C-Nucleosides: Synthetic Strategies and Biological Applications

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1. Introduction

While natural and synthetic *N*-nucleosides are vulnerable to enzymatic and acid-catalyzed hydrolysis of the nucleosidic bond, their *C*-analogues are much more stable. Several *C*-nucleosides are naturally occurring compounds, e.g., pseudouridine (isolated from the yeast *t*-RNA) and showdomycin (an antibiotic). Development of novel synthetic methodologies allowed the preparation of a large variety of synthetic analogues, which found numerous applications in medicinal chemistry and chemical biology. Most important biologically active *C*-nucleosides are the inhibitors of purine nucleosides phosphorylase or IMP dehydrogenase. A number of artificial aryl-*C*-nucleosides capable of π-stacking are being vigorously investigated as building blocks in chemical biology. In the past few years, several Artificial Expanded Genetic Information Systems (AEGIS)[1] have been successfully developed as prime examples of synthetic biology, a newly emerging interdisciplinary area, with the ultimate goal to design systems where high-level behaviors of the living matter are mimicked by artificial chemical systems.[2,3]

A large array of synthetic strategies toward *C*-nucleosides has been developed to date, and the compounds were used in a wide range of applications. Several reviews covering this area have appeared in the last 15 years.[4−11] However, some of them are very general reviews on nucleosides (with little focus on *C*-nucleosides), while others are very specialized, focusing only on some aspects of the *C*-nucleoside synthesis or applications. To date, no comprehensive review dealing with all synthetic approaches and assessment of their pros and cons has been published. In this comprehensive review article, a critical overview of all individual synthetic approaches and their merit is presented in context of the current needs of medicinal chemistry and chemical biology. Beside the synthetic approaches, applications of *C*-nucleosides in medicinal chemistry (e.g., antiviral or antitumor agents), chemical biology (e.g., studying of certain enzyme reactions and extension of the genetic alphabet), and other areas (e.g., fluorescent labeling and artificial DNA constructs, etc.) are summarized and critically evaluated, and some prospective future developments both in the synthesis and in potential applications are outlined.

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Jan Štambaský was educated at the Institute of Chemical Technology (ICT), Prague, Czech Republic (M.Sc. in 2003). After a short stint with Dr. M. Hocek at the Institute of Organic Chemistry and Biochemistry (IOCB), Academy of Sciences of the Czech Republic, Prague, he joined Prof. P. Kočovský at the University of Glasgow, U.K., and worked on new modular synthetic approaches towards *C*-nucleosides utilizing transition metal catalyzed and enzymatic reactions. He received his Ph.D. from the University of Glasgow in 2008 and then started his professional career in green-energy business in his home country. Expansion of his activities led him to setup of a new company NovaEnergo Ltd. in December 2008, where he is pursuing development and utilization of advanced biochemical approaches enhancing the yield and overall efficiency of the biogas and biomethane production processes. In 2009 he was appointed a member of the executive board of the European Biogas Association.

Michal Hocek was educated at the Institute of Chemical Technology (ICT), Prague, Czech Republic (M.Sc. in 1993) and earned his Ph.D. at Institute of Organic Chemistry and Biochemistry (IOCB) of the Academy of Sciences of the Czech Republic (ASCR), Prague, with Prof. A. Holý in 1996. After a postdoctoral stay at UCL Louvain-la-Neuve (Belgium) with Prof. L. Ghosez in 1997, he returned to IOCB, where he started his independent research and became a group leader in 2003. In 2006 he completed his habilitation at the ICT, Prague, where he now serves as an external Associate Professor; in the same year he received his D.Sc. degree. In 2007 he was appointed the head of the Senior Research Group in Bioorganic & Medicinal Chemistry at the IOCB. His current research interests include development of synthetic methodologies based on transition metal-catalyzed reactions, heterocyclic chemistry, and bioorganic and medicinal chemistry of modified nucleosides, nucleotides, and nucleic acids.

2. C-Nucleosides in Chemical Biology

The structure of duplex DNA is based on the complementary Watson−Crick hydrogen bonding patterns of **A**−**T** and **G**−**C** pairs (Chart 1).[12] Replacement of the natural nucleobases by diverse surrogates has become very popular in recent years.[13] The original aim just to investigate the structure and function of nucleic acids (NA) was extended toward three main goals: (1) formation of stabilized duplexes,[14] (2) design of universal nucleobases not discriminating between the complementary bases,[15] and (3) extension of the genetic alphabet.[16] The utilization of small organic molecules (nucleoside and nucleotide analogues) in studying enzyme mechanisms (mainly polymerases or enzymes of nucleic acid metabolism) is another important area of application. Because of the increased stability and modified properties, *C*-nucleosides have been extensively studied and many promising examples of their use in chemical biology were reported.

Pavel Kočovský was raised and educated in Prague, Czechoslovakia (now Czech Republic). He received an M.Sc. in 1974 from the Institute of Chemical Technology (ICT), Technical University, Prague, where he did his diploma work with Prof. O. Červinka in the area of asymmetric reactions. He obtained a Ph.D. in 1977 from the Czechoslovak Academy of Sciences, Institute of Organic Chemistry and Biochemistry (IOCB), Prague, where he worked on steroid chemistry under the guidance of Dr. V. Černý and Prof. F. Šorm. He was then appointed to an academic position at the same Institute, which he held for thirteen years (1977−1990). During this period, he also taught various advanced courses at Charles University, Prague. He did his postdoctoral work with Prof. J. E. McMurry at Cornell University, Ithaca, NY, U.S.A. (1983−1984), and later spent a sabbatical year with Prof. J.-E. Bäckvall at the University of Uppsala, Sweden (1989−1990). In January 1991 he moved to the U.K. and started a new academic career, first at the University of Leicester, where he spent almost nine years, obtained a D.Sc. (1993), and raised in the ranks to full professor. In 1999 he moved to the University of Glasgow as the Sir William Ramsay Professor of Chemistry. His research interests span organic and organometallic chemistry, stereoselective reactions, asymmetric catalysis, reaction mechanisms, and synthesis of functional molecules.

2.1. Extension of the Genetic Alphabet

The quest for an extension of the genetic alphabet is a complex project of paramount importance. Expanding the current four-base code to six bases (by adding one additional base-pair) would offer 216 combinations of three-letter codons, which could ultimately encode proteins containing nonbiogenic amino acids and thus engineer unnatural properties. It is generally accepted that the high-fidelity and efficient

Chart 1. Natural Watson−Crick Base Pairs

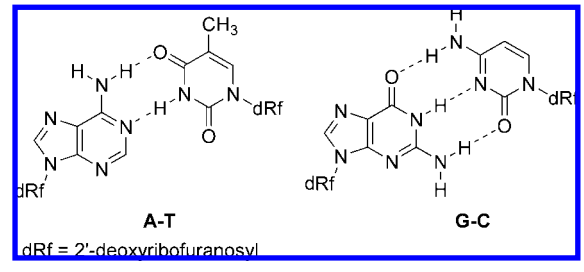
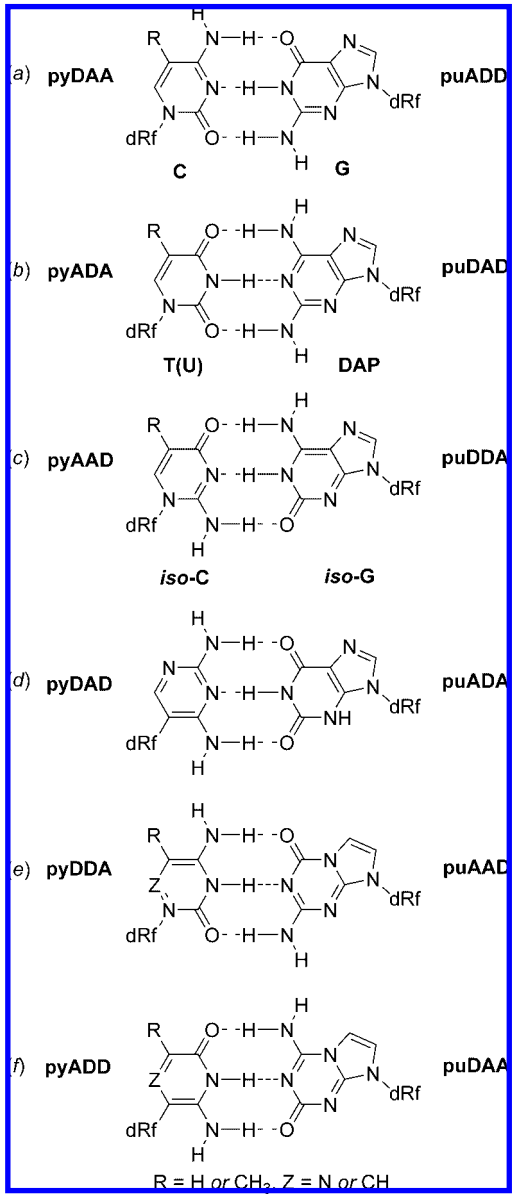


Chart 2. Base-Pairing by Hydrogen Bonding



replication is the key step in the extension of the genetic alphabet, while the transcription and translation are not as demanding in terms of fidelity. Therefore, the major efforts are focused on the development of a stable third base-pair that would be efficiently replicated with high fidelity.[17] Recent efforts have resulted in designing and construction of a number of candidate base-pairs that are stable within the DNA duplex. However, the enzymatic replication is a much more challenging problem and, as a result, only very few of these artificial base-pairs have been efficiently and selectively replicated to date. The candidate base-pairs draw upon unnatural hydrogen-bonding topologies as well as upon the shape complementarity,[18] hydrophobic forces,[19] metal-bridged base-pairing,[20] and even covalent cross-linking.[21]

2.1.1. Artificial Base-Pairs Based on Hydrogen Bonding

The concept of hydrogen-bonding patterns and shape complementarity was pioneered by Benner (e.g., isoguanosine, *iso*-**G**; isocytidine, *iso*-**C**; Chart 2, entry c).[18] Further development has led to the introduction of other donor−acceptor (**D**−**A**) purine−pyrimidine pairs[22] and finally to a generalization of the Watson−Crick nucleobases pairs.[23] In the most general form, the Watson−Crick base-pair joins a six-membered heterocyclic ring (pyrimidine or analogues) with a fused five-/six-membered ring system (purine or analogues) via three H-bonds (Chart 2). Two interbase H-bonds are formed between exocyclic functional groups, whereas one is formed between the heteroatoms of the heterocycles. Donor and acceptor hydrogen-bonding patterns are assigned **D** and **A**, respectively. With three H-bonds, 8 (2^3) H-bonding patterns and 16 independently replicable bases are conceivable within the Watson−Crick geometry, but only 6 of them are readily accessible (Chart 2). In practice, pyrimidine analogues presenting the **pyDAD**, **pyDDD**, and **pyADD** (d–f). H-bonding patterns are difficult to prepare.[24] Furthermore, in order to attain good stacking capabilities, the bases need to be aromatic, and therefore the ring system requires a junction to the carbohydrate in the form of a *C*-glycoside (i.e., a *C*-nucleoside). Several heterocyclic base analogues might meet these criteria. The 6-aminopyridin-2(1*H*)-one structure, which formally presents the correct H-bonding pattern, did not appear to be suitable because it is readily oxidized. Adding an additional N-atom decreases the susceptibility to oxidation but creates an unacceptable tautomeric ambiguity, resulting in low fidelity of the pairing.[25]

Finally, the **pyADD** and **pyDDA** patterns were implemented in the pyrazine ring, while the original purine ring had to be changed to the pyrrolo[3,2-a]triazol ring (Chart 2, entries e, f, $Z = N$). Although different heterocycles can support individual hydrogen-bonding patterns, only some representations of the same pattern are suitable for the artificial genetic systems (Chart 3).[26]

The ability of NA polymerase enzymes to catalyze the template-directed synthesis of duplex oligonucleotides containing some of these artificial base-pairs has been investigated.[27,28] The most important result of these efforts is that the *C*-nucleoside linkage itself has no influence on the enzymatic recognition of the base-pairs with DNA polymerases.[29] The *iso*-**G** and *iso*-**C** base-pairs were successfully

Chart 3. *C*-Glycosidic Heterocycles Capable of Implementing the pyDAD Hydrogen-Bonding Pattern

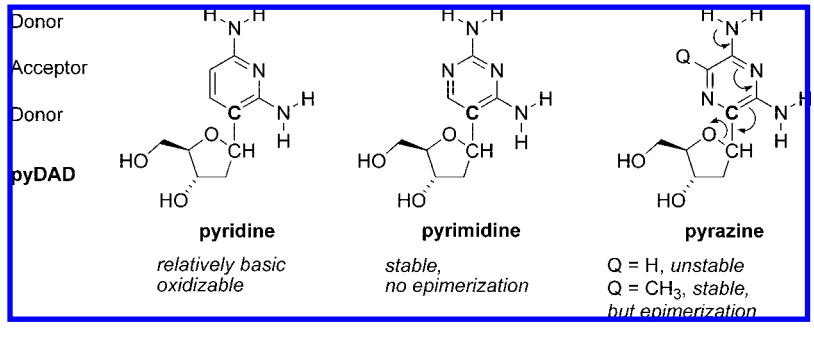
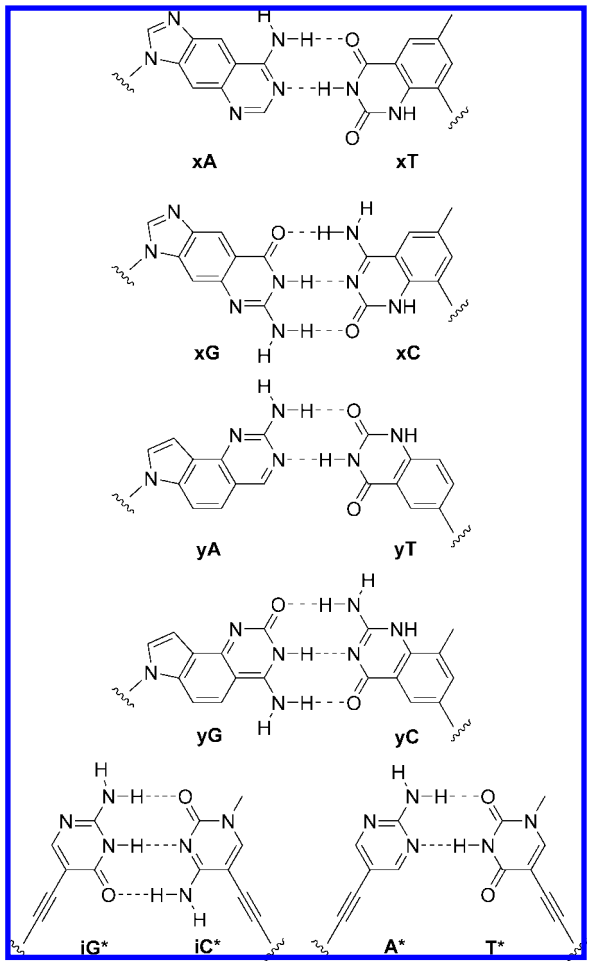
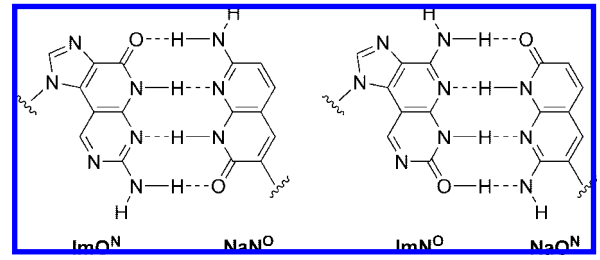


Chart 4. Extended Base-Pairs



incorporated into DNA as complementary base-pairs with the Klenow fragment of DNA polymerase I (KF) from *Escherichia coli*.[30] Furthermore, an additional set of codon−anticodon (*iso*-**C**)/(*iso*-**G**) was introduced and successfully employed to incorporate iodotyrosine (an unnatural amino acid) into a polypeptide.[16a] These encouraging results have triggered a quest for replication of an AEGIS by polymerase chain reaction (PCR). HIV reverse transcriptase was found to be a suitable polymerase for amplification of a six-letter genetic alphabet. One variant of a clinical mutant was found to be suitable (Y188L) and has been further engineered. These improvements eliminated residual nuclease activity and generated a doubly changed HIV reverse transcriptase (Y188L-E478Q) [or the doubly changed HIV reverse transcriptase Y188L-E478Q]. This mutant was able to amplify a DNA containing a **pyDAD−puADA** pair (d in Chart 2) in the PCR reaction. These artificial base-pairs were retained through multiple cycles of amplification. Longer PCR incubation times were required to produce full-length strands than those typical for the natural base-pairs. This successful PCR amplification was the first example of a six-letter genetic code replication.[31] A successful practical application has also been developed, based on polymerase incorporation of AEGIS components. EraGen Biosciences (www.eragen.com) has developed a process where a primer having a fluorescently tagged *iso*-**C** is targeted against a specific region of the SARS-virus DNA sequence. In the real-time PCR, the polymerase incorporates a fluorescence-quencher-tagged *iso*-**G** opposite to *iso*-**C**, thus quenching the fluorescence in the case when SARS virus is present.

Chart 5. Base-Pairs Based on Four H-Bonds



These studies have led to a very important conclusion, namely, that incorporation of *C*-nucleosides into a DNA duplex does not necessarily have a negative effect on the duplex stability.[32] However, because of the inherent population of minor tautomers, this genetic system is not stable in longer term and its in vivo applicability is therefore limited.

A further breakthrough in the field of artificial base-pairs with H-bonding patterns based on *C*-nucleosides was reported by Kool (Chart 4). The natural base-pair analogues, in which the fusion of a benzo-ring increases their size by ca. 2.4 Å (**xA**, **xT**, **xC**, **xG**), were reported three decades ago.[33] However, only recently, Kool introduced the idea of size-expanded genetic systems by using these structures.[34,35] These *linear* expanded analogues form stable base-pairs (Chart 4), and in template, they encode for selective incorporation of natural dNTPs into DNA not only in vitro but also in vivo in bacteria.[36] More recently, a double helix of size-expanded DNA (xDNA), containing all the size-expanded base-pairs, has been prepared.[37] This work has shown that a new, expanded helix adopts β-structure, the right-handed-twisting variant that is the most common natural form of DNA. In a similar manner, Kool introduced *angular* expanded analogues (**yA**, **yT**, **yC**), which exhibit an even better duplex stability when incorporated into DNA.[38] Another type of extended DNA pair was recently reported by Inouye,[39] based on the acetylene-linked *C*-nucleosides bearing pyrimidine heterocycles capable of forming Watson−Crick-like H-bonds (**iG*−iC*** and **A*−T***).

Two interesting pairs of extended imidazolopyridopyrimidines and naphthyridine *C*-nucleosides (**ImO^N/NaN^O** and **ImN^O/NaO^N**) were prepared[40] by Minakawa and Matsuda (Chart 5). Their four-H-bond interactions ensure extra stable duplexes and moderately selective recognition and incorporation[41] by Klenow fragment polymerase (although natural dATP was incorporated against **NaN^O** with almost identical efficiency as that of **ImO^N**TP).

Hirao[42] introduced the nucleobases **y**[43] and **v**[44] (Chart 6) and showed that d**y**TP is incorporated into DNA template opposite to d**x** more efficiently than any natural substrate.[45] Further optimization of the complementary base gave structure **s**. The d**y**TP was incorporated into the template opposite to d**s** with higher efficiency and a 3-fold higher selectivity than opposite to d**x**.[46] The efficiency and fidelity of **y**−**v** pairing were as high as in natural base-pairs. The RNA sequence containing two consecutive **y** bases was successfully transcribed from DNA template containing two **v** bases. The **y**−**s** pair was used for in vitro incorporation of chlorotyrosine into a protein.[47]

An interesting alternative to H-bonds was studied by Sekine,[48] who endeavored to employ halogen bonding for specific base-pairing of artificial nucleosides. Out of several halogenated benzene and pyridine pairs, the most stable and selective binding was found for difluoroiodobenzene (**2FI**)

Chart 6. Hirao's Pyridone Base-Pairs

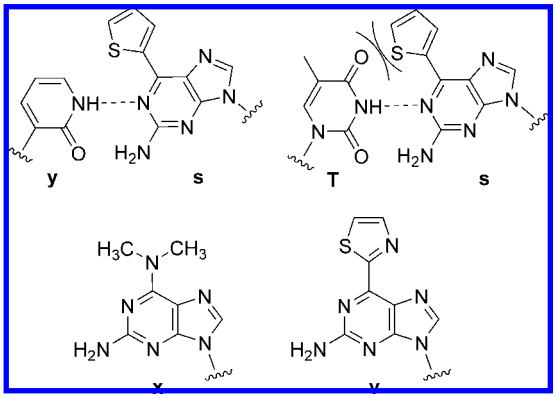


Chart 7. Proposed Halogen-Bonding Base-Pair

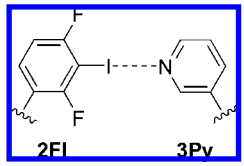
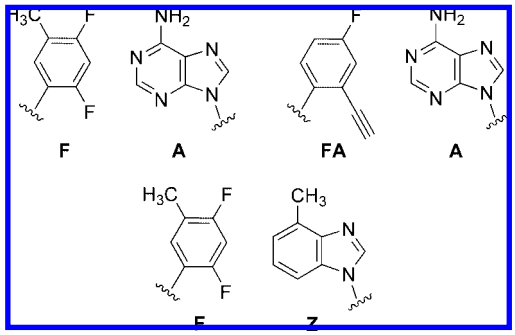


Chart 8. First Generation of Hydrophobic Hetero-Pairs



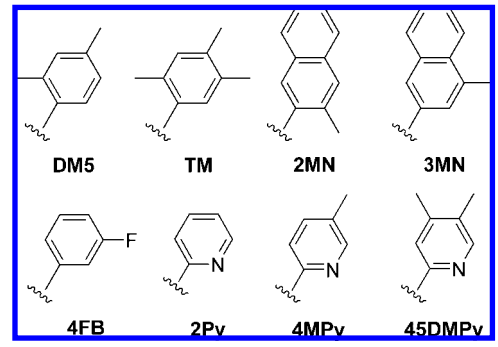
and pyridine (**3Py**) pair, but no evidence for the halogen bond was provided (Chart 7).

