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SYNTHESIS OF CHIRAL CARBOCYCLIC NUCLEOSIDES

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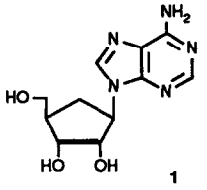
1. INTRODUCTION

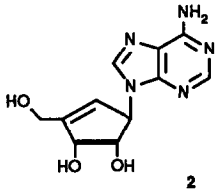
Nucleoside analogues display a wide range of biological activities[1] and have attracted particular attention as anti-tumour[2] and anti-viral[3] agents. Consequently, extensive modifications have been made to both the heterocyclic base and the sugar moiety. Replacement of the furanose ring oxygen by carbon is of particular interest since the resulting *carbocyclic nucleosides* possess greater metabolic stability to the phosphorylase enzymes which cleave the glycosidic linkage of normal nucleosides.

Although certain carbocyclic nucleosides occur in nature they were first described in 1966 with Shealy and Clayton's synthesis[4] of the racemic carbocyclic analogue (±) **1** of adenosine. Two years later the (-) enantiomer, named aristeromycin, was isolated as a metabolite of *Steptomyces citricolor*[5]. Synthetic interest was renewed in 1981 with the isolation from *Ampullariella regularis* of the structurally more diverse neplanocin family of carbocyclic nucleosides[6-8] and in particular the cyclopentenyl derivative neplanocin A **2**.



1

aristeromycin



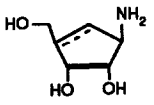
2

neplanocin A

The first enantiospecific synthesis was provided by Ohno *et al.* [9] in 1983 with a chemicoenzymatic approach to (-) aristeromycin **1** and (-) neplanocin A **2**. This synthesis still utilised the stepwise construction of the heterocyclic base onto a cyclopentylamine **3** which had featured in Shealy and Clayton's original approach, and which had been extensively employed in providing a wide range of racemic carbocyclic nucleoside analogues. These *linear* chemical syntheses and the biological properties of these early racemic analogues and of the natural products **1** and **2** were reviewed in 1986 by Marquez and Lim[10].

In the last five years nucleoside analogues have been investigated with renewed urgency in the search for agents effective against the Human Immunodeficiency virus (HIV), the causative agent of the AIDS epidemic. More effective treatment has also been sought for other viral infections, in particular Herpes Simplex virus (HSV types 1 and 2), Varicella Zoster virus (VZV), Cytomegalovirus (CMV) and Epstein-Barr virus (EBV), which can prove lethal to AIDS patients and other immunocompromised individuals. This has resulted in an explosion of synthetic activity in the field of carbocyclic nucleosides and the discovery of several derivatives with potent anti-viral activity. Thus, carbocyclic BVDU **4** is being developed for the treatment of HSV1 and VZV infections,[11] while carbocyclic 2'-*ara*-fluoro-

guanosine **5** is exceptionally effective against HSV1 and HSV2[12,13]. The latter compound **5** established carbocyclic nucleosides as more than simply metabolically stable versions of active furanose nucleosides since its furanose parent **6** showed only weak anti-herpes activity.



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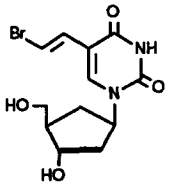

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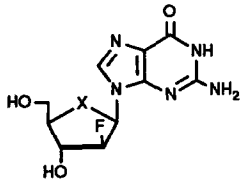
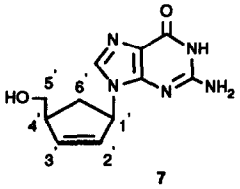


5 X=CH_2
6 X=O

The unsaturated derivative carbovir **7** has also attracted much attention[14] with activity against HIV comparable to that of AZT. Carbocyclic derivatives also now include cyclohexyl and cyclobutyl derivatives with the latter showing particularly promising anti-viral properties. For example, carbocyclic oxetanocin G **8** displays broad-spectrum anti-viral activity against HIV and herpes viruses[15,16]. Other recent developments include substitution of cyclopentyl derivatives at the previously unexplored 1'[17], 4'[18] and 6'[19-28] positions. The biosynthesis of aristeromycin has also begun to be unravelled[29].



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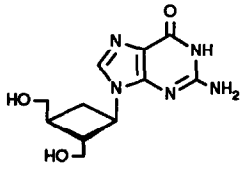


8

The pharmaceutical importance of these newer analogues has focused attention on more efficient and flexible syntheses, with the emphasis on *convergent* approaches in which the intact heterocyclic base is coupled directly to a suitably functionalised carbocyclic moiety. Furthermore, the realisation that the biological activity normally resides in one enantiomer,[12,30-32] and the increasing demand for new drug substances to be enantiomerically pure, has made the development of routes to *chiral* carbocyclic nucleosides of paramount importance. It is these approaches that are the subject of this review which covers the literature received up to mid 1991.

Throughout this review carbocyclic analogues and their precursors will be identified using the same numbering system used to describe their furanose isosteres with the carbon replacing the furan ring oxygen being designated as C-6' (see structure **7**). In structural formulae the common nucleoside bases adenine, guanine, cytosine, hypoxanthine, thymine and uracil will be abbreviated as A, G, C, H, T and U respectively, whilst B will be used to represent a general nucleoside base.

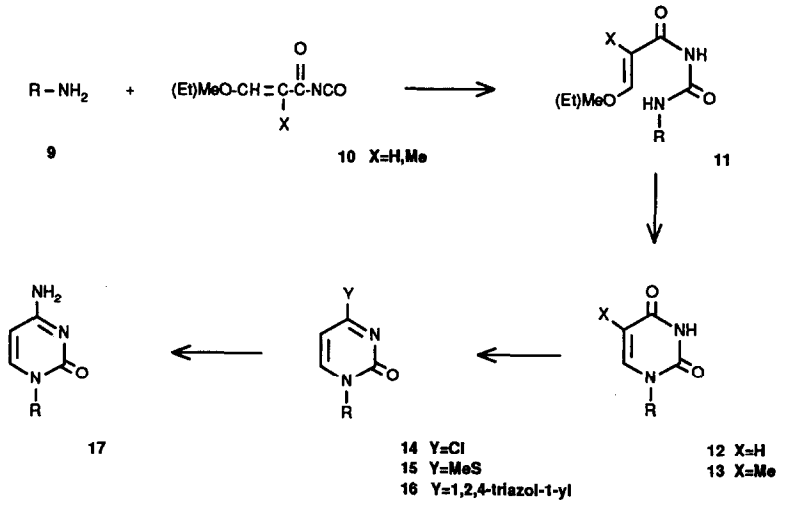
2. LINEAR APPROACHES

Linear approaches to chiral carbocyclic nucleosides rely on the construction of the heterocyclic base onto a suitable chiral cyclopentylamine. Before detailing these approaches a brief description will be given of the chemistry involved in the construction of the pyrimidine and purine moieties.

(a) Pyrimidines

Synthesis of uridine and thymidine derivatives employs methodology developed originally by Shaw and Warrener[33] (Scheme 1). Thus, reaction of the carbocyclic amine **9** with an acryloyl isocyanate **10** provides the intermediate acryloyl urea **11** which is then cyclised with concentrated ammonia, or with acid catalysis, to afford the uridine **12** or thymidine **13** analogues.

SCHEME 1



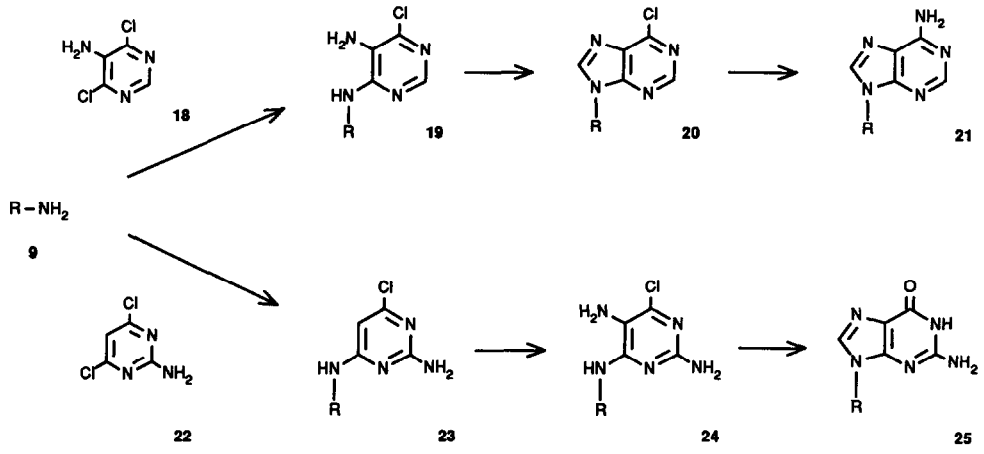
Cytidine derivatives **17** are derived from the corresponding uridines **12** by ammonolysis of either 4-chloro **14**,4-methylthio **15** or 4-(1,2,4-triazol-l-yl) **16** intermediates.

(b) Purines

Construction of the purine bases is based on the Traube synthesis (Scheme 2). Adenosine derivatives are prepared from the cyclopentylamine **9** in three stages. Thus, reaction with the

dichloropyrimidine **18** affords the diamino derivative **19** which is cyclised with triethylorthoformate to give the 6-chloro purine **20**. Ammonolysis of the chloro function then provides adenosine analogues **21**.

SCHEME 2

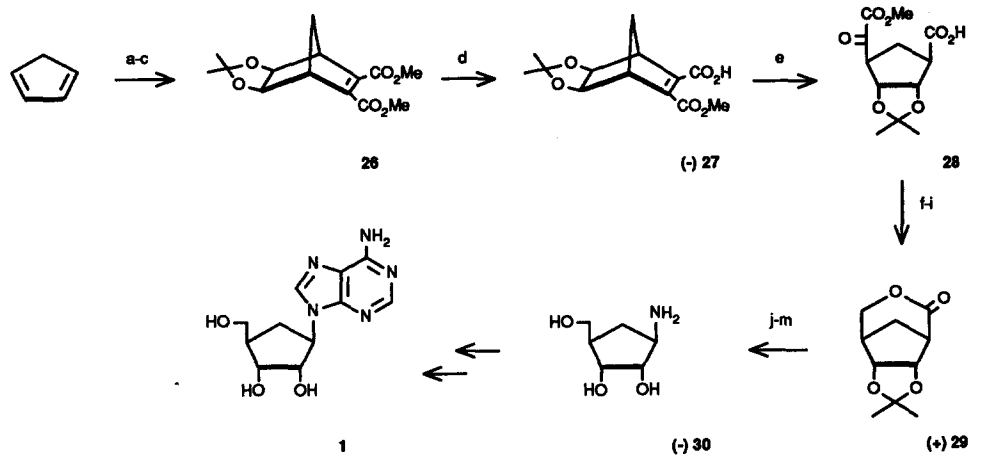


Synthesis of the guanine base requires two extra stages to introduce the 5-amino moiety. Reaction of the amine **9** with the pyrimidine **22** affords the diamine **23** and the 5-amino group is then introduced by a diazotization/reduction sequence. The resulting triamine **24** is then cyclised and the chloro function hydrolysed to provide guanosine analogues **25**.

2.1 Linear approaches to aristeromycin and other saturated carbocyclic nucleosides

Access to chiral carbocyclic nucleosides was first gained by Ohno *et al.*[9] with a chemicoenzymatic synthesis of (-) aristeromycin **1** *via* the enantiomerically pure amino triol (-) **30** (Scheme 3). Thus, pig liver esterase was employed to asymmetrically hydrolyse the meso diester **26** to give a quantitative yield of the half ester (-) **27** showing ee *ca* 80%. Decarboxylative ozonolysis then afforded the keto acid **28** which was transformed in four stages into the bicyclic lactone (+) **29**. Recrystallisation readily provided this key intermediate in optically pure form. Opening of the lactone with ammonia followed by acetylation, Hofmann degradation and deprotection completed this 13 stage synthesis of the chiral amino triol (-) **30** from cyclopentadiene (overall yield *ca* 11%). Construction of the adenine base then afforded (-) aristeromycin **1** identical in all respects with the natural product (overall yield for 16 stages from cycopentadiene ca 5%). The chiral lactone (+) **29** was also used to prepare (-) neplanocin A **2** (see Section 2.2).

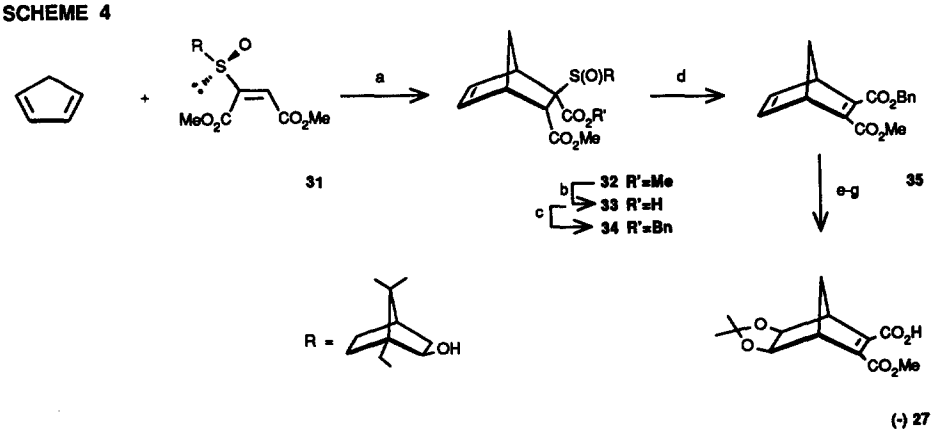
SCHEME 3



Reagents : (a) dimethyl acetylenedicarboxylate (b) OsO_4 (c) Me_2CO (d) pig liver esterase (e) O_3 (f) $NaBH_4$ (g) $NaIO_4$ (h) $NaBH_4$ (i) Ac_2O (j) NH_3 (k) Ac_2O (l) $Pb(OAc)_4$ (m) 2N HCl.

More recently, Koizumi *et al* have outlined alternative routes to the chiral Ohno intermediates **27** and **29** utilising asymmetric Diels-Alder reactions. The first approach[34] employed (R_S)-2-(10-isobornylsulphinyl) maleate **31** as a chiral equivalent of dimethyl acetylenedicarboxylate in a longer but more efficient approach to the half ester (-) **27** (Scheme 4). Thus, Diels-Alder reaction of this chiral dienophile with cyclopentadiene gave almost exclusively the *exo*-sulphoxide **32** which was selectively demethylated to give the carboxylic acid **33**. Conversion to the benzyl ester **34** was followed by elimination of the chiral auxiliary to afford the diene **35**. Cis-hydroxylation and subsequent acetonation and debenzylation completed this seven stage synthesis of the half-ester (-) **27** (ee ≥92%, overall yield *ca* 40%).

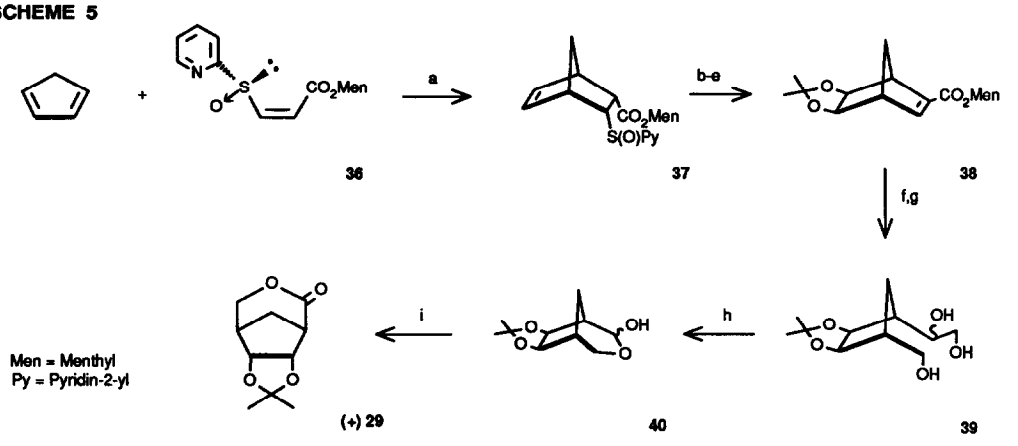
SCHEME 4



Reagents : (a) $ZnCl_2$,CH_2Cl_2,-20° (b) $AlBr_3$,Me_2S (c) BnBr,NaH (d) DBU (e) OsO_4 (f) Me_2CO,H^+ (g) cyclohexa-1,3-diene,Pd/C.

Another chiral dienophile, (S_S)-menthyl-3-(2-pyridylsulphinyl)acrylate **36**, was utilised in Koizumi's second approach[35] which provided efficient access to the lactone (+) **29** (Scheme 5). Reaction of **36** with cyclopentadiene gave the *endo* cycloadduct **37** with high diastereoselectivity (de ≥ 96%) and this product was transformed into the unsaturated ester **38** in four stages. Ozonolysis of **38** followed by lithium aluminium hydride reduction then provided the triol **39**. Cleavage of the diol moiety with sodium metaperiodate gave the lactol **40** as an anomeric mixture which on Collins oxidation provided the Ohno lactone (+) **29**. This nine stage sequence afforded (+) **29** in 22% overall yield.

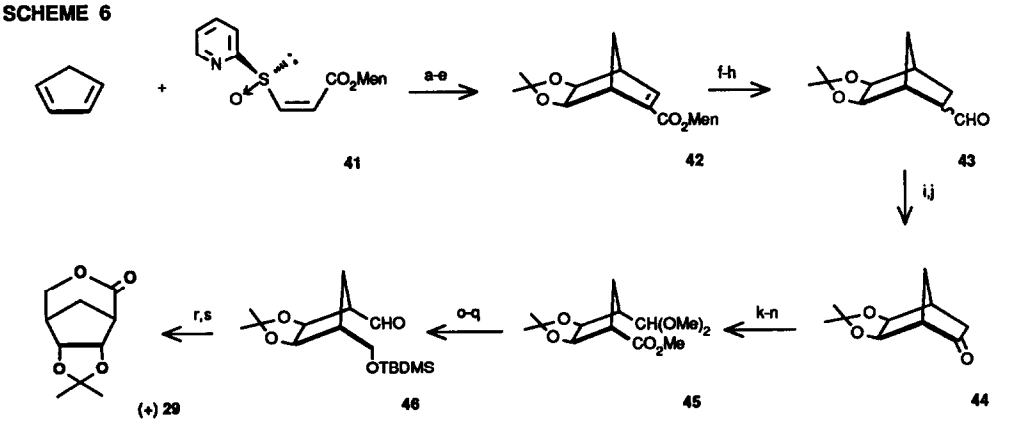
SCHEME 5



Reagents: (a) $Et_2AlCl,CH_2Cl_2,-78^o$ (b) OsO_4 (c) Me_2CO,H^+ (d) mCPBA (e)DBU (f) O_3 then Me_2S (g) $LiAlH_4$ (h) $NaIO_4$ (i) Collins reagent.

Koizumi[35] has also employed the diastereomer **41** of the chiral dienophile **36** in an alternative approach to (+) **29** but this route is of little practical value in view of the 19 stages involved (Scheme 6).

SCHEME 6

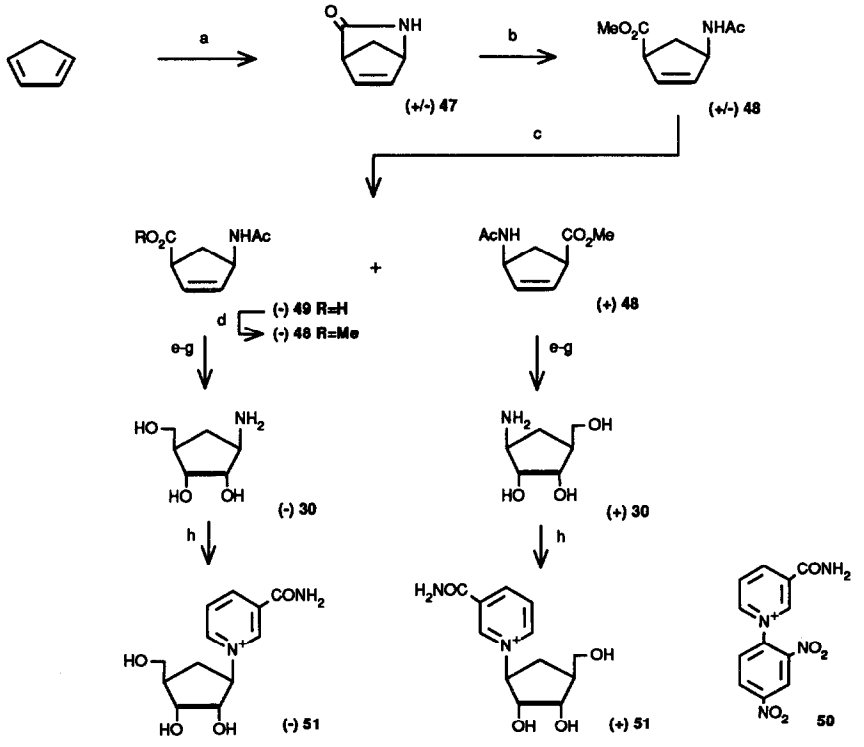


Reagents :(a) $Et_2AlCl,CH_2Cl_2,-78^o$ (b) OsO_4 (c) Me_2CO,H^+ (d) mCPBA (e) DBU (f) H_2,Pd/C (g) $LiAlH_4$ (h) PCC
(i) TBDMSOTf,NEt_3 (j) O_3 then Me_2S then Me_2CO,H^+ (k) TBDMSOTf,NEt_3 (l) O_3 (m) DOWEX(H^+) (n) CH_2N_2
(o) $LiAlH_4$ (p) TBDMSCl,imidazole,DMAP (q) Me_2CO,H^+ (r) aq AcOH (s) Collins reagent

Thus, the unsaturated ester **42** was obtained as before and converted into the ketone **44** *via* the aldehyde **43**. Ozonolysis of the silyl enol ether of **44** followed by esterification with diazomethane gave the ester **45** which was transformed into (+) **29** *via* the aldehyde **46**. A similar asymmetric Diels-Alder approach to the Ohno lactone (+) **29** has been outlined by Helmchen *et al.*[36]

Sicsic *et al.*[32,37] have utilised pig liver esterase to effect an enantioselective hydrolysis of the acetamidoester (±) **48** and hence gain access to *both* enantiomers of the amino triol **30** (Scheme 7). Racemic **48** is available from cyclopentadiene in four stages *via* the bicyclic lactam **47** and pig liver esterase was found to selectively hydrolyse the (-) enantiomer to provide the acid (-) **49** (ee 97%) in 47% yield. The unreacted dextrorotatory ester (+) **48** was recovered in 43% yield (ee 87%). Re-esterification of the acid (-) **49** to give the ester (-) **48**, followed by cis -hydroxylation, reduction of the ester moiety and acidic hydrolysis of the amide protection gave the amino triol (-) **30** showing identical optical rotation to that reported by Ohno. This nine stage synthesis from cyclopentadiene (overall yield *ca* 8%) represents the most direct route to (-) **30** yet reported. Similar transformation of (+) **48** provided (+) **30**. Reaction of these amino triol enantiomers with **50** afforded the carbocyclic nicotinamide analogues (-) and (+) **51**.

SCHEME 7

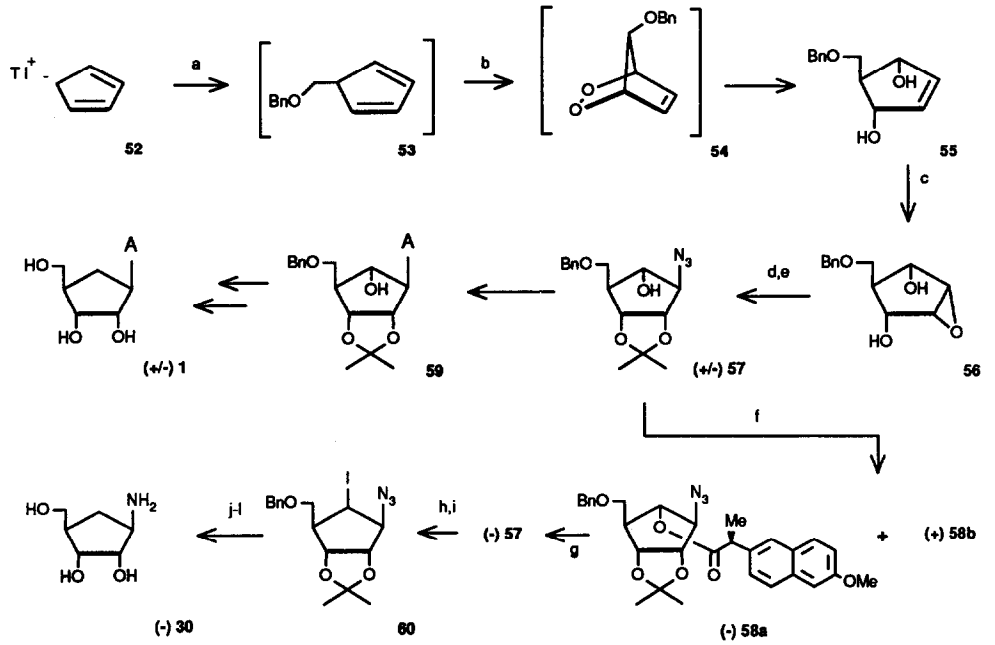


Reagents : (a) Tosyl cyanide then AcOH (b) MeOH/HCl then Ac_2O (c) pig liver esterase (d) MeOH/HCl (e) OsO_4 (f) $LiBH(Et)_3$ (g) 6N HCl (h) 50 .

