55. Nucleotides

Part IL[1])

Synthesis and Characterization of Cordycepin-Trimer-Vitamin and -Lipid Conjugates Potential Inhibitors of HIV-1 Replication

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Dedicated to Prof. Dr. *Richard Neidlein* on the occasion of his 65th birthday

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The syntheses of biodegradable 2′- and 5′-ester and 2′- and 5′-carbonate conjugates of the antivirally active 3′-deoxyadenylyl-(2′–5′)-3′-deoxyadenylyl-(2′–5′)-3′-deoxyadenosine (cordycepin-trimer core) with the vitamins, E, D_2, and A and the lipids 1,2-di-*O*-palmitoylglycerol and 1,2-di-*O*-hexadecylglycerol were achieved first by preparation of the trimeric educts **19–21** (*Scheme 1*). Secondly, these substances were condensed with the lipophilic residues *via* a succinate or carbonate linker and then deprotected by β-elimination of the npeoc and npe protecting groups and acid treatment for detritylation without harming the ester and carbonate functions, respectively (*Scheme 2*). Metabolically stable cordycepin-trimer-vitamin and -lipid conjugates are a new class of bioconjugates that inhibit HIV-1-induced syncytia formation with IC_{50} values of 7, 18, and 24 μM for **39**, **29**, and **42**, respectively, and inhibit HIV-1 reverse transcriptase (RT) activity from 14 to 96% (see *Table*). Of the nine conjugates tested, inhibition of HIV-1 replication by **28**, **29**, **32**, **40**, and **42** may be attributed in part to the activation of the RNase L/PKR antiviral pathways. Trimer conjugate **42** showed the greatest inhibition of HIV-1 replication, *i.e.*, a 120-fold decrease in HIV-1-induced syncytia formation and an 88% inhibition of HIV-1 reverse transcriptase (RT). This inhibition of replication of HIV-1 by **42** can be attributed in part to the activation of recombinant, human RNase L. The inhibition of HIV-1 replication by the cordycepin-trimer-vitamin and -lipid conjugates is significantly greater than that observed for the (2′–5′) A-trimer core or cordycepin-trimer core.

Introduction. – The antiviral activity of interferon is associated with two different reaction cascades: the (2′–5′)oligo A cascade and the protein kinase pathway both of which are finally leading to the inhibition of protein synthesis [2–5].

The presence of dsRNA or RNA stem-loop structures, *e.g.* in the transacting response element (TAR)-RNA sequence of HIV-1 [6] activates a (2′–5′)oligo A synthetase which is able to produce 2′,5′-connected oligoadenylate 5′-triphosphates from ATP [7]. The trimer possesses the best features to activate the latent RNase L which degrades finally viral and cellular mRNA, thereby inhibiting protein synthesis. However, (2′–5′)oligo A is also rapidly inactivated by two different nucleases.

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On the other hand, binding of dsRNA to the p68 kinase (PKR) results in autophosphorylation of the enzyme, followed by phosphoryl transfer to eIF-2(eucaryotic initiation factor-2), whereby eIF-2-P is incapable of recycling and, consequently, protein synthesis initiation is halted [8].

With the discovery of the (2′–5′)oligo A system, a novel chemotherapeutic possibility for the control of virus or cell growth seemed to be found. One of the modified (2′–5′)A analogues is the cordycepin-trimer core d$^{3'}$(A2′p5′A2′p5′A) [9] [10] which was found to be a biologically active substance with metabolic stability and without toxicity to cells [11]. Surprisingly, the cordycepin analogues do not stimulate (2′–5′)A-dependent RNase L activity [12] [13], although they inhibit HIV production. The target of (2′–5′)d$^{3'}$(A-A-A) or (2′–5′)d$^{3'}$(pA-A-A) was found to be the HIV-1 reverse transcriptase (RT) [13]. Treatment of HIV-1-infected H9 cells with as little as 1 μM (2′–5′)d$^{3'}$(A-A-A) or (2′–5′)d$^{3'}$(A-A-A) resulted in an almost total inhibition of virus production. The natural compounds (2′–5′)(A-A-A) and its triphosphate were without any antiviral effect up to a concentration of 10 μM [14].

It has been demonstrated that the tRNA^{Lys,3} acts as primer for the RT in the HIV system [15]. The HIV-1 RT binds to the anticodon region of tRNA^{Lys,3} which contains 4 uridine moieties (one of them is modified) in a row. This complex formation is weakened by (2′–5′)d$^{3'}$(pA-A-A) [14]. Detailed biochemical aspects are described and discussed in [16].

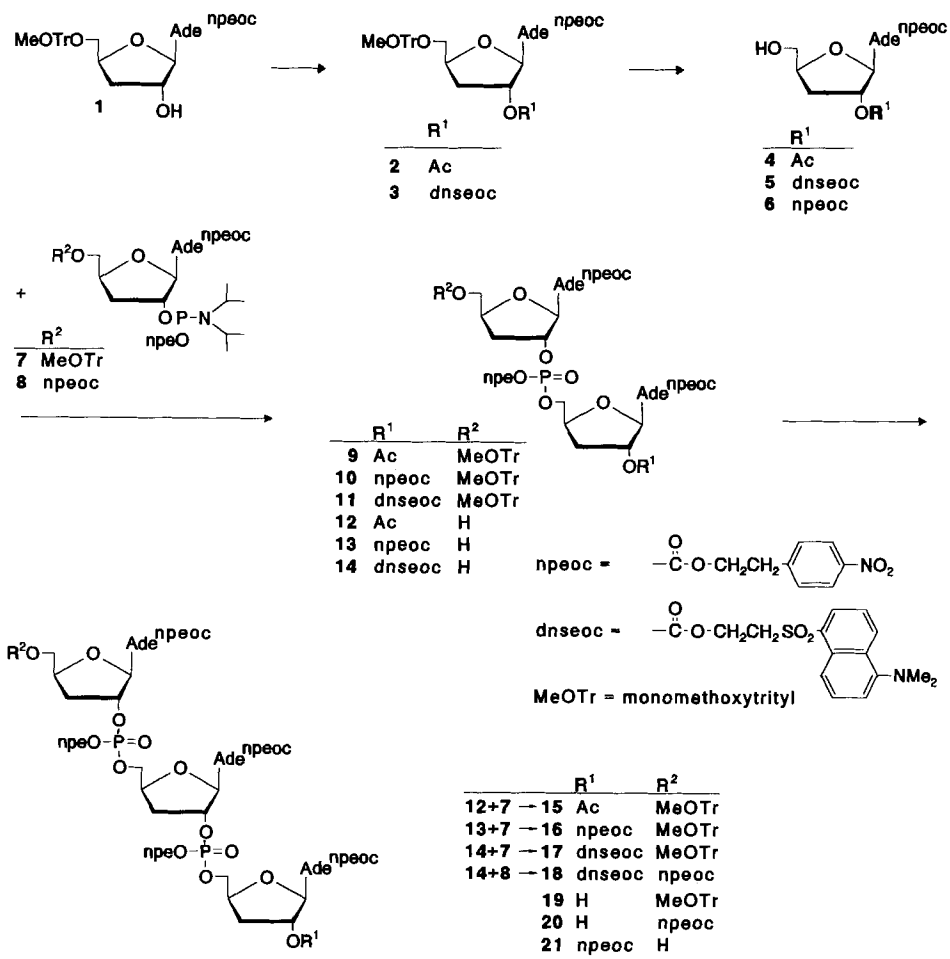
The major disadvantage in the application of oligonucleotides is their polarity which does not allow them to penetrate easily through the cell membrane. Therefore, previous reports [17–20] describe the improvement of cell uptake by conjugate formation. Our goal in this direction is to attach lipophilic groups *via* a succinyl or carbonyl spacer to the sugar moiety of (2′–5′)d$^{3'}$(A-A-A). It was recently found that the 2′-*O*- and 5′-*O*-cholesterol conjugates of (2′–5′)d$^{3'}$(A-A-A) exhibit a highly increased anti-HIV-1 activity which can be up to 1000-fold in comparison with (2′–5′)d$^{3'}$(A-A-A) [21]. This fact is most likely attributed to an improved cellular uptake of these conjugates bearing a hydrophobic handle. These promising results led to the synthesis of other cordycepin-trimer conjugates carrying vitamin E, D_2, and A and lipids [22–24] *via* a succinate or carbonate linker at the 2′-*O*- and 5′-*O*-position of the terminal ends.

The attachment of the vitamins and lipids [22–24] through an ester or carbonate linkage was chosen for a good biodegradation, recently also described by *Polushin* and *Cohen* [25]. Therefore, a special blocking-group strategy was necessary, using the 2-(4-nitrophenyl)ethyl (npe), the 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) [26], and the dansylethoxycarbonyl (dnseoc) [27] group for a unified protection cleavable by a β-elimination process without harming the ester functions. The multistep syntheses will be reported here. The various reaction products have been characterized by several physical data, and the anti-HIV-1 properties of the conjugates have been explored.

Synthesis. – The chemical solution syntheses of the cordycepin trimers carrying vitamins and lipids [22–24] at the 2′-*O*- and 5′-*O*-terminal ends *via* a succinyl (**28–33**) and carbonyl spacer (**39–43**) were achieved by the phosphoramidite approach. Four protecting-group strategies were applied for the preparation of different trimer conjugates starting from trimeric educts. A straightforward two-step deprotection procedure allowed the isolation of the different conjugates in good yields.

Thus various 2′-*O*-protected monomers were prepared by reaction of the starting material 3′-deoxy-5′-*O*-(monomethoxytrityl)-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine (**1**) [10] with acetic anhydride to give **2** or with 2-dansylethyl chloroformate hydrochloride (= 2-{[5-(dimethylamino)naphthalen-1-yl]sulfonyl}ethyl chloroformate hydrochloride; dnseocCl·HCl) [27] and 1-methyl-1*H*-imidazole to give **3** (96%) which were detritylated using 2% TsOH in CH_2Cl_2/MeOH 4:1 to **4** (76%) and **5** (82%), respectively. The differently 2′-*O*-protected cordycepins **4**–**6** [10] were then condensed with 3′-deoxy-5′-*O*-(monomethoxytrityl)-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 2′-[2-(4-nitrophenyl)ethyl *N*,*N*-diisopropylphosphoramidite] (**7**) [28] to give, on subsequent oxidation, **9**–**11** and, after detritylation, the dimers **12**–**14**. For further chain elongation, these dimers were treated with the phosphoramidite **7** [28] or **8**, and, after oxidation with I_2/H_2O/pyridine, the corresponding fully protected trimers **15**–**18** were obtained in very good yields. To obtain the 2′-OH trimers, the 2′-*O*-acetyl and

