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New Developments in the Enantioselective Synthesis of Cyclopentyl Carbocyclic Nucleosides

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1. INTRODUCTION

Nucleosides are fundamental building blocks of biological systems which are sequentially phosphorylated by kinases into their mono-, di-, and triphosphates.[1,2] The resultant nucleotides are processed

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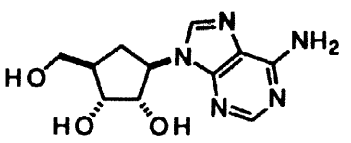
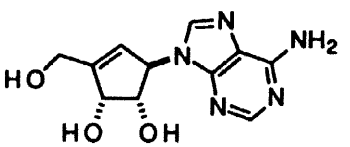
into nucleic acids by polymerases.[1,2] The search for nucleoside analogs which function as non-toxic, selective inhibitors of kinases and polymerases for the control of viral diseases and cancer has been the subject of intense research.[3-6] Nucleoside analogs which are good substrates for cellular kinases, but resistant to other host enzymes such as phosphorylases which cleave the glycosidic bond of natural nucleosides are essential for the development of useful therapeutic agents. One important discovery has been that replacement of the oxygen in the sugar portion of the nucleoside with a methylene (CH_2) unit results in carbocyclic nucleoside analogs which are highly resistant to phosphorylases.[7]

While the carbocyclic analog of adenosine was first described by Shealy[8] in 1966 it was the discovery that the natural carbocyclic nucleosides aristeromycin **1**[9] and neplanocin A **2**[10] display antibiotic and antitumor activity which sparked the search for other carbocyclic nucleoside analogs with biological activity. Subsequently, other synthetic carbocyclic nucleosides with important therapeutic properties were discovered. Particularly carbovir **3**,[11] the structurally related 1592U89 **4**[12] as well as BCA **5**[13] have been shown to be inhibitors of the human immunodeficiency virus (HIV), the causative agent for the acquired immune deficiency syndrome (AIDS). Phase III clinical trials indicate that 1592U89 succinate reduces viral load in HIV infected patients by >99% after 12 weeks of dosing. Of equal importance are the significant increases in CD4 counts (average increase from baseline of 352 to 450 after 12 weeks of dosing) and an absence of toxic side effects in the patients treated.[14]

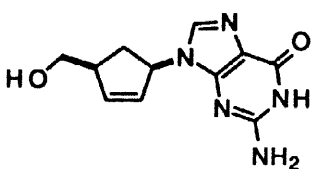
Figure 1



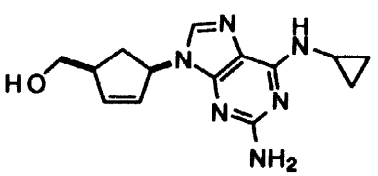
1 aristeromycin



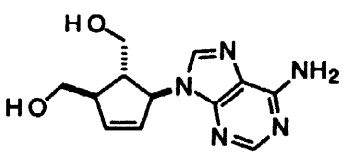
2 neplanocin A



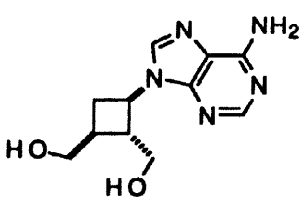
3 carbovir



4 1592U89 (abacavir)



5 (–)-BCA



6 Cyclobut A

While the exact mechanisms of these antivirals are not completely understood, they are prodrugs which are sequentially phosphorylated by cellular kinases to the corresponding triphosphates.[15] The triphosphate is incorporated into the replicating viral DNA chain by HIV reverse transcriptase, and chain termination results since there is no 3' hydroxyl for further elongation of the chain.[16] In addition, the 5' triphosphate or the oligonucleotide may act as a competitive inhibitor of the reverse transcriptase.

Although promising new antiviral agents have been discovered, the search for potent inhibitors of a variety of viral infective agents continues.[3-6] There is a need for new inhibitors of HIV, cytomegalovirus (CMV), herpes simplex virus type 1 (HSV-1), type 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and hepatitis B virus (HBV), since viral opportunistic infections of these types can prove fatal to patients

whose immune systems are compromised by AIDS or other causes.[17] The intense search for clinically useful carbocyclic nucleosides has resulted in a wealth of new approaches for their synthesis, and most importantly, their enantioselective synthesis. Recent developments in the area of enantioselective approaches to carbocyclic nucleosides is the subject of this review. This review covers the literature from the beginning of 1994 to mid 1997 with selected earlier examples included for historical reference or because of special significance. The reader is referred to other excellent earlier reviews for coverage of the literature prior to 1994.[3-6]

2 METHODS FOR COUPLING THE HETEROCYCLIC BASE WITH THE CARBOCYCLIC PSEUDO SUGAR

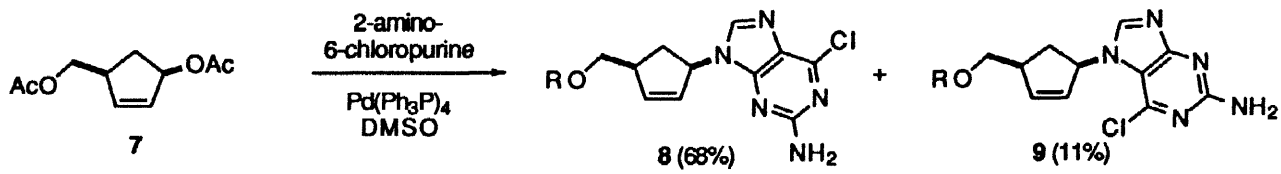
There are two fundamental approaches for the construction of carbocyclic nucleosides: 1) convergent attachment of an intact heterocyclic base with an appropriately functionalized carbocyclic ring by substitution and 2) linear construction of the heterocycle from an amine substituent on the carbocycle.

2.1 Direct Coupling of the Base with the Carbocyclic Pseudo Sugar

Direct substitution can be accomplished by several methods: 1) palladium catalyzed displacement of an allylic ester or carbonate; 2) Mitsunobu coupling with a cycloalkanol; 3) nucleophilic displacement of a halide ion or activated hydroxyl such as a mesylate, tosylate, or triflate; 4) ring opening of an epoxide; or 5) Michael addition to an olefin activated by a carbonyl or other electron withdrawing group. Direct coupling of a heterocyclic base provides a more convergent approach to carbocyclic nucleosides, but introduces the problem of regioselectivity with respect to attack by the base. With purines, attachment at the N9, N7 and N3 nitrogens is possible and is often observed as is the case in natural nucleoside synthesis. This issue will be addressed in more detail later. Adenine is often attached directly, although protection of the 6-amino group is sometimes beneficial. Guanine has a low solubility in organic solvents and is typically introduced by attachment of 2-amino-6-chloropurine followed by hydrolytic displacement of the 6-chloride.[18]

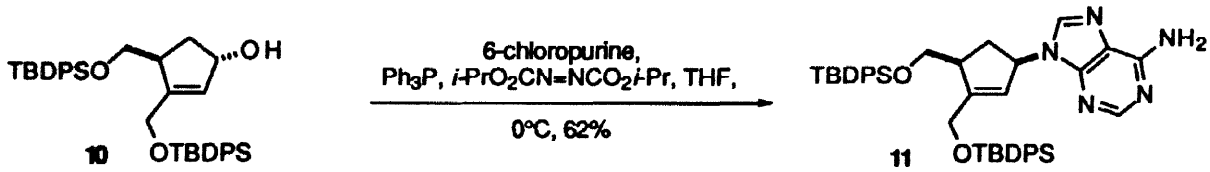
2.1.1 Palladium catalyzed displacement of an allylic ester or carbonate. One highly useful strategy for the convergent coupling of the two fragments of carbocyclic nucleosides is the palladium (0) catalyzed substitution of allylic esters and carbonates (Scheme 1). The reaction, which was pioneered by Trost,[19] proceeds with retention of configuration, although allylic rearrangement can result due to attack of the heterocyclic anion at the more sterically accessible end of the allyl metal complex. Palladium catalyzed couplings have been widely employed in carbocyclic nucleoside synthesis, particularly for dideoxy analogs such as carbovir and 1592U89 (abacavir).[20] A variety of Pd(0) catalysts have been employed.

Scheme 1



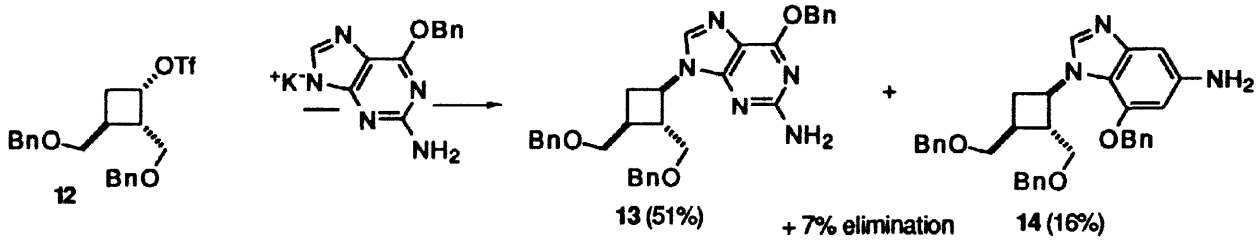
2.1.2. Mitsunobu coupling. Another of the most useful and common methods for the connection of the carbocyclic sugar and the heterocyclic base is the Mitsunobu coupling (Scheme 2).[21] Activation of a hydroxyl by a complex formed from an azodicarboxylate and triphenylphosphine allows direct substitution of the alcohol.[22] The relative high acidity of the the NH on the aromatic base makes it a useful partner in the Mitsunobu coupling.

Scheme 2



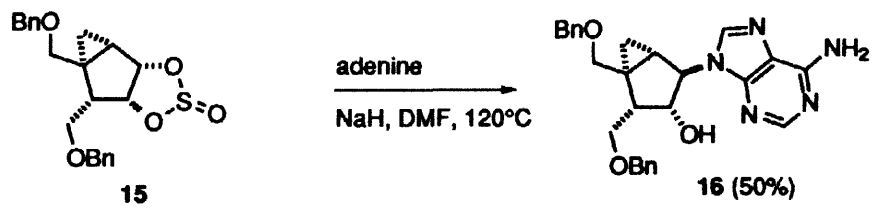
2.1.3. Nucleophilic displacement of a halide ion or activated alcohol. Direct S_N2 displacements of halides, but more commonly mesylates, tosylates and triflates have been utilized in coupling of the carbocycle to the heterocycle as illustrated in the synthesis of the carbocyclic oxetanocin analogue **13** in Scheme 3.[23] Competing elimination is a potential complication in this approach, particularly since higher temperatures are often required to achieve substitution.

Scheme 3



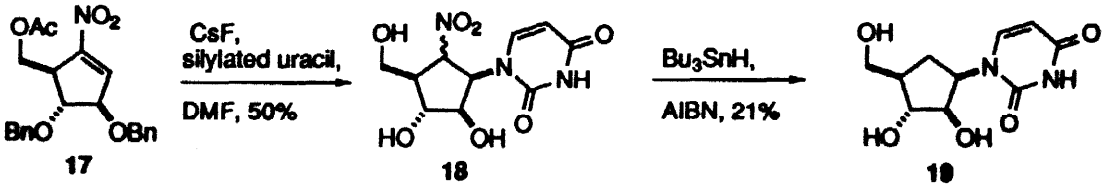
2.1.4. Ring opening of an epoxide or cyclic sulfate. Epoxides, cyclic sulfates and sulfites are useful electrophiles for the coupling of the key fragments in carbocyclic nucleoside synthesis as shown in Scheme 4.[24]

Scheme 4



2.1.5 Michael addition to an activated olefin. A limited number of examples of Michael additions for coupling of heterocycle and carbocycle have been reported. Nitro olefins function well in this regard as shown in Scheme 5.[25]

Scheme 5

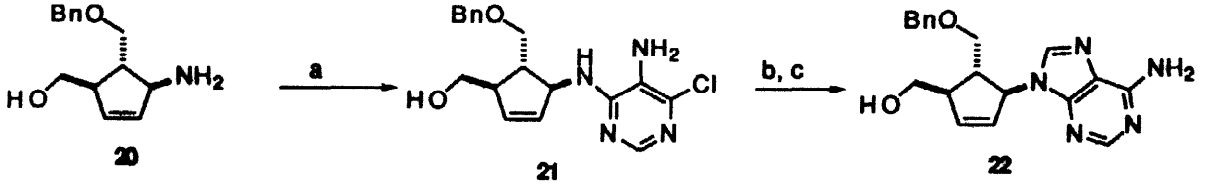


2.2 Construction of the heterocyclic base from an Aminocycloalkane.

The heterocyclic base of carbocyclic nucleosides can also be introduced through a linear strategy in which an amino group on the carbocycle is used to construct a heterocycle.[18,26-29] The amino group becomes the N9 of a purine moiety or the N1 of a pyrimidine.

2.2.1. Synthesis of purines. The synthesis of adenine derivatives is accomplished by reaction of a substituted cycloalkylamine with 5-amino-4,6-dichloropyrimidine to prepare the cycloalkylaminopyrimidine which can be condensed with triethyl or trimethyl orthoformate to provide the 6-chloropurine (Scheme 6). Displacement of the chloride with ammonia provides the adenine derivative in good overall yields.[26]

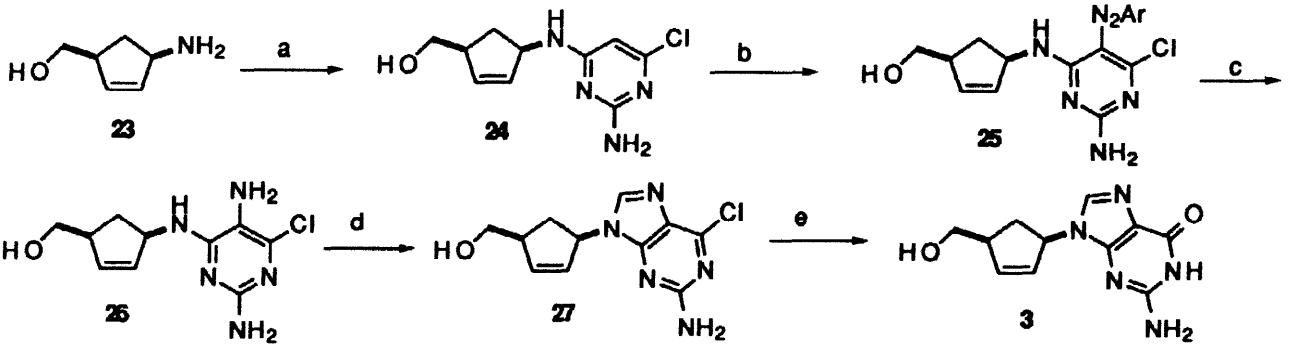
Scheme 6



a) 5-amino-4,6-dichloropyrimidine, Et_3N, 82%. b) $(EtO)_3CH$, HCl, 86%. c) NH_3, MeOH, 77%.

Guanines can be synthesized in a similar sequence by the reaction of the cycloalkylamine with 2-amino-4,6-dichloropyrimidine to give the cycloalkylaminopyrimidine (see Scheme 7). Reaction with 4-chlorobenzene-

Scheme 7

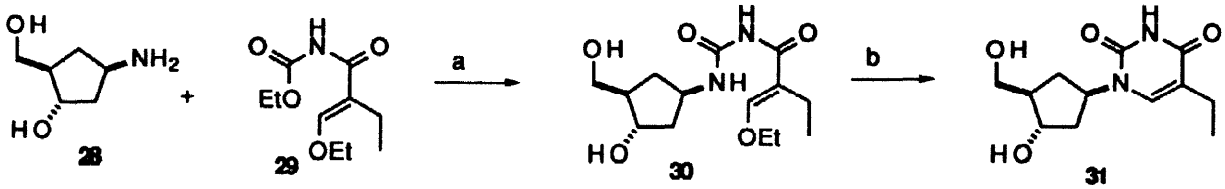


a) 2-amino-4,6-dichloropyrimidine, *i*-Pr_2NEt, BuOH, reflux, 80%. b) 4-$ClC_6H_4N_2^+Cl^-$, HOAc, NaOAc, H_2O, 69%. c) Zn, HOAc, EtOH, H_2O, 50%. d) $(EtO)_3CH$, HCl, H_2O. e) NaOH, H_2O, reflux, 74%

diazonium chloride followed by reduction with zinc provides the diaminopyrimidine. The aminopyrimidine is then converted to the 2-amino-6-chloropurine by the condensation with triethylorthoformate in the presence of acid. Displacement of the chloride with aqueous base completes the five step construction of the guanine.[27] Other nucleophiles such as amines, alkoxides, etc. can be used to incorporate a variety of substituents at the 6-position of the guanine (or adenine).

2.2.2 Synthesis of pyrimidines. Pyrimidines can be prepared by the reaction of a cycloalkylamine with 3-ethoxy-N-carboethoxy-2-ethylacrylamide to give the intermediate acryloylurea **30** which can be readily converted to the pyrimidine **31** by an acid or base catalyzed addition-elimination (Scheme 8).[28] Overall yields for the pyrimidine annelation are quite good. A variety of substituents can be incorporated at the 5-position of the pyrimidine by this approach.

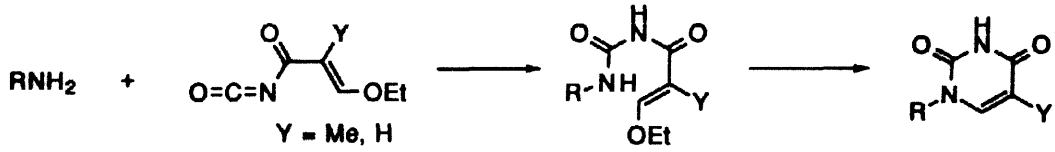
Scheme 8



a) Et_3N, dioxane. b) 2% 2N HCl in dioxane. ca. 80% overall.

Pyrimidines can also be prepared from an amino group by addition of an isocyanate to access a similar acylurea to **30** above (Scheme 9).[29] Cyclization to the pyrimidine can be carried out with either base or acid.

Scheme 9



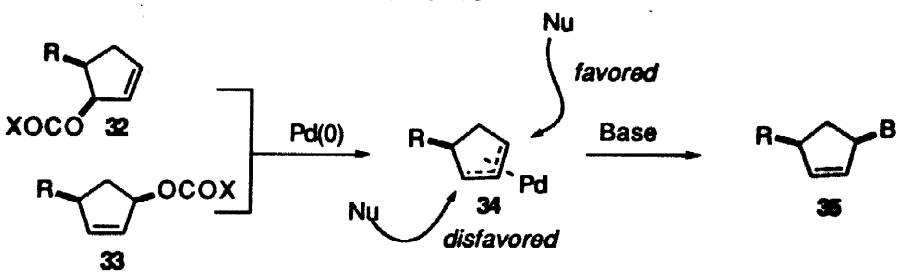
3. CYCLOPENTYL CARBOCYCLIC NUCLEOSIDES

3.1 Palladium catalyzed approaches to cyclopentenyl carbocyclic nucleosides.

Palladium catalyzed substitutions of allylic leaving groups have found wide application in carbocyclic nucleoside synthesis. An allylic ester, carbonate or epoxide is treated with a palladium (0) catalyst to generate an intermediate allyl palladium complex **34** which reacts with an anion of a purine or pyrimidine (Scheme 10). Three points are worth note. 1) Either of two regioisomeric allyl esters **32** or **33** can in principle provide access to the same palladium complex. 2) The palladium complex undergoes nucleophilic attack at the less hindered carbon. 3) Since palladium first displaces the allylic ester and then a nucleophile displaces palladium, the overall substitution reaction occurs with retention of configuration, although allylic rearrangement can occur.[30] The use of an epoxide or carbonate as the leaving group precludes the need for an external base to deprotonate the

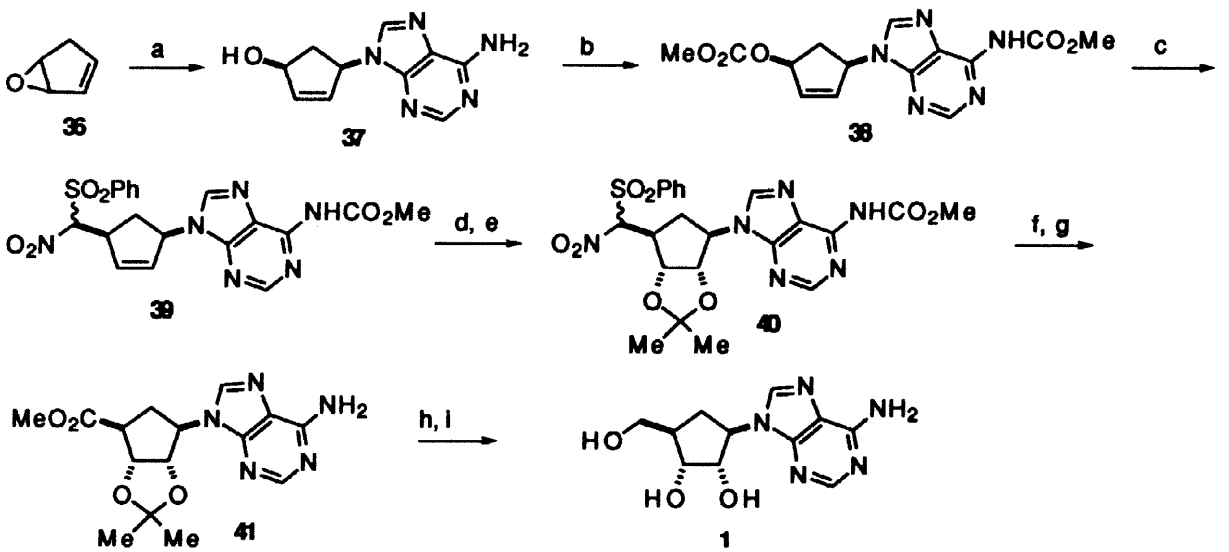
heterocyclic base. Since carboxylates are less basic, a stoichiometric amount of base must be added to deprotonate the heterocyclic base when esters are utilized as the leaving group.

