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SYNTHESIS OF [3′(O)→5′(C)]-OXYACETAMIDO LINKED NUCLEOSIDES

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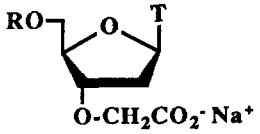
Summary : A convenient procedure has been developed for the preparation of non-ionic, achiral [3′(O)→5′(C)]-oxyacetamido analogues using the 4-methoxytrityl (MMTr) group for the protection of exocyclic amino function of 2′-deoxyadenosine, 2′-deoxycytidine and 2′-deoxyguanosine, and the 5′-azido group has been used as the masked 5′-amino function. The 5′-azido function could be reduced quantitatively without affecting the [3′(O)→5′(C)]-oxyacetamido function. The MMTr group was found to be stable during the formation of the [3′(O)→5′(C)]-oxyacetamido linkage [§]. The MMTr group could be easily removed from the hetero dimeric and trimeric nucleosides **15a, 19a and 19b** *by warming in 80% aqueous acetic acid for 5 min at 100 °C without any depurination. These have been exemplified through the preparation of 5′-d(H_2N-T§T-OH)-3′* **14,** *5′-d(H_2N-T§A-OH)-3′* **18,** *5′-d(H_2N-C§T§A-OH)-3′* **22a,** *5′-d(H_2N-G§T§A-OH)-3′* **22b.** *Detailed spectroscopic data have been used to corroborate their structures.*

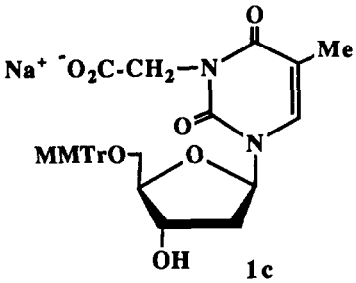
Recently there has been a growing interest in the synthesis of oligodeoxynucleotides with modified internucleotide linkages[1]. These analogues of oligo-DNA are expected to act as "antisense" repressors of the transcriptional and translational level of gene expression[2] and as models for the study of nucleic acid structure and function. Some of them have also shown antiviral activity *in vitro*[3]. On the other hand, oligonucleotide analogues in which the carbohydrate, purine and pyrimidine moieties are the same as those of natural polynucleotides but the internucleotide phosphate linkage has been replaced with flexible aliphatic, non-ionic, achiral spacers (7.1 Å)[9] as those of natural polynucleotides have received a poor attention, despite the reports that some of them actually show the desired hypochromicity comparable to the natural oligo-DNA and bind to the complementary DNA sequence by Watson-Crick base pairing[6,7].

Some of the DNA analogues reported in the second category todate contain carboxymethyl[5], carbamate[6], acrylamide[7], carbonate[4] and silyl[8] groups as internucleoside linkages. While carbonate, carbamate, and silyl internucleoside linkages are shorter than those required for nucleobases to form Watson-Crick base pairing, the acetate ester and oxyacetamido linkages however fulfil this criteria. DNA analogues containing acetate ester linkages, however, suffer from their instability and poor solubility under physiciological condition. We therefore decided to develop routes to the synthesis of DNA analogues containing all four naturally-occurring nucleobases with [3′(O)→5′(C)]-oxyacetamide linkage since they are expected to be more stable to alkaline hydrolysis than the oligonucleosides with acetate ester linkages[5].

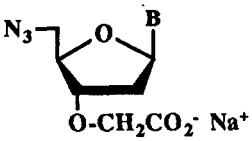
First synthesis of [3′(O)→5′(C)]-oxyacetamido-linked dimer of thymidine was reported in 1974 by Jones and coworkers[9] in 40 % yield in two steps by the condensation of the pyridinium salt of 3′-O-carboxymethyl-5′-O-triphenylmethyl thymidine **1a** with 5′-amino-5′-deoxythymidine **9** followed by



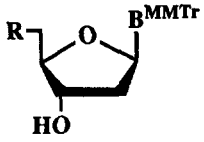
1a : R = Tr
1b : R = MMTr



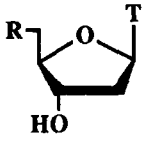
1c



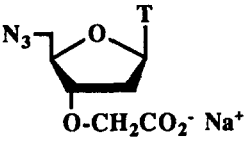
6a : B = C^{MMTr}
6b : B = G^{MMTr}
6c : B = C
6d : B = G



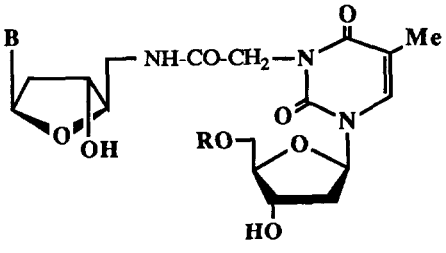
2a : B = A; R = OH
2b : B = C; R = OH
2c : B = G; R = OH
3a : B = A; R = OTs
3b : B = C; R = OTs
3c : B = G; R = OTs
4a : B = A; R = N_3
4b : B = C; R = N_3
4c : B = G; R = N_3
5a : B = A; R = NH_2
5b : B = C; R = NH_2
5c : B = G; R = NH_2



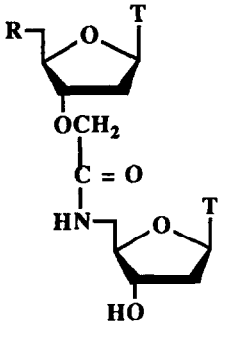
7 : R = OTs
8 : R = N_3
9 : R = NH_2



10



11a : B = T; R = MMTr
11b : B = A^{MMTr}; R = MMTr
11c : B = C^{MMTr}; R = MMTr
12a : B = T; R = H
12b : B = A; R = H
12c : B = C; R = H



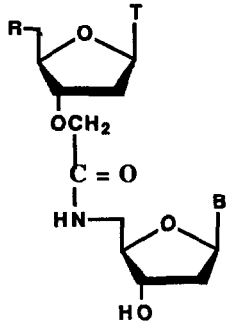
13 : R = N_3
14 : R = NH_2

detritylation. 3′-O-carboxymethyl-5′-O-triphenylmethyl thymidine **1a** was prepared[9] in DMSO solution by the reaction of $ClCH_2CO_2^-$ Na^+ with 5′-O-triphenylmethyl thymidine in presence of NaH at ~20 °C. Our attempts to prepare 3′-O-carboxymethyl-5′-O-[4-monomethoxytriphenylmethyl]thymidine **1b** by an identical procedure[9] gave exclusively an N^3-carboxymethylated product **1c**. 5′-azido-5′-deoxythymidine **8** however under a similar condition (experimental) gave 3′-O-carboxymethyl derivative **10**. UV spectroscopic data failed to distinguish between N^3-carboxymethylated thymidine **1c** (λ_{max} 268 nm) and 3′-O-carboxymethylated product **10** (λ_{max} 266 nm) unambiguously. ^{1}H-NMR showed that the resonance for $CH_2CO_2^-$ in **1c** and **10** absorbed at δ4.32 and 3.91, respectively. ^{13}C-NMR however clearly showed (Table 1) that the C-3′ in 3′-O-carboxymethyl derivative **10** went downfield by ~8 ppm relative to the parent compound **8**. This was not the case for **1c** relative to 5′-O-[4-monomethoxytriphenylmethyl]thymidine, both of them gave ^{13}C absorptions at ~72 ppm. Similarly, a comparison of δ^{13}C for $-CH_2CO_2^-$ showed that it absorbed at 45.2 and 69.7 ppm in **1c** and **10**, respectively, showing unambiguously the presence of the $-N^3-CH_2CO_2^-$ in the former and the 3′-O-$CH_2CO_2^-$ group in the latter (Table 1). The foregoing observations clearly established that the ^{1}H-NMR data alone should be treated with caution, whereas ^{13}C-NMR data are more conclusive regarding the unambiguous distinction between $-N^3-CH_2CO_2^-$ *versus* 3′-O-$CH_2CO_2^-$ substituted products. It is also clear from the above discussion that it is the 5′-substituent (5′-O-MMTr *versus* 5′-azido) which seems to determine the nature of reaction product formed [$N^3-CH_2CO_2^-$ *versus* 3′-O-$CH_2CO_2^-$] in the carboxymethylation reaction.

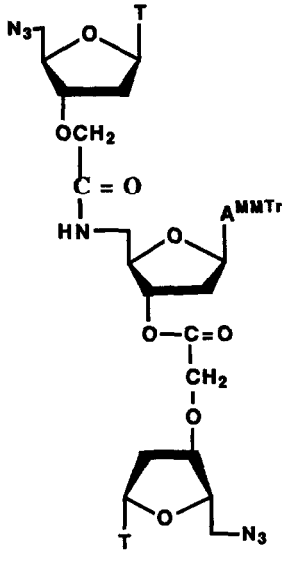
In view of the above results, we decided to emply the 5′-azido group as the masked 5′-NH_2 function for the synthesis of the DNA analogues with [3′(O)→5′(C)]-5′-deoxy oxyacetamido linkages *(vide infra)*. The synthesis of the DNA analogues with [3′(O)→5′(C)]-5′-deoxy oxyacetamido linkages also requires appropriate non-base sensitive exocyclic protecting groups, which should be intact during the formation of the ether and amide bonds, and can be removed conveniently without any depurination at the end of the synthesis. The MMTr group for exocyclic amino protection of guanosine was first introduced by Hata and coworkers[10]. Similarly, the exocyclic amino function of adenosine was protected with the MMTr[11] or DMTr[12] group. We have also used the acid sensitive MMTr group in this work as the exocyclic amino protecting group for 2′-deoxycytidine, 2′-deoxyadenosine and 2′-deoxyguanosine. The MMTr group can be removed either with $ZnBr_2$ in dry nitromethane or by warming with 80 % aqueous acetic acid at 100 °C for 5 min without causing any depurination of nucleosides. We have prepared the MMTr protected nucleosides **2a-c** in 83, 86 and 78 % yield, respectively, by employing the transition-protection methodology using trimethylsilyl chloride devised by Jones and coworkers[13]. Subsequently, the 5′-azido nucleosides **4a-c**, and **8** were prepared by treating the 5′-O-tosylated products **3a-c** or **7** with NaN_3 (2.4 equiv) and LiCl (2.4 equiv) in DMF or DMSO at 70 - 100 °C for 2 h in ~90 % yield. These 5′-azido-2′,5′-dideoxynucleosides can be formally considered as protected 5′-amino-5′-deoxynucleosides since the 5′-azido functions in monomeric nucleosides **4a-c**, **8**, in dimeric [3′(O)→5′(C)]-5′-deoxy oxyacetamido nucleosides **13** [**9** + **10** → **13**], **15a** [**5a** + **10** → **15a**], and **16** [**15a** → **16**], and in trimeric [3′(O)→5′(C)]-5′-deoxy nucleosides **19a** [**6a** + **17** → **19a**], **19b** [**6b** + **17** → **19b**], **20a** [**19a** → **20a**], and **20b** [**19b** → **20b**] could be specifically reduced using a slightly modified condition of Staudinger and coworkers[14] to give the corresponding 5′-amino-5′-deoxy monomers **5a-c** and **9**, dimers **14** and **17**, and trimers **21**, **22a** and

22b, respectively, in good yields [Ph_3P (1.1 equiv.) to the solution of 5′-azidonucleosides at ~0 °C, then stirring overnight at ~20 °C followed by methanolic ammonia treatment for one day (experimental)].

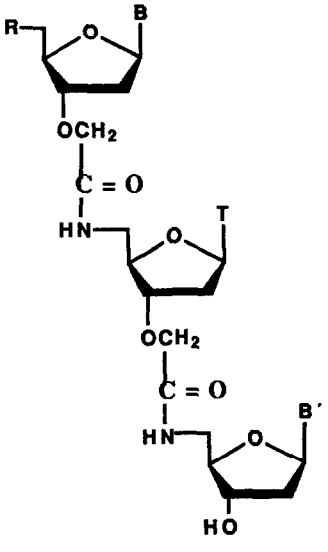
The carboxymethylation of the 3′-hydroxyl function of the 5′-azido-5′-deoxynucleosides **4b-c**, and **8** have been made by a slight modification of Jones and coworkers′ procedure[9] in order to avoid the formation of bis-carboxymethylated nucleosides. This modified procedure involves chilling of the DMSO solution of 5′-azido-5′-deoxynucleosides **4b-c** and **8**, followed by the addition of NaH, and $ClCH_2COO^-Na^+$ at ~20 °C for 1-3 days. This gave only 3′-O-monocarboxymethylated products **6a-b** and **10** in over 85 % yield in average.



