Nucleotides

Part LIX[1])

Synthesis, Characterization, and Biological Activities of New Potential Antiviral Agents: (2′–5′)Adenylate Trimer Analogs Containing 3′-Deoxy-3′-(hexadecanoylamino)adenosine at the 2′-Terminus

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Based upon 3′-amino-3′-deoxyadenosine (**15**), its protected 3′-hexadecanoylamino derivative **22** was chosen as starting material for the synthesis of a series of new modified 2′–5′-adenylate trimers **33**–**36** as potential antiviral agents. All (2′–5′)A trimer analogs **33**–**36** inhibit HIV-1 replication as measured by the inhibition of syncytia formation and inhibition of HIV-1 reverse transcriptase activity. Compound **34** inhibits HIV-1 reverse transcription by 100% and subsequently inhibits expression of HIV-1 p24. However, compound **35** acts differently, since it does not inhibit HIV-1 reverse transcription, HIV-1 integrase, or HIV-1 p24 expression. Therefore, **35** appears to exert its inhibitory effect at a later stage of HIV-1 replication, *i.e.*, the budding process.

1. Introduction. – The discovery of the natural (2′–5′)-oligoA system [3] initiated broad studies of the biochemical mechanism of interferon [4] and much activities to synthesize new types of potentially antivirally active compounds by chemical modification of (2′–5′)-linked oligoadenylates and oligonucleotides. Numerous derivatives of (2′–5′)-oligonucleotides [5–14] were modified at the sugar moiety, at the heterobase and at the internucleotide linkages, respectively, by chemical means to improve, *e.g.*, the permeability of oligoadenylates through the eucaryotic cell membranes as well as to prevent the high sensitivity of the oligonucleotides to nucleases. Thus, in comparison to the native pppA2′p5′A2′p5′A, new adenylate trimers carrying an amino group [12] [13] at the ribose moiety instead of the 3′-OH or 5′-OH function improved the enzymatic stability and revealed promising biological effects. Our recent efforts have been focussed in the same direction by synthesizing modified (2′–5′)adenylate trimers carrying a 3′-deoxy-3′-palmitoylamino group at the 2′-terminal unit.

2. Syntheses. – The successful synthesis of the four new trimers **33**–**36** was based on the availability of 3′-amino-3′-deoxyadenosine (**15**) for which several synthetic approaches have been described in literature. Till 1989 when *Samano* and *Robins* [2]

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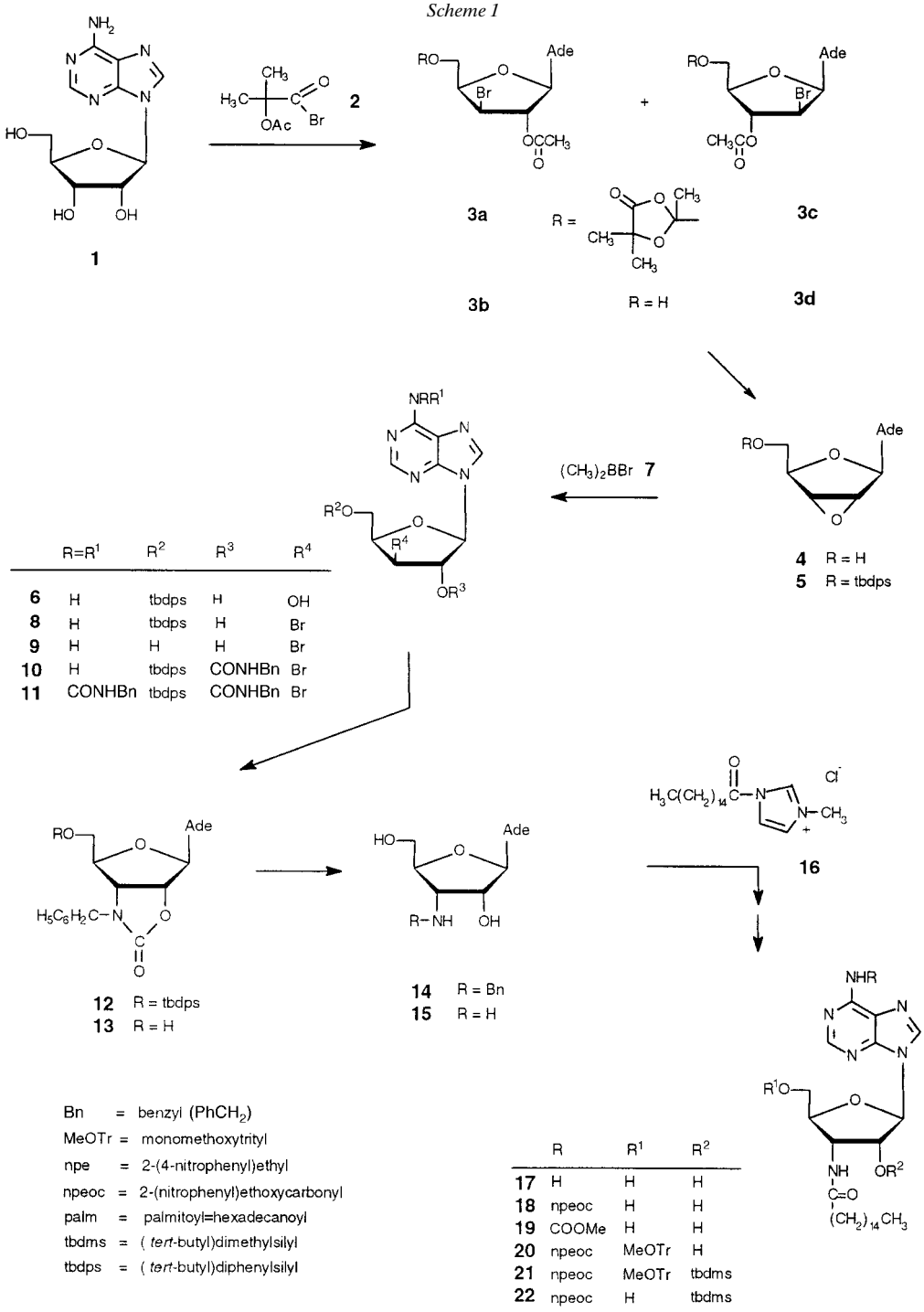
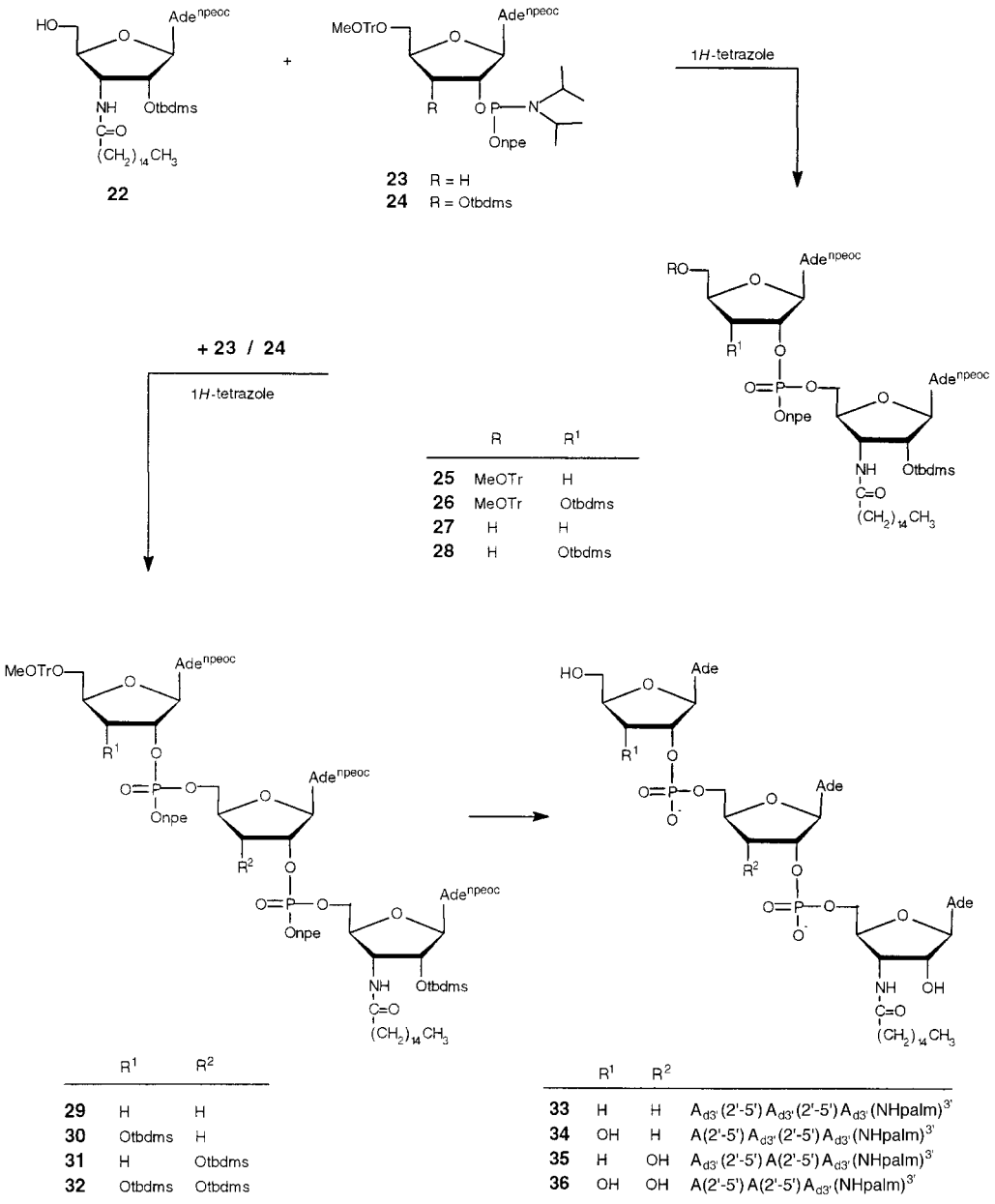
reported an efficient nine-step synthesis of **15** in a 66% overall yield, this biologically active compound was isolated either from microbiological cultures or was prepared in very low yields (< 2–20%) by chemical means, as, *e.g.* by transformation [15] [16] of adenosine into 3′-azido-3′-deoxyadenosine (12 steps, overall yields < 5%) and further reduction to the 3′-amino component [17], or by coupling reactions of suitable protected purine bases with glucose or xylose derivatives [18] [19] (overall yield < 20%). More efforts by *Robins et al.* [20] led in 1992 to another seven-step synthesis of **15** starting from adenosine *via* a stereoselective inversion (oxidation/reduction) at C(3′), triflation, azide displacement, and reduction to amine resulting, however, in a much lower overall yield.

We chose the first route [2] starting from adenosine (**1**), but realized that the described synthetic approach has to be discussed in more detail, since, in our hands, most steps have to be modified to achieve good yields of **15** (*Scheme 1*). It is recommended to treat dry **1** first with freshly prepared α-acetoxyisobutyryl bromide (**2**) [21] [22] in '*moist*' MeCN [2] [23] [24] leading to a mixture of 9-(2-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)- and 9-(3-*O*-acetyl-2-bromo-2-deoxy-β-D-arabinofuranosyl)adenines **3a**–**d** in which the 5′-OH group is present either in the orthoester function derived from 2,5,5-trimethyl-1,3-dioxol-4(5*H*)-one (**3a**, **3c**) or in unprotected form (**3b**, **3d**) [15] [16]. The dioxolone and acetyl protecting groups can either be sequentially removed by mild acidic treatment to give from **3a** the hydrolysed compound **3b** and finally **4** [15] [16] [25], or the mixture of the *trans*-3′(2′)-bromo-2′(3′)-acetoxy derivatives **3a**–**d** was directly treated without further separation with *Dowex 1* × *2* (OH^-) resin in MeOH to give 2′,3′-anhydroadenosine (**4**) in high yield [23–26]. In larger scale experiments, we obtained compound **4** with small contaminations of *9*-(β-D-xylofuranosyl)adenine [27] which could be removed by recrystallization which is actually not necessary since the next step yielding 2′,3′-anhydro-5′-*O*-[(*tert*-butyl)diphenylsilyl]anhydroadenosine (**5**) by silylation with (*tert*-butyl)chlorodiphenylsilane (tbdps-Cl) in pyridine required purification by silica-gel chromatography to give **5** in 87% and the corresponding xylofuranosyl derivative **6** in 6% yield. The anhydroadenosine **5** was then submitted to a regiocontrolled epoxide-ring-opening reaction with bromodimethylborane (**7**; Me_2BBr) at −78° to give **8** in 90% yield (TLC monitoring). The reagent **7**, useful for cleavage of various cyclic ethers, was prepared from BBr_3 and Me_4Sn at −55° under inert-gas atmosphere and final distillation by known procedures [28–31]. During the epoxide-cleavage reaction, the bulky (*tert*-butyl)diphenylsilyl group of **5** was not attacked by Me_2BBr, in contrast to some (*tert*-butyl)dimethylsilyl (tbdms) ethers which readily reacted with Me_2BBr at room temperature [28]. Furthermore, **8** was obtained by treatment of 9-(3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (**9**) [11] [22] with tbdps-Cl in pyridine within 19 h in 89% isolated yield. In subsequent reactions, the 2′-OH group of **8** was selectively protected by treatment with benzyl isocyanate under Et_3N activation for 3 days at room temperature [2] [32] to give compound **10** in 93% yield after flash chromatography (silica gel). The reaction time could be shortened to a few hours if **8** was first suspended in THF/MeCN and then reacted with benzyl isocyanate and Et_3N at 80° to give, within 15 min, a clear solution; further stirring for 75 min and usual workup gave **10** (78% yield) and some unreacted starting material **8** (14%). The reaction was accompanied by formation of little N^6,N^6 doubly protected adenosine derivative **11** (4%) due to the

