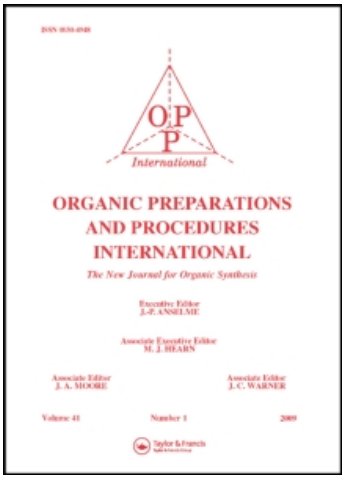

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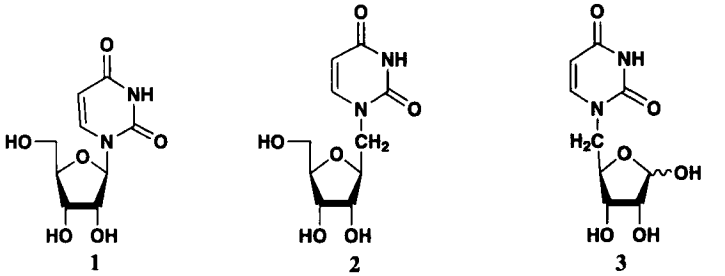
INTRODUCTION

Both naturally occurring and synthetic analogs of nucleosides possess significant antibacterial, antiviral and antitumor activities.[1-3] There is a special class of nucleosides derivatives, in which the nucleobase and the sugar are separated by a carbon bridge, thus making them more resistant to hydrolytic or enzymatic cleavage compared to the relatively reactive aminal linkage of common nucleosides. In addition to greater conformational flexibility and rotational freedom, the base moiety is located further away from the other nucleoside recognition sites, like the sugar ring oxygen and hydroxy groups. In oligonucleotides composed of these modified nucleosides, the distance between backbone and base moieties is increased thus lowering the electrostatic repulsion by maintained ability to build Watson-Crick base pairs with a natural DNA or RNA strain.

Such special nucleosides can be divided into *1'-homonucleosides* and *reversed nucleosides* (*Scheme 1*). *1'-Homonucleosides* are compounds, in which C-1' of the carbohydrate and a nitrogen (1'-homo-*N*-nucleosides) or a carbon atom (1'-homo-*C*-nucleosides) of the



Scheme 1

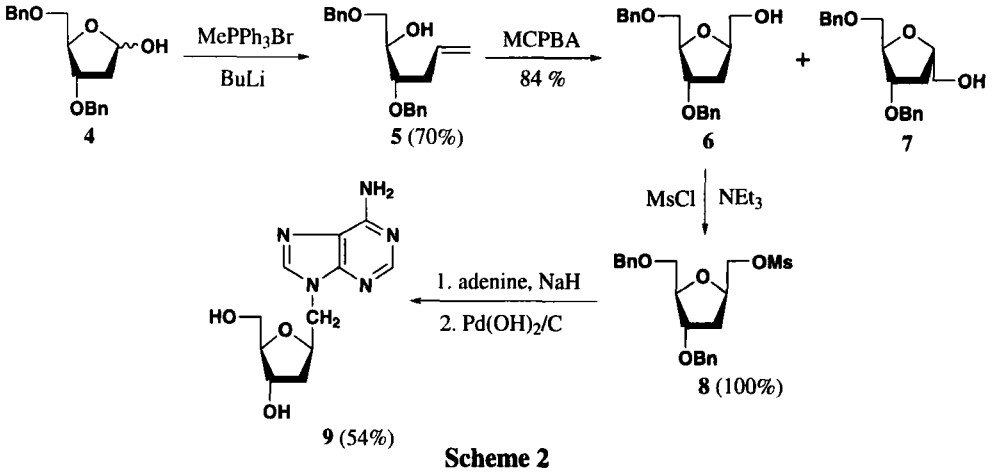
heterocyclic nucleobase are linked *via* a methylene group. In *reversed nucleosides* the methylene bridge between the sugar and the base is constituted from the C-5' of the furanose. Although both classes are non-glycosidic nucleoside analogs, a major difference between them is that *reversed nucleosides* still possess an anomeric center (although not involved in the nucleobase linkage) and *1'-homonucleosides* do not. The presence of an anomeric effect in a natural nucleoside is one of the most important factors which contributes to the conformational behavior of the nucleoside and, hence, to its biological features. These physiological properties may change dramatically, if the anomeric aminal function is removed from the nucleoside. The exchange of the furanose by a carbocyclic five-membered ring (carbocyclic nucleosides)[4-6] and the linkage of the sugar C-1 to a carbon atom of the nucleobase (*C*-nucleosides)[7-9] are other possibilities for the removal of the *N*-glycosidic linkage besides the introduction of a carbon bridge between the base and carbohydrate parts. These resulting *1'-homonucleosides* and *reversed nucleosides* are closely related structurally, but their synthetic approaches are completely different. *Reversed nucleosides* are usually obtained by nucleophilic substitution of the carbohydrate's 5-hydroxyl group by the nucleobase, whereas *1'-homonucleosides* are in principal derivatives of *C*-glycosides.[10-12] The preparation and transformation of these special nucleosides have never been summarized before and will be discussed in this review.

