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Disaccharide nucleosides

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Abstract. Structural features and biological properties of natural disaccharide nucleosides and related compounds are considered. The main methods for the synthesis of these compounds are described and their advantages and disadvantages are discussed. These methods include condensations of a protected disaccharide with a heterocyclic base or of a protected nucleoside with an activated monosaccharide. The bibliography includes 172 references.

I. Introduction

Disaccharide nucleosides constitute an important group of natural compounds, but in contrast to ordinary nucleosides, it is their disaccharide rather than monosaccharide moiety that is linked to a heterocyclic base. Over one hundred such compounds and their derivatives have been isolated from various sources.[1] These compounds manifest a broad spectrum of biological (including antibacterial, fungicidal, herbicidal, antitumour and antiviral) activities. The review by Lerner[2] published in 1991 provides a detailed description of the structures of disaccharide nucleoside antibiotics and the approaches to the synthesis of some of them (the works cited therein were published up to 1988). Since that time, many new publications devoted to this problem have appeared in the current literature. Disaccharide nucleosides occur in nature not only in the free state, but also as components of biopolymers, such as poly(ADP-ribose) and tRNA which play an important role in the vital activities of living organisms. The first part of the present review is devoted to analysis of structural peculiarities and biological activities of natural disaccharide nucleosides and their analogues. The second part deals with the description of general methods for the synthesis of disaccharide nucleosides, *i.e.*, the formation of O- and N-glycosidic bonds.

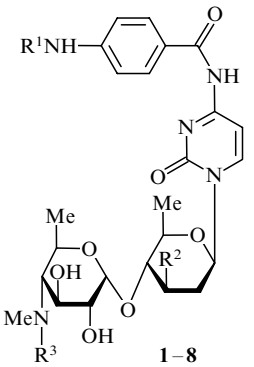
II. Structures and properties of natural disaccharide nucleosides

1. Low-molecular-mass disaccharide nucleosides

A sufficiently large number of disaccharide nucleosides and related compounds are found among antibiotics, which has significantly stimulated the interest in their investigation. The structures and biological activities of nucleoside antibiotics were reviewed by Isono[3,4] in 1988 and 1991. The methods for their isolation and structural elucidation and some approaches to their synthesis are surveyed by Buchanan and Wightman.[5] Some of the published data on the synthesis of complex nucleoside antibiotics are summarised in the reviews by Garner[6] and Knapp.[7]

The structures of nucleoside antibiotics are extremely diverse[2–5] and their elucidation is rather a complicated task. In addition to a heterocyclic base and two monosaccharide residues, these compounds contain various functional substituents, such as acyl and alkyl groups as well as phosphate and sulfate residues, fatty acids, amino acids and peptides. Their degradation by acid and alkaline hydrolysis or methanolysis, periodate oxidation and subsequent reduction yields fragments the structures of which can be established by physicochemical methods. At present, the structures of many complex antibiotics are determined mainly by NMR spectroscopy and mass spectrometry supplemented by hydrolysis and oxidative degradation.

The first disaccharide nucleoside antibiotic amicetin (**1**) was isolated from *Streptomyces sp.* in the early 1950's; [8] however, its structure was established only in the 1960's.[9,10] Its structural analogues, *viz.*, the antibiotics bamicetin (**2**), plicacetin (**3**),[11]



1–8

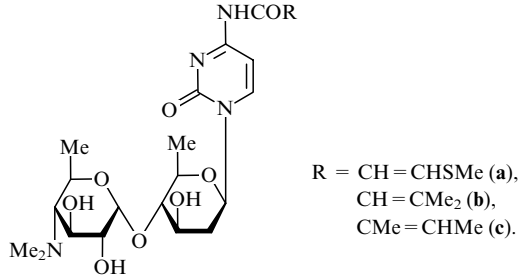
Compound	R^1	R^2	R^3
Amicetin (**1**)	$COCMe(NH_2)CH_2OH$	H	Me
Bamicetin (**2**)	$COCMe(NH_2)CH_2OH$	H	H
Plicacetin (**3**)	H	H	Me
Norplicacetin (**4**)	H	H	H
Oxamicetin (**5**)	$COCMe(NH_2)CH_2OH$	OH	Me
Oxyplicacetin (**6**)	H	OH	Me
SF2457 (**7**)	$COCHMeNH_2$	OH	H
Cytosaminomycin B (**8**)	Me	OH	Me

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norplicacetin (**4**),[12] oxamicetin (**5**),[13] oxyplicacetin (**6**),[14] SF2457 (**7**)[15] and cytosaminomycin (**8**)[16] were isolated and characterised starting from 1958. The presence of an α-(1→4)-glycoside bond between 4-methylamino- or 4-dimethylamino-4,6-dideoxy-D-glucose and 2,6-dideoxy- or 2,3,6-trideoxyhexose is the most characteristic feature of this group of antibiotics. The amino group of cytosine is acylated by *p*-aminobenzoic acid to which an (+)-α-methylserine or D-alanine residue is attached. The amicetin group antibiotics inhibit bacterial peptidyl transferase[17,18] and are active against gram-negative and gram-positive bacteria.

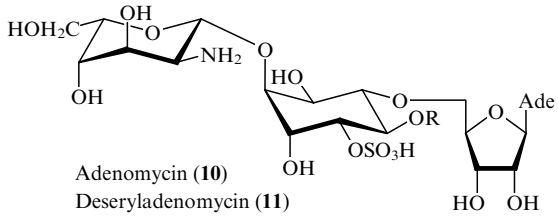
Oxyplicacetin **6** analogues, *viz*., cytosaminomycins A, C and D (**9a–c,** respectively) have been isolated recently.[16,19] In contrast to the antibiotics **1–8**, the amino group of cytosine in cytosaminomycins **9** is acylated by unsaturated acids.



R = CH=CHSMe (**a**),
CH=CMe$_2$ (**b**),
CMe=CHMe (**c**).

Cytosaminomycins (**9a–c**)

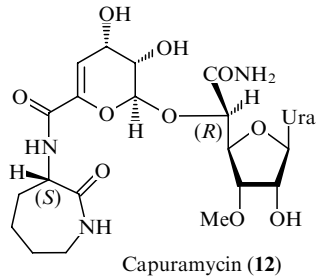
Adenomycin (**10**)[20] produced by *Streptomyces griseoflavus* is not formally related to disaccharide nucleosides, since it is devoid of the disaccharide fragment. It contains adenosine, (−)-*chiro*-inositol and L-gulosamine as well as L-serine.[20] This antibiotic inhibits growth of gram-positive and gram-negative bacteria and is endowed with antitumour activities. Yet another structurally similar compound, *viz*., deseryladenomycin (**11**)[21] isolated from *Str*. *pseudogriseolus,* possesses insecticidal properties.



Adenomycin (**10**)
Deseryladenomycin (**11**)

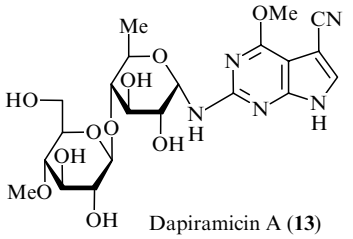
R = COCH(NH$_2$)CH$_2$OH (**10**), H (**11**).

The antibiotic capuramycin (**12**)[22] isolated from *Str*. *griseus* contains uracil and a derivative of L-talofuranuronamide glycosylated by 4-deoxy-D-*erythro*-hex-4-enuronic acid; its carboxylic group is linked to 2(*S*)-aminocaprolactam through an amide bond. The antibiotic **12** is active against certain streptococci and mycobacteria. Capuramycin was the first natural product which was found to contain caprolactam as a substituent.

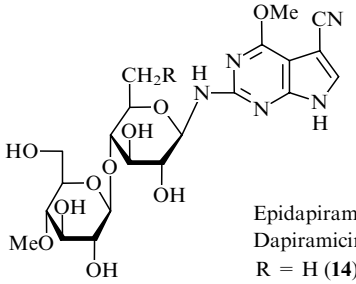


Capuramycin (**12**)

Dapiramicins (**13–15**) isolated from *Micromonospora sp*. contain 7-deazaguanine.[23,24] Its exocyclic amino group is involved in the formation of the N-glycosidic bond between the heterocyclic base and the disaccharide fragment (4′-*O*-methylcellobiose or 4′-*O*-methyl-6-deoxycellobiose). This bond is α in dapiramicin A (**13**) and β in the antibiotics **14** and **15**. It is believed that the configuration of the N-glycosidic bond determines the biological activities of dapiramicins. Dapiramicin A (**13**) exhibits strong fungicidal properties, while epidapiramicin A (**14**) and dapyramicin B (**15**) are less active.[24]



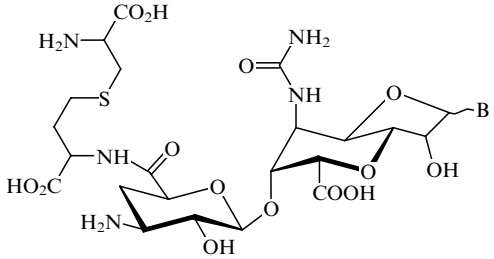
Dapiramicin A (**13**)



Epidapiramicin A (**14**)
Dapiramicin B (**15**)
R = H (**14**), OH (**15**).

