Nucleotides

Part LVII [1])

Synthesis of Phosphoramidite Building Blocks of 2′-Amino-2′-deoxyribonucleosides: New Compounds for Oligonucleotide Synthesis

by **Beate Greiner** and **Wolfgang Pfleiderer***

Fakultät für Chemie, Universität Konstanz, Postfach 5560, D-78434 Konstanz

The chemical synthesis of 2′-amino-2′-deoxyribonucleosides of uracil, cytosine, adenine, and guanine, and their conversion into suitably protected 3′-phosphoramidite building blocks **35**–**40** for oligonucleotide synthesis are described. The aglycone and the 2′-amino functions were protected using the 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) group. The synthesis of the 3′-*O*-succinyl (3′-*O*-(3-carboxypropanoyl))-substituted starting nucleoside **41** is described and its behavior examined in solution and on solid phase with regard to an anticipated migration during 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) deprotection. Oligonucleotides were prepared using the new building blocks, and their hybridization properties were studied by UV-melting techniques.

1. Introduction. – In recent years, antisense oligomers have emerged as a promising new therapeutic paradigm. The basic requirements for effective antisense oligomers are sufficiently strong hybridization with the RNA sense strand, stability against enzymatic degradation, and sufficient cellular uptake [2–4]. The search for derivatives which fulfill these requirements has led to the introduction of a huge variety of modifications in the phosphodiester backbone, at the bases, and at the sugar moieties of oligomers.

Modification of the 2′-position in oligomers is especially interesting, as increased thermal stability of duplex structures with RNA have been observed for 2′-fluoro or 2′-*O*-alkyl derivatives [5][6]. The first poly(2′-amino-2′-deoxyuridylic acid) and poly-(2′-amino-2′-deoxycytidylic acid) were synthesized enzymatically by *Eckstein* and co-workers [7], showing increased resistance to enzymes. Besides, it was observed that poly-(2′-amino-2′-deoxyuridylic acid) did not form a duplex with poly(rA), and the duplex of poly(2′-amino-2′-deoxycytidylic acid)/poly(rI) was less stable than the unmodified duplex. The effects of 2′-amino substitution of nucleosides on oligomer-hybridization properties have not been sufficiently studied and are more interesting for further investigations, also against the background of catalytic ribozymes [8–10].

We report here the synthesis of suitably protected 2′-amino-2′-deoxyribonucleotide phosphoramidite building blocks and their use in the solid-phase synthesis of 2′-amino-modified oligomers using the npe/npeoc strategy [11][12]. The aglycones and the 2′-amino function were protected using the 2-(4-nitrophenyl)ethyl (npe) and the 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) groups which proved to be very efficient for the protection of amino groups in the 3′- [13–15] and 5′-position of nucleosides [16] as well

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as protection of the exocyclic amino groups of the bases in the synthesis of oligoribonucleotides [17], oligoarabinonucleotides [18], and 2′-amino-2′-deoxyarabino oligonucleotides [19].

2. Syntheses. – The key building blocks for the synthesis of npe/npeoc-protected 2′-amino-2′-deoxycytidine, -guanosine, and -uridine (*Scheme 1*) were the 5′-*O*-(4-methoxytrityl) (MeOTr)- and 5′-*O*(4,4′-trityl)(($MeO)_2$Tr)-protected 2′-azido-2′-deoxyuridine derivates **3** and **4**, respectively, which were synthesized using a slightly modified literature procedure [20]. Thus, 5′-*O*-(MeOTr)- and 5′-*O*-(($MeO)_2$Tr)-2,2′-anhydrouridine (**1** and **2**, resp.) were reacted with LiN_3 in the dark [21–24] to give the corresponding 2′-azido-2′-deoxy derivates **3** and **4**, respectively (*Scheme 1*).

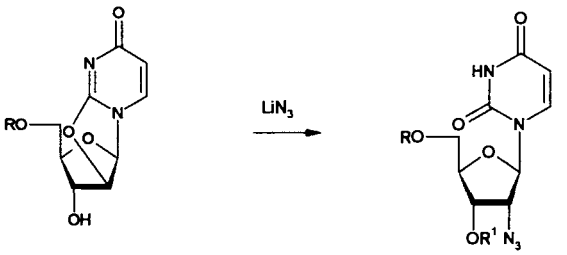
Conversion of the acetylated uridines **5** and **6** to the corresponding cytidines was carried out using the tetrazolide method [28–30] resulting in 2′-azido-2′-deoxy-5′-*O*-(4-methoxytrityl)- (**8**) and 2′-azido-2′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)cytidine (**9**) in high yield. Incomplete deprotection of the 3′-acetyl group in the conversion of **5** to **8** led to a mixture of 3′-*O*-acetyl-2′-azido-2′-deoxy-5′-*O*-(4-methoxytrityl)cytidine (**7**) and **8** (43%).

The subsequent introduction of the npeoc group into **8** and **9** was achieved by reaction of 3-methyl-1-{[2-(4-nitrophenyl)ethoxy]carbonyl}-1*H*-imidazol-3-ium chloride [26] in CH_2Cl_2 solution in the presence of 4-(dimethylamino)pyridine (DMAP) as activator to give, with simultaneous protection of the 4-NH_2 and 3′-OH groups, compounds **10** and **11**, respectively. *Staudinger* reduction of the N_3 group in **10** and **11** led *via* migration of the npeoc group to 2′-deoxy-N^4-{[2-(4-nitrophenyl)ethoxy]carbonyl}-5′-*O*-(4-methoxytrityl)-2′-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)cytidine (**12**) and 2′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-N^4-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2′-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)cytidine (**13**). Due to the lability of the npeoc group under basic conditions PPh_3 in THF/H_2O [31] was used instead of PPh_3 in NH_4OH/dioxan/pyridine [25].

In the uridine series, the N_3 function of the key building blocks **3** and **4** was reduced by *Staudinger* reduction to give 2′-amino-2′-deoxy-5′-*O*-(4-methoxytrityl)- (**15**) and 2′-amino-2′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)uridine (**16**) [20][25], respectively (*Scheme 1*). Selective protection of the 2′-amino function of **15** and **16** with the npeoc group was performed at 0° using 2-(4-nitrophenyl)ethyl chloroformate [26] in pyridine to give the 2′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-2′-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)- (**17**) and 2′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-2′-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)-uridine (**18**) in 79 and 87% yield, respectively. Another approach in which the 3′-OH-function of **3** was protected with the npeoc group to give 2′-azido-2′-deoxy-5′-*O*-(4-methoxytrityl)-3′-*O*-{[2-(4-nitrophenyl)ethoxy]carbonyl}uridine (**14**), followed by the *Staudinger* reduction, also led to **17**, due to migration of the npeoc group [27] to the amino function, to form a thermodynamically more stable carbamate structure than the original carbonate function.

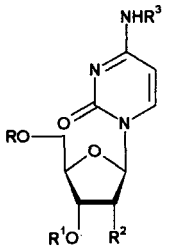
The synthetic problems concerned with the synthesis of the 2′-amino-2′-deoxyguanosine series prompted us to make use of a transglycosidation reaction [32–35]. The sugar donor **19** was prepared by detritylation of **18** with 6% AcOH in CH_2Cl_2/MeOH 4:1 in 88% yield (*Scheme 1*). The transglycosidation reaction required transient protection of O^6-(npe)-guanine [36][37] and **19**, which was achieved by refluxing in

Scheme 1

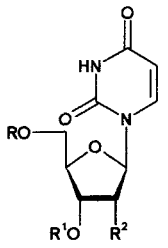


	R
1	MeOTr
2	$(MeO)_2Tr$

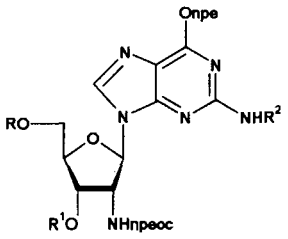
	R	R^1
3	MeOTr	H
4	$(MeO)_2Tr$	H
5	MeOTr	Ac
6	$(MeO)_2Tr$	Ac



	R	R^1	R^2	R^3
7	MeOTr	Ac	N_3	H
8	MeOTr	H	N_3	H
9	$(MeO)_2Tr$	H	N_3	H
10	MeOTr	npeoc	N_3	npeoc
11	$(MeO)_2Tr$	npeoc	N_3	npeoc
12	MeOTr	H	NHnpeoc	npeoc
13	$(MeO)_2Tr$	H	NHnpeoc	npeoc



	R	R^1	R^2
14	MeOTr	npeoc	N_3
15	MeOTr	H	NH_2
16	$(MeO)_2Tr$	H	NH_2
17	MeOTr	H	NHnpeoc
18	$(MeO)_2Tr$	H	NHnpeoc
19	H	H	NHnpeoc
20	tms	tms	NHnpeoc



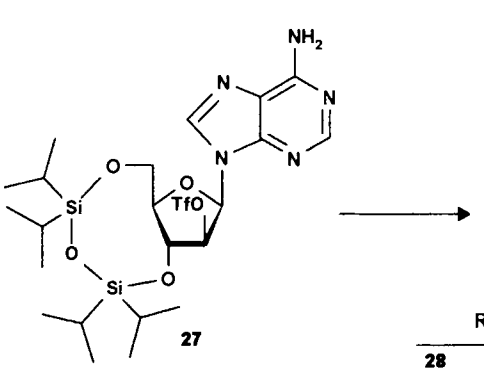
	R	R^1	R^2
21	tms	tms	tms
22	H	H	H
23	tipds		H
24	tipds		npeoc
25	H	H	npeoc
26	$(MeO)_2Tr$	H	npeoc

hexamethyldisilazane (HMDS)/bis(trimethylsilyl)acetamide (BSA)/MeCN, followed by the addition of trimethylsilyl triflate (tms-Tf) as promoter to give, after workup, the desired 2′-deoxy-O^6-[2-(4-nitrophenyl)ethyl]-2′-({[2-(4-(nitrophenyl)ethoxy]carbonyl}-amino)guanosine (**22**) in 85% yield. The structure assignment of the glycosidic linkage

in **22** was checked by ROESY-NMR indicating the β-D-configuration. When the disilylation step was omitted, the silylated derivatives **20** and **21**, respectively, could be isolated. To protect the aglycone amino function of **22**, the sugar OH groups were first protected using *Markiewicz*'s reagent (1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane; tipds Cl_2), giving **23** in 73% yield, followed by acylation with 2-(4-nitrophenyl)ethyl carbonochloridate in pyridine to give the fully protected nucleoside **24**. Desilylation with F^- ions [38] afforded 2′-deoxy-O^6-[2-(4-nitrophenyl)ethyl]-N^2-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2′-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)guanosine (**25**), which was then protected at the 5′-OH position with $(MeO)_2$TrCl/DMAP in pyridine to give the desired nucleoside **26**.

The 2′-amino-2′-deoxyadenosine series was synthesized starting from 2′-azido-2′-deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)adenosine (**28**) which was prepared by a multistep procedure as described in [32], except that the (trifluoromethyl)sulfonylation step was slightly modified. The (trifluoromethyl)sulfonyl group of **27** was then displaced by nucleophilic attack with LiN_3 in DMF to yield **28** in 90% yield (*Scheme 2*). Reduction of the N_3 group in **28** to **29** was performed *a*) by radical reduction using 2,2′-azobis[isobutyronitrile] (AIBN) and Bu_3SnH [32], *b*) by *Staudinger* reduction with PPh_3 in THF/H_2O, or *c*) PPh_3 in NH_4OH/dioxan/pyridine. In the latter procedure, partial ring opening at the 5′-position was observed resulting in **30** as by-product. The simultaneous protection of the aglycone and the 2′-NH_2 functions was carried out using 3-methyl-1-{[2-(4-nitrophenyl)ethoxy]carbonyl}-1*H*-imidazol-3-ium chloride in CH_2Cl_2 solution and DMAP as activator. When an insufficient amount of DMAP was used, monoacylated product **32** was also isolated besides the desired compound **31**. Desilylation of **31** with F^- ions (→**33**) and further treatment with $(MeO)_2$TrCl/DMAP in pyridine gave **34** in 86% yield.