Scheme 10



The first example of direct substitution of a heterocyclic base on a carbocycle through a palladium catalyzed substitution was reported by Trost in a racemic synthesis of aristeromycin (Scheme 11).[19] Reaction of the cyclopentadiene monoepoxide **36** with $Pd(OAc)_2$ and adenine gave the cyclopentenol **37**. No indication of N9 versus N7 selectivity is noted. The derived allylic carbonate **38** was subjected to a second palladium catalyzed substitution with phenylsulfonylnitromethane anion to provide the *cis* 3,5-disubstituted cyclopentene **39**. The nitrosulfone serves as a surrogate hydroxymethyl group. Dihydroxylation of the olefin **39** followed by protection of the diol gave the acetonide **40**. Conversion of the nitrosulfone **40** to its nitronate and subsequent ozonolysis produced the ester **41** which was readily transformed to (±)-aristeromycin **1**.

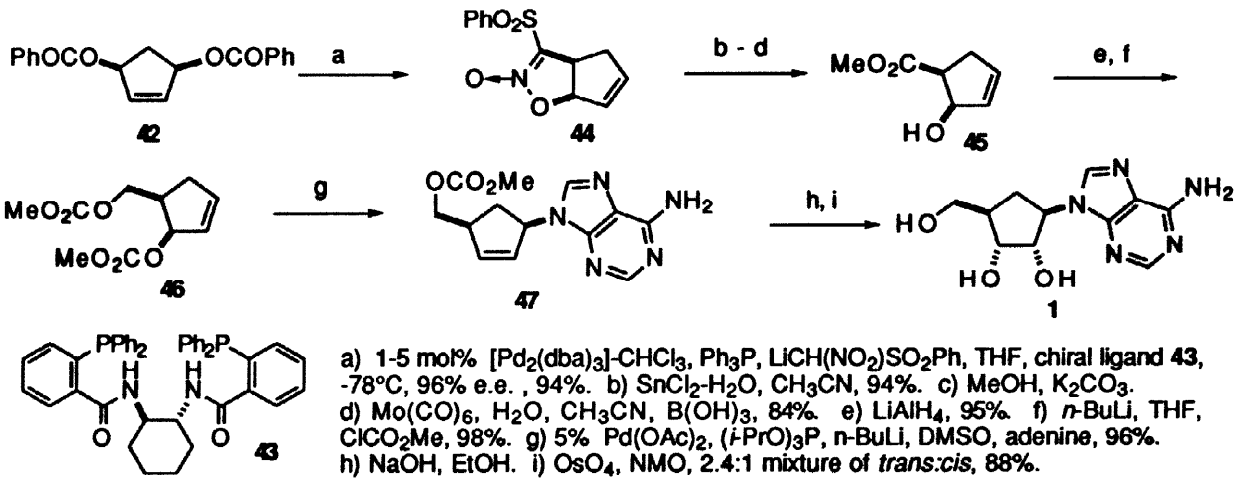
Scheme 11



a) 0.6 mol% $Pd(OAc)_2$, 6 mol % $(i\text{-PrO})_3P$, 1.2 mol % *t*-BuLi, adenine, 1:1 THF:DMSO, 67%. b) $ClCO_2Me$, pyr, CH_2Cl_2, 85%. c) 5 % $[Pd_2(dba)_3]$-$CHCl_3$, 50% PPh_3, $LiCH(NO_2)SO_2Ph$, THF, 82%. d) $KMnO_4$, NaOH, H_2O. e) p-TsOH, $Me_2C(OMe)_2$, 45% 2 steps. f) NH_4OH, MeOH, 81%. g) NaOMe, MeOH, O_3, -78°C, 70%. h) $i\text{-Bu}_2AlH$, CH_2Cl_2, C_6H_6, 82%. i) 1.5 M HCl, 80°C then Dowex IX8-50 (OH form), 70%.

A second generation synthesis by Trost attempted to address the difficulty of introducing the hydroxymethyl substituent and also the need for an enantioselective approach (Scheme 12).[31] A highly imaginative asymmetric desymmetrization reaction in which the chiral ligand **43** was used in the palladium (0) coupling of phenylsulfonylnitromethane with *cis* dibenzoate **42** produced the isoxazoline-2-oxide **44** in high enantiomeric purity. Conversion of **44** to the bis-carbonate **46** was accomplished in five steps to set the stage for incorporation of the heterocyclic base. Palladium (0) catalyzed coupling of the bis-carbonate **46** with adenine produced the carbonate **47** which was converted to aristeromycin by hydrolysis of the carbonate and subesquent dihydroxylation. No indication of N7-N9 selectivity is noted in the palladium catalyzed coupling reaction. The dihydroxylation afforded a 2.4:1 mixture of the *cis*-diols with aristeromycin as the major product.

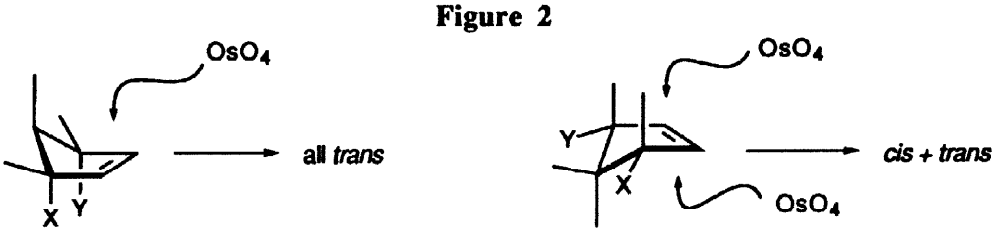
Scheme 12



a) 1-5 mol% $[Pd_2(dba)_3]$-$CHCl_3$, Ph_3P, $LiCH(NO_2)SO_2Ph$, THF, chiral ligand **43**, -78°C, 96% e.e., 94%. b) $SnCl_2$-H_2O, CH_3CN, 94%. c) MeOH, K_2CO_3. d) $Mo(CO)_6$, H_2O, CH_3CN, $B(OH)_3$, 84%. e) $LiAlH_4$, 95%. f) *n*-BuLi, THF, $ClCO_2Me$, 98%. g) 5% $Pd(OAc)_2$, $(i\text{-}PrO)_3P$, n-BuLi, DMSO, adenine, 96%. h) NaOH, EtOH. i) OsO_4, NMO, 2.4:1 mixture of *trans*:*cis*, 88%.

A rationale for the stereoselectivity of dihydroxylation in 3,5-disubstituted cyclopentenes which is based on the conformation of the cyclopentene has been proposed by Katigiri.[32] When the cyclopentene is in the quasi-axial conformation as is the case with heteroatoms at the 3 and 5 positions, e.g. diester **42** (Figure 2; X = Y = OCOPh), dihydroxylation occurs *trans* to the substituents due to both a steric effect and orbital stabilization, the "Cieplak effect". When one or more carbon substituents are at the 3 or 5 positions as in carbonate **47**, the cyclopentene adopts a quasi- equatorial conformation and a much less selective reaction occurs.

Figure 2

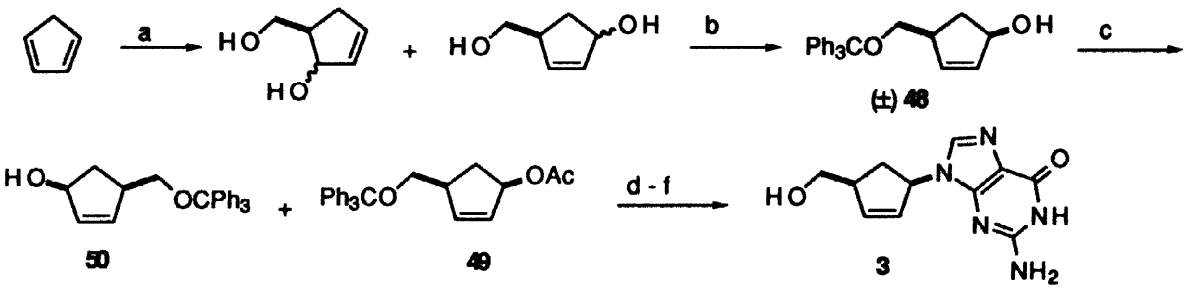


Other enantioselective approaches which utilize the palladium catalyzed substitution of cyclopentenol esters or carbonates with purines and pyrimidines have also been reported. The syntheses have been divided into two categories: a) Enantioselective approaches based on enzymatic or chemical resolution of an intermediate and b) Enantioselective syntheses through asymmetric synthesis.

3.1.1. Enzymatic or chemical resolution of an intermediate. Both chemical resolution by preparation of diastereomeric salts or chromatographically separable diastereomers as well as enzymatic resolution of *meso* intermediates and enzymatic resolution of chiral, racemic mixtures have been utilized in the enantioselective synthesis of carbocyclic nucleosides. Resolution of *meso* intermediates offer the advantage that all the material can be resolved, i.e. half is not lost as the "undesired" enantiomer.

Roberts began a synthesis of (-)-carbovir by exploiting the known Prins reaction[33] of cyclopentadiene with aqueous formaldehyde to produce a mixture of *cis* and *trans* 4-hydroxymethylcyclopent-2-en-1-ol and 5-hydroxymethylcyclopent-2-en-1-ol (Scheme 13)[34] The racemic trityl ether **48** was obtained by selective protection of the primary alcohol and chromatographic separation of the mixture. The racemic alcohol was resolved enzymatically to access acetate **49** in 95% e.e. Palladium catalyzed coupling of acetate **49** with 2-amino-6-chloropurine provided carbovir **3** after removal of the trityl ether and displacement of the chloride.

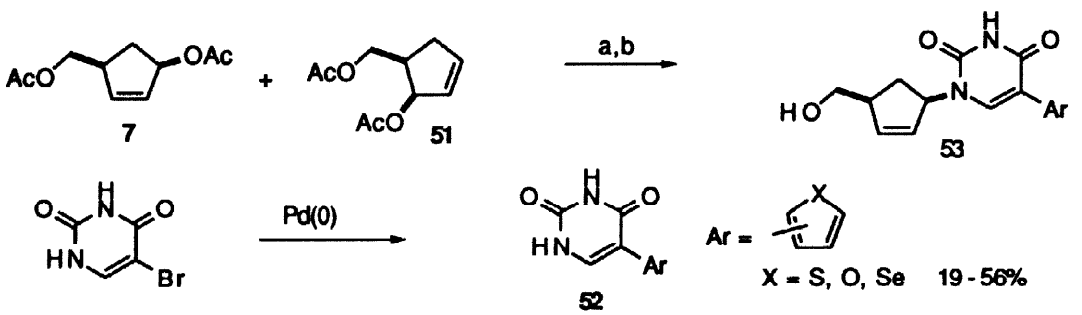
Scheme 13



a) CH_2O, HCO_2H; NaOH. b) Ph_3CCl, separation. c) Vinyl acetate, *Pseudomonas, fluorescens* lipase, 95% e.e. d) 2-amino-6-chloropurine, NaH, DMF, $Pd(PPh_3)_4$, THF, 49%. e) H_2O, HOAc, 96%. f) NaOH, H_2O, 66%.

A mixture of the isomeric *cis* diacetates **7** and **51** was coupled to several aryl substituted pyrimidines by Gronowitz (Scheme 14).[35] Interestingly, if a mixture of the *cis* and *trans* diacetates was utilized in the coupling reaction, the *cis* substituted carbocyclic nucleosides could be selectively crystallized from the product mixture as an alternative to separation of the mixture of the starting acetates.

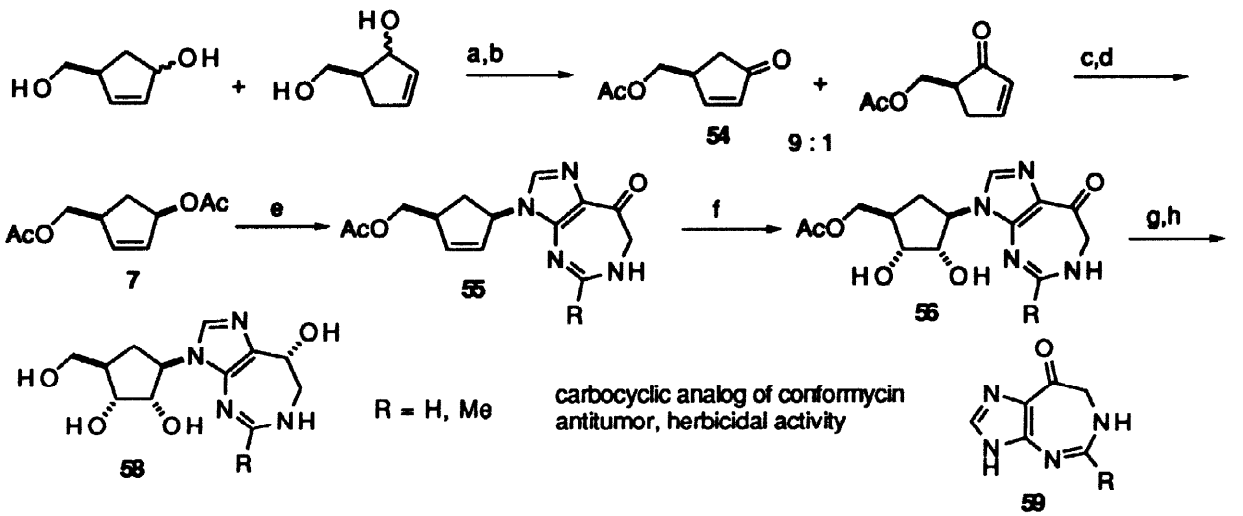
Scheme 14



a) NaH, $Pd(Ph_3P)_4$, pyrimidine **52**, 50 - 70%. b) MeOH, Et_3N.

The mixture of hydroxymethylcyclopentenols can be converted to predominantly the diacetate 7 as shown in Scheme 15 below.[36] Iodine oxidation of the diols gave a 9:1 mixture of two enones with 54 as the major product. Reduction of the ketone with Dibal-H and conversion of the resultant diols to the diacetates resulted in the formation of diacetate 7 as 85% of the product. Exposure of the diacetate to palladium (0) and the diazepine 59 allowed preparation of the carbocyclic analog of conformycin in modest yields.

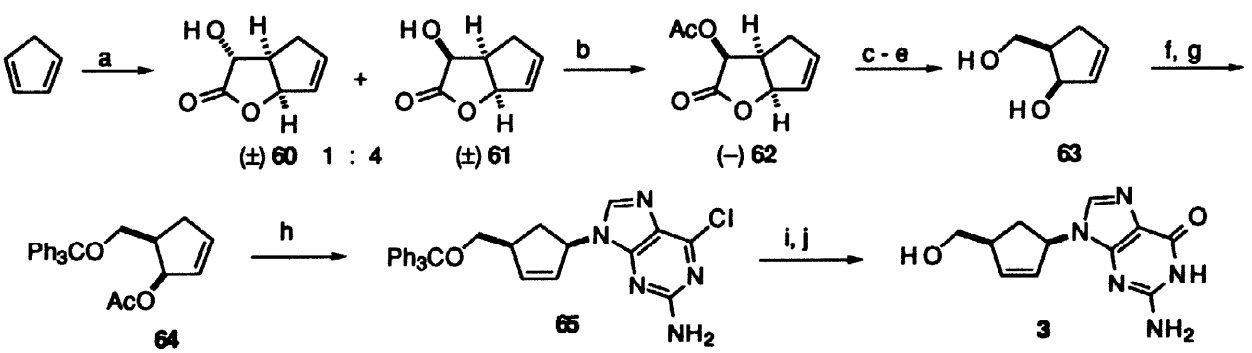
Scheme 15



a) I_2. b) Ac_2O, Et_3N, 37%. c) *i*-Bu_2AlH. d) Ac_2O, Et_3N, 47%. e) CsF, Et_3N, $Pd(PPh_3)_4$, **59**. 17% R = H, 42% R = Me. f) OsO_4. g) NaOMe. h) $NaBH_4$, 13%.

The lactones **60** and **61** (Scheme 16), the products of a Prins reaction between cyclopentadiene and glyoxalic acid, have also been utilized in enantioselective approaches to carbovir and aristeromycin.[37] The initially formed 1:4 mixture of lactones **60** and **61** can be separated by chromatography. The major isomer **61** was resolved enzymatically by esterification with vinyl acetate and *Pseudomonas flourescens* lipase to yield the

Scheme 16

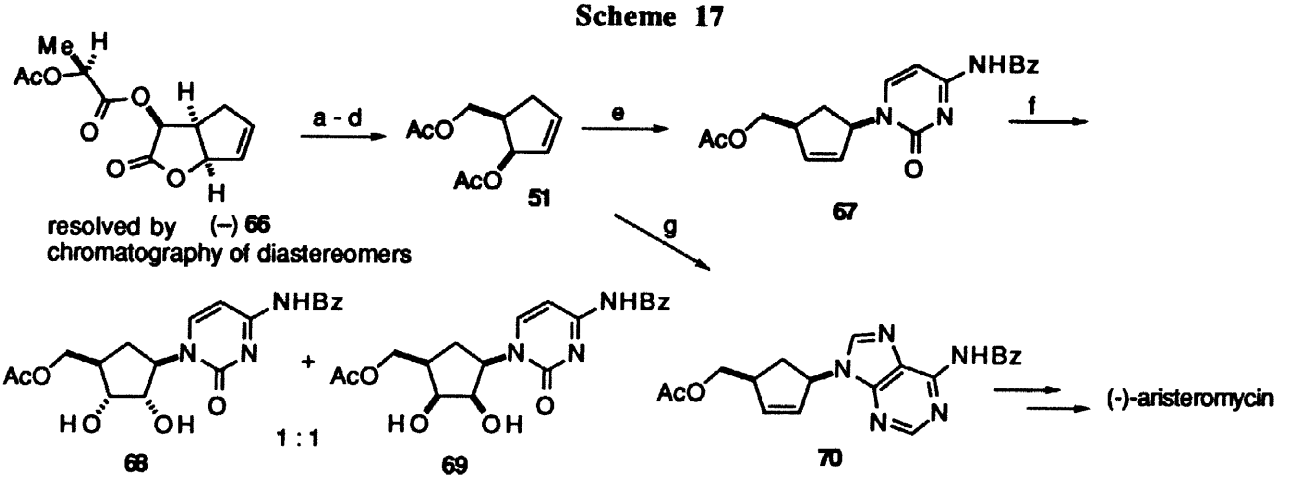


a) Glyoxalic acid, H_2O, 4d, 65%. b) Vinyl acetate, *Pseudomonas, fluorescens* lipase, 40% conversion, 95% e.e. c) $LiAlH_4$, THF. d) $NaIO_4$, Et_2O-H_2O. e) $NaBH_4$, MeOH, 50% 3 steps. f) Ph_3CCl, Et_3N, DMAP, CH_2Cl_2. g) Ac_2O, C_5H_5N. h) 2-amino-6-chloropurine, NaH, DMF, $Pd(PPh_3)_4$, THF, 49%. i) H_2O, HOAc, 96%. j) NaOH, H_2O, 66%.

acetate **62** (95% e.e.). A three step sequence involving reduction of the lactone, oxidative cleavage of the resultant triol and further reduction to diol **63** proceeded in 50% overall yield. Diol **63** was processed to (-)-carbovir in five steps in a similar manner to that discussed previously.

Lactone **61** can also be resolved by conversion of the secondary alcohol to its 2-acetoxypropionate **66** followed by chromatographic separation of the diastereomers (Scheme 17). Lactone **66** can be converted to diacetate **51** in a similar manner as described above. Exposure of acetate **51** to $Pd(Ph_3P)_4$ and N(4)-benzoylcytosine provided the carbocyclic nucleoside **67** which underwent a non-selective dihydroxylation to diols **68** and **69**. A formal synthesis of aristereomycin was also completed from **51**.[38]

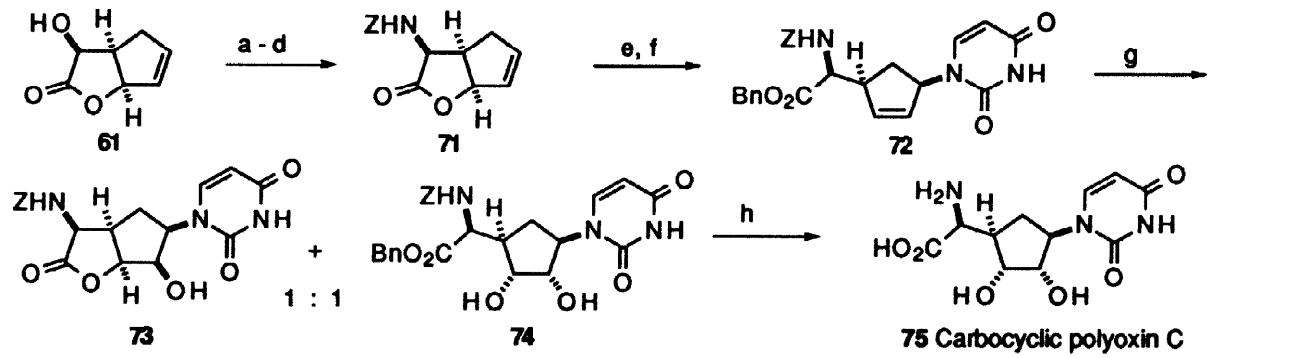
Scheme 17



a) $LiAlH_4$, THF. b) $NaIO_4$, Et_2O-H_2O. c) $NaBH_4$, MeOH. d) Ac_2O, C_5H_5N, DMAP, 30% 4 steps. e) Cesium salt of N(4)-benzoylcytosine, DMF, $Pd(PPh_3)_4$, 55°C, 85%. f) OsO_4, trimethylamine-N-oxide, 70-77%. g) Cesium salt of N(6) benzoylpurine, DMF, $Pd(PPh_3)_4$, 55°C, 48% + 13% N(7) isomer.

