Russian Journal of Bioorganic Chemistry, Vol. 26, No. 6, 2000, pp. 407–413. Translated from Bioorganicheskaya Khimiya, Vol. 26, No. 6, 2000, pp. 452–459.

The *S,X*-Acetals in Nucleoside Chemistry: II.[1] The Synthesis of 3'-*O*-Methylthiomethylribonucleosides

A. E. Pechenov*, S. G. Zavgorodny[2], V. I. Shvets*, and A. I. Miroshnikov****

**Lomonosov State Academy of Fine Chemical Technology, pr. Vernadskogo 86, Moscow, 117571 Russia*

***Shemyakin–Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, ul. Miklukho-Maklaya 16/10, GSP-7, Moscow, 119871 Russia*

Received December 14, 1999; in final form, January 17, 2000

Abstract—3'-*O*-Methylthiomethyl derivatives of ribonucleosides were synthesized from the selectively protected nucleosides by the action of a dimethyl sulfide–benzoyl peroxide mixture in acetonitrile or a dimethyl sulfoxide–acetic anhydride–acetic acid mixture.

Key words: ribonucleosides, methylthiomethylation, thioacetals, Pummerer's rearrangement

INTRODUCTION

In recent years, a number of laboratories have paid significant attention to the development of synthesis methods and the study of the properties of *O*-methylthiomethyl derivatives of nucleosides [2–13]. This problem has taken on particular importance since the reports on the use of wide-ranging synthetic possibilities of *O,S*-acetals in the nucleoside series [3–8, 11].

The following three methods for the introduction of the *O*-methylthiomethyl group are the most important:

1. Use of the dimethyl sulfide–benzoyl peroxide system [3, 4, 13].

2. Use of the Pummerer rearrangement (dimethyl sulfoxide–acetic anhydride system) either in its classical variant, in the presence of tertiary alcohols [8], or in modified variants using primary and secondary alcohols and acetic acid [5–7, 11]; AcOH is added in order to inhibit the oxidation process, which sharply decreases the yield of the target products [14, 15].

3. Treatment of corresponding alcoholates with methylthiomethyl chloride [2, 11].

Method 1 [16] has been used for the synthesis of 3'- and 5'-*O*-methylthiomethyl-2'-deoxyribonucleosides [3, 4] and 2'-*O*-methylthiomethylribonucleosides [12].

Method 2 has been applied successfully for obtaining 3'- and 5'-*O*-methylthiomethyl-2'-deoxyribonucleosides and 2'- and 5'-*O*-methylthiomethylribonucleosides [1, 5–7].

Method 3 elicited a certain controversy in the literature [3, 4]. In the case of nucleosides, it appears to be of no general use despite efforts to improve it [10, 11] following the controversy.

RESULTS AND DISCUSSION

Methods 1 and 2 have exhibited approximately equal efficiencies in the synthesis of 2'-*O*-methylthiomethylribonucleosides [1, 12]. In this work, therefore, we compared their efficiencies for obtaining 3'-*O*-methylthiomethylribonucleosides.

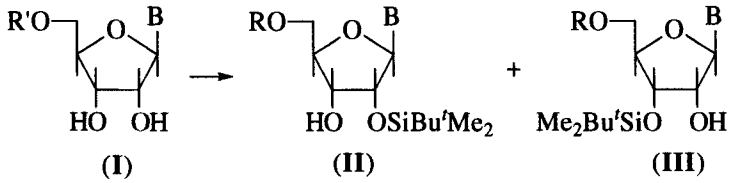
Starting ribonucleosides (**Ia**)–(**Ig**) were transformed into 2',5'-*O*-disubstituted protected derivatives by the action of *tert*-butyldimethylsilyl chloride, silver nitrate, and pyridine in tetrahydrofuran (Scheme 1) by a procedure similar to that described in [17]. The resulting mixtures of isomers (**II**) and (**III**) were then separated. Thus, derivatives (**IIa**) and (**IIc**) were isolated as described in [17, 18], whereas (**IIb**) and (**IIIb**) were separated by recrystallization. The use of different protective groups for 2'- and 5'-hydroxyls is expedient when the resulting *O,S*-acetals are used further in the synthesis of other nucleoside derivatives. In our case, the dimethoxytrityl protection of 5'-hydroxyl was shown in [17] to be inappropriate for further modification of the methylthiomethyl group, and, therefore, we chose acetyl group for this purpose. The silylation of (**Id**)–(**Ig**) resulted in isomer mixtures, and we succeeded in the separation of only (**IId**)/(**IIId**) and (**IIe**)/(**IIIe**) pairs, with pure (**IId**) and (**IIe**) being used in further syntheses.

Nucleosides (**IIa**)–(**IId**) were methylthiomethylated by methods 1 and 2 (Scheme 2). Method 2 provided for relatively lower yields (Table 1), which can be explained by the more rigorous conditions and the slower progress of the reaction than in the case of using method 1. However, both methods provided less efficiency than that achieved in the case of obtaining 2'-*O*-methylthiomethyl derivatives (cf. [1, 12]). The type of 5'-*O*-protective group also affected the product yield (see [14]); this is evident from a comparison of transformations (**IIc**) → (**Vc**) and (**IId**) → (**Vd**) (Table 1).

