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Synthesis of 2′-*O*-alkylnucleosides

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Abstract. The published data on the synthesis of 2′-*O*-alkylnucleosides are reviewed. The known methods are systematised and their advantages and disadvantages are discussed. The bibliography includes 174 references.

I. Introduction

Synthesis of modified oligonucleotides is a popular trend in the modern organic chemistry of nucleic acids. The introduction of modified fragments into the oligonucleotide chain allows one to solve diverse problems, such as the enhanced transport of DNA fragments through cell membranes, the increase in their resistance against nucleases and the increase in thermodynamic stabilities of various NA duplexes. The introduction of chemically reactive groups into oligonucleotides allows the preparation of various conjugates with peptides, dyes, *etc*. Post-synthetic random modifications or modifications at the 3′- and/or 5′-ends of oligonucleotides are possible in principle, but direct incorporation of a modified unit into a predetermined position of an oligomeric chain in the course of oligonucleotide synthesis is the most versatile approach.

This review surveys the synthesis of modified nucleosides containing alkoxy groups at positions 2′ of the carbohydrate moieties. These compounds are used as precursors of monomeric components in oligonucleotide synthesis. Preparation of now commercially available building blocks for the oligoribonucleotide synthesis, of conformationally locked nucleic acids (LNA) (their synthesis is not confined to the alkylation of the 2′-hydroxy group) and 2′-*O*-(β-D-ribofuranosyl)nucleosides (for reviews see Refs 1 and 2) are not considered here.

Modified oligonucleotides containing an alkoxy group at the 2′-position of the carbohydrate moiety cannot be prepared by modification of natural oligonucleotides. The only possible approach is the synthesis of a modified monomer and its incorporation into the oligonucleotide chain in the course of automated oligonucleotide synthesis.

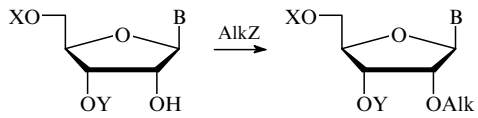
2′-*O*-Methyladenosine was isolated for the first time from a natural source in 1959;[3] approaches to the synthesis of this class of compounds were developed soon thereafter (in 1965 – 1966).[4 – 6]

In the past decade, modified oligonucleotides containing an alkoxy group in position 2′ of the carbohydrate fragment are actively employed as antisense probes. The results of these studies are summarised in several books[7 – 9] and reviews.[10 – 13] It was demonstrated that 2′-*O*-methyloligonucleotides form duplexes with RNA which are kinetically and thermodynamically more stable and simultaneously more sensitive to mismatches than non-modified oligoribonucleotides,[14] which makes them indispensable tools in antisense biotechnology. Besides, 2′-alkyloligonucleotides are used in the design of ribozymes[15] which are more resistant to nuclease digestion than their natural counterparts, and in studies of the processing of genetic material.[16 – 19] 2′-*O*-(3-Aminopropyl)-oligonucleotides are especially resistant against 3′-exonucleases due to the interaction of the amino group with the metal-binding domain. This was demonstrated by X-ray diffraction analysis using the Klenow fragment from *E. coli* as an example.[20] 2′-*O*-(2-Aminoethyl)oligonucleotides are the most potent inhibitors of the *in vivo* gene expression according to the antigenic mechanism, *viz*., the formation of a triplex with genomic DNA, in comparison with other known modified analogues of nucleic acids.[21,22] Oligonucleotides containing chemically reactive groups in position 2′ of the carbohydrate fragment are used for conjugation with various compounds, *e.g*., fluorophores[23] (these conjugates are used for structural analyses of various RNAs), electrochemically active compounds[24] (design of DNA analysers), metal ion complexes[25] (chemical nucleases), DNA and RNA duplexes with covalently linked chains.[26,27]

The alkylation of the 2′-hydroxy group of nucleosides usually follows a nucleophilic substitution mechanism.

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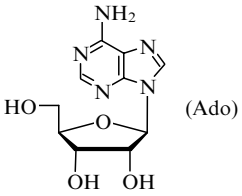
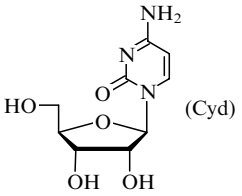
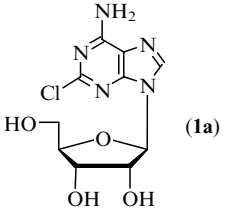
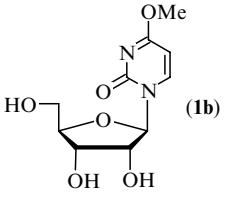
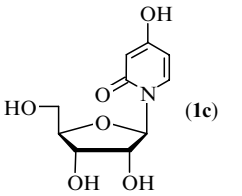
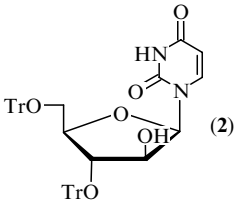


X, Y are H or protective groups; B is a heterocyclic base; AlkZ is an alkylating reagent.

Blocking of reaction centres of heterocyclic bases, 3′- and 5′-hydroxy groups to avoid side reactions is the central problem in the synthesis of 2′-*O*-alkylnucleosides. The choice of suitable protective groups still remains a topical problem. The majority of currently known alkylation procedures imply the use of strong organic or inorganic bases, therefore classical protective groups are not always compatible with the reaction conditions.

The review considers recent advances in the synthesis of 2′-*O*-alkylnucleosides and historically significant methodologies. Such a choice of literature sources is determined by the fact that the main approaches to the synthesis of 2′-*O*-alkylnucleosides have been known since the 1970's – 1980's. However, modified 2′-*O*-alkyloligonucleotides came into use only in the early 1990's. Studies in this field have led to the development of novel methods for the synthesis of 2′-*O*-alkylnucleoside and optimisation of the existing methods.

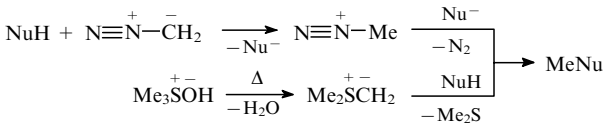
Table 1. Alkylation of the 2′-hydroxy group of nucleosides with diazomethane in the H_2O – DME system.

Nucleoside	Yield (%)	Ref.
 (Ado)	40	4
	27	28
	38	29
	20	30
	22 [a]	33
 (Cyd)	25	28
 (**1a**)	30 – 40	32
 (**1b**)	37	31
 (**1c**)	0	34
 (**2**)	90 [b]	35

Note. Hereinafter, Tr = Ph_3C. [a] The alkylation by diazoethane gave a mixture of ethyl and methyl derivatives (~ 1 : 1); [b] the yield of 2′-*O*,3-*N*-dimethyl-3′,5′-di-*O*-tritylarabinouridine is indicated.

II. Alkylation of nucleosides with diazomethane and trimethylsulfonium hydroxide

The alkylation procedures of nucleosides with diazomethane and trimethylsulfonium hydroxide have been proposed at different times, but here we consider them together because these reactions follow similar mechanisms. In addition, both these methods have only a historical significance at present.

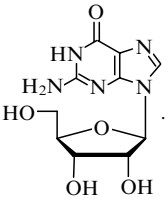


Broom and Robins [4] have synthesised 2′-*O*-methyladenosine by treatment of adenosine with diazomethane in aqueous dimethoxyethane (Table 1) and these results were reproduced by different authors.[28 – 35] Later, diazomethane was used for the alkylation of other nucleosides (Cyd, **1a** – **c**, see Table 1). The reaction with diazoethane proceeds in a similar way,[33] but a mixture of methyl and ethyl derivatives is formed in a ~ 1 : 1 ratio. The formation of methyl ethers is rationalised by solvent participation. Alkylation of 3′,5′-di-*O*-tritylarabinouridine (**2**) under similar conditions led to the dialkylation product, *viz*., 2′-*O*,3-dimethyl-3′,5′-di-*O*-tritylarabinouridine.[35] With 3-deazauridine (**1c**), the reaction proceeded selectively with the heterocyclic base (see Table 1).[34]

The use of trimethylsulfonium hydroxide as an alkylating reagent in the synthesis of 2′-*O*-methylnucleosides was proposed and developed by Kinoshita *et al*. in 1978 – 1980 [36 – 38] (Table 2).

Table 2. Alkylation of the 2′-hydroxy group of nucleosides with oxonium derivatives and trimethyl phosphate in DMF at 110 °C.

Nucleoside	Alkylating reagent	Yield (%)	Ref.
Cyd	$Me_3\overset{+}{S}\,OH^-$	30	36, 37
Cyd	$Me_3\overset{+}{S}\,OH^-$	28	38
Ado	$Me_3\overset{+}{S}\,OH^-$	20	38
Guo	$Me_3\overset{+}{S}\,OH^-$	11	38
Ado	$Me_3PhN^+\,OH^-$	6	39
Cyd	$Me_3PhN^+\,OH^-$	26	39
Ado	$(MeO)_3PO$	22	40
Cyd	$(MeO)_3PO$	28	40
Ado	$Me_3\overset{+}{S}\,OH^-$ (see [a])	5 – 10	41
Cyd	$Me_3\overset{+}{S}\,OH^-$ (see [a])	5 – 10	41

Note. Guo =  .

[a] The reaction was carried out in DMSO with $B(OH)_3$ addition at 110 °C.

This alkylating reagent is less reactive than diazomethane; therefore, the reaction is carried out in DMF at 110 °C. The alkylation with trimethylanilinium hydroxide [39] and trimethyl phosphate [40] gave similar results. An attempt to use trimethylsulfonium iodide [38] resulted in compounds in which only the heterocyclic base was alkylated. The addition of boric acid to trimethylsulfonium hydroxide also led to the alkylation of heterocyclic bases.[41]

The main disadvantage of both methods is their low selectivity, since the alkylation products of both the sugar residue and the heterocyclic base are formed. These possess similar chromatographic mobilities, which impedes separation of the reaction products. The yields of the target products are usually low.

III. Alkylation of nucleosides with methyl iodide in the presence of silver(I) oxide

Historically, the alkylation of nucleosides with methyl iodide in the presence of Ag_2O was the first method for the preparation of 2′-*O*-methylnucleosides. Furukawa *et al.*[6] performed the alkylation of 3′,5′-di-*O*-trityluridine (**3a**) devoid of protective groups in the heterocyclic base; therefore, the reaction partly involved the uracil residue (Table 3). This method was not further used until the early 1980's when this was rekindled for the alkylation of nucleosides with 3′- and 5′-hydroxy groups blocked by the 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl protective group (TIPDS, the Markiewicz protection) and the protected heterocyclic base (Table 3, compounds **3b**–**f**, **4a**,**b**, **5**).

