Approaches to the synthesis of heterocyclic *C*-nucleosides

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This review is focused on the synthetic strategies to heterocyclic *C*-nucleosides and covers the literature from 2011 to 2021. The main attention is paid to the following three approaches: the direct C—C coupling of a carbohydrate moiety with a preformed aglycon unit, the construction of a (pseudo)sugar residue on a pre-formed aglycon, and the construction of an aglycon on a pre-formed (pseudo)sugar. In each Section, the literature data are categorized in terms of the size of aglycon from simple to complex, the advantages and drawbacks of the reviewed approaches are discussed.

Key words: *C*-nucleosides, heterocycles, Remdesivir, convergent synthesis, divergent synthesis.

Analogs of natural nucleosides and nucleotides constituting a large class of compounds found wide applications in medicinal chemistry due mainly to their ability to compete with natural nucleosides as the building blocks for the synthesis of DNA and RNA.[1] To date, there are more than 30 such compounds were approved for the treatment of viral, cancer, bacterial, fungal, and some other diseases.[2—5]

Among the structural analogs of natural nucleosides that yet not entered clinical trials but exhibit *in vitro* biological activities, there are purine, pyrimidine, and pyrazine derivatives. It was shown[6] that the minimum inhibitory concentrations of the compounds of diazine family against different mycobacterium strains are lower than those of the comparator drugs (pyrazinamide and isoniazid). Abnormal purine nucleosides also show tuberculostatic activity.[7]

Natural nucleosides consist of aglycon (a nucleobase of purine (adenosine, guanine) or pyrimidine (thymine, uracil, cytosine) families) and a pentose sugar residue (ribose or 2′-deoxyribose) bonded by the C—N covalent bond. Consequently, the replacement or modification of these structural units can lead to the analogs of natural nucleosides.[8] To date, a wide variety of such modifications are in the arsenal of synthetic organic chemists. First, this is the replacement of the purine/pyrimidine unit by other (het)aryl residues. At the same time, it should be emphasized that formally the compounds obtained by such modifications are more correctly called

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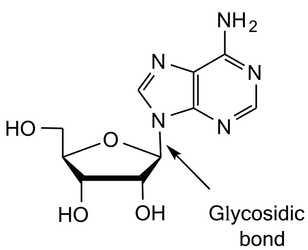
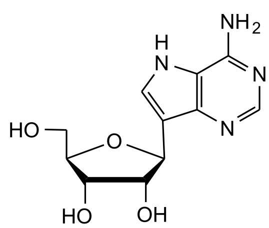
C-glycosyl compounds rather than *C*-nucleosides. Nevertheless, the term *C*-nucleosides is very popular in scientific literature. In this review, for the clarity the term *C*-nucleoside is referred to any compounds with C—C glycosidic bond, since from the viewpoint of biological activity in the cited publications they considered as the analogs of natural nucleosides. Second, the chemical modifications of natural nucleoside analogs involve the replacement of the ribose residue with alternative sugar units, introduction of carbocyclic moieties in the nucleosides as pseudoribose ring, replacement of endocyclic oxygen atom with other heteroatoms, *etc.*[8,9] The possibility to modify the glycosidic bond between aglycon and sugar residue is considered less frequently. Until recently, only limited data on a "shift" of this bond to other carbon atom of pseudoribose unit were available.[10,11]

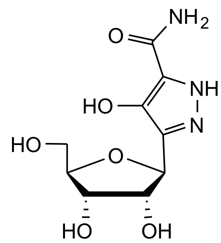
N-Nucleoside



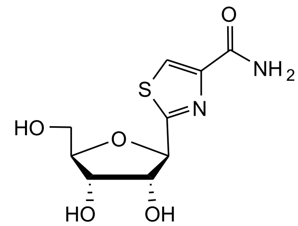
C-Nucleoside



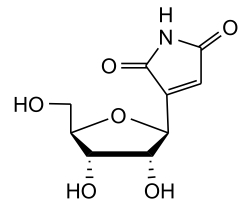
Since in some cases the C—N glycosidic bond, especially in purine deoxynucleosides, can be unstable to phosphorolysis with phosphorylases, the concept of *C*-nucleosides was introduced.[12—14] In *C*-nucleosides, the aglycon and sugar units are linked by the C—C covalent bond, which significantly increases metabolic stability of these compounds.[15] Among the synthesized *C*-nucleosides, the derivatives with promising antitumor and antiviral activities, *e.g.*, tiazofurin,[16] showdomycin,[17] formycin A and B analogs,[18] and pirazofurin,[19] were found. Recently, the interest in this class of the compounds significantly increased since *C*-nucleoside analog Remdesivir was approved by U.S. Food and Drug Administration for the treatment of COVID-19 and demonstrated direct antiviral effect by inhibiting RNA-dependent PNA polymerase (RdRp).[20,21]



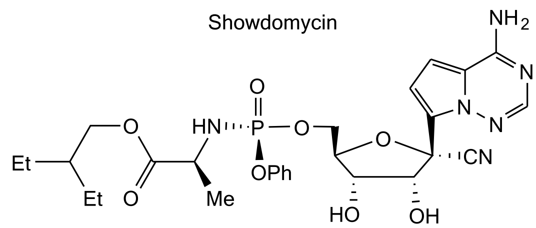
Pirazofurin



Tiazofurin



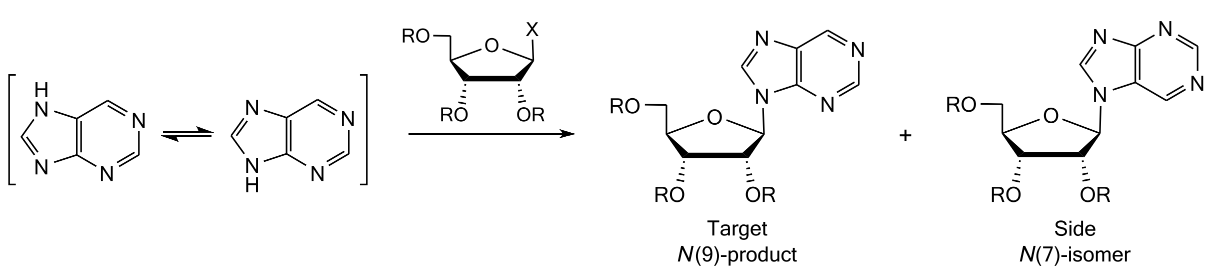
Showdomycin



Remdesivir

One of the key differences between the *C*-nucleoside synthesis and the *N*-nucleoside synthesis is the formation of the corresponding covalent bond between aglycon and carbohydrate residue. Thus, in the case of *N*-nucleoside the common approach to the C—N bond formation is the ribosylation of the nucleobase with sugars bearing the living group (halogen atom, OMe or OBn group).[22] The drawback of this method is the lack of regiospecificity because the prototropic tautomerism gave rise to side *N*(7)-ribosylated product (Scheme 1), and, in some cases, even more complex *N*(1)- and *N*(3)-regioisomers.[23]

Scheme 1



The C—C bond formation in *C*-nucleoside synthesis occurred regiospecifically, at the same time preliminary functionalization of both aglycon and sugar is required. The present review provided the analysis of the approaches to the *C*-nucleoside synthesis and strategies to the formation of the key C—C bond between aglycon and sugar. The main strategies towards *C*-nucleosides can be divided into three following groups: (1) the direct C—C coupling of the functionalized carbohydrate and aglycon, (2) the construction of a sugar residue on a pre-formed aglycon, and (3) the construction of an aglycon on a pre-formed sugar (Fig. 1).

The majority of the publications devoted to the *C*-nucleoside synthesis deals with the direct C—C bond formation between functionalized aglycon and carbohydrate. The articles on the construction of an aglycon on a pre-formed carbohydrate unit are in the second place. This is followed by the rarely applied approach to *C*-nucleosides *via* the construction of a sugar residue on a pre-formed aglycon.

The direct C—C coupling of the functionalized aglycon and carbohydrate can be achieved by the Pd-catalyzed reactions (the Suzuki, Sonogashira, and Heck reactions), by activation of the halogenated aglycon with the Grignard reagents followed by the reaction with (pseudo)ribonolactone, as well as using more exotic methods, *e.g.*, the electrochemical activation. The construction of an aglycon on a preformed (pseudo)riboside is often based on the cyclocondensation and cycloaddition reactions involving acetylene- and nitrile-substituted carbohydrate precursors that results in heterocyclic systems. The construction of a sugar residue on a pre-formed aglycon is the least common due approach apparently to it gives access to a limited scope of ribosides. Mainly, this approach is used to synthesize *C*-nucleosides with acyclic sugar residues.

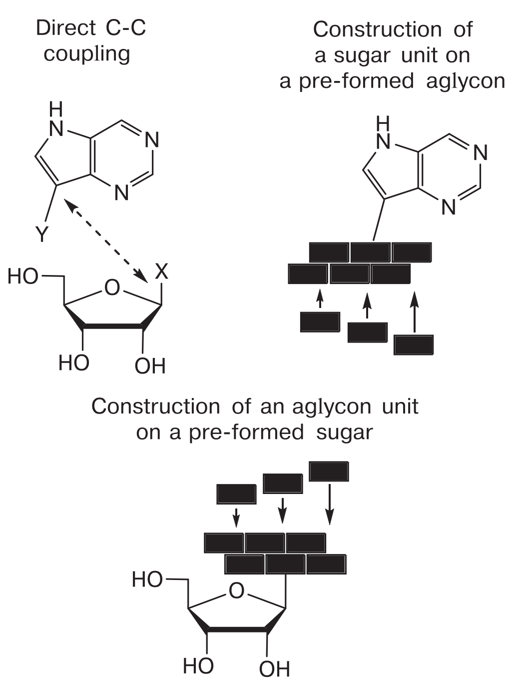


Fig. 1. Synthetic approaches to *C*-nucleosides.

According to the above approaches, the present review is divided into three large Sections in each of which the data are presented in the following order: simple aromatic aglycons, heterocyclic derivatives, and fused heterocyclic systems. The bibliography includes 109 references 83% of which were published in the last 10 years and 35% were reported in the last 5 years.

1. *C*-Nucleoside synthesis by the direct C—C coupling

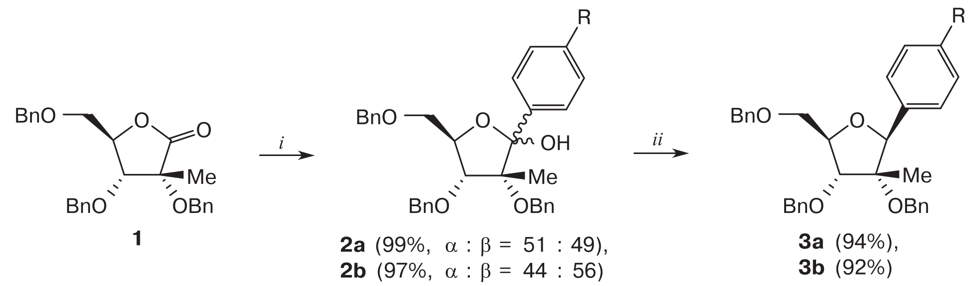
1.1. Reactions involving organometallic reagents

The most common approach to the *C*-nucleoside synthesis is the direct coupling of the preliminary functionalized carbohydrate and aglycon (see Fig. 1). This strategy is mainly implemented using the halogenated aglycons, which are converted to active carbanions by treatment with magnesium metal, the Grignard reagents, and some other methods. In these reactions, (pseudo)ribonolactone serves generally as an electrophile. The addition reactions gave hemiketals, which are further transformed to the target *C*-nucleosides.

Hocek and coworkers,[24] considering the structures of such well-known prodrugs as Sofosbuvir and Valopicitabine bearing 2′-*C*-methyl group synthesized their structural analogs, namely, benzene and pyridine 2′-*C*-methyl-*C*-ribonucleosides and -nucleotides (Schemes 2 and 3).

It is of note that in the inseparable mixtures of anomers **2a** and **2b** kept in DMSO-d_6 at 4 °C epimerization occurred, and after 2 weeks the ratio of anomers changed in favor of β-anomer (α : β = 31 : 69 for **2a** and α : β = 8 : 92 for **2b**). Reduction of the originally obtained mixtures of α- and β-anomers of compounds **2a** (α : β = 51 : 49) and **2b** (α : β = 44 : 56) using the $Et_3SiH/BF_3 \cdot Et_2O$ system in CH_2Cl_2 gave

Scheme 2



2, 3: R = H (**a**), Br (**b**)

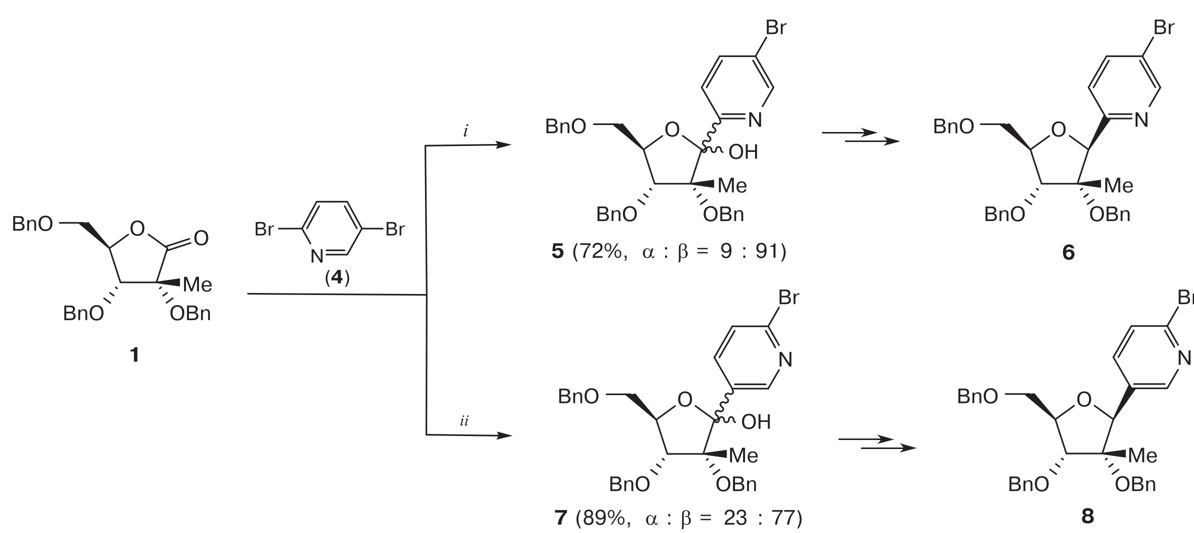
Reagents and conditions: *i.* 1) RC_6H_4Br, BuLi (1.1 equiv.), THF, –78 °C, 2) MeOH; *ii.* Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 → 20 °C, 5 min.

exclusively β-isomers of the target *C*-nucleosides **3a,b**. Hocek and coworkers[24] explained the observed stereoselectivity in terms of the formation of a planar oxocarbenium cation intermediate, which is then reduced by Et_3SiH.

The C—C coupling reactions of 2,5-dibromopyridine **4** and compound **1** to synthesize pyridine *C*-nucleosides (see Scheme 3) were carried out in the presence of BuLi in either toluene or diethyl ether. The reaction performed in toluene gave lower yield of the product than in Et_2O but proceeded with good β-stereoselectivity. In toluene, the C—C coupling reaction proceeded at the position 2 of 2,5-dibromopyridine to give compound **5** and in coordinating solvent Et_2O the reaction proceeded at the position 5 of 2,5-dibromopyridine to afford regioisomer **7**. Hemiketals **5** and **7** were transformed in the target *C*-nucleosides **6** and **8** by treatment with lithium bis(trimethylsilyl)amide (LiHMDS) followed by the reduction of the obtained acetates with $Et_3SiH/BF_3 \cdot Et_2O$.

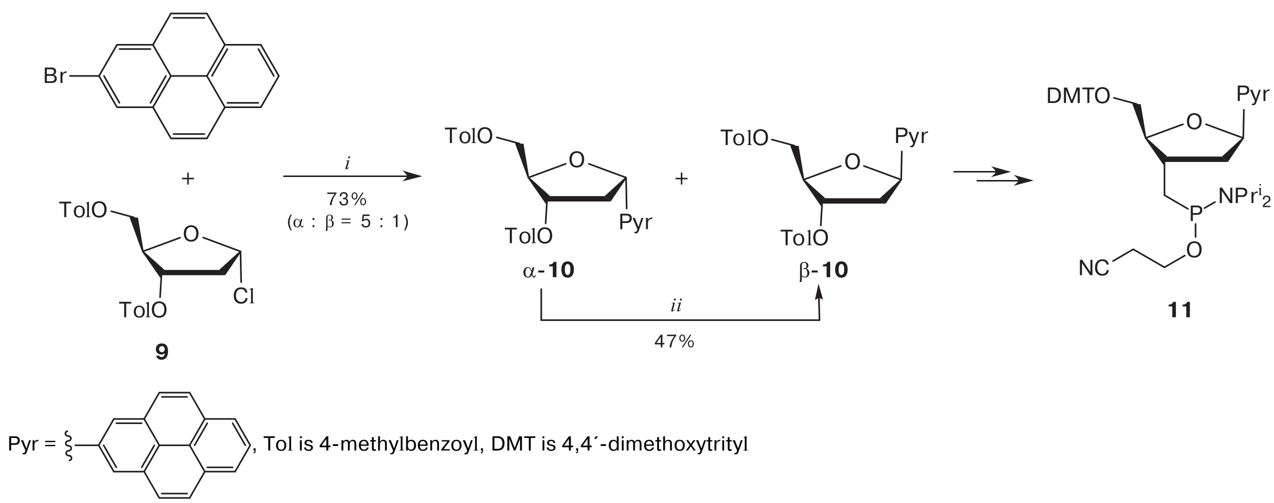
Leumann and coworkers[25] synthesized 2-pyrenyl-*C*-nucleosides using 2-pyrenylmagnesium bromide (Scheme 4). The obtained mixture of α- and β-anomers α-**10** and β-**10** was subjected to acid-catalyzed epimerization to give the target β-*C*-nucleoside β-**10**. Further transformations afforded phosphoramidite **11**, which was incorporated into oligodeoxynucleotides using standard automated DNA synthesis.

Scheme 3



Reagents and conditions: *i.* 1) BuLi (1.1 equiv.), toluene, –78 °C, 10 min, 2) MeOH; *ii.* **4**, BuLi (1.1 equiv.), diethyl ether, –78 °C, 10 min, 2) MeOH.

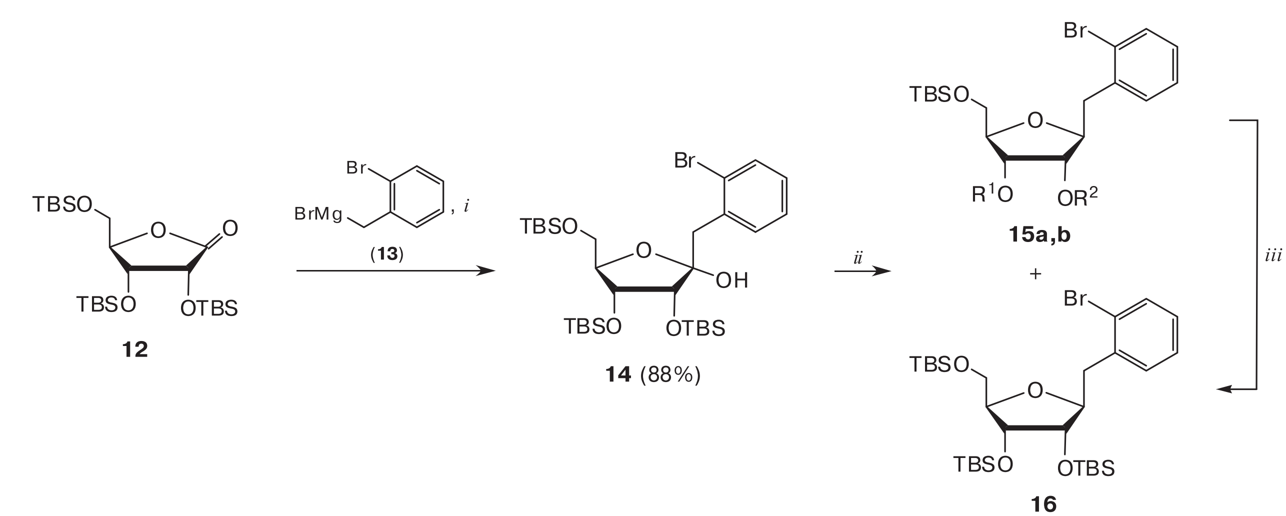
Scheme 4



Reagents and conditions: *i*. 1) Mg, THF, 55 °C, 2) CuI, 0 → 20 °C, 3) 55 °C; *ii*. CF_3CO_2H, $PhSO_3H$, reflux, 12 h.

Hocek and coworkers,[26] synthesized the 2-substituted benzyl *C*-ribonucleosides as the carba analogs of phosphoribosylanthranilate, a key intermediate in tryptophan biosynthesis. The synthesis involved the reaction of ribonolactone **12** with the Grignard reagent **13** (Scheme 5)[26]. The C—C bond forming reaction proceeded smoothly and stereoselectively to give α-hemiketal **14** in high yield (88%). It is of note that the reaction was carried out at room temperature under air and can be scaled up to 10-g load. The subsequent reduction of hemiketal **14** gave intermediate **16** in 36% yield in an inseparable mixture with two by-products **15a**,**b**. The mixture of partially silylated derivatives **15a**,**b** was converted into the fully silylated nucleoside **16** by silylation. Compound **16** was tested for the inhibition of PriA isomerase from *Mycobacterium tuberculosis* and showed no significant enzyme inhibition up to concentrations of 0.5 mmol L^{-1}.

Scheme 5



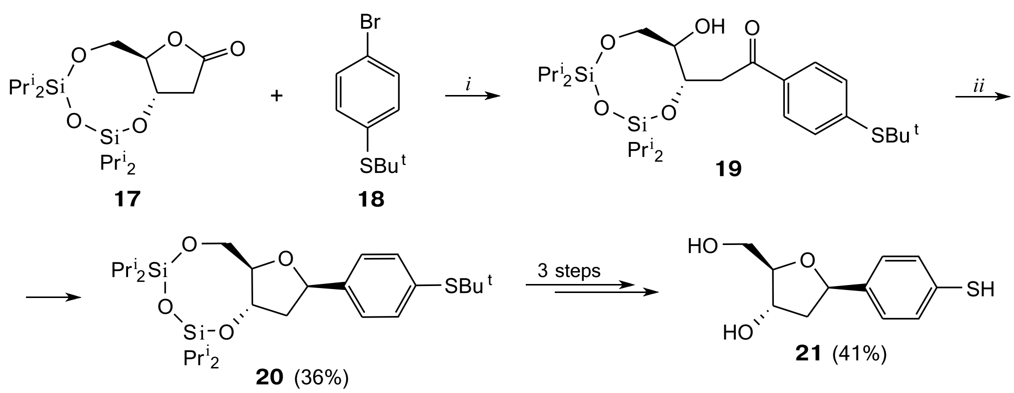
TBS is Bu^tMe_2Si
15: R^1 = H (**a**), TBS (**b**); R^2 = TBS (**a**), H (**b**)

Reagents and conditions: *i*. THF, 20 °C, 1 h, *ii*. Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C, 10 min; *iii*. TBSCl, imidazole, DMF, 24 h.

Hatano and coworkers[27] reported the synthesis of mercapto *C*-nucleosides **20** and **21** (Scheme 6). The reaction of the protected 2-deoxyribonolactone **17** with organolithium derivative generated *in situ* by treatment of precursor **18** with BuLi is accompanied with the lactone ring opening. The thus obtained hydroxy ketone **19** was selectively reduced with the ring closure to obtain product **20** as β-anomer. The subsequent deprotection using tetrabutylammonium fluoride (TBAF) (95%), treatment with NpsCl (74%, NpsCl is $2\text{-}O_2NC_6H_4SCl$), and reduction with EtSH/NEt_3 gave the target product **21**. In the last reduction step, significant amount (50%) of disulfide dimer was also obtained. Disulfide dimer was easily converted to the target compound **21** by treatment with mercaptoethanol in MeOH.

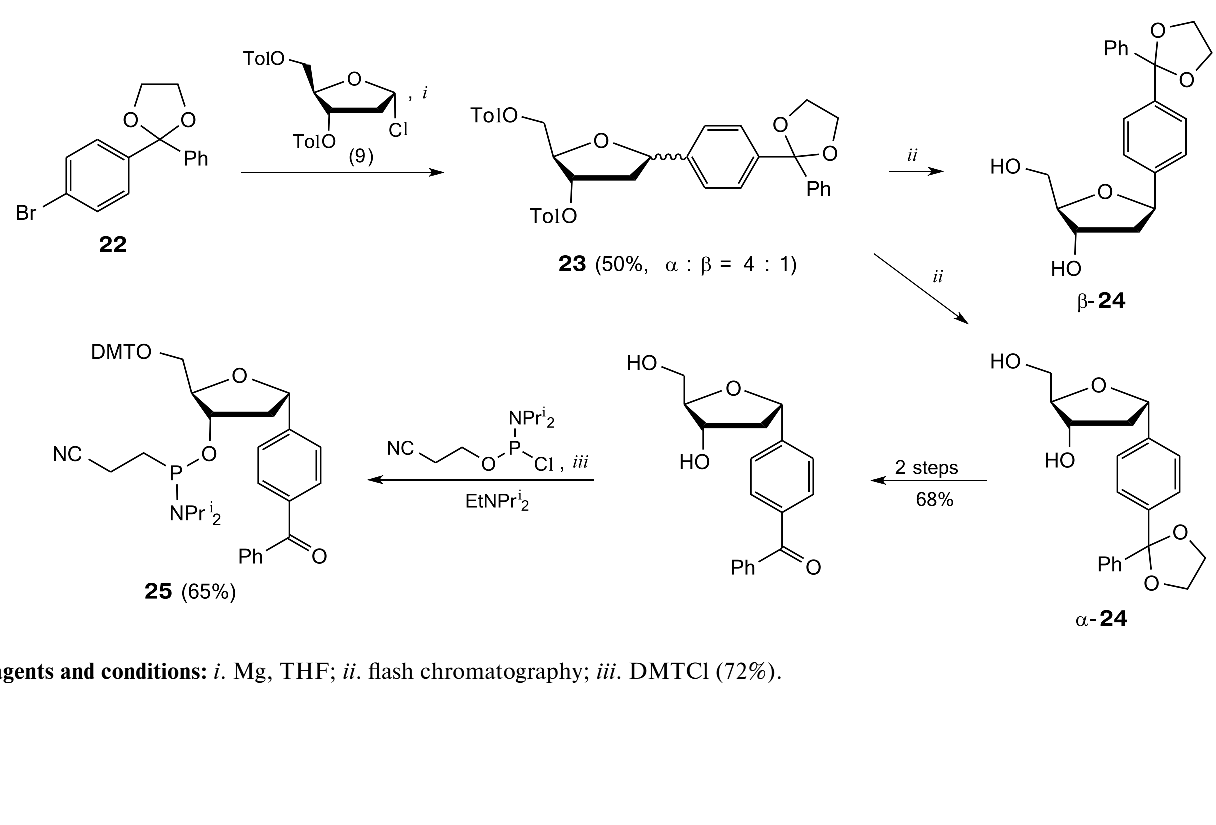
Weinberger and Wagenknecht[28] used 1,3-dioxolane **22** derived from 4-bromobenzophenone to synthesize benzophenone *C*-nucleosides (Scheme 7). Treatment of compound **22** with magnesium gave the Grignard reagent, which reacted with the Hoffer´s chlorosugar **9** to give product **23** as a mixture of α- and β-anomers. Anomers α-**23** and β-**23** were separated by flash chromatography and deprotected.

Scheme 6



Reagents and conditions: *i*. BuLi (1 equiv.); *ii*. Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2, −78 °C.

Scheme 7



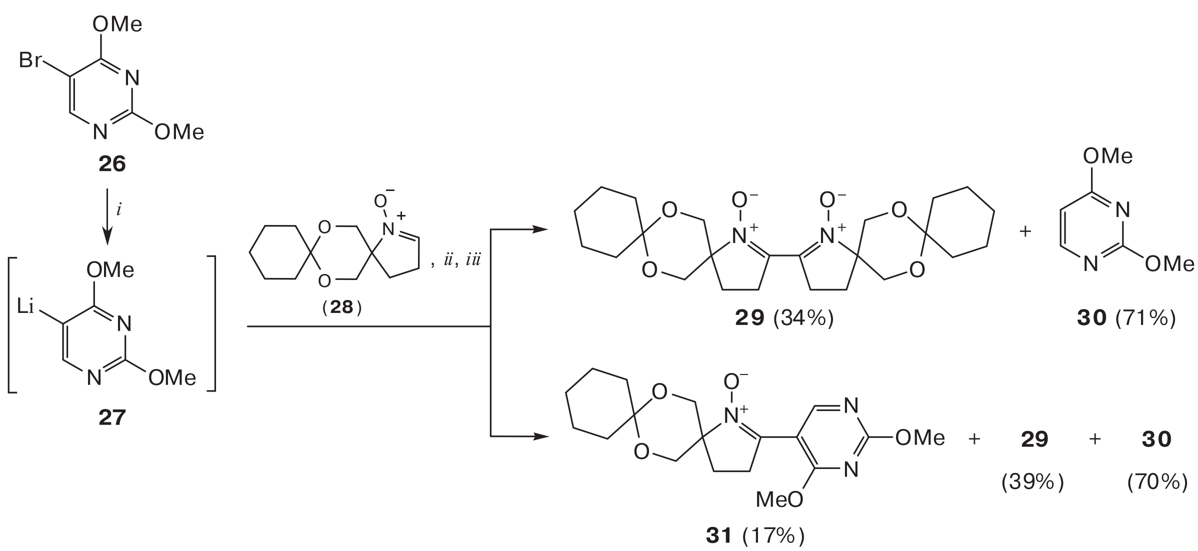
Reagents and conditions: *i*. Mg, THF; *ii*. flash chromatography; *iii*. DMTCl (72%).

It was found that the selectivity was shifted to α-**23**. Due to the better synthetic accessibility, α-stereoisomer α-**24** was subjected to phosphorylation to prepare the target *C*-nucleoside phosphoramidite **25**. The low yield of β-anomer β-**23** on the C—C coupling step is the significant disadvantage of this method because exactly this type of the bonding is characteristic of natural nucleosides. Phosphoramidite **25** was used to synthesize oligonucleotides.

Synthesis of pseudouridine analogs was described (Schemes 8 and 9).[29] It was found that the coupling of protected 5,5-bis(hydroxymethyl)-1-pyrroline 1-oxide **28** as a sugar mimic with organolithium species **27** generated by lithiation of bromo derivative **26** gave unwanted dimer **29**. The target product **31** was obtained as a minor product using 2 equiv. of Bu^tLi (see Scheme 8). The authors rationalized the choice of Bu^tLi to mediate the C—C bond forming reaction instead of commonly used Bu^nLi in terms of avoiding the addition reaction of Bu^nLi to keto nitrones since Bu^tLi did not undergo the addition under the reported conditions.

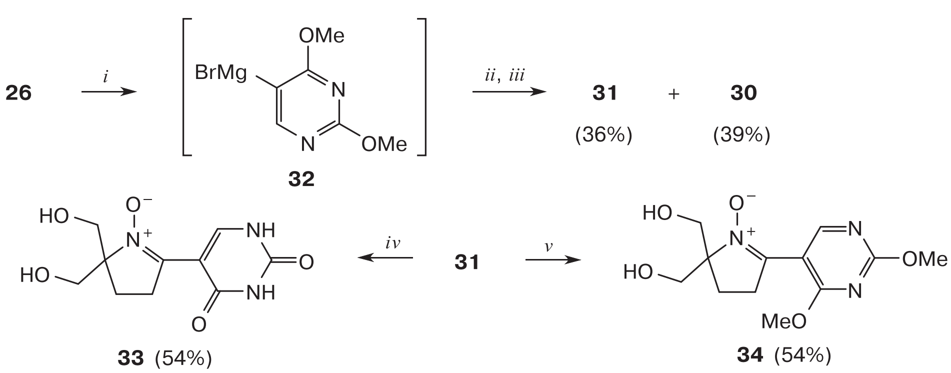
In turn, organomagnesium intermediate **32** generated by treatment of aryl bromide **26** with magnesium in THF in the presence of $(CH_2)_2Br_2$ reacted

Scheme 8



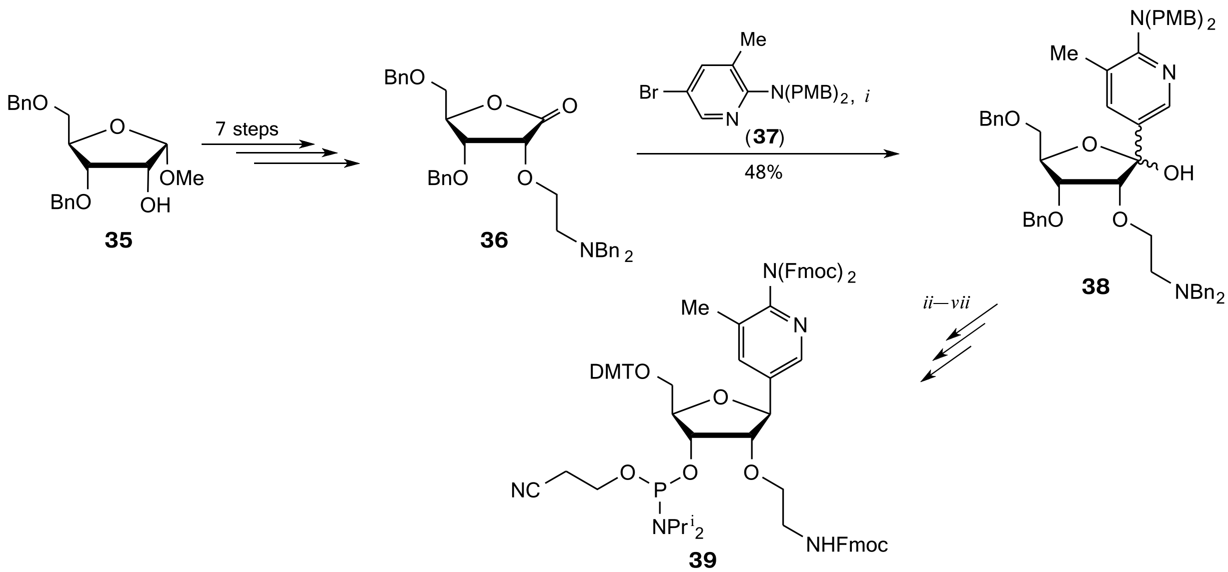
Reagents and conditions: *i*. 1) Bu^tLi (1.7 *M* in pentane), THF, –78 °C, 30 min, 2) **27** (**27** : Bu^tLi = 1 : 1.2 or 1 : 2); *ii*. THF, –78 → 20 °C, 3 h; *iii*. $Cu(OAc)_2$, NH_3 (aqueous), 1,4-dioxane, CH_2Cl_2, ~20 °C, 24 h.

Scheme 9



Reagents and conditions: *i*. Mg, $(CH_2)_2Br_2$, THF, reflux, 3 h; *ii*. **28**, THF, –10 °C, 2 h; *iii*. $Cu(OAc)_2$, NH_3 (aqueous), 1,4-dioxane, CH_2Cl_2, 20 °C, 24 h; *iv*. NaI, AcOH, 70 °C, 30 min; *v*. AcOH, 80 °C, 30 min.

Scheme 10



PMB is 4-$MeOC_6H_4CH_2$; Fmoc is fluorenylmethoxycarbonyl

Reagents, conditions, and yields: *i*. BuLi (1 equiv.), THF, –78 °C; *ii*. Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2, –78 °C, 26 h, 57%; *iii*. CF_3CO_2H, ~20 °C, 5 h, 85%; *iv*. BCl_3, CH_2Cl_2, –78 °C, 7 h, 88%; *v*. Pd/C, MeOH, 50 °C, 18 h; *vi*. 1) TMSCl, pyridine, ~20 °C, 2 h; 2) FmocCl, MeCN (anhydrous), ~20 °C, 4 h; 3) KF, H_2O, ~20 °C, 20 min; *vii*. DMTCl, 20 °C, 2 h, 78%; *viii*. $NC(CH_2)_2OP(Cl)NPr^i_2$, NPr_2^iEt, CH_2Cl_2, ~20 °C, 2 h, 82%.

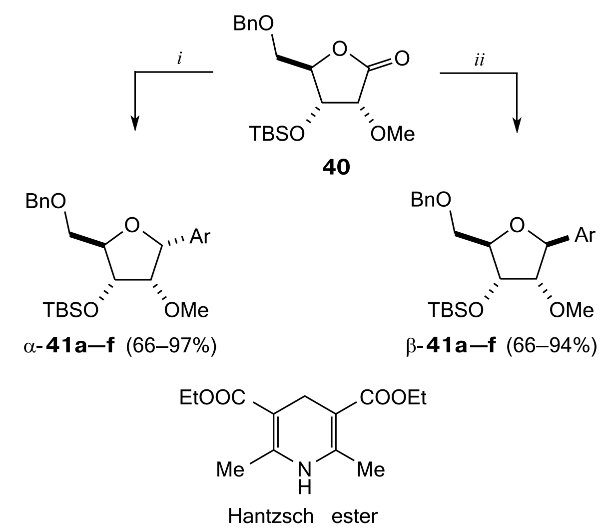
with *N*-oxide **28** to afford compound **31** in 36% yield (see Scheme 9).

Thus, the C—C coupling of compounds **26** and **28** *via* the organomagnesium intermediate **32** is more promising, however even under these conditions by-product **30** is formed in high yield. Deprotection of compound **31** resulted in pseudouridine analogs **33** and **34**.

Brown and coworkers[30] synthesized phosphoramidite **39** (Scheme 10). The key lactone intermediate **36** for the C—C coupling was obtained from compound **35** in 7 steps. The yields in each of the steps were 72—99%. The C—C coupling of lactone **36** with bromopyridine **37** in the presence of BuLi produced hemiketal **38** in moderate yield (48%). The low yield of compound **38** was explained by the formation of side hydrolysis products. The Fmoc and DMT protective groups were chosen because their permit to incorporate phosphoramidite **39** into triplex-forming oligonucleotides (TFOs).

