# AIDS-Driven Nucleoside Chemistry

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## Contents

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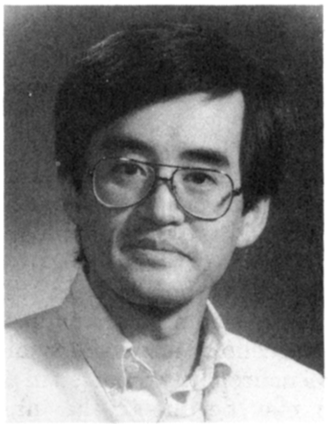

Masami Okabe, born in Yokahama, Japan (1955), received his B.S. and Ph.D. degrees from Waseda University working with Professor Masaru Tada. He has held post-doctoral appointments at Columbia University, working with Professors K. Nakanishi and G. Stork, as well as at the State University of New York at Stony Brook. At Stony Brook, he worked in the laboratory of Professor I. Ojima. In 1987 he joined the Chemical Synthesis Department at Hoffmann-La Roche, Inc. (Nutley, NJ) where he is currently a Research Investigator. His research interests involve organic reactions and mechanisms.

## I. Introduction

The finding that dideoxynucleosides, such as ddC (2′,3′-dideoxycytidine, **1**),[1] ddI (2′,3′-dideoxyinosine, **2**),[1] and AZT (3′-azido-3′-deoxythymidine, **3**),[2] are potentially effective therapeutic agents for the treatment of the acquired immune deficiency syndrome (AIDS) has triggered explosive new developments in the chemistry of these compounds and their analogs. To date, AZT (**3**), ddI (**2**), and ddC (**1**) are the only approved drugs for the treatment of AIDS. However, a number of other dideoxynucleosides, such as d4T (2′,3′-didehydro-3′-deoxythymidine, **4**)[3,4] and AZddU (3′-azido-2′,3′-dideoxyuridine, **5**)[5] have gone through at least preliminary clinical studies.

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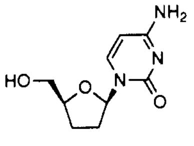
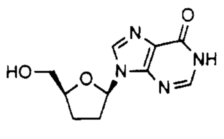
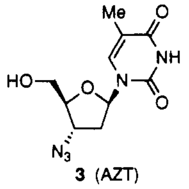


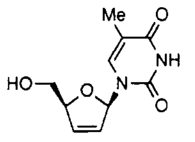
1 (ddC)



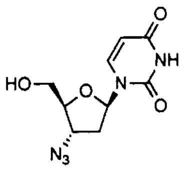
2 (ddI)



3 (AZT)



4 (d4T)



5 (AZddU)

The exact mechanism of action of each of these agents is not yet fully understood. In general, these dideoxynucleosides **6** are pro-drugs and are sequentially phosphorylated by cellular enzymes (kinases) to the corresponding 5′-triphosphate **9** (Scheme I). The efficiency of this phosphorylation process can account for some of the differences in activity of these molecules. This triphosphate is then incorporated into the replicating viral DNA chain by the HIV reverse transcriptase; chain termination results since a hydroxy group at the C3′-position required for further elongation is not present. In addition, the dideoxynucleoside 5′-triphosphate **9**, or even the terminated oligonucleotide, may act as a competitive inhibitor of the HIV reverse transcriptase. The delineation of the biochemical pathways which take place for each dideoxynucleosides is a complicated process that is under study by a number of laboratories.[6]

Unfortunately, the dideoxynucleoside triphosphates **9**, as well as the intermediate mono- and diphosphates **7** and **8**, often have affinity for other cellular enzymes; this affinity is thought to cause some of the undesired side effects observed in patients being treated with these drugs. For example, the bone marrow toxicity observed in AZT-treated patients is thought to arise from inhibition of the cellular enzyme, thymidylate kinase. The peripheral neuropathy reported in patients taking ddC and ddI may be due to the inhibition of the mitochondrial DNA polymerases.[6]

A challenge in recent years has been to discover dideoxynucleosides or analogs which are substrates of the cellular kinases, and subsequently as the triphosphate **9**, capable of binding to the HIV reverse transcriptase. However, these triphosphates at the same time must be incompetent as substrates for host enzymes. In addition, reports of AZT resistance[7] have prompted researchers to propose that multidrug regimens may be the most promising treatment for this disease. Enormous progress has been made in the synthesis of new dideoxynucleosides and their analogs due to the urgent need for better, as well as for a variety of, therapeutic agents for the treatment of AIDS.

The purpose of this review is to present highlights of the recent developments in the synthesis of anti-HIV dideoxynucleosides and their analogs, including oxetanocin. Efforts have primarily focused on modification of the carbohydrate portion of these molecules, since the cellular kinases are more tolerant of these changes than changes within the base moiety. Substitution at the C5′ position, as well as modifications of the heterocyclic base will not be within the scope of this review. A number of reviews regarding general nucleoside chemistry,[8–11] as well as two aimed more specifically at AIDS,[17,18] have been published previously. While the opportunistic viral infections associated with AIDS, such as those caused by cytomegalovirus (CMV) and herpes simplex virus (HSV), have initiated additional research into new nucleoside-type antiviral agents, this area has recently been reviewed[12] and will not be included. Several broad reviews on targets and strategies for AIDS chemotherapy have also recently appeared in the literature.[13–16] The literature has been surveyed through October 1991. Throughout this manuscript, the location of each substituent under consideration is described as $\alpha$ when it lies below the plane of the ring system and $\beta$ when it lies above it. The wedged lines indicate the absolute stereochemistry, and the bold lines (hashed or solid) indicate only the relative stereochemistry.

## *II. 2′,3′-Dideoxynucleosides and Their Analogs from Nucleosides*

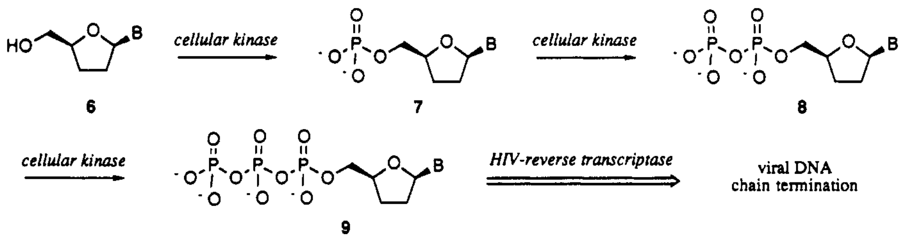
The synthesis of dideoxynucleosides and analogs from nucleosides has been studied extensively. The ribonucleoside-based synthesis is quite attractive since ribonucleosides are commercially available and not as expensive as their 2′-deoxy counterpart. The ribonucleoside with a modified base can also be readily prepared in an efficient manner. However, if available, 2′-deoxyribonucleosides provide a quick entry to the synthesis of dideoxynucleosides and 3′-substituted analogs.

### A. Dideoxynucleosides (Including Unsaturated Analogs)

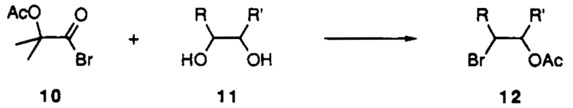
#### *1. Ribonucleosides with α-Acetoxyisobutyryl Bromide (Mattocks Reaction)*

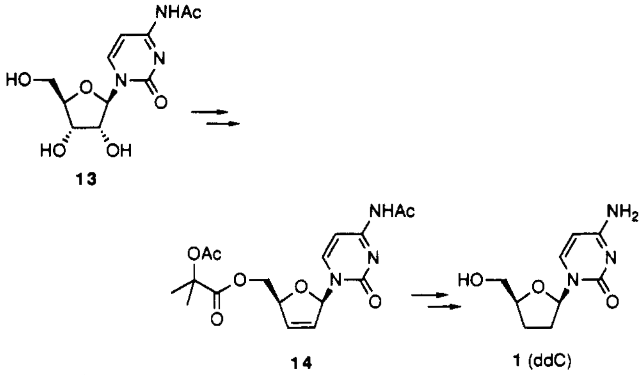
The Mattocks reaction,[19] the abnormal reaction of 1,2-diols with $\alpha$-acetoxyisobutyryl bromide **10** to furnish

**Scheme I**

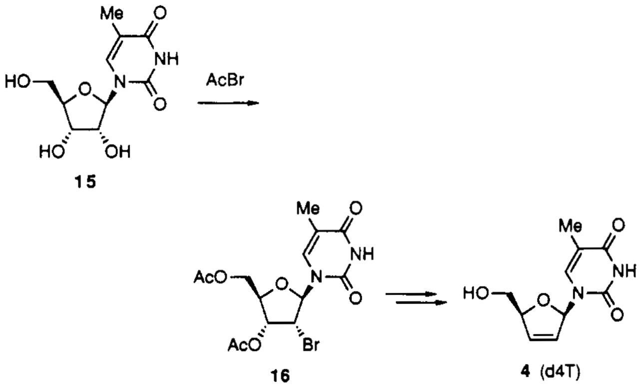


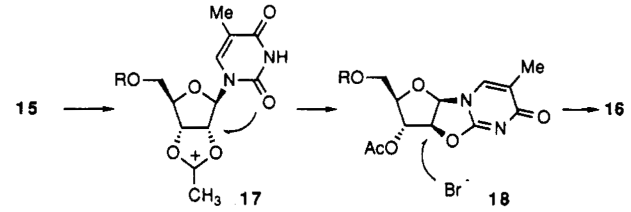
the bromo acetate 12, was reexamined by Moffatt and co-workers[20] and successfully applied to nucleoside chemistry.[20-22] The reductive elimination of the resulting bromo acetate 12 furnished 2′,3′-unsaturated 2′,3′-dideoxynucleosides, such as 14, by using a chromous ion complex,[23] electrochemical reduction,[24,25] zinc/acetic acid,[26] and zinc/copper couple.[27] The zinc/copper protocol appeared to be the most versatile and this procedure has been employed for the synthesis of ddA (6, B = adenine),[27] ddC (1),[28] ddG (6, B = guanine),[29] and ddI (2).[29] The unsaturated nucleosides, such as 14, were converted to dideoxynucleosides by catalytic hydrogenation on Pd–carbon[27,28,30] or on Raney Ni.[29] A direct conversion of the bromo acetate into the dideoxynucleoside by catalytic hydrogenation was not satisfactory due to the concomitant formation of the corresponding monodeoxynucleoside.[21] Recently, the selectivity of this direct reduction has been improved by utilizing aqueous acetonitrile as solvent and a NaOAc–Na$_2$CO$_3$ mixture as base in the hydrogenation.[31]





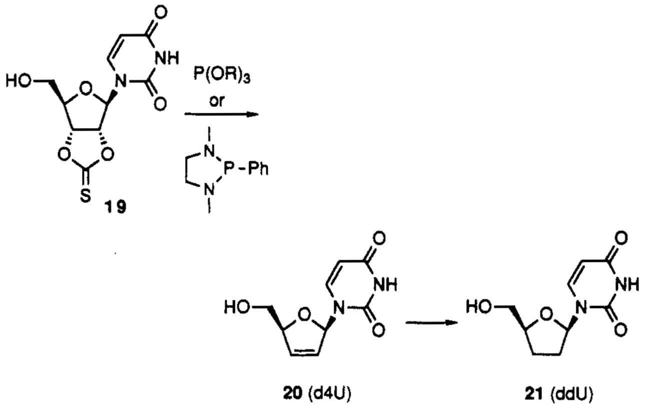
A variant of the Mattocks reaction using acetyl bromide[32] has been successfully applied to the synthesis of d4T (4).[30] The Mattocks reaction of uridine analogs (such as 15) is not only regiospecific but also stereospecific to give *cis*-2′α-bromo-3′α-acetoxy nucleosides (such as 16) due to the anchimeric assistance of the oxygen at the 2-position in the pyrimidine. In the case of other nucleosides, such as 13, or purine nucleosides, the formation of the bromo acetate was usually not regiospecific and a mixture of trans bromo acetates was obtained. The corresponding bromo acetate could be prepared by the treatment of adenosine with tetraacetoxysilane and phosphorus tribromide in the presence of boron trifluoride etherate.[33]





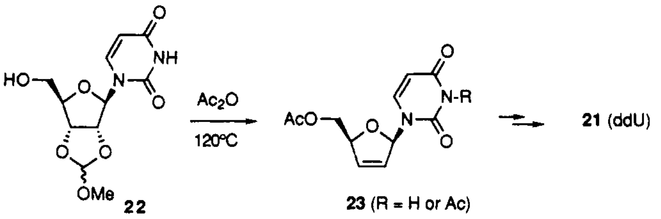
### 2. Cyclic Thionocarbonates with P(OR)$_3$, etc. (Corey–Winter Reaction)

Corey–Winter reaction[34] using trimethyl phosphite was unsuccessfully applied to the synthesis of ddU (21) due to extensive N-methylation of the base moiety.[35] This problem was avoided by careful exclusion of oxygen from the reaction mixture, and d4U (20) was obtained in high yield from the cyclic thionocarbonate 19.[36] Use of triethyl phosphite or 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine[37] also circumvents this problem.[30,38,39] The latter reagent has some advantages since the reaction can be carried out at lower temperature.[37] This procedure has been applied to the synthesis of ddA, ddG, and ddT (6, B = thymine) as well.[38]



### 3. Fragmentation of Cyclic Orthoformates (Eastwood Olefination)

The original Eastwood olefination procedure,[40,41] in which a five-membered cyclic orthoformate fragments in the presence of acid catalyst to give the corresponding olefin, failed to provide the desired unsaturated nucleoside (such as 23) when applied to compounds such as 22. However, using acetic anhydride as the solvent (Ando's modification[42]) the cyclic orthoformate 22 was successfully converted to ddU (21).[30,43] Attempts to prepare other dideoxynucleosides such as ddC (1) and ddA by this procedure were failed due to cleavage of N–glycosyl bond.[43] Recently, the use of hydrous zirconium oxide as a catalyst and tributylamine as a stabilizer in this reaction was reported; through this modification d4T (4) and the tribenzyl derivative of 2′,3′-dideoxy-2′,3′-didehydroadenosine (d4A) were successfully prepared.[44]



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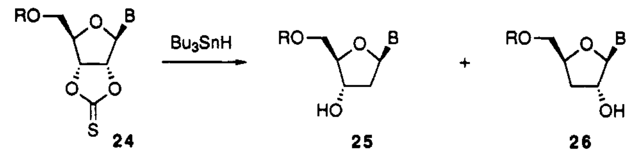
23 (R = H or Ac)

21 (ddU)

### 4. Radical Reaction (Barton Deoxygenation)

The removal of the 3′-hydroxy group of 2′-deoxyribonucleosides by Barton deoxygenation has been accomplished and provides a quick route to the dideoxynucleosides,[45–49] although the availability of the starting material is often limited. Starting from readily available ribonucleosides two procedures employing the Barton deoxygenation have been reported. The first involves the cyclic thionocarbonate 24, which upon treatment with tributyltin hydride gave a mixture of the corresponding monodeoxygenated products 25 and 26.[39,46]



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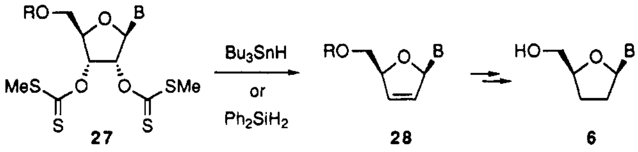
These products were again subjected to the deoxygenation procedure to afford dideoxynucleoside 6. The second, more versatile method involves treatment of the bisxantate 27 with tributyltin hydride to afford the 2′,3′-unsaturated dideoxynucleoside 28 in high yield.[38] Similar conversions of 2′,3′-dichloronucleosides[50] and 2′-chloro- or 2′(3′)-bromo-3′(2′)-[(phenoxythiocarbonyl)oxy]nucleosides[51,52] have also been reported. Although the Barton deoxygenation is conveniently and widely utilized, the requirement for tributyltin hydride is problematic as it results in tin contamination of the final product. Additional steps are usually required to ensure that the final product is free from this toxic contaminant. Recently, diphenylsilane was shown to be a suitable substitute for toxic tributyltin hydride; this method has been applied to the synthesis of ddA and ddU (21).[53]



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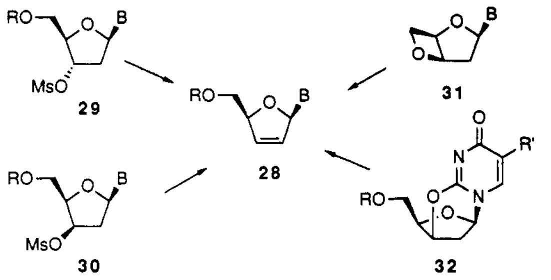
### 5. Other Methods

Introduction of 2′,3′ unsaturation via base-promoted elimination of the mesylates 29 and 30, the oxetane 31, and the anhydride 32 has been studied in 1960s.[54–57] Recently, syntheses of 2′,3′-didehydro-2′,3′-dideoxyguanosine (d4G)[58] and d4T (4)[59] using this procedure were published.

