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THE UNIVERSITY OF ALBERTA

SYNTHESES OF AMINO-SUGAR NUCLEOSIDES AND DERIVATIVES

BY

MIRNA CERDA

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

SYNTHESES OF AMINO-SUGAR NUCLEOSIDES AND DERIVATIVES

submitted by MIRNA CERDA in partial fulfillment of the requirements for the degree of MASTER OF SCIENCE in Chemistry.

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A.R. Morgan (External Examiner)

Date ...August 6th 1987.....

To

Vicente and my Family

ABSTRACT

The purpose of this study was to introduce hydroxyurea and urea functionalities on the amino-sugar moiety of a nucleoside, since these classes of compounds have shown promising biological properties. Uridine (**10**) was used as the starting nucleoside and 2'-amino-2'-deoxyuridine (**95**), our key intermediate, was prepared as described in the literature.

a) Carbamate Route: In this route, 2'-amino-2'-deoxyuridine was converted to its 2'-ethyl carbamate derivative (**96**) and then to the N2',O3' cyclic carbamate derivative (**103**). Opening of (**103**) was effected with NH_3/H_2O in a steel bomb at 70°C to provide (**97**). However, efforts to prepare (**98**) were unsuccessful.

b) Carbamoyl Chloride Route: When the 3',5'-O-protected amino-sugar nucleoside (**109**) was treated with 1 molar equivalent of phosgene and triethylamine the desired carbamoyl chloride derivative (**110**) and dimer (**111**) were obtained in a 1:1 ratio. We found that by reacting (**109**) with an excess of phosgene in the presence of benzyloxyamine hydrochloride and triethylamine, (**115**) was obtained as the major product. Hydrogenolysis of this compound and subsequent deprotection of the 3' and 5' hydroxyl groups afforded the (**98**).

c) Isocyanate Route: (95) Was treated with methylisocyanate and benzylisocyanate to provide (104) and (113), respectively, in high yields.

When (113) was subjected to hydrogenolysis, (97) was obtained in almost quantitative yield.

A smooth and efficient procedure for the preparation of 3'-amino-3'-deoxyadenosine has been developed. Conversion of adenosine (6) to its 2',3'-anhydro derivative (87) and subsequent opening of the epoxide function using 1 M HBr/DMF solution afforded (116) in high yield. Selective protection of the 5'-hydroxyl group was carried out using tert-butyldiphenylsilylchloride. (117) Was subjected to reaction with benzylisocyanate and triethylamine to afford (118). Base-promoted intramolecular nucleophilic cyclization of (118) gave (119). Deprotection and basic hydrolysis of (119) proyided (120). Hydrogenolysis of (120) afforded 3'-amino-3'-deoxyadenosine in ~60% overall yield from adenosine.

ACKNOWLEDGEMENTS

I would like to thank Dr. M.J. Robins for his patience, encouragement and support during the course of this work, and Dr. J.S. Wilson for helpful discussions and proofreading of this manuscript.

Thanks are due to the members of the support staff of the Chemistry Department for their assistance, especially to Ms. Diane Dowhaniuk for the typing of this thesis.

I am especially grateful to my husband, Vicente Samano, for his continuous help and support and to my Mother for her constant love and encouragement.

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INTRODUCTION

A. GENERAL INTRODUCTION AND SURVEY OF AMINO-SUGAR NUCLEOSIDES.

The history of the determination of the structures and functions of RNA and DNA began in 1868, when F. Miescher[1] isolated a material rich in phosphorous from nuclei of pus cells and from the sperm of salmon. This material was first called nuclein. Altmann[2] continued Miescher's investigations and first used the term nucleic acid. He developed methods for the preparation of protein-free nucleic acid from yeast as well as from animal tissues. Later, Kossel and Neumann[3] described a method for the preparation of nucleic acid from thymus glands. The discovery, isolation and characterization of the constituent parts of nucleic acids was due to the outstanding work of Piccard[4], Kossel[5], Neumann[5], Steudel[6], Levene[7] and Ascoli[8].

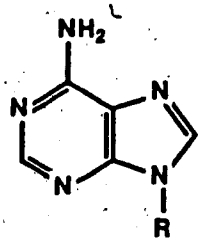
Nucleic acids are the substances most intimately linked with the transmission and utilization of genetic information in all living organisms. There are two major types of nucleic acid: ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). DNA and some RNA's are very large polymeric molecules of high molecular

weight and both are essential for the biosynthesis of proteins.

Acidic hydrolysis of either RNA or DNA was shown to yield phosphoric acid, a sugar and a mixture of purine and pyrimidine bases. The sugar isolated from RNA hydrolysis was ribose, while deoxyribose (2-deoxy-D-erythro-pentose) was obtained from DNA hydrolysates. The major bases obtained from DNA were the purines: adenine (**1**) and guanine (**2**) and the pyrimidines cytosine (**3**) and thymine (**4**). RNA yielded mainly adenine, guanine, cytosine, and another pyrimidine base, uracil (**5**).

Mild degradation of a nucleic acid afforded a mixture of acids known as nucleotides. Each nucleotide contained the elements of one purine or pyrimidine base, one phosphate unit, and one pentose unit. The phosphate unit may be selectively removed by futher careful hydrolysis to convert a nucleotide into a nucleoside.

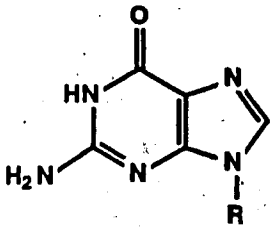
The nucleosides which occurred in RNA were adenosine (**6**), guanosine (**7**), cytidine (**8**) and uridine (**10**). Those in DNA were 2'-deoxyadenosine (**11**), 2'-deoxyguanosine (**12**), 2'-deoxycytidine (**13**) and thymidine (**9**).



1 R=H

6 R=R'

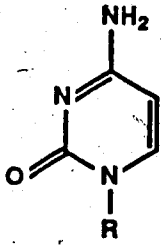
11 R=R"



2 R=H

7 R=R'

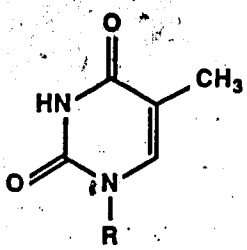
12 R=R"



3 R=H

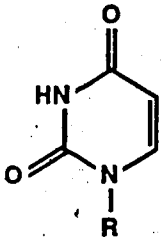
8 R=R'

13 R=R"



4 R=H

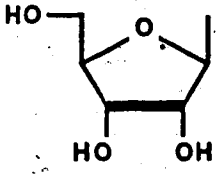
9 R=R"



5 R=H

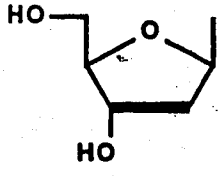
10 R=R'

R' =



RIBOSE

R" =



2-DEOXY-D -RIBOSE

The position of attachment of the sugar to the heterocyclic base in nucleosides was originally a difficult problem that was later solved by ultraviolet spectra comparison[9-11].

The DNA molecule is a double helix that carries the genetic message in a complementarily redundant form. The backbone of each helix consists of repeating units of deoxyribose sugar and phosphate. The backbones are linked by hydrogen bonds between pairs of four kinds of base: adenine, guanine, thymine and cytosine. The bases are the "letters" in which the genetic message is written. Because adenosine invariably pairs with thymine and guanine with cytosine, the two strands carry complementarily equivalent information[12,13,14].

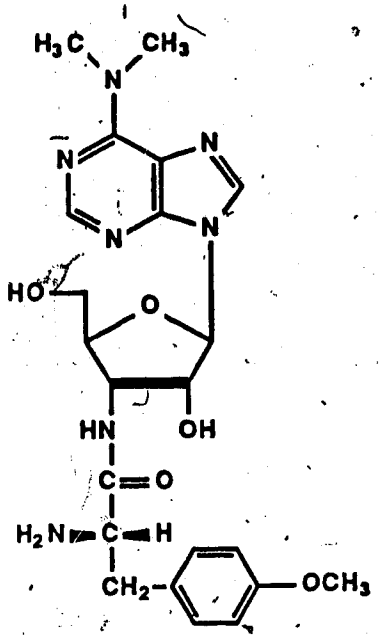
The code is transcribed when DNA directed synthesis of molecules of RNA occurs. The order of bases in the new RNA chains is determined by bases pairing with those on a strand of the template DNA. RNAs, in turn, direct this genetically coded synthesis of proteins.

Because nucleosides and nucleotides are fundamental building blocks of DNA and RNA, nucleoside analogs have been synthesized as anticancer and antiviral chemotherapeutic agents. Nucleoside analogs

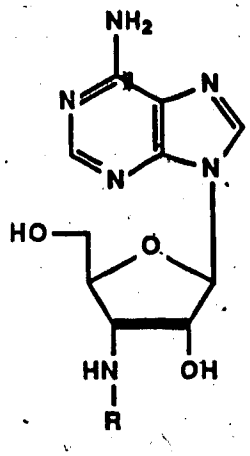
have chemical structures slightly different from natural nucleosides. If this "foreign" nucleoside is incorporated into the nucleic acid of a cancer cell, it could interfere with metabolism and be fatal to the cell. Viral nucleic acids could be attacked in the same way, thus, stimulating a search for this class of compounds.

A number of naturally occurring nucleoside antibiotics have been found which have an amino-sugar moiety[18,19]. Puromycin (**19**) is the well known and extensively studied terminator of peptide biosynthesis. It was isolated from the culture filtrates of Streptomyces albo-niger in 1952, and was first synthesized by Baker et al.[30] in 1955. The structurally related family of 3'-amino-3'-deoxyadenosine (**20**) and 3'-N-acetyl (**21**) and aminoacyl derivatives were discovered and studied somewhat later[18]. The discovery[20] and synthesis[21] of 2'-amino-2'-deoxy guanosine (**22**) as an amino-sugar nucleoside antibiotic exemplifies this class of 2'-amino nucleosides[22-25]. Purine and pyrimidine nucleoside antibiotics with more complex and/or pyranosyl amino-sugar portions also are known[18,26].

The 5'-amino nucleosides were relatively easy to prepare since reactions at the primary 5'-hydroxyl group are in general facile and mechanistically

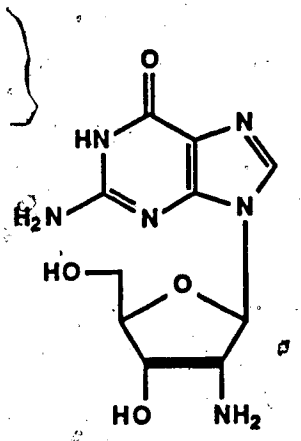


19



20 R=H

21 R=$COCH_3$



22

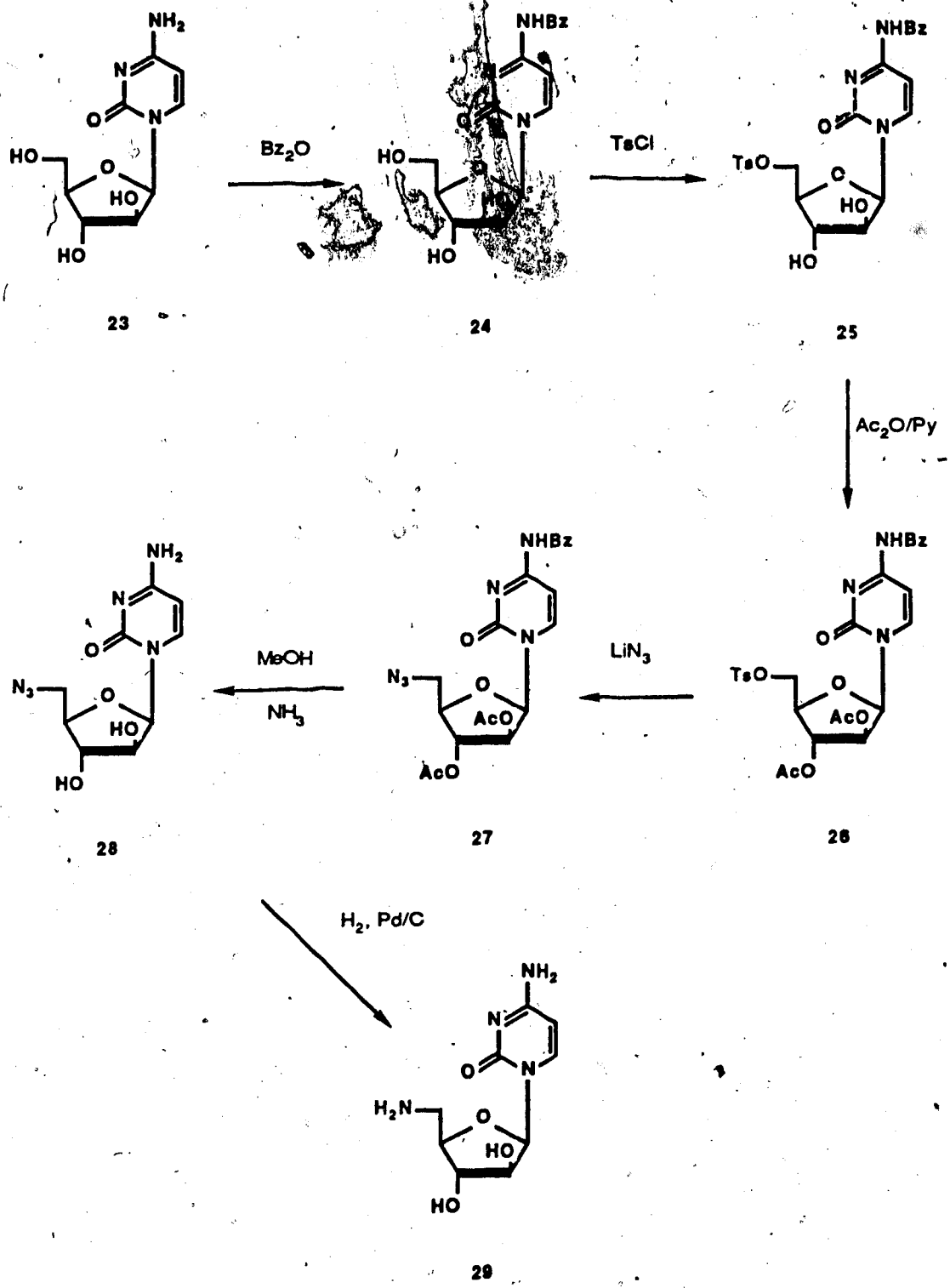
simple. In this regard, the preparation of 5'-amino nucleosides has been accomplished via direct S_N2 displacement reactions of 5'-sulfonate esters by azide ion in aprotic dipolar solvents. Catalytic reduction transformed the 5'-azide compounds into the desired 5'-aminonucleosides. This general method has been applied to the purine and pyrimidine series with success.[27-29] (SCHEME I).

The preparation of 2'- and 3'-aminonucleosides involved the differentiation between two secondary hydroxyl groups on the sugar. This was further complicated by steric hindrance from the base.

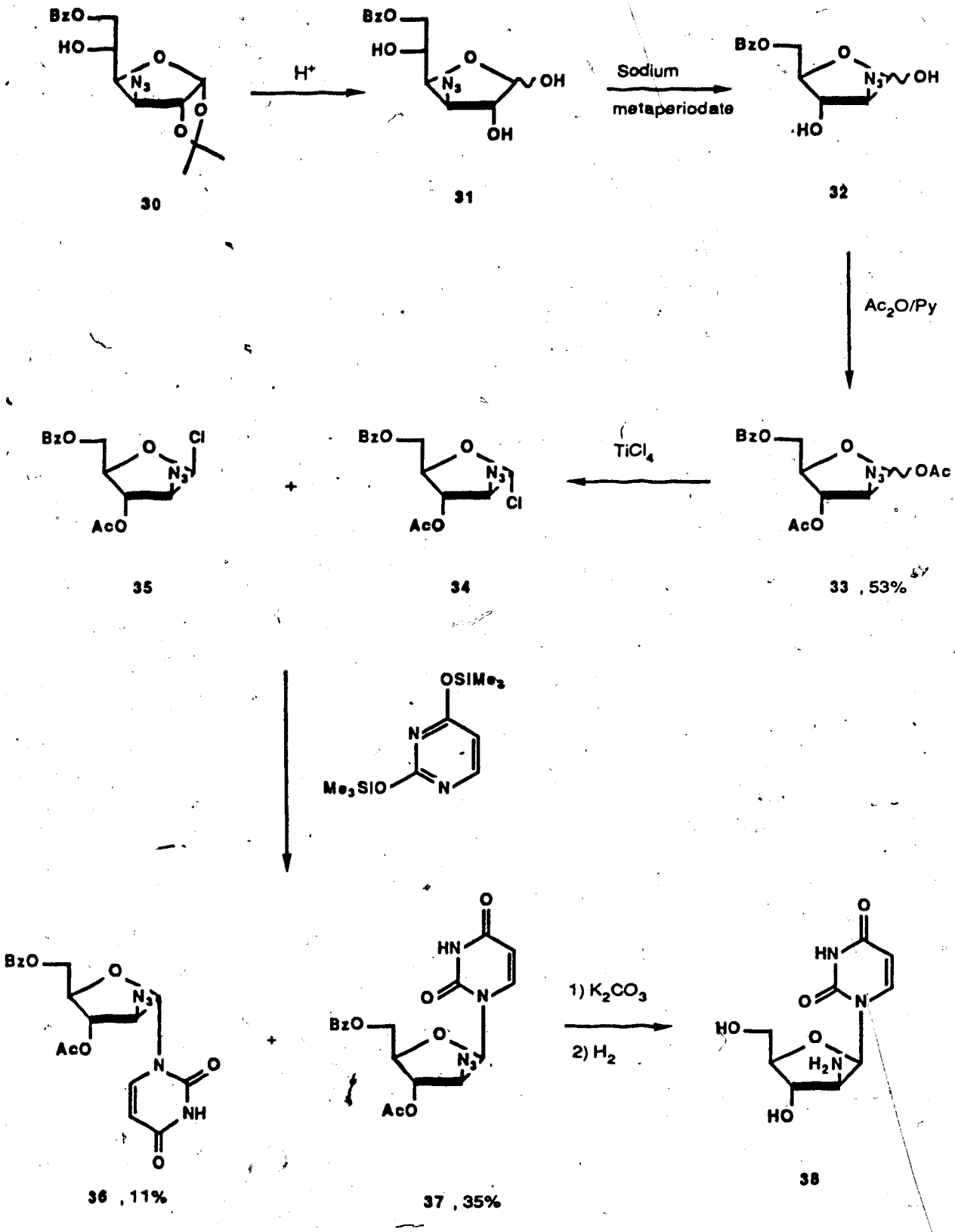
Three general types of synthetic approaches to 2'- and 3'-amino-sugar nucleosides have been employed. The first and most extensively used method of nucleoside construction involved coupling of a preformed sugar and the heterocyclic base. This approach was utilized in the synthesis of puromycin[30], and has recently been employed in the preparation of 1-(2-amino-2-deoxy-β-D-arabinofuranosyl)uracil [2'-amino-2'-deoxyspongo-uridine][31] (38). The major disadvantage to this approach was that both β and α anomers were produced. (SCHEME II).

A second synthetic strategy involved elaboration of the heterocyclic base on a functionalized

SCHEME I


NH2
N
O
N
HO
O
HO
HO
23
Bz2O
NHBz
24
TsCl
TsO
25
Ac2O/Py
26
LiN3
N3
27
MeOH
NH3
28
H2, Pd/C
H2N
29
AcO

SCHEME II

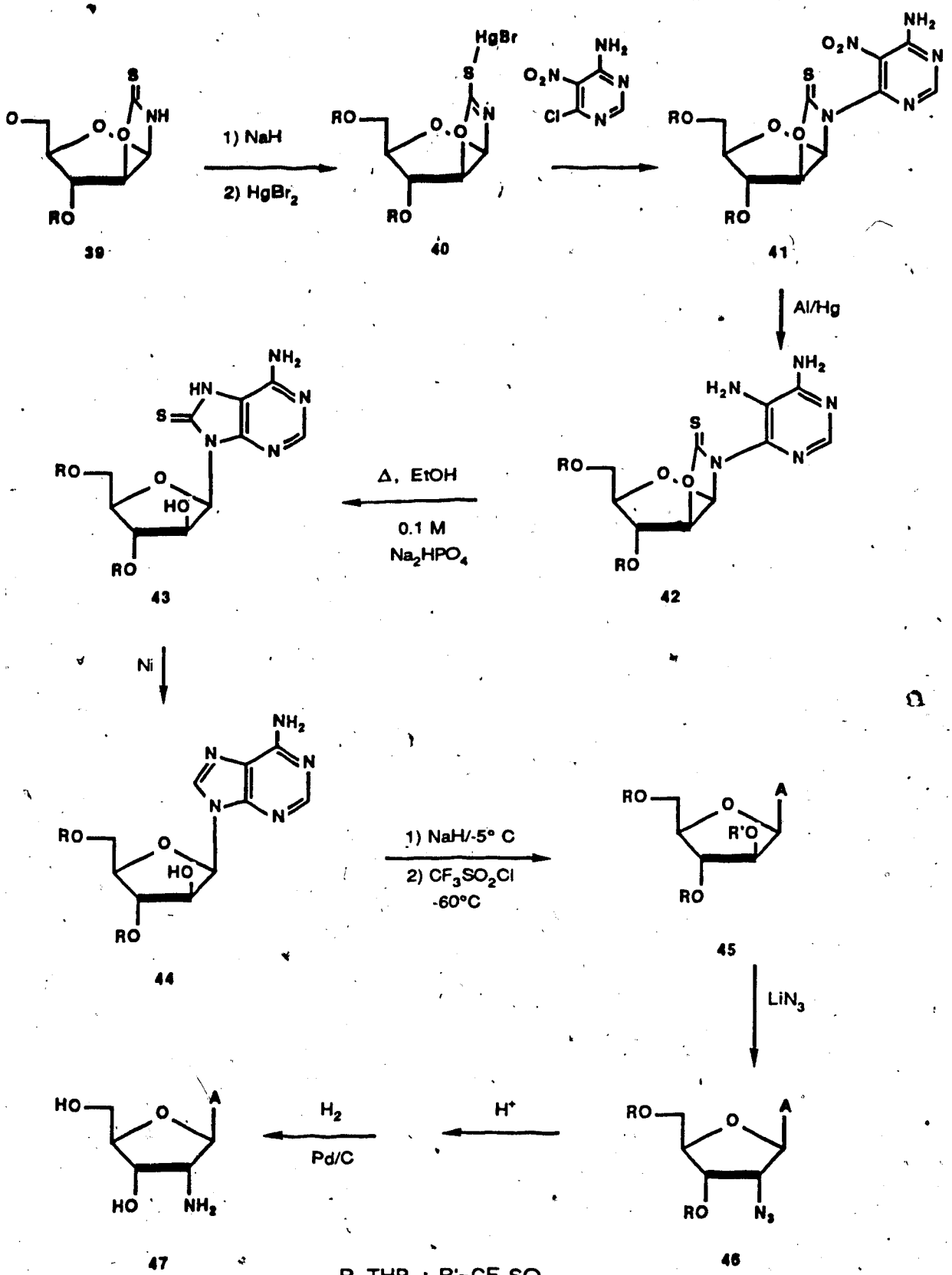

BzO
HO
O
N3
O
O
H+
OH
OH
Sodium
metaperiodate
OH
HO
30
31
32
Ac2O/Py
Cl
AcO
TiCl4
OAc
35
34
33 , 53%
OSIMe3
Me3SIO
N
HN
NH
1) K2CO3
2) H2
H2N
36 , 11%
37 , 35%
38

carbohydrate derivative. A recent example of this approach was the preparation of 2'-amino-2'-deoxyadenosine (**47**) from the oxazolidinethione derivative (**39**) obtained by treatment of D-arabinose with acidic aqueous potassium thiocyanate solution. Elaboration of the suitably protected purine cyclonucleoside derivative was followed by activation of the arabino 2'-hydroxyl by trifluoromethanesulfonylation. Displacement of the trifluoromethanesulfonate by azide followed by hydrogenolysis and deprotection gave the desired amino-sugar nucleoside product (**47**) (SCHEME III).