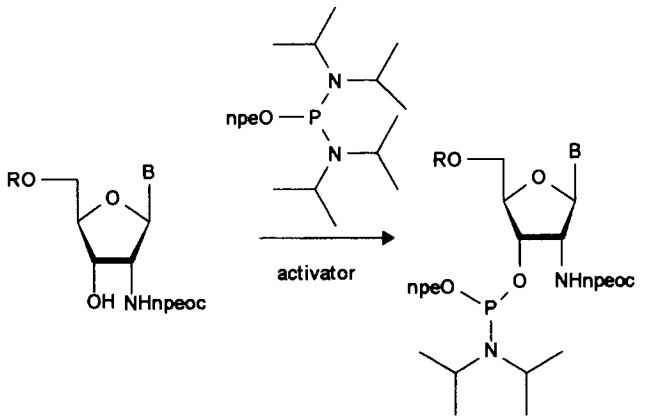
Scheme 2



	R	R^1	R^2	R^3
28	tipds		N_3	H
29	tipds		NH_2	H
30	H	tipdsOH	NH_2	H
31	tipds		NHnpeoc	npeoc
32	tipds		NHnpeoc	H
33	H	H	NHnpeoc	npeoc
34	$(MeO)_2$Tr	H	NHnpeoc	npeoc

The partially protected nucleosides **12**, **13**, **17**, **18**, **26**, and **34** were converted into their corresponding 3′-*O*-[2-(4-nitrophenyl)ethyl]phosphoramidites **35**–**40** by reaction with 2-(4-nitrophenyl)ethyl phosphorodiamidite [39] under 1*H*-tetrazole and/or pyridine-hydrochloride activation [40–42] (*Scheme 3*). However, with pyridine hydrochloride as activator, the obtained yields were *ca.* 10% higher.

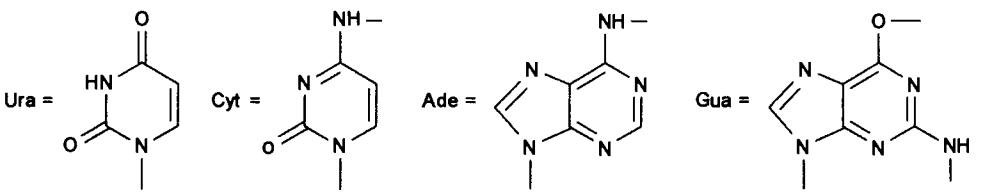
Scheme 3



	R	B	Activator[a]
12	MeOTr	Cyt^{npeoc}	tet
13	$(MeO)_2Tr$	Cyt^{npeoc}	pyHCl
17	MeOTr	Ura	tet
18	$(MeO)_2Tr$	Ura	pyHCl
24	$(MeO)_2Tr$	Gua$^{npe}_{npeoc}$	pyHCl
30	$(MeO)_2Tr$	Ade^{npeoc}	tet, pyHCl

	R	B
35	MeOTr	Cyt^{npeoc}
36	$(MeO)_2Tr$	Cyt^{npeoc}
37	MeOTr	Ura
38	$(MeO)_2Tr$	Ura
39	$(MeO)_2Tr$	Gua$^{npe}_{npeoc}$
40	$(MeO)_2Tr$	Ade^{npeoc}

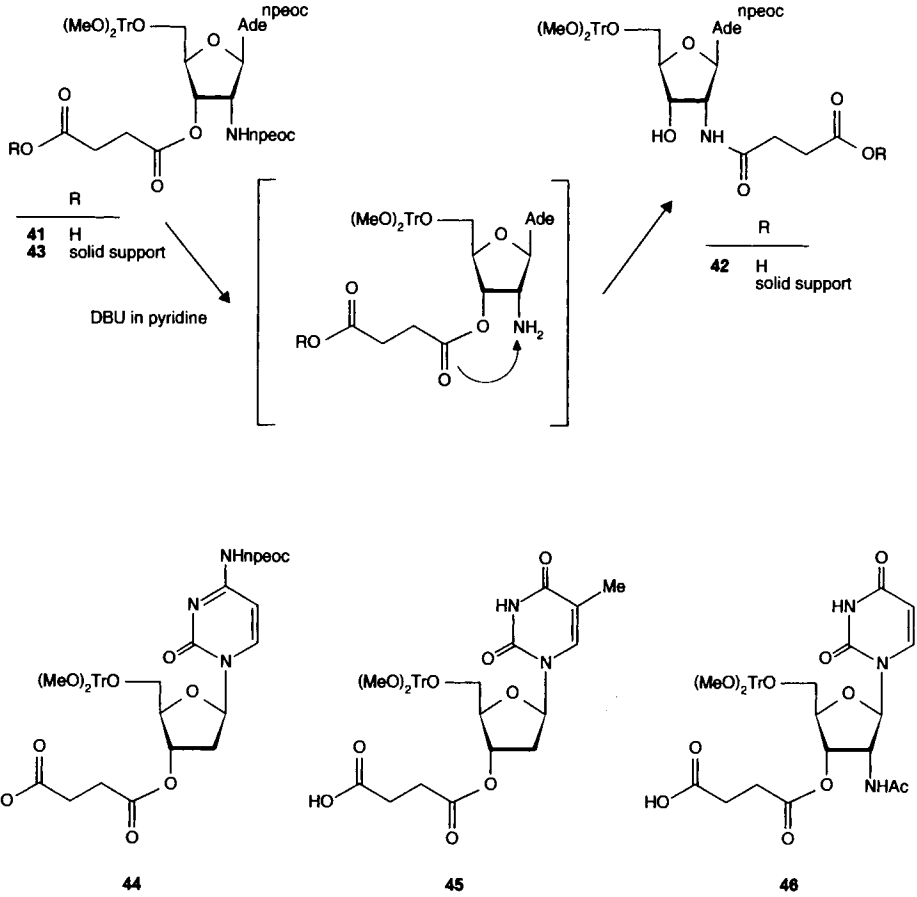
[a]) tet = 1*H*-tetrazole; pyHCl = pyridine hydrochloride



For solid-phase synthesis, 2′-*N*-(npeoc)-3′-*O*-succinyl-derivatized solid supports could not be used as starting nucleoside, due to the tendency of the npeoc group to migrate (*Scheme 4*). As a consequence of this amide-bond formation during the solid-

phase synthesis, it was assumed that after the npe/npeoc deprotection step with DBU, the synthesized oligomer could not be cleaved from the solid support by treatment with concentrated NH_3 solution.

Scheme 4



To confirm the prediction, 5′-*O*-protected 3′-*O*-(3-carboxypropanoyl)-2′-*N*-(npeoc)-adenosine derivative **41** was synthesized by reaction of **34** with succinic anhydride/DMAP in dry CH_2Cl_2. This was then treated with DBU *a*) in solution or *b*) on the solid support. *a*) After treatment of **41** with DBU in pyridine for 2 days, followed by neutralization with AcOH, compound **42** was isolated. Characterization by ^{1}H-NMR showed two characteristic signals at 5.78 ppm (HO–C(3′)) and 8.23 ppm (CONH–C(2′)).

b) Compound **41** was reacted with 500-Å LCAMA-CPG (= (long-chain alkyl)-methylamine-controlled pore glass) [11][12][17] using 2-{[(2-(2-cyanoethoxy)-2-oxoethylidene]amino}-1,1,3,3-tetramethyluronium tetrafluoroborate (TOTU) and *N*-methylmorpholine as coupling reagents in MeCN to give the solid support **43** with a loading of 14 μmol/g.

Successive treatment of **43** with DBU, 3% Cl_3CCOOH, and concentrated ammonia solution did not result in the release of nucleoside from the support confirming the expected migration (*Scheme 4*). Therefore, 3′-*O*-(3-carboxypropanoyl)-2′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-N^4-{[2-(4-nitrophenyl)ethoxy]carbonyl}cytidine (**44**), 3′-*O*-(3-carboxypropanoyl)-5′-*O*-(4,4′-dimethoxytrityl)thymidine (**45**) [17], and 2′-acetamido-3′-*O*-(3-carboxypropanoyl)-5′-*O*-(4-methoxytrityl)uridine (**46**) [43] were used instead as starting compounds in the solid-support synthesis. As a consequence, the prepared oligomers **47**–**55** have a deoxynucleoside at their 3′-end.

The oligomers **47**–**55** (*Table 1*) were synthesized using the solid-phase phosphoramidite apporach developed by *Caruthers* and co-workers [44–47]. Four chemical steps and intermediate washing steps were necessary for each elongation step. At first, the terminal $(MeO)_2Tr$ group was cleaved with 3% Cl_3CCOOH in CH_2Cl_2. The average coupling efficiency was monitored by absorption measurement of the released $(MeO)_2Tr$ solutions. During the coupling step, 0.1M nucleoside phosphoramidite (see **35**–**40**) and 0.5M activation reagent in MeCN were delivered to the solid support. After the condensation, unreacted OH functions were blocked by capping (15 s) with Ac_2O/2,6-dimethylpyridine/1-methyl-1*H*-imidazole in THF. The phosphite-triester bridge was oxidized with 0.05M I_2 in THF/pyridine/H_2O for 25 s. After the last synthesis cycle, the support was treated with 3% Cl_3COOH/CH_2Cl_2 and then with 1M DBU in MeCN for 12 h to remove all protecting groups. The oligonucleotide was cleaved from the support by treatment with concentrated NH_3 solution for 2.5 h, and the resulting solution was lyophilized. Completeness of deprotection and the quality of the synthesized oligonucleotides were confirmed by reversed-phase HPLC. The crude oligomers **48** and **54** were also analyzed by polyacrylamide-gel electrophoresis indicating one main product and no failure sequences.

Based on our experience from solid-support synthesis of oligoarabinonucleotides [38], α-arabinooligonucleotides [36], β-oligoarabinoaminonucleotides [19], affording coupling times of 600 and 1200 s, respectively, we checked coupling times of 900 and 1800 s. It turned out that a coupling time to 1800 s is not advisable, especially for the syntheses of longer oligonucleotides, due to more side reactions. Preliminary experiments

Table 1. *Synthesized Oligonucleotides*

Sequence (5′→3′)[a]	*t*[s][b]
$U_nC_nA_ndC$ (**47**)[c]	900; 1800
$C_nC_nC_n$ C_nC_ndC (**48**)[c]	900; 1800
$U_nU_nU_n$ $U_nU_nU_n$ dt (**49**)[d]	270
$A_nA_nA_nA_nA_n$UNHAc (**50**)[d]	420
$C_nC_nC_n$ $C_nC_nC_n$ $C_nC_nC_n$ C_nC_ndC (**51**)[c]	1800
$C_nA_nC_n$ C_nGA_n GGC_n C_nGG C_nGdC (**52**)[c]	dN: 45; N_n: 900
d(GGT TCC A_nTG CA_nT GGA_n A_nCC) (**53**)[c]	dN: 45; N_n: 900
d(GGU_n U_nCC A_nU_nG CA_nU_n GGA_n A_nCC) (**54**)[c]	dN: 45: N_n: 1800
$G_nG_nU_n$ $U_nC_nC_n$ $A_nU_nG_n$ $C_nA_nU_n$ $G_nG_nA_n$ A_nC_ndC (**55**)[d]	dN: 45, N_n: 420

[a]) $N_n = N_{d2'n}$ = 2′-Amino-modified 2′-deoxynucleotides; $dN = N_{d2'}$ = 2′-unsubstituted 2′-deoxynucleotides; for convenience, the hyphens representing the phosphodiester linkages are omitted. [b]) *t* = Coupling time. [c]) 1*H*-Tetrazole activation. [d]) Pyridine-hydrochloride activation.

with pyridine hydrochloride [42] as activator are very promising since they allow a substantial shortening of the coupling time.

3. Hybridization Experiments. – The stabilities of duplexes formed between oligomers **51**, **52**, **57**, or **59**, and a complementary DNA target **58** or **60** as well as between the self-complementary sequences **53**–**56** were studied by measuring the melting profiles and determining the melting temperatures as an informative parameter. The experiments were carried out in Na_2HPO_4/NaH_2PO_4 buffer pH 7.4 with 0.5 OD oligonucleotide (*Table 2*).

Table 2. *Oligonucleotides and Their* T_m *Values*

Sequence (5′→3′)[a])	c [Na^+]	T_m [°C]
d(GGT TCC ATG CAT GGA ACC) (**56**)[b])	0.15	65.5
d(GGT TCC A_nTG CA_nT GGA_n A_nCC) (**53**)[c])	0.15	48.6
d(GGU_n U_nCC A_nU_nG CA_nU_n GGA_n A_nCC) (**54**)	0.15	22.7
d(GGU_n U_nCC A_nU_nG CA_nU_n GGA_n A_nCC (**54**)[c])	0.3	22.2
$G_nG_nU_n$ $U_nC_nC_n$ $A_nU_nG_n$ $C_nA_nU_n$ $G_nG_nA_n$ A_nC_ndC (**55**)	0.12	n.o
$G_nG_nU_n$ $U_nC_nC_n$ $A_nU_nG_n$ $C_nA_nU_n$ $G_nG_nA_n$ A_nC_ndC (**55**)	0.024	n.o.
d(CCC CCC CCC CCC) (**57**)[b])	0.15	61.6
d(GGG GGG GGG GGG) (**58**)[b])		
$C_nC_nC_n$ $C_nC_nC_n$ $C_nC_nC_n$ C_nC_ndC (**51**)	0.12	n.o.
d(GGG GGG GGG GGG) (**58**)[b])		
d(CAC CAG CGG CGC) (**59**)[b])	0.15	62.8
d(GCG CCG TCG GTG) (**60**)[b])		
$C_nA_nC_n$ C_nA_nG C_nGG C_nGdC (**52**)	0.15	29.7
d(GCG CCG TCG GTC) (**60**)[b])		

[a]) $N_n = N_{d2'n}$ = 2-Amino-modified 2′-deoxynucleotide, $dN = N_{d2'}$ = 2′-unsubstituted 2′-deoxynucleotides; for convenience, the hyphens representing the phosphodiester linkages are omitted. [b]) Sequences **56** and **57**–**60** were synthesized by the npe/npeoc strategy [17]. [c]) Purified by HPLC. [d]) n.o.: not observed.