[1] For communication I, see [1].

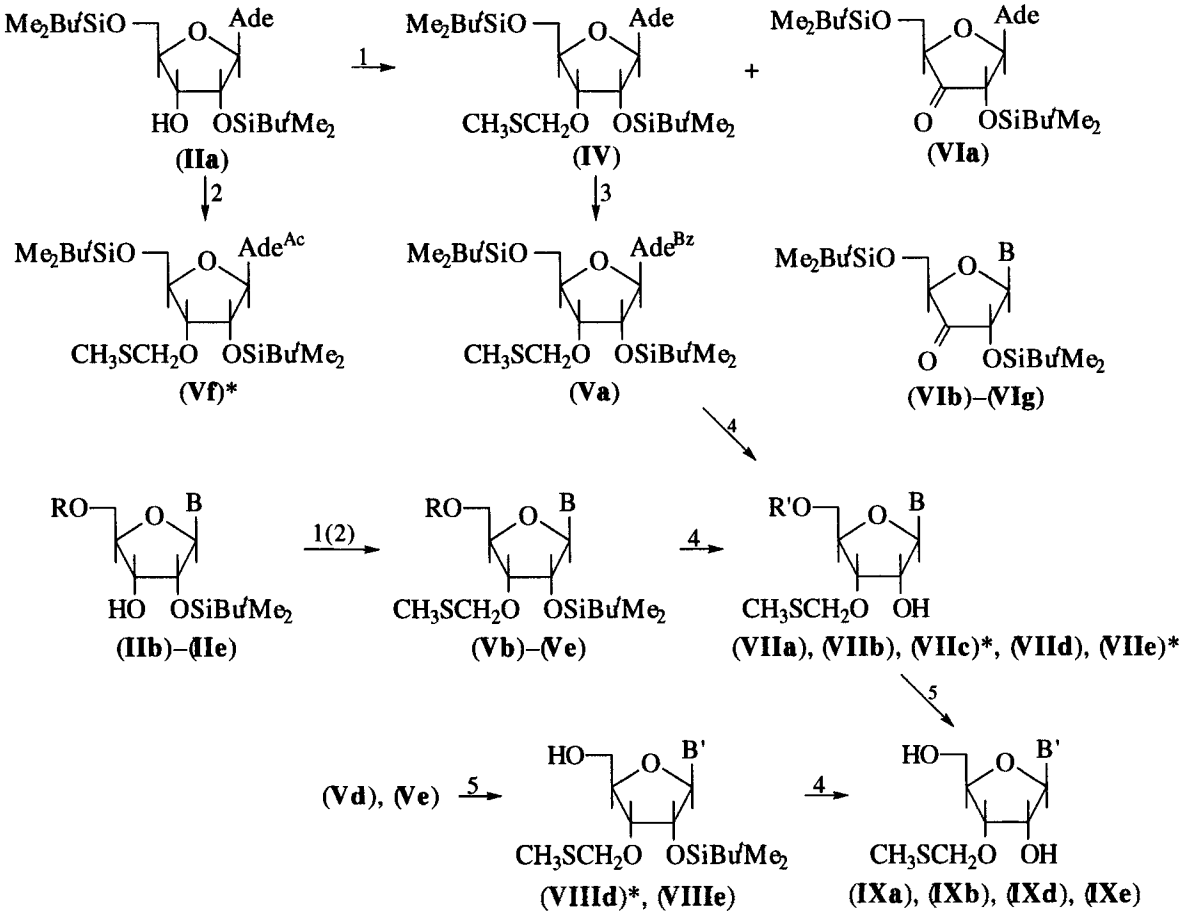
[2] To whom correspondence should be addressed; phone +7 (095) 330-7247; e-mail: kou@ibch.siobc.ras.ru.

1068-1620/00/2606-0407$25.00 © 2000 MAIK "Nauka/Interperiodica"



a: B = Ade, R' = H, R = SiBu^{t}Me$_2$; **d**: B = BzCyt, R' = R = Ac;
b: B = BzGua, R' = H, R = SiBu^{t}Me$_2$; **e**: B = Ura, R' = R = Ac;
c: B = BzCyt, R' = H, R = SiBu^{t}Me$_2$; **f**: B = BzAde, R' = R = Ac;
g: B = IbGua, R' = R = Ac;
Ib, isobutyryl

Scheme 1.



a: B = BzAde, B' = Ade, R = SiBu^{t}Me$_2$, R' = H; **d**: B = BzCyt, B' = Cyt, R = R' = Ac;
b: B = BzGua, B' = Gua, R = SiBu^{t}Me$_2$, R' = H; **e**: B = B' = Ura, R = R' = Ac;
c: B = BzCyt, B' = Cyt, R = SiBu^{t}Me$_2$, R' = H; **f**: B = AcAde, R = SiBu^{t}Me$_2$.
1—Me_2S, $(BzO)_2/CH_3CN$; 2—DMSO, Ac_2O, AcOH; 3—BzCl/Py; 4—$Bu_4N^+F^-$/THF; 5—NH_3/MeOH.
THF, tetrahydrofuran.
*These compounds were obtained and characterized; however, they were not used in further transformations

Scheme 2.

