1), rt, 75%; (t) Pd(OH)$_2$/C, cyclohexene, MeOH, reflux, 63%.

cyclohexenyl carbanucleosides also employ (*R*)-(−)-carvone as chiral starting material and has several points of coincidence (Scheme 12). Once the synthetic intermediate **129** is available, this product is further transformed into the allylic alcohol **135**, which is coupled either with adenine or 2-amino-6-chloropurine under Mitsunobu-type conditions to give the corresponding advanced carbanucleosides precursors **136** and **137**, respectively, that after cleavage of the corresponding protecting groups affords adenosine and guanosine derivatives **D-125** and **D-126**, respectively [46,47]. As can be observed in Scheme 12, both enantiomers of each nucleic base have been synthesized from the same starting material (D-A, L-A, D-G, L-G). Guanosine derivative **D-126** results to be a potent and highly selective antiviral agent

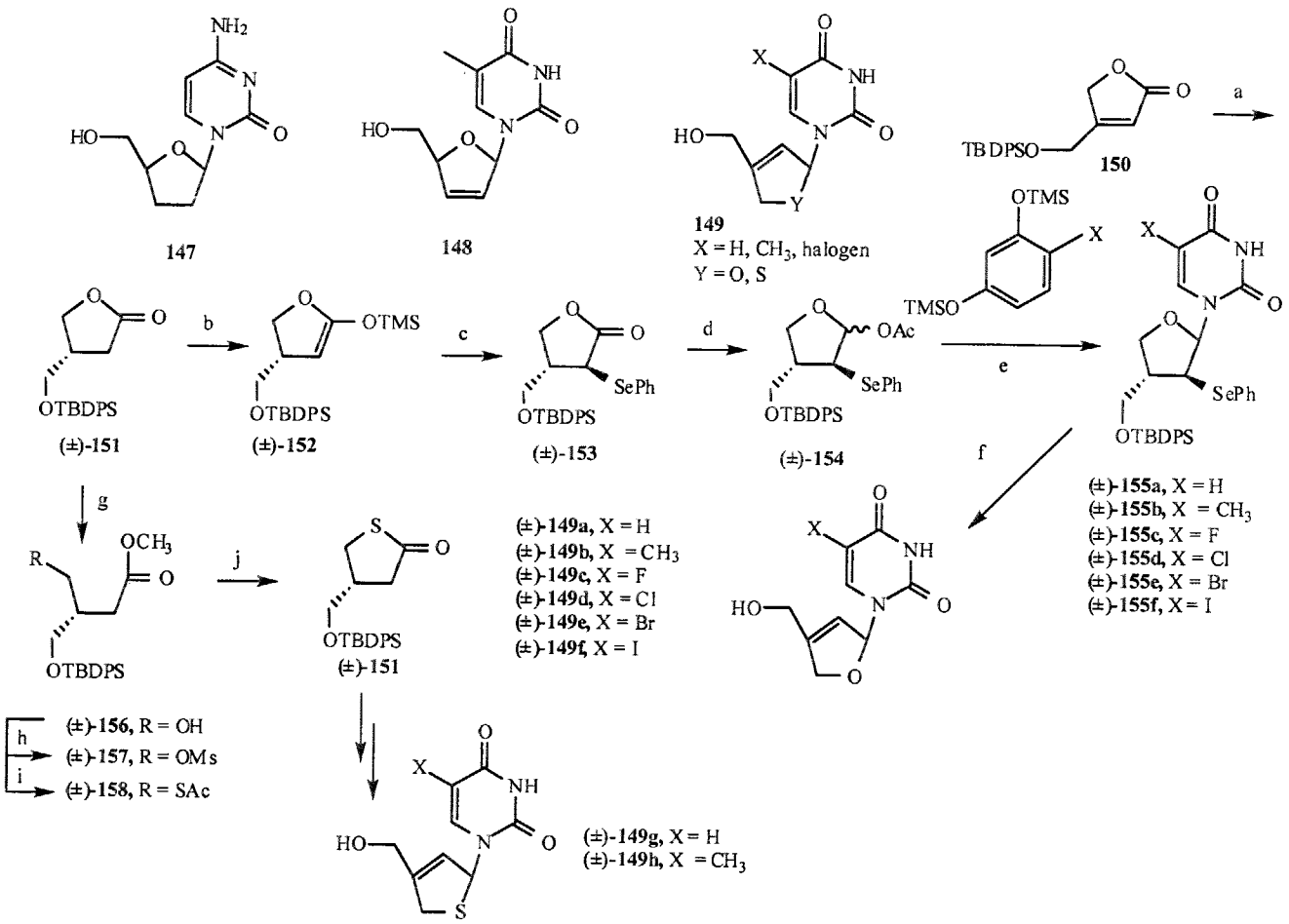


Scheme 12. Reagents and Conditions: (a) *n*-BuLi, TMP, Et_2AlCl, PhH-PhMe (1:1), 0 °C, 3 h, 71%; (b) 9-BBN, THF, 0 °C, then H_2O_2, 2 N NaOH, 74%; (c) TBDMSCl, Imidazole, DMF, rt, 70%; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 92% for **131**, 98% for **141**; (e) 10% Pd/C, HCO_2NH_4, MeOH, reflux, 76%; (f) MnO_2, CH_2Cl_2, rt 48% and 47% recovery starting material; (g) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C → rt, 91 % for **135**, 75% for **144**; (h) adenine, DEAD, PPh_3, dioxane, rt, 66% for **136**, 40% for **145**, 2-amino-6-chloropurine, DEAD, PPh_3, dioxane, rt, for **137** and **146**; (i) TFA/H_2O, rt,.78% for **D-125**, 46% from **135** for **D-126**, K_2CO_3, MeOH, rt for **L-125**, 58% from **144** for **146** followed by NH_3/MeOH, 80 °C, 2 days 73% for **L-126**; (j) Bz_2O, DMAP, CH_2Cl_2, 0 °C, 98%; (k) TBAF (1 equiv), THF, rt, 74%; (l) TBAF, THF, rt, 86%; (m) PDC, CH_2Cl_2, rt, 48%.

