93. Nucleotides

Part XLVIII[1])

Synthesis of 2′-Amino-2′-deoxyarabinonucleoside Phosphoramidite Building Blocks

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Chemical syntheses of 2′-amino-2′-deoxyarabinonucleosides of uracil, thymine, cytosine, adenine, and guanine and their conversion into suitably protected 3′-phosphoramidite building blocks **24–28** for oligonucleotide synthesis are described. The 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) group was used for protection of the aglycon and the 2′-amino functions.

1. Introduction. – Various arabinonucleosides, especially arabinosylcytosine (aC) and arabinosyladenine (aA) have interesting antiviral and antitumor activities [2]. Although aC is a potent drug against human acute myeloblastic leukemia [3–5], its usefulness is limited by its deficient stability against deamination by cytidine deaminase, forming inactive arabinosyluracil (aU). It has been found that 1-(2-azido-2-deoxy-β-D-arabinofuranosyl)cytosine and 1-(2-amino-2-deoxy-β-D-arabinofuranosyl)cytosine are stable against cytidine deaminase, showing similar biological activities as aC [6–8]. Due to the significance of these nucleosides, it may be of interest to introduce 2′-amino-2′-deoxyarabinonucleosides into oligonucleotides, especially because the introduction of 2′-amino-2′-deoxy**ribo**nucleosides of uracil and cytosine led to increased resistance against enzymatic degradation by snake-venom phosphodiesterase [9]. On the other hand, this structural modification is, however, also associated with a reduced hybridization of the oligonucleotide strands [10]. So 2′-amino-2′-deoxy**arabino**oligonucleotides may combine the higher stability against exonucleases with improved ability of hybridization.

For this reason, we would like to report the syntheses of suitably protected 2′-amino-2′-deoxyarabinonucleoside phosphoramidite building blocks. The synthesis of the starting 2′-amino-2′-deoxy-β-D-arabinonucleosides were performed according to literature. Protection of the aglycons and the 2′-amino function was achieved in the usual manner by the 2-(4-nitrophenyl)ethyl (npe) and the 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) group which have already been proven to be very efficient for the synthesis of oligodeoxynucleotides [11] and oligoarabinonucleotides [12].

2. Syntheses. – The synthetic approach towards the two series of 2′-amino-2′-deoxyarabinosylpyrimidines and -purines was based on two different strategies. The modified

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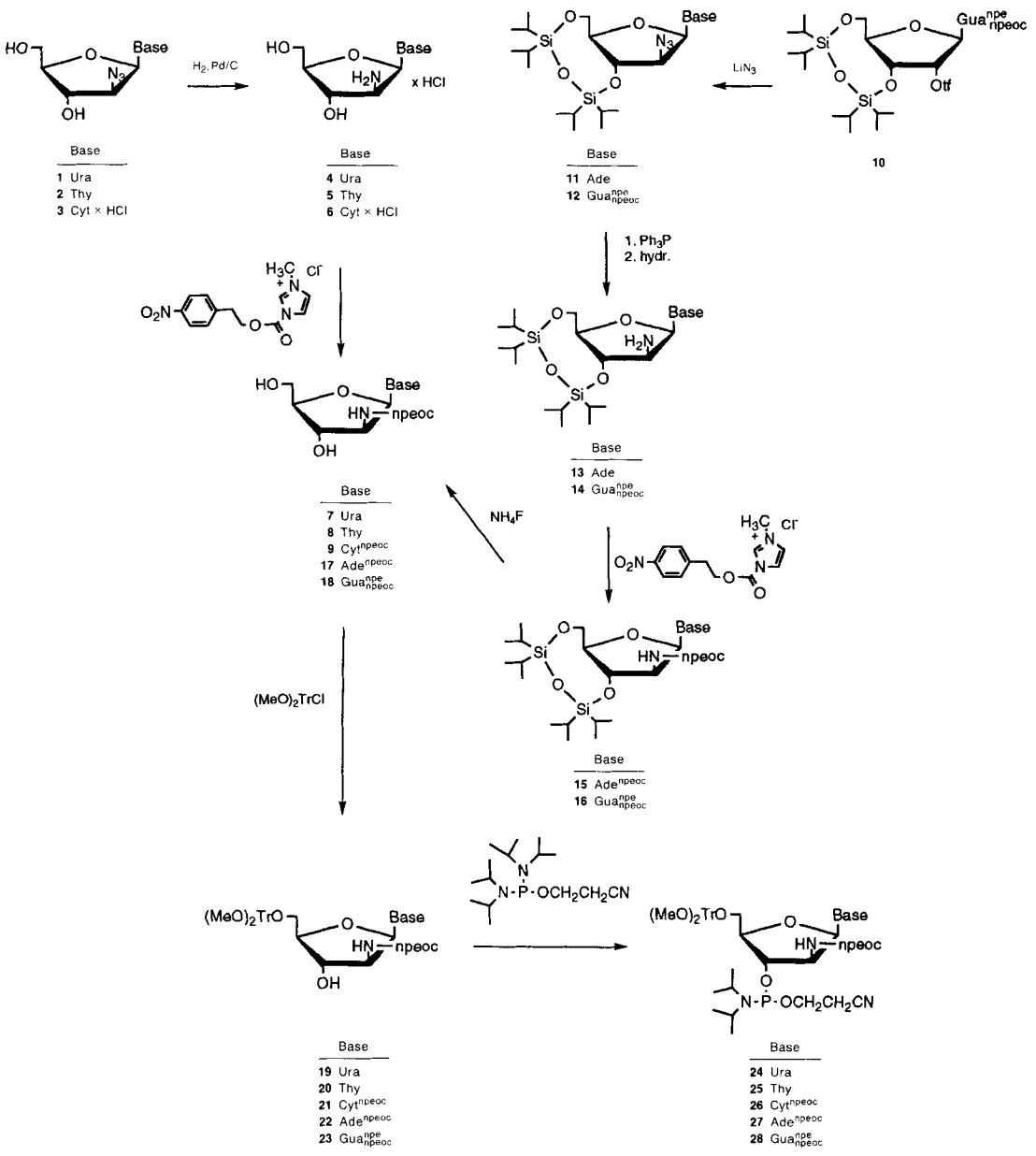
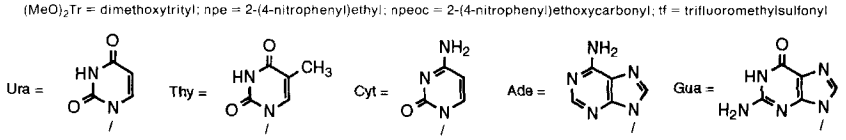
Scheme