A photosensitized electron-transfer reaction has been applied to the selective deoxygenation of the secondary alcohol of the uridine derivative 33.[60] This chemistry was recently used in the synthesis of purine 3′-azido-2′,3′-dideoxynucleosides.[61] Other methods involving the deiodonation of 3′-iodonucleosides,[62,63] desulfurization of 3′-mercaptonucleosides,[64] or iodine-catalyzed elimination of vicinal iodo mesylates[65] have been reported. Enzymatic transdideoxyribosylations have also been described.[66,67]



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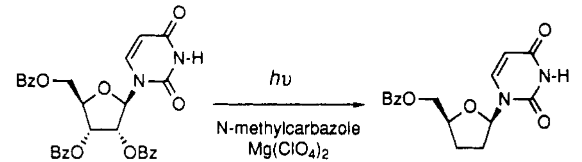

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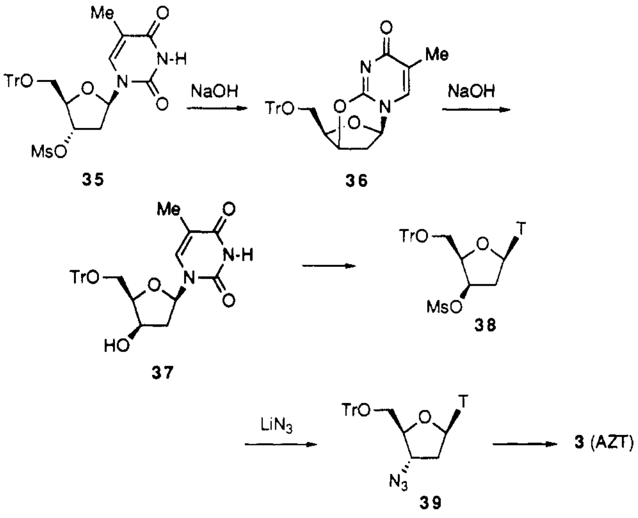
## B. Substituted Dideoxynucleosides

### 1. Nucleophilic Substitution

A variety of substituted nucleosides has been prepared via nucleophilic substitution and tested for their anti-HIV activity. In the original synthesis of AZT (3), the 3′-hydroxy group of thymidine (40) was inverted to give the 3′β-hydroxy compound 37 via the 2,3′-anhydronucleoside 36.[68,69] Then, the 3′β-hydroxy group was activated and displaced by azide to give AZT (3).[70] Using this procedure, other 3′-substituted dideoxynucleosides have been prepared.[58,71]



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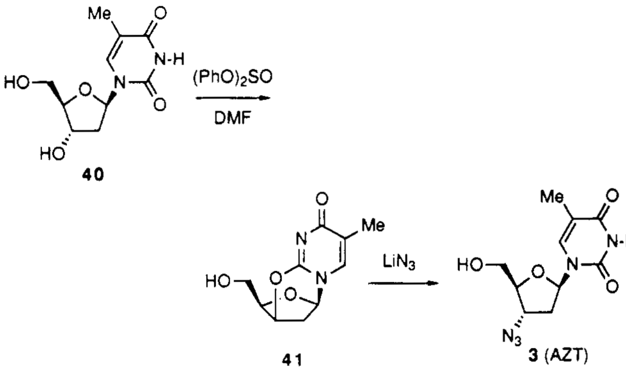
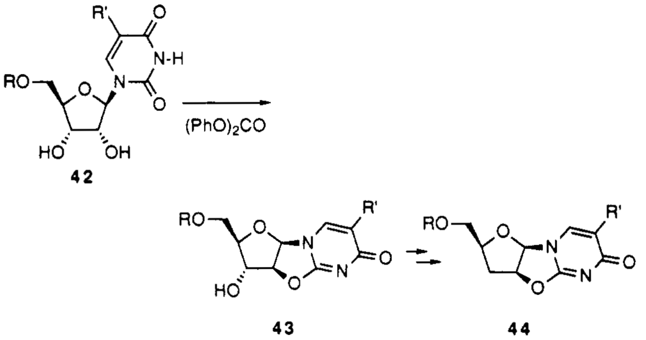
3 (AZT)

The 2,3′-anhydronucleoside 41 itself can be the precursor for the nucleophilic substitution.[72,73] Recently, a two-step synthesis of AZT (3) has been reported,[74] in which diphenyl sulfite was employed as a condensation reagent to give the 2,3′-anhydronucleoside 41 as depicted. The 5′-O-protected derivatives of 41 have also been prepared in one step by Mitsunobu reaction of thymidine (40).[75,76] Reaction of (diethylamido)sulfur trifluoride (DAST) with a 5′-protected 2′-deoxynucleoside has also been reported to give the 2,3′-anhydronucleoside.[77]

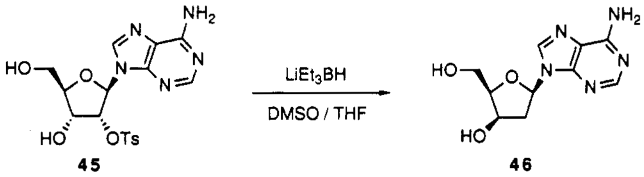
The corresponding 2,2′-anhydro-3′-deoxynucleosides 44 have been prepared in a multistep sequence from



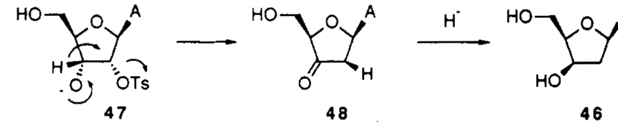
ribonucleosides **42** via Barton deoxygenation of **43**. The 2,2′-anhydronucleoside **44** is a precursor to the 2′α-substituted 2′,3′-dideoxynucleosides[78] or can be hydrolyzed to the 2′β-hydroxy-3′-deoxynucleosides.[79]



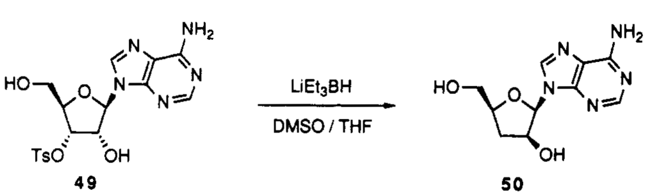
As mentioned above, the inversion of hydroxy groups in pyrimidine nucleosides has been achieved via anhydronucleosides such as **41** and **44**. However, in the case of purine nucleosides, such contribution from the base portion can not be expected. This difficulty was overcome by Hansske and Robins in an extraordinary manner.[80] The 2′-monotosylate of adenosine **45** was treated with excess lithium triethylborohydride; the 2′-deoxy-3′β-hydroxy compound **46** was isolated in 98% yield. On the basis of experiments using specifically



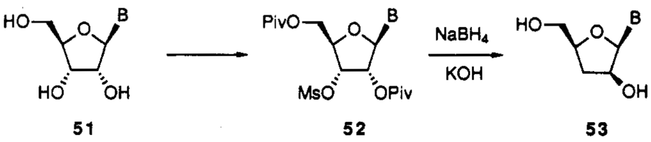
labeled 2′- and 3′-deuterio-2′-*O*-tosyladenosines and lithium triethylborodeuteride, this reaction was shown to involve a clean [1,2]-hydride shift from the C3′ to C2′ with accompanying inversion of the C2′ center to give the 3′-ketone **48**, which was stereoselectively reduced in situ by the hydride to give **46**.[80] The isomeric



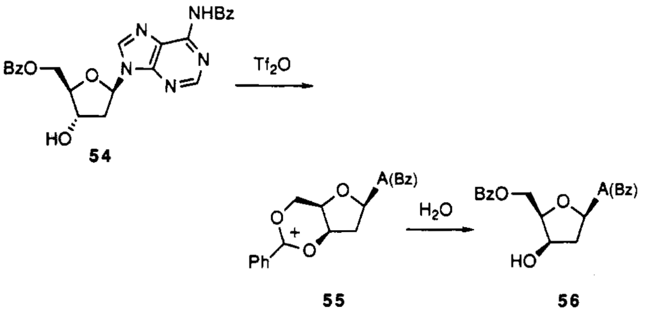
3′-*O*-tosylate **49** also underwent a similar rearrangement to give 3′-deoxy-2′β-hydroxy compound **50** in 82% yield.[80] These deoxynucleosides have been utilized for the preparation of 2′α- and 3′α-substituted dideoxynucleosides.[58,81-84]



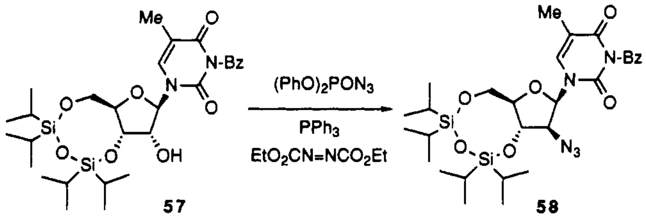
The synthesis of 3′-deoxy-2′β-hydroxynucleosides (such as **50**) by the method mentioned above[80] was not straightforward due to the multistep synthesis of the requisite 3′-tosylates (such as **49**). Kawana et al. have recently reported a two-step transformation of ribonucleosides into their 3′-deoxy-2′β-hydroxy analogs **53**,[85] which consisted of regioselective acylation followed by mesylation of 3′-hydroxy group in a one-pot manner; deprotection, rearrangement, and reduction also took place in one pot. This procedure was successfully applied to uridine, cytidine, adenosine, and guanosine, and **53** was obtained in 40–60% overall yield. In the case of 3′-sulfonates, contrary to the 2′-sulfonates, the reaction may involve the elimination of the 3′-sulfonate instead of the [1,2]-hydride shift to give the enolate which is subsequently reduced to give **53**.[83,86]



Alternatively, 2′-deoxy-3′β-hydroxy purine nucleosides **56** were prepared ingeniously from the corresponding 5′-*O*-benzoyl-2′-deoxynucleosides **54** by taking advantage of the anchimeric assistance of the 5′-*O*-carbonyl function.[87,88]



The nucleophilic substitution from the α-face of the nucleoside is usually an easy task since there is no steric or electronic hindrance to the incoming nucleophile. In the case of purine nucleosides, attacks from the β-face are still possible[81,89] despite the greater hindrance compared to the α-face. In contrast, pyrimidine nucleosides resist such transformation since the incoming nucleophile should compete with the favorable intramolecular attack of the 2-carbonyl group of the pyrimidine base. This problem has been solved by protecting the N3 of the base with a benzoyl group. This reduces the nucleophilicity of the 2-carbonyl group, and an azide group was successfully introduced from the β-face to afford **58**.[90] Here, diphenyl phosphorazidate was employed instead of highly toxic and explosive hydrogen azide.



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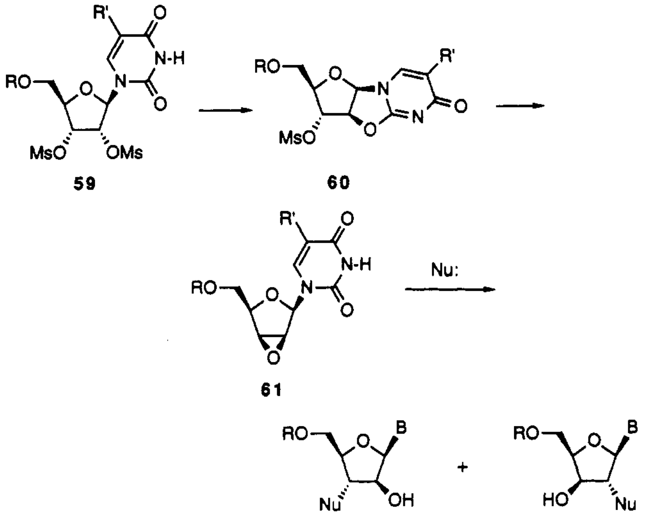
## 2. Epoxide Opening

Since the β-epoxide of pyrimidine nucleosides **61** are readily obtained via 2,2′-anhydronucleosides **60**,[91] the epoxide opening of **61** has been studied extensively. Exclusive formation of 3′α-substituted 2′β-hydroxynucleosides **62** have been reported by the introduction of hydrogen,[92] methyl,[92] ethynyl,[58,93,94] cyano,[94-96] and 1,3-dithian-2-yl[94,97] groups. On the other hand, reactions of **61** with azide,[98,99] sulfide,[100] selenide,[101] and 1,2,4-triazole[102] gave mixtures of **62** and **63**.