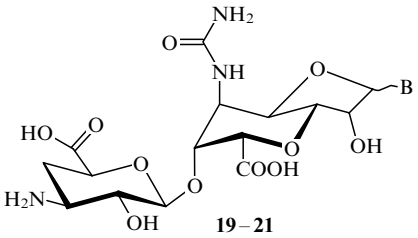
Ezomycins (**16–21**) isolated from the cultural medium of *Streptomyces sp*. and possessing fungicidal activities[25] belong to the group of nucleoside antibiotics which includes higher monosaccharides; the β-anomers **16** and **17** are more active.

A characteristic structural feature of ezomycins **16–21** is the presence of N- or C-glycosides of 3,7-anhydrooctofuranuronic acid glycosylated by ezoaminuronic acid which is linked with L-cystathionine in the case of compounds **16–18**.[25–27] Ezomycins A$_2$, B$_2$ and C$_2$ (**19–21**) do not contain this amino acid.[26] Compounds **17**, **18** and **20**, **21** contain 5-substituted uracil and can therefore be regarded as pseudouridine derivatives. Under mild conditions, ezomycins B$_1$ and B$_2$ (**17**, **20**) are easily anomerised into thermodynamically more stable ezomycins C$_1$ and C$_2$ (**18**, **21**).[27] Similar interconversions in acidic media are typical of pseudouridine. The α-configuration of compounds **18** and **21** was established based on circular dichroism (CD) and NMR spectroscopic studies. The ease of anomerisation of pseudouridine derivatives accounts for the formation of ezomycins C$_1$ and C$_2$ (**18**, **21**) during the isolation of compounds B$_1$ and B$_2$ (**17**, **20**) from biological objects.



16–18

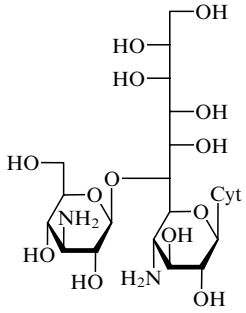
Compound	B
Ezomycin A$_1$ (**16**)	β-Cytosin-1-yl
Ezomycin B$_1$ (**17**)	β-Uracil-5-yl
Ezomycin C$_1$ (**18**)	α-Uracil-5-yl



19–21

Compound	B
Ezomycin A_2 (**19**)	β-Cytosin-1-yl
Ezomycin B_2 (**20**)	β-Uracil -5-yl
Ezomycin C_2 (**21**)	α-Uracil -5-yl

Anthelmycin (or hikizimycin, **22**) was isolated from *Str. longissimus* and *Str. hikiziensis*.[28,29] Analysis of the degradation products of compound **22** revealed that the latter contains cytosine, 3-amino-3-deoxy-D-glucopyranose (canosamine) and 4-aminoundecose (hikosamine).[29,30] The β-configurations of O- and N-glycosidic bonds of both amino sugars were established by NMR spectroscopy. The antibiotic **22** manifests antiparasitic and fungicidal properties and inhibits prokaryotic and eukaryotic peptidyl transferase.[31]



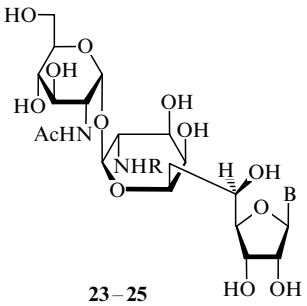
Anthelmycin or hikizimycin (**22**)

Many disaccharide nucleoside antibiotics contain fatty acid residues.

The microorganism *Str. lysosuperificus* is a producer of tunicamycins (**23**).[32] This group of antibiotics contains uracil, an undecose derivative (tunicamine) glycosylated by *N*-acetyl-D-glucosamine and a higher fatty acid residue.[33] At least ten tunicamycin derivatives **23** differing in acyl residues have been described.[33] α,β-Unsaturated acids are usually present as *trans*-isomers. Tunicamycins possess antibacterial and antiviral activities and effectively inhibit the biosynthesis of glycoproteins and peptidoglycans.[34,35]

The antibiotics streptovirudins (**24**) isolated from *Str. griseoflavus* are structurally similar to tunicamycins, they contain dihydrouracil along with uracil.[36]

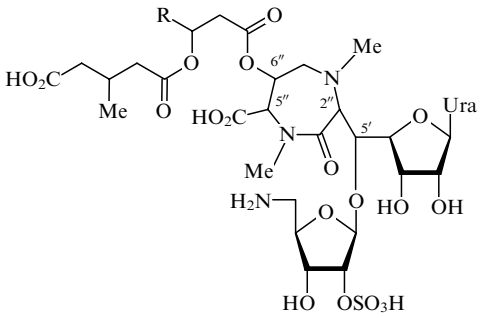
Corynetoxins (**25**), which are structurally similar to tunicamycins, were isolated from the pasture crops-damaging bacterium *Corynebacterium rathay* by Australian scientists.[37,38]



23–25

Compound	B	R
Tunicamycins I–X (**23**)	uracil-1-yl	$COCH=CH(CH_2)_nPr^i$, $n = 7–11$; $COCH=CH(CH_2)_nMe$, $n = 10–13$; $CO(CH_2)_{11}Pr^i$
Streptovirudins A_1, B_1, B_{1a}, C_1, D_1 (**24**)	uracil-1-yl	$COCH=CH(CH_2)_nPr^i$, $n = 6–8$; $COCH=CH(CH_2)_nBu^s$, $n = 6, 8$
Streptovirudins A_2, B_2, B_{2a}, C_2, D_2 (**24**)	dihydro-uracil-1-yl	$COCH=CH(CH_2)_nPr^i$, $n = 6–8$; $COCH=CH(CH_2)_nBu^s$, $n = 6, 8$
Corynetoxins (**25**)	uracil-1-yl	$COCH=CH(CH_2)_nBu^s$, $n = 10, 12$; $COCH_2CH(OH)(CH_2)_nBu^s$, $n = 10, 12$

The lipid-containing nucleoside antibiotics liposidomycins A I, B and C (**26a–c,** respectively) were isolated from *Str. griseosporeus*.[39,40] Liposidomycins **26** contain uridine glycosylated by 5-amino-5-deoxy-D-ribofuranose, 1,4-diazepane and β-hydroxy fatty acids acylated by 3-methylglutaric acid. The configuration of the double bonds of the lipid moiety of liposidomycin A I is *cis*.[40] It is of note that the absolute configuration of the chiral centres 5″ and 6″ has not been finally established yet. A series of papers devoted to the stereoselective synthesis of the disaccharide[41] and 1,4-diazepan-3-one[42–46] fragments and their comparison with the degradation products of liposidomycin have been published recently.[45,46] This enabled the determination of configurations of the other two chiral centres, *viz*., 5′(*S*) and 2″(*S*).[41,46]



Liposidomycins (**26a–c**)

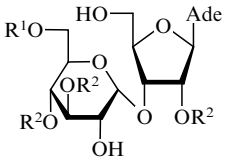
R = $(CH_2)_3CH=CHCH_2CH=CHC_5H_{11}$ (**a**), $(CH_2)_8Pr^i$ (**b**), $(CH_2)_{10}Me$ (**c**).

A series of liposidomycins produced by *Streptomyces sp*. SN-1061M have recently been discovered.[47] In contrast to liposidomycin A I, liposidomycin A II does not contain a sulfate group, while liposidomycin A III lacks the 3-methylglutaric acid residue and liposidomycin A IV is devoid of both substituents. Like tunicamycins, liposidomycins control the synthesis of glycoproteins and peptidoglycans[35,48] and inhibit bacterial translocase;[41,48] their cytotoxicities are significantly lower than those of tunicamycins.[48] Liposidomycins A II and A IV contain no sulfate groups and manifest high antimicrobial activities.[47]

A series of biologically active *O*-hexopyranosyl ribonucleosides (**27–29**), which are not related to antibiotics, have been isolated from various natural sources.

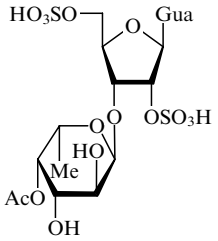
The adenosine derivatives adenophostins A and B (**27a**,**b**) are produced by the microorganism *Penicillum brevicompactum*.[49,50] Compounds **27** are the strongest agonists of receptors of inositol triphosphate which plays a crucial role in the release of Ca^{2+} ions (see Refs 51 and 52). The presence of an α-glycosidic bond between the glucopyranose and ribofuranose residues is a characteristic structural feature of adenophostins (**27**). A vast variety of analogues of compounds **27** have been synthesised and their structure–activity relationships have been studied.[53–55] The presence, in adenophostins (**27**), of an adenine residue is essential

for the manifestation of their biological activity. Adenophostin A derivatives where adenine is lacking or replaced by other heterocyclic bases are less active.[55]



Adenophostins (**27a**,**b**)

R^1 = H (**a**), Ac (**b**);
R^2 = PO_3H_2.

