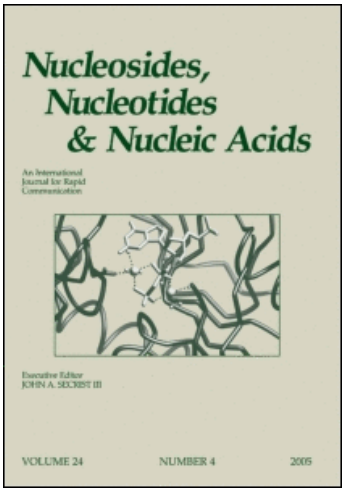


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# S,*X*-Acetals in Nucleoside Chemistry. III[1]. Synthesis of 2'-and 3'-O-Azidomethyl Derivatives of Ribonucleosides

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NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(10–12), 1977–1991 (2000)

# *S,X*-ACETALS IN NUCLEOSIDE CHEMISTRY. III[1]. SYNTHESIS OF 2'- AND 3'-*O*-AZIDOMETHYL DERIVATIVES OF RIBONUCLEOSIDES

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**Abstract.** 2'- and 3'-*O*-azidomethyl derivatives of ribonucleosides were obtained by splitting the corresponding methylthiomethyl derivatives of ribonucleosides with bromine or $SO_2Cl_2$ followed by lithium azide treatment.

## INTRODUCTION

Modification of methylthiomethyl (MTM) function[2] in *O*-MTM derivatives of nucleosides enables synthesis of potential antivirals, oligonucleotide analogues with formacetal internucleoside linkages, nucleosides containing new protective groups, reporter groups, *etc*[3-6]. The most abundant direction of the MTM group modification is splitting C-S bond with a halogenating agent and subsequent displacement of a halogen ion in the formed halogenomethyl derivative with various nucleophiles.

The following methods of MTM group scission are currently known in the nucleoside chemistry.

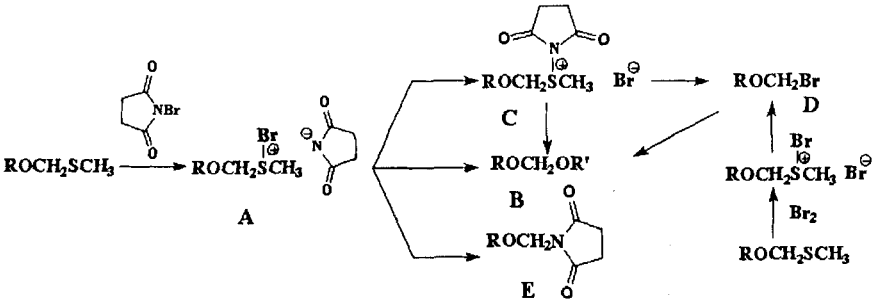
1. Treatment with N-halogensuccinimide *per se* (a)[3,4] or in the presence of electrophilic catalysts (b)[7,8].

This paper is dedicated to the memory of Professor A.A. Krayevsky.

2. Cleavage of MTM group with halogens[5,9-14].
3. Cleavage with sulfuryl chloride[5,15].
4. Solvolysis catalyzed by heavy metal salts[5].

Method 1a was first employed for the substitution of a methylthio group in nucleoside *O*-methylthiomethyl derivatives for alkoxy group (preparation of thymidine di- and trimers having internucleosidic (3'-5') methylene bonds), although possible complications in this case were quite clear due to the reaction mechanism (scheme 1). It is evident that the first intermediate A can be transformed not only into the required product B (either directly or through the related intermediate C and α-bromomethyl ether D), but also into the succinimidomethyl derivative E. The efficiency of this method previously described[3] was disproved by Veeneman *et al.* [4,7]. Really, the required product yield was 11%, when *N*-bromosuccinimide (NBS) was used, and 33% in case of *N*-iodosuccinimide (NIS), along with predominant formation of the corresponding 3'-*O*-succinimidomethyl derivative. Apparently, for this reason the method considered had a limited application[6,16]. In this connection we would like to mention that in spite of a statement[6,16], we have never used NBS for this purpose[5,9,11].

The employment of trifluoromethanesulphonic acid (TfOH) as a catalyst along with NIS for cleavage of the MTM group (method 1b) promotes to improve significantly the yields of required products. Obviously, acid eliminates succinimide anion from the set of competing nucleophiles. Thus, NIS - carboxylic acid treatment of MTM derivatives gives acyloxy ones in good yields[17]. This method, however, cannot be employed, when the presence of TfOH drastically decreases the nucleophility of the reagent ($N_3^-$, $CN^-$, $PhO^-$, *etc.*).




**SCHEME 1**

Shortly afterwards method 2 (bromine use) was proposed, which was free of method 1 drawbacks (see scheme 1). Its efficiency was confirmed by synthesis of a wide

range of $OCH_2X$ derivatives of nucleosides [5,6,9-11,13,14]. At the same time iodine application was proposed to cover the same purpose, but only for a limited number of compounds [12].

Noteworthy, in all above cases of the replacement of $CH_3S$ group by others, active reagents are the derivatives of the nucleosides A, C, D (scheme 1). Certain difficulties arise due to existence of strong electrophiles and the nucleophile (protected nucleic base) within the molecule. It is no mere chance that almost in all the works, where method 1 was used, the results were obtained only for the thymidine derivatives – the weakest nucleophiles among natural nucleosides. Since the attempts to employ this method (method 1b) for purine nucleosides faced certain difficulties, it was proposed[18] to carry out the reaction with a high excess of TfOH and at low temperatures. This allowed obtaining formacetal analogues of purine-purine dinucleotides[18] with good yields, but did not solve the problem of anionic nucleophile use.



There are at least two ways to improve the yield. First, it is shortening of free existence of *O*-halogenomethyl derivative of the nucleoside. Second, a decrease in the electrophilic activity of the given derivative, resulted from the employment of worse leaving groups (*e.g.* chlorine instead of bromine or iodine).

