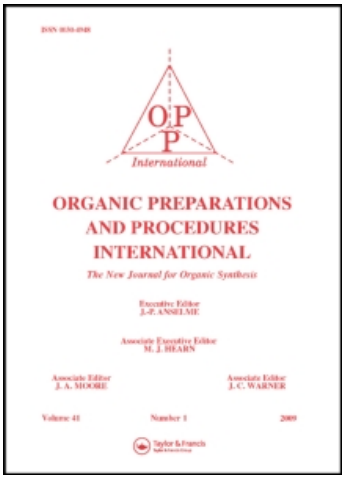

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THE CHEMISTRY OF 4',5'-UNSATURATED NUCLEOSIDES. A REVIEW

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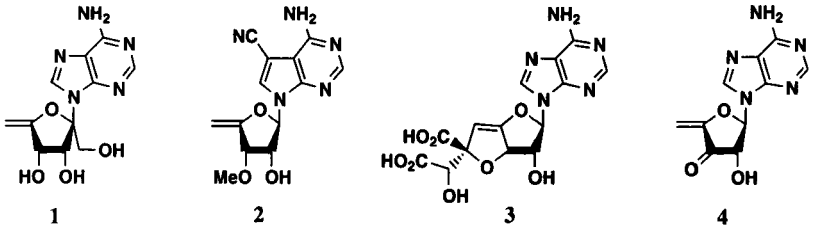
INTRODUCTION

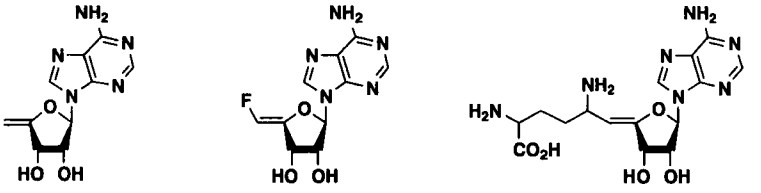
4',5'-unsaturated nucleosides, characterized by an exocyclic C-C double bond next to the ring oxygen in the carbohydrate moiety, represent a class of nucleosides, which combines several extraordinary properties. They display very often powerful biopotency, interfering in specific metabolic pathways. They also possess interesting chemical properties, resulting from the reactivity of the enol ether function, which offers numerous possibilities for multifold transformations.



Scheme 1

There are several examples of naturally occuring 4',5'-unsaturated nucleosides (*Scheme* 1). The nucleoside antibiotic angustmycin A (decoyinine) **1**,[3,4] isolated from cultures of *streptomyces hygroscopicus*, displays antibacterial and antitumor activity. The pyrrolo[2,3-d]pyrimidine nucleoside mycalisine A **2**[5,6] was found in extracts of the marine sponge *mycale sp.* It inhibits the cell division of fertilized starfish eggs. Griseolic acid A **3**[7,8] is a nucleotide phosphodiesterase inhibitor isolated from the culture broth of *streptomyces griseoaurantiacus*. The enone **4**[9,10] is one of the key intermediates during the reversible hydrolytic cleavage of *S*-adenosyl-L-homocysteine (SAH, AdoHcy) to adenosine and L-homocysteine, catalyzed by SAH hydrolase. This enzyme regulates biological methylation reactions indirectly by preventing the intracellular accumulation of SAH, which is a strong feedback inhibitor of *S*-adenosyl-L-methionine(SAM, AdoMet)-dependent methyltransferases.[11,12] This means, that inhibition of SAH hydrolase leads to the subsequent suppression of all SAM-dependent methylation reactions, including those which are required for the maturation of viral mRNA.[13] Since inhibi-

tion of SAH hydrolyse could be directly correlated with inhibition of viral replication,[14] it has been recognized as an attractive target for mechanism-based antiviral chemotherapy. Several 4',5'-unsaturated nucleosides act as inhibitors of SAH hydrolase, because they are accepted as alternative substrates on the basis of their similarity to metabolic intermediate **4**. To these synthetic SAH hydrolase inhibitors belong 4',5'-didehydro-5'-deoxyadenosine (**5**),[15,16] its 5'-fluoro derivative (**6**, MDL 28,842, ZDDFA)[17,18] and the 4',5'-didehydrosinefungin derivative (**7**, A9145C)[1,19] (*Scheme* 2).



Scheme 2

Compound **5** was also found to inhibit adenosine deaminase.[20] Furthermore it is probably one of the fission products of coenzyme B_{12} (5'-deoxyadenosylcobalamine) after enzymatic Co-C bond breakage.[21] Compound **6** possesses powerful antitumor[22] and antimalarial[23] activity.

This review illustrates the diverse possibilities in the preparation and transformation of 4',5'-unsaturated nucleosides.