It is apparent that unnatural base-pairs that are paired via H-bonding patterns offer promising approaches to expanding the genetic alphabet. However, there are some inherent limitations to their selective replication in DNA, due to the population of minor tautomeric forms of the unnatural bases that form mispairs.[49]

2.1.2. Artificial Base-Pairs Based on Hydrophobic Interactions

Kool was the first to observe that H-bonds are not absolutely necessary for efficient base-pairing and introduced a new concept of hydrophobic interactions.[19,50] The first nucleoside analogue of this kind was difluorotoluene **F**, as an isostere of thymine (Chart 8).[51] Furthermore, the corresponding TTP isoster d**F** triphosphate (d**F**TP), lacking the functionality for H-bonding, was selectively incorporated by DNA polymerases into DNA, opposite to **A** in the template.[52] A heated debate[53] then began as to whether or not some kind of H-bond is formed between **F** and **A**, which ended with the conclusion that it is just a hydrophobic interaction.[54] Somewhat analogous nucleobase **FA**[55] was also found to efficiently pair with **A**. Later on, by studying incorporation and extension using the new base pair **F**/**Z**,[56] lacking the minor-groove H-bond interactions, a new important observation was made that the shape complementarity (without any H-bonds) is sufficient for selective replication; however, for

Chart 9. Artifial Nucleobases Forming Selective Self-Pairs and Efficiently Incorporated by DNA Polymerases



further extension of the growing chain, minor-groove interactions are crucial. More recent work of Kuchta[57] on purine analogues has also confirmed these results. Mechanistic aspects of DNA replications were intensively studied as well.[57]

Kool has further continued the systematic research[58] on halogenated aromatic *C*-nucleosides (i.e., dichloro-, dibromo-, and diiodotoluene) and nonhalogenated toluene to find that these nucleobase surrogates exert increased packing (compared to T) in DNA duplex. Several combinations of related halogenated[59,60] or even nonhalogenated[61] aromatic nucleobase analogues have been found to form stable base-pairs. Recently, the halogenated *C*-nucleosides have been used on numerous occasions[62] as probes in chemical biology to assess the reactivity and/or mechanism of action of polymerases, reverse transcriptase, or thymidine kinase.

The concept of hydrophobic nucleobase-pairs was further elaborated on by Romesberg. By systematic study of diverse substituted benzene, naphthalene, pyridine, and other *C*- and *N*-nucleoside analogues, he has developed a plethora of novel self-pairs and heteropairs. In order to prevent the formation of mis-pairs with canonical nucleobases and to increase the hydrophobicity, one or several methyl groups were often introduced to the artificial aromatic nucleobase-surrogate. At first, Romesberg focused on finding base-pairs forming stable duplexes; later on, he optimized the base-pairs for enzymatic replication and extension. The first generation of hydrophobic base-pairs was based on self-pairs of isocarbostyril and azaindole *N*-nucleosides that formed stable duplexes,

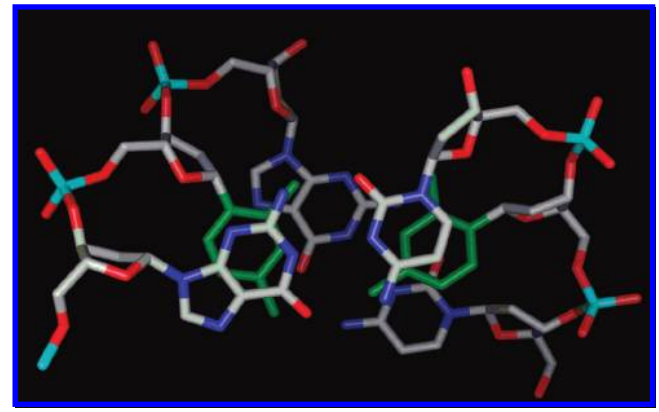


Figure 1. Energy-minimized model structure of the duplex containing the **DM5** self-pair. Intrastrand stacking of the **DM5** (shown in green) self-pair (left). Reprinted with permission from ref 64b. Copyright 1989 American Chemical Society.

Chart 10. Third Generation of Hetero-Pairs Efficiently Replicated and Extended by DNA Polymerases

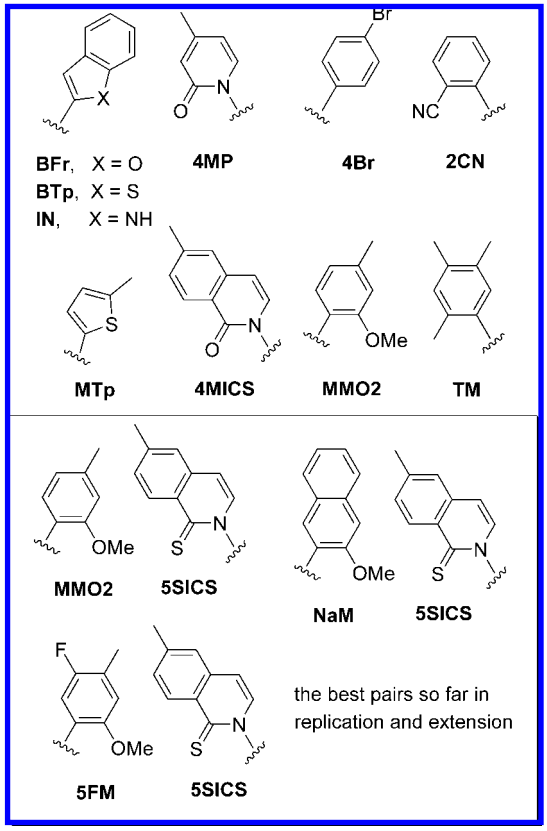
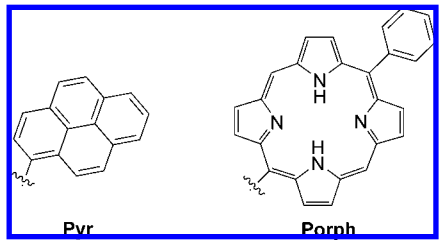


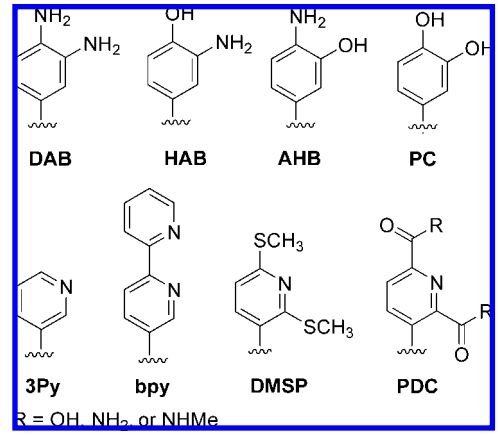
Chart 11. Examples of Extended Aryl-*C*-Nucleosides Complementary to Abasic Sites of Damaged DNA



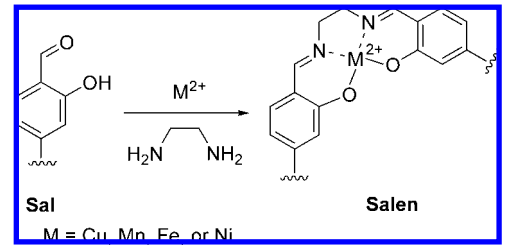
where the two extended heterocycles interacted by $\pi-\pi$ stacking within the DNA duplex.[63] The second generation was based on small methylated or fluorinated benzenes (i.e., **DM5**, **TM**, **2MN**, **3MN**, or **4FB**) that formed stable duplexes where the self-pair was held together only by hydrophobic forces and stacking with the neighboring base-pairs (Chart 9, Figure 1).[64] Some of these self-pairs were replicated by DNA polymerase (usually by the Klenow fragment) with reasonable efficiency and good fidelity. However, due to the lack of minor-groove interactions, the extension of the chain (incorporation of the next dNTP) did not work efficiently in any of these cases.

Therefore, the search for the next generation of artificial nucleobases focused on heterocycles and aromatic rings with additional H-bond accepting functional groups (i.e., oxo, methoxy, etc.). Several types of pyridine *C*-nucleosides have been examined, mostly as self-pairs, to find that **2Py**[65] and later even better **4MPy** and **45DMPy**[66] were replicated and extended with relatively good efficiency and fidelity (Chart 9). In parallel, new heteropairs were investigated, with the aim to find several successful combinations, e.g., benzofuran (**BFr**), benzothiophene (**BTp**), and indole (**IN**) with pyridone (**4MP**);[67] bromobenzene (**4Br**) with

Chart 12. Examples of Metal-Chelating *C*-Nucleoside "Bases" Forming Base-Pairs by Metal Coordination

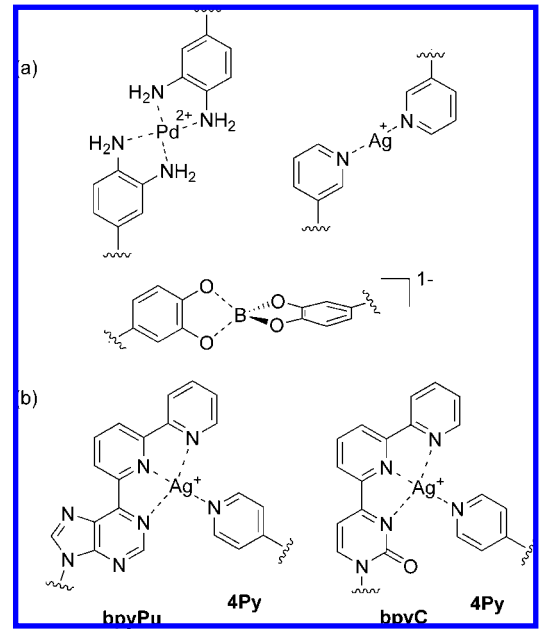


Scheme 1. Salen-Based Pair



benzonitrile (**2CN**);[68] methylthiophene (**MTp**) with isocarbostyril (**4MICS**);[69] and methoxytoluene (**MMO2**) with **TM**[70] (Chart 10), which were all efficiently replicated with high fidelity but proved to be much less efficiently extended. The last generation started with the discovery of the **MMO2/5SICS** pair that, for the first time, exhibited efficient replication and extension with high fidelity.[71] The latter pair was very recently further improved by introduction of a fluorine atom or by annulation of another benzene ring, and the resulting **5FM** or **NaM** were identified as the best complementary bases for **5SICS**, showing an almost natural-like replication and transcription in terms of efficiency and fidelity.[72]

Chart 13. Typical Examples of Homo- (a) and Hetero- (b) Metalla-Base-Pairs



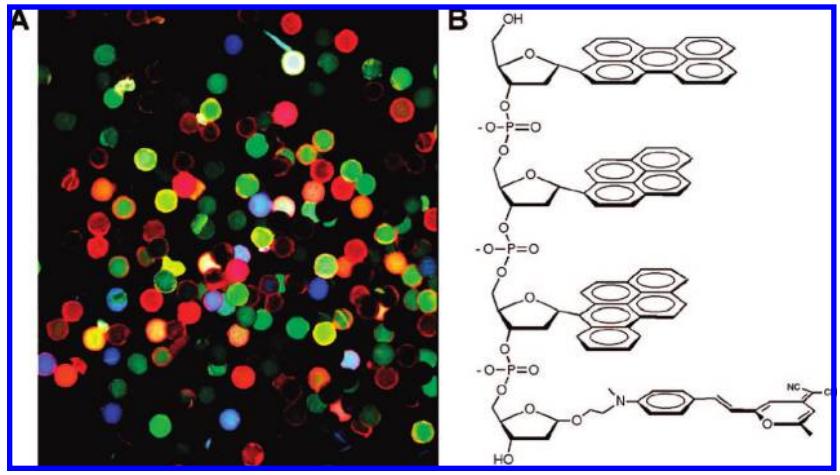


Figure 2. Multispectral oligodeoxyfluorosides. (A) Image from a 4096-member tetramer ODF library on PEG-polystyrene beads, taken with 340−380 nm excitation. (B) Structure of a typical ODF tetramer; this sequence is EYBK (listed in 5′ → 3′ direction). Reprinted with permission from ref 99. Copyright 1989 American Chemical Society.

Biaryl-*C*-nucleosides have also been systematically studied by several groups. They are of particular interest because of their largely extended stacking, which results in the formation of very stable duplexes.[73] Both theoretical calculations[74] and experimental (NMR structure) results[75] confirmed that they form a stacked-pair within B-DNA duplex. On the other hand, incorporation of bulky biaryl *C*-nucleoside into a duplex opposite to a purine or pyrimidine nucleobase causes a local disruption of the stacking.[76] Recently, a donor- and acceptor-modified biphenyl *C*-nucleoside-containing oligonucleotide was employed[75] for recognition of another hydrophobic modification in the opposite strand or even of a bulge or single-strand region. Interestingly, self-pairs of cyclohexylphenyl *C*-nucleosides were found to stabilize the DNA duplex even more strongly[77] than the biphenyl moieties, which demonstrates that hydrophobic forces could contribute as efficiently as the stacking to the stability of the duplex.

Very recently, analogous phenanthrenyl *C*-nucleosides have also been incorporated into DNA as fluorophores and to increase the stability of the duplex.[78] To date, the biaryl-*C*-nucleosides have been used as model systems for biophysical studies directed toward DNA-based materials but their enzymatic incorporation is unlikely to proceed, and therefore, they cannot be regarded as good candidates for extension of the genetic alphabet. In addition, oligoaryl *C*-nucleosides have been used by Kool[79] for the construction of fluorescent oligonucleotide probes (vide infra).

Extended aromatic systems have also been designed as complementary nucleobases for abasic sites of damaged DNA. Representative examples of stable duplexes containing **Pyr**[80] or **Porph**[81] *C*-nucleosides (Chart 11) or substituted indole *N*-nucleosides[82] opposite to abasic sites clearly show that the ON probes containing those extended artificial nucleobases can be employed as probes for sensing the damaged DNA strands.

2.1.3. Artificial Base-Pairs Based on Metal Bridges

Unnatural nucleobases capable of binding metal ions can, a priori, replace their natural counterparts in DNA.[20] Surely, metal-containing base-pairs could be incorporated into DNAs at desired positions. When the bond energy of metal coordination is compared with that of H-bonding, one ligand−metal bond should compensate for two or three H-bonds. Metal ions incorporated in this way could serve at least five purposes: (1) regulation of thermal stability of high-order structures of DNA (duplex, triplex, etc.); (2) construction of one-dimensional metal arrays in direct stacked contact along the DNA helix axis with interesting chemical and physical properties, with applications as molecular wires[83] or as single-molecule magnets;[84] (3) generation of metal-dependent functions, such as redox or photochemical catalysis; (4) assembly of DNA duplexes at the junctions to form two- or three-dimensional DNA networks; or (5) labeling of DNA with metal ions for analytical purposes.

Interactions of the DNA helix with various metal salts and complexes have been well-documented, as well as the effect of subsequent stability enhancement, presumably originating from the metal coordination.[85] The first artificial metal ligand-type nucleoside **DAB** (so-called "ligandoside") was described in 1999 by Shionoya[86] (Chart 12). Since then, other nucleosides having mono- to tridentate ligands for metal-mediated base-pairing have been reported.[86b] The *C*-glycosidic connection is the preferred feature in this class of artificial nucleosides. To date, several *C*-nucleosides (Chart 12) and a number of *N*-nucleosides have been shown to form metal-mediated base-pairs in DNA.[83−95]

The novel salicylaldehyde *C*-nucleoside **Sal** was recently developed, and after its incorporation into DNA in the presence of a metal cation and ethylenediamine, it was shown to form the salen complex **Salen** (Scheme 1). This new "ligandoside" features an interesting combination of metal coordinating groups and a covalent cross-link[87] and was used in the construction of arrays of up to 10 consecutive metal centers within the DNA duplex.[88]

The pseudonucleobase moiety can form a stable metal complex with a linear, trigonal-planar, square-planar, tetrahedral, or octahedral geometry. Among these geometries, the linear, trigonal-planar, and square-planar arrangements mimic the flat, H-bonded natural base-pair geometry; the square-planar, linear, and tetrahedral complexes (Chart 13) of Ag(I),[89,90] B(III),[91] Co(II),[92] Cu(II),[93,87] Fe(III),[87] Hg(II),[94] Mn(III),[87] Ni(II),[92,87] and Pd(II)[86,95] have been reported to date. Because it is very unlikely that a polymerase would be able to utilize metal complexation for the recognition of base-pairs during replication of transcrip-

tion, the metallobase-pairs will probably find applications in the chemically constructed DNA-based materials (molecular wires, nanoparticles, etc.) rather than in chemical biology.

2.1.4. Conclusions and Outlook of Artificial Base-Pairs

Recent studies have shown that the base-pairs based on H-bonding inherently face the problems of fidelity due to the population of minor tautomers.[26] A possible solution is the combination of H-bonding with steric factor exemplified by Hirao in **y**−**s** pair (Chart 6) that is so far the most efficient and selective in PCR amplification.[42−47] A very promising approach is also the use of extended **xN** or **yN** nucleobases[34−38] that are replicated with high fidelity. However, they can be combined with the natural nucleobases only to a very limited extent, so that they represent an alternative parallel genetic system rather than an extension of the current genetic alphabet. More promising are the hydrophobic base-pairs,[50−72] where the problems of extension associated with the lack of minor-groove interactions are being successfully addressed in the last generations of pairs (i.e., **5FM/5SICS**, Chart 10).[71,72] Along with further fine-tuning of the artificial base-pairs, real applications in transcription and later in encoding of proteins containing noncoded amino acids can be expected in the near future. The ultimate goal of creation of an artificial organism, fully operating on an extended 6-bases genetic code, is a long-term but not unrealistic project.

2.2. Other Applications in Chemical Biology

Apart from the use of *C*-nucleosides for investigation of the specificity and selectivity of DNA polymerases (this aspect was discussed in previous chapters), only a handful of applications in other directions of chemical biology have been elucidated to date. Very recently, He[96] reported a smart use of ONs containing trifluoromethyldiazirine−benzene−*C*-nucleoside that, upon UV irradiation, generates a highly reactive carbene intermediate, which forms an interstrand cross-link of dsDNA. A similar approach (with the diazirine moiety linked to the 5-position of U in the major groove of DNA) was used by Carell[97] for cross-linking of DNA with proteins. Apparently, this approach can be used as a tool for (1) studying interactions of nucleic acids with proteins; (2) conjugation of nucleic acids with proteins; or (3) inhibition of some DNA/RNA-processing enzymes. Therefore, further development in this field is highly desirable.

Oligonucleotide arrays of several (2−6) α-aryl- or α-oligoaryl-*C*-deoxyribonucleoside units in a DNA-like chain were introduced by Kool[79] and named "oligodeoxyfluorosides" (ODFs). These units can be easily constructed on an ON-synthesizer in a combinatorial way to produce libraries of ODFs with the emission maxima covering the whole visible spectral region (Figure 2). Kool assumes that the DNA backbone encourages close interactions of these flat aromatic species (similar to stacking of natural DNA bases), allowing for highly efficient electronic communication of excitation energy, which results in multiple forms of energy transfer, including FRET, exciplex, excimer, H-dimer, and other mechanisms.[98] Very recently, these ODFs were successfully employed[99] for fluorescence staining of cells and zebra fish embryos.

3. Medicinal Chemistry of C-Nucleosides

3.1. Natural *C*-Nucleosides

Pseudouridine (**Ψ**, Chart 14) is the most abundant natural *C*-nucleoside present in most tRNA and rRNA structures,[100] where it has been shown to stabilize RNA duplex.[101] It is formed in a unique way by a post-translational isomerization within RNA, catalyzed by pseudouridine synthases.[102] None of the derivatives or analogues of **Ψ** has been reported to have significant biological activity at a therapeutically useful level. However, somewhat related to **Ψ** is the natural antibiotic Showdomycin.[103] Its antibiotic and cytotoxic

Chart 14. Structure of Natural *C*-Nucleosides Ψ and Showdomycin

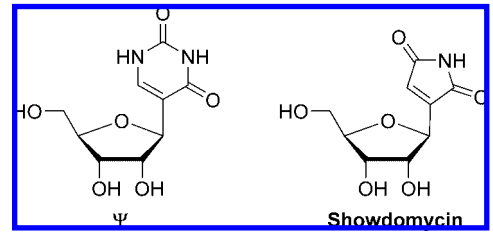


Chart 15. Examples of *C*-Nucleoside Analogues of Biologically Active Compounds

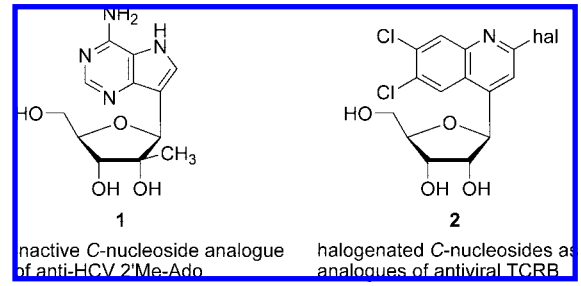


Chart 16. Structures of Formycins A and B and OFB

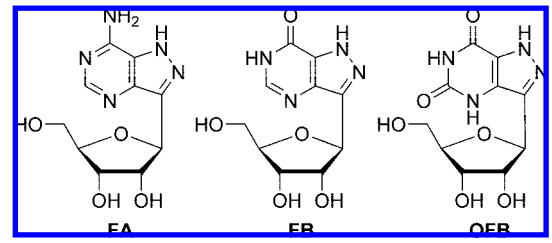
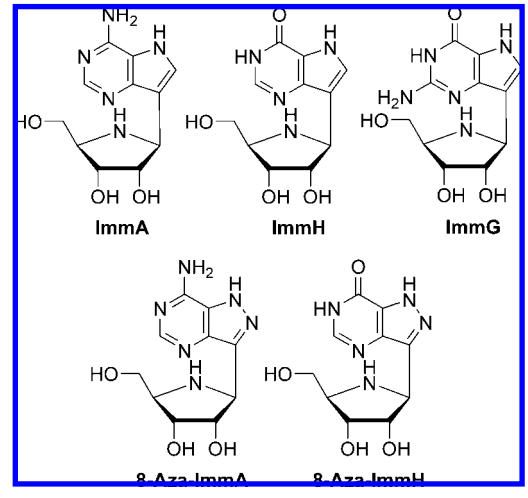
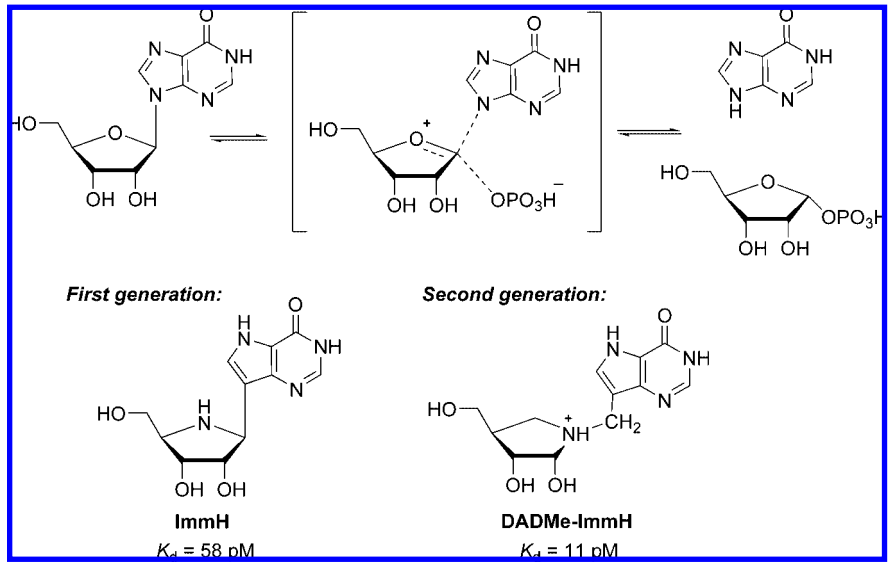


Chart 17. Structures of Immucilins



Scheme 2. Mechanism of PNP and Development of the First and Second Generations of Immucilins



properties have been known for decades but only in 1979 was its mechanism of action successfully addressed and shown[104] to involve inhibition of nucleoside transport into the cell.