The third general category involved chemical transformation of preformed nucleosides. Three subtypes may be noted in this area. Chemical manipulations of the carbohydrate moiety only are exemplified by the conversion of adenosine to 2'-amino-2'-deoxyadenosine (**47**) and 3'-amino-3'-deoxyadenosine (**20**) described by Mengel and Wiedner[24,33] (SCHEME X).

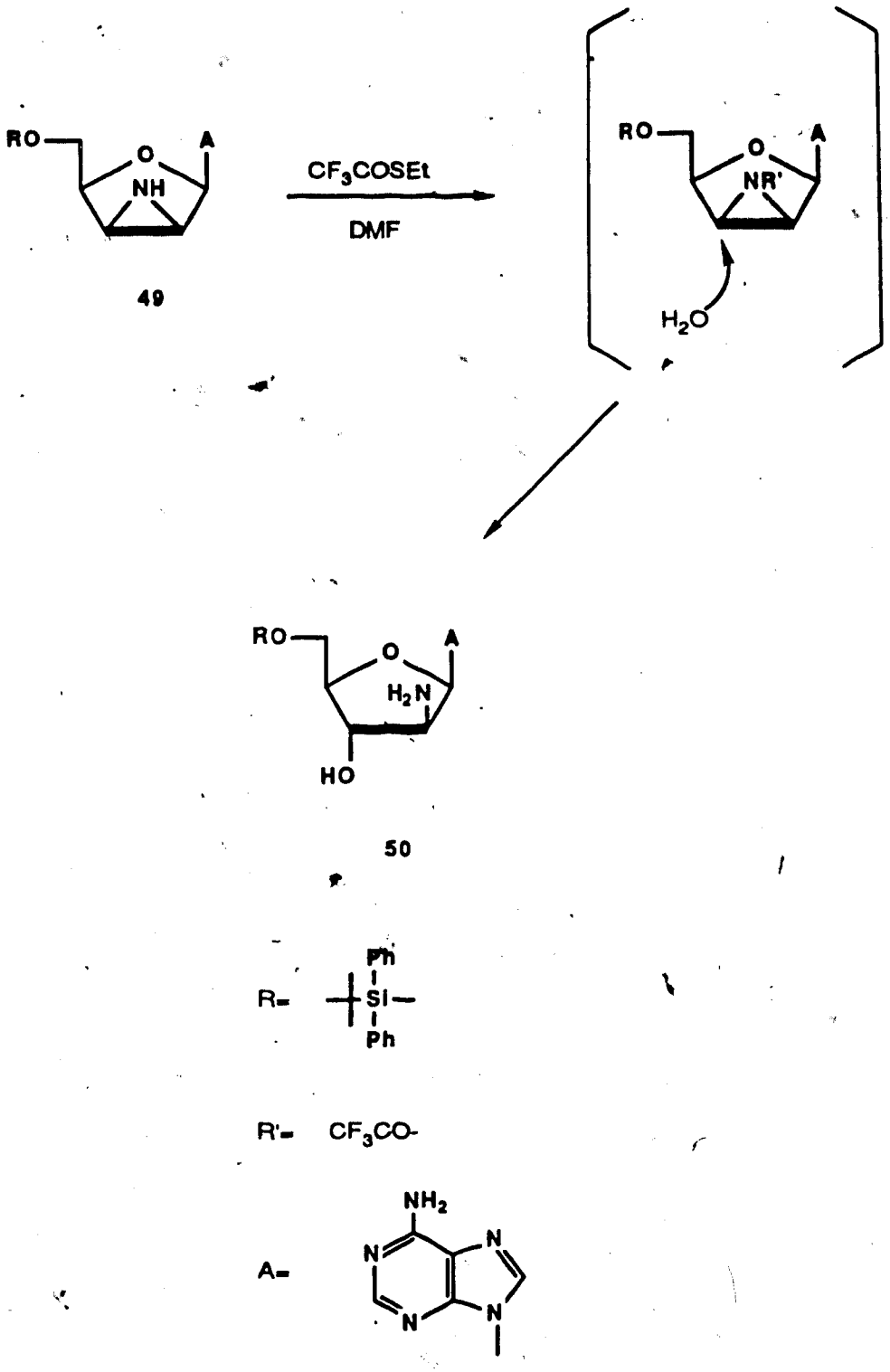
The 2',3'-anhydro (epoxide) group has been employed for many years in nucleoside chemistry[19], and recently the corresponding parent 2',3'-epimino (aziridine) function has been reported[33] for the preparation of 2'-amino-2'-deoxyarabinoadenosine (**50**) (SCHEME IV). The epimino function (**49**) was found to be much more stable than the corresponding oxirane group

SCHEME III



39 40 41 42 43 44 45 46 47

SCHEME IV

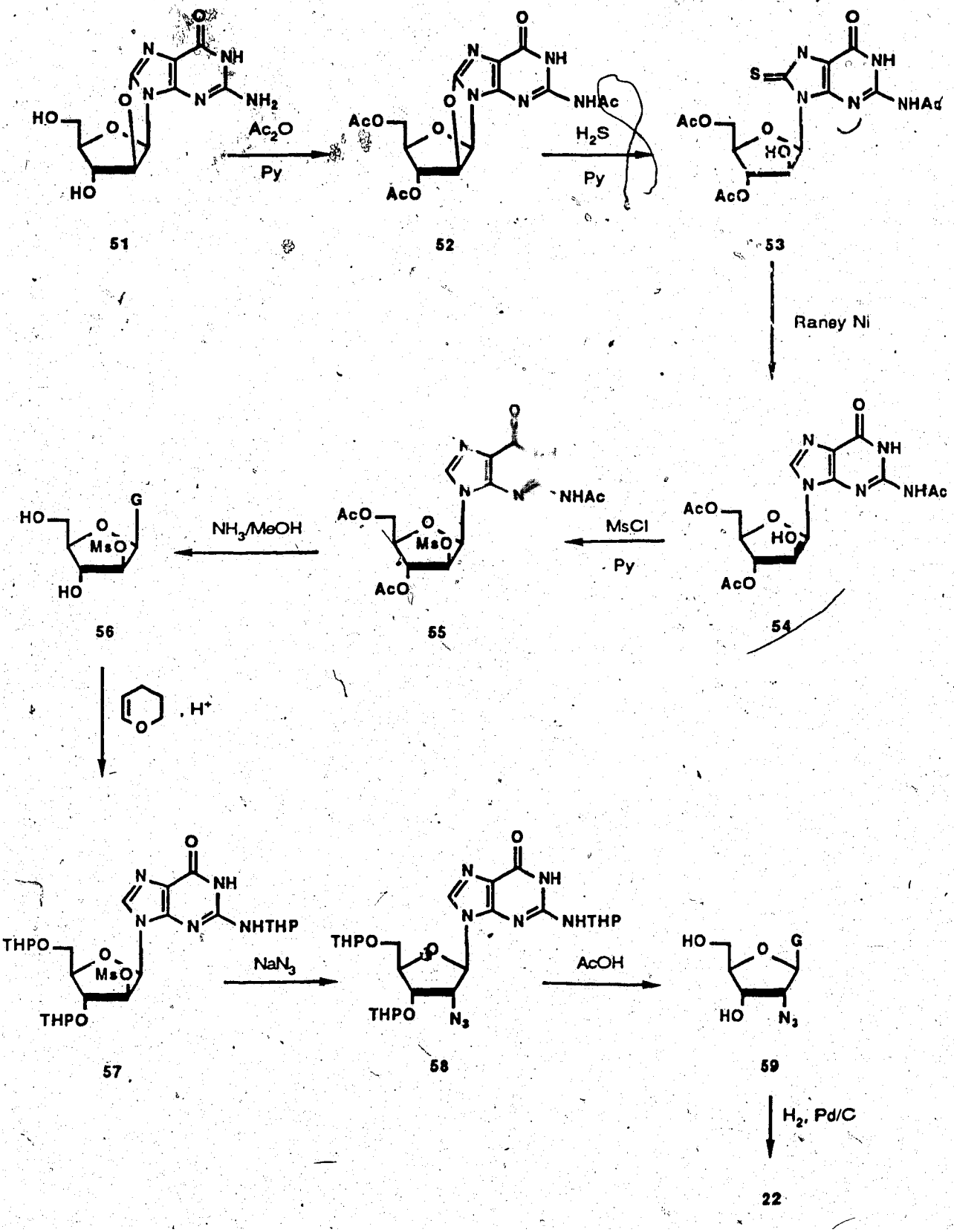

RO
O
A
NH
CF3COSEt
DMF
49
RO
O
A
NR'
H2O
RO
O
A
H2N
HO
50
R=
Ph
Si
Ph
R'= CF3CO-
A=
NH2
N
N
N
N

and was not opened by direct treatment with several nucleophiles. Activation by trifluoroacetylation of the imino nitrogen proved to be successful. In this way, treatment of the 5'-protected 2',3'-aziridine (49) nucleoside with excess ethylthio trifluoroacetate gave the desired ring opened compound. After deprotection and purification 2'-amino-2'-deoxyarabinoadenosine (50) was obtained in 49% yield[33].

Carbohydrate transformations which involved participation of the heterocyclic base (cyclonucleoside intermediates) have been widely exploited by Ikehara and co-workers. A recent report[89] detailed conversion of guanosine to the antibiotic 2'-amino-2'-deoxyguanosine (22), and involved initial bromination at C-8 of the purine base and 2'-hydroxyl activation by p-toluenesulfonylation to give the O-8→C-2'-cyclonucleoside (51). Attack by hydrosulfide at C-8 of the derivative (52) gave the 8-thione (53). Desulfurization was followed by methanesulfonylation of the 2'-hydroxyl and subsequent displacement of mesylate by azide. Deprotection, and hydrogenolysis gave the 2'-amino-sugar antibiotic (22) (SCHEME V).

Finally, examples of the use of pyrimidine base participation (cyclonucleoside intermediates) to functionalize the sugar moiety followed by glycosyl

SCHEME V


Ac2O
Py
H2S
Py
Raney Ni
MsCl
Py
NH3/MeOH
. H+
NaN3
AcOH
H2, Pd/C
51
52
53
54
55
56
57
58
59
22

cleavage are known. Routes which involved either isolation of sugar intermediates followed by coupling with a new base[34] or direct catalyzed trans-glycosylation[35] have been reported by Eckstein and co-workers. The formation of α-anomers was again noted in the latter examples.

B. UREA AND HYDROXY-UREA NUCLEOSIDE DERIVATIVES.

Ribonucleotide reductase is an allosterically regulated enzyme present in all cells that make DNA. It catalyzes the formation of deoxyribonucleotides from ribonucleotides[36] In Escherichia coli the enzyme consists of an $\alpha_2\beta_2$ complex between two non-identical subunits: proteins B1 and B2, of molecular weights 160000 and 78000 respectively. Protein B1 contains binding sites for the ribonucleoside diphosphate substrates and for the nucleoside triphosphate effectors and it also has oxidation-reduction active disulfides, which donate the electrons necessary for the reduction. Protein B2 consists of two apparently identical polypeptide chains, each with a molecular weight of 39000, and also contains two iron atoms and a tyrosine free radical. The two nonidentical irons stabilize the radical. This is localized in the aromatic ring of the tyrosine residue of the polypeptide chain and is a prerequisite for enzyme activity.

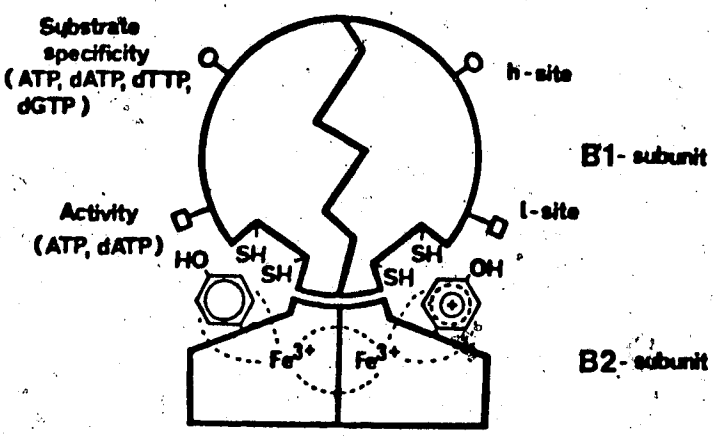


FIG. A. Model of ribonucleoside diphosphate reductase from E. coli.

A similar general construct of ribonucleotide reductase has been found in mammalian cells.[40]

Hydroxyurea was first synthesized by Dresler and Stain[38] in 1869, but it was not until 1928 that it was shown to be biologically active. It is a highly specific low-molecular-weight inhibitor of ribonucleotide reductases, and therefore, of DNA synthesis. Hydroxyurea has shown anti-leukemia and anti-tumor properties and has also found limited application in the treatment of dermatological disorders.

In studies using homogeneous E. coli reductase in vitro the drug was shown to scavenge the tyrosine

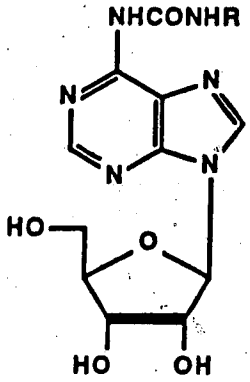
free-radical of protein B2 which resulted in an inactive enzyme[39]. Hydroxyurea also can inhibit RNA and protein synthesis, but to a lesser degree. It is antimitotic and cytotoxic depending on the concentration used, the duration of exposure, and the sensitivity of the organism. Also, several hydroxyurea analogs have been shown to inhibit DNA synthesis.[40]

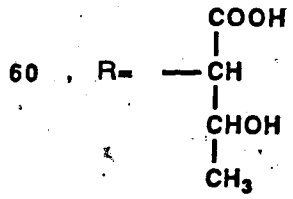
Hydroxyurea is easily obtained (in 53-73% yield) by the reaction of ethyl carbamate with hydroxylamine hydrochloride.[41]

$$H_2NCO_2C_2H_5 + NH_2OH \cdot HCl \xrightarrow{NaOH} H_2NCONHOH + NaCl + C_2H_5OH$$

However, nucleoside analogs bearing a hydroxyurea function have not been described in the literature. Among the known naturally occurring nucleoside analogs only two have been found to possess a urea function. These are the ureidopurine nucleosides, N-[(9-β-D-ribofuranosylpurin-6-yl)carbamoyl]threonine (**60**) and N-[(9-β-D-ribofuranosylpurin-6-yl)carbamoyl]glycine (**61**).

Compound (**60**), a hyper-modified nucleoside, was isolated and characterized from the transfer RNA (tRNA) of many organisms[43-45]. It was also isolated as a free nucleoside from human and rat urine[46]. The glycine analog (**61**), has been isolated from yeast tRNA.





Even though (**60**) and (**61**) showed poor biological and pharmacological activity, some of their analogs stimulate cell division and differentiation in plant tissues (cytokinin activity). Several of them also exerted growth inhibitory effect on cells of leukemic origin grown in culture[47,48].

Two methods have been developed for the synthesis of 6-ureido purines and 6-ureidopurine nucleosides[47-52].

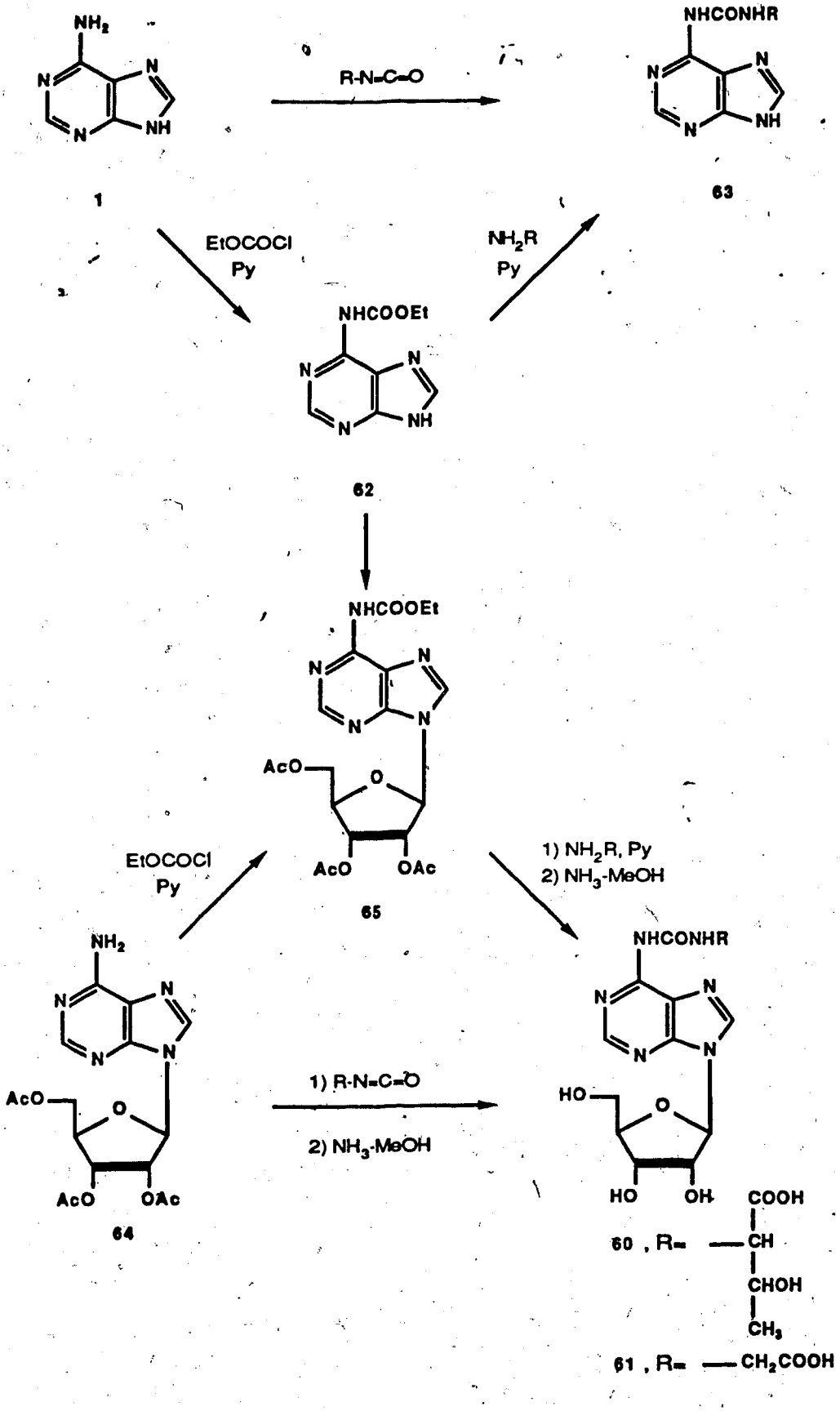
Method A: Urethan Route.

In this route the key intermediates, ethyl purine-6-carbamate (**62**) and ethyl 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purin-6-carbamate (**65**) were prepared by the reaction of ethyl chlorocarbonate with adenine and tri-O-acetyladenosine (**64**) respectively (SCHEME VI). Displacement of the ethoxyl group of urethan (**62**) with 2 molar equivalents of amino acids and amines in pyridine at 120°C for 6 h gave the desired ureido-purine, generally in good yields. Analogous displacement of the ethyl purine-6-carbamate ribonucleoside (**65**) yielded the tri-O-acetyl derivative of 6-ureidopurine nucleosides, which upon treatment with 4 N methanolic ammonia at ambient temperature for 8 h gave the desired nucleosides in good yield.

Method B: Isocyanate Route.

Some of the 6-ureidopurines and their nucleosides were prepared by the reactions of various isocyanates with the amino group of adenine and tri-O-acetyl-adenosines (SCHEME VI). Protected amino acids were converted to the corresponding isocyanates by reacting with $COCl_2$ in PhMe at 85-90°. Adenine (**1**) then was allowed to react with an appropriate isocyanate to give

SCHEME VI


NH2
N
N
NH
1
R-N=C=O
NHCONHR
63
EtOCOCl
Py
NH2R
Py
NHCOOEt
62
AcO
O
AcO
OAc
65
1) NH2R, Py
2) NH3-MeOH
EtOCOCl
Py
64
1) R-N=C=O
2) NH3-MeOH
HO
OH
COOH
60 , R= CH
CHOH
CH3
61 , R= CH2COOH

6-ureidopurines along with some 6-ureido-9-carbamoylpurines and 9-carbamoylpurines. The reaction of isocyanates with (**64**) gave the desired 6-ureidopurine ribonucleosides. The urethan method proved to be better than the isocyanate procedure in terms of yield and ease of isolation of the products.

