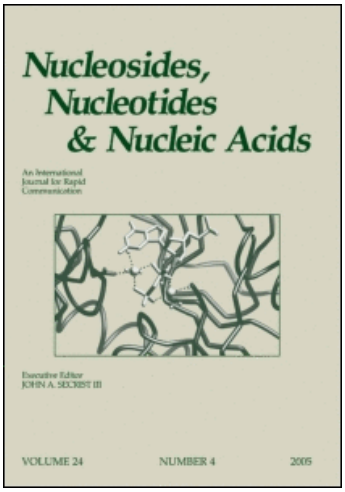

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Synthesis of 1-Deazaadenosine Analogues of (2'→5') ApApA

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SYNTHESIS OF 1-DEAZAADENOSINE ANALOGUES OF (2'→5') ApApA

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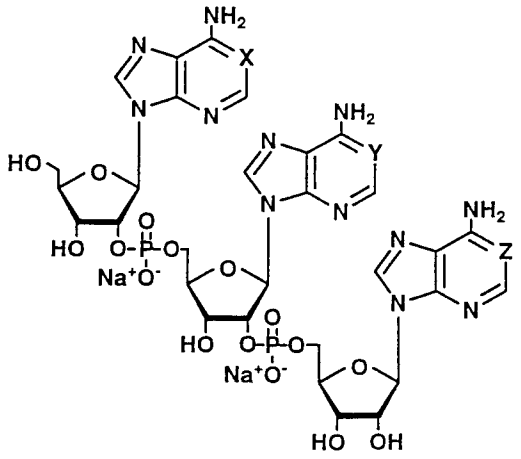
ABSTRACT: Synthesis of (2'→5')ApApA analogues containing 1-deazaadenosine at different positions is described (**32-34**). The approach used the phosphotriester methodology in solution and utilized 3'-*O*-benzoylated derivatives of the N^6-protected 5'-*O*-monomethoxytrityl-1-deazaadenosine as starting material.

INTRODUCTION

The 5'-triphosphates of 2'→5'-oligoadenylates [ppp(A2'p)$_n$5'A, n≥2; mainly trimers; 2'→5'A] are implicated at least in one of the mechanisms of antiviral actions of interferon (for review, see[1]). The 2'→5'A binds to and subsequently activates a latent endoribonuclease (RNase L) resulting in the cleavage of virus mRNA and eventually in the inhibition of virus replication. A wide variety of 2'→5'A analogues



	X	Y	Z
A (32)	C	N	N
B (33)	N	N	C
C (34)	N	C	N

Dedicated to Prof. Y. Mizuno on the occasion of his 75th birthday

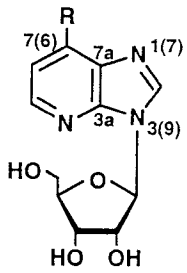
have been synthesized in order to establish the binding sites of the 2'→5'A molecule to RNase L. Thus, the replacement of adenosine by inosine[2-4] or 1,N^6-etheno-adenosine[5] resulted in dramatic decrease of biological activities. From these data, it has been reasoned that the adenine 6-amino group and possibly its N^1 nitrogen atom may be of crucial importance for the binding to and the activation of RNase L[3,4]. In order to study the relative importance of nitrogen-1 as binding site of each of the adenine bases of (2'→5')pppApApA in biochemical events the synthesis of those trimers was initiated in which one of the nucleotide fragment is sequentially replaced by 1-deazaadenosine (c^1A). In this paper the synthesis of 1-deazaadenosine analogues (A-C) of (2'→5') ApApA is described.

RESULTS AND DISCUSSION

Oligodeoxyribonucleotides containing 1-deaza-2'-deoxyadenosine have recently been prepared by solid-phase synthesis to generate Hoogsteen-duplex DNA[6]. The solid-phase oligoribonucleotides using P(III)-chemistry has also been established[7,8]. For the synthesis of the (2'→5') trimers phosphotriester methodology was chosen[9].

NMR-Data and Glycosyl Bond Conformation of 1-Deazaadenosine.

1-Deazaadenosine (**1a**)[10,11] was prepared either chemically by the very efficient method of Mizuno[12,13] (cf. Ref.[14]) or obtained by microbiological transglycosylation[15]. During the course of this work, various 6-substituted 1-deazapurine ß-D-ribofuranosides, *viz.*, 6-nitro (**1b**), 6-chloro (**1c**)[13], and 6-benzamido (**2**) were synthesized. All these compounds were characterized by ^{1}H- and ^{13}C-NMR spectra (Tables 1, 2, and 3). The assignment of most resonances was made by 2D [^{1}H,^{13}C] correlation spectra and in doubtful cases, e.g., of OH-5' in c^1A, resolved by homo-decoupling experiments.



1a: R = NH_2 (c^1A)
1b: R = NO_2
1c: R = Cl

Systematic numbering; purine numbering in parenthesis.

TABLE 1. ^{1}H-NMR Chemical Shifts (δ), Multiplicities, and Coupling Constants (J) [Hz] of 1-Deazaadenosine Derivatives[a].

Compd.	H-6[b] H-1[c]	H-5[b] H-2[c]	H-2[b] H-8[c]	H-1'	H-2'	H-3'	H-4'	H-5'/H-5''
1a	6.39d	7.78d	8.25s	5.87d	4.71m	4.13m	3.98m	3.67/3.56m
1b	8.04d	8.69d	9.11s	6.15d	4.61m	4.21m	4.00m	3.70/3.60m
1c	7.52d	8.36d	8.95s	6.09d	4.65m	4.21m	4.00m	3.70/3.62m
2	7.89d	8.35d	8.69s	6.07d	4.72m	4.21m	4.02m	3.71/3.60m
2*	7.89d	8.35d	8.64s	6.08d	4.71g	4.20q	4.02m	3.71/3.61m
3*	7.80d	8.24d	8.60s	6.04d	4.69m	4.19m	4.00m	3.72/3.58dd
4	6.40d	7.82d	7.85s	5.78d	5.52g	4.40d	4.36s	3.92/3.70m
5	5.75d	7.60d	8.11s	5.96d	4.70t	4.48m	4.32d	3.47/3.20dd
6	5.68d	7.52d	7.72s	5.74d	5.02m	4.26d	4.20s	3.82/3.52dd
7	8.28d	8.44d	8.22s	6.08d	4.84t	4.20d	4.27m	3.28/3.15m
8	8.20d	7.97d	8.23s	6.06d	4.80m	4.40m	4.45m	3.47/3.24dd
9	-	-	8.23s	6.68d	6.51t	6.15m	4.62m	3.61d
10*	8.12d	8.34d	8.66s	6.52d	6.18m	4.66m	4.26m	-
11*	-	8.30d	8.67s	6.22d	5.36m	5.73m	4.25m	-
12	-	-	-	6.64d	6.49t	6.11m	4.61m	3.62d
13	-	-	-	6.49d	6.13t	5.00m	4.34m	3.58/3.46dd
14	-	-	-	6.17d	5.18t	5.70dd	4.60m	3.55/3.38dd
15*	-	-	8.41s	5.64d	6.74m	6.18t	4.56m	-
16*	-	-	8.39s	6.08d	5.29m	5.64m	4.40m	-
18*	-	8.24d	8.80s	6.42d	5.96m	5.80m	4.42m	-
23	-	-	-	6.06d	6.40m	6.40m	4.62s	4.05m

