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CHEMICAL MODIFICATIONS OF NATURAL NUCLEOSIDES

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Abstract

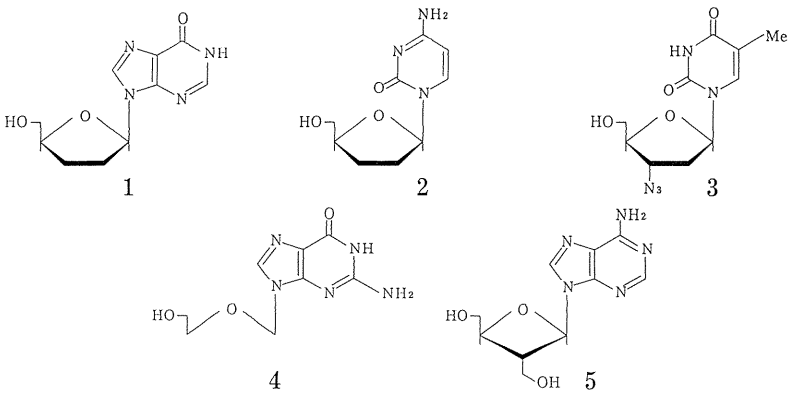
Some chemical modifications of natural nucleosides based on the general organic chemistry have been carried out. Base catalyzed elimination reactions at the 2′,3′-positions of purine and pyrimidine nucleosides proved to be regiospecific. In the pyrimidine series, the resulting 2′,3′-olefins with a leaving group at the C-2′ readily formed the corresponding 3′-deoxy-2′-keto-nucleosides, an entirely new class of bioorganic substances.

Exploratory experiments aiming at base-sugar cyclization at the 4′-positions of nucleosides led to the N^3,$C_{4'}$-cyclization with concomitant decyclization of the base moiety in adenosine series, while in the pyrimidine series the first synthesis of O^2,$C_{4'}$-cyclonucleosides was achieved. Synthetic studies on the hitherto unexploited nitrogen-bridged cyclonucleosides were extensively conducted. The major topics cover (a) general synthesis of 2,3′-imino and (substituted-imino) pyrimidine nucleosides, (b) regio and stereospecific synthesis of some reversed nucleosides through protected pyrimidine 6,5′-*N*-cyclonucleosides, (c) general synthesis of purine 8,5′-*N*-cyclonucleosides, (d) synthesis and chemistry of purine 8,2′- and 8,3′-long-bridged cyclonucleosides, (e) hydrolytic cleavage of the nitrogen bridge in the 2,2′- and 2,3′-(substituted-imino) pyrimidine nucleosides, (f) molecular rearrangements through the fission of the glycosidic bond in the general *N*-bridged cyclonucleosides, (g) strain-assisted hydrolysis of the nitrogen bridge of a pyrimidine multi-cyclic *N*-cyclonucleoside and (h) synthesis and chemistry of piperidine sugar uracil nucleosides. The final topic presents the synthesis and chemistry of 3-deoxy-3-nitro-hexopyranosyl nucleosides in both pyrimidine and purine series. The major results are stereoselective Michael addition reactions of various nucleophiles to the 3-nitro-2,3-unsaturated sugar nucleosides in both cases.

Contents

1. General Introduction

Recent studies in the area of nucleic acids components have covered the physico-chemical analyses of the sugar conformations and base-sugar conformations related to the tertiary structures of natural nucleic acids[1] and synthetic chemistry, which includes chemical modifications of the base or sugar moiety of natural nucleosides (or nucleotides) aiming at biological and/or optical models or therapeutic agents.[2-4] The recent improvements in solid phase RNA synthesis[5] have facilitated site-specific incorporation of modified nucleosides into ribozyme sequences. It has enabled determination of the functional group requirements of several bases found to be essential for catalytic activity.[6] The stereoselective synthesis of anomerically pure natural and unnatural nucleosides is a permanent target of general organic



chemists.[7] Furthermore, the finding that dideoxynucleosides such as 2′,3′-dideoxycytidine (ddC, **2**),[8] 2′,3′-dideoxyinosine (ddI, **1**),[8] 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T)[9,10], and 3′-azido-3′-deoxythymidine (AZT, **3**)[11] are potentially effective therapeutic agents for the treatment of AIDS has triggered explosive synthesis of modified nucleosides including extremely aberrant analogues with a ring-opened (e.g. Acyclovir, **4**)[12] or ring-contracted sugar part (e.g. Oxetanocin, **5**).[12]

Thus, in the past over two decades interdisciplinary demand for unnatural nucleosides has extended the reach of organic chemistry into the areas that were previously within the domain of biology. The author presents here *topically* some chemical modifications of natural and unnatural nucleosides which have been carried out principally from the viewpoint of 1) exploitation of useful chemical reactivities especially stemming from chemical or physicochemical correlations between the base and sugar parts, 2) applicability of common synthetic methods in general organic chemistry and 3) discovery of biologically active clue compounds.

2. Regioselective Elimination Reactions at the 2′,3′-Position of Nucleosides

2.1. Introduction

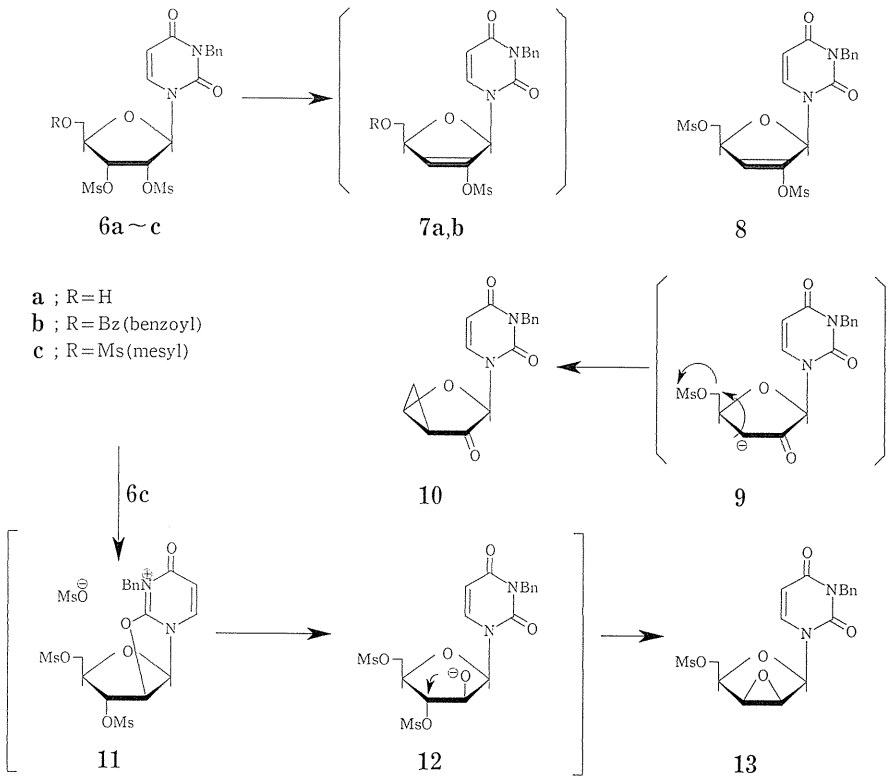
Although unsaturated-sugar nucleosides are useful intermediates for the transformations of the sugar moiety of nucleosides, examples of their use in synthesis were limited[13] at the point of the year 1970. In the pyrimidine series, 2′,3′-[9,14] and 3′,4′-unsaturated nucleosides[15] have been obtained by base-catalyzed elimination reactions. An elegant synthesis of 4′,5′-unsaturated uridine was also reported.[16] However, similar investigations on the introduction of a 2′,3′-unsaturated bond into the ribonucleosides were quite few.[17,18] We could predict the regioselectivity in the β-elimination reactions at the 2′,3′-position owing to the influence by the electron-withdrawing nucleobase, i.e., the more acidic H-2′ should be extracted by the base to extrude the 3′-leaving group when both C-2′ and C-3′ carry a leaving group. This assumption spurred us to examine the direction of base-catalyzed elimination reactions on N^3-protected uridine derivatives, where cyclonucleoside formation was considered less probable.

2.2. Elimination Reactions on the Di- and Trimesylated Derivatives of N^3-Benzyluridine

Thus, we have prepared 3-benzyl-2′,3′-di-*O*-mesyluridine (**6a**), 5′-*O*-benzoyl-3-benzyl-2′,3′-di-*O*-mesyluridine (**6b**) and 3-benzyl-2′,3′,5′-tri-*O*-mesyluridine (**6c**) as substrates for β-elimination (**Scheme 1**).[19] As expected, treatment of **6a** with excess amount of sodium benzoate in DMF at 100°C gave 1-(3′-deoxy-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**7a**), which was converted into crystalline 1-(3′-deoxy-2′,5′-di-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil (**8**). Similar treatment of **6b** gave **7b** which was also derived to **8**, while compound **6c** gave **6b** and **7b** in the same reaction. When compound **8** was treated with potassium carbonate in hot DMF, *endo*-3-(3-benzyluracil-1-yl)-2-oxabicyclo[3.1.0]-4-oxocyclohexane (**10**) was obtained as the major product, which must have formed through a 2′-ketone intermediate (**9**). Similar treatment of **6c** gave, unexpectedly, 1-(2′,3′-epoxy-5′-*O*-mesyl-β-D-lyxosyl)-3-benzyluracil (**13**) as the major product but no olefinic compound. Compound **13** must have formed via an intermediary 2,2′-cyclonucleoside (**11**). As far as the substance **6c** is concerned, two synchronous reaction paths are now obvious.

This piece of work revealed that (1) *the base induced β-elimination occurs selectively to leave a leaving group at C-2′*, (2) *the electronegative mesyl group and base moiety and their steric hindrance would regio- and stereoselectively regulate electrophilic reactions at the 2′,3′-olefinic bond* and (3) *the mesyl group might be chemically modified without difficulty.*

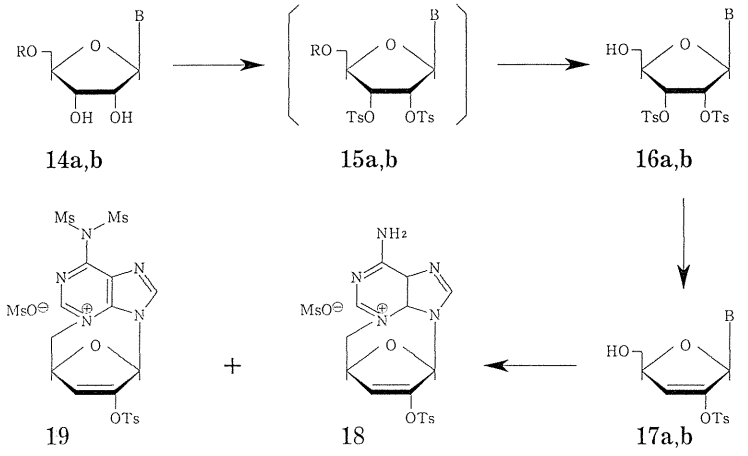
Scheme 1

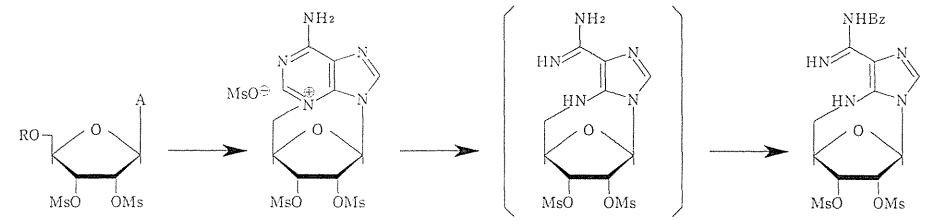


2.3. *Introduction of a 2′,3′-Double Bond into Purine Ribonucleosides*

The study was extended to similar elimination reactions with the derivatives of some purine ribonucleosides in order to establish the generality of the selective 2′-hydrogen abstraction[20] (**Scheme 2**). 2′,3′-Di-*O*-tosyladenosine (**16a**) was synthesized from 5′-*O*-acetyladenosine (**14a**)[21] through compound **15a**, while the corresponding inosine analogue **16b** was prepared from 5′-*O*-benzoyl-2′,3′-*O*-isopropylideneinosine through deisopropylidenation, ditosylation and hydrolysis. Compounds **16a,b** were now allowed to react with sodium

Scheme 2





methoxide/DMF at 100°C to give 9-(3′-deoxy-2′-*O*-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)-adenine (**17a**) and its hypoxanthine analogue **17b** in 55 and 37% yield, respectively, regenerating some starting material. It must be noted that the reaction did not occur at ambient temperature in contrast with the reported similar elimination reaction of 3'-*O*-tosyl-2′-deoxyadenosine. Treatment of **17a** with mesyl chloride easily gave the cyclonucleosides **18** and **19**, the first purine 3,5′-cyclonucleosides having a double bond in the sugar moiety. Interestingly, the ^{1}H NMR spectrum of **19** retained the characteristic furanose-ene proton resonances[20] as in the case of **17a**. This seems to explain the extremely facile cyclization at N^3, by which no substantial steric strain is generated to cause a conformational modification in the unsaturated sugar skeleton.

In pursuit of more economical substrates for β-elimination, 2′,3′,5′-tri-*O*-mesyladenosine (**20a**) directly obtainable from adenosine was first chosen. However, all the attempts to substitute the 5′-*O*-mesyl group with benzoate anion in order to obtain the water-insoluble 5′-*O*-benzoate (**20b**) collapsed, compound **23** being obtained as the major product together with very minor **20b** after benzoylation of the water-soluble product fraction. Thus, in this case the notorious intramolecular 3,5′-quaternization dominated to afford the intermediates **21** and **22**.

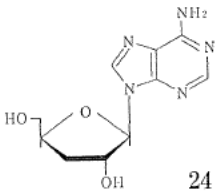
2.4. *Biomimetic Synthesis of 3′-Deoxy-2′-oxo Pyrimidine Nucleosides*

The above mentioned regioselective elimination reactions triggered by the 2′-hydrogen abstraction and the facile formation of the 2′-ketonucleoside **10** strongly suggested the possibility of the synthesis of 3′-deoxy-2′-keto pyrimidine nucleosides [1-(3′-deoxy-β-D-*glycero*-pentofuran-2′-ulosyl)pyrimidines]. This sort of chemical modifications are quite important in view of the observation that the antibiotic 3′-deoxyadenosine (cordycepin, **24**) is formed from adenosine in cultures of *Cordyceps militaris*.[22]

For this biological reduction process, a 2′,3′-en-2′-ol (**25**) formed *via* a trans-elimination of a molecule of water from adenosine was proposed as an intermediate.[22]

Hence, we prepared 1-(5′-*O*-benzoyl-2′,3′-di-*O*-mesyl-β-D-lyxofuranosyl)uracil (**26a**),[23] its analogues (**26b,c**[23] and **26d**[24]) and 1-(5′-*O*-benzyl-2′,3′-di-*O*-mesyl-β-D-lyxofuranosyl)uracil (**26e**)[25] starting from 1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**26**, R = Bz, R_1 = R_2 = OH)[26] and its 5′-*O*-benzyl analogue (**26**, R = Bn, R_1 = R_2 = OH).[25] It was considered that in these lyxofuranosyl substances, interaction between the base and sugar moiety to form a cyclonucleoside is in principle prohibited (**Scheme 3**).