Whereas the 'natural' enantiomer (-) **51** displayed interesting anti-bacterial and anti-fungal properties, the 'unnatural' (+) enantiomer was devoid of activity. A more recent enzymatic resolution of the lactam (±) **47** will be described later (see Section 2.2).

Chemical resolution was employed in the Syntex approach[38] to carbocyclic nucleosides to complete a formal synthesis of (-) aristeromycin **1** and provide an alternative route to the chiral amino triol (-) **30** (Scheme 8). The symmetrical ene-diol **55** was obtained from thallium cyclopentadienide **52** in a 'one-pot' sequence involving alkylation with benzyl chloromethyl ether to give **53** followed by cycloaddition of singlet oxygen and *in situ* reduction of the resulting endo peroxide **54**. Hydroxyl directed epoxidation of the olefin **55** gave exclusively the epoxide **56** which on opening with azide ion, followed by acetonation, afforded the racemic azido alcohol (±) **57** in 33% overall yield from **52**. Resolution was then achieved by esterification of (±) **57** with naproxen to give diastereoisomeric esters (-)**58a** and (+)**58b** which were separable by silica gel chromatography. Saponification of the (-) diastereomer provided the required (-) enantiomer of **57**. Racemic **57** was converted in eight stages and 31% overall yield, *via* the 6'α-hydroxy intermediate **59**, into (±) aristeromycin **1** and clearly (-) **57** could be elaborated in the same way to provide the optically pure natural product.

SCHEME 8

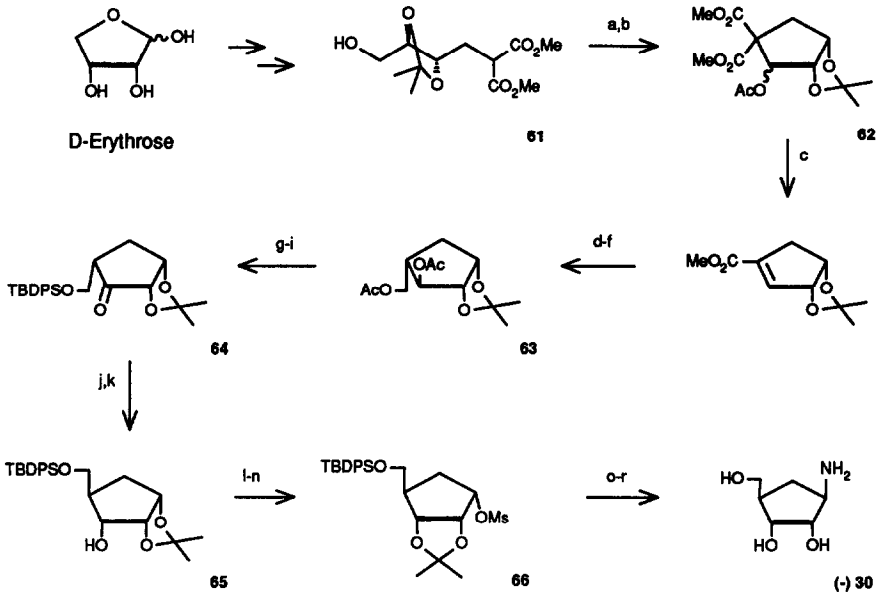


Reagents : (a) $BnOCH_2Cl$, -20° (b) $^1O_2$, rose bengal, thiourea, -5° (c) mCPBA (d) NaN_3 (e) Me_2CO,H^+ (f) Naproxen acid Cl (g) NaOH (h) Tf_2O (i) LiI (j) H_2, Pd/C (k) aq AcOH (l) Na/NH_3.

In addition, (-) **57** was converted in five stages into the chiral amino triol (-) **30**. Thus, activation of the hydroxyl function as a triflate followed by displacement with lithium iodide gave the azido iodide **60** which was reduced and deprotected to afford (-) **30**. If the 'one-pot' transformation of **52** into **55** is considered as one stage then this synthesis of (-) **30** from cyclopentadiene involves 12 steps but procedes in only 3.3% overall yield. However, this approach to carbocyclic nucleosides does provide access to novel derivatives substituted at C-6'[24]. Also the potential of the epoxide **56** to provide carbocyclic nucleoside derivatives in a *convergent* manner has been demonstrated by reaction with the sodium salt of adenine to give, after acetonation, (±) **59** in 25% yield[38].

Another route to the amino triol (-) **30** has been reported by Tadano *et al.*[39] starting from D-erythrose, but it is of little practical value because of the 24 stages involved (Scheme 9). The route is noteworthy only for the novel construction of the cyclopentane ring by intramolecular aldol condensation **61**→**62**. The protected carbocyclic-β-L-arabinofuranose intermediate **63** was obtained in 12 stages, and its conversion into (-) **30** required a further 12 stages and inversion at three of the four asymmetric centres. Oxidation to the 3-keto derivative **64** enabled C-4 to be epimerised on silica gel and borohydride reduction of the ketone function then gave the required *ribo* configuration at C-3 (**65**). Finally, inversion at C-1 was achieved by azide displacement of the mesylate **66**. Deprotection followed by reduction of the azide moiety then completed this transformation of D-erythrose into (-) **30**.

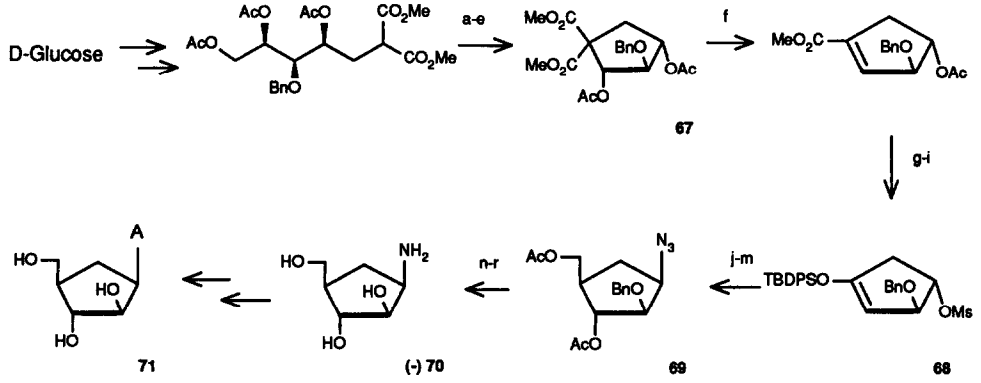
SCHEME 9



Reagents : (a) PCC (b) Ac_2O (c) aq DMSO,NaCl (d) DIBAL (e) BH_3/THF (f) Ac_2O (g) NaOMe (h) TBDPSCl (i) PCC (j) silica gel (k) $NaBH_4$ (l) aq AcOH,MeOH (m) Me_2CO,H^+ (n) MsCl (o) NaN_3 (p) TBAF (q) H^{+2} (r) H_2,Raney Ni.

The same workers[40] have described an even more protracted synthesis of the chiral *arabino* amino triol (-) **70** and hence of enantiomerically pure cyclaridine **71**, a compound with interesting anti-tumour and anti-viral properties (Scheme 10). Intramolecular aldol condensation was again employed to provide the intermediate **67** in 17 stages from D-glucose. Elaboration to the protected cyclopentene mesylate **68** then allowed the azide moiety to be introduced with inversion of configuration. In this case the required configuration at C-3 and C-4 was achieved by a highly stereoselective hydroboration of the double bond to give, after acetylation, the protected azido triol **69**. Reduction of the azide and deprotection to the amino triol (-) **70**, followed by construction of the adenine base completed this 30 stage synthesis of (+) cyclaridine **71**.

SCHEME 10

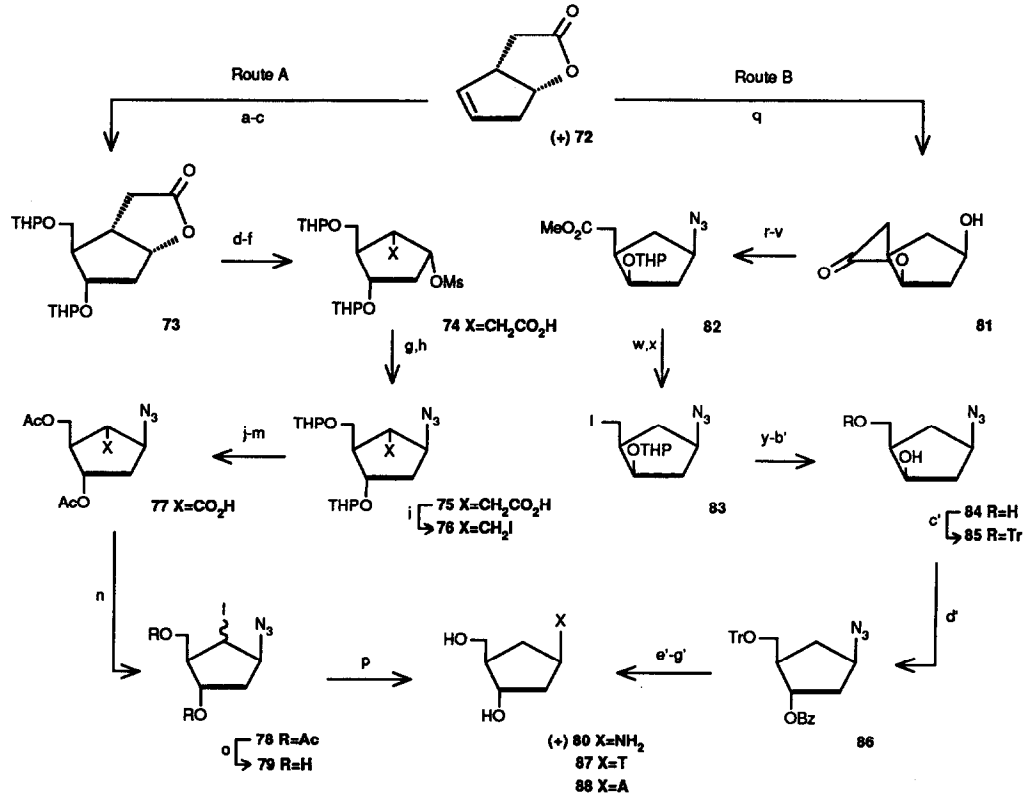


Reagents : (a) NaOMe (b) $NaIO_4$ (c) Ac_2O (d) Amberlite IR120(H^+) (e) Ac_2O (f) aq DMSO,NaCl (g) DIBAL (h) TBDMSCl (i) MsCl (j) NaN_3 (k) TBAF (l) BH_3/THF (m) Ac_2O (n) H_2S,aq pyridine (o) Ac_2O (p) $Pd(OH)_2$/C,cyclohexene (q) Ac_2O (r) H^+.

2'-Deoxy carbocyclic nucleosides are of particular interest as potential antiviral agents, and whilst these derivatives are most effectively prepared in a convergent manner (see Section 3.2) a number of more lengthy linear approaches have also been investigated. The chiral amino diol (+) **80** is an obvious precursor to such derivatives but only Béres *et al.*[25,42,43] have employed this intermediate. The commercially available unsaturated bicyclic lactone (+) **72** was the chiral starting material for this work and two strategies for its conversion to (+) **80** were explored (Scheme 11).

The first approach[42] (route A) employed a regio- and stereospecific Prins addition of formaldehyde to the double bond of (+) **72** to introduce the 3-hydroxy and 4-hydroxymethyl functions and give, after THP protection, the lactone **73**. Hydrolysis of the lactone ring provided a 1α-hydroxyl group which enabled the required 1β-azido moiety to be introduced by displacement of the mesylate **74** but left a troublesome acetic acid residue at C-6. Removal of this unwanted functionality required five stages plus a change from THP to acetyl protection and was achieved by successive iododecarboxylations of the acids **75** and **77** using iodobenzene diacetate. Earlier approaches to the removal of the acetic acid fragment were much less efficient[41]. Catalytic hydrogenation of the iodo azide **79** completed this 16 stage transformation of (+) **72** into the amino diol (+) **80** in 6% overall yield.

SCHEME 11



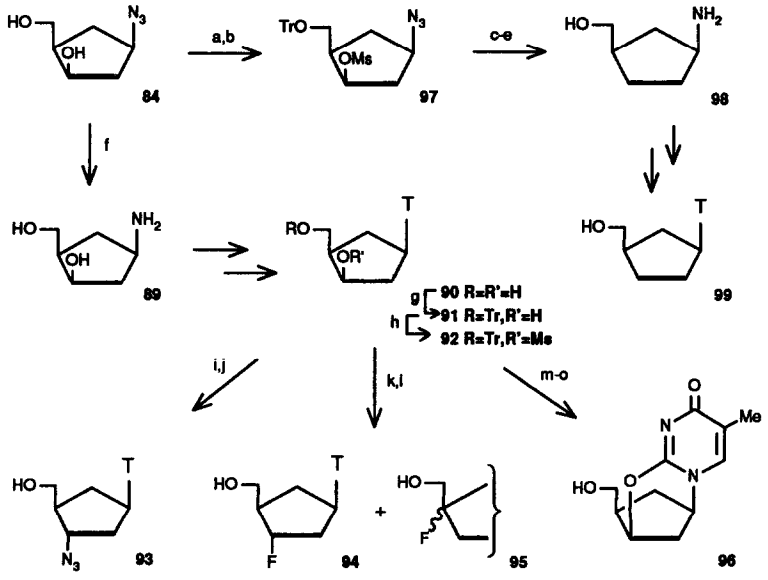
Reagents : (a) $(CH_2O)_n,H^+$ (b) Amberlite IR120(H^+) (c) DHP,H^+ (d) LiOH (e) CH_2N_2 (f) MsCl (g) NaN_3 (h) LiOH (i) IBDA,I_2 (j) pTSA (k) Ac_2O (l) mCPBA (m) PDC (n) IBDA,I_2 (o) K_2CO_3 (p) H_2,Pd/C (q) $Hg(OAc)_2$,$NaBH_4$ (r) Ph_3PI_2 (s) NaN_3 (t) LiOH (u) CH_2N_2 (v) DHP,H^+ (w) LiOH (x) IBDA (y) pTSA (z) Ac_2O (a') mCPBA (b') K_2CO_3 (c') TrCl (d') PPh_3,DEAD,$PhCO_2H$ (e') K_2CO_3 (f') pTSA (g') H_2 ,Pd/C.

The second approach[25,42] (route B) required the removal of only one carbon atom, with the lactone ring being utilised to provide the C-4 hydroxymethyl moiety and oxygen functionality at C-3. Functionalisation at C-1 was achieved by a highly regio- and stereoselective hydroxylation of the double bond of (+) **72** affording the 1β-hydroxy lactone **81** in 64% yield. The 1β-azido group was introduced with the required net retention of configuration by a double inversion *via* an intermediate 1α-iodide. Hydrolysis of the lactone ring and protection gave the ester **82**, which was hydrolysed to the carboxylic acid and the extra carbon atom was then removed by iododecarboxylation. The resulting iodomethyl derivative **83** was converted into the azido diol **84**, and inversion at C-3 was achieved by a Mitsunobu reaction on the trityl protected derivative **85** to give the 3-*ribo*-benzoate **86**. Finally, deprotection and reduction of the azide group completed the synthesis of the amino diol (+) **80**. This approach was one stage longer than route A and proceeded in lower overall yield (4%) but it did allow access to other 3'-substituted 2'-deoxy carbocyclic nucleosides (see below).

The amino diol (+) **80** was used to prepare (+) carbocyclic thymidine **87** and (+) carbocyclic 2'-deoxy-adenosine **88**. The thymidine derivative **87** displayed good *in vitro* activity against HSV1, HSV2 and Vaccinia virus while the adenosine analogue **88** was ten-fold less active[25]. The 'unnatural' (-) enantiomer of **87** was prepared in a similar manner starting from (-) **72** and was shown to have no anti-viral activity.

The intermediate azido diol **84** from route B has been used to prepare a number of other interesting carbocyclic thymidine derivatives, including carbocyclic versions (**93, 94, 99**) of compounds of interest in the treatment of AIDS (Scheme 12). Reduction of the azide moiety of **84** afforded the amino diol **89**, which was converted into (-) carbocyclic *xylo*-thymidine **90**[25]. Selective monotritylation of this derivative gave the secondary alcohol **91**. Mesylation to give **92** followed by azide displacement and de-tritylation yielded (+) carbocyclic AZT **93**. A sample of (-) carbocyclic 3'-deoxy-3'-fluoro-thymidine **94** was obtained *via* reaction of the alcohol **91** with diethylaminosulphur trifluoride (DAST) but this material was contaminated with an inseparable 4'-fluoro isomer **95** (configuration at C-4' unknown)[44]. An alternative synthesis of **94** has been reported by Griengl *et al* (see below). Reaction of the alcohol **91** with iodine and triphenylphosphine gave a 3'-*ribo*-iodo intermediate which cyclised on treatment with base to give, after deprotection, (+) carbocyclic 2,3'-*O*-anhydrothymidine **96**[25]. The 2,3-dideoxy amino alcohol **98** was prepared from **84** *via* reduction of the intermediate azido mesylate **97** and was used to prepare (-) carbocyclic 3'-deoxy-thymidine **99**. Unlike their furanose parents, compounds **93** and **99** were found to be devoid of activity against HIV and a variety of other viruses, as was the *xylo* derivative **90**[25].

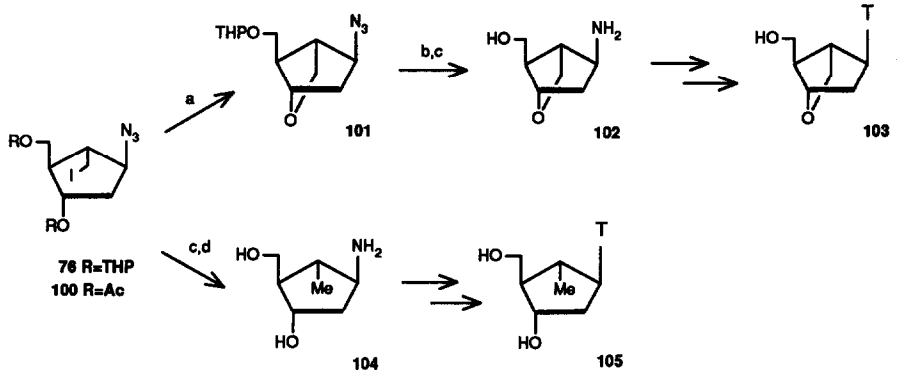
SCHEME 12



Reagents : (a) TrCl (b) MsCl (c) NaI,Zn (d) pTSA (e) H_2,Pd/C (f) aq NH_2NH_2,Pd/C (g) TrCl (h) MsCl (i) NaN_3 (j) pTSA (k) DAST (l) HCO_2H (m) Ph_3P,I_3,pyridine (n) DBU (o) pTSA .

The iodomethyl intermediates **76, 100** from route A have also been used to prepare two further novel carbocyclic thymidine analogues[25] (Scheme 13). Compound **76** was found to cyclise in high yield (90%) to the oxabicyclo [2.2.1] heptane **101** on treatment with *m*-chloroperbenzoic acid in dichloromethane in the presence of sodium bicarbonate. This reaction has been exploited to provide the unusual carbocyclic thymidine derivative **103** *via* the amine **102**. Simultaneous reduction of the azido and iodo functions of compound **100** with tri-*n*-butyl tin hydride afforded, after deacetylation, the amino diol **104** which was elaborated into (+) carbocyclic 6'-α-methyl-thymidine **105**. These two derivatives **103, 105** showed no anti-viral activity.

SCHEME 13

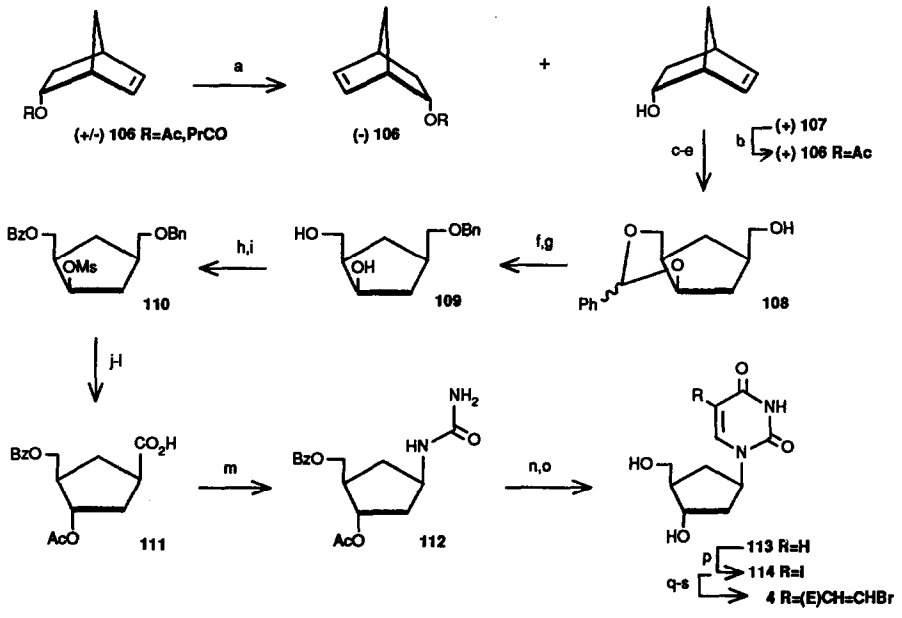


Reagents : (a) mCPBA (b) aq AcOH (c) nBu_3SnH (d) NH_3/MeOH .

Griengl *et al.*[45] have gained access to either enantiomer of 2'-deoxy carbocyclic nucleosides *via* enzymatic resolution of an *endo* norbornenyl ester (±) **106** (Scheme 14). Lipase from *Candida cylindracae* was found to more rapidly hydrolyse the (+) enantiomer of **106** to provide (+) **107** with ee *ca* 90%. Enrichment of the recovered ester by a second treatment with the enzyme afforded (-) **106** showing ee *ca* 86% while re-acetylation of (+) **107** provided (+) **106**. In this way both enantiomers of **106** could be readily prepared in multigram quantities. Ozonolysis of (+) **106** with reductive work-up followed by benzylidene protection of the resulting triol afforded the alcohol **108**. Benzyl protection of the remaining hydroxyl function followed by hydrolysis of the benzylidene moiety afforded the crystalline diol **109** which after recrystallisation was obtained optically pure. Selective benzoylation of the primary hydroxyl group followed by mesylation of the secondary one then provided the mesylate **110**. Displacement of this sulphonate ester with acetate gave the required *ribo* configuration at C-3 and this was followed by removal of the benzyl protection and oxidation to give the carboxylic acid **111**. Curtius degradation and trapping of the resulting isocyanate with gaseous ammonia afforded the urea **112** which was converted in two stages into (+) carbocyclic 2'-deoxy-uridine **113** (overall yield 3.5% for 14 stages from (±) **106**). Further elaboration of the pyrimidine base afforded (+) carbocyclic IDU **114** and (+) carbocyclic BVDU

4. The 'unnatural' (-) enantiomers of these derivatives were similarly prepared starting from (-) **106**. Against HSV1, (+) **4** and (+) **114** were shown to possess similar potent activity to their furanose parents. However, against HSV2, whereas (+) **4** showed similar weak activity to BVDU, (+) **114** was much less effective than IDU. Interestingly some activity was also observed in the 'unnatural' (-) enantiomers. The intermediate **108** has also been employed to prepare (-) carbocyclic 2′-deoxy-*xylo*-uridine[45b].