The results can be summarized as follows: the incorporation of the 2′-amino groups has a strong destablization effect on thermal stability. For the duplex **52**/**60**, the T_m was decreased from 62.8° for the unmodified duplex to 29.7° by incorporation of five 2′-amino-2′-deoxycytidines and two 2′-amino-2′-deoxyadenosines. In case of the duplex **51**/**58**, where **51** was a completely 2′-amino-modified oligomer, no melting point could be observed. In the series of the self-complementary sequences **53**–**56**, the melting point decreases from 65.5° for the unmodified duplex to 48.6° by exchange of the four 2′-deoxyadenosine with 2′-amino-2′-deoxyadenosine moieties (see **53**) and decreased further to 22.7° by incorporation of eight 2′-amino-2′-deoxynucleosides (four $A_{d2'n}$ and four $U_{d2'n}$; see **54**). For the completely 2′-amino-modified self-complementary sequence, **55** no melting point could be observed.

Previous studies indicate that 2′-amino-2′-deoxynucleoside [48] and short oligonucleotides thereof [49] exist primarily in the 2′-*endo*-conformation which should favor DNA/DNA duplex with a B-form geometry, whereas DNA/RNA duplex preferentially adopt an A-form geometry derived from 2′-*exo*-conformations of the basic nucleosides. These expectations could not be observed in the presented investigations, since we found in all cases of hybridizations decreased T_m values due to destabilizing effects resulting probably

from electrostatic interactions between the 2′-amino and the negatively charged phosphodiester function, and unknown secondary effects perturbing a normal duplex structure as also described by *Shabarova* and co-workers [24], *Miller et al.* [49], and *Eckstein* and co-workers [50].

4. Physical Data. – All newly synthesized compounds were characterized in the usual manner by elemental analysis, UV, ^{1}H-NMR, and in some cases, by IR and ^{31}P-NMR spectra (see *Exper. Part*).

Experimental Part

General. Products were dried under high vacuum. TLC: precoated silica gel thin-layer sheets *F1500 LS 254* from *Schleicher & Schüll*. Flash chromatography (FC): silica gel (*Baker*, 30–60 μm), 0.3–0.4 bar. HPLC: *Merck Hitachi L-6200, D-2000* chromatointegrator, detection at 260 nm (*Uvikon 730 SLC*, Fa. *Kontron*); column *RP-18 Lichrospher* (125 × 4 mm, 5 μm, *Merck*); flow rate 1 ml/min; mobile phase: *A*, 0.1M aq. (Et_3NH)OAc buffer (pH 7); *B*, *A* + MeCN 1:1; gradient: 0 min 95% *A*; 2 min 95% *A*; 32 min 60% *A*; 37 min 100% *B*; 40 min *B*; 45 min 95% *A*; 50 min 50% *A*. UV/VIS: *Perkin-Elmer, Lambda 15*; λ_{max} in nm (log ε). Melting curves: *Perkin-Elmer Lambda 2*; temp. control by *Peltier* element; programmer *PTP-6*. IR: *Perkin-Elmer* model *1600* series FTIR; CH_2Cl_2 solns.; in cm^{-1}. ^{1}H-NMR: *Bruker AC 250*; δ in ppm rel. to DMSO. ^{31}P-NMR: *Joel 400 MHz*; in ppm rel. to H_3PO_4.

1. *2′-Azido-2′-deoxy-5′-O-(4-methoxytrityl)uridine* (**3**). A suspension of **1** [20][21–23] (2.66 g, 5.33 mmol) and LiN_3 [51] (653 mg, 13.3 mmol) was dissolved in dry DMF (50 ml) at 130°, and benzoic acid (651 mg, 5.33 mmol) was added. Further equiv. of LiN_3 (3 × 13.3 mmol) were added gradually every 30 min. The mixture was poured into ice-water (50 ml), washed with H_2O (30 ml) and $CHCl_3$ (3 × 50 ml). The combined org. layers were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified twice by FC (toluene/AcOEt 2:1 → 1:1): 2.06 g (71%) of **2**. Colorless foam. UV (MeOH): 260 (3.99), 230 (4.22). IR (CH_2Cl_2): 2120. ^{1}H-NMR ((D$_6$)DMSO): 11.44 (*s*, NH); 7.69 (*d*, H–C(6)); 7.21–7.39 (*m*, 12 H, MeO*Tr*); 6.91 (*d*, 2 H *o* to MeO); 6.00 (*d*, H–C(1′)); 5.36 (*d*, HO–C(3′)); 4.36–4.49 (*m*, H–C(3′)); 4.24–4.29 (*m*, H–C(2′)); 3.89–3.95 (*m*, H–C(4′)); 3.73 (*s*, MeO); 3.24–3.29 (*m*, 2 H–C(5′)). Anal. calc. for $C_{29}H_{27}N_5O_6 \cdot 1/2$ PhMe (587.64): C 66.42, H 5.32, N 11.92; found: C 65.79, H 5.31, N 11.74.

2. *2′-Azido-2′-deoxy-5′-O-(4,4′-dimethoxytrityl)uridine* (**4**) [24]. A mixture of **3** (1 g, 1.89 mmol) and LiN_3 [51] (463 mg, 9.46 mmol) in dry DMF (10 ml) was heated in the dark at 120° for 16 h and evaporated. The residue was dissolved in AcOEt (50 ml), washed with sat. $NaHCO_3$ soln. (2 × 50 ml) and brine (2 × 50 ml), dried ($MgSO_4$), and evaporated. The residue was purified by FC ($CHCl_3$/MeOH 49:1, 19:1, and 9:1): 712 mg (66%) of **4**. Colorless foam. UV (MeOH): 262 (4.05), 233 (4.37). IR (CH_2Cl_2): 2119. ^{1}H-NMR ((D$_6$)DMSO): 11.44 (*s*, NH); 7.69 (*d*, H–C(6)); 7.12–7.29 (*m*, 9 H, (MeO)$_2$*Tr*); 6.83 (*m*, 4 H *o* to MeO); 6.00 (*d*, H–C(1′)); 5.73 (*d*, HO–C(3′)); 5.34 (*d*, H–C(5)); 4.43 (*d*, H–C(2′)); 4.26 (*m*, H–C(3′)); 3.96 (*m*, H–C(4′)); 3.72 (*s*, 2 MeO); 3.21 (*m*, 2 H–C(5′)). Anal. calc. for $C_{30}H_{29}N_3O_7$ (571.59): C 63.04, H 5.11, N 12.25; found: C 63.06, H 5.17, N 11.83.

3. *3′-O-Acetyl-2′-azido-2′-deoxy-5′-O-(4-methoxytrityl)uridine* (**5**). To a soln. of **3** (1.7 g, 3.14 mmol) in dry pyridine (15 ml), Ac_2O (1.6 g, 1.5 ml, 15.7 mmol) was added and stirred at r.t. for 8 h. After addition of MeOH (2 ml), the soln. was evaporated *in vacuo*, the residue dissolved in AcOEt (30 ml) and washed with sat. $NaHCO_3$ soln. (2 × 30 ml). The org. layer was dried ($MgSO_4$), evaporated *in vacuo*, and co-evaporated with toluene to remove remaining pyridine. The residue was purified by FC (CH_2Cl_2 + 1 → 2% MeOH): 1.3 g (71%) of **5**. Colorless foam. UV (MeOH) 260 (4.05), 231 (4.26). IR (CH_2Cl_2): 2115. ^{1}H-NMR ((D$_6$)DMSO): 11.50 (*s*, NH); 7.66 (*d*, H–C(6)); 7.20–7.38 (*m*, 12 H, MeO*Tr*); 6.90 (*d*, 2 H*o* to MeO); 5.80 (*d*, H–C(1′)); 5.55 (*d*, H–C(5)); 5.30–5.32 (*m*, H–C(3′)); 4.70–4.72 (*m*, H–C(2′)); 4.09–4.14 (*m*, H–C(4′)); 3.74 (*s*, MeO); 3.27–3.37 (*m*, 2 H–C(5′)); 2.09 (*s*, Ac). Anal. calc. for $C_{31}H_{29}N_5O_7 \cdot 1/2\ H_2O$ (592.61): C 62.83, H 4.93, N 11.82; found: C 63.00, H 5.14, N 11.28.

4. *3′-O-Acetyl-2′-azido-2′-deoxy-5′-O-(4,4′-dimethoxytrityl)uridine* (**6**). As described in *Exper. 3*, with **4** (8 g, 13.97 mmol) and Ac_2O (7.14 g, 6.6 ml, 69.98 mmol) in dry pyridine (60 ml, r.t. 15 h; 7 ml MeOH). Purification by FC (toluene/AcOEt 1:1): 7:3 g (91%) of **5**. Colorless foam. UV (MeOH): 262 (4.04), 234 (4.38). IR (CH_2Cl_2): 2119. ^{1}H-NMR ((D$_6$)DMSO): 11.50 (*s*, NH); 7.69 (*d*, H–C(6)); 7.20–7.38 (*m*, 9 H, (MeO)$_2$*Tr*); 6.90 (*d*, 4 H *o* to MeO); 5.80 (*d*, H–C(1′)); 5.55 (*d*, H–C(5)); 5.30–5.32 (*m*, H–C(3′)); 4.70 4.72 (*m*, H–C(2′)); 4.09–4.14

(*m*, H–C(4')); 3.72 (*s*, 2 MeO); 3.27–3.37 (*m*, 2 H–C(5')); 2.09 (*s*, Ac). Anal. calc. for $C_{32}H_{31}N_6O_8$ (613.63): C 62.64, H 5.09, N 11.41; found: C 62.46, H 5.23, N 11.14.

5. *3'-O-Acetyl-2'-azido-2'-deoxy-5'-O-(4-methoxytrityl)cytidine* (**7**). To a soln. of **5** (500 mg, 0.86 mmol) in dry pyridine (15 ml), 2-chlorophenyl phosphorodichloridate (526 mg, 0.346 ml, 2.14 mmol) and 1*H*-1,2,4-triazole (326 mg, 4.71 mmol) were added and stirred at r.t. for 16 h. The soln. was evaporated *in vacuo*, dissolved in $CHCl_3$, washed with sat. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. The residue was dissolved in dioxan (10 ml) and 25% aq. NH_3 soln. (5 ml), and stirred at r.t. for 2 h. The mixture was submitted to FC (CH_2Cl_2/MeOH 19:1 and 9:1): 180 mg (36%) of **7**, followed by 200 mg (43%) of **8**.

Data of **7**: Colorless foam. UV (MeOH): 269 (3.97), 230 (4.31). IR (CH_2Cl_2): 2119. ^{1}H-NMR ((D$_6$)DMSO): 7.63 (*d*, H–C(6)); 7.17–7.32 (*m*, 12 H, MeO*Tr*); 6.87 (*d*, 2 H *o* to MeO); 5.85 (*d*, H–C(1')); 5.69 (*d*, H–C(5)); 5.24–5.29 (*m*, H–C(3')); 4.40–4.47 (*m*, H–C(2')); 4.06–4.07 (*m*, H–C(4')); 3.80 (*s*, MeO); 3.28–3.38 (*m*, 2 H–C(5')); 2.04 (*s*, Ac). Anal. calc. for $C_{31}H_{30}N_6O_6 \cdot {}^1/_2\,H_2O$ (591.63): C 62.99, H 5.11, N 14.20; found: C 63.05, H 5.24, N 13.52.