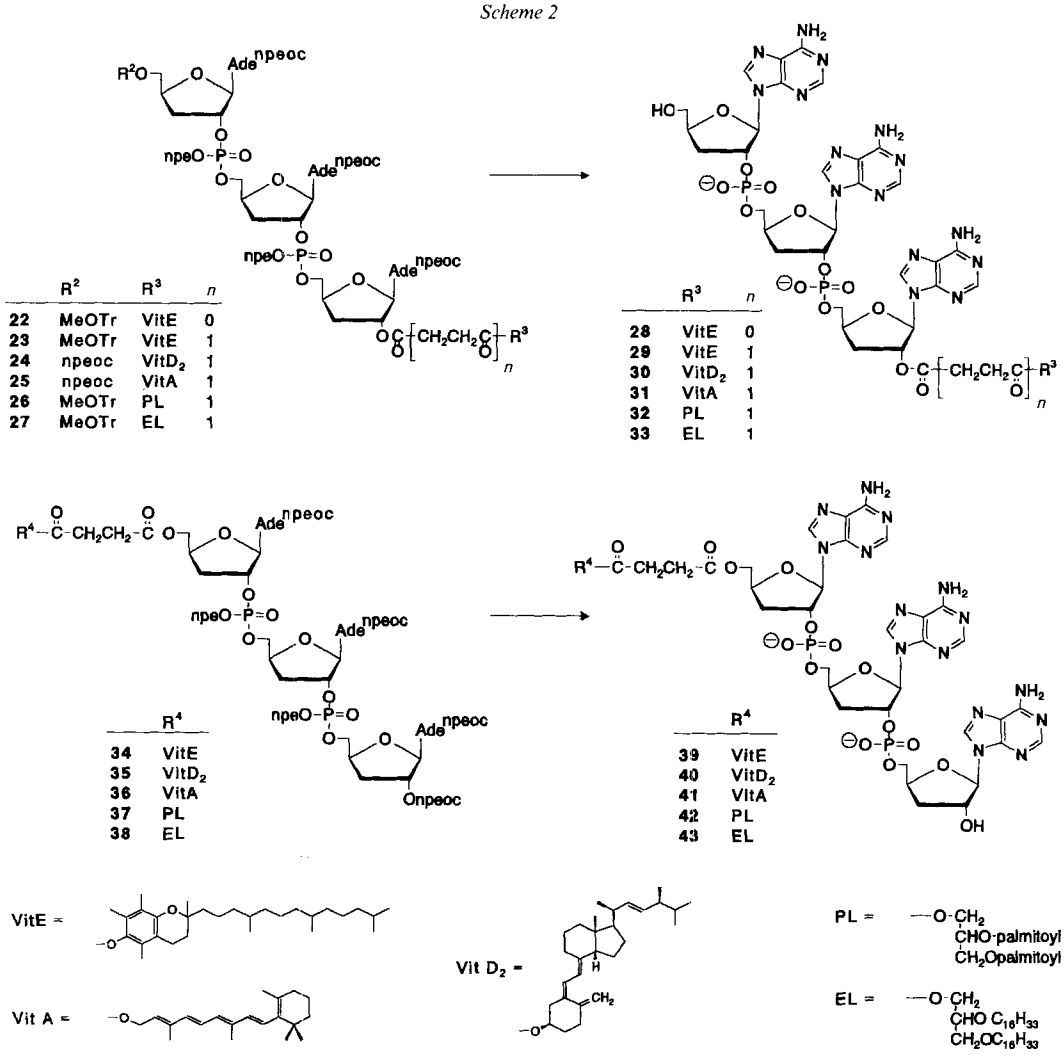
Scheme 1



2′-*O*-npeoc protected compounds **15** and **16** were treated with K_2CO_3 in abs. MeOH to give compound **19** in 75 and 69% yield, respectively. Another possibility to get the 2′-OH building blocks **19** and **20** was the selective β-elimination of the dnseoc group in compounds **17** and **18** with diluted 1,8-diazabicyclo[5.3.0]undec-7-ene (DBU) in abs. pyridine. Finally, the starting material for the 5′-*O*-conjugates is trimer **21** which was prepared by acid treatment of compound **16**.

For the synthesis of the vitamin E conjugate attached *via* a carbonate function, 2-*ambo*-α-tocopheryl chloroformate had to be prepared from vitamin E and trichloromethyl chloroformate. The acylation of the trimer **19** with 2-*ambo*-α-tocopheryl chloroformate in presence of 1-methyl-1*H*-imidazole resulted in the fully protected conjugate **22** (*Scheme 2*). The succinate-linked conjugates **23**–**27** resulted from a one-pot

Scheme 2



reaction of **19** or **20** first with succinic anhydride and 4-(dimethylamino)pyridine (DMAP) and followed by esterification applying the carbodiimide method with the vitamins E, D_2, and A, and with 1,2-di-*O*-palmitoylglycerol [22] [23] and 1,2-di-*O*-hexadecylglycerol [23] [24]. The vitamin D_2 and A conjugates **24** and **25** afforded a unified npeoc-protection compatible with the acid lability of these compounds; the final deblocking to **30** and **31**, respectively, was achieved by β-elimination with DBU removing the npe and npeoc groups. In the case of **22**, **23**, **26**, and **27**, further detritylation by AcOH was necessary after the DBU treatment yielding **28**, **29**, **32**, and **33**, respectively. Formation and deblocking of the trimer 5′-*O*-conjugates took place in a similar manner: the 5′-OH building block **21** was first modified with succinic anhydride and subsequently esterified with the vitamins E, D_2, and A and with the lipids in the presence of *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (EDC) as condensing agent to give compounds **34**–**38**. Deblocking was performed with 0.5M DBU in abs. pyridine leading to the conjugates **39**–**43**. The free cordycepin conjugates were isolated as colourless (**39**, **40**, **42**, **43**, **28**–**30**, **32**, and **33**) and pale yellow (**31** and **41**) powders by washing the solids with abs. MeCN. The free vitamin A conjugates, however, turned out to show some instability in aqueous solution hydrolysing into their corresponding succinates as shown by HPLC studies.

Biochemical Application. – Covalent conjugation of vitamin D_2, vitamin E, and palmitoyl and hexadecyl lipids to the 2′- or 5′-OH groups of cordycepin-trimer core with either a succinyl or carbonyl linker has produced a new group of inhibitors of HIV-1 replication (*Table*). All cordycepin-trimer-vitamin and -lipid conjugates tested (**28**–**30**, **32**, **33**, **39**, **40**, **42**, **43**) inhibited HIV-1-induced syncytia formation more than that observed in the presence of cordycepin, cordycepin-trimer core, or the monomeric cordycepin-vitamin and -lipid conjugates (*Table*) [29]. IC_{50} Values for syncytia formation were 7, 18, and 24 μM for trimer conjugates **39**, **29**, and **42**, respectively, compared to IC_{50} values of 125 and *ca.* 260 μM for the cordycepin-trimer core and monomeric cordycepin, respectively. Therefore, conjugation of vitamin E or lipid groups to the cordycepin-trimer core increased the anti-HIV-1 activity *ca.* 10-fold. Total inhibition of HIV-1 replication by trimer conjugates **19**, **39**, and **43** was observed at 100 μM and 300 μM.

Of the nine cordycepin-trimer conjugates tested, the cordycepin-trimer 5′-(di-*O*-palmitoylglyceryl succinate) **42** was the most potent inhibitor of HIV-1 replication, *i.e.*, a 120-fold decrease in syncytia formation and an 88% inhibition of HIV-1 RT (*Table*). The corresponding cordycepin-trimer 2′-(di-*O*-palmitoylglyceryl succinate) **32** inhibited HIV-1-induced syncytia formation 30-fold and inhibited HIV-1 RT 78%. However, neither **32** nor **42** activated human recombinant RNase L. Three of the cordycepin-trimer conjugates (**28**, **29**, and **40**) inhibited both HIV-1-induced syncytia formation (60-, 20-, and 8-fold, resp.) and HIV-1 RT (52, 70, and 14%), and also activated the antiviral enzyme RNase L (11, 12, and 12%). Conjugates **32** and **42** increased PKR expression 8 and 24%, respectively. Conversely, **28** decreased PKR expression. The decrease in PKR expression by **28** could be a consequence of mRNA degradation by an activated RNase L (*Table*). The 42% decrease in PKR expression by **28** may represent a reciprocal control over gene expression in which there is activation of PKR, *via* the NF-κB/IFN-β pathway, which can indirectly stimulate the (2′–5′)oligo A synthetase/RNase L system by increasing expression of (2′–5′)oligo A synthetase [30]. Based upon the observations that *i*) inhibition

Table. *Inhibition of HIV-1 Replication and Biological Activities of Cordycepin-Trimer-Vitamin and -Lipid Conjugates* **28**–**30**, **32**, **33**, **39**, **40**, **42**, *and* **43**[a])

		Inhibition of syncytia formation[b])	Inhibition of HIV-1 RT activity [%][c])	Activation of RNase L[d])	PKR Expression[e]) ([%] change)
28	Cordycepin-trimer 2′-(vitamin E carbonate)[f])	60	52	11	−42
29	Cordycepin-trimer 2′-(vitamin E succinate)[f])	20	70	12	n.t.[i])
30	Cordycepin-trimer 2′-(vitamin D_2 succinate)[g])	12	85	0	n.t.[i])
32	Cordycepin-trimer 2′-(2,3-di-*O*-palmitoylglyceryl succinate)[f])	30	78	0	+8
33	Cordycepin-trimer 2′-(2,3-di-*O*-hexadecylglyceryl succinate)[f])	15	77	0	n.t.[i])
39	Cordycepin-trimer 5′-(vitamin E succinate)[f])	10	96	0	n.t.[i])
40	Cordycepin-trimer 5′-(vitamin D_2 succinate)[h])	8	14	12	n.t.[i])
42	Cordycepin-trimer 5′-(2,3-di-*O*-palmitoylglyceryl succinate)[f])	120	88	0	+24
43	Cordycepin-trimer 5′-(2,3-di-*O*-hexadecylglyceryl succinate)[f])	30	59	0	n.t.[i])
	(2′–5′)d^3(A-A-A)[h])	4.8	96	12	−22
	(2′–5′)A-A-A[h])	3	33	50	n.t.[i])

[a]) Compounds were tested at 300 μM.

[b]) Inhibition of HIV-1 replication was determined by syncytia formation (fold reduction in infection). The mean of triplicate determinations is shown; variance did not exceed 5–10%.

[c]) Percent inhibition of HIV-1 reverse transcriptase (HIV-1 RT) activity. Control values for HIV-1 RT activity ranged from 24000 to 33000 cqm. The mean of duplicate determinations is shown; variance did not exceed 5–10%.

[d]) Activation of recombinant RNase·L was measured as the percent hydrolysis of [^{32}P]poly(U) in the presence of cordycepin-trimer 2′-*O*- and 5′-*O*-vitamin and -lipid conjugates (10 μM). The mean of duplicate determinations is shown; variance did not exceed 5–10%.

[e]) PKR Expression as measured by western blot analyses as described [29].

[f]) Test compound was dissolved in 0.1M $(Et_3NH)OAc$, pH 7.0. Data were normalized to a $(Et_3NH)OAc$ control.

[g]) Test compound was dissolved in MeOH; final concentration of MeOH in the assays was 10%. Data were normalized to a 10% MeOH control.

[h]) Test compound was dissolved in H_2O. Data were normalized to a H_2O control.

[i]) n.t. = not tested.

of HIV-1-induced syncytia formation and HIV-1 RT activity by conjugates **32** and **42** occurred independently of activation of RNase L, *ii*) pleiotropic effects other than activation of the RNase L by AA-ether-A have also been observed independently of RNase L activation in the prevention of HIV-1 replication in peripheral blood lymphocytes, and *iii*) (2′–5′)oligo A can be produced far in excess of that required to activate RNase L, we speculate on the existence of an acataleptic mechanism whereby the addition of select cordycepin-trimer-vitamin and -lipid conjugates and/or naturally occurring, biologically active (2′–5′)oligo A species can modulate expression of PKR [31] [32]. The expression of (2′–5′)oligo A synthetase and the activity of PKR are currently under investigation to further elucidate their roles during HIV-1 replication.

