https://doi.org/10.1070/RCR5013

Synthesis and biological activity of aza and deaza analogues of purine nucleosides

Elena S. Matyugina, Sergey N. Kochetkov, Anastasia L. Khandazhinskaya

Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, ul. Vavilova 32, 119991 Moscow, Russian Federation

Analogues and derivatives of nucleic acid components have been used as key drugs in different areas of medicine over the past decades. The replacement of one or more nitrogen atoms of the heterocyclic base with a CH group affords deazapurine nucleoside analogues, and the replacement of the methine group with a nitrogen atom gives azapurine derivatives. A combination of aza and deaza moieties in the purine base leads to aza(deaza)-modified bases. Some nucleoside analogues were found to exhibit pronounced anticancer and antiviral activity. The synthesis and evaluation of biological activity of aza- and deazapurine nucleoside analogues have attracted interest from researchers four decades ago. This review describes and integrates the studies concerning certain aspects of the synthesis and(or) activity of various representatives of this class of compounds. The structure – biological activity relationships are analyzed. The successful approaches to the design of aza- and deazapurine nucleoside analogues are considered. A comparison is given for the methods of chemical and enzymatic synthesis of these compounds.
The bibliography includes 161 references.

Contents

1. Introduction 1454
2. Spectrum of biological activities of aza and deaza analogues of purine nucleosides 1455
3. Chemical synthesis 1459
3.1. Condensation of a heterocyclic base with a carbohydrate moiety 1459
3.1.1. The C – N bond formation 1459
3.1.2. The C – C bond formation. Synthesis of 9-deazapurine nucleosides 1473
3.2. Synthesis of deaza- and azapurine nucleoside analogues *via* the construction of the heterocyclic base 1477
3.2.1. 1-Deazapurine nucleoside analogues 1477
3.2.2. 3-Deazapurine nucleoside analogues 1478
3.2.3. 7-Deazapurine nucleoside analogues 1478
3.2.4. 9-Deazapurine nucleoside analogues 1479
3.2.5. 2-Azapurine nucleoside analogues 1482
3.3. Synthesis of acyclic and carbocyclic deaza- and azapurine nucleoside analogues 1483
4. Chemical-enzymatic synthesis 1486
5. Conclusion 1488
6. List of acronyms and designations 1488

This review is dedicated to the blessed memory of our collegue and friend Sergei Nikolaevich Mikhailov, a prominent scientist in chemistry of nucleic acids, dearly departed on November 5, 2020.

1. Introduction

Heterocyclic bases of nucleosides and nucleotides not only have an important structural role in DNA and RNA but are also involved in numerous key metabolic processes, acting as cofactors or regulators of diverse types of reactions. Currently, analogues and derivatives of nucleic acid components, in particular those modified at the heterocyclic base, are used in anticancer, antibacterial, antifungal and antiviral therapy. Modifications of nucleobases can exert a significant effect on their interaction with relevant targets, playing an essential role in the spectrum of activity of the analogues.

One of the known structural modifications of naturally occurring purine nucleosides is based on the replacement of one or several nitrogen atoms of the heterocyclic base with the methine group. This modification affords deazapurine nucleoside analogues (1-deaza, 3-deaza, 7-deaza, 9-deaza, 1,7-dideaza derivatives, *etc.*) exhibiting antitumour and antiviral properties. Another type of modifications of the purine base involves the replacement of the methine group, primarily at the 2 and 8 positions, with a nitrogen atom giving rise to 2-aza- and 8-azapurine nucleoside analogues, respectively. Compounds of this group possess strong antitumour activity. A combination of aza and deaza moieties in the purine base gives rise to another type of modified purine bases. Nucleoside analogues bearing bases of this type, *e.g.*, 7-deaza-8-azaadenosine, 6-chloro-1-deaza-8-azapurine nucleosides, 4-aza-7,9-dideazaadenosine, *etc.*, exhibit high antiviral activity.

The synthesis of aza- and deazapurine nucleoside analogues and the evaluation of their biological activity have attracted attention about four decades ago. More than a hundred articles and several reviews concerning certain aspects of the synthesis and(or) activity of different representatives of this class were published during these years. Thus, a few examples of the synthesis of deazapurine nucleosides are available in the reviews,[1,2] which describe the synthesis of different nucleoside analogues. The review by Budow and Seela [3] considerers 2-azapurine nucleosides containing imidazo[4,5-*d*][1,2,3]triazine or related compounds as the heterocyclic base and describes different methods for their synthesis, in particular, reaction sequences involving the ring opening and closure of purine nucleo-

Received 4 December 2020
© 2021 Uspekhi Khimii, ZIOC RAS, Russian Academy of Sciences and IOP Publishing Limited

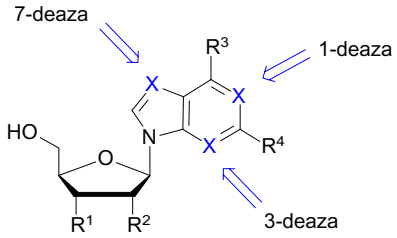
sides or the direct glycosylation of 2-azapurine nitrogen base with halide of the ribose moiety. Seela and Peng[4] compared different methods of glycosylation of 7-deazapurines (pyrrolo[2,3-*d*]pyrimidines). Metabolic transformations of compounds containing the 7-deazapurine moiety were analyzed in the review by McCarty and Bandarian,[5] and the spectrum of their biological activities was considered in the publications.[6,7] 9-Deazapurine nucleosides are mentioned in the reviews[8,9] dealing with strategies for the synthesis and biological properties of different C-nucleosides. The reviews[10,11] focused on the synthesis and biological activity of immucillins and related compounds. The reviews on the enzymatic synthesis of aza(deaza)purine nucleosides are lacking. Several examples of the synthesis of 1,3-deaza- and 3-deazaadenosines, analogues of 7-deazaguanine, 7-deaza-8-aza- and 5-aza-7-deazapurines are briefly mentioned in the reviews[12–14] concerning biotechnological or chemical-enzymatic methods for the synthesis of naturally occurring nucleosides and their analogues. Data on different aspects of antiviral activity of deazapurine nucleoside derivatives were summarized by Vittori *et al.*[15]

Therefore, the available data on aza- and deazapurine nucleoside analogues are to a large extent scattered. This review aims to close this gap by systematically considering the structure – biological activity relationships of these compounds, critically assessing the current state of approaches to their design and comparing the chemical and enzymatic methods of their synthesis.

2. Spectrum of biological activities of aza and deaza analogues of purine nucleosides

There are numerous approaches to the modification of naturally occurring purine nucleosides both at the heterocyclic base and the carbohydrate moiety.[16,17] One of the most well-known structural modifications is based on the replacement of one or several nitrogen atoms of the purine base by the methine group. These result in deazapurine nucleoside analogues with broad-spectrum biological activity (Fig. 1).

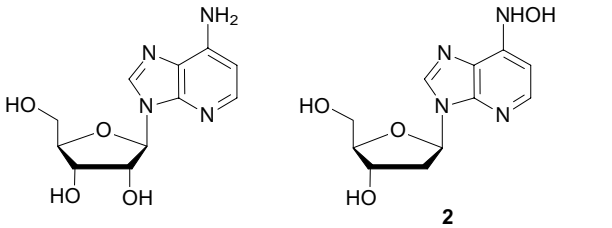
The replacement of the N(1) atom of the heterocyclic base affords 1-deazapurine nucleosides. 1-Deazaadenosine **1** and its analogues are known to act as adenosine receptor agonists and exhibit strong antitumour activity in mouse leukemia cells (P388, L1210).[18,19] The 6-Hydroxylamino derivative of 2′-deoxy-1-deazaadenosine **2**, being an inhibitor of adenosine deaminase (ADA) with an inhibitory constant (K_i) of 0.27 μmol L^{-1} (hereinafter μM),[20] significantly enhanced *in vitro* antitumour activity of adenine arabinoside (ara-A).[21,22]



X = N or CH (deaza); R^1 and R^2 = H, OH, F; R^3 and R^4 = H, NH_2, OH

Figure 1. Structure of purine and 1(3 or 7)-deazapurine nucleosides.

Structures 1, 2



1-Deazaadenosine, **1** **2**

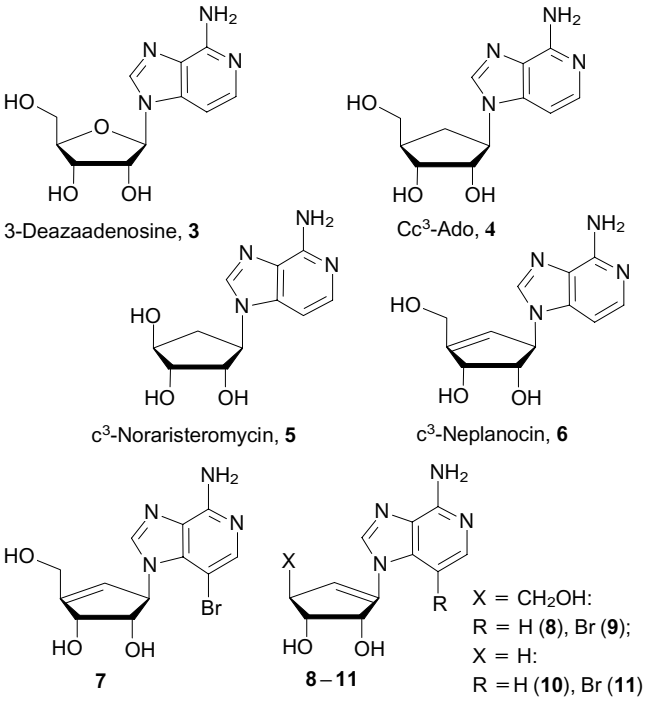
3-Deazaadenosine **3** was synthesized for the first time by Montgomery's research group.[23] This compound showed high biological activity by inhibiting the cellular enzyme S-adenosylhomocysteine hydrolase (SAH hydrolase), a known target for antiviral, antiparasitic and anticancer drugs.[24] More recently, the same research group[15,25] found that carbocyclic 3-deazaadenosine (Cc^3-Ado, **4**) has inhibitory activity against SAH hydrolase with K_i = 5 nM and antiviral activity against herpes simplex virus 1 and vaccinia virus with a half-maximal inhibitory concentration (IC_{50}) of 0.9 and 0.007 μM, respectively. 3-Deazaadenosine **3** and its carbocyclic analogues — Cc^3-Ado (**4**), 3-deazanoraristeromycin (c^3-noraristeromycin, **5**) and 3-deazaneplanocin A (c^3-neplanocin A, **6**) — inhibit the human immunodeficiency virus type 1 production *via* the suppression of the p24 protein synthesis in peripheral blood mononuclear cells infected with the A012 virus strain at a concentration of 0.15, 0.14, 0.01 and 3.48 μM, respectively.[15]

High antiviral activity of 3-bromo-3-deazaneplanocin (**7**), enantiomers of 3-deaza-1′,6′-isoneplanocin (**8**) and 3-bromo-3-deaza-1′,6′-isoneplanocin (**9**) and their analogues **10** and **11** lacking the 4′-hydroxymethyl group was reported by Schneller and co-workers.[26–28] Compound **7** exhibited activity against influenza A and B viruses (the effective concentration that inhibits virus replication by 50% (EC_{50}) was < 0.09 and 0.16 μM, respectively), parainfluenza virus (EC_{50} = 0.5 μM), *etc.*[26] Isoneplanocin analogues **8** and **9** displayed activity against the Ebola virus (EC_{50} = 0.1 – 0.3 μM), human cytomegalovirus (EC_{50} = 0.1 μM), hepatitis B virus (HBV, EC_{50} = 3.35 μM), norovirus (EC_{50} = 1.9 μM) and measles (EC_{50} = 0.29 – 0.38 μM).[27] Compounds **10** and **11** lacking the 4′-hydroxymethyl group inhibited the Ebola virus

E.S.Matyugina. Ph.D. in Chemistry, Senior Researcher at the EIMB RAS.
E-mail: matyugina@gmail.com
Current research interests: synthesis of modified nucleoside and nucleotide analogues, medicinal chemistry.
S.N.Kochetkov. Academician, Doctor of Chemical Sciences, Professor, Head of the Laboratory at the same Institute.
E-mail: kochet@eimb.ru
Current research interests: development of specific regulators of biological processes, in particular antiviral drugs; molecular virology, bioorganic chemistry.
A.L.Khandazhinskaya. Ph.D. in Chemistry, Senior Researcher at the same Institute.
E-mail: khandazhinskaya@bk.ru
Current research interests: synthesis of modified nucleoside and nucleotide analogues, development of depot forms of antiviral drugs of nucleoside nature, medicinal chemistry.

Translation: T.N.Safonova

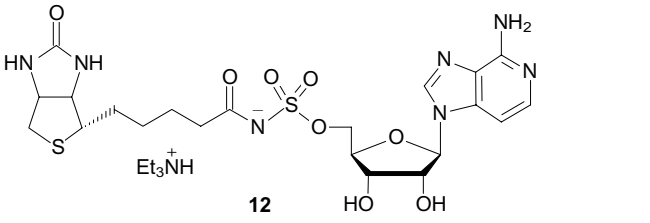
Structures 3 – 11



(EC_{50} = 0.3 – 0.4 μM) and human cytomegalovirus (EC_{50} < 0.05 μM).[28]

The research group headed by Professor Aldrich[29] used 3-deazaadenosine to synthesize the bisubstrate inhibitor of biotin protein ligase, which catalyzes post-translational biotinylation of proteins and regulates *Mycobacterium tuberculosis* lipid metabolism. Compound **12**, which is a acylsulfonamide-linked conjugate of 3-deazaadenosine and biotin, exhibited antimycobacterial activity (the minimum inhibitory concentration required to inhibit mycobacterial cell growth by 90% (MIC_{90}) is 1.56 μM).

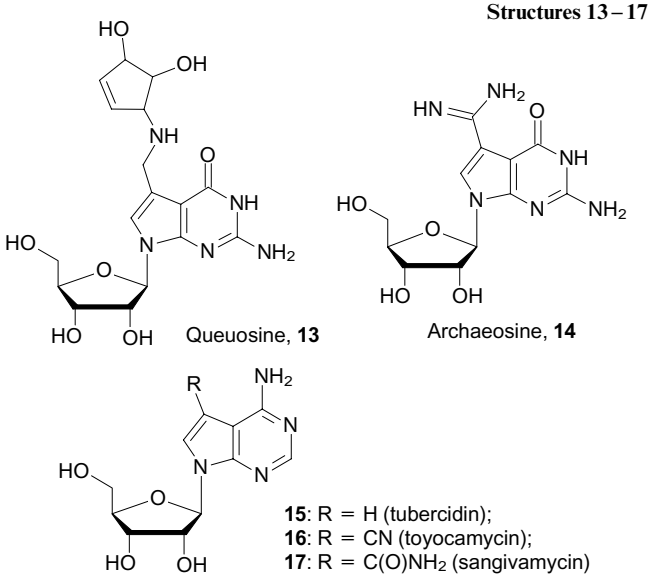
Structure 12



7-Deazapurine derivatives are an important group of biologically active purine nucleoside analogues. Some 7-deazapurine nucleosides occur in nature. For example, queuosine (**13**)[30,31] and archaeosine (**14**)[32] are involved in some prokaryotic (eukaryotic) and archaeal tRNA, respectively. The natural antibiotics tubercidin (**15**), toyocamycin (**16**) and sangivamycin (**17**) exhibited significant antitumour activity in *in vivo* assays.[15,33,34]

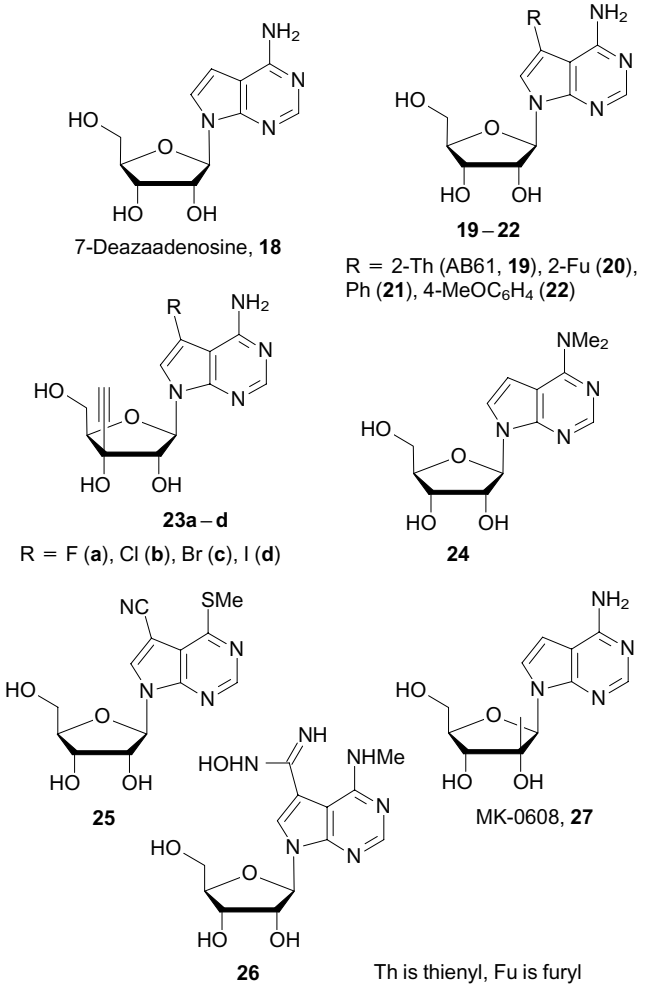
7-Deazanucleosides have a number of advantages compared to conventional nucleosides. For example, tubercidin (**15**) is resistant to adenosine deaminase and purine nucleoside phosphorylase — the enzymes involved in essential metabolic processes.[35,36] Numerous structural modifications of 7-deazapurine nucleosides were aimed at searching for anticancer and antiviral agents.[7] 7-Deazaadenosine derivatives (**18**), 7-hetaryl-7-deazaadenosine nucleosides

Structures 13 – 17



19 – **22**, showed a strong nanomolar cytostatic effect in a large panel of cancer cell lines.[7,37] The mechanism of action of 7-thienyl-substituted 7-deazaadenosine (commercial code AB61, **19**) was studied in detail. This mechanism involves the efficient phosphorylation of the molecule in cancer cells, thereby providing the selectivity. The resulting ribonucleo-

Structures 18 – 27



side triphosphate was incorporated into cellular RNA and DNA and caused the blocking of translation and DNA damage.[38]

3′-Ethynyl-7-halogen-substituted 7-deazaadenosine analogues **23a** – **d** exhibited significant antiproliferative activity. The inhibitory concentrations in different cancer cell lines (L1210, HeLa and CEM) varied from 0.014 to 0.056 μM. The 3′-ethynyl-7-chloro derivative of 7-deazaadenosine **23b**, displaying the highest activity, was also studied *in vivo* in mouse metastatic breast cancer cells (MDA-MB-231-LM2 line). This compound was found to inhibit tumour cell proliferation and reduce the formation of lung metastases.[39]

The C(6)- and C(7)-substituted 7-deazapurine nucleosides exhibited significant antiviral activity;[7] however, many of these derivatives were toxic for cells and cannot be considered as potential therapeutic agents. 6-(*N*,*N*-Dimethylamino)-7-deazaadenosine **24** (EC_{50} = 7.0 μM, CC_{50} = 300 μM)† was chosen as a candidate for the subsequent optimization of the structure. This compound is non-toxic in hepatitis C virus replicon assays. Toyocamycin derivatives **25** and **26** containing the 4-methylthio group and the 7-carboxamide oxime substituent, respectively, showed significant antiviral activity and selectivity (EC_{50} = 0.4 μM, CC_{50} = 250 μM for **25** and EC_{50} = 0.6 μM, CC_{50} = 200 μM for **26**).[40]

The cytotoxicity of 7-deazapurine nucleosides was reduced by means of different modifications of the carbohydrate moiety. 2′-Methyl-7-deazaadenosine (MK-0608, **27**) exhibited high antiviral activity and low cytotoxicity (EC_{50} = 0.27 μM, CC_{50} > 100 μM) and was under clinical trials as the anti-HCV agent; however, the trials were stopped for unknown reasons.[7,41]

7-Thioamide analogues of 7-deazaadenosine **28** – **31** showed activity against human cytomegalovirus (HCMV) with EC_{50} in a range of 0.5 – 1.6 μM combined with toxicity in human Foreskin fibroblast (HFF) cell culture.[42] The submicromolar inhibitory activity against Dengue virus — a representative of the *Flaviviridae* family — was found for 6-methyl-7-deazapurine ribonucleoside **32** (EC_{50} = 0.877 μM); however, it was toxic to human fibroblasts (MRC-5 and BJ cell lines).[43,44] The 2′-C-ethynyl-substituted analogue of 7-deazaadenosine (NITD008, **33**) showed the best selectivity: EC_{50} = 0.64 μM and CC_{50} > 100 μM.[45] Further studies demonstrated that NITD008 was phosphorylated *in vivo* to triphosphate and inhibited DENV RNA-dependent RNA-polymerase.[7,46] However, this compound was toxic in mouse models treated for more than one week.[45] 7-Ethynyl-substituted 7-deazaneplanocin **34** exhibited antiviral activity against HBV (EC_{50} = 1.8 μM, CC_{50} > 300 μM), including mutant virus strains resistant to lamivudine and adefovir.[47] 2′-Fluorine-substituted 7-deazapurine nucleosides **35** and **36** inhibit human immunodeficiency virus at low concentrations (EC_{50} = 0.5 – 0.7 μM) and can be considered as potential candidates for the optimization of the structure to search for potential anti-HIV agents.[48]

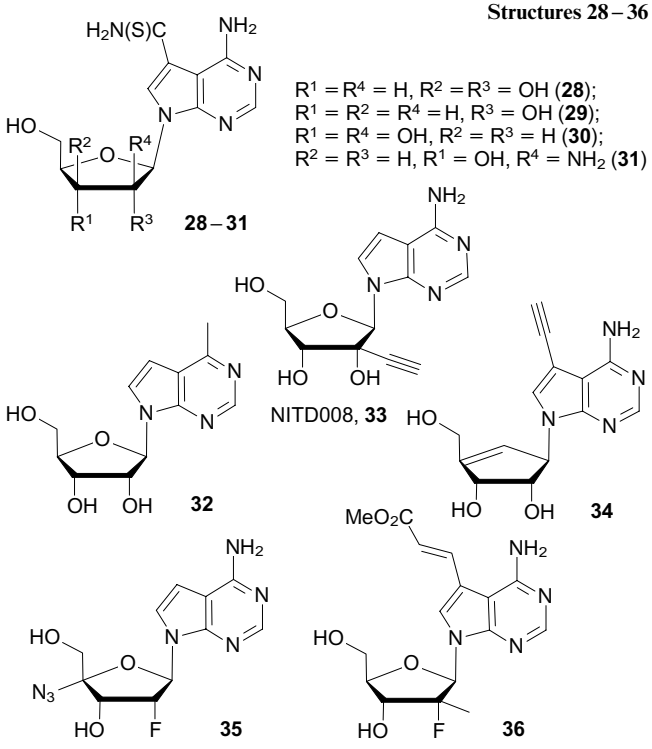
Another type of modification of purine bases is based on the replacement of the methine group (the C(2) or C(8) atom) by a nitrogen atom giving azapurine nucleosides or the simultaneous replacement of the methine group by a nitrogen atom and *vice versa*, resulting in the formation of azadeaza derivatives (Fig. 2).

8-Azaadenosine **37**, 8-azainosine **38** and 8-azaguanosine **39** were shown to have antitumour activity *in vivo*.[23] These 8-azanucleosides are phosphorylated by kinases and can interrupt RNA synthesis.[49]

In a series of 1-deaza-8-azapurine nucleosides, 2′,3′-dideoxy derivatives **40** and **41** were found to be strong inhibitors of adenosine deaminase (with K_i = 0.01 – 0.05 μM), α-anomer **40** being more than five times more active than β-anomer **41**. The α-anomer of 2′-deoxy-6-chloro-1-deaza-8-azaadenosine **42** exhibited antiviral activity against poliovirus and coxsackievirus (EC_{50} = 9 and 27 μM, respectively).[50] Ribo and deoxyribo analogues of 6-chloro-1-deaza-8-azaadenosine **43** and **44** showed antiproliferative activity in different human and murine tumour cell lines (P388, L1210, B16, LoVo), but they were much less active than 1-deazaadenosine **1**.[51]

7-Deaza-8-azapurine nucleosides exhibit a broad range of biological activities, such as antiparasitic, antitumour and antiviral activity.[52,53] Allopurinol (**45**) is a bright example of biologically active 7-deaza-8-azapurine bases. This compound is approved for the treatment of gout and also exhibits activity against several types of leishmania and trypanosomas.[54] Significant antiviral activity against HBV and HCMV was found for the 6-methoxy derivative of

Structures 28 – 36



† CC_{50} is the cytotoxic concentration that causes the death of 50% of cells.

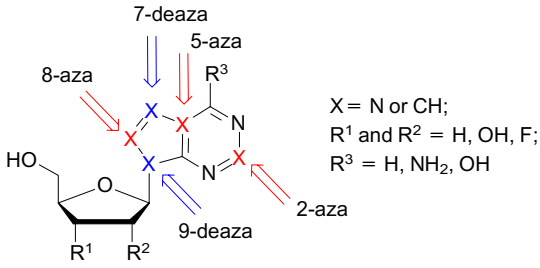
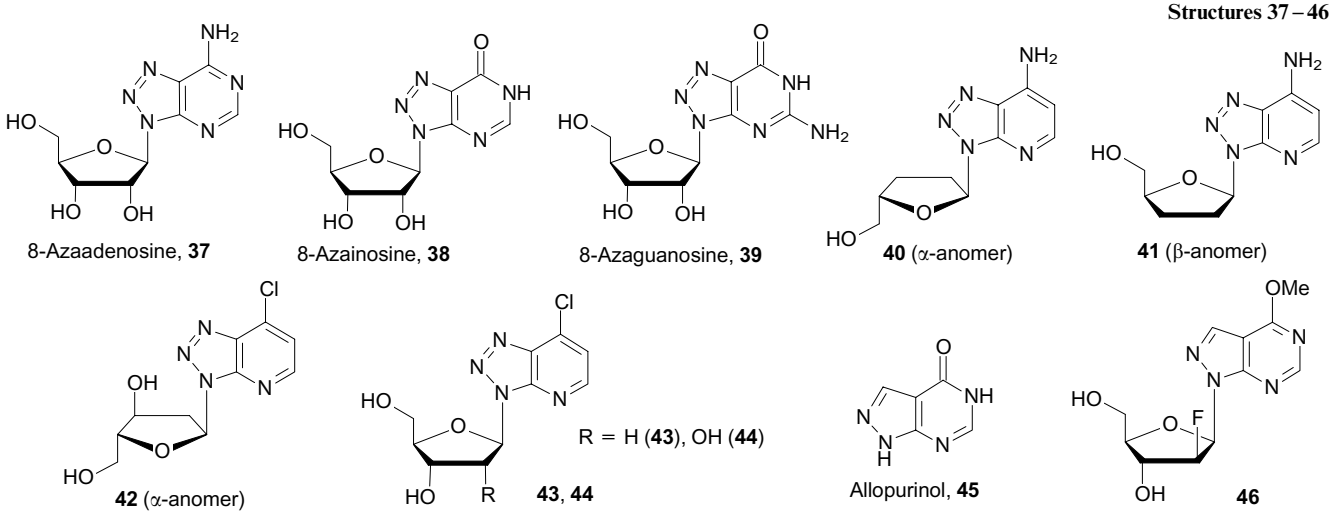


Figure 2. Structure of 2(5 or 8)-aza- and 7(9)-deazapurine nucleosides.

Structures 37 – 46

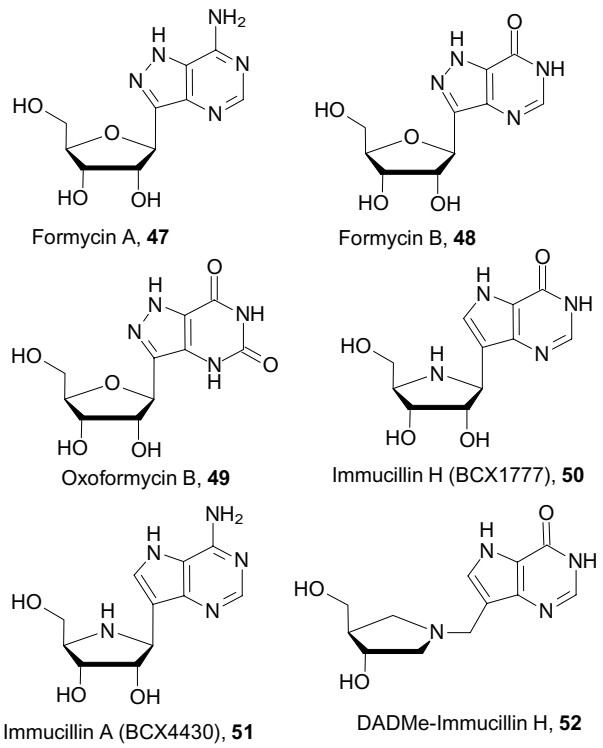


2′-deoxy-2′-fluoro-7-deaza-8-azaadenosine **46**, with EC_{50} of 0.42 and 0.98 μM, respectively.[55]

The natural antibiotics formycins **47** – **49** are 8-aza-9-deazapurine analogues of adenosine (formycin A), inosine (formycin B) and xanthosine (oxoformycin B), respectively. These compounds have antibacterial and cytostatic properties and also efficiently inhibit purine nucleoside phosphorylases (PNPs).[8, 56]

The discovery of C-nucleoside analogues by Schramm's research group[11, 57] was an important breakthrough in the rational design of chemotherapeutic agents. Immucillins[58] were found to be transition state inhibitors for PNPs. Compound **50** (immucillin H, also known as BCX1777, mundesine, forodesine) was approved in Japan for the treatment of relapsed and refractory peripheral T-cell lymphoma.[59] Currently, immucillin A (**51**, BCX4430, galidesivir) is under clinical trials as an antiviral agent against filoviruses;[59, 60] DADMe-immucillin H (**52**, BCX4208, ulodesine), as a drug for the treatment of gout.[59]

Structures 47 – 52



Another representative of azadeazapurines is Remdesivir (**53**). This drug is based on 4-aza-7,9-dideazaadenosine (Fig. 3). It was developed by Gilead Sciences and was initially intended for the treatment of diseases caused by representatives of filoviruses, namely, by the Ebola and Marburg viruses.[61] More recently, it was found that this compound exhibits antiviral activity against a broad range of single-stranded RNA viruses: respiratory syncytial virus, Junín virus, Lassa fever virus, Nipah virus, Hendra virus and coronaviruses (including MERS and SARS viruses).[62, 63] Remdesivir was shown to inhibit human coronavirus (CoV) and related animal viruses *in vitro* and *in vivo*.[64, 65]

Therefore, different deaza, aza and azadeaza analogues of purine nucleosides are convenient tools to act on enzymes as the targets for anticancer therapy and also for the treatment of infections caused by viral, bacterial and parasitic pathogens. A significant practical value of these compounds generates a need to develop efficient and selective methods for their synthesis, allowing the preparation of potential agents in required amounts. Main methods for the chemical and biotechnological synthesis of various deaza, aza and azadeaza analogues of purine nucleosides are considered in subsequent sections. Examples are given of the classical methods, which have been described for the first time in the 20th century and were commonly used at

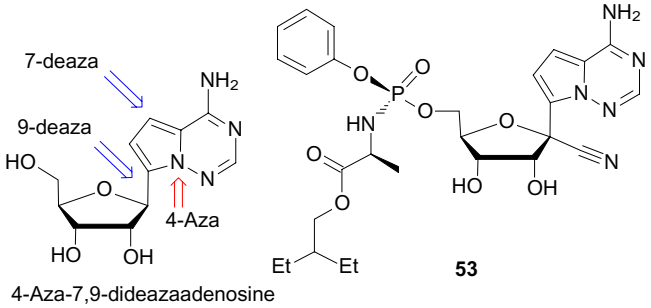


Figure 3. Structures of 4-aza-7,9-dideazaadenosine and the drug Remdesivir (**53**).

that time and which are still relevant, as well as of modern approaches.

3. Chemical synthesis

There are two main strategies for the synthesis of nucleosides:

— the condensation of a heterocyclic base with a carbohydrate moiety,

— the construction of a heterocyclic base at the amino group or another appropriate substituents at the 1′ position of carbohydrate.

Both strategies are applicable to the synthesis of aza and deaza analogues of purine nucleosides. The following ribose derivatives, which are traditionally used in nucleoside synthesis, are utilized as the carbohydrate moiety: ribofuranoses acetylated at all hydroxyl groups, fully protected deoxyribo- and ribofuranosyl 1-halides, ribonolactones, *etc*. The key distinguishing feature of the synthesis of aza and deaza analogues is the use of appropriate precursors of heterocyclic bases. It was shown that the change in the reactivity of purine analogues due to their aza and deaza modifications can be compensated by the introduction of particular substituents. This Section presents examples of the synthesis of the main types of aza and deaza analogues of purine nucleosides using different methods.

3.1. Condensation of a heterocyclic base with a carbohydrate moiety

3.1.1. The C – N bond formation

The following methods are most commonly used for the condensation of a heterocyclic base with a carbohydrate moiety: the fusion, reactions in the presence of Lewis acids, reactions involving metal salts and the silyl-Hilbert – Johnson reaction (the Vorbrüggen method).

3.1.1.1. Fusion

This method is based on the reaction of purines and their analogues with peracetylated sugars. The reaction is generally performed with heating in the presence of catalytic amounts of Lewis acids, which facilitate the formation of the electrophilic cation of the sugar. This method is also applicable to acidic heterocyclic systems, such as substituted or annulated imidazoles, purines, triazoles and pyrazoles. The product yield in this reaction is rarely higher than 60%. The method is more suitable for the synthesis of ribonucleoside analogues, while the synthesis of 2′-deoxyribonucleosides gives rise to two or more anomers.

