Synthesis of Thymidine, Uridine, and 5-Methyluridine Nucleolipids: Tools for a Tuned Lipophilization of Oligonucleotides

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Dedicated to Prof. Dr. *Jürgen Liebscher*, Berlin, and Cluj, Romania

Three pyrimidine nucleosides, uridine (**1**), 5-methyluridine (**6**), and 2′-deoxythymidine (**11**), were converted to amphiphilic nucleolipids. Compounds **1** and **6** were lipophilized by introduction of symmetric ketal moieties with various carbon chain lengths (*i.e.*, 5–17). Two ketal derivatives, **2b** and **7a**, were additionally further hydrophobized by *N*(3)-farnesylation. 2′-Deoxythymidine was alkylated at N(3) with a cetyl (= hexadecyl) residue, either directly or, after complete orthogonal protection of the sugar OH groups, by *Mitsunobu* reaction with hexadecan-1-ol. Some of the nucleolipids were subsequently converted to their 2-cyanoethyl phosphoramidites (5′ or 3′), one of which was used for an exemplary synthesis of a lipo-oligonucleotide. The sequence of this lipo-oligonucleotide is an encoded manifestation of *Pythagoras*' law, created with a key table in which the letters of the alphabet, the numbers from 0 to 9 as well as the mostly used mathematical symbols are allocated to a ribonucleic acid triplet of the genetic code.

1. Introduction. – In several recent reports, we described the synthesis of lipo-oligonucleotides and their incorporation into artificial lipid bilayers with the aim of a new DNA biosensor technology [1][2]. In this context, we could show that an equilibrium exists obviously between bilayer-bound DNA duplexes and nanoscale aggregates, which freely diffuse within the *cis* compartment of an optically transparent microfluidic sample carrier with perfusion capabilities [1]. It is conceivable that the bias of this equilibrium depends *i*) on the lipophilicity of the hydrophobic head group of the lipo-oligonucleotide, and *ii*) on the hydrophilicity as well as on the chain length of the appending oligonucleotide moiety, a relation which we have earlier defined as *amphiphilic ratio* [3]. We found that a particular DNA dodecamer can be immobilized within an artificial lipid bilayer, composed of 1-palmitoyl-2-oleyl-*sn*-glycero-3-phosphoethanol-amine (POPE)/1-palmitoyl-2-oleyl-*sn*-glycero-3-phosphocholine (POPC) 8:2 (*w*/*w*), most efficiently, when the terminal lipophilic part of the lipo-oligonucleotide contains a double-chained lipid with a sufficient alkyl chain length [1][4][5]; on the other hand, a relatively short and mono-tailed lipid, *e.g.*, geranyl or farnesyl groups, attached to the 5′-terminal nucleotide residue of the lipo-oligonucleotide, leads to a relatively easy wash-out of the bilayer-immobilized dodecamer [2]. One has to keep in mind, however, that appending extremely lipophilic nucleolipid moieties to a short DNA sequence might promote the formation of high-molecular-weight aggregates of

the lipo-oligonucleotides in favor of a lipid-bilayer incorporation. We, therefore, prepared a series of phosphoramidite building blocks of 2′-deoxythymidine, uridine, and 5-methyluridine for an automated solid-phase DNA synthesis, carrying symmetric ketal moieties with varying alkyl chain lengths [4][5] or single-chained lipids at the pyrimidine base. One of the phosphoramidites prepared will be used for the representative synthesis of a lipo-oligonucleotide. In the following, all phosphoramidites will be used for the synthesis of lipo-oligonucleotides with a standardized DNA chain length, which is not an easy task regarding their purification. The oligomers will then be immobilized in an artificial lipid bilayer. The retention times, t_R values, of the lipo-oligonucleotides within this bilayer upon perfusion will be studied later. We expect useful insight into the equilibrium mentioned above and, therewith, into new possibilities for an optimization of our novel DNA biosensor technique [6]. In a further study, we will prepare lipo-oligonucleotides with a selected lipophilic head group (nucleolipid) but with DNA sequences of various chain lengths and study their stability within a lipid bilayer towards perfusion. *si*RNSs carrying nucleolipids as those reported here may show a significantly improved delivery *in vivo* [7]; cholesterol residues, which have often been used for this purpose, bind very tightly into bilayer membranes, thus hampering an effective transfection of an appending nucleic acid.

2. Results and Discussion. – 2.1. *Hydrophobization of Uridine* (**1**) *and 5-Methyluridine* (**6**) *by Long-Chain Ketal Groups.* Uridine (**1**) and 5-methyluridine (**6**) were reacted with symmetrical long-chain ketones in acidic medium (DMF) and gave the ketals **2a**–**2e** and **7a**–**7c**, respectively. For this purpose, two different synthetic protocols [3][8] were applied (see *Exper. Part*). Partly, the compounds were then directly converted to their phosphoramidites **3** and **8**, respectively, or first *N*(3)-farnesylated and then phosphitylated to furnish **5** (*Scheme 1*) and **10** (*Scheme 2*), respectively. All compounds were characterized by multinuclear NMR and UV spectroscopy as well as by elemental analyses. Assignments of ^{13}C-NMR resonances was performed with the help of DEPT-135 spectra as well as by spectra simulation.