Urea derivatives of amino-sugar nucleosides have not been employed in the literature as biochemical probes in cellular reactions, perhaps due to the fact that urea itself (H_2NCONH_2) did not show biological activity when compared with hydroxyurea. However, since the finding of nitrosoureas as one of the most significant groups of anticancer agents that have been developed[53], ureidosugar nucleosides have been prepared as intermediates in the synthesis of nitrosoureido-nucleosides[54].

The key intermediates in the preparation of ureido-sugar nucleosides are the amino-sugar nucleosides, that can be prepared by any of the methods mentioned earlier. The amino-sugar nucleosides can then be converted to the urea derivatives by reaction with the corresponding isocyanates[55-58]. This method resembled that used in the isocyanate route described in Scheme VI.

C. 3'-AMINO-3'-DEOXYADENOSINE

3'-Amino-3'-deoxyadenosine (**20**) is a naturally occurring purine nucleoside antibiotic. It was first isolated from the culture filtrate of Helminthosporium s.p. 125[59] and Cordyceps militaris[60] and has exhibited antitumor properties. 3'-Amino-3'-deoxyadenosine inhibited RNA polymerase but not DNA polymerase. It has also been used to study the aminoacylation step in protein synthesis[61].

Compound (**20**) was first prepared by a lengthy chemical synthesis from adenine and D-xylose by Baker and co-workers in 1955[62]. In this 20-step approach, compound (**20**) was obtained in 3% overall yield.

Most of the syntheses reported for the preparation of (**20**) involve the elaboration of a suitably protected 3-amino-3-deoxy-D-ribofuranose unit, which then was converted to the desired nucleoside by coupling with the corresponding heterocyclic base. Several procedures have been published for the synthesis of 3-amino-3-deoxy-D-ribose[63-68].

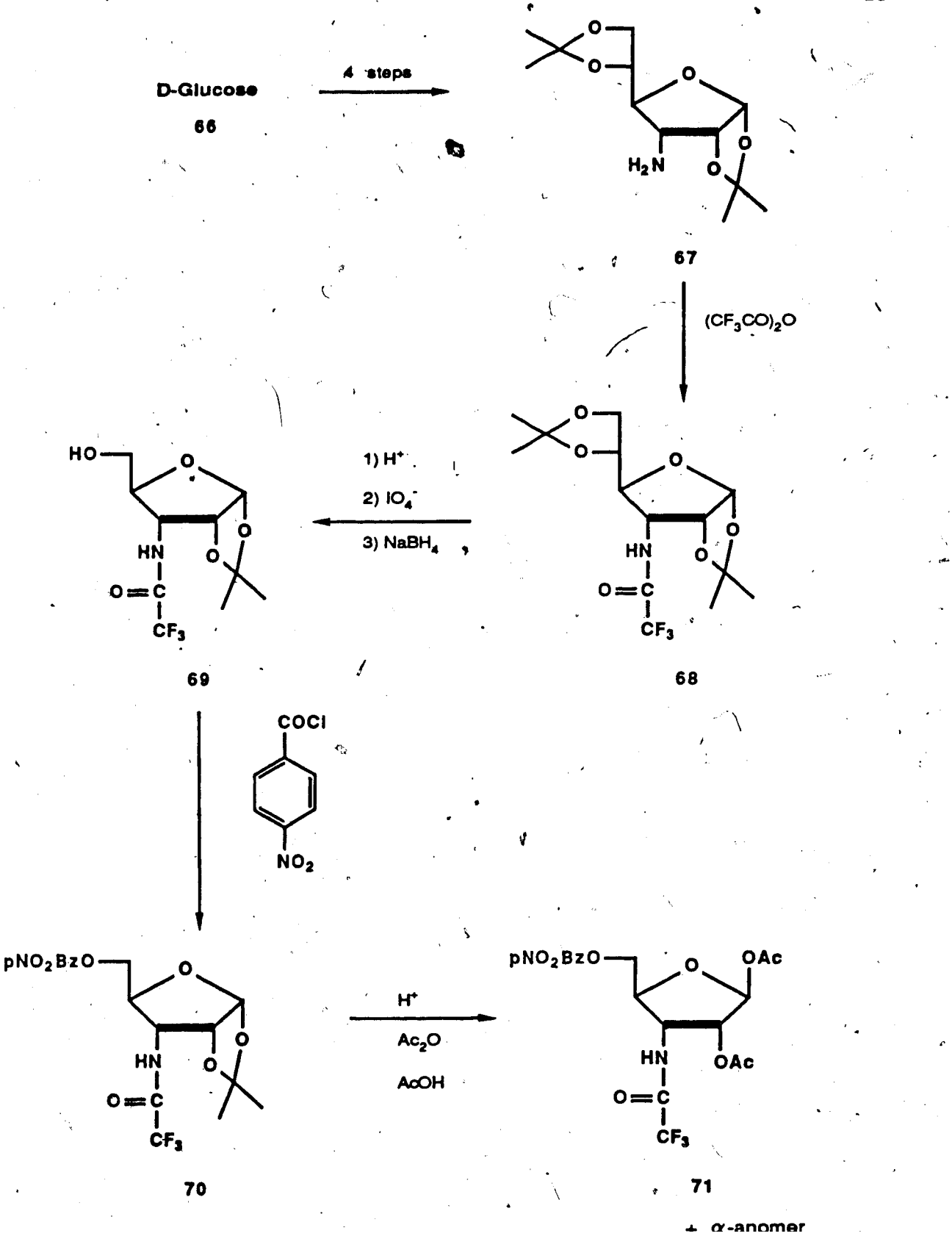
Two main routes have been developed for preparation of the suitably protected 3-amino-3-deoxy-D-ribofuranose derivatives. In one approach[67], D-glucose (**66**) was converted by a multi-step procedure

into the D-ribose derivative 71 in 24% overall yield from 67 (SCHEME VII).

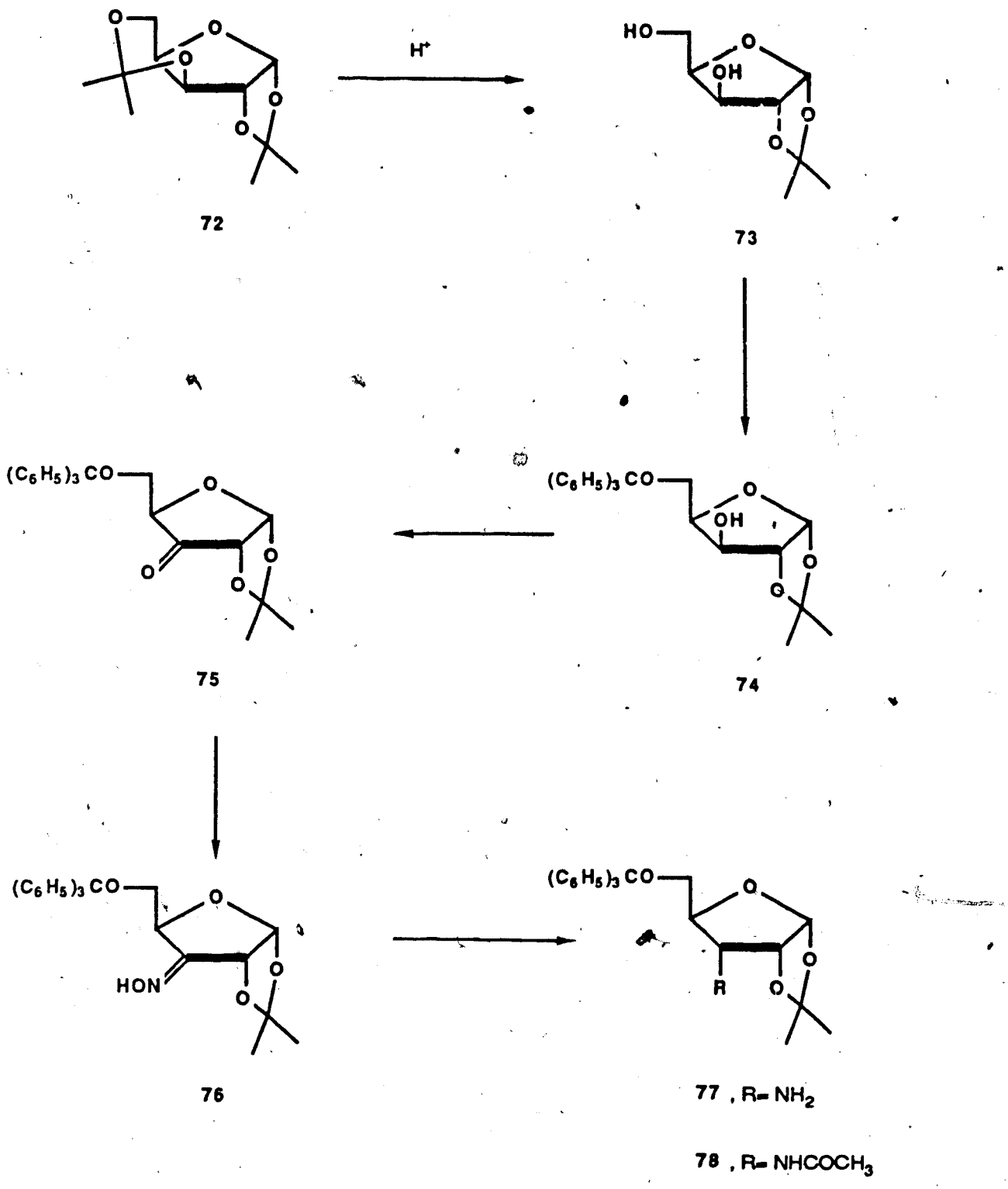
In the other approach, D-xylose was processed[62,64] to afford a similar D-ribose derivative. In this method, 1,2-O-isopropylidene-α-D-xylofuranose (73), readily obtained by hydrolysis of 1,2;3,5-di-O-isopropylidene-α-D-xylofuranose (72), was treated with triphenylchloromethane to protect the primary alcohol group. Oxidation of (74) by dimethyl sulfoxide-acetic anhydride provided the keto derivative (75). The oxime (76) generated from (75) was reduced by lithium aluminium hydride to 3-amino-3-deoxy-1,2-O-isopropylidene-5-O-triphenylmethyl-α-D-ribofuranose (77), isolated as the acetamido derivative (78). Hydrolysis of (78) afforded 3-amino-3-deoxy-D-ribose as the crystalline hydrochloride in an overall yield of about 45% based on (73) (SCHEME VIII).

Recently, Ozols et al.[66] elaborated a convenient method of converting D-xylose into a 3-azido derivative of D-ribose. This method consisted of the esterification of the 3-OH group of 1,2-isopropylidene-5-O-(4-methylbenzoyl)-α-D-xylofuranose (79) with trifluoromethanesulfonic anhydride. This was followed by nucleophilic substitution of the triflate function

SCHEME VII


D-Glucose
66
4 steps
67
(CF3CO)2O
68
1) H+
2) IO4-
3) NaBH4
69
COCl
NO2
70
H+
Ac2O
AcOH
71
pNO2BzO
OAc
HN
CF3
± α-anomer

SCHEME VIII



72

73

74

75

76

77 , R= NH_2

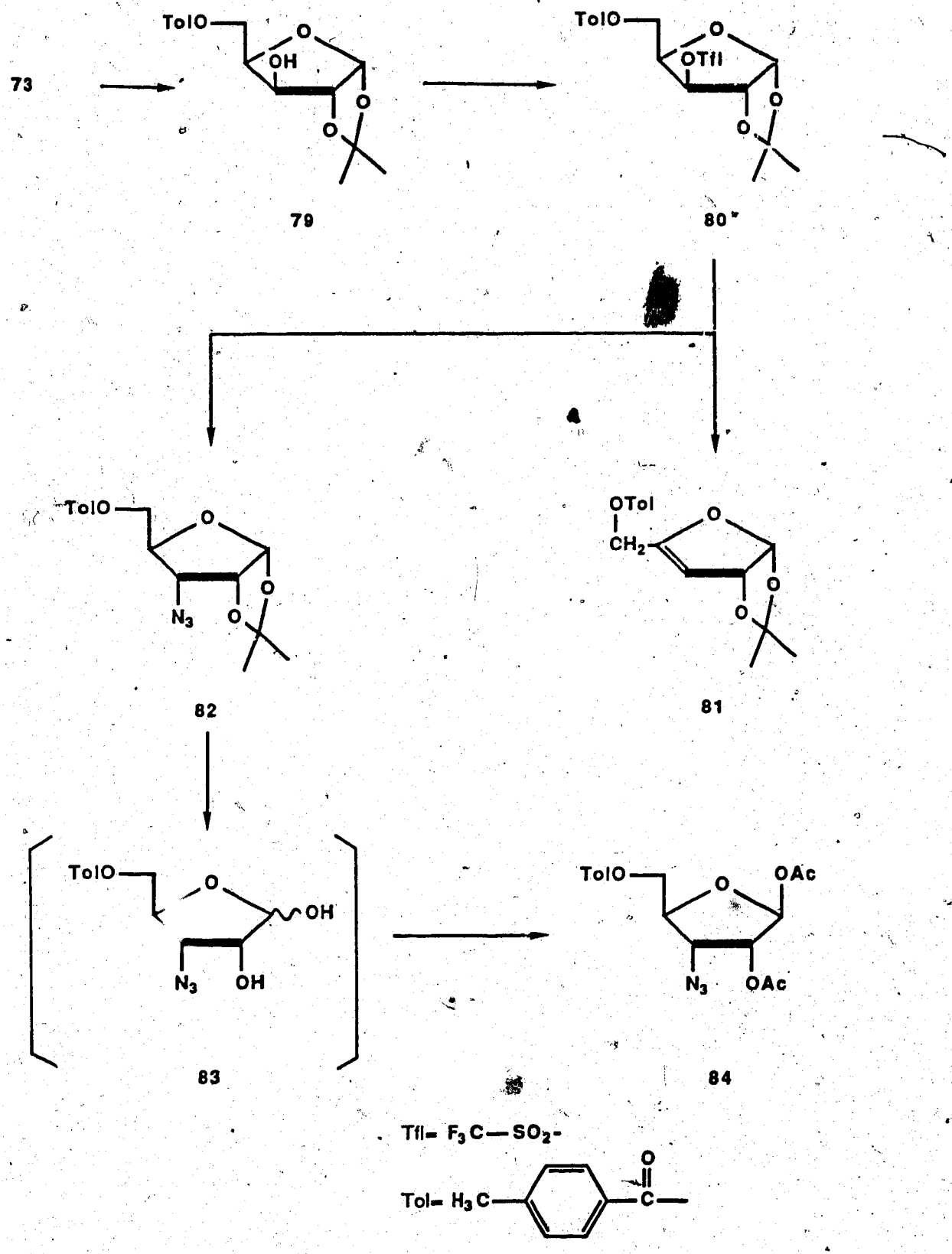
78 , R= $NHCOCH_3$

with lithium azide. The overall yield of product from the initial sugar (**73**) was 36% (SCHEME IX).

As can be observed in the last examples, the preparation of these sugar intermediates required many steps and reported yields are low. Furthermore, the subsequent condensation reactions with the heterocyclic bases and deprotection to afford the desired amino-sugar nucleosides resulted in poor yields of the final products.

3'-Amino-3'-deoxyadenosine also has been prepared by a 12 step synthesis using adenosine as starting material[24,69]. Treatment of 2',3'-O-methoxyethylideneadenosine (**85**) with excess pivalic acid chloride in refluxing pyridine gave a mixture composed primarily of 6-pivalamido-9-(3-chloro-3-deoxy-2-O-acetyl-5-O-pivalyl-β-D-xylofuranosyl)purine (**86a**) and 6-pivalamido-9-(3-chloro-3-deoxy-5-O-pivalyl-2-O-[4,4-dimethyl-3-pivalyloxypent-2-enoyl]-β-D-xylofuranosyl)purine (**86b**) in high combined yield. Methanolic sodium methoxide converted this mixture to 9-(2,3-anhydro-β-D-ribofuranosyl)adenine (adenosine ribo-epoxide) (**87**) in greater than 60% overall yield from adenosine. Benzoylation of (**87**) in pyridine gave the N^6,N^6,$O^{5'}$-tribenzoate (**88**). The crude product of the reaction of (**88**) with sodium benzoate-DMF was treated

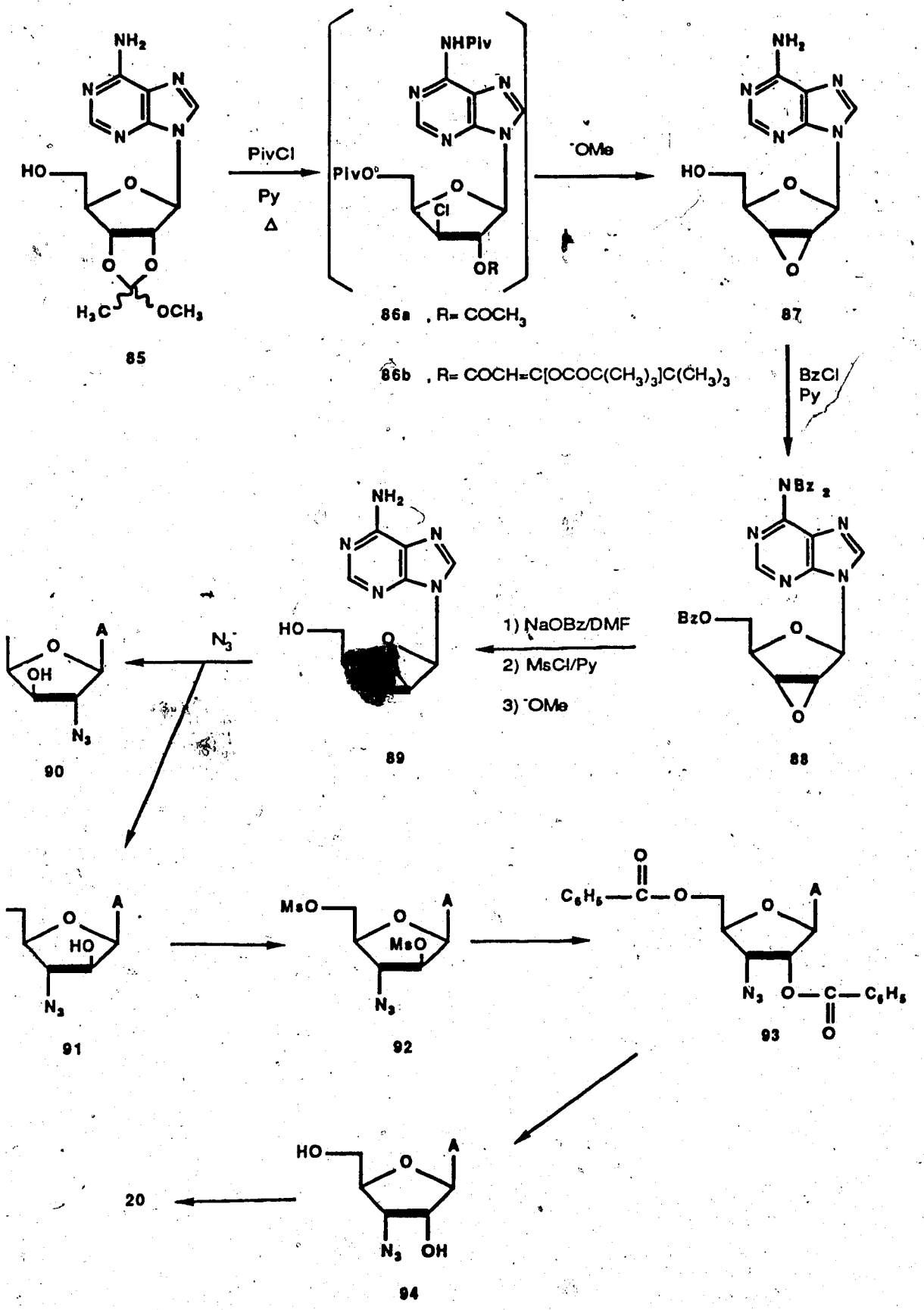
SCHEME IX


73
TolO
OH
O
O
O
79
TolO
OTfl
O
O
O
80
TolO
N3
O
O
O
82
OTol
CH2
O
O
O
81
TolO
OH
N3
OH
O
83
TolO
OAc
N3
OAc
O
84
Tfl= F3C—SO2-
Tol= H3C
O
C

with methanesulfonyl chloride in cold pyridine to give a monomesylate, which was converted to 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (**89**) by methanolic sodium methoxide. Nucleophilic opening of the derived lyxo epoxide (**89**) with azide gave the 3'-azido arabino isomer (**91**) as the major product and a minor amount of the 2'-azido xylo isomer (**90**). Hydroxyl activation by methanesulfonylation followed by S_N2 displacement of mesylate with benzoate, deblocking and hydrogenolysis provided the desired amino-sugar nucleoside (**20**) in 5% overall yield from adenosine.

Although these major efforts have been made for the preparation of 3'-amino-3'-deoxyadenosine, thus far, no good chemical synthesis in terms of yield and ease of reactions has been published.

