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2',3'-O-Phosphonoalkylidene Derivatives of Ribonucleosides: Synthesis and Reactivity

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Abstract: A novel type of nucleotide analogues, the 2',3'-O-(1-diethylphosphono)alkylidene derivatives of ribonucleosides was prepared by redox reaction of diethyl chlorophosphite with various nucleoside orthoesters. Some of these compounds undergo interesting rearrangements when treated with nucleophiles. The configuration of the title compounds was determined by 2D-ROESY experiments. Biological activity of partially protected nucleotide analogues is also discussed.

Nucleotide analogues represent a potent pool of biologically active compounds. Some of them act, after enzymatic phosphorylation, as antimetabolites at the level of nucleoside di- or triphosphates. Preformed nucleoside phosphates, however, undergo rapid enzymatic dephosphorylation during penetration through the cellular membrane. Phosphonate-based nucleotides containing P-C bond[1] instead of ester P-O linkage represent isopolar, enzymatically resistant nucleotide analogues that are in the foreground of interest of many laboratories.[2] A class of nucleoside phosphonic acids containing a phosphonomethyl group attached to the hydroxyl group of nucleosides by a stable ether bond was already investigated in our laboratory.[3,4] Among these compounds, the O-phosphonomethyl derivatives of acyclic nucleoside analogues[5] were found to be efficient antivirals.

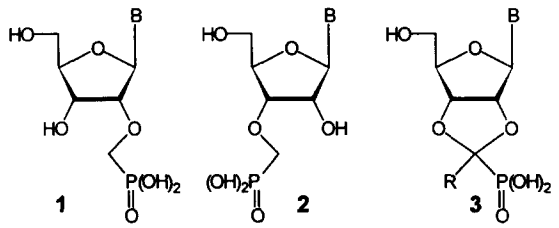

Figure 1

In agreement with our previous communication,[6] we report here a novel type of isopolar, non-isosteric, conformationally restricted nucleotide analogues related to 2'(3')-O-phosphonomethylribonucleosides[4] **1** and **2**. The novel compounds, 2',3'-O-phosphonoalkylidene ribonucleosides **3** (Figure 1) containing cyclic phosphonoformylacetal or 1-phosphonoketal moieties, can exist in epimeric pairs due to the chirality of the carbon atom bearing phosphoryl group in the position 2 of annel 1,3-dioxolane ring.

Several procedures for the preparation of cyclic acetals of formylphosphonic acid have been described so far; however, none of these procedures has ever been applied in nucleoside chemistry. As the first, we examined the reaction of quarternary ammonium formals[7] with trialkyl phosphites. Thus, the 2',3'-O-(dimethylamino)-methyleneuridine derivative **4**, prepared from 5'-O-trityluridine by reaction with dimethylformamide dimethylacetal in DMF, was quarternized by iodomethane. Subsequent treatment of the formed 2',3'-O-(trimethylammonium)-methylene-5'-O-trityluridine iodide **(5)** with trimethyl phosphite afforded a moderate yield of 2',3'-O-(dimethyl-

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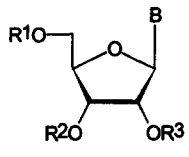
phosphono)methylene-3-N-methyl-5'-O-trityluridine (**6**) (see Table 1). In a further experiment we explored a procedure[8] based on an acid-catalyzed transacetalization of diethoxymethyldiphenylphosphine oxide with appropriate diol. Reactions of this type, when performed with diethyl diethoxymethanephosphonate and 5′-O-protected ribonucleoside **7**, completely failed.

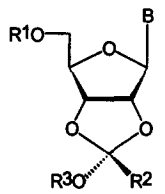
Table 1. Substrates and Products



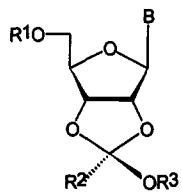
Compound	R^1	R^2	R^3	B
4	Tr	$=CHN(CH_3)_2$		U
5	Tr	$=CHN^+(CH_3)_3I^-$		U
6	Tr	$=CHP(O)(OCH_3)_2$		$U^{3\text{-N-Me}}$
7	TBDPS	H	H	U^{BOM}

Finally, we examined the reaction of diethyl chlorophosphite with various trialkyl orthoesters known to give corresponding acetals of formylphosphonic acid only when orthoformates were used. The orthoesters of other carboxylic acids were reported to react with chlorophosphines as well as chlorophosphites resulting in formation of esters of phosphinic or phosphorous acid.[9] Surprisingly, in our hands the reaction of various types of nucleoside 2',3'-orthoesters (see Table 2) with diethyl chlorophosphite proceeded very smoothly to afford appropriately protected nucleoside phosphonic acid derivatives (see Table 3) as the only products.

Table 2. 2',3'-Orthoesters of Nucleosides (in the case of epimerically pure compounds, prefix *R*- or *S*- is used commonly with the numbering).



R-epimer



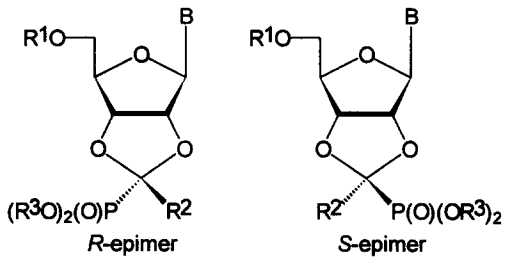
S-epimer

Compound	R^1	R^2	R^3	B
8R	TBDPS	H	CH_3	A^{Bz}
9aR	TBDPS	H	C_2H_5	A^{Bz}
9b	TBDPS	H	C_2H_5	G^{Bz}
9c	TBDPS	H	C_2H_5	C^{Bz}
9d	TBDPS	H	C_2H_5	U

Table 2. 2',3'-Orthoesters of Nucleosides (continuation).

Compound	R^1	R^2	R^3	B
9e	TBDPS	H	C_2H_5	T
10a	TBDPS	CH_3	C_2H_5	A^{Bz}
10b	TBDPS	CH_3	C_2H_5	G^{Bz}
10c	TBDPS	CH_3	C_2H_5	C^{Bz}
10d	TBDPS	CH_3	C_2H_5	U
10e	TBDPS	CH_3	C_2H_5	T
11a	TBDPS	C_6H_5	C_2H_5	A^{Bz}
11b	TBDPS	C_6H_5	C_2H_5	G^{Bz}
11c	TBDPS	C_6H_5	C_2H_5	C^{Bz}
11d	TBDPS	C_6H_5	C_2H_5	U
11e	TBDPS	C_6H_5	C_2H_5	T
12	H	H	CH_3	A^{Bz}
13	Bz	H	CH_3	A^{Bz}
14	TBDPS	$ZNHCH_2$	C_2H_5	A^{Bz}
15	TBDPS	$BzOCH_2$	CH_3	A^{Bz}
16	TBDPS	$BzOCH_2CH_2$	CH_3	A^{Bz}
17a	TBDPS	$BrCH_2$	C_2H_5	A^{Bz}
17e	TBDPS	$BrCH_2$	C_2H_5	T
17f	TBDPS	$BrCH_2$	C_2H_5	T^{BOM}

Table 3. 2′,3′-*O*-Phosphonoalkylidene Derivates of Nucleosides.



Compound	R^1	R^2	R^3	B
18a	TBDPS	H	C_2H_5	A^{Bz}
18b	TBDPS	H	C_2H_5	G^{Bz}
18c	TBDPS	H	C_2H_5	C^{Bz}
18d	TBDPS	H	C_2H_5	U
18e	TBDPS	H	C_2H_5	T
19a	TBDPS	CH_3	C_2H_5	A^{Bz}
19b	TBDPS	CH_3	C_2H_5	G^{Bz}

Table 3. 2′,3′-*O*-Phosphonoalkylidene Derivates of Nucleosides (continuation).

Compound	R^1	R^2	R^3	B
19c	TBDPS	CH_3	C_2H_5	C^{Bz}
19d	TBDPS	CH_3	C_2H_5	U
19e	TBDPS	CH_3	C_2H_5	T
19f	TBDPS	CH_3	C_2H_5	T^{BOM}
20a	TBDPS	C_6H_5	C_2H_5	A^{Bz}
20b	TBDPS	C_6H_5	C_2H_5	G^{Bz}
20c	TBDPS	C_6H_5	C_2H_5	C^{Bz}
20d	TBDPS	C_6H_5	C_2H_5	U
20e	TBDPS	C_6H_5	C_2H_5	T
21	Bz	H	C_2H_5	A^{Bz}
22	H	H	C_2H_5	A^{Bz}
23	TBDPS	$ZNHCH_2$	C_2H_5	A^{Bz}
24	TBDPS	NH_2CH_2	C_2H_5	A^{Bz}
25	TBDPS	$TfAcNHCH_2$	C_2H_5	A^{Bz}
26	TBDPS	$BzOCH_2$	C_2H_5	A^{Bz}
27	TBDPS	$BzOCH_2CH_2$	C_2H_5	A^{Bz}
28a*S*	TBDPS	$BrCH_2$	C_2H_5	A^{Bz}
28e*S*	TBDPS	$BrCH_2$	C_2H_5	T
28f	TBDPS	$BrCH_2$	C_2H_5	T^{BOM}
29*S*	TBDPS	$ClCH_2$	C_2H_5	A^{Bz}
30a	H	H	H	A
30b	H	H	H	G
30c	H	H	H	C
30d	H	H	H	U
30e	H	H	H	T
31a	H	CH_3	H	A
31b	H	CH_3	H	G
31c	H	CH_3	H	C
31d	H	CH_3	H	U
31e	H	CH_3	H	T
32a	H	C_6H_5	H	A
32b	H	C_6H_5	H	G
32c	H	C_6H_5	H	C
32d	H	C_6H_5	H	U
32e	H	C_6H_5	H	T

The starting 2',3'-O-alkoxyalkylidene derivatives of nucleosides **8-17** were prepared according to currently used procedures. The ribonucleosides with exocyclic amino groups were *N*-benzoylated by Jones procedure[10] (adenosine and guanosine derivatives) or by Watanabe procedure[11] (cytidine derivatives). For the 5'-hydroxyl

protection, the *tert*-butyldiphenylsilyl group[12] was utilized. Subsequent transformation of 5'-silylated compounds into 2′,3′-orthoesters **8-11** and **14-17** was made by modified standard procedures[13] in dichloromethane in the presence of 4-toluenesulfonic acid. The 6-*N*,5'-*O*-dibenzoyl-2',3'-*O*-methoxymethyleneadenosine (**13**) was prepared in the reverse manner: 6-*N*-benzoyladenosine was converted to the 2',3'-*O*-methoxymethylene derivative **12** and then protected at the 5'-position with a benzoyl group.[14] The ratio of nucleoside orthoester epimers was established by HPLC, and their *R*- or *S*-configuration was assigned according to ^{1}H and ^{13}C NMR and 2D-ROESY NMR experiments. The ratio of *R*- and *S*-epimer was equal in almost all cases. Only 2′,3′-*O*-alkoxymethylene derivatives of adenosine **8*R***, **9a*R*** were found to be predominantly the *R*-epimers.

The results of the reaction of nucleoside orthoesters **9-11** with two equivalents of diethyl chlorophosphite in acetonitrile under argon are summarized in the Table 4. We found the reactivity of nucleoside orthoesters to depend both on the nature of nucleobase and the type of orthoester moiety (given in the order of decreasing reactivity): $T \approx U > G^{Bz} > C^{Bz} > A^{Bz}$ and 2′,3′-*O*-(1-ethoxy-1-phenylmethylene)≈2′,3′-*O*-(1-ethoxyethylidene)->>2′,3′-*O*-ethoxymethylene. Throughout this whole series of phosphonates, the *S*-epimer was found to be the major one.

Table 4. Synthesis of 2′,3′-*O*-Phosphonoalkylidene Derivatives of Ribonucleosides.

R	B	Temperature (°C)	Orthoester (% of *S*-epimer[a])	Phosphonate (% of *S*-epimer[a])	Yield[b] (%)
H	A^{Bz}	reflux	**9a*R*** (-)	**18a** (75)	91
	G^{Bz}	20	**9b** (52)	**18b** (64)	63
	C^{Bz}	reflux	**9c** (17)	**18c** (71)	60
	U	20	**9d** (52)	**18d** (71)	52
	T	0 to 20	**9e** (52)	**18e** (74)	74
CH_3	A^{Bz}	20	**10a** (55)	**19a** (91)	98
	G^{Bz}	0 to 20	**10b** (60)	**19b** (91)	83
	C^{Bz}	0 to 20	**10c** (60)	**19c** (89)	66
	U	-40 to 20	**10d** (56)	**19d** (89)	72
	T	-40 to 20	**10e** (57)	**19e** (89)	78
C_6H_5	A^{Bz}	20	**11a** (55)	**20a** (91)	96
	G^{Bz}	0 to 20	**11b** (55)	**20b** (80)	77
	C^{Bz}	0 to 20	**11c** (55)	**20c** (89)	91
	U	-40 to 20	**11d** (55)	**20d** (91)	85
	T	-40 to 20	**11e** (55)	**20e** (86)	84

[a] according to ^{1}H NMR spectra; [b] isolated yield of the phosphonate.

In the case of 2′,3′-O-alkoxymethylene derivatives of adenosine **8*R***, **9a*R***, and **13**, as the orthoesters with the lowest reactivity, we examined their reaction with diethyl chlorophosphite in more details. We tried to influence the reaction course by addition of various effectors with respect to increase in rate as well as to control

of the epimeric ratio of formed 2',3'-*O*-(1-phosphonoalkylidene) derivatives **18a** and **21** (for the results see Table 5).

Table 5. Phosphonylation of 2′,3′-*O*-alkoxymethylene derivatives of adenosine by diethyl chlorophosphite in the presence of various effectors.

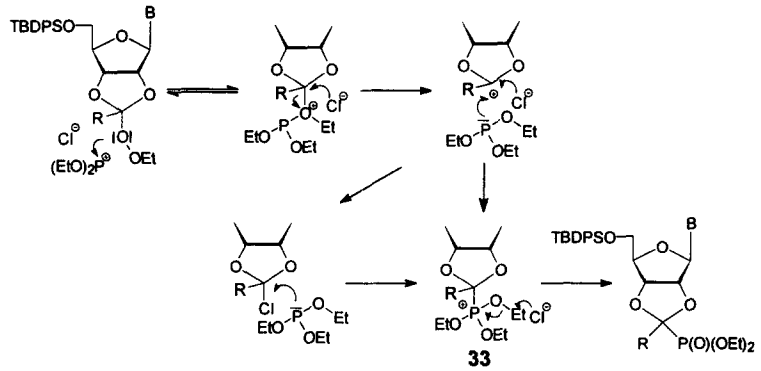
Entry	Effector	Orthoester	Temperature (°C)	Time	Phosphonate	Yield[a] (%)	*S*-epimer[b] (%)
1	-	**13**	50	12 h	**21**	57 [c]	75
2	DIPEA	**13**	50-100	8 h	no reaction	-	-
3	MPO	**13**	50-100	8 h	no reaction	-	-
4	NaI	**13**	50	80 min	**21**	54 [c]	75
5	$BF_3 . Et_2O$	**9aR**	20	35 min	**18a**	67	80
6	$SnCl_4$	**9aR**	20	10 min	**18a**	76	71
7	AgOTf	**8R**	20	5 min	**18a**	49	69
8	AgOTf	**8R**	0	25 min	**18a**	83	70
9	TMSOTf (0.2 ekv.)	**8R**	50	6 h	**18a**	67	75
10	TMSOTf	**8R**	20	5 min	**18a**	46	70
11	TMSOTf	**8R**	0	5 min	**18a**	79	66
12	TMSOTf	**8R**	-20	3.5 h	**18a**	33 [d]	71
13	TMSOTf[e]	**8R**	20	20 h	**18a**	64	66

[a] determined by HPLC; [b] determined by NMR spectroscopy; [c] isolated yield; [d] 10 % of the starting orthoester remained in the mixture; [e] triethyl phosphite was used as the phosphonylating agent instead of diethyl chlorophosphite.

The presence of molecular sieves (to neutralize the traces of HCl that could catalyse the reaction) did not influence the reaction rate or yield. On the contrary, the sterically hindered diisopropylethylamine or non-nucleophilic 4-methoxypyridine-*N*-oxide used as the bases caused complete inhibition of the reaction (Entry 2, 3); both compounds can probably act as electrophile scavengers. The use of *in situ* prepared diethyl iodophosphite or diethyl trifluoromethanesulfonyloxyphosphite from diethyl chlorophosphite and sodium iodide or silver trifluoromethanesulfonate, respectively, led to the significant acceleration of the reaction because of the increase of the polarization of P-X bond (Entry 4, 7, 8). Furthermore, we found that Lewis acids, boron trifluoride diethyl etherate, tin tetrachloride, and trimethylsilyl trifluoromethanesulfonate, if present in the equimolar amount, strongly accelerate the reaction course (Entry 5, 6, 9, 10, 11, 12). As far as the stereoselectivity of the reaction is concerned, neither low reaction temperature in the presence of Lewis acid nor epimeric composition of the starting nucleoside orthoester possessed any influence on the ratio of *R*- and *S*-epimer of phosphonates; the *S*-epimer always prevailed. These findings support the proposed S_N1 mechanism; a nucleophile (P^{III} species) comes to the planar carbocation reaction centre from the sterically less hindered site.

As far as the reaction mechanism is concerned, the formation of phosphonium cation **33** (Scheme 1) during the reaction of trialkyl orthoformates with diethyl chlorophosphite (Arbuzov-related type of reaction) was suggested by Dietsche.[9] On the basis of our experiments, this reaction seems to be a strongly-electrophile-promoted type. We found that the extent of diethyl chlorophosphite heterolysis due to the polarization of the P-Cl bond, i.e. the formation of positively charged P^{III} species is essential to drive the reaction. This can be supported by our findings that more polarizable phosphites, $(EtO)_2P\text{-}I$ and $(EtO)_2P\text{-}OSO_2CF_3$ (see Table 5, Entry 4, 7, 8) are much more reactive than diethyl chlorophosphite itself. The Lewis acids, which can both increase the extent of heterolysis of diethyl chlorophosphite and activate the orthoester moiety, were also found to accelerate dramatically the reaction rate, however, only their equimolar amount is effective. For explanation of the reaction

mechanism we originally supposed the formation of triethyl phosphite (from 2',3'-*O*-ethoxymethylene derivatives and diethyl chlorophosphite) as an intermediate which could react in the next step with an activated orthoester moiety. However, an experiment with triethyl phosphite and TMSOTf revealed a significantly lower reaction rate than in the presence of diethyl chlorophosphite (see Table 5, Entry 13).