6. *2'-Azido-2'-deoxy-5'-O-(4-methoxytrityl)cytidine* (**8**). As described in *Exper. 5*, with **6** (500 mg, 0.86 mmol), *o*-chlorophenyl phosphorodichloridate (526 mg, 0.346 ml, 2.14 mmol) and 1*H*-1,2,4-triazole (326 mg, 4.71 mmol) in dry pyridine (15 ml; r.t., 16 h). The soln. was evaporated *in vacuo*, dissolved in $CHCl_3$, washed with sat. $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was dissolved in dioxane (10 ml) and 25% aq. NH_3 soln. (10 ml), and stirred at r.t. for 15 h. The soln. was evaporated *in vacuo* and the residue purified by FC (CH_2Cl_2/MeOH 95:5, 19:1, and 9:1): 446 mg (96%) of **8**. UV (MeOH): 272 (3.95), 230 (4.31). IR (CH_2Cl_2): 2119. ^{1}H-NMR ((D$_6$)DMSO): 8.03–8.65 (2 br. *s*, NH_2); 7.69 (*d*, H–C(6)); 7.22–7.40 (*m*, 12 H, MeO*Tr*); 6.89 (*d*, 2 H *o* to MeO); 5.93 (*d*, H–C(1')); 5.74–5.78 (*d*, HO–C(3')); 5.54 (*d*, H–C(5)); 4.35–4.44 (*m*, H–C(2')); 4.06–4.10 (*m*, H–C(3')); 3.94–3.97 (*m*, H–C(4')); 3.73 (*s*, MeO); 3.26–3.34 (*m*, 2 H–C(5')). Anal. calc. for $C_{29}H_{28}N_6O_5 \cdot {}^1/_2\,H_2O$ (549.59): C 62.36, H 5.41, N 17.19; found: C 62.09, H 5.21, N 16.92.

7. *2'-Azido-2'-deoxy-5'-O-(4,4'-dimethoxytrityl)cytidine* (**9**). As described in *Exper. 6*, with **6** (1 g, 1.63 mmol), 2,5-dichlorophenyl phosphorodichloridate (1.14 g, 4.07 mmol) and 1*H*-1,2,4-triazole (281 mg, 4.07 mmol) in dry pyridine (20 ml; stirring 16 h). Purification was achieved by FC (toluene/AcOEt 1:1, toluene/AcOEt 1:1 + 2% MeOH, toluene/AcOEt/MeOH 5:4:1): 870 mg (93%) of **9**. Colorless foam. UV (MeOH): 271 (3.85), 236 (3.96). IR (CH_2Cl_2): 2128. ^{1}H-NMR ((D$_6$)DMSO): 8.00–8.61 (2 br. *s* NH_2); 7.71 (*d*, H–C(6)); 7.12–7.43 (*m*, 9 H, $(MeO)_2$*Tr*); 6.89 (*d*, 4 *o* to MeO); 5.93 (*d*, H–C(1')); 5.74–5.78 (*d*, HO–C(3')); 5.54 (*d*, H–C(5)); 4.35–4.44 (*m*, H–C(2')); 3.99–4.06 (*m*, H–C(3')); 3.94–3-97 (*m*, H–C(4')); 3.71 (*s*, 2 MeO); 3.26–3.34 (*m*, 2 H–C(5')). Anal. calc. for $C_{30}H_{30}N_6O_6 \cdot {}^1/_2\,H_2O$ (579.62): C 62.17, H 5.39, N 13.62; found: C 62.19, H 5.42, N 13.84.

8. *2'-Azido-2'-deoxy-5'-O-(4-methoxytrityl)*-N^4,*3'-O-bis{[2-(4-nitrophenyl)ethoxy]carbonyl}cytidine* (**10**). To a soln. of **8** (266 mg, 0.418 mmol) in dry CH_2Cl_2 (10 ml) was added a cat. amount of DMAP, molecular sieve, and 3-methyl-1-{[2-(4-nitrophenyl)ethoxy]carbonyl}-1*H*-imidazol-3-ium chloride (390 mg, 1.25 mmol). The suspension was vigorously stirred at r.t. for 3 d, afterwards filtered, and evaporated *in vacuo*. The residue was purified by FC (toluene/AcOEt 1:1, toluene/AcOEt/MeOH 5:4:1): 309 mg (quant.) of **10**. Colorless foam. UV (MeOH): 269 (4.37), 236 (4.46). IR (CH_2Cl_2): 2119. ^{1}H-NMR ((D$_6$)DMSO): 10.92 (*s*, N*H*npeoc); 8.08–8.17 (*m*, H–C(6), 4 H *o* to NO_2); 7.52–7.61 (2*d*, 4 H *m* to NO_2), 7.12–7.36 (*m*, 12 H, MeO*Tr*); 6.86–6.92 (*m*, H–C(5), 2 H *o* to MeO); 5.83 (*d*, H–C(1')); 5.24 (*t*, H–C(3')); 4.72 (*m*, H–C(2')); 4.33–4.48 (*m*, 2 OCH_2CH$_2$); 4.16 (*m*, H–C(4')); 3.72 (*s*, MeO); 3.30 (*m*, 2 H–C(5')); 3.07–3.08 (*m*, 2 OCH$_2$CH_2). Anal. calc. for $C_{47}H_{42}N_8O_{13}$ (926.89): C 60.90, H 4.57, N 12.09; found: C 61.18, H 4.73, N 11.60.

9. *2'-Azido-2'-deoxy-5'-O-(4,4'-dimethoxytrityl)*-N^4,*3'-O-bis{[2-(4-nitrophenyl)ethoxy]carbonyl}cytidine* (**11**). As described in *Exper. 8*, with **9** (1 g, 2.83 mmol), 3-methyl-1-{[2-(4-nitrophenyl)ethoxy]carbonyl}-1*H*-imidazol-3-ium chloride (2.65 g, 8.51 mmol) and DMAP, molecular sieve in dry CH_2Cl_2 (10 ml; r.t., 3 d). Purification by FC ($CHCl_3$, $CHCl_3$/MeOH 49:1): 2.23 g (86%) of **11**. Colorless foam. UV (MeOH): 270 (4.27), 236 (3.86). IR (CH_2Cl_2): 2119. ^{1}H-NMR ((D$_6$)DMSO): 10.80 (*s*, N*H*npeoc); 8.03–8.21 (*m*, H–C(6), 4 H *o* to NO_2); 7.19–7.72 (2*m*, 15 H, 4 H *m* to NO_2, $(MeO)_2$*Tr*, N*H*npeoc, H–C(5)); 6.72–6.93 (*m*, 4 H *o* to MeO); 5.86 (*d*, H–C(1')); 5.23 (*m*, H–C(3')); 4.71 (*m*, H–C(2')); 4.23–4.49 (*m*, 2 OCH_2CH$_2$); 4.17 (*m*, H–C(4')); 3.72 (*s*, 2 MeO); 3.30 (*m*, 2 H–C(5')); 3.07 (*m*, 2 OCH$_2$CH_2). Anal. calc. for $C_{48}H_{44}N_8O_{14} \cdot {}^3/_2\,H_2O$ (983.95): C 58.89, H 4.81, N 11.38; found: C 58.60, H 4.74, N 11.79.

10. *2'-Deoxy-5'-O-(4-methoxytrityl)*-N^4-*{[2-(4-nitrophenyl)ethoxy]carbonyl}-2'-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)cytidine* (**12**). A soln. of **10** (2.1 g, 2.4 mmol) was stirred with Ph_3P (758 mg, 2.89 mmol) in dry THF (25 ml) at r.t. overnight. H_2O was added and stirring continued for 3 d. After evaporation, the residue was dissolved in AcOEt, dried ($MgSO_4$), and once again evaporated *in vacuo*. The residue was purified by FC ($CHCl_3$/MeOH 99:1, 98:2, $CHCl_3$/MeOH 95:5): 1.96 g (91%) of **12**. Colorless foam. UV (MeOH): 272 (4.06), 235 (4.28). ^{1}H-NMR ((D$_6$)DMSO): 10.83 (*s*, N*H*npeoc); 8.03–8.19 (*m*, H–C(6), 4 H *o* to NO_2); 7.22–7.65

(*m*, 16 H, MeO*Tr*, 4 H *m* to NO_2); 6.80–6.91 (*m*, H–C(5), 2 H *o* to MeO); 5.95 (*d*, H–C(1')); 5.60 (*d*, HO–C(3')); 4.33–4.37 (2*m*, 2 OCH_2CH_2, H–C(3'), H–C(2')); 4.02–4.04 (*m*, H–C(4')); 3.73 (*s*, MeO); 3.11–3.34 (*m*, 2 H–C(5')); 3.07–3.08 (*m*, 2 OCH_2CH_2). Anal. calc. for $C_{47}H_{44}N_6O_{13}$ · PhMe (993.04): C 65.31, H 5.28, N 8.48; found: C 64.83, H 5.23, N 7.98.

11. *2'-Deoxy-5'-*O*-(4,4'-dimethoxytrityl)-*N^4*-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2'-({[2-(4-nitrophenyl)-ethoxy]carbonyl}amino)cytidine* (**13**). As described in *Exper. 10*, with **11** (1.6 g, 1.87 mmol), Ph_3P (586 mg, 2.2 mmol), and dry dioxane (20 ml; r.t., 15 h). FC (petroleum ether/acetone 4:1, 2:1, and 1:1): 1.28 g (47%) of **13**. Colorless foam. UV (MeOH): 270 (4.36), 236 (4.04). ^{1}H-NMR ((D_6)DMSO): 10.80 (*s*, N*H*npeoc); 8.03–8.21 (*m*, H–C(6), 4 H *o* to NO_2); 7.19–7.69 (*m*, 14 H, $(MeO)_2$*Tr*, 4 H *m* to NO_2, N*H*npeoc); 6.72–6.93 (*m*, H–C(5), 4 H *o* to MeO); 5.94 (*d*, H–C(1')); 5.56 (*d*, HO–C(3')); 4.18–4.37 (*m*, 2 OCH_2CH_2, H–C(3'), H–C(2')); 4.02 (*m*, H–C(4')); 3.73 (*s*, 2 MeO); 3.15–3.34 (*m*, 2 H–C(5')); 2.92–3.12 (2*m*, 2 OCH_2CH_2). Anal. calc. for $C_{48}H_{46}N_6O_{14}$ (930.93): C 61.93, H 4.98, N 9.03; found: C 62.36, H 5.19, N 8.90.

12. *2'-Azido-2'-deoxy-5'-*O*-(4-methoxytrityl)-3'-*O*-{[2-(4-nitrophenyl)ethoxy]carbonyl}uridine* (**14**). As described in *Exper. 8*, with **3** (337 mg, 0.622 mmol), 3-methyl-1-{[2-(4-nitrophenyl)ethoxy]carbonyl}-1*H*-imidazol-3-ium chloride (337 mg, 1.081 mmol), a cat. amount of DMAP, and molecular sieve in dry CH_2Cl_2 (15 ml). Purification by FC (CH_2Cl_1 + 1 → 5% MeOH): 324 mg (71%) of **14**. Colorless foam. UV (MeOH): 263 (4.03), 234 (4.35). IR (CH_2Cl_2): 2119. ^{1}H-NMR ((D_6)DMSO): 11.51 (*s*, N*H*npeoc); 8.14 (*d*, 2 H *o* to NO_2); 7.63 (*d*, H–C(6)); 7.54 (*d*, 2 H *m* to NO_2); 7.19–7.37 (*m*, 12 H, MeO*Tr*); 6.88 (*m*, 2 H *o* to MeO); 5.76 (*d*, H–C(1')); 5.55 (*d*, H–C(5)); 5.22 (*m*, H–C(3')); 4.75 (*m*, H–C(2')); 4.37–4.48 (*m*, OCH_2CH_2); 4.09–4.12 (*m*, H–C(4')); 3.72 (*s*, MeO); 3.26–3.30 (*m*, 2 H–C(5')); 3.06–3.11 (*m*, OCH_2CH_2). Anal. calc. for $C_{38}H_{34}N_6O_{10}$ (734.73): C 62.12, H 4.66, N 11.44; found: C 61.44, H 4.76, N 11.17.

13. *2'-Amino-2'-deoxy-5'-*O*-(4-methoxytrityl)uridine* (**15**). As described in *Exper. 10*, with **3** (322 mg, 0.564 mmol) and Ph_3P (464 mg, 1.77 mmol) in pyridine (50 ml), dioxane (50 ml), and 25% aq. NH_3 soln. (50 ml), at r.t., 15 h. Purification by FC ($CHCl_3$, $CHCl_3$ + 10% MeOH): 290 mg (95%) of **15**. Colorless foam. UV (MeOH): 262 (3.99), 230 (4.10). ^{1}H-NMR ((D_6)DMSO): 7.69 (*d*, H–C(6)); 7.16–7.41 (*m*, 12 H, MeO*Tr*); 6.90 (*d*, 2 H *o* to MeO); 5.64 (*d*, H–C(1')); 5.39 (*m*, HO–C(3'), H–C(5)); 4.39 (*m*, H–C(2')); 3.96 (*m*, H–C(3'), H–C(4')); 3.75 (*s*, MeO); 3.09–3.46 (2*m*, 2 H–C(5')). Anal. calc. for $C_{29}H_{27}N_5O_6$ · ½ H_2O (524.58): C 66.40, H 5.76, N 7.88; found: C 66.04, H 5.85, N 8.33.