3.2. Mechanism-Based Biologically Active C-Nucleosides

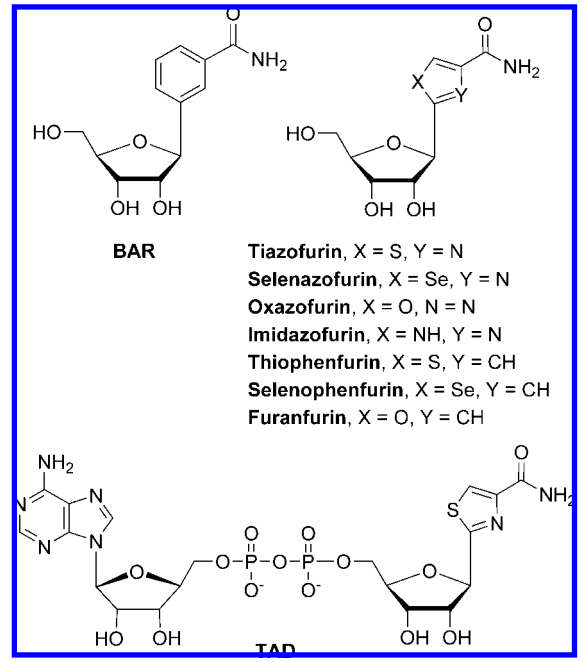
C-Nucleosides (as well as standard *N*-nucleosides) can in principle target any enzymes of the nucleic acid metabolism. Purine nucleoside analogues can, in addition, inhibit a wide range of enzymes that use purine-based cofactors (i.e., kinases, oxidoreductases, GPCR, and tubulin, etc.) and act as agonists or antagonists of purinoceptors. The major advantage of *C*-nucleosides is the stability toward cleavage of the nucleosidic bond due to the replacement of the nucleosidic C−N bond by the nonhydrolyzable C−C bond. Therefore, they are expected to be resistant to enzymatic cleavage. Replacement of the N atom by C in the position of the nucleosidic bond often dramatically changes the properties of the heterocyclic moiety. Thus, for example, replacement of pyrimidine by pyridine or replacement of purine by pyrrolopyrimidine dramatically changes the tautomeric populations and acidobasic properties of the heterocycles and functional groups (OH, NH_2). This phenomenon is manifested by a recent example of a laborious multistep synthesis of 9-deazaadenine-2′C-methylribonucleoside **1** (a carba analogue of the strong anti-HCV agent 2′C-methyladenosine[105]), which was found to be completely inactive,[106] presumably due to the change of the tautomeric population and basicity of the amino group. Several types of halogenated indole and quinoline *C*-nucleosides **2** were prepared[107] by Townsend as analogues of the antiviral TCRB[108] (Chart 15). Some of them showed nonselective antiviral activity against HCMV but accompanied by cytotoxicity in most instances.

3.2.1. Inhibitors of Nucleolytic Enzymes

Natural antibiotics formycins (in particular **FA**, **FB**, and oxoformycin B **OFB**, Chart 16) have been known since the early 1960s to possess antibiotic and cytotoxic properties; their antiparasitic activity (antimalarial, antischisostoma, etc.) was unraveled later. Being purine nucleoside analogues, their mechanism of action is quite complex and may involve effects on several pathways in parallel. However, these compounds proved[109] to be strong inhibitors of purine nucleoside phosphorylase (PNP) and nucleosidases, and this is probably the major part of their activity.

The discovery of immucillins, a new class of PNP inhibitors (Chart 17), was a triumph of rational drug design based on physical organic chemistry.[110] Schramm has systematically studied kinetic isotope effects of nucleoside analogues as inhibitors of PNP in combination with crystal structures,[111] molecular modeling, and experimental enzymology,[112] and after several iterations and structural improvements, he came up with the aza-*C*-nucleosides immucillins A, H, and G and their 8-aza-analogues as the first generation of potent cytostatics (Chart 17).[110] By further structural refining and deeper insight into the reaction mechanism (Scheme 2), Schramm developed a second generation (this time not based on *C*-nucleosides) of picomolar inhibitors of human PNP, namely, DADMe-ImmH

Chart 18. Structures of Some *C*-Nucleoside Inhibitors of IMPDH



(Scheme 2).[113] Several compounds of this class are now in advanced stages of clinical trials as cytostatics.

3.2.2. Inhibitors of Oxidoreductases

Nicotinamide-adenine dinucleotide (NAD) is the major cofactor of oxidoreductase enzymes. Many arylcarboxamide *C*-nucleosides can act as analogues of nicotinamide ribonucleoside and inhibit some oxidoreductases. Thus, inosine 5′-monophosphate dehydrogenase (IMPDH) catalyzes conversion of inosine 5′-monophosphate (IMP) to xanthosine 5′-monophosphate (XMP) and is the rate-limiting enzyme in de novo biosynthesis of guanylate. Inhibition of IMPDH and subsequent decrease in the concentration of guanine nucleotides interrupts the DNA and RNA synthesis in tumor cells. Tiazofurin (Chart 18) is a potent cytostatic,[114] which underwent clinical trials[115] and was found to be biotransformed to **TAD** (analogous to NAD), which then inhibits IMPDH.[116,117] The same mechanism has been demonstrated for benzamide ribonucleoside (**BAR**).[118] Further studies revealed that selenazofurin[119] exhibits even higher activity, while some other heteroanalogues (e.g., oxazofurin, imidazofurin,[120] selenophenfurin,[121] thiophenfurin, and furanfurin[122]) that exert similar levels of cytostatic effects act via the same mechanism.

3.2.3. Conclusions and Outlook in Medicinal Chemistry

It was demonstrated by numerous examples that a simple replacement of the labile nucleosidic bond of antiviral or antitumor nucleosides by the C−C bond to form *C*-nucleoside analogues of the parent bioactive compounds usually leads to a decrease or even complete lack of activity. The reason is the change of the acidobasic properties and tautomeric population of the modified nucleobase that significantly modulates the interactions with enzymes. Considering the very complex mechanisms of action of most nucleoside drugs, involving transport, phosphorylations up to triphosphate, and final inhibition of DNA or RNA polymerase, the structural change may block any of these steps, thereby suppressing the activity. On the other hand, synthesis and high-throughput screening of large series or libraries of *C*-nucleoside derivatives may reveal novel lead compounds with different mechanism of action. However, to our knowledge, no attempt on synthesis and screening of *C*-nucleoside libraries has been reported to date. In addition, a new mechanism based on the biologically active *C*-nucleosides could be discovered by rational drug design (especially for inhibition of single enzymes of nucleotide metabolism). Undoubtedly, development of new, efficient synthetic methodology will stimulate further research in this direction and hopefully unearth novel biologically active compounds.

4. Synthesis of C-Nucleosides

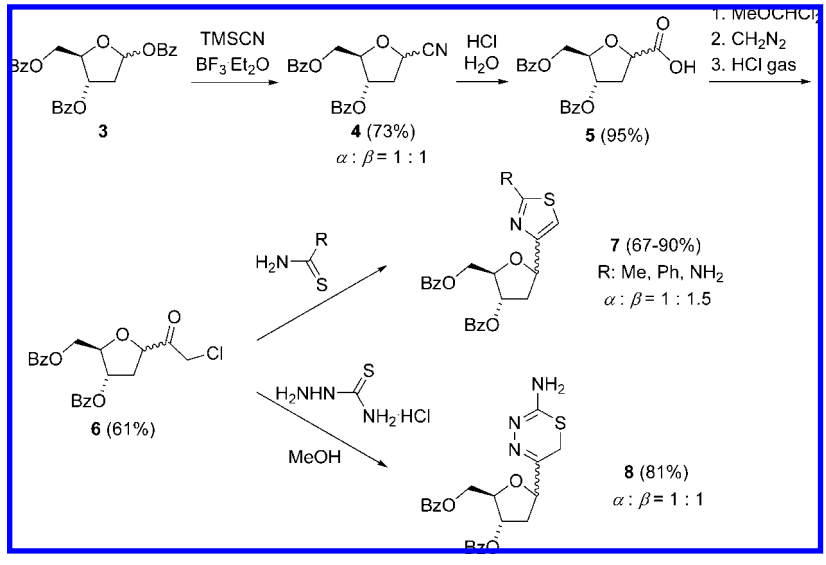
Since the Cohn discovery of the first *C*-nucleoside pseudouridine **Ψ**, these natural products and their artificial analogues became an important part of research. The low natural abundance of *C*-nucleosides, together with a high desire for their analogues, stimulated a focused interest in this class of compounds. Many synthetic strategies have been developed and summarized in excellent reviews.[6−11] Different approaches may be employed to classify these strategies. We would like to present the following scheme in this chapter, regarding the structural features of *C*-nucleosides: (A) Connection of an appropriate functional group to an anomeric position of a preformed carbohydrate moiety, followed by a construction of the aglycon unit; (B) connection of an appropriate functional group to a preformed aglycon, followed by a construction of the carbohydrate moiety; (C) a direct coupling of a preformed carbohydrate moiety with an aglycon; (D) modification of the existing *C*-nucleoside; and (E) modular approaches.

4.1. Construction of an Aglycon Unit upon a Carbohydrate Moiety

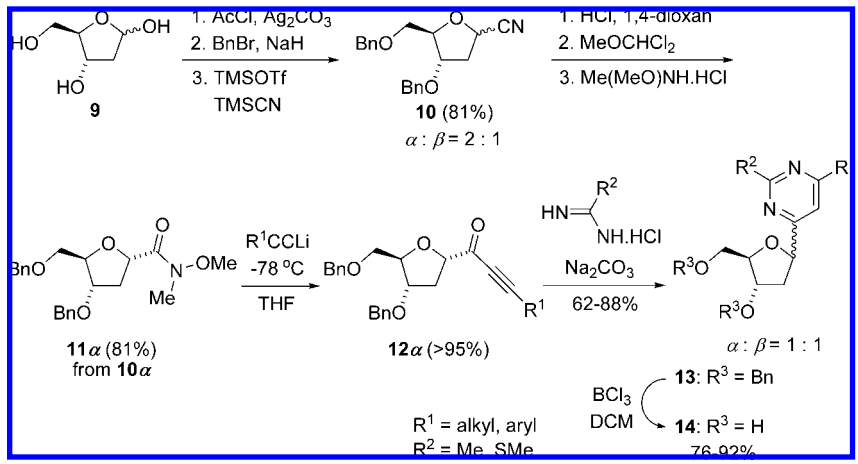
4.1.1. Introduction of the Nitrile Group and its Heterocyclizations

The first synthetic strategy for the introduction of an appropriate functional group onto a preformed carbohydrate is often utilized to construct heterocycles.[123] A classical example is the introduction of the CN-group (Scheme 3). For example, Baldwin and co-workers introduced the CN group to the fully benzoylated carbohydrate **3** with trimethylsilyl cyanide,[124] and the resulting mixture of nitrile anomers **4** was hydrolyzed to afford carboxylic acid **5**. This precursor was converted into the chloroacetyl derivative **6** by the sequence

Scheme 3. Introduction of the CN Group Followed by Heterocylic Ring Construction I



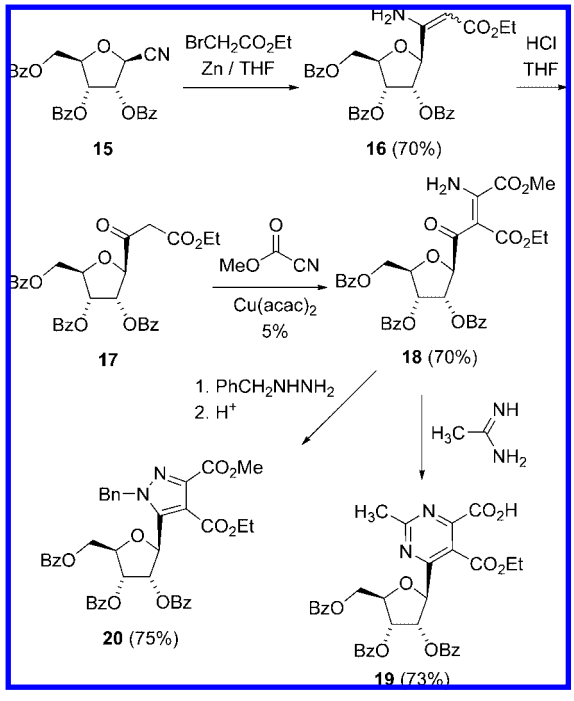
Scheme 4. Introduction of the CN Group Followed by Heterocylic Ring Construction II



of reactions with α,α-dichloromethyl methyl ether, diazomethane, and HCl. Subsequent cyclization with thioamide nucleophiles produced the substituted thiazoles **7** in moderate-to-good yields. Cyclization with semithiocarbazide afforded aminothiadiazole **8** as a mixture of anomers in good yield.

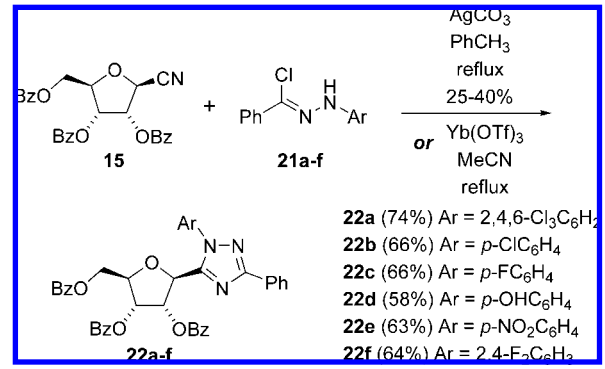
The latter cyano-group introduction was nonstereoselective, affording an equimolar mixture of both anomers. However, the carboxylic acid **5** is suitable for a chromatographic separation of the anomers, offering an opportunity to carry out the subsequent reactions with pure diastereoisomers. A higher yielding and partially stereoselective cyano-group introduction (Scheme 4) commenced with benzylation of ribose **9**, followed by transformation into the corresponding nitrile anomers **10**, which were successfully separated. Nitrile **10α** was hydrolyzed and the resulting acid was converted into the Weinreb amide **11α**, whose reaction with lithium acetylide afforded the propargyl ketone **12α**. Treatment of the latter derivative with amidoimidates produced pyrimidines **13** as a 1:1 mixture of anomers in good yield. Clearly, the isomerization in the last step shows that the attempted stereocontrol in the earlier steps was redundant.[125]

Scheme 5. Construction of Pyrimidines 19 and Pyrazoles 20

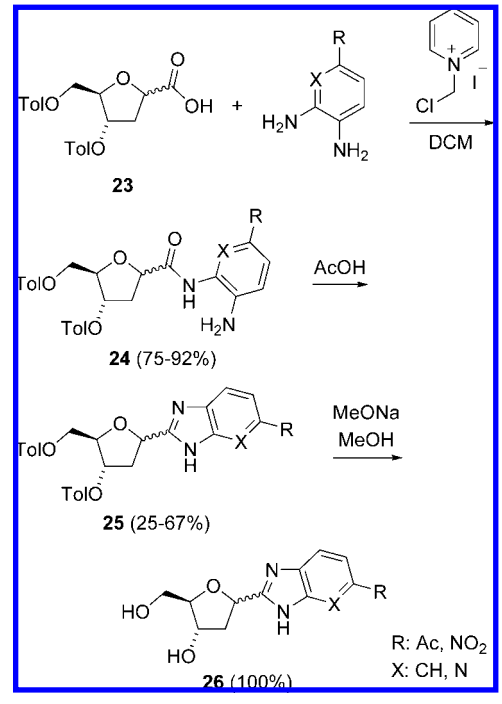


Protected 1-cyano-β-D-ribofuranose **15** was employed in the synthesis of pyrimidines by Veronse (Scheme 5).[126] Reformatsky reaction produced β-iminoester **16**,[127] whose hydrolysis afforded the unstable β-ketoester **17**, which was immediately treated with methyl cyanoformate in the presence of copper(II) catalyst to give diester **18** in good overall yield. Subsequent cyclization of **18** with ami-

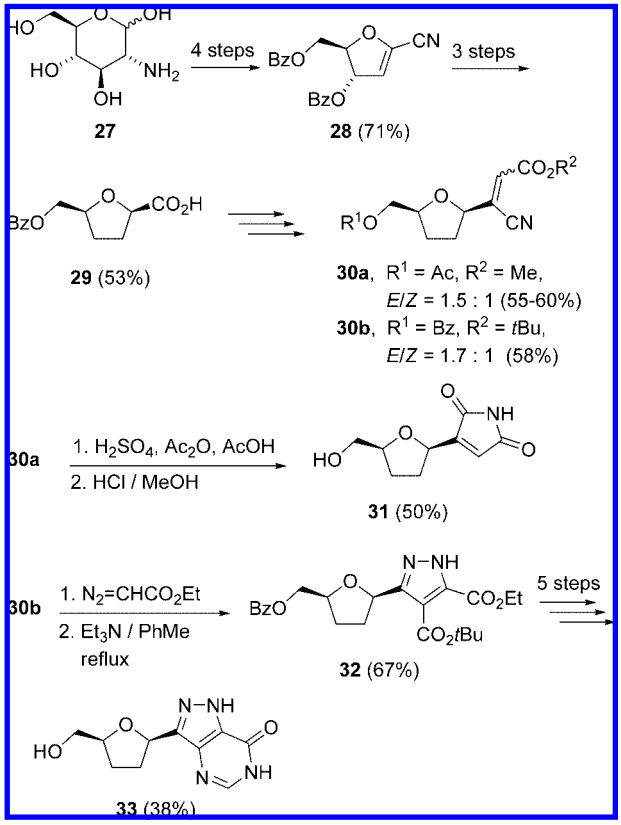
Scheme 6. Cycloaddition to Nitrile and Construction of 1,2,4-Triazoles 22



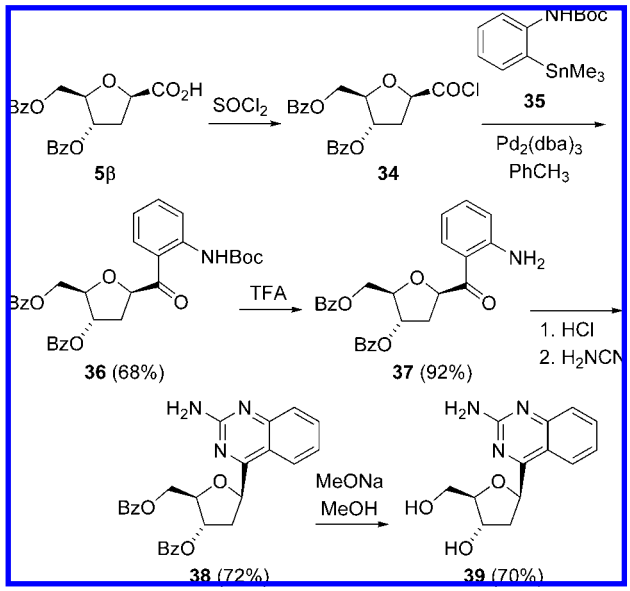
Scheme 7. Construction of Benzimidazole Rings



Scheme 8. Construction of Dideoxyshowdomycin 31 and Dideoxyformycin B 33



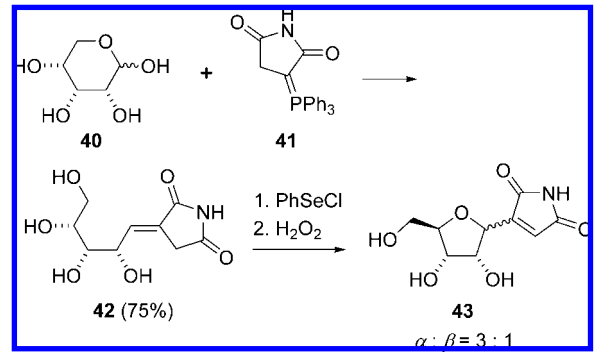
Scheme 9. Construction of Diastereopure Benzopyrimidines 39



doimidates or benzylhydrazine furnished the protected pyrimidine- and pyrazole-*C*-nucleosides **19** and **20**, respectively.

Al-Masoudi reported on a procedure employing β-cyano functionality in a cycloaddition reaction.[128] Here, protected 1-cyano-β-D-ribofuranose **15** (obtained stereoselectively due to neighboring-group participation in the ribo series) was treated with various hydrazonyl chlorides **21** in the presence of Lewis acids to afford 1,2,4-triazoles **22** in good yields when ytterbium triflate was used (Scheme 6).

Scheme 10. Wittig-Type Chemistry in the Synthesis of Showdomycin 43



Benhida developed a similar approach employing the toluoylated acid **23**[129] (Scheme 7) in the reaction with a variety of diamines mediated by Mukaiyama reagent (chloromethylpyridinium iodide).[130] The resulting amides **24** were cyclized under acidic conditions to the corresponding benzo- and pyrido-imidazoles **25**. Basic deprotection with sodium methanolate afforded *C*-nucleosides **26** in moderate overall yields. The diastereoselectivity of the reactions was fully dependent on the initial cyano group introduction.

This strategy was also employed in the synthesis of dideoxynucleosides. Jung reported on a synthesis utilizing the purified β-anomer of the protected acid **29**, readily available from glucosamine **27** in seven steps and 37% overall yield (Scheme 8).[131] Acid **29** was converted into the common intermediate, cyanoester **30**, by a cyanation reaction, followed by the Wittig-type reaction with the appropriate triphenylphosphorane. Various ester functionalities were utilized in the cyanoester **30**, which was either cyclized and deprotected to afford dideoxyshowdomycin **31** in the way of Ohno's synthesis of showdomycin[132] or submitted to cyclization with ethyl diazoacetate to give pyrazole diester **32**. The end game in the synthesis of dideoxyformycin B (**33**) required five final steps.