Treatment of the more accessible substrate **26b** with sodium benzoate under controlled conditions permitted isolation of 1-(5′-*O*-benzoyl-3′-deoxy-2′-*O*-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)uracil (**27a**) in a low yield. Similar treatment of **26a-c** under more drastic conditions gave directly 1-(5′-*O*-benzoyl-3′-deoxy-β-D-*glycero* pentofuran-2′-ulosyl)uracil (**28a**) in ca. 20% yield together with resinous products,[23] while compound **26d** with the same reagent gave a 60% yield of **28a**.[24] A heterogeneous reaction of **26e** with potassium carbonate in acetonitrile permitted isolation of **27c** in 50% yield.[25] The parent ketonucleoside **28c** was finally obtained by treatment of **28a** with triethylamine in MeOH (36%)[24] or by hydrogenolysis of **28b** (97%).[25]



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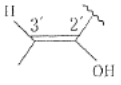

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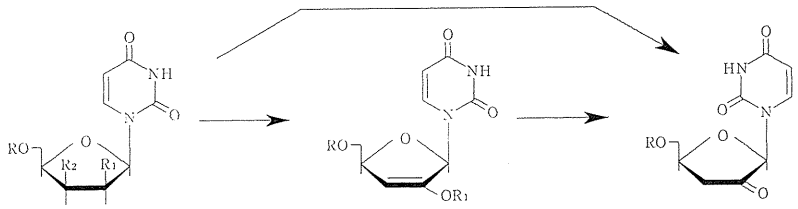
Scheme 3



26a, R=Bz,
$R_1=R_2=OMs$
b, R=Bz,
$R_1=OTs$, $R_2=OMs$
c, R=Bz,
$R_1=OMs$, $R_2=OTs$
d, R=Bz,
$R_1=OBz$, $R_2=OMs$
e, R=Bn,
$R_1=R_2=OMs$

27a, R=Bz
$R_1=Ts$
b, R=Bz
$R_1=Ms$
c, R=Bn
$R_1=Ms$

28a, R=Bz
b, R=Bn
c, R=H

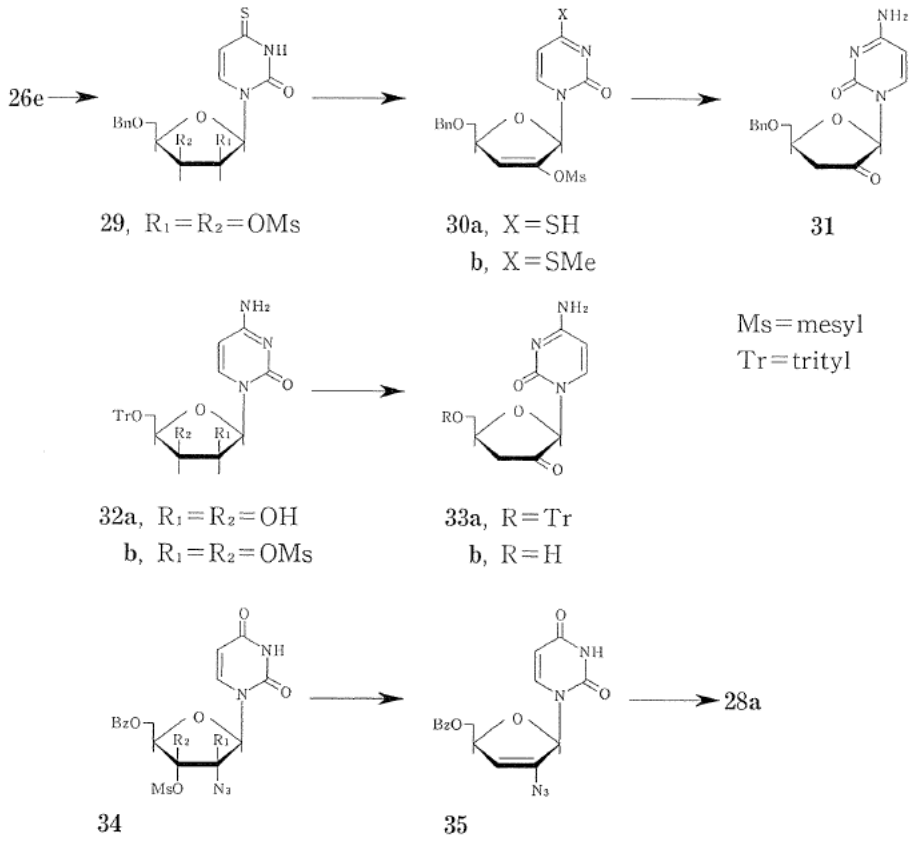
Bz=benzoyl
Bn=benzyl
Ts=tosyl
Ms=mesyl

The synthesis of similar 3′-deoxy-2′-keto-cytidine started first from the uridine derivative **26e** to evade the notorious trouble generally experienced in the manipulation of cytidine analogues (**Scheme 4**).[25] Compound **26e** was converted into 1-(5′-*O*-benzyl-2′,3′-di-*O*-mesyl-β-D-lyxofuranosyl)-4-thiouracil (**29**), which was treated with potassium carbonate in acetonitrile to give 1-(5′-*O*-benzyl-3′-deoxy-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-4-thiouracil (**30a**) (66%). 4-Methylthio-1-(5′-*O*-benzyl-3′-deoxy-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-2(1H)-pyrimidinone (**30b**) obtained by methylation of **30a** was treated with ethanolic ammonia to give directly a 82% yield of 1-(5′-*O*-benzyl-3′-deoxy-β-D-*glycero*-pentofurn-2′-ulosyl)cytosine (**31**), whose hydrogenolytic deprotection failed however. Hence, the known 5′-*O*-trityl-lyxosyl cytosine (**32a**)[27] was dimesylated to compound **32b**, which was treated with sodium benzoate to afford the cytosine ketonucleoside **33a**. Deprotection of **33a** with the use of 80% acetic acid gave the parent compound **33b** in 45% yield.

The unusual ease with which the eno-furanosides **27** and **30b** can be converted into the ketonucleosides **28a,b** and **31** suggests the presence of *anchimeric assistance by the ionized base moiety* (an interspacial repercussion between the ionized pyrimidine-2-carbonyl and the electron-rich sulfonyl or benzoyl group). *It must be added that compounds 28c and 33b proved to be two of the rare members which exist in the syn-conformation on the basis of CD-spectral criteria.*

Another route to the ketonucleoside **28a** was also exploited by us: β-elimination of compound **34** gave the 2′-azido olefine **35** (64%), which was converted into **28a** by hydrogenolysis (55%).[28]

Scheme 4



3. Base-Sugar Cyclization at the 4′-Position of Nucleosides

3.1. Introduction

Since Todd and coworkers reported 2′,3′-*O*-isopropylidene-2,5′-anhydrocytidine tosylate in 1951 as the first base-sugar cyclized nucleoside,[29] 2,2′-, 2,3′-, 2,5′-, 6,5′-, 6,2′-anhydro pyrimidine nucleosides[30] and analogous purine 8-cyclonucleosides[31] have been described and proved to be useful intermediates for chemical modifications of base and sugar moieties in natural nucleosides. The cyclonucleosides have themselves served as prominent models for physico-chemical studies on the base-sugar conformations in nucleosides and nucleotides.[32-34] Some anhydro nucleosides with nitrogen and sulfur bridges have also been obtained.[31,35] Clearly, the last target in cyclonucleoside chemistry must be the one involving cyclization at the 4′-position in nucleosides. In this field, 5′-bromo-5′-deoxy-2′,3′-*O*-isopropylidene-N^3,4′-cycloadenosine bromide was recorded in 1968 in a synthetic study related to the total synthesis of angustmycin A.[36] I herein summerize the results of our synthetic studies along this line.

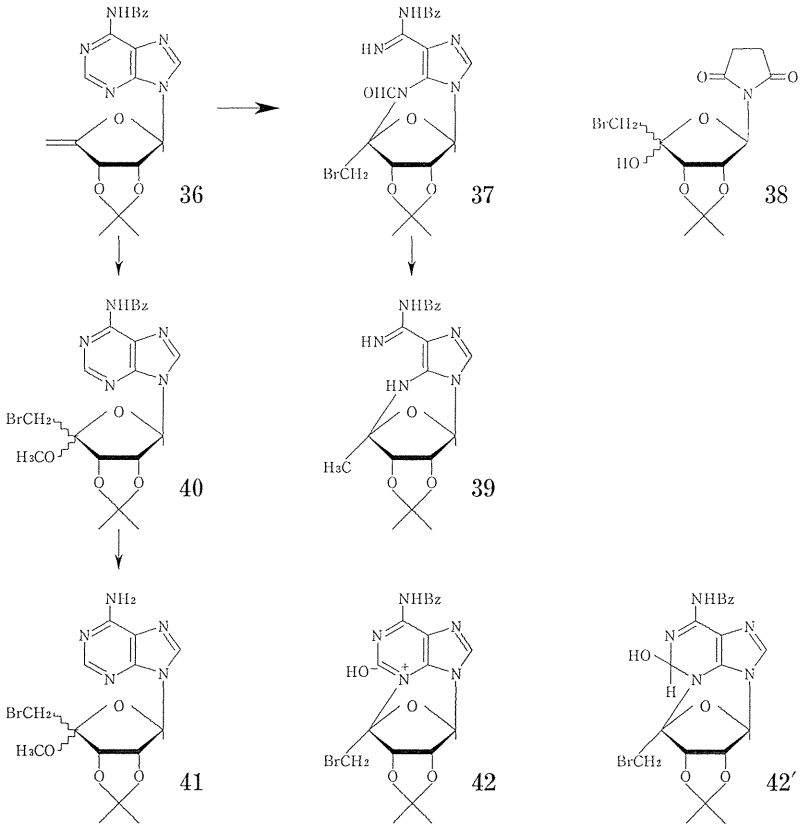
3.2. *Cyclization-Decyclization Reaction of a 4′,5′-Didehydroadenosine Derivative. A New Route to the Chemical Modification of Adenosine*

One of the imaginable methods to chemically manipulate the 4′-position of nucleosides is an electrophilic reaction at the 4′,5′-double bond to generate a 4′-carbocation which should be stabilized by the adjacent oxygen atom. Thus, addition of hypobromous acid generated *in situ* from *N*-bromosuccinimide (NBS) and water to 6-benzamido-9-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)purine (**36**) gave N^5,4′-anhydro-(5′-deoxy-5′-bromo-2′,3′-*O*-isopropylidene-α-L-lyxosyl)-4-benzoylcarboxamidino-5-(*N*-formyl)-amino-imidazole (**37**) (yellow crystals) and bromohydrin nucleoside **38** in 20 and 12% yield, respectively, together with other decomposition products (**Scheme 5**).[37]

Catalytic hydrogenation of **37** gave N^5,4′-anhydro-(5′-deoxy-2′,3′-*O*-isopropylidene-α-L-lyxosyl)-4-benzoylcarboxamidino-5-aminoimidazole (**39**). Final evidence for the acyclic nature of the base moiety and the N^5,4′-cyclic nature of **37** and **39** was provided by mass spectrometry (**Scheme 6**).[37]

In both cases, benzoyl cation (m/z 105) appeared as base peaks, which precluded a cyclic base structure conjugated with a phenyl group for these compounds. Both compounds

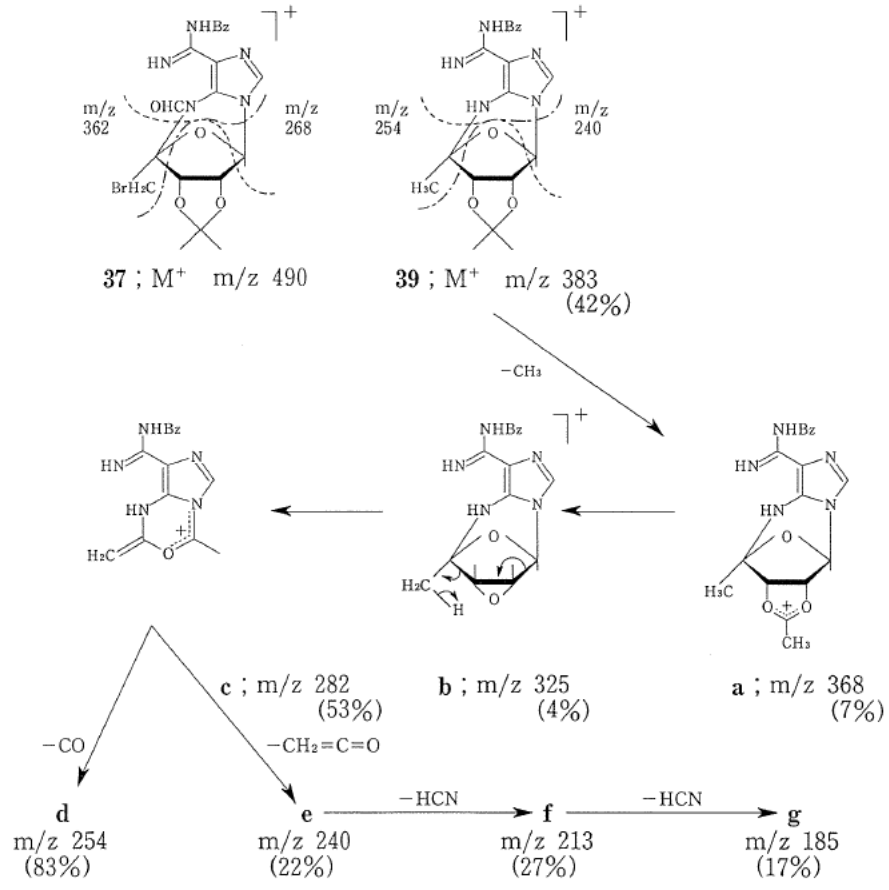
Scheme 5



exhibited characteristic fragment ions produced by cleavages along the dotted and dashed lines as shown in **Scheme 6**. On the other hand, analogous reaction of **36** with NBS/MeOH gave 9-(2′,3′-*O*-isopropylidene-4′-methoxy-4′-bromomethylene-β-D-*erythro*-furanosyl)-N^6-benzoyladenine (**40**) in 60% yield. Compound **40** was debenzoylated to compound **41** with the use of methanolic ammonia.

Acid-catalayzed cleavage of adenine is known to give 4-aminoimidazole-5-carboxamidine[38] which can also be derived from adenine 3-N-oxide.[38] However, the hydrolysis conditions used are usually too vigorous to be applied without depurination. While in our case the plausible intermediate **42** or **42′** could not be isolated, their intermediacy was probable on the basis of other observations. The formation of **37** represents the first *N*,4′-cyclization with concomitant facile ring cleavage of the base moiety in purine nucleoside derivatives and would provide, together with the unique fragmentation patterns in mass spectrometry themselves, a new route to the chemical modifications of purine nucleosides.

Scheme 6



3.3. *Synthesis and Properties of Some Pyrimidine 2,4′-Cyclonucleosides*[39,40]

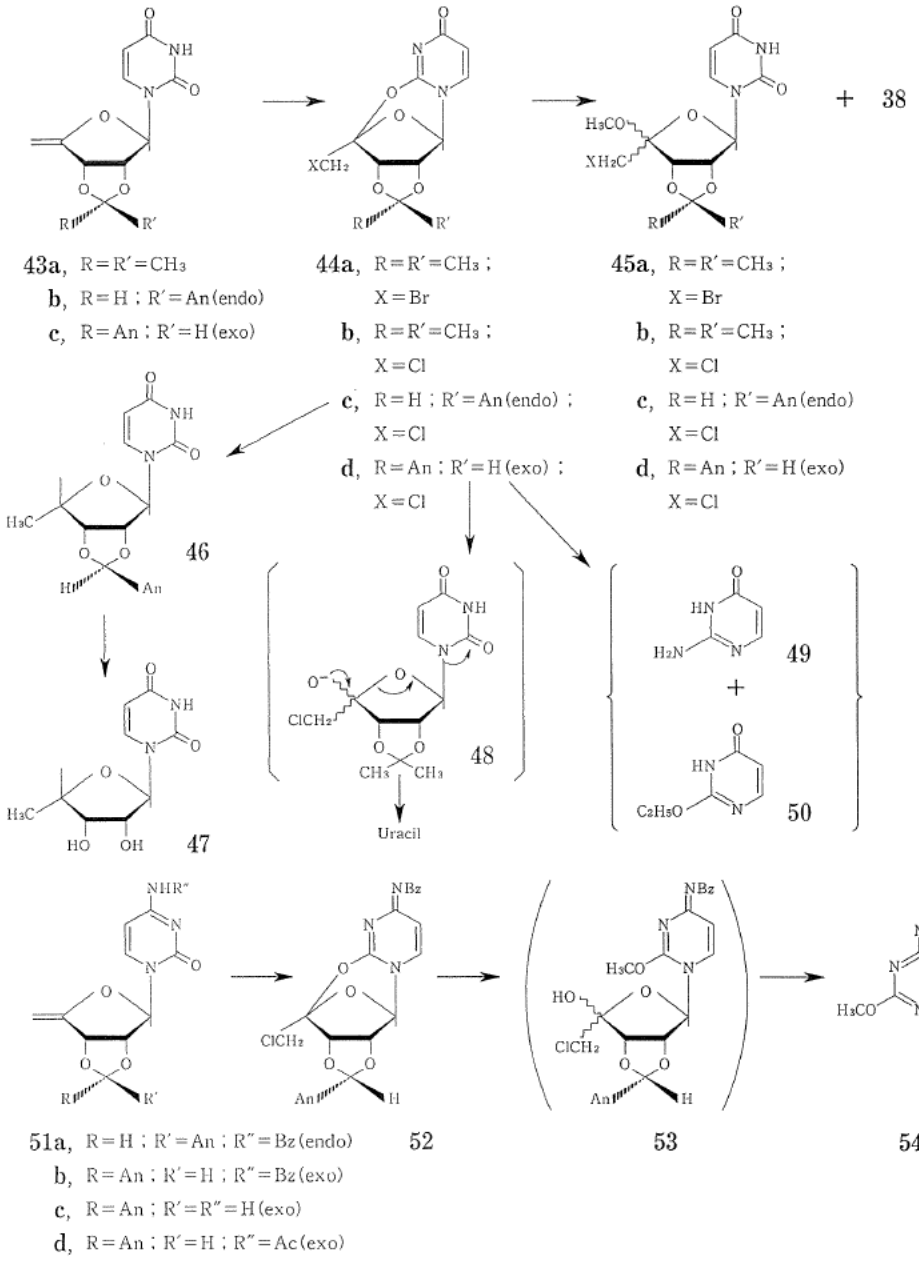
Treatment of 1-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (**43a**)[41] with hypobromous acid generated from NBS and water gave 2,4′-didehydro-1-(5′-bromo-5′-deoxy-2′,3′-*O*-isopropylidene-α-L-lyxosyl)uracil (**44a**) (35%) and the succinimide nucleoside **38** (17%).[39] Methanolysis of **44a** gave 1-(2′,3′-*O*-isopropylidene-4′-methoxy-4′-bromomethylene-β-D-*erythro*-furanosyl)uracil (**45a**). After this trial, we chose to use tert-butyl hypochlorite instead of hypobromous acid to evade the formation of the by-product **38**. Moreover, the former reagent can be used in dry media, thus precluding ionic side reactions. Thus, **43a** with t-butyl hypochlorite gave 2,4′-didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-isopropylidene-α-L-lyxosyl)uracil (**44b**) in 60% yield. Similarly, the cyclonucleosides **44c,d** were obtained in fair yields from the olefins **43b,c** (**Scheme 7**).[40]