33

Scheme 1

An attempt to capture the phosphonium ion as the intermediate of the phosphonylation reaction by ^{31}P NMR techniques was undertaken with the reaction of 2',3'-*O*-(1-ethoxyethylidene) derivative of adenosine **10a** with diethyl chlorophosphite in CD_3CN. Only signal assigned to unreacted P^{III} starting compound (diethyl chlorophosphite, δ_P 168.08 ppm), and two additional signals of immediately formed P^V product **19a** ($\delta_{P(R)}$ 15.97 ppm and $\delta_{P(S)}$ 15.85 ppm) were observed. No signal that could be assigned to the P^{IV+} cation (expected δ_P 53-56 ppm)[15] was found.

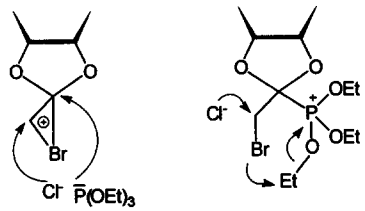
In order to obtain free nucleoside phosphonic acids we removed the protecting groups from prepared phosphonates by a standard methodology used in nucleotide chemistry.[16] The key step in deprotection procedure, removal of ethyl ester groups from phosphonate moiety was accomplished by bromotrimethylsilane treatment; this compound as a relatively strong Lewis acid could cause the epimerisation. It was found that according to the ratio of *R/S* epimers of protected phosphonates **18** - **20** and the deprotected counterparts **30** - **32**, no epimerization on the chiral carbon atom was observed.

Because of formation of epimeric pairs of phosphonates, we studied the possibility of separation of the *R* and *S* epimers by TLC and HPLC techniques. We found that only the epimeric diethyl phosphonomethylene derivatives of adenosine **22** were separable on silica gel (elution with gradient of ethanol in chloroform) and also by RP HPLC. Uridine **18d** and 5-methyluridine **18e** derivatives can be resolved by RP HPLC, however, after 5′-desilylation no more separation could be achieved. In the case of fully deprotected phosphonates **30**, the epimers of pyrimidine compounds **30c** - **30e** were separated completely by RP HPLC, while the purine derivatives **30a, 30b** showed only a "shoulder-like" separation. An attempt to separate epimeric phosphonates on Dowex 1x2 in acetate form was successful only for cytidine derivative **30c**.

We also attempted to prepare 2',3'-O-phosphonoalkylidene derivatives of ribonucleosides bearing a substituent in the ω-position of the alkylidene chain. Thus, the trialkyl orthoesters of ω-substituted carboxylic acids (triethyl bromoorthoacetate[17] prepared by bromination of triethyl orthoacetate with bromine in pyridine, and triethyl benzyloxycarbonylaminoorthoacetate[18], trimethyl benzoyloxyorthoacetate and trimethyl 3-benzoyloxy-orthopropionate prepared by two-step procedure[19] from corresponding nitriles) were used for the synthesis of ω-substituted alkylidene nucleoside orthoesters **14**, **15**, and **16**. These compounds were found to react readily with an excess of chlorodiethyl phosphite in acetonitrile to afford phosphonates **23**, **26**, and **27** in good yields. It is interesting that phosphonylation of benzoyloxyethylidene derivative **15** with chlorodiethyl phosphite required reflux for several hours while the similar reaction performed with benzoyloxypropylidene derivative **16** was complete within 15 hrs at room temperature. The 2-benzyloxycarbonylaminoethylidene derivative **23** was

transformed into the N-trifluoroacetyl derivative **25** by hydrogenolysis on Pd/C in ethanol-acetic acid mixture followed by acylation of the free aminogroup of compound **24** with ethyl trifluoroacetate.

The reaction of 2-bromoethylidene derivatives **17a, 17e,** and **17f** with diethyl chlorophosphite proceeded ambiguously, and two major side-products were isolated and characterized. In the case of 2-bromoethylidene-adenosine derivative **17a**, six equivalents of diethyl chlorophosphite is required to afford, besides expected 2-bromo-1-diethylphosphonoethylidene derivative **28a*S*** (12 %), a phosphonoethylidene derivative **19a** (28 %), and 2-chloro-1-diethylphosphonoethylidene derivative **29*S*** (12 %). An attempt to increase the reaction rate by the addition of sodium iodide to the reaction mixture (formation of more reactive diethyliodophosphite *in situ*) resulted in phosphonoethylidene derivative **19a** as the major product again. Similarly, the use of silver trifluoromethanesulfonate (*in situ* formation of highly reactive diethyl trifluoromethanesulfonylphosphite) at low temperature (-40 to 0 °C) led, besides formation of the expected 2-bromo-1-diethylphosphonoethylidene derivative **28a*S*** (19 %), to the phosphonoethylidene derivative **19a** (13 %). When the reaction was performed with the 2',3'-*O*-(2-bromo-1-ethoxyethylidene)-5-methyluridine derivative **17e** and diethyl chlorophosphite at low temperature (-40 to 20 °C), the 2-bromo-1-diethylphosphonoethylidene derivative **28e*S*** was produced in moderate yield (50 %) together with some amount of diethylphosphonoethylidene derivative **19e** (8 %). Surprisingly, phosphonylation of 3-*N*-benzyloxymethyl-2',3'-*O*-(2-bromo-1-ethoxyethylidene)-5-methyluridine derivative **17f** with four equivalents of diethyl chlorophosphite resulted, after 2 days at room temperature, in a low yield of both diethylphosphonoethylidene derivative **19f** (8 %) and 2-bromo-1-diethylphosphonoethylidene derivative **28f** (10%).



34 **35**

Figure 2

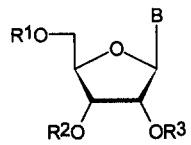
The presence of a bromo substituent in the α-position to the carbonium reaction center can lead to the formation of epibromonium intermediate **34** (Figure 2) which can react either directly with the phosphite under formation of the desired 2-bromo derivative **28**, or can be attacked by chloride anion under formation of the 2-chloro derivative **29**. The 2-chloroethylidene derivative **29** could be also generated from the phosphonium intermediate **35**; the reaction is driven by the attack of chloride anion to the carbon atom bearing the bromo substituent followed by cyclic transfer of bonds under splitting off the bromoethane. However, from the observed preferred formation of ethylidene derivatives **19** and the necessity to use an excess of diethyl chlorophosphite for the complete conversion, occurence of side-reactions as well as a more complicated redox mechanism is evident.

Within our effort to prepare phosphonates bearing a substituent in the 2-position of ethylidene side chain, we studied the reaction of 2',3'-*O*-(2-bromo-1-ethoxyethylidene)-5'-*O*-*tert*-butydiphenylsilyl-5-methyluridine (**17e**) and 2',3'-*O*-(2-bromo-1-diethylphosphono)uridine derivatives **28e** and **28f** with various nucleophiles. An attempt to substitute bromo atom in the 2',3'-*O*-(2-bromoethoxyethylidene)-5-*O*-*tert*-butyldiphenylsilyl--5-methyluridine (**17e**) for azido group by heating with sodium azide in DMF (150 °C, 10 h) or in DMSO (100 °C, 30 h) was unsuccesful. Only unchanged starting bromo compound **17e** was isolated from the reaction mixture. In addition, no degradation of the 2-bromoethylidene derivative **17e** was observed in the presence of strong base as potassium *tert*-butoxide or DBU in THF (3 days at room temperature). Therefore, these conditions were utilized for the protection of thymine moiety in the 3-N position of the derivative **17e** by benzyloxymethyl group. Thus, the addition of benzylchloromethyl ether to the compound **17e** in THF in the presence of DBU, afforded smoothly the 3-N-benzyloxymethyl derivative **17f** in quantitative yield. This method of N-protection of pyrimidine heterocycle is a variant to those employing potassium carbonate in DMF or acetone.[20] The observed resistance of 2-bromoethylidene orthoesters towards nucleophiles could be explained by the presence of a strongly electronegative orthoester moiety. The low reactivity of the similar system, the 5'-deoxy-5'-iodo derivatives of nucleosides substituted in 4'-position with an electron-withdrawing substituent, was reported earlier.[21,22]

In contrast to the resistance of 2',3'-*O*-(2-bromo-1-ethoxyethylidene)-5-methyluridine (**17e**) against nucleophilic substitution, extensive changes concerning the whole nucleotide skeleton during reaction with nucleophiles were observed in the case of 2',3'-*O*-(2-bromo-1-diethylphosphonoethylidene)-5-methyluridine (**28e**) (for the products see compounds inTable 6). The treatment of compound **28e** with potassium *t*-butoxide or sodium ethoxide in DMF at room temperature resulted in a fast and quantitative cleavage of nucleoside bond. An

experiment performed in a similar way with potassium *t*-butoxide in THF at 0 °C afforded a mixture of 2'(3')-*O*--acetyl-5'-*O*-*tert*-butyldiphenylsilyl-5-methyluridine (**36** and **37**; 32 %, in a 2:5 ratio of 2'- *versus* 3'-isomer) and 2',3'-*O*-(2-bromo-1-ethylphosphonoethylidene) derivative **38** (56 %). Treatment of compound **28e** with potassium fluoride in DMF at 130 °C for 6 h (only 5'-desilylation occurred at room or elevated temperature) provided 5-methyluridine (**39**, 39 %) and 3-*N*-ethyl-5-methyluridine (**40**, 35 %). No reaction of derivative **28e** with sodium azide in DMF at room temperature was observed; however, after heating of the reaction mixture (130 °C for 1 h) the starting material disappeared completely. The monoester **38** (6 %), a mixture of 2'(3')-O-phosphonoacetyl derivatives **41** and **42** (6 %), and 2,2'-anhydro-3'-O-phosphonoacetyl derivative **43** (64 %) were isolated from the mixture. Treatment of the compound **43** with 0.5M sodium hydroxide in water-dioxane mixture afforded 2,2'--anhydro-5'-*tert*-butyldiphenylsilyl-5-methyluridine (**44**), then 1-(5-*tert*-butyldiphenylsilyl-β-D-arabinofuranosyl)-thymine (**45**) on subsequent reaction, and finally 1-(β-D-arabinofuranosyl)thymine (**46**)[23] (Figure 3).

Table 6. Products of the Reaction of phosphonate **28e** with Nucleophiles.



Compound	R^1	R^2	R^3	B
36	TBDPS	Ac	H	T
37	TBDPS	H	Ac	T
38	TBDPS	=CH(CH_2Br)P(O)(OEt)(OH)		T
39	H	H	H	T
40	H	H	H	$T^{3\text{-N-Et}}$
41	TBDPS	C(O)CH_2P(O)(OEt)(OH)	H	T
42	TBDPS	H	C(O)CH_2P(O)(OEt)(OH)	T

The formation of 2,2'-anhydro ring in the reaction of compound **28e** with azide supposes an attack of the azido anion on hydrogen atom in the position 3-N of thymine moiety followed by attack of the oxygen atom in the position 2 on 2'- or 3'-carbon atom of the sugar ring. The 2',3'-phosphonoformal moiety serves as a leaving group under its rearrangement to the 2'(3')-phosphonoacetyl group.

On the contrary, the 3-N-benzyloxymethyl derivative **28f** where no 2,2'-anhydro ring was formed, the

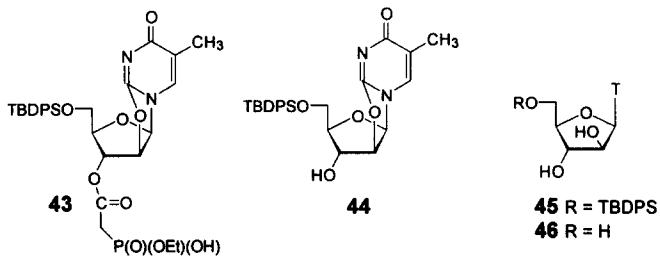


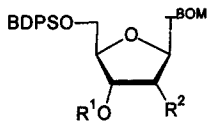
Figure 3

heating with sodium azide in DMF at 110 °C for 4 h resulted in the mixture of 2'(3')-O-phosphonoacetyl--5'-O-*tert*-butyldiphenylsilyl derivatives **47** and **48** with *ribo*-configuration of the sugar moiety (45 %, in a 3:5 ratio of 2'- *versus* 3'-isomer; see Table 7).

In order to verify the correctness of assingment of the chemical shifts of O-phosphonoacetyl moiety of compounds **43**, **47**, and **48** we prepared derivative **51** containing O-phosphonoacetyl group. We treated the 3-*N*-benzyloxymethyl-5'-*O*-*tert*-butyldiphenylsilylthymidine (**49**) with chloroacetyl chloride, and the formed 3'-*O*-chloroacetyl derivative **50** was then reacted with triethyl phosphite in xylene under reflux to afford the 3-*N*-benzyloxymethyl-5'-*O*-*tert*-butyldiphenylsilyl-3'-*O*-diethylphosphonomethylcarbonylthymidine (**51**, 83 %).

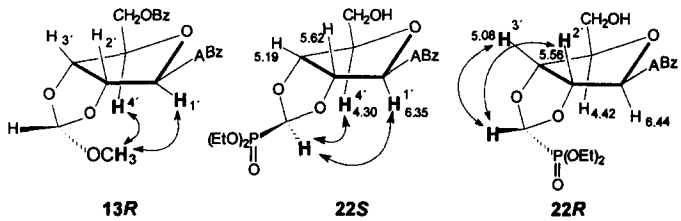
The structures of all compounds were determined by ^1H and ^{13}C NMR spectroscopic data (see Tables 8-16).The assignment of the proton signals was done according to the chemical shifts and signal multiplicity and confirmed by 2D-COSY spectra[24]. Proton chemical shifts and coupling constants were obtained from expanded 1D spectra according to first-order analysis. The configurational assignment of orthoesters and phosphonates was confirmed by proton 2D-ROESY spectra[25,26,27] of selected compounds (see Scheme 2). Carbon chemical shifts were obtained from ^{13}C NMR spectra measured by APT[28,29] technique. The coupling constants J(C,P) were obtained from doublets of carbon signals in ^{13}C NMR spectra.

Table 7. Products of the Reaction of Phosphonate **28f** with Sodium Azide and Related Compounds.



Compound	R^1	R^2
47	$C(O)CH_2P(O)(OEt)(OH)$	OH
48	H	$OC(O)CH_2P(O)(OEt)(OH)$
49	H	H
50	$C(O)CH_2Cl$	H
51	$C(O)CH_2P(O)(OEt)_2$	H

The configuration of 2',3'-O-methoxymethylene derivative **13*R*** and that of the pair of epimeric 2',3'-O-diethylphosphonoderivatives **22*R*** and **22*S*** were determined by 2D-ROESY spectra. The *R*-configuration of 2',3'-O-methoxymethylene derivative **13*R*** was determined from the intensive ROE-cross peak of the methoxy group and the proton H-1', and a weak cross peak with the proton H-4'. In the case of the epimeric pair of phosphonates, the *R*-epimer **22*R*** showed ROE-cross peaks of proton O-C**H**$(P(O)(OEt)_2)$-O with H-2' and H-3' ribose protons, and steric contacts of OCH_2 protons of the phosphonate group with H-1' proton. For the *S*-epimer **22*S***, ROE-cross peaks of proton O-C**H**$(P(O)(OEt)_2)$-O with ribose H-1' and H-4' were observed. The configurational assignment is also supported by chemical shift differences of ribose protons in epimeric pairs: the proximity of the bulk $O{=}P(OR)_2$ group induces downfield shifts (cca 0.1 ppm) of H-1' and H-2' protons in *R*-epimer **22*R***, and of H-2' and H-3' protons in *S*-epimer **22*S***.



13*R* **22*S*** **22*R***

Scheme 2

Inhibition of cell growth in the presence of prepared phosphonates was tested on cell line L 1210, L 929 and HeLa S3. While free phosphonic acids **30 - 32** showed no activity, the presence of 5'-silylated dialkyl phosphonates **18 - 20** causes a dramatic and yet unclear effect. The formation of "precipitate" and/or "emulsion" was observed and the count of cells was even lower than in inoculum (10^5 cells); it means that the compounds causes release of the cells from their monolayer (in the case of L1210 cells).This effect can be suppressed by the addition of γ-cyclodextrin as a solubilizer of lipophilic compounds.

The antiviral effects of the nucleotide analogues prepared in this study were investigated in the laboratory of Professor E. De Clercq, Catholic University, Leuven (Belgium). None of the nucleotide analogues **30 - 32** showed any significant *in vitro* antiviral activity against a standard series of DNA viruses and retroviruses.

Table 8. ^{1}H NMR Chemical Shifts (ppm) of 2′,3′-*O*-Alkoxyalkylidene Derivates of Nucleosides[a].