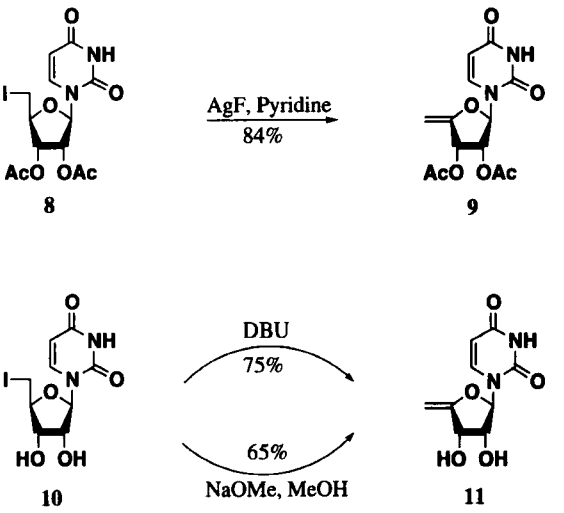
I. SYNTHESIS OF 4',5'-UNSATURATED NUCLEOSIDES

1. Base- or Fluoride-Promoted Elimination Reactions

a) Dehydrohalogenation

The first synthesis of a 4',5'-unsaturated nucleoside was accomplished in 1966 by silver fluoride promoted elimination reaction of the 5'-iodo substituted uridine **8** (*Scheme* 3).[24] Since then, dehydrohalogenation has become the most common method for the preparation of 4',5'-unsaturated nucleosides, because of the easy introduction of halogen atoms into the 5'-position of nucleosides.

E2 elimination of hydrogen iodide is also possible under base catalysis and in the absence of protecting groups in the sugar moiety. The uridine derivative **10** can be transformed into **11** with the aid of DBU[25] or sodium methoxide[26] (*Scheme* 3). Besides these two, a variety of bases like DBN,[3,27-31] potassium *tert*-butoxide[25,31,32] and potassium hydroxide[33] have been applied for the synthesis of 4',5'-unsaturated nucleosides. Other fluoride promoters such as potassium fluoride,[34] tetraethylammonium fluoride[35] or tetrabutylammonium fluoride[34] have also been used. With these reagents, the base- or fluoride promoted dehydrohalogenation of 5'-halogenated nucleosides led to 4',5'-unsaturated derivatives of adenosine,[3,15,26,27,29,30,32,36-39] guanosine,[26,28,30] uridine,[24-26,31,35,40,41] cytidine[3,31] and thymidine.[26,31,33-35,41,42] Two examples deal with the preparation of the rare 4',5'-unsaturated carbocyclic (*carba*-)nucleosides.[28,32] In most cases, iodine is used as the leaving group, but other halogens such as bromine[31,39,42] and fluorine[43,44] can also be eliminated.

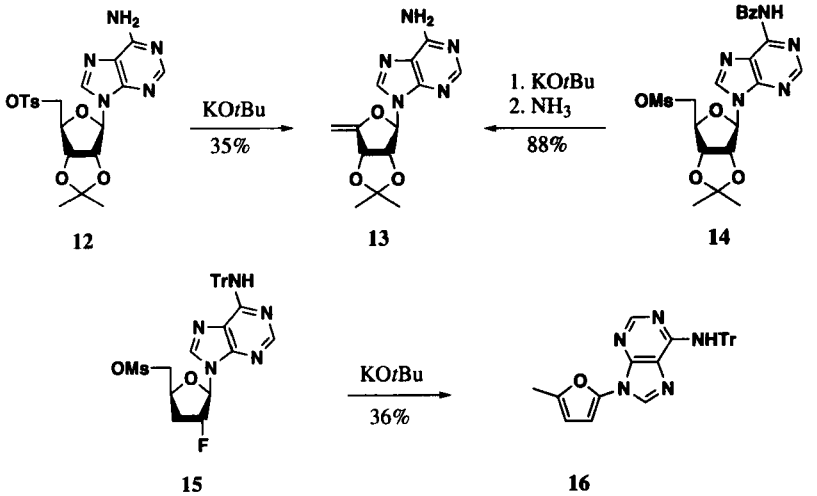


8 9 10 11

Scheme 3

b) Sulfonate Elimination

Sulfonyl groups in the 5'-position of nucleosides can also act as leaving groups in base-catalyzed E2 elimination reactions. Since the 5'-halogenation of nucleosides often proceeds through the corresponding 5'-sulfonyl intermediate, elimination of the sulfonyl derivatives seems to be a more direct approach. Reaction of the tosylated adenosine **12**[16,45] or the mesylated adenosine **14**[35,46-48] with potassium *tert*-butoxide leads in both cases to the vinylic nucleoside **13** (*Scheme* 4). As is also true for the dehydrohalogenation, the yield of the elimination step is limited by the instability of the starting compound and its ability to undergo nucleophilic displacement reactions leading to cyclonucleosides. In the case of purine nucleosides, this N^3,5'-cyclization can be supressed by benzoylation of the amino group as in **14**, which decreases the nucleophilicity of N^3. As demonstrated by comparison of the transformation of the two sulfonylated nucleosides **12** and **14** to **13**, this results in a drastic yield increase.