The C—C bond forming reaction to synthesize nucleosides **41a—f** was carried out by reacting the corresponding (het)aryllithium derivatives with ribonolactone **40** (Scheme 11).[31] Deoxygenation of the product mixtures in the presence of $BF_3 \cdot Et_2O$ and Et_3Si gave the target C(1)-arylated riboses **41a—f**

Scheme 11



Compounds **41**	Ar	α : β ratio Method *i*	α : β ratio Method *ii*
41a	Ph	20 : 1	1 : >20
41b	2-FC_6H_4	20 : 1	1 : >20
41c	3-thienyl	20 : 1	1 : 10
41d	6-methoxypyridin-3-yl	20 : 1	1 : 17
41e	quinolin-3-yl	>20 : 1	1 : 15
41f	5-bromopyridin-3-yl	>20 : 1	1 : 2

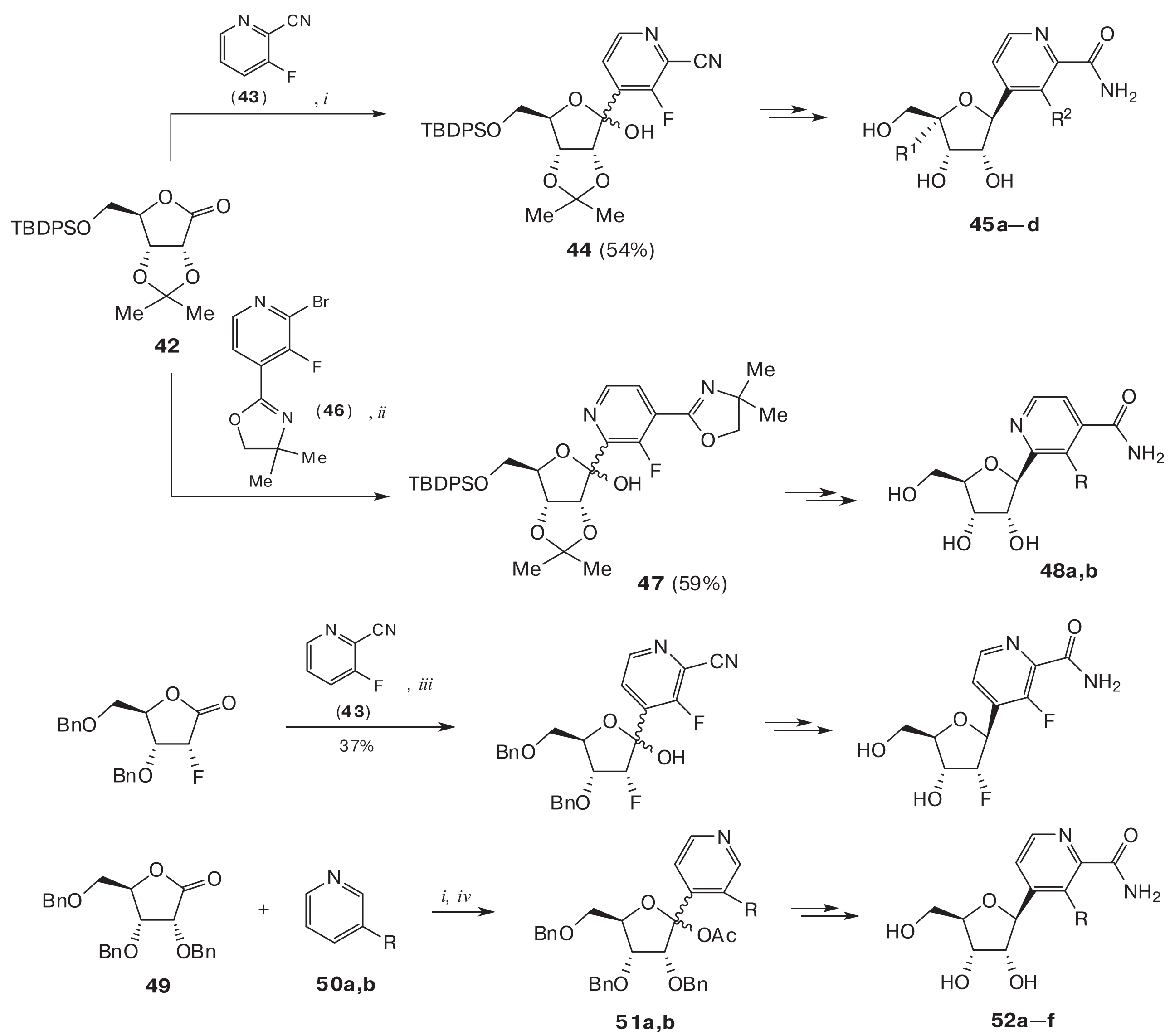
TBS is Bu^tMe_2Si

Reagents and conditions: *i*. 1) ArLi, 2) $BF_3 \cdot Et_2O$, Et_3SiH; *ii*. 1) ArLi, 2) $BF_3 \cdot Et_2O$, Hantzsch ester.

as the α-anomers exclusively. It is of note that MacMillan and coworkers[31] were the first to use the Hantzsch ester as the reductant to obtain the desired β-anomers of *C*-nucleosides **41a—f**.

Pyridine, pyridazine, and pyrimidine *C*-nucleosides as Favipiravir analogs were synthesized by Wang *et al.* (Scheme 12).[32] It is of note that *C*-nucleosides **44** and **51a,b** were synthesized using LDA for generating the lithium intermediates. This allowed the protonated derivatives **43** and **50a**,**b** to react with the protected lactones. The reaction of lactone **42** with lithium intermediate derived from **43** gave product **44** as a mixture of anomers the ratio of which was not given. The reaction of pyridines **50a,b** with lactone **49** carried out under similar conditions gave rise to derivatives **52a—f**. *C*-Nucleosides **48a**,**b**

Scheme 12



TBDPS is Bu^tPh_2Si
45: R^1 = H, R^2 = H (**a**), OMe (**b**), OH (**c**); R^1 = R^2 = F (**d**)
48: R = F (**a**), OH (**b**)
50, 51: R = Cl (**a**), Br (**b**)
52: R = H (**a**), Cl (**c**), Br (**d**), Me (**b**), vinyl (**e**), ethynyl (**f**)

Reagents and conditions: *i*. LDA (1 equiv.), THF, –78 °C; *ii*. BuLi (1 equiv.), THF, –78 °C, 2 h; *iii*. 3-fluoropicolinonitrile, LDA (1.01 equiv.), THF, –78 °C, 1 h; *vi*. lithium bis(trimethylsilyl)amide (LiHMDS), Ac_2O.

were synthesized from lactone **42** and bromopyridine **46** activated for the C—C coupling by treatment with BuLi.

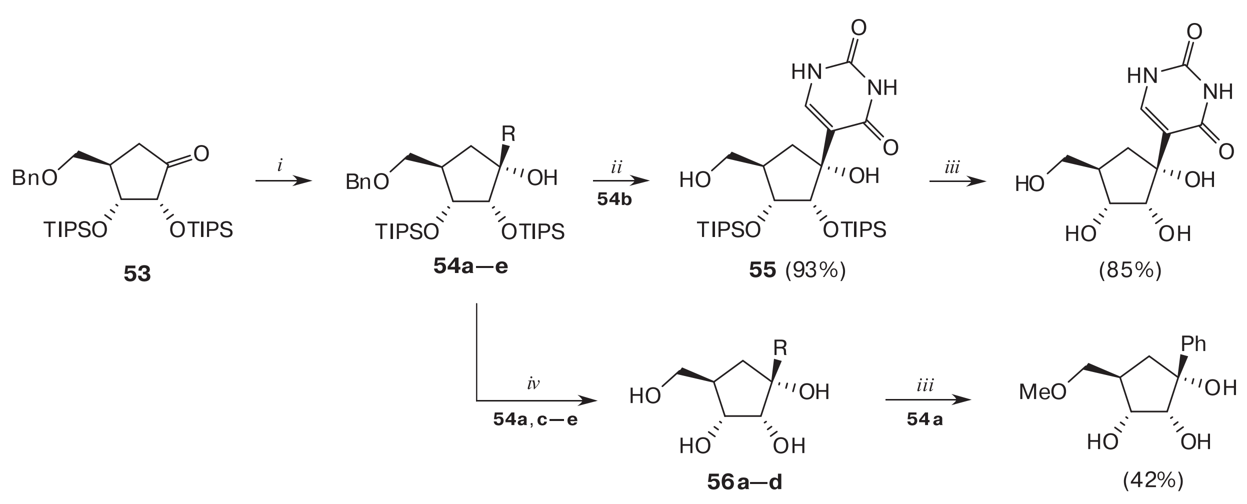
The inhibitory activity of 5´-*O*-triphosphate derived from compound **45a** against RdRp of hepatitis C virus (HCV), rhinovirus, and norovirus was evaluated. The half-maximal inhibitory concentrations (IC_{50}) of triphosphate of **45a** against RdRp of HCV, rhinovirus, and norovirus equal respectively to 5.3, 4.0, and 3.5 μmol L^{-1} indicated that compound **45a** may have the potential to be a broad-spectrum antiviral agent if it can be phosphorylated in infected cells. The anti-influenza activity of the synthesized compounds was determined in Madin—Darby canine kidney (MDCK) epithelial cells infected with influenza strain H1N1. Compound **45a** has activity and cytotoxicity comparable to Favipiravir (EC_{50} 1.9 μmol L^{-1} for **45a** and 2.7 μmol L^{-1} for Favipiravir). Compound **45c** exhibits even better inhibitory activity (EC_{50} = 1.3 μmol L^{-1}) but its cytotoxicity is several times higher (half-maximal cytotoxic concentration CC_{50} = 2.0 μmol L^{-1}) than that of compound **45a** and Favipiravir (CC_{50} > 400 μmol L^{-1}).

Maier *et al.*[33] described diastereoselective synthesis of carbocyclic *C*-nucleosides based on lithium and magnesium salts derived from aglycons and cyclopentane **53** synthesized from norbornadiene in four steps (Scheme 13).

Metobo *et al.*[34] developed a convenient synthetic procedure towards azoloazine *C*-nucleosides *via* direct C—C coupling of different lactones and activated azolotriazines. *C*-Nucleosides modified at the C(1´) atom of the carbohydrate unit are of special interest. Taking into account previously studied structurally related compounds with biological activity, Metobo *et al.*[34] synthesized 1´-substituted tubercidin *C*-nucleoside analogs (Scheme 14).[34] Lactone **49** reacted with lithium derivative generated by treatment of bromopyrrolotriazine **57** with BuLi to give hemiacetal **58** as a 3 : 1 anomeric mixture in 38% yield (see Scheme 14, method *A*). The yield of compound **58** was increased to 60% when *N*-protected derivative of **57** was used (see Scheme 14, method *B*).

The stereochemical outcome of the addition of hemiketal **58** to nucleophiles in the presence of different Lewis acids at different temperatures was

Scheme 13

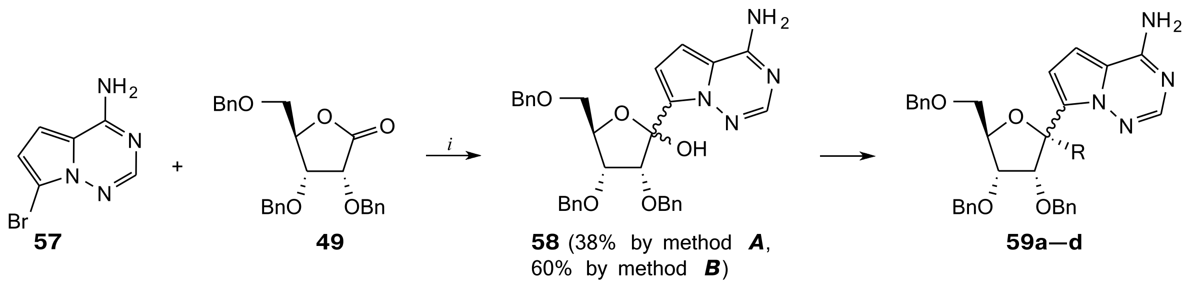


TIPS is $Pr^{i}{}_{3}Si$

Compound	R	Yield (%)		Compound	R	Yield (%)	
54, **56**		**54**	**56**	**54**, **56**		**54**	**56**
54a, **56a**	Ph	55	92	**54c**, **56b**	Bu	38	92
54b	2,4-bis(benzyloxy)-pyrimidin-5-yl	45	—	**54d**, **56c**	Bn	79	93
				54e, **56d**	thiazol-4-yl	90	53

Reagents and conditions: *i*. 1) PhLi (1.5 equiv.), THF, 0 °C (for **54a**); 2,4-bis(benzyloxy)-5-bromopyrimidine, BuLi (1 equiv.), THF, –78 °C, 2) **53**, –78 → 20 °C (for **54b**); BuMgCl (1.5 equiv.), THF, 0 → 20 °C (for **54c**); BnMgCl (1.5 equiv.), THF, 0 → 20 °C (for **54d**); 4-bromothiazole, $Pr^{i}MgCl \cdot LiCl$ (1.07 equiv.) (for **54e**); *ii*. H_2, Pd/C, EtOH, 80 °C; *iii*. TBAF, THF, ~20 °C; *iv*. 1) TBAF, THF, ~20 °C, 2) H_2 (50 bar), $Pd(OH)_2/C$, THF, 70 °C.

Scheme 14



59: R = CN (**a**), $CH_2CH=CH_2$ (**b**), Me (**c**), H (**d**)

Reagents and conditions: *i*. Method ***A***: 1) **57**, BuLi (3.3 equiv.), THF, –78 °C; 2) **49**, 3 h; Method ***B***: 1) **57**, $(ClSiMe_2CH_2)_2$ (1.2 equiv.), NaH (2.2 equiv., 60% suspension in mineral oil), BuLi (3.3 equiv.), THF, –78 °C, 2) **49**, 1 h.

Table 1. Stereoselectivity of the synthesis of compounds **59**

Compound	Nucleophile	Lewis acid	*T*/°C	*t*/h	Yield of **59** (%)	α : β
59a	TMSCN	TMSOTf	0	2	76	43 : 57
59a	TMSCN	TMSOTf	–78	3	65	15 : 85
59a	TMSCN	$BF_3 \cdot Et_2O$	–78	3	58	11 : 89
59b	AllylTMS	$BF_3 \cdot Et_2O$	–78	2	55	13 : 87
59b	AllylTMS	$BF_3 \cdot Et_2O$	0	2	75	26 : 74
59c	$AlMe_3$	$BF_3 \cdot Et_2O$	0	3	45	50 : 50
59d	Et_3Si	$BF_3 \cdot Et_2O$	0	1	82	5 : 95

studied (Table 1). It was found that the reaction temperature was the key parameter in the synthesis of nitrile **59a**. Thus, at 0 °C, the reaction proceeded with good yield but non-stereoselectively. Lowering the reaction temperature to –78 °C and replacement of TMSOTf with $BF_3 \cdot Et_2O$ increased the reaction selectivity though decreased the yield of product **59a**. Lowering the reaction temperature also improved stereoselectivity of the formation of allyl derivative **59b**. In contrast, this approach was unsuccessful in the case of compound **59c**. The reaction at 0 °C afforded the 1 : 1 anomeric mixture of **59c** and at –78 °C the conversion was less than 5%. High β-stereoselectivity was achieved only when Et_3SiH in the presence of $BF_3 \cdot Et_2O$ was used for the anomeric reduction of hemiketal **58**.

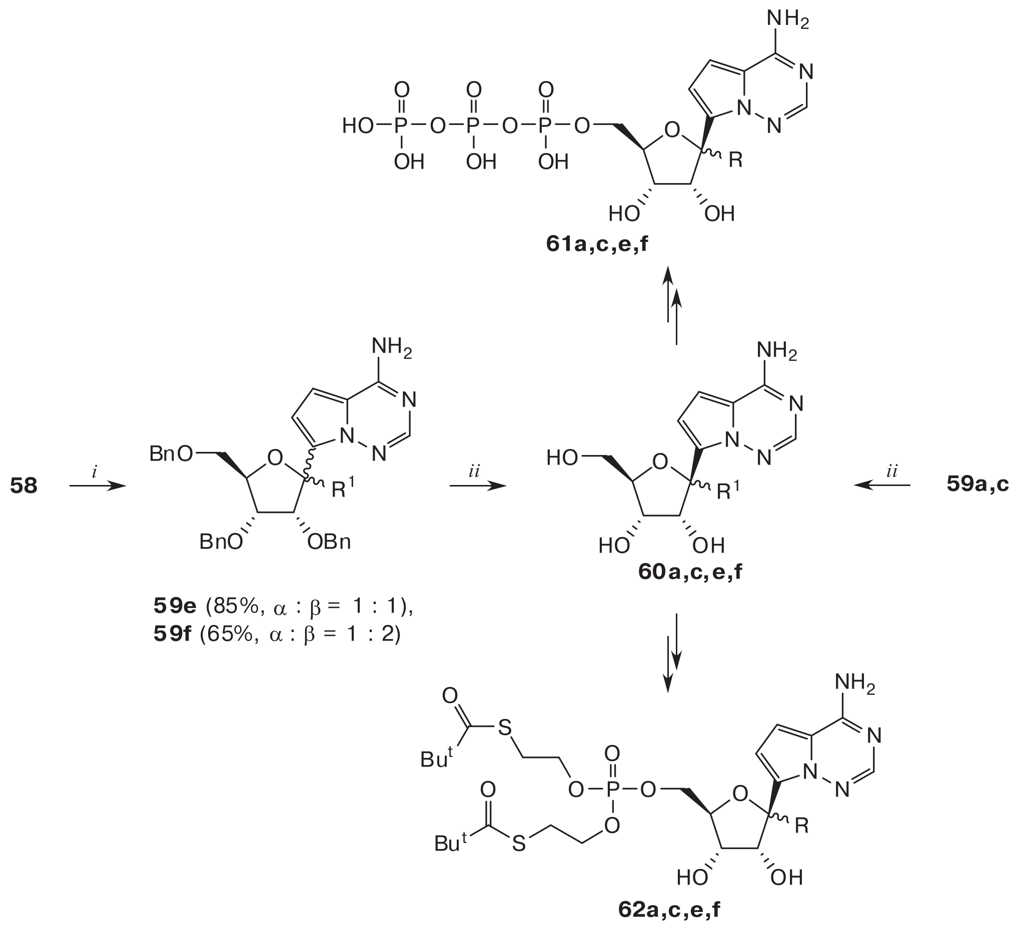
Removal of benzyl protective groups in compound **59d** using BCl_3 at –78 °C gave *C*-nucleoside in 78% yield.

Cho and coworkers[35] synthesized 1′-vinyl and 1′-ethynyl derivatives **59e,f**. From compounds **59e,f**, phosphorylated prodrugs **61 62** were prepared for biological evaluation (Scheme 15). The yields of compounds **60—62** are not given.[35]

Nucleosides **60a**,**c,e,f** were tested against several RNA viruses. The highest activity against HCV, yellow fever, Dengue virus type 2, parainfluenza virus type 3, and coronavirus SARS-CoV was demonstrated by compound **60a** with EC_{50} = 4.1, 11, 9.46, 1.71, and 2.24 μmol L^{-1}, respectively. Prodrug **62a** exhibited the most potent inhibitory activity against RdRp of hepatitis C virus with the half-maximal effective concentration (EC_{50}) and IC_{50} values of 0.085 and 5.6 μmol L^{-1}, respectively.

Cho and coworkers[36] synthesized 2′-*C*-methyl-*C*-nucleoside analogs of adenosine **65a**,**b**, **68**, uridine **69**, and cytidine **70** (Scheme 16). It is of note that the C—C coupling of ribonolactone **1** and bromo aglycons **57** and **63** in the presence of 3.3 equiv. of BuLi afforded compounds **64a,b** in the yields of 56 and 60%, respectively. The reaction with bis(methylthio) derivative **66** and equimolar amount of BuLi gave product **67** in 85% yield. It was found that coupling of lactone **1** with 5-bromo-2,4-di-*tert*-butoxypyrimidine proceeded with the ribose ring opening that required two additional steps to synthesize compound **69**.

Scheme 15



59: R = $CH=CH_2$ (**e**), C≡CH (**f**)
60—62: R = CN (**a**), Me (**c**), $CH=CH_2$ (**e**), C≡CH (**f**)

Reagents and conditions: *i.* CH_2=CHMgBr (6 equiv.) (for **59e**) or HC≡CMgCl (6 equiv.) (for **59f**), THF, 0 → 20 °C, 2 h, 2) MsOH (cat.), CH_2Cl_2, ~20 °C, 3 h; *ii.* BCl_3 or BBr_3 (4—8 equiv.), CH_2Cl_2, −78 °C, 1 h.

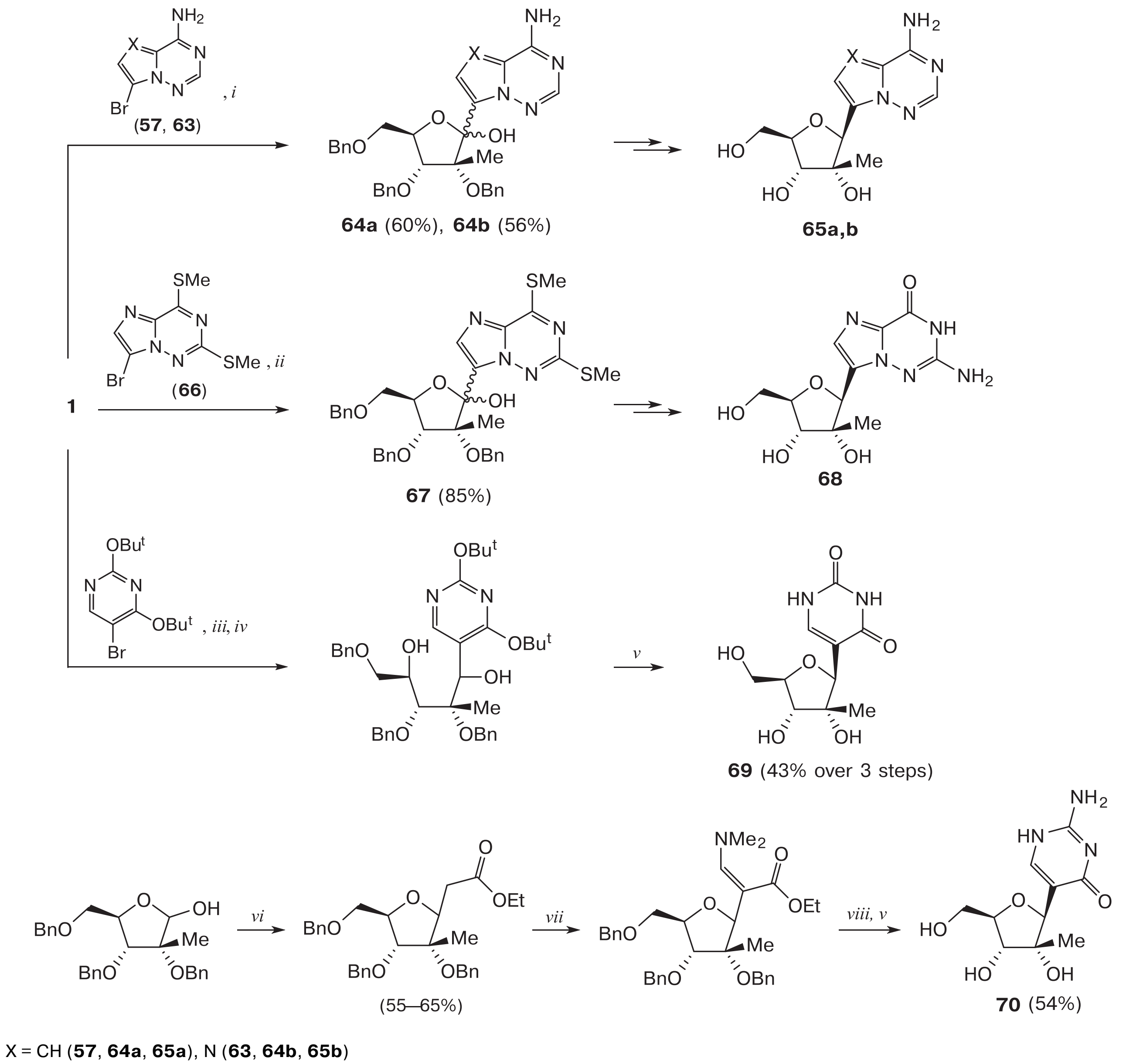
Of the synthesized *C*-nucleosides, only adenosine analogs **65a**,**b** showed activity against subgenomic GT1b HCV replicon with the EC_{50} 20-fold higher than those of the corresponding *N*-nucleosides. The most potent activity was demonstrated by compounds **65a** and **68** (IC_{50} = 0.31 and 0.19 μmol L^{-1} *vs* IC_{50} = 0.30 and 0.25 μmol L^{-1} for the corresponding *N*-nucleosides).

Reaction of lactone **1** and bromo heterocycle **57** in the presence of 3.3 equiv. of BuLi and 1 equiv. of $(ClSiMe_2CH_2)_2$ produced 1′-cyano-2′-*C*-methyl 4-aza-7,9-dideazaadenosine **71** (Scheme 17).[37] Compound **71** efficiently inhibited replication of hepatitis C virus (IC_{50} = 0.29 μmol L^{-1}). A phosphoramidate-type monophosphate prodrug derived from compound **71** was found to exhibit respectable replicon activity against GT1b HCV (EC_{50} = = 1.05 μmol L^{-1}).

Kirschberg and coworkers[38] synthesized 2′-fluoro-2′-*C*-methyl *C*-nucleoside **74** inhibiting HCV polymerase (Scheme 18). The IC_{50} value of 5′-*O*-triphosphate derived from compound **74** against nonstructural protein 5B (NS5B, RNA polymerase) found in the wild-type genotype 1b (GT1b) replicon of the hepatitis C virus was equal to 0.42 μmol L^{-1}.

At present, several methods to construct the nucleoside core of remdesivir are known. These methods gave the products of the C—C coupling of aglycon with riboside in the yields ranging from 25 to 69%.[20,34,35,39—42]

Scheme 16

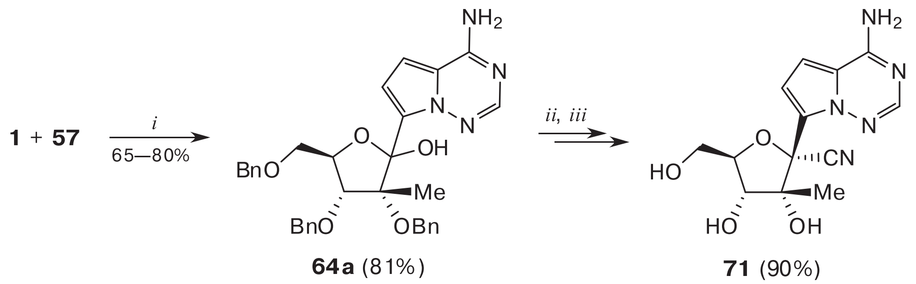


Reagents and conditions: *i*. 1) **57** or **63**, $(ClSiMe_2CH_2)_2$ (1.2 equiv.), 2) BuLi (3.3 equiv.), THF, −78 °C, 3) **1**, 1 h; *ii*. 1) **66**, BuLi, (1.0 equiv.), THF, −78 °C, 2) **1**, 1 h; *iii*. 1) 5-bromo-2,4-di-*tert*-butoxypyrimidine, BuLi (1.0 equiv.), THF, −78 °C, 2) **1**, 1 h; 3) $NaBH_4$ (4 equiv.), MeOH, 0 °C, 1 h; *iv*. HCl—EtOH (1 : 10 v/v), ~20 °C, 2 h; *v*. H_2, 10% Pd/C, 54%; *vi*. Ph_3PCHCO_2Et (1.5—2.5 equiv.), MeCN, microwave irradiation, 180 °C, 1 h; *vii*. Bredereck's reagent $Me_3COCH(NMe_2)_2$ (1.5 equiv.), toluene, 120 °C, 6 h; *viii*. guanidine (10 equiv.), MeOH, ~20 °C, 24 h.

Xue *at al.*[43] suggested to add secondary amines in the reaction mixture to stabilize the lithium aglycon intermediate and improve the yield of the target product **58** (Scheme 19). Additives of sterically hindered secondary amines (Table 2, entries *4—7*) were beneficial for improving the yield of the target product **58** up to 74%. When the reaction was carried out in the presence of tertiary diisopropylethylamine, the yield of product **58** decreased to 49%. The effect of the solvent : reactant ratio on the yield of the target product was also evaluated. It was found that the optimal concentration of the reactants is 0.2 mol L^{-1}.

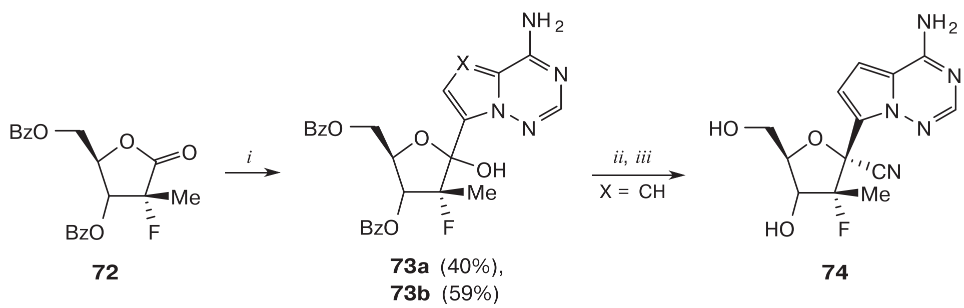
Convergent synthesis of imidazo[2,1-*f*][1,2,4]-triazin-4-amine *C*-nucleoside by the direct C—C

Scheme 17



Reagents, conditions, and yields: *i.* $(ClSiMe_2CH_2)_2$ (1 equiv.), BuLi (3.3 equiv.), THF, –78 °C, 1 h; *ii.* TMSCN (6 equiv.), TMSOTf (4 equiv.), CH_2Cl_2, $-15 \to 0$ °C, 2 h, 93%; *iii.* BCl_3 (3 equiv.), CH_2Cl_2, 0 °C, 1 h.

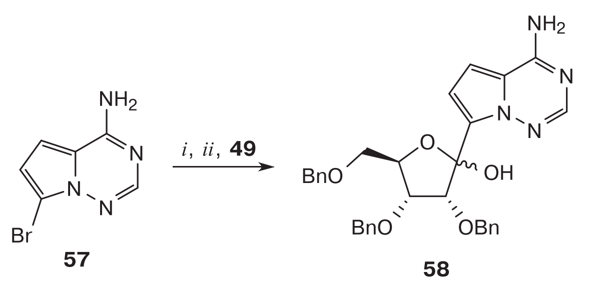
Scheme 18



73: X = CH (**a**), N (**b**)

Reagents, conditions, and yields: *i.* 1) **57** or **63** (1 equiv.), $(ClSiMe_2CH_2)_2$ (1.02 equiv.), THF, –78 °C, 1.6 *M* BuLi (1.1 equiv.), 2) **72**; *ii.* TMSCN, $In(OTf)_3$, dichloroethane, 58% (β : α = ~95 : 5); *iii.* concentrated aqueous NH_3, MeOH, 60%.

Scheme 19



Reagents and conditions: *i.* $(ClSiMe_2CH_2)_2$; *ii.* 1) R_2NH, BuLi, THF, –78 °C, 2 h, 2) **49**.

coupling of bromo heterocycle **75** and ribonolactone **77** in the presence of BuLi was described (Scheme 20)[44].

Guanosine derivatives **68** and **80** were synthesized similarly (Scheme 21).[44]

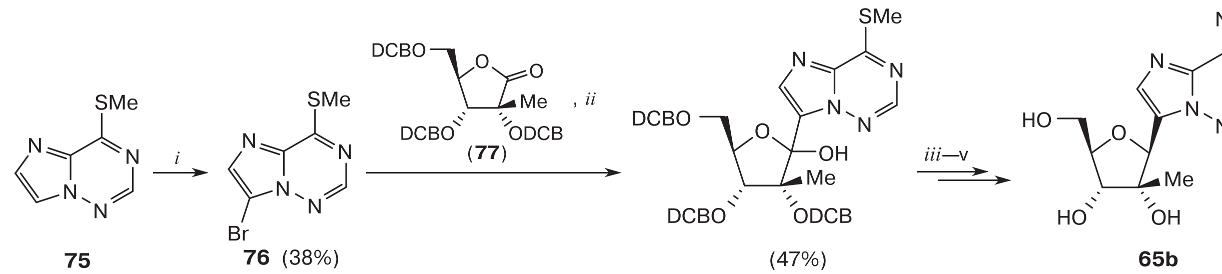
Draffan and coworkers[44] noted that the C—C coupling of ribonolactone **77** with less stable lithium intermediate generated from bromides **79** should be carried out at lower temperature (–100 °C; see Scheme 22) than the reaction with more stable anion of compound **76** (–78 °C; see Scheme 20). An alternative approach to *C*-nucleoside **80** is shown in Scheme 22.

Liu *at al.*[45] described an efficient synthesis of α- and β-*C*-nucleosides with high anomeric selectivity

Table 2. Effect of the amine additives on the yield of compounds **58**

Entry	Amine	Yield of **58** (%)
1	Diethylamine	41
2	Dipropylamine	45
3	Dibutylamine	54
4	Diisopropylamine	74
5	Diisobutylamine	71
6	Dicyclohexylamine	70
7	2,2,6,6-Tetramethylpiperidine	74
8	Diisopropylethylamine	49

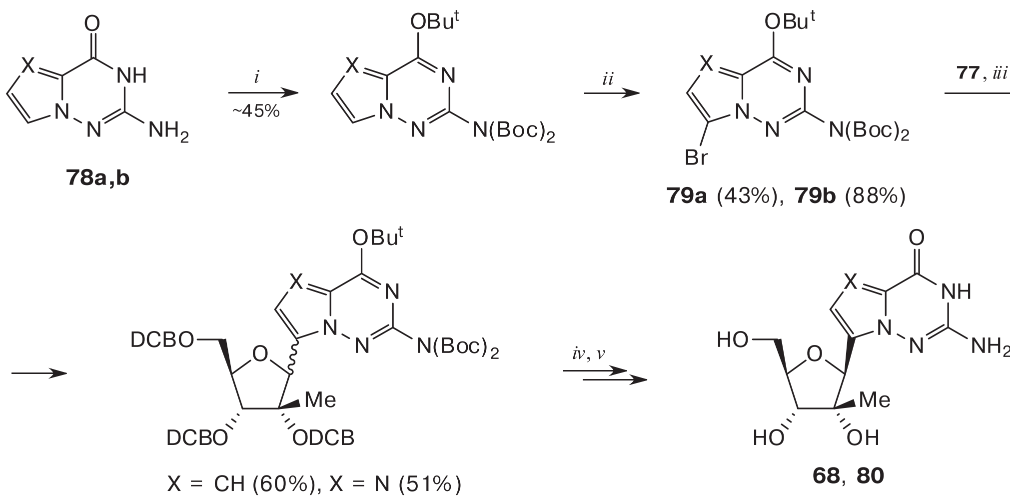
Scheme 20



DCB is 2,4-$Cl_2C_6H_3CH_2$

Reagents and conditions: *i* NBS, DMF, 86 °C, 1 h; *ii*. 1) BuLi (2 equiv.), –78 °C, THF, 2) **77**, –78 °C; *iii*. NH_3 in MeOH, 20 °C → reflux; *iv*. $BF_3 \cdot Et_2O$, Et_2SiH, CH_2Cl_2, –78 → 20 °C, 3 h; *v*. H_2, 10% Pd/C, 60 °C, 18 h, NaOAc, MeOH—CH_2Cl_2 (9 : 1), AcOH.

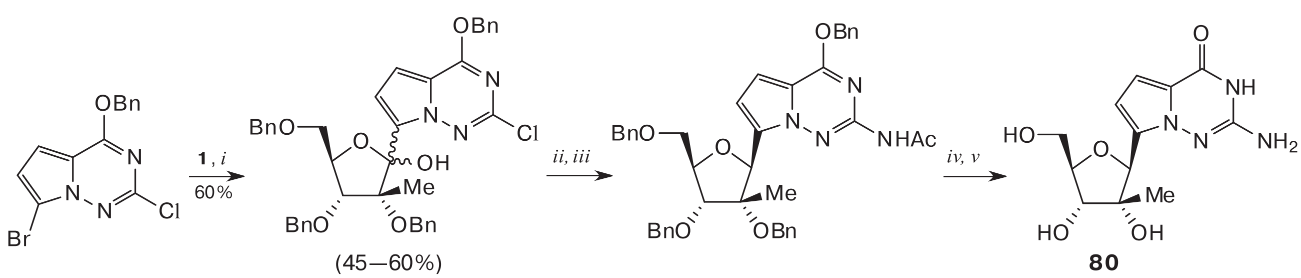
Scheme 21



X = CH (**78a**, **79a**, **80**), N (**68**, **78b**, **79b**)

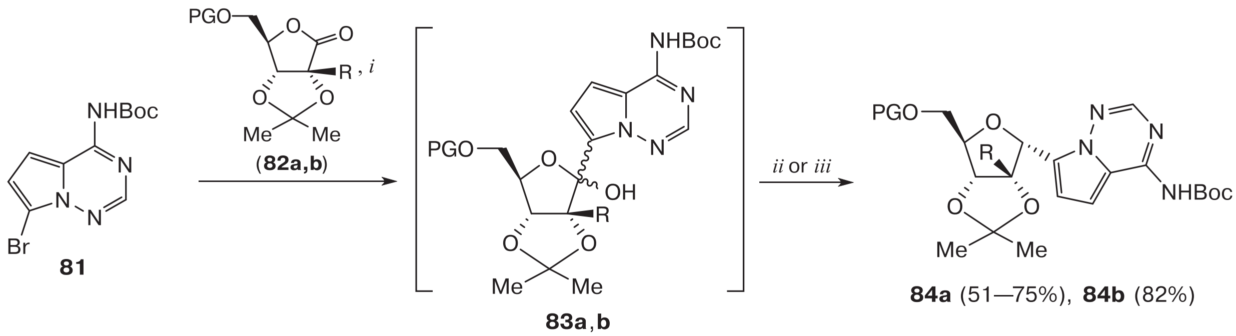
Reagents and conditions: *i*. Et_3N, DMAP, Boc_2O, MeCN, ~20 °C, 46 h; *ii*. NBS, dichloroethane, –10 → 0 °C, 1 h; *iii*. 1) BuLi (1.1 equiv.), THF, –100 °C, 79a or 79b, 2) 77; *iv*. $BF_3 \cdot OEt_2$, Et_3SiH, MeCN, –78 → 20 °C, 3 h; *v*. H_2 (4.3 bar), 10% Pd/C, 60 °C, 18 h, NH_4OAc, MeOH—EtOAc (13 : 2) (for 80) or BBr_3, –78 → –30 °C (for 68).

Scheme 22



Reagents and conditions: *i*. 1) BuLi (2 equiv.), –100 °C, 2-methyltetrahydrofuran, 2) **1**, –100 °C. *ii*. $BF_3 \cdot Et_2O$, Et_3SiH, CH_2Cl_2, –78 °C, 15 min; *iii*. $MeC(O)NH_2$, $Pd_2(dba)_2$, XantPHOS, Cs_2CO_3, 130 °C, 1 h; *iv*. H_2, 10% Pd/C, MeOH, 20 → 50 °C, 70 h; *v*. NaOMe, 20 → 80 °C.

Scheme 23



PG is 2-naphthylmethyl (Nap)
82—84: R = Me (**a**), H (**b**)

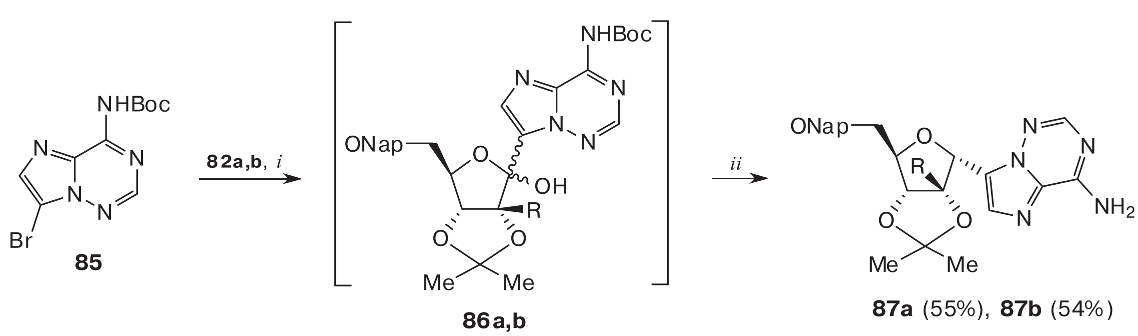
Reagents, conditions, and yields: *i*. 1) **81**, LDA, THF, –30 °C, 50 min, 2) BuLi, –78 °C, 5 min, 3) **82**, –78 °C, 2 h; *ii* for **83a**. Et_3SiH, $BF_3 \cdot Et_2O$, MeCN, –40 °C, 2 h, 51%; *iii*. Et_3SiH, TMSOTf, CH_2Cl_2, –78 °C, 2 h, **84a** — 75%, **84b** — 82%.

from *N*(6)-Boc-protected purine analogs (Scheme 23). Lithiation of compound **81** and subsequent nucleophilic addition of the protected lactones **82** to lithium intermediates were studied under different conditions. The high yields of the target *C*-nucleosides **84** were achieved only using 5′-*O*-Nap-protected ribonolactone **82**, LDA for generation of the lithium intermediate from bromide **81**, and the Et_3SiH/TMSOTf system for the reduction of hemiketal **83**. When other protective groups (PG = TBS, TBDPS) and other reagents for activation of bromide **81** (NaH, BuLi, LiHMDS) were used, these transformations were unsuccessful. High α-selectivity was confirmed by the ROESY analysis.