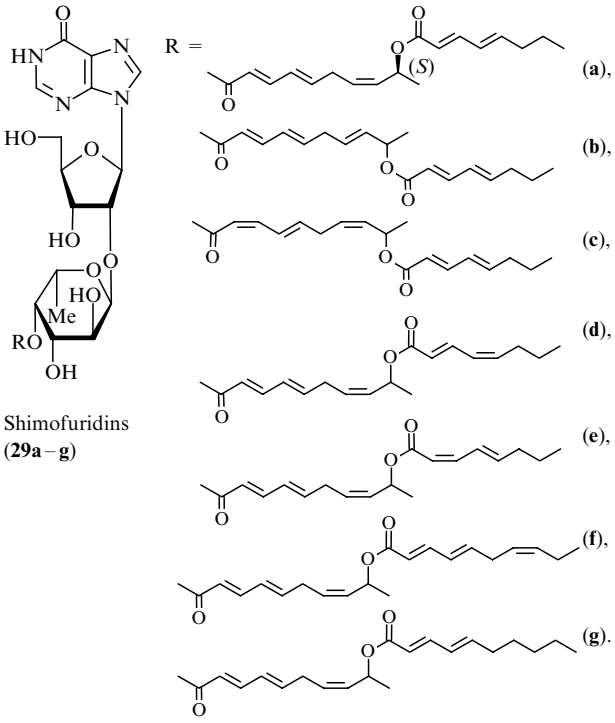


HF-7 (**28**)

A neuroactive compound HF-7 (**28**) was isolated from the venom of the spider *Hololena curta* and its chemical synthesis was carried out.[56] Compound **28** is an anionic nucleoside and, similar to adenophostins **27**, affects intracellular concentrations of Ca^{2+} ions in nervous tissues.

Sea algae, invertebrates (sponges, tunicata, molluscs) and symbiotic microorganisms (bacteria, fungi, microalgae, *etc*.) represent an abundant source of biologically active compounds as potential medicinal drugs.[57] Thus 9-(β-D-arabinofuranosyl)adenine, which possesses antiviral activity, was isolated from sea sponges as early as the 1950's. Several examples of disaccharide nucleosides from different marine organisms can be given.

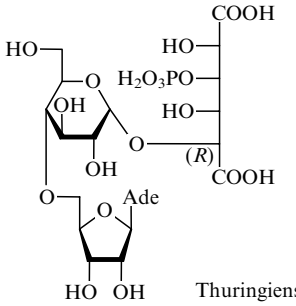
Thus a group of Japanese investigators have isolated a series of disaccharide nucleosides, *viz*., shimofuridins A–G (**29a**–**g**, respectively), which differ in the geometries of the double bonds and the lengths of the hydrocarbon chains of the acyl residues.[58,59] The configuration of the chiral centre (*S*) was established only for shimofuridin A.[58] 2′-*O*-α-L-Fucopyranosylinosine is the main structural element of shimofuridins. Shimofuridin A is active against gram-positive bacteria and manifests antifungal activity.



Shimofuridins (**29a**–**g**)

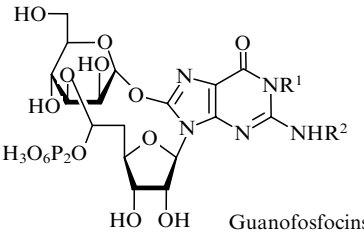
5′-*O*-α-D-Glucopyranosyl derivatives of tubercidin and toyocamycin, which contain 7-deazaadenosine and 7-cyano-7-deazaadenosine, respectively, were isolated from blue-green algae.[60] These compounds possess fungicidal properties and manifest cytotoxic activities. The crustacean *Ligia exotica* serve as a source of 3′-*O*-α-D-glucopyranosylinosine.[61] Disaccharide nucleosides were also isolated from plants. Thus an N^6-benzyl adenosine derivative glucosylated in the 3′-*O*-position is formed in petunia seedlings grown on an artifical medium in the presence of N^6-benzyladenine.[62]

Let us consider some structurally similar analogues of disaccharide nucleosides where the nucleoside fragment and the monosaccharide residue are linked through a non-O-glycosidic bond in more detail. Thuringiensin (or β-exotoxin, **30**) isolated from *Bacillus thuringiensis* simultaneously by two independent groups of investigators is an example.[63,64] This is built of adenosine linked to α-D-glucopyranose through an ether bond and a phosphorylated allaric acid.[65] The α-configuration of the O-glycosidic bond and the (*R*)-configuration of the C(2) atom of allaric acid have been established. Thuringiensin (**30**) possesses insecticidal properties and manifests pronounced cytotoxic activity. Compound **30** inhibits DNA-dependent RNA polymerase in prokaryotes and eukaryotes.[66]



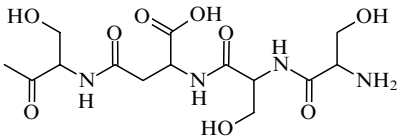
Thuringiensin (**30**)

The recently discovered antibiotics guanofosfocins (**31a**–**c**) have unusual structures.[67,68] Guanofosfocin A (**31a**) was isolated from *Streptomyces sp*. and guanofosfocins B (**31b**) and C (**31c**), from *Trichoderma sp*. They contain a hemiacetal bond between the monosaccharide residues. Guanofosfocins (**31**) inhibit chitin synthetase and are effective antifungal agents. However, these compounds are highly labile, which significantly complicates their synthesis and further studies.[68,69]

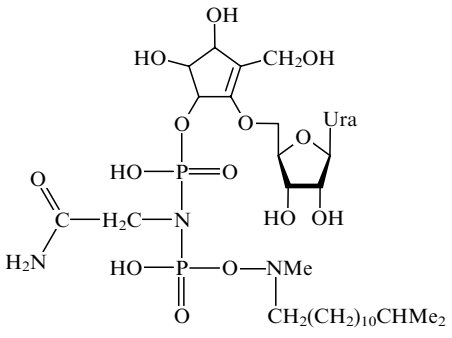


Guanofosfocins (**31a**–**c**)

R^1 = Me (**a**), H (**b**); R^2 = H;

R^1 = H, R^2 =  (**c**).

By way of illustration, the antibiotic EM 2487 (**32**) isolated from *Streptomyces sp*. represents a carbocyclic analogue of a disaccharide nucleoside.[70] Its cyclopentene fragment is linked to



EM 2487 (**32**)

uridine through an ether bond. The antibiotic **32** manifests pronounced anti-HIV activity.[71]

Even a brief survey demonstrates the diversity of structural peculiarities and biological activities of disaccharide nucleosides. In conclusion, special mention should be made of the studies devoted to the chemical synthesis of some of the compounds mentioned above. Complete syntheses of plicacethin (**3**),[72] capuramycin (**12**),[73] hikizimycin (**22**),[74] tunicamycin V (**23**) [75–77] and thuringiensin (**30**) [78] have been performed and approaches to the synthesis of fragments of the most complex antibiotics ezomycin A_1 (**16**) [79,80] and liposidomycin C (**26**) have been developed.[41–46,81,82] The syntheses of adenophostin (**27**), HF-7 (**28**) and shimofuridin A (**29**) will be considered in detail in the second part of the review. The development of methods for the synthesis of guanofosfocins (**31**) and EM 2487 (**32**) still presents a problem for modern bioorganic chemistry.

2. Disaccharide nucleosides as structural elements of biopolymers

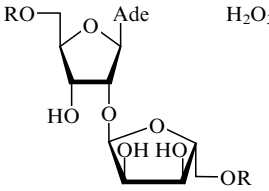
Purine disaccharide nucleosides with two O-glycosidically linked ribofuranose residues were identified as components of poly(ADP-ribose) and transfer RNA.

An enzyme responsible for the conversion of nicotinamide adenine dinucleotide (NAD^+) into a homopolymer, poly(ADP-ribose), with simultaneous release of nicotinamide was discovered in eukaryotic cell nuclei in the 1960's.[83–85] The polymer is covalently linked to histones and other nuclear proteins, as a rule, through glutamic acid and, less frequently, through aspartic acid.[84,85] Its multifaceted biological role is highlighted in a review.[84] Thus it is known that poly(ADP-ribose) is involved in structural modulation of chromatin, in replication, transcription and repair of DNA and in cell differentiation. In-depth studies on intracellular functions of poly(ADP-ribose) are currently underway.

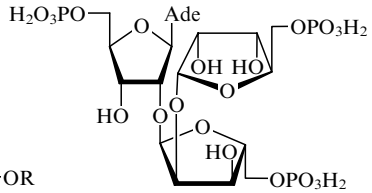
Molecules of poly(ADP-ribose) both isolated from natural sources and synthesised *in vitro* using the corresponding poly(ADP-ribose) polymerase have a branched structure and contain over 200 monomeric units.[86,87] Their linear fragments contain 20–50 units and alternate with branched fragments, which probably confer stability on the conformation of the biopolymer.

The degradation of poly(ADP-ribose) is mediated by two enzymes, *viz*., ADP-ribosyl protein lyase and poly(ADP-ribose) glycohydrolase.[83,84] The former is involved in the hydrolysis of the bond between the protein and the ADP ribose fragment. Glycohydrolase, which is endowed with both exo- and endoglycosidase activities, cleaves the bonds between ribofuranose and adenosine resulting in ADP ribose.[84,88]

Accessibility of polymerase enables an easy synthesis of poly(ADP-ribose) *in vitro*. Enzymatic hydrolysis of poly(ADP-ribose) synthesised *in vitro* by snake venom phosphodiesterase yields compound **33**; its structure was established by NMR spectroscopy.[89–91] Treatment of compound **33** with alkaline phosphatase results in 2′-*O*-α-D-ribofuranosyl adenosine (**34**). The absence of a signal for the 2′-hydroxy group of the adenosine residue in the ^1H NMR spectrum of the latter in DMSO-d_6 suggests the presence of a 1″→2′-glycosidic bond between the ribofuranose and adenosine residues.[91] The configurations of the O-glycosidic bond were established by ^{13}C NMR spectroscopy of compound **33** and anomeric methyl D-ribofuranosides.[89] A comparison of the spin–spin coupling constants $J_{1',2'}$ in the diphosphate **33**, methyl-β- and -α-D-ribofuranosides ($J_{1',2'}$ = 4.2, 1.2 and 4.5 Hz, respectively) confirmed the α-configuration of the O-glycosidic bond.[91] The structure of the nucleoside **35** localised in the branching point was also established using physicochemical methods.[92]

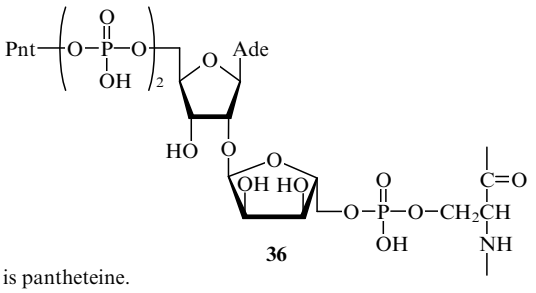


33: R = PO_3H_2;
34: R = H.