Compound	H-1′	H-2′	H-3′	H-4′	H-5′a	H-5′b	R^2	O-CH_2-CH_3		Base
8*R*	6.44	5.59	5.12	4.44	3.92	3.82	6.13	OCH_3: 3.39		NH: 11.25, H-2: 8.69, H-8: 8.61
9a*R*	6.46	5.57	5.12	4.47	3.92	3.83	6.20	3.67	1.23	NH: 11.23, H-2: 8.71, H-8: 8.62
9b*R*	6.31	5.36	5.39	4.43	3.88	3.84	6.17	3.65	1.19	NH: 12.16 a 11.57, H-8: 8.21
9b*S*	6.24	5.27	5.53	4.28	3.87	3.85	6.23	3.55	1.12	NH: 12.17 a 11.62
9c*R*	5.97	5.09	4.86	4.42	3.97	3.87	6.10	3.63	1.18	NH: 11.30, H-6: 8.24, H-5: 7.30
9c*S*	5.86	5.07	4.88	4.29	3.98	3.84	6.16	3.52	1.12	NH: 11.30, H-6: 8.25, H-5: 7.30
9d*R*	5.94	5.03	4.84	4.31	3.89	3.84	6.10	3.59	1.16	NH: 11.40, H-6: 7.72, H-5: 5.52
9d*S*	5.81	5.04	4.89	4.15	3.90	3.82	6.16	3.52	1.11	NH: 11.40, H-6: 7.71, H-5: 5.51
9e*R*	5.96	5.02	4.85	4.28	3.91	3.85	6.11	3.59	1.16	NH: 11.40, H-6: 7.53, CH_3: 1.66
9e*S*	5.80	5.03	4.92	4.13	3.90	3.83	6.16	3.52	1.11	NH: 11.40, H-6: 7.51, CH_3: 1.67
10a*R*	6.46	5.57	5.08	4.45	3.88	3.79	1.57	3.68	1.21	NH: 11.25, H-2: 8.65, H-8: 8.07
10a*S*	6.37	5.63	5.20	4.34	3.87	3.76	1.68	3.50	1.10	NH: 11.25, H-2: 8.62, H-8: 8.06
10b*R*	6.30	5.38	5.34	4.42	3.88	3.78	1.54	3.66	1.19	NH: 12.15 a 11.58, H-8: 8.23
10b*S*	6.23	5.32	5.46	4.28	3.88	3.78	1.65	3.48	1.07	NH: 12.15 a 11.58, H-8: 8.21
10c*R*	5.96	5.06	4.80	4.42	3.96	3.85	1.51	3.67	1.15	NH: 11.32, H-6:8.24,H-5:7.30
10c*S*	5.84	5.11	4.83	4.30	3.98	3.83	1.59	3.56	1.08	NH:11.33,H-6: 8.25, H-5: 7.33
10d*R*	5.95	5.03	4.80	4.29	3.90	3.84	1.51	3.59	1.15	NH: 11.25, H-6: 7.71, H-5: 5.49
10d*S*	5.79	5.09	4.88	4.16	3.90	3.81	1.59	3.45	1.08	NH: 11.25, H-6: 7.70, H-5: 5.52
10e*R*	5.95	5.01	4.82	4.27	3.90	3.84	1.52	3.59	1.14	NH: 11.40, H-6: 7.50, CH_3: 1.64
10e*S*	5.79	5.07	4.90	4.13	3.90	3.82	1.62	3.45	1.08	NH: 11.40, H-6: 7.52, CH_3: 1.68
11a*R*	6.63	5.67	5.20	4.64	3.95	3.86	7.40	3.62	1.21	NH: 11.30, H-2: 8.73, H-8: 8.61
11a*S*	6.47	5.84	5.42	4.31	3.89	3.77	7.40	3.49	1.13	NH: 11.30, H-2: 8.68, H-8: 8.64
11b*R*	6.47	5.48	5.40	4.60	3.91	3.88	7.40	3.59	1.19	NH: 12.14 a 11.54, H-8: 8.27
11b*S*	6.36	5.54	5.69	4.17	3.88	3.84	7.40	3.47	1.10	NH: 12.16 a 11.58, H-8: 8.23
11c*R*	6.12	5.16	4.91	4.59	4.03	3.91	7.40	3.55	1.15	NH: 11.35, H-6: 8.29, H-5: 7.30
11c*S*	5.90	5.34	5.05	4.27	4.00	3.86	7.40	3.42	1.11	NH: 11.35, H-6: 8.27, H-5: 7.30
11d*R*	6.07	5.11	4.91	4.47	3.95	3.88	7.40	3.51	1.13	NH: 11.40, H-6: 7.76, H-5: 5.53
11d*S*	5.86	5.53	5.07	4.09	3.90	3.82	7.40	3.44	1.11	NH: 11.40, H-6: 7.75, H-5: 5.54
11e*R*	6.07	5.10	4.92	4.43	3.95	3.89	7.40	3.50	1.13	NH: 11.40, H-6: 7.50, CH_3: 1.66
11e*S*	5.83	5.30	5.08	4.06	3.90	3.82	7.40	3.44	1.11	NH: 11.40, H-6: 7.52, CH_3: 1.69
13*R*	6.45	5.68	5.25	4.66	4.63	4.51	6.17	OCH_3: 3.40		NH: 11.24, H-2: 8.70, H-8: 8.69
17a*R*	6.53	5.76	5.26	4.53	3.88	3.76	3.80	3.78	1.23	NH: 11.27, H-2: 8.67, H-8: 8.61
17a*S*	6.48	5.78	5.33	4.51	3.91	3.80	3.87	3.58	1.16	NH: 11.27, H-2: 8.70, H-8: 8.63
17e*R*	5.90	5.18	4.94	4.32	3.92	3.84	3.73	3.67	1.17	NH: 11.40, H-6: 7.55, CH_3: 1.67
17e*S*	5.87	5.25	5.02	4.30	3.91	3.83	3.78	3.53	1.11	NH: 11.40, H-6: 7.52, CH_3: 1.69
17f*R*	5.92	5.17	4.96	4.36	3.95	3.83	3.76 3.73	3.68	1.18	[b]
17f*S*	5.89	5.23	5.04	4.36	3.94	3.83	3.79	3.54	1.11	[c]

[a] aromH: multiplet δ8.05-7.50, tBu: singlet δ1.0; [b] N-CH_2OPh: doublet δ5.29, 5.22, aromH,H-6: multiplet δ7.60 (5H), δ7.36-7.48 (6H), δ7.20-7.32 (6H); [c] N-CH_2OPh: doublet δ5.29, 5.23, aromH, H-6: multiplet δ7.60 (5H), δ7.36-7.48 (6H), δ7.20-7.32 (6H).

Table 9. ^{1}H NMR Coupling Constants (Hz) of 2′,3′-*O*-Alkoxyalkylidene Derivates of Nucleosides.

Compound	1′,2′	2′,3′	3′,4′	4′,5′a	4′,5′b	5′a,5′b	Other J[a]
8*R*	2.7	7.3	3.9	5.6	6.3	11.0	
9a*R*	2.7	7.3	3.9	5.6	6.3	11.0	
9b*R*	2.0	7.1	4.2	4.9	7.1	11.2	
9b*S*	1.5	6.3	4.2	4.5	7.0	11.2	
9c*R*	2.2	7.1	3.7	5.1	6.1	11.0	H-6,H-5 = 7.6
9c*S*	1.7	6.3	3.7	4.0	6.1	11.0	H-6,H-5 = 7.6
9d*R*	2.9	7.3	4.4	4.9	5.8	11.0	H-6,H-5 = 8.1
9d*S*	2.2	6.3	4.4	4.4	6.1	11.0	H-6,H-5 = 8.1
9e*R*	3.0	7.3	4.4	4.9	5.9	11.0	H-6,CH_3 = 1.2
9e*S*	2.4	6.3	4.4	4.1	5.9	11.0	H-6,CH_3 = 1.2
10a*R*	2.0	7.1	3.7	5.4	6.4	11.2	
10a*S*	1.5	6.3	3.7	5.3	6.4	11.2	
10b*R*	1.7	7.1	3.4	5.0	6.0	11.0	
10b*S*	1.6	6.3	3.9	5.0	6.0	11.0	
10c*R*	2.2	7.1	3.4	4.6	6.1	11.2	H-6,H-5 = 7.6
10c*S*	1.5	6.3	3.4	4.2	6.1	11.2	H-6,H-5 = 7.6
10d*R*	2.0	7.3	4.2	4.2	5.9	11.2	H-6,H-5 = 8.1
10d*S*	1.2	6.6	4.1	4.2	6.1	11.2	H-6,H-5 = 8.1
10e*R*	2.9	7.0	4.2	4.2	5.9	11.2	H-6,CH_3 = 1.2
10e*S*	2.4	6.6	4.4	4.4	6.1	11.2	H-6,CH_3 = 1.2
11a*R*	2.7	7.1	3.7	5.6	6.6	11.0	
11a*S*	2.0	6.6	3.4	5.6	6.6	11.0	
11b*R*	2.0	7.1	2.9	5.1	7.3	11.2	
11b*S*	1.5	6.6	4.2	4.5	7.3	11.2	
11c*R*	2.2	7.1	3.4	4.9	6.1	11.2	H-6,H-5 = 7.8
11c*S*	1.7	6.3	3.4	4.4	6.3	11.2	H-6,H-5 = 7.8
11d*R*	2.7	7.1	4.1	4.9	6.4	11.0	H-6,H-5 = 8.1
11d*S*	2.0	6.6	4.1	4.6	6.6	11.0	H-6,H-5 = 8.1
11e*R*	2.9	7.0	4.2	4.6	6.1	11.0	H-6,CH_3 = 1.2
11e*S*	2.2	6.6	4.2	4.6	6.3	11.0	H-6,CH_3 = 1.2
13*R*	3.2	7.3	3.9	4.2	6.1	11.5	
17a*R*	2.2	7.1	3.2	5.9	6.3	11.0	
17a*S*	2.0	6.8	3.4	5.4	6.8	11.0	
17e*R*	2.4	7.3	3.7	4.6	6.1	11.2	H-6,CH_3 = 1.2
17e*S*	2.0	7.0	4.4	4.4	6.3	11.0	H-6,CH_3 = 1.2
17f*R*	2.4	7.1	3.7	4.6	6.3	11.0	[b]
17f*S*	2.0	7.0	4.2	4.5	6.3	11.0	[c]

[a] $J(CH_2,CH_3)$ = 7.1 Hz; [b] CH_2Br: J(gem) = 11.5, N-CH_2: J(gem) = 9.8; [c] N-CH_2: J(gem) = 9.8.

Table 10. ^{13}C NMR Chemical Shifts (ppm) of 2′,3′-*O*-Alkoxyalkylidene Derivates of Nucleosides[a].

Compound	C-1′	C-2′	C-3′	C-4′	C-5′	O-C-O	O-CH_2 O-CH_3	CH_3	R^2	C-2	C-4	C-5	C-6	C-8	CH_3
8*R*	89.88	83.43	81.05	86.88	64.15	118.74	52.12	--	--	151.79	150.76	125.99	151.70	141.30	--
9a*R*	89.77	83.44	81.00	86.71	64.15	118.07	60.52	15.11	--	151.78	150.75	125.98	151.71	141.20	--
9b*R*	89.66	84.12	80.65	87.51	64.90	117.98	60.51	15.14	--	147.80	147.84	121.39	155.15	141.50	--
9b*S*	88.58	82.63	80.24	86.84	64.69	116.75	59.29	15.10	--	147.80	147.84	121.49	155.11	141.50	--
9c*R*	95.26	84.34	81.17	87.90	64.53	117.62	60.29	15.11	--	154.42	163.86	96.44	147.58	--	--
9c*S*	94.22	83.52	80.39	87.09	64.20	116.00	59.11	15.08	--	154.42	163.85	96.40	147.60	--	--
9d*R*	92.77	83.62	80.78	86.76	64.47	117.83	60.38	15.11	--	150.44	163.37	101.96	142.81	--	--
9d*S*	92.05	82.64	80.08	86.01	64.17	116.68	59.07	15.03	--	150.44	163.34	101.89	142.89	--	--
9e*R*	91.91	83.29	80.58	86.18	64.37	117.96	60.38	15.11	--	150.48	163.98	109.80	138.15	--	12.03
9e*S*	91.27	82.40	79.87	85.44	64.10	116.80	59.06	15.02	--	150.48	163.96	109.84	138.01	--	12.03
10b*R*	89.63	84.06	80.81	87.70	64.94	125.01	58.08	15.19	22.16	147.85	148.00	121.43	155.19	142.00	--
10b*S*	89.01	84.30	81.36	87.72	64.84	124.70	57.36	15.22	24.19	147.86	148.00	121.49	155.15	142.00	--
10c*R*	95.50	84.50	81.16	87.93	64.55	124.64	57.94	15.09	21.92	154.51	163.85	96.30	147.40	--	--
10c*S*	95.02	85.10	81.72	87.93	64.34	124.28	57.32	15.25	23.90	154.51	163.93	96.32	147.42	--	--
10e*R*	91.88	83.40	80.55	86.11	64.40	125.03	58.11	15.03	21.77	150.52	163.99	109.81	137.94	--	12.00
10e*S*	91.67	84.02	81.19	86.25	64.20	124.73	57.32	15.23	24.01	150.49	164.03	109.73	138.29	--	12.04
11a*R*	89.71	83.80	81.62	86.74	64.13	124.44	58.96	14.99	b	151.77	150.77	126.03	151.71	141.14	--
11a*S*	89.18	84.28	82.21	86.36	63.89	123.96	58.56	15.10	c	151.77	150.75	126.11	151.63	141.14	--
11b*R*	88.66	84.43	81.37	87.68	64.96	124.30	58.83	14.99	b	147.79	147.82	121.43	155.12	141.25	--
11b*S*	88.64	84.72	81.78	87.08	64.76	123.78	58.41	15.07	c	147.79	147.82	121.47	155.10	141.25	--
11c*R*	95.18	84.72	81.76	87.93	64.59	123.88	58.74	14.94	b	154.53	163.89	96.35	147.50	--	--
11c*S*	94.95	85.47	82.30	87.54	64.40	123.43	58.33	15.12	c	154.53	163.97	96.35	147.65	--	--
11d*R*	92.76	83.98	81.34	86.77	64.54	124.15	58.83	14.89	b	150.50	163.36	101.94	142.91	--	--
11d*S*	92.70	84.72	81.94	86.53	64.36	123.67	58.35	15.12	c	150.45	163.44	101.82	143.30	--	--
11e*R*	91.92	83.64	81.08	86.12	64.42	124.26	58.85	14.89	b	150.47	163.97	109.81	138.15	--	12.05
11e*S*	91.88	84.44	81.75	85.94	64.28	123.77	58.36	15.12	c	150.53	164.04	109.65	138.57	--	12.05
13*R*	89.99	83.34	80.78	84.09	64.45	118.85	52.20	--	--	151.94	150.76	125.95	151.80	141.30	--
17a*R*	89.79	84.47	82.50	86.99	63.89	123.98	58.19	15.05	33.57	151.76	150.77	125.90	151.55	143.69	--
17a*S*	89.38	84.65	82.53	86.71	63.92	123.40	58.11	15.11	33.71	151.77	150.75	125.96	151.64	143.69	--
17e*R*	92.35	84.59	81.89	86.60	64.33	123.80	58.17	14.98	33.55	150.52	164.03	109.71	138.42	--	12.03
17e*S*	92.07	84.84	82.00	86.29	64.25	123.28	57.99	15.11	33.63	150.48	160.04	109.73	138.53	--	12.05
17f*R*	93.60	84.75	81.99	87.02	64.28	123.79	58.14	14.98	33.62	150.66	162.98	108.95	137.97	--	12.64
17f*S*	93.24	84.94	82.04	86.67	64.21	123.24	58.04	15.12	33.57	150.65	162.98	108.99	137.86	--	12.63

[a] aromC: δ165.80, 133.50-128.00, *t*Bu: δ26.60, 18.90; [b] aromC: δ137.20, 129.40, 128.00 (2C), 125.90 (2C); [c] aromC: δ137.80, 129.40, 128.00 (2C), 125.90 (2C).

Table 11. ^{1}H NMR Chemical Shifts (ppm) of 2′,3′-*O*-Diethylphosphonoalkylidene Derivates of Nucleosides[a].

Compound	H-1′	H-2′	H-3′	H-4′	H-5′a	H-5′b	R^2	$O-CH_2-CH_3$		Base
18a*R*	6.53	5.60	5.29	4.52	3.89	3.79	5.50	4.21	1.31	NH: 11.26, H-2: 8.67, H-8: 8.61
18a*S*	6.43	5.65	5.37	4.41	3.92	3.81	5.87	4.14	1.27	NH: 11.27, H-2: 8.66, H-8: 8.62
18b*R*	6.39	5.32	5.56	4.47	3.87	3.84	5.43	4.18	1.29	NH: 12.16 a 11.62, H-8: 8.24
18b*S*	6.29	5.26	5.65	4.37	3.93	3.93	5.76	4.12	1.25	NH: 12.16 a 11.62, H-8: 8.22
18c*R*	5.98	5.13	4.97	4.48	3.98	3.85	5.37	4.17	1.28	NH: 11.35, H-6: 8.28, H-5: 7.30
18c*S*	5.93	5.18	5.08	4.36	4.01	3.87	5.74	4.11	1.25	NH: 11.35, H-6: 8.24, H-5: 7.30
18d*R*	5.95	5.09	4.95	4.37	3.89	3.82	5.39	4.16	1.27	NH: 11.41, H-6: 7.75, H-5: 5.51
18d*S*	5.87	5.12	5.03	4.23	3.93	3.85	5.72	4.11	1.25	NH: 11.42 ,H-6: 7.71, H-5: 5.54
18e*R*	5.93	5.07	4.95	4.34	3.90	3.82	5.40	4.16	1.27	NH: 11.40, H-6: 7.55, CH_3: 1.64
18e*S*	5.85	5.09	5.02	4.21	3.92	3.85	5.73	4.11	1.25	NH: 11.41, H-6: 7.52, CH_3: 1.67
19a*S*	6.40	5.76	5.40	4.39	3.88	3.73	1.66	4.11	1.25	NH: 11.25, H-2: 8.64, H-8: 8.59
19b*S*	6.28	5.37	5.54	4.32	3.95	3.92	1.64	4.07	1.22	NH: 12.18 a 11.60, H-8: 8.23
19c*R*	6.00	5.15	4.93	4.58	3.96	3.84	1.40	4.15	1.27	NH: 11.32, H-6: 8.26, H-5: 7.30
19c*S*	5.86	5.27	5.08	4.36	3.99	3.81	1.58	4.09	1.24	NH: 11.32, H-6: 8.26, H-5: 7.30
19d*R*	6.05	5.40	5.12	4.48	3.88	3.81	1.40	4.14	1.27	NH: 11.40, H-6: 7.75, H-5: 5.55
19d*S*	5.81	5.25	5.04	4.22	3.90	3.79	1.58	4.08	1.24	NH: 11.39, H-6: 7.74, H-5: 5.54
19e*R*	6.02	5.12	4.98	4.46	3.90	3.85	1.41	4.15	1.27	NH: 11.40, H-6: 7.51, CH_3: 1.64
19e*S*	5.80	5.21	5.08	4.21	3.91	3.80	1.58	4.07	1.24	NH: 11.39, H-6: 7.56, CH_3: 1.68
19f*R*	5.86	5.27	5.08	4.27	3.95	3.80	1.59	4.15	1.24	H-6: 7.75, CH_2N: 5.98, CH_3: 1.77
19f*S*	5.82	5.23	5.10	4.25	3.94	3.79	1.59	4.11	1.23	H-6: 7.60, CH_2N: 5.28, CH_3: 1.23
20a*R*	6.64	5.43	5.13	4.65	3.90	3.80	7.50	4.20	1.24	NH: 11.23, H-2: 8.68, H-8:8.54
20a*S*	6.39	5.93	5.64	4.16	3.88	3.73	7.50	4.10	1.18	NH: 11.25, H-2: 8.64, H-8: 8.61
20b*R*	6.50	5.12	5.42	4.64	3.97	3.95	7.50	4.11	1.22	NH: 12.12 a 11.52, H-8: 8.26
20b*S*	6.24	5.51	5.89	4.08	3.92	3.86	7.50	4.01	1.15	NH: 12.15 a 11.58, H-8: 8.24
20c*R*	6.07	4.94	4.78	4.59	4.00	3.90	7.50	4.10	1.20	NH: 11.26, H-6: 8.28, H-5: 7.30
20c*S*	5.83	5.45	5.27	4.13	3.98	3.81	7.50	4.00	1.16	NH: 11.34, H-6: 8.24, H-5: 7.30
20d*R*	6.03	4.91	4.80	4.48	3.91	3.82	7.50	4.10	1.19	NH: 11.35, H-6: 7.75, H-5: 5.51
20d*S*	5.77	5.42	5.23	3.94	3.88	3.77	7.50	4.00	1.16	NH: 11.38, H-6: 7.73, H-5: 5.54
20e*R*	6.04	4.91	4.82	4.45	3.91	3.84	7.50	4.12	1.20	NH: 11.37, H-6: 7.50, CH_3: 1.67
20e*S*	5.74	5.41	5.27	3.96	3.90	3.79	7.50	4.01	1.17	NH: 11.40, H-6: 7.50, CH_3: 1.68
21*R*	6.52	5.70	5.37	4.74	4.60	4.50	5.50	4.20	1.30	NH: 11.24, H-2: 8.69, H-8: 8.66
21*S*	6.44	5.72	5.43	4.62	4.64	4.50	5.88	4.13	1. 26	NH: 11.24, H-2: 8.70, H-8: 8.67
22*R*[b]	6.44	5.56	5.08	4.42	3.59	3.57	5.34	4.20	1.31	NH: 11.21, H-2: 8.77, H-8: 8.71
22*S*[b]	6.35	5.62	5.19	4.30	3.60	3.57	5.84	4.13	1.27	NH: 11.24, H-2: 8.78, H-8: 8.70
23*S*[c]	6.37	5.75	5.35	4.46	3.84	3.72	3.60; 3.54	4.12	1.26	NH: 11.25 and 7.80, H-2: 8.60, H-8: 8.58
25*S*[c]	6.35	5.78	5.40	4.43	3.83	3.67	3.79; 3.73	4.15	1.28	NH: 11.24 and 9.77, H-2: 8.66, H-8: 8.59
26*S*[c]	6.49	5.80	5.48	4.38	3.83	3.67	4.81; 4.65	4.18	1.28	NH: 11.25, H-2: 8.63, H-8: 8.60
27*S*[c]	6.46	5.88	5.44	4.42	3.81	3.65	4.59; 2.25	4.13	1.26	NH: 11.25, H-2: 8.62, H-8: 8.57
28a*S*	6.55	5.86	5.47	4.61	3.90	3.75	3.95	4.15	1.27	NH: 11.23, H-2: 8.71, H-8: 8.59
28e*S*	5.92	5.34	5.14	4.48	3.92	3.81	3.87	4.11	1.25	NH: 11.40, H-6: 7.58, CH_3: 1.70
28f*R*[c]	5.99	5.39	5.16	4.70	3.94	3.79	3.90	4.16	1.26	H-6: 7.82, CH_2N: 5.96, CH_3: 1.78
28f*S*[d]	5.93	5.36	5.17	4.52	3.95	3.80	3.89	4.09	1.24	H-6: 7.71, CH_2N: 5.26, CH_3: 1.74
29*S*	6.51	5.86	5.47	4.55	3.89	3.75	4.06	4.15	1.26	NH: 11.23, H-2: 8.70, H-8: 8.59

[a] aromH: multiplet δ8.05-7.50, *t*Bu: singlet δ1.0-0.95; [b] 5′-OH: triplet δ5.19; [c] $O-CH_2-N$: doublets δ6.00, 5.95; [d] $O-CH_2-N$: doublets δ5.30, 5.20.