SCHEME X



85

86a , R= $COCH_3$

86b , R= $COCH{=}C[OCOC(CH_3)_3]C(CH_3)_3$

87

88

89

90

91

92

93

94

RESULTS AND DISCUSSION

A. UREA AND HYDROXYUREA NUCLEOSIDE DERIVATIVES

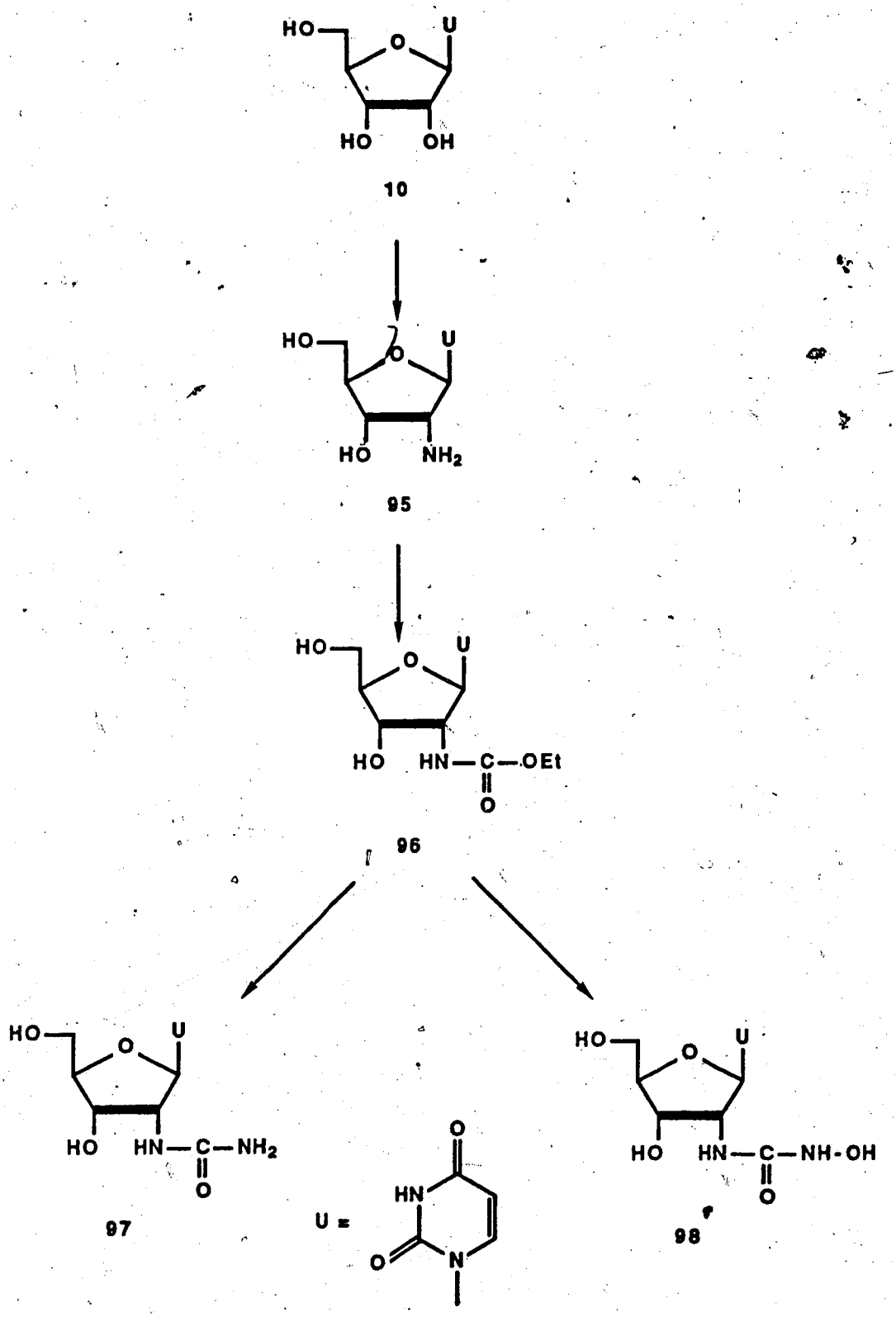
The important biological and pharmacological properties of hydroxyureas encouraged us to investigate the introduction of this functionality and model urea controls into the amino-sugar moiety of a nucleoside. The sugar portion of pyrimidine ribonucleosides is easily functionalized at the 2' position via participation of the heterocyclic base (cyclonucleoside formation). Therefore, uridine (**10**) was chosen as the starting nucleoside for the preparation of 2'-(carbamoyl)amino-2'-deoxyuridine (**97**) and 2'-(hydroxycarbamoyl)amino-2'-deoxyuridine (**98**).

Our first synthetic plan involved the use of 2'-amino-2'-deoxyuridine (**95**) as the key intermediate, followed by formation of the 2'-ethylcarbamate derivative (**96**), and subsequent displacement of the ethoxyl group by ammonia and hydroxylamine to afford the desired products (SCHEME XI).

2'-Amino-2'-deoxyuridine (**95**) has been prepared from uridine (**10**), as reported by several research groups[70-73].

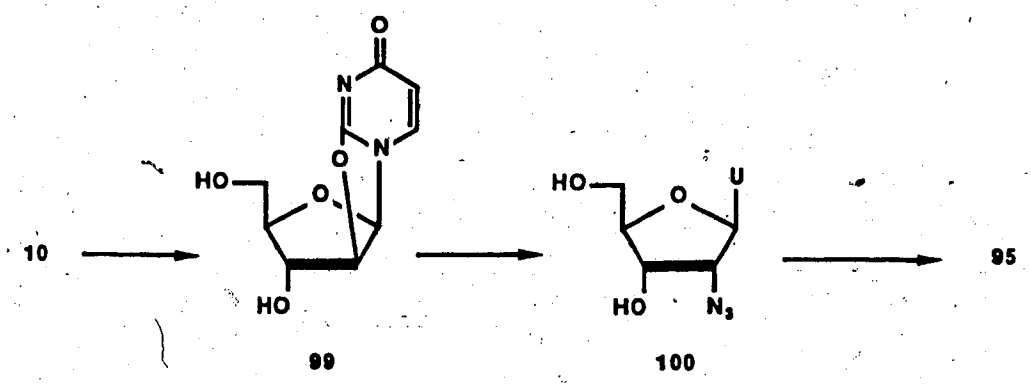
Following Hampton and Nichol's procedure[70], the O2,C2'-cyclouridine [2,2'-anhydro-1-(β-D-arabinofuran-

SCHEME XI


HO
O
U
HO
OH
10
HO
O
U
HO
NH2
95
HO
O
U
HO
HN—C—OEt
O
96
HO
O
U
HO
HN—C—NH2
O
97
U =
HN
O
O
N
HO
O
U
HO
HN—C—NH-OH
O
98

osyl)uracil] (**99**) was obtained by treatment of uridine with diphenyl carbonate and sodium bicarbonate in dimethylformamide (DMF) at 150°C. Crystallization of the crude product from MeOH afforded pure (**99**) in 81% yield. The melting point and spectral properties of this compound were identical with those reported in the literature. This anhydronucleoside (**99**) was opened, as described by Moffatt and coworkers[73], via the nucleophilic attack of lithium azide in hexamethylphosphoroamide (HMPA) at 150°C in the presence of benzoic acid. After purification, the desired product 2'-azido-2'-deoxyuridine (**100**) was obtained as a reasonably pure syrup in 50% yield. Subsequent reduction of the azido group in the presence of 5% Pd.C gave crystalline 2'-amino-2'-deoxyuridine (**95**) in 95% yield (SCHEME XII).

SCHEME XII



With the amino-sugar nucleoside (95) in hand we were ready to attempt the preparation of the carbamate derivative (96). Since it is known that chlorocarbonates (101) react with primary amines to produce carbamates (102)[74], this approach was used for the preparation of (96)[75].

$$\underset{(101)}{ROCOCl} + R'NH_2 \longrightarrow \underset{(102)}{ROCONHR'}$$

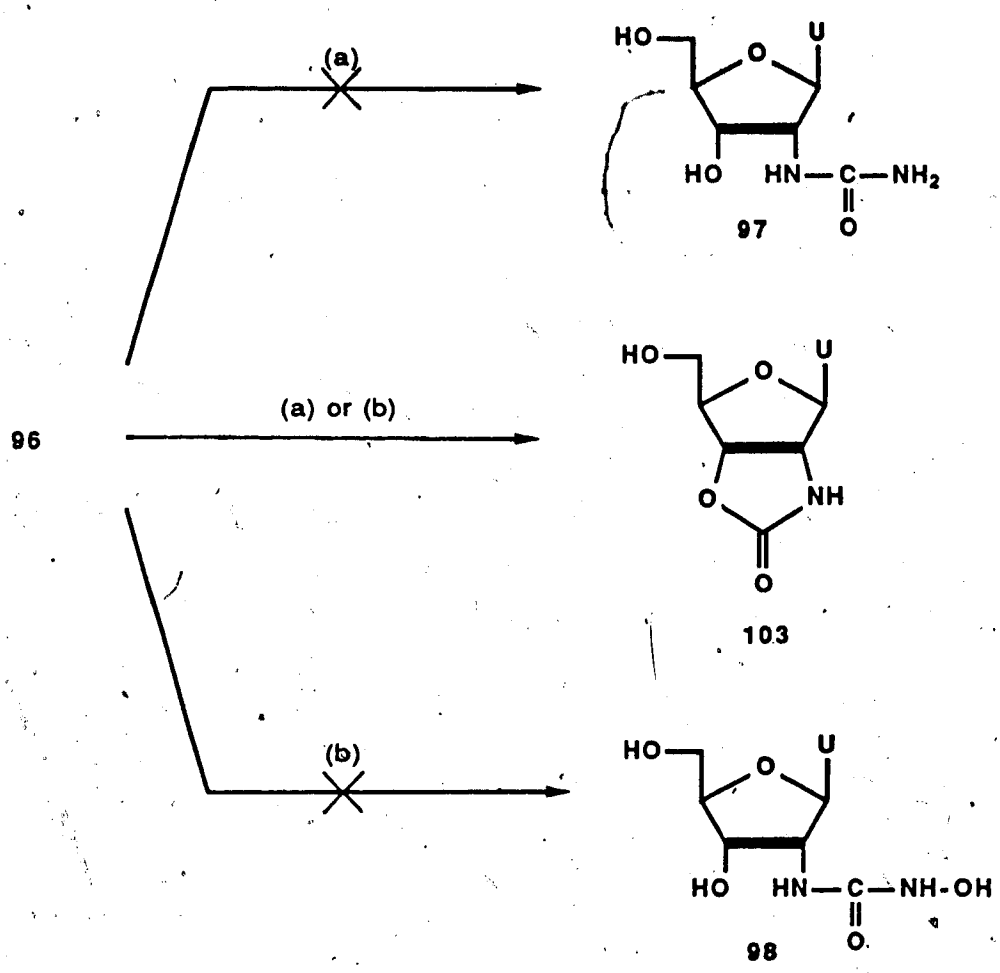
Treatment of unprotected amine (95) with ethyl chloroformate in pyridine and a catalytic amount of Et_3N provided a complex mixture of products, probably arising from side reactions of the ethyl chloroformate with the 3' and 5' hydroxyl groups. In order to avoid this complication, nucleoside (95) was protected using hexamethyldisilazane. The resulting crude trimethylsilylated product was subjected to the reaction conditions described above, using acetonitrile as the solvent. After deprotection, purification using ion exchange chromatography, and crystallization, a pure compound was obtained in 90% yield. This compound was identified as (96) by ^1H NMR as well as other spectroscopic methods. The ^1H NMR spectrum of (96)

shows, among other signals, a doublet at δ 6.88 that exchanges at a slow rate with D_2O (indicating the presence of the NH proton of the carbamate[76]) and the ethoxyl proton triplet at δ 1.26 and quartet at δ 4.04.

Having prepared compound (**96**), the next step in our synthetic route involved displacement of the ethoxyl group of the carbamate. Since analogous displacements on a urethan moiety have been performed in the synthesis of hydroxyurea itself[41] and ureido purine nucleosides[48-51], we thought that similar reaction conditions would afford our target molecules.

In an attempt to prepare ureidonucleoside (**97**), carbamate (**96**) was treated with ammonium hydroxide at ambient temperature to give a product in quantitative yield. Similarly, carbamate (**96**) was treated with hydroxylamine hydrochloride and sodium hydroxide at ambient temperature[41]. This reaction proceeded to give the same product in almost quantitative yield. Analysis of the ^1H NMR and mass spectra of the resulting product showed that these two reactions failed to give the desired products (**97**) and (**98**), but instead (**103**) was obtained in both cases (SCHEME XIII). Absence of the signal for the 3'-hydroxyl proton in the ^1H NMR spectrum of (**103**) indicated that substitution at this position had occurred.

SCHEME XIII



a) NH_3 / H_2O / 3 days

b) $NH_2OH.HCl$ / NaOH / 3 days

Disappearance of the ethoxyl hydrogen signals showed that displacement of this group had taken place, and the expected signals for introduction of the ureido functionalities were not observed. In the mass spectrum, a peak of m/z 269 corresponded to M^+ for structure (**103**). The spectral data obtained for (**103**) from both reactions were identical. A recrystallized sample of (**103**) gave satisfactory elemental analysis and UV spectral data.

Compound (**103**) obviously resulted from intramolecular cyclization of carbamate (**96**) under basic conditions. Analogous cyclizations have been reported to occur during the preparation of nitroso-ureidonucleosides[56].

At this point, it was decided to attempt the opening of cyclic carbamate (**103**). When (**103**) was treated with a 40% aqueous solution of methylamine at ambient temperature, a more polar product began to be formed. The structure of this compound (which was purified by chromatography on silica gel plates) was confirmed to be the expected methylureidonucleoside (**104**) by comparison of tlc mobilities and ^1H NMR, UV and mass spectra with those of an authentic sample prepared by the isocyanate route (SCHEME XXI) and fully identified as compound (**104**).

Encouraged by the smooth opening of (103) with methylamine, compound (103) was treated with ammonium hydroxide at ambient temperature for several days. A parallel reaction was carried out in which (103) was allowed to stand in an aqueous solution of hydroxylamine hydrochloride and sodium hydroxide at ambient temperature.

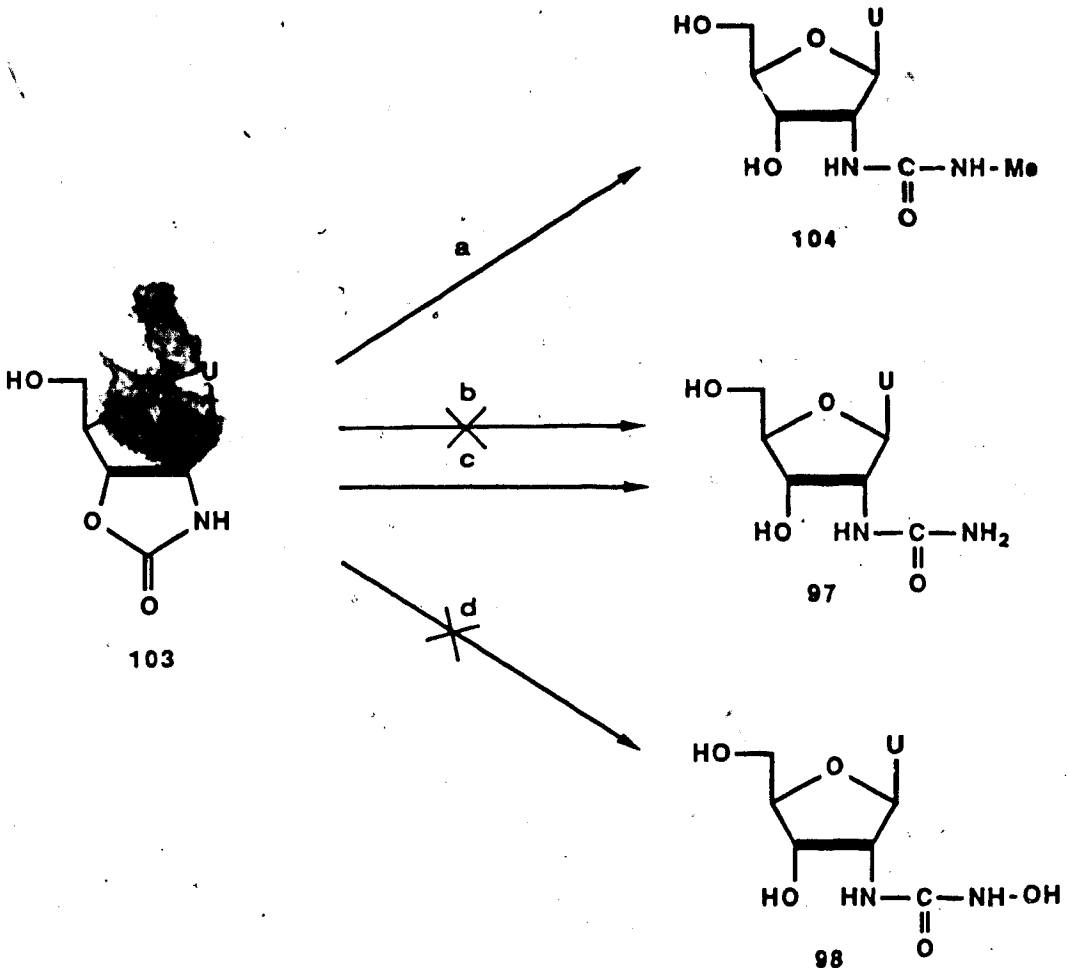
Unfortunately, both approaches were unsuccessful and starting material was recovered. This indicated that more drastic conditions would be required for the opening of (103). A reaction mixture containing cyclic carbamate (103) dissolved in ammonium hydroxide was heated at 70°C in a steel bomb for several days. Progress of the reaction was monitored by tlc and slow formation of a more polar compound was observed. Isolation of this compound was carried out using chromatography on silica gel plates and the crude powder obtained was recrystallized from MeOH/Et_2O to give a microcrystalline powder in 70% yield from (103). The mass spectrum of this compound by the Fast Atom Bombardment technique showed an m/z 287 ($M^+ + 1$) ion as expected for our desired compound (97). Its ^1H NMR spectrum also was in agreement with the structure of this compound displaying a one-proton exchangeable doublet at δ 5.8 corresponding to the free 3'-hydroxyl

group. A sharp singlet at δ 6.8 that integrated for two hydrogens showed the presence of an $-NH_2$ group in the molecule. Compound (**97**) was further characterized on the basis of its UV and ^{13}C spectra and its elemental analysis.

However, when we attempted the preparation of hydroxyureido nucleoside (**98**) by treatment of compound (**103**) with hydroxylamine hydrochloride and sodium hydroxide at high temperature for three days, only starting material was recovered (SCHEME XIV). The failure to prepare hydroxyureido compound (**98**) from cyclic carbamate (**103**) under these conditions indicated to us that an alternative method would be required to solve this problem.

Since (**103**) arose by the intramolecular participation of the 3'-hydroxyl group of (**96**) under basic reaction conditions, we thought that protection of the 3'- and 5'-hydroxyls would prevent this reaction and allow displacement of the ethoxyl group by hydroxylamine. For this purpose, carbamate (**96**) was selectively 3',5'-O-protected using 1,1,3,3-tetra-isopropyl-1,3-dichlorodisiloxane[77]. After purification, the resulting compound (**105**) was obtained as a yellowish oil in high yield. Identification of

SCHEME XIV



a) $MeNH_2$ / H_2O / ambient temperature

b) NH_4OH / ambient temperature

c) NH_4OH / 70°C / steel bomb

d) $NH_2OH.HCl$ / NaOH / H_2O / ambient temperature or Δ

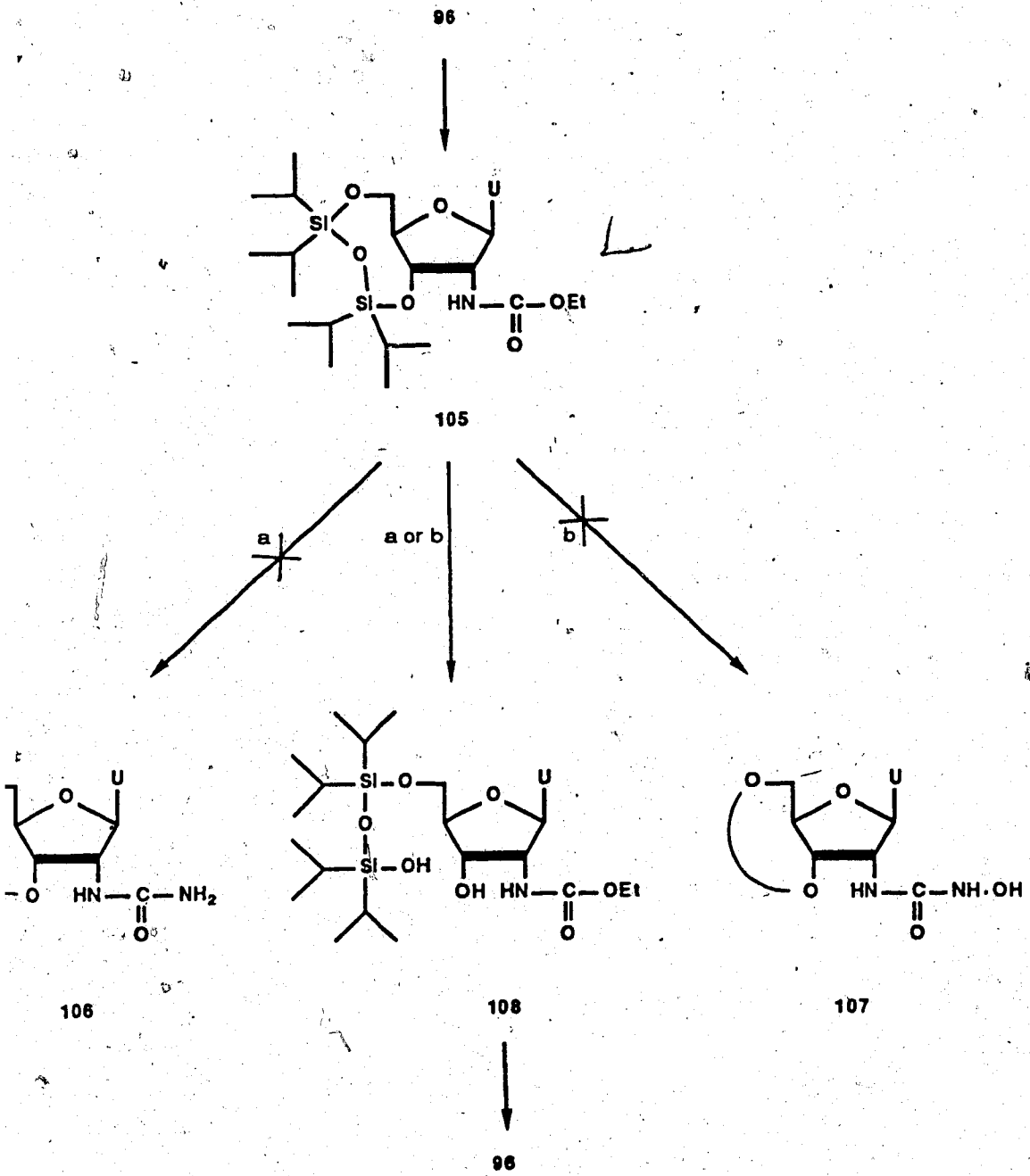
this compound was achieved by examination of its ^1H NMR, UV and mass spectral data.

When compound (105) was subjected to usual reaction conditions for preparation of ureido (106) and hydroxyureido (107) derivatives, one main product resulted from each reaction. These two products had the same chromatographic mobilities and spectral data. The mass spectrum of this compound revealed that the protecting group was still attached (M^+ m/z 574). Its ^1H NMR spectrum showed that the ethoxyl group was present. Two new signals, both readily exchangeable singlets, also were present in the spectrum. These observations indicated that the expected displacement reaction did not take place, but instead deprotection at the 3'-position had occurred to yield compound (108).