15a : B = A^{MMTr}; R = N_3
16 : B = A; R = N_3
17 : B = A^{MMTr}; R = NH_2
18 : B = A; R = NH_2



15b



19a : B = C^{MMTr}; B′ = A^{MMTr}; R = N_3
19b : B = G^{MMTr}; B′ = A^{MMTr}; R = N_3
21 : B = G^{MMTr}; B′ = A^{MMTr}; R = NH_2
20a : B = C; B′ = A; R = N_3
20b : B = G; B′ = A; R = N_3
22a : B = C; B′ = A; R = NH_2
22b : B = G; B′ = A; R = NH_2

Several different condensation methods have been attempted for preparation of di- and tri-nucleosides. The simplest condensation method using 4Å molecular sieves[15] at 140 °C did not work in our hands, only depurinated product could be isolated. The DCC condensation method[9] was found to be slow (1-3 days) and gave only ~50 % isolated yield of the product. More active condensing agent such as the mixture of 1-mesitylenesulfonyl chloride and 1-methylimidazole[16] in pyridine gave relatively more undesired side product such as **15b** [**5a** + **10** → **15a** + **15b** (2 : 3 ratio)]. The use of pyridinium salt of **10** in the condensation reaction with **5a** gave the trimeric-ester **15b** as the most predominant product. König's peptide condensation method[17] using DCC, 1-hydroxybenzotriazole and N-ethylmorpholine in dry DMF was found to provide an optimum condition giving the dimers **13** and **15a**, and the trimers **19a** and **19b** in 50 - 70% yields.
Deprotection of 5'-azido-5'-deoxy-3'-oxyacetamido-[3'(O)→5'(C)] linked dimer **13** was simply carried out by reduction using the Ph_3P procedure (experimental) to give fully deprotected **14** in 85 % yield. Dimer **15a** was deprotected by (i) detritylation with $ZnBr_2$ (68%), (ii) reduction, followed by an extraction between an aqueous and lipophilic phase (experimental) to give **18** (83 %). Alternatively, **15a** was deprotected in the following manner: (i) reduction to **17** (80%), and then (ii) detritylation with 80% aqueous acetic acid at 100 °C followed by a work up (experimental) gave pure **18** (86%). Trimers **19a**, and **19b** were deprotected first by reduction, followed by purification by column chromatography, and detritylation with 80% aqueous acetic acid at 100 °C, and then a simple work up (experimental) gave pure products **22a** (95%) and **22b** (92%), respectively. Alternatively, trimers **19a** and **19b** were deprotected first by detritylation with 80% aqueous acetic acid at 100 °C, followed by reduction gave, upon work up (experimental), products **22a** and **22b**. The dimers **13**, **15a** , and **16** , and in trimers **19a** , **19b** , **20a** , and **20b** were stable in methanolic ammonia, aqueous ammonia, 0.3 M sodium hydroxide and 1M hydrochloric acid for 24 at room temperature.

Finally, N^3-carboxymethylated thymidine **1c** was also condensed with 5'-amino-5'-deoxythymidine **9**, 5'-amino-5'-deoxy-N^6-MMTr-adenosine **5a**, 5'-amino-5'-deoxy-N^4-MMTr-cytidine **5b**, under a standard condition (experimental) to give the [N^3(C)→5'(C)] linked dimers **11a-c**, respectively. The 5'-O-MMTr group from **11a-c**, was easily removed by the treatment of $ZnBr_2$ or by 80% aqueous acetic to give the deprotected [N^3(C)→5'(C)] linked dimers **12a-c** in high yield.

UV, ^{1}H-NMR, ^{13}C-NMR, IR and mass spectroscopic data finally corroborated the structures of **12a-c**, **14**, **18**, **22a**, and **22b** (experimental).

NMR spectroscopic characterization of intermediates and products

The resonances of the sugar protons were assigned by means of homonuclear decoupling experiments and also by performing 2D Double Quantum Filter COSY (2D DQF COSY). 2D NOE spectroscopy has provided the information about the spatial proximities between a base and its own sugar.

The lower field proton at C-5' was assigned as the H-5' proton and the higher field proton was assigned as the H-5'' proton in accordance to the suggestion of Remin and Shugar[18]. When δ(H2') was different from

δ(H2′), the discrimination between the H2′ and H2″ protons were made using the rules devised by Rinkel and Altona[19].

The presence of the [N^3(C) → 5′(C)] linkage in dimers **12a-c** and the [3′(O)→5′(C)]-oxyacetamido linkage in **13, 14, 16, 18, 20a, 20b, 22a,** and **22b** were shown both by ^{1}H and ^{13}C-NMR spectroscopy. The CH_2 protons absorb at ~4.4 ppm for N^3-derivatives **12a-c** and ~4.0 ppm for O-3′ derivatives. The carbonyl group absorbs at ~170 ppm for the dimers **12a-c** and at ~173 ppm for the 5′-azido and 5′-amino compounds. The N^3-CH_2 group absorb at ~44 ppm for the dimers **11a-c** and **12a-c** whereas 3′-O-CH_2- group in the 5′-azido and 5′-amino derivatives with [3′(O)→5′(C)] linkage absorb at ~69 ppm. The C-3′ carbons with 3′-O-$CH_2CO_2^-$ function (as in compounds **6c, 6d and 10**), or with 3′-O-CH_2CONH- group as in [3′(O)→5′(C)]-linked **13, 14, 17, 18, 20a, 20b, 22a,** and **22b** absorb at ~80 ppm.

The reduction of the 5′-azido to 5′-amino function in monomeric, dimeric and trimeric compounds were shown by the consecutive upfield shift of the neighbouring H-5′ and H-5″ protons, beside the disappearence of azido stretching vibration at ν_{max} ~2090 cm^{-1} in the IR spectra. For the compounds 5′-N_3T **8** and 5′-NH_2T **9**, the H-5′ and H-5″ protons experience an upfield shift of 0.7 and 0.6 ppm respectively upon reduction. For the dimers, 5′-N_3T§A **16** and 5′-NH_2T§A **18** [§ denotes 3′(O)→5′(C)]-oxyacetamido linkage] , the upfield shift of the H-5′ and H-5″ protons of the thymidine residue upon reduction is respectively of 0.26 and 0.31 ppm. In 5′-N_3T§T **13** and 5′-NH_2T§T **14**, the upfield shift H-5′ and H-5″ protons is of 0.51 and 0.55 ppm, respectively. Due to the overlap of the resonances of the H-5′, H-5″ protons of the constituent units of the trimers, the exact chemical shifts could not be determined, but the upfield shift induced by the reduction could be seen on the 2D ^{1}H-^{1}H COSY spectra.

A comparison of the $J_{4',5'}$ and $J_{4',5''}$ of the thymidine residue in dimers 5′-N_3T§A **16** ($J_{4',5'}$ = 3.9 Hz, $J_{4',5''}$ = 5.6 Hz) and 5′-NH_2T§A **18** ($J_{4',5'}$ = 3.9 Hz, $J_{4',5''}$ = 9.0 Hz) shows that the reduction of the 5′-azido function to the 5′-amino group leads to a large increase in the $J_{4',5''}$ coupling by 3-4 Hz. The $J_{4',5'}$ and $J_{4',5''}$ coupling in the 5′-azido derivatives are of the same order of magnitude as found for dimers with [N^3(C)→5′(C)] linkages **12a-c**. The difference of 0.5 Hz observed in the coupling constants are probably due to the difference in the electronegativity between an oxygen and nitrogen atom. The same tendency could be observed for 5′-N_3T **8** and 5′-NH_2T **9** and, 5′-N_3T§T **13** and 5′-NH_2T§T **14** (see experimental part). The conformational behavior around the C4′-C5′ bond is monitored by means of the $J_{4',5'}$ and $J_{4',5''}$ coupling[20]. The presence of an 5′-amino group influences the rotamer population around the C4′-C5′ bond in comparison with those of 5′-azido derivatives (Table 2). It is clear from the Table 2 that 5′-hydroxy in **12a-c** and 5′-azido terminal enforces the C4′-C5′ bond preferentially in γ^+ conformation (~50% γ^+) while the γ^t orientation is preferrred in the compounds with the 5′-amino function. The C-5′ chemical shifts in ^{13}C NMR spectroscopy have also been used, in addition to IR spectroscopy, in distinguishing between the presence of a 5′-azido and 5′-amino group: the δC-5′ absorbs at ~53 ppm in the 5′-azido derivatives, while it absorbs at ~43 ppm for the 5′-amino derivatives (Compare δC-5′ in **8** (53 ppm) and **9** (43.8 ppm); **13** (53.3 ppm) and **14** (43.4 ppm); **16** (53.2 ppm) and **18** (42.9 ppm); **20a** (53.3 ppm) and **22a** (42.9 ppm); **20b** (53.3 ppm) and **22b** (42.8 ppm).

Table 1 : *Comparison of some specific ^{13}C-NMR chemical shifts (ppm)+*

	δC-3' linked to 3'-O-CH_2CO	δC-3' linked to 3'-OH	δ-CH_2CO linked N3 or O-3'
5'-O-MMTr-T	-	72.2	
1c	-	71.3	45.2
8	-	72.0	
10	80.6	-	69.7
6c	80.8	-	69.6
6d	81.4	-	70.1
12a	-	71.6 & 72.1	44.9
12b	-	71.6 & 73.0	44.9
12c	-	71.6 & 72.6	44.9
13	81.9	72.7	69.4
14	82.1	72.7	69.4
16	81.7	72.7	69.3
18	81.8	72.7	69.4

+ see experimental section for complete spectroscopic data

Table 2 : *Estimation of the rotamer distribution across C4'-C5' [γ] # for different [3'(O)→5'(C)]-oxyacetamido linked nucleosides*

	γ+	γ-	γt
5'-N_3T (**8**)	48	11	41
5'-NH_2T (**9**)	18	22	60
5'-OH-T¤T (**12a**)	51	13	36
5'-OH-T¤A (**12b**)	50	11	39
5'-OH-T¤C (**12c**)	50	14	36
5'-N_3T§T (**13**)	48	15	37
5'-NH_2T§T (**14**)	10	13	77
5'-N_3T§A (**16**)	47	14	39
5'-NH_2T§A (**18**)	10	13	77

¤ signifies [N^3(C)→5'(C)] linkage in dimers **12a-c**

§ signifies [3'(O)→5'(C)] linkage in dimers **13 -18, & 19-22.**

calculation were made using equations given in reference 20. A correction factor of 0.3 Hz were made on the observed coupling constants to account for the difference in electronegativity between an oxygen and nitrogen atom.

Experimental

^{1}H-NMR spectra were recorded at 90 and 270 MHz with Jeol FX 90Q and Jeol GX 270 spectrometers, respectively, using tetramethylsilane (set at 0 ppm) or dry acetonitrile (set at 2.0 ppm) as internal standard in δ scale. The protected compounds were recorded in $CDCl_3$ or in a mixture of $CDCl_3$ and CD_3OD, the unprotected compounds were evaporated in 99.8% D_2O and then dissolved in 0.5 ml of 99.96% D_2O. One and two dimensionnal ^{1}H and ^{13}C NMR spectra were recorded on a Jeol GX 270 MHz. 2D ^{1}H-^{1}H double quantum filtered cosy (2D DQF COSY) were recorded using the basic pulse sequence[21]. 128 scans were acquired for each t_1 value. A sinus square window was applied on a zero filled matrix and the spectra were symmetrized. Two dimensionnal ^{1}H-^{13}C chemical shift correlation spectra were recorded using standard pulse sequence. UV absorption spectra were recorded with a Varian-Cary 2200 spectrophotometer in ethanol

for the protected compounds and in water (pH 6.5) for the unprotected ones. Reactions were monitored on Merck precoated silica gel 60 F_{254} (0.25 mm) plates in the following systems : (A) methanol / dichloromethane (1 / 9, v / v); (B) methanol / dichlotromethane (3 / 7, v / v); (C) acetonitrile / water (17 / 3, v/v); (D) n-butanol / ethanol / water (16 / 2 / 5, v / v). The IR spectra of azido derivatives were recorded with a Perkin Elmer 298 Infrared Spectrophotometer.