Table 12. ^{1}H NMR Coupling Constants (Hz) of 2′,3′-*O*-Diethylphosphonoalkylidene Derivates of Nucleosides.

Compound	1′,2′	2′,3′	3′,4′	4′,5′a	4′,5′b	5′a,5′b	P,CH	P,OCH[a]	Other J
18a*R*	2.2	6.3	3.7	5.4	6.3	10.7	28.6	7.6	
18a*S*	2.4	6.3	3.9	5.4	6.3	10.7	28.3	7.6	
18b*R*	1.7	6.3	4.4	4.6	6.8	11.0	28.8	7.6	
18b*S*	1.7	6.1	4.4	5.9	5.9	--	28.6	7.6	
18c*R*	1.7	6.3	3.7	4.6	6.1	11.0	28.6	7.1	H-6,H-5 = 7.8
18c*S*	1.7	6.3	3.7	4.6	6.1	11.0	28.3	7.3	H-6,H-5 = 7.8
18d*R*	2.0	6.3	4.2	4.6	6.1	11.0	28.8	7.5	H-6,H-5 = 8.1; H-5,NH = 2.2
18d*S*	2.2	6.3	4.4	4.6	6.1	11.0	28.1	7.5	H-6,H-5 = 8.1; H-5,NH = 2.2
18e*R*	2.4	6.6	4.2	4.6	5.9	11.0	29.0	7.8	H-6,CH_3 = 1.2
18e*S*	2.7	6.3	4.4	4.6	5.9	11.0	28.1	7.8	H-6,CH_3 = 1.2
19a*S*	2.0	6.4	3.2	6.1	6.3	10.7	--	7.3	P,CH_3 = 10.2
19b*S*	2.0	6.3	3.9	4.9	7.0	11.6	--	7.5	P,CH_3 = 10.5
19c*R*	2.0	6.3	3.2	5.0	6.0	10.5	--	7.5	P,CH_3 = 10.7; H-6,H-5 = 7.6
19c*S*	1.7	6.3	3.2	4.8	5.9	10.5	--	7.5	P,CH_3 =10.3 ; H-6,H-5 = 7.6
19d*R*	2.0	6.3	4.0	5.0	6.0	10.7	--	7.8	P,CH_3 = 10.7;H-6,H-5 = 8.0; H-5,NH = 2.0
19d*S*	2.2	6.3	3.9	5.1	6.3	10.7	--	7.8	P,CH_3 = 10.3; H-6,H-5 = 8.0; H-5,NH=2.2
19e*R*	2.4	6.6	4.6	5.0	7.0	10.7	--	7.5	P,CH_3 = 10.7; H-6,CH_3 = 1.0
19e*S*	2.4	6.6	3.6	5.1	7.0	10.7	--	7.5	P,CH_3 =10.3; H-6,CH_3 = 1.2
19f*R*	2.4	6.6	3.7	5.5	5.5	11.0	--	7.8	P,CH_3 = 10.3; H-6,CH_3 = 1.0
19f*S*	2.2	6.6	3.7	5.1	5.9	11.0	--	7.8	P,CH_3 = 10.3; H-6,CH_3 = 1.2
20a*R*	2.0	6.3	3.7	5.9	6.4	10.8	--	7.8	
20a*S*	1.7	6.1	3.9	6.1	6.3	10.8	--	7.8	
20b*R*	1.5	6.3	4.2	4.6	7.3	11.2	--	7.3	
20b*S*	1.5	6.1	4.6	4.1	8.0	11.2	--	7.3	
20c*R*	1.5	6.3	3.7	4.4	6.0	11.2	--	7.5	H-6,H-5 = 7.8
20c*S*	1.5	6.1	3.7	4.4	6.1	11.2	--	7.5	H-6,H-5 = 7.8
20d*R*	1.9	6.3	4.2	5.0	6.1	10.8	--	7.5	H-6,H-5 = 8.1; H-5,NH = 2.2
20d*S*	1.9	6.1	4.2	5.1	6.3	10.8	--	7.5	H-6,H-5 = 8.1; H-5,NH = 2.2
20e*R*	2.2	6.6	4.2	5.0	6.3	11.0	--	7.8	H-6,CH_3 = 1.0
20e*S*	2.2	6.3	4.2	4.9	6.1	10.7	--	7.8	H-6,CH_3 = 1.2
21*R*	2.4	6.3	4.1	4.4	5.6	12.0	28.3	7.8	
21*S*	2.7	6.3	4.1	4.1	5.6	12.0	27.8	7.8	
22*R*[b]	2.9	6.1	2.7	4.6	4.6	12.2	28.6	7.8	H-5′,OH = 5.3
22*S*[b]	2.9	6.1	2.9	5.1	5.1	11.9	28.6	7.8	H-5′,OH = 5.3
23*S*	2.2	6.6	3.4	5.4	6.6	10.7	--	7.1	P,CCH_2 = 6.6 and 6.4
25*S*	1.5	6.3	2.9	5.9	6.8	10.7	--	7.1	P,CCH_2 = 6.63 and 5.9
26*S*	1.8	6.4	3.3	6.1	6.6	10.0	--	7.1	P,CCH_2 = 2.4
27*S*	2.0	6.6	2.9	6.3	6.6	10.7	--	7.1	
28a*S*	2.2	6.8	3.2	6.3	6.3	10.7	--	7.3	
28e*S*	2.4	6.8	3.6	5.9	6.3	11.0	--	7.5	H-6,CH_3 = 1.2
28f*R*[c]	2.2	7.1	3.5	5.6	6.5	10.7	--	7.8	H-6,CH_3 = 1.0
28f*S*[d]	2.2	7.1	3.4	5.6	6.4	10.7	--	7.8	H-6,CH_3 = 1.2
29*S*	2.2	6.8	3.2	6.3	6.3	10.7	--	7.3	

[a] $J(CH_2,CH_3)$ = 7.1.

Table 13. ^{13}C NMR Chemical Shifts (ppm), Coupling Constants (Hz), and ^{31}P NMR Chemical Shifts (ppm) of 2′,3′-*O*-Diethylphosphonoalkylidene Derivates of Nucleosides[a].

Compound	C-1′	C-2′	C-3′	C-4′	C-5′	O-C-O	R^2	C-2	C-4	C-5	C-6	C-8	CH_3	P
18a*R*	88.16	84.27 (7.8)	82.84 (6.6)	85.66	63.92	102.53 (194.4)	--	151.77	150.78	125.99	151.65	143.77	--	13.07
18a*S*	88.20	84.16 (4.5)	82.34 (3.9)	84.40	63.82	101.08 (194.3)	--	151.77	150.78	125.96	151.70	143.77	--	13.01
18b*R*	87.51	85.79 (8.8)	81.96 (8.2)	86.46	64.69	102.36 (195.3)	--	147.83	147.90	121.45	155.14	139.00	--	13.10
18b*S*	88.09	84.58 (4.4)	81.93 (4.0)	84.73	64.87	100.43 (194.4)	--	147.83	147.87	121.49	155.14	139.00	--	12.88
18c*R*	93.90	86.47 (7.5)	82.76 (7.8)	87.09	64.29	101.98 (195.3)	--	154.50	164.00	96.47	147.55	--	--	13.05
18c*S*	94.06	85.47 (2.0)	82.49 (2.0)	85.88	64.29	100.79 (194.4)	--	154.50	163.98	96.47	147.55	--	--	13.25
18d*R*	91.62	85.71 (8.8)	82.52 (6.8)	85.94	64.31	102.36 (195.3)	--	150.48	163.41	101.89	143.06	--	--	13.13
18d*S*	91.62	84.55 (4.2)	82.05 (3.4)	84.55	64.25	100.69 (194.3)	--	150.51	163.41	102.01	142.98	--	--	13.02
18e*R*	90.95	85.35 (7.5)	82.44 (7.3)	85.39	64.27	102.45 (195.3)	--	150.44	163.99	109.70	138.30	--	12.00	13.14
18e*S*	90.65	84.20 (5.0)	81.82 (5.2)	83.80	64.17	100.65 (193.4)	--	150.48	163.96	109.84	138.14	--	12.04	12.99
19a*S*	89.33	85.66	83.86	86.60	63.66	111.41 (200.2)	22.54 (20.5)	151.76	150.80	126.06	151.76	142.80	--	15.75
19b*S*	88.45	86.32	82.97	87.54	64.83	111.28 (201.2)	22.85 (20.5)	147.90	147.96	121.54	155.18	139.00	--	15.58
19c*R*	93.61	85.70 (5.0)	82.21 (5.0)	86.43	64.35	110.91 (200.0)	22.48 (21.5)	154.55	164.00	96.35	147.65	--	--	15.72
19c*S*	95.03	87.16	83.83	88.10	64.26	110.66 (200.2)	22.57 (21.5)	154.55	164.00	96.34	147.64	--	--	16.02
19d*S*	92.84	86.39	83.46	87.16	64.20	111.11 (199.2)	22.61 (20.5)	150.50	163.46	101.86	143.24	--	--	15.81
19e*S*	91.82	86.06	83.42	86.49	64.03	111.27 (199.2)	22.69 (20.5)	150.52	164.05	109.73	138.41	--	12.03	15.77
19f*R* [c]	93.20	86.18	83.31	86.80	64.03	110.64 (186.5)	22.50 (20.5)	150.16	162.36	108.89	137.80	--	12.54	15.50
19f*S* [c]	93.16	86.28	83.42	86.87	64.10	111.17 (200.2)	22.59 (20.5)	150.64	162.98	108.95	137.84	--	12.62	15.82
20a*R*	88.33	82.64	82.31	84.42	63.75	110:60 (202.0)	b	151.70	150.78	126.00	151.50	143.00	--	12.87
20a*S*	88.63	85.98	84.01	86.18	63.77	111.23 (202.2)	b	151.71	150.78	126.01	151.56	143.00	--	13.93
20b*R*	86.88	82.62	82.21	85.05	64.85	110.50 (202.2)	b	147.80	147.84	121.51	155.12	139.00	--	13.16
20b*S*	87.99	86.55	83.11	86.77	64.87	110.88 (203.1)	b	147.80	147.84	121.57	155.15	139.00	--	13.78
20c*R*	94.00	82.90	82.20	85.05	64.30	110.40 (202.0)	b	154.54	164.97	96.34	147.86	--	--	12.82
20c*S*	94.72	87.36	84.10	87.41	64.31	110.62 (202.2)	b	154.54	164.02	96.34	147.86	--	--	14.15
20d*S*	92.59	86.28	83.77	86.71	64.26	110.88 (202.2)	b	150.46	163.45	101.79	143.44	--	--	13.94
20e*R*	91.10	84.57 (6.5)	82.26 (6.0)	85.62	64.09	111.04 (196.4)	b	150.47	164.05	109.66	138.68	--	12.00	12.92
20e*S*	91.89	85.79	83.75	86.41	64.24	111.02 (200.3)	b	150.47	164.05	109.61	138.68	--	12.03	13.92
21*R*	88.45	84.97 (8.0)	82.68 (7.8)	82.77	64.15	102.56 (193.7)	--	151.92	150.77	125.91	151.80	143.61	--	12.96
21*S*	88.09	84.11 (5.3)	81.89 (4.3)	81.56	64.10	100.96 (194.4)	--	151.93	150.77	125.91	151.81	143.61	--	12.78
22*R*	88.60	84.87 (7.5)	83.58 (8.6)	85.93	61.49	102.06 (194.4)	--	151.95	150.64	125.83	152.03	143.33	--	13.02

Table 13. ^{13}C NMR Chemical Shifts (ppm), Coupling Constants (Hz), and ^{31}P NMR Chemical Shifts (ppm) of 2′,3′-*O*-Diethylphosphonoalkylidene Derivates of Nucleosides[a] (continuation).

Compound	C-1′	C-2′	C-3′	C-4′	C-5′	O-C-O	R^2	C-2	C-4	C-5	C-6	C-8	CH_3	P
22*S*	88.25	84.27 (4.3)	82.69 (4.3)	85.10	61.42	100.88 (194.4)	--	151.93	150.68	125.86	151.99	143.84	--	13.08
28a*S*	89.07	86.35	84.59	86.43	63.72	110.19 (197.3)	34.03 (40.0)	151.76	150.79	126.00	151.57	142.80	--	11.63
28e*S*	92.28	86.25	84.17	86.75	64.25	110.06 (197.3)	34.11 (10.0)	150.54	164.10	109.65	138.87	--	12.03	15.70
28f*R*	93.05	86.50	84.12	86.70	64.10	110.00 (196.0)	34.10 (40.0)	150.20	162.37	108.84	138.30	--	12.54	11.50
28f*S*	93.39	86.60	84.21	86.85	64.17	109.96 (196.3)	34.13 (40.0)	150.68	163.01	108.89	138.29	--	12.62	11.72
29*S*	88.90	86.14	84.48	86.26	63.68	110.79 (198.3)	44.40 (39.1)	151.77	150.80	126.00	151.60	142.20	--	13.11

[a] aromC: δ165.80, 133.50-128.0, P-OCH_2CH_3: doublets δ63.50-62.90 (J = 6.8), doublets δ16.50-16.20 (J = 4.9), *t*Bu: δ26.60, 18.90; [b] P-Oarom: doublet δ137.30 (J = 19.5), 129.30, 128.20 (2C), 126.30 (2C); [c] aromC: δ138.30, 128.30 (2C), 127.60, 127.42 (2C), O-CH_2-N: δ71.22 (*S*), δ70.38 (*R*).

Table 14. ^1H NMR Chemical Shifts (ppm) of 2′,3′-*O*-Phosphonoalkylidene Derivates of Nucleosides (in D_2O).

Compound	H-1′	H-2′	H-3′	H-4′	H-5′a	H-5′b	R^2	Base
30a*R*	6.28	5.35	5.02	4.66	3.87	3.23	5.22	H-2: 8.28, H-8: 8.12
30a*S*	6.18	5.39	5.12	4.44	3.90	3.85	5.43	H-2: 8.23, H-8: 8.07
30b*R*	6.14	5.33	5.02	4.57	3.80	3.78	5.21	H-8: 7.94
30b*S*	6.06	5.37	5.13	4.37	3.85	3.80	5.39	H-8: 7.92
30c*R*	5.84	4.98	4.88	4.27	3.91	3.85	5.10	H-6: 7.70, H-5: 6.02
30d*R*	5.95	5.08	4.87	4.48	3.85	3.79	5.15	H-6: 7.79, H-5: 5.86
30d*S*	5.89	5.10	4.96	4.29	3.90	3.83	5.31	H-6: 7.75, H-5: 5.87
30e*R*	5.96	5.10	4.88	4.44	3.87	3.80	5.17	H-6: 7.61, CH_3: 1.90
30e*S*	5.89	5.09	4.97	4.26	3.91	3.85	5.33	H-6: 7.56, CH_3: 1.89
31a*S*	6.21	5.50	5.25	4.53	3.82	3.78	1.77	H-2: 8.26, H-8: 8.10
31b*S*	6.10	5.54	5.23	4.46	3.79	3.74	1.74	H-8: 7.94
31c*R*	5.93	5.21	4.96	4.50	3.85	3.80	1.48	H-6: 7.78, H-5: 6.03
31c*S*	5.88	5.17	4.99	4.38	3.86	3.78	1.68	H-6: 7.73, H-5: 6.02
31d*R*	6.00	5.19	4.96	4.51	3.85	3.80	1.47	H-6: 7.79, H-5: 5.88
31d*S*	5.92	5.20	5.00	4.38	3.86	3.78	1.68	H-6: 7.78, H-5: 5.87
31e*R*	6.00	5.19	4.97	4.47	3.85	3.80	1.48	H-6: 7.62, CH_3: 1.90
31e*S*	5.93	5.20	5.01	4.34	3.86	3.79	1.68	H-6: 7.60, CH_3: 1.89
32a*R*	6.43	5.15	4.81	4.74	3.81	3.75	7.50	H-2: 8.20, H-8: 8.05
32a*S*	5.85	5.56	5.33	4.30	3.76	3.72	7.50	H-2: 8.04, H-8: 7.99
32b*R*	6.32	5.17	4.85	4.68	3.80	3.75	7.50	H-8: 7.90
32b*S*	5.89	5.63	5.36	4.24	3.74	3.71	7.50	H-8: 7.82

Table 14. ^{1}H NMR Chemical Shifts (ppm) of 2′,3′-*O*-Phosphonoalkylidene Derivates of Nucleosides (in D_2O) (continuation).