For further identification, compound (108) was subjected to deprotection using one molar equivalent of tetra-n-butylammonium fluoride[78]. The resulting product was purified and its identity confirmed to be (96) by tlc migration and ^1H NMR, UV, and mass spectral comparisons with an authentic sample (SCHEME XV).

We then decided to study a different approach to hydroxyureido nucleoside (98). Treatment of acyl halides with ammonia or amines is a very general

SCHEME XV


96
105
a
a or b
b
106
108
107
96
a) NH4OH / MeOH
b) NH2OH.HCl / NaOH / H2O / MeOH

reaction for the preparation of amides[78]. When phosgene ($COCl_2$) is used as the acyl halide, a carbamoyl chloride is the initial product.

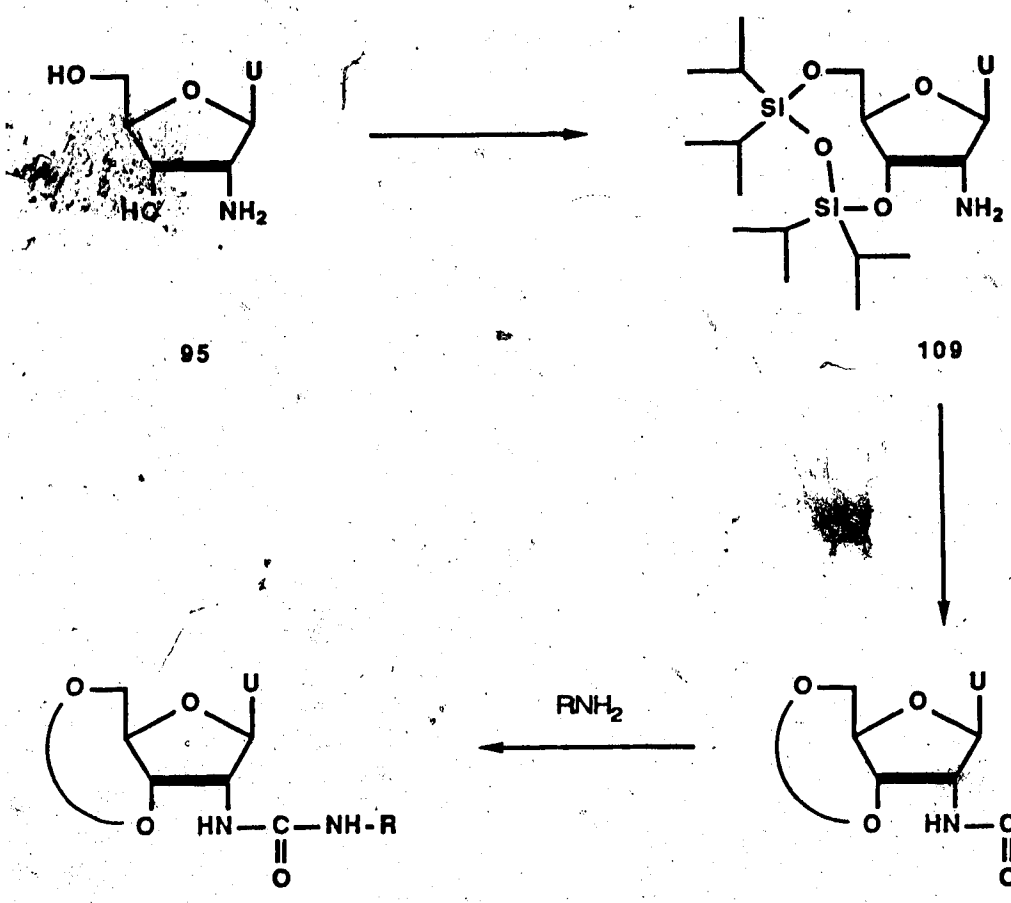
$$RNH_2 + COCl_2 \longrightarrow RNHCOCl + HCl$$

Introduction of this functionality at the 2'-position by reaction of the amino-sugar nucleoside (**95**) with $COCl_2$ would give a carbamoyl chloride nucleoside derivative (**110**) that subsequently could be used to acylate a suitable primary amine to give our desired compound (**107**) (SCHEME XVI).

As illustrated in Scheme XVI, the first step in this route was selective protection of the 3'- and 5'-hydroxyls of compound (**95**). Treatment of (**95**) with 1,1,3,3-tetraisopropyl-1,3-dichlorodisiloxane[77] under standard conditions gave the 3',5'-O-protected amino-sugar nucleoside (**109**) in 75% yield. The moderate yield obtained might have resulted from side reactions involving the 2'-NH_2 group.

An improvement in the preparation of (**109**) was achieved when 2'-azido-2'-deoxyuridine (**100**) was converted to 2'-azido-3',5'-O (1,1,3,3-tetraisopropyl-

SCHEME XVI



95

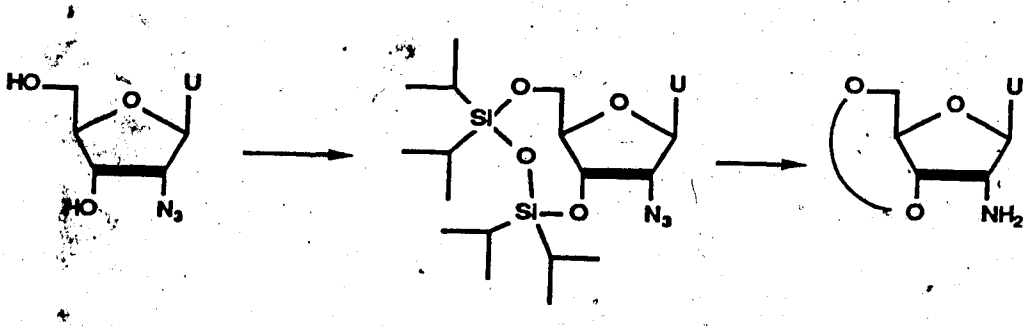
109

110

107 , R= OH

disilox-1,3-diyl)-2'-deoxyuridine (**114**) quantitatively under the same reaction conditions. Subsequent reduction of the azido group using 5% Pd.C afforded (**109**), also in quantitative yield (SCHEME XVII). In this manner a very high yield method to generate the key intermediate (**109**) has been developed.

SCHEME XVII



100 114 109

In order to perform the next reaction, a phosgene solution of known concentration was prepared by bubbling phosgene gas into alcohol-free, freshly distilled chloroform. Treatment of amino-sugar derivative (**109**) with one molar equivalent of phosgene and 3 molar equivalents of triethylamine (Et_3N) in ethanol-free chloroform provided a mixture of two products in about 1:1 ratio (tlc). The faster moving compound was identified by its chromatographic mobility as the desired compound (**110**).

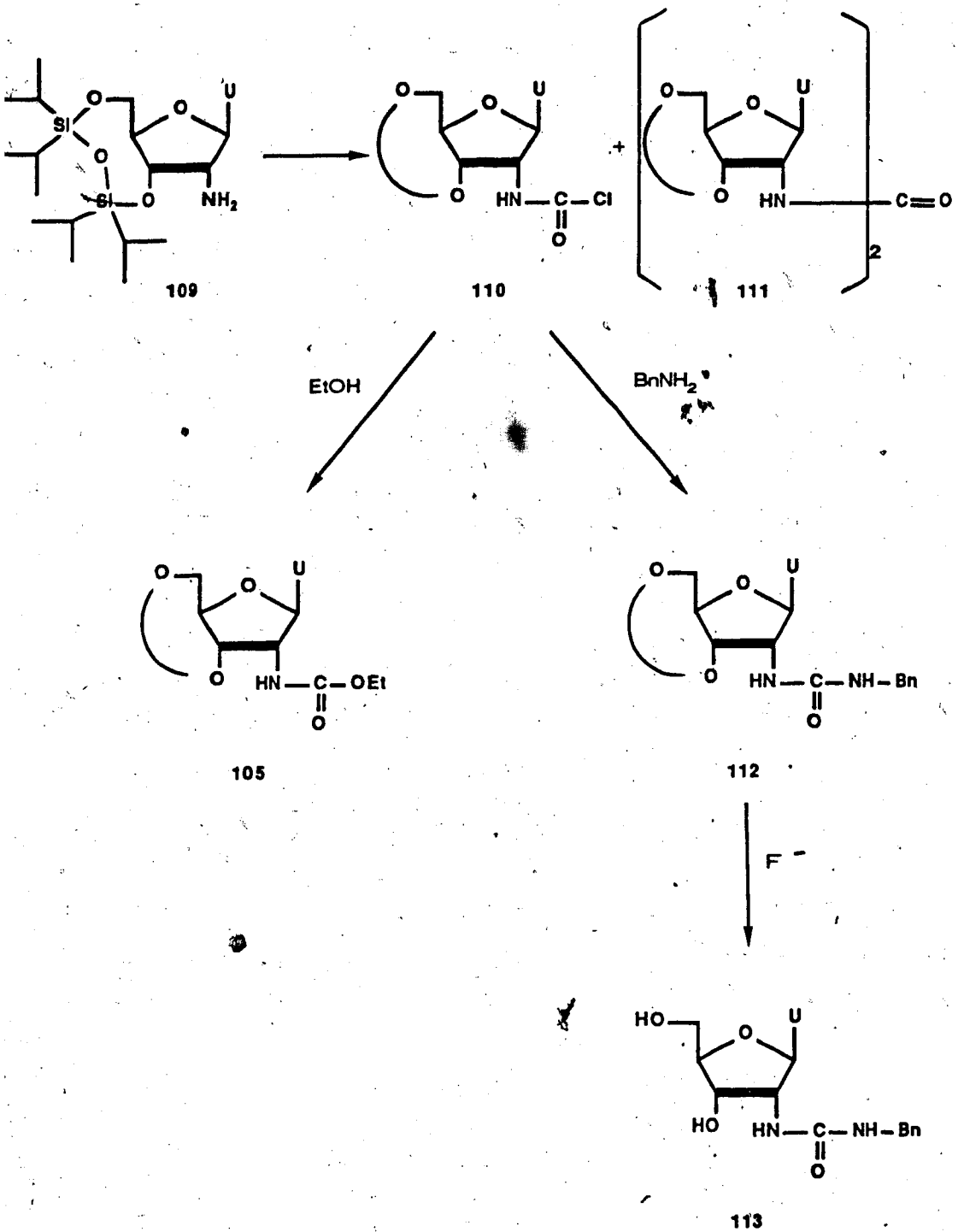
The second product of this reaction was purified by chromatography on silica gel plates and identified by its spectroscopic data. The high m/z molecular ion observed in the FAB mass spectrum ($M^+ + 1 = 997$) and the observation of only ten signals in the ^{13}C NMR spectrum were compatible with the structure of dimer (**111**) [MW = 996]. ^1H NMR data are in agreement with this proposed structure.

When (**110**) was stirred in EtOH at room temperature, total conversion of (**110**) to ethyl carbamate derivative (**105**) was observed by the tlc and confirmed by ^1H NMR spectroscopy. Similarly, the reaction of (**110**) with benzylamine afforded a compound that had ^1H NMR spectral data in harmony with structure (**112**).

After deprotection of (**112**) using tetra-n-butyl ammonium fluoride, the compound obtained had identical chromatographic mobilities and spectroscopic data to those of an authentic sample prepared by the isocyanate route (SCHEME XXI) and fully identified as (**113**) (SCHEME XVIII).

Dimer (**111**) resulted from reaction of a molecule of the carbamoyl chloride derivative (**110**) with a molecule of the starting 2'-amino compound (**109**). However, we found that by varying the concentration of

SCHEME XVIII



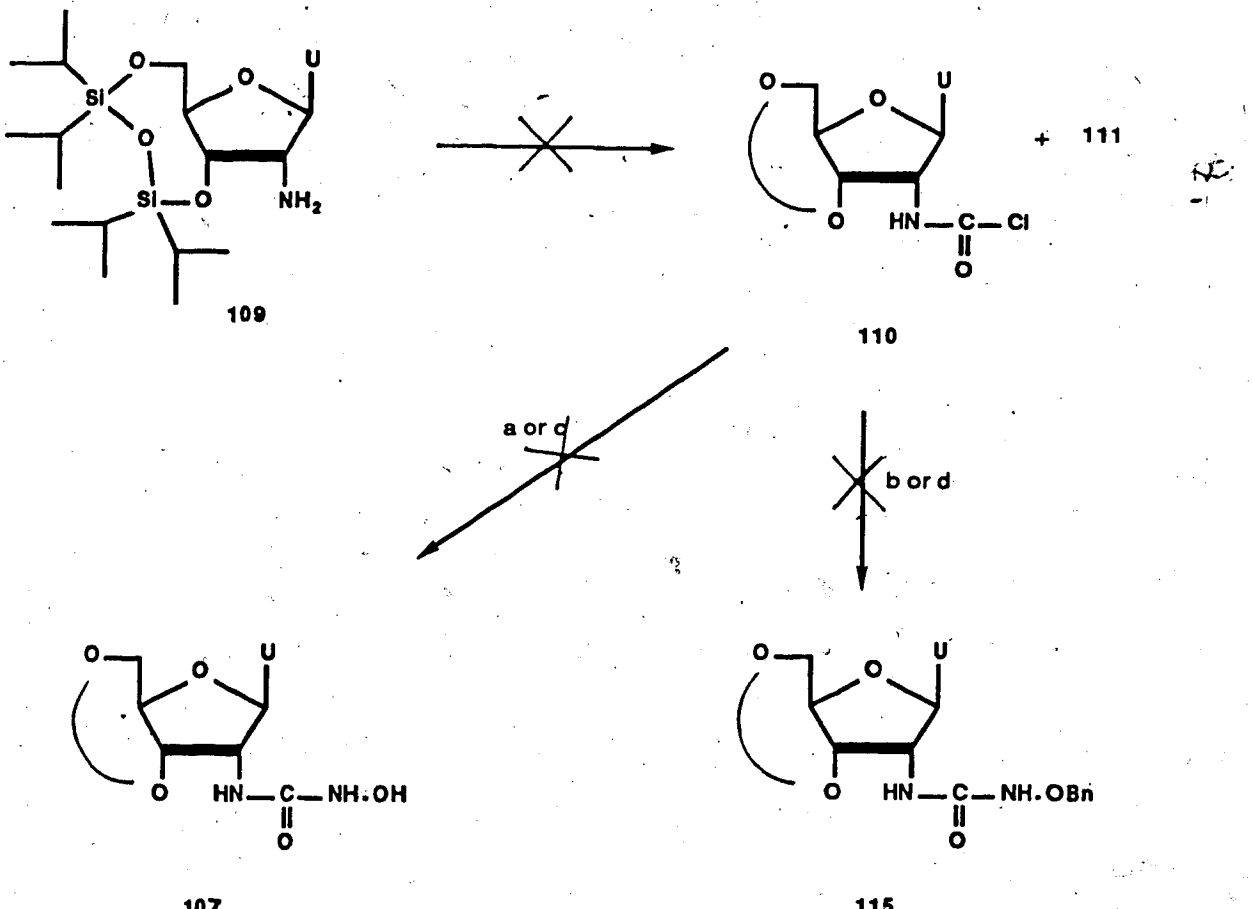
phosgene in the reaction mixture we could control the ratio of the products obtained. Thus, addition of 0.5 molar equivalent of phosgene provided dimer (**111**) almost quantitatively. On the other hand, if an excess of phosgene is used, carbamoyl chloride derivative (**110**) is the predominant product.

Efforts to isolate and characterize compound (**110**) were unsuccessful and indicated that further reactions should be carried out using the crude material. Having prepared the carbamoyl chloride nucleoside derivative (**110**), the next step called for reaction of this compound with a suitable primary amine. The amines chosen were: a) hydroxylamine hydrochloride, which would afford the hydroxyureido nucleoside (**107**), and b) benzyloxyamine hydrochloride, since the expected benzyloxyureido derivative should then be hydrogenolized easily to provide the hydroxyureido product (**107**).

The carbamoyl chloride derivative (**110**) was prepared using an excess of phosgene. After evaporation of the volatile materials <u>in vacuo</u> at ambient temperature, the crude product was subjected to reaction with hydroxylamine hydrochloride and triethylamine in chloroform. A parallel reaction was carried out using benzyloxyamine hydrochloride.

Unfortunately, neither of these reactions gave satisfactory results. When pyridine was used as the solvent no improvement was observed (SCHEME XIX).

SCHEME XIX



In our next attempt, we decided to carry out the preparation of (**107**) from (**109**) *in situ*, as follows. Treatment of amino nucleoside (**109**) with 4-molar equivalents of phosgene, 5-equivalents of Et_3N and 2-equivalents of hydroxylamine hydrochloride at 0°C for 3 h gave decomposition products and unreacted starting material only. However, when this reaction was repeated using benzyloxyamine hydrochloride, a predominant product along with small amount of dimer (**111**) was observed by tlc. The crude mixture was purified by column chromatography and a reasonably pure compound was obtained in 35% yield. This compound had an ^1H NMR spectrum that clearly showed the presence of a benzyl group and a downfield exchangeable singlet corresponding to the new NH function. The mass spectrum of this compound displayed a molecular ion peak at m/z 634 in harmony with the expected benzyloxyureido derivative (**115**). ^{13}C NMR and UV data for this compound are in agreement with structure (**115**).

Hydrogenolysis of (**115**) was carried out in 95% EtOH using 5% Pd•C. From this reaction two products were obtained. The mixture was separated and the compounds identified on the basis of their ^1H NMR spectra as well as other spectroscopic methods.

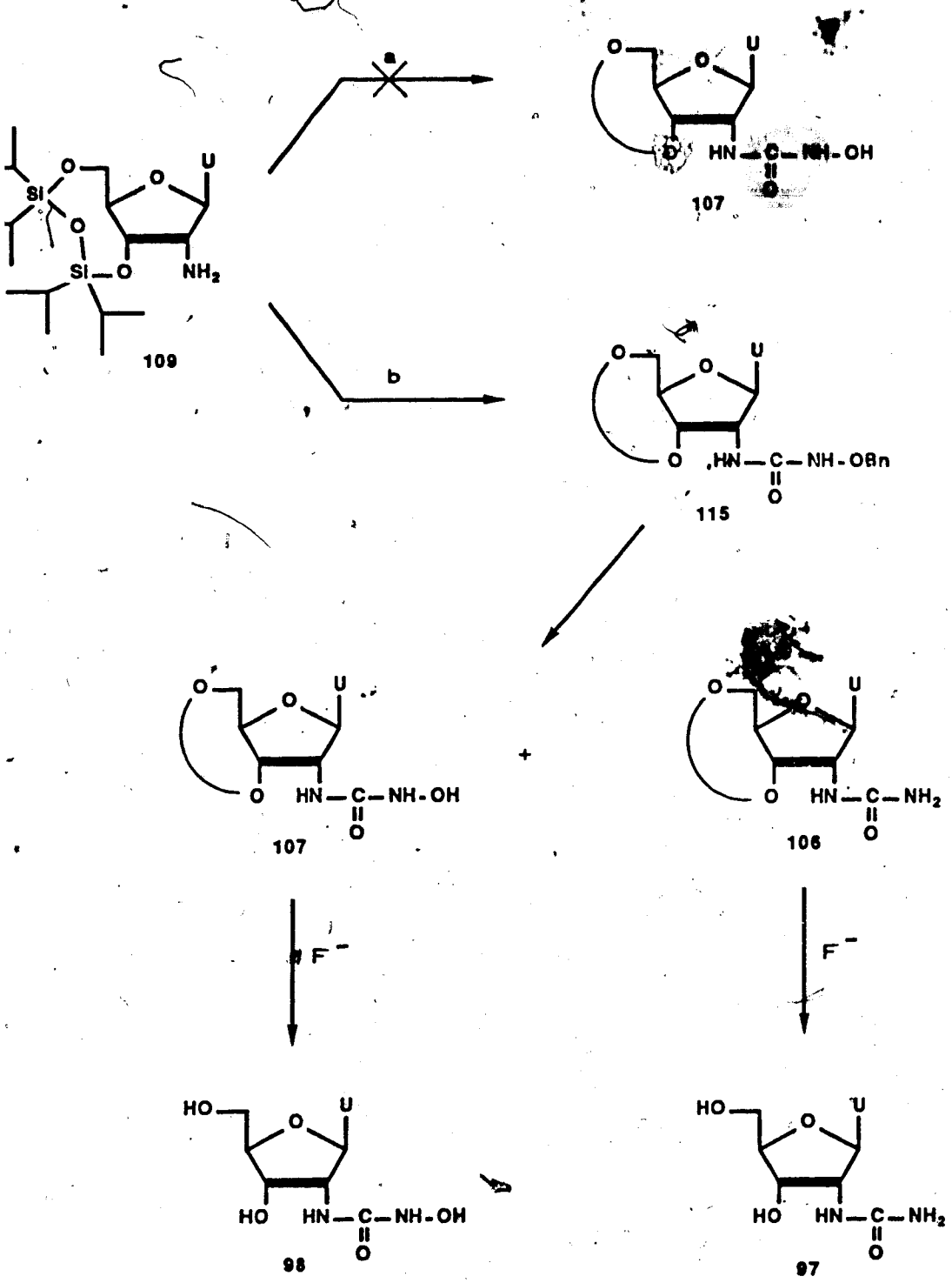
The ^{1}H NMR spectrum of the major compound did not show the signals corresponding to the benzyl group and displayed a new downfield exchangeable signal compatible with the structure of the expected product (**107**). This compound, obtained in 45% yield, gave satisfactory UV, mass and ^{13}C NMR spectral data.

The minor product of this reaction was identified by its ^{1}H NMR spectrum as the ureidonucleoside (**106**). Deprotection of this product by tetra-n-butylammonium fluoride afforded a compound that had spectroscopic data and chromatographic mobility identical to those of (**97**).

In the last step of our synthetic route, compound (**107**) was subjected to deprotection using tetra-n-butylammonium fluoride in THF at ambient temperature. After a few minutes, a solid began to separate from the solution and tlc showed total conversion of (**107**) to (**98**). The identity of (**98**) as 2'-(N-hydroxycarbamoyl)amino-2'-deoxyuridine was established on the basis of its ^{1}H and ^{13}C NMR, UV, and mass spectral data (SCHEME XX).

The reaction of amines with isocyanates occurs readily to give ureas, as described in Scheme VI. We decided to apply this method to the preparation of some ureidosugar nucleoside derivatives.