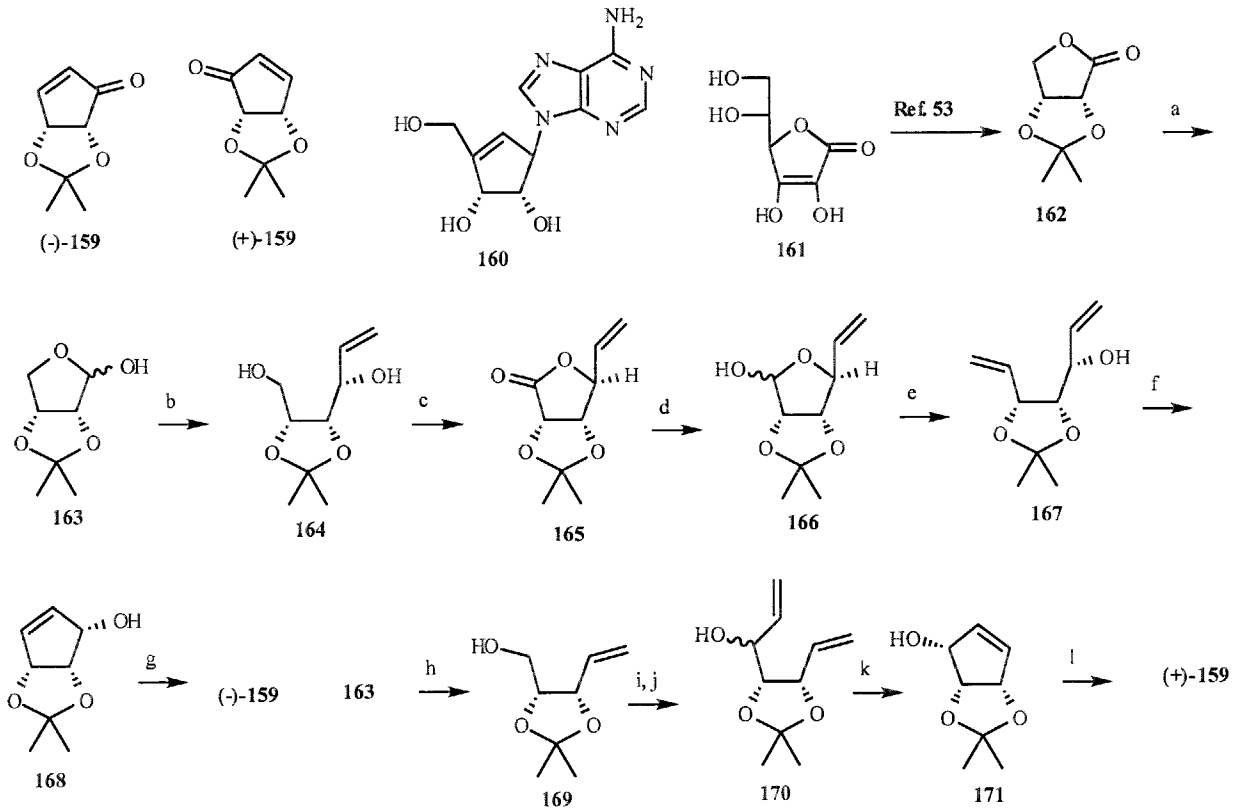
with effectiveness similar to the commonly employed drugs for the treatment of herpes infection, acyclovir and ganciclovir. The selectivity presented for these drugs make them good candidates for *in vivo* assays. It deserves to pointing out that both enantiomers exhibit almost the same potency as antiviral agents. Docking experiments with HSV-1 thymidine kinase (TK) shows that both enantiomers fit well in the active site when the conformation is flipped to that with a pseudo equatorial oriented base moiety. This constitutes an interesting example because the enzyme interacting with same efficacy at the active site can recognize both enantiomers. These results are in agreement with previous studies, in which inversion of configuration occurs when hexitol nucleosides are co-crystallized with HSV-1 TK. Very recently, Herdewijn *et al.* have reported that incorporation of cyclohexenyl carbanucleosides into oligonucleotides produces a remarkable heteroduplex stabilization [48]. Certainly, incorporation of one, two, or three unit of **D-125** in the DNA strand produces an increment of *T*m in +1.1, +1.6, and +5.2 °C, respectively. Interestingly, the stabilization effect of anhydrohexitol **102** (B = adenine) is two-fold higher than **D-125** [48]. However, the oligoadenilate-poly(dT) complex is significantly more stable than the corresponding anhydrohexitol oligoadenilate-poly(dT) complex. As cyclohexenyl carbanucleosides have structural similarities compared with natural furanosyl nucleic acids, they produce similar conformational changes than conventional nucleosides. In addition, since cyclohexenyl carbocyclic nucleosides combine the advantages of stabilizing heteroduplex complexes, of being stable in serum, and of activating RnaseH, these properties make these compounds good candidates for antisense evaluation in cellular systems. It is interesting to notice that **102** (B = adenine) is recognized by a number of DNA polymerases, especially by the B-family, however, in any case no more than two consecutive triphosphate derivative can be incorporate [49].

Cyclopentenyl Carbanucleosides

A very motivating novel class of nucleosides analogues are apio and thioapio dideoxydidehydronucleosides derivatives [50]. Although these drugs cannot be considered



Scheme 13. Reagents and Conditions: (a) H_2, 10% Pd/C, EtOAc, 99%; (b) LiHMDS, THF, -78 °C, then TMSCl, rt; (c) PhSeBr, THF, -78 °C, 77% from **151**; (d) i. DIBAL, PhMe, -78 °C, ii. Ac_2O, py, rt, 85%; (e) NH_4SO_4 (cat), HMDS, 140-150 °C → rt, then HMDS removal, 1,2-dichloroethane, 5 °C, TMSOTf, 90% for **155a**, 63% for **155b**, 62% for **155c**, 69% for **155d**, 91% for **155e**, 68% for **155f**; (f) CH_2Cl_2, 30% H_2O_2, rt, then TBAF, THF, 0 °C, 84% for **149a**, 44% for **149b**, 44% for **149c**, 90% for **149d**, 90% for **149e**, 45% for **149f**; (g) 1 N NaOH, 1 h, then $(CH_3)_2SO_4$, DMSO, 1 h, 89%; (h) MsCl, py, rt; (i) KSAc, DMF, rt, 7 h, 86% from **156**; (j) NaOH, H_2O, EtOH, 50 °C, 2.5 h, then DCC, DMAP, CH_2Cl_2, 30 min, 70%.



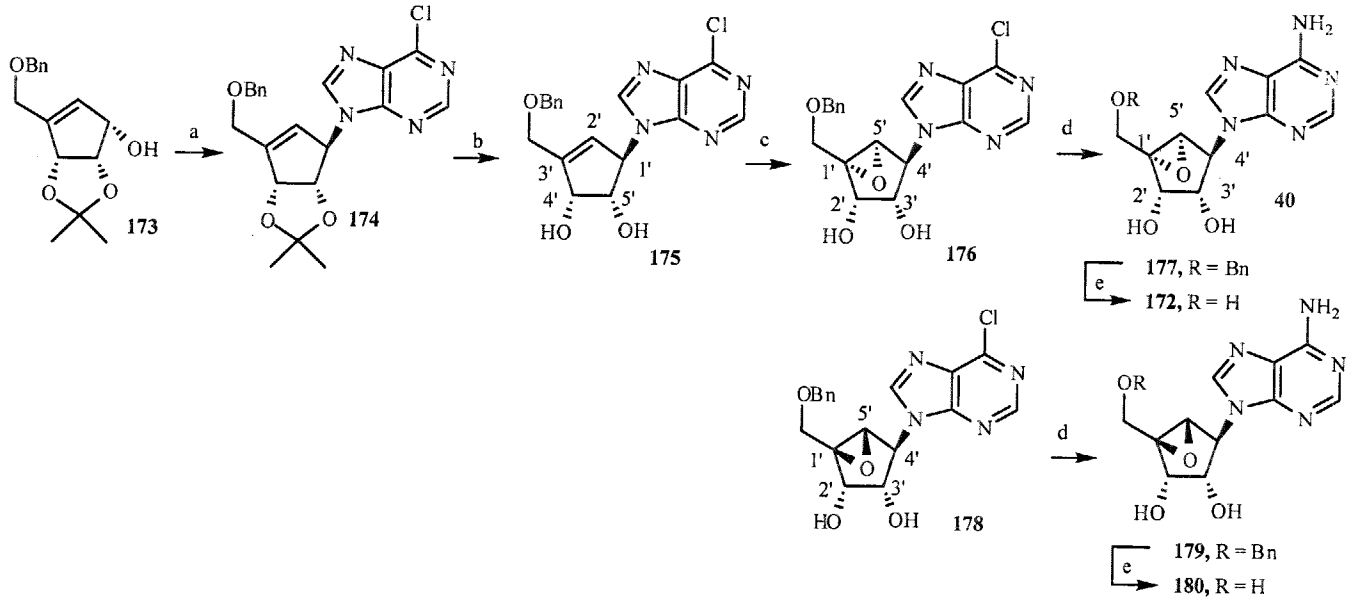
Scheme 14. Reagents and conditions: (a) DIBAL-H, PhMe, –78 °C, 81%; (b) CH_2=CHMgBr, THF, –78 °C, 100%; (c) TPAP, NMNO, CH_2Cl_2, 0 °C, 66%; (d) DIBAL-H, PhMe, –78 °C, 84%; (e) 60% NaH, DMSO, THF, PPh_3CH_3Br, 0 °C → rt, 88%; (f) Grubbs catalyst, $CHCl_3$, rt, 2 h, 89%; (g) MnO_2, CH_2Cl_2, rt, 5 h, 83%; (h) Ph_3PCH_3Br, NaH, DMSO, THF, rt, overnight, 72%; (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h, then NEt_3→ rt; (j) CH_2=CHMgBr, THF, –78 °C, 1 h, 63%; (k) Grubbs catalyst, $CHCl_3$, rt, 2 h, 77%; (l) MnO_2, CH_2Cl_2, rt, 15 h, 81%.