Table 1. The methylthiomethylation of 3'-hydroxyl groups in ribonucleosides

Product	Starting compound	Load		Method	Yield, %	Mp, °C	R_f (system)
		g	mmol				
(IV)	**(IIa)**	0.99	1.0	1	64	133.5–134**	0.60 (A)
(VIa)					20	165–167**	0.56 (A)
(Va)	**(IV)**	1.25	2.24	BzCl	98	–	–
(Vb)	**(IIb)**	1.23	2.0	1	62	149.5–150***	0.71 (A)
		0.62	1.0	2	52		
(Vc)	**(IIc)**	1.73	3.0	1	52		0.56 (B)
(VIc)*					25	174–176****	0.52 (B)
(Vd)	**(IId)**	1.42	2.81	1	46	–	0.54 (B)
		0.51	1.0	2	36		
(Ve)	**(IIe)**	1.60	4.0	1	46	–	0.66 (A)
		0.37	0.91	2	37		
(Vf)	**(IIa)**	0.22	0.44	2	37	66–68*****	0.74 (A)

* Ketonucleoside **(VIc)** was obtained as a by-product at the stage of a chromatographic separation of the reaction mixture after methylthiomethylation.

** From acetonitrile.

*** From toluene–hexane.

**** From chloroform–hexane.

***** From hexane.

The methylthiomethylation reaction performed according to methods 1 or 2 and leading to the target products **(IV)** and **(Vb)**–**(Vf)** is always accompanied by the formation of **(VI)**. In the majority of cases, these by-product ketonucleosides cannot be separated from the target product by the usual chromatography on silica gel. We isolated two such oxidation products, **(VIa)** and **(VIc)**. However, we managed to obtain pure target products another way, by using the instability of **(VI)**, particularly under alkaline conditions [14]. To this end, mixtures resulting from the methylthiomethylation by method 1 and a preliminary chromatographic purification were kept in a 10% solution of triethylamine in anhydrous tetrahydrofuran for 1–2 days. This treatment resulted in the degradation of ketonucleosides and the precipitation of the corresponding nucleic bases, which were identified by TLC comparison with independent samples. The reaction mixtures acquired a brown to black color due to the destruction of unsaturated sugar, the second degradation (β-elimination) product [14]. Under the more drastic reaction conditions of method 2, the degradation of these by-products took place partially during the course of the alkylation reaction itself and reached its end in the process of the treatment of the reaction mixtures.

Products **(V)** of the methylthiomethylation reactions according to methods 1 and 2 were identical (TLC and NMR). The only exception was the transformations of **(IIa)** by method 2. It resulted in **(Ve)** and comprised two simultaneous processes: the methylthiomethylation of 3'-hydroxyl and the acetylation of the base amino group. On the other hand, the methylthiomethylation reaction of **(IIa)** by method 1 afforded **(IV)**, which was transformed into the *N*-benzoyl derivative **(Va)** in an almost quantitative yield.

The removal of silyl and acyl protective groups led to a set of partially [**(VIIa)**–**(VIIe)**, **(VIIId)**, and **(VIIIe)**] and completely [**(IXa)**, **(IXb)**, **(IXd)**, and **(IXe)**] deprotected 3'-*O*-methylthiomethylnucleosides.

The structure of methylthiomethyl derivatives **(IV)**, **(Va)**–**(Vf)**, **(VIIa)**–**(VIIe)**, **(VIIId)**, **(VIIIe)**, **(IXa)**, **(IXb)**, **(IXd)**, and **(IXe)** was convincingly confirmed by their physicochemical characteristics (Tables 2, 3).

All the compounds synthesized exhibit in their ^{1}H NMR spectra resonances from protons of the CH_3S and OCH_2S groups, sugar residue, and protective groups (Table 3). The characteristic resonance from 3'-H has a doublet of doublets or pseudotriplet form in both protected and deprotected derivatives. The resonance from 2'-H is transformed from a doublet of doublets (pseudotriplet) into a multiplet upon the deprotection of 2'-hydroxyl. Note also that the chemical shifts of other resonances nearly coincide with those in the spectra of similar 2'-*O*-methylthiomethylribonucleosides [1].

The target products **(IXa)**, **(IXb)**, **(IXd)**, and **(IXe)** were characterized by mass spectrometry and UV spectroscopy (Table 2). Their UV spectra indicate the intactness of the nucleic base structure.

Thus, we showed that methylthiomethylation by dimethyl sulfide–benzoyl peroxide and dimethyl sulfoxide–acetic anhydride–acetic acid reagent systems

Table 2. Yields and physicochemical characteristics of 3'-*O*-methylthiomethylnucleosides

Compound	Starting compound	Load		Method of isolaton*	Yield, %	Mp, °C (from methanol)	UV spectrum**, λ_{max}, nm (ε)	Mass spectrum
		mg	mmol					
(IXa)	**(VIIa)**	110	0.255	C	85	207–208	257.0(14600) 259.4(14600) 259.4(14800)	328.1 $(M + H)^+$
(IXb)	**(VIIb)**	323	0.722	C	85	235–236***	256.4(12000) 252.6(13400) 264.6(11300)	344.1 $(M + H)^+$
(IXd)	**(VIId)**	200	0.455	D	98	–	279.4(13000) 270.4(8900) 271.6(8900)	304.2 $(M + H)^+$ 326.1 $(M + Na)^+$ 342.2 $(M + K)^+$
(IXe)	**(VIIIe)**	350	0.836	B	87	143–144	260.8(10100) 261.2(10100) 262.4(7000)	304.2 $(M)^+$ 327.1 $(M + Na)^+$

* See the Experimental section.