Compd.	δ and J(OH-2')	δ and J(OH-3')	δ and J(OH-5')	Ph	NH
1a	5.37 d (6.4)	5.14 d (4.1)	6.06 s	-	6.49 s
1b	5.59 d (5.6)	5.27 d (4.6)	5.13 t (5.4)	-	-
1c	5.54 d (5.9)	5.25 d (4.8)	5.19 t (5.5)	-	-
2	5.53 d (6.1)	5.40 d (4.7)	5.38 t (5.6)	7.50-8.07 m	10.48 s
2*	5.63 d (6.1)	5.25 d (4.7)	5.41 q (5.5)	7.54-8.08 m	7.49 s
3*	5.50 d (5.2)	5.24 d (4.0)	5.41 s	-	10.13 s
7	-	-	-	7.72-8.06 m	9.32 s
10*	-	5.82 d (6.0)	-	6.80-8.09 m	10.58 s
11*	6.01 d (6.5)	-	-	6.80-8.10 m	10.52 s
16*	5.98 d (6.5)	-	-	6.76-8.08 m	-
18*	-	-	-	6.78-8.08 m	9.90 s

[a]Spectra were measured in $CDCl_3$ rel. to TMS; the compounds with asterisk were measured in DMSO-d_6. [b]Systematic numbering. [c]Purine numbering.

TABLE 2. $^{1}H,^{1}H$-Coupling Constants [Hz] and Chemical Shifts (δ) of 1-Deazaadenosine Derivatives[a].

Compd.	J(1,2)	J(1',2')	J(2',3')	J(3',4')	J(4',5')	J(5',5")
1a	5.6	6.4	6.0	1.0		
1b	5.3	5.2	4.8	4.0		
1c	5.2	5.5	5.4	3.4		
2*	5.5	5.9	5.5	3.0		
2*	5.5	5.9	5.5	3.0	3.5	11.0
3	5.8	6.0	5.2	3.2	3.5	12.0
4	5.5	7.5	5.0	<1.0	<1.0	12.5
5	6.0	6.5	6.5	<1.0	4.0	11.0
6	5.5	7.0	5.0	<1.0	<1.0	12.5
7	5.5	5.5	5.5	2.0	4.0	11.0
8	5.8	6.0	4.6	b)	4.0	11.0
9*	b)	6.0	6.0	3.0	3.5	
10*	5.5	4.0	5.0	5.5		
11	5.5	5.5	6.0	4.5	4.5	
12	b)	6.0	6.0	3.5	3.0	
13	b)	5.0	5.0	4.0	3.5	10.0
14*	b)	6.2	6.0	2.0	3.0	11.0
15*	b)	5.5	5.0	5.0	4.0	
16*	b)	6.3	6.3	5.0	5.0	
18	5.5	5.5				
23	b)	5.0		<1.0	4.5	

[a] See a) of Table 1. [b] Not determined owing to overlap.

TABLE 3. ^{13}C-NMR Chemical Shifts (δ) of 1-Deazapurine ß-D-Ribofuranosides[a,b]

Compd.	C-1[b] C-6[c]	C-2[b] C-5[c]	C-4[b] C-3a[c]	C-5[b] C-7a[c]	C-6[b] C-7[c]	C-8[b] C-2[c]
1a	102.4	144.2	146.5	123.9	147.5	140.1
1b	112.2	144.8	150.3	127.2	143.8	147.8
1c	116.8	144.7	133.5	133.2	147.4	144.6
2[d]	109.2	144.8	147.2	131.2	137.4	142.6

Compd.	C-1'	C-2'	C-3'	C-4'	C-5'
1a	88.7	72.9	71.2	86.3	62.2
1b	88.0	73.9	70.0	85.5	61.0
1c	87.8	73.6	70.3	85.6	61.2
2[d]	88.0	73.9	70.6	85.7	61.6

[a] In DMSO-d_6 rel. to TMS. [b] Purine numbering. [c] Systematic numbering. [d] In $CDCl_3$ rel. to TMS.

The ^{1}H-NMR-data for **1a** and **1c** correlate well with those previously published[13,16]. Assignments of quaternary ^{13}C aglycone signals C-4, C-5, and C-6 (purine numbering) are based on the cumulative data for para-substituted pyridine derivatives[17] and are in excellent agreement with the data for related 2'-deoxy-ß-D-ribofuranosides[18].

From Table 1 it is noteworthy that the OH-5' resonance signal of **1a** is unusually deshielded and falls outside the range observed for other 6-substituted 1-deazapurine ribosides. This deshielding may result from an intramolecular 5'-OH···N^3-hydrogen bonding and consequently from the *syn*-conformation at the glycosyl bond. The *syn*-conformation of compound **1a** has already been detected by Mizuno et al.[16] using NOE-spectroscopy. We have also used ^{1}H-NMR NOE difference spectroscopy[19] for a more detailed conformational analysis with respect to the *syn/anti* equilibrium of different 1-deazapurine ribosides (Table 4).

As it can be seen the NOE data reveal a strong dependence of the N-glycosyl bond conformation upon the nature of the 6-substituent. A linear correlation of the *syn*-conformer population *vs.* the σ_{para} Hammett constants[20] for the substituents was found[19].