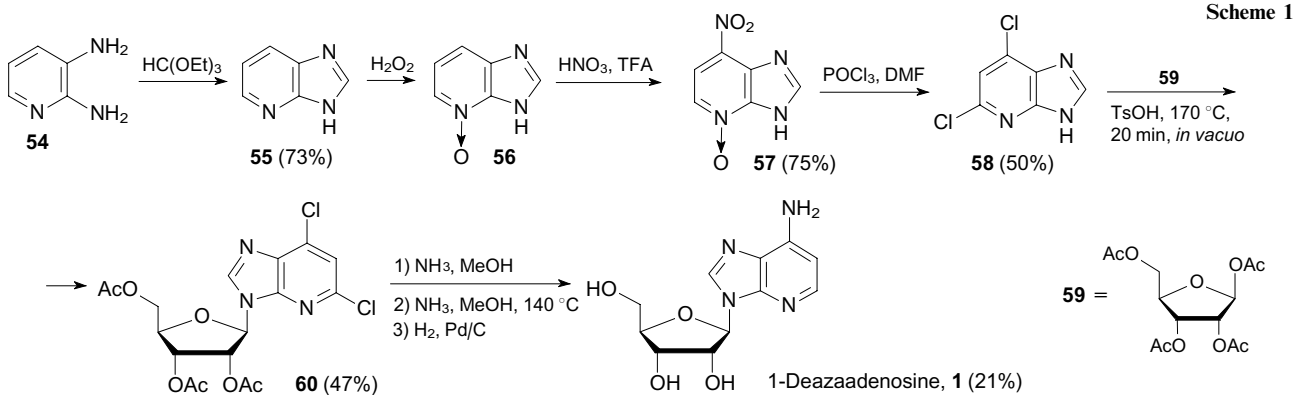
In the 1980s, different deazapurine ribonucleosides were prepared by the fusion in the presence of *p*-toluenesulfonic acid (TsOH). The first step of the synthesis of 1-deazaadenosine **1** involves the condensation of the starting 2,3-diaminopyridine (**54**) with triethyl orthoformate giving imidazo[4,5-*b*]pyridine **55** in 73% yield (Scheme 1). Compound **55** was oxidized with hydrogen peroxide to form N-oxide **56** followed by the nitration of the latter with a mixture of nitric and trifluoroacetic acids (TFA). The application of this combination of acids instead of the previously used mixture of nitric and acetic acids made it possible to increase the yield of 7-nitroimidazo[4,5-*b*]pyridine 4-oxide (**57**) to 75%.[21] Compound **57** was treated with phosphorus oxychloride in dimethylformamide to prepare 5,7-dichloro-3*H*-imidazo[4,5-*b*]pyridine **58** in 50% yield. The fusion of dichloro derivative **58** with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**59**) in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded protected 2,6-dichloro-1-deazaadenosine **60**. The treatment of compound **60** with ammonia in methanol at room temperature in order to remove acetyl moieties followed by heating at 140 °C and the final catalytic hydrogenolsis accompanied by the elimination of the chlorine atom gave 1-deazaadenosine **1**; the overall yield over the last three steps was 21%.[66]

The synthesis of 1-deazaadenosine (**1**) from diacetyl-1-deazaadenine **61** (Scheme 2) proved to be more efficient. Compound **61** was fused with ribose tetraacetate **59** in the presence of a catalytic amount of *p*-toluenesulfonic acid at 165 °C *in vacuo* for 2 h to prepare tetraacetylated nucleoside analogue **62**. This reaction product was isolated by silica gel column chromatography in 40% yield. The deprotection of compound **62** using sodium methoxide in methanol afforded 1-deazaadenosine (**1**) in 32% overall yield.[66]

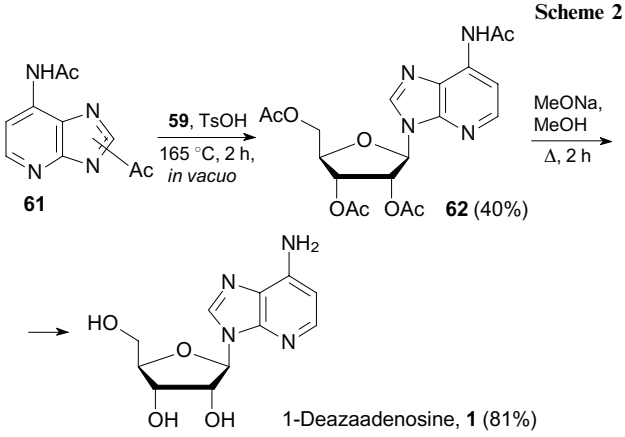
1,7-Dideazaadenosine **63** was synthesized from 1*H*-pyrrolo[2,3-*b*]pyridine (Scheme 3).[67] In the first step, 1*H*-pyrrolo[2,3-*b*]pyridine (**64**) was oxidized with *m*-chloroperoxybenzoic acid (m-CPBA) in dichloromethane to the corresponding N-oxide, which was nitrated with nitric acid in TFA at 0 °C. The treatment of intermediate 4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide with PCl_3 in ethyl acetate produced 4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine (**65**) in 29% yield over three steps. The hydrogenation of intermediate **65** with Raney nickel (Ni-Ra) in methanol and acetic acid under high pressure gave 4-amino-1*H*-pyrrolo[2,3-*b*]pyridine (**66**).

However, several attempts to synthesize the target 1,7-dideazaadenosine by the direct glycosylation of compound **66** failed. Hence, the authors developed an alternative approach starting from 4-amino-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (**67**), which was prepared by the hydrogenation of 4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine (**65**) in trifluoroacetic acid under high pressure in the presence of

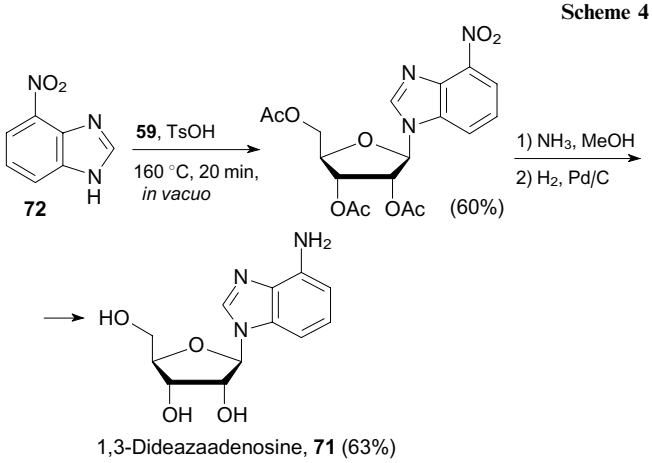
Scheme 1



Scheme 2



Scheme 4

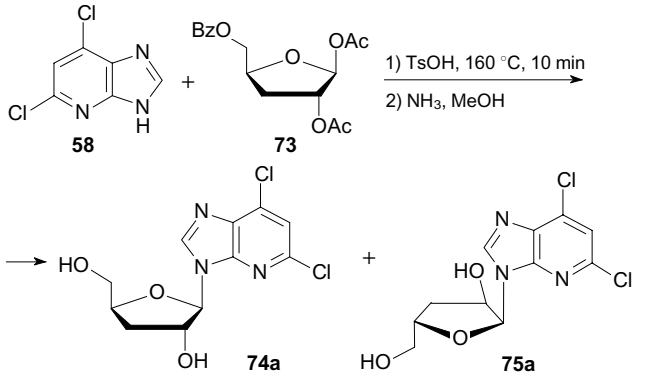


palladium, 10%, on carbon (10% Pd/C) as the catalyst. The subsequent acetylation with acetic anhydride gave a mixture of triacetyl and diacetyl derivatives. The latter compound was isolated by silica gel chromatography and then subjected to alkaline hydrolysis with dilute NaOH in ethanol. 4-N-Acetyl derivative **68** was isolated from the reaction mixture by silica gel chromatography and fused with ribose tetraacetate **59** in the presence of a catalytic amount of *p*-toluenesulfonic acid at 135 °C *in vacuo* for 40 min. 1-β-D-Ribofuranosyl derivative **69** was isolated by silica gel chromatography and oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in refluxing xylene giving tetraacetylated 1,7-dideazaadenosine **70**. The protecting groups were removed using the method described above, resulting in the formation of target product **63**.[67]

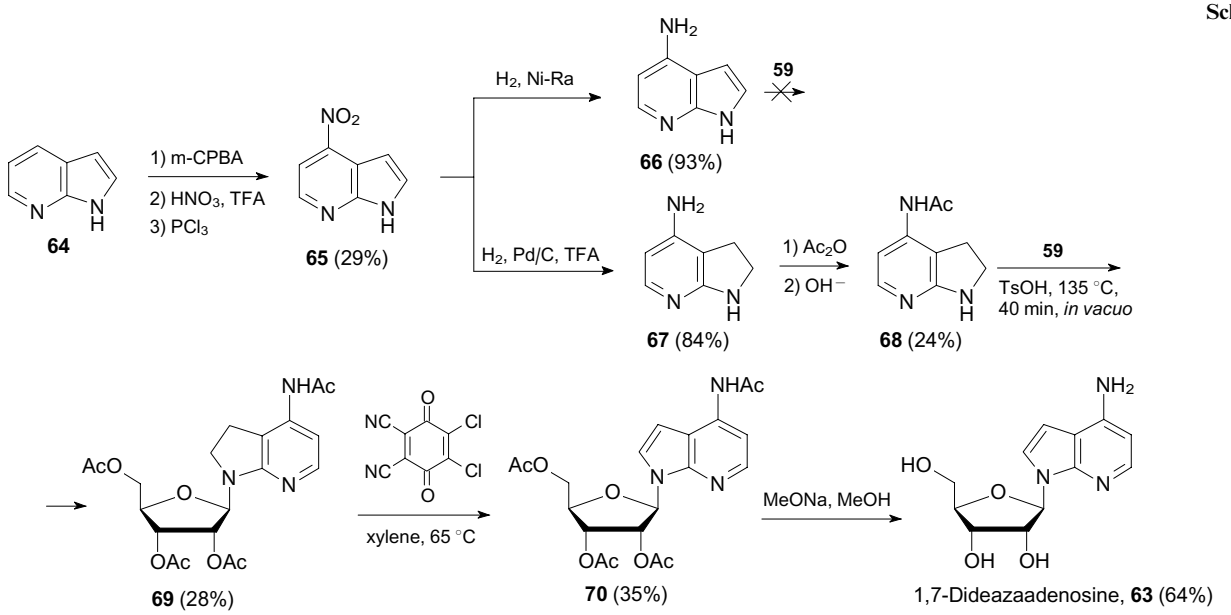
1,3-Dideazaadenosine (**71**) was synthesized from 4-nitrobenzimidazole (**72**) in three steps.[21] The fusion of compound **72** with ribose tetraacetate **59** followed by deacetylation with ammonia in methanol at room temperature and the catalytic hydrogenation in the presence of Pd/C afforded target nucleoside **71** in 38% yield over two steps (Scheme 4).[21]

Attempts to prepare deoxyribonucleosides by the fusion resulted in the formation of two or more products. Thus, the fusion of 2,6-dichloro-1-deazapurine (5,7-dichloro-3*H*-imidazo[4,5-*b*]pyridine, **58**) with 1,2-di-*O*-diacetyl-5-*O*-benzoyl-3′-deoxy-β-D-ribofuranose (**73**) in the presence of a catalytic amount of *p*-toluenesulfonic acid produced a mixture of β- and α-anomers in a ratio of 2 : 1 in 81% overall yield (Scheme 5). The removal of protecting groups with ammonia in methanol at room temperature gave 2,6-dichloro-1-deazapurine nucleosides **74a** and **75a** (the yield of the mixture was 85%).[2, 68]

Scheme 5



Scheme 3



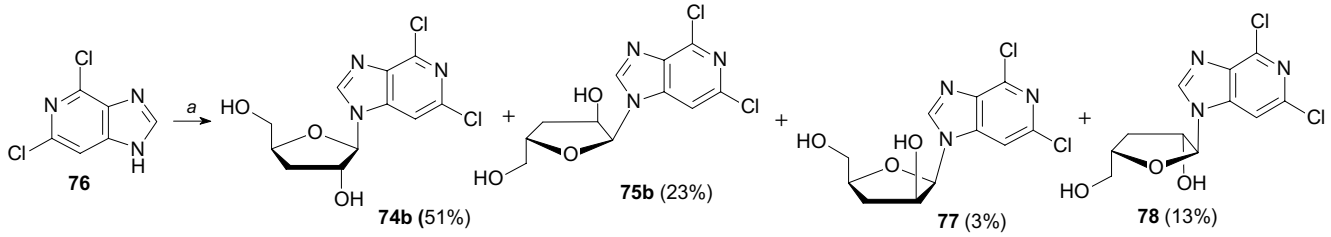
A similar fusion of 2,6-dichloro-3-deazapurine (4,6-dichloro-1*H*-imidazo[4,5-*c*]pyridine, **76**) with 3′-deaxyribofuranose **73** affords a mixture of four 3-deazapurine nucleosides in 90% overall yield (Scheme 6). The treatment of this mixture with ammonia in methanol at room temperature for 24 h allows the removal of the benzoyl and acetyl protecting groups to obtain four 2,6-dichloro-3-deazapurine nucleosides: β- and α-ribofuranose derivatives **74b**, **75b** and β- and α-arabinofuranose derivatives **77**, **78**.[2,69]

3.1.1.2. Reactions in the presence of Lewis acids

Another approach to the synthesis of deazaadenosines is based on the glycosylation with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**59**), which was performed at room temperature in acetonitrile using tin chloride as the acid catalyst. These reactions with all purine bases afforded only β-anomers.[2] The fusion of 5-chloro-7-nitro-3*H*-imidazo[4,5-*b*]pyridine (**79**) with ribose tetraacetate **59** in the presence of *p*-toluenesulfonic acid failed to produce the desired outcome.[2] In order to synthesize 2-chloro-1-deazaadenosine (**80**) and 1-deazaadenosine (**1**) from the same starting compounds, the ribosylation was performed in dry acetonitrile in the presence of freshly distilled tin chloride at room temperature for 12 h. Protected 5-chloro-7-nitro-1-(β-D-ribofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine (**81**) was isolated in 46% yield. The deacetylation with ammonia in methanol and the catalytic reduction of the nitro group with Raney nickel under high pressure afforded 2-chloro-1-deazaadenosine **80**, which was hydrogenated in the presence of Pd/C to give compound **1** (Scheme 7).[66]

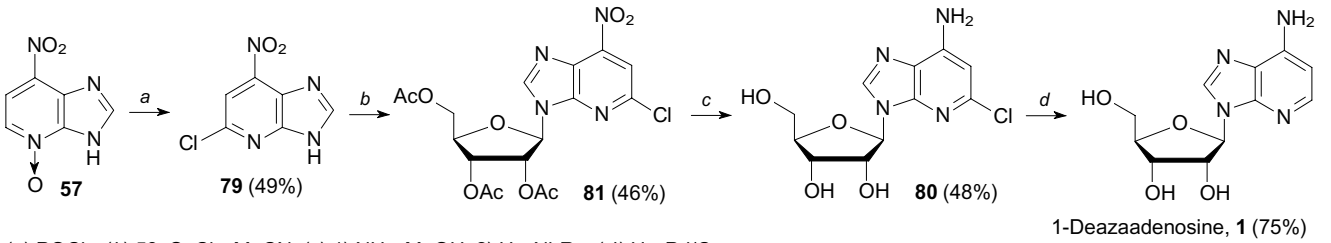
The synthesis of 3-deazaadenosine **3** from cheap and readily available 3,4-diaminopyridine (**82**) is presented in Scheme 8.[70] The cyclization involving triethyl orthoformate and formic acid gave 1*H*-imidazo[4,5-*c*]pyridine (**83**), which was oxidized with *m*-chloroperoxybenzoic acid to form N-oxide **84**. The treatment of the latter compound with phosphorus oxychloride was accompanied by the reduction giving 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (**85**) in high yield. This heterocyclic base was subjected to the reaction with ribose tetraacetate **59** in acetonitrile in the presence of tin chloride, and then protected nucleoside **86** was treated with an ammonia solution in methanol to prepare 4-chloronucleoside analogue **87**. The nucleophilic substitution of the chlorine atom by ammonia in methanol at 65 °C did not produce target 3-deazaadenosine, as opposed to 6-chloropurines. This problem was overcome using nucleophilic substitution by hydrazone followed by the reduction with

Scheme 6



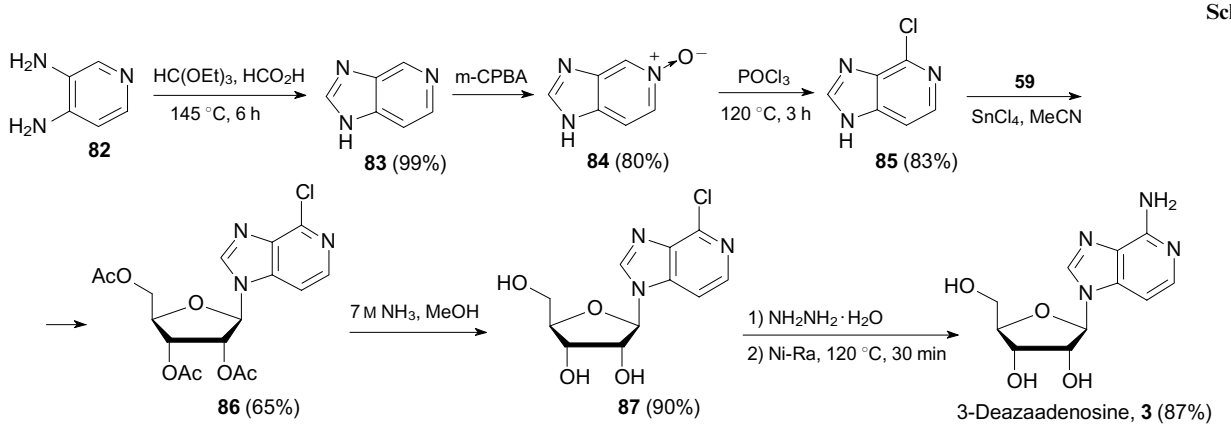
(*a*) 1) **73**, TsOH, 160 °C, 10 min; 2) NH_3, MeOH

Scheme 7



(*a*) $POCl_3$; (*b*) **59**, $SnCl_4$, MeCN; (*c*) 1) NH_3, MeOH; 2) H_2, Ni-Ra; (*d*) H_2, Pd/C

Scheme 8



Raney nickel.[71] Product **3** was obtained in 34% overall yield over seven steps.

3.1.1.3. Use of metal salts

This approach is based on the reaction of metal salts of heterocyclic bases with protected ribose halides. Initially, silver salts were used in this method.[72] In further studies, researchers gave preference to mercury salts of heterocyclic bases because of their lower polarity and, consequently, better solubility in organic solvents and higher reactivity compared to silver salts. Mercury salts of purines react with equivalent amounts of carbohydrate moieties giving kinetically favourable N(3)-nucleosides, which are rearranged on heating with $HgBr_2$, $HgCl_2$ or $Hg(CN)_2$ into thermodynamically controlled stable analogues of naturally occurring N(9)-nucleosides and some N(7)-nucleosides.[73]

An example of the use of mercury cyanide in the condensation is the synthesis of 1-deazaguanosine **88**, which was described in 1978 by the research group headed by Townsend[74] (Scheme 9). Ethyl 7-chloroimidazo[4,5-*b*]pyridine-5-carbamate (**89**) was treated with *N*,*O*-bis(trimethylsilyl)acetamide (BSA). The resulting silyl derivative was dissolved in benzene in the presence of mercury cyanide and heated to reflux. Then ribofuranosyl bromide **90** was added and the mixture was heated at reflux for 1 h. After the crystallization, condensation product **91** was isolated in 80% yield. The deprotection with sodium methoxide in a mixture of methanol and tetrahydrofuran at 40 °C afforded ethyl 3-(D-ribofuranosyl)-7-chloroimidazo[4,5-*b*]pyridine-5-carbamate (**92**). The reaction of **92** with sodium benzoxide in benzyl alcohol on heating followed by the hydrogenolysis made it possible to synthesize target 1-deazaguanosine **88** in 30% overall yield over the last two steps.

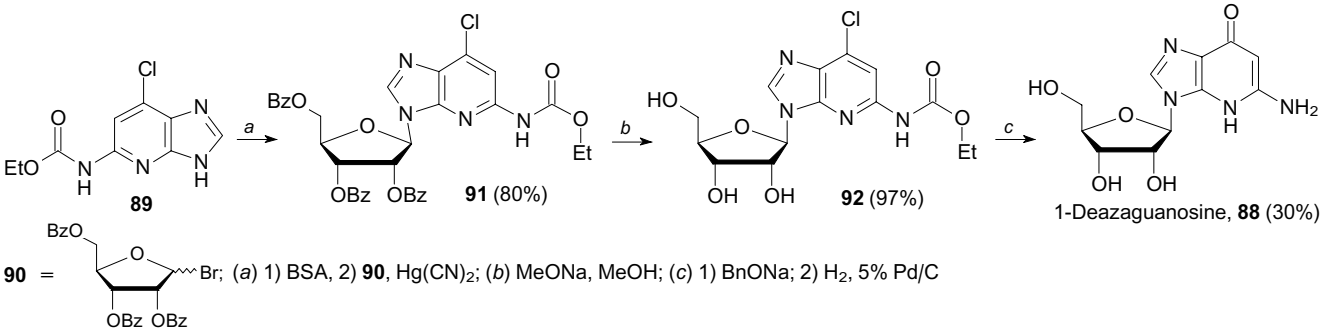
Currently, procedures using mercury salts are rarely employed because, apart from moderate yields of reaction products and complex reaction mixtures, traces of mercury impurities, which have strong biocidal properties, can give false data on biological activity of the synthesized nucleoside analogues.[75]

In more recent studies, the synthesis of nucleoside analogues was more often performed using purine salts or related heterocyclic systems, which were prepared *in situ* by the treatment with sodium hydride or related bases. These salts react with precursors of the carbohydrate moiety, such as 1-α-chloro-2-deoxy-3,5-di-*O*-*p*-toluylribofuranose (**93**) or 1-α-bromo-2,3,5-tri-*O*-benzyl-D-arabinofuranose (**94**), in acetonitrile giving the corresponding β-nucleosides *via* the S_N2 substitution of the α-halogen atom at the 1 position of the carbohydrate moiety by a heterocyclic base. For example, 4,6-dichloroimidazo[4,5-*c*]pyridine (**76**) was transformed into the sodium salt by the treatment with sodium hydride in acetonitrile. Then 2-deoxyribofuranose **93** was added and the resulting solution was stirred at 50 °C for 2 h. The subsequent treatment of protected nucleoside **95** with ammonia in methanol afforded 2′-deoxy-2-chloro-3-deazaadenosine analogue **96** in 44% overall yield (Scheme 10).[76] This method was also applied to synthesize 2′-deoxy-2-chlorotubericidine in 36% overall yield and 2′-deoxytubericidine in 60% overall yield.[76]

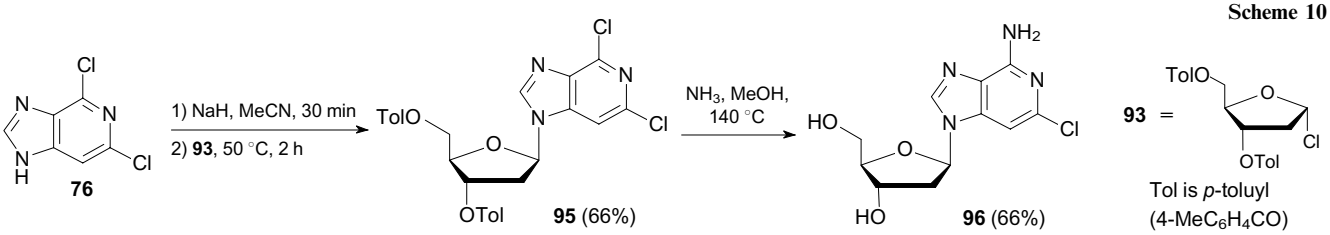
4-Azido-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (**97**) was treated in a similar manner with sodium hydride in dimethylformamide on cooling to 0 °C. The resulting solution was allowed to warm to room temperature, 2-deoxyribofuranose **93** was added, and the mixture was stirred at ambient temperature overnight. The synthesized azidonucleoside **98** was reduced with trimethylphosphine in tetrahydrofuran followed by acid hydrolysis using the Staudinger method; the deprotection with ammonia in methanol afforded 2′-deoxy-7-iodo-1,7-dideaza-β-D-adenosine (**99**) in 23% overall yield (Scheme 11).[77]

An efficient approach is based on the glycosylation of 4-methoxy-2-methylthio-1*H*-pyrrolo[2,3-*d*]pyrimidine (**100a**) under phase-transfer catalysis conditions. The conventional glycosylation of (*e.g.*, the Hilbert – Johnson method) is not applicable to this compound because the pyrimidine moiety is more nucleophilic than the pyrrole moiety. 4-Methoxy-2-methylthio-1*H*-pyrrolo[2,3-*d*]pyrimidine (**100a**) is easily glycosylated with bromide **94** in the presence of benzyltriethylammonium chloride (TEBAC) and 50% aqueous sodium hydroxide to form a mixture of the β- (**101a**) and α-anomers (**102a**) of the target nucleoside (Scheme 12).[78]

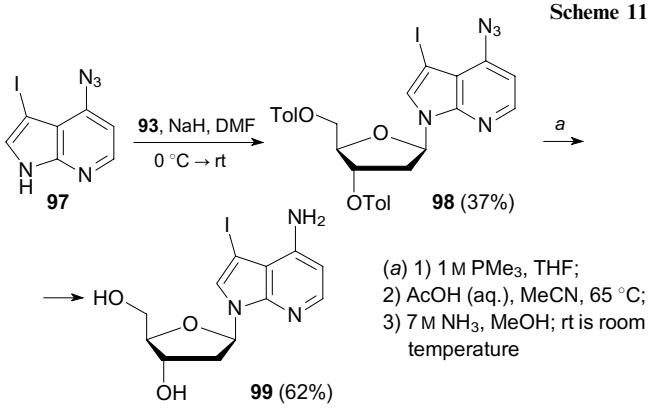
Scheme 9



Scheme 10



Scheme 11



In the presence of phase-transfer catalysts, 7-deaza- and 3,7-dideazapurine analogues **100a – d** (see Refs 79 and 80) are easily transformed into mixtures of the corresponding β- and α-nucleosides with the former prevailing (Scheme 13). It is worth noting that the concentrations of the phase-transfer catalyst [79] and NaOH [78, 80] affect the ratio of the β- and α-anomers **101** and **102**. A lower concentration of tetra-*n*-butylammonium hydrosulfate used as the catalyst (0.2 mol. *versus* 1 mol.) facilitates the formation of the β-anomer.[79] Apparently, an increase in the concentration of tetra-*n*-butylammonium hydroxide leads to the equilibrium formation of 1-β-chloride from 1-α-chloro-2,3,5-tri-*O*-benzyl-D-arabinofuranose (**103**), in which the chlorine atom is then replaced by the N-anion of the heterocyclic base *via* the S_N2 mechanism; consequently, the corresponding α-nucleoside is produced in a larger amount (see also the ratio of the β- and α-anomers in Scheme 12).[78, 81]

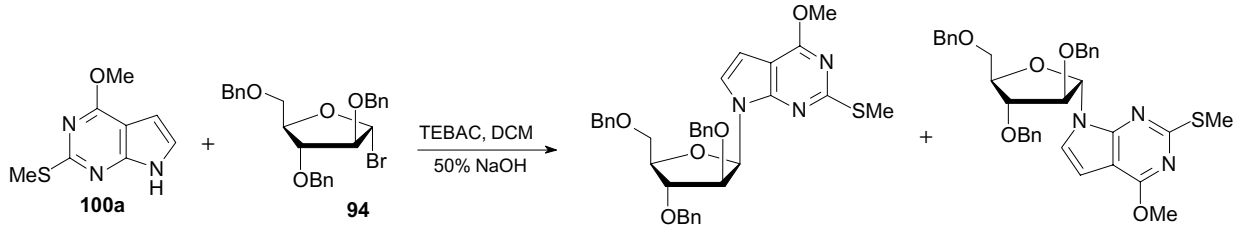
The reaction of pyrazolopyrimidine **104** with arabinofuranose **94** in the presence of KOH and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) as the phase-transfer catalyst affords a mixture of N(9)-substitution products, β-anomer **105** and α-anomer **106**, and also N(8)-substitution product **107** (Scheme 14).[82]

The treatment of 4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine (**65**) with KOH and TDA-1 resulted in its *in situ* transformation into the corresponding potassium salt, which reacted with deoxyribofuranose **93** to form protected β-nucleoside **108** in good yield (Scheme 15).[81]

Benzotriazole **109** is transformed in a similar fashion into a mixture of N(1)-nucleoside **110** and N(2)-nucleoside **111** (Scheme 16).[83] In this work, alternative reaction conditions were proposed using sodium hydride in acetonitrile. The products were obtained in the same yields.

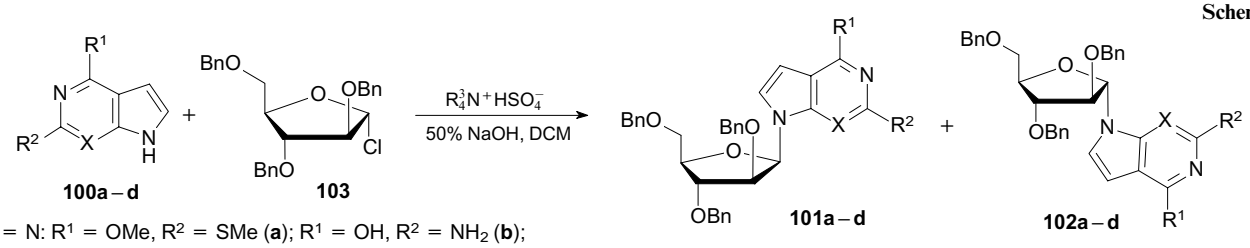
The glycosylation of 6-amino-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine **112** using TDA-1 (Scheme 17) was described by Ren *et al.*[84] Target N(9)-β-glycosylated compound **113** was obtained in moderate yield, and α-anomer **114** was isolated as a by-product. It is surprising that the N(8)-glycosylated compound was not detected. The protecting groups were removed with sodium methoxide at ambient temperature, and nucleoside analogues **115** and **116** were obtained in 91 and 89% yields, respectively. Purine 2′-deoxy-7-deaza-8-azanucleoside derivatives **117 – 120** were synthesized by the reaction at the 6-methoxy group using potassium hydroxide, ammonium hydroxide, hydrazine and hydroxylamine, respectively.