In an independent study, we showed that a 2′-*O*-linked cordycepin-trimer-folic acid conjugate inhibits HIV-1-induced syncytia formation, HIV-1 RT, and activates RNase L [33]. Uptake and subsequent anti-HIV-1 activity of nucleotide-lipid conjugates were reported in [34]. The increased inhibition of HIV-1 replication by the cordycepin-trimer-vitamin and -lipid conjugates compared to the cordycepin-trimer core could be attributed to either uptake by reporter-mediated endocytosis and/or direct membrane fusion [34] [35]. In view of the enhanced uptake of phosphorothiotate/phosphodiester (2′–5′)A derivatives we observed in HIV-1 infected cells [36], studies are currently under way to determine the mechanism of uptake of the cordycepin-vitamin and -lipid conjugates.

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Experimental Part

General. See [29].

Bioassay. Assays measuring HIV-1-induced syncytia formation, HIV-1 reverse transcriptase activity, activation of RNase L, and PKR expression were accomplished as described [29].

1. *2′-O-(2-Dansylethoxycarbonyl)-3′-deoxy-5′-O-(monomethoxytrityl)-N⁶-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**3**). To an ice-cooled suspension of 2-dansylethyl chloroformate hydrochloride [27] (1.512 g, 4 mmol) in abs. CH_2Cl_2 (20 ml) were given 1-methyl-1*H*-imidazole (822 mg, 10 mmol) and some molecular sieve (4 Å). Then 3′-deoxy-5′-*O*-(monomethoxytrityl)-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine (**1**) [10] (1.434 g, 2 mmol) was added, and the mixture was kept at 4° for 18 h. Then the mixture was filtered, the filtrate evaporated, and the residue purified by FC (silica gel, 18 × 3.5 cm, toluene/AcOEt 1:1→1:1 + 1% MeOH): 1.955 g (96%) of **3**. Amorphous solid. UV (MeOH): 342 (sh, 3.61), 272 (sh, 4.47), 264 (4.56), 239 (sh, 4.41). ^{1}H-NMR ((D$_6$)DMSO): 10.65 (*s*, NH); 8.59–8.50 (*m*, H–C(8), H–C(2), H–C(2)(dns)); 8.22–8.13 (*m*, *o* to NO_2, H–C(4)(dns), H–C(8)(dns)); 7.72–7.58 (*m*, *m* to NO_2, H–C(3)(dns), H–C(7)(dns)); 7.26–7.12 (*m*, MeO*Tr*, H–C(6)(dns)); 6.78 (*d*, 2 H *o* to MeO); 6.10 (*'s'*, H–C(1′)); 5.52 (*m*, H–C(2′)); 4.38 (*m*, H–C(4′), OC*H*$_2$CH$_2$, OCH$_2$CH$_2$dns); 3.89 (*'t'*, OCH$_2$C*H*$_2$dns); 3.69 (*s*, MeO); 3.15–3.07 (*m*, OCH$_2$C*H*$_2$, 2 H–C(5′)); 2.77–2.50 (*s*, *m*, Me$_2$N(dns), H–C(3′)); 2.00 (*dd*, H–C(3′)). Anal. calc. for $C_{54}H_{51}N_7O_{12}S$ (1022.1): C 63.46, H 5.03, N 9.59; found: C 63.17, H 5.15, N 9.78.

2. *2′-O-Acetyl-3′-deoxy-N⁶-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**4**). A soln. of twice in abs. pyridine co-evaporated **1** (4.30 g, 6 mmol) and Ac_2O (8.4 ml, 30 mmol) in abs. pyridine (11 ml) was kept at r.t. for 3 h. MeOH (5.5 ml) was added and the mixture stirred for further 1.5 h and then evaporated. The residue was dissolved in $CHCl_3$ (200 ml) and washed with sat. $NaHCO_3$ soln. (2 × 100 ml) and the org. layer dried ($MgSO_4$), evaporated, and co-evaporated with toluene to give *2′-O-acetyl-3′-deoxy-5′-O-(monomethoxytrityl)-N⁶-[2-(4-nitrophenyl)-ethoxycarbonyl]adenosine* (**2**), which was detritylated without further purification as follows: The residue was dissolved in CH_2Cl_2/MeOH 4:1 (120 ml) containing 2% of TsOH·H_2O and kept at r.t. for 10 min. Then the mixture was diluted with $CHCl_3$ (100 ml) and washed with sat. $NaHCO_3$ soln. (2 × 150 ml), the aq. phase re-extracted with $CHCl_3$, the combined org. layer dried ($MgSO_4$) and evaporated, and the residue purified by FC (silica gel, 18 × 3 cm, toluene/AcOEt 1:1→1:1 + 5% MeOH): 1.754 g (60%) of **4** and 480 mg (16%) of contaminated **4**. Amorphous solid. UV (MeOH): 273 (sh, 4.37), 267 (4.43). ^{1}H-NMR ((D$_6$)DMSO): 8.95 (*s*, NH); 8.71, 8.17–8.13 (2*s*, *d*, H–C(8), H–C(2), 2 H *o* to NO_2); 7.43 (*d*, 2 H *m* to NO_2); 5.99 (*d*, H–C(1′)); 5.56 (*m*, H–C(2′)); 4.95 (*m*, OH–C(5′)); 4.61–4.52 (*m*, H–C(4′), OC*H*$_2$CH$_2$); 4.10 (*m*, H–C(5′)); 3.70 (*m*, H–C(5′)); 3.15 (*t*, OCH$_2$C*H*$_2$); 2.90 (*m*, H–C(3′)); 2.20 (*m*, H–C(3′)); 2.12 (*s*, AcO). Anal. calc. for $C_{21}H_{22}N_6O_8$ (486.4): C 51.85, H 4.56, N 17.28; found: C 52.21, H 4.64, N 16.97.

3. *2′-O-(2-Dansylethoxycarbonyl)-3′-deoxy-N⁶-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**5**). Compound **3** (3.369 g, 3.3 mmol) was stirred at r.t. in CH_2Cl_2/MeOH 4:1 (70 ml) containing 2% of TsOH·H_2O for 15 min. Then the mixture was diluted with $CHCl_3$ (200 ml) and washed with sat. $NaHCO_3$ soln. (3 × 100 ml), the aq. phase re-extracted with $CHCl_3$, the combined org. layer dried ($MgSO_4$) and evaporated, and the residue diluted with small amounts of $CHCl_3$ and precipitated twice in Et_2O (2 × 250 ml): 2.021 g (82%) of **5**. Yellow powder. UV

(MeOH): 343 (sh, 3.61), 263 (4.55). ^{1}H-NMR ((D$_6$)DMSO): 10.63 (*s*, NH); 8.62–8.51 (2*s*, 1*d*, H–C(8), H–C(2), H–C(2)(dns)); 8.21–8.14 (*m*, 2 H *o* to NO_2, H–C(4)(dns), H–C(8)(dns)); 7.76–7.59 (*m*, 2 H *m* to NO_2, H–C(3)(dns), H–C(7)(dns)); 7.27 (*d*, H–C(6)(dns)); 6.07 (*d*, H–C(1′)); 5.34 (*m*, H–C(2′)); 5.06 (*t*, OH–C(5′)); 4.45 (*m*, 2 OCH_2CH$_2$, OCH_2CH$_2$dns); 4.38 (*m*, H–C(4′)); 3.88 (*t*, OCH$_2$CH_2dns); 3.6, 3.5 (2*m*, 2 H–C(5′)); 3.11 (*t*, OCH$_2$CH_2); 2.81 (*s*, *m*, Me$_2$N(dns), H–C(3′)); 2.00 (*dd*, H–C(3′)). Anal. calc. for $C_{34}H_{35}N_7O_{11}S$ (749.8): C 54.47, H 4.71, N 13.08; found: C 54.36, H 4.83, N 13.00.

4. *3′-Deoxy-*N^6*,5′-*O*-bis-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 2′-[2-(4-Nitrophenyl)ethyl* N,N*-Diisopropylphosphoramidite]* (**8**). A mixture of **6** [10] (510 mg, 0.8 mmol), bis(diisopropylamino)[2-(4-nitrophenyl)-ethoxy]phosphane [28] (636 mg, 1.6 mmol) and 1*H*-tetrazole (28 mg, 0.4 mmol) in abs. THF/dioxane 2:1 (15 ml) was kept under N_2 at r.t. for 18 h. Then further bis(diisopropylamino)[2-(4-nitrophenyl)ethoxy]phosphane (318 mg, 0.8 mmol) and 1*H*-tetrazole (14 mg, 0.2 mmol) in abs. THF/dioxane 2:1 (6 ml) were added. The mixture was stirred at r.t. for 24 h, evaporated, and diluted with $CHCl_3$ (120 ml), the soln. washed with sat. $NaHCO_3$/NaCl soln. (60 ml), the aq. phase re-extracted with $CHCl_3$, the combined org. layer dried ($MgSO_4$) and evaporated, and the residue purified by FC (silica gel, 13 × 3 cm, petroleum ether/acetone 4:1→3:1→2:1→1:1): 522 mg (70%) of **8**. Amorphous solid. UV (CH_2Cl_2): 271 (sh, 4.64), 267 (4.66). ^{1}H-NMR ($CDCl_3$): 8.7, 8.20–8.00 (*s*, *m*, H–C(8), H–C(2), NH, 6 H *o* to NO_2); 7.5–7.25 (*m*, 6 H *m* to NO_2); 6.10 (*s*, H–C(1′)); 4.95–4.85 (*m*, H–C(2′)); 4.65 (*m*, H–C(4′)); 4.6–4.2 (*m*, 3 OCH_2CH$_2$); 4.0–3.8 (*m*, 2 Me$_2$CHN); 3.65–3.5 (*m*, 2 H–C(5′)); 3.2–2.9 (*m*, 3 OCH$_2$CH_2); 2.3–2.0 (*m*, 2 H–C(3′)); 1.1 (*m*, 2 *Me*$_2$CHN). ^{31}P-NMR ($CDCl_3$): 149.84, 149.03. Anal. calc. for $C_{42}H_{48}N_9O_{19}P$ (933.9): C 54.02, H 5.18, N 13.50; found: C 53.72, H 5.35, N 12.98.