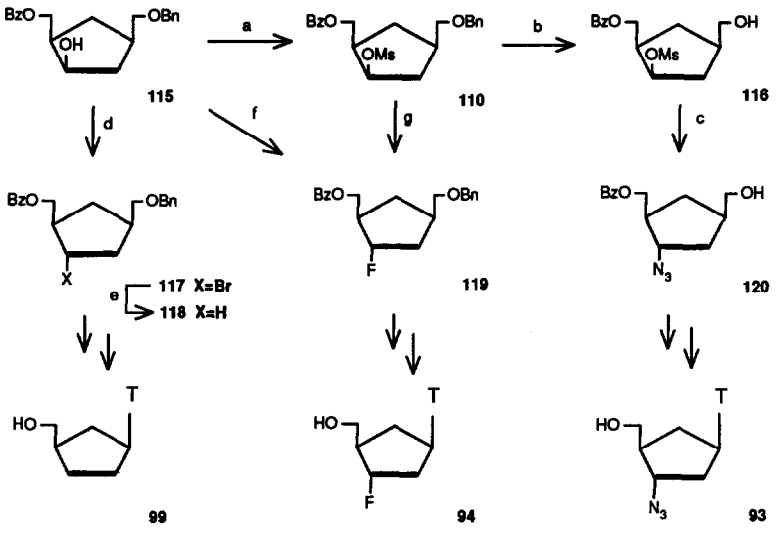
SCHEME 14



Reagents : (a) lipase (b) Ac_2O (c) O_3 (d) $LiAlH_4$ (e) $PhCH(OMe)_2,HBF_4$ (f) BnBr,KH (g) H^+ (h) BzCl (i) MsCl (j) CsOAc (k) H_2,Pd/C (l) PDC (m) DPPA (n) 3-ethoxyacryloyl chloride (o) aq NH_3 (p) I_2,HNO_3 (q) methyl acrylate,$Pd(OAc)_2,PPh_3,NEt_3$ (r) KOH (s) NBS,$KHCO_3$.

Griengl has also utilised the intermediate alcohol **115** and derived mesylates **110, 116** to provide alternative routes to the chiral carbocyclic thymidines **93, 94** and **99** (Scheme 15). Thus, reaction of **115** with bromine and triphenylphosphine afforded the 3-*ribo*-bromo derivative **117** which was reduced to give the 3-deoxy compound **118**. This intermediate was then elaborated as before to provide (-) carbocyclic 3'-deoxy-thymidine **99**[46]. Introduction of the 3'-*ribo*-fluoro substituent was achieved either by reaction of the alcohol **115** with DAST or by displacement of the mesylate **110** with potassium fluoride/18-crown-6 to give **119** and hence (-) carbocyclic 3'-deoxy-3'-fluoro-thymidine **94**[46]. Finally, azide displacement of the mesylate **116** afforded the intermediate **120** which in turn was converted into (+) carbocyclic AZT **93**[47].

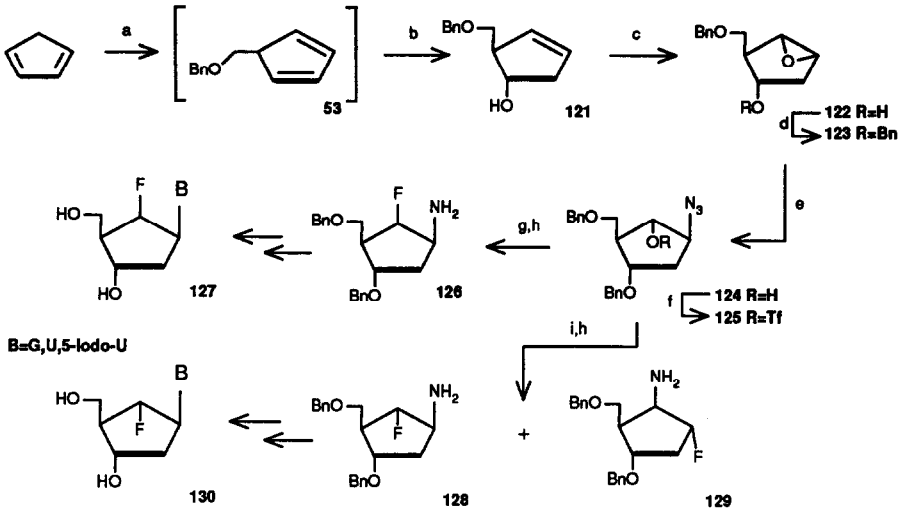
SCHEME 15



Reagents : (a) MsCl (b) H_2/Pd (c) NaN_3 (d) Ph_3P/Br (e) Bu_3SnH (f) DAST (g) KF

Replacement of the furanose oxygen of nucleosides by a methylene group provides an additional site for substitution of carbocyclic nucleosides and 6'-*fluoro* derivatives have attracted particular attention. In the 2'-deoxy series we have developed short and efficient routes to both 6'α-, and 6'β-fluoro derivatives *via* the key intermediate chiral epoxide **123**[13,19,20,49] (Scheme 16). Alkylation of cyclopentadiene with benzylchloromethyl ether to give **53** followed by *in situ* asymmetric hydroboration afforded a 39% yield of the cyclopentenol **121** showing ee ≥98%. Hydroxyl directed epoxidation and benzyl protection then gave the epoxide **123**. Opening of this epoxide with azide ion was highly regioselective providing the azido alcohol **124** in 85% yield. Activation of the alcohol as its triflate **125** and treatment with tetra-*n*-butyl ammonium fluoride introduced fluorine with inversion of configuration to give, after reduction of the azide moiety, the fluoro amine **126**. Construction of the required nucleoside base then provided 2'-deoxy-6'β-fluoro carbocyclic nucleosides **127**. In contrast, reaction of the alcohol **124** with DAST gave, after reduction of the azide function, a separable *ca* 2:3 mixture of isomeric fluoro amines **128** and **129**. The unexpected introduction of fluorine with retention of configuration and partial migration was explained by participation of the azide group in the DAST reaction. Elaboration of the required fluoro amine **128** afforded 2'-deoxy-6'α-fluoro analogues **130**. Whereas in the pyrimidine series both 6'α- and 6'β-fluoro substitution of carbocyclic IDU destroyed anti-herpes activity[20], in the purine series the potent activity of carbocyclic 2'-deoxy-guanosine against HSV1 and HSV2 was retained in the 6'α-fluoro derivative (**130**, B=guanine) but largely abolished in the 6'β-fluoro isomer[13]. Compound **130** (B=guanine) was also particularly effective against HSV1 and HSV2 *in vivo* in the mouse systemic model being >30 x more active than acyclovir.

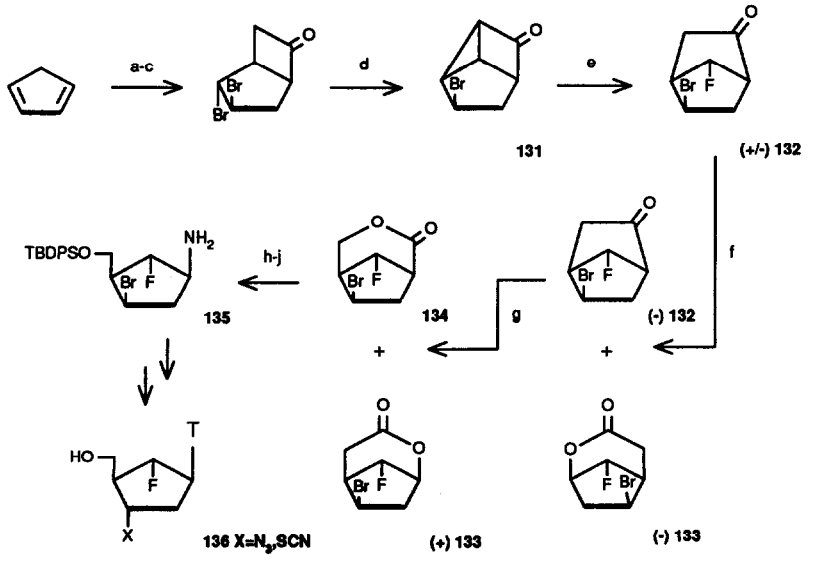
SCHEME 16



Reagents : (a) Na,THF,-5° then $BnOCH_2Cl$,-45° (b) (-) Di-isopinocampheylborane,-60°then H_2O_2,NaOH (c) t-BuOOH,vanadylacetylacetonate (d) BnBr,NaH (e) NaN_3 (f) TfCl (g) TBAF (h) H_2,Lindlar (i) DAST.

Roberts *et al.*[22] have developed an alternative approach to 2'-deoxy-6'α-fluoro derivatives which relies on an enzymatic kinetic resolution of the racemic ketone (±) **132** (Scheme 17).

SCHEME 17

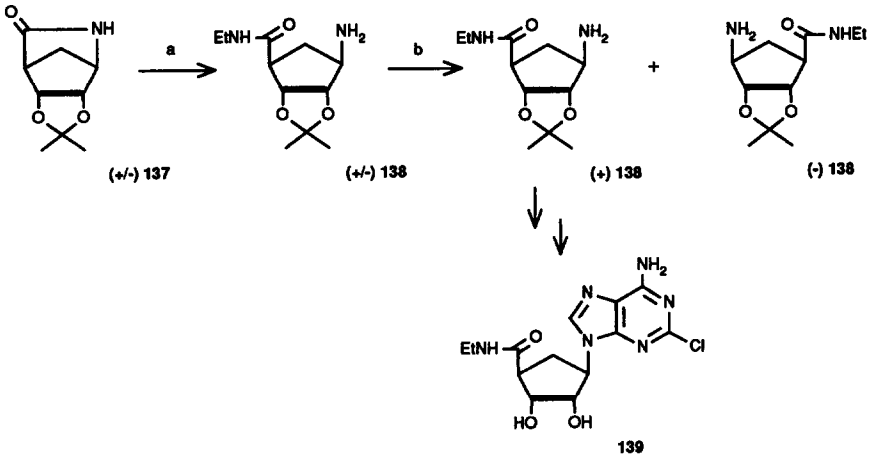


Reagents : (a) $Cl_2CHCOCl$,NEt_3 (b) Zn,AcOH (c) Br_2 (d) NaHMDS (e) NEt_3.3HF (f) Acinetobacter NCIB 9871 (g) mCPBA (h) NH_3 (i) TBDPSCl (j) $PhI(OCOCF_3)_2$.

This ketone was prepared from cyclopentadiene in five stages *via* fluoride opening of the tricyclic intermediate **131** and was incubated with the bacterium *Acinetobacter* NCIB 9871 until half of the starting material had been consumed. The unwanted enantiomer was thereby selectively oxidised to the lactone (-) **133** while the required enantiomer (-) **132** was recovered in 30% yield and with ee >90%. Chemical Baeyer-Villiger oxidation of (-) **132** occurred with opposite regioselectivity to the enzymatic oxidation giving the lactones **134** and (+) **133** in a ratio of 3.5:1. Compound **134** was converted in three stages into the bromo fluoro amine **135** which was transformed by construction of the thymine base and displacement of the bromine by azide into the 6'α-fluoro derivative **136** (X = N_3) of carbocyclic AZT. The 3'-thiocyanate derivative **136** (X = SCN) was similarly prepared.

Another area in which the metabolic stability of carbocyclic analogues has been exploited is that of anti-hypertensive adenosine agonists[48]. 5'-N-ethylcarboxamido-adenosine (NECA) is a potent adenosine A_2 agonist and Chen *et al.*[48a] have developed an efficient route to chiral 2-substituted derivatives of NECA involving chemical resolution (Scheme 18). The lactam (±) **137** was firstly opened with ethylamine in a steel bomb at 140° to give the racemic amine (±) **138** in 95% yield. This amine was then efficiently resolved with (+) dibenzoyltartaric acid to afford the enantiomers (+) and (-) **138** each showing ee >90%. The 'natural' (+) enantiomer was elaborated to give the 2-chloro analogue **139** of carbocyclic NECA and the chloro function was then displaced with a variety of amines to give a range of 2-amino derivatives. These derivatives were selective adenosine A_2 agonists and displayed the expected improved stability.

SCHEME 18

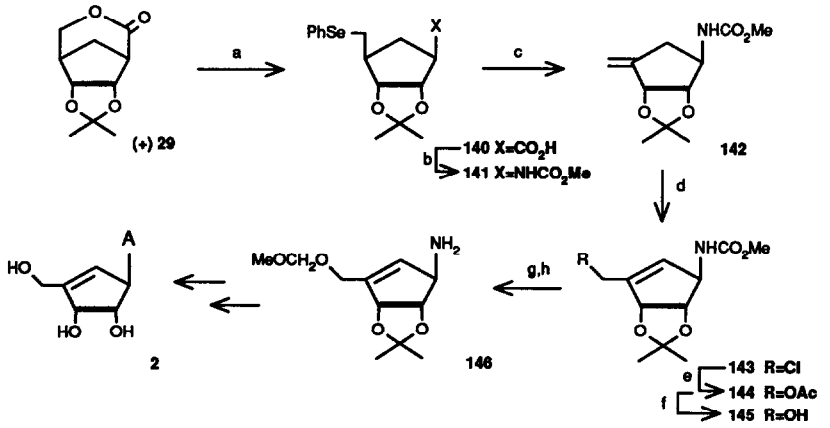


Reagents : (a) $EtNH_2$, 140° (b) resolution with (+) dibenzoyltartaric acid .

2.2 Linear approaches to neplanocin A and other unsaturated carbocyclic nucleosides

(-) Neplanocin A **2** was first synthesised by Ohno *et al.*[9] who utilised the chiral lactone (+) **29** to prepare the key intermediate cyclopentenylamine **146** (Scheme 19). Opening of the lactone ring with sodium phenyl selenide afforded the carboxylic acid **140** which was elaborated *via* a Curtius rearrangement into the methyl carbamate **141**. Oxidation followed by *syn* elimination of the resulting selenoxide then provided the exo-methylene derivative **142**. Chlorination of **142** with *t*-butyl hypochlorite gave the allylic chloride **143** which was converted into the required alcohol **145** *via* the acetate **144**. Protection of the hydroxyl group and hydrolysis of the carbamate completed this 17 stage synthesis of the cyclopentenylamine **146** from cyclopentadiene (overall yield *ca.* 6%). Construction of the adenine base then provided (-) neplanocin A **2** identical with the natural product (overall yield for 21 stages from cyclopentadiene ca 2.5%). The amine **146** has subsequently been employed to prepare a variety of cyclopentenyl nucleoside analogues[50].

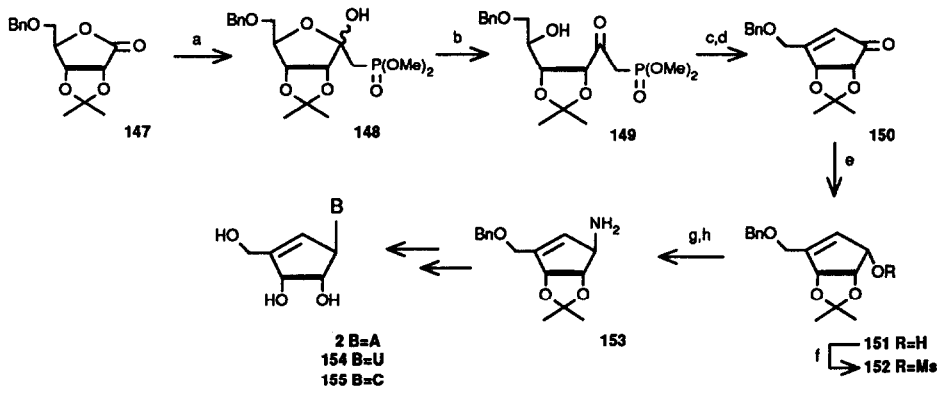
SCHEME 19



Reagents : (a) PhSeNa (b) $ClCO_2Et$, then aq NaN_3, then benzene,90°, then MeOH,90° (c) O_3,-78° then pyridine,40° (d) tBuOCl,HCO_2Me,-78° (e) NaOAc (f) Na_2CO_3,MeOH (g) $MeOCH_2Cl$ (h) KOH .

Marquez *et al.*[51] have developed a shorter route to a similar cyclopentenylamine intermediate **153** starting from D-ribonolactone (Scheme 20). Reaction of the protected ribonolactone **147** with lithium dimethyl methylphosphonate afforded the hemiketal **148** which was converted with sodium methoxide into the keto phosphonate **149**. Oxidation of the hydroxyl group of **149** followed by Wadsworth-Emmons cyclisation gave the cyclopentenone **150**. Sodium borohydride reduction of this ketone occurred exclusively from the less crowded convex β-face to give the 1α-alcohol **151** which was next activated as the mesylate **152**. Displacement with azide ion followed by reduction completed this 10 stage synthesis of the amine **153** from D-ribonolactone (overall yield *ca* 10%). This was used to prepare (-) neplanocin A **2** and also cyclopentenyluridine **154**[52] and cyclopentenylcytidine **155**[52,53]. The cytidine derivative **155** displays promising *in vivo* anti-tumour activity[50,53]. Sulphonate esters of the alcohol **151** have also been used to prepare cyclopentenyl nucleosides in a convergent manner (see Section 3.1).

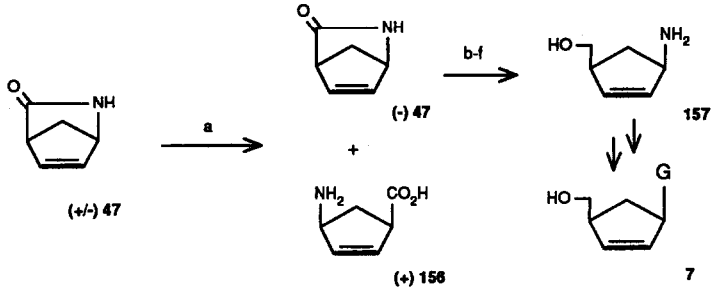
SCHEME 20



Reagents : (a) $LiCH_2P(O)(OMe)_2$ (b) NaOMe (c) CrO_3 (d) K_2CO_3,18-crown-6 (e) $NaBH_4$,$CeCl_3$ (f) MsCl (g) LiN_3 (h) H_2,Lindlar.

The, 2,3'-unsaturated carbocyclic guanosine derivative carbovir **7** has attracted much attention as a potent and selective inhibitor of HIV. Roberts *et al*[54] have developed a linear chemicoenzymatic synthesis of (-) **7** in which the bicyclic lactam **47** is resolved using whole cell preparations (Scheme 21). Thus, incubation of (±) **47** with *Pseudomonas solanacearum* NCIB 40249 (ENZA-20) until 55% conversion had occurred resulted in selective hydrolysis of the (+) enantiomer to the amino acid (+) **156** while the required lactam enantiomer (-) **47** was recovered with ee >98%. (-) **47** was converted in five stages into the amino alcohol **157** and hence into (-) carbovir **7**. An enantiocomplementary hydrolysis of (±) **47** was provided by incubation with *Rhodhococcus equi* NCIB 40213 (ENZA-1) which gave (+) **47** (ee >98%) and hence access to 'unnatural' enantiomers. Alternative approaches to (-) **7** will be described later (see Sections 3.2, 4 and 5.2).

SCHEME 21



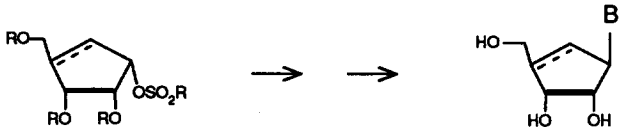
Reagents : (a) ENZA-20 (b) H^+ (c) MeOH,H^+ (d) Ac_2O (e) $Ca(BH_4)_2$ (f) H^+.

3. CONVERGENT APPROACHES

Convergent syntheses of carbocyclic nucleosides, which bring together the functionalised carbocyclic ring and the intact heterocyclic base, are generally more efficient and versatile than the linear approaches as they avoid the laborious stepwise construction of each purine or pyrimidine moiety. The convergent approaches that have been developed have employed three distinct strategies. These involve coupling the heterocyclic base B with the chiral carbocyclic moiety by:-

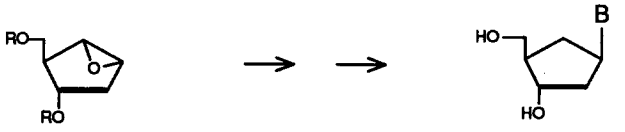
(a) Nucleophilic displacement of an activated hydroxyl group.

e.g.



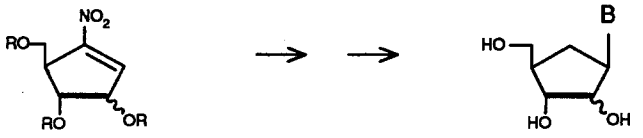
(b) Nucleophilic opening of an epoxide

e.g.



(c) Michael addition to an α,β-unsaturated nitro compound.

e.g.

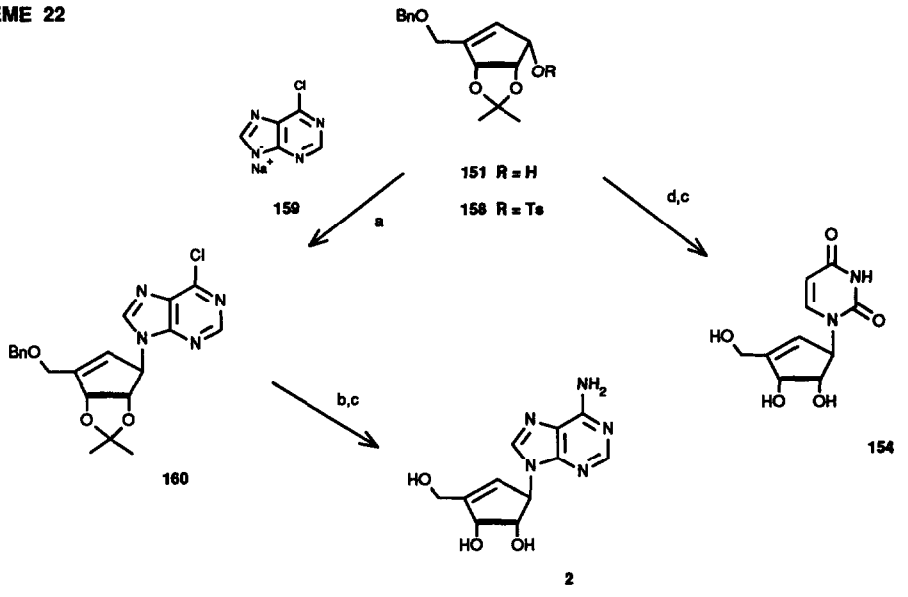


3.1 Nucleophilic displacement of an activated hydroxyl group

The first convergent synthesis of a carbocyclic nucleoside was reported by Marquez and Tseng[51,55] who utilised displacement of an allylic tosylate in an 11 stage synthesis of (-) neplanocin A **2** (Scheme 22). This sequence employed the chiral alcohol **151** prepared as described earlier from D-ribonolactone. Activation of this alcohol as its tosylate **158** and coupling with the sodium salt **159** of 6-chloropurine in acetonitrile at 50° afforded the protected carbocyclic nucleoside **160** in 31% yield. Ammonolysis of

the chloro function followed by simultaneous removal of the benzyl and isopropylidene groups with BCl_3 afforded (-) neplanocin A **2** (1.5% overall yield from D-ribonolactone). Similarly, coupling of the tosylate **158** with uracil in the presence of potassium carbonate in dimethylsulphoxide gave, after deprotection, cyclopentenyluridine **154**.