A notable property of **44a-d** is their unusually high acid lability as expected from the unique polycyclic structures having a bridged 1,3-dioxane component. Thus, treatments with rather strong organic or inorganic acids resulted in decomposition to afford only uracil, while brief contact of **44a** with dry, neat acetic acid gave quantitatively a stereoisomeric mixture of 1-(4′-acetoxy-4′-bromomethylene-2′,3′-*O*-isopropylidene-β-D-*erythro*-furanosyl)uracil (unpublished). Finally nitromethane, a very weak acid, was found to be an excellent catalyst for methanolysis of **44b** to give 1-(4′-chloromethylene-2′,3′-*O*-isopropylidene-4′-methoxy-β-D-*erythro*-furanosyl)uracil (**45b**) and its analogues **45c,d**. While in each methanolysis reaction one 4′-stereomer was isolated as crystals, isolation of the counterpart was abandoned. Hydrogenolysis of **44c** gave 1-(5′-deoxy-2′,3′-*O*-endo-anisylidene-α-L-lyxofuranosyl)uracil (**46**), which was also obtained from **43b** by similar hydrogenation. Compound **46** was deprotected to the known parent compound, 1-(5′-deoxy-α-L-lyxofuranosyl)uracil (**47**).[41] Neutral hydrolysis of **44b** in a mixture of acetone and water gave only uracil, most probably through the intermediate **48**. Reaction of **44b** with ethanolic ammonia at ambient temperature formed isocytosine (**49**) and 3,4-dihydro-4-keto-2-ethoxypyrimidine (**50**). *The behavior of a 2,4′-cyclo uracil nucleoside toward amines seems to be analogous to those of 2,5′-anhydro uracil nucleosides,*[40,42] 4′-hydroxy anion having accelerated the deglycosidation as in **48**.

In the cytidine series, we prepared N^4-benzoyl-1-(5-deoxy-2,3-*O*-endo(and exo)-anisylidene-β-D-*erythro*-pent-4-enofuranosyl)cytosine (**51a** and **51b**), 1-(5-deoxy-2,3-*O*-exo-anisylidene-β-D-*erythro*-pent-4-enofuranosyl)cytosine (**51c**) and N^4-acetyl-1-(5-deoxy-2,3-*O*-exo-anisylidene-β-D-*erythro*-pent-4-enofuranosyl)cytosine (**51d**) as substrates for the similar cyclization. Compond **51b** with t-butyl hypochlorite gave crystalline N^4-benzoyl-2,4′-didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-exo-anisylidene-α-L-lyxosyl)cytosine (**52**) in a fair yield. Formation of analogous cyclonucleosides from **51a** and **51d** were suggested by TLC, but their isolations were unsuccessful. Compound **52** is the second cytidine 2-cyclonucleoside with a 4-imino (not immonium) structure after 2,3′-anhydro-1-(2′,5′-di-*O*-trityl-β-D-xylofuranosyl)cytosine synthesized by Mizuno and coworkers.[43] Methanolysis of **52** in the presence of nitromethane also proceeded smoothly to give, unexpectedly, 2-methoxy-4-benzamidopyrimidine (**54**) but no 4′-methoxy compound (s)! *This methanolysis reaction was 100% specific and in sharp contrast to the behavior of uracil analogues.*

The cyclonucleosides **44** and **52** showed distinct negative ORD and/or CD Cotton effects at the 260–280 nm region indicating their syn-conformation. *It must be emphasized that the ORD curve of **44b** is an approximate mirror image to that of 6,5′-cyclo-6-hydroxyuridine*[32a] *and hence it could better serve as an optical model of syn-conformation than that of 2,5′-anhydrouridine.*[32a] *To add, this piece of work has introduced the concept of "didehydro" instead of "anhydro" compounds into the genre of cyclonucleosides.*

Scheme 7


+ 38
43a, R=R′=CH3
b, R=H ; R′=An(endo)
c, R=An ; R′=H(exo)
44a, R=R′=CH3 ; X=Br
b, R=R′=CH3 ; X=Cl
c, R=H ; R′=An(endo) ; X=Cl
d, R=An ; R′=H(exo) ; X=Cl
45a, R=R′=CH3 ; X=Br
b, R=R′=CH3 ; X=Cl
c, R=H ; R′=An(endo) X=Cl
d, R=An ; R′=H(exo) X=Cl
46
47
48
Uracil
49
+
50
51a, R=H ; R′=An ; R″=Bz(endo)
b, R=An ; R′=H ; R″=Bz(exo)
c, R=An ; R′=R″=H(exo)
d, R=An ; R′=H ; R″=Ac(exo)
52
53
54

4. Synthesis and Properties of Nitrogen-Bridged Cyclonucleosides

4.1. Introduction

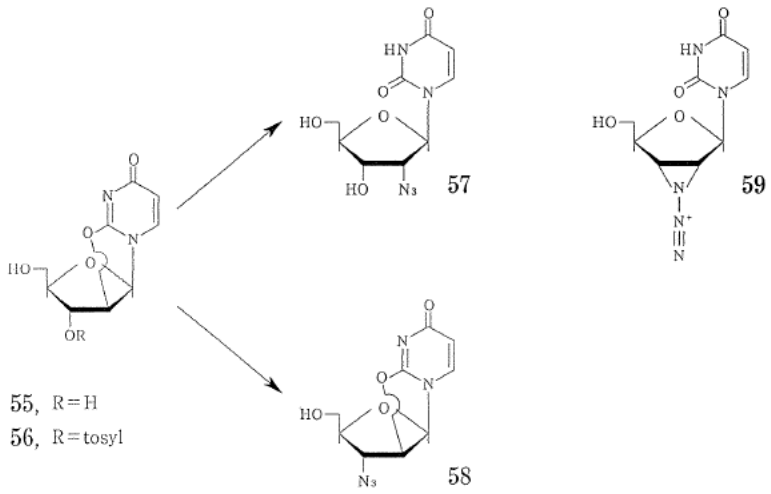
As described in the paragraph 3.1, cyclonucleosides are important modified nucleosides not only as optical models but also as synthetic intermediates. Epimerization of the 2′- or 3′-hydroxyl of the pyrimidine nucleosides can usually be achieved by hydrolysis of 2,2′-[30] or 2,3′-anhydro[30] bridges, leaving the nucleobase intact, while hydrolysis of 6,2′-anhydro pyrimidine nucleosides[44] causes epimerization at the C-2′ with concomitant introduction of a hydroxyl onto the C-6 of the base. Hydrogenolysis of purine 8,2′-*S*-cyclonucleosides gives the corresponding 2′-deoxynucleosides with the intact aglycone.[31] In contrast with the studies related to the synthesis and chemistry of oxygen- and sulfur-bridged nucleosides as exemplified above, the recorded synthesis of nitrogen isostere was quite limited and no chemistry inherent in the *N*-cyclonucleosides was disclosed until the beginning of the 1970's. This general situation spurred us to study the synthesis and chemistry of *N*-cyclonucleosides. *The working hypothesis was that the common C-N bond is intrinsically stable under hydrolytic conditions, but this stability may cause, on the contrary, an "unexpected" molecular reorganization of a N-cyclonucleoside under reasonably forcing conditions.*

4.2. Synthesis of 2,3′-Imino-1-(β-D-lyxofuranosyl)uracil and Its Derivatives

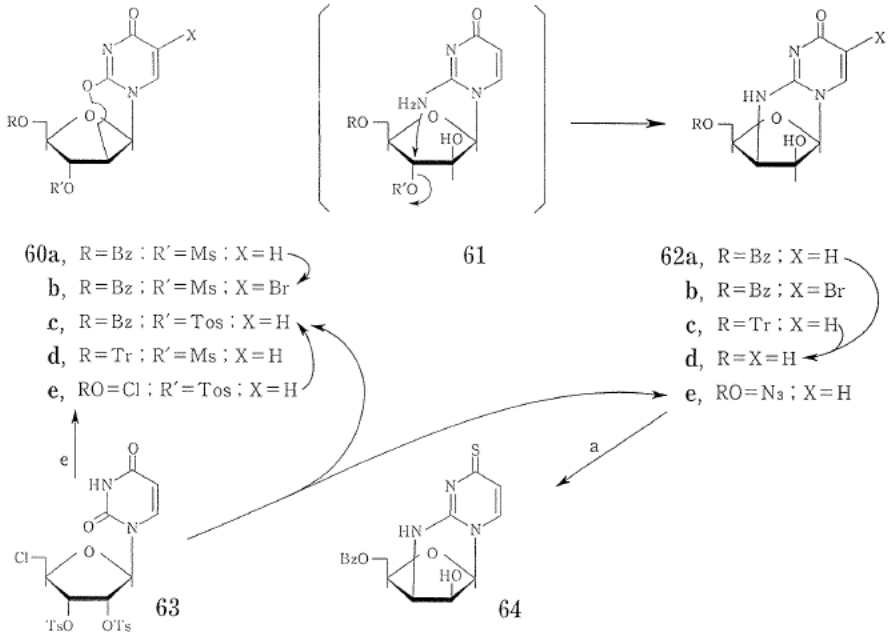
Introduction of an azide group followed by reduction has long been one of the standard methods for the synthesis of aminosugars and aminosugar nucleosides, while the use of other aspects of an azide reaction for the alterations of nucleosides is notably missing; an azide is known to have multiple reactivity leading to a nitrene, imine and/or triazole depending upon reaction conditions and the character of substrate.[45] Moffatt et al.[46] showed that the reaction of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (**55**) with lithium azide gives 2′-azido-2′-deoxyuridine (**57**), while Hirata[47] obtained 2,2′-anhydro-1-(3′-azido-3′-deoxy-β-D-arabinofuranosyl)uracil (**58**) from compound **56** and sodium azide (**Scheme 8**). For the latter reaction, an azidonium intermediate **59** was proposed by Fox et al.[48] without any direct evidence. The proposed intermediate **59** was, however, interesting since it suggested eventual synthesis of a compound with a "down" 2,3-imino function under appropriate conditions.

In such a complex situation of azide chemistry in the nucleoside field, we prepared several derivatives of uracil 2,2′-anhydro nucleosides (**60a-e**) (**Scheme 9**).[49] Reaction of 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**60a**) with ammonium azide generated *in situ* at 90°C gave, unexpectedly, 2,3′-imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**62a**), which was also obtained from **60c**. Similarly, compound **60b** as well as **60d** gave the corresponding 2,3′-imino nucleoside **62b** and **62c**, respectively, while similar treatment of **60e** gave **62e**, which was more conveniently obtainable from **63**. Clearly, ammonium azide became the source of ammonia: ammonia gradually released from ammonium azide at 90°C was instantaneously intercepted by **60** to give **62** in moderate to good yields through the intermediate **61**. The merit of this method of imino-bridging is conservation of the 5′-*O*-benzoyl group even under the basic conditions used. Thus, the thiation product **64** from **62a** could be easily isolated. Deprotection of **62a** and **62c** gave the parent compound **62d**, which, however, resisted hydrolytic cleavage of the imino-bridge using 3N KOH aiming at "up" amination at the 3′-position.

Scheme 8



Scheme 9



4.3. *Intramolecular Thermal Reactions of the Derivatives of 5′-Azido-5′-deoxyuridine. Regio- and Stereospecific Synthesis of Reversed Nucleosides Carrying a Substituted Five-Membered Heterocycle*

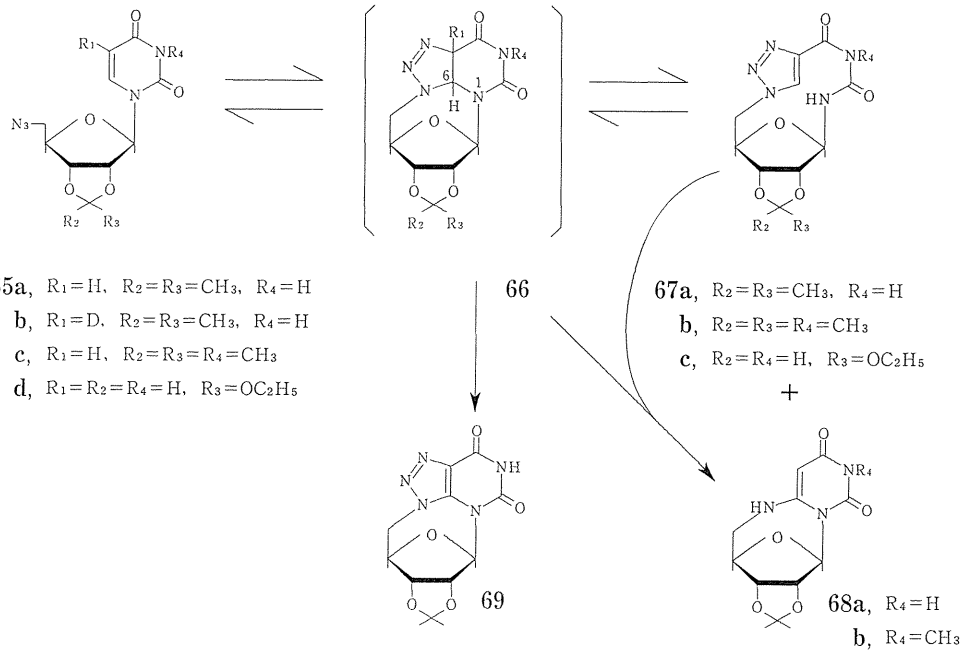
Synthetic exploitation of pyrimidine as dipolarophiles or dienophiles is important in view of the great variability of the expected products and the direct use of natural nucleosides with a given stereochemistry involving, among others, that of anomeric position. From this point of view, 1-(5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)uracil (**65a**)[50] (**Scheme 10**) is a readily accessible, simple model compound for roughly evaluating the reactivity of the "naked" 5,6-double bond with 1,3-dipoles.

Heating **65a** in dry toluene at 110°C gave N^1,5′-anhydro-N^{ω}-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-4-allophanoyl-1,2,3-triazole (**67a**) (80%) and 6,5′-imino-1-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)uracil (**68a**) (5.3%).[51,52] In search for the most plausible intermediate **66** for the formation of **67a** and **68a**, **65a** and DDQ were heated in toluene to give the known 8-azaxanthine derivative **69**[53] and **68a**, no trace of **67a** being detected. On heating **67a** with DDQ as above, the concurrent formation of **68a** and **69** was observed.

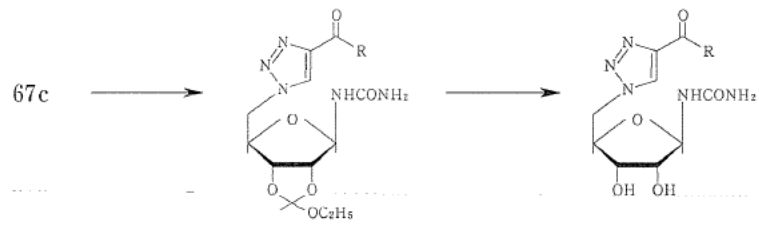
These results indicated that **66** and **67a** are interconvertible at this temperature and the immediate precursor of **68a** is **66**. Partial reversion of **67a** to **65a** was also observed when **67a** was heated in dioxane at 110°C.