6-N-MMTr-2′-deoxyadenosine (2a): 2′-deoxyadenosine (2.51 g, 10 mmol) was dried by coevaporation with dry pyridine and taken up in dry pyridine (100 ml). After transient protection with trimethylsilyl (TMS) group (6 eq. TMS-Cl) followed by addition of MMTr-Cl (6.16 g, 20 mmol) the reaction mixture was stirred for 3 days at ~20 °C. After sodium bicarbonate extraction the organic layer was evaporated and taken up in dioxane (100 ml). Aqueous ammonia (~ 20 ml) was added dropwise, until the solution remained clear, and the reaction mixture was stirred overnight. Upon distillation of all the volatile matters, the solid residue was purified on silica gel column, giving the desired compound in 83% yield (4.33 g). ^{1}H-NMR ($CDCl_3$): 7.93 (s, 1H) H–8; 7.73 (s, 1H) H-2; 7.25 (m, 14H) arom; 6.21 (dd, 1H) H-1′; 4.67 (m, 1H, $J_{2',3'}$ = 4.88 Hz) H-3′; 4.1 (s, 1H) H-4′; 3.8 (m, 2H) H-5′, H-5″; 3.72 (s, 3H) OCH_3; 2.93 (m, 1H) H–2′; 2.21 (m, 1H) H-2″. R_f (A) = 0.33. UV (Et OH) λ_{max} = 275 nm; 283 nm (sh), λ_{min} = 246 nm.

4-N-MMTr-2′-deoxycytidine (2b): 2′-deoxycytidine (0.227 g, 1 mmol) was 5′-O-monomethoxytritylated as described for **1a** giving the protected nucleoside (0.43g) in 86% yield. ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.5 (d, 1H, $J_{5,6}$ = 8.07 Hz) H–6; 7.32–6.6 (t, 14H) arom.; 6.01 (t, 1H) H-1′; 5.85 (d, 1H) H-5; 4.33 (m, 1H, $J_{3',4'}$ = 3.91 Hz) H-3′; 3.92 (m, 1H) H-4′; 3.79 (s, 3H) OCH_3; 3.72 (m, 2H) H-5′, H-5″ ; 2.28 (m, 2H) H-2′, H-2″. R_f (A) = 0.21. UV (EtOH) λ_{max} = 281 nm; λ_{min} = 249 nm.

6-N-MMTr-2′-deoxyguanosine (2c): 2′-deoxyguanosine (0.27 g, 1 mmol) was 5′-O-monomethoxytritylated as described for **1a** in 78 % yield (0.5 g). ^{1}H-NMR ($CDCl_3$+ CD_3OD): 7.77 (s, 1H) H–8; 7.32–6.75 (m, 14 H) arom; 5.64 (t, 1H) H–1′; 4.29 (m, 1H) H-3′; 3.85 (m, 1H) H-4′; 3.77 (s, 3H) OCH_3; 3.65 (m, 2H) H-5′, H-5″ ; 1.97 (m, 2H) H-2′, H-2″. R_f (A) = 0.09. UV (EtOH) λ_{max} = 262, 278 nm, λ_{min} = 247 nm.

5′-O-(4-Toluenesulfonyl)-6-N-MMTr-2′-deoxyadenosine (3a): Compound **2a** (1.04 g, 1.99 mmol) was tosylated as described for **7** giving the title compound **3a** (1.07 g) in 82 % yield. ^{1}H-NMR ($CDCl_3$): δ = 7.94 (s, 2H) H-8, H-2; 7.72-6.7 (m, 18) arom; 6.35 (t, 1H) H-1′; 4.62 (m, 1H) H-3′; 4.19 (m, 3H) H-4′, H-5′, H-5″ ; 3.76 (s, 3H) OCH_3; 2.7 (m, 2H) H-2′, H-2″; 2.37 (s, 3H) CH_3. R_f (A) = 0.45. UV (EtOH) λ_{max} = 268, 275 nm; 286 nm (sh); λ_{min} = 238 nm.

5′-O-(4-Toluenesulfonyl)-4-N-MMTr-2′-deoxycytidine (3b): Compound **2b** (0.48 g, 0.96 mmol) was tosylated as described for **7** yielding the title compound (0.48 g, 77 %). ^{1}H-NMR ($CDCl_3$): 7.7-6.79 (m, 18 H) arom; 6.31 (dd, 1H) H-1′, 5.07 (d, $J_{5',6'}$= 7.56 Hz, 1H) H-5; 4.24 (m, 1H) H-3′; 4.13 (m, 2H) H-5′, H-5″ ; 3.79 (s, 3H) OCH_3; 2.74-1.69 ppm (m, 5H) CH_3, H-2′, H-2″. R_f (A) = 0.37. UV (EtOH): λ_{max} = 275 nm; 270 nm (sh), λ_{min} = 252 nm.

5′-O-(4-Toluenesulfonyl)-2-N-MMTr-2′-deoxyguanosine (3c): Compound **2c** (0.27 g, 0.5 mmol) was tosylated as described for **7** giving the title compound (0.21 g) in 78 % yield. ^{1}H-NMR ($CDCl_3$): 7.7-6.65 (m, 19H) arom, H-8; 5.63 (t, 1H) H-1′, 4.32-3.8 (m, 4H) H-3′, H-4′, H-5′, H-5″ ; 3.67 (s, 3H) OCH_3; 2.49-1.76 ppm (m, 5H) CH_3, H-2′, H-2″. R_f (A) = 0.34. UV (EtOH): λ_{max} = 262 nm; 272 nm (sh); λ_{min} = 247nm.

5′-O-(4-Toluenesulfonyl)thymidine (7): Thymidine (0.24 g, 1 mmol) was coevaporated with dry pyridine and taken up in dry pyridine (10 ml). After chilling the solution to 0 °C, 4-toluenesulofonyl chloride (0.25 g, 1.3 mmol) was added and the reaction mixture was kept at ~ 5 °C for 2 days. The reaction mixture was quenched by addition of methanol and partitioned between dicloromethane and sodium bicarbonate. The dichloromethane phase was evaporated, coevaporated with toluene giving a foam which was purified by silica column chromatography yielding the desired compound (0.32 g, 80 %). ^{1}H-NMR.($CDCl_3$ + CD_3OD): 7.68–7.2 (m, 5H) arom. and H–6; 6.15 (t, 1H) H-1′; 4.3-3.9 (m, 4H) H-3′, H-4′, H-5′, H-5″ ; 2.37 (s, 3H) CH_3; 2.13 (m, 2H) H-2′, H-2″. R_f (A) = 0.32. UV (EtOH) λ_{max} = 265 nm; 272 nm (sh); λ_{min} = 241 nm.

5′-Azido-5′-deoxythymidine (8): Dry **7** (1.2 g, 3 mmol) was dissolved in dry DMF (40 ml). LiCl (0.31 g, 7.2 mmol) and NaN_3 (0.44 g, 7.2 mmol) were added and the reaction mixture was refluxed at 100

°C for 2 h. After evaporation of DMF the solid residue was chromatographed on silica column, giving **8** in 82 % yield (0.8 g, 2.4 mmol). ^{1}H-NMR (D_2O): 7.49 (q, 1H, $J_{H\text{-}6,CH3}$ = 1.2 Hz) H-6; 6.23 (t, 1H, $J_{1'2'}$ = 6.8 Hz, $J_{1'2''}$ = 6.8 Hz) H-1'; 4.43 (m, 1H, $J_{2'3'}$ = 6.8 Hz, $J_{2''3'}$ = 4.7 Hz, $J_{3'4'}$ = 4.1 Hz) H-3'; 4.03 (m, 1H, $J_{4'5'}$ = 3.7 Hz, $J_{4'5''}$ = 5.7 Hz) H-4'; 3.65 (dd, 1H) H-5'; 3.51 (dd, 1H, $J_{5'5''}$ = 13.6 Hz) H-5''; 2.42 (ddd, 1H, $J_{2'2''}$ = 14.7 Hz) H-2'; 2.31 (ddd, 1H) H-2''; 1.84 (d, 3H) CH_3. ^{13}C-NMR (D_2O): δ = 167.36 (C-4); 152.77 (C-2); 138.52 (C-6); 112.71 (C-5); 86.48 (C-1'); 85.91 (C-4'); 72.21 (C-3'); 52.99 (C-5'); 39.36 (C-2'); 12.74 (CH_3). R_f (A) = 0.25. UV (EtOH): λ_{max} = 265 nm, λ_{min} = 233 nm. IR (nujol): ν_{max} = 2092 cm^{-1}. MS (FAB$^-$): calc. for (M-H)$^-$ 266.0889, found 266.0892.

5'-Azido-6-N-MMTr-5',2'-dideoxyadenosine (4a): Dry **3a** (1.07 g, 1.58 mmol) was dissolved in dry DMSO (5 ml) and refluxed together with NaN_3 (0.36 g, 5.85 mmol) for 1-2 h. The reaction mixture was evaporated and purified on silica gel column giving **4a** (0.79 g, 93 %). ^{1}H-NMR.($CDCl_3$ + CD_3OD): 8.02 (s, 1H) H-8; 7.99 (s, 1H) H-2; 7.35-7.1 (m, 12 H) arom; 6.8 (d, 2H) arom; 6.37 (t, 1H) H-1', 4.56 (m, 1H) H-3', 4.04 (m, 1H) H-4'; 3.76 (s, 3H) OCH_3; 3.57 (m, 2H) H-5', H-5''; 3.05-2.25 ppm (m, 2H) H-2', H-2''. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 84.7 (C-4'); 83.83 (C-1'); 71.21 (C-3'); 51.7 (C-5'); 39.46 (C-2'). R_f (A) = 0.42. UV (EtOH) λ_{max} = 276 nm; 283 nm (sh); λ_{min} = 246 nm.IR (nujol): ν_{max} = 2092 cm^{-1}. MS (FAB$^-$): calc. for (M-H)$^-$ 547.2206, found 547.2211.

5'-Azido-4-N-MMTr-5',2'-dideoxycytidine (4b): Dry **3b** (0.73 g, 1.11 mmol) was converted to the target compound as described for **8** (0.55 g, 95 %). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.3-6.87 (m, 13 H) arom, H-6; 6.7 (d, 2H) arom; 6.31 (t, 1H) H-1'; 5.10 (d, 1H, $J_{H\text{-}6,H\text{-}5}$ = 7.6 Hz) H-5; 4.29 (m, 1H) H-3'; 4.06 (m, 1H) H-4'; 3.79 (s, 3H) OCH_3; 3.57 (m, 2H) H-5',H-5''; 2.76-1.79 ppm (m, 2H) H-2', H-2''. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 85.57 (C-4'); 84.05 (C-1'); 70.07 (C-3'); 51.65 (C-5'); 40.44 (C-2'). R_f (A) = 0.36. UV (EtOH): λ_{max} = 278 nm; λ_{min} = 250 nm. IR (nujol): ν_{max} = 2092 cm^{-1}. MS (FAB$^-$): calc. for (M-H)$^-$ 523.2094, found 523.2106.

5'-Azido-2-N-MMTr-5',2'-dideoxyguanosine (4c): Dry **3c** (3.1 g, 4.5 mmol) was prepared using a procedure described for **3b** in 90 % yield (2.26 g). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.54 (s, 1H) H-8; 7.3-7.14 (m, 12 H) arom, 6.80 (d, 2H) arom; 5.66 (t, 1H) H-1'; 4.17 (m, 1H) H-3'; 3.83 (m, 1H) H-4'; 3.69 (s, 3H) OCH_3; 3.19 (m, 2H) H-5', H-5''; 2.23-1.59 (m, 2H) H-2', H-2''.^{13}C-NMR ($CDCl_3$ + CD_3OD): 84.43 (C-4'); 84.05 (C-1'); 70.94 (C-3'); 51.82 (C-5'); 38.11 (C-2'). R_f (A) = 0.27. UV (EtOH) λ_{max} = 267 nm; 283 nm (sh); λ_{min} = 246 nm. IR (nujol): ν_{max} = 2092 cm^{-1}. MS (FAB$^-$): calc. for (M-H)$^-$ 563.2155, found 563.2161.

