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Synthesis of Carbocyclic Nucleosides

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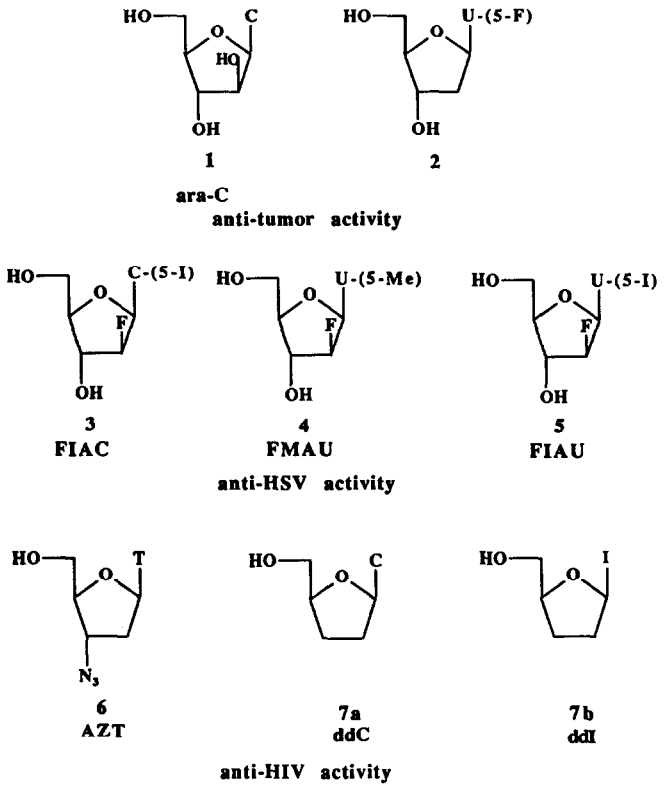
Abbreviations : **A**, Adenine; **ADA**, Adenosine deaminase; **AdoHcy**, S-Adenosyl-L-homocysteine; **AdoMet**, S-Adenosyl-L-methionine; **AIDS**, Acquired immunodeficiency syndrome; **ara-C**, Arabinocytidine; **AZT**, 3'-Azido-3'-deoxythymidine; **Bn**, Benzyl; **BVDU**, 5-Bromovinyl-2'-deoxyuridine; **Bz**, Benzoyl; **C**, Cytosine; **C-araFGua**, Carbocyclic arabino-5-fluoroguanosine; **C-BVDU**, Carbocyclic 5-Bromovinyl-deoxyuridine; **2'-CdG**, Carbocyclic 2'-deoxyguanosine; **C-IDU**, Carbocyclic 5-Iodo-deoxyuridine; **C-NECA**, Carbocyclic 5'-N-Ethylcarboxamidoadenosine; **DAST**, Diethylaminosulfur trifluoride; **DBU**, 1,8-Diazabicyclo-[5.4.0]undec-7-ene; **DCC**, 1,3-Dicyclohexylcarbodiimide; **DEAD**, Diethylazodicarboxylate; **ddC**, 2',3'-Dideoxycytidine; **ddI**, 2',3'-Dideoxyinosine; **DHP**, 3,4-Dihydro-2H-pyran; **DIBAL-H**, Diisobutylaluminium hydride; **DMF**, Dimethylformamide; **DMSO**, Dimethyl sulfoxide; **DNP**, 2,4-Dinitrophenol; **DPPA**, Diphenylphosphoryl azide; **EBV**, Epstein-Barr virus; **FIAC**, 2'-Fluoro-5-iodo-1-β-D-arabinofuranosylcytosine; **FIAU**, 2'-Fluoro-5-iodo-1-β-D-arabinofuranosyluracil; **FMAU**, 2'-Fluoro-5-methyl-1-β-D-arabinofuranosyluracil; **G**, Guanosine; **H**, Hypoxanthine; **HCMV**, Human cytomegalovirus; **HIV**, Human immunodeficiency virus; **HSV**, Herpes simplex virus; **HMPA**, Hexamethylphosphoramide; **IBDA**, Iodobenzene diacetate; **IDU**, 5-Iodo-2'-deoxyuridine; **IVDU**, 5-Iodovinyl-2'-deoxyuridine; **LDA**, Lithium diisopropylamide; **mCPBA**, m-Chloroperbenzoic acid; **Ms**, Mesyl; **NBA**, N-Bromoacetamide; **NBS**, N-bromosuccinimide; **PCC**, Pyridinium chlorochromate; **PDC**, Pyridinium dichromate; **PLE**, Pig liver esterase; **pTS acid**, p-Toluenesulfonic acid; **T**, Thymine; **TBAF**, Tetrabutylammonium fluoride; **TBDPSCl**, tert-Butyl-diphenylsilyl chloride; **TIPS**, 1,1,3,3-tetraisopropyl-disiloxane; **TrCl**, Trityl chloride; **Ts**, Tosyl; **U**, Uracil; **VO(acac)2**, Vanadyl acetylacetonate; **VZV**, Varicella zooster virus.

1. INTRODUCTION

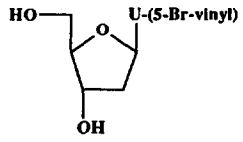
The chemistry of natural nucleosides and their analogs has been widely studied as potential anti-viral, fungicidal, and anti-cancer agents. For example, 1-β-D-arabinofuranosylcytosine (ara-C)[1] **1** and 5-fluoro-2'-deoxyuridine[2-5] **2** display some anti-cancer activities (Figure 1) ; 2'-fluoro-5-iodo-1-β-D-arabinofuranosyl cytosine (FIAC) **3**, 2'-fluoro-5-methyl-1-β-D-arabinofuranosyluracil (FMAU) **4**, and 2'-fluoro-5-iodo-1-β-D-arabinofuranosyluracil (FIAU) **5**, exhibited anti HSV properties[6-9]. And lastly, some nucleosidic substances showing activity against HIV-1[10,11], at least *in vivo*, have been described, but only 3'-azido-3'-deoxythymine (AZT)[12] **6**, 2',3'-dideoxycytidine (ddC) **7a** and 2',3'-dideoxyinosine (ddI) **7b** have been used for the treatment of HIV infection.

FIGURE 1

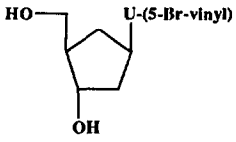


The inhibition of herpes virus by certain nucleosides is well known. The selectivity of these compounds, inhibitors of the replication of HSV-1 virus, depends on their preferential activation (phosphorylation) by the viral enzyme thymidine kinase.[14] However, these nucleosides are also substrates for phosphorylases, enzymes which cleave the N-glycosidic bond between the heterocycle moiety and the sugar.[15] In order to avoid these enzymatic degradations and to improve the antiviral activities of nucleosides, a great number of modifications has been carried out on both the sugar and the heterocycle. The replacement of the oxygen of the furan ring by a methylene group, leads to the synthesis of carbocyclic analogs of nucleosides. Thus, many carbocyclic nucleosides have been synthesized that exhibit biological activity as well as resistance to phosphorylases. As expected, the carbocyclic analogs of BVDU **8**, C-BVDU **9**, IDU **10**, and C-IDU **11** (Figure 2) are not substrates for phosphorylases[16,17] while they maintain their *in vitro* activities against HSV-1.[18] Similarly, the cyclopentane analog of adenosine **12**, C-adenosine or aristeromycin **13** is far less active as substrate of the S-adenosylhomocysteine hydrolase than adenosine. The fact that C-adenosine **13** is a potent inhibitor of this enzyme ($Ki = 5x10^{-9}M$) shows the necessity of the 3'-hydroxyl group for the enzymatic reaction, the replacement of the furanose ring with a cyclopentane ring does not affect binding by the enzyme.[19] De Clercq et al.[20] have shown that the isosteric replacement of the oxygen of furanose by a CH_2 results in a better enzymic resistance[20] and a decrease in the toxicity[21] of the carbocyclic analogs.

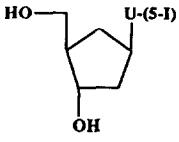
FIGURE 2



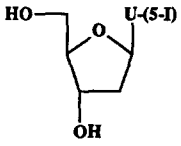
BVDU, 8



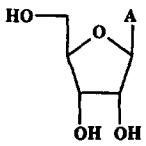
C-BVDU, 9



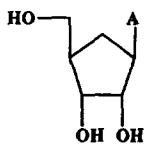
C-IDU, 11



IDU, 10



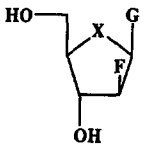
Adenosine, 12



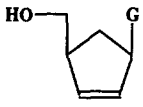
C-adenosine, 13
Aristeromycin

For the past six years, research on the chemistry of the carbocyclic nucleoside analogs has directed towards the development of agents showing activities against HIV, HSV types 1 & 2, VZV, HCMV and EBV. The carbocyclic analog of BVDU **9** has some activity against HSV and VZV[22] and carbocyclic 2'-*ara*-fluoroguanosine **14** is more active against HSV-1 and HSV-2[23,24] than its natural nucleoside analog **15** (Figure 3). Carbovir, **16** (C-2',3'-didehydro-2',3'-dideoxyguanosine)[25] shows interesting *anti*-HIV activity *in vitro* and neplanocin A, **17**, is an antibiotic with anti-cancer activity (especially against leukemia).

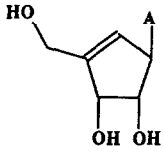
FIGURE 3



14 X = CH_2
15 X = O
anti-HSV



Carbovir, **16**
anti-HIV



Neplanocin A, **17**
antibiotic agent

The pharmaceutical importance of carbocyclic nucleoside analogs prompted new syntheses of these compounds. We describe below a new approach for the chemistry of these compounds possessing the ribo-, arabino-, and xylo-configuration (by analogy with the natural nucleosides) of the cyclopentane ring. We will review the strategies of synthesis reported in the literature up to end 1993, for each configuration of the five membered ring carbocyclic nucleosides. We will focused on the synthesis of aristeromycin, C-deoxyribo-nucleosides, carbovir, and neplanocin A which have important biological properties.

2. COUPLING PROCEDURES OF THE HETEROCYCLE MOIETY

All the syntheses of carbocyclic nucleosides are carried out first by formation of a functionalized cyclopentane and then by coupling of a purine or pyrimidine heterocycle or of one of their precursors. The

functionalized cyclopentane, by analogy with β-D-nucleosides, must have certain structural features that will direct the design of the precursors. It must have :

* an hydroxymethyl group or derivatices in the 4' position
* in the 1' position, a group that could react with a precursor of the heterocycle (amine, leaving group, epoxide, etc).

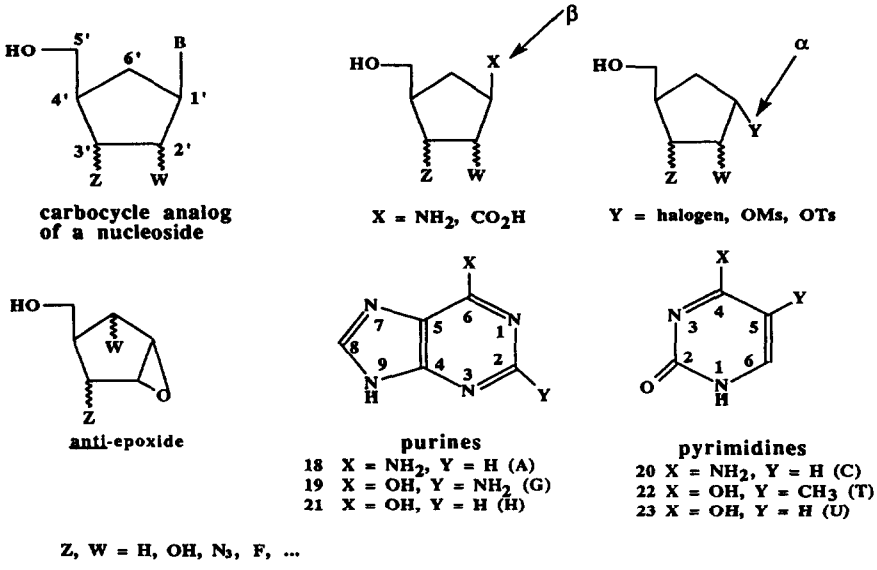
Remarks:

i) By analogy with the natural nucleosides, a substituent is designated to be in β orientation if it is *cis* to the 4'-hydroxy-methyl group in the cyclopentane. It is said to be α if it is *trans* to this function.

ii) In the structures of nucleoside analogs, bases are indicated adenine **18**, guanine **19**, cytosine **20**, hypoxanthine **21**, thymine **22**, and uracil **23**, by the abbreviations A, G, C, H, T, U, respectively, whereas the abbreviation B will be used in general to represent a heterocycle moiety (Figure 4).

iii) The numbering system of the carbocyclic analogs agrees with the numbering employed for nucleosides.

FIGURE 4



Two approaches can be used to couple a purine or a pyrimidine to the carbocycle :

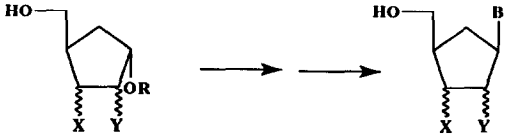
1) Nucleophilic substitution of a labile α group on the carbocycle by the heterocycle moiety,

2) Construction of heterocyclic bases around a 1'-β-amino function or a 1'-β-acidic function on the carbocycle.

2-1. Direct introduction of the heterocycle onto the carbocyclic moiety

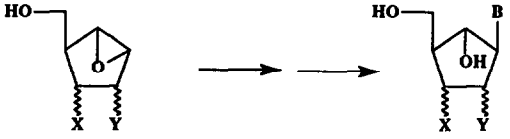
Generally the literature distinguishes four main ways to introduce a purine or a pyrimidine directly to a functionalized cyclopentane :

a) by nucleophilic displacement of an activated α hydroxyl group (MsO, TsO)



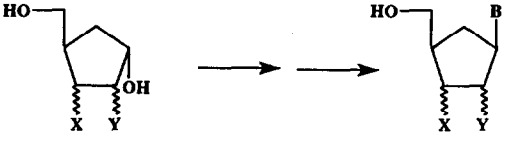
R = Ms, Ts; X, Y = H, OH, F, ...

b) by ring opening of an epoxide



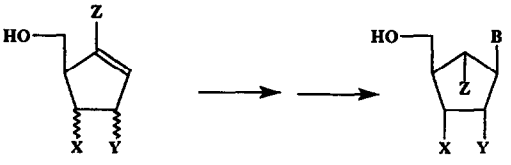
X, Y = H, OH, F, ...

c) by a Mitsunobu reaction



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

d) by a Michael 1,2-addition



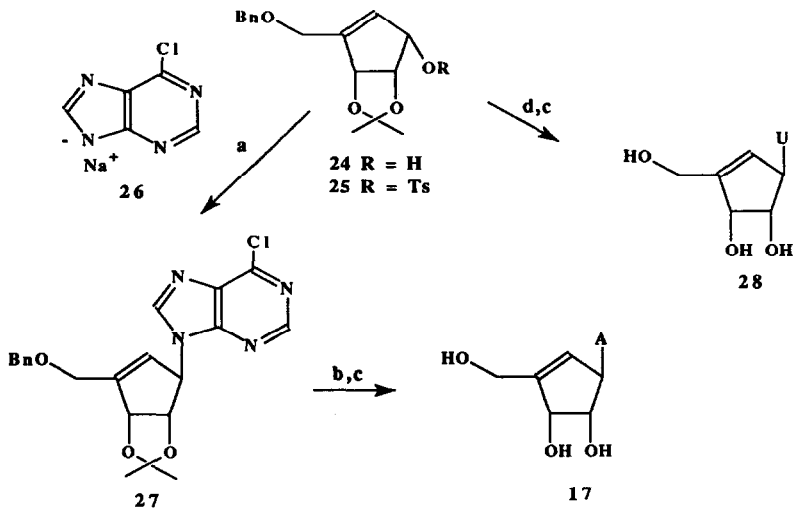
X, Y = H, OH, F, ...; Z = NO_2

Specific examples of these approaches are given below :

a) Nucleophilic substitution of an activated hydroxyl group :

The first synthesis of a carbocyclic nucleoside by coupling of a heterocycle moiety to a functionalized cyclopentane by means of a tosylate was reported by Marquez et al.[27,28] and led to the formation of (-)-neplanocin **17** (Scheme 1). Alcohol **24** has been prepared stereospecifically from D-ribonolactone. The formation of the tosylate **25** and its coupling with the sodium salt of 6-chloropurine **26** in acetonitrile gave **27**. Ammonolysis of the chloro group and then deprotection of the hydroxyl groups gave (-)-**17** neplanocin . The use of pyrimidine allowed the preparation of neplanocin analogs **28** by the same route. Also this method has been used to prepare nucleosides with modified carbocyclic nucleosides.[29-34] as shown in scheme 2.

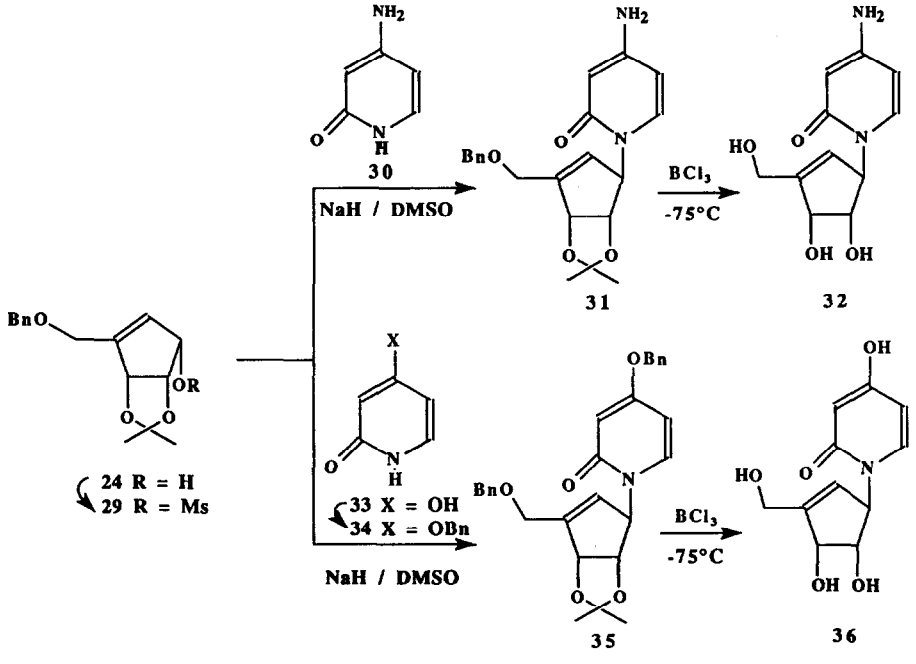
SCHEME 1



Reagents : a) 26, CH_3CN, 50°C b) NH_3/MeOH, 60°C c) BCl_3, -75°C d) Uracil, K_2CO_3

Thus, Copp et al.[33] have synthesized C-3-deazacytosine, **32**, and C-3-deazauridine **36** neplanocin analogs.

SCHEME 2

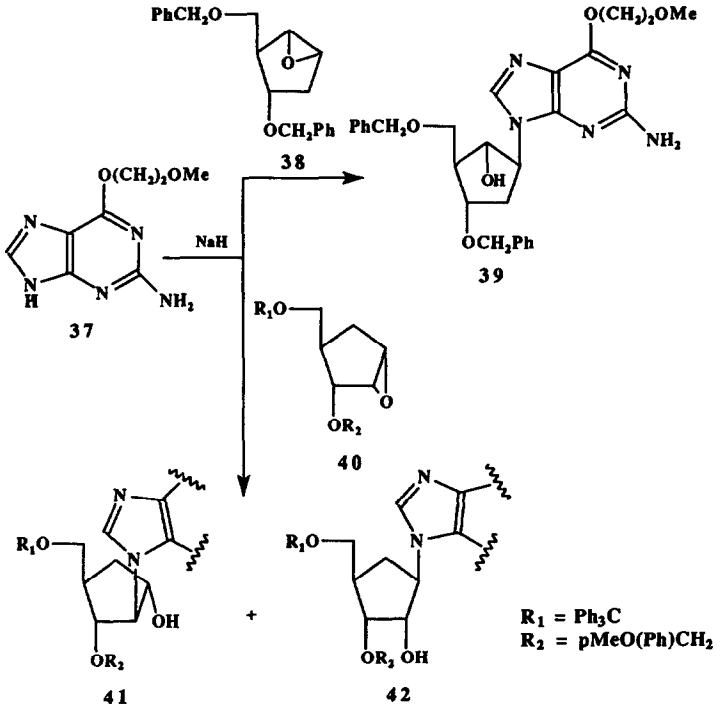


b) By opening of an α epoxide :

Opening of an α epoxide is effected by a purine or a pyrimidine salt under basic catalysis. This method is interesting since it leads to the formation of an hydroxyl in the α position. Nucleophilic attack on the epoxide can occur at two sites and leads to a mixture of isomers. The opening of the cyclopentoxide by uracil, thymine, or even adenine is well documented.[35-38] The only example described in the literature of reaction of the epoxide and a guanine[37] salt indicates a poor yield for the reaction. Biggadike et al.[39] have improved this synthesis using the protected guanine, **37**, 2-amino-6-methoxyethoxypurine (Scheme 3). The reaction of the protected guanine **37** with the epoxide **38** gave the predominating protected derivative **39** in 60% yield. In contrast, under the same conditions, opening of the racemic epoxide **40** is far less regioselective and leads to a mixture of alcohols **41** and **42** in a ratio of 3:2.

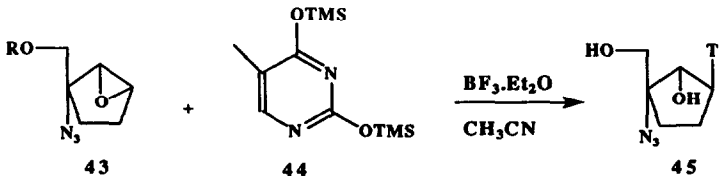
The limits of this method employed elsewhere[40-43] are lack of regioselectivity in the opening of the epoxide ; the stereochemical course of the opening is governed by steric and electronic effects of groups (in an α position relative to the oxirane). At present, only the anti-epoxide (relative to the 4'-OH group) is of interest for the synthesis of carbocyclic analogs of nucleosides.