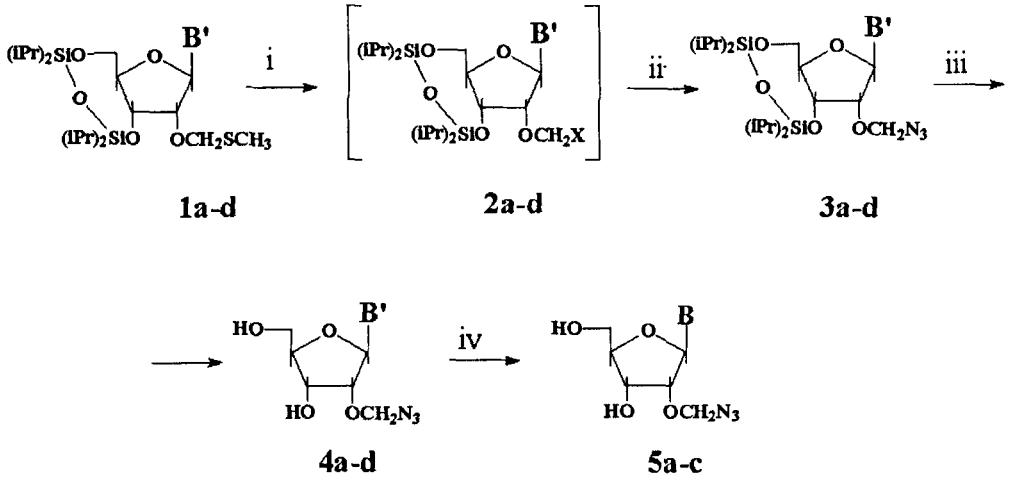
The first was successfully realized in[5,9,11], by selection of the experimental conditions and will be discussed elsewere. Nevertheless, the yield of $OCH_2X$ derivatives of purine nucleosides was lower than for pyrimidine ones. Therefore there were made some attempts to use *O*-chloromethyl derivatives. These derivatives are usually obtained when treated the corresponding *O*-MTM derivatives with sulfuryl chloride[2c] (method 3) that provides good results on *N,S*-acetals – nucleic base derivatives[19] and on *O,S*-acetals – nucleoside derivatives [5,15].

Method 4 is much less used owing to a long reaction time, limited set of nucleophiles and potential side reactions occurred due to protected nucleic base [5].

Thus, we can conclude that method 2 being universal is the most suitable almost in all the cases. In certain cases method 3 gives good results.

## RESULTS AND DISCUSSION

In the present work we synthesized 2'-*O*-azidomethyl (scheme 2) and 3'-*O*-azidomethyl (scheme 3) derivatives of ribonucleosides by cleavage the parent methylthiomethyl derivatives followed by lithium azide treatment.




**1a-d** **2a-d** **3a-d**

**4a-d** **5a-c**

a: B=Ade, B'=BzAde; b: B=Gua, B'=IbuGua; c: B=Cyt, B'=BzCyt; d: B=B'=Ura; X=Br, Cl;

(i) $Br_2$ ($SO_2Cl_2$)/$C_2H_4Cl_2$; (ii) $LiN_3$/DMF; (iii) $Bu_4N^+F^-$/THF; (iv) $NH_3$/MeOH

Ibu – isobutyryl.

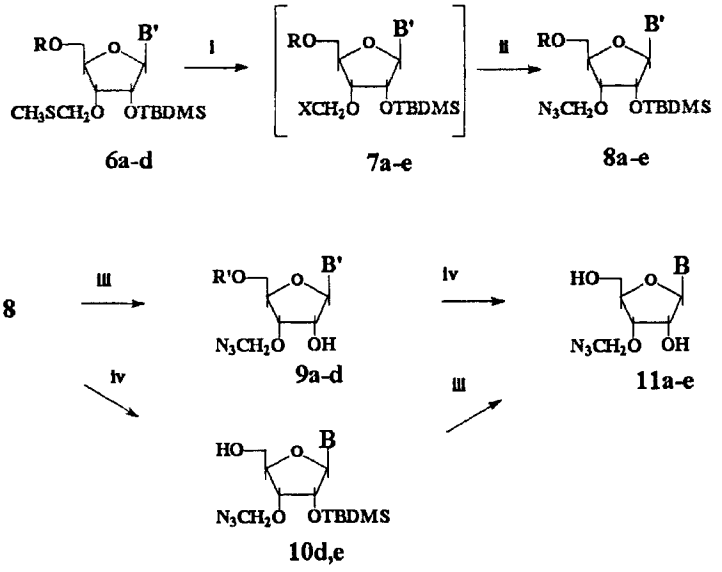
**SCHEME 2**

Synthesis of these compounds was based on our previous data concerning 2'-deoxyribo series[5,9,11]. On one hand, azidomethyl group incorporation can be easily controlled by IR spectrometry. On the other hand, this group can be removed under specific and mild conditions (triphenylphosphine in aqueous pyridine at ~20°C[5]) or used to obtain other derivatives or analogues of nucleosides [20,21].

According to scheme 2, 2'-*O*-methylthiomethyl derivatives of ribonucleosides [22] **1a-d** were converted into their 2'-*O*-halogenomethyl derivatives **2a-d,** if treated with molecular bromine or with sulfuryl chloride in dry dichloroethane. These halogenomethyl derivatives reacted then *in situ* with lithium azide (dissolved in dimethylformamide). After conventional work-up and purification the corresponding 2'-*O*-azidomethyl derivatives **3a-d** were obtained.

As scheme 3 shows 3'-*O*-methylthiomethyl derivatives of ribonucleosides[1] **6a-d** were converted in the same manner into the corresponding azidomethyl derivatives **8a-e,** when treated with molecular bromine or with sulfuryl chloride, and then with lithium azide.

*Cleavage of the MTM group of properly protected derivatives of adenosine* **1a**, **6a**, cytidine **1c**, **6c,** and uridine **1d**, **6d** with bromine gives the best results compared with




a: B=Ade, B'=BzAde, R=TBDMS, R'=H; b: B=Gua, B'=BzGua, R=TBDMS, R'=H; c: B=Cyt, B'=BzCyt, R=TBDMS, R'=H; d: B=B'=Ura, R=R'=Ac; e: B'=B=5-Cl-Ura, R=Ac; X=Br, Cl; TBDMS- *tert*-butyldimethylsylil.