Beigelman *et al.*[51] made an attempt to synthesise 2′-*O*-methylcytidine from 5′-*O*-dimethoxytrityl-3′-*O*-*tert*-butyldimethylsilyl-N^4-isobutyrylcytidine (**4c**), which is an intermediate product in the preparation of building blocks for the oligoribonucleotide synthesis. This attempt was unsuccessful, since the alkylation was accompanied by the 3′→2′ migration and partial removal of the silyl protective group; 2′,3′-di-*O*-methylcytidine and 3′-*O*-methylcytidine were formed as side products. Hodge and Sinha [52] have synthesised 2′-O-methyl, -ethyl, -allyl, -propyl and -pentyl nucleoside derivatives **4d**,**f** (the reaction was carried out in the presence of 0.1–0.2 equiv. of pyridine). The yields of 2′-*O*-alkylnucleosides decreased with an increase in the size of the alkyl group but remained at a sufficiently high level. Special mention should be made of the fact that this approach is suitable for large-scale (tens of grams) syntheses (see Table 3, compound **4d**).[52]

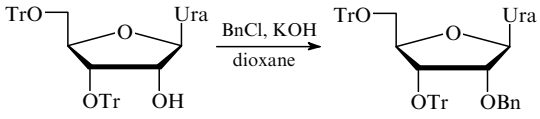
Today, the alkylation with methyl iodide in the presence of silver(I) oxide has proved to be a fairly efficient approach to the synthesis of pyrimidine 2′-*O*-alkylnucleosides. At the same time, it is seldom used for the synthesis of purine derivatives. It is of note that the methylation of partially protected 2-thiouridine (**6**) [53] gave a complex mixture, which may be due to the interaction of Ag_2O with the thioketone group and subsequent alkylation of the heterocyclic base.

IV. Alkylation of nucleosides in the presence of bases

1. The use of alkali metal hydroxides

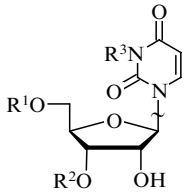
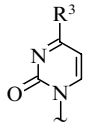
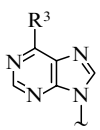
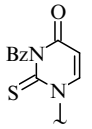
There are two approaches to the alkylation of nucleosides in the presence of alkali metal hydroxides: the reaction may be carried out in non-aqueous or in aqueous media.

In the mid-1960's, Reese *et al.*[5] performed the alkylation of 3′,5′-di-*O*-trityluridine (**3a**) with benzyl chloride in the presence of potassium hydroxide in dry dioxane, which resulted in protected 2′-*O*-benzyluridine (**7**) (Table 4).



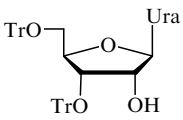
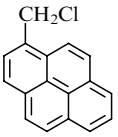
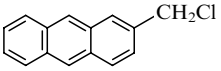
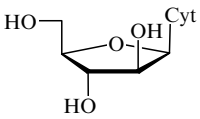
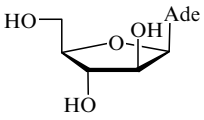
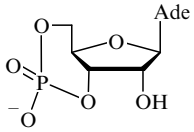
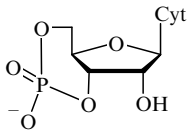
3a **7**

Table 3. Alkylation of the 2′-hydroxy group of nucleosides with methyl iodide in the presence of Ag_2O.

Nucleoside	R^1	R^2	R^3	Compound No.	Nucleoside : MeI : Ag_2O	Reaction conditions	Yield (%)	Ref.
	Tr	Tr	H	**3a**	1 : 15 : 5	Me_2CO, 20 °C, 72 h	50	6
	TIPDS		$Cl_3CCMe_2OC(O)$	**3b**	1 : 100 : 5	40 °C, 7 h	93	42
	TIPDS		Bz	**3c**	1 : 15 : 10	Me_2CO, 20 °C	86	43
	TIPDS		Bz	**3c**	1 : 26 : 2.9	PhH, 40 °C, 16 h	85	44, 45
	TIPDS		Bz	**3c**	1 : 26 : 2.9	PhH, 40 °C, 16 h	40	46
	TIPDS		2,4-$(NO_2)_2C_6H_3S$	**3d**	1 : 10 : 8	Me_2CO, 20 °C, 16 h	94	47
	TIPDS		2-$NO_2C_6H_4S$	**3e**	1 : 10 : 8	Me_2CO, 20 °C, 16 h	92	47
	TIPDS		4-$MeOC_6H_4C(O)$	**3f**	1 : 7 : 8	40 °C, 5 h	100	48
	TIPDS		2-$NO_2C_6H_4O$	**4a**	1 : 20 : 10	Me_2CO, 20 °C, 72 h	81	49
	TIPDS		BzNH	**4b**	1 : 26 : 2.9	PhH, 40 °C, 4 h	69	44, 45
	TIPDS		BzNH	**4b**	1 : 20 : 3	PhH, 20 °C, 2 h	98	50
	DMTr	TBDMS	Pr^iCONH	**4c**	–	–	26	51
	DMTr	H	BzNH	**4d**	1 : 25 : (1.5–2.5)	PhMe, 0 °C, 5–17 h	see [a]	52
	DMTr	H	4-$Bu^tC_6H_4OCH_2C(O)NH$	**4f**	1 : 25 : (1.5–2.5)	PhMe, 0 °C, 5–17 h	see [a]	52
	TIPDS		Cl	**5**	1 : 26 : 2.9	PhH, 40 °C, 1 h	66	44, 45
	TIPDS		Cl	**5**	1 : 26 : 2.9	PhH, 40 °C, 4 h	40	46
	TIPDS		–	**6**	–	–	see [b]	53

Note. Hereinafter, DMTr = $(4\text{-}MeOC_6H_4)_2PhC$, TBDMS = Bu^tMe_2Si. [a] The yields of the alkylation products with methyl, ethyl, propyl, allyl and pentyl iodides are 93%, 83%, 75%, 79% and 50%, respectively; [b] the product was not isolated from the reaction mixture.

Table 4. Alkylation of the 2′-hydroxy group of nucleosides in the presence of alkali metal hydroxides.

Nucleoside	Compound No.	Alkylating reagent	Nucleoside : alkylating reagent : sodium hydroxide	Reaction conditions	Yield (%)	Ref.
	**3a**	BnCl	1 : 1.2 : 5	dioxane, Δ	60	5
			1 : 1.1 : 10	benzene – dioxane, Δ, 2 h	65 [a]	54
			1 : 1.1 : 10	benzene – dioxane, Δ, 2 h	48 [a]	55
Cyd		$(MeO)_2SO_2$	1 : 30 : 100	H_2O, 20 °C, 5 h	22	56
		$(MeO)_2SO_2$	1 : 10 : 50	H_2O, 20 °C, 5 h	12	57
Ado		$(MeO)_2SO_2$	1 : 6 : 30	H_2O – DME, 20 °C, 7 h	25	58
	**8**	$(MeO)_2SO_2$	1 : 30 : 100	H_2O, 20 °C, 5 h	5	59
		$(MeO)_2SO_2$	1 : 2 : 45	H_2O, 20 °C, 10 h	8 [b]	60
		$(EtO)_2SO_2$	1 : 2 : 45	H_2O, 20 °C, 10 h	6 [b]	60
		$(MeO)_2SO_2$	1 : 6 : 30	H_2O – DME, 20 °C, 7 h	20 [b]	61
	**9**	$(MeO)_2SO_2$	1 : 6 : 30	H_2O – DME, 20 °C, 7 h	10	62
	**10a**	MeI	1 : 10 : 3	H_2O – DMF, 20 °C, 3 h	50	63
		EtI	1 : 10 : 3	H_2O – DMF, 20 °C, 3 h	40	63
	**10b**	MeI	1 : 10 : 3	H_2O – DMF, 20 °C, 3 h	62	63
		EtI	1 : 10 : 3	H_2O – DMF, 20 °C, 3 h	30	63

Note: Hereinafter, Ura is the uracil residue, Cyt is the cytosine residue, Ade is the adenine residue. [a] The yield over two steps (alkylation and detritylation) is indicated; [b] the yield over two steps (protection of 5′- and 3′-hydroxy groups and alkylation) is indicated.

The advantage of this method is that the heterocyclic base is not alkylated; however, the yields of the steps of the synthesis of the starting compound (3′,5′-di-*O*-trityluridine) do not exceed 30% – 45%. Later, in the 1990's, the alkylation was performed with more complex alkyl halides.[54, 55]

In the early 1970's, it was proposed [56] to use dialkyl sulfates as alkylating reagents in the presence of alkali metal hydroxides in aqueous media (see Table 4, compounds **8**, **9**). It was shown [56] that at pH > 13, no alkylation of the heterocyclic base occurs. The alkylation of adenosine and cytidine 3′,5′-cyclophosphates (**10a**,**b**) with alkyl halides in water – organic media has been described.[63] No side alkylation products at the 5′- and 3′-hydroxy groups were formed, which resulted in higher yields and facilitated the chromatographic isolation of the reaction products.

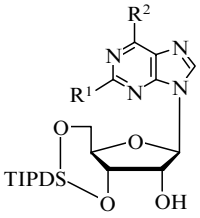
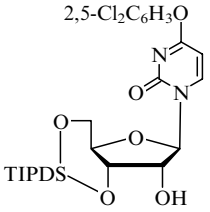
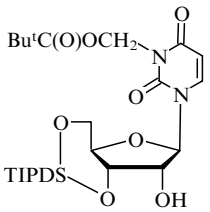
As can be seen from Table 4, the alkylation of the nucleoside **3a** in non-aqueous media gives fairly good yields even in the case of rather complex alkyl halides, but drastic reaction conditions significantly restrict the use of this method. Alkylation by dialkyl sulfates and alkyl iodides in aqueous and water – organic media proceeds as a rule with low yields and is of low practical value.

2. The use of organic bases

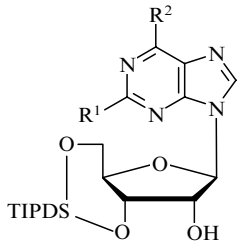
Alkylation of nucleosides in the presence of organic bases was first proposed by Sproat *et al.*[64 – 70] (Table 5). The alkylation of partially protected nucleosides with alkyl halides was carried out in the presence of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BDDDP) (see Ref. 71). This reaction and subsequent extraction are not accompanied by the formation of hydroxides; therefore, the protective groups of heterocyclic bases are preserved. It is of note that in addition to the known groups, *e.g.*, compounds **11a**,**b**,**d**, **12**, novel protective groups were introduced, *viz.*, the pivaloyloxymethyl group (compound **13**) for the protection of the N^3-position of uracil and the *tert*-butyldiphenylsilyl group (compound **11c**) for the blocking of the O^6-position of guanine (see Table 5). The pivaloyloxymethyl protective group is more stable than the conventional benzoyl group. In addition, the N^3-pivaloyloxymethyl derivative **13** is obtained in a higher yield than the N^3-benzoyl derivative. The use of the *tert*-butyldiphenylsilyl protective group made it possible to increase the total yield and to reduce the number of steps in the synthesis of 2′-*O*-propargylguanosine, since the 3′- and 5′-hydroxy groups and the O^6 atom of the heterocycle are deprotected simultaneously under the action of tetrabutylammonium fluoride.[64]

The alkylation of compound **14a** was accompanied by a side reaction at the exocyclic amino group; compound **14b** did not undergo alkylation under these conditions.[64]

Table 5. Alkylation of the 2′-hydroxy group of nucleosides in the presence of BDDDP.