5. *3′-Deoxy-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-2′-*O*-acetyl-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**9**). A mixture of **4** (486 mg, 1 mmol), **7** [28] (1.82 g; 1.8 mmol), and 1*H*-tetrazole (350 mg, 5 mmol) was stirred in dry MeCN (3 ml) under N_2 at r.t. for 4 h. Then it was oxidized with a I_2 soln. (I_2 (500 mg) in pyridine (3 ml), CH_2Cl_2 (1 ml), and H_2O (1 ml)) until no colour change was detected. The mixture was stirred for 15 min, diluted with $CHCl_3$ (120 ml), and washed with a $Na_2S_2O_3$/NaCl soln. (2 × 60 ml), the aq. phase re-extracted with $CHCl_3$, the combined org. layer dried ($MgSO_4$), evaporated, and co-evaporated with toluene, and the residue purified by FC (silica gel, 22 × 3 cm, $CHCl_3$→$CHCl_3$/MeOH 195:5): 1.37 g (96%) of **9**. Amorphous solid. UV (MeOH): 272 (sh, 4.75), 267 (4.79), 237 (4.45). ^{1}H-NMR ($CDCl_3$): 8.68–8.02 (*m*, 2 H–C(8), 2 H–C(2), 2 NH, 6 H *o* to NO_2); 7.46–7.20 (*m*, 6 H *m* to NO_2, 12 H of MeO*Tr*); 6.80 (2 H *o* to MeO); 6.20 (*d*, H–C(1′)); 6.02 (*s*, H–C(1′)); 5.72, 5.45 (2*m*, 2 H–C(2′)); 4.56–4.24 (2*m*, 2 H–C(4′), 3 OCH_2CH$_2$, 2 H–C(5′)); 3.78 (*s*, MeO); 3.40 (*dd*, 2 H–C(5′)); 3.19–3.00 (*m*, 3 OCH$_2$CH_2); 2.73–1.91 (4*m*, 4 H–C(3′)); 2.14 (*s*, Ac). Anal. calc. for $C_{68}H_{64}N_{13}O_{20}P \cdot H_2O$ (1432.3): C 57.02, H 4.64, N 12.71; found: C 56.51, H 4.63, N 12.31.

6. *3′-Deoxy-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-2′-*O*-(2-dansylethoxycarbonyl)-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**11**). As described in *Exper. 5*, with **5** (1.79 g, 2.39 mmol), **7** [28] (3.63 g, 3.59 mmol), 1*H*-tetrazole (837 mg, 11.95 mmol), anh. MeCN (6 ml; 4 h), and I_2 soln. Workup with CH_2Cl_2 (200 ml) and $Na_2S_2O_3$/NaCl soln. (2 × 80 ml) and purification by FC (silica gel, 22.5 × 3.5 cm, $CHCl_3$→$CHCl_3$/MeOH 195:5): 3.62 g (90%) of **11**. Amorphous solid. UV (CH_2Cl_2): 345 (sh, 3.65), 274 (sh, 4.76), 266 (4.84), 239 (sh, 4.58). ^{1}H-NMR ((D$_6$)DMSO): 10.61 (br., 2 NH); 8.6–8.4 (*m*, 2 H–C(8), 2 H–C(2), H–C(2)(dns)); 8.2–7.95 (*m*, 6 H *o* to NO_2, H–C(4)(dns), H–C(8)(dns)); 7.7–7.1 (*m*, 6 H *m* to NO_2, H–C(3)(dns), H–C(7)(dns), 12 H of MeO*Tr*, H–C(6)(dns)); 6.67 (*d*, 2 H *o* to MeO); 6.26, 6.20, 6.06, 6.03 (4*s*, 2 H–C(1′)); 5.55–5.35 (2*m*, 2 H–C(2′)); 4.5–4.05 (2*m*, 2 H–C(4′), 3 OCH_2CH$_2$, 4 H–C(5′), OCH_2CH$_2$dns); 3.88 (*t*, OCH$_2$CH_2dns); 3.68 (*s*, MeO); 3.2–2.0 (*m*, 3 OCH$_2$CH_2, 4 H–C(3′)); 2.77 (*s*, Me$_2$N(dns)). Anal. calc. for $C_{81}H_{77}N_{14}O_{23}PS$ (1677.6): C 57.99, H 4.63, N 11.69; found: C 57.63, H 4.73, N 11.34.

7. *3′-Deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-2′-*O*-acetyl-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**12**). As described in *Exper. 3*, with **9** (1.41 g, 1 mmol) and CH_2Cl_2/MeOH 4:1 (20 ml) containing 2% of TsOH·H_2O (30 min). Workup with $CHCl_3$ (200 ml) and sat. $NaHCO_3$ soln. (2 × 100 ml). FC (silica gel, 17 × 3 cm, $CHCl_3$→$CHCl_3$ + 2%MeOH→$CHCl_3$ + 2.5% MeOH→$CHCl_3$ + 3% MeOH→$CHCl_3$ + 4% MeOH→$CHCl_3$ + 5%MeOH): 1.095 g (96%) of **11**. Amorphous solid. UV (MeOH): 273 (sh, 4.75), 267 (4.80). ^{1}H-NMR ((D$_6$)DMSO): 10.61 (*s*, 2 NH); 8.62–8.52 (*m*, 2 H–C(8), 2 H–C(2)); 8.31–8.06 (*m*, 6 H *o* to NO_2); 7.61–7.40 (*m*, 6 H *m* to NO_2); 6.20–6.12 (*m*, 2 H–C(1′)); 5.70 (*m*, H–C(2′)); 5.26 (*m*, OH–C(5′)); 5.10 (*m*, H–C(2′)); 4.38–4.15 (*m*, 2 H–C(4′), 3 OCH_2CH$_2$, 2 H–C(5′)); 3.64, 3.47 (2*m*, 2 H–C(5′)); 3.10–2.93 (2*m*, 3 OCH$_2$CH_2); 2.60–2.08 (*m*, 4 H–C(3′), Ac).

8. *3′-Deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-2′-*O*-(2-dansylethoxycarbonyl)-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**14**). As described in *Exper. 3*, with **11** (200 mg, 0.12 mmol) and CH_2Cl_2/MeOH 4:1 (2.4 ml) containing 2% of TsOH·H_2O (1.5 h). Workup with $CHCl_3$ (30 ml) and sat. $NaHCO_3$ soln. (2 × 20 ml). FC (silica gel, 15.5 × 1 cm, $CHCl_3$→$CHCl_3$ + 1% MeOH→$CHCl_3$ + 4% MeOH): 146 mg (87%) of **14**. Amorphous solid. UV (CH_2Cl_2): 348 (sh, 3.67), 289 (sh, 4.31), 273 (sh, 4.75), 266 (4.83). ^{1}H-NMR ((D$_6$)DMSO): 10.6 (*m*, 2 NH); 8.6–8.4 (*m*, 2 H–C(8), 2 H–C(2), H–C(2)(dns)); 8.2–8.0 (*m*, 6 H *o* to NO_2, H–C(4)(dns), H–C(8)(dns)); 7.65–7.2 (*m*, 6 H *m* to NO_2, H–C(3)(dns), H–C(7)(dns), H–C(6)(dns)); 6.10, 6.14, 6.08, 6.06 (4*s*, 2 H–C(1′)); 5.45, 5.25 (2*m*, 2 H–C(2′)); 5.10 (*t*, OH–C(5′)); 4.45–4.0 (2*m*, 2 H–C(4′), 3 OCH_2CH$_2$, 4 H–C(5′), OCH_2CHdns); 3.88 (‘*t*’, OCH$_2$CH_2dns); 3.65, 3.40 (2*m*, 2 H–C(5′)); 3.0 (*t*, 2 OCH$_2$CH_2); 2.85 (*q*, OCH$_2$CH_2); 3.33 (2*s*, Me$_2$N(dns)); 2.5–2.0 (*m*, 4 H–C(3′)). Anal. calc. for $C_{61}H_{61}N_{14}O_{22}PS \cdot 1/4CH_2Cl_2$ (1426.5): C 51.57, H 4.35, N 13.75; found: C 51.25, H 4.44, N 13.58.

9. *3′-Deoxy-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-2′-*O*-acetyl-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**15**). As described in *Exper. 5*, with **12** (800 mg, 0.7 mmol), **7** [28] (1.276 g, 1.26 mmol), 1*H*-tetrazole (245 mg, 3.5 mmol), anh. MeCN/CH_2Cl_2 5:1 (3 ml; 4.5 h), and I_2 soln. Workup with $CHCl_3$ (120 ml) and $Na_2S_2O_3$/NaCl soln. (2 × 60 ml) and purification by FC (silica gel, 19.5 × 3 cm, $CHCl_3$→$CHCl_3$ + 3% MeOH): 1.391 g (96%) of **15**. Amorphous solid. UV (CH_2Cl_2): 273 (sh, 4.94), 267 (4.98), 237 (sh, 4.64). ^{1}H-NMR ((D$_6$)DMSO); 10.61 (*s*, 3 NH); 8.59–8.44, 8.14–7.97, 7.59–7.10 (3*m*, 3 H–C(8), 3 H–C(2), 10 H *o* to NO_2, 10 H *m* to NO_2, 12 H of MeO*Tr*); 6.76 (*d*, 2 H *o* to MeO); 6.26–6.09 (*m*, 3 H–C(1′)); 5.66–5.34 (*m*, 3 H–C(2′)); 4.4–4.05 (2*m*, 3 H–C(4′), 5 OCH_2CH$_2$, 4 H–C(5′)); 3.68 (*s*, MeO); 3.15–2.85 (2*m*, 5 OCH$_2$CH_2, 2 H–C(5′)); 2.65–2.00 (*m*, 6 H–C(3′), Ac). Anal. calc. for $C_{95}H_{90}N_{20}O_{31}P_2 \cdot H_2O$ (2087.8): C 54.65, H 4.34, N 13.42; found: C 54.26, H 4.43, N 12.94.

10. *3′-Deoxy-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)-ethyl]}→5′}-3′-deoxy-*N^6*,2′-*O*-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**16**) [10]. As described in *Exper. 5*, with **13** [21] (647 mg, 0.5 mmol), **7** [28] (912 mg, 0.9 mmol), 1*H*-tetrazole (175 mg, 2.5 mmol), anh. MeCN/CH_2Cl_2 4:1 (2.5 ml; 6 h), more **7** (200 mg, 0.2 mmol; 16 h), and I_2 soln. Workup with $CHCl_3$ (120 ml) and $Na_2S_2O_3$/NaCl soln. (2 × 6 ml) and purification by FC (silica gel, 20 × 3 cm, $CHCl_3$→$CHCl_3$ + 2.5% MeOH→$CHCl_3$ + 3% MeOH): 916 mg (82%) of **16** (physical data: [10]). Amorphous solid. UV (CH_2Cl_2): 273 (sh, 4.95), 267 (4.99), 237 (sh, 4.62). ^{1}H-NMR ($CDCl_3$): 8.69–8.52, 8.23–7.97 (2*m*, 3 H–C(8), 3 H–C(2), 3 NH, 12 H *o* to NO_2); 7.46–7.22 (*m*, 12 H *m* to NO_2, 12 H of MeO*Tr*); 6.79 (*d*, 2 H *o* to MeO); 6.19–5.99 (*m*, 3 H–C(1′)); 5.7–5.3 (*m*, 3 H–C(2′)); 4.58–4.21 (*m*, 3 H–C(4′), 6 OCH_2CH$_2$); 3.77 (*s*, MeO); 3.5–1.6 (*m*, 6 OCH$_2$CH_2, 6 H–C(5′), 6 H–C(3′)).

