Preprint: Kozak W., Demkowicz S., Daśko M., Rachon J., Rak J., Modifications at the C(5) position of pyrimidine nucleosides, RUSS CHEM REV, 2020, 89 (3), 281–310
DOI: 10.1070/RCR4919

Modifications at the C-5 position of pyrimidine nucleosides

Witold Kozak,[a] Sebastian Demkowicz,[b] Mateusz Daśko,[c] Janusz Rachon,[b] Janusz Rak[a*]

[a]Laboratory of Biological Sensitizers, Faculty of Chemistry, University of Gdańsk, Wita Stwosza 63, 80-308 Gdańsk, Poland

[b]Department of Organic Chemistry, Faculty of Chemistry, Gdańsk University of Technology, Narutowicza 11/12, 80-233 Gdańsk, Poland

[c]Department of Inorganic Chemistry, Faculty of Chemistry, Gdańsk University of Technology, Narutowicza 11/12, 80-233 Gdańsk, Poland

Abstract

This review summarizes the state of knowledge on the selected chemical methods of C-5-modifications of uridine and cytidine derivatives and may serve as a useful tool for synthetic chemists to choose an appropriate synthetic protocol. The synthesis of 5-substituted uracil derivatives is gaining more and more interest because of their possible applications in medicine and pharmacy. Modifications at the C-5 position of pyrimidine nucleosides can enhance their biostability, bioavailability or/and biological activity. Among the C-5-modified nucleosides, 5-halogenopyrimidines exhibit anticancer, antiviral, radio- and photosensitizing properties. Besides 5-halogeno-substituted derivatives, there are other examples of nucleosides, with confirmed biological activity, containing a C–C bond at the C-5 position in the pyrimidine ring. In the recent decades, scientists have made great progress in the field of cross-coupling reactions. Among them, nickel-catalyzed processes provide a broad spectrum of synthetic methods that are based on less toxic and cheaper starting materials. This review summarizes the synthetic approaches, based not only on the coupling or halogenation reactions, that enable 5-substituted pyrimidine nucleosides to be

obtained. Moreover, the importance of the considered systems for medicine and pharmacy is shortly discussed.
Keywords: modified nucleosides, DNA, pyrimidine, uridine, cytidine

Contents

1. Introduction

Synthesis of 5-substituted uracil derivatives is gaining more and more interest because of their biological properties.[1-3] Chemical modification at the C-5 position of pyrimidine nucleosides can enhance their biostability and bioavailability or change the behavior in an organism.[4,5] Among the C-5-modified nucleosides, 5-halogenopyrimidines exhibit anticancer, antiviral, radio- and photosensitizing properties. Research, carried out with these compounds, revealed important information regarding their cellular biochemistry and affinity towards transporter proteins and, moreover, with their help enzyme-substrate specific interactions have been elucidated.[6,7]

There are several drugs based on 5-halogeno-modified pyrimidine nucleosides (Fig. 1) available on the market e.g. 5-iodo-2'-deoxyuridine (**5IdU**) **1** – known under the Stoxil and Herplex Liquifilm trade names – used against feline herpes virus (FHV-1)[8] or 1-hexylcarbamoyl-5-fluorouracil (Carmofur) **2** – employed against resected colorectal cancer.[9] 5-Fluorouracil-based compounds are popular antimetabolites, among which 5-fluoro-2'-deoxyuridine (FUDR) (**5FdU**) **3** is a well-known anticancer drug used in colorectal, kidney and stomach cancer therapy.[10] 5-Fluorocytidine derivative **4** – emtricitabine – is used in the treatment of human immunodeficiency virus (HIV).[11] In addition, 5-chlorouridine derivatives are also known to possess anti-HIV activity.[12] Furthermore, 5-halogenopirymidine nucleosides are active against the varicella-zoster virus (VZV).[13]

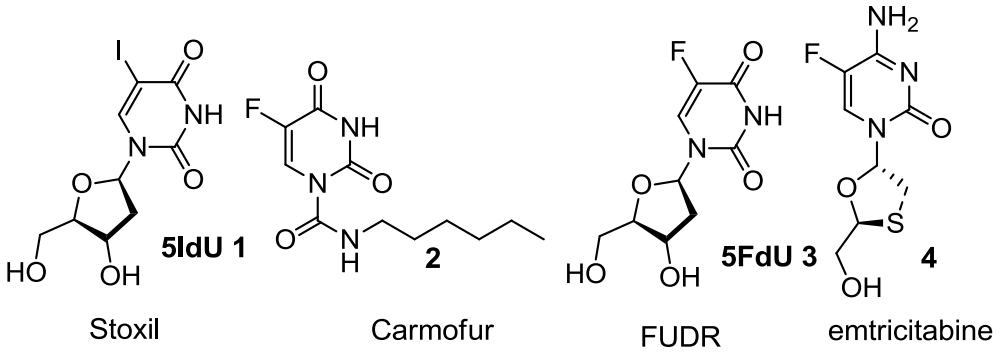


Figure. 1. Examples of registered drugs based on 5-halogeno-modified pyrimidines **1**-**4**.

Besides 5-halogeno-substituted derivatives, there are some other examples of nucleosides with confirmed biological activity containing a C–C bond at the C-5 position in the pyrimidine ring (Fig. 2). One of them, 5-trifluoromethyl-2'-deoxyuridine (**5CF$_3$dU**) **5** – known as Viroptic – is used against herpes simplex virus (HSV-1 and HSV-2)[14,15] and in combination with tipiracil (Lonsurf) **6** against metastatic colorectal cancer.[16] Another example is a nucleoside that consists of the 5-bromovinyluracil moiety connected to D-arabinose – sorivudine **7** – known under the Usevir or Brovavir trade names.[17] This substance is a potent anti-HSV-1, VZV and Epstein–Barr virus (EBV) drug. Some other examples of 5-substituted nucleosides

with confirmed biological activities are: 5-ethynyl-2'-deoxyuridine **8** (against herpes simplex-1 strain LYON and KOS),[18] telbivudine **9** – L-isomer of thymidine (anti-HBV),[19] stavudine **10** (anti-HIV),[20] zidovudine **11** (anti-HIV),[21] edoxudine **12** (anti-HSV)[22] (Fig. 2).

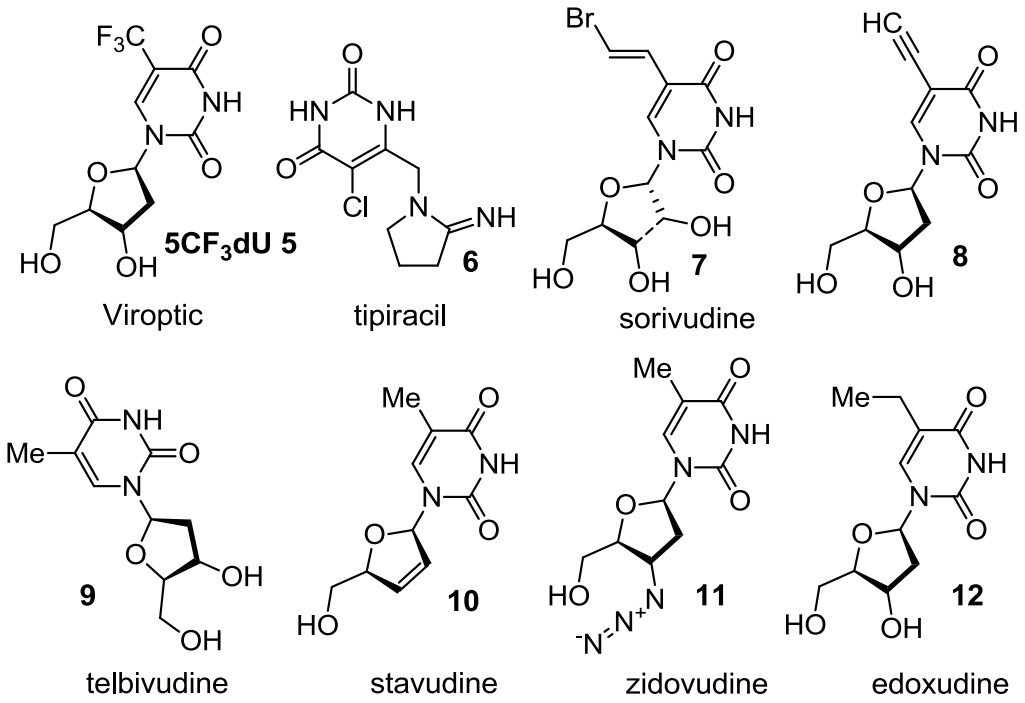


Figure 2. Chemical structures of selective biologically active uridine derivatives bearing a C-C bond at the C-5 position along with the structure of tipiracil **5**–**12**.

Another interesting features of 5-substituted nucleosides are their radio- and photosensitizing properties associated with an ability to undergo dissociative electron attachment (DEA)[23] and photo-induced electron transfer (PET), respectively.[24] These phenomena occur in DNA labeled with uracil nucleosides possessing a substantial electron affinity and relatively weak C-5–X bond or the consecutive bond within the X substituent.[25,26] Note, that hydrated electrons (e_{aq}^-), the second most abundant product of water (the main constituent of every cell) radiolysis,[27] attach to high electron affinity sites in DNA (to radiosensitizing nucleosides in the labeled DNA) and trigger a low-barrier or barrierless DEA if the mentioned above bonds are sufficiently weak, which makes hydrated electron transfer an irreversible process.[28,29] DEA itself, in turn, produces reactive radicals, which in secondary hydrogen transfer reactions

leads to strand breaks or cross-links.[30,31] Although e_{aq}^- easily attaches to native DNA, a competitive protonation of the anions formed on pyrimidines (sites of the highest electron affinity in the native DNA) prevents the formation of strand breaks.[32] The protonation is not an issue for the labeled DNA due to the swift dissociation triggered by electron attachment (DEA). The most thoroughly studied compound in this class of nucleosides is 5-bromo-2'-deoxyuridine (**5BrdU**) **13**,[33,34] which easily incorporates into DNA during its replication or repair.[35] As a result, cells labeled with **5BrdU 13** are 3-4 times more sensitive to ionizing radiation than those from the control.[36-39] Another examples of such compounds are: 5-thiocyanato- **14**, 5-selenocyanato- **15**, 5-trifluoromethanesulfonyl- (**5OTf**) **16** or 5-iodo-4-thio-2'-deoxyuridine **17**.[40-42]

As far as PET is concerned, it was demonstrated that the maximum yield of photoinduced damage (SSB) occurs for DNA sequences such as 5'-GAA**5BrdU,** in which the photosensitizer (**5BrdU 13**) is separated from guanine by two adenines.[43,44] Such configuration assures the most efficient electron transfer between the photoexcited **5BrdU 13** (the photooxidant) and guanine of the lowest ionization potential among the native nucleobases.[45] The ground state **5BrdU 13** anion formed due to such long-range ET undergoes dissociation similar to that observed for DEA triggered by the described above e_{aq}^- attachment to the labeled DNA.[46] A similar PET process was observed for the oligonucleotide labeled with 5-bromo-2'-deoxycytidine (**5BrdC**) **18** (Fig. 3).[47] On the other hand, a photoinduced formation of intra-strand thiethane is probably responsible for cytotoxicity of 4-thiothymidine **19** incorporated into cellular DNA.[1,48]

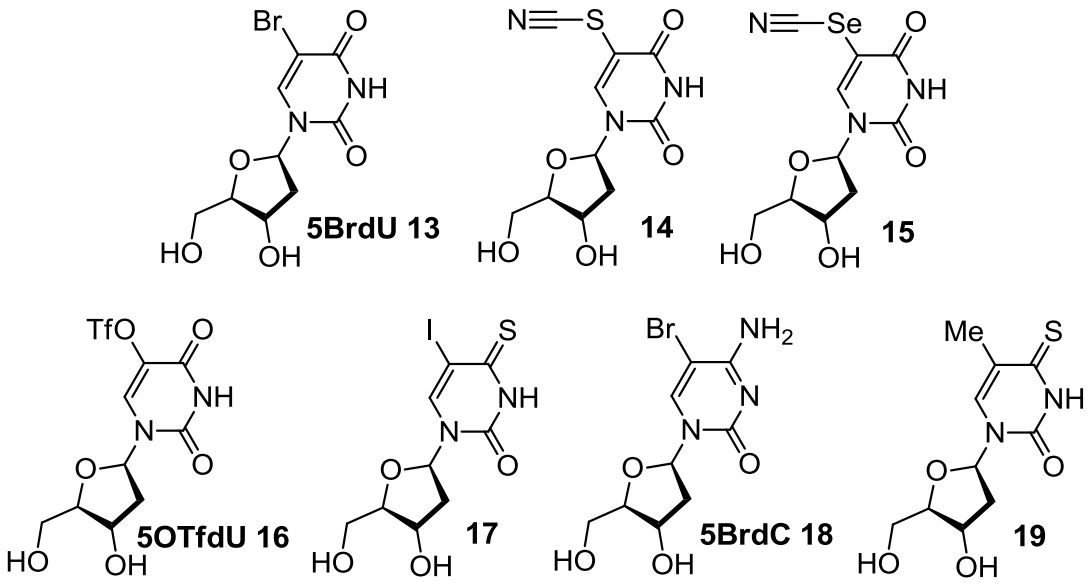


Figure 3. Structures of potential radio- and photosensitizers **13**–**19**.

In the current review, we gathered selected methods of chemical modification at the C-5 position of pyrimidine nucleosides. Taking into account the above-mentioned, it is clear that many biologically active pyrimidine nucleosides contain a C–C bond or halogen atom at the C-5 position. Therefore, it is essential to possess a wide range of distinct methods for their synthesis. Scientists have made great progress in the field of cross-coupling reactions in the recent decades.[49] Among them, nickel-catalyzed processes provide a broad spectrum of synthetic applications that are based on less toxic and cheaper starting materials.[49] Many of the coupling reactions proceed in aqueous solutions, which make them environmentally friendly.[50,51] It is worth of noticing, that in the synthesis of 5-substituted pyrimidine nucleosides not only coupling or halogenation reactions should be considered. Indeed, various synthetic methods for the introduction of a wide range of other substituents at the C-5 position are described in the recent literature. During the chemical synthesis of such compounds, chemists often have to decide whether to protect hydroxyl groups present in the sugar unit. In many cases it is inevitable. On one hand, the overall synthetic procedure is extended then to additional protection and deprotection steps, but on the other hand, protected intermediates become more hydrophobic, which usually facilitates the purification step. This review, in an accessible way, summarizes the state of knowledge about the selected chemical methods of C-5 modifications of

uridine and cytidine derivatives. To the best of our knowledge, previous review papers concerning this topic appeared in 1972[52] and 1988.[53]

Abbreviations:

5BrC – 5-bromocytidine,

5BrdC – 5-bromo-2'-deoxycytidine,

5BrdU – 5-bromo-2'-deoxyuridine,

5BrU – 5-bromouridine,

5CF_3dU – 5-trifluoromethyl-2'-deoxyuridine,

5ClC – 5-chlorocytidine,

5CldC – 5-chloro-2'-deoxycytidine,

5CldU – 5-chloro-2'-deoxyuridine,

5ClU – 5-chlorouridine,

5FdU – 5-fluoro-2'-deoxyuridine,

5FU – 5-fluorouridine,

5IC – 5-iodocytidine,

5IdC – 5-iodo-2'-deoxycytidine,

5IdU – 5-iodo-2'-deoxyuridine,

5IU – 5-iodouridine,

5MedU – 5-methyl-2'-deoxyuridine,

5NH_2dC – 5-amino-2'-deoxycytidine,

5NH_2dU – 5-amino-2'-deoxyuridine,

5NH_2U – 5-aminouridine,

5NO_2dC – 5-nitro-2'-deoxycytidine,

5NO_2dU – 5-nitro-2'-deoxyuridine,

5NO_2U – 5-nitrouridine,

5OHdC – 5-hydroxy-2'-deoxycytidine,

5OHdU – 5-hydroxy-2'-deoxyuridine,

5OHU –5-hydroxyuridine,

5OTfdU – 5-trifluoromethanesulfonyl-2'-deoxyuridine,

5OTfU – 5-trifluoromethanesulfonyluridine,

5SHdU – 5-mercapto-2’-deoxyuridine,

ACN – acetonitrile,

BAIB – [bis(acetoxy)-iodo]benzene,

bpy – 2,2’-bipyridine,

CAN – ceric ammonium nitrate,

m-CPBA – *m*-chloroperoxybenzoic acid,

dba – dibenzylideneacetone,

DEA – dissociative electron attachment,

DIPEA – diisopropylethylamine,

DMA – *N*,*N*-dimethylacetamide,

DMDO – dimethyldioxirane,

DMF – dimethylformamide,

DMP – Dess–Martin periodinane,

DMSO – dimethylsulfoxide,

DMTr – 4,4’-dimethoxytrityl,

DNA – deoxyribonucleic acid,

DTT – dithiothreitol,

EBV – Epstein–Barr virus,

EDC – 1,2-dichloroethane,

EDTA – ethylenediaminetetraacetic acid,

FHV – feline herpes virus,

HIV – human immunodeficiency virus,

HMDS – 1,1,1,3,3,3-hexamethyldisilazane,

HSV – herpes simplex virus,

LDA – lithium diisopropylamide,

MMTr – 4-methoxytrityl,

MW – microwave,

NADPH – nicotinamide adenine dinucleotide,

NBS – *N*-bromosuccinimide,

NCS – *N*-chlorosuccinimide,

NIS – *N*-iodosuccinimide,

OTf – trifluoromethanesulfonyl,

PTABS – 1,3,5-triaza-7-phosphaadamantane butane sulfonate,

PTAPS – 1,3,5-triaza-7-phosphaadamantane propane sulfonate,

SMBI – sodium monobromoisocyanurate,

SSB – a maximum yield of photoinduced damage,

TBAF – *t*-butylammonium fluoride,

TBDMS – *tert*-butyldimethylsilyl,

TEMPO – 2,2,6,6-tetramethyl-1-piperidinyloxyl,

TFA – trifluoroacetic acid,

TMCS – trimethylchlorosilane,

THF – tetrahydrofuran,

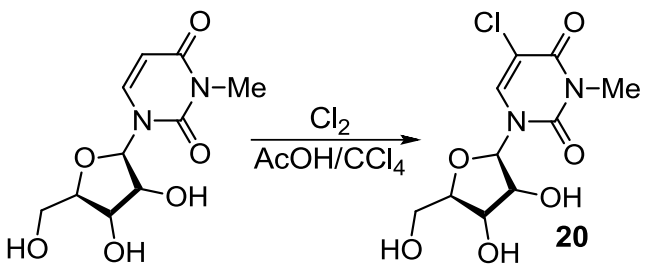
TMEDA – *N*,*N*,*N'*,*N'*-tetramethylethylenediamine,

VZV – varicella-zoster virus.

2. Halogenation

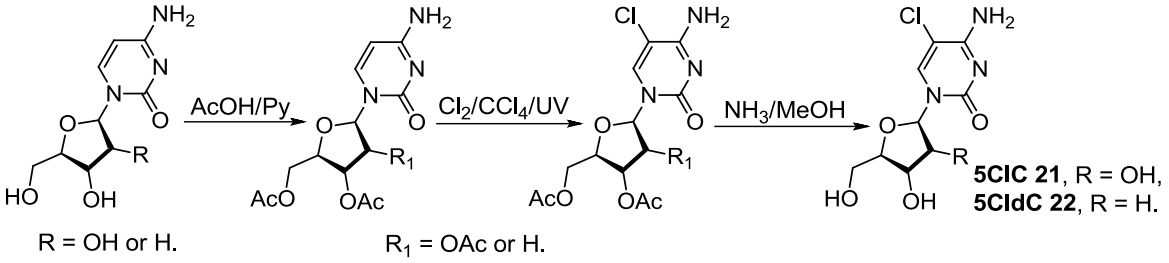
2.1. Chlorination

The first report for the synthesis of 5-chlorouridine derivative appeared in the *Journal of the American Chemical Society*. Visser *et al.* obtained 5-chloro-3-methyluridine **20** (Scheme 1) in a 35% yield in a reaction between 3-methyluridine and chlorine in acetic acid.[54]



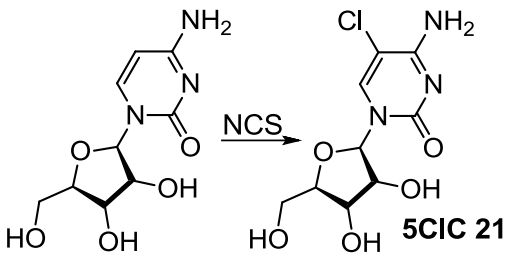
Scheme 1. Synthesis of 5-chloro-3-methyluridine **20**.

Fukuhara and Visser obtained 5-chlorocytidine (**5ClC**) **21** by the three-step protocol (Scheme 2). At first, cytidine was transformed into its tetraacetate analog, which was submitted to the radical reaction with chlorine. After a deprotection step with ammonia in methanol, the product was crystallized from ethanol. The overall yield of the process was 41%.[55] Three years later the same synthetic protocol was used by Frisch and Visser for the first time synthesis of 5-chloro-2'-deoxycytidine (**5CldC**) **22** (Scheme 2) with a 62% yield.[56]



Scheme 2. Synthesis of 5-chlorocytidine **5ClC 21** and 5-chloro-2'-deoxycytidine **5CldC 22**.

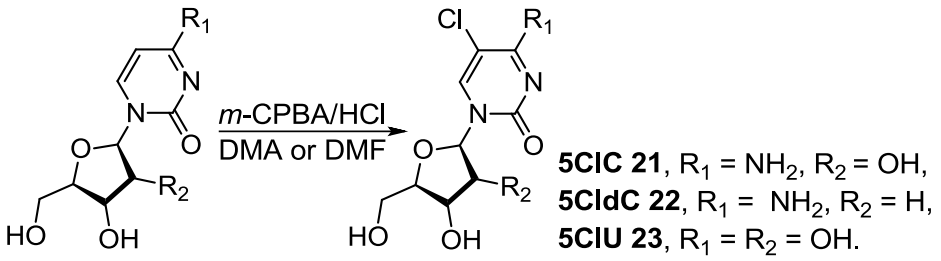
Another valuable method for the introduction of chlorine substituent at the C-5 position of cytidine with use of *N*-chlorosuccinimide (NCS) in an inert solvent was first reported in 1969 (**5ClC 21**, Scheme 3). However, the authors of the patent did not provide precise synthetic procedure and yield of the product.[57]



Scheme 3. Synthesis of **5ClC 21** with use of NCS.

Kikugawa *et al.* modified the method depicted in Scheme 3, by carrying out the reaction of cytidine with NCS in a glacial acetic acid in 105 °C. Authors obtained, after crystallization from ethanol, **5ClC 21** and 5-chlorouridine (**5ClU**) **23** in 61% yields in both cases.[58]

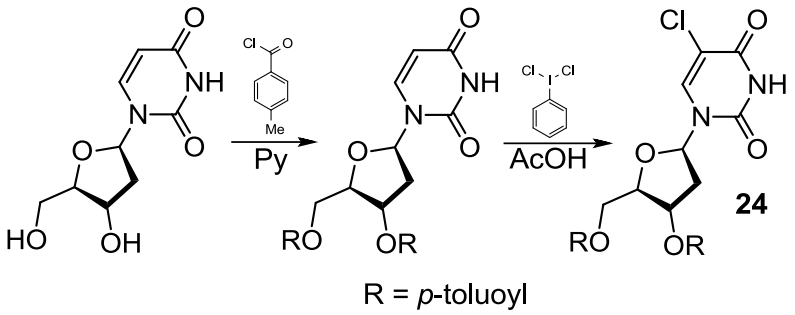
A different attitude towards chlorination at the C-5 position was described by Ryu and MacCoss.[59] The reaction proceeded with a treatment of cytidine, 2'-deoxycytidine or uridine with *m*-chloroperoxybenzoic acid (*m*-CPBA) in the presence of HCl in *N*,*N*-dimethylacetamide (DMA) at room temperature (Scheme 4). Compounds **5ClC 21**, **5CldC 22** and **5ClU 23** were obtained in 56, 75 and 90% yields, respectively. Comparing to previously given examples, this chlorination protocol has few advantages. Reactions are carried out in mild conditions, yields are better and times of the reactions are relatively short (3 h).



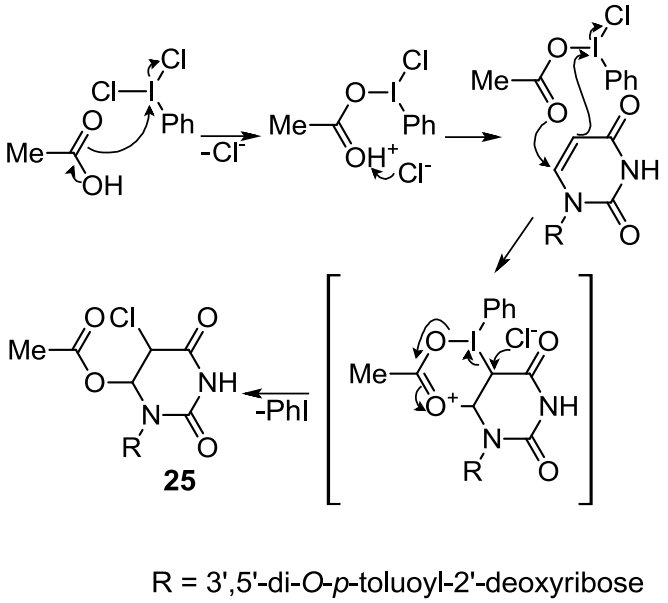
Scheme 4. Synthesis of 5-halogenonucleosides **21**–**23** with use of *m*-CPBA/HCl system.