Nucleoside	R^1	R^2	Compound No.	Alkylating reagent	Nucleoside : alkyl halide : BDDDP	Reaction time /h	Yield (%)	Ref.
	H	2,5-$Cl_2C_6H_3O$	**11a**	MeI	1 : 1.2 : 1.2	6	63	65
	H	2,5-$Cl_2C_6H_3O$	**11a**	MeI	1 : 1.2 : 1.2	6	–	66
	H	2,5-$Cl_2C_6H_3O$	**11a**	$HC\equiv CCH_2Br$	1 : 1.25 : 1.2	2	57	68
	H	2,5-$Cl_2C_6H_3O$	**11a**	$MeCH=CHCH_2Br$	1 : 1.2 : 1.2	6	70 – 75 [a]	68
	Cl	2,5-$Cl_2C_6H_3O$	**11b**	MeI	1 : 1.2 : 1.2	6	68	65
	Cl	2,5-$Cl_2C_6H_3O$	**11b**	MeI	1 : 1.2 : 1.2	6	70	66
	Cl	2,5-$Cl_2C_6H_3O$	**11b**	$MeCH=CHCH_2Br$	1 : 1.2 : 1.2	6	70 – 75 [a]	66
	NH_2	TBDPS – O	**11c**	MeI	1 : 2.5 : 5	3	48	67
	NH_2	TBDPS – O	**11c**	MeI	1 : 2 : 2	3	49	64
	NH_2	TBDPS – O	**11c**	$CH_2=CHCH_2Br$	1 : 2.5 : 5	3	51	67
	NH_2	TBDPS – O	**11c**	$CH_2=CHCH_2Br$	1 : 2 : 2	3	51	64
	NH_2	TBDPS – O	**11c**	$HC\equiv CCH_2Br$	1 : 2 : 2	3	51	64
	NH_2	TBDPS – O	**11c**	$N\equiv CCH_2Br$	1 : 2 : 2	3	47	64
	NH_2	TBDPS – O	**11c**	EtO_2CCH_2Br	1 : 2 : 2	3	48	64
	Cl	2-$NO_2C_6H_4O$	**11d**	MeI	1 : 2 : 2	3	61	64
	Cl	2-$NO_2C_6H_4O$	**11d**	$CH_2=CHCH_2Br$	1 : 2 : 2	3	51	64
	Cl	2-$NO_2C_6H_4O$	**11d**	$HC\equiv CCH_2Br$	1 : 2 : 2	3	71	64
	Cl	2-$NO_2C_6H_4O$	**11d**	$N\equiv CCH_2Br$	1 : 2 : 2	3	70	64
	Cl	2-$NO_2C_6H_4O$	**11d**	$N\equiv CCH_2Br$	1 : 2 : 2	3	61	69
	Cl	2-$NO_2C_6H_4O$	**11d**	EtO_2CCH_2Br	1 : 2 : 2	3	62	64
			**12**	MeI	1 : 1.2 : 1.2	6	–	66
			12	$HC\equiv CCH_2Br$	1 : 1.25 : 1.2	2	61	68
			12	$N\equiv CCH_2Br$	1 : 2 : 2	3	64	69
			12	EtO_2CCH_2Br	1 : 2 : 1.5	1	90	70
			**13**	$HC\equiv CCH_2Br$	1 : 1.25 : 1.2	2	48	68
			13	$N\equiv CCH_2Br$	1 : 2 : 2	3	65	69

Note. The yield of compound **11c** is indicated over two steps (alkylation and desilylation). Hereinafter, TBDPS is Bu^tPh_2Si; [a] the yields over two steps (alkylation and reduction of the crotyl residue to the butyl residue) are indicated.



14a,**b**

$R^1 = NH_2$, $R^2 = Ph_2NCO_2$ (**a**); $R^1 = Pr^iCONH$, $R^2 = Ph_2NCO_2$ (**b**).

It was also shown [64] that the introduction of the carbamoyl protective group at the exocyclic N^2 atom of guanosine decelerates the alkylation reaction and strongly decreases the yields.

Nearly all the works from Sproat's laboratory are methodologically flawless: as a rule, all reactions proceed with high yields and result in the formation of single products. The syntheses are multistep, but the total yields are rather high. The main disadvantage of this method is the high cost of BDDDP; therefore, the preparation of compounds in gram quantities using this method is hardly possible. These works are also interesting with respect to the application of novel protective groups for the heterocyclic bases.

3. The use of alkali metal hydrides

With alkali metal hydrides as the bases, the alkylation may be carried out with both the unprotected and the partially protected nucleoside. In the former case, the selectivity of the reaction involving the 2′-hydroxy group is due to its higher acidity in comparison with the 3′- and particularly the 5′-hydroxy group.[72] Nevertheless, this is accompanied by the formation of side products including the 3′-isomer with similar chromatographic mobilities; therefore, protected adenosine derivatives are sometimes used (Table 6). In the case of other (especially, pyrimidine) nucleosides, the alkylation partly involves the heterocyclic base. The use of alkali metal hydrides as the bases demands careful selection of protective groups, since some of them are unstable under the reaction conditions. In addition, post-synthetic workup results in the formation of alkali metal hydroxides, which precludes the application of certain standard protective groups. Nevertheless, at present this approach is one of the most popular ones.

The method proposed by Robins *et al.*[32] back in 1966 and recently employed by Yano *et al.*[73] in which 2-amino-6-chloro-

Table 6. Alkylation of the 2′-hydroxy group of nucleosides in the presence of sodium hydride.

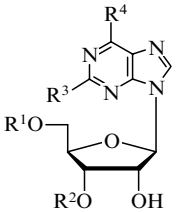
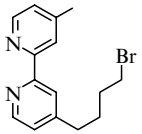
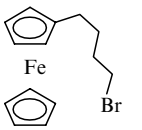
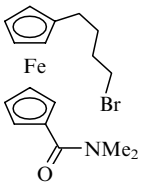
Nucleoside	R^1	R^2	R^3	R^4	Alkylating reagent [a]	Nucleoside : alkylating reagent : sodium hydride	Reaction conditions	Yield (%)	Ref.
	H	H	H	NH_2	MeI	1 : 1.15 : 0.75	DMF, 0 °C, 4 h	42	73
	H	H	H	NH_2	MeI	1 : 1.03 : 1.2	DMF, 0 °C, 3.5 h	23	74
	H	H	H	NH_2	MeI	1 : 1.1 : 1.6	DMF, 0 to 20 °C, 10 h	25 [b]	75
	H	H	H	NH_2	EtI	1 : 21 : 1	DMF, 0 to 20 °C, 10 h	3.5 [b]	75
	H	H	H	NH_2	AllBr	–	–	–	76
	H	H	H	NH_2	AllBr	1 : 1.1 : 1	DMF, 20 °C, 18 h	66 [c]	77
	H	H	H	NH_2	EtO_2CCH_2Br	–	–	–	78
	H	H	H	NH_2	EtO_2CCH_2Br	–	DMF	22 [d]	79
	H	H	H	NH_2	$PhthN(CH_2)_3Br$	1 : 1.15 : 1.5	DMF, 30 °C, 17 h	17	80
	H	H	H	NH_2	$PhthN(CH_2)_5Br$	–	DMF, 0 – 5 °C	21 [b]	81
	H	H	H	NH_2	$PhthN(CH_2)_{2-4}Br$	–	DMF	–	82
	H	H	H	NH_2	$Me(CH_2)_8Br$	–	DMF	–	82
	H	H	H	NH_2	$Im(CH_2)_3Br$	–	DMF	–	82
	H	H	H	NH_2	$TsS(CH_2)_6Br$	–	DMF	23	83, 84
	H	H	H	NH_2	$Ph(CH_2)_2OTs$	1 : 1 : 1.2	DMF, 0 °C, 3 h; 60 °C, 16 h	15	85
	H	H	H	NH_2		1 : 1.2 : 1.3	DMF, −5 °C, 24 h	18	86
	H	H	H	NH_2		1 : 1.1 : 0.5	DMF, 20 °C, 18 h	45	87
	H	H	H	NH_2		1 : 0.9 : 0.5	DMF, 35 °C, 48 h	30	88
	H	H	NH_2	NH_2	AllBr	1 : 1.1 : 1	DMF, 20 °C, 18 h	77 [c]	77
	H	H	NH_2	NH_2	$BnO(CH_2)_nBr$ (n = 2, 3)	–	DMF	48, 50	89
	H	H	NH_2	NH_2	$PhthN(CH_2)_3Br$	1 : 1.15 : 1.5	DMF, 30 °C, 17 h	–	80
	H	H	NH_2	NH_2	C_4H_9Br	–	DMF, 5 h	–	90
	H	H	NH_2	NH_2	$C_7H_{15}Br$	–	DMF, 5 h	–	90
	H	H	NH_2	NH_2	$C_{10}H_{21}Br$	–	DMF, 5 h	–	90
	H	H	NH_2	NH_2	$C_{16}H_{33}Br$	–	DMF, 5 h	–	90

Table 6 (continued).