The optimized conditions were applied to the reaction of bromo heterocycle **85** with lactones **82a**,**b** (Scheme 24). This reaction smoothly gave intermediates **86a**,**b**; however, reduction of hemiketals **86** was not as good as the reduction of **83**, and the target products **87a**,**b** were obtained in moderate yields of 54 and 55%, respectively. It should be noted that the *N*-Boc-protective group was unstable under conditions used for hemiketal reduction.

Reaction of *O*(5)-benzyl-protected lactones **88a**,**b** with bromo heterocycle **81** carried out under similar conditions gave hemiketals **89a,b** (Scheme 25).[45] Reduction of hemiketals **89a,b** with Et_3SiH in the presence of either $BF_3 \cdot Et_2O$ at –10 °C (see Scheme 25, conditions *iii*) or TMSOTf at –78 °C (conditions *ii*) resulted in the target α-anomers **90a**,**b** in good yields. Treatment of hemiketals **89a,b** with $Et_3SiH/BF_3 \cdot Et_2O$ at elevated temperatures (conditions *iv*) enabled not

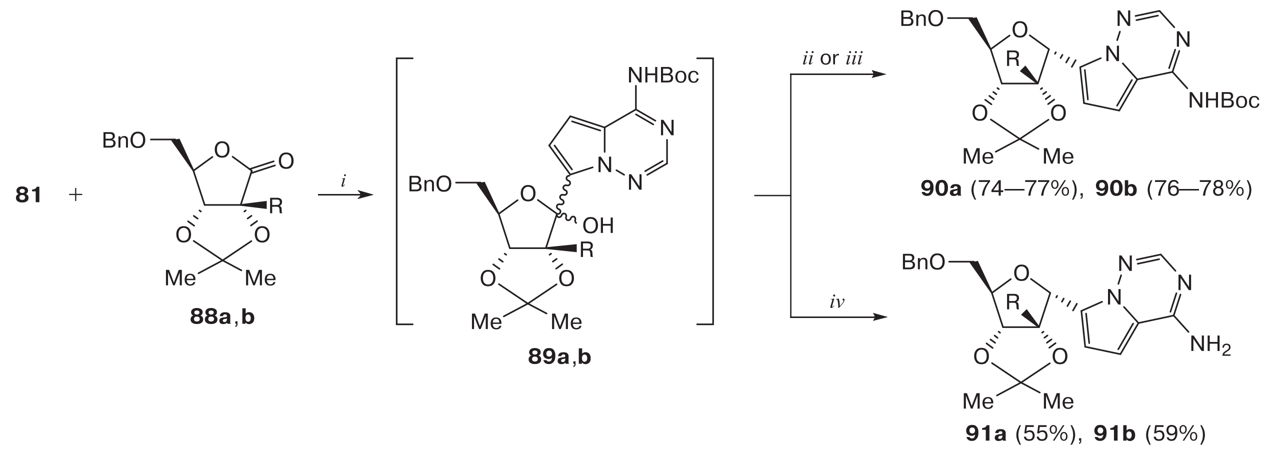
Scheme 24



86, 87: R = Me (**a**), H (**b**)

Reagents and conditions: *i*.1) **85**, LDA (1.3 equiv.), THF, –30 °C, 2) **82**, BuLi (2.5 equiv.), –78 °C; *ii*. $BF_3 \cdot Et_2O$, Et_3SiH, MeCN, –40 → 20 °C.

Scheme 25



88—91: R = Me (**a**), H (**b**)

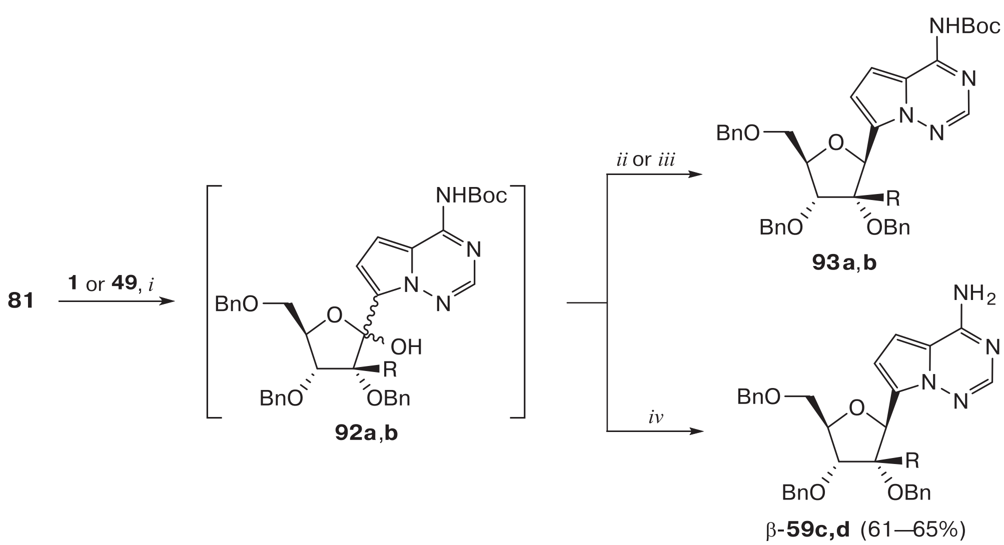
Reagents, conditions, and yields: *i*. 1) **81**, LDA (1.3 equiv.), THF, –30 °C, 2) **88**, BuLi (2.5 equiv.), –78 °C; *ii*. TMSOTf, Et_3SiH, CH_2Cl_2, –78 °C; *iii*. $BF_3 \cdot Et_2O$, Et_3SiH, CH_2Cl_2, –10 °C; *iv*. $BF_3 \cdot Et_2O$, Et_3SiH, CH_2Cl_2, 0 → 20 °C.

only the reduction of hemiketal but also the removal of the Boc-protective group to afford products **91a,b**.[45]

Possibility to synthesize β-*C*-nucleosides under the above-described conditions was exemplified by the reaction of per-*O*-benzylated lactones **1** and **49** with bromo heterocycle **81** (Scheme 26).[45] It was found that those reactions proceeded with high β-stereoselectivity and gave either *N*-Boc-protected (**93**) or deprotected (**59**) β-*C*-nucleosides depending of the conditions used for the reduction of the intermediate hemiketals **92**.

De Jonghe and coworkers[46] described the synthesis of pyrrolo[2,1-*f*][1,2,4]triazine *C*-nucleosides. The authors initially attempted the direct C—C-coupling of 9-bromo-4-aza-7,9-dicarbaadenine **57**

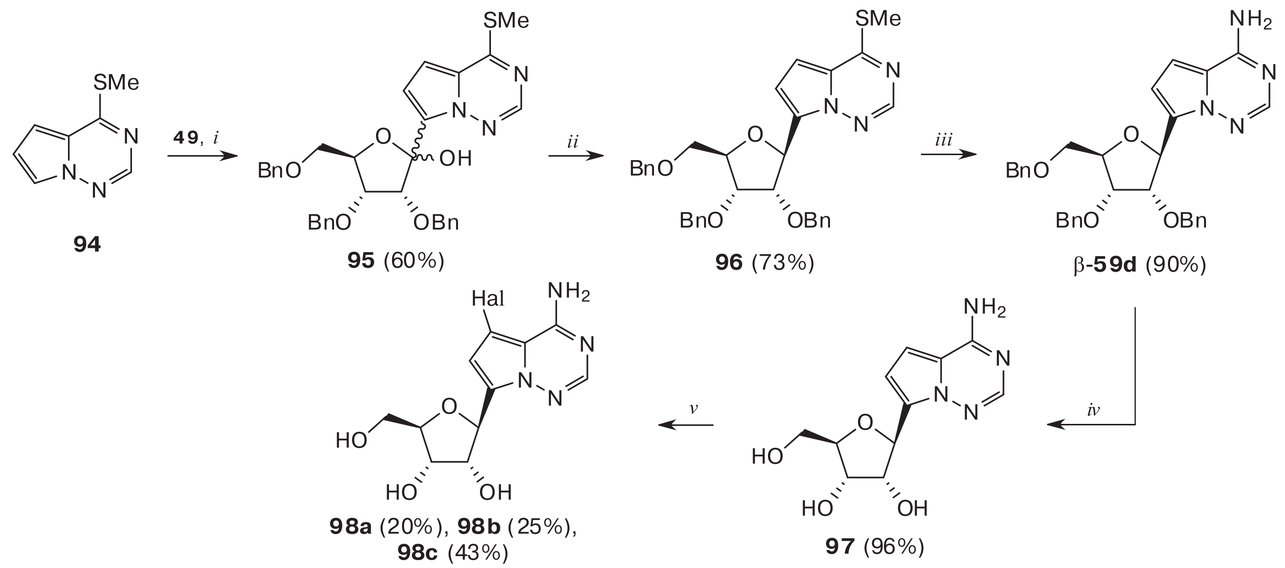
Scheme 26



R = Me (**92a**, **93a**, β-**59c**), H (**92b**, **93b**, β-**59d**)

Reagents, conditions, and yields: *i*. 1) **1** or **49**, LDA (1.3 equiv.), THF, –30 °C, 2) BuLi (2.5 equiv.), –78 °C, 3) **81**, –78 °C; *ii* for **93a**. Et_3SiH, TMSOTf, CH_2Cl_2, –78 °C, 80%; *iii*. Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2 –10 °C, **93a** — 81%, **93b** — 87%; *iv*. Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 → 20 °C.

Scheme 27



98: Hal = Cl (**a**), Br (**b**), I (**c**)

Reagents and conditions: *i*. LDA (1.5 equiv.), THF, –78 °C; *ii*. $BF_3 \cdot Et_2O$, Et_3SiH, CH_2Cl_2, 0 °C; *iii*. 7 *M* NH_3, MeOH, 100 °C; *iv*. H_2, $Pd(OH)_2/C$, AcOH, ~20 °C; *v*. *N*-halogenosuccinimide (NHalS), DMF, 0 °C.

and per-benzylated ribonolactone **49** (see Scheme 14, method *A*). This reaction gave the anomeric mixture in a very low yield. The authors suggested that the low yield of the target product was due to the presence of the unprotected exocyclic amino group in **57** and decided to switch to an alternative nucleobase, 4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazine **94**, rather than to protect the exocyclic amino group (Scheme 27). Hemiketal **95** synthesized by the C—C bond forming reaction between aglycon and ribonolactone was subjected to anomeric reduction to prepare exclusively β-anomer **96**. Before the removal of the benzyl protective groups, the methylthio group was replaced with the NH_2 group. Halogenation of *C*-nucleoside **97** with *N*-halosuccinimides gave chloro, bromo, and iodo derivatives **98a—c**. The iodine atom in compound **98c** was replaced with the CN group by the $Pd(PBu^t{}_3)_2$-catalyzed cross-coupling reaction with zinc cyanide.

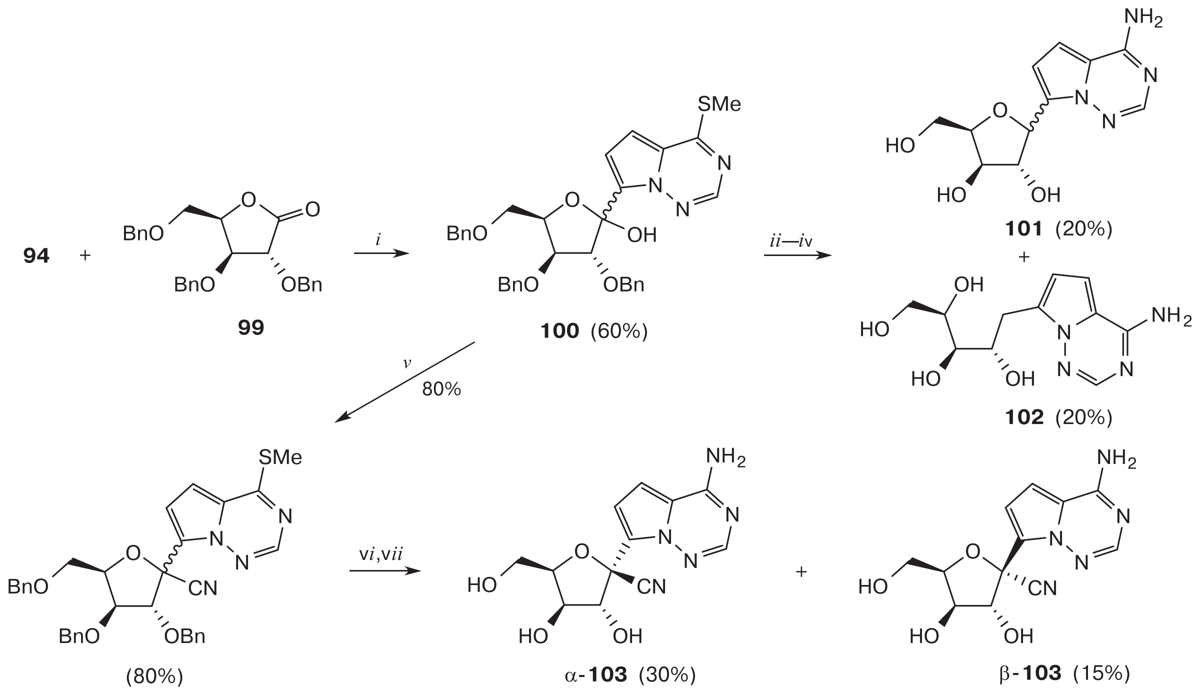
Compound **97** showed high *in vitro* cytotoxicity against human hematological and solid cancer cell lines. The exact molecular target of these compounds is currently unknown.

Underexplored xylo-*C*-nucleosides (3′-epimers of ribonucleosides) were studied by Herdewijn and coworkers.[47] The C—C coupling of compounds **94** and **99** gave a mixture of epimers **100** in 60% yield (Scheme 28). The stereoisomeric ratio was given only for a product of the reduction of 1′-hydroxy group in **100** (α : β = 2 : 3). The removal of the benzyl protective groups by the $Pd(OH)_2$-catalyzed hydrogenolysis in acetic acid gave rase to a mixture of xylo-*C*-nucleoside **101** and a ring opening product **102**. The yield of target xylo-*C*-nucleoside β-**101** increased to 62% when compound **100** was deprotected with $Pd(OH)_2/C$ in refluxing EtOH. These conditions also gave α-anomer α-**101** in 18% yield. Introduction of the CN group into the position 1′ of compound **100** and subsequent deprotection proceeded with good yields on each step to give products **103** (see Scheme 28).

Activity of compounds **101** and **103** against a panel of tumor cell lines was studied. Compound **101** was found to possess a micromolar antiproliferative activity against the human leukemia HL-60 and lung cancer NCI-H460 cells. In contrast, no significant cytotoxicity was observed for compound β-**103**.

Herdewijn and coworkers[48] synthesized threosyl *C*-nucleosides (Scheme 29). The C—C coupling of ribonolactone **104** with 4-(methylthio)pyrrolo[2,1-*f*]-[1,2,4]triazine (**94**) as an aglycon activated with LDA gave hemiketal **105** as a mixture of anomers in 70% yield. Reduction of the hydroxy group, replacement of the SMe group with the amino group, and depro-

Scheme 28



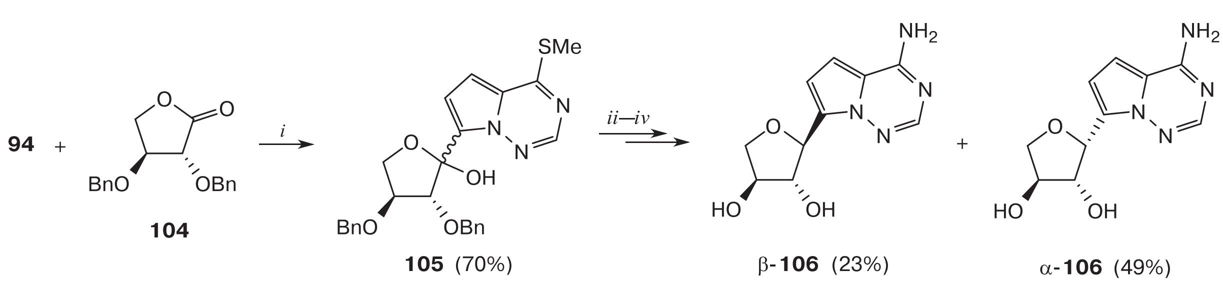
Reagents, conditions, and yields: *i.* LDA, THF, –78 °C, 3 h; *ii.* Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C, 1 h, 85%; *iii.* NH_3, MeOH, 100 °C, 12 h, 85%; *iv.* H_2, $Pd(OH)_2/C$, AcOH, ~20 °C, 48 h; *v.* TMSOTf, TMSCN, CH_2Cl_2, 0 °C, 2.5 h; *vi.* NH_3/MeOH, 100 °C, ~18 h, 86%; *vii.* BCl_3, CH_2Cl_2, 0 → 20 °C, 2.5 h.

tection of the benzyl groups afforded compound **106** as a mixture of α- and β-anomers in 72% yield. Anomers α-**106** and β-**106** were separated by column chromatography. The synthesized *C*-nucleosides were phosphorylated at the 3′-position with the yields of about 70% at each step.

Immucillins are an important group of *C*-nucleosides showing antitumor and antimalarial activity. The most important immucilins are compounds **110** (BCX-1777) and **111** (BCX-4430). Synthesis of compounds **109** and **110** *via* the multi-step construction of the aglycon on the pre-formed sugar unit was described by Herdewijn and coworkers.[49]

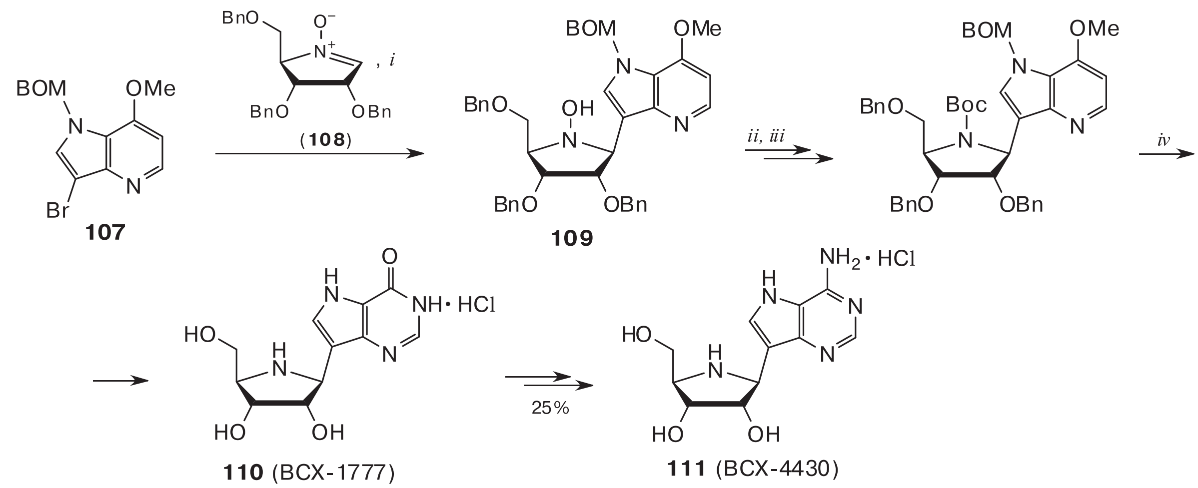
Zhang *et al.*[50] developed improved procedure to synthesize compounds **110** and **111** *via* the C—C bond forming reaction between aglycon **107** and *N*-oxide **108**, a synthetic equivalent of ribonolactone, under basic conditions (Scheme 30). No yield of compound **109** was given because it was subjected to reduction without purification. Due to low stability, the obtained intermediate was immediately treated with Boc_2O under basic conditions. The major isomer

Scheme 29



Reagents, conditions, and yields: *i.* LDA (1.07 equiv.), THF, –78 °C, 3 h; *ii.* Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C, 40 min, 94%; *iii.* NH_3, MeOH, 100 °C, 12 h, 92%; *iv.* cyclohexene, $Pd(OH)_2/C$, EtOH, reflux, ~18 h.

Scheme 30



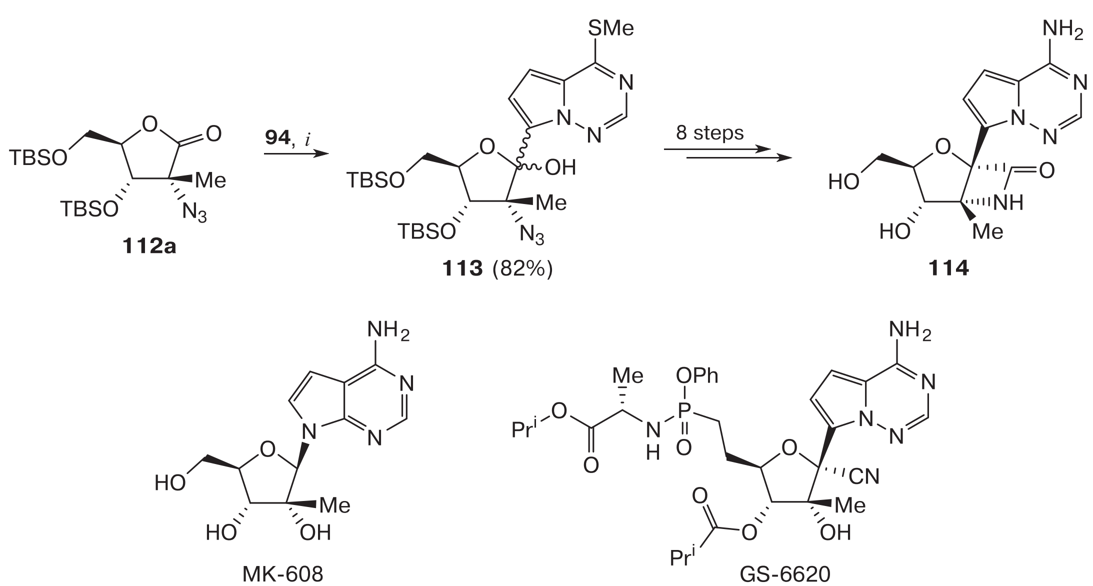
BOM is bemzyloxymethyl

Reagents, conditions, and yields: *i*. 1) **107**, BuLi (2.16 equiv.), MeOBu^t, −20 °C; 2) **108**, −20 °C; *ii*. Zn, MeOH—AcOH (1 : 5), reflux; *iii*. Boc_2O, NaOH, THF—H_2O (2 : 1), ~20 °C, 38% (over 3 steps); *iv*. HCl (conc.), reflux.

of *N*-Boc-derivative was isolated by column chromatography. Subsequent deprotection afforded compound **110** (70%) after recrystallization. Compound **110** (BCX-1777) was transformed to derivative **111** (BCX-4430) by the following reaction sequence that involved protection of the functional groups, replacement of the carbonyl group with the chlorine atom, the CuBr-catalyzed Ullmann-type amination, and deprotection. Since this reaction sequence involved less steps than the procedure described by Herdewijn and coworkers[49] and only 2—3 chromatographic steps for purification, this approach is very attractive for the large-scale synthesis.

C-Nucleoside **114** (Scheme 31) bearing 1´,2´-β-lactam moiety was designed as the hybrid scaffold of MK-608 and GS-6620.[51] Compound **114** is a potential hepatitis C virus NS5B polymerase inhibitor. The role of aglycon was played by compound **94**, which

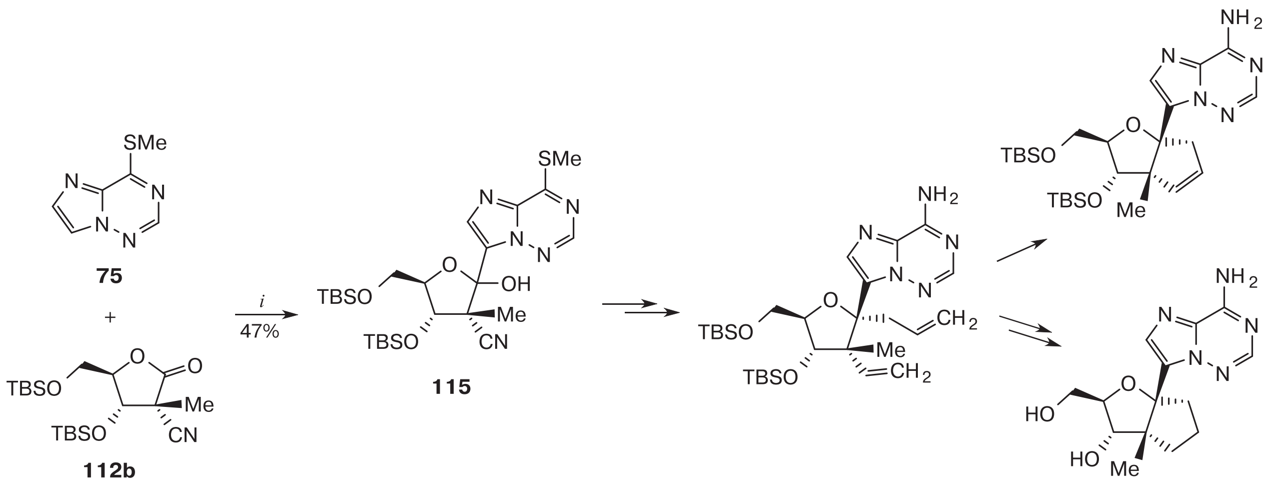
Scheme 31



TBS is Bu^{t}Me$_2$Si

Reagents and conditions: *i*. LDA (1.1 equiv.), THF, −78 → −20 °C, 40 min.

Scheme 32

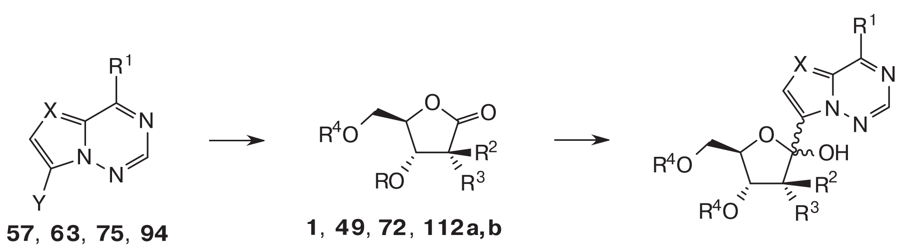


Reagents and conditions: *i*. LDA (1.1 equiv.), THF, –78 → –20 °C, 40 min.

was lithiated using LDA and subjected to the coupling with ribonolactone **112a** to give hemiketal **113** in 82% yield (see Scheme 31).

Dang and coworkers[52] used lactone **112b** as the starting material to synthesize 1′,2′-cyclopenta-fused *C*-ribonucleosides (Scheme 32). The charac-

Scheme 33



Aglycon	X	Y	R^1
57	CH	Br	NH_2
63	N	Br	NH_2
75	N	H	SMe
94	CH	H	SMe

Lactone	R^2	R^3	R^4
1	Me	OBn	Bn
49	H	OBn	Bn
72	Me	F	Bz
112a	Me	N_3	TBS
112b	Me	CN	TBS

Table 3. Conditions and outcome of the C—C-coupling of lactones **1**, **49**, **72**, and **112a,b** with aglycons **57**, **63**, **75**, and **94**

Aglycon	Lactone	Reaction conditions	Yield of *C*-nucleoside (%)	Ref.
57	**1**	1) $(ClSiMe_2CH_2)_2$, 2) BuLi, –78 °C	**64a** (60)	36
57	**49**	1) $(ClSiMe_2CH_2)_2$, 2) NaH, BuLi, –78 °C	**58** (60)	35
57	**72**	1) $(ClSiMe_2CH_2)_2$, 2) BuLi, –78 °C	**73a** (40)	38
63	**1**	1) $(ClSiMe_2CH_2)_2$, 2) BuLi, –78 °C	**64b** (56)	36
63	**72**	1) $(ClSiMe_2CH_2)_2$, 2) BuLi, –78 °C	**73b** (59)	38
75	**112a**	LDA, THF, –78 °C	(59)[5]	51
75	**112b**	LDA, THF, –20 °C	**115** (47)	52
94	**1**	LDA, THF, –78 °C	(32)	53
94	**49**	LDA, THF, –78 °C,	**95** (60)	53
94	**112a**	LDA, THF, –20 °C	**113** (82)	51

teristic feature of this synthesis is protection of the hydroxy groups as TBS ether instead of more common benzyl protection.

We compared the yields of the target products of the C—C coupling achieved in the reactions of different azoloazine aglycons and functionalized ribonolactones (Scheme 33, Table 3).

For aglycon **57**, the highest yield of the target *C*-nucleosides **58** and **64a** was achieved in its reaction with lactones **49** and **1**; in contrast, in the reaction of aglycon **57** with lactone **72** the yield of *C*-nucleoside **73a** was 40%. In the reactions with aglycon **63**, the best results were demonstrated by lactones **1** and **72**. The yields of *C*-nucleosides **64b** and **73b** in these reactions reached ~60%. In the reactions with aglycon **94**, the yields of the target products depended on the nature of the substituents at the position 2′ of lactone. Thus, the reaction of aglycon **94** with 2′-azido-2′-methyl-substituted lactone **112a** gave *C*-nucleoside **113** in 82% yield, whereas for 2′-benzyloxy-2′-methyl derivative **1** the yield dropped to 32%. In the case of aglycon **75**, the best results were obtained with 2′-azido-2′-methyl-substituted lactone **112a**. The replacement of the azide group with nitrile one (compound **112b**) decreased the yield of the target product **115** to 47%. In all cases, the C—C coupling products were synthesized as the mixtures of anomers, the ratios of which were not given.

Thus, the direct C—C coupling of aglycon and (pseudo)ribonolactone in the presence of organometallic reagents or relatively strong bases is the reasonably common strategy to access *C*-nucleosides. Typical reaction conditions are as follows: THF, BuLi (1—3.5 equiv.), −78 °C. In some cases, the halogenated aglycons were activated by refluxing with magnesium turnings, using a mixture of NaH and either BuLi or Bu^tLi. As the solvents, anhydrous toluene, methyl *tert*-butyl ether, and diethyl ether can be used. It is of note that such base as LDA can transform aglycons containing no halogen atoms into carbanions, wherein the lesser excess of the base should be used (from 1 to 1.5 equiv.).

1.2. Pd-Catalyzed *C*-glycosylation

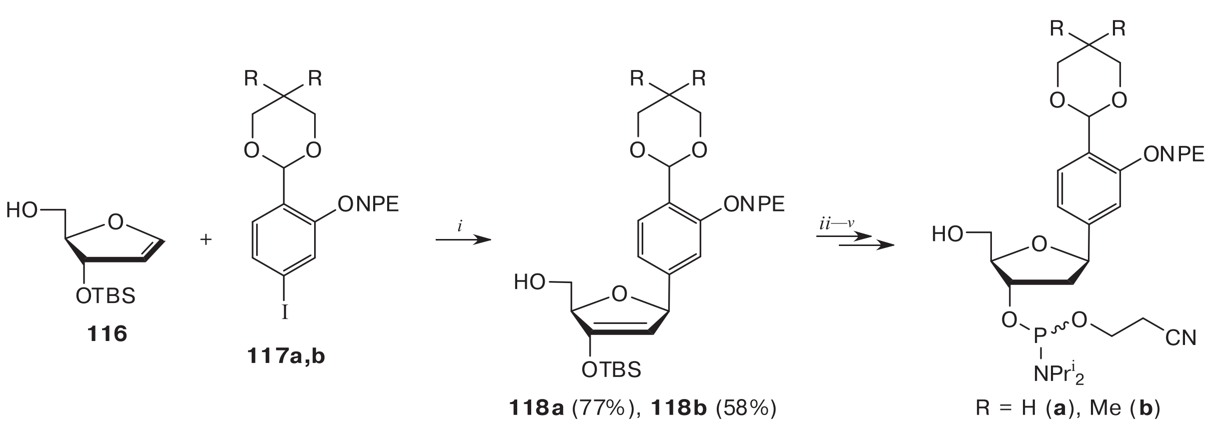
Another strategy to direct formation of the glycosidic bond between preliminary functionalized aglycon and (pseudo)riboside is the Pd-catalyzed reactions. To realize this strategy, the halogen-containing aglycons and carbohydrates with unsaturated units are mainly used.

This approach can be exemplified by the synthesis of *C*-nucleosides **118** by the reaction of iodo derivative **117** with glycal **116** catalyzed by the $Pd(OAc)_2/AsPh_3$ system (Scheme 34).[54]

Another example of the Pd-catalyzed syntheses of *C*-nucleosides is the Suzuki reaction of compounds **120a**,**b** with different (het)arylboronic acids to give the target carbocyclic *C*-nucleosides **121a—g** in high yields (75—99%) (Scheme 35).[33]

An efficient synthesis of alkynyl *C*-nucleosides by the Sonogashira coupling for the preparation of

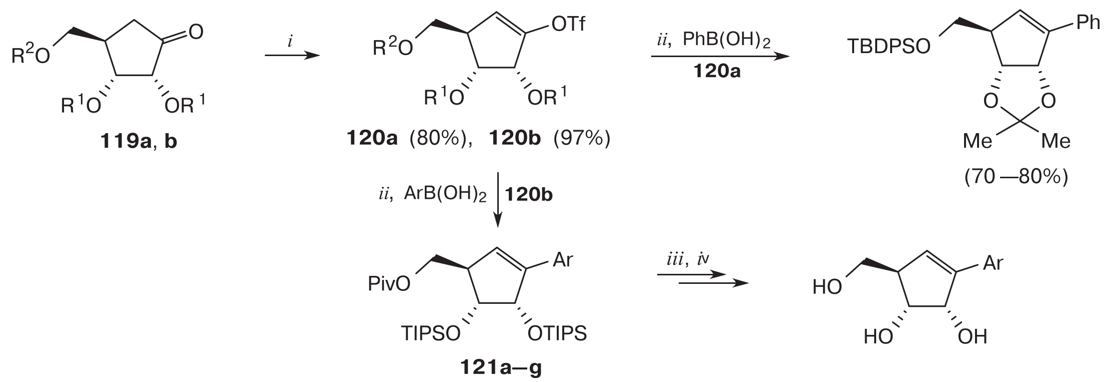
Scheme 34



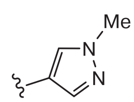
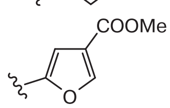
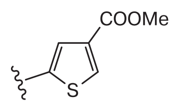
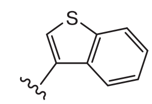
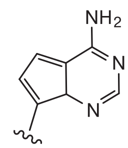
NPE is 2-(4-nitrophenyl)ethyl
117, 118: R = H (**a**), Me (**b**)

Reagents and conditions: *i.* $Pd(OAc)_2$, $AsPh_3$, Ag_2CO_3, $CHCl_3$, 70 °C. *ii.* $Et_3N \cdot 3HF$, THF, 0 °C, 10 min; *iii.* $NaBH(OAc)_3$, MeCN, 0 °C; *iv.* DMTCl, pyridine, ~20 °C; *v.* $NC(CH_2)_2OP(NPr^i_2)_2$, Pr^i_2NH, tetrazole, MeCN, ~20 °C.

Scheme 35



119, 120: R^1 = Pr^i, R^2 = Bu^tPh_2Si (TBDPS) (**a**); R^1 = $Pr^i{}_3Si$ (TIPS), R^2 = $Bu^tC(O)$ (Piv) (**b**)

Compound **121**	Ar	Yield (%)
a	Ph	92
b	2,4-$F_2C_6H_3$	76
c		87
d		81
e		99
f		75
g		87

Reagents and conditions: *i*. 1) LDA, THF, –78 °C, 2) $PhNTf_2$, –78 → 20 °C; $(Me_3Si)_2NK$ (KHMDS), *N*-(5-chloro-2-pyridyl)-bis(trifluoromethanesulfonamide) (the Comins′ reagent), THF, –78 → 20 °C; *ii*. $Pd(dppf)Cl_2$, K_3PO_4, $MeO(CH_2)_2OMe$ (DME), H_2O, 80 °C; *iii*. TBAF, THF, ~20 °C; *iv*. MeONa, MeOH, 65 °C.

DNA-based polyfluorophores was described by Kool and coworkers[55] (Scheme 36). The authors revealed the excess of the starting compound **122** (1.5 equiv.) to compensate for the oxidative Glaser homocoupling.[56,57]

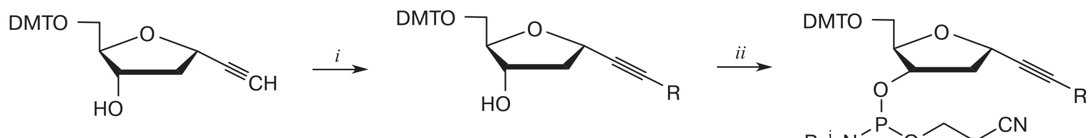
C-Nucleosides **123a—f** were used to synthesize the DNA-based polyfluorophores. These compounds could be used as fluorescent labels or probes in multiple DNA applications.

Modified Sonogashira coupling was used to synthesize derivatives **126a—f** (Scheme 37).[58] The strategy involved the coupling of alkynyl-substituted hydrocarbons **125a—f**, aroyl chlorides, and 1,4-dithiane-2,5-diol. The reaction conditions were optimized: the highest yields could be achieved in anhydrous HCl ethanol solution. However, prolongation of the reaction time caused the decrease in the yield due apparently to the decomposition of sugar in acidic solution. Under optimized conditions using the one-pot procedure, the target products were synthesized in 70—86% yields.

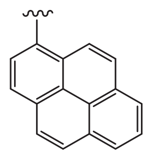
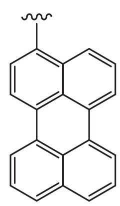
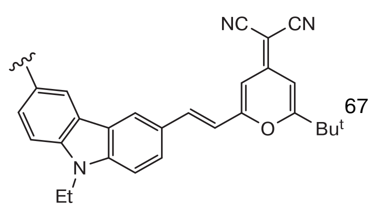
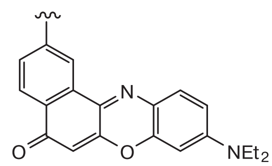
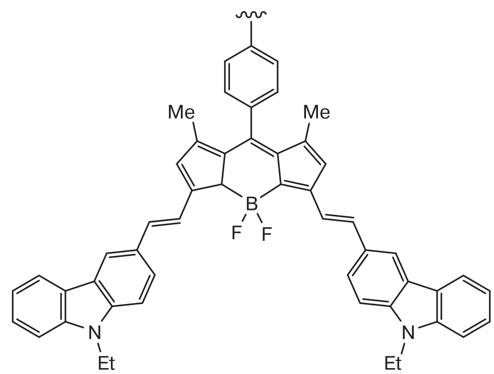
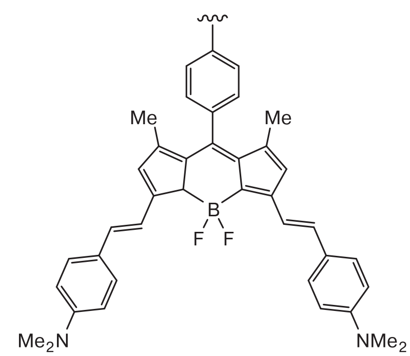
Sato and Matsuda[59] reported the synthesis of *C*-nucleosides by the Heck reaction (Scheme 38). 3′-Keto derivative **129** was prepared by the reaction of glycal **116** and 2-amino-4-fluoro-3,5-diiodopyridine **127** catalyzed by $Pd(OAc)_2$ and Ph_3As. The reaction regio- and stereoselectively gave the only product **128**, which was further transformed to 3′-hydroxy derivative **129** by stereoselective reduction. Phosphoramidite **130** was synthesized from (pseudo)-nucleoside **129** in three steps in 12% overall yield.