SCHEME XX



a) $NH_2OH.HCl$ / Et_3N / $COCl_2$ / $CHCl_3$

b) $BnONH_2.HCl$ / Et_3N / $COCl_2$ / $CHCl_3$

When amino-sugar nucleoside (**95**) was treated with methylisocyanate in MeOH at ambient temperature, a single product was obtained. This compound was identified as (**104**) by examination of its ^{1}H and ^{13}C NMR, UV, and mass spectra and elemental analysis data.

In its FAB mass spectrum, compound (**104**) (mw = 300) exhibited a protonated molecular ion peak at m/z 301. Its ^{1}H NMR spectrum showed a doublet at δ 2.86 for the methyl protons and a quartet for the NH of the urea, among other signals. The elemental analysis values and the UV spectral data also support the structure of (**104**) as 2'-(N-methylcarbamoyl)amino-2'-deoxyuridine.

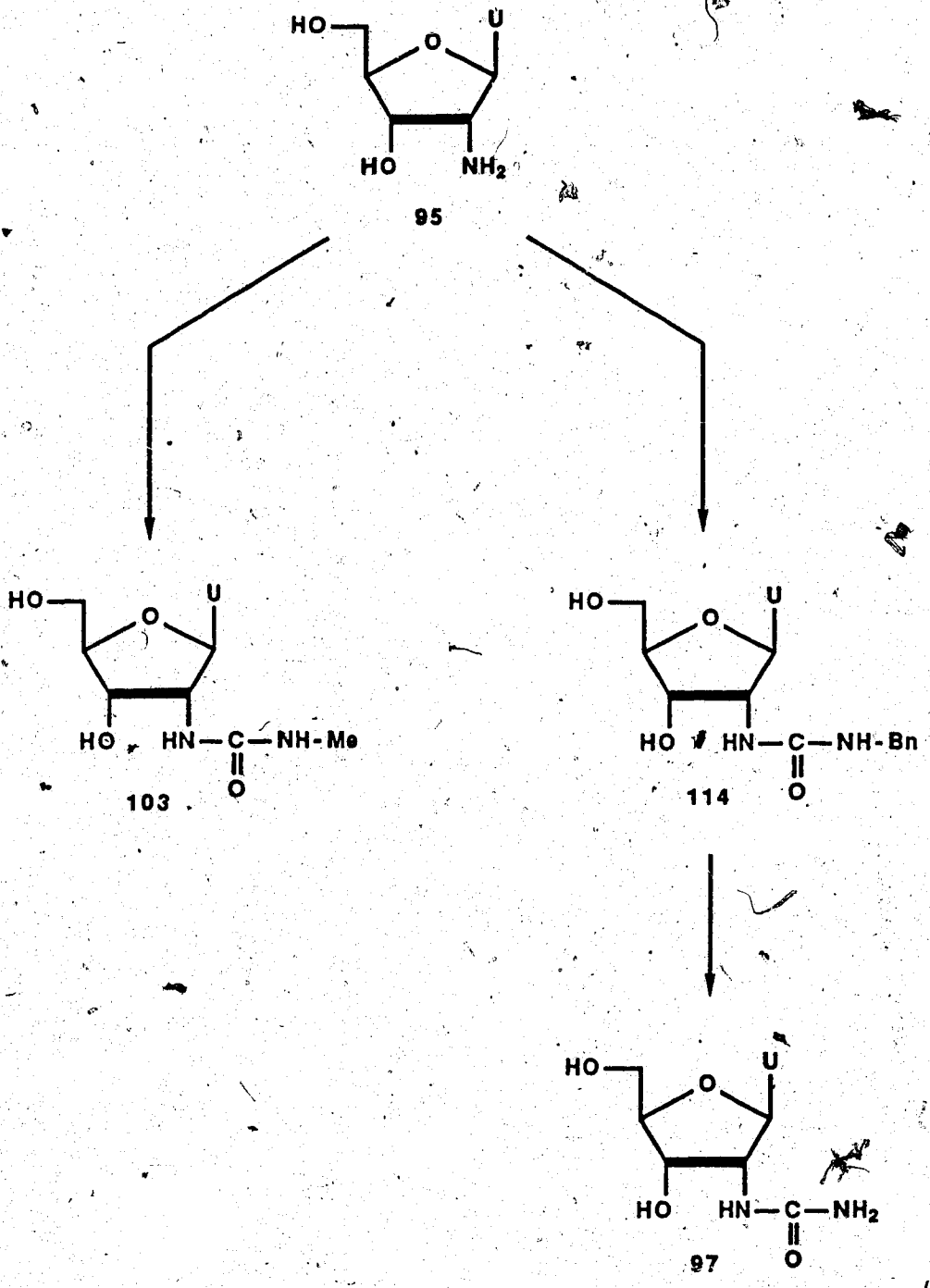
Because the yield obtained in the preparation of ureido nucleoside (**97**) from cyclic carbamate (**103**) with ammonium hydroxide was not very satisfactory, we decided to use the isocyanate approach as a new synthetic route to prepare (**97**).

Protection of amino-sugar nucleoside (**95**) was carried out using hexamethyldisilazane. The resulting crude trimethylsilylated product was dissolved in acetonitrile and allowed to react with benzylisocyanate at ambient temperature. Deprotection was effected using 29% ammonium hydroxide to afford a product in 92% yield after crystallization from MeOH/Et_2O. This

compound was identified as (113) by ^{1}H and ^{13}C NMR, UV and mass spectral and elemental analysis.

When benzylureido nucleoside (113) was subjected to hydrogenolysis in 95% EtOH using 5% Pd•C, a single product was obtained in almost quantitative yield. This compound was purified, recrystallized from MeOH/Et_2O, and identified as ureidonucleoside (97) by examination of its ^{1}H and ^{13}C NMR, UV, and mass spectral and elemental analysis data. This method proved to be superior in providing an efficient and short synthetic route to ureidonucleoside (97) from amino-sugar nucleoside (95) in high yield (SCHEME X[illegible].

SCHEME XXI


HO
O
U
HO
NH2
95
HO
O
U
HO
HN—C—NH-Me
O
103
HO
O
U
HO
HN—C—NH-Bn
O
114
HO
O
U
HO
HN—C—NH2
O
97

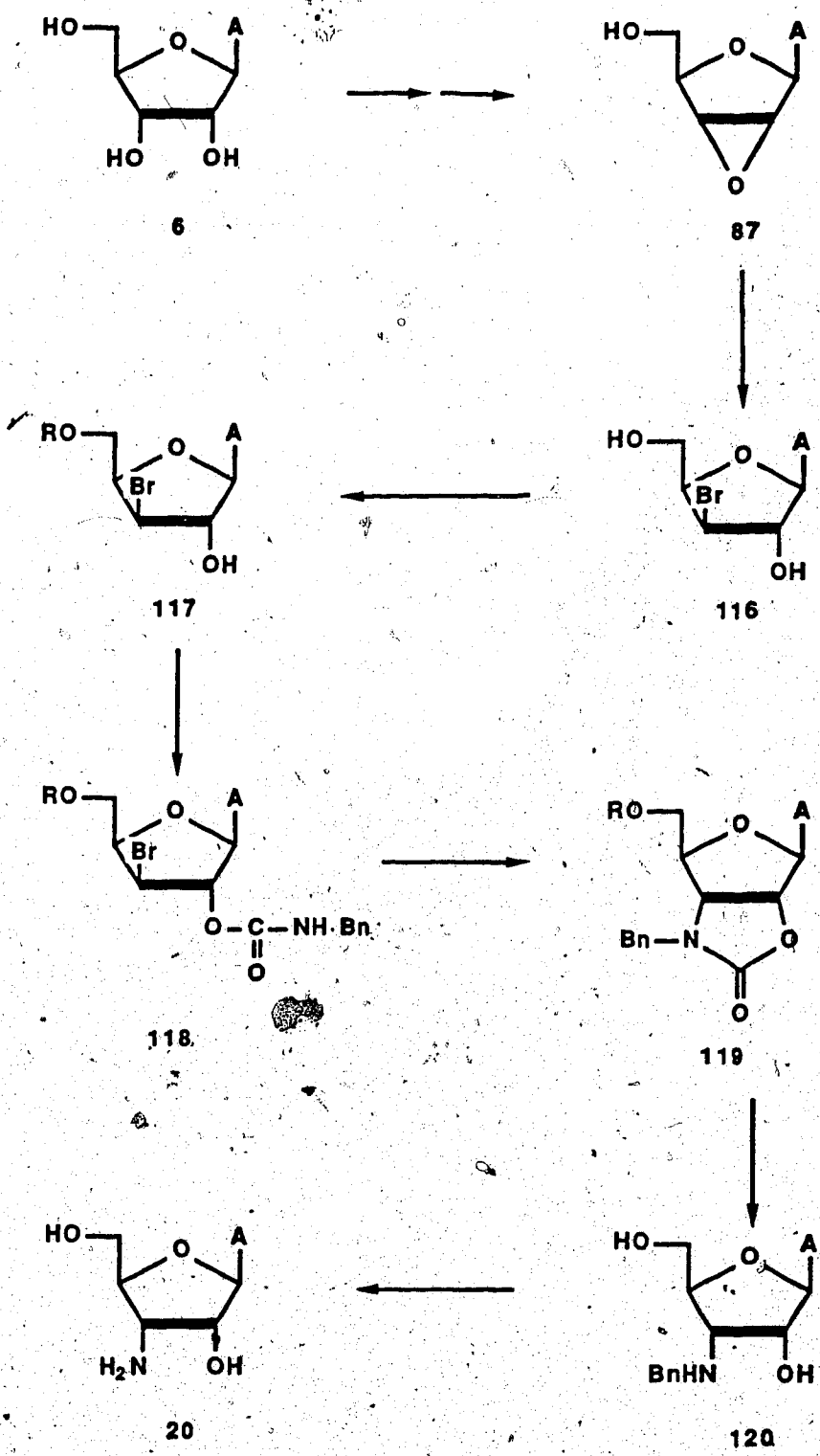
B. 3'-AMINO-3'-DEOXYADENOSINE

Since the antibiotic 3'-amino-3'-deoxyadenosine has been rather difficult to prepare in reasonable yield, we became interested in developing a synthetic route that would provide an efficient entry to this nucleoside analog.

A high yield conversion of adenosine to its 2',3'-epoxyderivative (**87**) using α-acetoxyisobutyryl bromide was recently developed in this laboratory[80]. This conversion combined with a method reported by Mengel and co-workers[81] for the opening of epoxide (**87**) using a solution of HBr in DMF was expected to afford (**116**) in reasonably good yield. Examination of this compound led us to the proposal that, by proper functionalization of (**116**), 3'-substituted ribonucleosides could be prepared via 3'-bromoxylo-adenosine.

Our synthetic plan involved selective protection of the 5'-hydroxyl group of (**116**) followed by reaction of the 2'-hydroxyl group with benzyl isocyanate to generate carbamate (**118**). Intramolecular nucleophilic cyclization of this carbamate followed by basic hydrolysis and hydrogenolysis of the benzyl group would afford our target product 3'-amino-3'-deoxyadenosine (**20**) (SCHEME XXII).

SCHEME XXII



Treatment of 1-mmol of dried adenosine (**6**) in 20-mL of dry acetonitrile with 2-mL of acetonitrile/water (100:1) and then 4-mmol of α-acetoxyisobutyryl bromide provided two major product fractions[80]. Treatment of this mixture with Dowex 1X2(OH^-) resin in absolute methanol gave one product cleanly (92% yield overall from adenosine) which was identified as 9-(2,3-anhydro-β-D-ribofuranosyl)adenine (**87**)[80].

A modified procedure using a 1 M solution of HBr in DMF for the opening of epoxide (**87**) afforded an improved yield of 3'-bromoxylo-adenosine (**116**). Efforts to purify this compound by column chromatography on silica gel were unsuccessful. Therefore we decided to carry out the next trahsformation on the crude material. An analytical sample of (**116**) was obtained by purification on silica gel plates and recrystallization from water. The spectroscopic data of this compound confirmed the structure of (**116**).

The 5' hydroxyl group of crude (**116**) was selectively protected using tert-butyldiphenylsilyl chloride[82] in pyridine at room temperature. After work-up, purification by silica gel column chromatography and recrystallization from THF/CH_3CN

compound (**117**) was obtained in 82% overall yield from epoxide (**87**).

It is known that carbamates can be prepared by treatment of alcohols with isocyanates. Therefore, 5'-O-protected-3'-bromoxylo-adenosine (**117**) was dissolved in CH_3CN/THF (1:1), and allowed to react with benzylisocyanate in the presence of triethylamine. Several preliminary reactions had to be carried out in order to find the best reaction conditions that would afford (**118**) in good yields. In our study of this reaction we found that absence of base resulted in no reaction. On the other hand, a large excess of triethylamine promoted side reactions of the benzylisocyanate and the amino group at the 6-position of the heterocyclic base. An excellent yield of (**118**) was obtained when 1-mmol of (**117**) was reacted with 2-mmol of benzylisocyanate and 1.5-mmol of triethyl amine at ambient temperature. Purification and crystallization from Skellysolve B/$CHCl_3$ provided (**118**) in 90% yield. The identity of this compound was established on the basis of its ^1H and ^{13}C NMR, UV, and mass spectral, and elemental analysis data.

In our next step, intramolecular nucleophilic cyclization of carbamate (**118**) was tried using sodium hydride in THF at ambient temperature. Unfortunately,

under these conditions the desired cyclic carbamate was not formed. Instead, the 5'-O-protected-2',3'-epoxide (**121**) was obtained and identified by analysis of its ^{1}H NMR and mass spectra.

When this reaction was carried out under dry conditions at lower temperature (-20°C), the desired cyclic carbamate (**119**) was produced in high yield with formation of only a very small amount of by-product (**121**) (tlc). Separation of these compounds was tried unsuccessfully by chromatography on silica gel. When the mixture of these two products was subjected to deprotection using tetra-n-butylammonium fluoride, the resulting deprotected compounds (**122**) and (**87**) had quite different Rf values that easily allowed their separation.

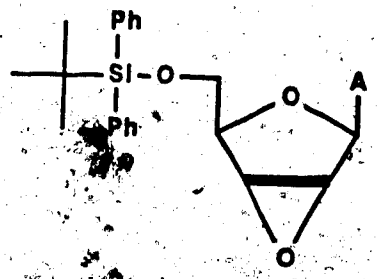
A reaction sequence in which purification was deleted gave (**122**) in 94% yield from (**118**). Compound (**122**) had ^{1}H and ^{13}C NMR, UV, and mass spectral and elemental analysis data consistent with its proposed structure.

Basic hydrolysis of (**122**) in a solution of 0.5 N NaOH in H_2O/THF at ambient temperature provided 3'-benzylamino-3'-deoxyadenosine (**120**) in essentially quantitative yield. When this reaction was carried out at reflux temperature, we found that reaction times

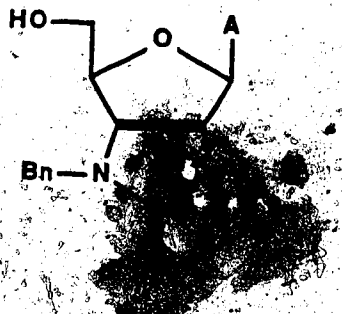
were shorter, but general decomposition and glycosyl bond cleavage were observed (tlc). After purification on a column of Dowex 1X2(OH^-)[87] resin and crystallization from $CHCl_3$/MeOH, compound (120) was obtained in 92% yield.

Morr and co-workers[84] had reported the preparation of compound (120) by reaction of 3'-amino-3'-deoxyadenosine (20) with PhCHO and $NaBH_4$ in acetate buffer. The spectroscopic data obtained from our pure sample of (120) agrees with that reported.

In the final step of our synthetic route, removal of the benzyl group from compound (120) was achieved by atmospheric hydrogenolysis in 95% EtOH at ambient temperature using 5% Pd·C. After purification of the product on a column of Dowex 1X2(OH^-) and crystallization from H_2O/MeOH, 3'-amino-3'-deoxyadenosine (20) was obtained in essentially quantitative yield.



121



122

TABLE 1. ^{13}C NMR DATA OF URIDINE COMPOUNDS

Compound	C-2	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	Others
10[a]	150.77	163.12	101.12	140.75	87.73	73.56	69.91	84.86	60.88	
95	151.08	163.06	101.85	140.77	87.92	57.49	71.31	85.91	61.58	
96	151.05	163.45	102.44	141.13	86.52	56.69	70.36	86.21	61.67	CO 147.38, CH_2 60.59, CH_3 14.72
103	150.77	164.11	102.16	142.58	93.39	61.40	79.55	86.59	61.16	CO 158.18
104	151.33	163.78	102.44	141.69	86.93	55.39	70.69	86.54	61.95	CO 158.59, CH_3 26.47
113[c]	150.96	163.10	101.91	140.99	86.63	54.96	70.74	86.17	61.72	CO 157.44, CH_2 42.75
97	151.28	163.70	102.34	141.49	86.49	55.11	70.93	86.46	61.93	CO 158.58
114[b]	149.98	163.15	101.33	140.07	88.01	64.46	70.32	84.18	60.12	
111[b]	151.04	163.62	102.62	139.39	85.92	53.44	70.69	85.05	63.62	CO 157.53
115[b]	150.39	162.95	101.95	141.78	88.21	53.20	70.62	83.38	62.95	CO 158.91, CH_2 77.49
107[b]	150.40	162.96	101.86	141.89	88.31	53.04	70.91	83.59	63.20	CO 160.69
98	150.77	162.96	101.92	140.90	86.58	54.14	70.57	86.11	61.57	CO 160.36

[a] Literature values[88]

[b] Isopropyl groups appeared in the range of 12 to 17 ppm

[c] Phenyl groups appeared in the range of 126 to 128 ppm

TABLE 2. ^{13}C NMR DATA OF ADENOSINE COMPOUNDS

Compound	C-2	C-4	C-5	C-6	C-8	C-1'	C-2'	C-3'	C-4'	C-5'	Others
6[a]	152.31	149.00	119.30	156.09	139.87	87.90	74.41	70.59	85.83	61.60	
87	152.79	149.06	118.44	155.82	139.87	82.01	57.73	58.59	81.13	60.80	
116	152.59	148.92	118.81	155.83	139.15	88.40	79.47	52.86	80.11	62.48	
117[b]	152.63	149.12	118.74	155.88	138.11	88.37	79.84	53.03	79.80	65.28	
118[b]	153.27	149.51	118.32	156.12	138.40	86.12	80.27	49.45	81.07	65.52	CO 154.99, CH_2 43.98
119[b]	153.12	149.06	119.26	156.71	140.85	89.63	79.56	60.63	85.41	63.85	CO 156.23, CH_2 46.77
122[b]	152.25	149.21	119.22	156.72	140.33	89.83	79.66	61.08	85.59	61.57	CO 156.34, CH_2 46.52
120[b]	153.41	149.40	119.71	156.47	140.85	90.51	73.20	58.85	84.66	62.30	CH_2 51.80
20	152.61	149.04	119.23	156.11	139.74	89.42	74.95	52.52	85.68	61.16	

[a]Literature values[88]

[b]For the tert-butyldiphenylsilyl protecting group: CH_3 appeared from 26 to 27 ppm, quaternary carbon from 18 to 19 ppm, and phenyl groups in the range of 126 to 135 ppm

EXPERIMENTAL

A. GENERAL PROCEDURES.

Melting points were determined on a Reichert microstage apparatus and are uncorrected. Mass spectra (MS) were determined by the Mass Spectrometry Laboratory of this department. High resolution MS measurements (EI) were done on a Kratos MS-50 instrument with computer processing at 70 eV using a direct probe for sample introduction. Fast atom bombardment (FAB) MS were recorded on a Kratos MS-9 instrument at low resolution. Nuclear magnetic resonance (NMR) spectra were determined on Bruker WH-400, WH-360, WH-300 or WH-200 spectrometers operating in the FT mode, with Me_4Si as internal standard in Me_2SO-$\underline{d}_6$ solutions. Ultraviolet (UV) spectra were recorded on a Hewlett Packard 8450 A diode array spectrophotometer and infrared (IR) spectra on a Nicolet 7199 FT(IR) instrument. Elemental analyses were determined by the Microanalytical Laboratory of this department.

All solvents used were of reagent grade and were purified according to the methods described in reference 85 if used as reaction media. Solvents used

for chromatography, extraction, and other purposes were purified by simple distillations. All dried solvents were stored over Davidson 3 Å and 4 Å molecular sieves purchased from the Fisher Scientific Company. Evaporations were effected using a IKa-Heizbad HB-250 rotating evaporator under water aspirator or mechanical oil pump vacuum at 40°C or cooler. Thin layer chromatography (TLC) was performed on E. Merck chromatographic sheets (silica gel 60 F_{254}, layer thickness 0.2 mm, catalogue 5775) with sample observation under UV light (2537 Å). Preparative TLC was performed on glass plates coated with Merck silica gel PF 254. The solvents used for TLC were different ratios of methanol-chloroform (A, 1:9; B, 2:8), ethanol-chloroform (C, 2:98; D, 5:95) and (E) the upper phase of EtOAc-nPrOH-H_2O (4:1:2). Silica gel column chromatography was performed using Terochem silica gel (100 mesh up: 5%, 100-200 mesh: 47.6%, 200 mesh down: 47.4%) or Merck silica gel 60 (230-400 mesh).

Ion exchange chromatography was carried out on Dowex 1X2 resin (200-400 mesh) in the hydroxide form and Dowex 50 W-X8 resin (20-50 mesh) in the H^+ form.

O2,O2'-Anhydro-1-(β-D-arabinofuranosyl)uracil (2,2'-cyclouridine) (**99**) was prepared as described by Hampton and Nichol[70] with an improved yield of 81%.

2'-amino-2'-deoxy uridine (**95**) was prepared by the method of Moffatt and coworkers.[73] 9-(2,3-Anhydro-β-D-ribofuranosyl)adenine (2',3'-anhydroadenosine) (**87**) was prepared as described.[80] 9-(3-Bromo-3-deoxy-β-D-xylofuranosyl)adenine (**116**) was prepared by an improved modification of the general procedure of Mengel and Wiedner.[81]

B. SYNTHESIS.

2'-Deoxy-2'-(ethoxycarbonyl)aminouridine (**96**).

Method A: (see page 79 for Method B).