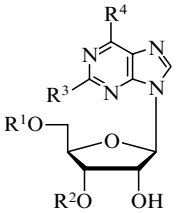
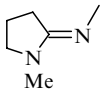
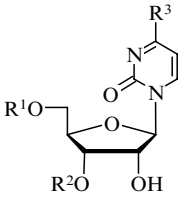
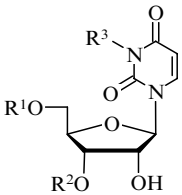
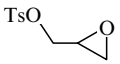
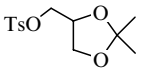
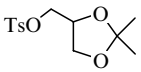
Nucleoside	R^1	R^2	R^3	R^4	Alkylating reagent [a]	Nucleoside : alkylating reagent : sodium hydride	Reaction conditions	Yield (%)	Ref.
	H	H	NH_2	NH_2	$MeO((CH_2)_2O)_n(CH_2)_2I$ (n = 0, 1, 2, 4)	–	DMF, 5 h	–	90
	H	H	NH_2	OH	AllBr	–	–	–	76
	H	H	NH_2	Cl	MeI	–	DMF, −20 °C	45 [e]	91
	H	H	NH_2	$2\text{-}NO_2C_6H_4(CH_2)_2O$	MeI	1 : 1.9 : 0.9	DMF, −45 to 20 °C, 3 h	22	75
	H	H	NH_2	$2\text{-}NO_2C_6H_4(CH_2)_2O$	EtI	1 : 8 : 0.9	DMF, −50 to −15 °C, 6 h	13	75
	Tr	H	H	OMe	BnCl	1 : 42 : 1.5	PhH – dioxane, 20 °C	41	92
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	H	OMe	$MeO(CH_2)_2Br$	1 : 1.15 : 1	THF, Δ	78	93
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$		OBn	$MeO(CH_2)_2Br$	1 : 1.15 : 1	THF, Δ	93	93
	H	H	NH_2	–	MeI	1 : 1.03 : 1.2	DMF, 0 °C, 3.5 h	–	74
	H	H	NH_2	–	MeI	1 : 1.1 : 1.6	DMF, 0 to 20 °C, 10 h	25 [b]	75
	H	H	NH_2	–	EtI	1 : 21 : 1	DMF, 0 to 20 °C, 10 h	14 [b]	75
	H	H	NH_2	–	BnCl	1 : 30 : 5	DMF, 20 °C	12	94
	TIPDS		$NHCOPr^i$	–	MeI	–	DMF	79	95
	Tr	Tr	NHBz	–	BnCl	1 : 2 : 2	PhH – dioxane, 20 °C	48	96
	DMTr	H	$NC(CH_2)_2$	–	MeI	1 : 8 : 1.6	DMF, −50 to −15 °C, 6 h	33	75
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–	MeI	1 : 1.15 : 1	THF, Δ	98	93
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–	AllBr	1 : 1.15 : 1	THF, Δ	88	93
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–	PrBr	1 : 1.15 : 1	THF, Δ	67	93
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–	Pr^iBr	1 : 1.15 : 1	THF, Δ	20	93
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–	EtO_2CCH_2Br	1 : 1.15 : 1	THF, Δ	97	93
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–		1 : 1.15 : 1	THF, Δ	72	93
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–	 *R*-isomer	1 : 1.15 : 1	THF, Δ	34	93
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–	 *S*-isomer	1 : 1.15 : 1	THF, Δ	35	93
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–	$PhthN(CH_2)_4Br$	1 : 1.15 : 1	THF, Δ	64	93
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–	$MeO(CH_2)_2Br$	1 : 1.15 : 1	THF, Δ	83	93

Table 6 (continued).

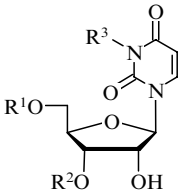
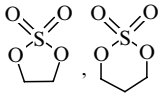
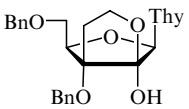
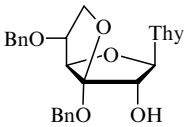
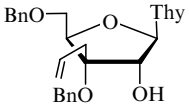
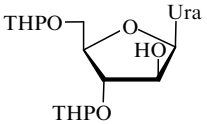
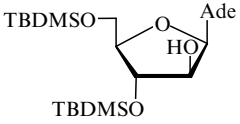
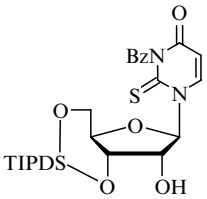
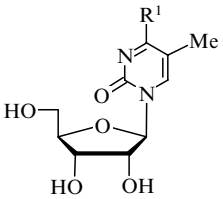
Nucleoside	R^1	R^2	R^3	R^4	Alkylating reagent [a]	Nucleoside : alkylating reagent : sodium hydride	Reaction conditions	Yield (%)	Ref.
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–	$MeO((CH_2)_2O)_n(CH_2)_2Br$ (n = 1, 2, 3)	1 : 1.15 : 1	THF, Δ	89, 76, 24	93
	$2,4\text{-}Cl_2C_6H_3CH_2$	$2,4\text{-}Cl_2C_6H_3CH_2$	$BnOCH_2$	–	$C_{10}H_{21}O((CH_2)_2O)_3(CH_2)_2Br$	1 : 1.15 : 1	THF, Δ	61	93
		TIPDS	$BnOCH_2$	–	MeI	1 : 10 : 1.2	DMF, 0 °C, 2 h	71 [f]	97
		TIPDS	$BnOCH_2$	–	EtO_2CCH_2Br	1 : 5 : 2.2	DMF, −5 °C, 1.5 h	98	98
		TIPDS	TrS	–	$Bu^tO_2CCH_2Br$	1 : 4 : 4	THF, 18 h	78	99
	H	H	$BnOCH_2$	–		–	DMF, −45 to 20 °C	63, 50	100, 101
	Tr	Tr	H	–	BnCl	1 : 20 : 10	DMF, 20 °C	33 [g]	102
	Tr	Tr	H	–	BnCl	1 : 20 : 0.9	DMF, 20 °C	60	103
	–	–	–	–	MeI	1 : 7.4 : 2	CH_2Cl_2, 36 °C, 23 h	62	104
	–	–	–	–	MeI	1 : 2.6 : 7.5	CH_2Cl_2, 20 °C, 48 h	62	105
	–	–	–	–	MeI	1 : 5 : 3	THF, 0 °C, 2 h	84	106
	–	–	–	–	AllBr	1 : 2 : 2	THF, 20 °C, 17 h	40	107, 108
	–	–	–	–	AllBr	1 : 2.5 : 2.5	THF, 20 °C, 16 h	32	107, 108

Table 6 (continued).

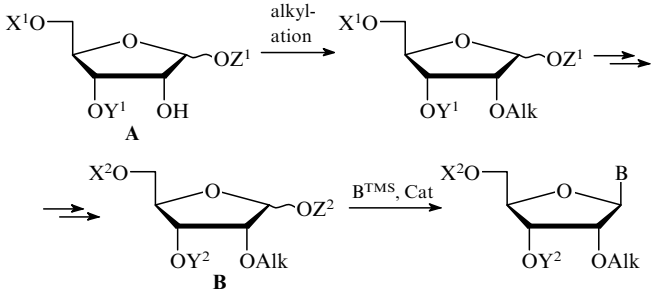
Nucleoside	R^1	R^2	R^3	R^4	Alkylating reagent [a]	Nucleoside : alkylating reagent : sodium hydride	Reaction conditions	Yield (%)	Ref.
	–	–	–	–	MeI	–	PhH	–	53
	NH_2	–	–	–	AllBr	–	–	–	76
	OH	–	–	–	AllBr	–	–	–	76

Note. [a] Abbreviations: Im, imidazolyl, Phth, phthaloyl; [b] The yield for a three-step synthesis (protection of the heterocyclic base, dimethoxytritylation, alkylation) is indicated; [c] the yield of a mixture of 2′- and 3′-isomers is indicated; [d] the yield over two steps (Markiewicz protection and alkylation) is indicated; [e] the total yield over two steps is indicated; [f] the yield over two steps (alkylation and desilylation) is indicated; [g] the yield of 2′-*O*-benzyl-3′,5′-di-*O*-trityl-3-benzyluridine is indicated.

purine riboside was used as the starting compound seems to be a very promising approach to the large-scale synthesis of 2′-*O*-alkylguanosine derivatives. The total yield of alkylation and hydrolysis to 2′-*O*-alkylguanosine is ~ 45%; the use of expensive reagents is avoided.

V. Preparation of 2′-*O*-alkylnucleosides by glycosylation of heterocyclic bases

The data on the synthesis of 2′-*O*-alkylnucleosides by glycosylation of heterocyclic bases are summarised in Tables 7 and 8. This involves two steps, *viz*., the alkylation of a partially protected carbohydrate and the glycosylation itself. In some cases, the alkylation of the 2-hydroxy group of the carbohydrate **A** is followed by a series of transformations in order to obtain the glycosyl donor **B**.



B^{TMS} is a silylated heterocyclic base;
X^1, X^2, Y^1, Y^2, Z^1, Z^2 are protective groups.

The synthesis of 2′-*O*-alkylnucleosides by glycosylation of heterocyclic bases was proposed in the early 1970's by Haines.[109] 2′-*O*-Methyluridine was synthesised starting from the partially protected β-D-ribopyranoside **15**, the total yield being as low as 5%.

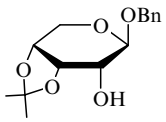
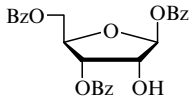
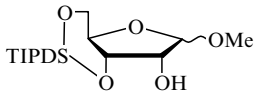
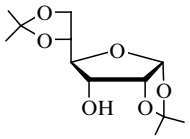
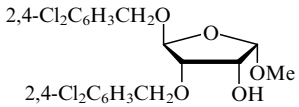
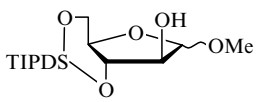
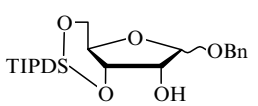
In the early 1980's, Imbach *et al.*[110, 111] performed the synthesis of pyrimidine 2′-*O*-methylnucleosides (total yield 50% – 55%) starting from the accessible 1,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**16**). Later, this approach was used by Cook *et al.*[112] for the synthesis of 2′-*O*-methyluridines containing various substituents at C^5. The use of $CF_3SO_3SiMe_3$ instead of $SnCl_4$ as a glycosylation catalyst made it possible to increase the yields of target nucleosides in some cases (see Table 8).

Keller and Haner [113] carried out the alkylation of the partially protected β-D-ribofuranoside (**17**) with *tert*-butyl bromoacetate in the presence of sodium hydroxide under conditions of phase-transfer catalysis. The desilylation with methanol and sulfuric acid was accompanied by transesterification of the *tert*-butyl ester and partial anomerisation. The glycosylation of thymine and adenine derivatives was stereoselective, the total yield was 15%.

Parmentier *et al.*[114] have succeeded in obtaining methyl 2-*O*-methyl-D-ribofuranoside in four steps without the isolation of intermediate products (yield ~ 75%). If the intermediate products had to be isolated in each step, the total yield decreased to 8%.

Cook *et al.*[78, 79] have performed the alkylation of the partially protected methyl β-D-riboside (**19**) (see Table 7) with ethyl bromoacetate. Subsequent glycosylation according to Vorbrüggen [121] gave the target nucleoside (see Table 8).

Table 7. Synthesis of protected 2-*O*-alkylcarbohydrates as precursors of 2′-*O*-alkylnucleosides.