$(MeO)_2Tr$ = dimethoxytrityl; npe = 2-(4-nitrophenyl)ethyl; npeoc = 2-(4-nitrophenyl)ethoxycarbonyl; tf = trifluoromethylsulfonyl



pyrimidine nucleosides **4–6** were prepared from the corresponding ribonucleosides which were first converted by the procedure of *Matsuda et al.* [13] [14] into 1-(2-azido-2-deoxy-β-D-arabinofuranosyl)uracil (**1**), 1-(2-azido-2-deoxy-β-D-arabinofuranosyl)thymine (**2**), and 1-(2-azido-2-deoxy-β-D-arabinofuranosyl)cytosine (**3**), respectively. The azido group of the latter was then reduced by hydrogenation over Pd/C in HCl/MeOH to yield **4–6** as crystalline products [6] [13] [15]. The subsequent introduction of the 2-(4-nitrophenyl)-ethoxycarbonyl (npeoc) group worked best with 3-methyl-1-[2-(4-nitrophenyl)ethoxy-carbonyl]-1*H*-imidazol-3-ium chloride [16] as acylating agent. In DMF solution and under 4-(dimethylamino)pyridine catalysis, this reagent protected the 2′-amino group selectively leading to **7** and **8** in yields of 75 and 79%, respectively. In the case of 1-(2-amino-2-deoxy-β-D-arabinofuranosyl)cytosine (**6**), the amino group of the aglycon and the sugar moiety could be blocked simultaneously, if the 3′- and 5′-hydroxy functions were silylated first by refluxing in hexamethyldisilazane (HMDS) to achieve a transient protection [17]. After acylation of the amino groups, the OH functions were desilylated with NH_4F yielding 1-{2-deoxy-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-D-arabino-furanosyl}-N^4-[2-(4-nitrophenyl)ethoxycarbonyl]cytosine (**9**) in 65% yield.

The syntheses of the 2′-amino-2′-deoxy-β-D-arabinopurine nucleosides were performed from appropriately protected precursors. The N^2-[2-(4-nitrophenyl)ethoxy-carbonyl]-O^6-[2-(4-nitrophenyl)ethyl]-2′-*O*-(trifluoromethylsulfonyl)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)guanosine (**10**) [18] and 9-[2-azido-2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]adenine (**11**) [19] resulted from multistep procedures already described in literature. The trifluoromethyl-sulfonyl group of **10** was displaced by nucleophilic attack of LiN_3 in DMF yielding 9-[2-azido-2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofurano-syl]-N^2-[2-(4-nitrophenyl)ethoxycarbonyl]-O^6-[2-(4-nitrophenyl)ethyl]guanine (**12**) in 92% yield. Reduction of the azido group of **11** and **12** was performed by *Staudinger* reaction with Ph_3P in THF leading to the iminophosphorane. The following hydrolysis at elevated temperatures gave the 2′-amino compounds **13** and **14**. However, **14** could not be isolated in pure form without contamination of triphenylphosphine oxid. The 2′-amino functions of **13** and **14** were blocked by treatment with 3-methyl-1-[2-(4-nitrophenyl)-ethoxycarbonyl]-1*H*-imidazol-3-ium chloride in CH_2Cl_2 to form **15** and **16**. Deprotection of the 3′,5′-hydroxy groups with NH_4F in MeOH at 60° led to **17** and **18** in yields of 91 and 79%, respectively.

Reaction of **7–9**, **17**, and **18** with dimethoxytrityl chloride in pyridine gave selectively the 5′-tritylated compounds **19–23** in yields of 80–90%. Conversion into the corresponding 3′-(2-cyanoethyl *N*,*N*-diisopropylphosphoramidites) **24–28** was achieved by reaction with (2-cyanoethoxy)bis(diisopropylamino)phosphine [20] under 1*H*-tetrazole activation in high yields.

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

Experimental Part

General. Products were dried under high vacuum. TLC: precoated silica gel thin-layer sheets *60 F254* from *Merck*. Flash chromatography (FC): silica gel (*Baker*, 30–60 μm), 0.3–0.4 bar. M.p.: *Gallenkamp* melting-point apparatus; no corrections. UV/VIS: *Perkin-Elmer, Lambda 15*; λ_{max} in nm ($\log\varepsilon$). ^{1}H-NMR: *Bruker AC 250*; δ in ppm rel. to Me_4Si.

1. *1-(2-Amino-2-deoxy-β-D-arabinofuranosyl)uracil Hydrochloride* (**4**) [15]. A suspension of 1-(2-azido-2-deoxy-β-D-arabinofuranosyl)uracil (**1**; 2.69 g, 10 mmol) [14] [15] and 5% Pd/C (200 mg) in halfsat. methanolic HCl (50 ml) was hydrogenated in a shaking apparatus at 1 atm. After 16 h, the mixture was filtered through *Celite*. The catalyst was washed with H_2O/MeOH 1:1 (3 × 20 ml). The product precipitated from the combined filtrates as colorless needles. The needles were washed with EtOH and Et_2O: 2.40 g (86%) of **4**. M.p. 200° (dec.). UV (H_2O): 260 (3.98). ^{1}H-NMR ((D$_6$)DMSO): 11.40 (*s*, H–N(3)); 8.55 (*s*, NH_3^+–C(2′)); 7.90 (*d*, H–C(6)); 6.12 (*s*, OH–C(3′)); 6.01 (*d*, H–C(1′)); 5.63 (*d*, H–C(5)); 4.23 (*t*, H–C(2′)); 3.9–3.6 (*m*, H–C(3′), H–C(4′), 2 H–C(5′)). Anal. calc. for $C_9H_{13}N_3O_5 \cdot HCl \cdot H_2O$ (297.7): C 36.31, H 5.42, N 14.12; found: C 36.26, H 5.44, N 14.10.