** The parameters of UV spectra are given at pH 1, 7, and 13.

*** From methanol–water.

permits the preparation of 3'-*O*-methylthiomethylribonucleosides in satisfactory yields. The first method is preferred for this purpose.

EXPERIMENTAL

Melting points were not corrected. For TLC, Kieselgel 60 F_{254} precoated plates (Merck, Germany) and chromatographic systems (A) 9 : 1 chloroform–methanol and (B) 27 : 1 chloroform–methanol were used. Silica gel L 40/100 (Kavalier, Czech Republic) was used for column chromatography. Nucleosides, chlorotrimethylsilane, and Dowex 50Wx8-200 were from Sigma (United States); benzoyl peroxide, *tert*-butyldimethylchlorosilane, and tetrabutylammonium fluoride trihydrate were from Fluka (Switzerland); and dimethyl sulfoxide (DMSO) was from Merck (Germany). Other reagents and solvents were of domestic production.

UV, ^{1}H NMR, and MALDI TOF mass spectra were measured on a Shimadzu UV-160 spectrophotometer (Japan), a Bruker DRX-500 spectrometer (Germany), and a Vision 2000 (Thermo Bioanalysis Corp., UK) spectrometer, respectively.

Nucleosides **(Ia)**–**(Ic)** were synthesized in yields of 75–80% as described in [19]. **(Id)**, **(If)**, and **(Ig)** were obtained from nucleosides bearing the corresponding protective groups on the exocyclic amino group of the base, and **(Ie)** was prepared from uridine with ethoxymethylene protection of 2'- and 3'-hydroxyls [20] by procedures similar to those in [21, 22]; the yields were 50–70%.

Nucleosides (Ia)–(Ig) were silylated by analogy with [17]. *tert*-Butyldimethylsilyl chloride (1.2 mmol per each silyl group to be entered) and, then, a solution of silver nitrate (1.2 mmol per each silyl group to be entered) in anhydrous pyridine (1 ml) were added dropwise under stirring to a suspension of a nucleoside (1 mmol) in THF (10 ml). The reaction mixture was stirred at 20°C for 2–4 h while being monitored by TLC. An additional quantity of the silylating mixture was added if required. The silver chloride precipitate was filtered off, and the filtrate was evaporated. The residue was treated with an aqueous solution of sodium bicarbonate (10 ml) and extracted with chloroform (3 × 10 ml). The combined extracts were dried with anhydrous sodium sulfate and evaporated, and the products were separated by chromatography on silica gel. The separation conditions of mixtures of isomers **(II)** and **(III)** are given below.

2',5'-Di-*O*-*tert*-butyldimethylsilyladenosine (IIa) and 3',5'-di-*O*-*tert*-butyldimethylsilyladenosine (IIIa) were obtained from **(Ia)** and separated by chromatography on silica gel in ether; **(IIa)**, yield 61.3%, R_f 0.53 (A); **(IIIa)**, yield 23.0%, R_f 0.45 (A).

***N*^{2}-Benzoyl-2',5'-di-*O*-*tert*-butyldimethylsilylguanosine (IIb) and *N*^{2}-benzoyl-3',5'-di-*O*-*tert*-butyldimethylsilylguanosine (IIIb)** were obtained from **(Ib)**. The mixture of isomers after chromatographic purification on silica gel was dissolved in chloroform, and **(IIb)** was precipitated by the gradual addition of hexane. The mother liquor was evaporated and recrystallized from methanol to give **(IIIb)**. This procedure was repeated several times. There resulted **(IIb)**, yield 41%, R_f 0.66 (A), mp 115–116°C, and **(IIIb)**, yield 45.9%, R_f 0.60 (A), mp 117–120°C. A solution of **(IIIb)** in a 9 : 1 pyridine–water mixture was kept for