Scheme 12



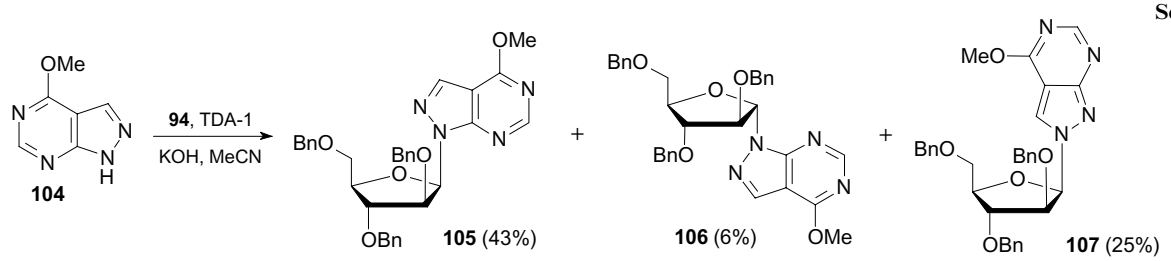
DCM is dichloromethane

Scheme 13

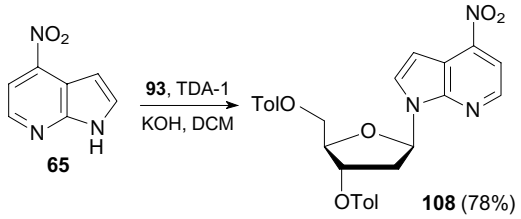


X = N: R^1 = OMe, R^2 = SMe (**a**); R^1 = OH, R^2 = NH_2 (**b**);
X = CH, R^2 = H: R^1 = NH_2 (**c**), Cl (**d**); R^3 = Alk

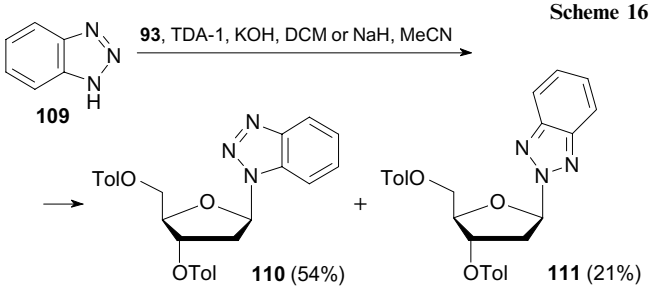
Scheme 14



Scheme 15



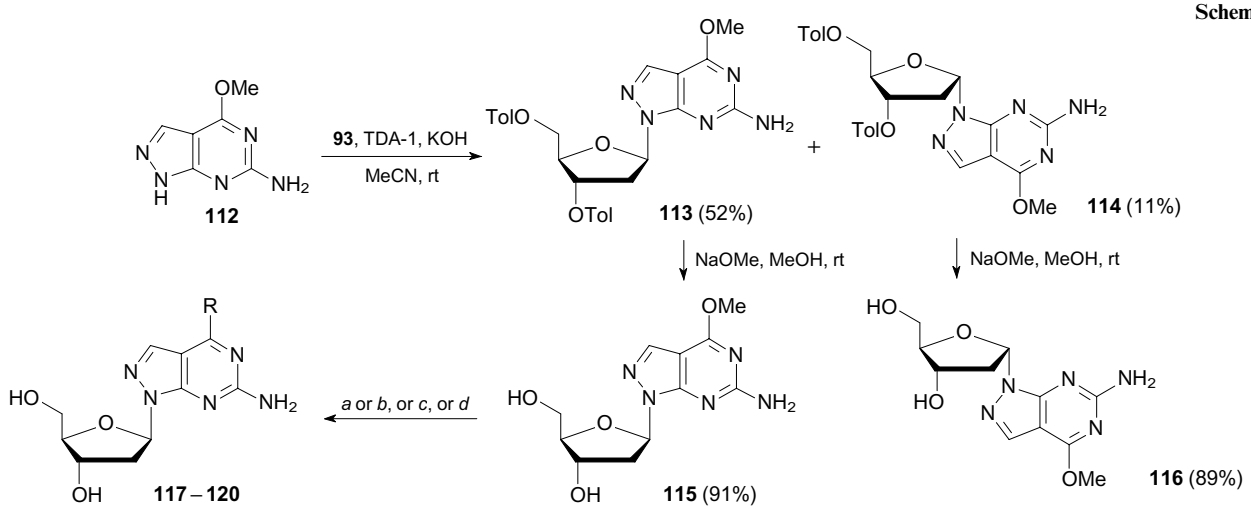
Scheme 16



In many cases, the treatment of the reaction mixture with K_2CO_3 in the presence of TDA-1 in acetonitrile gives products in much higher yields compared to the reactions under standard heterogeneous conditions, such as the 50% NaOH – $Bu^n_4NHSO_4$ – DCM system.[85]

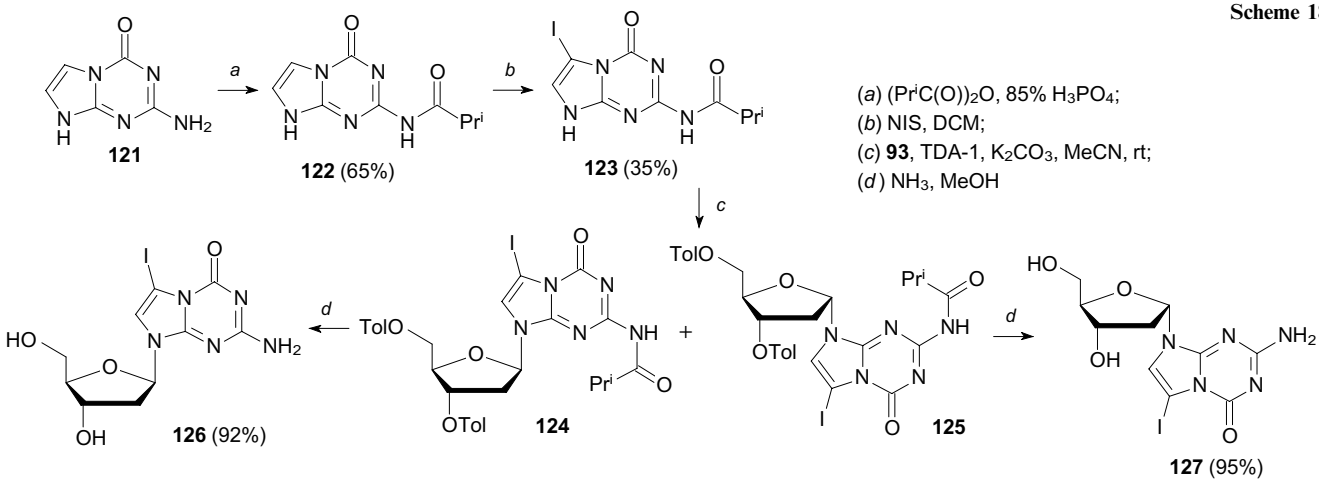
The glycosylation of unsubstituted 5-aza-7-deazaguanine (**121**) under different conditions invariably causes the formation of anomeric mixtures in moderate yields.[84] In order to enhance the solubility of substrates in organic solvents, improve the stereoselectivity of the reaction and increase the product yield, 5-aza-7-deazaguanine (**121**) was treated with a mixture of isobutyric anhydride and phosphoric acid giving *N*(2)-isobutyryl-5-aza-7-deazaguanine (**122**).[86] The subsequent reaction with *N*-iodosuccinimide (NIS) in anhydrous dichloromethane at room temperature afforded *N*(2)-isobutyryl-7-iodo-5-aza-7-deazaguanine (**123**) as a single isomer in 35% yield.[87] Similar reactions with NIS in anhydrous DMF or with ICl in an aqueous AcONa solution did not give the target product. Intermediate *N*(2)-isobutyryl-7-iodo-5-aza-7-deazaguanine (**123**) was glycosylated with 2-deoxyribofuranosyl chloride[88] (**93**) in the presence of potassium carbonate and TDA-1 to form a mixture of β-D- (**124**) and α-D-anomers (**125**) in a ratio of 3 : 2 (^{1}H NMR spectroscopy and HPLC data) in 95% overall yield (Scheme 18).[87] Attempts to isolate individual anomers by column chromatography failed. The mixture was treated with ammonia in methanol. However, after deprotection, attempts to separate the anomeric mixtures

Scheme 17

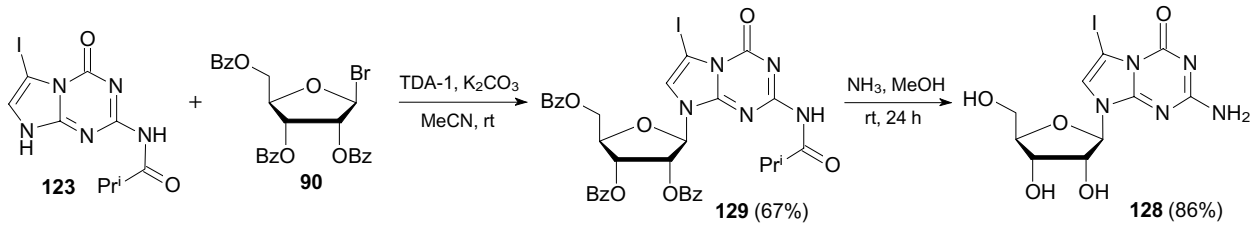


R = OH (**117**, 88%), NH_2 (**118**, 65%), $NHNH_2$ (**119**, 70%), NHOH (**120**, 55%); (*a*) 2 M KOH, rt (for **117**); (*b*) 25% NH_4OH, 80 °C (for **118**); (*c*) 80% NH_2NH_2, 70 °C (for **119**); (*d*) 50% NH_2OH, 60 °C (for **120**)

Scheme 18



Scheme 19



by column chromatography were unsuccessful.[87] To accomplish the separation, the mixture of protected anomers **124** and **125** was dissolved in hot methanol, and only β-anomer **124** crystallized on cooling (31% yield). The mother liquor was concentrated, and α-anomer **125** crystallized (27% yield) from a mixture of ethyl acetate and petroleum ether. The isolated anomers were deprotected using an ammonia solution in methanol, and nucleosides **126** and **127** were obtained in 92 and 95% yields, respectively, in the final step with an optical purity (enantiomeric excess, *ee*) $\geqslant$99% (see Scheme 18). In an alternative procedure for the isolation of the α-anomer (not shown in Scheme 18), the crystallization of the β-anomer was followed by the treatment of the mother liquor with ammonia in methanol giving an inseparable mixture of nucleosides in 87% yield. The 5′-OH groups of these nucleosides were protected with 4,4′-dimethoxytrityl (DMT) groups. This made it possible to isolate the DMT derivative of α-D-nucleoside (40% yield) and its β-D-analogue (12%) by silica gel column chromatography. The reaction with trichloroacetic acid produced target nucleosides in 91% yield.[89]

This method was also used to prepare 7-iodo-5-aza-7-deazaguanosine (**128**) (Scheme 19).[89] 1-*O*-Acetyl-2,3,5-tri-*O*-benzoylribofuranose was stored with a 30% HBr solution in acetic acid overnight. The resulting bromide **90** caused the glycosylation of nucleobase anions at room temperature in acetonitrile in the presence of potassium carbonate and TDA-1. The glycosylation of 5-aza-7-deazaguanine **121** gave the product in low yield (10%). On the contrary, the reaction using *N*(2)-isobutyryl-7-iodo-5-aza-7-deazaguanine (**123**) afforded protected β-D-nucleoside **129** in 67% yield (see Scheme 19). The protecting groups were removed with NH_3 in MeOH at room temperature, and iodinated ribonucleoside **128** was isolated in high yield. Therefore, the glycosylation of nucleobase anions is more efficient if the pyrrole or imidazole ring contains electron-withdrawing substituents, *e.g.*, halogen atoms; the same was observed in the synthesis of pyrrolo[2,3-*d*]pyrimidine nucleosides.[90]

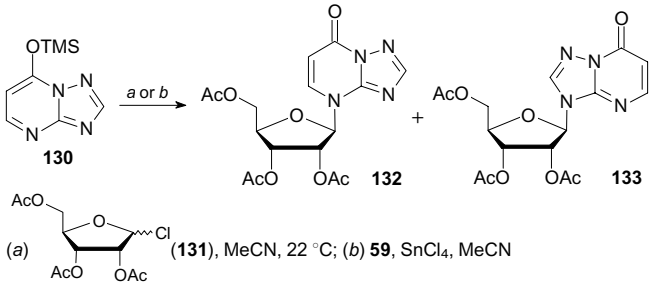
3.1.1.4. Silyl-Hilbert – Johnson reaction (Vorbrüggen method)

The method for the glycosylation developed by Vorbrüggen and co-workers[91–96] involves the condensation of trimethylsilyl derivatives of nucelobases or their N-acetylated derivatives with fully acetylated monosaccharides in the presence of Lewis acids. Trimethylsilyl derivatives of nucelobases are readily soluble in commercially available solvents, such as 1,2-dichloroethane (DCE) and acetonitrile, and can be easily prepared by the reaction with hexamethyldisilazane or trimethylchlorosilane. Anhydrous tin(IV) chloride, trimethylsilyl trifluoromethanesulfonate (trimethylsilyl triflate, TMSOTf) or boron trifluoride etherate ($BF_3 \cdot Et_2O$) are commonly employed as the catalysts.

Fully acetylated monosaccharides are generally used as glycosylating agents. Acetylated methyl glycosides can also be utilized. It is assumed that Lewis acid induces the formation of the C(1)-carbonium ion, which is stabilized in the presence of the ester group at the C(2) atom to form the acyloxonium ion.[91] The nucleophilic attack of the trimethylsilyl derivative on the heterocyclic base occurs stereospecifically to form the natural β-D-glycosidic bond. The reactions with 2-deoxy monosaccharides or derivatives with protecting groups at the C(2) position generally afford a mixture of α- and β-anomers.[97]

Silylated [1,2,4]triazolo[1,5-*a*]pyrimidine **130** reacts with 1-chloro-2,3,5-tri-*O*-acetylribofuranose **131** in acetonitrile at room temperature (method *a*) to form a mixture of products **132** and **133** [at the N(3) and N(9) atoms, respectively] in a ratio of 3 : 2 in 38% overall yield. Meanwhile, the reaction with ribose tetraacetate **59** in the presence of $SnCl_4$ (method *b*) affords a mixture of the same products in a ratio of 84 : 16 in 55% overall yield (Scheme 20).[98]

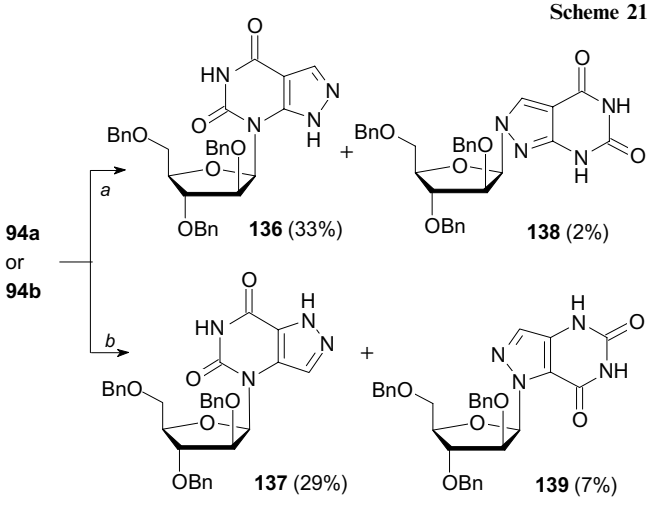
Scheme 20



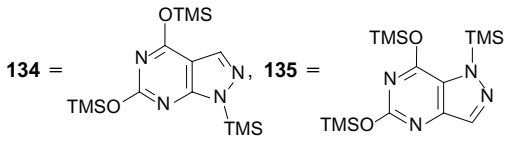
Silylated pyrazolouracils **134** (see Ref. 99) and **135** (see Ref. 100) react with halide **94** in the presence of $SnCl_4$ giving the corresponding N(3)-β-nucleosides **136** and **137** as the major products and a small amount of isomeric N(8)- and N(7)-β-nucleosides **138** and **139** (Scheme 21).

The method was developed for the synthesis of nucleoside analogues bearing fluorinated pyrrolo[2,3-*b*]pyridine and pyrrolo[2,3-*d*]pyrimidine heterocyclic bases. 5-Amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile (**140**) was used as the starting compound[101] instead of unstable unsubstituted 2-amino-1*H*-pyrrole that is difficult to synthesize. The *tert*-butyl protecting group and the electron-withdrawing cyano substituent significantly enhance stability of this heterocycle. The heating of reagent **140** with 1,1,1,5,5,5-hexafluoropentane-2,4-dione in acetic acid under reflux afforded substituted pyrrolopyridine **141**, while the reaction with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine in acetic acid at 0 °C gave compound **142** (Scheme 22).[101] The *tert*-butyl group at the N(1) atom of pyrrolo[2,3-*b*]pyridine **141** and pyrrolo[2,3-*d*]pyrimidine **142** was removed in 60% sulfuric acid. Compounds **143** and **144** were prepared in moderate yields. The glycosylation of these compounds with 1-*O*-methyl-2,3,5-tri-*O*-acetylribofuranose **145** was performed

Scheme 21



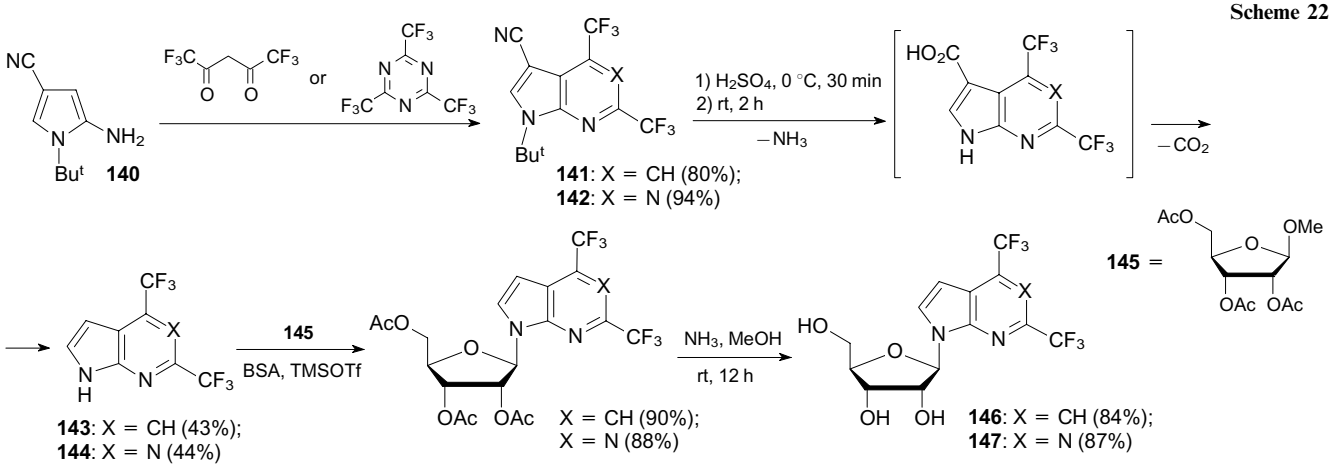
(*a*) **134**, $SnCl_4$, DCE; (*b*) **135**, $SnCl_4$, DCE;



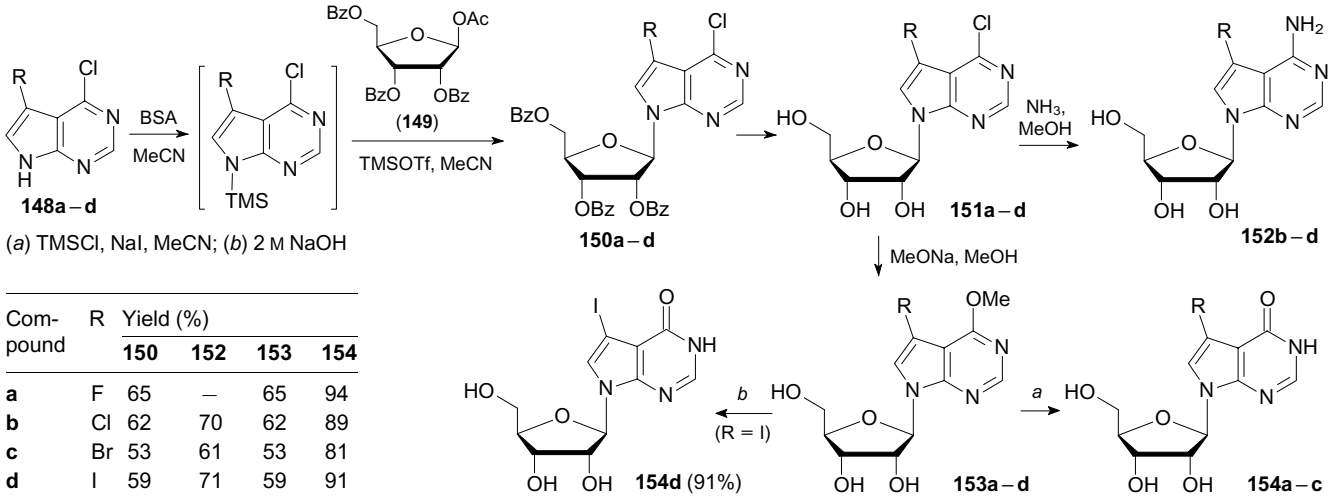
by the silyl-Hilbert – Johnson method in dichloromethane using BSA for the preliminary silylation of heterocyclic moieties. Trimethylsilyl triflate was utilized as the catalyst for glycosylation. The deprotection with ammonia in methanol afforded products **146** and **147** in high yields (see Scheme 22).[101]

7-Deazaadenosine and 7-deazainosine β-D-nucleosides and related β-L-nucleosides were synthesized by the silylation of 7-halogenated 6-chloro-7-deazapurines **148a – d** with BSA (1.2 equiv.) in anhydrous acetonitrile at room temperature followed by the addition of 1.2 equiv. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose) in the presence of TMSOTf at 80 °C (as exemplified by β-D-ribofuranose derivative **149** in Scheme 23).[102] It was found that the use of 1.2 equiv. of TMSOTf brought the reaction to the completion within 1 h. Glycosylation products **150a – d** were obtained in moderate yields. These conditions differ from those used for more sensitive 7-halogenated 2-amino-6-chloro-7-deazapurines, the reactions of which required the heating at 40 – 50 °C overnight.[90] Attempts to perform the glycosylation of unsubstituted 6-chloro-7-deazapurine (4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine) with no electron-withdrawing substituents at the 4 position (the 7 position according to nucleoside nomenclature) under similar con-

Scheme 22



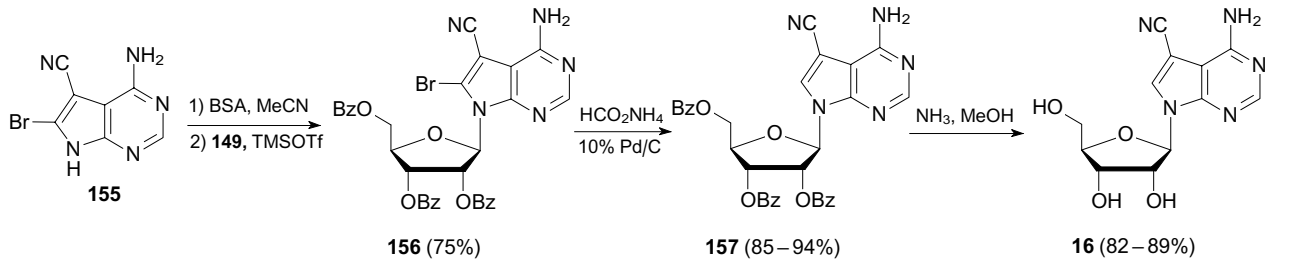
Scheme 23



(*a*) TMSCl, NaI, MeCN; (*b*) 2 M NaOH

Compound	R	Yield (%)			
		150	**152**	**153**	**154**
a	F	65	–	65	94
b	Cl	62	70	62	89
c	Br	53	61	53	81
d	I	59	71	59	91

Scheme 24



ditions using the same protected ribofuranoses were unsuccessful.

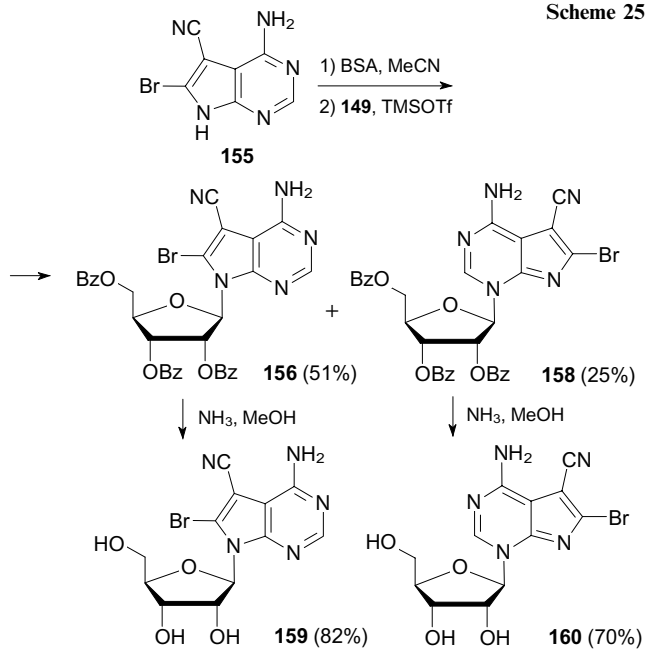
Bio *et al.*[103] observed a similar effect in the glycosylation of 5-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine with 2′-*C*-methyl-1,2,3,5-tetra-*O*-benzoyl-D-ribofuranose. Evidently, the electron-withdrawing character of 7-halogen substituents is a prerequisite for the successful silylation and glycosylation involving 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- or 1,2,3,5-tetra-*O*-benzoyl-D-ribofuranoses. The use of the isopropylidene-protected carbohydrate moiety is more favourable in the case of nucleobases unsubstituted at the 7 position.[104] Another approach involves the synthesis of bromine- or iodine-containing compounds followed by the halogen reductive elimination. The deprotection afforded target ribonucleosides **151a – d**.[102] 7-Halogenated tubercidin derivatives **152b – d** were synthesized using an ammonia solution in methanol. The reaction was performed in an autoclave at 120 °C overnight. The corresponding 7-halogenated β-L-tubercidin derivatives were prepared in a similar manner. The deprotection with a 0.5 M sodium methoxide solution in methanol at room temperature was accompanied by the replacement of the chlorine atom at the 6 position by the methoxy group. The latter group was replaced by the oxo group using the following two approaches: the treatment of compounds **153a – d** with a mixture of trimethylchlorosilane and sodium methoxide in acetonitrile or the heating under reflux in an aqueous alkaline solution (see Scheme 23). The former approach proved to be successful for compounds **153a – c** bearing 7-fluoro, 7-chloro or 7-bromo substituents but led to the partial deiodination of compound **153d**. For this reason, the demethylation of 7-iodo derivative **153d** was performed in alkaline conditions, allowing the synthesis of target nucleoside **154d** in 91% yield.[102]

7-Iodo derivatives are valuable intermediates for the introduction of alkynyl or aminoalkynyl substituents because they can be used as the starting compounds in Pd-catalyzed cross-coupling reactions. This method was applied to prepare 7-alkynyl- and 7-aminoalkynyl-7-deazapurine ribonucleosides. The reaction was performed in anhydrous DMF in the presence of tetrakis(triphenylphosphine)palladium(0), copper(I) iodide and triethylamine under a nitrogen atmosphere; the yields of alkynyl derivatives were 68 – 81%.[102]

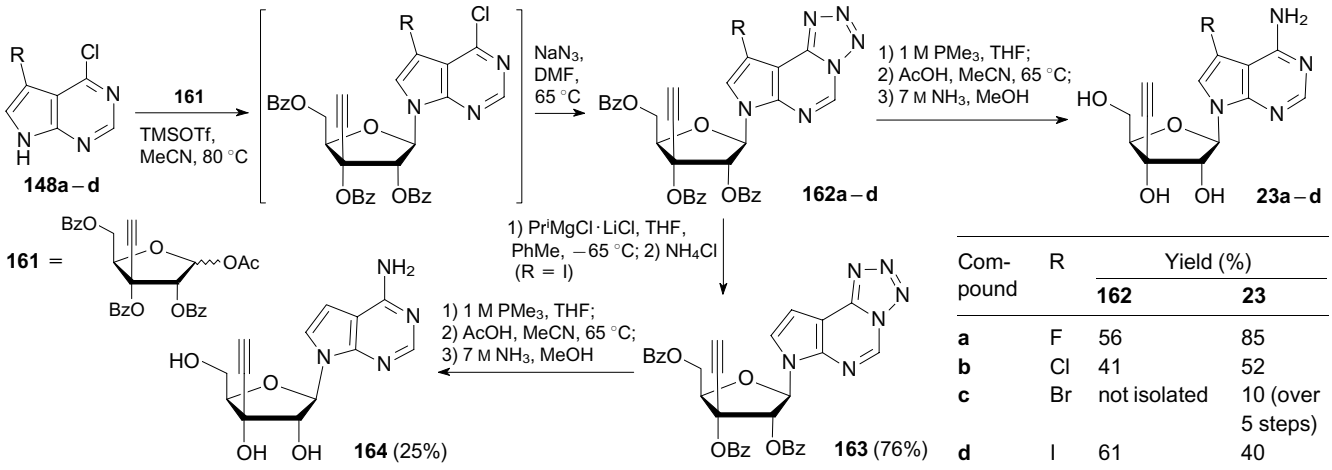
The Vorbrüggen method was used to prepare toyocamycin and its analogues.[105] 4-Amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine (**155**) was silylated with BSA (2 equiv.) in dry acetonitrile under an argon atmosphere at room temperature (Scheme 24). After 15 min, 1 equiv. of ribofuranose **149** and 3 equiv. of TMSOTf were added, and the reaction mixture was stirred at 80 °C for 3 h to bring the reaction to the completion. The simple treatment of the mixture gave 4-amino-6-bromo-7-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)-5-cyanopyrrolo[2,3-*d*]pyrimidine (**156**) in good yield. The debromination was accomplished by heating compound **156**, ammonium formate and 10% Pd/C under reflux in ethanol for 3 h to prepare 4-amino-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-cyanopyrrolo[2,3-*d*]-pyrimidine (**157**). The deprotection of the latter compound was performed with an ammonia solution in methanol under standard conditions to obtain toyocamycin (**16**).[105]

A decade later, Leonard *et al.*[106] made an attempt to reproduce this method. The authors silylated 4-amino-6-bromo-5-cyano-7*H*-pyrrolo[2,3-*d*]pyrimidine (**155**)[107] with BSA (2 equiv.) in dry acetonitrile at room temperature. Then 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose **149** (1 equiv.) and trimethylsilyl triflate (3 equiv.) were added, and the resulting solution was kept at 80 °C for 3 h. As opposed to the previously published example,[105] two major reaction products were separated by flash chromatography: N(9)-substitution product **156** was isolated in 51% yield; N(3)-substitution product **158**, in 25% yield (2 : 1 ratio). The reaction was repeated several times under the same conditions to confirm the product ratio. Nucleosides **159** and **160** were isolated after deprotection with a saturated ammonia solution in methanol (Scheme 25). The formation of two regioisomeric glycosylation products was confirmed by Huang and Bobek[108] using the same heterocyclic base but performing the glycosylation with azido sugar. This method was applied to prepare two glycosylation products, the structures of which were confirmed by ^{1}H and ^{13}C NMR spectroscopy and X-ray diffraction. The catalytic dehaloge-

Scheme 25



Scheme 26



Compound	R	Yield (%)	
		162	**23**
a	F	56	85
b	Cl	41	52
c	Br	not isolated	10 (over 5 steps)
d	I	61	40

nation of the protected compound was performed by heating the mixture under reflux in ethanol for 3 h with ammonium formate and 10% Pd/C (see Scheme 24). Toyocamycin (**16**) and its isomer were obtained after the debenzoylation with an ammonium solution in methanol.

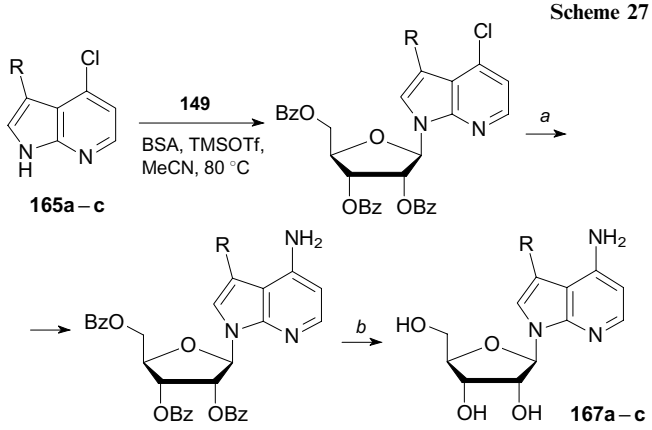
Recently, the Vorbrüggen glycosylation[1] was used to synthesize 7-halogenated 7-deazaadenosine derivatives from 4-chloro-5-halo-7*H*-pyrrolo[2,3-*d*]-pyrimidines **148a – d** and benzoyl-protected 3′-*C*-ethynyl-β-D-ribose acetate **161** (Scheme 26).[39] In this method, the benzoyl protection of hydroxyl groups of ribose was preferable compared to the acetyl protection. The following scheme was proposed for the efficient introduction of the 6-amino group into the molecule.[109, 110] The nucleophilic substitution of the chlorine atom at the 6 position by sodium azide afforded azide derivatives **162a – d**, which can rather easily be isolated in pure form due to a significant difference in the polarity caused by the major tetrazole isomer. The Staudinger reduction followed by the deprotection gave 6-amino derivatives **23a – d**. To dehalogenate the iodine atom at the 7 position, intermediate **162d** was subjected to I – Mg exchange using Pr^{i}MgCl · LiCl[111, 112] followed by the treatment with a saturated ammonium chloride solution giving compound **163**. The latter compound was transformed into product **164** under the conditions presented in Scheme 26.

The Vorbrüggen glycosylation performed under the conditions described above[39] made it possible to transform substituted pyrrolo[2,3-*b*]pyridines into the corresponding ribonucleosides (Schemes 27 and 28).[77] The starting 3-substituted 4-chloro- (**165a – c**, see Scheme 27) and 4-azido-1*H*-pyrrolo[2,3-*b*]pyridines (**166a – c**, see Scheme 28) were prepared in two steps from 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine, which can also be efficiently glycosylated. It is worth noting that regioisomeric N(7)-nucleosides were absent among the isolated products. The stereo- (β configurations) and regiochemistry (substitution at the N(1) atom) of the final nucleoside analogues **167a – c** and **168a – c** was established using 2D ^{1}H – ^{1}H and ^{1}H – ^{13}C NMR spectroscopy (nuclear Overhauser effect spectroscopy (NOESY) and heteronuclear multiple bond correlation (HMBC) experiments, respectively). The overall yields with respect to the starting bases are given in Schemes 27 and 28. The structure of nucleoside analogue **167c** with X = I was additionally confirmed by X-ray diffraction.

