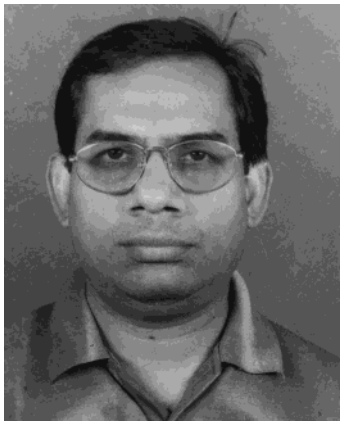
Azidonucleosides: Synthesis, Reactions, and Biological Properties

Tanmaya Pathak[†]

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

Received September 14, 2001

Contents



Tanmaya Pathak, born in 1958 in Kolkata, India, obtained his M.Sc. degree from Jadavpur University, India. After a brief stay at the research center of Organon (India) Ltd., he did his doctoral research with Prof. Jyoti Chattopadhyaya, Uppsala University, Sweden (1988). He joined the National Chemical Laboratory, Pune, India, as a scientist in 1991 after two years of postdoctoral research with Prof. David Gani, Southampton University, UK (and later St.-Andrews University, UK). He spent 1997 at the University of Karlsruhe, Germany, in the laboratory of Prof. Herbert Waldmann as an Alexander von Humboldt Fellow. His research focuses on nucleoside and carbohydrate modifications with a biological perspective. He also takes special interest in the use of enzymes in organic synthesis. At present he is Associate Professor in the Department of Chemistry of the Indian Institute of Technology, Kharagpur, India.

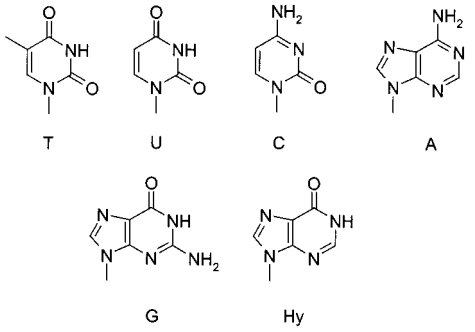
1. Introduction

Although the synthesis of modified nucleosides has been of interest for over four decades, the finding that 3′-azido-3′-deoxythymidine or AZT **1.001** is a therapeutic agent[1] for the treatment of acquired immunodeficiency syndrome (AIDS) has triggered explosive

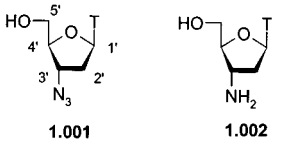
[†] Phone: (03222)-83342/82251. Fax: (03222)-82252. E-mail: tpathak@chem.iitkgp.ernet.in.

10.1021/cr0104532 CCC: $39.75
Published on Web 05/08/2002

new developments in the synthetic chemistry of nucleosides. The area of nucleoside modification has been reviewed extensively.[2−10] Specialized reviews on the synthesis of sugar-modified nucleosides, such as ketonucleosides,[11] 3′-branched nucleoside analogues,[12] AIDS-driven nucleoside chemistry,[13] bicyclic heterocyclic nucleosides,[14] imidazole and benzimidazole nucleosides,[15] thio- and selenosugar-modified nucleosides,[16−18] nucleoside analogues with axial chirality,[19] *C*-nucleosides,[10,20−24] isoxazolinyl- and isoxazolidinyl-nucleoside analogues,[25] acyclonucleosides,[26−30] C-branched nucleoside analogues,[31] D- and L-enantiomers of the oxathiolane and dioxolane nucleosides,[32] carbocyclic nucleosides,[33−36] nucleosides with a six-membered carbohydrate moiety,[37−39] nucleoside antibiotics,[40,41] azanucleosides,[42] boron-containing nucleosides,[43,44] L-nucleosides,[45,46] 2′,3′-dideoxynucleosides,[47,48] 4′,5′-unsaturated nucleosides,[49] C-alkenylation of pyrimidine nucleosides,[50] anomeric spironucleosides,[51] isonucleosides,[52] nucleosides fluorinated in the sugar moiety,[53−56] and dialdehyde derivatives of nucleosides,[57] have also appeared.

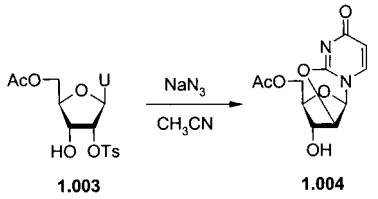


Surprisingly, a review on nitrogen-containing sugar-modified nucleosides has not appeared so far despite the important role that **1.001** has played[1] in proliferating research in the area of nucleoside modification. Moreover, it was reported that **1.001** was converted to 3′-amino-3′-deoxythymidine or AMT **1.002** in some cells and the triphosphate of **1.002** also

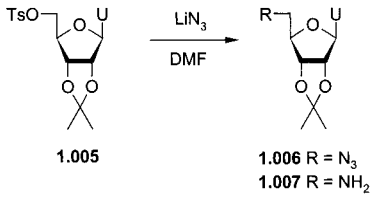


caused DNA chain termination.[58] This observation led us to initiate research in the specialized area of the synthesis of aminonucleosides.[59−64] Since all azidonucleosides are potential starting materials for the corresponding aminonucleosides, it was imperative for us to compile information on the synthesis and chemistry of azidonucleosides. This exercise has resulted in this review. Syntheses of azidonucleosides in the early years to the mid-1970s have been reviewed to a great extent by Moffatt.[3] The developments that have taken place over the last 2.5 decades in this area will be discussed in this review. We will concentrate mainly on the modification of the carbohydrate moiety of nucleosides. However, nucleobase modification of azidonucleosides will be mentioned to highlight the compatibility of nucleoside azides to various reaction conditions. As for the biological properties of azidonucleosides, most of these compounds have been found to be inactive. In section 8 we will focus on azidonucleosides only with positive activities.

Todd and co-workers reported[65] that 5′-*O*-acetyl-2′-*O*-tosyluridine **1.003** on treatment with NaN_3 in acetonitrile produced 2,2′-*O*-anhydro-1-(5′-*O*-acetyl-*β*-D-arabinosyl)uracil **1.004**. The nonformation of any



azide derivative was ascribed to the low solubility of NaN_3 in acetonitrile.[65] Four years later, Horwitz and co-workers successfully synthesized 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine **1.006** from 5′-*O*-tosyl-2′,3′-*O*-isopropylideneuridine **1.005** by treating the latter with LiN_3 in dry DMF at 100 °C.[66] The main purpose of this synthesis was to access aminonucleoside **1.007**.[66] Since then numerous azidonucleosides



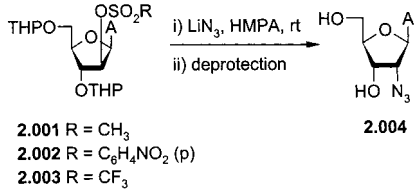
have been synthesized for accessing various aminonucleosides until the anti-HIV of **1.001** was reported,[1] arousing great interest in the synthesis of an array of azidonucleosides and their synthetic as well as biological properties.

2. 2′-Azido-2′-deoxynucleosides

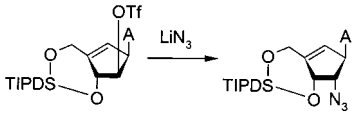
2.1. Synthesis

2.1.1. Nucleophilic Displacement by Azide

A straightforward synthesis of 2′-azido-2′-deoxyadenosine **2.004** could be achieved through direct nucleophilic displacement reactions at the 2′-position of a suitably protected 2′-sulfonate of *arabino*-furanosyladenines **2.001**−**2.003**. The mesylate **2.001** and

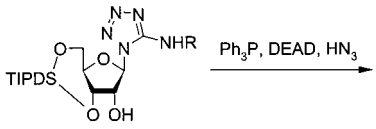


nosylate **2.002** exhibited only a poor tendency to undergo nucleophilic displacement with azide ion. The triflate **2.003** has proven to be more effective and with LiN_3 produced **2.004** in high yield without any side reaction.[67−69] To synthesize 2′-(*S*)-azido-2′-deoxyneplanocin A derivative **2.006**, 3′,6′-protected 2′-*O*-triflyl-*arabino*-neplanocin A **2.005** has been treated

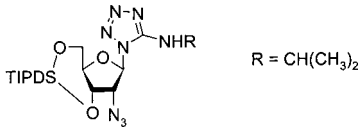


2.005 2.006

with LiN_3.[70] In both these cases configurations at C-2′ were inverted because of the backside attack by azide nucleophile. However, when partially protected (alkylamino)tetrazole nucleoside **2.007** was treated with Ph_3P, DEAD, and HN_3, the corresponding 2′-azido-2′-deoxy-*ribo*-nucleoside **2.008** was obtained with retention of configuration.[71]

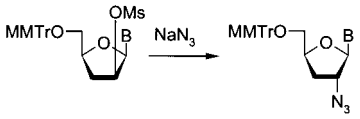


2.007



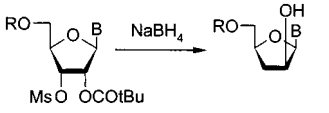
2.008

Mesylated derivatives **2.009** and **2.010**, however, underwent smooth azidolysis to furnish 2′-azido-2′,3′-dideoxyuridine **2.011** and 2′-azido-2′,3′-dideoxyadenosine **2.012**.[72] A general route to 2′-azido-2′-

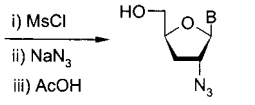


2.009 B = U **2.011**
2.010 B = N^6-monomethoxytrityl adeninyl **2.012**

deoxy-*ribo*-nucleosides **2.015**−**2.019** has been devised via key intermediates **2.014**. The deoxy derivative **2.014** was obtained by deoxygenative [1,2]-hydride shift and β-elimination reactions of sulfonylated *ribo*-derivatives **2.013**. Treatment of substrates **2.014** with



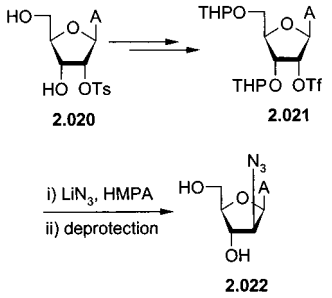
2.013 **2.014**



2.015 B = U
2.016 B = C
2.017 B = A
2.018 B = G
2.019 B = Hy

R = MMTr or DMTr

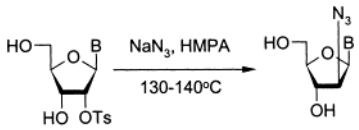
MsCl, followed by conventional S_N2 substitution and deprotection, produced **2.015**−**2.018**. Guanosine derivative **2.018**, on treatment with aqueous $NaNO_2$ and HCO_2H, produced xanthine analogue **2.019**.[73] A facile conversion of adenosine into 2′-azido-2′-deoxy-*arabino*-furanosyladenine **2.022** has been reported.



2.020 **2.021**

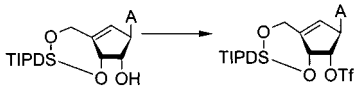
2.022

The starting material of this conversion, triflate **2.021**, was however prepared through a multistep sequence starting from tosylate **2.020**. The reactivity of **2.021** toward LiN_3 was comparable to that of *arabino*-derivative **2.003**.[74] It was shown later that the tosylate derivatives **2.020** and **2.023** on reaction

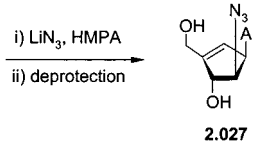


2.020 B = A **2.022**
2.023 B = G **2.024**

with NaN_3 in HMPA at high temperature produced **2.022** and **2.024**, respectively, in poor yields.[75] Similarly, partially protected neplanocin A derivative **2.025** was converted to 2′-azido-2′-deoxyneplanocin A **2.027** via triflate **2.026**.[70] In a similar fashion, 3′,5′-

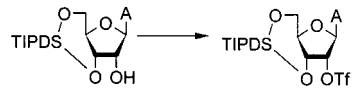


2.025 **2.026**

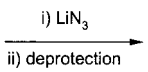


2.027

bisprotected adenosine **2.028** was readily converted to the 2′-*O*-triflate **2.029**, which was reacted with LiN_3; the product after desilylation produced **2.022**.[70]



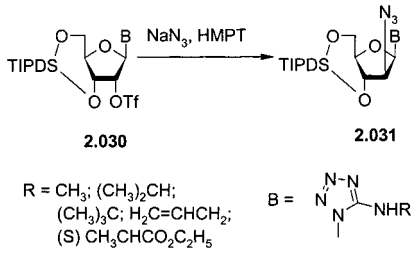
2.028 **2.029**



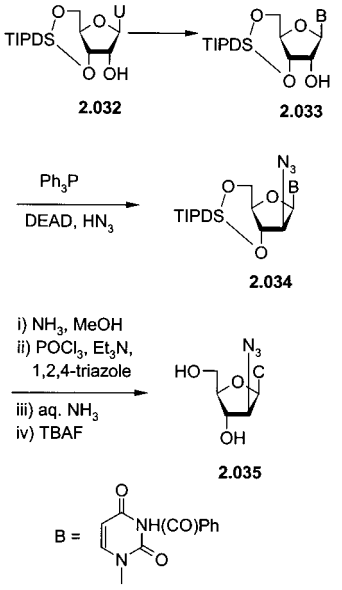
2.022

3′,5′-Disilyl-protected triflate derivatives of the (alkylamino)tetrazole nucleosides, **2.030**, were readily transformed to 2′-azido-2′-deoxy *arabino*-derivatives **2.031**.[71]

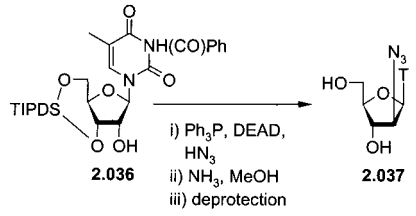
It has been generally recognized that the intramolecular nucleophilic attack of the C-2 carbonyl group of the uracil base on the 2′-position having a leaving group is predominant rather than the intermolecular nucleophilic substitution. If the nucleophilicity of the C-2 carbonyl oxygen could be reduced, the direct S_N2



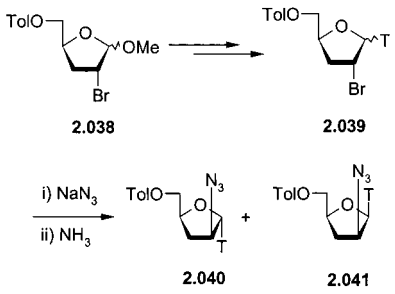
reaction at the 2′-position of uridine would be realized. Thus, 3′,5′-bisprotected uridine **2.032** was benzoylated to afford **2.033**. Compound **2.033** on reaction



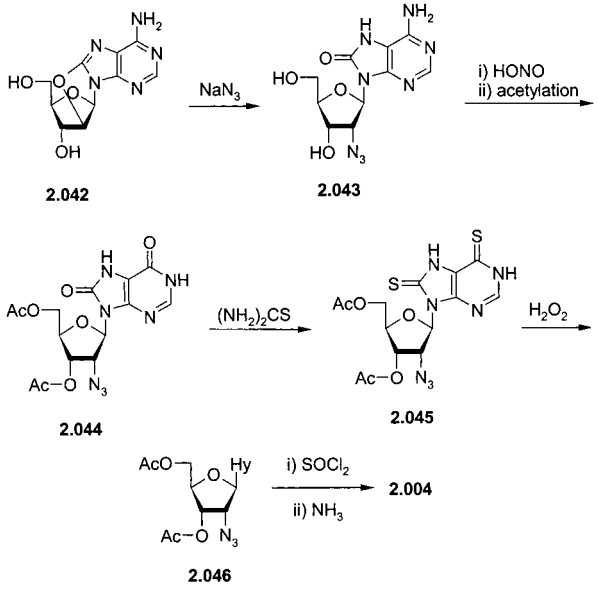
with Ph_3P, DEAD, and DPPA produced the *arabino*-derivative **2.034**. This was then deprotected and converted to *arabino*-derivative **2.035**.[76] A similar approach has been employed for the synthesis of 2′-azido-2′-deoxy-*arabino*-thymidine **2.037** from partially protected *ribo*-furanosylthymine derivative **2.036**.[77]



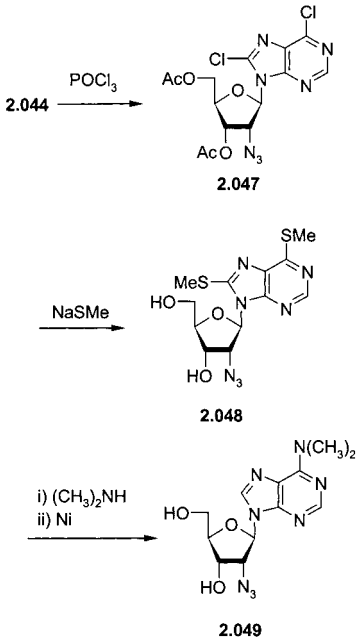
The anomeric mixture of 1-(2-bromo-2,3-dideoxy-5-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranosyl)-thymine **2.039**, which was synthesized from sugar derivative **2.038**, was treated with NaN_3. The products were deprotected to furnish α- and *β*-isomers of 2-azido-2,3-dideoxy-*threo*-pentofuranosylthymine, **2.040** and **2.041**, respectively.[78] A different route has been devised for the synthesis of **2.004**. The azido group was introduced at the C-2′ position by reacting 8,2′-*O*-cycloadenosine **2.042** with NaN_3 to produce the 8-oxo-2′-azide **2.043**. Stepwise conversion of **2.043** to 8-oxoinosine **2.044** followed by thiation led to the



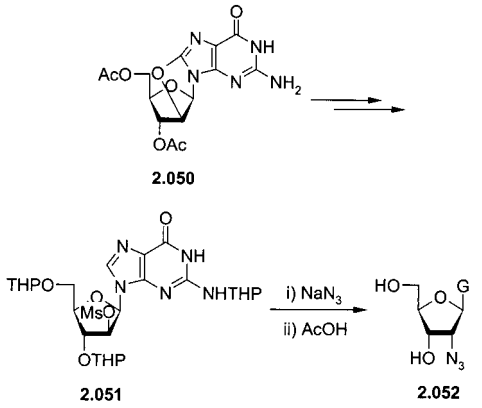
formation of 6,8-disulfanyl derivative **2.045**. Oxidation of **2.045** furnished inosine derivative **2.046**.



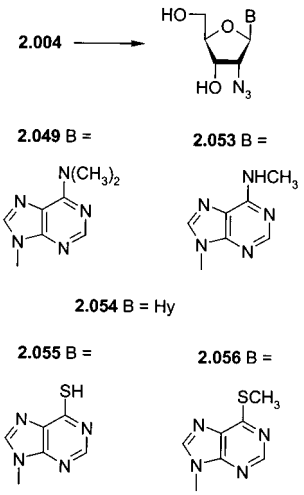
Amination of **2.046** produced 2′-azido-2′-deoxy-*ribo*-adenosine **2.004**.[79] Alternatively, **2.044** was converted to 6,8-bis(methylsulfanyl) derivative **2.048** via dichloride **2.047**. Dimethylamination followed by reduction of **2.048** furnished *N*-6-dimethyladenosine product **2.049**.[79] 8,2′-*O*-Anhydroguanosine **2.050**, on the other



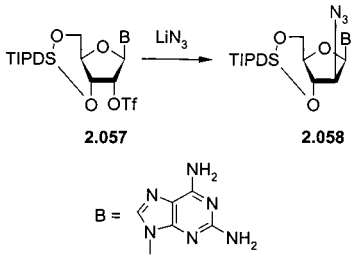
hand, was converted to *arabino*-derivative **2.051**, which was converted into the azido derivative **2.052**. Compound **2.052** acted as a starting material for the



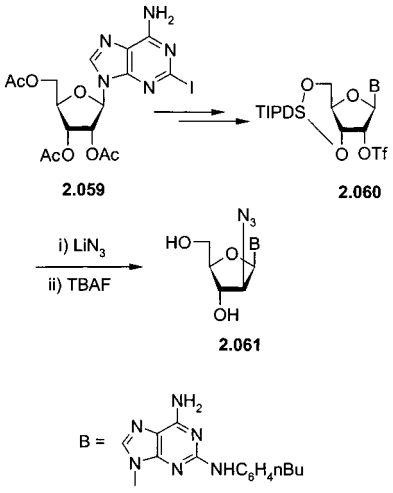
aminonucleoside antibiotic puromycin (2′-amino-2′-deoxyguanosine).[80] Azidonucleoside **2.004** acted as a versatile intermediate for the synthesis of several new purine-based 2′-azido-2′-deoxy derivatives. Thus, the syntheses of 6-monomethylamino (**2.053**), 6-dimethylamino (**2.049**), 6-sulfanyl (**2.055**), and 6-methylsulfanyl (**2.056**) purine nucleosides and inosine



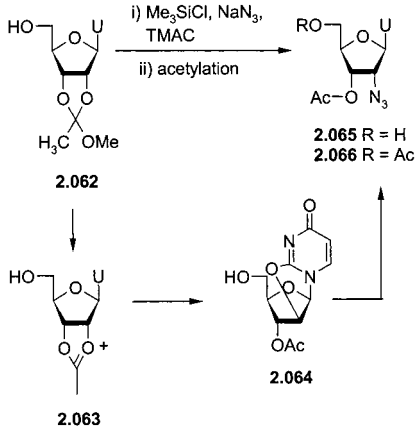
2.054 have been reported.[81] Displacement of sulfonate esters was used further for the conversion of 2,6-diaminopurine nucleoside **2.057** to 2′-azido *arabino*-derivative **2.058**.[82] It has been reported that 2-(*p*-*n*-butylanilino)-2′-deoxyadenosine-5′-triphosphate (BuAdATP) was a selective and potent inhibi-



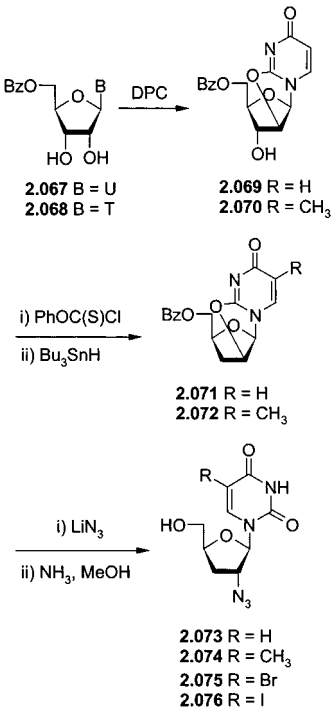
tor of eukaryotic pol α but did not inhibit pols δ and ϵ. Therefore, BuAdATP has been widely used for discrimination and identification of enzymes in the pol α family. To synthesize 9-(2-azido-2-deoxy-β-D-*arabino*furanosyl)-2-(*p*-*n*-butylamino)adenine **2.061**, 2-iodoadenosine derivative **2.059** was converted to the protected and trifluorosulfonylated BuAdA derivative **2.060**, which was converted to the desired azido derivative **2.061**.[83]



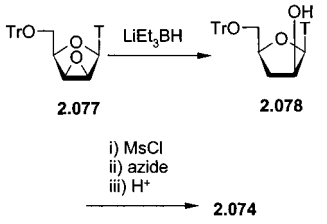
A facile synthesis of **2.065** has been reported from an easily accessible starting material, **2.062**. 2′,3′-*O*-Methoxyethyleneuridine **2.062** on treatment with excess NaN_3 in the presence of Me_3SiCl and TMAC at elevated temperature produced **2.066** after acetylation. With regard to the mechanism of this conversion, intermediacy of Me_3SiN_3 has been ruled out because **2.062** on treatment of this reagent did not produce **2.065**. It was therefore concluded that Me_3SiCl converted **2.062** to the oxocarbonium ion intermediate **2.063**, which very easily formed the 2,2′-*O*-anhydro derivative **2.064**. Azide ion attacked the C-2′ position of **2.064** to furnish **2.065**.[84,85]



2,2′-*O*-Anhydronucleosides have been used directly in the synthesis of various new azidonucleosides. Thus, 2,2′-*O*-anhydro-5′-*O*-benzoyluridine **2.069** was prepared from 5′-*O*-benzoyluridine **2.067** and converted to the 3′-deoxy analogue **2.071** by imidazolylthiocarbonylation followed by Bu_3SnH reduction. Treatment of **2.071** with LiN_3 followed by saponification afforded 2′-azido-2′,3′-dideoxyuridine **2.073**. In a similar fashion, thymidine analogue **2.074** has been synthesized via intermediates **2.070** and **2.072** starting from **2.068**. The halogeno analogues **2.075** and **2.076** were synthesized from uridine derivatives.[86] An



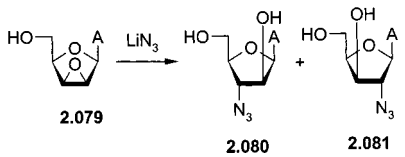
alternative route has been devised for the synthesis of **2.074**. *Lyxo*-epoxide **2.077** was opened selectively at the C-3′ position to furnish **2.078**, which on



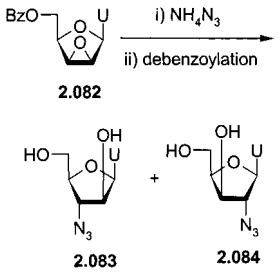
mesylation followed by azidolysis and deprotection produced **2.074**.[87] 2,2′-*O*-Anhydro-3′,5′-di-*O*-benzyl-*lyxo*-furanosyluracil, obtained from the corresponding 2′-deoxy-2′-iodo-*xylo*-furanosyluracil, on reaction with NaN_3 afforded the 2′-azido-2′-deoxy-3′,5′-di-*O*-benzyl-*xylo*-furanosyluracil.[88]

2.1.2. Opening of Nucleoside Epoxides by Azide

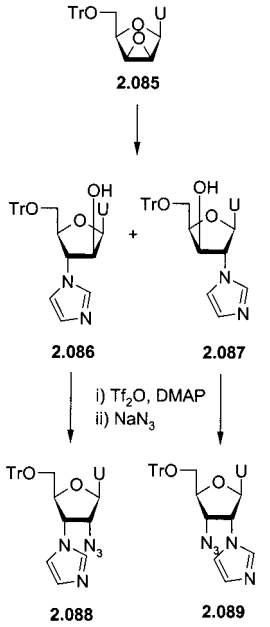
In addition to sulfonate esters and 2,2′-*O*-anhydro derivatives of nuclosides, epoxides of nucleosides should also act as efficient starting materials for the preparation of azidonucleosides. However, this is not a suitable method for the synthesis of 2′-azido-2′-deoxynucleosides because the epoxides are cleaved preferentially at the C-3′ site. For example, *lyxo*-furanosyladenine **2.079** on treatment with LiN_3 produced a mixture of *arabino*-**2.080** and *xylo*-**2.081**



in 79% and 8% isolated yields, respectively.[89] Reactions of 5′-*O*-benzoyl-2′,3′-*O*-anhydrouridine **2.082** with NH_4N_3 generated a mixture of **2.083** and **2.084**, but the isomers were not separated.[90] The composition of the reaction products **2.083** and **2.084** was later studied by a reversed-phase HPLC system, which separated *arabino*-**2.083** and *xylo*-**2.084** isomers that were formed (section 3.2.3).



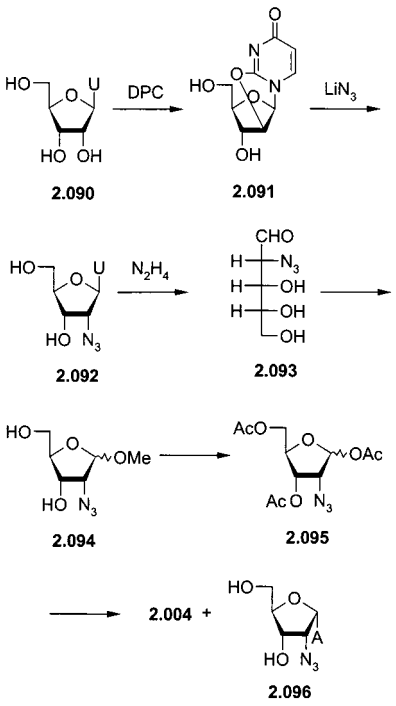
Azide-containing imidazol-1-yl-2′,3′-dideoxyuridines have been synthesized as follows. Oxirane **2.085** was cleaved with imidazole to produce **2.086** and **2.087**. Compounds **2.086** and **2.087** were sulfonylated, and the sulfonate esters were treated with NaN_3 separately to generate **2.088** and **2.089**, respectively.[91]



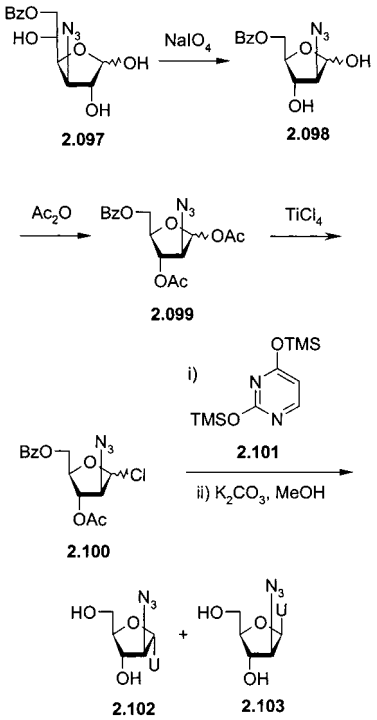
2.1.3. From Azidosugars

Since the ring opening of purine nucleoside epoxides favors attack at the C-3′ position over the 2′-position, it was necessary to develop a new methodology for accessing 2′-azido-2′-deoxynucleosides. Thus, easily accessible 2′-azido-2′-deoxyuridine **2.092** from uridine **2.090** via 2,2′-*O*-anhydrouridine **2.091** was treated with N_2H_4 to obtain 2-azido-2-deoxy-D-ribose **2.093**. Conversion of **2.093** to methyl glycoside **2.094** under standard conditions followed by acetylation furnished **2.095**. Diacetate **2.095** on coupling with partially protected adenine followed by deacetylation produced an anomeric mixture of **2.004** and **2.096**.[92]

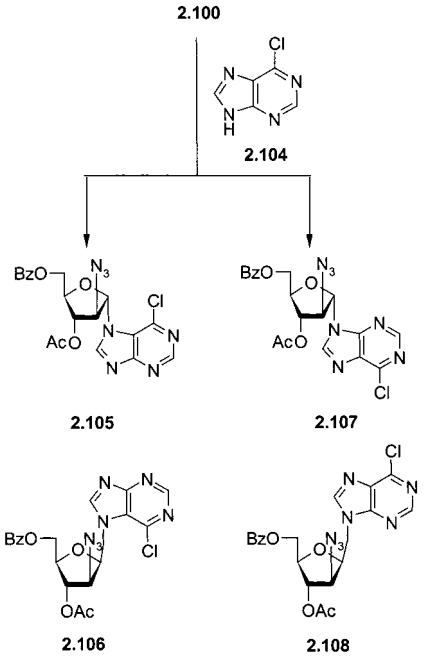
To synthesize less easily accessible *arabino*-nuclesides, such as **2.034**, **2.035**, **2.037**, etc., a new route has been designed using azidosugars as the starting materials. Thus, 6-*O*-benzoyl-3-azido-3-deoxy-D-glucofuranose **2.097**, obtained from diacetone D-glucose,



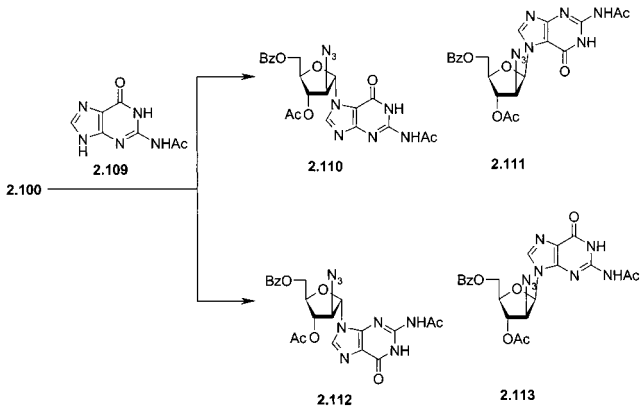
was oxidized with $NaIO_4$ to produce, in one step, the *arabino*-derivative **2.098**. Acetylation furnished di-



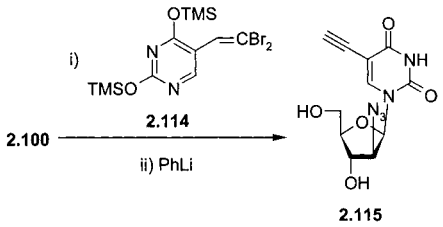
acetates **2.099**, which on treatment with $TiCl_4$ generated an anomeric mixture of chlorosugars **2.100**. Coupling of **2.100** with silylated uracil **2.101**, followed by deprotection, produced α- and *β*-anomers **2.102** and **2.103**, respectively.[93] A detailed study on the coupling of 6-chloropurine **2.104** with chlorosugar **2.100**, however, has shown that four isomeric nucleosides, α- and *β*-anomers of N-7-substituted purines **2.105** and **2.106**, respectively, and α- and *β*-anomers of N-9-substituted purines **2.107** and **2.108**, respec-