SCHEME 3



The opening of an epoxide in the presence of an acid catalyst has been far less studied.[44,45] Epoxide **43** has been treated with bis(trimethylsilyl)thymine **44** and a Lewis acid catalysis to give the cyclopentane nucleoside **45** in 58% yield (Scheme 4).

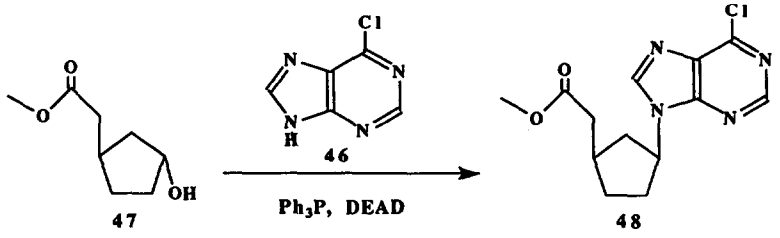
SCHEME 4



c) By a Mitsunobu reaction :

A secondary alcohol can be replaced by a purine using Mitsunobu conditions [(Ph)3P, DEAD]; the reaction takes place with an inversion of configuration. The addition of 6-chloropurine **46** to the α-alcohol **47** under standard Mitsunobu conditions[46] (room temperature, 20% excess of the heterocycle, (Ph)3P, DEAD) leads to derivative **48** in 80% yield (Scheme 5). This method has been applied to other heterocycles (guanine[47], thymine[46]) ; in these cases the 6-oxo- and 2-amino- functional groups of guanine and the 3-NH of thymine must first be protected.

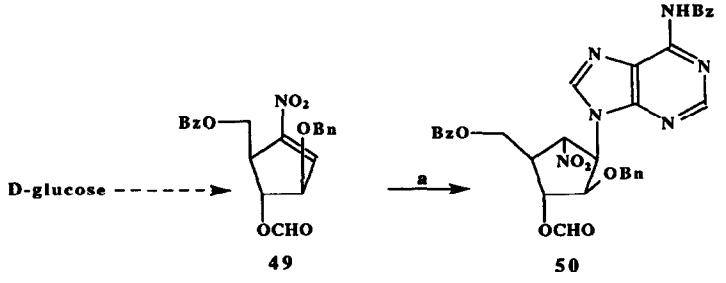
SCHEME 5



d) By a Michael addition

Kitagawa et al.[48,49] have developed a new aproach for the synthesis of carbocycles. They utilized the Michael addition of a purine to a nitrocyclopentene derivative, **49**, prepared from D-glucose (Scheme 6).

SCHEME 6



Reagents : a) KF / 18-crown-6 / DMF, N^6-benzoyladenine

The addition of the N^6-benzoyl adenine is carried out using KF and a crown ether (KF,

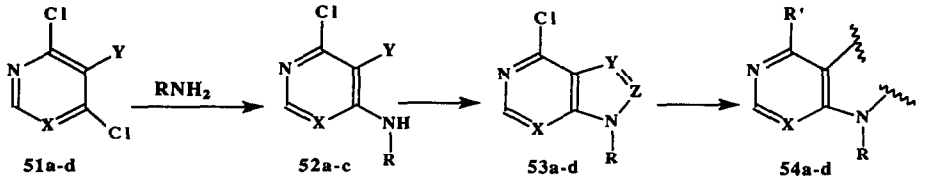
18-crown-6) in DMF. The expected product **50** is obtained in 15 steps from D-glucose.

2-2. Construction of purine and pyrimidine carbocyclics via precursors to these heterocycles

a) Construction of purines :

Purine carbocycles[50-54] are synthesized by reaction of purine precursors of these heterocycles and a functionalized cyclopentylamine RNH_2 (Scheme 7). The cyclopentylamine, RNH_2, can be converted into pyrimidylamino derivative **52** with the pyrimidine derivative **51**. Depending on the choice of Y and Z, ring-closure leads to the formation of modified 6-chloropurines, **53**, containing pyrrole, imidazole or triazole rings. Reaction of the chlorine with ammonia or hydroxide leads to derivatives of adenine or hypoxanthine, **54**. Ring closure of the bicyclic system **52** is effected by : (i) spontaneous cyclization under acid catalysis. In the case of **52c**; 7-deazapurine analog **53c** is obtained. (ii) by reaction of **52a**, **52c**, with triethylorthoformate and an acid catalysis to produce imidazole products **53a** and **53d**. (iii) by diazotition of **52a** to give the 8-azapurine analogue **53b**.

SCHEME 7



51a-d **52a-c** **53a-d** **54a-d**

	X	Y
a)	N	NH_2
b)	N	NO_2
c)	N	$CH_2CH(OEt)_2$
d)	CH	NO_2

	X	Y
a)	N	NH_2
b)	N	$CH_2CH(OEt)_2$
c)	CH	NH_2

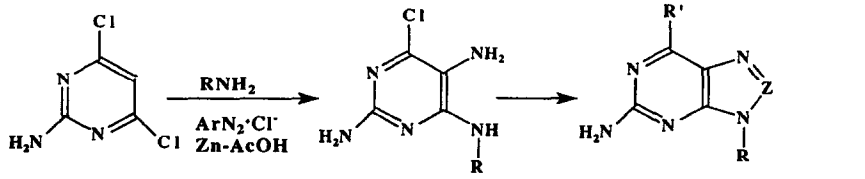
	X	Y	Z
a)	N	N	CH
b)	N	N	N
c)	N	CH	CH
d)	CH	N	CH

	X	R'
a)	N	NH_2
b)	N	OH
c)	CH	NH_2
d)	CH	OH

R= functionalized cyclopentane

Carbocycles with a guanine heterocycle and related analogs are obtained by similar procedures and from 2-amino-4,6-dichloropyrimidine **55** (Scheme 8). The 5-amino function was introduced by a phenyldiazo coupling followed by reduction with nascent hydrogen to yield compound **56**. Heterocyclic ring closure leads to derivative **57**, and substitution of the 6-chlorine allows the preparation of various guanine derivatives.

SCHEME 8



55 **56** **57 R' = Cl; Z = N, CH**

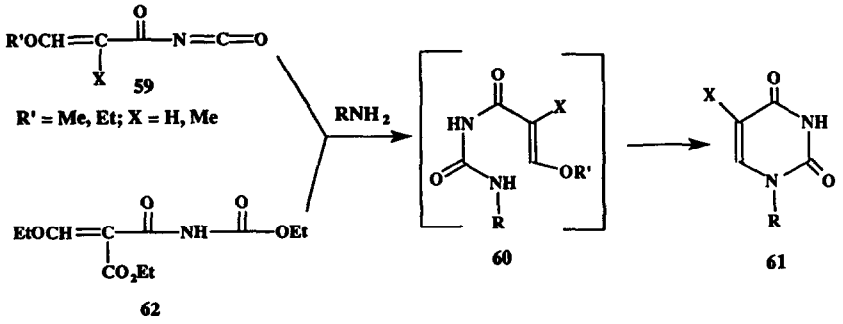
R= functionalized cyclopentane

58 R' = OH, NH_2, SH, Me
Z = N, CH

b) Construction of pyrimidines :

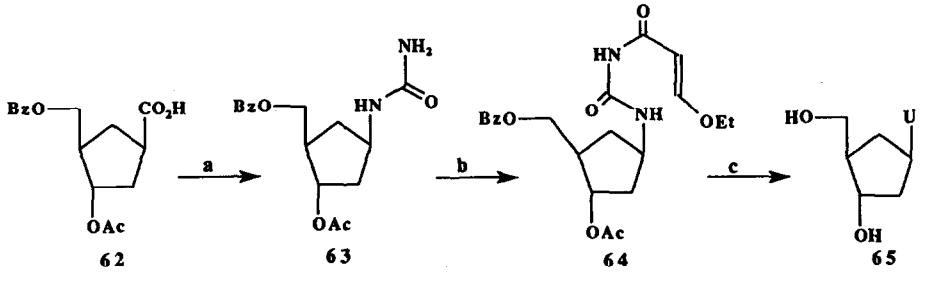
Pyrimidines[55-57] are often synthesized by the method reported by Shaw and Warrener[58,59] (Scheme 9). Isocyanate **59** reacts with a cyclopentylamine RNH_2 to give an acryloylurea intermediate **60**, which leads to the cyclic compound **61** under acidic or basic conditions. When X = H in **59**, the heterocycle will be uracil, and when X = Me, it will be thymine. The same result is obtained by reaction of RNH_2 with 3-ethoxy-N-2-bis(ethoxycarbonyl)acrylamide **62**, which leads to analog **61** in which X = CO_2Et.

SCHEME 9



Few publications[60-63] report formation of a pyrimidine by the Curtius degradation. Balzarini et al.[63] use this method to synthesise the carbocyclic analog of the 2'-deoxyribouracil **65** (Scheme 10). The Curtius degradation transforms a 1'-β-carboxylic acid group, *via* a carboxylic chloride, into a carboxylic azido group with diphenylphosphoryl azide (DPPA). This intermediate heated in an inert solvent (toluene) forms an isocyanate which reacts *in situ* with ammonia to give the substituted urea **63**. The acylation of **63** by a 3-ethoxyacroyloyl chloride gives **64**, which closes under basic conditions. The carbocyclic analog of the uracil **65** is then obtained.

SCHEME 10

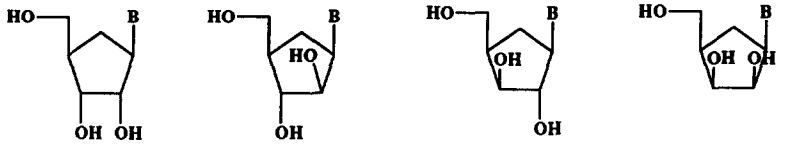


Reagents : a) DPPA; NH_3 b) 3-ethoxyacroyloyl chloride c) aqueous NH_3

3. SYNTHESIS OF FUNCTIONALIZED CYCLOPENTYLAMINE WITH RIBO, ARABINO, OR XYLO C-2',3' CONFIGURATIONS

Recently, many carbocyclic nucleoside analogs with various configurations (ribo, arabino, xylo, lyxo) have been synthesized[64-66] as well as other derivatives. The biological properties of these new compounds have also been evaluated (Figure 5). Having described the methods for coupling purine and pyrimidine with functionalized cyclopentylamines, we will now discuss methods for the syntheses of carbocycles with different configurations at C-2' and C-3'.

FIGURE 5



3-1. Carbocyclic analogs of ribofuranosylnucleosides : aristeromycin

The ribofuranosyl carbocyclic analogs have been widely studied, especially the carbocyclic analog of adenosine, aristeromycin **13** (Figure 2). This compound was first synthetized by Shealy and Clayton[67,68] in 1966 in the racemic form. Aristeromycin **13** is the most known potent inhibitor of the enzyme, S-adenosyl-L-homocysteine (AdoHcy) hydrolase, which plays an important role in methylation (AdoMet) dependant biological reactions. For several years, this enzyme represented a target for antiviral chemotherapy.[69] A close correlation exists between the antiviral potential of analogs of adenosine and their inhibition of AdoHcy Hydrolase.[19,70]

Various strategies have been developed to synthesize this compound (Figure 6a). The majority of the literature methods start with rigid bicyclic systems. The precursors of these syntheses fall into five groups that define the strategy of the synthesis.

Route a : Utilizes a bicyclic system of type [C-C] obtained from a Diels-Alder cycloaddition of dienophile of type [C=C] and cyclopentadiene (Syntheses of Shealy, of Arita, etc).

Route b : Utilizes a bicyclic system of type [C-N] obtained by a Diels-Alder cycloaddition of a dienophile of type [C=N] and a cyclopentadiene (Syntheses of Vince, of Saksena, etc).

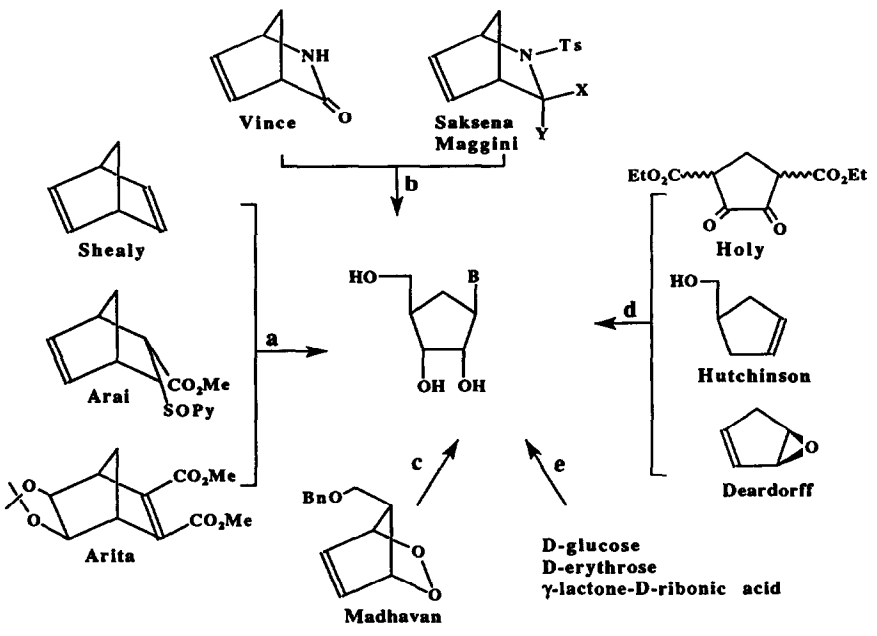
Route c : Utilizes a bicyclic system of type [O-O] obtained by a Diels-Alder cycloaddition of singlet oxygen $^1O_2$ and cyclopentadiene (Synthesis of Madhavan).

Route d : Utilizes a functionalized cyclopentane (Syntheses of Holy, etc).

Route e : From D-glucose and its derivatives (Syntheses of Tadano, etc).

We will present below several examples to illustrate each approach and will concentrate on the functionalized cyclopentane that will be coupled later with the heterocycle base.

FIGURE 6a

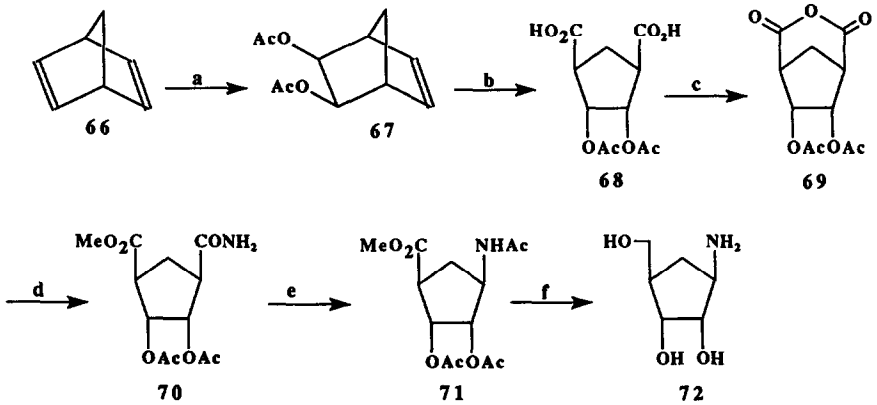


Method a : Bicyclic system of type [C-C]

i) Procedure of Shealy and Clayton[67,68]

The cis hydroxylation of 2,5-norbornadiene (**66**) followed by protection of the hydroxyl groups led to the diacetate **67** (Scheme 11). Oxidative cleavage of the double bond of **67** by a solution of potassium permanganate led to diacid **68**.

SCHEME 11



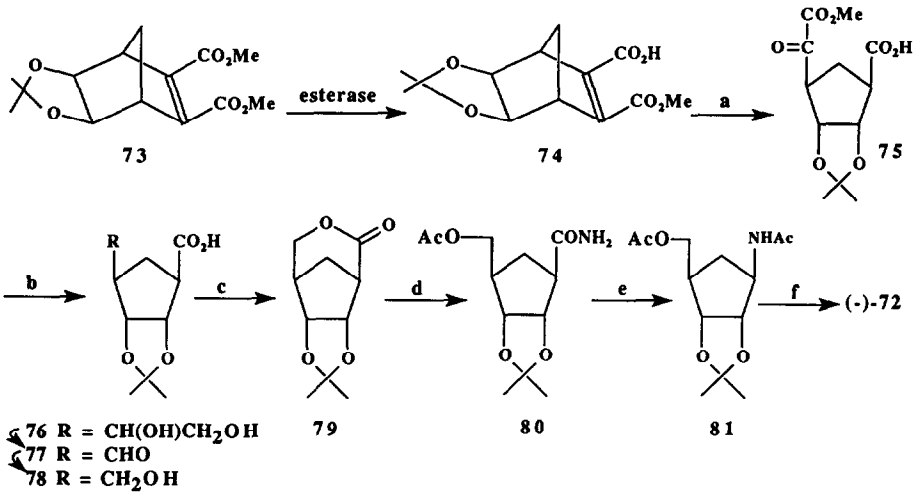
Reagents : a) $KMnO_4$ then Ac_2O/pyridine b) $KMnO_4$ c) ethoxyacetylene d) NH_3/MeOH e) Br_2/NaOH, MeOH/HCl then Ac_2O/pyridine f) $LiBH_4$ then HCl

Treatment of **68** with ethoxyacetylene yielded the anhydride **69**. Ammonolysis under anhydrous conditions gives the (±)-2α,3α-diacetoxy-4-β-carbamoyl-1-β-cyclopentanecarboxylic acid **70**. It is worth mentioning that the opening of the anhydro ring of **69** led to racemic **70**. After Hofmann degradation of **70**, protection of the acid and amine groups, compound **71** was reduced by lithium borohydride to **72**. The cyclopentylamine **72** with a ribo configuration was then treated with an adenine precursor **51**. A precursor of type **72** has also been prepared by Marschner et al..[167]

ii) Procedure of Ohno[71]

Ohno et al. have improved the procedure of Shealy using an enantioselective synthesis to prepare an asymmetric compound by means of an hydrolase (*Pig Liver Esterase*, PLE) on a prochiral[72] or on a meso compound[73] (Scheme 12). The main step of this synthesis is the asymmetric hydrolysis of meso diester **73** by means of PLE to an asymmetric acid **74** (80% yield). After ozonolysis of **74**, the α-ketoester **75** is obtained quantitatively. After a series of reductions, the alcohol **78** was obtained by reaction with acetic anhydride; (S)-lactone **79** was then isolated. Ammonolysis, followed by acetylation of the hydroxyl group, provided the carbamoyl derivative **80**. Hofmann degradation of **80** to **81** with lead tetraacetate and deprotection gave the cyclopentylamine **72** in good enantiomeric purity.

SCHEME 12

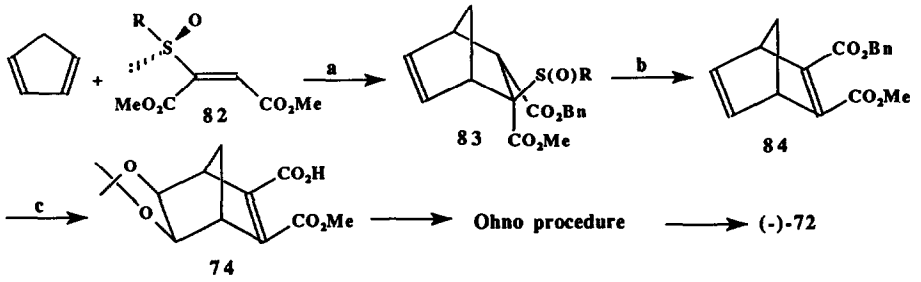


Reagents : a) O_3, b) $NaBH_4$; $NaIO_4$ c) Me_2CO, H^+ d) NH_3 then Ac_2O/pyridine e) $Pb(OAc)_4$ then tBuOH f) aqueous HCl

iii) Synthesis by Koïzumi[74,75]

This chiral synthesis is a new approach to the enantiomerically pure **74**. The asymmetric reaction of (Rs)-2-(10-isobornylsulphinyl)maleate **82** with cyclopentadiene yielded the cycloadduct **83**, which was transformed after six steps to the asymmetric acid **74** (Scheme 13). The Ohno procedure was then used to transform of **74** to the chiral **72** cyclo-pentylamine.

SCHEME 13



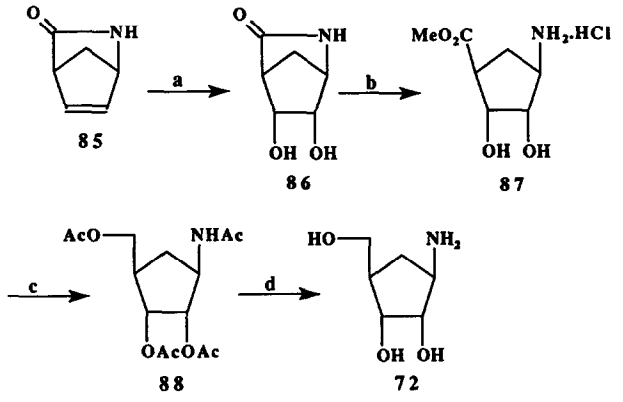
Reagents : a) $ZnCl_2$, -20°C; $AlBr_3$, Me_2S; BnBr, NaH b) DBU c) OsO_4; Me_2CO, H^+; H_2, Pd/C

Method b : Bicyclic system of type [C-N]

i) Synthesis by Vince

The Vince method[76] (Scheme 14) is one of several direct approaches to access carbocycles with the ribo configuration. Diels-Alder cycloaddition of cyclopentadiene and p-toluenesulfonylcyanide[77,78] led to lactam **85**. cis-Hydroxylation of **85** by osmium tetroxide gave cis-diol **86**. Methanolysis of this diol gave (±)methyl-4-β-amino-2α,3α-dihydroxy-1-β-cyclopentanecarboxylate hydrochloride **87**. Acetylation, reduction, and acetylation then produced **88**.

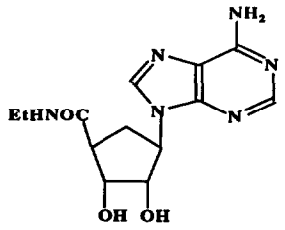
SCHEME 14



Reagents : a) OsO_4 b) MeOH/HCl c) Ac_2O/pyridine; $LiBH_4$; Ac_2O/pyridine d) aqueous HCl

Acid hydrolysis of the aminotriol **88** provided the cyclopentylamine **72**. This method is rapid and, depending on the type of heterocycle base used, it allows access to a great number of carbocyclic analogs of nucleosides[79-81]. It has been used for the synthesis of the carbocyclic 5'-N-ethyl-carboxamido-adenosine[82] (C-NECA) **89** (Figure 6b).