Blocked carbohydrate	Compound No.	Alkylating reagent	Yield of the alkylation product (%)	Ref.
	**15**	CH_2N_2	88	109
	**16**	CH_2N_2, $BF_3 \cdot Et_2O$ CH_2N_2, $BF_3 \cdot Et_2O$	74 71	110, 111 112
	**17**	$BrCH_2CO_2Bu^t$, NaOH, $BnBu_3N^+Cl^-$ MeI, NaH $BrCH_2CO_2Et$, NaH, DMF, 20 °C, 3 h	67 [a] 75 74	113 114 115
	**18**	MeI, NaH 1) $HC \equiv CCH_2Br$, NaH; 2) $B_{10}H_{14}$	80 55	42 116
	**19**	$BrCH_2CO_2Et$, NaH, DMF	95	78, 79
	**20**	MeI, BDDDP MeI, NaH	42 [b] 96 [a]	117, 118 117, 118
	**21**	MeI, NaH $CH_2=CHCH_2OC(O)Cl$, DMAP, $Pd(OAc)_2$, Ph_3P	70 87	119 119

[a] The yield for the alkylation of the β-anomer is indicated; [b] the yield for the alkylation of the α-anomer is indicated.

Table 8. Glycosylation of heterocyclic bases with 2-*O*-alkylcarbohydrates.

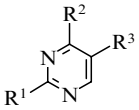
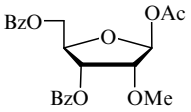
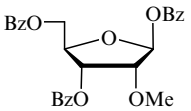
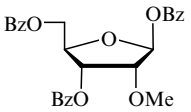
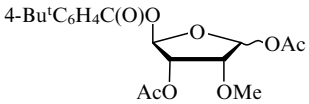
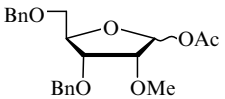
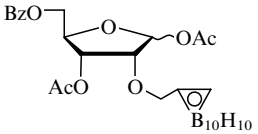
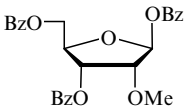
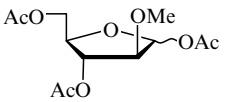
Heterocyclic base	R^1	R^2	R^3	Glycosyl donor	Reaction conditions	Yield of the β-nucleoside (%) (α : β ratio)	Ref.
	OTMS	OTMS	H		$SnCl_2$, $(CH_2Cl)_2$, 20 °C, 24 h	24	109
	OTMS	OTMS	H		$SnCl_4$, 20 °C	74 70	110 111
	OTMS	OTMS	H		TMS – OTfl, MeCN, 20 °C, 0.5 h	75	112
	OTMS	OTMS	H		20 °C, 16 h	55 – 70	42
	OTMS	OTMS	H		TMS – OTfl, MeCN, 20 °C, 2 – 3 h	65 (1 : 4)	114
	OTMS	OTMS	H		TMS – OTfl, MeCN, 20 °C, 4 h	71	116
	OTMS	OTMS	Me		TMS – OTfl, MeCN, 20 °C, 0.5 h	55	112
	OTMS	OTMS	Me		TMS – OTfl, $(CH_2Cl)_2$, 20 °C, 9 days	37 (2 : 3)	117, 118

Table 8 (continued).

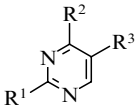
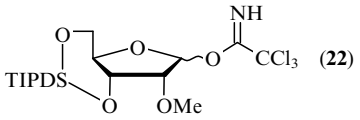
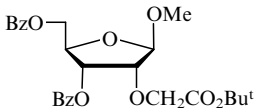
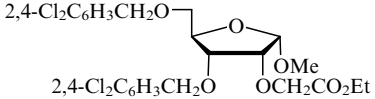
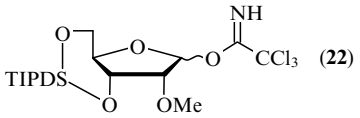
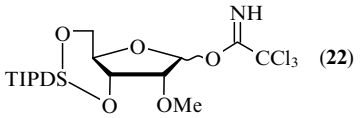
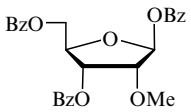
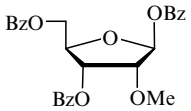
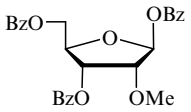
Heterocyclic base	R^1	R^2	R^3	Glycosyl donor	Reaction conditions	Yield of the β-nucleoside (%) (α : β ratio)	Ref.
	OTMS	OTMS	Me	 (**22**)	TMS – OTfl, MeCN, 20 °C, 5 min TMS – OTfl, $(CH_2Cl)_2$, 20 °C	94 93	119 121
	OTMS	OTMS	Me		TMS – OTfl, 20 °C, 30 min	79	113
	OTMS	OTMS	Me		BSA, TMS – OTfl, $(CH_2Cl)_2$, Δ	44	78, 79
	OTMS	OTMS	CH_2N_3	 (**22**)	TMS – OTfl, MeCN, 20 °C, 5 min	62	120
	OTMS	OTMS	CH_2NPhth	 (**22**)	TMS – OTfl, MeCN, 20 °C, 5 min	61	120
	OTMS	OTMS	CF_3		TMS – OTfl, MeCN, 20 °C, 30 min	62	112
	OTMS	OTMS	F		TMS – OTfl, MeCN, 20 °C, 30 min	68	112
	OTMS	OTMS	NO_2		TMS – OTfl, MeCN, 20 °C, 30 min	56	112

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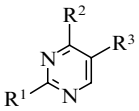
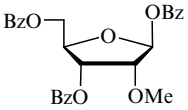
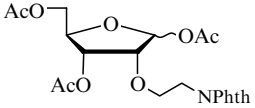
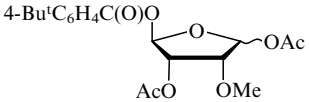
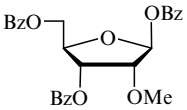
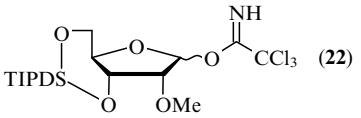
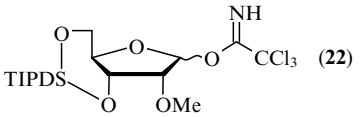
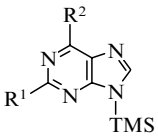
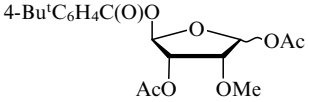
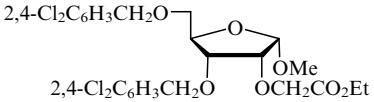
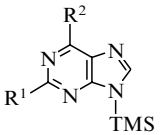
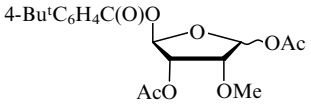
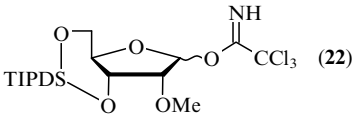
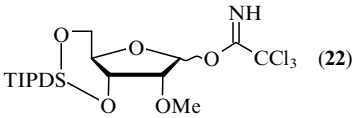
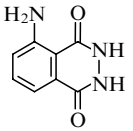
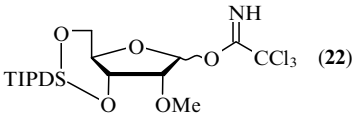
Heterocyclic base	R^1	R^2	R^3	Glycosyl donor	Reaction conditions	Yield of the β-nucleoside (%) (α : β ratio)	Ref.
	OTMS	OTMS	CN		TMS – OTfl, MeCN, 20 °C, 30 min	88	112
	OTMS	OTMS	I		TMS – OTfl, $(CH_2Cl)_2$, −20 to 0 °C, 3 h	82 (1 : 2)	115
	OTMS	NHAc	H		20 °C, 16 h	55 – 70	42
	OTMS	NHBz	H		$SnCl_4$, 20 °C	70	110, 111
	OTMS	NHBz	Me	 (**22**)	TMS – OTfl, MeCN, 20 °C, 5 min	95	119
	STMS	OTMS	Me	 (**22**)	TMS – OTfl, MeCN, 20 °C, 5 min	71	120
	H	NHBz	–		TMS – OTfl, MeCN, Δ, 3 – 5 h	55 – 70	42
	H	NHBz	–		$SnCl_4$	63	113

Table 8 (continued).

Heterocyclic base	R^1	R^2	R^3	Glycosyl donor	Reaction conditions	Yield of the β-nucleoside (%) (α : β ratio)	Ref.
	$NHC(O)CH_2OPh$	NH_2	–		TMS – OTfl, MeCN, Δ, 3 – 5 h	55 – 70	42
	$NHC(O)CH_2OPh$	H	–	 (**22**)	TMS – OTfl, MeCN, 20 °C, 5 min	77	119
	$NHC(O)Bu^t$	$4\text{-}NO_2C_6H_4(CH_2)O$	–	 (**22**)	TMS – OTfl, MeCN, 20 °C, 5 min	86	119
	–	–	–	 (**22**)	TMS – OTfl, MeCN, 20 °C, 5 min	80	119

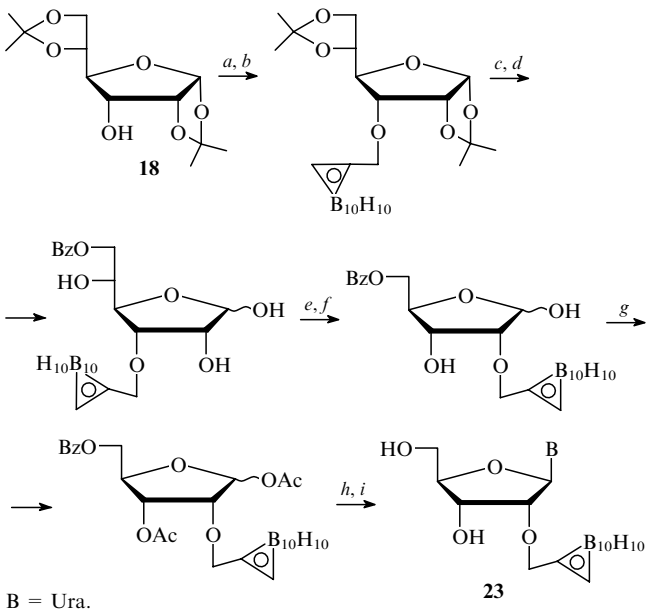
Note. Abbreviations: TMS – OTfl, trimethylsilyl trifluoromethanesulfonate; BSA, *N,O*-bis(trimethylsilyl)acetamide.