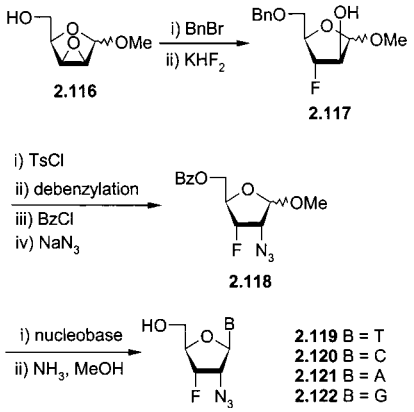
tively, are formed. Similarly, condensation of **2.100** with 2-acetamidohypoxanthine **2.109** also produced



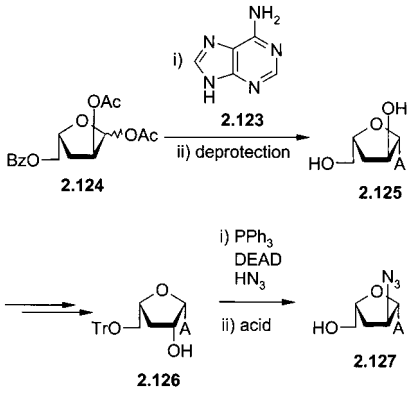
four isomers, **2.110**−**2.113**.[94] Heterocycle-modified pyrimidines, such as **2.114**, can be coupled with chlorosugar **2.100** to produce, after dehydrobromination, acetylenic azidonucleoside **2.115** along with its α-anomers.[95]



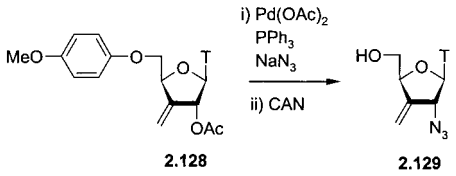
Four 2′-azido-2′,3′-dideoxy-3′-fluoro-D-*ribo*-furanosides of natural nucleobases have been synthesized. The starting epoxide **2.116** was protected and fluorinated at C-3′ to produce fluorosugars **2.117**. Tosylation, debenzylation, and benzoylation followed by treatment with NaN_3 converted **2.117** to the azidofluoro intermediate **2.118**. Condensation of **2.118** with nucleobases followed by deprotection furnished *ribo*-nucleosides **2.119**−**2.122** (only *β*-isomers shown).[96]



Condensation reactions of nucleobases with sugars have paved the way for the synthesis of virtually any synthetic azidonucleoside. For example, unnatural β-L-enantiomer 2-azido-2,3-dideoxy-β-L-derivative **2.127** has been synthesized. Coupling of adenine **2.123** with 1,2-di-*O*-acetyl-3-deoxy-5-*O*-benzoyl-L-*erythro*-pentofuranose **2.124** followed by deprotection produced β-L-nucleoside **2.125**. Synthetic manipulation of **2.125** inverted the configuration of 2′-OH to furnish **2.126**, which was converted to **2.127** in the



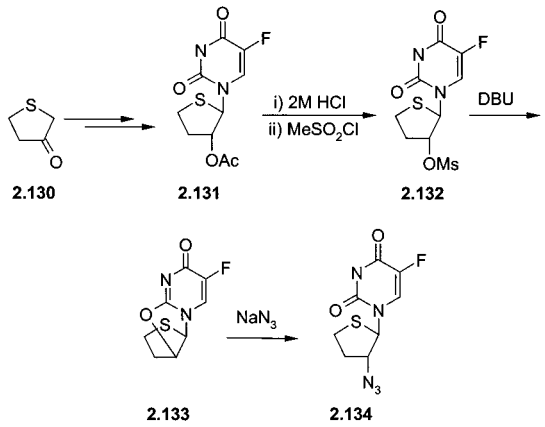
usual way.[97] In an attempt to synthesize 3′-branched azidonucleoside, **2.128**, obtained from the corresponding sugar, was treated with NaN_3 in the presence of $Pd(OAc)_2$ and Ph_3P. The palladium-catalyzed substitution of the allylic acetate of **2.128** by azide ion followed by deprotection furnished **2.129**. This reaction occurred at the acetoxy-bearing carbon with retention of configuration via a (π-allyl)palladium complex, so that the azido group was introduced on the α-face.[98]



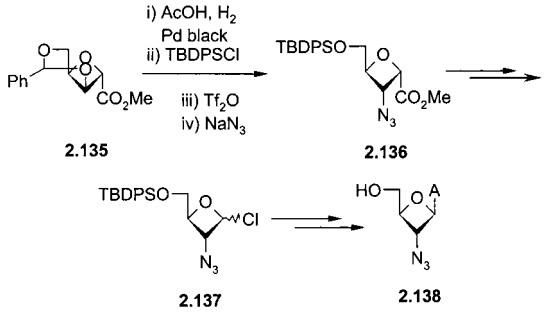
2.1.4. Carbohydrate Ring Modified 2′-Azido-2′-deoxynucleosides

Syntheses of neplanocin A derivatives **2.006** and **2.027** have been discussed in section 2.1.1 in connection with the effectiveness of various leaving groups toward azide displacement reactions.

To synthesize nucleosides from 5-fluorouracil and 2-amino-2,3-dideoxy-4-thio-DL-*glycero*-tetrofuranose, it was necessary to develop a route to the corresponding 2′-azido-2′,3′-dideoxytetrose derivative **2.134**. The starting ketone **2.130** was converted, in two steps, to protected nucleoside **2.131** using Pummerer rearrangement as one of the key steps. Deprotection of **2.131** followed by mesylation afforded **2.132**, which was converted to anhydro derivative **2.133** using DBU. Reaction of **2.133** with NaN_3 afforded **2.134** and their enantiomers.[99]



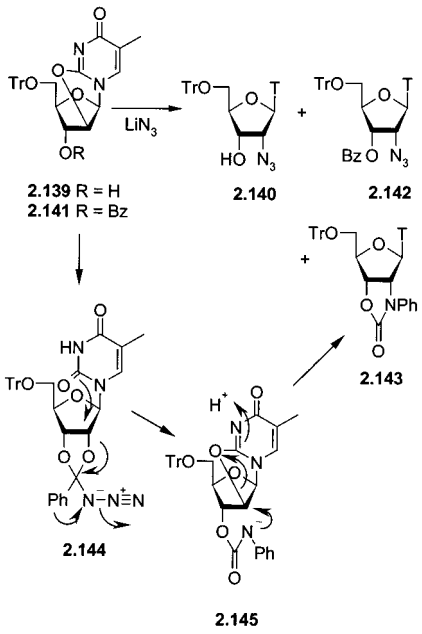
Benzylideneoxetane **2.135** was converted to the azidooxetane derivative **2.136** in three steps. Compound **2.136** was converted by the Barton modification of the Hunsdiecker reaction to a 1:1 epimeric mixture of chlorides **2.137**, which on treatment with adenine gave an anomeric mixture of the protected nucleoside. Deprotection followed by separation afforded azidooxetane nucleoside **2.138**.[100]



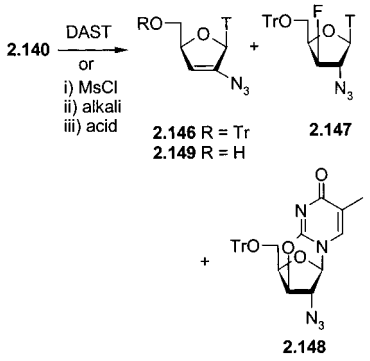
2.2. Reactions

2.2.1. Addition of Nucleophiles

Although 2,2′-*O*-anhydrothymidine derivative **2.139**, on treatment with LiN_3, furnished the expected 2′-azido-2′-deoxy derivative **2.140**, the 2,2′-*O*-anhydro-3′-*O*-benzoyl derivative **2.141**, under similar conditions, afforded a mixture of **2.140**, azidobenzoate **2.142**, and the oxazolidinone **2.143**, along with debenzoylated starting material **2.139**. The rather surprising formation of **2.143** would involve a 2′,3′-benzoxonium transient intermediate, which would give rise to the masked acyl azide **2.144**. The latter can undergo the Curtis rearrangement, yielding **2.145**, which produced **2.143** via an intramolecular nucleophilic attack. Reaction of **2.140** with DAST produced three products, namely, vinyl azide **2.146**,

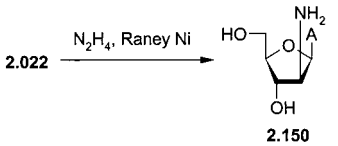


fluoro azido compound **2.147**, and the 2,3′-*O*-anhydro derivative **2.148**. Mesylation of azido alcohol **2.140** followed by treatment with alkali and deprotection, on the other hand, exclusively furnished 2′-azido-2′,3′-didehydro-2′,3′-dideoxythymidine **2.149**.[101]

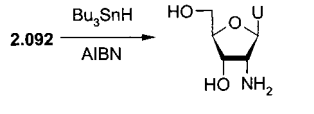


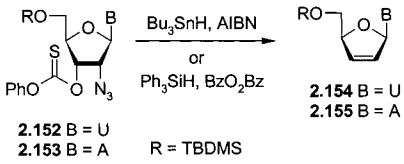
2.2.2. Reduction

There are several reports on the hydrogenation of azidonucleosides. Reduction of **2.022** with Raney Ni, in the presence of N_2H_4, produced amino derivative **2.150**.[102] Unprotected azidouridine **2.092** has been



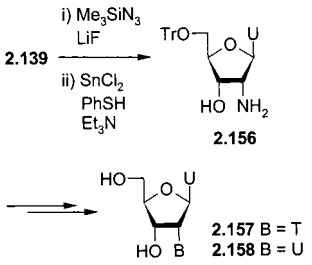
reduced by Bu_3SnH in a mixture of *N*,*N*-dimethylacetamide and benzene to aminonucleoside **2.151** in high yield. TBDMS- or TIPDS-protected azidouridines can also be reduced efficiently using the same reagent in bezene.[103] However, 3′-*O*-(phenoxythiocarbonyl)-2′-azidouridine **2.152** and the corresponding adenosine derivative **2.153**, on treatment with Bu_3SnH or Ph_3SiH, underwent direct radical-mediated hydrogenolysis to give protected 2′,3′-didehydro-2′,3′-dideoxyuridine **2.154** and the corresponding adenosine derivative **2.155**, respectively, via loss of the azido



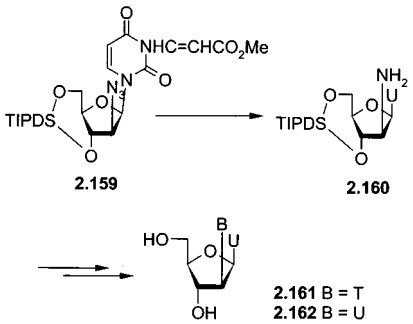


group from an incipient C-3′ radical. Reduction of azides to amines with Bu_3SnH is known,[103] but the hydrogenolytic deazidation with Ph_3SiH in the absence of amine formation appears to be novel. These results are in harmony with loss of radical species during the mechanism-based inactivation of *ribo*-nucleotide reductases with several 2′-substituted nucleoside 5′-phosphates.[104]

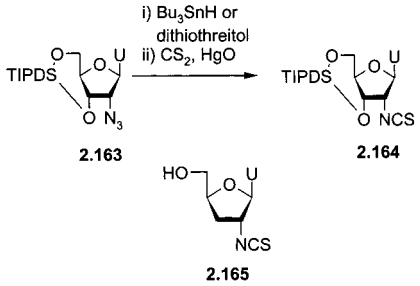
Since 2′,3′-dideoxynucleosides with the nucleobases at C-3′ or C-2′ (isonucleosides) have drawn much attention, pentofuranoses with two nucleobases have been synthesized. The required starting material **2.156** was prepared from the azido alcohol **2.140**. The



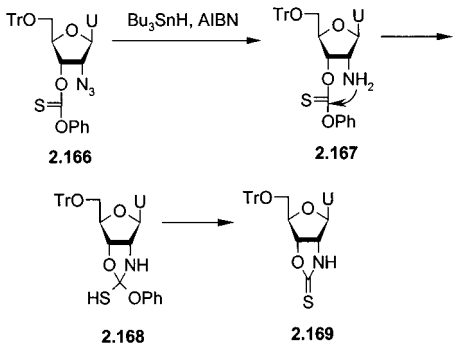
latter was obtained in this case by treating **2.139** with Me_3SiN_3. Reduction of **2.140** with the $SnCl_2$, PhSH, and Et_3N system furnished the amino alcohol **2.156**. Through standard manipulation **2.156** was converted to thymidine **2.157** or uridine **2.158**. Similarly, reduction of the azido function, followed by the removal of the N-3 protection of **2.159** by excess pyrrolidine produced **2.160**. The thymine or uracil ring was constructed at the C-2′ position of **2.160** to furnish **2.161** or **2.162**, respectively.[105]



Suitably protected 2′-azido-2′-deoxyuridine **2.163** was reduced to the corresponding amino derivative, which was reacted with CS_2 in the presence of HgO to yield isothiocyanatouridine **2.164**. Similarly, 2′-azido-2′,3′-dideoxyuridine **2.015** was converted to **2.165**.[106] Interestingly and in contrast to the forma-



tion of **2.154** from **2.152**,[104] azidothiocarbonyl derivative **2.166**, on treatment with Bu_3SnH, produced exclusively **2.169** and no 2′,3′-didehydro derivative. The most plausible explanation for the formation of **2.169** is that the 2′-azido group was reduced much more rapidly than the 3′-*O*-phenoxythiocarbonyl group. The amino derivative **2.167** thus formed attacked the thiocarbonyl carbon intramolecularly, leading to the formation of **2.168**, which eliminated a molecule of phenol to yield **2.169**.[106]

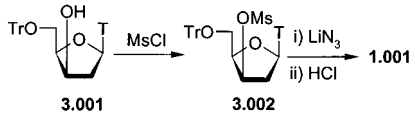


3. 3′-Azido-3′-deoxynucleosides

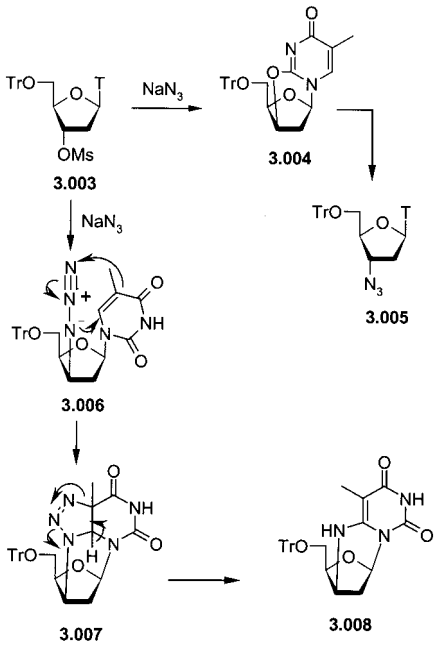
3.1. 3′-Azido-3′-deoxythymidine (AZT)

3.1.1. Synthesis from Thymidine

To study the "replacement of mesyloxy group by nucleophiles, such as azide..." Horwitz and co-workers reacted 1-(2-deoxy-3-*O*-mesyl-5-*O*-trityl-*β*-D-lyxosyl)thymine **3.002**, obtained from **3.001** via mesyla-

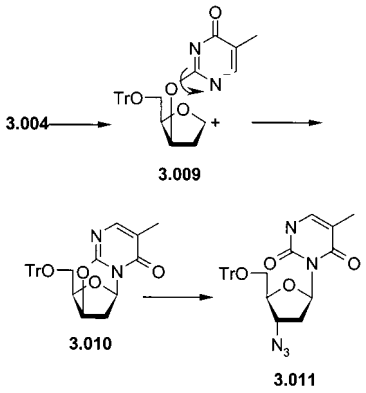


tion, with LiN_3. The crude product on detritylation afforded **1.001**. This was the first reported synthesis of **1.001**.[107] In an attempt to develop a methodology for the large-scale synthesis of **1.002** via **3.005**, 3′-*O*-mesyl-5′-*O*-tritylthymidine **3.003** was heated under reflux with NaN_3 to afford **3.005** in 41% yield. The "down" azido derivative **3.005** was formed via 2,3′-*O*-anhydronucleoside **3.004**. However, this reaction produced a more polar side product, **3.008**, via the "up" azidonucleoside **3.006** in almost equal amount. It has been proposed that a nucleophilic attack by the root nitrogen of the azido group at C-6, followed by a series of electron shifts, produced the triazolino intermediate **3.007**. This intermediate afforded **3.008** on loss of a molecule of N_2.[108] The lack of stereocontrol in the formation of azidonucleosides from **3.003** has been highlighted by other groups as well.[109]



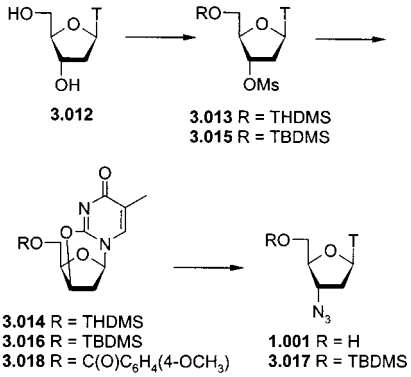
An alternative approach to nucleophilic displacement of sulfonate esters was considered where the *threo* isomer **3.001** was treated directly with the PPh_3–CBr_4–LiN_3 system. The reaction predominantly produced **3.005** with some amount of the anhydro derivative **3.004**.[110]

Interestingly, during the course of preparation of **1.001** from **3.004**, formation of an N-3 isomer of **1.001**, compound **3.011**, in 2−4% yield has been detected. A plausible mechanism of formation of **3.011** would be through the cleavage of the glycosidic linkage in **3.004**. The intermediate **3.009** would undergo N-1 to N-3 glycosylation to produce isomeric 2,3′-*O*-anhydro derivative **3.010**. Compound **3.010** on azidolysis would afford **3.011**.[111,112]



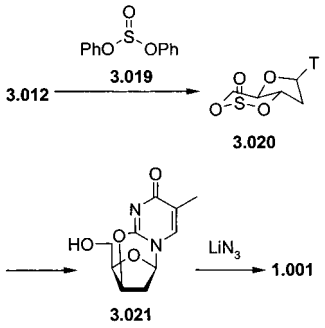
2,3′-*O*-Anhydrothymidines turned out to be the intermediate of choice for the synthesis of **1.001**. 2,3′-*O*-Anhydro-5′-*O*-monomethoxytritylthymidine (MMTr instead of Tr in **3.004**) on treatment with Me_3SiN_3 and BF_3–Et_2O directly furnished **1.001**.[113] However, the acid lability of the glycosidic bond of deoxynucleosides necessitated the use of 5′ protecting groups, removable under milder conditions. Thus 5′-*O*-thexyldimethyl derivative **3.013**, prepared from thymidine

3.012, was converted to **3.014** on treatment with DBU. 2,3′-*O*-Anhydro derivative **3.014** on reaction with NaN_3, followed by deprotection with DOWEX 50 (H^+), afforded **1.001**.[114] Similarly TBDMS-protected derivative **3.016**, obtained from **3.015**, on reaction with LiN_3 produced the protected azidothymidine **3.017**.[115]



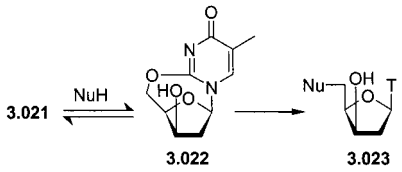
A very efficient route to **1.001** using a base-labile 5′ protecting ester group has been designed. The key step was a one-pot transformation of thymidine **3.012** into 2,3′-*O*-anhydro-5′-*O*-(*p*-methoxybenzoyl)thymidine **3.018** using the Ph_3P, DIAD, and *p*-methoxybenzoic acid system. Ring opening of **3.018** with azide ion and 5′-O-deprotection with NaOMe furnished **1.001** in more than 70% overall yield.[116]

To avoid the problem of protection−deprotection of the 5′-hydroxy group, a procedure for the direct conversion of **3.012** to 2,3′-*O*-anhydrothymidine **3.021** has been developed. Thus, **3.012** on heating with a 4-fold excess of diphenyl sulfite **3.019** at 156 °C in *N*,*N*-dimethylacetamide solution in the presence of a catalytic quantity of 1-methylimidazole afforded **3.021** in almost 65% yield. It is reasonable to assume that the reaction proceeded via a cyclic sulfite intermediate, **3.020**. Compound **3.021** on treatment with

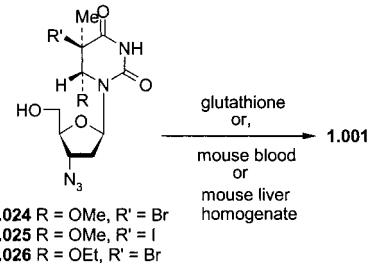


LiN_3 produced **1.001** in 71% yield.[117] It should, however, be noted that, under nucleophilic reaction conditions, **3.021** is partially converted into isomeric 2,5′-*O*-anhydro derivative **3.022**, which would be expected readily to undergo nucleophilic attack at C-5′ to produce **3.023**. It is, therefore, "usually advisable" to protect the 5′-hydroxy function of **3.021** before carrying out nucleophilic substitution reactions at C-3′.[118]

The 5-halogeno-6-alkoxy-5,6-dihydro-3′-azido-3′-deoxythymidines **3.024**−**3.026** have been designed as prodrugs, which would generate **1.001** in biological

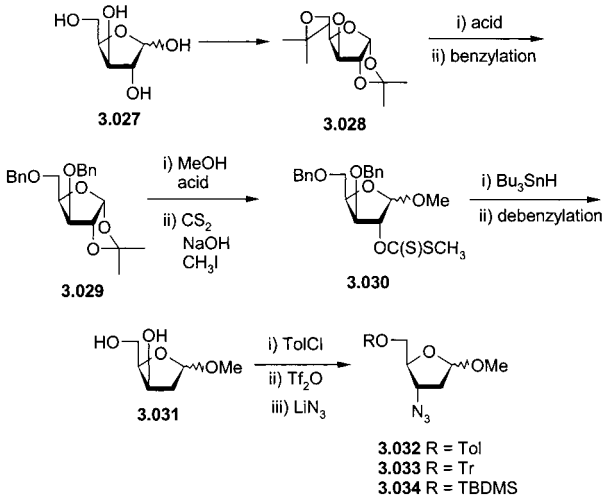


systems. Regeneration of the 5,6-double bond to give **1.001** upon incubation of **3.024**−**3.026** with glutathione, mouse blood, or mouse liver homogenate was dependent on the nature of the 5-halogeno substituent (I > Br).[119]



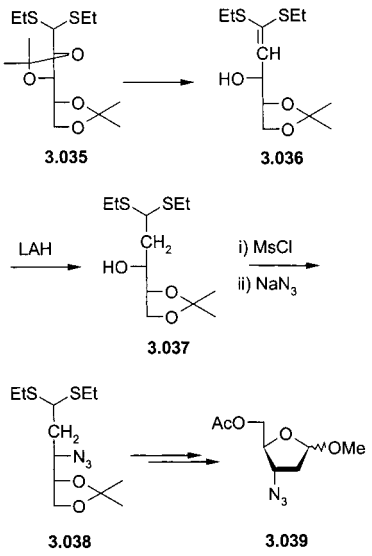
3.1.2. Synthesis from Carbohydrates

Increasing commercial demand for **1.001** led to the search for alternative and cheaper methodologies for its synthesis because thymidine **3.012** was too expensive a starting material. In almost all cases D-xylose **3.027** was considered to be the sugar of choice because of the in-built "up" configuration of the C-3 hydroxy group. This configuration is essential for the insertion of the azido group from the α-face of the furanose ring. Thus, a fully protected starting material, bisisopropylidenexylose **3.028**, synthesized from **3.027**, was selectively deprotected at the 3′,5′-sites, and the product was benzylated to give **3.029**. Compund **3.029** was easily converted to a mixture of methyl glycosides, which were converted to dithionocarbonates **3.030**. Deoxygenation of **3.030** with Bu_3SnH followed by debenzylation afforded **3.031**. The diol **3.031** was converted to 3′-azido-2′,3′-dideoxy-D-*ribo*-furanose derivative **3.032** through a sequence of standard reactions.[120] A comparable scheme of reactions has generated the 5-*O*-trityl derivatives **3.033** or the 5-*O*-TBDMS derivatives **3.034** from **3.027**.[121,122]

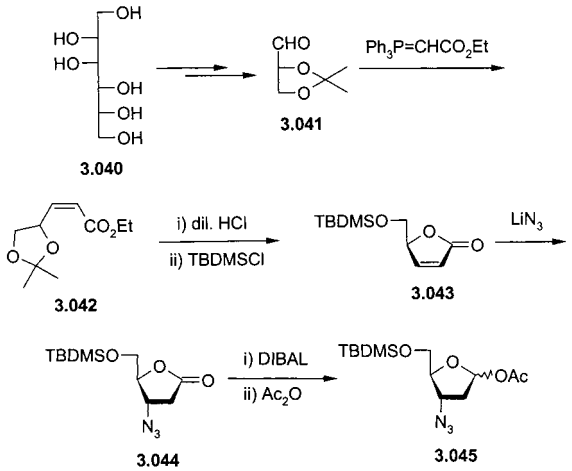


Using a different approach, 2,3:4,5-di-*O*-isopropyli-

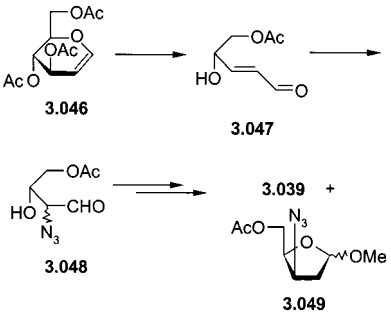
dene-D-xylose diethyldithioacetal **3.035**, on treatment with nBuLi, afforded ketene dithioacetal **3.003**. This was reduced in situ to afford 2-deoxy derivative **3.037**. Mesylation of **3.037** followed by treatment with azide afforded fully protected azidosugar **3.038**. An anomeric mixture of methyl 5-*O*-acetylazidosugars **3.039** was obtained from **3.038** via standard manipulation.[123]



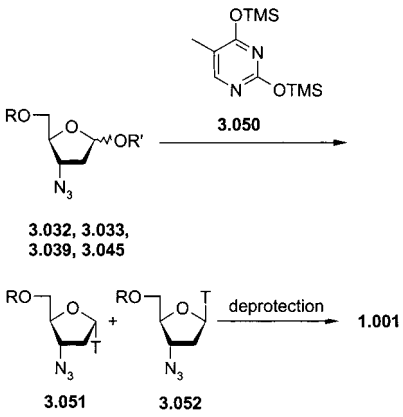
Carbohydrates other than xylose **3.027** have also been used as starting materials for the synthesis of **1.001**. The D-glyceraldehyde **3.041**, which can be readily prepared from D-mannitol **3.040** in two steps, was treated with (carbethoxymethylene)triphenylphosphorane. The *Z*-isomer **3.042** on treatment with diluted HCl, followed by protection, furnished the key intermediate, the α,*β*-unsaturated lactone **3.043**. An azido group was introduced at the 3-position of **3.043** in a stereoselective fashion with LiN_3 to afford exclusively the "down" azido derivative **3.044**. The bulky protecting group at the C-5 site inhibited the formation of any "up" azido derivative by blocking the *β*-face of the lactone **3.043**. Reduction of **3.044** followed by acetylation produced an anomeric mixture of **3.045**.[124] The α,*β*-unsaturated aldehyde **3.047**,



prepared from triacetyl-D-glucal **3.046** also reacted with the azide ion in a Michael fashion. However, in this case, in the absence of any stereocontrol, a mixture of isomers **3.048** was obtained. Compounds **3.048** after standard manipulations afforded **3.039** and the "up" azido derivatives **3.049**.[125,126]

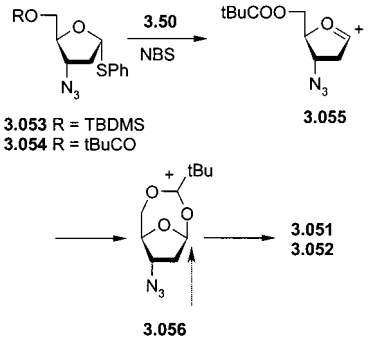


Although there was no shortage of ideas[124−126] for the synthesis of 3-azido-2,3-dideoxy-*ribo*-furanoses, the crucial step of glycosylation of these carbohydrate derivatives **3.032**, **3.033**, **3.039**, and **3.045** with bistrimethylsilyl-protected thymine **3.050** resulted in the formation of a mixture of α- and *β*-anomers **3.051** and **3.052**, respectively.[127] The *β*-anomer **3.052** on

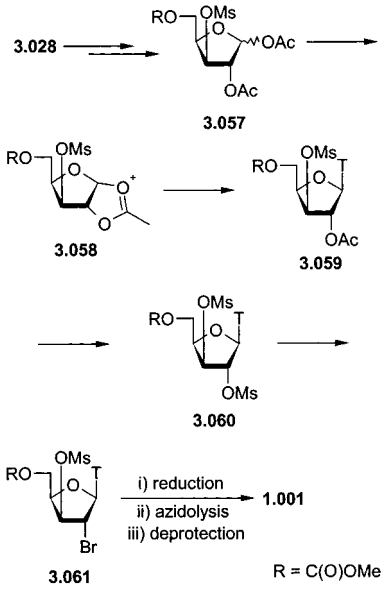


deprotection produced **1.001**. However, the overall low yield of the final product **1.001** made these methods less useful from a practical point of view. Several attempts have been made to improve the efficiency of the coupling step in favor of the *β*-anomer. For example, a comparative study on the coupling pattern of two differently protected 1-thiopentofuranosides, **3.053** and **3.054**, has revealed that by changing 5-O-protection from TBDMS (in **3.053**) to pivaloyl (in **3.054**) the ratio of α- and *β*-anomers (such as **3.051** and **3.052**) changed from 2:1 to 4:1. The significant increase in α-selectivity for coupling of **3.054** with **3.050** may be attributed to the formation of intermediate **3.056** due to acyl participation in carboxonium ion **3.055**. This result clearly indicated the influence of the 5-O protecting group in the anomeric selectivity of the coupling reaction.[128]

The problem of nonselective *β*-glycosylation of **3.050** with 3-azido-2,3-dideoxysugars was circumvented by coupling the former with an appropriately functionalized derivative of xylose **3.027** first and then carrying out deoxygenation (C-2′) and azidolysis (C-3′). The major advantage of synthesizing the *xylo*-nucleoside first is that the process affords a high degree of stereoselectivity for the *β*-anomer during condensation with a nucleobase, due to the participa-

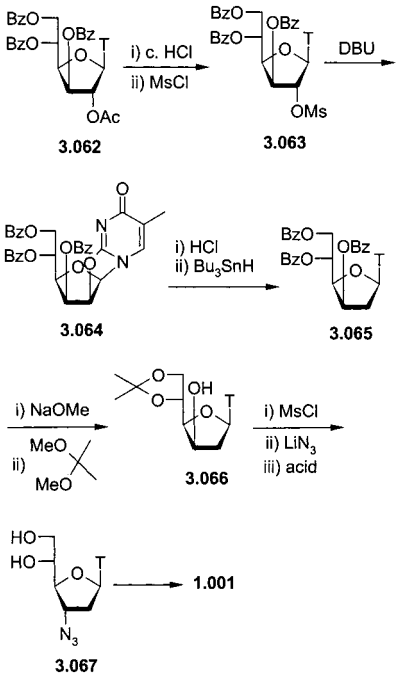


tion of the 2-*O*-acyl protecting group.[129] There are several reports on the use of this strategy.[130−134] The following sequence of reactions can be considered as a representative example. 1,2-Di-*O*-acetyl-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-*xylo*-furanose, obtained from **3.028**, was condensed with **3.050** to obtain the *β*-D-*xylo*-derivative **3.059**. The carboxonium ion intermediate **3.058** determines the stereoselectivity of the coupling stage by allowing nucleophile to attack the C-1 position from the *β*-face of the furanose system. Deacetylation of **3.059** with methanolic HCl followed by mesylation of the 2′-hydroxy group produced 2′,3′-di-*O*-mesyl derivative **3.060**. Treatment of **3.060** with K_2CO_3 generated a 2,2′-*O*-anhydro derivative, which on reaction with LiBr afforded bromo derivative **3.061**. Debromination of **3.061** with Bu_3SnH followed by azidolysis and deprotection produced **1.001**.[135]