I. SYNTHESIS OF 1'-HOMONUCLEOSIDES

1. Preparation of 1'-Homo-N-nucleosides

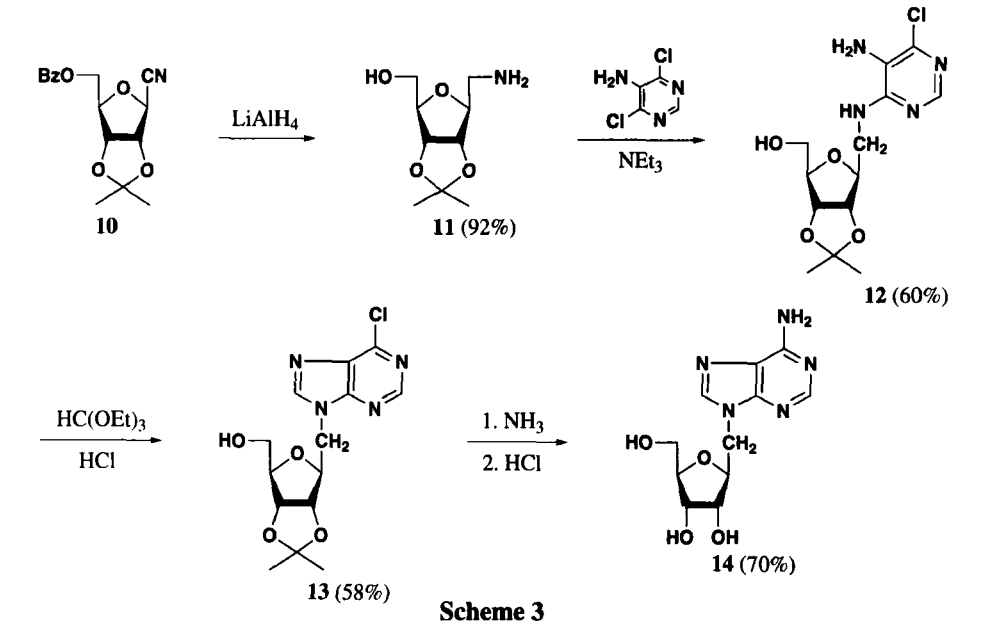
1'-Homonucleosides are in general higher sugar homologs of their natural counterparts. This is also true for 5'-homonucleosides, which are characterized by an additional methylene group between C-5' and the primary hydroxy group.[13,14] Other homonucleosides (2'-homonucleosides[15,16] and 3'-homonucleosides[16,17]), in which the methylene group is interposed between C-2' or C-3' and the corresponding hydroxy function, belong rather to the class of nucleosides with branched-chain sugar moieties. The introduction of a methylene group into the furanose between the ring oxygen and C-1',[18] C-1' and C-2',[19] C-2' and C-3',[20] C-3' and C-4' [21] and C-4' and the ring oxygen[22] leads to homonucleosides with hexopyranose moieties. Finally, homonucleosides with ring-expanded nucleobases, bearing an additional methylene group in the aromatic heterocycle, are also known.[23] Out of all these different homonucleosides, only 1'-homo derivatives possess a *C-glycosidic effect*, resulting in an extremely stable linkage between sugar and nucleobase.

In principle, there are two major methods for the synthesis of 1'-homo-*N*-nucleosides. One possibility is the introduction of the complete nucleobase by nucleophilic substitution of a leaving group at the exocyclic methyl group of a *C*-glycoside. By this method, the preparation of 1'-homonucleosides has been described by displacement of *C*-glycoside tosylates,[24-27] mesylates,[28] bromides,[29] iodides[30], pyridinium salts[31] and hydroxy groups (under Mitsunobu conditions).[32,33] An especially short approach to 1'-homo-deoxynucleosides is depicted in *Scheme 2*.[28] The 2-deoxyribose derivative **4** was converted in two steps to a mixture of the two C-glycosides **6** and **7** by a Wittig-ring opening/epoxidation-ring closure sequence. Compound **6** was transformed into its *O*-mesyl derivative **8**, which was then treated with sodium hydride and adenine to afford 1'-homodeoxyadenosine (**9**).