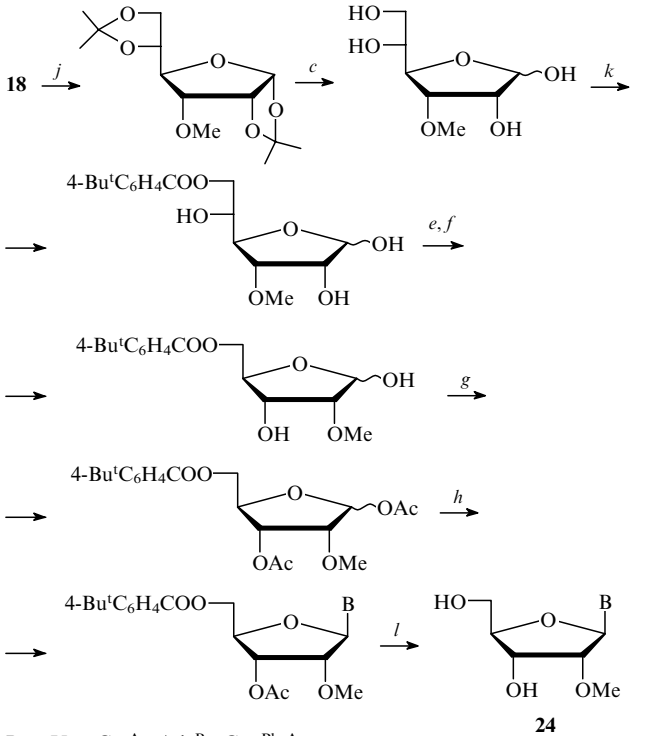
Both anomers of 1-*N*-(2-*O*-methyl-D-arabinofuranosyl)thymine were prepared from the blocked carbohydrate **20** by Gotfredsen *et al.*[117,118] (see Table 7). It should be noted that no alkylation of the α-anomer of the monosaccharide derivative occurred in the presence of sodium hydride, whereas the yield of the alkylation product in the presence of BDDDP was only 42%. In the case of the β-anomer, the reaction with sodium hydride as a base was virtually quantitative.

In 1994, Chanteloup *et al.*[119] published a paper, which described conversion of compound **21** into the *O*-trichloroacetimidate **22**. The latter served as a stereoselective and a high-yielding donor (see Table 8). The total yield was 35%–45%. Later, the glycosylation of compound **22** was studied in more detail.[120] It is known [122] that glycosylation with β-D-ribofuranose *O*-trichloroacetimidates follows the S_N2 mechanism with inversion of configuration of the C^1 atom. This suggests that the synthesis of the target β-nucleoside requires the α-anomer of the *O*-trichloroacetimidate. However, the thermodynamically and kinetically more stable β-anomer [yields 39% (α : β = 7 : 93) and 77% (α : β = 1 : 99), respectively] is predominantly formed in the presence of NaH and DBU (diazabicycloundecene). The α-anomer was predominantly formed only with K_2CO_3 as the base (total yield 71%, α : β = 93 : 7). Hence, this approach can be used for the synthesis of both α- and β-nucleosides.

An elegant synthesis of 2′-*O*-alkylnucleosides **23** and **24** (total yields 35%–40%) from the commercially available allofuranose derivative **18** has been described (Scheme 1).[51,116]

Scheme 1





(*a*) NaH, Br; (*b*) $B_{10}H_{14}$; (*c*) H^+; (*d*) BzCl; (*e*) $NaIO_4$; (*f*) Py, H_2O; (*g*) Ac_2O, Py; (*h*) B^{TMS}, TMS–OTfl; (*i*) MeONa, MeOH; (*j*) MeI, NaH; (*k*) 4-Bu^{t}C$_6$H$_4$COCl, Py; (*l*) NaOH.

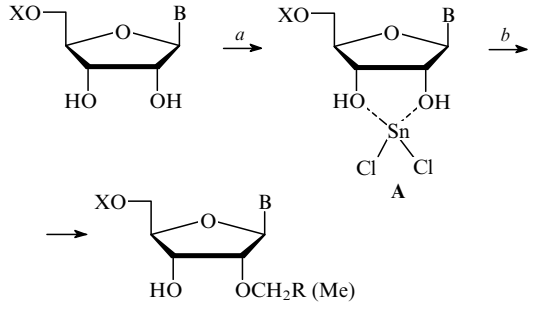
An elegant synthesis of 2′-*O*-alkylnucleosides **23** and **24** (total yields 35%–40%) from the commercially available allofuranose derivative **18** has been described (Scheme 1).[51,116]

Although glycosylation is rather tedious and is seldom used, it is appropriate for the synthesis of 2′-*O*-alkylated ribothymidine [78,79,112,113,118–120] and large-scale syntheses of modified 2′-*O*-alkylnucleosides.

Glycosylation is the limiting step. It often proceeds non-stereoselectively and yields a mixture of α- and β-anomers. In addition, it strongly depends on the nature of the substituent at the C(2′) atom and does not always give satisfactory yields of target products in the case of purine bases.

VI. Alkylation of the activated *cis*-diol group of nucleosides in the presence of transition metal compounds

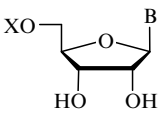
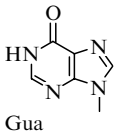
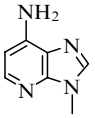
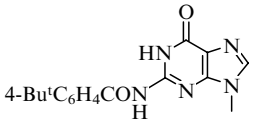
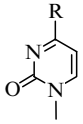
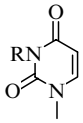
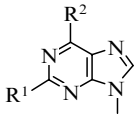
In the alkylation of the *cis*-diol group of nucleosides with alkyl halides or diazoalkanes in the presence of transition metal compounds (Tables 9–11), the transition metal is activated due to complex formation. In this case, the reaction may be carried out with nucleosides with non-protected 2′- and 3′-hydroxy groups. The main advantage of this approach is that the reaction proceeds in the absence of a base, which eliminates the necessity to protect the imino groups of the heterocyclic bases and functional groups of alkyl halides. However, the alkylation by this method yields considerable amounts of 3′-isomers which are hardly separable from the target 2′-*O*-alkylnucleosides owing to their similar chromatographic mobilities. In some cases, the isomeric mixture can be separated by crystallisation; more often, the modified nucleoside is first subjected to 5′-*O*-dimethoxytritylation and then to chromatography. The best ratio of the 2′- and 3′-isomers was achieved by alkylation of nucleosides in the presence of tin chloride [123–134] (see Table 9). In this reaction, it is the tin derivative **A** initially formed that undergoes alkylation.



(*a*) $SnCl_2$; (*b*) $RCHN_2$ or MeI.

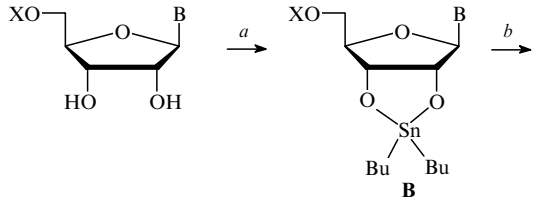
Yet another alkylation procedure in the presence of tin derivatives was proposed by Wagner *et al.*[135] The starting compound is treated consecutively with dibutyltin dichloride and dibutyltin oxide and alkyl halide with 2′,3′-*O*-dibutylstannylene nucleosides **B** as intermediates. Later, this method was used for

Table 9. Alkylation of the activated *cis*-diol group of nucleosides with diazomethane in the presence of $SnCl_2$.

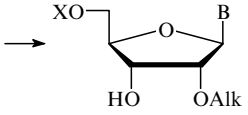
Nucleoside	X	B	Nucleoside : alkylating reagent : $SnCl_2$	Reaction conditions	Yield of the 2′-isomer (%) (2′ : 3′ ratio)	Ref.
Ado			1 : 3 : 0.18	MeOH – DME, 20 °C	38 (1.7 : 1)	123
			1 : 3 : 0.06	MeOH – DME, 20 °C	30 (1 : 2)	124
			1 : 3 : 0.02	DME, 20 °C, 8 h	27 [a]	125
Urd			1 : 3 : 0.06	MeOH – DME, 20 °C	40 (~2 : 1)	124
			1 : 3 : 0.02	DME, 20 °C, 8 h	30 [a]	125
Cyd			1 : 3 : 0.18	MeOH – DME, 20 °C	74 (2 : 1)	123
			1 : 3 : 0.06	MeOH – DME, 20 °C	35 (5 : 1)	124
			1 : 3 : 0.02	DME, 20 °C, 8 h	34 [a]	125
			1 : 3 : 0.2	MeOH – DME, 20 °C	67 (6.2 : 1) [b]	126
Guo			1 : 3 : 0.06	MeOH – DME, 20 °C	15 (1 : 1)	124
			1 : 3 : 0.02	DME, 20 °C, 8 h	16 [a]	125
1a			–	EtOH – DME, 20 °C	34 [c]	127
			1 : 3 : 0.02	DME, 20 °C, 8 h	21 [a]	125
1c			1 : 3 : 0.11	MeOH – DME, 20 °C	40 (5 : 1)	35
	H		1 : 3 : 0.02	DME, 20 °C, 8 h	21 [a]	131
	TBDPS	Gua	1 : 3 : 0.18	MeOH – DME, 50 °C	22 (1 : 2)	128
	DMTr	Ura	1 : 3 : 0.2	DMF, 50 °C, 8 h	41	129
	H		1 : 3 : 0.2	MeOH – DME, 20 °C, 8 h	20 (2 : 1)	130
	DMTr	Ade	1 : 1.6 : 0.04	DMA [d], DMSO, CH_2Cl_2, dioxane, −10 °C, 45 min	63 (2 : 1)	131
	DMTr		1 : 3 : 0.2	DMF, 50 °C, 8 h	43	129
	DMTr		R = NHBz	1 : 3 : 0.2	DMF, 50 °C, 8 h	49	129
			R = NPEOC(O)NH [e]	1 : 1.6 : 0.04	DMA, DMSO, CH_2Cl_2, dioxane, −10 °C, 45 min	87 (14 : 1)	131
	DMTr		R = H	1 : 1.6 : 0.04	DMA, DMSO, CH_2Cl_2, dioxane, −10 °C, 45 min	74 (4.3 : 1)	131
			R = Bz	1 : 1.6 : 0.04	DMA, DMSO, CH_2Cl_2, dioxane, −10 °C, 45 min	65 (2.2 : 1)	131
	H		$R^1 = NH_2$; R^2 = OEt	–	–	7	132
	H		$R^1 = R^2 = NH_2$	1 : 3 : 0.2	DMF, 50 °C, 24 h	51 (~1 : 1)	133
	DMTr		R^1 = H; R^2 = NHBz	1 : 3 : 0.2	DMF, 50 °C, 8 h	36	129
	DMTr		R^1 = NPEOC(O)NH; R^2 = ONPE	1 : 1.6 : 0.04	DMA, DMSO, CH_2Cl_2, dioxane, −10 °C, 45 min	79 (4 : 1)	131
	Tr		R^1 = H; R^2 = NHTr	1 : 1.1 : 0.25	DMF, 0 °C, 18 h	21 [f]	134

Note. [a] Alkylation with $PhCHN_2$; [b] alkylation with MeI; [c] the yield over two steps (alkylation and amination) is indicated; [d] DMA, dimethylacetamide; [e] NPE = 4-$NO_2C_6H_4(CH_2)_2$; [f] alkylation with Me_3SiCHN_2.

the synthesis of various 2′-*O*-alkylnucleosides [135–145] (see Table 10).