2. *1-(2-Amino-2-deoxy-β-D-arabinofuranosyl)thymine Hydrochloride* (**5**). As described in *Exper. 1*, with 1-(2-azido-2-deoxy-β-D-arabinofuranosyl)thymine (**2**; 850 mg, 3.0 mmol) [14], 5% Pd/C (40 mg) in MeOH/HCl (40 ml). After 16 h, H_2O (30 ml) was added. After removal of catalyst and solvent, the residue was crystallized from i-PrOH: 852 mg (86%) of **5**. M.p. 225° (dec.). UV (H_2O): 266 (3.97). ^{1}H-NMR ((D$_6$)DMSO): 11.39 (*s*, H–N(3)); 8.50 (*s*, NH_3^+–C(2′)); 7.79 (*s*, H–C(6)); 6.10 (*s*, OH–C(3′)); 6.05 (*d*, H–C(1′)); 5.72 (*s*, OH–C(5′)); 4.26 (*t*, H–C(2′)); 3.9–3.6 (*m*, H–C(3′), H–C(4′), 2 H–C(5′)); 1.80 (*s*, Me). Anal. calc. for $C_{10}H_{15}N_3O_5 \cdot HCl$ (293.7): C 40.89, H 5.49, N 14.31; found: C 40.90, H 5.55, N 14.06.

3. *1-(2-Amino-2-deoxy-β-D-arabinofuranosyl)cytosine Dihydrochloride* (**6**) [6] [13]. As described in *Exper. 1*, with 1-(2-azido-2-deoxy-β-D-arabinofuranosyl)cytosine hydrochloride (**3**; 1.60 g, 5.3 mmol) [14], 5% Pd/C (100 mg) in MeOH/HCl (50 ml) and H_2O (20 ml). After 20 h, H_2O (40 ml) was added. After removal of catalyst and solvent, the residue was crystallized from EtOH: 1.38 g (83%) of **6**. M.p. 195° (dec.; [13]: m.p. 192°). UV (H_2O): 269 (3.96), 226 (3.93). ^{1}H-NMR ((D$_6$)DMSO): 9.86 (*s*, NH–C(4)); 8.79 (*s*, NH–C(4)); 8.63 (*s*, NH_3^+–C(2′)); 8.25 (*d*, H–C(6)); 6.20 (*d*, H–C(5)); 6.00 (*d*, H–C(1′)); 4.23 (*t*, H–C(2′)); 3.97–3.60 (*m*, H–C(3′), H–C(4′), 2 H–C(5′)). Anal. calc. for $C_9H_{14}N_4O_4 \cdot 2\,HCl$ (315.2): C 34.30, H 5.12, N 17.77; found: C 33.99, H 5.07, N 17.25.

4. *1-{2-Deoxy-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-D-arabinofuranosyl}uracil* (**7**). A soln. of **4** (1.49 g, 5.0 mmol) and 4-(dimethylamino)pyridine (610 mg, 5.0 mmol) in dry DMF (20 ml) was treated with 4 Å molecular sieve by stirring for 20 min. Then 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride (1.71 g, 6.0 mmol) [16] was added, and the mixture was stirred at r.t. for 20 h. The precipitate was filtered off and washed with dry DMF. The combined filtrates were evaporated and purified by FC (toluene/AcOEt 1:1 to toluene/AcOEt/MeOH 5:5:1). The product fractions were concentrated to 50 ml to yield a precipitate: 1.63 g (75%) of **7**. UV (MeOH): 265 (4.31). ^{1}H-NMR ((D$_6$)DMSO): 11.30 (*s*, H–N(3)); 8.21 (*d*, 2 H *o* to NO_2); 7.72 (*d*, H–C(6)); 7.60, 7.22 (2*d*, NH–C(2′)); 7.51 (*d*, 2 H *m* to NO_2); 6.06 (*d*, H–C(1′)); 5.58 (*m*, H–C(5), OH–C(3′)); 5.39 (*t*, OH–C(5′)); 4.3–4.0 (*m*, OCH_2CH_2, H–C(2′), H–C(3′)); 3.8–3.6 (*m*, H–C(4′), 2 H–C(5′)); 2.98 (*m*, OCH_2CH_2). Anal. calc. for $C_{18}H_{20}N_4O_9$ (436.4): C 49.54, H 4.62, N 12.84; found: C 49.38, H 4.88, N 12.38.

5. *1-{2-Deoxy-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-D-arabinofuranosyl}thymine* (**8**). As described in *Exper. 4*, with **5** (174 mg, 0.6 mmol), 4-(dimethylamino)pyridine (73 mg, 0.6 mmol) and 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride (224 mg, 0.72 mmol). FC (toluene/AcOEt 1:1 to toluene/AcOEt/MeOH 5:5:1). The product fractions were concentrated to 20 ml to yield a precipitate: 213 mg (79%) of **8**. UV (MeOH): 269 (4.30). ^{1}H-NMR ((D$_6$)DMSO): 11.24 (*s*, H–N(3)); 8.20 (*d*, 2 H *o* to NO_2); 7.62 (*s*, H–C(6)); 7.60–7.41 (*m*, 2 H *m* to NO_2, NH–C(2′)); 6.02 (*d*, H–C(1′)); 5.54 (*d*, OH–C(3′)); 5.37 (*t*, OH–C(5′)); 4.25–3.98 (*m*, H–C(2′), H–C(3′), OCH_2CH_2); 3.79–3.54 (*m*, H–C(4′), 2 H–C(5′)); 2.92 (*m*, OCH_2CH_2); 1.71 (*s*, Me). Anal. calc. for $C_{19}H_{22}N_4O_9$ (450.4): C 50.67, H 4.92, N 12.44; found: C 50.52, H 5.04, N 12.27.