Using commercially available 1,2,3-tri-*O*-acetyl-5-deoxy-β-D-ribofuranose (**169**) and 1-*O*-acetyl-2,5-di-*O*-benzoyl-3-deoxy-α(β)-D-ribofuranose **170** as precursors of the carbohydrate moiety, the method allows the synthesis of 5′-deoxy- and 3′-deoxy analogues of 7-iodo-1,7-dideazaadenosine **171** and **172** from compound **166d** in 21 and 19% overall yields, respectively (Scheme 29).[77]

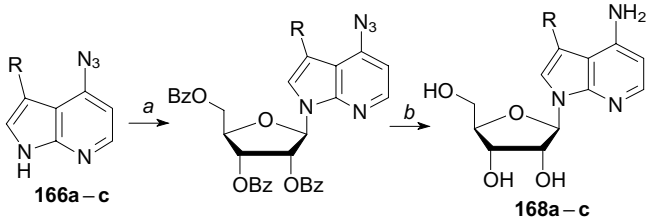
The efficient synthesis of 3,6-difluoro-3-deazapurine **173** from commercially available 3-chloro-2,4,5,6-tetrafluoropyridine (**174**) was performed in ten steps and gave the target product in 25% overall yield.[113] The glycosylation of 3,6-difluoro-3-deazapurine **173** was accomplished using three different carbohydrate synthons: 1,2,3,5-tetra-*O*-benzoyl-β-D-ribofuranose (**175**), 1,2,3,5-tetra-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranose (**176**) and 1,2-di-*O*-acetyl-3-

Scheme 27



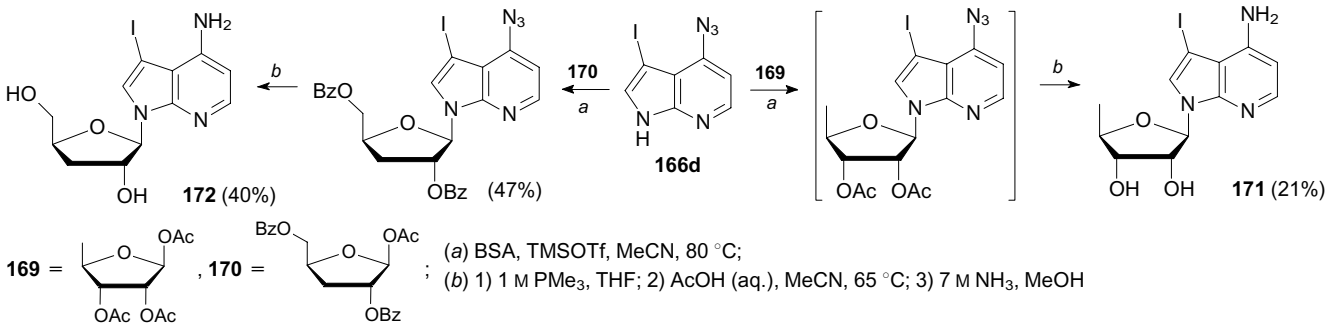
(*a*) 1) NaN_3, 15-crown-5, DMF, 110 °C; 2) 1 M PMe_3, THF; 3) AcOH (aq.), MeCN, 65 °C; (*b*) 7 M NH_3, MeOH; R = Cl (**a**, 33%), Br (**b**, 20%), I (**c**, 13%)

Scheme 28

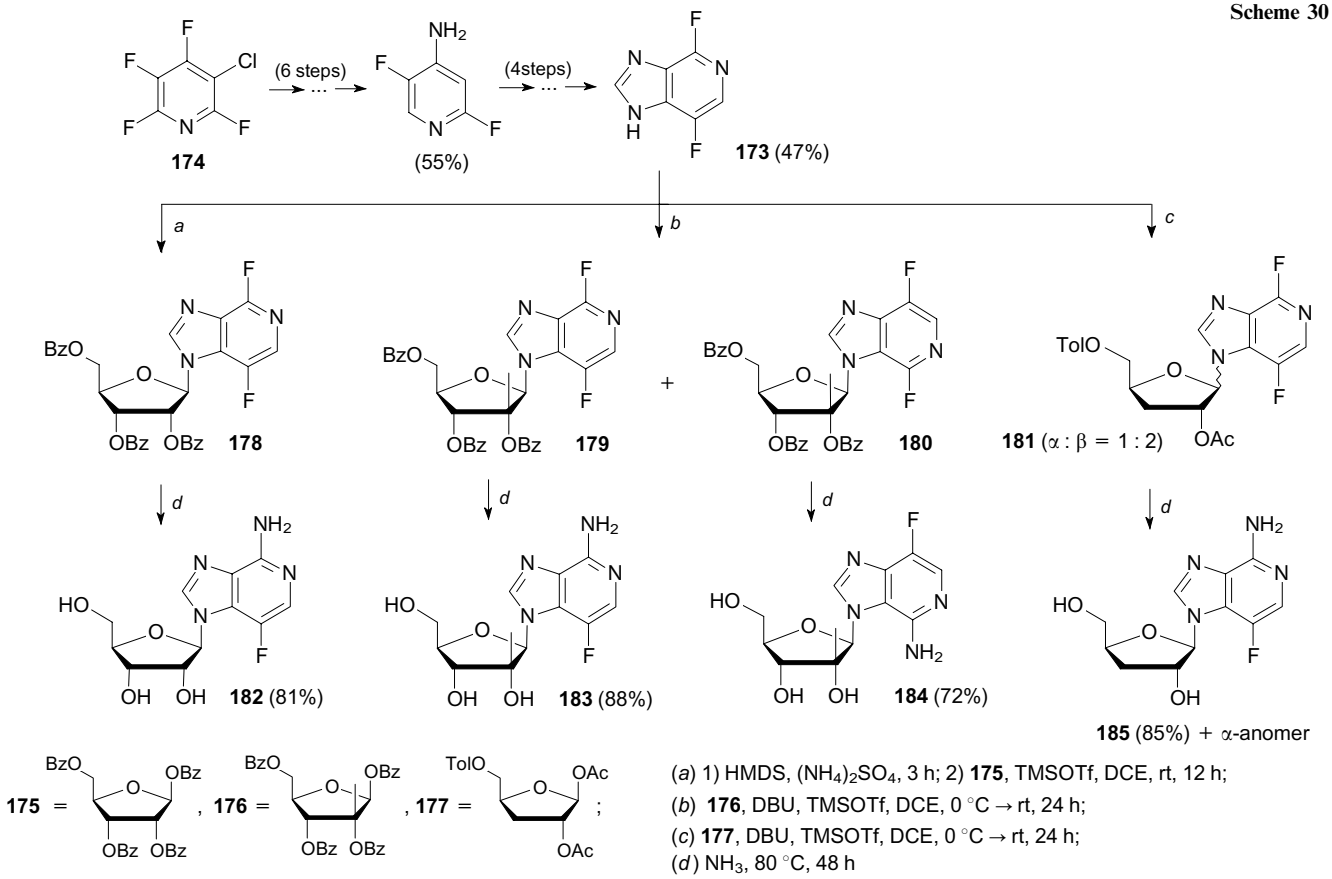


(*a*) **149**, BSA, TMSOTf, MeCN, 80 °C;
(*b*) 1) 1 M PMe_3, THF; 2) AcOH (aq.), MeCN, 65 °C;
3) 7 M NH_3, MeOH; R = F (**a**, 20%), CN (**b**, 60%), NO_2 (**c**,12%)

Scheme 29



Scheme 30



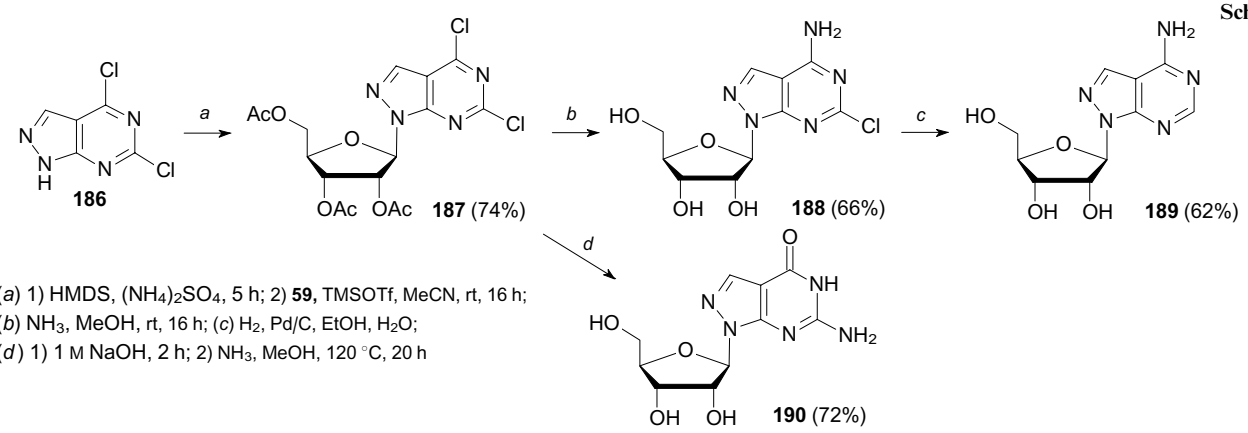
deoxy-5-*O*-(4-methylbenzoyl)-β-D-ribofuranose (**177**) (Scheme 30).[113]

The Vorbrüggen glycosylation involving the silylated base and 1,2,3,5-tetra-*O*-benzoyl-β-D-ribofuranose (**175**) in the presence of TMSOTf was selective and gave protected nucleoside analogue **178** in 70% yield. On the contrary, attempts to perform the glycosylation of protected 2-*C*-methylribose **176** under similar conditions or in the presence of $SnCl_4$ failed. Hence, the reaction of 3,6-difluoro-3-deazapurine **173** with 1,2,3,5-tetra-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranose (**176**) was carried out in dichloroethane in the presence of TMSOTf and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). This made it possible to prepare a mixture of compounds **179** and **180** as substitution products at the N(9) and N(7) atoms in a ratio of 5 : 1 in 84% overall yield. The isomers were separated by flash column chromatography (SiO_2; 3% EtOAc in dichloroethane as the eluent). Under the same conditions, the reaction of 3,6-difluoro-3-deazapurine **173** with deoxyribose analogue **177** afforded a mixture of the α- and β-anomers of **181** (1 : 2 ratio) in 70% yield. Protected nucleoside analogues **178** – **181** were treated with liquid ammonia at 80 °C. The complete deprotection and the formation of nucleosides **182** – **185** were observed after 48 h. The products were isolated in high yields. Neither an increase in the reaction time (to 96 h) nor an increase in the temperature (to 110 °C) led to the formation of diamino derivatives.

The Vorbrüggen method was used to synthesize 7-deaza-8-azapurine nucleosides[114, 115] shown in Scheme 31.

Readily available 4,6-dichloropyrazolo[3,4-*d*]pyrimidine (2,6-dichloro-7-deaza-8-azapurine, **186**) was silylated on heating in hexamethyldisilazane (HMDS) in the presence of ammonium sulfate. Then 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**59**) and trimethylsilyl triflate were added. The reaction afforded 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-4,6-dichloropyrazolo[3,4-*d*]pyrimidine (**187**) as the major product.[114] The treatment of this compound with an ammonia solution in methanol at room temperature gave

Scheme 31

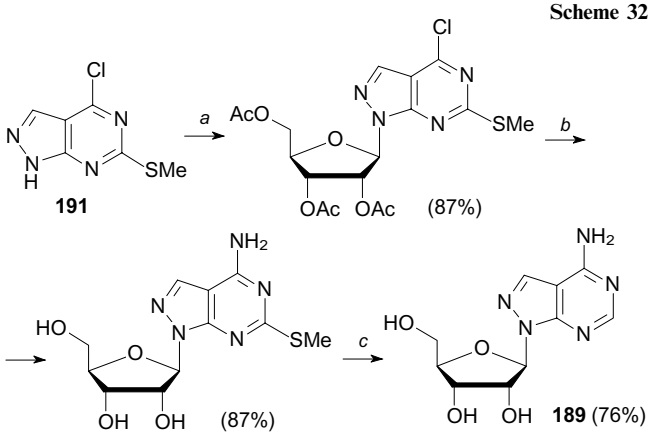


(*a*) 1) HMDS, $(NH_4)_2SO_4$, 5 h; 2) **59**, TMSOTf, MeCN, rt, 16 h;
(*b*) NH_3, MeOH, rt, 16 h; (*c*) H_2, Pd/C, EtOH, H_2O;
(*d*) 1) 1 M NaOH, 2 h; 2) NH_3, MeOH, 120 °C, 20 h

4-amino-6-chloro-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (**188**), and the subsequent dehalogenation with Pd/C under a hydrogen atmosphere produced 4-amino-(1-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (7-deaza-8-azaadenosine **189**, 41% yield over two steps). 8-Aza-7-deazaguanosine **190** was synthesized by the treatment of dichloropyrazolopyrimidine **187** with a refluxing aqueous sodium hydroxide and ethanol and then with ammonia in methanol at 120 °C for 20 h; the yield of the product was 72% over two steps. The reaction of intermediate **188** with an aqueous dimethylamine or methylamine solution at room temperature gave the corresponding 2,6-disubstituted aminonucleosides in 78 – 79% yields.

The yield of 7-deaza-8-azaadenosine **189** prepared by this method was low. Hence, a similar method was proposed for the synthesis of this compound from 4-chloro-6-methylthiopyrazolo[3,4-*d*]pyrimidine **191** (Scheme 32).[114] As a result, the overall yield of product **189** was increased from 30 to 58%.

Scheme 32



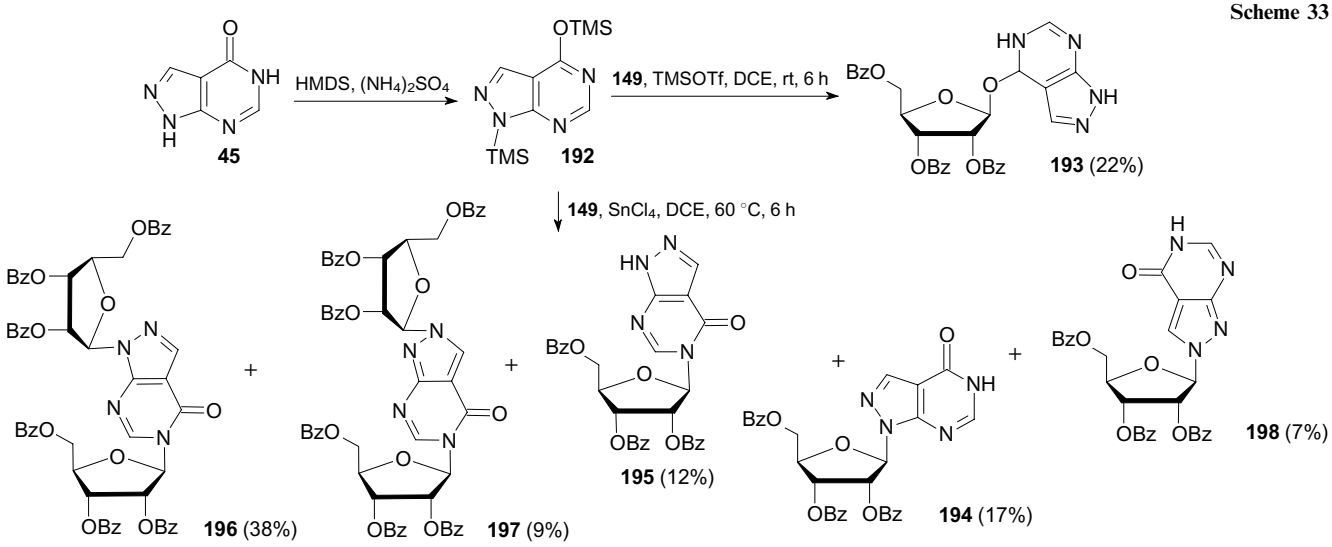
(*a*) 1) HMDS, $(NH_4)_2SO_4$, 5 h; 2) **59**, TMSOTf, MeCN, rt, 16 h;
(*b*) NH_3, MeOH, 100 °C, 16 h; (*c*) Ni-Ra, EtOH, H_2O

Different conditions of the glycosylation of allopurinol (7-deaza-8-azahypoxanthine) were compared. Attempts to synthesize nucleoside analogues by the glycosylation of non-silylated allopurinol with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**149**) or 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**59**) in the presence of $SnCl_4$ under different conditions did not lead to success.[115] Hence, in the first step allopurinol (**45**) was heated in HMDS under reflux in the presence of ammonium sulfate to prepare bis(trimethylsilyl) derivative **192** (Scheme 33). The reaction of compound **192** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**149**) in dichloroethane in the presence of trimethylsilyl triflate as the catalyst gave mainly O(6)-addition product **193**, while N(9)- and N(1)-nucleosides **194** and **195** were present in minor amounts. The same reaction on heating in the presence of tin tetrachloride afforded a mixture of N(1),N(9)- and N(1),N(8)-disubstitution products **196** and **197** and N(9)-, N(1)- and N(8)-nucleosides **194**, **195** and **198**. The mixture was separated by preparative thin-layer chromatography or HPLC. The benzoyl protecting groups were removed with sodium methoxide in methanol giving the corresponding free allopurinol ribosides in 53 – 88% yields.[115] The reaction of bis(trimethylsilyl)allopurinol with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**59**) in the presence of $SnCl_4$ (dichloroethane, 60 °C, 4 h) or boron trifluoride etherate (dioxane, reflux, 30 min) afforded identical mixtures of products bearing three monoribosides (the replacement at the N(9), N(1) and N(8) atoms) and N(1),N(9) and N(1),N(8)-bisribosides in a ratio of 2 : 2 : 1. As opposed to bisribosides, which are easily isolated by preparative silica gel thin-layer chromatography, attempts to separate a mixture of monoribosides to individual components failed.[115]

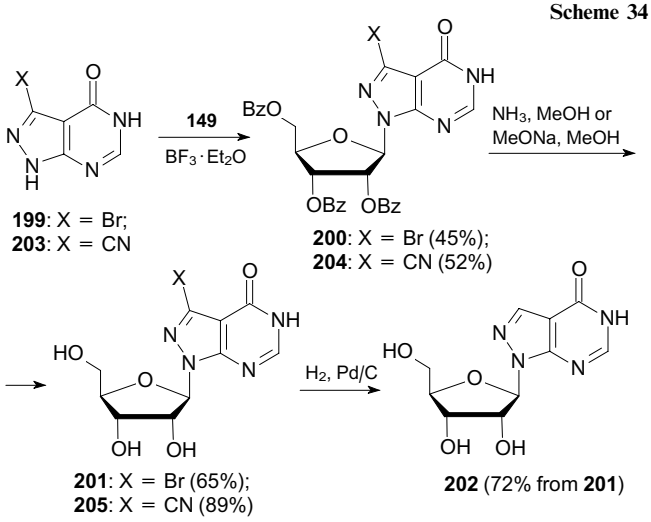
Attempts were made to use the Vorbrüggen method to synthesize 3-substituted allopurinol ribonucleosides.[116] However, as applied to these compounds, this approach proved to be less efficient. Thus, the glycosylation of the trimethylsilyl derivative of 3-bromoallopurinol (7-bromo-7-deaza-8-azahypoxanthine) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**149**) in the presence of trimethylsilyl triflate afforded the N(1)-glycosylated isomer as the major product that formed within the first hours of the reaction (TLC data). The heating of this isomer for one week led to its rearrangement into thermodynamically more stable 3-bromo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyrazolo[3,4-*d*]pyrimidin-4-(5*H*)-one (the N(9)-glycosylated isomer); however, the product was obtained in low yield (29%).

The alternative method for the glycosylation (Scheme 34) is based on the reaction of non-silylated 3-bromoallopurinol **199** with ribofuranose **149** in the presence of $BF_3 \cdot Et_2O$ in refluxing nitromethane for 90 min. Under these conditions, the formation of the N(1)-glycosylated isomer was not observed, the N(8) isomer was present in trace amounts, while the yield of the target N(9)-isomer **200** increased to 45%. The debenzoylation of the latter with

Scheme 33



Scheme 34



ammonia in methanol afforded 3-bromoallopurinol ribonucleoside **201**, which was transformed into allopurinol ribonucleoside (7-deaza-8-azainosine **202**) by the dehalogenation in the presence of Pd/C.

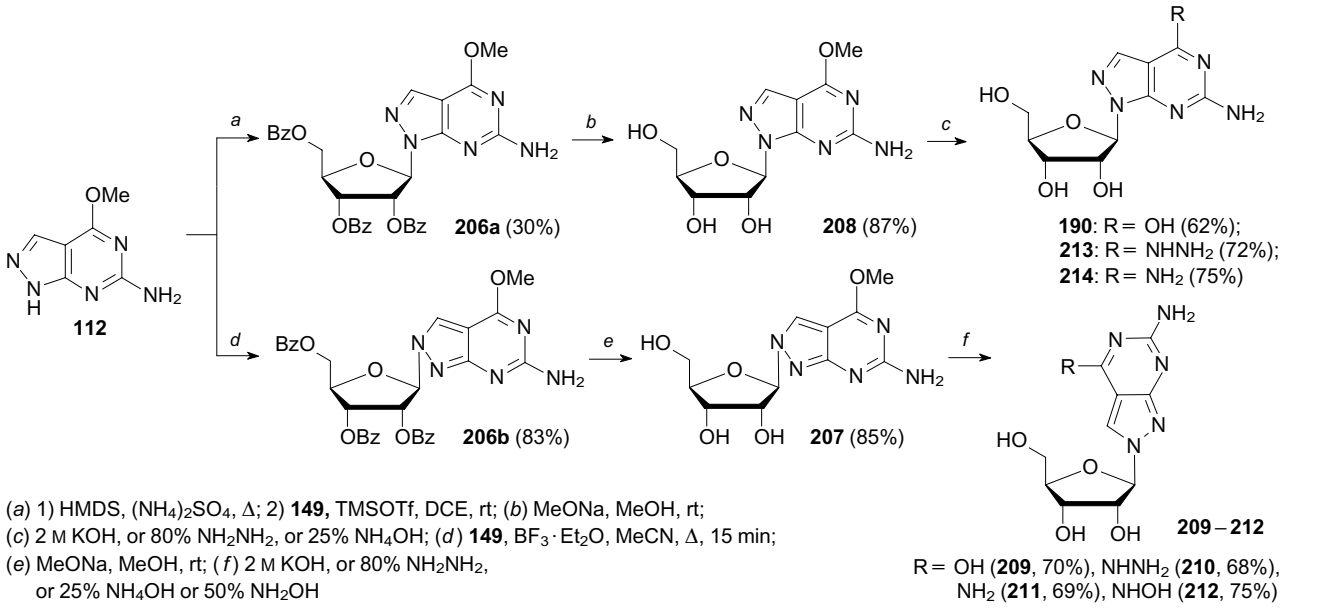
The glycosylation of presilylated 3-cyanoallopurinol **203** catalyzed by trimethylsilyl triflate produced protected 3-cyanoallopurinol ribonucleoside **204** in 46% yield (not shown in Scheme 34); the glycosylation of 3-cyanoallopurinol **203** under reflux with $BF_3 \cdot Et_2O$ in benzonitrile for 15 min afforded the same product **204** in 52% yield. The removal of benzoyl groups with sodium methoxide in methanol gave 4-(5*H*)-oxo-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine-3-carbonitrile (**205**) in high yield (see Scheme 34). Different transformations involving the Br atom and the CN group provided the synthesis of a series of new of 3-substituted allopurinol nucleoside analogues functionalized by amino, methylamino, dimethylamino, carboxamide, thiocarboxamide and carboxamidine groups.[116]

Ren *et al.*[84] compared different methods of glycosylation of 6-amino-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**112**). The reaction of this compound with ribofuranose **149** in the presence of tin tetrachloride did not afford the desired glycosylation product. Hence, the reaction was performed using trimethylsilyl triflate as the catalyst and HMDS and BSA as the silylating agents in acetonitrile, nitromethane and 1,2-dichloroethane. The best results (30% yield of N(9)-nucleoside **206a**) was achieved in the glycosylation of the HMDS-silylated purine base in the presence of TMSOTf in freshly distilled 1,2-dichloroethane, which was performed overnight at room temperature. The reaction using a boron trifluoride etherate solution as Lewis acid at high temperature in acetonitrile afforded N(8)-nucleoside **206b** in 83% yield, while the formation of the N(9)-glycosylated compound under these conditions almost did not occur (Scheme 35). The subsequent removal of benzoyl protecting groups using a methanolic solution of sodium methoxide gave 6-methoxy-7-deaza-8-azapurine nucleosides **207** and **208** (see Scheme 35). The treatment of these compounds with an aqueous potassium hydroxide solution afforded 7-deaza-8-azaguanosine derivatives **209** and **190**. Similarly, the heating of key intermediates **207** and **208** with ammonia, hydrazine or hydroxylamine solutions gave **210** – **214** (see Scheme 35).[84]

Unlike the above-described method, the glycosylation of 6-amino-3-iodo-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (2-amino-6-methoxy-7-iodo-7-deaza-8-azapurine, **215**) with ribofuranose **149** in the presence of $SnCl_4$ or TMSOTf afforded complex mixtures containing the N(9)-glycosylated product in trace amounts. The use of boron trifluoride etherate as the catalyst for this reaction in acetonitrile at room temperature allowed the isolation of target N(9)-glycosylated product **216** in 28% yield (Scheme 36).[84] 3,6-Dibromo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**217**) was glycosylated with ribofuranose **149**, without the protection of the oxo group. The heating of **149** under reflux in acetonitrile in the presence of boron trifluoride etherate for 15 min gave tri-*O*-benzoylnucleoside **218** in high yield. As in the above example, 7-deaza-8-azapurine nucleosides **219** and **220** were isolated in excellent yields after the removal of benzoyl protecting groups using a methanolic solution of sodium methoxide or ammonia. 6-Methoxy derivative **220** was treated with an aqueous potassium hydroxide solution to prepare 7-iodo-7-deaza-8-azaguanosine **221** or with an ammonia solution in the case of diaminopurine analogue **222** (see Scheme 36).[84]

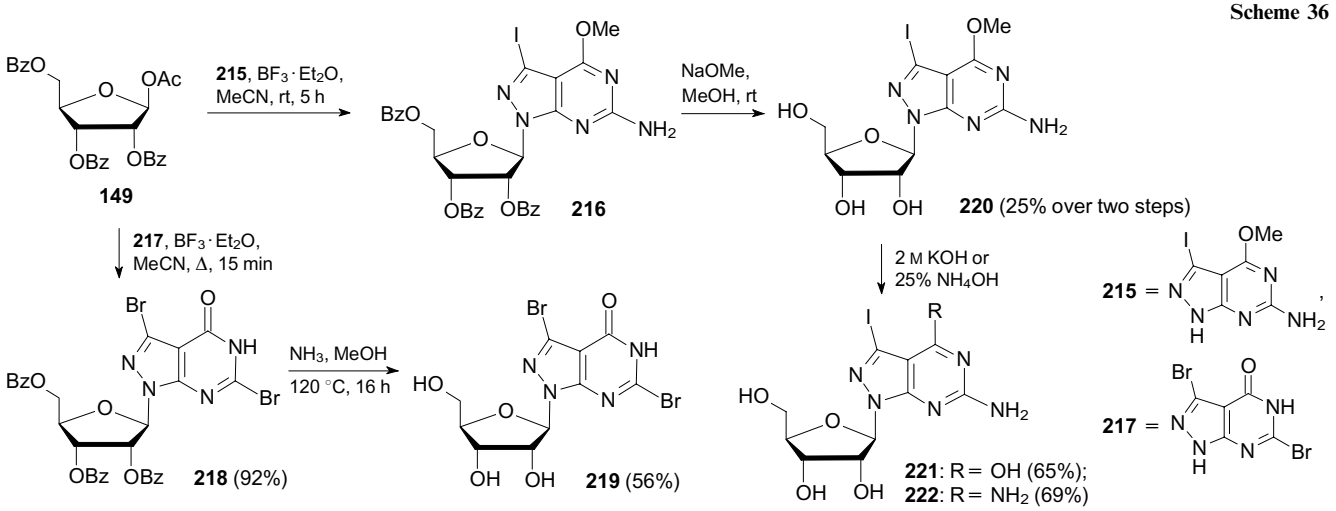
6-Methoxy-7-iodo derivative **220** is a convenient starting compound for the introduction of aromatic or alkynyl

Scheme 35



(*a*) 1) HMDS, $(NH_4)_2SO_4$, Δ; 2) **149**, TMSOTf, DCE, rt; (*b*) MeONa, MeOH, rt;
(*c*) 2 M KOH, or 80% NH_2NH_2, or 25% NH_4OH; (*d*) **149**, $BF_3 \cdot Et_2O$, MeCN, Δ, 15 min;
(*e*) MeONa, MeOH, rt; (*f*) 2 M KOH, or 80% NH_2NH_2,
or 25% NH_4OH or 50% NH_2OH

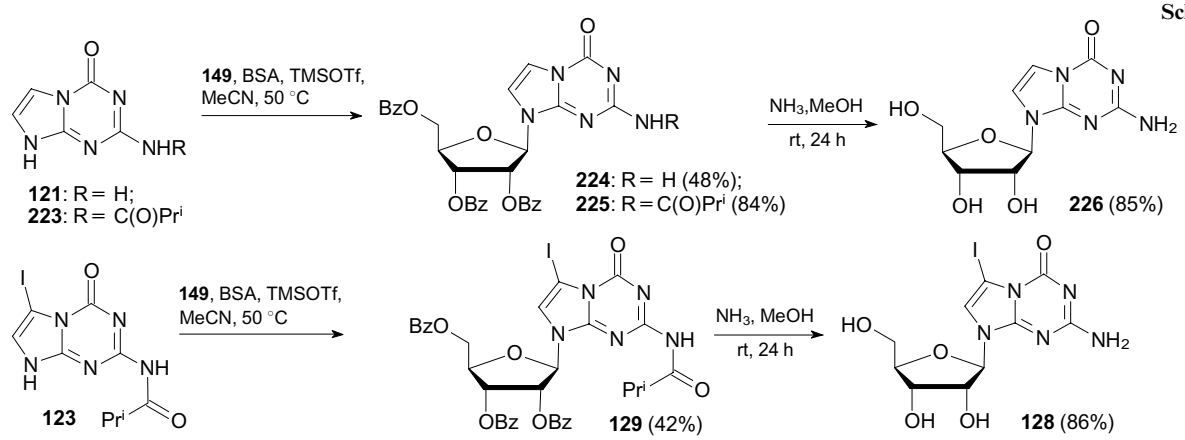
Scheme 36



substituents *via* Pd-catalyzed cross-coupling reactions.[84] The reaction of this compound with 2-(tri-n-butylstannyl)-furan catalyzed by bis(triphenylphosphine)palladium(II) chloride in DMF at 90°C produced the 7-furanyl derivative in 90% yield. The tetrakis(triphenylphosphine)palladium(II) ($Pd(PPh_3)_4$) chloride-catalyzed reaction with phenylboronic acid in the dimethoxyethane (DME)–water mixture (2 : 1) gave the target 7-phenyl-substituted product in 80% yield. 7-Alkynylated products (ethynyl- and *N*-(trifluoroacetyl)aminopropynyl derivatives) were synthesized in high yields using the appropriate alkynes under Sonogashira coupling conditions. Under Pd-catalyzed cross-coupling conditions, 7-deaza-8-azaguanine derivatives containing an iodine atom at the 7 position give products in very low yields. Consequently, the protection of the 6-oxo group by the methyl moiety is necessary for the activation of a halogen atom at the 7 position in C–C bond formation reactions.[84]

The Vorbrüggen method was successfully applied to the glycosylation of 5-aza-7-deazaguanine **121** (Scheme 37). It is worth noting that the protection of the amino group in starting compound **223** led to a significant increase in the yield of the target 5-aza-7-deazariboguanosine. Thus, the yield of compound **225** was 84% *versus* the 48% yield of its analogue **224** bearing the unprotected base (see Scheme 37).[89] The deprotection using conventional methods gave 5-aza-7-deazariboguanosine **226**. Attempts to subjected this compound to iodination with *N*-iodosuccinimide failed. The synthesis of 7-iodo-5-aza-7-deazariboguanosine **128** in the presence of TDA-1 and potassium carbonate was described in Section 3.1.1.3 (see Scheme 19). This compound was also prepared from the same starting compounds by the Vorbrüggen method. 7-Iodo-5-aza-7-deazaguanine **123** with the protected amino group was silylated using BSA and then, without isolation, was glycosylated with ribofuranose **149** in the presence of TMSOTf in acetonitrile at 50 °C for 16 h. After the removal of the solvent, glycosylation product **129** was isolated in 42% yield by column chromatography. However, due to the presence of unidentified products in the reaction mixture, the isolation and purification of the target compound were time consuming.[89]

Scheme 37



The deprotection using a conventional method gave 7-iodo-5-aza-7-deazariboguanosine **128** in high yield.

2-Deoxy-7-iodo-5-aza-7-deazaguanosine **126**, its α-D-anomer **127** (see Scheme 18) and 7-iodo-5-aza-7-deazaguanosine **128** (see Scheme 19) serve as the starting compounds for the synthesis of various derivatives. Alkynes (Sonogashira reaction) or boronic acid derivatives (Suzuki – Miyaura reaction) are utilized as reactants.[89]

In summary of the above, it is worth noting that the glycosylation of silylated heterocyclic bases in the presence of trimethylsilyl triflate is a selective and efficient (40 – 90% yields) method for the synthesis of N(9)-ribonucleoside analogues from most of 7-deaza, 1,7-dideaza, 7-deaza-8-aza and 5-aza-7-deaza analogues of purine bases containing a halogen atom at the 2, 6 or 7 position. Similar reactions in the presence of tin tetrachloride are often less selective and afford mixtures of products at the N(3), N(9) and N(8) atoms or do not give the desired products. The use of boron trifluoride etherate in the glycosylation of 7-deaza-8-azahypoxanthine and its substituted analogues led to a significant increase in the yield of the target products.