Table 3. ^{1}H NMR spectra of 3'-*O*-methylthiomethylnucleosides*

Compound	H6 or H8 ($J_{6,5}$)	H5 or H2	OCH_2S ($J_{a,b}$)	SCH_3	H1' ($J_{1',2'}$)	H2' ($J_{2',3'}$)	H3' ($J_{3',4'}$)	H4'	H5' ($J_{H5'a,H5'b}$; $J_{4',5'a}$; $J_{4',5'b}$)	Other
(IV)	8.34s	8.17s	4.84; 4.70dd (11.8)	2.17s	6.07d (5.2)	4.76pt (4.7)	4.40pt (3.3)	4.25m	4.03; 3.84ddd (11.3; 3.4; 2.7)	5.50 (NH_2); 0.97, 0.81 (2 × Bu^{t}Si); 0.16, 0.15, –0.03, –0.17 (4 × MeSi)
(Va)	8.82s	8.38s	4.85; 4.70dd (11.5)	2.18s	6.16d (4.9)	4.76pt (4.9)	4.41pt (3.3)	4.28m	4.04; 3.87ddd (11.4; 3.3; 2.7)	9.02 (NH); 8.07–7.50 (Ph); 0.98, 0.81 (2 × Bu^{t}Si); 0.17, 0.16, –0.02, –0.18 (4 × MeSi)
(Vb)	8.04s	–	4.88; 4.73dd (11.6)	2.19s	5.93d (5.8)	4.54pt (4.6)	4.46pt (3.0)	4.24m	3.94; 3.83ddd (11.6; 2.4; 2.0)	12.10, 8.59 (2 × NH); 7.92–7.54 (Ph); 0.95, 0.83 (2 × Bu^{t}Si); 0.14, 0.14, 0.00, –0.16 (4 × MeSi)
(Vc)	8.59d (7.0)	~7.5*	4.75; 4.53dd (11.6)	2.14s	5.87s	4.34d (4.0)	4.23dd (8.0)	4.30d	4.14; 3.84dd (11.6; <1)	8.75 (NH); 7.95–7.50 (Ph); 0.99, 0.93 (2 × Bu^{t}Si); 0.26, 0.18, 0.16, –0.14 (4 × MeSi)
(Vd)	8.29d (7.3)	~7.5*	4.75; 4.43dd (11.9)	2.18s	5.76s	4.44d (4.0)	4.09dd (8.8)	4.49dpt	4.53; 4.39ddd (12.5; 3.3; 1.5)	8.80 (NH); 7.90–7.50 (Ph); 2.10 (CH_3CO); 0.95 (Bu^{t}Si); 0.28, 0.16 (2 × MeSi)
(Ve)	7.67d (8.2)	5.73d	4.79; 4.53dd (11.9)	2.13s	5.73d** (2.4)	4.32m*** (4.5)	4.13dd (7.0)	4.37m	4.45; 4.33ddd (12.5; 3.7; 2.5)	8.05 (NH); 2.13 (CH_3CO); 0.92 (Bu^{t}Si); 0.15, 0.11 (2 × MeSi)
(Vf)	8.67s	8.36s	4.84; 4.67dd (11.7)	2.17s	6.13d (5.0)	4.72pt (4.6)	4.40pt (4.1)	4.27m	4.04; 3.85ddd (11.5; 3.2; 2.8)	8.48 (NH); 2.62 (CH_3CO); 0.98, 0.81 (2 × Bu^{t}Si); 0.17, 0.16, –0.02, –0.18 (4 × MeSi)
(VIIa)	8.77s	8.73s	4.87; 4.83dd (11.5)	2.16s	6.07d (6.4)	4.86m (4.9)	4.39dd (3.4)	4.13m	3.73; 3.62dddd (12.2; 4.3; 3.7)	11.20 (NH); 8.08–7.53 (Ph); 5.73 (2'-OH); 5.27 (5'-OH)
(VIIb)	8.31s	–	4.85; 4.82dd (11.6)	2.15s	5.92d (6.7)	4.69m (4.9)	4.32dd (2.8)	4.05m	3.68; 3.59m (12.2)	12.37, 11.94 (2 × NH); 8.09–7.53 (Ph); 5.66 (2'-OH); 5.19 (5'OH)
(VIIc)	8.49d (7.3)	7.35d	4.78; 4.70dd (11.3)	2.11s	5.83d (3.4)	4.26m (4.9)	4.16pt (5.8)	4.06m	3.76; 3.60dddd (11.9; 3.4; 3.1)	11.20 (NH); 8.08–7.53 (Ph); 5.27 (5'-OH); 5.59 (2'-OH)
(VIId)	8.11d (7.0)	~7.6*	4.81; 4.76dd (11.9)	2.19s	5.86d (2.8)	4.45m	4.27m	4.43–4.39m		8.75 (NH); 7.95–7.50 (Ph); 3.86 (2'-OH); 2.14 (CH_3CO)
(VIIe)	7.45d (8.0)	5.75d	4.78s	2.21s	5.75d** (3.6)	4.42–4.26m				8.53 (NH); 3.17 (2'-OH); 2.13 (CH_3CO)
(VIIIf)	7.87d (7.5)	5.73d	4.78; 4.70dd (11.6)	2.10s	5.79d (5.2)	4.33pt (4.6)	4.12pt (4.3)	3.99m	3.67; 3.57dddd (11.6; 3.4; 3.0)	7.14 (NH_2); 5.19 (5'-OH); 0.83, 0.02, 0.00 (Bu^{t}Si, 2 × MeSi)
(VIIIg)	7.65d (8.2)	5.73d	4.84; 4.64dd (11.5)	2.19s	5.56d (4.9)	4.60pt (4.1)	4.24–4.20m		3.98; 3.80dddd (12.4; 2.5; 1.6)	8.01 (NH); 2.78 (5'-OH); 0.90, 0.10, 0.08 (Bu^{t}Si, 2 × MeSi)
(IXa)	8.36s	8.15s	4.87; 4.82dd (11.5)	2.15s	5.90d (6.7)	4.80m (4.9)	4.33dd (2.8)	4.10m	3.70; 3.59dddd (11.9; 3.2; 3.7)	7.35 (NH_2); 5.61 (2'OH); 5.56 (5'-OH)
(IXb)	7.96s	–	4.84; 4.80dd (11.3)	2.14s	5.72d (6.4)	4.59m (4.9)	4.27dd (3.3)	4.00m	3.63; 3.56dddd (11.9; 4.3; 3.7)	10.60 (NH); 6.47 (NH_2); 5.56 (2'-OH); 5.16 (5'-OH)
(IXc)	7.85d (7.3)	5.75d	4.79; 4.72dd (11.6)	2.12s	5.79d (4.9)	4.16m (4.9)	4.12pt (4.9)	3.96m	3.67; 3.55dddd (11.9; 3.1; 3.4)	7.16 (NH_2); 5.42 (2'-OH); 5.16 (5'-OH)
(IXd)	7.88d (8.2)	5.68d	4.82; 4.75dd (11.5)	2.12s	5.80d (5.8)	4.23m (4.9)	4.17pt (3.7)	3.98m	3.64; 3.57dddd (12.2; 3.4; 3.1)	11.34 (NH); 5.52 (2'-OH); 5.21 (5'-OH)