An interesting method for utilizing iodobenzene dichloride as a chloride anion source was introduced in 1981.[60] With its help Robins *et al.* obtained 3',5'-di-*O*-*p*-toluoyl-5-chloro-2'-deoxyuridine **24** (Scheme 5) in a 94% yield. A major benefit of this method was a very short reaction time (15 minutes) with keeping the yield on an excellent level. A plausible mechanism of the reaction could be based on the consideration of Liu *et al.*[61] Although their two propositions were related to the reaction of iodobenzene dichloride with alkenes in the presence of DMF it is possible to adapt these schemes to the described case. Thus, two alternative pathways can be suggested. First mechanism comprises a nucleophilic attack of an acetic acid molecule on iodobenzene dichloride, followed by deprotonation. Such obtained crucial intermediate (confirmed with ^{1}H NMR and LC-MS analysis) reacts in the next step with 3',5'-di-*O*-*p*-toluoyl-2'-deoxyuridine to eventually afford 5-chloro-6-acetoxy-5,6-dihydro analog of 2'-deoxyuridine **25** (Scheme 6). The second hypothetic mechanism premises a reaction between 3',5'-di-*O*-*p*-toluoyl-2'-deoxyuridine and iodobenzene

dichloride to form chloronium cation, which, in the next step, reacts as an electrophile with an acetic acid molecule. After deprotonation compound **25** is formed (Scheme 6). According to the proposition of the authors, compound **25** can undergo an extra elimination step to form the desired product **24**, which is possible due to increased acidity of the H-5 proton.



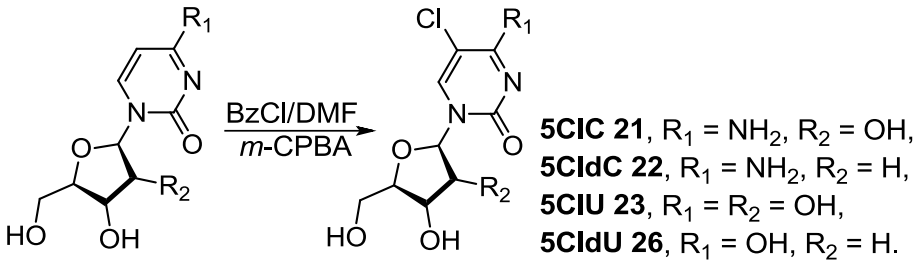
Scheme 5. Synthesis of 3',5'-di-*O*-*p*-toluoyl-5-chloro-2'-deoxyuridine **24** with use of iodobenzene dichloride.



Scheme 6. Plausible mechanism for the synthesis of compound **25** with use of iodobenzene dichloride in AcOH.

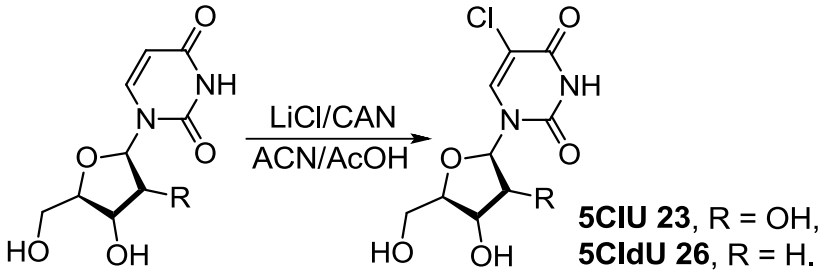
In 1989, **5ClC 21**, **5ClU 23** and their 2'-deoxy analogs (**22** and **26**) were obtained *via* the oxidative chlorination of appropriate nucleosides with chloride cation, generated *in situ* from the reaction of benzoyl (BzCl) or acetyl chloride (AcCl) with

DMF to produce the chloride anion, which was oxidized in the next step with *m*-CPBA solution in DMF (Scheme 7).[62] The reactions were carried out at room temperature without protection of hydroxyl groups within sugar moiety giving the products in 44–54% yields.



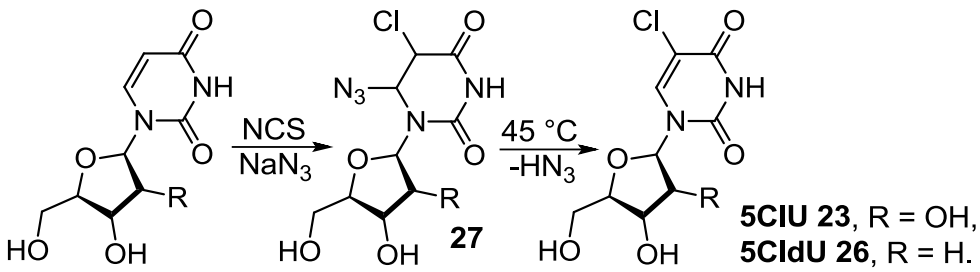
Scheme 7. Synthesis of 5-chloro nucleosides **21**–**23** and **26** with use of BzCl/DMF/*m*-CPBA system.

Ceric ammonium nitrate (CAN) is a very useful oxidizing agent in laboratory practice. For instance, it oxidizes secondary alcohols to ketones,[63] benzylic alcohols to aldehydes,[63] sulfides to sulfoxides[64]. CAN has also received much attention in the carbon–halogen bond formation reaction.[65] A reaction of acetylated nucleosides with lithium chloride, mediated by CAN, afforded the corresponding 5-chloro derivatives **23** and **26** in 94 and 95% yields, respectively (Scheme 8).[66] Chlorination was performed in acetonitrile (ACN)/AcOH solution at 80 °C for 6 h. The addition of AcOH significantly improved the kinetics of the reaction and shortened it even four times.



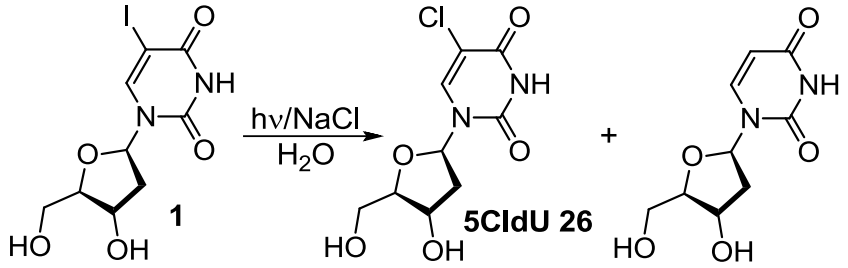
Scheme 8. Synthesis of 5-chloro nucleosides **23** and **26** catalyzed by CAN.

A mild and highly efficient chlorination method was proposed by Kumar *et al.* They used NCS as the chloride anion source.[67] Acetylated or non-acetylated uridines, when treated at room temperature with NCS, generated chloronium cations that subsequently reacted with NaN_3 to give 5-chloro-6-azido-5,6-dihydro-intermediates **27** (Scheme 9). These analogs were then converted to their 5-chloro derivatives **5ClU 23** and **5CldU 26** by mild heating to 45 °C.



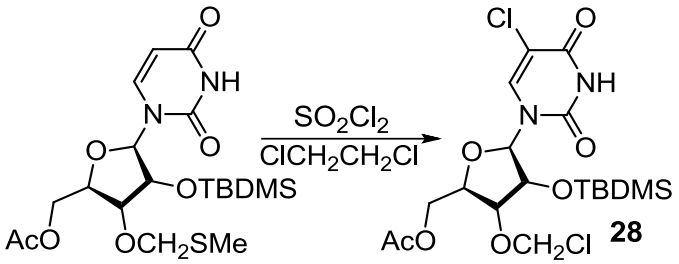
Scheme 9. Synthesis of 5-chlorouridines, **23** and **26**, in the presence of NCS and NaN_3.

A very essential observation was reported in 1999. It was found that a DNA fragment, having **5IdU 1** in its structure, can undergo a halogen exchange at the sp2 carbon of **1** mediated by photoirradiation (Scheme 10). Researchers managed to substitute iodine atom in **5IdU 1** with chlorine and bromine, but with fluoride they failed.[68] Reaction goes through plausible $S_{RN}1$ mechanism, that comprises the creation of an excited state of 5-iodo-2'-deoxyuridine, which in the second step reacts with chloride anion to form a corresponding radical anion.[69,70] The reaction can terminate to 2'-deoxyuridine or to **5CldU 26**, which means it is not selective from the chemical point of view. The authors declare to obtain **5CldU 26** and 2'-deoxyuridine in 19 and 30% yields, respectively, in a 4 M NaCl solution irradiated with a transilluminator (302 nm) for 10 minutes, reaching the consumption of **5IdU 1** at 49% level. In this case a halogen-elimination dominates over a halogen-exchange reaction.



Scheme 10. Photochemical synthesis of 5-chloro-2'-deoxyuridine **5CldU 26** from **5IdU 1** by the presumed $S_{RN}1$ mechanism.

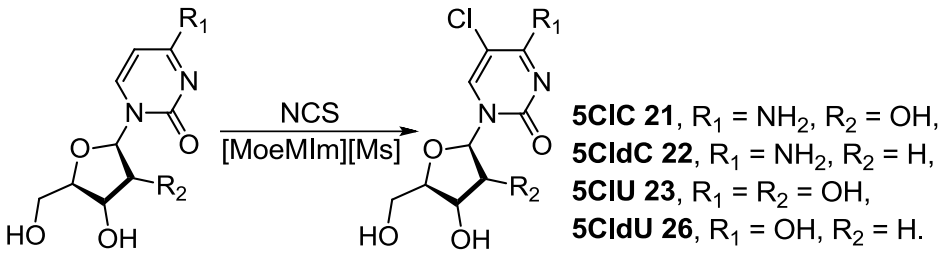
In 2000 Zavgorodny noticed , when trying to obtain 3'-*O*-chloromethyl derivative of uridine from its 3'-*O*-methylthiomethyluridine analog, an additional chlorination side reaction at the C-5 position in pyrimidine base occurred giving compound **28** in an unstated yield (Scheme 11).[71] In this case it was undesirable and unexpected, but in the chemical literature one can find examples of using SO_2Cl_2 as a chlorinating agent for uridine derivatives.[72,73] The use of SO_2Cl_2 in the presence of $FeCl_3$ for the uracil chlorination was reported much earlier.[74] In the same conditions of the reactions, the authors mentioned that when 2'-*O*-methylthiomethyluridine analog was treated with SO_2Cl_2 no chlorination at the C-5 position in pyrimidine moiety was observed.



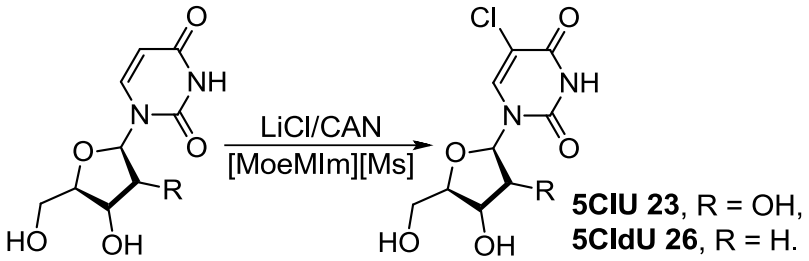
Scheme 11. Synthesis of 5-chlorouridine derivative **28** in the presence of SO_2Cl_2 in 1,2-dichloroethane.

In 2009, Kumar's research group published two articles describing very efficient and environmental friendly novel chlorination methods of uridine, cytidine and their 2'-deoxy analogs with use of ionic liquids as solvents. However, in fact they modified already existing protocols. In first example, C-5 chlorination was achieved

through the treatment of appropriate nucleoside with NCS in an ionic liquid, thus omitting the use of the catalyst i.e. AcOH (Scheme 12).[75] The reactions proceeded in very good yields in all cases (84–92%). The highest yields were achieved at 50 °C, in case of uridine and cytidine, while using the 1-methoxyethyl-3-methylimidazolium methanesulfonate ([MoeMIm][Ms]) ionic liquid. The second work published in the same year is related to the CAN-mediated method.[76] ACN/AcOH solution, previously used as a solvent mixture, was replaced by an ionic liquid (Scheme 13). Although the yields for the **5ClU 23** and **5CldU 26** were relatively low (30 and 58%), the authors managed to obtain **5CldU 26**, which was not accessible through the already reported CAN-based method. The highest yields were achieved again with use of the [MoeMIm][Ms] ionic liquid.



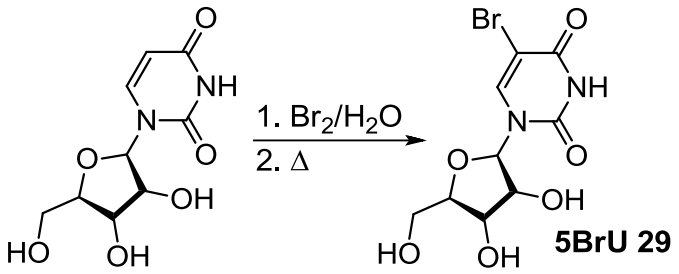
Scheme 12. Synthesis of 5-chloro nucleosides, **21**–**23** and **26**, in the presence of NCS in [MoeMIm][Ms] ionic liquid.



Scheme 13. CAN-mediated synthesis of 5-chlorouridines, **23** and **26**, in [MoeMIm][Ms] ionic liquid.

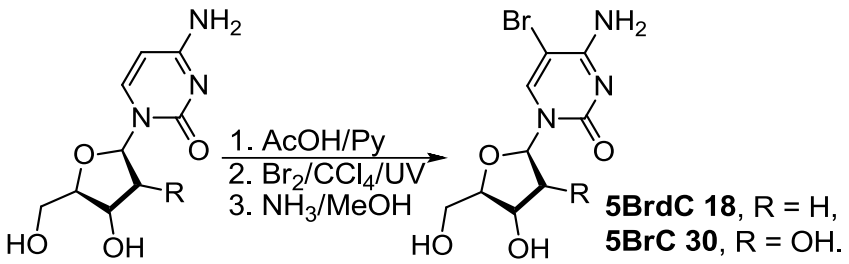
2.2. Bromination

The very first example of bromination of uridine at the C-5 position was reported in *Berichte der Deutschen Chemischen Gesellschaft*.[77] Levene and La Forge treated uridine with bromine water to afford 5-bromouridine (**5BrU**) **29** (Scheme 14) in an unstated yield.



Scheme 14. A first synthesis of **5BrU 29**.

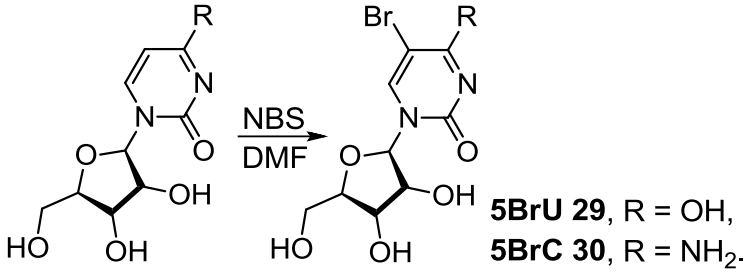
The same synthetic protocol as described for chlorination reactions[55,56] (Scheme 2) was used to synthesize 5-bromocytidine (**5BrC**) **30** and its 2'-deoxy derivative, **5BrdC 18**, in 70 and 62% yields, respectively, with the difference that instead of chlorine, bromine was used (Scheme 15).



Scheme 15. Synthesis of **5BrdC 18** and **5BrC 30**.

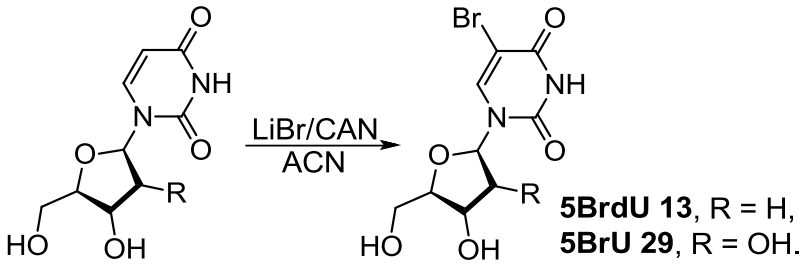
In 1969, Srivastava and Nagpal brominated uridine and cytidine by treating them with *N*-bromosuccinimide (NBS) in DMF (Scheme 16). They obtained **5BrU 29**

and **5BrC 30** in 62 and 83% yields, respectively.[78] A similar bromination reaction can be performed in a moderate yield with NBS in ACN.[79]



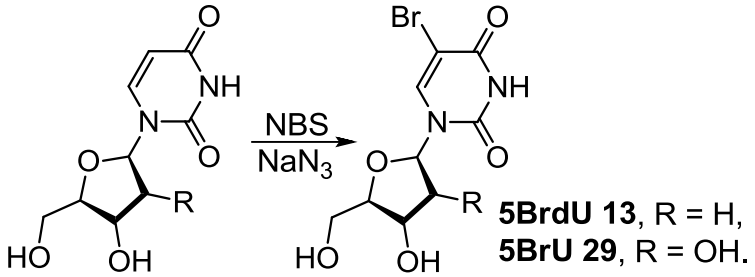
Scheme 16. Synthesis of **5BrU 29** and **5BrC 30** with use of NBS.

Utilizing a very similar synthetic procedure mediated by CAN (Scheme 8), it is possible to obtain 5-bromonucleosides **13** and **29** in excellent yields up to 91% (Scheme 17). In this case the reaction times were shorter than for the 5-chloro nucleosides (1.5 h in both cases) and the presence of AcOH in the reaction mixtures was not needed.[66]



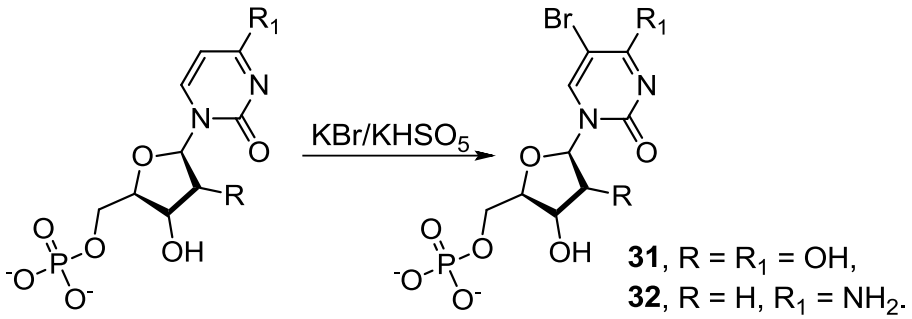
Scheme 17. Synthesis of 5-bromonucleosides **13** and **29** catalyzed by CAN.

Bromination can be performed with NBS/NaN_3 in 1,2-dimethoxyethane as it was described by Kumar *et al.* The only difference was that in order to obtain **5BrdU 13** and **5BrU 29** longer reaction times were required comparing to the chlorination, done with the same procedure (Scheme 9). **5BrdU 13** and **5BrU 29** were synthesized in excellent 95 and 90% yields, respectively (Scheme 18).[67]



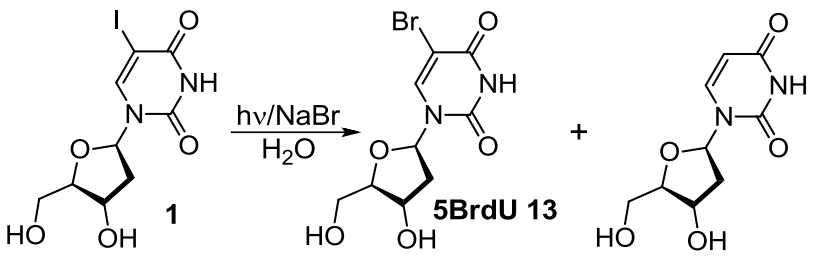
Scheme 18. Synthesis of 5-bromouridines **13** and **29** in the presence of NBS and NaN_3.

A different approach to bromination reaction was proposed by Ross and Burrows in 1994. They described the use of $KBr/KHSO_5$ system as an effective and convenient way to introduce a bromine atom at the C-5 position of a pyrimidine base. A presumed halogenating agent is Br_2, created *in situ* from Br^-/HSO_5^-. In the paper authors described the successful bromination of uridine-5'-monophosphate **31** and 2'-deoxycytidine-5'-monophosphate **32** in unstated yields (Scheme 19).[80]



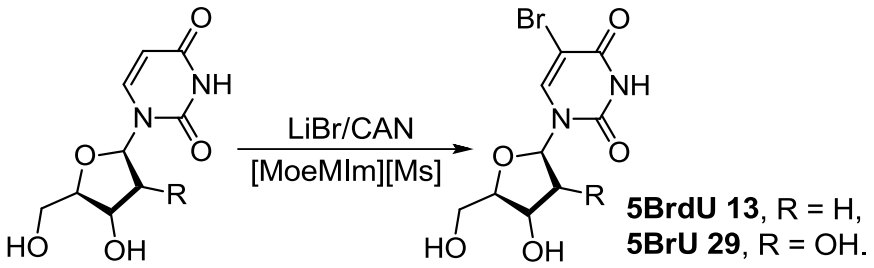
Scheme 19. Synthesis of 5-bromonucleotides **31** and **32** with use of $KBr/KHSO_5$ system.

Kawai *et al.* obtained **5BrdU 13** with the same synthetic protocol as for **5CldU 26** (Scheme 10). **5IdU 1**, photoirradiated with a transilluminator (302 nm) in an aqueous 4 M NaBr solution, was this time consumed to a greater extent of 87% giving **5BrdU 13** as the major product (48% yield) and 2'-deoxyuridine (39% yield) (Scheme 20).[68] In this case a halogen-exchange reaction dominated over the halogen-elimination process.

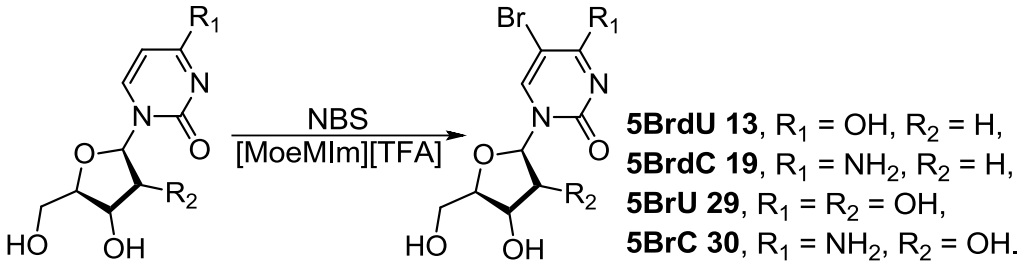


Scheme 20. Photochemical synthesis of **5BrdU 13** from **5IdU 1** by the presumed $S_{RN}1$ mechanism.

As it was described in section 2.1, ionic liquids are great media to perform halogenation reactions . With their help it was possible to obtain 5-bromo derivatives of nucleosides and 2'-deoxynucleosides in very good to excellent yields (80–98%) (Scheme 21 and 22). All the ionic liquids used in these methods were successfully recovered and reused in further reactions.[75,76]



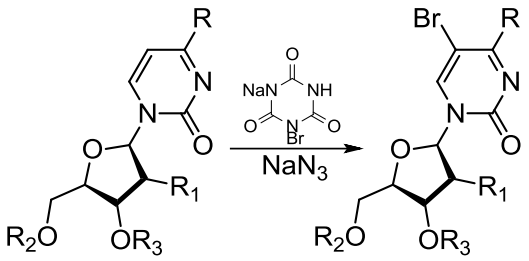
Scheme 21. Synthesis of 5-bromonucleosides **13** and **29** mediated by CAN in [MoeMIm][Ms].



Scheme 22. Synthesis of 5-bromonucleosides, **13**, **19**, **29**, **30**, in the presence of NBS in the ionic liquid – [MoeMIm][TFA].

Sodium monobromoisocyanurate (SMBI) is a commercially available reagent similar to NBS. It is a urea trimer and is expected to be environmentally friendly. In

2013, Maity and Stromberg published a facile application of SMBI, assisted by NaN_3, as a brominating system for pyrimidine nucleosides. The authors also investigated the reaction without the addition of NaN_3 to the reaction mixture, but they isolated the desired products in very low yields. N_3^- anion acts as a great leaving group at the C-6 position in *in situ* formed 5-bromo-6-azido-5,6-dihydro intermediates, similarly to the reaction pictured in Scheme 9. Researchers managed to obtain a series of 5-bromo derivatives in moderate to excellent yields (59–93%) (Scheme 23).[81] This method is applicable both to the protected and unprotected pyrimidine and purine nucleosides. Its unique advantage is the possibility to brominate the 4,4'-dimethoxytrityl (DMTr) or 4-methoxytrityl (MMTr) protected nucleosides, which is not possible with other synthetic protocols due to the lability of DMTr and MMTr protecting groups in acidic conditions. According to the authors it is the first literature example of bromination reaction of such type.

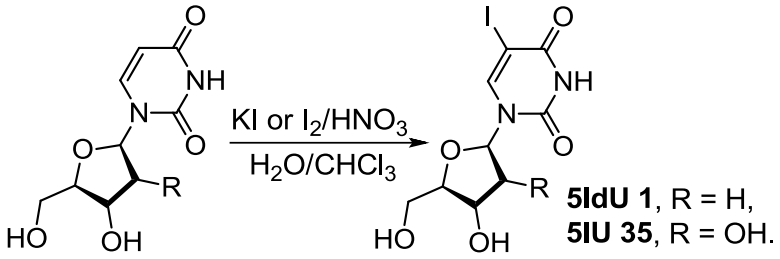


5BrdU 13, R = OH, R_1 = R_2 = R_3 = H,
5BrdC 19, R = NH_2, R_1 = R_2 = R_3 = H,
5BrU 29, R = OH, R_1 = OH, R_2 = R_3 = H,
5BrC 30, R = NH_2, R_1 = OH, R_2 = R_3 = H,
33, R = OH, R_1 = OCH_3, R_2 = R_3 = H,
34, R = NH_2, R_1 = OCH_3, R_2 = R_3 = H.