5'-Amino-5'-deoxythymidine (9): Dry compound **8** (0.053 g, 0.2 mmol) was dissolved in dry pyridine (1ml). This solution was chilled to 0 °C followed by addition of Ph_3P (0.57 g, 0.21 mmol).The reaction mixture was stirred at 0 °C for 1 h and at ~20 °C overnight. Methanolic ammonia (1 ml) was added and stirred for further period of a day. The reaction mixture was evaporated, coevaporated with toluene, partitioned between water and dichloromethane.The aqueous phase contained the pure product (0.047 g, quantitative)). ^{1}H-NMR (D_2O) : 7.37 (q, 1H, $J_{H\text{-}6,CH3}$ = 1.2 Hz) H-6; 6.18 (t, 1H, $J_{1'2'}$ = 6.8 Hz, $J_{1'2''}$ = 6.7 Hz) H-1'; 4.33 (m, 1H, $J_{2'3'}$ = 6.9 Hz, $J_{2''3'}$ = 4.4 Hz, $J_{3'4'}$ = 4.3Hz) H-3'; 3.90 (m, 1H, $J_{4'5'}$ = 4.6 Hz, $J_{4'5''}$ = 7.7 Hz) H-4'; 2.95 (dd, 1H, $J_{5'5''}$ = 13.5Hz) H-5'; 2.86 (dd, 1H) H-5''; 2.36 (ddd, 1H, $J_{2'2''}$ = 14.5 Hz) H-2'; 2.28 (ddd, 1H) H-2''; 1.82 (d, 3H) CH_3. ^{13}C-NMR.(D_2O): 169.07 (C-4); 153.98 (C-2); 138.63 (C-6); 112.78 (C-5); 87.31 (C-1'); 86.72 (C-4'); 72.74 (C-3'); 43.82 (C-5'); 39.15 (C-2'); 12.87 (CH_3). R_f (B) = 0.07. UV (H_2O): λ_{max} = 260 nm; λ_{min} = 233 nm. MS (FAB$^-$): calc. for (M-H)$^-$ 240.0984, found 240.0960.

5'-Amino-6-N-MMTr-5',2'-dideoxyadenosine (5a): Compound **4a** (0.55 g, 1 mmol) was reduced using a procedure described for **8**. Evaporating the reaction mixture, the solid residue was purified on silica gel column, giving the target compound (0.55 g, 96 %). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.99 (s, 1H) H-8; 7.84 (s, 1H) H-2; 7.3-7.01 (m, 12H) arom, 6.77 (d, 2H) arom; 6.29 (t, 1H) H-1'; 4.57 (m, 1H) H-3'; 3.95 (m, 1H) H-4'; 3.76 (s, 3H) OCH_3; 2.98 (m, 2H) H-5', H-5''; 2.90-2.20 (m, 2H) H-2', H-2''. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 86.38 (C-4'); 83.51 (C-1'); 71.16 (C-3'); 43.2 (C-5'); 38.33 (C-2'). R_f (B) = 0.17. UV (EtOH): λ_{max} = 275 nm; 283 nm (sh); λ_{min} = 246 nm. MS (FAB$^-$): calc. for (M-H)$^-$ 521.2301, found 521.2334.

5'-Amino-4-N-MMTr-5',2'-dideoxycytidine (5b): Compound **4b** (0.095 g, 0.18 mmol) was reduced using a procedure described for **8** giving the target compound (0.09 g, 94 %). ^{1}H-NMR.($CDCl_3$ + CD_3OD): 7.4-6.79 (m, 15H) arom, H-6; 6.05 (t, 1H) H-1'; 5.13 (d, 1H, $J_{H\text{-}6,H\text{-}5}$ = 7.17 Hz) H-5;

4.12 (m, 1H) H-3'; 3.9 (m, 1H) H-4'; 3.79 (s, 3H) OCH_3; 2.9 (m, 2H) H-5', H-5''; 2.52-1.9 (m, 2H) H-2', H-2''. ^{13}C-NMR ($CDCl_3$, CD_3OD): 86.92 (C-4'); 86.05 (C-1'); 71.05 (C-3'); 43.47 (C-5'); 40.66 (C-2'). R_f (B) = 0.16, UV (EtOH): λ_{max} = 277 nm; λ_{min} = 247nm. MS (FAB^-): calc. for $(M-H)^-$ 497.2189, found 497.2157.

5'-Amino-2-N-MMTr-5',2'-dideoxyguanosine (5c): Compound **4c** (0.11 g, 0.2 mmol) was converted to the amino derivative (0.49 g, 0.18 mmol) as described for **8**. ^{1}H-NMR.($CDCl_3$ + CD_3OD): 7.41-6.75 (m, 15H) arom, H-8; 5.61 (t, 1H) H-1'; 4.0-3.6 (m, 5H) H-3', H-4', OCH_3; 2.61 (m, 2H) H-5', H-5''; 2.21-1.70 (m, 2H) H-2', H-2''. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 87.40 (C-4'); 84.20 (C-1'); 71.32 (C-3'); 43.37 (C-5'); 39.63 (C-2'). R_f (B) = 0.07. UV (EtOH): λ_{max} = 262, 278 nm; λ_{min} = 247 nm. MS (FAB^-): calc. for $(M-H)^-$ 537.2250, found 537.2224.

5'-O-MMTr-N^3-carboxymethyl-5'-deoxythymidine (sodium salt) (1c): It was prepared with a modification of Gait and coworkers' procedure[9]. 5'-O-MMTr-thymidine (0.26 g, 0.5 mmol) was taken up in dry DMSO. The solution was frozen with ice-bath, and NaH (0.04 g, 1.5 mmol) was added, the reaction mixture was allowed to warm up to ~20 °C, and then $ClCH_2COO^-Na^+$ (0.064 g, 0.55 mmol) was added. The reaction mixture was stirred for 3 days at ~20 °C. Ethanol / water (1/ 1, v/v) was added and the pH was adjusted to 7 with 1 M HCl. The reaction mixture was evaporated and loaded on silica gel column, and eluted with a mixture of dichloromethane and methanol, giving the target compound (0.24 g, 94 %). Compound **1c** (0.02 g, 0.033 mmol) was deprotected, in order to get an NMR spectra with improved resolution, in 80 % aq. AcOH at ~20 °C for 2h. The reaction mixture was evaporated, coevaporated with toluene and taken up in H_2O, extracted twice with CH_2Cl_2, giving the corresponding 5'-OH derivative of **1c** (0.01 g, 90 %). ^{1}H-NMR (D_2O) : 7.53 (d, 1H, $J_{H-6,CH3}$ = 1.25 Hz) H-6; 6.17 (t, 1H, $J_{1',2'}$ = 6.7 Hz, $J_{1',2''}$ = 6.6 Hz) H-1'; 4.33 (m, 1H, $J_{2',3'}$ = 6.8, $J_{2'',3'}$ = 4.0 Hz, $J_{3',4'}$ = 3.9 Hz) H-3'; 4.32 (s, 2H) CH_2; 3.89 (m, 1H, $J_{4',5'}$ = 3.5 Hz, $J_{4',5''}$ = 5.2 Hz) H-4'; 3.71 (dd, 1H, $J_{5',5''}$ = 12.5 Hz) H-5'; 3.63 (dd, 1H) H-5''; 2.26 (ddd, 1H, $J_{2',2''}$ = 14.2 Hz) H-2'', 2.23 (ddd, 1H) H-2'; 1.79 (d, 3H) CH_3. ^{13}C-NMR: 175.78 (C=O); 166.25 (C-4); 152.79 (C-2); 136.86 (C-6); 111.78 (C-5); 87.85 (C-4'); 87.25 (C-1'); 71.60 (C-3'); 62.42 (C-5'); 45.85 (CH_2); 40.07 (C-2'); 13.49 (CH_3). R_f (B) = 0.33; R_f (D) = 0.54. UV (EtOH): λ_{max} = 268 nm; λ_{min} = 251 nm.

5'-Azido-3'-O-carboxymethyl-5'-deoxythymidine (sodium salt) (10): · DMSO solution of 5'-Azido-5'-deoxythymidine **8** (0.27 g, 1 mmol) was chilled before addition of NaH (0.084 g, 3.5 mmol) and 1 h later $ClCH_2COO^-Na^+$ (0.13 g, 1.1 mmol). During the 3 days reaction no bis-product was observed. The work up and chromatography was performed like in the above reference, giving the target compound (0.28 g, 80 %). ^{1}H-NMR (D_2O): 7.50 (d, 1H, $J_{H-6,CH3}$ = 1.2 Hz) H-6; 6.22 (dd, 1H, $J_{1',2'}$ = 7.2 Hz, $J_{1',2''}$ = 6.8 Hz) H-1', 4.20 (m, 2H, $J_{2',3'}$ = 6.3 Hz, $J_{2'',3'}$ = 3.6 Hz, $J_{3',4'}$ = 3.6 Hz, $J_{4',5'}$ = 3.4 Hz, $J_{4',5''}$ = 5.7 Hz) H-3',H-4'; 3.91 (s, 2H) CH_2; 3.67 (dd, 1H, $J_{5',5''}$ = -13.6 Hz) H-5'; 3.54 (dd, 1H) H-5''; 2.45 (ddd, $J_{2',2''}$ = 14.5 Hz) H-2''; 2.35 (ddd, 1H) H-2'; 1.83 ppm (d, 3H) CH_3. ^{13}C-NMR (D_2O): 178.33 (C=O); 167.43 (C-4); 152.77 (C-2); 138.58 (C-6); 112.74 (C-5); 86.71 (C-1'); 84.09 (C-4'); 80.68 (C-3'); 69.72 (CH_2); 36.75 (C-2'); 12.71 (CH_3). R_f (B) = 0.42; R_f (D) = 0.41. UV (H_2O): λ_{max} = 266 nm; λ_{min} = 235 nm. IR (nujol): ν_{max} = 2092 cm^{-1}. MS (FAB^-): calc. for $(M-H)^-$ 370.0740, found 370.0739.

5'-Azido-3'-O-carboxymethyl-4-N-MMTr-5',2'-dideoxycytidine (sodium salt) (6a): The target compound (0.57 g, 0.94 mmol) was prepared from 5'-Azido-N^4-MMTr-5',2'-dideoxycytidine **4b** (0.58 g, 1.11 mmol) using the procedure described for the thymidine analogue **10**, but the reaction time was 1 day instead of 3 days. Compound **6a** (0.04 g, 0.066 mmol) was deprotected, in order to get the NMR spectra with improved resolution , in 80 % aq. acetic acid at 100 °C for 10 min, and the usual work up gave 5'-Azido-3'-O-carboxymethyl-5',2'-dideoxycytidine (sodium salt) **6c** (0.040 g, 94 %). ^{1}H-NMR (D_2O): 7.84 (d, 1H, $J_{H-5,H-6}$ =7.6 Hz) H-6; 6.33 (t, 1H, $J_{1',2'}$ = 7.2 Hz, $J_{1',2''}$ = 6.2 Hz) H-1'; 6.13 (d, 1H) H-5; 4.34 (m, 1H, $J_{2',3'}$ = 6.3 Hz, J $_{2'',3'}$ = 3.3 Hz) H-3'; 4.29 (m, 1H, $J_{4',5'}$ = 3.6 Hz, $J_{4',5''}$ = 5.4 Hz) H-4'; 4.04 (s, 1H) CH_2; 4.03 (s, 1H) CH_2; 3.79 (dd, 1H, $J_{5',5''}$ = -13.5 Hz) H-5'; 3.67 (dd, 1H) H-5''; 2.61 (ddd, 1H, $J_{2',2''}$ = 14.2 Hz) H-2''; 2.37 (m, 1H) H-2'. ^{13}C-NMR (D_2O): 178.41 (C=O); 166.80 (C-4); 157.89 (C-2); 142.96 (C-6); 97.47 (C-5); 87.55 (C-1'); 84.04 (C-4'); 80.77 (C-3'); 69.63 (CH_2); 53.42 (C-5'); 37.41 (C-2'). R_f (B) = 0.29; R_f (D) = 0.5.UV (EtOH): λ_{max} = 278 nm; λ_{min} = 250 nm. IR(nujol): ν_{max} = 2092 cm^{-1}. MS (FAB^-): calc. for $(M-H)^-$ 309.0948, found 309.0941.

5'-Azido-3'-O-carboxymethyl-2-N-MMTr-5',2'-dideoxyguanosine (6b): The target compound was prepared from **4c** (0.9 g. 1.6 mmol), using the procedure described for **10**, in 80 % yield (0.83 g). Compound **6b** (0.04 g, 0.062 mmol) was deprotected and worked up to give 5'-Azido-3'-O-carboxymethyl-

5',2'-dideoxyguanosine **6d** (0.02g, 93 %). ^{1}H-NMR.(D_2O): 7.87 (s, 1H) H-8; 6.20 (t, 1H, $J_{1',2'}$ = 7.2 Hz, $J_{1',2''}$ = 6.4 Hz) H-1'; 4.30 (m, 1H, $J_{2',3'}$ = 6.2 Hz, $J_{2'',3'}$ = 3.4 Hz) H-3'; 4.24 (m, 1H, $J_{4',5'}$ = 6.1 Hz, $J_{4',5''}$ = 4.0 Hz) H-4'; 3.90 (s, 2H) CH_2; 3.61 (dd, 1H, $J_{5',5''}$ = 13.3 Hz) H-5''; 3.51 (dd, 1H) H-5''; 2.82 (m, 1H, $J_{2',2''}$ = 13.9 Hz) H-2'; 2.56 (ddd, 1H) H-2''. ^{13}C-NMR (D_2O): 178.08 (C=O); 159.85 (C-6); 155.24 (C-2); 152.94 (C-4); 138.66 (C-8); 119.42 (C-5); 85.76, 85.04 (C-1', C-4'); 81.42 (C-3'); 70.10 (CH_2); 53.78 (C-5'); 37.19 (C-2'). R_f (B) = 0.18; R_f (D) = 0.52. UV (EtOH): λ_{max} = 261, 278 nm; 257nm (sh); λ_{min} = 247, 273 nm. IR (nujol): ν_{max} = 2092 cm^{-1}. MS (FAB$^-$): calc. for (M-H)$^-$ 349.1009, found 349.1001.