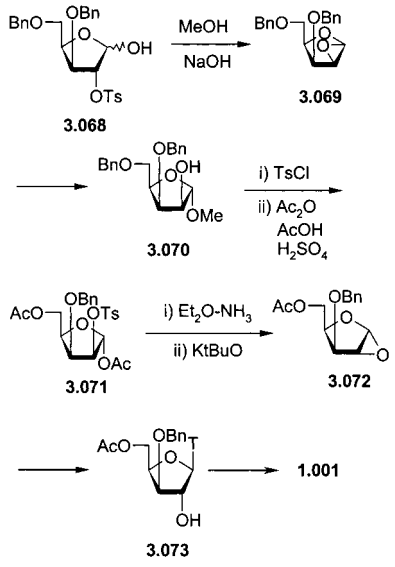


A methodology has also been developed using *gluco*-derivative **3.062**, which on deacetylation followed by mesylation produced **3.063**. 2,2′-*O*-Anhydro derivative **3.064** was obtained by treating **3.063** with DBU. Chlorination at C-2′ of **3.064** followed by reduction furnished **3.065**. Debenzoylation of **3.065** followed by isopropylidenation produced **3.066**. The usual chemical manipulation afforded azidonucleoside **3.067**. Oxidation of **3.067** with Dowex 1 (IO_4^-) resin followed by reduction with Dowex 1 (BH_4^-) resin produced **1.001**.[136]

More recently, the synthesis of a new, potentially viable intermediate for the preparation of **1.001** has



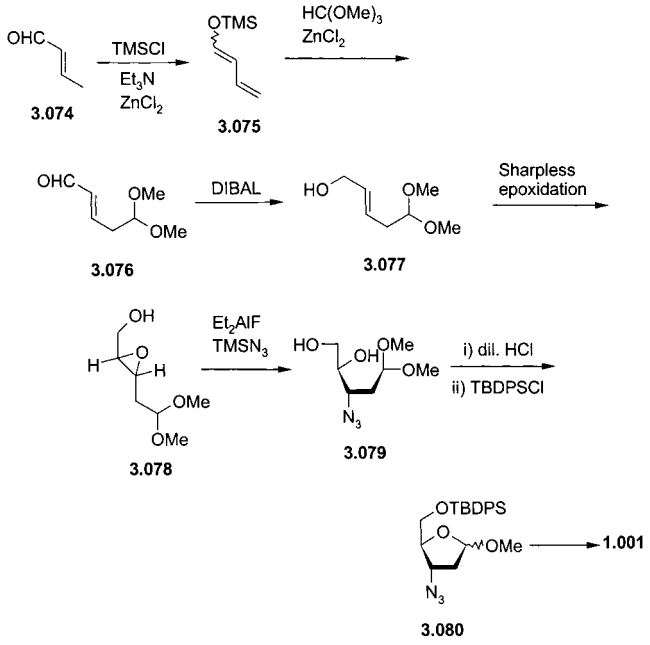
been reported. 3,5-Di-*O*-benzyl-2-*O*-tosyl-D-*xylo*-furanose **3.068**, obtained from D-xylose **3.027** in four steps, was converted to methyl 3,5-di-*O*-benzyl-α-D-*lyxo*-furanoside **3.070** via epoxide **3.069**. Tosylation of **3.070** followed by acetolysis furnished diacetate **3.071**. Selective deacetylation of **3.071** and treatment of the product with tBuOK afforded epoxide **3.072**. Condensation of **3.072** with **3.050** gave nucleoside **3.073**.[137]



3.1.3. Synthesis from Non-Carbohydrate Precursors

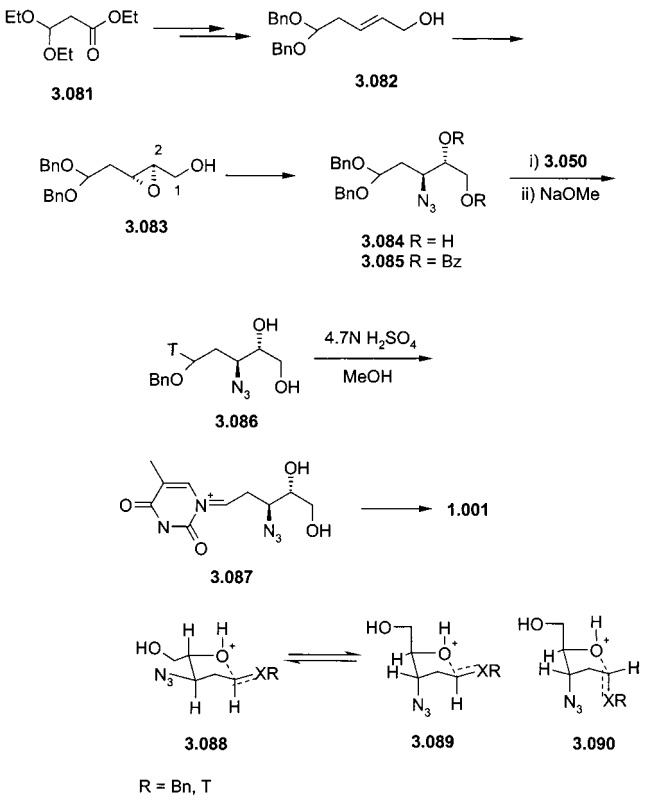
A synthetic protocol that permits the stereoselective construction of **1.001** from inexpensive, non-carbohydrate precursors is of immense importance. A stereospecific total synthesis of **1.001** has been reported, starting from crotonaldehyde **3.074**. 1-(Trimethylsilyloxy)-1,3-butadiene **3.075** was condensed with methyl orthoformate to give the enal acetal **3.076**. Reduction of **3.076** afforded the allylic alcohol **3.077**. The chirality necessary for the final product

was introduced by treating **3.077** with D-(−)-diisopropyl tartrate, tBuOOH, and $Ti(OiPr)_4$ to afford the desired epoxy alcohol **3.078** in >95% ee. The regioselective opening of the epoxide **3.078** was promoted by Et_2AlF with $TMSN_3$. The azido diol **3.079** thus obtained was cyclized under acidic conditions, and the anomeric mixture was isolated as 5-*O*-*tert*-butyldiphenylsilyl derivatives **3.080**. The azido sugar

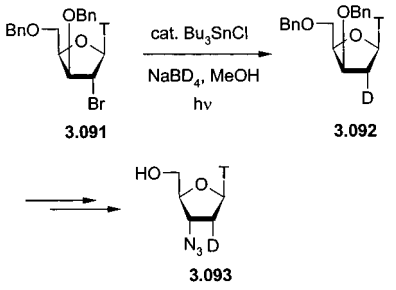


was converted to **1.001** in the usual way.[138] In another paper, 3,3-diethoxypropanoate **3.081** was converted to the dibenzyloxyallyl alcohol **3.082**. Under Sharpless asymmetric epoxidation conditions, the allylic alcohol **3.082** was oxidized to the 2(*S*),3(*R*)-epoxy alcohol in >97% ee. The azido group was introduced regioselectively to C-3 by treatment of **3.083** with $Ti(OiPr)_4$ and Me_3SiN. The azido alcohol **3.084** thus obtained was converted to dibenzoate **3.085**. Compound **3.085**, on coupling with **3.050**, followed by debenzoylation afforded a diastereomeric mixture of **3.086**. When exposed to concentrated acidic conditions, **3.086** cyclized to give exclusively the *β*-anomer **1.001** in 67% yield, based on the recovered starting material. The diastereomeric mixture **3.086** underwent cyclization presumably via one iminium ion intermediate, **3.087**. However, *β*-selectivity of cyclization has been attributed to the "gauche effect", which predicts that transition state **3.089** would be favored over **3.090** because in **3.089**, the C−C bond containing the azido group and the partially charged hydroxyl group have a gauche arrangement. Once the rotamer population around this bond is fixed, then the transition state **3.089** should dominate over **3.090** since the latter is disfavored due to a severe 1,3-interaction between the azido and XR group.[139]

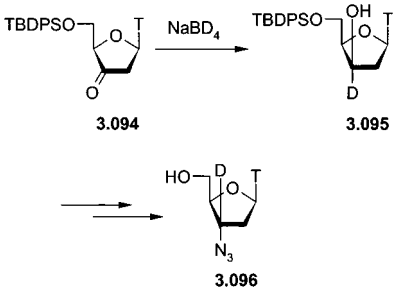
Synthesis of **1.001** from xylose has been applied to the synthesis of deuterium-labeled AZT, which was useful in the conformational analysis based on proton NMR. 1-(2-Bromo-3,5-di-*O*-benzyl-2-deoxy-*β*-D-*xylo*-furanosyl)thymine **3.091** was dehalogenated photolytically using $NaBD_4$ and a catalytic amount of



Bu_3SnCl, resulting in the formation of 2′(*R*)-2′-deoxy-2′-deuterio derivative **3.092**. The delivery of the deuterium from the α-face was expected due to the crowded *β*-face. (2′*R*)-Deuterioazidothymidine **3.093**



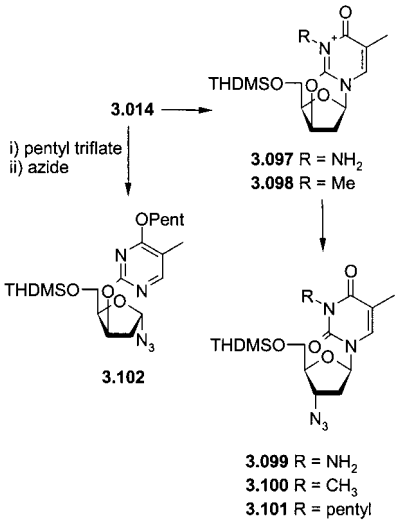
was obtained from **3.092** through the usual reactions. 1-(3-Azido-2,3-dideoxy-3-deuterio-*β*-D-*ribo*-furanosyl)-thymine **3.096** has also been synthesized. In this case, the 2′-ketothymidine **3.094** was reduced with $NaBD_4$ to produce the *threo*-derivative **3.095**. Compound **3.095** was converted to **3.096** under the usual reaction conditions.[140,141] There are several reports on the synthesis of tritium-labeled AZT.[142−144]

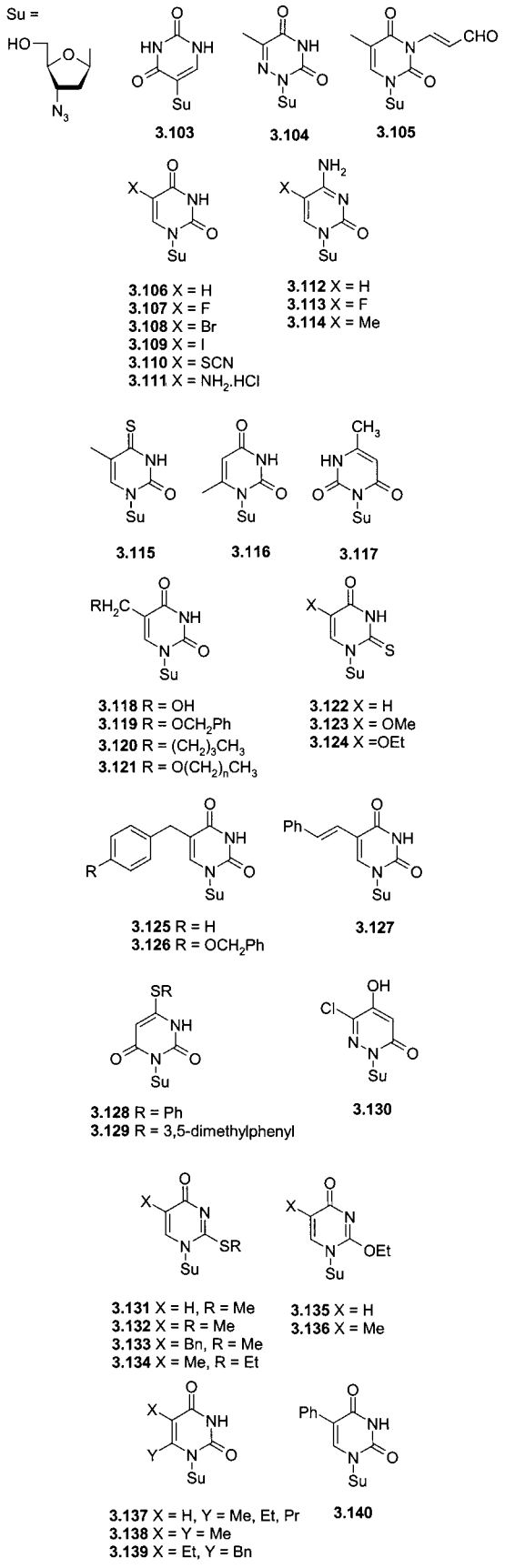


3.2. Synthesis of Other 3′-Azido-3′-deoxynucleosides

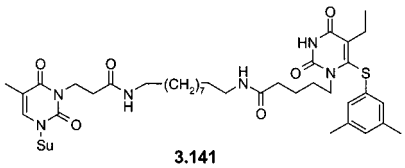
*3.2.1. 3′-Azido-2′,3′-dideoxy-*ribo*-furanosylnucleosides Other than AZT*

Since it has been shown[145] that several analogues of **1.001** substituted at the N-3 position are active against HIV and are less toxic than AZT, a study on the quarternization of the N-3 imino ether nitrogen of anhydronucleoside **3.014** was taken up. Separate reactions of **3.014** with *O*-(mesitylenesulfonyl)-hydroxylamine or CH_3OTf generated pyrimidinium salts **3.097** and **3.098**, which reacted with azide ion to give the N-3-substituted AZTs **3.099** and **3.100**, respectively. In contrast, alkylation of **3.014** with pentyl triflate occurred at both N-3 and O-4 positions, leading, after treatment with NaN_3, to the expected **3.101** and novel **3.102**. The extent to which competing O-4 alkylation occurred was found to be sensitive to steric factors, increasing in the order of MeOTf < EtOTf < pentylOTf < iPrOTf.[146,147] Several 3′-azido-2′,3′-dideoxypyrimidine-like analogues have been synthesized to study their biological properties. Most of these base-modified analogues such as **3.103**,[148] **3.104**−**3.114**,[149] **3.115**,[150] **3.116** and **3.117**,[151] **3.118** and **3.119**,[152] **3.120**,[153] **3.121**,[154,155] **3.122**−**3.124**,[156] **3.125** and **3.126**,[157] **3.127**,[158] **3.128** and **3.129**,[159] **3.130**,[160] **3.131**−**3.134**,[161] **3.135** and **3.136**,[162] **3.137**−**3.139**,[163] and **3.140**[164] have been synthesized using methodologies which have already been discussed during the synthesis of **1.001** (section 3.1). In each case, only the β-isomer is shown. Some of these compounds have however been synthesized by reacting either **1.001** or **3.106** with special reagents. A selection of these transformations has been discussed in section 3.3. To test the concept that HIV RT could be effectively inhibited by "mixed site inhibitors", a series of conjugates such as the (N-3 and C-5) AZT−HEPT conjugates **3.141**−**3.143** were synthesized.[165] Several other heterocycles have also been attached to azidosugar to synthesize novel azidonucleosides such as **3.144**,[166] **3.145** and **3.146**,[167] **3.147** and **3.148**,[168] **3.149**−**3.151**,[169,170] and **3.152**[171] to study their biological activities.

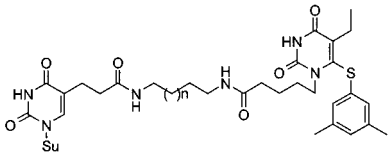




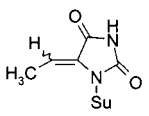
In the area of purine or purine-type nucleosides several novel structural modifications have been reported. 6-Dimethylamino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-furanosyl)purine **3.155** has been synthesized from the *xylo*-derivative **3.153** via nucleoside



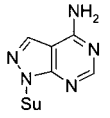
3.141



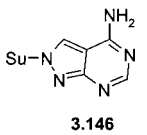
3.142 n = 1
3.143 n = 7



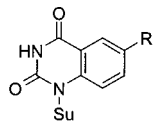
3.144



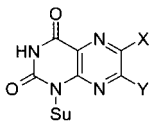
3.145



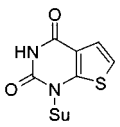
3.146



3.147 R = H
3.148 R = Me

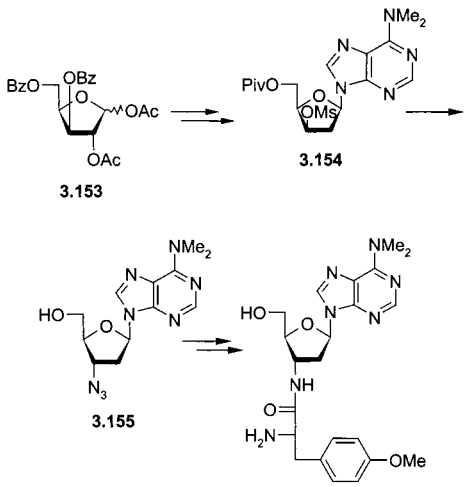


3.149 X = Y = H
3.150 X = Y = Me
3.151 X = Y = Ph



3.152

intermediate **3.154**. Compound **3.155** has been used in the preparation of 2′-deoxypuromycin **3.156**.[172]

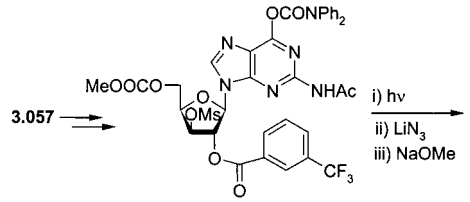


3.153

3.154

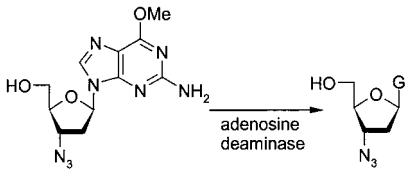
3.155

2-Amino-9-(3-azido-2,3-dideoxy-*β*-D-*erythro*-pentofuranosyl)-6-methoxy-9*H*-purine **3.158** and 3′-azido-2′,3′-dideoxyguanosine **3.159** have been synthesized from a common intermediate, **3.157**, obtainable from the *xylo*-derivative **3.057**. In this case, however, deoxygenation of the C-2′ site of the *m*-trifluorobenzoate ester **3.157** was carried out photolytically. Subsequent azidation and deprotection converted **3.157** to **3.158**. The other target molecule, **3.159**, was obtained by treating **3.158** with adenosine deaminase.[173]



3.057

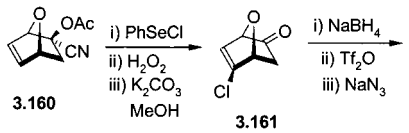
3.157



3.158

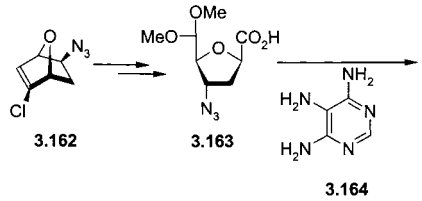
3.159

To synthesize a new C-nucleoside, (1*R*)-1-*C*-(6′-amino-7′*H*-purin-8′-yl)-1,4-anhydro-3-azido-2,3-dideoxy-D-*erythro*-pentitol **3.166**, (+)-(1*R*,2*R*,4*R*)-2-*endo*-cyano-7-oxabicyclo[2.2.1]hept-5-en-2-*exo*-yl acetate or the "naked sugar" **3.160** has been used as a starting material. The one-pot transformation of **3.160** to the chloroenone **3.161** was achieved via addition of benzeneselenyl chloride, oxidative elimination, and saponification. Reduction of **3.161** followed by triflylation and azidolysis produced the *exo*-azido derivative **3.162**. Conversion of **3.162** to *ribo*-hexouronic acid **3.163** was achieved in multiple steps, and the latter was condensed with 4,5,6-triaminopyrimidine **3.164** to afford the amide **3.165**. Heating **3.165** in the presence of excess CsF, followed by generation of the 5′-aldehyde function and its reduction, gave **3.166**.[174]



3.160

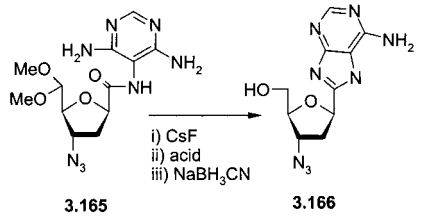
3.161



3.162

3.163

3.164

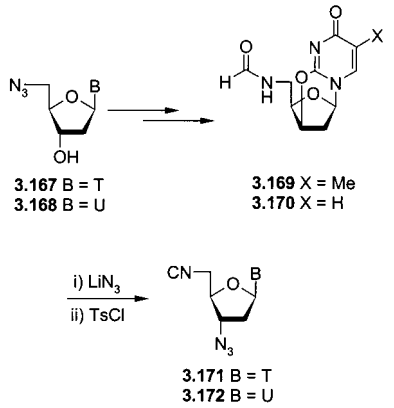


3.165

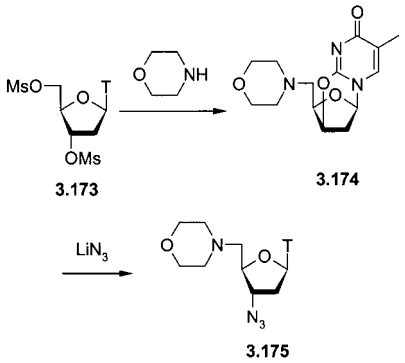
3.166

3.2.2. 5′-Modified Analogues of 3′-Azidonucleosides

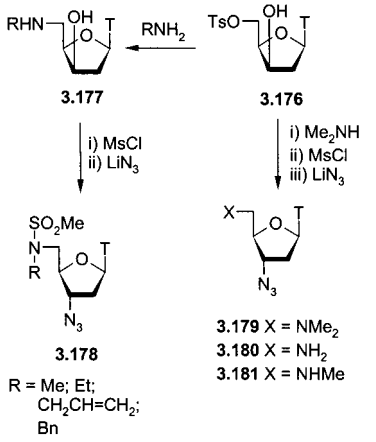
5′-Azido-5′-deoxythymidine **3.167** and the corresponding 2′,5′-dideoxyuridine **3.168** were converted to 2,3′-*O*-anhydro derivatives **3.169** and **3.170**, respectively. These compounds were treated consecutively with LiN_3 and TsCl to generate 3′-azido-5′-isocyano-3′,5′-dideoxythymidine **3.171** and 2′,3′,5′-trideoxyuridine **3.172.**[175] 5′-Deoxy-5′-*N*-morpholino-2,3′-*O*-anhydrothymidine **3.174**, which was obtained



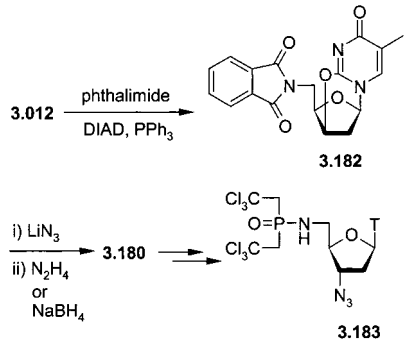
in one step by treating dimesylthymidine **3.173** with neat morpholine, on treatment with LiN_3 produced 3′,5′-disubstituted thymidine **3.175**.[59] A series of 5′-



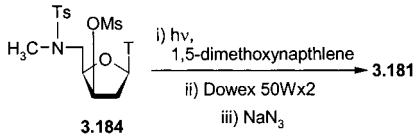
N-methanesulfonyl derivatives of 3′-azido-5′-alkylamino-3′,5′-dideoxythymidine has been synthesized. The first step involved the reaction of **3.176** with an appropriate amine to produce **3.177**, which on mesylation followed by treatment with LiN_3 produced **3.178**. The *N*,*N*-dimethylamino derivative **3.179** was



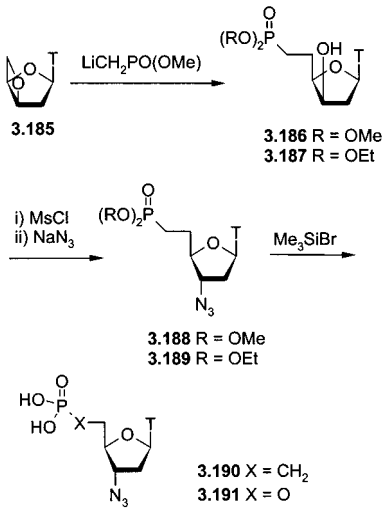
also synthesized in a similar fashion.[176] Thymidine **3.012** was converted to **3.182** in a single-pot reaction. Compound **3.182** underwent ring opening using LiN_3 to give 5′-protected azido derivative, which was deprotected to generate **3.180**. Phosphoramidate **3.183** was synthesized from **3.180**.[177] Selective photolysis of 5′-*N*-tosylamide **3.184** was carried out by UV radiation (>300 nm) in aqueous acetonitrile in the presence of 1,5-dimethoxynaphthalene as



an electron donor. The product thus obtained was converted to **3.181**.[178]

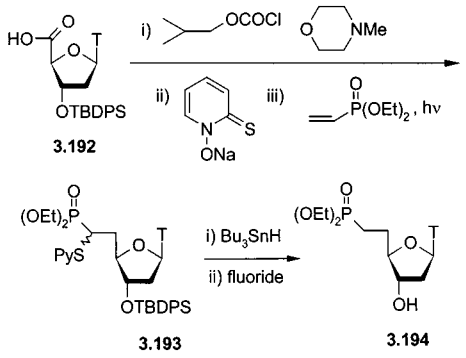


Emphasis on the search for prodrugs of **1.001** led to the synthesis of a phosphonate analogue, **3.190**, which is an isostere of 5′-phosphate **3.191**. BF_3–OEt_2-mediated cleavage of oxetane **3.185** with $LiCH_2$–PO-$(OMe)_2$ led to the formation of **3.186**. Mesylation of **3.186** and azide displacement converted **3.186** to **3.188**, which on deprotection generated phosphonate **3.190**.[179] A different approach utilized the 3′-*O*-

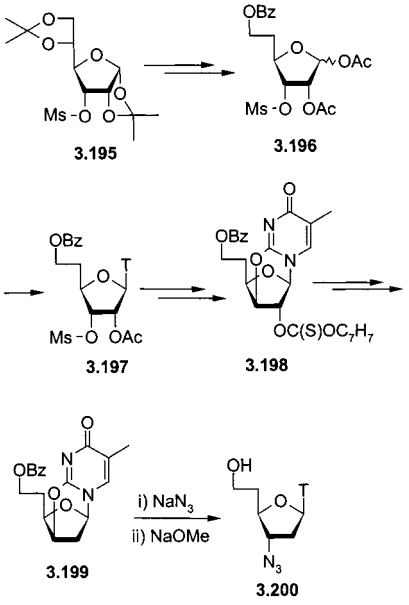


TBDPS-protected uronic acid derivative **3.192**, where the bulky TBDPS group permits a stereoselective formation of a carbon−carbon bond using the 4′-carbon radical. Thus, **3.192** generated **3.193**, which was reductively converted to **3.194**. Compound **3.194** was converted to **3.190** via intermediates **3.187** and **3.189**.[180]

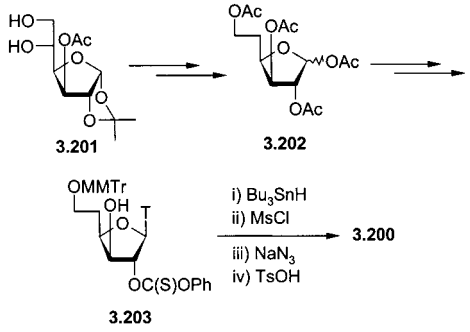
Enhanced lipophilicity of homonucleosides compared to their parent analogues generated a few interesting synthetic routes to 1-(3-azido-2,3,5-trideoxy-*β*-D-*allo*furanosyl)thymine **3.200**. In one approach, allofuranose derivative **3.195** was converted to the key intermediate, a mixture of diacetates **3.196**, which was coupled with **3.050** to give **3.197**. Formation of the 2,3′-*O*-anhydro derivative and simultaneous deacetylation of C-2′ followed by the thiocarbonylation afforded **3.198.** The radical deoxygenation of the 2′-*O*-(4-methylphenyloxy)thiocarbonyl deriva-



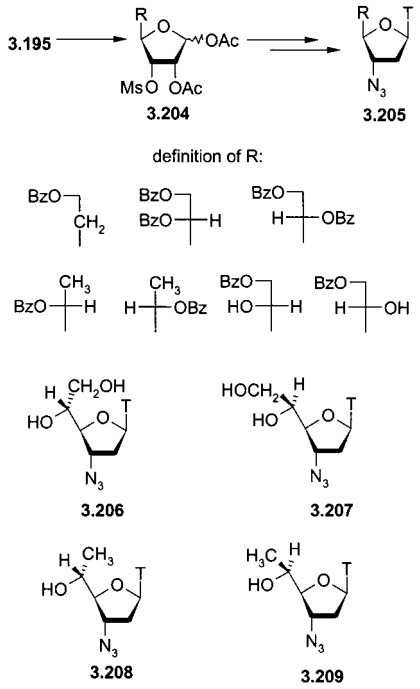
tive **3.198** afforded **3.199**, which was converted to **3.200** through known reaction sequences.[181] In an alternative approach a mixture of 5-deoxy-*gluco*furanose pentaacetates **3.202**, synthesized from 3-*O*-



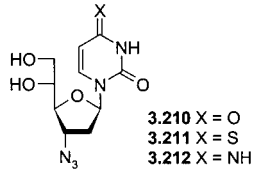
acetyl-2,3-*O*-isopropylidene-α-D-*gluco*furanose **3.201** was utilized. Coupling of **3.202** with **3.050**, followed by the usual synthetic manipulations, afforded the modified nucleoside **3.203**. A higher homologue of AZT, **3.200**, was obtained from **3.203** through reduction, mesylation, azidolysis, and deprotection.[182]



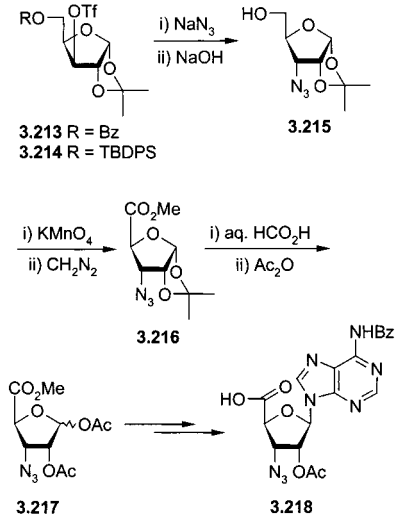
To develop a general strategy for the preparation of the side-chain analogues of **1.001**, compound **3.195** was converted to an anomeric mixture of 1,2-di-*O*-acetyl-6-*O*-benzoyl-5-deoxy-3-*O*-mesyl-D-*allo*furanoses **3.204**, which produced protected derivatives **3.205**. Compounds **3.205** on deprotection afforded



3.200 and **3.206**−**3.209**.[183] The synthesis of compounds **3.210**−**3.212**, related to **3.067**, has also been reported.[184]

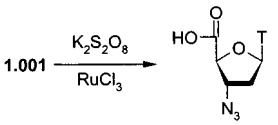


Treatment of triflate **3.213** with NaN_3 and debenzoylation afforded **3.215**. Azidosugar **3.215** was oxidized, and esterification afforded **3.216**. Deprotection under acidic conditions and acetylation produced a mixture of diacetates **3.217**, which was converted to **3.218**. Compound **3.218** was the key intermediate for the synthesis of a peptidyl nucleoside antibiotic, Chryscandin.[185]



1.001 was oxidized to the corresponding 5′-carboxylic acid **3.219** using $K_2S_2O_8$ and a catalytic

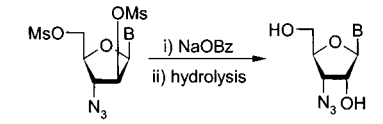
amount of $RuCl_3$ under basic conditions. Compound **3.219** was an important precursor for the preparation of a nucleoside-based amino acid,[186] which was used in the synthesis of amide-linked oligonucleosides.[187]



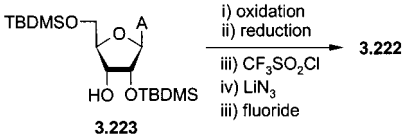
3.219

3.2.3. 3′-Azido-3′-deoxy-ribo-, -arabino-, *and* xylo-*furanosylnucleosides*

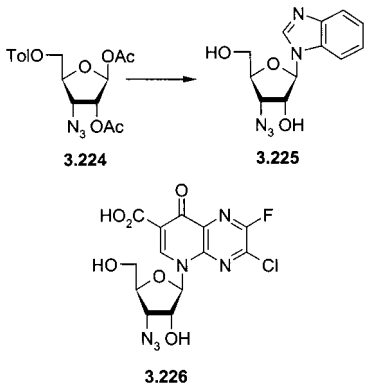
Treatment of azido dimesylate **3.220** with NaOBz, followed by hydrolysis, afforded 3′-azido-3′-deoxyuridine **3.221**.[188] Oxidation of 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)adenosine **3.223**, stereoselective reduction of the keto derivative from the α-face of the furanose ring, triflylation of the *xylo*-derivative, azide displacement, and deprotection gave 3′-azido-3′-deoxyadensine **3.222**.[68] Coupling of the appropriate heterocycles with 3-azido-3-deoxy-1,2-di-*O*-acetyl-5-*O*-(4-methylbenzoyl)-*β*-D-*ribo*furanose **3.224**, followed by deprotection, produced azidonucleoside **3.225**[189] or **3.226**.[190]