Compound	H-1′	H-2′	H-3′	H-4′	H-5′a	H-5′b	R^2	Base
32c*R*	6.08	4.81	4.68	4.62	3.90	3.76	7.50	H-6: 7.59, H-5: 5.98
32c*S*	5.67	5.26	5.13	4.12	3.78	3.73	7.50	H-6: 7.61, H-5: 5.96
32d*R*	6.09	4.91	4.71	4.59	3.85	3.73	7.50	H-6: 7.75, H-5: 5.83
32d*S*	5.75	5.31	5.13	4.15	3.79	3.74	7.50	H-6: 7.72, H-5: 5.84
32e*R*	6.10	4.85	4.68	4.58	3.86	3.77	7.50	H-6: 7.56, CH_3: 1.86
32e*S*	5.77	5.28	5.12	4.09	3.79	3.75	7.50	H-6: 7.54, CH_3: 1.88

Table 15. ^{1}H NMR Coupling Constants (Hz) of 2′,3′-*O*-Phosphonoalkylidene Derivates of Nucleosides (in D_2O).

Compound	1′,2′	2′,3′	3′,4′	4′,5′a	4′,5′b	5′a,5′b	P,CH	Other J
30a*R*	3.9	6.1	2.4	2.9	4.1	12.2	20.3	
30a*S*	3.4	6.3	3.9	3.7	4.9	12.4	19.8	
30b*R*	3.2	6.3	3.2	3.5	4.0	12.7	20.8	
30b*S*	2.7	6.3	4.0	3.9	4.6	12.7	20.3	
30c*R*	2.9	6.6	4.6	3.9	5.9	12.2	15.9	H-6,H-5 = 7.6
30d*R*	2.0	6.3	3.7	3.7	5.6	12.2	20.8	H-6,H-5 = 8.0
30d*S*	2.0	6.3	4.7	3.7	5.9	12.2	20.5	H-6,H-5 = 8.0
30e*R*	2.7	6.6	3.7	3.9	5.6	12.2	21.2	H-6,CH_3 = 1.0
30e*S*	2.9	6.3	4.9	3.9	5.6	12.2	20.5	H-6,CH_3 = 1.0
31a*S*	3.4	6.3	2.7	3.7	4.6	12.4	--	P,CH_3 = 9.3
31b*S*	2.9	6.3	2.9	3.9	5.6	12.4	--	P,CH_3 = 9.3
31c*R*	2.7	6.3	3.9	3.9	5.6	12.4	--	P,CH_3 = 10.0; H-6,H-5 = 8.0
31c*S*	2.7	6.3	3.7	3.7	5.9	12.4	--	P,CH_3 = 10.3; H-6,H-5 = 7.8
31d*R*	2.7	6.3	3.9	3.9	5.4	12.4	--	P,CH_3 = 9.8; H-6,H-5 = 8.0
31d*S*	2.7	6.3	3.7	3.7	5.9	12.4	--	P,CH_3 = 9.0; H-6,H-5 = 8.1
31e*R*	2.7	6.3	4.2	4.2	5.1	12.4	--	P,CH_3 = 9.8; H-6,CH_3 = 1.0
31e*S*	2.7	6.3	3.9	3.9	5.6	12.4	--	P,CH_3 = 9.3; H-6,CH_3 = 1.0
32a*R*	3.4	6.4	2.4	3.4	3.6	12.4	--	
32a*S*	2.4	6.1	2.7	4.2	3.4	12.4	--	
32b*R*	2.9	6.6	2.9	3.9	4.7	12.2	--	
32b*S*	2.7	6.1	3.2	3.9	4.9	12.7	--	
32c*R*	2.4	6.6	3.9	3.9	5.9	12.2	--	H-6,H-5 = 7.6
32c*S*	2.4	6.3	3.9	4.1	5.6	12.2	--	H-6,H-5 = 7.6
32d*R*	2.2	6.6	3.9	3.9	5.6	12.2	--	H-6,H-5 = 8.1
32d*S*	2.7	6.3	3.9	3.9	5.6	12.2	--	H-6,H-5 = 8.1
32e*R*	2.4	6.6	3.9	3.9	5.9	12.2	--	H-6,CH_3 = 1.0
32e*S*	2.9	6.3	3.9	3.9	5.4	12.4	--	H-6,CH_3 = 1.0

Table 16. ^{13}C NMR Chemical Shifts (ppm), Coupling Constants (Hz), and ^{31}P NMR Chemical Shifts (ppm) of 2′,3′-*O*-Phosphonoalkylidene Derivates of Nucleosides (in D_2O).

Compound	C-1′	C-2′	C-3′	C-4′	C-5′	O-C-O	R^2	C-2	C-4	C-5	C-6	C-8	CH_3	P
30a*R*	89.80	83.46 (7.8)	82.82 (9.8)	84.92	61.41	104.09 (179.7)	--	151.96	147.73	118.48	154.95	142.29	--	6.37
30a*S*	88.03	83.35 (6.8)	80.69 (6.8)	83.85	61.18	101.11 (180.7)	--	152.00	147.75	118.11	154.74	142.10	--	8.42
30b*R*	88.93	83.87 (8.8)	82.63 (9.8)	85.18	61.28	103.75 (180.7)	--	153.27	150.56	116.04	158.29	137.80	--	6.49
30b*S*	88.00	83.42 (6.8)	81.03 (6.8)	84.02	61.21	100.88 (182.6)	--	153.30	150.69	115.91	158.32	137.88	--	6.80
30c*R*	93.57	84.22 (8.8)	80.86 (7.8)	84.26	62.04	101.88 (172.9)	--	157.53	166.74	96.26	143.90	--	--	7.75
30d*R*	92.47	84.98 (8.8)	81.73 (9.8)	85.74	61.04	103.65 (181.6)	--	150.95	166.10	101.47	143.51	--	--	8.28
30d*S*	92.07	83.74 (7.8)	80.67 (7.8)	83.79	61.18	100.63 (182.6)	--	150.95	166.02	101.69	143.51	--	--	8.54
30e*R*	91.89	84.81 (8.8)	81.63 (8.8)	85.40	61.05	103.38 (181.6)	--	151.04	166.26	110:70	139.18	--	11.00	6.56
30e*S*	91.37	83.60 (7.8)	80.59 (7.8)	83.40	61.16	100.60 (182.6)	--	151.04	166.21	110.91	139.03	--	11.05	6.79
31a*S*	90.40 (2.0)	85.09	83.29	86.65 (0.7)	61.82	113.88 (189.5)	22.94 (18.6)	152.71	148.43	118.77	155.47	140.62	--	13.06
31b*S*	89.94 (2.0)	85.32	83.20	87.07 (0.7)	61.76	113.71 (189.5)	22.85 (18.6)	153.89	151.29	116.51	158.96	138.29	--	13.07
31c*R*	93.25	86.06 (6.8)	81.11 (6.0)	86.85	61.77	112.98 (200.0)	21.10 (18.0)	157.25	166.60	96.10	144.03	--	--	11.77
31c*S*	93.94 (2.0)	86.48	82.60	87.03 (0.7)	61.70	113.52 (190.4)	22.88 (19.5)	157.26	166.50	96.06	143.53	--	--	13.22
31d*R*	93.12	84.47 (6.8)	80.99 (5.9)	86.20	61.65	114.61 (200.0)	21.50 (18.0)	151.40	166.70	102.00	144.09	--	--	11.58
31d*S*	93.23 (2.0)	86.04	82.53	87.10 (0.7)	61.61	113.86 (189.5)	22.93 (19.5)	151.63	166.68	102.06	143.67	--	--	13.02
31e*R*	92.40	84.25 (6.5)	80.92 (6.8)	85.72	61.60	114.60 (200.0)	21.48 (18.0)	151.70	166.90	111.35	139.76	--	11.00	11.61
31e*S*	92.52 (2.0)	85.80	82.42	86.70 (0.7)	61.58	113.87 (189.5)	22.89 (19.6)	151.71	166.90	111.36	139.29	--	11.07	13.04
32a*R*	90.29	84.09 (7.8)	82.00 (7.8)	85.77	61.93	112.50 (185.0)	b	152.46	148.00	119.00	155.25	140.62	--	9.41
32a*S*	89.62	85.27 (2.0)	83.32 (2.0)	85.88	61.81	112.81 (188.5)	a	152.46	148.08	118.77	155.29	140.62	--	11.13

Table 16. ^{13}C NMR Chemical Shifts (ppm), Coupling Constants (Hz), and ^{31}P NMR Chemical Shifts (ppm) of 2′,3′-*O*-Phosphonoalkylidene Derivates of Nucleosides (in D_2O) (continuation).

Compound	C-1′	C-2′	C-3′	C-4′	C-5′	O-C-O	R^2	C-2	C-4	C-5	C-6	C-8	CH_3	P
32b*R*	89.55	84.14 (7.8)	82.09 (8.8)	86.02	61.87	112.34 (184.0)	b	153.83	151.16	116.64	158.94	138.42	--	9.44
32b*S*	89.11	85.51 (2.9)	83.37 (2.0)	86.11	61.75	112.73 (189.5)	a	153.79	151.21	116.55	158.94	138.27	--	11.18
32c*R*	93.59	85.45 (8.8)	81.70 (8.8)	86.42	61.98	112.00 (182.5)	b	156.80	166.20	102.34	143.48	--	--	9.50
32c*S*	93.44	86.84 (3.9)	82.93 (2.7)	86.15	61.88	112.88 (186.5)	a	156.89	166.14	96.21	143.56	--	--	11.34
32d*R*	93.25	84.75 (7.8)	81.47 (7.8)	86.45	61.70	111.73 (185.0)	b	151.48	166.68	101.96	144.21	--	--	9.41
32d*S*	92.32	86.08 (3.9)	82.79 (2.9)	86.04	61.59	112.78 (188.5)	a	151.60	166.64	102.14	143.64	--	--	11.06
32e*R*	92.17	83.86 (7.8)	80.64 (7.8)	85.53	61.15	112.69 (178.0)	b	151.01	166.40	110.60	139.39	--	11.01	9.24
32e*S*	90.99	85.14 (3.9)	81.95 (2.9)	85.07	61.06	112.92 (183.6)	a	151.18	166.33	110.87	138.63	--	11.06	11.01

[a] aromC.: doublet δ139.70 (J = 16.6), 128.90, 128.30 (2C), 126.70 (2C);[b] aromC: doublet δ138.80 (J = 14.0), 129.00, 128.40 (2C), 126.90 (2C)

EXPERIMENTAL

Unless stated otherwise, the solvents were evaporated at 40 °C and 2 kPa and the products were dried over phosphorus pentoxide at 50 - 70 °C and 13 Pa. The reactions were monitored by TLC on Silufol UV 254 foils (Kavalier Glassworks, Votice, Czech Republic) and visualized in UV light or by spraying with 1% solution of 4-(4-nitrobenzyl)pyridine in ethanol, subsequent heating and exposure to ammonia vapours (detection of dialkyl esters of phosphonic acids, deep blue spots). Preparative column chromatography (PLC) was carried out on 20 - 40 μm spherical silica gel (Tessek, Prague); the amount of adsorbent was 20 - 40 times higher than the weight of the separated mixture. Elution was performed at the rate of 40 ml/min. PLC and TLC was carried out with the following solvent systems (v/v): toluene - ethyl acetate 4:1 (T-1), 1:1 (T-2); toluene - acetone 1:1 (T-3); chloroform - ethanol 9:1 (C-1); ethyl acetate - acetone - ethanol - water 4:1:1:1 (H-1), 12:2:2:1 (H-3); 2-propanol - concentrated aqueous ammonia - water 7:1:2 (I, for ionic compounds). Preparative chromatography on reverse phase was carried out on a spherical octadecyl silica column (25x300 mm, 20 - 40 μm, Tessek, Prague); compounds were eluted with a linear gradient of methanol in water at 10 ml/min. Chromatography on DEAE-Sephadex A-25 was performed with linear gradient of 0-0.2M triethylammonium hydrogencarbonate in water, and chromatography on Dowex 1 X 2 (acetate form) was performed with linear gradient of 0-2M acetic acid in water. HPLC analysis was performed on a column of reverse phase (4 x 250 mm) Separon SGX C18 7 μm (Tessek, Prague), either isocratically by various concentration of methanol in 0.1M triethylammonium acetate or by gradient of methanol in the same buffer. The electrophoresis was made on a Whatman No. 3 MM paper or Whatman No. 1 in 0.1M triethylammonium hydrogencarbonate (pH 7.5) at 20 V/cm. The UV spectra were

recorded on PYE-Unicam SP 8000 spectrophotometer in water or in a methanol-water mixture (1:1, v/v) at pH 2, pH 7, and pH 12. Mass spectra (m/z) were recorded on ZAB-EQ (VG Analytical) instrument, using EI (electron energy 70 eV), FAB (ionisation by Xe, accelerating voltage 8 kV) or SIMS (ionization by Cs^+, accelerating voltage 35 kV) techniques, with glycerol and thioglycerol as matrices. ^1H and ^{13}C NMR spectra were measured on Varian Unity 500 instrument (^1H at 500 MHz, ^{13}C at 125.7 MHz) in hexadeuteriodimethyl sulfoxide and were referenced to the solvent signal ($\delta_H = 2.50$, $\delta_C = 39.7$). Sodium salts of phosphonic acids were measured in deuterium oxide, free phosphonic acids were measured in deuterium oxide containing sodium deuterioxide, with sodium 3-(trimethylsilyl)-1-propanesulfonate as internal standard. ^{31}P NMR spectra were recorded on Varian Unity 200 (81 MHz) spectrometer in deuterium oxide with H_3PO_4 as external standard.

General ***Methods A-G***

Method A*: Preparation of 5′-O-tert-Butyldiphenylsilyl Ribonucleosides. tert*-Butyldiphenylsilyl chloride[12] (6 ml, 22 mmol) was added under stirring to the suspension of nucleoside (20 mmol) in dry pyridine (200 ml), and the mixture was stirred for 24 hrs at room temperature under exclusion of moisture. The course of the reaction was checked by TLC in the system C-1. Reaction was quenched by absolute methanol (10 ml) and the mixture was concentrated under diminished presure. The residue was dissolved in chloroform (400 ml) and extracted with water (3 x 200 ml). The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was suspended in diethyl ether and sonicated for 15 minutes. The product was filtered off, washed with diethyl ether (3 x 50 ml) and dried over P_2O_5 *in vacuo* (60 °C, 13.5 Pa, 6 hrs).

Method B*: Preparation of 2′,3′-O-Alkoxyalkylidene Derivatives of Ribonucleosides.* Trialkyl orthoester (15 mmol) and 10% solution of *p*-toluenesulfonic acid in dioxane (0.5 ml) was added to the suspension of nucleoside (5 mmol) in dichloromethane (10 ml). The mixture was stirred usually for 16-24 hrs at room temperature (the course of the reaction was checked by TLC in the system C-1 after dilution of the sample with triethylammonium hydrogencarbonate-methanol mixture 1:1, v/v), than quenched by addition of triethylamine (2 ml, 14 mmol) at 0 °C, diluted with chloroform (200 ml), and extracted with water (3 x 100 ml). The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The product was purified by chromatography on silica gel (elution with gradient of 0-10% ethanol in chloroform, or of 0-50% acetone in toluene, 0.1% triethylamine).

Method C*: Preparation of 2′,3′-O-Phosphonoalkylidene Derivatives of Ribonucleosides.* Diethyl chlorophosphite[30] (0.29 ml, 2 mmol) was added to the solution of nucleoside orthoester (1 mmol) in dry acetonitrile (10 ml) under argon atmosphere at the starting temperature (see further in the text), and the solution was stirred at the reaction temperature (see further in the text). The course of the reaction was checked by TLC in the system C-1 after dilution of the sample with triethylammonium hydrogencarbonate-ethanol mixture 1:1, v/v). The reaction mixture was cooled down in a ice bath and quenched by addition of 1M triethylammonium hydrogencarbonate in 50% aqueous ethanol (50 ml), and concentrated under diminished pressure. The residue was co-evaporated with ethanol (2 x 50 ml) and toluene (1 x 50 ml). The product was purified by chromatography on silica gel (elution with gradient of 0-10% ethanol in chloroform, or of 0-50% acetone in toluene, 0.1% triethylamine).

Method D*: Cleavage of Phosphonate Esters.* Bromotrimethylsilane (1 equivalent per each ester group plus 1 equivalent per each active hydrogen in the molecule) was added to a solution of diester (1 mmol) in dry acetonitrile

(10 ml) at 0 °C. The reaction mixture was left aside overnight at room temperature and then evaporated to dryness (the course of the reaction was checked by TLC in the system C-1 and H-1 after dilution of the sample with triethylammonium hydrogencarbonate-ethanol mixture 1:1, v/v). The solid residue was treated with 2M triethylammonium hydrogencarbonate (5 ml) and ethanol (20 ml) for 5 min, the solution was evaporated and the residue was co-distilled with ethanol (3 x 20 ml). The crude nucleoside phosphonic acids (triethylammonium salts) were used for the further steps without purification.

***Method E**: Removal of the N- and O-Benzoyl Protecting Groups of Nucleoside Phosphonic Acids with Concentrated Aqueous Ammonia.* The benzoyl derivative (1 mmol) was dissolved in a mixture of concentrated aqueous ammonia (150 ml)- methanol (50 ml) and the solution was saturated with ammonia at 0 °C. The reaction mixture was stirred for 24 hrs at room temperature. The course of the reaction was checked by TLC in the system H-1 and I. After evaporation of the solvent, the residue was codistilled with dry toluene or pyridine (3 x 20 ml). The deacylated product was used without purification for the next reaction steps.

***Method F**: Removal of the N- and O-Benzoyl Protecting Groups of Nucleoside Phosphonic Acids with Sodium Methoxide in Methanol.* 2M Sodium methoxide (0.5 ml, 1 mmol) was added to the solution of benzoyl derivative (1 mmol) in absolute methanol (50 ml). The reaction mixture was stirred for 24 hrs at room temperature under exclusion of moisture. The course of the reaction was checked by TLC in the system H-1 and I. The reaction mixture was neutralized with Dowex 50 x 2 (H^+ form), the resin was filtered off, washed with methanol and the filtrate was concentrated *in vacuo*. The residue was codistilled with dry toluene or pyridine (3 x 20 ml). The deacylated product was used without purification for the next reaction steps.

***Method G**: Removal of 5′-O-tert-Butyldiphenylsilyl Protecting Groups.* The silyl derivative (1 mmol) was dissolved in 0.5M *tetra-n*-butylammonium fluoride in THF (10 ml, 5 mmol) and the mixture was stirred for 24 hrs at room temperature under exclusion of moisture. In case that the reaction mixture was not homogeneous, the mixture was concentrated under diminished pressure and pyridine (10 ml) was added. The course of the reaction was checked by TLC in the system C-1 (non-charged compounds) or in H-1 and I (ionic compounds). After evaporation of the solvent, the non-charged desilylated products were purified on silica gel (elution with gradient of 0-10% ethanol in chloroform, 0.1% triethylamine) while the desilylated phosphonic acids were purified on DEAE-Sephadex A-25 (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water).