FIGURE 6b

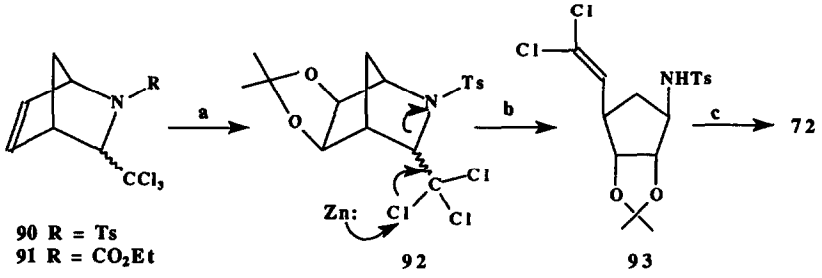


89

ii) Synthesis by Saksena

In 1980, Saksena[83] described the synthesis of racemic aristeromycin from racemic 2-azabicyclo-[2,2,1]-heptene **90** and **91**. After catalytic osmolysis of **90** and the formation of acetamide **92**, a reductive cleavage in the presence of activated zinc produced alkene **93**. Finally a sequence of reactions (ozonolysis, reduction, hydrolysis) leads to the carbocyclic ribo-NH_2 **72** (Scheme 15).

SCHEME 15



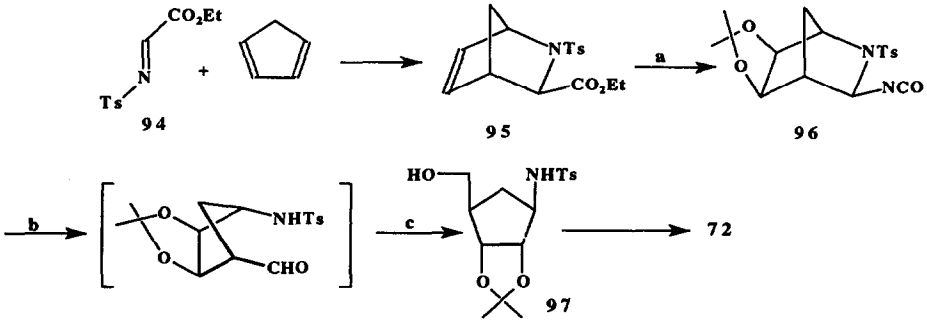
90 R = Ts
91 R = CO_2Et

92 **93**

Reagents : a) OsO_4; Me_2CO, H^+ **b)** Zn, H^+ **c)** O_3, $NaBH_4$, H^+

In 1990, Maggini et al.[84] improved Saksena's synthesis by using a stereoselective Diels-Alder reaction (Scheme 16). This cycloaddition was carried out between dienophile **94** and cyclopentadiene.

SCHEME 16



94 **95** **96**

97

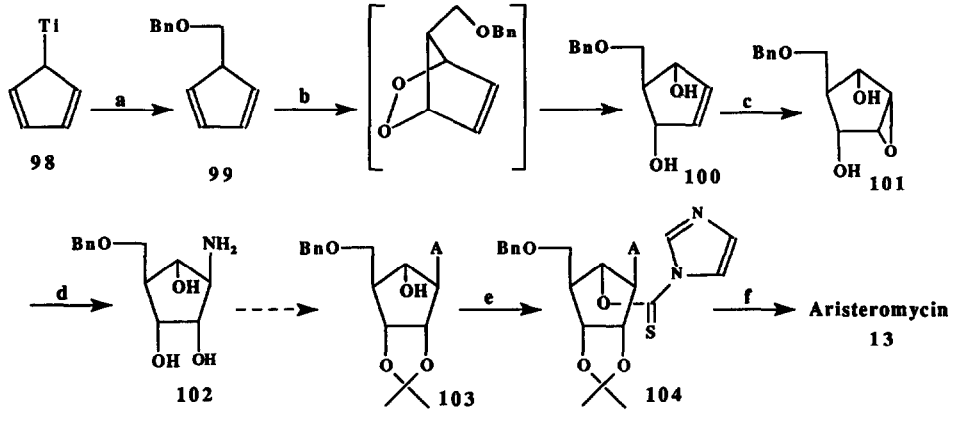
Reagents : a) OsO_4; Me_2CO, H^+; NaOH; $SOCl_2$; NaN_3; toluene **b)** BzOH; H_2, Pd/C 10% **c)** $NaBH_4$

The chiral cycloaddition yielded azanorbornene **95**, which was carried through a sequence of reactions (osmolysis, acetylation, basic hydrolysis, Curtius rearrangement) to yield isocyanate **96**. After catalytic hydrogenation and reduction, the alcohol **97** was isolated. Basic and acid hydrolysis then provided **72**. This approach to a carbocycle from the bicyclic system 2-azabicyclo-[2,2,1]-hept-5-ene has been applied by Katagiri et al.[85] to the synthesis of various carbocycles of ribofuranosyl structure.

Method c : Bicyclic system of type [O-O]

The addition of singlet oxygen to substituted cyclopentadiene **99**, followed by reduction *in situ* led to diol **100**. Stereoselective epoxidation then provided the symmetric epoxy-diol **101** (Scheme 17). Ring opening of the epoxide by azide ion, followed by hydrogenation, led to the trans aminoalcohol **102**. After a series of chemical steps to form the adenine moiety, the protected carbocycle **103** was obtained.[38] 6'-Dehydroxylation by preliminary reaction of the hydroxyl with N-N'-thiocarbonyldiimidazole gave **104**. Reduction of **104** by tributyl tin hydride followed by deprotection provided aristeromycin **13**. This method is very interesting since allows the preparation of a cyclopentane functionalized in positions 2',3' and 6'.

SCHEME 17

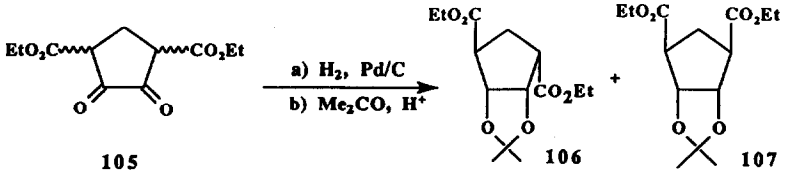


Reagents : a) $BnOCH_2Cl$ b) $^1O_2$, hv c) mCPBA d) NaN_3; H_2, Pd/C e) N,N'-thiocarbonyldiimidazole f) nBu_3SnH; H_2, $Pd(OH)_2/C$; H^+

Method d : Synthesis from functionalized cyclopentane

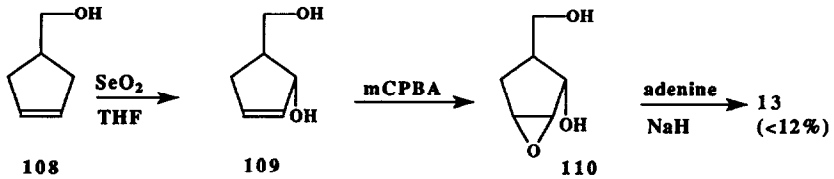
Up to now we have described the use of bicyclic [2,2,1] precursors for the synthesis of functionalized cyclopentylamines. The advantage of these rigid systems is the fixed configuration at C-1' and C-4'. Therefore, the synthetic problem addressed in the synthesis of carbocyclic-ribo-NH_2, where the precursors are cyclopentane structures, is the regioselectivity of various steps required to produce desired configurations at C-1' and C-4'. A synthesis described by Holy[86] using 2,3-cyclopentanedione-1,4-ethyl-dicarboxylate **105** is not regioselective (Scheme 18). In fact, catalytic hydrogenation (Pt or Raney Ni) leads, after acetylation, to a mixture of diastereoisomeric 2,3-dihydroxycyclopentane-1,4-diethyl-dicarboxylates (**106** and **107**), in which only the isomer **107** is used for the synthesis of a carbocyclic analog.

SCHEME 18



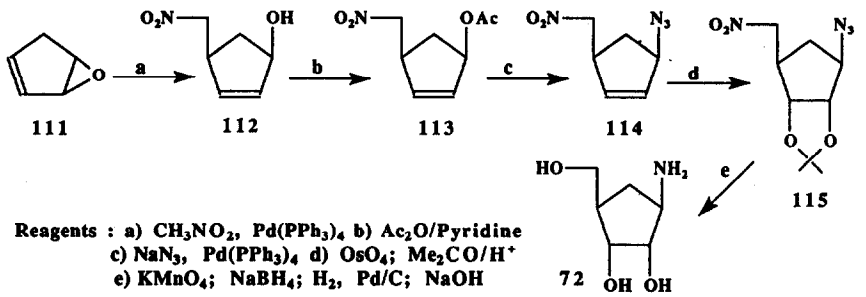
Hutchison et al.[87] have developed a rapid and stereoselective method for the synthesis of aristeromycin (Scheme 19). The main step in this synthesis is formation of an anti (or trans) epoxide relative to the 4'-hydroxymethyl group. The regioselective and stereoselective oxidation by SeO_2 of 1-hydroxymethyl-3-cyclopentene **108** produced diol **109**. Due to the presence of the allylic OH, the epoxidation of **109** by a peroxyacid led to the trans epoxide **110**. Nucleophilic opening of this epoxide gave a low yield of compound **13**.

SCHEME 19



An original method has been described by Deardorff[88] and by Trost.[89] It consists of the formation of aristeromycin from a monoepoxy-cyclopentadiene *via* the generation of a cationic (Π-allyl)Pd complex (Scheme 20). Reaction of the monoepoxy-cyclopentene **111** with nitromethane, under Pd(0)[90,91] catalysis, led to the nitromethyl adduct **112** by a 1,4 addition. After conversion to the acetate **113**, a reaction between **113** and NaN_3 (catalysed by Pd(0) complexes) led to the cis-azido compound **114**. A sequence of reactions (oxidation, protection) afforded the azido-nitro **115**. Four more steps then led to the carbocyclic-ribo-NH_2 **72**.

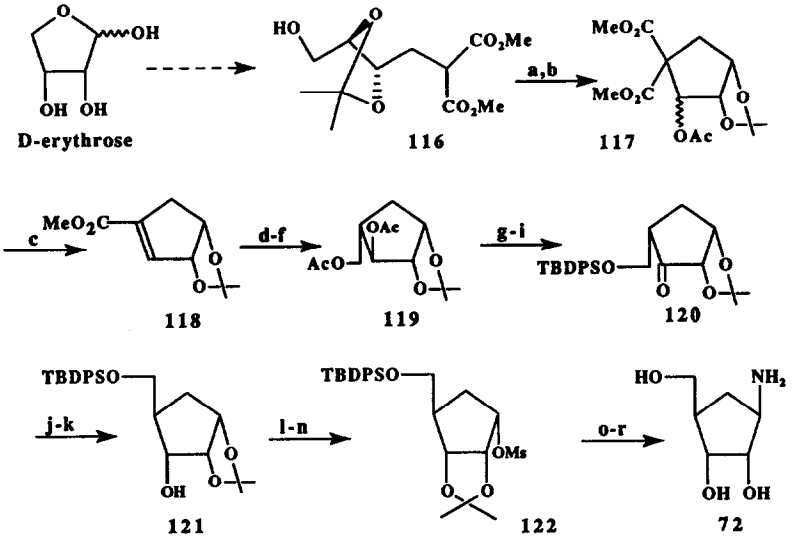
SCHEME 20



Method e : From the D-glucose, D-erythrose or the γ-lactone-D-ribonic acid

Another strategy for the synthesis of the aminotriol **72** has been described by Tadano et al.[92,93] starting from D-erythrose (Scheme 21).

SCHEME 21

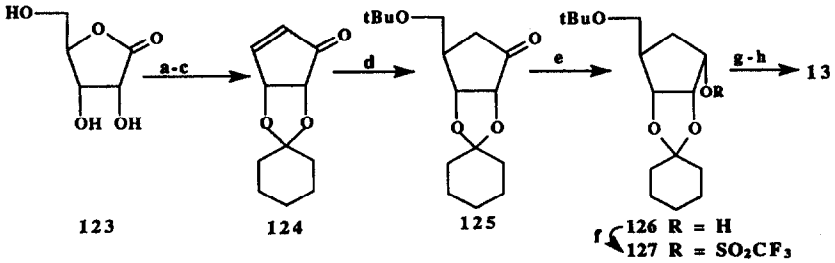


Reagents : a) PCC b) Me_2CO, H^+ c) DMSO, NaCl d) DIBAL-H e) BF_3/THF f) Ac_2O g) NaOMe h) TBDPSCl i) PCC j) silica gel k) $NaBH_4$ l) aqueous AcOH m) Me_2CO, H^+ n) MsCl o) NaN_3 p) TBAF q) H^+ r) H_2/Raney Ni

This reaction scheme needs 24 steps to produce the cyclopentylamine **72**. However, it is worth mentioning that the intramolecular aldol condensation **116** --> **117** (step b) forms the cyclopentane derivative. The intermediate **119** is obtained after 12 steps, and its conversion to (-)-**72** needs an additional 12 steps, after inversions of three of the four asymmetric centers. This synthesis leads therefore to a single enantiomer.

Starting from D-glucose, various teams[94-96] have obtained (-)-aristeromycin in 20 steps. A more direct way[97] begins with cyclopentenone **124** which is obtained from γ-lactone-D-ribonic acid **123** after four steps[98] (Scheme 22). Enone **124** treated with lithium cuprate generates the 4'-hydroxymethyl derivative **125**. After reduction of the cyclopentenone **125** and activation of the hydroxyl via triflate **127**, the coupling is carried out by addition of the adenine salt.

SCHEME 22



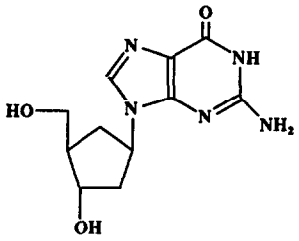
Reagents : a) cyclohexane, $FeCl_3$; $NaIO_4$, NaOH b) 2-propanol, pTS acid c) $CH_3PO(OMe)_2$, nBuLi, THF d) $(tBuOCH_2)_2CuLi$ e) DIBAL-H f) $(CF_3SO_2)_2O$/pyridine g) adenine, NaH h) CF_3CO_2H/H_2O

After deprotection, the chiral aristeromycin is isolated. This method has been widely applied.[29,32,34,99] The pyrimidine analogs[100-102] have been obtained by the Shealy method.[55] They are, however, far less studied. Two patents[103] describe the chemistry of aristeromycin and of the 3'-deazapurine derivative, obtained by enzymatic resolution of the racemic aristeromycin in a 5'-monophosphate form by an alkaline phosphatase.[180]

3-2. Carbocyclic analogs of deoxyribofuranosylnucleosides

Our introduction mentioned that carbocyclic analogs of deoxyribofuranosylnucleosides (C-BVDU **9**, C-IDU **11**, etc) had antiviral properties[18,23,24] especially of HSV type 1 & 2. The mechanism of inhibition of viral replication of hepatitis B by the 2'-deoxyguanosine carbocyclic analog (2'-CdG) **128** (Figure 7) was analyzed by Price et al.[104] Hepatitis B affects almost 300 million people around the world and increases the probability of developing liver cancer.

FIGURE 7



128

Additionally, this compound has anti-parasitical activities : it inhibits deoxyribonuclease, an enzyme that is essential for *Leishmania donovani*. The carbocyclic analogs of the deoxyribofuranosyl type comprise an important family of active compounds. The literature reports three important synthetic strategies to these compounds, each of which will be illustrated by examples:

Method a : From 5-norbornen-2-ol, endo or exo

Method b : From a chiral bicyclic [3,3,0] lactone

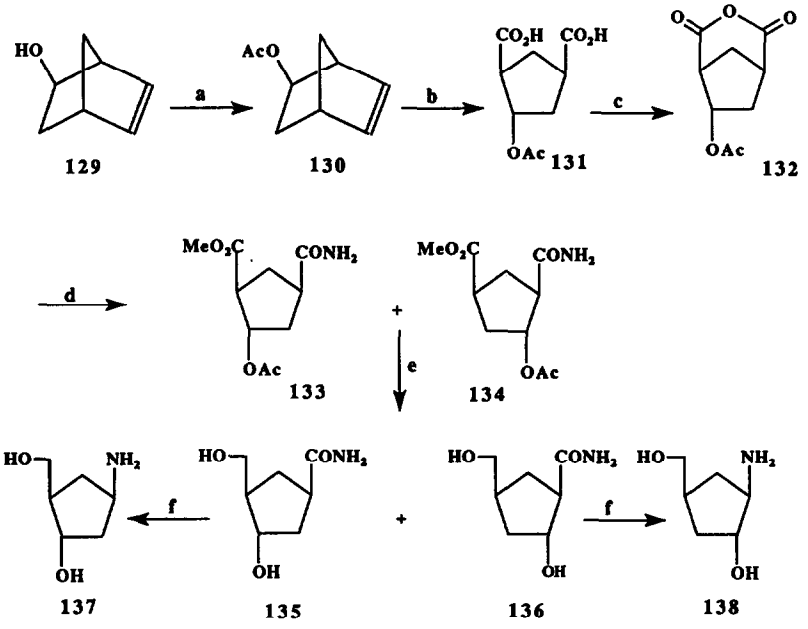
Method c : By dehydroxylation of a carbocyclic analog of the ribofuranosyl type

Method a : From the 5-norbornen-2-ol

Shealy and Clayton[106] were the first to use exo-5-norbornen-2-ol **129** as a precursor of a carbocycle (Scheme 23). Oxidation of the acetate (**130**) of exo-5-norbornen-2-ol with sodium permangante led to racemic cyclopentanedicarboxylic acid **131**. Treatment of **131** with acetic anhydride led to the cyclic anhydride **132**. A reaction sequence from **132** (opening of the anhydro, formation of an acid chloride, reaction with NH_3) allowed isolation of a mixture of amido-acid **133** and **134** which has given 2'- and 3'-C-deoxyribonucleosides respectively. A Hofmann degradation of the mixture gave, after protection of the formed amine, a mixture of acetamido ester **135** and **136**. After separation of the isomers, reduction by lithium borohydride of **135** gave the C-2'-deoxyribo-R-NH_2, **137**; and reduction of **136** led to the C-3'-deoxy isomer **138**.

This method has been employed for the synthesis of analogs with purines[106] and modified purines,[107] as well as for the synthesis of analogs with pyrimidines[55,56,100,108] and modified pyrimidines.[101,109] These methods are limited by the lack of regioselectivity at the stage of opening the cyclic anhydride which leads to a racemic mixture (**133**, **134**).

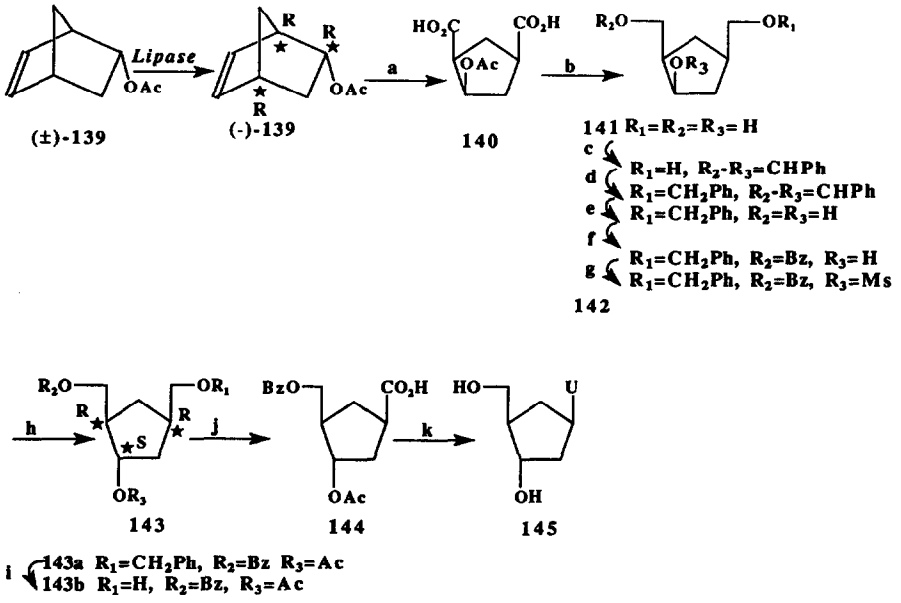
SCHEME 23



Reagents : a) Ac_2O/pyridine b) $NaMnO_4$ c) Ac_2O d) MeOH/H^+; $SOCl_2$; NH_3 e) $LiBH_4$ f) Br_2 / NaOH; MeOH/H^+

A new chiral approach has been developed by Griengl et al.[60,61,63] *via* a chemico-enzymatic step (Scheme 24). The endo-norbornenyl acetate **139** is obtained in large enantiomeric excess by an enzymatic resolution utilizing *Candida Cylindracea*.[110] By this approach, the (-)-acetate-(1R,2R,4R)-endo-bicyclo-[2,2,1]-hept-5-en-2-yl **139** has been isolated. Ozonolysis of **139** to **140** followed by reduction produced **141** with retention of configuration. A series of selective protections of this triol provides the protected carbocycle **142** (where $R_1 = CH_2Ph$, $R_2 = Bz$, $R_3 = Ms$). Inversion of configuration on the mesylated secondary alcohol **142** gave **143**. At this point, the compound becomes dextro (+) as in the natural series. After catalytic hydrogenation of the benzylether **143b** and oxidation, the acid, **144** was obtained. After a series of reactions (Curtius degradation, formation of an isocyanide, etc) the derivative of uracil **145** was isolated.