A synthesis of the core of the carbocyclic analog **75** of polyoxin C, an unusual natural nucleoside, has also been accomplished from the resolved lactone **61** (Scheme 18).[39] The secondary alcohol was transformed into the inverted bromide and subsequently to the amine via the azide to produce **71** after benzoylation. The

Scheme 18

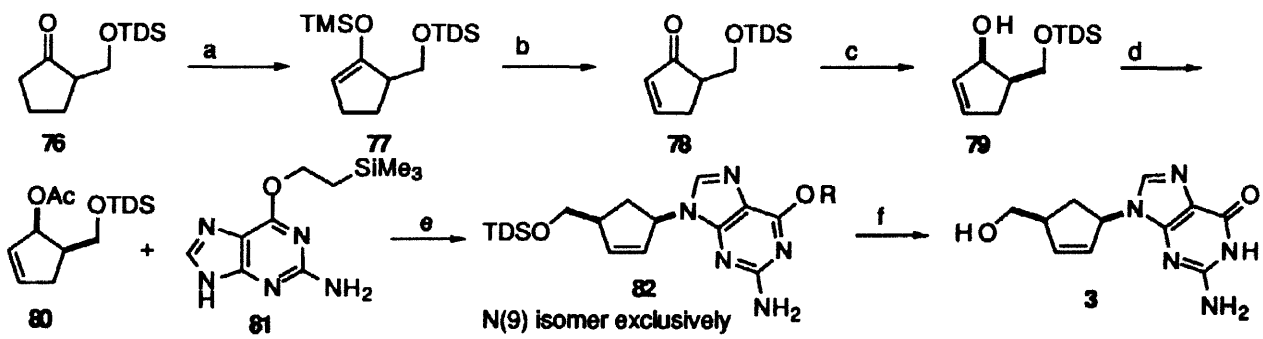


a) $ZnBr_2$, Ph_3P, DEAD, 60%. b) NaN_3, DMSO, 87%. c) PPh_3, THF-H_2O, 92%. d) BnOCOCl, $NaHCO_3$, THF-H_2O, 0°C, 94% e) Uracil, $(Me_3Si)_2NH$, Me_3SiCl, cat. $Pd(PPh_3)_4$, CH_3CN. f) BnBr, $NaHCO_3$, DMF, 50% 2 steps. g) OsO_4, NMO, THF, 90%. h) H_2, Pd/C, EtOH-H_2O, 100%.

palladium catalyzed substitution of the lactone carboxylate occurred readily on the illustrated diastereomer to provide the dideoxy uracil analog **72**. Dihydroxylation of the olefin proceeded with the anticipated low selectivity based on the Katigiri model and produced a 1:1 mixture of **73**:**74**. Hydrogenolysis of the benzyl protecting groups completed the synthesis of **75**.

Benneche and Gundersen[40] have reported a racemic synthesis of carbovir from ketone **76** (Scheme 19). Ketone **76** was converted to the enone **78** via palladium acetate oxidation of the silyl enolether **77**. The allylic acetate **80** was obtained by reduction of the enone **78** with 9-BBN and acylation of the resultant alcohol **79**. An extremely important observation was made in this and a related paper by Benneche and Gunderson:[41] the coupling of purines with allylic esters and carbonates gives a mixture of N9 and N7 isomers of the products. Earlier and some subsequent reports fail to recognize this limitation of the direct coupling although it is a common problem in natural nucleoside synthesis. Of equal importance was the recognition that incorporation of larger groups at the 6 position of the purine can substantially alter the regioselectivity of the coupling reaction. Thus, while 2-amino-6-chloropurine gives N9:N7 ratios in the 4 - 7:1 range depending on the substrate, 2-amino-6-trimethylsilylethoxypurine **81** resulted in the exclusive production of the N9 regioisomer **82**, the immediate precursor of carbovir.

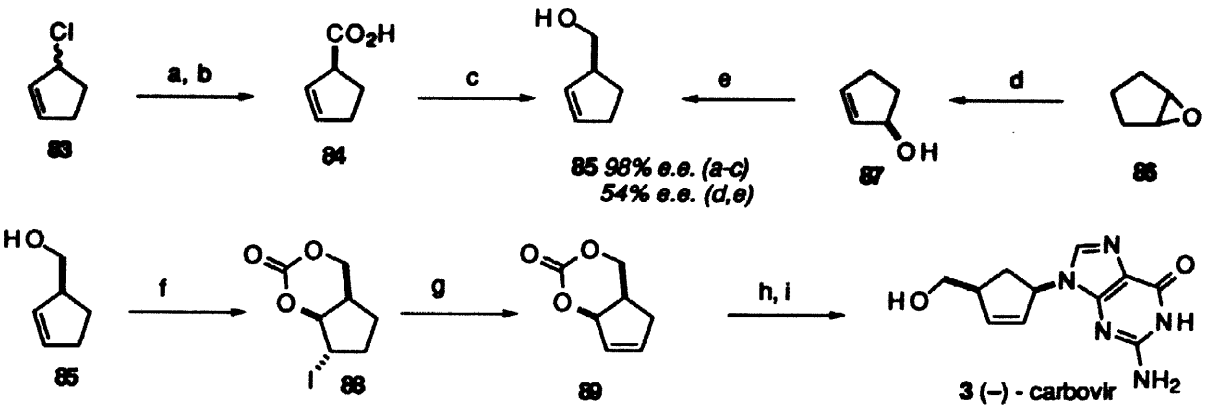
Scheme 19



a) LDA, TMSCl, THF, 95%. b) $Pd(OAc)_2$, CH_3CN, 75%. c) 9-BBN, THF, 66%. d) Ac_2O, DMAP, CH_2Cl_2, 91%. e) $Pd(PPh_3)_4$, LiH, DMF, 54%. f) Bu_4NF, CH_3CN, 70%.

Scheffold has described a different approach to the cyclic carbonate **89** which is a useful electrophile in palladium catalyzed substitution reactions (Scheme 20).[42] Carboxylic acid **84** was prepared from 1-chloro-2-cyclopentene. Crystallization of the α-phenethylamine salt of acid **84** gave the alcohol **85** in 98% e.e. after reduction of the acid. An enantioselective epoxide opening with vitamin B12 provided **85** in only 54% e.e. Alcohol **85** was transformed into the iodolactone **88** through an iodocarbonation reaction. Elimination of the iodide provided the cyclic carbonate **89** which was converted to (-)-carbovir through a palladium catalyzed substitution with 2-amino-6-chloropurine and subsequent hydrolysis. A similar strategy has also been used to prepare a series of pyrimidine carbocyclic nucleosides.[43]

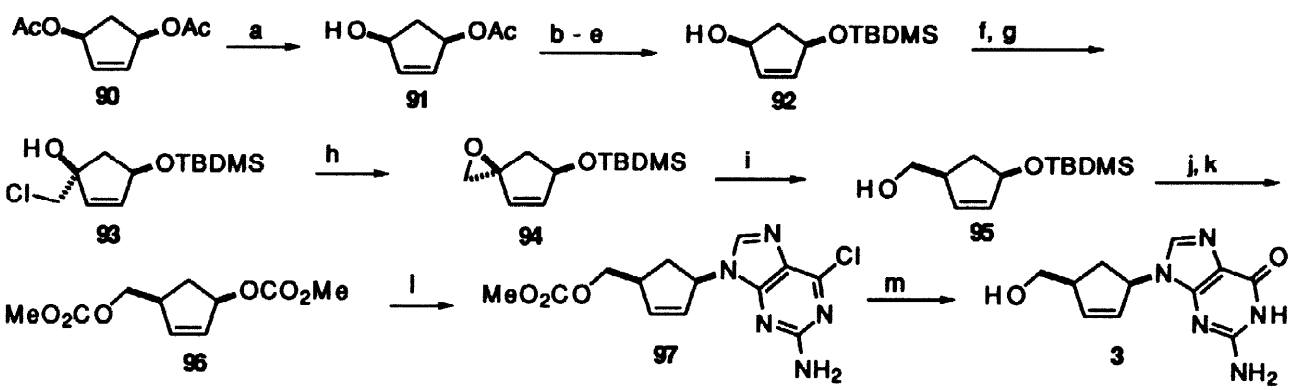
Scheme 20



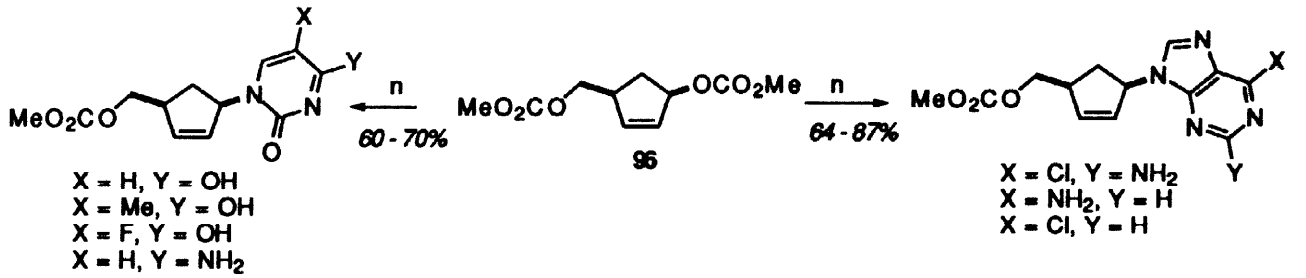
a) Mg, then CO_2, 85%. b) (-)-α-phenylethyl amine; recrystallization,16% overall of (-)-enantiomer. c) $LiAlH_4$, Et_2O, 64%. d) vitamin B12, 66%; 56% e.e. e) KH, ICH_2SnBu_3, THF; then BuLi, 49%. f) BuLi, then CO_2, then I_2, THF, 53%. g) DBU, CO_2, $PhCH_3$, 90°C, 63%. h) 2-amino-6-chloropurine, 10% allylpalladium chloride dimer, Ph_3P, THF, DMSO, 59%. i) 1N NaOH, reflux, 71%.

A synthesis of the dicarbonate **96** from the enzymatically resolved monoacetate **91** illustrated in Scheme 21 was reported by Nokami.[44] A series of protection-deprotection steps generated the alcohol **92**. Oxidation

Scheme 21



a) porcine pancreatic lipase (PPL). b) DHP, p-TsOH, CH_2Cl_2, 91%. c) KOH, H_2O, MeOH, 94%. d) *t*-$BuMe_2SiCl$, imid., DMF, 94%. e) Me_2AlCl (1.5 equiv.), CH_2Cl_2, -60°C, 74%. f) PCC, mol sieves, CH_2Cl_2, 87%. g) $ClCH_2I$, BuLi, THF, -78°C, 87%. h) MeOK, THF, -78°C. i) *i*-Bu_2AlH, hexane, -78°C, 77%. j) *n*-Bu_4NF, THF, 96%. k) MeO_2CCl, pyr, CH_2Cl_2, 91%. l) 2-amino-6-chloropurine, 3% $Pd(PPh_3)_4$, DMF, 62% plus 20% of the N(7) isomer. m) 1N NaOH, reflux, 83%. n) 3% $Pd(PPh_3)_4$, DMF, purine or pyrimidine.



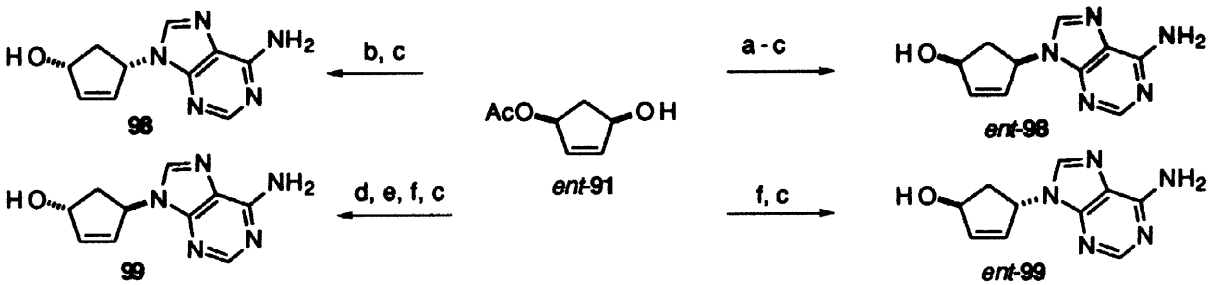
X = H, Y = OH
X = Me, Y = OH
X = F, Y = OH
X = H, Y = NH_2

X = Cl, Y = NH_2
X = NH_2, Y = H
X = Cl, Y = H

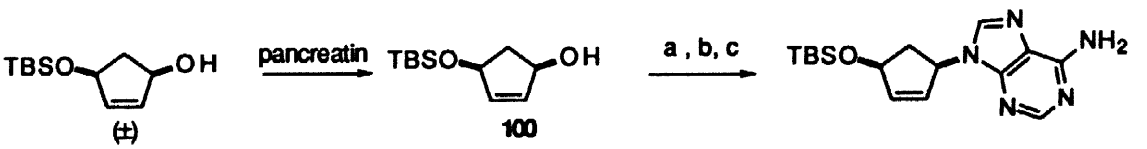
and treatment of the resultant ketone with chloromethyllithium provided the chlorohydrin **93**. Treatment of **93** with potassium methoxide followed by subsequent reduction of the epoxide produced the alcohol **95**. Deprotection and acylation gave the bis-carbonate **96**. A 3:1 mixture of the N9:N7 isomers **97** was obtained upon palladium catalyzed substitution with 2-amino-6-chloropurine. Hydrolysis of **97** yielded (-)-carbovir in 83% yield. Several other purine and pyrimidine carbocyclic nucleosides were also prepared from bis-carbonate **96**.

Two other groups have employed the enzymatically resolved monoacetate *ent*-**91** in the synthesis of the four stereoisomers of 5'-norcarbocyclic nucleosides (Scheme 22).[45,46] Dyatkina utilized both *ent*-**91** and the derived diethylphosphonate to prepare the enantiomeric *cis*-nucleoside analogs **98** and *ent*-**98**.[45] The *trans* isomers **99** and *ent*-**99** were synthesized by a Mitsunobu coupling. A subsequent report by Curran[46] noted low yield and low stereoselectivity when the diethylphosphonate of **91** was treated with adenine and $Pd(Ph_3P)_4$. This was attributed to participation by the acetoxy group in the π-allyl complex. To avoid acetoxy participation, the silyl ether **100** was converted to the diethylphosphonate and coupled to adenine in good yield.

Scheme 22



a) $(EtO)_2POCl$, imidazole, MeCN. b) 6-chloropurine, NaH, $Pd(Ph_3P)_4$, Ph_3P. c) NH_3, MeOH. d) *t*-$BuMe_2SiCl$, imidazole, MeCN. e) MeOH, NaOMe. f) 6-chloropurine, DEAD, Ph_3P.

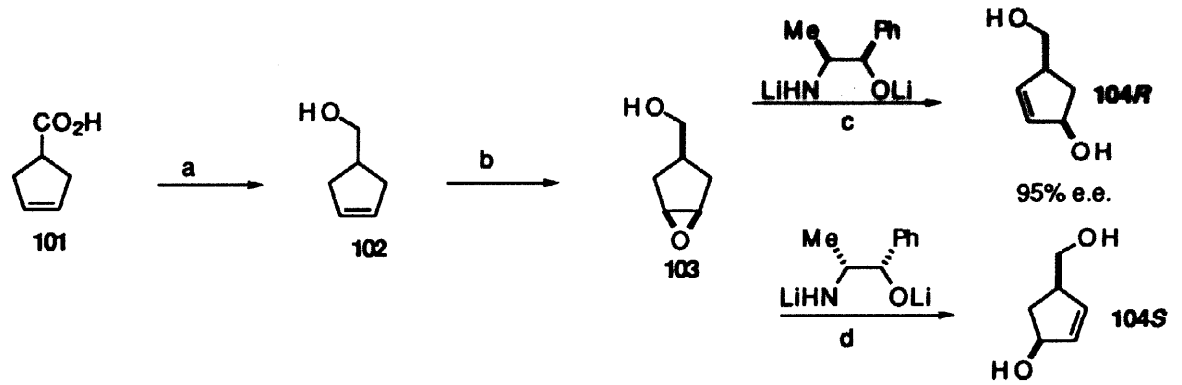


a) $(EtO)_2POCl$, imidazole, MeCN, 55%. b) 6-chloropurine, NaH, $Pd(Ph_3P)_4$, 47% N9, 5% N7, 17% N3 . c) NH_3, MeOH.

3.1.2. Enantioselective syntheses through asymmetric synthesis. More recently, asymmetric synthetic methods such as asymmetric cycloadditions, catalytic asymmetric desymmetrizations and auxiliary based asymmetric reactions, have been employed for the enantioselective synthesis of carbocyclic nucleosides.

Hodgson has reported the asymmetric synthesis of diols **104*R*** and **104*S*** from the unsaturated acid **101** (Scheme 23).[47] Reduction of the acid **101** to the alcohol **102** and subsequent Sharpless directed epoxidation gave the *meso* epoxy alcohol **103**. Exposure of epoxide **103** to dilithionorephedrine resulted in high levels of asymmetric induction in the resultant diols **104*S*,*R*** in good yields. The diols can be readily converted to the diacetates or dicarbonates which have been previously utilized in carbocyclic nucleoside synthesis.

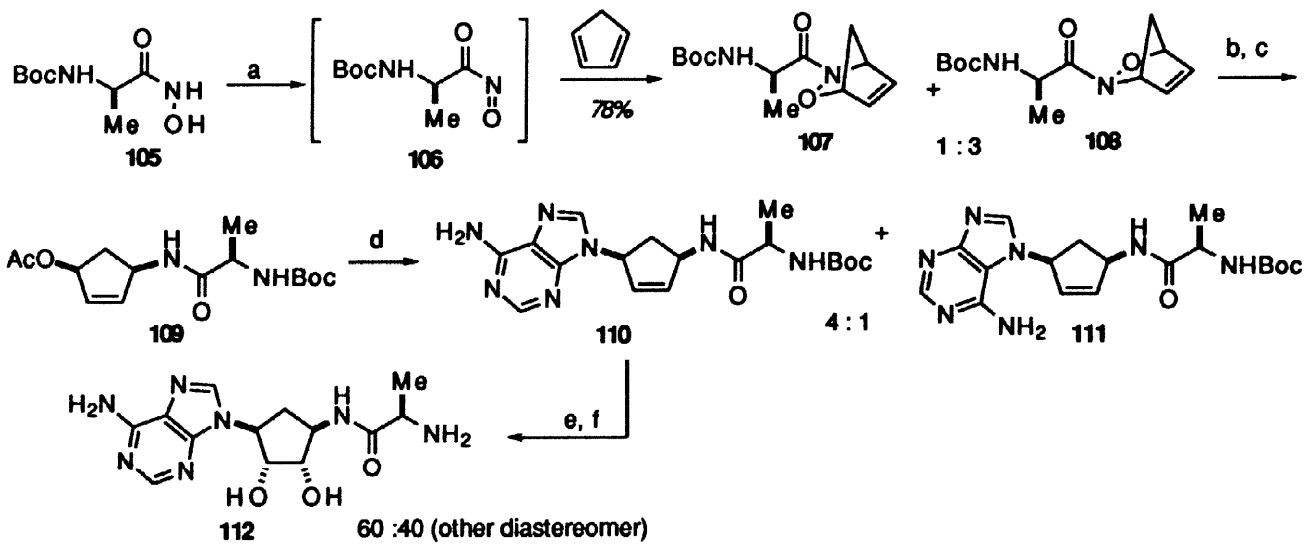
Scheme 23



a) $LiAlH_4$. b) *t*-BuOOH, cat. $VO(acac)_2$, CH_2Cl_2, 98%. c) 3 equiv, C_6H_6:THF (2:1), 0° - 25°C, 66%. d) 3 equiv, C_6H_6:THF (2:1), 0° - 25°C, 57%.

As shown in Scheme 24, an asymmetric cycloaddition of cyclopentadiene and the nitroso compound **106**, which can be prepared in situ from the hydroxylamine **105**, has been shown by Miller to result in a 1:3 mixture of cycloadducts **107:108**.[48-52] The major product **108** can be readily separated and converted to the *cis* disubstituted cyclopentene **109** by reductive cleavage of the N–O bond. Palladium catalyzed coupling of adenine to the carbocycle resulted in a 4:1 mixture of N9:N7 regioisomers **110:111** in 92% yield. Dihydroxylation of **110** produced a 60:40 mixture of diastereomeric nucleoside analogs with **112** as the major product.

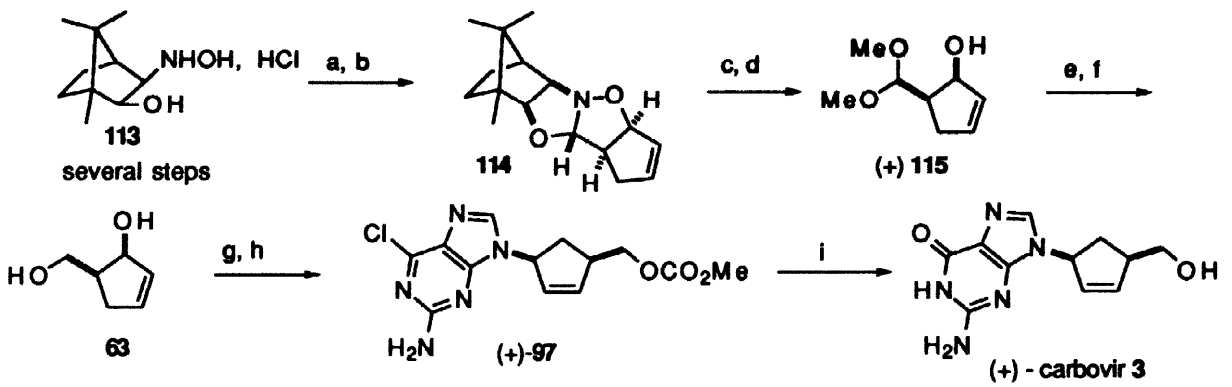
Scheme 24



a) $NaIO_4$. b) $Mo(CO)_6$, 89%. c) AcCl, pyr, CH_2Cl_2, 100%. d) NaH, adenine, DMF, $(Ph_3P)_4Pd$, 35-40°C, 92%. e) OsO_4, NMO. f) CF_3CO_2H, 90% 2 steps.

A concise approach to (+)-carbovir which relies on a an asymmetric cycloaddition has been accomplished by Langlois (Scheme 25).[53] The hydroxylamine hydrochloride **113** was prepared from borneol in several steps and subsequently treated with trimethylorthoformate to generate an oxazoline-N-oxide. The cycloadduct **114** was the only product obtained after direct exposure of the oxazoline-N-oxide to dicyclopentadiene. Oxidation of the nitrogen followed by treatment with acidic methanol produced the acetal **115** in 65% overall yield. Hydrolysis of the acetal followed by immediate reduction gave the diol **63** which was readily transformed into (+)-carbovir **3**.