To a suspension of 500 mg (2.06 mmol) of (**95**) in 8 mL of hexamethyldisilazane was added a drop of chlorotrimethylsilane and the stirred mixture was heated at reflux with exclusion of moisture until a clear solution was obtained. Excess silylating reagent was removed *in vacuo* with protection against moisture. The residual clear oil was dissolved in 25 mL of dry acetonitrile and cooled to 0°C. A 0.3 g (2.47 mmol) portion of 4-DMAP was added followed by 0.24 mL (2.5 mmol) of EtOCOCl and stirring was continued overnight at room temperature. The crude product obtained after deprotection by

stirring with 29% NH_3/H_2O overnight and evaporation was dissolved in H_2O and applied to a column of Dowex 50 (H^+). Elution with H_2O, evaporation and crystallization of the residue from MeOH with diffusion of Et_2O[86] gave 585 mg (90%) of (**96**): mp 233-235°C, uv (MeOH) max 261 nm (ε 8700), min 230 nm (ε 2600), (0.1 N HCl) max 261 nm (ε 8800), (0.1 N NaOH) max 260 nm (ε 6400); MS m/z 316.1152 (0.11%, $M^+ + 1$, $M^+ + H$ [$C_{12}H_{18}N_3O_7$] = 316.1145), 226.0593 (57%, $M^+ - 89$), 204.0870 (36%, $M^+ - B$), 141.0306 (6.6%, BHCHO), 113.0350 (83%, B + 2H), 112.0299 (27%, B + H), ^1H nmr (400 MHz) δ 1.26 (t, $J_{CH_2-CH_3}$ = 7 Hz, 3, CH_3), 3.65 (bs, 2, H-5', H-5"), 3.98 (bs, 1, H-4'), 4.04 (q, 2, CH_2), 4.16 (bs, 1, H-3'), 4.26 (bs, 1, H-2'), 5.22 (t, $J_{OH5'-5'} = J_{OH5'-5"}$ = 4.5 Hz), 5.64 (bs, 1, OH-3'), 5.73 (d, J_{5-6} = 8 Hz, 1, H-5), 5.94 (d, $J_{1'-2'}$ = 8.5 Hz, 1, H-1'), 6.88 (d, $J_{NH2'-2'}$ = 9 Hz, 1, NH-2'), 7.9 (d, 1, H-6), 11.5 (bs, 1, NH-3); Anal. calcd. for $C_{12}H_{17}N_3O_7$: C 45.72, H 5.44, N 13.33. Found: C 45.69, H 5.44, N 13.39.

2'-Amino-2',3'-N,O-carbonyl-2'-deoxyuridine (**103**).

A 20 mg (0.063 mmol) sample of (**96**) was dissolved in 7 mL of 29% NH_3/H_2O and the mixture was stirred at

ambient temperature for three days. Evaporation of the solvent in vacuo and crystallization of the residue from MeOH gave 17 mg (100%) of (**103**): mp 268-269°C; uv (MeOH) max 259 nm (ε 8200), min 228 nm (ε 1600), (0.1 N HCl) max 259 nm (ε 8000), (0.1 N NaOH) max 258 nm (ε 6000); MS m/z 269.0650 (0.55%, $M^+[C_{10}H_{11}N_3O_6]$ = 269.0648), 158.0456 (42%, M^+ - B), 141.0304 (4.7%, BHCHO), 113.0352 (48%, B + 2H), 112.0394 (1.2%, B + H); ^1H nmr (400 MHz) δ 3.65 (bs, 2, H-5', H-5"), 4.1 ("q", J = 4.5 Hz, 1, H-4'), 4.46 (dd, $J_{2'-1'}$ = 3 Hz, $J_{2'-3'}$ = 8 Hz, 1, H-2'), 5.0 (dd, $J_{3'-4'}$ = 4.5 Hz, 1, H-3'), 5.12 (bs, 1, OH-5'), 5.65 (d, $J_{5,6}$ = 8 Hz, 1, H-5), 5.74 (d, 1, H-1'), 7.68 (d, 1, H-6), 8.25 (s, 1, NH-2'), 11.4 (bs, 1, NH-3). Anal. calcd. for $C_{10}H_{11}N_3O_6$: C 44.62, H 4.12, N 15.61. Found: C 44.59, H 4.08, N 15.54.

2'-(Carbamoyl)amino-2'-deoxyuridine (**97**).

Method A:

A solution of 17 mg (0.059 mmol) of (**103**) in 7 ml of 29% NH_3/H_2O was sealed in a Parr steel bomb and heated at 70°C for three days. After cooling, the bomb was vented and solvent was removed in vacuo. The crude residue was chromatographed on a silica gel plate using

solvent (E). The silica which contained the product was scraped off the plate and eluted with 95% EtOH. Evaporation of the eluant and crystallization of the residue from MeOH with diffusion of Et_2O gave 12.7 mg (70%) of (97): mp 161°C (dec.); uv (MeOH) max 261 nm (ε 8200), min 230 nm (ε 2400), (0.1 N HCl) max 262 nm (ε 8000), (0.1 N NaOH) max 260 nm (ε 6600); MS (FAB) m/z 573 (0.83%, $2M^+ + 1$), 287 (34%, $M^+ + 1$, $M^+ + H$ $[C_{10}H_{15}N_4O_6]$ = 287, (CI) 287 (100%, $M^+ + 1$); ^1H nmr (400 MHz) δ 3.54 (dd, $J_{5'5"-4'}$ = 3 Hz, $J_{5'5"-OH5'}$ = 5 Hz, 2, H-5', H5"), 3.86 ("t", $J_{4'-5'}$ = 3 Hz, $J_{4'-3'}$ < 0.7 Hz, 1, H-4'), 3.98 (t, $J_{3'-2'} = J_{3'-OH3'}$ = 5 Hz, 1, H-3'), 4.25 (td, $J_{2'-1'} = J_{2'-NH2'}$ = 9 Hz, $J_{2'-3'}$ = 5 Hz, 1, H-2'), 5.12 (t, 1, OH-5'), 5.63 (d, J_{5-6} = 8 Hz, 1, H-5), 5.68 (s, 2, NH_2), 5.8 (d x 2, $J_{1'-2'}$ = 9 Hz, $J_{OH3'-3'}$ = 5 Hz, 2, H-1', OH-3'), 6.02 (d, 1, NH-2'), 7.84 (d, 1, H-6), 11.22 (s, 1, NH-3). Anal. calcd. for $C_{10}H_{14}N_4O_6 \cdot 3/4\ H_2O$: C 40.07, H 5.21, N 18.69. Found: C 40.24, H 5.13, N 18.84.

Method B:

A solution of 263 mg (0.69 mmol) of (113) in 95% EtOH was vigorously stirred in a hydrogen atmosphere with 5% Pd.C (100 mg) for 2 h. The mixture was

filtered and evaporated and the crude residue crystallized from MeOH with diffusion of ether to yield 190 mg (95%) of (**97**): mp 148-151°C. This product had UV, FAB and CI MS, 400 MHz ^{1}H nmr spectral data and tlc migration identical with those of the above product (**97**) of Method A. Anal. calcd. for $C_{10}H_{14}N_4O_6 \cdot \frac{1}{4} H_2O$: C 41.31, H 5.03, N 19.27. Found: C 41.25, H 5.10, N 19.53.

2'-Deoxy-2'-(N-methylcarbamoyl)amino uridine (**104**).

Method A:

To 200 mg (0.82 mmol) of (**95**) suspended in 4 mL of MeOH was added 48 µL (47 mg, 0.82 mmol) of methylisocyanate. The resulting solution was stirred at ambient temperature for 30 minutes and then evaporated to dryness in vacuo. The resulting off-white glass was crystallized from MeOH with diffusion of ether to yield 240 mg (99%) of (**104**): mp 190-191°C; uv (MeOH) max 262 nm (ε 8700), min 230 nm (ε 1500), (0.1 N HCl) max 262 nm (ε 8600), (0.1 N NaOH) max 260 nm (ε 7000); MS (FAB) m/z, 601 (2.5%, $2M^+ + 1$); 301 (75%, $M^+ + 1$, $M^+[C_{11}H_{16}N_4O_6] = 300$), ^{1}H nmr (200 MHz) δ 2.86 (d, J =

5 Hz, 3, CH_3), 3.96 (m, 2, H-5', H-5"), 4.27 ("t", $J_{4'-5'5"}$ = 3 Hz, $J_{4'-3'}$ < 0.7 Hz, 1, H-4'), 4.39 (t, $J_{3'-2"} = J_{5'-OH3'}$ = 5 Hz, 1, H-3'), 4.7 (td, $J_{2'-3'}$ = 5 Hz, $J_{2'-1'} = J_{2'-NH2'}$ = 9 Hz, 1, H-2'), 5.54 (t, $J_{OH5'-5',5"}$ = 5 Hz, 1, OH-5'), 6.06 (d, J_{5-6} = 8 Hz, 1, H-5), 6.19 (d x 2, $J_{OH3'-3'}$ = 5 Hz, $J_{1'-2'}$ = 9 Hz, 2, OH-3', H-1'), 6.23 (d, 1, NH-2'), 6.53 (q, J = 5 Hz, 1, -CO-NH-), 8.28 (d, 1, H-6), 11.65 (s, 1, NH-3). Anal. calcd. for: $C_{11}H_{16}N_4O_6 \cdot \frac{1}{4} H_2O$: C 43.35, H 5.46, N 18.38. Found: C 43.54, H 5.31, N 18.38.

Method B:

A solution of 5 mg (0.018 mmol) of (**103**) in 7 mL of 40% $MeNH_2/H_2O$ was stirred overnight at ambient temperature. The reaction mixture was concentrated in vacuo and the crude residue was purified by chromatography on a silica gel plate that was developed with solvent (E). The slower migrating product band was scraped off the plate and eluted with 95% EtOH to yield an off-white powder after evaporation of the eluate. This material was identified as compound (**104**) by mp, tlc, 200 MHz ^1H nmr and FAB MS comparisons.

2'-Deoxy-2'-(ethoxycarbonyl)amino-3',5'-O-(1,1,3,3-tetraisopropyl-1,3-diyl)uridine (105).

To 100 mg (0.317 mmol) of (96) dissolved in 5 mL of anhydrous pyridine was added 100 μL (99.9 mg, 0.317 mmol) of 1,1,3,3-tetraisopropyl-1,3-dichlorodisiloxane and the mixture was stirred overnight at ambient temperature. Pyridine was evaporated in vacuo and the residue was partitioned between $CHCl_3$ and H_2O. The organic phase was washed with 2 x 10 mL of cold 1 N HCl/H_2O, saturated $NaHCO_3/H_2O$, saturated $NaCl/H_2O$, dried (Na_2SO_4), filtered and evaporated. The crude residue was chromatographed on a column of silica gel using 5% solvent (D) as eluant. Evaporation of appropriate fractions gave a yellowish oil in quantitative yield with uv (MeOH) max 259 nm (ε 10400), min 229 nm (ε 4300), (0.1 N HCl) max 259 nm (ε 10300), (0.1 N NaOH) max 258 nm (ε 7900); MS m/z 557.2600 (0.74%, $M^+[C_{24}H_{43}N_3O_8Si_2]$ = 557.2589), 514.2044 (100%, M^+-ipr), 112.0273 (3.7%, B + H); ^1H nmr (400 MHz) δ 1.02 (m, 28, iPr x 4), 1.15 (t, J = 7 Hz, 3, CH_3), 3.98 (m, 5, CH_2, H-4', H5', H-5"), 4.36 (br, 1, H-3'), 4.45 (m, 1, H-2'), 5.64 (d, J_{5-6} = 8 Hz, 1, H-5), 5.71 (d, $J_{1'-2'}$ = 4.5 Hz, 1, H-1'), 7.36 (d, $J_{NH2'-2'}$ = 9 Hz, 1, NH-2'), 7.74 (d, 1, H-6), 11.36 (s, 1, NH-3).

2'-(N-Benzylcarbamoyl)amino-2'-deoxyuridine (113).

To a suspension of 250 mg (1.03 mmol) of 2'-amino-2'-deoxyuridine (95) in 4 mL of hexamethyldisilazane was added a drop of chlorotrimethylsilane and the stirred mixture was heated at reflux with exclusion of moisture until a clear solution was obtained. Excess silylating reagent was removed *in vacuo* with protection against moisture. The residual clear oil was dissolved in 15 mL of freshly distilled THF and cooled to 0°C. A 130 µL (140 mg, 1.05 mmol) portion of benzylisocyanate was added to the solution and stirring was continued overnight at ambient temperature. The crude product obtained after deprotection by stirring with 29% NH_3/H_2O overnight and evaporation, was chromatographed on a column of silica gel using 15% MeOH/$CHCl_3$ as the eluant. Evaporation of appropriate fractions and crystallization of the residue from MeOH with diffusion of Et_2O gave 356 mg (92%) of (113): mp 132-135°C; uv (MeOH) max 261 nm (ε 9700), min 231 nm (ε 3200), (0.1 N HCl) max 261 nm (ε 9400), (0.1 N NaOH) max 260 nm (8100); MS (FAB) m/z 753 (0.2%, $2M^+ + 1$), 377 (11%, $M^+ + 1$; $M^+ + H$ [$C_{17}H_{21}N_4O_6$] = 377.1461); ^1H nmr (400 MHz) δ 3.57 ("t", J = 4 Hz, 2, H-5', H-5"), 3.92 ("t", J = 3.5 Hz, $J_{4'-3'}$ < 0.7 Hz, 1, H-4'), 4.04 ("t", J =

4.5 Hz, 1, H-3'), 4.12 (dd, J_{CH_2-NH} = 6 Hz, $J_{gem\ CH_2}$ = 13 Hz, 1, H-CH), 4.17 (dd, 1, H-C-H), 4.36 (td, $J_{2'-3'}$ = 5 Hz, $J_{2'-1'} = J_{2'-NH2'}$ = 9 Hz, 1, H-2'), 5.15 (t, J = 5 Hz, 1, OH-5'), 5.65 (d, J_{5-6} = 8 Hz, 1, H-5), 5.85 (d x 2, 2, H-1', OH-3'), 6.12 (d, 1, NH-2'), 6.75 (t, 1, NH-CH_2); 7.25 (m, 5, Ph), 7.86 (d, 1, H-6). Anal. calcd. for $C_{17}H_{20}N_4O_6$ · [illegible]: C 53.61, H 5.43, N 14.71. Found: C 53.[illegible], N 14.86.

2'-Az[illegible]-deoxy-3',5'-O-(1,1,3,3-tetraisopropyldisilo[illegible]yl)uridine (**114**).

To a solution of 960 mg (3.56 mmol) of (**100**) in 80 mL of anhydrous pyridine was added 1.12 mL (1.12 g, 3.56 mmol) of 1,1,3,3-tetraisopropyl-1,3-dichlorodisiloxane and the mixture was stirred overnight at ambient temperature. Pyridine was evaporated in vacuo and the residue was partitioned between EtOAc and H_2O. The organic phase was washed with 2 x 50 mL of cold 1 N HCl/H_2O, saturated $NaHCO_3/H_2O$, saturated NaCl/H_2O, dried (Na_2SO_4), filtered and evaporated. The crude residue was purified by flash chromatography on silica gel using solvent (D) as eluant. Evaporation of appropriate fractions and crystallization of the residue from Et_2O/"Skellysolve-B" gave 1.8 g (98%) of

(114): mp 165-167°C; uv (MeOH) max 260 nm (ε 10500), min 229 nm (ε 1500), (0.1 N HCl) max 260 nm (ε 10400), (0.1 N NaOH) max 260 nm (ε 8000), MS m/z 468.1744 (100%, $M^+ - C_3H_7$ [$C_{18}H_{30}N_5O_6Si_2$] = 468.1734), 112.0271 (4.3%, B + H), ^1H nmr (400 MHz) δ 1.06 (m, 28, iPr x 4), 3.92 (m, 1, H-4'), 3.95 (dd, $J_{5'-4'}$ = 3 Hz, $J_{5'-5"}$ = 13 Hz, 1, H-5'), 4.1 (dd, $J_{5"-4'}$ = 3 Hz, 1, H-5"), 4.62 (m, 2, H-2', H-3'), 5.46 (d, $J_{1'-2'}$ = 0.6 Hz, 1, H-1'), 5.58 (d, J_{5-6} = 8 Hz, 1, H-5), 7.6 (d, 1, H-6), 11.42 (s, 1, NH-3). Anal. calcd. for $C_{21}H_{37}N_5O_6Si_2$: C 49.29, H 7.29, N 13.69. Found: C 49.10, H 7.42, N 13.97.

2'-Amino-2'-deoxy-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)uridine (109).

Method A:

To 11.9 mg (0.049 mmol) of (95) dissolved in 0.7 mL of anhydrous pyridine was added 16 μL (15.5 mg, 0.049 mmol) of 1,1,3,3-tetraisopropyl-1,3-dichlorodisiloxane and the mixture was stirred overnight at ambient temperature. Pyridine was evaporated in vacuo and the residue was partitioned between $CHCl_3$ and H_2O. The organic phase was washed with 2 x 10 mL of cold 1 N HCl/H_2O, saturated

$NaHCO_3/H_2O$, saturated $NaCl/H_2O$, dried (Na_2SO_4), filtered and evaporated. The crude residue was chromatographed on a column of silica gel using solvent (C) as the eluant. Evaporation of appropriate fractions gave 18 mg (75%) of (109) as a yellowish foam. Uv (MeOH) max 260 nm (ε 9700), min 230 nm (ε 500), (0.1 N HCl) max 256 nm (ε 9200), (0.1 N NaOH) max 262 nm (ε 6600). MS (NH_3-CI), m/z 486 (100%, M^+ + 1, M^+ + H $[C_{21}H_{40}N_3O_6Si_2]$ = 486.2456); ^1H nmr (400 MHz) δ 1.0 (m, 28, iPr x 4), 1.75 (br, 2, NH_2-2'), 3.47 (dd, $J_{2'-1'}$ = 4 Hz, $J_{2'-3'}$ = 6 Hz, 1, H-2'), 3.93 (m, 2, H-5', H-5"), 4.02 ("q", $J_{4'-3'} = J_{4'-5'} = J_{4'-5"}$ = 6 Hz, 1, H-4'), 4.27 ("t", 1, H-3'), 5.5 (d, 1, H-1'), 5.58 (d, J_{5-6} = 8 Hz, 1, H-5), 7.66 (d, 1, H-6), 12.6 (bs, 1, NH-3).

Method B:

A solution of 1.8 g (3.71 mmol) of (114) in 95% EtOH was vigorously stirred in a hydrogen atmosphere with 5% Pd•C catalyst (500 mg) for 12 hrs. The mixture was filtered and evaporated and the crude residue applied to a short column of silica gel. Elution with solvent (D) gave (109) as a yellowish foam in quantitative yield. This product had UV, CI MS, and

400 MHz ^1H nmr data and tlc migration identical with those of the above product (109) prepared by Method A.

N,N'-Bis-[2'-deoxy-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)uridin-2'-yl]urea (111).

To a solution of 26 mg (0.054 mmol) of (109) in 1 mL of $CHCl_3$ (alcohol free and 2 x distilled from CaH_2) was added 8.9 μL (16 mg, 0.16 mmol) of Et_3N and the solution was cooled to 0°C. A 17 μL (0.058 mmol) portion of $COCl_2$ (from a 3.4 M solution of $COCl_2$ in $CHCl_3$) was added to the solution and stirring was continued for 3 h. The reaction was quenched with EtOH and solvents were removed in vacuo. The crude residue was purified on a silica gel plate that was developed 3 times with 3% EtOH/$CHCl_3$. The slower migrating product band was scraped off the plate and eluted with $CHCl_3$. Evaporation of the eluate and crystallization of the residue from $CHCl_3$ gave 10.6 mg (40%) of (111): mp 257-259°C, uv (MeOH) max 259 nm (ε 9900), min 228 nm (ε 2500), (0.1 N HCl) max 259 nm (ε 10200), (0.1 N NaOH) max 259 nm (ε 7700); MS (FAB) m/z 997 (0.54%, $M^+ + 1$; $M^+ + H$ [$C_{34}H_{77}N_6O_{13}Si_4$] = 997.4626), 887 (37%, $M^+ + 1$ - Base); ^1H nmr (400 MHz) δ 1.0 (m, 28, iPr x 4), 3.75 (dt, $J_{4'-3'} = J_{4'-5'} = 4.5$ Hz, $J_{4'-5''} = 10$ Hz, 1,

H-4'), 3.86 (dd, $J_{5'-4'}$ = 4.5 Hz, $J_{5'-5"}$ = 10 Hz, 1, H-5'), 4.0 ("t", $J_{5"-5'} = J_{5"-4'}$ = 10 Hz, 1, H-5"), 4.35 (dd, $J_{3'-4'}$ = 4.5 Hz, $J_{3'-2'}$ = 8.5 Hz, 1, H-3'), 4.64 ("q", $J_{2'-1'} = J_{2'-3'} = J_{2'-NH2'}$ = 8.5 Hz, 1, H-2'), 5.63 (d, 1, H-1'), 5.66 (d, J_{5-6} = 8 Hz, 1, H-5), 6.47 (d, 1, NH-2'), 7.81 (d, 1, H-6), 11.29 (s, 1, NH-3).

2'-Deoxy-2'-(ethoxycarbonyl)amino-5'-O-(1,1,3,3-tetraisopropyldisiloxan-3-ol-1-yl)uridine (**108**).

To a solution of 70 mg (0.125 mmol) of (**105**) in 10 mL of MeOH/H_2O (1:1) was added 21 mg (0.3 mmol) of hydroxylamine hydrochloride and 20 mg (0.5 mmol) of sodium hydroxide. The mixture was stirred for 7 days at ambient temperature. The solvent was evaporated in vacuo and the residue dissolved in $CHCl_3$, filtered, evaporated and applied to a silica gel column that was eluted with 2% EtOH/$CHCl_3$. Evaporation of appropriate fractions gave 47 mg (65%) of (**108**) as a white powder. Uv (MeOH) max 262 nm, min 232 nm, MS (FAB) m/z 574 (3.6%, M^+ [$C_{24}H_{44}N_3O_9Si_2$] = 574.2616), 532 (1.4%, M^+ - iPr), 464 (13%, M^+ - B). ^1H nmr 400 MHz δ 0.98 (m, 28, iPr x 4), 1.1 (t, J = 7 Hz, 3, CH_3), 3.86 (br, 2, H-5', H-5"), 3.94 (q, J = 7 Hz, 2, CH_2), 3.97 (b s,

1, H-4'), 4.08 (bs, 1, H-3'), 4.19 (m, 1, H-2'), 5.6 (d, J_{5-6} = 8 Hz, 1, H-5), 5.62 (bs, 1, OH-3'), 5.88 (d, $J_{1'-2'}$ = 9 Hz, 1, H-1'), 6.12 (s, 1, Si-OH), 6.87 (d, $J_{NH2'-2'}$ = 9 Hz, 1, NH-2'), 7.72 (d, 1, H-6), 11.34 (s, 1, NH-3).