3.220 **3.221** B = U
3.222 B = A



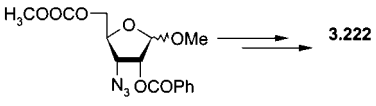
3.223



3.224 **3.225**

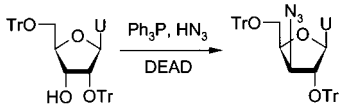
3.226

Similarly **3.222** has also been synthesized from the azidosugar **3.227**, which was obtained from **3.213**.[191]

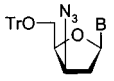


3.227

2′,5′-*O*-Bistrityluridine **3.228** can be transformed into the *xylo*-derivative **3.229** with the $Ph_3P-DEAD-HN_3$ combination. This reaction can also be used for the synthesis of the 3′-azido-2′,3′-dideoxy analogue **3.006** or **3.230**.[192]

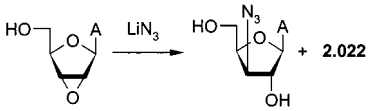


3.228 **3.229**

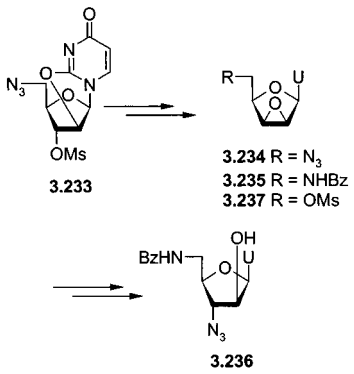


3.006 B = T
3.230 B = A

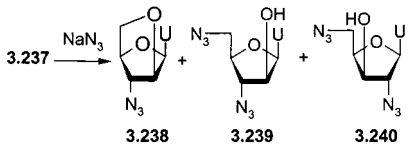
The importance of the 2′,3′-*O*-anhydro (oxirane) function in the synthesis of 3′-azido-3′-deoxynucleosides such as **2.080** and **2.083** has already been mentioned (section 2.1.2**)**. An elaborate study has established that the use of 10 equiv of NH_4N_3 in refluxing EtOH minimized the ring opening of **2.082** at C-2′ (7%). The regioselectivity of ring opening could be increased to 21% in favor of **2.084** by using less reagent (**2.082**:NH_4N_3 = 1:1.65). The same percentage of **2.084** has been obtained by conducting the reaction in DMF. It has been suggested that the epoxide ring opening proceeds through a "borderline-S_N2" transition state. Therefore, the increase in regioselectivity in favor of **2.083** with greater amounts of NH_4N_3 may be a result of an increase in the ionic strength of the solution, which is known to accelerate S_N1 reactions. The greater electron deficiency at C-2′ (due to inductive electron withdrawal by uracil at C-1′) of **2.082** is suppressed when a large excess of nucleophile is present. The increase in regioselectivity in favor of **2.084** (or reduction in the selectivity toward **2.083**) observed in DMF may be due to the higher nucleophilicity of azide ion in this solvent.[89,90,193−196] In addition, the *ribo*-epoxide **3.231** was cleaved with NaN_3 to produce essentially exclusively the *xylo*-isomer **3.232**. In large-scale experiments, the 2′-azido-2′-deoxy *arabino*-diastereomer **2.022** has been isolated in approximately 1% yield.[195] Treatment of the anhydronucleoside **3.233** with aqueous NaOH gave 1-(5-azido-5-deoxy-2,3-epoxy-*β*-D-*lyxo*-furanosyl)uracil **3.234**. The combined hydrogenolysis−benzoylation of **3.234** over Pd-black in the presence of Bz_2O afforded **3.235**. Compound **3.235** on reaction with NaN_3 produced **3.236** in high yield.[197] Direct treatment of 5′-*O*-mesyl-*lyxo*-uridine **3.237** with NaN_3 afforded a mixture of 2′,5′-anhydro-3′-azido-3′-deoxynucleoside **3.238** and 3′,5′-diazido-3′,5′-dideoxynucleoside **3.239** in 54% and 20% yields, respectively; the *xylo*-derivative **3.240** was also present



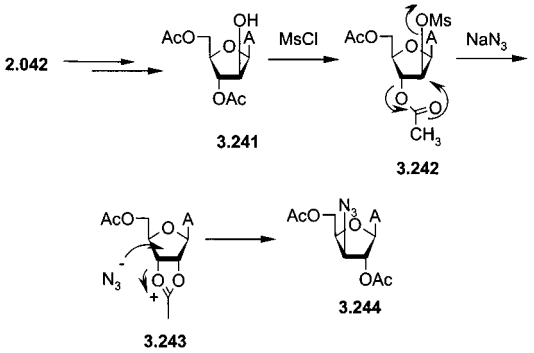
3.231 **3.232**



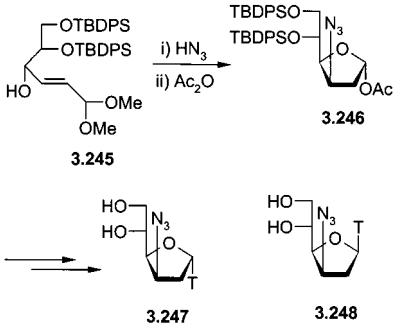
in the mixture in a minor amount.[197] Diacetyl *arabino*-derivative **3.241**, synthesized from 8,2′-*O*-anhydroadenosine **2.042** in multiple steps, was mesylated to afford **3.242**. When **3.242** was heated with NaN_3,



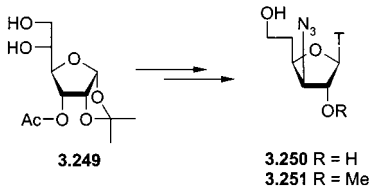
3.244 was the only product formed. The formation of **3.244** from **3.242** may be rationalized by invoking a carboxonium-type intermediate, **3.243**, which could be attacked from the β-face at the C-3′ atom. Deacetylation of **3.244** produced **3.232**.[81,198,199]



The product of Michael-type addition reaction of HN_3 to the α,β-unsaturated acetal **3.245** was isolated as the acetyl derivative **3.246**. The deoxy *arabino*-isomer **3.246**, on coupling with **3.050** followed by the

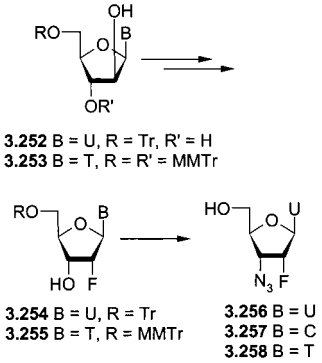


deprotection of the product, afforded α- and β-anomers **3.247** and **3.248**, respectively.[126] 1-(3-Azido-3,5-dideoxy-β-D-*xylo*-hexofuranosyl)thymine **3.250** and its 2′-*O*-methyl ether **3.251** have been synthesized from the *allo*hexofuranose derivative **3.249**.[182]

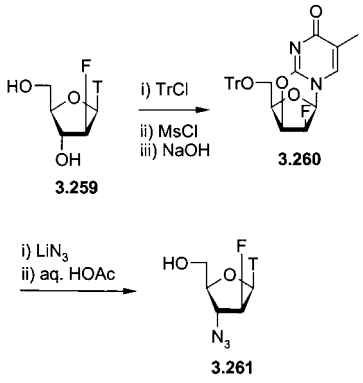


3.2.4.3′-Azido-2′-fluoro-2′,3′-dideoxynucleosides

2′-Deoxy-2′-fluoro-5′-*O*-trityluridine **3.254**, obtained from the *arabino*-derivative **3.252**, was used as the starting material for the synthesis of 3′-azido-2′,3′-dideoxy-2′-fluorouridine **3.256**. Cytidine analogue **3.257** has also been prepared.[200] Reactions of bisprotected thymidine analogue **3.253** with DAST, followed by detritylation and monomethoxytritylation, afforded **3.255** in poor yield. This intermediate, **3.255**, has been used for the preparation of **3.258**.[201]

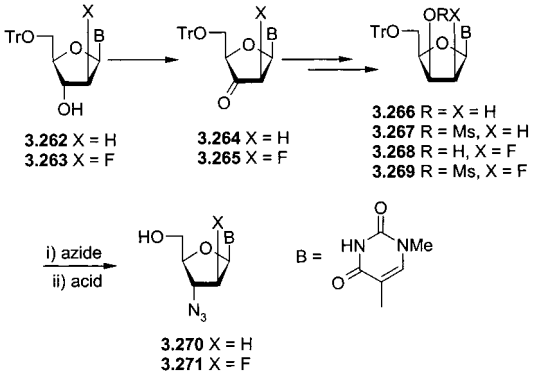


1-(3-Azido-2,3-dideoxy-2-fluoro-β-D-*arabino*-furanosyl)thymine or F-AZT **3.261** was synthesized from the fluoronucleoside **3.259** via the 2,3′-*O*-anhydro derivative **3.260**.[202] 1-Methyl-2′-deoxy-5′-*O*-tritylpseudo-

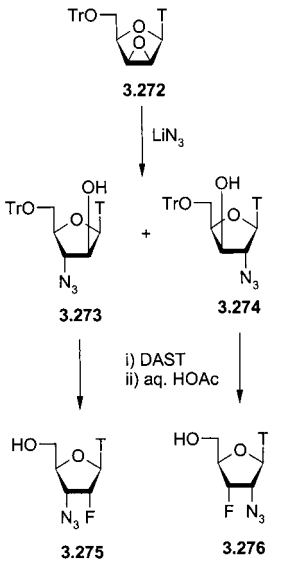


uridine **3.262** was oxidized with CrO_3, pyridine, and Ac_2O complex to the keto compound **3.264**, which was reduced to the *lyxo*-derivative **3.266**. Mesylation of **3.266** to **3.267** followed by azidolysis and deprotection afforded **3.270**. In a similar fashion, 1-methyl-5-(2-deoxy-2-fluoro-β-D-*arabino*-furanosyl)uracil **3.263** was converted into the 3′-azido analogue **3.271** via intermediates **3.265**, **3.268**, and **3.269**.[203]

When the *lyxo*-epoxide **3.272** was treated with LiN_3 in EtOH, both the 3′- and 2′-azido isomers **3.273** and **3.274** were obtained in about a 3:2 ratio. After

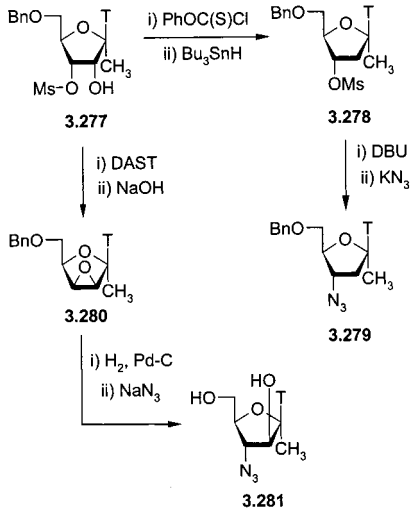


separation of these isomers, each one was converted to the corresponding *ribo*-fluorides **3.275** and **3.276**, respectively, by treatment with DAST, followed by detritylation.[204]

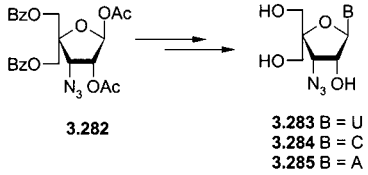


3.2.5. 3′-Azido-3′-deoxy-1′- or -4′-Modified Nucleosides

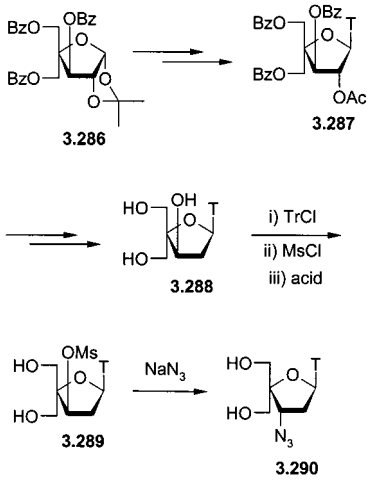
To synthesize 1-deoxypsicofuranosylnucleoside, 4-O-mesylated derivative **3.277** was deoxygenated at the C-3′ site to afford **3.278**. The usual chemical manipulations of **3.278** produced **3.279** in poor yield due to the instability of the glycosidic bond. Mesylate **3.277**



has also been converted to 3′-azido-3′-deoxy *arabino*-derivative **3.281** via epoxide **3.280**.[205] Glycosidation of 1,2-diacetyl-5-benzoyl-3-azido-4-*C*-[(benzoyloxy)-methyl]-3-deoxy-D-*erythro*-pentofuranose **3.282** with nucleobases and deprotection produced nucleosides **3.283**−**3.285**.[206] 1-(2-*O*-Acetyl-3,5-di-*O*-benzoyl-4-*C*-



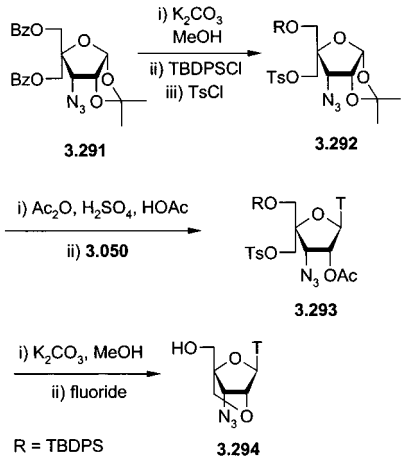
benzoyloxymethyl-α-L-*threo*-furanosyl)thymine **3.287**, synthesized from the 4-*C*-benzoyloxymethyl β-L-*threo*-derivative **3.286**, was converted to the 2′-deoxynucleoside analogue **3.288**. Tritylation of **3.288** followed by mesylation, detritylation, and nucleophilic substitution with azide furnished 1-(3′-azido-2′,3′-dideoxy-4′-*C*-hydroxymethyl-α-L-*glycero*-pentofuranosyl)thymine **3.290** in poor yield.[207] To synthesize a



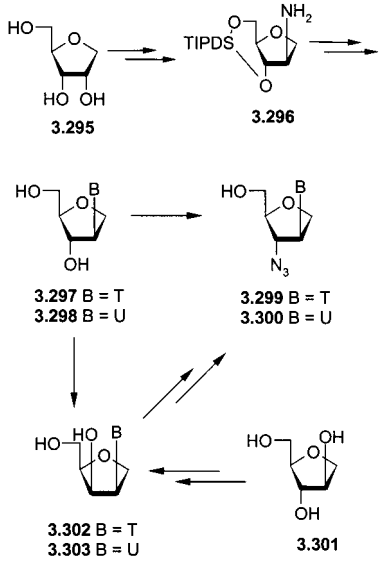
3′-azido-3′-deoxynucleoside, which has a locked N-conformation by formation of a methylene bridge between the 4′-carbon and 2′-oxygen atoms, the azidosugar **3.291** has been utilized as the starting material. Deprotection, selective protection, and tosylation converted **3.291** to **3.292**. Acetolysis of **3.292**, followed by coupling with **3.050**, gave **3.293**. Deacetylation and concomitant intramolecular nucleophilic displacement, followed by desilylation, transformed **3.293** to the desired locked azidonucleoside **3.294**.[208]

3.2.6. Carbohydrate Ring Modified 3′-Azido-3′-deoxynucleosides

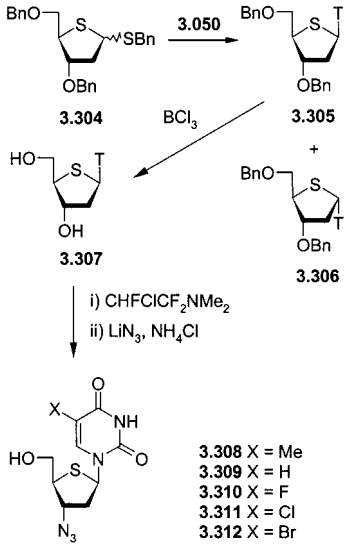
A conceptually new, hydrolytically stable, optically active analogue of **1.001**, 1,4-anhydro-3-azido-2,3-dideoxy-2β-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-D-arabinitol **3.299** has been synthesized. 1,4-Anhydro-D-ribitol **3.295** was converted to a suitably protected amino derivative, **3.296**, which was transformed to a thymidine analogue, **3.297**. Conversion of **3.297** to the azido derivative **3.299** was difficult because the 2,3′-*O*-anhydro intermediate was unusually stable to azide attack. Synthesis of **3.299** was, therefore, achieved by converting **3.297** to **3.302**, which can also be accessed from 1,4-anhydro-D-xylitol



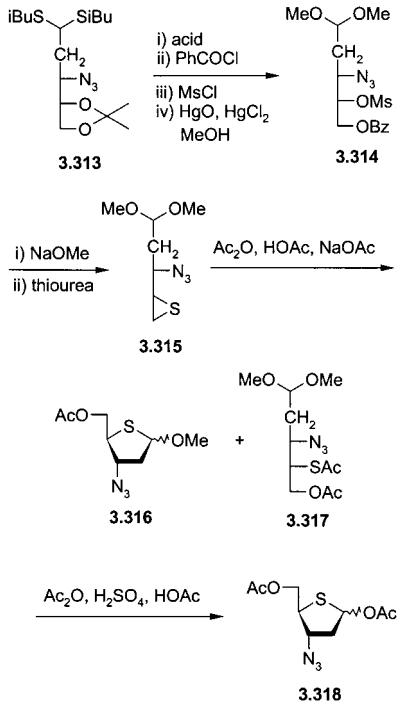
3.301. Similarly, the uracil derivative **3.300** has also been prepared.[209,210]



There has been increasing interest in the synthesis of nucleosides in which the furanose ring oxygen atom is replaced by a sulfur or nitrogen atom or a methylene group. Such a structural modification results in an increased resistance to phosphorolytic cleavage. Thus, the 4′-thio-2′-deoxynucleoside **3.305** and its α-anomer **3.306** have been synthesized by coupling the thiosugar **3.304** with **3.050**. The *β*-anomer **3.305** was separated and deprotected to generate free 4′-thiothymidine **3.307**, which was converted to the azido analogue **3.308**. The overall yield of the conversion is low probably because the presence of sulfur modified the reactivities of the hydroxyl groups.[211] The poor overall yield of **3.308** led to the preparation of 3-azido-2,3-dideoxy-4-thiosugar analogue **3.318** from D-xylose **3.027**. A multistep conversion of the D-*erythro*-pentose derivate **3.314** (for a comparison, see the preparation of **3.038**) to **3.315** gave the key intermediate for the introduction of a sulfur atom in the C-4 position. Thus, **3.315**, on treatment with NaOMe, afforded an epoxide, which on reaction with thiourea yielded the corresponding 4,5-epithio derivative **3.315**. The cyclized product **3.316** can be obtained from **3.315** along with **3.317**. The latter can be converted to the diacetate **3.318**.[212]



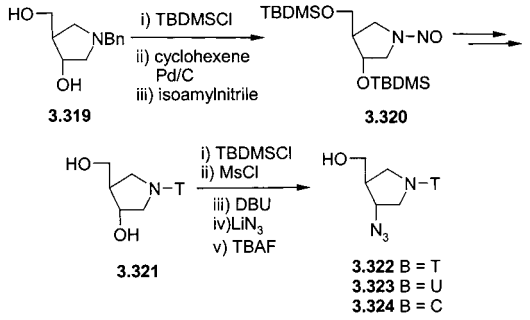
Both **3.316** and **3.318** can be used in the synthesis of **3.308** and other base-modified AZT analogues



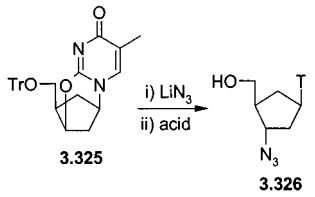
3.309−**3.312** in better overall yields.[211] Other groups have also reported the synthesis of 3-azido-4-thiosugars for the preparation of **3.308**.[213]

To modify the anomeric position with nitrogen substitution, *N*-benzylpyrrolidine diol **3.319** was protected, debenzylated, and nitrosated to produce *N*-nitroso derivative **3.320**. Reduction of nitroso to amino, followed by thymine ring construction and deprotection, furnished nucleoside **3.321**. The target azidonucleoside **3.322** was obtained from **3.321** via an established sequence of reactions.[214] The corresponding uracil and cytosine derivatives **3.323** and **3.324** have also been reported.[215,216]

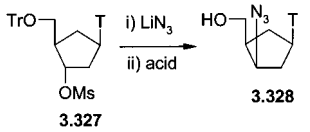
The C-2,3′-*O*-anhydrothymidine derivative **3.325** on treatment with LiN_3, followed by detritylation, afforded (±)-1-[(1*R*,3*S*,4*S*)-3-azido-4-(hydroxymeth-



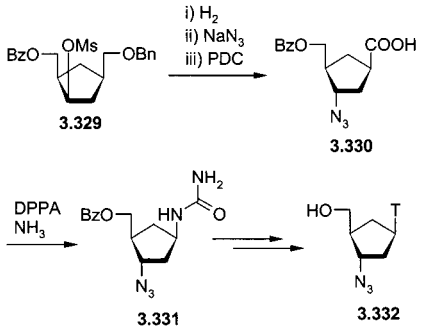
yl)cyclopentyl]-5-methyl-2,4-(1*H*,3*H*)-pyrimidinedione **3.326**. The mesylated derivative **3.327**, on the



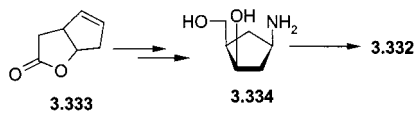
other hand, afforded the expected "up" azidonucleoside **3.328**.[217] All these compounds were, however, synthesized as racemic mixtures.



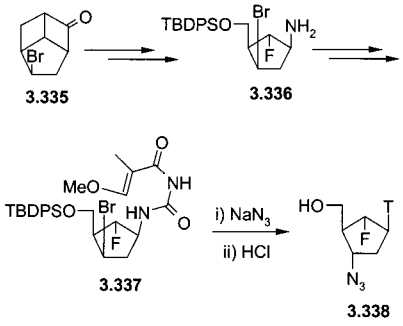
The synthesis of enantiomerically pure (+)-C-AZT **3.332** started from the mesylate **3.329**, which was converted to azido carboxylic acid derivative **3.330** in three steps. The urea derivative **3.331** was ob-



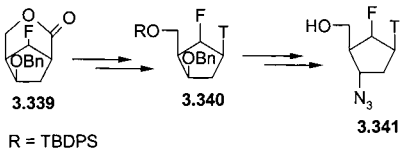
tained in optically pure form by treating **3.330** with DPPA and gaseous NH_3, followed by recrystallization. A thymine ring was constructed on **3.331** using the usual chemistry to obtain **3.332**.[218] This compound has also been synthesized starting from the unsaturated bicyclic lactone (+)-**3.333** via amino diol **3.334**.[219]



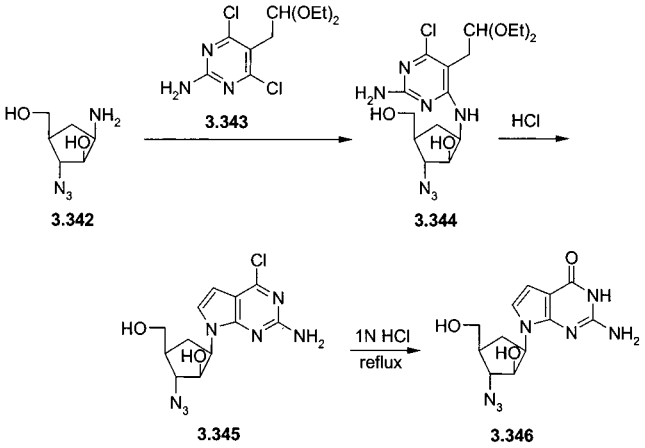
In an attempt to exchange the ring oxygen of **1.001** in the sugar unit for an isosteric fluoromethylene unit, the amino derivative **3.336**, obtained from the



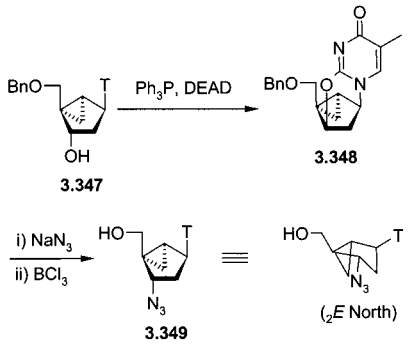
strained tricyclic ketone **3.335**, was converted to the bromo intermediate **3.337**. Displacement of the bromine atom by an azide ion followed by cyclization under acidic conditions afforded **3.338**. The other isomer, **3.341**, was synthesized from fluorolactone **3.339** via fluoronucleoside **3.340**.[220,221]



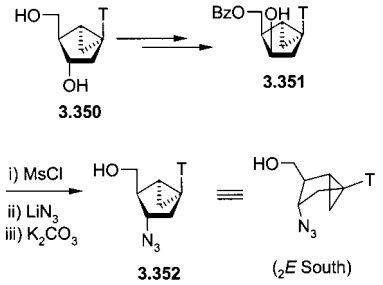
A pyrro[2,3-*d*]pyrimidin-4-one carbocyclic nucleoside, **3.346**, was synthesized by coupling azidocyclopentylamine **3.342** with pyrimidine **3.343**. Treatment of **3.344** with acid led to the formation of an aldehyde which cyclized directly to the chloro derivative **3.345**. Hydrolysis of **3.345** with 1N HCl afforded the 7-deazaguanine nucleoside **3.346**.[222]



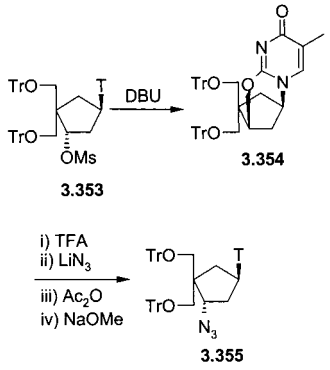
It has been suggested that the antipodal north conformation of **1.001** may be required for the strong interaction of AZT 5′-triphosphate with the target enzyme for the manifestation of its biological activities. It has also been proposed that the preference of **1.001** for the extreme $_3E$ (south) conformation is responsible for its potent anti-HIV activity. To resolve these issues, two conformationally rigid carbocyclic analogues of **1.001**, which are locked permanently into opposite $_2E$ (north) and $_3E$ (south) conformations, have been synthesized. Thus, (*N*)-methanocarba-AZT **3.349** was prepared from partially protected (*N*)-



methanocarbathymidine **3.347** via the anhydro derivative **3.348**. (*S*)-Methanocarba-AZT **3.352**, on the other hand, was prepared from **3.351**, which was obtained from (*S*)-methano-carbathymidine **3.350**.[223]

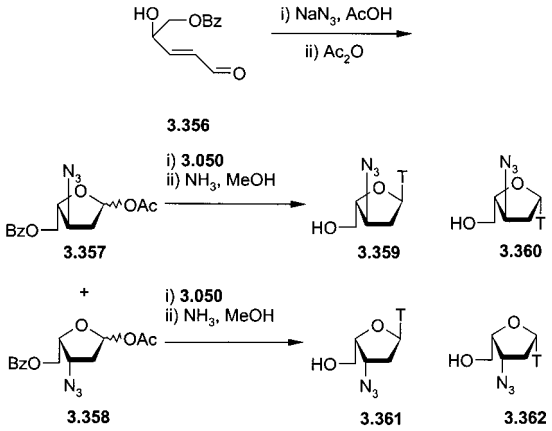


The (±)-*trans*-isomer **3.353** was converted to the *O*-anhydro derivative **3.354**, which after detritylation, azidation, acetylation, and deprotection afforded the (±)-*trans*-azidonucleoside **3.355**.[224]

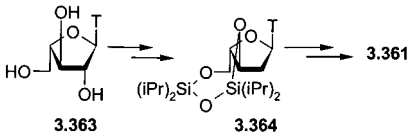


3.2.7. 3′-Azido-3′-deoxy-L-nucleosides

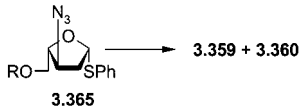
Since two enantiomeric forms of a biologically active compound often show differences in action and selectivity, preparation of the L-isomer of **1.001** was taken up. Michael-type addition of azide to (2*E*,4*R*)-5-(benzoyloxy)-4-hydroxy-2-pentenal **3.356**, followed by acetylation, produced after chromatographic purification, anomeric mixtures of L-*erythro*-pentofuranose **3.357** and L-*threo*-pentofuranose **3.358**. Coupling of **3.357** and **3.358** with **3.050** followed by methanolysis of the products generated the pairs **3.359**/**3.360** (L-AZT) and **3.361**/**3.362**, respectively.[126,225]



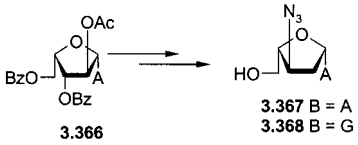
A different route was devised for the synthesis of **3.361** from the nucleoside **3.363**, which was converted



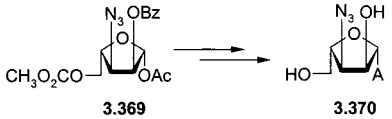
to **3.361** via the deoxy derivative **3.364**.[226] Coupling of L-enantiomers of 1-thiopentofuranoside **3.365** with **3.050** also produced **3.359** and **3.360**.[128] The usual



reaction sequence converted nucleoside **3.366** to 3′-azido-2′,3′-dideoxy-*β*-L-adenosine **3.367**.[97] Guanine derivative **3.368** has also been synthesized from



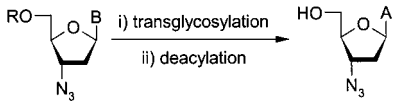
3.365 in multiple steps.[227] The synthesis of the enantiomer of **3.222** was realized by using L-azidosugar **3.369**, which was converted to 3′-azido-3′-deoxy-L-adenosine **3.370** in several steps.[191]



3.3. Reactions

3.3.1. Transglycosylation

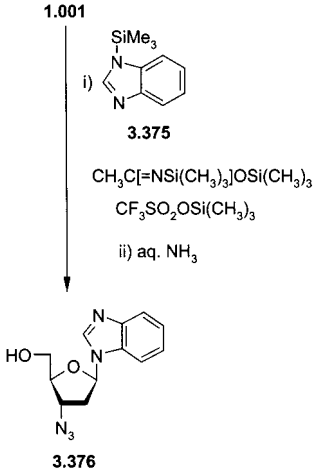
The transglycosylation of 5′-O-acetylated AZT **3.371** with silylated *N*-6-octanoyladenine using trimethylsilyl trifluoromethanesulfonate as a catalyst followed by deacylation produced **3.372** and its α-anomer. Silylated *N*-2-palmitoylguanine, on the other hand, produced **3.159** among other isomers.[228] Compound **3.376**, which is a 2′-deoxy analogue of **3.225**, has been



3.371 R = Ac, B = T
3.373 R = Bz, B = T
3.374 R = Ac, B = U

3.372

synthesized by transglycosylation of the persilylated derivative of **1.001** with silylated benzimidazole **3.375**.[189]

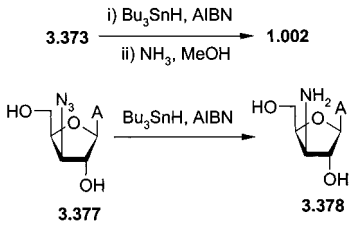


3.375

3.376

3.3.2. Reduction

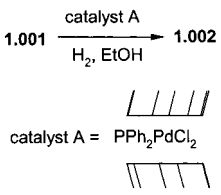
Some of the methods for the reduction of azide to amino groups have already been discussed in section 2.2. The 3′-azidonucleosides such as **3.373** and **3.377** have been reduced to **1.002** and **3.378**, respectively,



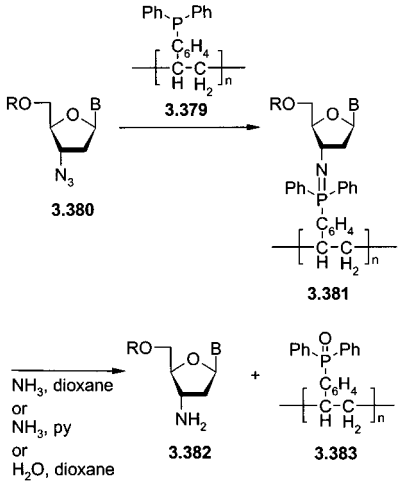
3.377

3.378

using Bu_3SnH.[229] Another method made use of hydrogenation by a heterogenized homogeneous catalyst, interlamellar montmorillonite diphenylphosphinepalladium(II) complex, to convert **1.001** to **1.002**.[230]



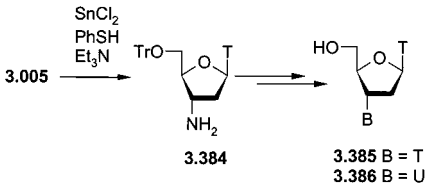
The reduction of azidonucleosides with Ph_3P represents one of the most convenient synthetic methods although separation of Ph_3PO, which is formed in the reaction, remains a problem. To avoid this inconvenience, a polymer-supported triarylphosphine, namely, polystyryldiphenylphosphine resin **3.379**, has been used successfully to convert a series of azidonucleosides represented by general structure **3.380** to amino derivatives **3.382** via intermediate **3.381**. The polymer-supported oxide derivative **3.383** can be removed through filtration.[231]