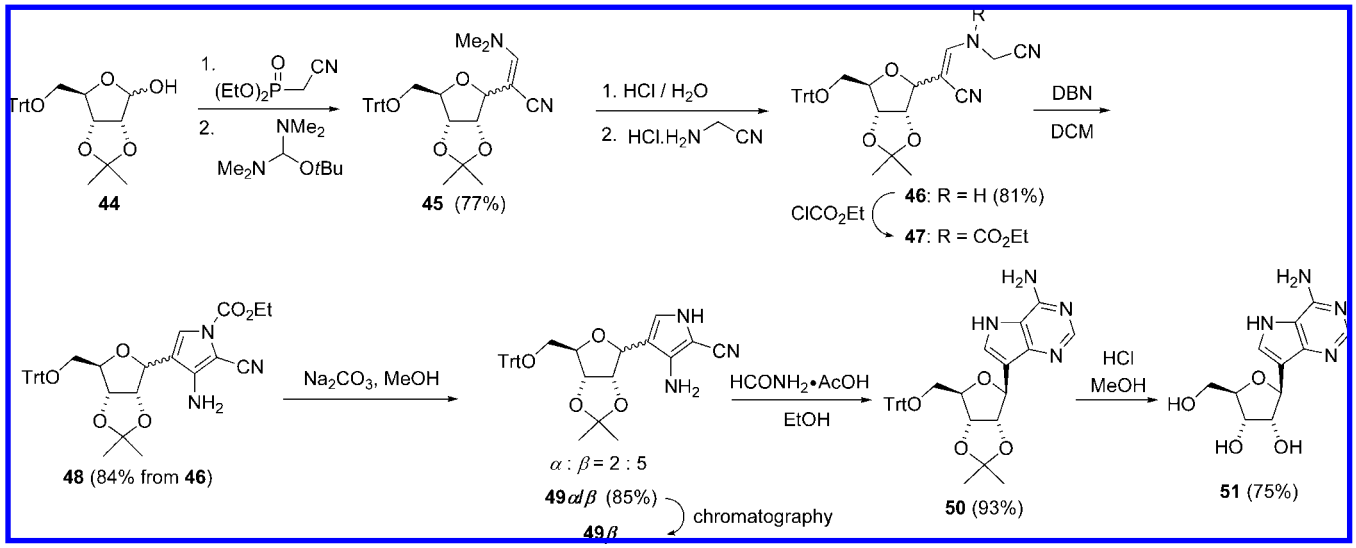
More recently, Gold reported on a procedure employing the purified β-anomer of protected acid **5** (Scheme 9).[133] The acid **5*β*** was converted into the corresponding acid chloride **34** and submitted to a palladium-catalyzed Stille coupling reaction with 2-trimethylstannyl aniline **35**. Removal of the protecting group gave aniline **37** in high yield. The cyclization with cyanamide, followed by deprotection, furnished the benzopyrimidine 2′-deoxyriboside **39**.

4.1.2. Wittig-Type Reactions

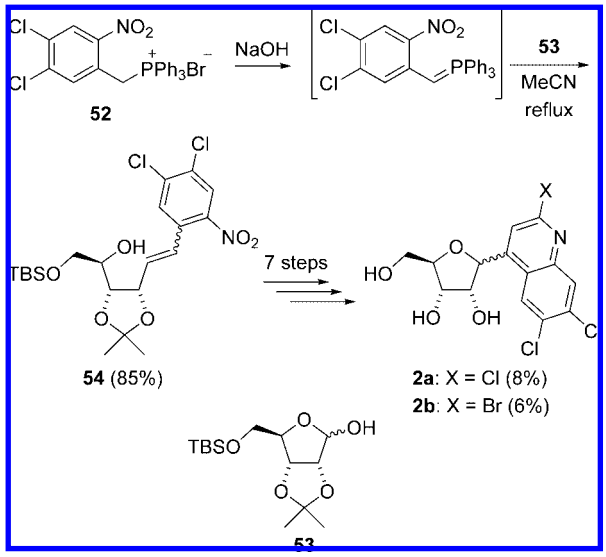
Another important strategy within the aglycon construction relies on the Wittig-type chemistry.[106,134] This approach is based on the reaction of a phosphorus ylide with an aldehyde function on the carbohydrate moiety. Thus, the reaction of ylide **41** with D-ribose **40** in boiling tetrahydrofuran produced compound **42** in 75% yield (Scheme 10). Selenoetherification, followed by oxidative elimination, afforded showdomycine **43*β*** and epi-showdomycine **43α** as a 1:3 mixture.[135]

The classical synthesis of 9-deazaadenosine **51** commenced with the functionality introduction via Horner−Wadsworth−Emmons reaction (Scheme 11).[136] Protected ribose **44** produced the corresponding ribosylacetonitrile intermediate on reaction with diethyl methylencyanophosphonate, whose treatment with *tert*-butoxy bis(dimethylamino)methane in dimethylformamide (DMF) gave enamine **45**. Acidic hydrolysis and reaction of the resulting enol with

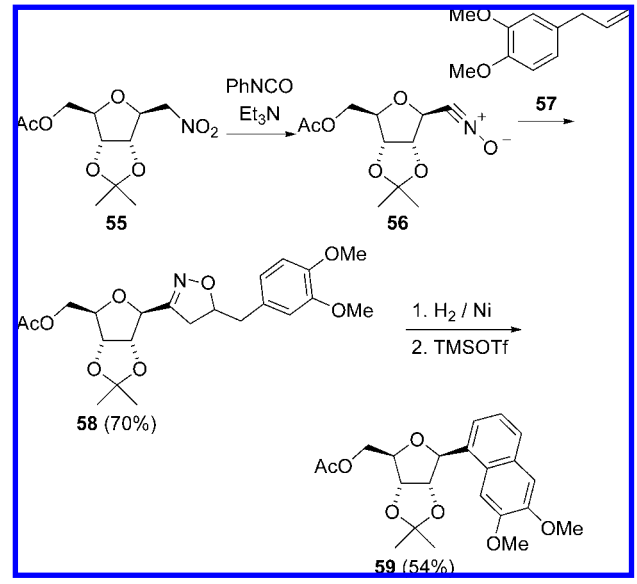
Scheme 11. Classical Synthesis of 9-Deazaadenosine 51



Scheme 12. Construction of Polyhalogenated Quinolines 2a−b



Scheme 13. 1,3-Dipolar Cycloadition in Construction of Aglycon Unit



aminoacetonitrile hydrochloride in an acetate buffer produced bisnitrile **46** in good yield over two steps. Protection of the secondary amino function with ethyl chloroformate afforded intermediate **47**, cyclization of which with an excess of DBN (1,5-diazabicyclo[4.3.0]non-5-ene) as a base produced the functionalized pyrrole **48** in good yield. After deprotection, the pyrrole anomers **49** were separated by using column chromatography. Pure β-D-anomer **49*β*** was cyclized with formamide acetate in boiling ethanol to produce the protected deazaadenosine **50**. Deprotection afforded the *C*-analogue of adenosine **51** in 22% overall yield in 10 steps from the protected ribose **44**.

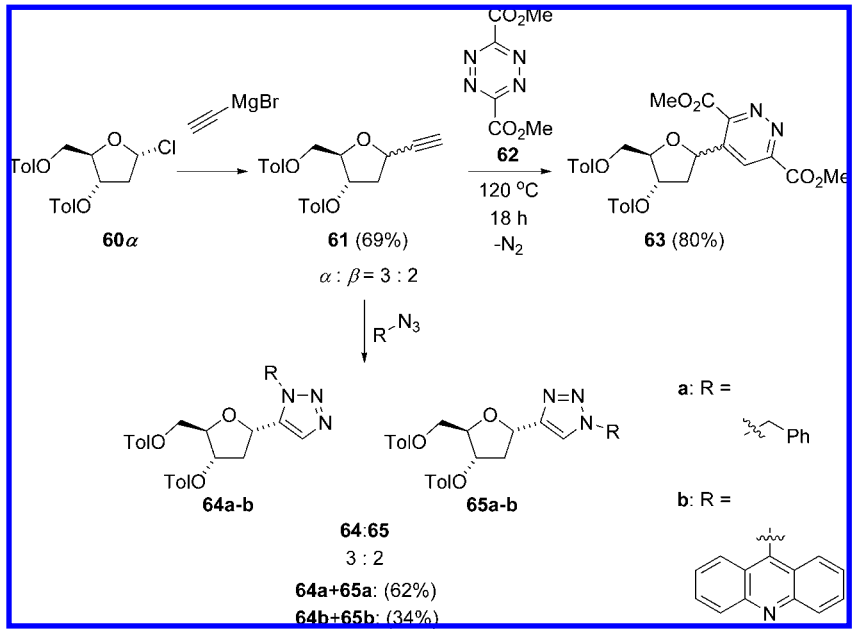
Wittig-type chemistry was also used by Townsend to construct polyhalogenated quinolines as potential antiviral agents (Scheme 12).[107c] Phosphonium bromide **52** was treated with sodium hydroxide and then directly coupled with protected ribose **53** to afford alkene **54** in good combined yield of two isomers (85%, *Z*/*E* = 12:1). This mixture was elaborated in seven steps into the desired *C*-nucleosides **2a** and **2b** bearing trichloroquinoline and bromodichloroquinoline aglycon, respectively. However, the overall yield was low.

4.1.3. Cycloadditions

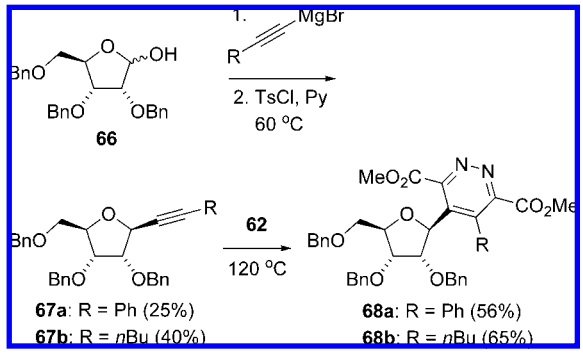
Cycloaddition reactions constitute an important strategy to be considered in the construction of aglycons. The first attempts were related to the total synthesis of showdomycin, where Diels−Alder cycloaddition reaction was used to construct the carbohydrate moiety with an appropriate functional group in the anomeric position.[132] In the same year (1984), Kozikowski employed a 1,3-dipolar cycloaddition reaction in the synthesis of artificial nucleoside analogues bearing an isoxazoline ring instead of ribose and in the total synthesis of (±)-blastomycinone.[137]

With this experience in hand, Kozikowski reported, shortly afterward, the first example of 1,3-dipolar cycloaddition in the synthesis of dimethoxynaphthyl *C*-nucleoside **59**.[138] The sequence commenced with the nitromethylene derivative **55**, which was first converted into the nitrile oxide **56**. Subsequent cycloaddition of the substituted allyl benzene **57** afforded isoxazoline **58**, whose reduction with Raney nickel gave the corresponding hydroxy ketone that was cyclized to the aryl *C*-nucleoside **59** on treatment with trimethylsilyl triflate (Scheme 13).

Scheme 14. Cycloadditions in Construction of Pyridazines 63 and Triazoles 64 and 65

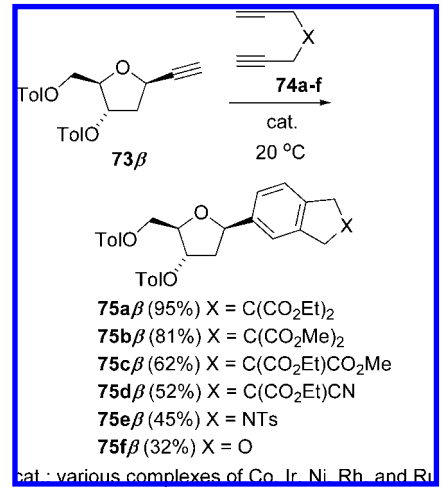


Scheme 15. Synthesis of Substituted Pyridazine Ribofuranosides 68

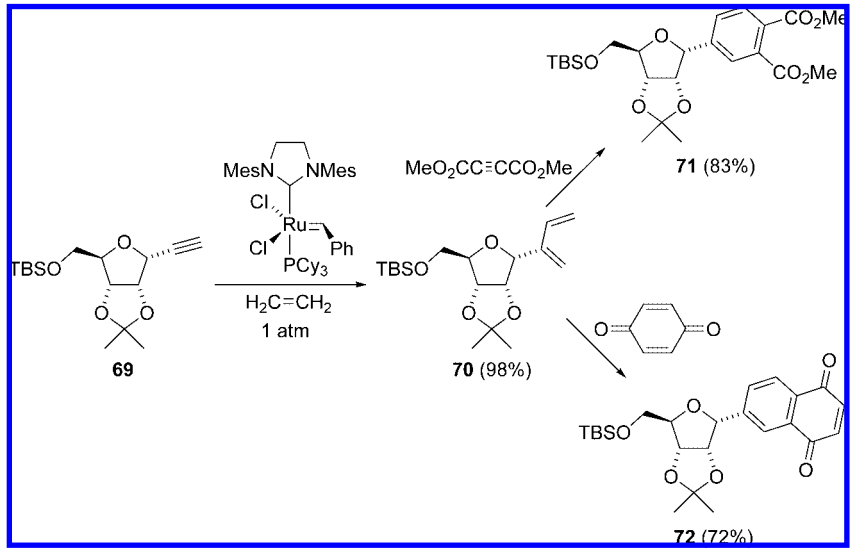


Other procedures have utilized an ethynyl group connected to the anomeric center. The key intermediate, ribofuranosylethyne **61**, can be prepared with various degrees of stereoselectivity, but the α-anomer is the predominant product in all these procedures. Wamhoff reported on the synthesis of pyridazine- and triazole-*C*-

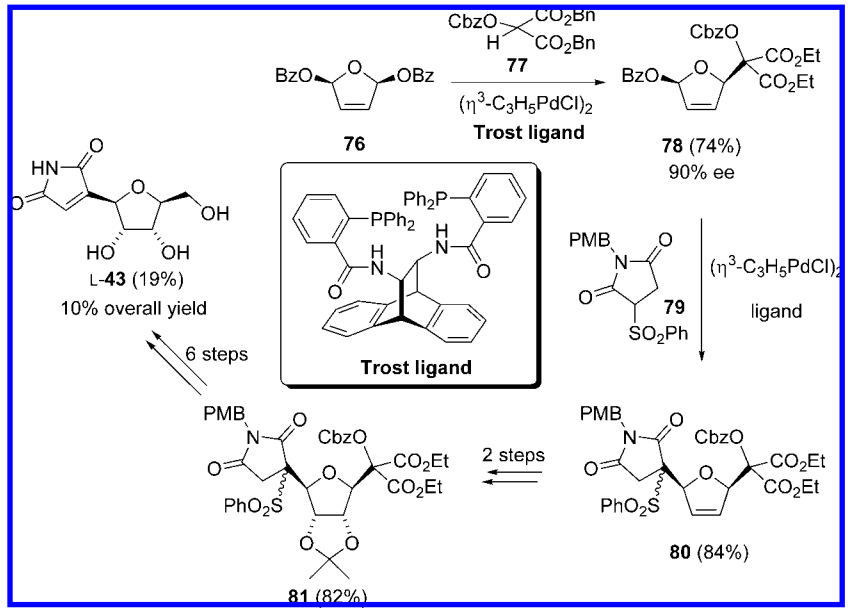
Scheme 17. Cyclotrimerization in Construction of *C*-Arylribosides 75



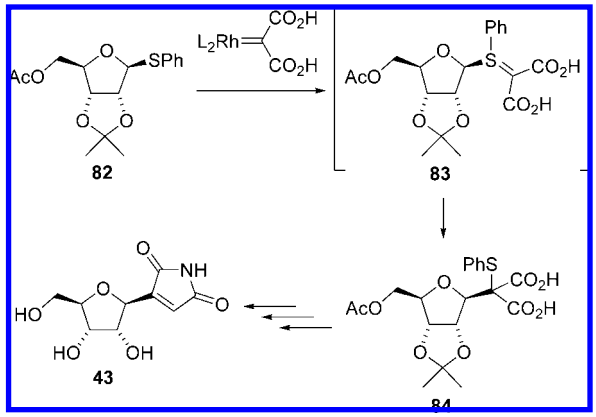
Scheme 16. Cross-Enyne Metathesis Followed by Diels−Alder Cycloaddition



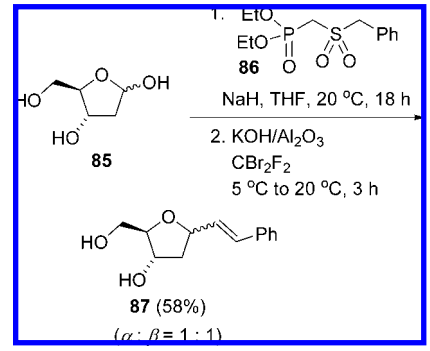
Scheme 18. Allylic Substitution in the Synthesis of L-Showdomycin



Scheme 19. Functialization of Protected Thioribose via Carbene Insertion



Scheme 20. HWE/Cyclization−Tandem-Halogenation/ Ramberg−Backlund Reaction



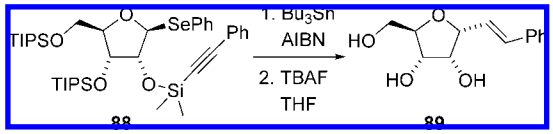
nucleosides (Scheme 14).[139] The α-anomer of the protected chlororibose **60α** was reacted with ethynylmagnesium bromide to afford toluoylated ribofuranosylethyne **61** as a mixture of anomers.[140] An influence of the protecting groups on anomeric population was observed: ester-based protecting groups (Ac, Bz, Tol = 4-Me-C_6H_4CO) gave mixtures with somewhat higher amounts of the desired *β*-anomers but still the undesired α-anomer was the major product. The anomeric mixture **61** was then submitted to the Diels−Alder cycloaddition reaction with dimethyl [1,2,4,5]-tetrazine-3,6-dicarboxylate **62**; the cycloadduct was formed readily and then underwent spontaneous decomposition under the Diels−Alder reaction conditions to give pyridazine **63**. The anomeric mixture of **61** was also submitted to a [3 + 2]-cycloaddition reaction with azides to afford practically equimolar (^{1}H NMR) mixtures of two possible regioisomers **64a−b** and **65a−b** in moderate yield. The regioselectivity was not influenced by steric effects as shown in the case of azidoacridine.

Dubreuil synthesized substituted pyridazine *C*-ribonucleosides **68** (Scheme 15)[141] from benzylated ribofuranose **66**, which was first treated with alkynylmagnesium bromides; the resulting *β*-anomers **67** were isolated and submitted to the Diels−Alder cycloaddition reaction with dicarboxylate **62**. The desired pyridazine *C*-ribonucleosides **68** were formed as pure *β*-anomers in moderate-to-good yield.

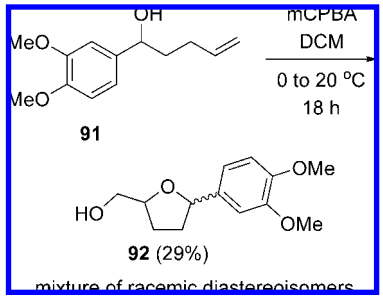
Kaliappan reported on a very efficient procedure leading to *C*-aryl glycosides (Scheme 16).[142] Application of this method to ribofuranosides was also investigated. The synthetic strategy was based on a cross-enyne metathesis, followed by Diels−Alder cycloaddition reaction. Thus, protected ribofuranosylethyne **69** was reacted with ethylene in the presence of Grubbs second-generation catalyst to give rise to diene **70** in high yield. On reaction with dimethyl ethynyldicarboxylate or benzoquinone, the latter derivative afforded α-*C*-nucleosides **71** and **72**, respectively. Since both the cross-metathesis and the cycloaddition were carried out in toluene at 80 °C, a two-reaction−one-pot procedure was carried out and was found to proceed without any significant difference in the isolated yield.

Cyclotrimerization leading to standard *C*-nucleosides was reported by Kotora (Scheme 17).[143] The anomeric mixture of toluoylated ribofuranosylethyne **73** was reacted with a range of diynes **74** to afford the expected products of cyclotrimerization **75a−f**. Various transition metal complexes were investigated to promote the reaction. The pure *β*-anomer **73*β*** gave cycloadducts **75a*β*−f*β*** in good yields. An analogous approach was reported by Yamamoto for the synthesis of various *C*-glycosides.[144] Homocyclotrimerization and oxidative homocoupling of **73*β*** were also employed as the key steps in the synthesis of tri- and disaccharide analogues.[145]

Scheme 21. Radical Cyclization in the Aglycon Unit Construction



Scheme 22. Nonstereoselective Synthesis of 2,5-Disubstituted Tetrahydrofuran



4.1.4. Other Methods for the Construction of the Aglycon Unit

Several other procedures leading to the structures fulfilling the definition of *C*-nucleoside have been developed. However, the practical utility of these procedures is low, as their versatility is low and/or the compounds produced are of a very limited use. Therefore, only a brief selection of these methods is presented herein.

Trost has developed a synthesis of L-showdomycin L-**43** based on the asymmetric palladium-catalyzed allylic substitution (Scheme 18).[146] This approach relies on desymmetrization of the *meso*-dibenzoate **76**, upon which were constructed both the hydroxymethyl and maleimide moieties. The hydroxymethyl part was introduced in the form of activated maleic diester **77**, whereas the maleimide moiety was introduced in the form of sulfonylsuccinimide **79**. In theory, either part, **77** or **79**, can be introduced in either order. However, Trost has found that the hydroxymethyl precursor **77** had to be introduced first, followed by the introduction of imide **79**, as the reversed order resulted in the formation of substantial amounts of side-products and poor stereocontrol. The unnatural L-configuration of the final product resulted from the enantioselective reaction of the *meso*-derivative **76**, catalyzed by a palladium compex of the Trost ligand (≤90% ee). With a different diphosphine ligand, the naturally D-configured intermediate D-**78** (≤76% ee) was obtained.[147] Once the building blocks had been attached to the dihydrofuran ring, they were elaborated into the final units of L-showdomycin L-**43** in 10 steps and 10% overall yield. Although the stereocontrol in this protocol is good, the main disadvantage here is the long elaboration of suitable precursors toward desired structures.