The Heck reaction of glycal **116** with phosphordiamidite **131** catalyzed by $Pd(OAc)_2$ and Ph_3As gave the mixture of the expected target product **132** (20%) and desilylated oxo nucleoside **133** (53%) (Scheme 39). Treatment of the mixture of compounds **132** and **133**

Scheme 36



Reagents and conditions: *i*. RX (X = Br (**123a**,**b**), I (**123c**,**e**,**f**), OTf (**123d**)), $Pd(PPh_3)_4$, CuI, NEt_3, DMF, 80 °C, 2.5 h; *ii*. $NC(CH_2)_2OP(Cl)NPr^i{}_2$, $EtNPr^i{}_2$, CH_2Cl_2, ~20 °C, 1.5 h.

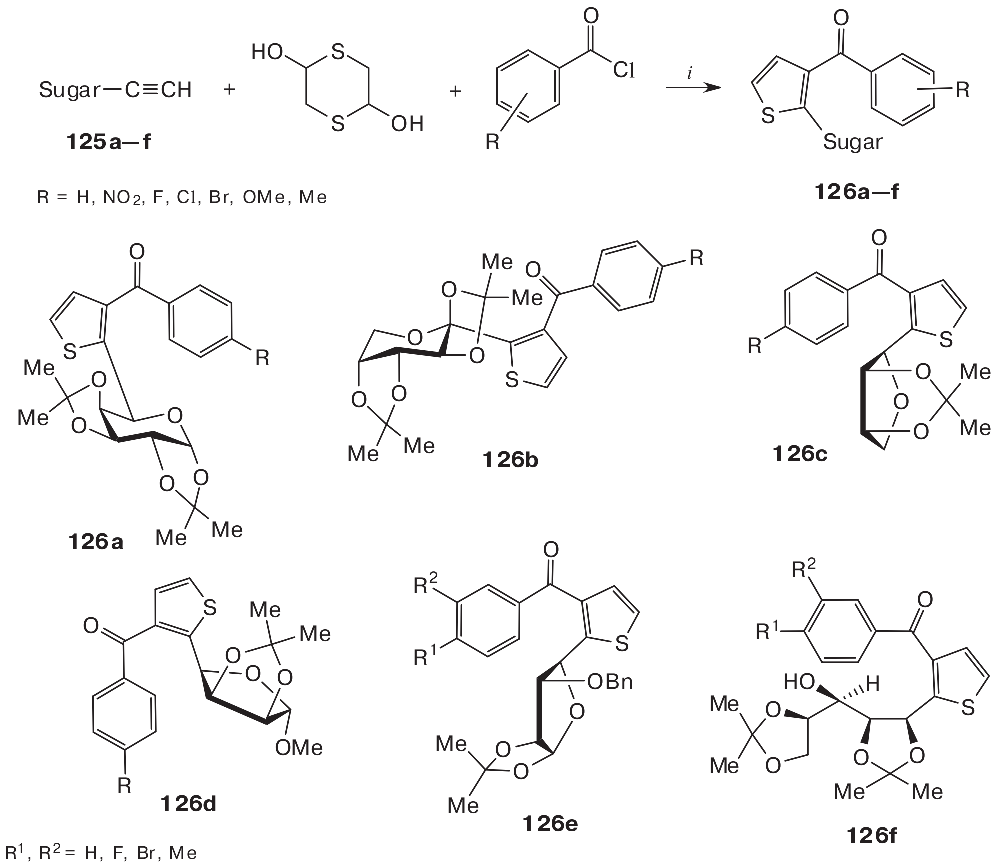
Compounds **123**, **124**	R	Yield (%) **123**	Yield (%) **124**
a		74	90
b		50	98
c		67	91
d		86	83
e		83	84
f		68	91

with $Et_3N \cdot 3HF$ provided oxo derivative **133** in 79% yield (over 2 steps). Further, compound **133** was transformed to pyridon-3-yl *C*-2′-deoxyribonucleosides **134a,b** in several steps. It should be underlined that the synthesis of *C*-deoxynucleoside **134b** by the Heck reaction of deoxyriboglycal **116** and 6-chloro-3-iodopyridin-2(1*H*)-one failed.[60]

Hocek and coworkers[61] described synthesis of 2,6-disubstituted pyridin-3-yl *C*-2′-deoxyribonucleosides **138** and **140** (Scheme 40). The Heck reaction of bromo-chloro-iodo-pyridines and glycal **116** in the presence of $Pd(OAc)_2$, $P(C_6F_5)_3$, and Ag_2CO_3 was accompanied by partial desilylation similarly to the reaction of glycal **116** with iodo pyridine **131** (see Scheme 39). The obtained mixtures were treated with $Et_3N \cdot 3HF$ to obtain fully deprotected ketones **137** and **139** as pure β-anomers. Subsequent stereoselective reduction gave compounds **138** and **140**. The synthesized *C*-nucleosides did not exert antiviral or cytostatic effects.

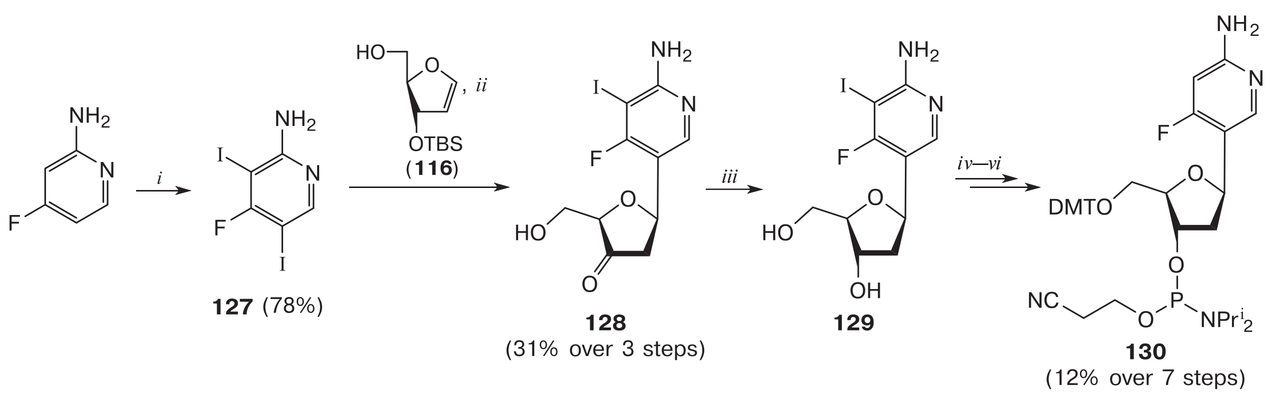
Hocek and coworkers[62] synthesized pyrimidin-5-yl *C*-2′-deoxyribonucleosides (Scheme 41). The Heck reaction was realized under the same conditions[61] using the $Pd(OAc)_2/P(C_6F_5)_3$ system. The

Scheme 37



Reagents and conditions: *i.* $Pd(PPh_3)_2Cl_2$ (1 mol.%), CuI (3 mol.%), Et_3N, 2) HCl, EtOH, heating.

Scheme 38

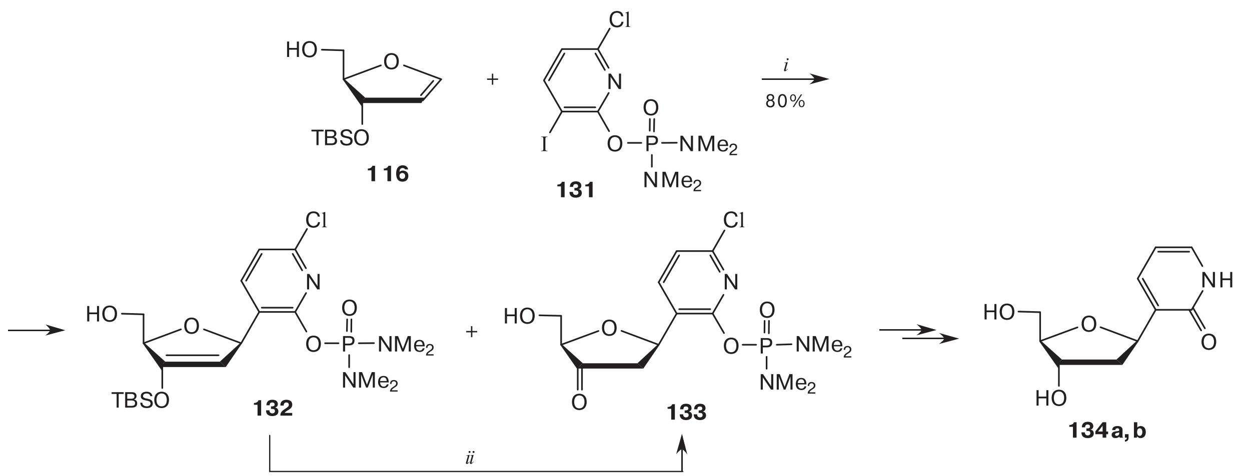


Reagents, conditions, and yields: *i.* NIS, AcOH; *ii.* 1) $Pd(OAc)_2$, Ph_3As, Et_3N, DMF, 65 °C, 2) $Et_3N \cdot 3HF$; *iii.* $NaBH(OAc)_3$, MeCN, AcOH (1 : 1); *iv.* H_2, Pd/C, MeOH, 90%; *v.* DMTCl, Et_3N, CH_2Cl_2, 92%; *vi.* $NC(CH_2)_2OP(Cl)NPr^i_2$, $EtNPr^i_2$, CH_2Cl_2, 61%.

reaction also proceeded with desilylation. Ketone **141** was prepared in 42% yield (over 2 steps). Reduction of ketone **141** afforded the target *C*-deoxyribonucleoside. Scaling up of the Heck reaction up to gram scale was emphasized.

Reaction between glycal **115** and 2-bromo-5-iodopyridine in the presence of $Pd(OAc)_2$ and $P(C_6F_5)_3$ gave derivative **142** in 53% yield exclusively as β-anomer (Scheme 42). Picolinamide *C*-nucleoside **143** was synthesized in seven steps in 2% overall yield.[63]

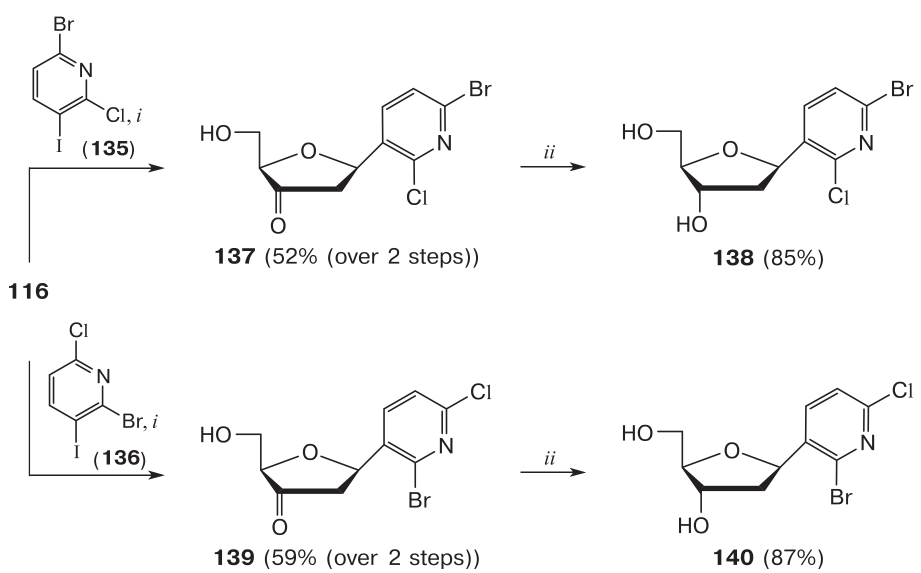
Scheme 39



134: R = H (**a**), Cl (**b**)

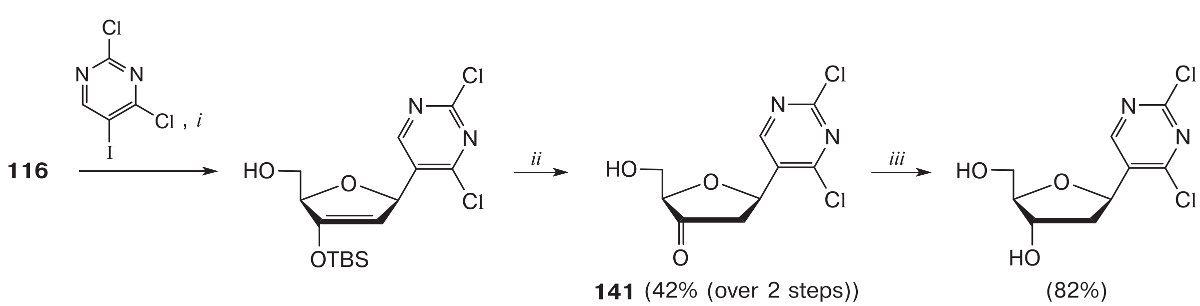
Reagents and conditions: *i*. $Pd(OAc)_2$, $AsPh_3$, Ag_2CO_3, $CHCl_3$, 70 °C, 12 h; *ii*. $Et_3N \cdot 3HF$, THF, ~20 °C, 12 h.

Scheme 40



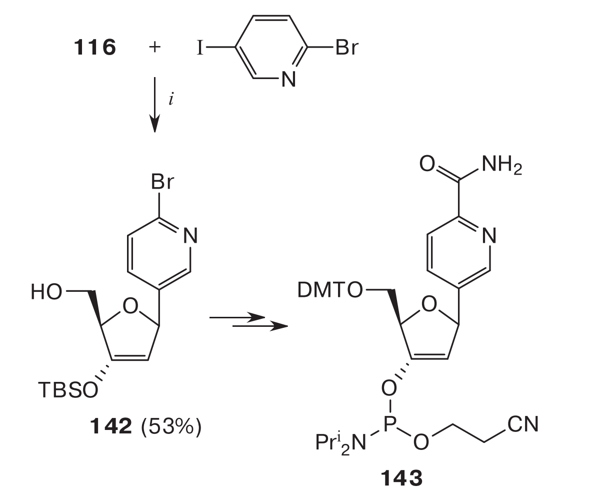
Reagents and conditions: *i*. 1) $Pd(OAc)_2$, $P(C_6F_5)_3$, Ag_2CO_3, $CHCl_3$, 70 °C, 10 h; 2) $Et_3N \cdot 3HF$, THF, ~20 °C, 15 min; *ii*. $NaBH(OAc)_3$, AcOH, MeCN, 0 °C, 5 min.

Scheme 41



Reagents and conditions: *i*. $Pd(OAc)_2$, $P(C_6F_5)_3$, Ag_2CO_3, $CHCl_3$, 70 °C, 10 h; *ii*. $Et_3N \cdot 3HF$, THF, 0 °C, 5 min; *iii*. $NaBH(OAc)_3$, MeCN, AcOH, 0 °C, 5 min.

Scheme 42



Reagents and conditions: *i*. $Pd(OAc)_2$, $P(C_6F_5)_3$, $CHCl_3$, Ar.

Serpi and coworkers[64] described the Heck reaction of 5-iodo aglycon **145** with protected ribofuranosyl glycal **144** catalyzed by the $Pd(OAc)_2/AsPh_3/EtNPr^i_2$ system. This reaction selectively afforded β-anomer **146** (Scheme 43). Compound **146** was transformed to 2′-deoxypseudoisocytidine **147** in three steps (see Scheme 43) in ~30% overall yield.

We like to give several additional examples of the Pd-catalyzed C—C bond formation between aglycon and riboside. Chiba and Inouye[65] used the Sonogashira reaction between 1-ethynyl-2-deoxyribose β-**122** and halogen-tethered pyrimidine and pyridine to synthesize alkynyl *C*-nucleosides **148a—f** in good yields (67—92%) (Scheme 44). Protection of the amino group (yields 56—93%) and subsequent phosphoramidation (yields 41—98%) furnished unnatural alkynyl *C*-pseudonucleotides **149a—f**.

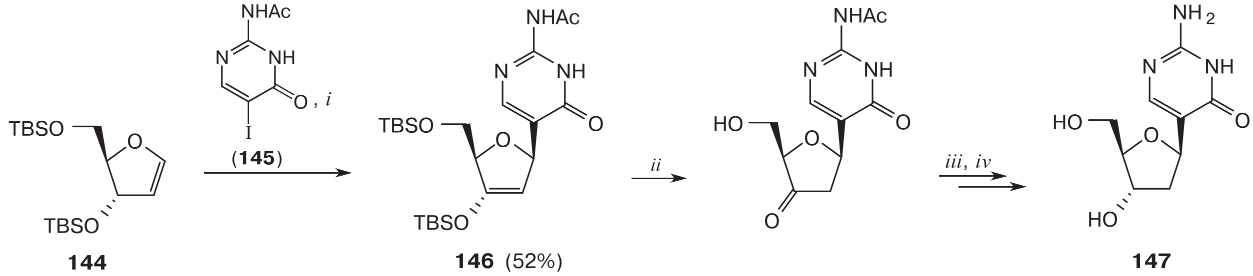
Lefoix *et al.*[66] were interested in the synthesis of pyrazolo[1,5-*a*][1,3,5]triazine *C*-nucleosides as deoxyadenosine analogs (Scheme 45). Different conditions for performing the Heck reactions between glycal **150** and iodopyrazolotriazine were tested. Thus, the solvent (MeCN, DMF, dioxane), the palladium source ($Pd(dba)_2$, $Pd_2(dba)_3$, Pd(OAc)), and the base (Bu_3N, Et_3N) were varied. However, the highest yield of the target compound **151** did not exceed 34%. Phosphoramidite **152** was used to synthesize 18-mer oligonucleotides, which incorporated one or two pyrazolotriazine *C*-nucleoside units.

Phthalimide *C*-nucleoside **155b** was synthesized by the Heck reaction of halogenated phthalimides **153a**,**b** and glycal **116** in the presence of the $P(C_6F_5)_3/Pd(OAc)_2/Et_3N$ catalytic system followed by the nitro group reduction (Scheme 46).[67] Nucleoside **155b** showed pronounced solvatochromic and solvatofluorochromic behavior. The absorption and fluorescence emission bands are red-shifted in solvents of high polarity; the largest bathochromic shift was observed in the solvents with hydrogen-bonding capabilities. Compound **155b** was further transformed to the corresponding phosphoramidite and used as the DNA building block in the synthesis of oligonucleotides.

The Heck coupling of glycal **150** and aglycon **156** catalyzed by the $Pd_2(dba)_3/AsPh_3/NBu_3$ system regio- and stereoselectively gave product **157** in high yield (Scheme 47).[46] Compound **157** was further converted to the corresponding 2′-deoxy- and 2′,3′-dideoxynucleosides **158** and **159**.

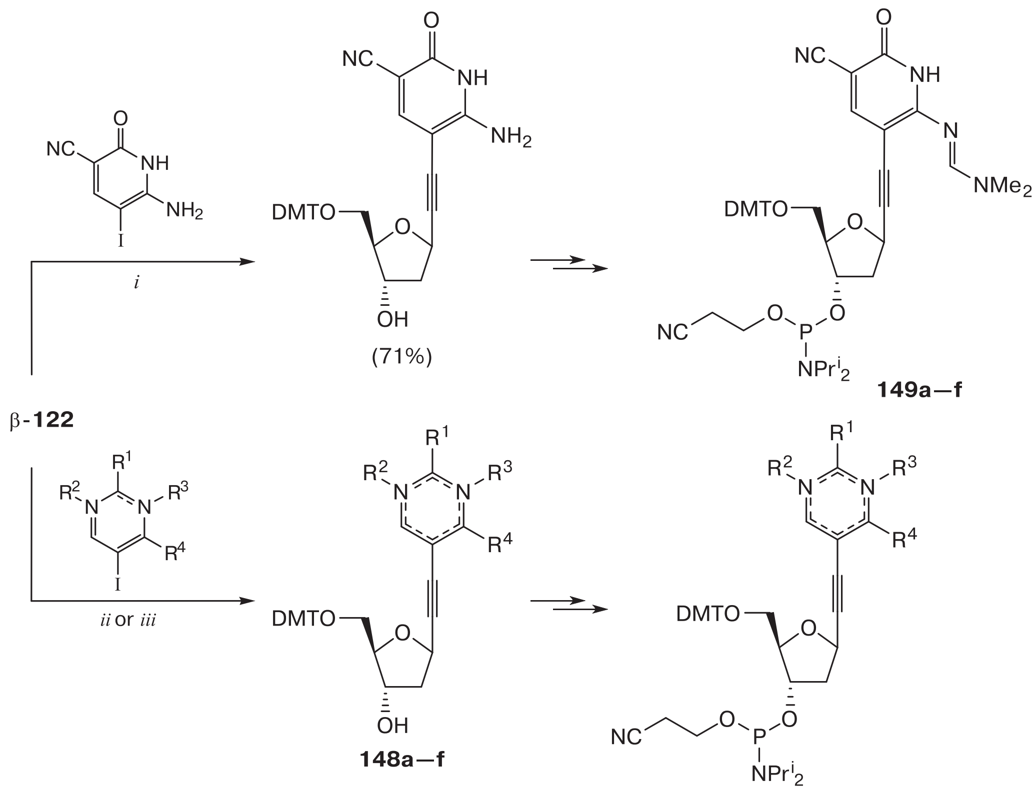
Thus, the Pd-catalyzed reactions are also reasonably common approach towards *C*-nucleosides. Realization of this approach requires halogenated aglycons, mainly, iodo derivatives. The most com-

Scheme 43



Reagents and conditions: *i*. *N*,*O*-bis(trimethylsilyl)acetamide, $Pd(OAc)_2$, $AsPh_3$, $EtNPr^i_2$, DMF, 80 °C, 24 h; *ii*. $C_6H_5N \cdot HF$, THF, ~20 °C, 12 h; *iii*. $NaBH(OAc)_3$, AcOH, MeCN, –15 → 20 °C, 2 h; *iv*. NH_3, MeOH, 0 → 20 °C, 6 h.

Scheme 44

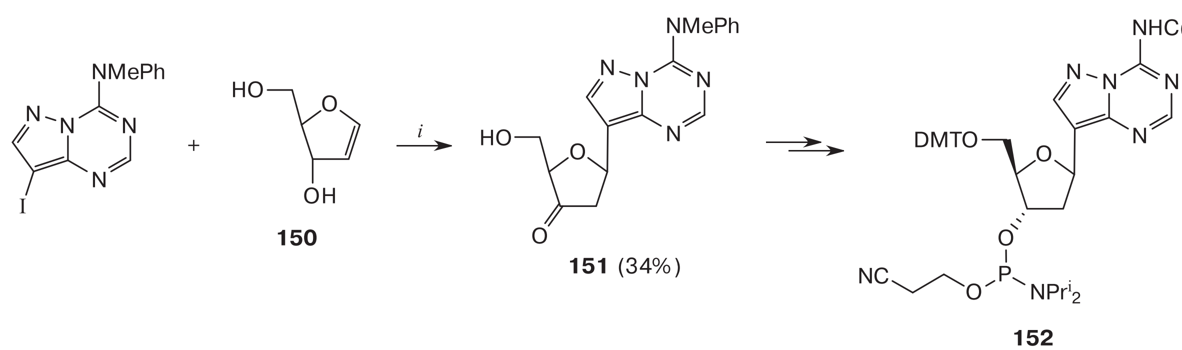


Compounds **148**	R^1	R^2	R^3	R^4	Yield (%)
a	OH	Me	H	OH	80
b	OH	Me	—	NH_2	67
c	NH_2	—	—	H	91
d	NH_2	—	H	OH	85
e	NH_2	—	—	NH_2	92
f	NH_2	Me	—	OH	86

Compounds **149**	R^1	R^2	R^3	R^4
a	OH	Me	H	OH
b		Me	—	NHC(O)Pr^i
c	$NCHNMe_2$	—	—	H
d	$NCHNMe_2$	—	H	OH
e	$NCHNMe_2$	—	—	$NCHNMe_2$
f	$NCHNMe_2$	Me	—	OH

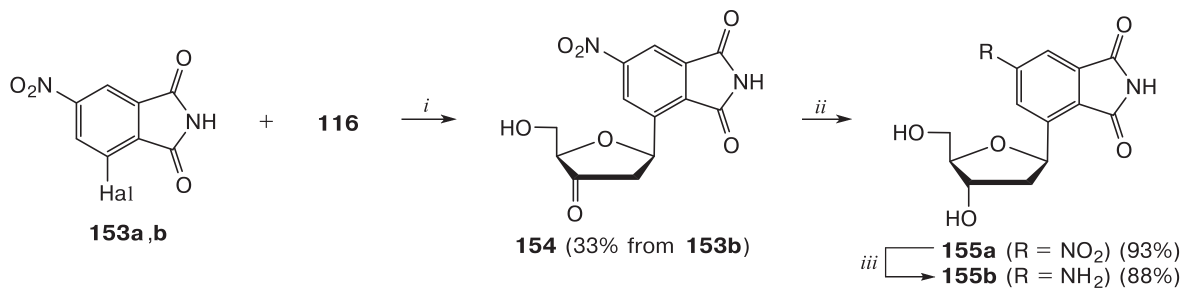
Reagents and conditions: *i*. $PdCl_2(PPh)_3$, CuI, $(Me_3Si)_2NH$ or Et_3N (for **148c**), DMF, N_2; *ii* (for **148a**). $Pd_2(dba)_3$, PPh_3, CuI, $NHPr^i{}_2$, DMF, N_2.

Scheme 45



Reagents and conditions: *i*. $Pd(dba)_2$, Et_3N, $AsPh_3$, MeCN.

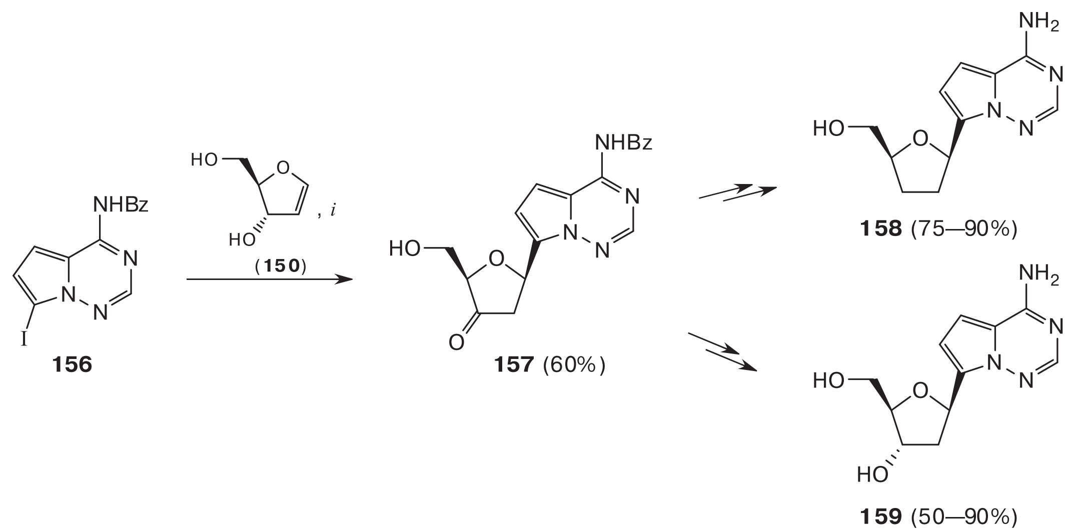
Scheme 46



153: Hal = Br (**a**), I (**b**)

Reagents and conditions: *i*. $P(C_6F_5)_3$, $Pd(OAc)_2$, Et_3N, MeCN, 82 °C; *ii*. $NaBH(OAc)_3$, HOAc—MeCN (2 : 1), 0 °C, 1 h; *iii*. NaSH, H_2O, EtOH, 78 °C, 1 h.

Scheme 47



Reagents and conditions: *i*. $Pd(dba)_2$, $AsPh_3$, NBu_3, DMF, 100 °C, 7 h.

mon source of Pd^0 is $Pd(OAc)_2$; less frequently $Pd(dppf)Cl_2$, $Pd(dba)_2$, and $Pd(PPh_3)_4$ are used. Other components of the catalytic system in these transformations are the ligand (*e.g.*, $AsPh_3$ and $P(C_6F_5)_3$) and the base (*e.g.*, Et_3N, $EtNPr^i_2$, and silver carbonate).

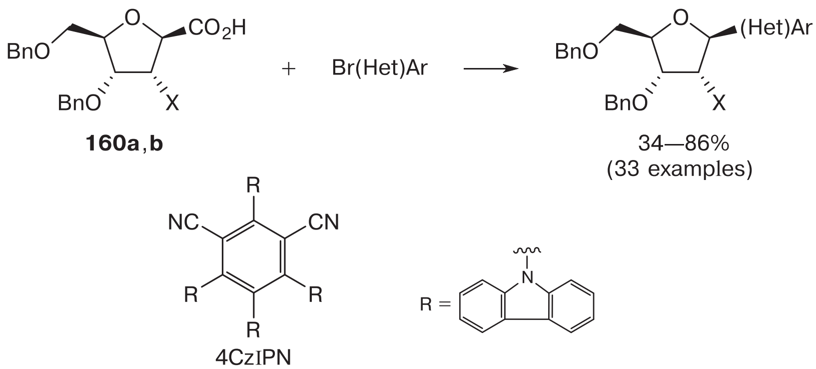
1.3. Non-standard approaches to the direct C—C coupling

In this Section, we exemplified the non-standard approaches of the C—C bond forming reactions between aglycon and carbohydrate. All these approaches are differed from each other in synthetic methods used for construction of the glycosidic bond.

Ma *et al.*[68] synthesized *C*-nucleosides *via* decarboxylative cross-coupling reaction involving ribosyl/deoxyribosyl acids with (het)aryl bromides in the presence of photoredox/nickel dual-catalyst (Scheme 48). Special experiments established the importance of visible light, photocatalyst, nickel catalyst, ligand, and base, since no formation of the desired cross-coupled product was observed in the absence of at least one of these reaction promoters. Moreover, the inhibition of the reactivity was observed in the presence of air oxygen and TEMPO (23—25% yields) thus suggesting the radical nature of the reaction.

The substituents (Het)Ar could be different substituted derivatives of benzene, naphthalene, benzofuran, indole, pyridine, benzomorpholine, thiazole,

Scheme 48



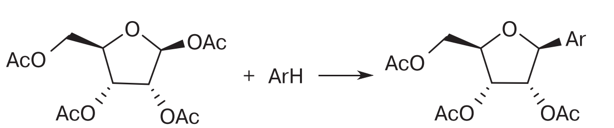
160: X = OBn (**a**), H (**b**)

Reagents and conditions: LEDs (blue light, 34 W), 4CzIPN (5 mol.%), $NiBr_2$ (10 mol.%), 2,2´-bipyridine (12 mol.%), K_2CO_3 (2 equiv.), DMF, N_2, 30 °C, 24 h.

and other mono- and bicyclic heteroaryl compounds. In addition to the mild reaction conditions, broad substrate scope, and good functional group compatibility, the most significant advantage of this transformation is the use of safe, bench-stable, and easily handled starting materials.[68]

Tachallait *et al.*[69] suggested straightforward and versatile synthesis of *C*-(het)aryl nucleosides *via* the $FeCl_3$-catalyzed Friedel—Crafts *C*-glycosylation (Scheme 49). It was found that no reaction occured in the presence of other iron salts and iron oxide (Fe_2O, $FeSO_4$) even with the increased catalyst loading (up to 50 mol.%) and at higher reaction temperatures as well as when CH_2Cl_2 was replaced with DMF. Nucleophiles ArH (see Scheme 49) were methoxybenzene and its 4-substituted derivatives, thiophene and furan derivatives, 2-methoxynaphthalene, and benzofuran. 2-Methoxynaphthalene and 3-(ethoxycarbonyl)furan *C*-glycosides were isolated exclusively as β-anomers. In the case of benzofuran, the reaction proceeded with good selectivity of β : α = 95 : 5. In other cases, β-anomers

Scheme 49

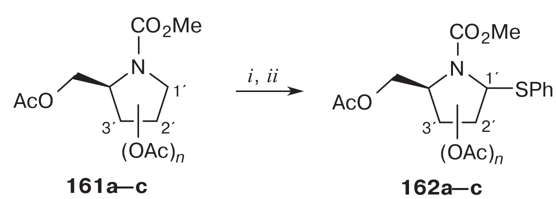


Reagents and conditions: $FeCl_3$ (10 mol.%), CH_2Cl_2, reflux, 10—30 min.

predominated only slightly, the product yields were 30—72%. The synthesized *C*-nucleosides showed interesting photophysical properties, including fluorescence. They can potentially can be used for RNA labeling to afford new biological probes and sensors.

Chiba and coworkers[70] described electrochemical synthesis of *C*-nucleosides based on unactivated prolinols. Firstly, the addition of thiophenol to prolinols **161a—c** was studied (Scheme 50). Interestingly, the relationship between the coupling yield, electron density at the position 1´, and pK_a of the carboxylic acid additives was observed. Additive of acetic acid caused a decrease in the yield with a decrease in the electron density at the position 1´ of the substrates;

Scheme 50

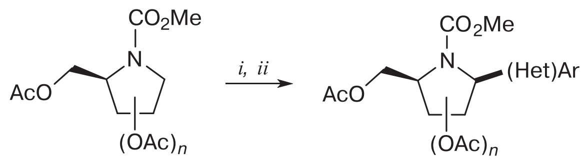


161, 162: 2´-deoxy (**a**), 3´-deoxy (**b**), 2´,3´-dideoxy (**c**)

RCO_2H	Yield of **162** (%)		
	162a	**162b**	**162c**
AcOH	94	64	24
Cl_2CHCO_2H	72	81	56
F_3CCO_2H	34	73	75

Reagents and conditions: *i.* 2.6 F mol^{-1}, 0.25 mA cm^{-2}, RCO_2H (50 mmol L^{-1}), 0 °C; *ii.* PhSH (5 equiv.), ~20 °C, glassy carbon anode, Pt cathode, $MeNO_2$—$LiClO_4$ (1.0 mol L^{-1}).

Scheme 51



161a—c (0.1 mmol)

Reagents and conditions: *i.* 1) 2.6 F mol^{-1}, 0.5 mA cm^{-2}, RCO_2H (R = Me, Cl_2CH, CF_3) (50 mmol L^{-1}), 0 °C; *ii.* (Het)ArH (5 equiv.), ~20 °C, glassy carbon anode, Pt cathode, $MeNO_2$—$LiClO_4$ (1.0 mol L^{-1}).

while in the case of TFA the reverse dependence was observed.

The developed conditions were used to synthesize a series of *C*-azanucleosides (Scheme 51). Different arenes, indoles, benzothiophene, benzofuran, and thiophene served as (het)aryls; the product yields varied from 45 to 84%. It was noted that in the case of 5-cyanoindole the yield of the target *C*-azanucleoside decreased to 14%. In contrast, the presence of the nitro group or the chlorine atom at position 7 of the starting indole has no effect on the yield and the corresponding products were obtained in the yields of 84 and 88%, respectively.

Comparatively rare sydnone *C*-nucleosides **164** and **166** were synthesized by Van Calenbergh and coworkers.[71] Two strategies, electrophilic and nucleophilic, for the generation of the C—C bond were explored (Scheme 52). Electrophilic glycosylation offered the advantage of operational simplicity and good yields; however, it is limited to benzyl protected ribofuranosides. Nucleophilic approach provided high stereoselectivity and compatible with different glycolactones.

Acyclo *C*-nucleosides were synthesized in high yields by the reaction of chlorophthalazine **167** with gluconic acid hydrazide and galactaric acid bishydrazide. Refluxing the reactants in EtOH enabled the cascade process that involved substitution of the chlorine atom and the 1,2,4-triazole ring closure[72] (Scheme 53).

Simple acyclic phosphorylated aza-*C*-nucleotides **171a—e** and **172** were synthesized by coupling of aldehydes **168** and **169** with amino phosphonates **170** (Scheme 54).[73]

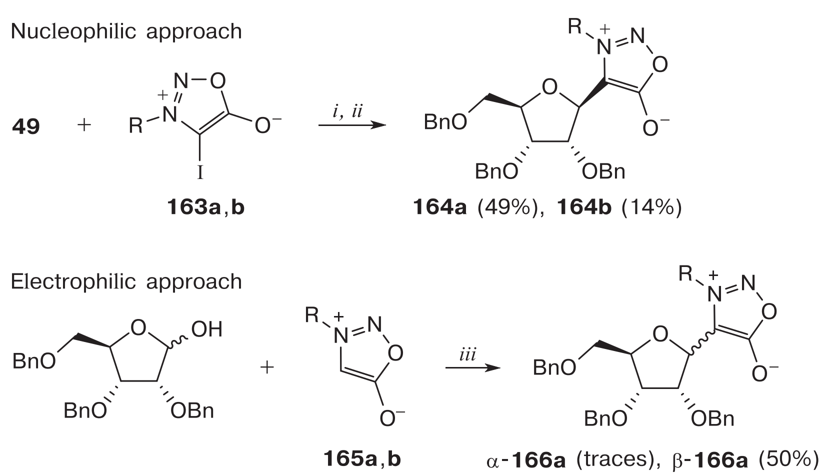
Derivatives **171f—g** were obtained by the reductive alkylation followed by deprotection.

Anthra[1,2-*d*]imidazole-6,11-dione *C*-nucleosides **174a—c** were synthesized by imidazole cyclization reaction of 1,2-diaminoanthraquinone **173** with various sugar- and azasugar-derived aldehydes[74] (Scheme 55).

Similar strategy was used to synthesize compounds **174d—h**. Condensation of 1,2-diaminoanthraquinone **173** with monochloroacetic acid and subsequent nucleophilic substitution of the chlorine atom with *N*-alkylamino aza-sugar gave compounds **174d—h** in the yields did not exceeding 48% (Scheme 56).

The approaches to the formation of the glycosidic bond between aglycon and carbohydrate unit de-

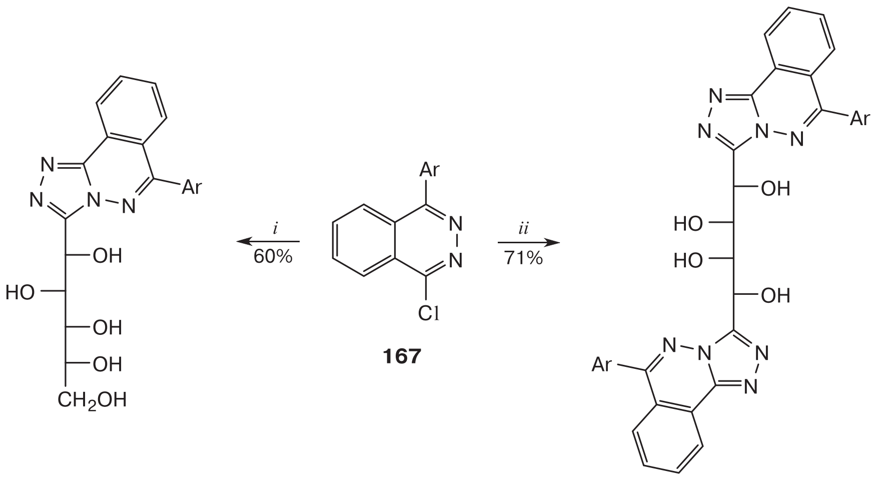
Scheme 52



162—166: R = 4-$MeOC_6H_4$ (**a**), Bn (**b**)

Reagents and conditions: *i.* $Pr^iMgCl \cdot LiCl$, THF, 0 °C; *ii.* $BF_3 \cdot Et_2O$, Et_3SiH, CH_2Cl_2, 0 °C; *iii.* $BF_3 \cdot Et_2O$, $CHCl_3$, reflux.