B = U; B = A; B = A^{ib}; B = C; B = C^{ib}

R = H; R = DMTr

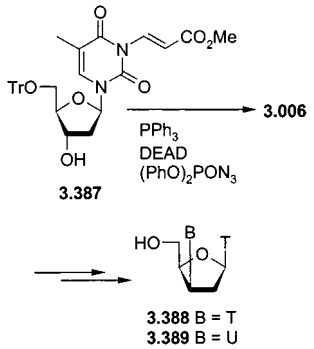
To synthesize uracil- and thymine-substituted thymidines, AZT derivative **3.005** was reduced to aminothymidine **3.384**, which was used in the preparation of 3′-thymin-1-yl and 3′-uracil-1-yl compounds **3.385** and **3.386**, respectively (see compounds **2.157**



3.384

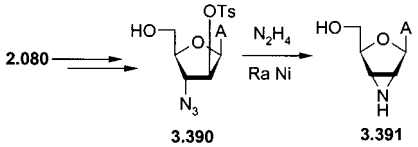
3.385 B = T
3.386 B = U

and **2.158)**. Similarly, an N-3-protected derivative of 5′-*O*-tritylthymidine **3.387** has been azidolyzed to **3.006**, which was converted to nucleosides **3.388** and **3.389** (see **2.161** and **2.162**).[105]



3.388 B = T
3.389 B = U

Reduction of the tosylate **3.390**, obtained from **2.080**, with intramolecular displacement−cyclization provided the aziridine nucleoside **3.391**. 3′-Azido-3′-

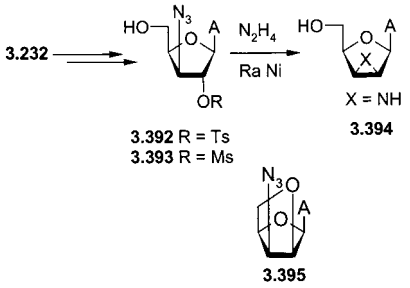


3.390

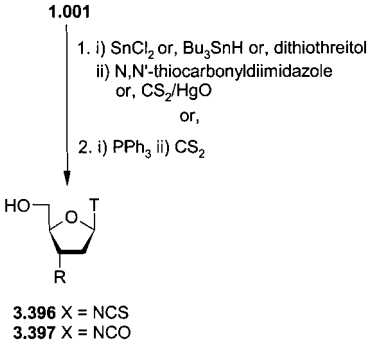
3.391

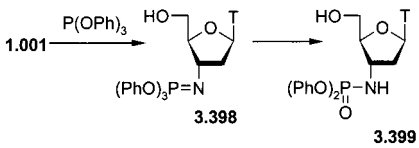
deoxy-2′-*O*-tosyl *xylo*-analogue **3.392**, on the other hand, on reduction furnished **3.394** as the major

product with a minute amount of the reduced product of **3.395**. The mesylate **3.393**, on treatment with NaH, produced 2′,5′-*O*-anhydroazidonucleoside **3.395**.[195]



Compound **1.001** can be converted to 3′-deoxy-3′-isothiocyanatothymidine **3.396** by using several combinations of reagents.[106] Using a solid-support approach, **3.396** as well as 3′-deoxy-3′-isocyanatothymidine **3.397** have been synthesized as the precursors for attaching fluorescent dyes at the C-3′ end of nucleosides.[232] **1.001** on reaction with triphenyl phosphite underwent reductive N-phosphorylation. The 3′-deoxy-3′-phosphoramidothymidine **3.399** formed via the phosphorimino intermediate **3.398**.[233]

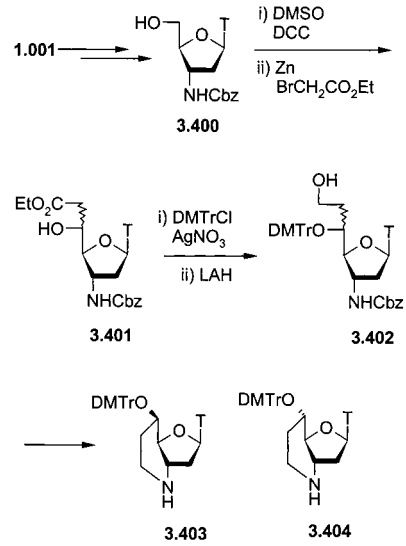


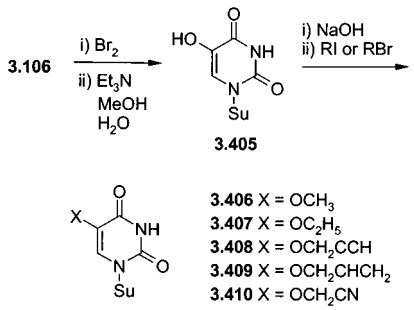


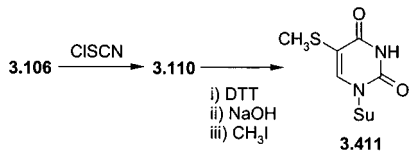
1.001 has been used as a starting material for the synthesis of conformationally locked nucleosides. Thus, **1.001** was converted to protected aminothymidine **3.400**. Oxidation of **3.400** followed by a Reformatsky reaction produced a mixture of **3.401**. Protection of the 5′-hydroxyl group and reduction of the ester function converted **3.401** to the alcohol **3.402**. Separation of isomers, followed by cyclization, produced the 5′(*R*)-isomer **3.403** and the 5′(*S*)-isomer **3.404**.[234]

3.3.3. Base Modification

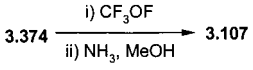
Treatment of the 5′-*O*-acetyl derivative of **3.108** with ammonia produced 5-amino derivative **3.111**. Methylamine or dimethylamine can also be used instead of ammonia to produce the *N*-alkylamino derivatives. Bromination of **3.106**, followed by treatment with Et_3N, MeOH, and H_2O, produced 5-hydroxy derivative **3.405**, which was alkylated to produce 5-alkoxy analogues **3.406**−**3.410**. The 5,6-double bond of **3.106** can be reacted with ClSCN to generate **3.110**. Treatment of **3.110** with DTT followed by methyl iodide in the presence of NaOH yielded 5-(methylthio) derivative **3.411**.[149]



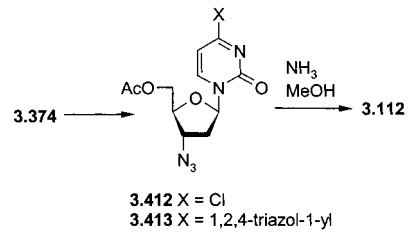




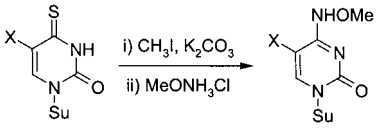
The C-6 site of **3.374** has been fluorinated with CF_3OF. Deacetylation of the product afforded **3.107**.[235]



Compound **3.374** can be converted to the 3′-azido-3′-deoxycytidine **3.112** via the 4-chloro **(3.412)** or 4-triazolyl (**3.413**) derivative.[235−237] Compounds **3.113** and **3.114** can also be prepared in a similar fashion.[149]



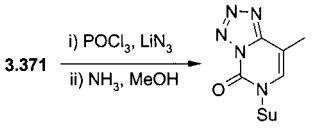
4-Thio derivatives **3.414** and **3.115** were methylated at C-4 and the SMe group was displaced by methoxyamine to afford nucleosides **3.415** and **3.416**, respectively.[238] Syntheses and biological studies of several 3′-azido-3′-deoxy-5-alkylated deoxycytidines have also been reported.[239,240]



3.414 X = H
3.115 X = Me

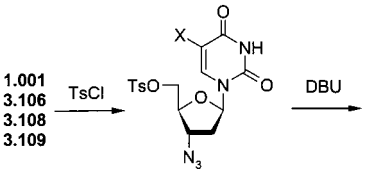
3.415 X = H
3.416 X = Me

An efficient method for the preparation of 6-(3-azido-2,3-dideoxy-β-D-*ribo*-furanosyl)-8-methyl-tetrazolo[1,5-*c*]pyrimidin-5(6*H*)-one **3.417** has been devised by treating **3.371** with $POCl_3$ in the presence of LiN_3, followed by deprotection.[241]

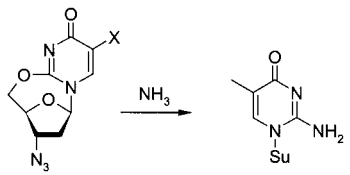


3.417

Tosylation of **1.001** afforded **3.418**. Tosylated derivative **3.418**, on treatment with DBU, furnished the 2,5′-*O*-anhydro derivative **3.422**. Ammonolysis of **3.422** in methanolic ammonia produced deoxyisocytidine analogue **3.426**. Similarly **3.106**, **3.108**, and **3.109** were converted to the anhydro compounds **3.423**−**3.425** via tosylates **3.419**−**3.421**.[242]



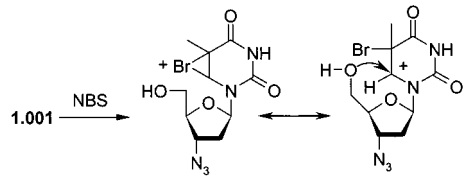
3.418 X = Me
3.419 X = H
3.420 X = Br
3.421 X = I



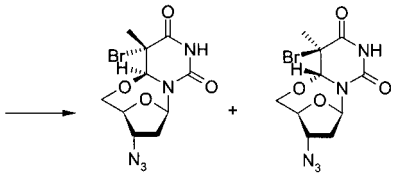
3.422 X = Me
3.423 X = H
3.424 X = Br
3.425 X = I

3.426

It has been demonstrated that the anti-HIV drugs with high lipophilicity and molecular weight lower than 400 improve brain permeability, through their enhanced ability to cross the blood−brain barrier by a nonfacilitated diffusion mechanism. To synthesize a more lipophilic variety of AZT, **1.001** was reacted with NBS to afford a mixture of (−)-*trans*-(5*S*,6*S*)-**3.429** and (+)-*trans*-(5*R*,6*R*)-**3.430**. The major component **3.429** was isolated from the mixture. These are formed through an ionic mechanism with an initial formation of 5,6-bromonium ion intermediates **3.427**, which underwent intramolecular nucleophilic

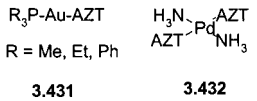


3.427 **3.428**

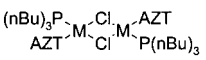


3.429 **3.430**

attack by the 5′-hydroxyl group (as shown in **3.428**) at the sterically less hindered C-6 position.[243] A novel class of metal complexes, **3.431**−**3.435**, has been prepared from N-3-deprotonated **1.001**.[244]

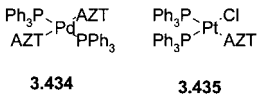


3.431 **3.432**



M = Pd, Pt

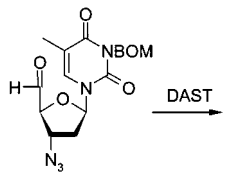
3.433



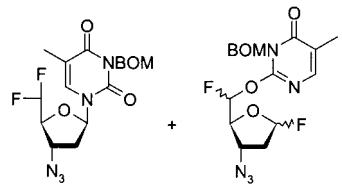
3.434 **3.435**

3.3.4. Fluorination

The reaction of pyrimidine nucleoside 5′-aldehydes **3.436** with DAST produced 5′-deoxy-5′,5′-difluoronucleoside **3.437** and a deglycosized product, **3.438**.[24]



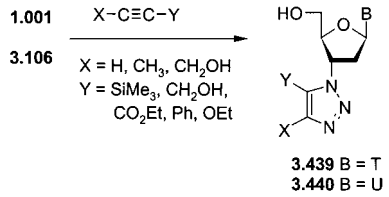
3.436



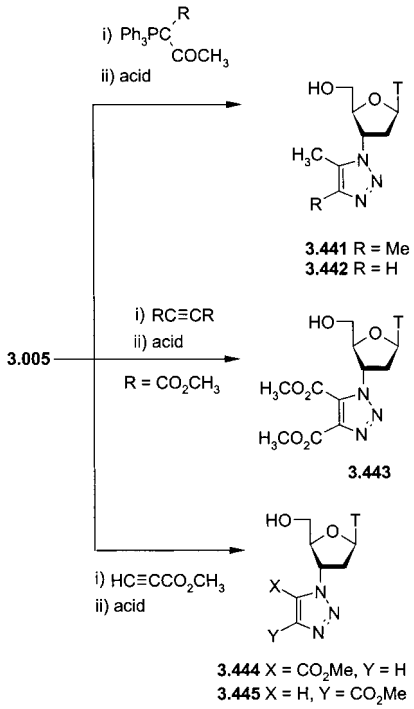
3.437 **3.438**

3.3.5. Cycloaddition

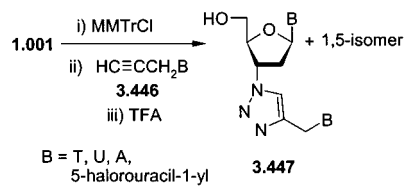
Cycloaddition of different acetylenic compounds on the azido function of **1.001** and **3.106** afforded products (general representations **3.439** and **3.440**) with a 1,2,3-triazol-1-yl substituent in the 3′-position.[246] In another paper, protected AZT **3.005** on reaction with 2-oxo-3-methylpropylidenetriphenylphosphorane and subsequent deprotection produced 4,5-dimethyl-1,2,3-triazol-1-yl derivative **3.441**. 2-Oxo-



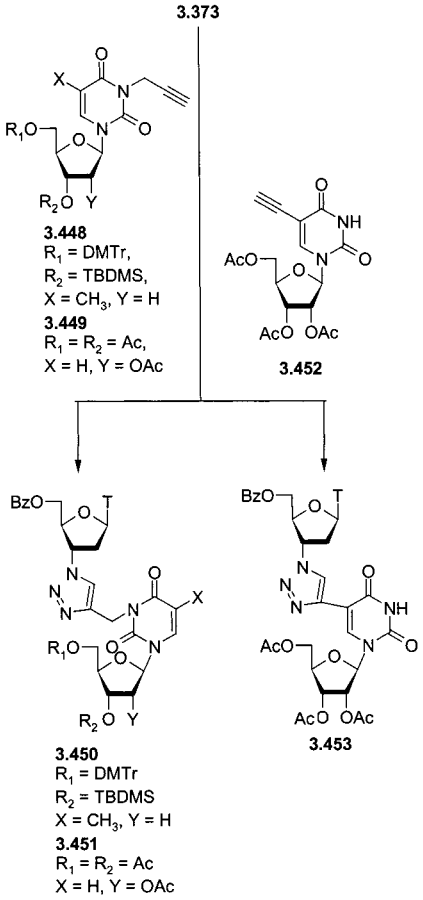
propylidenetriphenylphosphorane in a similar fashion produced the 5-methyl-1,2,3-triazole **3.442**. A positional isomer, 4-methyl-1,2,3-triazole, was not detected. On the other hand, reaction of **3.005** with dimethyl acetylenedicarboxylate followed by deprotection led to the formation of the triazole derivative **3.443**. Interestingly, cycloaddition of **3.005** with methyl propionate gave a mixture of two positional isomers, which were detritylated to afford **3.444** (minor) and **3.445** (major).[247] The cycloaddition reac-



tions of the suitably protected derivative of **1.001**, with *N*-9/*N*-1-propargylpurine/pyrimidine (general formula **3.446**) afforded a mixture of two regioisomers. Separation and deprotection afforded **3.447** as the major component.[248] A similar methodology

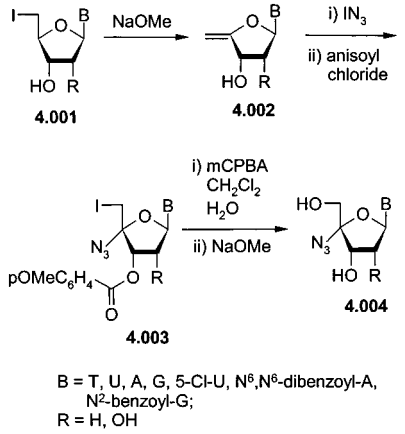


has been applied in the preparation of the *N*-3- or *C*-5-triazolyl-branched nucleoside dimers. The 5′-*O*-benzoyl derivative of AZT, **3.373**, was reacted with suitably protected *N*-3-propargylthymidine **3.448** or -uridine **3.449** to afford **3.450** and **3.451** as the major components, respectively. The *C*-5-propargyl derivative of uridine (**3.452**) in a similar fashion reacted with **3.373** to produce **3.453** as the major isomer.[249]

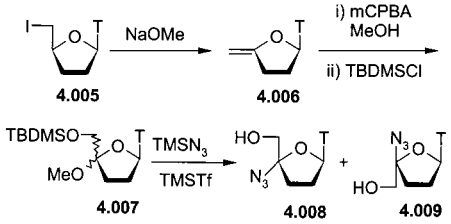


4. 4′-Azido-4′-deoxynucleosides

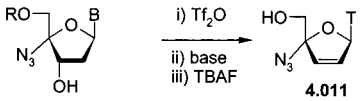
Because of the emergence of **1.001**-resistant HIV strains, attempts have been made to synthesize new nucleoside-based drugs, which should have distinct dissimilarity of structure to the current family of dideoxynucleosides. It would be hoped that virus variants elicited by any of the other nucleoside drugs would not be cross-resistant to such a compound. In this regard, the synthesis and biological evaluations of 4′-azidonucleosides have been envisaged. The key intermediates, 4′-olefinic derivatives **4.002**, have been synthesized from the 5′-deoxy-5′-iodonucleosides **4.001**. The reaction of IN_3 (generated in situ by ICl and NaN_3) with **4.002** afforded **4.003** (2′-*O*-*p*-methoxybenzoate derivative) as a major compound, where iodide added from the β-face of the double bond to give an iodonium ion intermediate which was opened on the α-side at 4′-C by azide ion. When a 4′-azido-3′-*O*-anisoyl-5′-deoxy-5′-iodonucleoside, **4.003**, was oxidized with mCPBA in the presence of water, a mixture of at least 12 products was obtained. This mixture was treated with NaOMe, and the final product **4.004** was isolated in yield varying from 35% to 71% in two steps. This oxidative displacement of the 5′-iodide was not successful in the 3′-deoxy series.



A different approach was considered in this case. The 4′-unsaturated thymidine derivative **4.006**, obtained from iododeoxythymidine **4.005**, on treatment with mCPBA in methanol afforded 4′-methoxy-3′-deoxythymidine **4.007** as a mixture of D- and L-isomers in



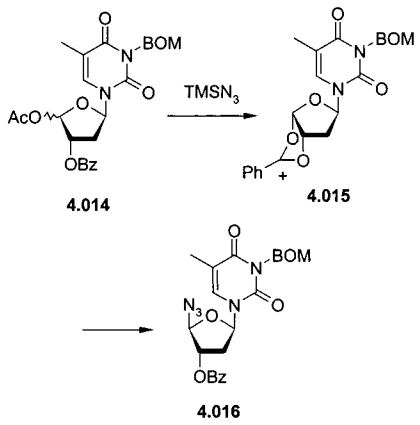
the ratio 1:3, respectively. The purified mixture was protected and the azide was introduced at the 4′-site by reacting the mixture with excess $TMSN_3$ in the presence of TMSTf. The 5′-silyl ether was cleaved concomitantly, and compound **4.008** and its 4′-epimer **4.009** were isolated in 37% and 25% yields, respectively. 5′-Protected 4′-azidothymidine **4.010** has been converted to 4′-azido-3′-deoxy-2′,3′-didehydrothymidine **4.011** in multiple steps using known reactions. 4′-Azidodeoxycytidine **4.012** and 4′-azidodeoxyinosine **4.013** have also been reported.[250a]



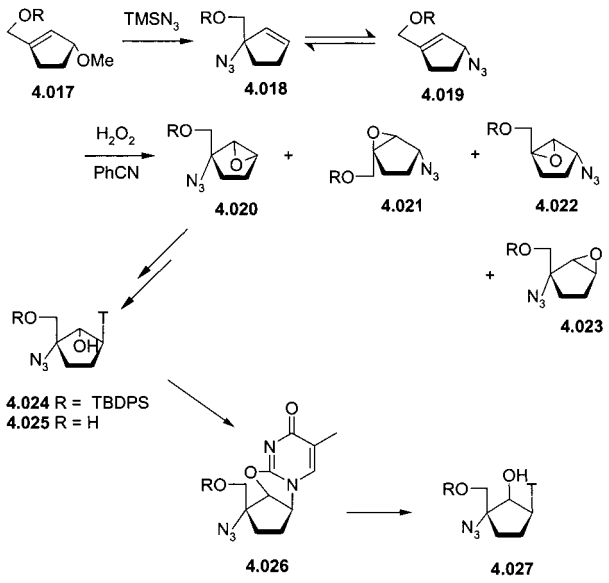
4.010 B = T, R = TBDMS
4.012 B = C, R = H
4.013 B = Hy, R = H

The tetrahydrofuranyl analogue **4.014** on reaction with $TMSN_3$ smoothly produced β-N-glycosylated furanoid nucleoside **4.016**. The reaction proceeded stereospecifically (only "up" azido) because of the formation of intermediate **4.015**.[251]

4′-Azido carbocyclic nucleosides have been synthesized because it was reported that the carbocyclic analogue of 2′-deoxy-2′-fluoro-*arabino*-furanosylguanine was 800 times more active against HSV than its oxa equivalent.[252] Treatment of (±)-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-3-methoxycyclopent-1-ene **4.017** with $TMSN_3$ gave an equilibrium mixture of allyl azides **4.018** and **4.019**. Epoxidation of the



mixture with peroxybenzimidic acid gave key epoxide **4.020** in poor yield along with three other products. Condensation of **4.020** with **3.050** furnished nucleoside **4.024**, which on deprotection afforded **4.025**. Inversion of configuration at C-6′ was accomplished by mesylation of **4.024** followed by treatment of the crude mesylate with aqueous base to give the deprotected diol **4.027**. The reaction undoubtedly proceeded via the 2,6′-*O*-anhydro derivative **4.026**.[252]

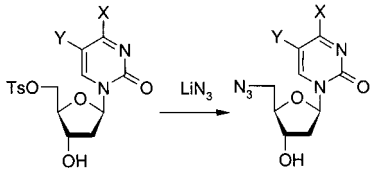


5. 5′-Azido-5′-deoxynucleosides

5.1. Synthesis

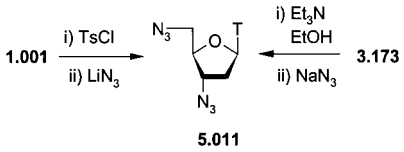
5.1.1. Nucleophilic Displacement

Nucleophilic displacement of 5′-*O*-sulfonate esters by azide is the most common method for the synthesis of 5′-azido-5′-deoxynucleosides. Thus, a range of tosylates, **5.001**−**5.005**, on treatment with LiN_3 produced azidonucleosides **5.006**−**5.010**, which were needed for the synthesis of the corresponding 5′-amino-5′-deoxynucleosides.[253] **1.001** was converted to diazidothymidine **5.011** in a similar fashion.[254a] Al-

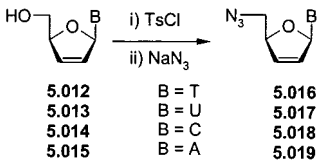


5.001	X = NH_2, Y = I	**5.006**
5.002	X = OH, Y = F	**5.007**
5.003	X = OH, Y = Cl	**5.008**
5.004	X = OH, Y = Br	**5.009**
5.005	X = OH, Y = I	**5.010**

ternatively, **5.011** was synthesized from the dimesylate **3.173** in two steps.[254b]

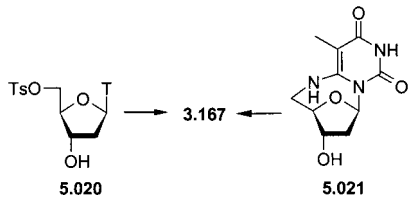


To synthesize new types of aminoacylnucleosides, intermediate azidonucleosides **5.016**−**5.018** have been synthesized by tosylating the free nucleosides **5.012**−**5.014**, respectively, and then by treating them with NaN_3. The yields of the tosylation step for compounds

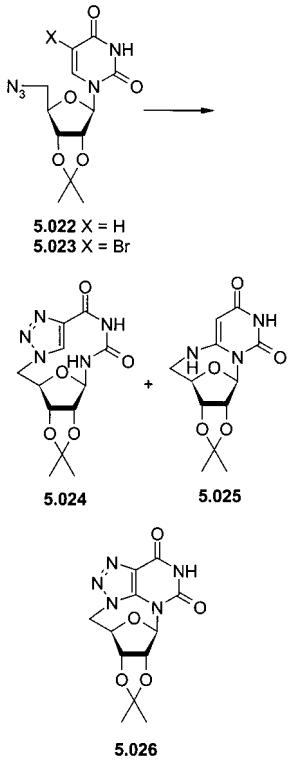


5.012	B = T	**5.016**
5.013	B = U	**5.017**
5.014	B = C	**5.018**
5.015	B = A	**5.019**

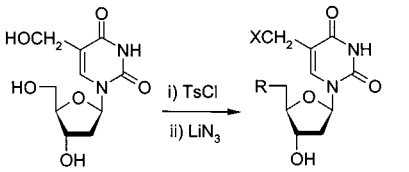
5.014 and **5.015** are low compared to those of **5.012** and **5.013**. Moreover, in the adenine series additional difficulties were anticipated because 5′-*O*-tosyladenosines tend to undergo intramolecular cyclization. Compound **5.015** was, therefore, subjected to direct introduction of azide by reacting it with a combination of $Ph_3P-CBr_4-LiN_3$.[255,256] Interestingly, treatment of 5′-*O*-tosylthymidine **5.020** with LiN_3 in DMF at reflux temperature afforded 6,5′-imino-5′-deoxythymidine **5.021**. It was suggested that compound



3.167 formed first, which underwent an intramolecular reaction[175] to form **5.021**. Similarly, uridine derivative **5.022** generated a mixture of **5.024** (80%) and **5.025** (∼5%). The 5-bromo derivative **5.023**, on the other hand, produced **5.026**.[108,257,258] An attempted synthesis of **5.033** from **5.027** was not efficient because tosylation of **5.027** with 1 equiv of tosyl chloride produced a mixture of **5.028**−**5.030** along with some unreacted starting material. Use of

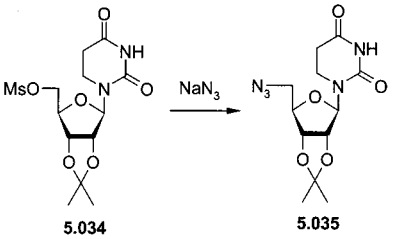


2 equiv of tosyl chloride exclusively yielded **5.029**. All possible azido compounds, **5.031**−**5.033**, have been

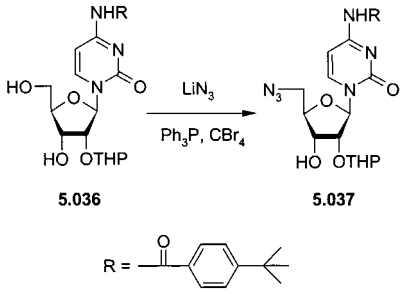


5.028 X = OTs, R = OH
5.029 X = R = OTs
5.030 X = OH, R = OTs
5.031 X = N_3, R = OH
5.032 X = R = N_3
5.033 X = OH, R = N_3

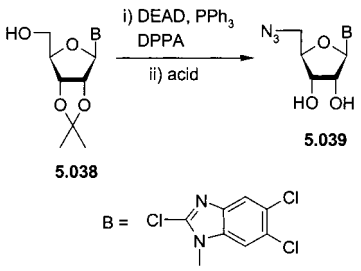
synthesized from **5.028**−**5.030**, respectively.[259] The 5,6-dihydrouridine mesylate **5.034** on treatment with NaN_3 produced the corresponding azidonucleoside **5.035**.[260]



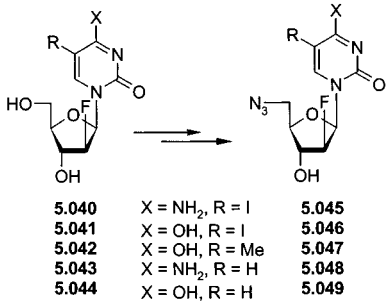
5′-Amino RNA oligomers may be readily conjugated to a variety of commercially available amine reactive fluorescent dyes. It was, therefore, necessary to synthesize partially protected azidonucleoside **5.037**, which would be converted to the corresponding amino derivative. 2′-Hydroxy- and N-4-protected cytidine **5.036** on treatment with LiN_3 in the presence of Ph_3P-CBr_4 produced the desired azido derivative **5.037**.[261]



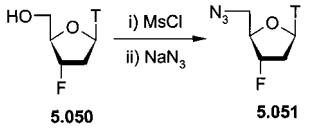
A 5′-azido-5′-deoxy 2,5,6-trichlorobenzimidazole *ribo*-nucleoside **5.039** has been synthesized by treating the 2′,3′-O-protected nucleoside **5.038** with the DEAD−Ph_3P−DPPA combination followed by deprotection.[262]



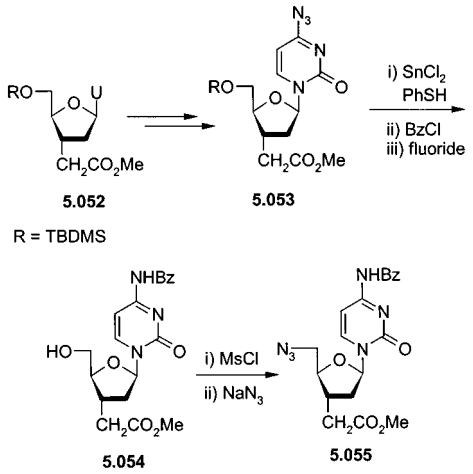
To determine if 5′-amination reduces or abolishes the antiviral activity of 2′-fluoro *arabino*-derivatives **5.040**−**5.044**, these compounds were converted to the azido intermediates **5.045**−**5.049**, respectively, via



tosylation and azidation.[263] Mesylation of **5.050**, followed by nucleophilic displacement with NaN_3, afforded 3′-fluoro-5′-azido-3′,5′-dideoxythymidine **5.051**.[264]

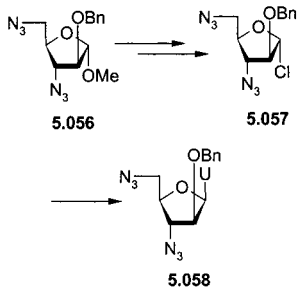


It was necessary to develop a methodology for the synthesis of monomeric blocks such as **5.054** for the construction of amide-linked dimers or oligomers containing deoxycytidine, Therefore, 5′-O-protected 3′-carbomethoxymethyl-2′,3′-dideoxyuridine **5.052** was converted to the 4-azido compound **5.053**. Reduction of **5.053**, followed by benzoylation and desilylation, afforded **5.054**. Mesylation of **5.054**, followed by the displacement of the mesylate by azide, provided the required building block **5.055**.[265]

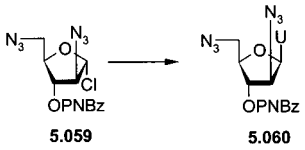


5.1.2. From Carbohydrates

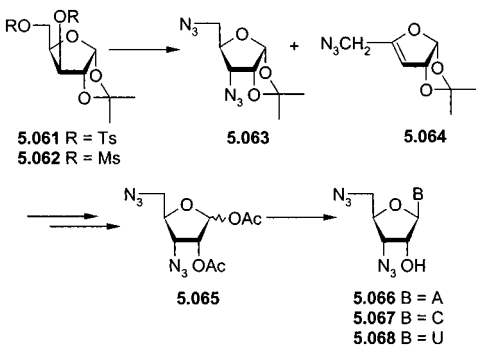
The diazidochlorosugar **5.057** obtained from the methyl glycoside **5.056** provided 2′-*O*-benzyl-3′,5′-diazido-3′,5′-dideoxy *arabino*-derivative **5.058** in poor



yield. The 2′,5′-diazidochlorosugar **5.059** on coupling with uracil afforded β-anomer **5.060** as the major product.[266] The 3′,5′-diazidoribose **5.063** can be ob-

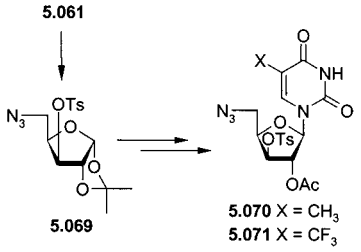


tained in moderate yield by treating the ditosylated or the dimesylated xylose derivative **5.061** or **5.062** with LiN_3. The olefinic compound **5.064** is also formed in the reaction mixture. Acetolysis of **5.063** provided the diacetates **5.065**, which on coupling with