Double irradiation experiments were utilized to identify the signals from H-2', H-3' and OH-3'.

2'-Deoxy-2'-(ethoxycarbonyl)aminouridine (96).

Method B: (See page 66 Method A)

A 20 mg (0.035 mmol) sample of (108) was dissolved in 3 mL of THF and 0.035 mL (0.035 mmol) of $nBu_4N^+F^-$ (as a 1 M solution in THF) was added. The mixture was stirred for 1 h at ambient temperature, evaporated, and the residue partitioned between Et_2O and H_2O. The aqueous phase was applied to a small column of Dowex 1X2(OH^-)[87] resin which was washed well with H_2O. Elution was effected with 15 mM aqueous tetraethylammonium bicarbonate solution (TEAB). After evaporation of the eluate in vacuo the residue was dissolved in H_2O and evaporated 4 times to remove residual TEAB. Crystallization of the residue from MeOH/Et_2O gave (96) in quantitative yield. This product had UV, MS and 400 MHz ^1H nmr spectral data,

and tlc migration identical with those of the product of Method A (96).

2'-(N-Benzyloxycarbamoyl)amino-2'-deoxy-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)uridine (115).

A solution of 200 mg (0.412 mmol) of (109) in 5 mL of $CHCl_3$ (alcohol free and 2 x distilled from CaH_2) was cooled to 0°C. A 287 µL (208 mg, 2.06 mmol) portion of Et_3N was added followed by 131 mg (0.82 mmol) of benzyloxyamine hydrochloride. The mixture was stirred until most of the solid dissolved, then 0.94 mL (1.6 mmol) of $COCl_2$ (from a 1.7 M solution of $COCl_2$ in $CHCl_3$) was added and stirring was continued for 1 h. Solvent was evaporated in vacuo and the crude residue was chromatographed on a column of silica gel using solvent (D) as eluant. Evaporation of appropriate fractions gave 93 mg (35%) of (115) that was used in the next reaction without further purification. This material had: uv (MeOH) max 259 nm, min 232 nm; MS m/z 634.2839 (2.3%, M^+ [$C_{29}H_{46}N_4O_8Si_2$] = 634.2854), 591.2304 (15%, M^+ - iPr), 91.0550 (100%, $PhCH_2^+$); ^1H nmr (300 MHz) δ 1.0 (m, 28, iPr x 4), [illegible] H-4', H-5', H-5"), 4.5 (m, 2, H-2', H-3'), 4.7 and [illegible] (d and d, J = 11 Hz, 1 + 1, CH_2), 5.68 (d, J_{5-6} = 8 Hz,

1, H-5), 5.72 (d, $J_{1'-2'}$ = 6 Hz, 1, H-1'), [illegible] d, $J_{NH2'-2'}$ = 7 Hz, 1, NH-2'), 7.48 (s, 5, Ph) [illegible]5 (d, 1, H-6), 9.5 (s, 1, NH-OBn), 11.4 (bs, 1, [illegible]).

2'-Deoxy-2'-(N-hydroxycarbamoyl)amino-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)uridine (107).

A solution of 50 mg (0.079 mmol) of (115) in 5 mL of 95% EtOH was vigorously stirred in a hydrogen atmosphere with 5% Pd.C catalyst (15 mg) for 4 h. The mixture was filtered, the filtrate evaporated and the crude residue applied to a column of silica gel. Elution with solvent (D) and evaporation of appropriate fractions followed by crystallization of the residue from 95% EtOH gave 19.3 mg (45%) of (107). mp 118-121°C; uv (MeOH) max 259 nm (ε 9800), min 228 nm (ε 2600), (0.1 N HCl) max 259 nm (ε 9400), (0.1 N NaOH) max 259 nm (ε 6900); MS (FAB) m/z 545 (14%, $M^+ + 1$), 544 (0.58%, M^+ $[C_{22}H_{40}N_4O_8Si_2]$ = 544.2385), 433 (24%, M^+ - B), ^1H nmr (360 MHz) δ 1.08 (m, 28, iPr x 4), 3.88 (m, 1, H-5'), 4.40 (m, 2, H-4', H-5"), 4.46 ("q", $J_{2'-1'} = J_{2'-3'} = J_{2'-NH2'}$ = 7 Hz, 1, H-2'), 4.58 (dd, $J_{3'-4'}$ = 5 Hz, $J_{3'-2'}$ = 7 Hz, 1, H-3'), 5.68 (d, J_{5-6} = 8 Hz, 1, H-5), 5.72 (d, 1, H-1'), 6.58 (d, 1, NH-2'), 7.76 (d, 1, H-6), 8.66 (s, 1, NH-OH), 8.85 (bs, 1, NH-OH), 11.32 (bs, 1, NH-3).

2'-Deoxy-2'-(N-hydroxycarbamoyl)amino-uridine (98).

To a solution of 17 mg (0.031 mmol) of (107) in 3 mL of THF was added 62 μL (0.062 mmol) of a 1 M solution of n-$Bu_4N^+F^-$ in THF. The solution was stirred for 10 min, solvent was removed in vacuo and the residue was partitioned between Et_2O and H_2O. The aqueous phase was applied to a column of Dowex 50 (H^+) resin and product was eluted with H_2O. After evaporation of the eluate in vacuo the residue was crystallized from MeOH/Et_2O to give 9 mg (96%) of (98). Uv (MeOH) max 261 nm, min 230 nm; MS (FAB) m/z 301 (1.8%, $M^+ - 1$, $M^+ - H$ [$C_{10}H_{13}N_4O_7$] = 301.07843), 111 (20.8%, B); ^1H nmr (360 MHz) δ 3.6 (br, 2, H-5', H-5"), 3.95 (br, 1, H-4'), 4.08 (br, 1, H-3'), 4.31 (td, $J_{2'-1'} = J_{2'-NH2'} = 8$ Hz, $J_{2'-3'} = 6$ Hz, 1, H-2'), 5.2 (br, 1, OH-5'), 5.15 (dd, $J_{1'-2'} = 8$ Hz, $J_{1'-6} = 2$ Hz), 5.9 (d, $J_{6-5} = 8$ Hz, 1, H-6), 6.0 (br, 1, OH-3'), 6.35 (d, 1, NH-2'), 7.9 (d, 1, H-5), 8.6 (s, 1, NH-OH), 8.85 (s, 1, NH-OH).

After spectroscopical analyses not enough compound was left for elemental analysis.

9-(3-Bromo-3-deoxy-β-D-xylofuranosyl)adenine (116).

A solution of 590 mg (2.37 mmol) of 9-(2,3-anhydro-β-D-ribofuranosyl)adenine (87)[80] in 55 mL of 1 M HBr/DMF was stirred at ambient temperature for 24 h, cooled to 0°C and 52 mL of 1 N $NaHCO_3/H_2O$ was added dropwise with vigorous stirring. Solvents were evaporated in vacuo and the crude residue was used in the next reaction without further purification. A pure sample of (116) for characterization was obtained by chromatography of the crude residue on a silica gel plate using solvent (E) followed by crystallization from H_2O. This sample of (116) had mp 131-133°C (Lit. mp[81] 131-132°C), uv (MeOH) max 259 nm (ε 15800), min 227 nm (ε 3600), (0.1 N HCl max 258 nm (ε 15400), (0.1 N NaOH) max 259 nm (ε 15100); MS m/z 329.0037 (0.78%, M^+ [$C_{10}H_{12}{}^{79}BrN_5O_3$] = 329.0124), 164.0573 (78%, BHCHO), 135.0547 (100%, B + H). ^1H nmr (400 MHz) δ 3.75 (m, 2, H-5', H-5"), 4.35 ("q", $J_{4'-3'} = J_{4'-5'} = J_{4'-5"} = 4.5$ Hz, 1, H-4'), 4.55 ("t", $J_{3'-2'} = J_{3'-4'} = 5$ Hz, 1, H-3'), 4.93 ("q", $J_{2'-1'} = J_{2'-3'} = J_{2'-OH2'} = 4.5$ Hz, 1, H-2'), 5.4 (t, $J_{OH5'-5'} = J_{OH5'-5"} = 5.5$ Hz, 1, OH-5'), 5.86 (d, 1, H-1'), 6.38 (d, $J_{OH2'-2'} = 5$ Hz, 1, OH-2'), 7.36 (s, 2, NH_2-6), 8.15 (s, 1, H-2), 8.32 (s, 1, H-8).

9-(3-Bromo-5-O-tert-butyldiphenylsilyl-3-deoxy-β-D-xylofuranosyl)adenine (117).

To a solution of 2.36 mmol of the crude (116) mixture in 15 mL of anhydrous pyridine was added 610 μL (649 mg, 2.36 mmol) of tert-butyldiphenylsilyl chloride and the mixture was stirred at ambient temperature for 12 h. H_2O (1 mL) was added and stirring was continued for 30 min. Solvents were evaporated in vacuo and the residue was partitioned between $CHCl_3$ and H_2O. The organic phase was washed with 2 x 50 mL of H_2O, saturated $NaHCO_3/H_2O$, saturated $NaCl/H_2O$, dried (Na_2SO_4), filtered and evaporated. The residue was chromatographed on a column of silica gel using solvent (D) as eluant. Evaporation of appropriate fractions and crystallization of the residue from THF/CH_3CN gave 1.1 g (82% overall yield from 87) of (117): mp 210-211°C; uv (MeOH) max 259 nm (ε 13800), min 233 nm (ε 700), (0.1 N HCL) max 258 nm (ε 13900), (0.1 N NaOH) max 259 nm (ε 13800); MS m/z 510.0614 [1.4%, M^+ - t-Bu; $M^+ - C_4H_9$ [$C_{22}H_{21}{}^{79}BrN_5O_3Si$] = 510.0597], 135.0560 (25%, B + H); ^1H nmr (400 MHz) δ 1.2 (s, 9, t-Bu), 4.4 (dd x 2, $J_{5'-4'} = J_{5''-4'} = 5$ Hz, $J_{5'-5''} = 11$ Hz, 2, H-5', H-5"), 4.54 ("q", $J_{4'-3'} = J_{4'-5'} = J_{4'-5''} = 5$ Hz, 1, H-4'), 4.62 (dd, $J_{3'-2'} = 4$ Hz, $J_{3'-4'} = 5$ Hz,

1, H-3'), 4.96 ("q", $J_{2'-OH2'} = J_{2'-1'} = 5$ Hz, 1, H-2'), 5.93 (d, 1, H-1'), 6.41 (d, 1, OH-2'), 7.34 (s, 2, NH_2-6), 7.4-7.7 (m, 10, Ph x 2), 8.1 (s, 1, H-2), 8.16 (s, 1, H-8). Anal. calcd. for $C_{26}H_{30}BrN_5O_3Si$: C 54.93, H 5.32, N 12.32; Found: C 54.73, H 5.12, N 12.45.

9-[2-O-(N-benzylcarbamoyl)-3-bromo-5-O-tert-butyldiphenylsilyl-3-deoxy-β-D-xylofuranosyl]adenine (118).

To a solution of 500 mg (0.88 mmol) of (118) in 50 mL of CH_3CN/THF (1:1) was added 220 μL (234 mg, 1.76 mmol) of benzylisocyanate and 180 μL (133 mg, 1.32 mmol) of Et_3N. The reaction mixture was stirred at ambient temperature for 48 h, solvents were evaporated in vacuo and the residue was chromatographed on a column of silica gel using solvent (D) as eluant. Evaporation of appropriate fractions and crystallization of the residue from "Skellysolve B"/$CHCl_3$ gave 0.55 g (90%) of (118): mp 178-179°C, uv (MeOH) max 259 nm (ε 14700), min 233 nm (ε 3100), (0.1 N HCl) max 258 nm (ε 14600), (0.1 N NaOH) max 259 nm (ε 14900); MS (FAB) m/z 702 (5.1%, $M^+ + 1$, $M^+ + H$ [$C_{34}H_{38}{}^{79}BrN_6O_4Si$] = 701.1829), 704 (6.8%, M + 1 = 703 [^{81}Br]), 135 (100%, B + H), 91 (92%, $PhCH_2$), 81 (10%,

^{81}Br), 79 (10%, ^{79}Br); ^1H nmr (400 MHz) δ 1.0 (s, 9, t-Bu), 3.98 (dd x 2, $J_{5'-4'} \simeq J_{5''-4'}$ = 5 Hz, $J_{5'-5''} \simeq$ 11 Hz, 2, H-5', H-5''), 4.12 and 4.16 (dd x 2, J_{CH_2-NH} = 6 Hz, $J_{gem\ CH_2}$ = 15 Hz, 2, CH_2), 4.5 ("q", $J_{4'-3'} = J_{4'-5'} \simeq J_{4'-5''}$ = 5 Hz, 1, H-4'), 4.88 (dd, $J_{3'-2'}$ = 4 Hz, $J_{3'-4'}$ = 5 Hz, 1, H-3'), 5.86 ("t", $J_{2'-1'}$ = 4 Hz, 1, H-2'), 6.14 (d, 1, H-1'), 7.1-7.3 (m, 18, Ph x 3, NH_2-6, NH-Bn), 8.1 (s, 1, H-2), 8.16 (s, 1, H-8). Anal. calcd. for $C_{34}H_{37}BrN_6O_4Si$: C 58.20, H 5.32, N 11.98; Found: C 58.01, H 5.25, N 12.08.

9-(3-Benzylamino-5-O-tert-butyldiphenylsilyl-2,3-O-N-carbonyl-3-deoxy-β-D-ribofuranosyl)adenine (**119**).

A 20 mg (0.42 mmol) sample of NaH (50% dispersion in mineral oil) was placed in a moisture-free three-neck round-bottom flask under a N_2 atmosphere. The oil was removed by rinsing with "Skellysolve B", and 40 mL of freshly distilled THF was added. The suspension was cooled to -20°C, 250 mg (0.36 mmol) of (**118**) in 5 mL of THF was added and stirring was continued for 12 h. The mixture was filtered on celite, the solvent was evaporated in vacuo and the crude residue was used in the next reaction without further purification. A pure sample for characterization of (**119**) was obtained by

chromatography on a silica gel plate using solvent (D) as eluant. This material had uv (MeOH) max 259 nm, min 233 nm; MS (FAB) m/z 621 (34%, $M^+ + 1$, $M^+ + H$ [$C_{34}H_{37}N_6O_4Si$] = 621.2646), 620 (12%, M^+), 135 (47%, B + H), 136 (47%, B + 2H); ^1H nmr (400 MHz) δ 0.84 (s, 9, t-Bu), 3.51 (dd, $J_{5'-4'}$ = 6 Hz, $J_{5'-5''}$ = 11 Hz, 1, H-5'), 3.6 (dd, $J_{5''-4'}$ = 5 Hz, $J_{5''-5'}$ = 11 Hz, 1, H-5"), 4.35 ("q", J = 4.5 Hz, 1, H-4'), 4.39 (d, $J_{gem\ CH_2}$ = 15 Hz, 1, CH_2), 4.55 (dd, $J_{3'-4'}$ = 4 Hz, $J_{3'-2'}$ = 8 Hz, 1, H-3'), 4.6 (d, 1, CH_2), 5.91 (dd, $J_{2'-1'}$ = 3 Hz, $J_{2'-3'}$ = 8 Hz, 1, H-2'), 6.38 (d, 1, H-1'), 7.36 (m, 17, Ph x 3, NH_2-6), 8.0 (s, 1, H-2), 8.27 (s, 1, H-8); IR ($CHCl_3$ cast) ν C = O 1763 cm^{-1}.

9-(3-Benzylamino-2,3-O-N-carbonyl-3-deoxy-β-D-ribofuranosyl)adenine (122).

A 0.36 mmol sample of crude (119) was dissolved in 40 mL of freshly distilled THF, 360 μL (0.36 mmol) of tetra-n-butylammonium fluoride (as a 1 M solution in THF) was added and the solution was stirred at ambient temperature for 1 h. Solvent was evaporated in vacuo and the residue was partitioned between H_2O and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ (2x) and the combined organic phase was washed with

saturated $NaHCO_3/H_2O$, saturated $NaCl/H_2O$, dried (Na_2SO_4), filtered and evaporated. The crude residue was purified by chromatography on a silica gel column using solvent (A) as eluant. Evaporation of appropriate fractions and crystallization of the residue from MeOH with diffusion of Et_2O gave 112 mg (94% yield overall from **118**) of (**122**): mp 229-230°C; uv (MeOH) max 258 nm (ϵ 14500), min 225 nm (ϵ 3300), (0.1 N HCl) max 257 nm (ϵ 14300), (0.1 N NaOH) max 258 nm (ϵ 13700); MS (FAB) m/z 383 (53%, $M^+ + 1$; $M^+ + H$ [$C_{18}H_{19}N_6O_4$] = 383.1468), 382 (1.3%, M^+), 135 (48%, B + H); ^1H nmr (360 MHz) δ 3.4 ("t", J = 3.5 Hz, 2, H-5', H-5"), 4.26 ("q", $J_{4'-3'} = J_{4'-5'} = J_{4'-5"} = 4$ Hz, 1, H-4'), 4.32 (d, J = 15 Hz, 1, gem CH_2), 4.36 (dd, $J_{3'-4'} = 4$ Hz, $J_{3'-2'} = 8$ Hz, 1, H-3'), 4.62 (d, 1, gem CH_2), 5.26 (bs, 1, OH-5'), 5.7 (dd, $J_{2'-1'} = 3$ Hz, $J_{2'-3'} = 8$ Hz, 1, H-2'), 6.32 (d, 1, H-1'), 7.35 (m, 7, Ph, NH_2-6), 8.12 (s, 1, H-2), 8.34 (s, 1, H-8); IR ($CHCl_3$ cast) ν C = O 1752 cm^{-1}. Anal. calcd. for $C_{18}H_{18}N_6O_4$: C 56.54, H 4.75, N 21.98. Found: C 56.20, H 4.54, N 21.74.

9-(3-Benzylamino-3-deoxy-β-D-ribofuranosyl)adenine (**120**).

To a solution of 112 mg (0.31 mmol) of (**122**) in 5

mL of THF was added 5 mL of 1 M NaOH. The reaction mixture was stirred at ambient temperature for 48 h and then treated with Amberlite IRC-50 (H^+) resin. The mixture was stirred for 1 h, filtered and evaporated to dryness. The crude residue was dissolved in H_2O and applied to a column of Dowex 1X2(OH^-) resin. The column was washed thoroughly with H_2O and product was eluted with 1% MeOH/H_2O. After evaporation of the eluate in vacuo the residue was crystallized from $CHCl_3$/MeOH to yield 96 mg (92%) of (120): mp 175-176°C, uv (MeOH) max 259 nm (ε 15700), min 229 nm (ε 3900), (0.1 N HCl) max 257 nm (ε 15500), (0.1 N NaOH) max 259 nm (ε 1500), MS m/z 356.1603 (0.8%, M^+ [$C_{17}H_{20}N_6O_3$] = 356.1597), 221.1051 (24%, M^+ - B), 136.0625 (93%, B + 2H), 91.0549 (100%, $PhCH_2$); ^1H nmr (400 MHz) δ 3.35 (m, 1, H-5'), 3.54 (m, 1, H-5"), 3.7 (m, 1, H-4'), 3.72 and 3.78 (dd x 2, J_{CH_2-NH} = 6 Hz, $J_{gem\ CH_2}$ = 15 Hz, 2, CH_2), 3.92 (dt $J_{3'-NH} = J_{3'-4'}$ = 3 Hz, $J_{3'-2'}$ = 6 Hz, 1, H-3'), 4.57 (dd, $J_{2'-1'}$ = 4 Hz, 1, H-2'), 5.27 (dd, $J_{OH5'-5'}$ = 5 Hz, $J_{OH5'-H5"}$ = 6 Hz, 1, OH-5'), 5.87 (bs, 1, OH-2'), 5.96 (d, 1, H-1'), 7.32 (m, 8, Ph, NH-Bn, NH_2-6), 8.12 (s, 1, H-2'), 8.35 (s, 1, H-8). Anal. calcd. for: $C_{17}H_{20}N_6O_3$: C 57.29, H 5.66, N 23.58. Found: C 57.01, H 5.69, N 23.70.

9-(3-Amino-3-deoxy-β-D-ribofuranosyl)adenine, (3'-Amino-3'-deoxyadenosine) 20.

To a solution of 90 mg (0.25 mmol) of (120) in 10 mL of 95% EtOH added 30 mg of 5% Pd.C catalyst and the suspension was vigorously stirred in a hydrogen atmosphere for 12 h. The catalyst was filtered on celite, solvent evaporated in vacuo and the crude residue was applied to a column of Dowex 1X2(OH^-) resin. The column was washed with H_2O and then eluted with 10% MeOH/H_2O. Evaporation of the eluant and crystallization of the residue from H_2O/MeOH gave 65 mg mg (97%) of (20). mp 259-261°C dec. (Lit. mp 259-260°C dec.[62]), uv (H_2O) max 259 nm (ε 14500), min 226 nm (ε 2100), (0.1 N HCl) max 256 nm (ε 15200), (0.1 N NaOH) max 259 nm (ε 14200); MS m/z 267.1197 (0.24%, M^+ + 1); 266.1130 (0.18%, M^+ [$C_{10}H_{14}N_6O_3$] = 266.1127), 136.0626 (100%, B + 2H); ^1H nmr (400 MHz) δ 1.66 (bs, 2, NH_2-3'), 3.47 (m, 1, H-5'), 3.57 (m, 1, H-5"), 3.73 (m, 2, H-4', H-3'), 4.28 (dd, $J_{2'-1'}$ = 3 Hz, $J_{2'-3'}$ = 5 Hz, 1, H-2'), 5.17 (t, $J_{OH5'-5'} = J_{OH5'-5"}$ = 5 Hz, 1, OH-5'), 5.77 (bs, 1, OH-2'), 5.94 (d, 1, H-1'), 7.3 (s, 1, NH_2-6), 8.15 (s, 1, H-2), 8.39 (s, 1, H-8).

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