6. *1-{2-Deoxy-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-D-arabinofuranosyl}-N^4-[2-(4-nitrophenyl)-ethoxycarbonyl]cytosine* (**9**). A suspension of **6** (315 mg, 1.0 mmol) in hexamethyldisilazane (10 ml) was refluxed for 6 h. After evaporation, the residue was co-evaporated with dry toluene and dissolved in dry CH_2Cl_2. After addition of 1.24 g (4.0 mmol) of 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride, the mixture was stirred at r.t. for 15 h. The precipitate was filtered off and washed with dry CH_2Cl_2. The combined filtrates were evaporated. The residue was dissolved in MeOH (10 ml), NH_4F (222 mg, 6.0 mmol) added, and after 1 h the solvent evaporated. The residue was purified by FC (toluene/AcOEt 1:1 to AcOEt/MeOH 1:2). The product

fractions were concentrated to 20 ml to yield a precipitate: 410 mg (65%) of **9**. UV (MeOH): 271 (4.39), 250 (4.35). ^{1}H-NMR ((D$_6$)DMSO): 11.44 (*s*, H–N(4)); 8.1 (*m*, 2 H *o* to NO$_2$, H–C(6)); 7.59 (*d*, 2 H *m* to NO$_2$); 7.48 (*d*, 2 H *m* to NO$_2$); 7.01 (*s*, NH–C(2′)); 6.88 (*d*, H–C(5)); 6.19 (*d*, H–C(1′)); 5.43 (*s*, OH–C(3′)); 5.21 (*s*, OH–C(5′)); 4.39 (*t*, OC*H*$_2$CH$_2$); 4.24–4.01 (*m*, H–C(2′), H–C(3′), OC*H*$_2$CH$_2$); 3.82–3.60 (*m*, H–C(4′), 2 H–C(5′)); 3.10 (*t*, OCH$_2$C*H*$_2$); 2.94 (*t*, OCH$_2$C*H*$_2$). Anal. calc. for C$_{27}$H$_{28}$N$_6$O$_{12}$ (628.6): C 51.59, H 4.49, N 13.37; found: C 51.76, H 4.61, N 13.74.

7. *9-[2-Azido-2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-*D*-arabinofuranosyl]-*N^2*-[2-(4-nitrophenyl)ethoxycarbonyl]-*O^6*-[2-(4-nitrophenyl)ethyl]guanine* (**12**). A soln. of **10** [18] (13.8 g, 13.8 mmol) in dry DMF (200 ml) was treated with LiN$_3$ (2.66 g, 54.3 mmol) with stirring at r.t. for 48 h. The solvent was evaporated, the residue dissolved in AcOEt (250 ml), washed with sat. NaHCO$_3$ soln. (40 ml) and sat. NaCl soln. (40 ml), dried (Na$_2$SO$_4$), and evaporated. Purification of the residue by FC (toluene to toluene/AcOEt 2:1) gave 11.3 g (92%) of **12**. Amorphous solid. UV (MeOH): 269 (4.54). ^{1}H-NMR (CDCl$_3$): 8.21 (*m*, 4 H *o* to NO$_2$); 8.00 (*s*, H–C(8)); 7.48 (*d*, 2 H *m* to NO$_2$); 7.39 (*d*, 2 H *m* to NO$_2$); 7.27 (*s*, NH–C(2)); 6.39 (*d*, H–C(1′)); 4.81 (*t*, OC*H*$_2$CH$_2$); 4.39 (*m*, OC*H*$_2$CH$_2$, H–C(2′), H–C(3′)); 4.12 (*m*, 2 H–C(5′)); 3.85 (*m*, H–C(4′)); 3.29 (*t*, OCH$_2$C*H*$_2$); 3.13 (*t*, OCH$_2$C*H*$_2$); 1.2–1.0 (*m*, 4 Me$_2$CH). Anal. calc. for C$_{39}$H$_{52}$N$_{10}$O$_{11}$Si$_2$ (893.1): C 52.45, H 5.87, N 15.68; found: C 52.30, H 5.93, N 15.35.

8. *9-[2-Amino-2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-*D*-arabinofuranosyl]adenine* (**13**). To a soln. of **11** [19] (4.06 g, 7.6 mmol) in THF (100 ml) was added with stirring Ph$_3$P (4.97 g, 19.0 mmol) which led to a spontaneous formation of N$_2$. After 2½ h, H$_2$O (5 ml) was added and stirring continued at 50° for 24 h. The mixture was diluted with AcOEt (150 ml), dried (Na$_2$SO$_4$), and evaporated. Hexane (15 ml) was added to the residue. Triphenylphosphine oxid crystallized as colorless needles. After 4 h, the needles were filtered off and washed with cold hexane. The combined filtrate was evaporated and the residue purified by FC (toluene/AcOEt 3:1 to AcOEt/MeOH 9:1): 3.18 g (82%) of **13**. Amorphous solid. UV (MeOH): 259 (4.17). ^{1}H-NMR ((D$_6$)DMSO): 8.11, 8.05 (2*s*, H–C(2), H–C(8)); 7.29 (*s*, NH$_2$–C(6)); 6.11 (*d*, H–C(1′)); 4.68 (*d*, H–C(3′)); 4.06 (*dd*, H–C(2′)); 3.83 (*dd*, H–C(5′)); 3.75 (*m*, H–C(4′), H–C(5′)); 1.56 (*s*, NH$_2$–C(2′)); 1.2–1.0 (*m*, 4 Me$_2$CH). Anal. calc. for C$_{22}$H$_{40}$N$_6$O$_4$Si$_2$ (508.8): C 51.94, H 7.92, N 16.52; found: C 51.49, H 7.80, N 16.49.

9. *9-{2-Deoxy-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-*D*-arabinofuranosyl}-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenine* (**15**). A mixture of **13** (3.05 g, 6.0 mmol), 4-(dimethylamino)pyridine (732 mg, 6.0 mmol), and 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride (7.48 g, 24.0 mmol) was stirred in dry CH$_2$Cl$_2$ (150 ml) at r.t. for 24 h. The solid was filtered off, the filtrate washed with sat. NaHCO$_3$ soln. (30 ml) and sat. NaCl soln. (30 ml), dried (Na$_2$SO$_4$), and evaporated. Purification of the residue by FC (toluene/AcOEt 3:2 to 2:3) gave 3.93 g (73%) of **15**. Amorphous solid. UV (MeOH): 267 (4.63). ^{1}H-NMR (CDCl$_3$): 8.68 (*s*, H–C(2) or H–C(8)); 8.18 (*d*, H–C(2) or H–C(8), 2 H *o* to NO$_2$); 8.06 (*d*, NH–C(6), 2 H *o* to NO$_2$); 7.46 (*d*, 2 H *m* to NO$_2$); 7.12 (*d*, 2 H *m* to NO$_2$); 6.22 (*d*, H–C(1′)); 5.21 (*d*, NH–C(2′)); 5.07 (*t*, H–C(2′)); 4.83 (*t*, H–C(3′)); 4.56 (*t*, OC*H*$_2$CH$_2$); 4.18 (*t*, OC*H*$_2$CH$_2$); 4.0–3.8 (*m*, H–C(4′), 2 H–C(5′)); 3.19 (*t*, OCH$_2$C*H*$_2$); 2.86 (*t*, OCH$_2$C*H*$_2$); 1.2–1.0 (*m*, 4 Me$_2$CH). Anal. calc. for C$_{40}$H$_{54}$N$_8$O$_{12}$Si$_2$ (895.1): C 53.67, H 6.08, N 12.52; found: C 53.36, H 6.08, N 12.38.