According to that, the c^{1}A adopts about 95% *syn* conformation (*cf.* Ref.[16]). Electron-donating 6-amino groups do facilitate the formation of intramolecular hydrogen bond between 5'-hydroxyl group and N^3-nitrogen atom. There is also a good correlation between the NOE on H-2' upon saturation of H-8 ($f_{2'8}$) as well as $f_{3'8}$ and the *syn/anti* equilibrium. This coincides with the observation[21] that the rather narrow *syn* region may be populated by the S-conformation of the furanose ring. It has been suggested that the *syn* conformation at the glycosyl bond is usually

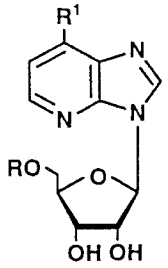
TABLE 4. NOE Data of 1-Deazapurine-ß-D-ribofuranosides Upon Irradiation of H-8.[a,b]

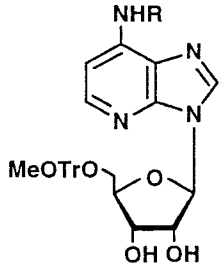
Compd.	NOE (%) H-1'	H-2'	H-3'	Compd.	NOE (%) H-1'	H-2'	H-3'
1a	10.3	2.5	-	**1c**	5.9	4.5	1.3
1b	4.4	4.7	1.5	**2**	6.4	3.9	0.9

[a]DMSO-d$_6$ at 23°C; [b]Purine numbering.

accompanied by a C-2'-*endo* (S) pucker of the furanose ring (for a more detailed discussion, see Ref.[22]). Indeed, the comparison of calculated[23] and experimental $^3J[H,H]$ coupling constants of furanose ring protons clearly shows that within the series of 6-substituted 1-deazapurine ribosides, *viz.*, NO_2, Cl, NHBz, and NH_2, the population of C-2' *endo* (S) conformation is increased.

Protecting Groups.- In order to synthesize the c^1A-building blocks for the preparation of the desired trimers, various protecting groups for 6-amino residue were introduced: (i) Benzoylation of c^1A using the protocol of transient protection[24] afforded the benzoate **2**.





	R	R^1
2	H	NHBz
3	H	NHNPEOC
4	H	N=CHN$(CH_3)_2$
5	MeOTr	NHMeOTr
6	MeOTr	NH_2

7: R = Bz
8: R = NPEOC

(ii) In a similar way reaction with 2-(4-nitrophenyl)ethoxycarbonyl (NPEOC) chloride[25] gave compound **3**. (iii) The dimethylaminomethylidene derivative **4** was prepared according to reference[26]. (iv) The reaction of c^1A with monomethoxytrityl chloride resulted in the formation of two compounds: the N^7,5'-O-bis-monomethoxytrityl derivative **5** (70% yield) and the 5'-O-monoprotected **6** (15% yield). Monomethoxytritylation of **4** gave a complex reaction mixture the separation of which by silica gel column chromatography proved to be difficult and, therefore, **4** was not further investigated.

In order to make the correct choice for the deblocking conditions of the protected trimers, model studies with compounds **2**, **3**, and **5** were performed. Deprotection of **2** in conc. aq. ammonia for 20 h at room temperature failed. Treatment of **2** with conc. aqueous ammonia at 60°C for 6 h resulted in complete debenzoylation yielding

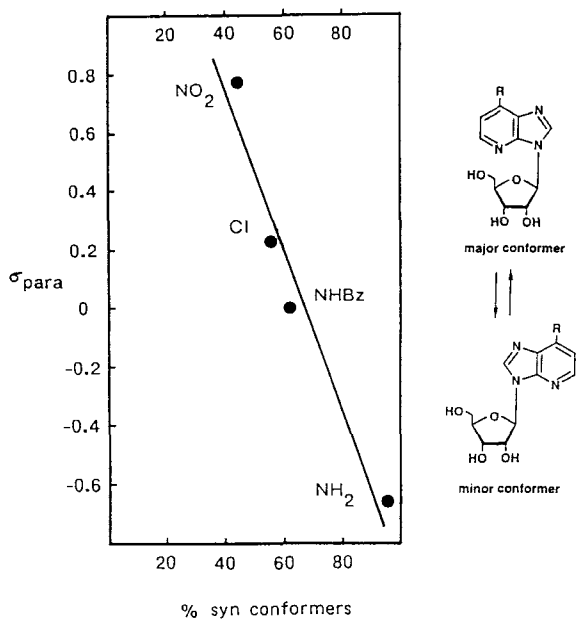
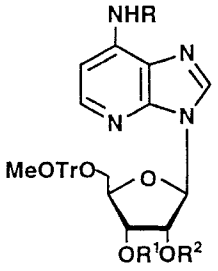


FIG. 1 Syn conformer populations of 1-deazapurine nucleosides as a function of Hammett constants of exocyclic substituents.

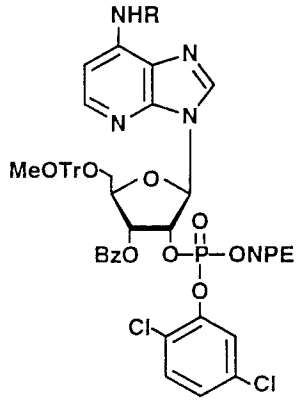
c^1A as the only reaction product. The half-life time of **2** with respect to deprotection under these conditions was found to be 125 min. The attempts of the deprotection of **2** with hydrazine hydrate in glacial acetic acid/pyridine[27] resulted in the formation of side products besides the expected c^1A that prevented this method of deblocking from further exploitation in oligomer synthesis. Next, treatment of the NPEOC derivative **3** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in pyridine at room temperature for 16 h resulted in complete deprotection affording c^1A as the only reaction product (*cf.* Refs. 25, 28). Finally, treatment of the bis-protected compound **5** with 2% p-toluenesulfonic acid in a mixture of CH_2Cl_2/MeOH (7:3, v/v) at room temperature for 1.5 h gave quantitatively the inital nucleoside **1a**.