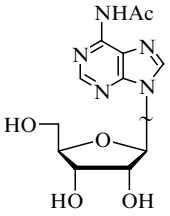
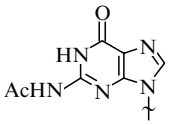
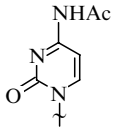
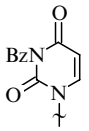
B



(*a*) Bu_2SnCl_2, Pr^i_2NEt or Bu_2SnO; (*b*) AlkHal.

The intermediate tin derivative **B** is much more stable than the derivative **A**. In addition to tin salts, other metal salts were

Table 10. Alkylation of the activated *cis*-diol group of nucleosides in the presence of equimolar amounts of dibutyltin dichloride or dibutyltin oxide.

Nucleoside	Alkylating reagent	Nucleoside : alkylating reagent	Reaction conditions	Yield of the 2′-isomer (%) (2′ : 3′ ratio)	Ref.
Urd	MeI	1 : 2	DMF, 20 °C, 18 h	35 (2 : 1)	135
	MeI	1 : 2	DMF, 20 °C, 18 h	7	136
	$H_2C=CHCH_2Br$	see [a]	DMF, Bu^n_4NBr, 20 °C	49 (1.8 : 1)	137
	$HC\equiv CCH_2Br$	1 : 2	DMF, 120 °C, 6 h	∼50 (∼1.5 : 1)	138, 139
	$PhthN(CH_2)_3Br$ [b]	–	–	16.8	80
	$PhthN(CH_2)_3Br$ [b]	–	DMF, 130 °C	14	140, 141
	$ClCH_2O(CH_2)_3Br$	1 : 1.3	$(CH_2Cl)_2$, 70 °C, 15 min	38 (1.25 : 1)	142
	BnCl	1 : 2	DMF, 100 °C, 1 h	31 (2 : 1)	135
Cyd	$PhthN(CH_2)_3Br$ [b]	–	–	16.8	80
	$ClCH_2O(CH_2)_3Br$	1 : 1.3	$(CH_2Cl)_2$, 70 °C, 15 min	51 (2.5 : 1)	142
	$ClCH_2O(CH_2)_3Br$	1 : 1.3	$(CH_2Cl)_2$, 70 °C, 15 min	60 (1.25 : 1)	142
	$ClCH_2O(CH_2)_3Br$	1 : 1.3	$(CH_2Cl)_2$, 70 °C	45 (1 : 0.4)	142
	2-$(BrCH_2)AQ$ [c]	see [d]	DMF, CsF, 20 °C, 48 h	31 (1.8 : 1)	143
	2-$(BrCH_2)AQ$ [c]	see [d]	DMF, CsF, 20 °C, 48 h	30 (1.8 : 1)	144
	2-$(BrCH_2)AQ$ [c]	1 : 2	DMF, 20 °C, 48 h	35 (1.4 : 1)	145

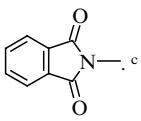
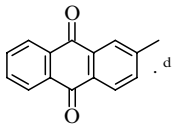
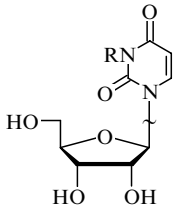
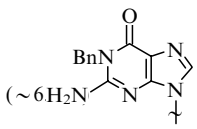
[a] The nucleoside : AllBr : Bu^n_4NBr ratio is 1 : 1.2 : 1.1; [b] PhthN = . [c] AQ = . [d] the nucleoside : 2-(bromomethyl)anthraquinone : CsF ratio is 1 : 2 : 2.5.

Table 11. Alkylation of the activated *cis*-diol group of nucleosides by trimethylsulfonium hydroxide in the presence of acetylacetonates.

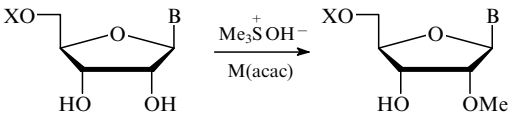
Nucleoside	M(acac)	Yield of the 2′-isomer (%) (2′ : 3′ ratio)	Ref.	Nucleoside	M(acac)	Yield of the 2′-isomer (%) (2′ : 3′ ratio)	Ref.
Cyd	Cu(acac)	60 (∼3 : 1)	148	 R = Me	Cu(acac)	18 (∼1.2 : 1)	148
	Mg(acac)	43 (10 : 1)	149	R = Me	Mg(acac)	65 (20 : 1)	149
Ado	Cu(acac)	45 (1 : 1)	148	R = Bn	Mg(acac)	62	149
	Mg(acac)	21 (∼2 : 1)	149		Ag(acac)		70
	Sr(acac)	75 (10 : 1)	91 [a]				91 [b]
Guo	Cu(acac)	18 (∼1.2 : 1)	148				
Urd	Mg(acac)	21 (20 : 1)	149				

Note. The reactions were carried out with the nucleoside : $Me_3S^+OH^-$: M(acac) ratio of 1 : 2 : 0.5 in DMF (70 °C, 1 h). [a] The nucleoside : $Me_3S^+OH^-$: Sr(acac) ratio in DMF (75 °C, 30 min) is 1 : 1.3 : 1.3; [b] the nucleoside : $Me_3S^+OH^-$: Ag(acac) ratio in DMF (70 °C, 2 h) is 1 : 1.3 : 1.3.

tested,[131, 146] but the degree of conversion in the alkylation and the ratio of the 2′- and 3′-isomers could not be increased.

It should be noted that sometimes the alkylation of the *cis*-diol group in the presence of cesium fluoride [147] affords larger amounts of the 2′-isomer. However, the addition of CsF in the alkylation of 2′,3′-*O*-dibutylstannylene-N^3-benzoyluridine slightly increased the selectivity, but the total yield of the reaction products decreased [144, 145] (see Table 10).

The methylation of nucleosides with trimethylsulfonium hydroxide in the presence of transition metal acetylacetonates (Cu, Co, Zn, *etc*.) (see Table 11) is less popular.[148, 149]



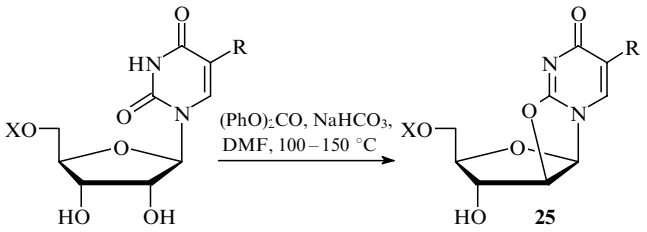
acac is the acetylacetone residue, M is the transition metal.

This approach eliminates the alkylation of heterocyclic bases (except for uracil) and provides high yields in certain cases. Later, it was shown [91] that the maximum selectivity of nucleoside alkylation is achieved in the presence of silver acetylacetonates (for protected guanosine), strontium acetylacetonate (for adenosine) and magnesium acetylacetonate (for cytidine and protected uridine).[149] Nevertheless, this procedure is hardly suitable for the introduction of other alkyl groups into nucleosides.

VII. Synthesis of pyrimidine 2′-*O*-alkylnucleosides from O^2,2′-anhydronucleosides

In addition to direct alkylation of ribonucleosides, pyrimidine 2′-*O*-alkylnucleosides are synthesised starting from O^2,2′-anhydrocyclonucleosides. This approach is attractive because the synthesis of the anhydrocycle results in both the activation of the C(2′) atom and elimination of the possibility of the reaction of the N^3 atom of the heterocyclic base.

The synthesis of the now commercially available O^2,2′-anhydrouridine and its derivatives is performed using different methods.[150, 151] Most often, this involves heating of uridine and its derivatives with diphenyl carbonate in the presence of sodium hydrogen carbonate as base. The O^2,2′-anhydrouridine derivatives **25** are easily purified by recrystallisation; the yields are ~ 90% (Table 12).



X is H or protective groups; R = H, Me.

It has been shown [152] that no alkoxylation of nucleosides with magnesium alkoxides occurs in the presence of blocked 3′-hydroxy groups, presumably due to the necessity of its involvement in the coordination of magnesium. Similar conclusions were made by Ross *et al*.[154] for the alkoxylation with trialkyl borates. It is suggested that if magnesium alkoxides are used, the 5′-hydroxy group was protected with the dimethoxytrityl group. Later,[153] the alkoxylation of anhydrouridine containing a non-protected 5′-hydroxy group with magnesium methoxide was carried out under similar conditions. If aluminium alkoxides and trialkyl borates are used, the alkoxylation at the C(2′) atom occurs with a free 5′-hydroxy group.[154, 157] Blommers *et al*.[158] did not synthesise alkoxides beforehand, but carried out a reaction with an alcohol in the presence of tetra(isopropoxy)titanium.

The alkoxylation of O^2,2′-anhydrouridine with trimethyl borate was successfully employed by other authors.[91, 159] Besides, the 2′-*O*-methylated product was obtained by the reaction of the fluorescent uridine analogue 1-(β-D-ribofuranosyl)-2,2′-anhydrobenzo[*g*]quinazoline-2,4(3*H*)-dione **26** with a twofold excess of $(MeO)_3B$ [$(MeO)_3CH$, $NaHCO_3$, MeOH].[160]

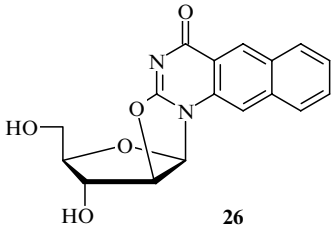
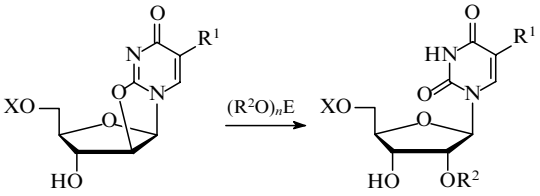


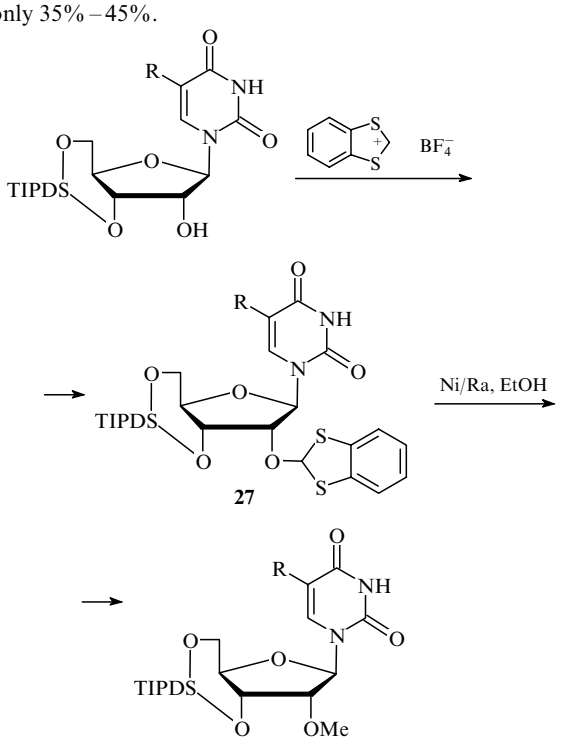
Table 12. Synthesis of pyrimidine 2′-*O*-alkylnucleosides from O^2,2′-anhydronucleosides.