10. *9-{2-Deoxy-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-*D*-arabinofuranosyl}-N^2-[2-(4-nitrophenyl)ethoxycarbonyl]-O^6-[2-(4-nitrophenyl)ethyl]guanine* (**16**). A soln. of **12** (4.47 g, 5.0 mmol) and Ph$_3$P (3.28 g, 12.5 mmol) in THF (50 ml) reacted under spontaneous formation of N$_2$. After stirring for 2 h, H$_2$O (5 ml) was added and the mixture refluxed for 24 h. The mixture was diluted with AcOEt (70 ml), dried (Na$_2$SO$_4$), and evaporated. The residue was purified by FC (toluene/AcOEt) to give on evaporation crude **14**, which was dried under high vacuum. To a soln. of crude **14** in dry CH$_2$Cl$_2$ (100 ml), 4-(dimethylamino)pyridine (610 mg, 5.0 mmol) and 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride (2.5 g, 8.0 mmol) were added. The mixture was stirred at r.t. for 17 h, then washed with sat. NaHCO$_3$ soln. (20 ml) and sat. NaCl soln. (20 ml), dried (Na$_2$SO$_4$), and evaporated. Purification of the residue by FC (toluene to toluene/AcOEt 1:2) gave 4.2 g (79%) of **16**. Amorphous solid. UV (MeOH): 269 (4.63). ^{1}H-NMR ((D$_6$)DMSO): 10.51 (*s*, NH–C(2)); 8.12 (*m*, 4 H *o* to NO$_2$, H–C(8)); 7.98 (*d*, 2 H *o* to NO$_2$); 7.58 (*m*, NH–C(2′), 4 H *m* to NO$_2$); 7.23 (*d*, 2 H *m* to NO$_2$); 6.22 (*d*, H–C(1′)); 4.8–3.8 (*m*, 3 OC*H*$_2$CH$_2$, H–C(2′), H–C(3′), H–C(4′), 2 H–C(5′)); 3.30 (*t*, OCH$_2$C*H*$_2$); 3.14 (*t*, OCH$_2$C*H*$_2$); 2.82 (*t*, OCH$_2$C*H*$_2$); 1.2–0.8 (*m*, 4 Me$_2$CH). Anal. calc. for C$_{48}$H$_{61}$N$_9$O$_{15}$Si$_2$ (1060.3): C 54.37, H 5.80, N 11.89; found: C 54.14, H 5.88, N 11.89.

11. *9-{2-Deoxy-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-N^6-[2-(4-nitrophenyl)-ethoxycarbonyl]adenine* (**17**). To a soln. of **15** (895 mg, 1.0 mmol) in MeOH (40 ml), NH$_4$F (520 mg, 14 mmol) was

added and the mixture stirred at 60° for 90 min. The solvent was evaporated, the residue treated with DMF (15 ml), the unsoluble material filtered off, and the filtrate dropped into ice-water (100 ml) to yield a fine, colorless solid. After filtration, the product was washed several times with H_2O and dried *in vacuo* over P_4O_{10}: 592 mg (91%). UV (MeOH): 267 (4.59). ^{1}H-NMR ((D$_6$)DMSO): 10.56 (*s*, NH–C(6)); 8.54 (*s*, H–C(2), H–C(8)); 8.15 (*d*, 2 H *o* to NO_2); 8.03 (*d*, 2 H *o* to NO_2); 7.59 (*d*, 2 H *m* to NO_2); 7.50 (*d*, NH–C(2′)); 7.21 (*d*, 2 H *m* to NO_2); 6.41 (*d*, H–C(1′)); 5.56 (*d*, OH–C(3′)); 5.27 (*t*, OH–C(5′)); 4.40 (*m*, 2 OCH_2CH$_2$); 4.16 (*m*, H–C(2′)); 4.00 (*m*, H–C(3′)); 3.8–3.6 (*m*, H–C(4′), 2 H–C(5′)); 3.13 (*t*, OCH$_2$CH_2); 2.75 (*m*, OCH$_2$CH_2). Anal. calc. for $C_{28}H_{28}N_8O_{11}$ (652.6): C 51.53, H 4.32, N 17.17; found: C 51.22, H 4.44, N 17.18.

12. *9-{2-Deoxy-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-N^2-[2-(4-nitrophenyl)-ethoxycarbonyl]-O^6-[2-(4-nitrophenyl)ethyl]guanine* (**18**). A soln. of 4.2 g (3.69 mmol) of **16** in MeOH (50 ml) was treated with NH_4F (888 mg, 24 mmol) by stirring at 60° for 2 h. The solvent was evaporated and the residue purified by FC (toluene/AcOEt 1:1 to AcOEt/MeOH 10:1). The product fractions were concentrated to 50 ml to yield a light yellowish precipitate: 2.56 g (79%) of **18**. UV (MeOH): 269 (4.60). ^{1}H-NMR ((D$_6$)DMSO): 10.42 (*s*, NH–C(2)); 8.28 (*s*, H–C(8)); 8.11 (*m*, 4 H *o* to NO_2); 7.99 (*d*, 2 H *o* to NO_2); 7.61 (*m*, 4 H *m* to NO_2); 7.40 (*m*, NH–C(2′)); 7.23 (*d*, 2 H *m* to NO_2); 6.21 (*d*, H–C(1′)); 5.54 (*d*, OH–C(3′)); 5.15 (*t*, OH–C(5′)); 4.78 (*t*, OCH_2CH$_2$); 4.33 (*m*, 2 OCH_2CH$_2$); 4.09 (*m*, H–C(2′)); 3.93 (*m*, H–C(3′)); 3.7–3.5 (*m*, H–C(4′), 2 H–C(5′)); 3.31 (*t*, OCH$_2$CH_2); 3.11 (*t*, OCH$_2$CH_2); 2.75 (*t*, OCH$_2$CH_2). Anal. calc. for $C_{36}H_{35}N_9O_{14}$ (817.7): C 52.88, H 4.31, N 15.42; found: C 52.62, H 4.36, N 14.96.

