38. Nucleotides

Part XLVI[1])

The Synthesis of Phospholipid Conjugates of Antivirally Active Nucleosides by the Improved Phosphoramidite Methodology

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The application of the improved phosphoramidite strategy for the synthesis of oligonucleotides using β-eliminating protecting groups to phospholipid chemistry offers the possibility to synthesize phospholipid conjugates of AZT (**6**) and cordycepin. The synthesis of 3′-azido-3′-deoxythymidine (**6**) was achieved by a new isolation procedure without chromatographic purification steps in an overall yield of 50%. Protected cordycepin (= 3′-deoxyadenosine) derivatives, the N^6,2′-bis[2-(4-nitrophenyl)ethoxycarbonyl]cordycepin (**12**) and the N^6,5′-bis[2-(4-nitrophenyl)ethoxycarbonyl]cordycepin (**13**) were prepared by known methods and direct acylation of N^6-[2-(4-nitrophenyl)ethoxycarbonyl]cordycepin (**9**), respectively. These protected nucleosides and the 3′-azido-3′-deoxythymidine (**6**) reacted with newly synthesized and properly characterized lipid-phosphoramidites **21**–**25**, catalyzed by 1*H*-tetrazole, to the corresponding nucleoside-phospholipid conjugates **26**–**38** in high yield. The deprotection was accomplished *via* β-elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in aprotic solvents to give analytically pure nucleoside-phospholipid diesters **39**–**51** as triethylammonium or sodium salts. The newly synthesized compounds were characterized by elemental analyses and UV and ^{1}H-NMR spectra.

1. Introduction. – It is well known that modified nucleosides play an important role in cancer chemotherapy and also act as antiviral compounds. Nucleoside derivatives provide seven of the nine antiviral licensed drugs in 1992 [2]. Today the only three clinically admitted medicaments against AIDS are modified nucleosides like dideoxycytidine (ddC), dideoxyinosine (ddI), and azidodeoxythymidine (AZT).

The high toxicity of AZT (3′-azido-3′-deoxythymidine; **6**) as a drug against HIV infection was the reason behind a number of investigations to synthesize lipophilic [3] or brain-targeting [4] prodrugs which might decrease the application dosages. On the other hand, cordycepin (3′-deoxyadenosine) exhibits, in form of its trimer, broad antiviral activity and functions as a competitive inhibitor of reverse transcriptase [5]. These results prompted us to apply the improved β-eliminating protecting-group strategy for the synthesis of phospholipid conjugates of these two interesting drugs.

Phospholipid conjugates of nucleosides have been known since *Paulus* and *Kennedy* [6] and *Agranoff et al.* [7] discovered in the early sixties the role of CDP diglycerides as carriers for the phosphatidyl residue in the biosynthesis of various phospholipids. Later on, lipid-diphosphate conjugates of modified nucleosides were used to enhance the membrane permeability of nucleoside drugs [8]. Synthetic lipid-monophosphate conjugates were first discovered by *Smrt* and *Hynie* [9] and, later on, a number of such

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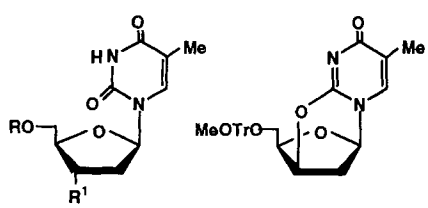
nucleoside prodrugs were prepared by the means of the phosphodiester [10] and phosphotriester methods [11], or by the phospholipase-D-catalyzed transesterification [12]. However, there is still no example where the phosphoramidite methodology is used for the synthesis of nucleoside-phospholipid conjugates.

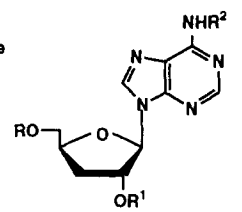
We applied this approach [13] to prepare phosphoramidites of lipids for coupling with the appropriately protected nucleosides. The 2-(4-nitrophenyl)ethyl (npe) and the 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) blocking groups [14] have been chosen for protection of the phosphate moiety as well as for the reactive functions of the nucleosides, since they give UV-detectable lipid-phosphoramidites and allow a simplified one-step deprotection procedure. These lipid-phosphoramidites could be easily purified by flash chromatography (FC) on neutral aluminium oxide with unpolar solvents like petroleum ether or Et_2O. The 1*H*-tetrazole-catalyzed coupling with the biologically active nucleoside was performed with an 1.5 to 2 molar excess of the phosphoramidite. The resulting phosphotriesters were purified by column chromatography (silica gel, toluene/AcOEt/MeOH) followed by precipitation from MeOH. In the last step, deprotection of the nucleoside phosphodiesters was achieved by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in aprotic solvents *via* β-elimination to give pure products in high yields.

2. Synthesis. – Azidodeoxythymidine **6** was prepared *via* a modified method of *Glinski et al.* [15], whereby the trityl protecting group has been changed to the monomethoxytrityl (MeOTr) function. In a one-pot reaction, thymidine (**1**) was tritylated (→ **2**) and mesylated to give 5′-*O*-(monomethoxytrityl)-3′-*O*-(methylsulfonyl)thymidine (**3**) [16] in high yield. Reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 at room temperature, analogous to *Secrist* [17], and crystallization afforded 2,3′-anhydro-5′-*O*-(monomethoxytrityl)thymidine (**4**) in 84% yield. Reaction with LiN_3 in DMF led to crude 3′-azido-3′-deoxy-5′-*O*-(monomethoxytrityl)thymidine (**5**) which gave, on treatment with TsOH after continuous extraction, crystalline AZT (**6**) in 71% yield. In the cordycepin series, the 2′,5′-di-*O*-acetyl derivative **7** [18] was treated with 3-methyl-1-[2-(4-

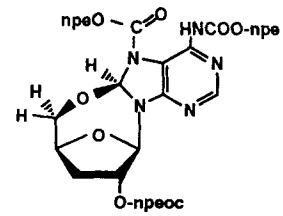


	R	R^1
1	H	OH
2	MeOTr	OH
3	MeOTr	Ms
5	MeOTr	N_3
6	H	N_3

4



	R	R^1	R^2
7	Ac	Ac	H
8	Ac	Ac	npeoc
9	H	H	npeoc
10	MeOTr	H	npeoc
11	MeOTr	npeoc	npeoc
12	H	npeoc	npeoc
13	npeoc	H	npeoc
15	npeoc	npeoc	npeoc



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MeOTr = Methoxytrityl, npe = 2-(4-nitrophenyl)ethyl, npeoc = 2-(4-nitrophenyl)ethoxycarbonyl

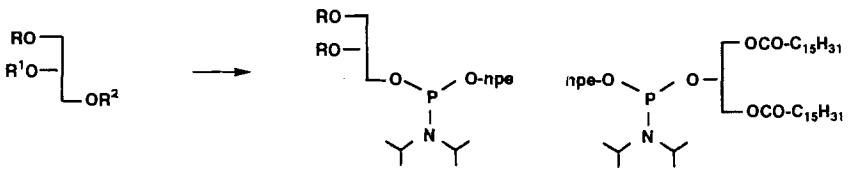
nitrophenyl)ethoxycarbonyl]-1*H*-imidazolium chloride [14] in CH_2Cl_2 to form in 95% yield N^6-[2-(4-nitrophenyl)ethoxycarbonyl]-2′,5′-di-*O*-acetylcordycepin (**8**), which was then deprotected with K_2CO_3 in MeOH to N^6-[2-(4-nitrophenyl)ethoxycarbonyl]-cordycepin (**9**) in 87% yield. This compound functioned as a central building block for the 3′- and the 5′-phospholipid conjugates. In the case of 5′-phospho-substituted cordycepin conjugates, the protection in the 2′-position was achieved in a three-step procedure by monomethoxytritylation of **9** to **10** in 80% yield, reaction with 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazolium chloride [14], activated by 4-(dimethylamino)pyridine (DMAP), to **11**, and subsequent deprotection with TsOH to generate N^6,2′-bis[2-(4-nitrophenyl)ethoxycarbonyl]cordycepin (**12**) [14] in an overall yield of 75%. Direct acylation of **9** with 2-(4-nitrophenyl)ethyl chloroformate [13] afforded, in 73% yield, N^6,5′-bis[2-(4-nitrophenyl)ethoxycarbonyl]cordycepin (**13**) as the main reaction product and two more by-products **14** and **15** which have been isolated chromatographically.

The formation of 7,8-dihydro-N^6,7,2′-*O*-tris[2-(4-nitrophenyl)ethoxycarbonyl]-8,5′-*O*-cyclocordycepin (**14**) was quite surprising because of the steric demand of the 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) group in the 6-position, but explainable by observations made by *Anzai* and coworkers during acylations of isopropylidene-adenosine [19]. Characteristically, **14** exhibits a *s* at 5.6 ppm in the ^{1}H-NMR spectrum due to H–C(8), and it also shows the characteristic bathochromic shift in its UV spectra, which has been reported for several 7,8-dihydropurines [20].

For the synthesis of the lipid building blocks, the racemic 1,2-*O*-diacylglycerines **16** and **17** have been prepared according to *Howe* and *Malkin* [21], and the 1,2-*O*-dialkylglycerines **18** and **19** *via* a slightly modified method originally developed by *Hermetter* and *Paltauf* [22] (*Scheme 1*). The preparation of the lipid-phosphoramidites **21**–**24** was performed in an inert gas atmosphere with diisopropyl(ethyl)amine, chloro(diisopropylamino)[2-(4-nitrophenyl)ethoxy]phosphane [23], and the anhydrous lipids **16**–**19** in 70–80% yield.

To exclude isomerization to the 1,3-*O*-diacyl derivatives, 1,3-*O*-dipalmitoylglycerine (**20**) was synthesized systematically [24] by acyl migration[2]) and transformed by phos-

Scheme 1



	R	R¹	R²
16	$C_{15}H_{31}CO$	$C_{15}H_{31}CO$	H
17	$C_{13}H_{27}CO$	$C_{13}H_{27}CO$	H
18	$C_{16}H_{33}$	$C_{16}H_{33}$	H
19	$C_{18}H_{37}$	$C_{18}H_{37}$	H
20	$C_{15}H_{31}CO$	H	$C_{15}H_{31}CO$

	R
21	$C_{15}H_{31}CO$
22	$C_{13}H_{27}CO$
23	$C_{16}H_{33}$
24	$C_{18}H_{37}$

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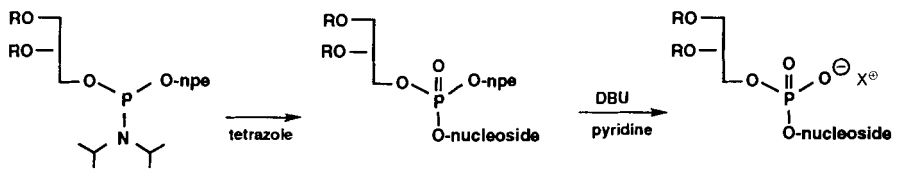
[2]) The thermal isomerization of 1,2-*O*-dipalmitoylglycerine (**16**) to 1,3-*O*-dipalmitoylglycerine (**20**) was achieved by heating **16** to 170° for 3 h and subsequent crystallization from petroleum ether according to [20b].

phitylation to **25** in 96% yield. Comparison of its ^{1}H-NMR data with those of **21** and **22** allowed a straightforward distinction between both series, also indicating that no isomerization had taken place under the applied reaction conditions.