35

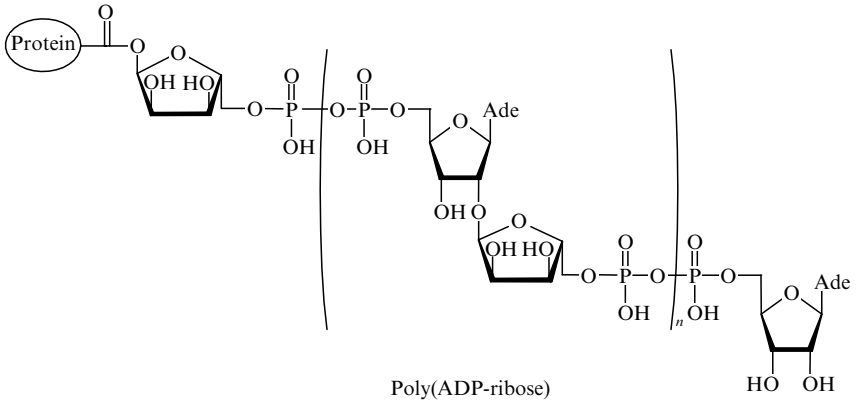
It is of note that compound **33** represents a fragment of the prosthetic group of compound **36** which is linked to the serine residue of bacterial citrate lyase [93,94] and malonate decarboxylase.[95] In contrast to poly(ADP-ribose), dephosphorylated coenzyme A is a precursor of compound **36**, while ATP is a contributor of an additional 5-phosphoribofuranose residue.[94,95]



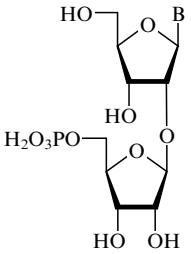
36

Pnt is pantheteine.

The purine disaccharide nucleosides **37** and **38** were isolated from lower eukaryotic initiator tRNAs ($tRNA_i^{Met}$) and several plant sources.[96,97] These minor nucleosides located in the steam of the T-loop of $tRNA_i^{Met}$ and occupy the 64th position in the primary structure of the molecule.[98–101] The 3′- and 5′-hydroxy groups of the nucleoside residue take part in the formation of internucleotide bonds. The site of the attachment of the ribofuranose residue to the nucleoside and the position of an additional phosphate group were established using periodate oxidation of mono- and dinucleotides containing fragments **37** and **38** with subsequent β-elimination under the action of cyclohexylamine.[99,100] In contrast to the monomeric unit of poly(ADP-ribose) (compound **33**), the additional ribofuranose residues in the disaccharide nucleosides **37** and **38** are linked to the nucleoside by a β-glycosidic bond.



Poly(ADP-ribose)



37: B = Ade;
38: B = Gua.

Total chemical synthesis of these minor nucleosides, *O*-β-D-ribofuranosyl-(1″→2′)-adenosine 5″-phosphate (**37**)[102] and *O*-β-D-ribofuranosyl-(1″→2′)-guanosine 5″-phosphate (**38**), has been carried out recently;[103] the synthesis of the α-anomer **33** has not been described so far.

The values of the spin–spin coupling constants of the natural disaccharide nucleoside **33** (see Ref. 91) and its synthetic isomer **37** as revealed by ^{1}H NMR spectroscopy are listed in Table 1.[102] These compounds possess similar coupling constants with the exception of $J_{1',2'}$ and $J_{3',4'}$ of the ribofuranose fragment.

Table 1. Experimental values of spin–spin coupling constants determined from the ^{1}H NMR spectra of compounds **33**[91] and **37**[102] (in D_2O).

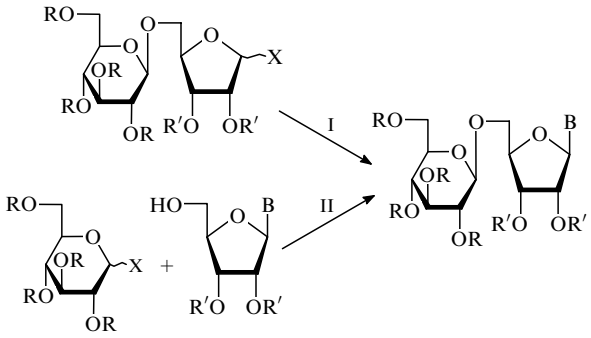
Coupling protons	*J* /Hz			
	fragment **33**		fragment **37**	
	Ado	α-ribosyl	Ado	β-ribosyl
1′–2′	5.5	4.6	6.4	1.2
2′–3′	5.1	6.4	5.5	4.6
3′–4′	3.7	0.7	3.1	6.4
4′–5′a	2.8	4.4	2.7	4.3
4′–5′b	3.8	4.1	3.7	5.7
5′a–5′b	−11.6	−11.3	−12.8	−11.6
5′a–P	4.3	5.8		6.4
5′b–P	4.8	4.4		7.0

It is believed that the presence of the disaccharide nucleosides **37** and **38** in position 64 is the most characteristic feature of lower eukaryotic $tRNA_i^{Met}$. According to data from X-ray diffraction analysis, the bulky 5″-phosphoribofuranosyl residue of the nucleoside **37** occupies a strictly definite position in the minor groove in the tertiary structure of yeast $tRNA_i^{Met}$ (see Ref. 104). The additional phosphate group forms a hydrogen bond with the 2-amino group of the vicinal guanosine residue G_{63}. After selective removal of the 5″-phosphoribofuranose residue (oxidation, β-elimination), tRNA begins to act as an elongator one, however, with a lower efficiency in comparison with native $tRNA_i^{Met}$ (see Refs 105 and 106). This suggests that the modification of the purine nucleoside **64** in $tRNA_i^{Met}$ plays a role in the discrimination of the initiation–elongation process of protein synthesis and thus prevents the formation of a tRNA complex with the elongation factor EF-1α and guanosine triphosphate characteristic of the elongation reaction.

The mechanisms of biosynthesis of modified nucleosides **37** and **38** have not been finally elucidated yet. It is hypothesised that adenosine and guanosine undergo post-transcriptional ribosylation in the precursor $tRNA_i^{Met}$ with involvement of 5-phosphoribosyl-1-pyrophosphate.[99]

III. General methods for the synthesis of disaccharide nucleosides

Disaccharide nucleosides can be synthesised by one of two routes. These consist of coupling of a protected disaccharide with a heterocyclic base derivative or the formation of an O-glycosidic bond between a nucleoside carrying one free hydroxy group and an activated monosaccharide.



X = Hal, OAcyl, SAlk, SPh *etc.*; B is heterocyclic base.

The choice of the order of formation of O- and N-glycosidic bonds is essential in the design of methods for the synthesis of disaccharide nucleosides. In each concrete case, the reaction sequence is determined by the structure and stability of final and intermediate products as well as by availability of starting compounds. Obviously, the use of readily available natural carbohydrates and nucleosides can significantly shorten the synthetic procedure. Special attention should be given to the choice of protective groups, estimation of their stability under various coupling conditions and stereoselectivity of formation of glycosidic bonds. The strategy and tactics of the syntheses of capuramycin (**13**), ezomycin A_1 (**16**), hikizimycin (**22**), tunicamycin (**23**), liposidomycin C (**26**) and thuringiensin (**30**) are reviewed by Knapp.[7]

1. Coupling of disaccharides with nucleic bases (N-glycosylation)

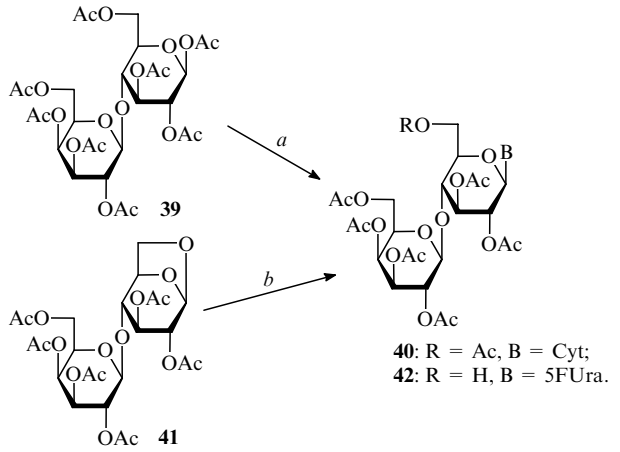
The classical methods for the synthesis of nucleosides[107] include coupling of acylglycosyl halides with silver or mercury salts of purine bases or with 2,4-dialkoxypyrimidines. A detailed account of the use of these methods in the first syntheses of disaccharide nucleosides starting from heterocyclic bases and derivatives of accessible natural disaccharides (lactose, maltose, cellobiose, melibiose, *etc.*) is given in a review by Lerner.[2] The yields in the coupling step did not usually exceed 50%. The main drawback of these methods is the necessity to prepare rather unstable glycosyl halides. Besides, the synthesis of purine derivatives demands the use of toxic mercury salts.