as carbanucleosides, the fact that the oxygen atom of the furanose ring moves to the C-2 position make these drugs not recognisable by adenosine deaminase, phosphorilases and hydrolases, behaviour found in carbanucleosides. These drugs were designed on the basis of the antiviral activities shown by 2',3'-dideoxycytidine (ddC, **147**) and 2',3'-dideoxy-2',3'-didehydrothymidine (d4T, **148**) by moving the oxygen atom and the double bond to form nucleosides analogues of general formula **149**. These compound were synthesized according to Scheme 13 starting from the known α,β-unsaturated lactone **150** [51]. All the **149** series is devoid of activity against HIV-1, HSV-1 and HSV-2, but the fluorouracil derivative (**149c**) is a potent anti-HCMV agent at the low micromolar level, while the rest of apio derivatives are moderately potent drugs against HCMV [50]. The thioapio nucleosides are not active against HCMV.

A very useful synthetic intermediate (compound **159**) is now available for the preparation of D- and L-cyclopentenyl carbocyclic nucleosides of pharmacological importance including the naturally occurring neplanocin A (**160**) and aristeromycin (**23**) [52]. Both enantiomers of **159** can be prepared from the same starting material, D-isoascorbic acid (**161**) as depicted in Scheme 14. **161** is easily transformed into the isopropyliden lactone **162** according to published procedures [53]. The levo-isomer **(-)-159** leads to D-carbocyclic nucleosides while the enantiomer **(+)-159** leads to the L-series [52].

Conformationally Constrained Carbanucleosides

Of special interest is the sugar conformation / biological activity studies made in a variety of carbocyclic nucleosides. In solution, the ribose unit exits in a dynamic equilibrium between the Northern-type geometry and the facing Southern-type geometry according to the concept of the pseudorotational cycle [54]. To the contrary, only one of these conformers is found in the crystalline structure, and only the Northern or Southern conformer is solely responsible for molecular recognition as well because only one form is present in the drug-enzyme complex. However, as the ribose ring is bendable and the conformation in solution may be unlike than that found in the solid state, any attempt to correlate sugar conformation with biological action would be flawed unless the crystal and the solution conformation are the same. A cyclopropane or epoxy ring can confer such rigidity to the sugar moiety that the equilibrium N ⇔ S is not observed indicating that the solution conformation is virtually identical to that found in the crystal [55]. However, the conformational restriction induced by an epoxy group at the C-2', C-3' positions fixes the sugar conformation far away from the Northern or Southern geometry that is required for biological activity. In carbocyclic nucleosides, the elimination of the oxygen atom of the furanose ring brings about a significant change in terms of stereoelectronic effects. Therefore, the anomeric effect as well as significant gauche interactions between this



Scheme 15. Reagents and conditions: (a) 6-chloropurine, PPh_3, DEAD, THF, rt, 1 h; (b) AcOH, 50 °C, 24 h, 40% from **173**; (c) *m*-CPBA, CH_2Cl_2, 0 °C → rt, 10 days, (d) NH_3/MeOH, 70 °C, 5 h, 75% for **177**, 63% for **179**; (e) H_2, 10% Pd/C, MeOH, 3 atm, 88% for **172**, 72% for **180**.

oxygen atom and any electronegative substituent at C-2' or C-3' is lacking. The naturally occurring carbocyclic nucleoside neplanocin C (**172**) [56-59], is a good prototype of a conformationally locked nucleoside analogue. This compound, isolated from *Ampullariela regularis*, is a minor component of the neplanocin family of antibiotics, and it is built on a [3.1.0]-bicyclic system, which allows it to exhibit the typical northern-type (N) conformation, specifically in the $_2E$ conformation that is very close to a pure $^3T_2$ (P = 0°) geometry as determined by the *P* value of the pseudorotational cycle (P value = 338.03° and ν_{max} = 21.89°) from the solved X ray structure [59]. The structure of neplanocin C was taken as lead drug for the development of a huge number of conformationally restricted carbanucleosides of biological importance [60-71]. The enantioselective synthesis of this valuable carbocyclic nucleoside has been recently achieved [72, 73] employing cyclopentenol **173** as advanced synthetic intermediate, which in turn, is available from D-ribonolactone in seven steps [72]. The critical step for the synthesis of neplanocin C is the epoxidation reaction, in which it is required ten days of reaction time to produce the neplanocin C precursor **176** and its diasteromer **178** in a 1:1 ratio. Both of these isomers are easily separated by column chromatography. The unusual stereochemical course of the epoxidation reaction, where the Hembest rule is not applicable, can be explained bearing in mind that the base in the *anti* position in **175** is almost 6 kcal/mol more stable that the *syn* conformer. Then, the electrophilic epoxidizing agent can also coordinate with the N-3 rather than exclusively with the hydroxyl groups affording equal amounts of **176** and **178**. The other critical point is the remarkable stability of the epoxy functionality under methanolic ammonia at high temperature to produce **177**. This fact had already been described in simpler and closely related carbanucleosides built in a [3.1.0]oxabicyclo systems [74]. As it was mentioned before several carbanucleosides has been synthesized on the basis of neplanocin C structure. Among them, it is worth pointing out the following conformationally rigid carbocyclic nucleosides: (a) the adenosine derivative of 2',3'-dideoxycarbanucleosides locked in the N geometry (**181**) is moderately active against HIV [60, 61]. The 5'-triphosphate of conformationally restricted carbocyclic analogues of AZT locked in the Northern conformation (**182**) is exclusively responsible for reverse transcriptase (RT) inhibition [62], while the 5'-triphosphate of its isomer rigid in the S geometry **183** ((S)-methanocarba-AZT) is devoid of activity against RT [62]. In addition, neither of these two rigid AZT analogues exhibit anti-HIV activity as such, and as the S geometry is the conformation needed for molecular recognition by kinases, it is reasonable that **182** is not efficiently phosphorylated, but it is very surprising that **183**, in spite of having the required S conformation (specifically $(_3E)$ conformation), is not capable of incorporation of phosphate either. This behavior might be attribute to the fact that the rigidity of this prodrug forces the thymine base to a *syn* orientation destabilizing the enzyme-substrate complex. These results explain why relatively flexible nucleosides prodrugs like AZT can be phsophorylated and then adopt the required N conformation to inhibit RT. (c) (N)-methanocarbathymidine (**184**) is an extremely potent drug against herpes simplex virus 1 and 2 (HSV1 and HSV2) and even more potent than acyclovir, a well known antiviral agent that is employed at the present time for treatment of herpetic infections [63, 64]. In addition, kinetics and crystal structure of **184** interacting with thymidine kinase from Herpes simplex virus type-1 has been conducted [75] demonstrating that the antiviral activity may be attributed to the thymidine salvage pathway [75]. (N)-methanocarbathymidine and (S)-methanocarbathymidine (**185**) also shows potential to be used as building block in antisense chemotherapy, in fact, when **184** replaces thymidine in DNA/RNA heteroduplexes an increment of thermodynamic stability is observed, while **185**, which is