* Spectra of **(IV)**, **(Va)**–**(Vf)**, **(VIId)**, **(VIIe)**, and **(VIIIe)** were measured in $CDCl_3$; those of **(VIIa)**–**(VIIc)**, **(VIIId)**, **(IXa)**–**(IXc)** and **(IXe)**, were taken in DMSO-d_6. Chemical shifts (δ, ppm, and spin–spin coupling constants (J, Hz)) are given. The integral intensities correspond to the number of protons indicated. Forms of resonances: s, singlet; d, doublet; dd, doublet of doublets; pt, pseudotriplet; ddd, doublet of doublets of doublets; dddd, doublet of doublets of doublets of doublets; dpt doublet of pseudotriplets; and m, multiplet. Resonances from Ph; from NH and NH_2; from 2'-OH, from 5'-OH; and from CH_3CO, CH_3, and Bu^{t}Me$_2$Si are multiplets, broad singlets, doublets or broad singlets, triplets or broad singlets, and singlets, respectively.

** Superposition of Ph.

*** Superposition of H5.

**** Superposition of H5'b.

2 days at 20°C. The resulting isomer mixture was repeatedly separated as described above. The total yields of (**IIb**) and (**IIIb**) were 60.5 and 21.6%, respectively.

N^4-Benzoyl-2',5'-di-*O*-*tert*-butyldimethylsilylcytidin (IIc) and N^4-benzoyl-3',5'-di-*O*-*tert*-butyldimethylsilylcytidine (IIIc) were obtained from (**Ic**). The mixture of isomers was separated by chromatography on silica gel in chloroform; (**IIc**), yield 61.2%, R_f 0.48 (B); (**IIIc**), yield 23.7%, R_f 0.24 (B).

5'-*O*-Acetyl-N^4-benzoyl-2'-*O*-*tert*-butyldimethylsilylcytidin (IId) and 5'-*O*-acetyl-N^4-benzoyl-3'-*O*-*tert*-butyldimethylsilylcytidine (IIId) were obtained from (**Id**). The mixture of isomers was separated by chromatography on a silica gel column eluted with a gradient of methanol concentration (from 0 to 3%) in chloroform; (**IId**), yield 64.9%, R_f 0.39 (B); (**IIId**), yield 30.1%, R_f 0.22 (B).

5'-*O*-Acetyl-2'-*O*-*tert*-butyldimethylsilyluridine (IIe) was obtained from (**Ie**). After chromatography on silica gel, the resulting mixture of (**IIe**) and (**IIIe**) was dissolved in chloroform and (**IIe**) was precipitated by the gradual addition of hexane until the oily (**IIIe**) began to precipitate. The yield of (**IIe**) was 69.2%, R_f 0.58 (A); R_f of (**IIIe**) was 0.52 (A). The mother liquor was evaporated and the residue was dissolved in a 9 : 1 pyridine–water mixture, kept for 2 days at 20°C, and evaporated. The separation of isomers was repeated, and a total yield of (**IIe**) of 82.0% was obtained.

The methylthiomethylation of 3'-hydroxyl groups of ribonucleosides. Method 1. A solution of a protected nucleoside, (**IIb**), (**IIc**), (**IId**), or (**IIe**),[3] in anhydrous acetonitrile (10–30 ml depending on the solubility of the nucleoside) was treated at 0°C with dimethyl sulfide (0.75 ml, 10 mmol) and, then, with benzoyl peroxide (970 mg, 4 mmol) in portions for 15–30 min under stirring. The mixture was stirred for 1–3 h at 0°C, the reaction was monitored by TLC, and the mixture was then evaporated, treated with 10% Na_2CO_3 (20 ml), and extracted with chloroform (3 × 20 ml). The combined extracts were dried with anhydrous sodium sulfate, evaporated, and chromatographed on a silica gel column eluted with 50 → 0% hexane in chloroform and then with 0 → 2% methanol in chloroform. Appropriate fractions were evaporated, dissolved in 10% triethylamine solution in THF (10 ml), kept for 1–2 days at 20°C, and evaporated. The residue was once more chromatographed on a silica gel column eluted with a 0 to 2% gradient of methanol in chloroform. (**Vb**)–(**Ve**) were obtained by the evaporation of the corresponding fractions.