The two cordycepin building blocks **12** and **13** and 3′-azido-3′-deoxythymidine (**6**) were coupled with 1.5 equiv. of the phosphoramidites **21**–**25** and 1*H*-tetrazole in CH_2Cl_2 and then oxidized by I_2/H_2O to the phosphotriesters **26**–**38** in high yields. All triesters have been isolated as glassy, colorless, analytically pure substances. High purity was necessary for the following aprotic deprotection reaction with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in pyridine, whereby the nucleoside-phospholipid diesters **39**–**51** were isolated as analytically pure colorless, powdery sodium and triethylammonium salts, respectively. Biochemical screening experiments with compounds **39**–**51** are under investigation.

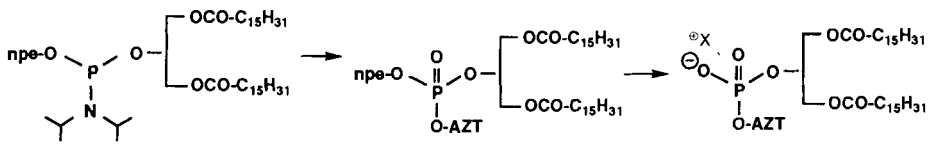
Scheme 2



	R
21	$C_{15}H_{31}CO$
22	$C_{13}H_{27}CO$
23	$C_{16}H_{33}$
24	$C_{18}H_{37}$

	R	Nucleoside
26	$C_{15}H_{31}CO$	AZT (= 5′$T_{d2′,3′}az^{3′}$)
27	$C_{13}H_{27}CO$	AZT
28	$C_{16}H_{33}$	AZT
29	$C_{18}H_{37}$	AZT
30	$C_{15}H_{31}CO$	5′npeoc$^6A_{d3′}$npeoc$^{2′}$
31	$C_{13}H_{27}CO$	5′npeoc$^6A_{d3′}$npeoc$^{2′}$
32	$C_{16}H_{33}$	5′npeoc$^6A_{d3′}$npeoc$^{2′}$
33	$C_{18}H_{37}$	5′npeoc$^6A_{d3′}$npeoc$^{2′}$
34	$C_{15}H_{31}CO$	2′npeoc$^6A_{d3′}$npeoc$^{5′}$
35	$C_{13}H_{27}CO$	2′npeoc$^6A_{d3′}$npeoc$^{5′}$
36	$C_{16}H_{33}$	2′npeoc$^6A_{d3′}$npeoc$^{5′}$
37	$C_{18}H_{37}$	2′npeoc$^6A_{d3′}$npeoc$^{5′}$

	R	Nucleoside	X
39	$C_{15}H_{31}CO$	AZT	Na
40	$C_{13}H_{27}CO$	AZT	Na
41	$C_{16}H_{33}$	AZT	Et_3NH
42	$C_{16}H_{37}$	AZT	Et_3NH
43	$C_{15}H_{31}CO$	5′$A_{d3′}$	Et_3NH
44	$C_{13}H_{27}CO$	5′$A_{d3′}$	Et_3NH
45	$C_{16}H_{33}$	5′$A_{d3′}$	Et_3NH
46	$C_{18}H_{37}$	5′$A_{d3′}$	Et_3NH
47	$C_{15}H_{31}CO$	2′$A_{d3′}$	Et_3NH
48	$C_{13}H_{27}CO$	2′$A_{d3′}$	Et_3NH
49	$C_{16}H_{33}$	2′$A_{d3′}$	Et_3NH
50	$C_{18}H_{37}$	2′$A_{d3′}$	Et_3NH



25 **38** **51** X = Na

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*). The comparison of the UV data of all nucleoside-phospholipid conjugates show that the deprotected, analytically pure conjugates exhibit the same extinction coefficient as the unmodified nucleosides themselves, a circumstance, which was not always considered in the literature.

Experimental Part

General. Pyridine was used at *p.a.* grade (*Merck*), all other solvents were purified by known methods [25]; mixtures *v/v*. TLC: Precoated SiO_2 thin-layer sheets (*Merck DC-SiO$_2$ 60 F 254*) and alumina oxide thin-layer sheets (*Merck DC-Alox 60 F 254 type E*). Prep. column chromatography (CC): silica gel (*Merck 60*, 0.063–0.2 mesh); flash column chromatography (FC): silica gel (*Baker*). M.p.: *Büchi* apparatus, model Dr. *Tottoli*; no corrections. p*K*: determination by the spectrophotometric method [26]. UV/VIS: *Lambda 5* (*Perkin-Elmer*); λ_{max} (log ε). ^{1}H-NMR: *Bruker-WM 250, AC 250* δ in ppm rel. to $SiMe_4$ or $CDCl_3$ ((D_6)DMSO). ^{31}P-NMR: *Joel JNM-GX400*; δ in ppm rel. to H_3PO_4. FAB-MS: *Finnigan MAT 312*.

1. *3′-O-(Methylsulfonyl)-5′-O-(monomethoxytrityl)thymidine* (**3**) [16]. Anal. pure **3** was isolated after chromatographical purification of the crude product described below (FC with toluene, then toluene/AcOEt 3:2). Colorless foam. TLC (SiO_2, toluene/AcOEt/MeOH 5:4:1): R_f 0.60. UV (MeOH): 229 (sh, 4.23), 264 (4.00), 281 (sh, 2.79). ^{1}H-NMR ($CDCl_3$): 8.77 (br., NH); 7.54 (*d*, *J* = 1.2, H–C(6)); 7.41–7.24 (*m*, 12 H, MeO*Tr*); 6.84 (*d*, 2 H *o* to MeO); 6.42 (*dd*, H–C(1′)); 5.39 (br. *m*, H–C(3′)); 4.32 (br. *m*, H–C(4′)); 3.80 (*s*, $MeSO_2$); 3.55–3.52 (*dd*, 1 H–C(5′)); 3.47–3.41 (*dd*, 1 H–C(5′)); 3.03 (*s*, MeO); 2.72–2.64 (*m*, 1 H–C(2′)); 2.53–2.44 (*m*, 1 H–C(2′)); 1.45 (*d*, *J* = 0.9, Me–C(5)). Anal. calc. for $C_{31}H_{32}N_2O_8S$ (592.7): C 62.86, H 5.44, N 4.73; found: C 62.74, H 5.41, N 4.79.

2. *2,3′-Anhydro-5′-O-(monomethoxytrityl)thymidine* (**4**). A soln. of thymidine (12.1 g, 50 mmol) and monomethoxytrityl chloride (MeOTrCl; 23.1 g, 75 mmol) was stirred in abs. pyridine (250 ml) for 16 h at 17°. The clear soln. was cooled to 0° and methanesulfonyl chloride (35 ml, 200 mmol) added in 30 min. The mixture was allowed to warm up in 2 h to r.t. and then dropped under vigorous stirring into ice-water (3500 ml), stirred for 30 min, filtered with suction and dried *in vacuo* to constant weight. The crude **3** (38 g) was dissolved in CH_2Cl_2 (400 ml) and stirred with DBU (12 ml) and molecular sieves (20 g) under anh. conditions for 20 h at 30–35°. The resulting orange soln. was decanted, treated with EtOH (100 ml), heated to slightly boiling, and then poured into Et_2O (*ca.* 800 ml) until turbidness appeared. After 4–5 h, yellowish crystals (17 g) were obtained. From the mother liquor, a second crop (3.9 g) was isolated after washing of the org. layer with H_2O/NaCl, drying ($MgSO_4$), evaporation, and a second crystallization: total yield 20.9 g (84%) of **4**. Yellowish crystals. TLC (SiO_2, $CHCl_3$/MeOH 9:1): R_f 0.31. M.p. 221°. UV (MeOH): 231 (4.32), 260 (sh, 3.84), 282 (sh, 2.95). ^{1}H-NMR ((D_6)DMSO): 7.39–7.12 (*m*, 12 H, MeO*Tr*); 6.90 (*d*, *J* = 0.9, H–C(6)); 6.77 (*d*, 2 H *o* to MeO); 5.45 (*d*, *J* = 3.7, H–C(1′)); 5.07 (br. *m*, H–C(3′)); 4.24–4.18 (*dt*, *J* = 2.4, 6.5, H–C(4′)); 3.75 (*s*, MeO); 3.30 (*dd*, *J* = 2.7, 1.5, 6.7, 2 H–C(5′)); 2.65 (br. *d*, *J* = 12.8, 1 H–C(2′)); 2.30 (*td*, *J* = 12.8, 1 H–C(2′)); 1.86 (*d*, *J* = 0.9, Me–C(5)). Anal. calc. for $C_{30}H_{28}N_2O_5$ (496.6): C 72.56, H 5.68, N 5.64; found: C 72.06, H 5.75, N 5.60.

3. *3′-Azido-3′-deoxy-5′-O-(monomethoxytrityl)thymidine* (**5**). Anal. pure **5** was isolated as a colorless foam after chromatographical purification of crude **5** described below (prep. TLC with $CHCl_3$/MeOH 99:1). TLC (SiO_2, toluene/AcOEt/MeOH 5:4:1): R_f 0.73. UV (MeOH): 228 (sh, 4.22), 265 (3.99). ^{1}H-NMR ($CDCl_3$): 8.46 (br. *s*, NH); 7.59 (*s*, H–C(6)); 7.46–7.26 (*m*, 12 H, MeO*Tr*); 6.80 (*d*, 2 H *o* to MeO); 6.26 (*d*, *J* = 6.4, H–C(1′)); 4.35 (*m*, H–C(3′)); 3.98 (*m*, H–C(4′)); 3.80 (*s*, MeO); 3.55 (*dd*, *J* = 2.7, 11.0, H–C(5′)); 3.33 (*dd*, *J* = 10.7, 2.7, 1 H–C(5′)); 2.40 (*m*, 2 H–C(2′)); 1.49 (*s*, Me–C(5)). Anal. calc. for $C_{30}H_{29}N_5O_5$ (539.6): C 66.78, H 5.42, N 12.98; found: C 66.77, H 5.51, N 12.82.

4. *3′-Azido-3′-deoxythymidine* (**6**) [27]. A soln. of **4** (10 g, 20 mmol) in abs. DMF (120 ml) was stirred with molecular sieves (20 g) and LiN_3 (10 g, 200 mmol) at 150° for 1 h. The solvent was removed (h.v.), the residue dissolved in AcOEt (300 ml), and the soln. washed with H_2O (4 × 150 ml), dried ($MgSO_4$), and evaporated: **5** as a brownish foam. The crude product was dissolved in CH_2Cl_2/MeOH (125 ml 4:1 (*v/v*)) and stirred with TsOH (1 g) for 6 h at r.t. The solvent was removed and the residue continuously extracted overnight (Na_2CO_3 (600 mg), H_2O (500 ml), AcOEt (500 ml)). The org. phase was evaporated and extracted again (H_2O, (300 ml), petroleum ether Et_2O 3:1 (500 ml)). The aq. phase was evaporated (30 ml) and **6** crystallized overnight at 4° (3.1 g). CC of the mother liquor and crystallization gave a second crop (700 mg). Total yield 3.8 g (73%) of **6**. Colorless crystals. TLC (SiO_2, $CHCl_3$/MeOH 9:1): R_f 0.63. M.p. 121–122° ([27]: 122–124°). UV (MeOH): 265 (4.00). ^{1}H-NMR ((D_6)DMSO): 11.3 (*s*, NH); 7.66 (*s*, H–C(6)); 6.07 (*t*, H–C(1′)); 5.21 (*t*, OH–C(5′)); 4.37 (*m*, H–C(3′)); 3.80 (*m*, H–C(4′)); 3.60 (*m*, 2 H–C(5′)); 2.42–2.19 (*m*, 2 H–C(2′)); 1.76 (*s*, Me–C(5)). Anal. calc. for $C_{10}H_{13}N_5O_4$ (267.2): C 44.94, H 4.90, N 26.21; found: C 44.96, H 4.83, N 26.12.