5'-O-MMTr-Thymidinylacetamido-[N^3(C)→5'(C)]-5'-deoxythymidine (11a): 5'-O-MMTr-N^3-carboxymethyl-5'-deoxythymidine **1c** (0.022 g, 0. 09 mmol) and 5'-amino-5'-deoxythymidine **9** (0.054 g, 0.1 mmol) were dried and taken up in dry DMF (1ml), 1-hydroxybenzotriazole (0.014 g, 0.1 mmol) N-ethylmorpholine and dicyclohexylcarbodiimide (0.042 g, 0.2 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at ~20 °C overnight. The reaction was quenched by addition of water, then evaporated and taken up in CH_2Cl_2. The precipitating dicyclohexylurea was filtered off and the solution was evaporated, then purified on silica gel column, giving the target compound (0.045 g, 63 %). R_f (A) = 0.15. UV (EtOH): λ_{max} = 267 nm; λ_{min} = 246nm.

Thymidinylacetamido-[N^3(C)→5'(C)]-5'-deoxythymidine (12a): The protected dimer **11a** (0.04 g, 0.05 mmol) was dissolved in 80 % aq. acetic acid and stirred for 2 h at ~20 °C. The reaction mixture was evaporated, coevaporated with water and partitioned between water and dichloromethane. The aqueous phase was again extracted with diethyl ether, then concentrated giving the title compound as crystal (0.023 g, 88 %). ^{1}H-NMR (D_2O): 7.58 (d, 1H, $J_{H\text{-}6,CH3}$ = 1.2 Hz) H-6 (T^1); 7.36 (d, 1H, $J_{H\text{-}6,CH3}$ = 1.2 Hz) H-6; 6.13 (t, 1H, $J_{1',2'}$ = 6.9 Hz, $J_{1',2''}$ = 6.5 Hz) H-1'(T^1); 6.08 (t, 1H, $J_{1',2'}$ = 7.1 Hz, $J_{1',2''}$ = 6.9 Hz) H-1' (T^2); 4.54 (s, 1H) CH_2; 4.49 (s, 1H) CH_2; 4.32 (m, 1H, $J_{2',3'}$ = 6.1 Hz, $J_{2'',3'}$ = 4.2 Hz) H-3'(T^1); 4.24 (m, 1H, $J_{2',3'}$ = 6.5 Hz, $J_{2'',3'}$ = 4.3 Hz) H-3'(T^2); 3.93 (m, 1H, $J_{4',5'}$ = 6.2 Hz, $J_{4',5''}$ = 4.5 Hz) H-4'(T^2); 3.89 (m, 1H, $J_{4',5'}$ = 3.5 Hz, $J_{4',5''}$ = 4.9) H-4'(T^1); 3.71 (dd, 1H, $J_{5',5''}$ = 12.4 Hz); H-5'(T^1); 3.62 (dd, 1H) H-5'(T^1); 3.46 (dd, 1H, $J_{5',5''}$ = -14.5 Hz) H-5'(T^2);3.37 (dd, 1H) H-5''(T^2); 2.25 (m, 1H, $J_{2',2''}$ = -14.1 Hz) H-2''(T^1); 2.22 (m, 1H) H-2'(T^1); 2.21 (m, 1H, $J_{2',2''}$ = 14.46 Hz) H-2''(T^2); 2.20 (ddd, 1H) H-2'(T^2); 1.77 (d, 3H) CH_3 (T); 1.71 (d, 3H) CH_3. ^{13}C-NMR (D_2O): 170.99 (C=O); 167.58 (C-4, T^2); 166.09 (C-4, T^1); 152.79 (C-2, T); 152.64 (C-2, T); 138.87 (C-6, T); 137.28 (C-6, T); 112.54 (C-5, T^2); 111.61 (C-5, T^1); 87.89 (C-4', T^1); 87.34 (C-1', T^1); 86.79 (C-1',T^2); 85.75 (C-4', T^2); 72.59 (C-3', T^2); 71.62 (C-3', T^1); 62.32 (C-5', T^1); 44.93 (CH_2); 42.0 (C-5', T^2); 39.98 (C-2', T^1); 39.18 (C-2', T^2); 13.35 (CH_3, T); 12.61 (CH_3, T). R_f (B) = 0.67. UV (H_2O): λ_{max} = 268 nm, 262 nm; λ_{min} = 236 nm.

5'-O-MMTr-thymidinylacetamido-[N3(C)→5'(C)]-N6-MMTr-5',2'-dideoxyadenosine (11b): 5'-O-MMTr-N3-carboxymethyl-5'-deoxythymidine (sodium salt) **1c** (0.113 g, 0.19 mmol) and N^6-MMTr-5'-amino-5',2'-dideoxyadenosine **5a** (0.1 g, 0.19 mmol) were condensed using a condition reported for **11a** giving the target compound **11b** in 50 % yield (0.1 g, 0.1 mmol). Rf (A) = 0.2. UV (EtOH): λ_{max} = 267 nm; λ_{min} = 245 nm. This was directly deprotected *(vide infra)* to give **12b.**

Thymidinylacetamido-[N^3(C)→5'(C)]-5',2'-dideoxyadenosine (12b): 5'-O-MMTr-Thymidinylacetamido-[N^3(C)→5'(C)]-N^6-MMTr-5',2'-dideoxyadenosine **11b** (0.044 g, 0.041 mmol) was dried and dissolved in ~ 0.1 M $ZnBr_2$ in dry nitromethane (1 ml) and the reaction mixture was stirred for 22 h at ~20 °C under argon. Aq. ammonia was added until the solution became clear. The volatile matters were evaporated and partitioned between water and dichloromethane.The aqueous phase was extracted twice with dichloromethane followed by diethyl ether. The aqueous phase was then evaporated giving the target compound (0. 014 g, 63 %). ^{1}H-NMR (D_2O, 270 MHz): 8.24 (s, 1H) H-8 (A); 8.19 (s, 1H) H-2 (A); 7.59 (s, 1H) H-6 (T); 6.37 (dd, 1H, $J_{1',2'}$ = 7.2 Hz, $J_{1',2''}$ = 6.2 Hz) H-1'(A); 6.17 (t, 1H, $J_{1',2'}$ = 7.0 Hz, $J_{1',2''}$ = 6.4 Hz) H-1'(T); 4.59 (s, 1H) CH_2; 4.54 (s, 1H) CH_2; 4.46 (m, 1H, $J_{2',3'}$ = 6.6 Hz, $J_{2'',3'}$ = 3.6 Hz, $J_{3',4'}$ = 3.4 Hz) H-3' (A); 4.38 (m, 1H, $J_{2',3'}$ = 6.4 Hz, $J_{2'',3'}$ = 4.4 Hz, $J_{3',4'}$ = 4.1 Hz) H-3'(T); 4.14 (m, 1H, $J_{4',5'}$ = 5.3 Hz, $J_{4',5''}$ = 4.2 Hz) H-4'(A); 3.95 (m, $J_{4',5'}$ = 3.5 Hz, $J_{4',5''}$ = 5.2 Hz) H-4' (T); 3.77 (dd, 1H, $J_{5',5''}$ = 12.5 Hz) H-5'(T); 3.69 (dd, 1H) H-5''(T) ; 3.60 (dd, $J_{5',5''}$ = -12.9 Hz) H-5' (A); 3.42 (dd, 1H) H-5''(A); 2.80 (m, 1H, $J_{2',2''}$ = 14.1 Hz) H-2'(A); 2.52 (ddd, 1H) H-2''(A); 2.30-2.25 (m, 2H, $J_{2',2''}$ = 14.3 Hz) H-2', H-2'' (T); 1.82 (d, 3 H, $J_{H6,CH3}$ =

1.2 Hz) CH_3. ^{13}C-NMR (D_2O): 170.92 (C=O); 166.01 (C-4, T); 156.42 (C-6, A); 153.29 (C-2, A); 152.52 (C-2, T); 149.83 (C-4, A); 141.76 (C-8, A); 137.19 (C-6, T); 120.30 (C-5, A); 111.52 (C-5, T); 87.86 (C-4′, T); 87.31 (C-1′, T); 86.45 (C-4′, A); 85.69 (C-1′, A); 72.99 (C-3′, A); 71.57 (C-3′, T); 62.38 (C-5′, T); 44.88 (CH_2); 42.12 (C-5′, A); 39.94 (C-2′, T); 39.72 (C-2′, A); 13.32 (CH_3). R_f (B) = 0.46. UV (H_2O): λ_{max} = 257 nm; λ_{min} = 226 nm.

Thymidinylacetamido-[N^3(C)→5′(C)]-N^4-MMTr-5′,2′-dideoxycytidine (11c): 5′-O-MMTr-N^3-carboxymethyl-5′-deoxythymidine (sodium salt) **1c** (0.09 g, 0.145 mmol) and 5′-amino-N^4-MMTr-5′,2′-dideoxycytidine **5b** (0.076 g, 0.145 mmol) were dried and coupled as for **11b** giving **11c** (0.08 g, 60 %). R_f (A) = 0.27. UV (EtOH): λ_{max} = 274, 269 nm; λ_{min} = 250 , 272 nm.

Thymidinylacetamido-[N^3(C)→5′(C)]-5′,2′-dideoxycytidine (12c): 5′-O-MMTr-Thymidinylacetamido-[N^3(C)→5′(C)]-N^4-MMTr-5′,2′-dideoxycytidine **11c** (0.07 g, 0.065 mmol) was dissolved in 80 % aq. acetic acid (1 ml) and refluxed at 100 °C for 10 mn. After the reaction mixture cooled to ~20 °C all the volatile matters were evaporated, giving a solid residue which was taken up in water and extracted twice with CH_2Cl_2, followed by diethylether. The aqueous phase gave **12c** (0.035 g, quantitative). ^{1}H-NMR (D_2O): 7.62 (q, 1H, $J_{H6,CH3}$ = 1.2 Hz) H-6 (T); 7.60 (d, 1H, $J_{H-5,H-6}$ = 7.6 Hz) H-6 (C); 6.19 (t, 1H) H-1′(T); 6.10 (dd, 1H, $J_{1',2'}$ = 6.7 Hz, $J_{1',2''}$ = 6.4 Hz) H-1′(C); 5.92 (d, 1H) H-5 (C); 4.59 (s, 1H) CH_2; 4.57 (s, 1H) CH_2; 4.39 (m, 1H, $J_{2',3'}$ = 5.7 Hz, $J_{2'',3'}$ = 4.6 Hz) H-3′(T); 4.27 (m, 1H, $J_{2',3'}$ = 6.7 Hz, $J_{2'',3'}$ = 4.1 Hz) H-3′(C); 4.00 (m, 1H, $J_{4',5'}$ = 3.6 Hz, $J_{4',5''}$ = 5.0 Hz) H-4′(T); 3.95 (m, 1H) H-4′(C); 3.78 (dd, 1H, $J_{5',5''}$ = 12.5) H-5′(T); 3.69 (dd, 1H) H-5′′(T); 3.48-3.46 (d, 2H) H-5′, H5′′ (C); 1.83 (s, 3H) CH_3. ^{13}C-NMR (D_2O): 170.92 (C=O); 167.05 (C-4, T); 165.97 (C-4, C); 158.12 (C-2, C); 152.56 (C-2, T); 142.91 (C-6, C); 137.23 (C-6, T); 111.54 (C-5, T); 97.19 (C-5, C); 87.96 (C-4′, C); 87.62 (C-1′, C); 87.33 (C-1′, T); 85.86 (C-4′, T); 72.65 (C-3′, C); 71.62 (C-3′, T);62.42 (C-5′, T); 44.86 (CH_2); 42.13 (C-5′, C); 40.15, 40.09 (C-2′, T,C); 13.40 (CH_3). R_f (B) = 0.28. UV (H_2O): λ_{max} = 268 nm; λ_{min} = 240 nm.