Method 2. A mixture of acetic anhydride (2.15 ml), acetic acid (0.65 ml), and dimethyl sulfoxide (3.15 ml) was added to a protected nucleoside (**IIa**), (**IIb**), (**IIc**), (**IId**), or (**IIe**). The reaction mixture was kept for 3 days at 20°C and monitored by TLC. After the end of the reaction, the mixture was poured into a cold 10% sodium carbonate solution under stirring. When the carbon dioxide ceased to evolve, the water layer was extracted with chloroform (3 × 20 ml). The combined extract was dried with sodium sulfate and evaporated in the vacuum of a water-jet pump and, then, an oil forvacuum pump. The dry residue was separated by chromatography on a silica gel column eluted with a 0–2% gradient of methanol in chloroform. The appropriate fractions were evaporated, and the products were recrystallized.

2',5'-Di-*O*-*tert*-butyldimethylsilyl-3'-*O*)-methylthiomethyladenosine (IV) and 9-(2,5-di-*O*-*tert*-butyldimethylsilyl-β-*D*-*erythro*-pentofuran-3-ulosyl)adenosine (VIa). A suspension of (**IIa**) (992 mg, 2 mmol) in acetonitrile (60 ml) was treated at 0°C with dimethyl sulfide (1.5 ml) and, in portions for 30 min, with benzoyl peroxide (1.94 g). After 15 min, the reaction mixture became clear and, after an additional 15 min, a precipitate was formed. Three hours after the addition of benzoyl peroxide, the precipitate was separated and recrystallized from acetonitrile to give (**VIa**); yield 195 mg (19.8%); R_f 0.56 (A). The mother liquor was treated as described in the general procedure (including triethylamine treatment) to give (**IV**), yield 707 mg (63.7%, accounting for recrystallization losses); mp 133.5–134°C; R_f 0.60 (A).

N^6-Benzoyl-2',5'-di-*O*-*tert*-butyldimethylsilyl-3'-*O*-methylthiomethyladenosine (Va). Benzoyl chloride (0.78 ml, 6.72 mmol) was added to a solution of (**IV**) (1.246 g, 2.24 mmol) in dry pyridine (15 ml). The mixture was kept at 20°C for 2 h, treated upon cooling with 3 ml of water and, 10 min later, with 4 ml of saturated ammonia, kept for 20 min, and evaporated. Saturated $NaHCO_3$ (20 ml) was added, and the mixture was extracted with chloroform (3 × 30 ml). The combined extracts were dried with sodium sulfate and evaporated, and the product was chromatographed on silica gel eluted with chloroform. The corresponding fraction gave (**Va**) after evaporation; yield 1.45 g (98%).

Desilylation of methylthiomethylnucleosides. A 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.1 ml per silyl group) was added to a solution of 1 mmol of (**Va**), (**Vb**), (**Vc**), (**Vd**), (**Ve**), or (**VIIIe**) (its synthesis is described below) in 3 ml of tetrahydrofuran. The reaction mixture was kept for 2 h at 20°C, evaporated, and the residue was chromatographed on a silica gel column. The corresponding fractions were evaporated, and the product [(**VIIa**), (**VIIb**), or (**VIIc**)] was recrystallized (method A). If the target product could not be recrystallized, the desilylation mixture was evaporated and the residue was dissolved in aqueous methanol and passed through a layer of Dowex 50W in NH_4^+-form. The filtrate was evaporated, and the resulting product [(**VIId**), (**VIIe**), or (**IXe**)] was purified by column chromatography on sil-

[3] The methylthiomethylation procedure of (**IIa**) differs from this one in some details and is given below when describing the syntheses of (**IV**) and (**VIa**).

ica gel (method B). The following derivatives were obtained:

N^6-Benzoyl-3'-*O*-methylthiomethyladenosine (VIIa); method A; mp 177–178°C (from methanol); yield 144 mg (83.4%) from 264 mg (0.4 mmol) of (**Va**).

N^2-Benzoyl-3'-*O*-methylthiomethylguanosine (VIIb); method A; mp 167–168°C (from aqueous methanol); yield 413 mg (82.4%) from 757 mg (1.12 mmol) of (**Vb**).

N^4-Benzoyl-3'-*O*-methylthiomethylcytidine (VIIc); method A; mp 163.5–164.5°C (from methanol); yield 83 mg (80.8%) from 160 mg (0.252 mmol) of (**Vc**).

5'-*O*-Acetyl-N^4-benzoyl-3'-*O*-methylthiomethylcytidine (VIId); method B; yield 260 mg (81.5%) from 400 mg (0.71 mmol) of (**Vd**).

5'-*O*-Acetyl-3'-*O*-methylthiomethyluridine (VIIe); method B; yield 136 mg (88.2%) from 205 mg (0.445 mmol) of (**Ve**).

3'-*O*-Methylthiomethyluridine (IXe). For the data, see Table 2.