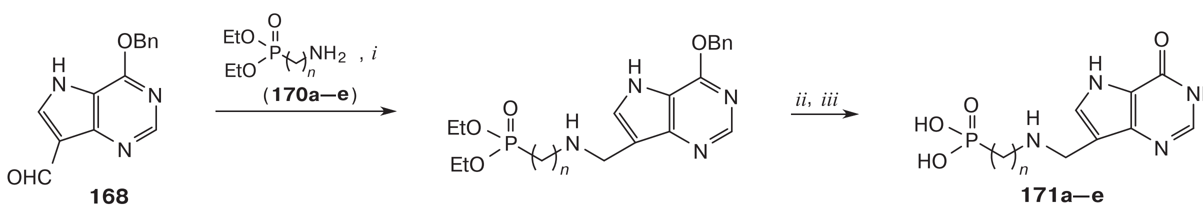
Scheme 53



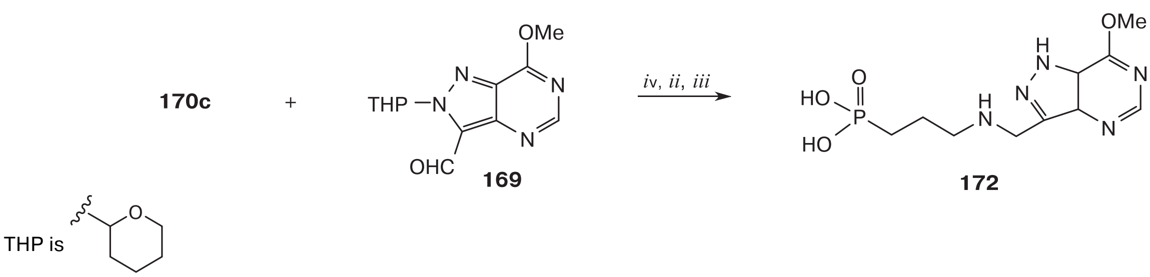
Ar is 2,4,6-$Me_3C_6H_2$

Reagents and conditions: *i*. gluconic acid hydrazide, EtOH, reflux, 4 h; *ii*. galactaric acid bishydrazide, EtOH (anhydrous), reflux, 5 h.

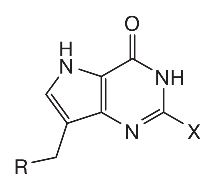
Scheme 54



170, 171: *n* = 1 (**a**), 2 (**b**), 3 (**c**), 4 (**d**), 5 (**e**)

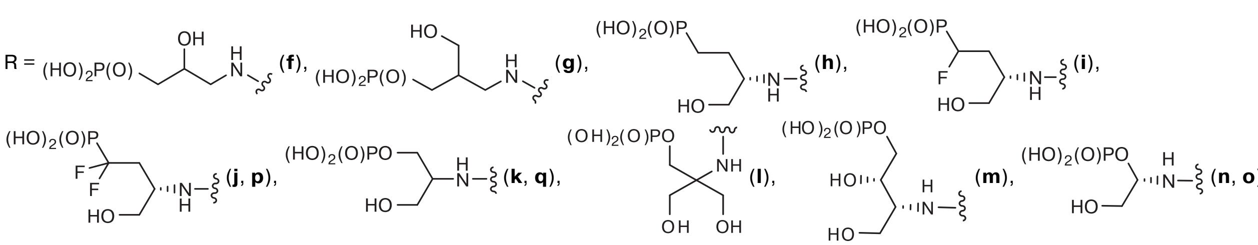


Reagents and conditions: *i*. $NaBH_4$, EtOH; *ii*. 35% HCl, 60 °C; *iii*. 48% HBr, 90 °C; *iv*. 2-picoline borane complex, MeOH.

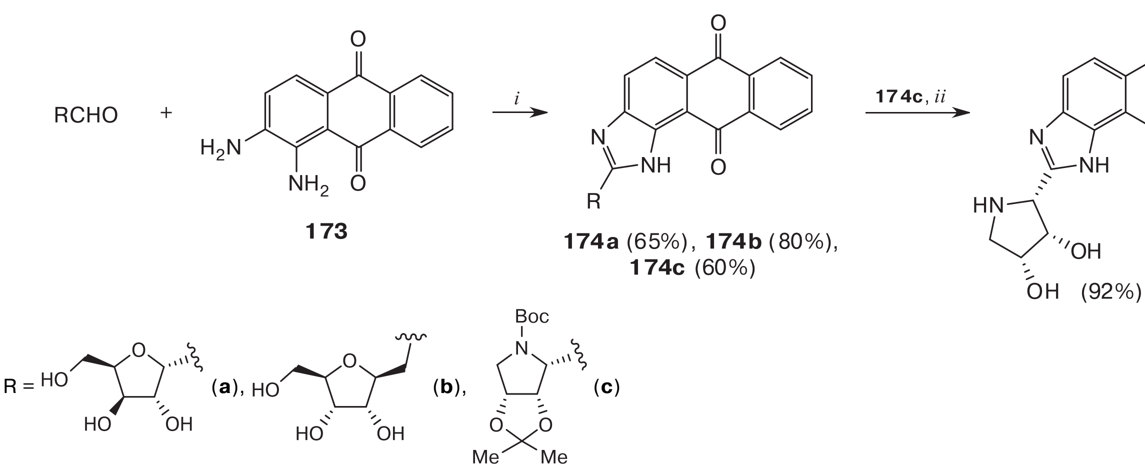


171f—q

171: X = H (**f—n**), NH_2 (**o**, **p**), Cl (**q**)

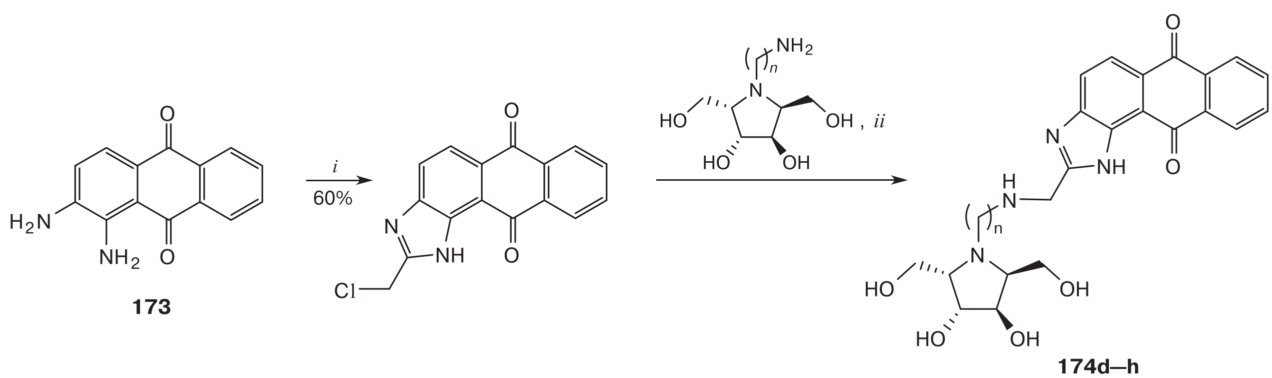


Scheme 55



Reagents and conditions: *i*. H_2SO_4, DMF, ~20 °C, 5 h; *ii*. HCl, 1,4-dioxane, 40 °C, 5 h.

Scheme 56



Compounds 174	*n*	Yield (%)	Compounds 174	*n*	Yield (%)
d	2	43	g	6	45
e	3	40	h	8	48
f	4	40			

Reagents and conditions: *i*. $ClCH_2CO_2H$, 90 °C, 1 h; *ii*. DMF, $EtNPr^i{}_2$, NaI, 70 °C, 3 h.

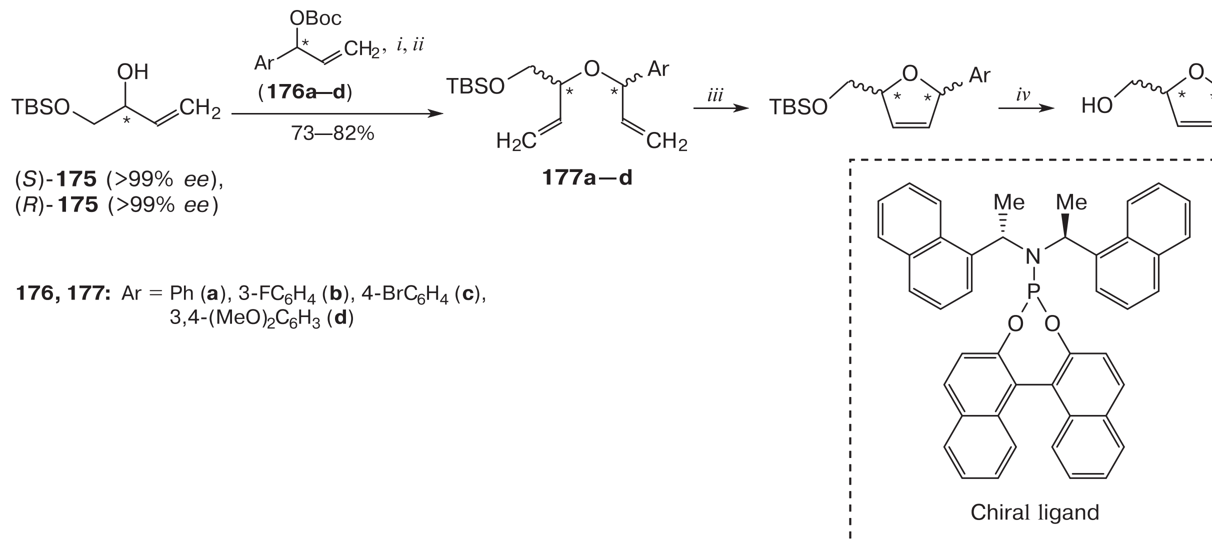
scribed in this Section are quite diverse and, in some cases, allow synthesis of the target *C*-nucleosides in good yield and high stereoselectivity. However, in terms of universality and applicability to a wide range of substrates these approaches are significantly inferior to more common methods that based on activation with the Grignard reagents and the Pd-catalyzed transformations.

2. Synthesis of *C*-nucleosides by construction of a sugar unit on a pre-formed aglycon

The next strategy towards *C*-nucleosides involved the construction of the carbohydrate unit on a pre-formed aglycon (see Fig. 1).

For instance, the iridium(I)-catalyzed allylation of enantiopure copper(I) alkoxide, generated from monoprotected diols (*R*)- and (*S*)-**175**, with enantiopure allylic carbonates (*R*)- and (*S*)-**176a—d** was used to synthesize *C*-nucleoside precursors **177a—d**[75] (Scheme 57). Configuration of products **177a—d** obtained by the stereocontrolled synthesis was predetermined by the absolute configuration of the starting substrates **175** and **176**. Compounds **177a—d** were converted to pseudoribosides under conditions of the standard ring-closing metathesis. Undoubted advantages of this approach are stereoselectivity and high yields of the target products (56—97%). However, the use of unique and expensive reagents limited a wide application of this approach. In addition, it

Scheme 57



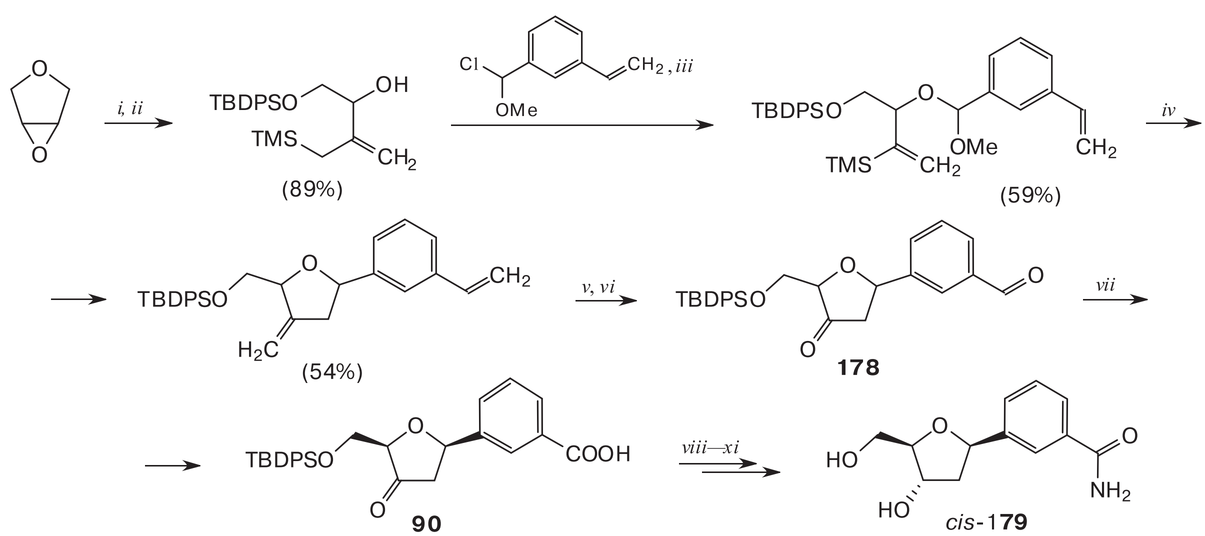
Reagents and conditions: *i*. BuLi; *ii*. 1) CuI, 2) **176a—d**, $[Ir(COD)Cl]_2$ (COD is 1,5-cyclooctadiene), chiral ligand, THF, $-40 \rightarrow 20$ °C, 16—20 h; *iii*. $(Cy_3P)_2Cl_2Ru{=}CHPh$ (1 mol.%), CH_2Cl_2, reflux, 3 h; *iv*. $Et_3N \cdot 3HF$, THF, ~20 °C, 16 h.

remains unclear whether this approach is applicable to the synthesis of heterocyclic *C*-nucleosides.

Synthesis of 2′-deoxy-*C*-glycosides based on the construction of the riboside unit on a pre-formed aglycon described by Midtkandal *et al.*[76] required 11 steps (Scheme 58). The obtained mixture of *cis* and *trans* isomers of compound **178** was separated by column chromatography, however attempted epimerization of *trans*-isomer to *cis*-isomer failed. The final *cis*-**179** was obtained in 11.2% overall yield.

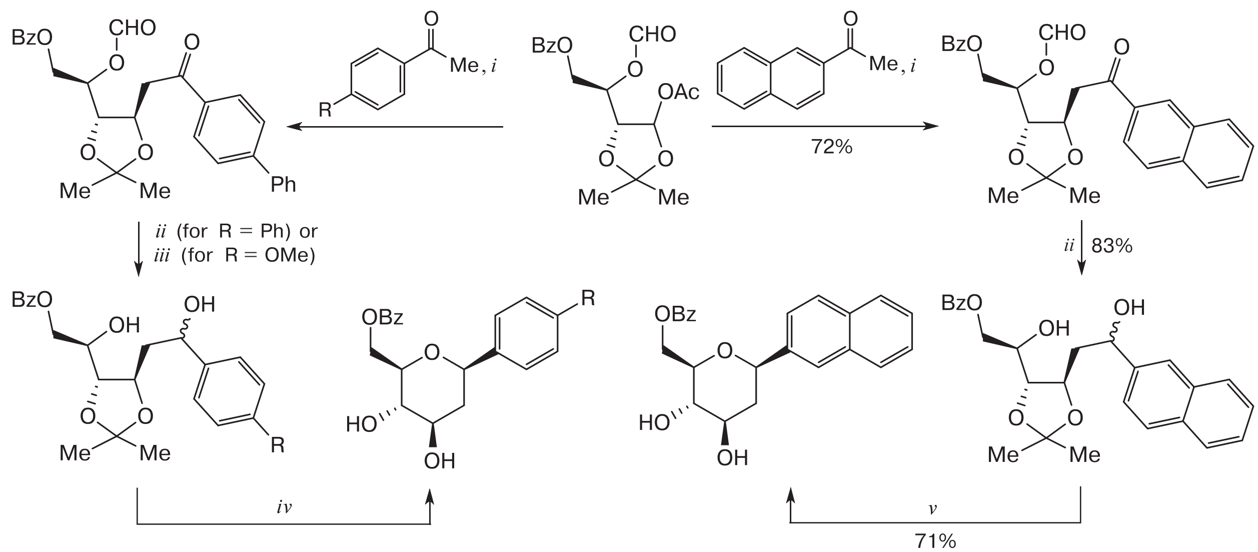
Compound *cis*-**179** was evaluated against a wide panel of the tumor cell lines but was found inactive.

Scheme 58



Reagents, conditions, and yields: *i*. $TMSCH_2Li$, THF, -78 °C; *ii*. TBDPSCl, Et_3N, DMAP, CH_2Cl_2, ~20 °C, 89% (over 2 steps); *iii*. Et_3N, CH_2Cl_2, $0 \rightarrow 20$ °C, 59%; *iv*. $TMSNTf_2$, CH_2Cl_2, -78 °C, 54% (*cis* : *trans* = 1.3 : 1); *v*. O_3; *vi*. PPh_3, CH_2Cl_2, 87% (resolution of the isomers by column chromatography gave *cis*-isomer in 50% yield); *vii*. $NaClO_2$, H_2O_2, 90%, NaH_2PO_4, MeCN, H_2O, 90%; *viii*. $SOCl_2$, PhMe; *ix*. NH_4OH, 95% (over 2 steps); *x*. TsOH, DMF, 60 °C, 56%; *xi*. $NaBH(OAc)_3$, AcOH, MeCN, 0 °C, 95%.

Scheme 59



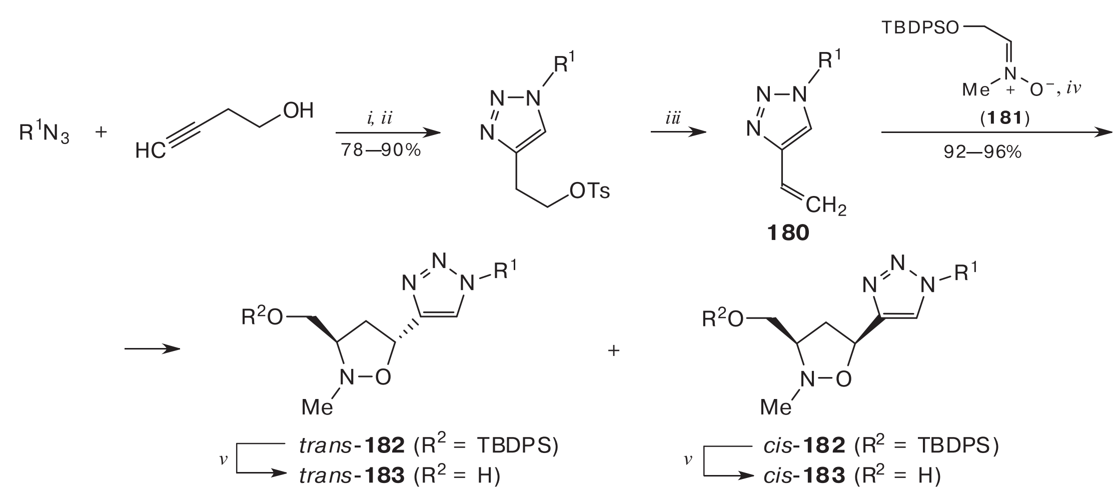
R = Ph, OMe

Reagents, conditions, and yields: *i*. Et_3N, TMSOTf, 0 °C, 67% (R = Ph), 73% (R = OMe); *ii*. $NaBH_4$, MeOH, 1 h, 81% (R = Ph); *iii*. 1) $NaHCO_3$, MeOH, 94%, 2) $NaBH_4$, MeOH, 1 h, 92%; *iv*. TMSOTf, MeCN, –20 °C, 78% (R = Ph) or –40 °C, 95% (R = OMe); *v*. $BF_3 \cdot Et_2O$, $MeNO_2$, –10 °C; *vi*. $NaHCO_3$, MeOH.

Stereoselective transformation of the sugar derivatives to *C*-glycosides was reported by Boto and coworkers.[77] The synthesized acyclic glycosides were modified to "construct" the cyclic riboside unit in good yield and excellent diastereoselectivity (Scheme 59). It was noted that this method of construction of the riboside moiety can be applied to substrates with high functionalization and conformational constraints.

1,3-Dipolar cycloaddition of *C*-vinyltriazoles **180** to *C*-(*tert*-butyldiphenylsilyl)oxy-*N*-methylnitrone **181** afforded a mixture of *cis* and *trans* isomeric *C*-nucleosides **182** in almost quantitative yields. The ratio of *cis* and *trans* isomers of triazolyl nucleosides **183** obtained by removal of the TBDPS protective varied from 1 : 1 to 1 : 1.3 depending on the substituent R^1 (Scheme 60).[78] Giofrè and coworkers[78]

Scheme 60



R^1 = Ph, Bn, 3-F_3C-4-ClC_6H_3, 4-$MeOC_6H_4$, 4-FC_6H_4, 2-pyridylmethyl, 2-naphthyl

Reagents and conditions: *i*. $CuSO_4 \cdot 5H_2O$, sodium ascorbate, Et_3N, 4 h, ~20 °C; *ii*. TsCl, Et_3N, CH_2Cl_2, ~20 °C, 12 h; *iii*. Bu^tOK, Bu^tOH, 40 °C, 12 h; *iv*. $CHCl_3$, microwave irradiation (150 W), 80 °C, 2 h; *v*. TBAF, THF, ~20 °C, 4—5 h.

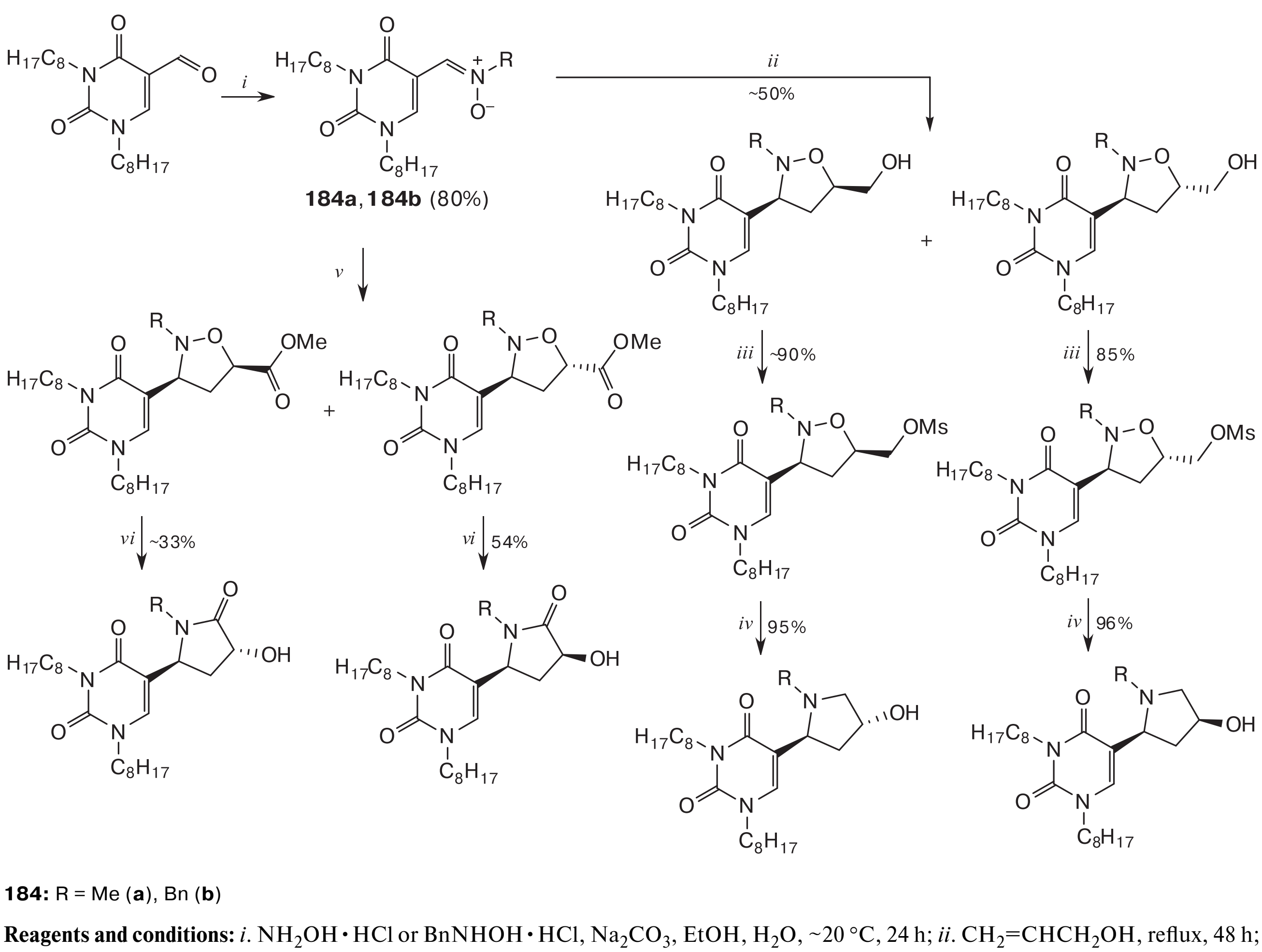
rationalized the absence of diastereoselectivity in terms of the *E-endo* attack of the dipolarophile on the nitrone, which leads to *cis* adducts, competing with the *E-exo* attack leading to *trans* adducts because of secondary orbital interactions exerted by the triazole ring.

Compounds *cis*-**183** bearing the phenyl and benzyl substituents R^1 showed antiproliferative activity. The growth inhibitory effect exerted by these compounds at a concentration of 100 μmol L^{-1} reached 50% in hepatocellular carcinoma (HepG2) and colorectal adenocarcinoma (HT-29) cells and increased up to 56% in the neuroblastoma (SH-SY5Y) cell line after 72 h of incubation.

1,3-Dipolar cycloaddition was also used to synthesize pyrrolidine *C*-azanucleoside analogs related to pseudouridine.[79] The main synthetic concept utilized for the synthesis of the target products is based on the construction of the pyrrolidine analogs of pseudocarbohydrate on an aglycon *via* nitrones **184a**,**b** (Scheme 61). The good yields of the majority of intermediates and target products are of note; however, the yields were reported for not all compounds synthesized. In general, this approach is convenient for the construction of the pyrrolidine ring in the position 5 of uracil. Using the appropriately substituted nitrones and alkenes, it is possible to synthesize a wide variety of pyrrolidine analogs of pseudouridine with different substituents and geometry.

Stereoselective synthesis of pyridazine *C*-nucleosides that involved the construction of the riboside unit from acyclic moiety in compounds **185** and **186** and subsequent one-pot transformation of the furan ring to the pyridazine scaffold was described by Cermola and coworkers[80] (Scheme 62). It is of note the yields of furyl ribosides is relatively low (30—35%).

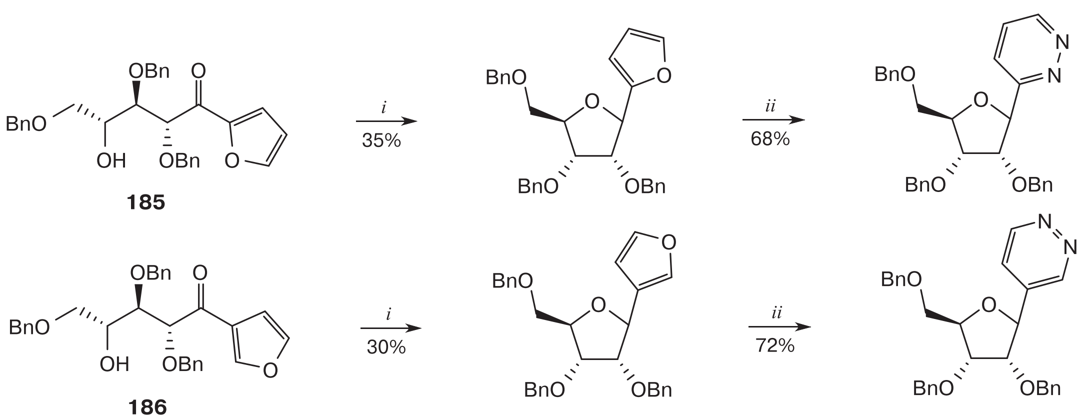
Scheme 61



184: R = Me (**a**), Bn (**b**)

Reagents and conditions: *i*. $NH_2OH \cdot HCl$ or $BnNHOH \cdot HCl$, Na_2CO_3, EtOH, H_2O, ~20 °C, 24 h; *ii*. $CH_2{=}CHCH_2OH$, reflux, 48 h; *iii*. MsCl, pyridine, ~20 °C, 12 h; *iv*. H_2, Pd/C, MeOH, ~20 °C, 48 h; *v*. $CH_2{=}CHCO_2Me$, toluene, 80 °C, 48 h; *vi*. H_2, Ranay Ni, MeOH, ~20 °C, 24 h.

Scheme 62



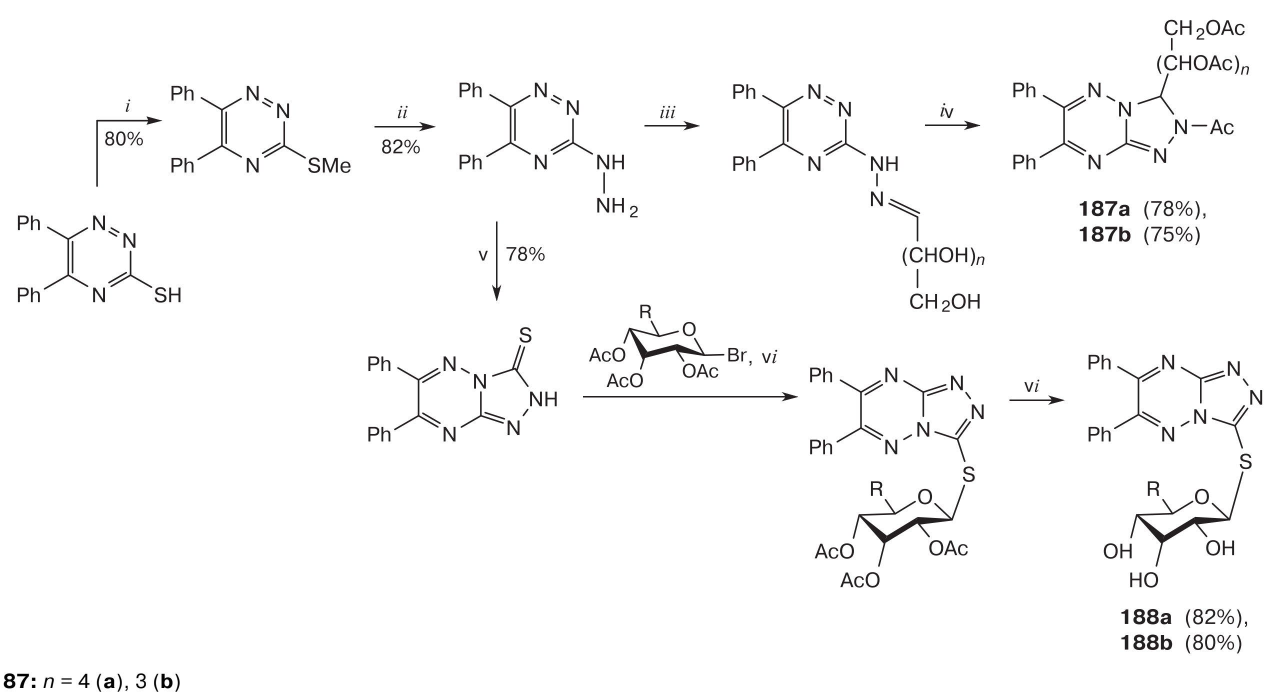
Reagents and conditions: *i*. Et_3SiH, MeCN, $BF_3 \cdot Et_2O$, $-40 \to 20$ °C, ~18 h; *ii*. 1) O_2, CH_2Cl_2, -20 °C, 90 min; 2) Et_2S, -20 °C, 2 h; 3) NH_2NH_2, THF, ~20 °C, 1 h.

Synthesis of thioglycoside and acyclic *C*-nucleoside of [1,2,4]triazines and [1,2,4]triazolo[4,3-*b*][1,2,4]-triazines was described[81] (Scheme 63). Good overall yields of *C*-nucleosides **187** synthesized in four steps (40±5%) and thioglycosides **188** prepared in five steps (32±5%) were achieved.

Sugar hydrazones **191** were synthesized by the reaction of compound **189** with equimolar amounts of aldoses **190** (Scheme 64).[82] Oxidative cyclization of hydrazones **191** and subsequent acylation of the resulted triazoloquinazolines **192** gave rise to polyacetoxyalkyl *C*-nucleosides **193**. This approach gave the target products in overall yields form 20 to 60%.

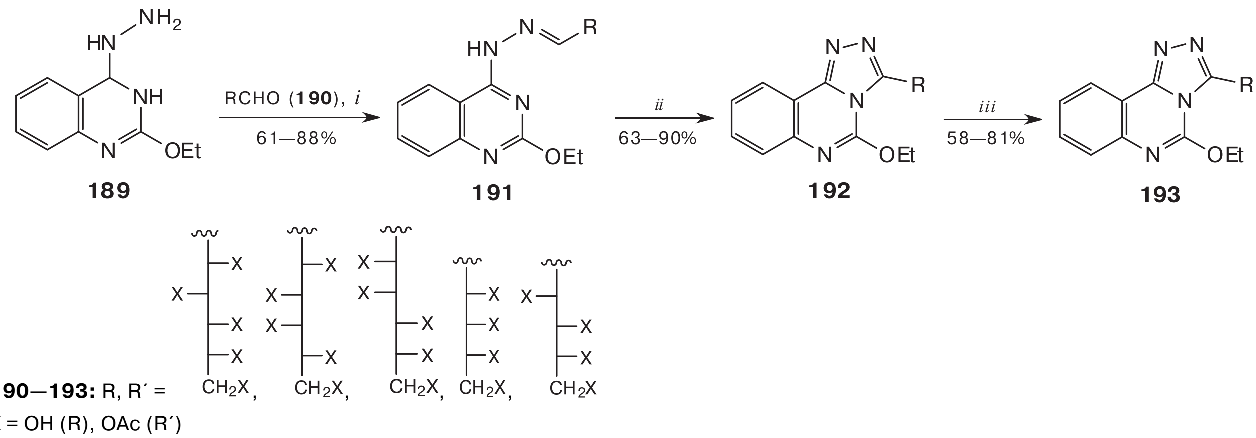
Chromeno[2,3-*b*]pyridine and [1,2,4]triazolo-[1,5-*a*]quinoline *C*-nucleoside analogs were synthesized either by the reaction of compound **194** with

Scheme 63



Reagents, conditions, and yields: *i*. MeI, K_2CO_3, acetone, ~20 °C; *ii*. N_2H_4, EtOH, reflux; *iii*. $HOCH_2(CHOH)_nCHO$, AcOH, EtOH, reflux, 85% ($n = 4$), 83% ($n = 3$); *iv*. Ac_2O, 90 °C; *v*. CS_2, KOH, EtOH, reflux; *vi*. KOH, acetone, ~20 °C, 81% (R = CH_2OAc), 79% (R = H); *vii*. NH_3, MeOH, 0 °C.

Scheme 64

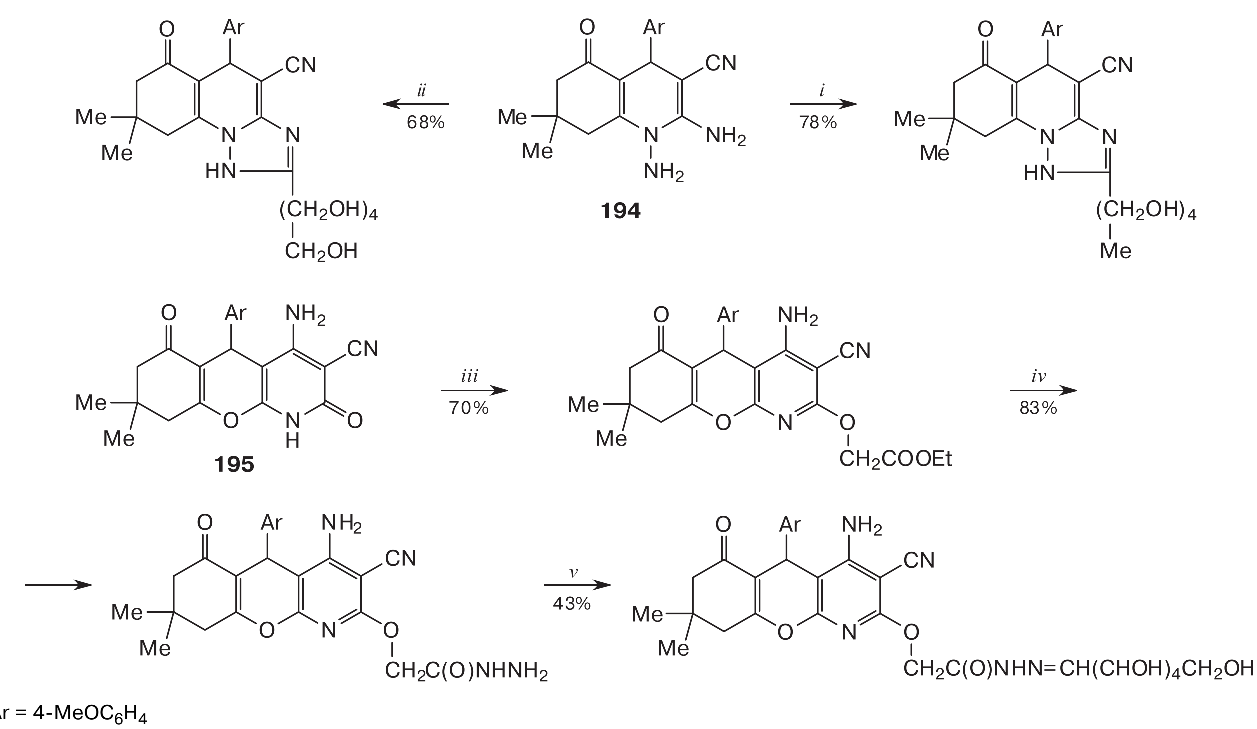


Reagents and conditions: *i*. **190**, EtOH, AcOH; *ii*. $FeCl_3$, EtOH; *iii*. Ac_2O, pyridine.

aldoses in the presence of iodine or by three-step construction of the acyclic unit on heterocycle **195** (Scheme 65).[83] This strategy for the *C*-nucleoside synthesis is very promising due to good yields of the target products, short reaction sequences, and available reagents used.

The strategy of the construction of the sugar unit on a pre-formed aglycon is generally applicable for the synthesis of *C*-nucleosides bearing the pseudoriboside (mainly acyclic) unit. The role of heterocyclic base is mainly played by simple aromatic derivatives and functionalization of the structure is impossible. Synthesis of compounds bearing functionalized purines/pyrimidines as aglycons and ribose/deoxyribose as the sugar units following this strategy is limited. These facts explained the smaller number of publications focusing on this approach compared to other strategies for constructing the *C*-nucleoside backbone.

Scheme 65



Reagents and conditions: *i*. L-rhamnose, I_2, AcOH; *ii*. D-glucose, I_2, AcOH; *iii*. $ClCH_2CO_2Et$; *iv*. N_2H_4; *v*. D-glucose.