SCHEME 24



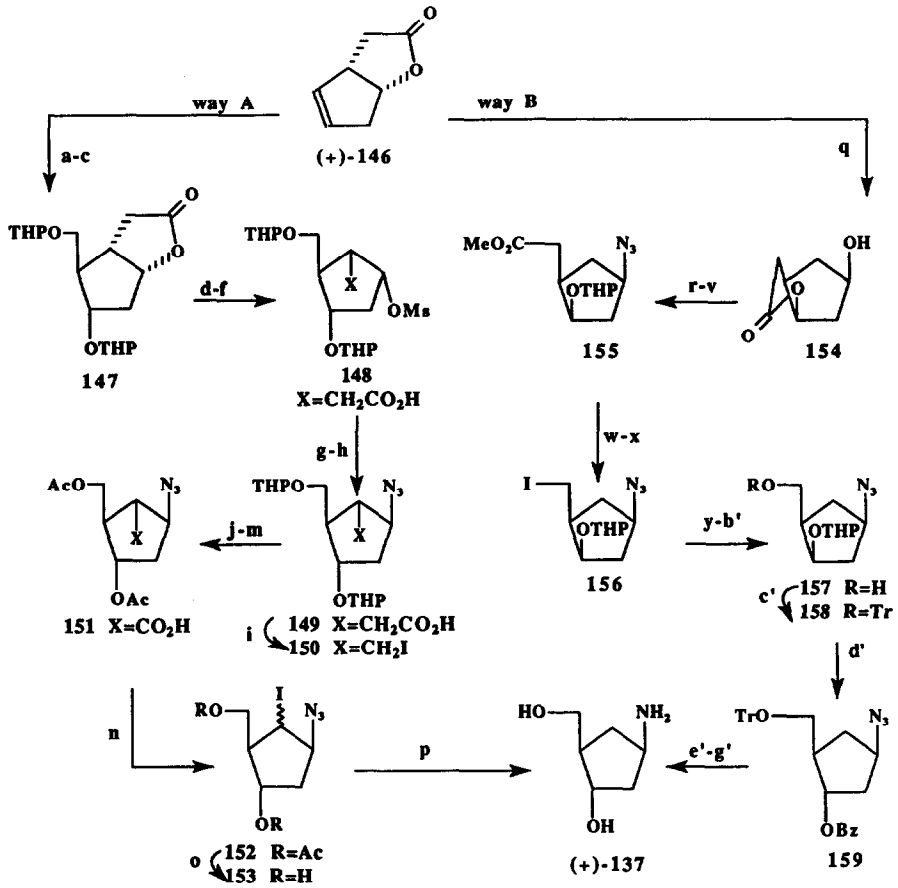
Reagents : a) O_3 b) $AlLiH_4$ c) $PhCH(OMe)_2$; HBF_4 d) KF, $PhCH_2Br$ e) H_2SO_4 f) BzCl/pyridine g) MsCl, Et_3N h) CsOAc, DMSO i) H_2, Pd/C j) PDC k) DPPA, toluene, 3-ethoxyacryloic acid chloride; NH_4OH

Method b : From a chiral bicyclic [3.3.0] lactone

Recently, Beres et al.[57,111,112] have developed an enantioselective synthesis of carbocycles by use of the chiral unsaturated lactone **146** (Scheme 25). The first approach[111-112] (way A) uses regioselective and stereoselective Prins addition of formaldehyde to the double bond of (±)-**146** to introduce 3-hydroxy and 4-hydroxymethyl functions and to give, after protection, the product **147**. Hydrolysis of the cyclic lactone produces a 1-α-hydroxyl derivative which, after mesylation, is substituted by azide ion to **149**, with concomitant formation of a group at C-5. Seven steps are needed to take this group off (using among others, iododecarboxylation reactions) and to obtain compound **153**. Catalytic hydrogenation of the iodoazide **153** led to the cyclopentylamine (±)-**137**.

The second approach[57,112] (way B) uses the lactone ring as a potential 4'-hydroxymethyl group. Azido group at C-1-β, introduced to **154** by a double inversion *via* a 1-α-iodo intermediate, produces **155**. The formation of the C-4-hydroxymethyl is carried out with a loss of one carbon atom by iododecarboxylation of **155**. The product **156** is transformed to azidodiol **157** and the inversion at C-3' is accomplished by a Mitsunobu's reaction which gives after protection, **159**. After deprotection and reduction of **159**, the chiral cyclopentylamine (+)-**137** is obtained.

SCHEME 25



Reagents : a) $(CH_2O)n$, H^+ b) amberlite H^+ c) DHP H^+ d) LiOH e) CH_2N_2 f) MsCl g) NaN_3 h) LiOH i) IBDA, I_2 j) pTsOH k) Ac_2O l) mCPBA m) PDC n) IBDA, I_2 o) K_2CO_3 p) H_2 Pd/C q) $Hg(OAc)_2$ r) Ph_3PI_2 s s) NaN_3 t) LiOH u) CH_2N_2 v) DHP, H^+ w) LiOH x) IBDA, I_2 y) pTsOH z) Ac_2O, pyridine a') mCPBA b') K_2CO_3 c') TrCl, pyridine d') PPh_3, DEAD, $PhCO_2H$ e')'K_2CO_3 f') pTSOH g') H_2 Pd/C

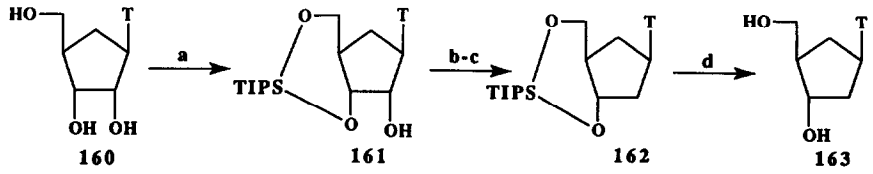
Method c : By dehydroxylation of a carbocyclic nucleoside

This method[39,102,113] consists of the reduction of O-phenoxy-thiocarbonyl ester (Scheme 26). Protection of the 3'-OH and 5'-OH of the C-ribothymine **160** has led to **161**. After activation and reduction, the deoxyanalog **162** was isolated, then its deprotection led to the 2'-deoxyribothymine carbocycle **163**.

Recently, Schneller et al[200] have described the (±)-3'-deoxy-araristeromycin. We have also reported[201] the synthesis of 3'-deoxyribonucleosides and their derivatives using direct addition of an heterocycle moiety to a protected 3-hydroxymethyl-1.5-epoxycyclopentane.

Literature reports a single approach *via* a precursor of cyclopentane[114] and two patents[115] describe the carbocyclic analogs of the 2'-deoxyribopyrimidines.

SCHEME 26

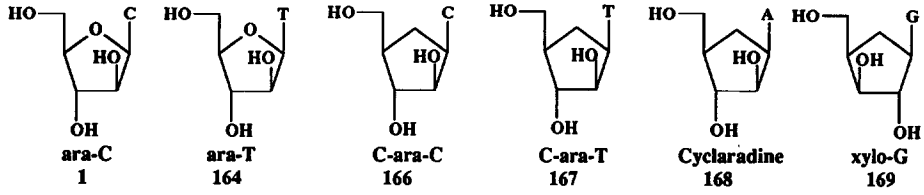


Reagents : a) $(iPr_2SiCl)_2O$ b) PhOC(S)Cl c) nBu_3SnH d) nBu_4NF

3-3. Carbocyclic analogs of arabino and xylofuranosyl nucleosides

Some *arabino* or *xylo* nucleosides show anticancer and antiviral activities. Important examples are *ara*-C **1** and *ara*-T **164** (Figure 8). The synthesis of carbocyclic analogues of these compounds, C-*ara*-C **166** and C-*ara*-T **167**, were carried out to improve their enzymatic resistance. Cyclaradine **168** is a potent anti-HSV agent. Also, few xylopurine nucleosides have as much anti-HSV[116] activity as the xyloguanosine carbocycle **169** (a few reports concern this configuration; and resulting compounds have no significant biological activity).

FIGURE 8

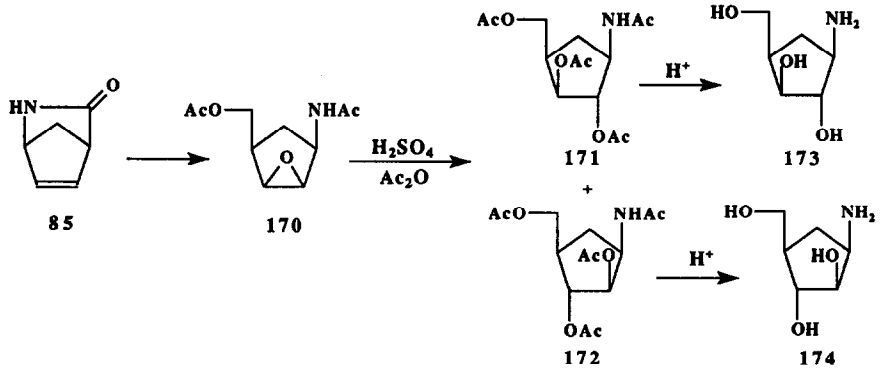


These syntheses were carried out using three methods.

Method a : Vince method

The hydrolysis of the epoxide **170**, which is easily obtained[76] from the lactam **85**, followed by an acetylation results in a mixture of compounds **171** and **172** (Scheme 27).

SCHEME 27

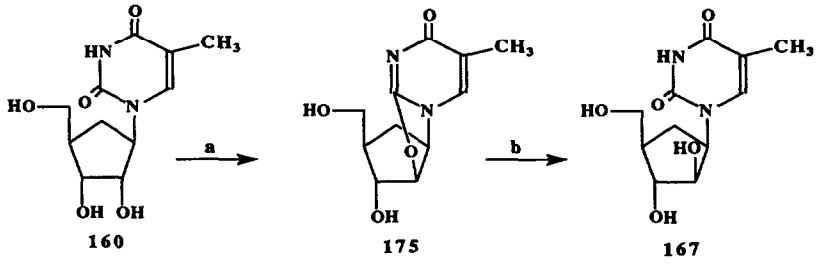


Deprotection of **171** gave a cyclopentylaminetriol **173** with a xylo configuration, whereas **172** provided the arabino isomer **174**. These cyclopentylamines form the carbocycles by reacting with the precursors of heterocycles bases. The above short procedure has been frequently employed for the formation of carbocyclic derivatives of purines.[78,116,117]

Method b : By inversion of configuration of the C-2'-OH

This method[100,118] leads only to compounds of the *arabino* configuration. It consists of the formation of an anhydro function between C-2' of the cyclopentane and the pyrimidine heterocyclic moiety (Scheme 28). C-ribo-thymine **160** has been converted into a 2,2'-anhydro derivative **175** by heat in the presence of diphenylcarbonate and of sodium hydrogencarbonate[119]. Basic hydrolysis led to the derivative **167** with the expected *arabino* configuration. This method can be used only with pyrimidines capable of forming such anhydro rings. These two methods of synthesis are the shortest reported and they allow the formation of chiral products. We also note the synthesis of cyclaradine **168** from the bicyclic lactone **146** (used by Beres and Griengl[57,111,112]) which was obtained from D-glucose or from 5-norbornen-2-one.[43] A patent[121] describes the synthesis of cyclaradine and of a guanine derivative. The configuration at 2' and 3'-deoxythreo[172] and 2',3'-dideoxyglycero[173] have been little studied, but examples of this series show little biological activity.

SCHEME 28



160 175 167

Reagents : a) PhOC(O)OPh, NaHCO3 b) NaOH

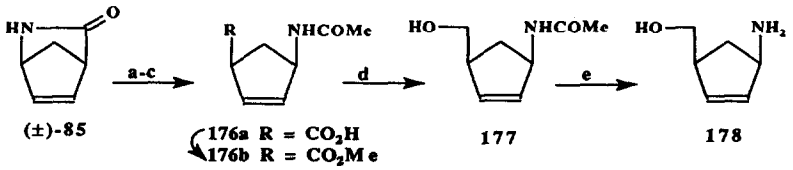
3-4. Carbovir and Neplanocin

a) Carbovir

Carbovir **16** (NCS 614846) (Figure 3) is a carbocyclic 2',3'-didehydro-2',3'-dideoxyguanosine derivative that has anti-HIV properties *in vitro*. This compound inhibits the infectivity and the replication of HIV in T cells at concentrations 200 to 400 fold below toxic levels. The anti-HIV activity of analogs of carbovir with purine (chloroadenine, adenine, hypoxanthine, 6-thiopurine, 6-chloroguanine) and pyrimidine groups has been evaluated by Vince et al.[122] Only carbovir, **16** , has significant activity *in vitro*.

The synthesis of (±)-carbovir starts with lactam, 2-azabicyclo-[2,2,1]-hept-5-en-3-one, **85** (Scheme 29). The lactam **85** is obtained[77] by the Diels-Alder reaction of p-toluenesulphonyl-cyanide and cyclopentadiene, followed by acid treatment of the cycloadduct. Hydrolysis of lactam **85** gives the amidoester **176b** after esterification and acetylation. This compound is reduced to the alcohol **177** by lithium borohydride. Deacylation with acidic conditions leads to the amino alcohol **178,** which can then be coupled with a guanine precursor.

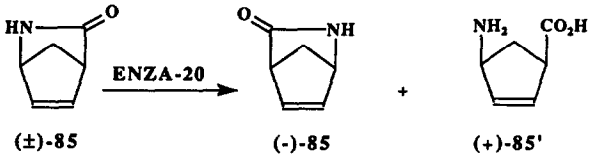
SCHEME 29



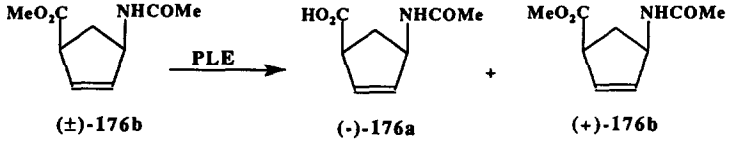
Reagents : a) H⁺ b) MeOH, H⁺ c) Ac_2O/Pyridine d) $LiBH_4$ e) H⁺

An improvement in this synthesis has been carried out by introduction of an enzymatic resolution step. Thus, Evans et al.[54,123] resolved the racemic lactam by incubation with *Pseudomonas Solanacearum* NCIB 40249 (ENZA-20), and obtained up to 55% of conversion (Scheme 30). The (+)-enantiomeric form is selectively hydrolyzed to (+)-aminoacid **85'**, whereas the (-)-lactam **85** is isolated unchanged and used for the synthesis of carbovir. The (±)-acetamidoester **176b** can be resolved enzymaticallythanks to the PLE enzyme[124] (Scheme 31).

SCHEME 30

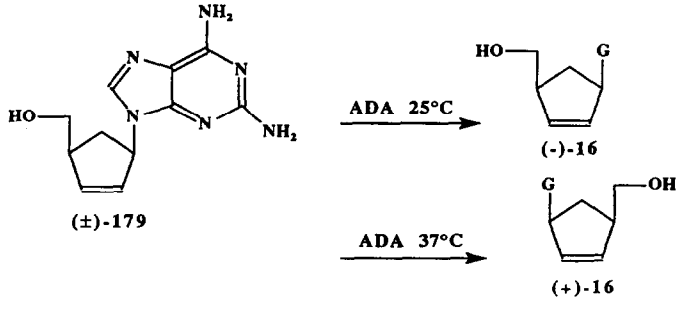


SCHEME 31



The PLE selectively hydrolyses the (-)-enantiomer to (-)-carboxylate amide **176a**. The (-)-carbovir can be prepared by the action of *adenosine deaminase*[125] (ADA) on 2,6-diaminopurine (±)-**179** (Scheme 32), which in turn can be synthesized as reported by Vince et al.[25] and, more recently by Exall et al.[26]

SCHEME 32

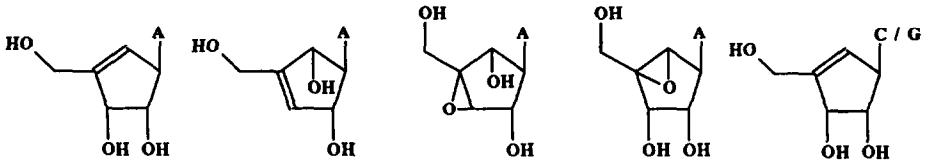


Hanrahan et al.[181] have worked out the enzymatic synthesis of antiviral agents such as carbovir. The biological activities of this compound prompted the synthesis of ^{14}C-marked carbovir by Kepler et al.,[128] with the objective of studying its metabolic fate. Some patents[129] protect the chemistry and biological activities of carbovir and its purine or pyrimidine derivatives.

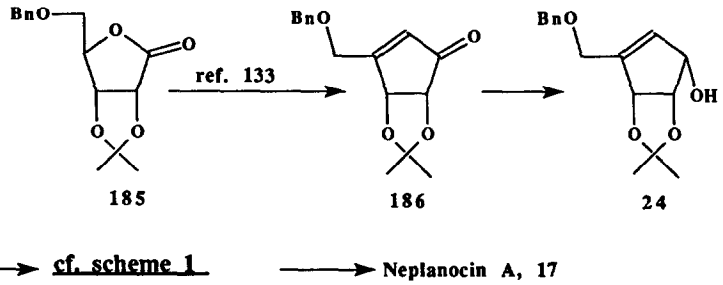
b) The neplanocins

The neplanocin family of antibiotics includes many molecules in which the modifications are on the cyclopentane (Figure 9). Among these various compounds, neplanocin A **17** has significant anti-leukemia activity.[130] The syntheses of compounds **180-184** are described in the literature[131,132] along with many other carbocyclic derivatives of neplanocin.[166] Neplanocin A can be prepared from bicyclic[71] systems or by asymmetric Diels-Alder reaction[74] of a dienophile on a cyclopentadiene. The most common synthesis of this compound is based on the preparation of 2-cyclopenten-1-one **186** from (+)-γ-lactone-D-ribonic acid[169] **185**, whose synthesis is reported by Lim and Marquez.[133] The stereoselective reduction of **186** produces the allylic alcohol **24** (Scheme 33).

FIGURE 9

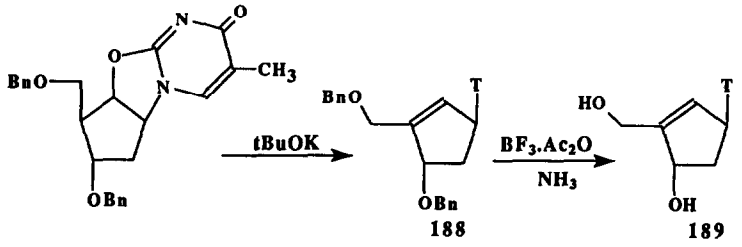


SCHEME 33



This procedure has been widely used[30,33,134-136] for the synthesis of analogs of neplanocin A with purines or pyrimidines groups and is protected by a patent.[137] The literature also mentions[40] how to get 2'-deoxypyrimidic analogue **189** of the neplanocin A; the key step of the synthesis is an intramolecular elimination by action of potassium *tert*-butoxide on the anhydro derivative **187** (Scheme 34). After deprotection of the intermediate **188**, the derivative **189** is isolated.

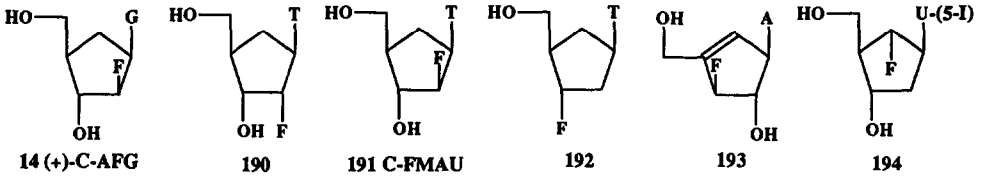
SCHEME 34



4. THE FLUORINATED CARBOCYCLIC ANALOGS OF NUCLEOSIDES

In 1986, Blackburn et al.[138] suggested that a fluoromethylene would be a better isosteric group than the methyl to replace the ring oxygen. Various teams have paid attention to the synthesis of 6'-fluorocarbocycles.[24,41,53,140,141] We have previously mentioned the anti-HSV activity of the fluorinated nucleosides FIAC **3**, the FMAU **4**, and FIAU **5** (Figure 1). A second interesting challenge for chemists, therefore, was the synthesis of carbocyclic analogs[23,141-144] in which the fluorine is in the 2'-position. For example, some fluorinated analogues of 2'-deoxyribonucleosdides or of neplanocin A have been synthesized[60,145-146] and their biological properties have been evaluated. Figure 10 displays some of the active fluorinated carbocycles. Fluorine has been used in place of hydrogen or hydroxyl group at various sites, in place of the oxygen of the ose, and on the heterocyclic base of nucleosides[147-151] (Figure 11).

FIGURE 10



Fluorine shows the following physico-chemical properties :

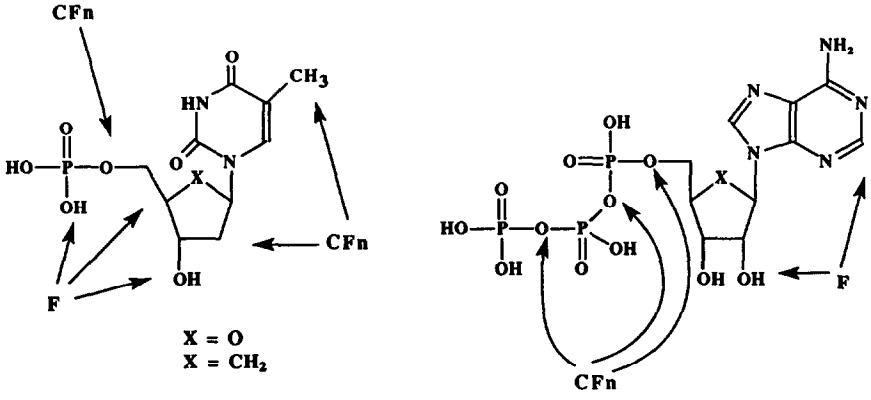
a) It is the most electronegative element among the halogens.

b) Its Van der Waals radius (1.35×10^{-10}m) is fairly close to that of hydrogen (1.10×10^{-10}m) so F will not disturb the geometry of the molecule.

c) The energy of a C-F bond (485 kJ/mole) is greater than that of C-H (413 kJ/mole) or of C-O (385 kJ/mole).

The introduction of a fluorine on the cyclopentane ring of a nucleosidic analog implies some modifications in the chemical and in its biological activity without an important change in the conformation of the fluorinated cyclopentane. Compound **14** (+)-C-*ara*FGua represents the first example of a fluorinated carbocyclic analog of an arabino purine nucleoside that has greater anti-HSV activity than the parent nucleoside **15** (cf Figure 3).