Building Block and Oligonucleotide Synthesis.- It was previously shown that the 3'-*O*-benzoyl protection in combination with 5'-*O*-monomethoxytritylation and the 2-(4-nitrophenyl)ethyl (NPE) group for phosphate protection is effective for (2'→5')

oligonucleotide synthesis[9,29,30]. The same strategy was studied for the synthesis of monomeric building blocks as well as the oligomers. Monomethoxytritylation of **2** and **3** gave the corresponding derivatives **7** and **8** in high yields. The method of selective 3'-*O*-benzoylation[9] using freshly destilled benzoyl chloride (1.2 eq.) in acetonitrile in the presence of Et_3N and DMAP was now carried out on compounds **7**, **8**, and **5** to give the respective 3'-*O*-benzoylated derivatives in the following yields: **11** (41%), **14** (58%), and **16** (53%). FAB mass spectra revealed the correct $(M + H)^+$ peaks (see Exp. Part).

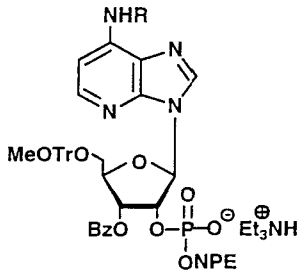


	R	R^1	R^2
9	Bz	Bz	Bz
10	Bz	H	Bz
11	Bz	Bz	H
12	NPEOC	Bz	Bz
13	NPEOC	H	Bz
14	NPEOC	Bz	H
15	MeOTr	Bz	Bz
16	MeOTr	Bz	H

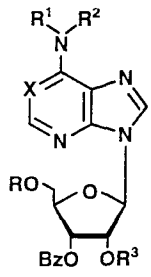


17 : R = Bz
19 : R = NPEOC
21 : R = MeOTr

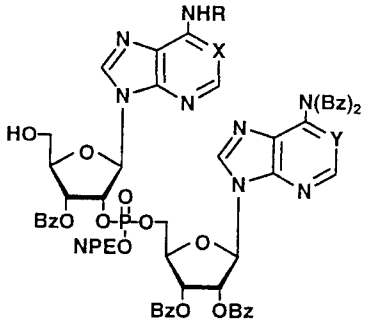
Then compounds **11**, **14**, and **16** were transformed to the corresponding phosphotriesters **17**, **19**, and **21**, and to the phosphodiesters **18**, **20**, and **22** under standard conditions[30]. Benzoylation of **10** and subsequent detritylation gave the 2'-terminal c^1A building block **23**. The synthesis of analogous adenosine building blocks **24a** and **24b** was described in ref.[30].



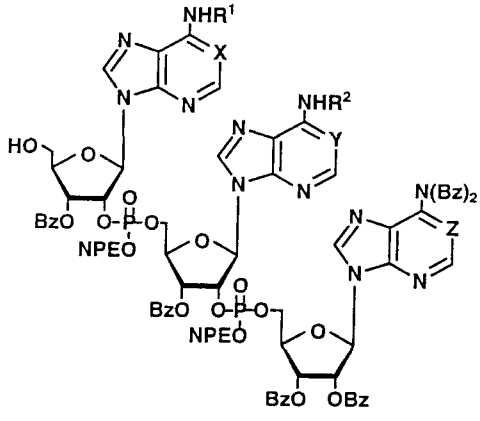
18 : R = Bz
20 : R = NPEOC
22 : R = MeOTr



	R	R^1	R^2	R^3	X
23	H	Bz	Bz	Bz	C
24a	MeOTr	Bz	H	NPEOP(O)O⁻	N
24b	H	Bz	Bz	Bz	N



	R	X	Y
25	Bz	N	C
26	NPEOC	C	N
27	Bz	N	N

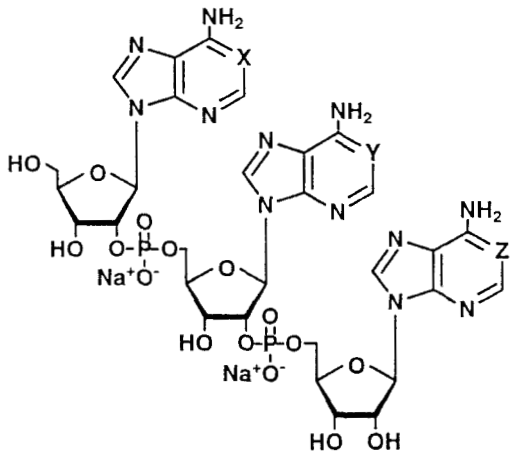


	R^1	R^2	X	Y	Z
28	Bz	Bz	C	N	N
29	H	Bz	C	N	N
30	Bz	Bz	N	N	C
31	Bz	NPEOC	N	C	N

The assembly of the trimers was performed by condensing (TPS-Cl/N-methylimidazole, 1:3, as an activating agent; $CHCl_3$ as a solvent[31,32]) the monomeric building blocks in different successions and combinations in order to synthesize the 5'-detritylated dimers **25**, **26** (see Exp. Part), and **27**. Next, the dimers thus obtained were reacted with the phosphodiesters **18**, **22**, or **24a** followed by detritylation to afford the partially blocked trimers **28**-**31**. In the case of **29**, detritylation (2% p-toluenesulfonic acid in CH_2Cl_2/MeOH, 7:3, v/v, at room

temperature for 2h) resulted in the formation of side products which seemed to be mainly chain-cleaved compounds[33].

Deprotection of **28** and **30** was performed by treatment with DBU followed by concentrated aqueous ammonia (40°C; 2h). Complex reaction mixtures were obtained from which the desired 2'→5'-trimers, $A_2(c^1A)$ (**32**) and $(c^1A)A_2$ (**33**) were isolated as Na^+ salts in 8 and 17% yield.



	X	Y	Z
32	C	N	N
33	N	N	C
34	N	C	N

An attempt to use the benzoate **18** for the synthesis of $A(c^1A)A$ (**34**) (condensation of **18** with **24b** and the dimer obtained with **24a**) resulted in the isolation of the trimer (**34**) in very low yield. Thus, exposure to concentrated ammonia at 40°C resulted in internucleotide cleavage (*cf.*[34]) especially in this latter case. Deprotection of **29** was performed by treatment with DBU, concentrated ammonia, and subsequent chromatography to afford the trimer $A_2(c^1A)$ (**32**) in 17% yield. Similar deprotection of **31** followed by chromatographic purification gave the trimer $A(c^1A)A$ (**34**) in 80% yield. The biological testing of the trimers **32-34** is in progress.