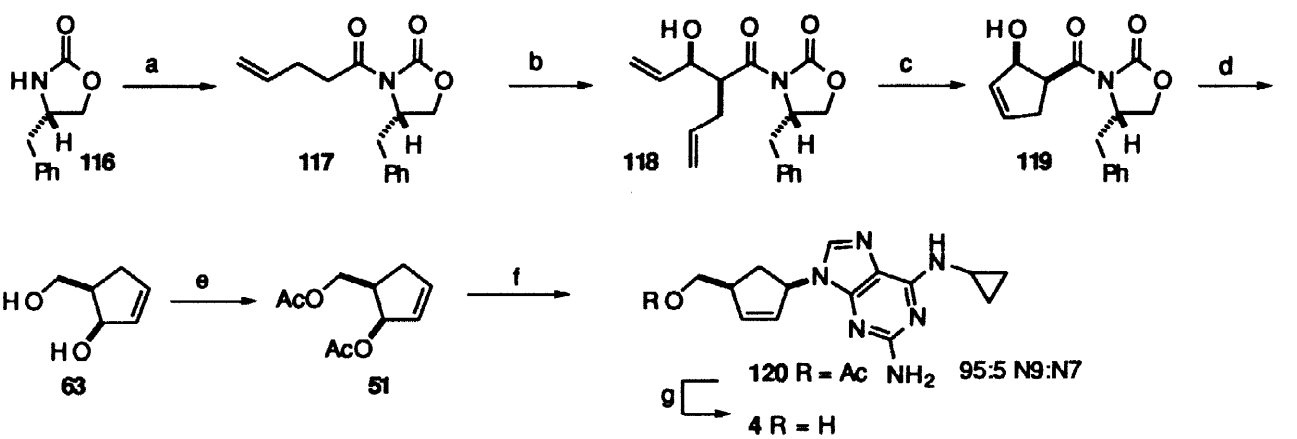
Scheme 25



a) $HC(OMe)_3$, CH_2Cl_2, $CaCO_3$, 40°C. b) cyclopentadiene, CH_2Cl_2, 40°C, 24h. c) m-CPBA, 0°C, 3h. d) CSA, MeOH, 20°C, 4h, 65% overall. e) CSA, CH_3CN, H_2O. f) $NaBH_4$, 0°C, 60% overall. g) $ClCO_2Me$, C_5H_5N, 0 - 20°C CH_2Cl_2. h) 2-amino-6-chloropurine, 5% $Pd(Ph_3P)_4$, THF-DMSO. i) 0.5 N NaOH, reflux.

A conceptually unique approach, which does not rely on cyclopentadiene as the initial starting material, was recently reported by Crimmins and King (Scheme 26).[20] The relative and absolute stereochemistry of the

Scheme 26

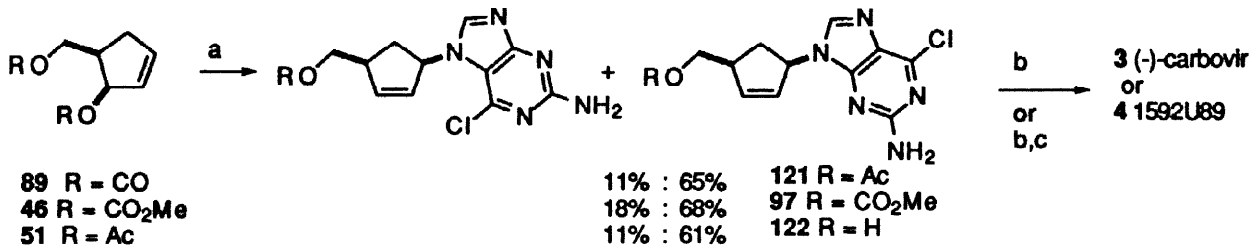


a) *n*-BuLi, CH_2=$CH(CH_2)_2CO_2COCMe_3$, THF, -78°C; 99%. b) Bu_2BOTf, Et_3N, CH_2Cl_2, CH_2=CHCHO, -78 °C, 82%. c) $Cl_2(Cy_3P)_2Ru$=CHPh; CH_2Cl_2, 97%. d) $LiBH_4$, MeOH, THF, 78%. e) Ac_2O, Et_3N, CH_2Cl_2, DMAP, 90%. f) $Pd(PPh_3)_4$, NaH, 2-amino-6-cyclopropylaminopurine,1:1 THF:DMSO, 62%. g) NaOH, H_2O, 95%.

carbocycle were established by exploiting an auxiliary mediated asymmetric aldol addition in combination with a Grubbs ring-closing metathesis reaction. The benzyloxazolidinone **116** was acylated with the mixed anhydride of 4-pentenoic acid and pivalic acid to produce the acyl oxazolidinone **117**. Asymmetric aldol condensation of the dibutylboron enolate of **117** with acrolein gave the aldol adduct **118** in >99% d.e. Exposure of **118** to the Grubbs catalyst closed the cyclopentene ring to form **119** which was reduced with lithium borohydride to remove the chiral auxiliary. The resultant diol **63** (>99.6% e.e.) was acetylated to access the diacetate **51**. Palladium catalyzed coupling of the diacetate **51** with 2-amino-6-cyclopropylaminopurine resulted in a highly regioselective formation (95:5 N9:N7) of the 1592U89 precursor **120**. The cyclopropylaminopurine was employed since use of 2-amino-6-chloropurine gave substantially lower regioselectivity in the coupling reaction.

Interestingly, the diacetate **51** and the cyclic carbonate **89** resulted in comparable levels of regioselectivity (85:15; N9:N7) while the dicarbonate gave only a 74:26 ratio of the N9:N7 products (Scheme 27). The major product in each case was converted to both (-)-carbovir and (-)-1592U89.

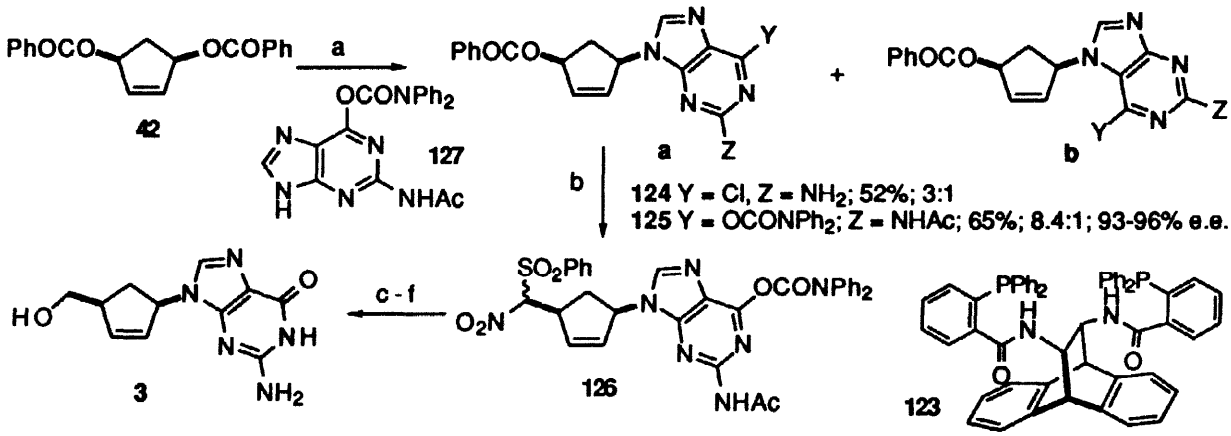
Scheme 27



a) $Pd(PPh_3)_4$, NaH, 2-amino-6-chloropurine,1:1 THF:DMSO. b) NaOH, H_2O. c) Cyclopropylamine, EtOH.

A recent report by Trost (Scheme 28) describes some improvements in the asymmetric desymmetrization reaction in the palladium catalyzed coupling with purines, particularly in the levels of conversion and the regio-

Scheme 28

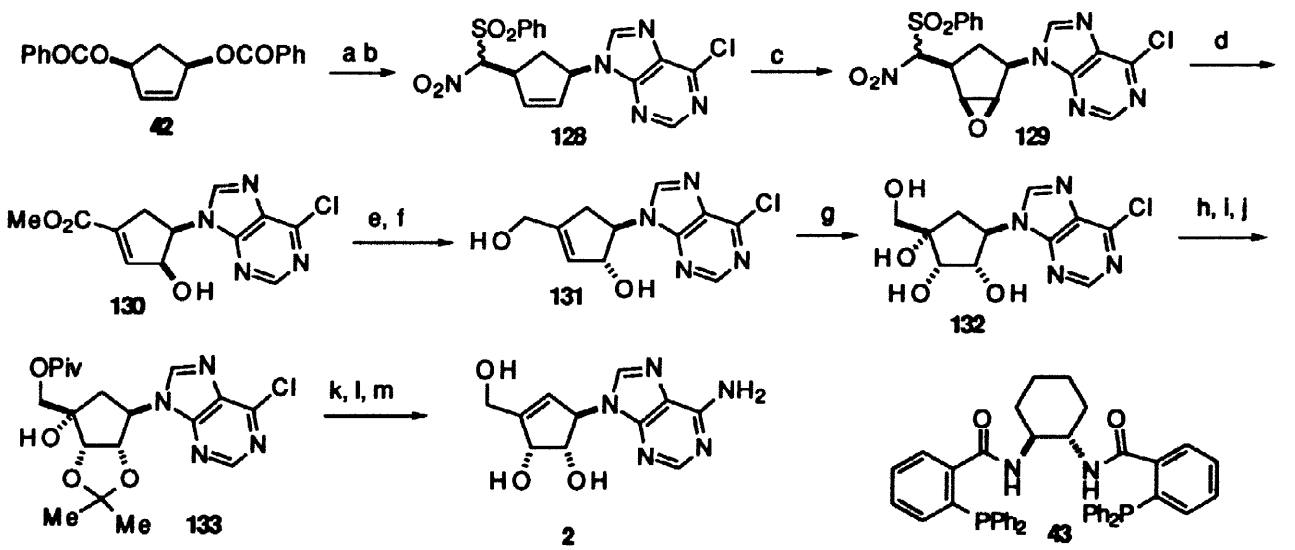


a) 1.5% $(C_3H_5PdCl)_2$, 4.5% diphosphine **123**, 3 equiv pempidine, DMSO:THF, 0°C, 59% N(9) isomer; 6% N(7) isomer; 93 - 96% e.e. b) 1.5 % $[Pd_2(dba)_3]$-$CHCl_3$, 12% PPh_3, THF, 97%. c) tetramethylguanidine. d) tetrabutylammonium oxone, Na_2CO_3. e) $Ca(BH_4)_2$, THF. f) NH_4OH. 61%.

selectivity.[54] Reaction of dibenzoate **42** with 2-amino-6-chloropurine [$(C_3H_5PdCl)_2$, ligand **123**] afforded a 3:1 mixture of N9:N7 isomers **124a**:**124b** when pempidine was used as the base. Tertiary amine bases gave superior results to inorganic bases and ligand **123** resulted in the highest levels of asymmetric induction. Additionally, an alternate guanine equivalent **127** was found to improve the N9:N7 selectivity to 8.4:1 in the formation of **125a** and **125b**. Oxidation of the tetramethylguanidine salt of **126** with *n*-Bu_4N-oxone followed by reduction with calcium borohydride and hydrolysis of the guanine protecting groups completed the synthesis of (-)-carbovir.

A similar strategy was utilized in a recent enantioselective synthesis of neplanocin A (Scheme 29).[55] The 6-chloropurine analog **128** was prepared in 94% e.e. by two successive allylic substitutions. The alkene **128** was epoxidized stereoselectively and the resultant epoxide **129** was rearranged to afford the allylic alcohol **130**. The hydroxyl was inverted under Mitsunobu conditions to give alcohol **131** which was dihydroxylated to provide triol **132**. Conversion to **133** was accomplished by ketalization, ketal isomerization and protection of the primary alcohol. The teriary alcohol was then dehydrated to provide (-)-neplanocin A after chloride displacement and deprotection.

Scheme 29

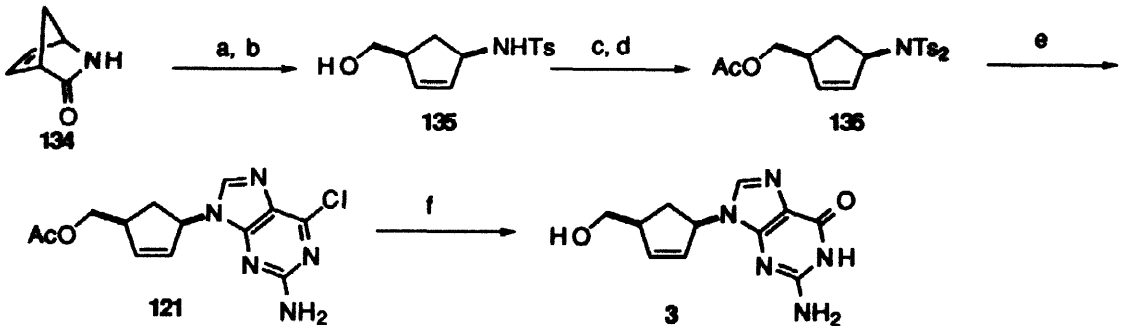


a) 1% $(dba)_3Pd_2$-CH_3Cl, 6-chloropurine, 3% **43**, Et_3N, THF, 25°C, 76% 94% e.e. b) 1.5 % $[Pd_2(dba)_3]$-$CHCl_3$, 4% PPh_3, $PhSO_2CH_2NO_2$, Et_3N, THF, 25°C, 95%. c) mCPBA, CH_2Cl_2, 73%. d) DBU, THF, MeOH, O_3, -78°C to 25°C, 67%. e) p-$O_2NC_6H_4CO_2H$, Ph_3P, DEAD, THF, 62%. f) *i*-Bu_2AlH, THF-CH_2Cl_2, -78°, 79%. g) 2% OsO_4, NMO, CH_3COCH_3, H_2O, 89%. h) $(MeO)_2CMe_2$, p-TsOH, 71%. i) $FeCl_3$-$6H_2O$, silica gel, CH_2Cl_2, 94%. j) Me_3COCl, C_5H_5N, 95%. k) SO_2Cl_2, C_5H_5N, DMF, 60%. l) NH_3, MeOH, 73%. m) HCl, H_2O, 91%.

Jung recently reported the use of an activated amine as a leaving group in a palladium catalyzed substitution.[56] The bicyclic lactam **134** (Scheme 30) was tosylated and the intermediate sulfonamide was reduced with sodium borohydride affording the hydroxyamide **135**. The primary alcohol was protected and the nitrogen was further activated by preparation of the bis-tosylamide **136**. Palladium catalyzed displacement of the bis-tosylamide with 2-amino-6-chloropurine gave **121** which was hydrolyzed to carbovir **3**. While this is a racemic synthesis, the bicyclic lactam is now commercially available as the single enantiomer through resolution.

Limited attempts have been made to prepare the lactam **134** in optically active form by an asymmetric cycloaddition.[57]

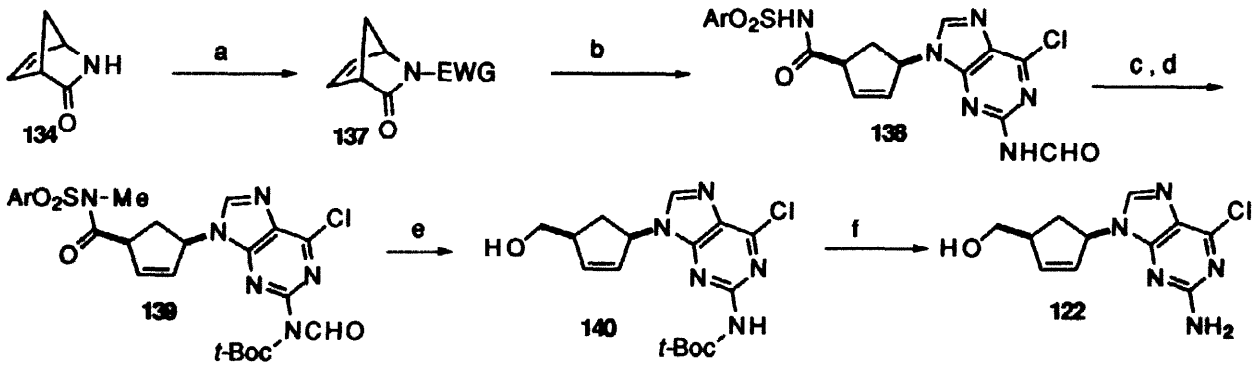
Scheme 30



a) p-$MeC_6H_4SO_2Cl$, NaH, 58%. b) $NaBH_4$, MeOH, 92%. c) Ac_2O, pyr, 100%. d) p-$MeC_6H_4SO_2Cl$, NaH, 75%. e) $Pd[P(O\text{-}i\text{-}Pr)_3]_4$, 1:1 THF:DMSO, 2-amino-6-chloropurine sodium salt, 68%. f) 0.5N NaOH, 75%.

The first example of use of a derivative of bicyclic lactam **134** directly in a palladium catalyzed coupling was recently reported by Katigiri.[58] Activation of the nitrogen of the bicyclic lactam **134** as the p-nitrobenzenesulfonamide **137** facilitated the palladium catalyzed conversion to **138** (Scheme 31). The corresponding [2.2.2] system failed to react. The sulfonamide **138** was reduced via **139** to **140** after protection of the 2-amino group of the purine and methylation of the sulfonamide nitrogen. The BOC group was removed to provide the key intermediate **122**.

Scheme 31



a) o-$NO_2C_6H_4SO_2Cl$, BuLi, THF, 83%. b) $Pd[P(O\text{-}i\text{-}Pr)_3]_4$, THF, 2- (formylamino)-6-chloropurine tetrabutylammonium salt, 55%. c) NaH, THF, 0°C; $t\text{-}Boc_2O$, 25 - 50°C; d) MeI, 25°C. e) $NaBH_4$, MeOH. f) AcOH, 50°C, 72% overall, 4 steps.

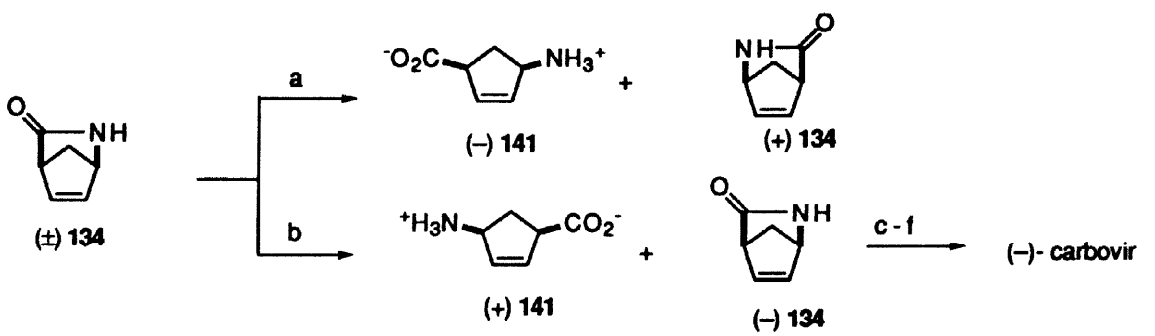
3.2 Other direct coupling approaches and syntheses utilizing classical heterocyclic base syntheses

Nucleophilic displacement of sulfonates, cyclic sulfates and sulfites as well as Mitsunobu type substitutions of alcohols which also occur with inversion have been commonly used in carbocyclic nucleoside synthesis. Similar problems to those encountered in palladium catalyzed couplings must be overcome to achieve efficient connection of the two fragments. Regioselectivity (N9 vs. N7 alkylation in purines) as well as competing elimination are potential complications, particularly since higher temperatures are often required to achieve substitution. Since many syntheses which use the approach of constructing the heterocyclic base from an amine on the carbocycle rely on a nucleophilic displacement to incorporate the nitrogen, these general areas have been combined.

The following section is subdivided based on how the carbocyclic subunit has been prepared: 1) Synthesis from a cycloaddition with cyclopentadiene a) [4+2] cycloaddition of cyclopentadiene with a C=N dienophile to form a bicyclic lactam intermediate, b) [4+2] cycloaddition of cyclopentadiene with a C=C dienophile to form a norbornene type derivative, c) [4+2] cycloaddition of cyclopentadiene with O_2 as the dienophile to proceed through 2-cyclopenten-1,4-diol. 2) Synthesis from a carbohydrate or amino acid or other chiral starting material.

3.2.1 Bicyclic lactams as intermediates to carbocyclic nucleosides. The byciclic lactam **134**, which is readily prepared from the cycloaddition product of cyclopentadiene and tosylcyanide by aqueous hydrolysis, has been a key building block in many syntheses of carbocyclic nucleosides.[59] Recent studies have demonstrated that lactam **134** can be enzymatically resolved to either enantiomer and the enantiomeric ring opened amino acid **141**.[60] The enantiomerically pure lactam **134** is now commercially available.[60]

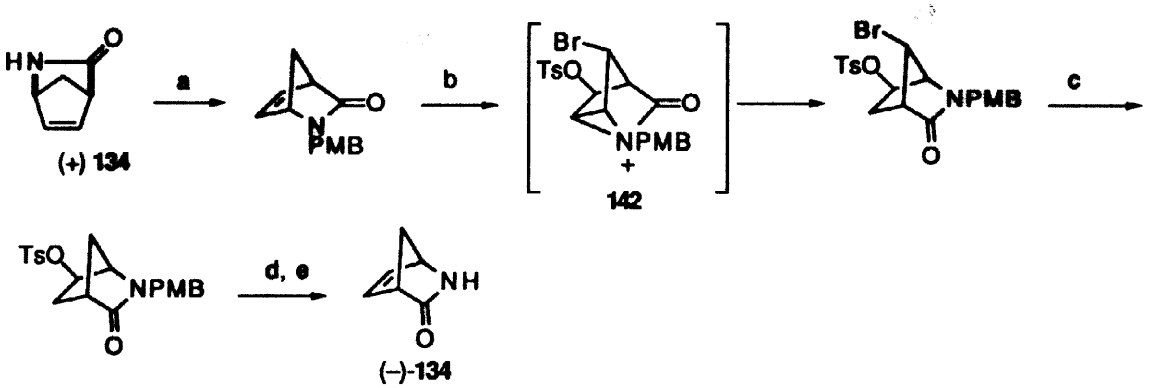
Scheme 32



a) *Pseudomonas flourescens* (ENZ A22). b) *Aureobacterium* (ENZ A25). c) $(t\text{-}BuO_2C)_2O$, DMAP, Et_3N, CH_2Cl_2. d) $NaBH_4$. e) CF_3CO_2H. f) standard guanine synthesis.