FIGURE 11



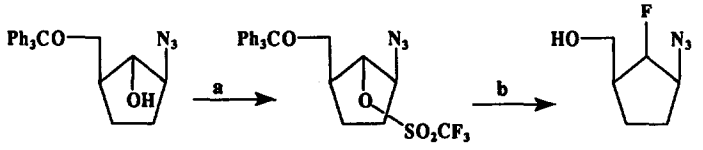
Methods for introducing the fluorine atom

Various methods can be employed :

Method a : Substitution of a nucleofuge[41,53,139,153] by a fluoride ion.

The fluorination agent often employed is Bu_4NF (Scheme 35) and by an SN_2 mechanism, gives a product with an inverted configuration. First, the azidoalcohol[153] **195** is activated by preparation of the triflate **196**. The triflate group is then displaced by the fluoride ion of $Bu_4N^+F^-$ to yield the fluoro-azide **197**.

SCHEME 35

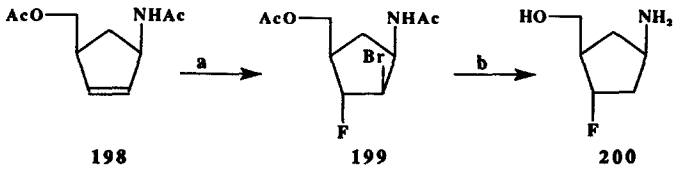


195 196 197

Reagents : a) $(CF_3SO_2)_2O$, pyridine b) TBAF, THF

Method b : By the combined action of hydrofluoric acid solution in pyridine (HF/Pyridine, Olah's reagent) and of N-bromosuccinimide on a double bond.[152,153] A synthesis of fluorinated carbocycles has been reported by Nakayama et al.[152] (Scheme 36) using this approach. *cis*-4-Acetamido-1-acetoxymethyl-2-cyclopentene **198** was treated with Olah's reagent[152] which led to the formation of the *trans*-bromofluoro compound **199**. The reduction of **199** by tributyltin hydride gave the cyclofluoropentylamine **200**. This method has be reviewed by Palmer and al.[159]

SCHEME 36



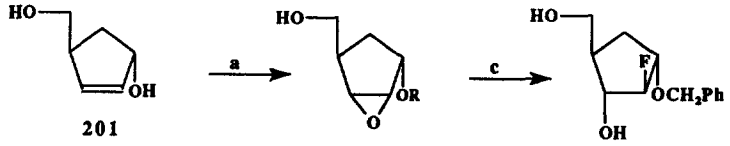
198 199 200

Reagents : a) HF/Pyridine, NBS b) $(Bu)_3SnH$

Method c : By opening of an epoxide.

The fluorination agent used to effect *trans*-addition is the HF-KF complex (Scheme 37). The selective tritylation of the primary alcohol of **201** and then epoxidation gave epoxide **202**. After protection of the secondary alcohol by benzylation, **203** was treated with a solution of potassium hydrogen difluoride. It is noteworthy that in addition to fluorination, detritylation took place and the fluoro diol **204** was obtained.

SCHEME 37



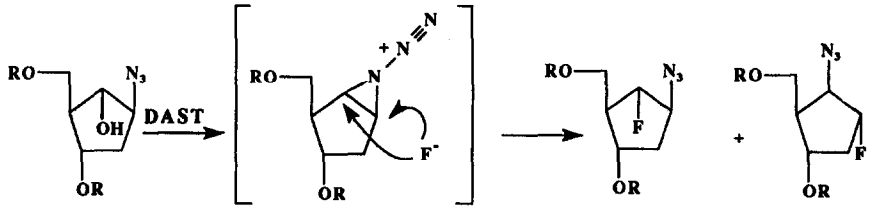
201

Reagents : a) TrCl; tBuOOH, toluene, $VO(acac)_2$ b) NaH, $PhCH_2Br$, nBu_4NI c) KHF_2

Method d : By reaction of an alcohol with DAST.

DAST is a fluorination agent[154,155] that allows conversion of an alcohol to a monofluorinated derivative, and of an aldehyde or a ketone to difluorinated derivatives. Fluorination by DAST is carried out under mild conditions and occurs normally with inversion of configuration; however, certain neighboring groups can result in retention of configuration[156] (Scheme 38).

SCHEME 38



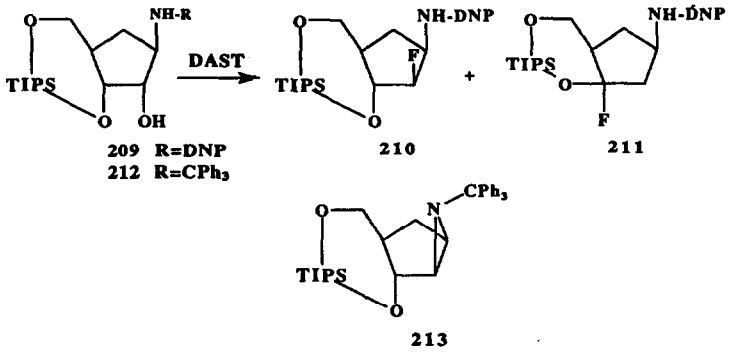
205 206 207 208

R = Ph_3C

The fluorination of azido-alcohol[53] **205** by DAST led to fluoro-azido compounds **207** with retention of configuration and also to **208**. The transient intermediate **206** would explain the migration of the azido group

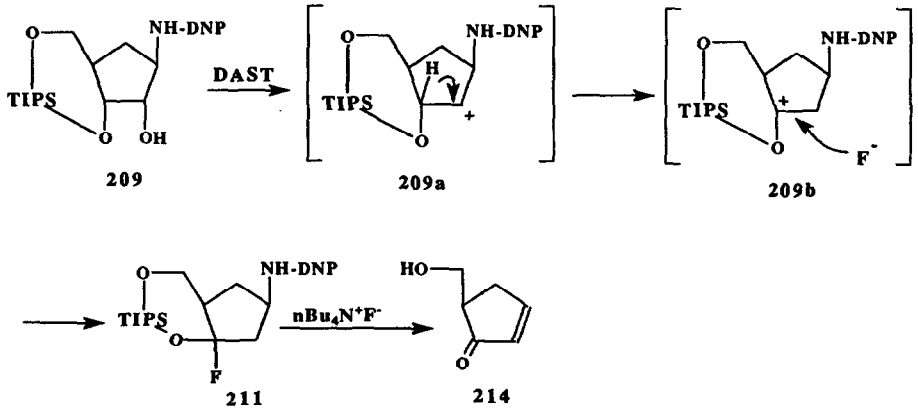
in **208**. Azide migration during fluorination by DAST has been utilized by Nicolaou et al.[157] in the chemistry of carbohydrates. The success of the fluorination also depends on the protecting groups on the amine and alcohol functions. Thus, in the case of an aminoalcohol[142] (Scheme 39), the amino function must be protected by an electrondrawing group to minimize participation of the amine nitrogen during fluorination.

SCHEME 39



After protection of the hydroxyls at C-3' and C-6' as their oxybis(diisopropylsilyl)ethers and the amine with a dinitrobenzene group (DNP), the fluorinated compound **210** with an inverted configuration was obtained as the main product. A small amount of **211** was also isolated. Its formation was explained as shown in Scheme 40. This mechanism implies migration of an α-hydrogen to stabilize carbocation **209a** and the attack by a fluoride ion (**209b**) from the less hindered side. On the other hand, if the amine is protected by a trityl group during the fluorination, only the aziridine **213** is isolated[142] (Scheme 39). It is noteworthy that the silyl ether (OTIPS) remains intact in the presence of DAST, which demonstrates that there is no free fluoride ion in the mixture. In fact, with another fluorinating agent, nBu_4NF, **211** is completely deprotected to **214**. It has been noted that some trialkylsilyl protecting groups are not resistant during fluorination by DAST.[158] Based on the various observations, the mechanism of fluorination by DAST cannot be classified as either SN_1 or SN_2.

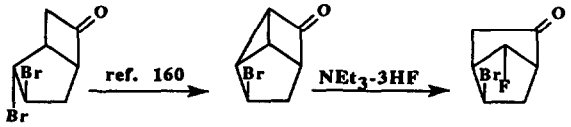
SCHEME 40



Method e : the opening of a strained ring system[140].

The use of Et_3N-HF[161] opened the strained tricyclic ketone **216** (obtained from compound **215**) (Scheme 41) to give the dihalogenated ketone **217**. The use of other sources of fluoride ion gave inferior results for this type of ring opening.

SCHEME 41



215 **216** **217**

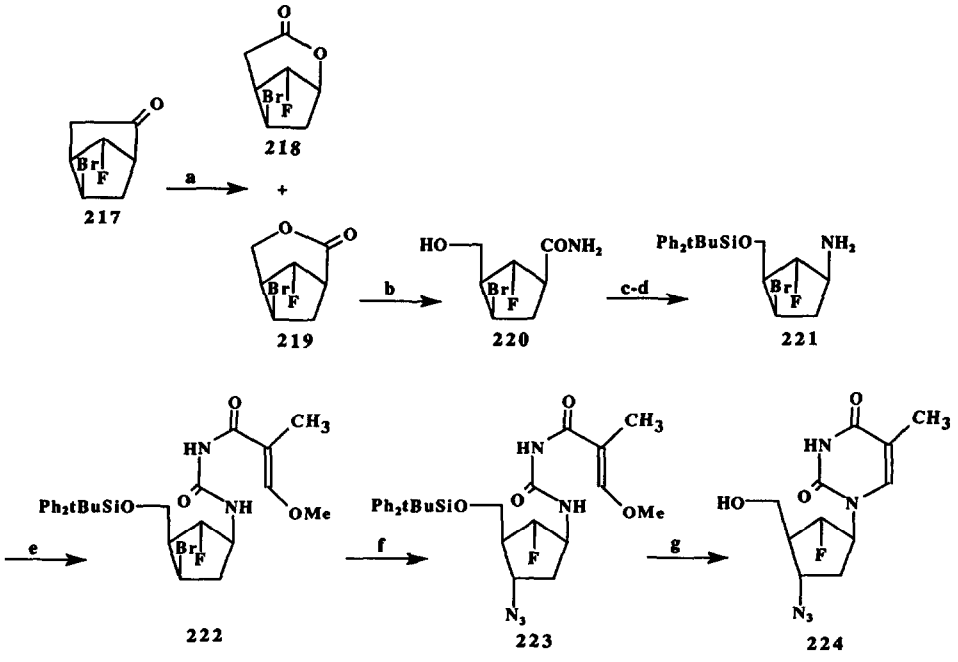
We now describe in detail, several interesting classes of fluorinated carbocyclic nucleosides analogs. These syntheses have been classified on the basis of location of the fluorine on the cyclopentane ring as well as on the fluorination technique.

4-1. Synthesis of C-6'-fluorinated carbocyclic nucleosides

i) Fletcher Synthesis[140]

This attractive synthesis allows preparation of C-6'-α and C-6'-β-fluorinated nucleosides (Scheme 42). Fluorine was introduced by method e.

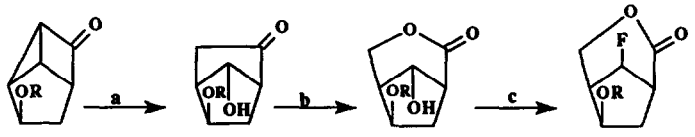
SCHEME 42



Reagents : a) mCPBA, $NaHCO_3$ b) liq. NH_3 c) $(Ph)_2tBuSiCl$ d) $PhI(OCOCF_3)_2$ e) MeOCH=C(Me)CONCO f) NaN_3 g) H^+

The dihalogeno ketone **217**, on Bayer-Villiger oxidation gave both **218** and **219**. Lactone **219** was then converted to amide **220** by liquid ammonia. A Hofmann reaction on amide **220** provided cyclopentylamine **221**. Initial condensation of an acrylic isocyanate derivative with **221** gave the bromo-fluoro intermediate **222**. After substitution of bromine by an azido group (compound **223**), deprotection, and then ring-closure gave 3'-β-azido-6'-α-fluorothymine **224**. An enzymatic catalysis of the Bayer-Villiger oxidation of ketone **217** has also been accomplished by Levitt et al.[163] To obtain the 6'-β-fluorinated isomer, a ring in tricycle **225** is first opened by aqueous THF to **226**. After a Bayer-Villiger reaction, the derived lactone **227** was fluorinated by DAST to yield **228** with an inverted configuration (Scheme 43).

SCHEME 43



225 **226** **227** **228**

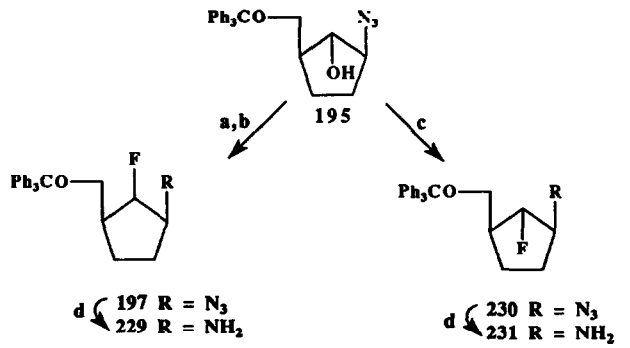
R = $PhCH_2$

Reagents : a) THF, H_2O b) Bayer-Villiger conditions c) DAST

ii) Synthesis by Roberts et al.[23,24,53,141,162]

A series of 2',3'-dideoxy-6'-α/β-fluorinated nucleosides has been synthesized. The key step in these syntheses is substitution of the hydroxyl by fluorine (Scheme 44), with α or β configurations depending on the type of fluorinating agent used. The fluorination of **195** with TBAF, *via* a triflate, gave β-fluoroazide **197**. After a catalytic hydrogenation of the azide function, the fluorinated cyclopentylamine **229** can be coupled to yield purines or pyrimidines. Fluorination of the azido-alcohol **195** with DAST provided the azido-fluoro compound **230**, with retention of configuration, which gave after hydrogenation of the azide, the 6'-α-fluoro-cyclopentylamine **231**. This compound was then coupled with appropriate precursors to yield purines or pyrimidines.

SCHEME 44

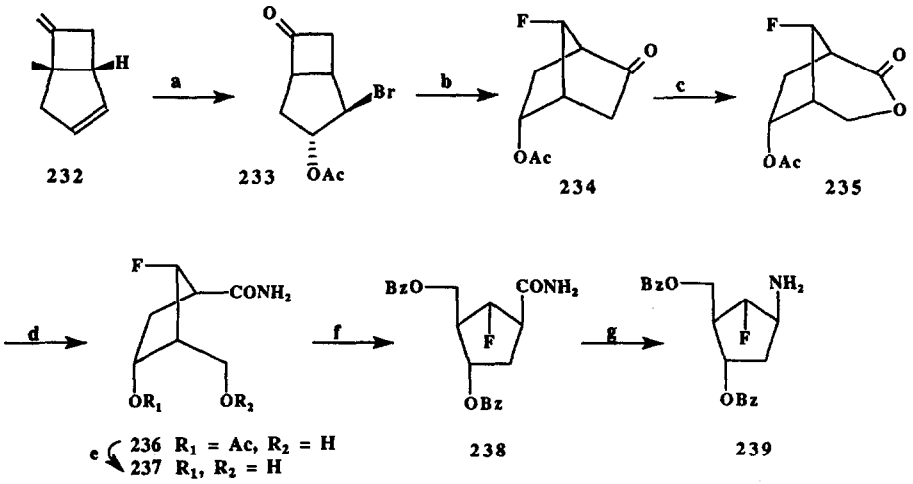


Reagents : a) $(CF_3SO_2)_2O$ / Pyridine b) TBAF c) DAST d) H_2, Lindlar cat.

* *Synthesis by Payne et al.*[139]

This attractive synthesis produces a 6'-α-fluorinated carbocycle from a bicyclic ketone (**232**, Scheme 45). The ketone **232** was converted to bromoacetate **233**. Treatment of the ester **233** with potassium *tert*-butoxide (resulting in a rearrangement and a Michaël addition) followed by substitution of a bromine by Et_3N-HF gave the fluoroester **234**. Bayer-Villiger oxidation then led to lactone **235**, which was converted to amide **236** by liquid ammonia. Hydrolysis of **236** led to diol **237** which provided, under Mitsunobu conditions, the dibenzoate **238**. Finally a Hofmann reaction on the amide yielded the fluorinated cyclopentylamine **239**, which can be elaborated further to give various heterocyclic bases.

SCHEME 45

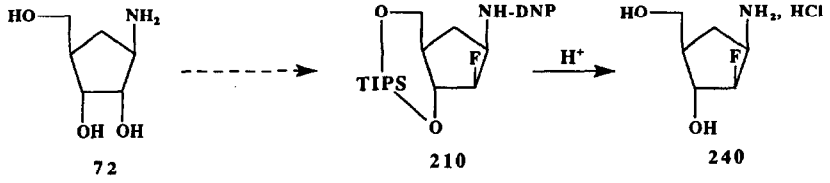


Reagents : a) NBA b) tBuOK, Et_3N-3HF c) mCPBA d) liq. NH_3 e) NH_3-MeOH f) PPh_3, $PhCO_2H$, $EtO_2N{=}NCO_2Et$ g) Hofmann's conditions

4-2. Synthesis of C-2'-fluorinated carbocyclic nucleosides

Several syntheses[23,141,142] have involved formation of carbocyclic nucleoside analogs possessing the C-2'-F-*arabino*-configuration. They all use the fluoro-aminodiol **72** (Scheme 46) whose synthesis we was described earlier[67,68] (Scheme 11). After the many steps shown in scheme 36, **210** was obtained. Acidic hydrolysis of the fluorinated amine **210** provides the fluorinated arabino carbocycle **240**.

SCHEME 46



Alternatively Borthwick et al.[143,144] synthesized the 2'-deoxy-2'-β-fluoro-*arabino*-cyclopentylguanine **14** (+)-C-AFG[165] from aristeromycin **13** by a three steps synthesis that involved:

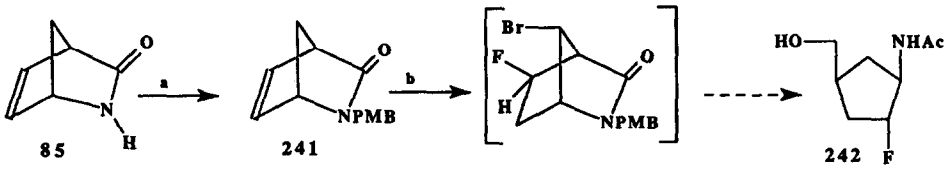
(i) protection of the 3'-OH and 5'-OH (as the TIPSether),

(ii) fluorination of the 2' hydroxyl with inversion of configuration by DAST,

(iii) transformation of the adenine moiety to guanine.

We also point out the synthesis of Palmer et al.[159] which led to 3'-deoxy-2'-α-fluoro-*ribo*-cyclopentylamine **242**. The protected bicyclic lactam **241**, was fluorinated by treatment with a mixture of NBS, Et_3N-3HF (Scheme 47). The substitution of bromine by hydrogen (by used of tributyltin hydride)left the fluorine intact. The other steps of this conversion to **242** are identical to those described in Scheme 29.

SCHEME 47



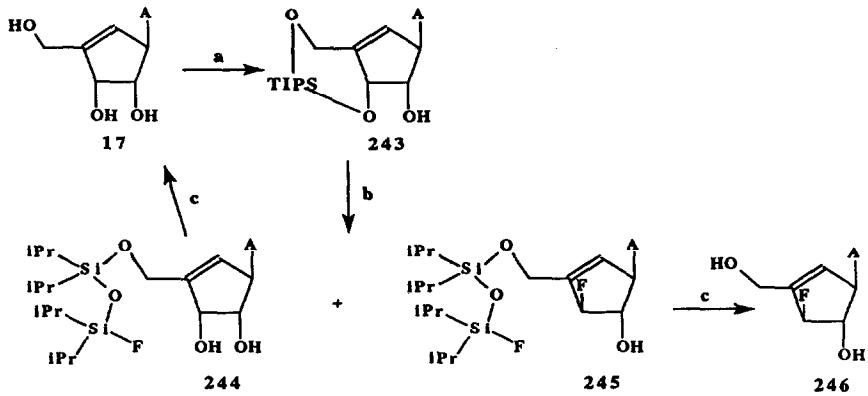
85 241 242

Reagents : a) 4-MeOC$_6$H$_4$CH$_2$Cl b) NBS, Et$_3$N-3HF

4-3. Synthesis of C-3'-fluorinated carbocyclic nucleosides

The fluorinations are accomplished by substitution of a mesylate in C-3'-β[60], by reaction of the C-3'-β-hydroxyl with DAST with inversion of configuration[145], or by replacement of a trimethylsilyl ether at C-3'-β by use of a DAST analog, the piperidine trifluorosulfide.[153] The synthesis of fluoro-neplanocin developed by Borthwick et al.[146] (Scheme 48) is representative of the approach.

SCHEME 48



17 243 244 245 246

Reagents : a) TIPSCl/ Et$_3$N b) DAST c) TBAF

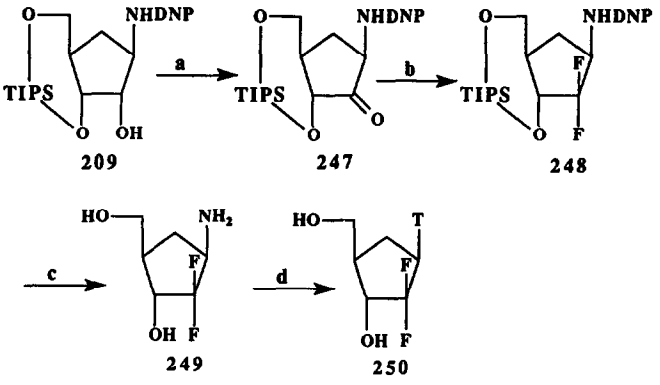
Simultaneous protection of the 3'-OH and 5'-OH of neplanocin A **17** by TIPS led to the derivative **243**. Reaction of **243** with DAST then provided a mixture of diol **244** and 3'-fluoro derivative **245**. However, when

the reaction was carried out at low temperature, the formation of **245** was mainly favored. Deprotection of **244** with a solution of $Bu_4N^+F^-$ gave the neplanocin **17** and deprotection of **245** gave the expected fluorinated product **246**. One patent[164] describes the chemistry of carbocyclic analogs of 3'-fluoro-2'-deoxyribo nucleosides.