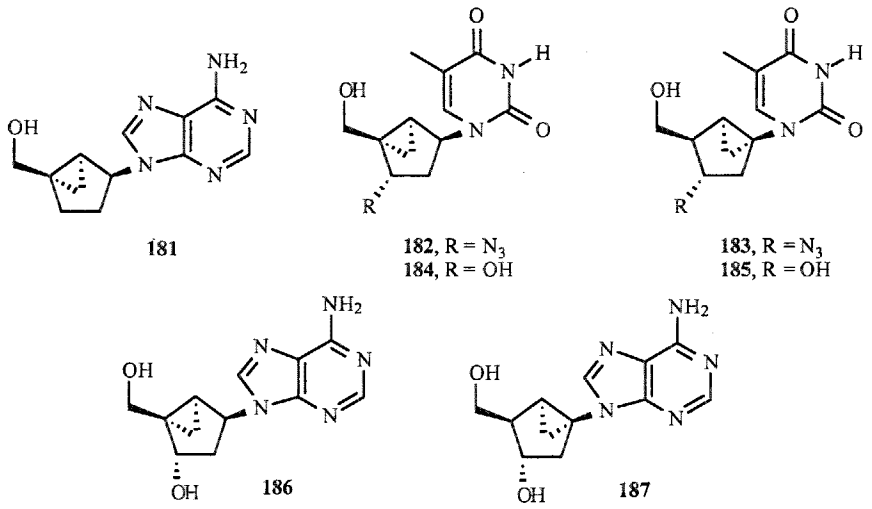
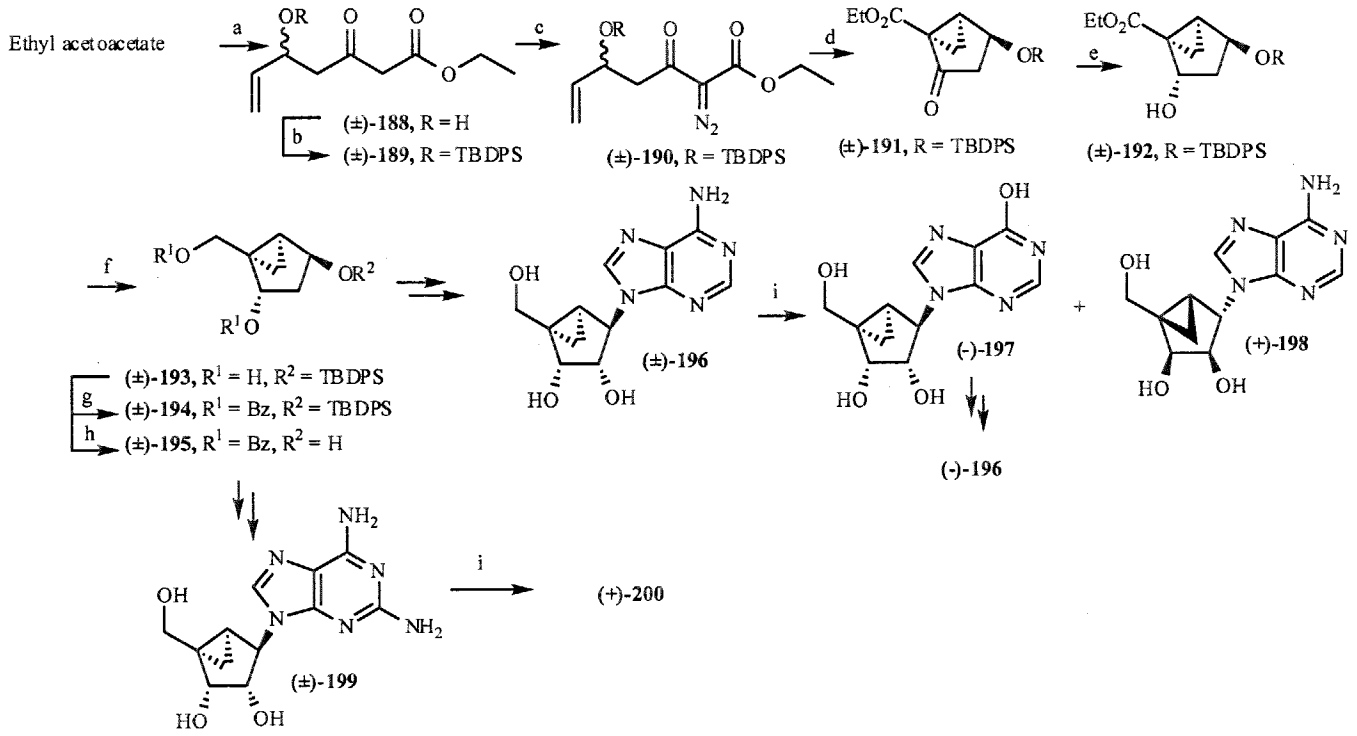


Fig. (1).

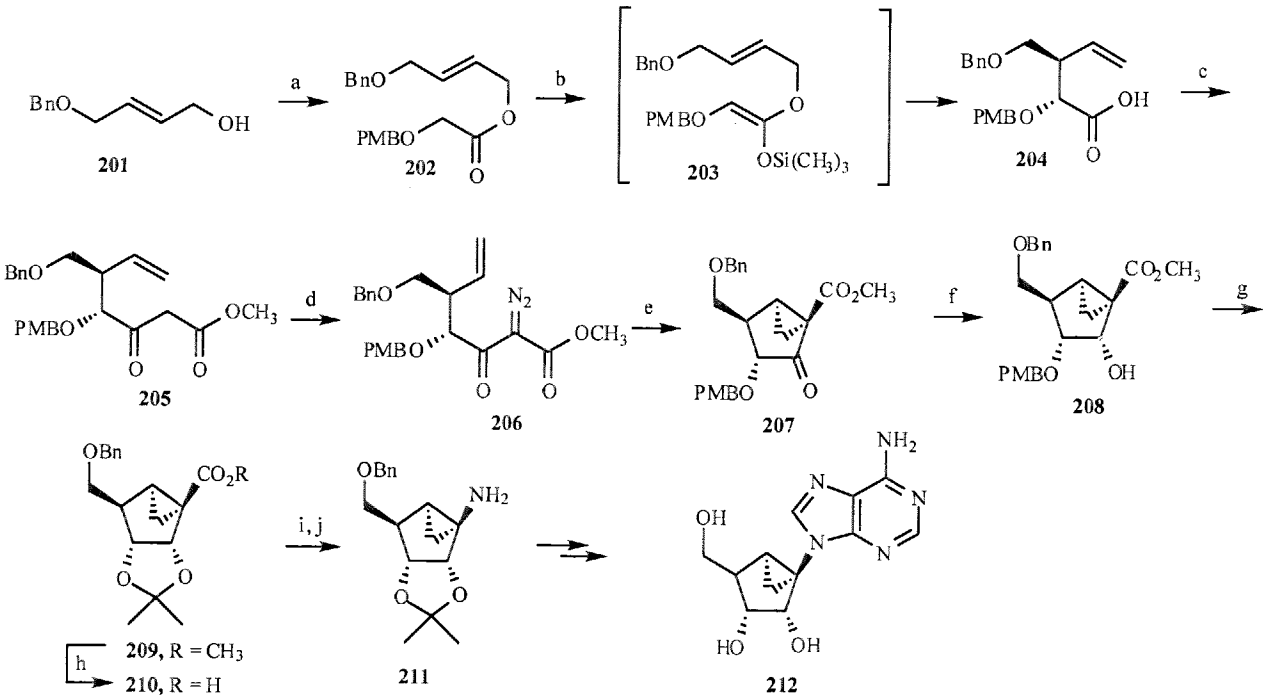
locked in the S geometry, produces an opposite destabilizing effect [65, 66]. Adenosine derivative (N)-methanocarba-2'-desoxyadenosine (**186**) is a substrate of adenosine deaminase (ADA), the enzyme responsible for catalyzing irreversible deamination of adenosine to inosine, this compound is deaminated 100 times faster than its antipodal rigid conformer **187**, (S)-methanocarba-2'-deoxyadenosine [67] (Figure **1**). ADA is a crucial enzyme in the purine metabolic pathway that appears at extremely high levels in tumoral lymphocytes, whereas it is not well expressed in several inherited immunodeficient diseases. In a rigorous study of preferential conformation for catalysis it is described that the N-type nucleosides form a stable complex with ADA [76]. Certainly, the N-locked carbanucleoside analogue **186** is deaminated 100-fold faster than the S-type analogue **187** [77]. One attractive application of the concept of lock conformation is the preparation of DNA duplexes bearing conformationally constrained abasic sugars to investigate the mechanism of base flipping by *Hha*I DNA (cytosine C5)-methyltransferase [78]. In conclusion, some of the Northern analogues prove to be extremely potent antiviral agents while the Southern derivatives exhibit vanishing inhibitory action.