SCHEME 22

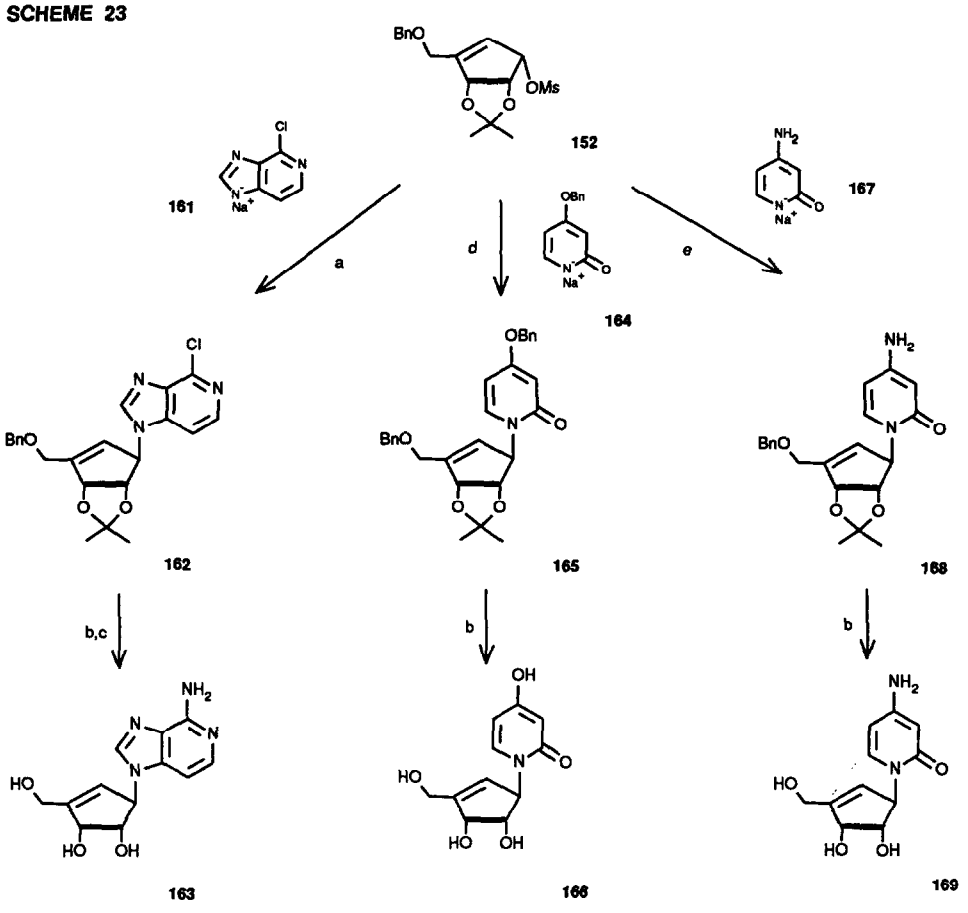


Reagents : (a) 159, CH_3CN, 50°, 42 hr (b) NH_3 /MeOH, 60° (c) BCl_3, -75° (d) Uracil, K_2CO_3, DMSO, RT.

Marquez has also employed this approach to prepare 3-deazapurine[56] and 3-deazapyrimidine[57] analogues (Scheme 23). Thus, coupling of the mesylate **152** with the sodium salt **161** of 6-chloro-3-deazapurine gave the desired coupled product **162** in 21% yield. Sequential deprotection of this material with BCl_3 followed by treatment with anhydrous hydrazine and immediate reduction with Raney nickel afforded 3-deaza-neplanocin A **163**, a powerful inhibitor of S-adenosylhomocysteine hydrolase[56]. This compound was less cytotoxic than neplanocin A and displayed potent *in vitro* activity against Vesicular Stomatitis, Parainfluenza type 3, Yellow Fever and Vaccinia viruses. *In vivo* activity was also demonstrated against Vaccinia in the mouse tailpox assay.

Coupling of the mesylate **152** with the 3-deazapyrimidines **164** and **167** resulted in *ca* 1:1 N:O alkylation with the desired N-alkylated products **165** and **168** being isolated in 27% and 36% yield respectively[57]. Deprotection of these materials with BCl_3 afforded 3-deaza-cyclopentenyluridine **166** and 3-deaza-cyclopentenylcytidine **169**. Unlike cyclopentenylcytidine **155**, these 3-deaza derivatives showed no useful anti-tumour or anti-viral activity.

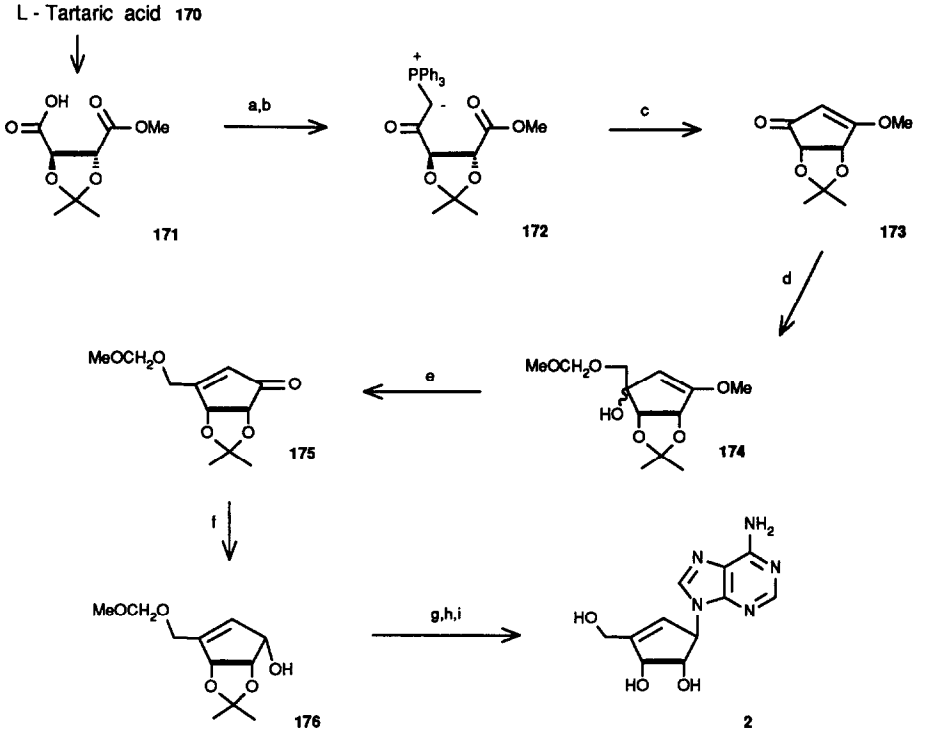
SCHEME 23



Reagents : (a) 161, CH_3CN, 80°, 6 hr (b) BCl_3, -75° (c) H_2NNH_2, Δ, then Raney Ni / H_2O, Δ (d) 164, DMF, 80°, 48 hr (e) 167,DMSO,rt,40 hr.

Bestmann and Roth's approach[58] to (-) neplanocin A **2** involved coupling of a similar allylic alcohol **176** with 6-chloropurine but under Mitsunobu conditions. The alcohol **176** was again obtained by reduction of the corresponding cyclopentenone **175** but this intermediate was now derived from L-tartaric acid **170** (Scheme 24). Thus the protected monomethyl tartrate **171** was converted *via* an intermediate ethyl thioester into the ylid **172** which under forcing conditions (150°, 110 bar, 80h) underwent intramolecular Wittig reaction to give the cyclopentenone **173** (35% from **171**). Epimerisation at the carbon bearing the keto ylid occurred during this cyclisation. Addition of (methoxymethoxy)methyl lithium to **173** gave the diastereoisomeric alcohols **174** which on treatment with acid furnished the cyclopentenone **175**. Reduction to the allylic alcohol **176** was followed by reaction with 6-chloropurine in the presence of triphenylphosphine/diethylazodicarboxylate which afforded the coupled product in 60% yield. Ammonolysis and deprotection completed this 12 stage synthesis of (-) neplanocin A **2** from L-tartaric acid (overall yield 4%).

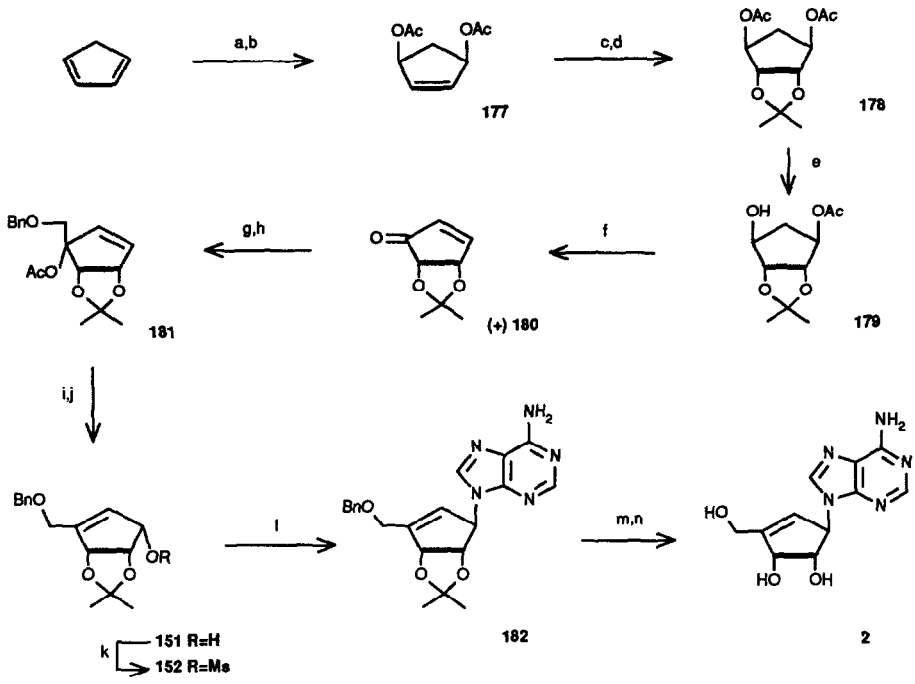
SCHEME 24



Reagents : (a) EtSH, DCC, DMAP (b) Methylenetriphenylphosphorane (c) PhMe,150°, 110bar, N_2 (d) $LiCH_2OCH_2OCH_3$, THF, -78° (e) Me_2CO, H^+ (f) $NaBH_4$, $CeCl_3$ (g) 6-chloropurine, PPh_3, DEAD, THF (h) NH_3, MeOH (i) H^+.

Johnson[59] employed a chemicoenzymatic approach to the same intermediate allylic alcohol **151** in his synthesis of (-) neplanocin A **2** from cyclopentadiene (Scheme 25). Singlet oxygen addition to cyclopentadiene followed by acetylation afforded the diacetate **177** which was hydroxylated with osmium tetroxide and then protected to give the acetonide **178**. Asymmetric hydrolysis of this meso diacetate with electric eel acetylcholinesterase gave an 80% yield of the mono ester **179** which was oxidised with Jones reagent to afford a 95% yield of the enone (+) **180** showing ee 98%[60]. This key intermediate and its enantiomer have also been prepared by optical resolution of (±) **180** using (+) N,S-dimethyl-S-phenylsulphoximine[60]. The key to Johnson's approach is the conversion of this simple enone into the allylic alcohol **151**. This was achieved by firstly reacting the enone (+) **180** with benzyloxymethyl lithium, and then protecting the resulting tertiary alcohol as its acetate **181**. Rearrangement of this allylic acetate with $PdCl_2(CH_3CN)_2$ followed by hydrolysis of the rearranged secondary acetate then provided the allylic alcohol **151** (78% from (+) **180**). The coupling stage was improved by reacting the mesylate **152** directly with adenine itself (K_2CO_3, 18-crown-6, DMF, 75°) to afford the protected derivative **182** in 46% yield. Debenzylation with $Pd(OH)_2$ and cyclohexene followed by hydrolysis of the isopropylidene group completed this 14 stage synthesis of (-) neplanocin A **2** (overall yield 11%).

SCHEME 25

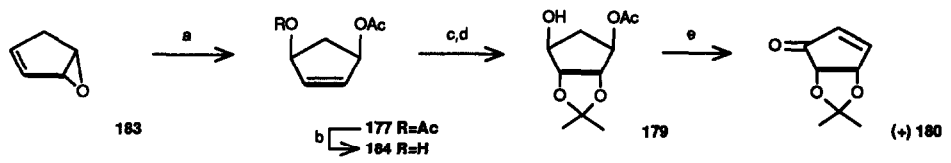


Reagents: (a) O_2 / hv, rose bengal (b) Ac_2O,py (c) 1mole% OsO_4, MeNO (d) Me_2CO, H^+ (e) electric eel acetylcholinesterase (f) Jones reagent (g) n-Bu_3SnCH_2OBn, nBuLi, THF, -78° (h) Ac_2O, Et_3N (i) 3mole% $PdCl_2(CH_3CN)_2$, benzoquinone, THF (j) K_2CO_3,MeOH (k) MsCl (l) Adenine, K_2CO_3, 18-crown-6, DMF (m) $Pd(OH)_2$, cyclohexene (n) H^+.

A similar chemicoenzymatic approach to the chiral enone (+) **180** has been reported by Deardorff *et al.*[61] who instead performed the enzymatic cleavage on the unsaturated diester **177** (Scheme 26). This diester was again derived from cyclopentadiene but *via* the mono epoxide **183**. Reaction of this epoxide with acetic anhydride in the presence of tetrakis(triphenylphosphine)palladium(O) afforded a 71% yield of the meso diester **177** which was then selectively hydrolysed with electric eel acetylcholinesterase to give the chiral alcohol **184** in 94% yield and showing ee >99%. This material was then converted into the enone (+) **180** *via* **179** in a yield of 59%.

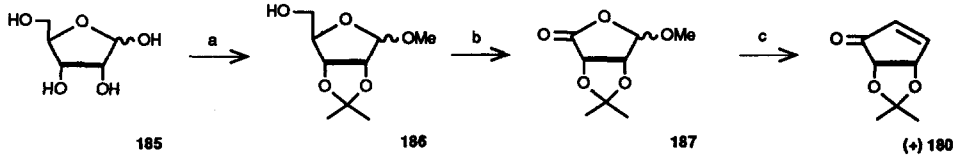
More recently, Borchardt *et al.*[62] have described an efficient three stage synthesis of (+) **180** starting from D-ribose **185** which procedes in 41% overall yield. The key step is the unusual PCC cleavage of the alcohol **186** to the lactone **187** (Scheme 27). D-Ribose **185** was first protected as the 2,3-isopropylidene methyl furanoside **186** and oxidation of this alcohol with PCC (4 eq) was found to furnish the lactone **187**. Reaction of **187** with lithium dimethyl methylphosphonate then provided the required enone (+) **180**. In this last stage the methoxide generated *in situ* during the opening of the lactone ring serves to catalyse the subsequent Wadsworth-Emmons cyclisation to (+) **180**.

SCHEME 26



Reagents : (a) Ac_2O, tetrakis(triphenylphosphine)palladium (0) (b) electric eel acetylcholinesterase (c) 2.8 mole% OsO_4, NMO, Me_2CO, H_2O (d) Me_2CO, $(MeO)_2CH_2CH_2CH_3$, pTSA (e) py,PCC, CH_2Cl_2.

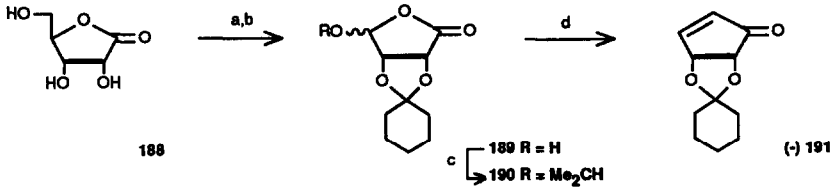
SCHEME 27



Reagents : (a) $Me_2C(OMe)_2$, MeOH, $HClO_4$ (b) PCC, PhH, 80°, overnight (c) $LiCH_2PO(OMe)_2$.

Borchardt *et al.*[63] have also employed this methodology to prepare the opposite cyclopentenone enantiomer (-) **191**, now with cyclohexylidene protection, and have utilised this material as a key intermediate in convergent approaches to both (-) aristeromycin **1** and (-) neplanocin A **2** (Scheme 29). The enone (-) **191** was readily prepared[64] from D-ribonolactone **188** in four stages and in 65% overall yield (Scheme 28). Thus, cyclohexylidene protection of **188** followed by periodate oxidation gave the hydroxylactone **189** which was converted with 2-propanol and pyridinium *p*-toluenesulphonate into the L-glycoside **190**. Reaction with lithium dimethyl methylphosphonate then completed the synthesis of (-) **191**. The intermediate **189** was also prepared in lower yield from D-gulonic acid-γ-lactone[63].

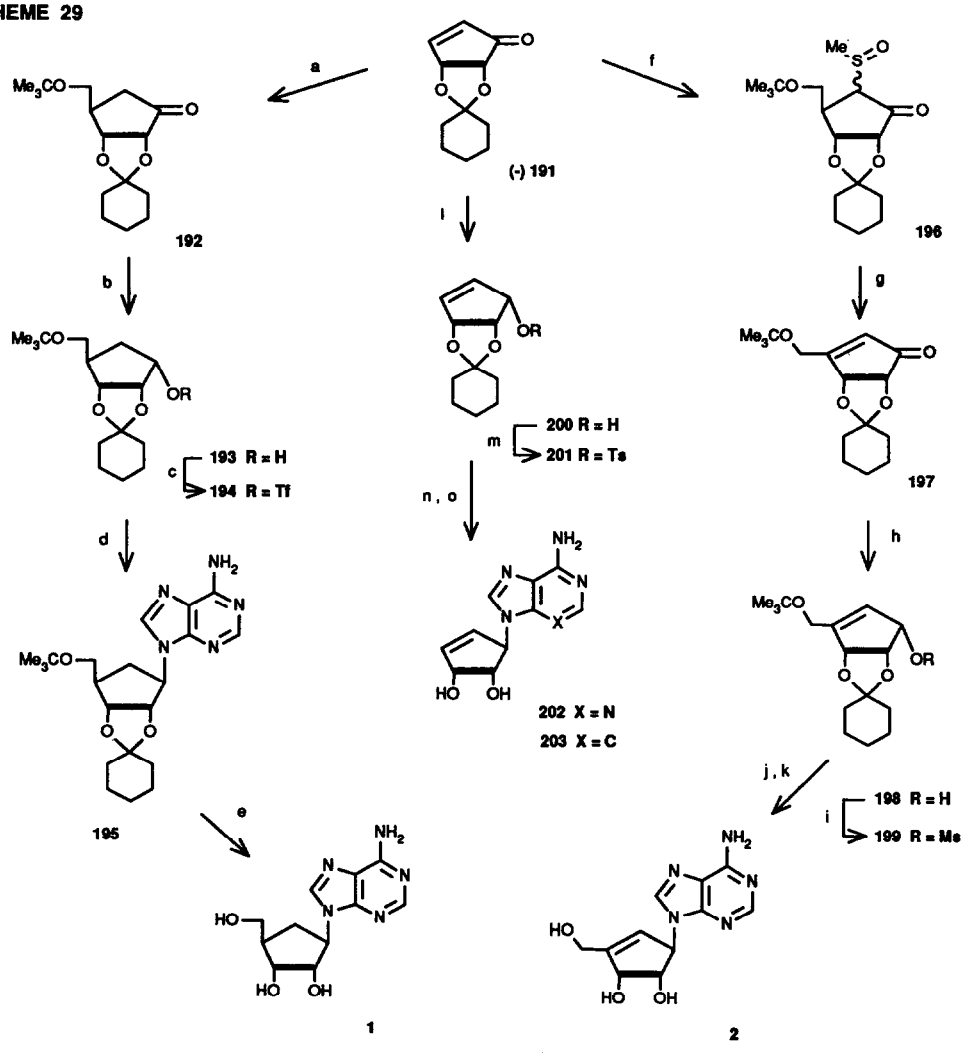
SCHEME 28



Reagents : (a) Cyclohexane, $FeCl_3$ (b) $NaIO_4$, H_2O, NaOH (c) 2-Propanol, py, pTSA (d) $CH_3PO(OMe)_2$, nBuLi, THF .

Conjugate addition of a hydroxymethyl equivalent to the enone (-) **191** provided access to both saturated and unsaturated carbocyclic nucleosides (Scheme 29). Thus, addition of lithium bis(*t*-butoxymethyl)cuprate to (-) **191** followed by quenching with acetic acid afforded the ketone **192** in 81% yield. DIBAL reduction of this ketone gave almost exclusively the 1α-alcohol **193** which was activated as its triflate **194** and coupled with the sodium salt of adenine in DMF at 0° to afford solely the N-9 alkylated product **195** in 46% yield. Acidic deprotection completed this nine stage synthesis of (-) aristeromycin **1** from D-ribonolactone (overall yield 18%). This represents the shortest and most efficient route to **1** yet described.

SCHEME 29



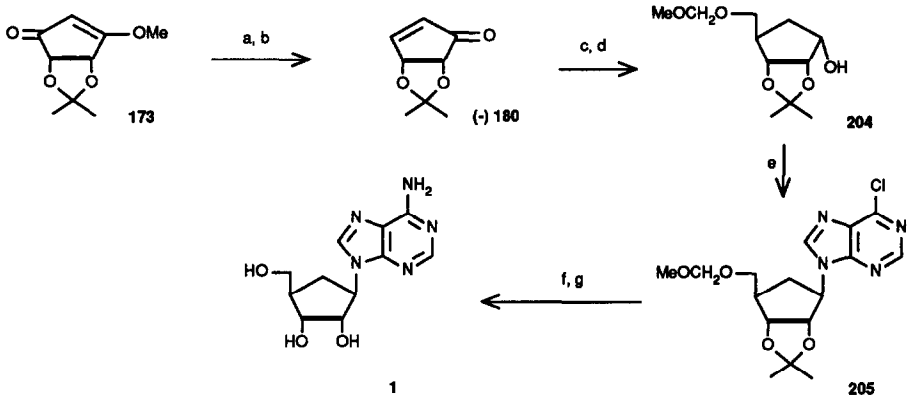
Reagents : (a) (t-BuOCH$_2$)$_2$CuLi (b) DIBAL (c) Tf$_2$O (d) Adenine, NaH, 18-crown-6, DMF (e) H$^+$ (f) (t-BuOCH$_2$)$_2$CuLi, MeSOCl (g) Toluene, CaCO$_3$, Δ (h) DIBAL (i) MsCl (j) Adenine, NaH, 18-crown-6, DMF (k) H$^+$ (l) NaBH$_4$, CeCl$_3$ (m) TsCl (n) Adenine, or 3-deaza-adenine, NaH, DMF then HCl.

Trapping of the conjugate addition product of (-) **191** and lithium bis(*t*-butoxymethyl)cuprate with methane sulphinyl chloride followed by pyrolytic syn-elimination of the resulting β-keto sulphoxide **196** in the presence of calcium carbonate afforded the cyclopentenone **197** in 64% yield. DIBAL reduction then gave the alcohol **198** which was coupled *via* its mesylate **199** with the sodium salt of adenine to afford, after deprotection, (-) neplanocin A **2** (overall yield 11% for 10 stages from D-ribonolactone).

The enone (-) **191** has also been stereospecifically reduced to the 1α-alcohol **200** which was coupled *via* its tosylate **201** with the sodium salts of adenine and 3-deaza-adenine to give, after deprotection, the neplanocin and 3-deaza-neplanocin analogues **202** and **203** respectively[64]. Both **202** and **203** are selective inhibitors of S-adenosylhomocysteine hydrolase and show similar anti-viral spectra to neplanocin A **2** but with reduced cytotoxicity[65].

Bestmann and Roth[66] have adopted a similar strategy to Borchardt in their recent synthesis of (-) aristeromycin **1**. They utilised the L-tartaric acid derived intermediate **173**, which had featured in their earlier synthesis of (-) neplanocin A **2** (Scheme 24), to gain access to the isopropylidene protected cyclopentenone (-) **180** (Scheme 30). Thus, borohydride reduction of **173** followed by treatment with *p*TSA afforded (-) **180** in 80% yield. The protected hydroxymethyl moiety was then introduced by conjugate addition of the higher order cyanocuprate derived from 2-thienyl-(cyano)-copper lithium and (methoxymethoxy)methyl lithium which afforded the required 1α-alcohol **204** in 89% yield. Coupling of this material with 6-chloropurine was effected under Mitsunobu conditions to give **205** in 56% yield. Ammonolysis and deprotection completed this 13 stage synthesis of (-) aristeromycin **1** from L-tartaric acid (overall yield 3%).

SCHEME 30

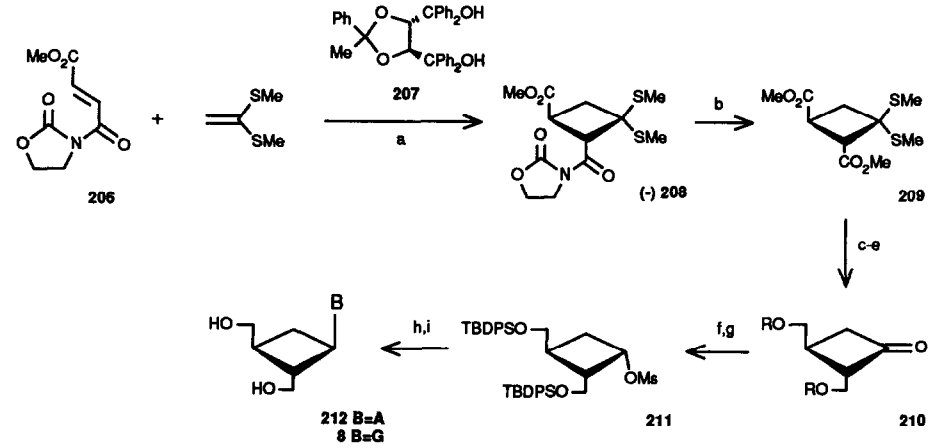


Reagents : (a) $NaBH_4$, $CeCl_3$ (b) pTSA, aq Me_2CO (c) (2-Th) $(MOMOCH_2)CuCNLi_2$, THF (d) $NaBH_4$, $CeCl_3$ (e) 6-chloropurine,Ph_3P,DEAD (f) NH_3, MeOH (g) HCl.