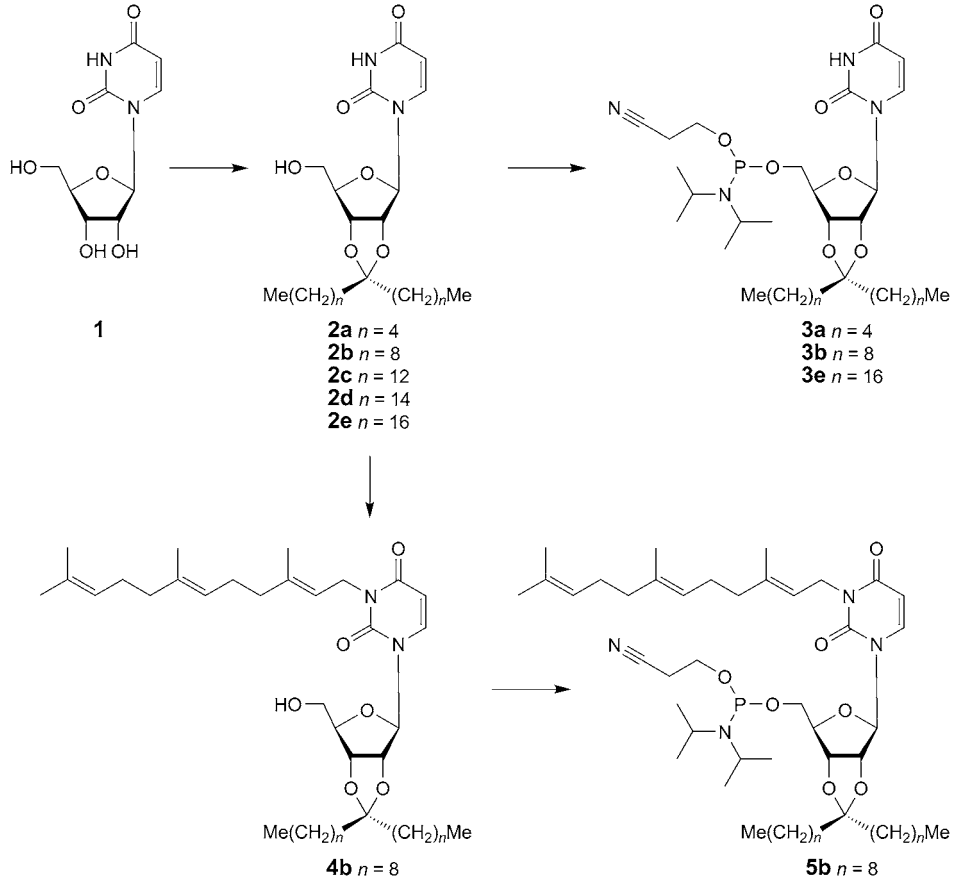
The novel phosphoramidites represent terminator molecules which can be attached once to the 5′-terminus of an oligonucleotide chain lending them a tuned lipophilicity as well as a protection against enzymatic 5′-exonucleolytic degradation.

Fig. 1 displays the R_f values of the various uridine- and methyluridine-containing ketals as a function of the carbon-chain length. It is obvious that the lipophilicity of the various ketals are not as strongly dependent from the alkyl-chain length as expected; the additional introduction of an all-(*E*) farnesyl (=(all-*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl) residue, however, enhances the lipophilicity of the resulting nucleolipid significantly. A similar result had been found for cyclic ketal derivatives of 5-fluorouridine [3].

Fig. 2 shows the chemical-shift differences ($\Delta\delta$) of ^{13}C-NMR resonances of C(1a″) and C(1b″) (for definition, see *Exper. Part*, *General*) of the corresponding ketal moieties as a function of the total carbon-chain length. It reveals that the longer the alkyl chain length gets, the higher is the difference of the chemical shifts of those C-atoms most adjacent to the pseudo-stereogenic center at the ketal C-atom.

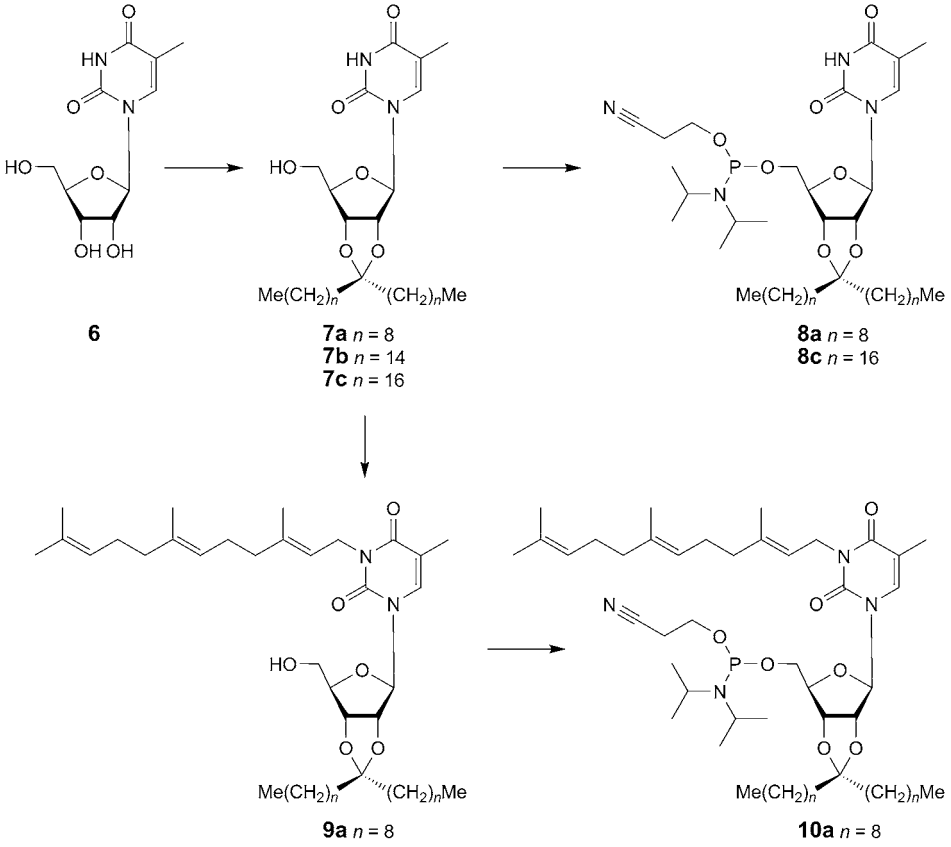
From the particular ^{13}C-NMR chemical shifts (see *Exper. Part*) of C(1a″) and C(1b″) of the ketals **2a**–**2e** and **7a**–**7c**, it can be seen that the increasing $\Delta\delta$ values

Scheme 1



result from a change of the C(1b″) (C_{exo}) resonances towards higher field, while the C(1a″) (C_{endo}) resonances remain almost constant. It is, therefore, assumed that steric interactions, arising from contacting *Van der Waals* radii of closely spaced H-atoms, lead to this increased shielding of the C-atoms attached to these H-atoms [9]. The steric perturbation of the C–H bond involved causes the charge to drift towards the C-atom. The bonding orbitals at the C-atom expand, and a paramagnetic shielding σ^{para} will arise according to the *Karplus–Pople* equation [10]. This points to decreasing C(1a″)–$C_{(ketal)}$–C(1b″) (Φ) bond angles with increasing alkyl-chain length due to increasing *Van der Waals* interactions along the two C-chains. We tentatively assume that, with increasing C-chain length (*i.e.*, **2a** → **2e**), both alkyl chains approach each other more and more due to increasing *Van der Waals* interactions. This causes an

Scheme 2



increasing steric perturbation of the C(1a″)–H and C(1b″)–H bonds with the above-mentioned consequences for the ^{13}C-NMR chemical shifts (*Fig. 3*).