A novel synthetic approach for access to bicyclo[3.1.0]hexane carbocyclic nucleosides that employs

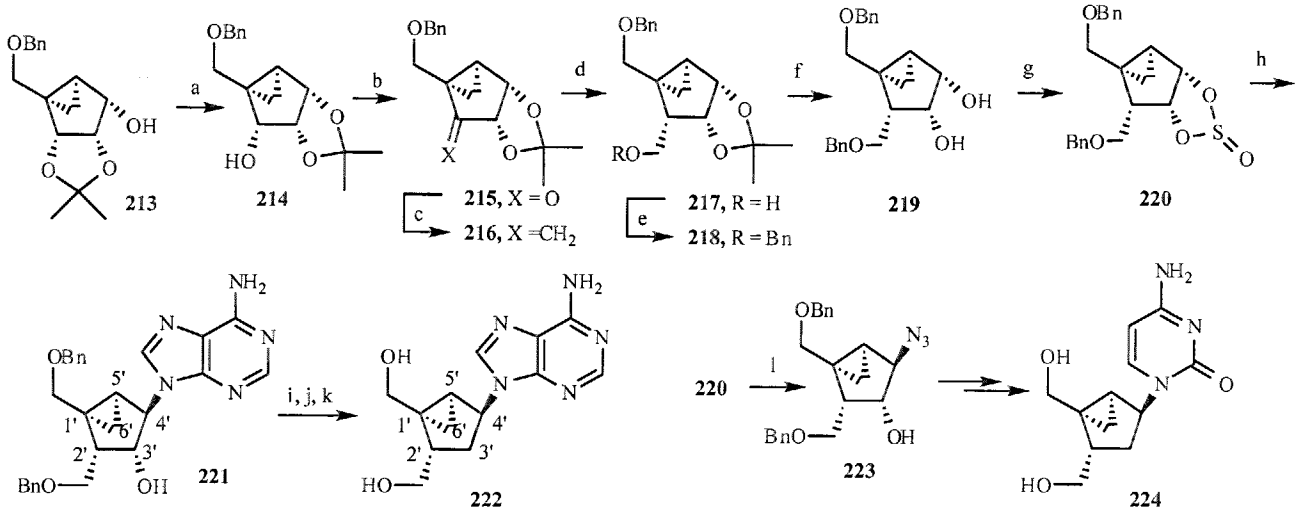


Scheme 16. Reagents and conditions: (a) LDA, THF, -78 °C, CH_2=CHCHO; (b) ^{t}BuPh$_2$SiCl, CH_2Cl_2, 53% from ethyl acetoacetate; (c) TsN_3, Et_3N, MeCN, 99%; (d) $CuSO_4$, cyclohexane, Δ, 61%; (e) $NaBH_4$, MeOH, rt; (f) $LiAlH_4$, Et_2O, 79% from **184**; (g) BzCl; (h) *n*-Bu_4NF, THF; (i) adenosine deaminase, 80%.

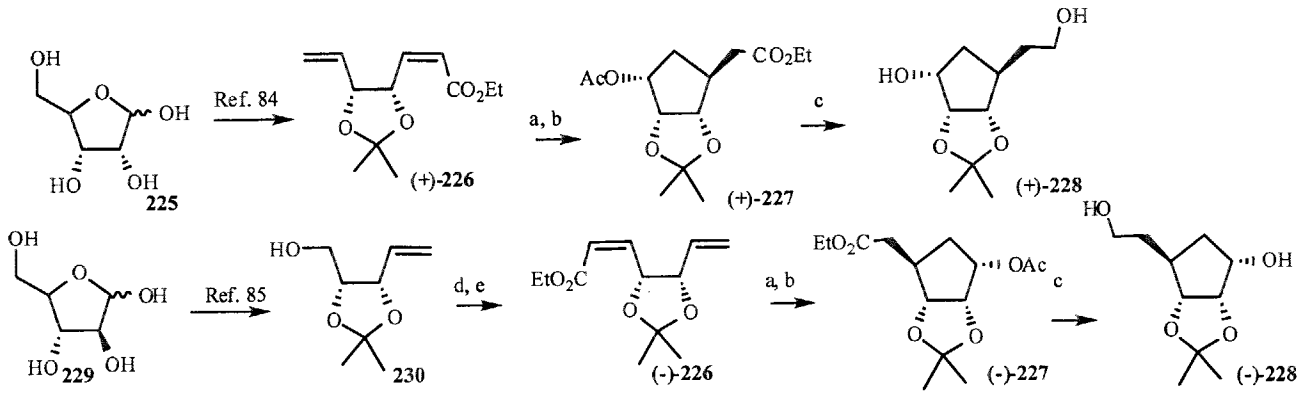
an intramolecular cyclopropanation as key step has been recently reported [79]. In this strategy, a carbene generated from an appropriate β-ketoester gives rise with high diastereoselectivity to the desired carbocyclic ring in an elegant and efficient way. The natural enantiomers of the adenosine and guanosine are obtained with the use of ADA to discriminate the "natural" carbanucleosides. Therefore, (±)-**199** is irreversible deaminated to give the corresponding guanosine derivative **(+)-200**, while **(±)-196** to the inosine derivative **(-)-197** plus the unnatural adenoside **(+)-198**. (-)-**197** is converted back into carbocyclic **(-)-196** by known procedures (Scheme 16) [79]. With the use of this intramolecular carbene insertion on a double bond is also possible to access to the rigid S conformers [80]. As is illustrated in Scheme 17, this reaction provides the required bicyclo[3.1.0]hexane ring that is further transformed into the cyclopentylamine precursor. The allylic alcohol **201** is employed as starting material. The critical synthetic step in this synthetic approach are the Claisen rearrangement reaction on **202** via the intermediate **203** to produce **204**, the



Scheme 17. Reagents and conditions: (a) $PMBOCH_2COOH$, DCC, DMAP, CH_2Cl_2, 99%; (b) i. LDA, THF, ii. TMSCl, Et_3N, 91%; (c) i. carbonyldiimidazole, THF, ii. $LiCH_2CO_2CH_3$, THF, 90%; (d) TsN_3, Et_3N, MeCN, 95%; (e) cupric acetylacetonate, cyclohexane, 52%; (f) $NaBH_4$, MeOH/CH_2Cl_2, (2:1), 91%; (h) $CuSO_4$, H_2SO_4 (cat), Me_2CO, 93%; (i) 1.0 N NaOH, MeOH, 100%; (j) i. $(PhO)_2PON_3$, Et_3N, PhH, ii. 2.0 N NaOH, THF, 64%.