4-4. Synthesis of gem-difluorinated carbocyclic nucleosides

The only synthesis reported is the one of Borthwick et al.[141] (Scheme 49). The oxidation **209** to **247** and fluorination of this ketone by DAST gave the difluorinated derivative **248**. Deprotection and coupling of **249** with the thymine precursor provided the difluorinated carbocyclic analog **250.**

SCHEME 49



Reagents : a) DCC, DMSO b) DAST c) OH^-, then H^+ d) DBU, EtOCH=C(Me)CONCO then H_2SO_4

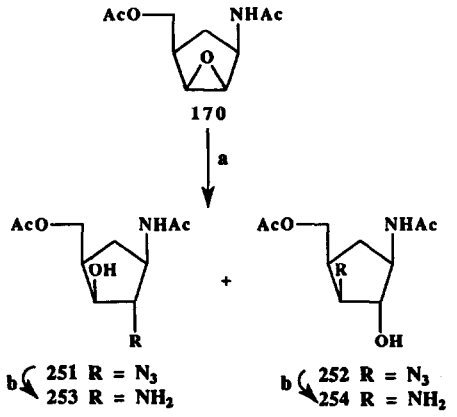
5 - CARBOCYCLES SUBSTITUTED BY OTHER FUNCTIONAL GROUPS

We now outline several syntheses of carbocyclic analogs of nucleosides functionalized on the cyclopentane ring by amino, azido, or other groups.

5-1. The azido and amino carbocyclic nucleoside analogs

These compounds were synthesized for the first time by Daluge and Vince.[170] Their syntheses involve trans-opening of epoxide **170** by azide ion (Scheme 50). As expected both azido derivatives **251** and **252** were obtained due to the two possible sites of attack. After hydrogenation, the amino alcohols **253** and **254** were isolated. They were then coupled to precursors of purines or pyrimidines.

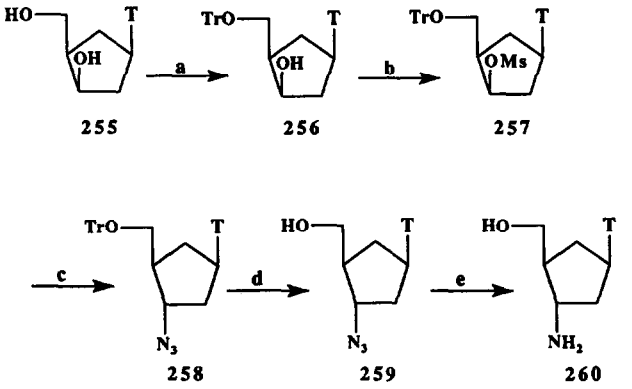
SCHEME 50



Reagents : a) NaN_3 b) H_2, Pd/C

The carbocyclic analog of AZT[171] has also been synthesized (Scheme 51). Tritylation of the primary hydroxyl of carbocycle **255** to give **256** followed by activation of the secondary hydroxyl by mesylation gave the mesylate derivative **257**. Displacement of the labile group at β-C-3' of **257** by azide ion gave the protected azido-carbocycle **258**. Finally, deprotection led to the carbocyclic analog **259** of AZT. Hydrogenation of the azido function also provided the amino carbocycle **260**.

SCHEME 51



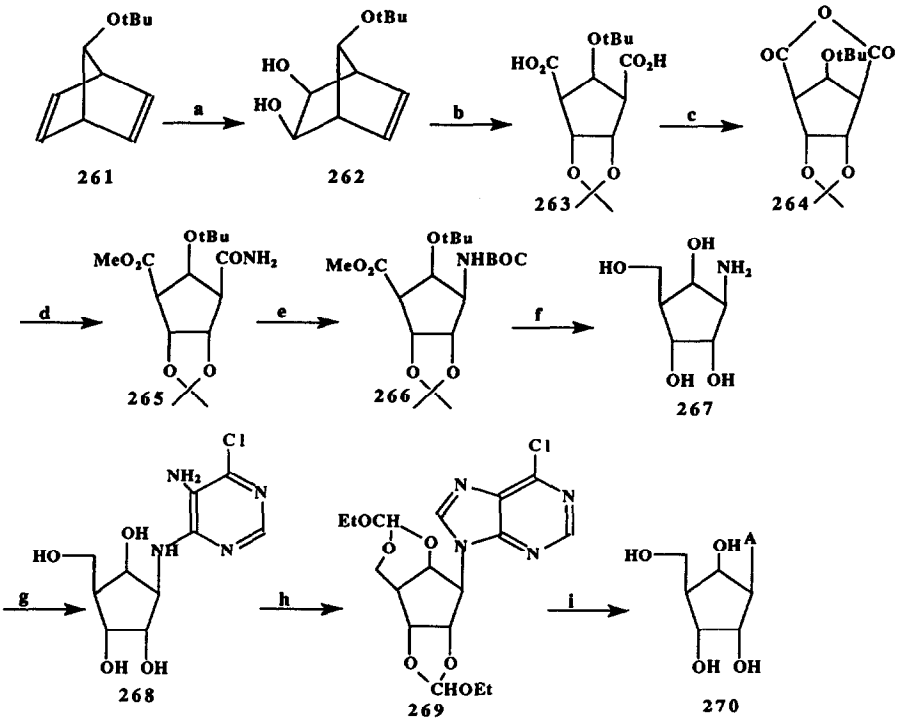
Reagents : a) TrCl/pyridine b) $MsCl/CH_2Cl_2$ c) NaN_3 d) H^+ e) H_2 Raney Ni

5-2. Synthesis of 6'-β-hydroxyribonucleosides

In view of the the biological importance of aristeromycin and neplanocin A derivatives, the synthesis of 6'-β-hydroxyaristeromycin **270** was developed.[174-175] One of the approaches described in literature started with 7-*tert*-butoxynorbornadiene **261**. Oxidation with potassium permanganate led to exodiol **262** (Scheme 52). After protection of the 1,2-diol, oxidative cleavage of the double bond provided the *meso* diacid **263**,

which was transformed to the anhydride **264** by reaction with DCC in pyridine. The cyclic anhydride was then transformed, *in situ*, to the monoacid, which when esterified gave product **265**. A Hofmann reaction gave the BOC amino-ester **266** with retention of configuration. Reduction of the ester followed by total deprotection gave the cyclopentylamine tetrol **267**. This compound was transformed to intermediate **268** with 5-amino-4,6-dichloropyrimidine. Ring-closure to the imidazole cycle required protection of the 2', 3', 5' and 6'-OH. Ammonolysis of **269** and acidification of the derivative gave the expected carbocycle **270**.

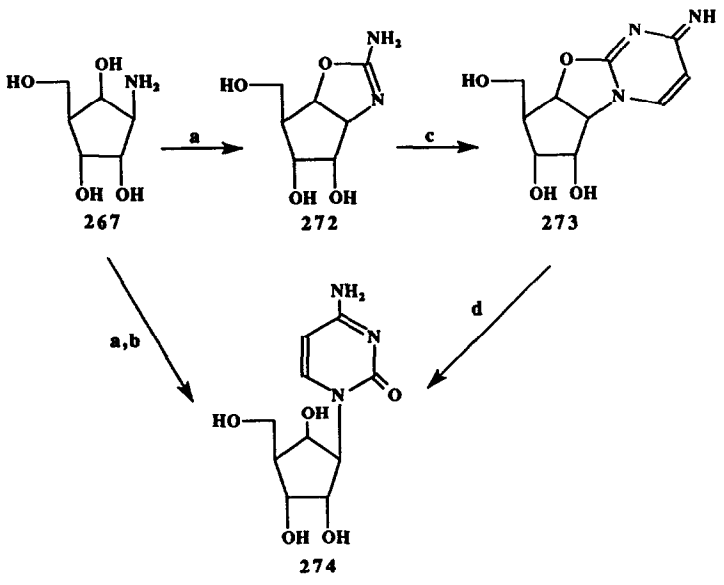
SCHEME 52



Reagents : a) $KMnO_4$ b) Me_2CO, $CuSO_4$; aq. $KMnO_4$ c) DCC, pyridine d) NH_3; CH_2N_2 e) $Pb(OAc)_4$, t BuOH, Δ f) $Ca(BH_4)_2$; HCl, MeOH g) 5-amino-4,6-dichloropyrimidine h) $CH(OEt)_3$ i) NH_3 then HCl

The synthesis of cytosine derivatives has also been accomplished[175] (Scheme 53). The heterocycle moiety was formed in two steps from the cyclopentylamine tetrol **267** *via* the reaction *in situ* of cyanoacetylene with oxazoline intermediate **272**.

SCHEME 53



Reagents : a) BrCN b) cyanoacetylene, NH_4OH c) cyanoacetylene, $CH_3CON(CH_3)_2$ d) NH_4OH

5-3. Carbocycles without the 5'-methyl

Carbocyclic nucleoside analogs possessing a C-4'-β-OH instead of the 4'-hydroxymethyl group were synthesized by Coe et al.[176] This route (Scheme 54) utilized the Pd(0) directed coupling of heterocycle bases to epoxy-cyclopentene **111** and led[177a] to the corresponding cyclopentenol **275**. Recently, a chemo-enzymatic[177b] resolution of **275** led to the optically active 5'-noraristeromycin **276**. The reaction of **275** with borane/basic hydrogen peroxide gave the 2'- and 3'-deoxy-noraristeromycin analogs[178d]. The 5'-noraristeromycin[178] **276** has this type of structure (Figure 12) and has been synthesized using this procedure.

SCHEME 54

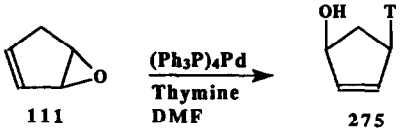
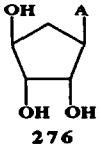


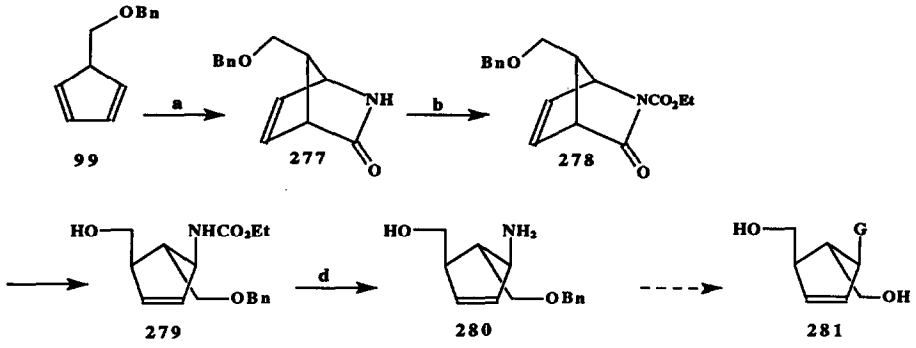
FIGURE 12



5-4. Synthesis of a carbocyclic analog derivated from carbovir

Compound **281** is another analog of carbovir. Its synthesis[179] is shown in Scheme 55.

SCHEME 55



Reagents : a) TsCN b) LDA / HMPA then $ClCO_2Et$ c) $NaBH_4$ d) KOH, H_2O

The precursor **99**, after reaction with tosylcyanide and acidification of the cycloadduct provided the lactam **277**. Ethoxycarbonylation of **277** with diisopropyl lithium led to carbamate **278**. A reductive cleavage of which gave **279**. After total deprotection, the cyclopentylamine **280** was obtained. The classical method for the build-up of guanine around the amino function provided the carbovir analog **281**.

6- Biological activity of carbocyclic nucleosides

The mechanism of action and metabolic fate of carbocyclic nucleosides are similar to those nucleosides. The antiviral activity depends on various factors including penetration into the cell, phosphorylation steps, catabolism, etc. A rational approach to antiviral chemotherapy exploits the biochemical differences that exist between viral and cellular properties. Most of the therapeutic agents used today for the treatment of viral infections are structural analogs known to block the metabolism of the viral nucleic acids. Different steps of the replication cycle of a virus are good potential targets for anti-viral agents :

1) adsorption of the virion to the cellular membrane by specific receptors of the host cell.

2) penetration and uncoating.

3) expression of the genome and synthesis of the proteins. [The genetic message is contained in the nucleus as DNA (or RNA). After its integration, the DNA is transcribed to mRNA which goes into the cytoplasm where the translation into proteins occurs *via* the tRNA. The mechanisms of replication and transcription involved the polymerisation of the nucleosides (in their triphosphate form) in the DNA monocatenar matrix utilizing viral and cellular polymerases.]

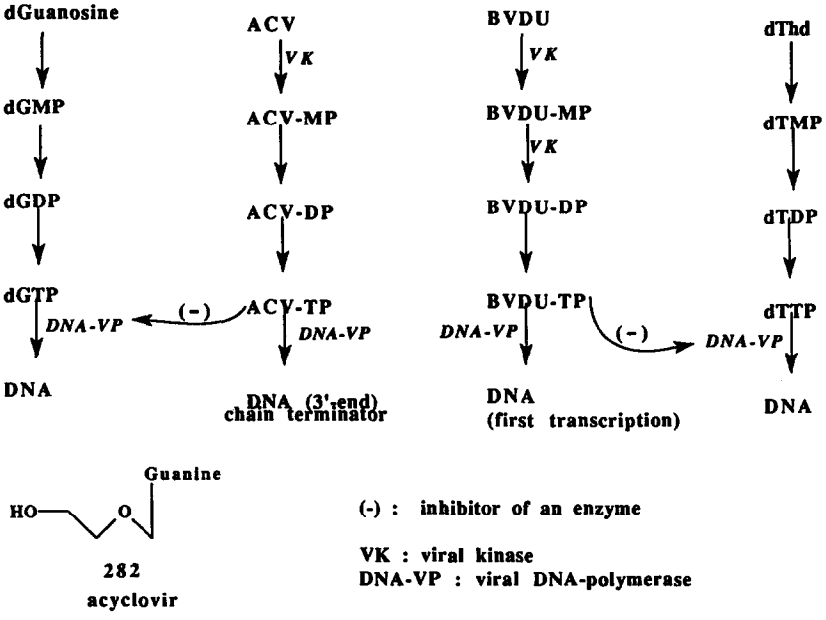
4) assembling of the new virion.

5) budding.

The main targets for the nucleoside analogs in anti-viral chemotherapy are the intracellular elements of replication of the genome and the synthesis of the proteins. The problems met by potential drugs are their selectivity, the possible cellular resistance towards these agents, the transport of the drug (transition through

cellular membranes) and their metabolism. The selectivity of agents in chemotherapy is due to the preferential inhibition of viral enzymes during nucleosidic metabolism. The active form of these compounds is the triphosphorylated analog. Nucleosides are phosphorylated by viral or cellular kinases. Thus acyclovir **282** (and also BVDU **8**) is a potent anti-HSV agent, which is monophosphorylated by the herpes thymidine kinase (Figure 13).

FIGURE 13



The ACV-MP is then phosphorylated by cellular kinases (GMP) to ACV-DP, and then to ACV-TP by other cellular enzymes. The ACV-TP is an inhibitor of the DNA polymerase of HSV ; it is a competitive inhibitor of the natural substrate dGTP. Furthermore ACV-TP can be incorporated and act as a chain terminator.

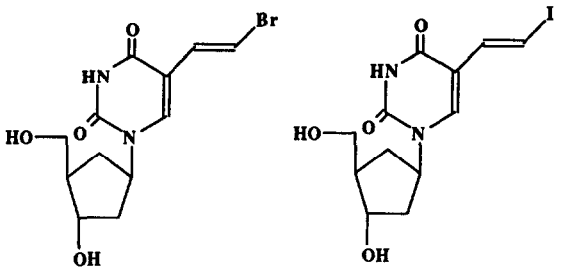
BVDU, **8**, is mono and diphosphorylated by viral kinases into BVDU-DP. After triphosphorylation by means of a cellular enzyme, BVDU-TP inhibits viral DNA-polymerases. Added to the problems of resistance, due to the genetic mutations of the virus, it is easy to understand the difficulty in developing an agent active toward virus (HSV, HCMV, HIV) which only partially utilize cellular mechanisms. The nucleoside analogs, as agents of antiviral chemotherapy, have been very thoroughly reported in recent literature.[64-66,182-186] We will mention a few biological properties of the carbocyclic analogs, which are most active against viruses and retroviruses.

6-1. The carbocyclic analogs of 2'-deoxyuridine

The carbocyclic analogs of both BVDU **9** and IVDU **283** (Figure 14) are good inhibitors[187,188] of HSV-1 replication. Both are also completely resistant toward cleavage by dThd and uridine phosphorylases[17]. The (+) and (-) enantiomers of these two compounds inhibit viral replication. The (+) enantiomer is 10 times

more active than the (-). Despite this fact, the two enantiomers have similar affinities for HSV-1 thymidine kinase (Ki = 0.09μM and 0.09μM, respectively, for (+)-C-BVDU and (+)-C-IVDU; and Ki = 0.16μM and 0.19μM, respectively, for the (-)-C-BVDU and (-)-C-IVDU). The inhibition of thymidine kinase is competitive. It is the first example in which both enantiomeric forms have important enzymatic affinities.

FIGURE 14

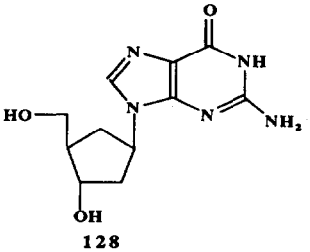


C-BVDU **C-IVDU**
9 **283**

6-2. The carbocyclic analog of 2'-deoxyguanosine

The carbocyclic analog of 2'-deoxyguanosine (Figure 15) (CdG) shows a broad spectrum of antiviral activity and is active against HSV, HCMV and HBV. To try to understand the mechanism of action of this compound against HSV, studies have been conducted, based on the rate of incorporation of [^{3}H]-CdG in cellular or viral DNA and of the interaction of CdG-TP with cellular or HSV α, β, γ-DNA polymerases.[189] These tests show that CdG.TP is a better substrate for viral DNA polymerases than for cellular polymerases. Moreover, it is a competitive inhibitor for the incorporation of the natural nucleoside analog into the DNA by cellular or viral polymerase DNA. Price et al.[104] have shown that this compound inhibits hepatitis B viral replication. It is incorporated into the DNA and does not act as a chain terminator. Kinetic analyses of dG-TP and CdG-TP show that it is a competitive inhibitor of the natural analog. At low concentrations, hepatitis B viral polymerase seems to be selectively inhibited. Finally, we note the inhibition *in vitro* of the growth of promastigotes[105] of *Leishmania donovani*.

FIGURE 15



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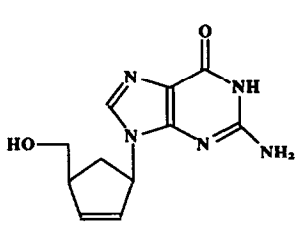
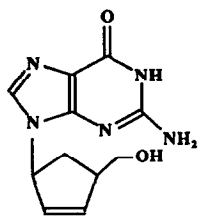
6-3. Carbovir

The anti-HIV activity of carbovir (Figure 16) has been compared to activities of other substances used in the treatment of AIDS. The accompanying table[190] lists the IC_{50} and CD_{50} values for the principal nucleoside analogs used in anti-retroviral (anti-HIV) chemotherapy. The (-)-enantiomer of carbovir is twice as active as the racemic form[190] and 75 times more active than the (+)-enantiomer.[191] This fact indicates that the major part of the antiviral activity is found in the (-)-enantiomer.

FIGURE 16



1'R,4'S-(-)-carbovir

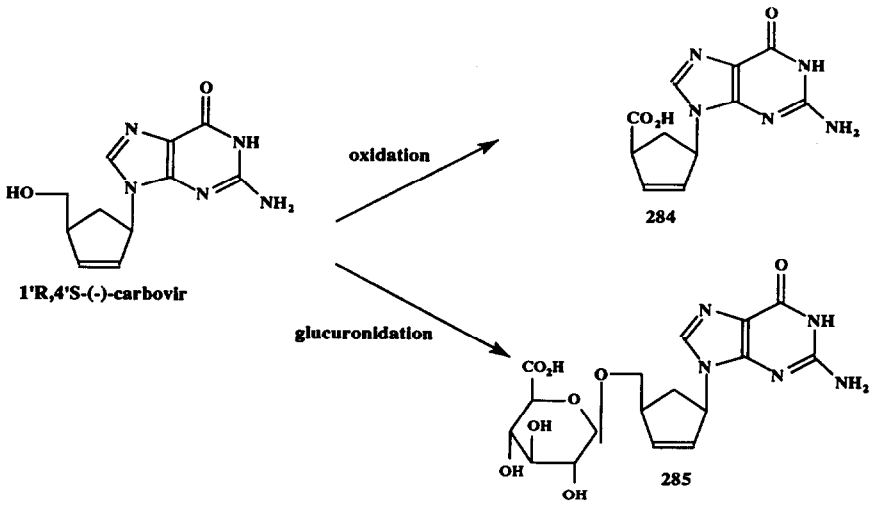


1'S,4'R-(+)-carbovir

cells	MT-4		C8166		JM	
	IC_{50}	ID_{50}	IC_{50}	ID_{50}	IC_{50}	ID_{50}
	μg/ml		μg/ml		μg/ml	
(-) carbovir	0.31	100	0.12	>100	0.13	100
(±) carbovir	0.52	100	-	-	-	-
ddC	0.001	100	0.004	>100	0.005	10
AZT	0.003	10	0.03	>100	>100	>100

The selectivity is probably due to the specific inhibition of viral reverse transcriptase by the triphosphorylated form of carbovir. Shannon and Vince[192] have shown that carbovir is anabolized to the mono, di, and triphosphates and to G-TP in CEM cells *via* the hypoxanthine-guanine phosphoribosyl-transferase enzyme (HGPRT). However, the mechanism has not been completely elucidated yet. (-)-Carbovir TP is a potent inhibitor of the HIV-1 reverse transcriptase, with a Ki similar to that found for AZT. Study of the chain elongation,[194] shows that (-)-carbovir-TP terminates transcription at identical positions to those found for the dideoxyguanosine-TP nucleoside analog. Carbovir acts as a competitive inhibitor of natural dNu-TP. Finally, Patanella et *al.*[193] have pointed out that oxidation of the 4'-CH_2OH to the corresponding 4'-COOH **284** metabolite (Scheme 56) is the main route of metabolisation of carbovir. Alcohol-dehydrogenase and aldehyde-dehydrogenase would be responsible for this bio-transformation. Another metabolic pathway of carbovir leads to the glucoronide **285**. Recent studies have reported some metabolisms of carbovir.[203]

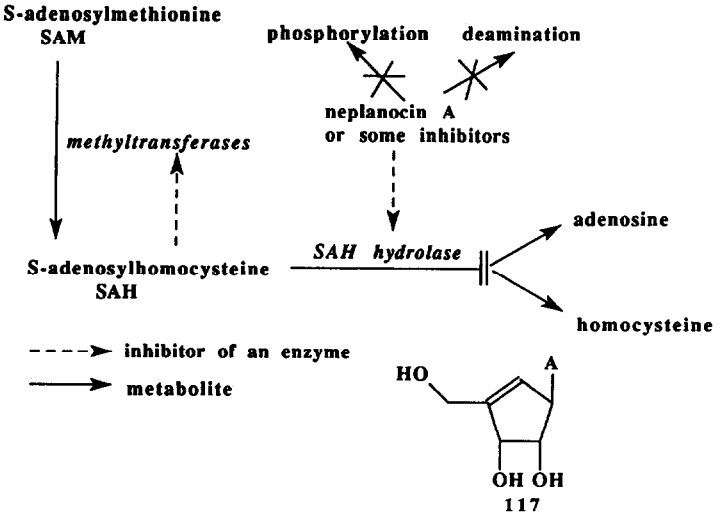
SCHEME 56



6-4. Neplanocin A

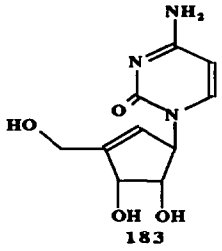
Neplanocin A **117** (Scheme 57) has a wide range of biological activities.[195] It likely is an inhibitor of S-adenosyl-L-homocysteine hydrolase (AdoHcy hydrolase). This enzyme is very important in regulating S-adenosylmethionine (SAM) dependent methylation reactions. The methyltransferases can be considered as potential targets for therapeutic agents. These transferases are necessary for the maturation of the mRNA. Inhibition of methyl transferases *via* alteration of metabolism of the AdoHcy can therefore induce inhibition of methylation reactions used for mRNA viral processes[195].