Scheme 23. Synthesis of 5-bromonucleosides (**13**, **19**, **29**, **30**, **33**, **34**) with use of SMBI/NaN_3 system.

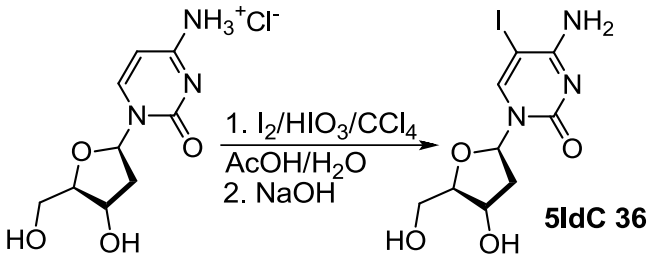
2.3. Iodination

First reports of successful iodination of pyrimidine nucleosides were published by Prusoff *et al.* Scientists synthesized 5-iodouridine (**5IU**) **35** and **5IdU 1** in 66 and 56% yields, respectively, by refluxing uridine or 2'-deoxyuridine with KI or I_2 for 2 h in an HNO_3 aqueous solution (Scheme 24).[7,82]



Scheme 24. Iodination of uridine and 2'-deoxyuridine with KI or I_2 in the presence of HNO_3 as an oxidizing agent.

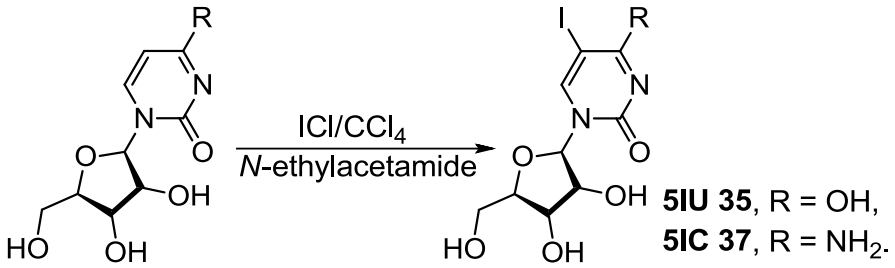
A very first synthetic procedure for obtaining 5-iodo-2'-deoxycytidine (**5IdC**) **36** was described in 1961.[83] In that time all known iodination systems, useful for uridines, led to the cleavage of *N*-glycosidic bond in cytidines. A breakthrough method was proposed by Chang and Welch. Iodic acid, chosen as the oxidizing agent, unlike citric acid, did not affect the *N*-glycosidic bond of a substrate. The authors mixed 2'-deoxycytidine hydrochloride, iodic acid, iodine and CCl_4 and stirred it in an AcOH aqueous solution (Scheme 25) for 1.5 h. After brief workup, a remaining residue was diluted in water and the pH was adjusted to 10. Raw product was crystallized from water to obtain **5IdC 36** in an overall 68% yield. The same procedure, starting from cytidine hemisulfate, was performed in order to obtain 5-iodocytidine (**5IC**) **37**.[84]



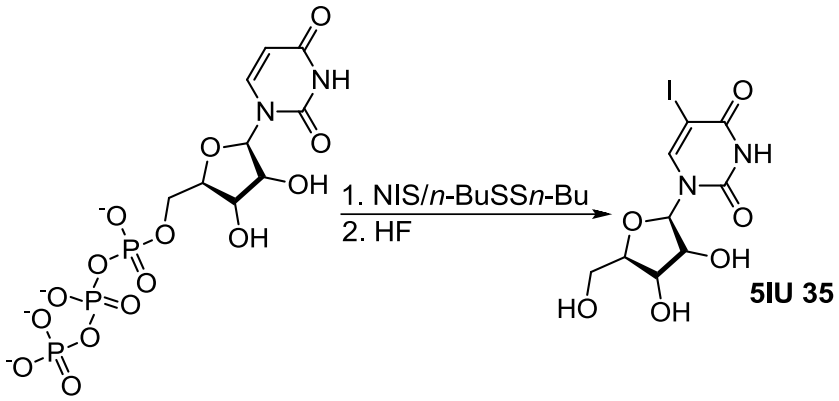
Scheme 25. First reported synthesis of **5IdC 36**.

5IU 35 and **5IC 37** were synthesized likewise *via* a treatment of uridine and cytidine with an iodine monochloride (ICl) solution in CCl_4 in *N*-ethylacetamide in an unstated and 85% yields, respectively (Scheme 26). Furthermore, the same group of researchers afforded **5IU 35** starting from uridine-5'-triphosphate in a tetraethylammonium salt, which underwent a reaction with *N*-iodosuccinimide (NIS)

in DMSO in the presence of *n*-butyl disulfide. The isolated product, 5-iodouridine-5'-triphosphate, was degraded by 60% HF acid (1 h, 0 °C) to provide **5IU 35** in an unstated yield (Scheme 27).[85]

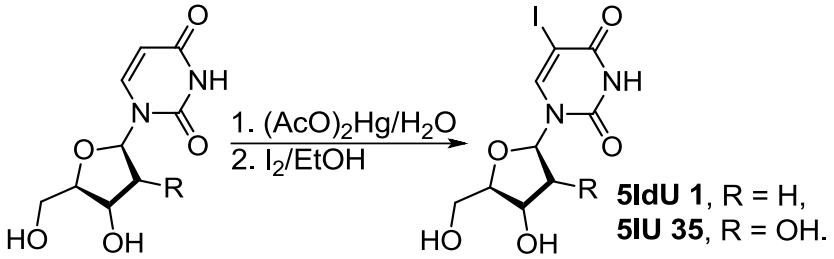


Scheme 26. Synthesis of **5IU 35** and **5IC 37** in the presence of ICl.



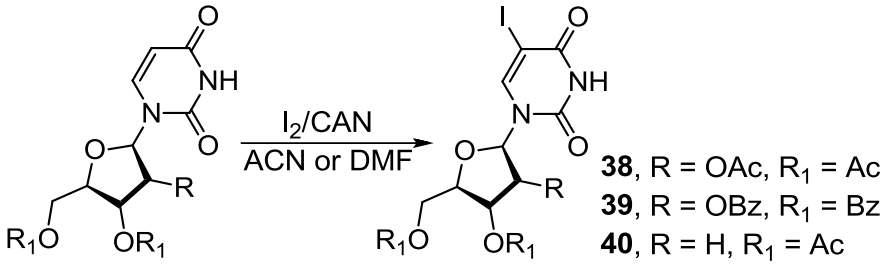
Scheme 27. Synthesis of **5IU 35** in the presence of NIS and *n*-butyl disulfide followed by the degradation with 60% HF.

An original, but inefficient attempt towards introducing the iodine at the C-5 position was shown by Dale *et al.* In the first step uridine or its 2'-deoxy analog were mercurated with mercuric acetate in sodium acetate aqueous solution. Mercuric derivatives, obtained in this manner, were subsequently iodinated with I_2 in ethanol affording the desired products **1** and **35** in poor yields (3%) (Scheme 28).[86]



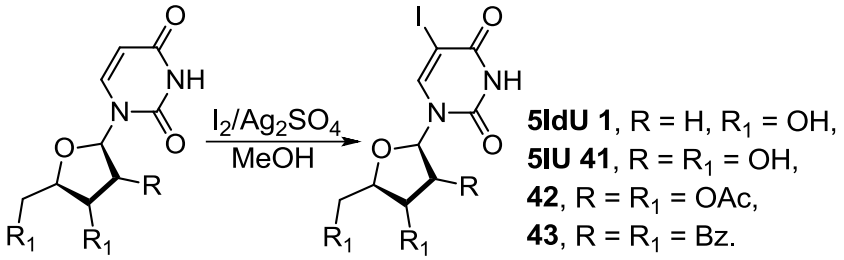
Scheme 28. Two-step iodination procedure for obtaining 5-iodouridines **1** and **35**.

In 1988, Asakura and Robins used, for the first time, CAN as a catalyst in the iodination reaction. Protected uridines were treated with iodine in the presence of CAN in ACN or DMF. Desired raw products were crystallized from ethanol to obtain compounds **38**–**40** in excellent yields (91–97%) (Scheme 29).[87] In ref. 66, cited in sections 2.1 and 2.2, the same authors broadened a variety of iodinating agents by introducing NaI an LiI without worsening yields of the desired products. LiI turned out to be as effective as I_2 within the same reaction time (1 h), whereas reactions with NaI lasted much longer, up to 8 h.



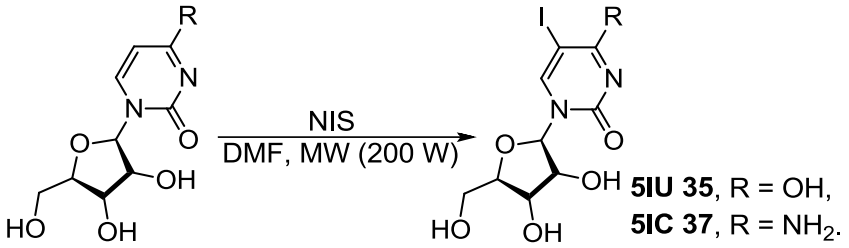
Scheme 29. Synthesis of 5-iodouridine derivatives **38**–**40** with use of the CAN approach.

Protected and unprotected uridines can be iodinated with I_2 in the presence of silver sulfate in MeOH. According to the authors, this facile and very fast protocol enables to obtain 5-iodo derivatives **1** and **41**–**43** in very good to excellent yields (71–98%) in usually less than 12 minutes (Scheme 30).[88]



Scheme 30. Synthesis of 5-iodouridines **1** and **41**–**43** with the I_2/Ag_2SO_4 system.

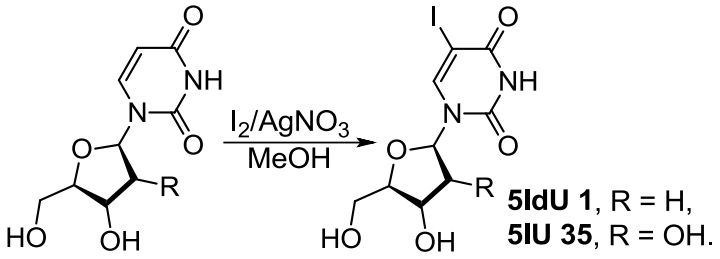
A very useful modification of the halogenation technique shown in Schemes 3 and 16 was reported in 2003. As it was discovered earlier, NIS is not reactive towards uridines nor cytidines comparing to NCS or NBS.[85] Apparently, when microwave-assisted, the reaction proceeded giving corresponding products **35** and **37** in very good 65 and 72% yields, respectively (Scheme 31).[89] The protection of 3'- and 5'-hydroxyl groups was not needed.



Scheme 31. Microwave-assisted iodination of uridine and cytidine with use of NIS.

5-Iodination of different pyrimidine nucleosides can also be performed in the same manner as presented in Schemes 12, 13, 21 and 22 with use of NIS or LiI/CAN system in ionic liquids.[75,76]

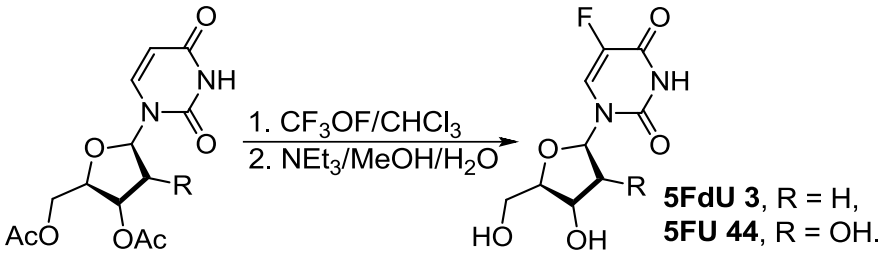
Recently a well-known mild $I_2/AgNO_3$ protocol was adapted to iodinate uridines.[90] Scientists obtained **5IU 1** and **5IdU 35** in quantitative yields (3 h, 40 °C), which were used as starting materials in further coupling reactions (Scheme 32).[91-93]



Scheme 32. Synthesis of 5-iodouridines **1** and **35** with the $I_2/AgNO_3$ system.

2.4. Fluorination

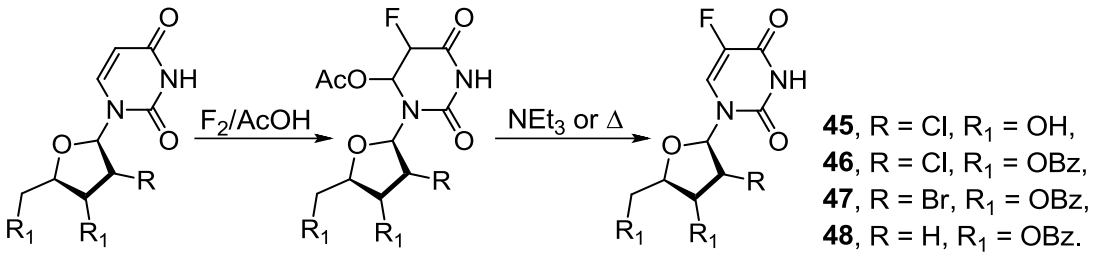
Robins and Naik presented the first, direct fluorination method for the synthesis of 5-fluoro nucleosides with use of trifluoromethyl hypofluorite as a fluorinating agent. Acetylated 2'-deoxyuridine or uridine were treated with CF_3OF in chloroform/fluorotrichloromethane solution at −78 °C. In the second step, upon the addition of triethylamine methanolic solution in water, a molecule of CF_3OH is eliminated and hydroxyl groups are simultaneously deprotected affording final products **5FdU 3** and 5-fluorouridine (**5FU**) **44** in 80 and 55% yields, respectively (Scheme 33).[94] This methodology was also successfully adapted to fluorinate cytidines.[95]



Scheme 33. Synthesis of 5-fluorouridines, **3** and **44**, with use of CF_3OF.

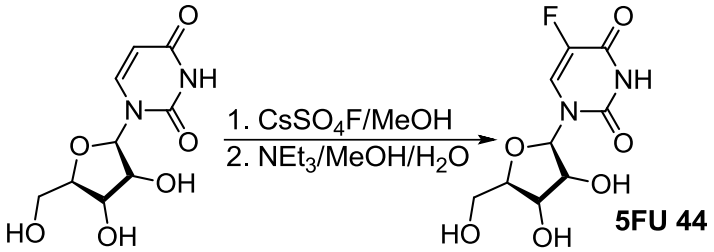
Protected or unprotected uridines can be transformed into their corresponding 5-fluoro-analogs with a solution of elemental fluorine in AcOH followed by heating or refluxing in NEt_3 (Scheme 34).[96] The reaction goes through the 5,6-dihydro-intermediate, generated *in situ*, which, upon the action of NEt_3, is converted to a final

product. Corresponding 5-fluoro derivatives **45**–**48** were isolated in moderate to very good yields (48–82%).



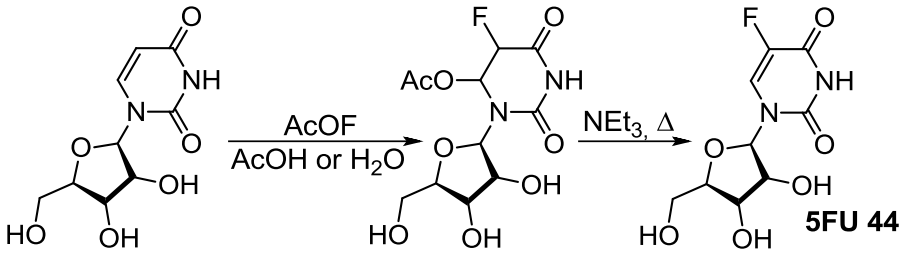
Scheme 34. Synthesis of 5-fluorouridines **45**–**48** with use of saturated solution of F_2 in AcOH.

Further development of fluorination techniques led to the discovery of caesium fluoroxysulfate ($CsSO_4F$) – a convenient and stable reagent for introducing the fluorine atom into the molecule's constitution at room temperature. $CsSO_4F$ was successfully used as a 5-fluorinating agent for uridine, which corresponds with the above-mentioned CF_3OF (both compounds are from the same hypofluorite family). $CsSO_4F$ mediated method allowed to obtain **5FU 44** in a 79% yield (Scheme 35).[97]



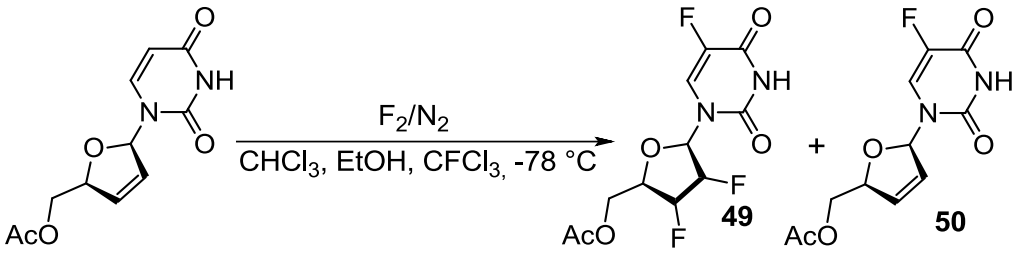
Scheme 35. Synthesis of **5FU 44** with use of $CsSO_4F$.

Another variation of the reaction of pyrimidine nucleosides with hypofluorites was proposed by Visser *et al.* This scientific team used acetyl hypofluorite to generate the 5,6-dihydro-intermediates, which are described as stable and possible to isolate using column chromatography. Such obtained 5-fluoro-6-acetoxy-5,6-dihydrouridine was then treated with NEt_3 to eventually give **5FU 44** (Scheme 36).[98] Moreover, the authors submitted a very interesting and in-detailed discussion of the stereochemistry of the 5,6-dihydro-intermediates that are furnished during this kind of reactions.



Scheme 36. Synthesis of **5FU 44** with use of AcOF.

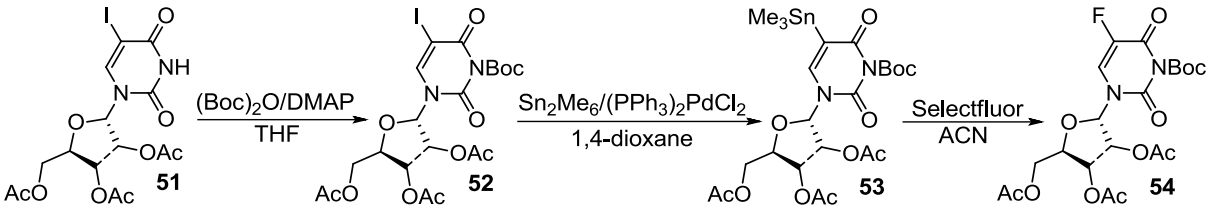
In 1994, Coe *et al.* proposed the direct fluorination reaction of 5'-*O*-acetyl-2',3'-didehydro-2',3'-dideoxyuridine in the presence of F_2 and EtOH as the proton donor (Scheme 37). The reaction proceeds through the electrophilic *syn*-addition to the 5,6-double bond[99] of the pyrimidine nucleoside. In this case, formed 5,6-dihydro-intermediates were impossible to isolate, which was in contrary to the reaction of uridines with the F_2/AcOH, as described in ref. 96, where such entities could be isolated in good yields. Moreover, the authors claimed that this was a first example of the stereospecific *cis*-addition of fluorine to 2',3'-double bond within the sugar moiety (see compound **49** in Scheme 37) and a first example of the reaction with elemental fluorine, where the *N*-glycosidic bond degradation was to a negligible extent.[100] According to this method compounds **49** and **50** were obtained in 15 and 32% yields, respectively.



Scheme 37. Synthesis of 5-fluorouridines **49** and **50** with use of elemental fluorine and EtOH as the proton donor.

Selectfluor is a specific fluorinating reagent and a trademark of Air Products and Chemicals. It is a derivative of 1,4-diazabicyclo[2.2.2]octane and was first described by Banks *et al.*[101] As a fluorine donor it was utilized for the

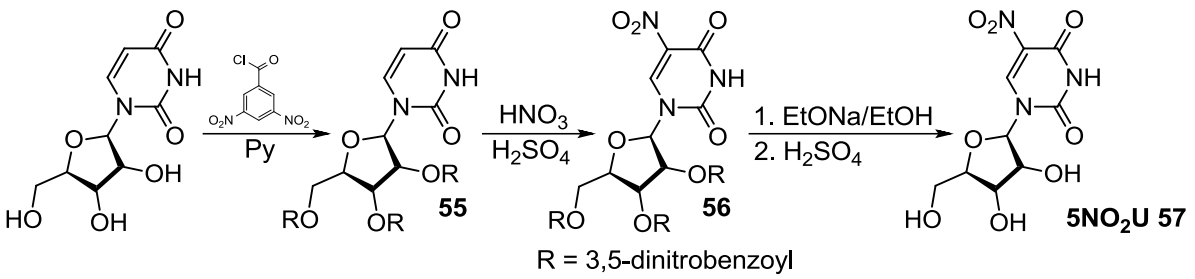
fluorodestannylation reaction of 3-*N*-Boc-5-trimethylstannyl-2',3',5'-tri-*O*-acetyl arabinosyl uridine **53**, prepared from its analog – 5-iodo-2',3',5'-tri-*O*-acetyl arabinosyl uridine **51**. In the first step compound **52** was Boc-protected (10% yield), then a stannyl moiety was introduced at the C-5 position in the presence of palladium catalyst (30% yield) and finally **53** was treated with the Selectfluor to provide 5-fluoro-analog **54** (Scheme 38) (30% yield).[102]



Scheme 38. Indirect fluorination of 2',3',5'-tri-*O*-acetyl-5-iodouridine **51** with use of Selectfluor.

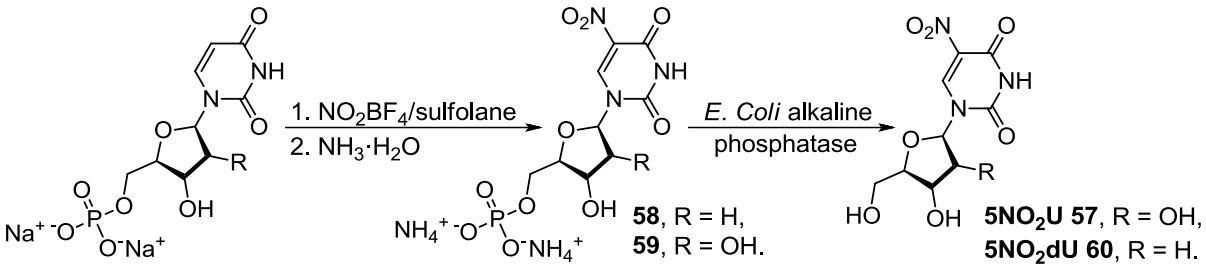
3. Nitration

A very first report of the nitration reaction at the C-5 position of uridine was published by Wempen *et al.*[103] The authors, just from the beginning, indicated the difficulties of introducing a nitro moiety into the structure of a pyrimidine nucleoside. They had to face a cleavage of the *N*-glycosidic bond as well as an oxidation of 4'-hydromethyl group to carboxyl moiety. In order to avoid these synthetic issues they protected the 2'-, 3'- and 5'-hydroxyl groups with a 3,5-dinitrobenzoyl chloride. Such protected derivative **55** was then nitrated in the fuming HNO_3 in the presence of H_2SO_4 affording 5-nitro-analog **56**, which was eventually deprotected with use of sodium ethoxide to give 5-nitrouridine (**5NO$_2$U**) **57** in an overall 43% yield (Scheme 39).



Scheme 39. A first example of an indirect 5-nitration of uridine **57** with use of the fuming nitric acid.

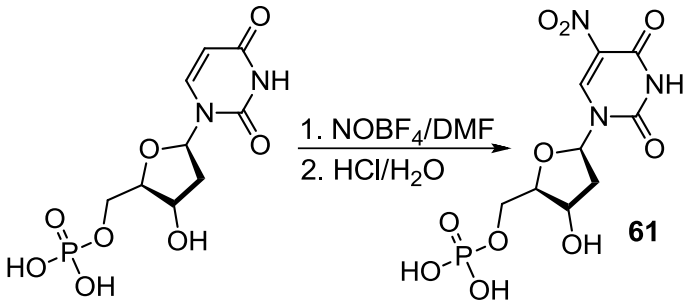
Another nitration method one can found in the chemical literature is concerned with nitronium tetrafluoroborate (NO_2BF_4). However, attempts of nitration of uridine and 2'-deoxyuridine with this mild reagent in sulfolane were unsuccessful. Even if the hydroxyl groups from a sugar moiety were protected with acetyls or isopropylidene, in all cases, the major product occurred to be 5-nitrouracil.[104] Similar nitrating conditions, applied to the 2'-deoxyuridine-5'-monophosphate or uridine-5'-monophosphate, followed by a conversion to their ammonium salts, led to the corresponding 5-nitro derivatives **58**–**59** in low to moderate yields (authors didn't indicate precise yields, they gave a range from 28 to 42%). In the next step, compounds **58**–**59** were enzymatically dephosphorylated with use of *Escherichia Coli* alkaline phosphatase, giving 5-nitro-2'-deoxyuridine (**5NO$_2$dU**) **60** in a 58% yield and **5NO$_2$U 57** in an unstated yield (Scheme 40).[104]



Scheme 40. Synthesis of 5-nitrouridines **57** and **60** with use of NO_2BF_4 and *E. Coli* alkaline phosphatase.