Ichikawa *et al.*[67]employed displacement of a mesylate of a chiral cyclobutanol by an alkali metal salt of a purine base in the first synthesis of chiral carbocyclic oxetanocin derivatives (Scheme 31). The key feature of this approach was the generation of a properly functionalised chiral cyclobutane derivative using an asymmetric [2+2] cycloaddition reaction catalysed by a chiral titanium reagent.

The chiral titanium reagent was generated *in situ* from dichlorodiisopropoxytitanium and the L-tartaric acid derived chiral diol **207**. Cycloaddition of the acryloyl oxazolidinone **206** with 1,1-bis(methylthio)ethylene in the presence of the above chiral titanium catalyst gave the cyclobutane (-) **208** in 83% yield and with ee >98%. Reaction of (-) **208** with dimethoxymagnesium in methanol provided the diester **209** in 96% yield. Reduction of this diester with lithium aluminium hydride and TBDPS protection of the resulting diol followed by hydrolysis of the thioketal function with NCS/silver nitrate afforded the cyclobutanone **210** (R=TBDPS) in 86% overall yield. Stereoselective reduction of this ketone was achieved using DIBAL in toluene at -78° to give the required 1α-alcohol in 82% yield. Activation of this alcohol as its mesylate **211** and coupling with the sodium salt of adenine in DMF at 140° afforded the N-9 substituted adenine in 46% yield which was then deprotected to give carbocyclic oxetanocin A **212**. Similarly, the mesylate **211** was reacted with the lithium salt of 2-amino-6-methoxyethoxypurine to give a 30% yield of coupled product which was deprotected to afford carbocyclic oxetanocin G **8**. These carbocyclic oxetanocin derivatives show great promise as potent broad spectrum anti-viral agents[15,16,67,68].

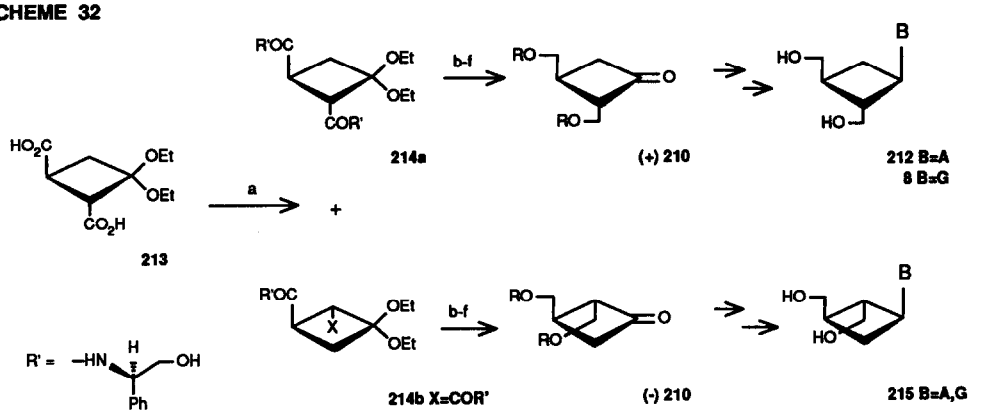
SCHEME 31



Reagents : (a) $Ti(iPrO)_2Cl_2$ (b) $(MeO)_2Mg$ (c) $LiAlH_4$ (d) TBDPSCl (e) NCS,$AgNO_3$ (f) DIBAL,-78° (g) MsCl (h) adenine,NaH,DMF,140° or 2-amino-6-(2-methoxy)ethoxypurine,LiH,DMF (i) H^+.

More recently Bisacchi *et al.*[68] have gained access to *both* enantiomers of carbocyclic oxetanocins *via* chemical resolution of the diacid **213** (Scheme 32). Thus, DCC mediated coupling of **213** with R-(-)-2-phenylglycinol afforded the diastereoisomeric bis-amides **214a** and **214b** which were readily separated by crystallisation. These diastereomers were then converted in five stages into the enantiomeric cyclobutanones (+) and (-) **210** (R=Bz). The remainder of the synthesis parallelled that of Ichikawa with the purine bases being introduced by displacement of a 1α-sulphonate ester. In this way (+) **210** provided carbocyclic oxetanocins A **212** and G **8** whilst (-) **210** afforded the 'unnatural' enantiomers **215**. These studies revealed that the anti-herpes activity resides solely in the 'natural' enantiomers.

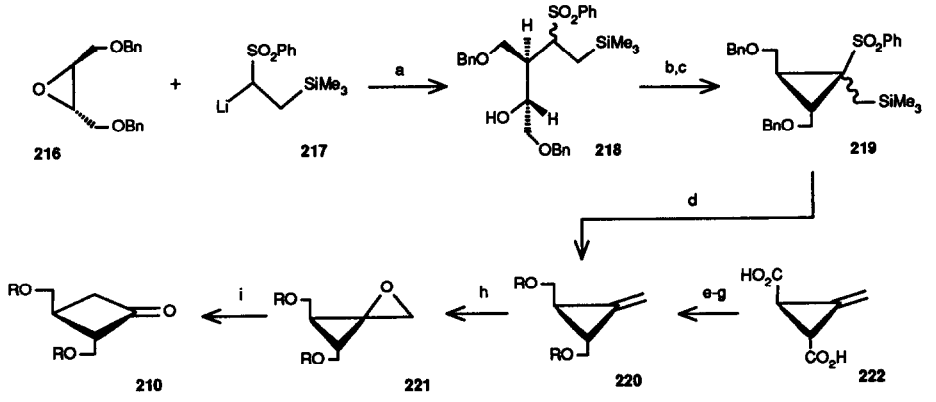
SCHEME 32



Reagents : (a) R-(-)-2-phenylglycinol,DCC (b) TBDMSCl (c) N_2O_4,NaOAc (d) $LiBH_4$ (e) BzCl (f) H_2SO_4 .

Hsiao and Hannick[69] have reported a completely different approach to the chiral cyclobutanone **210** *via* an intermediate methylenecyclopropane **220**. Two routes to this intermediate were described (Scheme 33). The first route began with the chiral epoxide **216** which was opened with the lithio derivative **217** to give a 75% yield of the alcohol **218** as an inseparable mixture of diastereoisomers. Mesylation of this alcohol followed by deprotonation with LDA afforded the cyclopropane **219** in 82% yield. Elimination of benzenesulphonyltrimethylsilane by reacting **219** with tetra-*n*-butyl ammonium fluoride then gave the

SCHEME 33

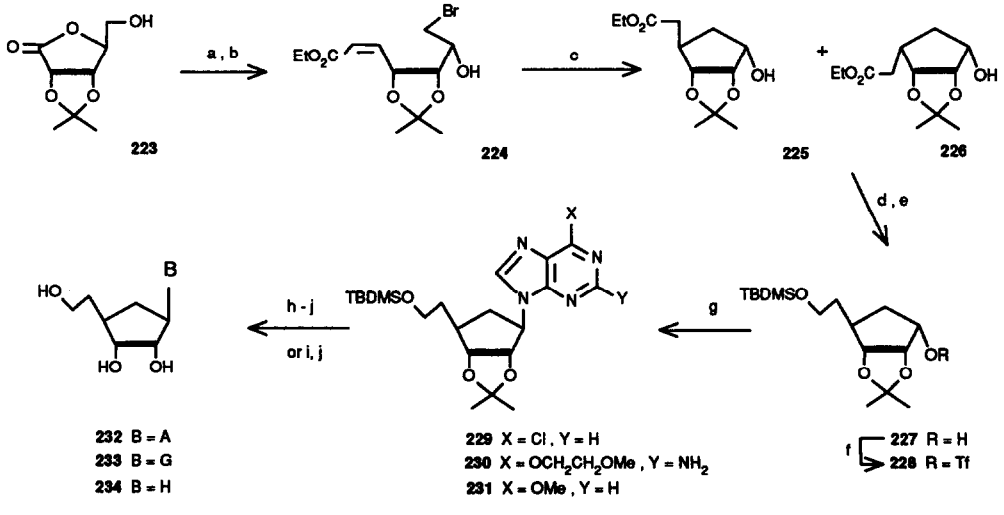


Reagents: (a) Et_2O,-78° to 25° (b) MsCl (c) LDA,THF,-78° to 25° (d) TBAF,THF,reflux (e) MeOH,H^+ (f) DIBAL (g) BnCl,NaH or TBDPSCl (h) mCPBA (i) catalytic LiI, CH_2Cl_2,0° .

methylenecyclopropane **220** (R=Bn) in 91% yield. The second route started from the (+) enantiomer **222** of Feist's acid[70]. The methylenecyclopropanes **220** (R=Bn, TBDPS) were thereby obtained in three stages and in high yield by DIBAL reduction of the dimethyl ester of **222** followed by protection of the resulting diol. Conversion of the methylenecyclopropane **220** into the Ichikawa cyclobutanone **210** was achieved by epoxidation to the unstable oxaspiropentane **221** which was cleanly isomerised with catalytic lithium iodide to afford **210** in excellent yield.

Jones and Roberts[71] utilised displacement of a secondary triflate by lithium salts of purine bases in their approach to chiral 5'-*homo*-carbocyclic nucleosides (Scheme 34). The carbocyclic moiety was derived from L-ribonolactone *via* a radical cyclisation process. Thus, isopropylidene L-ribonolactone **223** was firstly brominated with NBS/triphenylphosphine and the lactone then reduced with DIBAL. Wittig reaction of the resulting lactol with (carbethoxymethylene) triphenylphosphorane provided the bromo acrylate **224** in 55% yield from **223**. Formation of the primary radical from **224** with tri-*n*-butyltin hydride/AIBN resulted in rapid cyclisation to give the isomeric cyclopentanols **225** and **226** in a ratio of 6:1 in 89% yield. DIBAL reduction of this mixture followed by selective TBDMS protection of the resulting primary hydroxyl function afforded a 71% yield of the required 1α-alcohol **227**. Activation of this alcohol as its triflate **228** and coupling with the lithium salt of 6-chloropurine gave the required N-9 isomer **229** in 46% yield but some N-7 alkylation (9%) was also observed. Reaction of **228** with 2-amino-6-methoxyethoxypurine and 6-methoxypurine afforded the required products **230** (26%) and **231** (38%) but even more N-7 alkylation was observed in these cases (26% and 36% respectively). Ammonolysis of **229** followed by deprotection afforded (-) 5'-*homo*-aristeromycin **232** in 70% yield. The guanosine **233** and inosine **234** analogues were derived from **230** and **231** in 80% and 42% yield respectively. These 5'-*homo*-carbocyclic nucleosides showed disappointing biological activity.

SCHEME 34

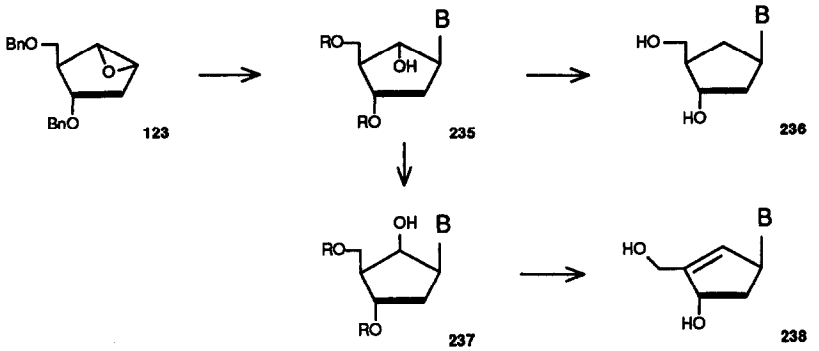


Reagents : (a) NBS , Ph_3P (b) DIBAL , then Ph_3PCHCO_2Et (c) Bu_3SnH,AIBN (d) DIBAL (e) TBDMSCl (f) Tf_2O
(g) 6-chloropurine, or 2-amino-6-methoxyethoxypurine, or 6-methoxypurine/LiH (h) NH_3/MeOH (i) TBAF (j) H^+ .

3.2 Nucleophilic opening of an epoxide

Following the discovery at Glaxo[72,73] of potent HSV1 and VZV activity in carbocyclic BVDU **4** we sought an efficient convergent approach to this and other chiral 2'-deoxy carbocyclic nucleosides. Having demonstrated that the readily available chiral epoxide **123** undergoes ring opening by azide ion at C-1 with high regioselectivity (Scheme 16) we envisaged that opening of **123** with purine or pyrimidine bases could provide 2'-deoxy carbocyclic nucleosides **236** in a short convergent manner (Scheme 35). Furthermore, the intermediate 6'α-hydroxy derivatives **235** (R=H) would also be of interest in their own right and could in turn provide access to novel 6'β-hydroxy **237** (R=H) and 4',6'-unsaturated analogues **238**.

SCHEME 35

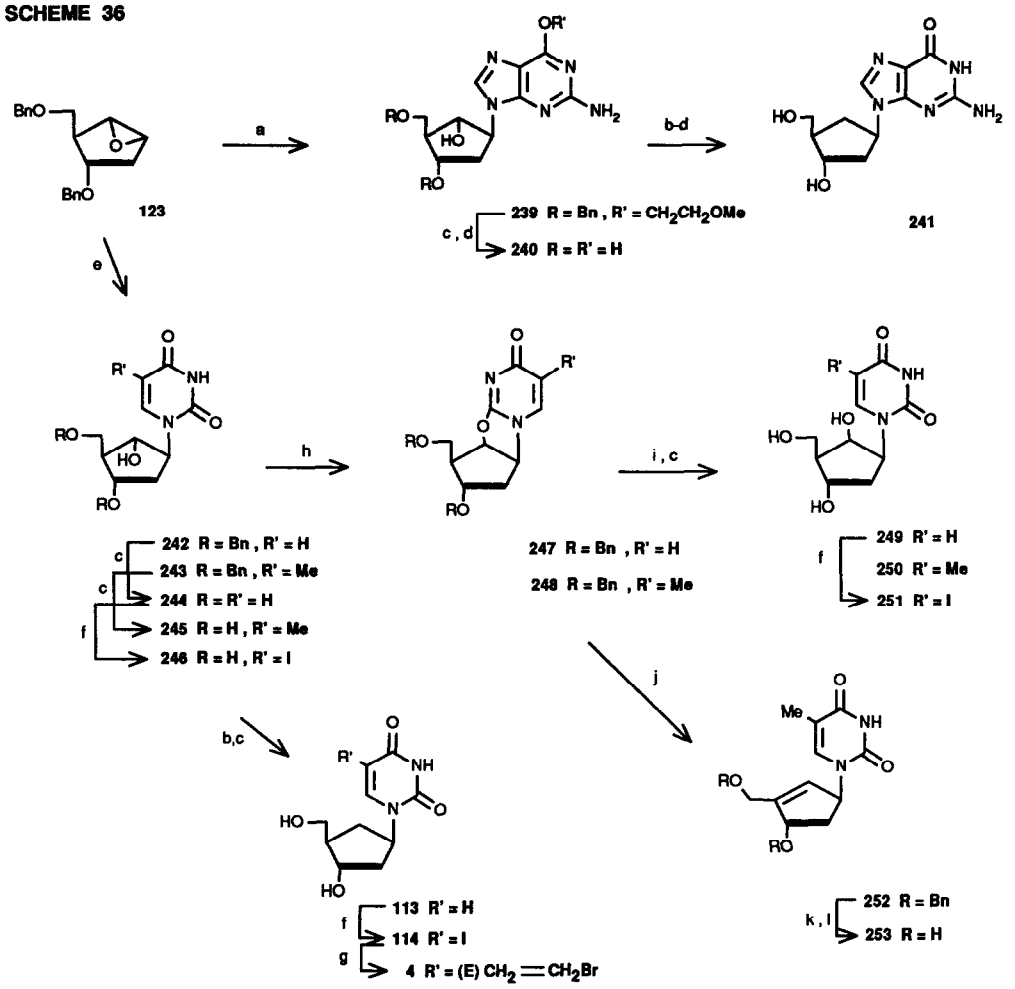


Ring opening of the epoxide **123** with 2-amino-6-methoxyethoxypurine in the presence of lithium hydride in DMF at 140° indeed occurred with high regioselectivity to afford the 6'α-hydroxy derivative **239** in 60% yield[74] (Scheme 36). It is noteworthy that whereas displacement of sulphonate esters by purines often gives large amounts of unwanted N-7 alkylation, this opening of the epoxide **123** gives the required N-9 alkylation with high selectivity. Deoxygenation of the alcohol **239** *via* tri-*n*-butyl tin hydride reduction of its 6'-*O*-phenoxythiocarbonyl derivative followed by hydrogenolytic debenzylation and hydrolysis of the methoxyethoxy moiety completed this 8 stage synthesis of (+) carbocyclic 2'-deoxy-guanosine **241** from cyclopentadiene (overall yield 10%). This compound displays potent activity against HSV1 and HSV2[31,74]. Approaches to this derivative by enzymatic resolution and from aristeromycin will be described later (see Sections 4 and 5.2).

Opening of the epoxide **123** with uracil and thymine afforded the alcohols **242** and **243** in 63% and 70% yield respectively[74]. Deoxygenation and deprotection of **242** gave (+) carbocyclic 2'-deoxy-uridine **113** in 54% yield which was then iodinated to provide (+) carbocyclic IDU **114** and hence (+) carbocyclic BVDU **4**[75].

Debenzylation of **242** and **243** afforded the 6'α-hydroxy derivatives **244**[76] and **245**[26] respectively and subsequent iodination of **244** gave 6'α-hydroxy carbocyclic IDU **246**[76]. Similarly, debenzylation of **239** followed by hydrolysis of the methoxyethoxy protection afforded the 6'α-hydroxy derivative **240** of carbocyclic 2'-deoxy-guanosine[76].

SCHEME 36



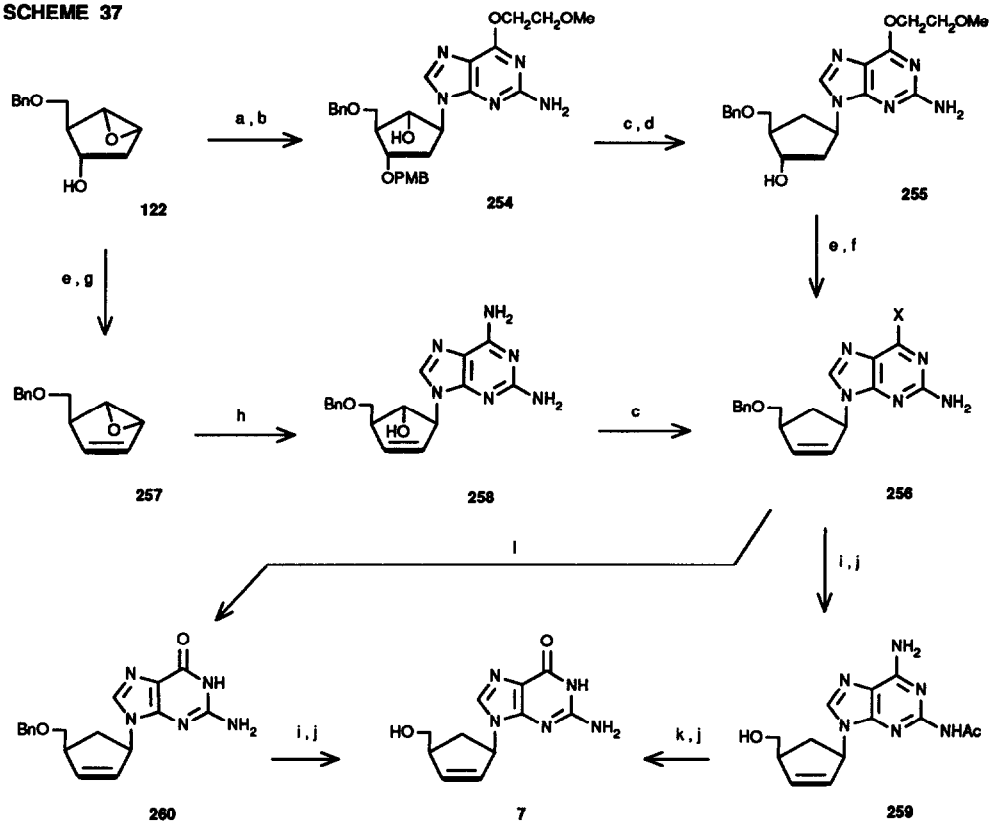
Reagents : (a) 2-Amino-6-methoxyethoxypurine (b) PhOCSCl, then nBu_3SnH,AIBN (c) H_2, Pd/C (d) 3M HCl (e) Uracil or thymine, NaH, DMF (f) I_2, HNO_3 (g) Methyl acrylate, $Pd(OAc)_2$, PhP_3, Et_3N, then NaOH, then K_2CO_3, NBS (h) $(PhO)_2CO$ (i) NaOH, aq MeOH (j) $KOBu^t$ (k) $BF_3.Et_2O$, Ac_2O (l) NH_3/MeOH.

In the pyrimidine series, 6'β-hydroxy derivatives were prepared by inversion of the 6'α-hydroxy isomers *via* 2,6'-anhydro intermediates. Thus, treatment of **242** and **243** with diphenylcarbonate in DMF at 150° afforded in high yield the anhydro derivatives **247** and **248** respectively which on hydrolysis and debenzylation provided the 6'β-hydroxy analogues **249**[76] and **250**[26]. Iodination of **249** gave the 6'β-hydroxy derivative **251**[76] of carbocyclic IDU.

The anhydro derivative **248** underwent a facile intramolecular elimination on treatment with potassium-*t*-butoxide in DMF to provide the 4',6'-alkene **252** in 46% yield[26]. Two step deprotection of this material by acetolysis with acetic anhydride/BF_3 followed by methanolysis of the resulting diacetate then gave (-) cyclopentenylthymidine **253** in 8 stages from cyclopentadiene.

More recently, Jones *et al.*[77] in these laboratories have utilised the chiral epoxide **122** to provide *two* new routes to the anti-HIV compound (-) carbovir **7** (Scheme 37). Thus, *p*-methoxybenzyl protection of **122** followed by epoxide opening with 2-amino-6-methoxyethoxypurine gave the 6'α-hydroxy derivative **254** which on deoxygenation followed by selective deprotection with DDQ gave the 3'-alcohol **255**. Activation of this alcohol as its mesylate and treatment with methoxyethoxide in DMF then provided the protected 2',3'-olefin **256** (X=$OCH_2CH_2OCH_3$). Alternatively, the double bond was introduced before the purine base. Thus, treatment of the mesylate of **122** with tetra-*n*-butyl ammonium fluoride gave the allylic epoxide **257** which was opened with 2,6-diaminopurine to afford the 6'α-hydroxy intermediate **258** which on deoxygenation gave **256** (X=NH_2). Debenzylation of this material was achieved by acetolysis with acetic anhydride/BF_3 followed by methanolysis and the resulting alcohol **259** was diazotised and treated with ammonia in methanol to give (-) carbovir **7**. Alternatively **256** (X=$OCH_2CH_2OCH_3$) was treated with aluminium triiodide to afford **260** which was then debenzylated to provide **7**.