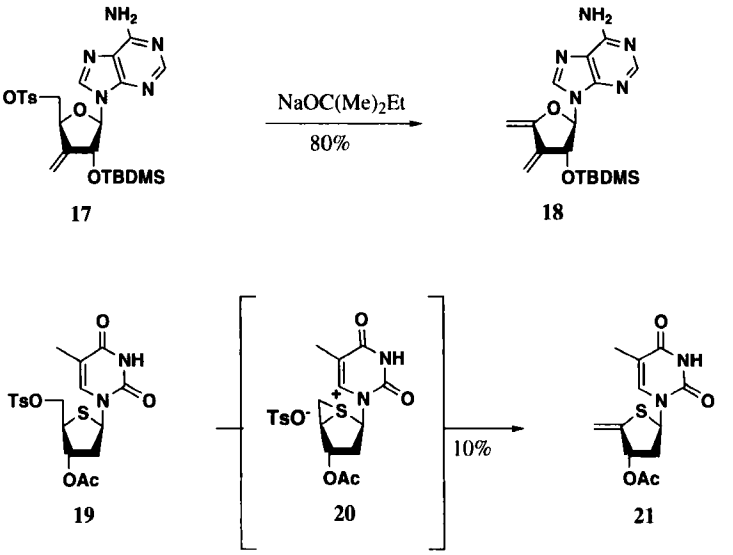


12 13 14 15 16

Scheme 4

In the special case of 3'-deoxynucleosides bearing a halogen atom[46] or a acetyloxy group[36] at carbon 2', attempts to prepare a 4',5'-unsaturated nucleoside by elimination of appropriate leaving groups at C-5' always lead to methyl- and nucleobase substituted furans like **16** (*Scheme* 4).[46]

Other 4',5'-unsaturated nucleosides have also been prepared by elimination of 5'-O-mesylated[49,50] or tosylated[27,50-54] precursors. One of these is the adenosine derivative **18**, bearing two conjugated *exo*-methylene functions (*Scheme* 5).[27] It should be an interesting diene for Diels-Alder reactions.



Scheme 5

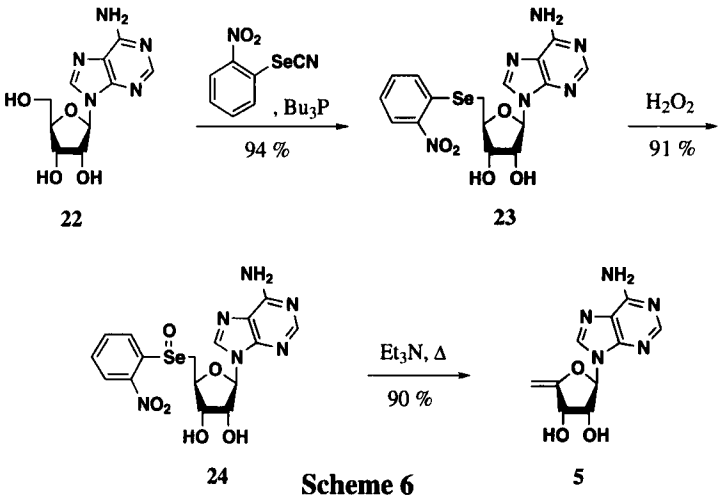
Application of the 5'-O-sulfonyl elimination also enables the preparation of the only known 4',5'-didehydro-4'-thio (*thia*-)nucleoside **21** (*Scheme* 5).[54] Because of the absence of the normally required base, the bicyclic episulfonium ion **20** was proposed as reactive intermediate.

2. Thermal Elimination Reactions

a) Selenoxide Elimination

The unsaturation of the 4',5'-position of nucleosides may also be accomplished by thermal *syn* elimination of 5'-arylselenoxides.[5,55-59] Such compounds are usually obtained by oxidation of 5'-arylselenides, which can be prepared from precursors either with a halogen atom or an unprotected hydroxy group in the 5'-position. The latter approach is demonstrated by the concise 3-step approach to 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**5**) from adenosine (**22**) in *Scheme* 6.[55]

An additional advantage of this approach is, that hydroxyl-protecting groups, which are not compatible with the conditions of base-promoted eliminations may be used. The application of this selenoxide elimination allowed the synthesis of two deuterated analogs of **5**, bearing a deuterium atom either in the E or in the Z position of the C-C double bond instead of the corresponding hydrogen.[57]



Scheme 6

b) Sulfoxide Elimination

A special approach has been developed for the reliable preparation of 4',5'-didehydro-5'-fluoronucleosides like **27**. In principle, **27** is obtainable as mixture of E- and Z-isomers by base-promoted dehydrofluorination of the difluoride **26**, but the *gem*-difluorination of aldehyde **25** with DAST proceeds only in 18 % yield.[43,44] In view of the importance of **27** as precursor of the potential pharmaceutical MDL 28,842 (ZDDFA) **6**, McCarthy et al.[43,44] introduced a new approach to such vinyl fluorides utilizing the *fluoro*-Pummerer reaction[60-63] as key step. Herein the arylsulfoxide **29** is transformed into a diastereomeric mixture of α-fluoro thioethers **30** by fluorine insertion with DAST. Further oxidation with *m*-CPBA yields again a sulfoxide **31**, which can be reacted to **27** by thermal *syn*-elimination of sulfenic acid.[43,44] Recently it was shown, that the thioether **28** can be converted directly into the α-fluoro thioether **30** with DAST and antimony trichloride[64] or xenon difluoride[65] (*Scheme* 7).