5. *2′,5′-Di-O-acetyl-3′-deoxy-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**8**). To a soln. of **7** [18] (3.8 g, 10 mmol) in abs. CH_2Cl_2 (70 ml), 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazolium chloride [14] (6 g, 19 mmol) was added. After stirring under anh. conditions for 40 h at r.t., the yellow mixture was evaporated, dissolved in a small volume of CH_2Cl_2, and purified by FC (silica gel, 3.5 × 18 cm, toluene, 250-ml fractions,

toluene/AcOEt 4:1 to 1:1): 5.3 g (100%) of **8**. Colorless foam. For anal. purposes, chromatographically pure material was dissolved in AcOEt and added dropwise into Et_2O at 0°. TLC (SiO_2, toluene/AcOEt/MeOH 5:4:1): R_f 0.47. UV (MeOH): 266 (4.44). ^{1}H-NMR ($CDCl_3$): 8.70 (*s*, H–C(8) or H–C((2)); 8.50 (*d*, 2 H, *o* to NO_2); 8.11 (*s*, H–C(2) or H–C(8)); 7.43 (*d*, 2 H *m* to NO_2); 6.09 (*d*, J = 1.2, H–C(1′)); 5.73 (*d*, J = 5.8, H–C(2′)); 4.65 (*m*, H–C(4′)); 4.54 (*t*, CH_2CH_2O); 4.45 (*dd*, J = 12.2, 2.7, 1 H–C(5′)); 4.25 (*dd*, J = 11.7, 5.5, 1 H–C(5′)); 3.16 (*t*, CH_2CH_2O); 2.70 (*ddd*, 1 H–C(3′)); 2.20 (*dd*, 1 H–C(3′)); 2.16 (*s*, Ac); 2.06 (*s*, Ac). Anal. calc. for $C_{23}H_{24}N_6O_9$ (528.5): C 52.27, H 4.58, N 15.90; found: C 51.95, H 4.57, N 15.64.

6. *3′-Deoxy-*N^6*-[2(4-nitrophenyl)ethoxycarbonyl]adenosine* (**9**) [14]. A soln. of **8** (1.06 g, 2 mmol) in abs. MeOH (10 ml) was stirred with K_2CO_3 (28 mg, 0.2 mmol) at r.t. After 1 h, **9** began to precipitate and after 3 h, the suspension was treated with Et_2O (10 ml) and AcOH (30 µl), then stirred for another 15 min, and filtered with suction. The crude product was dried in an exsiccator: 780 mg (87%). M.p. 117°. Recrystallization from MeOH (120 ml) afforded anal. pure **9**: 500 mg (78%). TLC (SiO_2, toluene/AcOEt/MeOH 5:4:1): R_f 0.2. M.p. 121° ([14]: 124°). UV (pH 0): 267 (4.43). UV (pH 4): 268 (4.39), 272 (sh, 4.37). UV (pH 8): 268 (4.39), 272 (sh, 4.36), 398 (sh, 3.79). UV (pH 13): 290 (4.47). pK_a = 1.85, 10.78. ^{1}H-NMR ((D$_6$)DMSO): 10.6 (br. *s*, NH); 8.7 (*s*, H–C(8) or H–C(2)); 8.6 (*s*, H–C(2) or H–C((8)); 8.15 (*d*, 2 H *o* to NO_2); 7.6 (*d*, 2 H *m* to NO_2); 6.0 (*s*, H–C(1′)); 5.7 (*d*, OH–C(2′)); 5.05 (*t*, OH–C(5′)); 4.55 (br. *m*, H–C(2′)); 4.35 (*t*, H–C(4′), CH_2CH_2O); 3.7 (*m*, 1 H–C(5′)); 3.5 (*m*, 1 H–C(5′)); 3.1 (*t*, CH_2CH_2O); 2.25 (*m*, 1 H–C(2′)); 1.9 (*m*, 1 H–C(2′)).

7. *3′-Deoxy-*N^6*,5′-*O*-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**13**), *3′-Deoxy-7,8-dihydro-*N^6*,7,2′-*O*-tris[2-(4-nitrophenyl)ethoxycarbonyl]-8,5′-*O*-cycloadenosine* (**14**) *and 3′-Deoxy-*N^6*,2′-*O*,5′-*O*-tris[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**15**). A soln. of **9** (1 g, 2.25 mmol) in abs. pyridine (8 ml) was cooled to −30° and treated within 30 min with a soln. of 2-(4-nitrophenyl)ethyl chloroformate [14] (1.5 g, 6.5 mmol) in abs. CH_2Cl_2 (4 ml, anh. conditions, syringe). The mixture was warmed up to −10° and stirred for 30 min. After a second addition of 2-(4-nitrophenyl)ethyl chloroformate (800 mg, 3.5 mmol) in abs. CH_2Cl_2 (4 ml) at −10° and stirring for another 70 min at −10°, the soln. was treated with sat. $NaHCO_3$ soln. (50 ml) and extracted with $CHCl_3$ (100 ml). The org. layer was washed again with sat. $NaHCO_3$ soln. (2 × 50 ml) and then the $NaHCO_3$ layer back-extracted with $CHCl_3$ (50 ml). The combined org. phase was dried ($MgSO_4$), evaporated, and co-evaporated with toluene (2 × 20 ml) to remove pyridine. Separation of the three products was achieved by FC (silica gel (65 g), 3.5 × 15 cm, toluene, gradient toluene/AcOEt/MeOH). The resulting products were purified by crystallization from MeOH to give **13** (1.05 g, 73%) and by prep. TLC to give **14** (110 mg, 6%) and **15** (200 mg, 11%).

13: TLC (SiO_2, toluene/AcOEt/MeOH 5:4:1): R_f 0.42. TLC (SiO_2, toluene/acetone 8:2): R_f 0.05. M.p. 157°. UV (MeOH): 266 (4.55). ^{1}H-NMR ((D$_6$)DMSO): 10.58 (*s*, NH); 8.62 (*s*, H–C(8) or H–C(2)); 8.49 (*s*, H–C(2) or H–C((8)); 8.13 (2*d*, 2 H *o* to NO_2); 7.55 (2*d*, 4 H *m* to NO_2); 5.99 (*d*, J = 1.6, H–C(1′)); 5.79 (*d*, OH–C(2′)); 4.70 (br. *m*, H–C(2′)); 4.51 (br. *m*, H–C(4′)); 4.41–4.21 (*m*, 2 H–C(5′), 2 CH_2CH_2O); 3.12–3.00 (2*t*, 2 CH_2CH_2O); 2.25 (*m*, 1 H–C(3′)); 2.03 (*m*, 1 H–C(3′)). Anal. calc. for $C_{28}H_{27}N_7O_{11}$ (637.6): C 52.75, H 4.27, N 15.38; found: C 52.66, H 4.29, N 15.34.

14: TLC (SiO_2, toluene/acetone 4:1): R_f 0.30. UV (MeOH): 217 (4.64), 224 (sh, 4.58), 272 (4.59). ^{1}H-NMR ($CDCl_3$): 9.20 (br. *s*, NH); 8.29 (*s*, H–C(2)); 8.18–8.11 (*m*, 6 H *o* to NO_2); 7.38 (*m*, 6 H *m* to NO_2); 6.37 (*s*, H–C(8)); 5.65 (*s*, H–C(1′)); 5.46 (*s*, H–C(2′)); 4.77 (*m*, H–C(4′)); 4.60–4.33 (*m*, 3 CH_2CH_2O); 3.52 (br. *m*, 2 H–C(5′)); 3.16–3.06 (*m*, 3 CH_2CH_2O); 2.35–2.25 (*m*, 1 H–C(3′)); 2.19–2.05 (*m*, 1 H–C(3′)). FAB-MS (3-nitrobenzyl alcohol matrix): 832 (MH$^+$). Anal. calc. for $C_{37}H_{35}N_8O_{15}$ (831.7): C 53.43, H 4.24, N 13.47; found: C 52.96, H 4.14, N 13.32.

15: TLC (SiO_2, toluene/acetone 4:1): R_f 0.19. UV (MeOH): 267 (4.68), 270 (sh, 4.66). ^{1}H-NMR ($CDCl_3$): 8.69 (*s*, H–C(8) or H–C(2)); 8.26 (br. *s*, NH); 8.15 (*m*, 6 H *o* to NO_2); 8.06 (*s*, H–C(2) or H–C(8)); 7.37 (*m*, 6 H *m* to NO_2); 6.12 (*d*, J = 1.2, H–C(1′)); 5.55 (*d*, H–C(2′)); 4.60–4.20 (*m*, H–C(4′), 2 H–C(5′), 3 CH_2CH_2O); 3.70–3.60 (*m*, 3 CH_2CH_2O); 2.60 (*m*, 1 H–C(3′)); 2.20 (*m*, 1 H–C(3′)). FAB-MS (3-nitrobenzyl alcohol matrix): 832 (MH$^+$). Anal. calc. for $C_{37}H_{35}N_8O_{15}$ (831.7): C 53.43, H 4.24, N 13.47; found: C 53.39, H 4.17, N 13.38.

8. *Lipid-phosphoramidites* **21**–**25**: *General Method.* A soln. of the appropriate lipid **16**–**20** (3 mmol) in CH_2Cl_2 (15 ml) was treated with *N*-ethyldiisopropylamine (12 mmol) and solid chloro(diisopropylamino)[2-(4-nitrophenyl)ethoxy]phosphane (**23**) [23] (1.6 g, 4.5 mmol) under Ar. After stirring for 1 h at r.t., the solvent was evaporated to a small volume and, after addition of pentane (150 ml), the yellow soln. was extracted with sat. NaCl/$NaHCO_3$ soln. (3 × 30 ml). The org. phase was dried ($MgSO_4$) and evaporated and the yellow oil dried (h.v.). After purification by FC (alox (30 g), neutral, 3.5 × 4 cm, with petroleum ether, petroleum ether/Et_2O or petroleum ether/AcOEt), the lipid-phosphoramidites **21**–**25** were isolated as yellowish oils.