EXPERIMENTAL SECTION

General. Low resolution FAB mass spectra were obtained on a Kratos MS50TC (England) spectrometer from samples dissolved in DMSO with glycerol as matrix under Xe atoms bombardment (6-8 KeV). The UV-spectra were recorded on a Specord UV-VIS spectrophotometer (Carl Zeiss, Germany). ^{1}H-NMR spectra were recorded on a AC 250 spectrometer (Bruker, Germany) with tetramethylsilane as an internal standard (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet).

^{1}H-NMR spectra of trimers **32**, **33**, and **34** were measured in D_2O at 23°C; the chemical shifts (δ) and coupling constants (J) are reported in ppm rel. to external TMS and Hz, respectively. NOE Spectra were measured on an AC-250 spectrometer (Bruker, Germany) as described in ref.[19]. Thin layer chromatography (TLC) was carried out on silica gel F 1500 LS 254 plates (Schleicher & Schull, Germany). Solvent systems used: EtOAc-hexane, 1:1 (A); EtOAc-hexane, 7:5 (B); $CHCl_3$-MeOH, 24:1 (C); $CHCl_3$-MeOH, 19:1 (D); $CHCl_3$-MeOH, 9:1 (E); $CHCl_3$-MeOH, 4:1 (F); $CHCl_3$-MeOH-Et_3N, 9:0.2:0.8 (G); 2-PrOH-conc. NH_3-H_2O, 17:1:2 (H), n-BuOH-HOAc-H_2O, 5:3:2 (I). Column chromatography was performed on silica gel L 40/100 μ and 100/400 μ (Chemapol, Czechoslovakia). Melting points were determined with a Boethius (Germany) apparatus and are uncorrected. The solutions of compounds in organic solvents were dried with anhydr. Na_2SO_4 for 4h. The reactions were performed at room temperature, unless stated otherwiese. The nomenclature of oligonucleotides follows the (2'→5')-direction throughout the manuscript.

7-(Benzoylamino)-N^3-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (2).
Trimethylsilyl chloride[10,11] (1.14 mL, 9.01 mmol) was added to a solution of 1-deazaadenosine **1a** (0.32 g, 1.20 mmol) in anh. pyridine (3 mL) and the reaction mixture was stirred for 15 min. Benzoyl chloride (0.42 mL, 3.6 mmol) was then added and stirring was continued for 2h. The reaction mixture was cooled to 0°C and water (1.2 mL, 0°C) was added under stirring. After 5 min, concentrated aquaeous ammonia (2.4 mL) was added and stirring was continued for 30 min. The reaction mixture was evaporated and the residue was partitioned between water (30 mL) and $CHCl_3$ (30 mL). The organic layer was dried, evaporated, and the residue was crystallized from water to give colorless crystals (0.39 g, 87%); m.p. 228-230°C; R_f 0.4 (E); UV (MeOH) λ_{max} nm (lg ϵ): 282 (4.35). FAB MS m/z 371 $(M + H)^+$.

7-{[2-(4-Nitrophenyl)ethoxycarbonyl]amino}-N^3-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (3).
Trimethylsilyl chloride (0.63 g, 5.8 mmol) was added to a solution of 1-deazaadenosine **1a**, (0.22 g, 0.83 mmol) in anh. pyridine (2 mL) and the reaction mixture was stirred for 2h. Then, 2-(4-nitrophenyl)ethylchloroformate[25] (0.45 g, 1.96 mmol) was added and stirring was continued for 1h at 0°C and another 2h at room temperature. The reaction mixture was cooled to 0°C and water (0.78 mL, 0°C) was added under stirring. After 5 min, concentrated aqueous ammonia (1.56 ml) was added and stirring was continued for 30 min. The reaction mixture was

evaporated and the product was purified by silica gel column chromatography (70 ml). Elution was performed with a linear gradient (0→10%, v/v, 600 mL) of MeOH in $CHCl_3$. The fractions containing the product were collected, evaporated, and crystallized from EtOH to give colorless crystals (0.29 g, 77%); m.p. 193-195°C; R_f 0.5 (D); UV (MeOH) λ_{max} nm (lg ϵ): 267 (4.47), 276sh (4.42). FAB MS m/z 460 $(M + H)^+$.

7-{[(Dimethylamino)methylidene]amino}-N^3-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (4).

To a solution of 1-deazaadenosine **1a** (0.02 g, 0.075 mmol) in anh. DMF (0.4 ml), N,N-dimethylformamide dimethyl acetal (0.1 ml) was added and the mixture was kept for 4 days. The reaction mixture was evaporated, the residue was dissolved in $CHCl_3$ (0.2 mL), and precipitated in hexane (20 mL). The resulting precipitate was collected by filtration and dried *in vacuo* to give colorless **4** (0.02 g, 83%); m.p. 84-86°C, R_f 0.4 (F); UV (MeOH) λ_{max} nm (lg ϵ): 309 (4.54). FAB MS m/z 322 $(M + H)^+$.

Reaction of 1-Deazaadenosine with Monomethoxytrityl Chloride.

A solution of 1-deazaadenosine **1a** (0.11 g, 0.41 mmol), monomethoxytrityl chloride (0.21 g, 0.68 mmol) and 4-dimethylaminopyridine (6 mg, 0.052 mmol) in anh. pyridine (2 mL) was stirred for 12 h and then poured into a mixture of ice and water (150 mL) under vigorous stirring. The resulting precipitate was collected by filtration, washed with water, and dried *in vacuo*. The products (**5** and **6**) were purified on a silica gel (70 mL) column eluting with a linear gradient of methanol in EtOAc (0→5%, v/v; 1 L).

7-(Methoxytriphenylmethylamino)-N^3-[5-*O*-(methoxytriphenylmethyl)]-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (5).

Compound **5** (0.22 g, 70%) isolated as an amorphous powder; m.p. 131-133°C, R_f 0.6 (C). UV (MeoH) λ_{max} nm (lg ϵ): 270 (4.51), 287 (4.54). FAB MS m/z 811, 273 $(M + H)^+$.