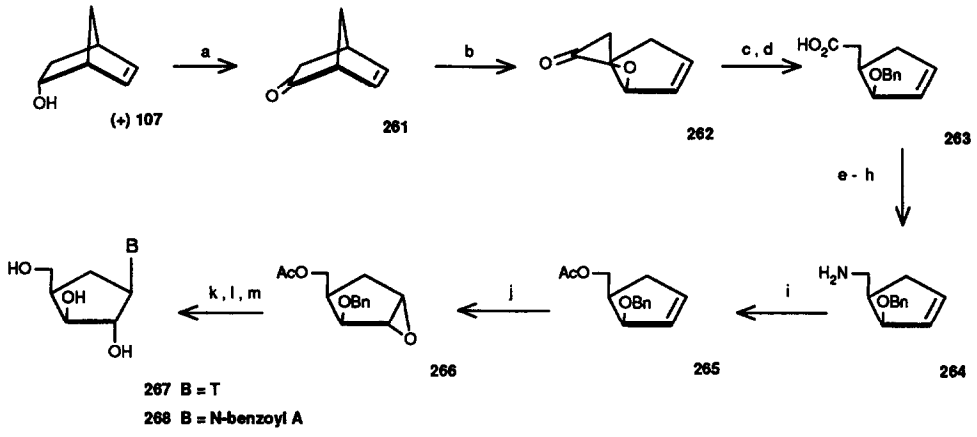
SCHEME 37



Reagents : (a) p-Methoxybenzyl chloride, NaH, TBAI (b) 2-amino-6-methoxyethoxypurine, LiH (c) PhOCSCl, DMAP then nBu_3SnH (d) DDQ (e) MsCl (f) $NaOCH_2CH_2OMe$, DMF (g) TBAF (h) 2, 6-diaminopurine, NaH (i) $BF_3.Et_2O$, Ac_2O (j) NH_3/MeOH (k) $NaNO_2$, aq AcOH (l) AlI_3, CH_3CN.

Nucleophilic opening of an epoxide has also been recently adopted by Griengl *et al.*[78] to gain convergent access to chiral *xylo*-carbocyclic analogues. The key epoxide intermediate **266** was prepared in six stages from the previously described enzymatically enriched norbornenol (+) **107** (ee 90%) (Scheme 38). Thus, oxidation of this alcohol to the ketone **261** followed by Baeyer-Villiger reaction under acidic conditions gave the rearranged lactone **262**. Saponification of this material and benzyl protection of the liberated secondary hydroxyl group afforded the carboxylic acid **263** which was converted into the amine **264** by Curtius degradation. Reaction of **264** with sodium nitrite/acetic acid in dichloromethane gave the acetate **265** in 46% yield and epoxidation of this olefin then provided the required α-epoxide **266** in 82% yield. This epoxide was opened with thymine and N-6 benzoyladenine to furnish the protected *xylo*-carbocyclic nucleosides in 41-46% yield. Recrystallisation at this point provided these intermediates enantiomerically pure. Finally, removal of the acetate and benzyl protecting groups completed the synthesis of the *xylo*-derivatives **267** and **268.**

SCHEME 38



Reagents : (a) $(COCl)_2$, DMSO (b) H_2O_2, H^+ (c) aq KOH (d) BnBr (e) Ethylchloroformate, NEt_3 (f) NaN_3 (g) Toluene, Δ (h) H_2O (i) $NaNO_2$,AcOH (j) mCPBA (k) Thymine or N-6 benzoyladenine, NaOH or K_2CO_3, DMF (l) NH_3/MeOH (m) H_2, Pd/C

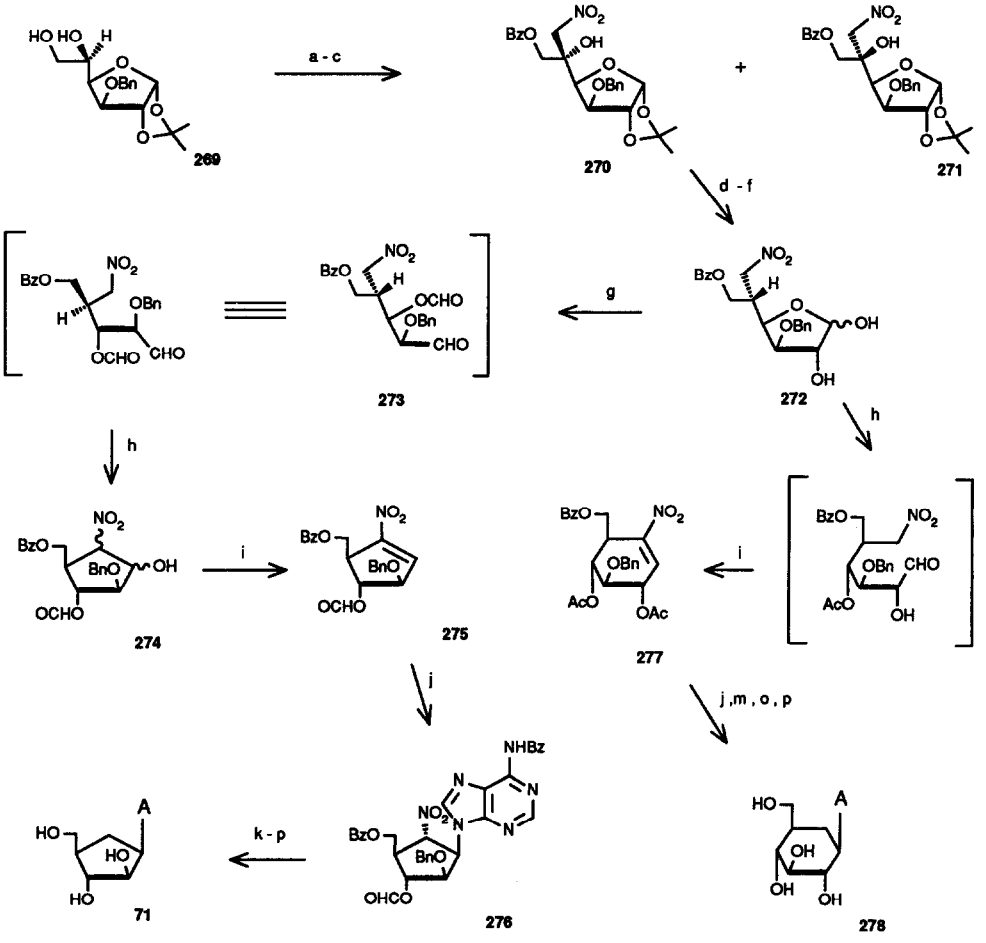
3.3 Michael addition to an α,β-unsaturated nitro compound

Kitagawa *et al.* have developed a novel but lengthy convergent approach to chiral carbocyclic nucleosides which involves the Michael addition of a purine base to an optically pure nitro-cyclopentene[79,80] or nitro-cyclohexene[81], both of which were derived from D-glucose.

Selective benzylation of the primary hydroxyl group of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose **269** followed by Swern oxidation and addition of nitromethane to the resulting ketone gave the isomeric nitro-alcohols **270** and **271** in 40% and 21% yield respectively from **269**[82] (Scheme 39).

Acetylation of **270** was followed by treatment with sodium borohydride which displaced the acetoxy group with inversion of configuration. Subsequent removal of the isopropylidene protection then gave the diol **272**. Cleavage of this diol with lead tetraacetate and cyclisation of the resulting unstable nitro-aldehyde **273** using potassium fluoride/18-crown-6 in DMF afforded the nitro-cyclopentanol **274**[83] which was then dehydrated to the required nitro-cyclopentene **275**[79]. Addition of N-6 benzoyladenine to **275** in the presence of potassium fluoride/18-crown-6 furnished the coupled nitro-carbocyclic nucleoside **276** in 80% yield. Removal of the formyl group from **276** and replacement with the more stable ethoxyethyl ether protection then allowed the nitro group to be removed with tri-*n*-butyl tin hydride/AIBN. Finally, sequential removal of the ethoxyethyl, benzoyl and benzyl protecting groups afforded (+) cyclaridine **71** (31% from nitro-cyclopentene **275**, ca 2 % overall yield for 19 stages from D-glucose).

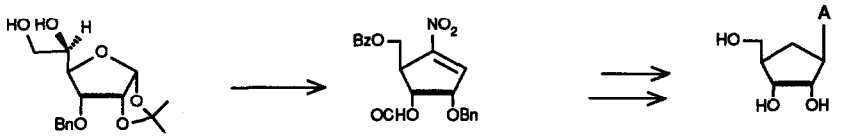
SCHEME 39



The same intermediate nitrofuranose **272** was also used to gain access to the cyclohexyl adenine derivative **278**[81] (Scheme 39). Thus, treatment of **272** with potassium fluoride/18-crown-6 in DMF followed by acetylation with acetic anhydride in the presence of *p*-toluene sulphonic acid gave the nitro-cyclohexene **277**[84] in 80% yield. Michael addition of N-6 benzoyladenine to **277** followed by removal of the nitro group and deprotection as before provided (-) carbocyclic 9-β-D-glucopyranosyladenine **278**.

Kitagawa *et al.*[80] have also used this approach to prepare (-) aristeromycin **1** from D-glucose in 21 stages and in 4% overall yield (Scheme 40). This route required inversion of D-glucose at C-3 but elaboration of the resulting epimer **279** of **269** to (-) aristeromycin **1** *via* the nitro-olefin **280** exactly paralleled that described above for (+) cyclaridine **71**.

SCHEME 40

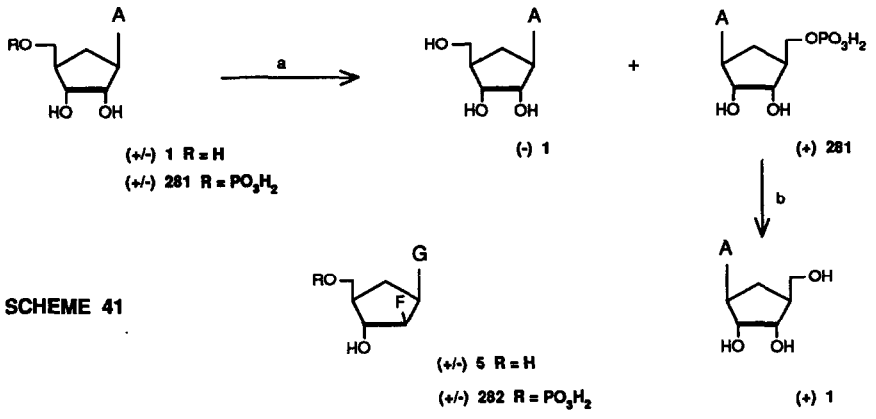


279 **280** **1**

4. ENZYMATIC RESOLUTION OF RACEMIC CARBOCYCLIC NUCLEOSIDES.

Enzymatic resolution of carbocyclic nucleosides has so far been confined to purine derivatives with the enzymes 5'-ribonucleotide phosphohydrolase and adenosine deaminase being employed to effect enantioselective hydrolysis of 5'-monophosphate and 6-amino/6-chloro derivatives respectively.

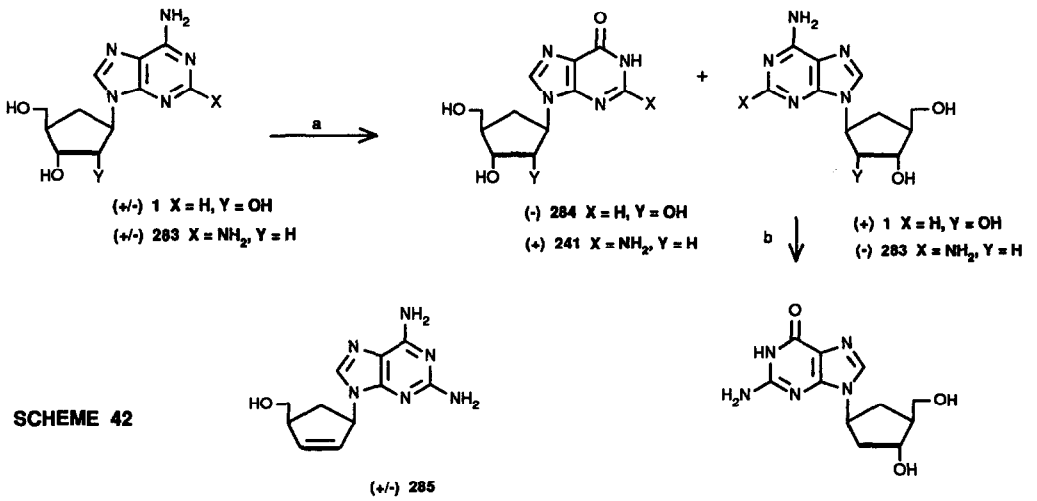
This approach was first applied by De Clercq *et al.*[30] to resolve (±) aristeromycin **1** (Scheme 41). This racemic material was chemically converted into its 5'-monophosphate (±) **281** which was then treated with 5'-ribonucleotide phosphohydrolase from *Crotalus atrox* venom in glycine buffer containing $MgCl_2$ at pH9 for 5h at 37°. The natural (-) enantiomer was thereby selectively hydrolysed to provide (-) aristeromycin **1** while the dextrorotatory monophosphate (+) **281** was recovered. Treatment of this recovered monophosphate (+) **281** with alkaline phosphatase then gave (+) aristeromycin. Evaluation of the anti-viral, anti-tumour and cytotoxic properties of the two enantiomers showed that the biological activity of aristeromycin resides exclusively in the natural isomer (-) **1**. We employed a similar procedure[12] to resolve the potent anti-herpetic carbocyclic 2'-*ara*-fluoro-guanosine (±) **5**, but the initial phosphorylation to provide the racemic 5'-monophosphate (±) **282** was also achieved enzymatically using thymidine kinase isolated from HSV1. Once again, 5'-ribonucleotide phosphohydrolase displayed good enantioselectivity despite the presence of the 2'-*ara*-fluoro substituent in this carbocyclic substrate. The anti-viral activity was found to be predominantly associated with the 'natural' (+) enantiomer of **5**.



SCHEME 41

Reagents : (a) 5 '-ribonucleotide phosphohydrolase (b) alkaline phosphatase

Adenosine deaminase (ADA) has also been found to be remarkably tolerant of unusual structural features both in the carbocyclic moiety and in the purine base. This enzyme normally deaminates adenosine to inosine but it is also capable of catalysing the hydrolysis of other leaving groups at the 6-position of the purine ring[85]. The use of this enzyme to resolve carbocyclic derivatives was first described by Secrist *et al*[31]. Thus, incubation of racemic aristeromycin (±) **1** with ADA afforded (-) carbocyclic inosine (-) **284** and the (+) enantiomer of **1** was recovered (Scheme 42). Similarly, treatment of the racemic 2,6-diaminopurine derivative (±) **283** with ADA provided the anti-herpetic (+) carbocyclic 2'-deoxy-guanosine (+) **241**, which crystallised from the chilled reaction mixture, while (-) **283** was recovered. This 'unnatural' enantiomer (-) **283** was hydrolysed only slowly by ADA but prolonged treatment with higher concentration of the enzyme provided (-) carbocyclic 2'-deoxy-guanosine (-) **241**.



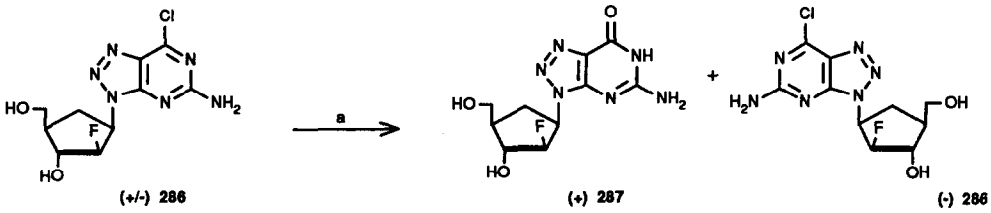
SCHEME 42

Reagents : (a) ADA, 25°, 2-3hr (b) ADA, 37°, 72hr

Again, the anti-viral activity was found to reside principally in the 'natural' (+) enantiomer of **241**. Using a similar protocol, ADA has been used to obtain the (+) and (-) enantiomers of carbovir **7** from the racemic 2,6-diaminopurine precursor (±) **285**[86].

The versatility of this enzyme has further been illustrated in these laboratories[87] with the enantioselective hydrolysis of the 6-chloro derivative (±) **286** (Scheme 43). Here the enzyme tolerates the 2-amino and 8-aza functionality in the heterocyclic base and the 2'-fluoro substituent in the carbocyclic ring to afford (+) carbocyclic 2'-*ara*-fluoro-8-aza-guanosine (+) **287**, a compound displaying potent activity against HSV1, HSV2 and VZV[87]. An alternative approach to (+) **287** from aristeromycin will be described later (see Section 5.2).

SCHEME 43



Reagents : (a) ADA

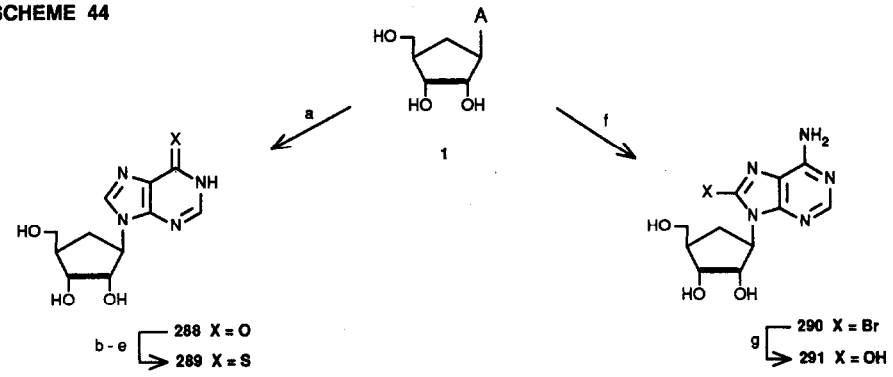
5. SYNTHESES FROM ARISTEROMYCIN AND NEPLANOCIN A.

As with most natural products, the discovery of aristeromycin **1** and neplanocin A **2** was followed by chemical modifications to obtain closely related analogues. More recently, however, the availability of aristeromycin in quantity, by large scale fermentation, has made this natural product an attractive starting material for the production of a variety of more diverse anti-viral carbocyclic derivatives in optically pure form.

5.1 Synthesis of closely related analogues.

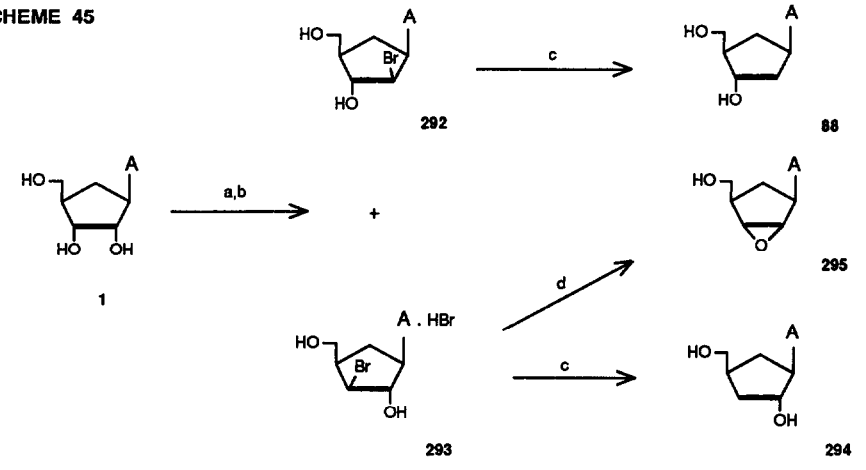
The first analogues of aristeromycin were described by Marumoto *et al.*[88] who applied standard nucleoside chemistry to make modifications in the purine base (Scheme 44) and in the carbocyclic moiety (Scheme 45). Thus, treatment of the natural product with nitrous acid afforded carbocyclic inosine **288** which was further elaborated *via* a 6-chloro intermediate into the 6-thio analogue **289** (Scheme 44). Bromination of **1** gave the 8-bromo derivative **290** which on hydrolysis provided 8-hydroxy-aristeromycin **291.** Reaction of aristeromycin with acetyl bromide in acetonitrile, followed by treatment with HBr afforded a separable 1:5 mixture of 2'-bromo **292** and 3'-bromo **293** derivatives (Scheme 45). Hydrogenolysis of **292** and **293** then provided the 2'-deoxy **88** and 3'-deoxy **294** derivatives respectively. The 2',3'-*ribo* epoxide **295** was also prepared by treatment of **293** with sodium methoxide in methanol.

SCHEME 44



Reagents : (a) HNO_3 (b) BzCl, py (c) $SOCl_2$, DMF (d) thiourea EtOH, Δ (e) NaOMe, MeOH (f) Br_2 (g) 1N HCl, Δ .

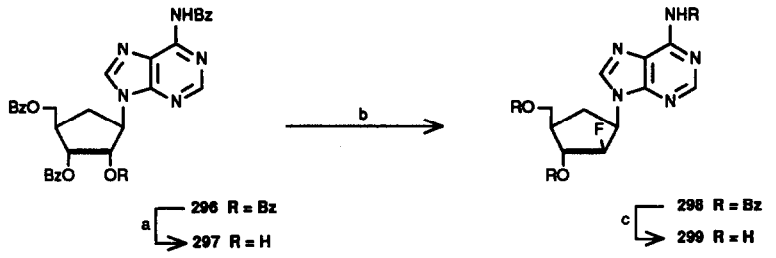
SCHEME 45



Reagents : (a) AcBr, CH_3CN (b) HBr, MeOH (c) H_2, Pd/C (d) NaOMe, MeOH .

The potent anti-herpes activity displayed by carbocyclic 2'-*ara*-fluoro-guanosine **5** lead us to investigate the introduction of the important 2'-*ara*-fluoro substituent into aristeromycin[89]. Whereas attempts to introduce this substituent into intact furanose nucleosides had previously met with very limited success we were able to efficiently prepare 2'-*ara*-fluoro-aristeromycin **299** using DAST (Scheme 46). Thus, selective 2'-debenzoylation of the tetrabenzoyl derivative **296** with potassium *t*-butoxide in THF at -35° afforded the alcohol **297** which was reacted with DAST to give the protected fluoro derivative **298** in 55% yield. Debenzoylation then completed this four stage synthesis of **299**. This derivative showed anti-herpes activity in its own right but was also a valuable intermediate in the synthesis of (+) **5** (see Section 5.2).

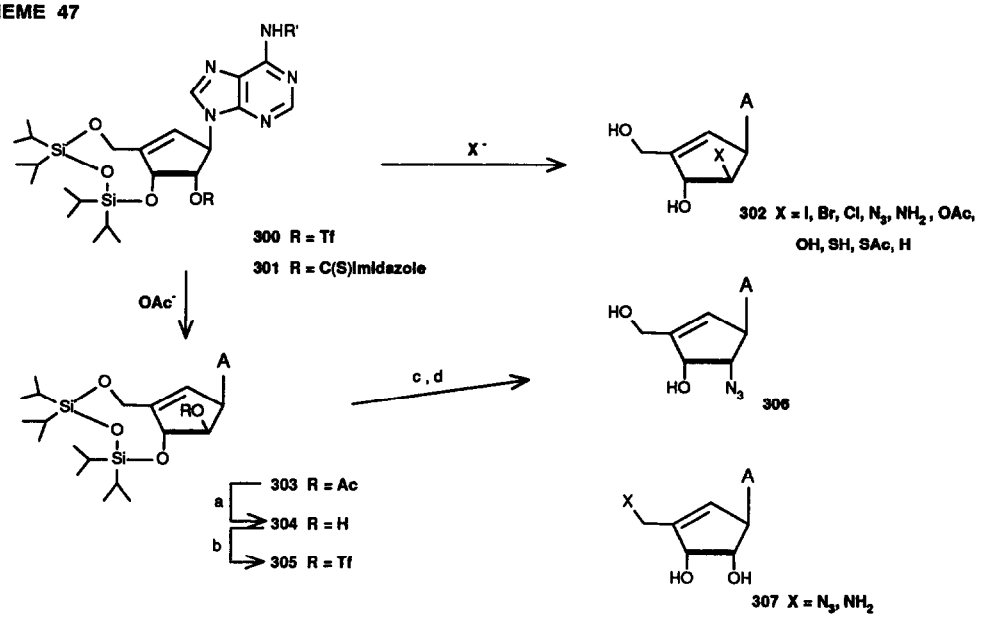
SCHEME 46



Reagents : (a) KOBu^t, THF (b) DAST (c) NH_3/MeOH .

Ueda *et al.*[90] have utilised nucleophilic displacement of a 2'-*O*-triflate moiety to gain access to a range of 2'-substituted analogues of neplanocin A (Scheme 47). The 3' and 5' hydroxyl functions of the natural product (or its N-6 benzoyl derivative) were first simultaneously blocked using 1,3-dichloro-1,1,3,3,-tetraisopropyldisiloxane (TIPS protection) allowing the 2'-hydroxyl then to be activated as the triflate **300** (R'=H or Bz). Displacement of this triflate with a variety of nucleophiles provided, after deprotection, the 2'-*ara* substituted neplanocins **302**. The 2'-deoxy derivative (**302**, X=H) was obtained *via* tri-*n*-butyl tin hydride reduction of the intermediate 2'-*ara*-bromo or iodo derivatives or alternatively *via* a similar reduction of the 2'-*ribo*-*O*-thiocarbonylimidazoyl derivative **301** (R'=Bz)[91]. An X-ray crystal structure was obtained on the 2'-mercapto derivative (**302**, X=SH) which confirmed the *arabino* configuration[92].