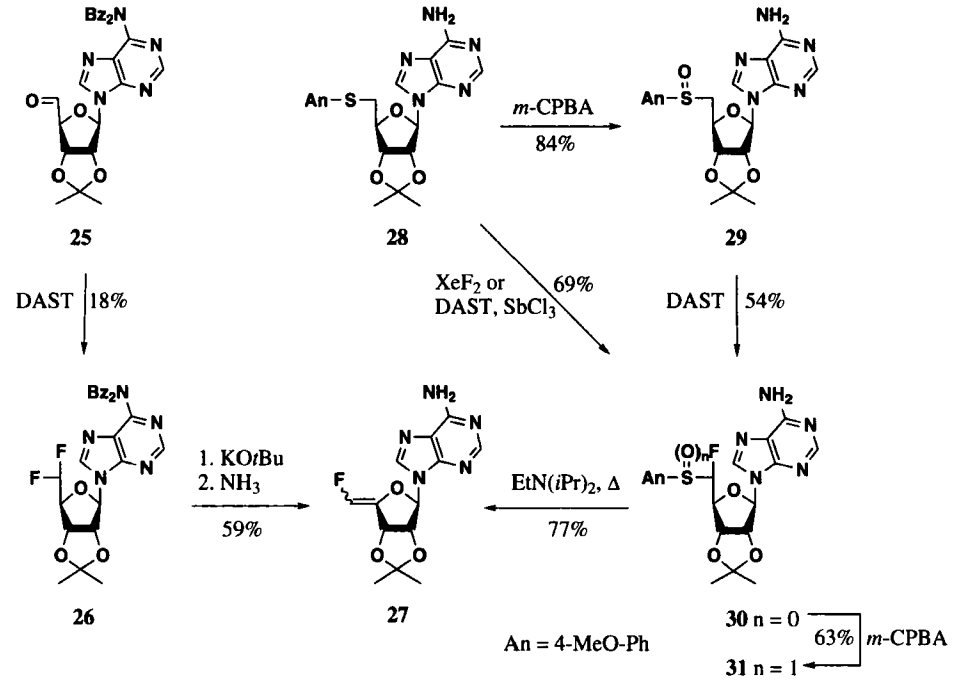
The employment of the *p*-anisylidene sulfoxide allows the fluoro-analog of the Pummerer rearrangement to proceed without any catalyst,[43,44,61,62] other sulfoxides require the support of a lewis acid like antimony trichloride.[60,63] With this valuable method other 4',5'-didehydro-5'-fluoro-[65-68] and 5'-methoxynucleosides[65] have also been prepared, two of them representing 4',5'-didehydro-5'-fluoro analogs of the *carba*-nucleoside antibiotic aristeromycin.[67,68]

The preparation of the related 4',5'-didehydro-5'-chloro nucleosides follows a different scheme.[43,69] Herein the 5'-sulfides may be transformed directly to α-chlorosulfoxides, whose subsequent thermolysis leads to the desired vinyl chlorides. *Scheme* 8 demonstrates that although the chlorination / oxidation step leads to a mixture of the diastereomers **33** and **34**, their thermolysis proceeds in a highly *syn*-selective manner.[69]

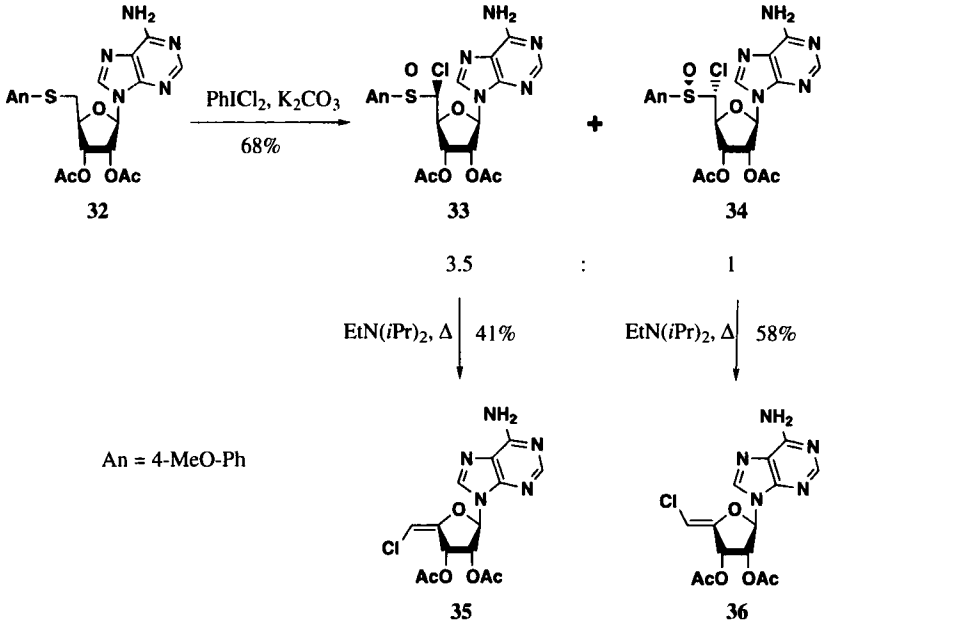
The sulfoxide method also made possible the first total synthesis of griseolic acid **3**.[7]

3. Wittig-type Reactions

The 5'-aldehydes are also valuable intermediates for the preparation of 4',5'-unsaturated nucleosides through non-eliminative transformations. Their Wittig reaction with appropriate