(R)-6-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-methoxymethyleneadenosine (**8*R***)

Compound **8*R*** was prepared according to ***Method B*** from 6-N-benzoyl-5′-O-*tert*-butyldiphenylsilyl-adenosine[10,12] (3.05 g, 5.0 mmol) and trimethyl orthoformate. Yield 2.93 g (90 %). For $C_{35}H_{37}N_5O_6Si$ (651.8) calculated: 64.50 % C, 5.72 % H, 10.74 % N; found: 63.74 % C, 5.74 % H, 10.90 % N. MS (FAB): 674 (M + Na), 652 (M + H^+), 620 (M - OMe).

(R)-6-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-ethoxymethyleneadenosine (**9a*R***)

Compound **9a*R*** was prepared according to ***Method B*** from 6-N-benzoyl-5′-O-*tert*-butyldiphenylsilyladenosine[10,12] (9.15 g, 15 mmol) and triethyl orthoformate. Yield 3.19 g (96 %). For $C_{36}H_{39}N_5O_6Si$ (665.8) calculated: 64.94 % C, 5.90 % H, 10.52 % N; found: 64.86 % C, 5.68 % H, 10.30 % N. MS (FAB): 688 (M + Na), 666 (M + H^+), 620 (M - OEt).

2-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-ethoxymethyleneguanosine (**9b**)

Compound **9b** was prepared according to ***Method B*** from 2-N-benzoyl-5′-O-*tert*-butyldiphenylsilyl-guanosine[10,12] (2.00 g, 3.2 mmol) and triethyl orthoformate. Yield 3.34 g (98 %, 52 % of *S*-epimer). For $C_{36}H_{39}N_5O_7Si$ (681.8) calculated: 63.42 % C, 5.77 % H, 10.27 % N; found: 62.97 % C, 5.82 % H, 10.14 % N. MS (FAB): 704 (M + Na), 682 (M + H^+), 636 (M - OEt).

4-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-ethoxymethylenecytidine (**9c**)

Compound **9c** was prepared according to ***Method B*** from 4-N-benzoyl-5′-O-*tert*-butyldiphenylsilyl-cytidine[11,12] (2.68 g, 4.6 mmol) and triethyl orthoformate. Yield 2.85 g (97 %, 17 % of *S*-epimer). For $C_{35}H_{39}N_3O_7Si$ (641.8) calculated: 65.50 % C, 6.12 % H, 6.55 % N; found: 65.69 % C, 6.15 % H, 6.63 % N. MS (FAB): 664 (M + Na), 642 (M + H^+), 596 (M - OEt).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-ethoxymethyleneuridine (**9d**)

Compound **9d** was prepared according to ***Method B*** from 5′-O-*tert*-butyldiphenylsilyluridine[12] (3.70 g, 7.6 mmol) and triethyl orthoformate. Yield 3.86 g (94 %, 52 % of *S*-epimer). For $C_{28}H_{34}N_2O_7Si$ (538.7) calculated: 62.43 % C, 6.36 % H, 5.20 % N; found: 62.40 % C, 6.35 % H, 5.11 % N. MS (FAB): 493 (M - OEt).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-ethoxymethylene-5-methyluridine (**9e**)

Compound **9e** was prepared according to ***Method B*** from 5′-O-*tert*-butyldiphenylsilyl-5-methyluridine[12] (2.50 g, 5.0 mmol) and triethyl orthoformate. Yield 1.93 g (70 %, 52 % of *S*-epimer). For $C_{29}H_{36}N_2O_7Si$ (552.7) calculated: 63.02 % C, 6.57 % H, 5.07 % N; found: 63.54 % C, 6.71 % H, 4.71 % N. MS (FAB): 507 (M - OEt).

6-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-ethoxyethylidene)adenosine (**10a**)

Compound **10a** was prepared according to ***Method B*** from 6-N-benzoyl-5′-O-*tert*-butyldiphenylsilyl-adenosine[10,12] (3.05 g, 5.0 mmol) and triethyl orthoacetate. Yield 3.33 g (98 %, 55 % of *S*-epimer) For $C_{37}H_{41}N_5O_6Si$ (679.8) calculated: 65.37 % C, 6.08 % H, 10.30 % N; found: 64.78 % C, 5.76 % H, 9.78 % N. MS (FAB): 680 (M + H^+), 634 (M - OEt).

2-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-ethoxyethylidene)guanosine (**10b**)

Compound **10b** was prepared according to ***Method B*** from 2-N-benzoyl-5′-O-*tert*-butyldiphenylsilyl-guanosine[10,12] (2.82 g, 4.5 mmol) and triethyl orthoacetate. Yield 3.03g (97 %, 60 % of *S*-epimer) For $C_{34}H_{41}N_5O_7Si$ (695.8) calculated: 63.87 % C, 5.94 % H, 10.06 % N; found: 64.00 % C, 6.04 % H, 9.78 % N. MS (FAB): 718 (M + Na), 696 (M + H^+), 650 (M - OEt).

4-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-ethoxyethylidene)cytidine (**10c**)

Compound **10c** was prepared according to ***Method B*** from 4-N-benzoyl-5′-O-*tert*-butyldiphenylsilyl-cytidine[11,12] (2.65 g, 4.5 mmol) and triethyl orthoacetate. Yield 2.75 g (93 %, 60 % of *S*-epimer). For $C_{36}H_{41}N_3O_7Si$ (655.8) calculated: 65.93 % C, 6.30 % H, 6.41 % N; found: 65.88 % C, 6.39 % H, 6.29 % N. MS (FAB): 678 (M + Na), 656 (M + H^+), 610 (M - OEt).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-(1-ethoxyethylidene)uridine (**10d**)

Compound **10d** was prepared according to ***Method B*** from 5′-O-*tert*-butyldiphenylsilyluridine[12] (2.2 g, 4.5 mmol) and triethyl orthoacetate. Yield 2.24 g (90 %, 56 % of *S*-epimer). For $C_{29}H_{36}N_2O_7Si$ (552.7) calculated: 63.02 % C, 6.57 % H, 5.07 % N; found: 62.38 % C, 6.27 % H, 4.73 % N. MS (FAB): 507 (M - OEt).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-(1-ethoxyethylidene)-5-methyluridine (**10e**)

Compound **10e** was prepared according to ***Method B*** from 5′-O-*tert*-butyldiphenylsilyl-5-methyluridine[12] (2.0 g, 4.0 mmol) and triethyl orthoacetate. Yield 1.80 g (80 %, 57 % of *S*-epimer). For $C_{30}H_{38}N_2O_7Si$ (566.7) calculated: 63.58 % C, 6.76 % H, 4.94 % N; found: 63.79 % C, 6.81 % H, 4.72 % N. MS (FAB): 521 (M - OEt).

6-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-ethoxy-1-phenylmethylene)adenosine (**11a**)

Compound **11a** was prepared according to ***Method B*** from 6-N-benzoyl-5′-O-*tert*-butyldiphenylsilyl-adenosine[10,12] (6.1 g, 10.0 mmol) and triethyl orthobenzoate. Yield 7.0 g (94 %, 55 % of *S*-epimer). For $C_{42}H_{43}N_5O_6Si$ (741.9) calculated: 67.99 % C, 5.84 % H, 9.44 % N; found: 67.86 % C, 6.02 % H, 8.87 % N. MS (FAB): 764 (M + Na), 742 (M + H^+), 694 (M - OEt).

2-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-ethoxy-1-phenylmethylene)guanosine (**11b**)

Compound **11b** was prepared according to ***Method B*** from 2-N-benzoyl-5′-O-*tert*-butyldiphenylsilyl-guanosine[10,12] (3.13 g, (5.0 mmol) and triethyl orthobenzoate. Yield 3.01 g (79 %, 55 % of *S*-epimer). For $C_{42}H_{43}N_5O_7Si$ (757.9) calculated: 66.56 % C, 5.72 % H, 9.24 % N; found: 65.83 % C, 5.67 % H, 9.07 % N. MS (FAB): 758 (M + H^+), 712 (M - OEt).

4-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-ethoxy-1-phenylmethylene)cytidine (**11c**)

Compound **11c** was prepared according to ***Method B*** from 4-N-benzoyl-5′-O-*tert*-butyldiphenylsilyl-cytidine[11,12] (2.93 g, 5.0 mmol) and triethyl orthobenzoate. Yield 2.76 g (77 %, 55 % of *S*-epimer. For $C_{41}H_{43}N_3O_7Si$ (717.9) calculated: 68.60 % C, 6.04 % H, 5.85 % N; found: 67.87 % C, 6.08 % H, 5.73 % N. MS (FAB): 672 (M - OEt).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-(1-ethoxy-1-phenylmethylene)uridine (**11d**)

Compound **11d** was prepared according to ***Method B*** from 5′-O-*tert*-butyldiphenylsilyluridine[12] (2.4 g, 5.0 mmol) and triethyl orthobenzoate. Yield 2.09 g (68 %, 55 % of *S*-epimer). For $C_{34}H_{38}N_2O_7Si$ (614.8) calculated: 66.43 % C, 6.23 % H, 4.56 % N; found: 66.27 % C, 6.43 % H, 4.19 % N. MS (FAB): 569 (M - OEt).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-(1-ethoxy-1-phenylmethylene)-5-methyluridine (**11e**)

Compound **11e** was prepared according to ***Method B*** from 5′-O-*tert*-butyldiphenylsilyl-5-methyluridine[12] (2.5 g, 5.0 mmol) and triethyl orthobenzoate. Yield 1.77 g (56 %, 55 % of *S*-epimer). For $C_{35}H_{40}N_2O_7Si$ (628.8) calculated: 66.86 % C, 6.41 % H, 4.46 % N; found: 66.86 % C, 6.55 % H, 4.26 % N. MS (FAB): 583 (M - OEt).

6-N,5′-O-Dibenzoyl-2′,3′-O-methoxymethylenadenosine (**13**)

Benzoyl cyanide (650 mg, 5 mmol) and triethylamine (0.14 ml, 1 mmol) was added to the solution of 6-N-benzoyl-2′,3′-O-methoxymethyleneadenosine[31] (**12**, 1.65 g, 4 mmol) in dichloromethane (10 ml), and the mixture was stirred at room temperature 40 min under exclusion of moisture. The course of the reaction was checked by TLC in the system C-1. The reaction was quenched by absolute methanol (5 ml) and concentrated

under diminished pressure. The residue was dissolved in chloroform (200 ml) and extracted with water (3 x 100 ml). The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. Chromatography on silica gel (elution with gradient of 0-50% acetone in toluenue, 0.1% triethylamine) afforded 1.70 g (65 %, 63 % of *R*-epimer) of compound **13**. For $C_{26}H_{23}N_5O_7$ (517.5) calculated: 60.35 % C, 4.48 % H, 13.53 % N; found: 59.17 % C, 4.47 % H, 13.17 % N. MS (FAB): 540 (M + Na), 518 (M + H^+), 486 (M - OMe).

6-N-Benzoyl-2′,3′-O-(2-bromo-1-ethoxyethylidene)-5′-O-tert-butyldiphenylsilyladenosine (**17a**)

Compound **17a** was prepared according to ***Method B*** from 6-N-benzoyl-5′-O-*tert*-butyldiphenylsilyl-adenosine[11,12] (6.1 g, 10.0 mmol) and triethyl orthobromoacetate[17]. Yield 7.43 g (98 %, 70 % of *S*-epimer). For $C_{37}H_{40}BrN_5O_6Si$ (758.7) calculated: 58.57 % C, 5.31 % H, 9.23 % N; found: 58.19 % C, 5.36 % H, 8.72 % N. MS (FAB): 780, 782 (M + Na), 758, 760 (M + H^+).

2′,3′-O-(2-Bromo-1-ethoxyethylidene)-5′-O-tert-butyldiphenylsilyl-5-methyluridine (**17e**)

Compound **17e** was prepared according to ***Method B*** from 5′-O-*tert*-butyldiphenylsilyl-5-methyluridine[12] (6.75 g, 13.6 mmol) and triethyl orthobromoacetate[17]. Yield 7.04 g (80 %, 58 % of *S*-epimer). For $C_{30}H_{37}BrN_2O_7Si$ (645.6) calculated: 55.81 % C, 5.78 % H, 4.34 % N; found: 55.83 % C, 5.84 % H, 3.90 % N. MS (FAB): 667, 669 (M + Na), 645, 647 (M + H^+), 599, 601 (M - OEt).

3-N-Benzyloxymethyl-2′,3′-O-(2-bromo-1-ethoxyethylidene)-5′-O-tert-butyldiphenylsilyl-5-methyluridine (**17f**)

Benzylchloromethyl ether (1.3 ml, 9 mmol) and DBU (1.8 ml, 12 mmol) was added to the solution of bromoethylidene derivate **17e** (3.9 g, 6.0 mmol) in acetonitrile (50 ml) at 0 °C. The mixture was left aside for 24 hrs at room temperature under exclusion of moisture. The course of the reaction was checked by TLC in the system T-1. The excess of the reagent was destroyed by absolute methanol (10 ml) and the mixture was concentrated under diminished pressure. The residue was dissolved in chloroform (200 ml) and extracted with 10% citric acid (2 x 50 ml). The chloroform layer was dried over magnesium sulfate and the solvent was evaporated. Chromatography on silica gel (elution with gradient of 0-5 % acetone in toluene) afforded 4.30 g (93 %, 63 % of *S*-epimer) of compound **17f**. For $C_{38}H_{45}BrN_2O_8Si$ (765.8) calculated: 59.60 % C, 5.92 % H, 3.66 % N; found: 59.02 % C, 5.95 % H, 3.79 % N. MS (FAB): 787, 789 (M + Na), 765, 767 (M + H^+), 719, 721 (M - OEt).

6-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-diethylphosphonomethyleneadenosine (**18a**)

Compound **18a** was prepared according to ***Method C*** (20°C to b.p. of acetonitrile) from the ethoxymethylene derivative **9a** (19.8 g, 30 mmol). Yield 20.74 g (91 %, 75 % of *S*-epimer). For $C_{38}H_{44}N_5O_8PSi$ (757.9) calculated: 60.22 % C, 5.85 % H, 9.24 % N; found: 59.33 % C, 5.82 % H, 8.99 % N. MS (FAB): 758 (M + H^+), 620 (M - $P(O)(OEt)_2$).

2-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-diethylphosphonomethyleneguanosine (**18b**)

Compound **18b** was prepared according to ***Method C*** (20 °C) from the ethoxymethylene derivative **9b** (5.1 g, 7.5 mmol). Yield 3.65 g (63 %, 64 % of *S*-epimer). For $C_{38}H_{44}N_5O_9PSi$ (773.9) calculated: 58.98 % C, 5.73 % H, 9.05 % N; found: 58.76 % C, 5.75 % H, 8.58 % N. MS (FAB): 774 (M + H^+), 636 (M - $P(O)(OEt)_2$).

4-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-diethylphosphonomethylenecytidine (**18c**)

Compound **18c** was prepared according to ***Method C*** (20 °C to b.p. of acetonitrile) from the ethoxymethylene derivative **9c** (2.51 g, 3.9 mmol). Yield 1.71 g (60 %, 71 % of *S*-epimer). For $C_{37}H_{44}N_3O_9PSi$ (733.8)

calculated: 60.56 % C, 6.04 % H, 5.73 % N; found: 60.31 % C, 5.99 % H, 5.59 % N. MS (FAB): 734 (M + H^+), 596 (M - $P(O)(OEt)_2$).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-diethylphosphonomethyleneuridine (**18d**)

Compound **18d** was prepared according to ***Method C*** (20 °C) from the ethoxymethylene derivative **9d** (3.62 g, 6.2 mmol). Yield 2.04 g (74 %, 71 % of *S*-epimer). For $C_{30}H_{39}N_2O_9PSi$ (630.7) calculated: 57.13 % C, 6.23 % H, 4.44 % N; found: 56.38 % C, 6.23 % H, 4.45 % N. MS (FAB): 642 (M + Na), 631 (M + H^+), 493 (M - $P(O)(OEt)_2$).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-diethylphosphonomethylene-5-methyluridine (**18e**)

Compound **18e** was prepared according to ***Method C*** (0 to 20 °C) from the ethoxymethylene derivative **9e** (2.23 g, 4.0 mmol). Yield 2.01 g (74 %, 74 % of *S*-epimer). For $C_{31}H_{41}N_2O_9PSi$ (644.7) calculated: 57.75 % C, 6.41 % H, 4.34 % N; found: 57.67 % C, 6.37 % H, 4.21 % N. MS (FAB): 645 (M + H^+), 507 (M - $P(O)(OEt)_2$).

6-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-diethylphosphonoethylidene)adenosine (**19a**)

Compound **19a** was prepared according to ***Method C*** (20 °C) from the ethoxyethylidene derivative **10a** (0.67 g, 0.98 mmol). Yield 0.75 g (98 %, 91 % of *S*-epimer). For $C_{39}H_{46}N_5O_8PSi$ (771.9) calculated: 60.69 % C, 6.01 % H, 9.07 % N; found: 60.58 % C, 5.94 % H., 8.74 % N. MS (FAB): 772 (M + H^+), 634 (M - $P(O)(OEt)_2$).

2-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-diethylphosphonoethylidene)guanosine (**19b**)

Compound **19b** was prepared according to ***Method C*** (0 to 20 °C) from the ethoxyethylidene derivative **10b** (2.13 g, 3.1 mmol). Yield 2.00 g (83 %, 91 % of *S*-epimer). For $C_{39}H_{46}N_5O_9PSi$ (787.9) calculated: 59.45 % C, 5.88 % H, 8.89 % N; found: 59.45 % C, 5.97 % H, 8.44 % N. MS (FAB): 810 (M + Na), 788 (M + H^+), 650 (M - $P(O)(OEt)_2$).

4-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-diethylphosphonoethylidene)cytidine (**19c**)

Compound **19c** was prepared according to ***Method C*** (0 to 20 °C) from the ethoxyethylidene derivative **10c** (2.09 g, 3.16 mmol). Yield 1.56 g (66 %, 89 % of *S*-epimer). For $C_{38}H_{46}N_3O_9PSi$ (747.9) calculated: 61.03 % C, 6.20 % H, 5.62 % N; found: 60.70 % C, 6.27 % H, 5.44 % N. MS (FAB): 770 (M + Na), 748 (M + H^+), 610 (M - $P(O)(OEt)_2$).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-(1-diethylphosphonoethylidene)uridine (**19d**)

Compound **19d** was prepared according to ***Method C*** (-40 to 20 °C) from the ethoxyethylidene derivative **10d** (0.64 g, 1.16 mmol). Yield 0.54 g (72 %, 89 % of *S*-epimer). For $C_{31}H_{41}N_2O_9PSi$ (644.7) calculated: 57.75 % C, 6.41 % H, 4.34 % N; found: 58.09 % C, 6.47 % H, 4.18 % N. MS (FAB): 667 (M + Na), 645 (M + H^+), 507 (M - $P(O)(OEt)_2$).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-(1-diethylphosphonoethylidene)-5-methyluridine (**19e**)

Compound **19e** was prepared according to ***Method C*** (-40 to 20 °C) from the ethoxyethylidene derivative **10e** (1.47 g, 2.6 mmol). Yield 1.34 g (78 %, 89 % of *S*-epimer). For $C_{32}H_{43}N_2O_9PSi$ (658.8) calculated: 58.34 % C, 6.58 % H, 4.25 % N; found: 58.81 % C, 6.66 % H, 4.15 % N. MS (FAB): 681 (M + Na), 659 (M + H^+), 521 (M - $P(O)(OEt)_2$).