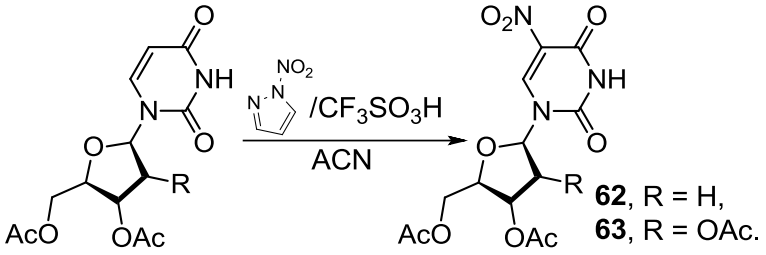
Two of the nitration methods described above caused an extensive cleavage of the *N*-glycosidic bond, which was a problem of great importance. Even if the

2'-, 3'- and 5'-hydroxyl groups were protected products were obtained in rather low to moderate yields. A nitrosating reagent – (nitrosonium tetrafluoroborate) $NOBF_4$ – was investigated against its capability of indirect introducing of a nitro group at the C-5 position of nucleosides.[105] It turned out that a short-term treatment (5 minutes) of 2'-deoxyuridine-5'-monophosphate, in its acid form, with an excess of $NOBF_4$ in anhydrous DMF gave, after acidification with HCl, 5-nitro-2'-deoxyuridine-5'-monophosphate **61** in an excellent 95% yield (Scheme 41). Moreover, the authors didn't exclude the possibility of a 3'-*O*-nitration product to arise, but by the use of short period reaction times, they eliminated it completely.



Scheme 41. Indirect synthesis of 5-nitro-2'-deoxyuridine-5'-monophosphate **61** with use of $NOBF_4$.

1-Nitropyrazole in the presence of Lewis or Brønsted acid is an efficient agent for nitration of aromatic compounds.[106] While investigating the mechanism of the reaction and the influence of the acid catalyst, it turned out that a triflic acid (CF_3SO_3H) can be used effectively in this procedure as well. According to the authors, a proper nitrating agent seems to be an *N*-protonated *N*-nitropyrazole, which transfers the nitro group to i.e. nucleosides. Giziewicz *et al.* performed successful attempts of nitrating the acetyl-protected uridine and 2'-deoxyuridine with 1-nitropyrazole/CF_3SO_3H system affording compounds **62** and **63** in 78 and 97% yields, respectively (Scheme 42).[107] However, despite excellent yields, the reaction is much more time-consuming than other methods. Disregarding the protection and deprotection phases, nitration step lasts for 72 h.

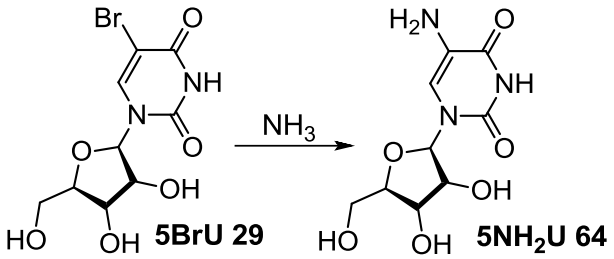


Scheme 42. Synthesis of 5-nitrouridines **62** and **63** with use of 1-nitropyrazole/CF_3SO_3H system.

According to the chemical literature, there are no examples of direct nitration of cytidines. Such compounds can be obtained i.e. through the S_n2 reaction of 4-mesyl-5-nitrouridines with ammonia in water[108] or by glycosylation of silylated 5-nitrocytosines with protected 1-chloropentofuranose[109].

4. Amination

The first literature example for the synthesis of 5-aminouridine (**5NH$_2$U**) **64** was reported by Roberts and Visser. **5BrU 29** was treated with liquid ammonia in a bomb tube for 5 days in 50 °C. After this time the tube was opened and NH_3 was removed by boiling it off. Raw product was crystallized from 2-propanol/H_2O mixture to furnish **5NH$_2$U 64** in a 63% yield (Scheme 43).[110]



Scheme 43. The first report for the synthesis of **5NH$_2$U 64**.

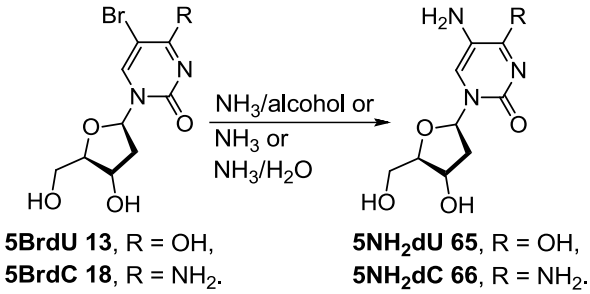
The first synthesis of 5-amino-2'-deoxyuridine (**5NH$_2$dU**) **65** was published in *The Journal of Biological Chemistry*. Beltz and Visser treated **5BrdU 13** with liquid ammonia in anhydrous alcohol for 7 days in 55 °C. They obtained raw product **65**,

which was crystallized from anhydrous alcohol to provide **5NH$_2$dU 65** in a very poor 8% yield (Scheme 44).[111]

Later scientists modified this reaction by using 3–4 times more of liquid ammonia (8 mL for 1 g of a substrate) without using alcohol as a solvent at the same time. It resulted in shortening the reaction time from 7 days to 24 h and the yields of **5NH$_2$dU 65** were significantly improved (up to 74%) (Scheme 44).[112] It is worth noting that **5NH$_2$dU 65** was purified here on a preparative column chromatography and the yield suggests, that previously mentioned purifying method (crystallization) may not be suitable. Nevertheless, such improvement of the yield with shortening the reaction time and keeping almost identical condition of the process at the same time may surprise.

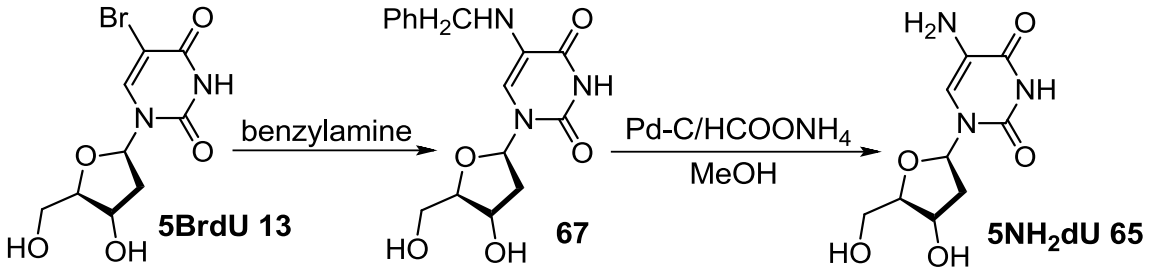
It is also possible to obtain **5NH$_2$dU 65** in a very poor 6% yield by treating **5BrdU 13** with ammonia aqueous solution in a screw cap vial for 4 days in 55 °C (Scheme 44).[113] Furthermore, the authors mentioned, without giving any details, that the same synthetic procedure performed on the **5IdU 1** gave **5NH$_2$dU 65** as well. From the synthetic point of view this method is not recommended. Ferrer *et al.* only investigated this in order to explain problems, which they faced during the deprotection reactions of the oligonucleotides obtained by using the phosphotriester method. According to them, lowering the temperature of the reaction to 37 °C prevented 5-halogenouridines from an undesirable substitution with amino moiety.

In 2010, 5-amino-2'-deoxycytidine (**5NH$_2$dC**) **66** was obtained by Barawkar *et al*. successfully using the similar protocol described by Beltz and Visser[112] **5NH$_2$dC 66** was isolated with use of the flash column chromatography in a 38% yield as pale-yellow solid (Scheme 44).[114]



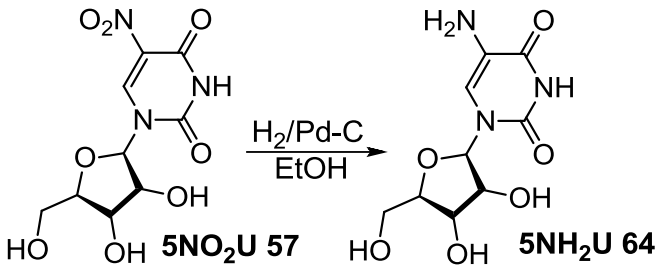
Scheme 44. Synthesis of **5NH$_2$dU 65** and **5NH$_2$dC 66** from their 5-bromo-analogs.

A great alternative for the reactions presented in Scheme 44 is a benzylamination/reduction approach. **5BrdU 13**, when heated with benzylamine, gives 5-benzylamino-2'-deoxyuridine **67**. Subsequent hydrogenolysis of **67** in the presence of Pd-C catalyst and ammonium formate, led to **5NH$_2$dU 65** quantitatively (Scheme 45).[115] The advantages of this procedure over the nucleophilic substitution of a halogen atom with ammonia are as follows: a) yields are improved from poor/moderate to quantitative; b) there is no need to handle with liquid ammonia; c) long lasting processes are shortened to overall 5–6 h.



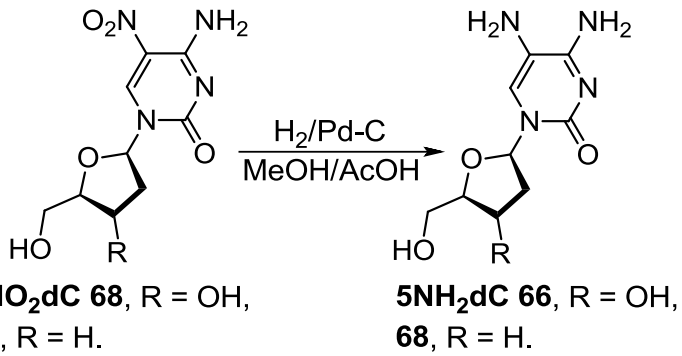
Scheme 45. Synthesis of **5NH$_2$dU 65** through the benzylamination/reduction approach.

A distinct methodology for synthesizing the 5-amino-substituted nucleosides is the reduction of 5-nitro derivatives. One of the first examples of such reaction was described in ref. 103. **5NO$_2$U 57** underwent a hydrogenation on the Pd-C catalyst in ethanol. Raw product was crystallized from 2-propanol/H_2O mixture to obtain **5NH$_2$U 64** in a 22% yield (Scheme 47).



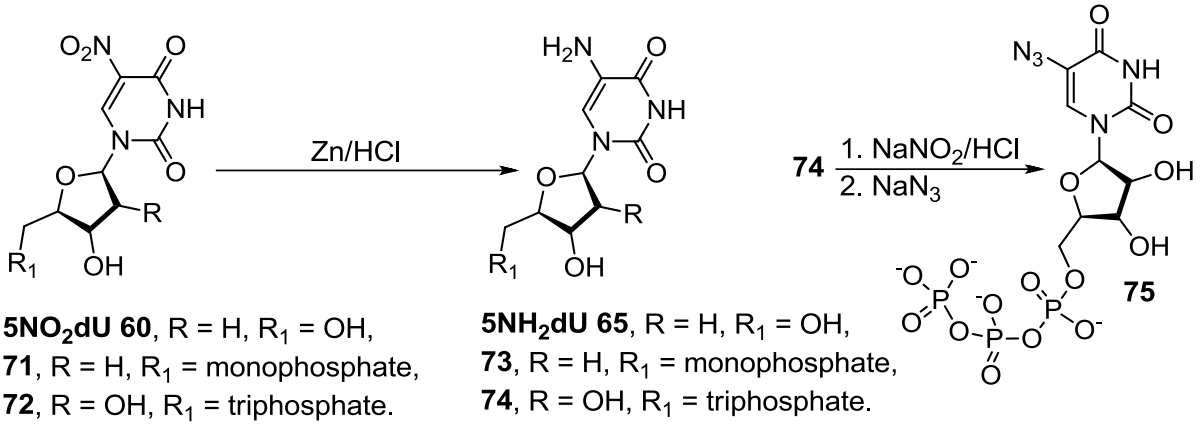
Scheme 47. Hydrogenation of **5NO$_2$U 57** on the Pd-C catalyst.

Not only 5-nitrouridines can be converted to 5-amino-analogs by using H_2/Pd-C system, 5-nitrocytidines are susceptible to these reaction as well. Compounds **5NH$_2$dC 66** and **70** were synthesized in 95 and 85% yields by treating 5-nitro-2'-deoxycytidine (**5NO$_2$dC**) **68** or 5-nitro-2',3'-dideoxycytidine **69** with H_2/Pd-C in methanol (in case of **5NO$_2$dC 68** an addition of AcOH was used) (Scheme 48).[109]



Scheme 48. Hydrogenation of 5-nitrocytidines **68** and **69** on the Pd-C catalyst.

The third type of reduction of a nitro group at the C-5 position in nucleosides, found in the literature, is a widely used Zn/HCl method. The reduction of 5-nitrocytidines with this protocol is problematic due to the instant protonation of the amino group present in the pyrimidine base of cytidine. Therefore the only examples one can find are associated with 5-nitrouridines. On the other hand, the first thing noteworthy is that the Zn/HCl method can be adapted to both uridine nucleosides and nucleotides. Treating **5NO$_2$dU 60**,[115] 5-nitro-2'-deoxyuridine-5'-monophosphate **71**[116] or 5-nitrouridine-5'-triphosphate **72**[117] with granulated zinc in HCl gave corresponding 5-amino-analogs **5NH$_2$dU 65** and **73–74** in 60–70% (overall yield for conversion of 5-nitrouridine-5'-monophosphate to compound **71**, calculated on the basis of known extinction coefficient) and 37% (overall yield for conversion of uridine-5'-triphosphate to 5-azidouridine-5'-triphosphate **75**), respectively (Scheme 49). Compound **74** was additionally transformed into its 5-azido derivative **75** *via* the *in situ* creation of a diazonium salt followed by the addition of NaN_3.

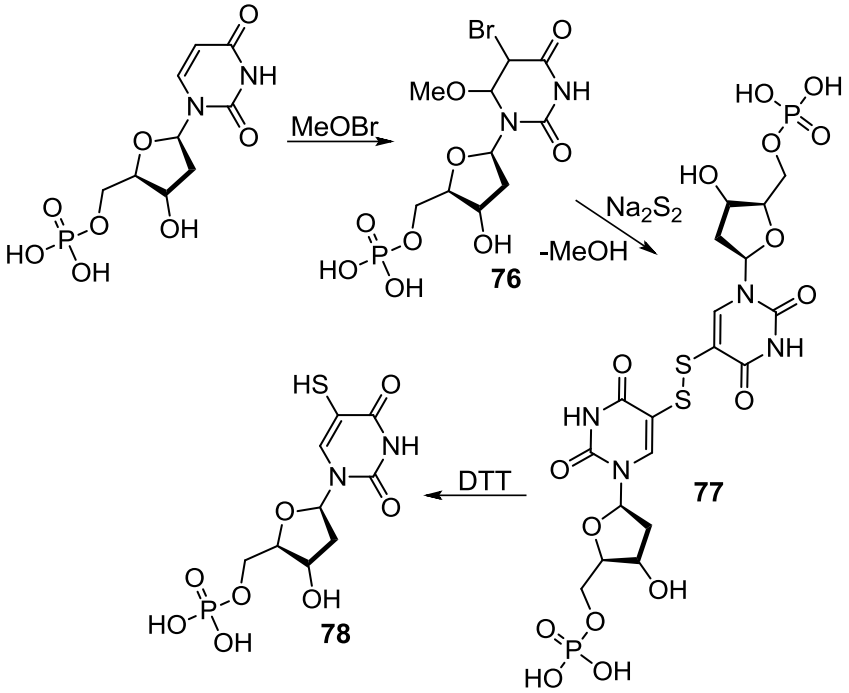


Scheme 49. Reduction of **5NO$_2$dU 60** and 5-nitronucleotides **71**–**72** with use of Zn/HCl system and synthesis of 5-azido derivative **75**.

5. Sulfanylation, selenylation and telluration

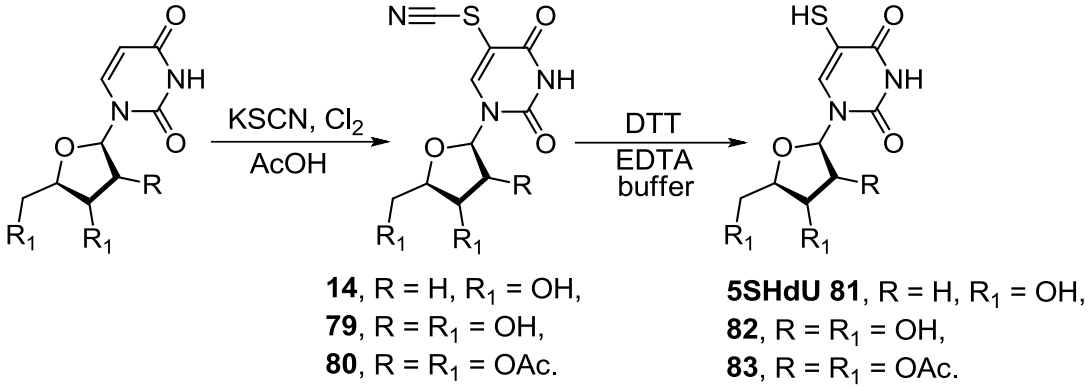
5.1. Sulfanylation

The very first attempts for obtaining 5-mercapto-analogs of nucleosides engaged chemical or enzymatical glycosylation of an appropriate modified base with a modified sugar moiety.[118119] The earliest example of the direct sulfanylation at the C-5 position in pyrimidine nucleosides found in the literature comes from 1970.[120] 2'-deoxyuridine-5'-monophosphate treated with methyl hypobromite (MeOBr) gave 5,6-dihydro-intermediate **76**, which was isolated and crystallized from MeOH/Et$_2$O mixture. Upon the reaction with sodium disulfide, compound **76** was transformed to **77**. Further treatment with dithiothreitol (DTT) resulted in a fast reduction to 5-mercapto-2'-deoxyuridine-5'-monophosphate **78** in an overall yield of 68% (Scheme 50).



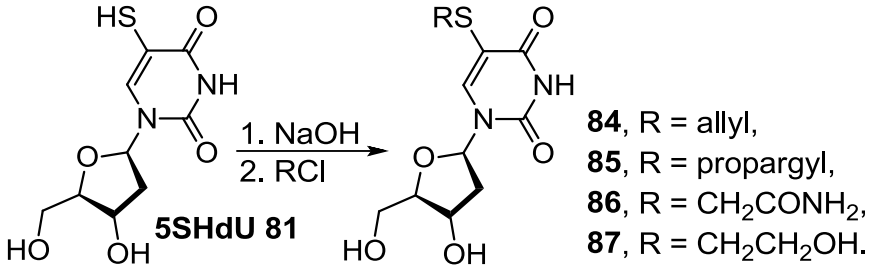
Scheme 50. Synthesis of 5-mercapto-2'-deoxyuridine-5'-monophosphate **78** from 2'-deoxyuridine-5'-monophosphate.

In 1972, Nagamachi *et al.* proposed the synthesis of 5-thiocyanato-analogs **14** and **79**–**80** with subsequent possibility of their reduction to 5-mercapto derivatives **81**–**83**.[121] In the first step, uridine derivatives were added to a mixture of glacial acetic acid and potassium thiocyanate, saturated with an appropriate amount of chlorine gas. Thiocyanogen chloride, generated *in situ* in this reaction, is the appropriate thiocyanating agent. After 1 h, the reactions were quenched upon the addition of cyclohexene and raw 5-thiocyanato-analogs **14** and **79**–**80** were crystallized from ethanol to furnish pure products in 48–96% yields (Scheme 51). The highest yield (96%) was reached for the 2',3',5'-tri-*O*-acetyl-protected uridine **80**. Subsequent reduction of 5-thiocyanatouridines was performed with DTT in EDTA buffer in 2-minute reaction time to furnish 5-mercapto derivatives **81**–**83** in unstated yields (Scheme 51).



Scheme 51. Synthesis of 5-thiocyanato and 5-mercapto analogs of uridine **81**–**83**.

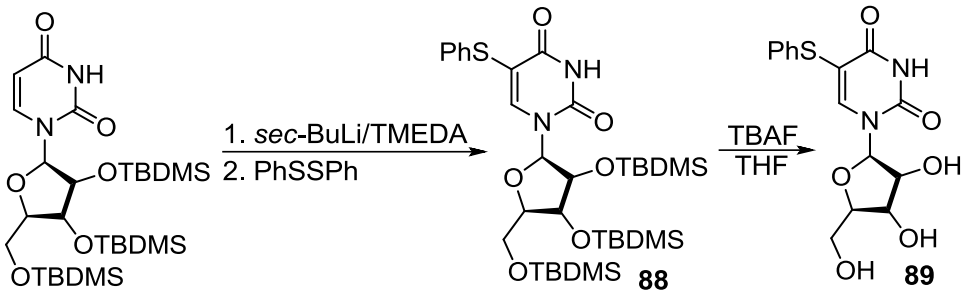
Among the sulfur derivatives of pyrimidine nucleosides, particular attention was paid to their 5-(alkylsulfanyl) analogs. Several different centers, where the alkylation reaction can proceed in nucleosides, makes this process difficult to perform. Taking into account the fact that a proton from the thiol group at the C-5 position is more acidic than protons from the 2'-deoxyribose moiety, it is possible to quantitatively generate the 2'-deoxyuridyl sulfide anion with sodium hydroxide without protecting the 3'- and 5'-hydroxyl groups at the same time. Such anion underwent the alkylation reaction with different alkyl halides, to provide compounds **84**–**87** in very good 78–90% yields (Scheme 52).[122]



Scheme 52. Synthesis of 5-(alkylsulfanyl) derivatives of 2'-deoxyuridine **84**–**87**.

It is also possible to furnish 5-substituted uridine derivatives using a lithiation reaction. Lithiation at the C-5 or C-6 positions is strongly affected by the chemical constitution of a nucleoside. For example, a reaction between 2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine and lithium diisopropylamide (LDA) gives mostly C-6 lithiated product, whereas 2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)uridine provides no

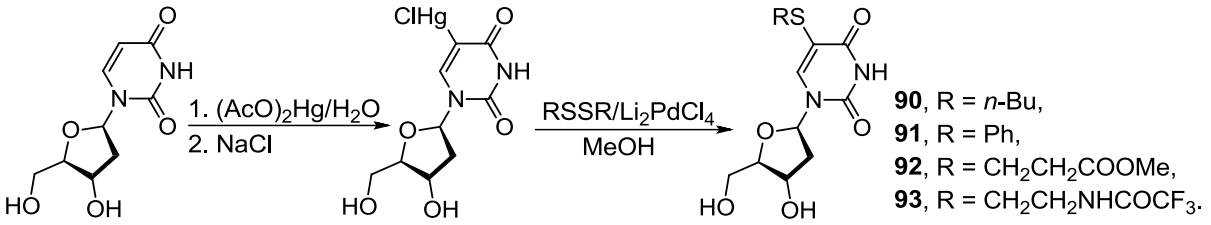
lithiation products when treated with LDA. The reason for that is twofold: a) too low basicity of LDA to deprotonate the H-5 and b) the C-6 position is not available due to sterical issues triggered by the 2'-*O*-*tert*-butyldimethylsilyl (2'-*O*-TBDMS) protecting group. Lithiation at the C-5 position of 2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)uridine with *sec*-BuLi, much stronger base than LDA, in the presence of *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) followed by subsequent reaction with PhSSPh led to the 2',3',5'-protected 5-phenylthiouridine **88** (Scheme 53) in a 66% yield. It is worth noting that researchers managed to reach C-5 lithiation levels up to 86% when using *sec*-BuLi/TMEDA system. The removal of the protecting groups could be finally performed by treating compound **88** with TBAF in THF to obtain 5-phenylthiouridine **89** in a 90% yield.[123]



Scheme 53. Synthesis of 5-phenylthiouridine **89** with use of *sec*-BuLi/TMEDA system.

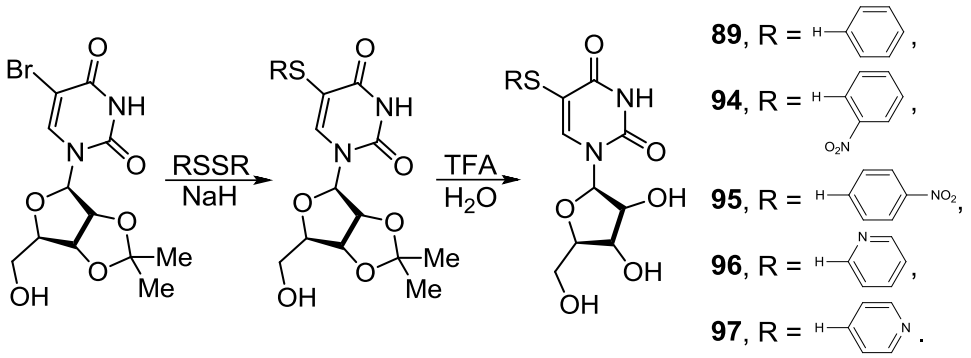
Another way to introduce the alkyl- or arylsulfanyl substituent into the nucleoside structure is the reaction of 5-mercurated analogs with disulfide in the presence of lithium palladium chloride. 5-Mercurinucleosides are easily available *via* a reaction of a corresponding nucleoside with mercury acetate in water.[124] In 1989, Bergstrom *et al.* used this methodology to synthesize derivatives of 2'-deoxyuridine **90**–**93**. Treating 5-chloromercuri-2'-deoxyuridine with dialkyl or diphenyl disulfides in the presence of 1 equivalent of Li_2PdCl_4 in methanol overnight led to obtain the corresponding analogs **90**–**93** in moderate (46–73%) yields (Scheme 54).[125] May it be mentioned that when authors used more polar disulfides – like 3,3'-dithiodipropionic

acid or 2,2-dithiodiethanol – 2 equivalents of Li_2PdCl_4 were needed to initialize the reactions.