Scheme 1


1
2
3a
3b
3c
3d
R = H
4 R = H
5 R = tbdps
(CH3)2BBr 7
6 H tbdps H OH
8 H tbdps H Br
9 H H H Br
10 H tbdps CONHBn Br
11 CONHBn tbdps CONHBn Br
12 R = tbdps
13 R = H
14 R = Bn
15 R = H
16
17 H H H
18 npeoc H H
19 COOMe H H
20 npeoc MeOTr H
21 npeoc MeOTr tbdms
22 npeoc H tbdms
Bn = benzyl (PhCH2)
MeOTr = monomethoxytrityl
npe = 2-(4-nitrophenyl)ethyl
npeoc = 2-(nitrophenyl)ethoxycarbonyl
palm = palmitoyl=hexadecanoyl
tbdms = (tert-butyl)dimethylsilyl
tbdps = (tert-butyl)diphenylsilyl

Scheme 2



more severe reaction conditions. In the next step, the intramolecular nucleophilic ring closure of the *N*-benzylcarbamate derivative **10** was achieved by treatment with 80% NaH in DMF for 1 h at $-5°$ and 30 min at room temperature to give three derivatives: the anticipated oxazolidinone **12** in only 13%, the corresponding 5′-*O*-desilylated

compound **13** in 56% yield, and 10% of 3′-*N*-(benzylamino)-3′-deoxyadenosine **14**. Further studies on the interconversion of **10** to **13** by variation of the reaction conditions to 4 h at $-5°$ and 1 h at room temperature proceeded with ring closure and complete cleavage of the 5′-*O*-tbdps group to yield crystalline **13** in 87%. On the other hand, removal of the silyl group of pure **12** could also be performed with $Bu_4NF \cdot 3\ H_2O$ in THF leading in 88% to **13**. Hydrolysis of the oxazolidinone ring of **13** and subsequent decarboxylation was performed with aq. 1N NaOH at room temperature to give the desired 3′-*N*-(benzylamino)-3′-deoxyadenosine (**14**). To shorten the time-consuming synthesis from **10** to **14**, a two-step reaction was developed, treating **10** first with 80% NaH in the described manner followed by $Bu_4NF \cdot 3\ H_2O$ to cleave the 5′-*O*-tbdps group completely. The mixture was then purified by flash chromatography, and the resulting mixture of **13** and **14** was then treated with aq. 1N NaOH and THF for 5 days; neutralization with *Amberlite* (H^+) resin and isolation of **14** by *Dowex 1 × 2* (OH^-) column chromatography ($MeOH/H_2O$) gave **14** in 56% yield from **10**. The benzyl group of **14** was finally removed by hydrogenolysis in presence of 5% Pd/C catalyst under vigorous stirring for 4 days leading to 3′-amino-3′-deoxyadenosine (**15**) in 69% isolated yield as colourless crystals. In our preparative-scale synthesis of **15** starting from adenosine (**1**), we were able to reach an overall yield of 53% over 8 steps (**1** → **14**). Including the last debenzylation step (**14** → **15**; 69%), we can claim only 37% (**1** → **15**) instead of 66% obtained by *Samano* and *Robins* [2].

The introduction of the hexadecanoyl (palmitoyl) residue into the 3′-amino position of **15** was performed almost quantitatively with the acylating agent **16**, which was prepared from hexadecanoyl chloride and 1-methyl-1*H*-imidazole in dry DMF in 90% yield as a colorless powder. The subsequent protection of the 6-NH_2 function of **17** by the npeoc group required a transient protection of the sugar OH groups by silylation with 1-(trimethylsilyl)-1*H*-imidazole in abs. CH_2Cl_2, then treatment with 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride [33], and finally cleavage of the silyl groups in pyridine/H_2O to give crystalline 3′-deoxy-3′-(hexadecanoylamino)-N^6-2-[(4-nitrophenyl)ethoxycarbonyl]adenosine (**18**) in 87% yield. Desilylation by the common Et_3N/MeOH treatment was less successful and proceeded with partial transesterification of the N^6-npeoc into the N^6-(methoxycarbonyl) group [34] forming **19** as a by-product. Finally, the required building block **22** resulted from subsequent reactions involving selective monomethoxytritylation of the 5′-OH group of **18** (→ **20**; 88%), then introduction of the (*tert*-butyl)dimethylsilyl (tbdms) group at the 2′-OH position (→ **21**; 95%), followed by treatment with 2% TsOH in CH_2Cl_2/MeOH 4:1 to cleave off the MeOTr group (→ **22**; 89%).

The other two building blocks for the oligonucleotide syntheses were derived from 3′-deoxy-5′-*O*-(monomethoxytrityl)-N^6-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine [35] and 3′-*O*-[(*tert*-butyl)dimethylsilyl]-5′-*O*-(monomethoxytrityl)-N^6-[2-(4-nitrophenyl)-ethoxycarbonyl]adenosine [6] by phosphitylation with 2-(4-nitrophenyl)ethyl tetraisopropylphosphonodiamidite [6] [36] to give the corresponding 2′-phosphoramidites **23** and **24** in high yields, respectively.

The first condensation reactions between the starting 5′-OH component **22** and **23** or **24,** respectively, in a mixture of abs. MeCN and abs. CH_2Cl_2 in the presence of 1*H*-tetrazole and subsequent oxidation by I_2 in pyridine/H_2O/CH_2Cl_2 led to the corresponding fully protected dimers $A_{d^{3'}}\varphi A_{d^{3'}}$ $(NHpalm)^{3'}$ (**25**) and $A\varphi A_{d^{3'}}$ $(NHpalm)^{3'}$

($\varphi = PO_3(Onpe)^{2-}$) (**26**), respectively, in excellent quantitative yields. Detritylation of these intermediates with 2% TsOH in CH_2Cl_2/MeOH 4:1 afforded in yields of *ca.* 90% the 5′-OH components **27** and **28**, respectively, which were then separately condensed again with the phosphoramidites **23** and **24**, respectively in an analogous manner. The four fully protected (2′–5′)adenylate trimers $A_{d3'}\varphi A_{d3'}\varphi A_{d3'}(NHpalm)^{3'}$ **29** (96%), $A\varphi A_{d3'}\varphi A_{d3'}(NHpalm)^{3'}$ **30** (91%), $A_{d3'}\varphi A\varphi A_{d3'}(NHpalm)^{3'}$ **31** (97%), and finally $A\varphi A\varphi A_{d3'}(NHpalm)^{3'}$ **32** (94%) were obtained, after purification by FC (silica gel), as colorless foams.

The final removal of the various protecting groups from the four trimers **29**–**32** was achieved by subsequent treatment first with 0.5M DBU (= 1.8-diaza-bicyclo[5.4.0]undec-7-ene) in abs. MeCN to eliminate the 2-(4-nitrophenyl)ethyl (npe) and 2-(4-nitrophenyl)ethoxycarbonyl groups, then with Bu_4NF in THF to remove the (*tert*-butyl)dimethylsilyl groups, and finally with AcOH to cleave the monomethoxytrityl residue at the 5′-end of the trimers. The purity of the newly synthesized (2′–5′)-adenylate trimers **33**–**36** carrying 3′-deoxy-3′-(hexadecanoylamino)adenosine at the 2′-terminus was checked by TLC and HPLC (*Fig. 1*), and the composition was proven by FAB-MS (*Fig. 2*).

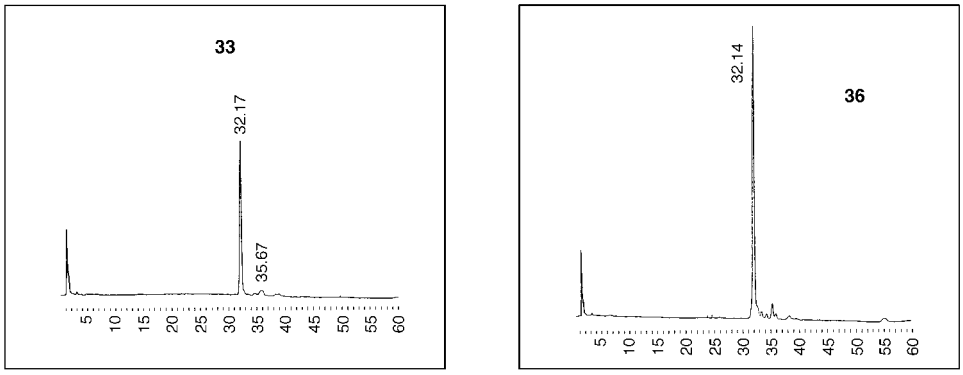


Fig. 1. *HPLC Analysis of* $A_{d3'}(2'-5')A_{d3'}(2'-5')A_{d3'}(NHpalm)^{3'}$ (**33**) *and* $A(2'-5')A(2'-5')A_{d3'}(NHpalm)^{3'}$ (**36**). Conditions: *RP 18* column; for elution gradient, see *Exper. Part*.

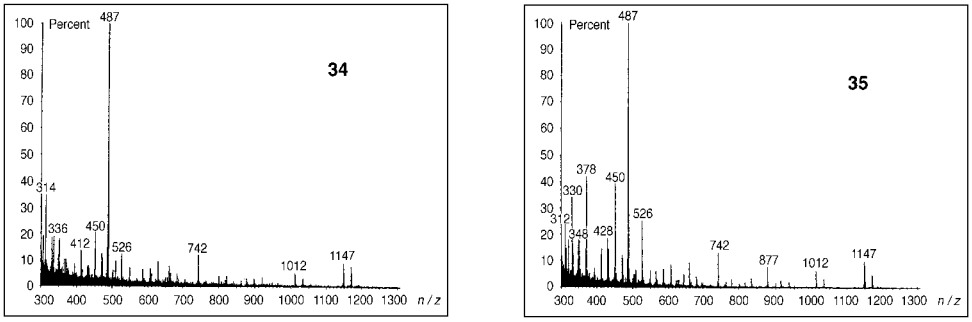


Fig. 2. *FAB-MS of* $A(2'-5')A_{d3'}(2'-5')A_{d3'}(NHpalm)^{3'}$ (**34**) *and* $A_{d3'}(2'-5')A(2'-5')A_{d3'}(NHpalm)^{3'}$ (**35**). $[M+H]^+$ 1147, $[M+Na]^+$ 1169 (matrix DMSO/3-nitrobenzyl alcohol).

3. Biological Applications. – In a previous publication [1], we described the inhibition of HIV-1 replication in SupT1 cells treated with 5′-terminally (hexadecanoylamino)-substituted (2′–5′)adenylyl-3′-deoxyadenylyl trimer core derivatives. In this study, we report the inhibition of HIV-1 replication by 2′-terminal (hexadecanoylamino)-substituted (2′–5′)adenylyl-3′-deoxyadenylyl trimer cores. Replacement of the 3′-OH with the 3′-(hexadecanoylamino) group produced trimer derivatives that inhibited HIV-1 replication as determined by the inhibition of HIV-induced syncytia formation and HIV-1 reverse transcriptase (RT) activity (*Table 1*). The inhibition of syncytia formation for compounds **33**–**36** was 91, 99, 91, and 21%, respectively. In this study, the substitution of the (hexadecanoylamino) group at the 3′-hydroxy terminus of **33**, **34** and **35** resulted in derivatives that were markedly more potent than compound **36**.