(i) $Br_2$ ($SO_2Cl_2$)/$C_2H_4Cl_2$; (ii) $LiN_3$/DMF; (iii) $Bu_4N^+F^-$/THF; (iv) $NH_3$/MeOH

**SCHEME 3**

sulfuryl chloride almost in every case, together with a longer reaction time in the latter case. The cytidine derivatives reaction was performed at room temperature, lower temperature was required for other derivatives. The bromine-assisted cleavage was inefficient in case of guanosine derivatives. Azidomethyl derivatives **3b** and **8b** were obtained by treatment of starting nucleosides **1b** and **6b** with sulfuryl chloride and then with lithium azide with appropriate yields (84% and 53%, respectively). Despite the statement of paper[16] in similar cases we used the related procedures in our earlier papers[5,9,11].

An interesting result was obtained when protected 3'-*O*-methylthiomethyluridine was treated with sulfuryl chloride. Chlorination of the nucleic base also proceeds in position 5 in addition to the main reaction. The product of the reaction **8e** was obtained with 79% yield. In case of protected 2'-*O*-methylthiomethyluridine **1d** the undesirable reaction was not observed, evidently, due to the protecting group influence.

The obtained azidomethyl derivatives **3a-d**, **8a-e** were deprotected, providing particularly **4a-c**, **9a-c**, **10d**, **10e** and fully deprotected nucleosides **4d**, **5a-c**, **11a-e**. The

identity of the derivatives was confirmed by their physical and chemical properties.

In the $^1$H NMR spectra the resonances previously assigned to the methylthio group were no longer apparent. The coupling constants of $OCH_2N$ methylene protons were changed to 8.6-9.2 Hz compared to 11.3-12.0 Hz for $OCH_2S$ protons in the starting compounds. Chemical shifts and multiplicity of the signals of other protons changed insufficiently compared to similar 2'- and 3'-*O*-methylthyomethyl derivatives. In the $^1$H NMR spectra of 5-chlorouridine derivatives **8e**, **10e** and **11e** no resonance assigned to H5 was observed, the resonance assigned to H6 became singlets and shifted downfield at 0.4-0.55 ppm compared to compounds **8d**, **10d** and **11d**, in which the nucleic base did not change.

The IR spectra of the obtained compounds showed a characteristic band at 2130-2140 $cm^{-1}$.



Final compounds **4a**, **5a-5c** and **11a-11d** were UV spectroscopically identical to the parent nucleosides. The mass spectrometry data also confirmed the composition, except for compound **11e**, where the molecular ion was not observed. The $^1$H NMR and UV spectra along with the elemental analysis data allowed us to propose that the derivative **11e** was obtained as a solvate with THF risen from crystallization.

Thus, it was shown that cleavage of 2'- and 3'-*O*-methylthiomethyl group of protected adenosine, cytidine and uridine with bromine or sulfuryl chloride gives approximately equal yields of the corresponding azidomethyl derivatives, in case of guanosine derivatives satisfactory results were obtained only with sulfuryl chloride.

## EXPERIMENTAL

The melting points are uncorrected. TLC was conducted on Kieselgel 60 $F_{254}$ (Merck). Chromatography was performed on columns of silica gel L40/100 (Kavalier). IR spectra were recorded on Hitachi IR Spectrophotometer Model 270-50 and UV spectra - on Shimadzu UV-160. $^1$H NMR spectra were recorded on Bruker DRX-500 spectrometer operating at 500 MHz. Tetramethylsilane was used as internal reference. Mass spectra were obtained on Vision 2000 spectrometer (method MALDI TOF) (Thermo Bioanalysis Corp.). All solvents (analytical grade) were distilled and dried before use. Bromine was distilled over concentrated $H_2SO_4$.

**General route for bromine cleavage (Method *A*).**

Bromine (1.2 eq) was added to solution of 1 mmol of nucleoside **1a-d**, **6a-d** in 3 ml (for **1b** in 40 ml) of dry 1,2-dichloroethane at –10°C (for **1c** and **6c** at 20°C). After 10-30 min the solution of lithium azide (6 eq) in 2 ml of dimethylformamide was added to the reaction mixture. The mixture was poured into 20 ml of saturated aqueous $NaHCO_3$ after 30 min at 20°C and extracted with chloroform (3x20 ml). Combined chloroform extracts were dried over $Na_2SO_4$ and concentrated at reduced pressure. The residue was applied on silica gel column and washed with gradient (0→2%) methanol in chloroform. Desired fractions were evaporated and nucleosides **3a-d** and **8a-d** were obtained (details are listed below).

**General route for sulfuryl chloride cleavage (Method *B*).**

Sulfuryl chloride (2.2 eq, two portions within 1 h) was added to solution of nucleoside in 3 ml (for **1b** in 40 ml) of dry 1,2-dichloroethane at 0°C. After 2-3 h lithium azide solution (10 eq) in 3 ml DMF was added. After 30 min at 20°C an aqueous work-up and purification were performed, as listed above, yielding nucleosides **3a-d**, **8a-c** and **8e**.



**2'-*O*-Azidomethyl-$N^6$-benzoyl-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-adenosine (3a)** was prepared from 673 mg (1 mmol) of **1a** by Method *A* to give 436 mg (65%) of **3a**. Processing of 337 mg (0.5 mmol) of **1a** by Method *B* gave 207 mg (62%) of **3a**. $^1$H NMR ($CDCl_3$) δ : 9.02 (1H, br. s, NH), 8.80 (1H, s, H8), 8.32 (1H, s, H2), 8.10-7.45 (5H, m, arom.), 6.12 (1H, s, H1'), 5.07 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.7 Hz), 4.99 (1H, d, Hb, $OCH_2N$), 4.79 (1H, dd, H3', $J_{3',4'}$=9.6 Hz), 4.61 (1H, d, H2', $J_{2',3'}$=4.6 Hz ), 4.19 (1H, m, H4'), 4.27 (1H, dd, H5'a, $J_{H5'a,H5'b}$=13.3 Hz), 4.06 (1H, dd, H5'b), 1.22 (28H, m, *i*PrX4).