14. *2'-Amino-2'-deoxy-5'-*O*-(4,4'-dimethoxytrityl)uridine* (**16**). As described in *Exper. 10*, with **4** (6.0 g, 10.5 mmol) and Ph_3P (8.26 g, 31.49 mmol) in pyridine (100 ml), dioxane (100 ml), and 25% aq. NH_3 soln. (100 ml), at r.t., 15 h. Purification by FC ($CHCl_3$/MeOH 49:1, 19:1, 4:1): 5.89 g (94%) of **16**. Colorless foam. UV (MeOH): 263 (4.03), 234 (4.35). ^{1}H-NMR ((D_6)DMSO): 7.60 (*d*, H–C(6)); 7.12–7.39 (*m*, 9 H, $(MeO)_2$*Tr*); 6.83 (*m*, 4 H *o* to MeO); 5.64 (*d*, H–C(1')); 5.39 (*m*, H–C(5), HO–C(3')); 4.45 (*d*, H–C(2')); 3.95 (*m*, H–C(4'), H–C(3')); 3.72 (*s*, 2 MeO); 3.09–3.46 (*m*, 2 H–C(5')). Anal. calc. for $C_{30}H_{31}N_3O_7$ · ½ H_2O (5.54.61): C 64.97, H 5.82, N 7.58; found: C 64.87, H 5.79, N 7.51.

15. *2'-Amino-2'-deoxy-5'-*O*-(4-methoxytrityl-2'-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)uridine* (**17**). To a cooled soln. (ice-water) of **15** (1 g, 1.94 mmol) in dry pyridine (50 ml), 2-(4-nitrophenyl)ethyl carbonochloridate (669 mg, 2.91 mmol) was added. After 15 min stirring at low temp., the ice-bath was removed, and stirring was continued for 1 h at r.t. The mixture was evaporated *in vacuo* and co-evaporated three times with toluene. The residue was pre-adsorbed on silica gel (2 g) and purified by FC (toluene, toluene/AcOEt 1:1 → +2% MeOH): 790 mg (79%) of **17**. Amorphous solid. UV (MeOH): 265 (4.26), 230 (4.30). ^{1}H-NMR ((D_6)DMSO): 11.39 (*s*, NH); 8.14 (*d*, 2 H *o* to NO_2); 7.63 (*d*, H–C(6)); 7.54 (*d*, 2 H *m* to NO_2); 7.12–7.41 (*m*, 13 H, MeO*Tr*, N*H*npeoc); 6.90 (*d*, 2 H *o* to MeO); 5.85 (*d*, H–C(1')); 5.61 (*d*, HO–C(3')); 5.41 (*d*, H–C(5)); 3.98–4.2 (*m*, H–C(3'), H–C(2'), H–C(4'), OCH_2CH_2); 3.73 (*s*, MeO); 3.16–3.24 (*m*, 2 H–C(5')); 2.97–3.09 (*t*, OCH_2CH_2). Anal. calc. for $C_{38}H_{36}N_4O_{10}$ (708.73): C 64.40, H 5.12, N 7.91; found: C 64.23, H 5.31, N 7.38.

16. *2'-Deoxy-5'-*O*-(4,4'-dimethoxytrityl)-2'-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)uridine* (**18**). As described in *Exper. 15*, with **16** (3.79 g, 6.93 mmol), 2-(4-nitrophenyl)ethyl carbonochloridate (1.76 g, 7.64 mmol) in dry pyridine (60 ml). Purification by FC (toluene/AcOEt 1:1, $CHCl_3$/MeOH 19:1): 4.43 g (87%) of **18**. Amorphous solid. UV (MeOH): 266 (4.29), 235 (4.37). ^{1}H-NMR ((D_6)DMSO): 11.40 (*s*, NH); 8.19 (*d*, 2 H *o* to NO_2); 7.63 (*d*, H–C(6)); 7.54 (*d*, 2 H *m* to NO_2); 7.12–7.39 (*m*, 10 H, $(MeO)_2$*Tr*, N*H*npeoc); 6.89 (*m*, 4 H *o* to MeO); 5.89 (*d*, H–C(1')); 5.63 (*d*, HO–C(3')); 5.41 (*m*, H–C(5)); 4.12–4.39 (*m*, H–C(2'), H–C(3'), OCH_2CH_2); 4.01 (*m*, H–C(4')); 3.72 (*s*, 2 MeO); 3.12–3.31 (*m*, 2 H–C(5')); 3.09 (*t*, OCH_2CH_2). Anal. calc. for $C_{39}H_{38}N_4O_{11}$ (738.76): C 63.58, H 5.20, N 7.60; found: C 63.16, H 5.43, N 7.77.

17. *2'-Deoxy-2'-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)uridine* (**19**). A soln. of **18** in 6% TFA in CH_2Cl_2/MeOH 4:1 (50 ml) was stirred at r.t. for 3 h and then evaporated. The residue was washed several times with Et_2O and dried: 2.21 g (88%) of **19**. Amorphous solid. UV (MeOH): 264 (4.21). ^{1}H-NMR ((D_6)DMSO):

11.33 (*s*, NH); 8.14 (*d*, 2 H *o* to NO_2); 7.88 (*d*, H–C(6)); 7.53 (*d*, 2 H *m* to NO_2); 6.98 (*d*, N*H*npeoc); 6.65 (br. *s*, HO–C(5')); 5.87 (*d*, H–C(1')); 5.67 (*d*, H–C(5)); 5.35 (br. *s*, HO–C(3')); 4.18–4.20 (*m*, H–C(2'), OCH_2CH_2); 4.05 (*m*, H–C(3')); 3.88 (*m*, H–C(4')); 3.56 (*m*, 2 H–C(5')); 2.97 (*t*, OCH_2CH_2). Anal. calc. for $C_{18}H_{20}N_4O_6 \cdot H_2O$ (455.39): C 47.58, H 4.88, N 12.32; found: C 47.24, H 4.47, N 11.62.

18. *2'-Deoxy-2'-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)-3',5'-bis-*O*-(trimethylsilyl)uridine* (**20**). Dry **19** (136 mg, 0.312 mmol) and O^6-[2-(4-nitrophenyl)ethyl]guanine (190 mg, 0.561 mmol) [36][37] were dissolved in MeCN (20 ml), and a cat. amount of $(NH_4)_2SO_4$ and HMDS (0.4 ml) were added. After refluxing for 1 h, a clear soln. was obtained, the soln. was evaporated *in vacuo*. The residue was dissolved again in dry MeCN (20 ml) and Me_3Si-Tf (90 mg, 74 µl, 0.406 mmol) was added. After refluxing for 3.5 h, the soln. was evaporated *in vacuo*, the residue dissolved in $CHCl_3$ and washed with sat. $NaHCO_3$ soln. (2 × 30 ml), dried ($MgSO_4$), and evaporated. The resulting residue was purified by FC ($CHCl_3$/MeOH 49:1, 19:1, 9:1): 68 mg (38%) of **20**. Colorless foam. UV (MeOH): 264 (4.28). ^{1}H-NMR ((D_6)DMSO): 11.34 (*s*, NH); 8.12 (*d*, 2 H *o* to NO_2); 7.79 (*d*, H–C(6)); 7.52 (*d*, 2 H *m* to NO_2); 7.35 (*d*, N*H*npeoc); 5.85 (*d*, H–C(1')); 5.68 (*d*, H–C(5)); 4.21–4.32 (*m*, H–C(2'), OCH_2CH_2); 4.16–4.18 (*m*, H–C(3')); 3.85 (*m*, H–C(4')); 3.63–3.72 (*m*, 2 H–C(5')); 2.95–3.00 (*m*, OCH_2CH_2); 0.20–0.10 (*s*, 2 Me_3Si). Anal. calc. for $C_{24}H_{36}N_4O_9Si_2$ (580.75): C 49.64, H 6.25, N 9.65, C 50.27, H 6.25, N 10.16.

19. *2'-Deoxy-2'-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)-*O^6*-[2-(4-nitrophenyl)ethyl]-*N^2*,3',5'-*O*-tris-(trimethylsilyl)guanosine* (**21**). As described in *Exper. 18*, with **19** (100 mg, 0.229 mmol) and O^6-[2-(4-nitrophenyl)ethyl]guanine (139 mg, 0.412 mmol) in dry MeCN (5 ml), HMDS (74 mg, 96 µl, 0.458 mmol), and BSA (93 mg, 112 µl, 0.458 mmol), refluxing for 1 h. After evaporation, the residue was dissolved in MeCN (15 ml) and Me_3Si-Tf (90 mg, 74 µl, 0.312 mmol) was added and the mixture refluxed for 15 h. Purification by FC ($CHCl_3$/MeOH 49:1 and 19:1, $CHCl_3$/MeOH 9:1, $CHCl_3$/MeOH 4:11): 68 mg (35%) of **21**. Colorless foam. UV (MeOH): 275 (4.54), 253 (4.42). ^{1}H-NMR ((D_6)DMSO): 8.16 (*d*, 2 H *o* to NO_2); 8.05 (*d*, 2 H *o* to NO_2); 7.96 (*s*, H–C(8)); 7.61 (*d*, 2 H *m* to NO_2); 7.56 (*d*, N*H*npeoc); 7.46 (*d*, 2 H *m* to NO_2); 6.51 (br. *s*, NH_2); 5.84 (*d*, H–C(1')); 4.81–4.83 (*m*, H–C(2')); 4.63–4.68 (*m*, OCH_2CH_2); 4.13–4.18 (*m*, H–C(3'), OCH_2CH_2); 3.85 (*m*, H–C(4')); 3.67 (*m*, 2 H–C(5')); 3.15–3.26 (*m*, OCH_2CH_2); 2.85–2.93 (*m*, OCH_2CH_2); 0.03–0.07 (*m*, 3 Me_3Si). Anal. calc. for $C_{36}H_{52}N_8O_{10}Si_3$ (841.11): C 51.41, H 6.23, N 13.32; found: C 51.31, H 5.85, N 13.33.

20. *2'-Deoxy-2'-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)-*O^6*-[2-(4-nitrophenyl)ethyl]guanosine* (**22**). A soln. of **19** (512 mg, 1.17 mmol), O^6-[2-(4-nitrophenyl)ethyl]guanine (562 mg, 1.28 mmol) [36], HMDS (755 mg, 976 µl, 4.68 mmol), and $(NH_4)_2SO_4$ in dry MeCN (25 ml) was heated under reflux, until a clear soln. was obtained (1 h). Then Me_3Si-Tf (318 mg, 260 µl, 1.4 mmol) was added, and heating under reflux was continued for 4 h. To remove the Me_3Si groups, after evaporation *in vacuo*, the residue was dissolved in MeOH, and NH_4F (217 mg, 5.85 mmol) was added. The mixture was stirred for 2 min, then silica gel (3 g) was added and evaporated. Purification by FC (toluene/AcOEt 1:1, toluene/AcOEt 1:1 + 1 → 5% MeOH): 634 mg (85%) of **22**. Colorless foam. UV (MeOH): 276 (4.43), 253 (4.33). ^{1}H-NMR ((D_6)DMSO): 8.16 (*d*, 2 H *o* to NO_2); 8.08 (*d*, 2 H *o* to NO_2); 7.98 (*s*, H–C(8)); 7.61 (*d*, 2 H *m* to NO_2); 7.45 (*d*, 2 H *m* to NO_2); 7.17 (*d*, N*H*npeoc); 6.46 (br. *s*, NH_2); 5.80 (*d*, H–C(1')); 5.60 (*d*, HO–C(3')); 5.19 (*t*, HO–C(5')); 4.57–4.75 (*m*, H–C(2'), OCH_2CH_2); 4.09–4.14 (*m*, H–C(3'), OCH_2CH_2); 3.92 (*m*, H–C(4')); 3.55 (*m*, 2 H–C(5')); 3.25 (*t*, OCH_2CH_2); 2.92 (*t*, OCH_2CH_2). Anal. calc. for $C_{36}H_{52}N_8O_{10}Si_3 \cdot H_2O$ (654.59): C 51.38, H 4.62, N 17.12; found: C 51.11, H 4.68, N 16.46.

21. *2'-Deoxy-2'-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)-*O^6*-[2-(4-nitrophenyl)ethyl]-3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,2-diyl)guanosine* (**23**). To soln. of **22** (811 mg, 1.27 mmol) in dry pyridine (10 ml), 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane was added and stirred overnight. After evaporation, the residue was purified by FC (toluene/AcOEt 1:1, toluene/AcOEt 1:1 + 1% MeOH): 790 mg (73%) of **23**. Colorles foam. UV (MeOH): 275 (4.42), 255 (4.32). ^{1}H-NMR ((D_6)DMSO): 8.03–8.21 (1*s*, 2*d*, H–C(8), 4 H *o* to NO_2); 7.59 (*d*, 2 H *m* to NO_2); 7.51 (*d*, N*H*npeoc); 7.45 (*d*, 2 H *m* to NO_2); 6.46 (br. *s*, NH_2); 5.78 (*d*, H–C(1')); 4.61–4.79 (*m*, H–C(2'), OCH_2CH_2); 4.50 (*m*, H–C(3')); 4.12 (*t*, OCH_2CH_2); 3.89 (*m*, 2 H–C(5'), H–C(4')); 3.25 (*t*, OCH_2CH_2); 2.92 (*t*, OCH_2CH_2); 0.78–1.13 (*m*, 2 $(Me_2CH)_2Si$). Anal. calc. for $C_{36}H_{54}N_8O_{11}Si_2 \cdot {}^1/_2\,H_2O$ (8.76.09): C 53.47, H 6.33, N 12.79; found: C 53.92, H 6.52, N 12.04.