Thionucleoside **82** served as a starting material in the synthesis of D-showdomycin **43** (Scheme 19): on reaction with the rhodium carbene derived from malonate, **82** was converted into intermediate **83**, which then underwent a rearrangement to produce **84**; further elaboration in several steps afforded showdomycin **43**.[148]

Another sequence that can be potentially regarded as an approach to *C*-nucleoside derivatives utilized the unprotected 2′-deoxyribose **85**, whose reaction with phosphonate **86** gave an equimolar mixture of anomers of *C*-nucleoside **87** in a two-step−one-pot protocol. The reaction itself consists of four consecutive steps involving Horner−Wadsworth−Emmons olefination, followed by cyclization, tandem bromination, and Ramberg−Bäcklund reaction (Scheme 20).[149]

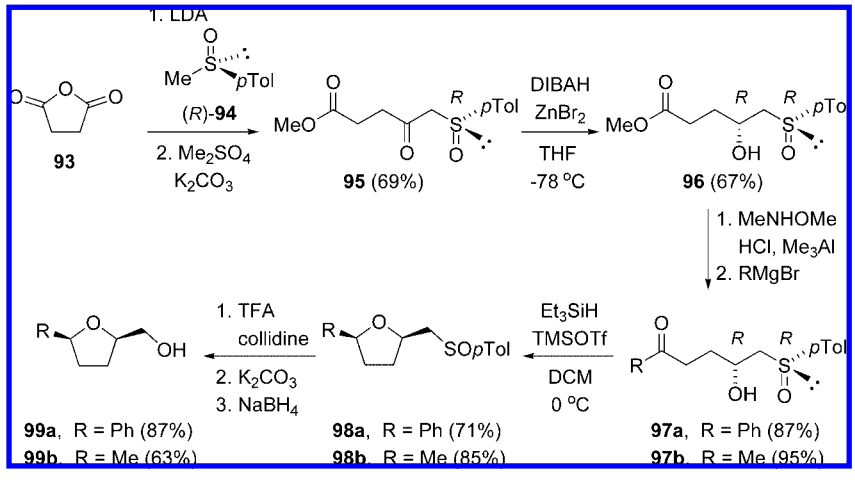
Stork has used his intramolecular radical cyclization method for the silicon-tethered alkynes to stereoselectively synthesize *C*-ribofuranosides. Owing to the mechanism of the reaction, the diastereoselectivity strictly depends on the alkyne position: with the ribose substrate **88**, the α-anomer **89** becomes the only product of the reaction (Scheme 21).[150]

4.2. Construction of a Carbohydrate Moiety upon an Aglycon Unit

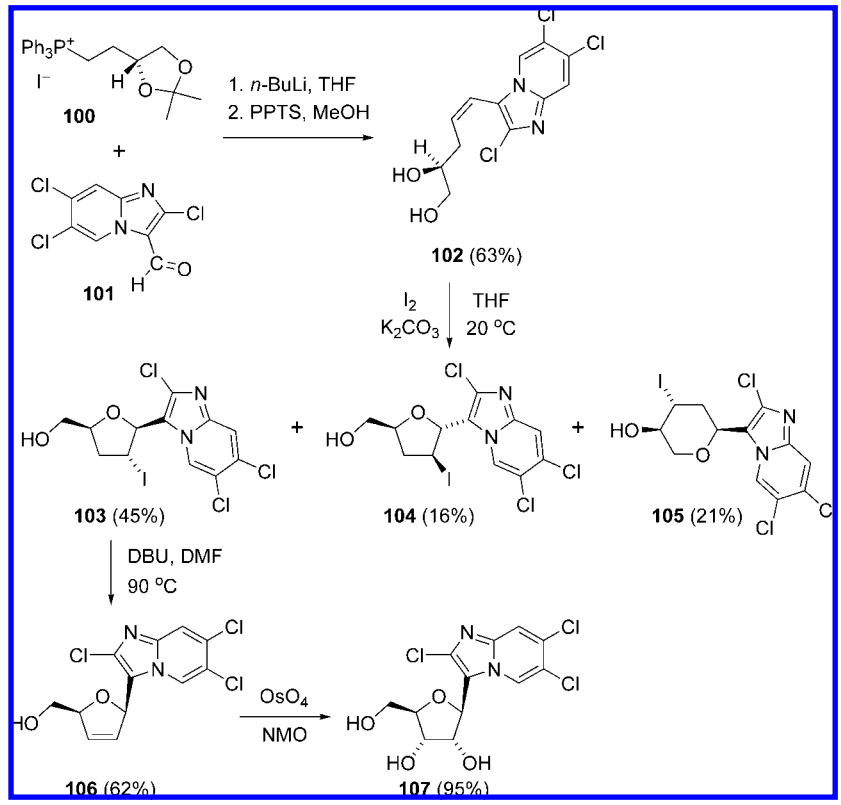
The logical complement to the synthetic strategy based on the building of an aglycon unit upon a carbohydrate moiety is the construction of a carbohydrate moiety upon an aglycon, or the synthesis of a carbohydrate moiety followed by the aglycon construction. These strategies are not very common as they require construction of up to four stereogenic centers.

The former strategy utilizes the carbohydrate moiety containing all the stereocenters and has been applied to several total syntheses of *C*-nucleosides.[132] Thus, Vogel reported on synthesis of the *C*-nucleoside intermediate **90**, containing all the stereochemical features required for the biologically attractive 3′-azido-2′,3′-dideoxy-*C*-nucleo-

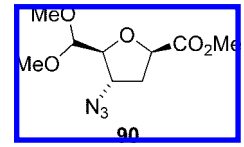
Scheme 23. Hydroxysulfinyl Ketones in Stereoselective Synthesis of 2,5-Disubstituted Tetrahydrofurans



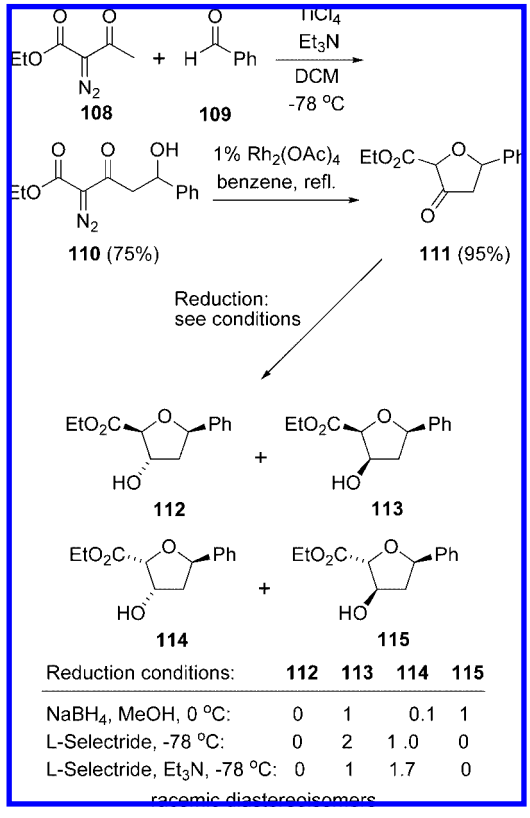
Scheme 24. Construction of a Carbohydrate Moiety upon an Aglycon Unit



sides.[151] The ester functionality of this common intermediate was elaborated into a range of *C*-nucleosides.

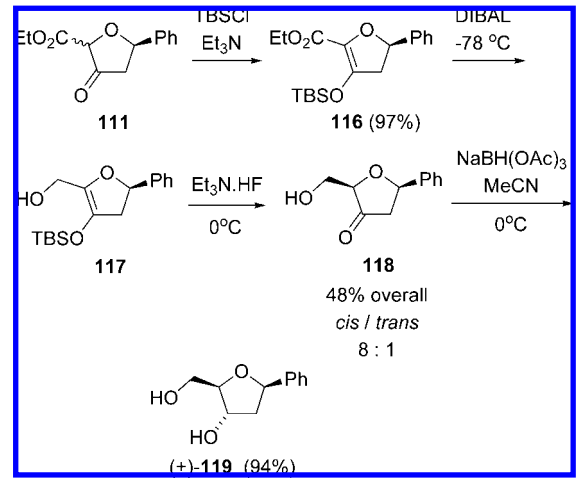


Scheme 25. Carbene in Carbohydrate Moiety Construction and Nonselective Reduction

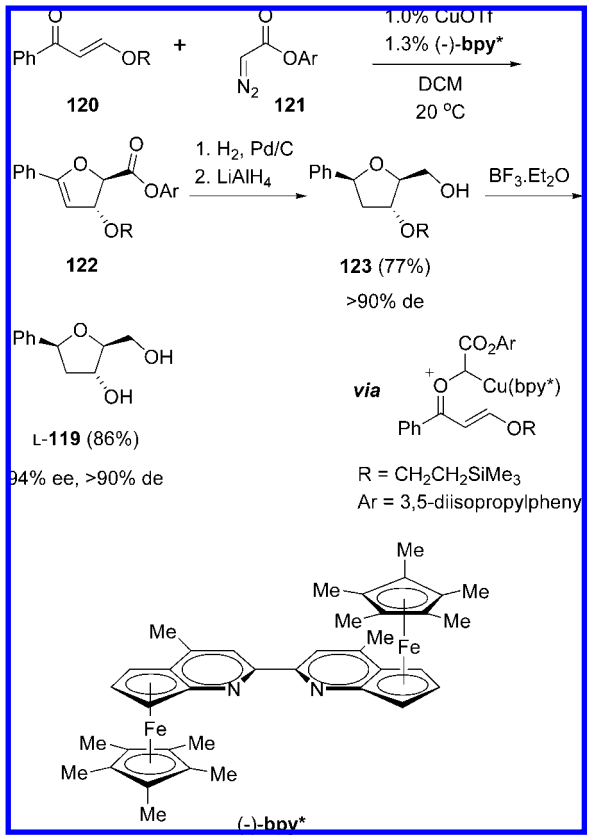


2′,3′-Dideoxy-*C*-nucleosides should receive a special attention among *C*-nucleosides analogues. They possess a structural feature of 2,5-disubstituted tetrahydrofuran and, thus, share the synthetic methodology with a variety of natural compounds.[10] A nonstereoselective synthesis of racemic diastereoisomers has been reported (Scheme 22),[152] starting with the unsaturated alcohol **91**, which was submitted to epoxidation, followed by an in situ oxirane-ring-opening and cyclization to give 2,5-disubstituted tetrahydrofuran **92**.

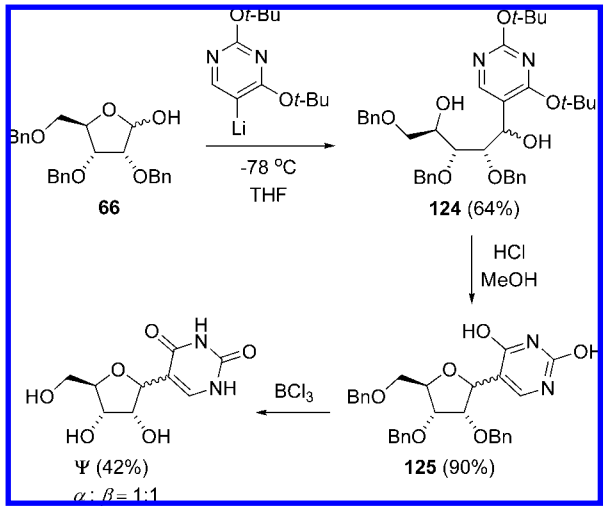
Scheme 26. Carbene in Carbohydrate Moiety Construction; Two Consecutive Reductions



Scheme 27. Copper-Catalyzed Asymmetric [4 + 1]-Cycloaddition of Enones with Diazo Compounds to Form 2′-Deoxy-*C*-nucleoside L-119

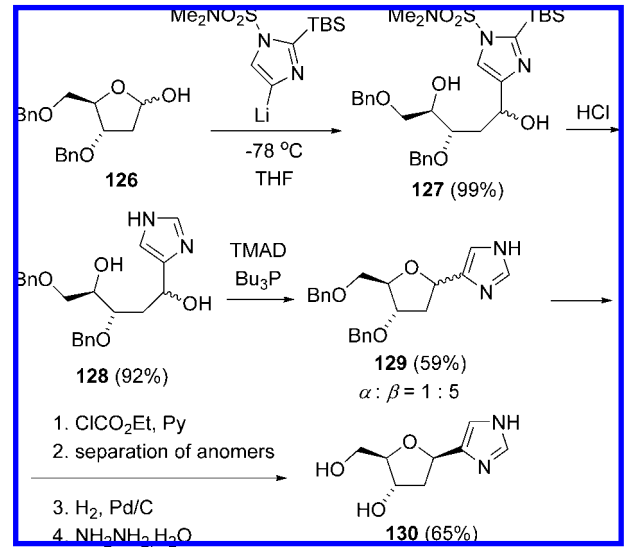


Scheme 28. Coupling of Protected Ribofuranose 66 and Organolithium Derivate Followed by Acid-Catalyzed Cyclization

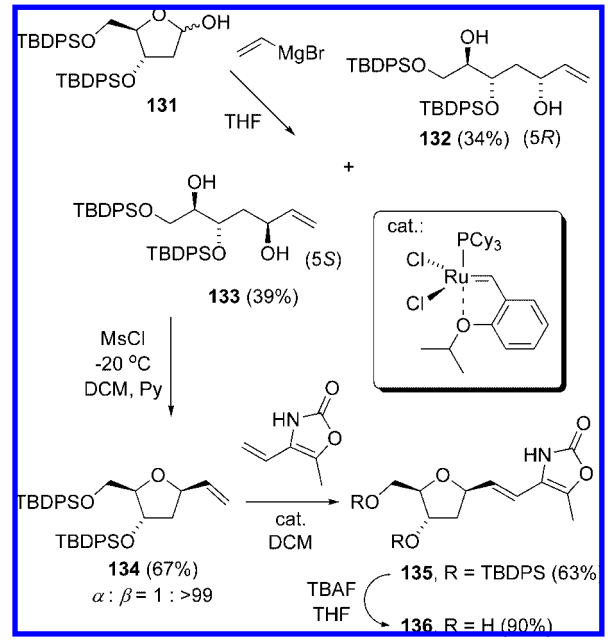


A stereoselective synthesis of tetrahydrofurans (and tetrahydropyrans) that can be regarded as a blueprint for the synthesis of dideoxy *C*-nucleosides was developed by Carreño (Scheme 23).[153] In this approach, succinic anhydride **93** was first reacted with a lithium salt of the enantiopure (*R*)-methyl-*p*-tolylsulfoxide **94**, and the resulting acid was methylated with dimethyl sulfate to give *β*-ketosulfoxide **95**. A highly diastereoselective reduction of **95** was obtained by using diisobutylaluminum hydride (DIBAL-H) in the presence (or absence) of $ZnBr_2$; the reported diastereoselectivity exceeded 98% diastereomeric excess (de). The resulting hydroxysulfinyl ester **96** was then transformed into

Scheme 29. Coupling of Protected 2′-Deoxyribofuranose and Organolithium Nucleophile Followed by Cyclization under Mitsunobu Conditions



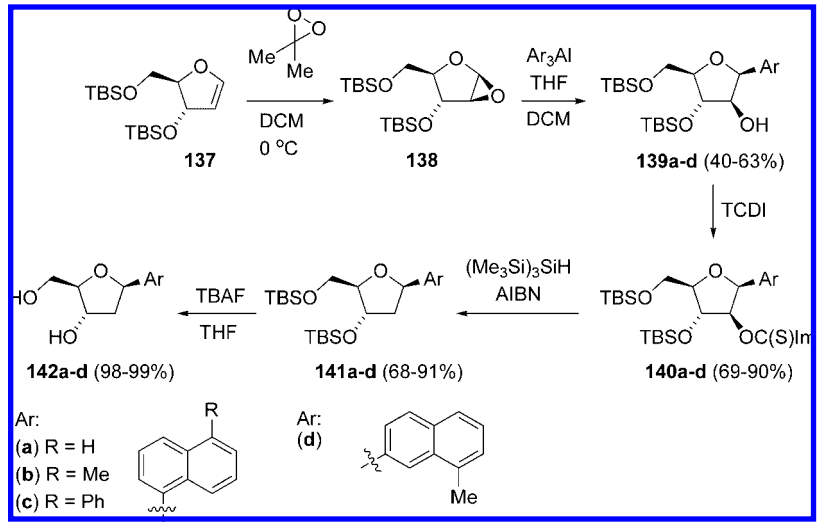
Scheme 30. Introduction of Vinyl Group to Protected 2′-Deoxyribofuranose Followed by Cross-Metathesis



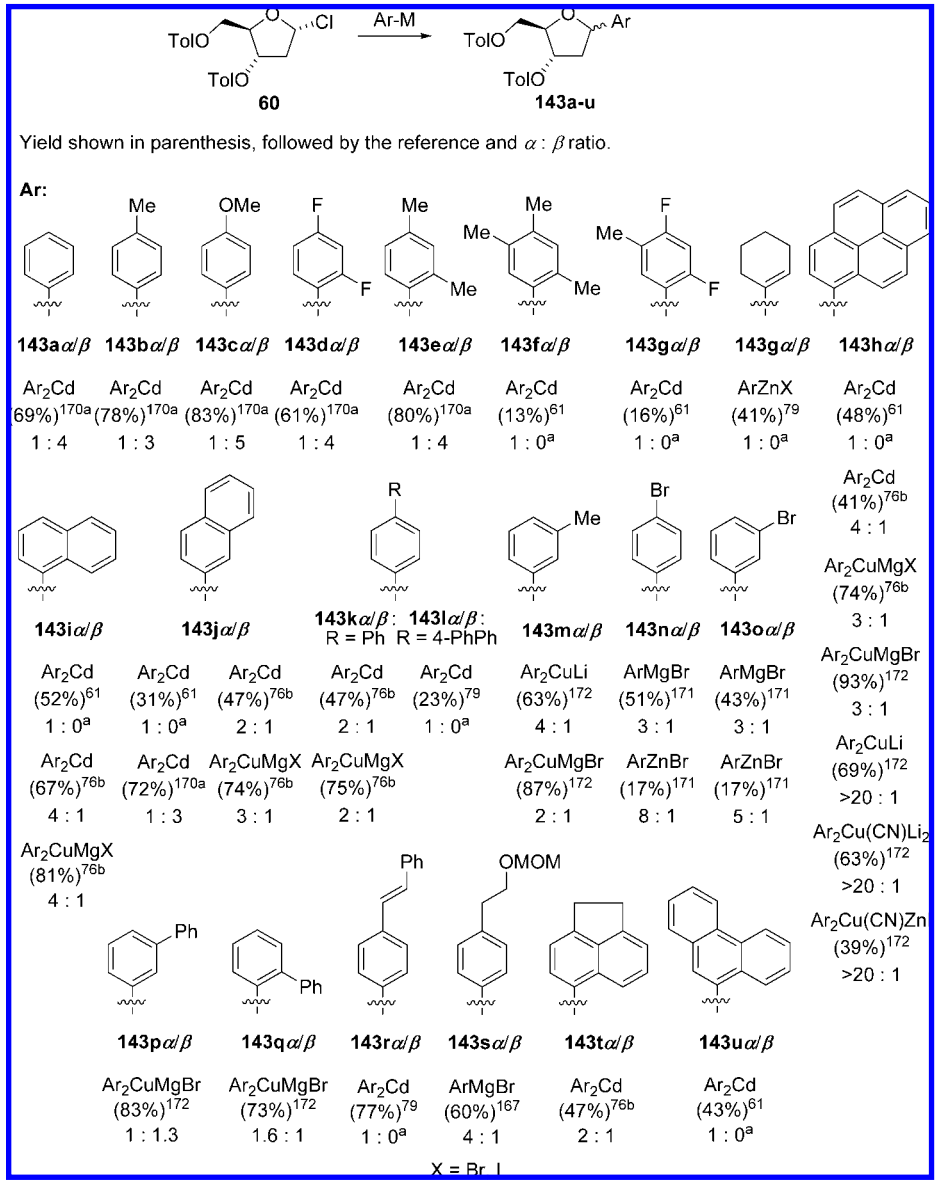
the corresponding Weinreb amide as a versatile intermediate, suitable for reactions with a variety of arylmagnesium bromides to afford the corresponding hydroxysulfinyl ketones, e.g., **97**. Reductive cyclization then afforded tetrahydrofurans **98a**,**b**. The diastereoselectivity of this cyclization was determined in the crude reaction mixture only in the case of phenyl substituent (72% de); only the major diastereoisomers **98a**,**b** were isolated. Finally, the Pummerer reaction of **98a**,**b**, followed by reduction, resulted in the formation of the desired 2′,3′-dideoxy-*C*-nucleosides **99a**,**b**. The enantiomeric series, starting with (*S*)-methyl *p*-tolylsulfoxide, was also reported.

The classical route to the construction of a carbohydrate moiety upon an aglycon was reported by Townsend (Scheme 24).[154] In his protocol, he utilized Wittig olefination of the heterocyclic aldehyde **101** with the phosphonium iodide **100**, followed by deprotection, which gave rise to diol

Scheme 31. Nucleophilic Addition to Protected 1,2-Anhydrofuranose

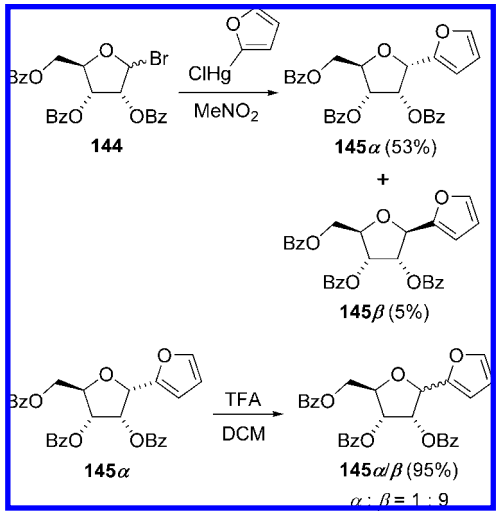


Scheme 32. Coupling of Hoffer's Chlorosugar with Various Organometallic Reagents



102. The subsequent iodocyclization of the latter alkenol **102** was extensively optimized to maximize the yield of the desired iodotetrahydrofuran **103**. Elimination of iodine, followed by standard stereoselective dihydroxylation of the resulting dihydrofuran **106**, afforded ribofuranose **107** in 17% yield over all four steps.