3. Synthesis of *C*-nucleosides by construction aglycon on a pre-formed sugar unit

Another approach towards *C*-nucleosides is based on the reaction sequences that allow construction of an aglycon on a pre-formed carbohydrate unit bearing the functional groups able to participate in cyclocondensation and cycloaddition reactions.

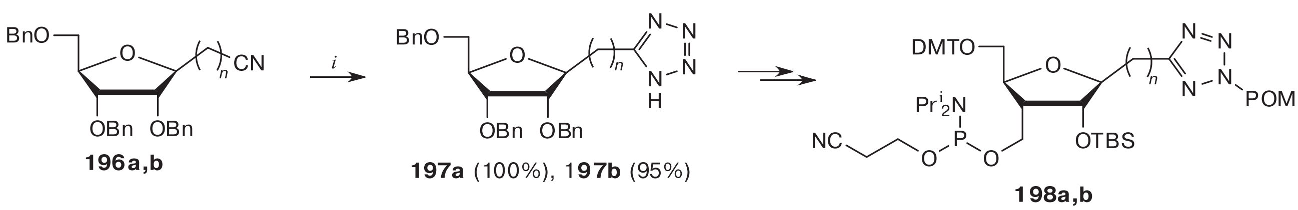
Thus, *C*-nucleosides **197a**,**b** were synthesized in almost quantitative yields by cycloaddition of sodium azide to the nitrile group of protected ribosides **196a**,**b** (Scheme 66). The introduction of acyloxymethyl group as *N*-protective groups in the tetrazole ring allowed subsequent phosphorylation of the 3´-OH group of the sugar residue to give the target compounds **198a** and **198b** in the yields of 16 and 33.8%, respectively, over 6 steps.[84]

Ribosides **199a—d** derived from D-glucose were used as the starting material for the construction of aglycon based on the nitrile group to prepare tiazofurin analogs **201a—d**[85] (Scheme 67). The key intermediates **200a—d** were synthesized by the one-pot reaction that involved the addition of hydrogen sulfide to the nitrile group, the azide reduction, and spontaneous *O*,*N*-shift of the acyl group. It was shown that this one-pot sequence was a general approach to a variety of 2-amido-D-ribofuranosyl thiocarboxamides **200a—d**. Compounds were the convenient intermediates for the thiazole synthesis *via* the reaction with ethyl bromopyruvate.

Compounds **201a—d** demonstrated high *in vitro* cytotoxicity against chronic myelogenous leukemia K562 cell lines with IC_{50} = 0.15—2.69 μmol L^{-1}. Among solid tumor cell lines, human colorectal adenocarcinoma cells (HT29) were sensitive only to compound **201d**, while cervical cancer cell-derived HeLa cells were sensitive to compounds **201a**,**b**,**d**. Only compound **201a** was cytotoxic against human breast cancer cell line MCF-7.

Similarly strategy for the construction of aglycon on a nitrile group of riboside was used by Popsavin and coworkers[86] to synthesize 2-(β-D-xylofuranosyl)-thiazole-4-carboxamide **204** (Scheme 68) and two tiazofurin analogs **208a,b** with 5-hydroxymethyl-2-

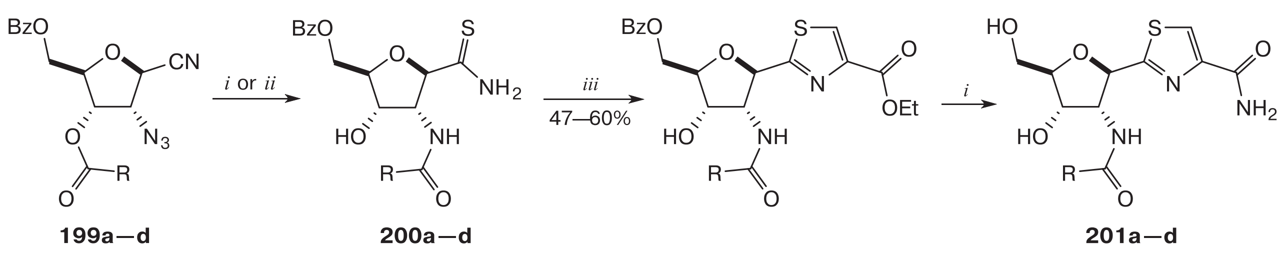
Scheme 66



POM is $CH_2OC(O)Bu^t$
196—198: *n* = 0 (**a**), 2 (**b**)

Reagents and conditions: *i*. NaN_3, Et_3N, DMF, 130 °C, 2 h (for **197a**) or microwave irradiation, 130 °C, 2 h (for 1**97b**).

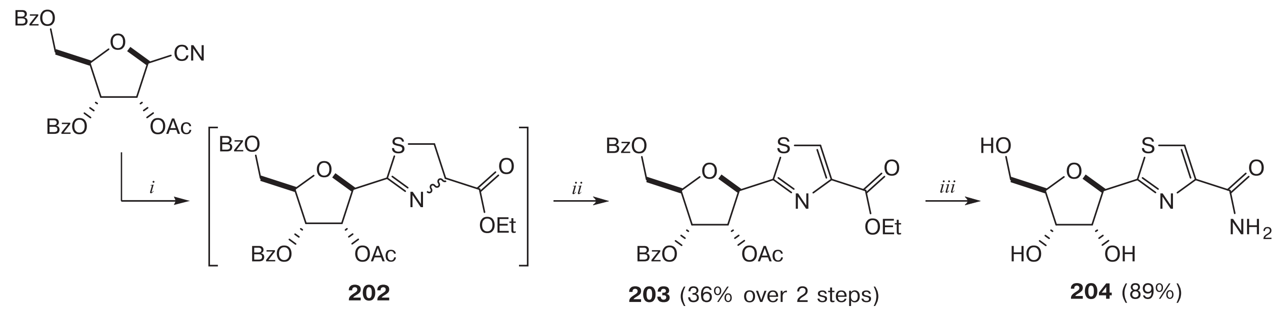
Scheme 67



Compounds 199—201	R	Yield (%) 200	201
a	C_5H_{11}	99	66
b	C_7H_{15}	92	49
c	C_8H_{19}	87	81
d	$C_{11}H_{23}$	92	80

Reagents and conditions: *i*. H_2S, pyridine, ~20 °C; *ii*. H_2S, DMAP, EtOH, ~20 °C; *iii*. $BrCH_2COCO_2Et$, EtOH, reflux; *iv*. NH_3, MeOH, ~20 °C.

Scheme 68



Reagents and conditions: *i*. $HSCH_2CH(NH_2)CO_2Et$, Et_3N, MeOH, ~20 °C, 2 h; *ii*. 1) $BrCCl_3$, DBU, CH_2Cl_2, 0 °C, 5 h; 2) 4 °C, 68 h; *iii*. NH_3, MeOH, ~20 °C, 6 days.

methyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol moiety (Scheme 69). It is of note that intermediate **202** was obtained as an inseparable mixture of C(4)-epimers and was immediately treated with bromotrichloromethane and DBU to give thiazole **203**. The yields of intermediates **207a,b** (see Scheme 69) were somewhat higher (50—54%) than those of compound **203** (36%).

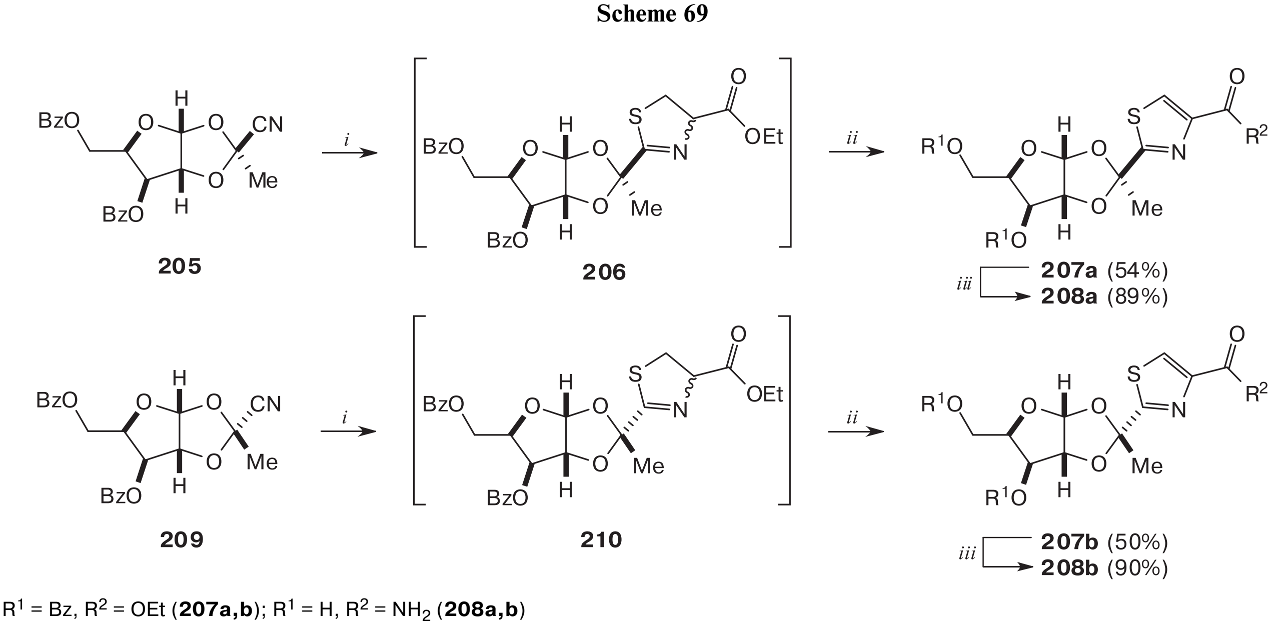
Compounds **208a,b** demonstrated submicromolar activities against four tumor cell lines (K562, HL-60, Jurkat, and HeLa).

The same strategy was successful in the synthesis of acyclic nucleosides 213 and 214, the tiazofurin analogs (Scheme 70). The key synthetic step was the condensation of compound 211 derived from D-arabinose with cysteine ethyl ester hydrochloride to afford C-epimeric thiazoline, which was treated with bromotrichloromethane and DBU to give thiazole **212**.[87]

Pure α- and β-anomers of glycosylcyanide **216** (the synthesis of which was established in hundred-gram scale in 93% yield) were used to synthesize *C*-nucleosides **217—220** bearing tetrazole, 1,2,4-oxadiazole, and 1,3,4-oxadiazole as the aglycon mimics (Scheme 71).[88] Most synthetic steps gave the yields of at least 70—80%.

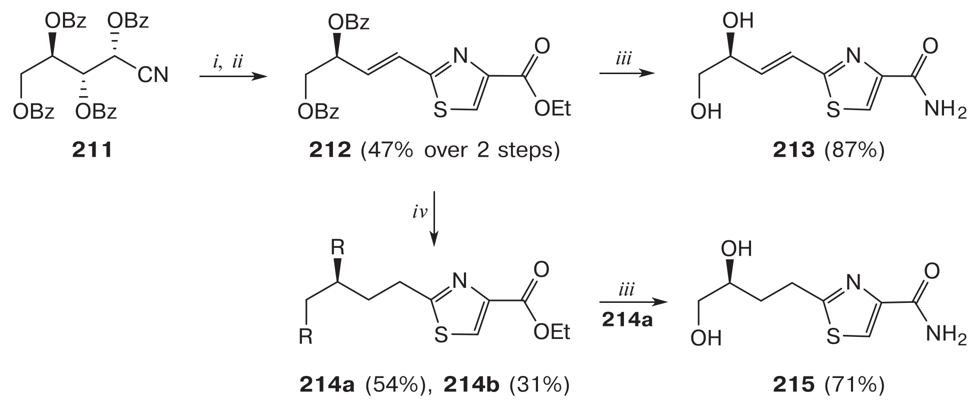
Tetrahydrofuranyl alkynes **221**, **223**, **225**, and **227** were involved in Cu-catalyzed cycloaddition reaction with different furanyl azides and adamantyl azide.[89] It should be noted that treatment of stereoisomeric alkynes **221**, **223**, and **225** with azides

Scheme 69



Reagents and conditions: *i*. $HSCH_2CH(NH_2)CO_2Et$, Et_3N, MeOH, ~20 °C, 2 h (for **206**) or 3.5 h (for **210**); *ii*. 1) $BrCCl_3$, DBU, CH_2Cl_2, 0 °C, 5 h, 2) 4 °C, 4 days (for **207a**) or 18 h (for **207b**); *iii*. NH_3, MeOH, ~20 °C, 7 days (for **208a**) or 6 days (for **208b**).

Scheme 70



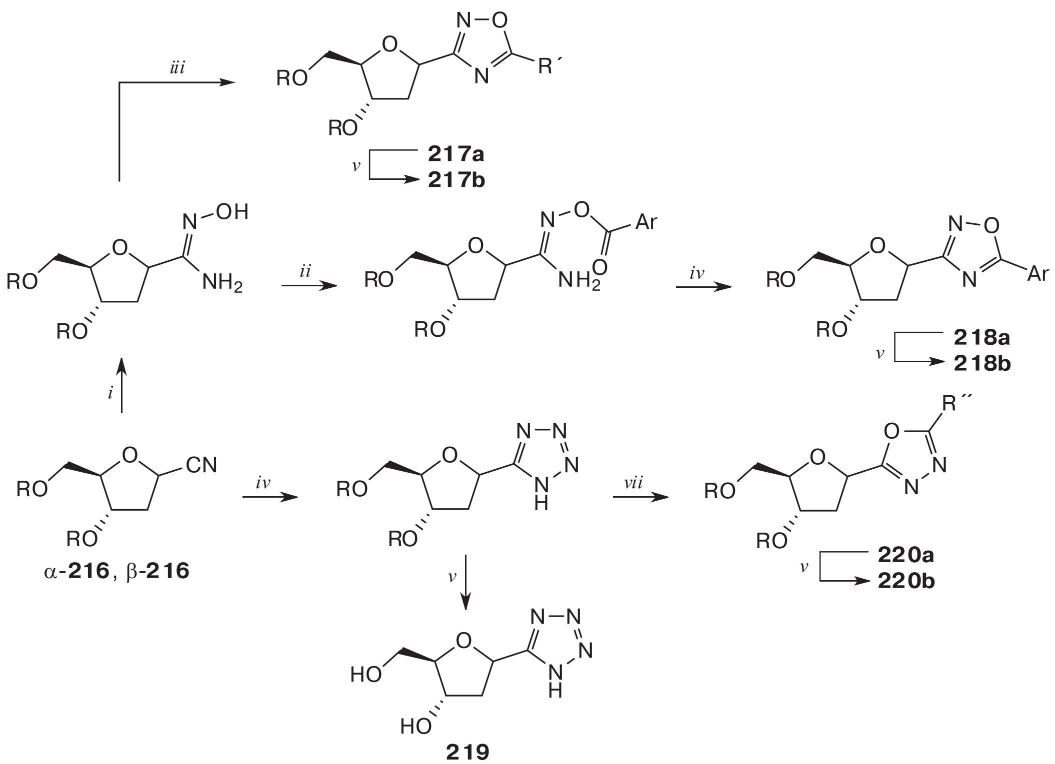
214: R = OBz (**a**), H (**b**)

Reagents and conditions: *i*. $HSCH_2CH(NH_2)CO_2Et$, Et_3N, MeOH, ~20 °C, 2 h; *ii*. 1) $BrCCl_3$, DBU, CH_2Cl_2, 0 °C, 5 h; 2) 4 °C, 17 days; *iii*. NH_3, MeOH, ~20 °C, 6 days (for **213**) or 16 days (for **215**); *iv*. H_2, 10% Pd/C, EtOH, ~20 °C, 72 h.

afforded the corresponding 1,2,3-triazolyl *C*-nucleosides **222b**, **224a—c**, and **226b**,**c** in 58—75% yields (Scheme 72).

Sabat *et al.*[90] synthesized alkynyl derivative **231** by the similar Barbier reaction between the fully protected ribose **230** and ethyl iodopropiolate **229**

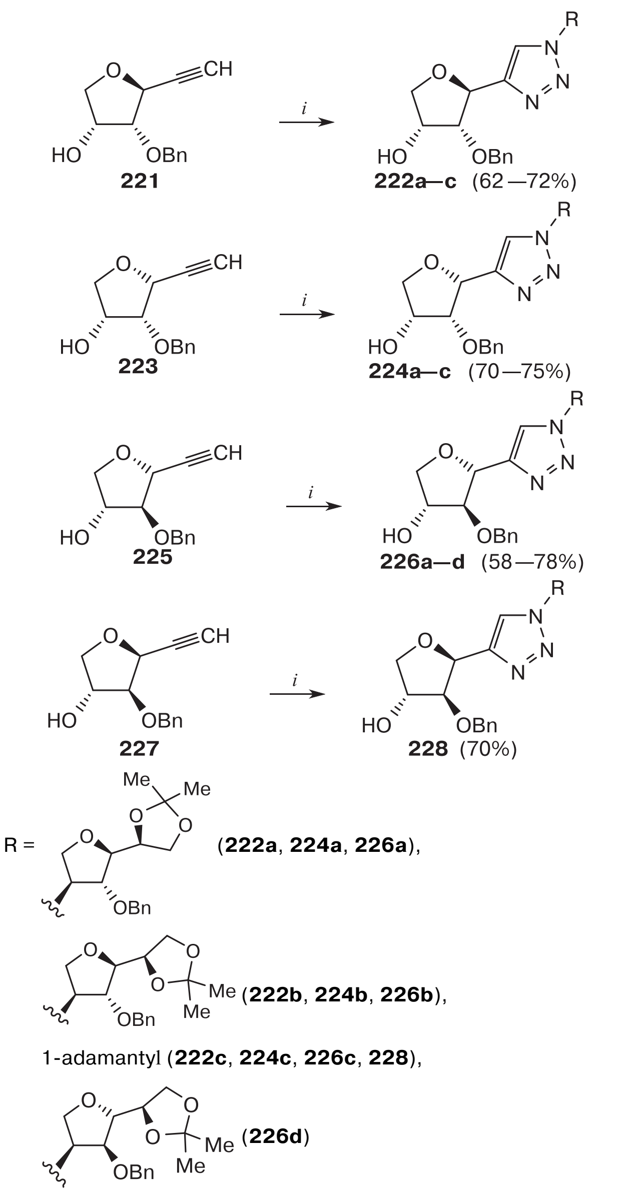
Scheme 71



R = *p*-Tol (**216**, **217a**, **218a**, **220a**), H (**217b**, **218b**, **220b**)
217a,b: R´ = Me, Bu^i, Bu^t, CF_3
218a,b: Ar = Ph, *p*-Tol
220a,b: R´´ = Me, Bu^i, Bu^t, CF_3, Ph, *p*-Tol

Reagents and conditions: *i*. $NH_2OH \cdot HCl$, DIPEA, EtOH, reflux, 1 h; *ii*. ArC(O)Cl, 1,4-dioxane, ~20 °C, 16 h; *iii*. $CH(OMe)_3$, $BF_3 \cdot Et_2O$ 110 °C, 3 h or $(R'CO)_2O$, $BF_3 \cdot Et_2O$, 110 °C or CF_3CO_2H, CH_2Cl_2, ~20 °C, 5 h; *iv*. KOH, DMSO, ~20 °C, 6 h; *v*. NaOMe, CH_2Cl_2—MeOH (3 : 2), ~20 °C, 16 h; *vi*. NaN_3, Cu, $CuSO_4$, DMF, 120 °C, 16 h; *vii*. $(R''CO)_2O$, hydroquinone, reflux, 1 h or R″C(O)Cl, pyridine, 90 °C, 2 h.

Scheme 72



Reagents and conditions: *i*. RN_3, $CuSO_4 \cdot 5H_2O$, (+)-L- ascorbic acid sodium salt, Bu^tOH-H_2O (1 : 1), ~20 °C, 6—8 h.

(Scheme 73). The subsequent Huisgen cycloaddition, aminolysis, and deprotection gave rise to ribavirin derivative SRO-91.

The key intermediates **232** bearing the alkyne unit were synthesized in high yields by the intramolecular Nicholas reaction catalyzed by $Co_2(CO)_8$ (Scheme 74).[91] Subsequent Cu^I-cycloaddition proceeded with high yields to give triazolyl *C*-nucleosides **233a—g**.[91]

One-pot synthesis of aryl pyrazole *C*-nucleosides analogs of Pyrazofurin by the three-component coupling of sugar alkynes **234a—j**, benzoyl chlorides, and hydrazine hydrate was described by Liu *et al.*[92] (Scheme 75). The reaction conditions were optimized by varying the catalyst, base, solvent, and the reaction time. When the reaction was carried out under the optimal conditions, in the presence of the $PdCl_2(PPh_3)_2$/CuI system as a catalyst, Et_3N as a base, and THF as a solvent, the yield of the target products bearing the ribose unit reached 70—90%.

The developed procedure was further used to synthesize a series of thiophene *C*-nucleosides in 65—80% yields (Scheme 76).[93]

Bicyclic lactones (+)-**235a** and (±)-**235b** and their derivatives reacted with aminoguanidine bicarbonate under basic conditions to give rise to 3-aminotriazole *C*-nucleosides **237—239**[94,95] (Scheme 77). Compounds **236a,b** are the suitable precursors for the synthesis of such biologically active compounds as showdomycin and its carba analogs.

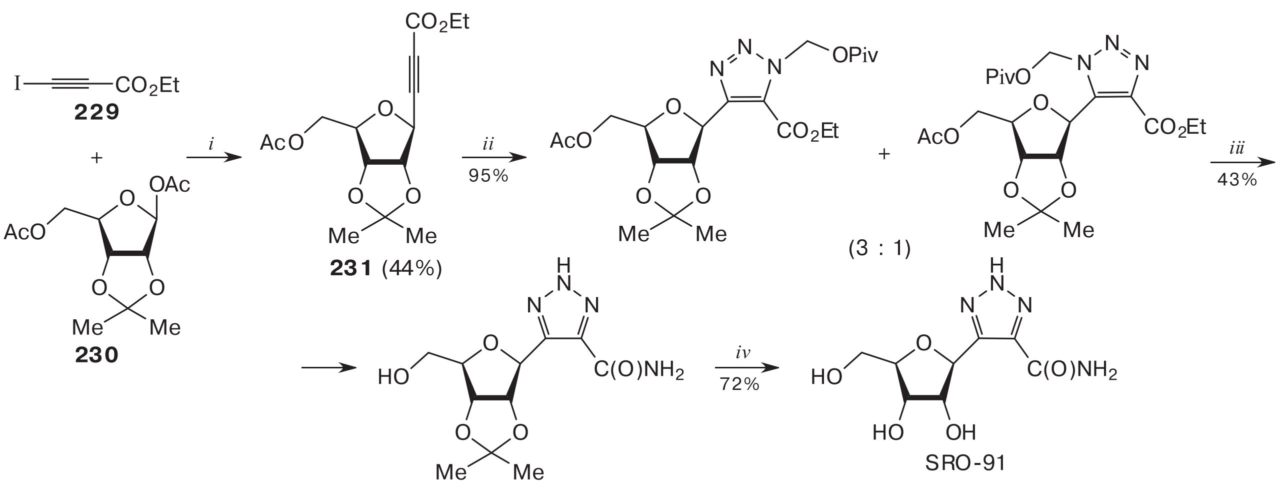
Solarte *et al.*[96] involved alkyne **231** in the cycloaddition reaction with benzyl azide. Deprotection of *C*-nucleoside precursors **240a** and **241b** and conversion of the ethoxycarbonyl moiety to the amide group afforded the target products **240b** and **241b** (Scheme 78).

The tandem ene/intramolecular Sakurai cyclization was used to synthesize *C*-glycoside **243**, a structural analog of tiazofurin[97] (Scheme 79). Compound **242** was also used as a starting material in the synthesis of other pyranosyl *C*-nucleosides. However, the yields on each synthetic step were low, therefore, this method is of low interest for the synthesis of a wide range of the *C*-nucleoside and *C*-glycoside derivatives.

Sequential construction of aglycon unit in six steps from compound **244** gave pyridazine *C*-nucleosides **248a**,**b** (Scheme 80).[32] It is of note that the reaction of hydrazone **245** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) resulted in a mixture of expected pyridazine **246** and its *N*-methyl derivative **247**. Compounds **246** and **247** were separated by flash chromatography. Next, compounds **246** and **247** were transformed to amides and then subjected to desilylation. The overall yields of compounds **248a** and **248b** were 5.7 and 5.3%, respectively (over 6 steps).

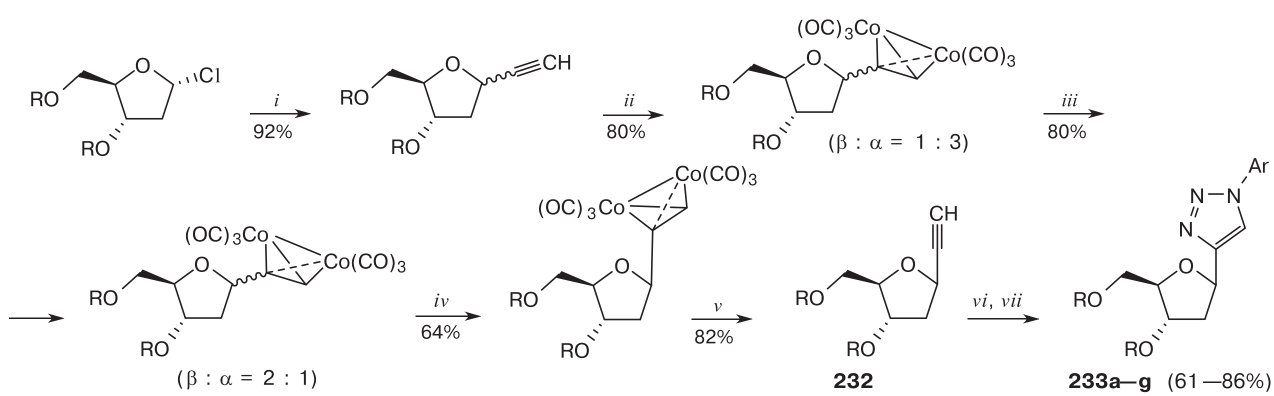
Wang *et al.*[32] did not limit themselves to the use of pyridazine as the aglycon. Pyrimidine *C*-nucleoside **249** was synthesized through the Weinreb amide (Scheme 81). The overall yield of the target compound **250** was 3.5%.

Scheme 73



Reagents and conditions: *i*. In^0, CH_2Cl_2, reflux, 3 days; *ii*. $PivOCH_2N_3$, toluene, reflux, 24 h; *iii*. aqueous NH_3, 1,4-dioxane, reflux, 48 h; *iv*. Dowex 50WX8, MeOH, H_2O, 50 °C, ~18 h.

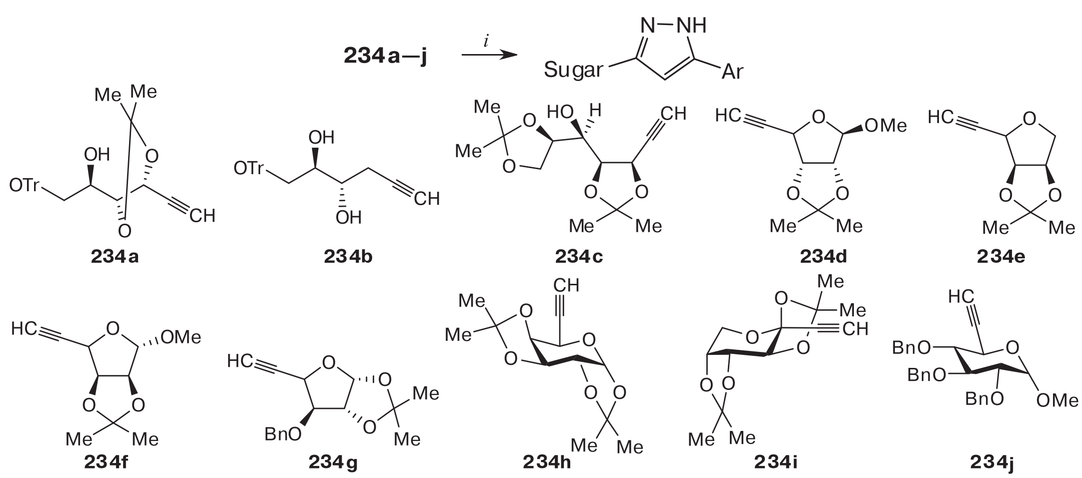
Scheme 74



233: Ar = 4-$Me_2NC_6H_4$ (**a**), 3,5-$(MeO)_2C_6H_3$ (**b**), 1-naphthyl (**c**), anthracen-2-yl (**d**), pyren-1-yl (**e**), 2-NCC_6H_4 (**f**), 4-$O_2NC_6H_4$ (**g**)

Reagents and conditions: *i*. HC≡CMgCl, THF, ~20 °C, 3 h; *ii*. $Co_2(CO)_8$, CH_2Cl_2, ~20 °C; *iii*. 1) $BF_3 \cdot OEt_2$, –78 °C, 1 h, 2) Et_3N, ~20 °C; *iv*. column chromatography; *v*. I_2, THF, 0 °C; *vi*. THF, CuI, Et_3N, ArN_3, 60 °C, 30 min; *vii*. MeONa, MeOH.

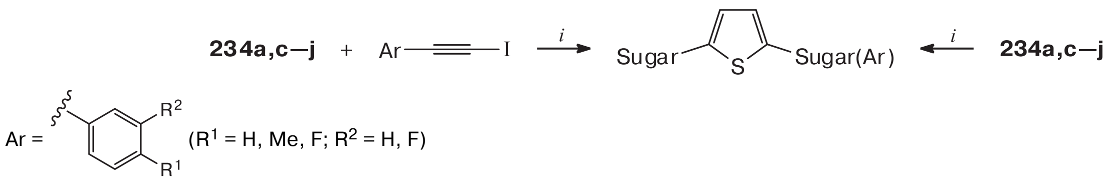
Scheme 75



Ar = XC_6H_4; X = H, Me, OMe, F, Cl, Br

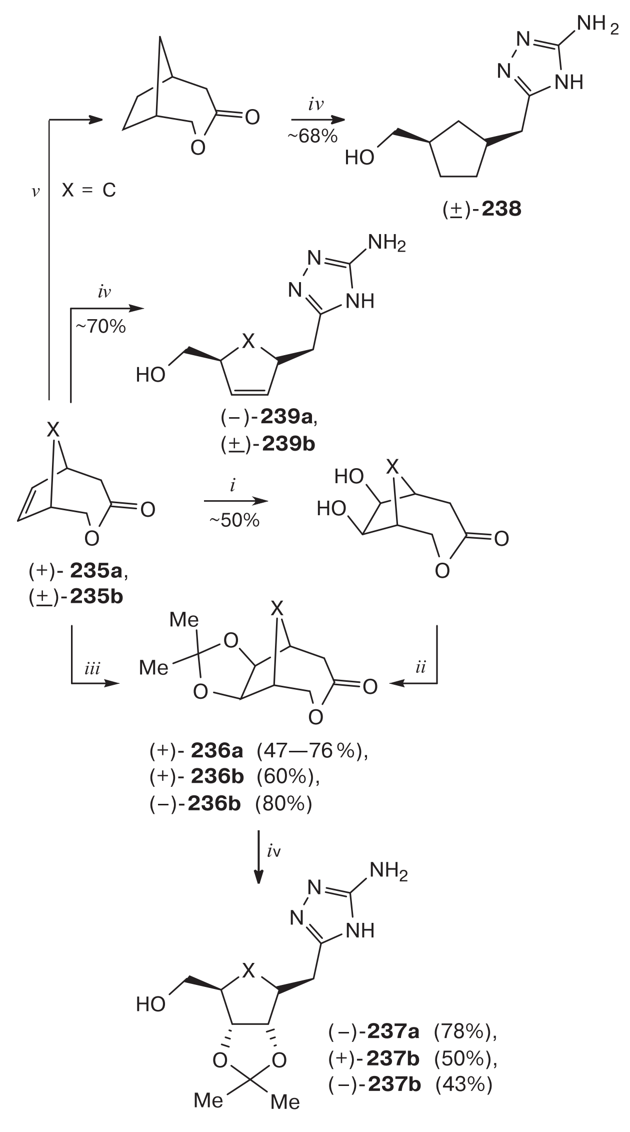
Reagents and conditions: *i*. 1) ArC(O)Cl, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, 2) N_2H_4, EtOH.

Scheme 76



Reagents and conditions: *i*. 1) $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, ~20 °C, 2) $Na_2S \cdot 9H_2O$, KOH, 60 °C.

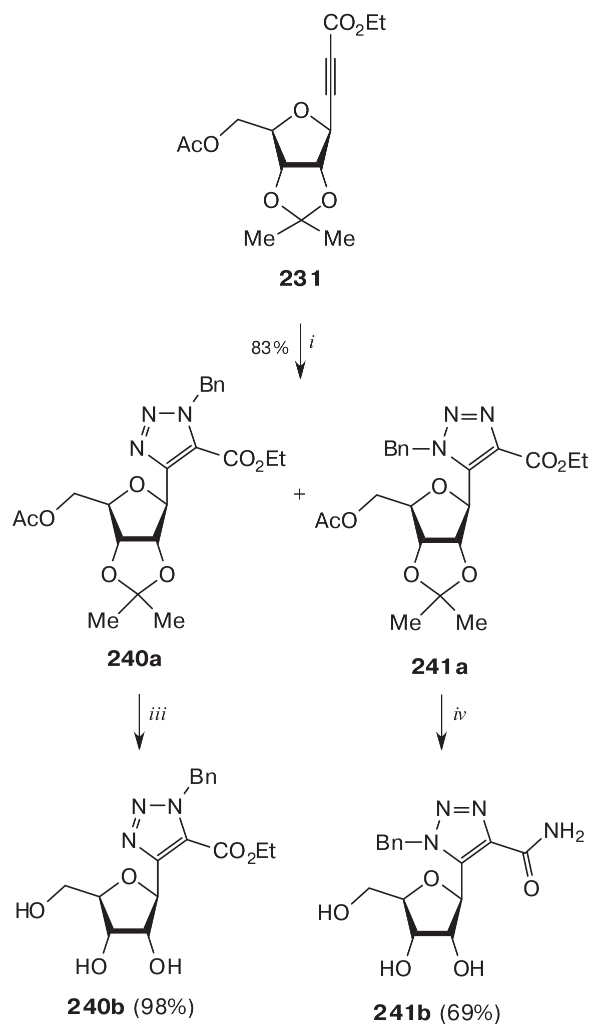
Scheme 77



235—237, 239: X = O (**a**), CH_2 (**b**)

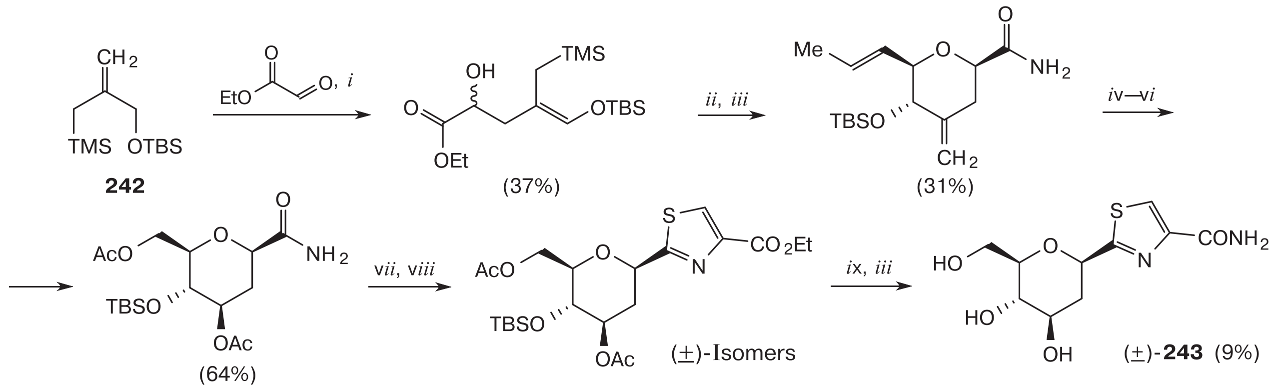
Reagents and conditions: *i*. 4-methylmorpholine 4-oxide (NMO), OsO_4, CH_2Cl_2, Bu^tOH, ~20 °C; *ii*. 2-methoxypropene or 2,2-dimethoxypropane, TsOH, acetone, ~20 °C; *iii*. 1) NMO, OsO_4, CH_2Cl_2, Bu^tOH, ~20 °C, 2) $AlCl_3$, acetone, ~20 °C; *iv*. aminoguanidine bicarbonate, pyridine, reflux; *v*. H_2, Pd/C, AcOEt, ~20 °C.

Scheme 78



Reagents and conditions: *i*. BnN_3, toluene, reflux, 24 h; *ii*. Dowex 50 (H^+), MeOH, H_2O, 50 °C, 6 h; *iii*. 1) NH_3 (gas), MeOH, –10 °C, 8 h (yield 83%), 2) Dowex (H^+), MeOH, H_2O.

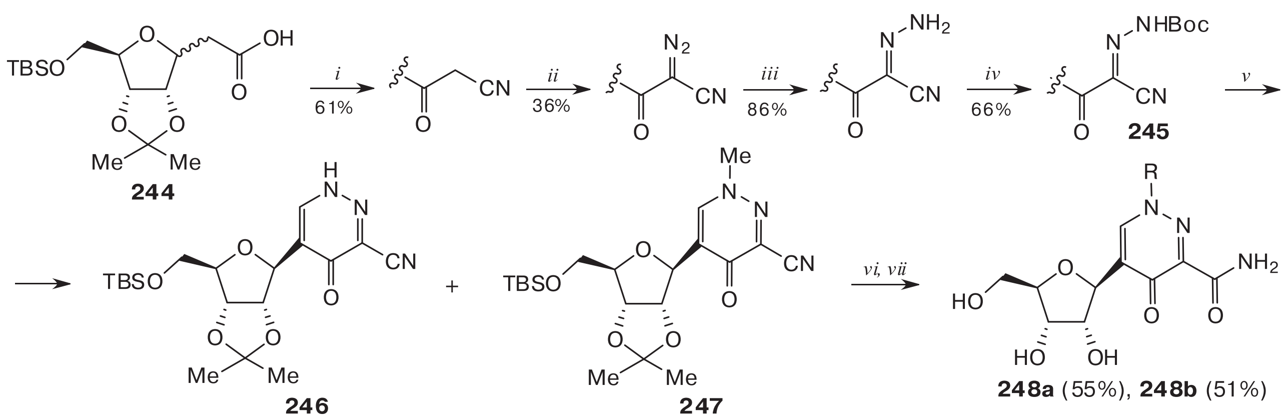
Scheme 79



TMS is Me_3Si

Reagents and conditions: *i*. Et_2AlCl, CH_2Cl_2; *ii*. MeCH=CHCHO, $BF_3 \cdot Et_2O$, CH_2Cl_2; *iii*. NH_3 (gaseous), MeOH; *iv*. 1) O_3, MeOH, CH_2Cl_2, 2) Me_2S; *v*. $NaBH_4$, MeOH; *vi*. Ac_2O, pyridine; *vii*. P_2S_5, toluene; *viii*. $BrCH_2C(O)CO_2Et$, 4 Å molecular sieves, EtOH (anhydrous); *ix*. TBAF, THF.