This is the first synthesis of a *N*-bridged nucleoside by triazoline decomposition. The same experiment using a 5-deuterated azide (**65b**) also gave **67a** and **68a**, indicating a net 1,3-shift of D-5 to N^{ω}.[51] Analogous thermal reaction using **65c** gave **67b** and **68b** in 55 and 8% yield, respectively.[52] For the purpose of obtaining the deprotected form of **67a** under milder acidic conditions, **65d** was synthesized and subjected to the similar thermal reaction to

Scheme 10



Scheme 11



70a, R=OCH_3 **71a**, R=OCH_3
b, R=NH_2 **b**, R=NH_2

give **67c** as a major product.[52] Several trials for the selective deprotection of **67a** or **67c** led to decomposition.

Availability of **67a** and **67c** in good to excellent yield and the presence of the multifunctional allophanoyl chain (-CO-NH-CO-NH-) gave an impetus to further transformations. Heating **67a** or **67c** in refluxing methanol allowed regioselective methanolysis to afford 5-(4-methoxycarbonyl-1,2,3-triazol-1(1H)-yl)-5-deoxy-2,3-*O*-isopropylidene-1-ureido-1-β-D-ribofuranose (**72a**) (**Scheme 12**) or its 2,3-*O*-ethoxymethylene analogue (**70a**) (**Scheme 11**).

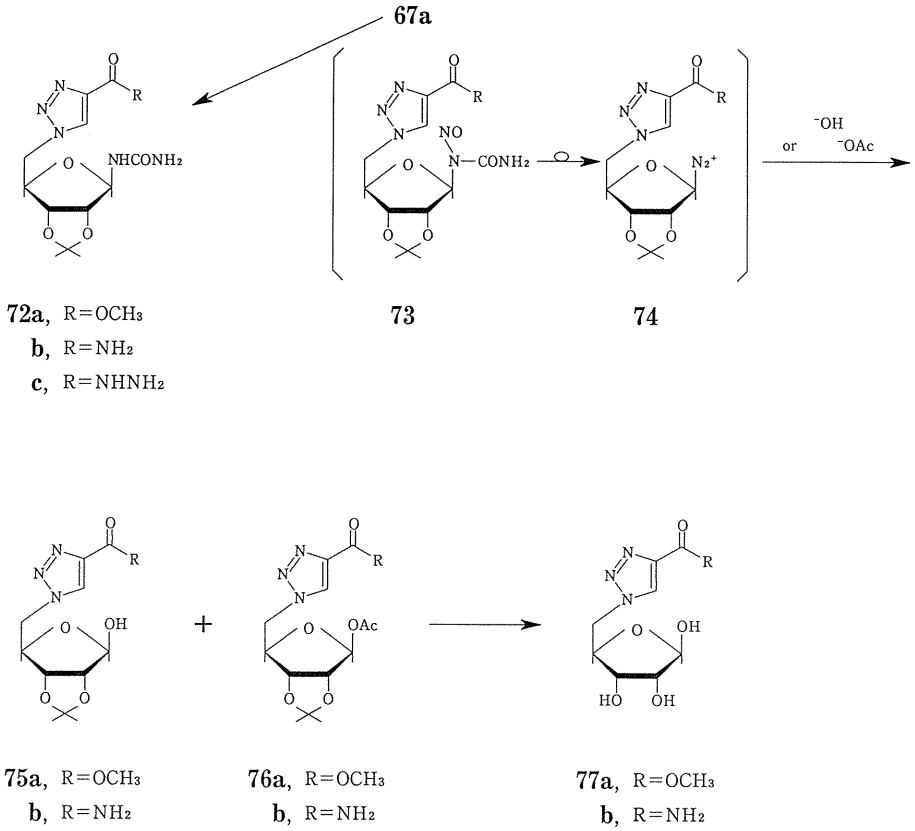
This initial finding was encouraging in view of the recent, broad scope of synthesis of nucleosides containing five-membered polyazaheterocycles[54] and also of the multiple implications endowed to "reversed" nucleosides.[54] Compound **67c** with NH_3/EtOH gave 5-(4-carboxamido-1,2,3-triazol-1(1H)-yl)-5-deoxy-2,3-*O*-ethoxymethylene-1-ureido-1-β-D-ribofuranose (**70b**) in 80% yield. Careful deprotection of **70a,b** gave the corresponding reversed nucleosides (**71a,b**). Compound **67a** with ethanol saturated with ammonia and with very dilute ethanolic hydrazine gave **72b** and **72c**, respectively. Treatment of **72a** with $NaNO_2$/80% AcOH gave 5-(4-methoxycarbonyl-1,2,3-triazol-1(1H)-yl)-5-deoxy-2,3-*O*-isopropylidene-1-β-D-ribofuranose (**75a**) and its 1-*O*-acetyl analogue (**76a**). Deprotection of **75a** or the double deprotection of **76a** with 90% trifluoroacetic acid yielded 5-(4-methoxycarbonyl-1,2,3-triazol-1(1H)-yl)-5-deoxy-1-β-D-ribofuranose (**77a**). Similar chemical modification of **72b** gave the corresponding analogue **75b**, **76b** and **77b**.

*This is the first example of transformation through an anomeric diazo species in the area of nucleosides or carbohydrates and the strict retention of the anomeric configuration is surprising. The overall result provides not only a short route to the cyclonucleosides such as **69** or **68** but also allows the use of the C_4-C_5-C_6 unit in the uracil skeleton as a "masked" synthon for reversed nucleosides carrying substituted polyazaheterocycles that are bonded to the sugar moiety at a defined position.*[55] It must be added that similar thermal reaction of the 5-bromo derivative of **65a** gave only compound **69** (**Scheme 10**).[53] A study on the steric requirement for the cleavage between N^1 and C-6 of the pyrimidine part of the intermediate **66** was also carried out using a more simpler model system.[56]

4.4. Convenient Synthesis of Purine 8,5′-Imino Cyclonucleosides

Limiting the view point to the cyclonucleoside synthesis in the purine series, the accumulated data have demonstrated the possibility of bonding the 8-position of the base with C-2′, C-3′ and C-5′ of the sugar through a heteroatom (O, S or limitedly N)[31,57] or directly with C-5′.[58] In contrast with the synthesis and chemical studies in the area of oxygen and sulfur-

Scheme 12



72a, R=OCH_3
b, R=NH_2
c, R=$NHNH_2$

73 **74**

75a, R=OCH_3
b, R=NH_2

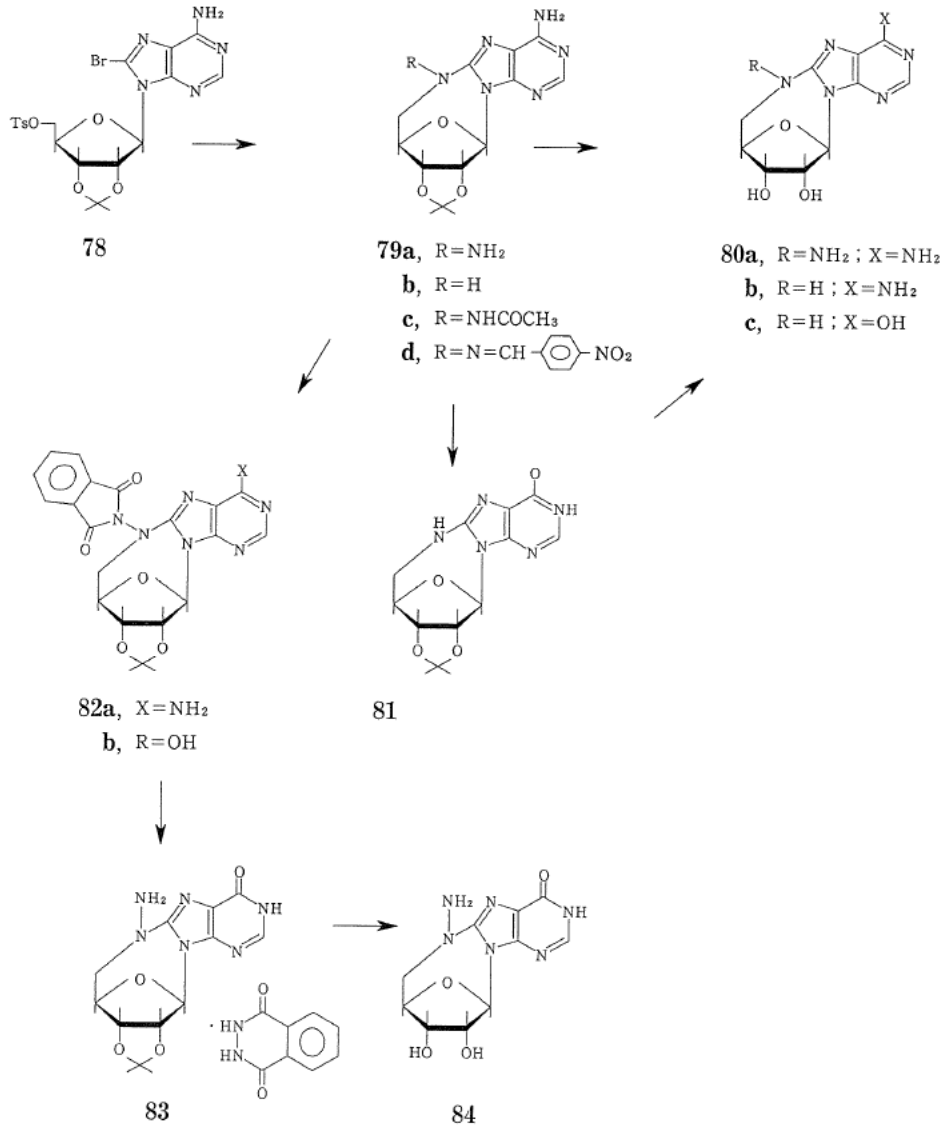
76a, R=OCH_3
b, R=NH_2

77a, R=OCH_3
b, R=NH_2

bridged nucleosides, the recorded synthesis of nitrogen isostere was quite limited: only four 8,2′-imino cyclonucleosides were known[57a,b] later in the 1970's. Difficulty in synthesizing 8,5′- or 8,3′-imino purinenucleosides stems from the facile intramolecular quaternization between the N^3 of the base and C-5′ or C-3′ carrying a leaving group.

8-Aminoadenosine is known to exhibit significant inhibition of sarcoma 180 ascite cells and is resistant toward adenosine deaminase.[59] 8-Aminopurinenucleosides also attracted much interest because of their structural similarity to a paralytic marine toxin, saxitoxin.[60] These findings gave an impetus to the extensive synthesis of a variety of 8-aminopurinenucleosides and their analogues.[61] In view of these facts, synthesis of purine 8,5′-iminonucleosides and analogues which are restricted in an anti-conformation seemed to be of primary importance, and I herein describe a simple and effective synthesis of this class of compounds from 2′,3′-*O*-isopropylidene-5′-*O*-tosyl-8-bromoadenosine (**78**)[62] and hydrazine as the nitrogen source (**Scheme 13**).[63] Compound **78** was treated with a large excess of hydrazine at room temperature to give 8,5′ aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**79a**) in 90% yield. Compound **79a** was derived to compounds **79c-d** to confirm its 8,5′-aminimno structure. Oxidation of **79a** with iodine pentoxide gave a 95% yield of

Scheme 13



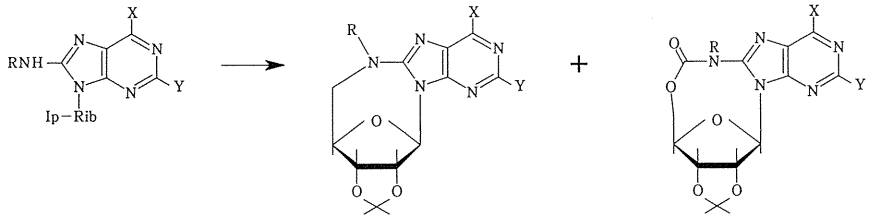
8,5′-iminonucleoside **79b**. Compounds **79a,b** were deprotected to the corresponding parent compounds **80a,b**. Diazotization of **79a** gave 8,5′-imino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**81**), which was deblocked to 8,5′-imino-9-(5′-deoxy-β-D-ribofuranosyl)hypoxanthine (**80c**). Compound **79a** with phthalic anhydride gave the 8,5′-phthalimidimino analogue (**82a**), which was diazotized to **82b**. Treatment of **82b** with

hydrazine gave the 8,5′-aminimno hypoxanthine analogue (**83**) as a phthalazin-1,4-dione complex which was deprotected to the parent compound **84**. A similar study was conducted in the guanosine series.[64]

Later on, these series of works were developed to the "Systematic General Synthesis of Purine 8,5′-Imino and Substituted-Imino Cyclonucleosides"[65,66] using common dehydration methods [Method A: $(PhO)_2CO$ (1.5 equiv.)/DMF, 135°C, 2 h; Method B: N,N′-Carbonyldiimidazole (CDI) (1.5 equiv.)/DMF, 125°C, 2 h; Method C: Diethyl azodicarboxylate (1.5 equiv.)/Ph_3P (1.5 equiv.)/THF, room temp., 10 h]. The three dehydration methods were applied to the substrates **85a-i**, and the results were compared (**Scheme 14**).

Although the yields depended upon the substrate species and no significant difference between the three methods was not detected, a new type of cyclonucleosides were discovered. Thus, the reaction of **85h** with diphenyl carbonate gave 8,5′-(*N*-benzylcarbamoyloxy)-2-dimethylaminomethylidene-9-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)guanine (**87a**). Similarly, compound **85j** with diphenyl carbonate or CDI yielded its *N*-allyl analogue (**87b**). The carbamate ester function in **87b** was unaffected by the weakly acidic conditions used to remove the dimethylaminomethylidene function, and compound **87c** was obtained in a high yield. It was further confirmed that a carbamate ester such as **87** is unlikely to be an intermediate for the 8,5′-imino cyclization. The formation of compounds **87** suggested *the possibility of spanning nucleoside molecules with a longer bridge to expand the range of the*

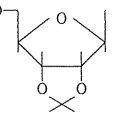
Scheme 14



85	X	Y	R
a	NH_2	H	Me
b	OH	H	Me
c	NH_2	H	Bn
d	OH	H	Bn
e	NH_2	H	Al
f	OH	H	Al
g	OH	NH_2	Bn
h	OH	DMAMA	Bn
i	OH	NH_2	Al
j	OH	DMAMA	Al

86	X	Y	R
a	NH_2	H	Me
b	OH	H	Me
c	NH_2	H	Bn
d	OH	H	Bn
e	NH_2	H	Al
f	OH	H	Al
g	OH	DMAMA	Bn
h	OH	NH_2	Bn
i	OH	NH_2	Al

87	X	Y	R
a	OH	DMAMA	Bn
b	OH	DMAMA	Al
c	OH	NH_2	Al

Me=methyl
Bn=benzyl
Al=allyl
DMAMA=
dimethylaminomethylideneamino
Ip–Rib= 

models of base-sugar conformation. An X-ray study revealed that compound ***87b*** *has an unprecedented base-sugar torsion angle.*[67,68]

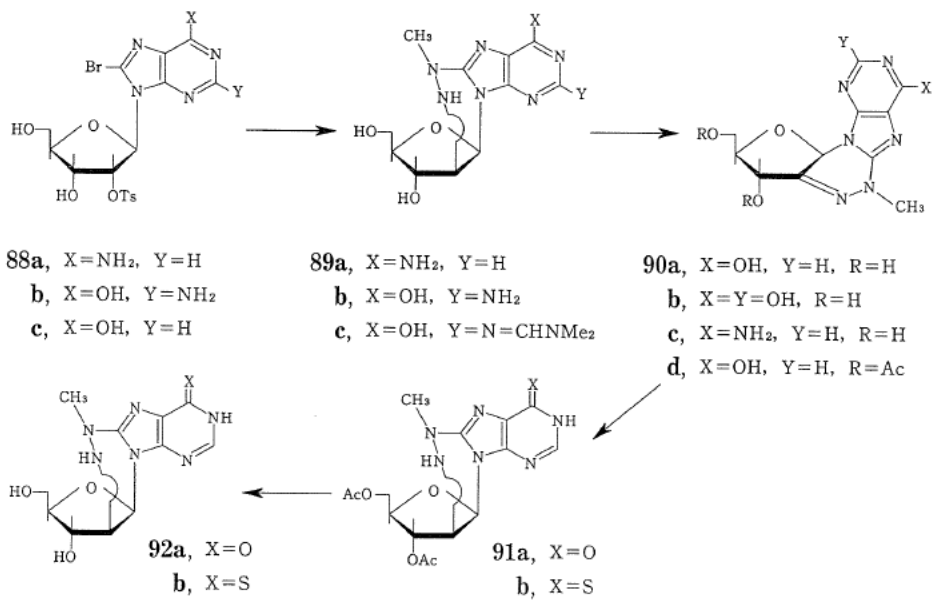
4.5. Long-Bridged Cyclonucleosides

Among the hitherto known, large number of pyrimidine and purine cyclonucleosides, notably missing members are those having a base-sugar bridge constructed by multiple atoms. A few of such compounds were synthesized by us (Paragraph 4.4., compound **87**). In view of the numerous theoretically possible base-sugar conformations in natural nucleosidic materials, it is important to try to expand the presently limited bounds of the model conformations by bonding the base and sugar moieties with a reasonably longer chain. This type of cyclonucleosides might also be useful as a new type of synthetic intermediates for bifunctionalization at the base and sugar moieties, depending upon the chemical properties of the bridge. Herein described are the syntheses and reactions of some purine 8-*N*-cyclonucleosides having a diatomic bridge.