The (+)- enantiomer has also been converted into the (–)-enantiomer through intermediate **142** in an effort to recover the unused antipode.[61]

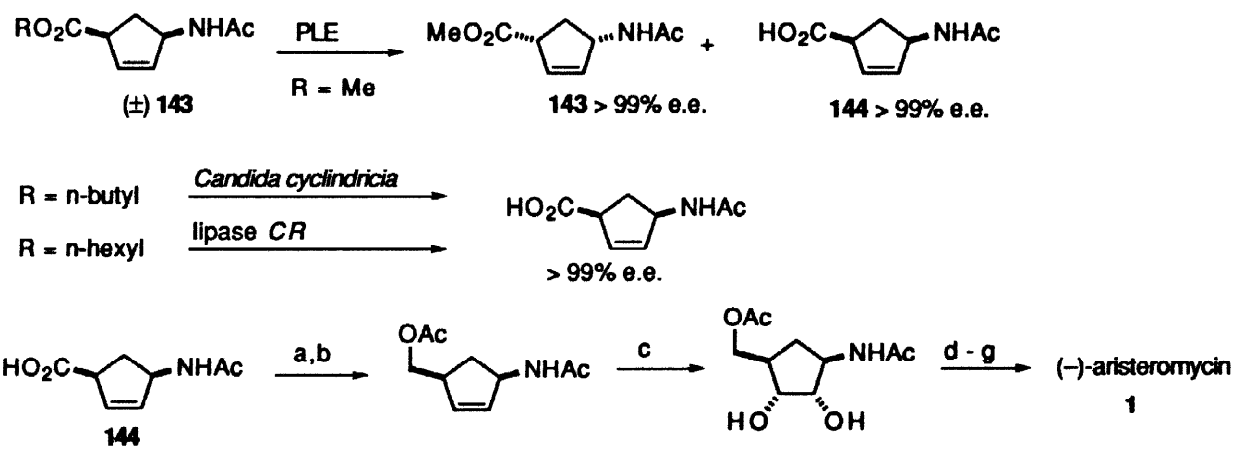
Scheme 33



a) PMBCl, KOH, phase transfer, 95%. b) NBS, p-TsOH, 74%. c) Bu_3SnH, AIBN, $PhCH_3$. d) t-BuO^-K^+, DMSO. e) $Ce(NH_4)_2(NO_3)_6$, 45% for 3 steps.

The ring opened amino esters **143** have also been resolved enzymatically by selective hydrolysis of one enantiomer by a lipase to provide the amido ester **143** and the amido acid **144** in >99% e.e.[62] The resolved acid **144** has been converted to (–)-aristeromycin in 6 steps.[63]

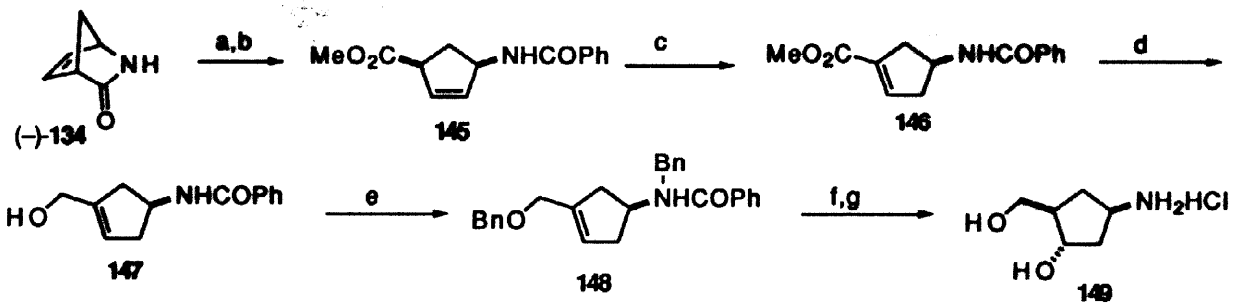
Scheme 34



a) $Ca(BH_4)_2$. b) Ac_2O, pyr. c) OsO_4, NMO, 1:1; mixture of diastereomers. d) HCl, heat. e) 5-amino-4,6-dichloropyrimidine, Et_3N. f) $(EtO)_3CH$, HCl. g) NH_3

The enantiomerically pure lactam **134** was converted to the versatile amino diol **149** as shown in Scheme 35.[64] Activation of the amide nitrogen with benzoyl chloride allowed the efficient hydrolysis to ester **145**. Exposure of the ester **145** to DBU resulted in isomerization of the alkene to the conjugated ester **146**. The ester **146** was reduced with i-Bu_2AlH to afford the allylic alcohol **147** which was treated with base and benzyl bromide to provide the benzyl ether **148**. Regioselective and stereoselective hydroboration of the alkene of **148** followed by removal of the protecting groups gave the aminodiol **149**.

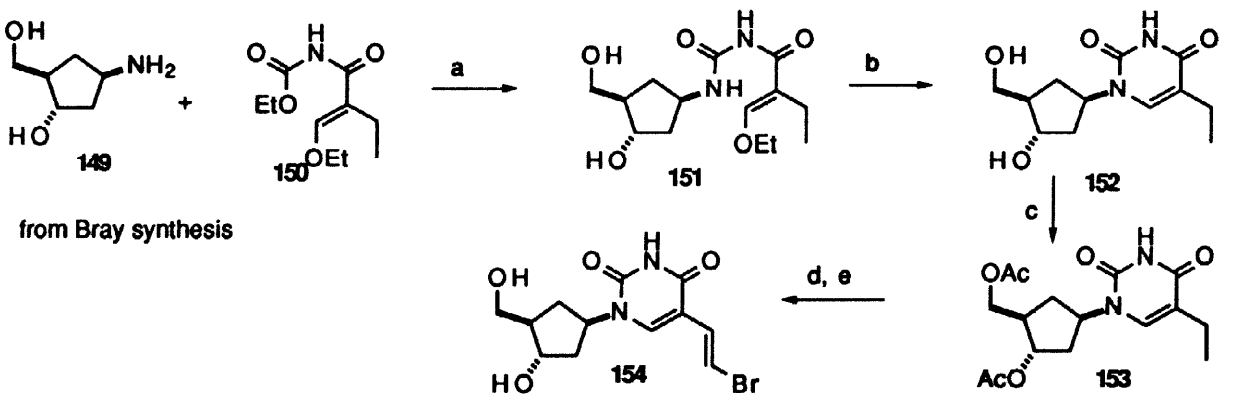
Scheme 35



a) PhCOCl, pyr., 90%. b) H_2SO_4, MeOH, 95%. c) DBU, CH_2Cl_2, 95%. d) *i*-Bu_2AlH, CH_2Cl_2,$PhCH_3$, 93%. e) BnBr, $PhCH_3$, NaOH, R_4NX, 90%. f) BH_3-Me_2S, 2,3-dimethyl-3-butene, H_2O_2, NaOH, 95%. g) H_2, Pd/C, n-PrOH.

The aminodiol **149** has recently been used in a synthesis of the anti VZV carbocyclic nucleoside BVDU **154**.[65] The aminodiol **149** was condensed with the carbethoxyacrylamide **150** to provide the pyrimidine precursor **151**. Treatment of **151** with dilute HCl gave a high yield of the pyrimidine **152**. The diol of **152** was converted to the diacetate **153**. Exposure of **153** to NBS in dioxane resulted in bromination and dehydrobromination to yield **154** after hydrolysis of the acetates.

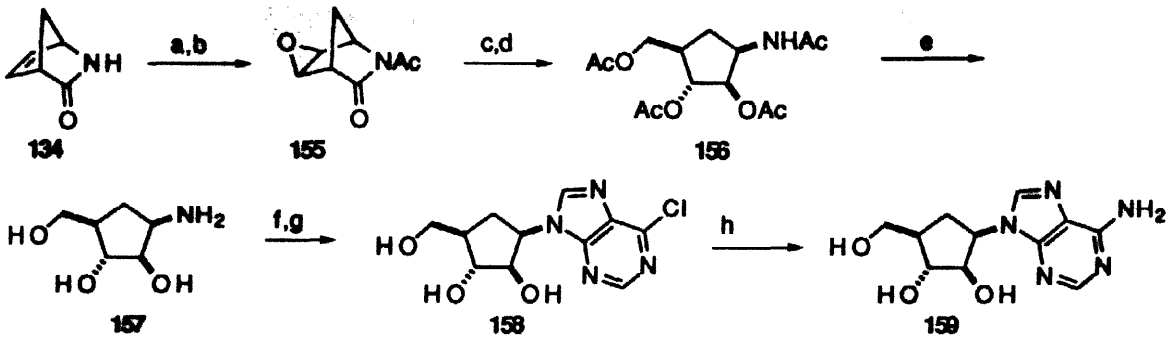
Scheme 36



a) Et_3N, dioxane, 100%. b) 2% 2N HCl in dioxane, 100%. c) Ac_2O, DMAP, dioxane, 77.5%. d) NBS, dioxane, 84%. e) NaOH, EtOH, 99%.

The carbocyclic analog **159** of cyclaridine has also been synthesized from the bicyclic lactam **134**.[66] Acetylation of the nitrogen of **134** and subsequent stereoselective epoxidation of the alkene gave the epoxide **155**. Reduction of the lactam followed by acetylation of the resultant alcohol effected an assisted epoxide opening to produce the tetraacetate **156**. The acetates were hydrolyzed and the aminotriol **157** was transformed to the carbocyclic nucleoside **159** by a classical adenine synthesis.

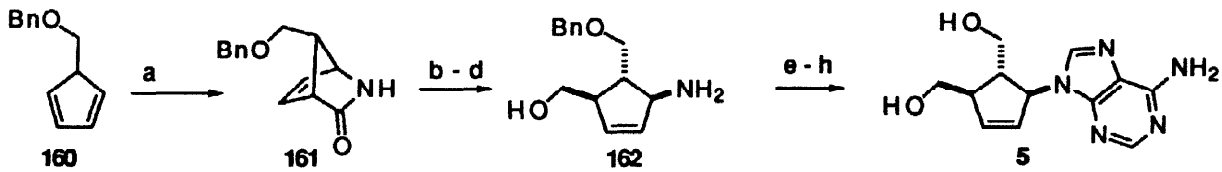
Scheme 37



a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 78%. b) m-CPBA, $CHCl_3$, 65%. c) $NaBH_4$, MeOH, 83%. d) Ac_2O, pyridine, 63%. e) 2N HCl, 70%. f) 5-amino-4,6-dichloropyrimidine, Et_3N, 70%. g) $(EtO)_3CH$, 2N HCl, 70%. h) NH_3, dioxane, 100%

In his original synthesis of BCA **5** Katigiri utilized a cycloaddition of tosylcyanide with substituted cyclopentadiene **160** to access lactam **161**, albeit in low yield.[67] The lactam was activated by acylation, reductively cleaved and the carbamate hydrolyzed to give amine **162**. A standard purine synthesis completed the synthesis of BCA **5**.

Scheme 38

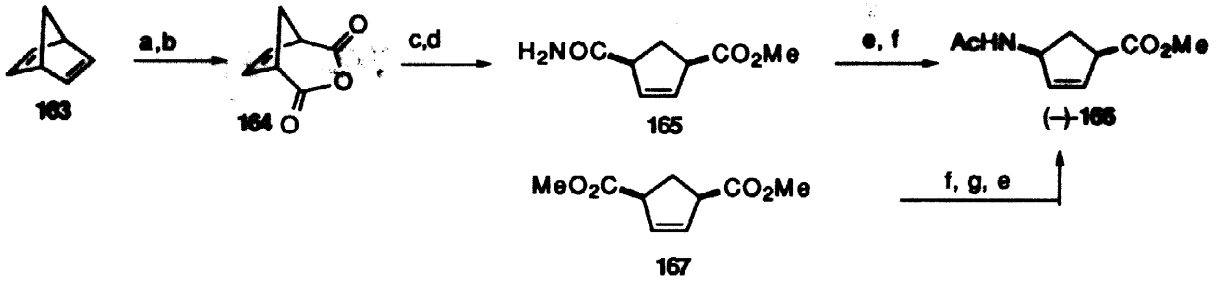


a) TsCN, then H_2O, 27% plus 2 other cycloadducts. b) LDA, THF, $ClCO_2Et$, 59%. c) $NaBH_4$, MeOH, 83%. d) KOH, MeOH, 86%. e) 5-amino-4,6-dichloropyrimidine, Et_3N, 82%. f) $(EtO)_3CH$, HCl, 86%. g) NH_3, MeOH, 77%. h) BCl_3, CH_2Cl_2, 83%.

3.2.2 Synthesis from bicyclic [2.2.1] heptenes. Several approaches to the carbocyclic subunit from bicyclic [2.2.1] heptenes have been reported. Ready availability of starting materials in large quantities make this an attractive approach. However, the need to cleave the bicyclic system and the requirement that one carbon be excised from the cleavage product increases the overall number of steps through this strategy.

Norbornadiene **163** has been utilized as the starting material in two recent enzyme mediated enantioselective syntheses of useful carbocycles.[68 - 70] The selective ozonolysis of norbornadiene **163** with a subsequent oxidative workup and formation of the cyclic anhydride afforded the symmetrical anhydride **164**.[68] The anhydride was converted to both the amide-ester **165** and the diester **167**. Amide **165** was treated with $Pb(OAc)_4$ to effect a Hofmann degradation to provide the cyclopentene amide **166** after resolution with naproxen esterase. Diester **167** was also resolved with the same enzyme to the half acid ester with good levels of enantiomeric excess. Further transformation to the amide **166** was accomplished through the amide **165**.

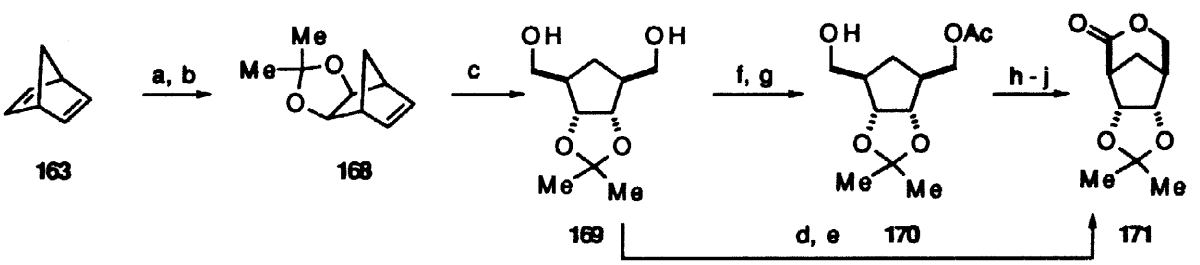
Scheme 39



a) O_3, -78°C, 5h, Ag_2O. b) DCC, CH_2Cl_2, 40%. c) NH_3. d) $SOCl_2$, Na_2CO_3, MeOH, 75%. e) $Pb(OAc)_4$, HOAc. f) naproxen esterase, 40%, 94% e.e. g) $SOCl_2$, NH_3

Another approach from norbornadiene has also been reported.[69,70] Selective dihydroxylation of norbornadiene and protection of the diol provided acetonide **168** which was ring cleaved to the known diol **169**. The meso diol **169** was oxidized enantioselectively with HLADH to produce Ohno's lactone **171**, but in low yield. Alternatively, enantioselective hydrolysis of the diacetate of **169** with lipase SAM-2 gave the monoacetate **170** in excellent yields and high enantiomeric excess. The monoacetate was readily converted in high yield to Ohno's lactone **171** which has been previously converted to carbocyclic nucleosides.[71]

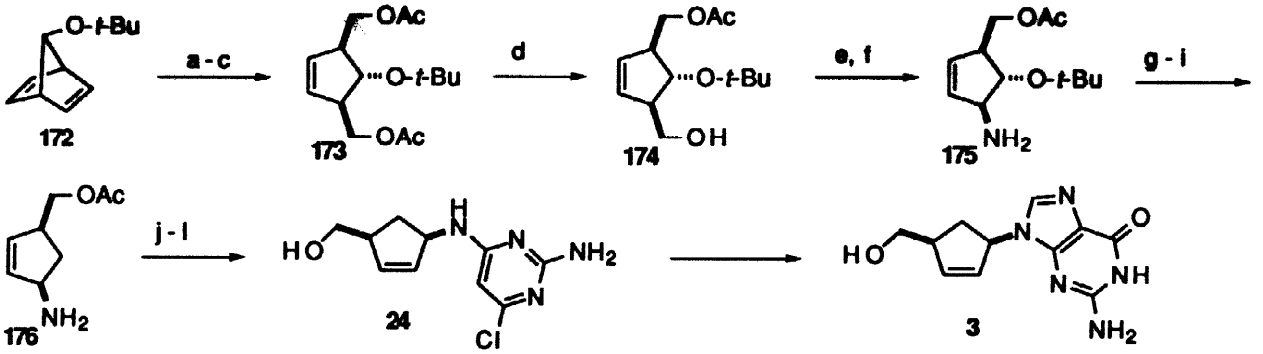
Scheme 40



a) $KMnO_4$. b) $(MeO)_2CMe_2$, p-TsOH, Me_2CO. c) O_3, then $NaBH_4$, 72% overall. d) HLADH, NAD^+, FMN, pH 9 buffer. e) PCC, 25% 2 steps, 100% e.e. f) Ac_2O, Et_3N, DMAP. g) Lipase SAM-2/VA, 94% yield, >99% e.e. h) PDC, DMF. i) K_2CO_3, MeOH. j) Ac_2O, pyr.

Tanaka has converted the substituted norbornadiene **172** into carbocyclic systems useful for the synthesis of a variety of nucleoside analogs.[72,73] Selective ozonolysis of the less hindered alkene followed by reductive workup and protection of the alcohols gave the diacetate **173**. The *meso* diacetate was exposed to *Rhizopus delemar* lipase to provide the monoacetate **174** in high yield and enantiomeric excess. Oxidation of the primary alcohol to the carboxylic acid and subsequent Hofmann degradation with diphenylphosphorazidate afforded the amine **175**. The *t*-butoxy substituent was excised by hydrolysis of the *t*-butyl ether, conversion of the alcohol to the thiocarbonate and subsequent reduction with Bu_3SnH. The amino ester **176** which resulted was transformed to (-)-carbovir by a classical purine synthesis.

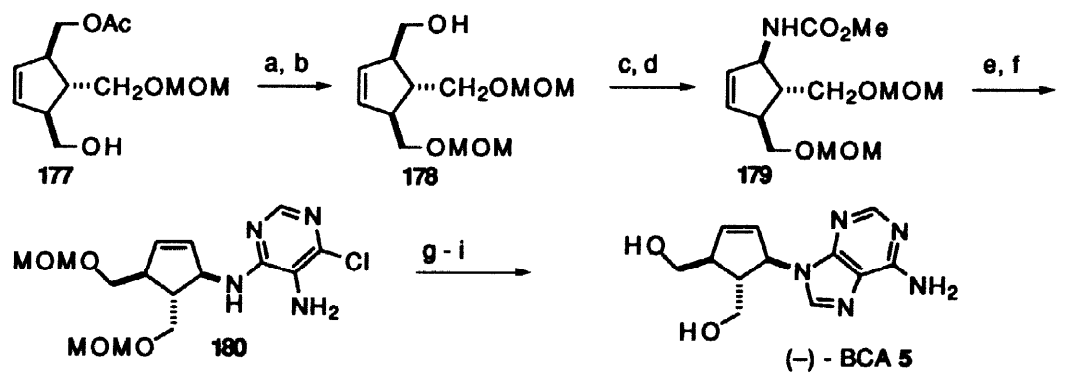
Scheme 41



a) O_3, CH_2Cl_2. b) $NaBH_4$. c) Ac_2O, 50% 2 steps +10% cleavage of other alkene . d) *Rhizopus delemar* Lipase, 95%. e) Jones reagent. f) diphenylphosphorazidate, Et_3N, then MeOH, 50%. g) $TiCl_4$. h) PhOCSCl. i) Bu_3SnH, AIBN, 92%. j) K_2CO_3, MeOH, 85% k) KOH. l) 2-amino-4,6-dichloropyrimidine, 45%.

The monoacetate **177**, obtained in an analogous manner to **174** above, was utilized in an asymmetric synthesis of (-)-BCA **5**. Protection of the primary alcohol **177** as the MOM ether and hydrolysis of the acetate gave alcohol **178**. Oxidation and Hofmann degradation as above resulted in the formation of the carbamate **179**. The carbamate was hydrolyzed and the resultant amine was converted to (-)-BCA **5** through a linear adenine synthesis.[72]

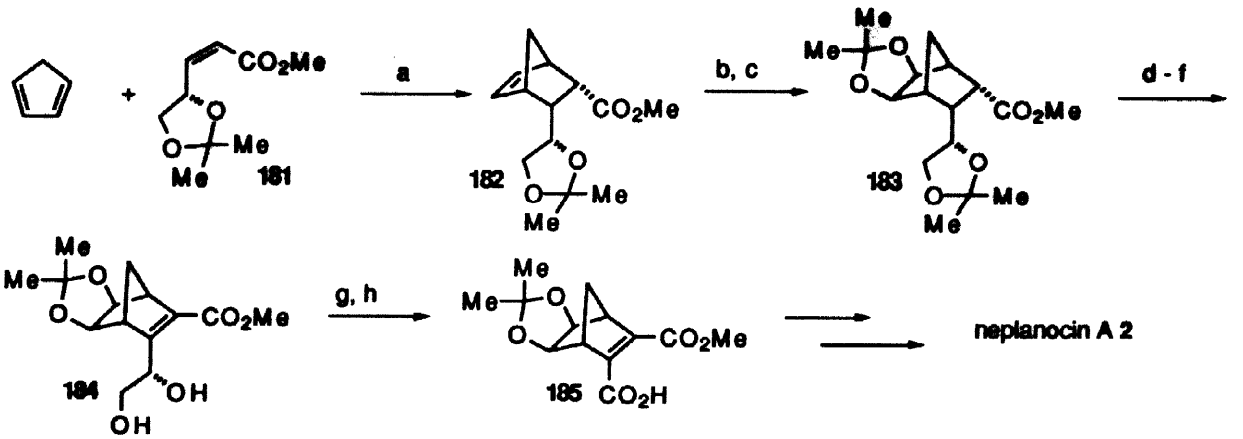
Scheme 42



a) MOMCl. b) K_2CO_3, MeOH, 85%. c) PCC, then $NaClO_2$. d) diphenylphosphorazidate, Et_3N, then MeOH, 48%. e) KOH. f) 5-amino-4,6-dichloropyrimidine, 57%. g) $(EtO)_3CH$. h) NH_3, 74% i) HCl, MeOH, 95%.