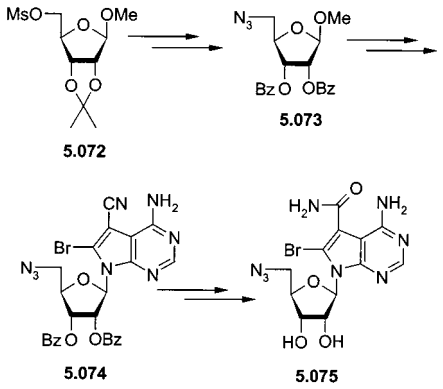


appropriate nucleobases, followed by deprotection, afforded the adenine, the cytosine, and the uracil

derivatives **5.066**, **5.067**, and **5.068**, respectively.[267] The monoazidosugar **5.069** was synthesized in excellent yield from **5.061**. Pyrimidine derivatives **5.070** and **5.071** have been synthesized from the diacetates obtained from **5.069**.[268]

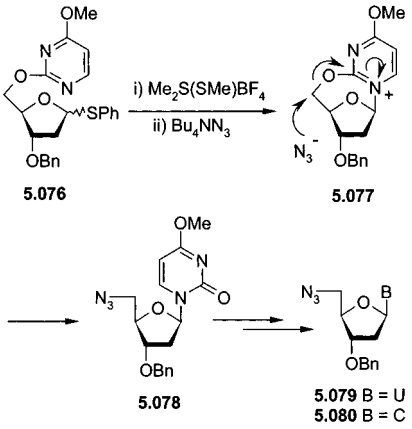


Nonphosphorylatable pyrrolo[2,3-*d*]pyrimidine azidonucleosides have been synthesized as follows. The 5-*O*-mesyl group of **5.072** was displaced by an azido group, and the product was hydrolyzed and benzoylated to provide the dibenzoate **5.073**. Acetolysis of **5.073** followed by coupling of the diacetate with silylated 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine gave protected nucleoside **5.074** as the single product, which on deprotection afforded **5.075**.[269]

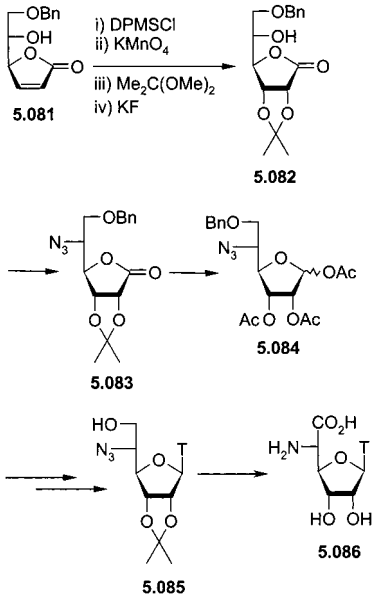


5′-Azido-5′-deoxypyrimidine nucleosides have been synthesized employing intramolecular glycosylation. The substrate for the intramolecular glycosylation, **5.076**, on treatment with Bu_4NN_3 in the presence of dimethyl(methylthio)sulfonium tetrafluoroborate afforded the 5′-azido derivative **5.078**. Formation of the intermediate **5.077** allows the nucleophile to attack the 5′-end to produce **5.078**. Treatment of **5.078**, either with Dowex 50W (H^+) or with NH_3–MeOH, yielded the uracil or the cytosine derivative **5.079** or **5.080**, respectively.[270]

To synthesize Polyoxin J, it was necessary to develop a route to generate the nucleoside moiety deoxypolyoxin C **5.086**. The unsaturated lactone **5.081** was converted to the partially protected alcohol **5.082** in four steps. Treatment of **5.082** with 2-fluoro-1-methyl-pyridinium tosylate and LiN_3 afforded the azidolactone **5.083**. Partial reduction of the lactone followed by acetolysis produced an anomeric mixture of the triacetates **5.084**. The usual coupling of **5.084** with **3.050**, debenzylation, and acetonation produced



the azido alcohol **5.085**, which could be converted to **5.086** via known routes.[271]

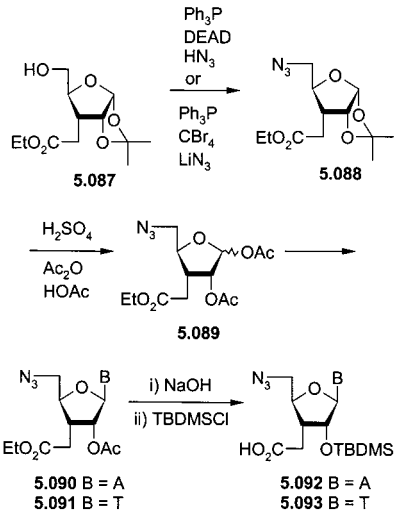


The ethyl ester of 3-(carboxymethyl)-3-deoxy-D-*ribo*-furanose **5.087**, obtained from the 1,2-*O*-isopropylidene-3-ketopentofuranose derivative in multiple steps, was converted to the 5-azido-5-deoxy-3-(carboxymethyl)-D-*ribo*-furanose analogue **5.088**. Acetolysis of **5.088** afforded a mixture of diacetates **5.089**, which were coupled with nucleobases to provide branched-chain nucleosides **5.090** and **5.091**. Ester saponification and protecting group manipulation provided the TBDMS-protected 5′-azido-5′-deoxy derivatives of 3′-(carboxymethyl)-3′-deoxy-*ribo*-nucleosides **5.092** and **5.093**. These compounds are useful precursors for the preparation of amide-linked oligo-*ribo*-nucleosides.[272]

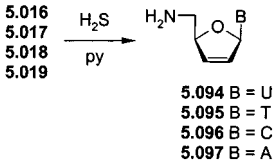
5.2. Reactions

5.2.1. Reduction

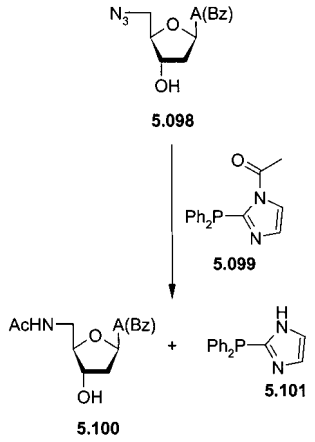
Aminonucleosides **5.094**−**5.097** were prepared in high yields from the corresponding azidonucleosides



5.016−**5.019** by selective reduction with H_2S in pyridine.[273]

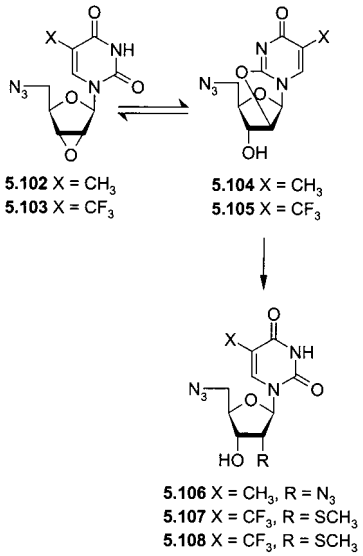


To develop a "traceless" Staudinger reaction (nucleophilic attack of a phosphine on an azide), a phosphine reagent has been designed for the selective formation of amides from azides. Thus, imidazole phosphine **5.099** reacted with **5.098** in wet THF to produce the *N*-acetylated product **5.100** in high yield and **5.101** as the side product. This preliminary study may yield new methods for peptide couplings.[274]

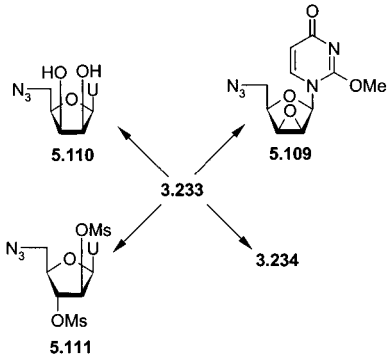


5.2.2. Addition of Nucleophiles

1-(2-*O*-Acetyl-5-azido-5-deoxy-3-*O*-tosyl-*β*-D-*xylo*-furanosyl)thymine **5.070**, on treatment with a mixture of NaN_3 and NH_4Cl, produced 1-(2,5-diazido-2,5-dideoxy-*β*-D-*ribo*-furanosyl)thymine **5.106** via the intermediates epoxide **5.102** and 2,2′-*O*-anhydro derivative **5.104**. Similarly, the treatment of **5.070** or **5.071** with NaSMe produced **5.107** or **5.108**, respectively. These reactions also proceed via the formation of the epoxides **5.102** and **5.103**, which are in equilibrium with the more favored **5.104** and **5.105**, respectively. [268]

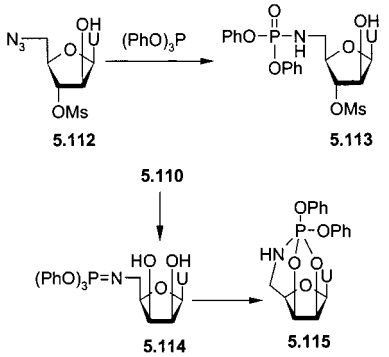


5′-Azido-5′-deoxy-3′-*O*-mesyl-2,2′-*O*-anhydrouridine **3.233** has been used as an intermediate for the synthesis of various 5′-azido-5′-deoxynucleosides. Thus, treatment of **3.233** with aqueous NaOH afforded **3.234**, whereas reaction with NaOMe produced 1-(5-azido-5-deoxy-2,3-epoxy-*β*-D-*lyxo*-furanosyl)-2-*O*-methyluracil **5.109**. The *lyxo*-derivative **5.110** was obtained by heating **3.233** under reflux in water or in dilute HCl. The ring opening of **3.233** with acidic ion exchanger followed by mesylation yielded the dimesyl *arabino*-derivative **5.111**.[197]

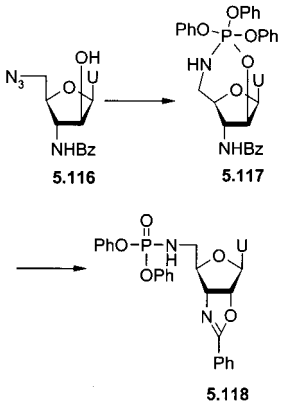


5.2.3. Phosphorylation

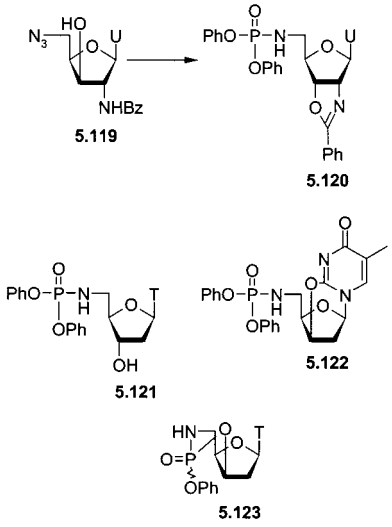
While the reaction of **5.112** with $(PhO)_3P$ produced the expected product **5.113**, the reaction of *lyxo*-derivative **5.110** under similar conditions afforded the tricyclic product **5.115**. The reaction is believed



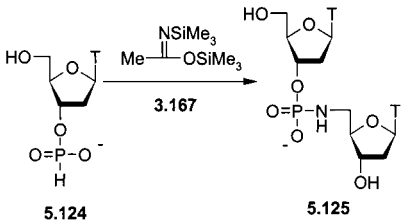
to proceed via initially formed phosphite imine **5.114**. It is well-known that the rate of solvolysis of esters of phosphoric acid is profoundly enhanced by a neighboring nucleophilic group. Therefore, when the benzamido derivative **5.116** was reacted with $(PhO)_3P$, oxazoline **5.118** was formed. The reaction proceeded



through a presumed intermediate, **5.117**, which underwent an intramolecular nucleophilic attack at the C-2′ site. Similarly, the regioisomer **5.119** afforded **5.120**.[275] The reactions of $(PhO)_3P$ with azidonucleosides continued to generate interest, which led to the synthesis of compounds **5.121**−**5.123**.[244]

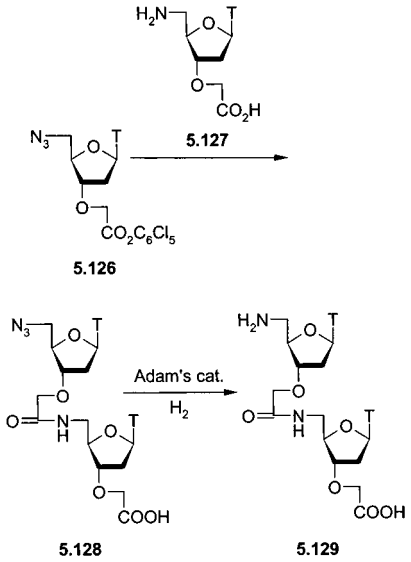


Phosphoramidates, which can be obtained with particular ease by condensing azides with silyl phosphites, are of interest as analogues of biologically important phosphates. Equimolar amounts of 5′-azido-5′-deoxythymidine **3.167** and thymidine-3′-phosphite **5.124**, in the presence of bis(trimethylsilyl)-acetamide. produced dinucleotide **5.125** in high yield.[276]



5.2.4. Dimerization

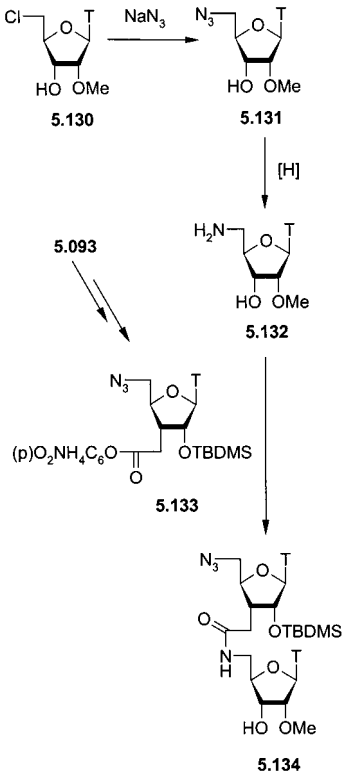
The pentachlorophenyl ester of 5′-azido-3′-*O*-carboxymethyl-5′-deoxythymidine **5.126** was coupled with aminocarboxymethylthymidine **5.127** to obtain the amide-linked dimer **5.128**. Reduction of **5.128** provided **5.129**, which was polymerized to give poly(5′-amino-3′-*O*-carboxymethyl-5′-deoxythymidine).[277] Several other oxyacetamido analogues having a 5′-azido group as the masked amino function have been synthesized, and their detailed spectral data have been reported.[278]



To synthesize 3′-CH_2CONH-5′-linked nucleoside analogues of small oligonucleotides, 1-(5-amino-5-deoxy-2-*O*-methyl-*β*-D-*ribo*furanosyl)thymine **5.132** has been synthesized from the chloro derivative **5.130** in two steps via azidonucleoside **5.131**. Condensation of **5.132** with the active ester **5.133** obtained from **5.093** provided dimeric **5.134**. Several such small oligomers have been synthesized using similar strategies where the 5′-azido-5′-deoxy function provided masked 5′-amino-5′-deoxy residues for chain extension at the 5′-end.[279]

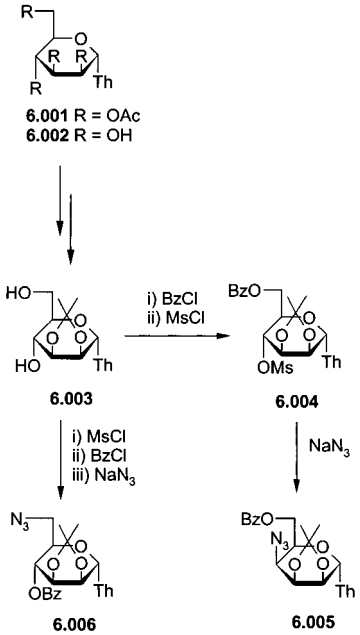
6. Pyranosylazidonucleosides

9-*β*-D-Glucopyranosyladenine, a hexopyranosyl nucleoside, was the first nucleoside ever synthesized.[280] Since then, a number of purine and pyrimidine hexopyranosylnucleosides have been prepared. Although a greater level of biological interest has been generated by pentofuranosylnucleosides over the years, a number of naturally occurring and synthetic hexopyranosylnucleosides are also known. For example, 1-(2-deoxy-*β*-D-*arabino*-hexopyranosyl)thymine was recognized many years ago to be an inhibitor of a pyrimidine nucleoside phosphorylase from Ehrlich ascites tumor.[281] 9-*β*-D-Fucopyranosyladenine has been reported to be an inhibitor of the development of leukemia cells L **1210.**[281] More recently, the



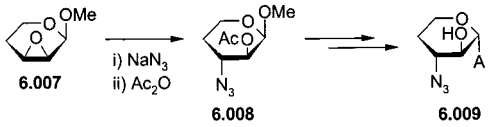
synthesis of new hexopyranosylnucleosides has drawn attention because several hexopyranosylnucleoside analogues have been reported as potential anti-HIV agents.[37−39,281]

To synthesize aminodeoxynucleosides of talose and mannose, it was necessary to synthesize the azido derivatives. The starting material 7-(2,3,4,6-tetra-*O*-acetyl-α-D-*manno*pyranosyl)theophylline **6.001** was obtained by condensing the pentaacetate carbohydrate and the nucleobase. Selective acetonation of **6.002** afforded 2′,3′-*O*-isopropylidene compound **6.003**. Selective benzoylation followed by mesylation of the

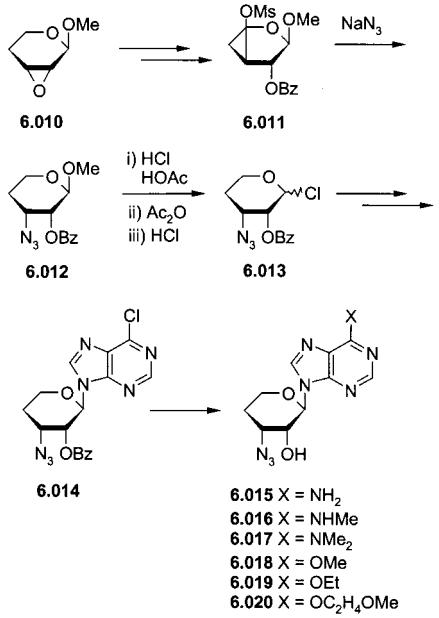


4′-hydroxy group of **6.003** gave **6.004**. Displacement of the mesylate of **6.004** by azide produced the 4′-azido-4′-deoxy derivative **6.005**. In an alternative approach, the diol **6.003** was treated with 1 equiv of mesyl chloride at low temperature followed by benzoylation. The resulting product was reacted with NaN_3 to provide the 6′-azido-6′-deoxy derivative **6.006**.[282]

As part of a program on the development of pyranosylazidonucleosides with chemotherapeutic value, several azidodeoxypentopyranosylnucleosides have been synthesized. Opening of the epoxide **6.007** with NaN_3, followed by protection of the free hydroxyl group, led to pentopyranose **6.008**. Condensation of **6.008** with adenine, followed by deprotection, gave nucleoside **6.009**.[283]

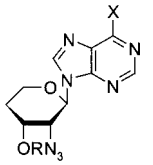


The *erythro*-isomer of **6.009** has also been synthesized. The sugar component **6.012** was prepared from 2,3-*O*-anhydro-4-deoxy-β-DL-*erythro*-pentopyranoside **6.010** (only the D series is depicted here). The mesyl derivative **6.011** was prepared from **6.010** in several steps and was then reacted with NaN_3 to obtain **6.012**. The glycosyl chloride **6.013**, obtained from **6.012** in three steps, was condensed with 6-chloropurine to give nucleoside **6.014**. Treatment of **6.014** with propanolic NH_3 furnished **6.015**.[284]



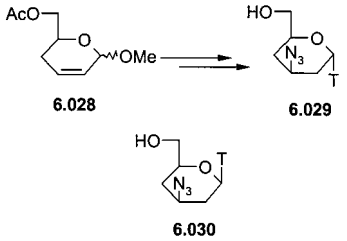
A series of 6-substituted purine 3′-azidodeoxypentopyranoses, **6.015**−**6.020**, were prepared in 75−98% yields by heating **6.014** with the corresponding nucleophiles. Similarly, 6-substituted purine 2′-azidodeoxypentopyranoses **6.022**−**6.027** have been prepared from **6.021**.[285]

The AZT analogues **6.029** and **6.030** have been prepared from the racemic acetate **6.028** by using a



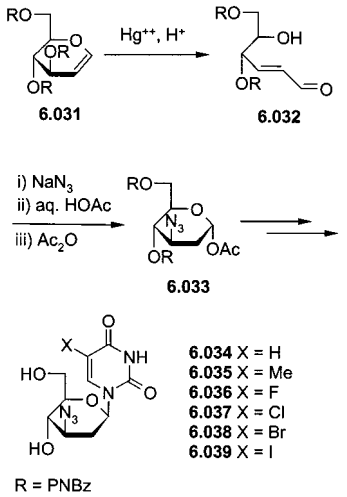
6.021 X = Cl, R = Bz
6.022 X = NH_2, R = H
6.023 X = NHMe, R = H
6.024 X = NMe_2, R = H
6.025 X = OMe, R = H
6.026 X = OEt, R = H
6.027 X = OC_2H_4OMe, R = H

sequence of azidation, acetylation, coupling with **3.050**, and deprotection.[286]



6.028 **6.029** **6.030**

In continuation with the effort of accessing pyranosyl analogues of AZT, α,*β*-unsaturated D-sugar aldehyde **6.032**, prepared from tri-*O*-acetyl-D-glucal **6.031**, was converted into 1-*O*-acetyl-3-azido-2,3-dideoxy-α-D-*arabino*-pyranose derivative **6.033** by reaction with NaN_3 in a mixture of aqueous HOAc. Reactions of **6.033** with silylated pyrimidines followed by deprotection with the NH_3−MeOH system afforded 3′-azido-2′,3′-dideoxy-*β*-D-*arabino*-hexopyranosylnucleosides **6.034**−**6.039**.[287]



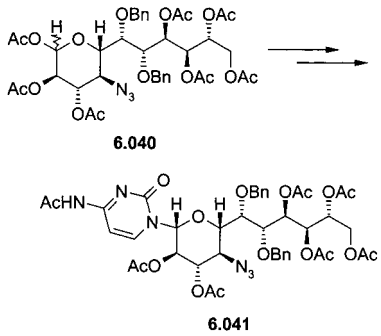
6.031 **6.032** **6.033**

6.034 X = H
6.035 X = Me
6.036 X = F
6.037 X = Cl
6.038 X = Br
6.039 X = I

R = PNBz

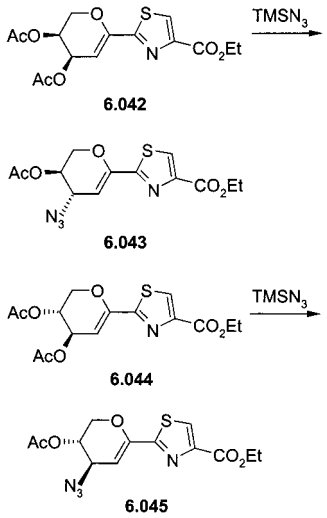
Anthelmintic agent hikizimycin is composed of a cytosine base, kanosamine, and hikosamine, where the cytosine is attached directly to hikosamine. To synthesize the 4-aminoundecosylnucleoside moiety, the peracetylated anomeric mixture **6.040** was condensed with bis(trimethylsilyl)cytosine and the product was acetylated to afford the fully protected nucleoside **6.041**.[288]

Ethyl 2-(3,4-di-*O*-acetyl-2-deoxy-L-*erythro*- and -D-*threo*-pent-1-enopyranosyl)thiazole-4-carboxylates



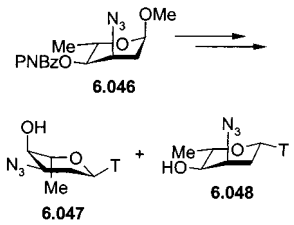
6.040 **6.041**

6.042 and **6.044**, respectively, on reaction with $TMSN_3$ produced L-*threo* **6.043** and D-*threo* **6.045** in the presence of a Lewis acid. The regio- and stereoselective reactions proceeded with the Lewis acid-mediated formation of a carbocation, and the stereochemistry of the incoming azide nucleophile was determined by the neighboring 4′-acetoxy group to generate these less common thiazole *C*-nucleosides.[289]



6.042 **6.043** **6.044** **6.045**

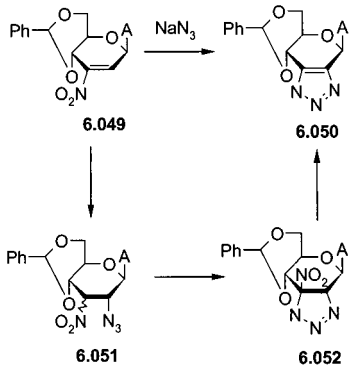
In an attempt to synthesize a new *β*-L-*ribo*-hexopyranosyl analogue of AZT, α-L-*ribo*-hexopyranoside **6.046** was coupled with thymine to afford after deprotection 1-(3-azido-2,3,6-trideoxy-α- and -*β*-L-*ribo*-hexopyranosyl)thymines **6.047** and **6.048**.[290,291]



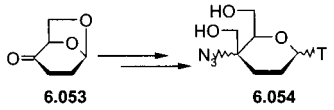
6.046 **6.047** **6.048**

The treatment of the vinylnitro-modified nucleoside **6.049** with NaN_3 gave 2,3-(1,2,3-triazolo) derivative **6.050**. One plausible route for the formation of **6.050** is the initial attack of azide ion to Michael acceptor **6.049** to form **6.051**, which changed to intermediate

6.052 and underwent elimination to produce **6.050**.[292]



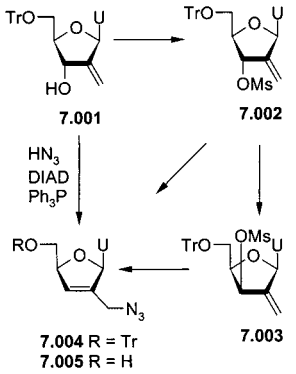
There is a brief paper on the synthesis of 3′- and 4′-C-branched-chain sugar nucleoside analogues such as **6.054** from the ketoanhydro carbohydrate **6.053**.[293]



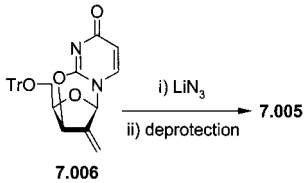
7. Branched-Chain Azidonucleosides

7.1. 2′-*C*- and 3′-*C*-Azidomethyl-2′-olefinic Nucleosides

Reactions of **7.001** or **7.002** with HN_3 in the presence of PPh_3 and DIAD produced exclusively **7.004**. "Up" mesylate **7.003** obtained from **7.002** also afforded **7.004**.[294] This interesting reaction has been

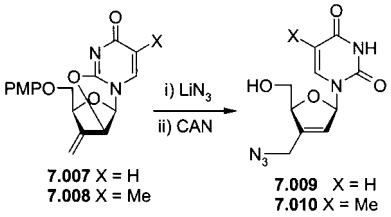


explored further by others. For example, heating 2,3′-*O*-anhydrouridine derivative **7.006** in the presence of excess LiN_3 resulted in the formation of **7.004**, which was deprotected to give **7.005**. The 2,2′-*O*-

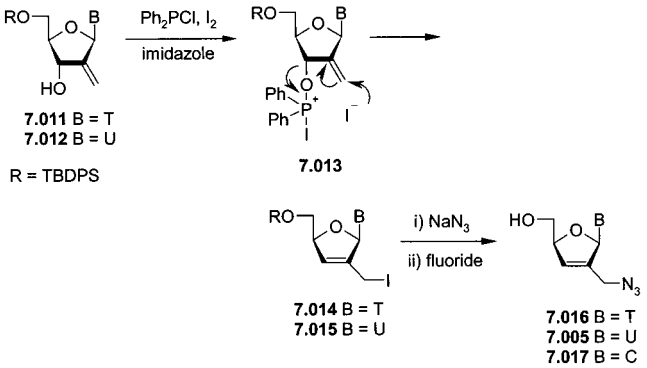


anhydronucleosides **7.007** and **7.008** on reaction with LiN_3, followed by deprotection of the *p*-methoxyphenyl group by CAN, afforded 3′-branched compounds **7.009** and **7.010**, respectively.[98,295]

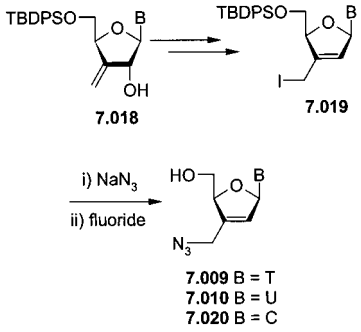
Reactions of **7.011** and **7.012** with 1.2 equiv of freshly distilled Ph_2PCl and 2.1 equiv of imidazole



followed by the addition of 1.2 equiv of I_2 gave the primary allylic iodides **7.014** and **7.015**, respectively,



via a plausible intermediate, **7.013**. Treatment of **7.014** and **7.015** with NaN_3 followed by deprotection afforded **7.016** and **7.005**, respectively. The corresponding cytidine derivative **7.017** was obtained from **7.005**.[296] A similar strategy generated 3′-*C*-azidomethylnucleosides **7.009**, **7.010**, and **7.020** from the corresponding 3′-*C*-methylenenucleosides **7.018** via iodo derivatives **7.019**.[297]

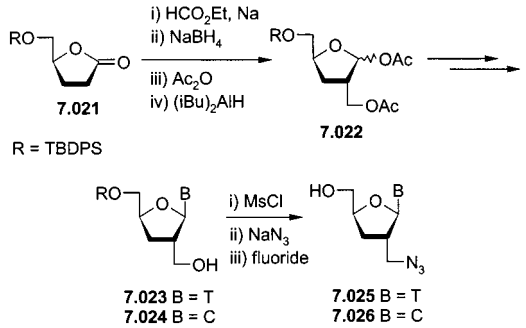


7.2. 2′(3′)-*C*-Azidomethyl-2′(3′)-deoxynucleosides

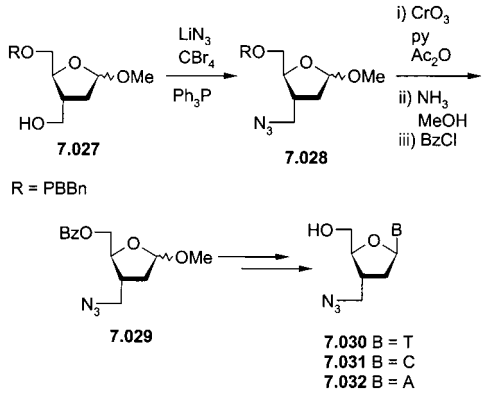
Nucleosides having a branched-chain sugar, such as oxetanocin A[13] or 2′,3′-dideoxy-3′-*C*-hydroxymethylcytidine, has shown activity against HIV. These findings intensified the interest in nucleosides with branched-chain carbohydrate moieties carrying azido groups at the end of the chain.[298]

One such synthesis started from protected (*S*)-4-hydroxymethyl-γ-butyrolactone **7.021**, which was converted to D-*erythro*-pentofuranose diacetates **7.022** in multiple steps. Condensation of **7.022** with silylated nucleobases and selective deprotection afforded 2′-*C*-hydroxymethylnucleosides **7.023** and **7.024**. The free primary hydroxy groups of **7.023** and **7.024** were converted to an azido function, and deprotection afforded 2′-*C*-azidomethyl-2′,3′-dideoxynucleosides **7.025** and **7.026**, respectively.[298]

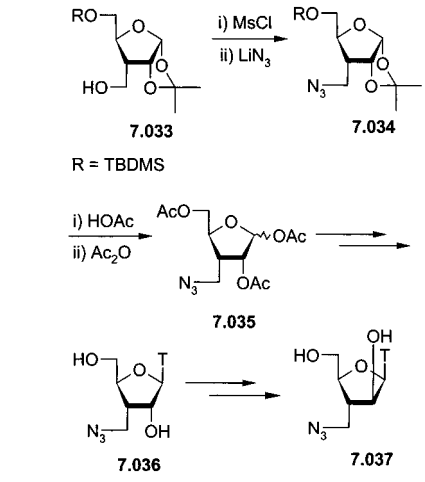
To synthesize 3′-*C*-azidomethyl-2′,3′-dideoxynucleosides, the 3′-*C*-hydroxymethyl furanoside **7.027** was



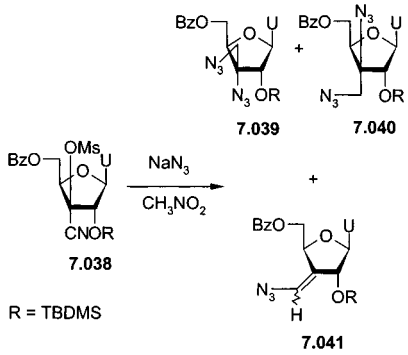
converted to the corresponding 3′-*C*-azidomethyl furanoside **7.028** using $Ph_3P-CBr_4-LiN_3$. Silylated purine and pyrimidine bases were subsequently glycosylated with **7.029** obtained from **7.028** to afford, after deprotection, nucleosides **7.030**−**7.032** along with the corresponding α-anomers.[299]