This steric shift δ_{st} is, according to a model of *Grant* [11], depending on the proton–proton repulsive force ($F_{HH}(r_{HH})$) which is a function of the proton–proton distance r_{HH} and of the angle θ between the H–H axis and the pertubated C–H bond:

$$\delta_{st} = \text{const. } F_{HH}(r_{HH}) \cos\theta$$

2.2. *Hydrophobization of 2′-Deoxythymidine by Long, Single-Chain Alkyl Groups at N(3)*. In a further approach, we attempted the synthesis of thymidine derivative carrying a long, single-chain long alkyl group at N(3) of the nucleobase. For this purpose, 2′-deoxythymidine (**11**) was first reacted with cetyl bromide (1-bromohexadecane) under basic reaction conditions (K_2CO_3, DMF) and yielded the *N*(3)-cetyl

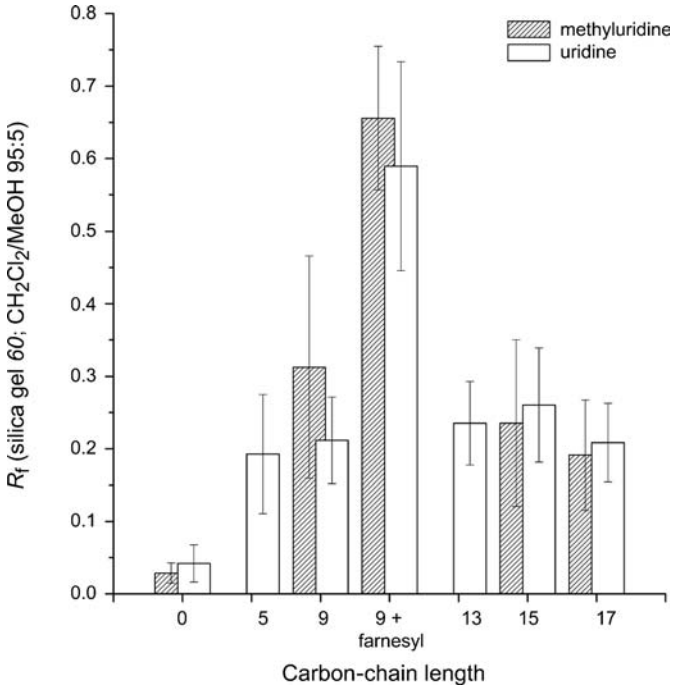


Fig. 1. R_f *Values of ketals* **2a**–**2e** *and* **7a**–**7c** *as a function of carbon-chain length*

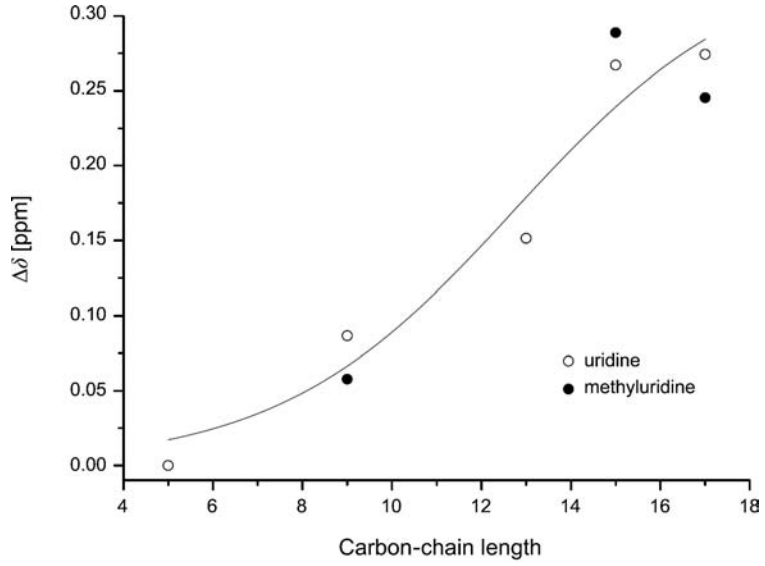


Fig. 2. $\Delta\delta$ *Values of* ^{13}*C-NMR resonances of C(1″) of ketals* **2a**–**2e** *and* **7a**–**7c** *as a function of carbon-chain length*

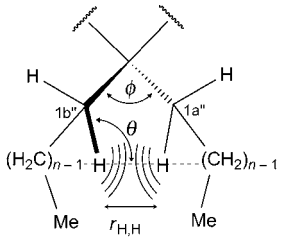


Fig. 3. *Sketch of the ketal moiety demonstrating the steric clash of H–C(1a″) and H–C(1b″)*

derivative **12**. Its UV maximum (267 nm) resembled that of compound **11**, and established *N*- and not *O*-alkylation.

In the following, 2′-deoxythymidine was *N*(3)-alkylated with hexadecan-1-ol (cetyl alcohol) applying *Mitsunobu* reaction conditions. In a preceeding publication [4], we showed that, for a *Mitsunobu* alkylation [12] of a nucleoside, the latter should be fully protected at all OH functions to avoid side reactions. Therefore, we first protected the 5′-OH group of 2′-deoxythymidine (→**13**; *Scheme 3*), followed by protection of the 3′-OH group with a *tert*-butyl(diphenyl)silyl (TBDPSi) group (→**14**). When a *Mitsunobu* reaction was performed (Ph_3P, THF, diisopropyl azodicarboxylate (DIAD), cetyl alcohol, room temperature) with the 5′-protected compound **13**, subsequent ESI mass spectrum of the product isolated exhibited a correct molecular-ion peak ($[M+H]^+$ 713.5 Da). ^{1}H-NMR Analysis, however, showed clearly two sets of signals of corresponding to CH_2 groups as well as a signal of an additional OH group besides that of 3′-OH. Repeated chromatography as well as intensive drying at 40° in high vacuum gave the same results with respect to ESI mass spectrometry and NMR spectroscopy. Therefore, it was assumed that a relatively stable adduct of the *N*(3)-cetyl compound **13** with 1 equiv. of cetyl alcohol had been formed.