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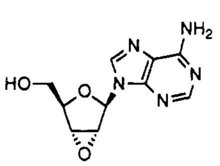
The epoxide openings of the α- [103-105] or β-epoxide[106] of adenosine (**64** and **65**) by azide,[103,106] bromide,[104] fluoride,[103] and hydride[105] have also been reported to give exclusively 3′-substituted adenosine analogs. In the opening of the β-epoxide **65** with lithium aluminum hydride, however, a small amount of the regioisomer resulting from substitution at C2′ was observed.[107] The requisite α- and β-epoxides were prepared by using the Mattocks reaction on adenosine,[21,27] and oxidation–reduction–condensation of the 2′β-hydroxy analog of adenosine,[108] respectively. The products of the epoxide openings have been converted further to a variety of nucleoside analogs, such as **66**,[97] **67**,[95] **68**,[106] and **69**.[104]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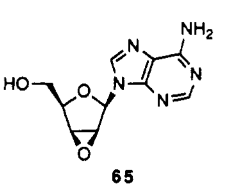
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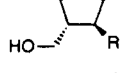
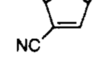

66 (R = H or OH)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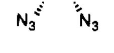
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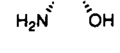
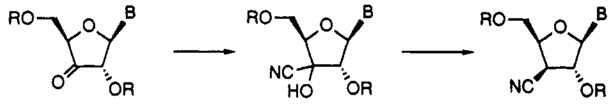
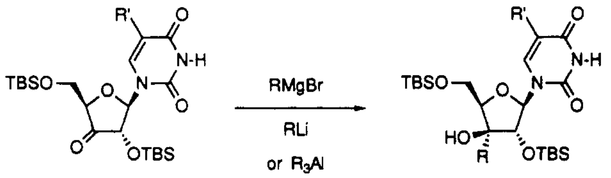

69

## 3. Via Ketonucleoside

The 2′- and 3′-ketonucleosides (such as **70**) have been converted into the cyanohydrins.[109-112] The tertiary alcohol can be removed by Barton deoxygenation to give stereoselectively β-cyanonucleosides (e.g. **72**). The corresponding 3′α-cyano isomers were obtained by base-catalyzed epimerization.[95,109,111]


70 71 72

The reactions of Grignard, organolithium, and organoaluminum reagents with 2′- or 3′-keto pyrimidine nucleosides (e.g. **73**) have been reported to occur exclusively from the α-face to give α-alkylated β-hydroxynucleosides (such as **74**).[113-117] In the case of 2′-ketone **75**, reaction with Grignard reagents gave ca. 1:1 mixture of **76** and **77**.[115,116]



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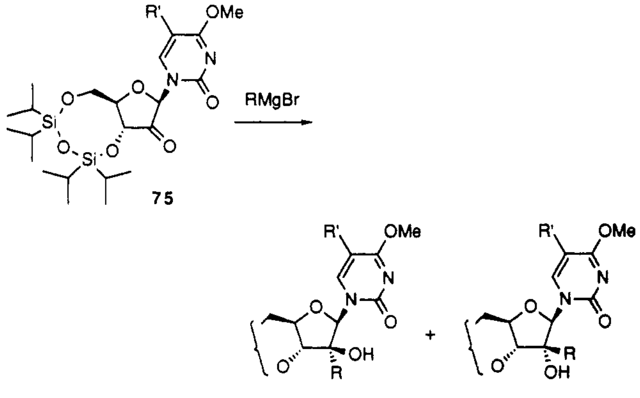
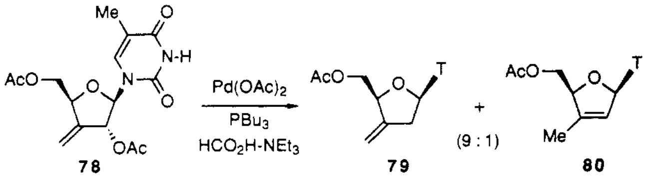


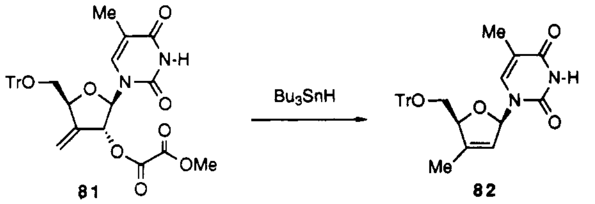
75 76 77

The Wittig reaction of 2′- and 3′-ketonucleosides has been reported.[118-121] The synthesis of 2′-deoxy-2′-(fluoromethylene)nucleosides has also been described.[122] The resulting methylidene nucleosides **78** and **81** were subjected to deoxygenation. The palladium-catalyzed reduction[123] of the allylic acetate **78** gave 2′-deoxy-3′-methylidenenucleoside **79** as a major product (**79**:**80** = 9:1).[118] On the other hand, deoxygenation of 2′-*O*-methyl oxalyl ester **81** gave 2′,3′-didehydro-3′-methylnucleoside **82** as the sole product.[118] The latter deoxygenation developed by Dolan and MacMillan[124] has also been applied to the deoxygenation of tertiary



78 79 80

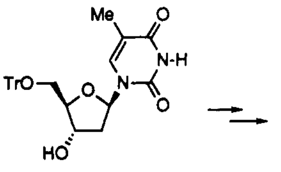
alcohols **77** to give exclusively $2'\beta$-alkyl-$2'$-deoxynucleosides.[115,116]



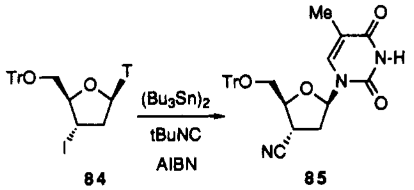
**81** **82**

### *4. Radical Reaction*

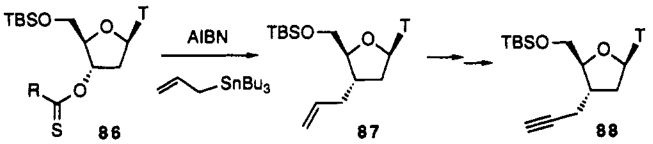
Stork's radical cyanation[125] has been successfully applied to the iodide **84** to give $3'\alpha$-cyano-$3'$-deoxythymidine (**85**) stereospecifically.[126] The related reaction with $2'$-deoxyadenosine, however, gave ca. 1:1 mixture of $3'\alpha$- and $3'\beta$-cyano-$2',3'$-dideoxyadenosine.[127] The allyl group can be introduced by the same strategy to give **87**[128-130] which has been converted to nucleosides (such as **88**) conformationally similar to AZT (**3**).[129]



**83**



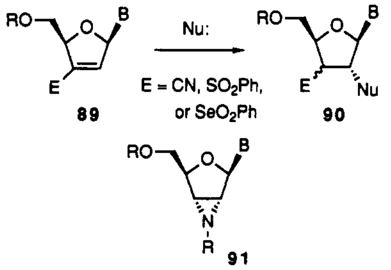
**84** **85**



**86** **87** **88**

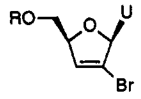
### *5. Others*

Michael addition reactions of the electron-deficient $2',3'$-ene nucleosides **89** with a variety of nucleophiles have been studied.[100,101,110,131] The nucleophile exclusively attacks from the $\alpha$-face, but the protonation of C3′ is not always stereoselective, usually resulting in a mixture of stereoisomers **90**. The selenone substituent of **90** acted as a leaving group to give aziridines **91** and other three-membered ring products by intramolecular substitutions.[101,131]

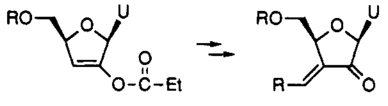


**89** **90** **91**

The palladium-catalyzed cross-coupling of the vinyl bromide **92**[132] and the aldol reaction of $2'$-enolate **93**[133] have also been reported. These starting materials were prepared by selenoxide eliminations.[132-134]

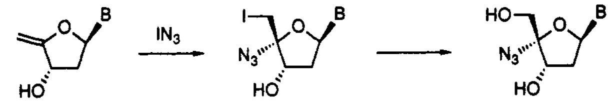


**92**



**93** **94**

More recently, $4'$-azido-$2'$-deoxynucleoside **97** was prepared via the regio- and stereoselective addition of iodine azide to the unsaturated nucleoside **95**.[135]

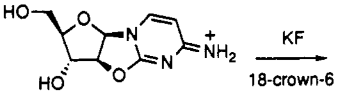


**95** **96** **97**

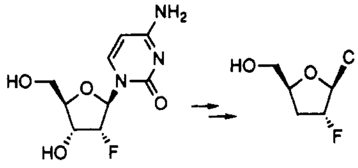
## C. Fluorinated Dideoxynucleosides

The methodologies for the synthesis of nucleosides fluorinated in the carbohydrate moiety have been reviewed by Herdewijn in 1989.[136] Hence, only chemistry which has recently appeared in the literature will be discussed.

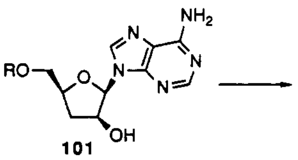
Since the fluoride ion is a poor nucleophile, vigorous reaction conditions are frequently required to introduce fluorine into a nucleoside. Furthermore yields of the desired products are often low due to the fluoride ion catalyzed elimination. Potassium fluoride can be activated by crown ethers, and this reagent successfully transformed the 2,2′-anhydrocytidine **98** into the $2'\alpha$-fluoride **99** in 40% yield.[137] Despite the high temperature and modest yields, this method appears to be a general solution to the fluorination problem. The fluoronucleoside **99** was converted to dideoxy-$2'\alpha$-fluorocytidine (**100**) by Barton deoxygenation.[138] The use of triflate as a leaving group[139] allowed the preparation of the $2'\alpha$-fluoride **103** under mild conditions in 78% yield.[140]



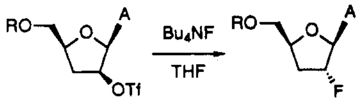
**98**



**99** **100**

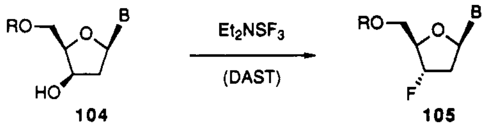


**101**

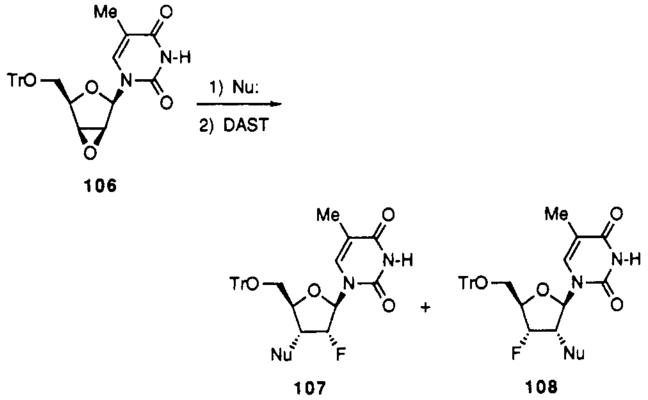


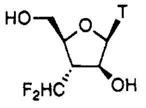
**102** **103**

Recently, (diethylamido)sulfur trifluoride (DAST) has been employed extensively; this method appears to be quite general for the introduction of fluorine from the α-face of the nucleoside.[136] A variety of 3′α-fluorodideoxynucleosides **105**[47,141] and 2′α-fluorodideoxynucleosides (such as **103**)[98,141] have been prepared in good yield using DAST.

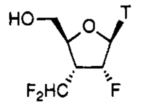


By a combination of the β-epoxide-opening reaction and fluorination with DAST, 2′(3′)α-fluoro-3′(2′)α-substituted-nucleosides **107** (and **108**) can be obtained. The epoxide **106** was opened by the action of KHF$_2$, and the resulting regioisomers were treated with DAST to afford 2′α,3′α-difluoride **107** (Nu = F) in 42% overall yield.[98] Preparations of **109**–**112** via the epoxide opening of **106** with 4,5-dihydro-2-lithio-5-methyl-1,3,5-dithiazine have also been reported.[142]

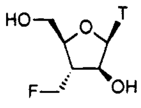




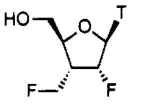
**109**



**110**

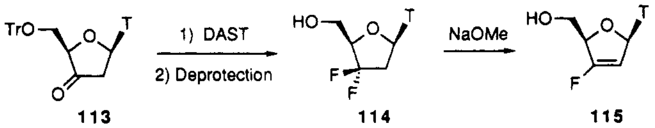


**111**

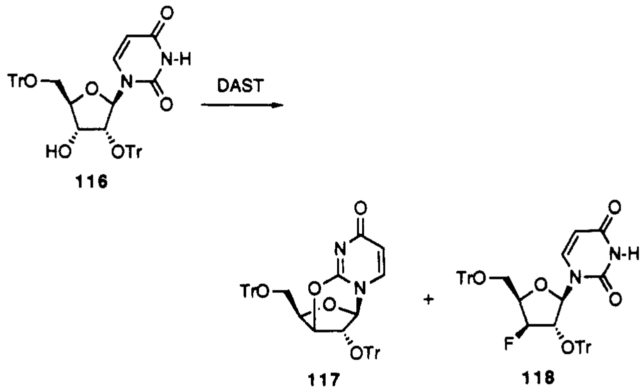


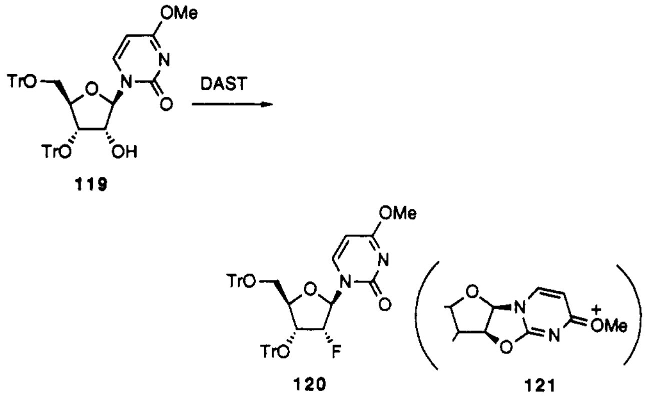
**112**

The reaction of 3′-ketothymidine **113** with DAST in CH$_2$Cl$_2$ at reflux overnight gave, after deprotection, 3′,3′-difluoride **114**.[143] Treatment of **114** with NaOMe provided 3′-fluoro-2′,3′-ene nucleoside **115** in 62% yield.[141]

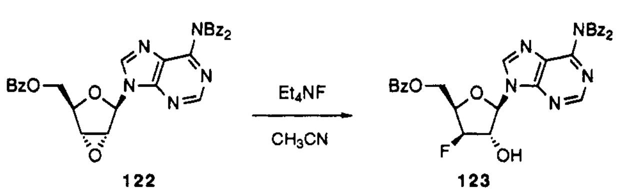


Despite its widespread use, only a few reports have dealt with the use of DAST for the preparation of β-fluoronucleosides.[81,136,144] The difficulties generally resulted from the neighboring participation of the $O^2$ atom of pyrimidines or the $N^3$ atom of purines. The reaction of 2′,5′-di-O-trityluridine **116** with 1 equiv of DAST gave 2,3′-anhydrouridine **117** as the sole product. On the other hand, addition of 2 equiv of DAST appeared to give the 3′β-fluoronucleoside **118** (40%) with concomitant formation of **117** (33%).[144] The reaction of 3′,5′-di-O-trityluridine again gave 2,2′-anhydrouridine exclusively without formation of any fluorinated product. When the base portion was protected with a methoxy group, fluorination of **119** with 4 equiv of DAST proceeded well, and the fluorinated product **120** with the unexpected α-configuration was obtained in 94% yield. Apparently, double inversion via the anhydro species **121** took place.[144]

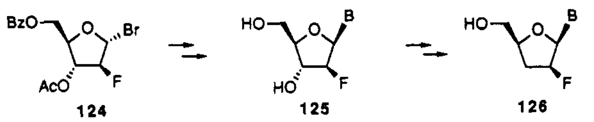




In the case of adenosine, a 3′β-fluorine has been successfully introduced by the opening of the α-epoxide **122** in 60% yield.[103] Bis-N-benzoylation of the adenine portion is essential in order to prevent the formation of $N^3$,3′-cyclonucleoside.