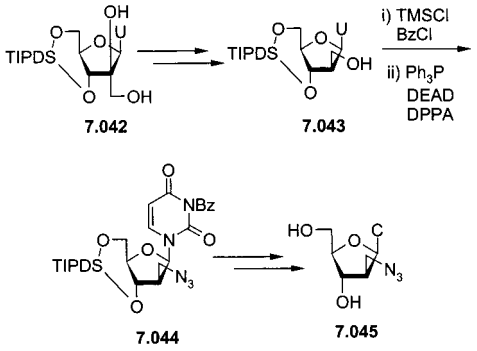
The partially protected 3′-deoxy-3′-*C*-hydroxymethyl-*ribo*-furanose **7.033** was converted to the corresponding azido derivative **7.034**. Deprotection of **7.034** under acidic conditions, followed by acetylation, afforded the triacetates **7.035**. Nucleoside **7.036** was obtained from **7.035** in the usual way. Deoxynucleoside **7.030** or the *arabino*-analogue **7.037** has been obtained from **7.036** using methodologies discussed earlier.[300]



A study was taken up on the usefulness of alkylidene carbenes as intermediates for the synthesis of branched-chain nucleosides functionalized with azido groups. The fully protected 3′-α-mesyloxynitrile of uracil **7.038** was treated with NaN_3 in CH_3NO_2 to afford after laborious chromatographic purifications a mixture of the diazidonucleosides **7.039** and **7.040** (18% and 11% yields, respectively) and vinylazidonucleosides **7.041** (15% yield). The change of solvent from CH_3NO_2 to CH_2Cl_2 afforded **7.041** in 33% yield and **7.039** and **7.040** in 16% and 6% yields, respectively.[301]



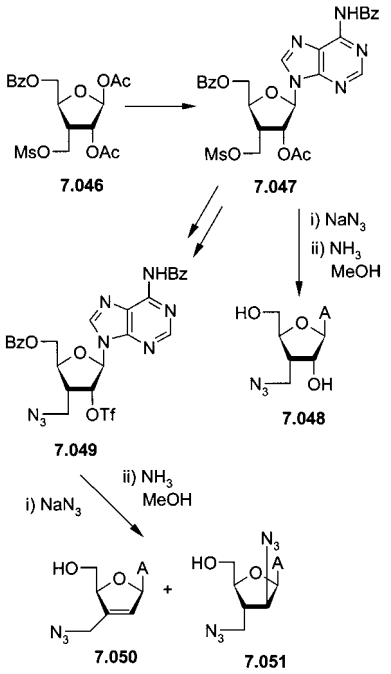
The tertiary alcohol group of the branched nucleoside **7.042** was removed by the radical deoxygenation of the corresponding cyclic thionocarbonate. The reaction occurred regio- and stereoselectively to produce **7.043**. For the introduction of the azido group at the 2′-branched chain, the N-3 position of **7.043** was protected to avoid the formation of an anhydronucleoside. The resulting nucleoside on reaction with DPPA as the azide source afforded **7.044**. After debenzoylation, **7.044** was converted to 2′-*C*-azidomethyl-2′-deoxy-*arabino*-cytosine **7.045**.[302]



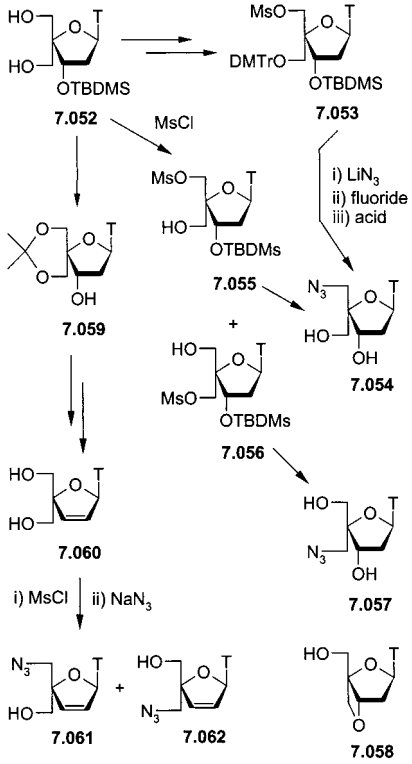
3-C-Mesyloxymethyl-*ribo*-furanose derivative **7.046** was converted to *N*-6-benzoyladenosine homologue **7.047** in the usual way. Treatment of **7.047** with NaN_3, followed by standard deprotection, afforded 3′-*C*-azidomethyl-3′-deoxyadenosine **7.048**. Triflate **7.049** obtained in overall poor yield from **7.047**, on reaction with LiN_3, followed by deprotection afforded unsaturated branched-chain nucleoside **7.050** and the diazidoadenine derivative **7.051**.[303]

7.3. 4′-*C*-Azidomethylnucleosides

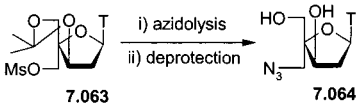
Since the triphosphate of 4′-azidothymidine was shown[250a,304] to be a potent competitive inhibitor of thymidine triphosphate incorporation by HIV RT, 4′-substituted nucleosides became a subject of interest. Diol **7.052** was selectively protected and mesylated



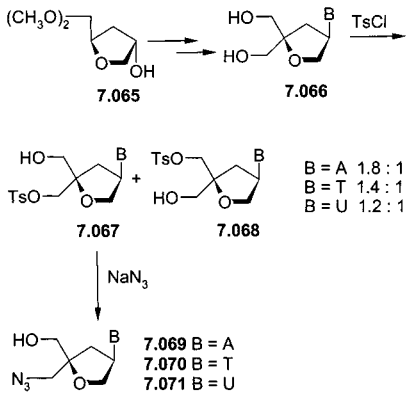
to **7.053**. Treatment of **7.053** with LiN_3, followed by deprotection, afforded azidomethyl derivative **7.054**.



Direct reaction of **7.052** with 1 equiv of MsCl afforded a 1:1 mixture of **7.055** and **7.056**. Treatment of this mixture with LiN_3 gave a mixture of three compounds, which were isolated and identified as **7.054**, **7.057**, and **7.058**. The loss of the silyl protecting group under these conditions is noteworthy. Dehydrodiol **7.060**, obtained from partially protected **7.059**, was converted to azidomethyl compounds **7.061** and **7.062** in a ratio of 1:1.[305] Reactions of isopropylidene derivative **7.063** with azide gave, on deprotection, compound **7.064**, which was the *C*-3′-stereoisomer of **7.057**.[306]

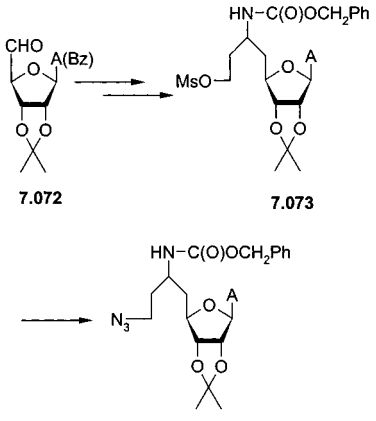


The role of the oxygen at the 3′-position appears to be critical in terms of antiviral activity for some of these compounds. Whether this role could be assumed by an endocyclic oxygen appeared worthy of investigation. For the synthesis of such a modified nucleoside, the rearranged deoxysugar 2(*R*)-(dimethoxymethyl)tetrahydrofuran-4(*S*)-ol **7.065** was coupled with nucleobases. Hydrolysis of the product, followed by a sequential aldol condensation and Cannizaro reaction, gave the desired bishydroxymethyl compounds **7.066**. Selective tosylation of **7.066** afforded a mixture of **7.067** and **7.068**; the ratio of the products is dependent on the size of the nucleobases. Treatment of **7.067** with NaN_3 produced nucleosides **7.069**−**7.071**.[307]

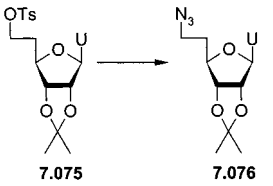


7.4. Other Alkylazido-Modified Nucleosides

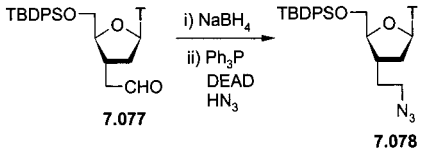
Precursors of sinefungin, a nucleoside antibiotic, has been prepared by chain extension of the blocked adenosine 5′-aldehyde **7.072**. During such a synthesis, the mesylate of **7.073** was displaced with an azide to obtain **7.074**.[308]



A 6′-azido-6′-deoxyhomouridine derivative has been synthesized for generating nitrogen radicals with a 1,5-relationship to H-3′ necessary for the biomimetic modeling of the abstraction of H-3′ by *ribo*-nucleotide reductase. Tosylated homouridine **7.075**, on treatment with NaN_3, afforded the 6′-azido derivative **7.076**.[309]



To synthesize 3′-C-branched thymidine for coupling with near-infrared oxazine fluorescent dye, 3′-*C*-azidoethylthymidine **7.078** has been prepared from the aldehyde **7.077** through reduction and azidation.[310]



8. Biological Properties

2′-Azido-2′-deoxynucleosides. Compound **2.022** possesses cytotoxic and antiviral properties comparable to those of *arabino*-furanosyladenine.[74] Nucleoside **2.061** did not significantly inhibit the growth of murine leukemic P 388 cells in culture, although its triphosphate was shown to be a potent and selective inhibitor of cellular pol α.[83] Compound **2.127** inhibited HBV replication at concentrations ranging between 2.2 and 5.0 μM.[97] Oxetane nucleoside **2.138** showed significant antiviral activity against HIV (RF strain) in vitro.[100] Didehydronucleoside **2.149** showed moderate inhibitory activity against HIV-1 and HIV-2 in MT-4 cells.[101]

3′-Azido-3′-deoxynucleosides. **1.001**, as a triphosphate, inhibits the reverse transcriptase of HTLV-III/LAV. It blocked the expression of the p24 *gag* protein of HTLV-III/LAV in H9 cells following exposure to virus and also completely blocked viral replication as assessed by reverse transcriptase production in normal human peripheral blood mononuclear cells exposed to HTLV-III. Finally, at concentrations of **1.001** that block the in vitro infectively and cytopathic effect of HTLV-IIIB, the in vitro immune functions of normal T cells remain basically intact.[1] Since the publication of this result, innumerable papers have been published on the biological properties of **1.001**, and the compound today is one of the most important components of the drugs used for treating AIDS patients.[58,311] A detailed discussion on the mode of action of AZT and the possible reasons for its toxicity is now available.[311] It should, however, be pointed out that at least one group of scientists has questioned the usefulness of AZT as an anti-AIDS drug and has in fact proposed[312] that "...AZT causes immunodeficiency, lymphoma, muscle atrophy and dementia".

Compound **3.067** was significantly active against HSV-1 (IC_{50} = 2 μg/mL) with low toxicity.[136] Base-modified nucleosides **3.105**−**3.114**[149,150] were tested against HIV-1 and were found to have significant antiviral activity. There seems to be no clear relationship between the antiviral activity and either the electron-withdrawing or the electron-donating capacity of the substituents at the 5-position of the nucleoside analogues.[149] The biochemical pharmacology of the lower homologue of **1.001**, 3′-azido-2′,3′-dideoxyuridine **3.106**, has been discussed in detail.[311] The 4-thio derivative **3.115** manifested modest anti-HIV activity in ATH8 cells. When **3.115** and **1.001** were compared for their inhibitory effects on the cytopathogenicity of HIV in ATH8 cells, **3.115** proved to be significantly less potent in protecting this culture against virus.[150,235] 5-Benzyloxymethylnucleoside **3.119** has cytotoxic activity in vitro. It inhibits the thymidine incorporation into the DNA of CaOV cells.[152] Another 5-modified nucleoside, **3.127**, was tested using HIV-1 (Kenya) infected human MOLT4 cells and was found to be active with ED_{50} values of 5 μg/mL (AZT anti HIV-1 with an ED_{50} value of 0.02 μg/mL).[158] S-1-alkylated 2-thiouracil derivatives **3.132** and **3.134** showed activity against HIV-1, but this activity is most likely due to a small impurity of **1.001**.[161] Nucleoside conjugates **3.141**−**3.143** displayed anti-HIV activity, but they had no effect on the replication of the HIV-2 or HIV-1 strain with the Y181C mutation. These compounds interact preferentially with the hydrophobic pocket of the RT.[165] Purine derivative **3.158** is active against both HIV-1 and HIV-2 in vitro,[313,314] and **3.159** inhibited the replication of HIV in vitro.[315,316] 5′-Aminonucleoside **3.180** is far (2500-fold) less active than **1.001**.[177] Hexofuranosylnucleoside **3.207** is slightly active against HSV-1, HSV-2, and VV.[183] Carbocyclic nucleoside **3.328** showed modest activity against HSV-1 in Vero cells.[217] Compound **3.338** was tested for antiviral activity on HIV (RF strain) infected MT4 cells and showed weak activity.[221] The 5′-triphosphates of **3.349** and **3.352** were evaluated directly as RT inhibitors. The results showed that inhibition of RT occurred only with the triphosphate of **3.349**. This inhibition was equipotent to and kinetically indistinguishable from that produced by the triphosphate of **1.001**.[223] **3.360** is ∼10000 times less active against HIV than **1.001**.[225] Nucleoside **3.367** inhibited HBV replication at concentrations ranging between 2.2 and 5.0 μM.[97] Base-modified nucleosides **3.405** demonstrated significant anti-HIV-1 activity, whereas **3.406**, **3.407**, **3.408**, and **3.410** showed moderate antiviral activity.[149] Substitution at C-5 with an alkyl function greater than C-2 including bromovinyl substitution reduced the antiviral potency significantly.[240] Cytosine derivatives **3.415** and **3.416** showed very low anti-HIV activity. 4-Thionucleoside **3.414**, however, showed a noticeable anti-HIV activity on CEM-C113 cell lines.[238] The 2,5′-*O*-anhydronucleosides **3.422**−**3.425** demonstrated significant anti-HIV activity, but they were somewhat less active than **1.001**. The cytotoxicity of **3.422** is less than that of **1.001**. 2-Amino-modified AZT analogue **3.426** also demonstrated anti-HIV activity. Experiments suggested that the basis of the antiviral activity of **3.422**−**3.425** did not depend on their conversion to **1.001**, **3.106**, **3.108**, or **3.109**, respectively, but the anhydro compounds appear to be active per se. Nucleoside **3.422** was also found to be most active against Rauscher−Murine leukemia virus in cell culture.[242] Interestingly, **3.429** exhibited antiviral activity similar to that of **1.001**, and there

is no significant difference of cytotoxicities of **1.001** and **3.429**. On the other hand, **3.429** is 55.5 times more lipophilic than **1.001**. It is important to note that **3.429** remains unchanged during all stability assays.[243] Metal complexes of AZT, such as **3.431** (R = Me and Ph) and **3.435** showed anti-HIV activity very similar to that of **1.001**. Metal complex **3.431** (R = Me) also exhibited antiinflammatory activity.[244]

4′-Azidonucleosides. All of the 4′-azido-2′-deoxy-β-D-nucleosides were potent inhibitors of HIV. Modifications at the 2′- or 3′-position of the 4′-substituted 2′-deoxynucleosides tended to diminish activity. Further evaluation of 4′-azidothymidine **4.004** (B = T, R = H) in H9, PBL, and MT-2 cells infected with HIV demonstrated an inhibitory profile similar to that of **1.001**. However, **4.004** (B = T, R = H) retained its activity against HIV mutants, which were resistant to **1.001**.[250] Interestingly, despite the presence of a 3′-hydroxyl group, **4.004** (B = T, R = H) too can act as a chain terminator besides being a potent RT inhibitor. The presence of an azido group at the 4′-position induces a strong preference for an unusual N-type conformation of the furanose ring, and this may be a factor in the mechanism of DNA chain termination.[250b]

5′-Azido-5′-deoxynucleosides. Trichlorobenzimidazole derivative **5.039** had significant activity against human cytomegalovirus in plaque but had little activity against HSV-1.[262] Diazido-*ribo*-nucleosides **5.066**−**5.068** showed low antibacterial activity against 19 bacterium species.[267]

Pyranosylnucleosides. The antiviral activity on vaccinia and Sindbis viruses show that **6.009** is only active on the VV.[283] Nucleoside **6.048** inhibited the HIV replication more effectively than AZT and exerted no cytotoxic effect on the cells.[290]

Branched-Chain Azidonucleosides. 4′-Azidomethylnucleoside **7.057** showed low anti-HIV activity.[305] Azidomethylnucleosides **7.069**−**7.071** exhibited low in vitro inhibitory activity. It is not clear whether the low activity is due to the difficulty associated with intracellular conversion to their triphosphates or to the weak competitive inhibition of the HIV RT by the triphosphate or both.[307]

9. Concluding Remarks

The discovery of the anti-HIV activity of one single molecule, namely, AZT, has catalyzed the proliferation of research in the area of azidonucleosides. It is clear from the impressive number of publications that the attempted search for a better therapeutic agent than AZT triggered the synthesis of an array of modified nucleosides carrying azido groups at various positions of their carbohydrate moieties. Initial problems of using only a few naturally occurring nucleosides as starting materials and their prohibitive costs have been circumvented by using modified carbohydrates as synthons. However, the absence of any rigorously defined structure−activity relationships between the positions of azido groups in azidonucleosides and their biological properties has led to the random incorporation of an azido function at every conceivable site of the carbohydrate moiety of nucleosides. The approach resulted in the discovery of 4′-azidothymidine **4.004** (B = T, R = H), which demonstrated an inhibitory profile similar to that of **1.001**. The more significant point is that **4.004** retained its activity against HIV mutants which were resistant to **1.001**.[250] A pyranosyl nucleoside, **6.048**, structurally unrelated to AZT, inhibited the HIV replication more effectively than AZT and exerted no cytotoxic effect on the cells.[290] More recently, the synthesis of a prodrug, **3.429**, has been reported, which exhibited antiviral activity similar to that of **1.001** but was much more lipophilic than the latter.[243] One important conclusion to be drawn from the examples cited above is that the discovery of a new biologically active azidonucleoside is often a discontinuous jump in an otherwise monotonic series of analogues and the new nucleoside is hard to design. The unresolved problems associated with the severe toxicity of AZT[311] will, nevertheless, continue to drive research in the area of the synthesis of new azidonucleosides.

10. Abbreviations

Ac	acetyl
AIBN	2,2-azobisisobutyronitrile
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	*p*-methoxybenzyl
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cb	benzyloxycarbonyl
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.5.0]undec-5-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMAP	dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMTr	dimethoxytrityl
DPC	diphenyl carbonate
DPMS	diphenylmethylsilyl
DPPA	diphenylphosphoryl azide
DTT	dithiothreitol
ee	enantiomeric excess
Et	ethyl
HIV	human immunodeficiency virus
HBV	hepatitis B virus
HMPA	hexamethylphosphoric triamide
HMPT	hexamethylphosphorous triamide
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus
LAH	lithium aluminum hydride
LAV	lymphadenopathy-associated virus
mCPBA	*m*-chloroperbenzoic acid
Me	methyl
MMTr	monomethoxytrityl
Ms	methanesulfonyl (mesyl)
NBS	*N*-bromosuccinimide
PBBn	*p*-bromobenzyl
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Piv	pivaloyl
PMP	*p*-methoxyphenyl
PNBz	*p*-nitrobenzoyl
Py	pyridine

RT	reverse transcriptase
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TIPDS	1,1,3,3-tetraisopropyldisiloxane-1,3-diyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THDMS	thexyldimethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl
TMAC	tetramethylammonium chloride
TMSTf	trimethylsilyl trifluoromethanesulfonate
$TMSN_3$	trimethylsilyl azide
tosyl	*p*-toluenesulfonyl (Ts)
TPP	triphenylphosphine
Tr	triphenylmethyl (trityl)
Ts	*p*-toluenesulfonyl (tosyl)
VV	vaccinia virus

11. Acknowledgments

I thank Drs. H. Bazin, A. Foldesi, B. Ravindran, M. S. Shashidhar, and Prof. S. R. Kotha for their help. I am thankful to Dr. Sanjib Bera for providing me with several reading materials and to Dr. N. N. Joshi for correcting the manuscript. I gratefully acknowledge the financial support from the Department of Science and Technology, New Delhi, India. I am indebted to my wife Babli and sons Inca and Harappa for their support during the preparation of the manuscript.

12. References

(1) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.
(2) Fox, J. J. *Pure Appl. Chem*. **1969**, *18*, 223.
(3) Moffatt, J. G. *Nucleoside Analogs: Chemical, Biological, and Medicinal Applications*; NATO Advanced Study Institutes Series, Series A; Plenum Press: New York, 1979; Vol. A26, p 71.
(4) Ueda, T. Synthesis and reaction of pyrimidine nucleosides. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1988; Vol. 1, p 1.
(5) Srivastava, P. C.; Robins, R. K.; Meyer, R. B., Jr. Synthesis and properties of purine nucleosides and nucleotides. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1988; Vol. 1, p 113.
(6) De las Heras, F. G.; Camarasa, M. J.; Fiandor, J. In *Recent Progress in the Chemistry and Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, Germany, 1990; p 321.
(7) Minamoto, K. *Mem. Sch. Eng., Nagoya Univ.* **1997**, *48*, 91; *Chem. Abstr*. **1997**, *127*, 66000.
(8) Czernecki, S.; Valery, J. M. Sugar-modified pyrimidine nucleoside analogs with potential antiviral activity. In *Carbohydrate Drug Design*; Witczak, Z. J., Nieforth, K. A., Eds.; Dekker: New York, 1997; p 495.
(9) Jung, M. E.; Nichols, C. J.; Kretschik, O.; Xu, Y. *Nucleosides Nucleotides* **1999**, *18*, 541.
(10) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700.
(11) Antonakis, K. *Adv. Carbohydr. Chem. Biochem*. **1984**, *42*, 227.
(12) Sterzycki, R. Z.; Martin, J. C.; Wittman, M.; Brankovan, V.; Yang, H.; Hitchcock, M. J.; Mansuri, M. M. *Nucleosides Nucleotides* **1991**, *10*, 291.
(13) Huryn, D. M.; Okabe, M. *Chem. Rev*. **1992**, *92*, 1745.
(14) Pfleiderer, W. Syntheses and reactions of bicyclic heterocyclic nucleosides and nucleotides. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum: New York, 1994; Vol. 3, p 145.
(15) Shaw, G. The synthesis and chemistry of imidazole and benzimidazole nucleosides and nucleotides. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum: New York, 1994; Vol. 3, p 263.
(16) Wnuk, S. F. *Tetrahedron* **1993**, *49*, 9877.
(17) Robins, M. J.; Wnuk, S. F. *Phosphorus, Sulfur Silicon Relat. Elem*. **1994**, *95* and *96*, 71.
(18) Yokoyama, M. *Synthesis* **2000**, 1637.
(19) Zemlicka, J. *Nucleosides Nucleotides* **1997**, *16*, 1003.
(20) Knutsen, Lars J. S. *Nucleosides Nucleotides* **1992**, *11*, 961.
(21) Watanabe, K. A. The chemistry of C-nucleosides. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum: New York, 1994; Vol. 3, p 421.
(22) Chaudhuri, N. C.; Ren, R. X. F.; Kool, E. T. *Synlett* **1997**, 341.
(23) Shaban, M. A. E.; Nasr, A. Z. *Adv. Heterocycl. Chem*. **1997**, *68*, 223.
(24) Sheban, M. A. E. *Adv. Heterocycl. Chem*. **1998**, *70*, 163.
(25) Pan, S.; Amankulor, N. M.; Zhao, K. *Tetrahedron* **1998**, *54*, 6587.
(26) Chu, C. K.; Cutler, S. J. *J. Heterocycl. Chem*. **1986**, *23*, 289.
(27) El Ashry, E. S. H.; El Kilany, Y. *Adv. Heterocycl. Chem*. **1997**, *68*, 1.
(28) El Ashry, E. S. H.; El Kilany, Y. *Adv. Heterocycl. Chem*. **1997**, *67*, 391.
(29) El Ashry, E. S. H.; El Kilany, Y. *Adv. Heterocycl. Chem*. **1998**, *69*, 129.
(30) Gao, H.; Mitra, A. K. *Synthesis* **2000**, 329.
(31) Jorgensen, P. N.; Wengel, J. *Stud. Nat. Prod. Chem*. **1997**, *19* (Structure and Chemistry (Part E)), 511.
(32) Beach, J. W. Carbohydrate templates for the synthesis of 3′-heteronucleosides. In *Carbohydrate Drug Design*; Witczak, Z. J., Nieforth, K. A., Eds.; Dekker: New York, 1997; p 523.
(33) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 517.
(34) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611.
(35) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.
(36) Zhu, X.-F. *Nucleosides, Nucleotides Nucleic Acids* **2000**, *19*, 651.
(37) Herdewijn, P.; Van Aerschot, A.; Balzarini, J.; De Clercq, E. *Nucleosides Nucleotides* **1991**, *10*, 119.
(38) Herdewijn, P. *Spec. Publ.—R. Soc. Chem*. **1997**, *198* (Anti-Infectives), 316.
(39) Herdewijn, P. Anhydrohexitols as conformationally constrained furanose mimics, design of an RNA-receptor. In *Carbohydrate Mimics*; Chapleur, Y., Ed.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998; p 553.
(40) Knapp, S. *Chem. Rev*. **1995**, *95*, 1859.
(41) Zhang, D.; Miller, M. J. *Curr. Pharm. Des*. **1999**, *5*, 73.
(42) Yokoyama, M.; Momotake, A. *Synthesis* **1999**, 1541.
(43) Soloway, A. H.; Zhuo, J.-C.; Rong, F.-G.; Lunato, A. J.; Ives, D. H.; Barth, R. F.; Anisuzzaman, A. K. M.; Barth, C. D.; Barnum, B. A. *J. Organomet. Chem*. **1999**, *581*, 150.
(44) Lesnikowski, Z. J.; Shi, J.; Schinazi, R. F. *J. Organomet. Chem*. **1999**, *581*, 156.
(45) Wang, P.; Hong, J. H.; Cooperwood, J. S.; Chu, C. K. *Antiviral Res*. **1998**, *40*, 19.
(46) Graciet, J.-C. G.; Schinazi, R. F. *Adv. Antiviral Drug Des*. **1999**, *3*, 1.
(47) Dueholm, K. L.; Pedersen, E. B. *Synthesis* **1992**, 1.
(48) Converso, A.; Siciliano, C.; Sindona, G. *Targets Heterocycl. Syst*. **1998**, *2*, 17.
(49) Lamberth, C. *Org. Prep. Proced. Int*. **1999**, *31*, 379.
(50) Nasonov, A. F.; Korshunova, G. A. *Russ. Chem. Rev*. **1999**, *68*, 483.
(51) Chatgilialoglu, C. *Farmaco* **1999**, *54*, 321.
(52) Walczak, K. *Pol. J. Chem*. **1999**, *73*, 1613.
(53) Herdewijn, P.; Van Aerschot, A.; Kerremans, L. *Nucleosides Nucleotides* **1989**, *8*, 65.
(54) Pandiewicz, Krzysztof W.; Watanabe, Kyoichi A. *J. Fluorine Chem*. **1993**, *64*, 15.
(55) Lamberth, Clemens. *Recent Res. Dev. Synth. Org. Chem*. **1998**, *1*, 1.
(56) Pankiewicz, Krzysztof. *Carbohydr. Res*. **2000**, *327*, 87.
(57) Ermolinsky, B. S.; Mikhailov, S. N. Russ. *J. Bioorg. Chem*. **2000**, *26*, 429.
(58) Balzarini, J. *Pharm. World Sci*. **1994**, *16*, 113.
(59) Sakthivel, K.; Kumar, R. Krishna; Pathak, T. *Tetrahedron* **1993**, *49*, 4365.
(60) Sakthivel, K.; Bera, S.; Pathak, T. *Tetrahedron* **1993**, *49*, 10387.
(61) Sakthivel, K.; Pathak, T.; Suresh, C. G. *Tetrahedron* **1994**, *50*, 13251.
(62) Bera, S.; Pathak, T.; Langley, G. J. *Tetrahedron* **1995**, *51*, 1459.
(63) Sakthivel, K.; Pathak, T. *Tetrahedron* **1996**, *52*, 4877.
(64) Bera, S.; Pathak, T. *Tetrahedron* **1999**, *55*, 13051.
(65) Brown, D. M.; Todd, A. *J. Chem. Soc*. **1958**, 4242.
(66) Horwitz, J. P.; Tomson, A. J.; Urbanski, J. A.; Chua, J. *J. Org. Chem*. **1962**, *27*, 3045.
(67) Ranganathan, R. *Tetrahedron Lett*. **1977**, 1291.
(68) Robins, M. J.; Hawrelak, S. D.; Hernandez, A. E.; Wnuk, S. F. *Nucleosides Nucleotides* **1992**, *11*, 821.
(69) Butke, G.; Quiggle, K.; Chladek, S. *J. Carbohydr., Nucleosides, Nucleotides* **1980**, *7*, 63.
(70) Fukukawa, K.; Uedao, T.; Hirano, T. *Chem. Pharm. Bull*. **1983**, *31*, 1582.
(71) Knotz, H.; Zbiral, E. *Liebigs Ann. Chem*. **1986**, 1736.
(72) Wu, J. C.; Pathak, T.; Tong, W.; Vial, J. M.; Remaud, G.; Chattopadhyaya, J. *Tetrahedron* **1988**, *44*, 6705.
(73) Kawana, M.; Kuzuhara, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 469.
(74) Ranganathan, R.; Larwood, D. *Tetrahedron Lett*. **1978**, 4341.