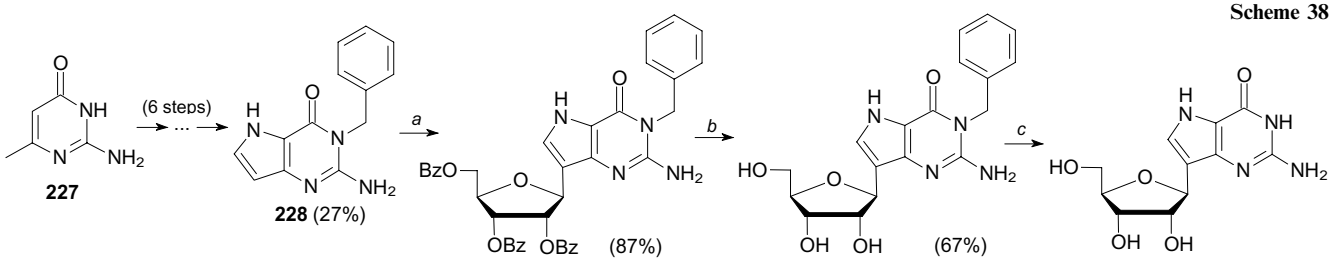
3.1.2. The C – C bond formation. Synthesis of 9-deazapurine nucleosides

N(1)-Benzyl-9-deazaguanine **228** was synthesized from commercially available 2-amino-6-methyl-4(3*H*)-oxopyrimidine (**227**) in six steps (Scheme 38).[117] Heterocyclic base **228** was fused with ribofuranose **149** in the presence of tin tetrachloride in nitromethane, the protecting groups were removed and the target 9-deazaguanosine **229** was isolated in 19% overall yield.[117]

The nucleophilic substitution of hydroxyl-protected ribonolactones is currently widely employed in the synthesis of 9-deazapurine nucleosides, which are C-nucleosides.[8, 9, 118 – 123] The use of C-nucleophiles, such as lithio(het)arenes, results in the C – C bond formation through intermediate lactol. The subsequent deoxygenation at the C(1′) atom with Lewis acids (*e.g.*, $BF_3 \cdot OEt_2$) generates the oxocarbenium ion. The reduction of this intermediate with various silanes gives C-nucleosides resembling canonical nucleosides. The stereochemistry of the reduction of the oxocarbenium ion is determined by the conformation and stability of the ion, which, in turn, depends on the nature of substituents at the C(2′), C(3′) and C(5′) atoms.[9]

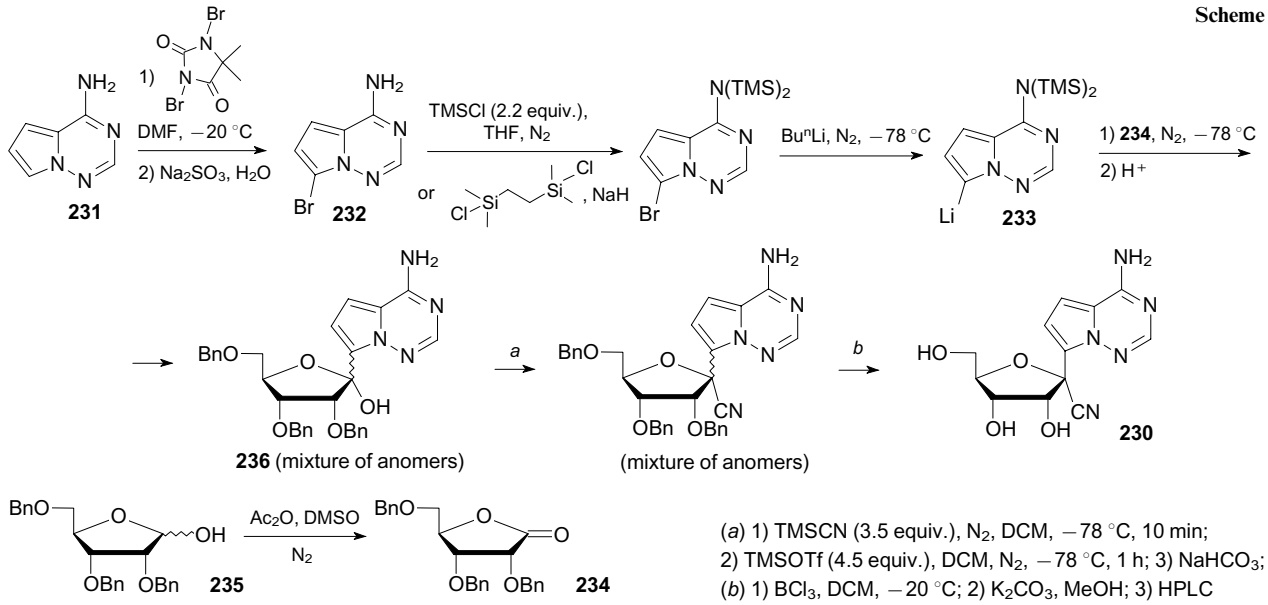
1′-Cyano-4-aza-7,9-dideazaadenosine **230** (Scheme 39), which is the active component of Remdesivir, can be synthesized in several steps from ribose according to the method proposed by Cho and co-workers[119 – 121] (Gilead Sciences, Inc). 4-Aminopyrrolo[2,1-*f*][1,2,4]triazine (**231**) was brominated, the amino group of compound **232** was protected with trimethylsilyl chloride, and the compounds was subjected to the halogen – lithium exchange with n-butyllithium at −78 °C giving intermediate **233**. Then lactone **234**, which was prepared by oxidation of tribenzylribose **235** with a mixture of acetic anhydride and dimethyl sulfoxide, was added to compound **233**. The treatment of the reaction mixture with a weakly acidic aqueous solution gave an anomeric mixture of **236** in 25% yield. The product yield was increased to 60% using alternative glycosylation conditions, such as 1,2-bis(chlorodimethylsilyl)ethane for the protection of the amino group, sodium hydride, the subsequent treatment with n-butyllithium and the addition of lactone. To introduce the cyano group, a mixture of 1′ isomers of **236** was treated with an excess of trimethylsilyl cyanide in dichloromethane at −78 °C for 10 min. Then trimethylsilyl triflate was added, and the mixture was stirred for 1 h and neutralized with an aqueous potassium hydrogen carbonate solution. The target β-anomer was purified by reversed-phase HPLC. The benzyl protecting groups were removed with boron trichloride in dichloromethane at −20 °C, and the excess of boron trichloride was treated with a mixture of potassium carbonate and methanol.

Scheme 38



(*a*) **149**, $SnCl_4$, $MeNO_2$; (*b*) MeONa, MeOH; (*c*) cyclohexene, MeOH

Scheme 39

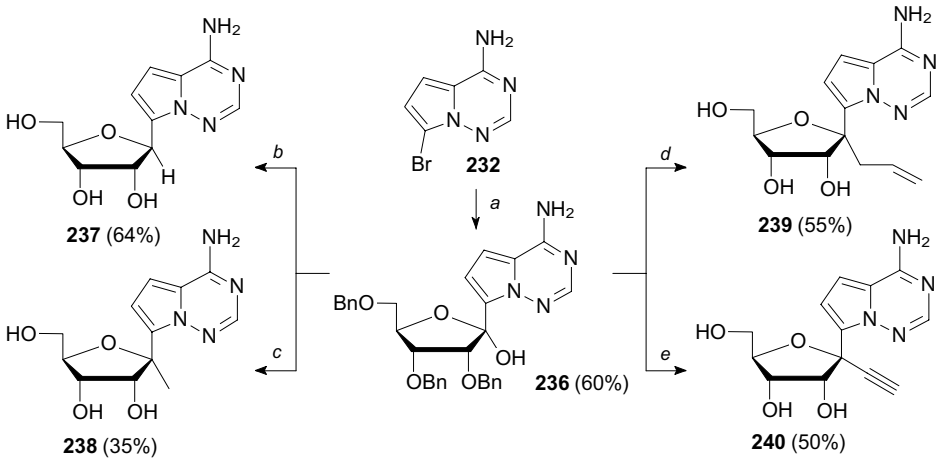


Other 4-aza-7,9-dideazaadenosine analogues were synthesized in a similar way through the formation of the same hemiacetal **236** (Scheme 40).[119] Unsubstituted 4-aza-7,9-dideazaadenosine **237** was synthesized by the anomeric reduction of hemiacetal **236** in the presence of triethylsilane and boron trifluoride etherate. The reaction performed at 0 °C afforded a mixture of the β- and α-anomers in a ratio of 95 : 5. The benzyl protecting groups were completely removed using boron trichloride; the overall yield of 4-aza-7,9-dideazaadenosine **237** over three steps was 40%.[119] The synthesis of 1′-methyl-4-aza-7,9-dideazaadenosine **238** using trimethylaluminium and boron trifluoride etherate at 0 °C gave a mixture of the β- and α-anomers in 45% yield (1 : 1 ratio); at a lower temperature, the conversion was much lower (< 5%).[119] Meanwhile, 1′-allyl-4-aza-7,9-dideazaadenosine **239** was synthesized using allyltrimethylsilane in the presence of boron trifluoride etherate. The dependence of the ratio of β- and α-anomers of the final nucleoside on the reaction temperature was described: at 0 °C, the mixture was obtained in 76% yield in a ratio of 74 : 26; at −78 °C, the product yield was 70% and the ratio was 87 : 13.[119]

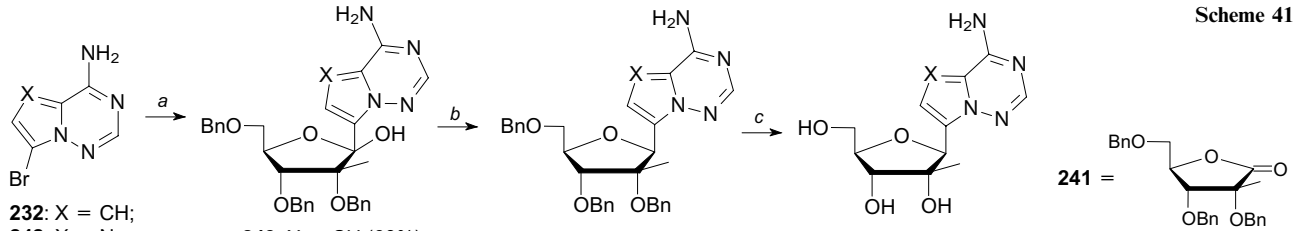
A similar procedure was developed for the synthesis of 1′-ethynyl-4-aza-7,9-dideazaadenosine **240**.[120] Initially, hemiacetal **236** was treated with an excess of ethynylmagnesium chloride in THF at a temperature from 0 to 20 °C for 2 h. Then a catalytic amount of methanesulfonic acid in dichloromethane was added and the mixture was kept for 3 h at room temperature; the yield of the mixture of the β- and α-anomers (2 : 1 ratio) was 65% (Scheme 40). The reaction with vinylmagnesium bromide under the same conditions (not shown in Scheme 40) afforded 1′-vinyl-4-aza-7,9-dideazaadenosine as an equimolar mixture of β- and α-anomers in 85% yield. In all cases, the protecting groups were removed using boron trichloride in dichloromethane at low temperature.[120]

2′-C-Methyladenosine analogues were synthesized from 2′-*C*-methylribonolactone **241** according to the same method (Scheme 41).[120] The addition of 3 equiv. of Bu^nLi to a cold suspension of the bromine-containing heterocycle (bromopyrrolotriazine **232** or bromoimidazolotriazine **242**) in THF in the presence of 1,4-dichloro-1,1,4,4-tetramethyldisilylethane led to both the protection of the free amino group and the bromine–lithium exchange. Lithium was then involved in the reaction with lactone giving hemiacetal **243** or **244** as an equilibrium mixture of anomers. It is worth noting that the subsequent reduction of this mixture with triethylsilane and boron trifluoride etherate was stereoselective and afforded exclusively the target anomer. The

Scheme 40



Scheme 41



232: X = CH;
242: X = N

243: X = CH (60%);
244: X = N (56%)

X = CH, N
(35 – 85%)

245: X = CH;
246: X = N

(*a*) 1) $Me_2ClSi(CH_2)_2SiMe_2Cl$, Bu^nLi, THF, −78 °C; 2) **241**; (*b*) $BF_3 \cdot OEt_2$, Et_3SiH, DCM, 20 °C, 16 h; (*c*) BCl_3, DCM, −78 °C, 1 h or H_2, 10% Pd/C, AcOH, 20 °C

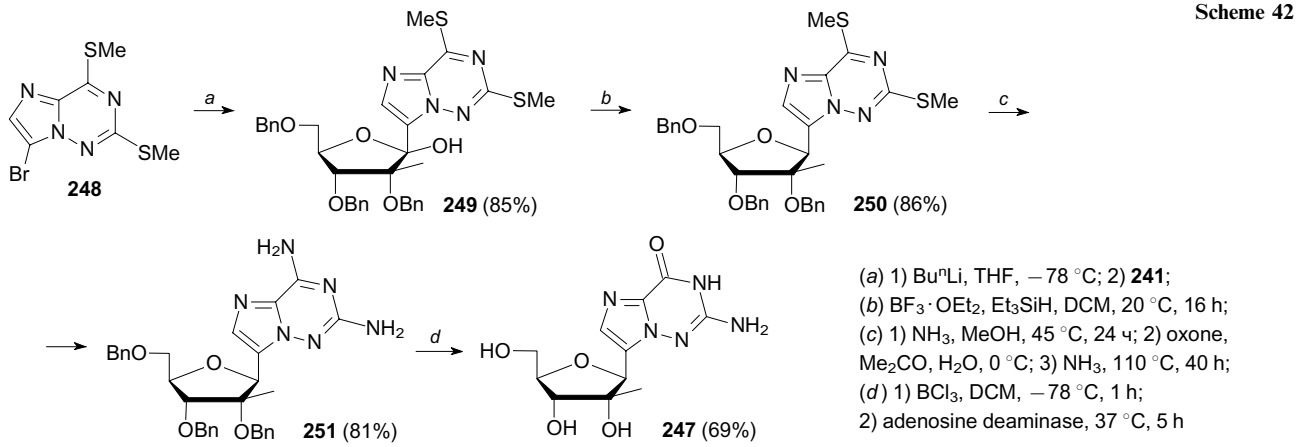
O-debenzylation *via* hydrogenolysis or using BCl_3 gave the target nucleosides: 2′-*C*-methyl-4-aza-7,9-dideazaadenosine **245** or 2′-*C*-methyl-4-aza-9-deazaadenosine **246**.[120, 121] 2′-*C*-Methyl-4-aza-9-deazaadenosine was synthesized from 7-bromo-4-(methylthio)imidazo[2,1-*f*]-[1,2,4]triazine and 2,3,5-tris(dichlorobenzyl)-2′-*C*-methylribonolatone.

The synthesis of 2′-*C*-methyl-4-aza-9-deazaguanosine **247** involved the reaction of bis(methylthio)bromoimidazolotriazine **248** and ribonolatone **241** as the first step (Scheme 42).[120] The resulting compound **249** was reduced to β-C-nucleoside **250**. As in the above cases, the reaction was highly stereoselective. The treatment of the reaction mixture with a 7 M ammonia solution in methanol at 45 °C led to the replacement of the sulfur atom only at the 6 position. An attempt to prepare a diamino-substituted product by increasing the reaction temperature (to 110 °C) failed. Therefore, the 2-methylthiol group was oxidized to more reactive sulfone using oxone (the triple salt $2\,KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$). The subsequent treatment with gaseous ammonia at 110°C in a high-pressure steel reactor produced 2,6-diamino derivative **251**. After deprotection, the diaminopurine nucleoside analogue was treated with adenosine deaminase giving 2′-*C*-methyl-4-aza-9-deazaguanosine **247** (see Scheme 42).[120]

In the alternative method for the synthesis of 2′-*C*-methyl-4-aza-7,9-dideazaguanosine **252**, the glycosylation was performed using a mixture of 4-benzyloxy-2-chloropyrrolo[2,1-*f*][1,2,4]triazines containing bromine atoms at the 9 and 7 positions (3 : 1 ratio), which was prepared in two steps from 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine.[122] It was found that the C(7) isomer is inactive in the glycosylation, which made it possible to introduce the mixture into the reaction without the separation. The glycosylation of the mixture with perbenzylated lactone **241** afforded intermediate **253** in 60% yield and this intermediate was reduced to β-nucleoside **254**. The replacement of the chlorine atom at the 2 position by the acetamide group led to the partial removal of the benzyl moiety from the hydroxyl group of the purine base. The hydrogenolysis of the resulting mixture led to the removal of the remaining benzyl groups, and the cleavage of the acetamide moiety under basic conditions gave 2′-*C*-methyl-4-aza-7,9-dideazaguanosine **252** (Scheme 43).[122]

The above-described methods involving *n*-butyllithium enabled the synthesis of 1′-cyano-4-aza-7,9-dideazaadenosine **230**; however, instability of the yields, low selectivity, the necessity of using cryogenic temperatures and chiral column chromatography hinder the scale-up of this method. More recently, the synthesis of Remdesivir (**53**) was improved,[123] thereby allowing the isolation of a single isomer on a scale sufficient for preclinical trials of efficacy and toxicity (Scheme 44). The treatment with PhMgCl and TMSCl provided the amino group protection and served to remove acidic protons. The glycosylation was performed using iodo derivative **255** instead of the bromine-containing base, which, in combination with the complex $Pr^iMgCl \cdot LiCl$, facilitated the metal – halogen exchange. The subsequent addition of ribonolactone **241** at −20 °C gave glycosylation product **236** in 40% yield. Milder reagents and lower temperatures enabled the large-scale synthesis of the target product in a stable yield. The treatment of nucleoside analogue **236** with a mixture of TMSCN, TMSOTf and TfOH at −78 °C gave the corresponding 1′-cyano derivative in 85% yield and an anomeric ratio > 95 : 5. The addition of TfOH to the reaction mixture is a key factor providing high yields and selectivity in favour of the target β-anomer. The benzyl protection was removed by the treatment of the reaction mixture with boron trichlor-

Scheme 42



248

249 (85%)

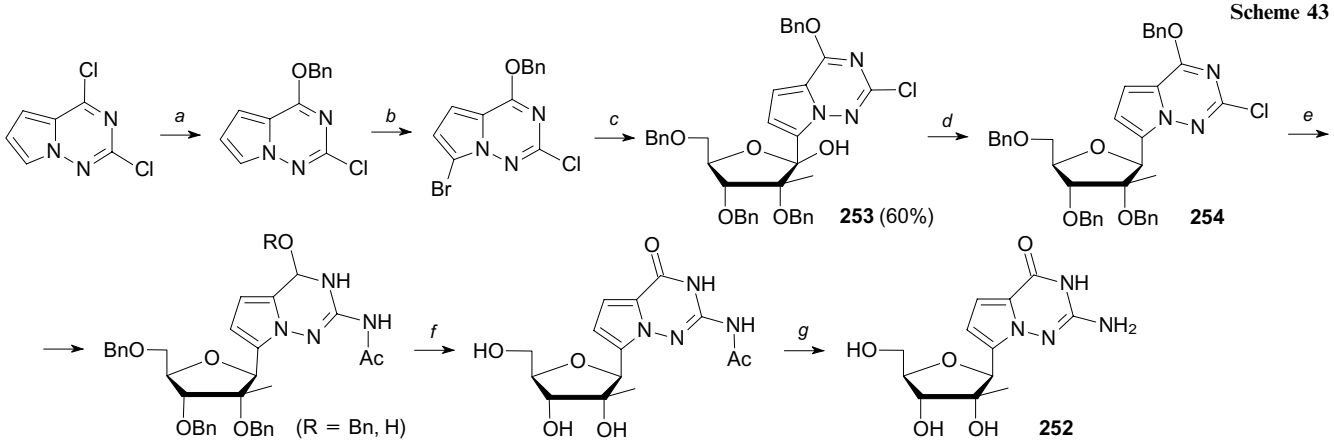
250 (86%)

251 (81%)

247 (69%)

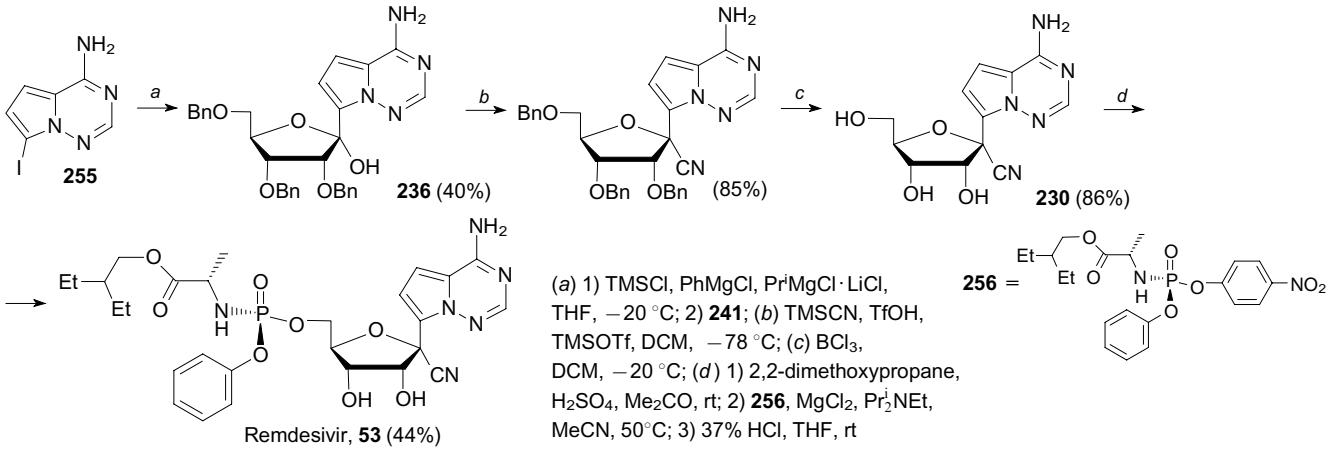
(*a*) 1) Bu^nLi, THF, −78 °C; 2) **241**;
(*b*) $BF_3 \cdot OEt_2$, Et_3SiH, DCM, 20 °C, 16 h;
(*c*) 1) NH_3, MeOH, 45 °C, 24 ч; 2) oxone, Me_2CO, H_2O, 0 °C; 3) NH_3, 110 °C, 40 h;
(*d*) 1) BCl_3, DCM, −78 °C, 1 h;
2) adenosine deaminase, 37 °C, 5 h

Scheme 43



(*a*) BnOH, Bu^{n}Li, THF, −10 °C; (*b*) NBS, DCM, −10 °C; (*c*) 1) Bu^{n}Li, 2-Me-THF, −100 °C; 2) **241**; (*d*) $BF_3 \cdot OEt_2$, Et_3SiH, DCM, −78 °C, 15 min; (*e*) $AcNH_2$, $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, 130 °C; (*f*) H_2, 10% Pd/C, MeOH, 50 °C, 70 h; (*g*) NaOMe, 80 °C; NBS is *N*-bromosuccinimide, dba is dibenzylideneacetone, Xantphos is 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Scheme 44

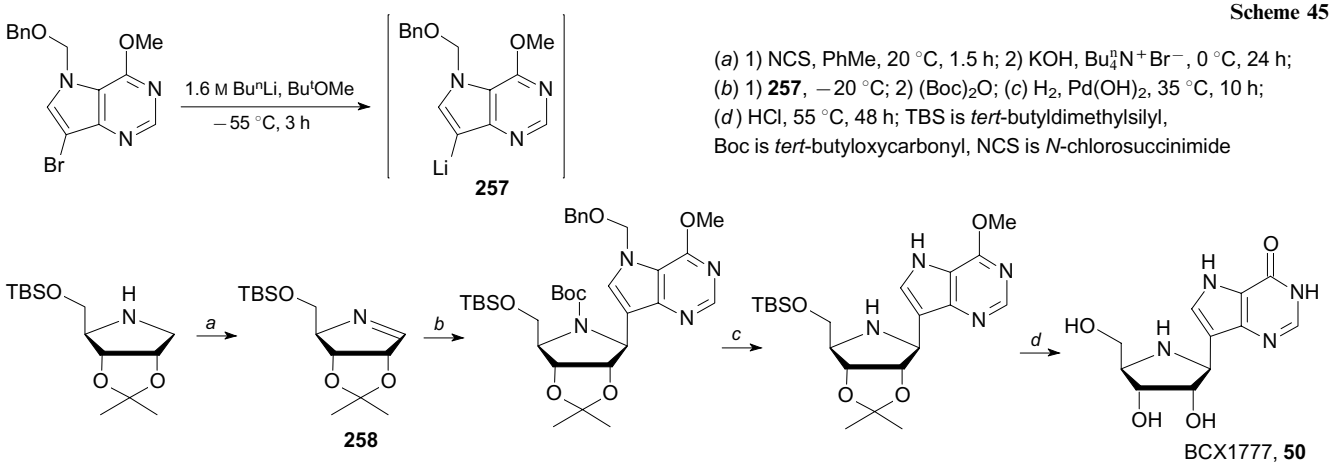


(*a*) 1) TMSCl, PhMgCl, Pr^{i}MgCl · LiCl, THF, −20 °C; 2) **241**; (*b*) TMSCN, TfOH, TMSOTf, DCM, −78 °C; (*c*) BCl_3, DCM, −20 °C; (*d*) 1) 2,2-dimethoxypropane, H_2SO_4, Me_2CO, rt; 2) **256**, $MgCl_2$, Pr^i_2NEt, MeCN, 50°C; 3) 37% HCl, THF, rt

ide. Product **230** was isolated by crystallization. The synthesis of target Remdesivir involved the protection of 2′,3′-hydroxyl groups using 2,2-dimethoxypropane in the presence of sulfuric acid. The yield of the protected nucleoside was 90%. The 2′,3′-isopropylidene protection significantly improved the product yield compared to that from the unprotected nucleoside (70% *versus* 40%). In this case, the reaction with the individual S_P isomer of nitrophenoxide precursor **256** in the presence of $MgCl_2$ and Hünig's base afforded the corresponding prodrug in 70% yield as a single S_P isomer.[124] The deprotection of 2′,3′-hydroxyl groups with concentrated HCl in THF occurred with a yield of 69%. The stereochemistry of the synthesized Remdesivir (**53**) was established by X-ray diffraction.[123]

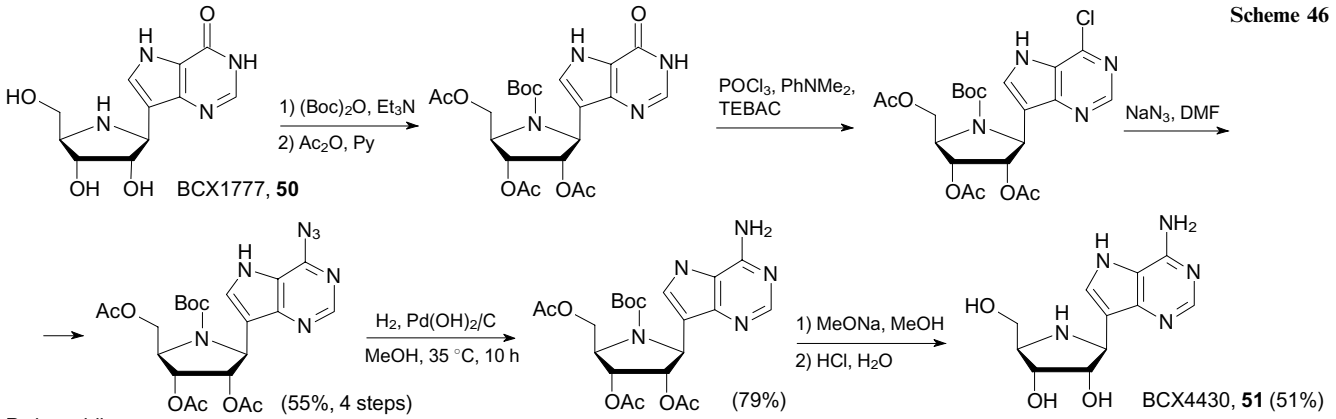
The authors of the Refs 125 and 126 described for the first time the addition of lithium derivative of 9-deazagua-

Scheme 45



(*a*) 1) NCS, PhMe, 20 °C, 1.5 h; 2) KOH, $Bu^n_4N^+Br^-$, 0 °C, 24 h; (*b*) 1) **257**, −20 °C; 2) $(Boc)_2O$; (*c*) H_2, $Pd(OH)_2$, 35 °C, 10 h; (*d*) HCl, 55 °C, 48 h; TBS is *tert*-butyldimethylsilyl, Boc is *tert*-butyloxycarbonyl, NCS is *N*-chlorosuccinimide

Scheme 46



nine **257** to carbohydrate cyclic imine **258** giving the pyrrolidine analogue of 9-deazaguanosine BCX1777 {7-[(2*S*,3*S*,4*R*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidin-2-yl]-3*H*-pyrrolo[3,2-*d*]pyrimidin-4-(5*H*)-one hydrochloride, **50**} (Scheme 45). More recently, this method was scaled-up,[60] which allowed the Sigma-Aldrich to produce 9-deazaguanosine analogue **50** using the seven-step synthesis on the industrial scale with isolation of intermediates in four steps.

The 9-deazaadenosine analogue BCX4430 (**51**) was synthesized from compound **50** through a sequence of transformations in seven steps in 22 – 25% overall yield (Scheme 46).[60] A comparison of the strategies of the synthesis of various immucillin analogues is given in the reviews of Wierzchowski *et al.*[10] and Merino *et al.*[11]

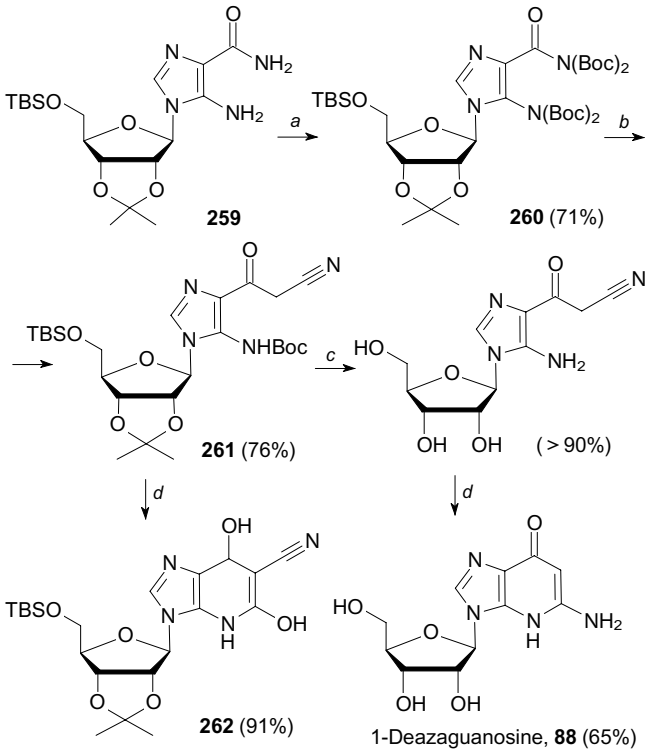
3.2. Synthesis of deaza- and azapurine nucleoside analogues *via* the construction of the heterocyclic base

1-(β-D-Ribofuranosyl)imidazoles bearing appropriate substituents at the 4 and 5 positions of the imidazole ring often serve as the starting compounds in the synthesis of 1-deaza- and 3-deazapurine nucleosides. A combination of the 5-amino- and 4-carboxamide groups results in the formation of 1-deazaguanosine. The presence of the 5-ethynyl moiety and the 4-carboxamide group allows the synthesis of 3-deazaguanosine and 3-deazainosine, and the closure of 5-ethynyl and 4-carbonylnitrile substituents affords 3-deazaadenosine. Currently, the synthesis of 7-deazapurine nucleosides by the construction of a heterocyclic base [127] is used rather rarely because of the development of more efficient methods.[4] 9-Deazapurine nucleosides and their analogues were synthesized from (D-ribofuranosyl)-2-formylacetonitrile or 2′,3′,5′-protected 1-hydroxyribofuranosides. This method can be used to prepare almost all types of deaza- and azapurine nucleosides. Therefore, it seems reasonable to consider examples of the synthesis of representatives of different classes although most of the cited studies were published more than two decades ago.

3.2.1. 1-Deazapurine nucleoside analogues

In 2000, Kojima and co-workers [128, 129] reported the method for the four-step synthesis of 1-deazaguanosine **88** from 2′,3′,5′-protected 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide **259** (Scheme 47). The authors compared two methods for the synthesis of tetra(*tert*-butyloxycarbonyl) derivative **260**. Di(*tert*-butyl) dicarbonate and a catalytic amount of dimethylaminopyridine were used in both cases. In one case, the reaction was performed in acetonitrile (the yield of target product **260** was 46%); in another one, in 1,2-dichloroethane in the presence of an excess of triethylamine on heating to 75 °C (71% yield). 4-Cyanoethyl derivative **261** was synthesized by the reaction of compound **260** with the acetonitrile anion generated from acetonitrile and *n*-butyllithium. The heating of protected compound **261** at reflux under basic conditions gave 1-cyano-1-deazaxanthosine derivative **262** as the major cyclization product in a rather high yield. The treatment of compound **261** with an aqueous trifluoroacetic acid solution resulted in the complete deprotection with a quantitative yield. The subsequent heating at reflux under basic conditions made it possible to isolate the target 1-deazaguanosine **88** in good yield.