9. *(2*RS*)-2,3-Bis(hexadecanoyloxy)propyl 2-(4-Nitrophenyl)ethyl* N,N*-Bis(1-methylethyl)phosphoramidite* (= *2,3-Di-*O*-palmitoylglycer-1-yl 2-(4-Nitrophenyl)ethyl* N,N*-Diisopropylphosphoramidite*; **21**). From **16** (1.71 g,

3 mmol) [20]: 2 g (76%) of **21**. TLC (alox, neutral, toluene/AcOEt 98:2): R_f 0.85. ^{1}H-NMR ($CDCl_3$): 8.15 (*m*, 2 H *o* to NO_2); 7.40 (*m*, 2 H *m* to NO_2); 5.16 (*quint.*, CH_2CHCH_2(1)); 4.37–4.10 (*m*, CH_2CHCH_2(1)); 3.89–3.45 (*m*, CH_2CH_2O, CH_2CHCH_2(1), 2 Me_2CH); 3.00 (*t*, CH_2CH_2O); 2.30 (*t*, 2 $Me(CH_2)_{13}CH_2CO$); 1.60 (br. *m*, 2 $Me(CH_2)_{12}CH_2CH_2CO$); 1.25 (br. *m*, 2 $Me(CH_2)_{12}CH_2CH_2CO$); 1.10 (4*s*, 2 Me_2CH); 0.87 (*t*, 2 $Me(CH_2)_{14}CO$). ^{31}P-NMR ($CDCl_3$): 149.3, 149.1.

10. *(2RS)-2,3-Bis(tetradecanoyloxy)propyl 2-(4-Nitrophenyl)ethyl* N,N-*Bis(1-methylethyl)phosphoramidite* (= *2,3-Di-O-myristoylglycer-1-yl 2-(4-Nitrophenyl)ethyl* N,N-*Diisopropylphosphoramidite*; **22**). From **17** (5.12 g, 10 mmol) [20]: 7 g (87%) of **22**. TLC (alox, neutral, toluene/AcOEt 98:2): R_f 0.85. ^{1}H-NMR ($CDCl_3$): 8.12 (*m*, 2 H *o* to NO_2); 7.36 (*d*, 2 H *m* to NO_2); 5.12 (br. *m*, CH_2CHCH_2(1)); 4.34–3.42 (*m*, CH_2CHCH_2(1), CH_2CH_2O, 2 Me_2CH); 2.97 (*t*, CH_2CH_2O); 2.26 (*t*, 2 $Me(CH_2)_{11}CH_2CO$); 1.57 (*m*, 2 $Me(CH_2)_{10}CH_2CH_2CO$); 1.22 (*m*, 2 $Me(CH_2)_{10}CH_2CH_2CO$); 1.07 (4*s*, 2 Me_2CH); 0.85 (*t*, 2 $Me(CH_2)_{12}CO$). ^{31}P-NMR ($CDCl_3$): 149.2, 149.0.

11. *(2RS)-2,3-Bis(hexadecyloxy)propyl 2-(4-Nitrophenyl)ethyl* N,N-*Bis(1-methylethyl)phosphoramidite* (= *2,3-Di-O-hexadecylglycer-1-yl 2-(4-Nitrophenyl)ethyl* N,N-*Diisopropylphosphoramidite*; **23**). From **18** (3.24 g, 6 mmol) [21]: 4.3 g (85%) of **23**. TLC (alox, neutral, toluene/AcOEt 98:2): R_f 0.9. ^{1}H-NMR ($CDCl_3$): 8.17–8.13 (*m*, 2 H *o* to NO_2); 7.41–7.38 (*m*, 2 H *m* to NO_2); 3.95–3.39 (*m*, CH_2CHCH_2(1), CH_2CH_2O, 2 $Me(CH_2)_{14}CH_2O$, 2 Me_2CH); 3.01 (*t*, CH_2CH_2O); 1.54 (*m*, $Me(CH_2)_{13}CH_2CH_2O$); 1.25 (*m*, 2 $Me(CH_2)_{13}CH_2CH_2O$); 1.16–1.09 (4*s*, 2 Me_2CH); 0.87 (*t*, 2 $Me(CH_2)_{15}O$). ^{31}P-NMR ($CDCl_3$): 147.8.

12. *(2RS)-2,3-Bis(octadecyloxy)propyl 2-(4-Nitrophenyl)ethyl* N,N-*Bis(1-methylethyl)phosphoramidite* (= *2,3-Di-O-octadecylglycer-1-yl 2-(4-Nitrophenyl)ethyl* N,N-*Diisopropylphosphoramidite*; **24**). From **19** (5.97 g, 10 mmol) [21]: 6.3 g (70%) of **24**. TLC (alox, neutral, petroleum ether/Et_2O 9:1): R_f 0.8. ^{1}H-NMR ($CDCl_3$): 8.16–8.13 (*m*, 2 H *o* to NO_2); 7.41–7.38 (*m*, 2 H *m* to NO_2); 3.95–3.39 (*m*, CH_2CHCH_2(1), CH_2CH_2O, 2 $Me(CH_2)_{16}CH_2O$, 2 Me_2CH); 3.01 (*t*, CH_2CH_2O); 1.54 (*m*, 2 $Me(CH_2)_{15}CH_2CH_2O$); 1.25 (*m*, 2 $Me(CH_2)_{15}CH_2CH_2O$); 1.16–1.09 (4*s*, 2 Me_2CH); 0.87 (*t*, 2 $Me(CH_2)_{17}O$). ^{31}P-NMR ($CDCl_3$): 147.8. Anal. calc. for $C_{53}H_{101}N_2O_6P$ (893.4): C 71.26, H 11.40, N 3.14; found: C 71.79, H 11.28, N 3.05.

13. *2-(Hexadecanoyloxy)-1-[(hexadecanoyloxy)methyl]ethyl 2-(4-Nitrophenyl)ethyl* N,N-*Bis(1-methylethyl)phosphoramidite* (= *1,3-Di-O-palmitoylglycer-2-yl 2-(4-Nitrophenyl)ethyl* N,N-*Diisopropylphosphoramidite*; **25**). From **20** (1.71 g, 3 mmol)[2]: 2.5 g (96%) of **25**. TLC (alox, neutral, toluene/AcOEt 98:2): R_f 0.9. ^{1}H-NMR ($CDCl_3$): 8.15 (*m*, 2 H *o* to NO_2); 7.40 (*d*, 2 H *m* to NO_2); 4.2–3.4 (*m*, $(CH_2)_2CH$(1), CH_2CH_2O, 2 Me_2CH); 3.0 (*t*, CH_2CH_2O); 2.29 (*t*, 2 $Me(CH_2)_{13}CH_2CO$); 1.62–1.34 (br., 2 $Me(CH_2)_{12}CH_2CH_2CO$); 1.25 (*m*, 2 $Me(CH_2)_{12}CH_2CH_2CO$); 1.16–1.07 (4*s*, 2 Me_2CH); 0.85 (*t*, 2 $Me(CH_2)_{14}CO$). ^{31}P-NMR ($CDCl_3$): 149.95. Anal. calc. for $C_{49}H_{89}N_2O_8P$ (865.2): C 68.02, H 10.37, N 3.24; found: C 65.71, H 10.02, N 3.50.

14. *AZT-Phosphotriesters* **26**–**29** *and* **38**: *General Procedure*. A soln. of **6** (4 mmol) in abs. MeCN (15 ml) was treated under inert gas with a soln. of the appropriate lipid-phosphoramidite **21**–**25** (6 mmol) and 1*H*-tetrazole (20 mmol). After 1 h at r.t., the mixture was oxidized with I_2 in pyridine/H_2O/CH_2Cl_2 3:1:1 until no further decolorization occurred. The brown soln. was diluted with $CHCl_3$ (150 ml) and extracted with $Na_2S_2O_3$ soln. (10 g of $Na_2S_2O_3$ in 500 ml of sat. NaCl soln., 30 ml). The colorless org. phase was dried ($MgSO_4$), evaporated, coevaporated with toluene to remove pyridine (3 × 20 ml), and applied as CH_2Cl_2 soln. onto a FC column (silica gel (80 g), toluene, 5.5 × 10 cm, toluene/AcOEt 1:1 with MeOH gradient). The products were precipitated from MeOH (for **28** at −30°) and filtered with suction to give anal. pure material.

15. *3'-Azido-3'-deoxythymidine 5'-[(2RS)-2,3-Bis(hexadecanoyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**26**). From **6** (200 mg, 0.75 mmol): 520 mg (67%) of **26**. TLC (SiO_2, toluene/AcOEt/MeOH 5:4:1): R_f 0.85. M.p. 38–39°. UV (MeOH): 265 (4.26). IR (KBr): 2110 (N_3). ^{1}H-NMR ($CDCl_3$): 9.14 (br. *d*, NH); 8.17 (*m*, 2 H *o* to NO_2); 7.39 (*m*, 2 H *m* to NO_2); 7.27 (*s*, H–C(6)); 6.14 (*m*, H–C(1')); 5.22 (*m*, CH_2CHCH_2(1)); 4.34–3.89 (*m*, H–C(3'), H–C(4'), 2 H–C(5'), CH_2CHCH_2(1), CH_2CH_2O); 3.11 (*t*, CH_2CH_2O); 2.43–2.28 (*m*, 2 H–C(2'), 2 $Me(CH_2)_{13}CH_2CO$); 1.92 (*s*, Me–C(5)); 1.60 (*m*, 2 $Me(CH_2)_{12}CH_2CH_2CO$); 1.25 (br. *m*, 2 $Me(CH_2)_{12}CH_2CH_2CO$); 0.87 (*t*, 2 $Me(CH_2)_{14}CO$). ^{31}P-NMR ($CDCl_3$): −0.34, −0.51. Anal. calc. for $C_{53}H_{87}N_6O_{13}P$ (1047.3): C 60.79, H 8.37, N 8.03; found: C 60.86, H 8.25, N 7.89.

16. *3'-Azido-3'-deoxythymidine 5'-[(2RS)-2,3-Bis(tetradecanoyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**27**). From **6** (1.1 g, 4.12 mmol): 3.6 g (88%) of **27**. TLC (SiO_2, toluene/AcOEt/MeOH 5:4:1): R_f 0.61. M.p. 25°. UV (MeOH): 266 (4.26). IR (KBr): 2110 (N_3). ^{1}H-NMR ($CDCl_3$): 9.03 (br. *d*, NH); 8.17 (*m*, 2 H *o* to NO_2); 7.40 (*m*, 2 H *m* to NO_2); 7.28 (*s*, H–C(6)); 6.13 (2*t*, H–C(1')); 5.23 (br. *quint.*, CH_2CHCH_2(1)); 4.36–3.95 (*m*, H–C(3'), H–C(4'), 2 H–C(5'), CH_2CHCH_2(1), CH_2CH_2O); 3.06 (br. *t*, CH_2CH_2O); 2.43–2.27 (*m*,

2 H–C(2'), 2 $Me(CH_2)_{11}CH_2CO$); 1.91 (*s*, Me–C(5)); 1.58 (br. *m*, 2 $Me(CH_2)_{10}CH_2CH_2CO$); 1.25 (*m*, 2 $Me(CH_2)_{10}CH_2CH_2CO$); 0.87 (*t*, 2 $Me(CH_2)_{12}CO$). ^{31}P-NMR ($CDCl_3$): –0.46, –0.63. Anal. calc. for $C_{49}H_{79}N_6O_{13}P$ (991.2): C 59.38, H 8.03, N 8.48; found: C 59.51, H 8.11, N 8.48.