Scheme 18. Reagents and conditions: (a) *p*-TsOH, Me_2CO, 56 °C, 2 h, 57%; (b) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 100%; (c) $CH_3P(Ph)_3Br$, *n*-BuLi, THF, 0 °C, 30 min, 90%; (d) BH_3.THF, $NaBO_3$-H_2O, 99%; (e) BnBr, NaH; (f) 1.0 N HCl, MeOH-THF, reflux, 88%; (g) NEt_3, $SOCl_2$, 0 °C, 5 min, 80%; (h) adenine, NaH, DMF, 18-crown-6, 50%; (i) CS_2, ICH_3, NaH; (j) Et_3B, n-Bu_3SnH; (k) Pd black, HCO_2H, 61%; (l) NaN_3, DMF, 100 °C, 10 h, 81%.

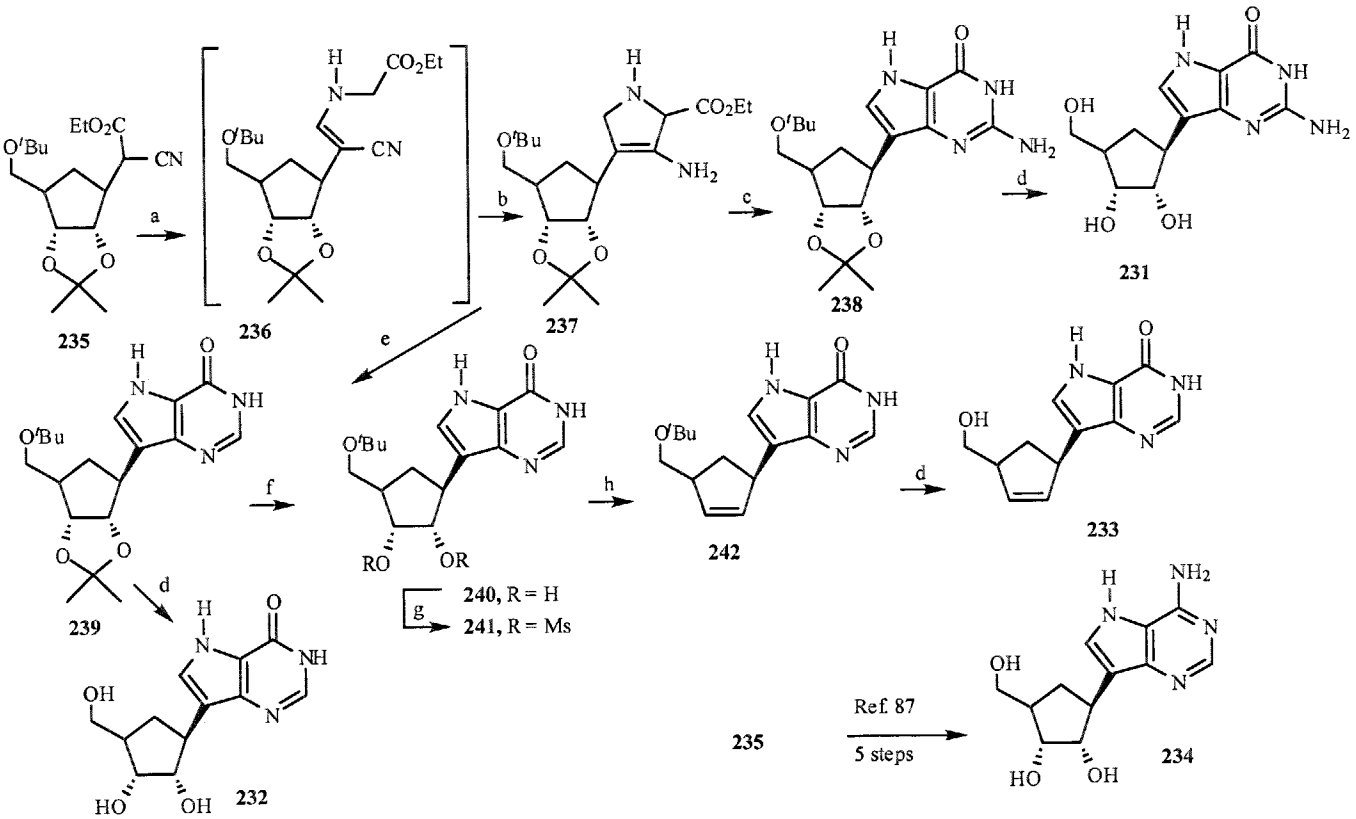


Scheme 19. Reagents and conditions: (a) $Hg(OAc)_2$, AcOH, 20 °C, 12 h; (b) $NaBH(OMe)_3$, CH_2Cl_2, 20 °C, 24 h, 53% from **(+)-226** and from **(–)-226** ; (c) $LiAlH_4$, THF, reflux, 5 h, 87% for **(+)-228** and for **(–)-228**; (d) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –50 °C → 20 °C, 30 min; (e) $Ph_3P{=}CHCO_2Et$, EtOH, $PhCO_2H$ (1%), 0 °C → 20 °C, 24 h, 75% from **230**.

incorporation of two nitrogen atoms by a diazo transfer reaction, and the thermolysis of **206** to produce the rigid bicyclo[3.1.0]hexane template **207**, which after three synthetic step is converted into the cyclopentyl amine **211** that following a linear strategy leads to the adenosine derivative **212** locked in the Southern conformation. Another interesting example of conformationally locked carbanucleosides in the N geometry is the preparation of ring-expanded oxetanocin analogues [81,82]. The synthetic strategy followed for the preparation of these carbanucleosides employs a regioselective opening reaction of the cyclic sulfite **220** as key step. The synthesis begins with the readily available cyclopentanyl alcohol **213**, which in turn is prepared from **173** [65]. Then, on reaction either with adenine or azide ion, **220** is transformed into the desired carbocyclic nucleoside precursor **221** or the cyclopentylazide **223** with high diastereoselectivity. The hydroxymethyl group at the C-3' results to be a bad substituent in terms of the antiviral activity [81].