Table 1. *Inhibition of HIV-1 Replication and Biological Activities of (2′–5′)Adenylyl/3′-Deoxyadenylyl Trimer Derivatives* [a]) **33**–**36**

	R^1	R^2	Inhibition of HIV-1 replication [%]	
			Syncytia [b])	RT [c])
33	H	H	91	54
34	OH	H	99	50
35	H	OH	91	78
36	OH	OH	21	0

[a]) Compounds **33**–**36** were tested at 100 μM. [b]) Inhibition of HIV-1 replication as determined by HIV-1-induced syncytia formation (%) for each compound. The number of syncytia/10^4 cells was 324 ± 3 for the control SupT1 cells. The mean of duplicate determinations is shown; variance did not exceed 5–10%. [c]) Inhibition of reverse transcriptase (HIV-1 RT) activity. Control values for HIV-1 RT activity averaged 4325 dpm. The mean of duplicate determinations is shown; variance did not exceed 5–10%.

We have also studied the effects of compounds **34** and **35** on HIV-1 reverse transcription by PCR amplification, inhibition of HIV-1 integrase, and the inhibition of HIV-1 p24 antigen expression. Compound **34**, but not compound **35**, completely inhibited PCR amplification of HIV-1 partial reverse transcripts (*Table 2*). Again, these data demonstrate the significance of the position of the adenylyl and 3′-deoxyadenylyl groups in these trimer core derivatives as related to the inhibition of

Table 2. *Effect of (2′–5′)A Derivatives on Critical Stages of the HIV-1 Replicative Cycle*

	R^1	R^2	Inhibition [%] of		
			HIV-1 PCR [a])	Integrase [b])	Expression of p24 [c])
34	OH	H	100	0	100
35	H	OH	0	0	0

[a]) Inhibition of HIV-1 reverse transcription was measured by PCR amplification partial reverse transcripts. 100% indicates no amplification, 0% indicates amplification by one or more primer sets. Concentrations of **34** and **35** were 100 μM. [b]) HIV-1 Integrase assays were done by integration by the HIV-1 genome by endonucleolytic cleavage of two terminal nucleotides from the 3′-ends of the viral DNA. 100% inhibition is based on a comparison to AZT 5′-monophosphate; 0% indicates no inhibition of integrase activity. Concentrations of **34** and **35** were 1000 μM. [c]) Inhibition of expression of p24 antigen was determined by Western blotting. Concentrations of **34** and **35** were 300 μM.

HIV-1 RT. Because compound **34** inhibited HIV-1 reverse transcription as determined by PCR, the expression of p24 antigen was also inhibited (*Table 2*). However, compound **34** did not inhibit HIV-1 integrase. Although compound **35** inhibited HIV-1 replication as determined by inhibition of HIV-1-induced syncytia formation and HIV-1 RT assays, this inhibition of HIV-1 replication exhibited by compound **35** can not be attributed to the inhibition of HIV-1 reverse transcription, HIV-1 integrase, or p24 antigen expression (*Table 2*). Therefore, compound **35** may affect the budding process required for HIV-1 replication.

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Experimental Part

General. TLC: Precoated silica gel thin-layer sheets *60 F_{254}* from *Merck*; precoated cellulose thin-layer sheets *F1440/LS 254* from *Schleicher & Schüll.* Flash chromatography (FC): silica gel for FC, *J. T. Baker* (Ø 40 μm). HPLC: *Merck-Hitachi, L-6200-Intelligent* pump, *D-2000* chromatointegrator, detection at 260 nm (*Uvikon 730SLC*, Fa. *Kontron*); column *RP18* (*LiChrospher* 125 × 4 mm, 5 μm, *Merck 50943*); flow rate 1 ml/min; mobile phase: A = 0.1M (Et_3NH)OAc buffer (pH 6.9)/MeCN 1 : 1, B = 0.1M (Et_3NH)OAc buffer (pH 6.9), gradient for **33**–**36**: 0 min, 50% A/50% B; 5 min, 50% A/50% B; 35 min, 100% A; 40 min, 100% A. M.p.: *Gallenkamp* or *Büchi* (model Dr. *Tottoli*) melting-point apparatus; no corrections. UV/VIS: *Perkin-Elmer Lambda* 5; λ_{max} in nm (log ε). ^{1}H-NMR: *Bruker WM 250, AC 250;* δ in ppm rel. to $CDCl_3$ or (D_6) DMSO as internal standard. ^{31}P-NMR: *Jeol JM GX-400;* δ in ppm rel. to 85% H_3PO_4 soln. Fast-atom-bombardment (FAB) MS: *Finnigan MAT 312/AMD-5000*, matrix DMSO/3-nitrobenzyl alcohol.

Bioassay. Assays measuring HIV-1-induced syncytia formation, HIV-1 reverse transcriptase activity, HIV-1 RT PCR amplification, HIV-1 integrase, and expression of p24 antigen were accomplished as previously described [1].

1. *2-Acetoxy-2-methylpropanoyl Bromide* (**2**). 1.1. *2-Acetoxy-2-methylpropanoyl Chloride* [21] [22]. Acetyl chloride (240 g, 3.06 mol) was added within 40 min under stirring and ice-cooling to 2-hydroxy-2-methylpropanoic acid (120 g, 1.15 mol). Then, the mixture was stirred for further 10 min at 0° and 20 min at r.t. until the gas evolution had ceased. The mixture was heated under reflux for 2 h, excess acetyl chloride was then removed by destillation (at 10–12 Torr). The yellowish residue (= 2-acetoxy-2-methylpropanoic acid) was cooled to r.t., then thionyl chloride (117 g, 0.987 mol) was added dropwise within 15 min, and the mixture was heated once more under reflux for 2 h. The resulting 2-acetoxy-2-methylpropanoyl chloride was then isolated by destillation at 67–69°/8–10 Torr ([21]; 55–56°/6 Torr): 175 g (93%). n_D^{25} 1.4272 ([21]: n_D^{25} 1.4278). ^{1}H-NMR ($CDCl_3$): 2.10 (*s*, MeCOO); 1.60 (*s*, Me_2C).

1.2. *2-Acetoxy-2-methylpropanoyl Bromide* (**2**) [21] [22]. To dried (8 h at 150°/high vacuum) LiBr (108 g, 1.25 mol), anh. AcOEt (375 ml) was added, and the mixture was stirred at r.t. until LiBr was dissolved. Then, 2-acetoxy-2-methylpropanoyl chloride (164 g, 1 mol) was added in one portion, and the suspension was stirred at 80° for 2 h. After cooling to r.t., the colourless precipitate (LiCl) was removed by filtration, and the soln. was concentrated to 1/3 of the volume. The residue was distilled at 74–83°/10–12 Torr: **2** (109 g, 52%) ([22]: 63%; b.p. 75–77°/12 Torr]. Colorless liquid. ^{1}H-NMR ($CDCl_3$): 2.11 (*s*, MeCOO); 1.57 (*s*, Me_2C).

2. *9-(2,3-Anhydro-β-*D*-ribofuranosyl)adenine (= Adenosine Epoxide*; **4**). Dry adenosine (13.36 g, 50 mmol) was suspended in abs. MeCN (200 ml) and MeCN/H_2O 99 : 1 (20 ml), **2** (24 ml, 60 mmol) was added, and the mixture was stirred at r.t. A homogeneous soln. was obtained after 45 min, and after 1 h, AcOEt (160 ml) was added and the mixture washed twice with $NaHCO_3$ soln. (120 ml). The aq. phase was reextracted with AcOEt (5 × 60 ml) and the combined org. phase dried (Na_2SO_4) and evaporated to give an amorphous solid of four intermediates, namely *9-(2-*O*-acetyl-3-bromo-3-deoxy-5-*O*-(2,4,4-trimethyl-5-oxo-1,3-dioxolan-2-yl)-β-*D*-xylofuranosyl)adenine* (**3a**), *9-(2-*O*-acetyl-3-bromo-3-deoxy-β-*D*-xylofuranosyl)adenine* (**3b**), *9-(3-*O*-acetyl-2-bromo-2-deoxy-5-*O*-(2,4,4-trimethyl-5-oxo-1,3-dioxolan-2-yl)-β-*D*-arabinofuransoyl)adenine* (**3c**), and *9-(3-*O*-acetyl-2-bromo-2-deoxy-β-*D*-arabinofuranosyl)adenine* (**3d**) which were suspended in abs. MeOH (200 ml) without further isolation. *Dowex 1 × 2* (OH^-, 200–400 mesh; washed with abs. MeOH and dried *in vacuo*; 50 g) was added and the mixture stirred vigorously at r.t. for 15 min. The mixture was heated until the precipitated product was dissolved, filtered hot from *Dowex*, washed with hot MeOH (3 × 50 ml), then cooled

to r.t., and evaporated to 1/3 of the volume. To complete the crystallization of **4**, the mixture was cooled to 4° over night, filtered off by suction, and dried at 50°/high vacuum: **4** (10.33 g, 83%) ([17]: 92%). Colorless powder. M.p. 180° (dec.). TLC (CH_2Cl_2/MeOH 4:1): R_f 0.56. UV (MeOH): 258 (4.15), 209 (4.29). ^{1}H-NMR ((D_6)DMSO): 8.32 (*s*, H–C(8)); 8.16 (*s*, H–C(2)); 7.33 (*s*, NH_2); 6.20 (*s*, H–C(1′)); 5.06 (*t*, OH–C(5′)); 4.45 (*d*, H–C(2′)); 4.21 (*d*, H–C(3′)); 4.17 (*t*, H–C(4′)); 3.55 (*m*, 2 H–C(5′)). Anal. calc. for $C_{10}H_{11}N_5O_3$ (249.2): C 48.19, H 4.45, N 28.10; found: C 48.01, H 4.63, N 28.27.

For anal. purposes, a small amount of the mixture **3a**–**d** was suspended in abs. MeOH and filtered from insoluble material to give the two isomers **3a**/**3c** as solid. Thereof, 145 mg were re-crystallized from EtOH (10 ml) to give pure **3a** (104 mg, 72%). M.p. 171–172° ([15] [16]: 171–172°). TLC (CH_2Cl_2/MeOH 9:1): R_f 0.53. UV (MeOH): 258 (4.17), 208 (4.28). ^{1}H-NMR ((D_6)DMSO): 8.25 (*s*, H–C(8)); 8.15 (*s*, H–C(2)); 7.38 (*s*, NH_2); 6.14 (*d*, H–C(1′)); 5.91 (*t*, H–C(2′)); 4.91–4.88 (*dt*, H–C(3′)); 4.49–4.46 (*m*, 2 H–C(5′)); 2.09 (*s*, MeC=O); 1.72 (*s*, $MeC(O_2)$); 1.48, 1.45 (2*s*, Me_2C). Anal. calc. for $C_{18}H_{22}BrN_5O_7$ (500.3): C 43.21, H 4.43, N 14.00; found: C 43.09, H 4.49, N 14.06.

3. *9-{2,3-Anhydro-5-*O*-[(*tert*-butyl)diphenylsilyl]-β-*D*-ribofuranosyl}-adenine (= 5′-*O*-[(*tert*-Butyl)diphenylsilyl]adenosine Epoxide*; **5**). In dry pyridine (3 × 20 ml), not recrystallized **4** (6.23 g, 25 mmol) was co-evaporated, the residue suspended in dry pyridine (75 ml), then (*t*-Bu)Ph_2SiCl (8.25 g, 30 mmol) added, and the mixture stirred at r.t. for 16 h. The mixture was poured into ice-water (100 ml) and extracted with AcOEt (200 ml). The aq. phase was washed with AcOEt (2 × 100 ml) and the combined org. phase dried (Na_2SO_4), evaporated, and co-evaporated with toluene (3 × 30 ml) and CH_2Cl_2 (2 × 20 ml). Purification by FC (silica gel, 10 × 5 cm, 1% MeOH/CH_2Cl_2 (400 ml), 1.5% MeOH/CH_2Cl_2 (400 ml), 2% MeOH/CH_2Cl_2 (1.2 l; elution of **5**), 3% MeOH/CH_2Cl_2 (400 ml; elution of **5**), 4% MeOH/CH_2Cl_2 (400 ml; elution of **6**)) gave **5** (10.56 g, 87%) and **6** (753 mg, 6%; formation due to crude **4**) as colorless foams.

Data of **5**: TLC (CH_2Cl_2/MeOH 9:1; 2 developments): R_f 0.69. UV (MeOH): 259 (4.13), 208 (4.56). ^{1}H-NMR ((D_6)DMSO): 8.24 (*s*, H–C(8)); 8.01 (*s*, H–C(2)); 7.54–7.21 (*m*, Ph_2Si, NH_2); 6.24 (*s*, H–C(1′)); 4.46 (*d*, H–C(2′)); 4.32 (*t*, H–C(3′)); 4.23 (*d*, H–C(4′)); 3.85 (*m*, 1 H–C(5′)); 3.65 (*m*, 1 H–C(5′)); 0.89 (*s*, Me_3C). Anal. calc. for $C_{26}H_{29}N_5O_3Si$ (487.6): C 64.04, H 5.99, N 14.36; found: C 64.06, H 6.15, N 14.25.