Heating 8-bromo-2′-*O*-tosyladenosine (**88a**)[69] with methylhydrazine in methanol gave 8,2′-(N^{α}-methylhydrazo)-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (**89a**) (85%) (**Scheme 15**).[70] Similarly, compound **88b**[69] was converted into the guanine analogue (**89b**), which was derived to more soluble **89c**. Compounds **89a,b** with nitrous acid gave another type of cyclonucleosides, 2′,N^{β}-didehydro-8,2′-(N^{α}-methylhydrazo)-9-(2′-deoxy-β-D-arabinofuranosyl)hypoxanthine (**90a**) and its xanthine analogue (**90b**), respectively. Compound **90a** was acetylated to **90d**, which was reduced to **91a**. Thiation of **91a** gave **91b**. Compound **91a,b** were deprotected to the corresponding parent compounds **92a,b**.

The high yield synthesis of **89a** spurred us to examine further transformations. The methylhydrazo bridge should intrinsically be stable under hydrolytic conditions, and hence we aimed to cleave the glycosidic bond for further recombination transformations. Thus,

Scheme 15



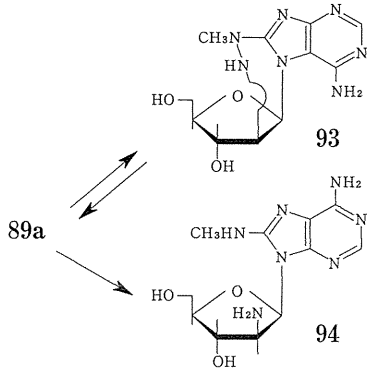
prolonged heating of **89a** in a 5:1 mixture of methanol and concentrated hydrochloric acid gave an equilibrium mixture of **89a** and 8,2′-(N^{α}-methylhydrazo)-7-(2′-deoxy-β-D-arabinofuranosyl)adenine (**93**) (**Scheme 16**). Catalytic hydrogenolysis of **89a** gave 2′-amino-8-(methylamino)-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (**94**). *This is the first synthesis of an aminosugar nucleoside via a cyclonucleoside.*

We next attempted to construct a *N*-methyloxamido bridge between C-8 and C-2′ of adenosine (**Scheme 17**).[70] Reaction of **88a** with *N*-methylhydroxylamine gave 8-[(methylamino)oxy]-9-(2′-*O*-tosyl-β-D-ribofuranosyl)adenine (**95**), 8,2′-(N^{α}-methyloxamido)-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (**96**) and 8-(methylamino)-9-(β-D-arabinofuranosyl)adenine (**97**). Compound **97** formed from **96** by reduction with *N*-methylhydroxylamine. The strong CD extrema near the major UV absorptions of **89a,b, 92a** and **96** reflect their high anti-conformations in solution. *The conversion of **89a** to **94** or of **96** to **97** exemplifies the importance of such cyclonucleosides with a breakable diatomic bridge in terms of epimerizing bifunctionalization.*

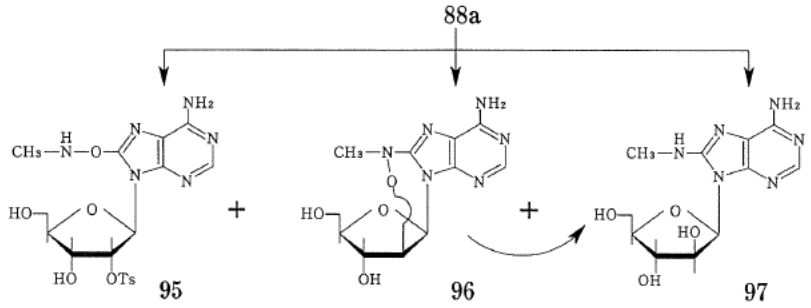
This line of work was then extended to spanning the C-8 and C-3′ of some purine nucleosides with the similar diatomic bridges (**Scheme 18**).[71] Reaction of 8-bromo-3′-*O*-[(2,4,6-triisopropylphenyl)sulfonyl]adenine (**98a**)[69] with methylhydrazine gave compound **99a** quantitatively. Similarly, **98b** was converted into **99b**. Heating **99a** under basic conditions gave 8,3′-(N^{α}-methylhydrazo)-9-(3′-deoxy-β-D-xylofuranosyl)adenie (**100a**) (25%) and 9-[2′,3′-(methylamino)epimino]-2′,3′-dideoxy-β-D-lyxofuranosyl]adenine 8,*N*-cyclonucleoside (**101a**) (33%). In recent years, a small number of nucleosides with a 2′,3′-aziridine ring were synthesized by Robins and coworkers[72] and by us.[28] The former authors synthesized 9-(2,3-epimino-2,3-dideoxy-β-D-ribofuranosyl)adenine and its lyxofuranosyl isomer principally from a biological interest by analogy with natural products having a fused aziridine ring such as mitomycin C. Compound **99b** was similarly converted into **100b** (21%) and **101b** (35%).

Compound **100a** with diphenyl carbonate gave another tricyclic cyclonucleosides, 9-[3′,5′-[*N*-(methylamino)azetidino]-3′,5′-dideoxy-β-D-xylofuranosyl]adenine 8,*N*-cyclonucleoside (**106**). Hydrogenolysis of **100a** gave the aminosugar nucleoside **102**. Compounds **101a,b** were acetylated to the corresponding 5′-*O*-acetyl derivatives (**103a,b**), which were then reduced to 5′-*O*-acetyl-8,2′-(N^{α}-methylhydrazo)-9-(2′,3′-dideoxy-β-D-arabinofuranosyl)adenine (**104a**) and the hypoxanthine analogue (**104b**). These were deprotected to **105a,b**. An aziridine is generally known to be labile to acid: protonation at the nitrogen atom

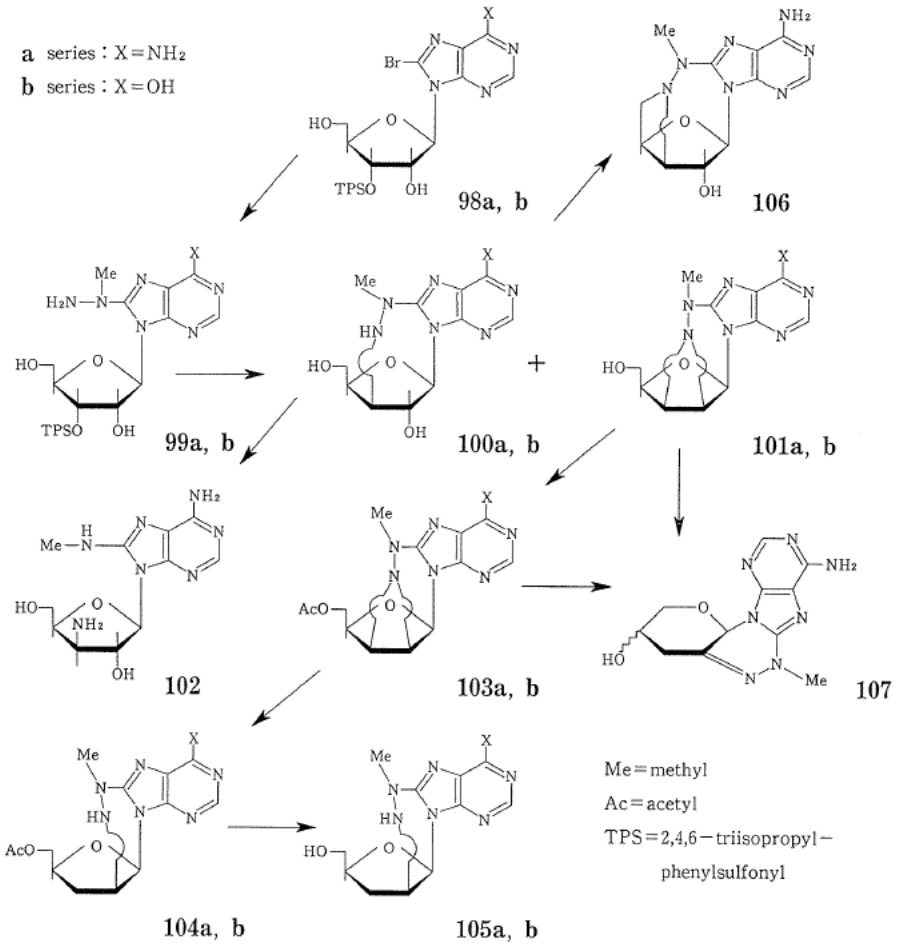
Scheme 16



Scheme 17



Scheme 18

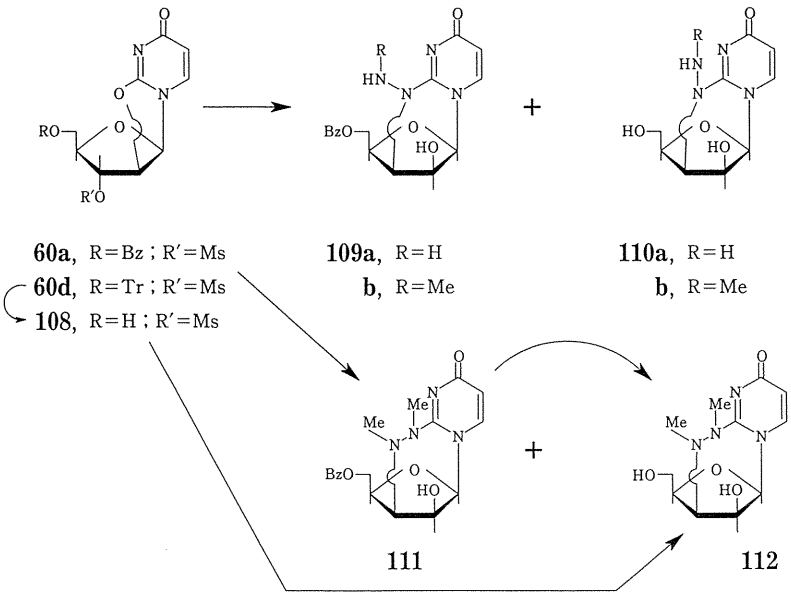


is usually followed by ring opening with introduction of a nucleophile. Treatment of **101a** with 1N HCl/MeOH afforded 2′,N^{β}-didehydro-8,2′-(N^{α}-methylhydrazo)-9-(2′,3′-dideoxypyranosyl)adenine (**107**) as the major product, which was also obtained from **103a** in the same reaction. The net result of the conversion of **101a** into **107** is the fission and recombination of the anomeric bond with skeletal rearrangement involving hydrogrn transfer from C-2′ to C-3′. *Such a furanose to pyranose conversion was unprecedented in the field of cyclonucleoside chemistry and spurred us to further transformations along this line.*[73]

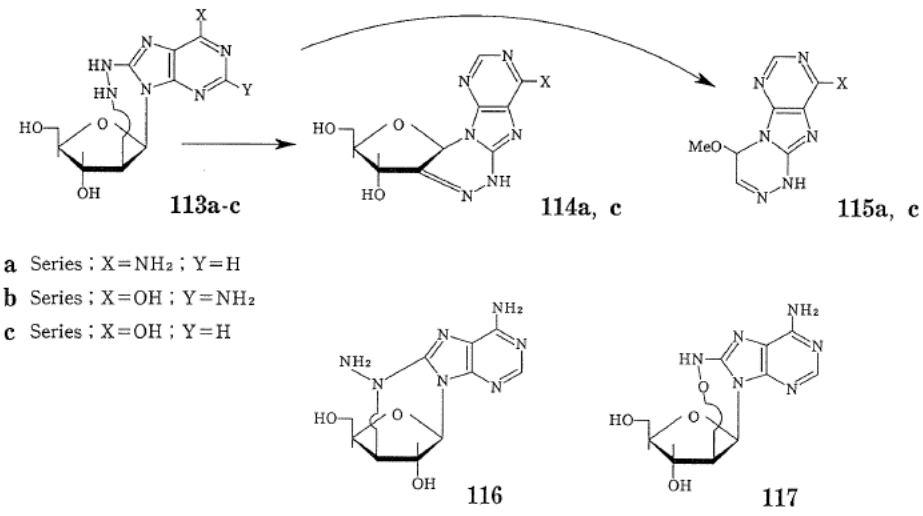
A preliminary examination was carried out to probe the possibility of spanning the C-2 and C-3′ of pyrimidine nucleosides (**Scheme 19**).[74] Reaction of **60a** with hydrazine monoacetate gave 2,3′-aminimino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**109a**) in 70% yield. Similarly, **60a** with methylhydrazine monoacetate gave **109b** in a good yield, substitution by the amino group having occurred probably owing to the steric hindrance by the methyl in contrast with the foregoing cases of purine nucleosides. On the other hand, reactions of **60a** with 1,2-dimethylhydrazine monoacetate under forcing conditions gave 2,3′-(N^{α},N^{β}-dimethylhydrazo)-1-(5′-*O*-benzoyl-3′-deoxy-β-D-lyxofuranosyl)uracil (**111**) and its deblocked form (**112**) in unspecified low yields. Compound **112** is obtainable more economically from **108**. Although the possibility of diatomic bridging between the C-2 and C-3′ was confirmed, further experimental scrutiny involving the choice of the substrates would be needed for applied chemistry of long-bridged pyrimidine nucleosides.

In view of the known oxidative nitrogen release from carbocycles containing a "naked" hydrazo group during various radical reactions,[75] we were particularly intrigued by the unequivocal synthesis of cyclonucleosides having a hydrazo bridge. Compounds **88a-c** (**Scheme 15**) with hydrazine gave the corresponding 8,2′-hydrazo-9-(2′-deoxy-β-D-arabinofuranosyl)-purines (**113a-c**) in good yields (**Scheme 20**).[76] Compounds **113a,c** were oxidized to **114a,c** with the use of hypobromous acid, while sodium methoxide catalyzed aerial oxidation of

Scheme 19



Scheme 20



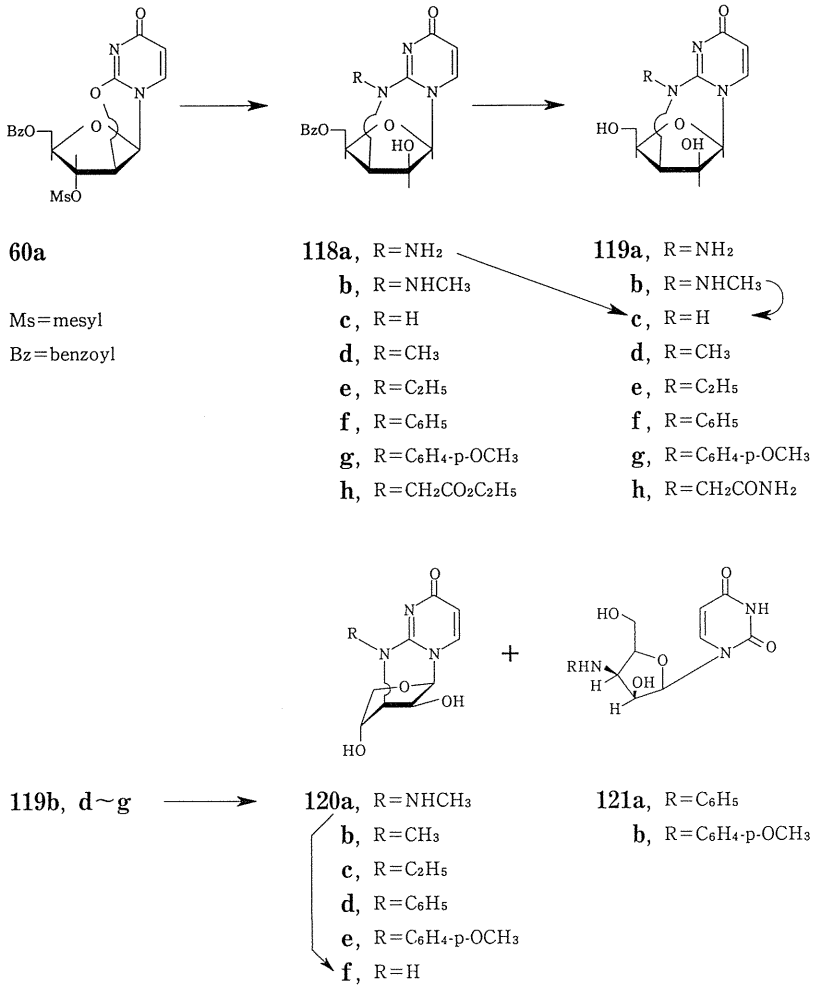
113a,c in methanol formed the corresponding 9-substituted-4-methoxy-1H-triazino[3,4-e]purines (**115a,c**) via **114a,c** by an unknown mechanism. Compound **98a** (**Scheme 18**) with hydrazine gave the 8,3′-aminimino nucleoside **116**, while **88a** with hydroxylamine gave the 8,2′-oxamido nucleoside **117** through 8-hydroxylamino-2′-*O*-tosyladenosine.