Miscellaneous

Very recently, a simple procedure for the preparation of precursors of both enantiomers of 5'-*homo*-aristeromycin has

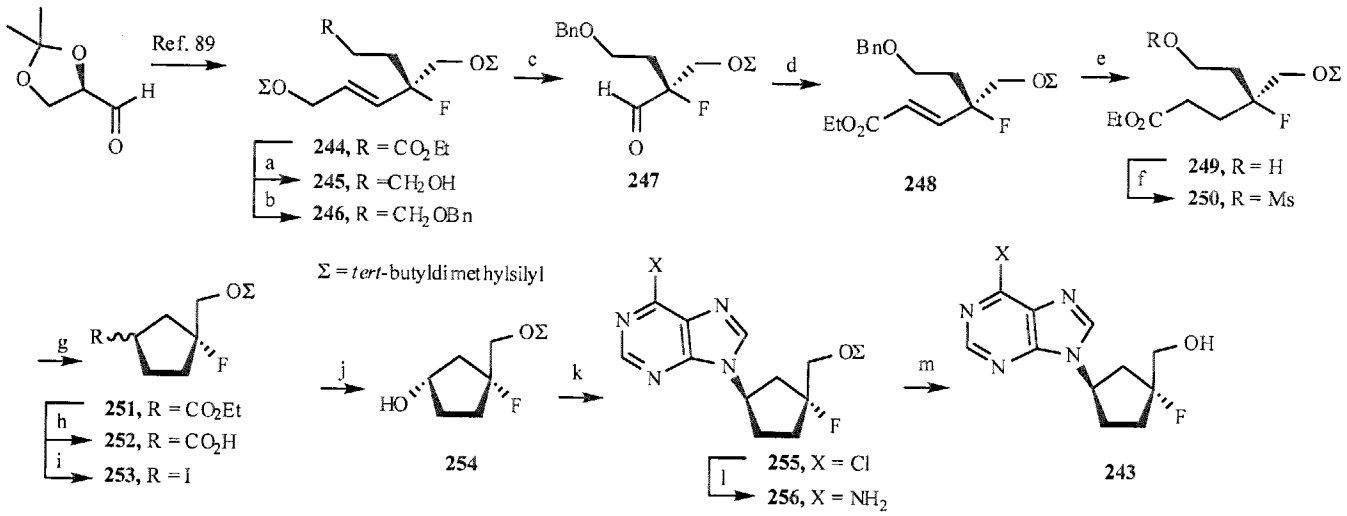


Scheme 20. Reagents and conditions: (a) i. DIBAL-H, Et_20, –78 °C, 10 min, ii. $H_2NCH_2CO_2Et.HCl$, MeOH, 2 h; (b) i. $ClCO_2Et$, DBU, CH_2Cl_2, 2 h, ii. NaOMe, MeOH, 40 min, 41% from **235**; (c) i. $BzN{=}C{=}S$, CH_2Cl_2, ii. MeI, DBN, iii. NH_3/MeOH, 90 °C, 16 h, 57%; (d) CF_3CO_2H/H_2O (2: 1, v/v), 50 °C, 3 h, 68% for **231**, 68% for **232**, 60% for **233**; (e) $HC(=NH)NH_2.HOAc$, EtOH, reflux, 4 days, 81%; (f) HCl (c), MeOH, rt, 2 h, 72%; (g) MsCl, py, rt, 4 h, 76%; (h) Te, Et_3BHLi, THF, 50 °C, 7 h, 65%.

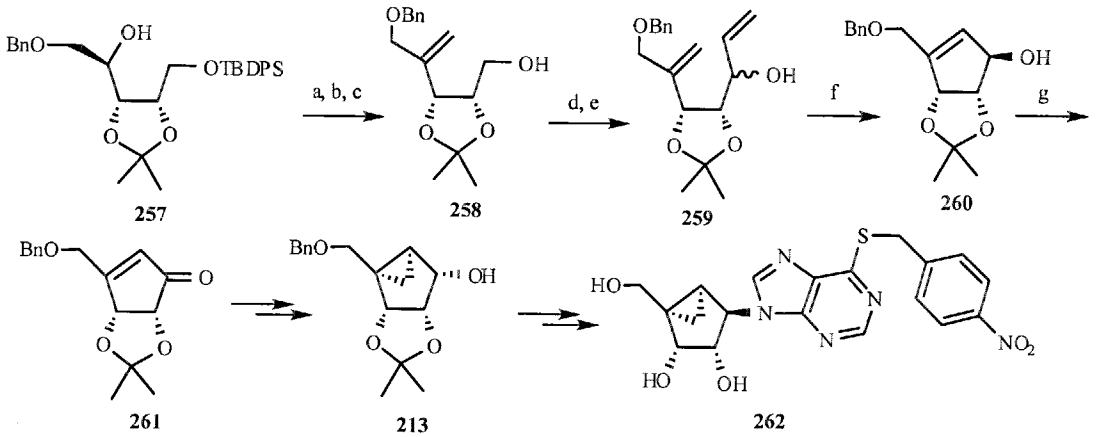
been reported [83]. In fact, (–)-(1*R*,2*R*,3*S*,4*R*)- and (+)-(1*S*,2*S*,3*R*,4*S*)-4-hydroxyethylcyclopentane-1,2,3-triol (compounds **(–)-228** and **(+)-228**, respectively), are useful template for the synthesis of unnatural and natural aristeromycin [83]. The advances intermediates are straightforwardly obtained from D-ribose [84] in three steps and D-arabinose in two steps [85] (Scheme 19).

A very promising field in the design of carbanucleosides is the preparation of carbocyclic *C*-nucleosides, in which the nitrogen atom of the bases bonded to the pseudosugar ring is replaced by a carbon atom [86,87]. Compounds **231-234** emerge as attractive members of this family of drugs. The preparation of this particular class of carbanuclesides is outlined in Scheme 20 starting from the intermediate **235** that is readily prepared from D-ribonolactone [87]. Unfortunately, these drugs are not effective against HIV. Another interesting carbanucleoside is the fluor-containing unnatural isomer of 2',3'-dideoxyadenosine **243**. L-(1'S,3'S)-9-[3-Fluoro-3-(hydroxymethyl)cyclopentan-1-yl] adenine is synthesized in 14 steps from 2,3-isopropyliden-D-glyceraldehyde as chiral source [88] via the known advanced intermediate **244** [89]. The antiviral action of this drug is not reported [88] (Scheme 21).

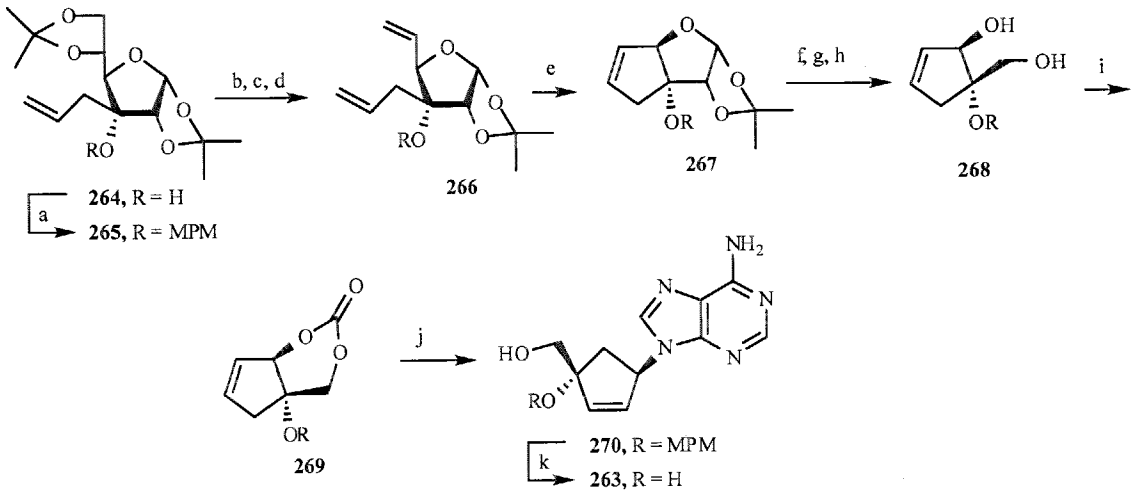
A novel synthetic approach to access to carbocyclic rings has been developed by Jacobson *et al.* [90] starting from the synthetic intermediate **257**, which is straightforwardly prepared from D-ribonolactone [91]. The critical step in this novel methodology to prepare the well-known ketone **261** is a ring closure metathesis reaction on **259** to produce the cyclopentenyl alcohol **260** as a major product and its diastereoisomer **173** (Scheme 22). Ketone **261** was further transformed into the ring-constrained cyclopentenyl alcohol **213** in order to obtain conformationally rigid carbanucleosides such as **262**. This compound is able to inhibit nucleoside transport by the equilibrative transporters at the low nanomolar level [90]. Conformationally