Two applications of asymmetric Diels-Alder reactions in the synthesis of carbocyclic nucleosides have appeared recently. Ortuno used the chiral dienophile **181**, derived from D-mannitol, in a Diels-Alder reaction with cyclopentadiene to prepare the *endo* adduct **182** in 78% yield.[74,75] The alkene of **182** was stereoselectively dihydroxylated and the diol was converted to the acetonide to yield **183**. Introduction of unsaturation into the bicyclic system through organoselenium chemistry and selective hydrolysis of the acyclic ketal produced diol **184**. Oxidative cleavage of the diol gave the acid **185** which was an intermeidate in the Ohno synthesis of neplanocin A.[71]

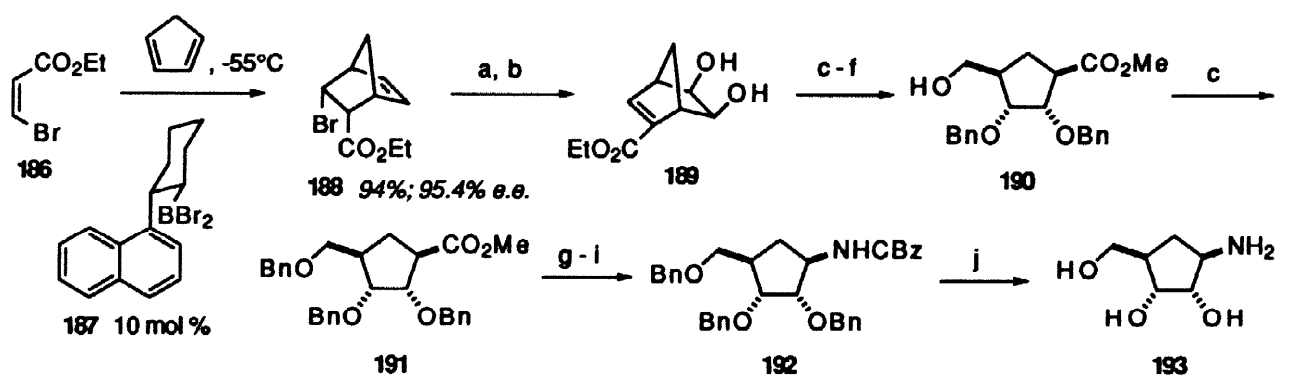
Scheme 43



a) Et_2AlCl, CH_2Cl_2, 78%. b) OsO_4, NMO, H_2O, THF, t-BuOH, 81%. c) $(MeO)_2CMe_2$, acetone, HCl, MeOH, 91%. d) LDA, THF, PhSeBr. e) H_2O_2, HOAc, 0°C to 25°C, 72%. f) 90% HOAc, 85%. g) $NaIO_4$, THF-H_2O, 92%. h) $NaClO_2$, $NaHPO_4$, 2-methyl-2-butene, t-BuOH, H_2O, 84%.

Leahy recently accomplished an asymmetric Diels-Alder reaction between cyclopentadiene and ethyl 3-bromoacrylate **186** in the presence of the chiral Lewis acid **187** which resulted in the formation of the *endo* adduct **188** in 94% yield and 95.4% e.e.[76] Dihydroxylation of the alkene of **188** and elimination of HBr gave the diol **189**. The diol was converted to **190** by protection of the diol as the dibenzyl ether, cleavage of the bicyclic system and esterification. The methyl ester **191** was transformed into the corresponding acyl azide which when heated in the presence of benzyl aalcohol resulted in a Curtius rearrangement to afford carbamate **192**. Deprotection of **192** provided the versatile ribo-carbocyclic nucleoside precursor **193**.

Scheme 44



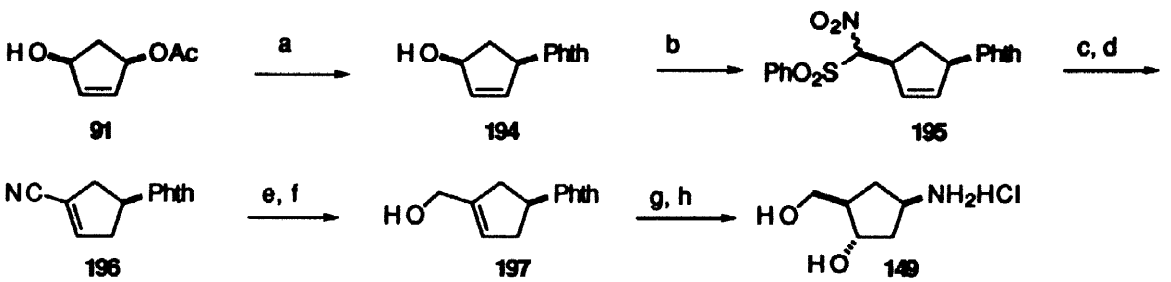
a) OsO_4; NMO; 74%. b) DBU, 97%. c) BnBr, Ag_2O, 3A sieves, 80%. d) O_3, $LiBH_4$. e) $NaIO_4$. f) Br_2, $NaHCO_3$, MeOH, 66% 3 steps. g) NH_2NH_2. h) N_2O_4. i) PhH, BnOH, heat; 67% 3 steps. j) Na, NH_3, 61%.

3.2.3 Syntheses derived from 2-cyclopenten-1,4-diol. Several syntheses of carbocyclic nucleosides from 2-cyclopenten-1,4-diol derivatives which involve palladium catalyzed coupling of the heterocyclic base directly to the carbocycle are included in an earlier section. The use of 2-cyclopenten-1,4-diol as a starting material in other

approaches including other palladium catalyzed substitutions is covered here. The monoacetate of 2-cyclopenten-1,4-diol **91** can be obtained enantiomerically enriched by enzymatic resolution.

In a second approach to the carbocyclic pseudo sugar of 2'-deoxy analogs, Bray, et al. exposed the monoacetate **91** to sodium phthalimide and a Pd(0) catalyst to obtain the imide **194**.[64] The Trost protocol was then used to introduce the carbon required for the 5'-hydroxymethyl. The nitrosulfone **195** was reduced with $TiCl_3$ and then exposed to DBU to prepare the nitrile **196**. Hydrolysis of the nitrile and reduction of the resultant acid provided the imide **197**. Stereoselective hydroboration followed by hydrolysis of the phthalimide completed the synthesis of the carbocyclic amine **149**.

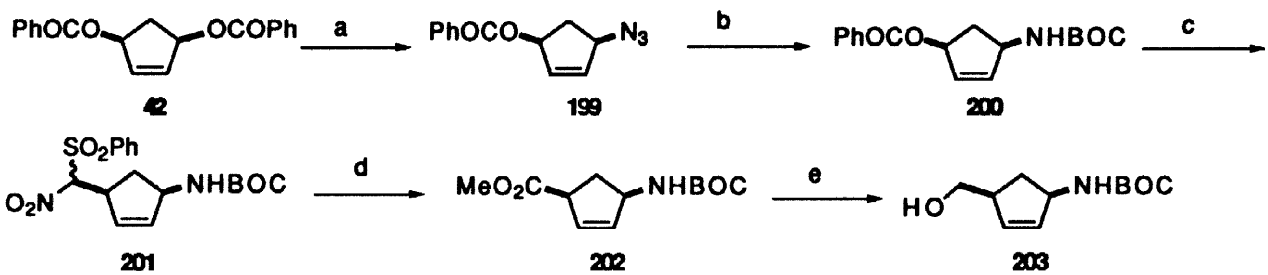
Scheme 45



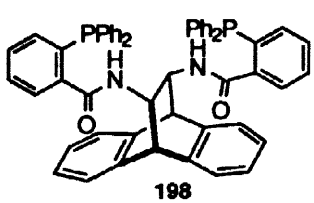
a) NaPhth, $Pd(PPh_3)_4$, DMSO, THF, 82%. b) CH_3COCN, DMAP, THF, $(allylPdCl)_2$, $PhSO_2CH_2NO_2$, THF, 86% c) $TiCl_3$, HCl, MeOH, 92%. d) DBU, DMF, 55%. e) HCl, HOAc. f) $(COCl)_2$, THF, $NaBH_4$. DMF. g) BH_3-Me_2S, 2,3-dimethyl-3-butene, H_2O_2, NaOH, 85%. h) H_2NNH_2, MeOH, HCl, 95%.

A similar strategy has been applied to the synthesis of the dideoxy amido alcohol **203** by Trost[77] utilizing an asymmetric desymmetrization of the dibenzoate **42**. Treatment of dibenzoate **42** with sodium azide in the presence of Pd(0) and Pd the chiral ligand **198** provided the azide **199** in >98% e.e. Reduction of the azide and protection of the resultant amine afforded the amide **200**. A second palladium catalyzed substitution

Scheme 46



a) $[Pd_2(dba)_3]$-$CHCl_3$, THF, chiral ligand **198**, NaN_3, -78°C, >98% e.e., 62%. b) Ph_3P, di-*t*-butyl-BOC-dicarbonate, K_2CO_3, 88%. c) 0.5% $[Pd_2(dba)_3]$-$CHCl_3$, 4 mol% Ph_3P, $PhSO_2CH_2NO_2$, 96%. d) tetrabutylammonium oxone, NaOH, $CsCO_3$, MeOH 45%. e) $LiBH_4$, 73%.

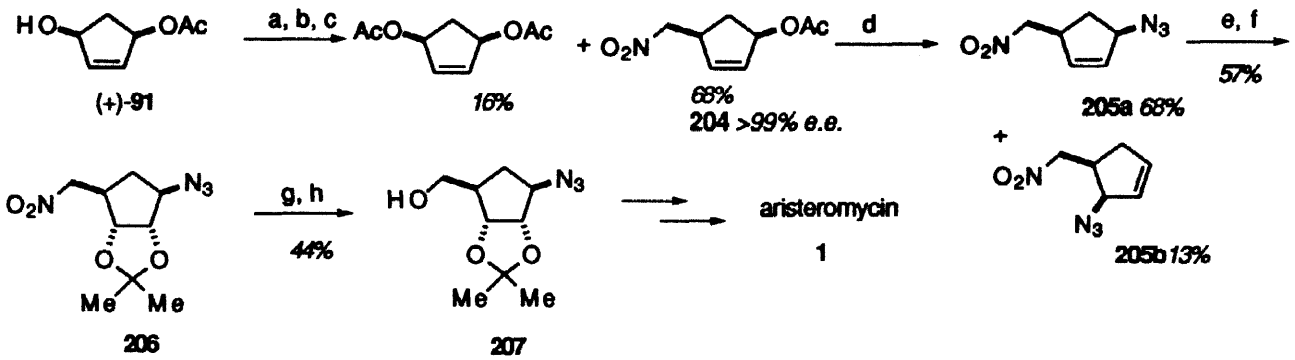


198

yielded the nitrosulfone **201** which was converted to the nitronate and oxidatively cleaved to give the methyl ester **202**. The target amide **203** was then obtained by hydride reduction of the ester. The five step, enantioselective synthesis rapidly constructs a precursor for the synthesis of dideoxy didehydro carbocyclic nucleosides.

Deardorff[78] recently reported the synthesis of the azide **207** which has previously been converted to aristeromycin. The monoacetate **91** was subjected to two successive palladium (0) catalyzed substitutions leading to the azide **205a** good yield. Nitromethane functions well as a one carbon nucleophile in the palladium catalyzed coupling. The alkene **205a** was stereoselectively dihydroxylated and the resultant diol was protected as its acetonide **206**. Oxidative cleavage of the nitro group accessed an aldehyde which was reduced to the alcohol **207**.

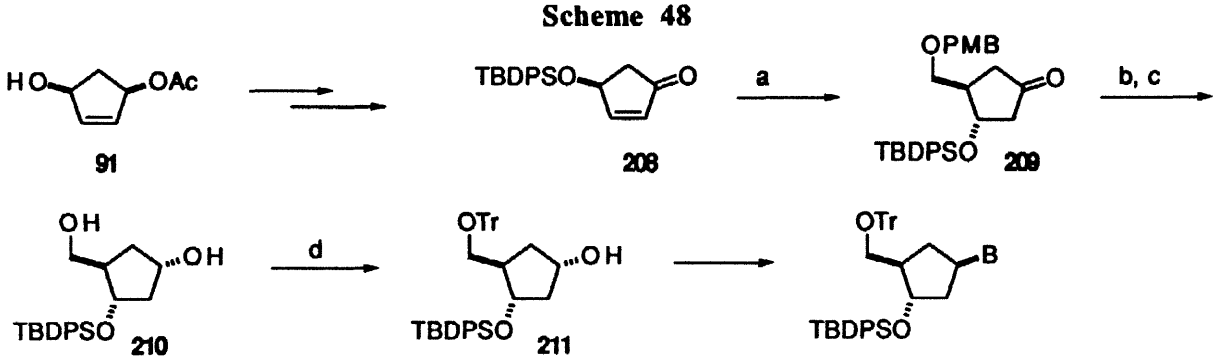
Scheme 47



a) CH_3NO_2, $(dba)_3Pd_2$-$CHCl_3$; $P(O\text{-}i\text{-}Pr)_3$, 50 °C, 60%. b) EtOCOCl, pyr. c) Pd(0) CH_2Cl_2, CH_3NO_2. d) NaN_3, $Pd(Ph_3P)_4$, THF, H_2O. e) OsO_4, NMO. f) p-TsOH, $(MeO)_2CMe_2$. g) $KMnO_4$, KOH, MeOH. h) $NaBH_4$.

Borthwick employed the resolved monoacetate **91** to prepare the silyloxy enone **208**.[79] A conjugate addition of the α-alkoxy higher order mixed cuprate proceeded stereoselectively to give **209**. The p-methoxy benzyl ether was removed to effect a directed hydride reduction of the ketone and provide diol **210** with excellent stereoselectivity. Selective protection of the primary alcohol required the use of the trityl ether to

Scheme 48

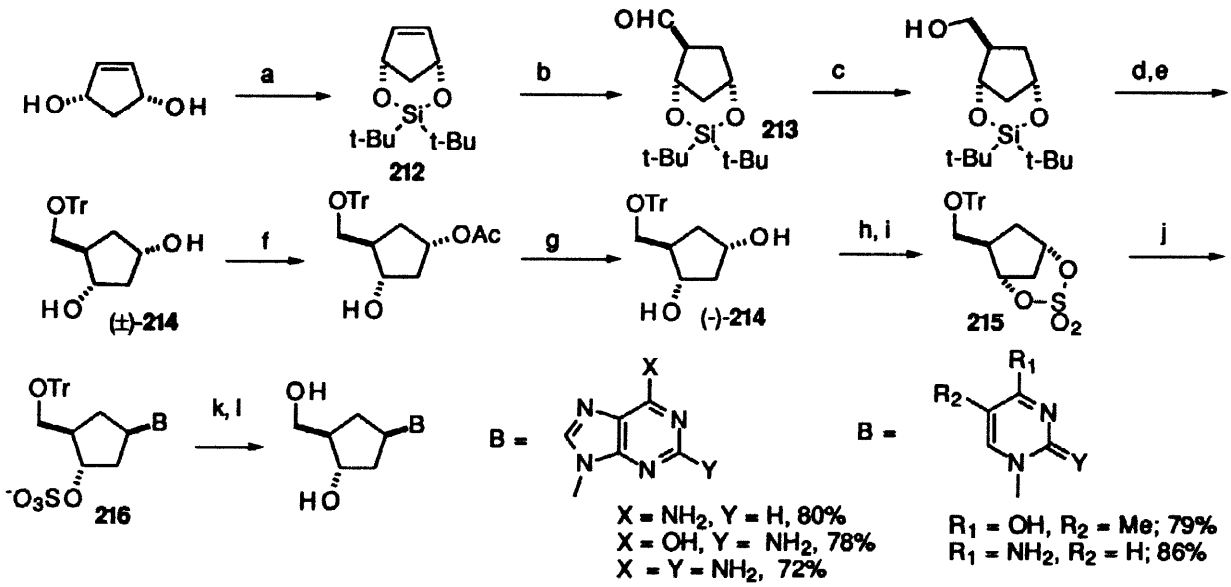


a) (2-Th)$(PMBOCH_2)CuCNLi_2$, 67%. b) DDQ, CH_2Cl_2, 86%. c) $NaBH(OAc)_3$, EtOAc, 75%. d) Ph_3CCl, DMAP, CH_2Cl_2, 80%.

achieve high selectivity in the construction of 211. The alcohol 211 could be readily converted to a variety of 2'-deoxy analogs by direct Mitsunobu coupling with heterocyclic bases.

A related approach by Moser and Lang[80] begins by protecting 2-cyclopenten-1,4-diol as the cyclic siloxane 212. Efficient rhodium (I) hydroformylation of the alkene incorporated the 5'-carbon in the form of aldehyde 213 which was reduced to the alcohol. Tritylation of the primary alcohol and hydrolysis of the siloxane produced the diol 214 which was enzymatically resolved in good yield and excellent enantiomeric excess as the monoacetate. The acetate was then hydrolyzed back to the enantiomerically pure diol 214 which was transformed into the cyclic sulfate 215 for coupling to a variety of heterocyclic bases. The intermediate sulfates 216 were readily hydrolyzed to the nucleoside analogs with aqueous acid.

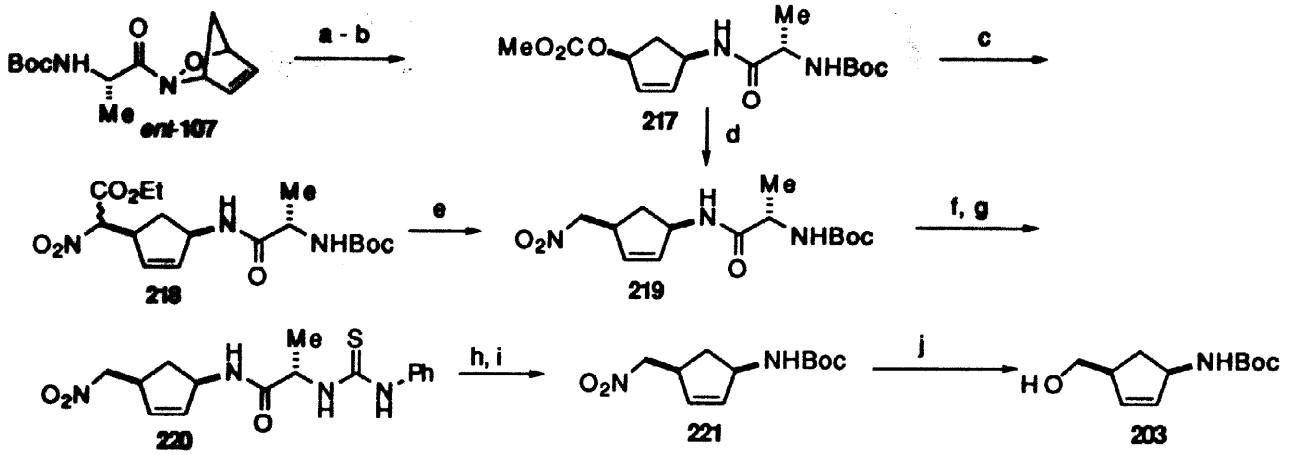
Scheme 49



a) $(t\text{-Bu})_2Si(OSO_2CF_3)_2$, lutidine, CH_2Cl_2, 80%. b) 0.4 mol% $RhCl(Ph_3P)_3$, THF, H_2, CO, 80 bar, 95%. c) $NaBH_4$, THF, H_2O, 98%. d) Ph_3CCl, DMAP, Et_3N, CH_2Cl_2, 88%. e) *n*-Bu_4NF, THF, 100%. f) vinyl acetate, *pseudomonas flourescens* lipase, >99% e.e., 43%. g) MeOH, $H_2NCH_2CH_2NH_2$, 95%. h) $SOCl_2$, Et_3N, CH_2Cl_2, 100%. i) MeCN, CCl_4, 1.5 mol % $RuCl_3$, $NaIO_4$, 100%. j) base, DBU, 80%. k) MeOH, HCl, 87%. l) NH_3, MeOH, 100%.