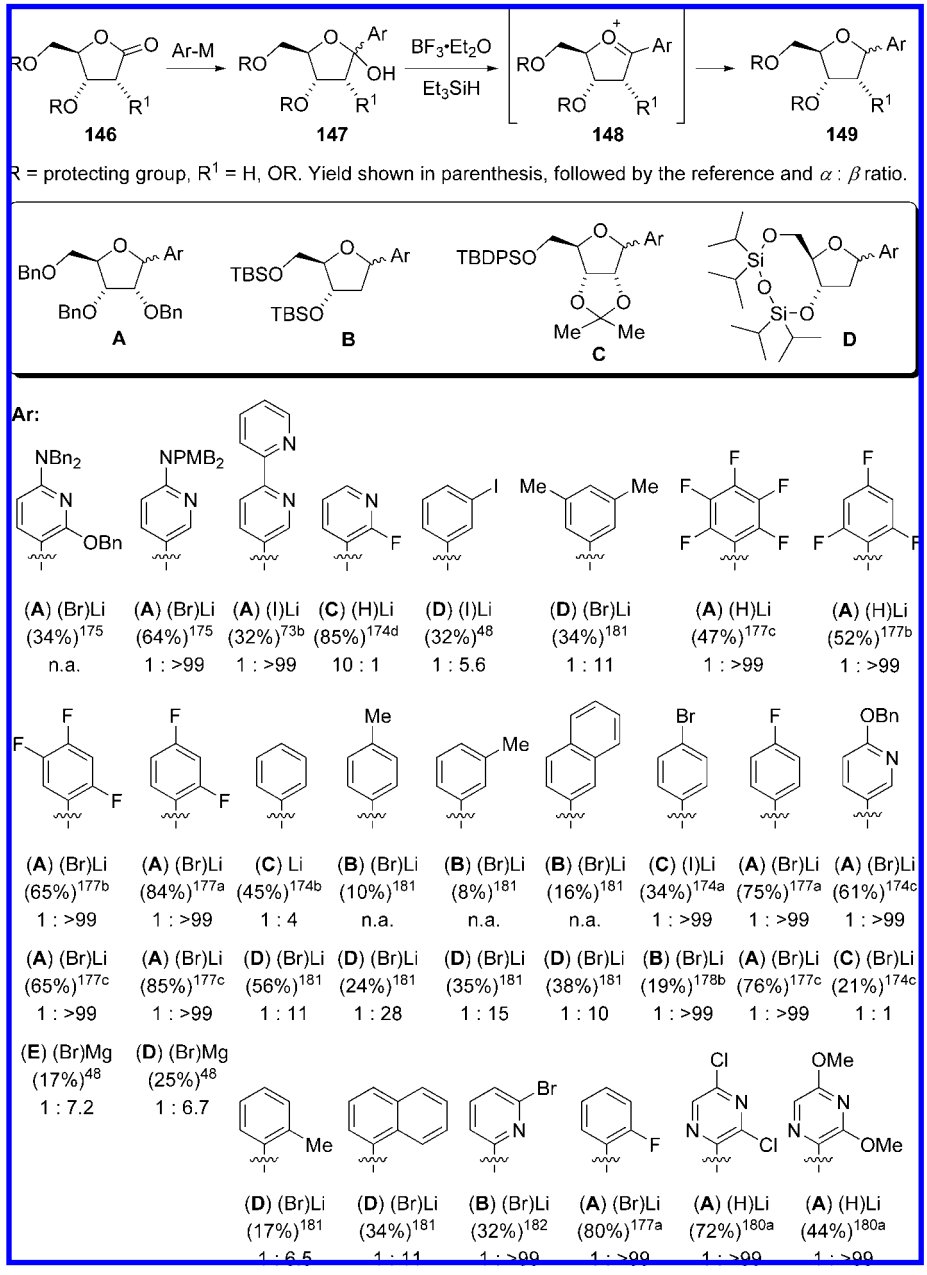
Scheme 33. Furanylmercury−Bromose Coupling Followed by Epimerization



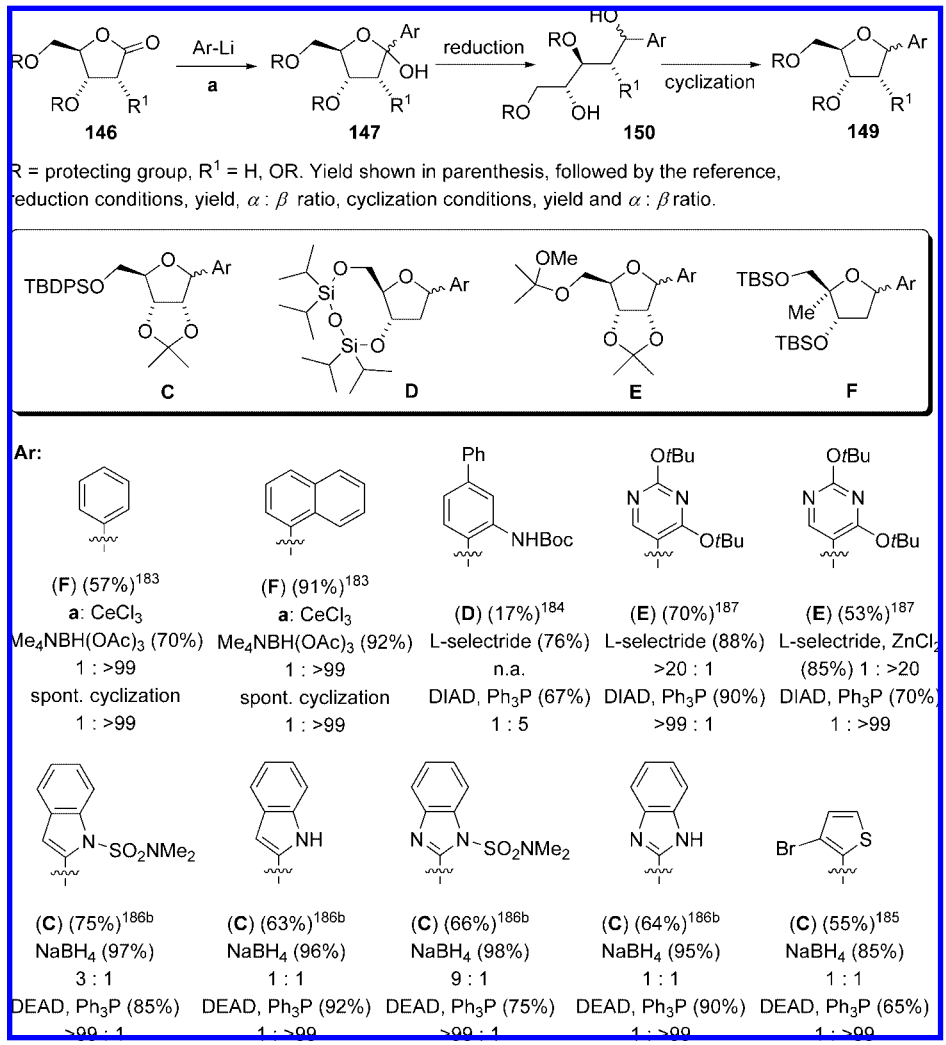
The last example within this strategy employs carbene chemistry, and the first attempts have been reported by Calter.[155] Here, aldol reaction of **108** with arylaldehyde **109** was employed as the key step, followed by the Rh-catalyzed cyclization of the resulting **110** via the corresponding metallocarbene (Scheme 25) to ketoester **111**, reduction of which can, a priori, afford racemic diastereoisomers **112**−**115**. However, the desired natural 2′-deoxy-β-D-ribofuranoside **112** was not detected in the crude product. The *cis*-ketoester **111** was also isolated as a single diastereoisomer prior to reduction but turned out to be configurationally unstable.

Sequential reduction of the keto ester **111** was also investigated (Scheme 26).[155b] First, **111** was transformed into the corresponding silyl enol ether **116** and the ester function was reduced with DIBAL-H to afford the primary alcohol **117**. Diastereoselective cleavage of the silyl enol ether group was then carried out by treatment with triethylammonium fluoride to produce ketone **118** in moderate yield

Scheme 34. Nucleophilic Addition to Furanolactones Followed by Silane Reduction



Scheme 35. Nucleophilic Addition to Furanolactones Followed by Mitsunobu Cyclization



and good diastereoselectivity (77% de). The final reduction of **118** with sodium triacetoxyborohydride afforded racemic diol **119** with the configuration of natural 2′-deoxy-β-ribofuranose.

There have been several attempts to follow this strategy, but these have met with only a modest success.[155c,d] A new carbene cycloaddition approach was developed recently by Fu (Scheme 27).[156] Here, the asymmetric copper-catalyzed cycloaddition of diazoester **121** to enone **120** was employed as the key-reaction, giving rise to dihydrofuran **122** with ≤85% ee. Stereoselective hydrogenation of the latter derivative **122**, followed by reduction of the ester function, afforded tetrahydrofuran **123** (>90% de), whose deprotection gave the desired 2′-deoxy-*C*-nucleoside L-**119** in good overall yield (66%, 4 steps) and good stereoselectivity. The overall enantio- and diastereoselectivity (94% ee and 20:1 dr) is the result of the purification procedures after the first enantioselective step. However, the practical utility of this efficient procedure is limited by the availability of the chiral ligand (−)-bpy* used in the copper-catalyzed cycloaddition. Migaud[157] has recently published a novel diastereoselective approach to pyranosyl-*C*-nucleosides using the ene/intramolecular Sakurai cyclization reaction followed by ozonization.

4.3. Direct Coupling of a Carbohydrate Moiety with a Preformed Aglycon Unit

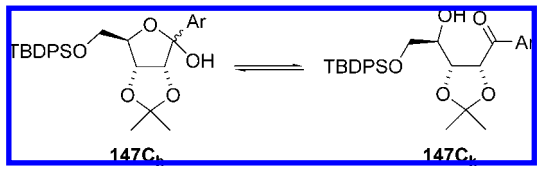
The synthetic strategy of the direct coupling of a protected carbohydrate moiety with a preformed aglycon nucleophile represents the most common synthetic approach to the construction of *C*-nucleoside backbone.[6d] There are six different reaction tactics within this strategy: (1) nucleophilic addition to the aldehyde function of a carbohydrate; (2) nucleophilic addition to 1,2-anhydrofuranoses; (3) coupling of nucleophiles with halogenoses; (4) nucleophilic addition to furanolactones; (5) Heck coupling; and (6) Lewis acids-mediated electrophilic substitution.

4.3.1. Nucleophilic Addition to the Aldehyde Function of a Carbohydrate

Addition of organometallic reagents to the aldehyde functionality in the carbohydrate moiety leads to a mixture of diastereoisomeric diols **124** in good yields. Subsequent cyclization to **125** proceeds under acidic conditions in a nondiastereoselective fashion (Scheme 28),[118a,158] so that the resulting pseudouridine (**Ψ**) was obtained as a 1:1 anomeric mixture.

The intermediate diol **128**, obtained in two steps from the protected deoxyribose **126**, was cyclized diastereoselectively under Mitsunobu conditions to produce anomeric mixture

Scheme 36. Hemiacetal/Keto Equilibrium



129. The subsequent N-protection, separation of anomers, and deprotection afforded the 2′-deoxyribofuranoside **130** in 34% overall yield (Scheme 29).[159] With an optimized Mitsunobu-based cyclization, reported recently, the analogous pyrazole derivatives were prepared with ≤92% de.[160]

A novel approach within this strategy was recently demonstrated by Rothman in the synthesis of oxazolone ethenyl *C*-nucleosides (Scheme 30).[161] Protected deoxyribofuranose **131** was converted into a mixture of chromatographically separable diols **132** and **133** on reaction with vinylmagnesium bromide. Mesylation of the (5*R*)-diastereoisomer **133** was followed by a spontaneous, highly diastereoselective cyclization in the 5(O)^n-*exo*-tet manner,[162] to give rise to the tetrahydrofuran derivative **134** as a single diastereoisomer. The exocyclic double bond was utilized in the cross-metathesis reaction, using the Hoveyda−Grubbs first-generation catalyst. Deprotection of the resulting product **135** furnished the desired oxazolone *C*-nucleoside **136*β*** in 15% overall yield from **131**; the corresponding α-anomer was obtained from **132** in a similar manner in 11% overall yield.

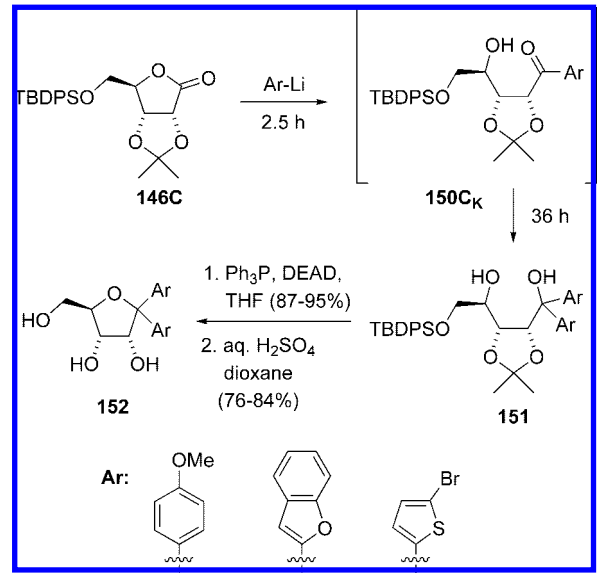
4.3.2. Nucleophilic Addition to 1,2-Anhydrofuranoses

A conceptually different approach was recently developed by Seitz (Scheme 31),[163] starting with epoxidation of the furanose glycal **137** with dimethyldioxirane, which gave rise to anhydrofuranose **138**, whose oxirane ring was stereoselectively opened by various triarylalanes to afford arabinofuranoses **139**; triarylalanes were found to be superior to aryldimethylalanes, as they gave substantially better isolated yields. Arabinofuranoses **139** thus obtained were then deoxygenated at 2′-position in two steps by using the Barton procedure. Final deprotection of the resulting **141** gave 2′-deoxyribofuranose-*C*-nucleosides **142** in moderate overall yields and excellent diastereoselectivities. The need of 3 equiv of the aryl building block (Ar_3Al) may be prohibitive in the case of more complex aryl moieties.

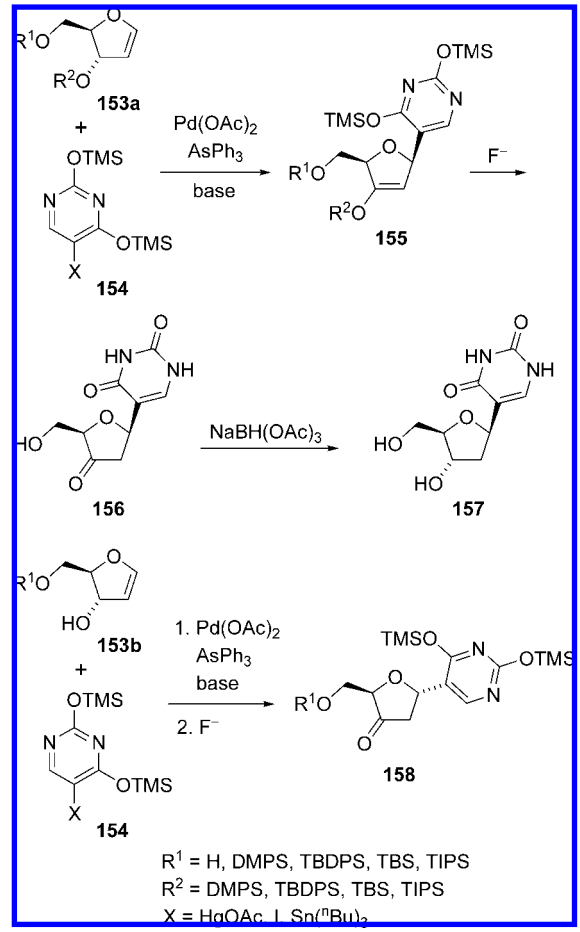
4.3.3. Couplings of Nucleophiles with Halogenoses

A coupling reaction of protected carbohydrates with soft organometallic reagents is the oldest method for the construction of the *C*-glycoside bond[164] and has become an important approach to *C*-nucleosides as well. Both protected ribosyl and 2-deoxyribosyl bromides or chlorides may be used as starting materials. Among them, Hoffer's chlorosugar (1-chloro-2-deoxy-3,5-bis[*O*-(*p*-toluoyl)]-α-D-ribofuranose **60**)[165] became one of the most widely used building blocks. The typical reaction procedure features a coupling reaction of halogenose and an organometallic reagent based on cadmium,[55,166] zinc, mercury, magnesium,[167,168] and even lithium.[169] The yields are generally low, determined by the nature of the organometallic reagent (Scheme 32).[170,171] The α-anomer is the major product in all cases, regardless of the variation of the metal, solvent, temperature, or reaction conditions. To obtain the more desirable, naturally configured *β*-anomer, an acid-catalyzed epimerization is, therefore,

Scheme 37. Formation of C1′-Disubstituted *C*-Nucleosides

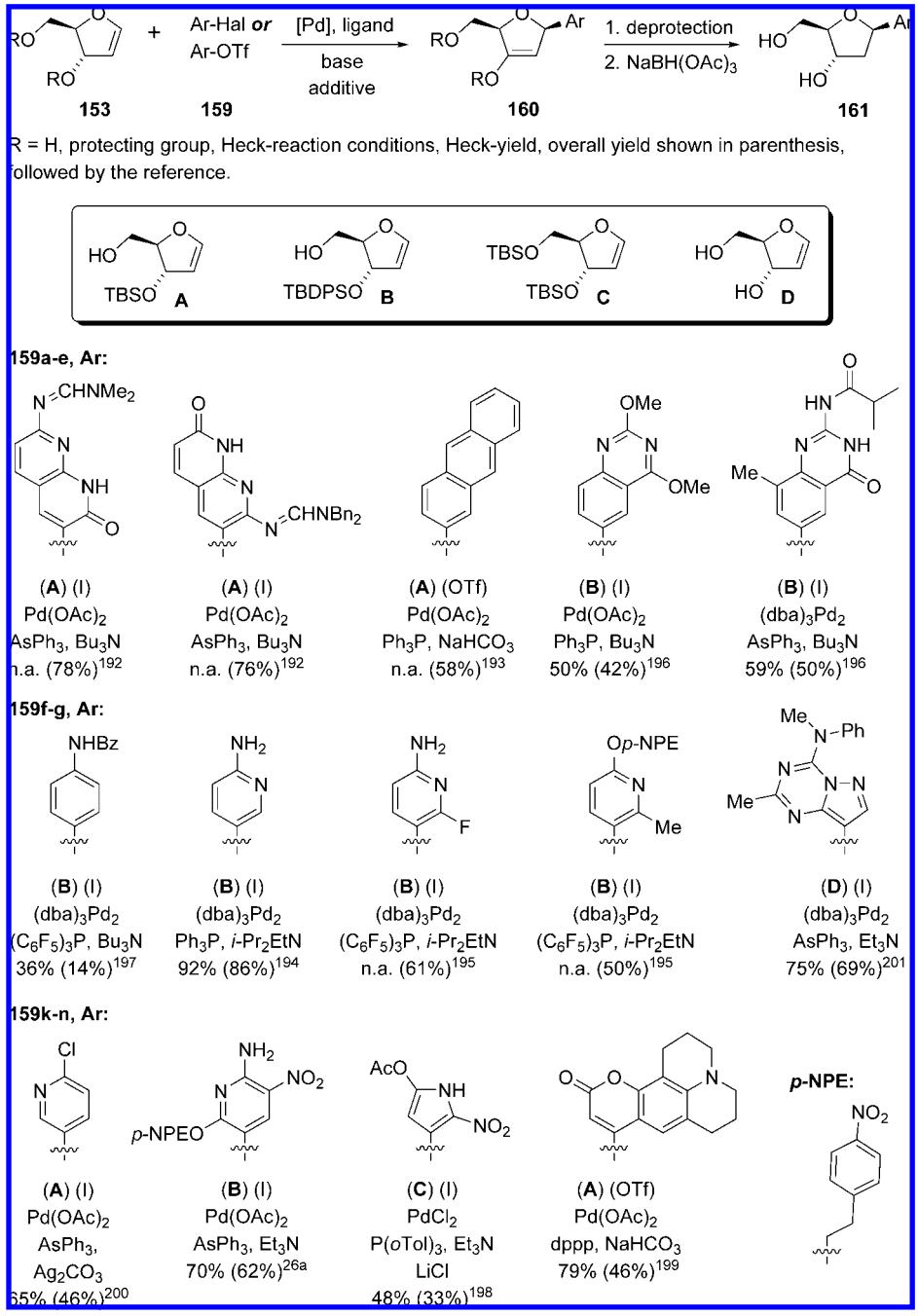


Scheme 38. Heck-Type Coupling of Furanoid Glycals with an Aglycon Precursor and Heck-Enol Deprotection Followed by Stereoselective Reduction



normally required as an additional step. In spite of the unfavorable stereochemical outcome, the synthetic approach utilizing the halogenose-coupling reaction has been further optimized. Seitz reported an environmentally friendly organometallic reagent based on mixed magnesium-cuprate (Normant cuprate). The use of this organometallic reagent substantially improved the isolated yield of the anomeric mixture, which again, in combination with subsequent

Scheme 39. Examples of Heck Coupling Approach Followed by Deprotection and Reduction



isomerization, renders this method competitive, owing to its simplicity (Scheme 32).[76b,172]

1-Halogeno-ribofuranoses are also suitable building blocks in this strategy as demonstrated by the reaction of furanylmercury chloride with bromoribose **144** to give a separable anomeric mixture with predominant α-anomer **145α**, which was isolated and submitted to the acid-catalyzed epimerization (via an open-chain benzylic-type cation) to afford *β*-anomer in 80% de purity (Scheme 33).[173]

4.3.4. Nucleophilic Addition to Furanolactones

Addition of an organometallic nucleophilic reagent across the lactone functionality is the most frequent synthetic tactic to construct the new C−C anomeric bond in the case of *C*-ribonucleosides, and one of the most frequent approaches to the synthesis of 2′-deoxy-*C*-ribonucleosides (together with the Heck coupling).

Thus, reaction of the protected lactone **146** with an aryl- or (heteroaryl)lithium reagent at low temperature is known to produce the expected hemiketal **147** (which usually exists as an equilibrium mixture of the open form and two hemiketal anomers). Two methods have been developed for the subsequent reduction of the hemiketal function to afford the desired *C*-nucleoside **149** (Scheme 34). The older method features deoxygenation of hemiketal **147** by a Lewis acid (typically boron trifluoride etherate), followed by reduction of the oxonium intermediate **148**, usually with triethylsilane. As a rule, the latter reduction proceeds with good-to-excellent stereoselectivity, giving rise to the desired *β*-anomers as major or as sole products.[48,73,174−182] The stereoselectivity depends on the nature of the aglycon unit and, most

importantly, on the protecting groups in the carbohydrate unit (Scheme 34). Only in the case of some pyridine organometallics, significant amounts of α-anomers were formed.[174d] The major side-reaction in the additions to 2′-deoxyribonolactones **B** is the double elimination, leading to the corresponding furan derivatives.

Alternatively, the hemiketals arising from the addition of the organometallics can be reduced to the corresponding diols and then cyclized to ethers. Thus, hemiketal **147** was reduced by a complex hydride to afford diol **150** that was cyclized under Mitsunobu conditions to the desired nucleoside analogue **149** (Scheme 35).[183−187] The stereoselectivity of this reaction sequence can be controlled in different ways. Thus, Benhida reported on the stereoselective sequence of reduction of hemiketals **147** with borohydride, followed by Mitsunobu cyclization of the intermediate diols **150** bearing indole, imidazole, and benzimidazole moiety.[186] The stereoselectivity was found to be controlled by the presence and the nature of the *N*-protecting group on the heterocycle and can reach up to 80% de. Thus, for instance, hemiketal **147** bearing a benzimidazole or indole moiety, protected by dimethylaminosulfonyl group, was reduced with borohydride, and the resulting diol **150**, formed quantitatively, was cyclized upon Mitsunobu conditions to afford the α-anomer (**149**). On the other hand, removal of the protecting group gave rise to the *β*-anomer **149** as the sole product.