**2'-*O*-Azidomethyl-$N^2$-isobutyryl-3',5'-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)guanosine (3b)** was prepared from 734 mg (1.14 mmol) of **1b** by Method *B* and recrystallized from 1,2-dichloroethane to give 610 mg (84%) of **3b**, m.p. 115-117°C dec. Method *A* for 300 mg (0.46 mmol) of **1b** gave 35 mg (12%) of **3b**. $^1$H NMR ($CDCl_3$) δ : 11.9 (1H, br. s, NH), 8.03 (1H, br. s, NH), 8.01 (1H, s, H2) , 5.95 (1H, s, H1'), 5.12 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=9.2 Hz), 4.85 (1H, d, Hb, $OCH_2N$), 4.51 (1H, dd, H3', $J_{3',4'}$=9.2 Hz), 4.35 (1H, d, H2', $J_{2',3'}$=4.6 Hz ), 4.15 (1H, m, H4'), 4.28 (1H, dd, H5'a, $J_{H5'a,H5'b}$=13.3 Hz), 4.03 (1H, dd, H5'b), 2.61 (1H, m, C<u>H</u>$(CH_3)_2$), 1.10 (28H, m, *i*PrX4).

**2'-*O*-Azidomethyl-$N^4$-benzoyl-3',5'-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)cytidine (3c)** was prepared from 490 mg (0.76 mmol) of **1c** by Method *A* to give 374

mg (77%) of **3c**. $^1$H NMR ($CDCl_3$) δ : 8.37 (1H, d, H6, $J_{6,5}$=6.9 Hz), 7.90-7.50 (6H, m, arom. and H5), 5.13 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.7 Hz), 4.99 (1H, d, Hb, $OCH_2N$ b), 5.85 (1H, s, H1'), 4.33 (1H, dd, H5'a, $J_{H5'a,H5'b}$=13.8 Hz), 4.25-4.20 (3H, m, H2', H3', H4'), 4.03 (1H, dd, H5'b), 1.1 (28H, m, *i*Prx4).

**2'-*O*-Azidomethyl-3',5'-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)uridine (3d)** was prepared from 273 mg (0.5 mmol) of **1d** by Method *B* to give 244 mg (90%) of **3d**. Treatment of 160 mg (0.29 mmol) of **1d** by Method *A* gave 139 mg (88%) of **3d**. $^1$H NMR ($CDCl_3$) : 9.01 (1H, br. s, NH), 7.90 (1H, d, H6, $J_{6,5}$=8.2 Hz), 5.69 (1H, d, H5), 5.02 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.87 (1H, d, Hb, $OCH_2N$), 5.73 (1H, s, H1'), 4.16 (1H, d, H2', $J_{2',3'}$=4.5 Hz), 4.22 (1H, dd, H3', $J_{3',4'}$=9.6 Hz), 4.14 (1H, m, H4'), 4.15 (1H, dd, H5'a, $J_{H5'a,H5'b}$=13.6 Hz), 3.80 (1H, dd, H5'b), 1.1 (28H, m, *i*Prx4).

**3'-*O*-Azidomethyl-$N^6$-benzoyl-2',5'-bis-*O*-*tert*-butyldimethylsilyladenosine (8a)** was prepared from 462 mg (0.7 mmol) of **6a** by Method *A* to give 360 mg (79%) of **8a**. Treatment of 462 mg (0.7 mmol) of **6a** by Method *A* gave 327 mg (71%) of **8a**. $^1$H NMR ($CDCl_3$) δ : 9.02 (1H, br. s, NH), 8.82 (1H, s, H8), 8.36 (1H, s, H2), 8.1-7.5 (5H, m, arom.), 6.15 (1H, d, H1', $J_{1',2'}$=5.2 Hz), 4.98 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.8 Hz), 4.79 (1H, pt, H2', $J_{2',3'}$=4.3 Hz), 4.64 (1H, d, Hb, $OCH_2N$), 4.34-4.28 (2H, m, H3', H4'), 4.05 (1H, dd, H5'a, $J_{H5'a,H5'b}$=11.5 Hz, $J_{4',5'a}$=3.0 Hz, $J_{4',5'b}$=2.5 Hz), 3.88 (1H, dd, H5'b), 0.97, 0.92 (2x9H, 2s, 2x*t*BuSi), 0.17, 0.16, -0.02, -0.19 (4x3H, 4s, 4xMeSi).

**3'-*O*-Azidomethyl-$N^2$-benzoyl-2',5'-bis-*O*-*tert*-butyldimethylsilylguanosine (8b)** was prepared from 473 mg (0.7 mmol) of **6b** by Method *B* and recrystallized from toluene-hexane to give 250 mg (53%) of **8b**, m.p. 182.5-183°C dec. $^1$H NMR ($CDCl_3$) δ : 8.55 (1H, br. s, NH), 8.03 (1H, s, H8), 7.9-7.6 (5H, m, arom.), 5.93 (1H, d, H1', $J_{1',2'}$=5.8 Hz), 4.99 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.67 (1H, d, Hb, $OCH_2N$), 4.55 (1H, dd, H2', $J_{2',3'}$=4.6 Hz), 4.32 (1H, pt, $J_{3',4'}$=3.0 Hz), 4.29 (1H, m, H4'), 3.95 (1H, dd, H5'a, $J_{H5'a,H5'b}$=11.6 Hz, $J_{4',5'a}$=2.6 Hz, $J_{4',5'b}$=2.1 Hz), 3.84 (1H, dd, H5'b), 0.95, 0.83 (2x9H, 2s, 2x*t*BuSi), 0.15, 0.15, 0.0, -0.16 (4x3H, 4s, 4xMeSi).

**3'-*O*-Azidomethyl-$N^4$-benzoyl-2',5'-bis-*O*-*tert*-butyldimethylsilylcytidine (8c)** was prepared from 318 mg (0.5 mmol) of **6c** by Method *A* to give 256 mg (81%) of **8c**. Treatment of 318 mg (0.5 mmol) of **6c** by Method *B* gave 214 mg (68%) of **8c**. $^1$H NMR ($CDCl_3$) δ : 8.60 (1H, br. s, NH), 8.54 (1H, d, H6, $J_{6,5}$=7.0 Hz), 7.93-7.55 (6H, m, arom. and H5), 5.87 (1H, d, H1', $J_{1',2'}$=1.5 Hz), 4.88 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.48 (1H,

d, Hb, $OCH_2N$), 4.36 (1H, dd, H2', $J_{2',3'}$=4.0 Hz), 4.32 (1H, m, H4'), 4.15 (1H, dd, H5'a, $J_{H5'a,H5'b}$=11.9 Hz, $J_{4',5'a}$=0.9 Hz, $J_{4',5'b}$=1.5 Hz), 4.13 (1H, dd, H3', $J_{3',4'}$=7.6 Hz), 3.87 (1H, dd, H5'b), 0.99, 0.93 (2x9H, 2s, 2x*t*BuSi), 0.25, 0.19, 0.17, 0.14 (4x3H, 4s, 4xMeSi).