R^1	X	$(R^2O)_nE$	Nucleoside : $(R^2O)_nE$ ratio	Reaction conditions	Yield (%)	Ref.
H	DMTr	$(MeO)_2Mg$	1 : 4	DMF, 100 °C, 4 h	88	152
H	DMTr	$(EtO)_2Mg$	1 : 6	DMF, 100 °C, 16 h	61	152
H	DMTr	$(Pr^nO)_2Mg$	1 : 6	DMF, 100 °C, 16 h	62	152
H	DMTr	$(AllO)_2Ca$	1 : 40	DMF, 100 °C, 16 h	42	152
H	H	$(MeO)_2Mg$	1 : 4	MeOH, Δ, 5 h	92	153
H	H	$(MeO)_3B$	1 : 2	$(MeO)_3CH$, $NaHCO_3$	86–97	154
Me	H	$(MeO)_3B$	–	MeOH	93	154
H	H	$[PhthN(CH_2)_3O]_3B$	–	–	18	154
Me	H	$[PhthN(CH_2)_2O]_3B$	1 : 2	THF, 150 °C, 24 h	21	155
Me	TBDPS	$[PhthN(CH_2)_3O]_3B$	1 : 2	$BH_3 \cdot THF$, $(CH_2OH)_2$, $NaHCO_3$, 150 °C, 16 h	50	77, 156
H	H	$[MeO(CH_2)_2O]_3Al$	1 : 3	$MeO(CH_2)_2OH$, Δ, 48 h	91	157
H	DMTr	$PhthN(CH_2)_2OH$	1 : 5.8	$Ti(OPr^i)_4$, $NaHCO_3$ (cat), THF, 140 °C, 48 h	32	158

VIII. Other methods for the synthesis of 2′-*O*-alkylnucleosides

A modified procedure for a two-step methylation of nucleosides involving alkylation with 1,3-benzodithiolium tetrafluoroborate and subsequent reduction of the intermediate product **27** over Raney nickel was proposed by Sekine *et al.*[161] This excludes the necessity of protecting the heterocyclic base and the amino groups additionally introduced into the heterocycle, but the overall yield is only 35% – 45%.



27

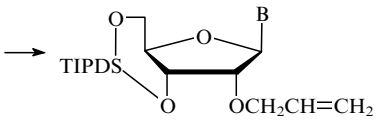
R = H, $CH_2N(Bn)CH_2CO_2Et$.

Sproat *et al.*[162] have succeeded in developing an efficient procedure for the synthesis of 2′-*O*-alkylnucleosides by alkylating nucleosides with 3′- and 5′-hydroxy groups protected (the Markiewicz protective group) with allyl ethyl carbonate in the presence of a Pd(0) complex. A 2,5-dichlorobenzyl protective group was used to protect the OH group of the heterocycles.[66] The degree of conversion in the allylation of compounds **11a**,**b** and **12**[163] was 90% in 30 min and no side products were formed. However, this reaction can only be used for the synthesis of allyl ethers, since it proceeds *via* the intermediate allylpalladium(0) complexes. Later, this approach was used by Froehler *et al.*[164] for the preparation of 2′-*O*-allyl derivatives of 5-(propyn-1-yl)uridine and 5-(propyn-1-yl)cytidine.

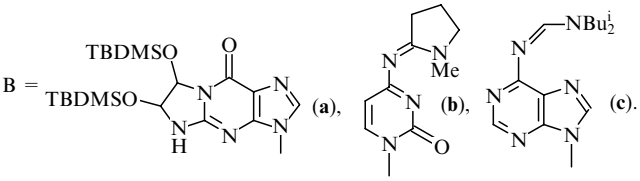
Sproat *et al.*[165] have designed novel protective groups for heterocyclic bases which made it possible to reduce the number of steps in the synthesis of the 2′-*O*-allyl derivatives **28a** – **c** and to increase the overall yields of the target products, especially, in the case of the guanosine derivative **28a**.



29a – **c**



28a – **c**

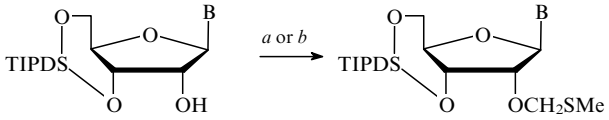
B = 

Direct allylation of the TIPDS-protected cytidine and adenosine derivatives (**29b**,**c**) is also possible, whereas earlier alkylation of uridine and inosine derivatives followed by transamination had to be performed.

A similar allylation procedure in which tetrakis(triphenylphosphine)palladium was used as a catalyst was proposed by Kumar *et al.*[166] This procedure allowed the alkylation of nucleosides bearing only the 5′-hydroxy protected group. With a 2.5-fold excess of allyl ethyl carbonate, the yields of the target allylation products of 5′-*O*-dimethoxytrityluridine and 5′-*O*-dimethoxytrityl-N^4-benzoylcytidine were ~ 60%, whereas in the case of the stoichiometric ratio of the reactants the reaction involved predominantly the heterocyclic base (90%).

Subsequent modification of the allyl derivatives leading to the introduction of the aldehyde groups was repeatedly employed in different laboratories.[167 – 170]

The alkylation of compounds **30** with dimethyl sulfide in the presence of dibenzoyl peroxide (yield 55% – 70%) has been carried out.[171, 172] Later,[173] compounds **31** were prepared by the reaction with DMSO and acetic anhydride in the presence of acetic acid.

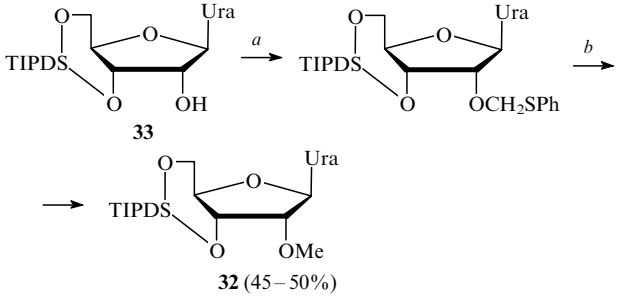


30 **31**

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

(*a*) Me_2S, Bz_2O_2, 2,6-lutidine; (*b*) DMSO, Ac_2O, AcOH.

This approach was used [51] in a two-step synthesis of the 2′-*O*-methyluridine derivative **32** by alkylation of compound **33** with methyl phenyl sulfide and subsequent desulfurisation.

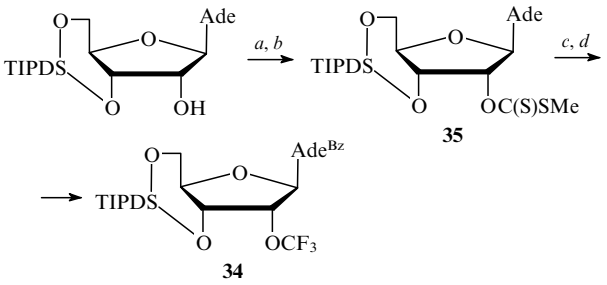


33

32 (45 – 50%)

(*a*) MeSPh, Bz_2O_2, dimethylaminopyridine; (*b*) Bu_3SnH, Bz_2O_2.

Matsuda *et al.*[174] have synthesised 2′-*O*-trifluoromethyladenosine **34** *via* the intermediate 2′-methyl xanthate **35**.



(*a*) BuLi, CS_2, −78 °C; (*b*) MeI, −78 °C; (*c*) BzCl, Py; (*d*) HF, Py, 1,3-dibromo-5,5-dimethylhydantoin.

The yield calculated over two steps was as low as 24% due to the formation of side products and partial removal of the Markiewicz protective group under the reaction conditions.

IX. Conclusion

The data considered above suggest that currently the methods for the synthesis of 2′-*O*-alkylnucleosides are well-developed, especially for the simplest representatives of this type of modified nucleoside, *viz*., 2′-*O*-methylnucleosides. Presumably, the main application of 2′-*O*-alkylnucleosides consists in their incorporation into oligonucleotides. The majority of modified oligonucleotides prepared from 2′-*O*-alkylnucleosides meet the major requirement, *viz*., the ability to form stable duplexes with the complementary regions of nucleic acids.

At present, the synthesis of 2′-*O*-alkylnucleosides is performed using two ideologically different approaches. One of them entails the maximum protection of all reactive centres of the molecule and, as a consequence, involves many steps. The other, in contrast, is aimed at the reduction of steps, which inevitably results in side reactions and, correspondingly, complicates the chromatographic separation of the reaction mixture. It should be noted that the total yield of the target product in the former approach is higher, as a rule. The advantage of the latter approach consists in the reduction of the time and cost of the synthesis.

Currently, the methods of nucleoside alkylation with diazomethane and trimethylsulfonium hydroxide, as well as with dialkyl sulfates in aqueous media, have only a historical significance. The most efficient procedure for the preparation of pyrimidine 2′-*O*-alkylnucleosides is the synthesis *via* O^2,2′-anhydronucleosides and treatment with alkyl iodides in the presence of silver(I) oxide.[43] The alkylation of pyrimidine nucleosides with alkyl halides in the presence of transition metal derivatives can be recommended only for those cases where the reactants contain groups sensitive to strong bases, since this procedure yields a large amount of the 3′-isomer.

Alkylation in the presence of alkali metal hydrides is the method of choice for adenosine and its derivatives. It is of note that this method excludes the protection of 3′- and 5′-hydroxy groups as well as the functional groups of the heterocyclic base.

The use of cyclic sulfates as alkylating reagents is especially attractive, since the alkylation product can be subjected to further nucleophilic substitution.[91,92]

The alkylation of uridine and thymidine in the presence of alkali metal hydrides affords considerable amounts of the 3′-isomers. Therefore, the 3′- and 5′-hydroxy groups as well as the heterocyclic base should be protected. If this approach is chosen, 2′-*O*-alkylcytidine is prepared preferably by transamination of 2′-*O*-alkyluridine.

The optimum procedure for the synthesis of 2′-*O*-alkylguanosine and its derivatives proposed by Sproat *et al*.[64] is rather costly and cost reduction is hardly possible. The alkylation of 9-(β-D-ribofuranosyl)-6-chloro-2-aminopurine and subsequent conversion of the reaction product into guanosine derivatives is a promising alternative to this method.[91] However, the conditions of this reaction were not optimised and the possibility of its application in large-scale syntheses was not investigated. The use of transglycosylation is another promising approach;[91] however, this reaction is extremely sensitive to both the structure of the aglycon and the substituent at the C(2′) atom of the carbohydrate fragment and will hardly ever be used as a versatile procedure.

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