7-Amino-N^3-[5-*O*-(4-methoxytriphenylmethyl)-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (6).

Compound **6** (0.03 g, 15%) isolated as an amorphous powder; m.p. 210-214°C; R_f 0.3 (D); UV (MeOH) λ_{max} nm (lg ϵ): 270 (3.32), 287 (3.41). FAB MS m/z 539, 273 $(M + H)^+$.

7-(Benzoylamino)-N^3-[5-*O*-(4-methoxytriphenylmethyl)-(ß-D-ribofuranosyl]-3H-imidazo[4,5-b]pyridine (7).

A solution of **2** (0.35 g, 0.95 mmol) and 4-methoxytrityl chloride (0.38 g, 1.23 mmol) in anh. pyridine (7 mL) was stirred for 12 h and then poured into a mixture of ice and water (300 mL) under vigorous stirring. The resulting precipitate was collected by filtration, washed with water, and dried *in vacuo*. The product was purified on a silica gel column (100 mL) eluting with a linear MeOH gradient (0→10%, v/v; 1 L) in $CHCl_3$ to give **7** as an amorphous powder (0.47 g, 79%; m.p. 108-111°C; R_f 0.4 (D). UV (MeOH) λ_{max} nm (lg ϵ): 230 (4.66), 280 (4.66). FAB MS m/z 643, 273, 369, 353 $(M + H)^+$.

7-{[2-(4-Nitrophenyl)ethoxycarbonyl]amino}-N^3-[5-*O*-(4-methoxytriphenylmethyl)-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (8).

Compound **8** was prepared as described above, starting from 0.24 g (0.52 mmol) of **3** to give a colorless solid (0.29 g, 78%); m.p. 102-105°C (EtOH); R_f 0.8 (D). UV (MeOH) λ_{max} nm (lg ϵ): 267 (4.56), 276sh (4.50). FAB MS m/z 732, 273 $(M + H)^+$.

Benzoylation of 7-(Benzoylamino)-N^3-[5-*O*-(4-methoxytriphenylmethyl)-(ß-D-ribofuranosyl)]-3H-imidazo[4,5-b]pyridine (7) with Benzoyl Chloride.

To the stirred solution of compound **7** (0.32 g, 0.5 mmol) in a mixture of anh. MeCN (7.5 mL), Et_3N (0.9 mL, 6.47 mmol) and 4-dimethylaminopyridine (DMAP) (4 mg, 0.04 mmol), freshly distilled benzoyl chloride (0.08 g, 0.069 mL, 0.6 mmol) was added. After stirring for 30 min, the reaction mixture was poured into a mixture of ice and water (200 mL) under vigorous stirring. After the ice was melted, the resulting precipitate was collected by filtration, washed with water, and dried *in vacuo*. The products (**9-11**) were chromatographed on a silica gel column (70 mL) eluting with a linear EtOAc gradient (20→60%, v/v; 500 mL) in hexane.

7-(Benzoylamino)-N^3-[(2,3-*O*-dibenzoyl)-5-*O*-(4-methoxytriphenymethyl)]-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (9).

The fractions containing **9** were pooled, evaporated, dissolved in EtOAc, and precipitated from hexane to give a solid (0.04 g, 10%); m.p. 94-98°C; R_f 0.3 (A); UV (MeOH) λ_{max} nm (lg ϵ): 230 (4.80), 279 (4.52).

7-(Benzoylamino)-N^3-[(2-*O*-benzoyl)-5-*O*-(4-methoxytriphenylmethyl)-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (10).

Compound **10** was isolated as colorless solid (0.06 g, 15%); m.p. 109-114°C; R_f 0.2

(A); UV (MeOH) λ_{max} nm (lg ϵ): 230 (4.64), 280 (4.45)]. FAB MS m/z 747, 273, 457 $(M + H)^+$.

7-(Benzoylamino)-N^3-[(3-*O*-benzoyl)-5-O-(4-methoxytriphenylmethyl)]-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (11).
Compound **11** was obtained as colorless solid (0.15 g, 41%); m.p. 113-116°C; R_f 0.2 (A); UV (MeOH) λ_{max} nm (lg ϵ): 230 (4.64), 280 (4.45). FAB MS m/z 747, 273 $(M + H)^+$.

Benzoylation of 7-{[2-(4-Nitrophenyl)ethoxycarbonyl]amino}-N^3-{[5-*O*-(4-methoxytriphenylmethyl)]-(ß-D-ribofuranosyl)}-3H-imidazo[4,5-b]pyridine (8).
The reaction was performed as described above, starting from 0.22 g (0.30 mmol) of **8** giving compounds **12-14**.

7-{[2-(4-Nitrophenyl)ethoxycarbonyl]amino}-N^3-[(3-*O*-benzoyl)-5-*O*-(4-methoxytriphenylmethyl)-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (14).
Compound **14** was isolated as colorless solid (0.16 g, 58%); m.p. 106-108°C, R_f 0.3 (B); UV (MeOH) λ_{max} nm (lg ϵ): 232 (4.43), 267 (4.44), 276sh (4.39). FAB MS m/z 836 $(M + H)^+$.

7-{[2-(4-Nitrophenyl)ethoxycarbonyl]amino}-N^3-[2-*O*-(benzoyl)-5-*O*-(4-methoxytriphenylmethyl)-(ß-D-ribofuranosyl)]-3H-imidazo[4,5-b]pyridine (13).
Colorless solid (30 mg, 11%); m.p. 109-116°C; R_f 0.4 (B); UV (MeOH) λ_{max} nm (lg ϵ): 232 (4.44), 267 (4.45), 277sh (4.40). FAB MS m/z 836, 273 $(M + H)^+$.

7-{[2-(4-Nitrophenyl)ethoxycarbonyl]amino}-N^3-[2,3'-di-*O*-(benzoyl)-5-*O*-4-methoxytriphenylmethyl)-(ß-D-ribofuranosyl)]-3H-imidazo[4,5-b]pyridine (12).
Colorless solid (12 mg, 4%); m.p. 97-100°C; R_f 0.5 (B); UV (MeOH) λ_{max} nm (lg ϵ): 230 (4.63), 267 (4.51), 276sh (4.46. FAB MS m/z 940, 273 $(M + H)^+$.