3.2.4 [4+2] Cycloadditions of cyclopentadiene and R-N=O dienophiles. Miller employed a chiral acyl nitroso dienophile derived from alanine in a cycloaddition with cyclopentadiene to prepare the adduct *ent*-107 as described earlier (see Scheme 22).[81] The N–O bond was reductively cleaved and the resultant alcohol was protected as a methyl carbonate to form carbonate 217. A palladium (0) catalyzed substitution led to the nitro ester 218 which was decarboxylated to the nitromethyl derivative 219. Removal of the *t*-BOC and subsequent conversion of the amine to the thioimide 220 facilitated amide hydrolysis and further prepartion of the carbamate 221. Finally, oxidative cleavage of the nitronate and reduction of the intermediate aldehyde with sodium borohydride gave the hydroxy carbamate 203 also prepared by Trost.[77]

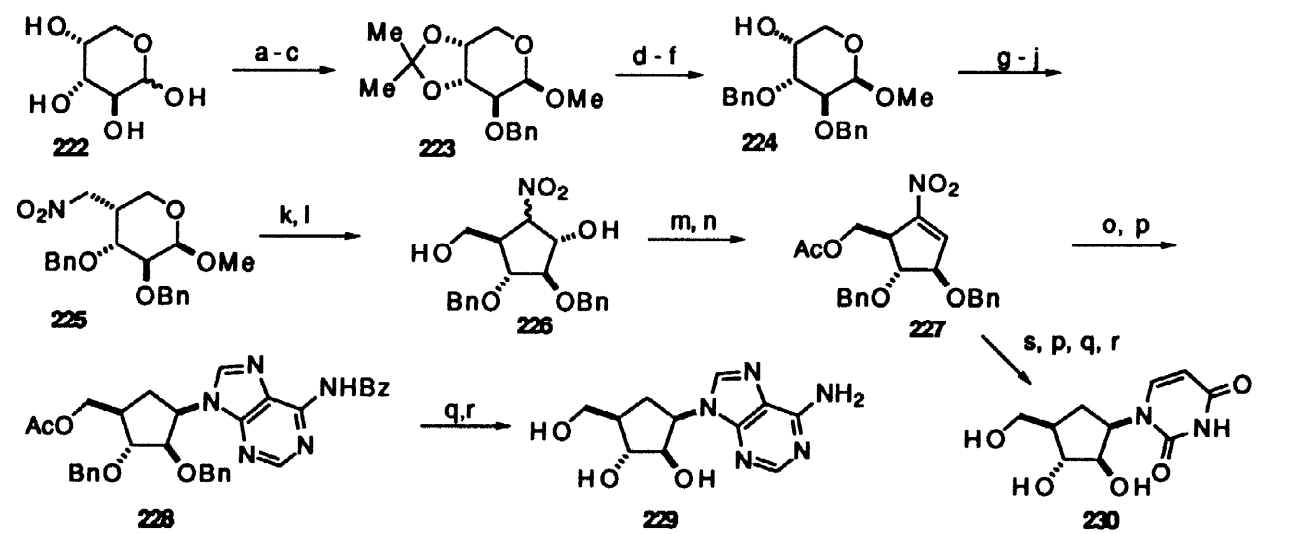
Scheme 50



a) $Mo(CO)_6$, 89%. b) $(CO_2Me)_2O$, DMAP, CH_2Cl_2, 97%. c) $EtO_2CCH_2NO_2$, CH_3CN, $(Ph_3P)_4Pd$, 96%. d) $Pd(PPh_3)_4$, CH_3NO_2, 60-65%. e) LiCl, DMSO, 45-50%. f) TFA, CH_2Cl_2. g) PhN=C=S, 89%, 2 steps. h) TFA. i) Boc_2O, Et_3N. j) MeOH, $PhCH_3$, EtOAc, t-BuOK, $KMnO_4$, -30 to -40 °C; $NaBH_4$, 37%.

3.2.5 Synthesis from carbohydrates and amino acids. Several recent syntheses of carbocyclic nucleosides have been accomplished by starting with natural carbohydrates and amino acids, the "chiral pool". The Yoshikawa synthesis of some 2'-β-carbocyclic nucleosides began with the transformation of D-arabinose **222** to the methyl protected form **223**.[82] Hydrolysis of the acetonide and selective protection of the 3'-hydroxyl as the benzyl ether gave the alcohol **224**. The alcohol of **224** was oxidized and the ketone was exposed to the enolate of nitromethane to afford **225** after dehydration and conjugate reduction of the conjugate nitro olefin. An

Scheme 51

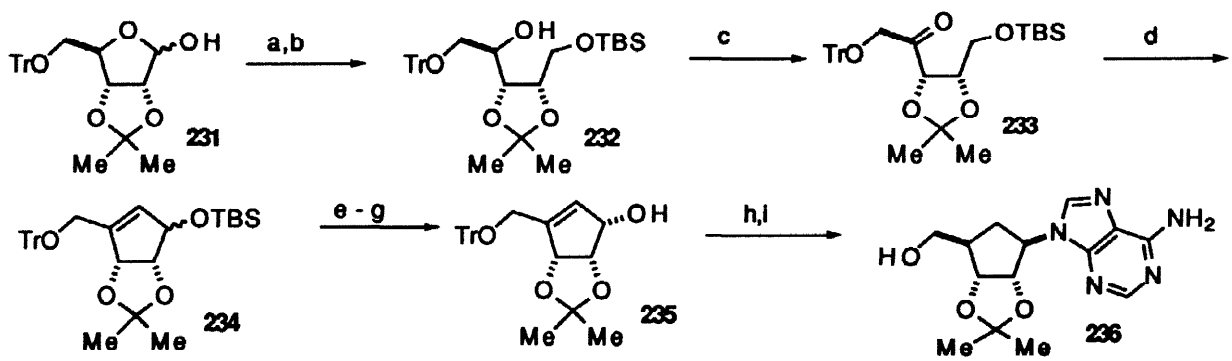


a) HCl, MeOH. b) $(MeO)_2CMe_2$, p-TsOH, DMF. c) BnCl, NaH, DMF, 100%. d) 80% HOAc, 50°C. e) Bu_2SnO, $PhCH_3$. f) BnBr, CsF, DMF, 100%. g) $(COCl)_2$, CH_2Cl_2, Et_3N, DMSO. h) CH_3NO_2, KF, 18-Cr-6, DMF, 72%. i) p-TsOH, Ac_2O. j) $NaBH_4$, EtOH, 85%. k) con HCl, CH_3CO_2H, 57%. l) CsF, DMF, 86%. m) p-TsOH, Ac_2O. n) pyridine, 82%. o) N6-benzoyladenine, DMF, CSF, 85%. p) Bu_3SnH, AIBN, 21%. q) NaOMe, MeOH, 88%. r) Pd/H_2, EtOAc, HOAc, 94%. s) CsF, silylateduracil, DMF, 50%.

interesting ring contraction was then executed by hydrolysis of the acetal which effected an aldol addition of the nitronate on the resultant aldehyde. Dehydration of the alcohol through the acetate generated the nitro olefin **227**. The heterocyclic base was then incorporated by a Michael addition with the aid of CsF. The nitro group was reductively removed in low yield with Bu_3SnH to yield **228** which was deprotected to complete the synthesis of (+)-cyclaridine **229**. The nitro oelfin **227** was also used in the preparation of the pyrimidine analog **230**.

D-Ribose was used as the starting material in two recent syntheses of carbocyclic nucleosides: the Ohira[83] synthesis of (-)-aristeromycin and the Chu[84] synthesis of some L-carbocyclic nucleoside analogs. The Ohira synthesis begins by conversion of the acetonide **231**, which is derived from D-ribose, to the alcohol **232** by reduction of the aldehyde and protection of the primary alcohol. Oxidation of the secondary alcohol produced the ketone **233**. Next, a very interesting C–H insertion reaction was employed to close the carbocyclic ring. Treatment of the ketone **233** the lithium anion of trimethylsilyldiazomethane resulted in a 55-65% yield of the diastereomeric cyclopentenes **234** by C–H insertion of the intermediate vinyl carbene. The diastereomeric mixture was converted to the single allylic alcohol **235** by an oxidation-reduction sequence. Direct incorporation of adenine through a Mitsunobu coupling produced the (-)-aristeromycin acetonide **236**.

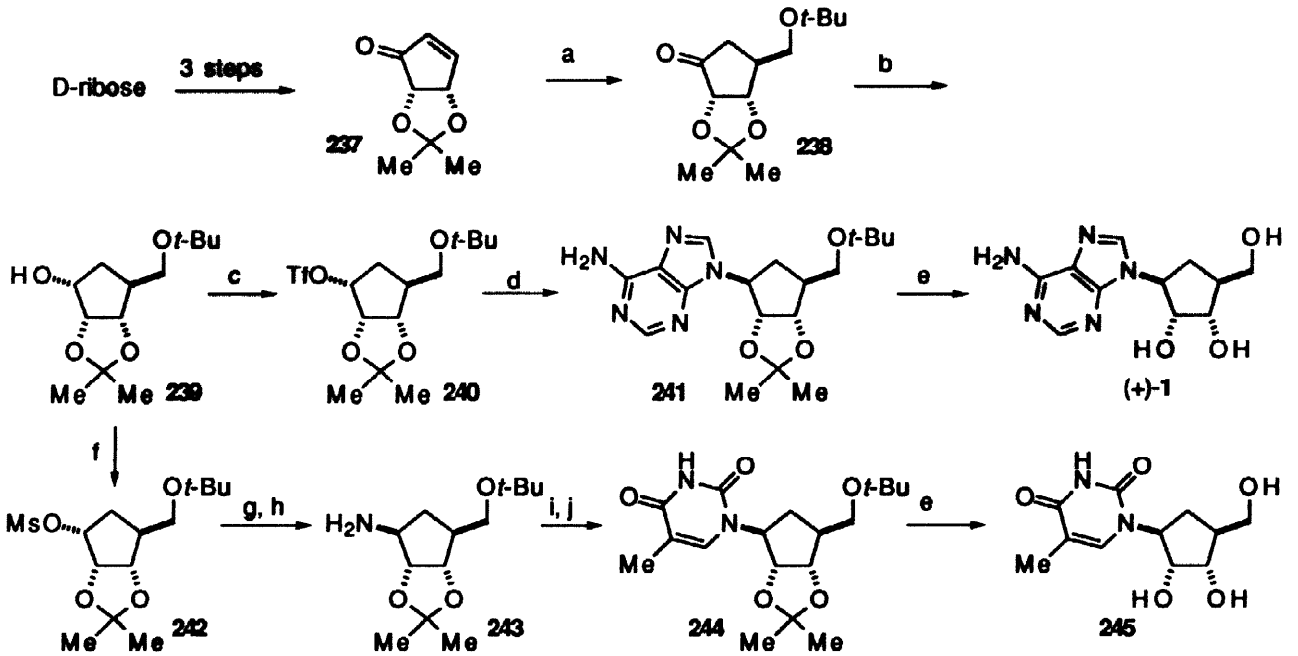
Scheme 52



a) $LiAlH_4$, Et_2O, 85%. b) t-$BuMe_2SiCl$, imidazole, DMF, 97%. c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 89%. d) $TMSC(Li)N_2$, THF, 0°C, 55-65%, 0°C. e) Bu_4NF, THF, 69%. f) PDC, CH_2Cl_2, 80%. g) $LiAlH_4$, THF, 87%. h) adenine, Ph_3P, DEAD, THF, 52%. i) HCl, MeOH, 100%.

L-Carbocyclic nucleoside analogs[84] have been constructed from the enone **237** which had been previously prepared from D-ribose.[85] Addition of the homocuprate derived from *t*-butyloxymethyllithium to enone **237** served to incorporate the 5'-hydroxymethyl. The ketone was stereoselectively reduced to the alcohol **239** which was readily transformed to the triflate **240**. Direct displacement of the triflate with the sodium salt of adenine afforded the nuleoside analog **241** but in low yield. Hydrolysis of the protecting groups completed the synthesis of (+)- aristeromycin. In an effort to improve the yield of the coupling to the heterocyclic base, the alcohol **239** was mesylated and the mesylate was displaced with lithium azide in 89% yield. Reduction of the azide yielded the amine **243** which produced the L-thymidine carbocyclic nucleoside **245** through a standard pyrimidine synthesis.

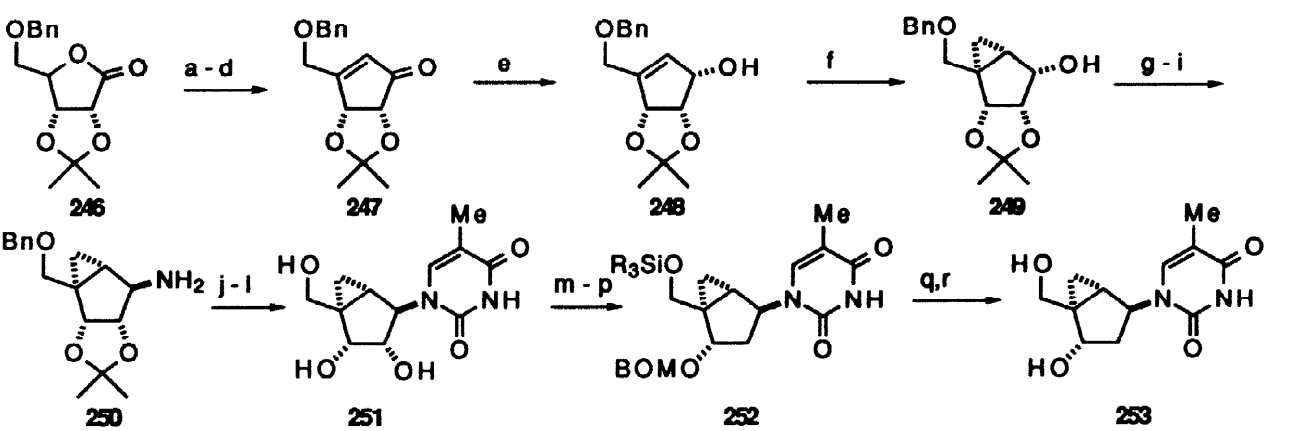
Scheme 53



a) $(t\text{-BuOCH}_2)_2\text{CuLi}$, t-BuOMe, THF, -30°C, 87%. b) $i\text{-Bu}_2\text{AlH}$, CH_2Cl_2, -78°C, 82%. c) $(CF_3SO_2)_2O$, pyr, 0°C, 97%. d) adenine, NaH, 18-cr-6, DMF, 32%. e) CF_3CO_2H, H_2O, 80%. f) MsCl, Et_3N, CH_2Cl_2, 100%. g) LiN_3, DMF, 140°C, 89%. h) 5% Pd/C, EtOH, 20 psi. i) β- methoxy-α-methacryloyl isocyanate, DMF, 88% 2 steps. j) 30% NH_4OH, EtOH, 85%.

Two different groups have independently prepared several conformationally restricted cyclopentyl nucleosides from ribonolactone **246**. Marquez[86] had previously converted ribonolactone **246** to the cyclopent-

Scheme 54

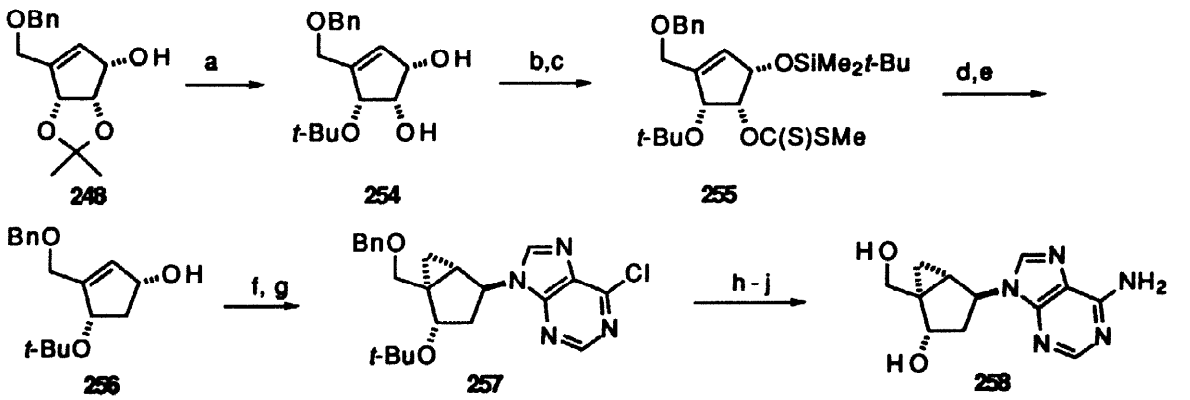


a) $LiCH_2P(O)(OCH_3)_2$. b) $NaOCH_3$. c) CrO_3-pyr. d) K_2CO_3, 18-crown-6. e) $NaBH_4$, $CeCl_3$. f) Zn/Cu, CH_2I_2, 73%. g) TsCl, Et_3N, CH_2Cl_2, DMAP, 77%. h) NaN_3, DMF, 70°C, 88%. i) H_2, Lindlar's cat., 100%. j) $CH_3OCH{=}C(CH_3)CONCO$, CH_2Cl_2, -78°C, 95%. k) 0.2 N HCl, EtOH, H_2O, 80%. l) H_2, 10% Pd/C, AcOEt, MeOH, (84% e.e.). m) $i\text{-Pr}_3SiCl$, imidazole, DMF, 67%. n) BOMCl, DBU, CH_3CN, 85%. o) $CH_3C_6H_4OC(S)Cl$, DMAP, Et_3N, CH_2Cl_2, 90%. p) 1. Bu_3SnH, AIBN, DME, 80°C; 2. preparative HPLC, 65%, 100% e.e. q) n-Bu_4NF, THF, 99%. r) H_2, 10% Pd/C, NaOMe, 88%.

enone **247** during his synthesis of neplanocin A. A stereoselective reduction of the enone produced the allylic alcohol **248**. Altmann[87] subsequently converted the allylic alcohol **248** to the cyclopropane **249** under Simmons-Smith conditions. The secondary hydroxyl was tosylated, the tosylate displaced with azide and the resultant azide was reduced to the aminocyclopentane **250**. A standard pyrimidine synthesis followed by removal of the protecting groups provided the carbocyclic nucleoside **251**. The 2'-deoxy analog **253** was prepared from **251** by selective protection of the 5' and 3' hydroxyls and radical reduction of the 2'thiocarbonate.

Marquez has prepared the adenine derivative as well as other analogs[86,88] as shown in Scheme 55. The allylic alcohol **248** obtained as described above was selectively converted to the diol **254** with Me_3Al. Selective protection of the allylic hydroxyl followed by conversion of the 2'-hydroxyl to its xanthate gave **255**. Reductive removal of the 2'-xanthate and removal of the 1'- silyl ether provided the key allylic alcohol **256**. A directed cyclopropanation of **256** followed by Mitsunobu coupling of 6-chloropurine and the alcohol generated the protected adenosine analog **257** which was readily converted to the desired **258**.

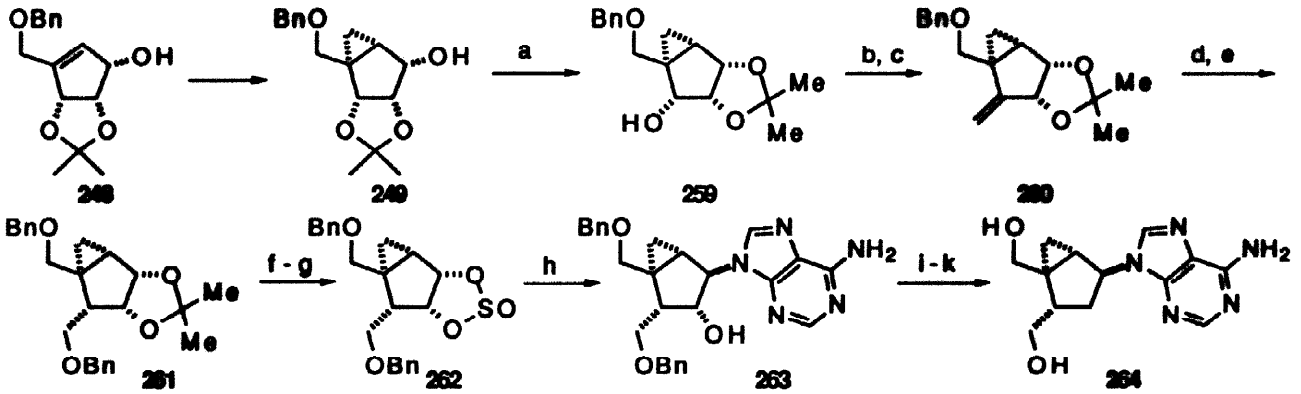
Scheme 55



a) $AlMe_3$, CH_2Cl_2; -78°C, 54%. b) t-$BuMe_2SiCl$, imidazole, DMF, 87%. c) CS_2, NaH, MeI, THF, 82%. d) Bu_3SnH, AIBN, $C_6H_5CH_3$, 77%. e) n-Bu_4NF, THF, 92%. f) Sm, $HgCl_2$, THF, CH_2I_2, 96%. g) Ph_3P, DEAD, 6-chloropurine, THF, 58%. h) NH_4OH, dioxane, 76%. i) BCl_3, CH_2Cl_2; -78°C. j) NH_4OH, 70%.

The 3'-hydroxymethyl derivative **264** has also been synthesized from bicyclic alcohol **249** as shown in Scheme 56.[89] Acid catalyzed rearrangement of the acetonide **249** produced the acetonide **259** in good yield. Oxidation of the alcohol and methylenation of the resultant ketone gave the methylene cyclopentane **260**. The 3'-hydroxymethyl was incorporated by stereoselective hydroboration of the exocyclic olefin followed by benzylation of the primary alcohol to give **261**. The acetonide of **261** was hydrolyzed and the diol transformed to the cyclic sulfite **262**. In a novel coupling reaction, the cyclic sulfite was regioselectively opened by the sodium salt of adenine to produce **263** in good yield. Removal of the benzyl protecting groups gave the adenosine analog **264**.

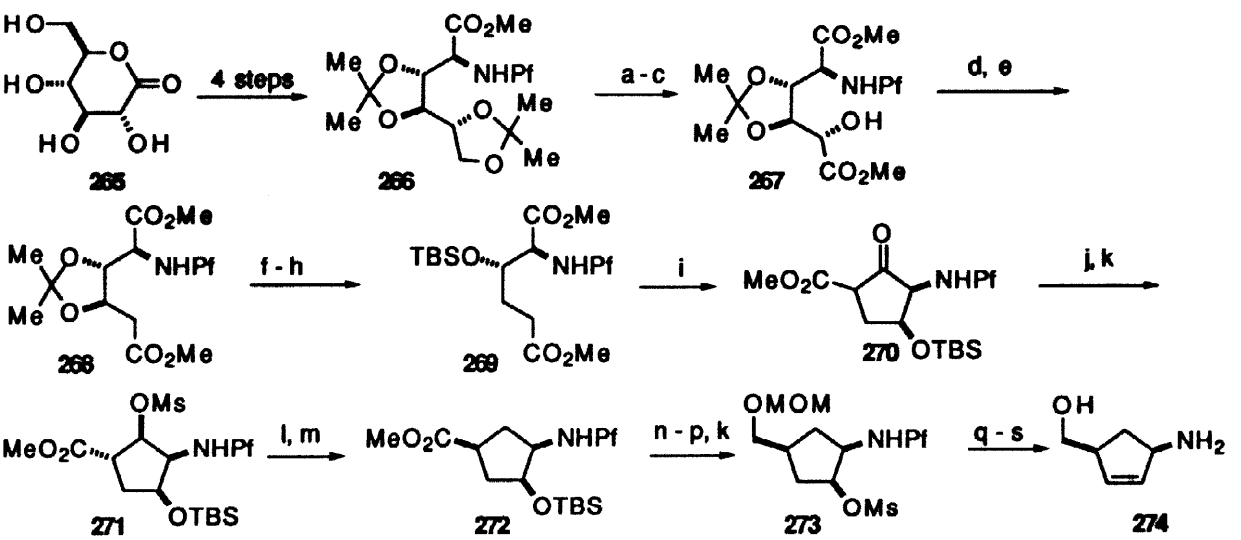
Scheme 56



a) p-TsOH, acetone, 50°C, 57%. b) Pr_4NRuO_4, NMO, CH_2Cl_2, 100%. c) $CH_3(Ph_3P)_3Br$, n-BuLi, THF, 0°C, 90%. d) BH_3-RHF, THF, 0°C; $NaBO_3$, 90%. e) BnBr, Bu_4NI, NaH, THF, 80°C, 88%. f) 1N HCl, MeOH, THF, 50°C, 100%. g) $SOCl_2$, Et_3N, 0°C, 100%. h) adenine, NaH, 18-cr-6, DMF, 120°C, 72h, 50%. i) CS_2, NaH, MeI, THF, 0°C. j) Bu_3SnH, Et_3B, C_6H_6, 73%. k) Pd, HCOOH, MeOH, 83%.