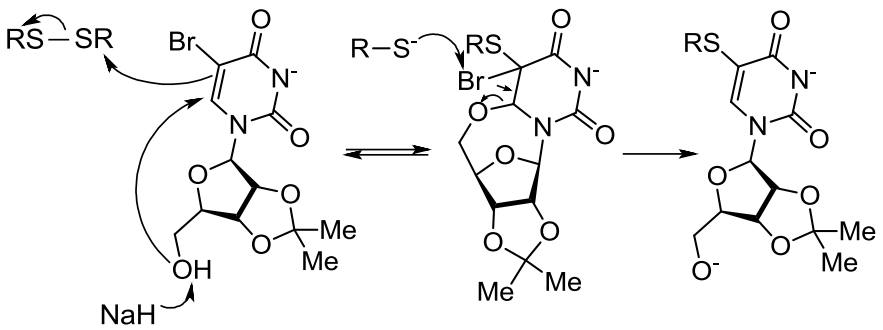


Scheme 54. Indirect synthesis of 5-(alkyl/arylsulfanyl) derivatives of 2'-deoxyuridine **90**–**93**.

To synthesize 5-(arylsulfanyl) derivatives of uridine one can start from 2',3'-*O*-isopropylidene-5-bromouridine. Its reaction with disulfides in the presence of sodium hydride in dry DMF gave a series of 5-(arylsulfanyl) derivatives **89** and **94**–**97** in 27–81% yields (Scheme 55).[126] Diaryl disulfides bearing strong electron-withdrawing substituents in the aryl rings (i.e. NO_2 group) reacted much faster than their diphenyl or di-2-pirydynyl analogs (1 h comparing to 48 and 72 h). The authors devoted a great deal of effort trying to explain the possible mechanism of this reaction. They evaluated the effect of 1-*N* substituent on the process and came to the conclusion that the influence of 5'-OH group in 2'-deoxyribose or the 2'-OH group in the β-D-arabinofuranose is crucial. After deprotonation, these moieties are involved in the nucleophilic attack to form the O^6,5'- or O^6,2'-cyclo-5,6-dihydro-carboanion intermediates, which are then stabilized by the reaction with electrophiles. Subsequent debromination and β-elimination give the final product. What's interesting, even the non-brominated 2',3'-*O*-isopropylideneuridine or 1-β-D-arabinofuranosyluracil could undergo this type of reaction (the only mechanistic difference is attributed to the deprotonation reaction instead of debromination). The proposed mechanism of the described reaction presented by researchers is presented in Scheme 56.

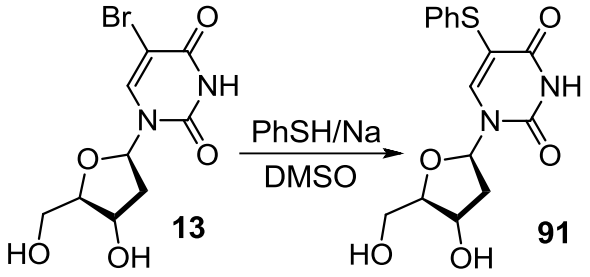


Scheme 55. Synthesis of 5-(arylsulfanyl) derivatives of uridine **89** and **94**–**97**.



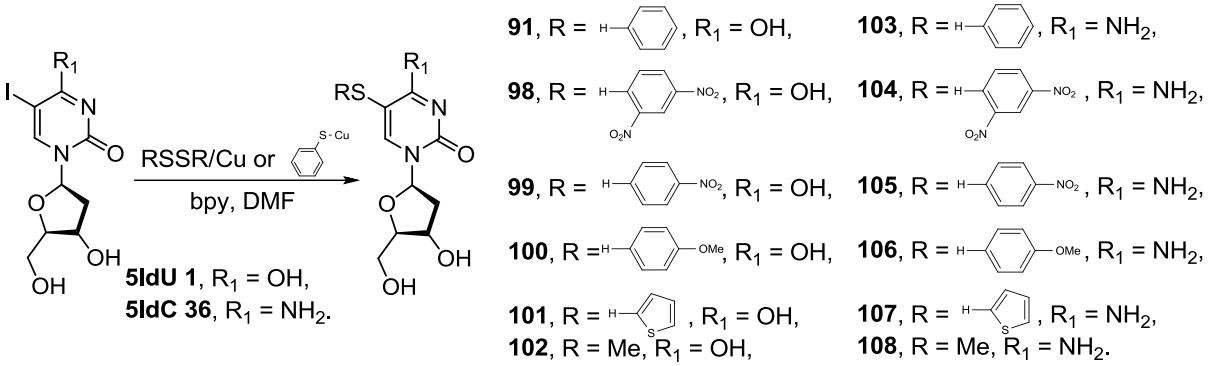
Scheme 56. The plausible mechanism for the synthesis of 5-(arylsulfanyl) derivatives of uridine.

In 2006, Zeng *et al.* used thiophenol (PhSH) in the presence of sodium in DMSO to obtain 5-phenylthio-2'-deoxyuridine **91** in a 47% yield starting from **5BrdU 13** (Scheme 57).[127] This reaction is very interesting from the mechanistic point of view. Sodium reacts with PhSH and DMSO at the same time giving sodium thiophenolate and dimsyl sodium, respectively. Taking into account the work of Nampalli *et al.*[128] it is expected that when the ratio of PhSH to DMSO is 1 : 3, the major product would be 5-dimsyl-2'-deoxyuridine but when the ratio is changed to 3 : 2; 5-phenylthio-2'-deoxyuridine **91** is obtained in majority. The function of DMSO is twofold: a) it supports the solubility of **5BrdU 13** and b) it solvates sodium cations, what makes the thiophenolate anions more reactive.

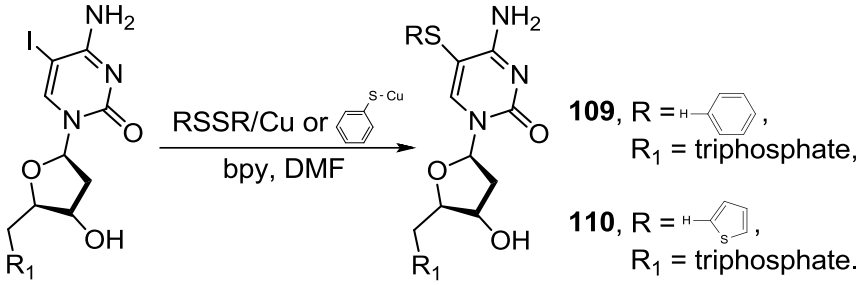


Scheme 57. Synthesis of 5-phenylthio-2'-deoxyuridine **91** with use of PhSH/Na system in DMSO.

One of the latest approach towards modifying the pyrimidine base in nucleosides with an alkyl/arylsulfanyl moiety is the Cu-promoted sulfanylation.[129] Unprotected **5IdU 1** and **5IdC 36** treated with dialkyl- or diaryldisulfides/Cu or copper(I) thiophenolate, in the presence of 2,2'-bipyridine (bpy) in DMF at 80–120 °C for 1–8 h, furnished the corresponding derivatives **91**, **98**–**108** in poor to moderate yields (18–58%) (Scheme 58). The same methods were adapted for modification of 5-iodo-2'-deoxycytidine-5'-triphosphate in 7 and 24% yields, respectively (compounds **109**–**110**, Scheme 59). The yields for **109**–**110** were poor but, according to the authors, it was the first time to modify 2'-deoxycytidine-5'-triphosphate in this way in the chemical literature (Scheme 59).



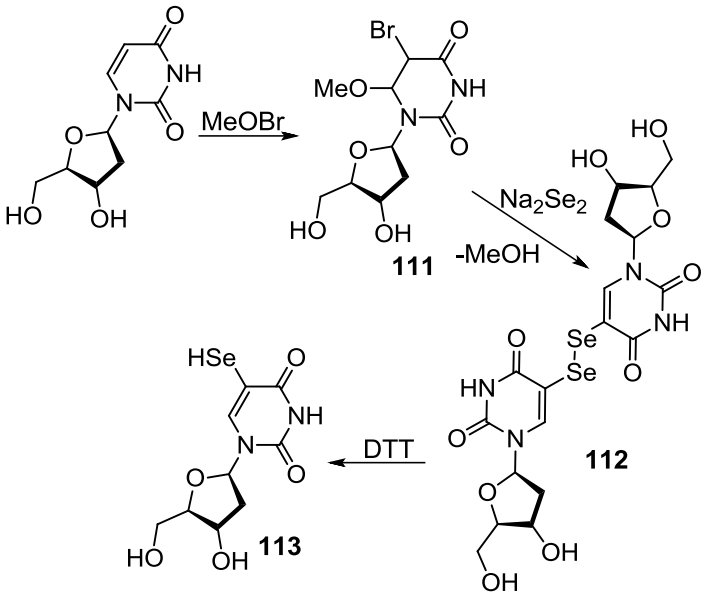
Scheme 58. Synthesis of compounds **91**, **98**–**108** with use of Cu-mediated alkyl/arylsulfanylation.



Scheme 59. Synthesis of 5-arylsulfanyl-2'-deoxycytidine-5'-triphosphates **109**–**110**.

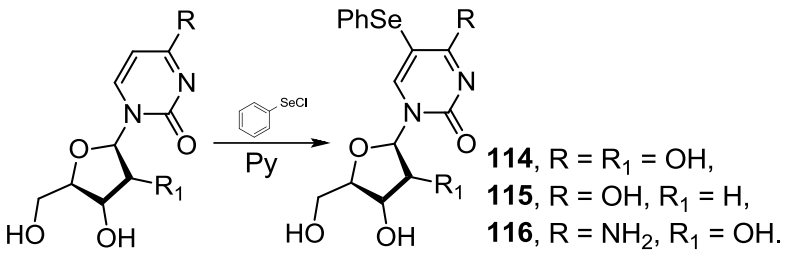
5.2. Selenylation

First report about 5-selenium-substituted derivatives of uridine comes from the same research group that described the first chemical method for sulfanylation of uridines in 1970.[120] Similarly, 2'-deoxyuridine was treated with methyl hypobromite (MeOBr) to provide the 5,6-dihydro-intermediate **111**, which upon the reaction with sodium diselenide converted to **112**. Subsequent reduction with DTT resulted in 5-hydroseleno-2'-deoxyuridine **113** (Scheme 60). However, authors didn't isolate it, admitting that such hydroseleno derivatives were slowly decomposing upon acidic conditions, which made a purifying process more difficult.[130] The arise of compound **113** was confirmed by IR and ^{1}H NMR spectroscopy and by a comparison with similar spectra collected for corresponding thioanalog **78** (see Scheme 50).



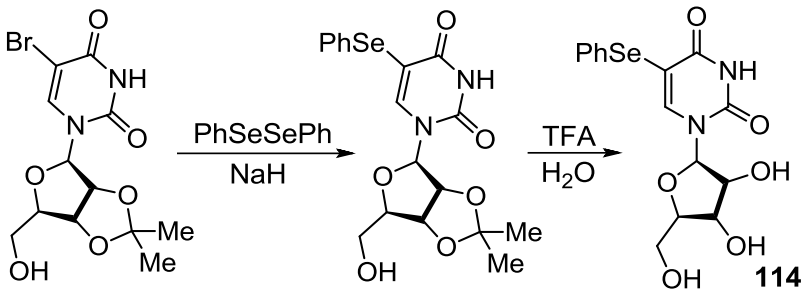
Scheme 60. The first chemical *in situ* synthesis of 5-hydroseleno-2'-deoxyuridine **113**.

Schinazi *et al.* proposed direct synthesis of 5-phenylselenenyl analogs of uridine and cytidine by treating nucleoside substrates with phenylselenenyl chloride in pyridine. After 24 h desired products **114**–**116** were isolated from reactions mixtures in 38–49% yields (Scheme 61).[131] Although a mechanism of this process is unknown, a very good article by Zima and Liotta concerning a discussion over the reaction of unsaturated ketones with phenylselenenyl chloride in pyridine can shed some light on its mechanistic aspects.[132] A plausible mechanism comprises: a) a nucleophilic attack of pyridine at the C-6 position followed by enolization, b) electrophilic attack of phenylselenenyl chloride at the C-5 position and c) elimination of pyridinium hydrochloride.



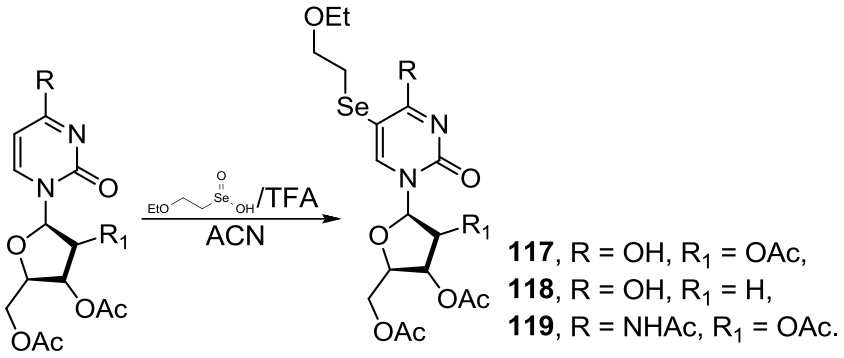
Scheme 61. Direct synthesis of 5-phenylselenenyl derivatives **114**–**116**.

It is also possible to introduce the phenylselenenyl moiety at the C-5 position of pyrimidine nucleosides *via* an approach presented earlier in this paper.[126] In this case 2',3'-*O*-isopropylidene-5-bromouridine treated with diphenyl diselenide in the presence of NaH at 90 °C gave, after deprotection, the desired 5-phenylselenouridine **114** in a 43% yield (Scheme 62).

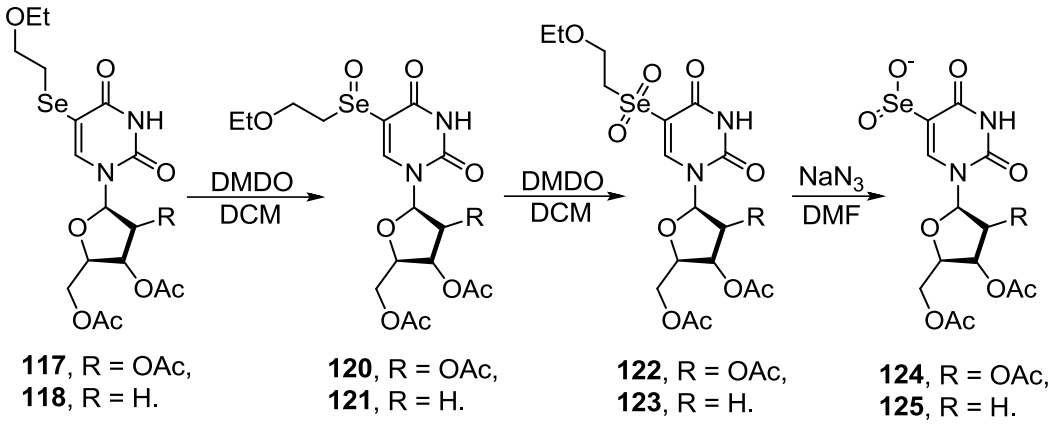


Scheme 62. Synthesis of 5-phenylselenouridine **114**.

A very interesting work was published in 2010 by Abdo *et al.* Based on their own experience with alkaneseleninic acids as great electrophiles towards phenols or indols,[133134] they managed to adapt this procedure to nucleosides. Reactions between 2-ethoxyethaneseleninic acid and appropriate acetyl-protected nucleosides in the presence of catalytic amounts of TFA gave the corresponding products **117**–**120** in 46–61% yields (Scheme 63). Authors decided also to alter the conditions of the reaction to water. This time they used the non-protected substrates to afford final products in similar to slightly better yields (38–71%) comparing to the results achieved in ACN. Furthermore, compounds **117** and **118** were oxidized with dimethyldioxirane (DMDO) to corresponding selenoxides **120**–**121** and selenones **122**–**123**. Additionally, selenones were transformed into seleninic acids **124**–**125** *via* nucleophilic dealkylation with use of NaN_3 in DMF (Scheme 64).[135]

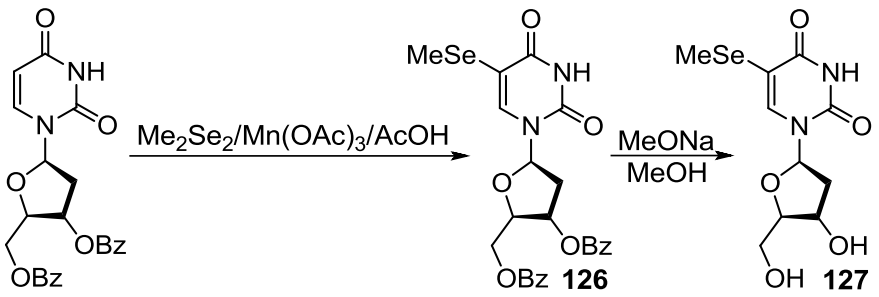


Scheme 63. Synthesis of 5-selenoethers **117**–**119** from acetyl-protected nucleosides.



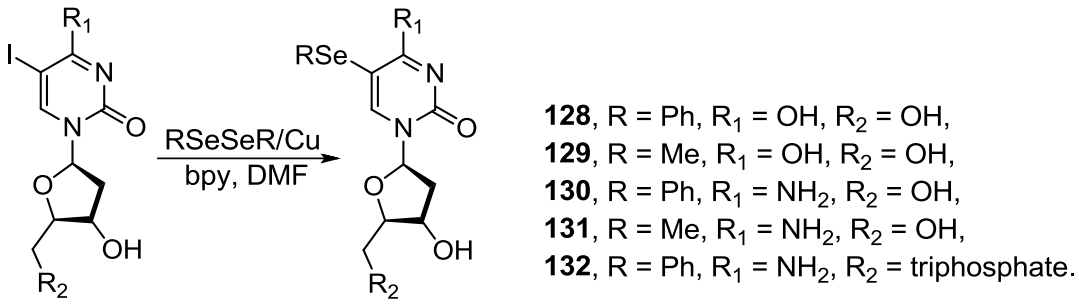
Scheme 64. Transformations of 5-selenylated compounds **117**–**118** to their corresponding sulfoxides **120**–**121**, selenones **122**–**123** and seleninic acids **124**–**125**.

A first report concerning synthesis of 5-alkylselenyl nucleosides comes from 2009. Hassan *et al.* screened several Lewis acids to find the best agent, that could interact with dimethyldiselenide to initiate the alkyl selenylation process. It turned out that manganese(III) acetate was the most effective. Treating 3',5'-di-*O*-benzoyl-2'-deoxyuridine with MeSeSeMe in the presence of $Mn(OAc)_3$ in AcOH at 90 °C for 36 h afforded the 5-methylselenyl analog **126** in a 56% yield (Scheme 65).[136] To furnish the non-protected 5-methylseleno derivative **127**, quantitative removal of the protecting groups with MeONa in MeOH was performed.



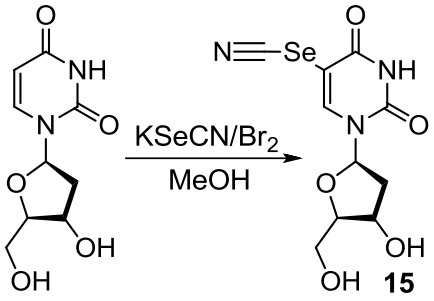
Scheme 65. Direct 5-alkyl selenylation of 3',5'-di-*O*-benzoyl-2'-deoxyuridine with use of $Mn(OAc)_3$.

It is also possible to modify the C-5 position of nucleosides and nucleotides with the similar methodology to that described in section **5.1**.[129] Treating **5IdU 1** or **5IdC 36** with diphenyl- or dimethyldiselenide in the presence of Cu and bpy in DMF, gave the corresponding 5-substituted analogs **128**–**131** in 11–50% yields (Scheme 66). The same reaction applied to 5-iodo-2'-deoxycytidine-5'-triphosphate afforded its 5-selenylated derivative **132** in a 34% yield (Scheme 66).



Scheme 66. Synthesis of 5-alkyl/arylseleno nucleosides **128**–**131** and nucleotide **132** with use of Cu/bpy system.

In 2018, Rak's research team managed to synthesize 5-selenocyanato-2'-deoxyuridine **15**. They adapted a selenocyanation method published by Agenäs.[137] A reaction between 2'-deoxyuridine and a cyanogen $(SeCN)_2$ – obtained *in situ* from KSeCN and Br_2 – in MeOH gave the 5-selenocyanato derivative **15** in a very poor 6% yield (Scheme 67). Such yield value was probably due to very weak solubility of 2'-deoxyuridine in MeOH and thus, its low conversion.[40]

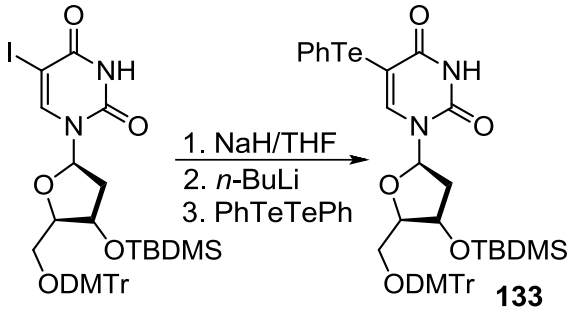


Scheme 67. Synthesis of 5-selenocyanato-2'-deoxyuridine **15** with use of KSeCN/Br_2 system.

5.3. Telluration

The only literature report concerning 5-telluro nucleoside derivatives comes from 2011. Sheng *et al.* synthesized 3'-*O*-TBDMS-5'-DMTr-5-phenyltelluro-2'-deoxyuridine **133** by treating 3'-*O*-TBDMS-5'-DMTr-5-iodo-2'-deoxyuridine with NaH, *n*-BuLi and finally with PhTeTePh (Scheme 68). Compound **133** was isolated in a 64% yield. It is noteworthy that in the purification step authors had to face the

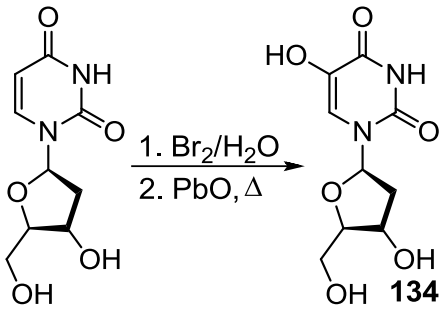
problem of separating the desired product from its 6-PhTe isomer. Furthermore **133** was converted to its 3'-phosphoramidite derivative and, in the next step, was coupled to a previously designed DNA sequence in an overall yield of about 71%.[138]



Scheme 68. Synthesis of 3'-*O*-TBDMS-5'-DMTr-5-phenyltelluro-2'-deoxyuridine **133**.

6. Hydroxylation

The first report for the synthesis of 5-hydroxy-2'-deoxyuridine (**5OHdU**) **134** was submitted by Beltz and Visser.[139] Researchers treated 2'-deoxyuridine with bromine water, followed by subsequent addition of lead(II) oxide. Heating at reflux for 30 minutes followed by chilling to 0 °C resulted in precipitation of lead(II) bromide. The final product **134** was isolated in a 30% yield (Scheme 69). Due to the fact that a chemist has to handle with toxic lead(II) compounds, this method is not recommended.

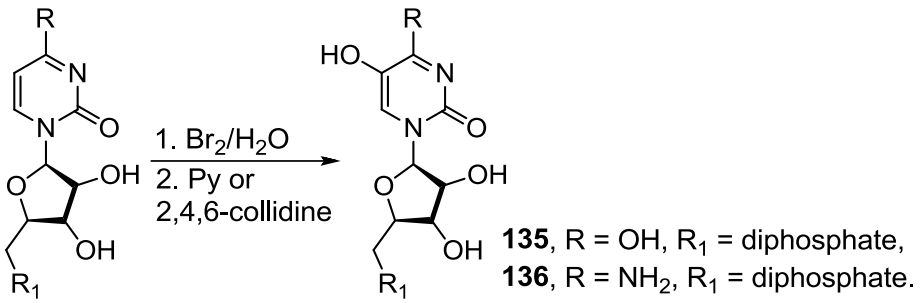


Scheme 69. The first synthetic procedure for 5-hydroxy-2'-deoxyuridine **134**.