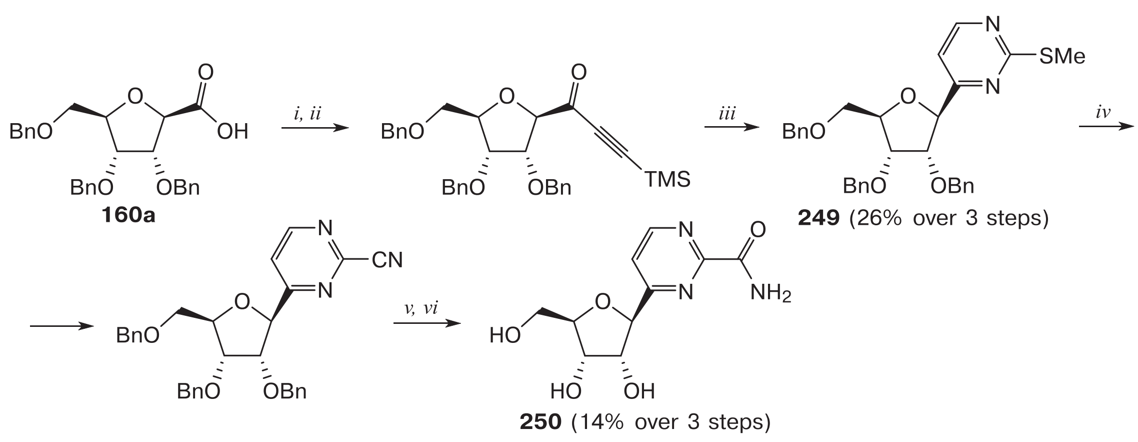
Scheme 80



248: R = H (**a**), Me (**b**)

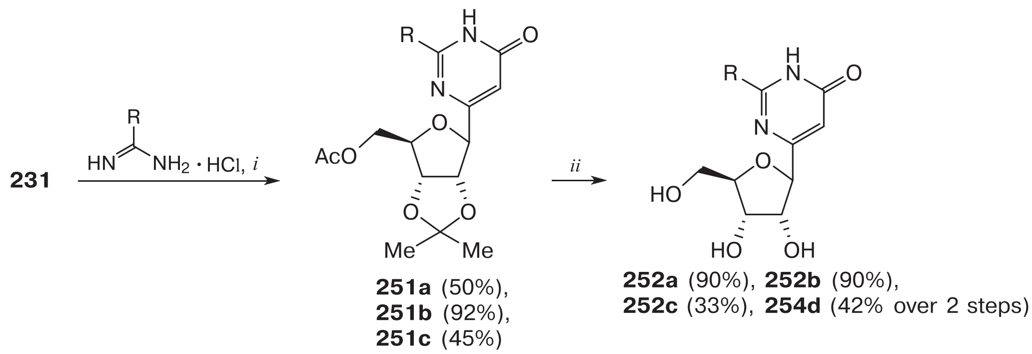
Reagents, conditions, and yields: *i*. BuLi, MeCN; *ii*. TfN_3, Et_3N, MeCN; *iii*. PMe_3, THF, H_2O; *iv*. Boc_2O, pyridine; *v*. $Me_2NCH(OMe)_2$, THF, 12 h; *vi*. Et_3N, H_2O_2, MeOH, 83%; *vii*. 80% aqueous CF_3CO_2H.

Scheme 81



Reagents, conditions, and yields: *i*. 2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), $EtNPr^i_2$, MeON(H)Me, CH_2Cl_2, 8 h, 82%; *ii*. 1) $Me_3SiC{\equiv}CLi$, THF, –78 °C, 2) ~20 °C, 3 h; *iii*. $MeO_2C(S)NH_2 \cdot HCl$, MeCN, 80 °C, 3 h, 32% (over 2 steps); *iv*. 1) MCPBA, CH_2Cl_2, 3 h, 92%; 2) KCN, DMSO, ~18 h, 63%; *v*. H_2O_2, NH_4OH, MeOH, 1 h, 57%; *vi*. BCl_3, CH_2Cl_2, 0 °C, 4 h, 41%.

Scheme 82



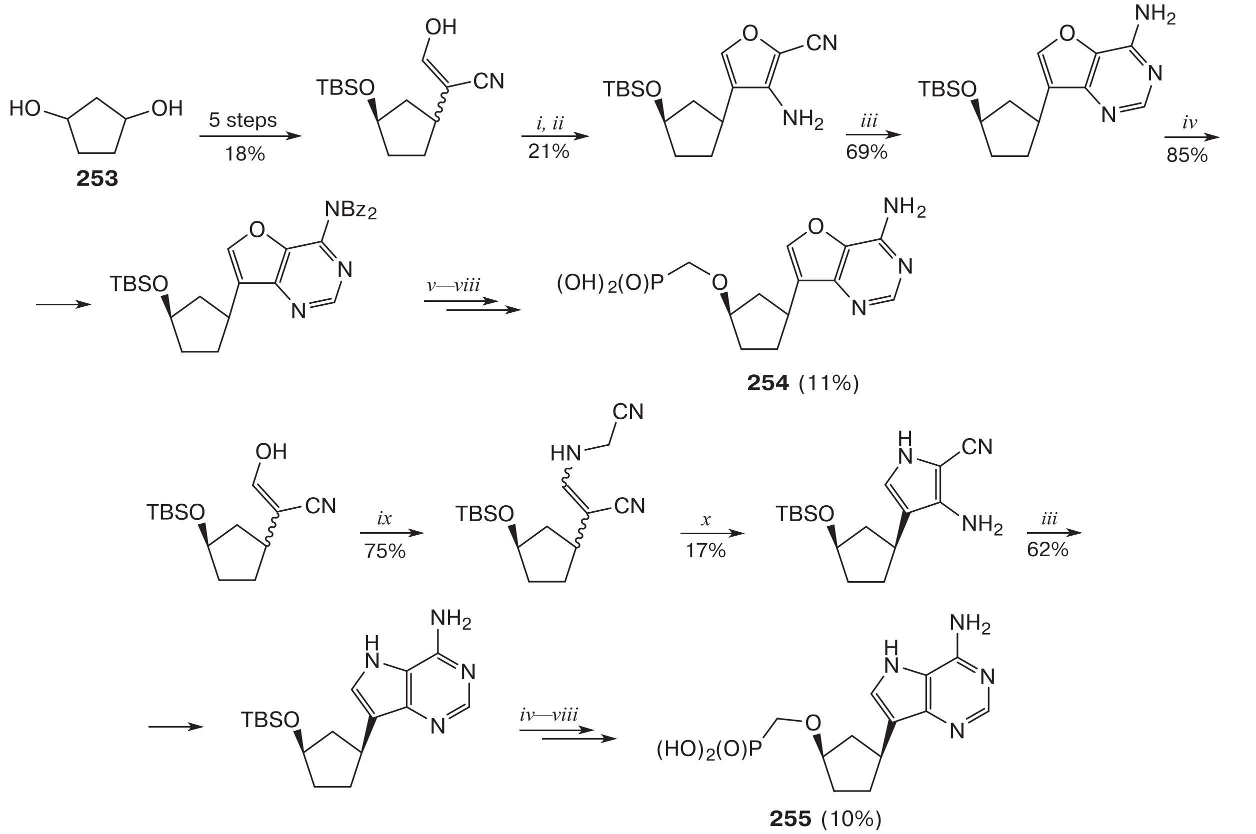
253, **254**: R = SMe (**a**), Me (**b**), Ph (**c**), O (**d**)

Reagents and conditions: *i*. Na_2CO_3, MeCN, H_2O (0.5 mol.%), 80 °C, 4 h; *ii*. MeOH—H_2O (8 : 2), Dowex H^+, 16 h.

Legrave *et al.*[98] optimized the conditions of condensation of different amidines and alkynyl ribose derivative **231** and synthesized *C*-nucleoside precursors **251a—c**. Subsequent deprotection gave the target derivatives **252a—c** (Scheme 82).

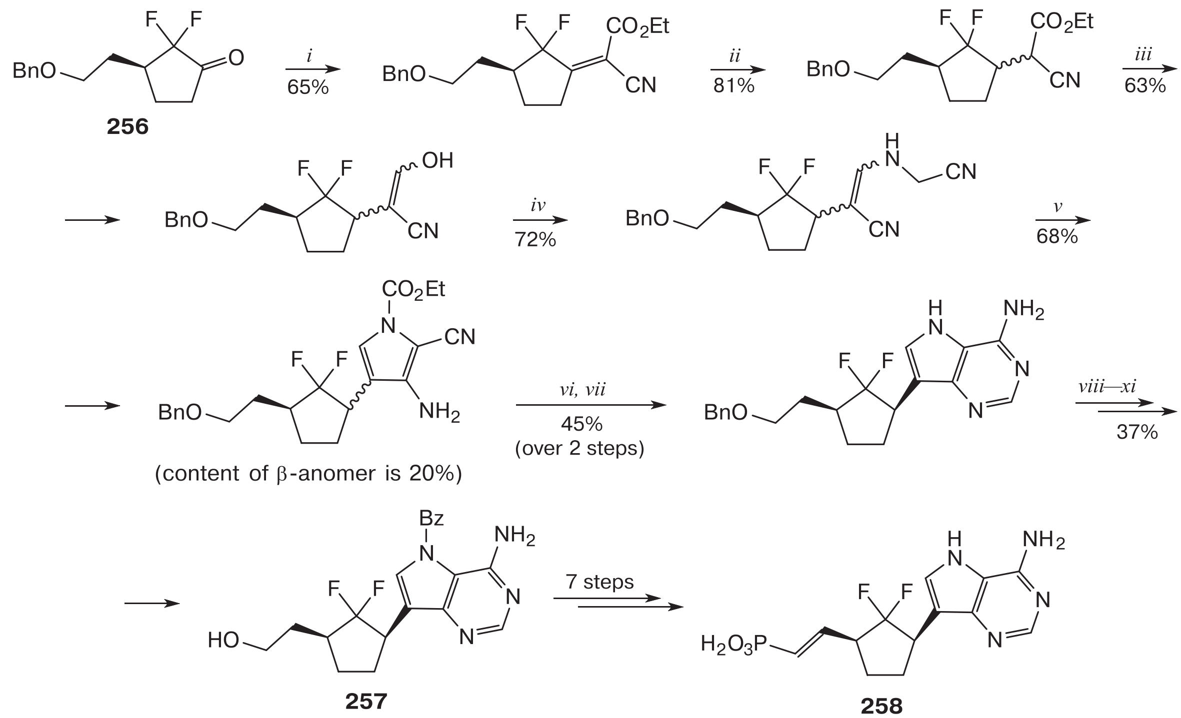
Synthesis of *C*-nucleosides by the construction of the aglycon unit on the carbohydrate mimic **253** was studied.[99—102] Synthesis of phosphorylated 9-deazaadenosine and 7-oxa-7,9-dideazaadenosine *C*-nucleosides **254** and **255** is shown in Scheme 83.[102] The

Scheme 83



Reagents and conditions: *i*. $ClCH_2CN$, Cs_2CO_3, DMF; *ii*. LDA, –70 °C, THF; *iii*. $CH(NH)NH_2 \cdot AcOH$, EtOH; *iv*. BzCl, pyridine; *v*. TBAF, THF; *vi*. $(EtO)_2POCH_2OTf$, Bu^tOLi, THF; *vii*. NH_3, MeOH, ~20 °C; *viii*. TMSBr, 2,6-lutidine, MeCN; *ix*. $H_2NCH_2CN \cdot H_2SO_4$, NaOAc, MeOH; *x*. 1) ClC(O)OEt, DBU, CH_2Cl_2; 2) DBU, CH_2Cl_2; 3) K_2CO_3, EtOH.

Scheme 84



Reagents and conditions: *i*. $NCCH_2CO_2Et$, Bu^tOK, EtOH; *ii*. H_2, 10% Pd/C, MeOH; *iii*. DIBAL-H, Et_2O; *iv*. H_2NCH_2CN, NaOAc, MeOH; *v*. 1) ClC(O)OEt, DBU, CH_2Cl_2, 2) DBU; *vi*. K_2CO_3, EtOH; *vii*. $CH(NH)NH_2 \cdot AcOH$, EtOH; *viii*. BCl_3, CH_2Cl_2; *ix*. TBSCl, imidazole, CH_2Cl_2; *x*. BzCl, pyridine; *xi*. TBAF, THF.

target products were obtained in low amounts due to multi-step synthesis and low yields.

To widen a series of biologically active carbocyclic nucleosides, Kim and Hong[101] synthesized 6′,6′-difluoro-5′-deoxycarbocyclic-9-deazaadenosine *C*-nucleoside **257**. Compound **257** was further converted to phosphonate **258** (Scheme 84). The starting compound **256** was synthesized in ten steps in 15% overall yield. Despite the relatively high yields in each synthetic step (see Scheme 84), this synthetic approach is of low interest.

Nevertheless, this method was applied for the synthesis of other *C*-nucleoside derivatives[100] (Scheme 85). The starting lactone **259** was synthesized from 1,4-dihydroxy-2-butene in four steps in 49% overall yield. Lactone **259** was transformed in eight steps to carbocyclic 4-*N*-dibenzyl diazaadenosine *C*-nucleoside **260** in 7.2% overall yield. Compound **260** was further phosphorylated to give prodrugs **261—264**.

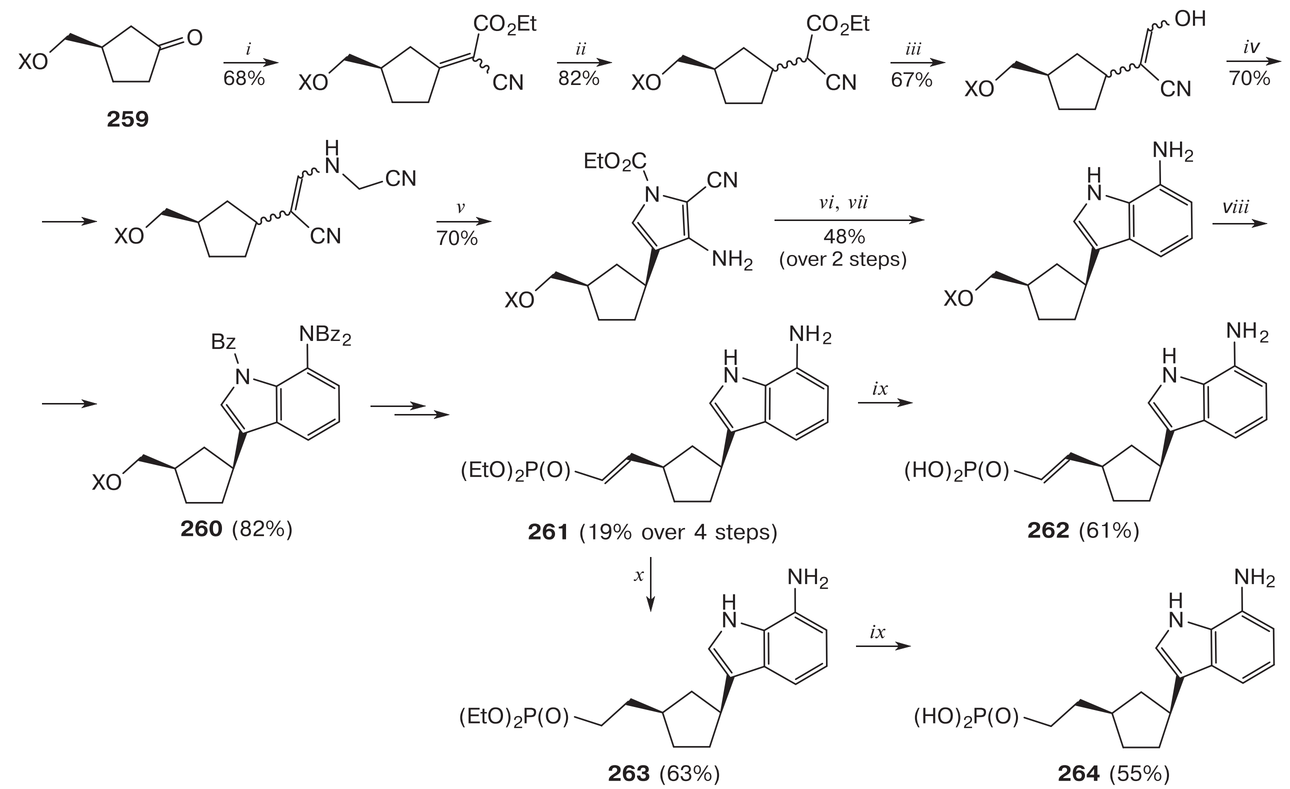
4′-Trifluoromethylated carbocyclic nucleoside **266** was synthesized similarly *via* intermediate **265** (Scheme 86).[99] The yield of nucleoside **266** was 1.7% over seven steps.

Vogel and coworkers[103] synthesized *C*-nucleosides **270** and **271** in high yields (76—90%) from fully protected *C*-ribosides **268a—c** by the reaction of the aldehyde group with different CH-acidic compounds followed by construction of the aglycon unit using two sequential cyclocondensations (Scheme 87).

Analogous approach was used to convert protected aldehyde **272** to thienopyrimidinone **273** in four steps in 20% overall yield (Scheme 88). Aldehyde **272** was also transformed to methylthiopyrimidine *C*-nucleoside **276** (see Scheme 88). First, aldehyde **272** was converted to 2-deoxy acetylenic ketones **274a**,**b**, which were further transformed to pyrimidines **275a**,**b**. Deprotection of compound **275a** afforded *C*-nucleoside **276**. No yields of compounds **274a**,**b** are given.[103]

Reaction of compound **267** with alkynyl organometallic compounds followed by the Dess—Martin oxidation gave intermediates **277a,b** (Scheme 89). Compounds **277a,b** were involved in the reactions

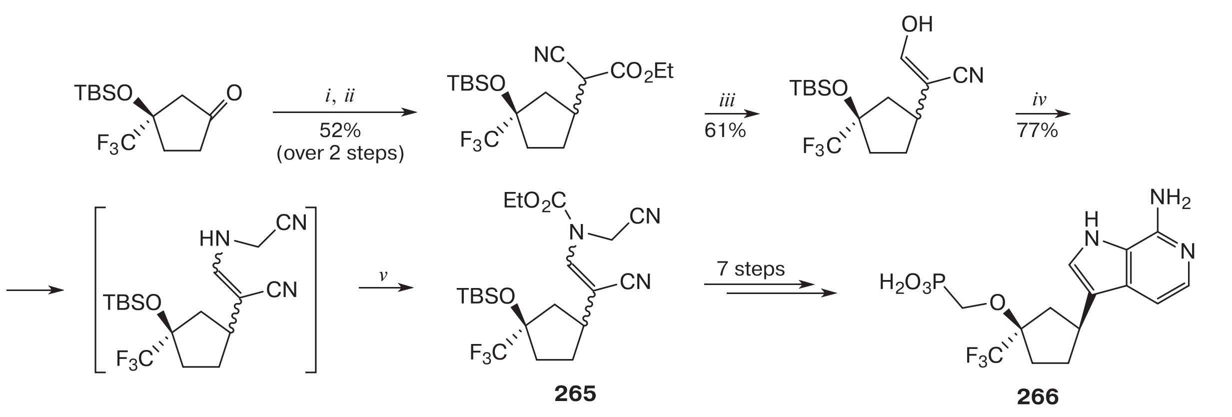
Scheme 85



X = Bu^{t}Me$_2$Si

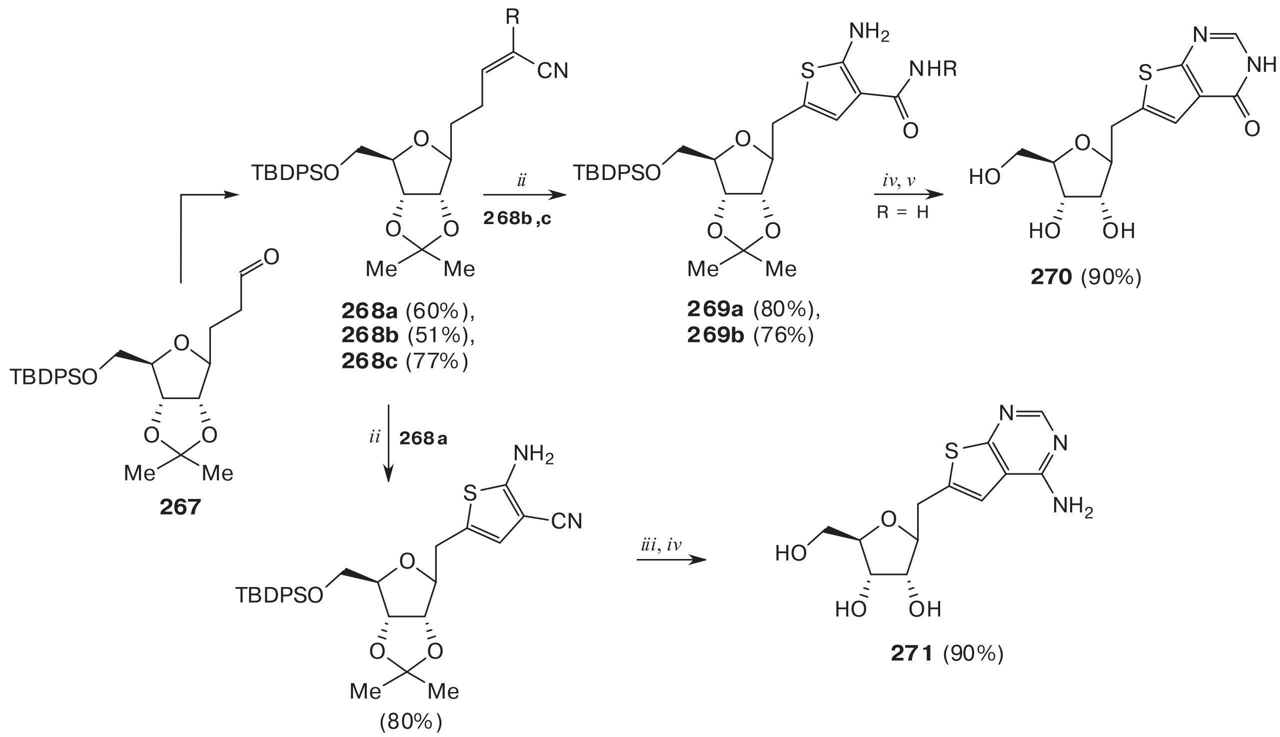
Reagents and conditions: *i*. $NCCH_2CO_2Et$, Bu^{t}OK, EtOH; *ii*. H_2, 10% Pd/C, MeOH; *iii*. DIBAL-H, Et_2O; *iv*. H_2NCH_2CN, NaOAc, MeOH; *v*. 1) ClC(O)OEt, DBU, CH_2Cl_2; 2) DBU; *vi*. K_2CO_3, EtOH; *vii*. $CH(NH)NH_2 \cdot AcOH$, EtOH; *viii*. BzCl, pyridine; *ix*. TMSBr, 2,6-lutidine, MeCN; *x*. 10% Pd/C, cyclohexene, MeOH.

Scheme 86



Reagents and conditions: *i*. $NCCH_2CO_2Et$, Bu^{t}OK, EtOH; *ii*. H_2, 10% Pd/C, MeOH; *iii*. DIBAL-H, Et_2O; *iv*. $H_2NCH_2CN \cdot H_2SO_4$, NaOAc, MeOH; *v*. ClC(O)OEt, DBU, CH_2Cl_2.

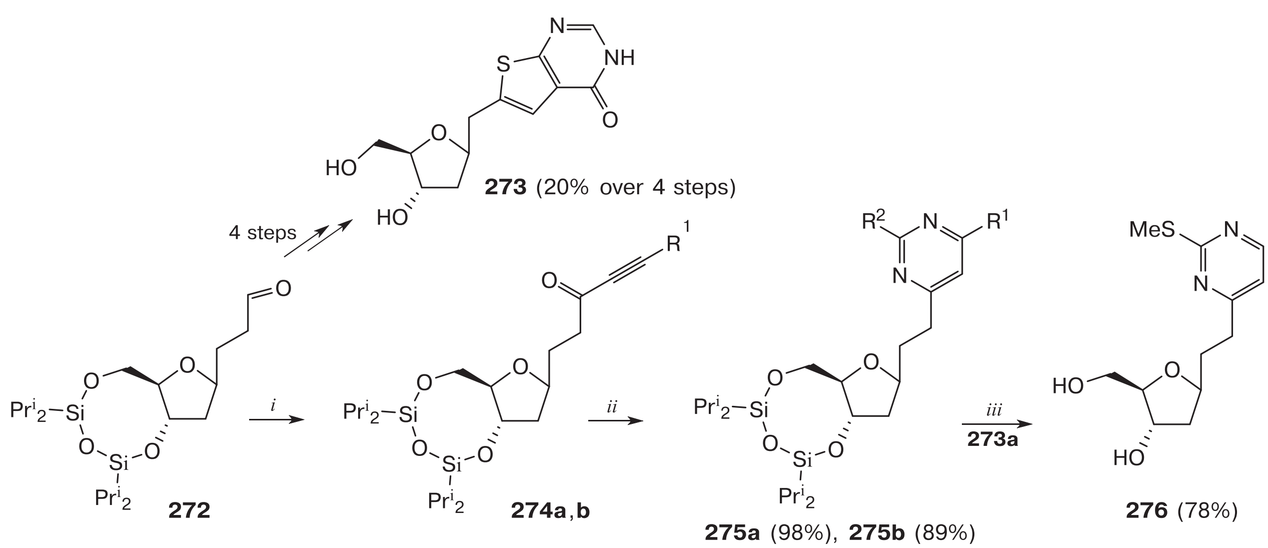
Scheme 87



268: R = CN (**a**), $CONH_2$ (**b**), 4-$MeOC_6H_4NHC(O)$ (**c**)
269: R = H (**a**), 4-$MeOC_6H_4$ (**b**)

Reagents and conditions: *i*. CH acids, Al_2O_3, toluene (anhydrous), reflux, 2—16 h; *ii*. S_8, Et_3N, DMF, ~20 °C, 2 h; *iii*. 1) $HC(OEt)_3$, reflux, 2 h, 2) $EtOH/NH_3$, reflux, 2 h; *iv*. 90% aqueous CF_3CO_2H, CH_2Cl_2, ~20 °C; *v*. $HC(OEt)_3$, DMF (anhydrous), reflux, 7—10 h.

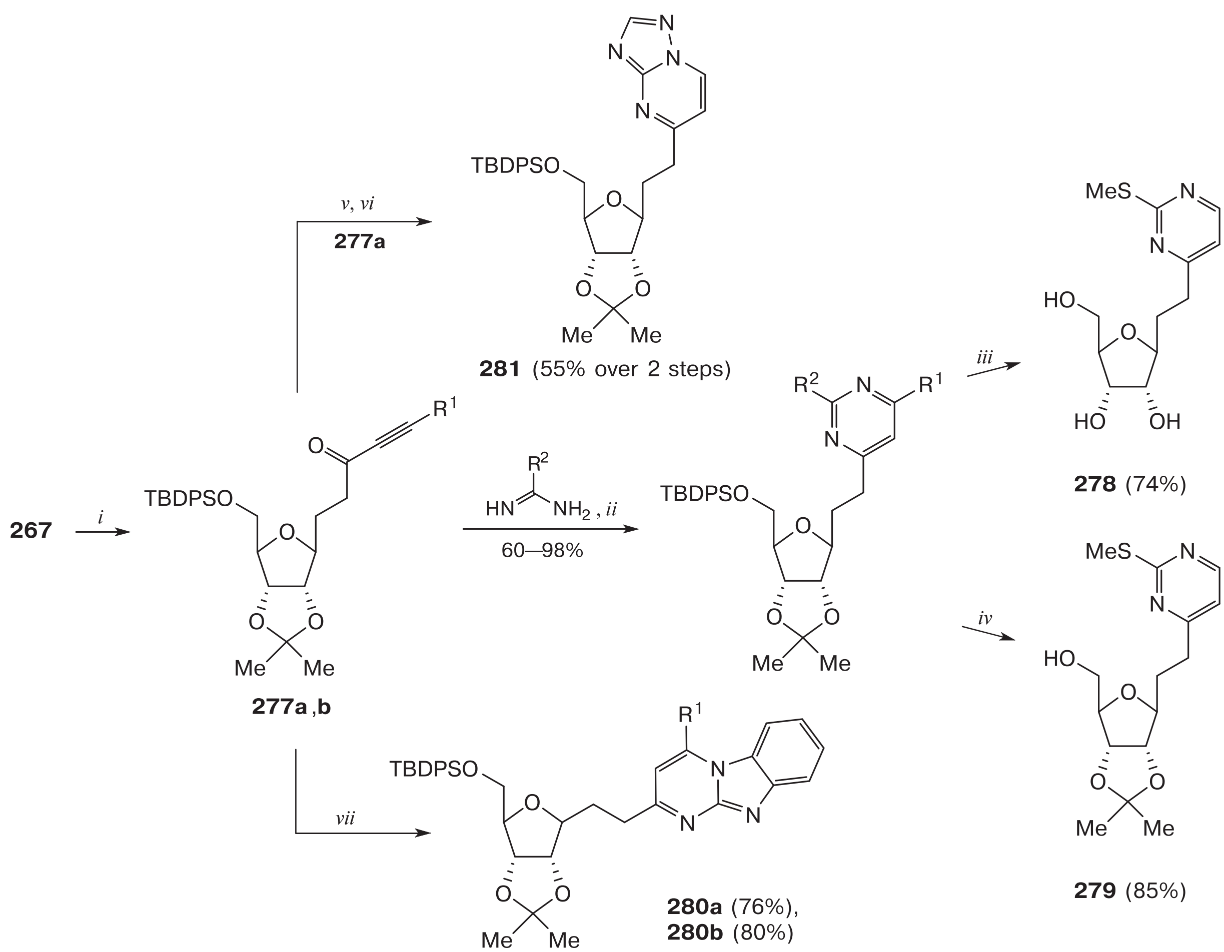
Scheme 88



274: R^1 = H (**a**), Ph (**b**)
275: R^1 = H, R^2 = SMe (**a**), R^1 = Ph, R^2 = Me (**b**)

Reagents and conditions: *i*. 1) CH≡CEtMgBr or PhC≡CLi, THF (anhydrous), ~20 °C, 4 h, 2) the Dess—Martin oxidation; *ii*. $MeSC(NH)NH_2 \cdot H_2SO_4$ (for **274a**) or $MeC(NH)NH_2 \cdot HCl$ (for **274b**), H_2O (cat.), Na_2CO_3, AcOEt, reflux, 3—24 h; *iii*. Bu_4NF, 1,4-dioxane, ~20 °C, 24 h.

Scheme 89



277, 280: R^1 = H (**a**), Ph (**b**); R^2 = Me, Ph, SMe

Reagents and conditions: *i*. 1) HC≡CMgBr or PhC≡CLiMgBr, THF (anhydrous), ~20 °C, 4 h, 2) the Dess—Martin oxidation; *ii*. acetamidinium chloride, benzamidinium chloride, or *S*-methylisothiouronium, H_2O (cat.), Na_2CO_3, AcOEt, reflux, 2—24 h; *iii*. Bu_4NF, 1,4-dioxane, ~20 °C, 4 h; *iv*. 1 *M* HCl, EtOH, ~20 °C, 12 h. *v*. 4*H*-1,2,4-triazol-3-amine, EtOH (anhydrous), reflux, 4 h; *vi*. 1 *M* NaOMe in MeOH, ~20 °C, 1 h; *vii*. 1) 1*H*-benz[*d*]imidazol-2-amine, EtOH (anhydrous), reflux, 2 h, 2) 1 *M* NaOMe in MeOH, ~20 °C, 1 h.

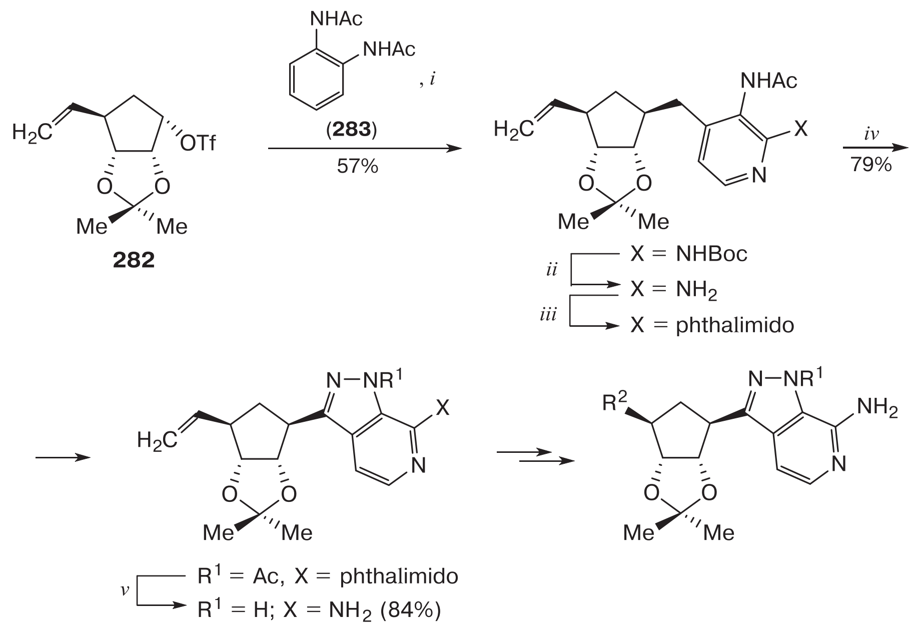
with various diamines to afford *C*-nucleosides **278—281** with the pyrimidine, triazolopyrimidine, and benzimidazopyrimidine scaffolds as the aglycons.[103]

Schneller and coworkers[104] developed an efficient synthesis of a series of carbocyclic formycin derivatives structurally related to 3-deazaaristeromycin. This approach is characterized by high yields on each step (Scheme 90).

Smellie and Paton[105] synthesized nitrile oxide **284** from D-ribose in four steps in 85% overall yield. Compound **284** was used as a starting material for constructing the aglycon unit by cycloaddition reactions (Scheme 91). The developed procedure towards benzazole *C*-nucleosides is an effective alternative to current synthetic routes to furanosylbenzazoles owing to small number of steps and good yields.

Zhang and coworkers[106] described efficient synthesis of indolizine *C*-nucleoside analogs by one-pot three-component coupling of sugar alkynes **234a**,**c—i**, pyridines, and α-bromo carbonyl compounds. Optimization of the reaction conditions revealed that refluxing in THF in the presence of cesium carbonate for 2 h is the most efficient. Under the optimal conditions, a series of derivatives **285** were obtained in high yields of 76—95% (Scheme 92).

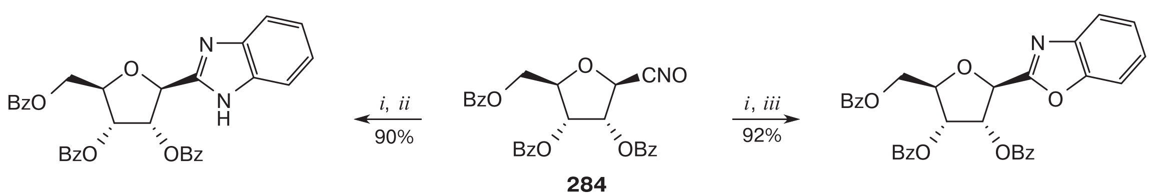
Scheme 90



R^1 = H, Me, R^2 = CH_2OH, CH_2CH_2OH

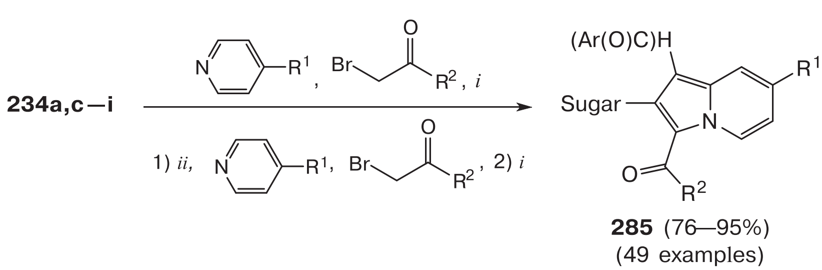
Reagents, conditions, and yields: *i*. 1) **283**, THF, −78 °C, 2) BuLi, 3) **282**, ~20 °C; *ii*. CF_3CO_2H (20 equiv.), 0 → 20 °C, 5 h; *iii*. phthalic ahydride, toluene, 50 °C, 24 h, 80% (over 2 steps); *iv*. KOAc, Ac_2O, isoamyl nitrite, benzene, reflux; *v*. NH_3, MeOH, ~20 °C, ~18 h.

Scheme 91



Reagents and conditions: *i*. NCS, pyridine, $CHCl_3$, 40 °C; *ii*. 1,2-$(H_2N)_2C_6H_4$, EtOH, reflux, 5 h; *iii*. 2-$HOC_6H_4NH_2$, EtOH, reflux, 5 h.

Scheme 92

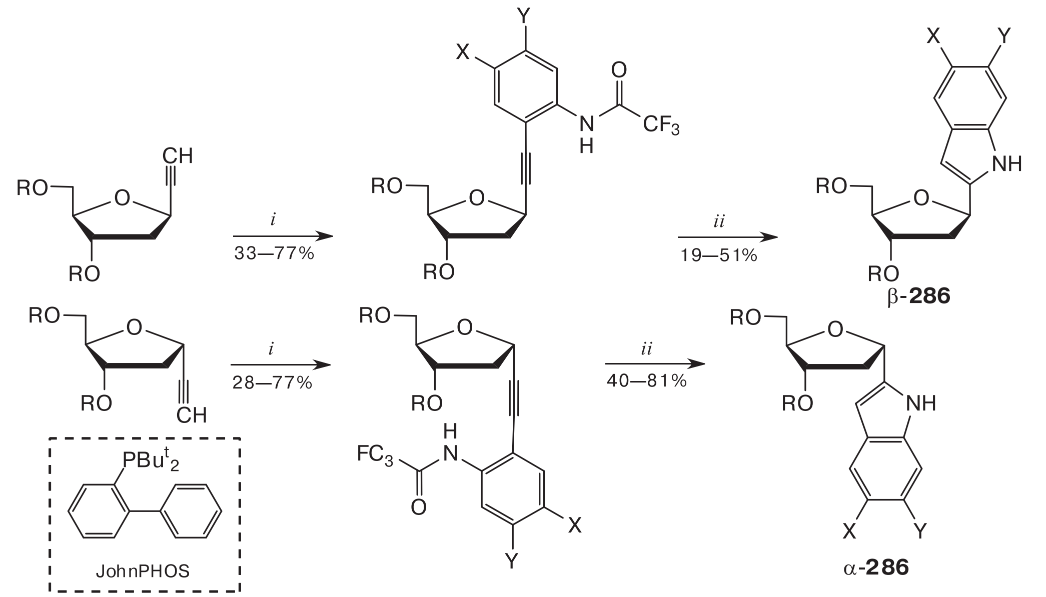


R^1 = H, CN, R^2 = Ph, OEt, Bu^t; Ar = 4-ClC_6H_4, 2-MeC_6H_4

Reagents and conditions: *i*. Cs_2CO_3, THF, reflux; *ii*. ArC(O)Cl, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N.