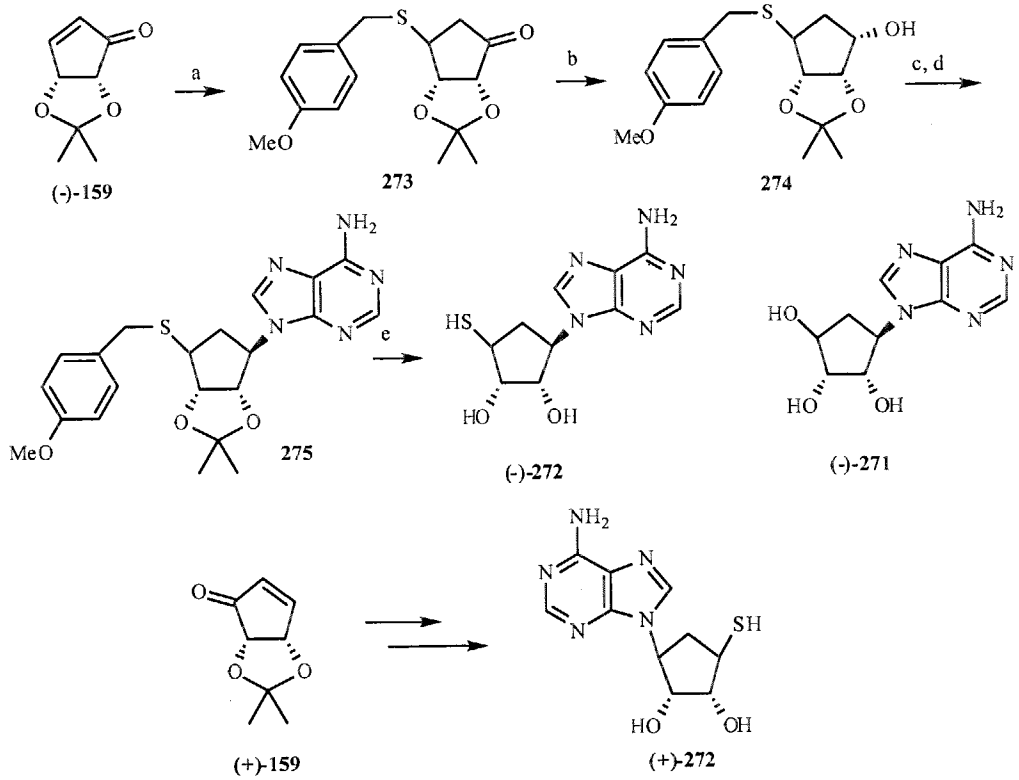
Scheme 21. Reagents and conditions: (a) $LiAlH_4$, THF, –40 °C → –35 °C, 90 min, 95%; (b) NaH, THF, 0 °C → rt, 1 h, then BnBr, TBAI, 0 °C to rt, overnight, 74%; (c) O_3, MeOH, –78 °C, 45 min, then Me_2S, 0 °C, 2 h, 50%; (d) $(EtO)_2P(O)CH_2CO_2Et$/NaHMDS, THF, –78 °C, 1 h, 80%; (e) H_2, 10% Pd/C, cyclohexane, rt, 24 h, 95%; (f) MsCl, Py, CH_2Cl_2, 0 °C → rt, 24 h, 85%; (g) NaH, THF, reflux, 16 h, 75%; (h) NaOH/H_2O, EtOH, rt, 5 h, then AcOH, 0 °C, 81%; (i) $Pb(OAc)_4$, CCl_4, hν, reflux, 15 min, then I_2, CCl_4, hν, reflux, 2 h, 82%; (j) $NaHCO_3$, 15% (v/v) H_2O/ HMPA, 100 °C, 16 h, 40%; (k) 6-chloropurine, PPh_3, DEAD, rt, 6 h, 80%; (l) NH_3/MeOH, 100 °C, 2.5 h, 83%; (m) TBAF, THF, rt, 30 min, 98%.



Scheme 22. Reagents and conditions: (a) $(COCl)_2$, DMSO, THF, –78 °C, then TEA, rt; (b) PPh_3CH_3Br, n-BuLi, THF; (c) TBAF, CH_3CN; (d) $(COCl)_2$, DMSO, THF, –78 °C, then TEA, rt; (e) CH_2=CHBr, THF, –78 °C, (f) Grubbs catalyst, CH_2Cl_2; (g) MnO_2, $CHCl_3$.



Scheme 23. Reagents and conditions: (a) MPM-Br/NaH, THF, rt, 6 h, 86%; (b) 0.8% H_2SO_4, MeOH, rt, 10 h, 75%; (c) $MeSO_2Cl$, Et_3N, DMAP, CH_2Cl_2, rt, 1 h; (d) NaI, EtCOMe, reflux, 8 h, 64%; (e) Grubbs catalyst, CH_2Cl_2, rt, 6 h, 80%; (f) 0.4% H_2SO_4, dioxane, reflux, 2 h; (g) $NaIO_4$, CH_2Cl_2, SiO_2, rt, 1 h, 69%; (h) $NaBH_4$, MeOH, rt, 1 h, 70%; (i) Im-CO-Im, PhH, reflux, 4 h, 69%; (j) 6-aminopurine, $Pd(PPh_3)_4$, DMSO, THF (1:1), 45 °C, 2 h, 54%; (k) DDQ, CH_3CN/H_2O, rt, 2 h, 72%.



Scheme 24. Reagents and conditions: (a) 4-methoxy-α-toluenethiol, K_2CO_3, THF, 99%;(b) BH_3.THF, 60%; (c) DIAD, PPh_3, 6-chloropurine, THF; (d) NH_3, MeOH, 110 °C, 71%; (e) TFA, PhOH, reflux, 75%.

constrained adenosine derivatives have been designed as ligands at adenosine receptors (A_1, A_{2A}, A_{2B}, and A_3) and nucleotide receptors (P2) [92, 93].

An elegant synthetic approach for the preparation of a carbovir hydroxylated analogue (**263**) has been recently published [94]. This compound was synthesized starting from 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose via the intermediate **264** [95]. In this case, a RCM reaction was employed as a key step in order to form the carbocyclic ring. The preparation of **263** is illustrated in Scheme 23.

5'-Norcarbanucleosides are found to have important biological properties, in which 5'-*nor*-aristeromycin (**271**) arises as the main member of this family of nucleoside analogues. For instance, the enantiomer of this compound ((+)-**271**) exhibits potent action against hepatitis B virus [96]. On the basis of these results, several analogues of this product have been prepared [97]. The enantiomer analogue of

5'-*nor*-aristeromycin, in which the C-4' is lacking, proves to be 10-fold more potent than **(+)-271** against HBV [97]. It is an interesting example the preparation of a mercapto analogue of both enantiomers of 5'-*nor*-aristeromycin (**(–)-272** and **(+)-272**, respectively [98]. This compounds are prepared from either **(-)-159** or **(+)-159** to afford the natural or unnatural isomer, respectively. Only **(–)-272** was moderately active against vaccinia virus [98] (Scheme 24).

CONCLUSIONS

The essential idea for the design and synthesis of carbocyclic nucleosides is the production of a metabolically stable glycosidic bond not affected by phosphorylases and hydrolases. Moreover, structural conformational variations due to the lack of gauche and anomeric effects should be avoid to a minimum in order to have recognizable nucleosides analogues.

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