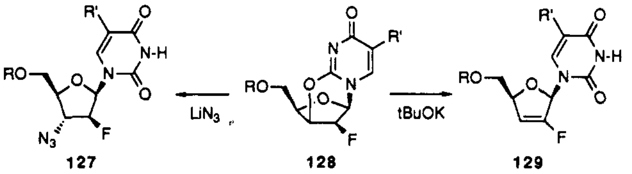


The introduction of a fluorine atom in the β-configuration at the C2′-position of nucleosides is very difficult, because of neighboring-group participation of the base portion, although not impossible.[81] The process developed by Fox, which involves the reaction of the bromide **124** with the appropriate silylated base to give 2′β-fluoro nucleosides **125**,[145] is still the method of choice. Barton deoxygenation has been applied to give 2′β-fluorodideoxynucleosides **126**.[138,141,146,147] The



124 125 126

2′β-fluoro analog of AZT **127** was prepared from **125** via 2,3′-anhydronucleoside **128**.[146,147] The 2′-fluoro-2′,3′-ene nucleoside **129** has also been prepared by base-catalyzed elimination.[98,138,147] The 2′β,3′α-difluoride **130** was prepared by HF/AlF$_3$ treatment of **128**[98] or by the reaction of **131** with DAST.[138]



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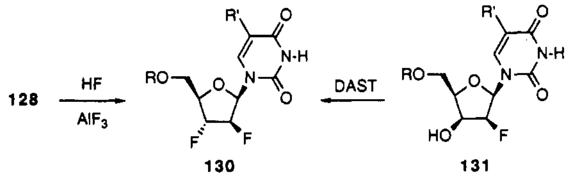


130 131

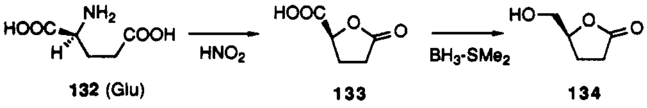
## *III. De Novo Synthesis of Dideoxynucleosides and Their Analogs*

Since chemistry based on DNA nucleosides obtained from limited natural sources can be inimical to the broad application of modified nucleosides in AIDS therapy, schemes utilizing abundant raw materials to construct the sugar portions of modified nucleosides have been targeted for investigation. Because of its convergent nature, this strategy can be extended to the preparation of a variety of modified nucleosides from one precursor, since there are so many modified nucleoside bases available.

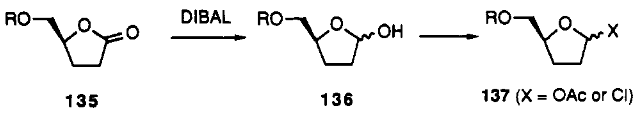
### A. Dideoxynucleosides and Substituted Dideoxynucleosides

#### *1. Dideoxynucleosides*

The butyrolactone **134**, a logical precursor of 2,3-dideoxynucleosides, has been previously prepared from L-glutamic acid,[148,149] from D-mannitol,[150] and from D-ribonolactone.[151-153] Fewer steps and the low cost of L-glutamic acid make the route from this material preferred. The nitrous acid deamination of L-glutamic acid (**132**), which proceeds with full retention of configuration due to the participation of the neighboring α-carboxylate group,[154] followed by selective reduction of the carboxylic acid **133** with borane–dimethyl sulfide readily affords the lactone **134**.[149]

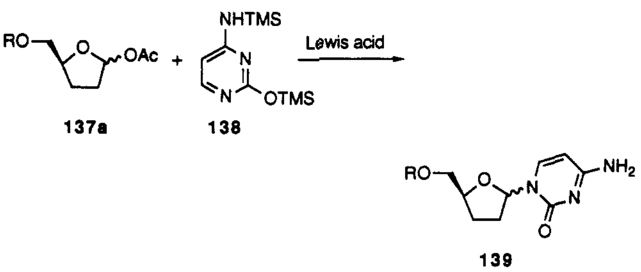


132 (Glu) 133 134



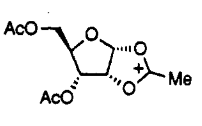
135 136 137 (X = OAc or Cl)

The protected lactone **135** was reduced with DIBAL to the corresponding lactol **136**, which was then converted to the requisite sugar portion, acetate **137a** (X = OAc)[155-158] or chloride **137b** (X = Cl).[159] The acetate **137a** has been coupled with silylated pyrimidines (such as **138**)[155-157] and purine[157,158] bases in the presence of Lewis acids such as ethylaluminum dichloride,[155] trimethylsilyl bromide,[157] and trimethylsilyl triflate.[156,158] The chloride has also been treated with the anions of purine bases.[159] The resulting anomeric mixture of nucleosides **139** (usually ca. 1:1) could be separated chromatographically. The assignment of anomeric configuration can be made easily on the basis of characteristic $^1$H NMR features; the H4′ proton of an α-anomer appears at a lower field than that of a β-anomer and the H5′ protons of an α-anomer appear at a higher field than those of a β-anomer, due to the anisotropic effect of the bases.[155,158,160-163] The enantiomers of dideoxynucleosides have also been prepared from the antipode, D-glutamic acid.[155]



137a 138 139

This convergent process provides a quick route to the preparation of a variety of dideoxynucleosides. However, the need for chromatographic separation makes this process unamenable to scaleup. This problem has been addressed in several ways. In Vorbrüggen's method for the synthesis of β-ribonucleosides, the formation of the 1,2-acyl oxonium species **140** determined the exclusive formation of β-anomers.[164,165] These synthetic ribonucleosides have been converted to the dideoxynucleosides by the methods mentioned previously. In the case of 2′-deoxyribonucleosides, on the other hand, no such participation of 2-*O*-acyl group can be applied. Therefore, the 3-hydroxy group has been employed for this purpose; the 3-*O*-thiobenzoate[166] and 3-*O*-[2-(methylsulfinyl)ethyl][167] groups have been reported to give stereoselectively the β-anomers via **141** and **142**, respectively. The possbility of using a 2,3-dideoxyribose with a substituent at the 2-position, which would not only direct the condensation toward the formation of the β-anomer but also be disposable, has been explored. Phenylselenyl[168] and arylsulfenyl[169] groups have served this purpose, and high β-selectivities have been achieved in the synthesis of d4T (**4**). However, the requisite precursor **145** has to be separated from its epimer **146** chromatographically.



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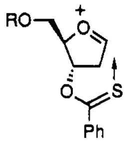

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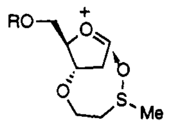

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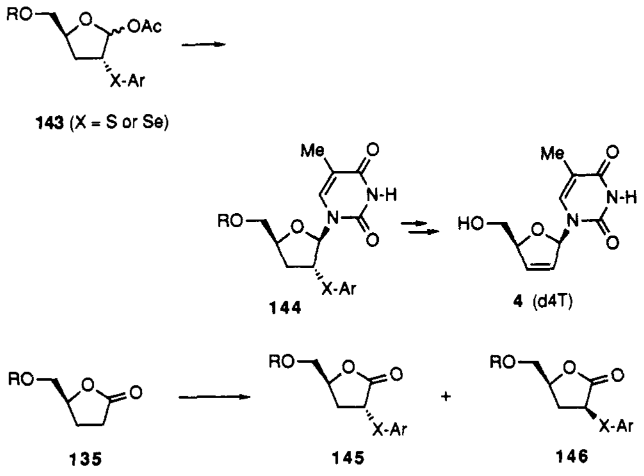
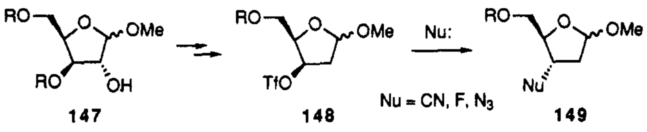
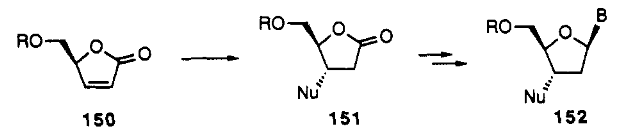


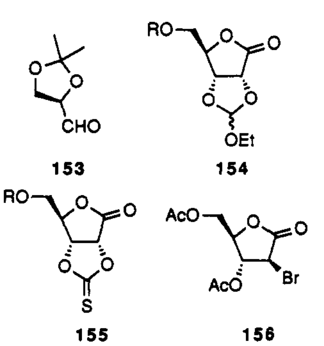
## 2. Substituted Dideoxynucleosides

The triflate **148** was prepared via Barton deoxygenation of the suitably protected xylose **147**. The nucleophilic substitution of **148** with azide,[170,171] cyanide,[171,172] and fluoride[171] afforded, after further transformations, 3′α-substituted deoxythymidines.

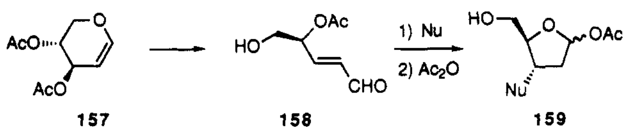


The butenolide **150** has been also an attractive starting material for preparing 3′α-substituted nucleosides **151** (Nu = alkyl,[156] azido,[173] and cyano[155]). Five methods of preparing **150** are reported. A synthesis from L-glutamic acid involved introduction of a double bond by selenium chemistry.[174] Another used the D-glyceraldehyde derivative **153** which can be prepared from D-mannitol.[175] The other three started with D-ribonolactone, and **150** was prepared by pyrolysis of the cyclic orthoformate **154**,[152] by Raney nickel reduction of the cyclic thiocarbonate **155**,[176] or by the NaHSO$_3$-induced elimination of the bromoacetate **156**.[177] The susceptibility of the butenolide **150** to racemization is a drawback of this strategy.[155,174]

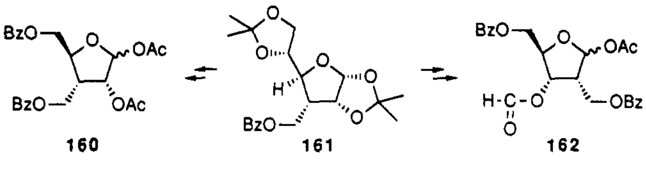


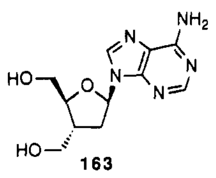


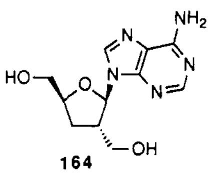
A method utilizing Michael additions to α,β-unsaturated sugar aldehydes has also been developed. Phthalimide stereoselectively added to **158** to give the furanose **159**.[178] However, a poor stereoselectivity was reported in the case of a corresponding Michael addition of azide.[162,179]



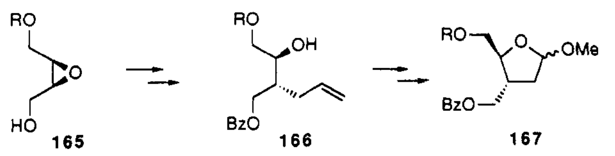
The branched sugar **161** which was prepared in four steps from diisopropylidene-D-glucose provided the glycons **160** and **162** through the selective cleavage of either vicinal diol functionality.[180,181] These sugar portions were further converted into 3′α-(hydroxymethyl)- and 2′α-(hydroxymethyl)deoxyadenosines and the corresponding dideoxy analogs **163** and **164**.[181] The 3′α-(hydroxymethyl)-3′-deoxy sugar (such as **160**) was also prepared in a more efficient manner from commercially available 1,2-O-isopropylidene-α-D-xylose.[182]



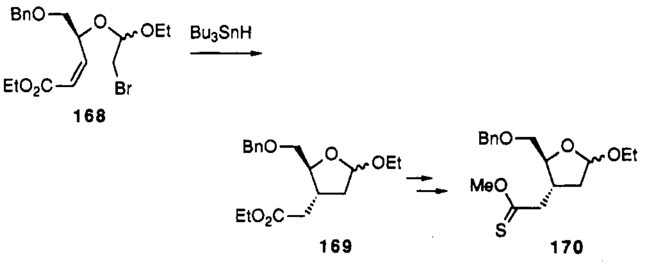




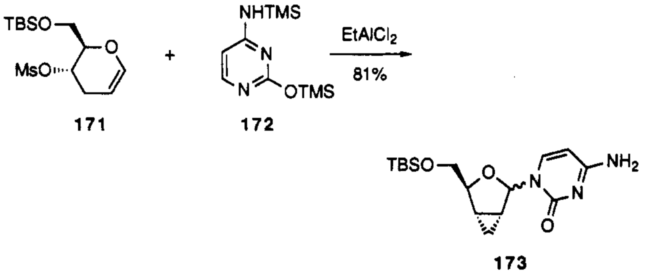
The 3′α-(hydroxymethyl)dideoxynucleoside **163** has been also prepared from a noncarbohydrate starting material.[161] The chiral epoxy alcohol **165**, readily prepared via Sharpless epoxidation, was regioselectively alkylated at C3 to give **166**, after protection. The construction of the furanose **167** was achieved via oxidative cleavage of the double bond. No stereochemical control was observed in the formation of the glycosyl bond.



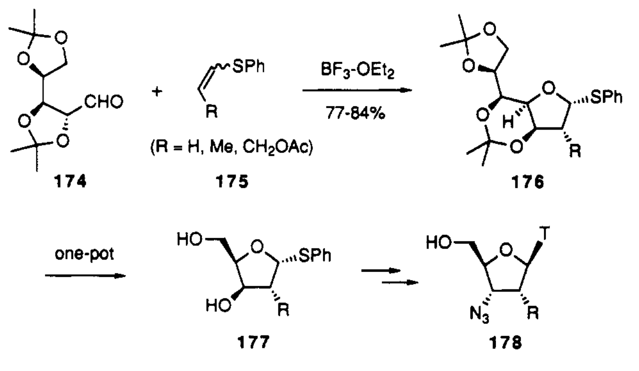
Radical cyclization of the bromide **168** proceeded with high stereoselectivity to give exclusively the trans product **169**.[183] The cis double bond is reported to be crucial for good stereochemical control in the radical cyclization.[184,185] The coupling of the ester **169** with bis-TMS-thymine showed only moderate β-selectivity. However, the corresponding thioester acetate **170** gave the β-nucleoside with very high selectivity.[183] The strong anchimeric assistance of a thiocarbonyl group (such as **141**) has been also reported in a related system.[166]



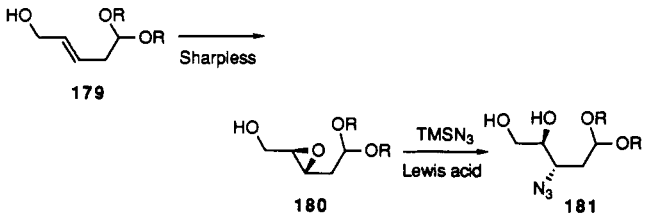
The bicyclic nucleoside **173** has been prepared via homologous Ferrier reaction of the mesylate **171**, which was prepared from tri-*O*-acetyl-D-glucal in 60% yield.[186] The stereochemistry of the three-membered ring was completely controlled by the configuration of the mesylate **171**. However, no stereochemical control was observed at the anomeric center. A similar reaction with the corresponding β-mesylate was unsuccessful.