22. *2'-Deoxy-*N^2*-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2'-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)-*O^6*-[2-(4-nitrophenyl)ethyl]-3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)guanosine* (**24**). As described in *Exper. 15*, with **23** (800 mg, 0.914 mmol), 2-(4-nitrophenyl)ethyl carbonodichloridate (1.05 g, 4.57 mmol), and molecular sieve in dry pyridine (25 ml, vigorously stirred at 0° for 30 min; r.t., 3 d). Purification by FC (toluene/AcOEt 1:1): 685 mg (70 %) of **24**. Colorless foam. UV (MeOH): 268 (4.57), 213 (4.62). ^{1}H-NMR ((D_6)DMSO): 10.33 (*s*, N*H*npeoc); 8.36 (*s*, H–C(8)); 8.02–8.19 (*d*, 4 H *m* to NO_2); 7.41–7.65 (*d*, 4 H *m* to NO_2, N*H*npeoc); 5.86 (*d*, H–C(1')); 4.71–4.89 (*m*, H–C(2'), H–C(3'), OCH_2CH_2); 4.32 (*t*, OCH_2CH_2); 4.16 (*t*, OCH_2CH_2); 3.83–4.11 (*m*, 2 H–C(5'), H–C(4')); 3.29 (*t*, OCH_2CH_2); 3.12 (*t*, OCH_2CH_2); 2.92 (*t*, OCH_2CH_2); 0.81–1.12

(*m*, 2 $(Me_2CH)_2Si$). Anal. calc. for $C_{48}H_{61}N_6O_{15}Si_2$ (1060.24): C 54.38, H 5.80, N 11.89; found: C 54.82, H 5.89, N 11.66.

23. *2'-Deoxy-N²-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2'-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)-O⁶-[2-(4-nitrophenyl)ethyl]guanosine* (**25**). To a soln. of **24** (200 mg, 0.187 mmol) in dry THF (5 ml), $Bu_4NF \cdot 3H_2O$ (129 mg, 0.412 mmol) and AcOH (239 mg, 227 µl, 4.12 mmol) were added. After stirring for 3 d, the soln. was diluted with AcOEt and washed twice with sat. $NaHCO_3$ soln., dried, and evaporated *in vacuo*. The residue was purified by FC ($CHCl_3$/MeOH 49:1, $CHCl_3$/MeOH 19:1, toluene/AcOEt 1:1 + 1% MeOH): 119 mg (78%) of **25**. Colorless foam. UV (MeOH): 268 (4.64), 213 (4.67). ^{1}H-NMR ((D_6)DMSO): 10.33 (*s*, NHnpeoc); 8.34 (*s*, H–C(8)); 7.98–8.19 (*d*, 4 H *m* to NO_2); 7.35–7.61 (*d*, 4 H *m* to NO_2); 7.15 (*d*, NHnpeoc); 5.91 (*d*, H–C(1')); 5.59 (*d*, HO–C(3')); 5.01 (*t*, HO–C(5')); 4.68–4.83 (*m*, H–C(2'), OCH_2CH_2); 4.32 (*t*, OCH_2CH_2); 4.28 (*m*, H–C(3')); 4.16 (*t*, OCH_2CH_2); 3.98 (*m*, H–C(4')); 3.49–3.71 (*m*, 2 H–C(5')); 3.26 (*t*, OCH_2CH_2); 3.12 (*t*, OCH_2CH_2); 2.92 (*t*, OCH_2CH_2). Anal. calc. for $C_{32}H_{35}N_9O_{14} \cdot H_2O$ (847.75): C 52.32, H 4.40, N 14.87; found: C 52.45, H 4.42, N 14.89.

24. *2'-Deoxy-5'-O-(4,4'-dimethoxytrityl)-N²-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2'-({[2-(4-nitrophenyl)-ethoxy]carbonyl}amino)-O⁶-[2-(4-nitrophenyl)ethyl]guanosine* (**26**). To a soln. of **25** (940 mg, 1.149 mmol) in dry pyridine (10 ml), 4,4'-dimethoxytrityl chloride (492 mg, 1.26 mmol) and molecular sieve (4 Å) were added. After stirring overnight, filtration and evaporation gave a residue which was dissolved in $CHCl_3$, washed twice with sat. $NaHCO_3$ soln. and brine, and dried ($MgSO_4$). After evaporation, the residue was purified by FC (toluene/AcOEt 1:1): 686 mg (53%) of **26**. Colorless foam. UV (MeOH): 269 (4.19), 236 (4.11), 216 (4.40). ^{1}H-NMR ((D_6)DMSO): 10.28 (*d*, NHnpeoc); 8.22 (*s*, H–C(8)); 8.08–8.18 (*m*, 6 H *o* to NO_2); 7.13–7.68 (*m*, 16 H, $(MeO)_2Tr$, NHnpeoc, 6 H *m* to NO_2); 6.73 (*m*, 4 H *o* to NO_2); 5.81 (*d*, H–C(1')); 5.61 (*d*, HO–C(3')); 4.91 (*m*, H–C(2')); 4.74 (*t*, OCH_2CH_2); 4.28–4.39 (*m*, H–C(4'), OCH_2CH_2); 4.18 (*m*, OCH_2CH_2); 3.69 (*s*, 6 H *o* to 2 MeO); 3.31 (*m*, 2 H–C(5'), OCh_2CH_2); 3.16 (*t*, OCH_2CH_2); 2.93 (*t*, OCH_2CH_2). Anal. calc. for $C_{57}H_{52}N_9O_{16}$ (867.08): C 61.18, H 4.68, N 11.26; found: C 60.98, H 4.82, N 10.98.

25. *3,5-O-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl-9-{2-O-[(trifluoromethyl)sulfonyl]-β-D-arabinofuranosyl}adenine* (**27**) [32][38]. A soln. of 9-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl-β-D-arabinofuranosyl]-adenine [32][38] (10 g, 19.6 mmol) and DMAP (7.2 g, 58.5 mmol) in dry CH_2Cl_2 (140 ml) was cooled under N_2 to −30° to −50°. After stirring for 30 min, diluted trifluoromethanesulfonyl anhydride (Tf_2O; 6.96 g, 4 ml, 24.5 mmol in CH_2Cl_2 (5 ml)) was dropped slowly to the soln. Stirring was continued for 15 min, and the mixture was allowed to reach r.t. and stirred further for 30 to 45 min. The mixture was poured into ice-water (250 ml), washed with sat. $NaHCO_3$ soln. (200 ml), brine (200 ml), and CH_2Cl_2 (90 ml). The combined org. layers were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. Purification by FC ($CHCl_3$/MeOH 49:1): 11.7 g (93%) of **27**. Colorless foam. UV (MeOH): 258 (4.15). ^{1}H-NMR ((D_6)DMSO): 8.29–8.07 (2*s*, H–C(8), H–C(2)); 7.46 (br. *s*, NH_2); 6.47 (*d*, H–C(1')); 6.05 (*t*, H–C(2')); 5.65 (*t*, H–C(3')); 4.11–4.21 (*m*, H–C(4')); 3.82–4.01 (*m*, 2 H–C(5')); 0.83–1.18 (*m*, 2 $(Me_2CH)_2$). Anal. calc. for $C_{23}H_{38}F_3N_5O_7SSi_2$ (641.80): C 43.04, H 5.97, N 10.91; found: C 43.06, H 5.92, N 10.40.

26. *2'-Azido-2'-deoxy-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)adenosine* (**28**) [32]. To a soln. of **27** (1.7 g, 2.69 mmol) in dry DMF (80 ml), LiN_3 [51] (656 mg, 13.4 mmol) was added. After stirring at r.t. for 2 h, the mixture was poured into ice-water (150 ml), diluted with AcOEt (100 ml), and washed several times with brine (100 ml). The combined org. layers were dried ($MgSO_4$) and evaported *in vacuo*: 1.28 g (90%) of **28**. Colorless foam. UV (MeOH): 258 (4.19). IR (CH_2Cl_2). 2121. ^{1}H-NMR ((D_6)DMSO): 8.05, 8.22 (2*s*, H–C(8), H–C(2)); 7.39 (*s*, NH_2); 5.81 (*d*, H–C(1')); 5.44 (*dd*, H–C(3')); 5.00 (*d*, H–C(2')); 3.85–4.12 (*m*, 2 H–C(5'), H–C(4')); 0.89–1.21 (*m*, 2 $(Me_2CH)_2Si$). Anal. calc. for $C_{22}H_{38}N_8O_4Si_2 \cdot {}^1/_2$ AcOEt (566.81): C 48.81, H 7.47, N 19.77; found: C 48.21, H 7.04, N 19.73.

27. *2'-Amino-2'-deoxy-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)adenosine* (**29**) [32]. 27.1. *Radical Reduction*. To a soln. of **28** (200 mg, 0.374 mmol) in dry toluene (5 ml), Bu_3SnH (248 µl, 272 mg, 0.935 mmol) was added dropwise *via* a syringe. The mixture was stirred for 15 min under N_2. Then, a cat. amount of AIBN was added and the mixture heated under reflux for 90 min. For the workup, the mixture was evaporated *in vacuo*, dissolved in H_2O/AcOEt and washed with AcOEt (20 ml), sat. $NaHCO_3$ soln. (20 ml), and AcOEt (20 ml). The combined org. layers were dried ($MgSO_4$), evaporated, and the resulting residue was purified by FC ($CHCl_3$/MeOH 19:1): 157 mg (82%) of **29**.

27.2. Staudinger *Reduction* [30][31]. To a soln. of **28** (1.63 g, 3 mmol) in dry THF (80 ml), PPh_3 (1 g, 3.96 mmol) was added. The mixture was stirred for 7 h at r.t., finally H_2O was added and stirring continued overnight. For workup, the soln. was evaporated, dissolved in AcOEt, dried ($MgSO_4$), and evaporated. The crude product was purified by FC (CH_2Cl_2/MeOH 19:1, 9:1): 1.44 g (94%) of **29**.

27.3. Staudinger *Reduction with PPH_3 in Dioxane/Pyridine* [25]. A mixture of **28** (11.6 g, 21.7 mmol) and PPh_3 (17 g, 65 mmol) in pyridine (250 ml), aq. ammonia (250 ml), and dioxane (70 ml) was stirred at r.t. for 24 h and evaporated *in vacuo*. The resulting residue was dissolved in AcOEt, dried ($MgSO_4$), and purified by FC ($CHCl_3$/MeOH 19:1, 9:1, 4:1): 4.3 g (39%) of **29** and 4.4 g (40%) of **30**.

Data of **29**. Colorless foam. UV (MeOH): 259 (4.16). ^{1}H-NMR ((D$_6$)DMSO): 8.23, 8.07 (2*s*, H–C(8), H–C(2)); 7.29 (br. *s*, NH_2); 5.72 (*d*, H–C(1′)); 4.81 (*d*, H–C(3′)); 3.88–4.01 (*m*, H–C(4′), 2 H–C(5′), H–C(2′)); 2.10 (br. *s*, NH_2); 0.89–1.13 (*m*, 2 (Me_2CH)$_2$). Anal. calc. for $C_{22}H_{40}N_6O_4Si_2$ (508.77): C 51.94, H 7.92, N 16.52; found: C 48.50, H 7.99, N 16.53.

Data of **30**. Amorphous solid. UV (MeOH): 258 (4.18). ^{1}H-NMR ((D$_6$)DMSO): 8.21, 8.10 (*s*, H–C(8), H–C(2)); 7.26 (br. *s*, NH_2); 6.09 (*s*, HO–C(5)); 5.71 (*d*, H–C(1′)); 5.49 (br. *s*, SiOH); 3.78–4.11 (*m*, H–C(4′), 2 H–C(5′), H–C(2′), H–C(3′)); 1.98 (br. *s*, NH_2); 0.89–1.13 (*m*, 2 (Me_2CH)$_2$). Anal. calc. for $C_{22}H_{42}N_6O_4Si_2 \cdot {}^1/_2\ H_2O$ (528.79): C 49.97, H 8.39, N 15.89; found: C 50.11, H 7.81, N 15.66.