In 1968 in a book entitled *Synthetic Procedures in Nucleic Acid Chemistry.*

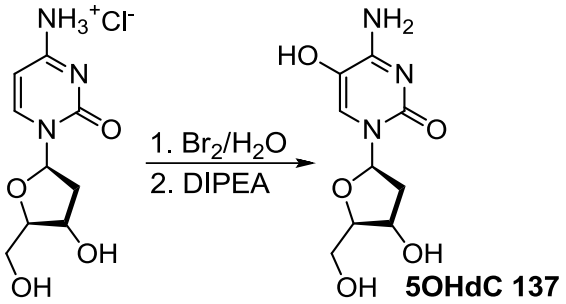
Vol. 1. Preparations of Purines, Pyrimidines, Nucleosides, and Nucleotides appeared a note that treating uridine-5'-diphosphate with bromine water and pyridine had given the corresponding 5-hydroxyuridine-5'-diphosphate analog **135** (Scheme 70).[140]

5 years later Eaton and Hutchinson synthesized 5-hydroxycytidine-5'-diphosphate **136**, in a 34% yield, by the reaction of cytidine-5'-diphosphate with bromine water and 2,4,6-collidine (Scheme 70).[141] Moreover, they proposed a possible mechanism for the 5-hydroxy derivative formation. It comprises an addition of hypobromous acid, formed *in situ* in the bromine water, to the 5,6-double bond in the pyrimidine ring. The bromine atom at the C-5 position in such obtained bromohydrin intermediate can be substituted with a hydroxyl group and, from this 5,6-dihydroxy derivative, elimination of water leads to 5-hydroxynucleoside. Interestingly, when pyridine was used instead of 2,4,6-collidine, deamination reaction occurred and 5-hydroxyuridine-5'-diphosphate was the major product.



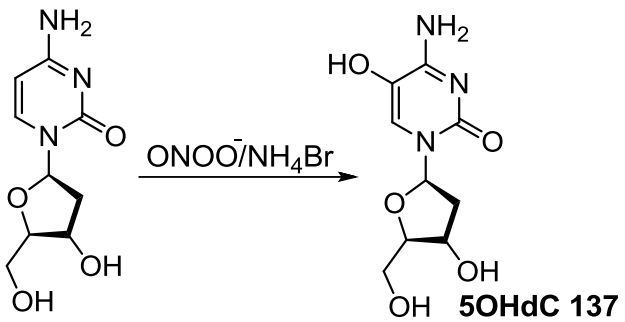
Scheme 70. Synthesis of 5-hydroxycytidine and uridine diphosphates **135**–**136** in bromine water in the presence of pyridine or 2,4,6-collidine.

In 1998, the same synthetic protocol as for compound **136** was used for the synthesis of 5-hydroxy-2'-deoxycytidine (**5OHdC**) **137**. The starting material was the 2'-deoxycytidine hydrochloride and instead of 2,4,6-collidine, *N*,*N*-diisopropylethylamine (DIPEA) was used. The yield of the reaction was 40% (Scheme 71).[142]



Scheme 71. Synthesis of **5OHdC 137** in the presence of DIPEA.

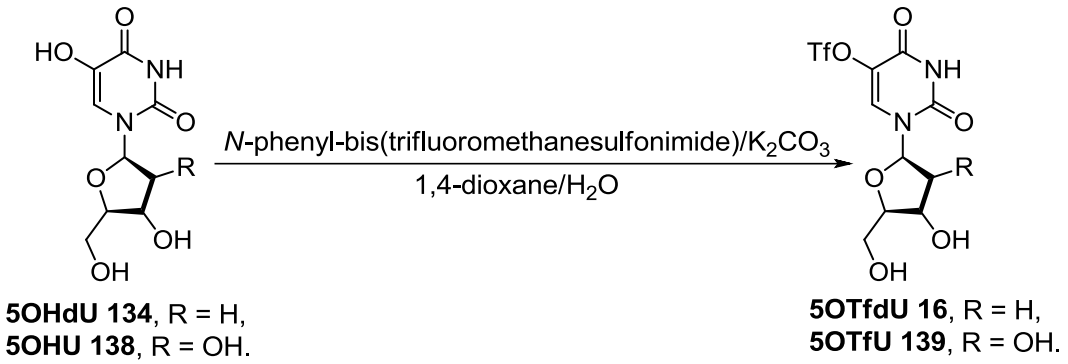
In 2008, a group of scientists was evaluating a synthesis of peroxynitrite ($ONOO^-$) from $^{\bullet}NO$ and $^{\bullet}O_2^-$ in cells.[143] These two species are formed upon actions of enzymes – nitric oxide synthase and NADPH oxidase or xanthine oxidoreductase, respectively. Peroxynitrite itself is very reactive and in the presence of NH_4Br it presumably forms hypobromous acid, which can undergo an addition reaction to the 5,6-double bond of nucleoside, as it was described earlier in this section, giving eventually a 5-hydroxynucleoside after a treatment with base. In the laboratory, peroxynitrite can be generated from $NaNO_2$ subjected to acidified H_2O_2 solution.[144] 2'-Deoxycytidine added to the $ONOO^-$ solution in phosphate buffer in the presence of NH_4Br afforded **5OHdC 137** in an unstated yield (Scheme 72).



Scheme 72. Synthesis of **5OHdC 137** with use of $ONOO^-/NH_4Br$ system.

5OHdU 134 or 5-hydroxyuridine (**5OHU**) **138** can be easily converted to their 5-trifluoromethanesulfonyl analogs without needing to protect the hydroxyl groups in the sugar unit. Crisp and Flynn performed reactions of compounds **134** and **138** with *N*-phenyl-bis(trifluoromethanesulfonimide) in 1,4-dioxane/water mixture in the

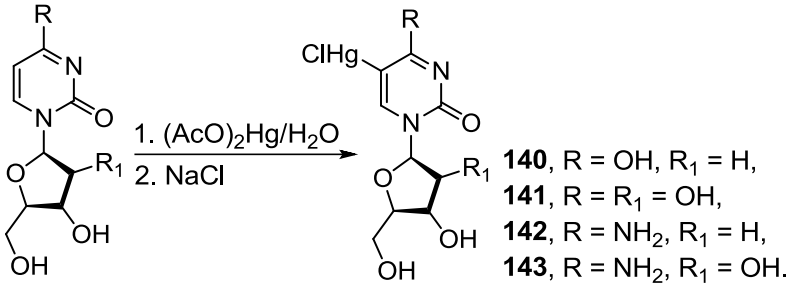
presence of potassium carbonate. Procedures were carried out in mild conditions at room temperature for 24 h yielding triflates **5OTfdU 16** and 5-trifluoromethanesulfonyluridine (**5OTfU**) **139** in 98 and 54% yields, respectively (Scheme 73).[145146]



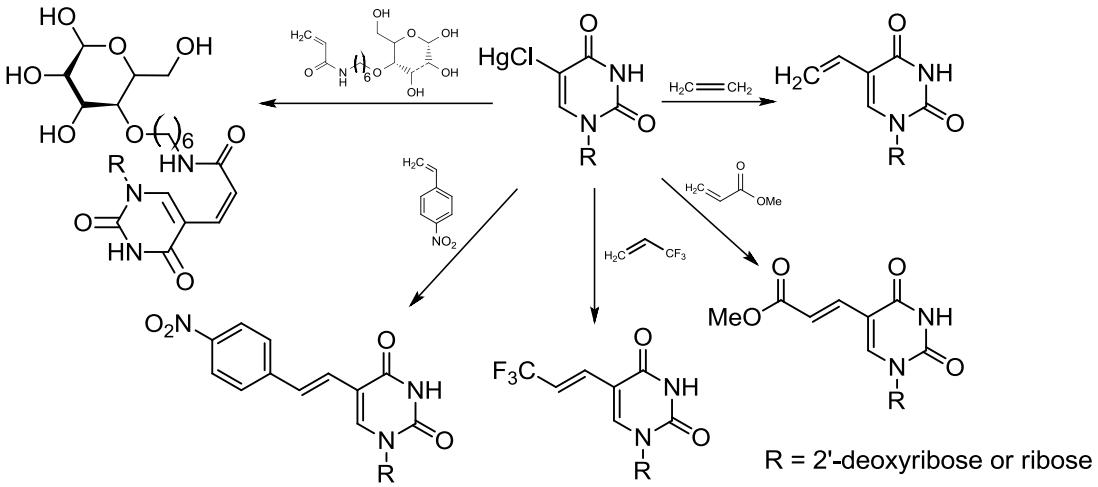
Scheme 73. Synthesis of triflates **16** and **139** with use of *N*-phenyl-bis(trifluoromethanesulfonimide)/K_2CO_3 system.

7. Metallation

Probably one of the most explored 5-metal nucleosides are their 5-mercuri analogs. In 1975, Dale *et al.* synthesized 5-mercuriuridine and cytidine and their 2'-deoxy derivatives.[124] A reaction between appropriate nucleoside with mercury(II) acetate, followed by the addition of a sodium chloride aqueous solution gave 5-chloromercuri nucleosides **140**–**143** (Scheme 74). By means of these compounds, *via* a reaction with olefins in the presence of Li_2PdCl_4 in MeOH, it was possible to obtain a vast group of C-5-alkylated nucleosides. Some examples of such reactions are presented below (Scheme 75).[147-151]

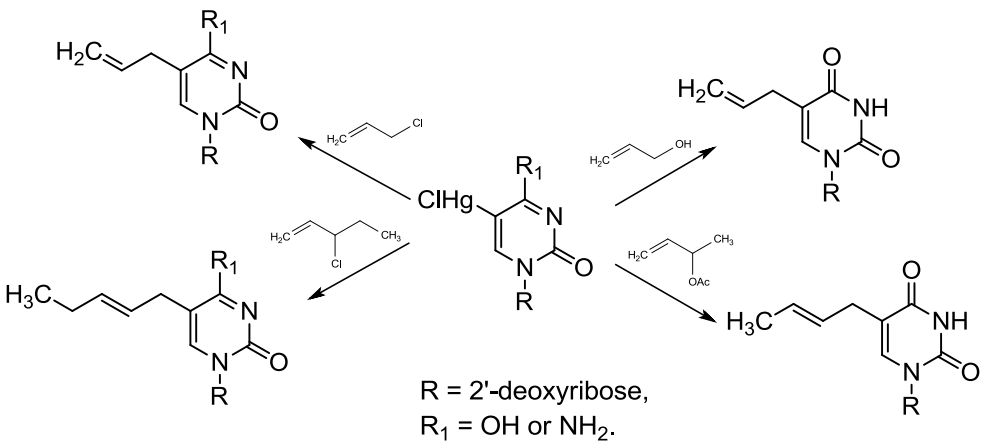


Scheme 74. Synthesis of 5-chloromercuri nucleosides **140–143** with use of mercury(II) acetate/NaCl system.



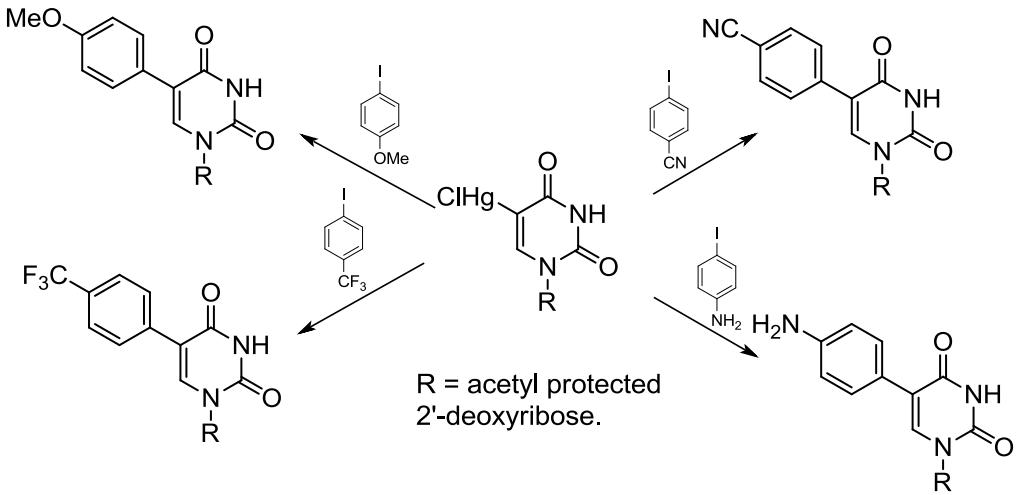
Scheme 75. The C-5 alkylation of 5-chloromercuri uridines with vinyl olefins with use of Li_2PdCl_4 in MeOH.

Several amendments were made to this process in which instead of olefins, allylic chlorides, alcohols and acetates were used. Bergstrom *et al.* synthesized a wide series of 5-alkyl-substituted pyrimidine nucleosides in poor to very good yields (5–84%). Some example reactions are shown in Scheme 76.[152] It is worth noticing that some of the reactions presented in this publication gave non-intuitive products. Authors, based on the Heck's reports,[153] described Li_2PdCl_4 as a catalyst and the reason for this allylic rearrangement. Generally, good to very good yields of reactions were obtained for alkenes with lower electron density. On the other hand, yields were much poorer for alkenes with electron-donating groups.



Scheme 76. The C-5 alkylation of 5-chloromercuri nucleosides with allylic derivatives with use of Li_2PdCl_4 in MeOH.

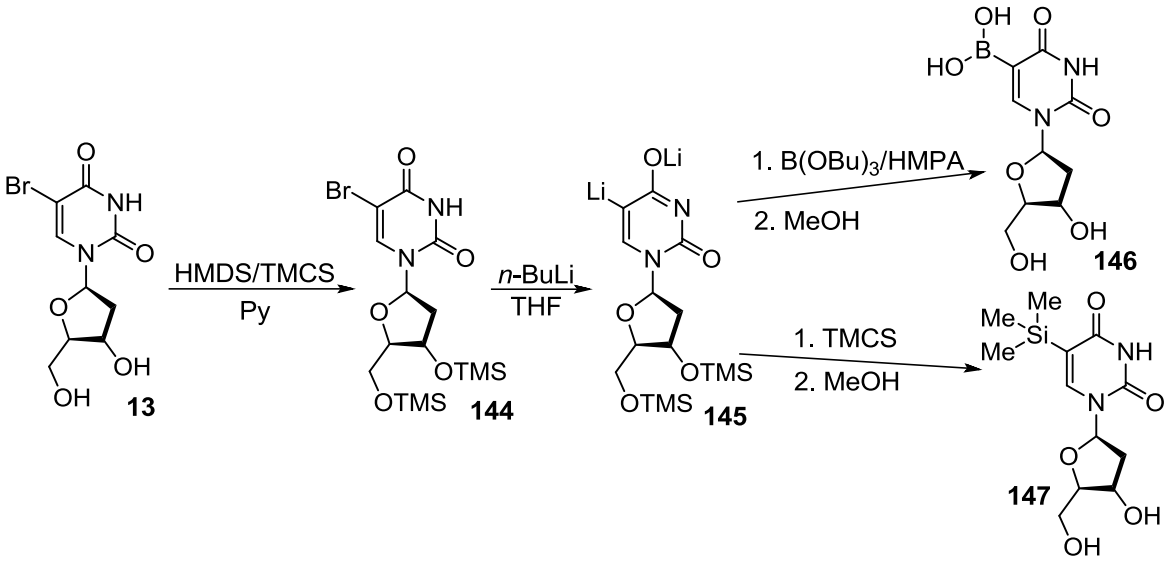
Starting from acetyl-protected 5-mercuri derivatives, it is also possible to obtain C-5 arylated uridines. In this case an appropriate 5-mercuri derivative was treated with *p*-substituted iodobenzene in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] in THF/diglyme mixture for 12 h at 120 °C to provide 3',5'-di-*O*-acetyl-5-arylated-2'-deoxyuridines in 40–70% yields (Scheme 77).[154,155] Reaction proceeded also with non-protected 5-mercuri nucleosides as starting materials but with poorer yields, which was due to their much lower solubility in THF.



Scheme 77. The C-5 arylation of 5-chloromercuri nucleosides with iodobenzene derivatives in the presence of $Pd(PPh_3)_4$ in THF/diglyme mixture.

Moreover, as it was shown before in Schemes 28 and 54 (see refs 86 and 125), starting from 5-mercuri derivatives, one can afford corresponding 5-iodo and 5-(alkylsulfanyl) nucleosides.

In 1985, Schinazi and Prusoff obtained 5-boro and 5-trimethylsilyl derivatives of 2'-deoxyuridine. Treating **5BrdU 13** with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and trimethylchlorosilane (TMCS) in pyridine furnished 3',5'-di-(*O*-trimethylsilyl)-5-bromo-2'-deoxyuridine **144**. Subsequent treatment with *n*-BuLi at −50 °C led to the *in situ* lithiated compound **145**, which was in the next step mixed with tri-*n*-butyl borate in the presence of hexamethylphosphoramide or trimethylsilyl chloride followed by the addition of methanol to hydrolize 3',5'-trimethylsilyl ethers. Compounds **146** and **147** were obtained in 12 and 26% yields, respectively (Scheme 78).[156]

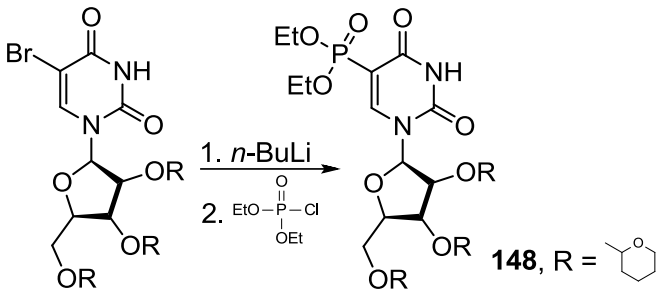


Scheme 78. Synthesis of 5-boro- **146** and 5-trimethylsilyl-2'-deoxyuridine **147** with use of the lithiation approach.

8. Phosphonylation

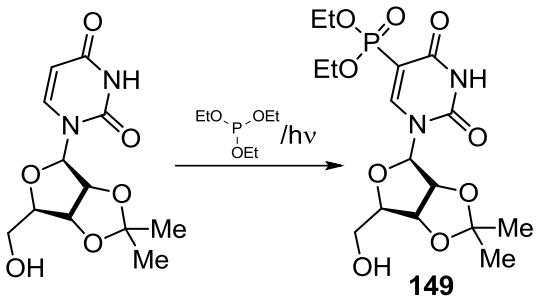
The first literature report on 5-phosphono nucleoside comes from 1986. Researchers subjected the 2',3',5'-tri-*O*-(tetrahydro-2-pyranyl)-5-bromouridine to the reaction with *n*-BuLi in THF at −78 °C for 1 h. In the next step they treated the *in situ* lithiated

intermediate with diethyl chlorophosphate for 5 h to afford the desired product **148** in a 38% yield (Scheme 79).[157] Tetrahydropyranyl ethers are one of the earliest entities applied for protecting alcohols. Their stability against basic conditions, combined with easy removal, make them attractive in organic synthesis.



Scheme 79. Phosphonylation of 5-bromo derivative of uridine with diethyl chlorophosphate.

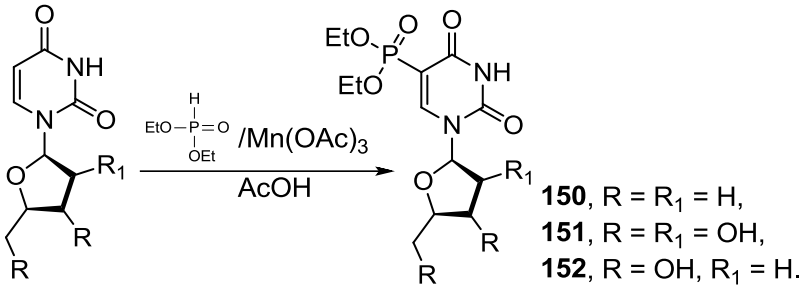
The same research group proposed a diverse phosphonylation reaction. Irradiating 2',3'-*O*-isopropylideneuridine with a low-pressure mercury lamp generated an excited state, which reacted with triethyl phosphite in DMF/ACN mixture to provide a radical intermediate, which in the next step disproportionated to ethyl radical and 2',3'-*O*-isopropylideneuridine-5-phosphonate **149** in a 56% yield (Scheme 80).[158] Overall reaction time was 6 days, which makes it difficult to handle.



Scheme 80. Photochemical synthesis of 5-diethylphosphono derivative **149**.

A highly efficient method for 5-phosphonylation of nucleosides was published in 2013.[159] It assumes the use of dialkyl H-phosphonate in the presence of manganese(III) acetate. In this oxidative cross-coupling reaction, a phosphonyl radical,

generated *in situ*, acts as an electrophile. Kim *et al.* synthesized three derivatives of uridine **150**–**152**, by heating the substrates with diethyl H-phosphonate in the presence of $Mn(OAc)_3$ in AcOH for 3 h, in very good to excellent yields (68–91%) (Scheme 81). During the reaction it is important to keep the temperature not higher than 50 °C, because of the possible formation of *N*-glycosidic bond cleavage byproducts.



Scheme 81. Synthesis of 5-diethylphosphono derivatives of uridine **150**–**152** with use of oxidative cross-coupling reaction.

Taking into account the three above-described phosphonylation methods, the mild protocol proposed by Kim *et al.* gives a facile and fast access to 5-phosphono nucleosides and additionally to some uracil and purine derivatives with good to excellent yields.

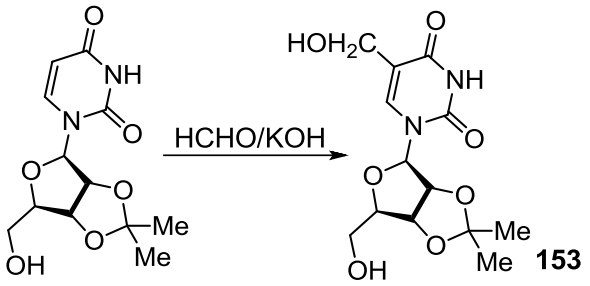
9. C–C bond formation

One of the most chemically explored area in the modification of nucleosides at the C-5 position is the C–C bond formation. In sections 9.1–9.4 we listed the most popular and synthetically useful methodologies for performing hydroxymethylation, formylation, carboxylation and heterocoupling reactions.

9.1. Hydroxymethylation

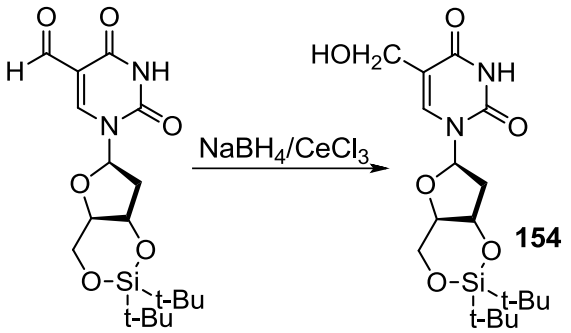
In 1966, Scheit described the synthesis of 5-hydroxymethyl derivative of 2',3'-*O*-isopropylideneuridine. Treating the 2',3'-protected uridine with paraformaldehyde in

0.5 M KOH solution afforded compound **153** in an 85% yield (Scheme 82).[160] Later, this synthetic procedure was modified by using NEt_3 instead of KOH aqueous solution.[161,162]



Scheme 82. Synthesis of 5-hydroxymethyl derivative of uridine **153**.

A different approach toward introducing the hydroxymethyl moiety into the nucleoside constitution comprises the reduction of its formyl precursor. An example method is based on treating the 5-formyl-2'-deoxyuridine derivative with sodium borohydride in the presence of cerium(III) chloride in MeOH. The reaction was finished after 1 h giving the final product **154** in a 78% yield (Scheme 83).[162]

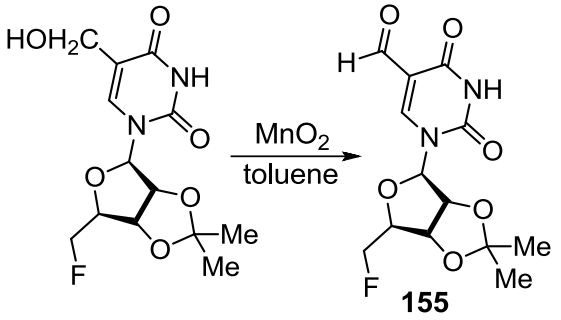


Scheme 83. Synthesis of 5-hydroxymethyl derivative **154** from its 5-formyl analog.

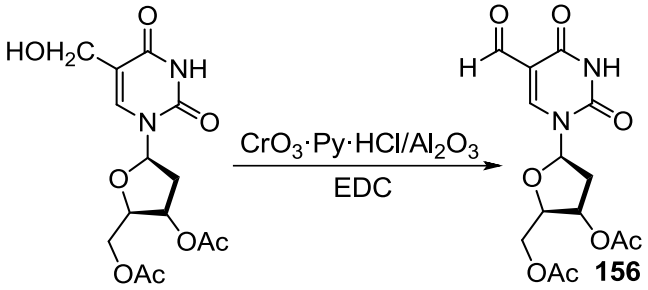
9.2. Formylation

The 5-hydroxymethyl moiety can be oxidized in various ways to a 5-formyl substituent. The most popular synthetic protocols are shown in Schemes 84–87.[163-166] The highest yields were reached in case of the oxidation with pyridinium chloroformate and Dess–Martin periodinane (DMP), 72 and 77% yields, respectively

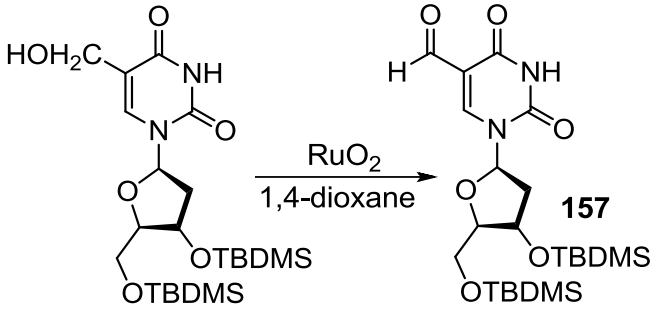
(Schemes 85 and 87). Oxidation reaction with MnO_2 and RuO_2 were performed in moderate 34 and 45% yields, respectively (Schemes 84 and 86).