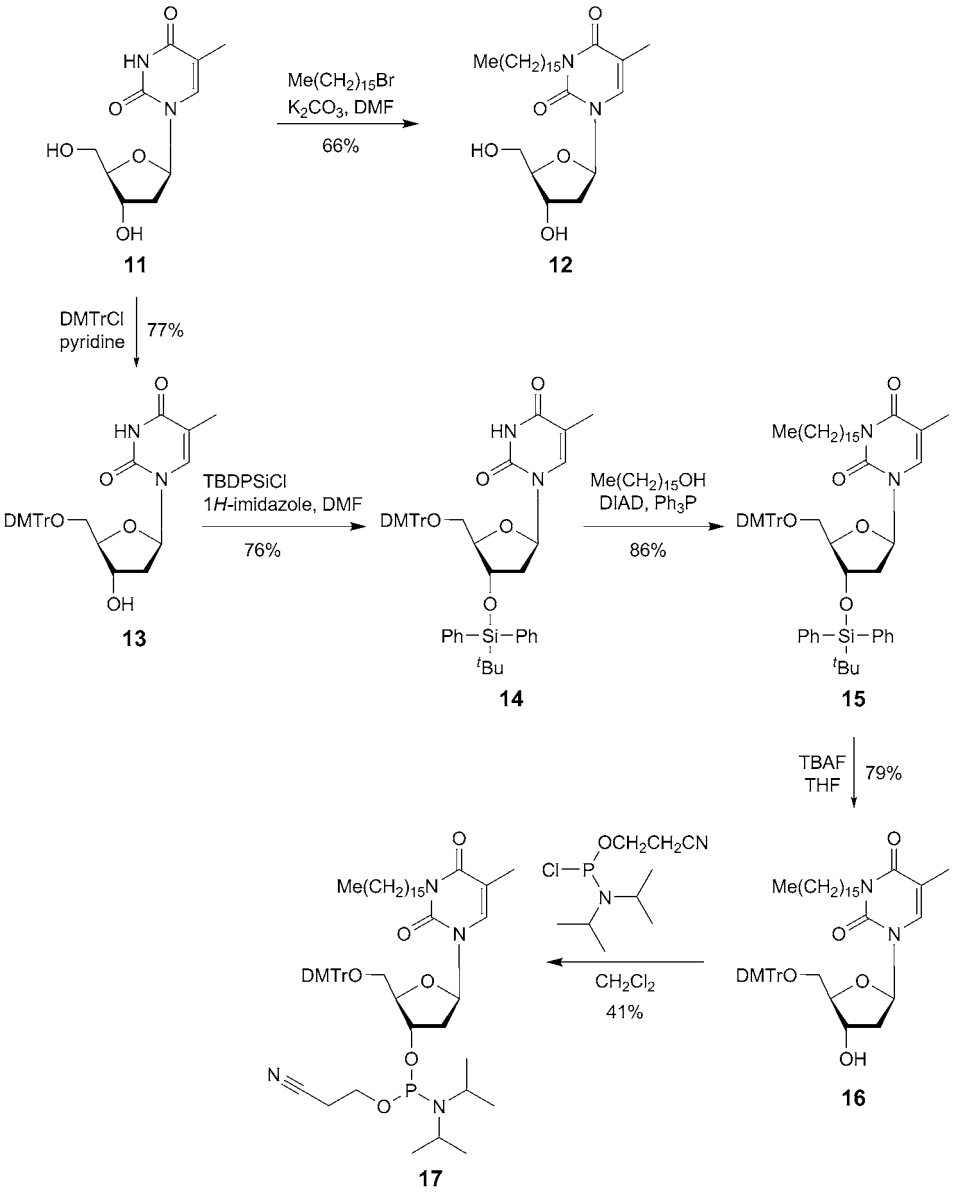
Next, we performed a *Mitsunobu* reaction on the fully protected compound **14**. This reaction was performed under various reaction conditions. The best results were obtained when all reagents (**14**, DIAD, Ph_3P, THF) were mixed at room temperature, and then stirred further overnight at room temperature. In this case, the yield obtained after purification of the reaction product **15** amounts to moderate 50%. All new compounds provided expected NMR spectra as well as elemental analyses values, and they did not exhibit aggregation reactions with cetyl alcohol.

Next, compound **15** was desilylated by reaction with Bu_4NF (TBAF) in THF to yield compound **16**, which was then phosphitylated to give the phosphoramidite **17**. Compound **17** can be used for the solid-phase synthesis of oligonucleotides, which carry one or more lipophilization sites at any pre-determined position of the sequence (*Scheme 3*).

2.3. *Representative Lipo-Oligonucleotide Synthesis Using the Phosphoramidite* **8a**. To test the practical applicability of lipophilic phosphoramidites as described above, we used compound **8a** for the preparation of a 24-mer carrying the nucleolipid **7a** at the 5′-terminus. For this purpose, we have chosen a special sequence which is derived from the *Pythagoras*' law with the help of the following encoding *Table*.

This *Table* presents an exemplary code for alphabetical letters, numbers from 0 to 9 and the most frequently used mathematical symbols in form of ribonucleic acid triplets of the genetic code. The code presented in the *Table* represents one possible key. This

Scheme 3



allocation can be principally changed; the number of permutations N for the assignments is:

$$N = n!/(n-k)! = 64! \approx 1.3 \cdot 10^{89}$$

where n is the number of triplets and k is the number of symbols.

Table. *Encryption Table to Encode a Message into RNA*

		2. Base			
		U	C	A	G
1. Base	U	UUU ≡ A	UCU ≡ E	UAU ≡ I	UGU ≡ M
		UUC ≡ B	UCC ≡ F	UAC ≡ J	UGC ≡ N
		UUA ≡ C	UCA ≡ G	UAA ≡ K	UGA ≡ O
		UUG ≡ D	UCG ≡ H	UAG ≡ L	UGG ≡ P
	C	CUU ≡ Q	CCU ≡ U	CAU ≡ Y	CGU ≡ 2
		CUC ≡ R	CCC ≡ V	CAC ≡ Z	CGC ≡ 3
		CUA ≡ S	CCA ≡ W	CAA ≡ 0	CGA ≡ 4
		CUG ≡ T	CCG ≡ X	CAG ≡ 1	CGG ≡ 5
	A	AUU ≡ 6	ACU ≡ /	AAU ≡ :	AGU ≡ !
		AUC ≡ 7	ACC ≡ Σ	AAC ≡ +	AGC ≡ √
		AUA ≡ 8	ACA ≡ =	AAA ≡ -	AGA ≡ sin
		AUG ≡ 9	ACG ≡ ●	AAG ≡ ²	AGG ≡ cos
	G	GUU ≡ tan	GCU ≡ π	GAU ≡ (	GGU ≡ ∞
		GUC ≡ $\int$	GCC ≡ α	GAC ≡)	GGC ≡ Δ
		GUA ≡ |	GCA ≡ β	GAA ≡ exp	GGA ≡ Λ
		GUG ≡ <	GCG ≡ >	GAG ≡ γ	GGG ≡ ∂

Pythagoras' law, in an encoded form using the above-mentioned encryption code, is given by the RNA sequence **18**.