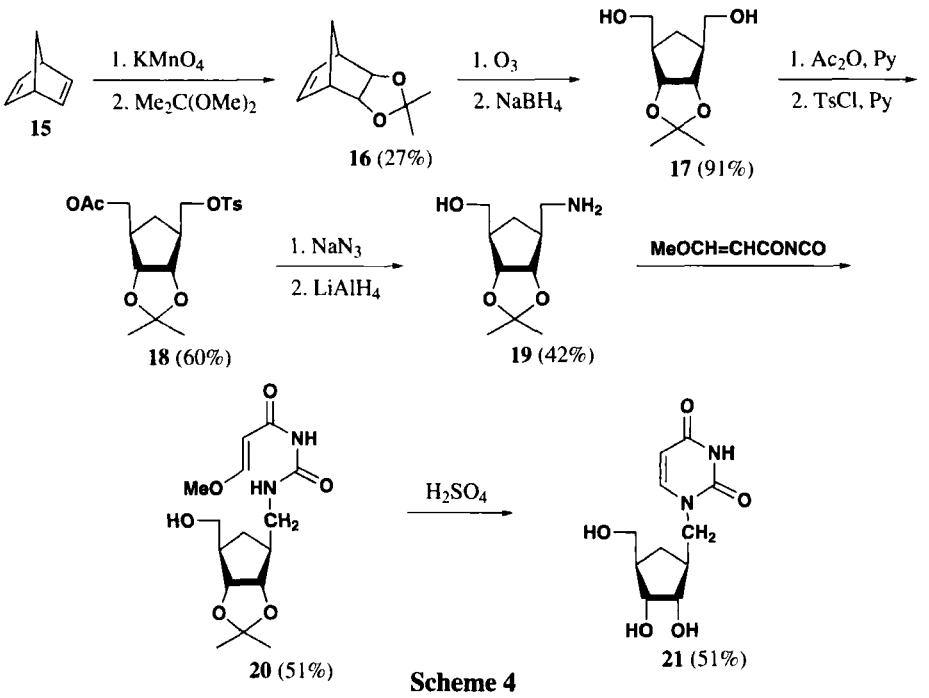
Scheme 2

Another possibility is the *de novo* construction of the nucleobase. For this approach, primary amines such as **11** are important intermediates because they were utilized in several syntheses of 1'-homoadenosine,[34-37] -cytidine,[34,38] -uridine[30,34,38] and -thymidine.[39,40] The coupling of **11** with 5-amino-4,6-dichloropyrimidine led to **12**, which could be further transformed to 1'-homoadenosine (**14**) by purine cyclization, ammonolysis and deprotection (*Scheme 3*).[36] The biocatalytic oxidative cyclization of an acyclic nucleoside to a 1'-homo-*N*-nucleoside was achieved by the aerobic bacterium *Acetobacter suboxydans*.[41] In addition, the synthesis of 1'-bis-homonucleosides in which the carbohydrate and nucleobase are connected via an ethylene linker has been described.[32,40,42-49]



Scheme 3

The connection of three-membered,[50-53] four-membered,[54-56] five-membered[57-64] and six-membered[65,66] carbocyclic sugars and aza-sugars[67] to nucleobases across a methylene bridge furnished 1'-homonucleoside derivatives. *Scheme 4* shows an approach to the carbocyclic congener of homouridine **21** from commercially available norbornadiene (**15**).[58] The key intermediate is the amino alcohol **19**, which was treated with β-methoxyacryloyl isocyanate. Cyclization of the resulting acryloyl urea **20** in acidic medium led to concomitant hydrolysis of the isopropylidene protecting group, thus affording the carbocyclic 1'-homonucleoside **21**.

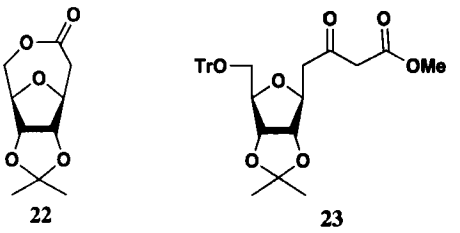


Scheme 4

1'-Homo-*N*-nucleosides are compounds with a carbon linker between a nitrogen atom of the nucleobase and the sugar. Nucleoside derivatives in which these parts are joined *via* another one-atom bridge consisting of a nitrogen,[68] oxygen[69-72] or sulfur atom[73] are known as well.