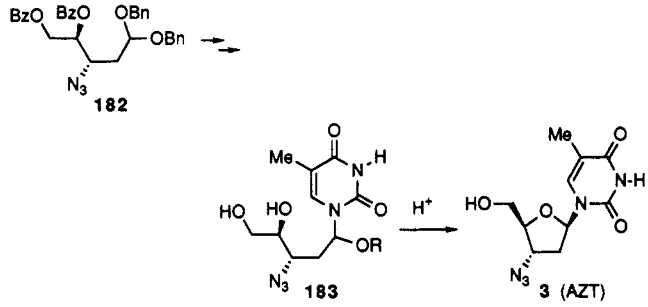
Lewis acid catalyzed condensation of the aldehyde **174** with vinyl sulfides **175** proceeded with high stereoselectivity to provide exclusively the furanoside **176**. This was converted into 2-deoxy-1-thiopentofuranoside **177** in a one-pot procedure.[187] *N*-Bromosuccinimide (NBS) was found to promote the coupling of these thio-sugars with bis(trimethylsilyl)thymine (bis-TMS-thymine) to form preferentially the α-anomers. The minor β-anomers have been converted to the 2′,3′-disubstituted nucleosides such as **178**.[188]



Two reports on de novo syntheses of AZT from noncarbohydrate starting materials (i.e. crotonaldehyde[189] and ethyl vinyl ether[190]) were reported recently. Both approaches utilized a Sharpless epoxidation of the allylic alcohol **179** to introduce the necessary chirality. The regioselective Lewis acid catalyzed opening of the epoxy alcohol **180** with azide furnished the azide diol **181** which has all the required stereochemistry except that of the anomeric position. However, the coupling of the corresponding furanoside of **181** with bis-TMS-thymine was reported to proceed nonstereospecifically.[162,171,173,189,190] DIBAL reduction of the epoxide **180** has also been reported to proceed regioselectively to afford a precursor of ddC (**1**).[191]



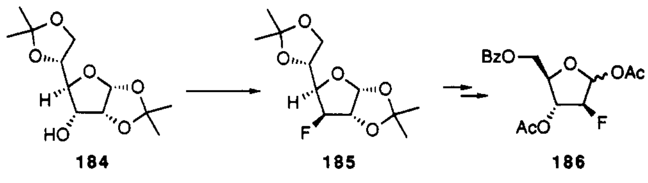
Hager and Liotta[190] noticed that only the β-anomer was formed under kinetic conditions when the azide diol **181** cyclized to the corresponding furanoside. Encouraged by this observation, coupling of bis-TMS-thymine with **182** was followed by deprotection to afford the acyclic nucleoside **183**, which should be capable of undergoing similar cyclization to that of **181**. In fact, **183** did cyclize to give exclusively the β-anomer of AZT (**3**) in 67% yield, based on recovered starting material.[190] Even though the yield is not high, this new strategy opens new possibilities to control the stereochemistry of the glycosyl bond of dideoxynucleosides.

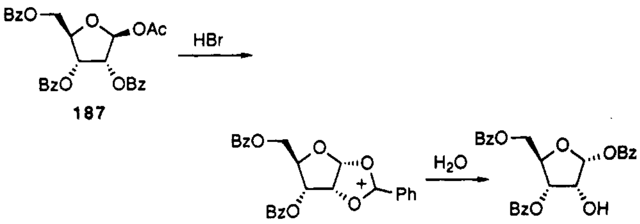


### 3. Fluorinated Dideoxynucleosides

In the late 1970s, 2′β-fluoro-2′-deoxynucleosides **125** were found to be active against DNA viruses by Watanabe and Fox.[192] Since then, a variety of 2′β-fluoronucleosides has been prepared. Because the introduction of a fluorine atom in the β configuration at the C2′-position of a nucleoside is very difficult, 2′β-fluoro-nucleosides have been prepared solely by de novo synthesis.

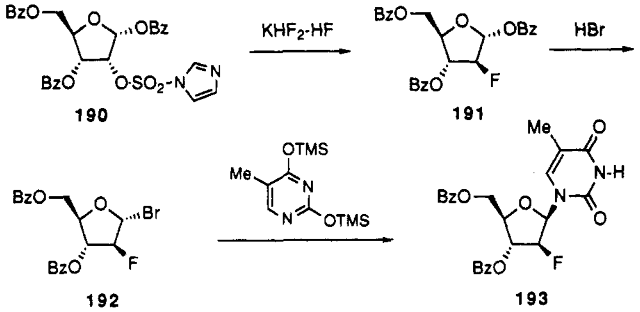
The requisite 2β-fluorofuranoside **186** has been prepared from the protected hexose **184** via introduction of a fluorine followed by cleavage of the 1,2-diol of **185**.[140,145,193] A more straightforward procedure starts with ribose. Treatment of the protected ribose **187** with HBr followed by the addition of water prompts the migration of the benzoyl group from C2 to C1 via **188** to give the crystalline product **189** which has a free C2 hydroxy group for selective manipulation.[194] The direct fluorination of **189** with DAST[136] was not successful. However, treatment of the imidazolesulfonate **190** with $KHF_2$–HF gave the fluoro sugar **191** in 63% yield.[195] Bromination of the anomeric position proceeded stereospecifically to afford only the α-anomer **192** due to





187 188 189

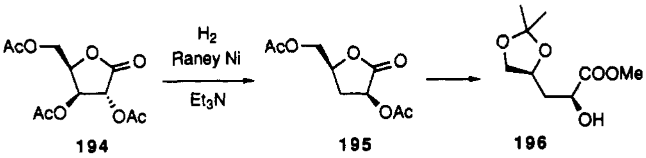
a strong directing effect of the 2-fluorine.[195-197] Subsequent reaction of the bromide **192** with bis-TMS-thymine in refluxing $CHCl_3$ gave exclusively the β-nucleoside **193** via an $S_N2$ mechanism.[196]



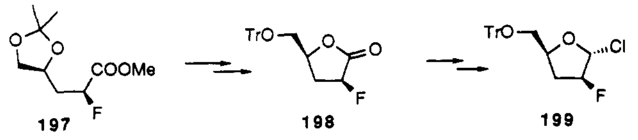
190 191 192 193

The acetate **186** and the bromide **192** have been utilized to prepare a variety of 2′β-fluorodideoxynucleosides (such as **126**).[98,138,140,141,146,147,158,198]

The above procedure relied on a Barton deoxygenation for the final conversion into dideoxynucleosides. Unfortunately, this reaction often results in toxic tin contamination of the final product. Therefore, a different approach was taken.[197] The crystalline lactone **194**, prepared from D-xylose in 65% yield, was subjected to catalytic hydrogenation using Raney Ni in the presence of $Et_3N$. This procedure gave the 3-deoxy lactone **195** in 92% yield via elimination of the 3-acetoxy group.[199] The alcohol **196** was converted into the fluoride **197** in multistep sequence. After lactonization, DIBAL reduction of **198**, and chlorination afforded the α-chloride **199** stereospecifically. The coupling of **199** with bis-TMS-*N*-acetylcytosine proceeded with high β-selectivity to give the 2′β-fluoro analog of ddC.[197]

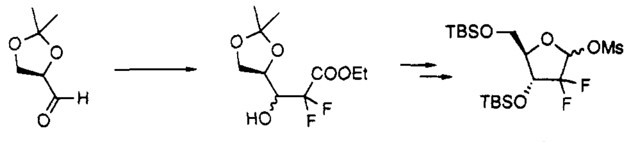


194 195 196



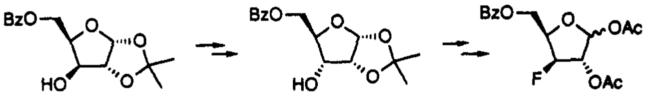
197 198 199

Reformatsky reaction of bromodifluoroacetate with the aldehyde **200** afforded the alcohol **201**.[200,201] After chromatographic separation, **201** was further converted into the 2,2-difluoro sugar **202**. The coupling of the mesylate **202** with silylated bases proceeded poorly providing the α-anomers as major products.[201]



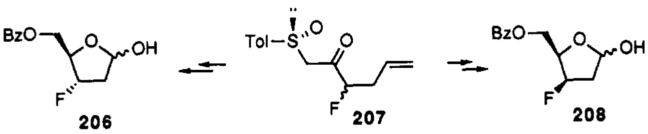
200 201 202

Compared to the 2′β-fluoronucleosides, nucleosides with 3′β-fluorine have been explored less. The protected xylose **203** was converted to the protected ribose **204** via an oxidation–reduction sequence. Fluorination of **204** with DAST proceeded well to give the required 3′β-fluoro sugar **205**. The 3′β-fluoro analog of ddG has been prepared from **205**.[202]



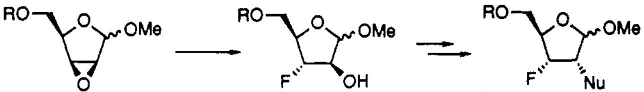
203 204 205

Starting with (*R*)-methyl 4-methylphenyl sulfoxide, the diastereomers **207** were prepared. After separation, each isomer was reduced with DIBAL to the corresponding alcohol with high asymmetric induction by the sulfinyl auxiliary. The 5-hydroxy group was established via Pummerer rearrangement, and oxidative cleavage of the double bond afforded 3α-fluoro- or 3β-fluoro dideoxy sugar (**206** or **208**).[203]



206 207 208

The 3α-fluoro-3-deoxy- and 2α-azido-3α-fluorodideoxyfuranosides **211** have been prepared via epoxide opening of **209** and subsequent nucleophilic substitutions. These sugars **211** were converted to a variety of 3′α-fluoronucleosides.[163]

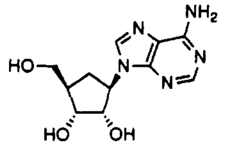


Nu = OBz, $N_3$

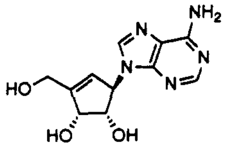
209 210 211

## B. Carbocyclic Analogs

Carbocyclic nucleosides are considered nucleoside analogs in which the furanose ring is replaced by a cyclopentane ring. Their synthesis was reviewed by Marquez and Lim in 1986.[204] Reviews on aristeromycin (**212**)[205] and neplanocin A (**213**),[206] carbocyclic analogs of adenosine isolated from natural sources, appeared in 1989. Hence, we will discuss here only the chemistry which has recently appeared in the literature.



**212** (Aristeromycin)

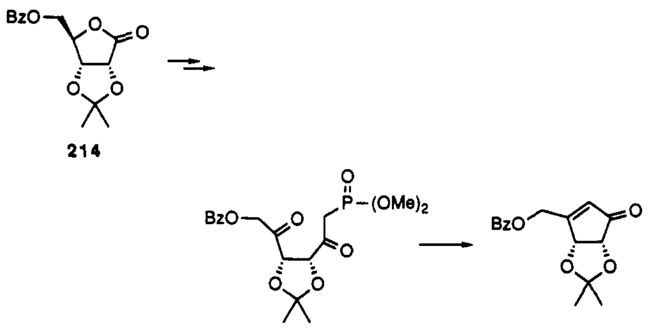


**213** (Neplanocin A)

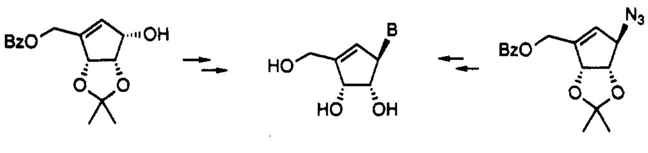
### 1. Neplanocin A and Analogs

Marquez et al. have published a number of papers on the synthesis of neplanocin A (**213**) and its analogs

**218**.[207-210] Treatment of the ribonolactone derivative **214** with dimethyl (lithiomethyl)phosphonate, followed by oxidation gave the diketone **215**, which underwent intramolecular cyclization to the desired cyclopentenone **216**. Partial racemization of **215** was observed in this cyclization. The enantiomerically pure **216** was isolated in 35% yield by removal of the crystalline racemate.[207] The last chiral center was constructed by the stereoselective reduction of **216** to the $\alpha$ allylic alcohol **217**, followed by $S_N2$ displacement with $LiN_3$ or the sodium salt of the corresponding heterocyclic base.

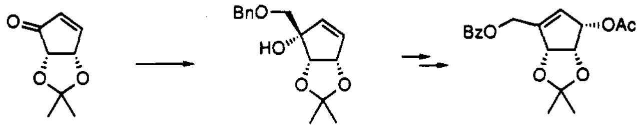


**214** **215** **216**

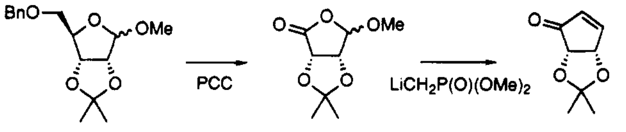


**217** **218** **219**

Alternatively, the requisite $\alpha$ allylic alcohol **217** has been made from the chiral enone **220**.[211] Treatment of **220** with [(benzyloxy)methyl]lithium afforded the tertiary allylic alcohol **221**. The $\alpha$-allylic acetate **222** was obtained via palladium catalyzed isomerization of the corresponding tertiary acetate of **221**. The chiral enone **220** was prepared via enzymatic hydrolysis of prochiral diacetates.[211,212] More recently, a three-step procedure from ribose was reported: PCC oxidation of the ribose derivative **223** to the lactone **224** followed by reaction with dimethyl (lithiomethyl)phosphonate furnished the requisite enone **220** in 41% overall yield.[213]

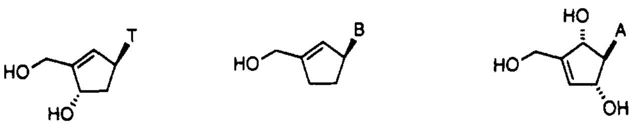


**220** **221** **222**



**223** **224** **220**

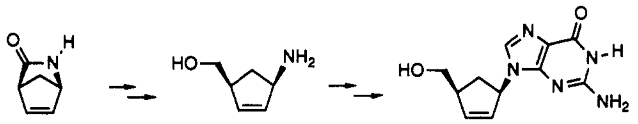
The syntheses of the deoxy analog **225**,[214] the dideoxy analog **226**,[215] and racemic neplanocin F (**227**)[216] have also been reported recently.