Stereoselective formation of the N-glycosidic bond is the key step in the synthesis of nucleosides. This problem is considered in detail in several reviews.[107–111] The presence of a participating 2-*O*-acyl group in the monosaccharide ensures stereoselective formation of 1,2-*trans*-products; in other cases, mixtures of α- and β-anomers are formed. These regularities hold also for the reactions involving disaccharides.

A procedure proposed by Vorbruggen[108,110,111] has replaced virtually completely the previously employed methods for the synthesis of nucleosides and their analogues. This consists of the interactions of silyl derivatives of heterocyclic bases with peracylated sugars in aprotic solvents in the presence of Lewis acids ($SnCl_4$ or trimethylsilyl trifluoromethanesulfonate, TMSOTf). The use of this approach has significantly simplified the reaction procedure and increased the yields of the target products.

Thus the glycosylation of bis(trimethylsilyl)cytosine [$(TMS)_2$-Cyt] by octaacetyllactose (**39**), octaacetylcellobiose and octaacetylmaltose in the presence of $SnCl_4$ in boiling dichloroethane occurred at a sufficiently high rate (2 h) and afforded disaccharide nucleosides (*e.g.*, lactosylcytosine **40**) in high yields (60%–90%).[112] The use of acylglycosyl chlorides resulted in the formation of regioisomers.[112] The glycosylation of the silyl derivative of 5-fluorouracil $(TMS)_2$-5FUra by 1,6-anhydrolactose hexaacetate (**41**) required more drastic conditions (boiling in

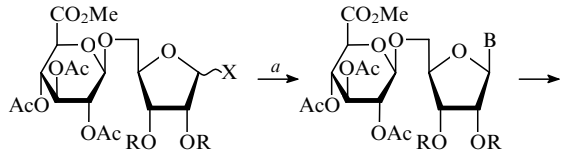
acetonitrile, 10 h); the yield of the β-anomer **42** was 35%.[113] Peracylated tri- and tetrasaccharides can also be involved in the coupling.[112]



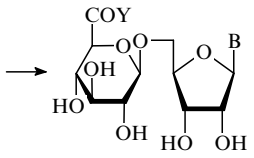
(*a*) $(TMS)_2$ – Cyt, $SnCl_4$, DCE (1,2-dichloroethane), Δ, 2 h;
(*b*) $(TMS)_2$ – 5FUra, $SnCl_4$, MeCN, Δ, 10 h.

The reaction of octaacetylcellobiose with a silyl derivative of theophylline was carried out under similar conditions ($SnCl_4$, acetonitrile, 75 °C, 16 h) and gave 7-(hepta-*O*-acetyl-β-cellobiosyl)theophylline in 90% yield.[114]

Preparation of 5′-*O*-glucuronides of the known antitumour nucleosides, 5-fluorouridine and 5-fluorocytidine, has been described.[115] The coupling of the glycosyl chloride **43** with a trimethylsilyl derivative of 5-fluorocytosine (boiling in acetonitrile, 24 h) resulted in the disaccharide nucleoside **44** in 49% yield. Under similar conditions (boiling in 1,2-dichloroethane, 35 min), the peracetylated disaccharide **45** reacted much faster; the products **46** were obtained in 90% yield. Removal of protective groups gave the free acid **47** or the amide **48**.



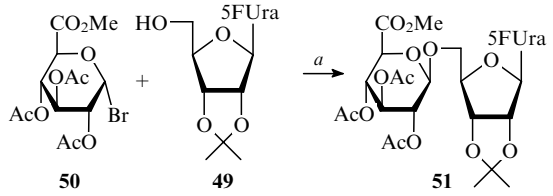
43: X = α- or β-Cl, R = Bz;
45: X = β-OAc, R = Ac.
44: R = Bz, B = 5FCyt;
46: R = Ac, B = 5FCyt, 5FUra.



47: Y = OH; **48**: Y = NH_2;
B = 5FCyt, 5FUra.

(*a*) $(TMS)_2$ – 5FCyt or $(TMS)_2$ – 5FUra, $SnCl_4$, MeCN or DCE.

An alternative route to the synthesis of 5′-*O*-glycosylribonucleosides entailed the Koenigs – Knorr *O*-glycosylation of 2′,3′-*O*-isopropylidene-5-fluorouridine (**49**) by glucuronosyl bromide **50**; the yield of the disaccharide nucleoside **51** was 65%. However,



50 **49** **51**

(*a*) Ag_2O, C_6H_6 – MeCN, Δ, 16 h.

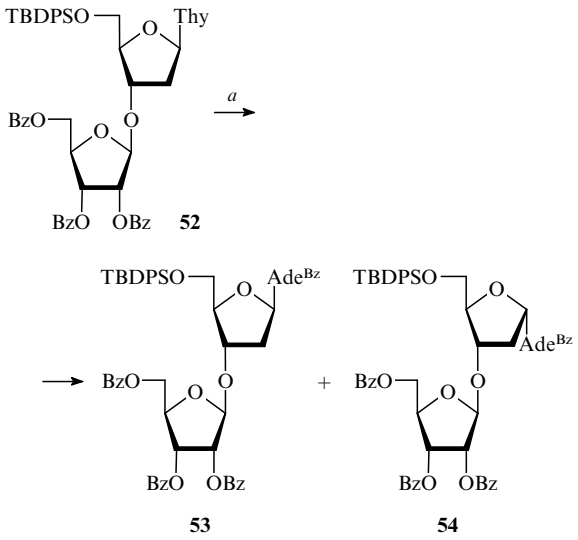
subsequent removal of the 2′,3′-*O*-isopropylidene group in an acidic medium (boiling in 80% AcOH, 30 min) was accompanied by a significant cleavage of the O-glycosidic bonds and the formation of the target product in a low yield.

A comparison of these approaches to the synthesis of 5′-*O*-glycosylribonucleosides has demonstrated a salient advantage of the Vorbruggen *N*-glycosylation by acetate **45** which is also employed in the synthesis of purine disaccharides. Thus the coupling of bis(trimethylsilyl)hypoxanthine with peracetylated 5-*O*-(β-D-glucopyranosyl)-β-D-ribofuranose and subsequent deacetylation gave 5′-*O*-(β-D-glucopyranosyl)inosine.[116]

At present, the synthesis of disaccharide nucleosides is usually performed by the Vorbruggen procedure. Thus the disaccharide fragment of the antibiotic liposidomycin (**26**)[41] and some of its derivatives have recently been synthesised using this method.[117] The reaction of fully protected 1-*O*-acetyl-5-*O*-(5-azido-5-deoxy-β-D-ribofuranosyl)-D-allofuranose or -L-talofuranose derivatives with bis(trimethylsilyl)uracil in the presence of TMSOTf in acetonitrile was carried out under mild conditions (room temperature, 3 h); the yields were up to 70%. Similar glycosylation was used[53,54,118] in the synthesis of numerous analogues of adenophostin (**27**).

In all cases studied, *N*-glycosylation by furanose derivatives occurs under milder conditions and at much faster rates than by pyranoses. The best results were obtained when 1-*O*-acetyl sugars were used.

Substitution of heterocyclic bases is an alternative route to the synthesis of disaccharide nucleosides.[111] A mixture of compounds **53** and **54** was prepared starting from a thymine disaccharide (compound **52**[119]) and a 1.5-fold excess of bis(trimethylsilyl)-N^6-benzoyladenine, the overall yield of the reaction products being 68%.[120] As expected, the β- and α-anomers **53** and **54** are formed in a 1 : 2 ratio in the absence of a participating group at the C(2′) atom.



TBDPS is *tert*-butyldiphenylsilyl;
(*a*) $(TMS)_2$ – Ade^{Bz}, TMSOTf, MeCN, Δ, 2.5 h.