3-N-Benzyloxymethyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-diethylphosphonoethylidene)-5-methyluridine (**19f**)

Compound **19f** was obtained according to ***Method C*** (-40 to 20 °C) from the 2-bromoethylidene derivative **17f** (0.38 g, 0.5 mmol) and 4 equivalents of diethyl chlorophosphite. Chromatography on silica gel (elution with gradient of 0-5% acetone in toluene) and on reverse phase (elution with linear gradient of methanol in water) afforded 0.03 g (8 %, 80 % of *S*-epimer). For $C_{40}H_{51}N_2O_{10}PSi$ (778.9) calculated: 61.68 % C, 6.60 % H, 3.60 % N; found: 61.34 % C, 6.28 % H, 3.66 % N. MS (FAB): 779 (M + H^+), 641 (M - $P(O)(OEt)_2$).

6-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-diethylphosphono-1-phenylmethylene)adenosine (**20a**)

Compound **20a** was prepared according to ***Method C*** (20 °C) from the ethoxyphenylmethylene derivative **11a** (2.6 g, 3.5 mmol). Yield 2.90 g (96 %, 91 % of *S*-epimer). For $C_{44}H_{48}N_5O_8PSi$ (834.0) calculated: 63.37 % C, 5.80 % H, 8.40 % N; found: 63.20 % C, 5.75 % H, 7.98 % N. MS (FAB): 856 (M + Na), 834 (M + H^+), 696 (M - $P(O)(OEt)_2$).

2-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-diethylphosphono-1-phenylmethylene)guanosine (**20b**)

Compound **20b** was prepared according to ***Method C*** (0 to 20 °C) from the ethoxyphenylmethylene derivative **11b** (2.78 g, 3.67 mmol). Yield 2.41 g (77 %, 80 % of *S*-epimer). For $C_{44}H_{48}N_5O_9PSi$ (850.0) calculated: 62.18 % C, 5.69 % H, 8.24 % N; found: 61.72 % C, 5.75 % H, 8.00 % N. MS (FAB): 872 (M + Na), 810 (M + H^+), 712 (M - $P(O)(OEt)_2$).

4-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-diethylphosphono-1-phenylmethylene)cytidine (**20c**)

Compound **20c** was prepared according to ***Method C*** (0 to 20 °C) from the ethoxyphenylmethylene derivative **11c** (2.28 g, 3.17 mmol). Yield 2.37 g (91 %, 89 % of *S*-epimer). For $C_{43}H_{48}N_3O_9PSi$ (809.9) calculated: 63.77 % C, 5.97 % H, 5.19 % N; found: 63.90 % C, 5.89 % H, 5.19 % N. MS (FAB): 832 (M + Na), 810 (M + H^+), 672 (M - $P(O)(OEt)_2$).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-(1-diethylphosphono-1-phenylmethylene)uridine (**20d**)

Compound **20d** was prepared according to ***Method C*** (-40 to 20 °C) from the ethoxyphenylmethylene derivative **11d** (1.8 g, 2.9 mmol). Yield 1.75 g (85 %, 91 % of *S*-epimer). For $C_{36}H_{43}N_2O_9PSi$ (706.8) calculated: 61.18 % C, 6.13 % H, 3.96 % N; found: 60.88 % C, 6.17 % H, 3.92 % N. MS (FAB): 729 (M + Na), 569 (M - $P(O)(OEt)_2$).

5′-O-tert-Butyldiphenylsilyl-2′,3′-O-(1-diethylphosphono-1-phenylmethylene)-5-methyluridine (**20e**)

Compound **20e** was prepared according to ***Method C*** (-40 to 20 °C) from the ethoxyphenylmethylene derivative **11e** (0.74 g, 1.18 mmol). Yield 0.84 g (84 %, 86 % of *S*-epimer). For $C_{37}H_{45}N_2O_9PSi$ (720.8) calculated.: 61.65 % C, 6.29 % H, 3.89 % N; found: 61.41 % C, 6.16 % H, 3.77 % N. MS (FAB): 743 (M + Na), 583 (M - $P(O)(OEt)_2$).

6-N,5′-O-Dibenzoyl-2′,3′-O-diethylphosphnomethyleneadenosine (**21**)

Compound **21** was prepared according to ***Method C*** (20 to 50 °C) from the methoxymethylene derivative **13** (0.60 g, 1.16 mmol). Yield 0.41 g (57 %, 75 % of *S*-epimer). For $C_{29}H_{30}N_5O_{10}P$ (623.6) calculated: 55.86 % C, 4.85 % H, 11.23 % N; found: MS (FAB): 624 (M + H^+), 486 (M - $P(O)(OEt)_2$).

(R) 6-N-Benzoyl-2′,3′-O-diethylphosphonomethyleneadenosine (**22*R***)
(S)-6-N-Benzoyl-2′,3′-O-diethylphosphonomethyleneadenosine (**22*S***)

Compounds **22*R*** and **22*S*** were prepared according to ***Method G*** from the phosphonate **18a** (17.7 g, 23.4 mmol). Chomatography on silica gel (elution with chloroform, 0.1% TEA) afforded 2.8 g (23 %) of faster compound **22*R***, and 7.6 (62 %) of slower compound **22*S***. MS (FAB): 542 (M + Na), 520 (M + H^+), 382 (M - $P(O)(OEt)_2$).

6-N-Benzoyl-2′,3′-O-(2-benzyloxycarbonylamino-1-diethylphosphonoethylidene)-5′-O-tert-butyldiphenylsilyl-adenosine (**23**)

6-N-Benzoyl-5′-O-*tert*-butyldiphenylsilyladenosine [10,12] (1.21 g, 1.98 mmol) was treated with triethyl benzyloxycarbonylaminoorthoacetate[18] (0.62g, 2 mmol) and 3M HCl in DMF (1 ml) in dichloromethane (20 ml) for 15 hrs at room temperature. The orthoester **14**, isolated by silicagel chromatography in a yield of 1.04 g (63 %), was subsequently converted into the phosphonate **23** according to ***Method C*** (20 °C, 4 equivalents of diethyl chlorophosphite). Yield 0.92 g (80 %, 95 % of *S*-epimer). MS (FAB): For $C_{47}H_{53}N_6O_{10}PSi$ (920.333009) found: 921.340834 (M + H^+).

6-N-Benzoyl-2′,3′-O-(1-diethylphosphono-2-trifluoroacetylaminoethylidene)-5′-O-tert-butyldiphenylsilyl-adenosine (**25**)

Compound **23** (0.92 g, 1.0 mmol) in the mixture of ethanol-acetic acid (20 ml, 4:1, v/v) was hydrogenated (15 p.s.i.) for 15 hrs in the presence of 10% Pd on charcoal (0.10 g). The course of the hydrogenation was checked by TLC in system C-1. The catalyst was removed by filtration through Celite, the filtrate was concentrated under diminished pressure, and oily residue was coevaporated three times with toluene to remove traces of acetic acid. The free amino compound **24** was dissolved in dry dichloromethane (10 ml) and treated with ethyl trifluoroacetate (1.42 g, 10 mmol) for 20 hrs at room temperature. Chromatography on silica gel (elution with gradient of 0-10% ethanol in chloroform) afforded the N-trifluoroacetyl derivative **25**. Yield 0.52 g (59 %, 94 % of *S*-epimer). MS (FAB): For $C_{41}H_{46}F_3N_6O_9PSi$ (882.278529) found: 883.286354 (M + H^+).

6-N-Benzoyl-2′,3′-O-(2-benzoyloxy-1-diethylphosphonoethylidene)-5′-O-tert-butyldiphenylsilyladenosine (**26**)

A solution of benzoyloxyacetonitrile[32] (51.5 g, 320 mmol) in a mixture of dry methanol (16 ml, 384 mmol) and diethyl ether (300 ml) was saturated with gaseous hydrogen chloride for 30 min at 0 °C, and the mixture was then left aside for 20 hrs at room temperature under exclusion of moisture. Crystalline methyl 3-benzoyloxyacetimidate hydrochloride was filtered off, washed with dry diethyl ether (3 l), and dried *in vacuo* over potassium hydroxide. Imino ester (64.3 g, 280 mmol) was then suspended in absolute methanol (150 ml) and dry diethyl ether (40 ml), and the mixture was heated at 40 °C for 16 hrs under exclusion of moisture. The crystalline ammonium chloride was filtered off, and the filtrate was diluted with cold 10% of water solution of sodium carbonate (300 ml) and extracted with diethyl ether (500 ml). The ether layer was washed with water (300 ml), dried over anhydrous magnesium sulfate, evaporated under diminished pressure and codistilled with dry toluene (3 x 200 ml). The obtained crude trimethyl 2-benzoyloxyorthoacetate was used for the subsequent reaction directly without additional purification. The treatment of 6-N-benzoyl-5′-O-*tert*-butyldiphenylsilyladenosine [10,12](3.05 g, 5.0 mmol) and the crude trimethyl 3-benzoyloxyorthopropionate (2 g) in dichloromethane (50 ml) with HCl in DMF according to the procedure described for compound **23** afforded 2.12 g (54 %)of 2-benzoyloxy--1-methoxyethylidene derivative **15**. The conversion of the orthoester **15** (2.09 g, 2.66 mmol) into the phosphonate

26 according to ***Method C*** (80 °C, 4 equivalents of diethyl chlorophosphite) afforded desired product **26**. Yield 1.12 g (47 %, 89 % of *S*-epimer). MS (FAB): For $C_{46}H_{50}N_5O_{10}PSi$ (891.306460) found: 892.314285 ($M + H^+$).

6-N-Benzoyl-2′,3′-O-(3-benzoyloxy-1-diethylphosphonopropylidene)-5′-O-tert-butyldiphenylsilyladenosine (**27**)

Benzoylchloride (127 ml, 1.1 mol) was added dropwise at 0°C within 3 hrs to the stirred mixture of freshly distilled 2-cyanoethanol (68 ml, 1 mol) and pyridine (97 ml, 1.2 mol) in THF (200 ml). The suspension was stirred for 20 hrs at room temperature under exclusion of moisture. The excess of benzoylchloride was destroyed by absolute methanol (10 ml), and pyridinium hydrochloride was filtered off. The filtrate was concentrated under diminished pressure, the residue was dissolved in diethyl ether (500 ml) and extracted with water (3 x 300 ml). The ether layer was dried over anhydrous magnesium sulfate, concentrated under diminished pressure, and codistilled with dry toluene (3 x 100 ml). The solution of the crude 3-benzoyloxypropionitrile in a mixture of dry methanol (50 ml,1.2 mol) and diethyl ether (500 ml) was saturated with gaseous hydrogen chloride for 30 min at 0 °C, and then was left aside for 20 hrs at room temperature under exclusion of moisture. Crystalline methyl 3-benzoyloxypropioimidate hydrochloride was filtered off, washed with dry diethyl ether (3 l), and dried over potassium hydroxide. Hydrochloride (64.3 g, 280 mmol) was then suspended in absolute methanol (150 ml) and dry diethyl ether (40 ml), and the mixture was heated at 40 °C under exclusion of moisture for 16 hrs. The crystalline ammonium chloride was filtered off, the filtrate was diluted with cold 10% water solution of sodium carbonate (300 ml), and extracted with diethyl ether (500 ml). The ether layer was washed with water (300 ml), dried over anhydrous magnesium sulfate, and codistilled with dry toluene (3 x 200 ml). The treatment of 6-N-benzoyl-5′-O-*tert*-butyldiphenylsilyladenosine[12,10] (1.23 g, 2.0 mmol) and the crude trimethyl 3-benzoyloxyorthopropionate (2 g) in dichloromethane (50 ml) with HCl in DMF according to the method described for compound **23** afforded 0.71 g (44 %) of 3-benzoyloxy-1-methoxypropylidene derivative **16**. The orthoester **16** (0.71 g, 0.89 mmol) was then converted according to ***Method C*** (20 °C, 4 equiv. of diethyl chlorophosphite) to the phosphonate **27**. Yield 0.31g (38 %, 91 % of *S*-epimer). MS (FAB): For $C_{47}H_{52}N_5O_{10}PSi$ (905.322110) found: 906.329935 ($M + H^+$).

(S)-6-N-Benzoyl-2′,3′-O-(2-bromo-1-diethylphosphonoethylidene)-5′-O-tert-butyldiphenylsilyladenosine (**28a*S***)

Compound **28a*S*** was prepared according to ***Method C*** (20 °C) from the 2-bromoethylidene derivative **17a** (0.38 g, 0.5 mmol) and 6 equivalents of diethyl chlorophosphite. Chromatography on silica gel (elution with gradient of 0-1% ethanol in chloroform) and on reverse phase (elution with linear gradient of methanol in water) afforded 0.05 g (12 %). For $C_{39}H_{45}BrN_5O_8PSi$ (850.7) calculated: 55.06 % C, 5.33 % H, 8.23 % N; found: 54.75 % C, 5.40 % H, 7.86 % N. MS (FAB): 851, 853 ($M + H^+$).

(S)-2′,3′-O-(2-Bromo-1-diethylphosphonoethylidene)-5′-O-tert-butyldiphenylsilyl-5-methyluridine (**28e*S***)

Compound **28e*S*** was prepared according to ***Method C*** (-40 to 20 °C) from the derivative **17e** (3.9 g, 6.0 mmol). Chromatography on silica gel (elution with gradient of 0-10% acetone in toluene) and on reverse phase (elution with linear gradient of methanol in water) afforded 2.31 g (52 %). For $C_{32}H_{42}BrN_2O_9PSi$ (737.7) calculated: 52.10 % C, 5.74 % H, 3.80 % N; found: 51.86 % C, 5.76 % H, 3.75 % N. MS (FAB): 759, 761 ($M + Na$), 737, 739 ($M + H^+$), 599, 601 ($M - P(O)(OEt)_2$).

3-N-Benzyloxymethyl-2′,3′-O-(2-bromo-1-diethylphosphonoethylidene)-5′-O-tert-butyldiphenylsilyl-5-methyl-uridine (**28f**)

Compound **28f** was prepared according to ***Method C*** (-40 to 20 °C) from the 2-bromoethylidene derivative **17f** (0.38 g, 0.5 mmol) and 4 equivalents of diethyl chlorophosphite. Chromatography on silica gel (elution with gradient of 0-5% acetone in toluene) and on reverse phase (elution with linear gradient of methanol in water) afforded 0.04 g (10 %, 82 % of *S*-epimer). For $C_{40}H_{50}BrN_2O_{10}PSi$ (857.8) calculated: 56.01 % C, 5.88 % H, 3.27 % N; found: 56.16 % C, 6.15 % H, 3.10 % N. MS (FAB): 857, 859 (M + H^+), 719, 721 (M - $P(O)(OEt)_2$).

(S)-6-N-Benzoyl-5′-O-tert-butyldiphenylsilyl-2′,3′-O-(1-diethylphosphono-2-chloroethylidene)adenosine (**29*S***)

Compound **29*S*** was obtained according to ***Method C*** (20 °C) from the 2-bromoethylidene derivative **17a** (0.38 g, 0.5 mmol) and 6 equivalents of diethyl chlorophosphite. Chromatography on silica gel (elution with gradient of 0-1% ethanol in chloroform) and on reverse phase (elution with linear gradient of methanol in water) afforded 0.05 g (12 %). For $C_{39}H_{45}ClN_5O_8PSi$ (806.3) calculated: 58.09 % C, 5.63 % H, 8.69 % N; found: 58.96 % C, 5.73 % H, 8.53 % N. MS (FAB): 805, 807 (M + H^+).

(S)-2′,3′-O-Phosphonomethyleneadenosine (**30a*S***)

Compound **30a*S*** was prepared according to ***Method D*** and ***F*** from the desilylated *S*-phosphonate **22*S*** (0.52 g, 1.0 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.30 g (79 %) of sodium salt of compound **30a*S***. MS (FAB): 382 (M + Na), 360 (M + H^+), 279 (M - $P(O)(OH)_2$). N/P: calculated: 5.00; found: 4.21.

(R)-2′,3′-O-Phosphonomethyleneadenosine (**30a*R***)

Compound **30a*R*** was prepared in the same manner as the compound **30a*S***, from the desilylated *R*-phosphonate **22*R*** (0.52 g, 1.0 mmol). Yield 0.26 g (68 %) of sodium salt of compound **30a*R***. MS (FAB): 382 (M + Na), 360 (M + H^+), 279 (M - $P(O)(OH)_2$). N/P: calculated: 5.00; found: 4.73.

2′,3′-O-Phosphonomethyleneguanosine (**30b**)

Compound **30b** was prepared according to ***Method D*** , ***E***, and ***G*** from the phosphonate **18b** (2.68 g, 3.46 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.89 g (65 %, 60 % of *S*-epimer) of sodium salt of compound **30b**. MS (FAB): 398 (M + Na), 376 (M + H^+). N/P: calculated: 5.00; found: 4.99.

(R)-2′,3′-O-Phosphonomethylenecytidine (**30c*R***)

Compound **30c*R*** was prepared according to ***Method D***, ***E***, and ***G*** from the phosphonate **18c** (1.35 g, 1.8 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.48 g (75 %, 70 % of *S*-epimer) of sodium salt of the mixture of epimeric compound **30c**. Rechromatography on Dowex 1 x 2 (acetate form, elution with linear gradient of 0-1M acetic acid in water) afforded 0.09 g of inner salt of the compound **30c*R***, m.p. > 300 °C (ethanol-water). For

$C_{10}H_{14}N_3O_8P$ (335.2) calculated: 35.83 % C, 4.21 % H, 12.54 % N; found: 35.98 % C, 4.19 % H, 12.52 % N. MS (FAB): 336 (M + H^+).

2′,3′-O-Phosphonomethyleneuridine (**30d**)

Compound **30d** was prepared according to ***Method D*** and ***G*** from the phosphonate **18d** (1.6 g, 2.5 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.72 g (80 %, 75 % of *S*-epimer) of sodium salt of compound **30d**.MS (FAB): 359 (M + Na), 337 (M + Na^+), 255 (M - $P(O)(OH)_2$). N/P: calculated: 2.00; found: 1.71.