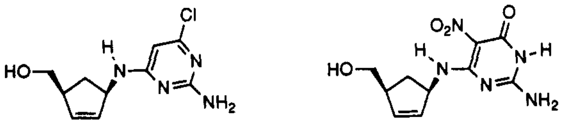
**225** **226** **227**

## 2. Carbovir

Carbovir (**230**), a dideoxy didehydro carbocyclic nucleoside, has proven to be a potent inhibitor of HIV-1 replication;[217] several papers on its synthesis have recently appeared. The versatile intermediate, chiral bicyclic lactam **228**, has been prepared via enzymatic resolution.[218] Hydrolytic cleavage of the lactam ring followed by hydride reduction gave the required amine **229**. Alternatively, acylation of the lactam **228** followed by reductive opening of the lactam ring furnished **229**.[219] The guanine portion was constructed via the reaction of **229** with 2-amino-4,6-dichloropyrimidine to give **231**,[217] or more directly with the 2-amino-6-chloro-5-nitro-4(3*H*)-pyrimidinone to give **232**.[220]

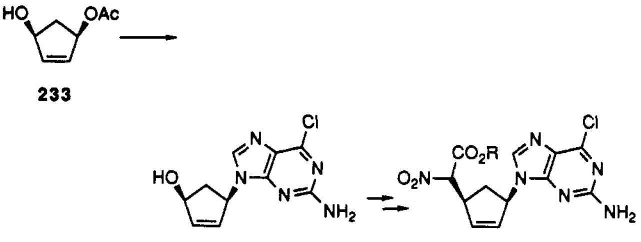


**228** **229** **230**



**231** **232**

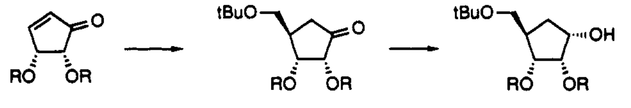
The chemistry reported by Trost[221] has also been applied to the synthesis of carbovir (**230**).[222] Treatment of the chiral allylic acetate **233** with the potassium salt of 2-amino-6-chloropurine under palladium catalysis gave **234**. The allyl alcohol **234**, after conversion to the corresponding carbonate, was again subjected to the palladium chemistry to afford the cis-1,4-disubstituted cyclopentene **235** regio- and stereospecifically. Conversion of the carboalkoxy(nitro)methyl group to a hydroxymethyl group proceeded rather poorly.



**233** **234** **235**

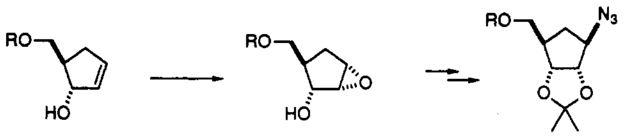
## 3. Other Carbocyclic Analogs

Several syntheses of aristeromycin (**212**)[205] and its analogs have been reported. The enone **236** was treated with lithium bis(*tert*-butoxymethyl)cuprate to afford the Michael adduct **237** stereospecifically. Reduction of the ketone **237** to the alcohol **238** also proceeded with high stereoselectivity. The hydroxy group of **238**, after activation as the triflate, was displaced with the sodium salt of adenine to give aristeromycin (**212**).[223]



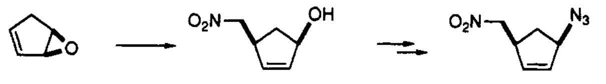
236 237 238

Two more reports on the racemic synthesis of the carbocyclic portion of aristeromycin[205] have appeared in the recent literature. The diol **239** prepared by a Prins reaction of cyclopentadiene, was treated with mCPBA to give the epoxide **240**. The regioselective opening of the epoxide **240** furnished the requisite azide **241** in 50% yield.[224]



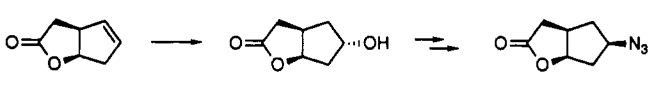
239 240 241

The palladium-catalyzed reaction[221] of cyclopentadiene monoepoxide (**242**) with nitromethane followed by a second palladium-catalyzed allylic substitution reaction afforded cis-1,4-substituted cyclopentene **244** which was also converted into **241** in several steps.[225]

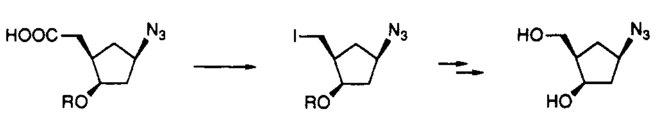


242 243 244

The chiral bicyclic lactone **245** has served as a starting material for 2′-deoxy carbocyclic nucleosides.[226-228] The highly regio- and stereoselective hydroxylation of **245** using $Hg(OAc)_2$ furnished the alcohol **246**. Displacement of the hydroxy group by azide followed by several chemical transformations gave **248**. The acetic acid side chain of **248** was transformed to an iodomethyl group via iododecarboxylation[229] in 80% yield. The iodomethyl compound **249** was then converted into hydroxymethyl derivative **250** oxidatively using mCPBA.[226] From this key intermediate **250**, several thymidine analogs have been prepared.[226-228]

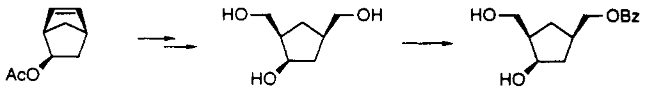


245 246 247



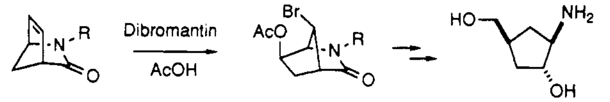
248 249 250

The optically active bicyclic acetate **251** prepared via enzymatic resolution gave on ozonolysis with reductive workup the triol **252**. Enantiomerically pure material was obtained by a single recrystallization of the monobenzylated triol **253**, which has also been converted into 2′-deoxy carbocyclic nucleosides.[230]



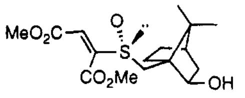
251 252 253

A precursor of the 3′-deoxy carbocyclic nucleoside **256** has been prepared from the bicyclic lactam **254**.[231] Bromination of **254** with 1,3-dibromo-5,5-dimethylhydantoin (dibromantin) in acetic acid afforded **255** via migration of the amido function. Hydrodebromination followed by standard transformations furnished the requisite amine **256**. Similarly, the 2α-fluoro analog was also prepared from **254**.[231]



254 255 256

Asymmetric Diels–Alder reaction of the maleate **257** with cyclopentadiene was reported recently[232] to produce, after several transformations, Ohno's half ester **258**[233] which is a known chiral precursor for the synthesis of carbocyclic nucleosides, such as aristeromycin (**212**) and neplanocin A (**213**).



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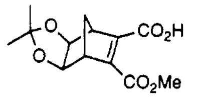

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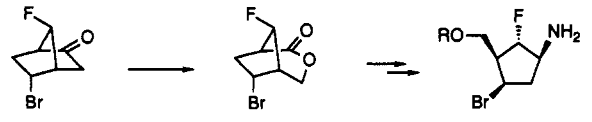
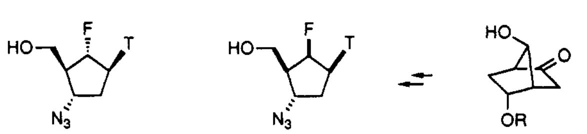
### 4. Fluorinated Carbocyclic Analogs

Fluorinated carbocyclic analogs of AZT (**262** and **263**), in which the ring oxygen atom in the sugar unit was replaced by an isosteric fluoromethylene unit, have been synthesized.[234-236] The regioselective Baeyer–Villiger oxidation of the chiral fluoro bicyclic ketone **259** (resolved via biological oxidation) afforded the lactone **260**.[235] Standard transformations, including Curtius rearrangement, furnished the chiral amine **261**. Construction of the thymine portion and displacement of the bromide by azide gave **262**. Starting from the racemic ketone **264**, the racemic β-fluoro analog **263** was prepared via similar transformations.[234,236]

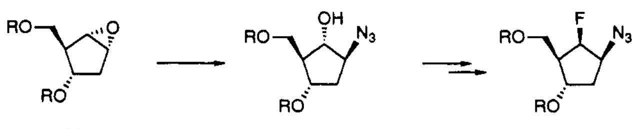


259 260 261



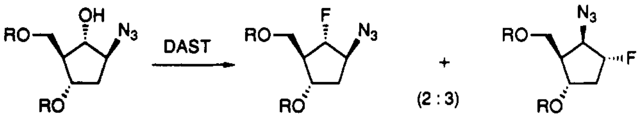
262 263 264

Cyclopentene oxide derivatives, such as **265**, are also versatile intermediates to prepare fluorinated carbocyclic nucleosides. Regioselective opening of the epoxide **265** with azide gave the alcohol **266**. Activation of the hydroxy group as triflate, followed by displacement with a fluorine atom produced the precursor of β-fluoro 2′-deoxy carbocyclic nucleosides **267**.[237] Treatment of the



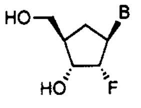
265 266 267

alcohol **266** with DAST gave a mixture of the fluorides **268** and **269**. Participation of the azide group obviously resulted in replacement of the hydroxy group by a fluorine atom with retention of configuration as well as migration of the azide group. The minor product **268** has been converted into α-fluoro 2′-deoxy carbocyclic nucleosides.[237] The corresponding racemic dideoxy carbocyclic[238] and carbocyclic ribose[239] versions have also been reported.

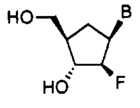


**266** **268** **269**

Carbocyclic nucleosides fluorinated at the C2′ position (**270**–**272**) have been prepared from the amino triol **273**[240,241] or aristeromycine (**212**)[242] by using standard transformations.



**270**



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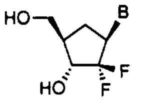

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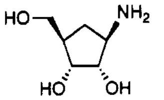


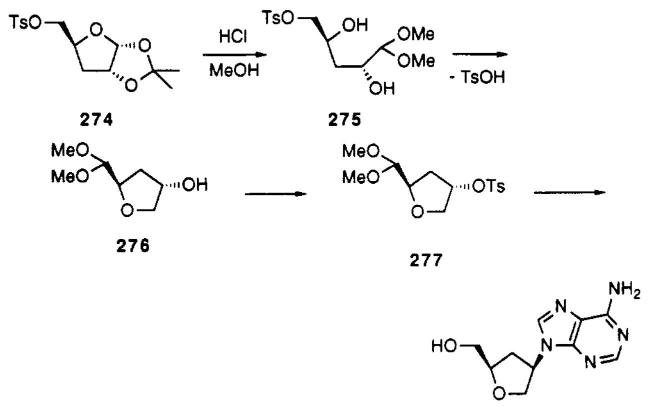
**273**

## C. Heterocyclic Analogs

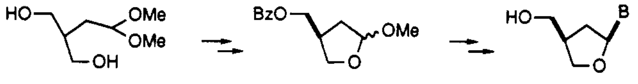
Several modifications of the 2′,3′-dideoxynucleoside framework in which the furanose oxygen atom is either transposed to a new position within the ring and/or replaced by another heteroatom have recently been reported. Interestingly, a number of these derivatives show potent anti-HIV activity.

Two series of such compounds are isomeric with the 2′,3′-dideoxynucleosides, but differ in the placement of the oxygen atom within the five-membered ring. The "iso-nucleosides", exemplified by iso-ddA (**278**) were designed to provide improved acid and enzymatic stability over conventional purine dideoxynucleosides.[243] Acid-mediated hydrolysis of the carbohydrate derivative **274**, followed by in situ cyclization afforded the furanose unit **276** in >95% yield. Conversion to the corresponding tosylate **277** was followed by displacement with adenine. The target compound **278** was generated by hydrolysis and reduction.[243] Among a series of these molecules containing the standard nucleobases, as well as some modified derivatives, the adenine (**278**) and guanine analogs were found to possess good anti-HIV activity.[244] Furthermore, the stability of these molecules was significantly enhanced when compared to the corresponding purine 2′,3′-dideoxynucleosides.

In a similar series, the apex oxygen atom of the parent dideoxynucleosides was transposed to the 2′-position to afford compounds **281**, as well as the corresponding α-anomers. The starting material **279**, derived from diethyl malonate and bromoacetaldehyde dimethyl acetal, was converted to an equal mixture of the furanose anomers **280** by acid treatment and benzoylation. Vorbrüggen reaction with the appropriate silylated base, followed by separation and deprotection yielded the 2′-oxa derivatives **281** of uridine, cytidine, and guanosine.[245] A synthesis of the optically active adenosine analog **281** utilizing a lipase-catalyzed transesterification of **279** has also been reported.[246]

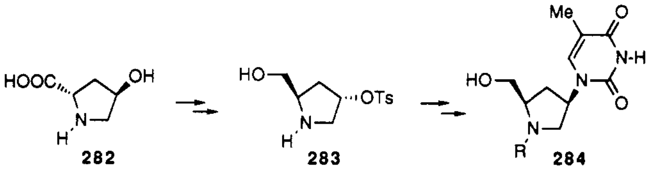


**278** (iso-ddA)



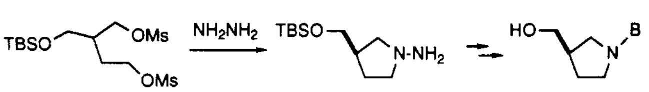
**279** **280** **281**

Incorporation of a nitrogen atom into the furanose ring provided a number of new 2′,3′-dideoxynucleoside variations. The 3′-azanucleoside series was prepared from *trans*-4-hydroxy-L-proline (**282**), since the cost of the obvious D series starting material is prohibitive. In a number of standard transformations, **282** was converted to the prolinol **283** with inversion of both chiral centers. The pyrimidine ring was incorporated by standard conditions to provide the aza analog of 3′-deoxythymidine **284** (R = H). Substitution of the nitrogen yielded a number of AZT-related structures **284** (R = OH, NO, and CN).[247] The corresponding purine analogs of **284** were also prepared recently.[248] An enantiomeric series of 3′-azadideoxynucleosides has also appeared in the literature.[249]



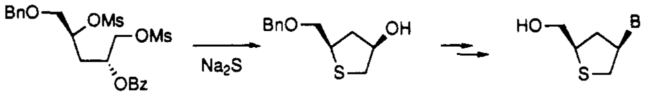
**282** **283** **284**

A further variation of the azadideoxynucleoside series involves linkage of the pyrrolidine ring to the nucleobase via the heteroatom (e.g. **287**). The required 1-aminopyrrolidine **286** was synthesized from the mesylate **285**. The thymidine, uridine, and cytidine analogs **287** were all generated from **286**.[250]



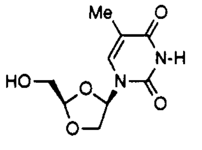
**285** **286** **287**

Introduction of a sulfur atom into the 3′-position of the furanose ring afforded structures such as **290**. Diacetone D-glucose was converted to the dimesylate **288** through a series of steps. Reaction with sodium sulfide provided the tetrahydrothiophene **289**. Inversion of the secondary hydroxy group, activation, and displacement with the appropriate nucleobase yielded the 3′-thiadideoxynucleoside analogs **290**. None of the sulfur-containing nucleosides were reported to exhibit anti-HIV activity.[251]