SCHEME 47

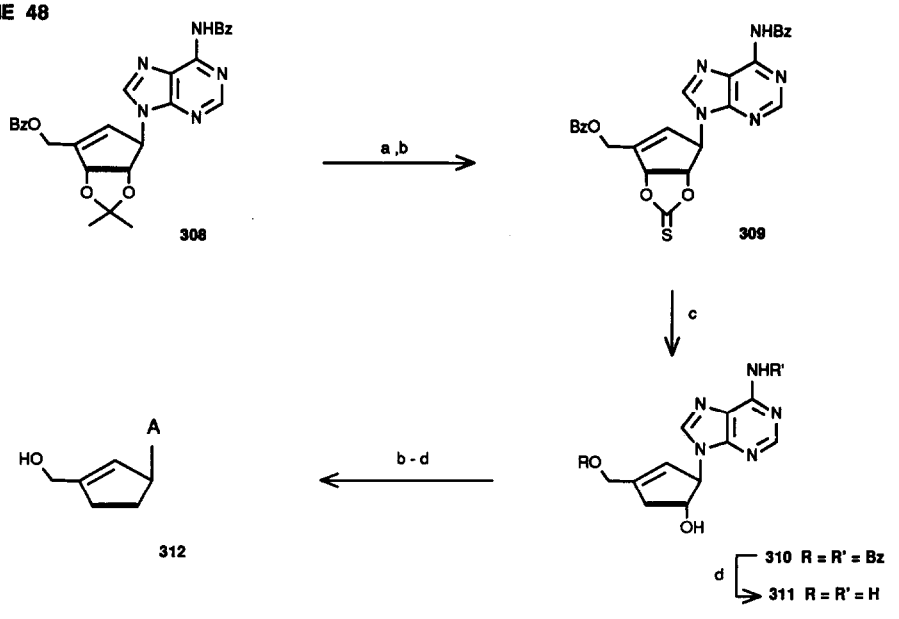


Reagents : (a) NEt_3, MeOH (b) TfCl (c) LiN_3, HMPA (d) TBAF .

Ueda[90] also detailed one example of a 2'-*ribo*-neplanocin derivative which was again obtained *via* triflate displacement (Scheme 47). Thus, deacetylation of the 2'-*ara*-acetate **303** provided the alcohol **304** which was then activated as its triflate **305**. Azide displacement of this triflate followed by desilylation afforded the 2'-*ribo*-azido derivative **306** of neplanocin A. Azido and amino substitution has also been reported at the 5' position **307** of neplanocin A[93].

3'-Deoxygenation of neplanocin A was also achieved by Ueda[91] *via* radical reduction of the 2',3'-cyclic thiocarbonate **309** (Scheme 48). Thus, removal of the isopropylidene group from the protected derivative **308** allowed **309** to be prepared using N,N'-thiocarbonyldiimidazole. Reduction of this derivative with tri-*n*-butyl tin hydride occurred selectively at the allylic C-3' centre to give the 3'-deoxy derivative **310** in 76% yield and debenzoylation then gave 3'-deoxy-neplanocin A **311**. More recently, interest in 2',3'-dideoxy nucleosides as potential anti-HIV agents prompted Marquez *et al.*[94] to further deoxygenate the intermediate **310** to provide 2',3'-dideoxy-neplanocin A **312**. A convergent route to this derivative was also described involving double deoxygenation of the cyclopentenol **151** at C-2' and C-3' followed by Mitsunobu coupling to introduce the purine base[94].

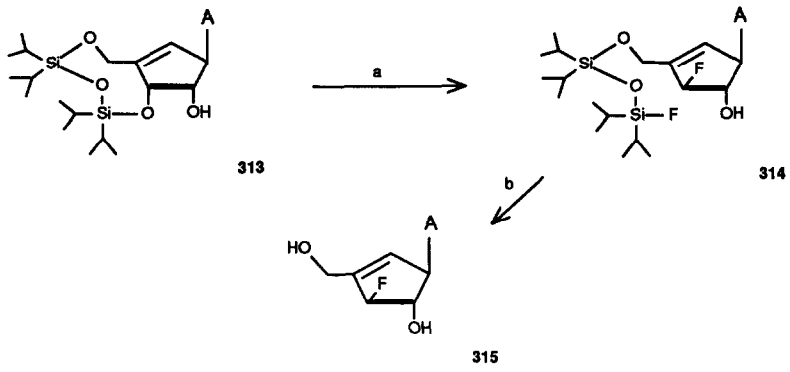
SCHEME 48



Reagents : (a) aq HCO_2H (b) N,N'-thiocarbonyldiimidazole, DMF (c) nBu_3SnH, AIBN (d) NH_3/MeOH.

An attempt by us to introduce a 2'-*ara*-fluoro substituent into neplanocin A instead afforded the 3'-*xylo*-fluoro derivative **315**[95] (Scheme 49). Thus, reaction of TIPS protected neplanocin A **313** with DAST/pyridine (1:1) in dichloromethane at 0° gave the 3'-fluoro derivative **314** in 60% yield. Whereas TIPS protection had previously proved compatible with DAST in saturated carbocyclic systems[49], cleavage at the allylic 3'-position occurred in this unsaturated derivative. Desilylation of **314** gave 3'-*xylo*-fluoro-neplanocin A **315**, the configuration being confirmed by X-ray crystallography.

SCHEME 49



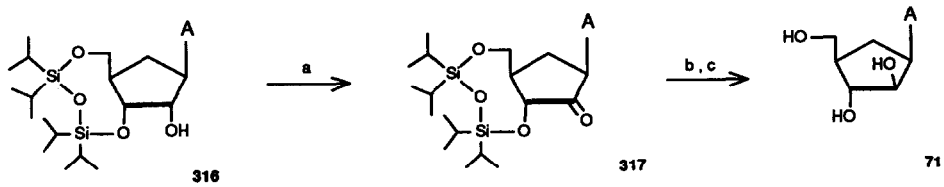
Reagents : (a) DAST, pyridine (b) TBAF

5.2 Production of chiral anti-viral derivatives from aristeromycin.

The emergence in recent years of a variety of carbocyclic *purine* nucleosides with potentially useful anti-viral activity has focused attention on the utilisation of aristeromycin **1** as starting material for the production of these derivatives in optically pure form. These studies have seen the natural product extensively modified both in the carbocyclic ring and in the purine moiety.

The most straightforward transformation was the Schering[96] conversion of **1** into its *arabino* derivative (+) cyclaridine **71**. Whereas the linear and convergent routes to **71** from D-glucose (see Sections 2.1 and 3.3) involved 30 and 19 stages respectively, this material was obtained from aristeromycin in just four stages (Scheme 50). Thus, Swern oxidation of TIPS protected aristeromycin **316** afforded the 2'-keto intermediate **317** and stereoselective reduction with *t*-butylamine-borane complex then effected the required inversion of configuration. Desilylation completed the conversion to (+) cyclaridine **71** (overall yield 43%). This process was much more efficient than an earlier one from Schering[97] in which the inversion at C-2' was effected by acetate displacement of a 2'-*O*-triflate derivative.

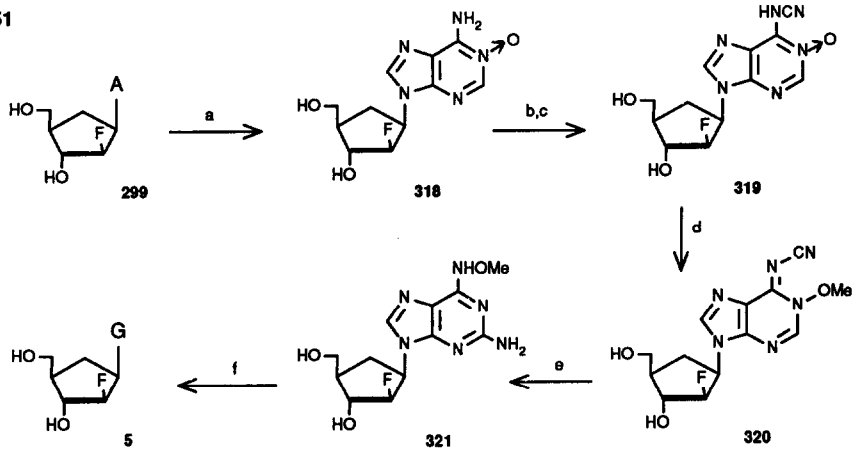
SCHEME 50



Reagents : (a) $(COCl)_2$, DMSO (b) t-butylamine, borane (c) TBAF

Transformation of aristeromycin into the potent anti-herpetic (+) carbocyclic 2'-*ara*-fluoro-guanosine **5** required introduction of the fluoro substituent and conversion of the adenine base to guanine. Having converted aristeromycin into its 2'-*ara*-fluoro derivative **299** (see Section 5.1), we completed the transformation to **5** with a six stage base interconversion[98] (Scheme 51). Treatment of **300** with mcpba gave the N-oxide **318** with was N-alkylated with cyanogen bromide to afford, after neutralisation of the intermediate tricyclic oxadiazole hydrobromide, the N-6-cyano derivative **319**. *O*-methylation of this material gave the methoxynitrile **320** which was converted into the 2-amino-6-methoxyamino derivative **321** *via* a Dimroth rearrangement. Acid hydrolysis of the methoxyamino moiety completed this 10 stage synthesis of (+) **5** from aristeromycin. Compound 5 displays remarkable *in-vivo* activity against HSV1 and HSV2 in the mouse systemic model being ≥70 x more effective than acyclovir[13].

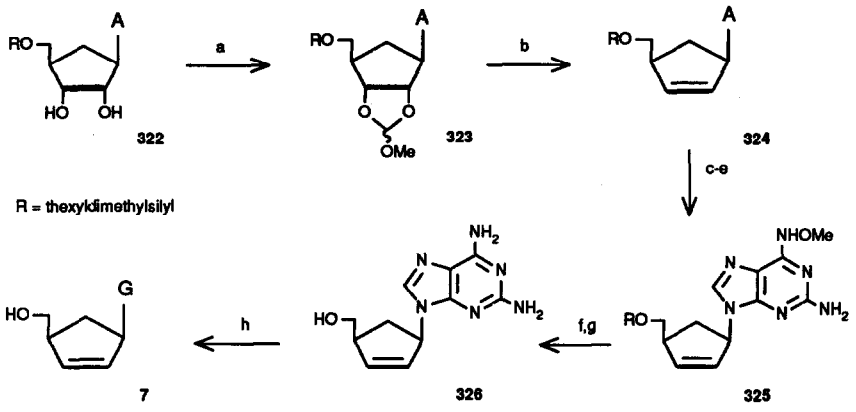
SCHEME 51



Reagents : (a) mCPBA (b) BrCN (c) NH_3,MeOH (d) MeI,NEt_3 (e) 1M NaOH then DOWEX(H^+) to pH 6.8 and EtOH reflux (f) H^+.

Two efficient syntheses of the active (-) enantiomer of the anti-HIV derivative carbovir **7** from aristeromycin **1** have also been developed in these laboratories[99]. In the first approach the 2',3'-unsaturation was introduced prior to the adenine to guanine base interconversion (Scheme 52). Selective protection of the 5'-hydroxyl function of **1** as the thexyldimethylsilyl ether **322** allowed the 2',3'-orthoester **323** to be prepared with trimethyl orthoformate and pyridinium tosylate as catalyst. Treatment of this orthoester with acetic anhydride then introduced the required 2',3'-double bond, but also acetylated the amino function. This acetyl group was removed with ammonia in methanol to afford the unsaturated adenine carbocycle **324**. The adenine moiety was modified as before to the 2-amino-6-methoxyamino derivative **325** but the acid instability of the unsaturated carbocyclic system precluded the direct hydrolysis of the 6-methoxyamino moiety. Instead this group was firstly reduced with aluminium amalgam to give, after removal of the silyl protection, the 2,6-diaminopurine **326** which was then hydrolysed using adenosine deaminase to complete this 9 stage conversion of **1** to (-) carbovir **7** (overall yield 30%). In the second approach, the use of aluminium amalgam and adenosine deaminase were avoided by introducing the 2',3' double bond after conversion of aristeromycin into carbocyclic guanosine. The overall yield for this route was slightly lower (21%). A sample of (-) **7** was converted into its 5'-triphosphate which was shown to be a powerful inhibitor of HIV reverse transcriptase.

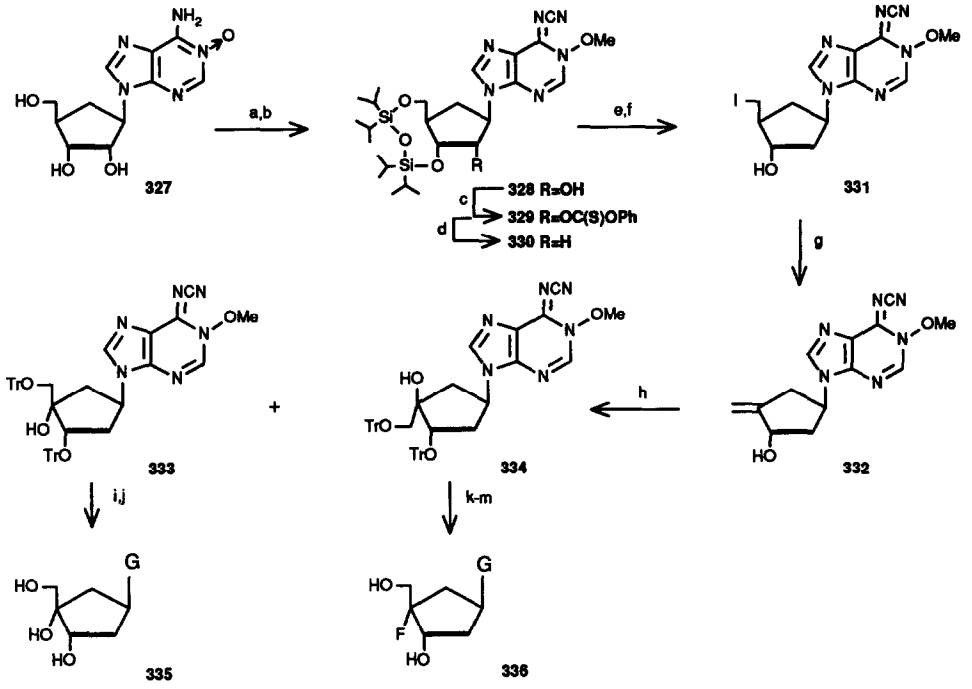
SCHEME 52



Reagents : (a) $CH(OMe)_3$,pyridinium tosylate (b) Ac_2O then NH_3,MeOH (c) mCPBA (d) BrCN,DMF then NEt_3 then MeI (e) DBU (f) Aluminium amalgam aq THF (g) H^+ (h) Adenosine deaminase .

Introduction of 4'α-hydroxyl and 4'α-fluoro substituents into carbocylic purine nucleosides has provided derivatives with potent anti-herpes activity,[18,100] and we have again exploited aristeromycin to obtain these derivatives in homochiral form. Access to the 4'α-hydroxyl **335** and 4'α-fluoro **336** derivatives of carbocyclic 2'-deoxy-guanosine was first gained by performing the modifications to the carbocyclic moiety while the purine base was at the intermediate methoxynitrile stage[100] (Scheme 53). Thus, reaction of aristeromycin N-oxide **327** with cyanogen bromide followed by *O*-methylation and TIPS protection afforded the intermediate **328** which was then deoxygenated *via* the thionocarbonate **329** to give the 2'-deoxy derivative **330**. Desilylation of **330** and reaction of the resulting diol with Rydon's reagent afforded the 5'-iodide **331** which on treatment with pyridine at 70° gave the 4',5'-olefin **332**. Osmylation of this derivative occurred predominantly from the β-face and afforded, after bis-tritylation, the separable 4'α **333** and 4'β **334** hydroxyl derivatives in a ratio of *ca* 1:6. The base interconversion was then completed by subjecting **333** to Dimroth rearrangement followed by acid hydrolysis to provide 4'α-hydroxy-2'-deoxy carbocyclic guanosine **335**. Treatment of the 4'β-hydroxy derivative **334** with DAST introduced fluorine with inversion of configuration and hence allowed 4'α-fluoro-2'-deoxy carbocyclic guanosine **336** to be obtained after Dimroth rearrangement and acid hydrolysis.

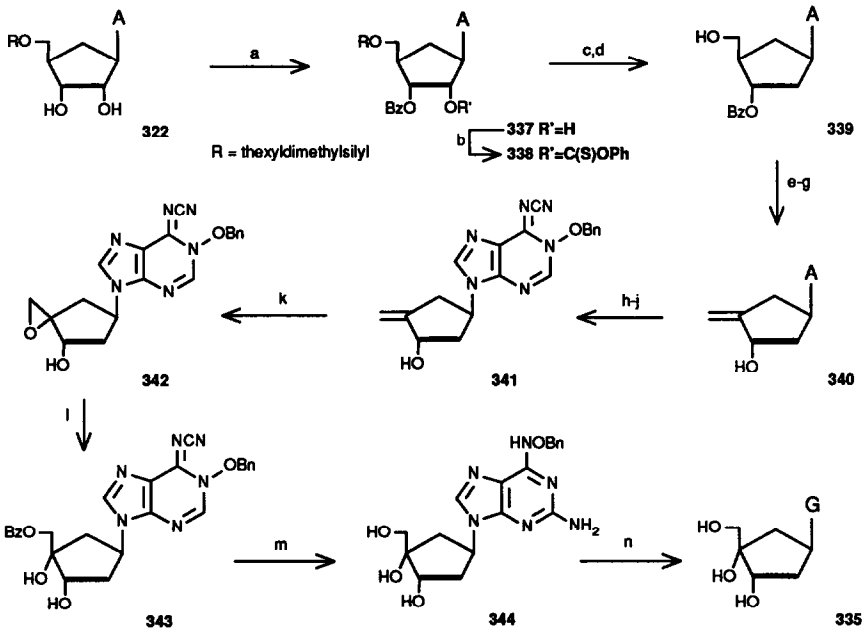
SCHEME 53



Reagents : (a) BrCN (b) MeI,NEt_3 then TIPSCl (c) PhOC(S)Cl (d) nBu_3SnH,AIBN (e) H^+ (f) $(PhO)_3P^+MeI^-$ (g) pyridine,70° (h) OsO_4 then TrCl (i) DBU (J) H^+ (k) DAST (l) DBU (m) H^+.

The 4'α-hydroxy derivative **335** shows particular promise as an anti-herpetic and therefore a second approach was sought in which the 4'-hydroxyl was introduced stereospecifically. This was accomplished by utilising the 3'-hydroxyl group to direct epoxidation of the 4',5'-double bond[101] (Scheme 54). In this approach the 2'-deoxygenation and the introduction of the 4',5'-unsaturation were performed prior to any purine base modification. Thus, treatment of the 5'-thexyldimethylsilyl ether **322** of aristeromycin with di-*n*-butyl tin oxide followed by benzoyl chloride afforded the 3'-benzoate **337** and the 2'-hydroxyl was then removed *via* the thionocarbonate **338** to give, after desilylation, the 2'-deoxy derivative **339**. Reaction of this alcohol with Rydon's reagent and base catalysed elimination of the resulting 5'-iodide afforded, after de-benzoylation, the 4',5'-olefin **340**. At this stage the adenine base was converted in three stages into the intermediate benzyloxynitrile **341**. Hydroxyl directed epoxidation of this olefin using *t*-butyl hydroperoxide and vanadyl acetylacetonate then furnished the required epoxide **342** in 98% yield. Opening of this epoxide with sodium benzoate /15-crown-5 in DMF afforded the 4'α-hydroxy-5'-benzoate **343** which underwent Dimroth rearrangement and debenzoylation to give **344** on treatment with potassium bicarbonate in refluxing aqueous ethanol. Acidic hydrolysis of the benzyloxyamino moiety completed this 15 stage synthesis of **335** from aristeromycin.

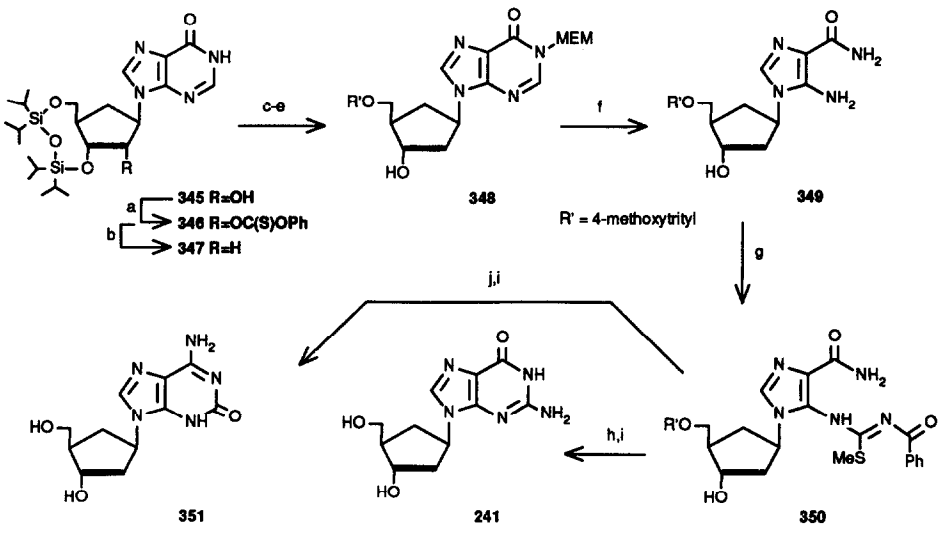
SCHEME 54



Reagents : (a) nBu_2SnO,BzCl (b) PhOC(S)Cl (c) nBu_3SnH,AIBN (d) TBAF (e) $(PhO)_3P^+MeI^-$ (f) DBN,pyridine,80° (g) Amberlite IRA 400 (OH^-) (h) mCPBA (I) BrCN (j) BnBr (k) tBuOOH,vanadyl acetylacetonate (l) NaOBz,BzOH,15-crown-5,DMF,55° (m) $KHCO_3$ (n) H^+.

An alternative adenine to guanine interconversion has been described by workers at Takeda[102]. This approach involves degradation of the purine base to an intermediate 5-aminoimidazole-4-carboxamide which is then cyclised to generate the guanine ring system. Aristeromycin **1** was converted into (+) carbocyclic 2'-deoxy-guanosine **241** using this methodology (Scheme 55). The natural product was firstly deaminated with nitrous acid to give carbocyclic inosine which was protected as its TIPS derivative **345**. The 2'-hydroxyl group was then removed *via* tri-*n*-butyl tin hydride reduction of the thionocarbonate **346** to afford the 2'-deoxy analogue **347**. The pyrimidine ring was activated by methoxymethylation at N-1 and, after desilylation and *4*-methoxytrityl protection of the 5'-hydroxyl group, the intermediate **348** was ring-opened with sodium hydroxide to give the imidazole **349**. Reaction of this amine with benzoyl isothiocyanate followed by methylation with dimethyl sulphate afforded the methylthio derivative **350**. Cyclisation of this material with 6N sodium hydroxide at reflux followed by detritylation completed the synthesis of the guanosine derivative **241**. Under milder conditions (0.1 N sodium hydroxide/aqueous ethanol/reflux) cyclisation of **350** afforded, after detritylation, the *iso*guanine derivative **351**. Carbocyclic guanosine was also prepared from aristeromycin using this methodology[102].

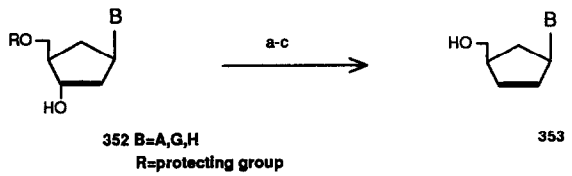
SCHEME 55



Reagents : (a) PhOC(S)Cl (b) nBu_3SnH,AIBN (c) MEMCl,NaH (d) TBAF (e) 4MeOTrCl (f) NaOH,aq EtOH (g) PhC(O)NCS then $(MeO)_2SO_2$ (h) 6N NaOH (i) aq AcOH (j) 0.1n NaOH .

Takeda have also taken their 2'-deoxy intermediates **352** and performed a second radical deoxygenation to remove the 3'-hydroxyl function and provide the 2',3'-dideoxy derivatives **353**[103] (Scheme 56).