5′-(UUU AAG AAC UUC AAG ACA UUA AAG) (**18**)

A back-transcription into a corresponding DNA following the regular base-pairing rules gives **19**:

3′-d(AAA TTC TTG AAG TTC TGT AAT TTC) (**19**)

Using the phosphoramidite **8a**, the lipo-oligonucleotide **20** as well as its cyanine-5-labelled complementary strand **21** were synthesized:

5′-d[(**7a**)(AAA TTC TTG AAG TTC TGT AAT TTC)] (**20**)

5′-d[(*Cy*-5)(GAA ATT ACA GAA CTT CAA GAA TTT)] (**21**)

Experiments towards spotting the lipo-oligonucleotide onto silanized glass plates to produce an non-visible microdot [13] with a hidden message, which can be visualized by addition of **21**, are in progress and will be published in due course. Moreover, the production of lipo-oligonucleotide-covered *Wilhelmy* plates for a specific nucleic acid isolation from a library, using a special *Dipcoater* technique [14], will be described later.

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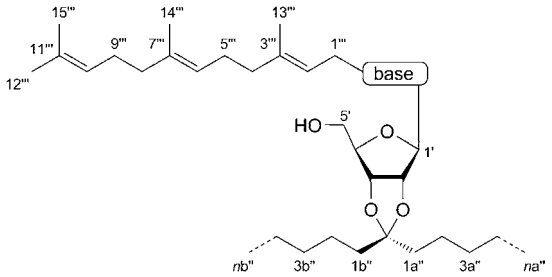
Experimental Part

General. Starting compounds and solvents were purchased from the appropriate suppliers and were used as obtained. Column chromatography (CC): silica gel *60* (SiO_2; *Merck*, Germany). TLC: Aluminum sheets, SiO_2 *60* F_{254}, 0.2-mm layer (*Merck*, Germany). M.p.: *Stuart*-SMP3 apparatus (Fa. *Bibby Scientific Ltd.*, UK-Staffordshire); uncorrected. UV Spectra: *Cary 6000i* spectrophotometer (*Varian*, D-Darmstadt); λ_{max} in nm, ε in M^{-1} cm^{-1}. NMR Spectra: *AMX-500* spectrometer (*Bruker*, D-Rheinstetten); ^1H: 500.14, ^{13}C: 125.76, and ^{31}P: 101.3 MHz; δ in ppm rel. to Me_4Si as internal standard for ^1H and ^{13}C nuclei, and external 85% H_3PO_4, *J* in Hz. Elemental analyses (C, H, N) of crystallized compounds were performed on a *VarioMICRO* instrument (Fa. *Elementar*, D-Hanau).



*2′,3′-*O*-(1-Pentylhexylidene)uridine* (=*1-[(3a*R,*4*R,*6*R,*6a*R*)-Tetrahydro-6-(hydroxymethyl)-2,2-dipentylfuro[3,4-*d*][1,3]dioxol-4-yl]pyrimidine-2,4(1*H,*3*H*)-dione*; **2a**). *Uridine* (**1**; 0.76 g, 3.1 mmol) was dissolved in anh. DMF (10 ml), and undecan-6-one (0.80 ml, 3.9 mmol) as well as 4M HCl in 1,4-dioxane (4 ml) and triethyl orthoformate ($HC(OEt)_3$; 1 ml) were added. The mixture was stirred for 24 h at r.t. Subsequently, the soln. was partitioned between CH_2Cl_2 (75 ml) and a sat. aq. $NaHCO_2$ soln. (50 ml). The org. phase was washed with dist. H_2O (100 ml) and separated. After drying (Na_2SO_4), the solvent was evaporated. Purification was performed by CC (SiO_2 *60*; column: 2 × 22 cm). A stepwise elution with 750 ml of CH_2Cl_2/MeOH 99 :1, followed by 250 ml of CH_2Cl_2/MeOH 95 :5 gave one main zone, from which, after evaporation and drying in high vacuum, **2a** (1.1 g, 2.69 mmol, 87%) was isolated. Colorless foam. R_f (SiO_2 *60*; CH_2Cl_2/MeOH 95 :5) 0.19. UV (MeOH): 260 (9.200). ^1H-NMR (500.13 MHz, (D_6)DMSO): 11.32 (*s*, H–N(3)); 7.77 (*d*, ^3J(6,5) = 8.2, H–C(6)); 5.83 (*d*, ^3J(1′,2′) = 2.5, H–C(1′)); 5.62 (*dd*, ^3J(5,6) = 8.0, ^4J(5,HN(3)) = 1.7, H–C(5)); 5.01 (*t*, ^3J(OH,5′) = 5.04, HO–C(5′)); 4.89 (*dd*, ^3J(2′,1′) = 2.8, ^3J(2′,3′) = 6.6, H–C(2′)); 4.74 ((*dd*, ^3J(3′,4′) = 3.5, ^3J(3′,2′) = 6.6, H–C(3′)); 4.06 (Ψq, ^3J(4′,5′) = ^3J(4′,3′) = 4.4, H–C(4′)); 3.56 (*m*, CH_2(5′)); 1.67 (*m*, CH_2(1a″)); 1.52 (*m*, CH_2(1b″)); 1.44 – 1.20 (*m*, CH_2(2a″ – 4a″, 2b″ – 4b″)); 0.86 (*m*, Me(5a″,5b″)). ^{13}C-NMR (125.76 MHz, (D_6)DMSO): 163.06 (C(4)); 150.26 (C(2)); 141.94 (C(6)); 116.631 (C(ketal)); 101.65 (C(5)); 91.20 (C(1′)); 86.66 (C(4′)); 83.79 (C(3′)); 80.73 (C(2′)); 61.34 (C(5′)); 36.34 (C(1″)); 31.34 (C(3a″)); 31.25 (C(3b″)); 23.19 (C(2a″)); 22.51 (C(2b″)); 21.91 (C(4a″)); 21.89 (C(4b″)); 13.76 (C(5″)). Anal. calc. for $C_{20}H_{32}N_2O_6$ (396.48): C 60.59, H 8.14, N 7.07; found: C 60.20, H 8.11, N 6.97.