17. *3'-Azido-3'-deoxythymidine 5'-[(2RS)-2,3-Bis(hexadecyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**28**). From **6** (400 mg, 0.9 mmol): 1.3 g (85%) of **28**. TLC (SiO_2, toluene/acetone 8:2): R_f 0.26. M.p. 41–42°. UV (MeOH): 266 (4.27). IR (KBr): 2110 (N_3). ^{1}H-NMR ($CDCl_3$): 9.13, 9.10 (2*s*, 2 H *o* to NO_2); 7.40 (*m*, 2 H *m* to NO_2); 7.35 (*s*, H–C(6)); 6.18 (*m*, H–C(1')); 4.40–3.96 (*m*, H–C(3'), H–C(4'), 2 H–C(5'), CH_2CHCH_2(1), CH_2CH_2O); 3.58–3.37 (*m*, CH_2CHCH_2(1), CH_2CHCH_2, 2 $Me(CH_2)_{14}CH_2O$); 3.15–3.08 (2*t*, CH_2CH_2O); 2.48–2.25 (*m*, 2 H–C(2')); 1.92 (*s*, Me–C(5)); 1.52 (*m*, 2 $Me(CH_2)_{13}CH_2CH_2O$); 1.25 (*m*, 2 $Me(CH_2)_{13}CH_2CH_2O$); 0.87 (*t*, 2 $Me(CH_2)_{15}O$). ^{31}P-NMR ($CDCl_3$): –0.31, –0.43. Anal. calc. for $C_{53}H_{91}N_6O_{11}P$ (1019.32): C 62.45, H 9.00, N 8.25; found: C 62.70, H 9.01, N 7.85.

18. *3'-Azido-3'-deoxythymidine 5'-[(2RS)-2,3-Bis(octadecyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**29**). From **6** (870 mg, 3.25 mmol): 2.9 g (83%) of **29**. TLC (SiO_2, toluene/acetone 8:2): R_f 0.24. M.p. 52–53°. UV (MeOH): 266 (4.24). IR (KBr): 2110 (N_3). ^{1}H-NMR ($CDCl_3$): 8.95–8.70 (br., NH); 8.19–8.14 (*m*, 2 H *o* to NO_2); 7.42–7.35 (*m*, 2 H *m* to NO_2, H–C(6)); 6.22–6.17 (*m*, H–C(1')); 4.40–3.96 (*m*, H–C(3'), H–C(4'), 2 H–C(5'), CH_2CHCH_2(1), CH_2CH_2O); 3.60–3.37 (*m*, CH_2CHCH_2(1), CH_2CHCH_2 2 $Me(CH_2)_{16}CH_2O$); 3.15–3.09 (2*t*, CH_2CH_2O); 2.43–2.30 (*m*, 2 H–C(2')); 1.92 (*s*, Me–C(5)); 1.51 (*m*, 2 $Me(CH_2)_{15}CH_2CH_2O$); 1.25 (*m*, 2 $Me(CH_2)_{15}CH_2CH_2O$); 0.87 (*t*, 2 $Me(CH_2)_{17}O$). Anal. calc. for $C_{57}H_{99}N_6O_{11}P$ (1975.43): C 63.66, H 9.28, N 7.82; found: C 64.09, H 9.52, N 7.42.

19. *Cordycepin-Phosphotriesters* **30–37**: *General Procedure*. A soln. of **12** or **13** (2 mmol) in abs. MeCN (10 ml) was treated under inert gas with a soln. of the appropriate lipid phosphoramidite **21–24** (3 mmol) in abs. CH_2Cl_2 (10 ml). To the clear colorless soln., 1*H*-tetrazole (8 mmol) was added and the mixture stirred for 90 min and subsequently oxidized with I_2/pyridine/H_2O/CH_2Cl_2 3:1:1 (1 g in 10 ml) until no more decolorization occurred. The dark soln. was stirred for another 15 min and decolorized by extraction with $CHCl_3$ (200 ml) and 10% $Na_2S_2O_3$ in sat. NaCl soln. (50 ml). The aq. phase was washed with CH_2Cl_2 (100 ml), the org. layer dried ($MgSO_4$), evaporated, and co-evaporated with toluene (2 × 20 ml), and the residue purified by FC (silica gel (70 g), toluene, 5.5 × 10 cm, 100-ml fractions, toluene/AcOEt 1:1 → toluene/AcOEt 1:1 with 5% MeOH). The product-containing fractions were evaporated, co-evaporated with MeOH, and treated with MeOH. The colorless precipitate was filtered with suction.

20. *3'-Deoxy-N^6,2'-O-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 5'-[(2RS)-2,3-Bis(hexadecanoyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**30**). From **12** (1.65 g, 2.5 mmol): 3.2 g (90%) of **30**. TLC (SiO_2, toluene/AcOEt/MeOH 5:4.5:0.5): R_f 0.32, 0.34 (diastereoisomers). UV (MeOH/CH_2Cl_2 1:1): 267 (4.66), 272 (sh, 4.64). ^{1}H-NMR ($CDCl_3$): 8.68 (*s*, H–C(8) or H–C(2)); 8.16–8.06 (*m*, H–C(2) or H–C(8), 6 H *o* to NO_2); 7.43–7.29 (*m*, 6 H *m* to NO_2); 6.08 (*s*, H–C(1')); 5.60 (*m*, H–C(2')); 5.15 (*quint.*, CH_2CHCH_2(1)); 4.54–4.02 (*m*, H–C(4'), 2 H–C(5'), CH_2CHCH_2(1), 3 CH_2CH_2O); 3.15–3.00 (*m*, 3 CH_2CH_2O); 2.70–2.51 (*m*, 1 H–C(3')); 2.32–2.19 (*m*, 1 H–C(3'), 2 $Me(CH_2)_{13}CH_2CO$); 1.59 (br. *m*, 2 $Me(CH_2)_{12}CH_2CH_2CO$); 1.25 (*m*, 2 $Me(CH_2)_{12}CH_2CH_2CO$); 0.87 (*t*, 2 $Me(CH_2)_{14}CO$). Anal. calc. for $C_{71}H_{101}N_8O_{20}P$ (1417.6): C 60.16, H 7.18, N 7.90; found: C 60.25, H 7.28, N 7.95.

21. *3'-Deoxy-N^6,2'-O-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 5'-[(2RS)-2,3-Bis(tetradecanoyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**31**). From **12** (1.59 g, 2.5 mmol): 3.05 g (77%) of **31**. TLC (SiO_2, toluene/AcOEt/MeOH 5:43.5:0.5): R_f 0.32, 0.34 (diastereoisomers). UV (MeOH/CH_2Cl_2 1:1): 267 (4.66), 271 (sh, 4.63). ^{1}H-NMR ($CDCl_3$): 8.72 (*s*, H–C(8) or H–C(2)); 8.33 (2*s*, NH); 8.21–8.09 (*m*, H–C(2) or H–C(8), 6 H *o* to NO_2); 7.47–7.27 (*m*, 6 H *m* to NO_2); 6.12 (*s*, H–C(1')); 5.63 (*m*, H–C(2')); 5.19 (*m*, CH_2CHCH_2(1)); 4.57–4.01 (*m*, H–C(4'), 2 H–C(5'), CH_2CHCH_2(1), 3 CH_2CH_2O); 3.20–3.02 (*m*, 3 CH_2CH_2O); 2.73–2.58 (*m*, 1 H–C(3')); 2.32–2.22 (*m*, 1 H–C(3'), 2 $Me(CH_2)_{11}CH_2CO$); 1.59 (br. *m*, 2 $Me(CH_2)_{10}CH_2CH_2CO$); 1.25 (*m*, 2 $Me(CH_2)_{10}CH_2CH_2CO$); 0.87 (*t*, 2 $Me(CH_2)_{10}CH_2CH_2CO$). ^{31}P-NMR ($CDCl_3$): –0.46. Anal. calc. for $C_{67}H_{93}N_8O_{20}P$ (1361.5): C 59.11, H 6.89, N 8.23; found: C 59.16, H 6.97, N 8.12.

22. *3'-Deoxy-N^6,2'-O-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 5'-[(2RS)-2,3-Bis(hexadecyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**32**). From **12** (1.27 g, 2 mmol): 2.3 g (83%) of **32**. TLC (SiO_2, toluene/AcOEt/MeOH 5:4.5:0.5): R_f 0.33. UV (MeOH/CH_2Cl_2 1:1): 267 (4.67), 272 (sh, 4.65). ^{1}H-NMR ($CDCl_3$): 8.69 (*s*, H–C(8) or H–C(2)); 8.17–8.07 (*m*, H–C(2) or H–C(8), NH, 6 H *o* to NO_2); 7.44–7.24 (*m*, 6 H *m* to NO_2); 6.10 (*d*, J = 1.5, H–C(1')); 5.58 (*m*, H–C(2')); 4.54–3.95 (*m*, H–C(4'), 2 H–C(5'), CH_2CHCH_2(1), 3 CH_2CH_2O); 3.58–3.33 (*m*, CH_2CHCH_2(1), 2 $Me(CH_2)_{14}CH_2O$); 3.17–3.00 (*m*, 3 CH_2CH_2O); 2.70–2.52 (*m*, 1 H–C(3')); 2.25–2.15

(*m*, 1 H–C(3′)); 1.49 (br. *m*, 2 $Me(CH_2)_{13}CH_2CH_2O$); 1.25 (*m*, 2 $Me(CH_2)_{13}CH_2CH_2O$); 0.87 (*t*, 2 $Me(CH_2)_{15}O$). Anal. calc. for $C_{71}H_{101}N_8O_{18}P$ (1389.6): C 61.37, H 7.62, N 8.06; found: C 61.40, H 7.60, N 8.06.

23. *3′-Deoxy-*N^6,*2′-*O*-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 5′-[(2*RS*)-2,3-Bis(octadecyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**33**). From **12** (1.15 g, 1.8 mmol): 2.3 g (88%) of **33**. TLC (SiO_2, toluene/AcOEt/MeOH 5:4.5:0.5): R_f 0.31, 0.35 (diastereoisomers). UV (MeOH/CH_2Cl_2 1:1): 267 (4.67), 272 (sh, 4.65). ^{1}H-NMR ($CDCl_3$): 8.69 (*s*, H–C(8) or H–C(2)); 8.17–8.07 (*m*, H–C(2) or H–C(8), NH, 6 H *o* to NO_2); 7.44–7.24 (*m*, 6 H *m* to NO_2); 6.08 (2*d*, J = 1.5, H–C(1′)); 5.57 (*m*, H–C(2′)); 4.54–3.95 (*m*, H–C(4′), 2 H–C(5′), CH_2CHCH_2(1), 3 CH_2CH_2O); 3.58–3.33 (*m*, CH_2CHCH_2(1), 2 $Me(CH_2)_{16}CH_2O$); 3.17–3.00 (*m*, 3 CH_2CH_2O); 2.70–2.51 (*m*, H–C(3′)); 2.25–2.15 (*m*, H–C(3′)); 1.49 (br. *m*, 2 $Me(CH_2)_{15}CH_2CH_2O$); 1.25 (*m*, 2 $Me(CH_2)_{15}CH_2CH_2O$); 0.87 (*t*, 2 $Me(CH_2)_{17}O$). Anal. calc. for $C_{78}H_{113}N_8O_{18}P$ (1445.7): C 62.31, H 7.88, N 7.75; found: C 62.23, H 7.89, N 7.83.