Rapoport accomplished a synthesis of the amino alcohol **274** from D-glucono-δ-lactone **265** (Scheme 57).[90] The bis-ketal **266** was prepared from **265** in 4 steps and subsequently converted to the diester **267** by selective hydrolysis and oxidation of the primary alcohol. Dehydroxylation of the hydroxy ester produced the ester **268**. Exposure of the β-alkoxy ester to KHMDS effected β-elimination and the resultant unsaturated ester was hydrogenated to generate the diester **269**. Treatment of diester **269** with KHMDS resulted in Dieckmann

Scheme 57

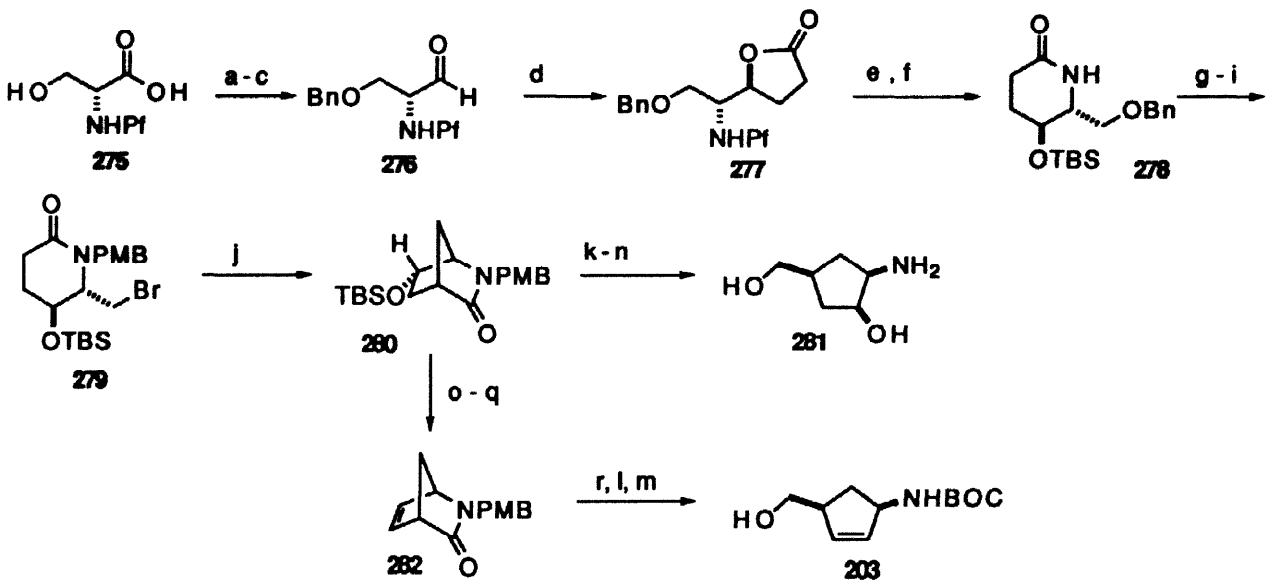


a) HCl, H_2O, 86%. b) Pt, O_2, 85%. c MeI. d) Tf_2O. e) LiI-$3H_2O$, 81%. f) KHMDS. g) t-$BuMe_2SiCl$, imidazole, 96%. h) H_2Pd/C, 92%. i) KHMDS, 95%. j) $NaBH_4$, MeOH, 86%. k) MsCl, 97%. l) NaH, 96%. m) H_2, Pt/C, 95%. n) $LiAlH_4$, 95%. o) MOMCl, 92%. p) Bu_4NF, 95%. q) NaH, $MeOCH_2CH_2OH$. r) PPTS, 89%. s) TFA, 79%.

condensation to the cyclopentanone **270**. The ketone was reduced and the resultant alcohol mesylated to afford **271**. The mesylate eliminated upon exposure to sodium hydride and the unsaturated ester was hydrogenated to the all *cis* **272**. Conversion of the silyloxy ether to the corresponding mesylate **273** followed by elimination gave the target amino alcohol **274** after removal of the protecting groups. Ultimately, all of the initial stereocenters are either removed or inverted during the synthesis.

Rapoport[91] has also prepared a carbocyclic precursor for carbocyclic nucleoside synthesis from the protected L-serine **275** (Scheme 58). Protection of the hydroxyl and adjustment of the acid oxidation state produced the aldehyde **276** which was exposed to a titanium homoenolate to arrive at the butyrolactone **277**. The nitrogen protecting group was cleaved resulting in a lactone-lactam rearrangment to afford lactam **278** after protection of the secondary alcohol. The benzyl ether was hydrogenolyzed and the resultant alcohol was converted to the primary bromide **279**. Exposure of the lactam to KHMDS effected an intramolecular alkylation to produce the functionalized bicyclic lactam **280**. The lactam was reduced and deprotected to provide the aminodiol **281**. The lactam **280** could also be transformed in a series of steps to the hydroxycarbamate **203**.

Scheme 58

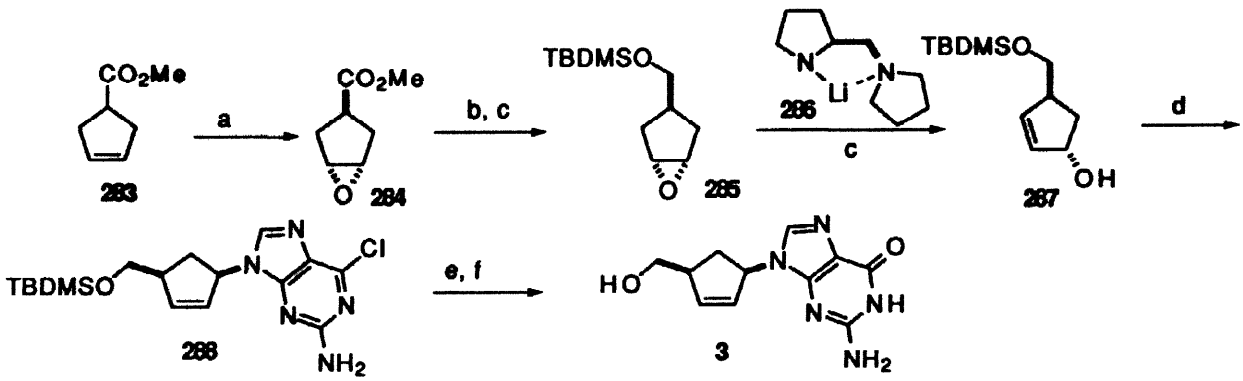


a) isoxazolidine, HOBT, DCC, 84%. b) Na, BnBr, Bu_4NI, 97%. c) $LiAlH_4$, aq. $KHSO_4$, 99%.
d) t-butyl-3-propionate, Zn-Cu, $TiCl_4$, $Ti(i\text{-}PrO)_4$, 6.5:1 *anti:syn*, 68% *anti* after recrystallization. e) H_2, Pd/C, 97%.
f) t-$BuMe_2SiCl$, imidazole, 92%. g) NaH, PMBBr. h) H_2, Pd/C, 100%. i) CBr_4, Ph_3P. j) KHMDS, 88%.
k) Na, NH_3, 95%. l) $(BOC)_2O$, pyr., DMF, 100%. m) $NaBH_4$, MeOH. n) HCl, CH_2Cl_2. o) Bu_4NF, 97%. p) Ph_3P, I_2, imidazole. q) DBU, 93%. r) $Ce(NH_4)_2(NO_3)_6$, H_2O.

3.2.6 Syntheses using asymmetric desymmetrizations. Two examples of the asymmetric desymmetrization of epoxide **285** have been reported for the asymmetric synthesis of carbocyclic nucleosides.[92,93] Asami[93] employed the ester **283**, available from dimethyl malonate and 1,4-dichloro-*cis*-2-butene, to prepare the epoxide **285** by epoxidation to give the intermediate **284** followed by reduction of the ester and protection of the resultant alcohol. The *meso* epoxide **285** was desymmetrized by exposure to the chiral amide base **286**. The

allylic alcohol **287** was generated in 74% yield and 83% e.e. Mitsunobu coupling of 2-amino-6-chloropurine with the allylic alcohol afforded the chloropurine **288** which yielded carbovir upon removal of the silyl ether and hydrolysis.

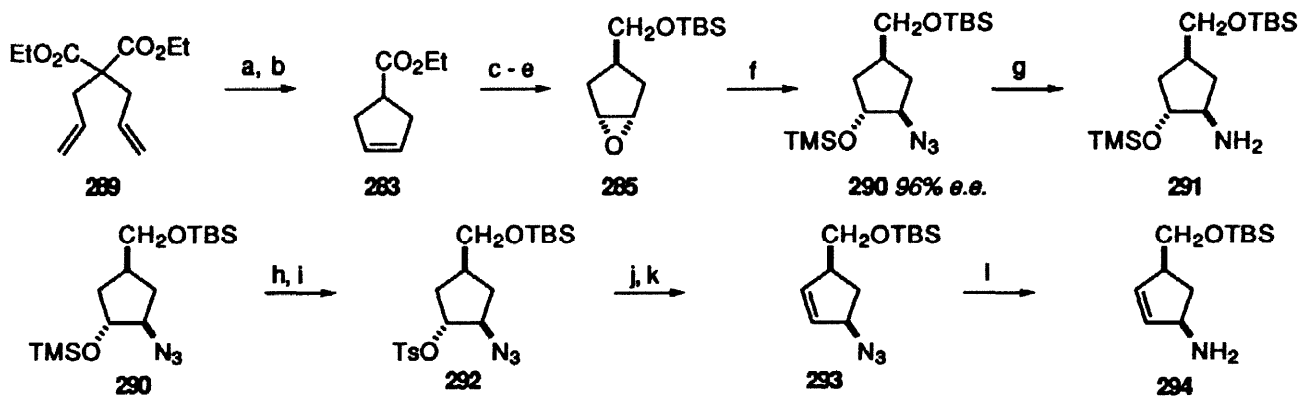
Scheme 59



a) m-CPBA, C_6H_{12}, 91%, 79% trans, 21% cis. b) $LiAlH_4$, 76%. c) t-$BuMe_2SiCl$, imidazole, DMF, 100%. 1.5 equiv **285**, THF, DBU, 25°C, 74%, 83% e.e. d) 2-amino-6-chloropurine, Ph_3P, DEAD, dioxane, 35%. e) n-Bu_4NF, THF, 92%. f) NaOH, H_2O, 89%.

Another desymmetrization of epoxide **285** has also appeared[94] Diallyl ethyl malonate underwent ring closing metathesis to **283** upon treatment with Nugent's catalyst. Epoxidation, reduction and protection as reported by Asami gave the epoxide **285**. Exposure of **285** to $TMSN_3$ and Jacobsen's catalyst provided a 96% e.e. of the azide **290**. Hydrogenation of the azide produced the amine **291** which is a useful intermediate for the synthesis of 3'-deoxycarbocyclic nucleosides.

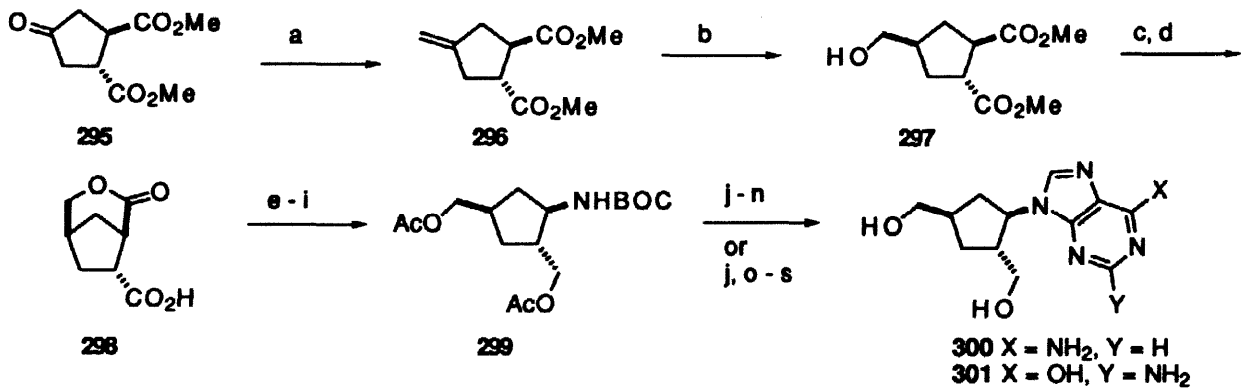
Scheme 60



a) NaCN, DMSO, 83%. b) 2 mol% tungsten catalyst, 4 mol % Et_4Pb, $PhCH_3$, 85%. c) mCPBA, 70%. d) $LiAlH_4$, THF, -78°C. e) TBSCl, imidazole, CH_2Cl_2, 90%. f) TMSCN, 2 mol% catalyst, Et_2O, 95%. g) H_2, Lindlar, 90°C, 93%. h) CSA, MeOH. i) TsCl, pyridine, 81%. j) NaSePh, THF, HMPA. k) H_2O_2, pyridine, 81%. l) $LiAlH_4$, Et_2O, 0°C, 88%.

3.2.7 Syntheses from C2 symmetric intermediates. Samuellson has used the enantiomerically pure keto diester **295**[95] in the synthesis of a series of bis-hydroxymethyl carbocyclic nucleosides.[95-97] The 2'α-hydroxymethyl analogs were prepared by olefination of the ketone **295** to give the exocyclic alkene **296**.[96] Hydroboration of the alkene provided the primary alcohol **297**. The esters were then hydrolyzed and the resultant diacid was exposed to acetic anhydride resulting in formation of the bridged lactone **298**. The lactone was readily converted to the amide with ammonia; the acid was reduced to the primary alcohol through the mixed anhydride and finally the amide was converted to **299** by a Hofmann degradation. The amide **299** was transformed to the nucleoside analogs **300** and **301** by standard adenine and guanine synthesis respectively.

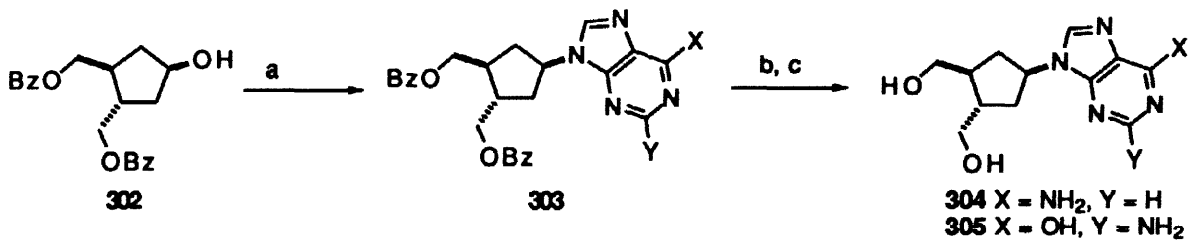
Scheme 61



a) Zn, CH_2Br_2, $TiCl_4$, 68%. b) BH_3-Me_2S, NaOH, H_2O_2, 92%. c) NaOH, MeOH. d) Ac_2O, pyr, 69%. e) NH_3, MeOH. f) EtOCOCl, Et_3N, DMF. g) $NaBH_4$. h) Ac_2O, pyr, 43%, 4 steps. i) $Pb(OAc)_4$, tBuOH, 86%. j) MeOH, HCl. k) 2,5-amino-4,6-dichloropyrimidine, Et_3N. l) $(MeO)_3CH$, HCl. m) HCl, H_2O. n) NH_3, 42%, 4 steps. o) 2-amino-4,6-dichloropyrimidine, Et_3N. p) 4-Cl-$C_6H_4N_2$+Cl-. q) Zn, HOAc. r) $(MeO)_3CH$, HCl. s) H_2O, HCl. 25% 6 steps.

The diester **295** was also easily refunctionalized to the alcohol **302**.[97] Mitsunobu coupling of the purines followed by removal of the protecting groups accessed the 3'α-hydroxymethyl analogs **304**, **305**.

Scheme 62

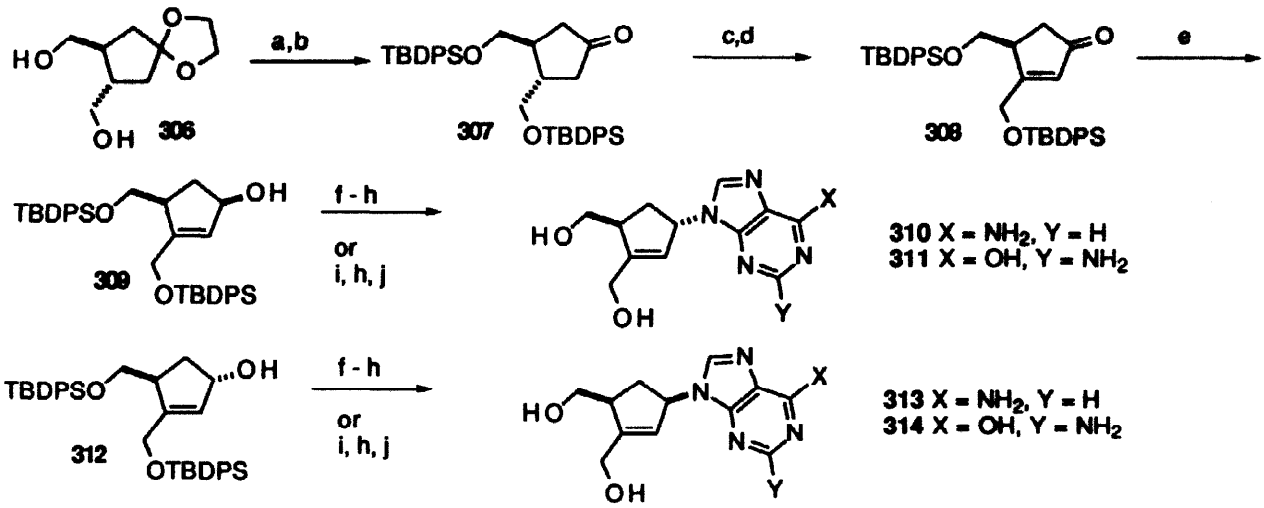


a) 6-chloropurine, Ph_3P, DEAD, THF, 0°C. b) NH_3, MeOH,dioxane. c) NaOH, MeOH, 52%, 40% overall.

In addition, the 3'α-hydroxymethyl-2',3'-dehydro analogs **313**, **314** could also be prepared from the same diester **295**. Protection of the ketone carbonyl of **295** and reduction of the esters gave the diol **306**. Protection of the hydroxyl groups as TBDPS ethers followed by hydrolysis of the ketal produced the ketone

307. Selenylation of the ketone and oxidative elimination of the selenide produced the enone 308. The ketone was reduced under Luche conditions to afford a 2:1 mixture of 309:312. Each of the allylic alcohols was independently coupled to adenine and 2-amino-6-chloropurine under Mitsunobu conditions ultimately providing the carbocyclic nucleoside analogs 310, 311, 313, and 314.

Scheme 63



a) t-BuPh$_2$SiCl, imidazole, DMF, 98%. b) p-TsOH, dioxane, H_2O, 50°C, 92%. c) LDA, PhSeBr, THF, -78°C, 74%. d) H_2O_2, CH_2Cl_2, 0°C. e) $NaBH_4$, $CeCl_3$, MeOH, CH_2Cl_2, 95%. f) 6-chloropurine, Ph_3P, DIAD, THF, 0°C, 62%; 58%. g) NH_3, MeOH, dioxane, 90%, 92%. h) Bu_4NF. i) 2-amino-6-chloropurine, Ph_3P, DIAD, THF, 0°C, 52%; 58%. j) 80% HCO_2H, 80°C, then NH_4OH, MeOH, 47%, 54%.

Summary. Carbocyclic nucleoside analogs have become an extremely important class of antiviral agents, particularly in view of the discovery of 1592U89 (abacavir) as a highly potent and clinically effective anti-HIV agent. The synthesis of carbocyclic nucleosides, especially enantioselective synthesis, has advanced dramatically in the last few years with a variety of new, efficient approaches being developed. Advances which rely on asymmetric synthetic methods have been particularly noteworthy. The low cost commercial availability of key chiral intermediates has also contributed substantially to synthetic advances. Nevertheless, new, more highly convergent and more practical syntheses are still needed because of the high dosing levels required and the strong demand for antivirals. Finally, while improvements have been made, the need for a general method for highly regioselective and high yielding coupling between purine and pyrimidine bases and the carbocyclic pseudosugar is an area which is in strong need of further development to improve the convergency of synthetic approaches.

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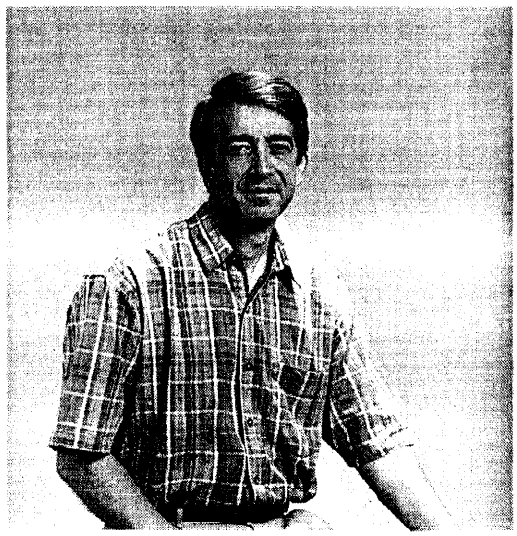
Biographical sketch



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