**5'-*O*-Acetyl-3'-*O*-azidomethyl-2'-*O*-*tert*-butyldimethylsilyluridine (8d)** was prepared from 323 mg (0.7 mmol) of **6d** by Method *A* to give 302 mg (95%) of **8d**. $^1$H NMR ($CDCl_3$) δ : 8.38 (1H, br. s, NH), 7.59 (1H, d, H6, $J_{6,5}$=8.2 Hz), 5.74 (1H, d, H5), 4.91 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.53 (1H, d, Hb, $OCH_2N$), 3.99 (1H, dd, H3', $J_{3',2'}$ and $J_{3',4'}$=6.4 and 4.6 Hz), 4.44-4.36 (3H, m, H4', H5'a, H5'b), 2.14 (3H, s, $CH_3CO$), 0.91 (9H, s, *t*BuSi), 0.14, 0.11 (2x3H, 2s, 2xMeSi).

**5'-*O*-Acetyl-3'-*O*-azidomethyl-2'-*O*-*tert*-butyldimethylsil-5-chlorouridine (8e)** was prepared from 231 mg (0.5 mmol) of **6d** by Method *A* and recrystallized from methanol to give 194 mg (79%) of **8e**, m.p. 96-97°C dec. $^1$H NMR ($CDCl_3$) δ : 7.98 (1H, s, H6), 4.88 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.8 Hz), 4.52 (1H, d, Hb, $OCH_2N$), 5.70 (1H, d, H1', $J_{1',2'}$=1.5 Hz), 4.32 (1H, dd, H2', $J_{2',3'}$=4.1 Hz), 3.98 (1H, dd, H3', $J_{3',4'}$=7.4 Hz), 4.44 (1H, m, H4'), 4.50 (1H, dd, H5'a, $J_{H5'a,H5'b}$=12.0 Hz, $J_{4',5'a}$=$J_{4',5'b}$=2.0 Hz), 4.42 (1H, dd, H5'b), 2.22 (3H, s, $CH_3CO$), 0.92 (9H, s, *t*BuSi), 0.17, 0.12 (2x3H, 2s, 2xMeSi).



**Desilylation of azidomethyl derivatives of ribonucleosides 3a-d and 8a-e.** TBAF•$3H_2O$ as 1 M solution in THF (1.1 eq for each silyl or 2.2 eq for siloxadiyl protecting group) was added to 1 mmol nucleoside solution in THF (3 ml) and the mixture was stirred for 1 h at room temperature. The solvent was evaporated at a reduced pressure. The residue was purified by chromatography on a silica gel column with methanol-chloroform (5:95→10:90, v/v) and the product was then recrystallized (Method *C*). If crystallization was impossible, the residue after desilylation was dissolved in water-methanol (proportions depend on solubility of the compound, up to pure methanol). This solution was applied to a column of Dowex 50W ($NH_4^+$ form). Elution was performed with water-methanol (up to pure methanol). The eluate was concentrated *in vacuo* and the residue was purified by chromatography on a column of silica gel to give the product (Method *D*). The compounds obtained are listed below.

**2'-*O*-Azidomethyl-$N^6$-benzoyladenosine (4a)** was obtained from 310 mg (0.464 mmol) of **3a** by Method *D* to give 152 mg (77%) of **4a**. $^1$H NMR (DMSO-$d_6$) δ : 11.18

(1H, br. s, NH), 8.78 (1H, s, H8), 8.76 (1H, s, H2), 8.10-7.50 (5H, m, arom.), 6.26 (1H, d, H1', $J_{1',2}$=5.5 Hz), 5.53 (1H, d, 3'-OH, $J$=5.0 Hz), 5.20 (1H, t, 5'-OH, $J$=5.5 Hz), 4.98 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=9.2 Hz), 4.88 (1H, pt, H2', $J_{2',3'}$=5.5 Hz), 4.76 (1H, d, Hb, $OCH_2N$), 4.43 (1H, m, H3'), 4.06 (1H, m, H4'), 3.75 (1H, m, H5'a, $J_{H5'a,H5'b}$=12.0 Hz), 3.63 (1H, m, H5'b).

**2'-*O*-Azidomethyl-$N^2$-isobutirylguanosine (4b)** was prepared from 490 mg (0.75 mmol) of **3b** by Method *C* to give 251 mg (82%) of **4b**, m.p. 158-159°C dec (methanol-water). $^1$H NMR (DMSO-$d_6$) δ : 12.10 (1H, s, NH), 11.65 (1H, s, NH), 8.30 (1H, s, H8), 6.00 (1H, d, H1', $J_{1',2}$=6.9 Hz), 5.45 (1H, d, 3'-OH, $J$=4.6 Hz), 5.13 (1H, t, 5'-OH, $J$=5.3 Hz), 4.93 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.7 Hz), 4.72 (1H, d, Hb, $OCH_2N$), 4.64 (1H, dd, H2', $J_{2',3'}$=4.6 Hz), 4.33 (1H, m, H3'), 3.99 (1H, m, H4'), 3.65 (1H, m, H5'a, $J_{H5'a,H5'b}$=11.9 Hz), 3.58 (1H, m, H5'b), 2.70 (1H, sep., $C\underline{H}(CH_3)_2$, $J$=5.2 Hz), 1.11 (6H, d, $CH(C\underline{H}_3)_2$).