24. *3′-Deoxy-*N^6,*5′-*O*-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 2′-[(2*RS*)-2,3-Bis(hexadecanoyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**34**). From **12** (831 mg, 1.3 mmol): 1.58 g (85%) of **34**. TLC (SiO_2, toluene/AcOEt/MeOH 5:4.5:0.5): R_f 0.31, 0.35 (diastereoisomers). UV (MeOH/CH_2Cl_2 1:1): 267 (4.65), 272 (sh, 4.63). ^{1}H-NMR ($CDCl_3$): 8.71, 8.70 (2*s*, H–C(8) or H–C(2)); 8.31 (NH); 8.16–8.08 (*m*, H–C(2) or H–C(8), 6 H *o* to NO_2); 7.47–7.28 (*m*, 6 H *m* to NO_2); 6.18, 6.14 (2*d*, H–C(1′)); 5.35 (*m*, H–C(2′)); 5.22 (*m*, CH_2CHCH_2(1)); 4.65–4.09 (*m*, H–C(4′), 2 H–C(5′), CH_2CHCH_2(1), 3 CH_2CH_2O); 3.20–3.06 (*m*, 3 CH_2CH_2O); 2.50–2.25 (*m*, 2 H–C(3′), 2 $Me(CH_2)_{13}CH_2CO$); 1.65 (br. *m*, 2 $Me(CH_2)_{12}CH_2CH_2CO$); 1.25 (*m*, 2 $Me(CH_2)_{12}CH_2CH_2CO$); 0.87 (*t*, 2 $Me(CH_2)_{12}CH_2CH_2CO$). Anal. calc. for $C_{71}H_{101}N_8O_{20}P$ (1417.6): C 60.16, H 7.18, N 7.90; found: C 60.16, H 7.59, N 7.61.

25. *3′-Deoxy-*N^6,*5′-*O*-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 2′-[(2*RS*)-2,3-Bis(tetradecanoyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**35**). From **12** (790 mg, 1.25 mmol): 1.61 g (91%) of **35**. TLC (SiO_2, toluene/AcOEt/MeOH 5:4.5:0.5): R_f 0.31, 0.35 (diastereoisomers). UV (MeOH/CH_2Cl_2): 267 (4.66), 272 (sh, 4.64). ^{1}H-NMR ($CDCl_3$): 8.71, 8.70 (2*s*, H–C(8) or H–C(2)); 8.61 (br., NH); 8.17–8.07 (*m*, H–C(2) or H–C(8), 6 H *o* to NO_2); 7.47–7.28 (*m*, 6 H *m* to NO_2); 6.21, 6.17 (*s*, *d*, H–C(1′)); 5.34 (*m*, H–C(2′)); 5.24 (*m*, CH_2CHCH_2(1)); 4.65–4.09 (*m*, H–C(4′), 2 H–C(5′), CH_2CHCH_2(1), 3 CH_2CH_2O); 3.20–3.06 (*m*, 3 CH_2CH_2O); 2.50–2.25 (*m*, 2 H–C(3′), 2 $Me(CH_2)_{11}CH_2CO$); 1.65 (br. *m*, 2 $Me(CH_2)_{10}CH_2CH_2CO$); 1.25 (*m*, 2 $Me(CH_2)_{10}CH_2CH_2CO$); 0.87 (*t*, 2 $Me(CH_2)_{12}CO$). Anal. calc. for $C_{67}H_{93}N_8O_{20}P$ (1361.5): C 59.11, H 6.89, N 8.23; found: C 58.76, H 6.85, N 8.26.

26. *3′-Deoxy-*N^6,*5′-*O*-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 2′-[(2*RS*)-2,3-Bis(hexadecyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**36**). From **12** (1.2 g, 2 mmol): 2.2 g (79%) of **36**. TLC (SiO_2, toluene/AcOEt/MeOH 5:4.5:0.5): R_f 0.51, 0.54 (diastereoisomers). UV (MeOH/CH_2Cl_2): 267 (4.66), 272 (sh, 4.64). ^{1}H-NMR ($CDCl_3$): 8.67, 8.66 (2*s*, H–C(8) or H–C(2)); 8.16–8.04 (*m*, H–C(2) or H–C(8), NH, 6 H *o* to NO_2); 7.44–7.31 (*m*, 6 H *m* to NO_2); 6.16 (2*s*, H–C(1′)); 5.30 (*m*, H–C(2′)); 4.70–3.95 (*m*, H–C(4′), 2 H–C(5′), CH_2CHCH_2(1), 3 CH_2CH_2O); 3.54–3.33 (*m*, CH_2CHCH_2(1), 2 $Me(CH_2)_{14}CH_2O$); 3.17–3.05 (*m*, 3 CH_2CH_2O); 2.50–2.20 (*m*, 2 H–C(3′)); 1.49 (br. *m*, 2 $Me(CH_2)_{13}CH_2CH_2O$); 1.25 (*m*, 2 $Me(CH_2)_{13}CH_2CH_2O$); 0.87 (*t*, 2 $Me(CH_2)_{15}O$). Anal. calc. for $C_{71}H_{101}N_8O_{20}P$ (1417.6): C 61.37, H 7.62, N 8.06; found: C 61.28, H 7.56, N 8.32.

27. *3′-Deoxy-*N^6,*5′-*O*-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 2′-[(2*RS*)-2,3-Bis(octadecyloxy)propyl 2-(4-Nitrophenyl)ethyl Phosphate]* (**37**). From **12** (1.26 g, 2 mmol): 2.3 g (80%) of **37**. TLC (SiO_2, toluene/AcOEt/MeOH 5:4.5:0.5): R_f 0.51, 0.54 (diastereoisomers). UV (MeOH/CH_2Cl_2): 267 (4.65), 272 (sh, 4.63). ^{1}H-NMR ($CDCl_3$): 8.67, 8.66 (2*s*, H–C(8) or H–C(2)); 8.16–8.04 (*m*, H–C(2) or H–C(8), NH, 6 H *o* to NO_2); 7.44–7.31 (*m*, 6 H *m* to NO_2); 6.16 (2*s*, H–C(1′)); 5.30 (*m*, H–C(2′)); 4.60–4.03 (*m*, H–C(4′), 2 H–C(5′), CH_2CHCH_2(1), 3 CH_2CH_2O); 3.54–3.33 (*m*, CH_2CHCH_2(1), 2 $Me(CH_2)_{16}CH_2O$); 3.17–3.05 (*m*, 3 CH_2CH_2O); 2.50–2.20 (*m*, 2 H–C(3′)); 1.49 (br. *m*, 2 $Me(CH_2)_{15}CH_2CH_2O$); 1.25 (*m*, 2 $Me(CH_2)_{15}CH_2CH_2O$); 0.87 (*t*, 2 $Me(CH_2)_{17}O$). Anal. calc. for $C_{75}H_{113}N_8O_{18}P$ (1445.7): C 62.31, H 7.88, N 7.75; found: C 62.25, H 7.98, N 7.71.

28. *3′-Azido-3′-deoxythymidine 5′-{2-(Hexadecanoyloxy)-1-[(hexadecanoyloxy)methyl]ethyl 2-(4-Nitrophenyl)ethyl Phosphate}* (**38**). According to *Exper. 14* from **6** (120 mg, 0.44 mmol): 400 mg (86%) of **38**. TLC (SiO_2, $CHCl_3$/MeOH 95:5): R_f 0.51. M.p. 38°. UV (MeOH): 266 (4.24). IR (KBr): 2110 (N_3). ^{1}H-NMR ($CDCl_3$): 9.15, 9.10 (2 br. *s*, NH); 8.13 (*m*, 2 H *o* to NO_2); 7.35 (*m*, 2 H *m* to NO_2); 7.26 (*s*, H–C(6)); 6.15–6.08 (2*t*, H–C(1′)); 4.73–4.66 (*m*, $(CH_2)_2CH$(1)); 4.43–3.92 (*m*, H–C(3′), H–C(4′), 2 H–C(5′), $(CH_2)_2CH$, CH_2CH_2O); 3.11–3.05 (2*t*, CH_2CH_2O); 2.40–2.23 (*m*, 2 H–C(2′), 2 $Me(CH_2)_{13}CH_2CO$); 1.87 (*s*, Me–C(5)); 1.55–1.43 (br. *m*, 2 $Me(CH_2)_{12}CH_2CH_2CO$); 1.32–1.00 (*m*, 2 $Me(CH_2)_{12}CH_2CH_2CO$); 0.84 (*t*, 2 $Me(CH_2)_{14}CO$). ^{31}P-NMR ($CDCl_3$): −0.97, −1.08. Anal. calc. for $C_{53}H_{87}N_6O_{13}P$ (1047.3): C 60.79, H 8.37, N 8.03; found: C 60.94, H 8.30, N 7.89.

29. *Deprotection of Acyloxy-Substituted AZT-Phosphotriesters to* **39**, **40**, *and* **51**: *General Procedure.* A soln. of the protected triesters **26**, **27**, or **38** (1 mmol) in MeCN (10 ml) and DBU (1 ml) was stirred for 45 min at r.t. The yellowish mixture was diluted with CH_2Cl_2 (300 ml) and extracted with 0.5M HCl (4 × 100 ml). The org. phase was washed with 10 mM $(Et_3NH)OAc$ buffer (2 × 50 ml) and H_2O (100 ml), dried ($MgSO_4$), and concentrated to a brownish oil. FC (silica gel (45 g), 3.5 × 10 cm, toluene/AcOEt/Et_3N 450:400:50, gradient up to 8% MeOH, 100-ml fractions). The colorless oil was dissolved in acetone (30 ml), filtered, and evaporated. This crude product was dissolved in acetone (10 ml) and treated with NaI soln. (300 mg/2 ml of acetone). The colorless precipitate was collected by centrifugation and washed twice with small amounts of acetone.

30. *3′-Azido-3′-deoxythymidine 5′-[Sodium (2*RS*)-2,3-Bis(hexadecanoyloxy)propyl Phosphate]* (**39**). From **26** (400 mg, 0.38 mmol): 260 mg (68%) of **39**. TLC (SiO_2, $CHCl_3$/MeOH 95:5 + 3% Et_3N): R_f 0.4. M.p. 160° (dec.). UV (MeOH): 265 (3.97). IR (KBr): 2110 (N_3). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO 1:1): 11.2 (*s*, NH(3)); 7.84 (*s*, H–C(6)); 6.23 (*t*, H–C(1′)); 5.12 (br. *m*, CH_2CHCH_2(1)); 4.54–3.91 (*m*, H–C(3′), H–C(4′), 2 H–C(5′), CH_2CHCH_2(1)); 2.48–2.23 (*m*, 2 H–C(2′), 2 Me$(CH_2)_{13}CH_2CO$); 1.89 (*s*, Me–C(5)); 1.54 (br. *m*, 2 Me$(CH_2)_{12}CH_2CH_2CO$); 1.25 (br. *m*, 2 Me$(CH_2)_{12}CH_2CH_2CO$); 0.87 (*t*, 2 *Me*$(CH_2)_{14}CO$). ^{31}P-NMR ($CDCl_3$/(D_6)DMSO 1:1): 1.38. Anal. calc. for $C_{45}H_{79}N_5NaO_{11}P \cdot H_2O$ (938.1): C 57.61, H 8.70, N 7.46; found: C 57.27, H 8.65, N 7.50.