13. *1-{2-Deoxy-5-*O*-(dimethoxytrityl)-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-uracil* (**19**). In dry pyridine, **7** (873 mg, 2.0 mmol) was co-evaporated 3 times and then dissolved in dry pyridine (30 ml). After addition of (MeO)$_2$TrCl (709 mg, 2.1 mmol), the mixture was stirred at r.t. for 24 h. The solvent was evaporated, the residue diluted with AcOEt (70 ml), and the soln. washed with sat. $NaHCO_3$ soln. (20 ml) and sat. NaCl soln. (20 ml), dried (Na_2SO_4), and evaporated. Purification by FC (toluene to toluene/AcOEt/MeOH 5:5:1) and co-evaporation with CH_2Cl_2 gave 1.26 g (85%) of **19**. Amorphous solid. UV (MeOH): 266 (4.35), 233 (4.46). ^{1}H-NMR ($CDCl_3$): 10.1, 9.6 (2*s*, H–N(3)); 8.1, 8.0 (2*d*, 2 H *o* to NO_2); 7.82 (*d*, H–C(6)); 7.4–7.1 (*m*, 9 H of Tr, 2 H *m* to NO_2); 6.81 (*m*, 4 H *o* to MeO); 6.31 (*m*, H–C(1′)); 6.09 (*m*, NH–C(2′)); 5.30 (*m*, H–C(5)); 4.4–4.1 (*m*, H–C(2′), H–C(3′), OCH_2CH$_2$); 3.91 (*m*, H–C(4′)); 3.8–3.5 (*m*, 2 MeO, 2 H–C(5′)); 3.03 (*t*, OH–C(3′)); 2.86 (*m*, OCH$_2$CH_2). Anal. calc. for $C_{39}H_{38}N_4O_{11}$ (738.8): C 63.41, H 5.18, N 7.58; found: C 63.11, H 5.43, N 7.49.

14. *1-{2-Deoxy-5-*O*-(dimethoxytrityl)-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-thymine* (**20**). As described in *Exper. 13*, with **8** (950 mg, 2.11 mmol) and (MeO)$_2$TrCl (749 mg, 2.21 mmol) in dry pyridine (30 ml). FC (toluene to toluene/AcOEt 1:3) gave 1.41 g (89%) of **20**. Amorphous solid. UV (MeOH): 271 (4.29), 232 (4.39). ^{1}H-NMR ((D$_6$)DMSO): 11.30 (*s*, H–N(3)); 8.19 (*d*, 2 H *o* to NO_2); 7.68 (*d*, NH–C(2′)); 7.51–7.24 (*m*, Tr, *m* to NO_2, H–C(6)); 6.90 (*d*, 4 H *o* to MeO); 6.18 (*d*, H–C(1′)); 5.60 (*d*, OH–C(3′)); 4.35–4.11 (*m*, H–C(2′), H–C(3′), OCH_2CH$_2$); 3.83 (*m*, H–C(4′)); 3.75 (*s*, 2 MeO); 3.32 (*m*, 2 H–C(5′)); 2.99 (*m*, OCH$_2$CH_2); 1.56 (*s*, Me). Anal. calc. for $C_{40}H_{40}N_4O_{11}$ (752.8): C 63.82, H 5.36, N 7.44; found: C 63.76, H 5.31, N 7.14.

15. *1-{2-Deoxy-5-*O*-(dimethoxytrityl)-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-N^4-[2-(4-nitrophenyl)ethoxycarbonyl]cytosine* (**21**). As described in *Exper. 13*, with **9** (319 mg, 0.5 mmol) and (MeO)$_2$TrCl (177 mg, 0.525 mmol) in dry pyridine (10 ml). FC (toluene/AcOEt 1:1 to toluene/AcOEt/MeOH 10:10:1) gave 370 mg (80%) of **21**. Amorphous solid. UV (MeOH): 273 (4.40), 237 (4.50). ^{1}H-NMR ((D$_6$)DMSO): 10.78 (*s*, NH–C(4)); 8.15 (*m*, 4 H *o* to NO_2, H–C(6)); 7.6–7.2 (*m*, 9 H of Tr, NH–C(2′), 2 H *m* to NO_2); 6.90 (*d*, 4 H *o* to MeO); 6.75 (*d*, H–C(5)); 6.21 (*d*, H–C(1′)); 5.62 (*s*, OH–C(3′)); 4.35 (*m*, H–C(2′), 2 OCH_2CH$_2$); 4.04 (*m*, H–C(3′)); 3.82 (*m*, H–C(4′)); 3.73 (*s*, 2 MeO); 3.32 (*m*, 2 H–C(5′)); 3.06 (*t*, OCH$_2$CH_2); 2.92 (*m*, OCH$_2$CH_2). Anal. calc. for $C_{48}H_{46}N_6O_{14}$ (930.9): C 61.93, H 4.98, N 9.03; found: C 61.87, H 5.02, N 9.13.

16. *9-{2-Deoxy-5-*O*-(dimethoxytrityl)-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenine* (**22**). As described in *Exper. 13*, with **17** (2.0 g, 3.06 mmol) and (MeO)$_2$TrCl (1.09 g, 3.22 mmol) in dry pyridine (30 ml). FC (toluene/AcOEt 2:1 to toluene/AcOEt/MeOH 5:5:1) gave 2.34 g (83%) of **22**. Amorphous solid. UV (MeOH): 267 (4.58), 235 (4.47). ^{1}H-NMR ($CDCl_3$): 8.67 (*s*, H–C(2) or H–C(8)); 8.23 (*m*, H–C(2) or H–C(8), 2 H *o* to NO_2); 8.11 (*s*, NH–C(6)); 8.02 (*d*, 2 H *o* to NO_2); 7.5–7.2 (*m*, 9 H of Tr, 2 H *m* to NO_2); 7.06 (*d*, 2 H *m* to NO_2); 6.76 (*m*, 4 H *o* to MeO); 6.38 (*d*, H–C(1′)); 5.85 (*d*, NH–C(2′)); 4.79 (*m*, H–C(2′)); 4.66 (*m*, H–C(3′), OCH_2CH$_2$); 4.03 (*m*, OCH_2CH$_2$, H–C(4′)); 3.78 (*s*, 2 MeO); 3.52 (*m*, 2 H–C(5′)); 3.17 (*t*, OH–C(3′), OCH$_2$CH_2); 2.78 (*t*, OCH$_2$CH_2). Anal. calc. for $C_{49}H_{46}N_8O_{13}$ (955.0): C 61.63, H 4.86, N 11.73; found: C 61.71, H 4.90, N 11.52.