2′,3′-O-Phosphonomethylene-5-methyluridine (**30e**)

Compound **30e** was prepared according to ***Method D*** and ***G*** from the phosphonate **18e** (1.7 g, 2.6 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.84 g (85 %, 75 % of *S*-epimer) of sodium salt of compound **30e**. MS (FAB): 373 (M + Na), 351(M + H^+), 269 (M - $P(O)(OH)_2$). N/P: calculated: 2.00; found: 2.12.

(S)-2′,3′-O-(1-Phosphonoethylidene)adenosine (**31a*S***)

Compound **31a*S*** was prepared according to ***Method D*** , ***F***, and ***G*** from the phosphonate **19a** (0.8 g, 1.5 mmol). Yield 0.53 g (89 %) of sodium salt of compound **31a*S***. MS (FAB): 396 (M + Na), 374 (M + H^+). N/P: calculated: 5.00; found: 4.71.

(S)-2′,3′-O-(1-Phosphonoethylidene)guanosine (**31b*S***)

Compound **31b*S*** was prepared according to ***Method D*** , ***F***, and ***G*** from the phosphonate **19b** (0.79 g, 1.0 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.33 g (80 %) of sodium salt of compound **31b*S***. MS (FAB): 412 (M + Na), 390 (M + H^+). N/P: calculated: 5.00; found: 4.62.

2′,3′-O-(1-Phosphonoethylidene)cytidine (**31c**)

Compound **31c** was prepared according to ***Method D*** , ***F***, and ***G*** from the phosphonate **19c** (1.17 g, 1.56 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.44 g (76 %, 90 % of *S*-epimer) of sodium salt of compound **31c**. MS (FAB): 372 (M + Na), 350 (M + H^+). N/P: calculated: 3.00; found: 2.60.

2′,3′-O-(1-Phosphonoethylidene)uridine (**31d**)

Compound **31d** was prepared according to ***Method D*** and ***G*** from the phosphonate **19d** (0.80 g, 1.50 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.16 g (72 %, 88 % of *S*-epimer) of sodium salt of compound **31d**. MS (FAB): 373 (M + Na), 351 (M + H^+). N/P: calculated: 2.00; found: 1.99.

2′,3′-O-(1-Phosphonoethylidene)-5-methyluridine (**31e**)

Compound **31e** was prepared according to ***Method D*** and ***G*** from the phosphonate **19e** (0.75 g, 1.14 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.33 g (72 %, 88 % of *S*-epimer) of sodium salt of compound **31e**. MS (FAB): 387 (M + Na), 365 (M + H^+). N/P: calculated: 2.00; found: 1.86.

2′,3′-O-(1-Phenyl-1-phosphonomethylene)adenosine (**32a**)

Compound **32a** was prepared according to ***Method D*** , ***E***, and ***G*** from the phosphonate **20a** (1.25 g, 1.50 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.51 g (74 %, 91 % of *S*-epimer) of sodium salt of compound **32a**. MS (FAB): 458 (M + Na), 436 (M + H^+), 354 (M - $P(O)(OH)_2$). N/P: calculated: 5.00; found: 4.96.

2′,3′-O-(1-Phenyl-1-phosphonomethylene)guanosine (**32b**)

Compound **32b** was prepared according to ***Method D*** , ***E***, and ***G*** from the phosphonate **20b** (1.80 g, 2.1 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.63 g (63 %, 78 % of *S*-epimer) of sodium salt of compound **32b**. MS (FAB): 474 (M + Na), 452 (M + H^+), 370 (M - $P(O)(OH)_2$). N/P: calculated: 5.00; found: 4.96.

2′,3′-O-(1-Phenyl-1-phosphonomethylene)cytidine (**32c**)

Compound **32c** was prepared according to ***Method D*** , ***E***, and ***G*** from the phosphonate **20c** (1.93 g, 2.4 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.89 g (85 %, 86 % of *S*-epimer) of sodium salt of compound **32c**. MS (FAB): 434 (M + Na), 330 (M - $P(O)(OH)_2$). N/P: calculated: 3.00; found: 2.56.

2′,3′-O-(1-Phenyl-1-phosphonomethylene)uridine (**32d**)

Compound **32d** was prepared according to ***Method D*** and ***G*** from the phosphonate **20d** (1.22 g, 1.7 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.43 g (58 %, 85 % of *S*-epimer) of sodium salt of compound **32d**. MS (FAB): 435 (M + Na), 413 (M + H^+), 331 (M - $P(O)(OH)_2$). N/P: calculated: 2.00; found: 1.94.

2′,3′-O-(1-Phenyl-1-phosphonomethylene)-5-methyluridine (**32e**)

Compound **32e** was prepared according to ***Method D*** and ***G*** from the phosphonate **20e** (0.61g, 0.85 mmol). The obtained crude phosphonic acid was purified on DEAE Sephadex (HCO_3^- form, elution with linear gradient of 0-0.2M triethylammonium hydrogen carbonate in water) and converted into the sodium salt on Dowex 50 x 2 (Na^+ form). Freeze-drying afforded 0.09 g (24 %, 71 % of *S*-epimer) of sodium salt of compound **32e**. MS (FAB): 449 (M + Na), 345 (M - $P(O)(OH)_2$). N/P: calculated: 2.00; found: 1.99.

(S)-2′,3′-O-(2-Bromo-1-ethylphosphonoethylidene)-5′-O-tert-butyldiphenylsilyl-5-methyluridine (**38S**)

Potassium *t*-butoxide (0.09 g, 0.80 mmol) was added to the solution of the 2-bromoethylidene derivate **28eS** (0.30 g, 0.40 mmol) in THF (5 ml) at 0 °C. The mixture was stirred 1 h at 0 °C under exclusion of moisture, and was deionized on Dowex 50 x 2 (H^+ form) in acetone. Chromatography on silica gel (elution with gradient of H-3 in ethyl acetate) afforded 0.16 g (56 %) of monoester **38S**. MS (FAB): 709, 711 (M + H^+). N/P: calculated: 2.00; found: 2.11.

^{1}H NMR: 11.38 s, 1H (NH); 7.65-7.60 m, 4H (aromH); 7.58 q, 1H, J(6,CH_3) = 1.2 (H-6); 7.48-7.35 m, 6H (aromH); 5.88 d, 1H, J(1',2') = 2.6 (H-1'); 5.16 dd, 1H, J(2',1') = 2.6, J(2',3') = 6.8 (H-2'); 5.04 dd, 1H, J(3',2') = 6.8, J(3',4') = 4.0 (H-3'); 4.33 m, 1H (H-4'); 3.95 d, 1H a 3.91 d, 1H, J(gem) = 12.5 (CH_2-Br); 3.88 dd, 1H, J(5'a,4') = 4.9, J(gem) = 11.0 (H-5'a); 3.82 m, 2H (P-OCH_2); 3.79 dd, 1H, J(5'b,4') = 6.1, J(gem) = 11.0 (H-5'b); 1.65 d, 3H, J(CH_3,6) = 1.2 (CH_3); 1.09 t, 3H, J(CH_3,CH_2) = 7.1 (CH_3); 0.98 s, 9H (t-Bu).

^{13}C NMR: 164.03 (C-4); 150.45 (C-2); 138.29 (C-6); 135.26 (2C), 135.20 (2C), 133.06, 132.88, 130.13 (2C), 128.13 (2C) a 128.05 (2C) (aromC); 111.62 d, J(C,P) = 160.6 (O-C-O); 109.80 (C-5); 91.34 (C-1'); 85.80 (C-4'); 85.75 (C-2'); 82.59 (C-3'); 64.44 (C-5'); 60.73 d, J(C,P) = 6.5 (P-OC); 39.40 (C-Br); 26.78 a 18.99 (t-Bu); 16.40 d, J(C,P) = 4.0 (CH_3); 11.99 (CH_3).

^{31}P NMR: 7.19.

2,2′-Anhydro-5′-O-tert-butyldiphenylsilyl-3′-O-ethylphosphonoacetyl-5-methyluridine (**43**)

Compound **43** was obtained as the major product from the 2-bromoethylidene phosphonate **28eS** (0.74 g, 1.0 mmol) when heated with sodium azide (0.65 g, 10 mmol) in DMF (10 ml) 1 h at 130 °C. Chromatography on silica gel (elution with 30% H-1 in H-3) afforded 0.40 g (64 %) of phosphonoacetyl derivate **43**. UV spectrum (λ_{max}, nm): 253 (pH 2), 253 (pH 12). IR spectrum (KBr): ν(C=O) ester: 1730s; ν(C=O), ν(C=C), ν(C=N) pyrimidone: 1671s, 1647s, 1574vs, 1486s,sh; ν(ring) phenyl: 1495s, 1428 s; δ_s(CH_3) *t*-butyl: 1390m, 1363w; ν(P=O): 1239s; phenyl on Si: 1114s; ν(C-O): 1106s, 1090s, 1063. MS (FAB): 651 (M + Na), 629 (M + H^+). N/P: calculated: 2.00; found: 1.93.

^{1}H NMR: 7.83 brs, 1H (H-6); 7.51 m, 4H, 7.44 m, 2H a 7.38 m, 4H (aromH); 6.39 d, 1H, J(1',2') = 5.9 (H-1'); 5.49 brd, 1H, J(2',1') = 5.9, J(2',3') = 0.5 (H-2'); 5.40 brd, 1H, J(3',2') = 0.5, J(3',4') = 2.7 (H-3'); 4.41 ddd, 1H, J(4',3') = 2.7, J(4',5'a) = 4.9, J(4',5'b) = 6.8 (H-4'); 3.73 m, 2H (P-OCH_2); 3.56 dd, 1H, J(5'a,4') = 4.9, J(gem) = 11.2 (H-5'a); 3.44 dd, 1H, J(5'b,4') = 6.8, J(gem) = 11.2 (H-5'b); 2.61 dd, 1H, J(P,CH) = 19.5, J(gem) = 12.2 (P-CHa); 2.57 dd, 1H, J(P,CH) = 19.3, J(gem) = 12.2 (P-CHb); 1.76 d, 3H, J(CH_3,6) = 1.2 (CH_3); 1.11 t, 3H, J(CH_3,CH_2) = 7.1 (CH_3); 0.90 s, 9H (t-Bu).

^{13}C NMR: 171.57 (C-2); 169.10 d, J(C,P) = 6.8 (C=O); 159.21 (C-4); 135.00 (4C), 132.59 a 132.43 (arom C); 132.38 (C-6); 130.13 (2C), 128.16 (2C) a 128.13 (2C) (aromC); 117.19 (C-5); 90.26 (C-1'); 86.18 (C-4'); 85.09 (C-2'); 75.64 (C-3'); 62.92 (C-5'); 59.36 d, J(C,P) = 5.9 (P-OC); 36.58 d, J(C,P) = 107.4 (P-C); 26.52 a 18.87 (t-Bu); 16.98 d, J(C,P)= 6.8 (CH_3); 13.65 (CH_3).

^{31} P NMR: 8.27.

2,2′-Anhydro-5′-O-tert-butyldiphenylsilyl-5-methyluridine (**44**)

The acyl compound **43** (0.10 g, 0.16 mmol) was stirred with 0.1M potassium hydroxide in 50% water dioxane (5 ml, 0.5 mmol) at room temperature 20 min. The course of the reaction was checked by TLC in system H-3. The mixture was neutralized with dry CO_2 and concentrated under diminished pressure. Chromatography on silica gel (elution with 10% ethanol in ethyl acetate) afforded 0.05 g (65 %) of the anhydro derivative **44**. UV spectrum (λ_{max}, nm): 253 (pH 2), 253 (pH 12). MS (FAB): 479 (M + H^+).

^{1}H NMR: 7.80 q, 1H, J(6,CH_3) = 1.2 (H-6); 7.55-7.48 m, 4H a 7.45-7.34 m, 6H (aromH); 6.32 d, 1H, J(1',2') = 5.6 (H-1'); 6.00 d, 1H, J(OH,3') = 4.4 (3'-OH); 5.23 dd, 1H, J(2',1') = 5.6, J(2',3') = 1.5 (H-2'); 4.42 ddd, 1H, J(3',2') = 1.5, J(3',4') = 3.2, J(3',OH) = 4.4 (H-3'); 4.18 ddd, 1H, J(4',3') = 3.2, J(4',5'a) = 4.6, J(4',5'b) = 6.9 (H-4'); 3.57 dd, 1H, J(5'a,4') = 4.6, J(gem) = 12.4 (H-5'a); 3.41 dd, 1H, J(5'b,4') = 6.9, J(gem) = 12.4 (H-5'b); 1.76 d, 3H, J(CH_3,6) = 1.2 (CH_3), 0.91 s, 9H (t-Bu).

^{13}C NMR: 171.66 (C-2); 159.25 (C-4); 135.15 (2C), 135.10 (2C), 132.78 a 132.61 (aromC); 132.41 (C-6); 130.12 (2C), 128.13 (2C) a 128.12 (2C) (aromC); 117.08 (C-5); 89.87 (C-1'); 88.48 (C-4'); 87.47 (C-2'); 74.30 (C-3'); 62.94 (C-5'); 26.53 a 18.90 (t-Bu); 13.64 (CH_3).

1-(5-O-tert-Butyldiphenylsilyl-β-D-arabinofuranosyl)thymine (**45**)

Compound **45** was obtained as the product from the acyl compound **43** (0.10 g, 0.16 mmol) when treated in 0.1M potassium hydroxide in 50% water dioxane (5 ml, 0.5 mmol). Chromatography on silica gel (elution with 75% ethyl acetate in toluene) afforded 0.02 g (25 %) of the arabinofuranosyl derivative **45**. MS (FAB): 497 ($M+H^+$).

^{1}H NMR: 11.30 s, 1H (NH); 7.68-7.62 m, 4H a 7.50-7.40 m, 6H (aromH); 7.29 q, 1H, J(6,CH_3) = 1.0 (H-6); 6.04 d, 1H, J(1',2') = 4.6 (H-1'); 5.57 d, 1H, J(OH,2') = 4.6 (2'-OH); 5.53 d, 1H, J(OH,3') = 4.6 (3'-OH); 4.04 td, 1H, J(2',1') = J (2',OH)=4.6, J(2',3') = 3.7 (H-2'); 4.00 ddd, 1H, J(3',2') = 3.7, J(3',4') = 4.2, J(3',OH) = 4.6 (H-3'); 3.90 dd, 1H, J(5'a,4') = 4.2, J(gem) = 11.0 (H-5'a); 3.86 dd, 1H, J(5'b,4') = 5.4, J(gem) = 11.0 (H-5'b); 3.83 dt, 1H, J(4',3') = J(4',5'a) = 4.2, J(4',5'b) = 5.4 (H-4'); 1.58 d, 3H, J(CH_3,6) = 1.0 (CH_3); 1.02 s, 9H (t-Bu).

^{13}C NMR: 164.12 (C-4); 150.75 (C-2); 138.13 (C-6); 135.45 (2C), 135.40 (2C), 133.38, 133.25, 130.27, 130.28 a 128.26 (4C) (aromC); 107.66 (C-5); 84.90 (C-1'); 83.64 (C-4'); 75.85 a 75.58 (C-2' a C-3'); 63.61 (C-5'); 26.91 a 19.24 (t-Bu); 12.34 (CH_3).

3-N-Benzyloxymethyl-3'-O-diethylphosphonoacetyl-5'-O-tert-butyldiphenylsilylthymidine (**51**)

Chloroacetyl chloride (0.12 ml, 1.5 mmol) and DIPEA (0.35 ml, 2.0 mmol) was added to the solution of protected thymidine **49** (0.60 g, 1.0 mmol) in dichloromethane (10 ml). The mixture was stirred 30 min at room temperature under exclusion of moisture. The course of the reaction was checked by TLC in system T-1. The mixture was decomposed by addition of absolute methanol (2 ml), diluted with chloroform (50 ml) and extracted with 10% citric acid (2 x 30 ml). The chloroform layer was dried over magnesium sulfate and the solvent was evaporated. Chromatography on silica gel (elution with gradient of 0-10% acetone in toluene) afforded 0.14 g (21%) of the 3'-O-chloroacetyl derivate **50**, which was heated with triethyl phosphite (0.20 ml, 1.2 mmol) in xylene (0.2 ml) 10 h at 130 °C. The mixture was diluted with water and applied to reverse phase (elution with linear gradient of methanol in water). Chromatography afforded 0.13 g (83 %) of phosphonate **51**. For: $C_{40}H_{51}N_2O_{10}PSi$ (778.9) calculated: 61.68 % C, 6.60 % H, 3.60 % N; found: 60.45 % C, 6.24 % H, 3.31 % N. MS (FAB): 779 ($M + H^+$).

^{1}H NMR: 7.63 m, 4H (aromH); 7.49 q, 1H, J(6,CH_3) = 1.0 (H-6); 7.48-7.40 m, 6H a 7.34-7.23 m, 5H (arom H); 6.26 dd, 1H, J(1',2'a) = 8.3, J(1',2'b) = 6.1 (H-1'); 5.34 d, 1H a 5.33 d, 1H, J(gem) = 12.2 (N-CH_2-O); 4.58 s, 2H (O-CH_2); 4.11 ddd, 1H, J(4',3') = 2.7, J(4',5'a) = 3.2, J(4',5'b) = 4.2 (H-4'); 4.06 m, 4H (P-OCH_2); 3.95 dd, 1H, J(5'a,4') = 3.2, J(gem) = 11.5 (H-5'a); 3.87 dd, 1H, J(5'b,4') = 4.2, J(gem) = 11.5 (H-5'b); 3.21 d, 2H, J(P,CH) = 11.2 (P-CH_2); 2.39 ddd, 1H, J(2'a,1') = 8.3, J(2'a,3') = 6.1, J(gem) = 14.2 (H-2'a); 2.35 ddd, 1H, J(2'b,1') = 6.1, J(2'b,3') = 2.7, J(gem) = 14.2 (H-2'b); 1.53 d, 3H, J(CH_3,6) = 1.0 (CH_3); 1.25 t, 6H, J(CH_3,CH_2) = 7.1 (CH_3); 1.02 s, 9H (t-Bu).

^{13}C NMR: 165.66 d, J(C,P) = 6.0 (C=O); 162.83 (C-4); 150.73 (C-2); 138.34, 135.29 (2C) a 135.12 (2C) (aromC); 134.81 (C-6); 132.91, 132.40, 130.33, 130.27, 128.36 (2C), 128.23 (4C), 127.65 a 127.49 (2C) (aromC);

109.35 (C-5); 84.99 (C-1'); 84.16 (C-4'); 74.91 (C-3'); 71.26 a 70.52 (O-C); 64.15 (C-5'); 62.23 d, J(C,P) = 5.9 (P-OC); 36.51 (C-2'); 33.65 d, J(C,P) = 128.9 (P-C); 26.82 a 19.04 (t-Bu); 16.30 d, J(C,P) = 6.8 (CH_3); 12.57 (CH_3). ^{31}P NMR: 20.85.

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