2. Preparation of 1'-Homo-C-nucleosides

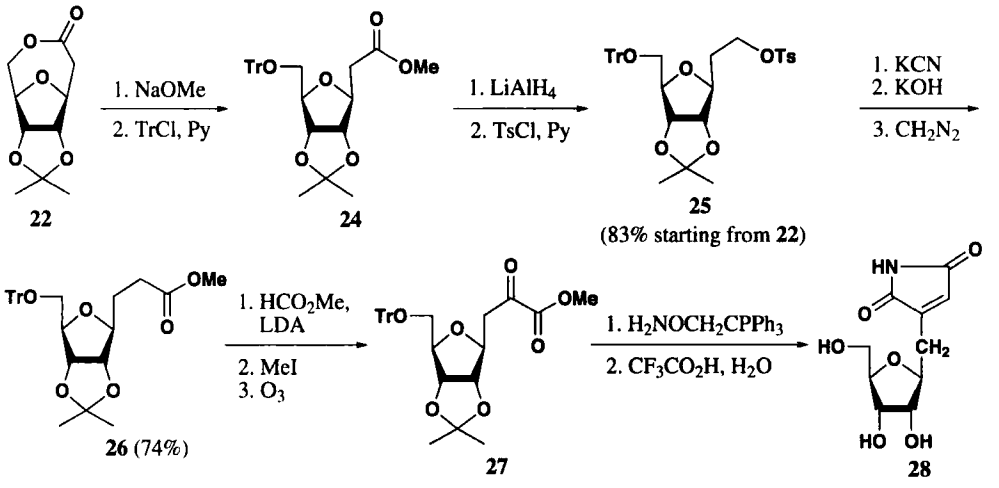
1'-Homo-*C*-nucleosides are compounds with a methylene bridge between a carbon atom of the nucleobase and C-1' of the furanose. There are in principle two possible pathways to such compounds. One approach employs special *C*-glycosides, which carry the sugar part of the desired nucleoside, as starting materials for the elaboration of the nucleobase. Two compounds which have found ample application are the tricyclic lactone **22**[74-79] and the β-ketoester **23**[80-83] (*Scheme 5*).



22 23

Scheme 5

Since the initial isolation of showdomycin from *Streptomyces showdoensis*, this *C*-nucleoside antibiotic has elicited considerable attention because of its significant antibacterial and antitumor activities and of its enzyme inhibitory abilities.[84] An efficient synthesis of its homolog **28** was worked out starting from lactone **22**, which after ring-opening and several chain-elongation steps led to the α-ketoester **27**. Wittig condensation of **27** with carbamoylmethylenetriphenylphosphorane gave the desired maleimide scaffold; the removal of the protecting groups afforded 1'-homoshowdomycin **28** (*Scheme 6*).[77]

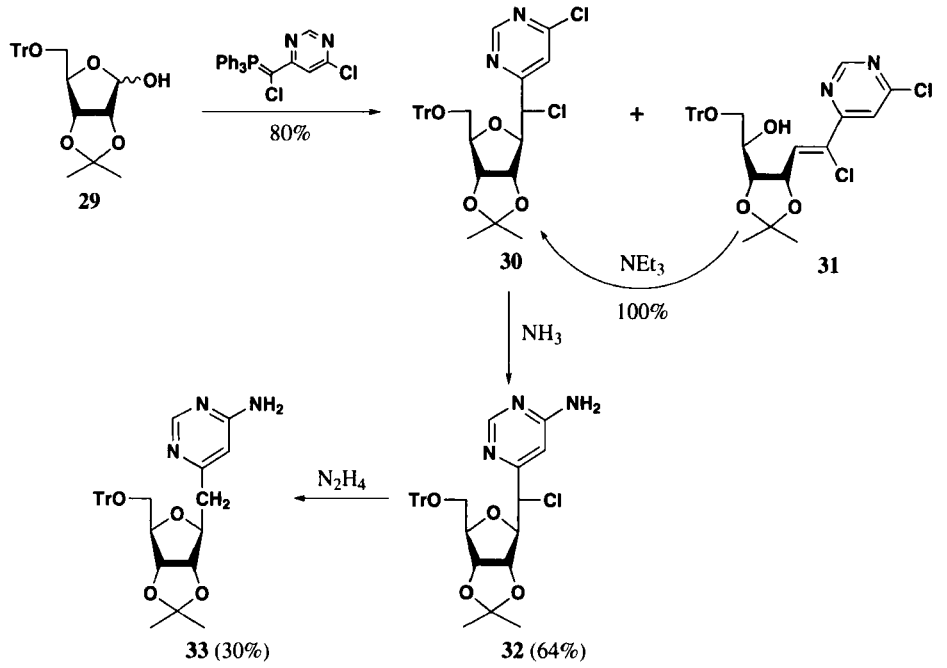


22 24 25 (83% starting from **22**) 26 (74%) 27 28 (56% starting from **26**)