*2′,3′-*O*-(1-Nonyldecylidene)uridine* (=*1-[(3a*R,*4*R,*6*R,*6a*R*)-Tetrahydro-6-(hydroxymethyl)-2,2-dinonylfuro[3,4-*d*][1,3]dioxol-4-yl]pyrimidine-2,4(1*H,*3*H*)-dione*; **2b**). Uridine (**1**; 0.76 g, 3.1 mmol) was dissolved in anh. DMF (10 ml), and nonadecan-10-one (1.11 g, 3.9 mmol), 4M HCl in 1,4-dioxane (4 ml), and $HC(OEt)_3$ (1 ml), as well as CH_2Cl_2 (6 ml), were added consecutively. The mixture was stirred for 24 h at r.t. Subsequently, the mixture was partitioned between an aq. sat. $NaHCO_3$ soln. (100 ml) and CH_2Cl_2 (100 ml). The org. layer was washed with dist. H_2O (100 ml), separated, dried (Na_2SO_4), and then evaporated to dryness. Purification of the raw product was performed by stepped-gradient CC (SiO_2 *60*, column: 6.5 × 10 cm). A stepwise elution with 800 ml of CH_2Cl_2/MeOH 99 :1, followed by 200 ml of CH_2Cl_2/MeOH 95 :5 gave one main zone, from which, after evaporation and drying in high vacuum, **2b** (1.50 g, 2.95 mmol, 95%) was isolated. Colorless foam. M.p. 69.8°. R_f (SiO_2 *60*; CH_2Cl_2/MeOH 95 :5) 0.21. UV (MeOH): 260 (9.600). ^1H-NMR (500.13 MHz, (D_6)DMSO): 11.33 (*s*, H–N(3)); 7.76 (*d*, ^3J(6,5) = 8.0, H–C(6)); 5.82 (*d*, ^3J(1′,2′) = 2.5, H–C(1′)); 5.62 (*d*, ^3J(5,6) = 8.0, H–C(5)); 5.02 (*m*, HO–C(5′)); 4.89 (*dd*, ^3J(2′,1′) = 2.5, ^3J(2′,3′) = 6.5, H–C(2′)); 4.73 (*dd*, ^3J(3′,4′) = 3.5, ^3J(3′,2′) = 6.5, H–C(3′)); 4.05 (Ψq,

$^3J(4',5') = {}^3J(4',3') = 4.2$, H–C(4')); 3.57 (*m*, CH_2(5')); 1.66 (*m*, CH_2(1a'')); 1.51 (*m*, CH_2(1b'')); 1.30–1.20 (*m*, CH_2(2a''–8a'', 2b''–8b'')); 0.85 (*m*, Me(9a'',9b'')). ^{13}C-NMR (125.76 MHz, (D_6)DMSO): 163.11 (C(4)); 150.28 (C(2)); 141.98 (C(6)); 116.63 (C(ketal)); 101.67 (C(5)); 91.23 (C(1')); 86.69 (C(4')); 83.82 (C(3')); 80.70 (C(2')); 61.35 (C(5')); 36.38 (C(1a'')); 36.29 (C(1b'')); 31.21 (C(7a'')); 31.19 (C(7b'')); 29.09 (C(3a'')); 29.04 (C(3b'')); 28.86 (C(4a'')); 28.83 (C(4b'')); 28.80 (C(5'')); 28.59 (C(6a'')); 28.58 (C(6b'')); 23.52 (C(2a'')); 22.88 (C(2b'')); 22.01 (C(8a'')); 22.00 (C(8b'')); 13.85 (C(9'')). Anal. calc. for $C_{28}H_{48}N_2O_6$ (508.69): C 66.11, H 9.51, N 5.51; found: C 65.86, H 9.50, N 5.21.

2',3'-O-*(1-Tridecyltetradecylidene)uridine* (=*1-[(3a*R,*4*R,*6*R,*6a*R*)-Tetrahydro-6-(hydroxymethyl)-2,2-ditridecylfuro[3,4-*d*][1,3]dioxol-4-yl]pyrimidine-2,4(1*H,*3*H*)-dione*; **2c**). Heptacosan-14-one (0.40 g, 1 mmol) was added to a soln. of anh. THF (14 ml), **1** (1.22 g, 5 mmol), TsOH (0.19 g, 1 mmol), and $HC(OEt)_3$ (0.85 ml, 5.1 mmol). The mixture was refluxed for 24 h (75°), and then Et_3N (0.6 ml) was added. To this mixture, ice-cold 4% aq. $NaHCO_3$ (50 ml) was added, and the mixture was stirred for 15 min at r.t. The mixture was washed with 100 ml of CH_2Cl_2 and 100 ml of dist. H_2O. The org. layer was dried (Na_2SO_4), filtered, and the solvent was evaporated. Compound **2c** was precipitated by addition of ice-cold MeOH on ice; the material was filtered and dried in high vacuum overnight: **2c** (65.6%, 0.41 g, 0.66 mmol). Colorless solid. M.p. 90.1°. R_f (SiO_2 *60*; CH_2Cl_2/MeOH 95:5) 0.24. UV (CH_2Cl_2): 260 (9.340). ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.32 (*d*, ^4J(HN(3),5) = 1.89, H–N(3)); 7.76 (*d*, ^3J(6,5) = 8.2, H–C(6)); 5.82 (*d*, ^3J(1',2') = 2.5, H–C(1')); 5.61 (*dd*, ^3J(5,6) = 8.2, ^4J(5,HN(3)) = 2.2, H–C(5)); 5.01 (*t*, ^3J(HO–C(5'),5') = 5.4, HO–C(5')); 4.88 (*dd*, ^3J(2',1') = 2.5, ^3J(2',3') = 6.6, H–C(2')); 4.73 (*dd*, ^3J(3',4') = 3.5, ^3J(3',2') = 6.6, H–C(3')); 4.05 (*Ψq*, ^3J(4',5') = ^3J(4',3') = 4.4, H–C(4')); 3.55 (*m*, CH_2(5')); 1.66 (*m*, CH_2(1a'')); 1.51 (*m*, CH_2(1b'')); 1.42–1.19 (*m*, CH_2(2a''–12a'', 2b''–12a'')); 0.85 (*m*, Me(13a'',13b'')). ^{13}C-NMR (125.76 MHz, (D_6)DMSO): 163.07 (C(4)); 150.26 (C(2)); 141.94 (C(6)); 116.62 (C(ketal)); 101.66 (C(5)); 91.22 (C(1')); 86.68 (C(4')); 83.81 (C(3')); 80.68 (C(2')); 61.34 (C(5')); 36.38 (C(1a'')); 36.22 (C(1b'')); 31.21 (C(11'')); 29.05 (C(3a'')); 28.99 (C(3b'')); 28.96–28.59 (C(4'')–C(10'')); 22.48 (C(2a'')); 22.86 (C(2b'')); 22.00 (C(12'')); 13.84 (C(13'')). Anal. calc. for $C_{36}H_{64}N_2O_6$ (620.90): C 69.64, H 10.39, N 4.51; found: C 69.77, H 10.74, N 3.92.