(75) Sato, A.; Imai, R.; Nakamizo, N.; Hirata, T. *Chem. Pharm. Bull.* **1979**, *27*, 821.
(76) Matsuda, A.; Yasuoka, J.; Ueda, T. *Chem. Pharm. Bull.* **1989**, *37*, 1659.
(77) Matsuda, A.; Yasuoka, J.; Sasaki, T.; Ueda, T. *J. Med. Chem.* **1991**, *34*, 999.
(78) Abdel-Megied, A. E. S.; Pedersen, E. B.; Nielsen, Carsten M. *Synthesis* **1991**, 313.
(79) Ikehara, M.; Maruyama, T.; Miki, H.; Takatsuka, Y. *Chem. Pharm. Bull.* **1977**, *25*, 754.
(80) Ikehara, M.; Maruyama, T. *Chem. Pharm. Bull.* **1978**, *26*, 240.
(81) Ikehara, M.; Takatsuka, Y. *Chem. Pharm. Bull.* **1978**, *26*, 985.
(82) Robins, M. J.; Zou, R.; Hansske, F.; Wnuk, S. F. *Can. J. Chem.* **1997**, *75*, 762.
(83) Tomikawa, A.; Sato-Kiyotaki, K.; Ohtsuki, C.; Hirai, T.; Yamaguchi, T.; Kawaguchi, T.; Yoshida, S.; Saneyoshi, M. *Nucleosides Nucleotides* **1998**, *17*, 487.
(84) Logue, M. W.; Han, B. H. *J. Org. Chem.* **1980**, *45*, 5000.
(85) Han, B. H.; Logue, M. W. *Proc. N. D. Acad. Sci.* **1980**, *34*, 5.
(86) Warshaw, J. A.; Watanabe, K. A. *J. Med. Chem.* **1990**, *33*, 1663.
(87) Van Aerschot, A.; Everaert, D.; Gosselin, G.; Peeters, O.; Blaton, N.; De Ranter, C.; Imbach, J. L.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *Antiviral Res.* **1990**, *14*, 357.
(88) Robles, R.; Rodriguez, C.; Izquierdo, I.; Plaza, M. T.; Mota, A.; Alvarez de Cienfuegos, L. *Tetrahedron: Asymmetry* **2000**, *11*, 3069.
(89) Mengel, R.; Wiedner, H. In *Nucleic Acid Chemistry*; Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1978; Vol. 2, p 499.
(90) Hummel, Charles F.; Carty, Robert P. *Nucleosides Nucleotides* **1983**, *2*, 249.
(91) Ariza, X.; Garces, J.; Vilarrasa, J. *Tetrahedron Lett.* **1992**, *33*, 4069.
(92) Hobbs, J. B.; Eckstein, F. *J. Org. Chem.* **1977**, *42*, 714.
(93) Bobek, M.; Martin, V. *Tetrahedron Lett.* **1978**, 1919.
(94) Bobek, M. *Carbohydr. Res.* **1979**, *70*, 263.
(95) Sharma, R. A.; Kavai, I.; Hughes, R. G., Jr.; Bobek, M. *J. Med. Chem.* **1984**, *27*, 410.
(96) Mikhailopulo, I. A.; Poopeiko, N. E.; Prikota, T. I.; Sivets, G. G.; Kvasyuk, E. I.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1991**, *34*, 2195.
(97) Gosselin, G.; Boudou, V.; Griffon, J.-F.; Pavia, G.; Pierra, C.; Imbach, J.-L.; Faraj, A.; Sommadossi, J.-P. *Nucleosides Nucleotides* **1998**, *17*, 1731.
(98) Czernecki, S.; Ezzitouni, A. *J. Org. Chem.* **1992**, *57*, 7325.
(99) Jones, J. O.; McElhinney, R. S. *J. Chem. Res., Synop.* **1984**, 146.
(100) Wang, Y.; Fleet, G. W. J.; Wilson, F. X.; Storer, R.; Myers, P. L.; Wallis, C. J.; Doherty, O.; Watkin, D. J.; Vogt, K.; Peach, J. M. *Tetrahedron Lett.* **1991**, *32*, 1675.
(101) Mikhailopulo, I. A.; Zaitseva, G. V.; Vaaks, E. V.; Balzarini, J.; De Clercq, E.; Rosemeyer, H.; Seela, F. *Liebigs Ann. Chem.* **1993**, 513.
(102) Robins, M. J.; Hawrelak, S. D. *Tetrahedron Lett.* **1978**, 3653.
(103) Samano, M. C.; Robins, M. J. *Tetrahedron Lett.* **1991**, *32*, 6293.
(104) Robins, M. J.; Wnuk, S. F.; Hernandez-Thirring, A. E.; Samano, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11341.
(105) Costa, A. M.; Faja, M.; Farras, J.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 1835.
(106) Zehl, A.; Cech, D. *Liebigs Ann./Recl.* **1997**, 595.
(107) Horwitz, J. P.; Chua, J.; Noel, M. *J. Org. Chem.* **1964**, *29*, 2076.
(108) Matsuda, A.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1980**, *45*, 3274.
(109) Colla, L.; Herdewijn, P.; De Clercq, E.; Balzarini, J.; Vanderhaeghe, H. *Eur. J. Med. Chem.—Chim. Ther.* **1985**, *20*, 295.
(110) Yamamoto, I.; Sekine, M.; Hata, T. *J. Chem. Soc., Perkin Trans. 1* **1980**, 306.
(111) Zeidler, J. M.; Kim, M. H.; Watanabe, K. A. *Nucleosides Nucleotides* **1990**, *9*, 629.
(112) Zaitseva, G. V.; Kvasyuk, E. I.; Vaaks, E. V.; Barai, V. N.; Bokut, S. B.; Zinchenko, A. I.; Mikhailopulo, I. A. *Nucleosides Nucleotides* **1994**, *13*, 819.
(113) Mandal, S. B.; Achari, B. *J. Chem. Res., Synop.* **1993**, 326.
(114) Maillard, M.; Faraj, A.; Frappier, F.; Florent, J. C.; Grierson, D. S.; Monneret, C. *Tetrahedron Lett.* **1989**, *30*, 1955.
(115) Matsuda, A.; Satoh, M.; Ueda, T.; Machida, H.; Sasaki, T. *Nucleosides Nucleotides* **1990**, *9*, 587.
(116) Czernecki, S.; Valery, J. M. *Synthesis* **1991**, 239.
(117) Rao, T. S.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1989**, 997.
(118) Joshi, B. V.; Reese, C. B. *Tetrahedron Lett.* **1992**, *33*, 2371.
(119) Kumar, R.; Wang, L.; Wiebe, L. I.; Knaus, E. E. *J. Med. Chem.* **1994**, *37*, 4297.
(120) Dyatkina, N. B.; Azhaev, A. V. *Synthesis* **1984**, 961.
(121) Gurjar, M. K.; Ashok, B.; Rao, A. V. R. *Indian J. Chem.* **1987**, *26B*, 905.
(122) Fleet, G. W. J.; Son, J. C. *Tetrahedron Lett.* **1987**, *28*, 3615.
(123) Gurjar, M. K.; Pawar, S. M.; Rao, A. V. R. *J. Carbohydr. Chem.* **1988**, *7*, 271.
(124) Chu, C. K.; Beach, J. W.; Ullas, G. V.; Kosugi, Y. *Tetrahedron Lett.* **1988**, *29*, 5349.
(125) Wengel, J.; Pedersen, E. B. *Synthesis* **1991**, 451.
(126) Wengel, J.; Lau, J.; Walczak, K.; Pedersen, E. B. *Nucleosides Nucleotides* **1991**, *10*, 405.
(127) Fleet, G. W. J.; Son, J. C.; Derome, A. E. *Tetrahedron* **1988**, *44*, 625.
(128) Sugimura, H.; Osumi, K.; Yamazaki, T.; Yamaya, T. *Tetrahedron Lett.* **1991**, *32*, 1813.
(129) Nakayama, C.; Saneyoshi, M. *Nucleosides Nucleotides* **1982**, *1*, 139.
(130) Meguro, H.; Orui, H.; Fujita, A. Jpn. Kokai Tokkyo Koho JP 01203399, 1989; *Chem. Abstr.* **1990**, *112*, 77872.
(131) Benhaddou, R.; Czernecki, S.; Valery, J. M.; Bellosta, V. *Bull. Soc. Chim. Fr.* **1991**, 108.
(132) Chen, Y.; Bauman, J. G.; Chu, C. K. *Nucleosides Nucleotides* **1992**, *11*, 693.
(133) Hrebanecky, H.; Holy, A. Eur. Patent EP 301908, 1989; *Chem. Abstr.* **1989**, *111*, 78550.
(134) Mustafin, A. G.; Gataullin, R. R.; Abdrakhmanov, I. B.; Spirikhin, L. V.; Tolstikov, G. A. *Russ. Chem. Bull.* **1998**, *47*, 2007.
(135) Wilson, J. D. U.S. Patent 4921950, 1990; *Chem. Abstr.* **1990**, 113, 132719.
(136) Hrebabecky, H.; Holy, A. *Carbohydr. Res.* **1991**, *216*, 179.
(137) Ning, J.; Kong, F. *Carbohydr. Res.* **2000**, *326*, 235.
(138) Jung, M. E.; Gardiner, J. M. *J. Org. Chem.* **1991**, *56*, 2614.
(139) Hager, M. W.; Liotta, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5117.
(140) Gurjar, M. K.; Lalitha, S. V. S.; Sharma, P. A.; Rao, A. V. R. *Tetrahedron Lett.* **1992**, *33*, 7945.
(141) Gurjar, M. K.; Kunwar, A. C.; Reddy, D. V.; Islam, A.; Lalitha, S. V. S.; Jagannadh, B.; Rao, A. V. R. *Tetrahedron* **1993**, *49*, 4373.
(142) Hill, J. A.; Freeman, G. A. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 277.
(143) Aggarwal, S. K.; Shalinsky, D. R.; Agrawal, K. C. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 1055.
(144) Sidorov, G. V.; Myasoedov, N. F.; Yasko, M. V. *J. Labelled Compd. Radiopharm.* **1994**, *34*, 339.
(145) Maillard, M.; Florent, J. C.; Lemaitre, M.; Begassat, F.; Bugnicourt, A.; Ferrieux, C.; Rombi, C.; Pacaud, E.; Thierry, D.; et al. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1469.
(146) Goulaouic, C.; Adams, D. R.; Chiaroni, A.; Riche, C.; Grierson, D. S. *J. Org. Chem.* **1993**, *58*, 3030.
(147) Saha, A. K.; Schairer, W.; Upson, D. A. *Tetrahedron Lett.* **1993**, *34*, 8411.
(148) Doboszewski, B.; Chu, C. K.; Van Halbeek, H. *J. Org. Chem.* **1988**, *53*, 2777.
(149) Lin, T. S.; Guo, Ji Y.; Schinazi, R. F.; Chu, C. K.; Xiang, J. N.; Prusoff, W. H. *J. Med. Chem.* **1988**, *31*, 336.
(150) Palomino, E.; Meltsner, B. R.; Kessel, D.; Horwitz, J. P. *J. Med. Chem.* **1990**, *33*, 258.
(151) Hrebabecky, H.; Holy, A.; De Clercq, E. *Collect. Czech. Chem. Commun.* **1990**, *55*, 1801.
(152) Bakhmedova, A. A.; Yartseva, I. V.; Zhukova, O. S.; Volosyuk, T. P.; Yurkevich, A. M.; Mel'nik, S. Y. *Bioorg. Khim.* **1992**, *18*, 444−448; *Chem. Abstr.* **1992**, *117*, 192247.
(153) Kjaersgaard, U.; Pedersen, E. B.; Nielsen, C.; El-Torgonman, A. M. *Acta Chem. Scand.* **1992**, *46*, 1016.
(154) Abdel-Megied, A. E. S.; Hansen, P.; Pedersen, E. B.; Nielsen, C.; Nielsen, C. M. *Arch. Pharm.* **1993**, *326*, 377.
(155) Abdel-Megied, A. E.; Pedersen, E. B.; Nielsen, C. *Monatsh. Chem.* **1998**, *129*, 99.
(156) El-Torgoman, A. M.; Motawia, M. S.; Kjaersgaard, U.; Pedersen, E. B. *Monatsh. Chem.* **1992**, *123*, 355.
(157) Pan, B. C.; Weng, Z. Y.; Chen, Z. H.; Rowe, E. C.; Chu, S. H. *J. Heterocycl. Chem.* **1990**, *27*, 1569.
(158) Yamaguchi, T.; Saneyoshi, M. *Nucleosides Nucleotides* **1992**, *11*, 373.
(159) El-Emam, A. A.; Pedersen, E. B.; Jacobsen, J. P.; Nielsen, C. *Bull. Soc. Chim. Fr.* **1993**, *130*, 817.
(160) Kasnar, B.; Wise, D. S.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. *Nucleosides Nucleotides* **1994**, *13*, 459.
(161) Zahran, M. A.; Abdel-Megied, A. E.-S.; Abdel-Rahman, A. A.-H.; El-Emam, A.; Pedersen, E. B.; Nielsen, C. *Heterocycles* **1995**, *41*, 2507.
(162) Abdel-Bary, H. M.; Abdel-Rahman, A. A.-H.; Pedersen, E. B.; Nielsen, C. *Monatsh. Chem.* **1995**, *126*, 811.
(163) Larsen, E.; Danel, K.; Vaaben, G. B.; El-Emam, A. A.; Pedersen, E. B.; Nielsen, C. *Acta Chem. Scand.* **1996**, *50*, 417.
(164) Krecmerova, M.; Hrebabecky, H.; Masojidkova, M.; Holy, A. *Collect. Czech. Chem. Commun.* **1996**, *61*, 478.
(165) Pontikis, R.; Dolle, V.; Guillaumel, J.; Dechaux, E.; Note, R.; HungNguyen, C.; Legraverend, M.; Bisagni, E.; Aubertin, A.-M.; Grierson, D. S.; Monneret, C. *J. Med. Chem.* **2000**, *43*, 1927.
(166) El-Barbary, A. A.; Khodair, A. I.; Pedersen, E. B. *Arch. Pharm.* **1994**, *327*, 653.
(167) Jeong, L. S.; Beach, J. W.; Chu, C. K. *J. Heterocycl. Chem.* **1993**, *30*, 1445.
(168) El-Barbary, A. A.; El-Brollosy, N. R.; Pedersen, E. B. *Heterocycles* **1994**, *38*, 2191.
(169) Cao, X.; Pfleiderer, W. *Nucleosides Nucleotides* **1994**, *13*, 773.

(170) Dunkel, M.; Pfleiderer, W. *Nucleosides Nucleotides* **1993**, *12*, 125.
(171) El-Barbary, A. A.; El-Brollosy, R.; Pedersen, E. B.; Nielsen, C. *Sulfur Lett.* **1996**, *20*, 31.
(172) Koizumi, F.; Oritani, T.; Yamashita, K. *Agric. Biol. Chem.* **1990**, *54*, 3093.
(173) Almond, M. R.; Collins, J. L.; Reitter, B. E.; Rideout, J. L.; Freeman, G. A.; St. Clair, M. H. *Tetrahedron Lett.* **1991**, *32*, 5745.
(174) Jeanneret, V.; Gasparini, F.; Pechy, P.; Vogel, P. *Tetrahedron* **1992**, *48*, 10637.
(175) Hiebl, J.; Zbiral, E.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1991**, *34*, 1426.
(176) Urjasz, W.; Celewicz, L.; Golankiewicz, K. *Nucleosides Nucleotides* **1996**, *15*, 1189.
(177) McGuigan, C.; Turner, S.; Mahmood, N.; Hay, A. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2445.
(178) Urjasz, W.; Celewicz, L. *J. Phys. Org. Chem.* **1998**, *11*, 618.
(179) Tanaka, H.; Fukui, M.; Haraguchi, K.; Masaki, M.; Miyasaka, T. *Tetrahedron Lett.* **1989**, *30*, 2567.
(180) Barton, D. H. R.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *Tetrahedron Lett.* **1989**, *30*, 4969.
(181) Hiebl, J.; Zbiral, E.; Balzarini, J.; De Clercq, E. *Nucleosides Nucleotides* **1991**, *10*, 521.
(182) Gautier, C.; Leroy, R.; Monneret, C.; Roger, P. *Tetrahedron Lett.* **1991**, *32*, 3361.
(183) Hiebl, J.; Zbiral, E.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1992**, *35*, 3016.
(184) Hrebabecky, H.; Holy, A. *Collect. Czech. Chem. Commun.* **1994**, *59*, 412.
(185) Yamashita, M.; Kawai, Y.; Uchida, I.; Komori, T.; Kohsaka, M.; Imanaka, H.; Sakane, K.; Setoi, H.; Teraji, T. *Tetrahedron Lett.* **1984**, *25*, 4689.
(186) Varma, R. S.; Hogan, M. E. *Tetrahedron Lett.* **1992**, *33*, 7719.
(187) Efimov, V. A.; Buryakova, A. A.; Chakhmakhcheva, O. G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1013.
(188) Popovkina, S. V.; Azhaev, A. V.; Kharshan, M. A.; Kraevskii, A. A.; Bobruskin, I. D.; Gottikh, B. P. *Bioorg. Khim.* **1979**, *5*, 546; *Chem. Abstr.* **1979**, *91*, 91902.
(189) Dyatkina, N. B.; Kraevskii, A. A.; Azhaev, A. V.; Yartseva, I. V. *Synthesis* **1985**, 410.
(190) Al-Masoudi, N. A.; Al-Soud, Y. A.; Ehrmann, M.; De Clercq, E. *Nucleosides Nucleotides* **1998**, *17*, 2255.
(191) Botta, O.; Moyroud, E.; Lobato, C.; Strazewski, P. *Tetrahedron* **1998**, *54*, 13529.
(192) Loibner, H.; Zbiral, E. *Justus Liebigs Ann. Chem.* **1978**, 78.
(193) Perlman, M. E.; Watanabe, K. A. *Nucleosides Nucleotides* **1987**, *6*, 621.
(194) Perlman, M. E.; Watanabe, K. A. *Nucleosides Nucleotides* **1989**, *8*, 145.
(195) Robins, M. J.; Hawrelak, S. D.; Kanai, T.; Siefert, J. M.; Mengel, R. *J. Org. Chem.* **1979**, *44*, 1317.
(196) Hollenberg, D. H.; Watanabe, K. A.; Fox, J. J. *J. Med. Chem.* **1977**, *20*, 113.
(197) Katalenic, D.; Skaric, V. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1065.
(198) Ikehara, M.; Maruyama, T.; Miki, H. *Tetrahedron* **1978**, *34*, 1133.
(199) Ikehara, M.; Maruyama, T.; Miki, H. *Tetrahedron Lett.* **1976**, 4485.
(200) Van Aerschot, A.; Herdewijn, P. *Bull. Soc. Chim. Belg.* **1989**, *98*, 937.
(201) Herdewijn, P.; Van Aerschot, A. *Bull. Soc. Chim. Belg.* **1989**, *98*, 943.
(202) Watanabe, K. A.; Harada, K.; Zeidler, J.; Matulic-Adamic, J.; Takahashi, K.; Ren, W. Y.; Cheng, L. C.; Fox, J. J.; Chou, T. C.; Zhu, Q. Y.; Polsky, B.; Gold, J. W. M.; Armstrong, D. *J. Med. Chem.* **1990**, *33*, 2145.
(203) Sochacka, E.; Nawrot, B.; Pankiewicz, K. W.; Watanabe, K. A. *J. Med. Chem.* **1990**, *33*, 1995.
(204) Huang, J. T.; Chen, L. C.; Wang, L.; Kim, M. H.; Warshaw, J. A.; Armstrong, D.; Zhu, Q. Y.; Chou, T. C.; Watanabe, K. A.; Matulic-Adamic, J.; Su, T. L.; Fox, J. J.; Polsky, B.; Baron, P. A.; Gold, J. W. M.; Hardy, W. D.; Zuckerman, E. *J. Med. Chem.* **1991**, *34*, 1640.
(205) Faivre-Buet, V.; Grouiller, A.; Descotes, G. *Nucleosides Nucleotides* **1992**, *11*, 1411.
(206) Surzhykov, S. A.; Dyatkina, N. B. *Bioorg. Khim.* **1993**, *19*, 722; *Chem. Abstr.* **1994**, *120*, 218370.
(207) Hrebabecky, H.; Holy, A. *Collect. Czech. Chem. Commun.* **1993**, *58*, 409.
(208) Obika, S.; Andoh, J.-I.; Sugimoto, T.; Miyashita, K.; Imanishi, T. *Tetrahedron Lett.* **1999**, *40*, 6465.
(209) Nari, V.; Purdy, D. F. *Heterocycles* **1993**, *36*, 421.
(210) Purdy, D. F.; Zintek, L. B.; Nair, V. *Nucleosides Nucleotides* **1994**, *13*, 109.
(211) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Med. Chem.* **1991**, *34*, 2782.
(212) Tber, B.; Fahmi, N.-E.; Ronco, G.; Villa, P.; Ewing, D. F.; Mackenzie, G. *Carbohydr. Res.* **1995**, *267*, 203.
(213) Ait, H.; Fahmi, N.-E.; Goethals, G.; Tber, B.; Payet, J.-M.; Ronco, G.; Villa, P. *J. Nat.* **1996**, *8*, 17.
(214) Lee, Y. H.; Kim, H. K.; Youn, I. K.; Chae, Y. B. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 287.
(215) Kim, H. K.; Lee, Y.; Young, I. K.; Chae, Y. B. *Korean J. Med. Chem.* **1995**, *5*, 68; *Chem. Abstr.* **1996**, *124*, 202916.
(216) Lee, Y.; Kim, H. K.; Young, I. K.; Chae, Y. B. *Korean J. Med. Chem.* **1995**, *5*, 66; *Chem. Abstr.* **1996**, 124, 202915.
(217) Shealy, Y. F.; O'Dell, C. A.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1986**, *29*, 483.
(218) Bodenteich, M.; Griengl, H. *Tetrahedron Lett.* **1987**, *28*, 5311.
(219) Beres, J.; Sagi, G.; Tomoskozi, I.; Gruber, L.; Baitz-Gacs, E.; Otvos, L.; De Clercq, E. *J. Med. Chem.* **1990**, *33*, 1353.
(220) Fletcher, C. A.; Hilpert, H.; Myers, P. L.; Roberts, S. M.; Storer, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1707.
(221) Highcock, R. M.; Hilpert, H.; Myers, P. L.; Roberts, S. M.; Storer, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1127.
(222) Legraverend, M.; Huel, C.; Zerial, A.; Lemaitre, M.; Bisagni, E. *Nucleosides Nucleotides* **1990**, *9*, 639.
(223) Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford, H., Jr.; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi, J. J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 2780.
(224) Hrebabecky, H.; Holy, A. *Collect. Czech. Chem. Commun.* **2000**, *65*, 395.
(225) Wengel, J.; Lau, J.; Pedersen, E. B.; Nielsen, C. M. *J. Org. Chem.* **1991**, *56*, 3591.
(226) Czernecki, S.; Le Diguarher, T. *Synthesis* **1991**, 683.
(227) Marchand, A.; Mathe, C.; Imbach, J.-L.; Gosselin, G. *Nucleosides, Nucleotides Nucleic Acids* **2000**, *19*, 205.
(228) Imazawa, M.; Eckstein, F. *J. Org. Chem.* **1978**, *43*, 3044.
(229) Pupeiko, N. E.; Prikota, T. I.; Mikhailopulo, I. A. *Synlett* **1991**, 342.
(230) Sharma, G. V. M.; Chandrasekhar, S. *Synth. Commun.* **1989**, *19*, 3289.
(231) Holletz, T.; Cech, D. *Synthesis* **1994**, 789.
(232) Stolze, K.; Koert, U.; Klingel, S.; Sagner, G.; Wartbichler, R.; Engels, J. W. *Helv. Chim. Acta* **1999**, *82*, 1311.
(233) Katalenic, D.; Zinic, M. *Nucleosides Nucleotides* **1998**, *17*, 1231.
(234) Wang, G. *Tetrahedron Lett.* **1999**, *40*, 6343.
(235) Lin, T. S.; Gao, Y. S.; Mancini, W. R. *J. Med. Chem.* **1983**, *26*, 1691.
(236) Lin, T. S.; Mancini, W. R. *J. Med. Chem.* **1983**, *26*, 544.
(237) Lin, T. S. In *Nucleic Acid Chemistry*; Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1991; Vol. 4, p 63.
(238) Czernecki, S.; Le Diguarher, T.; Valery, J. M. *Nucleosides Nucleotides* **1993**, *12*, 369.
(239) Lin, T. S.; Chen, M. S.; McLaren, C.; Gao, Y. S.; Ghazzouli, I.; Prusoff, W. *J. Med. Chem.* **1987**, *30*, 440.
(240) Chu, C. K.; Schinazi, R. F.; Ahn, M. K.; Ullas, G. V.; Gu, Z. P. *J. Med. Chem.* **1989**, *32*, 612.
(241) Ciszewski, K.; Celewicz, L.; Golankiewicz, K. *Biochem. Biophys. Res. Commun.* **1992**, *187*, 1545.
(242) Lin, T. S.; Shen, Z. Y.; August, E. M.; Brankovan, V.; Yang, H.; Ghazzouli, I.; Prusoff, W. H. *J. Med. Chem.* **1989**, *32*, 1891.
(243) Motura, M.; Salomon, H.; Moroni, G.; Wainberg, M.; Brinon, M. C. *Nucleosides Nucleotides* **1999**, *18*, 337.
(244) Pill, T.; Polborn, K.; Kleinschmidt, A.; Erfle, V.; Breu, W.; Wagner, H.; Beck, W. *Chem. Ber.* **1991**, *124*, 1541.
(245) Lloyd, A. E.; Coe, P. L.; Walker, R. T.; Howarth, O. W. *J. Fluorine Chem.* **1993**, *62*, 145.
(246) Wigerinck, P.; Van Aerschot, A.; Claes, P.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *J. Heterocycl. Chem.* **1989**, *26*, 1635.
(247) Hirota, K.; Hosono, H.; Kitade, Y.; Maki, Y.; Chu, C. K.; Schinazi, R. F.; Nakane, H.; Ono, K. *Chem. Pharm. Bull.* **1990**, *38*, 2597.
(248) Lazrek, H. B.; Taourirte, M.; Oulih, T.; Kabbaj, Y.; Barascut, J. L.; Imbach, J. L.; Almasoudi, N. A.; Pfleiderer, W. *Nucleosides Nucleotides* **1997**, *16*, 1073.
(249) Lazrek, H. B.; Engels, J. W.; Pfleiderer, W. *Nucleosides Nucleotides* **1998**, *17*, 1851.
(250) (a) Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440. (b) Prisbe, E. J.; Maag, H.; Verheyden, J. P. H.; Rydzewski, R. M. Structure-activity relationships among HIV inhibitory 4′-substituted nucleosides. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993; p 101.
(251) Teng, K.; Kharadwaj, R.; Cook, P. D. *Synlett* **1996**, 346.
(252) Maag, H.; Rydzewski, R. M. *J. Org. Chem.* **1992**, *57*, 5823.
(253) Lin, T.-S.; Prusoff, W. H. *J. Med. Chem.* **1978**, *21*, 106.
(254) (a) Lin, T.-S.; Prusoff, W. H. *J. Med. Chem.* **1978**, *21*, 109. (b) Lavandera, I.; Fernandez, S.; Ferrero, M.; Gotor, V. *J. Org. Chem.* **2001**, *66*, 4079.
(255) Adachi, T.; Yamada, Y.; Inoue, I.; Saneyoshi, M. *Carbohydr. Res.* **1979**, *73*, 113.
(256) Adachi, T.; Arai, Y.; Inoue, I.; Saneyoshi, M. *Carbohydr. Res.* **1980**, *78*, 67.
(257) Sasaki, T.; Minamoto, K.; Suzuki, T.; Sugiura, T. *J. Am. Chem. Soc.* **1978**, *100*, 2248.

(258) Sasaki, T.; Minamoto, K.; Suzuki, T.; Sugiura, T. *J. Org. Chem*. **1979**, *44*, 1424.
(259) Shiau, G. T.; Schinazi, R. F.; Chen, M. S.; Prusoff, W. H. *J. Med. Chem*. **1980**, *23*, 127.
(260) Skaric, V.; Katalenic, D.; Skaric, D.; Salaj, I. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2091.
(261) Kierzek, R.; Li, Y.; Turner, D. H.; Bevilacqua, P. C. *J. Am. Chem. Soc.* **1993**, *115*, 4985.
(262) Gudmundsson, K. S.; Drach, J. C.; Wotring, L. L.; Townsend, L. B. *J. Med. Chem*. **1997**, *40*, 785.
(263) Harada, K.; Matulic-Adamic, J.; Price, R. W.; Schinazi, R. F.; Watanabe, K. A.; Fox, J. J. *J. Med. Chem*. **1987**, *30*, 226.
(264) Van Aerschot, A.; Herdewijn, P.; Balzarini, J.; Pauwels, R.; De Clercq, E. *J. Med. Chem*. **1989**, *32*, 1743.
(265) Grunder-Klotz, E.; Just, G. *Nucleosides Nucleotides* **1994**, *13*, 1829.
(266) Unger, F. M.; Christian, R.; Waldstaetten, P. *Tetrahedron Lett*. **1979**, 605.
(267) Ozols, A.; Azhaev, A. V.; Kraevskii, A. A.; Ushakov, A. S.; Gnuchev, N. V.; Gottikh, B. P. *Synthesis* **1980**, 559.
(268) Al-Masoudi, N. A.; Pfleiderer, W. *Carbohydr. Res*. **1995**, *275*, 95.
(269) Sharma, M.; Li, Y. X.; Ledvina, M.; Bobek, M. *Nucleosides Nucleotides* **1995**, *14*, 1831.
(270) Sugimura, H.; Katoh, Y. *Chem. Lett*. **1999**, 361.
(271) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett*. **1984**, 405.
(272) Robins, M. J.; Doboszewski, B.; Timoshchuk, V. A.; Peterson, M. A. *J. Org. Chem*. **2000**, *65*, 2939.
(273) Adachi, T.; Yamada, Y.; Inoue, I. *Synthesis* **1977**, 45.
(274) Saxon, E.; Armstrong, J. I.; Bertozzi, C. R. *Org. Lett*. **2000**, *2*, 2141.
(275) Katalenic, D.; Skaric, V.; Klaic, B. *Tetrahedron Lett*. **1994**, *35*, 2743.
(276) Gibbs, D. E. *Tetrahedron Lett*. **1977**, 679.
(277) Gait, M. J.; Jones, A. S.; Jones, M. D.; Shepherd, M. J.; Walker, R. T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1389.
(278) Nyilas, A.; Glemarec, C.; Chattopadhyaya, J. *Tetrahedron* **1990**, *46*, 2149.
(279) Robins, M. J.; Doboszewski, B.; Nilsson, B. L.; Peterson, M. A. *Nucleosides, Nucleotides Nucleic Acids* **2000**, *19*, 69.
(280) Fischer, E.; Helferich, B. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 210.
(281) Hanessian, S.; Conde, J. J.; Khai, H. H.; Lou, B. *Tetrahedron* **1996**, *52*, 10827 and references therein.
(282) Leclercq, F.; Jumelet-Bach, J.; Antonakis, K. *Carbohydr. Res*. **1978**, *62*, 73.
(283) Bouchu, D.; Abou-Assali, M.; Grouiller, A.; Carret, G.; Pacheco, H. *Eur. J. Med. Chem.—Chim. Ther*. **1981**, *16*, 43.
(284) Carret, G.; Grouiller, A.; Pacheco, H. *Carbohydr. Res*. **1982**, *111*, 59.
(285) Carret, G.; Grouiller, A.; Chabannes, B.; Pacheco, H. *Nucleosides Nucleotides* **1986**, *5*, 331.
(286) Kaluza, Z.; Pedersen, E. B.; Nielsen, C. M.; Chmielewski, M. *Acta Chem. Scand*. **1990**, *44*, 294.
(287) Hansen, P.; Lau, J.; Pedersen, E. B.; Nielsen, C. M. *Liebigs Ann. Chem*. **1990**, 1079.
(288) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657.
(289) Kovacs, L.; Herczegh, P.; Batta, G.; Farkas, I. *Tetrahedron* **1991**, *47*, 5549.
(290) Sztaricskai, F.; Dinya, Z.; Batta, G.; Gergely, L.; Szabo, B. *Nucleosides Nucleotides* **1992**, *11*, 11.
(291) Sztaricsaki, F.; Dinya, Z.; Batta, G.; Gergely, L.; Szabo, B. *Nucleosides Nucleotides* **1993**, *12*, 263.
(292) Tsuboike, K.; Minamoto, K.; Mizuno, G.; Yanagihara, K. *Nucleosides Nucleotides* **1998**, *17*, 745.
(293) Ton-That, T. *Nucleosides Nucleotides* **1999**, *18*, 731.
(294) Hassan, A. A. A.; Matsuda, A. *Heterocycles* **1992**, *34*, 657.
(295) Czernecki, S.; Ezzitouni, A. *Tetrahedron Lett*. **1993**, *34*, 315.
(296) Ioannidis, P.; Classon, B.; Samuelsson, B.; Kvarnstroem, I. *Nucleosides Nucleotides* **1993**, *12*, 449.
(297) Ioannidis, P.; Classon, B.; Samuelsson, B.; Kvarnstroem, I. *Nucleosides Nucleotides* **1993**, *12*, 865.
(298) Ioannidis, P.; Classon, B.; Samuelsson, B.; Kvarnstroem, I. *Nucleosides Nucleotides* **1992**, *11*, 1205.
(299) Svansson, L.; Kvarnstroem, I.; Classon, B.; Samuelsson, B. *Nucleosides Nucleotides* **1992**, *11*, 1353.
(300) Lin, T. S.; Zhu, J. L.; Dutschman, G. E.; Cheng, Y. C.; Prusoff, W. H. *J. Med. Chem*. **1993**, *36*, 353.
(301) Perez-Perez, M.-J.; Camarasa, M.-J. *Tetrahedron* **1994**, *50*, 7269.
(302) Yoshimura, Y.; Satoh, H.; Sakata, S.; Ashida, N.; Miyazaki, S.; Matsuda, A. *Nucleosides Nucleotides* **1995**, *14*, 427.
(303) Mikhailopulo, I. A.; Poopeiko, N. E.; Tsvetkova, T. M.; Marochkin, A. P.; Balzarini, J.; De Clercq, E. *Carbohydr. Res*. **1996**, *285*, 17.
(304) Maag, H.; Prisbe, E. J.; Verheyden, J. P. H. Eur. Patent EP 371366, 1990; *Chem. Abstr*. **1990**, *113*, 191854.
(305) O-Yang, C.; Kurz, W.; Eugui, E. M.; McRoberts, M. J.; Verheyden, J. P. H.; Kurz, L. J.; Walker, K. A. M. *Tetrahedron Lett*. **1992**, *33*, 41.
(306) Hrebabecky, H.; Holy, A. *Collect. Czech. Chem. Commun*. **1993**, *58*, 1668.
(307) Jeon, G. S.; Nair, V. *Tetrahedron* **1996**, *52*, 12643.
(308) Lyga, J. W.; Secrist, J. A., III. *J. Org. Chem*. **1983**, *48*, 1982.
(309) Guo, Z.; Samano, M. C.; Krzykawski, J. W.; Wnuk, S. F.; Ewing, G. J.; Robins, M. J. *Tetrahedron* **1999**, *55*, 5705.
(310) Schoetzau, T.; Koert, U.; Engels, J. W. *Synthesis* **2000**, 707.
(311) Balzarini, J.; De Clercq, E. Biochemical pharmacology of nucleoside and non-nucleoside reverse transcriptase inhibitors active against HIV. In *Textbook of AIDS Medicine*; Merigan, T. C., Bartlett, J. G., Bolognesi, D., Eds.; Williams and Wilkins: Baltimore, MD, 1998; p 815.
(312) Duesberg, P.; Rasnick D. *Genetica* **1998**, *104*, 85.
(313) Averett, D. R. *J. Virol. Methods* **1989**, *23*, 263.
(314) Averett, D. R. *J. Virol. Methods* **1989**, *25*, 351.
(315) Hartmann, H.; Hunsmann, G.; Eckstein, F. *Lancet* **1987**, *1*, 40.
(316) Hartmann, H.; Vogt, M. W.; Durno, A. G.; Hirsch, M. S.; Hunsmann, G.; Eckstein, F. *AIDS Res. Hum. Retroviruses* **1988**, *4*, 457.

CR0104532