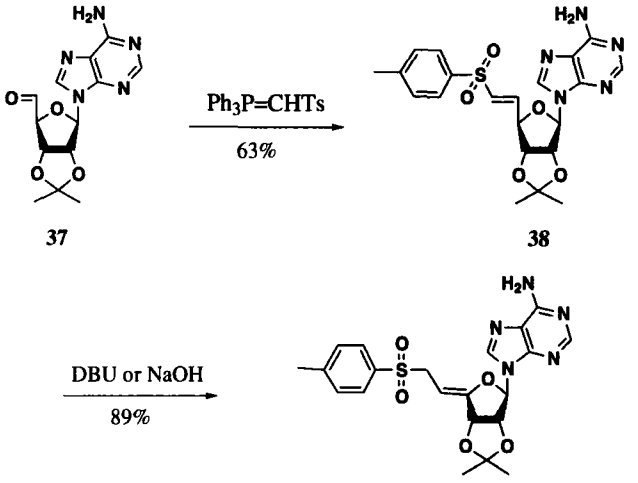
Scheme 7



Scheme 8

phosphoranes gives C-C coupling products, which can be isomerized under basic conditions to 4',5'-enol ethers.[70-72] The rearrangement of the vinyl sulfone **38** to the allyl sulfone **39** proceeds

under monophasic (DBU / THF) as well as under biphasic basic conditions (NaOH, H_2O, MeCN) (*Scheme* 9).[71]

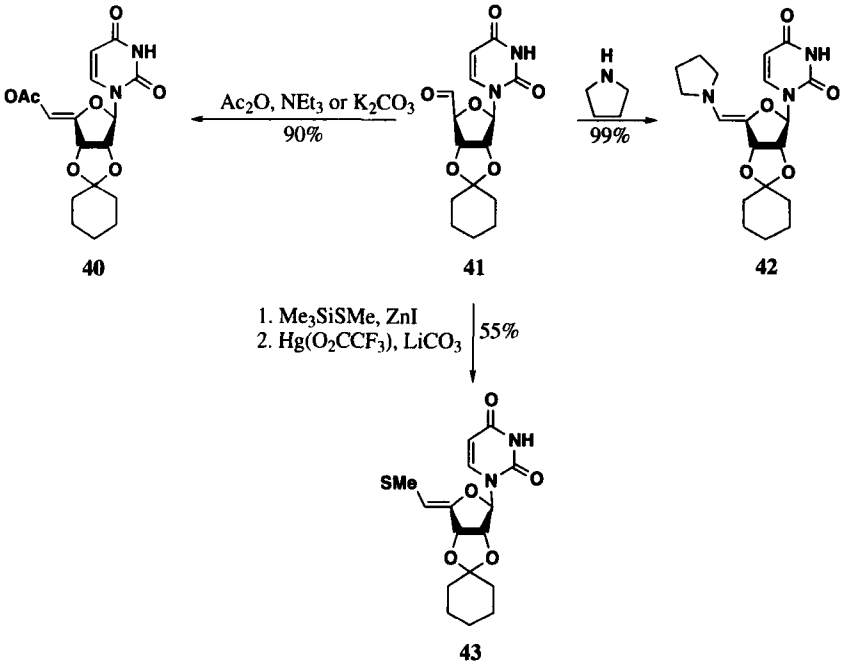


37 38 39

Scheme 9

4. Miscellaneous Methods

Nucleoside 5'-aldehydes are not only educts for the Wittig reaction, they are also appropriate starting materials for the synthesis of nucleoside 4',5'-enol acetates.[73-75] The treatment of aldehyde **41** with an excess of acetic anhydride and two equivalents of triethylamine[74] or potassium carbonate[75] affords the enol acetate **40** in high yield (*Scheme* 10).



40 41 42 43

Scheme 10

Nucleoside 4',5'-enamines like **42**[76] and vinyl sulfides as **43**[77] are also obtainable from the corresponding 5'-aldehyde through different base-catalyzed transformations (*Scheme* 10).

The following table lists all known 4',5'-unsaturated nucleosides, in which at least one substituent of the exocyclic C-C double bond is not identical with hydrogen. In those cases where the vinylic nucleosides have been obtained as E/Z-mixtures the table shows the predominant isomer.

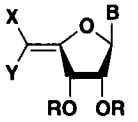


TABLE.