2',3'-O-*(1-Pentadecylhexadecylidene)uridine* (=*1-[(3a*R,*4*R,*6*R,*6a*R*)-Tetrahydro-6-(hydroxymethyl)-2,2-dipentadecylfuro[3,4-*d*][1,3]dioxol-4-yl]pyrimidine-2,4(1*H,*3*H*)-dione*; **2d**). Hentriacontan-16-one (0.45 g, 1.0 mmol) was added to a soln. of anh. THF (14 ml), **1** (1.22 g, 5 mmol), TsOH (0.19 g, 1.0 mmol), and $HC(OEt)_3$ (0.85 ml, 5.1 mmol). This mixture was refluxed for 24 h (75°), and Et_3N (0.6 ml) was added. The resulting mixture was poured into an aq. ice-cold 4% $NaHCO_3$ soln. (50 ml) and stirred for 15 min at r.t. The mixture was washed with CH_2Cl_2 (100 ml) and dist. H_2O (100 ml), dried (Na_2SO_4), filtered, and the solvent was evaporated. The residue was triturated with ice-cold MeOH on ice which gave **2d** (0.36 g, 0.54 mmol, 53.7%). Slightly yellowish solid which was dried in high vacuum. M.p. 93°. R_f (SiO_2 *60*; CH_2Cl_2/MeOH 95:5) 0.26. UV (CH_2Cl_2): 260 (8.350). ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.32 (*s*, H–N(3)); 7.77 (*d*, ^3J(6,5) = 8.0, H–C(6)); 5.83 (*d*, ^3J(1',2') = 2.5, H–C(1')); 5.62 (*d*, ^3J(5,6) = 8.0, H–C(5)); 5.01 (*t*, ^3J(HO–C(5'),5') = 5.0, HO–C(5')); 4.88 (*dd*, ^3J(2',1') = 2.5, ^3J(2',3') = 6.5, H–C(2')); 4.73 (*dd*, ^3J(3',4') = 3.5, ^3J(3',2') = 6.3, H–C(3')); 4.05 (*Ψq*, ^3J(4',5') = ^3J(4',3') = 4.4, H–C(4')); 3.55 (*m*, CH_2(5')); 1.66 (*m*, CH_2(1a'')); 1.51 (*m*, CH_2(1b'')); 1.41–1.16 (*m*, CH_2(2a''–14a'', 2b''–14a'')); 0.85 (*m*, Me(15a'',15b'')). ^{13}C-NMR (125.76 MHz, (D_6)DMSO): 162.69 (C(4)); 150.03 (C(2)); 141.49 (C(6)); 116.52 (C(acetal)); 101.45 (C(5)); 91.02 (C(1')); 86.44 (C(4')); 83.62 (C(3')); 80.50 (C(2')); 61.18 (C(5')); 36.32 (C(1a'')); 36.06 (C(1b'')); 30.90 (C(13'')); 28.77 (C(3a'')); 28.73 (C(3b'')); 28.66–28.28 (C(4'')–C(12'')); 23.18 (C(2a'')); 22.63 (C(2b'')); 21.66 (C(14'')); 13.46 (C(15'')). Anal. calc. for $C_{40}H_{72}N_2O_6$ (677.01): C 70.96, H 10.72, N 4.14; found: C 71.08, H 11.06, N 3.74.

2',3'-O-*(1-Heptadecyloctadecylidene)uridine* (=*1-[(3a*R,*4*R,*6*R,*6a*R*)-2,2-Diheptadecyltetrahydro-6-(hydroxymethyl)furo[3,4-*d*][1,3]dioxol-4-yl]pyrimidine-2,4(1*H,*3*H*)-dione*; **2e**). Pentatriacontan-18-one (0.5 g, 0.99 mmol) was added to a soln. of anh. THF (14 ml), **1** (1.22 g, 5 mmol), TsOH (0.19 g, 1.0 mmol), and $HC(OEt)_3$ (0.85 ml, 5.1 mmol). The mixture was refluxed for 24 h at 75°. Then, Et_3N (0.6 ml) was added, and the resulting mixture was poured into an ice-cold aq. 4% $NaHCO_3$ soln. (50 ml). This soln. was stirred for 15 min at r.t. The org. layer was washed with CH_2Cl_2 (100 ml) and dist. H_2O (100 ml), dried (Na_2SO_4), filtered, and the solvent was evaporated. The residue was triturated with ice-cold MeOH on ice, which gave the solid product. The colorless product was dried overnight in high vacuum to afford **2e** (0.45 g, 0.61 mmol, 61.4%). M.p. 89.7°. R_f (SiO_2 *60*; CH_2Cl_2/MeOH 95:5) 0.21. UV

(CH_2Cl_2): 260 (9.320). ^{1}H-NMR (500 MHz, (D_6)DMSO, 60°): 11.16 (*s*, H–N(3)); 7.74 (*d*, ^3J(6,5) = 8.0, H–C(6)); 5.84 (*d*, ^3J(1′,2′) = 2.5, H–C(1′)); 5.60 (*d*, ^3J(5,6) = 8.2, H–C(5)); 4.88 (*m*, H–C(2′), HO–C(5′), 2 H); 4.75 (*dd*, ^3J(3′,4′) = 3.5, ^3J(3′,2′) = 6.5, H–C(3′)); 4.07 (*Ψq*, ^3J(4′,5′) = ^3J(4′,3′) = 4.3, H–C(4′)); 3.53 – 3.63 (*m*, CH_2(5′)); 1.68 (*m*, CH_2(1a″)); 1.53 (*m*, CH_2(1b″)); 1.43 – 1.19 (*m*, CH_2(2a″ – 16a″, 2b″ – 16b″)); 0.86 (*m*, Me(17a″,17b″)). ^{13}C-NMR (125.76 MHz, (D_6)DMSO): 162.69 (C(4)); 150.03 (C(2)); 141.50 (C(6)); 116.52 (C(acetal)); 101.45 (C(5)); 91.02 (C(1′)); 86.44 (C(4′)); 83.62 (C(3′)); 80.50 (C(2′)); 61.18 (C(5′)); 36.32 (C(1a″)); 36.05 (C(1b″)); 31.19 (C(15″)); 28.76 (C(3a″)); 28.72 (C(3b″)); 28.79 – 28.25 (C(4″) – C(14″)); 23.17 (C(2a″)); 22.62 (C(2b″)); 21.66 (C(16″)); 13.46 (C(17″)). Anal. calc. for $C_{44}H_{80}N_2O_6$ (733.12): C 72.09, H 11.00, N 3.82; found: C 71.70, H 11.14, N 3.81.