*9-{5-*O*-[(*tert*-Butyl)diphenylsilyl]-β-*D*-xylofuranosyl}adenine* (**6**). M.p. 198–200°. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.43. UV (MeOH): 259 (4.17), 207 (4.59). ^{1}H-NMR ((D_6)DMSO): 8.25 (*s*, H–C(8)); 8.08 (*s*, H–C(2)); 7.61–7.31 (*m*, PhSi, NH); 5.93 (*d*, H–C(1′)); 5.57 (*d*, OH–C(2′)); 5.26 (*d*, OH–C(3′)); 4.64 (*q*, H–C(2′)); 4.34 (*q*, H–C(3′)); 4.03 (*q*, H–C(4′)); 3.94–3.73 (*m*, 2 H–C(5′)); 0.97 (*s*, Me_3C). Anal. calc. for $C_{26}H_{31}N_5O_4Si$ (505.7): C 61.76, H 6.18, N 13.85; found: C 61.81, H 6.18, N 14.09.

4. *Bromodimethylborane* (**7**) [28–30]. A dried (15 h at 100°) 25-ml flask was evacuated and then flushed with N_2 and equipped with a septum. A short-path distillation apparatus utilizing a preweighed dry (15 h at 100°) 50-ml two-necked flask as the receiver was stoppered with a septum. The 25-ml flask was cooled to −55° (i-PrOH/solid CO_2) and charged with BBr_3 (7 ml, 72.5 mmol; *Fluka*) under N_2. Me_4Sn (10 ml, 72.5 mmol; *Fluka*) was added dropwise by syringe within 60 min. The mixture was stirred for another 60 min at −50° (without N_2 stream!) and for additional 30 min at r.t. The bromodimethylborane (b.p. 32–36°; [27]: 31–32°] was separated from the by-product Me_2SnBr_2 by distillation at max. 100° bath temp., and the receiver was cooled to −35° from beginning of the distillation. Compound **7** (8.59 g, 98%; [27]: 84%) was mixed with CH_2Cl_2 to afford a 1.1–2.1M soln. of **7**, which was stored at −20° and used within few weeks for epoxide cleavage reactions.

5. *9-{3-Bromo-5-*O*-[(*tert*-butyl)diphenylsilyl]-3-deoxy-β-*D*-xylofuranosyl}adenine* (**8**) [17] [21] [25]. 5.1. To a cold (−78°; i-PrOH/solid CO_2), stirred soln. of pure **5** (4.88 g, 10 mmol) in dry CH_2Cl_2 (90 ml) under N_2, successively Et_3N (0.25 ml, 2 mmol) and 1.45M **7** in CH_2Cl_2 (14 ml, 20 mmol) were added. After 15 min. at −78°, the mixture was transferred by cannula into a vigorously stirred soln. of sat. $NaHCO_3$ soln. (200 ml) and then extracted with CH_2Cl_2 (100 ml). The org. phase was washed with NaCl soln. (200 ml) and the combined aq. phase with CH_2Cl_2 (4 × 100 ml). The org. layers were dried (Na_2SO_4) and evaporated. The solid residue was crystallized from EtOH to give pure **8** (5.14 g, 90%), after drying at 40°/high vacuum ([18]: 98% (crude); [21]: 96% (crude)). Colorless powder. M.p. 211–213° ([18]: 210–211°). TLC (CH_2Cl_2/MeOH 9:1; 2 developments): R_f 0.64. UV (MeOH): 259 (4.20), 206 (4.60). ^{1}H-NMR ((D_6)DMSO): 8.13 (*s*, H–C(8)); 8.08 (*s*, H–C(2)); 7.64 (*m*, 4 H, Ph_2Si); 7.47–7.34 (*m*, 6 H, Ph_2Si); 6.49 (*d*, OH–C(2′)); 5.90 (*d*, H–C(1′)); 4.94 (*q*, H–C(2′)); 4.60 (*m*, H–C(3′)); 4.53 (*m*, H–C(4′)); 4.00 (*m*, 2 H–C(5′)); 1.00 (*s*, *t*-Bu). Anal. calc. for $C_{26}H_{30}BrN_5O_3Si$ (568.5): C 54.93, H 5.32, N 12.32; found: C 54.59, H 5.38, N 12.21.

5.2. Pure **4** (6.86 g, 27.52 mmol) was dried by co-evaporations with abs. pyridine (3 × 20 ml). Abs. pyridine (100 ml), and (*t*-Bu)Ph_2SiCl (9.08 g, 33 mmol) were added, and the suspension was stirred at r.t. over night (18 h). H_2O (11 ml) was added. The mixture cleared within a few minutes and was stirred for another 30 min, evaporated, and co-evaporated with toluene (2 × 20 ml). The residue was diluted with CH_2Cl_2 (300 ml), the

soln. washed with H_2O (2×100 ml), sat. $NaHCO_3$ soln. (2×100 ml), and NaCl soln. (2×100 ml), dried (Na_2SO_4), and evaporated, and the residue dried *in vacuo* to give crude **5** (15.2 g, >100%). Without further purification, the quantity of crude compound **5** was halved, and each half was reacted separately in the same manner. Under N_2, crude **5** (7.6 g) was dissolved in abs. CH_2Cl_2 (300 ml) and cooled to $-65°$ (i-PrOH/solid CO_2). Et_3N (0.5 ml, 3.57 mmol) and a soln. of Me_2BBr (**7**; 24.88 mmol) in abs. CH_2Cl_2 (22 ml) were added successively. After 5 h at $-60°$ (TLC monitoring), the ratio **5**/**8** was *ca.* 1:3 to 2:3. The mixture was kept at $-15°$ overnight to allow the reaction to reach completion. The mixture was then poured into a vigorously stirred sat. $NaHCO_3$ soln. (600 ml) and extracted with CH_2Cl_2 (2×150 ml). The org. phases were washed with sat. NaCl soln. (500 ml), the aq. layer was re-extracted with CH_2Cl_2 (2×100 ml), and the combined org. phases were dried (Na_2SO_4) and evaporated. The residual powder was crystallized from THF/MeCN 1:1 (120 ml): **8** (10.44 g, 67% rel. to **4**). The mother liquour was purified by FC (silica gel, 13×3 cm, 2–20% EtOH/CH_2Cl_2) to give another 1.45 g of **8**. Overall yield of **8**: 11.89 g (76%, rel. to **4**).

5.3. In dry pyridine, 9-(3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (**9**) [11] [22] (2.2 g, 6.66 mmol) was co-evaporated (3×20 ml) and then dissolved in pyridine (40 ml). (*t*-Bu)Ph_2SiCl (1.83 g, 6.66 mmol) was added and stirred for 19 h at r.t. The reaction was stopped with H_2O (3 ml), the mixture stirred for further 30 min at r.t., and then evaporated. The residue was partitioned between CH_2Cl_2 (100 ml), and H_2O (60 ml), the org. phase washed with H_2O (2×60 ml), sat. $NaHCO_3$ soln. (100 ml) and NaCl soln. (100 ml), dried (Na_2SO_4), evaporated, and co-evaporated with toluene (3×40 ml), and the residue crystallized from MeCN/THF 5:7 (24 ml) to give, after drying at 40° *in vacuo*, **8** (3.36 g, 89%). Colourless powder.

6. *9-{2-*O*-[(Benzylamino)carbonyl]-3-bromo-5-*O*-[(*tert*-butyl)diphenylsilyl]-3-deoxy-β-*D*-xylofuranosyl}-adenine* (**10**). 6.1. To a soln. of **8** (4.45 g, 7.83 mmol) in abs. THF/MeCN 2:1 (150 ml), benzyl isocyanate (2 ml, 15.66 mmol) and Et_3N (1.6 ml, 11.75 mmol) were added and stirred at r.t. for 3 days. Then, EtOH (25 ml) was added and stirring continued for 30 min. After evaporation, the sirupy residue was purified by FC (silica gel, 6×5 cm, CH_2Cl_2 (elution of dibenzylurea), 1–5% EtOH/CH_2Cl_2 (2–5% EtOH, elution of pure **10**)) to give **10** (5.11 g, 93%). Colourless foam ([21]: 90%). TLC: R_f 0.47 (hexane/acetone 1:2), 0.36 (CH_2Cl_2/MeOH 19:1). R_f UV (MeOH): 262 (sh, 4.18), 259 (4.20). ^{1}H-NMR ((D$_6$)DMSO): 8.13 (*m* + *dt*, H–C(8), H–C(2), NH); 7.65 (*m*, 4 H, Ph_2Si); 7.48–7.13 (*m*, 13 H, NH_2, Ph, Ph_2Si); 6.14 (*d*, H–C(1′)); 5.87 (*t*, H–C(2′)); 4.90 (*t*, H–C(3′)); 4.51 (*q*, H–C(4′)); 4.17–3.98 (*m*, NHCH_2, 2 H–C(5′)); 1.02 (*s*, *t*-Bu). Anal. calc. for $C_{34}H_{37}BrN_6O_4Si$ (701.7): C 58.20, H 5.32, N 11.98; found: C 58.13, H 5.31, N 12.04.

6.2. *9-{N^6,N^6,2-*O*-Tris[(benzylamino)carbonyl]-3-bromo-5-*O*-[(*tert*-butyl)diphenylsilyl]-3-deoxy-β-*D*-xylofuranosyl}adenine* (**11**). To a suspension of **8** (2.84 g, 5 mmol) in abs. THF/MeCN 1:1 (20 ml), benzyl isocyanate (524 ml, 6 mmol) and Et_3N (1.25 ml, 10 mmol) were added and stirred at 80°. After 15 min, the mixture cleared, and after further stirring for 75 min at 80°, AcOH (524 ml, 9 mmol) was added and stirring continued for 15 min at r.t. The mixture was diluted with AcOEt (50 ml) and washed twice with H_2O (2×80 ml). The aq. phases were re-extracted with AcOEt (3×50 ml) and the combined AcOEt layers dried ($MgSO_4$) and evaporated. Purification by FC (silica gel, 26×2.5 cm, hexane/acetone 2:1 (800 ml → **11**), 1:1 (400 ml → **10**), and 1:2 (400 ml → **8**)) gave **11** (0.21 g, 4%), **10** (2.72 g, 78%) and unreacted **8** (0.4 g, 14%). Colourless foams. **11**: TLC: R_f 0.78 (hexane/acetone 1:2), 0.70 (CH_2Cl_2/MeOH 19:1). UV (MeOH): 262 (sh, 4.18), 259 (4.20). ^{1}H-NMR ($CDCl_3$): 8.13 (*m* + *dt*, H–C(8), H–C(2), NH); 7.65 (*m*, 4 H, Ph_2Si); 7.48–7.13 (*m*, 13 H, NH_2, Ph, $PhSi_2$); 6.14 (*d*, H–C(1′)); 5.87 (*t*, H–C(2′)); 4.90 (*t*, H–C(3′)); 4.51 (*q*, H–C(4′)); 4.17–3.98 (*m*, NHCH_2, 2 H–C(5′)); 1.02 (*s*, *t*-Bu). Anal. calc. for $C_{50}H_{51}BrN_8O_6Si$ (968.0): C 62.04, H 5.31, N 11.58; found: C 61.92, H 5.40, N 11.46.

7. *3′-(Benzylamino)-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-*N*,2′-*O*-carbonyl-3′-deoxyadenosine* (**12**), *3′-(Benzylamino)-3′-*N*,2′-*O*-carbonyl-3′-deoxyadenosine* (**13**), and *3′-(Benzylamino)-3′-deoxyadenosine* (**14**). 7.1. NaH (80% in mineral oil; 350 mg, 11.45 mmol) was washed 3 times with abs. Et_2O (20 ml), filtered by suction, and then added to a soln. of **10** (2.68 g, 3.82 mmol) in abs. DMF (38 ml) at $-5°$ (ice/NaCl). The mixture was stirred for 60 min at $-5°$ to 0° and 30 min at r.t., MeOH (40 ml) was added, the mixture stirred at r.t. for further 10 min, evaporated, and co-evaporated with MeOH (3×20 ml), and the residue dissolved in little CH_2Cl_2/MeOH 2:1. FC silica gel (6 g) was added, the mixture evaporated, and the residue applied to a column of FC (silica gel, 15×2.5 cm, 1–15% MeOH/CH_2Cl_2). The three product fractions were evaporated separately. Compound **12** was co-evaporated with CH_2Cl_2 to give 296 mg (13%) of **12** as colorless foam. The residue containing pure **13** was co-evaporated twice with MeOH/Et_2O 2:1 (20 ml) and led to 812 mg (56%) of **13** as colourless powder. Compound **14** was crystallized from CH_2Cl_2/MeOH 1:2 (15 ml) to give 130 mg (10%) of **14**. Overall yield: 79%.