28. *2′-Deoxy-*N^6*-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2′-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)-3′,5′-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)adenosine* (**31**) *and 2′-Deoxy-2′-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)adenosine* (**32**). As described in *Exper. 15*, with **29** (2 g, 3.9 mmol), 2-(4-nitrophenyl)ethyl carbonochloridate (3.6 g, 11.7 mmol), molecular sieve (4 Å), and a cat. amount of DMAP in dry CH_2Cl_2 (60 ml; carefully stirred at r.t. for 3 d). Purification by FC (toluene/AcOEt 1:1, toluene/AcOEt 1:1 + 1% MeOH): **31** was eluted first: 3 g (86%); then **32**: 219 mg (8%).

Data of **31**: Colorless foam. UV (MeOH): 266 (4.56), 277 (sh, 4.51). ^{1}H-NMR ((D$_6$)DMSO): 10.64 (br. *s*, NH_2); 8.63, 8.54 (2*s*, H–C(8), H–C(2)); 8.10–8.16 (*m*, 2*d*, 4 H *o* to NO_2); 7.66 (*d*, N*H*npeoc); 7.59 (*d*, 2 H *m* to NO_2); 7.49 (*d*, 2 H *m* to NO_2); 5.98 (*d*, H–C(1′)); 4.81–4.98 (*m*, H–C(2′), H–C(3′)); 4.38 (*t*, OCH_2CH_2); 4.12–4.82 (*m*, OCH_2CH_2); 3.82–4.01 (*m*, H–C(4′), 2 H–C(5′)); 3.10 (*t*, OCH_2CH_2); 2.79 (*t*, OCH_2CH_2); 0.78–1.13 (*m*, (Me_2CH)$_2$). Anal. calc. for $C_{40}H_{54}N_8O_{12}Si_2$ (895.09): C 53.68, H 6.08, N 12.52; found: C 53.16, H 6.16, N 12.21.

Data of **32**: Colorless foam. UV (MeOH): 261 (4.36). ^{1}H-NMR ((D$_6$)DMSO): 8.07–8.31 (*d*, 2*s*, H–C(2), H–C(8), 2 H *o* to NO_2); 7.63 (*d*, N*H*npeoc); 7.50 (*d*, 2 H *m* to NO_2); 7.35 (br. *s*, NH_2); 5.87 (*d*, H–C(1′)); 4.73–5.94 (*s*, H–C(2′)); 4.12–4.28 (*m*, 2 H–C(5′)); 3.84–3.98 (*m*, H–C(3′), H–C(4′), OCH_2CH_2); 2.79 (*t*, OCH_2CH_2); 0.75–1.35 (*m*, (Me_2CH)$_2$Si). Anal. calc. for $C_{31}H_{47}N_7O_8Si_2$ (701.93): C 53.05, H 6.75, N 13.97; found: C 52.45, H 6.74, N 13.38.

29. *2′-Deoxy-*N^6*-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2′-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)-adenosine* (**33**). As described in *Exper. 23*, with **31** (3 g, 3.35 mmol), AcOH (2.01 g, 1.9 ml, 33.5 mmol), and $Bu_4NF \cdot 3H_2O$ (2.6 g, 8.38 mmol) in dry THF (75 ml); stirring at r.t. for 16 h; dilution with AcOEt (100 ml), extraction with H_2O (100 ml), sat. $NaHCO_3$, brine (75 ml), and AcOEt (75 ml), dried. Purification by FC (toluene/AcOEt 1:1, toluene/AcOEt/MeOH 5:4:1): 2.25 g (quant.) of **33**. UV (MeOH): 266 (4.62). ^{1}H-NMR ((D$_6$)DMSO): 10.61 (*s*, N*H*npeoc); 8.60 (2*s*, H–C(2), H–C(8)); 8.06–8.19 (2*d*, 4 H *o* to NO_2); 7.59, 7.44 (2*d*, 4 H *m* to NO_2); 7.25 (*d*, N*H*npeoc); 6.04 (*d*, H–C(1′)); 5.70 (*d*, HO–C(3′)); 5.21 (*t*, HO–C(5′)); 4.82–4.98 (*m*, H–C(2′)); 4.38 (*t*, OCH_2CH_2); 4.23 (*m*, H–C(3′)); 4.08 (*t*, OCH_2CH_2); 4.01 (*m*, H–C(4′)); 3.50–3.72 (*m*, 2 H–C(5′)); 3.06–3.17 (*t*, OCH_2CH_2); 2.75–2.98 (*t*, OCH_2CH_2). Anal. calc. for $C_{28}H_{28}N_8O_{11} \cdot {}^1/_2\ H_2O$ (661.69): C 50.84, H 4.42, N 16.96; found: C 50.79, H 4.59, N 16.80

30. *2′-Deoxy-5′-*O*-(4,4′-dimethoxytrityl)-*N^6*-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2′-({[2-(4-nitrophenyl)-ethoxy]carbonyl}amino)adenosine* (**34**). As described in *Exper. 24*, with **33** (1.64 g, 2.5 mmol) and $(MeO)_2TrCl$ (932 mg, 2.75 mmol) in dry pyridine (70 ml); stirring at r.t. for 15 h. Purification by FC (toluene/AcOEt 1:1, toluene/AcOEt/MeOH 5:4:1): 2.05 g (86%) of **34**. UV (MeOH): 266 (4.59), 235 (4.49). ^{1}H-NMR ((D$_6$)DMSO): 10.62 (*s*, N*H*npeoc); 8.48, 8.49 (2*s*, H–C(8), H–C(2)); 8.01–8.18 (2*d*, 4 H *o* to NO_2); 7.58 (*d*, N*H*npeoc); 7.47 (*d*, 2 H *m* to NO_2); 7.36 (*d*, 2 H *m* to NO_2); 7.09–7.28 (*m*, 9 H, $(MeO)_2OTr$); 6.78–6.83 (*m*, 4 H *o* to OMe); 6.07 (*d*, H–C(1′)); 5.76 (*d*, HO–C(3′)); 5.04–5.15 (*m*, H–C(2′)); 4.32–4.77 (*m*, OCH_2CH_2, H–C(3′)); 4.08–4.18 (*m*, OCH_2CH_2, H–C(4′)); 3.25 (*d*, 2 H–C(5′)); 3.09 (*t*, OCH_2CH_2); 2.93 (*t*, OCH_2CH_2). Anal. calc. for $C_{49}H_{46}N_8O_{13}$ (954.959): C 61.63, H 4.68, N 11.03; found: C 62.38, H 4.88, N 11.47.

31. *2′-Deoxy-*N^4*-{[2-(4-nitrophenyl)ethoxy]carbonyl-5′-*O*-(4-methoxytrityl)}-2′-({[2-(4-nitrophenyl)etho-xy]carbonyl}amino)cytidine 3′-[2-(4-Nitrophenyl)ethyl Diisopropylphosphoramidite]* (**35**). To a soln. of **12** (500 mg, 0.555 mmol) in dry MeCN (5 ml), 2-(4-nitrophenyl)ethyl tetraisopropylphosphorodiamidite (441 mg, 1.11 mmol) [39] and a cat. amount of 1*H*-tetrazole (19 mg, 0.28 mmol) were added under N_2. After stirring at r.t. for 15 h, the mixture was diluted with $CHCl_3$ (25 ml), washed with sat. $NaHCO_3$ soln. (2 × 25 ml) and brine (25 ml). The org. layer was dried ($MgSO_4$), evaporated *in vacuo*, and purified by FC (petroleum ether/acetone 4:1, 3:1, 2:1, 1:1): 440 mg (66%) of **35**. Colorless foam. UV (MeOH): 269 (4.1), 236 (4.9). ^{1}H-NMR ((D$_6$)DMSO): 10.87 (*s*, N*H*npeoc); 8.04–8.16 (*m*, H–C(6), 6 H *o* to NO_2); 7.12–7.84 (*m*, 19 H, MeO*Tr*, H–C(5), 6 H *m* to

NO_2); 6.86 (*d*, 2 H *o* to MeO); 5.96 (*d*, H–C(1′)); 4.14–4.37 (2*m*, 3 OCH_2CH_2, H–C(2′), H–C(3′)); 3.83 (*m*, H–C(4′)); 3.70 (*s*, MeO); 3.07–3.23 (*m*, 2 H–C(5′)); 2.85–3.04 (2*m*, 2 OCH_2CH_2); 2.80–2.83 (*m*, OCH_2CH_2); 0.89–1.12 (*m*, 2 Me_2CH). ^{31}P-NMR ((D$_6$)DMSO): 150.96; 150.19. Anal. calc. for $C_{61}H_{65}N_8O_{16}P$ + 1/3 $CHCl_3$ (1236.57): C 59.54, H 5.32, N 9.06; found: C 60.11, H 5.41, N 8.61.

32. *2′-Deoxy-*N^4*-{[2-(4-nitrophenyl)ethoxy]carbonyl-5′-*O*-(4,4′-dimethoxytrityl)}-2′-({[2-(4-nitrophenyl)-ethoxy]carbonyl}amino)cytidine 3′-[2-(4-Nitrophenyl)ethyl Diisopropylphosphoramidite]* (**36**). To a soln. of **13** (500 mg, 0.555 mmol), 2-(4-nitrophenyl)ethyl tetraisopropylphosphorodiamidite (427 mg, 1.07 mmol) in dry MeCN (5 ml), a 0.5M pyridine hydrochloride soln. (0.54 ml) was added under N_2, and the mixture was stirred at r.t. for 15 h. The mixture was evaporated *in vacuo*, dissolved in $CHCl_3$, washed with sat $NaHCO_3$ soln., and brine, and dried ($MgSO_4$). After evaporation, the crude product was purified by FC (toluene/AcOEt 2:1, 1:1): 467 mg (75%) of **36**. Colorless foam. UV (MeOH): 268 (4.46), 238 (4.22). ^{1}H-NMR ((D$_6$)DMSO): 10.87 (*s*, N*H*npeoc); 8.04–8.16 (*m*, H–C(6), 6 H *o* to NO_2); 7.12–7.84 (*m*, 17 H, $(MeO)_2Tr$, H–C(5), 6 H *m* to NO_2, NHnpeoc); 6.86 (*d*, 4 H *o* to MeO); 5.96 (*d*, H–C(1′)); 4.14–4.37 (2*m*, 3 OCH_2CH_2, H–C(2′), H–C(3′)); 3.83 (*m*, H–C(4′)); 3.70 (*s*, 2 MeO); 3.07–3.23 (*m*, 2 H–C(5′)); 3.85–3.04 (2*m*, 2 OCH_2CH_2); 2.80–2.83 (*m*, OCH_2CH_2); 0.89–1.12 (*m*, 2 Me_2CH). ^{31}P-NMR ((D$_6$)DMSO 161.7 MHz): 151.79; 151.39. Anal. calc. for $C_{61}H_{67}N_8O_{17}P \cdot 1/2$ AcOEt (1287.29): C 59.72, H 5.56, N 8.70; found: C 59.66, H 5.62, N 9.20.

33. *2′-Deoxy-5′-*O*-(4-methoxytrityl)-2′-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)uridine 3′-[2-(4-Nitrophenyl)ethyl Diisopropylphosphoramidite]* (**37**). As described in *Exper. 31*, with **17** (810 mg, 1.14 mmol), 2-(4-nitrophenyl)ethyl tetraisopropylphosphorodiamidite (910 mg, 2.29 mmol) [39] and 1*H*-tetrazole (40 mg, 0.57 mmol) in dry MeCN (7.5 ml), stirring at r.t. for 15 h. Purification by FC (toluene/AcOEt 2:1, toluene/AcOEt 1:1): 909 mg (79%) of **37**. Colorless foam. UV (MeOH): 265 (4.45), 232 (4.35). ^{1}H-NMR ((D$_6$)DMSO): 11.45 (*s*, NH); 7.29 (*m*, 4 H *o* to NO_2); 7.66 (*m*, H–C(6)); 7.12–7.49 (*m*, 17 H, MeO*Tr*, 4 H *m* to NO_2, N*H*npeoc); 6.87 (*d*, 2 H *o* to MeO); 5.87 (*m*, H–C(1′)); 5.47 (*m*, H–C(5)); 3.99–4.95 (*m*, H–C(2′), H–C(3′), H–C(4′), 2 OCH_2CH_2); 3.71 (*s*, MeO); 2.85–3.21 (*m*, 2 OCH_2CH_2, 2 H–C(5′)); 0.91–0.94 (*m*, 2 Me_2CH). ^{31}P-NMR ($CDCl_3$): 148.65; 148.18. Anal. calc. for $C_{52}H_{57}N_6O_{13}P$ (1005.04): C 62.14, H 5.72, N 8.36; found: C 62.23, H 5.80, N 8.38.