11. *3′-Deoxy-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)-ethyl]}→5′}-2′-*O*-(2-dansylethoxycarbonyl)-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**17**). As described in *Exper. 5*, with **14** (211 mg, 0.15 mmol), **7** [28] (228 mg, 0.225 mmol), 1*H*-tetrazole (53 mg, 0.75 mmol), anh. MeCN/CH_2Cl_2 3:1 (2 ml; 4.5 h), more **7** (76 mg, 0.075 mmol; 18 h), and I_2 soln. Workup with $CHCl_3$ (50 ml) and $Na_2S_2O_3$/NaCl soln. (2 × 30 ml) and purification by FC (silica gel, 23 × 2 cm, $CHCl_3$→$CHCl_3$ + 2% MeOH→$CHCl_3$ + 2.5% MeOH): 299 mg (85%) of **17**. Amorphous solid. UV (CH_2Cl_2/MeOH): 340 (sh, 3.79), 272 (sh, 4.98), 266 (5.03). ^{1}H-NMR ((D$_6$)DMSO): 10.62–10.59 (*m*, 3 NH); 8.60–8.44 (*m*, 3 H–C(8), 3 H–C(2), H–C(2)(dns)); 8.21–7.96 (*m*, 10 H *o* to NO_2, H–C(4)(dns), H–C(8)(dns)); 7.69–7.10 (*m*, 10 H *m* to NO_2, H–C(3)(dns), H–C(7)(dns), 12 H of MeO*Tr*, H–C(6)(dns)); 6.75 (*d*, 2 H *o* to MeO); 6.26–6.05 (*m*, 3 H–C(1′)); 5.49–5.34 (*m*, 3 H–C(2′)); 4.45–3.80 (*m*, 3 H–C(4′), 5 OCH_2CH$_2$, 4 H–C(5′), OCH_2CH$_2$dns); 3.67 (*s*, MeO); 3.15–2.0 (*m*, 5 OCH$_2$CH_2, 2 H–C(5′), Me$_2$N(dns), 4 H–C(3′)). Anal. calc. for $C_{108}H_{103}N_{21}O_{34}P_2S \cdot H_2O$ (2351.2): C 55.17, H 4.50, N 12.51; found: C 54.86, H 4.43, N 12.33.

12. *3′-Deoxy-*N^6*,5′-*O*-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-2′-*O*-(dansylethoxycarbonyl)-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**18**). As described in *Exper. 5*, with **14** (141 mg, 0.1 mmol), **8** (131 mg, 0.14 mmol), 1*H*-tetrazole (35 mg, 0.5 mmol), anh. MeCN (5 ml; 3 h), more **8** (28 mg, 0.03 mmol; 4 h), and I_2 soln. Workup with $CHCl_3$ (80 ml) and $Na_2S_2O_3$/NaCl soln. (40 ml), FC (silica gel, 11 × 2 cm, $CHCl_3$→$CHCl_3$ + 3% MeOH→$CHCl_3$ + 4% MeOH→$CHCl_3$ + 5% MeOH), and then precipitation from Et_2O (60 ml): 204 mg (91%) of **18**. Yellow powder. UV (CH_2Cl_2/MeOH): 334 (sh, 3.76), 272 (sh, 5.01), 266 (5.06). ^{1}H-NMR ($CDCl_3$): 9.0–7.95 (*m*, 3 NH, 3 H–C(8), 3 H–C(2), H–C(2)(dns), 12 H *o* to NO_2, H–C(4)(dns), H–C(8)(dns)); 7.7–7.10 (*m*, 12 H *m* to NO_2, H–C(3)(dns), H–C(7)(dns), H–C(6)(dns)); 6.2–6.0 (*m*, 3 H–C(1′));

5.7–5.32 (*m*, 3 H–C(2′)); 4.7–3.7 (*m*, 3 H–C(4′), 5 OCH_2CH$_2$, 6 H–C(5′), OCH_2CH_2dns); 3.2–2.9 (*m*, 6 OCH$_2$CH_2, Me$_2$N(dns)); 2.9–2.1 (*m*, 6 H–C(3′)). Anal. calc. for $C_{97}H_{94}N_{22}O_{37}P_2S$ (2254.0): C 51.69, H 4.20, N 13.67; found: C 51.57, H 4.45, N 13.35.

13. *3′-Deoxy-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)-ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**19**). 13.1. To a soln. of **15** (207 mg, 0.1 mmol) in abs. MeOH/CH_2Cl_2 1:1 (4 ml) was added K_2CO_3 (7 mg, 0.05 mmol). The mixture was stirred at r.t. for 3 h, diluted with $CHCl_3$ (100 ml), and washed with phosphate buffer pH 7 (2 × 50 ml), the aq. phase re-extracted with $CHCl_3$, the combined org. layer dried ($MgSO_4$) and evaporated, and the residue purified by FC (silica gel, 16 × 2 cm, $CHCl_3$ → $CHCl_3$ + 1.5% MeOH → $CHCl_3$ + 4% MeOH): 153 mg (75%) of **19**.

13.2. As described in *Exper. 13.1*, with **16** (222 mg, 0.1 mmol), K_2CO_3 (10 mg, 0.07 mmol), and abs. MeOH/CH_2Cl_2 1:1 (4 ml; 2 h). Workup with $CHCl_3$ (100 ml) and 10% citric acid soln. (50 ml) and FC (silica gel, 16 × 2 cm, $CHCl_3$ → $CHCl_3$ + 1.5% MeOH → $CHCl_3$ + 4% MeOH): 140 mg (69%) of **19**.

13.3. First, **17** (140 mg, 60 μmol) was co-evaporated twice with abs. pyridine and then dissolved in abs. pyridine (1.2 ml). After addition of 0.1M DBU in abs. pyridine (1.2 ml), the mixture was kept at r.t. for 3 min. Then AcOH (5 drops) was added, the mixture diluted with $CHCl_3$ (40 ml) and washed with H_2O (2 × 20 ml), the aq. phase re-extracted with $CHCl_3$, the combined org. layer dried ($MgSO_4$), evaporated, and co-evaporated with toluene, and the residue purified by FC (silica gel, 19 × 1 cm, $CHCl_3$ → $CHCl_3$ + 3% MeOH → $CHCl_3$ + 4% MeOH → $CHCl_3$ + 5% MeOH): 106 mg (87%) of **19**. Amorphous solid. UV (CH_2Cl_2): 273 (sh, 4.95), 267 (4.99), 237 (sh, 4.64). ^{1}H-NMR ((D$_6$)DMSO): 10.60 (*s*, 3 NH); 8.60–8.45, 8.12–7.97, 7.59–7.10 (3*m*, 3 H–C(8), 3 H–C(2), 10 H *o* to NO_2, 10 H *m* to NO_2, 12 H of MeO*Tr*); 6.76 (*d*, 2 H *o* to MeO); 6.27–5.94 (*m*, 3 H–C(1′)); 5.82 (*m*, OH–C(2′)); 5.50–5.38 (*m*, 2 H–C(2′)); 4.69 (br., H–C(2′)); 4.5–4.1 (*m*, 3 H–C(4′), 5 OCH_2CH$_2$, 6 H–C(5′)); 3.68 (*s*, 3 H, MeO); 3.15–1.9 (*m*, 5 OCH$_2$CH_2, 6 H–C(3′)). Anal. calc. for $C_{93}H_{88}N_{20}O_{30}P_2 \cdot H_2O$ (2045.8): C 54.60, H 4.43, N 13.69; found: C 54.36, H 4.51, N 13.31.

14. *3′-Deoxy-*N^6*,5′-*O*-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**20**). As described in *Exper. 13.3*, with **18** (100 mg, 0.045 mmol), 0.05M DBU in abs. pyridine (1.8 ml; 3 min), and AcOH (5 drops). Workup with $CHCl_3$ (40 ml) and 10% citric acid soln. (20 ml). Purification by prep. TLC (silica gel, 20 × 40 cm, CH_2Cl_2 + 5% MeOH): 70 mg (80%) of **20**. Amorphous solid. UV (CH_2Cl_2): 272 (sh, 4.97), 267 (5.00). ^{1}H-NMR ($CDCl_3$): 9.3–7.9 (*m*, 3 NH, 3 H–C(8), 3 H–C(2), 12 H *o* to NO_2); 7.4–7.20 (*m*, 12 H *m* to NO_2); 6.2–5.9 (*m*, 3 H–C(1′)); 5.4 (*m*, 2 H–C(2′)); 5.0–4.1 (*m*, H–C(2′), OH–C(2′), 3 H–C(4′), 6 OCH_2CH$_2$, 6 H–C(5′)); 3.2–3.0 (*m*, 6 OCH$_2$CH_2); 2.5–2.1 (*m*, 6 H–C(3′)). Anal. calc. for $C_{82}H_{79}N_{21}O_{33}P_2$ (1948.6): C 50.54, H 4.09, N 15.09; found: C 50.29, H 4.28, N 14.77.

15. *3′-Deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*,2′-O-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**21**). As described in *Exper. 3*, with **16** (1.35 g, 0.609 mmol) and CH_2Cl_2/MeOH 4:1 (12 ml) containing 2% of TsOH·H_2O (50 min). Workup with $CHCl_3$ (100 ml) and sat. $NaHCO_3$ soln. (2 × 40 ml). FC (silica gel, 10 × 3.5 cm, $CHCl_3$ → $CHCl_3$ + 6% MeOH → CH_2Cl_3 + 7% MeOH): 1.093 g (92%) of **14**. Amorphous solid. UV (CH_2Cl_2): 272 (sh, 4.98), 267 (5.01). ^{1}H-NMR ((D$_6$)DMSO): 10.60 (*m*, 3 NH); 8.61–8.46 (*m*, 3 H–C(8), 3 H–C(2)); 8.15–7.99 (*m*, 12 H *o* to NO_2); 7.61–7.35 (*m*, 12 H *m* to NO_2); 6.20–6.12 (*m*, 3 H–C(1′)); 5.62, 5.38, 5.37 (3*m*, 3 H–C(2′)); 5.12 (*t*, OH–C(5′)); 4.5–4.0 (*m*, 3 H–C(4′), 6 OCH_2CH$_2$, 6 H–C(5′)); 3.6, 3.4, 3.2, 2.9, 2.7–2.0 (5*m*, 6 OCH$_2$CH_2, 6 H–C(3′)). Anal. calc. for $C_{82}H_{79}N_{21}O_{33}P_2$ (1948.6): C 50.54, H 4.09, N 15.09; found: C 50.04, H 4.22, N 14.65.

16. *3′-Deoxy-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)-ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]-2′-*O*-(2-*ambo*-α-tocopheryloxycarbonyl)adenosine* (**22**). The 2-*ambo*-α-tocopheryl chloroformate was synthesized as described in [29]. To a soln. of **19** (101 mg, 50 μmol) in abs. CH_2Cl_2 (2 ml) were added some pearls of molecular sieve (4 Å), 1-methyl-1*H*-imidazole (100 mg, 1.2 mmol) and 2-*ambo*-α-tocopheryl chloroformate (99 mg, 0.2 mmol). The mixture was kept at 4° for 20 h, then further 2-*ambo*-α-tocopheryl chloroformate (99 mg, 0.2 mmol) and 1-methyl-1*H*-imidazole (100 mg, 1.2 mmol) were added, and the mixture was kept at 4° for 20 h. Purification was achieved first by FC (silica gel, 17,5 × 1 cm, $CHCl_3$ → $CHCl_3$ + 4% MeOH), then by prep. TLC (silica gel, 2 plates 20 × 40 cm, $CHCl_3$ + 10% MeOH): 94 mg (76%) of **22**. Amorphous solid. UV (CH_2Cl_2): 273 (sh, 4.91), 267 (4.95), 238 (sh, 4.58). ^{1}H-NMR ((D$_6$)DMSO): 10.59 (*m*, 3 NH); 8.59–8.44 (*m*, 3 H–C(8), 3 H–C(2)); 8.14–7.97 (*m*, 10 H *o* to NO_2); 7.60–7.10 (*m*, 10 H *m* to NO_2,

12 H of MeO*Tr*); 6.75 (*d*, 2 H *o* to MeO); 6.32–6.10 (*m*, 3 H–C(1′)); 5.80, 5.49, 5.35 (3*m*, 3 H–C(2′)); 4.6–4.1 (*m*, 3 H–C(4′), 5 OCH_2CH$_2$, 4 H–C(5′)); 3.67 (*s*, MeO); 3.2–2.8 (*m*, 2 H–C(5′), 5 OCH$_2$CH_2); 2.8–0.75 (*m*, 6 H–C(3′), 49 H(tocopheryl)). Anal. calc. for $C_{123}H_{136}N_{20}O_{33}P_2$ (2484.5): C 59.46, H 5.52, N 11.28; found: C 59.31, H 5.67, N 10.82.