**2'-*O*-Azidomethyl-$N^4$-benzoylcytidine (4c)** was prepared from 323 mg (0.5 mmol) of **3c** by Method *C* to give 169 mg (84%) of **4c**, m.p. 114-116°C dec (methanol). $^1$H NMR (DMSO-$d_6$) δ : 11.25 (1H, s, NH), 8.55 (1H, d, H6, $J_{6,5}$=6.9 Hz), 8.10-7.50 (5H, m, arom.), 7.38 (1H, d, H5), 5.36 (1H, d, 3'-OH, $J$=5.9 Hz), 5.27 (1H, t, 5'-OH, $J$=4.8 Hz), 5.04 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.7 Hz), 4.96 (1H, d, Hb, $OCH_2N$), 5.91 (1H, d, H1', $J_{1',2}$=2.3 Hz), 4.19 (1H, pt, H2', $J_{2',3'}$=5.0 Hz), 4.15 (1H, m, H3'), 3.97 (1H, m, H4'), 3.82 (1H, m, H5'a, $J_{H5'a,H5'b}$=12.3 Hz), 3.66 (1H, m, H5'b).

**2'-*O*-Azidomethyluridine (4d)** was prepared from 200 mg (0.33 mmol) of **3d** by Method *D* to give 84 mg (85%) of **4d**. UV $\lambda_{max}$, nm: 261 (ε 9700) (pH1); 261 (ε 9800) (pH7); 261 (ε 6800) (pH 13). MALDI-MS : *m/z* 300.1 ($[M+H]^+$), 322.2 ($[M+Na]^+$). $^1$H NMR (DMSO-$d_6$) δ : 11.36 (1H, s, NH), 7.95 (1H, d, H6, $J_{6,5}$=8.2 Hz), 5.93 (1H, d, H1', $J_{1',2}$=5.0 Hz), 5.69 (1H, d, H5), 5.37 (1H, d, 3'-OH, $J$=5.5 Hz), 5.19 (1H, t, 5'-OH, $J$=5.0 Hz), 4.99 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.7 Hz), 4.71 (1H, d, Hb, $OCH_2N$), 4.22 (1H, pt, H2', $J_{2',3'}$=5.0 Hz), 4.16 (1H, m, H3'), 3.91 (1H, m, H4'), 3.71-3.55 (2H, m, H5'a,b).

**3'-*O*-Azidomethyl-$N^6$-benzoyladenosine (9a)** was prepared from 327 mg (0.5 mmol) of **8a** by Method *C* to give 200 mg (94%) of **9a**, m.p. 178-178.5°C dec (methanol). $^1$H NMR (DMSO-$d_6$) δ : 11.19 (1H, s, NH), 8.78 (1H, s, H8), 8.74 (1H, s, H2), 8.10-7.50 (5H, m, arom.), 6.07 (1H, d, H1', $J_{1',2'}$=6.2 Hz), 5.88 (1H, d, 2'-OH, $J$=5.8 Hz), 5.29 (1H, t, 5'-OH, $J$=5.6 Hz), 5.04 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.90 (1H, m, H2'), 4.87 (1H, d,

Hb, $OCH_2N$), 4.34 (1H, dd, H3', $J_{3',2'}$=4.8 Hz, $J_{3',4'}$=3.4 Hz), 4.15 (1H, m, H4'), 3.74 (1H, m, H5'a), 3.64 (1H, m, H5'b).

**3'-*O*-Azidomethyl-$N^2$-benzoylguanosine (9b)** was prepared from 210 mg (0.313 mmol) of **8b** by Method *C* 117 mg (84%) of **9b**, m.p. 165-166°C dec (methanol-water). $^1$H NMR (DMSO-$d_6$) δ : 12.36 (1H, br. s, NH), 11.92 (1H, br. s, NH), 8.30 (1H, s, H8), 8.08-7.53 (5H, m, arom.), 5.90 (1H, d, H1', $J_{1',2'}$=6.7 Hz), 5.77 (1H, d, 2'-OH, *J*=5.8 Hz), 5.19 (1H, br. s, 5'-OH), 5.02 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.85 (1H, d, Hb, $OCH_2N$), 4.70 (1H, m, H2'), 4.26 (1H, dd, H3', $J_{3',2'}$=4.6 Hz, $J_{3',4'}$=2.7 Hz), 4.06 (1H, m, H4'), 3.66 (1H, m, H5'a), 3.58 (1H, m, H5'b).

**3'-*O*-Azidomethyl-$N^4$-benzoylcytidine (9c)** was prepared from 300 mg (0.476 mmol) of **9c** by Method *C* to give 150 mg (78%) of **9c**, m.p. 149-150°C (dec) (methanol). $^1$H NMR (DMSO-$d_6$) δ : 11.24 (1H,br. s, NH), 8.48 (1H, d, H6, $J_{6,5}$=7.3 Hz), 8.4-7.5 (5H, m, arom.), 7.35 (1H, d, H5), 5.83 (1H, d, H1', $J_{1',2'}$=3.7 Hz), 5.73 (1H, d, 2'-OH, *J*=5.5 Hz), 5.30 (1H, t, 5'-OH, *J*=5.0 Hz), 4.93 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.76 (1H, d, Hb, $OCH_2N$), 4.28 (1H, m, H2'), 4.12 (1H, dd, H3', $J_{3',2'}$=4.6 Hz, $J_{3',4'}$=6.0 Hz), 4.09 (1H, m, H4'), 3.77 (1H, m, H5'a), 3.61 (1H, m, H5'b).

**5'-*O*-Acetyl-3'-*O*-azidomethyluridine (9d)** was prepared from 215 mg (0.472 mmol) of **6d** by Method *D* to give 150 mg (93%) of **8d**. $^1$H NMR ($CDCl_3$) δ : 8.73 (1H, br. s, NH), 7.45 (1H, d, H6, $J_{6,5}$=8.2 Hz), 5.74 (1H, d, H5), 4.89 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=9.0 Hz), 4.81 (1H, d, Hb, $OCH_2N$), 5.73 (1H, d, H1', $J_{1',2'}$=1.2 Hz), 4.40-4.35 (4H, m, H2', H4', H5'a,b), 4.21 (1H, pt, H3' *J*=4.4 Hz), 3.40 (1H, br. s, 2'-OH), 2.13 (3H, s, $CH_3CO$).