A more general stereocontrol was reported by Hanessian (Scheme 35):[187] Stereoselective reduction of hemiketal **147** was performed by using L-selectride alone (leading to α-anomer after the Mitsunobu cyclization) or with an addition of zinc chloride (affroding *β*-anomer). By using this protocol, Hanessian was able to prepare both anomers of pseudouridine **Ψ** in five steps from unprotected ribonolactone; the sequence involving the latter stereocontolled reduction, followed by Mitsunobu cyclization as the key features, represents an efficient route to **Ψα** (65%) and **Ψβ** (46%), each obtained as a single anomer.

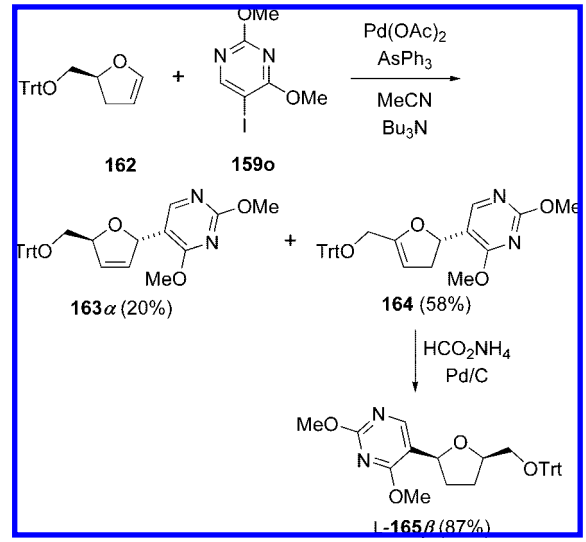
The adduct resulting from the reaction of aryllithium with protected ribonolactone can, in general, be isolated either as a hemiketal **147C$_h$** or as a hydroxy ketone **147C$_k$** (Scheme 36). Benhida found the hydroxy ketone as a stable and predominant product in the case of electronically rich aryl moiety.

The available ketone function was employed in the second addition of an excess of aryllithium to form the C1′-disubstituted *C*-nucleoside analogues **152** (Scheme 37).[188] Mitsunobu cyclization of diols **151** proceeded readily, owing to the effect of the two aryl groups, which induced selective activation of the benzylic hydroxyl function, and afforded the respective products **152** in high yields.

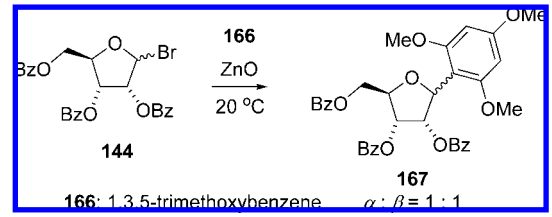
4.3.5. Heck Coupling

The Heck-type coupling reaction between the anomeric carbon of carbohydrate derivatives **153** and (hetero)aromatics **154** has evolved into the most important method for the synthesis of 2′-deoxy-*C*-nucleosides in the last 30 years;[6f] the first report came from Daves.[189a] In general, Heck reaction is highly regio- and stereoselective. When applied to glycals, whose double bond is electron-rich, the new *C*-glycosidic bond is formed selectively at the carbon adjacent to the oxygen (the anomeric carbon), and the initial attack occurs from the less sterically hindered face of the glycal ring to produce **155**. The stereocontrol can be further enhanced by the bulky protection group at 3-position, especially in

Scheme 40. Heck-Type Coupling in the Synthesis of 2′,3′-Dideoxy *C*-Nucleosides



Scheme 41. Lewis Acid-Catalyzed Glycosylation

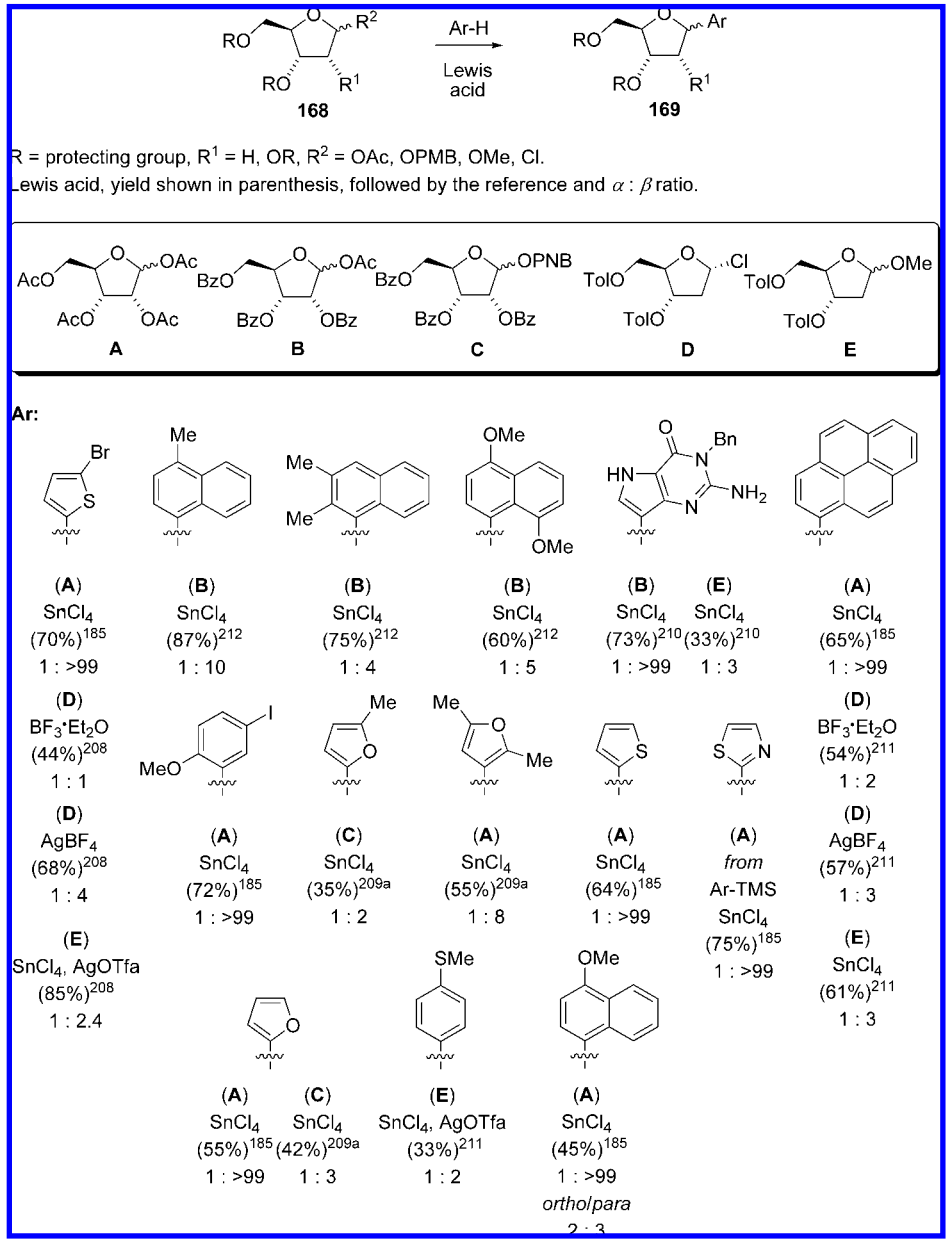


combination with the bulky Ph_3As ligand, so that the *β*-anomer **155** is formed exclusively. On the other hand, an unprotected 3-hydroxyl function drives the attack of the organopalladium species to occur from the opposite direction to give α-anomer **158** exclusively, presumably via coordination of the metal and steering its approach (Scheme 38).[190] In most cases, the 5′-unprotected-3′-protected glycals **A** or **B** (Scheme 39) are the best substrates, giving the best yields and *β*-selectivity. The carbonyl functionality is released (**155** → **156**) by the fluoride-mediated desilylation and subsequently reduced by sodium triacetoxyborohydride with high stereoselectivity to afford the desired 2′-deoxy-*C*-nucleoside **157** as a result of complexation of the hydride to the free 5′−OH, which steers the reduction of the carbonyl from the more hindered side.[35b,191]

Recent examples of utilization of the Heck-type reaction in the synthesis of *C*-nucleosides are summarized in Scheme 39.[26a,192−200] Raboisson employed the fully unprotected glycal **153D**, affording the desired *β*-anomer exclusively.[201] The crucial effect of Ag_2CO_3 on the efficiency of the Heck coupling was recently reported[200] for iodopyridine **159k**.

The Heck reaction was also used in the stereoselective synthesis of 2′,3′-dideoxy-*C*-nucleosides (Scheme 40),[202] starting with the enantiopure 2,3-dihydrofuran **162**, which was converted into a mixture of 2,3- and 2,5-dihydrofurans **163α**, and **164** on the Pd-catalyzed reaction with iodopyrimidine **159o**. Although the major product **164** lost its original chiral center, this was restored via a stereoselective hydrogenation that occurred from the less hindered face of the dihydrofuran ring, which gave rise to the unnatural L-carbohydrate L-**165*β***. The latter reaction sequence gave a similar yield as that leading to the naturally configured D-**165*β***.

Scheme 42. Lewis Acids-Mediated Electrophilic Substitution



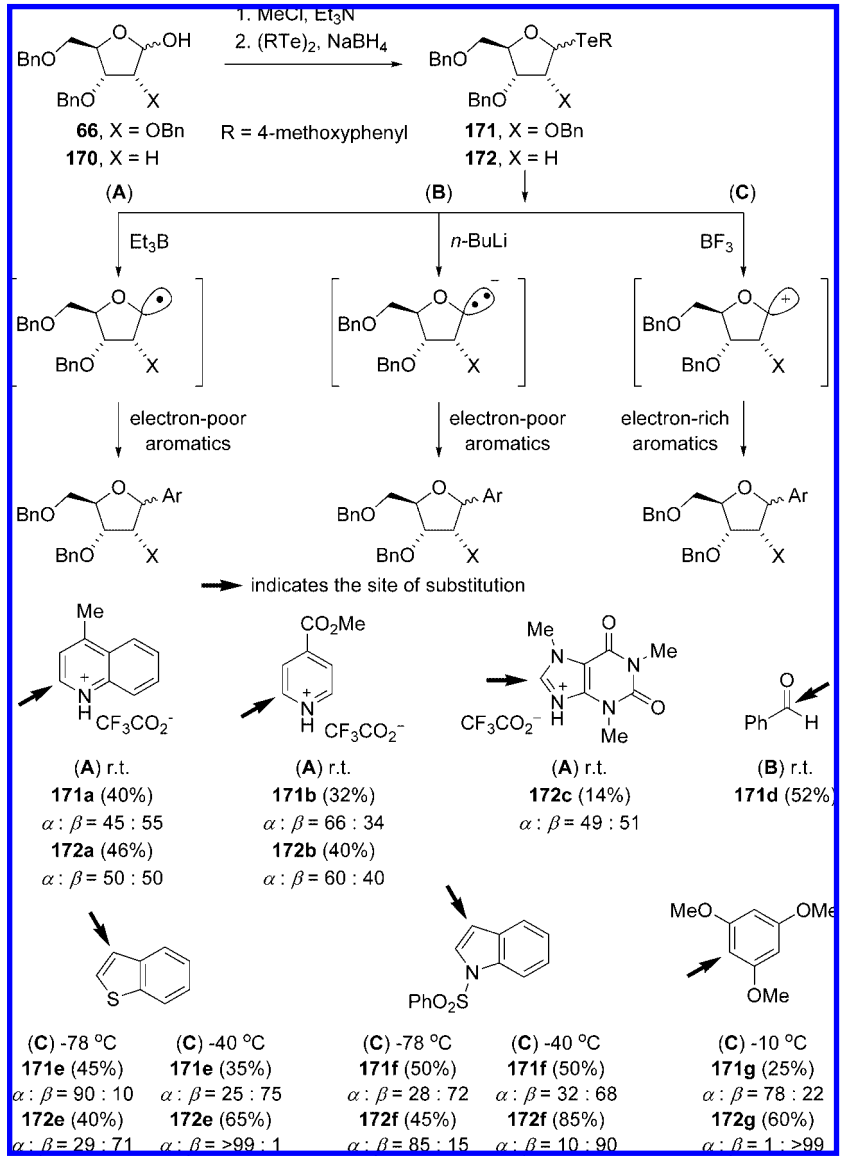
Several general observations have been made for the Heck-type coupling reaction of the glycal to the aglycon.[203] Palladium acetate and $(dba)_3Pd_2$ were found to be the most successful sources of palladium, and $AsPh_3$ was optimized as the ligand of choice. Standard solvents for the Heck reaction (DMF, MeCN, THF) have been employed in most cases. The most frequently used bases are Bu_3N, Et_3N, and iPr_2NEt. Inorganic bases, such as $NaHCO_3$, have only been used in a few cases.

4.3.6. Lewis Acids-Mediated Electrophilic Substitutions

Coupling reactions of a preformed carbohydrate and a (hetero)aryl, catalyzed by Lewis acids (i.e., a Friedel−Crafts type electrophilic substitution of the aromatic ring by the glycon), provide a simple route to *C*-nucleosides. The method was developed for the synthesis of *C*-glycosides of hexopyranoses.[204,205] Šorm utilized the Lewis acid-mediated coupling reaction in the synthesis of showdomycin **43** (vide infra, Scheme 45). Condensation of benzylated bromose **144** with *sym*-trimethoxybenzene **166** in the presence of zinc chloride gave *C*-nucleoside **167** (Scheme 41).[206] This protocol has then been applied to a broad range of electron-rich benzenes to afford equimolar mixtures of anomers of the products.[207]

The simplicity of the process is balanced with poor regioselectivity of the aglycon attack and with generally modest stereoselectivity of the anomeric C−C bond formation. Reference examples are shown for the reaction of protected carbohydrates **168** (ribofuranoses **168A**−**C** and 2′-deoxyribofuranoses **168D**−**E**) with a range of aglycon units (Scheme 42).[185,208−212] The regioselectivity is fully controlled by the nature of the aglycon unit, whereas diastereoselectivity and the yield are affected by the interaction of all three components, i.e., the protected carbohydrate, the aglycon unit, and the Lewis acid.[122,213] This Friedel−Crafts methodology is applicable only to some electron-rich arenes and heterocycles, and in some cases, it is accompanied by double arylation of the sugar to form the undesired 1,1-diaryl alcohols (**151**; a similar behavior was shown in Scheme 37).[214]

Scheme 43. Tellurides in *C*-Nucleoside Synthesis



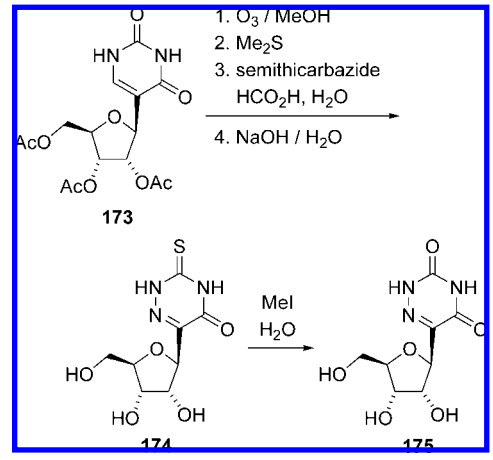
Tellurides are known as useful building blocks reactive toward electrophiles, nucleophiles, and radicals.[215] Togo and Yokoyama developed a procedure based on the coupling reaction of a carbohydrate anomeric radical, anion, and cation with an aglycon unit (Scheme 43).[216] The ribofuranose derivatives **66** and **170** were transformed into the corresponding anisyl tellurides and directly treated with either triethylborane, buthyllithium, or boron trifluoride, and then reacted with an appropriate aryl- or heteroarylaglycon unit. No stereoselective reaction was observed. The reactions of a mixture of anomers (route **A**) gave essentially the same results as in the cases where pure α- and β-anomer of telluride **171** and **172** had been employed in the reaction. The reactions of a cation (route **C**) resulted in a certain degree of stereoselectivity. However, these were of the same value as in the case of the thermodynamic equilibrium ratio obtained by epimerization mediated by boron trifluoride itself.

4.4. Modification of the Existing *C*-Nucleosides

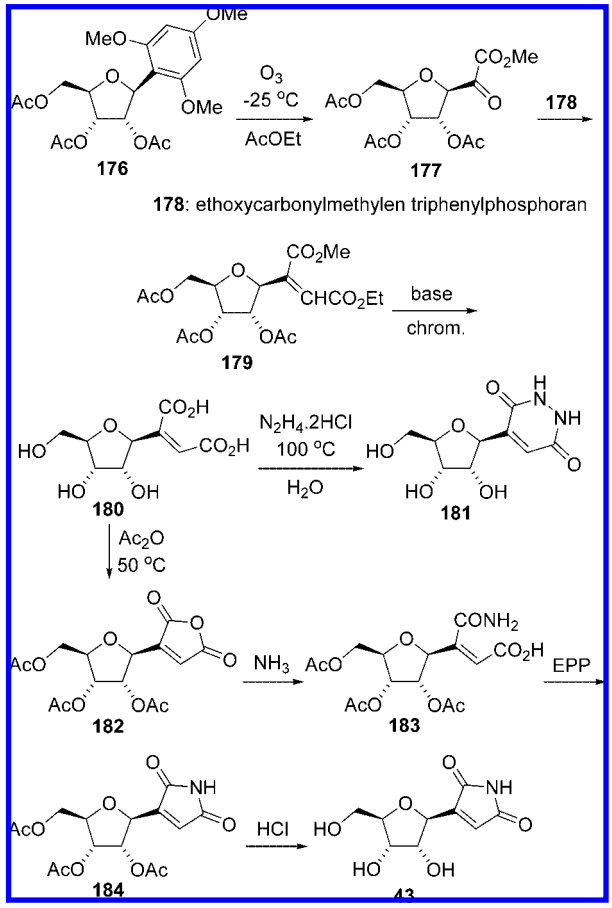
The last synthetic strategy to be discussed here is based on modification(s) of functional groups in the naturally occurring or synthetic *C*-nucleosides. These modifications may include either the aromatic or the carbohydrate part of the *C*-nucleoside, or both. The C−C bond between the aglycon and carbohydrate is kept intact during all transformations.[217]

This strategy was employed in the syntheses of analogues of the naturally occurring pseudouridine (Scheme 44).[218]

Scheme 44. Modification of Protected Pseudouridine 173



Scheme 45. First Synthesis of Showdomycin 43 and Its Pyridazine Analogue 181

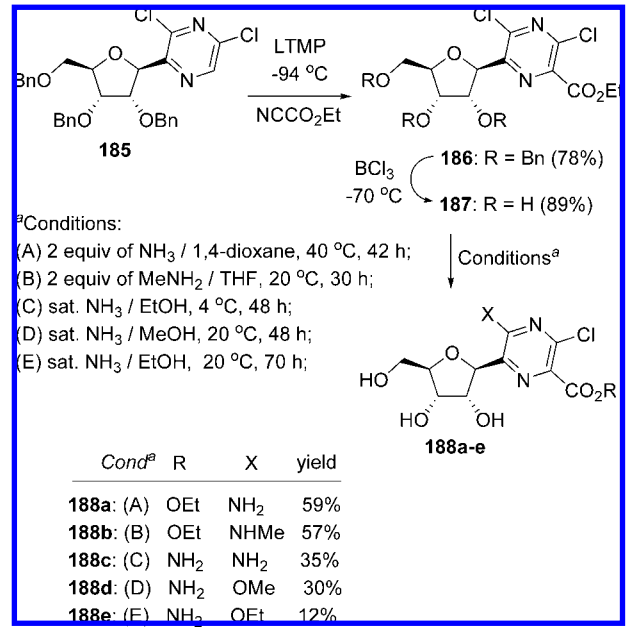


Protected pseudouridine **173** was transformed into thiatriazolone **174**, which was hydrolyzed to afford the 6-aza analogue of pseudouridine **175**. However, this approach, apparently quite promising, has not received overwhelming attention because the natural sources are very limited, in both quantity and structural diversity.

Šorm reported on the first synthesis of showdomycin (Scheme 45).[206] The parent *C*-nucleoside structure **176** was obtained by a Lewis acid-catalyzed condensation (vide supra, Scheme 41), followed by the separation and purification of the β-anomer by crystallization. The protected *C*-nucleoside **176** was ozonolyzed with reductive workup, and the resulting ketoester **177** was directly treated with phosphorane **178** in refluxing benzene, to give rise to the unsaturated ester **179**; the (*Z*/*E*) isomer ratio on the new double bond was 10:1. After alkaline hydrolysis, the desired (*Z*)-diacid **180** was separated by ion-exchange chromatography and then treated with hydrazine dihydrochloride to give pyridazine **181**. The conversion of the latter diacid **180** into showdomycin **43** was accomplished in four steps and 14% yield as follows: dehydration of **180** afforded anhydride **182**, whose reaction with ammonia produced maleamic acid **183**, which was dehydrated with ethyl polyphosphate in dimethylformamide to afford maleimide **184**. Final deprotection with 2% HCl in methanol gave showdomycin **43**.

A renaissance of this method has begun in the late 1990s. Many stereoselective methods were developed to construct *C*-nucleosides as shown in previous paragraphs of this chapter. The key feature of this approach is the stereoselective synthesis of a common intermediate, which can be elaborated into a number of *C*-nucleosides.

Scheme 46. Synthesis of Pyrazinoic-Ester *C*-Nucleosides 188



Cond[a]	R	X	yield
188a: (A)	OEt	NH_2	59%
188b: (B)	OEt	NHMe	57%
188c: (C)	NH_2	NH_2	35%
188d: (D)	NH_2	OMe	30%
188e: (E)	NH_2	OEt	12%

Townsend reported on the preparation and subsequent derivatization of pyrazinoic ester **186**.[219] Protected pyrazine *C*-nucleoside **185** was selectively lithiated by lithium 2,2,6,6-tetramethylpiperidide at low temperature and carboxylated by using ethyl cyanoformate; this was an optimized procedure as a number of standard carboxylation protocols failed. The ester **186** thus formed was debenzylated, and the resulting ribose derivative **187** was submitted to a variety of functionalization reactions. A range of potential chemotherapeutics **188a**−**188e** was thus prepared in three steps (Scheme 46).