4.6. Syntheses and Hydrolysis Reactions of 2,3′-(Substituted-imino) Pyrimidine Nucleosides[79,80]

It was shown in Paragraph 4.5. that the ≡C-NH- or >C=N- bridge bond in some adenine nucleosides is sufficiently stable under hydrolytic conditions to allow the fission-recombination of the glycosidic bond. In 1968 Fox and coworkers[77] reported that 2,3′-imino- and 2,3′-(substituted-imino)-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)thymines were stable under acid and basic conditions which readily cause a 2,3′-anhydro uracil nucleoside to react, and that hence an "up" 3′-amino-3′-deoxynucleoside could not be obtained from these imino nucleosides even under strongly alkaline conditions (7N KOH, room temperature, 3 weeks). Accordingly, we decided to challenge this problem (**Scheme 21**).[78] Compound **60a** with appropriate amines gave the corresponding 2,3′-(substituted-imino)-1-(3′-deoxy-β-D-lyxofuranosyl)uracils (**118a-h**), which were deprotected to **119a-h**. Compound **119c** was obtained directly from **118a** by treatment with isoamyl nitrite by an unknown mechanism or from **119b** by oxidation with m-chloroperbenzoic acid (MCPBA).

Prolonged heating of **119b** with a 1:1 mixture (v/v) of 6N NaOH and ethanol at 75–80°C gave 2,3′-[(methylamino)imino]-1-(3′-deoxy-β-D-lyxopyranosyl)uracil (**120a**). Similar treatment of **119d,e** gave the corresponding analogues **120b,c**. On the other hand, similar treatment of 2,3′-arylimino nucleosides **119f,g** gave the 2,3′-arylimino pyranosyl nucleosides (**120d,e**) and the 3′-arylamino-3′-deoxy-lyxofuranosyl nucleosides **121a,b** in similar yields. Thus, in the case of 2,3′-arylimino nucleosides the attack of a hydroxide anion occurred both at the C-2 and anomeric carbon. Formation of **121** is explicable by the aryl-promoted resonance stabilization of the intervening arylimino anion (Aryl-N^--).[78] *It must be*

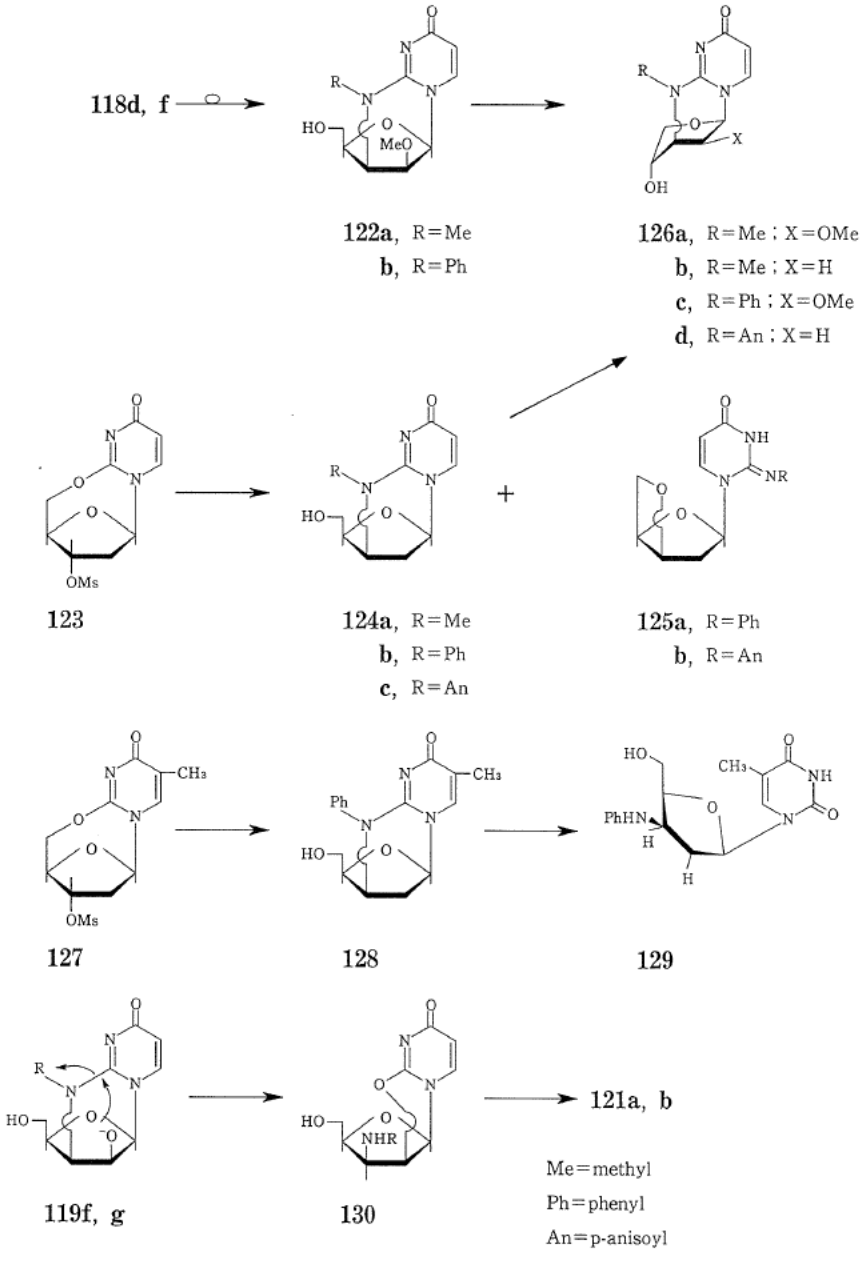
Scheme 21



*added that the isomerization of **119** to **120** occurred with retention of chirality:* the negative Cotton effects in the 243–262 nm region in the CD spectra of **119d,e** and **120b,c** coincided with the generally accepted notion of the syn-conformation of pyrimidine nucleosides.[78] Thus, this piece of work provided the *first example of the hydrolytic fission of the 2-(substituted-imino)-bridge and also of the glycosidic bond under alkaline conditions.*

Because the 2′-hydroxyl in common nucleosides is known to possess higher acidity under the influence of the rather electronegative heterocyclic base, further experiments were conducted to gain an insight into the role of a 2′-hydroxyl anion, using some 2,3′-(substituted-imino)pyrimidine nucleosides (**Scheme 22**).[79] Compounds **118d,f** (**Scheme 21**) were converted into 2′-methoxy analogues (**122a,b**), while the 2′-deoxy analogues (**124a,b,c**) were prepared from 2′-deoxyuridine *via* a 2,5′-anhydro intermediate **123**. Similar alkaline hydrolysis of **122a,b** and **124a-c** gave exclusively the corresponding isomerization products **126a-d**

Scheme 22


118d, f
122a, R=Me
b, R=Ph
126a, R=Me ; X=OMe
b, R=Me ; X=H
c, R=Ph ; X=OMe
d, R=An ; X=H
123
124a, R=Me
b, R=Ph
c, R=An
125a, R=Ph
b, R=An
127
128
129
119f, g
130
121a, b
Me=methyl
Ph=phenyl
An=p-anisoyl

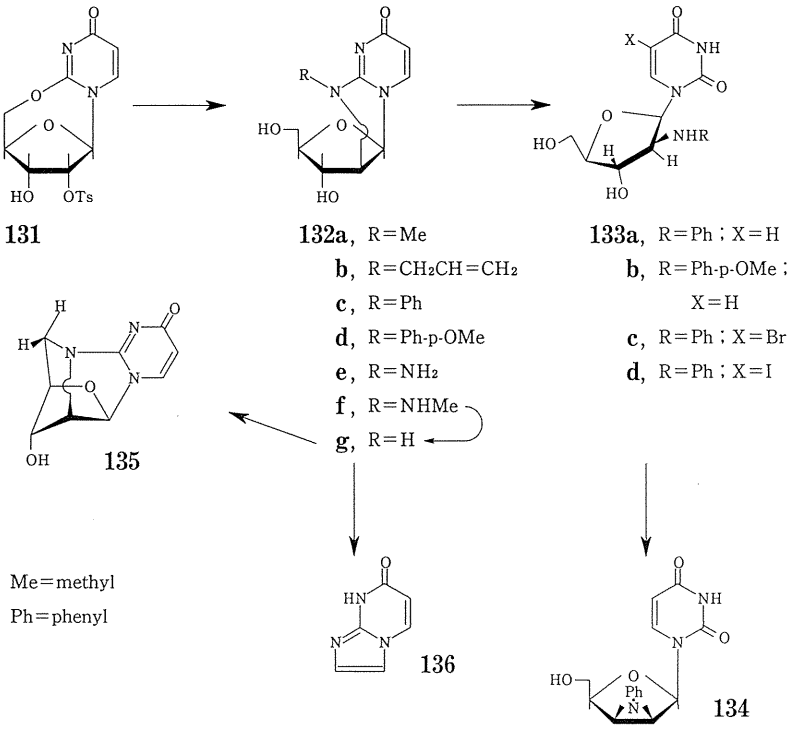
generally in better yields than the cases of **120** (**Scheme 21**) in far shorter reaction times. Treatment of the thymine analogue **128** obtained from **127** with another medium, 3N NaOH in neat EtOH, gave, surprisingly, a nearly quantitative yield of 1-(3′-anilino-2′-deoxy-β-D-*threo*-pentofuranosyl)thymine (**129**) but no isomerization product. On the basis of this observation, **119f** was treated with a more dilute ethanolic solution of NaOH (1N NaOH/EtOH) to afford **121a** almost exclusively (80%), suggesting an intramolecular mechanism for the formation of **121a**.

Thus, this piece of work corroborated the evidence that some of the basic nucleophiles such as hydroxide or alkoxide ion can directly attack the anomeric carbon in pyrimidine nucleosides. We also disclosed that the formation of **121a,b** from **119f,g** must have occurred through a 2,2′-anhydro nucleoside (**130**) formed by entropically favorable, intramolecular attack of the 2′-hydroxyl anion in **119f,g**. In contrast, the thymine analogue **128** underwent the C_2-N fission exclusively by the direct attack of an external hydroxide ion. This difference of reactivity between the uracil and thymine analogues might have stemmed from inductive effect by the 5-methyl, which would make the anomeric carbon less electrophilic.

4.7. Syntheses and Hydrolysis Reactions of 2,2′-Imino- and 2,2′-(Substituted-imino)pyrimidine Nucleosides

Dibutylstannylation of 2,5′-anhydrouridine followed by *in situ* tosylation gave a good yield of 2′-*O*-tosyl-2,5′-anhydrouridine (**131**) (**Scheme 23**)[80]. Reaction of **131** with methylamine, allylamine, aniline, p-anisidine, hydrazine, methylhydrazine, ammonia gave the corre-

Scheme 23



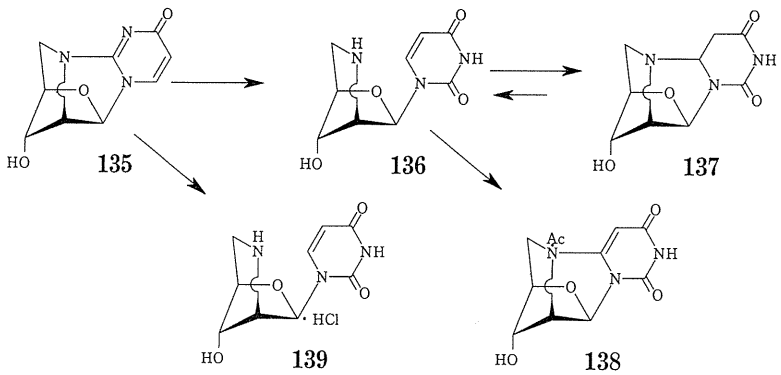
sponding 2,2′-(substituted-imino)- and 2,2′-imino-1-(2′-deoxy-β-D-arabinofuranosyl)uracils (**132a-g**). Compound **132g** was also obtainable from **132f** by MCPBA-oxidation. Alkaline hydrolysis, first conducted using **132a,b** and **132f**, resulted in complex decomposition: **132b** was used in the expectation that the known allyl to isopropenyl isomerization under strongly alkaline conditions[81] would occur to facilitate the hydrolysis of the resulting conjugated imino bridge.[78] In the event, the arylimino bridge in **132c,d** proved to be extraordinarily susceptible to alkaline hydrolysis: **132c** and **132d** could be quantitatively converted into 1-(2′-anilino-2′-deoxy-β-D-arabinofuranosyl)uracil (**133a**) and the 2′-p-anisidino analogue (**133b**) in 2 and 7 min, respectively, at room temperature by treatment with 2N NaOH-MeOH (1:1).

These reaction conditions are in sharp contrast with those applied to **119f,g**, i.e., 6N NaOH-EtOH (1:1); 75–80°C; 21 h for **119f** and 45 h for **119g**.[78] In both cases, cleavage of the more electronegative phenylimino bridge is faster. This unusually fast hydrolysis may reflect abnormal molecular distortion of **132c,d** as suggested by the close scrutiny of their general spectral data,[80] besides the proposed, aryl-promoted resonance stabilization of an intervening imino anion.[78] The Mitsunobu reaction[82] with **133a** gave 1-[2′,3′-dideoxy-2′,3′-(*N*-phenyl)epimino-β-D-lyxofuranosyl]uracil (**134**), the first pyrimidine nucleoside having an up" epimino group, while the same reaction with the use of **132g** gave 5′,*N*-anhydro-2,2′-imino-1-(2′-deoxy-β-D-arabinofuranosyl)uracil (**135**). This compound contains a highly strained 3-ring system (*vide infra*). Rather surprisingly, alkaline hydrolysis of **132g** gave solely, by unknown mechanism, a good yield of blue-fluorescent imidazo[1,2-a]pyrimidine-7(8H)-one (**136**). This cycloreversion like fragmentation is unprecedented in cyclonucleoside chemistry and needs a separate mechanistic study. Finally, **133a** were converted into its 5-bromo (**133c**) and 5-iodoanalogue (**133d**) for biological evaluation; they were of interest because they contain intact 5′- and 3′-hydroxyl groups necessary for incorporation into a nucleic acid.