Scheme 6

Another route to 1'-homo-*C*-nucleosides is the Wittig reaction between a sugar hemiacetal and the phosphorane of a nucleobase.[80,81,85-88] For example, the reaction between the protected ribose **29** and (6-chloropyrimidin-4-yl)methylenetriphenylphosphorane gave a mixture of the 1'-homo-*C*-nucleoside **30** and the ring-openend olefin **31**, which could be cyclized to **30** with the aid of a base in quan-

titative yields. Subsequent exchange of the aromatic chlorine by amine and removal of the aliphatic chlorine led to the 1'-homo-*C*-nucleoside **33**. (*Scheme 7*).[85,86,88]



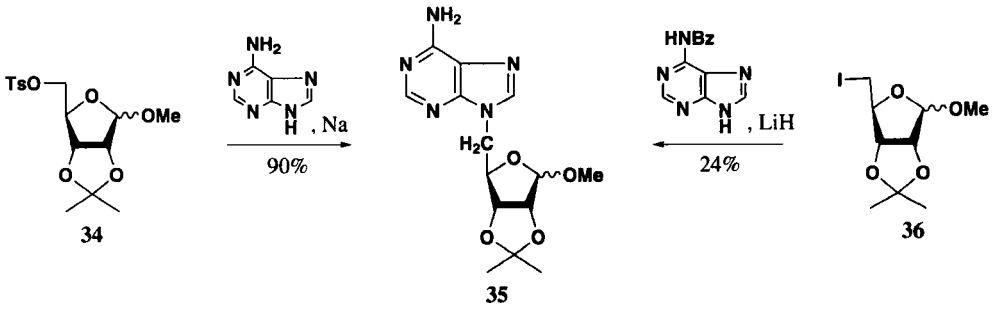
Scheme 7

The nucleophilic displacement of an anomeric sugar halide by a stabilized nucleobase-carbanion[87] and the dehydrative cyclization of acyclic *C*-nucleosides with *p*-toluenesulfonyl chloride[89,90] have also been described as alternative approaches to 1'-homo-*C*-nucleosides.

II. SYNTHESIS OF REVERSED NUCLEOSIDES

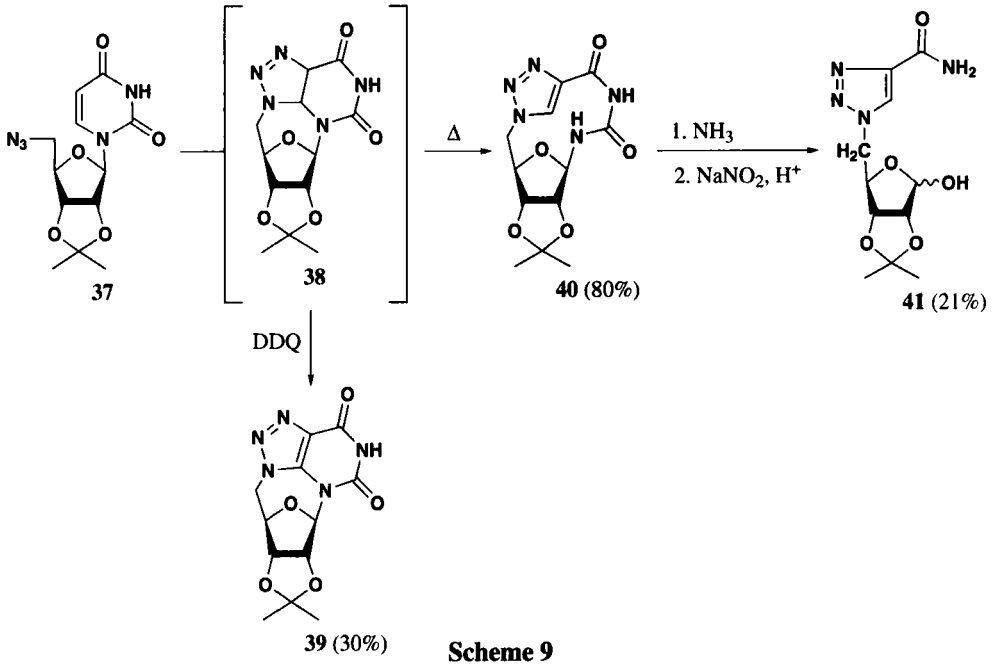
Nucleosides in which the adenine ring has been moved from the 1'-position to the 5'-position are resistant to degradation by the enzyme *Adenine deaminase*. These findings provide further evidence for the importance of the 5'-hydroxy group as a structural requirement for significant substrate activity of nucleosides.[91]

There are several routes to reversed nucleosides. One approach for the creation of the new C-N bond is the Mitsunobu reaction between the hydroxy function at C-5 of the ribofuranose with the nucleobase.[92] Another possibility is the transformation of this hydroxy group into a tosylate,[91,93-109] brosylate[110] or iodide[94,111] and the nucleophilic substitution of these groups by the nitrogen heterocycle, as demonstrated by the synthesis of the reversed adenosine **35** in *Scheme 8*.[109,111]