31. *3′-Azido-3′-deoxythymidine 5′-[Sodium (2*RS*)-2,3-Bis(tetradecanoyloxy)propyl Phosphate]* (**40**). From **27** (900 mg, 0.9 mmol): 550 mg (70%) of **40**. TLC (SiO_2, toluene/AcOEt/MeOH/Et_3N 4:3:2:1): R_f 0.49. M.p. 165° (dec.). UV (MeOH): 265 (3.97). IR (KBr): 2110 (N_3). ^{1}H-NMR ($CDCl_3$/CD_3OD 4:1): 7.54 (*s*, H–C(6)); 6.12 (*t*, H–C(1′)); 5.15 (br. *m*, CH_2CHCH_2(1)); 4.41–3.89 (*m*, H–C(3′), H–C(4′), 2 H–C(5′), CH_2CHCH_2(1)); 2.38–2.19 (*m*, 2 H–C(2′), 2 Me$(CH_2)_{11}CH_2CO$); 1.85 (*s*, Me–C(5)); 1.51 (br. *m*, 2 Me$(CH_2)_{10}CH_2CH_2CO$); 1.17 (br. *m*, 2 Me$(CH_2)_{10}CH_2CH_2CO$); 0.79 (*t*, 2 *Me*$(CH_2)_{12}CO$). ^{31}P-NMR ((D_6)DMSO): 4.67. Anal. calc. for $C_{41}H_{71}N_5NaO_{11}P$ (864.0): C 56.99, H 8.28, N 8.11; found: C 57.18, H 8.16, N 7.96.

32. *Deprotection of Alkoxy-Substituted AZT-Phosphotriesters to* **41** *and* **42**: *General Procedure.* A soln. of the protected triesters **28** or **29** (1 mmol) in MeCN/CH_2Cl_2 2:1 (15 ml) and DBU (1 ml) was stirred for 60 min at r.t. The yellowish mixture was diluted with CH_2Cl_2/MeOH 95:5 (300 ml) and extracted with 0.5M HCl (4 × 100 ml). The aq. phase was washed with CH_2Cl_2/MeOH 95:5 (100 ml) and the combined org. phase extracted with H_2O (100 ml), dried ($MgSO_4$), and evaporated. The colorless solid residue was suspended in acetone (10 ml) and treated with Et_3N (1 ml). After addition of CH_2Cl_2 (5 ml), a clear soln. resulted which was filtered and evaporated. The residue was suspended in MeCN/acetone 1:1 (10 ml), stirred for 1 h, filtered with suction, and washed with MeCN (10 ml).

33. *3′-Azido-3′-deoxythymidine 5′-[Triethylammonium (2*RS*)-2,3-Bis(hexadecyloxy)propyl Phosphate]* (**41**). From **28** (900 mg, 0.9 mmol): 780 mg (91%) of **41**. TLC (SiO_2, toluene/AcOEt/MeOH/Et_3N 4:3:2:1): R_f 0.5. M.p. 68–70° (dec.). UV (MeOH): 265 (3.97). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO 1:1): 11.9 (br., Et_3NH^+); 8.90 (br., NH(3)); 7.80 (*s*, H–C(6)); 6.29 (*t*, H–C(1′)); 4.50 (*m*, H–C(3′)); 4.13–3.92 (*m*, H–C(4′), 2 H–C(5′), CH_2CHCH_2(1)); 3.62–3.37 (*m*, CH_2CHCH_2(1), 2 Me$(CH_2)_{14}CH_2O$); 3.05 (*m*, $(MeCH_2)_3NH^+$); 2.36 (*m*, 2 H–C(2′)); 1.97 (*s*, Me–C(5)); 1.51 (*m*, 2 Me$(CH_2)_{13}CH_2O$); 1.25 (*m*, 2 Me$(CH_2)_{13}CH_2CH_2O$, $(MeCH_2)_3NH^+$); 0.87 (*t*, 2 *Me*$(CH_2)_{15}O$). ^{31}P-NMR ((D_6)DMSO/$CDCl_3$ 1:1): 0.45. Anal. calc. for $C_{51}H_{99}N_6O_9P$ (971.37): C 63.06, H 10.27, N 8.65; found: C 62.83, H 10.33, N 8.25.

34. *3′-Azido-3′-deoxythymidine 5′-[Triethylammonium (2*RS*)-2,3-Bis(octadecyloxy)propyl Phosphate]* (**42**). From **29** (1.08 g, 1 mmol): 930 mg (91%) of **42**. TLC (SiO_2, toluene/AcOEt/MeOH/Et_3N 4:3:2:1): R_f 0.5. UV (MeOH): 265 (3.99). ^{1}H-NMR ($CDCl_3$): 12.4 (br., Et_3NH^+); 8.40 (br., NH(3)); 7.80 (*s*, H–C(6)); 6.29 (*t*, H–C(1′)); 4.50 (*m*, H–C(3′)); 4.13–3.92 (*m*, H–C(4′), 2 H–C(5′), CH_2CHCH_2(1)); 3.62–3.37 (*m*, CH_2CHCH_2(1), 2 Me$(CH_2)_{16}CH_2O$); 3.05 (*m*, $(MeCH_2)_3NH^+$); 2.40–2.10 (*m*, 2 H–C(2′)); 1.97 (*s*, Me–C(5)); 1.51 (*m*, 2 Me$(CH_2)_{15}CH_2CH_2O$); 1.25 (*m*, 2 Me$(CH_2)_{15}CH_2CH_2O$, $(MeCH_2)_3NH^+$); 0.87 (*t*, 2 *Me*$(CH_2)_{17}O$). Anal. calc. for $C_{55}H_{107}N_6O_9P \cdot H_2O$ (1045.4): C 63.18, H 10.51, N 8.03; found: C 63.08, H 10.70, N 7.56.

35. *Deprotected Cordycepin-Phosphotriesters* **43**–**50**: *General Procedure.* A soln. of protected triesters **30**–**37** (0.5 mmol) in abs. pyridine (10 ml) was treated with DBU (2 mmol) for 24 h at r.t. The mixture was diluted with CH_2Cl_2/MeOH 4:1 (50 ml) and extracted with 8M HCl (150 ml). For a better separation of the phases, most of the aq. phase was discarded and the emulsion filled up with CH_2Cl_2/MeOH 4:1 (150 ml). The resulting org. layer was treated with methyloxirane (5 ml), stirred for *ca.* 15 min at r.t., dried ($MgSO_4$), and evaporated. The residue was suspended in MeCN (20 ml) and filtered with suction. This crude product (purity 90% by UV) was further purified by FC (silica gel (15 g), CH_2Cl_2/Et_3N 98:2, gradient up to 15% MeOH). The product-containing fractions were evaporated and the residue suspended in MeCN and filtered with suction.

36. *3′-Deoxyadenosine 5′-[Triethylammonium (2RS)-2,3-Bis(hexadecanoyloxy)propyl Phosphate]* (**43**). From **30** (700 mg, 0.5 mmol): 408 mg (83%) of **43**. TLC (SiO_2, CH_2Cl_2/MeOH 95:5 + 3% Et_3N): R_f 0.05. UV (MeOH/CH_2Cl_2 1:1): 259 (4.16). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO 1:1): 11.2 (br. *s*, Et_3NH^+); 8.25, 8.10 (2*s*, H–C(2) or H–C(8)); 7.05–6.90 (br., NH_2); 5.90 (*s*, H–C(1′)); 5.60 (br. *m*, OH–C(2′)); 5.05 (*m*, CH_2CHCH_2(1)); 4.50 (*m*, H–C(2′), H–C(4′)); 4.30–4.20 (*m*, 1 H–C(5′)); 4.10–3.80 (*m*, 1 H–C(5′), CH_2CHCH_2(1)); 2.95 (*q*, $(MeCH_2)_3NH^+$); 2.25–2.10 (*m*, 1 H–C(3′), 2 Me$(CH_2)_{13}CH_2CO$); 1.95 (*m*, 1 H–C(3′)); 1.90–1.80 (br. *m*, 2 Me$(CH_2)_{12}CH_2CH_2CO$); 1.30–1.10 (*m*, 2 Me$(CH_2)_{12}CH_2CH_2CO$, $(MeCH_2)_3NH^+$); 0.81 (*t*, 2 *Me*$(CH_2)_{14}CO$). Anal. calc. for $C_{51}H_{95}N_6O_{10}P$ (983.3): C 62.30, H 9.74, N 8.55; found: C 61.85, H 9.61, N 8.54.

37. *3′-Deoxyadenosine 5′-[Triethylammonium (2RS)-2,3-Bis(tetradecanoyloxy)propyl Phosphate]* (**44**). From **31** (660 mg, 0.5 mmol): 390 mg (86%) of **44**. TLC (SiO_2, CH_2Cl_2/MeOH 95:5 + 3% Et_3N): R_f 0.05. UV (MeOH/CH_2Cl_2 1:1): 259 (4.15). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO 1:1): 11.2 (br. *s*, Et_3NH^+); 8.24, 8.09 (2*s*, H–C(2), H–C(8)); 6.98–6.85 (br., NH_2); 5.90 (*s*, H–C(1′)); 5.60 (br. *m*, OH–C(2′)); 5.05 (*m*, CH_2CHCH_2(1)); 4.50 (*m*, H–C(2′), H–C(4′)); 4.30–4.20 (*m*, 1 H–C(5′)); 4.10–3.80 (*m*, 1 H–C(5′), CH_2CHCH_2(1)); 2.95 (*q*, $(MeCH_2)_3NH^+$); 2.25–2.10 (*m*, 1 H–C(3′), 2 Me$(CH_2)_{11}CH_2CO$); 1.95 (*m*, H–C(3′)); 1.90–1.80 (br. *m*, 2 Me$(CH_2)_{10}CH_2CH_2CO$); 1.30–1.10 (*m*, 2 Me$(CH_2)_{10}CH_2CH_2CO$, $(MeCH_2)_3NH^+$); 0.81 (*t*, 2 *Me*$(CH_2)_{12}CO$). Anal. calc. for $C_{47}H_{87}N_6O_{10}P$ (927.3): C 60.88, H 9.46, N 9.46; found: C 60.56, H 9.22, N 9.06.

38. *3′-Deoxyadenosine 5′-[Triethylammonium (2RS)-2,3-Bis(hexadecyloxy)propyl Phosphate]* (**45**). From **32** (350 mg, 0.25 mmol): 170 mg (71%) of **45**. TLC (SiO_2, CH_2Cl_2/MeOH 95:5 + 3% Et_3N): R_f 0.05. UV (MeOH/CH_2Cl_2 1:1): 259 (4.13). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO 1:1): 11.5 (br. *s*, Et_3NH^+); 8.30, 8.08 (2*s*, H–C(2), H–C(8)); 7.05 (br., NH_2); 5.89 (*s*, H–C(1′)); 5.61 (br. *m*, OH–C(2′)); 4.48 (*m*, H–C(2′), H–C(4′)); 4.05–3.95 (*m*, 1 H–C(5′)); 3.89–3.82 (*m*, 1 H–C(5′)); 3.20 (*m*, CH_2CHCH_2(1)); 3.45–3.25 (*m*, CH_2CHCH_2(1), 2 Me$(CH_2)_{14}CH_2O$); 3.05–2.90 (*q*, $(MeCH_2)_3NH^+$); 2.28–2.18 (*m*, 1 H–C(3′)); 1.95–1.89 (*m*, 1 H–C(3′)); 1.49 (br. *m*, 2 Me$(CH_2)_{13}CH_2CH_2O$); 1.20 (*m*, 2 Me$(CH_2)_{13}CH_2CH_2O$, $(MeCH_2)_3NH^+$); 0.75 (*t*, 2 *Me*$(CH_2)_{15}O$). Anal. calc. for $C_{51}H_{99}N_6O_8P \cdot 0.5\ H_2O$ (964.4): C 63.52, H 10.45, N 8.71; found: C 63.56, H 10.46, N 8.51.