17. *3′-Deoxy-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)-ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]-2′-*O*-{[2-(2-ambo-α-tocopheryloxycarbonyl)-ethyl]carbonyl}adenosine* (**23**). A mixture of **19** (100 mg, 0.049 mmol), succinic anhydride (6 mg, 0.059 mmol), and DMAP (8 mg, 0.064 mmol) in abs. CH_2Cl_2 (1.5 ml) was kept at r.t. for 3 h. Then *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (EDC; 23 mg, 0.123 mmol) and 2-*ambo*-α-tocopherol (65 mg, 0.147 mmol) were added. The mixture was kept at r.t. in the dark for 18 h, then diluted with $CHCl_3$ (60 ml), and washed with sat. $NaHCO_3$ (2 × 30 ml), the aq. phase re-extracted with $CHCl_3$, the combined org. layer dried ($MgSO_4$) and evaporated, and the crude product purified by FC (silica gel, 14 × 1 cm, $CHCl_3 \rightarrow CHCl_3$ + 4% MeOH): 100 mg (80%) of **23**. Amorphous solid. UV (CH_2Cl_2): 275 (sh, 4.91), 267 (4.97), 237 (sh, 4.61). ^{1}H-NMR ((D$_6$)DMSO): 10.60 (*m*, 3 NH); 8.57–8.44, 8.12–7.96, 7.58–7.09 (3*m*, 3 H–C(8), 3 H–C(2), 10 H *o* to NO_2, 10 H *m* to NO_2, 12 H of MeO*Tr*); 6.75 (*d*, 2 H *o* to MeO); 6.26–6.11 (*m*, 3 H–C(1′)); 5.75, 5.5, 5.35 (3*m*, 3 H–C(2′)); 4.5–4.15 (2*m*, 3 H–C(4′), 5 OCH_2CH$_2$, 4 H–C(5′)); 3.67 (*s*, MeO); 3.13–0.77 (*m*, 2 H–C(5′), 5 OCH$_2$CH_2, C(O)CH_2CH_2C(O), 6 H–C(3′), 49 H(tocopheryl)). Anal. calc. for $C_{126}H_{140}N_{20}O_{34}P_2$ (2540.6): C 59.57, H 5.55, N 11.03; found: C 59.24, H 5.55, N 10.95.

18. *3′-Deoxy-*N^6*,5′-*O*-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-2′-*O*-{[2-(ergocalciferyloxycarbonyl)ethyl]carbonyl}-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**24**). As described in *Exper. 17*, with **20** (146 mg, 0.075 mmol) succinic anhydride (12 mg, 0.12 mmol), and DMAP (16 mg, 0.135 mmol) in abs. CH_2Cl_2 (2 ml; 20 h). Then EDC (23 mg, 0.12 mmol) and vitamin D_2 (48 mg, 0.12 mmol) in abs. CH_2Cl_2 (2 ml; 3.5 h, N_2, darkness), more EDC (12 mg, 0.6 mmol) and vitamin D_2 (24 mg, 0.06 mmol; 18 h). Workup with CH_2Cl_2 (80 ml) and sat. NaCl soln. (2 × 30 ml). FC (silica gel, 12 × 2 cm, $CHCl_3 \rightarrow CHCl_3$ + 2% MeOH → $CHCl_3$ + 3.5% MeOH → $CHCl_3$ + 5% MeOH): 134 mg (74%) of **24**. Amorphous solid. UV (CH_2Cl_2): 272 (sh, 5.03), 267 (5.06). ^{1}H-NMR ($CDCl_3$): 8.7–8.0 (*m*, 3 NH, 3 H–C(8), 3 H–C(2), 12 H *o* to NO_2); 7.45–7.0 (*m*, 12 H *m* to NO_2); 6.2–4.85 (*m*, 3 H–C(1′), H–C(6)(VitD$_2$), H–C(7)(VitD$_2$), 3H–C(2′), H–C(22)(VitD$_2$), H–C(23)(VitD$_2$), 2 H–C(19)(VitD$_2$), H–C(3)(VitD$_2$)); 4.6–4.05 (*m*, 3 H–C(4′), 6 OCH_2CH$_2$, 6 H–C(5′)); 3.02–0.5 (*m*, 6 OCH$_2$CH_2, C(O)CH_2CH_2C(O), 6 H–C(3′), 36 H(VitD$_2$)). Anal. calc. for $C_{114}H_{125}N_{21}O_{36}P_2$ (2427.3): C 56.41, H 5.19, N 12.12; found: C 55.86, H 5.21, N 11.74.

19. *3′-Deoxy-*N^6*,5′-*O*-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]-2′-*O*-{[2-(retinoyloxycarbonyl)ethyl]carbonyl}adenosine* (**25**). As described in *Exper. 17*, with **20** (146 mg, 0.075 mmol) succinic anhydride (12 mg, 0.12 mmol), and DMAP (16 mg, 0.135 mmol) in abs. CH_2Cl_2 (2 ml; 20 h). Then EDC (26 mg, 0.135 mmol) and vitamin A (39 mg, 0.135 mmol) in abs. CH_2Cl_2 (2 ml; 4 h, N_2, darkness), more EDC (12 mg, 0.06 mmol) and vitamin A (19 mg, 0.06 mmol; 2 h). Workup with CH_2Cl_2 (80 ml) and sat. NaCl soln. (2 × 30 ml). FC (silica gel, 12 × 2 cm, $CHCl_3 \rightarrow CHCl_3$ + 2% MeOH → $CHCl_3$ + 3.5% MeOH → $CHCl_3$ + 5% MeOH): 140 mg (81%) of **24**. Amorphous solid. UV (CH_2Cl_2): 330 (4.67), 272 (sh, 4.99), 267 (5.02). ^{1}H-NMR ($CDCl_3$): 8.65–7.9 (*m*, 3 H–C(8), 3 H–C(2), 3 NH, 12 H *o* to NO_2); 7.45–7.24 (*m*, 12 H *m* to NO_2); 6.6, 6.25–6.0, 5.8–5.25 (3*m*, 3 H–C(1′), 5 CH=C(retinyl), 3 H–C(2′), H–C(14)(retinyl)); 4.75 (*d*, 2 H–C(15)); 4.7–4.1 (*m*, 3 H–C(4′), 6 OCH_2CH$_2$, 6 H–C(5′)); 3.2–3.0 (*m*, 6 OCH$_2$CH_2); 2.7–1.0 (*m*, C(O)CH_2CH_2C(O), 6 H–C(3′), 2 H–C(4)(retinyl), 2 H–C(2)(retinyl), 2 H–C(3)(retinyl), Me–C(9)(retinyl), Me–C(13)(retinyl), Me–C(5)(retinyl), 2 Me–C(1)(retinyl)). Anal. calc. for $C_{106}H_{111}N_{21}O_{36}P_2$ (2317.1): C 54.95, H 4.83, N 12.69; found: C 54.50, H 4.96, N 12.14.

20. *3′-Deoxy-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)-ethyl]}→5′}-3′-deoxy-2′-*O*-{[2-(2,3-di-*O*-palmitoylglycer-1-yloxycarbonyl)ethyl]carbonyl}-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**26**). As described in *Exper. 17*, with **19** (152 mg, 0.075 mmol), succinic anhydride (12 mg, 0.12 mmol), and DMAP (16 mg, 0.135 mmol) in abs. CH_2Cl_2 (3 ml; 18 h). Then EDC (29 mg, 0.15 mmol) and 1,2-di-*O*-palmitoylglycerol [22] [23] (85 mg, 0.15 mmol) in abs. CH_2Cl_2 (2 ml; 6 h), more EDC (15 mg, 0.075 mmol) and 1,2-di-*O*-palmitoylglycerol (42 mg, 0.075 mmol; 15 h). Workup with CHCl (80 ml) and sat. NaCl soln. (2 × 30 ml). FC (silica gel, 10 × 2 cm, $CH_2Cl_2 \rightarrow CH_2Cl_2$ + 1% MeOH → CH_2Cl_2 + 2.5%

MeOH → CH_2Cl_2 + 3% MeOH): 160 mg (80%) of **26**. Amorphous solid. UV (CH_2Cl_2): 272 (sh, 4.93), 267 (4.97), 239 (sh, 4.12). ^{1}H-NMR ($CDCl_3$): 8.7–7.9 (*m*, 3 H–C(8), 3 H–C(2), 10 H *o* to NO_2); 7.4–7.1 (*m*, 10 H *m* to NO_2, 12 H of MeO*Tr*); 6.75 (*d*, *o* to MeO); 6.2–6.0 (*m*, 3 H–C(1′)); 5.8–5.15 (*m*, 3 H–C(2′), H–C(2)(Glyc)); 4.6–4.1 (*m*, 3 H–C(4′), 5 OCH_2CH_2, 6 H–C(5′), 2 H–C(1)(Glyc), 2 H–C(3)(Glyc)); 3.72 (*s*, MeO); 3.45–2.1 (*m*, 5 OCH$_2$CH_2, C(O)CH_2CH_2C(O), 6 H–C(3′), 2 CH$_2$(α)(Palm)); 1.65 (*m*, 2 CH$_2$(β)(Palm)); 1.22 (*m*, 48 H(Palm)); 0.85 (*t*, 2 Me(Palm)). Anal. calc. for $C_{132}H_{158}N_{20}O_{37}P_2$ (2678.8): C 59.19, H 5.95, N 10.46, found: C 58.96, H 6.01, N 10.37.

21. *3′-Deoxy-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)-ethyl]}→5′}-3′-deoxy-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]-2′-*O*-{[2-(2,3-di-*O*-hexadecylglycer-1-yloxycarbonyl)ethyl]carbonyl}adenosine* (**27**). As described in *Exper. 17*, with **19** (152 mg, 0.075 mmol), succinic anhydride (12 mg, 0.12 mmol), and DMAP (16 mg, 0.135 mmol) in abs. CH_2Cl_2 (3 ml; 18 h). Then EDC (29 mg, 0.15 mmol) and 1,2-di-*O*-hexadecylglycerol [23] [24] (81 mg, 0.15 mmol) in abs. CH_2Cl_2 (2 ml; 6 h), more EDC (15 mg, 0.075 mmol) and 1,2-di-*O*-hexadecylglycerol (40 mg, 0.075 mmol; 15 h). Workup with $CHCl_3$ (80 ml) and sat. NaCl soln. (2 × 30 ml). FC (silica gel, 10.5 × 2 cm, CH_2Cl_2 → CH_2Cl_2 + 1% MeOH → CH_2Cl_2 + 2.5% MeOH): 129 mg (65%) of **27**. Amorphous solid. UV (CH_2Cl_2): 272 (sh, 4.93), 267 (4.96), 239 (sh, 4.62). ^{1}H-NMR ($CDCl_3$): 8.65–8.4, 8.2–7.9 (2*m*, 3 H–C(8), 3 H–C(2), 3 NH, 10 H *o* to NO_2); 7.4–7.1 (*m*, 10 H *m* to NO_2, 12 H of MeO*Tr*); 6.75 (*d*, 2 H *o* to MeO); 6.15–5.95 (*m*, 3 H–C(1′)); 5.75–5.2 (*m*, 3 H–C(2′)); 4.6–4.1 (*m*, 3 H–C(4′), 5 OCH_2CH$_2$, 6 H–C(5′), H–C(2)(Glyc)); 3.72 (*s*, MeO); 3.6–2.9 (*m*, 5 OCH$_2$CH_2, 2 CH$_2$(EL), 2 H–C(1)(Glyc), 2 H–C(3)(Glyc)); 2.7–2.1 (*m*, C(O)CH_2CH_2C(O), 6 H–C(3′)); 1.55, 1.22 (*m*, 56 H(EL)); 0.85 (*t*, 2 Me(EL)). Anal. calc. for $C_{132}H_{162}N_{20}O_{35}P_2$ (2650.8): C 59.81, H 6.16, N 10.57; found: C 59.33, H 6.24, N 10.59.