Scheme 8

The transformation of the 5-hydroxy group of the furanose into an azide function and its 1,3-dipolar cycloaddition with suitable alkenes and alkynes has also been successfully applied to the preparation of reversed nucleosides.[112-118] An interesting intramolecular version is shown in *Scheme 9*, where the 5'-azido group of **37** undergoes thermally-induced addition to the 5,6-double bond of the uracil moiety. The instable intermediate **38** can be oxidized to the isolizable cyclonucleoside **39**, but simple heating in toluene affords the macrocycle **40** through an unprecedented N^1–C^6 cleavage. Compound **40** can be transformed to the reversed triazole nucleoside **41** by ammonolysis and diazotization.[117,118] Furanosides with primary amine functions in the terminal position (C-5) could also be elaborated into reversed nucleosides by different methods.[93,113,114,119]



Scheme 9

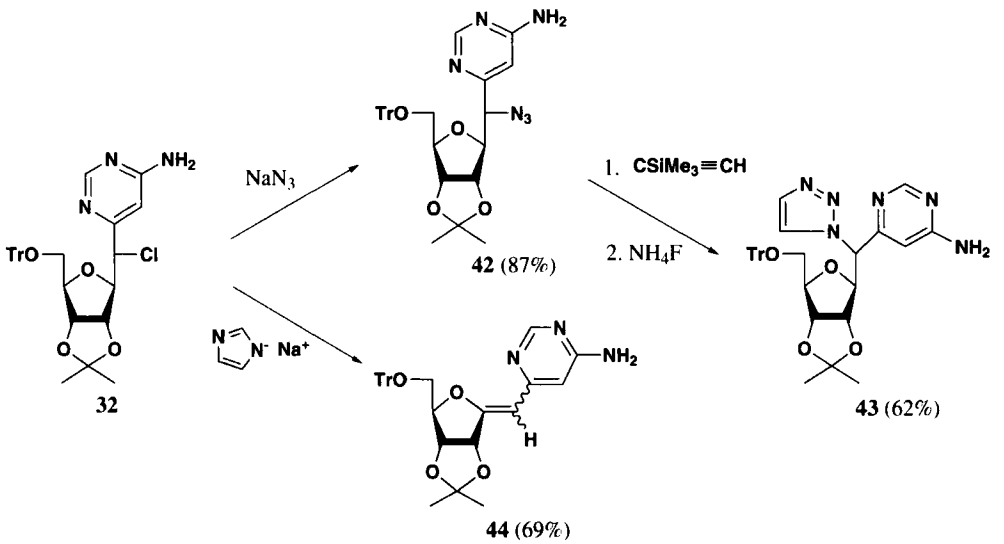
III. REACTIONS OF 1'-HOMONUCLEOSIDES

1. Reactions of 1'-Homo-N-nucleosides

Several 1'-homo-*N*-nucleosides have been converted into the corresponding nucleotides by phosphorylation of hydroxy groups of the sugar moiety.[24,39,40,120-122] The resulting 1'-homo-*N*-nucleotides could be incorporated into oligodeoxyribonucleotides (DNA fragments)[24,39,40,120,121] as well as into hammerhead ribozymes.[121] Some of these homo-nucleotide monomeres or oligomeres have been reported to exhibit efficient antiviral activity against herpes simplex virus type-1 by inhibition of its *Uracil-DNA glycosylase*.[120,121] The derivatization of functional groups in the nucleobase part of 1'-homo-*N*-nucleosides has also been described.[28,29,34,36,38,123]

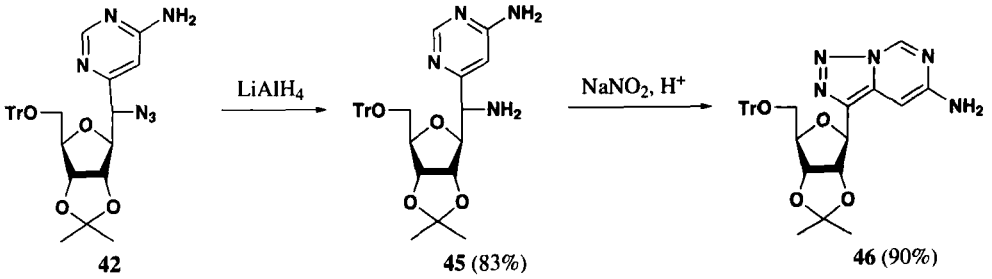
2. Reactions of 1'-Homo-C-nucleosides

The synthesis of unique "split" nucleosides is made possible starting from 1'-homo-*C*-nucleosides. "Split" nucleosides are analogs of purine nucleosides in which both five- and six-membered heterocycles of the purine are separated from each other. In this way, although the recognition elements for molecular interaction of the purine base are disconnected, they are still present. Upon a 1,3-dipolar cycloaddition with trimethylsilylacetylene, azide **42** was converted to the "split" nucleoside **43**. An attempt to introduce the second nucleobase of the desired "split" nucleoside by nucleophilic substitution of the secondary chloride **32**, led to the unsaturated 1'-homo-*C*-nucleoside **44**, in which the sugar and the carbon bridge are linked by a C-C double bond (*Scheme 10*).[85]