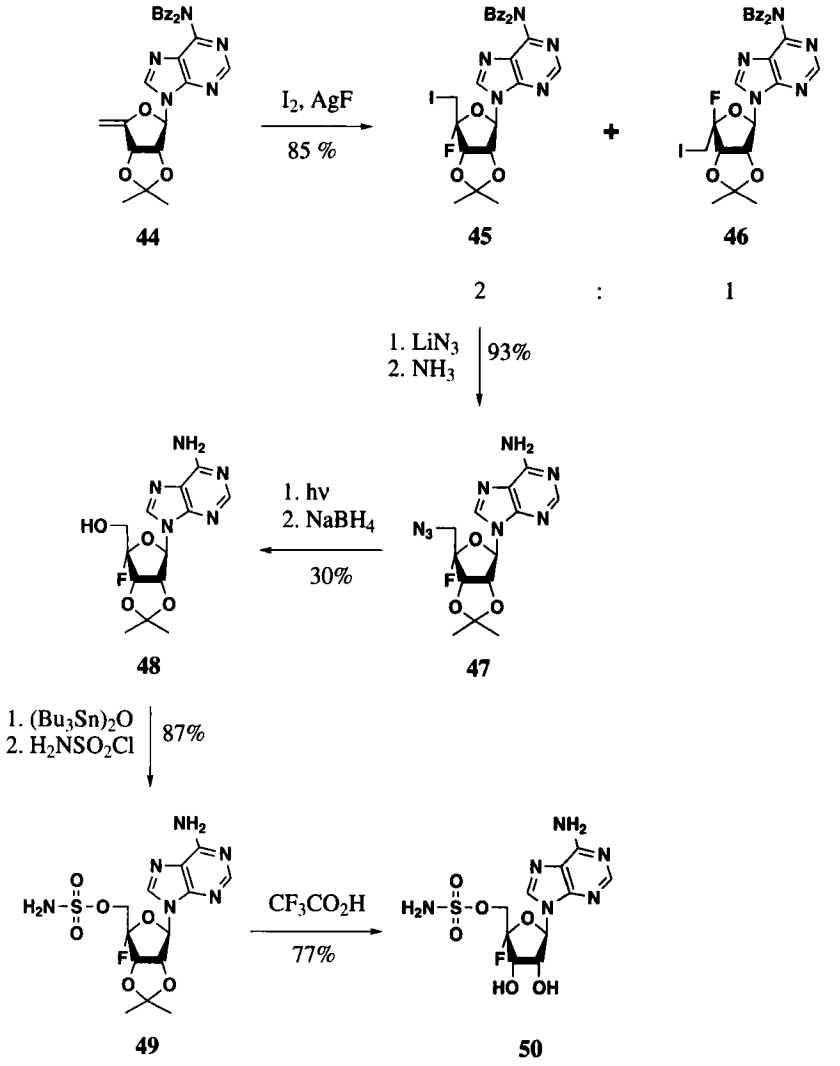
X	Y	Ref.	X	Y	Ref.
D	H	57	F	H	43, 44, 65, 66
H	Me	37, 52	F	Cl	43
HO_2CCH_2	H	72	H	Cl	43, 69
$TsCH_2$	H	70, 71	Cl	Cl	69
$TBDMSOCH_2$	H	42	H	I	46, 47
$(CH_2)_4N$	H	76	$(EtO)_2OP$	H	80
$PhCH_2CONH$	H	78	MeS	H	77
H	MeO	65	*i*BuS	H	77
AcO	H	73, 74, 75, 79	CN	AcO	73

II. REACTIONS OF 4',5'-UNSATURATED NUCLEOSIDES

1. Addition Reactions

a) Halogenation

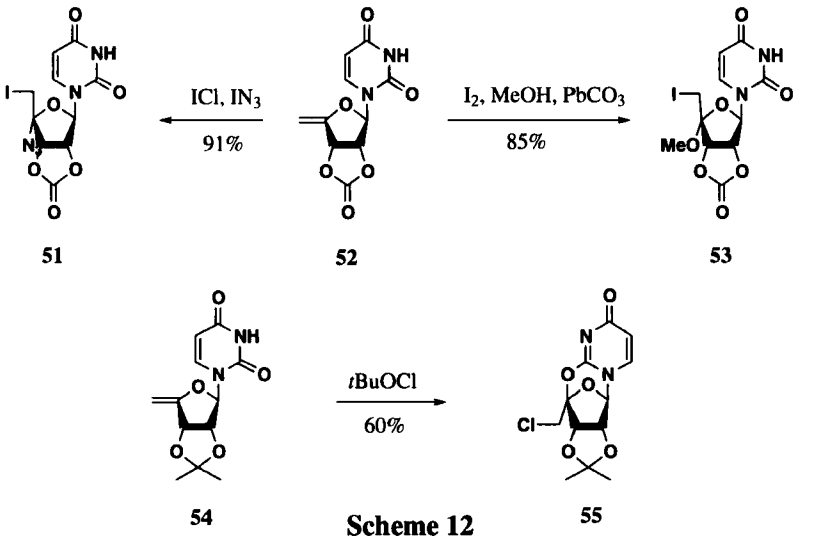
The isolation of the antitrypanosomal nucleoside antibiotic nucleocidin **50**[46-48] from the microorganism *streptomyces calvus* started a search for methods allowing the convenient modification of C-4' of nucleosides. The addition of halogen to the C-C double bond of 4',5'-unsaturated nucleosides seems to be an attractive tool for the introduction of substituents at C-4' and enables indeed the total synthesis of nucleocidin.[46-48] The reaction of **44** with iodine fluoride generated *in situ* from silver fluoride and iodine results in the regioselective formation of the two isomeric 4'-fluoro-5'-deoxy-5'-iodo nucleosides **45** and **46**, which can be separated by chromatography. Due to the electronic deactivation by the adjacent fluorine substituent, the 5'-iodo function of the β-D-ribo isomer **45** proved to be very resistant to nucleophilic displacement. While none of several oxygen nucleophiles gave a satisfactory reaction, at least the substitution with azide was possible. Therefore the desired 5'-O-sulfamoyl function is introduced via the azido- and hydroxy intermediates **47** and **48**. The deprotection of the isopropylidene group in **49** with trifluoroacetic acid leads finally to nucleocidin **50** (*Scheme* 11).[47,48]



Scheme 11

Besides iodine fluoride,[46-49,81,82] other halogens also undergo addition reactions with 4',5'-unsaturated nucleosides. *Scheme* 12 shows that the regio- and stereoselective addition of iodine azide[26,41] and iodine in methanol[29,83] allow the diverse functionalization of C-4'. Both addition products **51** and **53** were obtained without the formation of the corresponding α-L-lyxo epimers.

An explanation for the exclusive formation of the β-D-ribo product during certain addition reactions of 4',5'-unsaturated pyrimidine nucleosides is the occurrence of O^2,4'-cyclonucleoside intermediates. Using *tert*-butyl hypochlorite[50] or hypobromous acid[84] as dipolar addition reagents, the cyclization to stable O^2,4'-anhydro nucleosides like **55** can be achieved (*Scheme* 12). Such cyclonucleosides are quite sensitive to nucleophiles and therefore open additional possibilities for the functionalization of nucleosidic C-4'.