**3'-*O*-Azidomethyluridine (11d)** was obtained from 182 mg (0.44 mmol) of **10d** by Method *C* to give 107 mg (81%) of **11d**. UV $\lambda_{max}$ , nm: 262 (ε 10100) (pH1); 261 (ε 10100) (pH7); 262 (ε 7300) (pH 13). MALDI-MS : *m/z* 299.2 ($[M]^+$). $^1$H NMR (DMSO-$d_6$) δ : 11.34 (1H, br. s, NH), 7.86 (1H, d, H6, $J_{6,5}$=8.2 Hz), 5.78 (1H, d, H1', $J_{1',2'}$=6.1 Hz), 5.66 (1H, d, H5), 5.64 (1H, d, 2'-OH, *J*=5.8 Hz), 5.21 (1H, t, 5'-OH, *J*=5.2 Hz), 4.97 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.77 (1H, d, Hb, $OCH_2N$), 4.23 (1H, m, H2'), 4.10 (1H, dd, H3', $J_{3',2'}$=4.9 Hz, $J_{3',4'}$=3.7 Hz), 3.99 (1H, m, H4'), 3.64 (1H, ddd, H5'a, $J_{H5'a,H5'b}$=11.9 Hz, $J_{4',5'a}$= $J_{4',5'b}$=3.4 Hz), 3.57 (1H, ddd, H5'b).

**3'-*O*-Azidomethyl-5-chlorouridine (11e)** was prepared from 150 mg (0.335 mmol) of **10d** by Method *C* to give 74 mg (94%) of **5a**. M.p. 143-144°C dec (THF). UV

$\lambda_{max}$ , nm: 276 (ε 10600) (pH1); 276 (ε 10300) (pH7); 275 (ε 7600) (pH 13). Anal. calc. for $C_{10}H_{12}N_5O_6Clx0.8THF$: C, 40.51; H, 4.70; N 17.89; Cl, 9.06. Found: C, 40.31; H, 4.75; N, 17.87; Cl, 8.88. $^1$H NMR (DMSO-$d_6$) δ : 11.88 (1H, br.s, NH), 8.38 (1H, s, H6), 5.75 (1H, d, H1', $J_{1',2}$=4.9 Hz), 5.70 (1H, d, 2'-OH, $J$=5.8 Hz), 5.42 (1H, t, 5'-OH, $J$= 4.7), 4.97 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.78 (1H, d, Hb, $OCH_2N$), 4.28 (1H, m, H2'), 4.10 (1H, pt, H3', $J$=4.9 Hz), 4.04 (1H, m, H4'), 3.74 (1H, m, H5'a), 3.63 (4.2H, m, H5'b, THF), 1.79 (3.2H, m, THF).

**Removal of acyl protecting group**. Nucleosides **4a-c**, **8d**, **8e**, **9a-c** were dissolved in 5 ml of half-saturated methanolic ammonia. After 24 h (for **4b** and **9b** – 72 h) the mixture was evaporated and the product was purified by crystallization (Method *E*) or by chromatography on a column with silica gel (Method *F*), if crystallization was impossible. The compounds obtained are listed below. The yields and the melting points of deblocked compounds are listed in tables 1 and 2.



**2'-*O*-Azidomethyladenosine (5a)** was obtained from 140 mg (0.33 mmol) of **4a** by Method *E* to give 100 mg (94%) of **5a**. M.p. 116-117°C dec (methanol-chloroform 1:99). UV $\lambda_{max}$, nm: 257.2 (ε 14300) (pH1); 259.4 (ε 14400) (pH7); 259.6 (ε 14800) (pH 13). MALDI-MS : *m/z* 323.2 ([*M*+H]$^+$), 345.1 ([*M*+Na]$^+$). $^1$H NMR (DMSO-$d_6$) δ : 8.40 (1H, s, H8), 8.16 (1H, s, H2), 7.35 (2H, br. s, $NH_2$), 6.09 (1H, d, H1', $J_{1',2}$=6.4 Hz), 5.45 (2H, m, 5'-OH, 3'-OH), 4.93 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.69 (1H, d, Hb, $OCH_2N$), 4.82 (1H, pt, H2', $J_{2',3}$=5.1 Hz), 4.38 (1H, m, H3'), 4.03 (1H, m, H4'), 3.70 (1H, m, H5'a), 3.58 (1H, m, H5'b).

**2'-*O*-Azidomethylguanosine (5b)** was prepared from 97 mg (0.237 mmol) of **4b** by Method *E* to give 67 mg (84%) of **5b**. M.p. > 200°C dec (methanol). UV $\lambda_{max}$ , nm: 257 (ε 12300) (pH1); 253 (ε 13200) (pH7); 265 (ε 11300) (pH 13). MALDI-MS : *m/z* 339.0 ([*M*+H]$^+$), 365.0 ([*M*+Na]$^+$). $^1$H NMR (DMSO-$d_6$) δ : 10.60 (1H, br. s, NH), 7.95 (1H, s, H8), 6.45 (2H, br. s, $NH_2$), 5.40 5.89 (1H, d, H1', $J_{1',2}$=6.4 Hz), 4.92 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.72 (1H, d, Hb, $OCH_2N$), 4.59 (1H, pt, H2', $J_{2',3}$=5.0 Hz), 4.29 (1H, m, H3'), 3.95 (1H, m, H4'), 3.64 (1H, m, H5'a), 3.55 (1H, m, H5'b).

**2'-*O*-Azidomethylcytidine (5c)** was obtained from 150 mg (0.373 mmol) of **4c** by Method *E*. to give 93 mg (84%) of **5c**. M.p. 117-118°C dec (methanol-chloroform 1:9). UV $\lambda_{max}$ , nm: 279 (ε 13100) (pH1); 271 (ε 8500) (pH7); 271 (ε 8800) (pH 13).

MALDI-MS : *m/z* 299.0 ([*M*+H]$^+$). $^1$H NMR (DMSO-$d_6$) δ : 7.92 (1H, d, H6, $J_{6,5}$=7.3Hz), 7.17 (2H, two s, $NH_2$), 5.86 (1H, d, H1', $J_{1',2'}$=3.1 Hz), 5.47 (1H, d, H5), 5.27 (1H, d, 3'-OH, *J*=5.8 Hz), 5.13 (1H, t, 5'-OH, *J*=5.0 Hz), 4.97 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.6 Hz), 4.86 (1H, d, Hb, $OCH_2N$), 4.14-4.06 (2H, m, H2', H3'), 3.87 (1H, m, H4'), 3.8-3.6 (2H, m, H5'a,b).