Since a number of the existing procedures for construction of the anomeric C−C bond only exhibit moderate stereoselectivity, controlled epimerization would be highly desirable. Optimized procedures were reported for the *C*-nucleosides bearing both electron-donating (EDG) and electron-withdrawing groups (EWG).[220,221]

Stivers has developed two procedures. Thus, isomerization of glycosides with EDG can be catalyzed by trifluoroacetyl (TFA) (5%), whereas stronger acidic conditions are required for EWG substituted aglycons. A catalytic amount of a mixture of TFA and benzensulfonic acid proved to be optimal (Scheme 47). Examples of thermodynamic equilibrium distribution resulting from the epimerization are shown in Table 1.

Recently, the strategy of *C*-nucleoside modification was employed in the syntheses of the artificial DNA-nucleoside analogue d**xC** from d**xT** (Scheme 48).[36c] The starting d**xT** was transformed into its 4-thia analogue **190** and subsequent aminolysis afforded d**xC** in 74% overall yield.

Procedures for modification of the carbohydrate moiety have played an important role since the discovery of *C*-nucleosides.[222] Modification of the carbohydrate part of an easily accessible *C*-nucleoside remains the major route to compounds possessing modified (artificial) carbohydrate, such as the D4 modification in the Sartorelli preparation of D4-9-deazaguanosine (Scheme 49).[223] In this approach, 9-deazaguanosine **191** was treated with bis(trimethylsilyl)-azane in anhydrous DMF and then with isobutyric anhydride in pyridine to afford the *N*-protected 9-deazaguanosine **192**. Standard protection of the primary hy-

Scheme 47. Epimerization of *C*-Nucleosides 189

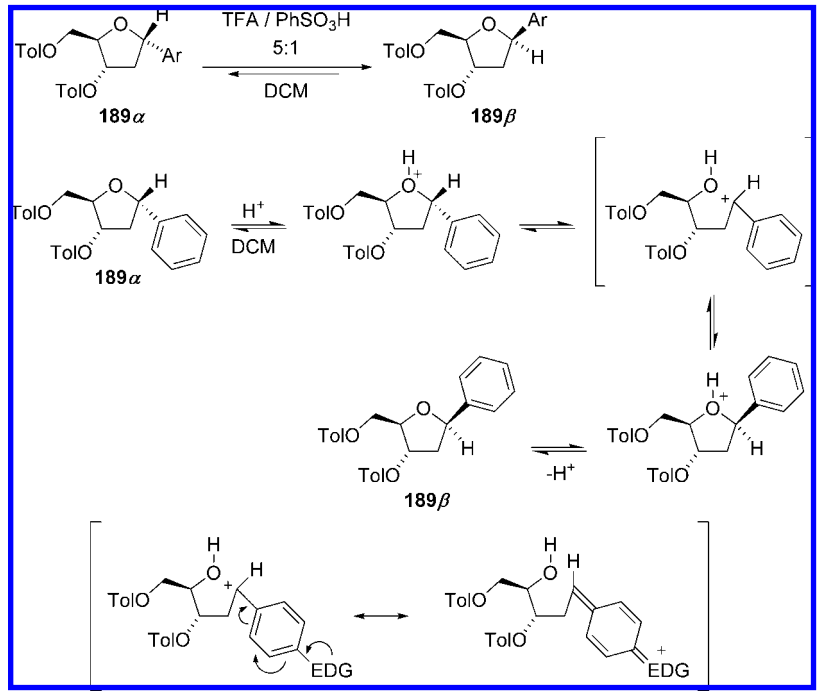
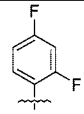
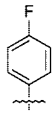
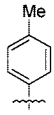
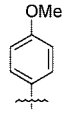


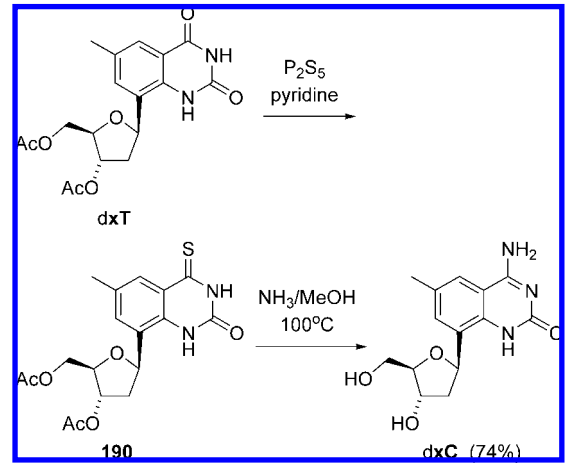
Table 1. Epimerization of α-*C*-nucleosides 189 (Scheme 47)

compound	Ar	conditions	α-isomer[a] (%)	β-isomer[a] (%)
189a		20 mol % catalyst 40 °C, 40 h	37	58
189b		12 mol % catalyst 40 °C, 20 h	35	54
189c		12 mol % catalyst 40 °C, 20 h	38	54
189d		12 mol % catalyst 40 °C, 20 h	27	65
189e		5 mol % catalyst 40 °C, 20 h	30	64
189f		5 mol % catalyst 23 °C, 2 h	20	78
189g		5 mol % catalyst 40 °C, 20 h	32	63

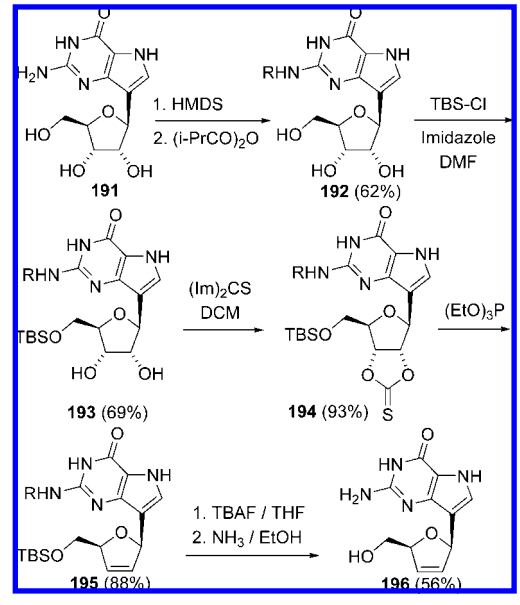
[a] Isolated yield.

droxyl function with *tert*-butyldimethylsilyl gave **193**, which was then converted into the cyclic thiocarbonate **194** by treatment with thiocarbonyl diimidazole. Deoxy-

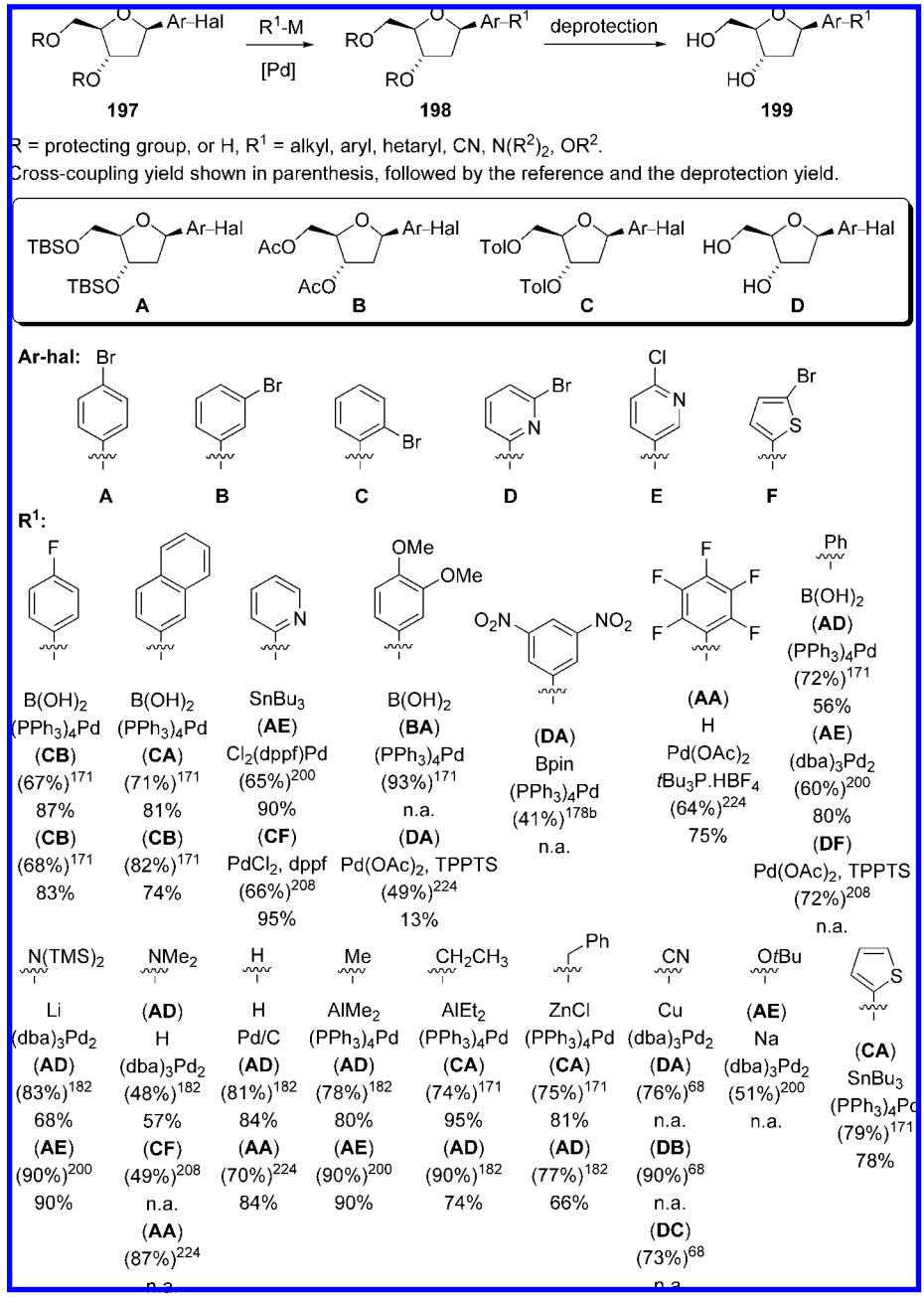
Scheme 48. Synthesis of dxC



Scheme 49. Modification of the Carbohydrate Moiety and Synthesis of D4 9-Deazaguanosine 196



Scheme 50. Cross-Coupling Modification of the Nucleobase Moiety



genation of the latter product with triethyl phosphite afforded dihydrofuran **195**, whose deprotection in two steps yielded D4-9-deazaguanosine **196**.

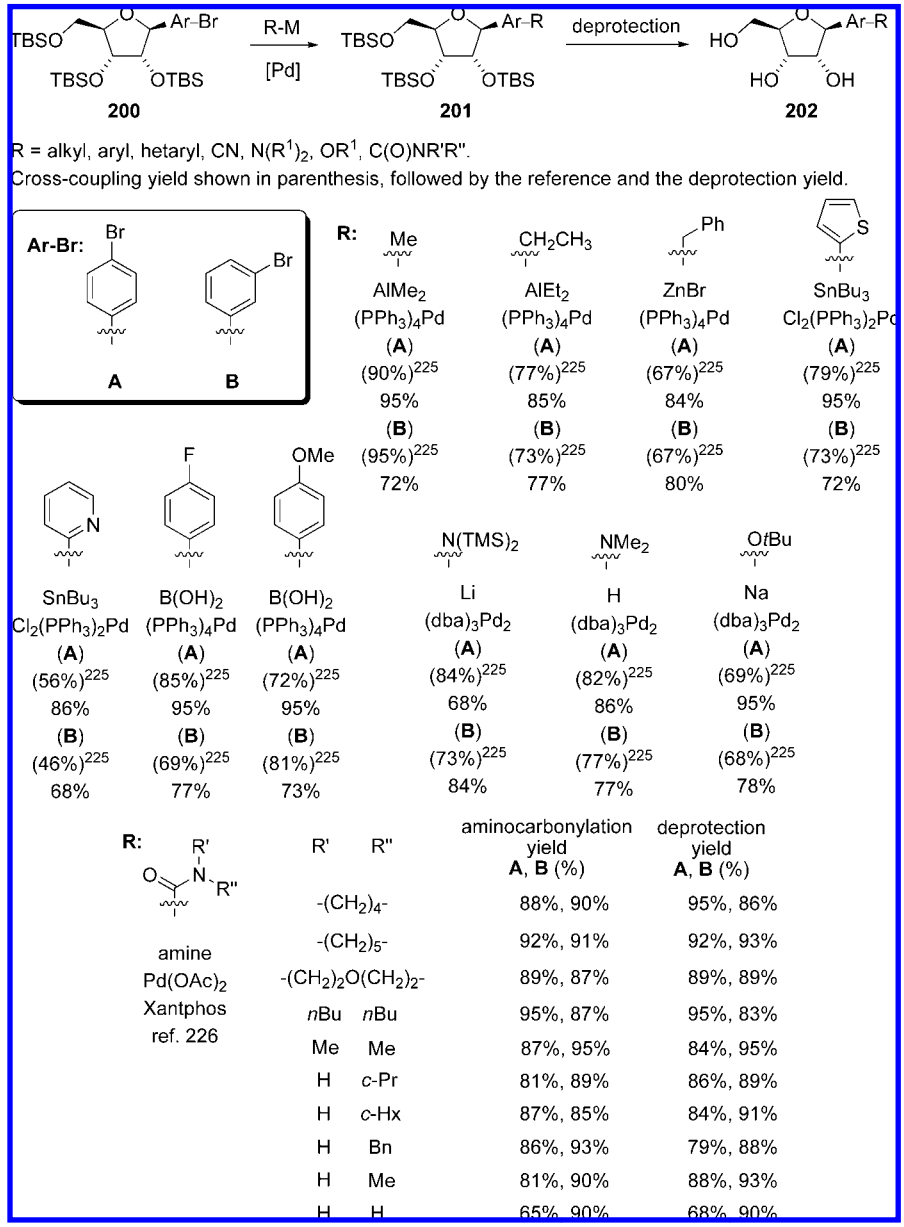
4.5. Modular Approaches

Modular approaches applicable to the synthesis of a variety of *C*-nucleosides are highly desirable for the diversity-oriented preparation of a larger series of derivatives without the need to optimize the difficult construction of the C−C "glycosidic" bond for every example. The three obvious variable modules are the carbohydrate part, the aromatic moiety, and the additional functional groups.

The first example of such a modular approach to *C*-nucleosides has been developed by Hocek: his protocol consists of the synthesis of haloaryl-*C*-nucleoside intermediates, followed by a functional group transformation to introduce various substituents. Thus, the protected 2′-deoxy-*C*-nucleosides **197** bearing brominated benzenes,[171,224] bromo- and chloropyridines,[182,200] and 2-bromothiophene[208] nucleobase were submitted to a wide range of palladium-catalyzed reactions (Scheme 50). These involved simple hydrogenolysis, cross-coupling reactions with trimethylalane and triethylalane, Suzuki−Miyaura coupling with a wide variety of boronic acids, Negishi coupling with benzylzinc chloride, Stille coupling with aryl tributyl stannanes, Hartwig−Buchwald aminations with lithium bis(trimethylsilyl)amide, methylamine, and dimethylamine, and Hartwig−Buchwald etherification with sodium *tert*-butoxide. The subsequent deprotection of the resulting product **198** gave 2′-deoxyribonucleosides **199** with a broad range of substitution patterns. Independently, the same approach was used by Leumann for the synthesis of biphenyl-*C*-nucleosides[178b] and by Romesberg for the synthesis of benzonitrile-*C*-nucleosides.[68]

Considerably less attention has been paid to the modification of *C*-nucleosides possessing the ribofuranose moiety.

Scheme 51. Cross-Coupling Modification of the Nucleobase Moiety of Ribofuranosides

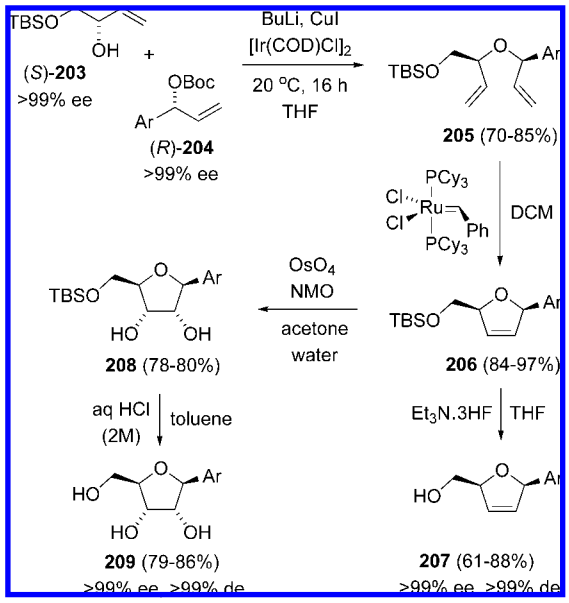


Palladium-catalyzed modifications of halogenated nucleobases of protected ribofuranosides **200** were recently developed by Hocek (Scheme 51).[225] As with the deoxyribo series, the fully silylated ribofuranosides bearing a bromophenyl nucleobase were submitted to a range of cross-coupling reactions with trimethylalane and triethylalane, Suzuki−Miyaura coupling with boronic acids, Negishi coupling with benzylzinc chloride, Stille coupling with aryl tributyl stannanes, Hartwig−Buchwald aminations with lithium bis(trimethylsilyl)amide, and dimethylamine, and Hartwig-Buchwald etherification with sodium *tert*-butoxide. The subsequent deprotection of **201** afforded the desired 1′-*C*-ribofuranosides **202** in good overall yields. The protected ribofuranosides **200** were also successfully submitted to palladium-catalyzed aminocarbonylation (Scheme 51)[226] with a range of primary and secondary amines under an atmospheric pressure of carbon monoxide. Extensive search for an efficient synthetic equivalent of ammonia was also carried out; the best results were obtained with ammonium chloride, which afforded the corresponding products in good yields, only slightly lower than those attained with (di)alkyl amines.

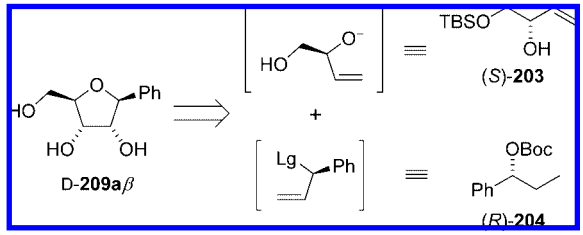
A conceptually new modular approach has been developed by Kočovský (Scheme 52).[227] His strategy relies on the carbohydrate construction that allows a combination of α-, *β*-, D-, L-ribofuranosides and their 1′,2′-didehydro-1′,2′-dideoxy (D4) analogues by using one methodology. Here, the silyl-protected enantiopure, commercially available diol **203** reacts with the Boc-functionalized branched aryl propenols **204**[228] in the iridium-catalyzed[229,230] stereospecific allylic substitution reaction,[231,232] affording diallyl ethers **205**. Utilizing the Grubbs first-generation catalyst, the ring-closing metathesis (RCM) reaction closes the cyclic ribofuranose core in good yields. Intermediates **206** can be either deprotected under mild conditions to form the corresponding D4 *C*-nucleoside analogues **207** or dihydroxylated to form the vicinal diols **208**. Simple acidic deprotection procedure furnished the desired 1′-*C*-ribofuranosides **209** in excellent overall yields.[227]

The enantiopurity and diastereopurity of all the products is based on the enantiopurity of the starting materials and conservation of the stereochemical integrity throughout all the transformations employed. From this point of view, the

Scheme 52. Iridium-Catalyzed Allylic Substitution Approach to D- and L-*C*-Ribofuranosides and Their D4 Analogues



Scheme 53. Chirality Source Retention in the Synthesis of Novel Ribofuranisides 209



most important is the first strategic connection, utilizing the stereocontrol exercised by the iridium catalyst in the allylic substitution.[233,234] The right choice of the right enantiomer of the starting material is very straightforward. For example in the case of 1′C-aryl ribofuranose, there are four stereocenters at carbons 1′, 2′, 3′, and 4′. The centers 2′ and 3′ (*syn*) are constructed in the last step, and the configuration fully depends on the configuration at centers 1′, and 4′. Thus, full stereocontrol can be easily attained: the protected diol (*S*)-**203** gives rise to D-ribofuranoses, whereas its enantiomer (*R*)-**203** serves as a precursor of L-ribofuranoses. α-Ribofuranoses arise from the (*S*)-,(*S*)-, and (*R*)-,(*R*)-combinations of enantiomers of diol **203** and carbonate **204**, whereas β-ribofuranosides result from the mixed (*S*)-,(*R*)-, and (*R*)-,(*S*)-configurations (Scheme 53).

This new methodology is suitable for the synthesis of 1′C-arylribofuranoses and their D4-analogues bearing non-*ortho*-substituted aromatics and heteroaromatics, lacking coordinating atoms (nitrogen).

5. Conclusions

Despite the plethora of synthetic approaches available for the construction of *C*-glycosidic bonds, there is no generally applicable, efficient, and fully stereoselective method. The buildup approaches are usually very laborious, multistep sequences with low overall yields and limited applicability in the synthesis of a series of compounds. Approaches based on the coupling of the aglycon unit with the carbohydrate part are generally shorter but inherently face problems of stereoselectivity and, again, none of them is applicable to a wider range of arene and heteroarene moieties. The coupling of (hetero)arylorganometallics with a halogenose usually gives rise to the undesired α-anomer as the major product (so that additional isomerization is required), and the reaction is often accompanied by elimination to form (hetero)arylfurans. Moreover, the most efficient organometallics in these couplings are the highly toxic diarylcadmium species. Additions of organometallics (usually aryllithium species) to lactones or lactols are more general but require another difficult step, namely, reduction of the resulting hemiacetal in the former case and the Mitsunobu cyclization of the diol in the latter instance. The Friedel−Crafts approach is efficient for electron-rich arenes but is often accompanied by problems associated with regioselectivity and side reactions. The Heck coupling of (hetero)aryl halides with glycals represents the mildest and most general methodology but often requires a time-consuming optimization of the catalytic system and reaction conditions.

Typically, for each target *C*-nucleoside class, several alternative methods need to be explored before a satisfactory route is identified. Therefore, the modular approaches based on either further modification of the haloaryl-*C*-nucleosides or allylic substitution−RCM sequence can be regarded as a valuable addition to the portfolio of available methods. Certainly, there is still a lot of space for development of stereoselective catalysis in the *C*-glycosidation reactions.

Further development of efficient and selective methodologies will allow a wider use of *C*-nucleosides in medicinal chemistry and chemical biology. Apart from the inhibition of relevant enzymes of nucleotide metabolism (PNP, nucleosidases, IMP dehydrogenase, etc.), the finding of new antiviral and antineoplastic activities and new mechanisms of action can be expected. The *C*-nucleoside will undoubtedly play an important role in the quest for the extension of the genetic alphabet and in development of alternative genetic systems.[235] Other possible fields of application in chemical biology will include construction of chemical probes for studying of enzyme mechanisms and fluorescence labeling.

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