Removal of the acyl protective groups. A solution of 1 mmol of a nucleoside [(**Vd**), (**Ve**), (**VIIa**), (**VIIb**), or (**VIId**)] in 5 ml of a semisaturated methanolic ammonia (methanol was saturated with gaseous ammonia at 0°C and twofold diluted with methanol) was kept for 1 day at 20°C [2 days in the case of (**VIIb**)]. The mixture was then evaporated, and the product was recrystallized (method C) or purified by chromatography on a silica gel column eluted with a gradient from 5 to 10% of methanol in chloroform (method D). The results of the deacylation of (**VIIb**), (**VIId**), and (**VIIe**) are given in Table 2.

3'-*O*-Methylthiomethyl-2'-*O*-*tert*-butyldimethylsilylcytidine (VIIId); method D; mp 217–218°C (from chloroform–hexane); yield 133 mg (89.7%) from 200 mg (0.355 mmol) of (**Vd**).

3'-*O*-Methylthiomethyl-2'-*O*-*tert*-butyldimethylsilyluridine (VIIIe); method D; mp 201–202°C (from methanol); yield 387 mg (92.4%) from 461 mg (1 mmol) of (**Ve**).

REFERENCES

1. Pechenov, A.E., Zavgorodny, S.G., Shvets, V.I., and Miroshnikov, A.I., *Bioorg. Khim.*, 2000, vol. 26, pp. 362–368.
2. Matteucci, M., *Tetrahedron Lett.*, 1990, vol. 31, pp. 2385–2388.
3. Veeneman, G.H., van der Marel, G.A., van den Elst, H., and van Boom, J.H., *Rec. Trav. Chim. Pays-Bas*, 1990, vol. 109, pp. 449–451.
4. Veeneman, G.H., van der Marel, G.A., van den Elst, H., and van Boom, J.H., *Tetrahedron*, 1991, vol. 47, pp. 1547–1562.
5. Oivanen, M., Viinamäki, T., Zavgorodny, S., Poliansky, M., Azhayev, A., van Aerschot, A., Herdewijn, P., and Lönnberg, H., *Collect. Czech. Chem. Commun.*, 1990, vol. 55, pp. 17–20.
6. Zavgorodny, S., Poliansky, M., Kriukov, V., Oksman, P., Hakala, H., Lönnberg, H., van Aerschot, A., Herdewijn, P., and Azhayev, A., *Nucleic Acids Res.*, 1991, vol. 19, p. 295.
7. Zavgorodny, S., Poliansky, M., Besidsky, E., Kriukov, V., Sanin, A., Pokrovskaya, M., Gurskaya, G., Lönnberg, H., and Azhayev, A., *Tetrahedron Lett.*, 1991, vol. 32, pp. 7593–7596.
8. Hsu, L.-Y., Wise, D.S., Kucera, L.S., Drach, J.C., and Townsend, L.B., *J. Org. Chem.*, 1992, vol. 57, pp. 3354–3358.
9. Jones, R.J., Lin, K.-Y., Milligan, J., Wadwani, S., and Matteucci, M., *J. Org. Chem.*, 1993, vol. 58, pp. 2983–2991.
10. Lin, K.-Y., Pudlo, J.S., Jones, R.J., Bishofberger, N., Matteucci, M.D., and Froehler, B.C., *Biomed. Chem. Lett.*, 1994, vol. 4, pp. 1061–1064.
11. Ducharme, Y. and Harrison, K.A., *Tetrahedron Lett.*, 1995, vol. 36, pp. 6643–6646.
12. Karpeisky, A., Gonzalez, C., Burgin, A.B., Usman, N., and Beigelman, L., *Nucleosides Nucleotides*, 1997, vol. 16, pp. 955–958.
13. He, G.-X. and Bishofberger, N., *Tetrahedron Lett.*, 1997, vol. 38, pp. 945–948.
14. Hansske, F., Madej, D., and Robins, M.J., *Tetrahedron*, 1984, vol. 40, pp. 125–135.
15. Gavagnin, M. and Sodano, G., *Nucleosides Nucleotides*, 1989, vol. 8, pp. 1319–1324.
16. Medina, J.C., Salomon, M., and Kyler, K.S., *Tetrahedron Lett.*, 1988, vol. 29, pp. 3773–3776.
17. Hakimelahi, G.H., Proba, Z.A., and Ogilvie, K.K., *Can. J. Chem.*, 1982, vol. 60, pp. 1106–1113.
18. Ogilvie, K.K., Beaucage, S.L., Schifman, N.L., Theriault, N.Y., and Sadana, K.L., *Can. J. Chem.*, 1978, vol. 56, pp. 2768–2780.
19. Van Boom, J.H. and Wreesmann, C.T.J., *Oligonucleotide Synthesis: A Practical Approach*, Gait, M.J., Ed., Oxford: IRL, 1984, pp. 153–182.
20. Eckstein, F. and Cramer, F., *Chem. Ber.*, 1965, vol. 98, pp. 995–997.
21. Griffin, B.E., Jarman, M., Reese, C.B., and Sulston, J.E., *Tetrahedron*, 1967, vol. 23, pp. 2301–2313.
22. Fromageot, H.P.M., Jarman, M., Reese, C.B., and Sulston, J.E., *Tetrahedron*, 1967, vol. 23, pp. 2315–2331.