4.8. Strain-Assisted, Unusually Facile Hydrolysis of the Nitrogen-Bridge of Compound 135[83]

The facile synthesis of compound **135** in the above paragraph allowed us to envisage strain-assisted hydrolysis of multi-cyclic *N*-bridged nucleosides. This compound proved to be instantaneously hydrolyzed to 1-(2′,5′-*N*-anhydro-5′-amino-2′,5′-dideoxy-β-D-arabinofuranosyl)uracil (**136**) with the use of 1:1 mixture of 1N NaOH and MeOH at room temperature (**Scheme 24**).[83]

Scheme 24



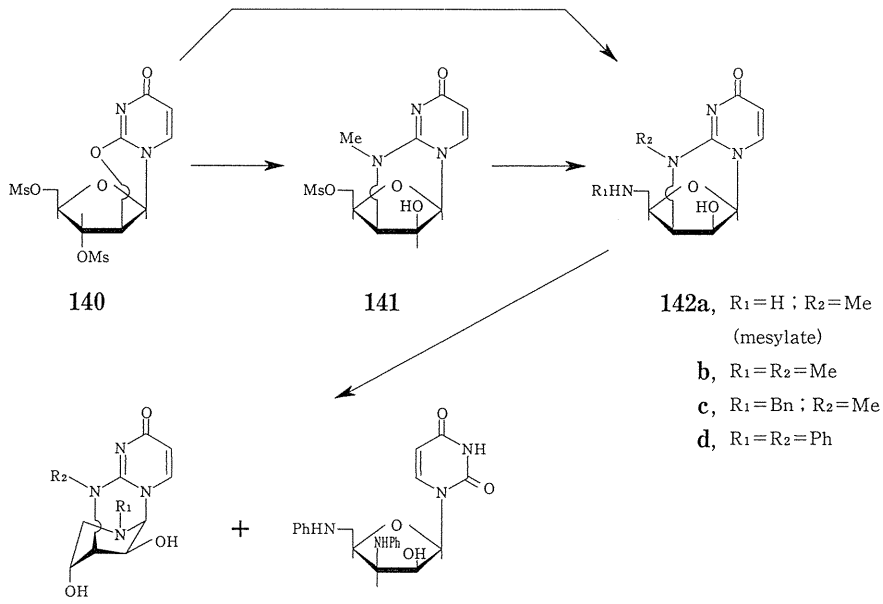
Treatment with 1M Et_3N/H_2O-MeOH (1:1) at room temperature is also sufficient for the quantitative hydrolysis (1.5 h). The hydrolysate **136** rapidly changed to 5′,*N*-anhydro-6,2′-imino-1-(2′-deoxy-β-D-arabinofuranosyl)-5,6-dihydrouracil (**137**) to attain finally an equilibrium between both, in favor of the latter. Compound **137** could be partially isolated as crystals, while **136** was isolated as a *N*-acetyl analogue. On the other hand, instantaneous contact of **135** with 1N HCl-MeOH (1:1) at room temperature afforded the hydrochloride **139** quantitatively. *The results described here represent the first hydrolytic cleavage of the formally alkyl-substituted imino bridge of a N-cyclonucleoside and also the first successful acidic fission of this type, leaving the glycosidic bond intact.* The newly formed aliphatic nitrogen heterocycle may be amenable to further transformations involving the C-N fission.

4.9. Synthesis of Some Piperidine Sugar Uracil Nucleosides with a 2,3′-(Substituted-imino) Bridge

At this stage, we were interested in the synthesis and biological evaluation of some 2,3′-substituted-imino uracil nucleosides having a piperidine-type sugar moiety, which seemed to be accessible from 2,3′-(substituted-imino)-lyxofuranosyluracils with a 5′-amino or 5′-(substituted-amino) group by similar isomerization reactions.[78,79] In view of the previous efforts to form nucleosides[84] or other glycosides[85] containing a pyrrolidine sugar, the synthesis of this type of compounds appeared to be most attractive (**Scheme 25**).[86,87]

Treatment of 2,2′-anhydro-1-(3′,5′-di-*O*-mesyl-β-D-arabinofuranosyl)uracil (**140**) with methylamine under mild conditions gave the 2,3′-methylimino nucleosides **141** which was

Scheme 25



140 **141**

142a, R₁=H ; R₂=Me (mesylate)
b, R₁=R₂=Me
c, R₁=Bn ; R₂=Me
d, R₁=R₂=Ph

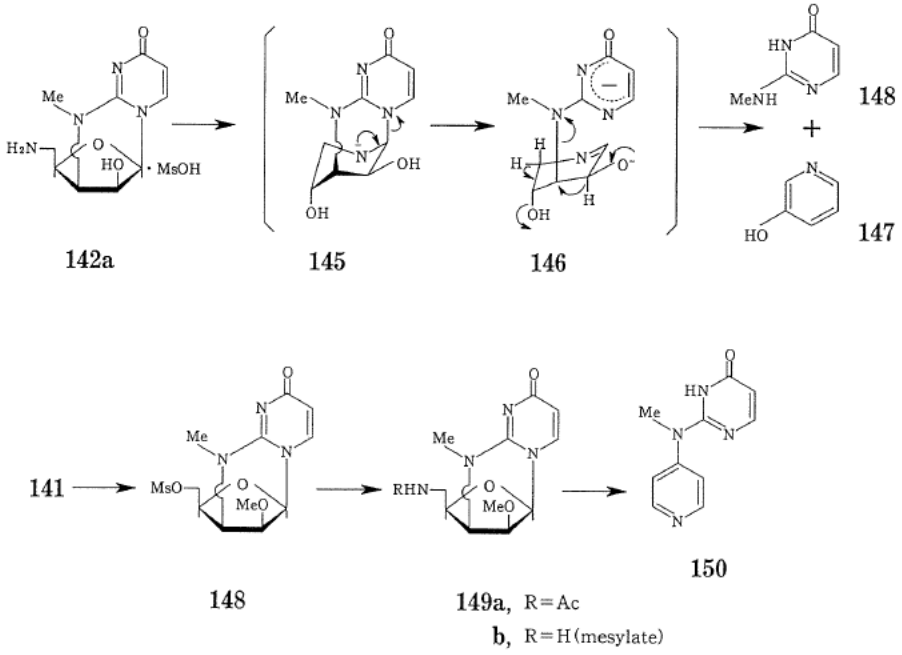
143a, R₁=R₂=Me
b, R₁=Bn ; R₂=Me
c, R₁=R₂=Ph

144

also obtainable directly from 2′,3′,5′-tri-*O*-mesyluridine. Compound **141** with excess of ammonia gave 1-(5′-amino-3′,5′-dideoxy-β-D-lyxofuranosyl)-2,3′-methyliminouracil (**142a**) as a crystalline methanesulfonate. Similarly, reaction of **141** with methylamine gave a high yield of 5′-methylamino analogue (**142b**). In the hope that a *N*-benzyl group would ultimately be removed by hydrogenolysis, 5′-benzylamino analogue **142c** was also synthesized, while compound **140** with aniline gave the 5′-anilino-2,3′-phenylimino analogue **142d** under forcing conditions.

Alkaline hydrolysis of **142b** in a 1:1 mixture of 6N NaOH and EtOH gave crystalline 1-(3′,5′-dideoxy-5′-methylamino-β-D-lyxopyranosyl)-2,3′-methyliminouracil (**143a**) in 24% yield, while compound **143b** was obtained by treating **142c** with 3N NaOH/EtOH. Similar treatment of **142d** gave 5′-anilino-2,3′-phenylimino analogue (**143c**) (26%) and 1-(3′,5′-dianilino-3′,5′-dideoxy-β-D-lyxofuranosyl)uracil (**144**) (10.4%). It was shown that the piperidine sugar nucleosides **143** are generally less stable than their oxygen analogues **120** under strongly alkaline conditions. When compound **142a** was similarly treated with 3N NaOH/EtOH, 3-hydroxypyridine (**147**) and N^2-methylisocytosine (**148**)[88] was obtained (**Scheme 26**). This reaction is unusual in that the sugar C-N bond was easily cleaved as judged by TLC at the earlier stage of the reaction and may be explicable in terms of elimination of the heterocyclic base from the sugar moiety as depicted in the formulae **145** and **146**: the drive toward delocalization of the 2′-hydroxyl anion would trigger a suprafacial [1,2]-hydride shift of H-2′ to C-3′ to remove the pyridine moiety (**146**). In order to check this hypothesis, other substrates **149a,b** in which the 2′-hydroxyl is blocked by the methyl group were synthesized from **141** through compound **148**. Compound **149b** was then subjected to the similar alkaline hydrolysis to afford N^2-methyl-N^2-(4-pyridino)isocytosine (**150**). The formation of **150** is explicable by aromatization of the sugar moiety through simple dehydration and elimination of methanol after fission of the anomeric bond of a transiently formed piperidine sugar

Scheme 26



nucleoside such as **145**. *Such chemical modifications of cyclonucleosides involving aromatization of the sugar part are unprecedented.*

5. Chemical Modifications of Nitrosugar Nucleosides

5.1. Introduction

It is well known that a number of nitro or nitroso group-containing organic molecules possess hazardous biological activities involving carcinogenicity,[89] while some nitro group-containing antibiotics of natural origin such as Chloramphenicol, 2-nitro-imidazole or Aureothin are known.[89] Although a consistent understanding of the biochemical role of the nitro group seems to be lacking, various biological oxidation-reduction processes involving nitrite or nitrate compounds are recorded.[89] Therefore, synthesis and biological evaluation of nitrosugar nucleosides are, at least in principle, important, especially in view of the history of nucleoside chemistry which has recorded the synthesis of numerous aminosugar nucleosides as potential therapeutic agents. In this context, the first synthesis of 2′,3′-dideoxy-3′-nitrothymidine and its 2′,3′-didehydro analogue as potential anti-AIDS substances has been reported recently by Hossain et al.[90,91]

Herein described are the results of our recent studies directed toward the synthesis of some 2,3-dideoxy-3-nitro-β-D-hexopyranosyl nucleosides substituted at the 2-position with nitrogen, sulfur and carbon nucleophiles. The 2-(substituted-amino) analogues of this class seemed to be especially attractive in view of the recorded antineoplastic activity of some aliphatic nitro compounds carrying a substituted amino group.[92] Feasibility of some other chemical modifications related to this class of compounds was also examined on the basis of common synthetic methods in general organic chemistry.

*5.2. Stereoselective Reactions of 1-(4,6-O-Benzylidene-2,3-didehydro-2,3-dideoxy-3-nitro-β-D-hexopyranosyl)uracil (**155**) with Some Nucleophiles*

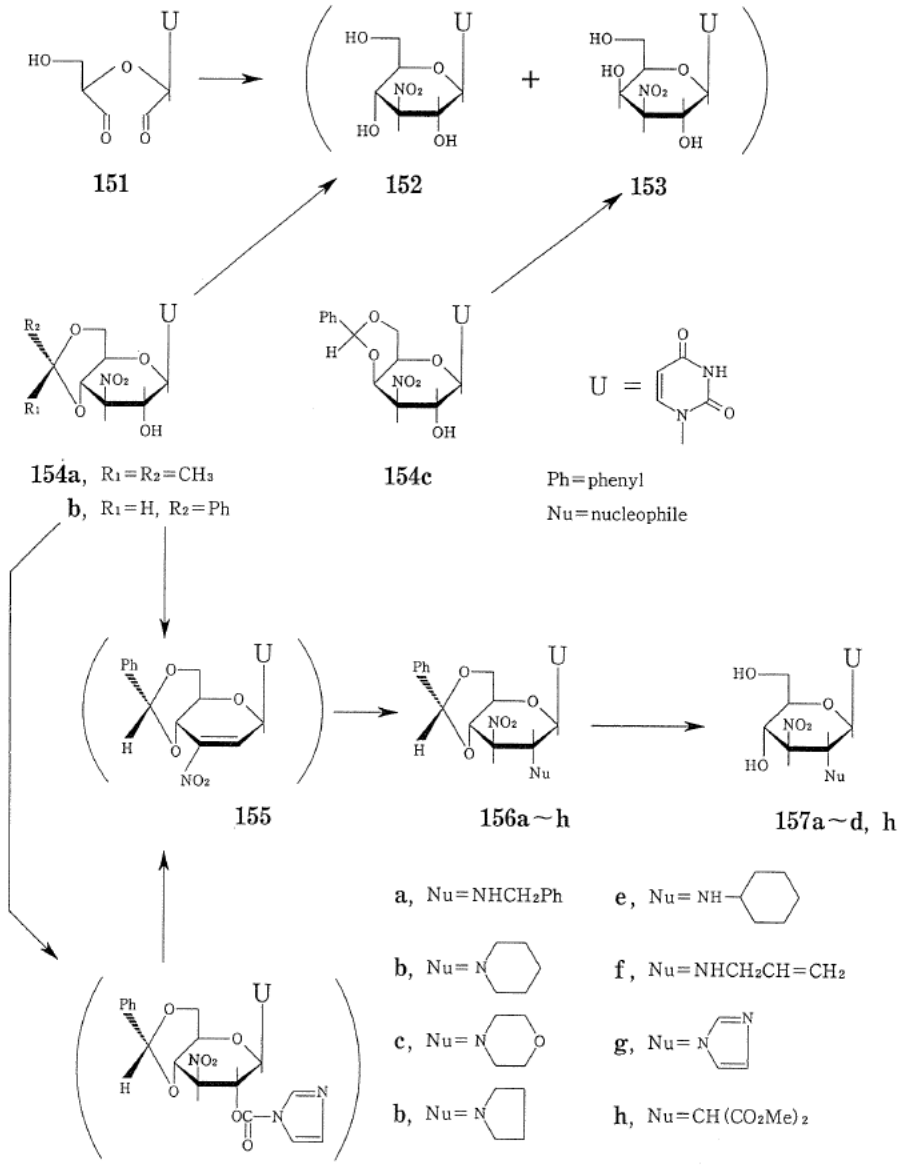
*– Michael Addition Reactions to the Nitroolefin **155***

For the purpose of generation of a 2,3-didehydro-2,3-dideoxy-3-nitro intermediate (**155**) (**Scheme 27**)[93,94] as a Michael acceptor, we first subjected the product[95] obtained from the dialdehyde and nitromethane to the usual isopropylidenation reaction. However, this reaction turned out to require unexpectedly drastic conditions. Although a selected experiment gave a 58% yield of 1-(3-deoxy-4,6-*O*-isopropylidene-3-nitro-β-D-glucopyranosyl)uracil (**154a**), this substance proved to be unstable, gradually regenerating 1-(3-deoxy-3-nitro-β-D-glucopyranosyl)uracil (**152**) in methanolic solution at room temperature.

Treatment of the TLC-pure nitronucleoside obtained from **151** with benzaldehyde/$ZnCl_2$ gave a mixture of two products, from which the major product (**154b**) was isolated in ca. 70% yield and used as the starting material. The minor product obtained in 15% yield proved to be 1-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-galactopyranosyl)uracil (**154c**).[96] Thus, the original nitronucleoside product was an inseparable mixture of two isomers.

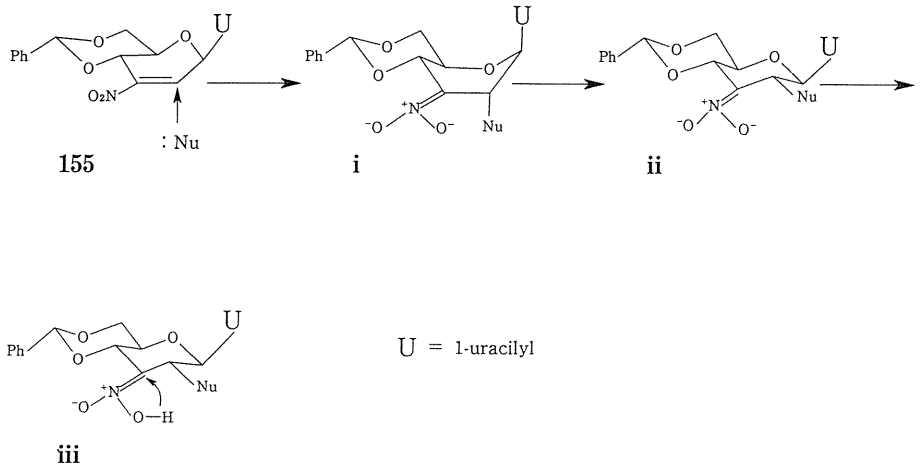
Compound **154b** in acetone was treated with methanesulfonyl chloride (MsCl) and then with excess amount of triethylamine at −18°C[97] to give the nitroolefin intermediate (**155**) as a less polar product, which was too unstable to be isolated in contrast with the reported isolation of various nitroolefins in the areas of hexopyranose sugars[98] and pentofuranosyl nucleosides.[90,91]

Scheme 27



Treatment of this reaction mixture with benzylamine gave 1-(2-benzylamino-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranosyl)uracil (**156a**). Similarly, its 2-piperidino (**156b**), 2-morpholino (**156c**), 2-pyrrolidino (**156d**), 2-cyclohexylamino (**156e**) and 2-allylamino analogues (**156f**) were obtained. The glucopyranosyl structures of these compounds are based upon the generally large $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ values in the ^{1}H NMR spectra. For

Scheme 28



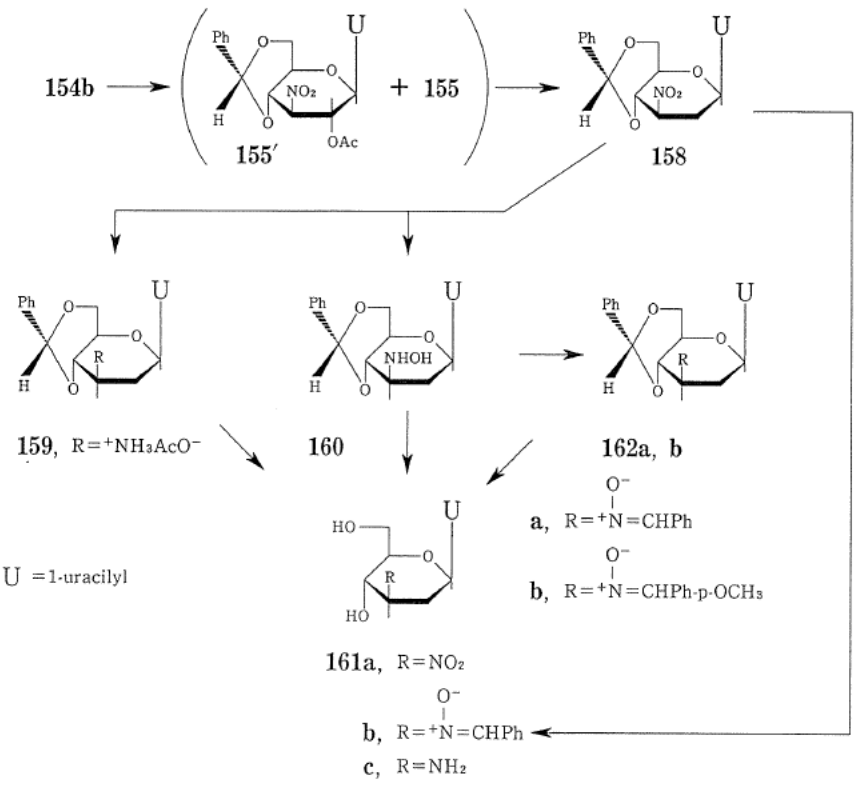
another purpose, **154b** in DMF was treated with *N,N'*-carbonyldiimidazole (CDI) to give, interestingly, the 2-imidazol-1-yl analogue (**156d**) quantitatively under gas evolution. This observation is explicable in terms of imidazocarbonylation of the 2-hydroxyl followed by elimination of imidazo-carboxylic acid which instantaneously released carbon dioxide. The nitroolefin thus formed reacted with the released imidazole to afford **156g**. Similarly, Michael addition of dimethylmalonate to **155** gave 2-*C*-dimethylmalonyl analogue **156h** in 55% yield. Debenzylidenation of **156a-d,h** with 90% TFA gave the corresponding 1-(2,3-dideoxy-3-nitro-2-substituted-β-D-glucopyranosyl)uracils **157a-d,h**, while the deprotected form of **156e**, **156f** as well as **156g** was too unstable to be isolated.