2. Coupling of monosaccharides with nucleosides (O-glycosylation)

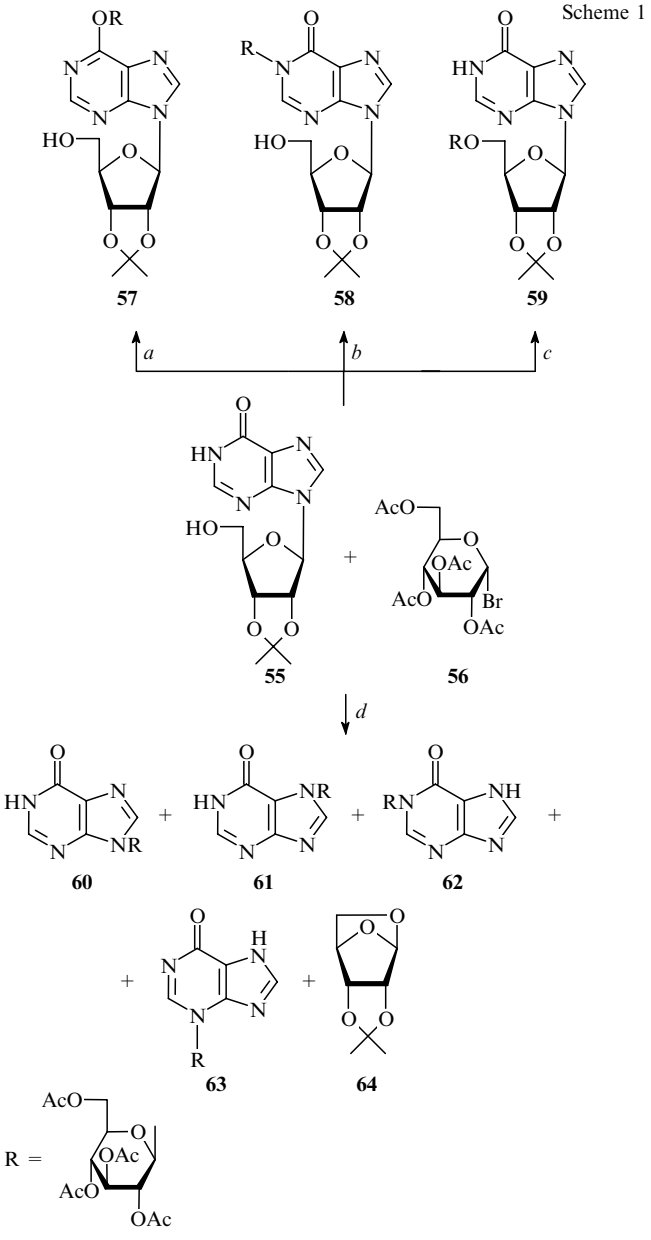
The formation of the O-glycosidic bond is considered in detail in the reviews devoted to carbohydrate chemistry.[121–123] Early syntheses of disaccharide nucleosides were carried out using the Koenigs – Knorr method or its modifications, *i.e.*, coupling of glycosyl halides with alcohols in the presence of mercuric or silver salts. As in the case of N-glycoside synthesis, the presence of a participating acyl group at the O(2) atom of a monosaccharide favours stereoselective formation of 1,2-*trans*-substituted products, while in its absence a mixture of α- and β-anomers is usually

formed. Directed synthesis of 1,2-*cis*-substituted products is a more complicated process.

Studies by Lichtenthaler *et al.*[124–126] have shown that the yields in the Koenigs–Knorr glycosylation of 2′,3′-*O*-isopropylidene nucleosides by per-*O*-acetylglycopyranosyl bromides strongly depend on the nature of the solvent and the promoter. The reaction of 2′,3′-*O*-isopropylideneinosine (**55**) with tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**56**) (Scheme 1) in the presence of silver carbonate in chloroform (24 h, 60 °C) gave predominantly the O^6-glycoside **57** (yield 66%); prolonged heating (3–4 days) gave the second product, *viz.*, N^9-glycoside **58**. The disaccharide nucleoside **59** was obtained in 41% yield when the reaction was carried out in the presence of a silver carbonate–silver perchlorate mixture in chloroform (24 h, 0 °C).[125]

Similar reactions of 2′,3′-*O*-isopropylideneadenosine and -guanosine afforded complex mixtures of products.[125] Thus the glycosylation of compound **55** in nitromethane in the presence of mercuric cyanide (2 days, 40 °C) yielded a mixture of all possible

Scheme 1

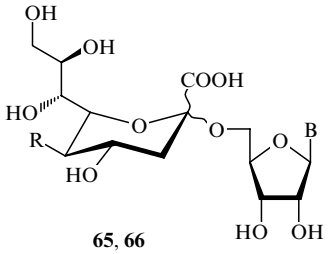


(*a*) Ag_2CO_3, $CHCl_3$, 60 °C, 24 h; (*b*) Ag_2CO_3, $CHCl_3$, 60 °C, 3–4 days; (*c*) Ag_2CO_3–$AgClO_4$, $CHCl_3$, 0 °C, 24 h; (*d*) $Hg(CN)_2$, $MeNO_2$.

N-glycopyranosylhypoxanthines **60**–**63** and 2,3-*O*-isopropylidene-1,5-anhydro-D-ribofuranose (**64**).[124]

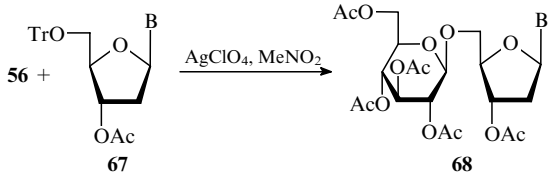
More encouraging results were obtained when this method was used in the synthesis of pyrimidine nucleosides. Thus the reaction of 2′,3′-*O*-isopropylideneuridine with glycosyl bromide **56** under identical conditions occurred at much faster rates (3 h, 55 °C) and gave a protected 5′-*O*-glucopyranosyluridine derivative in 73% yield.[126] Good yields of disaccharide derivatives were achieved upon glycosylation of 2′,3′-*O*-isopropylideneuridine with tetra-*O*-acetyl-α-D-galactopyranosyl bromide in the presence of mercuric cyanide.[126, 127] A similar reaction of 2′,3′-*O*-isopropylideneuridine with 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl bromide yielded a mixture of α- and β-anomers (2 : 1).[126]

As expected, the Koenigs–Knorr glycosylation of nucleosides by 3-deoxynon-2-ulosonic acid derivatives gave a mixture of α- and β-anomers; the overall yields of the derivatives **65** and **66** after deprotection were rather small.[128, 129]

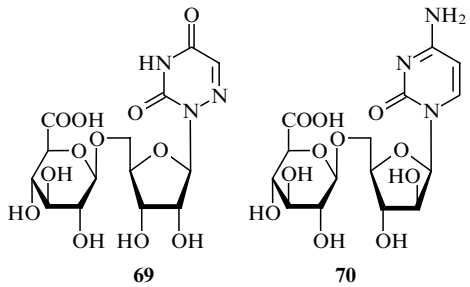


65: R = NHAc, B = Cyt, Hyp; **66**: R = OH, B = Ura, Cyt, 5FUra.

In some studies,[130–132] 5′-*O*-glucopyranosylnucleoside derivatives were synthesised using the Bredereck modification. The reactions of 5′-*O*-trityl-2′-deoxynucleosides (**67**) with glucosyl bromide **56** in nitromethane in the presence of silver perchlorate gave compounds **68** in 22% and 41% yields.[130] 5′-*O*-Glucuronides of 6-azauridine **69**[131] and 1-(β-D-arabinofuranosyl)cytosine **70**[132] were synthesised in a similar way; the yields in the coupling step were 38% and 20%, respectively.

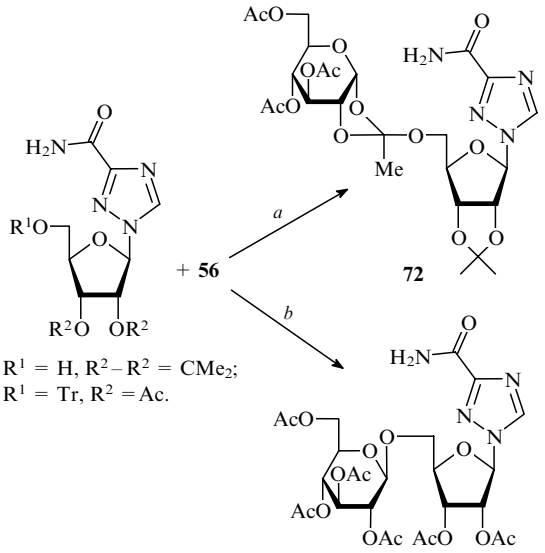


B = Cyt^{Ac}, Thy.



The glycosylation of ribavirin derivatives has been described.[133] The Koenigs–Knorr coupling of glucosyl bromide **56** with 2′,3′-*O*-isopropylideneribavirin (**71**) in the presence of silver carbonate and silver perchlorate gave a complex mixture; the orthoester **72** was isolated in 30% yield. At the same time, the Bredereck glycosylation of the trityl ether **73** afforded the disaccharide nucleoside **74** in 15% yield. Similar results were obtained in the glycosylation of compounds **71** and **73** by galactosyl bromide.[133] It is noteworthy that the formation of an orthoester derivative (27%) also took place upon Koenigs–Knorr coupling of tetra-*O*-acetyl-α-D-glucopyranosyl bromide

56 with 2′-deoxy-N^4-acetylcytidine in nitromethane in the presence of silver carbonate.[130]



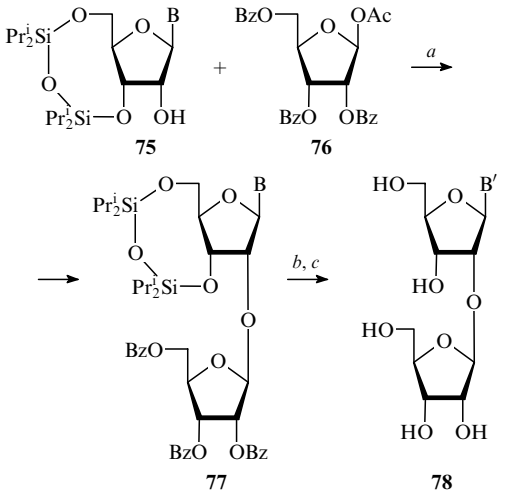
71: R^1 = H, R^2–R^2 = CMe_2;
73: R^1 = Tr, R^2 = Ac.

Tr is triphenylmethyl (trityl);
(*a*) Ag_2CO_3–$AgClO_4$, CH_2Cl_2; (*b*) $AgClO_4$, $MeNO_2$.