5′-Azido-thymidinylacetamido-[3′(O)→5′(C)]-5′-deoxythymidine (13): 5′-Azido-3′-O-carboxymethyl-5′-deoxythymidine (sodium salt) **10** (0.088g, 0.25 mmol) and 5′-amino-5′-deoxythymidine **9** (0.061 g, 0.25 mmol) were condensed as reported for **11a** yielding the target compound (0.062 g, 44 %) after silica gel column chromatography. ^{1}H-NMR (D_2O, 270 MHz): 7.50 (d, 1H, $J_{H-6,CH3}$ = 1.2 Hz) H-6 (T); 7.46 (d, 1H, $J_{H-6,CH3}$ = 1.3 Hz) H-6 (T); 6.21 (dd, 1H, $J_{1',2'}$ = 7.9 Hz, $J_{1',2''}$ = 6.2 Hz) H-1′(T^1); 6.17 (t, 1H) H-1′ (T^2); 4.37 (m, 1H) H-3′(T^2); 4.27-4.19 (m, 2H) H-3′, H-4′(T^1); 4.11 (s, 2H) CH_2; 4.06 (m, 1H)H-4′(T^2); 3.64 (dd, 1H, $J_{4',5'}$ = 4.0 Hz, $J_{5',5''}$ = 13.40 Hz) H-5′(T^1); 3.57-3.51 (m, 3H) H-5′′ (T^1), H5′, H5′′ (T^2); 2.45 (ddd, 1H, $J_{2',3'}$ = 3.0 Hz, $J_{2',2''}$ = 14.26 Hz) H-2′′(T^1); 2.39-2.29 (m, 3H) H-2′(T^1), H-2′, H-2′′ (T^2); 1.86 (m, 6H) CH_3, (T^1, T^2).^{13}C-NMR (D_2O): 173.47 (C=O); 167.41 (C-4, T^1, T^2); 152.73, 152.68 (C-2, T^1,T^2);138.90, 138.37 (C-6, T^1, T^2); 112.88 (C-5, T^1); 112.55 (C-5, T^2); 87.03 (C-1′, T^2); 86.71 (C-1′, T^1); 85.44 (C-4′, T^2); 83.84 (C-4′, T^1); 81.89 (C-3′, T^1); 72.69 (C-3′, T^2); 69.47 (CH_2); 53.35 (C-5′, T^1); 41.82 (C-5′, T^2); 39.12 (C-2′, T^2); 36.62 (C-2′, T^1); 12.71 (CH_3, T^1, T^2). R_f (B) = 0.38. UV (H_2O): λ_{max} = 269 nm; 290 nm (sh); λ_{min} = 235 nm, 245 nm. IR (nujol): ν_{max} = 2092 cm^{-1}. MS (FAB$^-$): calc. for (M-H)$^-$ 547.1901, found 547.1901.

5′-Amino-thymidinylacetamido-[3′(O)→5′(C)]-5′-deoxythymidine (14): 5′-Azido-thymidinylacetamido-[3′(O)→5′(C)]-5′-amino-5′-deoxythymidine **13** (0.038 g, 0.067 mmol) was coevaporated with dry pyridine and taken up in dry pyridine (0.4 ml). Ph_3P (0.02 g, 0.073 mmol) was added to the 0 °C solution and stirred at 0 °C for 1 h, followed by overnight stirring at ~20 °C. Methanolic ammonia (0.4 ml) was added quickly and the reaction mixture was stirred for further period of a day. The volatile matters were evaporated and the solid residue was purified on silica gel column, giving 5′-Amino-thymidinylacetamido-[3′(O)→5′(C)]-5′-deoxythymidine **14** (0.03 g, 0.056 mmol) in 85 % yield. ^{1}H-NMR (D_2O): 7.40 (d,1H, $J_{H6,CH3}$ =1.3 Hz) H-6 (T); 7.36 (d, 1H, $J_{H-6,CH3}$ = 1.1 Hz) H-6 (T); 6.12 (t, 1H) H-1′(T^1); 6.09 (t, 1H) H-1′(T^2); 4.33 (m, 1H) H-3′(T^2); 4.22-4.11 (m, 2H) H-3′, H-4′(T^1); 4.07 (s, 2H) CH_2; 4.01 (m, 1H, $J_{4',5'}$ = 6.7 Hz, $J_{4',5''}$ = 4.8 Hz) H-4′(T^2); 3.55 (dd, 1H, $J_{5',5''}$ = -14.3 Hz) H-5′(T^2); 3.47 (dd, 1H) H-5′′(T^2); 3.13 (dd, 1H, $J_{4',5''}$ = 4.3 Hz, $J_{5',5''}$ = -13.5 Hz) H-5′(T^1); 3.02 (dd, 1H, $J_{4'5''}$ = 8.4 Hz) H-5′′(T^1); 2.29-2.04 (m, 4H) H-2′,2′′(T^1, T^2); 1.81 (m, 6H) CH_3 (T^1, T^2). ^{13}C-NMR (D_2O): 173.40 (C=O); 167.63 (C-4, T^1, T^2); 152.81 (C-2, T^1, T^2); 139.28 (C-6, T^2);

138.82 (C-6, T^1); 112.68 and 112.54 (C-5, T^1, T^2); 87.97 (C-1', T^1); 87.01 (C-1', T^2); 85.44 (C-4', T^2); 83.34 (C-4', T^1); 82.14 (C-3', T^1); 72.71 (C-3', T^2); 69.43 (CH_2); 43.37 (C-5',T^1); 41.82 (C-5', T^2); 39.05 (C-2', T^2); 36.07 (C-2', T^1); 12.72 and 12.64 (CH_3, T^1,T^2).R_f (B) = 0.042. UV (H_2O): λ_{max} = 258 nm; 266 (sh), 241 nm (sh); λ_{min} = 231 nm, 235 nm. MS (FAB^-): calc. for $(M-H)^-$ 521.1996, found 521.1965.

5'-Azido-thymidinylacetamido-[3'(O)→5'(C)]-N^6-MMTr-5',2'-dideoxyadenosine (15a): 5'-Azido-3'-O-carboxymethyl-5'-deoxythymidine **10** (sodium salt) (0.174 g, 0.5 mmol) and 5'-amino-N^6-MMTr-5',2'-dideoxyadenosine **5a** were dried and condensed in DMF as described for **13** to give the title compound (0.3 g, 72 %). ^{1}H-NMR ($CDCl_3$): 8.00 (s, 1H) H-8 (A); 7.93 (s, 1H) H-2 (A); 7.35-7.16 (m, 12 H) arom; 7.32 (d, 1H, $J_{H\text{-}6,CH3}$ = 1.3 Hz) H-6 (T); 6.77 (d, 2H) arom; 6.3 (t, 1H) H-1'(A); 6.15 (dd, 1H, $J_{1',2'}$ = 7.6 Hz, $J_{1',2''}$ = 6.1 Hz) H-1'(T); 4.13 (m, 1H) H-3'(A); 4.09 (m, 1H) H-3'(T); 4.02 (s, 2H) CH_2; 3.95 (m, 2H) H-4'(T,A); 3.76 (s, 3H) OCH_3; 3.54 (dd, 1H, $J_{4',5'}$ = 3.4 Hz, $J_{5',5''}$ = 13.5 Hz) H-5'(T); 3.44 (m, 2H) H-5'(A), H-5''(T); 3.38 (dd, 1H, $J_{4',5''}$ = 3.4 Hz, $J_{5',5''}$ = 13.0 Hz) H-5''(A); 2.46- 2.36 (m, 2H) H-2', H-2''(A); 2.11-2.09 (m, 2H) H-2', H-2''(T); 1.89 (d, 3H) CH_3. R_f (A) = 0.61. UV (EtOH): λ_{max} = 270 nm; λ_{min} = 243 nm. IR (nujol): ν_{max} = 2092 cm^{-1}.

5'-Azido-thymidinylacetamido-[3'(O)→5'(C)]-N^6-MMTr-adenylylacetyl-[3'(O)→3'(C)]-5'-azido-thymidine (15b): When 5'-Azido-3'-O-carboxymethyl-5'-deoxythymidine **10** (sodium salt) (0.174 g, 0.5 mmol) and 5'-amino-N^6-MMTr-5',2'-dideoxyadenosine **5a** were dried and condensed in pyridine in presence of 1-mesitylenesulfonyl chloride (0.33 g, 1.5 mmol) and 1-methylimidazole (0.24 ml, 3 mmol) gives **15b** (0.17 g, 30 %). ^{1}H-NMR ($CDCl_3$): 7.95 (s, 1H)H-8 (A); 7.94 (s, 1H) H-2 (A); 7.28 (q, 1H, $J_{H\text{-}6,CH3}$ = 1.4 Hz) H-6 (T); 7.25 (q, 1H, $J_{H\text{-}6,CH3}$ = 1.5 Hz) H-6 (T); 7.21-7.11, 6.73 - 6.69 (m, 28 H) arom; 6.26 (dd, 1H) H-1'(A); 6.09 (t, 1H) H-1'(T); 6.06 (t, 1H) H-1'(T); 5.35 (m, 1H) H-3'(A); 4.25-4.14 (m, 2H) H-4'(A) and H-3'(T); 4.10-4.07 (m, 1H) H-3'(T); 4.09 (s, 2H) CH_2, 3.95 (s, 2H) CH_2; 3.90 - 3.80 (m, 2H) H-4'(T); 3.69 (s, 3H) OCH_3; 3.65 - 3.49 (m, 5H) H-5', H-5''(T), (T), and H-5'(A); 3.37 (dd, 1H) H-5''(A); 3.17 (m, 1H) H-2'(A); 2.49 (m, 1H) H-2''(A); 2.42- 2.28 (m, 2H) H-2'(T); 2.21 - 1.96 (m, 2H) H-2''(T); 1.84 (m, 6H) 2x CH_3. IR (nujol): ν_{max} = 2092 cm^{-1}. UV (EtOH): λ_{max} = 268 nm; λ_{min} = 242 nm.

5'-Amino-thymidinylacetamido-[3'(O)→5'(C)]-N^6-MMTr-5',2'-dideoxyadenosine (17): 5'-Azido-thymidinylacetamido-[3'(O)→5'(C)]-N^6-MMTr-5',2'-didedoxyadenosine **15a** (0.44 g, 0.53 mmol) was reduced using a procedure described for the preparation of **14** to give **17** (0.333 g, 80 %) after silica gel column chromatography. ^{1}H-NMR ($CDCl_3$): 8.03 (s, 1H) H-8 (A); 7.99 (s, 1H) H-2 (A); 7.35-7.20 (m, 13 H) arom, H-6 (T); ; 6.79 (d, 2H) arom; 6.33 (t, 1H, $J_{1',2'}$ = 6.4 Hz, $J_{1',2''}$ = 6.7 Hz) H-1'(A); 6.08 (t, 1H) H-1'(T); 4.42 (m, 1H, $J_{2',3'}$ = 4.0 Hz, $J_{2'',3'}$ = 3.5 Hz) H-3'(A); 4.09 (m, 2H) H-3'(T), H-4'(A); 4.04 (s, 1H) CH_2; 4.01 (s, 1H) CH_2; 3.88 (m, 1H) H-4'(T); 3.78 (s, 3H) OCH_3; 3.72 (m, 1H) H-5'(A); 3.52 (m, 1H) H-5''(A); 2.87-2.73 (m, 2H) H-5'(T), H-5''(T); 2.45-2.31 (m, 2H) H-2', H-2''(A); 2.26-2.18 (m, 2H) H-2', H-2''(T); 1.90 (s, 3H) CH_3. R_f (B) = 0.18. UV (EtOH): λ_{max} = 273 nm; λ_{min} = 243.