17. *9-{2-Deoxy-5-*O*-(dimethoxytrityl)-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-N^2-[2-(4-nitrophenyl)ethoxycarbonyl]-O^6-[2-(4-nitrophenyl)ethyl]guanine* (**23**). As described in *Exper. 13*, with

18 (2.04 g, 2.5 mmol) and $(MeO)_2TrCl$ (890 mg, 2.63 mmol) in dry pyridine (50 ml). FC (toluene/AcOEt 3:1 to AcOEt) gave 2.52 g (90%) of **23**. Amorphous solid. UV (MeOH): 269 (4.63), 236 (4.51). ^{1}H-NMR ($CDCl_3$): 8.0 (*m*, 4 H *o* to NO_2); 7.87 (*m*, H–C(8), 2 H *o* to NO_2); 7.43 (*s*, NH–C(2)); 7.38 (*d*, 2 H *m* to NO_2); 7.2–6.9 (*m*, 9 H of Tr, 4 H *m* to NO_2); 6.59 (*m*, 4 H *o* to MeO); 6.45 (*d*, NH–C(2′)); 6.12 (*d*, H–C(1′)); 5.12 (*m*, H–C(2′)); 4.6 (*m*, H–C(3′), OCH_2CH_2); 4.29 (*t*, OCH_2CH_2); 4.0–3.8 (*m*, H–C(4′), OCH_2CH_2); 3.61 (*s*, 2 MeO); 3.2 (*m*, 2 H–C(5′), OCH_2CH_2); 2.90 (*m*, OH–C(3′), OCH_2CH_2); 2.68 (*t*, OCH_2CH_2). Anal. calc. for $C_{57}H_{53}N_9O_{16}$ (1120.1): C 61.12, H 4.77, N 11.25; found: C 60.81, H 4.88, N 11.05.

18. *1-{2-Deoxy-5-*O*-(dimethoxytrityl)-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-uracil 3′-(2-Cyanoethyl* N,N-*Diisopropylphosphoramidite)* (**24**). A mixture of **19** (960 mg, 1.3 mmol), (2-cyanoethoxy)bis(diisopropylamino)phosphine (588 mg, 1.95 mmol), and of 1*H*-tetrazole (45 mg, 0.65 mmol) was stirred in dry CH_2Cl_2 (20 ml) under N_2 at r.t. for 24 h. After dilution with CH_2Cl_2 (60 ml), the soln. was washed with sat. $NaHCO_3$ soln. (20 ml) and sat. NaCl soln. (20 ml), dried (Na_2SO_4), and evaporated. The residue was purified by FC (toluene to toluene/AcOEt 1:1 with addition of 0.2% of Et_3N). The product fractions were evaporated and co-evaporated with dry CH_2Cl_2: 1.06 g (87%) of **24**. Amorphous solid. UV (MeOH): 265 (4.33), 234 (4.40). ^{1}H-NMR ($CDCl_3$): 10.3, 9.1 (2*s*, H–N(3)); 8.1 (2*d*, 2 H *o* to NO_2); 7.92, 7.79 (2*d*, H–C(6)); 7.4–7.2 (*m*, 9 H of Tr, 2 H *m* to NO_2); 6.86 (*m*, 4 H *o* to MeO); 6.54, 6.41 (2*d*, H–C(1′)); 6.18 (*m*, NH–C(2′)); 5.28 (*m*, H–C(5)); 4.7–4.4 (*m*, H–C(2′), H–C(3′)); 4.2 (*m*, OCH_2CH_2); 4.0 (*m*, H–C(4′)); 3.8–3.3 (*m*, 2 MeO, 2 H–C(5′), 2 Me_2CH, OCH_2CH_2CN); 3.1–2.9 (*m*, OCH_2CH_2); 2.62, 2.39 (2*t*, OCH_2CH_2CN); 1.3–0.9 (*m*, 2 Me_2CH). Anal. calc. for $C_{48}H_{55}N_6O_{12}P$ (939.0): C 61.40, H 5.90, N 8.95; found: C 60.98, H 6.11, N 9.08.

19. *1-{2-Deoxy-5-*O*-(dimethoxytrityl)-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-thymine 3′-(2-Cyanoethyl* N,N-*Diisopropylphosphoramidite)* (**25**). As described in *Exper. 18*, with **20** (1.43 g, 1.9 mmol), (2-cyanoethoxy)bis(diisopropylamino)phosphine (900 mg, 3.0 mmol), and 1*H*-tetrazole (70 mg, 1.0 mmol) in dry CH_2Cl_2 (15 ml). FC (toluene to toluene/AcOEt 1:2 with addition of 0.2% of Et_3N) gave 1.54 g (85%) of **25**. Amorphous solid. UV (MeOH): 269 (4.31), 232 (4.41). ^{1}H-NMR ($CDCl_3$): 8.61 (*s*, H–N(3)); 8.1, 8.0 (2*d*, 2 H *o* to NO_2); 7.51 (*s*, H–C(6)); 7.4–7.1 (*m*, 9 H of Tr, 2 H *m* to NO_2); 6.82 (*m*, 4 H *o* to MeO); 6.08 (*d*, H–C(1′)); 6.0 (*m*, NH–C(2′)); 4.5–4.0 (*m*, H–C(2′), H–C(3′), H–C(4′), OCH_2CH_2); 3.79 (*s*, 2 MeO); 3.8–3.3 (*m*, 2 H–C(5′), 2 Me_2CH, OCH_2CH_2CN); 3.11, 2.92 (2*t*, OCH_2CH_2); 2.58, 2.39 (2*t*, OCH_2CH_2CN); 1.65 (*s*,Me–C(5)); 1.3–0.9 (*m*, 2 Me_2CH). Anal. calc. for $C_{49}H_{57}N_6O_{12}P$ (953.0): C 61.76, H 6.03, N 8.82; found: C 61.91, H 6.07, N 8.60.