Scheme 47



(*a*) $(Boc)_2O$, DMAP, Et_3N; (*b*) $LiCH_2CN$; (*c*) TFA (aq.);
(*d*) $NaHCO_3$ (aq.), EtOH, 100 °C;
DMAP is 4-dimethylaminopyridine

3.2.2. 3-Deazapurine nucleoside analogues

Minakawa *et al.*[130] synthesized 3-deazainosine **263** starting from 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (**264**) (Scheme 48) with protected hydroxyl groups. The 5-amino group was replaced by an iodine atom using isoamylnitrile in diiodomethane. The resulting iodide **265** was subjected to cross-coupling with trimethyl[(tri-n-butylstannyl)ethynyl]silane in the presence of a palladium catalyst in acetonitrile followed by the deprotection with ammonia in methanol. The treatment of 1-(β-D-ribofuranosyl)-5-ethynylimidazole-4-carboxamide (**266**) with aqueous dimethylamine followed by the addition of a mixture of 50% aqueous acetic acid and ethanol (1 : 1 ratio) afforded target 3-deazainosine; after the crystallization, the yield of **263** was 64%.[131]

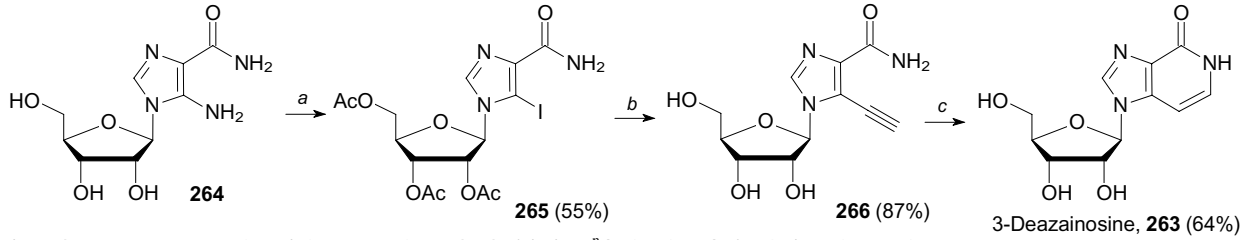
3-Deazaguanosine **267** was synthesized from the above-described 1-(β-D-ribofuranosyl)-5-ethynylimidazole-4-carboxamide (**266**) (Scheme 49).[131] After protection of hydroxyl groups and hydroxyamination with aqueous dimethylamine at 50 °C for several hours, hydroxylamine hydrochloride and acetic acid were added to the reaction mixture. This reaction afforded 1-[2,3,5-tris(*O*-*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-5-(2-hydroxyiminoethyl)imidazole-4-carboxamide (**268**) in 91% yield without the formation of by-products. Compound **268** was dehydrated with phenyl isocyanate in benzene; the resulting intermediate was heated in pyridine at 50 °C to form 1-[2,3,5-tris(*O*-*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-5-cyanomethylimidazole-4-carboxamide (**269**) in moderate yield. The ring closure was accomplished by refluxing in a 5% aqueous sodium carbonate solution in ethanol giving 6-amino-1-[2,3,5-tris(*O*-*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]imidazo[4,5-*c*]pyridin-4(5*H*)-one in 82% yield. The deprotection afforded target 3-deazaguanosine **267** in 78% yield.[131]

The reaction of ammonia with 1-(β-D-ribofuranosyl)-5-ethynylimidazole-4-carbonitrile (**270**) produces 3-deazaadenosine.[130] The preliminary protection of carbohydrate hydroxyl groups significantly reduces the amount of by-products, resulting in the formation of 2′,3′,5′-tri-*O*-TBS derivative **271** (Scheme 50). The treatment of the latter with ammonia in methanol gave 4-amino-1-[2,3,5-tris(*O*-*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]imidazo[4,5-*c*]pyridine in 76% yield; the subsequent deprotection furnished 3-deazaadenosine **3** in quantitative yield.[131]

3.2.3. 7-Deazapurine nucleoside analogues

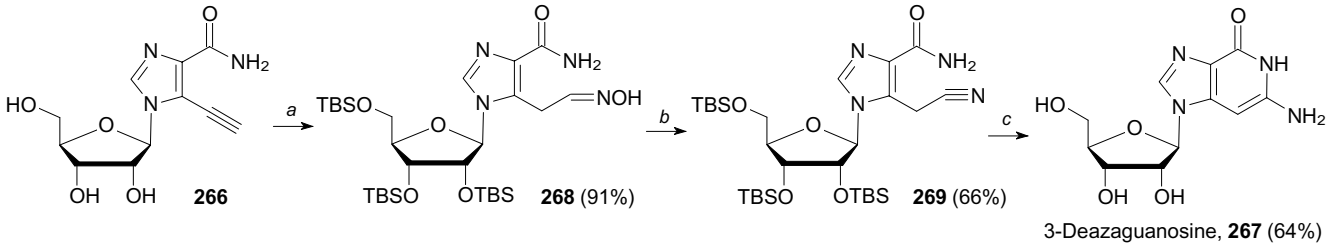
In 1963, Mizuno *et al.*[127] reported the synthesis of 7-deazapurine ribonucleoside (7-deazainosine, **272**) from 4-amino-5-(2,2-diethoxyethyl)-1*H*-pyrimidin-6-one (**273**) and 2,3,4-tri-*O*-acetyl-5-*O*-trityl-D-ribose (**274**) giving Schiff base as the intermediate. The condensation of the starting reagents in the presence of ammonium chloride afforded compound **275** (Scheme 51), and its deacetylation with ammonia in methanol led to the carbohydrate ring closure. The resulting compound **276** was again acetylated. Under acidic conditions, acetal **277** was hydrolyzed to aldehyde followed by

Scheme 48



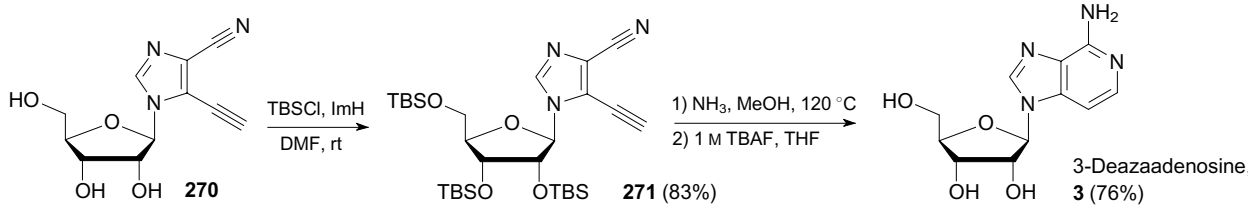
(*a*) 1) Ac_2O, Et_3N, DMAP, MeCN; 2) CH_2I_2, iso-$C_5H_{11}ONO$; (*b*) 1) $Bu^n_3SnC{\equiv}CTMS$, $(PhCN)_2PdCl_2$, MeCN; 2) NH_3, MeOH; (*c*) 1) Me_2NH, EtOH, 80 °C; 2) AcOH, EtOH, rt

Scheme 49

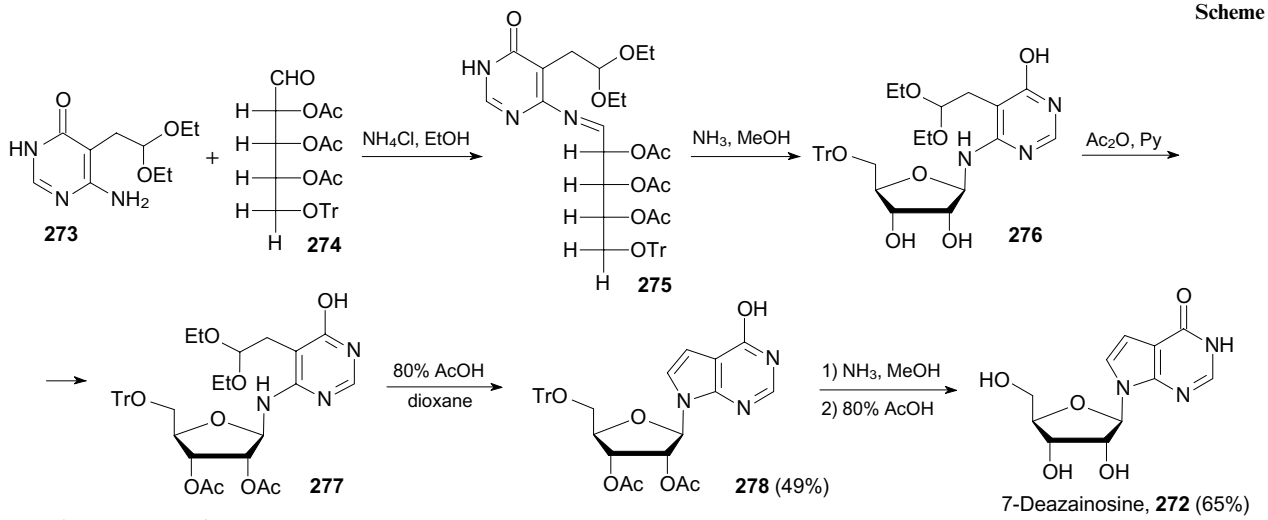


(*a*) 1)TBSCl, ImH, DMF, rt; 2) Me_2NH, EtOH, 50 °C; 3) $H_2NOH \cdot HCl$, AcOH, EtOH, rt; (*b*) PhNCO, PhH, rt; (*c*) 1) 5% Na_2CO_3, EtOH, 100 °C; 2) 1 M TBAF, THF; ImH is imidazole, TBAF is tetra-n-butylammonium fluoride

Scheme 50



Scheme 51



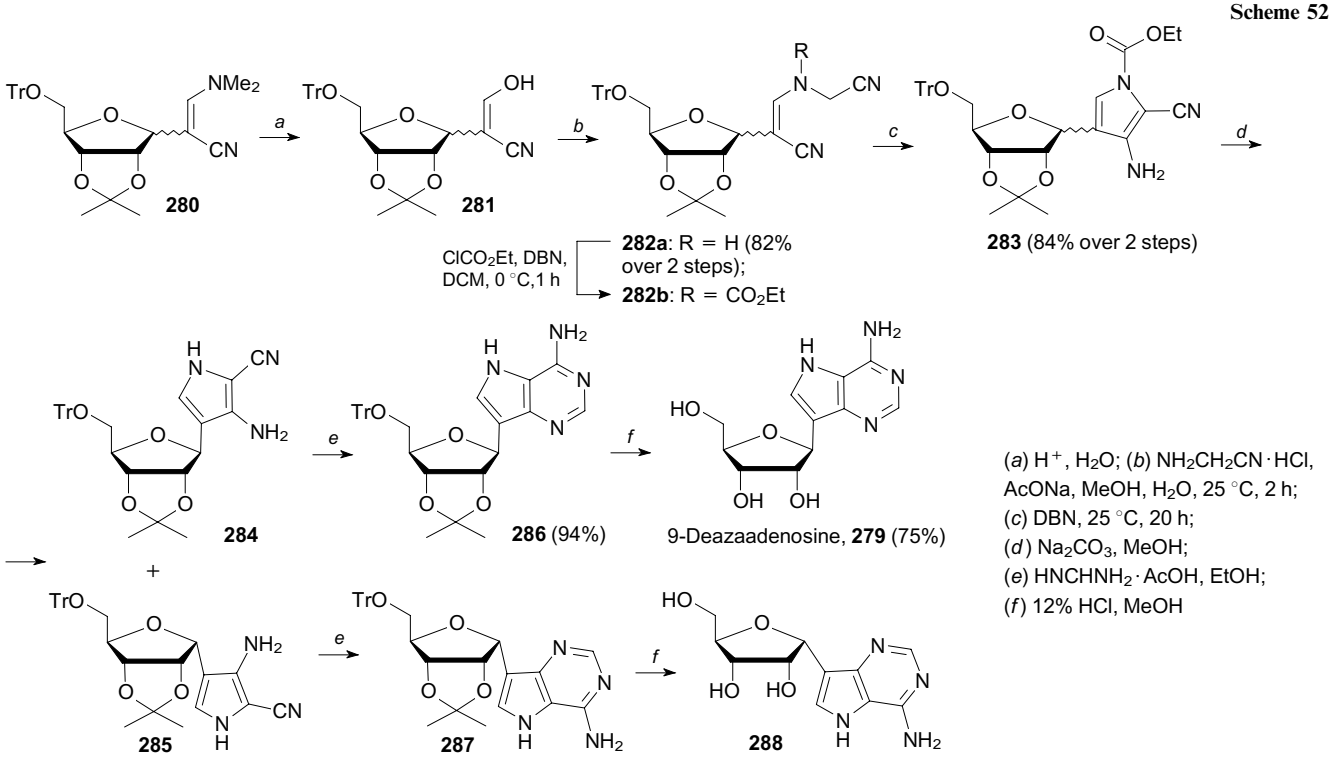
Tr is trityl (triphenylmethyl)

the cyclization giving 7-deazapurine nucleoside **278**. The deprotection of compound **278** gave 7-deazainosine **272**.[4]

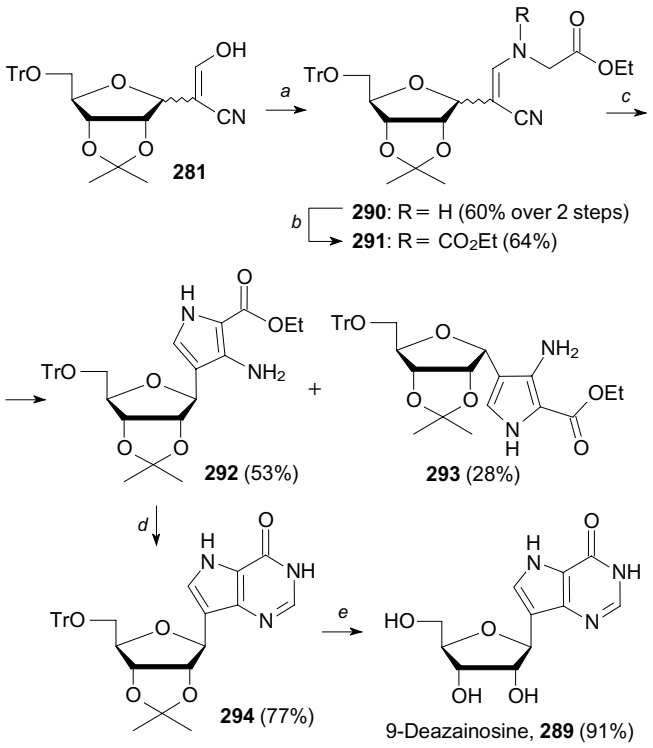
3.2.4. 9-Deazapurine nucleoside analogues

Lim and Klein [132] described the synthesis of 9-deazaadenosine **279** *via* the ring closure of the heterocyclic base (Scheme 52). The hydrolysis of the starting 2-(D-ribofuranosyl)-3-dimethylaminoacrylonitrile **280** (Ref. 133) with weak acid afforded 2-(D-ribofuranosyl)-2-formylacetonitrile **281**, which was treated with aminoacetonitrile hydrochloride in the presence of sodium acetate in aqueous methanol at 25 °C for 20 h. The NH group in the resulting enamine **282a** was protected by the treatment with ethyl chloroformate in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in dichloromethane. The cyclization of the peripheral substituent to pyrrole was accomplished by the treatment of the reaction mixture with an additional equivalent of DBN (25 °C, 20 h). The overall yield of *N*-carbethoxypyrrole **283**, isolated as a mixture of α and β isomers, was 84% (over two steps). The carbethoxy group was removed by the treatment of intermediate **283** with sodium carbonate in methanol (25 °C, 50 min) giving β (**284**) and α isomers (**285**) of 3-amino-2-cyanopyrrole in 85% overall yield and 5 : 2 ratio. The isomers were separated by silica gel column chromatography (toluene — ethyl acetate, 8 : 1, as the eluent). The heating of each isomer at reflux with formamidine acetate in ethanol for 5 h gave the corresponding isomer of pyrrolopyrimidine (**286** or **287**) in high yield. The final treatment of β isomer **286** with 12% HCl in MeOH (25 °C, 2 h) afforded 9-deazaadenosine **279**, which crystallized directly from the reaction mixture. α Isomer **288** was obtained in a similar way.

Scheme 52



Scheme 53



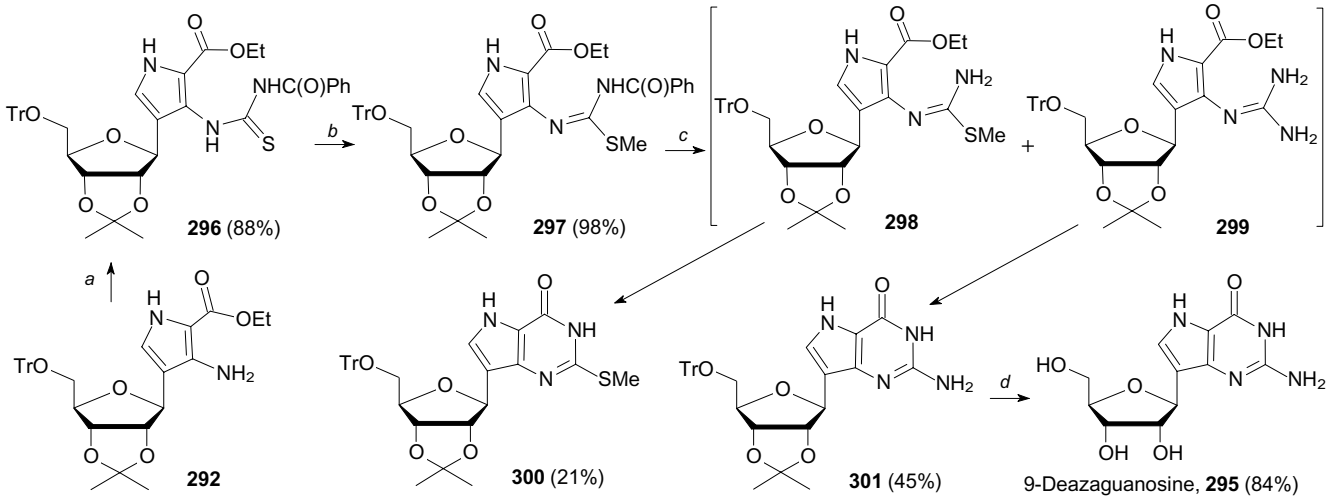
(*a*) $NH_2CH_2CO_2Et \cdot HCl$, AcONa, MeOH, H_2O, 25 °C, 2 h; (*b*) $ClCO_2Et$, DBN, DCM, 0 °C,1 h; (*c*) EtONa, EtOH, rt, 40 min; (*d*) $HNCHNH_2 \cdot AcOH$; (*e*) 6% HCl, MeOH

In the first step of the synthesis of 9-deazainosine **289** (Scheme 53),[134] 2-(D-ribofuranosyl)-2-formylacetonitrile **281** (see Ref. 133) was subjected to condensation with glycine ethyl ester hydrochloride in the presence of sodium acetate in aqueous methanol. During the reaction, crystalline enamine **290** precipitated. The crystallization from methanol afforded stereochemically pure product **290** in 60% yield over two steps. The protection of the NH group, required for the efficient pyrrole ring closure, was accomplished by the treatment of enamine **290** with ethyl chloroformate and DBN in dichloromethane. The preparative chromatography purification afforded carbamate **291** as a mixture of two major anomeric products with similar chromatographic mobility. Under the above-described conditions, the cyclization of this carbamate in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene occurred much more slowly (at least over 2 days for the completion of the process) and was complicated by the partial N-deacetylation of freshly prepared pyrrole giving a mixture of four products.

An alternative method was proposed based on the treatment of carbamate **291** with sodium ethoxide in ethanol. The subsequent chromatography purification allowed the isolation of two major products: β-anomer **292** and α-anomer **293**. The cyclization of β-anomer **292** to the corresponding pyrrolo[3,2-*d*]pyrimidine **294** was performed on prolonged heating (4 days) with formamidine acetate (5 equiv.) in refluxing ethanol. The column chromatography purification gave 3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine *C*-nucleoside **294** in good yield. The final deprotection of the β-anomer with a 6% methanolic solution of HCl at 25 °C for 50 min afforded 9-deazainosine **289** as the anomerically pure product in 91% yield.[134] The α-anomer of 3-amino-2-carbethoxypyrrole **293** was transformed into the corresponding α-nucleoside in a similar manner.[134]

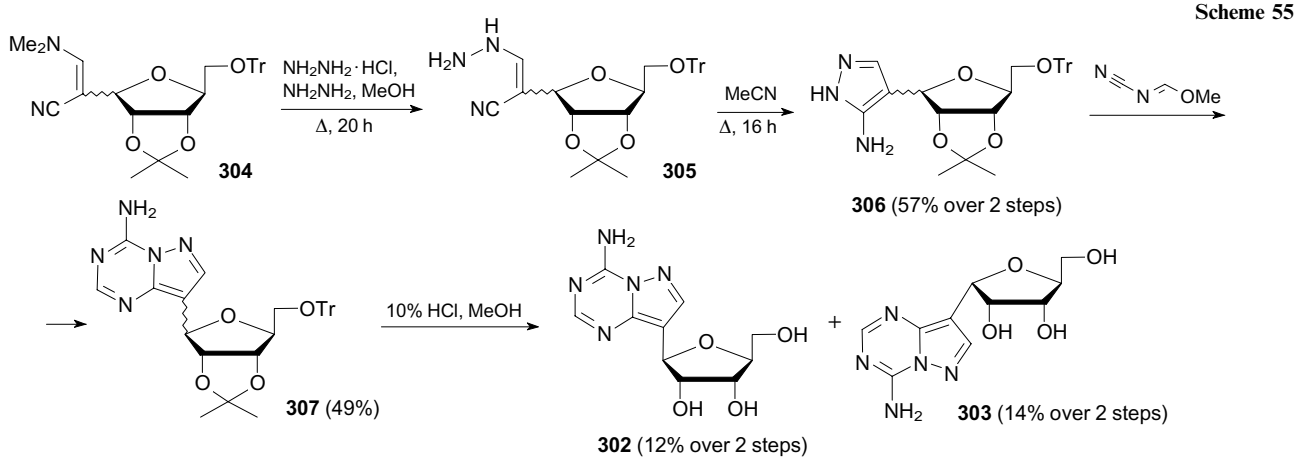
The synthesis of 9-deazaguanosine **295** (Scheme 54) [134] was started with the treatment of β-anomer **292** with benzoyl isothiocyanate in dichloromethane at 0 °C for 0.5 h. After the purification by silica gel column chromatography, 2-carbethoxy-3[(*N*-benzoylthiocarbamoyl)-amino]-1*H*-pyrrole **296** was isolated in high yield. The intermediate was subjected to S-methylation with iodomethane in the presence of DBN in chloroform. After the chromatography purification, S-methylisothioureido derivative **297** was obtained in nearly quantitative yield. The subsequent treatment of **297** with saturated ammonia in methanol at 100 °C overnight afforded a mixture of two major products **298** and **299**. The separation by silica gel column chromatography gave 7-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-2-methylthio-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (**300**) and protected 9-deazaguanosine **301**. The deprotection of the latter compound using 12% hydrochloric acid in methanol at low temperature for

Scheme 54



(*a*) Ph(O)CNS, CH_2Cl_2, 0 °C; (*b*) MeI, DBN, $CHCl_3$; (*c*) NH_3, MeOH, 90 °C, 16 h; (*d*) 12% HCl, MeOH

Scheme 55



1 h produced 9-deazaguanosine **295** as crystalline monohydrochloride in high yield.[134]

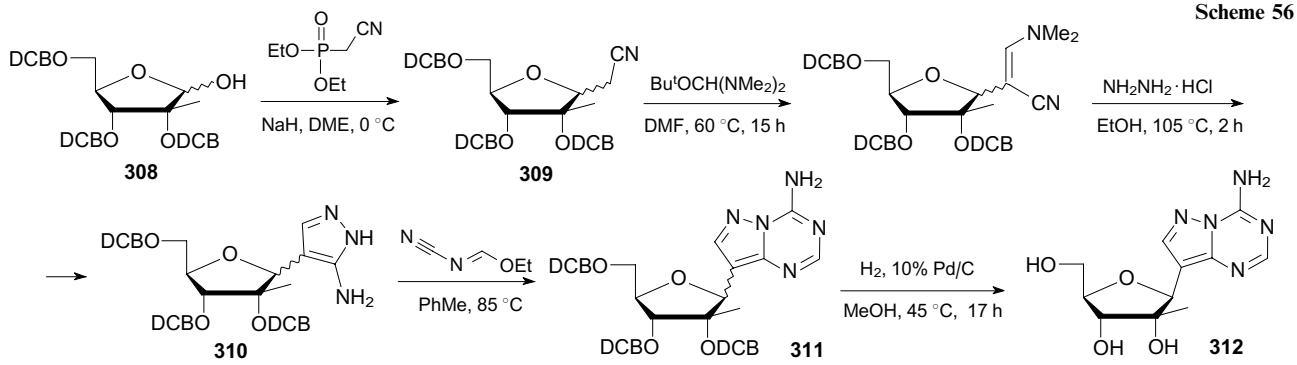
The procedure developed by Lim *et al.*[134] was used to synthesize L-9-deazaadenosine. However, in this case the overall yield of the nucleoside with respect to the starting 2-(L-ribofuranosyl)-3-dimethylaminoacrylonitrile[135] was significantly lower compared to that in the synthesis of D-nucleoside (5% *versus* 30%).[135]

This research group[135] used a sequence of transformations shown in Scheme 55 to prepare α-L- (**302**) and β-L-5-aza-9-deazaadenosines (**303**). The treatment of 2-(L-ribofuranosyl)-3-dimethylaminoacrylonitrile **304** with hydrazine and hydrazine monohydrochloride in refluxing aqueous ethanol afforded compound **305**, which was cyclized in refluxing acetonitrile to form aminopyrazole **306** as a mixture of α- and β-anomers. The reaction of this mixture with methyl *N*-cyanoformimidate in refluxing benzene produced an anomeric mixture of **307**, which was deprotected with hydrochloric acid in methanol giving free α-L- and β-L-nucleosides (**302** and **303**). The latter compounds were separated by silica gel column chromatography.[135] β-L-9-Deaza-5-azaadenosine **303** was obtained in low overall yield (7%).

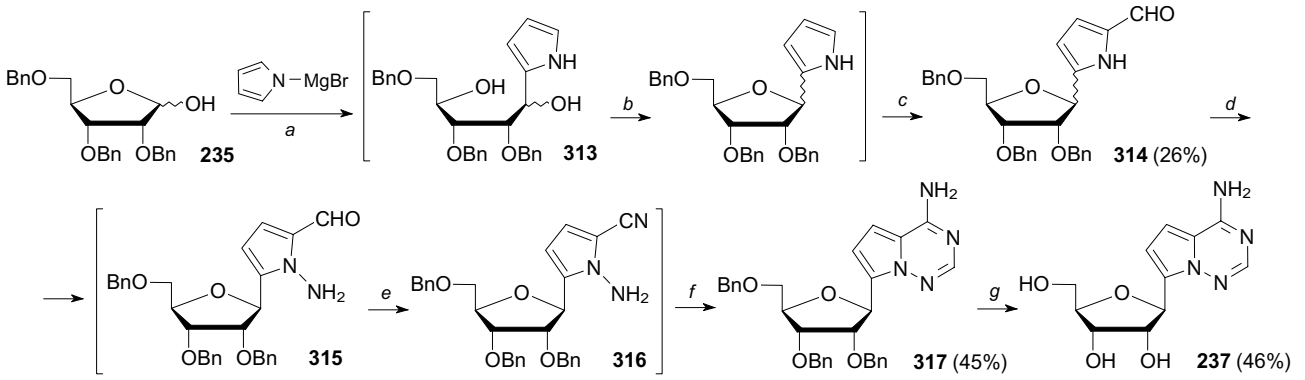
The condensation of 2,4-dichlorobenzyl (DCB)-protected 2-diethoxyphosphorylacetonitrile with riboside **308** afforded intermediate formylacetonitrile **309** as an anomeric mixture (Scheme 56).[122] In this step, the anomers were not separated because the product was found to undergo anomerization during the addition of dimethylamine and the subsequent formation of aminopyrazole **310**. The condensation of aminopyrazole **310** with ethyl cyanoimidoformate also gave an anomeric mixture of protected nucleosides. These nucleosides were separated. The β configuration of compound **311** was established by 2D nuclear Overhauser effect NMR spectroscopy by observing the coupling between the protons H(1′) and H(4′). Pyrazolotriazine adenosine analogue **312** was synthesized by the hydrogenolysis of the precursor.[122]

A 9-deazapurine nucleoside analogue, 4-aza-7,9-dideazaadenosine **237**, was synthesized through building up (Scheme 57).[136] The reaction of protected ribofuranose **235** with pyrrole magnesium bromide in dichloromethane at 0 °C for 1 h followed by the treatment of the reaction mixture with an aqueous solution of ammonium chloride afforded intermediate **313**, which was dehydrated *in situ* by the addition of trifluoroacetic acid. According to the TLC data, the reaction was completed within 1 h. The direct formylation of the aromatic pyrrole ring was accomplished by the Vilsmeier procedure. The reaction mixture was added dropwise, without separation and purification, to a solution of $POCl_3$ in DMF at 0 °C followed by the treatment with sodium acetate. The major product, pyrrole aldehyde **314**, was isolated by silica gel flash chromatography using 8 – 15% ethyl acetate in hexane as the eluent; the yield with respect to ribofuranose **235** was 26%. Sodium hydride was added to a solution of aldehyde **314** in tetrahydrofuran to form the anion followed by the amination with *O*-(mesitylenesulfonyl)hydroxylamine (MSH) at 0 °C for 45 min. The subsequent reaction of crude intermediate **315** with hydroxylamine-*O*-sulfonic acid (HOSA) followed by the *in situ* decomposition of intermediate oxime-*O*-sulfonate upon the addition of a mixture of a potassium hydroxide solution in cold water and dioxane (1 : 1) gave *N*-aminonitrile **316**. The latter compound was isolated by the extraction and used in the subsequent step without additional purification. Good conversion of *N*-aminonitrile **316**

Scheme 56

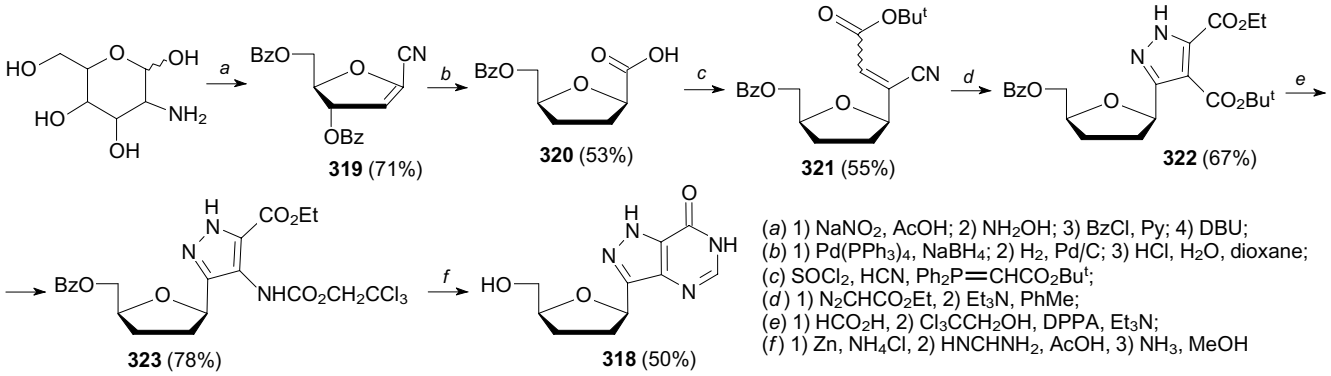


Scheme 57



(*a*) DCM, 0 °C; (*b*) TFA; (*c*) $POCl_3$, DMF, 0 °C; (*d*) NaH, MSH, THF, 0 °C; (*e*) HOSA, KOH, dioxane, H_2O; (*f*) $HNCHNH_2 \cdot AcOH$, DMA, 140 °C; (*g*) H_2, 10% Pd/C, AcOH

Scheme 58



(*a*) 1) $NaNO_2$, AcOH; 2) NH_2OH; 3) BzCl, Py; 4) DBU;
(*b*) 1) $Pd(PPh_3)_4$, $NaBH_4$; 2) H_2, Pd/C; 3) HCl, H_2O, dioxane;
(*c*) $SOCl_2$, HCN, $Ph_2P{=}CHCO_2Bu^t$;
(*d*) 1) N_2CHCO_2Et, 2) Et_3N, PhMe;
(*e*) 1) HCO_2H, 2) Cl_3CCH_2OH, DPPA, Et_3N;
(*f*) 1) Zn, NH_4Cl, 2) $HNCHNH_2$, AcOH, 3) NH_3, MeOH

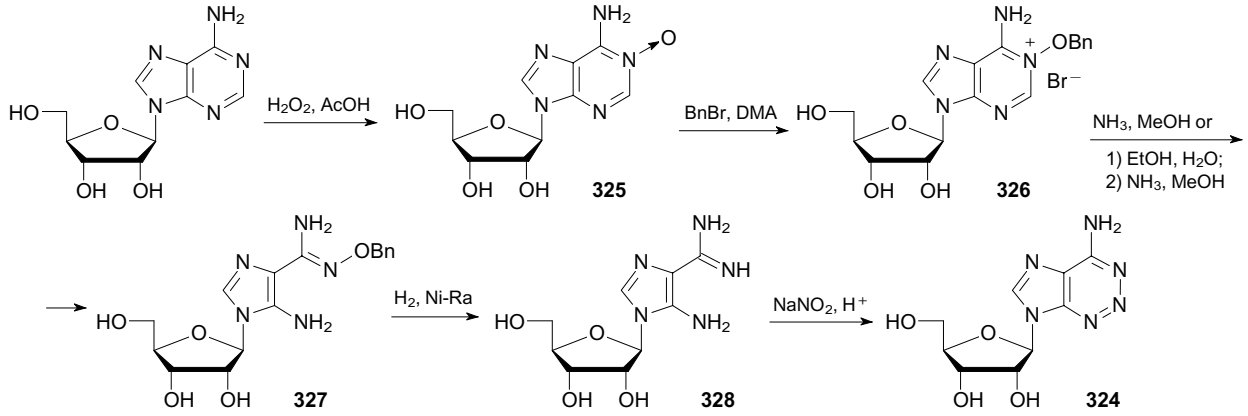
was achieved by the treatment of this compound with formamidine acetate in *N*,*N*-dimethylacetamide (DMA) at 140 °C for 1.5 h. The yield of protected nucleoside **317** after silica gel flash chromatography (chloroform – methanol, 99.5 : 0.5, as the eluent) was 45% with respect to aldehyde **314**. The synthesis of 4-amino-7-(β-D-ribofuranosyl)pyrrolo[2,1-*f*][1,2,4]triazine (**237**) was completed with the debenzylation in acetic acid over 10% Pd/C under a hydrogen atmosphere.[136]

The synthesis of 2′,3′-dideoxy-8-aza-9-deazainosine[137] **318** proceeded through the following key intermediates: nitrile **319**, which was produced from D-glucosamine in 71% overall yield over four steps, and anhydrodideoxygluconic acid **320**, derived from **319** in three steps in 53% overall yield (Scheme 58). The formation of acid chloride, the condensation with HCN and the Wittig reaction of intermediate acylnitrile gave cyano ester **321** as a mixture of *E* and *Z* stereoisomers (1.7 : 1 ratio) in 55 – 60% yield. The addition of ethyl diazoacetate to either isomer followed by heating in the presence of triethylamine in toluene (to eliminate HCN) afforded pyrazole diester **322** in good yield (67% from the *E* isomer, 60% from the *Z* isomer). The removal of the *tert*-butyl group with formic acid and the heating of the appropriate acid with diphenylphosphoryl azide (DPPA), 2,2,2-trichloroethanol and a base produced carbamate **323**. The reduction and subsequent condensation with formamidine in acetic acid afforded 5′-*O*-benzoyl-2′,3′-dideoxyformycin B in 56% yield. The final hydrolysis of benzoate produced 2′,3′-dideoxyformycin B **318** in 95% yield.

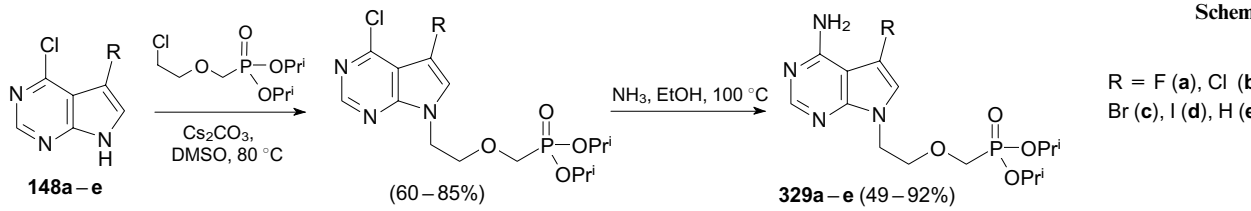
3.2.5. 2-Azapurine nucleoside analogues

The strategy commonly used for the synthesis of 2-azapurine nucleoside analogues involves a sequence of ring opening and closure reactions of a six-membered heterocyclic base of naturally occurring or synthetic purine nucleosides.[138] An example of this approach to the synthesis of 2-azaadenosine **324** is presented in Scheme 59. The oxidation of the adenosine with a mixture of hydrogen peroxide and acetic acid afforded N(1)-oxide **325**, which was treated with benzyl bromide in dimethylacetamide to form *N*(1)-(benzyloxy)adenosine bromide **326**. The ring opening of **326** in a neutral solution of aqueous ethanol followed by the treatment with ammonia in methanol or directly with ammonia in methanol produced compound **327**. The hydrogenolysis of the protecting group with Raney nickel gave 5-amino-1*H*-imidazole-4-carboxamidine ribonucleoside **328**, and its treatment with sodium nitrite in aqueous acetic or hydrochloric acid afforded target 2-azaadenosine **324** in 64% yield.[138] This method is also suitable for the synthesis of 2′-deoxy-2-azaadenosine and the arabino- and xyloadenosine analogues.[138] 7-Deaza-2,8-diazaadenosine and 2,8-diazaadenosine were synthesized in a similar way using 7-deaza-8-azaadenosine and 8-azaadenosine N(1)-oxides, respectively, as the starting compounds; however, the product yields were much lower compared to 2-azaadenosine **324**.[138] Alternative methods for the synthesis of 2-azapurine nucleoside analogues are described in detail in the review by Budow and Seela.[3]

Scheme 59



Scheme 60



R = F (**a**), Cl (**b**), Br (**c**), I (**d**), H (**e**)

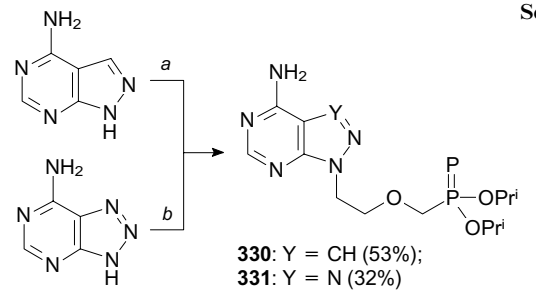
3.3. Synthesis of acyclic and carbocyclic deaza- and azapurine nucleoside analogues

Acyclic nucleoside or nucleotide analogues and carbocyclic nucleosides are assigned to individual classes of modified nucleosides. In these compounds, the glycosidic bond is absent and the carbohydrate moiety is replaced by an aliphatic or carbocyclic moiety. The chemical properties of these compounds are significantly different from those of conventional nucleosides. Special methods were developed for the synthesis of acyclic and carbocyclic deaza- and azapurine nucleoside analogues. These methods are briefly described below.