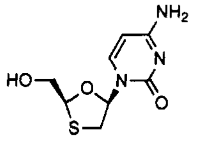


**288** **289** **290**

Dideoxynucleoside prototypes containing two heteroatoms within the carbohydrate framework have led to several promising anti-HIV agents, such as dioxolane-T (**291**)[252] and BCH-189 (**292**).[253] The dioxolane

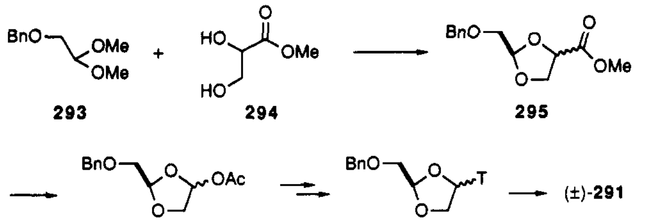


**291** (dioxolane-T)



**292** (BCH-189)

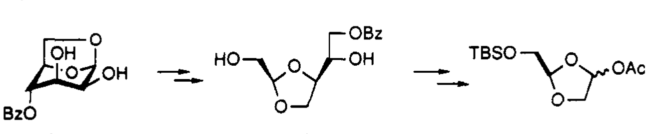
series is exemplified by oxygen atoms at the apex and 3′-position, as in **291**. Condensation of **293** with methyl glycerate **294** afforded **295**. Decarboxylation provided the acetate **296**, which when treated under Vorbrüggen conditions yielded a mixture of the diastereomers **297**. Separation and deprotection generated the anti-HIV agent (±)-dioxolane-T.[252]



**293** **294** **295**

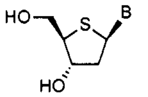
**296** **297**

An asymmetric synthesis of dioxolane-T (**291**) has been reported which utilizes 1,6-anhydro-D-mannose as starting material. Conversion to the diol **298** was followed by oxidative cleavage and reduction to provide **299** via benzoyl migration from the secondary to primary position. Functional group manipulation afforded an intermediate **300** similar to that used in the racemic synthesis.[254]

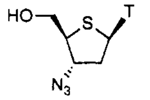


**298** **299** **300**

A number of analogs which contain a sulfur atom at the apex position were prepared as antiviral or anticancer agents. These include 2′-deoxynucleoside analogs **301**[255,256] and the sulfur analog of AZT **302**.[255]



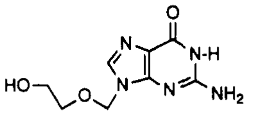
**301**



**302**

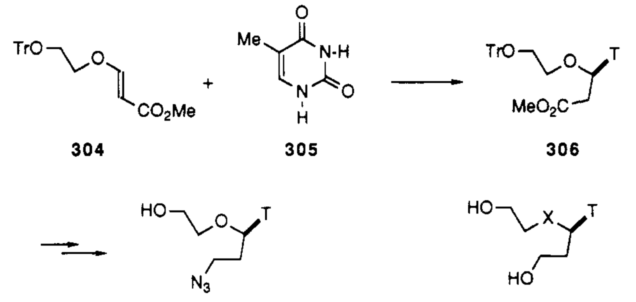
## D. Acyclic Analogs

The area of acyclic nucleosides has been widely explored due to the successful development of the antiherpes drug, acyclovir (**303**). As the topic of antiviral and anticancer acyclic nucleosides has been recently reviewed,[12] our focus will be on acyclic nucleosides synthesized expressly as anti-HIV agents.



**303** (Acyclovir)

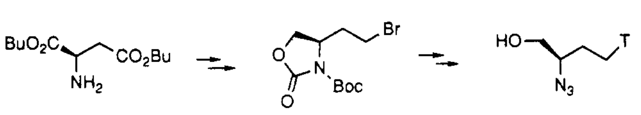
Among the acyclic nucleosides reported in the literature are those modeled after other known anti-HIV agents such as AZT (**3**) and the 2′,3′-dideoxynucleosides **6**. The acyclic AZT analog **307** was prepared by Michael addition of thymine **305** to the α,β-unsaturated ester **304**. Standard chemical manipulation afforded **307** in four subsequent steps. The 3′,4′-secothymidine as well as the sulfur analog **308** (X = O and S) were similarly prepared.[257]



**304** **305** **306**

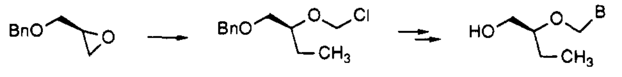
**307** **308**

The related AZT analog **311**, derived from (*R*)-aspartic acid, was reported in 1990.[258] The synthesis involved conversion of the dibutyl ester of (*R*)-aspartic acid (**309**) to the oxazolidinone **310**. Alkylation with thymine, deprotection, and further manipulation provided the parent **311**. A number of other acyclic AZT analogs in which the azide moiety was replaced by an amino-function, as well as the adenine derivative, were also prepared.[258]



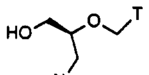
**309** **310** **311**

Seco derivatives of the 2′,3′-dideoxynucleosides **314** were prepared in optically active form using (*S*)-*O*-benzylglycidol (**312**) as starting material. Regiospecific epoxide opening was followed by chloromethylation to yield **313**. This precursor was used in coupling reactions



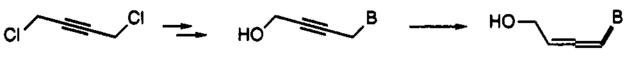
**312** **313** **314**

with the appropriate silylated nucleobase to afford acyclic derivatives (**314**) of ddA, ddC (**1**), ddG, and ddI (**2**).[259] A similar strategy was applied to a synthesis of the seco-AZT analog **315**.[260]



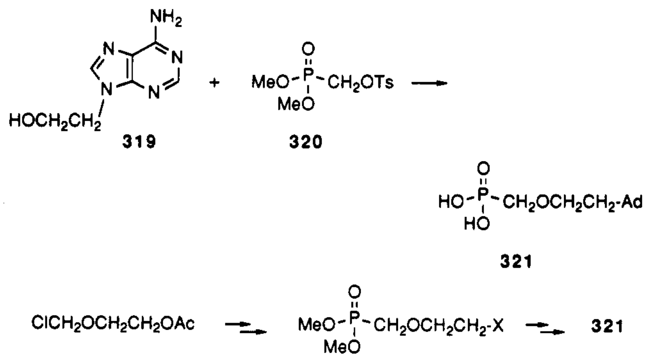
**315**

In 1988, the antiviral activity of adenallene (**318a**, B = adenine) and cytallene (**318b**, B = cytosine) were reported.[261] These molecules were viewed as analogs of the 2′,3′-dideoxynucleosides in that the allene moiety and the furanose ring served to situate the heterocyclic base and the hydroxymethyl substituents in a similar orientation.[262] Alkylation of the nucleobase with an acetylenic derivative **316**, was followed by hydrolysis to yield the alcohol **317**. Isomerization under basic conditions provided a mixture of **317** and the desired allene **318**. Using this strategy the allenic nucleosides **318** of adenine, cytosine, guanine, and hypoxanthine were prepared. The synthesis of the thymine derivative required protection of the N-3 nitrogen of the thymine moiety prior to isomerization.[263]



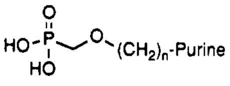
**316** **317** **318**

The 2-(phosphonylmethoxy)ethyl (PME) class of acyclic nucleosides (e.g. **321**) represents compounds with not only anti-HIV activity, but also inhibitory activity against other viruses (e.g. herpes simplex virus).[264] Two strategies for the synthesis of these molecules have been employed. Reaction of a protected adenine derivative **319** with a phosphonic acid synthon **320** generated, after deprotection, the desired product **321** in modest yield. More satisfactory was the condensation of adenine with an ethoxymethanephosphonic acid precursor (e.g. **323**). The starting material, (2-acetoxyethoxy)methyl chloride (**322**), was converted to the phosphonate **323**. Reaction with adenine, or another purine, and deprotection yielded **321**.[265]

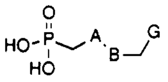


**319** **320** **321** **322** **323** (X = Br, Cl, OTs)

A number of related analogs aimed at defining the structure–activity relationships of this class of molecules were described by Kim and co-workers. Structures **324**–**327** were synthesized as above by reaction of an acyclic phosphonate with the appropriate purine.[266] The 3-fluoro-2-(phosphonylmethoxy)propyl derivative **328** was reported to possess potent and selective anti-HIV activity.[267] A large number of interesting acyclic nucleosides targeted as antiherpetic agents, but devoid of anti-HIV activity have also been synthesized.[268-272]

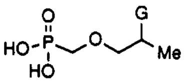


**324**



**325**

a A=B=CH$_2$
b A=CH$_2$, B=O
c A=S, B=CH$_2$



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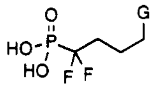

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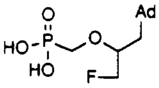


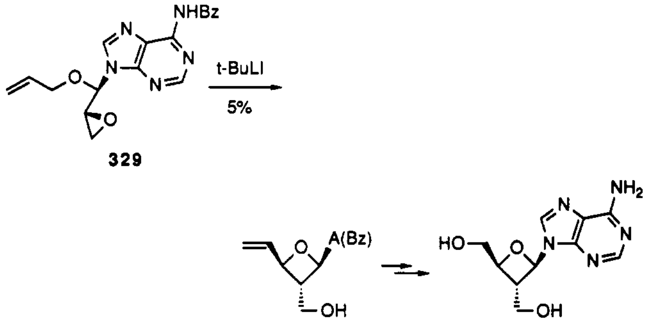
**328**

## *IV. Oxetanocin and Its Analogs*

The potent anti-HIV activity of oxetanocin-A (**331**),[273] which is the first natural product having an oxetanosyl-*N*-glycoside, has prompted a number of papers on the synthesis of this molecule and its analogs. This subject has been reviewed recently by Nishiyama and Yamamura.[274]

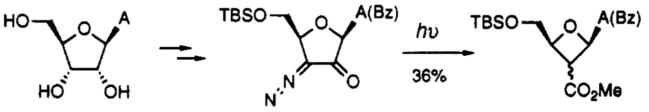
### A. Oxetanocin and Its Analogs

The first reported synthesis of oxetanocin-A (**331**) involves the formation of an acyclic nucleoside **329** from a readily available carbohydrate starting material.[275] The key step, formation of the oxetane **330** via the (allyloxy)carbanion generated from **329**, however, occurred in low yield.[276]



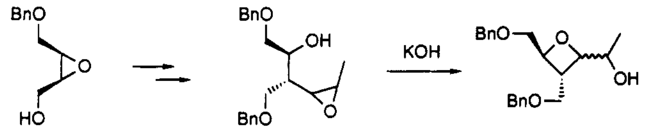
**329** **330** **331**

A ring contraction reaction has also been used to synthesize oxetanocin-A (**331**).[105] Norbeck and Kramer converted adenosine (**332**) to the diazo ketone **333** in five steps. Photochemical Wolff rearrangement afforded the oxetane **334** in 36% yield as a 2:1 mixture of α- and β-epimers. After separation, reduction, and deprotection of **334**, oxetanocin-A was prepared in 5% overall yield.



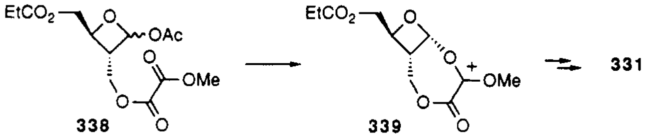
**332** **333** **334**

Construction of the requisite sugar portion has also been a strategy employed. The chiral epoxide **335** was utilized to prepare the acyclic derivative **336**. Oxetane formation took place to give **337** in 62% yield via intramolecular epoxide opening.[277] A similar strategy using intramolecular $S_N2$ displacement of a secondary mesylate has also been reported.[278,279] After further chemical transformations, the purine was introduced



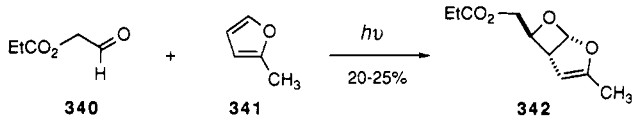
335 336 337

by Lewis acid catalyzed condensation of the acetate **338** with the silylated adenine. Great care in choice of protecting groups is necessary to achieve high $\beta$-selectivity in the coupling. The methyl oxalyl ester was found to promote the formation of the desired $\beta$-anomer presumably via **339**.[279] With benzoyl groups as protecting groups, only the $\alpha$-anomer was produced.[278] Use of a benzoyl group instead of the propionyl group in **338** significantly increased the $\alpha$-selectivity.[280]



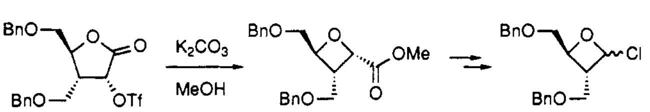
338 339

The racemic version has been achieved quite easily; irradiation of the aldehyde **340** with 2-methylfuran (**341**) gave the oxetane **342**, which was transformed in a one-pot reaction into racemic **338** in 45% yield via ozonolysis.[280]

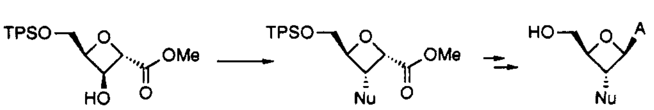


340 341 342

The lactone triflate **343**, prepared in 11 steps from diisopropylideneglucose, was used as a key intermediate in another synthesis of oxetanocin-A (**311**). Treatment of **343** with $K_2CO_3$ in methanol caused ring contraction with inversion of configuration at C2 to generate **344** in 56% yield.[281] The ring contractions of lactone triflates have been reported in detail in separate papers.[282,283] Conversion of **344** to the chlorooxetane **345** followed by introduction of adenine via nucleophilic substitution afforded epimeric mixtures of oxetanocin-A (**331**) in low yield.[281] The same strategy was applied more successfully to synthesize azido- and fluoro-substituted oxetanocin analogs **348** (Nu = $N_3$ and F).[284] The nucleophilic substitutions by azide and fluoride in the oxetane ring proceeded surprisingly well. Coupling of the corresponding chlorides with adenine was also achieved in good yields, due to the stabilization of the chloride by the electron-withdrawing substituents ($N_3$ and F).