SCHEME 57



Finally it should be noted that the cytosine analog (Ce-Cyd) **183** of neplanocin A also has a wide range of antiviral activities[166f,h] (Figure 17).

FIGURE 17



183

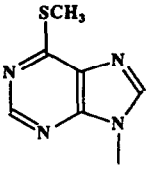
6-5. Conclusion

The carbocyclic analogs of nucleosides have a wide field of application in antiviral chemotherapy. The mode of action is mainly in the inhibition of a replication step of the virus, by direct inhibition of a viral enzyme as a chain terminator and/or by competitive inhibition. On top of this, these compounds are not substrates of phosphorylases, in contrast to the nucleoside analogs and have similar or superior biological activities. The existence of these agents as potents drugs in the treatment of various DNA and RNA viruses indicates that these compounds compose a very promising family. Studies on their metabolism[204] and on various active site requirements (of viral enzyme) should allow a better understanding of structure-activity relationships. With this better understanding at hand the development of new, improved, antiviral compound should be possible.

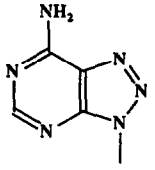
7-SYNOPTIC TABLE

The tables on the following pages summarize the cyclopentane analogs of nucleosides reported up to 1993. The columns list the heterocyclic bases (classical bases A/C/G/T/U or others I-XVI) and the rows identify the functionalised cyclopentanes. At the intersections, bibliographical references are noted.

Structures of heterocyclic bases of unusual functionalized cyclopentanes (column "others")



I



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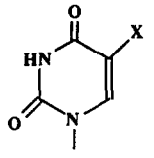
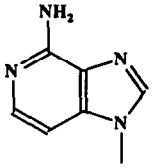
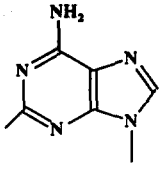


III

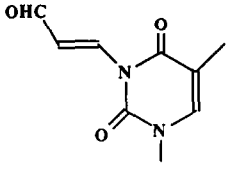
a X=H; b X=CH_3
c X=F; d X=Br; e X=I
f X=NH_2; g X=$NHCH_3$
h X=NHC_4H_9; i X=$N(CH_3)_2$
j X=CH_2OH; k X= CH=$CHCO_2Me$
l X= CH=CHBr



IV



V



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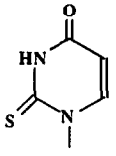
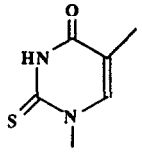
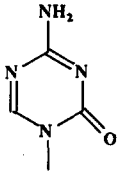


VII

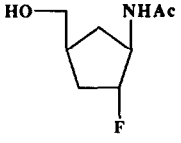


VIII

IX



X



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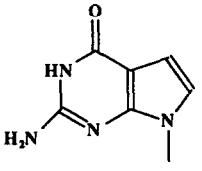

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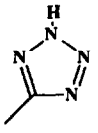
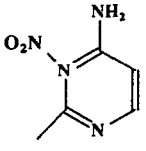


XIII



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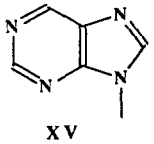
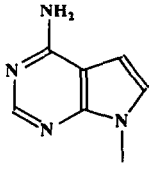
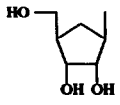
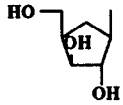
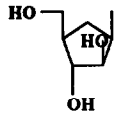
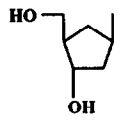
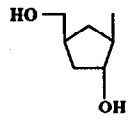
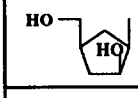
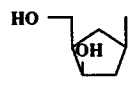
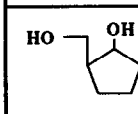
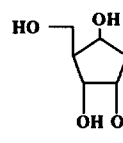
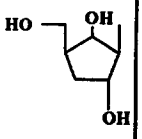
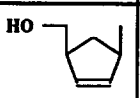
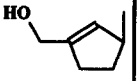
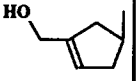
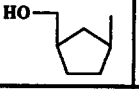
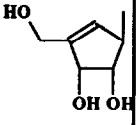
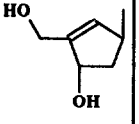
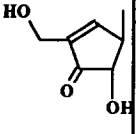
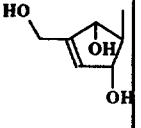


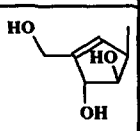
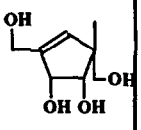
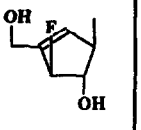
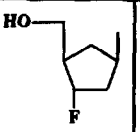
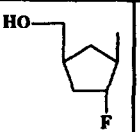
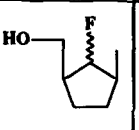
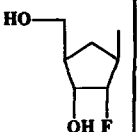
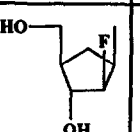
XV

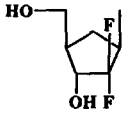
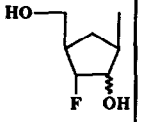
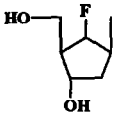
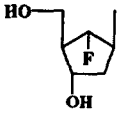
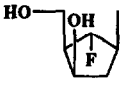
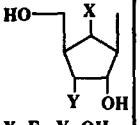
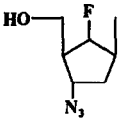
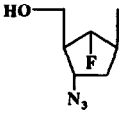


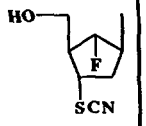
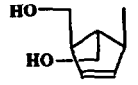
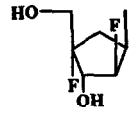
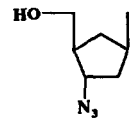
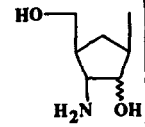
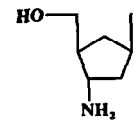
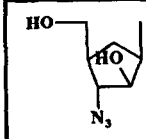
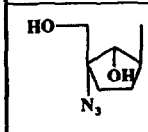
XVI

	Adenine	Guanine	Cytosine	Thymine	Uracil	Others
	29-30,34, 38,45,46, 68,71,76, 79-84, 86-89,92, 94-96,99, 167,173,	39	100,109, 166	102 108-109	55,101 109,173	I-> 68 II->79 IIIa-j->109 IIIc->101 IV->81,103 XIV->38b
	117,120	116		43		II->116 IV->117 V->116
	78,117,120 121	121	100	118		IV->20
	106, 112-113 178	104-105 113,117 174	100 109 115	57,60,102 108-109 111,115	39,55,56 63,101,109 114,115	IIIc,e,k,l-> 39,63,101, 114 V->107 VI->102
	106		100,109	108-109	55-56 101,109	IIIa-i->109 IIIc->101 XIV->201 XV->201
	200		100		172	VII->172
					61-62 172	VII->172
					171	IIId-e->171
	174		175			

	Adenine	Guanine	Cytosine	Thymine	Uracil	Others
	87					
	122,129	54,85 122,123, 125,127 128,129	122	122	122	
	166		166	44		
				145		
	42		173	108,173	173	VIII->173
	30,32,34 40,71,74 133-135 137	137	31,33 136,137 166	137	137	IX->98 IV->30,33 X->136
			166			
	166					
	199					

	Adenine	Guanine	Cytosine	Thymine	Uracil	Others
			166			
	31,166		31			
	146					
	153,164	164	164	145,153 164	164	
						XII->159
	53	53		53	53	
		24	141	141	141	
	143,144	23,24,144 165	141,142	142	141,142	IIIe->141 142

	Adenine	Guanine	Cytosine	Thymine	Uracil	Others
				141		
	153	153b		153b	153b	
		24			162	IIIe->141 162
	139	24		139	141,162	IIIe->141 162
				139		
 X=F, Y=OH X=OH, Y=F	41					
				140		
				140,163		

	Adenine	Guanine	Cytosine	Thymine	Uracil	Others
				163		
	179	179				
		141b				
				57,171	171	IIIe,j->171
	170					XI->170
					171	IIIe,l->171
		198				XI->198
				44		

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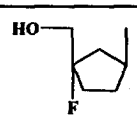				145		
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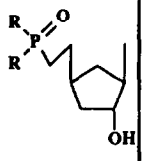
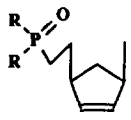
	42a,b					
	42b					

8. REFERENCES

1. Creasy, W. *Handb. Exp. Pharmacol.* **1975**, *38*, 232
2. Heidelberger, C. *Handb. Exp. Pharmacol.* **1975**, *38*, 193
3. Heidelberger, C.; Ansfield F. *Cancer Res.* **1963**, *23*, 1226
4. Carter,S. *Cancer Res.* **1972**, *30*, 1543
5. Harbers, E.; Chanduri, N.; Heidelberger, C. *J. Biol. Chem.* **1959**, *234*, 1255
6. Brodfuehrer, P.; Brundidge, S; Howell, J.;Howell, H.; Sapino, C.; Tann, C. *J. Org. Chem.* **1985**, *50*, 3644
7. Fox, J.; Reichman, U.; Watanabe, K. *Carbohyd. Res.* **1967**, *5*, 292
8. Fox, J.; Schinazi, R. ; Su, T-L. ; Watanabe, K. *J. Med. Chem.* **1986**, *29*, 151
9. Benigni, D.; Brodfuehrer, P.; Brundidge, S.; Howell, H.; Sapino, C. *J. Org. Chem.* **1988**, *53*, 85
10. De Clercq, E. *J. Med. Chem.* **1986**, *29*, 1561
11. Kim, C.; Marquez, V.; Broder, S.; Mitsuya, H.; Driscoll, J. *J. Med. Chem.* **1987**, *30*, 867

12. Gaertner, H.; Janta-Lipinski, M.; Langen, P.; Lehman, C.; Mathes, E.; Rosenthal, H.; Scholz, D. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 78
13. Yarchoan, R.; Klecker, R.; Weinhold, K.; Markham, P.; Lyerly, H.; Durack, D.; Gelmann, E.; Nusinoff, S.; Blum, R.; Barry, D.; Shearer, G.; Fischl, M.; Mitsuya, H.; Gallo, R.; Collins, J.; Bolognesi, D.; Myers, C.; Broder, S. *Lancet* **1986**, *i*, 575
14. Cheng, Y.; Dutschman, D.; De Clercq, E.; Jones, A.; Rahim, S.; Verhelst, G.; Walker, R. *Mol. Pharmacol.* **1981**, *20*, 230
15. Desgranges, C.; Razaka, G.; Drouillet, F.; Bricaud, H.; Herdewijn, P.; De Clercq, E. *Nucleic Acids Res.* **1984**, *12*, 2081
16. Herdewijn, P.; De Clercq, E.; Balzarini, J.; Vanderhaeghe, H. *J. Med. Chem.* **1985**, *28*, 50
17. De Clercq, E.; Desgranges, C.; Herdewijn, P.; Sim, I.; Walker, R. *Proceedings of the Eighth International Symposium on Medicinal Chemistry* (J. L. G. Nilsson and R. Dahlbom, Eds), Swedish Pharmaceutical Press, Stockholm, **1985**, 198
18. De Clercq, E.; Balzarini, J.; Bernaerts, R.; Herdewijn , P.; Verbruggen, A. *Biochem. Biophys. Res. Commun.* **1985**, *126*, 397
19. Guranowski, A.; Montgomery, J.; Cantoni, G.; Chiang, P. *Biochemistry* **1981**, *20*, 110
20. Bricaud, H.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol.* **1983**, 3583
21. Cookson, R.; Dudfield, P.; Newton, R.; Ravenscroft , P.; Scopes, D.; Cameron, J. *Eur. J. Med. Chem. Chim. Ther.* **1985**, *20*, 375
22. Boehme, R.; Storer, R.; Willianson, C.; Clemens, I.; Cameron, J.; *Abstracts of Paper, Interscience Conference on Antimicrobial Agents and Chemotherapy*, Atlanta, October **1990**, abstract 1088
23. Borthwick, A.; Butt, S.; Biggadike, K.; Exall, A.; Roberts, S.; Youds, P.; Kirk, B.; B. Booth, B.; Cameron, J.; Cox, S.; Marr, C.; Shill, M. *J. Chem. Soc., Chem. Commun.* **1988**, 656
24. Borthwick, A.; Kirk, B.; Biggadike, K.; Exall, A.; Butt, S.; Roberts, S.; Knight, D.; J. Coates, J.; Ryan, D. *J. Med. Chem.* **1991**, *34*, 907
25. Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17
26. Hayashi, M.; Yaginama, S.; Muto, N.; Tsujino, M. *Nucleic Acids Res. Symp. Ser.* **1981**, *34*, 675
27. Marquez, V.; Lim, M.; Tseng, C.; Markovac, A.; Priest, M.; Khan, M.; Kaskar, B. *J. Org. Chem.* **1988**, *53*, 5709
28. Tseng, C.; Marquez, V. *Tetrahedron Lett.* **1985**, *26*, 3669
29. Jones, M.; Roberts, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2927
30. Tseng, C.; Marquez, V.; Fuller, R.; Goldstein, B.; Haines, D.; McPherson, H.; Parsons, J.; Shannon, W.; Arnett, G.; Hollingshead, M.; Driscoll, J. *J. Med. Chem.* **1989**, *32*, 1442
31. Marquez, V.; Bodenteich, M.; Copp, R.; Lim, B. *Nucleic Acids Res. Symp. Ser.* **1990**, *22*, 35
32. Wolfe, M.; Anderson, B.; Borcherding, D.; Borchardt, R. *J. Org. Chem.* **1990**, *55*, 4712
33. Copp, R.; Marquez, V. *J. Med. Chem.* **1991**, *34*, 208
34. Wolfe, M.; Bartlett, W.; Borcherding, D.; Borchardt, R. *J. Med. Chem.* **1992**, *35*, 1782
35. Kondo, K.; Sato, T.; Takemoto, K. *Chem. Lett.* **1973**, 967
36. DiMenna, W.; Piantadosi, C.; Lamb, R. *J. Med. Chem.* **1978**, *21*, 1073
37. Martin, J.; Smee, D.; Verheyden, J. *J. Org. Chem.* **1985**, *50*, 755

38. a) Bindu Madhavan, G.; Martin, J. *J. Org. Chem.* **1986**, *51*, 1287 b) Palmer, C.; Parry, K.; Roberts, S. *Tetrahedron Lett.* **1990**, *31*, 279
39. Biggadike, K.; Borthwick, A.; Exall, A.; Kirk, B.; Roberts, S.; Youds, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1083
40. Biggadike, K.; Borthwick, A.; Exall, A. *J. Chem. Soc., Chem. Commun.* **1990**, 458
41. Bindu Madhavan, G.; McGee, D.; Rydzewski, R.; Boehme, R.; Martin, J.; Prisbe, E. *J. Med. Chem.* **1988**, *31*, 1798
42. a) Navé, J-F.; Wolff-Kugel, D.; Halazy, S. *Bioorg. Med. Chem. Letters* **1992**, *2*, 1483 b) Wolkk-Kugel, D.; Halazy, S. *Nucleosides & Nucleotides* **1993**, *12*, 279
43. Baumgartner, H.; Marscner, C.; Pucher, R.; Griengl, H. *Tetrahedron Lett.* **1991**, *32*, 611
44. Maag, H.; Rydzewski, R. *J. Org. Chem.* **1992**, *57*, 5823
45. Matsumura, F.; Nishiyama, Y.; Matsubara, K.; Nagahata, T.; Hoshino, H.; Seki, J. *Patent,* **EP 0330992** *Chem. Abstr.* : **1990**, 112, 235073w
46. Jenny, T.; Horlacher, J.; Previsani, N.; Benner, S. *Helv. Chim. Acta* **1992**, *75*, 1944
47. Jenny, T.; Schneider, K.; Benner, S. *Nucleosides & Nucleotides* **1992**, *11*, 1257
48. Yoshikawa, M.; Nakae, T.; Cha, B.; Yokokawa, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1989**, *37*, 545
49. Yoshikawa, M.; Okaichi, Y.; Cha, B.; Kitagawa, I. *Tetrahedron* **1990**, *46*, 7459
50. Shealy, Y.; O'Dell, C.; Arnett , G.*J. Med. Chem.* **1987**, *30*, 1090
51. Peterson, M.; Vince, R. *J. Med. Chem.* **1990**, *34*, 1214
52. Ben Cheikh, A.; Zemlicka, J. *Nucleosides & Nucleotides* **1987**, *6*, 265
53. Coe, D.; Myers, P.; Parry, D.; Roberts, S.; Storer, R. *J. Chem. Soc., Chem. Commun.* **1990**, 151
54. Evans, C.; Roberts, S.; Shoberm, K.; Sutherland, A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 589
55. Shealy, Y.; O'Dell, C. *J. Heterocyclic Chem.* **1976**, *13*, 1015
56. Shealy, Y.; O'Dell, C. *J. Heterocyclic Chem.* **1976**, *13*, 1041
57. Béres, J.; Sagi, G.; Tomoskozi, I.; Gruber, L.; Baitz-Gacs, E.; De Clercq, E. *J. Med. Chem.* **1990**, *33*, 1353
58. Shaw, G.; Warrener, R. *J Chem. Soc.* **1958**, 153
59. Shaw, G.; Warrener, R. *J. Chem. Soc.* **1958**, 157
60. Baumgartner, H.; Bodenteich, M.; Griengl, H. *Tetrahedron Lett.* **1988**, *29*, 5745
61. Bodenteich, M.; Griengl, H. *Tetrahedron Lett.* **1986**, *27*, 4291
62. Bodenteich, M.; Faber, K.; Penn, G.; Griengl, H. *Nucleosides & Nucleotides* **1987**, *6*, 233
63. Balzarini, J.; Baumgartner, H.; Bodenteich, M.; De Clercq, E.; Griengl, G. *J. Med. Chem.* **1989**, *32*, 1862
64. Roberts, S.; Biggadike, K.; Borthwick, A.; Kirk, B. *Topics in Medicinal Chemistry*, Ed P.R., Royal Society of Chemistry, **1988**, 172 (review)
65. Marquez, V.; Lim, M. *Med. Res. Rev.* **1986**, *6*, 1 (review)
66. a) Borthwick, A.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571 (review) b) Montgomery, J. *Antiviral Res.* **1989**, *12*, 113