SCHEME 56

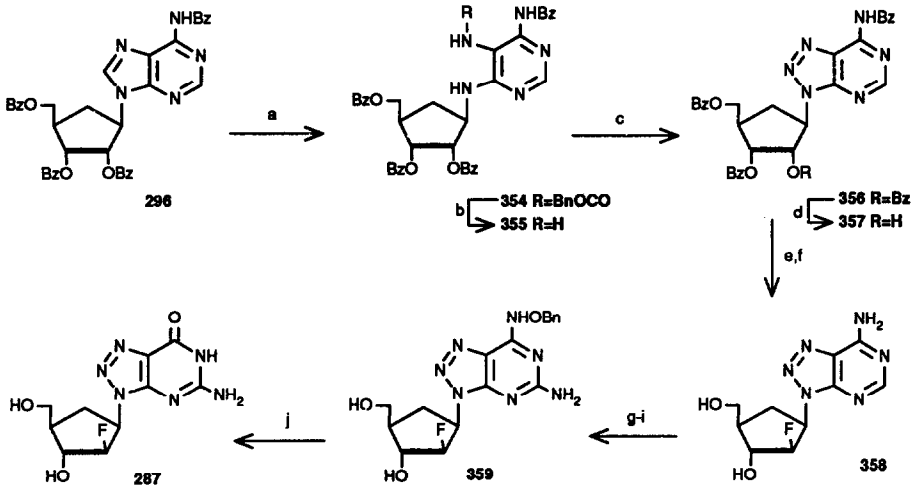


Reagents : (a) thiocarbonyl diimidazole,CH_2Cl_2 (b) nBu_3SnH,AIBN (c) deprotect

Finally, perhaps the most extensive modification yet made to aristeromycin is that developed in these laboratories to obtain (+) carbocyclic 2'-*ara*-fluoro-8-aza-guanosine **287**[87]. This synthesis required ring-opening and re-closure of both the imidazole and pyrimidine rings of the purine moiety as well as the introduction of the fluoro substituent into the carbocycle (Scheme 57). Opening of the imidazole ring was achieved by treatment of tetra-benzoyl aristeromycin **296** with dibenzylpyrocarbonate in aqueous THF to afford the protected diamine **354** in 83% yield. Hydrogenolysis of the benzyloxycarbonyl protection gave the diamine **355** which was then cyclised with nitrous acid to the protected 8-aza-aristeromycin **356**. The 2'-*ara*-fluoro substituent was again introducted *via* selective 2'-debenzoylation and reaction of the resulting alcohol **357** with DAST to afford, after debenzoylation, 2'-*ara*-fluoro-8-aza-aristeromycin **358**. The final 8-aza-adenine to 8-aza-guanine transformation exactly paralleled that described earlier for the

natural purine. Thus, conversion of **358** to its N-1 oxide followed by successive alkylations with cyanogen bromide and benzyl bromide allowed the Dimroth rearrangement to be conducted to afford the 6-benzyloxyamino derivative **359**. Acid hydrolysis completed the conversion to the (+) 8-aza-guanine **287**. Alternatively, the intermediate **358** was obtained by performing the adenine to 8-aza-adenine conversion on the protected 2'-*ara*-fluoro-aristeromycin **298**.

SCHEME 57



Reagents : (a) $O(CO_2Bn)_2$,aq THF (b) H_2,Pd/C (c) HNO_2,aq THF (d) $KOBu^t$,THF,-50° (e) DAST (f) NaOMe,THF,MeOH (g) mCPBA (h) BrCN,DMF then BnBr,NEt_3 (i) DBU (j) H^+ .

6. SUMMARY AND OUTLOOK

The last 5 years have seen carbocyclic nucleosides become established as an important class of anti-tumour and anti-viral agents. Whereas replacement of the furanose oxygen by carbon was once perceived as simply a means of improving metabolic stability, derivatives such as carbocyclic 2'-*ara*-fluoro-guanosine **5**[12,13] and carbovir **7**[14] have been discovered with potent anti-viral activity which is *not* shown by their furanose counterparts. The need to produce these and other carbocyclic derivatives enantiomerically pure has resulted in the wide variety of approaches described in this review. Whilst traditional linear approaches have continued to be explored, attention has focused increasingly on the development of more efficient and versatile convergent routes. Enzymes have also featured strongly in this area both to provide chiral intermediates and also to resolve intact carbocyclic nucleosides. Finally, the readily available natural product aristeromycin has emerged as an important starting material for the production of chiral carbocyclic purine derivatives.

Looking to the future, the inherent metabolic stability of carbocyclic nucleosides seems certain to ensure continued interest in this class of nucleoside analogue, and this interest has already begun to extend beyond anti-tumour and anti-viral applications. For example, adenosine agonists and antagonists display a variety of important CNS and cardiovascular actions,[104] and in this area carbocyclic A_2 agonists show promise as anti-hypertensives[48]. Also neplanocin A has been shown to posses anti-malarial properties,[105] and certain saturated carbocyclic derivatives have been claimed[106] to be active against *Pneumocystis carinii*, a major cause of death in AIDS patients. The availability of chiral carbocyclic nucleosides has now opened the way for carbocyclic *oligonucleotides* to be explored with possible exciting applications in the field of genetic engineering[107]. In this respect, fluoro-carbocyclic derivatives may prove valuable as n.m.r. probes of nucleic acid structure.

Elucidation[29] of the biosynthesis of aristeromycin and the neplanocins may allow novel analogues to be obtained from feeding experiments, while selective blocking of the biosynthesis could provide useful chiral intermediates. Finally, the recent discovery of the novel adenosine deaminase inhibitor adecypenol[108], the cyclopentenyl analogue of coformycin, suggests that further novel carbocyclic derivatives of biological importance are likely to be isolated from natural sources and these will undoubtedly present yet more challenges to the synthetic organic chemist.

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REFERENCES

1. Isono, K. *J. Antibiot.* **1988**, *41*, 1711.
2. (a) MacCoss, M.; Robins, M.J.; In *Chemistry of Antitumour Agents;* Wilman, D.E.V., Ed.; Blackie and Son: U.K., 1990; p261. (b) Robins, R.K.; Kini, G.D. *Ibid;* p299.
3. Robins, R.K.; Revankar, G.R.; In *Antiviral Drug Development;* De Clercq, E.; Walker, R.T., Eds.; Plenum: New York, 1988; p11.
4. Shealy, Y.F.; Clayton, J.D. *J. Am. Chem. Soc.* **1966**, *88*, 3885.
5. Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255.
6. Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *Ibid.* **1981**, *34*, 359.
7. Yaginuma, S.; Tsujino, M.; Muto, N.; Otani, M.; Hayashi, M.; Ishimura, F.; Fujii, T.; Watanabe, S.; Matsuda, T.; Watanabe, T.; Abe, J. *Curr. Chemother. Infect. Dis., Int. Congr.* **1980**, *2*, 1558.
8. Tsujino, M.; Yaginuma, S.; Fujii, T.; Hayano, K.; Matsuda, T.; Watanabe, T.; Abe, J. *Ibid.* **1980**, *2*, 1559.
9. Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049.
10. Marquez, V.E.; Lim, M-I. *Med. Res. Rev.* **1986**, *6*, 1.
11. Boehme, R.E.; Storer, R.; Williamson, C.; Clemens, I.R.; Cameron, J.M. *Abstracts of Papers,* Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, October 1990; Abstract 1088.
12. Borthwick, A.D.; Butt, S.; Biggadike, K.; Exall, A.M.; Roberts, S.M.; Youds, P.M.; Kirk, B.E.; Booth, B.R.; Cameron, J.M.; Cox, S.W.; Marr, C.L.P.; Shill, M.D. *J. Chem. Soc., Chem. Commun.* **1988**, 656.
13. Borthwick, A.D.; Kirk, B.E.; Biggadike, K.; Exall, A.M.; Butt, S.; Roberts, S.M.; Knight, D.J.; Coates, J.A.V.; Ryan, D.M. *J. Med. Chem.* **1991**, *34*, 907.
14. Vince, R.; Hua, M. *Ibid.* **1990**, *33*, 17.
15. Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ichikawa, Y-I.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1854.
16. Norbeck, D.W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J.J.; Erickson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. *J. Med. Chem.* **1990**, *33*, 1281.
17. Bodenteich, M.; Marquez, V.E. *Tetrahedron Lett.* **1990**, *31*, 5977.
18. Biggadike, K.; Borthwick, A.D. *J. Chem. Soc. Chem. Commun.* **1990**, 1380.
19. Biggadike, K.; Borthwick, A.D.; Exall, A.M.; Kirk, B.E.; Roberts, S.M.; Youds, P.; Slawin, A.M.Z.; Williams, D.J. *Ibid.* **1987**, 255.
20. Borthwick, A.D.; Evans, D.N.; Kirk, B.E.; Biggadike, K.; Exall, A.M.; Youds, P.; Roberts, S.M.; Knight, D.J.; Coates, J.A.V. *J. Med. Chem.* **1990**, *33*, 179.
21. Highcock, A.M.; Hilpert, H.; Myers, P.L.; Roberts, S.M.; Storer, R. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1127.
22. Levitt, M.S.; Newton, R.F.; Roberts, S.M.; Willetts, A.J. *J. Chem Soc., Chem. Commun.* **1990**, 619.
23. Cheikh, A.B.; Craine, L.E.; Recher, S.G.; Zemlicka, J. *J. Org. Chem.* **1988**, *53*, 929.
24. Madhavan, G.V.B.; McGee, D.P.C.; Rydzewski, R.M.; Boehme, R.; Martin, J.C.; Prisbe, E.J. *J. Med. Chem.* **1988**, *31*, 1798.
25. Béres, J.; Sági, Gy.; Tömösközi, I.; Gruber, L.; Baitz-Gács, E.; Otvös, L.; De Clercq, E. *Ibid.* **1990**, *33*, 1353.
26. Biggadike, K.; Borthwick, A.D.; Exall, A.M. *J. Chem. Soc., Chem. Commun.* **1990**, 458.
27. Coe, D.M.; Myers, P.L.; Parry, D.M.; Roberts, S.M.; Storer, R. *Ibid.* **1990**, 151.
28. Noble, S.A.; Beddall, N.E.; Beveridge, A.J.; Marr, C.L.P.; Mo, C.L.; Myers, P.L.; Penn, C.R.; Storer, R.; Woods, J.M. *Nucleosides Nucleotides* **1991**, *10*, 487.
29. (a) Parry, R.J.; Bornemann, V.; Subramanian, R. *J. Am. Chem. Soc.* **1989**, *111*, 5819. (b) Parry, R.J.; Haridas, K.; De Jong, R.; Johnson, C.R. *Tetrahedron Lett.* **1990**, *31*, 7549. (c) Parry R.J.; Haridas, K.; De Jong, R.; Johnson, C.R. *J. Chem. Soc. Chem. Commun.* **1991**, 740.
30. Herdewijn, P.; Balzarini, J.; De Clercq, E.; Vanderhaeghe, H. *J.Med. Chem.* **1985**, *28*, 1385.
31. Secrist, J.A. III; Montgomery, J.A.; Shealy, Y.F.; O'Dell, C.A.; Clayton, S.J. *Ibid.* **1987**, *30*, 746.
32. Ikbal, M.; Cerceau, C.; Le Goffic, F.; Sicsic, S. *Eur. J. Med. Chem.* **1989**, *24*, 415.
33. Shaw, G.; Warrener, R.N. *J. Chem. Soc.* **1958**, 157.
34. Arai, Y.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett.* **1988**, *29*, 6143.

35. Arai, Y.; Hayashi, Y.; Yamamoto, M.; Takayema, H.; Koizumi. T. *J. Chem. Soc., Perkin Trans. I* **1988**, 3133.
36. Helmchen, G.; Hady, A.F.A.; Hartmann, H.; Karge, R.; Krotz, A.; Sartor, K.; Urmann, M. *Pure Appl. Chem.* **1989**, *61*, 409.
37. Sicsic, S.; Ikbal, M.; Le Goffic, F. *Tetrahedron Lett.* **1987**, *28*, 1887.
38. Madhavan, G.V.B.; Martin, J.C. *J. Org. Chem.* **1986**, *51*, 1287.
39. Tadano, K.; Hoshino, M.; Ogawa, S.; Suami, T. *Ibid.* **1988**, *53*, 1427.
40. Tadano, K.; Kimura, H.; Ogawa, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1355.
41. Otvös, L.; Béres, J.; Sági, Gy.; Tömösközi, I.; Gruber, L. *Tetrahedron Lett.* **1987**, *28*, 6381.
42. Béres, J.; Sági, Gy.; Baitz-Gács, E.; Tömösközi, I.; Otvös, L. *Tetrahedron* **1988**, *44*, 6207.
43. Béres, J.; Sági, Gy.; Tömösközi, I.; Gruber, L.; Gulácsi. E.; Otvös, L. *Tetrahedron Lett.* **1988**, *29*, 2681.
44. Béres, J.; Sági, Gy.; Baitz-Gács, E.; Tömösközi, I.; Gruber, L.; Otvös, L. *Tetrahedron* **1989**, *45*, 6271.
45. (a) Balzarini, J.; Baumgartner, H.; Bodenteich, M.; De Clercq, E.; Griengl, H. *J. Med. Chem.* **1989**, *32*, 1861. (b) Bodenteich, M.; Faber, K.; Penn, G.; Griengl, H. *Nucleosides Nucleotides* **1987**, *6*, 233.
46. Baumgartner, H.; Bodenteich, M.; Griengl, H. *Tetrahedron Lett.* **1988**, *29*, 5745.
47. Bodenteich, M.; Griengl, H. *Ibid.* **1987**, *28*, 5311.
48. (a) Chen, J.; Grim, M.; Rock, C.; Chan, K. *Ibid.* **1989**, *30*, 5543. (b) Chen, J.; Hutchison, A.J. U.S. Patent Appl. 4, 954,504, 1990.
49. Biggadike, K.; Borthwick, A.D.; Evans, D.; Exall, A.M.; Kirk, B.E.; Roberts, S.M.; Stephenson, L.; Youds, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 549.
50. Arita, M.; Okumoto, T.; Saito, T.; Hoshino, Y.; Fukukawa, K.; Shuto, S.; Tsujino, M.; Sakakibara, H.; Ohno, M. *Carbohydr. Res.* **1987**, *171*, 233.
51. Marquez, V.E.; Lim, M-I.; Tseng, C.K.H.; Markovac, A.; Priest, M.A.; Khan, M.S.; Kaskar, B. *J. Org. Chem.* **1988**, *53*, 5709.
52. Lim, M-I.; Moyer, J.D.; Cysyk, R.L.; Marquez, V.E. *J. Med. Chem.* **1984**, *27*, 1536.
53. Marquez, V.E.; Lim, M-I.; Treanor, S.P.; Plowman, J.; Priest, M.A.; Markovac, A.; Khan, M.S.; Kaskar, B.; Driscoll, J.S. *Ibid.* **1988**, *31*, 1687.
54. Taylor, S.J.C.; Sutherland, A.G.; Lee, C.; Wisdom, R.; Thomas, S.; Roberts, S.M.; Evans, C. *J. Chem. Soc., Chem. Commun.* **1990**, 1120.
55. Tseng, C.K.H.; Marquez, V.E. *Tetrahedron Lett.* **1985**, *26*, 3669.
56. Tseng, C.K.H.; Marquez, V.E.; Fuller, R.W.; Goldstein, B.M.; Haines, D.R.; McPherson, H.; Parsons, J.L.; Shannon, W.M.; Arnett, G.; Hollingshead, M.; Driscoll, J.S. *J. Med. Chem.* **1989**, *32*, 1442.
57. Copp, R.R.; Marquez, V.E. *Ibid.* **1991**, *34*, 208.
58. Bestmann, H.J.; Roth, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 99.
59. Medich, J.R.; Kunnen, K.B.; Johnson, C.R. *Tetrahedron Lett.* **1987**, *28*, 4131.
60. Johnson, C.R.; Penning, T.D. *J. Am. Chem. Soc.* **1986**, *108*, 5655.
61. Deardorff, D.R.; Shambayati, S.; Myles, D.C.; Heerding, D. *J. Org. Chem.* **1988**, *53*, 3614.
62. Ali, S.M.; Ramesh, K.; Borchardt, R.T. *Tetrahedron Lett.* **1990**, *31*, 1509.
63. Wolfe, M.S.; Anderson, B.L.; Borcherding, D.R.; Borchardt, R.T. *J. Org. Chem.* **1990**, *55*, 4712.
64. Borcherding, D.R.; Scholtz, S.A.; Borchardt, R.T. *Ibid.* **1987**, *52*, 5457.
65. De Clercq, E.; Cools, M.; Balzarini, J.; Marquez, V.E.; Borcherding, D.R.; Borchardt, R.T.; Drach, J.C.; Kitaoka, S.; Konno, T. *Antimicrob. Agents Chemother.* **1989**, *33*, 1291.
66. Bestmann, H.J.; Roth, D. *Synlett.* **1991**, 751.
67. Ichikawa, Y.; Narita, A.; Shiozawa, A.; Hayashi, Y.; Narasaka, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1919.
68. Bisacchi, G.S.; Braitman, A.; Cianci, C.W.; Clark, J.M.; Field, A.K.; Hagen, M.E.; Hockstein, D.R.; Malley, M.F.; Mitt, T.; Slusarchyk, W.A.; Sundeen, J.E.; Terry, B.J.; Toumari, A.V.; Weaver, E.R.; Young, M.G.; Zahler, R. *J. Med. Chem.* **1991**, *34*, 1415.
69. Hsiao, C-N.; Hannick, S.M. *Tetrahedron Lett.* **1990**, *31*, 6609.

70. Doering, W. von E.; Roth, H.D. *Tetrahedron* **1970**, *26*, 2825.
71. Jones, M.F.; Roberts, S.M. *J. Chem. Soc., Perkin Trans. I* **1988**, 2927.
72. Scopes, D.I.C.; Newton, R.F.; Ravenscroft, P.; Cookson, R.C. Eur. Pat. 0104 066, 1988.
73. Cookson, R.C.; Dudfield, P.J.; Newton, R.F.; Ravenscroft, P.; Scopes, D.I.C.; Cameron, J.M. *Eur. J. Med. Chem.* **1985**, *20*,375.
74. Biggadike, K.; Borthwick, A.D.; Exall, A.M.; Kirk, B.E.; Roberts, S.M.; Youds, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1083.
75. Myers, P.I. Eur. Par. Appl. 0 418 007, 1991.
76. Borthwick, A.D.; Biggadike, K.; Exall, A.M. unpublished results.
77. Jones, M.F.; Myers, P.L.; Robertson, C.A.; Storer, R.; Williamson, C. *J. Chem. Soc., Perkin Trans I* **1991**, 2479.
78. Baumgartner, H.; Marschner, C.; Pucher, R.; Griengl, H. Tetrahedron Lett. **1991**, *32*, 611.
79. Yoshikawa, M.; Nakae, T.; Cha, B.C.; Yokokawa, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1989**, *37*, 545.
80. Yoshikawa, M.; Okaichi, Y.; Cha, B.C.; Kitagawa, I. *Tetrahedron* **1990**, *46*, 7459.
81. Kitagawa, I.; Cha, B.C.; Nakae, T.; Okaichi, Y.; Takinami, Y.; Yoshikawa, M. *Chem. Pharm. Bull.* **1989**, *37*, 542.
82. Yoshikawa, M.; Cha, B.C.; Nakae, T.; Kitagawa, I. *Ibid.* **1988**, *36*, 3714.
83. Yoshikawa, M.; Cha, B.C.; Okaichi, Y.; Kitagawa, I. *Ibid.* **1988**, *36*, 3718.
84. Yoshikawa, M.; Cha, B.C.; Okaichi, Y.; Takinami, Y.; Yokokawa, Y.; Kitagawa, I. *Ibid.* **1988**, *36*, 4236.
85. Wolfenden, R. *J. Am. Chem. Soc.* **1966**, *88*, 3157.
86. Vince, R.; Brownell, J. *Biochem. Biophys. Res. Commun.* **1990**, *168*, 912.
87. Borthwick, A.D.; Biggadike, K.; Kirk, B.E.; Storer, R.; Weir, N.G.; Baxter, A.D.; Mo, C.L. Eur. Pat. Appl. 0 410 660, 1991.
88. Marumoto, R.; Yoshioka, Y.; Furukawa, Y.; Honjo, M. *Chem. Pharm. Bull.* **1976**, *24*, 2624.
89. Biggadike, K.; Borthwick, A.D.; Exall, A.M.; Kirk, B.E.; Ward, R.A. *J. Chem. Soc., Chem. Commun.* **1988**, 898.
90. Fukukawa, K.; Ueda, T.; Hirano, T. *Chem. Pharm. Bull.* **1983**, *31*, 1582.
91. Fukukawa, K.; Ueda, T.; Hirano, T. *Ibid.* **1983**, *31*, 1842.
92. Kinoshita, K.; Hayashi, M.; Hirano, T.; Nakatsu, K.; Fukukawa, K.; Ueda, T. *Nucleosides Nucleotides* **1983**, *2*, 319.
93. Toyo Jozo Co. Japanese Patent 58 183 691, 1983; *Chem. Abstr.* **1984**, *100*, 103821f.
94. Marquez, V.E.; Tseng, C.K.H.; Treanor, S.P.; Driscoll, J.S. *Nucleosides Nucleotides* **1987**, 6, 239.
95. Borthwick, A.D.; Biggadike, K. *Tetrahedron Lett.* in press.
96. Nagabhushan, T.L.; Schumacher, D.P. Eur. Pat. Appl. 0 246 605, 1987.
97. Nagabhushan, T.L.; Krepski, L.; Reichert, P.; Tsai, H.; Ostrander, M.R.; Lieberman, M.; Schwartz, J.; Miller, G.H. *Abstracts of Papers*, 185th ACS National Meeting, Seattle, March 1983; CARB 27.
98. Borthwick, A.D.; Biggadike, K.; Holman, S.; Mo, C.L. *Tetrahedron Lett.* **1990**, *31*, 767.
99. Exall, A.M.; Jones, M.F.; Mo, C.L.; Myers, P.L.; Paternoster, I.L.; Singh, H.; Storer, R.; Weingarten, G.G.; Williamson, C.; Brodie, A.C.; Cook, J.; Lake, D.E.; Meerholz, C.A.; Turnbull, P.J.; Highcock, R.M. *J. Chem. Soc., Perkin Trans I* **1991**, 2467.
100. Borthwick, A.D.; Biggadike, K. Eur. Pat. Appl. 0 345 076, 1989.
101. Storer, R.; Paternoster, I.L.; Borthwick, A.D.; Biggadike, K. Eur. Pat. Appl. 0 430 518, 1991.
102. (a) Marumoto, R.; Taniyama, Y.; Fukuda, T. *Nucleic Acids Res. Symp. Ser.* **1987**, *18*, 37. (b) Taniyama, Y.; Marumoto, R. Eur. Pat. Appl. 0 219 838, 1986/7.
103. Taniyama, Y.; Hamana, T.; Marumoto, R.; Yamamoto, N. Eur. Pat. Appl. 0 236 935, 1987.
104. Williams, M. *Ann. Rev. Pharmacol. Toxicol.* **1987**, *27*, 315.
105. Whaun, J.M.; Miura, G.A.; Brown, N.D.; Gordon, R.K.; Chiang, P.K. *J. Pharmacol. Exper. Ther.* **1986**, *236*, 277.
106. Daluge, S.M. Eur. Pat. Appl. 0 368 640, 1990.
107. (a) Perbost, M.; Lucas, M.; Chavis, C.; Pompon, A.; Baumgartner, H.; Rayner, B.; Griengl, H.; Imbach, J-L. *Biochem. Biophys. Res. Commun.* **1989**, *165*, 742. (b) Szemző, A.; Szécsi, J.; Sági, J.; Otvös, L. *Tetrahedron. Lett.* **1990**, *31*, 1463. (c) Sági, J.; Szemző, A.; Szécsi, J.; Otvös, L. *Nucleic Acids Res.* **1990**, *18*, 2133. (d) Miyashita, O.; Taniyama, Y.; Fujisawa, Y.; Marumoto, R. *Nucleic Acids Res. Symp. Ser.* **1985**, *16*, 141.
108. (a) Omura, S.; Tanaka, H.; Kuga, H.; Imamura, N. *J. Antibiot.* **1986**, *39*, 309. (b) Tanaka, H.; Kawakami, T.; Yang, Z.B.; Komiyama, K.; Omura, S. *Ibid.* **1989**, *42*, 1722.