Data of **12**: TLC (CH_2Cl_2/MeOH 19:1): R_f 0.36. UV (MeOH): 258 (4.16), 261 (sh, 4.15), 207 (4.65). ^{1}H-NMR ((D$_6$)DMSO): 8.27 (*s*, H–C(8)); 8.12 (*s*, H–C(2)); 7.40–7.32 (*m*, 17 H, Ph_2Si, NH_2, Ph); 6.30

(*d*, H–C(1′)); 5.69 (*dd*, H–C(2′)); 4.66–4.26 (*m*, NCH_2, H–C(3′), H–C(4′)); 3.43–3.35 (*m*, 2 H–C(5′)). Anal. calc. for $C_{34}H_{37}N_6O_4Si \cdot 0.5\ H_2O$ (630.8): C 64.74, H 6.07, N 13.32; found: C 65.03, H 5.85, N 13.24.

7.2. NaH (80% in mineral oil; 176 mg, 5.76 mmol) was first treated with abs. Et_2O (3 × 20 ml), filtered by suction to remove the mineral oil and then added to the ice-cooled (−5°) soln. of **10** (1.35 g, 1.92 mmol) in abs. DMF (19 ml). The mixture was stirred for 4 h at −5° to 0° and 1 h at r.t. MeOH (4 ml) was added and the mixture evaporated under high vacuum, and co-evaporated with MeOH (3 × 20 ml). The residual solid was crystallized first from EtOH/H_2O 3:1 (20 ml) and then from MeOH/AcOEt 2:1 (15 ml) to give **13** (639 mg, 87%). Colourless crystals. M.p. 231–232° ([21]: 229–230° (MeOH/Et_2O)). TLC (CH_2Cl_2/MeOH 19:1, then hexane/acetone 1:2): R_f 0.21. UV (MeOH): 258 (4.18), 207 (4.45). ^{1}H-NMR ((D$_6$)DMSO): 8.33 (*s*, H–C(8)); 8.12 (*s*, H–C(2)); 7.43–7.32 (*m*, 7 H, NH_2, Ph); 6.30 (*d*, H–C(1′)); 5.69 (*dd*, H–C(2′)); 5.27 (*t*, OH–C(5′)); 4.63 (*d*, 1, NCH); 4.39–4.26 (*m*, H–C(3′), H–C(4′), 1 NCH); 3.42 (*t*, 2 H–C(5′)). Anal. calc. for $C_{18}H_{18}N_6O_4$ (382.4): C 56.54, H 4.75, N 21.98; found: C 56.62, H 4.76, N 21.80.

7.3. Pure **12** (295 mg, 0.474 mmol) was dissolved in abs. THF (25 ml), and $Bu_4NF \cdot 3\ H_2O$ (240 mg, 0.76 mmol) was added. After stirring for 2 h at r.t., the mixture was diluted with CH_2Cl_2 (100 ml), the soln. washed with H_2O (80 ml), sat. $NaHCO_3$ soln. (50 ml), and sat. NaCl soln. (50 ml), dried (Na_2SO_4), and evaporated, and the residue purified by FC (16 × 1.5 cm, packed with CH_2Cl_2/MeOH 19:1, elution with CH_2Cl_2/MeOH 19:1 (350 ml)). Treatment of the crude product with little MeOH/Et_2O gave, after evaporation and drying, **13** (160 mg, 88%). Colorless powder.

7.4. NaH (80% in mineral oil; 1.35 g, 45 mmol) was washed with hexane (3 × 15 ml), then suspended in dist. THF (250 ml), and cooled to −5° (ice/NaCl). Then, the soln. of **10** (15 g, 21.4 mmol) in dist. THF (250 ml) was added dropwise within 1 h and the mixture stirred for further 45 min at −5° and finally at r.t. for 20 h. The suspension was filtered over *Celite* over a glass suction filter (*D4*), the *Celite* washed with THF, and the filtrate dried and evaporated: 15.6 g of crude mixture containing mainly **12**, smaller amounts of **13**, and traces of **14** (by TLC). Without further purification steps, the mixture was dissolved in dist. THF (250 ml) and treated with $Bu_4NF \cdot 3\ H_2O$ (6.4 g, 20.28 mmol) at r.t. for 4 h. The mixture was concentrated *in vacuo* to 1/3 of its volume, diluted with $CHCl_3$ (500 ml), and transferred by cannula under vigorous stirring into H_2O (800 ml). The org. phase was separated, the aq. layer extracted with $CHCl_3$ (250 ml), the combined org. phase washed with $NaHCO_3$ and NaCl soln. (each 700 ml), dried (Na_2SO_4), and evaporated, and the residue dissolved in CH_2Cl_2/MeOH 9:1 and chromatographed by FC (13 × 5.5 cm, CH_2Cl_2/MeOH 9:1 (1 l) and 4:1, (0.5 l)). The obtained crude solid was dissolved in hot MeOH (30 ml), Et_2O (60 ml) was added, the mixture evaporated to 1/2 of its volume, cooled at −8° for 16 h, and the precipitate filtered off by suction, washed (Et_2O), and dried at 40°/high vacuum: **13** (3.65 g; 45% rel. to **10**). The mother liquor containing **13**/**14** was used without further purification for the next procedure.

Crystalline **13** (4.74 g, 12.4 mmol; isolated from the 15-g and a 5-g batch of **10**) was suspended together with the residue of the above mother liquor (**13**/**14**) in dist. THF (100 ml). NaOH (1N, 50 ml) was added and the emulsion stirred at r.t. for 3 d. Then, dist. THF (50 ml) and NaOH soln. (1N, 70 ml) were added once more, and the mixture was kept for another 2 d at r.t. under stirring. The mixture (pH 12.5) was neutralized with *Amberlite* (H^+) resin (*Amberlyst 15*, Fa. *Serva*), filtered, washed with H_2O and MeOH and evaporated. The residue was dissolved in H_2O and applied to a column of *Dowex 1 × 2* (OH^-) resin (17 × 3.5 cm, H_2O, H_2O/MeOH 1:1). The eluate was evaporated and the residue treated with hot MeOH (100 ml). Then $CHCl_3$ (60 ml) and H_2O (40 ml) were added. The mixture was concentrated to *ca.* 1/2 of its volume and cooled, and the precipitate collected by filtration, washed (Et_2O), and dried 40%/high vacuum: 3.18 g. Workup of the mother liquor finally yielded a total of 5.7 g (56%, 3 steps, rel. to **10**) of **14**. M.p. 170–173° ([32]: 175–176°). TLC (silica gel, i-PrOH/NH_3/H_2O 8:1:1): R_f 0.85. UV (MeOH): 259 (4.18). ^{1}H-NMR ((D$_6$)DMSO): 8.36 (*s*, H–C(8)); 8.12 (*s*, H–C(2)); 7.36–7.19 (*m*, 8 H, Ph, NH_2, HN–C(3′)); 5.96 (*d*, H–C(1′)); 5.89 (*d*, OH–C(2′)); 5.30 (*t*, OH–C(5′)); 4.57 (*m*, H–C(2′)); 3.92 (*m*, H–C(3′)); 3.78–3.70 (*m*, H–C(4′), PhCH_2); 3.55 (*m*, 1 H–C(5′)); 3.35 (*m*, 1 H–C(5′)). Anal. calc. for $C_{17}H_{20}N_6O_3 \cdot 0.5\ H_2O$ (365.4): C 55.88, H 5.79, N 23.00; found: C 56.15, H 5.63, N 23.19.

8. *9-(3-Amino-3-deoxy-β-*D*-ribofuranosyl)adenine (=3′-Amino-3′-deoxyadenosine*; **15**). To a soln. of **14** (1 g, 2.81 mmol) in 95% EtOH (120 ml) was added 5% Pd/C catalyst (700 mg). The suspension was vigorously stirred under H_2 (1 atm) for 4 days. The catalyst was filtered over *Celite* over a glass suction filter (*D4*), and the solid catalyst/*Celite* was then extracted with EtOH in a *Soxhlet* extractor for 48 h. The extract was evaporated and the residue applied to a column of *Dowex* 1 × 2 (OH^-) resin (15 × 3.5 cm, H_2O (1.4 l), H_2O/MeOH 1:9 (1 l), H_2O/MeOH 1:1 (1.5 l), and MeOH (2.5 l)). The product fraction was evaporated to 20 ml of the volume and cooled to −12°. The solid material was filtered off by suction and dried at 40°/high vacuum: **15** (514 mg, 69%). Colorless crystals. M.p. 262° ([29]: 259–261°). TLC (silica gel, i-PrOH/NH_3/H_2O 8:1:1): R_f 0.56. TLC

(silica gel, CH_2Cl_2/MeOH 6:1): R_f 0.37. UV (MeOH): 259 (4.14), 207 (4.22). ^{1}H-NMR ((D_6)DMSO): 8.37 (*s*, H–C(8)); 8.12 (*s*, H–C(2)); 7.29 (*s*, NH_2); 5.90 (*d*, H–C(1′)); 5.76 (br. *s*, OH–C(2′)); 5.17 (*t*, OH–C(5′)); 4.27 (*t*, H–C(2′)); 3.74–3.42 (*m*, 2 H–C(5′), H–C(3′), H–C(4′)); 1.68 (br. *s*, NH_2–C(3′)). Anal. calc. for $C_{10}H_{14}N_6O_3$ (266.3): C 45.11, H 5.30, N 31.56; found: C 44.68, H 5.31, N 31.72.

9. *1-Hexadecanoyl-3-methyl-1*H*-imidazolium Chloride* (**16**). To a soln. of hexadecanoyl chloride (2.75 g, 10 mmol) in dry DMF (80 ml), 1-methyl-1*H*-imidazole (820 mg, 10 mmol) in dry DMF (20 ml) was added at 0° within 10 min to form **16** as voluminous colourless precipitate. The mixture was stirred vigorously at 0° for further 15 min, filtered off by suction, washed with cooled Et_2O, and dried at 50°/high vacuum: 3.2 g (90%) of colourless powder. M.p. 162°. ^{1}H-NMR ((D_6)DMSO): 8.96 (*s*, 1 H); 7.58 (*s*, 1 H); 3.83 (*s*, Me); 2.17 (*t*, CH_2); 1.46 (*m*, CH_2); 1.22 (*s*, 12 CH_2); 0.84 (*t*, Me). Anal. calc. for $C_{20}H_{37}ClN_2O$ (357.0): C 67.29, H 10.45, N 7.85; found: C 67.20, H 10.43, N 7.76.

10. *3′-Deoxy-3′-(hexadecanoylamino)adenosine* (**17**). The susp. of **15** (250 mg, 0.94 mmol) in dry DMF (25 ml) was stirred at r.t. for 15 min, then **16** (400 mg, 1.12 mmol) was added and the mixture kept for 1 h at r.t. under vigorous stirring. During reaction, the precipitate was converted slowly into **17**. After 2 h, MeOH (25 ml) and H_2O (5 ml) were added. The mixture was stirred for further 10 min and filtered by suction and the solid washed with MeOH and Et_2O and dried (40°/high vacuum): 442 mg (93%) of **17**. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.43. UV(MeOH): 259 (4.14). ^{1}H-NMR ((D_6)DMSO): 8.40 (*s*, H–C(8)); 8.14 (*s*, H–C(2)); 7.89 (*d*, H–N(3′)); 7.33 (*s*, NH_2); 5.94 (*m*, H–C(1′), OH–C(2′)); 5.21 (*t*, OH–C(5′)); 4.45 (*m*, H–C(2′), H–C(3′)); 3.97 (*m*, H–C(4′)); 3.66 (*m*, 1 H–C(5′)); 3.51 (*m*, 1 H–C(5′)); 2.14 (*t*, CH_2); 1.47 (*m*, CH_2); 1.22 (*s*, $(CH_2)_{12}$); 0.84 (*t*, Me). Anal. calc. for $C_{26}H_{44}N_6O_4$ (504.7): C 61.88, H 8.79, N 16.65; found: C 62.09, H 8.85, N 16.07.