5'-Azido-thymidinylacetamido-[3'(O)→5'(C)]-5',2'-dideoxyadenosine (16): 5'-Azido-thymidinylacetamido-[3'(O)→5'(C)]-N^6-MMTr-5',2'-dideoxyadenosine **15a** (0.11 g, 0.132 mmol) was taken up in dry nitromethane (0.5 ml) and 0.1 M $ZnBr_2$ (3-5 ml) solution was added. The reaction mixture was stirred for 22 h at ~20 °C. After addition of aq. NH_3, all the volatile matters were evaporated and the solid residue was purified on silica gel column to give **16** (0.043 g, 68 %). ^{1}H-NMR (D_2O, 270 MHz): 8.21 (s, 1H) H-8 (A); 8.15 (s, 1H) H-2 (A); 7.34 (q, 1H, $J_{H6,CH3}$ = 1.1 Hz) H-6 (T); 6.35 (t, 1H, $J_{1',2'}$ = 6.3 Hz, $J_{1',2''}$ = 6.7 Hz) H-1'(A); 5.96 (dd, 1H, $J_{1',2'}$ = 8.0 Hz, $J_{1',2''}$ = 6.3 Hz) H-1'(T); 4.52 (m, 1H, $J_{2',3'}$ = 6.3 Hz, $J_{2'',3'}$ = 4.9 Hz, $J_{3',4'}$ = 4.1 Hz) H-3'(A); 4.15 (m, 1H, $J_{4',5'}$ = 6.3 Hz, $J_{4',5''}$ = 4.1 Hz) H-4'(A); 4.06 (m, 1H, $J_{2',3'}$ = 6.1 Hz , $J_{2'',3'}$ = 3.4 Hz, $J_{3',4'}$ = 4.1Hz) H-3'(T); 3.94 (m, 1H, $J_{4',5'}$ = 4.0 Hz, $J_{4',5''}$ = 5.6 Hz) H-4'(T); 3.94 (s, 2H) CH_2; 3.60 (dd, 1H, $J_{5',5''}$ = 14.4 Hz) H-5'(A); 3.47 (dd, 1H) H-5''(A); 3.46 (dd, 1H, $J_{5',5''}$ = -13.4 Hz) H-5'(T); 3.37 (dd, 1H) H-5''(T); 2.82 (m, 1H, $J_{2',2''}$ = 14.2 Hz) H-2'(A); 2.56 (ddd, 1H) H-2''(A); 2.21 (m, 1H, $J_{2',2''}$ = 14.0) H-2''(T); 2.14 (m, 1H) H-2'(T). ^{13}C-NMR (D_2O): 173.52 (C=O); 167.52 (C-4, T); 156.49 (C-6, A); 153.34 (C-2, A); 152.64 (C-2, T); 150.10 (C-4, A); 141.27 (C-8, A); 138.26 (C-6, T); 119.98 (C-5, A); 112.84 (C-5, T); 86.58 (C-1', T); 85.75 (C-4', A); 85.09 (C-1', A); 83.62 (C-4', T); 81.76 (C-3', T); 72.67 (C-3', A); 69.32 (CH_2); 53.18 (C-5', T); 41.23 (C-5', A); 39.40 (C-2', A); 36.45 (C-

2′, T); 12.71 (CH_3). R_f (B) = 0.49. UV (H_2O): λ_{max} = 258nm, λ_{min} = 228nm. IR(nujol): ν_{max} = 2092 cm^{-1}. MS (FAB^+): calc. for $(M+H)^+$ 558.2173, found 558.2143.

5′-Amino-thymidinylacetamido-[3′(O)→5′(C)]-5′,2′-dideoxyadenosine (18): 5′-Azido-thymidinylacetamido-[3′(O)→5′(C)]-5′,2′-dideoxyadenosine **16** (0.043 g, 0.082 mmol) was reduced as described for the preparation of **14** giving the target compound (0.034 g, 83%) after partitionating between dichloromethane and water. ^{1}H-NMR.(D_2O): 8.17 (s, 1H) H-8 (A); 8.06 (s, 1H) H-2 (A); 7.27 (q, 1H, $J_{H\text{-}6,CH3}$ = 1.2 Hz) H-6 (T); 6.28 (t, 1H, $J_{1',2'}$ = 6.6 Hz, $J_{1',2''}$ = 5.9 Hz) H-1′(A) ; 5.87 (t, 1H, $J_{1',2'}$ = 7.8 Hz, $J_{1',2''}$ = 6.6 Hz) H-1′(T); 4.50 (m, 1H, $J_{2',3'}$ = 4.9 Hz, $J_{2'',3'}$ = 6.3 Hz, $J_{3'4'}$ = 4.7 Hz) H-3′(A); 4.13 (m, 2H, $J_{2',3'}$ = 6.2 Hz, $J_{2'',3'}$ = 3.6 Hz, $J_{4',5'}$ = 6.0 Hz, $J_{4',5''}$ = 4.3 Hz) H-3′(T), H4′(A); 4.06 (m, 1H, $J_{4',5'}$ = 3.9 Hz, $J_{4',5''}$ = 9.0 Hz) H-4′(T); 3.57 (dd, 1H, $J_{5',5''}$ = 14.4 Hz) H-5′(A); 3.44 (dd, 1H) H-5′′(A); 3.42 (s, 1H) CH_2, 3.40 (s, 1H) CH_2; 3.20 (dd, 1H, $J_{5',5''}$ = 13.3 Hz) H-5′(T); 3.06 (dd, 1H) H-5′′(T); 2.77 (m, 1H, $J_{2',2''}$ = 14.1 Hz) H-2′(A); 2.54 (ddd, 1H) H-2′′(A); 2.25-2.19 (m, 2H, $J_{2',2''}$= 14.2 Hz) H-2′,H2′′ (T); 1.75 (d, 3H) CH_3.^{13}C-NMR (D_2O): 173.20 (C=O); 167.44 (C-4, T); 156.42 (C-6, A); 153.88 (C-2, A); 152.49 (C-2, T); 149.78 (C-4, A), 141.13 (C-8, A); 139.50 (C-6, T); 119.89 (C-5, A); 112.46 (C-5, T); 88.33 (C-1′, T); 85.90 (C-4′, A); 85.12 (C-1′, A); 81.86 (C-3′,C4′, T); 72.74 (C-3′, A); 69.36 (CH_2); 42.88 (C-5′, T); 41.37 (C-5′, A); 39.52 C-2′, A); 35.90 (C-2′, T); 12.58 (CH_3). R_f (D) = 0.17.UV (H_2O): λ_{max} = 260 nm, λ_{min} = 231 nm. MS (FAB^+): calc. for $(M+H)^+$ 532.2268, found 532.2271.

5′-Azido-N^4-MMTr-cytidinylacetamido-[3′(O)→5′(C)]-thymidinylacetamido-[3′(O)→5′(C)]-N^6-MMTr-5′,2′-dideoxyadenosine (19a): 5′-Amino-thymidinylacetamido-[3′(O)→5′(C)]-N^6-MMTr-5′,2′-dideoxyadenosine **17** (0.152 g, 0.19 mmol) and 5′-Azido-3′-O-carboxymethyl-N^4-MMTr-5′,2′-dideoxycytidine (sodium salt) **6a** (0.11 g, 0.19 mmol) were dried, condensed as described for the preparation of **13** giving the target compound (0.158 g, 61 %). ^{1}H-NMR ($CDCl_3$) : 7.94 (s, 1H) H-8 (A); 7.90 (s, 1H) H-2 (A); 7.26-7.05 (m, 25H) arom, H-6 (C); 7.23 (d, 1H, $J_{H\text{-}6,CH3}$ = 1.4 Hz) H-6 (T); 6.78-6.75 (d, 2H) arom; 6.72-6.69 (d, 2H) arom; 6.24 (t, 1H, $J_{1',2'}$ = 6.7 Hz, $J_{1',2''}$ = 6.1 Hz) H-1′(A); 6.10 (t, 1H, $J_{1',2'}$ = 8.2 Hz, $J_{1',2''}$ = 5.6 Hz) H-1′ (C); 5.84 (t, 1H) H-1′(T); 5.10 (d, 1H, $J_{H\text{-}5,H\text{-}6}$ = 7.6 Hz) H-5 (C); 4.36 (m, 1H, $J_{2',3'}$ = 6.3 Hz, $J_{2'',3'}$ = 3.6 Hz) H-3′(A); 4.09-3.86 (m, 5H) H-3′ (C), H-3′ (T), H4′ (C,T,A); 3.71 (s, 3H) OCH_3; 3.69 (s, 3H) OCH_3, 3.63-3.34 (m, 10 H) H-5′, H-5′′(C,T,A), 2 x CH_2; 2.72 (m, 1H, $J_{2',2''}$= 13.6 Hz) H-2′(A); 2.58-2.50 (m, 2H) H-2′, H-2′′(C); 2.36 (ddd, 1H) H-2′′(A); 2.28-2.20 (m, 2H) H-2′, H-2′′(T); 1.81 (d, 3H) CH_3 (T). R_f (A) = 0.37. UV (EtOH): λ_{max} = 275 nm; 283 (sh); λ_{min} = 245 nm. IR (nujol): ν_{max} = 2093 cm^{-1}.

5′-Azido-N^2-MMTr-guanosinylacetamido-[3′(O)→5′(C)]-thymidinylacetamido-[3′(O)→5′(C)]-N^6-MMTr-5′,2′-dideoxyadenosine (19b): 5′-Amino-thymidinylacetamido-[3′(O)→5′(C)]-N^6-MMTr-5′,2′-dideoxyadenosine **17** (0.152 g, 0.19 mmol) and 5′-Azido-3′-O-carboxymethyl-N^2-MMTr-5′,2′-dideoxyguanosine **6b** were condensed as described for **13**. Usual work-up and column chromathographic purification gave the target compound (0.2 g, 75 %). ^{1}H-NMR ($CDCl_3$): 7.91 (s, 1H) H-8 (A); 7.90 (s, 1H) H-2 (A); 7.47-7.03 (m, 29H) arom, H6 (T); 6.75-6.69 (m,4H) arom; 6.23 (t, 1H, $J_{1',2'}$ = 7.1 Hz, $J_{1',2''}$ = 6.2 Hz) H-1′ (A); 5.85 (t, 1H) H-1′(T); 5.64 (t, 1H) H-1′ (G); 4.36 (m, 1H) H-3′(A); 4.07-3.63 (m, 5H) H-4′(A), H-3′(T), H-4′(T), H-3′(G), H-4′(G); 3.90 (d, 2H) CH_2; 3.78 (d, 2H) CH_2; 3.65 (s, 3H) OCH_3; 3.63 (s, 3H) OCH_3, 3.55-3.37 (m, 6H) H5′, H5′′ (G,T,A); 2.77 (m, 1H) H-2′(A); 2.36 (m, 1H) H2′′ (A); 2.27-2.23 (m, 2H) H-2′, H2′′ (T); 1.98-1.67 (m,2H) H-2′, H2′′ (G); 1.81 (s, 3H) CH_3. R_f (A) = 0.15. UV (EtOH): λ_{max} = 268, 275 nm; λ_{min} = 245 nm. IR (nujol): ν_{max} = 2090 cm^{-1}.

5′-Azido-cytidinylacetamido-[3′(O)→5′(C)]-thymidinylacetamido-[3′(O)→5′(C)]-5′,2′-dideoxyadenosine (20a): Compound **19a** (0.07 g, 0.5 mmol) was dried and dissolved in 0.1 M solution of $ZnBr_2$ in dry nitromethane (4 ml) and the reaction mixture was stirred at ~20 °C for 2 days. The reaction was quenched by addition of aqueous ammonia. Volatile matters were removed from the reaction mixture and the residue was purified on a silica gel column to give **20a** (0.027 g, 70%)). ^{1}NMR. (D_2O): 8.24 (s, 1H) H-8 (A); 8.18 (s, 1H) H-2 (A); 7.71 (d, 1H, $J_{H\text{-}5,H\text{-}6}$ = 7.7 Hz) H-6 (C); 7.32 (d, 1H, $J_{H\text{-}6,\ CH3}$ = 1.2 Hz) H-6 (T); 6.36 (t, 1H, $J_{1',2'}$ = 6.3 Hz, $J_{1',2''}$ = 6.7 Hz) H-1′(A); 6.11 (dd, 1H, $J_{1',2'}$ = 7.7 Hz, $J_{1',2''}$= 6.1 Hz) H-1′(C); 6.02 (d, 1H) H-5 (C); 5.93 (dd, 1H, $J_{1',2'}$ = 7.8 Hz, $J_{1',2''}$= 6.1 Hz) H-1′(T); 4.51 (m, 1H, $J_{2',3'}$ = 6.3 Hz, $J_{2'',3'}$ = 4.9 Hz) H-3′(A); 4.20-4.12 (m, 3H) H-4′(A), H-3′,H-4′(C); 4.08-3.90 (m, 2H) H-3′, H-4′(T); 4.02 and 4.01 (s, 2H) CH_2; 3.97 and 3.96 (s, 2H)

CH_2; 3.62-3.45 (m, 4H) H-5',H-5''(C, A); 3.37-3.34 (d, 2H) H-5', H-5''(T); 2.80 (m, 1H, $J_{2',2''}$ = 14.3 Hz) H-2'(A); 2.55 (ddd, 1H) H-2''(A); 2.46 (m, 1H) H-2''(C); 2.31-2.09 (m, 3H) H-2' (C), H-2', H-2''(T); 1.80 (d, 3H) CH_3. ^{13}C-NMR (D_2O + CD_3OD): 173.36 (2 x C=O); 167.40 (C-4 T); 153.61 (C-2, A); 152.50 (C-2, T); 149.98 (C-4, A); 142.99 (C-6, C); 141.37 (C-8 A); 138.60 (C-6, T); 120.14 (C-5, A); 112.60 (C-5, T); 97.29 C-5, C); 87.64 (C-1', C); 86.97 (C-1', T); 85.92 and 85.14 (C-1'A, C-4'A); 83.82 and 83.26 (C-4' T, C-4' C); 81.88 (C-3' T, C-3' C), 72.69 (C-3', A); 69.33 and 69.28 (C=O); 53.30 (C-5' C); 41.86 and 41.35 (C-5' T, A); 39.55 (C-2' A); 37.39 (C-2' C); 36.33 (C-2' T); 12.69 (CH_3 T). R_f (D) = 0.33. UV (H_2O): λ_{max} = 264nm; λ_{min} = 232nm. IR (nujol): ν_{max} = 2092 cm^{-1}. MS (FAB^+): calc. for $(M+H)^+$ 824.3188, found 824.3156.