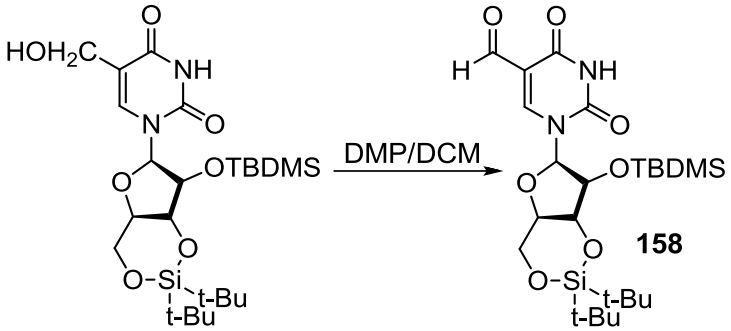
Scheme 84. Oxidation of 5-hydroxymethyl derivative of uridine with use of MnO_2.



Scheme 85. Oxidation of 5-hydroxymethyl derivative of 2'-deoxyuridine with use of pyridinium chlorochromate adsorbed on aluminum oxide.

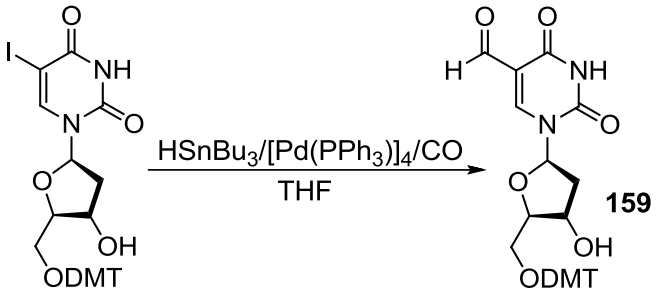


Scheme 86. Oxidation of 5-hydroxymethyl derivative of 2'-deoxyuridine with use of ruthenium (IV) oxide in 1,4-dioxane.



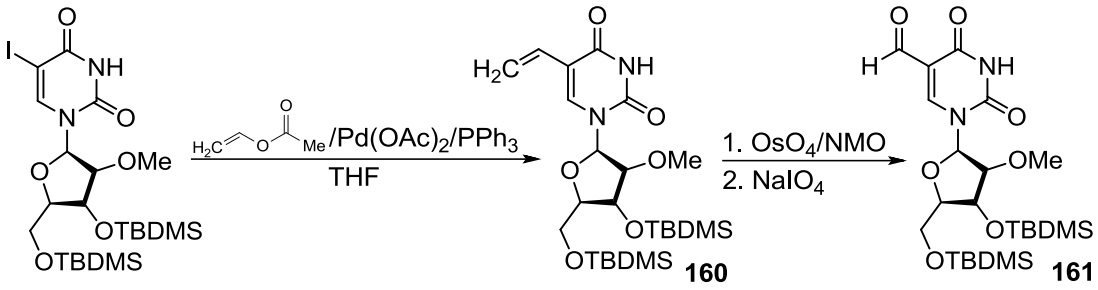
Scheme 87. Oxidation of 5-hydroxymethyl derivative of uridine with use of Dess–Martin periodinane.

In 1994, Crouch and Eaton described a synthesis of 5-formyl derivative **159** with use of facile modification of Stille coupling conditions.[167] An 8-hour reaction between 5-iodo derivative and CO in the presence of Pd(0) catalyst and tributyltin hydride led to 5'-DMTr-5-formyl-2'-deoxyuridine **159** in a 95% yield (Scheme 88).[168]

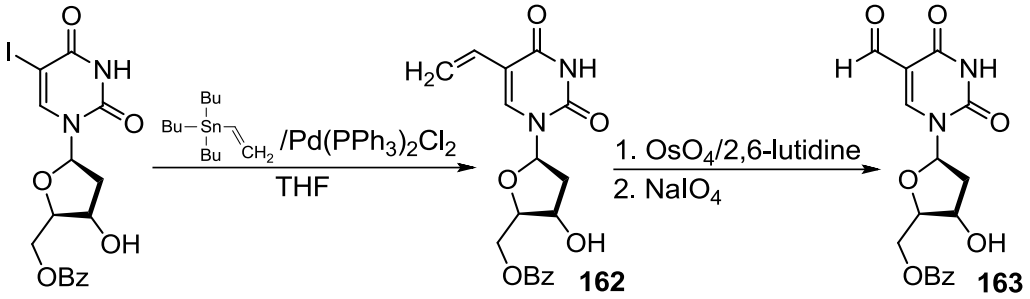


Scheme 88. Synthesis of 5-formyl derivative of 2'-deoxyuridine **159** with use of tributyltin hydride/Pd(0) catalyst.

Other two-step procedures, presented below, can be alternatives for the above-mentioned reaction, which requires the use of CO (Scheme 88). In the first step of presented methods, the 5-vinyl nucleoside analogs **160** or **162** were obtained and then subsequently subjected to dihydroxylation with OsO_4 in the presence of base. Such obtained vicinal diols are then cleaved by $NaIO_4$ to give compounds **161** or **163** in overall 35 and 77% yields, respectively (Schemes 89 and 90).[169,170] Despite the fact that these two reactions exclude the use of CO, they are tedious and time-consuming and the yields of the products are lower.

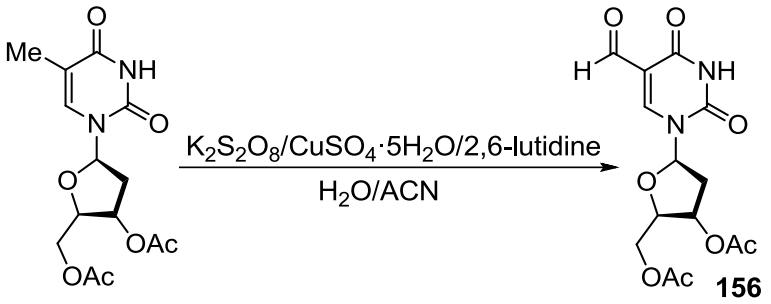


Scheme 89. Two-step synthesis of 5-formyl derivative of uridine **161**.



Scheme 90. Two-step synthesis of 5-formyl derivative of 2'-deoxyuridine **163**.

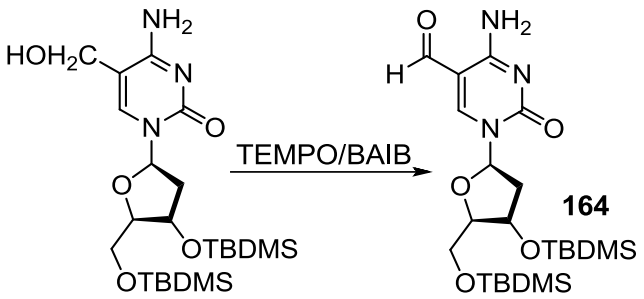
In 1993, Matsuda *et al.* described the direct synthesis of 5-formyl derivative **156** in a 52% yield by heating 3',5'-di-*O*-acetyl protected thymidine with potassium peroxysulfate in the presence of $CuSO_4$ and 2,6-lutidine (**Scheme 91**).[171]



Scheme 91. Synthesis of 5-formyl derivative **156** with use of potassium peroxysulfate and $CuSO_4$ in the presence of 2,6-lutidine.

A very efficient method for the 5-formyl derivative of 2'-deoxycytidine was reported by Sun *et al.* This research team modified an oxidation procedure of

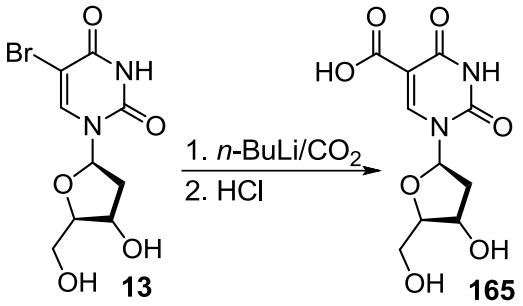
5-hydroxymethyl derivatives to 5-formyl analogs by using stoichiometric amounts of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and [bis(acetoxy)-iodo]benzene (BAIB). Treatment of 5-hydroxymethyl derivative of 2'-deoxycytidine gave its 5-formyl analog **164** in 1 h in an 82% yield (Scheme 92).[172] The precise mechanism of this oxidation method is unknown, but there are two very interesting articles that discuss this topic in details.[173,174]



Scheme 92. Synthesis of 5-formyl derivative **164** with use of TEMPO/BAIB system.

9.3. Carboxylation

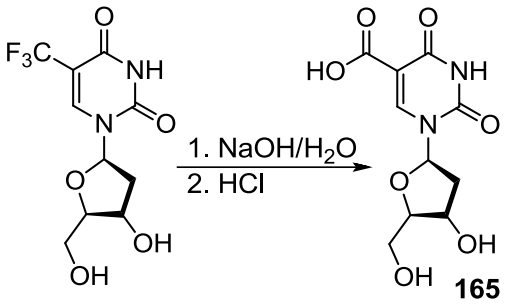
The first literature report concerning the synthesis of 5-carboxyl-2'-deoxyuridine comes from 1967. **5BrdU 13** subjected to the reaction with *n*-BuLi, followed by the addition of solid CO_2 and acidification with HCl, gave the desired product **165** in a 27% yield (Scheme 93).[175]



Scheme 93. Synthesis of 5-carboxyl-2'-deoxyuridine **165** with use of *n*-BuLi/CO_2.

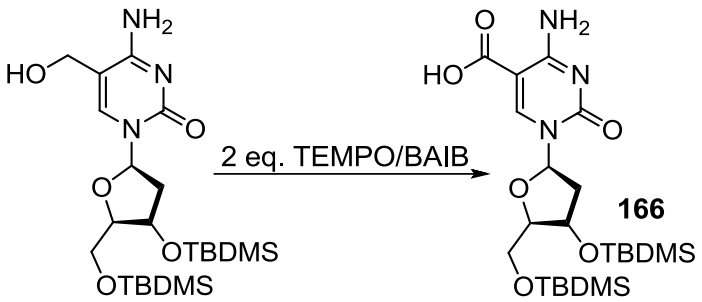
Another method of introducing the carboxyl moiety into the nucleoside structure is the alkaline hydrolysis of 5-trifluorothymidine. The plausible mechanism

comprises the arise of difluorohydroxy and hypothetical monofluorocarbonyl intermediates.[176] Treating 5-trifluoromethyl-2'-deoxyuridine with NaOH aqueous solution gave the desired product **165** in a 90% yield (Scheme 94).[177]



Scheme 94. Alkaline hydrolysis of 5-trifluoromethyl-2'-deoxyuridine with an NaOH aqueous solution.

It is also possible to get 5-carboxyl moiety by oxidizing the 5-hydroxymethyl substituent with TEMPO/BAIB system. As it was shown in Scheme 92, using stoichiometric amounts of TEMPO/BAIB, one can get an aldehyde. When using 2 equivalents of these reagents, a hydroxymethyl derivative is oxidized to carboxylic acid. In this case, the reaction between 5-hydroxymethyl-2'-deoxycytidine with TEMPO/BAIB gave the corresponding 5-carboxyl analog **166** (Scheme 95).[172]

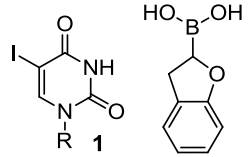
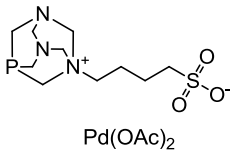
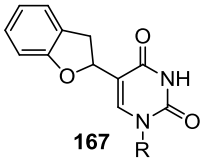
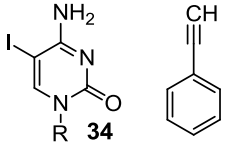
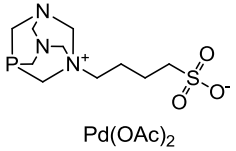
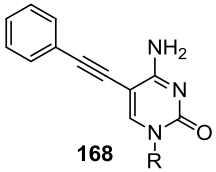
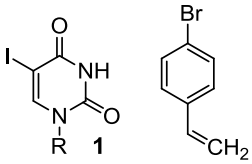
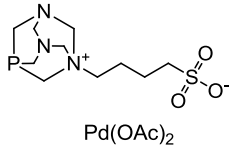
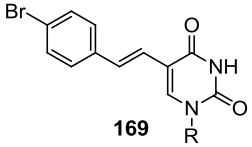
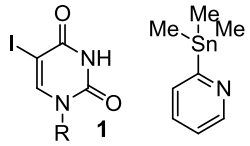
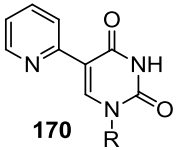
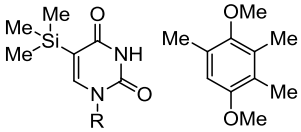
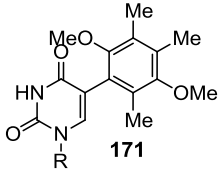


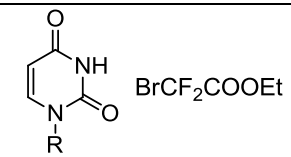
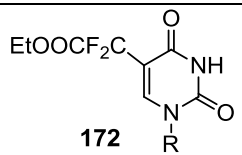
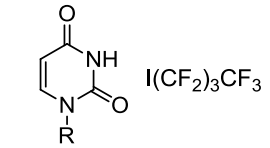
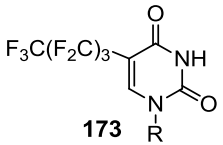
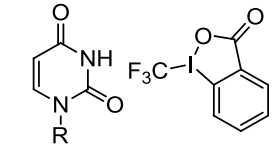
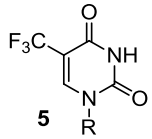
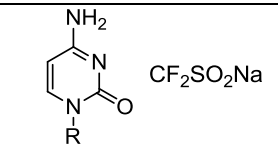
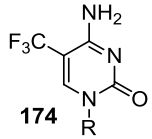
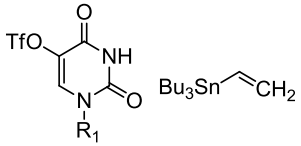
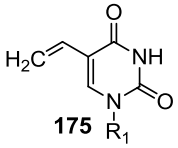
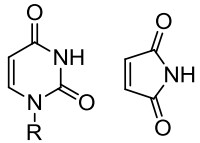
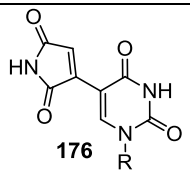
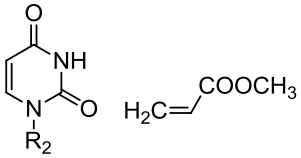
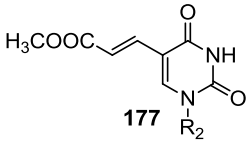
Scheme 95. Oxidation of 5-hydroxymethyl derivative of 2'-deoxycytidine with 2 equivalents of TEMPO/BAIB.

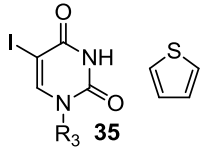
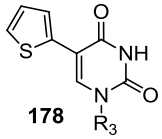
9.4. Heterocoupling reactions

All of the examples presented in Table 1 are variations of different heterocoupling approaches. C–C coupling reactions, in the context of nucleosides, are mainly catalyzed by Pd(0), but one can also find copper, iridium and ruthenium derivatives as catalysts. Some of such reactions are photo-catalyzed as well. Previously, in section **7** we showed examples of C–C bond formation with use of 5-halogenomercuri compounds in the presence of Li_2PdCl_4 (Schemes 74–76).

Table 1. Selected examples of the C–C bond formation at the C-5 position in pyrimidine nucleosides.

Entry	Substrates	Catalysts/Reagents	Product	Conditions	Yield [%]	Ref.
1				H_2O, 80 °C, 3 h	88	178
2				H_2O, ACN, 80 °C, 45 min	75	178
3				H_2O, ACN, 80 °C, 18 h	88	178
4		$PdCl_2(Ph_3P)_2$		1,4-dioxane, 90 °C, 1 h	83	179
5		irradiation at 310 nm		ACN, 40 °C, 48 h	15	180

6		*fac*-Ir(ppy)$_3$, irradiation at 460 nm	 **172**	DMSO, rt, 24 h	84	181
7		Ru(bpy)$_3$Cl$_2$, irradiation at 460 nm	 **173**	DMSO, rt, 24 h	44	182
8		CuI	 **5**	DMF, 40 °C, 23 h	73	184
9		*t*-BuOOH	 **174**	H_2O, rt, 3 h	73	185
10		Pd(PPh$_3$)$_4$, LiCl	 **175**	1,4-dioxane, reflux, 4 h	87	146
11		Pd(OAc)$_2$	 **176**	ACN, reflux, 17 h	10	186
12		Pd(OAc)$_2$, PhCO$_3$*t*-Bu	 **177**	ACN, rt, 53 h	74	187

13	 **35**	$Pd_2(dba)_3$, TBAF	 **178**	DMF, 100 °C, 1 h	98	188

R = 2'-deoxyribose, R_1 = acetyl-protected 2'-deoxyribose, R_2 = 2',3'-isopropylideneribose, R_3 = ribose.

In 2016, Bhilare *et al.* described the discovery of two phosphatriazene ligands (PTABS and PTAPS) that, along with $Pd(OAc)_2$, create very efficient catalysts for Suzuki–Miyaura, Sonogashira and Heck couplings. Their enhanced solubility in water gives the possibility to recycle the catalyst more easily and to avoid preparative column chromatography purification step. Non-protected 5-iodo nucleosides treated with PTABS, $Pd(OAc)_2$ and subsequently with 2-benzofuranyl boronic acid, phenyl acetylene or 4-bromostyrene, in the presence of NEt_3, gave compounds **167**–**169** in 88, 75 and 88% yields, respectively (Table 1, entries 1–3).[178]

5-Iodo-2'-deoxyuridine subjected to the reaction with 2-(trimethylstannyl)pyridine in the presence of $PdCl_2(PPh_3)_2$ in 1,4-dioxane afforded 5-(pirydyn-2-yl)-2'-deoxyuridine **170** in a 83% yield (Table 1, entry 4).[179]

C-alkylation reactions can be also performed under irradiation. Entries 5–7 show three different methodologies covering this topic. Al-Razzak *et al.* described the photochemical aromatic substitution regarding to the synthesis of uridine derivatives. A 5-trimethylsilyl-2'-deoxyuridine solution, obtained from 5-iodo-2'-deoxyuridine and HMDS, and 2,3-dimethyl-1,4-dimethoxybenzene was irradiated at 310 nm. The desired product **171** was isolated in a 25% yield (Table 1, entry 5).[180]

Fac-$Ir(ppy)_3$, a very efficient photoredox catalyst, was successfully used in the visible-light-induced coupling difluoroalkylation. He *et al.* synthesized compound **172**, starting from 2'-deoxyuridine and ethyl bromodifluoroacetate, in an 84% yield (Table 1, entry 6).[181]

The same research group published an article concerning the 5-perfluoroalkylation of uridines. When using the same protocol as for **172** they obtained compound **173** in a very poor yield. To resolve this problem, they used perfluoroalkyl iodide as substrate, instead of a bromide and $Ru(bpy)_3Cl_2$ as a catalyst. In the course of research, it turned out that DMSO is the most efficient solvent (comparing to DMF or ACN) and caesium carbonate was chosen as a base. Eventually, 5-perfluorinated analog **173** was obtained in a 44% yield (Table 1, entry 7).[182]

The next two examples, shown in Table 1, relate to 5-trifluoromethylation of nucleosides. The $–CF_3$ group is very crucial from the pharmaceutical and agrochemical point of view. This moiety is present in i.e. Viroptic (Fig. 2). There are two possible ways to synthesize 5-trifluoromethyl derivatives of nucleosides. The first method is the reaction of a nucleoside with Togni's reagent in the presence of copper(I) iodide. Togni's reagent is a facile trifluoromethylating agent and it is one of the first examples of stable hypervalent iodine derivatives.[183] It was successfully used in the 5-trifluoromethylation reaction of 2'-deoxyuridine in which 5-trifluoromethyl-2'-deoxyuridine **5** was obtained in a 73% yield (Table 1, entry 8).[184]

The second way to introduce the $–CF_3$ group into the structure of a nucleoside is the reaction with sodium trifluoromethanesulfinate in the presence of *t*-butyl hydroperoxide as a radical source. 2'-Deoxycytidine treated with the aforementioned system yielded 5-trifluoromethyl-2'-deoxycytidine **174** in a very good, 73% yield (Table 1, entry 9).[185]

Acetyl-protected 5-triflate derivatives (Scheme 73) can undergo various coupling reactions with terminal alkynes or organostannanes.[145,146] The example of organostannane palladium-triggered coupling to nucleoside triflate is shown in Table 1, entry 10. 3',5'-Di-*O*-acetyl-5-trifluoromethanesulfonyl-2'-deoxyuridine and ethenyltributylstannane were treated with $Pd(PPh_3)_4$ and LiCl in 1,4-dioxane at reflux for 4 h. Raw product was purified on the preparative column chromatography affording 3',5'-di-*O*-acetyl-5-ethenyl-2'-deoxyuridine **175** in an 87% yield. The authors indicated that the organostannanes, with both electron-donating and electron-withdrawing substituents, coupled to triflates with similar efficacy.

Itahara reported a possibility of introducing a maleimide moiety at the C-5 position of uracils and uridines. A reaction between 2'-deoxyuridine and maleimide in the presence of $Pd(OAc)_2$ gave the product **176** in a 10% yield (Table 1, entry 11). It is worth-noticing that in case of uracil derivatives yields of the final products were higher, up to 56%, when using re-oxidants such as AgOAc, $Na_2S_2O_8$ and $Cu(OAc)_2$.[186]

2',3'-Isopropylideneuridine subjected to methyl acrylate in the presence of $Pd(OAc)_2$ and *t*-butyl perbenzoate afforded the product **177** in a 74% yield (Table 1, entry 12).

Reaction was carried out at room temperature in a very good yield, which is convenient, nevertheless the time was longer comparing to other examples from Table 1.[187]

A very facile and efficient protocol for the synthesis of 5-aryluridines was introduced by Wnuk and coworkers.[188] Scientists coupled 5-iodonucleosides with furan or thiophene in the presence of tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] and TBAF in DMF at 100 °C for 1–2 h. Not only the yields of the products were good to excellent (45–98%), this method kept the *N*-glycosidic bond stable in case of 2'-deoxyuridine substrates. The reaction worked well with both protected and unprotected nucleosides and it avoided the use of toxic compounds. In an example, shown in entry 13 in Table 1, 5-iodouridine was treated with thiophene in the presence of $Pd_2(dba)_3$ and TBAF in DMF to give 5-(thiophen-2-yl)uridine **178** in a 98% yield.

10. Conclusions

In this review paper, we have collected together the most popular methods for the chemical modifications at the C-5 position of pyrimidine nucleosides. Taking into account that the C-5-modified pyrimidine nucleosides are vital for medicine and pharmacy, search for and development of rapid and efficient ways of synthesizing them are highly demanded.

5-Halogenonucleosides and their analogs with a C–C bond at the C-5 position exhibit anticancer, antiviral, radio- and photosensitizing properties. Moreover some of them are active against the HSV-1, HSV-2, VZV or EBV viruses. 5-substituted uridines and cytidines due to their structural similarity to the native nucleosides can be incorporated into DNA at the cellular level, which makes them good candidates for efficient chemotherapeutic agents. Moreover, radiotherapy, used in ca. 50% of cancer patients, as well as photodynamic therapy could benefit directly from the C-5-modified pyrimidine radio-/photosensitizers. To sum up, from the medical point of view, exploration of the therapeutic potential of the C-5-modified nucleosides should certainly continue.

Acknowledgements

J. Rak gratefully acknowledges the National Science Centre (NCN), Poland, for financial support (2014/14/A/ST4/00405).

Conflict of interest

The authors declare no conflict of interest.