The aforementioned data clearly demonstrate that the Koenigs–Knorr method and its modifications have been often employed for the glycosylation of 5′-hydroxy groups of nucleosides by glycopyranosyl bromide derivatives. These reactions are usually accompanied by the formation of side products; the yields of target disaccharide nucleosides (with rare exceptions) are rather low. The glycosylation of the 5′-hydroxy group of uridine derivatives by acylglycofuranosyl halides was used in the synthesis of analogues of the disaccharide fragment of liposidomycin.[41, 134]

Later, alternative methods of *O*-glycosylation of nucleosides were developed. A simple and efficient synthesis of disaccharide nucleosides has been performed which includes coupling of a peracylated monosaccharide with a partly protected nucleoside in the presence of Lewis acids under conditions similar to those used in the synthesis of alkyl β-D-ribofuranosides.[135]

Coupling of *N*-protected 3′,5′-*O*-tetraisopropyldisiloxane-1,3-diyl ribonucleosides (**75**)[136] with a small excess of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**76**) in the presence of $SnCl_4$ was stereospecific and afforded protected 2′-*O*-β-D-ribofuranosyl nucleosides (**77**).[137–140] This reaction was carried out



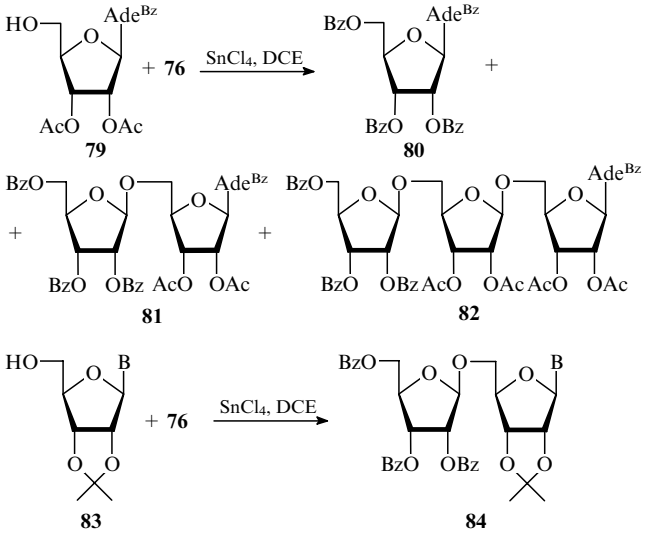
B = Ura, Thy, Cyt^{Bz}, Ade^{Bz}, Gua^{Bu^i}; B′ = Ura, Thy, Cyt, Ade, Gua;
(*a*) $SnCl_4$, DCE; (*b*) Bu_4NF, THF; (*c*) NH_3, MeOH.

under mild conditions (0 °C, 1,2-dichloroethane, 2 h for pyrimidine nucleosides, 7–16 h for purine derivatives); the yields of the target compounds **77** were 74%–82%.[138, 139] At room temperature, this reaction occurred faster (30 min), but the yields in the coupling steps were lower (40%–77%).[137, 140] After deprotection, the disaccharide nucleosides **78** were obtained in good overall yields.[137–140] The synthesis of the minor nucleosides **37** and **38** could be performed using this method.[102, 103]

The use of the above-described procedure ensures an easy and efficient synthesis of pyrimidine 3′-*O*-β-D-ribofuranosyl- [119] and 5′-*O*-β-D-ribofuranosyl-2′-deoxynucleosides [141, 142] as well as 5′-*O*-β-D-ribofuranosyl nucleosides.[143, 144] Other peracylated furanoses and pyranoses [145] (D- and L-arabinofuranose, D-erythrofuranose, 5-azido-5-deoxyribofuranose, D-ribopyranose) were successfully employed in the glycosylation of the nucleoside **75**.[145] The synthesis of numerous 2′-*O*-β-D-ribofuranosylnucleoside derivatives (**77**) containing various monosaccharide residues at O(2′) shows explicitly the versatility of the coupling based on the use of peracylated sugars as glycosyl donors in the presence of $SnCl_4$.

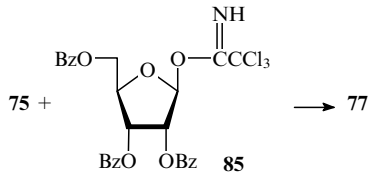
The stabilities of various protective groups in O-glycosylation have been studied.[141, 142] It was found that TMSOTf can be used as a Lewis acid. This glycosylation procedure was used in the synthesis of disaccharide fragments of liposidomycin (**26**).[134] It is of note that incorporation of 2′-*O*-β-D-ribofuranosylnucleosides and their analogues into synthetic oligonucleotides has found application in the studies of enzymes of nucleic acid metabolism.[146–150]

Despite good reproducibility of *O*-glycosylation in the presence of peracylated sugars, side reactions occur sometimes. For example, the synthesis of purine 5′-*O*-β-D-ribofuranosylnucleosides was sometimes accompanied by the formation of trisaccharide nucleosides.[144] Coupling of the nucleoside **79** with fully protected ribofuranose **76** in the presence of $SnCl_4$ yielded a mixture of mono-, di- and trisaccharide nucleosides (**80**–**82**) in 18%, 29% and 17% yields, respectively. The formation of compounds **80** and **82** is attributed to the instability of the N-glycosidic bond in the starting purine ribonucleoside **79** and/or in the disaccharide nucleoside **81** in the presence of $SnCl_4$.[144] The use of 2′,3′-*O*-isopropylidene derivatives **83** containing a more stable N-glycosidic bond has made it possible to avoid the formation of trisaccharide nucleosides and to obtain target purine 5′-*O*-ribofuranosylnucleosides (**84**) in 60%–65% yields.[144]



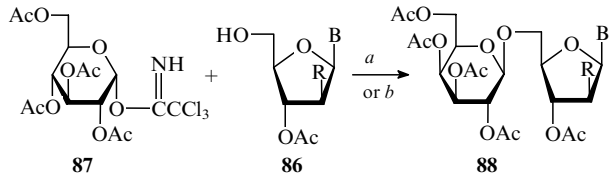
B = Ade^{Bz}, Gua^{Bu^i}.

Recently, sugar trichloroacetimidates have found application as glycosyl donors.[151] The coupling of nucleoside **75** (B = Ade^{Bz}) with trichloroacetimidate **85** in tetrahydrofuran was carried out under different conditions.[152]



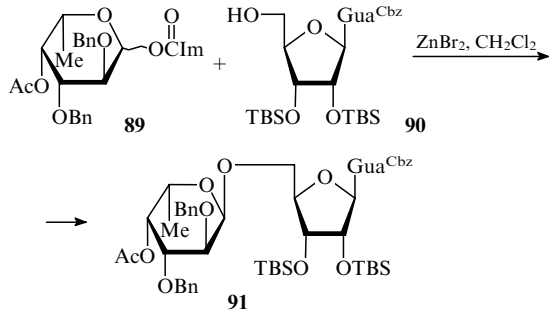
Conditions	TMSOTf, 0 °C	$BF_3 \cdot Et_2O$, 20 °C	TfOH, 0 °C
Yield (%)	64	57	93

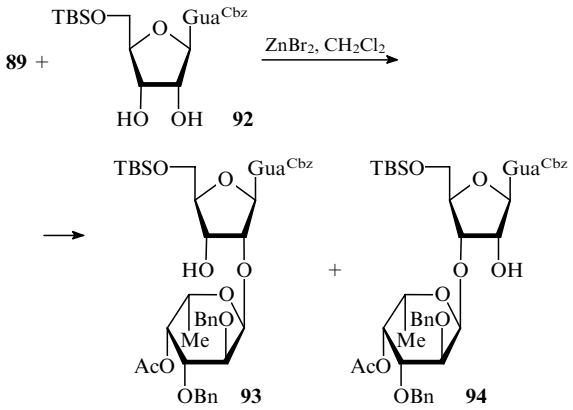
It was found[153, 154] that the glycosylation of the primary hydroxy group of the pyrimidine nucleosides **86** by trichloroacetimidate **87** is far less efficient. After activation with $BF_3 \cdot Et_2O$ (conditions *a*), the yields of the products **88** did not exceed 24%, whereas the use of TfOAg in $CHCl_3$ (*b*) made it possible to increase the yields up to 35%–41%.[153, 154] The acetylation of the free 5′-hydroxy group in nucleosides **86** is the main side reaction. Low reactivity of the primary 5′-hydroxy group with respect to *O*-glycosylation was attributed to the presence of a hydrogen bond with a 2-carbonyl group of the pyrimidine heterocycle observable in the ^1H NMR spectra in aprotic solvents.[153]



R = H: B = Cyt^{Ac}, Thy, 5FUra; R = OAc, B = Cyt^{Ac};
(*a*) $BF_3 \cdot Et_2O$, CH_2Cl_2; (*b*) TfOAg, $CHCl_3$.