5'-Amino-cytidinylacetamido-[3'(O)→5'(C)]-thymidinylacetamido-[3'(O)→5'(C)]-5',2'-dideoxyadenosine (22a): Compound **19a** (0.0371g, 0.027 mmol) was dissolved in 80% aq. acetic acid (1 ml) and refluxed at 100 °C for 5 min. The reaction mixture was evaporated several times with toluene and dry pyridine, then taken up in dry pyridine. Ph_3P (0.008 g, 0.03 mmol) was added when the reaction mixture was chilled down to 0 °C and stirred for 1 h at 0 °C and at RT overnight. Methanolic NH_3 was added (1 ml) with stirring for 1 day. All the volatile matters were evaporated and the residue was dissolved in water, extracted with CH_2Cl_2 and diethylether. The water phase was liophylized giving the product (0.019 g , 95%).^{1}H-NMR (D_2O): 8.27 (s, 1H) H-8 (A); 8.18 (s, 1H) H-2 (A); 7.57 (d, 1 H, $J_{H-5,H-6}$ = 7.5 Hz) H-6 (C); 7.35 (d, 1H, $J_{H-6,CH3}$ = 1.0 Hz) H-6 (T); 6.39 (t, 1H $J_{1',2'}$ = 6.3 Hz, $J_{1',2''}$ = 6.6 Hz) H-1'(A); 6.07 (t, 1H) H-1' (C); 5.96 (dd, 1H, $J_{1',2'}$ = 7.4 Hz, $J_{1',2''}$ = 6.3 Hz) H-1' (T); 5.95 (d, 1H) H-5 (C); 4.57 (m, 1H, $J_{2',3'}$ = 6.3 Hz, $J_{2'',3'}$ = 4.9 Hz) H-3'(A); 4.30-4.23 (m, 2H) H-3', H4' (C); 4.21-4.18 (m, 1H) H-4' (A); 4.15-3.96 (m, 2H) H-3', H-4' (T); 4.09 (s, 2H) CH_2; 4.02 (s, 2H) CH_2; 3.64 (dd, 1H, $J_{4',5'}$= 6.3 Hz, $J_{5',5''}$ = 14.4 Hz) H-5' (A); 3.55 (dd, 1H, $J_{4',5''}$= 4.3 Hz) H-5''(A); 3.42-3.39 (m, 2H) H-5',H-5''(T); 3.31 (dd, 1H, $J_{4',5'}$ = 3.6 Hz, $J_{5',5''}$ = 13.4 Hz) H-5'(C); 3.18 (dd, 1H, $J_{4',5''}$ = 8.5 Hz) H-5''(C); 2.86 (m, 1H, $J_{2',2''}$ = -14.0 Hz) H-2'(A); 2.62 (ddd, 1H) H-2''(A); 2.52-2.37 (m, 2H) H-2', H-2''(C); 2.31 (ddd, 1H, $J_{2'',3'}$ = 3.1 Hz, $J_{2',2''}$ = 14.2 Hz) H-2''(T); 2.20 (m, 1H, $J_{2',3'}$ = 6.4 Hz) H-2'(T); 1.81 (d, 3H) CH_3 T. ^{13}C-NMR (D_2O + CD_3OD): 173.32 and 173.25 (2 x C=O); 167.46 (C-4 T); 156.77 (C-6 A); 150.02 (C-4 A); 142.44 (C-6 C); 141.20 (C-8 A); 138.57 (C-6 T); 112.59 (C-5 T); 97.35 (C-5 C); 89.73 (C-1'C); 87.00 (C-1' T); 85.86 (C-1'A); 85.04 (C-4'A); 83.27 (C-4' T); 82.16 (C-3', C-4'C); 81.89 (C-3' T); 72.68 (C-3'A); 69.40 and 69.30 (C=O); 42.95 (C-5'C); 41.88 and 41.35 (C-5'T, C); 39.47 (C-2' A); 36.52 and 36.29 (C-2'T, C); 12.74 (CH_3 T). R_f (D) = 0.05. UV (H_2O): λ_{max} = 264 nm; λ_{min} = 232 nm. MS (FAB^+): calc. for $(M+H)^+$ 798.3284, found 798.3284.

5'-Azido-guanosinylacetamido-[3'(O)→5'(C)]-thymidinylacetamido [3'(O)→5'(C)]-5',2'-dideoxyadenosine (20b): Compound **19b** (0.20 g, 0.142 mmol) was dissolved in 80% aq. acetic acid (1 ml) and refluxed for 5 min at 100 °C. The reaction mixture was evaporated and coevaporated several times with toluene followed by water. The solid residue was partitioned between hot water, methanol and dichloromethane. The aqueous phase was evaporated until the product crystallized out (0.048 g, 80 %). ^{1}H-NMR (D_2O): 8.29 (s, 1H) H-8 (A); 8.22 (s, 1H) H-2 (A); 7.95 (s, 1H) H-8 (G); 7.41 (d, 1H, $J_{H-6,CH3}$ = 0.9 Hz) H-6 (T); 6.42 (t, 1H) H-1'(A); 6.23 (t, 1H) H-1'(G); 6.02 (t, 1H) H-1'(T); 4.55 (m, 1H) H-3'(A); 4.38 (m, 1H) H-3'(G); 4.31 (m, 1H)H-4'(G); 4.17 (m, 1H) H-4'(A); 4.13-3.99 (m, 2H) H-3', H-4'(T); 4.13 (s, 2H) CH_2; 4.04 (s, 2H) CH_2; 3.70-3.45 (m, 6H) H-5', H-5'' (G,T,A); 2.93-2.79 (m, 2H) H-2' (A), H-2' (G); 2.64-2.54 (m, 2H) H-2' (A), H-2'(G); 2.36 (m, 1H) H-2''(T); 2.22 (m, 1H) H-2'(T); 1.87 (s, 3H) CH_3. ^{13}C-NMR.(D_2O + CD_3OD): 173.34 (C=O); 173.17 (C=O); 167.20 (C-4, T); 156.28 (C-6,A); 155.10 (C-2, G); 154.01 (C-2, A); 152.75 (C-2, T); 150.03 (C-4, A); 141.24 (C-8, A); 138.59, 138.44 (C-6,T; C-8, G); 112.55 (C-5, T); 87.18 (C-1', T); 86.10 (C-4', A); 85.34, 85.13, 84.55 (C-1'(G), C-1'(A) & C-4'(G)); 83.36 (C-4', T); 82.33 (C-3', T); 81.97 (C-3', G); 72.85 (C-3', A); 69.37 (CH_2); 69.53 (CH_2); 53. 34 (C-5', G); 41.98, 41.54 (C-5', T, A); 39.80 (C-2', A); 36.68, 36.50 (C-2', G, T); 12.68 (CH_3, T). R_f (B) = 0.35. UV (H_2O): λ_{max} = 258 nm; λ_{min} = 229 nm. IR (nujol): ν_{max} = 2092 cm^{-1}. MS (FAB^+): calc. for $(M+H)^+$ 864.3250, found 864.3268.

5'-Amino-N^2-MMTr-guanosinylacetamido-[3'(O)→5'(C)]-thymidinylacetamido-[3'(O)→5'(C)]-N^6-MMTr-5',2'-dideoxyadenosine (21): Compound **19b** (0.20 g, 0.142 mmol) was reduced using a procedure described for **9**, subsequently, a silica gel column chromatography gave the target compound (0.188 g, 96 %).1H-NMR ($CDCl_3$ + CD_3OD): 7.97 (s, 1H) H-8 (A); 7.94 (s, 1H) H-2 (A); 7.34-7.08 (m,) arom, H-8 (G), H-6 (T); 6.79-6.67 (m, 4H) arom; 6.28 (t, 1H) H-1'(A); 5.84 (t, 1H) H-1'( ), 5.49 (s, 1H) H-1'( ); 4.45 8 m,1H) H-3'(A); 4.16-3.60 (m, 5H) H4'(A), H-3'(G, T), H-

4′(G,T); 3.75 (s, 2H) CH_2; 3.66 (s, 2H) CH_2; 3.42 (s, 6H) 2 x OCH_3; 3.54-2.95 (m, 6H) H-5′, H5′′ (G, T, A); 1.78 (s, 3H) CH_3. R_f (B) = 0.2. UV (EtOH): λ_{max} = 268, 275 nm; λ_{min} = 245 nm.

5′-Amino-guanosinylacetamido-[3′(O)→5′(C)]-thymidinylacetramido-[3′(O)→5′(C)]-5′,2′-dideoxyadenosine (22b): Compound **21** (0.112 g, 0.081 mmol) was detritylated as described for compound **19b**, which upon extraction gave the target compound (0.055 g, 88%). ^{1}H-NMR (D_2O, 270 MHz): 8.31 (s, 1H) H-8 (A); 8.20 (s, 1H) H-2 (A); 7.88 (s, 1H) H-8 (G); 7.39 (s, 1H) H-6 (T); 6.42 (t, 1H) H-1′(A); 6.24 (dd, 1H, $J_{1',2'}$ = 8.2 Hz, $J_{1',2''}$ = 6.2 Hz) H-1′(G); 6.01 (dd, 1H, $J_{1',2'}$ = 7.6 Hz, $J_{1',2''}$ = 6.5 Hz) H-1′(T); 4.63 (m, 1H) H-3′(A); 4.55-4.47 (m, 2H) H-3′, H-4′(G); 4.29 (m, 1H) H-4′(A); 4.26-4.14 (m, 2H) H-3′, H-4′(T); 4.26 (s, 2H) CH_2; 4.10 (s, 2H) CH_2; 3.77-3.37 (m, 6H) H-5′, H-5′′(G,T,A); 3.04-2.80 (m, 2H) H-2′(G,A); 2.77-2.61 (m, 2H) H-2′(G, A); 2.37 (ddd, 1H, $J_{2'',3'}$ = 3.13 Hz, $J_{2',2''}$ = -14.1 Hz) H-2′′(T); 2.25 (m, 1H) H-2′(T); 1.87 (s, 3H) CH_3. ^{13}C-NMR (D_2O + CD_3OD): 173.19 (2 x C=O); 167.14 (C-4, T); 159.81 (C-6, G); 156.42 (C-6, A); 154.90 (C-2, G); 153.95 (C-2, A); 152.35 (C-2, T); 149.93 (C-4, A); 141.16 (C-8, A); 139.08, 138.53 (C-6,T; C-8, G); 112.53 (C-5, T); 87.14 (C-1′, T); 86.02; 85.97 (C-1′, G; C-4′, A); 85.17 (C-1′, A); 83.31; 82.50 (C-4′, T; G); 81.92 (C-3′, G, T); 72.79 (C-3′, A); 69.49 (CH_2); 69.33 (CH_2); 42.87 (C-5′, G); 41.95, 41.50 (C-5′, T, A); 39.65 (C-2′, A); 36.34, 36.16 (C-2′, G, T); 12.62 (CH_3, T). R_f (D) = 0. UV (H_2O): λ_{max} = 258 nm; λ_{min} = 233 nm. MS (FAB$^+$): calc. for $(M+H)^+$ 838.3345, found 838.3343.

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