Scheme 10

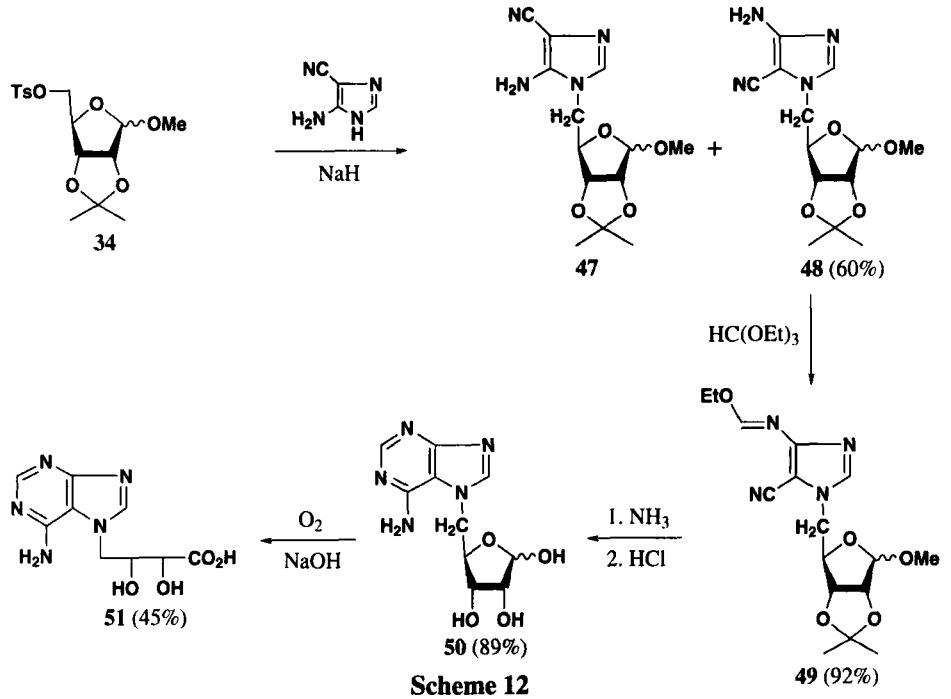
1'-Homo-*C*-nucleosides have also been used as efficient intermediates in the synthesis of special bicyclic *C*-nucleosides like **46**, which otherwise would be difficult to prepare (*Scheme 11*).[86,87]



Scheme 11

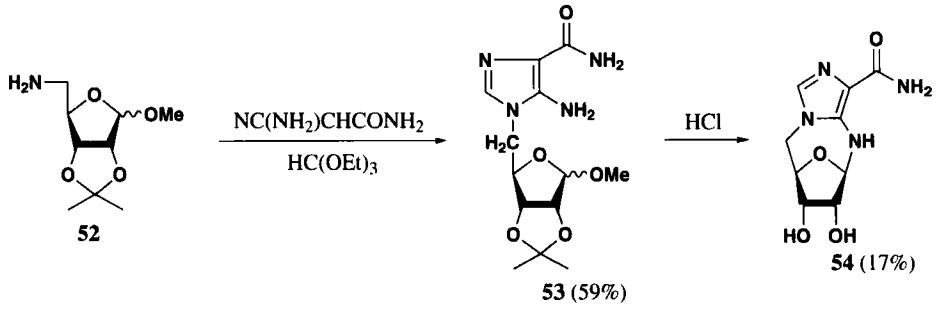
IV. REACTIONS OF REVERSED NUCLEOSIDES

Reversed nucleosides have been transformed into their acyclic open-chain analogs by oxidative ring-opening with oxygen in an alkaline medium[104-109] or with sodium periodate (often in the presence of a ruthenium catalyst).[92,96-100,103] Most of these investigations have been stimulated by the finding that the acyclic nucleoside D-eritadenine (lentinacin, 4-(adenin-9-yl)-2(*R*)-3(*R*)-dihydroxybutyric acid), a hypocholesterolemic substance isolated from the edible Japanese mushroom shiitake (*Lentinus edodes* SING.), strongly inhibits *S-adenosyl-L-homocysteine hydrolase*. Like other inhibitors of this enzyme, which is important for the regulation of biological methylations, eritadenine also exhibits a significant antiviral effect.[96] Thus unnatural derivatives of eritadenine became of interest. The reversed nucleoside **50**, which is obtainable in four steps from 4-amino-5-cyanoimidazole and the tosylated ribose **34**, was used as key intermediate in a short synthesis of the N^7 isomer **51** of D-eritadenine (*Scheme 12*).[104]