Benzoylation of 7-(4-Methoxytriphenylmethylamino)-N^3-[5-*O*-(4-methoxytriphenylmethyl)-(ß-D-ribofuranosyl)]-3H-imidazo[4,5-b]pyridine (5).
The reaction and workup was performed as described above, starting from 96 mg (0.12 mmol) of **5** yielding compounds **15** and **16** as amorphous solids.

7-(4-Methoxytriphenylmethylamino)-N^3-[5-*O*-(4-methoxytriphenylmethyl)-3-*O*-(benzoyl)-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (16).
Compound **16** was isolated as colorless solid (57 mg, 53%); m.p. 117-121°C; R_f 0.4

(B); UV (MeOH) λ_{max} nm (lg ϵ): 270 (4.52), 287 (4.55). FAB MS m/z 915, 273 (M + H)$^+$.

7-(4-Methoxytriphenylmethylamino)-N^3-[5-*O*-(4-methoxytriphenylmethyl)-2,3-di-*O*-(benzoyl)-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (15).
Colorless solid (20 mg, 17%); m.p. 114-117°C; R_f 0.7 (B). FAB MS m/z 1019 (M + H)$^+$.

7-(Benzoylamino)-N^3-{3-*O*-(benzoyl)-2-*O*-[2,5-dichlorophenyl-2-(4-nitrophenylethyl)-phosphato]-[5-*O*-(4-methoxytriphenylmethyl)]-(ß-D-ribofuranosyl)}-3H-imidazo[4,5-b]pyridine (17).
Phosphorylation of **11** (0.15 g, 0.2 mmol) with 2,5-dichlorophenyldi(triazolido)phosphate followed by treatment with 2-(4-nitrophenyl)ethanol was carried out as described earlier[30] affording the triester **17** as an amorphous powder (0.15 g, 75%). R_f 0.2 (B); UV (MeOH) λ_{max} nm (lg ϵ): 230 (4.95), 277 (4.80).

7-{[2-(4-Nitrophenyl)ethoxycarbonyl]amino}-N^3-{2-*O*-[2,5-dichlorophenyl-2-(4-nitrophenylethyl)-phosphato]-[5-*O*-(4-methoxytriphenylmethyl)]-(ß-D-ribofuranosyl)}-3H-imidazo[4,5-b]pyridine (19).
Similarly, starting from 0.08 g (0.095 mmol) of **14**, 0.09 g (78%) of the triester **19** was obtained as an amorphous powder. R_f 0.3 (B); UV (MeOH) λ_{max} nm (lg ϵ): 274 (4.58).

7-(4-Methoxytriphenylmethylamino)-N^3-{3-*O*-(benzoyl)-2-*O*-[2,5-dichlorophenyl-2-(4-nitrophenylethyl)-phosphato]-[5-*O*-(4-methoxytriphenylmethyl)]-(ß-D-ribofuranosyl)}-3H-imidazo[4,5-b]pyridine (21).
Similarly, starting from 57 mg (0.062 mmol) of **16**, 64 mg (80%) of the triester **21** was obtained as an amorphous powder. R_f 0.4 (B); UV (MeOH) λ_{max} nm (lg ϵ): 270 (4.55), 287 (4.56).

7-(Benzoylamino)-N^3-{3-*O*-(benzoyl)-5-*O*-(4-methoxytriphenylmethyl)-2-*O*-[2-(4-nitrophenylethyl)-phosphato]-(ß-D-ribofuranosyl)}-3H-imidazo[4,5-b]pyridine, Triethylammonium Salt (18).
Treatment of the triester **17** (0.11 g, 0.058 mmol) with p-nitrobenzaloxime followed by work up as described earlier[30] afforded the diester **18** as an amorphous powder (0.09 g, 85%). R_f 0.3 (G); UV (MeOH λ_{max} nm (lg ϵ): 230 (4.81), 278 (4.77).

7-[2-(4-Nitrophenyl)ethoxycarbonylamino]-N^3-{3-*O*-benzoyl-5-*O*-(4-methoxytriphenylmethyl)-2-*O*-[2-(4-nitrophenylethyl)-phosphato]-(ß-D-ribofuranosyl)}-3H-imidazo[4,5-b]pyridine, Triethylammonium Salt (20).
Similarly, starting from the triester **19** (0.09 g, 0.07 mmol), the diester **20** was obtained as an amorphous powder (0.064 g, 81%). R_f 0.3 (G); UV (MeOH) λ_{max} nm (lg ϵ): 267 (4.58), 276sh (4.56)].

7-(4-Methoxytriphenylmethylamino)-N^3-{5-*O*-(4-methoxytriphenylmethyl)-2-*O*-[2-(4-nitrophenylethyl)-phosphato]-(ß-D-ribofuranosyl)}-3H-imidazo[4,5-b]pyridine, Triethylammonium Salt (22).
In a similar way, starting from the triester **21** (64 mg, 0.05 mmol), the diester **22** was obtained as an amorphous powder (47 mg, 82%). R_f 0.4 (G); UV (MeOH) λ_{max} nm (lg ϵ): 270 (4.53), 287 (4.56).

7-(Dibenzoylamino)-N^3-[2,3-*O*-(dibenzoyl)-(ß-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (23).
Benzoylation of **10** (0.124 g, 0.17 mmol) followed by detritylation as described earlier[30] afforded a colorless solid (0.17 g, 66%); m.p. 190-191°C (EtOH); R_f 0.4 (B); UV (MeOH) λ_{max} nm (lg ϵ): 230 (4.68), 270 (4.42). FAB MS m/z 683 $(M + H)^+$.