34. *2′-Deoxy-5′-*O*-(4,4′-dimethoxytrityl)-2′-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)uridine 3′-[2-(4-Nitrophenyl)ethyl Diisopropylphosphoramidite]* (**38**). As described in *Exper. 32*, with **18** (1 g, 1.35 mmol), 2-(4-nitrophenyl)ethyl tetraisopropylphosphorodiamidite (1.07 g, 2.70 mmol) in dry MeCN (10 ml), 0.5M pyridine hydrochloride soln. (1.35 ml) [40]; stirring at r.t. for 15 h. Purification by FC (toluene/AcOEt 2:1, toluene/AcOEt 1:1): 1.26 g (90%) of **36**. Colorless foam. UV (MeOH): 261 (4.03), 234 (4.36). ^{1}H-NMR ((D$_6$)DMSO): 11.41 (*s*, NH); 8.02–8.20 (*m*, 4 H *o* to NO_2); 7.63 (*d*, H–C(6)); 7.54 (*d*, 4 H *m* to NO_2); 7.09–7.39 (*m*, 10 H, $(MeO)_2Tr$, N*H*npeoc); 6.86 (*m*, 4 H *o* to OMe); 5.89 (*d*, H–C(1′)); 5.43 (*m*, H–C(5)); 4.12–4.39 (*m*, H–C(2′), H–C(3′), H–C(4′), 2 OCH_2CH_2); 3.72 (*s*, 2 MeO); 2.75–3.45 (4*m*, 2 OCH_2CH_2, 2 H–C(5′)); 0.91–0.94 (*m*, 2 Me_2CH). ^{31}P-NMR ((D$_6$)DMSO): 148.74, 148.34. Anal. calc. for $C_{53}H_{59}N_6O_{14}P$ (1035.67): C 61.47, H 5.74, N 8.11; found: C 61.74, H 5.88, N 8.18.

35. *2′-Deoxy-5′-*O*-(4,4′-dimethoxytrityl)-*N^2*-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2′-({[2-(4-nitrophenyl)-ethoxy]carbonyl}amino)-*O^6*-[2-(4-nitrophenyl)ethyl]guanosine 3′-[2-(4-Nitrophenyl)ethyl Diisopropylphosphoramidite]* (**39**). As described in *Exper. 32*, with **26** (184 mg, 0.164 mmol), 2-(4-nitrophenyl)ethyl tetraisopropylphosphorodiamidite (130 mg, 0.329 mmol) stirring at r.t. for 15 h. Purification by FC (toluene/AcOEt 2:1, 1:1): 157 mg (67%) of **39**. Colorless foam. UV (MeOH): 269 (4.64), 236 (4.35). ^{1}H-NMR ((D$_6$)DMSO): 10.23 (*d*, N*H*npeoc); 8.01–8.28 (*m*, 8 H *o* to NO_2, H–C(8)); 7.09–7.72 (*m*, 18 H, $(MeO)_2Tr$, N*H*npeoc, 8 H *m* to NO_2); 6.63 (*m*, 4 H *o* to MeO); 6.02 (*m*, H–C(1′)); 5.12 (*m*, H–C(2′)); 4.78 (*m*, OCH_2CH_2); 4.55 (*m*, H–C(3′)); 4.39 (*m*, OCH_2CH_2); 4.12 (*m*, 2OCH_2CH_2); 3.82 (*m*, H–C(4′)); 3.65 (*m*, 2 H–C(5′), 2 MeO); 3.31 (*m*, OCH_2CH_2); 3.08 (*m*, OCH_2CH_2); 2.81 (*t*, OCH_2CH_2); 0.82–0.99 (*m*, 2 Me_2CH). ^{31}P-NMR ($CDCl_3$): 152.15; 151.57. Anal. calc. for $C_{71}H_{73}N_{11}O_{19}P$ (1415.41): C 60.25, H 5.20, N 10.89; found: C 60.16, H 5.48, N 10.30.

36. *2′-Deoxy-5′-*O*-(4,4′-dimethoxytrityl)-*N^6*-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2′-({[2-(4-nitrophenyl)-ethoxy]carbonyl}amino)adenosine 3′-[2-(4-Nitrophenyl)ethyl Diisopropylphosphoramidite]* (**40**). 36.2. *1H-Tetrazole Activation*. As described in *Exper. 31*, with **30** (500 mg, 0.523 mmol), 2-(4-nitrophenyl)ethyl tetraisopropylphosphorodiamidite (416 mg, 1.00 mmol) and 1*H*-tetrazole (18 mg, 0.262 mmol) in dry MeCN (20 ml), stirring at r.t. for 15 h. Purification by FC (petroleum/acetone 4:1 to 1:1): 503 mg (77%) of **40**.

36.2. *Pyridine-Hydrochloride Activation*. As described in *Exper. 32*, with **30** (714 mg, 0.748 mmol), 2-(4-nitrophenyl)ethyl tetraisopropylphosphorodiamidite (568 mg, 1.428 mmol) and 748 µl of a 0.5M pyridine hydrochloride soln. in MeCN (7 ml); stirring at r.t. for 15 h. Purification by FC (toluene/AcOEt 1:1): 777 mg (83%) of **40**. Colorless foam. UV (MeOH): 273 (4.63), 267 (4.66), 237 (4.48). ^{1}H-NMR ((D$_6$)DMSO): 10.61 (*s*, N*H*npeoc); 8.49 (*m*, H–C(8), H–C(2)); 8.08–8.28 (3*d*, 6 H *o* to NO_2); 7.58 (*d*, N*H*npeoc); 7.16–7.46 (*m*, 15 H, $(MeO)_2Tr$, 6 H *m* to NO_2); 6.79 (*d*, 4 H *o* to MeO); 6.08–6.12 (*m*, H–C(1′)); 5.12–5.29 (*m*, H–C(2′)); 4.42–4.61 (*m*, H–C(3′));

4.32–4.40 (*m*, OCH_2CH_2); 4.04–4.26 (*m*, 2 OCH_2CH_2, H–C(4')); 3.68 (*s*, 2 MeO); 3.39–3.49 (*m*, 2 H–C(5')); 3.14 (*t*, OCH_2CH_2); 2.76–2.98 (*m*, 2 OCH_2CH_2); 0.88–1.12 (*m*, 2 Me_2CH). ^{31}P-NMR ($CDCl_3$): 150.53; 150.99. Anal. calc. for $C_{63}H_{67}N_{10}O_{16}P$ (1251.54): C 60.47, H 5.40, N 11.19; found: C 60.37, H 5.44, N 11.11.

37. *3'-O-(3-Carboxypropanoyl)-2'-deoxy-5'-O-(4,4'-dimethoxytrityl)-N^6-{[2-(4-nitrophenyl)ethoxy]carbonyl}-2'-({[2-(4-nitrophenyl)ethoxy]carbonyl}amino)adenosine* (**41**). To a soln. of **34** (470 mg, 0.492 mmol) in dry CH_2Cl_2 (10 ml), succinic anhydride (63 mg, 0.652 mmol) and DMAP (86 mg, 0.707 mmol) were added. After stirring for 3 d, the soln. was diluted with CH_2Cl_2, extracted with phosphate buffer (pH 7; 2 × 65 ml), 10% citric acid (2 × 50 ml), and H_2O (2 × 50 ml). The combined org. layer was dried ($MgSO_4$) and evaporated: 493 mg (95%) of **41**. Amorphous solid. UV (MeOH): 274 (4.49), 266 (4.55), 236 (4.44). ^{1}H-NMR ((D_6)DMSO): 12.31 (*s*, COOH); 10.63 (*s*, NHnpeoc); 8.49 (*s*, H–C(8), H–C(2)); 8.08–8.17 (*2d*, 4 H *o* to NO_2); 7.83 (*d*, NHnpeoc); 7.18–7.58 (*m*, 9 H, $(MeO)_2Tr$, 4 H *m* to NO_2); 6.80 (*d*, 4 H *o* to MeO); 6.13 (*d*, H–C(1')); 5.32–5.49 (*m*, H–C(2'), H–C(3')); 4.35–4.42 (*m*, OCH_2CH_2); 4.03–4.22 (*m*, OCH_2CH_2, H–C(4')); 3.71 (*s*, 2 OMe); 3.08–3.26 (*m*, OCH_2CH_2); 2.93–2.97 (*m*, OCH_2CH_2); 2.51–2.67 (*m*, $OCCH_2CH_2CO$, H–C(5')). Anal. calc. for $C_{53}H_{50}N_8O_{16} + H_2O$ (1073.05): C 59.33, H 4.88, N 10.00; found: C 59.33, H 4.88, N 10.00.

38. *2'-[(3-Carboxypropanoyl)amino]-2'-deoxy-5'-O-(4,4'-dimethoxytrityl)adenosine* (**42**). To a soln. of **41** (100 mg, 0.101 mmol) in dry pyridine (8 ml), DBU (616 mg, 4 mmol) was added, and the mixture was stirred at r.t. for 2 d. After neutralization with AcOH (240 mg, 4 mmol), the soln. was diluted with $CHCl_3$ and dropped slowly into Et_2O. The precipitate was filtered and dried: 36 mg (53%) of **42**. Amorphous solid. UV (MeOH): 260 (4.02), 228 (4.24). ^{1}H-NMR ((D_6)DMSO): 8.21 (*d*, NH); 8.01, 8.18 (2*s*, H–C(8), H–C(2)); 7.17–7.49 (*m*, 9 H, $(MeO)_2Tr$); 6.31 (*d*, 4 H *o* to MeO); 5.98 (*d*, H–C(1')); 5.78 (br. *s*, HO–C(3')); 5.15–5.28 (*m*, H–C(2')); 4.39 (*m*, H–C(3')); 4.12 (*m*, H–C(4')); 3.73 (*s*, 2 MeO); 3.21–3.38 (*m*, 2 H–C(5')); 2.26–2.42 (*m*, $OCCH_2CH_2CO$). Anal. calc. for $C_{35}H_{36}N_6O_8 \cdot 2\,H_2O$ (704.74): C 59.65, H 5.72, N 11.92; found: C 59.40, H 5.73, N 11.46.

39. *Solid-Support Material* **43** *from 500-Å LCAMA-CPG.* A mixture of **41** (16 mg, 16 μmol), 500-Å LCAMA-CPG (100 mg), [11][12][17], TOTU (6 mg, 18 μmol) and *N*-methylmorpholine (5 μl, 45 μmol), in dry MeCN (3 ml) was gently shaken for 3 h. The CPG material was collected in a glass funnel and washed with MeOH, DMF, pyridine, MeOH, acetone, and Et_2O, and then dried. Determination of loading: A defined amount of **43** (6 mg) was treated in a 10-ml calibrated flask with 0.2M TsOH in MeCN (10 ml). After 1 min, the absorbance at 498 nm was measured against 0.2M TsOH in MeCN. The loading *L* [μmol/g] can be calculated by the formula $L = A \times 10 \times 14.4/m$ (A = absorbance at 498 nm; m weight of CPG material **43** in mg) and gave for **43**: $L = 14$ μmol/g.

40. *Assembly of Oligonucleotides.* Syntheses were carried out using an *Applied Biosystems 392 DNA/RNA* synthesizer. Nucleoside-functionalized CPG [17][43] material was packed into a small *ABI* column, and cycles of nucleotide addition were carried out by programmed series of reagent and solvent washes based on recommended procedures with the following main steps. *1)* 5'-*O*-$(MeO)_2$Tr-deprotection in 135 s; the eluate from this step was collected and the absorbance at 498 nm measured to determined the condensation yields. *2)* Coupling: 0.1M phosphoramidite and 0.5M activation reagent in dry MeCN, delivered in alternating reagent pushes with a subsequent waiting time (see *Table 1*). *3)* Capping: Ac_2O/2,6-dimethylpyridine/THF 1:1:8 and 1-methyl-1*H*-imidazole/THF 16:84, delivered in one 10-s push with a subsequent wait time of 5 s. *4)* Oxidation: 0.05M I_2 in THF/pyridine/H_2O 7:2:1, delivered in one 10-s push with a subsequent waiting time of 15 s. Then, a cleavage programme was carried out: *1)* Cleavage of the base-protecting groups: 1M DBU in MeCN delivered in several pushes and following waiting steps (total wait time: 12 h). *2)* Cleavage from the support: conc. NH_3 soln. delivered in one push with a consecutive wait time of 4 × 2400 s (total waiting time 2.5 h). The reaction soln., containing only the oligonucleotide and NH_3, was collected and, after determination of the isolated amount of oligonucleotide by measurement of the absorbance at 260 nm, lyophilized in a *Speed-vac* concentrator under high vacuum.

41. *Melting Curves.* Absorbance *vs.* temp. curves were measured at 260 nm in Na_2HPO_3/NaH_2PO_4 buffer at pH 7.0; Na^+ conc. 0.15M, 0.3M, 0.12M, and 0.024M.

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Received April 3, 1998