Commercially available 6-chloro-7-deazapurine (7*H*-pyrrolo[2,3-*d*]pyrimidine) derivatives **148a**–**e** were used as the starting compounds in the synthesis of acyclic 7-deaza-adenine analogue **329e** and its 7-halogenated derivatives **329a**–**d** (Scheme 60). The alkylation of these substrates with diisopropyl [(2-chloroethoxy)methyl]phosphonate[139] in the presence of caesium carbonate in DMSO at 80 °C followed by ammonolysis at 100°C afforded acyclic 7-deazaadenine analogue **329e** in 39% overall yield.[140] Acyclic 7-halo-7-deazaadenine phosphonates **329a**–**d** were prepared in good yields according to a similar procedure in two steps (see Scheme 60).[140]

Diisopropyl phosphonate of acyclic 7-deaza-8-azaadenosine derivative **330** was synthesized by heating diisopropyl [(2-chloroethoxy)methyl]phosphonate with the presynthesized 7-deaza-8-azaadenine sodium salt in DMF at 100 °C. The similar reaction of 8-azaadenine with the same alkylating agent using DBU as the base gave 8-azapurine derivative **331** in 32% yield (along with the related N(8)-regioisomer isolated in 32% yield) (Scheme 61).[140]

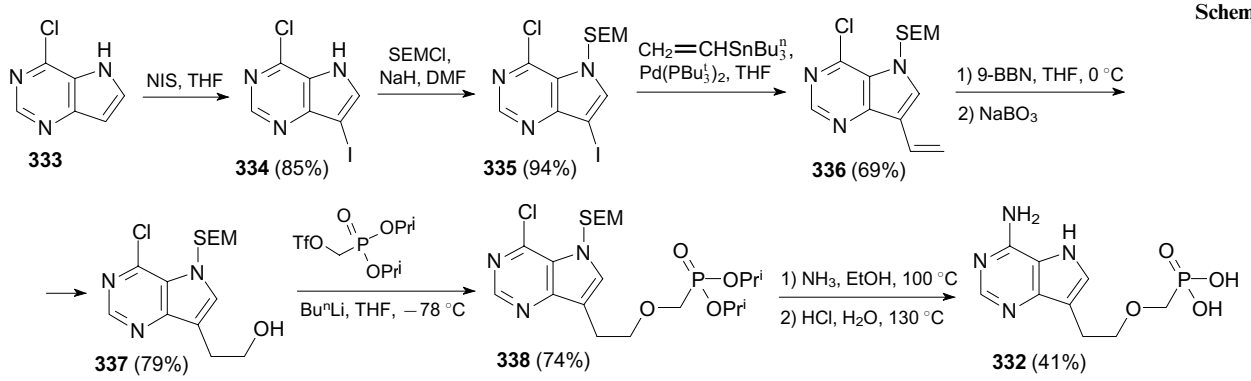
Scheme 61



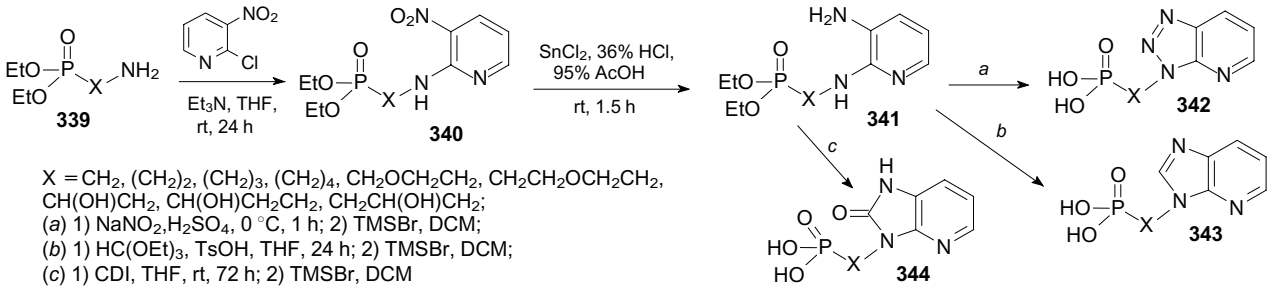
(*a*) 1) NaH, DMF, 80 °C; 2) $Cl(CH_2)_2OCH_2P(O)(OPr^i)_2$, DMF, 100°C; (*b*) $Cl(CH_2)_2OCH_2P(O)(OPr^i)_2$, DBU, DMF, 100 °C

The 9-deaza analogue of 9-(2-phosphonylmethoxyethyl)adenine (PMEA) **332** (Scheme 62) was synthesized using commercially available 6-chloro-9-deazapurine (4-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidine, **333**), which was iodinated with *N*-iodosuccinimide in THF to form 6-chloro-9-iodo-9-deazapurine **334** in high yield. After the introduction of the protecting group using SEMCl (SEM is 2-(trimethylsilyl)methoxyethyl ether) and sodium hydride in DMF, intermediate SEM derivative **335** was subjected to $Pd(Bu^n_3P)_2$–catalyzed Stille cross-coupling with tri-n-butylvinyltin in THF giving 9-vinyl-9-deazapurine **336**. The utilization of other palladium catalysts in the Stille reaction led to the formation of complex reaction mixtures containing the target product, the homocoupling product, the starting compound and its dehalogenated derivative in different ratios. The use of the 9-bromine-containing analogue (9-bromo-6-chloro-9-deazapurine) as the starting compound also resulted in a significant decrease in the yield of the desired intermediate. 9-(2-Hydroxyethyl)-9-deazapurine derivative **337** was synthesized in good yield by the hydroboration of compound **336** with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by the *in situ* oxidation with aqueous sodium perborate. The alkylation of compound **337** to phosphonate **338** was accomplished using $TfOCH_2P(O)(OPr^i)_2$ in the presence of n-butyllithium at low temperature. The treatment of phosphonate **338** with ammonia in ethanol gave the 9-deazaadenine derivative in good yield, and the simultaneous removal of SEM and isopropyl groups by microwave-assisted hydrolysis using a hydrochloric acid solution gave target phosphonic acid **332** in 56% yield.[140]

Scheme 62



Scheme 63



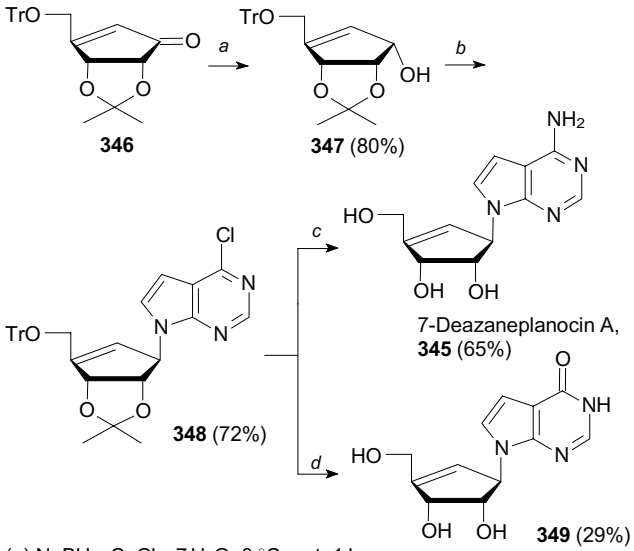
X = CH_2, $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$, $CH_2OCH_2CH_2$, $CH_2CH_2OCH_2CH_2$, $CH(OH)CH_2$, $CH(OH)CH_2CH_2$, $CH_2CH(OH)CH_2$;
(*a*) 1) $NaNO_2$,H_2SO_4, 0 °C, 1 h; 2) TMSBr, DCM;
(*b*) 1) $HC(OEt)_3$, TsOH, THF, 24 h; 2) TMSBr, DCM;
(*c*) 1) CDI, THF, rt, 72 h; 2) TMSBr, DCM

The reaction of aminoalkyl phosphonates **339** with 2-chloro-3-nitropyridine afforded diethyl [(3-nitropyridin-2-yl)amino]alkylphosphonates **340** in yields from 39 to 91% (Scheme 63). [141]

The reduction of the nitro group of compounds **340** furnished diethyl [(3-aminopyridin-2-yl)amino]alkylphosphonates **341**, which were used as key intermediates in the synthesis of nucleotide analogues. The diazotization of diethyl [(3-aminopyridin-2-yl)amino]alkylphosphonates followed by the spontaneous intramolecular cyclization produced diethyl 1,2,3-triazolo[4,5-*b*]pyridin-3-ylalkylphosphonates in 47–96% yields. 1-Deazapurine-containing analogues were synthesized by the reaction of the same intermediates with triethyl orthoformate in the presence of *p*-toluenesulfonic acid (32–99% yields). Imidazolone analogues of diethyl [(3-aminopyridin-2-yl)amino]alkylphosphonates **341** were prepared by the treatment with 1,1′-carbonyldiimidazole (CDI). However, under these conditions, only diethyl [(3-aminopyridin-2-yl)amino]alkylphosphonates were efficiently transformed into target nucleotide analogues. In the case of racemic phosphonates containing the hydroxyl group in the phosphonoalkyl chain, the reaction with 1,1′-carbonyldiimidazole produced a complex mixture of products. Several attempts to separate the reaction mixture on silica gel columns failed. The transformation of phosphonates containing the hydroxyl group in the phosphonoalkyl chain into imidazolones requires the prior protection of this group.[141] Phosphonic acids **342**–**344** were synthesized from respective diethyl phosphonates using trimethylbromosilane in dichloromethane (see Scheme 63).

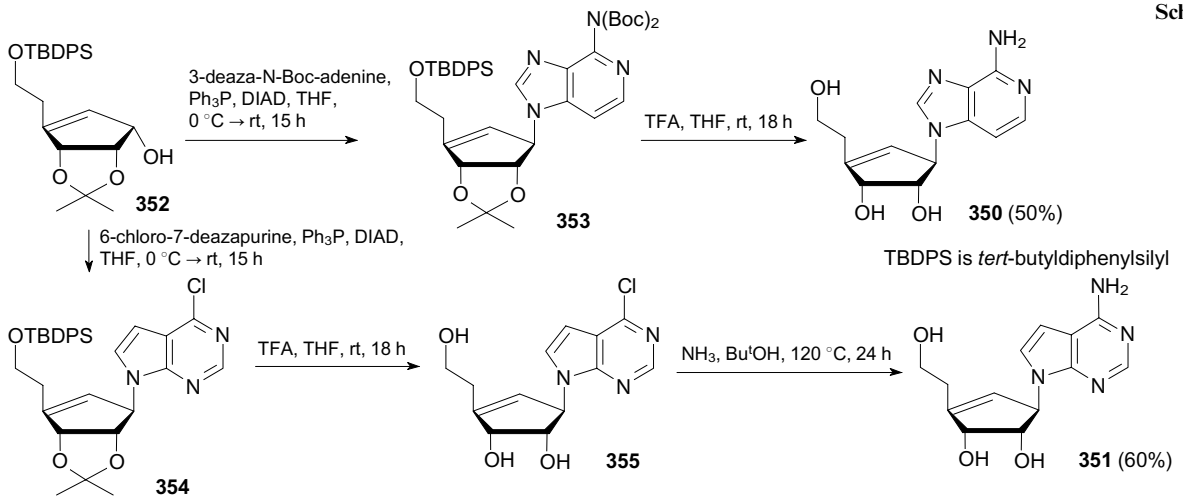
Carbocyclic aza- and deazapurine nucleoside analogues are often synthesized by the condensation of a heterocyclic base with a carbocyclic moiety under the Mitsunobu conditions.[142–144] Thus, 7-deazaneplanocin A (**345**) was prepared from key intermediate **346**, which was synthesized from D-ribose by an efficient procedure developed by Choi *et al.*[145] The reduction of the intermediate with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ afforded the precursor of the carbocyclic moiety (**347**) as a single diastereomer (Scheme 64). This precursor was subjected to condensation with 6-chloro-7-deazapurine under the standard Mitsunobu conditions giving the protected nucleoside analogue (**348**). The treatment of this compound with a methanolic solution of ammonia followed by acidic hydrolysis produced 7-deazaneplanocin A. Intermediate **348** was also transformed into respective carbocyclic 7-deazahypoxanthine derivative **349** by heating with 1 M HCl in 1,4-dioxane.[144]

Scheme 64

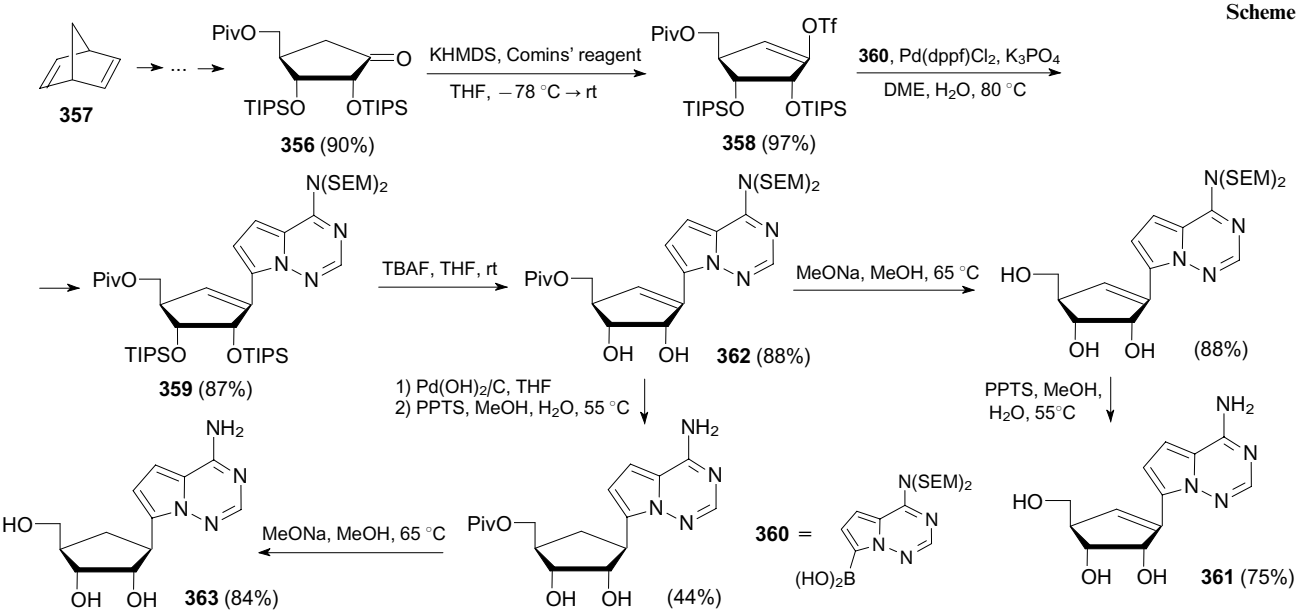


(*a*) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, 0 °C → rt, 1 h;
(*b*) 6-chloro-7-deazapurine, Ph_3P, DIAD, THF, 0 °C → rt, 15 h;
(*c*) 1) NH_3, MeOH, 120 °C, 40 h; 2) 2 M HCl, THF, MeOH, 55 °C, 15 h; 3) $NaHCO_3$; (*d*) 1 M HCl, 1,3-dioxane, 100 °C, 50 h;
DIAD is diisopropyl azodicarboxylate

Scheme 65



Scheme 66



dppf is 1,1′-bis(diphenylphosphino)ferrocene, PPTS is pyridinium *p*-toluenesulfonate

The homoneplanocin A analogues, compounds **350** and **351**, were synthesized from carbocyclic precursor **352** presynthesized from D-ribose (Scheme 65).[146] The carbocyclic moiety was subjected to condensation with 6-chloro-7-deazachloropurine or protected 3-deazaadenine under the Mitsunobu conditions. The deprotection of nucleoside analogues **353** and **354** with trifluoroacetic acid furnished 3-deazahomoneplanocin A (**350**) and 6-chloro derivative **355**, which was treated with ammonia in BuᵗOH giving 7-deazahomoneplanocin A (**351**).[144] This method was also used to prepare various 1-deaza-*N*-methanocarbaadenosine derivatives, which are adenosine A3 receptor agonists,[147] and L-3-deaza-, L-3-bromo-3-deaza- and L-5′-fluoro-5′-deoxy-3-deazaneplanocin analogues.[148]

Another example of the application of the condensation of a heterocyclic base with a carbocyclic moiety is the synthesis of carbocyclic 4-aza-7,9-dideazaadenosine analogues developed by Maier *et al.*[149] (Scheme 66).

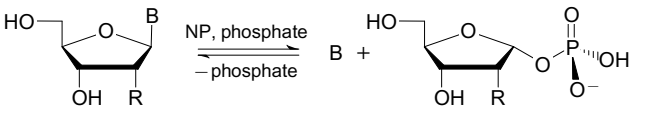
The proposed approach enables the selective synthesis of 4-aza-7,9-dideaza analogues of neplanocin A and aristeromycin. Substituted cyclopentanone **356**, the secondary hydroxyl groups of which are protected by triisopropylsilyl (TIPS) moieties and the primary hydroxyl group is protected by the pivaloyl (Piv) moiety, is a key intermediate in this method. This intermediate can be produced from available norbornadiene **357** as a racemate (in six steps) or an individual isomer (in ten steps).[149] The intermediate is quite stable to purification by column chromatography and storage at 25 °C for months. The complete conversion of intermediate **356** to enol triflate **358** was achieved in the presence of potassium hexamethyldisilazane (KHMDS) and Comins' reagent. Protected 4-aza-7,9-dideazaneplanocin A analogue **359** was synthesized by the Suzuki cross-coupling reaction of enol triflate **358** with hetarylboronic acid **360**, which was prepared from commercially available 7-bromopyrrolo[2,1-*f*][1,2,4]triazine-4-amine. The subsequent deprotection of compound **359** afforded the target 4-aza-7,9-dideaza analogue of neplanocin A **361** in 49% overall yield with respect to intermediate **356**. The hydrogenation of the double bond of the cyclopentene moiety of compound **362** and the subsequent deprotection gave 4-aza-7,9-dideazaaristeromycin **363** (37% yield over three steps).[149]

The above examples show the great potential of the chemical approach to the synthesis of aza and deaza analogues of different nucleosides.

4. Chemical-enzymatic synthesis

A highly efficient approach to the synthesis of naturally occurring nucleosides and their analogues is based on the transglycosylation reaction involving biocatalysts. This reaction is the transfer of the pentafuranose moiety of pyrimidine nucleosides to the purine heterocyclic base and backward. Two types of enzymes are mainly used as biocatalysts in nucleoside synthesis.[12–14] One type includes uridine phosphorylase (UP; EC 2.4.2.3), thymidine phosphorylase (TP; EC 2.4.2.4) and purine nucleoside phosphorylase (PNP; EC 2.4.2.1) from *Escherichia coli*. Nucleoside phosphorylases (NPs) *in vivo* catalyze reversible phosphorolysis of ribo- and deoxyribonucleosides in the presence of organic pyrophosphate giving free heterocyclic bases and ribo(deoxyribo)furanose phosphates (Scheme 67). The transglycosylation often involves pyrimidine nucleosides as donors of the pentafuranose moiety and purine heterocyclic bases as acceptors.[13]

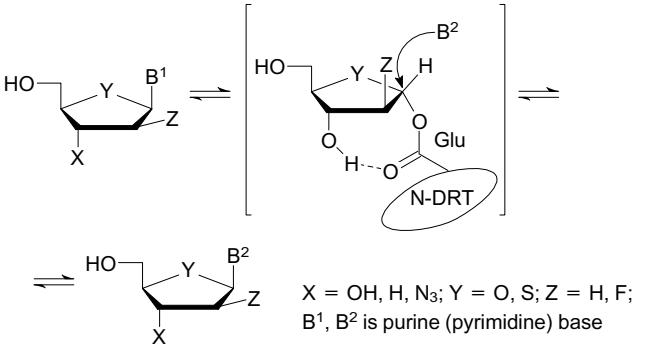
Scheme 67



R = H, OH; B is heterocyclic base

N-Deoxyribosyltransferases (N-DRT; EC 2.4.2.6) belong to another type of biocatalysts used in nucleoside synthesis. These enzymes catalyze the transfer of the 2′-deoxyribose moiety between the nucleoside and the heterocyclic base. In this process, deoxyribofuranose phosphate is not formed as an intermediate. The reaction proceeds through the formation of a transient complex, the 2-deoxy-α-D-ribofuranose moiety of which is covalently bound in the active site of the enzyme (Scheme 68).[12]

Scheme 68



X = OH, H, N_3; Y = O, S; Z = H, F; B^1, B^2 is purine (pyrimidine) base

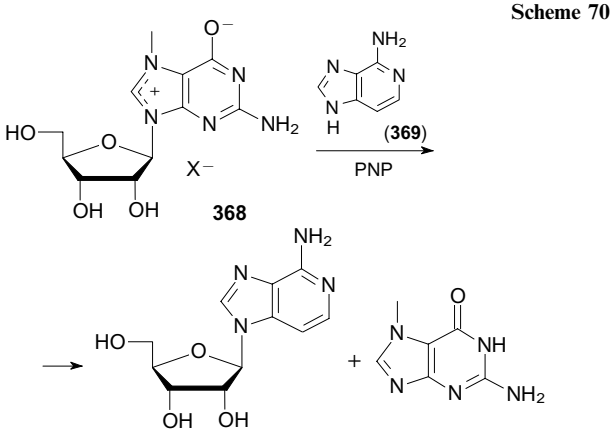
N-Deoxyribosyltransferases can be divided into two classes depending on the substrate specificity: class I enzymes (also called purine deoxyribosyltransferases, PDT) are specific for the transfer of deoxyribose between two purines; class II enzymes (called nucleoside deoxyribosyltransferases, NTD) catalyze the transfer of deoxyribose between purine or pyrimidine nucleosides but have a high affinity for deoxypyrimidine as the nucleoside donor.[150]

The chemical-enzymatic method involving nucleoside phosphorylases proved to be an efficient approach to the synthesis of diverse nucleoside analogues, in particular, aza and deaza derivatives. Purine nucleoside phosphorylases (in particular, AhPNP from *Aermonas hydrophila*) were used to synthesize numerous potentially active nucleoside analogues and those that are applied in therapy.[151]

The enzymes *E. coli* UP, TP and PNP were employed as catalysts in the synthesis of various ribo- and deoxyribo derivatives of 3-deazapurine, Depending on the donor of the pentafuranose moiety, uridine (R^1 = OH, R^2 = H) or thymidine (R^1 = H, R^2 = Me), the glycosidic bond is formed at the N(9) (compounds **364**, **365**) or N(7) atom (compounds **366**, **367**) of the heterocyclic base (Scheme 69).[14, 152]

3-Deazaadenosine **3** was synthesized using N(7)-methylguanosine **368** as the ribofuranose donor and 3-deazaadenine **369** as the acceptor (Scheme 70).[14, 153]

Scheme 70

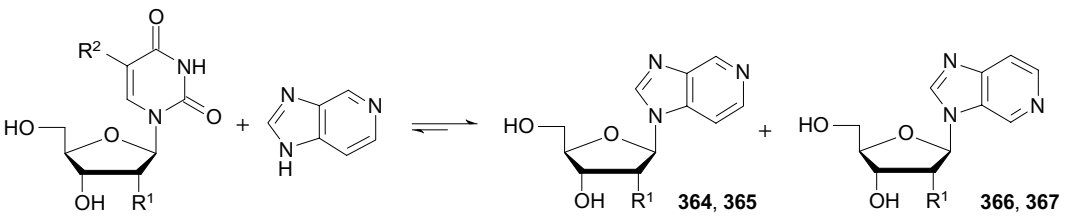


3-Deazaadenosine, **3**

Substituted benzimidazoles also proved to be good substrates in the transribosylation (guanosine as the donor) and transdeoxyribosylation (2′-deoxyriboguanosine as the donor) reactions catalyzed by *E. coli* BMT 1D/1A whole cells expressing PNP in required amounts.[154, 155] The reactions are characterized by high regioselectivity and afforded N(7)-β-D-glycosides, 1,3-deazanucleoside analogues **71** and **370**–**374**.[14]

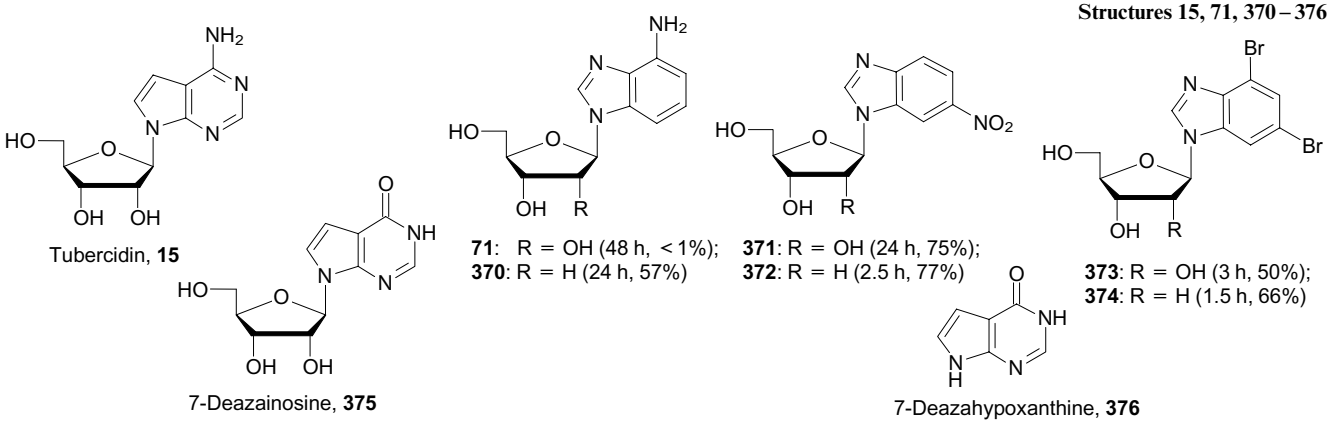
It is worth noting that *E. coli* PNP is the key enzyme in the synthesis of purine nucleosides and their analogues because it has a broad substrate specificity. Two nitrogen

Scheme 69

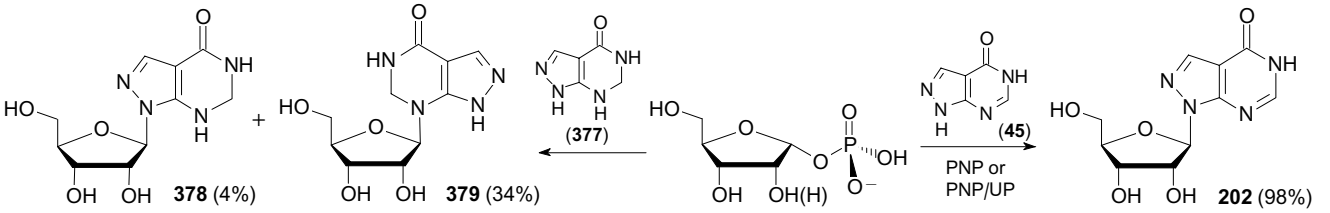


R^1 = OH, R^2 = H (64%, **364** : **366** = 5 : 1);
R^1 = H, R^2 = Me (26%, **365** : **367** = 1 : 3)

Structures 15, 71, 370 – 376



Scheme 71

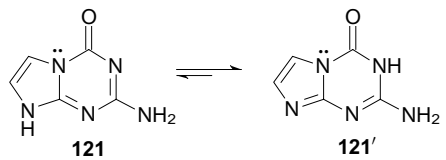


atoms of the five-membered ring play an important role in the binding of the heterocyclic base in the active site of the enzyme, one of the nitrogen atoms, when bound to the enzyme, enhancing the nucleophilicity of the second nitrogen atom.[12] It was shown that tubercidin **15** and 7-deazainosine **375**, having low affinity for the enzyme, are not substrates for PNP, whereas the free base 7-deazahypoxanthine **376** acts as an inhibitor of PNP and forms a stable complex with the enzyme.

Another hypoxanthine analogue, allopurinol **45**, a known inhibitor of xanthine oxidase,[156, 157] is an active substrate for *E. coli* PNP.[14, 158] Meanwhile, its metabolite, oxypurinol **377**, exhibits weak substrate properties, although the formation of N(9)- and N(3)-nucleosides **378** and **379** from this metabolite was detected (Scheme 71).

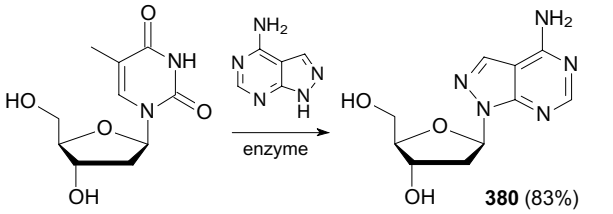
5-Aza-7-deazaguanine, which can exist in two tautomeric forms, **121** and **121′** (Scheme 72), has good substrate properties.[12, 159] The transglycosylation involving PNP produced 5-aza-7-deazaguanine deoxyriboside, arabinoside and deoxyfluororiboside with different efficiency (the yields were 63, 50 and 81%, respectively).[86, 159]

Scheme 72



Although nucleoside phosphorylases are most often used in the synthesis of nucleoside analogues, examples of the application of nucleoside transferases as biocatalysts are also known. Thus, in earlier studies, large-scale transglycosylation reactions of an excess of thymidine with 4-amino-

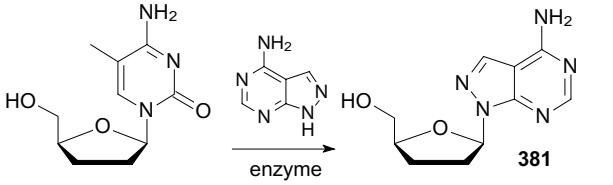
Scheme 73



pyrazolo[3,4-*d*]pyrimidine were catalyzed with nucleoside 2′- deoxyribosyltransferase (EC 2.4.2.6) from *Lactobacillus leichmannii*; these reactions afforded product **380** in quite high yield (Scheme 73).[160]

Nucleoside deoxyribosyltransferase II from *Lactobacillus leichmannii* also catalyzes the transfer of the 2′,3′-dideoxyriboside moiety from the 2′,3′-dideoxycytidine molecule to 4-aminopyrazolo[3,4-*d*]pyrimidine[161] giving 2′,3′-dideoxyribo-7-deaza-8-azaadenosine **381** (Scheme 74).

Scheme 74



Therefore, the enzymatic synthesis of aza and deaza analogues of purine nucleosides holds promise for respective bases, which are substrates for enzymes that catalyze transglycosylation reactions.

5. Conclusion

Deaza, aza and azadeaza analogues of purine nucleosides serve as convenient tools against various pathogens. In recent years, there has been an increasing interest in these compounds due to the emergence of drug resistance in long-known pathogens and the appearance of their new forms. This generates a need to develop highly efficient and selective methods for the synthesis of purine nucleoside analogues, which can be used to prepare potential drugs in required amounts. Currently, the majority of deaza, aza and azadeaza analogues of purine nucleosides are synthesized by chemical methods. Most of the methods for nucleoside synthesis are to some extent applicable to the preparation of their aza and deaza derivatives. In each particular case, the efficiency of the synthesis depends on the structures of the purine base and the carbohydrate moiety, as well as on the method used. The Vorbrüggen method (silyl-Hilbert–Johnson reaction) and fusion reactions in the presence of Lewis acids, which are used for the glycosidic bond formation in most of ribonucleoside analogues, are characterized by high selectivity along with high product yields. Reactions involving salt metals and biotechnological methods are, as a rule, more suitable for the synthesis of deoxyribonucleoside analogues. The enzymatic approach is becoming a convenient alternative to the chemical synthesis. Biocatalysts enable the synthesis of nucleoside analogues with high chemo-, regio- and stereoselectivity. This approach is regarded as environmentally more benign. Besides, enzymatic reactions make it possible to decrease the number of steps in the synthesis and to do without the protection of reactive functional groups. The biotechnological approach is suitable for the synthesis of naturally occurring nucleosides and their analogues modified at the heterocyclic base and(or) the carbohydrate moiety, is promising for scaling-up to the industrial production and, apparently, over time will displace chemical methods for the synthesis of these compounds.

This review was written with the financial support of the Russian Science Foundation (Project No. 19-74-10048).