11. *3′-Deoxy-3′-(hexadecanoylamino)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**18**). A suspension of **17** (182 mg, 0.36 mmol) in abs. CH_2Cl_2 (3.6 ml) was stirred for 20 min at r.t. Then, 1-(trimethylsilyl)-1*H*-imidazole (268 mg, 1.91 mmol) was added. After 20 min of vigorous stirring, the mixture cleared, and after another 10 min, the soln. was evaporated. The residue was taken up in abs. toluene (50 ml) and washed twice with 1% KH_2PO_4 soln. (30 ml, pH 4.55). The org. phase was diluted with CH_2Cl_2 (10 ml), dried (Na_2SO_4), and evaporated. For *N*^{6}-acylation, the residue was taken up in dry CH_2Cl_2 (5 ml), and 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride [33] (170 mg, 0.54 mmol) was added. After stirring at r.t. over night, the soln. was separated from the unsoluble reagent by suction. The residual sirup was dissolved in pyridine (4 ml), H_2O (2 ml) was added, and the emulsion was stirred at r.t. for 24 h, evaporated, and co-evaporated with toluene (3 × 20 ml) to remove pyridine. The residue was crystallized from MeOH (10 ml): 220 mg (87%) of colourless crystals. M.p. 167–169°. TLC (CH_2Cl_2/MeOH 19:1): R_f 0.25. UV (MeOH): 298 (sh, 3.59), 272 (sh, 4.39), 267 (4.42), 208 (sh, 4.49). ^{1}H-NMR ((D_6)DMSO): 10.61 (*s*, NH); 8.73 (*s*, H–C(8)); 8.62 (*s*, H–C(2)); 8.16 (*d*, 2 H *o* to NO_2); 7.90 (*d*, H–N(3′)); 7.62 (*d*, 2 H *m* to NO_2); 6.05 (*m*, H–C(1′)); 6.03 (*d*, OH–C(2′)); 5.12 (*t*, OH–C(5′)); 4.48 (*m*, H–C(2′), H–C(3′)); 4.39 (*t*, OCH_2CH_2); 3.99 (*m*, H–C(4′)); 3.70 (*m*, H–C(5′)); 3.53 (*m*, 1 H–C(5′)); 3.11 (*t*, OCH_2CH_2); 2.12 (*dt*, CH_2); 1.47 (*m*, CH_2); 1.22 (*s*, $(CH_2)_{12}$); 0.83 (*t*, Me). Anal. calc. for $C_{35}H_{51}N_7O_8$ (697.8): C 60.24, H 7.37, N 14.05; found: C 60.57, H 7.56, N 13.85.

12. *3′-Deoxy-3′-(hexadecanoylamino)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**18**) *and 3′-Deoxy-3′-(hexadecanoylamino)-*N^6*-(methoxycarbonyl)-adenosine* (**19**). As described for **18**, with **17** (252 mg, 0.5 mmol), 1-(trimethylsilyl)-1*H*-imidazole (383 mg, 2.73 mmol) in abs. CH_2Cl_2 (5 ml), 30 min, r.t., extraction with toluene (80 ml) and 1% KH_2PO_4 soln. (pH 4.55; 2 × 100 ml), evaporation. *N*^{6}-Acylation, with 3-methyl-1-[2-(4-nitrophenyl)ethoxycarbonyl]-1*H*-imidazol-3-ium chloride [33] (234 mg, 0.75 mmol) in abs. CH_2Cl_2 (10 ml), 18 h, r.t., filtration by suction, evaporation. For desilylation, the residue was dissolved in MeOH (15 ml), Et_3N (2 ml) added, the mixture stirred for 3 h at r.t. and then evaporated, and the residue crystallized from MeOH (20 ml): **18** (202 mg, 58%). The mother liquor was evaporated, purified by FC (silica gel, 5 × 2 cm, $CHCl_3$ and 1–2% MeOH/$CHCl_3$), and crystallized from MeOH: **18** (total 266 mg, 76%) and **19** (10 mg, 4%). Colourless crystals.

Data of **19**: M.p. 202–204°. TLC (CH_2Cl_2/MeOH 19:1): R_f 0.17. UV (MeOH): 272 (sh, 4.21), 266 (4.27). ^{1}H-NMR ((D_6)DMSO): 10.59 (*s*, NH); 8.73 (*s*, H–C(8)); 8.63 (*s*, H–C(2)); 7.90 (*d*, H–N(3′)); 6.05 (*m*, H–C(1′)); 6.02 (*d*, OH–C(2′)); 5.13 (*t*, OH–C(5′)); 4.48 (*m*, H–C(2′), H–C(3′)); 4.00 (*m*, H–C(4′)); 3.70 (*s*, MeO); 3.56–3.40 (*m*, 2 H–C(5′)); 2.14 (*t*, CH_2); 1.48 (*m*, CH_2); 1.22 (*s*, $(CH_2)_{12}$); 0.84 (*t*, Me). Anal. calc. for $C_{28}H_{46}N_6O_6$ (562.7): C 59.77, H 8.24, N 14.94; found: C 59.43, H 8.03, N 14.56.

13. *3′-Deoxy-3′-(hexadecanoylamino)-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**20**). To a soln. of **18** (520 mg, 0.745 mmol; co-evaporated 3 times with abs. pyridine (15 ml)) in abs. pyridine (12 ml), monomethoxytrityl chloride (MeOTrCl) (414 mg, 1.34 mmol) was added and kept at r.t. for 19 h. The mixture was diluted with $CHCl_3$ (100 ml), washed with phosphate buffer (pH 6.88; 2 × 80 ml), dried (Na_2SO_4), and evaporated. After co-evaporation with toluene (3 × 30 ml), the residue was taken up in little

$CHCl_3$ and purified by FC (silica gel, 11 × 2.5 cm, $CHCl_3$ (150 ml), 1% MeOH/$CHCl_3$ (500 ml)): 638 mg (88%) of **20**. Amorphous solid. TLC (CH_2Cl_2/MeOH 19:1): R_f 0.54. UV (MeOH): 296 (sh, 3.62), 272 (sh, 4.42), 267 (4.46), 234 (4.30). ^{1}H-NMR ($CDCl_3$): 8.69 (*s*, H–C(8)); 8.20 (*s*, H–C(2)); 8.16 (*d*, 2 H *o* to NO_2); 8.13 (*s*, NH); 7.42 (*d*, 2 H *m* to NO_2); 7.31–7.16 (*m*, 12 H, MeO*Tr*); 6.75 (*d*, 2 H *m* to MeO); 6.20 (*d*, H–N(3′)); 6.00 (*d*, H–C(1′)); 5.14 (*d*, OH–C(2′)); 4.89 (*m*, H–C(2′)); 4.56 (*m*, H–C(3′)); 4.52 (*t*, OC*H*$_2$CH$_2$; 4.42 (*m*, H–C(4′)); 3.75 (*s*, MeO); 3.46 (*m*, 2 H–C(5′)); 3.14 (*t*, OCH$_2$C*H*$_2$); 2.19 (*t*, CH_2); 1.57 (*m*, CH_2); 1.23 (*s*, $(CH_2)_{12}$); 0.85 (*t*, Me). Anal. calc. for $C_{55}H_{67}N_7O_9$ (970.2): C 68.09, H 6.96, N 10.11; found: C 67.94, H 7.03, N 10.02.

14. *2′*-O-*[(*tert*-Butyl)dimethylsilyl]-3′-deoxy-3′-(hexadecanoylamino)*-5′-O-*(monomethoxytrityl)*-N^6-*[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**21**). In abs. pyridine (20 ml), **20** (560 mg, 0.577 mmol) was dried by 2 co-evaporations. The residue was dissolved in abs. pyridine (15 ml), (*t*-Bu)Me$_2$SiCl (1.04 g, 6.92 mmol; 12-fold excess) and 1*H*-imidazole (943 mg, 13.85 mmol, 20-fold excess) were added, and after stirring at r.t. for 2 days, the mixture was partitioned between $CHCl_3$ (80 ml) and phosphate buffer (pH 7, 100 ml). The aq. layer was washed with $CHCl_3$ (3 × 60 ml), the combined org. phase dried (Na_2SO_4), evaporated, and co-evaporated with toluene (3 × 40 ml), and the residue purified by FC (15 × 2.5 cm, $CHCl_3$ (250 ml)): **21** (592 mg, 95%). Colourless foam. TLC (toluene/AcOEt 1:1): R_f 0.42. UV (MeOH): 294 (sh, 3.65), 272 (sh, 4.42), 267 (4.46). ^{1}H-NMR ($CDCl_3$): 8.69 (*s*, H–C(8)); 8.22 (*s*, H–C(2)); 8.17 (*d*, 2 H *o* to NO_2); 8.05 (*s*, NH); 7.46–7.17 (*m*, 14 H, 2 H *m* to NO_2, MeO*Tr*); 6.80 (*d*, 2 H *o* to MeO); 6.06 (*d*, H–C(1′)); 5.75 (*d*, H–N(3′)); 4.72–4.67 (*m*, H–C(2′), H–C(3′)); 4.52 (*t*, OC*H*$_2$CH$_2$); 4.18 (*m*, H–C(4′)); 3.76 (*s*, MeO); 3.49 (*m*, 2 H–C(5′)); 3.14 (*t*, OCH$_2$C*H*$_2$); 2.12 (*t*, CH_2); 1.54 (*m*, CH_2); 1.23 (*s*, $(CH_2)_{12}$); 0.89 (*s*, *t*-BuSi); 0.85 (*t*, Me); 0.10 (*s*, MeSi); 0.06 (*s*, MeSi). Anal. calc. for $C_{61}H_{81}N_7O_9Si$ (1084.4): C 67.56, H 7.53, N 9.04; found: C 67.36, H 7.64, N 8.80.

15. *2′*-O-*[(*tert*-Butyl)dimethylsilyl]-3′-deoxy-3′-(hexadecanoylamino)*-N^6-*[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* (**22**). Compound **21** (592 mg, 0.546 mmol) and 2% TsOH in CH_2Cl_2/MeOH 4:1 (12 ml) were stirred at r.t. After 30 min, the mixture was diluted with $CHCl_3$ (80 ml), washed with phosphate buffer (pH 6.88; 150 ml), dried (Na_2SO_4), and evaporated, and the residue submitted to FC (15 × 2.5 cm, $CHCl_3$ (200 ml), 1% MeOH/$CHCl_3$ (400 ml)): 396 mg (89%) of **22**. Colourless foam. TLC (CH_2Cl_2/MeOH 19:1): R_f 0.52. UV (MeOH): 286 (sh, 3.92), 271 (sh, 4.41), 267 (4.44), 212 (sh, 4.51). ^{1}H-NMR ($CDCl_3$): 8.72 (*s*, H–C(8)); 8.29 (br. *s*, NH); 8.28 (*s*, H–C(2)); 8.16 (*d*, 2 H *o* to NO_2); 7.42 (*d*, 2 H *m* to NO_2); 6.09 (*d*, H–N(3′)); 5.90 (*d*, H–C(1′)); 4.81 (*m*, OH–C(5′), H–C(2′)); 4.52 (*t*, OC*H*$_2$CH$_2$); 4.46 (*m*, H–C(3′)); 4.26 (*m*, H–C(4′)); 3.91 (*m*, 2 H–C(5′)); 3.14 (*t*, OCH$_2$C*H*$_2$); 2.22 (*t*, CH_2); 1.64 (*t*, CH_2); 1.23 (*s*, $(CH_2)_{12}$); 0.86 (*s*, *t*-Bu); 0.83 (*t*, Me); –0.01 (*s*, MeSiC); –0.04 (*s*, MeSi). Anal. calc. for $C_{41}H_{65}N_7O_8Si$ (812.1): C 60.64, H 8.07, N 12.07; found: C 60.92, H 8.30, N 11.83.