39. *3′-Deoxyadenosine 5′-[Triethylammonium (2RS)-2,3-Bis(octadecyloxy)propyl Phosphate]* (**46**). From **33** (700 mg, 0.49 mmol): 410 mg (86%) of **46**. TLC (SiO_2, CH_2Cl_2/MeOH 95:5 + 3% Et_3N): R_f 0.05. UV (MeOH/CH_2Cl_2 1:1): 260 (4.15). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO 1:1): 11.4 (br. *s*, Et_3NH^+); 8.27, 8.09 (2*s*, H–C(2), H–C(8)); 7.05 (br., NH_2); 5.90 (*d*, J = 1.4, H–C(1′)); 5.61 (br. *m*, OH–C(2′)); 4.48 (*m*, H–C(2′), H–C(4′)); 4.05–3.95 (*m*, 1 H–C(5′)); 3.89–3.82 (*m*, 1 H–C(5′)); 3.20 (*m*, CH_2CHCH_2(1)); 3.45–3.25 (*m*, CH_2CHCH_2(1), 2 Me$(CH_2)_{16}CH_2O$); 3.05–2.90 (*q*, $(MeCH_2)_3NH^+$); 2.28–2.18 (*m*, 1 H–C(3′)); 1.95–1.89 (*m*, 1 H–C(3′)); 1.49 (br. *m*, 2 Me$(CH_2)_{15}CH_2CH_2O$); 1.20 (*m*, Me$(CH_2)_{15}CH_2CH_2O$, $(MeCH_2)_3NH^+$); 0.75 (*t*, 2 *Me*$(CH_2)_{17}O$). Anal. calc. for $C_{55}H_{107}N_6O_8P \cdot 0.5\ H_2O$ (1020.5): C 64.76, H 10.66, N 8.24; found: C 64.59, H 10.53, N 8.12.

40. *3′-Deoxyadenosine 2′-[Triethylammonium (2RS)-2,3-Bis(hexadecanoyloxy)propyl Phosphate]* (**47**). From **34** (200 mg, 0.14 mmol): 106 mg (77%) of **47**. TLC (SiO_2, CH_2Cl_2/MeOH 95:5 + 3% Et_3N): R_f 0.05. UV (MeOH/CH_2Cl_2 1:1): 259 (4.14). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO 1:1): 10.9 (br. *s*, Et_3NH^+); 8.19, 8.10 (2*s*, H–C(2), H–C(8)); 7.00 (br., NH_2); 6.05 (*d*, J = 2.1, H–C(1′)); 5.40 (br. *m*, OH–C(5′)); 5.05 (*m*, CH_2CHCH_2(1)); 4.95 (*m*, H–C(2′)); 4.38 (*m*, H–C(4′)); 4.25 (*dd*, 1 H–C(5′)); 4.00 (*dd*, 1 H–C(5′)); 3.80–3.60 (*m*, CH_2CHCH_2(1)); 2.95 (*q*, $(MeCH_2)_3NH^+$); 2.55 (*m*, 1 H–C(3′)); 2.15–2.10 (*m*, 1 H–C(3′), 2 Me$(CH_2)_{13}CH_2CO$); 1.90–1.80 (br. *m*, 2 Me$(CH_2)_{12}CH_2CH_2CO$); 1.30–1.10 (*m*, 2 Me$(CH_2)_{12}CH_2CH_2CO$, $(MeCH_2)_3NH^+$); 0.79 (*t*, 2 *Me*$\{CH_2)_{14}CO$). Anal. calc. for $C_{51}H_{95}N_6O_{10}P \cdot H_2O$ (1001.3): C 61.17, H 9.76, N 8.39; found: C 61.05, H 9.83, N 8.49.

41. *3′-Deoxyadenosine 2′-[Triethylammonium (2RS)-2,3-Bis(tetradecanoyloxy)propyl Phosphate]* (**48**). From **35** (570 mg, 0.42 mmol): 320 mg (83%) of **48**. TLC (SiO_2, CH_2Cl_2/MeOH 95:5 + 3% Et_3N): R_f 0.05. UV (MeOH/CH_2Cl_2 1:1): 259 (4.16). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO 1:1): 11.0 (br. *s*, Et_3NH^+); 8.30, 8.02 (2*s*, H–C(2), H–C(8)); 7.60 (br., NH_2); 6.10 (*d*, J = 2.2, H–C(1′)); 5.05 (*m*, CH_2CHCH_2(1), H–C(2′)); 4.38 (*m*, H–C(4′)); 4.25 (*m*, 1 H–C(5′)); 4.00 (*dd*, 1 H–C(5′)); 3.80–3.60 (*m*, CH_2CHCH_2(1), br., OH–C(5′)); 2.95 (*q*, $(MeCH_2)_3NH^+$); 2.45 (*m*, 1 H–C(3′)); 2.15–2.10 (*m*, 1 H–C(3′), 2 Me$(CH_2)_{11}CH_2CO$); 1.90–1.80 (br. *m*, 2 Me$(CH_2)_{10}CH_2CH_2CO$); 1.30–1.10 (*m*, 2 Me$(CH_2)_{10}CH_2CH_2CO$, $(MeCH_2)_3NH^+$); 0.79 (*t*, 2 *Me*$(CH_2)_{12}CO$). Anal. calc. for $C_{47}H_{87}N_6O_{10}P \cdot H_2O$ (945.3): C 59.72, H 9.49, N 8.89; found: C 59.80, H 9.40, N 8.85.

42. *3′-Deoxyadenosine 2′-[Triethylammonium (2RS)-2,3-Bis(hexadecyloxy)propyl Phosphate]* (**49**). From **36** (700 mg, 0.5 mmol): 410 mg (86%) of **49**. TLC (SiO_2, CH_2Cl_2/MeOH 95:5 + 3% Et_3N): R_f 0.05. UV (MeOH/CH_2Cl_2 1:1): 259 (4.14). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO 1:1): 11.4 (br. *s*, Et_3NH^+); 8.15, 8.05 (2*s*, H–C(2), H–C(8)); 7.00–6.80 (br., NH_2); 6.05 (*s*, H–C(1′)); 5.45 (br. *m*, OH–C(5′)); 5.00 (*m*, H–C(2′)); 4.38 (*m*, H–C(4′)); 3.80–3.60 (*m*, CH_2CHCH_2(1)); 3.50–3.20 (*m*, 2 H–C(5′), CH_2CHCH_2(1), 2 Me$(CH_2)_{14}CH_2O$); 2.95 (*q*, $(MeCH_2)_3NH$); 2.50 (*m*, 1 H–C(3′)); 2.15–2.10 (*m*, 1 H–C(3′)); 1.90–1.80 (br. *m*, 2 Me$(CH_2)_{13}CH_2CH_2O$);

1.30–1.10 (*m*, 2 Me(C*H*$_2$)$_{13}$CH$_2$CH$_2$O, (*Me*CH$_2$)$_3$NH$^+$); 0.79 (*t*, 2 *Me*(CH$_2$)$_{15}$O). Anal. calc. for $C_{51}H_{99}N_6O_8P$ (955.4): C 64.10, H 10.44, N 8.80; found: C 64.19, H 10.50, N 8.63.

43. *3′-Deoxyadenosine 2′-[Triethylammonium (2RS)-2,3-Bis(octadecyloxy)propyl Phosphate]* (**50**). From **37** (720 mg, 0.5 mmol): 440 mg (87%) of **50**. TLC (SiO_2, CH_2Cl_2/MeOH 95:5 + 3% Et_3N): R_f 0.05. UV (MeOH/CH_2Cl_2 1:1): 259 (4.14). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO 1:1): 11.4 (br. *s*, Et_3NH^+); 8.15, 8.05 (2*s*, H–C(2), H–C(8)); 7.00–6.80 (br., NH_2); 6.05 (*s*, H–C(1′)); 5.45 (br. *m*, OH–C(5′)); 5.00 (*m*, H–C(2′)); 4.38 (*m*, H–C(4′)); 3.80–3.60 (*m*, CH_2CHCH_2(1)); 3.50–3.20 (*m*, 2 H–C(5′), CH_2CHCH_2(1), 2 Me(CH$_2$)$_{16}$C*H*$_2$O); 2.95 (*q*, (MeC*H*$_2$)$_3$NH$^+$); 2.50 (*m*, 1 H–C(3′)); 2.15–2.10 (*m*, 1 H–C(3′)); 1.90–1.80 (br. *m*, 2 Me(CH$_2$)$_{15}$C*H*$_2$CH$_2$O); 1.30–1.10 (*m*, 2 Me(C*H*$_2$)$_{15}$CH$_2$CH$_2$O, (*Me*CH$_2$)$_3$NH); 0.79 (*t*, 2 *Me*(CH$_2$)$_{17}$O). Anal. calc. for $C_{55}H_{107}N_6O_8P$ (1011.5): C 65.31, H 10.66, N 8.31; found: C 64.91, H 10.44, N 8.28.

44. *3′-Azido-3′-deoxythymidine 5′-{Sodium 2-(Hexadecanoyloxy)-1-[(hexadecanoyloxy)methyl]ethyl Phosphate}* (**51**). From **38** (210 mg, 0.2 mmol): 110 mg (55%) of **51**. M.p. 120°. TLC (SiO_2, $CHCl_3$/MeOH 95:5 + 3% Et_3N): R_f 0.5. UV (MeOH): 265 (3.94). IR (KBr): 2110 (N_3). ^{1}H-NMR ((D_6)DMSO/$CDCl_3$ 1:1): 11.2 (*s*, NH); 7.74 (*s*, H–C(6)); 6.15 (*t*, *J* = 6.4, H–C(1′)); 4.48–3.94 (*m*, H–C(3′), H–C(4′), 2 H–C(5′), (C*H*$_2$)$_2$C*H*(1)); 2.41–2.30 (*m*, 2 H–C(2′)); 2.20 (*t*, 2 Me(CH$_2$)$_{13}$C*H*$_2$CO); 1.81 (*s*, Me–C(5)); 1.46 (*m*, 2 Me(CH$_2$)$_{12}$C*H*$_2$CH$_2$CO); 1.17 (br. *m*, 2 Me(C*H*$_2$)$_{12}$CH$_2$CH$_2$CO); 0.80 (*t*, 2 *Me*(CH$_2$)$_{14}$CO). ^{31}P-NMR ((D_6)DMSO/$CDCl_3$ 1:1): 0.67. Anal. calc. for $C_{45}H_{79}N_5NaO_{11}P$ (920.3): C 58.74, H 8.65, N 7.61; found: C 58.73, H 8.92, N 7.13.

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