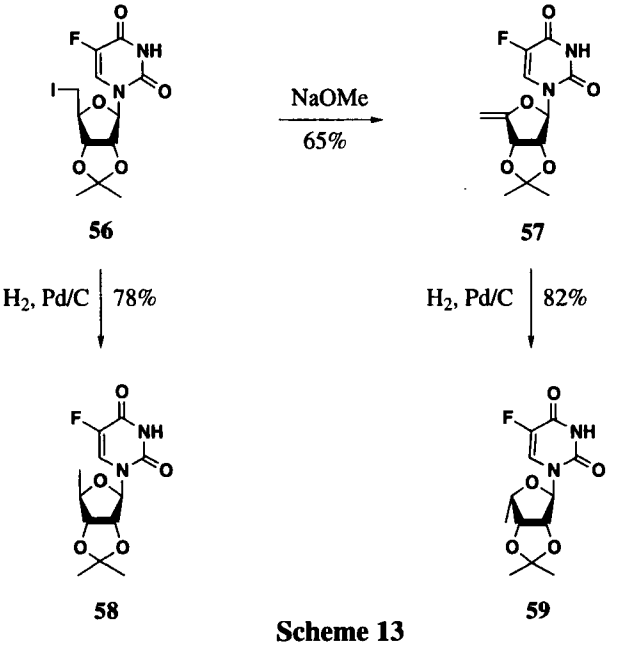


51 52 53 54 55

Scheme 12

b) Hydrogenation

The addition of hydrogen to the 4',5'-nucleosidic C-C double bond is an excellent method for the preparation of otherwise difficult to obtain 5'-deoxy-α-L-*lyxo* nucleosides.[16,33,40,53] *Scheme 13* shows that the L-*lyxo* nucleoside **59** is obtained by selective hydrogenation of the vinylic 5-fluorouridine **57**, whereas its D-*ribo* epimer **58** is formed exclusively by reduction of the 5'-iodo precursor **56**.[40]



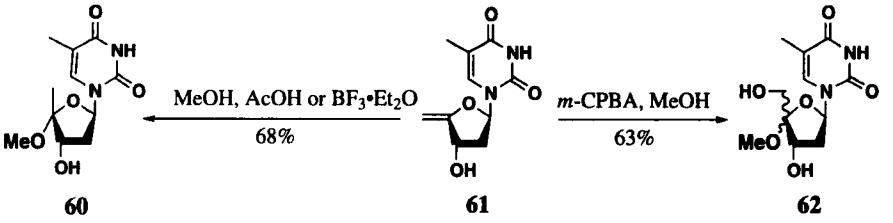
56 57 58 59

Scheme 13

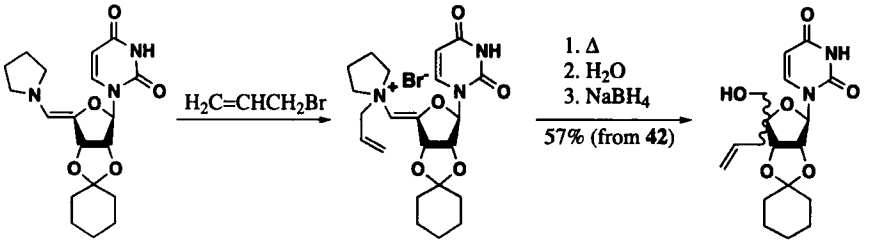
c) Various Addition Reactions

The diastereoselective introduction of alkoxy groups at C-4' of 4',5'-didehydro-5'-deoxythymidine (**61**) under mild acidic conditions (acetic acid or borontrifluoride etherate catalysis)

gives 5'-deoxy-4'-methoxythymidine (**60**).[85] Also interesting is the synthesis of 4'-methoxythymidine (**62**), achieved with *m*-chloroperbenzoic acid in methanol in an oxidation-substitution sequence (*Scheme* 14). In this case the C-C double bond is first oxidized to an epoxide, followed by *in situ* ring opening with methanol.[26,85]



60 **61** **62**

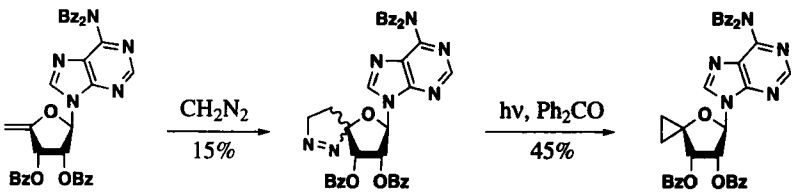


42 **63** **64**

Scheme 14

Besides the functionalization of C-4' with halogen, azide and alkoxy substituents shown above, 4',5'-unsaturated nucleosides also enable the introduction of alkyl side-chains at this important nucleosidic carbon centre. An example is the alkylation reaction of the enamine **42** with allyl bromide. The resulting ammonium salt **63** undergoes a Claisen-type rearrangement, during which the allyl group migrates from the quarternary nitrogen to C-4'. Aqueous hydrolysis of the intermediate iminium salt to an aldehyde and its subsequent sodium borohydride reduction leads to an 4'-allylated uridine **64** in an epimeric mixture (*Scheme* 14).[76]