16. *3′-Deoxy-5′-*O*-(monomethoxytrityl)*-N^6-*[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-[2′-{O^P-[2-(4-nitrophenyl)ethyl]}-5′]-2′-*O-*[(*tert*-butyl)dimethylsilyl]-3′-deoxy-3′-(hexadecanoylamino)*-N^6-*[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* ((MeOTr)(npeoc)^{6}A$_{d3'}$*φ*(npeoc)^{6}A$_{d3'}$(NHpalm)$^{3'}$(tbdms)$^{2'}$; **25**). A soln. (4 ml) of abs. MeCN/CH_2Cl_2 5:3, **22** (200 mg, 0.246 mmol), 3′-deoxy-5′-*O*-(monomethoxytrityl)-*N*^{6}-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 2′-[2-(4-nitrophenyl)ethyl diisopropylphosphoramidite] (**23**) [6] (448 mg, 0.442 mmol) and 1*H*-tetrazole (62 mg, 0.884 mmol) under N_2 was stirred for 2.75 h. Then I_2/H_2O/pyridine (0.5 g of I_2 in 5 ml of pyridine/H_2O/CH_2Cl_2 3:1:1) was added dropwise until the brown colour persisted. The mixture was stirred for further 10 min, diluted with $CHCl_3$ (80 ml), washed twice with $Na_2S_2O_3$/NaCl soln. (80 ml), dried (Na_2SO_4), evaporated, and co-evaporated with toluene (3 × 20 ml). Purification by FC (silica gel, 10 × 1.5 cm, $CHCl_3$, 1% MeOH/$CHCl_3$ 2% MeOH/$CHCl_3$) gave colourless amorphous **25** (428 mg, 100%). TLC (CH_2Cl_2/MeOH 19:1): R_f 0.63. UV (MeOH): 299 (sh, 4.01), 272 (sh, 4.76), 267 (4.80), 237 (sh, 4.49). ^{1}H-NMR ($CDCl_3$): 8.71 (*s*, H–C(8)); 8.64, 8.59 (2*s*, H–C(8)); 8.22–8.01 (*m*, 10 H, 2 × H–C(2), 2 NH, 3 × 2 H*o* to NO_2); 7.47–7.19 (*m*, 18 H, 3 × 2 H *m* to NO_2, MeO*Tr*); 6.79 (*m*, H–N(3′), 2 H *o* to MeO); 6.30, 6.20 (2*s*, H–C(1′)); 5.98 (*s*, H–C(1′)); 5.91 (*t*, H–C(2′)); 5.56, 5.47 (2 *t*, H–C(2′)); 4.68–4.18 (*m*, 11 H, H–C(3′), 2 OC*H*$_2$CH$_2$ (npeoc), POC*H*$_2$CH$_2$, 2 H–C(4′), 2 × 1 H–C(5′)); 3.78 (*s*, MeO); 3.38 (*m*, 2 × 1 H–C(5′)); 3.13 (*m*, 2 OCH$_2$C*H*$_2$ (npeoc), POCH$_2$C*H*$_2$); 2.61–2.08 (*m*, H–C(3′), CH_2); 1.51 (*m*, CH_2); 1.23 (2*s*, $(CH_2)_{12}$); 0.92 (*s*, *t*-Bu); 0.87 (*s*, Me); 0.12 (2*s*, MeSi); 0.08 (*s*, MeSi). Anal. calc. for $C_{88}H_{107}N_{14}O_{20}PSi$ (1740.0): C 60.75, H 6.20, N 11.27; found: C 60.81, H 6.19, N 10.98.

17. *3′-*O*-[(*tert*-Butyl)dimethylsilyl]-5′-*O*-(monomethoxytrityl)*-N^6-*[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-[2′-{O^P-[2-(4-nitrophenyl)ethyl]}-5′]-2′-*O-*[(*tert*-butyl)dimethylsilyl]-3′-deoxy-3′-(hexadecanoylamino)*-N^6-*[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* ((MeOTr)(npeoc)^{6}A(tbdms)$^{3'}$*φ*(npeoc)^{6}A$_{d3'}$(NHpalm)$^{3'}$-(tbdms)$^{2'}$; **26**). As described for **25**, with **22** (250 mg, 0.308 mmol), abs. MeCN (3.1 ml), abs. CH_2Cl_2 (1.9 ml), 1*H*-tetrazole (78 mg, 1.108 mmol), and 3′-*O*-[(*tert*-butyl)dimethylsilyl]-5′-*O*-(monomethoxytrityl)-*N*^{6}-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine 2′-[2-(4-nitrophenyl)ethyl diisopropylphosphoramidite] (**24**) [6]

(633 mg, 0.554 mmol) under N_2 for 2.25 h at r.t. Oxidation with I_2/pyridine/H_2O, extraction with $CHCl_3$ and $Na_2S_2O_3$/NaCl soln., drying (Na_2SO_4), purification by FC (silica gel, 11 × 1.5 cm, $CHCl_3$ (100 ml) 1% MeOH/$CHCl_3$ (200 ml)) gave 571 mg (99%) of **26**. Colourless foam. TLC (CH_2Cl_2/MeOH 19:1): R_f 0.56. UV (MeOH): 285 (sh, 4.40), 273 (sh, 4.73), 267 (4.77), 240 (sh, 4.47), 212 (sh, 4.94). ^{1}H-NMR ($CDCl_3$): 8.71–8.63 (*m*, 2 × H–C(8)); 8.39–7.90 (*m*, 10 H, 3 × 2 H *o* to NO_2, 2 × H–C(2), 2 NH); 7.46–7.07 (*m*, 18 H, 3 × 2 H *m* to NO_2, MeO*Tr*); 6.75 (2*d*, 2 H *o* to MeO); 6.32; 6.22 (2*d*, H–C(1′)); 5.93–5.80 (*m*, H–C(1′), H–N(3′)); 5.65 (*m*, H–C(2′)); 4.79–3.84 (*m*, 13 H, H–C(2′), 2 OCH_2CH$_2$ (npeoc), POCH_2CH$_2$, 2 × H–C(3′), 2 × 1 H H–C(4′), 2 × 1 H–C(5′)); 3.74, 3.73 (2*s*, MeO); 3.52–2.52 (*m*, 8 H, 2 × 1 H–C(5′), 2 CH$_2$CH_2 (npeoc), POCH$_2$CH_2); 2.09 (*m*, CH$_2$); 1.53 (*m*, CH$_2$); 1.21 (*s*, (CH$_2$)$_{12}$); 0.88 (2*s*, *t*-Bu); 0.84 (*s*, Me); 0.79 (2*s*, *t*-Bu); 0.07 to 0.03 (*m*, 2 MeSi). Anal. calc. for $C_{94}H_{121}N_{14}O_{21}PSi_2$ (1870.2): C 60.37, H 6.52, N 10.48; found: C 60.60, H 6.66, N 10.11.

18. *3′-Deoxy*-N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}-5′}-2′*-O-*[(*tert*-butyl)dimethylsilyl]-3′-deoxy-3′-(hexadecanoylamino)*-N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* ((npeoc)^{6}A$_{d^3}$*φ*(npeoc)^{6}A$_{d^3}$(NHpalm)$^{3'}$(tbdms)$^{2'}$; **27**). Compound **25** (369 mg, 0.212 mmol) was stirred at r.t. in CH_2Cl_2/MeOH 4:1 (4.5 ml) containing 2% of TsOH · H_2O for 20 min. Then, the mixture was diluted with $CHCl_3$ (40 ml) and washed with phosphate buffer (pH 6.8; 2 × 50 ml), the aq. phase re-extracted with $CHCl_3$ (3 × 40 ml), the combined org. layer dried (Na_2SO_4) and evaporated, and the residue purified by FC (silica gel, 11 × 1.5 cm, $CHCl_3$ (50 ml), 1% MeOH and 2% MeOH/$CHCl_3$ (each 200 ml)): 283 mg (91%) of **27**. Amorphous solid. TLC (CH_2Cl_2/MeOH 19:1): R_f 0.44. UV (MeOH): 297 (sh, 4.08), 271 (sh, 4.77), 267 (4.80), 208 (sh, 4.87). ^{1}H-NMR ($CDCl_3$): 8.78–8.69 (*m*, 2 × H–C(8)); 8.49–8.03 (*m*, 10 H, 3 × 2 H *o* to NO_2, 2 × H–C(2), 2 NH); 7.46 (*d*, 2 H *m* to NO_2); 7.45 (*d*, 2 H *m* to NO_2); 7.29 (*d*, 2 H *m* to NO_2); 6.13–5.85 (*m*, 2 × H–C(1′), H–N(3′)); 5.42 (*m*, H–C(2′)); 5.18, 4.84 (2*m*, H–C(2′)); 4.72–3.97 (*m*, 12 H, OH–C(5′), 2 OCH_2CH$_2$ (npeoc), POCH_2CH$_2$, H–C(3′), 2 × 1 H–C(4′), 2 × 1 H–C(5′)); 3.61 (*m*, 2 × 1 H–C(5′)); 3.18 (*m*, 2 OCH$_2$CH_2 (npeoc)); 2.94 (*m*, POCH$_2$CH_2); 2.70, 2.36 (2*m*, H–C(3′)); 2.16 (*m*, CH$_2$); 1.59 (*m*, CH$_2$); 1.24 (*s*, (CH$_2$)$_{12}$); 0.94 (2*s*, *t*-Bu); 0.87 (*t*, Me); 0.20 (*s*, MeSi); 0.15 (*s*, MeSi); 0.14 (*s*, MeSi); 0.10 (*s*, MeSi). ^{31}P-NMR ($CDCl_3$): −1.58; −1.75. Anal. calc. for $C_{68}H_{91}N_{14}O_{19}PSi$ (1467.6): C 55.65, H 6.25, N 13.36; found: C 55.50, H 6.27, N 13.19.

19. *3′*-O-*[(*tert*-Butyl)dimethylsilyl]*-N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-{2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}-5′}-2′*-O-*[(*tert*-butyl)dimethylsilyl]-3′-deoxy-3′-(hexadecanoylamino)*-N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* ((npeoc)^{6}A(tbdms)$^{3'}$*φ*(npeoc)^{6}A$_{d^3}$(NHpalm)$^{3'}$(tbdns)$^{2'}$; **28**). As described for **27**, with **26** (528 mg, 0.282 mmol) and CH_2Cl_2/MeOH 4:1 (6 ml) containing 2% of TsOH · H_2O. After stirring for 20 min at r.t. and workup with $CHCl_3$ (80 ml) and phosphate buffer (pH 6.8, 2 × 50 ml), FC (silica gel, 11 × 1.5 cm, $CHCl_3$ (100 ml), 1% MeOH/$CHCl_3$ (200 ml)) gave **28** (392 mg, 87%). Amorphous solid. TLC (CH_2Cl_2/MeOH 19:1): R_f 0.45. UV (MeOH): 285 (sh, 4.37), 270 (sh, 4.77), 267 (4.79). ^{1}H-NMR ($CDCl_3$): 8.87–7.94 (*m*, 12 H, 2 × H–C(8), 2 × H–C(2), 2 NH, 3 × 2 H *o* to NO_2); 7.44 (*m*, 2 × 2 H *m* to NO_2); 7.20, 7.09 (2*d*, 2 H *m* to NO_2); 6.15–5.49 (*m*, 4 H, 2 × H–C(1′), H–C(2′), H–N(3′)); 4.70–3.66 (*m*, 16 H, H–C(2′), 2 × H–C(3′), 2 OCH_2CH$_2$ (npeoc), POCH_2CH$_2$, 2 × H–C(4′), 2 × 2 H–C(5′), OH–C(5′)); 3.15 (*q*, 2 OCH$_2$CH_2); 2.81–2.08 (*m*, POCH$_2$CH_2, CH$_2$); 1.58 (*m*, CH$_2$); 1.22 (*s*, (CH$_2$)$_{12}$); 0.93–0.82 (*m*, 21 H, 2 *t*-Bu, Me); 0.20–0.03 (*m*, 2 SiMe$_2$). ^{31}P-NMR ($CDCl_3$): −0.96, −1.27. Anal. calc. for $C_{74}H_{105}N_{14}O_{20}PSi_2$ (1597.9): C 55.62, H 6.62, N 12.27; found: C 55.53, H 6.75, N 12.11.

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′}-2′*-O-*[(*tert*-butyl)dimethylsilyl]-3′-deoxy-3′-(hexadecanoylamino)*-N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* ((MeOTrO)(npeoc)^{6}A$_{d^3}$*φ*(npeoc)^{6}A$_{d^3}$*φ*(npeoc)^{6}A$_{d^3}$(Nhpalm)$^{3'}$(tbdms)$^{2'}$; **29**). To a soln. of **27** (100 mg, 0.068 mmol) in abs. MeCN (2 ml) and abs. CH_2Cl_2 (1 ml), 1*H*-tetrazole (17 mg, 0.244 mmol) and **23** [6] (124 mg, 0.122 mmol) were added under N_2. At r.t., the mixture was stirred for 3 h, oxidized with I_2/H_2O/pyridine (I_2 (0.5 g) in pyridine/H_2O/CH_2Cl_2 3:1:1 (5 ml)), then stirred for another 15 min, diluted with $CHCl_3$ (60 ml), and washed twice with sat. $Na_2S_2O_3$/NaCl soln. (50 ml). The aq. phase was re-extracted with $CHCl_3$ (3 × 40 ml), the combined org. phase dried (Na_2SO_4), evaporated, and co-evaporated with toluene (3 × 20 ml), and the residue purified by FC (silica gel, 9 × 1.5 cm, $CHCl_3$ (50 ml), 2% MeOH/$CHCl_3$ (200 ml)). The trimer fractions were evaporated and dried (30°/high vacuum): 157 mg (96%) of fully protected **29**. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.36. UV (MeOH): 285 (sh, 4.60), 271 (sh, 4.93), 267 (4.96), 243 (sh, 4.65), 209 (sh, 5.14). Anal. calc. for $C_{115}H_{133}N_{21}O_{31}P_2Si$ (2395.5): C 57.66, H 5.60, N 12.28; found: C 57.46, H 5.63, N 11.85.