References

1 E.Gemenetzidis, O.Shavorskaya, Y.-Z.Xu, G.Trigiante. *J. Dermatol. Treat.*, **24**, 209 (2013)

2 T.Onishi, C.Mukai, R.Nakagawa, T.Sekiyama, M.Aoki, K.Suzuki, H.Nakazawa, N.Ono, Y.Ohmura, S.Iwayama, M.Okunishi, T.Tsuji. *J. Med. Chem.*, **43**, 278 (2000)

3 N.Ashida, Y.Watanabe, S.Miura, F.Kano, S.Sakata, T.Yamaguchi, T.Suzutani, H.Machida. *Antiviral Res.*, **35**, 167 (1997)

4 C.Périgaud, G.Gosselin, J.L.Imbach. *Nucleosides Nucleotides*, **11**, 903 (1992)

5 E.De Clercq. *Pure Appl. Chem.*, **55**, 623 (1983)

6 J.R.Mercer, L.H.Xu, E.E.Knaus, L.I.Wiebe. *J. Med. Chem.*, **32**, 1289 (1989)

7 W.H.Prusoff, W.L.Holmes, A.D.Welch. *Cancer Res.*, **13**, 221 (1953)

8 H.E.Kaufman. *Proc. Soc. Exp. Biol. Med.*, **109**, 251 (1962)

9 N.Realini, C.Solorzano, C.Pagliuca, D.Pizzirani, A.Armirotti, R.Luciani, M.P.Costi, T.Bandiera, D.Piomelli. *Sci. Rep.*, **3**, 1035 (2013)

10 Y.Uchikubo, T.Hasegawa, S.Mitani, H.-S.Kim, Y.Wataya. *Nucleic Acids Symp. Ser.*, **2**, 245 (2002)

11 D.D.Richman. *Antiv. Ther.*, **6**, 83 (2001)

12 A.van Aershot, D.Everaert, J.Balzarini, K.Augustyns, L.Jie, G.Janssen, O.Peeters, N.Blaton, C.De Ranter, E.De Clercq, P.Herdewijn. *J. Med. Chem.*, **33**, 1833 (1990)

13 W.A.Cristofoli, L.I.Wiebe, E.De Clercq, G.Andrei, R.Snoeck, J.Balzarini, E.E.Knaus. *J. Med. Chem.*, **50**, 2851 (2007)

14 H.-J.Lenz, S.Stintzing, F.Loupakis. *Cancer Treat. Rev.*, **41**, 777 (2015)

15 E.De Clercq. *Antiviral Chem. Chemother.*, **23**, 93 (2013)

16 C.B.Burness, S.T.Duggan. *Drugs*, **76**, 1393 (2016)

17 R.J.Whitley. *Neurology*, **45**, S73–S75 (1995)

18 P.J.Barr, T.A.Hamor, R.T.Walker. *Acta Crystallogr. B*, **34**, 2799 (1978)

19 C.L.Lai, N.Leung, E.-K.Teo, M.Tong, F.Wong, H.Hann, S.Han, T.Poynard, M.Myers, G.Chao, D.Lloyd, N.A.Brown. *Gastroenterology*, **129**, 528 (2005)

20 P.-F.Lin, H.Samanta, R.E.Rose, A.K.Patick, J.Trimble, C.M.Bechtold, D.R.Revie, N.C.Khan, M.E.Federici, H.Li, A.Lee, R.E.Anderson, R.J.Colonno. *J. Infect. Dis.*, **170**, 1157 (1994)

21 R.M.Gulick, J.W.Mellors, D.Havlir, J.J.Eron, C.Gonzalez, D.McMahon, E.A.Emini. *New Eng. J. Med.*, **337**, 734 (1997)

22 S.L.Sacks, L.D.Tyrrell, D.Lawee, W.Schlech, M.J.Gill, F.Y.Aoki, A.Y.Martel, J.Singer. *J. Infect. Dis.*, **164**, 665 (1991)

23 R.Tashiro, H.Sugiyama. In *Radical and Radical Ion Reactivity in Nucleic Acid Chemistry*. (Eds M.M.Greenberg). John Wiley & Sons, Inc.: Hoboken, NJ, 2009, 163

24 S.B.Brown, E.A.Brown, I.Walker. *Lancet Oncol.*, **5**, 497 (2004)

25 L.Chomicz, M.Zdrowowicz, F.Kasprzykowski, J.Rak, A.Bounaugurio, Y.Wang, K.H.Bowen. *J. Phys. Chem. Lett.*, **4**, 2853 (2013)

26 S.Makurat, L.Chomicz-Mańka, J.Rak. *ChemPhysChem*, **17**, 2572 (2016)

27 L.Chomicz-Mańka, P.Wityk, Ł.Golon, M.Zdrowowicz, J.Wiczk, K.Westphal, M.Żyndul, S.Makurat, J.Rak. In *Handbook of Computational Chemistry*. (Eds J.Leszczynski). Springer Netherlands, 2015, 1

28 K.Westphal, K.Skotnicki, K.Bobrowski, J.Rak. *Org. Biol. Chem.*, **14**, 9331 (2016)

29 K.Westphal, J.Wiczk, J.Miloch, G.Kciuk, K.Bobrowski, J.Rak. *Org. Biol. Chem.*, **13**, 10362 (2015)

30 M.Rieber, M.Strasberg Rieber. *Cancer Biol. Ther.*, **7**, 1561 (2008)

31 T.Yan, Y.Seo, J.E.Schupp, X.Zeng, A.B.Desai, T.J.Kinsella. *Mol. Cancer Ther.*, **5**, 893 (2006)

32 J.Kohanoff, M.McAllister, G.A.Tribello, B.Gu. *J. Phys. Condens. Matter*, **29**, 383001 (2017)

33 D.Katz, E.Ito, F.Liu. *Int. J. Radiat. Oncol. Biol. Phys.*, **73**, 988 (2009)

34 C.J.McGinn, T.S.Lawrence. *Semin. Radiat Oncol.*, **11**, 270 (2001)

35 B.Goz. *Pharmacol Rev.*, **29**, 249 (1977)

36 W.C.Dewey, R.M.Humphrey. *Radiat. Res.*, **26**, 538 (1965)

37 R.Erikson, W.Szybalski. *Radiat. Res.*, **20**, 252 (1963)

38 L.L.Ling, J.F.Ward. *Radiat. Res.*, **121**, 76 (1990)

39 C.von Sonntag. In *The Chemical Basis of Radiation Biology*. Taylor & Francis, London, NY, 1987

40 S.Makurat, M.Zdrowowicz, L.Chomicz-Mańka, W.Kozak, I.E.Serdiuk, P.Wityk, A.Kawecka, M.Sosnowska, J.Rak. *RSC Adv.*, **8**, 21378 (2018)

41 M.Zdrowowicz, L.Chomicz, M.Żyndul, P.Wityk, J.Rak, T.J.Wiegand, C.G.Hanson, A.Adhitary, M.D.Sevilla. *Phys. Chem. Chem. Phys.*, **17**, 16907 (2015)

42 S.Makurat, P.Spisz, W.Kozak, J.Rak, M.Zdrowowicz. *Int. J. Mol. Sci.*, **20**, 1308 (2019)

43 T.Watanabe, T.Bando, Y.Xu, R.Tashiro, H.Sugiyama. *J. Am. Chem. Soc.*, **127**, 44 (2005)

44 M.Zdrowowicz, B.Michalska, A.Zylicz-Stachula, J.Rak. *J. Phys. Chem. B*, **118**, 5009 (2014)

45 L.Cupellini, P.Wityk, B.Mennucci, J.Rak. *Phys. Chem. Chem. Phys.*, **21**, 4387 (2019)

46 K.Westphal, S.Makurat, J.Rak. *J. Phys. Chem. B*, **121**, 9169 (2017)

47 M.Zdrowowicz, P.Wityk, B.Michalska, J.Rak. *Org. Biomol. Chem.*, **14**, 9312 (2016)

48 O.Reelfs, P.Karran, A.R.Young. *Photochem. Photobiol. Sci.*, **11**, 148 (2012)

49 V.Gayakhe, S.Bhilare, A.Yashmeen, I.J.S.Fairlamb, A.R.Kapdi. In *Palladium-Catalyzed Modification of Nucleosides, Nucleotides and Oligonucleotides*. (Eds A.R.Kapdi, D.Maiti, Y.S.Sanghvi). Elsevier, Amsterdam, 2018, 167

50 F.Christoffel, T.R.Ward. *Catal. Lett.*, **148**, 489 (2018)

51 A.Dadras, M.R.Naimi-Jamal, F.M.Moghaddam, S.E.Ayati. *Appl. Organomet. Chem.*, **32**, 3993 (2018)

52 N.K.Kochetkov, E.I.Budovskii. In *Organic Chemistry of Nucleic Acids*. Springer, Boston, MA, 1972, 269

53 T.Ueda. In *Chemistry of Nucleosides and Nucleotides*. Springer, Boston, MA, 1988, 1

54 D.W.Visser, G.Barron, R.Beltz. *J. Am. Chem. Soc.*, **75**, 2017 (1953)

55 T.K.Fukuhara, D.W.Visser. *J. Am. Chem. Soc.*, **77**, 2393 (1955)

56 D.M.Frisch, D.W.Visser. *J. Am. Chem. Soc.*, **81**, 1756 (1958)

57 GB Patent 1167605 (1969)

58 K.Kikugawa, I.Kawada, M.Ichino. *Chem. Pharm. Bull.*, **23**, 35 (1975)

59 E.K.Ryu, M.MacCoss. *J. Org. Chem.*, **46**, 2819 (1981)

60 M.J.Robins, P.J.Barr, J.Giziewicz. *Can. J. Chem.*, **60**, 554 (1982)

61 L.Liu, D.Zhang-Negrerie, Y.Du, K.Zhao. *Org. Lett.*, **16**, 436 (2014)

62 E.K.Ryu, J.N.Kim. *Nucleosides Nucleotides*, **8**, 43 (1989)

63 S.S.Kim, H.C.Jung. *Synthesis*, 2135 (2003)

64 M.Ali, D.Kriedelbaugh, T.Wencewicz. *Synthesis*, 3507 (2007)

65 V.Sridharan, J.C.Menendez. *Chem. Rev.*, **110**, 3805 (2010)

66 J.Asakura, M.J.Robins. *J. Org. Chem.*, **55**, 4928 (1990)

67 R.Kumar, L.I.Wiebe, E.E.Knaus. *Can. J. Chem.*, **72**, 2005 (1994)

68 K.Kawai, I.Saito, H.Sugiyama. *Tetrahedron Lett.*, **40**, 5721 (1999)

69 C.Galli, P.Gentili, Z.Rappoport. *J. Org. Chem.*, **59**, 6786 (1994)

70 C.Galli, P.Gentili, A.Guarnieri, S.Kobayashi, Z.Rappoport. *J. Org. Chem.*, **63**, 9292 (1998)

71 S.G.Zavgorodny, A.E.Pechenov, V.I.Shvets, A.I.Miroshnikov. *Nucleosides Nucleotides*, **19**, 1977 (2000)

72 A.Mieczkowski, P.Peltier, T.Zevaco, L.A.Agrofoglio. *Tetrahedron*, **65**, 4053 (2009)

73 A.Mieczkowski, P.Wińska, M.Kaczmarek, M.Mroczkowska, D.Garbicz, T.Pilżys, M.Marcinkowski, J.Piwowarski, E.Grzesiuk. *Chem. Pap.*, **72**, 981 (2018)

74 H.W.Barrett, I.Goodman, K.Dittmer. *J. Am. Chem. Soc.*, **70**, 1753 (1948)

75 V.Kumar, J.Yap, A.Muroyama, S.V.Malhotra. *Synthesis*, **23**, 3957 (2009)

76 V.Kumar, S.V.Malhotra. *Nucleosides Nucleotides*, **28**, 821 (2009)

77 P.A.Levene, F.B.La Forge. *Ber. Dtsch. Chem. Ges.*, **45**, 608 (1912)

78 P.C.Srivastava, K.L.Nagpal. *Experientia*, **26**, 220 (1969)

79 J.Brokeš, H.Hřebabecký, J.Beránek. *Collect. Czech. Chem. Commun.*, **44**, 439 (1979)

80 S.A.Ross, C.J.Burrows. *Tetrahedron Lett.*, **38**, 2805 (1997)

81 J.Maity, R.Stromberg. *Molecules*, **18**, 12740 (2013)

82 W.H.Prusoff. *Biochim. Biophys. Acta*, **32**, 295 (1959)

83 P.K.Chang, A.D.Welch. *Biochem. Pharmacol.*, **8**, 327 (1961)

84 P.K.Chang, A.D.Welch. *J. Org. Chem.*, **6**, 428 (1963)

85 D.Lipkin, F.B.Howard, D.Nowotny, M.Sano. *J. Biol. Chem.*, **238**, 2249 (1963)

86 R.M.K.Dale, D.C.Ward, D.C.Livingston, E.Martin. *Nucleic Acids Res.*, **2**, 915 (1975)

87 J.Asakura, M.J.Robins. *Tetrahedron Lett.*, **23**, 2855 (1988)

88 W.-W.Sy. *Synth. Commun.*, **20**, 3391 (1990)

89 L.Paolini, E.Petricci, F.Corelli, M.Botta. *Synthesis*, **7**, 1039 (2003)

90 W.-W.Sy, B.A.Lodge, A.W.By. *Synth. Commun.*, **20**, 877 (1990)

91 B.H.Le, J.C.Koo, H.N.Joo, Y.J.Seo. *Bioorganic Med. Chem.*, **25**, 3591 (2017)

92 B.H.Le, Y.J.Seo. *Bioorganic Med. Chem. Lett.*, **28**, 2035 (2018)

93 B.H.Le, Y.J.Seo. *Bull. Korean Chem. Soc.*, **39**, 1054 (2018)

94 M.J.Robins, S.R.Naik. *J. Am. Chem. Soc.*, **93**, 5277 (1971)

95 M.J.Robins, M.MacCoss, S.R.Naik, G.Ramani. *J. Am. Chem. Soc.*, **98**, 7381 (1976)

96 D.Cech, A.Holy. *Collect. Czech. Chem. Commun.*, **41**, 3335 (1976)

97 S.Stavber, M.Zupan. *J. Chem. Soc., Chem. Commun.*, 563 (1983)

98 G.W.M.Visser, R.E.Herder, P.Noordhuis, O.Zwaagstra, J.D.M.Herscheid, F.J.J.De Kanter. *J. Chem. Perkin Trans. 1*, 2547 (1988)

99 S.Rozen. *Acc. Chem. Res.*, **21**, 307 (1988)

100 P.L.Coe, R.R.Talekar, R.T.Walker. *J. Fluor. Chem.*, **69**, 19 (1994)

101 R.E.Banks, S.N.Mohialdin-Khaffaf, S.Lal, I.Sharif, R.G.Syvret. *J. Chem. Soc., Chem. Commun.*, 595 (1992)

102 C.-S.Yu, L.-W.Chiang, C.-H.Wu, Z.-K.Hsu, M.-H.Lee, S.-D.Pan, K.Pei. *Synthesis*, 3835 (2006)

103 I.Wempen, I.L.Doerr, L.Kaplan, J.J.Fox. *J. Am. Chem. Soc.*, **82**, 1624 (1960)

104 G.-F.Huang, P.F.Torrence. *J. Org. Chem.*, **42**, 3821 (1977)

105 R.K.Evans. *Biochemistry*, **26**, 269 (1987)

106 G.A.Olah, S.C.Narang, A.P.Fung. *J. Org. Chem.*, **46**, 2706 (1981)

107 J.Giziewicz, S.F.Wnuk, M.J.Robins. *J. Org. Chem.*, **64**, 2149 (1999)

108 M.Kovaliov, M.Weitman, D.T.Major, B.Fischer. *J. Org. Chem.*, **79**, 7051 (2014)

109 E.Colacino, G.Sindona, G.Gosselin, C.Mathé. *Nucleosides Nucleotides*, **22**, 2013 (2003)

110 M.Roberts, D.W.Visser. *J. Am. Chem. Soc.*, **74**, 668 (1952)

111 R.E.Beltz, D.W.Visser. *J. Biol. Chem.*, **226**, 1035 (1957)

112 D.A.Barawkar, R.K.Kumar, K.N.Ganesh. *Tetrahedron*, **48**, 8505 (1992)

113 E.Ferrer, C.Fàbrega, R.G.Garcia, F.Azorín, R.Eritja. *Nucleosides Nucleotides*, **15**, 907 (1996)

114 K.Gislason, S.T.Sigurdsson. *Eur. J. Org. Chem.*, **2010**, 4713 (2010)

115 S.Gourdain, C.Petermann, D.Harakat, P.Clivio. *Nucleosides Nucleotides*, **29**, 542 (2010)

116 R.K.Evans, B.E.Haley. *Biochemistry*, **26**, 269 (1987)

117 L.-M.Zhu, E.A.Carrey. *Bioorganic Med. Chem. Lett.*, **6**, 2513 (1996)

118 T.J.Bardos, M.P.Kotick, C.Szantay. *Tetrahedron Lett.*, **16**, 1759 (1966)

119 K.Baranski, T.J.Bardos, A.Bloch, T.I.Kalman. *Biochemical Pharmacol.*, **18**, 347 (1969)

120 L.Szabo, T.I.Kalman, T.J.Bardos. *J. Org. Chem.*, **35**, 1434 (1970)

121 T.Nagamachi, P.F.Torrence, J.A.Waters, B.Witkop. *J. Chem. Soc., Chem. Commun.*, **18**, 1025 (1972)

122 F.J.Dinan, T.J.Bardos. *J. Med. Chem.*, **23**, 569 (1980)

123 H.Hayakawa, H.Tanaka, K.Obi, M.Itoh, T.Miyasaka. *Tetrahedron Lett.*, **28**, 87 (1987)

124 R.M.K.Dale, E.Martin, D.C.Livingston, D.C.Ward. *Biochemistry*, **14**, 2447 (1975)

125 D.Bergstrom, P.Beal, A.Husain, R.Lind, J.Jenson. *J. Am. Chem. Soc.*, **111**, 374 (1989)

126 K.Hirota, T.Tomishi, Y.Maki, H.Sajiki. *Nucleosides Nucleotides*, **17**, 161 (1998)

127 Y.Zeng, H.Cao, Y.Wang. *Org. Lett.*, **8**, 2527 (2006)

128 S.Nampalli, I.Livshin, S.Kumar. *Nucleosides Nucleotides*, **18**, 697 (1999)

129 F.Botha, M.Slavíčková, R.Pohl, M.Hocek. *Org. Biomol. Chem.*, **14**, 10018 (2016)

130 S.Choi, T.I.Kalman, T.J.Bardos. *J. Med. Chem.*, **22**, 618 (1979)

131 R.F.Schinazi, J.Arbiser, J.J.S.Lee, T.I.Kalman, W.H.Prusoff. *J. Med. Chem.*, **29**, 1293 (1986)

132 G.Zima, D.Liotta. *Synth. Commun.*, **9**, 697 (1979)

133 M.Abdo, S.Knapp. *J. Am. Chem. Soc.*, **130**, 9234 (2008)

134 J.Oddershede, L.Henriksen, S.Larsen. *Org. Biomol. Chem.*, **1**, 1053 (2003)

135 M.Abdo, Y.Zhang, V.L.Schramm, S.Knapp. *Org. Lett.*, **12**, 2982 (2010)

136 A.E.A.Hassan, J.Sheng, J.Jiang, W.Zhang, Z.Huang. *Org. Lett.*, **11**, 2503 (2009)

137 L.B.Agenäs. *Acta Chem. Scand.*, **17**, 268 (1963)

138 J.Sheng, A.E.A.Hassan, W.Zhang, J.Zhou, B.Xu, A.S.Soares, Z.Huang. *Nucleic Acids Res.*, **39**, 3962 (2011)

139 R.E.Beltz, D.W.Visser. *J. Am. Chem. Soc.*, 77, 736 (1955)

140 D.W.Visser, P.Roy-Burman. In *Synthetic Procedures in Nucleic Acid Chemistry. Vol. 1. Preparations of Purines, Pyrimidines, Nucleosides, and Nucleotides*. (Eds W.W.Zorbach, R.St.Tipson). John Wiley & Sons Ltd., London-New York, 1968, 493

141 M.A.W.Eaton, D.W.Hutchinson. *Biochim. Biophys. Acta.*, **319**, 281 (1973)

142 J.Wang, K.-Y.Lin, M.D.Matteucci. *Tetrahedron Lett.*, **39**, 8385 (1998)

143 T.Suzuki, K.Ida, S.Uchibe, M.Inukai. *Bioorg. Med. Chem.*, **16**, 5146 (2008)

144 J.S.Beckman, J.Chen, H.Ischiropoulos, J.P.Crow. *Methods Enzymol.*, **233**, 229 (1994)

145 G.T.Crisp, B.L.Flynn. *J. Org. Chem.*, **58**, 6614 (1993)

146 G.T.Crisp, B.L.Flynn. *Tetrahedron Lett.*, **31**, 1347 (1990)

147 D.E.Bergstrom, J.L.Ruth. *J. Am. Chem. Soc.*, **98**, 1587 (1976)

148 C.F.Bigge, P.Kalaritis, J.R.Deck, M.P.Mertes. *J. Am. Chem. Soc.*, **102**, 2033 (1980)

149 D.E.Bergstrom, J.L.Ruth, P.A.Reddy, E.De Clercq. *J. Med. Chem.*, **27**, 279 (1984)

150 S.R.Sarfati, S.Pochet, J.-M.Neumann, J.Igolen. *J. Chem. Soc. Perkin Trans. 1.*, 1065 (1990)

151 Y.-M.Cho, F.Johnson. *Tetrahedron Lett.*, **35**, 1149 (1994)

152 D.E.Bergstrom, J.L.Ruth, P.Warwick. *J. Org. Chem.*, **46**, 1432 (1981)

153 R.F.Heck. *J. Am. Chem. Soc.*, **90**, 5531 (1968)

154 C.F.Bigge, M.P.Mertes. *J. Org. Chem.*, **46**, 1994 (1981)

155 G.Chang, M.P.Mertes. *J. Org. Chem.*, **52**, 3625 (1987)

156 R.F.Schinazi, W.H.Prusoff. *J. Org. Chem.*, **50**, 841 (1985)

157 M.Honjo, T.Maruyama, M.Horikawa, J.Balzarini, E.De Clercq. *Chem. Pharm. Bull.*, **35**, 3227 (1987)

158 T.Maruyama, M.Honjo. *Nucleosides Nucleotides*, **7**, 203 (1988)

159 S.H.Kim, S.H.Kim, C.H.Lim, J.N.Kim. *Tetrahedron Lett.*, **54**, 1697 (2013)

160 K.H.Cheit. *Chem. Ber.*, **99**, 3884 (1966)

161 K.Ikeda, S.Tanaka, Y.Mizuno. *Chem. Pharm. Bull.*, **23**, 2958 (1975)

162 Q.Dai, C.-X.Song, T.Pan, C.He. *J. Org. Chem.*, **76**, 4182 (2011)

163 G.Herrmann, D.Cech, G.Kowollik, P.Langen. *Z. Chem.*, **19**, 422 (1979)

164 A.V.Ivanov, A.R.Simonyan, E.F.Belanov, L.A.Aleksandrova. *Russ. J. Bioorg. Chem.*, **31**, 556 (2005)

165 S.Schiesser, T.Pfaffeneder, K.Sadeghian, B.Hackner, B.Steigenberger, A.S.Schröder, J.Steinbacher, G.Kashiwazaki, G.Höfner, K.T.Wanner, C.Ochsenfeld, T.Carell. *J. Am. Chem. Soc.*, **135**, 14593 (2013)

166 A.A.Tanpure, S.Balasubramanian. *ChemBioChem*, **18**, 2236 (2017)

167 J.K.Stille. *Angew. Chem.*, **25**, 508 (1986)

168 G.J.Crouch, B.E.Eaton. *Nucleosides Nucleotides*, **13**, 939 (1994)

169 H.Sun, M.L.T.Porro, M.M.Greenberg. *J. Org. Chem.*, **82**, 11072 (2017)

170 D.B.Gophane, B.Endeward, T.F.Prosner, S.T.Sigurdsson. *Org. Biomol. Chem.*, **16**, 816 (2018)

171 A.Matsuda, M.Inada, H.Nara, E.Ohtsuka, A.Ono. *Bioorg. Med. Chem. Lett.*, **3**, 2751 (1993)

172 Q.Sun, J.Sun, S.-S.Gong, C.-J.Wang, S.-Z.Pu, F.-D.Feng. *RSC Adv.*, **4**, 36036 (2014)

173 A.E.J.De Nooy, A.C.Besemer, H.van Bekkum. *Synthesis*, 1153 (1996)

174 M.Angelin, M.Hermansson, H.Dong, O.Ramström. *Eur. J. Org. Chem.*, 4323 (2006)

175 N.Isenberg, C.Heidelberger. *J. Med. Chem.*, **10**, 970 (1967)

176 M.F.Jones. *J. Pharm. Pharmacol.*, **33**, 274 (1981)

177 V.Guerniou, D.Gasparutto, S.Sauvaigo, A.Favier, J.Cadet. *Nucleosides Nucleotides Nucleic Acids*, **22**, 1073 (2003)

178 S.Bhilare, V.Gayakhe, A.V.Ardhapure, Y.S.Sanghvi, C.Schulzke, Y.Borozdina, A.R.Kapdi. *RSC Adv.*, **6**, 83820 (2016)

179 A.J.Gutierrez, T.J.Terhorst, M.D.Matteucci, B.C.Froehler. *J. Am. Chem. Soc.*, **116**, 5540 (1994)

180 L.A.Al-Razzak, D.Schwepler, C.J.Decedue, J.Balzarini, E.De Clercq. *J. Med. Chem.*, **30**, 409 (1987)

181 C.-Y.He, J.Kong, X.Li, X.Li, Q.Yao, F.-M.Yuan. *J. Org. Chem.*, **82**, 910 (2017)

182 B.-H.Zhang, J.-J.Kong, Y.Huang, Y.-G.Lou, X.-F.Li, C.-Y.He. *Chin. Chem. Lett.*, **28**, 1751 (2017)

183 P.Eisenberger, S.Gischig, A.Togni. *Chem. Eur. J.*, **12**, 2579 (2006)

184 Z.Fang, Y.Ning, P.Mi, P.Liao, X.Bi. *Org. Lett.*, 16, 1522 (2014)

185 D.Musumeci, C.Irace, R.Santamaria, D.Montesarchio. *Med. Chem. Commun.*, **4**, 1405 (2013)

186 T.Itahara. *Chem. Lett.*, **15**, 239 (1986)

187 K.Hirota, Y.Isobe, Y.Kitade, Y.Maki. *Synthesis*, 495 (1987)

188 Y.Liang, J.Gloudeman, S.F.Wnuk. *J. Org. Chem.*, **79**, 4094 (2014)