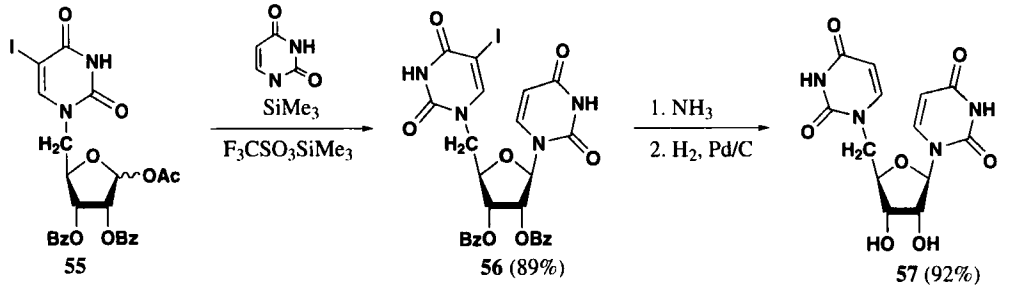
Scheme 12

Reversed nucleosides with an amino function in the nucleobase could be transformed into interesting cyclonucleosides under acidic conditions.[112-114] The cyclization occurs regioselectively, because final ring-closure to **54** involves attack by the heterocyclic amine on the anomeric center with displacement of the glycosidic hydroxy group (*Scheme 13*).[114]



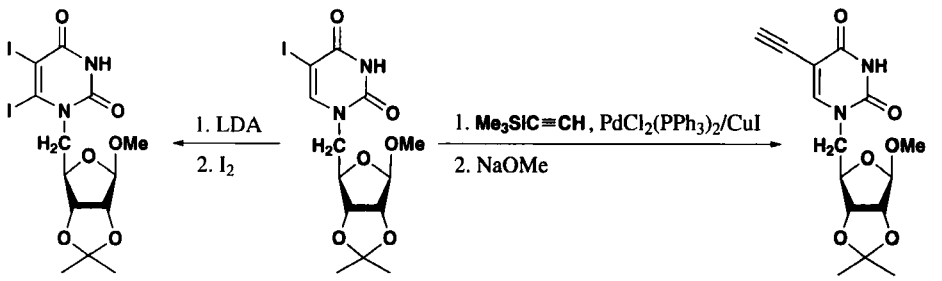
Scheme 13

The syntheses of "double-headed" nucleosides has been facilitated by application of reversed nucleosides as key intermediates.[95,124] "Double-headed" nucleosides are compounds with two identical or different nucleobases linked to C-1' (normal attachment) and to C-5' (reversed attachement) of a furanose. These modified nucleosides may simultaneous bind and recognize two complementary bases by Watson-Crick type base-pairing. Alternatively, "double-headed" nucleosides may interact with a polynucleotide using one base for pairing and the other as an intercalator stabilizing the base pair. "Double-headed" nucleosides have been prepared earlier in low yields by introduction of the reversed linked nucleobase into the 5'-position of a nucleoside.[125-127] A better way seems to be to form the two nucleosidic C-N bonds in opposite order, because the reversed nucleoside **55** was easily transformed into the "double-headed" nucleoside **56** by standard Vorbrüggen coupling. Subsequent sugar deprotection and iodine removal affords the interesting nucleoside **57** bearing two uracil bases in high yield (*Scheme 14*).[95]



Scheme 14

Finally, reversed nucleosides have been subject to further functionalization of the nucleobase. The reversed 5-iodo-uridine **59** could be converted into the 5,6-diiodo and 5-ethynyl derivatives **58** and **60** by standard lithiation or palladium-catalyzed cross-coupling methodologies (*Scheme 15*).[124]



58 (15%) **59** **60** (71%)

Scheme 15

V. CONCLUSION

As we have seen, there are several methods available for the preparation of nucleosides with a carbon bridge between both sugar and base components. The resulting 1'-homonucleosides and reversed nucleosides not only possess interesting biological properties but are also well suited for further chemical manipulations. The easy access to such important nucleoside derivatives like "split" and "double-headed" nucleosides, as well as special cyclonucleosides and bicyclic *C*-nucleosides demonstrates, that 1'-homonucleosides and reversed nucleosides are valuable intermediates in nucleoside chemistry.

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