20. *1-{2-Deoxy-5-*O*-(dimethoxytrityl)-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-N^4-[2-(4-nitrophenyl)ethoxycarbonyl]cytosine 3′-(2-Cyanoethyl* N,N-*Diisopropylphosphoramidite)* (**26**). As described in *Exper. 18*, with **21** (343 mg, 0.368 mmol), (2-cyanoethoxy)bis(diisopropylamino)phosphine (174 mg, 0.575 mmol), and 1*H*-tetrazole (13 mg, 0.192 mmol) in dry CH_2Cl_2 (5 ml). FC (toluene/AcOEt 2:1 to 1:3 with addition of 0.2% of Et_3N) gave 347 mg (83%) of **26**. Amorphous solid. UV (MeOH): 272 (4.42), 234 (4.59). ^{1}H-NMR ($CDCl_3$): 8.15 (*d*, 2 H *o* to NO_2); 8.02 (*d*, 2 H *o* to NO_2); 7.91 (*d*, H–C(6)); 7.55 (*s*, NH–C(4)); 7.40 (*d*, 4 H *m* to NO_2); 7.25 (*m*, 9 H of Tr); 7.10 (*d*, H–C(5)); 6.80 (*d*, 4 H *o* to MeO); 6.18 (*d*, H–C(1′)); 5.59 (*m*, NH–C(2′)); 4.64 (*m*, H–C(2′)); 4.42 (*t*, H–C(3′), OCH_2CH_2); 4.19 (*m*, H–C(4′)); 4.02 (*m*, OCH_2CH_2); 3.78 (*s*, 2 MeO); 3.7–3.4 (*m*, 2 H–C(5′), 2 Me_2CH, OCH_2CH_2CN); 3.21 (*t*, OCH_2CH_2); 2.79 (*t*, OCH_2CH_2); 2.58, 2.37 (2*t*, OCH_2CH_2CN); 1.3–0.9 (*m*, 2 Me_2CH). Anal. calc. for $C_{57}H_{63}N_8O_{15}P$ (1131.2): C 60.52, H 5.61, N 9.91; found: C 60.81, H 5.97, N 9.83.

21. *9-{2-Deoxy-5-*O*-(dimethoxytrityl)-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenine 3′-(2-Cyanoethyl* N,N-*Diisopropylphosphoramidite)* (**27**). As described in *Exper. 18*, with **22** (955 mg, 1.0 mmol), (2-cyanoethoxy)bis(diisopropylamino)phosphine (452 mg, 1.5 mmol), and 1*H*-tetrazole (35 mg, 0.5 mmol) in dry CH_2Cl_2 (10 ml). FC (toluene/AcOEt 1:1 to 1:2 with addition of 0.2% of Et_3N) gave 1.03 g (89%) of **27**. Amorphous solid. UV (MeOH): 266 (4.58), 235 (4.50). ^{1}H-NMR ($CDCl_3$): 8.69 (2*s*, H–C(2) or H–C(8)); 8.2 (*m*, NH–C(6), H–C(2) or H–C(8), 2 H *o* to NO_2); 8.0 (*d*, 2 H *o* to NO_2); 7.5–7.2 (*m*, 9 H of Tr, 2 H *m* to NO_2); 7.08 (*d*, 2 H *m* to NO_2); 6.79 (*m*, 4 H *o* to MeO); 6.41 (2*d*, H–C(1′)); 5.87 (2*d*, NH–C(2′)); 4.82 (*m*, H–C(2′)); 4.70 (*m*, H–C(3′)); 4.56 (*t*, OCH_1CH_2); 4.2–4.0 (*m*, OCH_2CH_2, H–C(4′)); 3.79 (*s*, 2 MeO); 3.7–3.4 (*m*, 2 H–C(5′), 2 Me_2CH, OCH_2CH_2CN); 3.20 (*t*, OCH_2CH_2); 2.78 (*t*, OCH_2CH_2); 2.56, 2.22 (2*t*, OCH_2CH_2CN); 1.2–1.0 (*m*, 2 Me_2CH). Anal. calc. for $C_{58}H_{63}N_{10}O_{14}P$ (1155.2): C 60.31, H 5.50, N 12.13; found: C 60.07, H 5.54, N 11.84.

22. *9-{2-Deoxy-5-*O*-(dimethoxytrityl)-2-[2-(4-nitrophenyl)ethoxycarbonylamino]-β-*D*-arabinofuranosyl}-N^2-[2-(4-nitrophenyl)ethoxycarbonyl]-O^6-[2-(4-nitrophenyl)ethyl]guanine 3′-(2-Cyanoethyl* N,N-*Diisopropylphosphoramidite)* (**28**). As described in *Exper. 18*, with **23** (560 mg, 0.5 mmol), (2-cyanoethoxy)bis(diisopropylamino)phosphine (226 mg, 0.75 mmol), and 1*H*-tetrazole (17 mg, 0.25 mmol) in dry CH_2Cl_2 (15 ml). FC (toluene to

toluene/AcOEt 1:2 with addition of 0.2% of Et_3N) gave 568 mg (86%) of **28**. Amorphous solid. UV (MeOH): 269 (4.64), 236 (4.53). ^{1}H-NMR ($CDCl_3$): 8.16 (*t*, 4 H *o* to NO_2); 7.96 (*m*, H–C(8), 2 H *o* to NO_2); 7.5–7.0 (*m*, 9 H of Tr, 6 H *m* to NO_2); 6.67 (*m*, 4 H *o* to MeO); 6.32 (*m*, H–C(1′)); 6.07 (*m*, NH–C(2′)); 5.0 (*m*, H–C(2′)); 4.7 (*m*, OCH_2CH_2, H–C(3′)); 4.41 (*m*, OCH_2CH_2); 4.1 (*m*, OCH_2CH_2, H–C(4′)); 3.71 (*s*, 2 MeO); 3.6–3.4 (*m*, 2 H–C(5′), 2 Me_2CH, OCH_2CH_2CN); 3.30 (*t*, OCH_2CH_2); 3.10 (*m*, OCH_2CH_2); 2.71 (*t*, OCH_2CH_2); 2.56, 2.22 (2*t*, OCH_2CH_2CN); 1.15–0.95 (*m*, 2 Me_2CH). Anal. calc. for $C_{66}H_{70}N_{11}O_{17}P$ (1320.3): C 60.04, H 5.34, N 11.67; found: C 59.85, H 5.37, N 11.40.

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