Thus, the present Michael addition reactions gave the thermodynamically more stable glucopyranosyl nucleosides. Probably owing to the steric hindrance by the base, the nucleophiles might have attacked the nitroolefin **155** from the α-side (axial attack) to yield transiently the boat-like *aci*-nitro intermediate **i**, which may flip to the more stable chair form **ii** (**Scheme 28**). After protonation of **ii** to yield **iii**, hydride shift must have occurred in thermodynamically favorable way to form **156**.

—Synthesis and reduction of 1-(4,6-O-Benzylidene-2,3-dideoxy-3-nitro-β-D-arabino-hexopyranosyl)uracil (158)

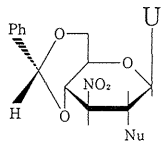
Synthesis and biological evaluation of nitrososugar and hydroxylaminosugar nucleosides seemed to be interesting, since these types of nucleosides as possible intermediates in the biological redox system have never appeared in the literature as contrasted with the various aminosugar nucleosides. Hence, we chose the title compound **158** as the simplest model substrate for stepwise reduction (**Scheme 29**).[93,94] Treatment of **154b** with acetic anhydride in pyridine gave a mixture of **155** and 2-acetate of **154b** (**155'**). This inseparable mixture was directly treated with $NaBH_4$ to give 1-(4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*arabino*-hexopyranosyl)uracil (**158**) in a high yield.[98] Reduction of **158** with tin powder/AcOH-EtOH gave the 3-amino analogue **159** as an acetate, while controlled reduction of **158** with

Scheme 29

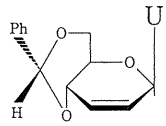


Zn powder/AcOH-EtOH permitted isolation of 1-(4,6-*O*-benzylidene-2,3-dideoxy-3-hydroxylamino-β-D-*arabino*-hexopyranosyl)uracil (**160**) in 73% yield. Compound **158** and **159** were deprotected to 1-(2,3-dideoxy-3-nitro-β-D-*arabino*-hexopyranosyl)uracil (**161a**) and its 3-amino analogue **161c**, respectively, with the use of 80% acetic acid, while similar treatment of **160** yielded 1-(2,3-dideoxy-3-N-benzylideneaminoxido-β-D-*arabino*-hexopyranosyl)uracil (**161b**) as a single product (quantitative in terms of TLC). The structural evidence for the nitrone **161b** was obtained as follows. Compound **160** was converted into the protected nitrone **162a** and **162b** by treatment with benzaldehyde and p-anisaldehyde, respectively, in acetic acid. The deprotected form of **162a** was identified with **161b**. Compound **162b** provided a distinct ^{1}H NMR signal for the nitrone methine proton at 7.78 ppm. *Compounds **161b** and **162a,b** are the first nitrone-sugar nucleosides to be recorded and suggest a novel scope of transformations.*

Very recently, some other Michael adducts (**163a-g**) were synthesized[99] from **155** and some sulfur nucleophiles as well as azide ion, and the deblocked forms of **163a,d,e,f** were fully characterized. Compound **163d** was converted with the use of tributyltin hydride-AIBN into 1-(4,6-*O*-benzylidene-2,3-dideoxy-2,3-didehydro-β-D-hexopyranosyl)uracil (**164**) by analogy with the 2,3-unsaturated pentofuranosyl nucleosides as anti-AIDS substances.[99]



163a~g



164

a, Nu=SMe
b, Nu=SEt
c, Nu=S⌒SH
d, Nu=SPh
e, Nu=SO_2Ph
f, Nu=S-⬡
g, Nu=N_3

5.3. Synthesis of Some New 3-Nitrohexopyranosyladenines and Related Compounds via a Nitroolefin Intermediate

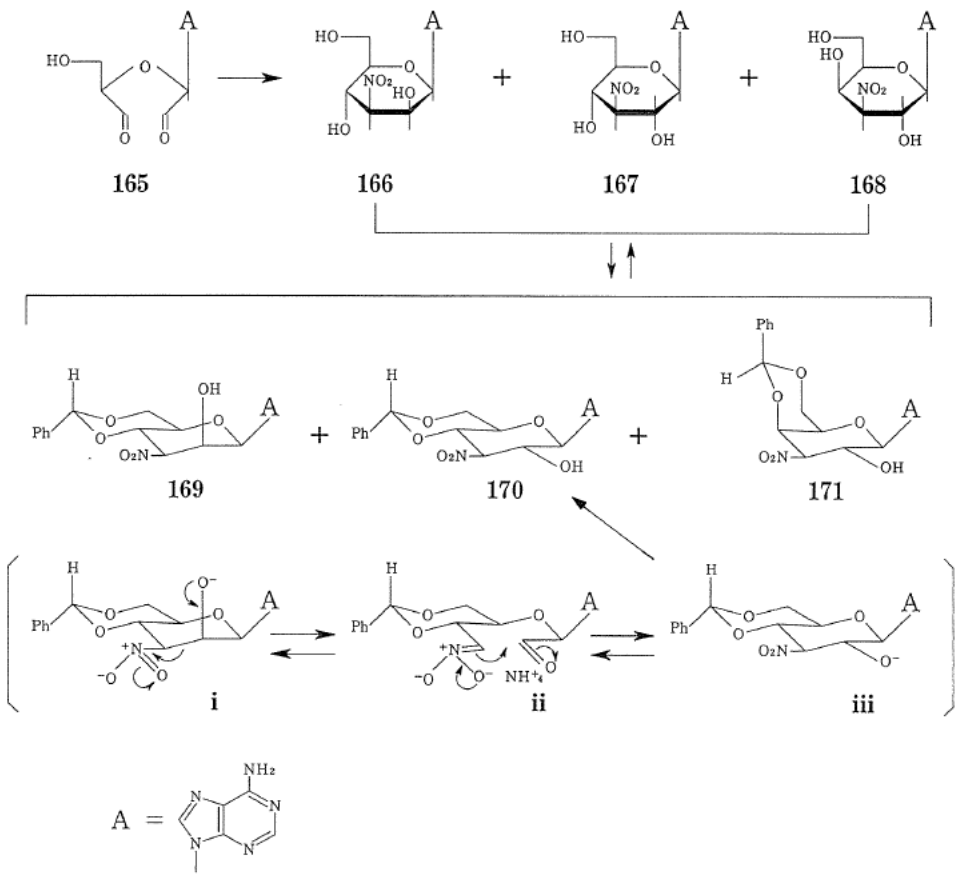
The work described in Paragraph 5.2. was extended to the adenine series (**Scheme 30**).[100] An inseparable diastereomeric mixture of 9-(3-deoxy-3-nitro-β-D-hexopyranosyl)adenines (**166—168**) obtained by the periodate-nitromethane procedure[101] (Henry reaction) was subjected to benzylidenation using benzaldehyde and zinc chloride to give 9-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-mannopyranosyl)adenine (**169**, 10%), the glucopyranosyl (**170**, 33%) and the galactopyranosyl analogues (**171**, 22%) as crystals. The structures of these isomers were established on the basis of the ^{1}H NMR data.

Interestingly, the *manno* isomer **169** is convertible into the thermodynamically more stable *gluco* isomer **170** by treatment with strong bases (7 N NH_3/MeOH, 100°C; or t-BuOK/DMF, room temperature). This observation is unprecedented in the area of nucleoside chemistry and explicable in terms of Retro-Henry reaction involving the intermediates **i**, **ii** and **iii**.

Compounds **169** and **171** were deblocked with the use of 90% TFA and the parent compounds **166** and **168** were obtained as a crystalline monohydrate and hydrochloride salt, respectively, while the deprotected form of **170** resisted crystallization.

Treatment of compound **170** with acetic anhydride in pyridine quantitatively gave 9-(4,6-*O*-benzylidene-2,3-didehydro-2,3-dideoxy-3-nitro-β-D-hexopyranosyl)adenine (**172**) as a rather unstable foam (**Scheme 31**). A mixture of **172**, 1.6 equivalent morpholine and 0.8 equivalent potassium fluoride in THF was heated to reflux for 2 h to give a 70% yield of 9-(4,6-*O*-benzylidene-2,3-dideoxy-2-(morpholin-1-yl)-3-nitro-β-D-glucopyranosyl)adenine (**173a**). Similarly, 2-(piperidin-1-yl) (**173b**, 71%), 2-allylamino (**173c**, 85%), 2-propargylamino (**173d**, 75%), 2-methoxycarbonylmethylamino (**173e**, 44%), 2-methylthio (**173f**, 30%) and 2-phenylthio analogues (**173g**, 71%) were obtained. Deprotection of **173** gave the corresponding 9-(2,3-dideoxy-3-nitro-2-substituted-β-D-glucopyranosyl)adenines **174a-d** and **174f** as a foam and **174g** as crystals. On the other hand, treatment of **172** with sodium azide gave 9-[4,6-*O*-benzylidene-2,3-didehydro-2,3-dideoxy-2,3-(1,2,3-triazolo)-β-D-glucopyranosyl]adenine (**175**), which might have formed through the 1,3-dipolar addition reaction of the azide followed by elimination of nitrous acid. However, another possibility that an initially formed Michael addition product having a 2-azido group changed to the intermediate **iv** (unusual azide insertion) can not be ruled out. Anyway, the formation of **175** is in contrast with the isolation of **163g** in the uracil series and is under mechanistic investigation. Compound **175** was deprotected to the parent compound **176** under controlled conditions. Thus,

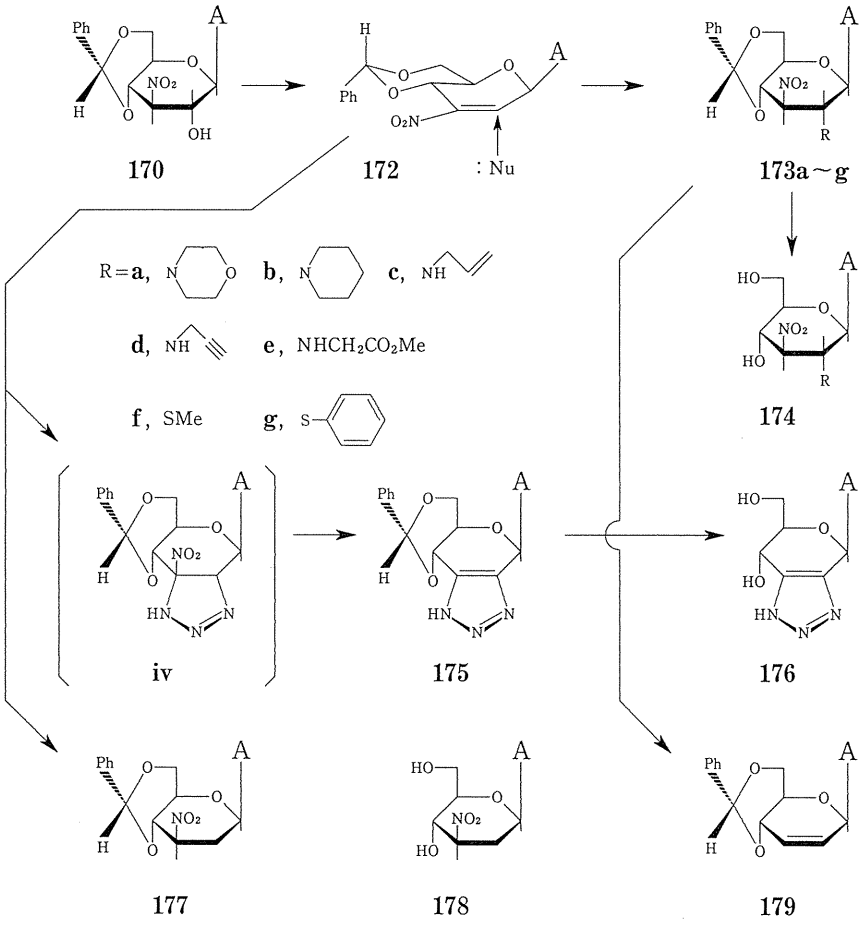
Scheme 30



as in the case of uracil series, *the Michael additions of nucleophiles to the nitroolefin* ***172*** *proceeded in stereoselective way.* This observation may also be explicable by the mechanism shown in **Scheme 28**.

The intermediate **172** was reduced to the 2-deoxy nucleoside **177** which was deprotected to the parent compound **178**, while compound **173g** with tributyltin hydride-AIBN afforded 9-(4,6-*O*-benzylidene-2,3-didehydro-2,3-dideoxy-β-D-hexopyranosyl)adenine (**179**). The formations of **177** and **179** suggest further important chemical modifications in the area of 2,3-dideoxy- and 2,3-didehydro-2,3-dideoxy-hexopyranosyl nucleosides as biological probes related to the functions of nucleic acids.

Scheme 31



6. Summary

(1) Base-induced elimination reactions at the 2′,3′-positions of purine and pyrimidine nucleosides proved to occur regioselectively to leave a leaving group at the C-2′ under the influence of the electronegative nucleobases. In the pyrimidine series, the resulting 2′,3′-olefins with a leaving group at the C-2′ readily formed the corresponding 3′-deoxy-2′-keto nucleosides. These are new species of nucleosidic compounds biomimetically formed on the analogy of formation of cordycepin from adenosine. (2) Base-sugar cyclization at the 4′-position was easily realized in both purine and pyrimidine nucleosides. Some pyrimidine 2,4′-cyclonucleosides proved to be optical models better than the pyrimidine 2,5′-anhydronucleosides and

would be useful intermediates for introducing various functional groups into the 4′-position of nucleosides. (3) General synthesis of *N*-bridged cyclonucleosides spanned between the base moiety and C-2′, C-3′ and C-5′ positions of the sugar part was achieved in both purine and pyrimidine series. Also, diatomic bridging between the base and sugar moieties was attained for the first time especially in the purine series. Various molecular reorganizations of these classes of compounds were found, and especially, the first hydrolytic cleavage of the nitrogen bridge was realized in some of the pyrimidine *N*-cyclonucleosides. Hydrolytic fission and recombination of the glycosidic bond accompanied by molecular rearrangements were also recorded for some of these *N*-cyclonucleosides. A new synthesis of some reversed nucleosides carrying a variously substituted triazole was also established using the molecular strain inherent in a condensed type of a pyrimidine *N*-cyclonucleoside. (4) Michael addition reactions of various nucleophiles to some protected derivatives of 2,3-didehydro-2,3-dideoxy-3-nitro-β-D-hexopyranosyl nucleosides occurred stereoselectively to give many biologically interesting compounds. The Retro-Henry reaction of a protected *manno*-pyranosyl adenine nucleoside to the *gluco* isomer was found. This discovery would facilitate access to the synthetic chemistry using the general hexopyranosyl nucleosides.

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