Synthesis of Dimers 25-27 and Trimers 28-31.
Synthesis of the dimers **25-27** and subsequently of the trimers **28-31** was performed by standard methodology consisting of (i) condensation of phosphodiesters **18**, **20**, or **24a** with 2'-terminal building blocks **23** or **24b** and subsequent detritylation, and (ii) condensation of individual dimers obtained with phosphodiesters **18**, **20**, **22**, or **24a** and subsequent detritylation. To a solution of the appropriate phosphodiester (0.11 mmol) and the 2'-terminal building block or dimer (0.1 mmol) in $CHCl_3$ (0.5 mL), 2,4,6-triisopropylbenzenesulfonyl chloride (0.3 mmol) and N-methylimidazole (0.9 mmol) were added and the reaction mixture was stirred for 30 min. The reaction mixture was poured into hexane (200 mL), the resulting precipitate was collected by filtration, dried *in vacuo*, and then dissolved in 2% solution of p-toluenesulfonic acid in CH_2Cl_2/MeOH (7:3, v/v; 15 mL). After stirring for 5 min (in the case of **29**, reaction time was 120 min), the solution was diluted with $CHCl_3$ (15 mL) and washed with 0.05 M phosphate buffer, pH 7.0 (2 x 30 mL). The organic layer was separated, dried, evaporated, and purified by silica gel column chromatography (60 mL). The product was eluted with a linear methanol gradient (0-5%, v/v; 2 x 300

mL) in chloroform. Appropriate fractions were collected, evaporated to a volume of 2 mL and precipitated into hexane (200 mL). The compounds were obtained as amorphous solids.

25: 71%; R_f 0.35 (C); UV (MeOH) λ_{max} nm (lg ε): 232sh (4.86), 276 (4.76).
26: 96%; R_f 0.34 (C); UV (MeOH) λ_{max} nm (lg ε): 267 (4.66), 277sh (4.63).
28: 70%; R_f 0.22 (C); UV (MeOH) λ_{max} nm (lg ε): 233 (4.89), 277 (4.79).
29: 66%; R_f 0.19 (C); UV (MeOH) λ_{max} nm (lg ε): 232 (4.84), 276 (4.72).
30: 67%; R_f 0.23 (C); UV (MeOH) λ_{max} nm (lg ε): 232sh (4.96), 276 (4.82).
31: 90%; R_f 0.21 (C); UV (MeOH) λ_{max} nm (lg ε): 267 (4.75), 277sh (4.74).

Deprotection of the trimers **28-31** was performed by the sequence deblocking of the phosphate group and subsequent treatment with methanol, saturated with ammonia at 0°C or conc. aqueous ammonia.

(2'→5')-Adenylyl-(2'→5')-adenylyl-(2'→5')-1-deazaadenosine, Sodium Salt (32). Procedure a: The trimer **28** (0.11 g, 0.054 mmol) was dissolved in 0.5 M solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in pyridine (16 mL) and stirred for 2h. After the addition of 1 M solution of HOAc in pyridine (8 mL), the mixture was evaporated and then coevaporated with pyridine (2 x 5 mL). The residue was dissolved in conc. ammonia (25 mL), kept at 40°C for 2h and evaporated. The residue was chromatographed on a DEAE-Sephadex A-25 (HCO_3^- form, 50 mL) column using a linear gradient of aqueous triethylammonium hydrogen carbonate (0.001→ 0.6 M; 500 mL, each). The product-containing fractions were collected, evaporated and precipitated as Na^+ salt[35] to give the trimer **32** (5 mg, 8%). R_f 0.3 (H); 0.07 (I); hypochromicity: 14%. ^{1}H-NMR (D_2O, purine numbering): 8.13, 8.05, 7.93, 7.90, and 7.72 (s, 5H, adenine H-8 and H-2, and H-8 of c^1A), 7.31 (d, 1H, J = 6.0 Hz, H-2 of c^1A), 6.03 (d, 1H, J = 4.5 Hz, H-1' of Np-), 5.96 (d, 1H, J = 6.0 Hz, H-1 of c^1A), 5.82 (d, 1H, J = 3.0 Hz, H-1' of -pNp-), 5.78 (d, 1H, J = 4.5 Hz, H-1' of -pN).

Procedure B: Compound **29** (60 mg, 0.031 mmol) was treated with DBU in pyridine (9 mL, 2h) and then with saturated methanolic ammonia (15 mL, 20h); isolation as above afforded the trimer **32** (6 mg, 17%).

1-Deazaadenylyl-(2'→5')-adenylyl-(2'→5')-adenosine, Sodium Salt (33). In a similar way, compound **30** (0.17 g, 0.08 mmol) was treated with DBU in pyridine (30 ml, 2h) and then with conc. ammonia (30 ml, 50°C, 5h); chromatography followed by precipitation as above gave the trimer **33** (16 mg, 17%). R_f 0.3 (H); 0.07 (I); hypochromicity: 22%. ^{1}H-NMR (D_2O, purine numbering):

8.09, 7.99 (2H), 7.87, and 7.69 (s, 5H, adenine H-8 and H-2, and H-8 of c^1A), 7.87 (d, 1H, J = 6.0 Hz, H-2 of c^1A), 6.54 (d, 1H, J = 6.5 Hz, H-1 of c^1A), 6.08 (d, 1H, J = 4.0 Hz, H-1' of Np-), 5.94 (d, 1H, J = 3.5 Hz, H-1' of -pNp-), 5.88 (d, 1H, J = 4.5 Hz, H-1' of -pN).

Adenylyl-(2'→5')-1-deazaadenylyl-(2'→5')-adenosine, Sodium Salt (34). Compound **31** (55 mg, 0.026 mmol) was treated with DBU in pyridine (20 mL) for 16h and worked up further as described for **29** to give the trimer **34** (23 mg, 80%). R_f 0.3 (H); 0.07 (I); hypochromicity: 27%. ^{1}H-NMR (D_2O, purine numbering): 8.16, 8.06, 8.00, 7.94, and 7.69 (s, 5H, adenine H-8 and H-2, and H-8 of c^1A), 7.64 (d, 1H, J = 6.0 Hz, H-2 of c^1A), 6.18 (d, 1H, J = 6.0 Hz, H-1 of c^1A), 6.07 (d, 1H, J = 4.0 Hz, H-1' of Np-), 6.00 (d, 1H, J = 3.5 Hz, H-1' of -pNp-), 5.78 (d, 1H, J = 3.5 Hz, H-1' of -pN).

Determination of Hypochromicity. To a solution containing 0.05 M Tris-HCl, 5 mM $MgCl_2$ and a specific amount of the trimer in the form of Na-salt (1 mL, optical density within 0.4-0.5; pH 8.8), the solution (50 μL) of snake venom phosphodiesterase (1 μg; Boehringer Mannheim, Germany) in the same buffer was added and the reaction mixture was incubated at 38°C until the absorbance reached the constant value. Hypochromicity was calculated as described in ref.[36].

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