67. Shealy, Y.; Clayton, J. *J. Am. Chem. Soc.* **1966**, *88*, 3885
68. Shealy, Y.; Clayton, J. *J. Am. Chem. Soc.* **1969**, *9*, 3075
69. De Clercq, E. *Biochem. Pharmacol.* **1987**, *36*, 2567
70. Cools, M.; De Clercq, E. *Biochem. Pharmacol.* **1989**, *38*, 1061
71. Arita, M.; Adachi, K.; Ito, Y.; Sawa, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049
72. Ohno, M.; Kobayashi, S.; Iimori, I.; Wang, Y.; Izawa, T. *J. Am. Chem. Soc.* **1981**, *103*, 2405
73. Ito, Y.; Shibata, T.; Arita, M.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 6739
74. Arai, Y.; Hayashi, Y.; Yamamoto, M.; Takayema, H.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3133
75. Arai, Y.; Kayashi, K.; Koizumi, T. *Tetrahedron Lett.* **1988**, *29*, 6143
76. Cermak, R.; Vince, R. *Tetrahedron Lett.* **1981**, *22*, 2331
77. Jagt, J.; VanLeusen, A. *J. Org. Chem.* **1974**, *39*, 564
78. Vince, R.; Daluge, S. *J. Med. Chem.* **1977**, *20*, 612
79. Vince, R.; Daluge, S. *J. Org. Chem.* **1980**, *45*, 531
80. Kam, B.; Oppenheimer, N. *J. Org. Chem.* **1981**, *46*, 3268
81. a) Montgomery, J.; Clayton, S.; Thomas, H.; Shannon, W.; Arnett, G.; Bodner, A.; Kion, I.; Cantoni, G.; Chiang, P. *J. Med. Chem.* **1982**, *25*, 626 b) Secrist, J.; Comber, R.; Gray, R.; Gilroy, R.; Montgomery, J. *J. Med. Chem.* **1993**, *36*, 2102
82. Chen, J.; Grim, M.; Rock, C.; Chan, K. *Tetrahedron Lett.* **1989**, *30*, 5543
83. Saksena, A. *Tetrahedron Lett.* **1980**, *21*, 133
84. Maggini, M.; Prato, M.; Scorrano, G. *Tetrahedron Lett.* **1990**, *31*, 6243
85. a) Katagiri, N.; Muto, M.; Nomura, M.; Higashikawa, T.; Kaneko, C. *Chem. Pharm. Bull.* **1991**, *39*, 1112 b) Katagiri, N.; Muto, M.; Kaneko, C. *Tetrahedron Lett.* **1989**, *30*, 1645
86. Holy, A. *Collect. Czech. Chem. Commun.* **1976**, *41*, 647
87. Huychison, A.; Grim, M.; Chen, J. *J. Heterocyclic Chem.* **1989**, *26*, 451
88. Deardorff, D.; Shulman, M.; Sheppeck, J. *Tetrahedron Lett.* **1989**, *30*, 6625
89. Trost, B.; Huo, G.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621
90. Trost, B.; Molander, G. *J. Am. Chem. Soc.* **1981**, *103*, 5969
91. Deardorff, D.; Myles, D.; MacFerrin, K. *Tetrahedron Lett.* **1985**, *26*, 5615
92. Tadano, K.; Hoshino, M.; Ogawa, S.; Suami, T. *Tetrahedron Lett.* **1987**, *28*, 2741
93. Tadano, K.; Hoshino, M.; Ogawa, S.; Suami, T. *J. Org. Chem.* **1988**, *53*, 1427
94. Yoshikawa, M.; Okaichi, Y.; Cha, B.; Kitagawa, I. *Tetrahedron* **1990**, *46*, 7459
95. Yoshikawa, M.; Okaichi, Y.; Cha, B.; Kitagawa, I. *Chem. Pharm. Bull.* **1989**, *37*, 2555
96. Tadano, K.; Hakuba, K.; Kimura, H.; Ogawa, S. *J. Org. Chem.* **1989**, *54*, 276
97. Wolfe, M.; Borcherding, D.; Borchardt, R. *Tetrahedron Lett.* **1989**, *7*, 1453
98. Borcherding, D.; Scholtz, S.; Borchardt, B. *J. Org. Chem.* **1987**, *52*, 5457
99. Parry, R.; Haridas, K. *Tetrahedron Lett.* **1990**, *31*, 7549
100. Shealy, Y.; O'Dell, C. *J. Heterocyclic Chem.* **1980**, *17*, 353
101. Shealy, Y.; Frye, J.; Dubois, N.; Shaddix, S.; Brockman, R. *J. Med. Chem.* **1981**, *24*, 1083
102. Lin, T.; Guo, J.; Zhang, X. *Nucleosides & Nucleotides* **1990**, *9*, 923

103. a) Chen, J.; Hutchison, A. *Patent*, **EP 267878** *Chem. Abstr.*: **1989**, 110, 75172f b) Montgomery, J.; Clayton, S. *Patent*, **EP 4387228** *Chem. Abstr.*: **1983**, 99, 105645m
104. Price, P.; Banerjee, R.; Jeffrey, A.; Acs, G. *Hepatology* **1992**, *16*, 8
105. Dong, Z.; Zhu, B.; Jeffrey, A. *Experimental Parasitology* **1992**, *75*, 257
106. Shealy, Y.; O'Dell, C. *Tetrahedron Lett.* **1969**, *27*, 2231
107. Shealy, Y.; O'Dell, C.; Shannon, W.; Arnett, G. *J. Med. Chem.* **1984**, *27*, 1416
108. Shealy, Y.; O'Dell, C.; Thorpe, M. *J. Heterocyclic Chem.* **1981**, *18*, 383
109. Shealy, Y.; O'Dell, C.; Shannon, W.; Arnett, G. *J. Med. Chem.* **1983**, *26*, 156
110. Eichberger, G.; Penn, G.; Faber, K.; Griengl, H. *Tetrahedron Lett.* **1986**, *27*, 2843
111. Otvos, L.; Béres, J.; Sagi, G.; Tomoskozi, I.; Graber, L. *Tetrahedron Lett.* **1987**, *28*, 6381
112. Béres, J.; Sagi, G.; Baitz-Gacs, E.; Tomoskozi, I.; Ouvos, L. *Tetrahedron* **1988**, *44*, 6207
113. Taniyama, Y.; Fukuda, T.; Marumoto, R. *Nucleosides & Nucleotides* **1992**, *11*, 529
114. Ravenscroft, P.; Newton, R.; Scopes, D. *Tetrahedron Lett.* **1986**, *27*, 747
115. a) Taniyama, Y.; Marumoto, R. *Patent* , **EP 0219838** *Chem. Abstr.* : **1988**, 108, 6350j b) Ravenscroft , P.*Patent*, **US 4658044** *Chem. Abstr.* : **1986**, 105, 62106j
116. Vince, R.; Turakhia, R.; Shannon, W.; Arnett, G. *J. Med. Chem.* **1987**, *30*, 2026
117. Vince, R.; Brownell, J.; Daluge, S. *J. Med. Chem.* **1984**, *27*, 1358
118. Lin, T.; Zhang, X.; Wang, Z-H.; Prusoff, W. *Synth. Commun.* **1988**, *18*, 925
119. Hampton, A.; Nichol, A. *Biochemistry* **1966**, *5*, 2076
120. Yoshikawa, M.; Nakae, T.; Cha, B.; Yokokawa, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1989**, *37*, 545
121. Vince, R. *Patent*, **EP 0042596** *Chem. Abstr.* : **1982**, 96, 181575s
122. Vince, R.; Hua, M.; Brownell, J.; Daluge, S.; Lee, F.; Shannon, W.; Lavelle, G.; Qualls, J.; Weislow, O.; Kiser, R.; Canonico, P.; Schultz, R.; Narayanan, V.; Mayo, J.; Shoemaker, R.; Boyd, M. *Biochem. Biophys. Res. Commun.* **1988**, *156*, 1046
123. Taylor, S.; Sutherland, A.; Lee, C.; Wisdom, R.; Thomas, S.; Roberts, S.; Evans, C. *J. Chem. Soc., Chem. Commun.* **1990**, 1120
124. a) Sicsic, S.; Ikbal, M.; Le Goffic, F. *Tetrahedron Lett.* **1987**, *28*, 1887 b) Ikbal, M.; Cerceam, C.; Le Goffic, F.; Sicsic, S. *Eur. J. Med. Chem.* **1989**, *24*, 415
125. Vince, R.; Brownell, J. *Biochem. Biophys. Res. Commun.* **1990**, *168*, 912
126. Exall, A.; Jones, M.; Mo, C.;Myers, P.; Paternoster, I.; Singh, H.; Storer, R.; Weingarten, G.; Williamson, C.; Brodie, A.; Cook, J.; Lake, D.; Meerholz, C.; Turnbull, P.; Highcock, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2467
127. Peel, M.; Sternbach, D.; Johnson, M. *J. Org. Chem.* **1991**, *56*, 4990
128. Gopinathan, M.; Kepler, J. *J. Label. Compounds & Radiopharma.* **1991**, *29*, 645
129. a) Vince, R.; Hua, M.; Myers, P.; Storer, R. *Patent* , **FR 2626002** *Chem. Abstr.* : **1990**, 112, 56589x b) A. Schwartz, A. *Patent*, **EP 0393499** *Chem. Abstr.* : **1990**, 113, 212581s
130. Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Ohani, M. *J. Antibiot.* **1981**, *34*, 359

131. Yaginuma, S.; Tsujino, M.; Muto, N.; Orani, M.; Hayashi, M.; Ishimura, F.; Fujii, T.; Watanabe, S.; Matsuda, T.; Watanabe, T.; J. Abe *Curr. Chemother. Infect. Dis., Proc. Int. Congr.* **1980**, *2*, 1558
132. Lim, M.; Moyer, D.; Cysyk, R.; Marquez, V. *J. Med. Chem.* **1984**, *27*, 1536
133. Lim, M.; Marquez, V. *Tetrahedron Lett.* **1983**, *24*, 5559
134. Medich, J.; Kunnen, K.; Johnson, C. *Tetrahedron Lett.* **1987**, *28*, 4131
135. Tseng, C.; Marquez, V. *Tetrahedron Lett.* **1985**, *31*, 3669
136. Lim, B.; Marquez, V.; Dobyns, K.; Cooney, D.; De Clercq, E. *Nucleosides & Nucleotides* **1992**, *11*, 1123
137. Marquez, V.; Driscoll, J.; Lim, M-I.; Tseng, C.; Haces, A.; Glazer, R. *Patent*, **WO 9009177** *Chem. Abstr.* : **1991**, 115, 867583n
138. Blackburn, G.; Dent, D. *J. Chem. Soc., Perkin Trans.1* **1986**, 913
139. Payne, A.; Roberts, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2633
140. Fletcher, C.; Hilpert, H.; Myers, P.; Roberts, S.; Storer, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1707
141. a) Borthwick, A.; Evans, D.; Kirk, B.; Biggadike, K.; Exall, A.; Youds, P.; Roberts, S.; Knight, D.; Coates, J. *J. Med. Chem.* **1990**, *33*, 179 b) Acheson, R.; Ansell, P. *J. Chem. Soc., Perkin Trans. I* **1987**, 1275
142. Biggadike, K.; Borthwick, A.; Evans, D.; Exall, A.; Kirk, B.; Roberts, S.; Stephenson, L.; Youds, P.; Slawin, A.; Williams, D. *J. Chem. Soc., Chem. Commun.* **1987**, 251
143. Biggadike, K.; Borthwick, A.; Exall, A.; Kirk, B.; Ward, R. *J. Chem. Soc., Chem. Commun.*, **1988**, 898
144. Borthwick, A.; Biggadike, K.; Holman, S.; Mo, C. *Tetrahedron Lett.* **1990**, *31*, 767
145. Béres, J.; Sagi, G.; Baitz-Gacs, E.; Tomoskozi, I.; Gruber, L.; Otvos, L. *Tetrahedron* **1989**, *45*, 6271
146. Borthwick, A.; Biggadike, K. *Tetrahedron Lett.* **1992**, *33*, 3237
147. Ikera, M.; Imura, J. *Chem. Pharm. Bull.* **1981**, *29*, 1034
148. Ikera, M.; Imura, J. *Chem. Pharm. Bull.* **1981**, *29*, 3281
149. Fox, J.; Greenberg, N.; Lopez, C.; Reichman, U.; Su, T-L.; Watanabe, K. *J. Med. Chem* **1984**, *27*, 91
150. De Clercq, E.; Griengl, H.; Rosenwirth, B.; Scharz, W.; Streicher, W.; Wanek, E. *J. Med. Chem.* **1987**, *30*, 1199
151. Arnett, G.; O'Dell, C.; Shannon, W.; Shealy, Y. *J. Med. Chem.* **1983**, *26*, 156
152. Olah, G.; Nojima, M.; Kerebes, I. *Synthesis* **1973**, 780
153. a) Nakayama, T.; Morizawa, Y.; Matsumara, Y.; Yasuda, A.; Uchida, K. *Nucleic Acids Res. Symp. Ser.*, **1989**, *21*, 73 b) Morizawa, Y.; Nakayama, T.; Matsumura, Y.; Uchida, K.; Yasuda, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2714
154. Middleton, W. *J. Org. Chem.* **1975**, *40*, 574
155. Markovskii, L.; Pashinik, V.; Kirsanov, A. *Synthesis*, **1973**, 787

156. Castillon, S.; Dessinges, A.; Faghih, R.; Lukacs, G.; Olesker, A.; Thang, T. *J. Org. Chem.* **1985**, *50*, 4913
157. Nicolaou, K.; Ladduwahetty, T.; Randall, J.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466
158. Card, P. *J. Carbohydr. Chem.* **1985**, *4*, 451
159. Palmer, C.; Parry, K.; Roberts, S.; Sik, V. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1021
160. a) Gilbert, J.; Luo, T.; Davis, R. *Tetrahedron Lett.* **1975**, 2545 b) Grudzinski, Z.; Roberts, S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1767
161. Franz, R. *J. Fluorine Chem.* **1980**, *15*, 423
162. Biggadike, K.; Borthwick, A.; Exall, A.; Kirk, B.; Roberts, S.; Youds, P.; Slawin, A.; Williams, D. *J. Chem. Soc., Chem. Commun.* **1987**, 255
163. Levitt, M.; Newton, R.; Roberts, S.; Willetts, A. *J. Chem. Soc., Chem. Commun.* **1990**, 619
164. Yoshitomi, M.; Toshiati, N.; Arita, Y.; Keiichi, U. *Patent* , **EP 277599** *Chem. Abstr.* : **1989**, 110, 39325z
165. Borthwick, A.; Evans, D.; Kirk, B.; Biggadike, K.; Stephenson, L. *Patent* , **EP 212956** *Chem. Abstr.* : **1987**, 107, 154170v
166. a) Russ, P.; Hegedus, L.; Kelley, J.; Barchi, J.; Marquez, V. *Nucleosides & Nucleotides* **1992**, *11*, 351 b) Marquez, V.; Bodenteich, M. *Nucleosides & Nucleotides* **1991**, *10*, 311 c) Bodenteich, M.; Marquez, V. *Tetrahedron Lett.* **1990**, *31*, 5977 d) S. Kim, S.; R. Fuller, R.; V. Marquez, V. *Nucleosides & Nucleotides* **1990**, *9*, 663 e) Paisley, S.; Wolfe, M.; Borchardt, R. *J. Med. Chem.* **1989**, *32*, 1418 f) Marquez, V.; Lim, M.; Treanor, S.; Plowman, J.; Priest, M.; Markovac, A.; Khan, M.; Kaskar, B.; Driscoll, J. *J. Med. Chem.* **1988**, *31*, 1687 g) Marquez, V.; Tseng, C.; Treanor, S.; Driscoll, J. *Nucleosides & Nucleotides* **1987**, *6*, 239 h) De Clercq, E.; Murase, J.; Marquez, V. *Biochem. Pharmacol.* **1991**, *41*, 1821
167. Marschner, C.; Penn, G.; Griengl, H. *Tetrahedron Lett.* **1990**, *31*, 2873
168. Shobern, K.; Roberts, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2419
169. Mashhood, S.; Ramesh, K.; Borchardt, R. *Tetrahedron Lett.* **1990**, *31*, 1509
170. a) Daluge, S.; Vince, R. *Tetrahedron Lett.* **1976**, *17*, 3005 b) Daluge, S.; Vince, R. *J. Org. Chem.* **1978**, *43*, 2311
171. a) Bodenteich, M.; Griengl, H. *Tetrahedron Lett.* **1978**, *28*, 5311 b) Hronowski, L.; Szarek, W. *J. Chem. Soc., Chem. Commun.* **1990**, 1547
172. Hronowski, L.; Szarek, W. *Can. J. Chem.* **1985**, *63*, 2787
173. a) Hronowski, L.; Szarek, W. *Can. J. Chem.* **1988**, *66*, 61 b) Béres, J.; Sagi, G.; Tomoskozi, J.; Gruber, L.; Gulacsi, E.; Otvos, L. *Tetrahedron Lett.* **1988**, *29*, 2681
174. a) Ben Cheikh, A.; Zemlicka, J. *Nucleosides & Nucleotides* **1987**, *6*, 265 b) Ben Cheikh, A.; Craine, L.; Recher, S.; Zemlicka, J. *J. Org. Chem.* **1988**, *53*, 929
175. Desai, D.; Ben Cheikh, A.; Zemlicka, J. *Tetrahedron Lett.* **1991**, *32*, 6281
176. a) Coe, D.; Hilpert, H.; Noble, S.; Peel, M.; Roberts, S.; Storer, R. *J. Chem. Soc., Chem. Commun.* **1991**, 312 b) Coe, D.; Orr, D.; Roberts, S.; Storer, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3378

177. a) Toyota, A.; Katagiri, N.; Kaneko, C. *Chem. Pharm. Bull.* **1992**, *40*, 1039 b) Merlo, V.; Reece, F.; Roberts, S.; Gregson, M.; Storer, R. *J. Chem. Soc., Perkin Trans 1* **1993**, 1717
178. a) Koya, M.; Schneller, S. Tetrahedron Lett. **1990**, *31*, 5861 b) Patil, S.; Schneller, S. *J. Med. Chem.* **1992**, *35*, 3372 c) Siddiqi, S.; Chen, X.; Schneller, S. *Nucleosides & Nucleotides* **1993**, *12*, 267 d) Koya, M.; Schneller, S. *J. Org Chem.* **1993**, *58*, 6471
179. a) Katagiri, N.; Shiraishi, T.; Sato, H.; Toyota, A.; Kaneko, C.; Yusa, K.; Oh-Hara, T.; Tsurno, T. *Biochem. Biophys. Res. Commun.* **1992**, *184*, 154 b) Katagiri, N.; Nomura, M.; Sato, H.; Kaneko, C.; Yusa, K.; Tsurno, T. *J. Med. Chem.* **1992**, *35*, 1882 c)Katagiri, N.; Shiraishi, T.; Toyota, A.; Sato, H.; Kaneko, C.; Aikawa, T. *Chem. Pharm. Bull.* **1993**, *41*, 1027
180. Herdewjin, P.; Balzarini, J.; De Clercq, E.; Vanderhaeghe, H. *J. Med. Chem.* **1985**, *28*, 1385
181. Hanrahan, J.; Hutchinson, D. *J. Biotechnol.* **1992**, 193
182. Périgaud, C.; Gosselin, G.; Imbach, J-L. *Nucleosides & Nucleotides* **1992**, *11*, 903 (review)
183. Marquez, V.; *ACS Symposium Series 401*, **1989**, J. C. Martin Editor (review)
184. a) Dolin, R. *Science* **1985**, *227*, 1296 (review) b) Isono, K. *Pharmacol. Ther.* **1991**, *52*, 269 c) Plunkett, W.; Saunders, P. *Pharmacol. Ther.* **1991**, *49*, 239
185. De Clercq, E.; Walker, R. *"Progress in Medicinal Chemistry"*, G. P. Ellis and G. B. West Eds **1986**, *23*, 187, Elsevier Science Publishers, Amsterdam (review)
186. a) De Clercq, E. *"Advances in Drug Research"*, Bernard Testa Ed. **1988**, *17*, 1 ; Harcourt Brace Jovanovich, Publishers, Londres et references therein. b) De Clercq, E. *Advances in Virus Research* **1993**, *42*, 1 c) De Clercq, E. *AIDS Res. Hum. Retrovirus* **1992**, *8*, 119 d) De Clercq, E. *Microbiol.* **1990**, *13*, 165
187. Balzarini, J.; Bernaerts, R.; Verbruggen, A.; De Clercq, E. *Mol. Pharmacol.* **1989**, *37*, 402
188. Balzarini, J.; De Clercq, E.; Baumgartner, H.; Bodenteich, M.; Griengl, H. *Mol. Pharmacol.* **1989**, *37*, 395
189. Parker, W.; Shaddix, S.; Allan, P.; Arnett, G.; Rose, L.; Shannon, W.; Shealy, Y.; Montgomery, J.; Secrist, J.; Bennett, L. *Mol. Pharmacol.* **1991**, *41*, 245
190. Coates, J.; Ingall, H.; Pearson, B.; Penn, C.; Storer, R.; Williamson, C.; Cameron, J. *Antiviral Res.* **1991**, 161
191. Carter, S.; Kessler, J.; Rankin, C. *Antimicrob. Agents Chemother.* **1990**, *34*, 1297
192. Bondoc, L.; Shannon, W.; Secrist, J.; Vince, R.; Fridland, A. *Biochemistry* **1990**, *29*, 9839
193. Patanella, J.; Walsh, J. *Drug Metab. Dispos.* **1992**, *20*, 912
194. Orr, D.; Figueiredo, H.; Mo, C-L.; Penn, C.; Cameron, J. *J. Biol. Chem.* **1992**, *267*, 4177
195. Borchardt, R.; Keller, B.; Patel-Thrombe, U. *J. Biol. Chem.* **1984**, *259*, 4353
196. Chiank, P.; Richards, H.; Cantoni, G. *Mol. Pharmacol.* **1977**, *13*, 939
197. Chiank, P.; Cantoni, G. *Biochem. Pharmacol.* **1979**, *28*, 1897
198. Legraverend, M.; Huel, C.; Zerial, A.; Lemaitre, M.; Bisagni, E. *Nucleosides & Nucleotides* **1990**, *9*, 639
199. Bodenteich, M.; Marquez, V. *Tetrahedron Lett.* **1989**, *30*, 4909
200. Frick, W.; Patil, S.; Gambino, A.; Schneller, S. *Tetrahedron Lett.* **1993**, *34*, 5541

201. a) Agrofoglio, L.; Condom, R.; Guedj, R.; Challand, R.; Selway, J. *Tetrahedron Lett.* **1993**, *34*, 6271 b) Agrofoglio, L.; Condom, R.; Guedj, R.; Challand, R.; Selway, J. *Nucleosides & Nucleotides* **1994**, *13*, 1147

202. Mohar, B.; Stimae, A.; Kobe, J. *Nucleosides & Nucleotides* **1993**, *12*, 793

203. a) Parker, W.; Shaddix, S.; Bowdon, B.; Rose, L.; Vince, R.; Shannon, W.; Bennett, L. *Antimicrob. Agents Chemother.* **1993**, *37*, 144 c) Miller, W.; Daluge, S.; Garvey, E.; Hopkins, S.; Reardon, J.; Boyd, F.; Miller, R. *J. Biol. Chem.* **1992**, *267*, 21220 d) Parker, W.; White, E.; Shaddix, S.; Ross, L.; Buckheit, R.; Germany, J.; Secrist, J.; Vince, R.; Shannon, W. *J. Biol. Chem.* **1991**, *266*, 1754

204. a) Oxenrider, K.; Bu, G.; Sitz, T. *Febs Letters* **1993**, *316*, 273 b) Zimmerman, C.; Remmel R.; Ibrahim, S.; Beers, S.; Vince, R. *Drg Metab. Dispos.* **1992**, *20*, 47 c) Smolenski, R.; Montero, C.; Duley, J.; Simmonds, H. *Biochem. Pharmacol.* **1991**, *42*, 1767 d) Ault-Riche, D.; Lee, Y.; Yuan, C.; Hasobe, M.; Wolfe, M.; Borcherding, D.; Borchardt, R. *Mol. Pharmacol.* **1993**, *43*, 989

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