22. *3′-Deoxyadenylyl-(2′→5′)-3′-deoxyadenylyl-(2′→5′)-3′-deoxy-2′-*O*-(2-*ambo*-α-tocopheryloxycarbonyl)adenosine* (**28**). A mixture of dry **22** (33 mg, 13 μmol) and DBU (50 mg, 332 μmol) in dry pyridine (1 ml) was kept at r.t. in the dark for 2 d. Then AcOH (60 mg, 1 mmol) was added and the mixture evaporated, then diluted with $CHCl_3$ (40 ml), and washed with H_2O (10 ml). The aq. phase was re-extracted with $CHCl_3$ and the combined org. layer dried ($MgSO_4$) and evaporated. To the residue was added 80% AcOH (5 ml). The mixture was kept at r.t. for 19 h and then lyophilized. The residue was washed and centrifugated several times with H_2O, MeCN, and Et_2O: 15 mg of **28** (321 *OD*). Colourless powder. HPLC (5% MeCN (0–2 min), 5–50% MeCN (2–20 min), 50–100% MeCN (20–40 min), and 100% MeCN (40–42 min) in 0.1M (Et_3NH)OAc buffer (pH 7)): t_R 35.7 min.

23. *3′-Deoxyadenylyl-(2′→5′)-3′-deoxyadenylyl-(2′→5′)-3′-deoxy-2′-*O*-{[2-(2-*ambo*-α-tocopheryloxycarbonyl)ethyl]carbonyl}adenosine* (**29**). As described in *Exper. 22*, with **23** (25 mg, 10 μmol) and DBU (38 mg, 250 μmol) in abs. pyridine (1 ml; 2 d), then AcOH (15 mg, 250 μmol). Workup with $CHCl_3$ (30 ml) and H_2O (10 ml). Then 80% AcOH (3 ml; 18 h), workup with H_2O and MeCN: 12 mg of **29** (250 *OD*). Colourless powder. HPLC (gradient as in *Exper. 22*): t_R 37.07 min.

24. *3′-Deoxyadenylyl-(2′→5′)-3′-deoxyadenylyl-(2′→5′)-3′-deoxy-2′-*O*-{[2-(ergocalciferyloxycarbonyl)-ethyl]carbonyl}adenosine* (**30**). A mixture of dry **24** (31 mg, 12.8 μmol) in 0.5M DBU in dry pyridine (380 μl) was kept at r.t. under N_2 in the dark for 2 d. Then 2M AcOH in abs. MeCN (100 μl) was added, the mixture evaporated and co-evaporated with dry toluene, and the residue treated with abs. MeCN, washed, and centrifugated several times with abs. MeCN and Et_2O: 16 mg of **30** which was contaminated with trimeric cordycepin. Colourless powder. HPLC (30% 0.1M (Et_3NH)OAc buffer (pH 7), 5% THF, 65% MeCN): t_R 5.26 min. Purification by prep. HPLC (*Lichrospher 100 RP18*, 10 μm, 25 × 2 cm; 60% MeCN (0–2 min) and 60–100% MeCN (2–32 min) in 0.1M (Et_3NH)OAc buffer (pH 7), 7 ml/min; t_R 28 min): 7 mg of **30** (237 *OD*) which showed a shoulder of a new by product in the chromatogram.

25. *3′-Deoxyadenylyl-(2′→5′)-3′-deoxyadenylyl-(2′→5′)-3′-deoxy-2′-*O*-{[2-(retinyloxycarbonyl)ethyl]-carbonyl}adenosine* (**31**). As described in *Exper. 24*, with **25** (52 mg, 22 μmol) and 0.5M DBU in dry pyridine (520 μl; 2 d, N_2, darkness), then 2M AcOH in abs. MeCN (140 μl). Workup with abs. MeCN: 27 mg of **31**, which was instable on aq. buffer (pH 7) treatment and decomposed into its cordycepin-trimer succinyl derivative within 45 min. Yellow powder. HPLC (30% 0.1M (Et_3NH)OAc buffer (pH 7), 5% THF, 65% MeCN): t_R 3.80 min.

26. *3′-Deoxyadenylyl-(2′→5′)-3′-deoxyadenylyl-(2′→5′)-3′-deoxy-2′-*O*-{[2-(2,3-di-*O*-palmitoylglycer-1-yloxycarbonyl)ethyl]carbonyl}adenosine* (**32**). As described in *Exper. 22*, with **26** (40 mg, 15 μmol) and 0.5M DBU in abs. pyridine (300 μl; 18 h), more abs. pyridine (300 μl; 18 h), then 2M AcOH in abs. MeCN (80 μl). Workup with $CHCl_3$ (40 ml) and H_2O (15 ml). Then 80% AcOH (7.5 ml; 16 h), workup with H_2O and MeCN: 14 mg of **32** (333 *OD*). Colourless powder. HPLC (15% 0.1M (Et_3NH)OAc buffer (pH 7), 30% THF, 55% MeCN): t_R 3.15 min.

27. *3′-Deoxyadenylyl-(2′→5′)-3′-deoxyadenylyl-(2′→5′)-3′-deoxy-2′-O-{[2-(2,3-di-O-hexadecylglycer-1-yloxycarbonyl)ethyl]carbonyl}adenosine* (**33**). As described in *Exper. 22*, with **26** (40 mg, 15 μmol) and 0.5M DBU in abs. pyridine (300 μl; 18 h), more abs. pyridine (300 μl; 20 h), then 2M AcOH in abs. MeCN (80 μl). Workup with $CHCl_3$ (40 ml) and H_2O (15 ml). Then 80% AcOH (7.5 ml; 16 h), workup with H_2O and MeCN: 19 mg of **33** (469 *OD*). Colourless powder. HPLC (15% 0.1M $(Et_3NH)OAc$ buffer (pH 7), 30% THF, 55% MeCN). t_R 4.58 min.

28. *3′-Deoxy-N⁶-[2-(4-nitrophenyl)ethoxycarbonyl]-5′-O-{[2-(2-ambo-α-tocopheryloxycarbonyl)ethyl]carbonyl}adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-N⁶-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-N⁶,2′-O-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**34**). As described in *Exper. 17*, with **21** (175 mg, 0.09 mmol), succinic anhydride (11 mg, 0.108 mmol), and DMAP (14 mg, 0.117 mmol) in abs. CH_2Cl_2 (4 ml; 20 h). Then EDC (45 mg, 0.234 mmol) and vitamin E (101 mg, 0.234 mmol; 7 h, darkness), more EDC (17 mg, 0.09 mmol), vitamin E (39 mg, 0.09 mmol), and DMAP (11 mg, 0.09 mmol; 18 h). Workup with $CHCl_3$ (70 ml) and 10% citric acid soln. (40 ml). FC (silica gel, 13 × 2 cm, $CHCl_3 \rightarrow CHCl_3$ + 5% MeOH → $CHCl_3$ + 6% MeOH): 183 mg (82%) of **34**. Amorphous solid. UV (CH_2Cl_2): 272 (sh, 4.97), 267 (5.00). ^{1}H-NMR ($CDCl_3$): 9.2–8.4, 8.15–7.9 (2*m*, 3 H–C(8), 3 H–C(2), 3 NH, 12 H *o* to NO_2); 7.4–7.15 (*m*, 12 H *m* to NO_2); 6.1–5.9 (*m*, 3 H–C(1′)); 5.6–5.2 (*m*, 3 H–C(2′)); 4.6–4.0 (*m*, 3 H–C(4′), 6 OCH_2CH_2, 6 H–C(5′)); 3.1–0.7 (*m*, 6 OCH_2CH_2, C(O)CH_2CH_2C(O), 6 H–C(3′), 49 H(tocopheryl)). Anal. calc. for $C_{115}H_{131}N_{21}O_{37}P_2$ (2461.4): C 56.12, H 5.36, N 11.95; found: C 56.15, H 5.50, N 11.49.

29. *3′-Deoxy-5′-O-{[2-(ergocalciferyloxycarbonyl)ethyl]carbonyl}-N⁶-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-N⁶-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-N⁶,2′-O-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**35**). As described in *Exper. 17*, with **21** (175 mg, 0.09 mmol), succinic anhydride (11 mg, 0.108 mmol), and DMAP (14 mg, 0.117 mmol) in abs. CH_2Cl_2 (4 ml; 4.5 h), more succinic anhydride (11 mg, 0.108 mmol) and DMAP (14 mg, 0.117 mmol; 17 h). Then EDC (45 mg, 0.234 mmol) and vitamin D_2 (93 mg, 0.234 mmol; 4 h, N_2, darkness), more EDC (10 mg, 0.05 mmol), DMAP (6 mg; 0.05 mmol), and vitamin D_2 (20 mg, 0.05 mol; 18 h). Workup with $CHCl_3$ (80 ml) and sat. $NaHCO_3$ soln. (40 ml). FC (silica gel, 13 × 2 cm, $CHCl_3 \rightarrow CHCl_3$ + 3% MeOH → $CHCl_3$ + 4% MeOH): 147 mg (67%) of **35**. Amorphous solid. UV (CH_2Cl_2): 267 (5.06). ^{1}H-NMR ($CDCl_3$): 9.2–7.9 (*m*, 3 NH, 3 H–C(8), 3 H–C(2), 12 H *o* to NO_2); 7.5–7.1 (*m*, 12 H *m* to NO_2); 6.2–4.7 (*m*, 3 H–C(1′), H–C(6)(VitD_2), H–C(7)(VitD_2), 3 H–C(2′), H–C(22)(VitD_2), H–C(23)(VitD_2), 2 H–C(19)(VitD_2), H–C(3)(VitD_2)); 4.65–4.1 (*m*, 3 H–C(4′), 6 OCH_2CH_2, 6 H–C(5′)); 3.2–0.5 (*m*, 6 OCH_2CH_2, C(O)CH_2CH_2C(O), 6 H–C(3′), 36 H(VitD_2)). Anal. calc. for $C_{114}H_{125}N_{21}O_{36}P_2$ (2427.3): C 56.41, H 5.19, N 12.12; found: C 56.43, H 5.41, N 11.23.