21. *3′*-O-*[(*tert*-Butyl)dimethylsilyl]-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-*[(*tert*-butyl)dimethylsilyl]-3′-deoxy-3′-(hexadecanoylamino)*-N^6*-[2-(4-nitrophe-*

nyl)ethoxycarbonyl]adenosine ((MeOTr)(npeoc)^{6}A(tbdms)$^{3'}\varphi$(npeoc)^{6}A$_{d^3}\varphi$(npeoc)^{6}A$_{d^3}$(NHpalm)$^{3'}$(tbdms)$^{2'}$; **30**). As described for **29**, with **27** (100 mg, 0.068 mmol), **24** [6] (140 mg, 0.122 mmol), and 1*H*-tetrazole (17 mg, 0.244 mmol) in a soln. (3 ml) of abs. MeCN/CH_2Cl_2 2:1 under N_2 (3 h, r.t.). FC (silica gel, 10 × 1.5 cm, $CHCl_3$ (50 ml), 2% MeOH/$CHCl_3$ (200 ml)) gave **30** (157 mg, 91%). TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.44. UV (MeOH): 286 (sh, 4.59), 271 (sh, 4.94), 267 (4.97), 243 (sh, 4.66). Anal. calc. for $C_{121}H_{147}N_{21}O_{32}P_2Si_2 \cdot H_2O$ (2543.8): C 57.13, H 5.90, N 11.56; found: C 56.85, H 5.74, N 11.52.

22. *3′-Deoxy-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-[2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}-5′]-3′-*O*-[(*tert*-butyl)dimethylsilyl]-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-[2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}-5′]-2′-*O*-[(*tert*-butyl)dimethylsilyl]-3′-deoxy-3′-(hexadecanoylamino)-*N^6*-[2-(4-nitrophenyl)-ethoxycarbonyl]adenosine* ((MeOTr)(npeoc)^{6}A$_{d^3}\varphi$(npeoc)^{6}A(tbdms)$^{3'}\varphi$(npeoc)^{6}A$_{d^3}$(NHpalm)$^{3'}$(tbdns)$^{2'}$; **31**). As described for **29**, with **28** (120 mg, 0.075 mmol), **23** [6] (137 mg, 0.135 mmol), and 1*H*-tetrazole (19 mg, 0.27 mmol) in abs. MeCN (2.4 ml) and abs. CH_2Cl_2 (1.2 ml) for 3 h at r.t. (N_2). Oxidation with I_2/pyridine/H_2O, and workup with $CHCl_3$ (80 ml) and $Na_2S_2O_3$/NaCl soln. (2 × 60 ml). FC (silica gel, 10 × 1.5 cm), $CHCl_3$ (50 ml), 2% MeOH/$CHCl_3$ (200 ml)) gave the fully protected **31** (184 mg, 97%). Amorphous solid. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.52. UV (MeOH): 285 (sh, 4.51), 272 (sh, 4.85), 267 (4.88), 240 (sh, 4.53), 208 (sh, 5.06). Anal. calc. for $C_{121}H_{147}N_{21}O_{32}P_2Si_2$ (2525.7): C 57.54, H 5.87, N 11.65; found: C 57.47, H 6.01, N 11.46.

23. *3′-*O*-[(*tert*-Butyl)dimethylsilyl]-5′-*O*-(monomethoxytrityl)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenylyl-[2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}-5′]-3′-*O*-[(*tert*-butyl)dimethylsilyl]-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]-adenylyl-[2′-{*O^P*-[2-(4-nitrophenyl)ethyl]}-5′]-2′-*O*-[(*tert*-butyl)dimethylsilyl]-3′-deoxy-3′-(hexadecanoylamino)-*N^6*-[2-(4-nitrophenyl)ethoxycarbonyl]adenosine* ((MeOTr)(npeoc)^{6}A(tbdms)$^{3'}\varphi$(npeoc)^{6}A(tbdms)$^{3'}\varphi$(npeoc)^6-A$_{d^3}$(NHpalm)$^{3'}$2′ **32**). As described for **29**, with **28** (120 mg, 0.075 mmol), **24** [6] (154 mg, 0.135 mmol), and 1*H*-tetrazole (19 mg, 0.27 mmol) in abs. MeCN/abs. CH_2Cl_2 2:1 (3.6 ml) under N_2 (4.5 h, r.t.). Oxidation with I_2/pyridine/H_2O, extraction with $CHCl_3$ (80 ml) and $Na_2S_2O_3$/NaCl soln. (2 × 60 ml), and purification by FC (silica gel, 11 × 1.5 cm $CHCl_3$ (100 ml), 2% MeOH/$CHCl_3$ (150 ml)) gave **32** (188 mg, 94%). Colorless foam. TLC (toluene/AcOEt/ MeOH 5:4:1): R_f 0.61. UV (MeOH): 286 (sh, 4.52), 271 (sh, 4.89), 267 (4.92), 242 (sh, 4.61), 208 (sh, 5.11). Anal. calc. for $C_{127}H_{161}N_{21}O_{33}P_2Si_3 \cdot H_2O$ (2674.0): C 57.05, H 6.14, N 11.00; found: C 56.82, H 6.24, N 11.01.

24. *3′-Deoxyadenylyl-(2′–5′)-3′-deoxyadenylyl-(2′–5′)-3′-deoxy-3′-(hexadecanoylamino)adenosine* (A$_{d^3}$-(2′–5′)A$_{d^3}$(2′–5′)A$_{d^3}$(NHpalm)$^{3'}$; **33**). At r.t., the soln. of **29** (70 mg, 29 mmol) in 0.5M DBU/MeCN (5.8 ml) was stirred for 24 h, then neutralized with 1M AcOH in MeCN (2.9 ml), stirred for another 15 min, and finally diluted with CH_2Cl_2 (2 ml) to dissolve the precipitate. TLC (silica gel, *Polygam* plates, AcOEt/(i-PrOH/NH_3/H_2O 7:1:2) 1:1): R_f 0.31. To split off the (*tert*-butyl)dimethylsilyl groups, the soln. was evaporated, $Bu_4NF \cdot 3\ H_2O$ (316 mg, 1 mmol) in THF (1 ml) added, and the mixture stirred for 41 h at r.t. and evaporated. TLC (cellulose, i-PrOH/NH_3/H_2O 8:1:1): R_f 0.68. The residue was washed several times with MeCN and lyophilized from MeOH/H_2O 1:1 (20 ml). The (MeOTr)A$_{d^3}$(2′–5′)A$_{d^3}$(2′–5′)A$_{d^3}$(NHpalm)$^{3'}$ was then detritylated with AcOH (4 ml) in MeOH (0.5 ml) and H_2O (0.5 ml) for 24 h at r.t., the mixture evaporated, and co-evaporated with MeOH/H_2O 1:1 (8 × 5 ml), and the residue lyophilized from dioxane/H_2O 2:1, then washed several times with MeCN, and lyophilized from EtOH/H_2O: **33** (8.6 mg). Colourless powder. TLC (cellulose, i-PrOH/NH_3/H_2O 8:1:1): R_f 0.56. ^{31}P-NMR ((D$_6$)DMSO): −1.52. HPLC: t_R 32.17 min (*Fig. 1*): FAB-MS 1154 [M + H + Na]$^+$.

25. *Adenylyl-(2′–5′)-3′-deoxyadenylyl-(2′–5′)-3′-deoxy-3′-(hexadecanoylamino)adenosine* (A(2′–5′)A$_{d^3}$(2′–5′)-A$_{d^3}$(NHpalm)$^{3'}$; **34**). As described for **33**, with **30** (70 mg, 27.7 mmol), 0.5M DBU/MeCN (5.5 ml), r.t., 25 h, 1M AcOH/MeCN (2.75 ml), 30 min. TLC (silica gel, *Polygam* plates, AcOEt/(i-PrOH/NH_3/H_2O 7:1:2) 1:1): R_f 0.41. $Bu_4NF \cdot 3\ H_2O$ (631 mg, 2 mmol) in THF (3 ml), 28 h at r.t. and 2 d at 8°. Then, the mixture was diluted with $CHCl_3$ (25 ml) and washed with sat. NaCl soln. (25 ml). The aq. phase was washed with $CHCl_3$ (2 × 20 ml). The combined org. layer was dried (Na_2SO_4) and evaporated. The residue was digested with MeCN (10 ml) and centrifuged (3000 r/min, 15 min) and the soln. decanted. The powder was washed twice with MeCN (centrifugation) and finally dissolved in MeOH (2 ml). TLC (cellulose, i-PrOH/NH_3/H_2O 8:1:1): R_f 0.64. AcOH (4 ml) and H_2O (0.5 ml) were added, the mixture was stirred at r.t. for 25 h, evaporated to 1/2 of its volume, and co-evaporated with MeOH (3 × 10 ml). The residue was treated with MeCN (10 ml), centrifuged (15 min, 3000 r/min), decanted and washed with H_2O (10 ml) and Et_2O (2 × 10 ml): **34** (10.8 mg) after drying (40°/high vacuum). Colourless powder. TLC (cellulose, i-PrOH/NH_3/H_2O 8:1:1): R_f 0.57. HPLC: t_R 32.69 min. FAB-MS: 1169 [M^+ H + Na]$^+$ (see *Fig. 2*).

26. *3′-Deoxyadenylyl-(2′–5′)-adenylyl-(2′–5′)-3′-deoxy-3′-(hexadecanoylamino)adenosine* (A$_{d^3}$(2′–5′)A(2′–5′)-A$_{d^3}$(NHpalm)$^{3'}$; **35**). As described for **33**, with **31** (70 mg, 27.7 mmol), 0.5M DBU/MeCN (5.5 ml), r.t., 40 h, 1M

AcOH/MeCN (2.75 ml), 30 min. TLC (silica gel, *Polygam* plates, AcOEt/(i-PrOH/NH_3/H_2O 7:1:2) 1:1): R_f 0.52. $Bu_4N \cdot 3\ H_2O$ (631 mg, 2 mmol) in THF (2 ml), 4 d at r.t., final evaporation. The residue was extracted with $CHCl_3$ (40 ml) and H_2O (40 ml), the aq. phase washed with $CHCl_3$ (2×30 ml), and the combined org. phase evaporated. The sirupy residue was washed with MeCN (3×2 ml) to give a colourless precipitate. TLC (cellulose, i-PrOH/NH_3/H_2O 8:1:1): R_f 0.79. MeOH (0.5 ml), H_2O (0.5 ml) and AcOH (4 ml) were added, and the mixture was stirred at r.t. for 24 h and co-evaporated with MeOH/H_2O (1:1, 5×10 ml) and NH_3/H_2O ($3 \times$ 5 ml). The residue was washed several times with EtOH and MeCN and lyophilized from H_2O: **35** (17 mg). Colourless powder. TLC (cellulose, *i*-PrOH/NH_3/H_2O 8:1:1): R_f 0.54. UV (MeOH): 259 (4.55). HPLC: t_R 31.52 min. FAB-MS: 1147 $[M+H]^+$, 1169 $[M+Na]^+$ (*Fig. 2*).

27. *Adenylyl-(2′–5′)-adenylyl-(2′–5′)-3′-deoxy-3′-(hexadecanoylamino)adenosine* ($A(2'-5')A(2'-5')A_{d3'}$-(NHpalm)$^{3'}$; **36**). As described for **33**, with **32** (70 mg, 26.4 mmol), 0.5M DBU/MeCN (5.3 ml), r.t., 24 h, 1M AcOH/MeCN (2.65 ml), 30 min. TLC (silica gel, *Polygam* plates, AcOEt/(i-PrOH/NH_3/H_2O 7:1:2) 1:1): R_f 0.59. $Bu_4NF \cdot 3\ H_2O$ (947 mg, 3 mmol) in THF (5 ml), 3 d at r.t., final evaporation. TLC (cellulose; i-PrOH/NH_3/H_2O 8:1:1): R_f 0.77. MeOH (0.5 ml), H_2O (0.5 ml), and AcOH (4 ml) were added, the mixture was stirred at r.t. for 23 h, evaporated, co-evaporated with MeOH/H_2O 1:1 (4×15 ml), and washed several times with EtOH. The residue was lyophilized from NH_3/H_2O: **36** (8.5 mg). Colourless powder. TLC (cellulose, *i*-PrOH/NH_3/H_2O 8:1:1): R_f 0.48. HPLC: t_R 32.14 min (*Fig. 1*). FAB-MS: 1164 $[M+H]^+$, 1185 $[M+Na]^+$.

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