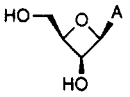


343 344 345



346 347 348

Kitagawa and co-workers synthesized oxetanocin derivatives **349**–**351** using oxetanocin-A (**331**) as starting material. Interestingly, the $\beta$-hydroxy analog **349** and simple oxetane **351** exhibited higher anti-HIV activity than the parent compound **331**.[285] The sugar portion of **350** has also been prepared. However, its glycosidation has not been successful due to ring expansion to the corresponding furanosyl derivative.[286]



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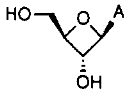

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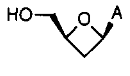
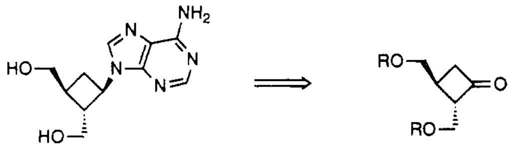


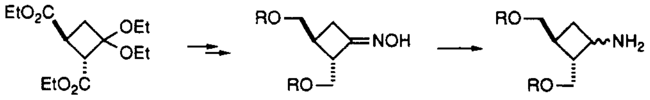
351

## B. Carbocyclic Oxetanocin Analogs

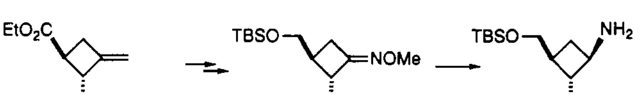
The carbocyclic analog of oxetanocin, known as cyclobut-A (**352**), has received considerable attention from researchers due to its broad spectrum of antiviral activities. Many of the reported syntheses use a disubstituted cyclobutanone, such as **353** as a key intermediate. The first synthesis of racemic material was reported by Honjo and co-workers in 1989.[287] 3,3-Diethoxy-1,2-cyclobutanedicarboxylate (**354**) was converted in several steps to **353**. The oxime **355** was generated and then reduced to provide a mixture of aminocyclobutanes **356**. Through classical transformations the amino function of the desired $\beta$-isomer was converted into the purine moiety to yield racemic cyclobut-A (**352**). More recently, the stereospecific reduction of a similar oxime **358** employing $NaBH_3(O_2CCF_3)$ was reported.[288]



352 (Cyclobut-A) 353

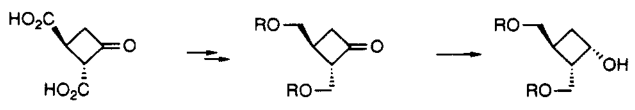


354 355 356



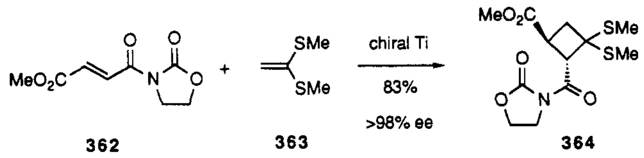
357 358 359

Enantiomerically pure **360** of both antipodes were prepared via resolution.[289] Stereoselective reduction of the cyclobutanone **353** using LS-Selectride afforded the alcohol **361**.[290] Activation of the alcohol as a tosylate and displacement by a purine precursor yielded, after further transformation, both enantiomers of cyclobut-A (**352**) and cyclobut-G.[289]

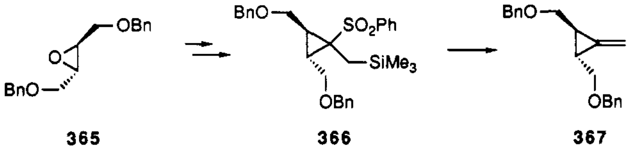


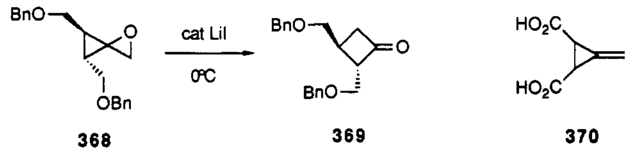
360 353 361

An asymmetric synthesis of these cyclobutane nucleosides has been reported by Ichikawa et al.[291] A thermal [2 + 2] cycloaddition of the oxazolidinone **362** and 1,1-bis(methylthio)ethylene (**363**) in the presence of a catalytic amount of a chiral titanium complex afforded the cyclobutane adduct **364** in 83% yield and in better than 98% ee. A series of transformations converted **364** to the cyclobutanone **353**. In a manner similar to those described above, cyclobut-A (**352**) and cyclobut-G were synthesized in optically pure form.

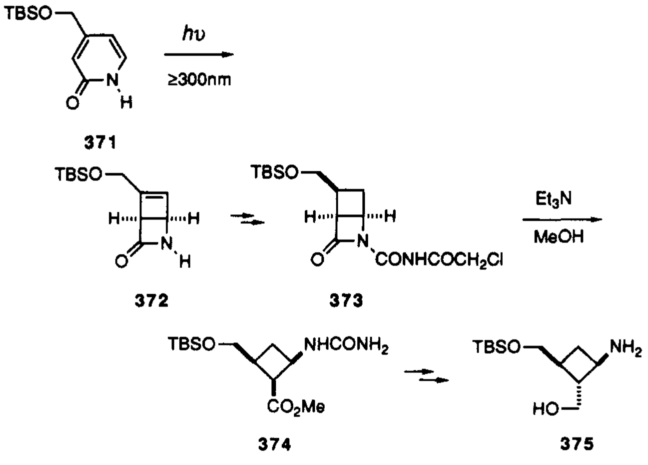


An oxaspiropentane rearrangement has also been used in the synthesis of the cyclobutanone intermediate **353**.[292] The cyclopropane derivative **366**, synthesized via the alkylation of 1-(phenylsulfonyl)-2-(trimethylsilyl)ethane with the chiral oxirane **365**, was converted to the oxaspiropentane **368**. Upon treatment with a catalytic amount of lithium iodide, the cyclobutanone **369** was formed in 96% yield. In a further modification of this strategy, Feist's acid **370** was resolved in optical pure form via a known procedure. Simple transformation afforded the methylenecyclopropane **367** which intercepts the first synthesis.

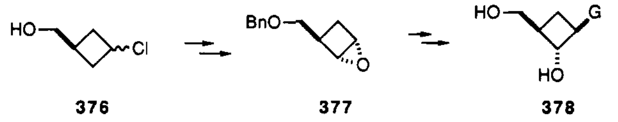




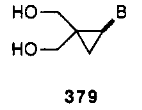
An interesting approach to a useful cyclobutylamine precursor **375** has been reported by Katagiri et al.[293] The substituted pyrimidine **371** was employed as starting material. Photolysis yielded the bicyclic derivative **372**, which was further elaborated to **373**. Opening of the $\beta$-lactam provided trisubstituted cyclobutane **374**, which upon simple transformations was converted to the racemic cyclobutylamine **375**. This intermediate can be used in the synthesis of purine as well as pyrimidine cyclobutane analogs.



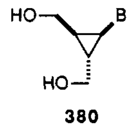
A derivative of cyclobut-G, the 2-hydroxy analog **378**, has been reported to effectively mimic the conformation of 2′-deoxyguanosine.[294] The synthesis involved regioselective opening of the $\alpha$-epoxide **377**, readily available from 1,1-cyclobutanedicarboxylic acid via the chloride **376**, with a purine nucleophile.



Cyclopropane analogs of oxetanocin (e.g. **379**[295] and **380**[296]) have also been prepared via Curtius rearrangement.



**379**

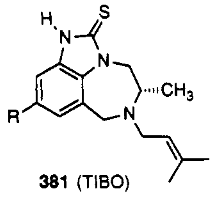


**380**

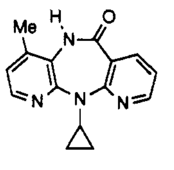
## V. Concluding Remarks

The past several years have witnessed explosive new developments in the design and synthesis of 2′,3′-dideoxynucleosides and their analogs. Improvements in the efficiency in the synthesis of existing therapies are a particularly important issue due to the need to limit cost. Furthermore, the need for novel, more effective agents has prompted an enormous amount of research. Table I represents the anti-HIV carbohydrate-modified nucleosides reported to date. Derivatives with changes within the nucleobase are not included. Due to the variations in testing protocols, no attempt has been made to compare the relative activity and merits of each molecule. As can be seen, a diverse group of structures including acyclic, cyclobutyl, and heterocyclic nucleosides, as well as classical 2′,3′-dideoxynucleosides, can possess anti-HIV activity.

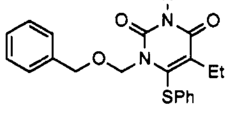
Recently, a new class of reverse transcriptase inhibitors has been described. These molecules are not substrate analogs, but act at a distinctly different site of the HIV reverse transcriptase than the dideoxynucleosides. Some of the reported structures with this allosteric inhibitory RT activity (**381**,[297] **382**,[298] **383**,[299,300] and **384**[301]) are shown below. Their usefulness in a clinical setting is currently under investigation.



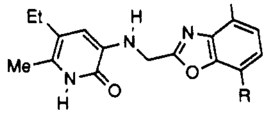
**381** (TIBO)



**382** (BI-RG-587)



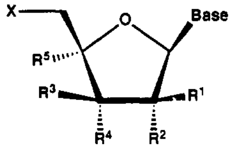
**383** (E-BPU)



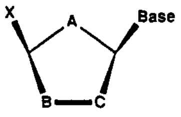
**384** (R = Me; L-697,639)
(R = Cl; L-697,661)

In addition to the HIV reverse transcriptase, a number of other viral proteins have been targeted as potential sites of intervention. Extremely potent

**Table I. Carbohydrate-Modified Anti-HIV Nucleosides**



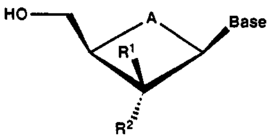
I



II

X - A - B - C - Base

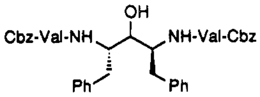
III



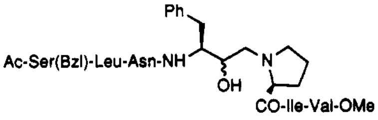
IV

| structure | substituents | reference |
|---|---|---|
| I | $R^1, R^2, R^3, R^4, R^5 = H$; $X = OH$; base = adenine, cytosine, 2,6-diaminopurine, guanine, inosine, thymine | 1, 309 |
| II | $A = O$; $B\text{–}C = CH{=}CH$; $X = CH_2OH$; base = adenine, cytosine, thymine | 3, 4, 308, 310, 311 |
| I | $R^1, R^2, R^3, R^5 = H$; $R^4 = N_3$; $X = OH$; base = adenine, cytosine, 2,6-diaminopurine, guanine, thymine, uracil | 2, 5, 81, 312, 313,314 |
| I | $R^1, R^2, R^3, R^5 = H$; $R^4 = OOH, SCN, NCS$; $X = OH$, base = thymine | 71 |
| I | $R^1 + R^3 = O$; $R^2, R^4, R^5 = H$; $X = OH$; base = cytosine | 92 |
| I | $R^1, R^2, R^3 = H$; $R^4 = OH$; $R^5 = NH_3$; $X = OH$; base = thymine | 135 |
| I | $R^1, R^2, R^3, R^5 = H$; $R^4 = F$; $X = OH$; base = thymine | 47 |
| I | $R^1 = F$; $R^2, R^3, R^4, R^5 = H$; $X = OH$; base = adenine, cytosine | 138, 146, 147, 81, 315 |
| I | $R^1, R^4 = F$; $R^2, R^3 = H$; $X = OH$; base = cytosine | 138 |
| II | $A = O$; $B\text{–}C = CH{=}CF$; $X = CH_2OH$; base = cytosine, thymine | 138 |
| I | $R^1, R^2, R^3, R^5 = H$; $R^4 = CH_2OH$; $X = OH$; base = cytosine, adenine | 161, 181 |
| I | $R^1, R^2, R^3, R^5 = H$; $R^4$ = pyrrol-1-yl; $X = OH$; base = thymine | 102 |
| II | $A = CH_2$; $B\text{–}C = CH{=}CH$; $X = CH_2OH$; base = 6-chloropurine, 2,6-diaminopurine, guanine | 217, 316 |
| II | $A = CH_2\alpha F$; $B = CH\alpha N_3$; $C = CH_2$; $X = CH_2OH$; base = thymine | 234 |
| II | $A = CH\alpha F$; $B, C = CH_2$; $X = CH_2OH$; base = thymine | 238 |
| II | $A = CH\alpha F$; $B, C = CH_2$; $X = OCH_2P_3O_9H_4$; base = thymine | 317 |
| II | $A, C = CH_2$; $B = O$; $X = CH_2OH$; base = adenine, guanine | 243, 244 |
| II | $A, B = CH_2$; $C = O$; $X = CH_2OH$; base = adenine | 246 |
| II | $A, B = O$; $C = CH_2$; $X = CH_2OH$; base = $\alpha$-cytosine, thymine | 252, 253, 254 |
| II | $A = O$; $B = S$; $C = CH_2$; $X = CH_2OH$; base = cytosine | 253 |
| III | $A\text{–}B\text{–}C = CH{=}C{=}CH$; $X = CH_2OH$; base = adenine, cytosine | 261 |
| III | $A = O$; $B, C = CH_2$; $X = CH_2PO_3H_2$; base = adenine, 2-aminopurine, 2,6-diaminopurine | 264 |
| III | $A = O$; $B = (CH_2)_2$; $C = CH_2$; $X = CH_2PO_3H_2$; base = guanine | 266 |
| III | $A = O$; $B = CH(CH_2F)$; $C = CH_2$; $X = CH_2PO_3H_2$; base = adenine, 2,6-diaminopurine, guanine | 267 |
| IV | $A = O$; $R^1 = H$; $R^2 = CH_2OH$; base = adenine | 273 |
| IV | $A = O$; $R^1 = H$; $R^2 = N_3$; base = adenine | 284 |
| IV | $A = O$; $R^1 = OH$; $R^2 = H$; base = adenine | 285 |
| IV | $A = O$; $R^1 = H$; $R^2 = OH$; base = adenine | 285 |
| IV | $A = O$; $R^1, R^2 = H$; base = adenine | 285 |
| IV | $A = CH_2$, $R^1 = H$; $R^2 = CH_2OH$; base = adenine, guanine | 288, 291 |

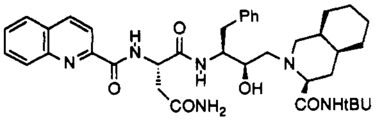
inhibitors of the HIV protease have been reported by a number of groups; some representative structures (**385**,[302] **386**,[303] **387**,[304] **388**,[305] and **389**[306]) are illustrated below. These molecules act by inhibition of the maturation step required for formation of infectious virus particles. Several of these compounds are reported to be undergoing clinical trials. Inhibitors of the HIV regulatory protein, TAT, as well as inhibitors of virion glycosylation and adsorption have also been disclosed.[13,15,307]



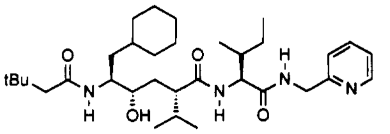
**385**



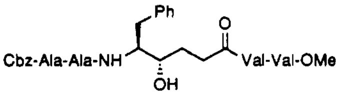
**386**



**387**



**388**



**389**

It is commonly believed that a multidrug regimen, each agent being targeted to a different viral process, will be the future of AIDS therapy. This strategy aims to circumvent the resistance problem, as well as to improve the overall therapeutic efficacy. The carbohydrate-modified nucleosides reviewed here and/or those emerging in the future will undoubtedly be a part of that treatment plan.

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