A simple two-step method for the selective synthesis of anomerically pure α- and β-(indol-2-yl)deoxyribosides α-**286** and β-**286** involved the Sonogashira reaction of 1α- and 1β-ethynyldeoxyribose and 2-haloanilines followed by the Pd-catalyzed cyclization to the corresponding indolyldeoxyribosides (Scheme 93).[107]

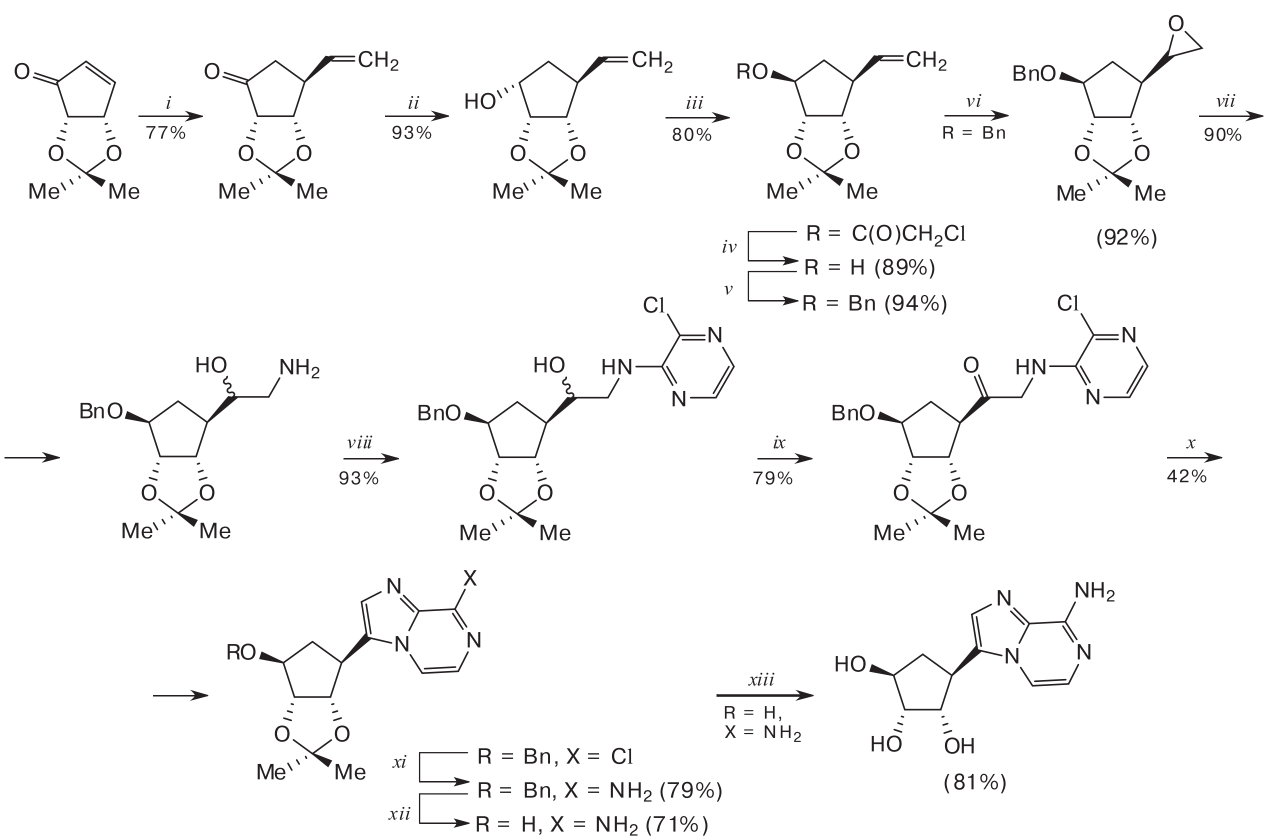
Scheme 93



R = 4-MeC$_6$H$_4$C(O), X = H, Cl, CO$_2$Me, Y = H, Cl

Reagents and conditions: *i*. 2-haloanilines, Pd(PPh$_3$)$_4$, Et$_3$N, MeCN, 70 °C; *ii*. Pd$_2$(dba)$_3$, JohnPHOS, MeCN, 120 °C.

Scheme 94



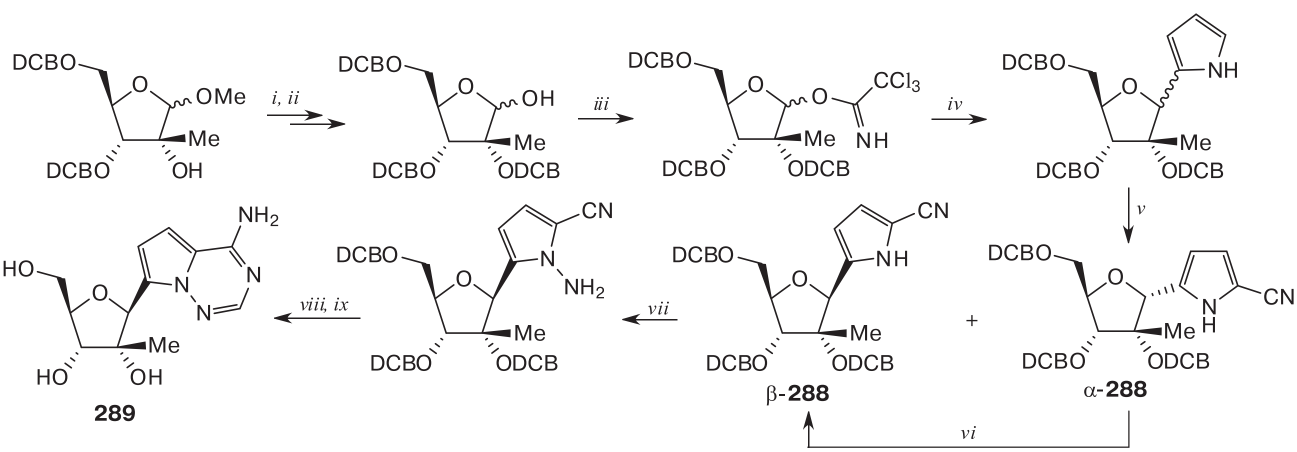
Reagents and conditions: *i*. CH$_2$CHMgBr, CuBr·Me$_2$S, TMSCl, HMPA, THF, –78 °C; *ii*. LiAlH$_4$, THF; *iii*. ClCH$_2$CO$_2$H, Ph$_3$P, diisopropyl azodicarboxylate (DIAD), THF; *iv*. LiOH·H$_2$O, THF, H$_2$O, 0 °C; *v*. BnBr, NaI, NaH, THF; *vi*. dimethyldioxirane (DMDO), acetone, 0 °C; *vii*. NH$_4$OH, 60 °C; *viii*. 2,3-dichloropyrazine, Et$_3$N, 1,4-dioxane; *ix*. DMSO, (CF$_3$CO)$_2$O, Et$_3$N, CH$_2$Cl$_2$; *x*. CF$_3$CO$_2$H, (CF$_3$CO)$_2$O, pyridine, toluene; *xi*. NH$_3$, MeOH, 130 °C; *xii*. cyclohexene, Pd(OH)$_2$/C, EtOH, reflux; *xiii*. 2 *M* HCl, MeOH.

Ye and Schneller[108] synthesized 5′-noraristeromycin *C*-nucleoside bearing imidazo[1,2-*a*]pyrazine aglycon mimic *via* the construction of aglycon on the sugar unit (Scheme 94). The yields were above 75% on almost all steps except for the key imidazole ring closure step that gave 42% product yield.

Draffan and coworkers[44] reported on the synthesis of compounds **289** (Scheme 95) and **290** (Scheme 96). Structural features of these compounds required the careful choice of synthetic approaches. Thus, compound **289** was synthesized by a highly modified approach developed by Patil *et al.*[109] Slow addition of pyrrole to compound **287** at low temperature (–78 °C) in the presence of $BF_3 \cdot Et_2O$ afforded a 1 : 1 anomeric mixture of the pyrrole nucleosides α-**288** and β-**288** in 80% yield (see Scheme 95). Modest improvement in β-selectivity was achieved at higher temperature (–50 °C; α : β = 1 : 2) but at the cost of the yield (60%). The mixture of α- and β-isomers **288** was separated by flash column chromatography and α-isomer was transformed to β-isomer by treatment with $BF_3 \cdot Et_2O$. Subsequent construction of the triazine unit and deprotection of the hydroxy groups of the riboside moiety gave the target *C*-nucleoside **289**.

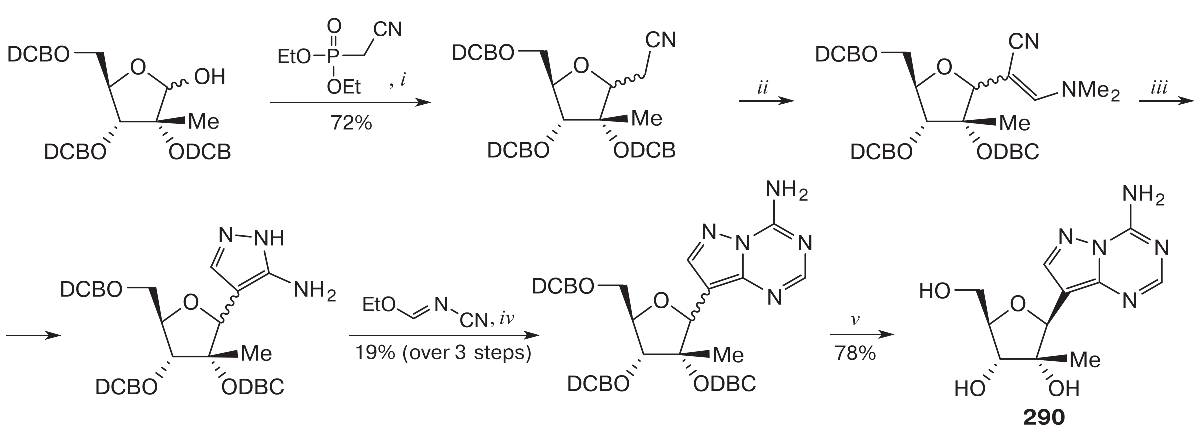
Convergent approach (see Section 1) was unapplicable to the synthesis of pyrazolo[1,5-*a*][1,3,5]-triazine *C*-nucleoside **290**, therefore this compound was synthesized by linear synthesis of aglycon on a sugar unit (Scheme 96).[44]

Scheme 95



Reagents, conditions, and yields: *i*. NaH, 2,4-dichlorobenzyl chloride; *ii*. $CF_3CO_2H-H_2O$ (9 : 1); *iii*. Cl_3CCN, Cs_2CO_3; *iv*. 1) 4 Å molecular sieves, CH_2Cl_2, 2 h, ~20 °C, 2) pyrrole, $BF_3 \cdot OEt_2$, –50 °C or –78 °C, 3) NH_3, MeOH, –78 °C; *v*. $ClSO_2NCO$, MeCN, DMF, 0 °C; *vi*. $BF_3 \cdot OEt_2$, CH_2Cl_2, reflux; *vii*. 1) NaH, THF, 0 °C, 2) $Ph_2P(O)ONH_2$, THF, 0 °C; *viii*. $CH(NH)NH_2 \cdot AcOH$, $MeC(O)NMe_2$, 140 °C, 1—2 h; *ix*. H_2, Pd/C (10%), 45 °C, 18 h, NaOAc, MeOH, AcOH.

Scheme 96



Reagents and conditions: *i*. NaH, DME, 0 → 20 °C; *ii*. $Bu^tOCH(NMe_2)_2$, DMF, 60 °C, 15 h; *iii*. $N_2H_4 \cdot HCl$, EtOH, 105 °C, 2 h; *iv*. EtOCH=NCN, 85 °C, toluene; *v*. H_2, 10% Pd/C, MeOH, 45 °C, 17 h.

It can be noted that the strategy of construction of aglycon on a pre-formed carbohydrate unit to synthesize *C*-nucleosides of various nature is common. The advantage of this approach is the possibility to synthesize the functionalized heterocyclic aglycons which is very important in the search for compounds with a given biological activity. However, the necessity to prepare preliminary (pseudo)ribosides bearing the moieties suitable for the subsequent aglycon synthesis significantly reduces the attractiveness of this strategy. The synthesis of these precursors often requires multi-step sequences thus negatively affecting the overall yields of the target *C*-nucleosides.

Conclusion

In the present review, three main strategies to the synthesis of *C*-nucleosides are described: the direct C—C coupling of the pre-formed aglycon and sugar, the construction of an aglycon unit on a pre-formed sugar, and the construction of a sugar unit on a preformed aglycon. Each strategy can be used for synthesizing the compounds, which are hardly accessible by other methods.

The direct C—C coupling under the Heck conditions enables synthesis of both 2´-deoxyribonucleosides[57—65], and carbocyclic *C*-nucleosides.[31] The undoubted advantage of this approach is no need to fully protect all hydroxy groups of (pseudo)sugar and amino and carbonyl groups of aglycon, which significantly increases the overall yield of the target *C*-nucleoside since no protection and deprotection steps are required.

Another C—C bond forming strategy involved the reactions either between ribonolactone and lithium intermediates or between the Grignard reagents and 1´-halogenated carbohydrates or ribonolactones. In all cases, the reactions gave the mixtures of α- and β-isomers separable by column chromatography. Application of this strategy is complicated by the need to carry out the reactions at low temperatures (–78÷–100 °C) in anhydrous solvents under an inert atmosphere to prevent hydrolysis of organometallic reagents and intermediates. Protection of the carbonyl and amino groups to reduce the formation of the side products is required as it was clearly shown by Metobo and coworkers.[34] Thus, Boc and TMS groups were found to be the suitable and convenient protective groups in the presence of which the yield could be increased from 10 to 82%.[45] The use of the excess of the base (the Grignard reagents or its analogs) for the aglycon activation is also important. In some cases, the yields of the target products equal to 20—40% achieved in the presence of 1 equiv. of the base could be increased to 65—90% by using 3.3 equiv. of the base. This strategy is the most promising in terms of small number of steps and good yields of the target products.

More exotic variants of the direct C—C coupling of aglycon and sugar were reported. For instance, electrochemical activation of the starting compounds,[68] photocatalytic reactions,[66] and Lewis-acid catalyzed glycosylation[67] were described. However, in most cases these methods are limited to only a specific class of compounds, did not provide high yields and required stereoselectivity.

The construction of an aglycon unit on a (pseudo)-sugar residue opens up the prospects to a wide range of various *C*-nucleosides. It is of note the method based on ribofuranyl alkynes[87,88,90] that provided both mono- and bicyclic[101,104,105] aglycon scaffolds in one-two synthetic steps in excellent yields. The drawback of this method is the use of expensive palladium catalysts. In other cases, the synthesis is multi-step, which inevitably leads to a decrease in the yield of the target compounds. Moreover, this strategy required the use of fully or partially protected starting (pseudo)sugars, which adds the additional protection/deprotection steps in the reaction sequence.

The construction of the sugar unit on an aglycon allows a selective synthesis of *C*-nucleosides, which are hardly accessible by a direct C—C coupling and other methods. It should be noted that the yields of *C*-nucleosides upon coupling of nitrones and vinyl azoles under electrochemical conditions increased up to 92—96%; while the reaction in refluxing solvent gave the target products in 75—85% yields.[76,77] This approach was used in the smallest number of works published over the past 10 years, which reflected its least promise due to limitations on structural diversity of the synthesized *C*-nucleosides, multi-step reaction sequences, the need in expensive catalysts, as well as due to availability of simpler approaches towards *C*-nucleosides.

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No human or animal subjects were used in this research.

The authors declare no competing interests.

References

1. E. de Clercq, *Acta Pharm. Sin. B*, 2012, **2**, 535; DOI: 10.1016/J.APSB.2012.10.001.
2. G. Niu, H. Tan, *Trends Microbiol.*, 2015, **23**, 110; DOI: 10.1016/J.TIM.2014.10.007.
3. E. De Clercq, G. Li, *Clin. Microbiol. Rev.*, 2016, **29**, 695; DOI: 10.1128/CMR.00102-15.
4. K. Peasley, *Med. Hypotheses*, 2000, **55**, 408; DOI: 10.1054/MEHY.2000.1077.
5. C. Simons, *Nucleoside Mimetics*: *Their Chemistry and Biological Properties*, CRC Press, Boca Raton, 2001, 204 pp.; DOI: 10.1201/9781482283143.
6. D. A. Gruzdev, V. V. Musiyak, G. L. Levit, V. P. Krasnov, V. N. Charushin, *Russ. Chem. Rev.*, 2018, **87**, 604; DOI: 10.1070/RCR4772.
7. E. V. Verbitskiy, G. L. Rusinov, V. N. Charushin, O. N. Chupakhin, *Russ. Chem. Bull.*, 2019, **68**, 2172; DOI: 10.1007/S11172-019-2686-X.
8. L. P. Jordheim, D. Durantel, F. Zoulim, C. Dumontet, *Nat. Rev. Drug Discovery*, 2013, **12**, 447; DOI: 10.1038/nrd4010.
9. E. S. Matyugina, S. N. Kochetkov, A. L. Khandazhinskaya, *Russ. Chem. Rev.*, 2021, **90**, 1454; DOI: 10.1070/RCR5013/XML.
10. L. Agrofoglio, E. Suhas, A. Farese, R. Condom, S. Richard Challand, R. A. Earl, R. Guedj, *Tetrahedron*, 1994, **50**, 10611; DOI: 10.1016/S0040-4020(01)89258-9.
11. V. E. Marquez, M. I. Lim, *Med. Res. Rev.*, 1986, **6**, 1; DOI: 10.1002/MED.2610060102.
12. J. Rodríguez, M. Comin, *Mini Rev. Med. Chem.*, 2005, **3**, 95; DOI: 10.2174/1389557033405331.
13. H. Wójtowicz-Rajchel, *J. Fluorine Chem.*, 2012, **143**, 11; DOI: 10.1016/J.JFLUCHEM.2012.06.026.
14. R. B. Stockbridge, G. K. Schroeder, R. Wolfenden, *Bioorg. Chem.*, 2010, **38**, 224; DOI: 10.1016/J.BIOORG.2010.05.003.
15. K. Temburnikar, K. L. Seley-Radtke, *Beilstein J. Org. Chem.*, 2018, **14**, 772; DOI: 10.3762/BJOC.14.65.
16. K. S. Ramasamy, R. Bandaru, D. Averett, *J. Org. Chem.*, 2000, **65**, 5849; DOI: 10.1021/JO000460A.
17. B. M. Trost, L. S. Kallander, *J. Org. Chem.*, 1999, **64**, 5427; DOI: 10.1021/JO990195X.
18. J. Zhou, M. Yang, S. W. Schneller, *Tetrahedron Lett.*, 2004, **45**, 8233; DOI: 10.1016/J.TETLET.2004.09.007.
19. X. Chen, S. W. Schneller, S. Ikeda, R. Snoeck, G. Andrei, J. Balzarini, E. De Clercq, *J. Med. Chem.*, 1993, **36**, 3727; DOI: 10.1021/JM00075A0303.
20. T. K. Warren, R. Jordan, M. K. Lo, A. S. Ray, R. L. Mackman, V. Soloveva, D. Siegel, M. Perron, R. Bannister, H. C. Hui, N. Larson, R. Strickley, J. Wells, K. S. Stuthman, S. A. Van Tongeren, N. L. Garza, G. Donnelly, A. C. Shurtleff, C. J. Retterer, D. Gharaibeh, R. Zamani, T. Kenny, B. P. Eaton, E. Grimes, L. S. Welch, L. Gomba, C. L. Wilhelmsen, D. K. Nichols, J. E. Nuss, E. R. Nagle, J. R. Kugelman, G. Palacios, E. Doerffler, S. Neville, E. Carra, M. O. Clarke, L. Zhang, W. Lew, B. Ross, Q. Wang, K. Chun, L. Wolfe, D. Babusis, Y. Park, K. M. Stray, I. Trancheva, J. Y. Feng, O. Barauskas, Y. Xu, P. Wong, M. R. Braun, M. Flint, L. K. McMullan, S. S. Chen, R. Fearns, S. Swaminathan, D. L. Mayers, C. F. Spiropoulou, W. A. Lee, S. T. Nichol, T. Cihlar, S. Bavari, *Nature*, 2016, **531**, 381; DOI: 10.1038/nature17180.
21. S. M. Reza Hashemian, T. Farhadi, A. A. Velayati, *Drug Des., Dev. Ther.*, 2020, **14**, 3215; DOI: 10.2147/DDDT.S261154.
22. M. Legraverend, *Tetrahedron*, 2008, **64**, 8585; DOI: 10.1016/J.TET.2008.05.115.
23. J. Boryski, *Nucleosides Nucleotides*, 1996, **15**, 771; DOI: 10.1080/07328319608002422.
24. A. Tokarenko, L. Poštová Slavětínská, B. Klepetářová, M. Hocek, *Eur. J. Org. Chem.*, 2015, 7962; DOI: 10.1002/EJOC.201501219.
25. F. Wojciechowski, J. Lietard, C. J. Leumann, *Org. Lett.*, 2012, **14**, 5176; DOI: 10.1021/OL302150A.
26. T. Kubelka, L. Slavětínská, M. Hocek, *Eur. J. Org. Chem.*, 2012, **2012**, 4969; DOI: 10.1002/EJOC.201200819.
27. A. Hatano, M. Okada, K. Dezaki, S. Hirai, *Tetrahedron*, 2015, **71**, 1095; DOI: 10.1016/J.TET.2014.12.085.
28. M. Weinberger, H. A. Wagenknecht, *Synthesis*, 2012, **44**, 648; DOI: 10.1055/S-0031-1289672.
29. M. Koszytkowska-Stawińska, E. Mironiuk-Puchalska, W. Sas, *Tetrahedron Lett.*, 2011, **52**, 1866; DOI: 10.1016/J.TETLET.2011.02.018.
30. C. Lou, M. Shelbourne, K. R. Fox, T. Brown, *Chem. Eur. J.*, 2011, **17**, 14851; DOI: 10.1002/CHEM.201102287.
31. M. Peifer, R. Berger, V. W. Shurtleff, J. C. Conrad, D. W. C. Macmillan, *J. Am. Chem. Soc.*, 2014, **136**, 5900; DOI: 10.1021/JA502205Q.
32. G. Wang, J. Wan, Y. Hu, X. Wu, M. Prhavc, N. Dyatkina, V. K. Rajwanshi, D. B. Smith, A. Jekle, A. Kinkade, J. A. Symons, Z. Jin, J. Deval, Q. Zhang, Y. Tam, S. Chanda, L. Blatt, L. Beigelman, *J. Med. Chem.*, 2016, **59**, 4611; DOI: 10.1021/ACS.JMEDCHEM.5B01933.
33. L. Maier, P. Khirsariya, O. Hylse, S. K. Adla, L. Černová, M. Poljak, S. Krajčovičová, E. Weis, S. Drápela, K. Souček, K. Paruch, *J. Org. Chem.*, 2017, **82**, 3382; DOI: 10.1021/ACS.JOC.6B02594.
34. S. E. Metobo, J. Xu, O. L. Saunders, T. Butler, E. Aktoudianakis, A. Cho, C. U. Kim, *Tetrahedron Lett.*, 2012, **53**, 484; DOI: 10.1016/J.TETLET.2011.11.055.
35. A. Cho, O. L. Saunders, T. Butler, L. Zhang, J. Xu, J. E. Vela, J. Y. Feng, A. S. Ray, C. U. Kim, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 2705; DOI: 10.1016/J.BMCL.2012.02.105.
36. A. Cho, L. Zhang, J. Xu, D. Babusis, T. Butler, R. Lee, O. L. Saunders, T. Wang, J. Parrish, J. Perry, J. Y. Feng, A. S. Ray, C. U. Kim, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4127; DOI: 10.1016/J.BMCL.2012.04.065.
37. A. Cho, L. Zhang, J. Xu, R. Lee, T. Butler, S. Metobo, V. Aktoudianakis, W. Lew, H. Ye, M. Clarke, E. Doerffler, D. Byun, T. Wang, D. Babusis, A. C. Carey, P. German, D. Sauer, W. Zhong, S. Rossi, M. Fenaux, J. G. McHutchison, J. Perry, J. Feng, A. S. Ray, C. U. Kim, *J. Med. Chem.*, 2014, **57**, 1812; DOI: 10.1021/JM400201A.

38. T. A. Kirschberg, S. Metobo, M. O. Clarke, V. Aktoudianakis, D. Babusis, O. Barauskas, G. Birkus, T. Butler, D. Byun, G. Chin, E. Doerffler, T. E. Edwards, M. Fenaux, R. Lee, W. Lew, M. R. Mish, E. Murakami, Y. Park, N. H. Squires, N. Tirunagari, T. Wang, M. Whitcomb, J. Xu, H. Yang, H. Ye, L. Zhang, T. C. Appleby, J. Y. Feng, A. S. Ray, A. Cho, C. U. Kim, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 1840; DOI: 10.1016/J.BMCL.2017.02.037.
39. D. Siegel, H. C. Hui, E. Doerffler, M. O. Clarke, K. Chun, L. Zhang, S. Neville, E. Carra, W. Lew, B. Ross, Q. Wang, L. Wolfe, R. Jordan, V. Soloveva, J. Knox, J. Perry, M. Perron, K. M. Stray, O. Barauskas, J. Y. Feng, Y. Xu, G. Lee, A. L. Rheingold, A. S. Ray, R. Bannister, R. Strickley, S. Swaminathan, W. A. Lee, S. Bavari, T. Cihlar, M. K. Lo, T. K. Warren, R. L. Mackman, *J. Med. Chem.*, 2017, **60**, 1648; DOI: 10.1021/ACS.JMEDCHEM.6B01594.
40. T. Vieira, A. C. Stevens, A. Chtchemelinine, D. Gao, P. Badalov, L. Heumann, *Org. Process Res. Dev.*, 2020, **24**, 2113; DOI: 10.1021/ACS.OPRD.0C00172.
41. US Pat. 10023600B2.
42. US Pat. 2010021425A1.
43. F. Xue, X. Zhou, R. Zhou, X. Zhou, D. Xiao, E. Gu, X. Guo, J. Xiang, K. Wang, L. Yang, W. Zhong, Y. Qin, *Org. Process Res. Dev.*, 2020, **24**, 1772; DOI: 10.1021/ACS.OPRD.0C00310.
44. A. G. Draffan, B. Frey, B. Pool, C. Gannon, E. M. Tyndall, M. Lilly, P. Francom, R. Hufton, R. Halim, S. Jahangiri, S. Bond, V. T. T. Nguyen, T. P. Jeynes, V. Wirth, A. Luttick, D. Tilmanis, J. D. Thomas, M. Pryor, K. Porter, C. J. Morton, B. Lin, J. Duan, G. Kukolj, B. Simoneau, G. McKercher, L. Lagacé, M. Amad, R. C. Bethell, S. P. Tucker, *ACS Med. Chem. Lett.*, 2014, **5**, 679; DOI: 10.1021/ML500077J.
45. T. Liu, Z. Zhu, H. Ren, Y. Chen, G. Chen, M. Cheng, D. Zhao, J. Shen, W. Zhu, B. Xiong, Y. L. Chen, *Org. Chem. Front.*, 2018, **5**, 1992; DOI: 10.1039/C8QO00165K.
46. Q. Li, E. Lescrinier, E. Groaz, L. Persoons, D. Daelemans, P. Herdewijn, S. De Jonghe, *ChemMedChem*, 2018, **13**, 97; DOI: 10.1002/CMDC.201700657.
47. P. Nie, E. Groaz, D. Daelemans, P. Herdewijn, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 1450; DOI: 10.1016/J.BMCL.2019.04.023.
48. P. Nie, E. Groaz, P. Herdewijn, *Eur. J. Org. Chem.*, 2019, 6666; DOI: 10.1002/EJOC.201901200.
49. G. B. Evans, R. H. Furneaux, G. J. Gainsford, V. L. Schramm, P. C. Tyler, *Tetrahedron*, 2000, **56**, 3053; DOI: 10.1016/S0040-4020(00)00194-0.
50. M. Zhang, F. Xue, J. Ou, Y. Huang, F. Lu, B. Zhou, Z. Zheng, X. Y. Liu, W. Zhong, Y. Qin, *Org. Chem. Front.*, 2020, **7**, 3675; DOI: 10.1039/D0QO01026J.
51. Q. Dang, Z. Zhang, Y. Bai, R. Sun, J. Yin, T. Chen, S. Bogen, V. Girijavallabhan, D. B. Olsen, P. T. Meinke, *Tetrahedron Lett.*, 2014, **55**, 5576; DOI: 10.1016/J.TETLET.2014.08.072.
52. Q. Dang, Z. Zhang, T. Chen, B. Tang, X. He, S. He, Y. Song, S. Bogen, V. Girijavallabhan, D. B. Olsen, P. T. Meinke, *Tetrahedron Lett.*, 2014, **55**, 5092; DOI: 10.1016/J.TETLET.2014.07.037.
53. Q. Li, E. Groaz, J. Rocha-Pereira, J. Neyts, P. Herdewijn, *Eur. J. Med. Chem.*, 2020, **195**, 112198; DOI: 10.1016/J.EJMECH.2020.112198.
54. M. Minuth, W. Frey, C. Richert, *Synlett*, 2014, **25**, 1438; DOI: 10.1055/S-0033-1341252.
55. D. K. Kölmel, L. J. Barandun, E. T. Kool, *Org. Biomol. Chem.*, 2016, **14**, 6407; DOI: 10.1039/C6OB01199C.
56. C. Glaser, *Ber. Dtsch. Chem. Ges.*, 1869, **2**, 422; DOI: 10.1002/CBER.186900201183.
57. C. Glaser, *Justus Liebigs Ann. Chem.*, 1870, **154**, 137; DOI: 10.1002/JLAC.18701540202.
58. Y. Luo, F. Gao, H. Liu, F. Zhang, Y. Zhao, *Synthesis*, 2020, **52**, 1435; DOI: 10.1055/S-0039-1690808.
59. K. Sato, A. Matsuda, *Curr. Protoc. Nucleic Acid Chem.*, 2019, **77**; DOI: 10.1002/CPNC.77.
60. H. Chapuis, T. Kubelka, N. Joubert, R. Pohl, M. Hocek, *Eur. J. Org. Chem.*, 2012, **2012**, 1759; DOI: 10.1002/EJOC.201101662.
61. T. Kubelka, L. Slavětínská, V. Eigner, M. Hocek, *Org. Biomol. Chem.*, 2013, **11**, 4702; DOI: 10.1039/C3OB40774H.
62. T. Kubelka, L. Slavtínská, M. Hocek, *Synthesis*, 2012, **44**, 953; DOI: 10.1055/S-0031-1289694.
63. R. A. Dengale, S. R. Thopate, T. Lönnberg, *ChemPlusChem*, 2016, **81**, 978; DOI: 10.1002/CPLU.201600258.
64. M. Serpi, R. De Biasi, F. Pertusati, M. Slusarczyk, C. McGuigan, *ChemistryOpen*, 2017, **6**, 424; DOI: 10.1002/OPEN.201700019.
65. J. Chiba, M. Inouye, *Curr. Protoc. Nucleic Acid Chem.*, 2015, **61**, 4.62.1; DOI: 10.1002/0471142700.NC0462S61.
66. M. Lefoix, G. Mathis, T. Kleinmann, J. C. Truffert, U. Asseline, *J. Org. Chem.*, 2014, **79**, 3221; DOI: 10.1021/JO5000253.
67. M. Weinberger, F. Berndt, R. Mahrwald, N. P. Ernsting, H. A. Wagenknecht, *J. Org. Chem.*, 2013, **78**, 2589; DOI: 10.1021/JO302768F.
68. Y. Ma, S. Liu, Y. Xi, H. Li, K. Yang, Z. Cheng, W. Wang, Y. Zhang, *Chem. Commun.*, 2019, **55**, 14657; DOI: 10.1039/C9CC07184A.
69. H. Tachallait, M. Safir Filho, H. Marzag, K. Bougrin, L. Demange, A. R. Martin, R. Benhida, *New J. Chem.*, 2019, **43**, 5551; DOI: 10.1039/C8NJ06300A.
70. K. Okamoto, M. Tsutsui, H. Morizumi, Y. Kitano, K. Chiba, *Eur. J. Org. Chem.*, 2021, 2479; DOI: 10.1002/EJOC.202100106.
71. J. Bouton, S. Van Calenbergh, J. Hullaert, *Org. Lett.*, 2020, **22**, 9287; DOI: 10.1021/ACS.ORGLETT.0C03523.
72. M. Abdel, A. El-Hashash, A. Youssef Soliman, I. E. El-Shamy, *Turk. J. Chem.*, 2021, **36**, 347; DOI: 10.3906/kim-1111-52.
73. K. Clinch, D. R. Crump, G. B. Evans, K. Z. Hazleton, J. M. Mason, V. L. Schramm, P. C. Tyler, *Bioorg. Med. Chem.*, 2013, **21**, 5629; DOI: 10.1016/J.BMC.2013.02.016.
74. Q. Wang, C. Ma, X. Li, X. Wang, R. Rong, C. Wei, P. Zhang, X. Li, *Carbohydr. Res.*, 2018, **460**, 29; DOI: 10.1016/J.CARRES.2018.02.012.

75. J. Štambaský, V. Kapras, M. Štefko, O. Kysilka, M. Hocek, A. V. Malkov, P. Kočovský, *J. Org. Chem.*, 2011, **76**, 7781; DOI: 10.1021/JO201110Z.
76. R. R. Midtkandal, P. Redpath, S. A. J. Trammell, S. J. F. MacDonald, C. Brenner, M. E. Migaud, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5204; DOI: 10.1016/J.BMCL.2012.06.069.
77. J. Miguélez, V. R. Batchu, A. Boto, *J. Org. Chem.*, 2012, **77**, 7652; DOI: 10.1021/JO301031T.
78. S. V. Giofrè, R. Romeo, C. Carnovale, R. Mancuso, S. Cirmi, M. Navarra, A. Garozzo, M. A. Chiacchio, *Molecules*, 2015, **20**, 5260; DOI: 10.3390/MOLECULES20045260.
79. E. Coutouli-Argyropoulou, S. Trakossas, *Tetrahedron*, 2011, **67**, 1915; DOI: 10.1016/J.TET.2011.01.020.
80. F. Cermola, S. Vella, M. Dellagreca, A. Tuzi, M. R. Iesce, *Molecules*, 2021, **26**, 2341; DOI: 10.3390/MOLECULES26082341.
81. W. A. El-Sayed, I. F. Nassar, A. A. H. Abdel-Rahman, *J. Heterocycl. Chem.*, 2011, **48**, 135; DOI: 10.1002/JHET.522.
82. M. A. El-Hashash, K. M. Darwish, S. A. Rizk, F. A. El-Bassiouny, *Glob. J. Health Sci.*, 2012, **4**, 174; DOI: 10.5539/GJHS.V4N1P174.
83. A. Ghoneim, A. El-Farargy, *Lett. Org. Chem.*, 2015, **12**, 13; DOI: 10.2174/1570178611666140304000403.
84. S. Harusawa, H. Yoneyama, D. Fujisue, M. Nishiura, M. Fujitake, Y. Usami, Z. Y. Zhao, S. A. Mcphee, T. J. Wilson, D. M. J. Lilley, *Tetrahedron Lett.*, 2012, **53**, 5891; DOI: 10.1016/J.TETLET.2012.08.082.
85. M. Popsavin, M. Svirčev, L. Torović, G. Bogdanović, V. Kojić, D. Jakimov, S. Spaić, L. Aleksić, V. Popsavin, *Tetrahedron*, 2011, **67**, 6847; DOI: 10.1016/J.TET.2011.06.090.
86. M. Popsavin, S. Spaić, M. Svirčev, V. Kojić, G. Bogdanović, V. Popsavin, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 6700; DOI: 10.1016/J.BMCL.2012.08.093.
87. M. Popsavin, V. Kojić, S. Spaić, M. Svirčev, G. Bogdanović, D. Jakimov, L. Aleksić, V. Popsavin, *Tetrahedron*, 2014, **70**, 2343; DOI: 10.1016/J.TET.2014.02.035.
88. S. Penjarla, S. Kumar Sabui, D. Sudhakar Reddy, S. Banerjee, P. Yella Reddy, S. Penta, Y. S. Sanghvi, *Bioorg. Med. Chem. Lett.*, 2020, **30**, 127612; DOI: 10.1016/J.BMCL.2020.127612.
89. P. V. Reddy, M. Saquib, N. N. Mishra, P. K. Shukla, A. K. Shaw, *Arkivoc*, 2014, Part iv, 170; DOI: 10.3998/ARK.5550190.P008.374.
90. N. Sabat, E. Migianu-Griffoni, T. Tudela, M. Lecouvey, S. Kellouche, F. Carreiras, F. Gallier, J. Uziel, N. Lubin-Germain, *Eur. J. Med. Chem.*, 2020, **188**, 112009; DOI: 10.1016/J.EJMECH.2019.112009.
91. S. S. Bag, S. K. Das, *Tetrahedron*, 2019, **75**, 3024; DOI: 10.1016/J.TET.2019.04.038.
92. H. Liu, Y. Liang, T. T. Jia, F. Han, F. Zhang, Y. Zhao, *Eur. J. Org. Chem.*, 2017, 1443; DOI: 10.1002/EJOC.201601506.
93. X. Zhou, T. Jia, Y. Luo, H. Liu, F. Zhang, Y. Zhao, *Org. Biomol. Chem.*, 2020, **18**, 1800; DOI: 10.1039/C9OB02717C.
94. D. A. Bianchi, R. Moran-Ramallal, N. Iqbal, F. Rudroff, M. D. Mihovilovic, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 2718; DOI: 10.1016/J.BMCL.2013.02.085.
95. F. Rudroff, D. A. Bianchi, R. Moran-Ramallal, N. Iqbal, D. Dreier, M. D. Mihovilovic, *Tetrahedron*, 2016, **72**, 7212; DOI: 10.1016/J.TET.2015.11.048.
96. C. Solarte, M. Dos Santos, S. Gonzalez, L. S. M. Miranda, R. Guillot, A. Ferry, F. Gallier, J. Uziel, N. Lubin-Germain, *Synthesis*, 2017, **49**, 1993; DOI: 10.1055/S-0036-1588409.
97. P. Redpath, K. A. Ness, J. Rousseau, S. J. F. Macdonald, M. E. Migaud, *Carbohydr. Res.*, 2015, **402**, 25; DOI: 10.1016/J.CARRES.2014.10.030.
98. G. Legrave, R. A. Youcef, D. Afonso, A. Ferry, J. Uziel, N. Lubin-Germain, *Carbohydr. Res.*, 2018, **462**, 50; DOI: 10.1016/J.CARRES.2018.04.005.
99. S. Kim, J. H. Hong, *Nucleosides, Nucleotides Nucleic Acids*, 2015, **34**, 848; DOI: 10.1080/15257770.2015.1079327.
100. E. Kim, J. H. Hong, *Nucleosides*, *Nucleotides Nucleic Acids*, 2015, **34**, 737; DOI: 10.1080/15257770.2015.1072636.
101. S. Kim, J. H. Hong, *Nucleosides*, *Nucleotides Nucleic Acids*, 2015, **34**, 708; DOI: 10.1080/15257770.2015.1071847.
102. S. Kim, E. Kim, C.-H. Oh, K. Ho Yoo, J. Hee Hong, *Bull. Korean Chem. Soc.*, 2014, 35; DOI: 10.5012/bkcs.2014.35.12.3502.
103. H. Waechtler, D. P. Fuentes, J. A. Q. Suarez, D. Michalik, A. Villinger, U. Kragl, C. Vogel, *Arkivoc*, 2012, Part iii, 110; DOI: 10.3998/ARK.5550190.0013.310.
104. Y. Zhang, W. Ye, H. Wang, S. W. Schneller, *Synthesis*, 2012, **44**, 723; DOI: 10.1055/S-0031-1289688.
105. I. A. S. Smellie, R. M. Paton, *Arkivoc*, 2012, Part i, 49; DOI: 10.3998/ARK.5550190.0013.905.
106. M. Kong, X. Zhou, Q. Chen, F. Zhang, Y. Zhao, *Carbohydr. Res.*, 2021, **505**, 108337; DOI: 10.1016/J.CARRES.2021.108337.
107. D. Neas, D. Hidasová, M. Hocek, M. Kotora, *Org. Biomol. Chem.*, 2011, **9**, 5934; DOI: 10.1039/C1OB05844D.
108. W. Ye, S. W. Schneller, *Synthesis*, 2014, **47**, 228; DOI: 10.1055/S-0034-1378910.
109. S. A. Patil, B. A. Otter, R. S. Klein, *Tetrahedron Lett.*, 1994, **35**, 5339; DOI: 10.1016/S0040-4039(00)73494-0.

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