6. List of acronyms and designations

ADA — adenosine deaminase,
Ara-A — adenine arabinoside,
9-BBN — 9-borabicyclo[3.3.1]nonane,
Boc — *tert*-butyloxycarbonyl,
BSA — *N*,*O*-bis(trimethylsilyl)acetamide,
CC_{50} — cytotoxic concentration that causes the death of 50% of cells,
CDI — 1,1′-carbonyldiimidazole,
dba — dibenzylideneacetone,
DBN — 1,5-diazabicyclo[4.0.3]non-5-ene,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCB — 2,4- dichlorobenzyl,
DCE — dichloroethane,
DCM — dichloromethane,
DENV — Dengue virus,
DMA — *N*,*N*-dimethylacetamide,
DMAP — 4-dimethylaminopyridine,
DME — dimethoxyethane,
DMT — 4,4′-dimethoxytrityl,
DPPA — diphenylphosphoryl azide,
dppf — 1,1′-bis(diphenylphosphino)ferrocene,
DRT — *N*-deoxyribosyltransferase,
EC_{50} — effective concentration that inhibits virus replication by 50%,
ee — enantiomeric excess,
Fu — furyl,
HBV — hepatitis B virus,
HCMV — human cytomegalovirus,
HCV — hepatitis C virus,
HIV-1 — human immunodeficiency virus type 1,
HMBC — heteronuclear multiple bond correlation spectroscopy,
HMDS — hexamethyldisilazane,
HOSA — hydroxylaminesulfonic acid,
HSV-1 — herpes simplex virus 1,
IC_{50} — half-maximal inhibitory concentration of the enzyme,
ImH — imidazole,
K_i — inhibitory constant,
m-CPBA — *m*-chloroperoxybenzoic acid,
MERS — Middle East respiratory syndrome,
MIC_{90} — minimum inhibitory concentration required to inhibit mycobacterial cell growth by 90%,
MSH — *O*-mesitylenesulfonylhydroxylamine,
NBS — *N*-bromosuccinimide,
Ni-Ra — Raney nickel,
NIS — *N*-iodosuccinimide,
NTD — nucleoside deoxyribosyltransferase,
NOESY — nuclear Overhauser effect NMR spectroscopy,
PDT — purine deoxyribosyltransferase,
Piv — pivaloyl,
PMEA — 9-(2-phosphonylmethoxyethyl)adenine,
PNP — purine nucleoside phosphorylase,
PPTS — pyridinium *p*-toluenesulfonate,
Py — pyridine,
rt — room temperature,
SAH — *S*-adenosylhomocysteine,
SARS — severe acute respiratory syndrome,
SEM — 2-(trimethylsilyl)ethoxymethyl,
TBAF —tetra-n-butylammonium fluoride,
TBDPS — *tert*-butyldiphenylsilyl,
TBS — *tert*-butyldimethylsilyl,
TDA-1 — tris[2-(2-methoxyethoxy)ethyl]amine,
TEBAC —benzyltriethylammonium chloride,
TFA — trifluoroacetic acid,
Tf — trifluoromethanesulfonyl,
Th — thienyl,
TIPS — triisopropylsilyl,
TMS — trimethylsilyl,
Tol — *p*-tolyl,
Tr — trityl (triphenylmethyl),
TsOH — *p*-toluenesulfonic acid,
VV — vaccinia virus.

References

1. H.Vorbruggen, C.Ruh-Polenz. In *Organic Reactions*. (Ed. L.A. Paquette). (New York: Wiley, 2000). Vol. 55. P. 1
2. G.Cristalli, S.Costanzi, C.Lambertucci, S.Taffi, S.Vittori, R.Volpini. *II Farmaco*, **58**, 193 (2003)
3. S.Budow, F.Seela. *Chem. Biodivers.*, **7**, 2145 (2010)
4. F.Seela, X.H.Peng. *Curr. Top. Med. Chem.*, **6**, 867 (2006)
5. R.M.McCarty, V.Bandarian. *Bioorg. Chem.*, **43**, 15 (2012)
6. L.M.De Coen, T.S.Heugebaert, D.Garcia, C.V.Stevens. *Chem. Rev.*, **116**, 80 (2016)
7. P.Perlikova, M.Hocek. *Med. Res. Rev.*, **37**, 1429 (2017)

8. J.Stambasky, M.Hocek, P.Kocovsky. *Chem. Rev.*, **109**, 6729 (2009)
9. K.Temburnikar, K.L.Seley-Radtke. *Beilstein J. Org. Chem.*, **14**, 772 (2018)
10. J.Wierzchowski, J.M.Antosiewicz, D.Shugar. *Mol. Biosyst.*, **10**, 2756 (2014)
11. P.Merino, T.Tejero, I.Delso. *Curr. Med. Chem.*, **15**, 954 (2008)
12. I.A.Mikhailopulo, A.I.Miroshnikov. *Acta Naturae*, **2**, 36 (2010)
13. I.A.Mikhailopulo, A.I.Miroshnikov. *Mendeleev Commun.*, **21**, 57 (2011)
14. I.A.Mikhailopulo. *Curr. Org. Chem.*, **11**, 317 (2007)
15. S.Vittori, D.Dal Ben, C.Lambertucci, G.Marucci, R.Volpini, G.Cristalli. *Curr. Med. Chem.*, **13**, 3529 (2006)
16. K.L.Seley-Radtke, M.K.Yates. *Antivir. Res.*, **154**, 66 (2018)
17. M.K.Yates, K.L.Seley-Radtke. *Antivir. Res.*, **162**, 5 (2019)
18. G.Cristalli, P.Franchetti, M.Grifantini, S.Vittori, T.Bordoni, C.Geroni. *J. Med. Chem.*, **30**, 1686 (1987)
19. D.K.Tosh, S.Crane, Z.Chen, S.Paoletta, Z.G.Gao, E.Gizewski, J.A.Auchampach, D.Salvemini, K.A.Jacobson. *ACS Med. Chem. Lett.*, **6**, 804 (2015)
20. G.Cristalli, M.Grifantini, S.Vittori, W.Balduini, F.Cattabeni. *Nucleosides Nucleotides*, **4**, 237 (1985)
21. I.Antonini, G.Cristalli, P.Franchetti, M.Grifantini, S.Martelli, F.Petrelli. *J. Pharm. Sci.*, **73**, 366 (1984)
22. G.Cristalli, S.Vittori, A.Eleuteri, M.Grifantini, R.Volpini, G.Lupidi, L.Capolongo, E.Pesenti. *J. Med. Chem.*, **34**, 2226 (1991)
23. R.D.Elliott, J.A.Montgomery. *J. Med. Chem.*, **20**, 116 (1977)
24. P.K.Chiang. *Pharmacol. Ther.*, **77**, 115 (1998)
25. J.A.Montgomery, S.J.Clayton, H.J.Thomas, W.M.Shannon, G.Arnett, A.J.Bodner, I.K.Kion, G.L.Cantoni, P.K Chiang. *J. Med. Chem.*, **25**, 626 (1982)
26. C.Liu, Q.Chen, S.W.Schneller. *Bioorg. Med. Chem. Lett.*, **22**, 5182 (2012)
27. C.Liu, Q.Chen, S.W.Schneller. *Bioorg. Med. Chem. Lett.*, **26**, 928 (2016)
28. C.Liu, R.Coleman, A.Archer, I.Hussein, T.L.Bowlin, Q.Chen, S.W.Schneller. *Bioorg. Med. Chem. Lett.*, **29**, 2480 (2019)
29. C.Shi, D.Tiwari, D.J.Wilson, C.L.Seiler, D.Schnappinger, C.C.Aldrich. *ACS Med. Chem. Lett.*, **4**, 1213 (2013)
30. R.C.Morris, M.S.Elliott. *Mol. Genet. Metab.*, **74**, 147 (2001)
31. D.Iwata-Reuyl. *Bioorg. Chem.*, **31**, 24 (2003)
32. J.M.Gregson, P.F.Crain, C.G.Edmonds, R.Gupta, T.Hashizume, D.W.Phillipson, J.A.McCloskey. *J. Biol. Chem.*, **268**, 10076 (1993)
33. C.Simons. *Nucleoside Mimetics: Their Chemistry and Biological Properties*. (Amsterdam: Gordon and Breach Science Publishers, 2001)
34. R.K.Robins, G.R.Revankar. *Advances in Anti Viral Drug Design*. (Greenwich: JAI Press, 1993)
35. R.H.Adamson, D.W.Zaharevitz, D.G.Johns. *Pharmacology*, **15**, 84 (1977)
36. A.Bloch, R.J.Leonard, C.A.Nichol. *Biochim. Biophys. Acta*, **138**, 10 (1967)
37. K.H.Schram, L.B.Townsend. *J. Carbohydr. Nucleosides Nucleotides,* **1**, 39 (1974)
38. P.Perlikova, G.Rylova, P.Naus, T.Elbert, E.Tloust'ova, A.Bourderioux, L.P.Slavetinska, K.Motyka, D.Dolezal, P.Znojek, A.Nova, M.Harvanova, P.Dzubak, M.Siller, J.Hlavac, M.Hajduch, M.Hocek. *Mol. Cancer Ther.*, **15**, 922 (2016)
39. F.Hulpia, S.Noppen, D.Schols, G.Andrei, R.Snoeck, S.Liekens, P.Vervaeke, S.Van Calenbergh. *Eur. J. Med. Chem.*, **157**, 248 (2018)
40. C.V.N.S.Varaprasad, K.S.Ramasamy, J.L.Girardet, E.Gunic, V.Lai, W.D.Zhong, H.Y.An, Z.Hong. *Bioorg. Chem.*, **35**, 25 (2007)
41. D.B.Olsen, A.B.Eldrup, L.Bartholomew, B.Bhat, M.R.Bosserman, A.Ceccacci, L.F.Colwell, J.F.Fay, O.A.Flores, K.L.Getty, J.A.Grobler, R.L.La Femina, E.J.Markel, G.Migliaccio, M.Prhavc, M.W.Stahlhut, J.E.Tomassini, M.MacCoss, D.J.Hazuda, S.S.Carroll. *Antimicrob. Agents Chemother.*, **48**, 3944 (2004)
42. S.H.Krawczyk, T.E.Renau, M.R.Nassiri, A.C.Westerman, L.L.Wotring, J.C.Drach, L.B.Townsend. *J. Med. Chem.*, **38**, 4115 (1995)
43. R.Wu, E.D.Smidansky, H.S.Oh, R.Takhampunya, R.Padmanabhan, C.E.Cameron, B.R.Peterson. *J. Med. Chem.*, **53**, 7958 (2010)
44. P.Perlikova, P.Konecny, P.Naus, J.Snasel, I.Votruba, P.Dzubak, I.Pichova, M.Hajduch, M.Hocek. *MedChemComm*, **4**, 1497 (2013)
45. Z.Yin, Y.L.Chen, W.Schul, Q.Y.Wang, F.Gu, J.Duraiswamy, R.R.Kondreddi, P.Niyomrattanakit, S.B.Lakshminarayana, A.Goh, H.Y.Xu, W.Liu, B.P.Liu, J.Y.H.Lim, C.Y.Ng, M.Qing, C.C.Lim, A.Yip, G.Wang, W.L.Chan, H.P.Tan, K.Lin, B.Zhang, G.Zou, K.A.Bernard, C.Garrett, K.Beltz, M.Dong, M.Weaver, H.D.He, A.Pichota, V.Dartois, T.H.Keller, P.Y.Shi. *Proc. Natl. Acad. Sci. USA*, **106**, 20435 (2009)
46. D.R.Latour, A.Jekle, H.Javanbakht, R.Henningsen, P.Gee, I.Lee, P.Tran, S.P.Ren, A.K.Kutach, S.F.Harris, S.M.Wang, S.J.Lok, D.Shaw, J.Li, G.Heilek, K.Klumpp, D.C.Swinney, J.Deval. *Antivir. Res.*, **87**, 213 (2010)
47. H.J.Kim, A.Sharon, C.Bal, J.N.Wang, M.Allu, Z.H.Huang, M.G.Murray, L.Bassit, R.F.Schinazi, B.Korba, C.K Chu. *J. Med. Chem.*, **52**, 206 (2009)
48. X.H.Guo, Y.J.Li, L.Tao, Q.Wang, S.Y.Wang, W.D.Hu, Z.L.Pan, Q.H.Yang, Y.M.Cui, Z.P.Ge, L.H.Dong, X.J.Yu, H.Y.An, C.J.Song, J.B.Chang. *Bioorg. Med. Chem. Lett.*, **21**, 6770 (2011)
49. J.A.Montgomery. *Med. Res. Rev.*, **2**, 271 (1982)
50. P.Franchetti, L.Messini, L.Cappellacci, G.A.Sheikha, M.Grifantini, P.Guarracino, A.Demontis, A.G.Loi, M.E.Marongiu, P.Lacolla. *Nucleosides Nucleotides*, **13**, 1739 (1994)
51. P.Franchetti, L.Cappellacci, M.Grifantini, G.Lupidi, G.Nocentini, A.Barzi. *Nucleosides Nucleotides*, **11**, 1059 (1992)
52. C.R.Petrie 3rd, H.B.Cottam, P.A.McKernan, R.K.Robins, G.R.Revankar. *J. Med. Chem.*, **28**, 1010 (1985)
53. H.B.Cottam, D.B.Wasson, H.C.Shih, A.Raychaudhuri, G.Dipasquale, D.A.Carson. *J. Med. Chem.*, **36**, 3424 (1993)
54. M.A.Pfaller, J.J.Marr. *Antimicrob. Agents Chemother.*, **5**, 469 (1974)
55. A.T.Shortnacy-Fowler, K.N.Tiwari, J.A.Montgomery, R.W.Buckheit, J.A.Secrist, F.A.Seela. *Helv. Chim. Acta*, **82**, 2240 (1999)
56. A.Bzowska. In *Modified Nucleosides: in Biochemistry, Biotechnology and Medicine*. (Ed. P.Herdewijn). (Weinheim: Wiley-VCH, 2008). P. 473
57. G.A.Kicska, L.Long, H.Horig, C.Fairchild, P.C.Tyler, R.H.Furneaux, V.L.Schramm, H.L.Kaufman. *Proc. Natl. Acad. Sci. USA*, **98**, 4593 (2001)
58. R.W.Miles, P.C.Tyler, R.H.Furneaux, C.K.Bagdassarian, V.L.Schramm. *Biochemistry*, **37**, 8615 (1998)
59. G.B.Evans, P.C.Tyler, V.L.Schramm. *ACS Infect. Dis.*, **4**, 107 (2018)
60. T.K.Warren, J.Wells, R.G.Panchal, K.S Stuthman, N.L.Garza, S.A.Van Tongeren, L.Dong, C.J.Retterer, B.P.Eaton, G.Pegoraro, S.Honnold, S.Bantia, P.Kotian, X.L.Chen, B.R.Taubenheim, L.S.Welch, D.M.Minning, Y.S.Babu, W.P.Sheridan, S.Bavari. *Nature (London)*, **508**, 402 (2014)

61. T.K.Warren, R.Jordan, M.K.Lo, A.S.Ray, R.L.Mackman, V.Soloveva, D.Siegel, M.Perron, R.Bannister, H.C.Hui, N.Larson, R.Strickley, J.Wells, K.S.Stuthman, S.A.Van Tongeren, N.L.Garza, G.Donnelly, A.C.Shurtleff, C.J.Retterer, D.Gharaibeh, R.Zamani, T.Kenny, B.P.Eaton, E.Grimes, L.S.Welch, L.Gomba, C.L.Wilhelmsen, D.K.Nichols, J.E.Nuss, E.R.Nagle, J.R.Kugelman, G.Palacios, E.Doerffler, S.Neville, E.Carra, M.O.Clarke, L.J.Zhang, W.Lew, B.Ross, Q.Wang, K.Chun, L.Wolfe, D.Babusis, Y.Park, K.M.Stray, I.Trancheva, J.Y.Feng, O.Barauskas, Y.L.Xu, P.Wong, M.R.Braun, M.Flint, L.K.McMullan, S.S.Chen, R.Fearns, S.Swaminathan, D.L.Mayers, C.F.Spiropoulou, W.A.Lee, S.T.Nichol, T.Cihlar, S.Bavari. *Nature (London)*, **531**, 381 (2016)
62. M.K.Lo, R.Jordan, A.Arvey, J.Sudhamsu, P.Shrivastava-Ranjan, A.L.Hotard, M.Flint, L.K.McMullan, D.Siegel, M.O.Clarke, R.L.Mackman, H.C.Hui, M.Perron, A.S.Ray, T.Cihlar, S.T.Nichol, C.F.Spiropoulou. *Sci. Rep.*, **7**, 43395 (2017)
63. T.P.Sheahan, A.C.Sims, R.L.Graham, V.D.Menachery, L.E.Gralinski, J.B.Case, S.R.Leist, K.Pyrc, J.Y.Feng, I.Trantcheva, R.Bannister, Y.Park, D.Babusis, M.O.Clarke, R.L.Mackman, J.E.Spahn, C.A.Palmiotti, D.Siegel, A.S.Ray, T.Cihlar, R.Jordan, M.R.Denison, R.S.Baric. *Sci. Transl. Med.*, 9 (2017)
64. M.L.Agostini, E.L.Andres, A.C.Sims, R.L.Graham, T.P.Sheahan, X.Lu, E.C.Smith, J.B.Case, J.Y.Feng, R.Jordan, A.S.Ray, T.Cihlar, D.Siegel, R.L.Mackman, M.O.Clarke, R.S.Baric, M.R.Denison. *mBio*, 9 (2018)
65. M.L.Holshue, C.DeBolt, S.Lindquist, K.H.Lofy, J.Wiesman, H.Bruce, C.Spitters, K.Ericson, S.Wilkerson, A.Tural, G.Diaz, A.Cohn, L.Fox, A.Patel, S.I.Gerber, L.Kim, S.Tong, X.Lu, S.Lindstrom, M.A.Pallansch, W.C.Weldon, H.M.Biggs, T.M.Uyeki, S.K.Pillai. *New Engl. J. Med.*, **382**, 929 (2020)
66. G.Cristalli, M.Grifantini, S.Vittori, W.Balduini, F.Cattabeni. *Nucleosides Nucleotides*, **4**, 625 (1985)
67. I.Antonini, F.Claudi, G.Cristalli, P.Franchetti, M.Grifantini, S.Martelli. *J. Med. Chem.*, **25**, 1258 (1982)
68. R.Volpini, S.Costanzi, S.Vittori, G.Cristalli, G.Lupidi. *Helv. Chim. Acta*, **82**, 2112 (1999)
69. R.Volpini, E.Camaioni, S.Costanzi, S.Vittori, G.Cristalli. *Helv. Chim. Acta*, **81**, 2326 (1998)
70. B.Zhang, S.De Graef, M.Nautiyal, L.P.Pang, B.Gadakh, M.Froeyen, L.Van Mellaert, S.V.Strelkov, S.D.Weeks, A.Van Aerschot. *Eur. J. Med. Chem.*, **148**, 384 (2018)
71. O.Bande, P.Herdewijn. *Eur. J. Org. Chem.*, 231 (2014)
72. E.Fischer, B.Helferich. *Ber. Dtsch. Chem Ges.*, **47**, 210 (1914)
73. M.Miyaki, B.Shimizu. *Chem. Pharm. Bull.*, **18**, 1446 (1970)
74. B.L.Cline, R.P.Panzica, L.B.Townsend. *J. Heterocycl. Chem.*, **15**, 839 (1978)
75. J.J.K.Novak, F.Sorm. *Collect. Czech. Chem. Commun.*, **27**, 902 (1962)
76. Z.Kazimierczuk, H.B.Cottam, G.R.Revankar, R.K.Robins. *J. Am. Chem. Soc.*, **106**, 6379 (1984)
77. C.Lin, F.Hulpia, C.F.da Silva, D.D.J.Batista, K.Van Hecke, L.Maes, G.Caljon, M.D.C.Soeiro, S.Van Calenbergh. *J. Med. Chem.*, **62**, 8847 (2019)
78. F.Seela, H.D.Winkeler. *J. Org. Chem.*, **47**, 226 (1982)
79. F.Seela, H.D.Winkeler. *Liebigs Ann. Chem.*, 1634 (1982)
80. W.Bourgeois, F.Seela. *J. Chem. Soc., Perkin Trans. 1*, 279 (1991)
81. F.Seela, R.Gumbiowski. *Heterocycles*, **29**, 795 (1989)
82. F.Seela, H.Winter. *Liebigs Ann. Chem.*, 105 (1991)
83. Z.Kazimierczuk, F.Seela. *Helv. Chim. Acta*, **73**, 316 (1990)
84. H.Ren, H.Y.An, J.C.Tao. *Molecules*, **24**, 983 (2019)
85. Z.Kazimierczuk, U.Binding, F.Seela. *Helv. Chim. Acta*, **72**, 1527 (1989)
86. H.Rosemeyer, F.Seela. *J. Org. Chem.*, **52**, 5136 (1987)
87. W.Q.Lin, X.M.Zhang, F.Seela. *Helv. Chim. Acta*, **87**, 2235 (2004)
88. V.Rolland, M.Kotera, J.Lhomme. *Synth. Commun.*, **27**, 3505 (1997)
89. P.Leonard, D.Kondhare, X.Jentgens, C.Daniliuc, F.Seela. *J. Org. Chem.*, **84**, 13313 (2019)
90. F.Seela, X.H.Peng. *J. Org. Chem.*, **71**, 81 (2006)
91. H.Vorbrüggen. In *Nucleoside Analogues. Chemistry, Biology, and Medical Applications* (Eds R.T.Walker, E.De Clercq, F.Eckstein). (New York: Plenum Press, 1979). P. 35
92. U.Niedballa, H.Vorbrueggen. *J. Org. Chem.*, **39**, 3668 (1974)
93. U.Niedballa, H.Vorbrueggen. *J. Org. Chem.*, **39**, 3654 (1974)
94. H.Vorbrüggen, B.Bennua. *Chem. Ber. Recl.*, **114**, 1279 (1981)
95. H.Vorbrüggen, G.Hofle. *Chem. Ber. Recl.*, **114**, 1256 (1981)
96. H.Vorbrüggen, K.Krolikiewicz, B.Bennua. *Chem. Ber. Recl.*, **114**, 1234 (1981)
97. K.A.Watanabe, O.H.Hollenberg, J.J.Fox. *J. Carbohydr. Nucleosides Nucleotides*, **1**, 1 (1974)
98. J.L.Barascut, C.Ollierdemarichard, J.L.Imbach. *J. Carbohydr. Nucleosides Nucleotides*, **3**, 281 (1976)
99. T.S.Rao, G.R.Revankar, R.S.Vinayak, R.K.Robins. *J. Heterocycl. Chem.*, **28**, 1779 (1991)
100. T.S.Rao, G.R.Revankar, R.S.Vinayak, R.K.Robins. *J. Heterocycl. Chem.*, **29**, 343 (1992)
101. V.O.Iaroshenko, Y.Wang, D.V.Sevenard, D.M.Volochnyuk. *Synthesis*, 1851 (2009)
102. F.Seela, X.Ming. *Tetrahedron*, **63**, 9850 (2007)
103. M.M.Bio, F.Xu, M.Waters, J.M.Williams, K.A.Savary, C.J.Cowden, C.H.Yang, E.Buck, Z.G.J.Song, D.M.Tschaen, R.P.Volante, R.A.Reamer, E.J.J.Grabowski. *J. Org. Chem.*, **69**, 6257 (2004)
104. L.G.Zhang, Y.L.Zhang, X.H.Li, L.H.Zhang. *Bioorg. Med. Chem.*, **10**, 907 (2002)
105. A.R.Porcari, L.B.Townsend. *Nucleosides Nucleotides*, **18**, 153 (1999)
106. P.Leonard, S.A.Ingale, P.Ding, X.Ming, F.Seela. *Nucleosides Nucleotides Nucleic Acids*, **28**, 678 (2009)
107. A.R.Porcari, L.B.Townsend. *Synth. Commun.*, **28**, 3835 (1998)
108. B.G.Huang, M.Bobek. *Carbohydr. Res.*, **308**, 319 (1998)
109. W.Y.Yu, E.J.Chory, A.K.Wernimont, W.Tempel, A.Scopton, A.Federation, J.J.Marineau, J.Qi, D.Barsyte-Lovejoy, J.N.Yi, R.Marcellus, R.E.Iacob, J.R.Engen, C.Griffin, A.Aman, E.Wienholds, F.L.Li, J.Pineda, G.Estiu, T.Shatseva, T.Hajian, R.Alawar, J.E.Dick, M.Vedadi, P.J.Brown, C.H.Arrowsmith, J.E.Bradner, M.Schapira. *Nat. Commun.*, **3**, 1 (2012)
110. L.C.Campeau, P.D.O'Shea. *Synlett*, 57 (2011)
111. P.Naus, O.Caletkova, P.Konecny, P.Dzubak, K.Bogdanova, M.Kolar, J.Vrbkova, L.Slavetinska, E.Tloust'ova, P.Perlikova, M.Hajduch, M.Hocek. *J. Med. Chem.*, **57**, 1097 (2014)
112. T.Brückl, I.Thoma, A.J.Wagner, P.Knochel, T.Carell. *Eur. J. Org. Chem.*, 6517 (2010)
113. K.Sakthivel, P.D.Cook. *Tetrahedron Lett.*, **46**, 3883 (2005)
114. H.B.Cottam, G.R.Revankar, R.K.Robins. *Nucleic Acids Res.*, **11**, 871 (1983)
115. F.W.Lichtenthaler, E.Cuny. *Chem. Ber. Recl.*, **114**, 1610 (1981)
116. H.B.Cottam, C.R.Petrie, P.A.Mckernan, R.J.Goebel, N.K.Dalley, R.B.Davidson, R.K.Robins, G.R.Revankar. *J. Med. Chem.*, **27**, 1119 (1984)
117. M.Hamann, C.Pierra, R.Storer, J.-P.Sommadossi, A.G.Loi, A.Cadeddu, M.Fanti, N.Boscu, F.Bassetti, M.Liuzzi, G.Gosselin. *Nucleic Acids Symp. Ser.*, **52**, 617 (2008)
118. A.Cho, L.J.Zhang, J.Xu, D.Babusis, T.Butler, R.Lee, O.L.Saunders, T.Wang, J.Parrish, J.Perry, J.Y.Feng, A.S.Ray, C.U.Kim. *Bioorg. Med. Chem. Lett.*, **22**, 4127 (2012)
119. S.E.Metobo, J.Xu, O.L.Saunders, T.Butler, E.Aktoudianakis, A.Cho, C.U.Kim. *Tetrahedron Lett.*, **53**, 484 (2012)

120. A.Cho, O.L.Saunders, T.Butler, L.Zhang, J.Xu, J.E.Vela, J.Y.Feng, A.S.Ray, C.U.Kim. *Bioorg. Med. Chem. Lett.*, **22**, 2705 (2012)
121. A.Cho, L.Zhang, J.Xu, R.Lee, T.Butler, S.Metobo, V.Aktoudianakis, W.Lew, H.Ye, M.Clarke, E.Doerffler, D.Byun, T.Wang, D.Babusis, A.C.Carey, P.German, D.Sauer, W.Zhong, S.Rossi, M.Fenaux, J.G.McHutchison, J.Perry, J.Feng, A.S.Ray, C.U.Kim. *J. Med. Chem.*, **57**, 1812 (2014)
122. A.G.Draffan, B.Frey, B.Pool, C.Gannon, E.M.Tyndall, M.Lilly, P.Francom, R.Hufton, R.Halim, S.Jahangiri, S.Bond, V.T.T.Nguyen, T.P.Jeynes, V.Wirth, A.Luttick, D.Tilmanis, J.D.Thomas, M.Pryor, K.Porter, C.J.Morton, B.Lin, J.M.Duan, G.Kukolj, B.Simoneau, G.McKercher, L.Lagace, M.Amad, R.C.Bethell, S.P.Tucker. *ACS Med. Chem. Lett.*, **5**, 679 (2014)
123. D.Siegel, H.C.Hui, E.Doerffler, M.O.Clarke, K.Chun, L.Zhang, S.Neville, E.Carra, W.Lew, B.Ross, Q.Wang, L.Wolfe, R.Jordan, V.Soloveva, J.Knox, J.Perry, M.Perron, K.M.Stray, O.Barauskas, J.Y.Feng, Y.L.Xu, G.Lee, A.L.Rheingold, A.S.Ray, R.Bannister, R.Strickley, S.Swaminathan, W.A.Lee, S.Bavari, T.Cihlar, M.K.Lo, T.K.Warren, R.L.Mackman. *J. Med. Chem.*, **60**, 1648 (2017)
124. Patent WO 2013084165A1 (2013)
125. G.B.Evans, R.H.Furneaux, T.L.Hutchison, H.S.Kezar, P.E.Morris Jr., V.L.Schramm, P.C.Tyler. *J. Org. Chem.*, **66**, 5723 (2001)
126. D.A.Babkov, A.N.Geisman, A.L.Khandazhinskaya, M.S.Novikov. *Russ. Chem. Rev.*, **85**, 308 (2016)
127. Y.Mizuno, M.Ikehara, K.A.Watanabe, S.Suzaki. *J. Org. Chem.*, 3331 (1963)
128. N.Kojima, N.Minakawa, A.Matsuda. *Tetrahedron*, **56**, 7909 (2000)
129. N.Minakawa, N.Kojima, A.Matsuda. *J. Org. Chem.*, **64**, 7158 (1999)
130. N.Minakawa, T.Takeda, T.Sasaki, A.Matsuda, T.Ueda. *J. Med. Chem.*, **34**, 778 (1991)
131. N.Minakawa, A.Matsuda. *Tetrahedron*, **49**, 557 (1993)
132. M.I.Lim, R.S.Klein. *Tetrahedron Lett.*, **22**, 25 (1981)
133. S.De Bernardo, M.Weigele. *J. Org. Chem.*, **42**, 109 (1977)
134. M.I.Lim, W.Y.Ren, B.A.Otter, R.S.Klein. *J. Org. Chem.*, **48**, 780 (1983)
135. C.Y.Liang, T.W.Ma, J.S.Cooperwood, J.F.Du, C.K.Chu. *Carbohydr. Res.*, **303**, 33 (1997)
136. S.A.Patil, B.A.Otter, R.S.Klein. *Tetrahedron Lett.*, **35**, 5339 (1994)
137. M.E.Jung, I.D.Trifunovich. *Tetrahedron Lett.*, **33**, 2921 (1992)
138. J.A.Montgomery, A.T.Shortnacy, S.D.Clayton. *J. Heterocycl. Chem.*, **14**, 195 (1977)
139. A.Holy, J.Gunter, H.Dvorakova, M.Masojidkova, G.Andrei, R.Snoeck, J.Balzarini, E.De Clercq. *J. Med. Chem.*, **42**, 2064 (1999)
140. M.Cesnek, J.Skacel, P.Jansa, M.Dracinsky, M.Smidkova, H.Mertlikova-Kaiserova, M.P.Soto-Velasquez, V.J.Watts, Z.Janeba. *ChemMedChem*, **13**, 1779 (2018)
141. A.Hartwich, N.Zdzienicka, D.Schols, G.Andrei, R.Snoeck, I.E.Glowacka. *Nucleosides Nucleotides Nucleic Acids*, **39**, 542 (2020)
142. K.C.K.Swamy, N.N.B.Kumar, E.Balaraman, K.V.P.P.Kumar. *Chem. Rev.*, **109**, 2551 (2009)
143. M.M.Yang, J.Zhou, S.W.Schneller. *Tetrahedron*, **62**, 1295 (2006)
144. G.Chandra, Y.W.Moon, Y.Lee, J.Y.Jang, J.Song, A.Nayak, K.Oh, V.A.Mulamoottil, P.K.Sahu, G.Kim, T.S.Chang, M.Noh, S.K.Lee, S.Choi, L.S.Jeong. *J. Med. Chem.*, **58**, 5108 (2015)
145. W.J.Choi, H.R.Moon, H.O.Kim, B.N.Yoo, J.A.Lee, D.H.Shin, L.S.Jeong. *J. Org. Chem.*, **6**9, 2634 (2004)
146. G.Chandra, M.S.Majik, J.Y.Lee, L.S.Jeong. *Org. Lett.*, **14**, 2134 (2012)
147. D.K.Tosh, A.Ciancetta, E.Warnick, R.O'Connor, Z.M.Chen, E.Gizewski, S.Crane, Z.G.Gao, J.A.Auchampach, D.Salvemini, K.A.Jacobson. *J. Med. Chem.*, **59**, 3249 (2016)
148. Q.Chen, A.Smith. *Bioorg. Med. Chem. Lett.*, **29**, 126613 (2019)
149. L.Maier, P.Khirsariya, O.Hylse, S.K.Adla, L.Cernova, M.Poljak, S.Krajcovicova, E.Weis, S.Drapela, K.Soucek, K.Paruch. *J. Org. Chem.*, **82**, 3382 (2017)
150. R.Anand, P.A.Kaminski, S.E.Ealick. *Biochemistry*, **43**, 2384 (2004)
151. M.Rabuffetti, T.Bavaro, R.Semproli, G.Cattaneo, M.Massone, C.F.Morelli, G.Speranza, D.Ubiali. *Catalysts*, **9**, 355 (2019)
152. T.A.Krenitsky, J.L.Rideout, E.Y.Chao, G.W.Koszalka, F.Gurney, R.C.Crouch, N.K.Cohn, G.Wolberg, R.Vinegar. *J. Med. Chem.*, **29**, 138 (1986)
153. W.J.Hennen, C.H.Wong. *J. Org. Chem.*, **54**, 4692 (1989)
154. I.A.Mikhailopulo, Z.Kazimierczuk, A.I.Zinchenko, V.N.Barai, V.V.Romanova, L.A.Eroshevskaya. *Nucleosides Nucleotides Nucleic Acids*, **14**, 477 (1995)
155. M.I.Kharitonova, I.D.Konstantinova, A.I.Miroshnikov. *Russ. Chem. Rev.*, **87**, 1111 (2018)
156. I.Chu, B.M.Lynch. *J. Med. Chem.*, **18**, 161 (1975)
157. J.Gao, X.Liu, B.Zhang, Q.Mao, Z.Zhang, Q.Zou, X.Dai, S.Wang. *Eur. J. Med. Chem.*, **190**, 112077 (2020)
158. I.V.Kulikova, M.S.Drenichev, P.N.Solyev, C.S.Alexeev, S.N.Mikhailov. *Eur. J. Org. Chem.*, 6999 (2019)
159. I.V.Fateev, K.V.Antonov, I.D.Konstantinova, T.I.Muravyova, F.Seela, R.S.Esipov, A.I.Miroshnikov, I.A.Mikhailopulo. *Beilstein J. Org. Chem.*, **10**, 1657 (2014)
160. M.G.Stout, D.E.Hoard, M.J.Holman, E.S.Wu, J.M.Siegel. *Methods Carbohydr. Chem.*, **7**, 19 (1976)
161. Patent WO 9006312 (1989)