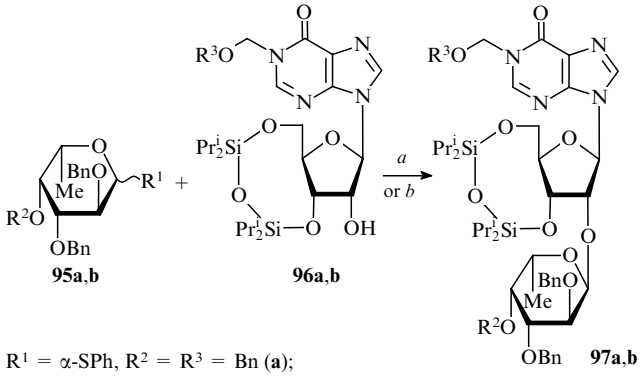
A series of isomeric α-L-fucopyranosylguanosines have been synthesised in order to establish the structure of the disaccharide nucleoside HF-7 (**28**).[56] L-Fucopyranosyl 1-*O*-imidazolecarboxylate **89** containing a benzyloxy group at the C(2) atom, which ensures good stereoselectivity in the formation of the α-glycosidic bond, was used as a glycosyl donor. The coupling of the nucleoside **90** with the glycosyl donor **89** in the presence of $ZnBr_2$ in CH_2Cl_2 gave the disaccharide nucleoside **91** in 80% yield. A mixture of 2′- and 3′-isomers **93** and **94** was prepared starting from nucleoside **92** under identical conditions (yields 38% and 40%, respectively). Compound **28** identical to the natural product was obtained upon removal of the silyl protective group in compound **94** with subsequent sulfation and hydrogenolysis. Attempts to use the glycosyl donor **89** for the glycosylation of the guanosine derivative **92** containing an additional 2′-*O*-*tert*-butyldimethylsilyl group failed, apparently due to the steric hindrance of the 3′-hydroxy group.[56]





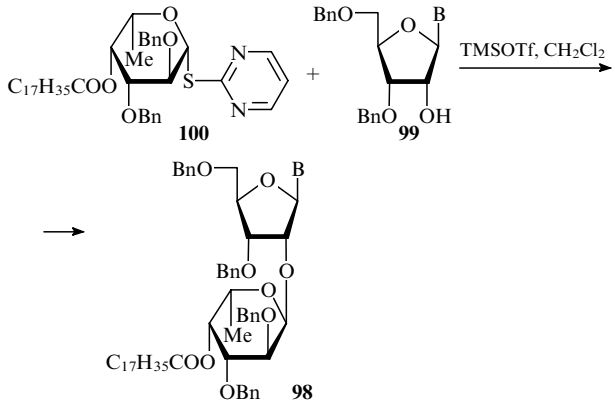
Im is imidazolyl; TBS is *tert*-butyldimethylsilyl.

The synthesis of the shimofuridin analogues **29** also included the formation of the O-glycosidic bond. The coupling of the phenyl 1-thioglycoside **95a** with a selectively protected inosine derivative **96a** in the presence of *N*-iodosuccinimide (NIS) and TfOH gave the product **97a** in a moderate yield of 37%.[155] If the heterocyclic base did not contain a protective group, no desired disaccharide nucleoside was formed. This can be attributed to the glycosylation at the O(6) of hypoxanthine, which was earlier observed by Lichtenthaler *et al.*[124, 126] The use of L-fucopyranose dibutyl phosphate **95b** as a glycosyl donor has been described; its reaction with the pivaloyl derivative **96b** in the presence of TMSOTf made it possible to increase the yield of the disaccharide **97b** to 53%.[156]



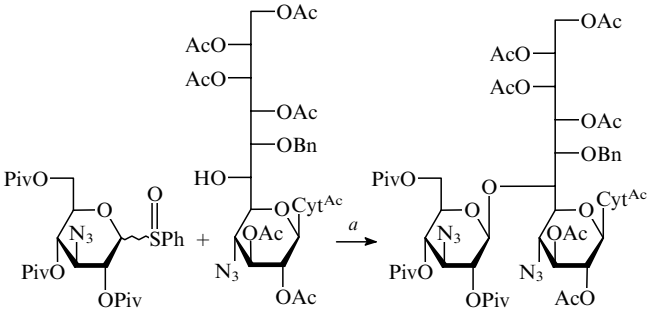
R^1 = α-SPh, R^2 = R^3 = Bn (**a**);
R^1 = α- or β-OP(O)$(OBu)_2$, R^2 = Ac, R^3 = Piv (**b**);
(*a*) NIS, TfOH, CH_2Cl_2; (*b*) TMSOTf, Et_2O, DCE.

The highest (90%) yields of α-L-fucopyranosylthymidine and -uridine **98** were achieved in the glycosylation of the pyrimidine nucleosides **99** by pyrimidin-2-yl 1-thiofucopyranoside **100** in the presence of trimethylsilyl triflate.[157, 158]



B = Thy, Ura.

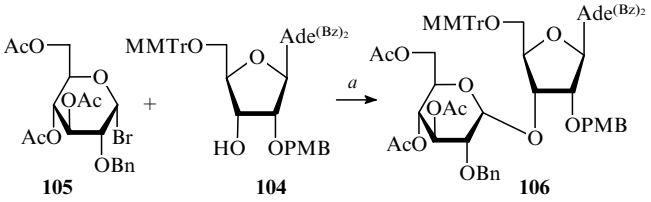
O-Glycosylation of the sterically hindered secondary hydroxy group in the nucleoside **101** was a problem in the synthesis of the antibiotic hikizimycin (**22**).[74] It was suggested to use glycosyl sulfoxides as glycosyl donors in the glycosylation of non-reactive alcohols.[121,159] Compound **103** was prepared from glycosyl sulfoxide **102** and the nucleoside **101** in a satisfactory yield (38%).[74] Deprotection and reduction of the azido groups afforded the target hikizimycin (**22**).



102 **101** **103**

(*a*) Tf_2O, PhMe.

Two different routes of the formation of disaccharide nucleosides were explored in the synthesis of the adenophostin derivatives (**27**).[160–163] The coupling of the selectively protected nucleoside **104** with the glycosyl bromide **105** in the presence of $AgClO_4$ and γ-collidine afforded the product **106** (yield 48%).[160] The use of Ag_2CO_3 as an *O*-glycosylation promoter as described earlier was ineffective.[126]

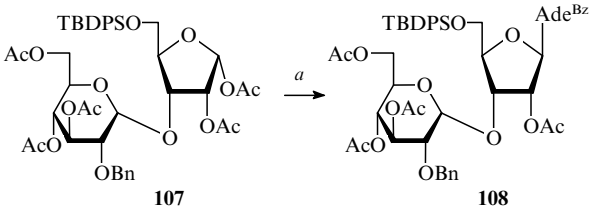


105 **104** **106**

MMTr is mono-*p*-methoxytrityl, PMB is *p*-methoxybenzyl;
(*a*) $AgClO_4$, γ-collidine, $CHCl_3$.

The synthesis of adenophostin A (**27**) starting from the disaccharide nucleoside **106** included the following steps: removal of the methoxybenzyl (oxidation by dichlorodicyanoquinone, DDQ), acid-labile monomethoxytrityl and acyl groups; *N*,*O*-monomethoxytritylation of the exocyclic amino group of adenine and primary hydroxy groups; phosphorylation, detritylation and hydrogenolysis in the presence of palladium black. The overall yield of adenophostin A was 22%.[160]

The Vorbruggen *N*-glycosylation of the bis(trimethylsilyl) derivative of N^6-benzoyladenine by the disaccharide glycosyl donor **107** (see Refs 161–163) is an alternative route to the synthesis of adenophostin **27**.[108–111] The yield of the disaccharide nucleoside **108** in the coupling step was significantly higher (71%) than in the former case; the overall yield of the product **27** was 28%.



107 **108**

(*a*) $(TMS)_2$–Ade^{Bz}, TMSOTf, DCE.

* * *

While considering the methods for the synthesis of disaccharide nucleosides, special mention should be made of the possibility of microbiological and enzymatic *O*-glycosylation. Some papers are devoted to the synthesis of *O*-hexopyranosyl derivatives of purine nucleosides[164,165] and 1-(β-D-arabinofuranosyl)cytosine[166] using various glycosidases. Thus the use of β-galactosidase and 4-nitrophenyl β-D-galactopyranoside as glycosyl donors has made it possible to synthesise *O*-galactosides of adenosine, guanosine, inosine, uridine, 2′-deoxyuridine and thymidine.[167–170] In these syntheses, the formation of 5′-O- and 3′-O-derivatives of galactopyranosyl nucleosides usually occurred. The glycosylation of thymidine and 1-(β-D-arabinofuranosyl)cytosine in the presence of glycosidases isolated from various sources using di- and polysaccharide donor substrates was studied.[171,172] The yields of disaccharide nucleosides in enzymatic glycosylation rarely exceeded 10%.

An analysis of the published data prompts a conclusion that the majority of natural disaccharide nucleosides[2] were synthesised by coupling of a protected disaccharide with a heterocyclic base. This synthetic route is more common, since *O*-glycosylation of nucleosides is sometimes concomitant with *N*-glycosylation of the heterocyclic base and hydrolysis of the N-glycosidic bond of purine nucleosides. In some cases, protective groups cause a further decrease in the stability of the N-glycosidic bond under reaction conditions. It is noteworthy that acid hydrolysis of the O-glycosidic bond in purine disaccharide nucleosides occurs simultaneously with apurinisation, whereas the fragmentation of pyrimidine disaccharides occurs exclusively at the O-glycosidic bond and yields a nucleoside and a monosaccharide.[141] Despite the aforementioned difficulties, efficient procedures for *O*-glycosylation of nucleosides that have been developed significantly simplify and supplement the first approach to the synthesis of disaccharide nucleosides.

In conclusion, it may be noted that several reliable and reproducible *N*- and *O*-glycosylation procedures are known, which enable successful synthesis of natural disaccharide nucleosides and their analogues.

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