**3'-*O*-Azidomethyl-2'-*O*-*tert*-butyldimethylsilyluridine (10d)** was prepared from 260 mg (0.57 mmol) of **8d** by Method *E* to give 197 mg (83%) of **10d**. $^1$H NMR ($CDCl_3$) δ : 7.57 (1H, d, H6, $J_{6,5}$=8.2 Hz), 5.74 (1H, d, H5), 5.53 (1H, d, H1', $J_{1',2'}$=5.8 Hz), 4.98 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.59 (1H, d, Hb, $OCH_2N$), 4.67 (1H, pt, H2', $J_{2',3'}$=4.6 Hz), 4.18 (1H, dd, H3', $J_{3',4'}$=3.7 Hz), 4.26 (1H, m, H4'), 3.99 (1H, ddd, H5'a, $J_{H5'a,H5'b}$=12.5 Hz, $J_{4',5'a}$= $J_{4',5'b}$=2.1 Hz), 3.80 (1H, ddd, H5'b), 2.81 (1H, dd, J $J_{5'-OH,5'a}$=3.0 Hz, $J_{5'-OH,5'b}$=7.3 Hz), 0.89 (9H, s, *t*BuSi), 0.09, 0.05 (2x3H, 2s, 2xMeSi).

**3'-*O*-Azidomethyl-2'-*O*-*tert*-butyldimethylsil-5-chlorouridine (10e)** was obtained from 200 mg (0.408 mmol) of **8e** by Method *F* to give 161 mg (88%) of **10e**. $^1$H NMR ($CDCl_3$) δ : 8.15 (1H, br. s, NH), 8.12 (1H, s, H6), 5.66 (1H, d, H1', $J_{1',2'}$=4.1 Hz), 4.97 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.8 Hz), 4.58 (1H, d, Hb, $OCH_2N$), 4.51 (1H, pt, H2', $J_{2',3'}$=4.6 Hz), 4.30 (1H, m, H4'), 4.20 (1H, pt, H3', $J_{3',4'}$=4.7 Hz), 4.09 (1H, m, H5'a), 3.88 (1H, m, H5'b), 2.40 (1H, br. s, 5'-OH), 0.91 (9H, s, *t*BuSi), 0.11, 0.10 (2x3H, 2s, 2xMeSi).

**3'-*O*-Azidomethyladenosine (11a)** was prepared from 160 mg (0.375 mmol) of **9a** by Method *E* to give 108 mg (89%) of **11a**. M.p. 173-173.5°C dec (methanol). UV $\lambda_{max}$, nm: 257 (ε 14500) (pH1); 259 (ε 14900) (pH7); 260 (ε 15000) (pH 13). MALDI-MS : *m/z* 323.2 ([*M*+H]$^+$), 345.1 ([*M*+Na]$^+$).$^1$H NMR (DMSO-$d_6$) δ : 8.37 (1H, s, H8), 8.16 (1H, s, H2), 7.36 (2H, s, $NH_2$), 5.90 (1H, d, H1', $J_{1',2'}$=6.4 Hz), 5.76 (1H, d, 2'-OH, *J*=6.4 Hz), 5.57 (1H, dd, 5'-OH, *J*=4.3, 7.0 Hz), 5.03 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.86 (1H, d, Hb, $OCH_2N$), 4.84 (1H, m, H2'), 4.29 (1H, dd, H3', $J_{3',2'}$=4.9 Hz, $J_{3',4'}$=2.7 Hz), 4.13 (1H, m, H4'), 3.71 (1H, m, H5'a), 3.61 (1H, m, H5'b).

**3'-*O*-Azidomethylguanosine (11b)**. There was dissolved 105 mg (0.237 mmol) of **9a** in 5 ml of half-saturated methanolic ammonia. The mixture was evaporated 72 h later, the residue was washed with chloroform (2x5 ml) and the product was purified by crystallization from methanol-water to give 69 mg (86%) of **11b**. M.p. 198-200°C dec. UV $\lambda_{max}$, nm: 257 (ε 11800) (pH1); 252 (ε 13400) (pH7); 265 (ε 11000) (pH 13).

MALDI-MS : *m/z* 338.4 ([*M*]$^+$), 361.2 ([*M*+Na]$^+$). $^1$H NMR (DMSO-$d_6$) δ : 10.6 (1H, br. s, NH), 7.93 (1H, s, H8), 6.46 (2H, br. s, $NH_2$), 5.70 (1H, d, H1', $J_{1',2'}$=6.7 Hz), 5.68 (1H, d, 2'-OH, *J*=6.1 Hz), 5.15 (1H, t, 5'-OH, *J*=5.5 Hz), 5.00 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.82 (1H, d, Hb, $OCH_2N$), 4.61 (1H, m, H2'), 4.21 (1H, dd, H3', $J_{3',2'}$=4.9 Hz, $J_{3',4'}$=3.1 Hz), 4.01 (1H, m, H4'), 3.62 (1H, m, H5'a), 3.55 (1H, m, H5'b).

**3'-*O*-Azidomethylcytidine (11c)** was prepared from 90 mg (0.244 mmol) of **9c** by Method *F* to give 63 mg (87%) of **11c**. UV $\lambda_{max}$, nm: 279 (ε 13100) (pH1); 270 (ε 9000) (pH7); 271 (ε 9000) (pH 13). MALDI-MS : *m/z* 299.1 ([*M*+H]$^+$).$^1$H NMR (DMSO-$d_6$) δ : 7.80 (1H, d, H6, $J_{6,5}$=7.3 Hz), 7.17 (2H, two s, $NH_2$), 5.77 (1H, d, H1', $J_{1',2'}$=5.2 Hz), 5.71 ( 1H, d, H5), 5.52 (1H, d, 2'-OH, *J*=6.1 Hz), 5.14 (1H, t, 5'-OH, *J*=5.2 Hz), 4.94 (1H, d, Ha, $OCH_2N$, $J_{a,b}$=8.9 Hz), 4.74 (1H, d, Hb, $OCH_2N$), 4.16 (1H, m, H2'), 4.05 (1H, pt, H3', $J_{3',2'}$= $J_{3',4'}$=4.9 Hz), 3.95 (1H, m, H4'), 3.65 (1H, ddd, H5'a, $J_{H5'a,H5'b}$=12.2 Hz, $J_{4',5'a}$= $J_{4',5'b}$=3.4 Hz), 3.55 (1H, ddd, H5'b).



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