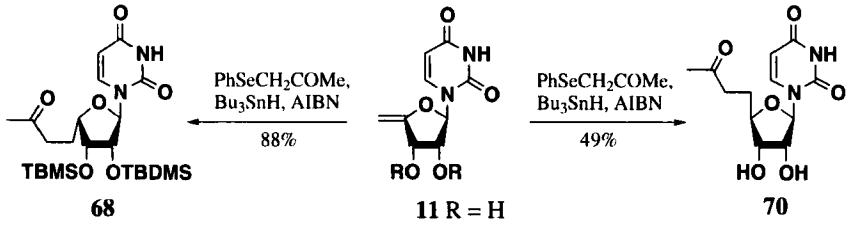
The cycloaddition of diazomethane to the 4',5'-unsaturated adenosine **65** produced a diastereomeric mixture of the unstable 4'-spiropyrazoline derivative **66**. Its sensitized photochemical extrusion of nitrogen provided the unique 4'-spirocyclopropane nucleoside **67** (*Scheme* 15).[86]



65 **66** **67**

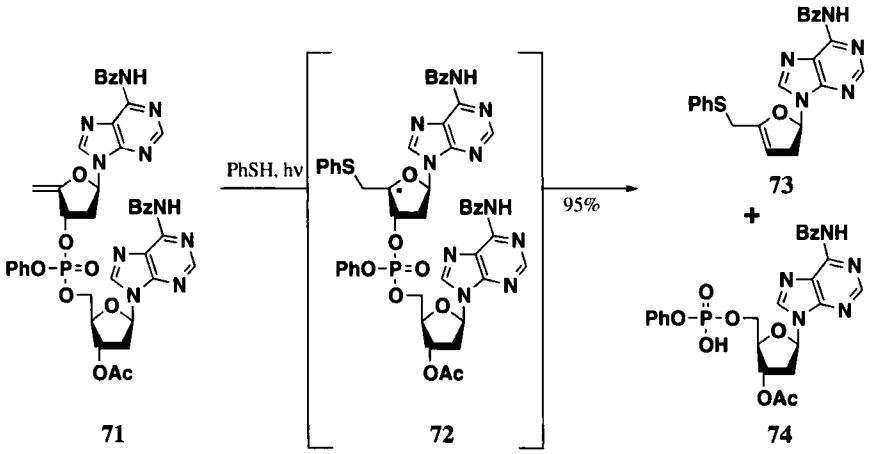
Scheme 15

The addition of carbon-centered radicals to the exocyclic enol ether moiety of unsaturated nucleosides represents an excellent method for the convenient elongation of the 4',5'-sidechain of nucleosides. Phenylseleno compounds are appropriate radical precursors for this C-C bond formation. It turns out that the protecting group at the C-2' and C-3' hydroxyl groups has a profound impact on the stereochemical outcome of the addition. In the radical reaction with phenylselenoacetone and tributyltin hydride the 3',4'-unprotected uridine **11** selectively yields the β-D-ribo product **70**, whereas its *tert*-butyldimethylsilyl protected derivative **69** produces exclusively the α-L-lyxo nucleoside **68** in high yield (*Scheme* 16).[87]



68 **11** R = H **70**

69 R = TBDMS



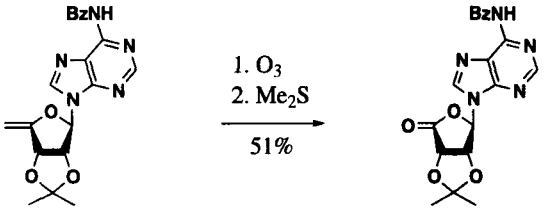
71 **72** **73** + **74**

Scheme 16

4',5'-Unsaturated nucleotides proved to be appropriate precursors for model studies on the mechanism of the anaerobic radical induced DNA strand cleavage.[88-91] Important intermediates hereby seem to be 4'deoxyribonucleotide radicals like **72**. The addition of benzenethiyl radicals to the dinucleotide **71** leads to the formation of radical **72**, which undergoes rapid fragmentation via a 3',4'-radical cation intermediate into the endocyclic enol ether **73** and one equivalent of the corresponding 5'-phosphorylated 2'-acetyldeoxyadenosine **74** (*Scheme* 16).[91] Because of the excellent ionic leaving ability of phosphate, the C-O bond cleavage is much faster than the competing hydrogen abstraction from thiophenol. In aqueous solution, **73** hydrolyzes directly under ribofuranose-ring opening to an acyclic ketoaldehyde, which was evidently found as a DNA strand scission product.

2. Other Reactions

4',5'-unsaturated nucleosides like **75** are readily converted into the corresponding base-labile nucleoside lactones **76** by standard ozonolysis (*Scheme* 17).[35]



75 **76**

Scheme 17

4',5'-nucleosidic olefines have also been used as building blocks in radical copolymerizations with maleic anhydride,[25] vinylene carbonate[25] and acrylic anhydride.[92] The strictly alternating arrangement of the resulting polyribonucleotide analogues originates from charge-transfer complexes of the monomer pairs during copolymerization.

III. CONCLUSION

As we have seen, there are several methods available for the installation of an *exo*-methylene group at the 4',5'-terminus of nucleosides. Its double bond provides an excellent handle for further chemical manipulations. This easy access to 4'-substituted or 5'-chain-elongated nucleosides makes 4',5'-unsaturated nucleosides especially valuable intermediates in nucleoside chemistry.

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