30. *3′-Deoxy-N⁶-[2-(4-nitrophenyl)ethoxycarbonyl]-5′-O-{[2-(retinyloxycarbonyl)ethyl]carbonyl}adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-N⁶-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-N⁶,2′-O-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**36**). As described in *Exper. 17*, with **21** (146 mg, 0.075 mmol), succinic anhydride (12 mg, 0.12 mmol), and DMAP (16 mg, 0.135 mmol) in abs. CH_2Cl_2 (2 ml; 20 h). Then EDC (26 mg, 0.135 mmol) and vitamin A (39 mg, 0.135 mmol) in abs. CH_2Cl_2 (2 ml; 4 h, N_2, darkness), more EDC (12 mg, 0.06 mmol) and vitamin A (19 mg; 0.06 mmol; 2 h). Workup with CH_2Cl_2 (80 ml) and sat. NaCl soln. (2 × 30 ml). FC (silica gel, 12 × 2 cm, $CHCl_3 \rightarrow CHCl_3$ + 2% MeOH → $CHCl_3$ + 3.5% MeOH → $CHCl_3$ + 5% MeOH): 142 mg (81%) of **36**. Amorphous solid. UV (CH_2Cl_2): 330 (4.68), 272 (sh, 4.99), 267 (5.02). ^{1}H-NMR ($CDCl_3$): 8.7–7.95 (*m*, 3 H–C(8), 3 H–C(2), 3 NH, 12 H *o* to NO_2); 7.45–7.2 (*m*, 12 H *m* to NO_2); 6.65, 6.25–5.95, 5.7–5.3 (3*m*, 3 H–C(1′), 5 CH=C(retinyl), 3 H–C(2′), H–C(14)(retinyl)); 4.75 (*d*, 2 H–C(15)); 4.7–4.0 (*m*, 3 H–C(4′), 6 OCH_2CH_2, 6 H–C(5′)); 3.2–3.0 (*m*, 6 OCH_2CH_2); 2.8–1.0 (*m*, C(O)CH_2CH_2C(O), 6 H–C(3′), 2 H–C(4)(retinyl), 2 H–C(2)(retinyl), 2 H–C(3)(retinyl), Me–C(9)(retinyl), Me–C(13)(retinyl), Me–C(5)(retinyl)); 1.00 (*s*, 2 Me–C(1)(retinyl)). Anal. calc. for $C_{106}H_{111}N_{21}O_{36}P_2$ (2317.1): C 54.95, H 4.83, N 12.69; found: C 54.74, H 5.03, N 12.16.

31. *3′-Deoxy-5′-O-{[2-(2,3-di-O-palmitoylglycer-1-yloxycarbonyl)ethyl]carbonyl}-N⁶-[2-(4-nitrophenyl)-ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-N⁶-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-N⁶,2′-O-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**37**). As described in *Exper. 17*, with **21** (117 mg, 0.06 mmol), succinic anhydride (7 mg, 0.072 mmol), and DMAP (10 mg, 0.078 mmol) in abs. CH_2Cl_2 (2 ml; 15 h), more succinic anhydride (7 mg, 0.072 mmol) and DMAP (10 mg, 0.078 mmol; 4 h). Then EDC (30 mg, 0.156 mmol) and 1,2-di-*O*-palmitoylglycerol [22] [23] (89 mg, 0.15 mmol) in abs. CH_2Cl_2 (2 ml; 6 h), more EDC (30 mg, 0.156 mmol), 1,2-di-*O*-palmitoylglycerol (89 mg, 0.15 mmol; 15 h), and DMAP (19 mg; 0.156 mmol; 15 h). Purification by FC (silica gel, 12 × 1 cm, $CH_2Cl_2 \rightarrow CH_2Cl_2$ + 2% MeOH → CH_2Cl_2 + 5% MeOH), the prep. TLC (silica gel, 40 × 20 cm, CH_2Cl_2 + 5%

MeOH): 107 mg (69%) of **37**. Amorphous solid. UV (CH_2Cl_2): 272 (sh, 4.97), 267 (5.00). ^{1}H-NMR ($CDCl_3$): 8.65–8.50, 8.25–7.95 (2*m*, 3 H–C(8), 3 H–C(2), 12 H *o* to NO_2); 7.45–7.2 (*m*, 12 H *m* to NO_2); 6.2–6.0 (*m*, 3 H–C(1′)); 5.7–5.2 (*m*, 3 H–C(2′), H–C(2)(Glyc)); 4.6–4.0 (*m*, 3 H–C(4′), 6 OCH_2CH_2), 6 H–C(5′), 2 H–C(1)(Glyc), 2 H–C(3)(Glyc)); 3.25-3.0 (*m*, 6 OCH_2CH_2); 2.8–2.1 (2*m*, $C(O)CH_2CH_2C(O)$, 6 H–C(3′), 2 $CH_2(\alpha)$(Palm)); 1.7–1.5 (*m*, 2 $CH_2(\beta)$(Palm)); 1.4–1.2 (*m*, 48 H(Palm)); 0.85 (*t*, 2 Me(Palm)). Anal. calc. for $C_{121}H_{149}N_{21}O_{40}P_2$ (2599.6): C 55.91, H 5.78, N 11.31; found: C 55.42, H 5.74, N 11.19.

32. *3′-Deoxy-5′-O-{[2-(2,3-di-O-hexadecylglycer-1-yloxycarbonyl)ethyl]carbonyl}-N^6-[2-(4-nitrophenyl)-ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{O^P-[2-(4-nitrophenyl)ethyl]}→5′}-3′-deoxy-N^6,2′-O-bis[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**38**). As described in *Exper. 17*, with **21** (117 mg, 0.06 mmol), succinic anhydride (7 mg, 0.07 mmol), and DMAP (10 mg, 0.078 mmol) in abs. CH_2Cl_2 (2 ml; 15 h), more succinic anhydride (7 mg, 0.07 mmol) and DMAP (10 mg, 0.078 mmol; 4 h). Then EDC (30 mg, 0.156 mmol) and 1,2-di-*O*-hexadecylglycerol (85 mg, 0.15 mmol) in abs. CH_2Cl_2 (2 ml; 6 h), more EDC (30 mg, 0.156 mmol), and 1,2-di-*O*-hexadecylglycerol (85 mg, 0.15 mmol) and DMAP (19 mg, 0.156 mmol; 15 h). Purification with FC (silica gel, 11.5 × 1 cm, $CH_2Cl_2 \rightarrow CH_2Cl_2$ + 2% MeOH → CH_2Cl_2 + 5% MeOH), then prep. TLC (silica gel, 20 × 40 cm, CH_2Cl_2 + 5% MeOH): 107 mg (69%) of **38**. Amorphous solid. UV (CH_2Cl_2): 272 (sh, 4.98), 267 (5.01). ^{1}H-NMR ($CDCl_3$): 8.75–7.8 (*m*, 3 H–C(8), 3 H–C(2), 3 NH, 12 H *o* to NO_2); 7.45–7.26 (*m*, 12 H *m* to NO_2); 6.2–5.95 (*m*, 3 H–C(1′)); 5.7–5.2 (*m*, 3 H–C(2′)); 4.7–4.0 (*m*, 3 H–C(4′), 6 OCH_2CH_2, 6 H–C(5′), H–C(2)(Glyc)); 3.7–2.1 (*m*, 6 OCH_2CH_2, 2 CH_2(EL), 2 H–C(1)(Glyc), 2 H–C(3)(Glyc), $C(O)CH_2CH_2C(O)$, 6 H–C(3′)); 1.65–0.85 (*m*, 62 H(EL)).

33. *3′-Deoxy-5′-O-{[2-(2-*ambo-*α-tocopheryloxycarbonyl)ethyl]carbonyl}adenylyl-(2′→5′)-3′-deoxyadenylyl-(2′→5′)-3′-deoxyadenosine* (**39**). A mixture of dry **34** (49 mg, 20 μmol) and DBU (37 mg, 240 μmol) in dry pyridine (1 ml) was kept at r.t. in the dark for 2 d. Then AcOH (40 mg, 0.67 mmol) was added and the mixture evaporated and co-evaporated with abs. toluene. The residue was treated with abs. MeCN to give a colourless powder and washed and centrifugated several times with 80% AcOH, H_2O, MeCN, and Et_2O: 27 mg of **39** (543 *OD*). Colourless powder. HPLC (30% 0.1M $(Et_3NH)OAc$ buffer (pH 7), 5% THF, 65% MeCN): t_R 8.91 min.

34. *3′-Deoxy-5′-O-{[2-(ergocalciferyloxycarbonyl)ethyl]carbonyl}adenylyl-(2′→5′)-3′-deoxyadenylyl-(2′→5′)-3′-deoxyadenosine* (**40**). As described in *Exper. 24*, with **35** (49 mg, 20 μmol) and 0.5M DBU in dry pyridine (480 μl; 2 d, N_2, darkness), then 2M AcOH in abs. MeCN (130 μl). Workup with abs. MeCN: 25 mg of **31** (564 *OD*). Colourless powder. HPLC (30% 0.1M $(Et_3NH)OAc$ buffer (pH 7), 5% THF, 65% MeCN): t_R 5.39 min.

35. *3′-Deoxy-5′-O-{[2-(retinyloxycarbonyl)ethyl]carbonyl}adenylyl-(2′→5′)-3′-deoxyadenylyl-(2′→5′)-3′-deoxyadenosine* (**41**). As described in *Exper. 24*, with **36** (40 mg, 17 μmol) and 0.5M DBU in dry pyridine (400 μl; 2 d, N_2, darkness), then 2M AcOH in abs. MeCN (110 μl). Workup with abs. MeCN: 20 mg of **41** which was unstable in aq. buffer (pH 7) and decomposed into its cordycepin-trimer succinyl derivative within 55 min. Yellow powder. HPLC (45% 0.1M $(Et_3NH)OAc$ buffer (pH 7), 5% THF, 50% MeCN): t_R 3.78 min.

36. *3′-Deoxy-5′-O-{[2-(2,3-di-O-palmitoylglycer-1-yloxycarbonyl)ethyl]carbonyl}adenylyl-(2′→5′)-3′-deoxyadenylyl-(2′→5′)-3′-deoxyadenosine* (**42**). As described in *Exper. 33*, with **37** (39 mg, 15 μmol) and 0.5M DBU in dry MeCN (300 μl) and abs. pyridine (200 μl; 2 d), then 2M AcOH in abs. MeCN (80 μl). Workup with 80% AcOH, H_2O, MeCN, and Et_2O: 13 mg of **42** (317 *OD*). Colourless powder. HPLC (15% 0.1M $(Et_3NH)OAc$ buffer (pH 7), 20% THF, 65% MeCN): t_R 5.06 min.

37. *3′-Deoxy-5′-O-{[2-(2,3-di-O-hexadecylglycer-1-yloxycarbonyl)ethyl]carbonyl}adenylyl-(2′→5′)-3′-deoxyadenylyl-(2′→5′)-3′-deoxyadenosine* (**43**). As described in *Exper. 33*, with **38** (39 mg, 15 μmol) and 0.5M DBU in dry MeCN (300 μl) and abs. pyridine (200 μl; 2 d), then 2M AcOH in abs. MeCN (80 μl). Workup with 80% AcOH, H_2O, MeCN, and Et_2O: 13 mg of **43** (322 *OD*). Colourless powder. HPLC (15% 0.1M $(Et_3NH)OAc$ buffer (pH 7), 20% THF, 65% MeCN): t_R 8.58 min.

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