5′-O-*{[Bis(1-methylethyl)amino](2-cyanoethoxy)phosphino}-2′,3′*-O-*(1-pentylhexylidene)uridine* (=*2-Cyanoethyl [(3a*R,*4*R,*6*R,*6a*R*)-6-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydro-2,2-dipentylfuro[3,4-*d*][1,3]dioxol-4-yl]methyl Bis(1-methylethyl)phosphoramidite*; **3a**). Compound **2a** (0.214 g, 0.3 mmol) was dissolved in dist. CH_2Cl_2 (15 ml). Under Ar, EtN(^{i}Pr)$_2$ (125 µl, 0.72 mmol) and (chloro)(2-cyanoethoxy)(diisopropylamino)phosphine (156 µl, 0.6 mmol) were then added, and the mixture was stirred for 17 min at r.t. The reaction was quenched by addition of an ice-cold aq. 5% $NaHCO_3$ soln. (12 ml), and the mixture was extracted with CH_2Cl_2 (15 ml). The combined org. layers were dried (1 min, Na_2SO_4), filtered, evaporated to dryness (25°), and the raw product was further dried in high vacuum at r.t. CC (SiO_2 *60*, column: 2 × 10 cm, CH_2Cl_2/acetone 8 : 2, containing 8 drops of Et_3N per l) gave one main zone which was pooled, evaporated, and dried in high vacuum: **3a** (0.13 g, 0.22 mmol, 71%). Colorless oil stored at −20°. R_f (SiO_2 *60*; CH_2Cl_2/acetone 8 : 2) 0.66. ^{31}P-NMR (202.45 MHz, $CDCl_3$): 149.40 (P_R), 149.30 (P_S).

5′-O-*{[Bis(1-methylethyl)amino](2-cyanoethoxy)phosphino}-2′,3′*-O-*(1-nonyldecylidene)uridine* (=*2-Cyanoethyl [(3a*R,*4*R,*6*R,*6a*R*)-6-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydro-2,2-dinonylfuro[3,4-*d*][1,3]dioxol-4-yl]methyl Bis(1-methylethyl)phosphoramidite*; **3b**). Compound **2b** (0.153 g, 0.3 mmol) was converted to **3b** as described for **3a**. Yield: 0.157 g (0.22 mmol, 73%). Colorless oil stored at −20°. R_f (silica *60*; CH_2Cl_2/acetone 8 : 2) 0.89. ^{31}P-NMR (202.45 MHz, $CDCl_3$): 149.46 (P_R), 149.37 (P_S).

5′-O-*{[Bis(1-methylethyl)amino](2-cyanoethoxy)phosphino}-2′,3′*-O-*(1-heptadecyloctadecylidene)uridine* (=*2-Cyanoethyl [(3a*R,*4*R,*6*R,*6a*R*)-6-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydro-2,2-diheptadecylfuro[3,4-*d*][1,3]dioxol-4-yl]methyl Bis(1-methylethyl)phosphoramidite*; **3e**). Compound **2e** (0.22 g, 0.3 mmol) was converted to **3e** as described for **3a**. Yield: 0.1 g (0.17 mmol, 57%). Colorless oil stored at −20°. R_f (SiO_2 *60*; CH_2Cl_2/acetone 8 : 2) 0.81. ^{31}P-NMR (202.45 MHz, $CDCl_3$): 149.46 (P_R), 149.38 (P_S).

2′,3′-O-*(1-Nonyldecylidene)-3-[(2*E,*6*E*)-3,7,11-trimethyl-2,6,10-dodecatrien-1-yl]uridine* (=*1-[(3a*R,*4*R,*6*R,*6a*R*)-Tetrahydro-6-(hydroxymethyl)-2,2-dinonylfuro[3,4-*d*][1,3]dioxol-4-yl]-3-[(2*E,*6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]pyrimidine-2,4(1*H,*3*H*)-dione*; **4b**). Compound **2b** (0.5 g, 0.98 mmol) was dissolved in anh. DMF (14 ml), and K_2CO_3 (1 g, 7.24 mmol) was added. Subsequently, under Ar, (*E*,*E*)-farnesyl bromide (0.35 ml, 1.1 mmol) was added dropwise within 10 min. The mixture was stirred for 24 h at r.t. under the exclusion of light. Then, the mixture was filtered and partitioned between dist. H_2O (225 ml) and CH_2Cl_2 (150 ml). The org. phase was separated, dried (Na_2SO_4), and filtered. The soln. was evaporated to dryness and further dried in high vacuum. CC (SiO_2 *60*, column: 2 × 27 cm, CH_2Cl_2 and MeOH, 99 : 1) and evaporation of the main fractions gave **4b** (0.533 g, 0.75 mmol, 77%). Colorless oil. R_f (SiO_2 *60*; CH_2Cl_2/MeOH 95 : 5) 0.59. UV (MeOH): 260 (7010). ^{1}H-NMR (500.13 MHz, (D_6)DMSO): 7.81 (*d*, ^3J(6,5) = 8.0, H–C(6)); 5.87 (*d*, ^3J(1′,2′) = 2.2, H–C(1′)); 5.74 (*d*, ^3J(5,6) = 8.0, H–C(5)); 5.11 (*t*, ^3J(HO–C(5′),5′) = 6.5, HO–C(5′)); 5.08 – 5.00 (*m*, H–C(2‴,6‴,10‴)); 4.87 (*dd*, ^3J(2′,1′) = 2.5, ^3J(2′,3′) = 6.6, H–C(2′)); 4.73 (*dd*, ^3J(3′,4′) = 3.0, ^3J(3′,2′) = 6.5, H–C(3′)); 4.41 – 4.38 (*m*, CH_2(1‴)); 4.09 (*Ψq*, ^3J(4′,5′) = ^3J(4′,3′) = 4.2, H–C(4′)); 3.61 – 3.51 (*m*, CH_2(5′)); 2.03 (*m*, CH_2(5‴)); 2.00 – 1.92 (*m*, CH_2(8‴,9‴)); 1.92 – 1.87 (*m*, CH_2(4‴)); 1.73 (*s*, Me(13‴)); 1.69 – 1.66 (*m*, CH_2(1a″)); 1.63 (*s*, Me(12‴)); 1.54 (*s*, Me(14‴)); 1.51 (*m*, CH_2(1b″)); 1.42 – 1.18 (*m*, CH_2(2a″ – 8a″, 2b″ – 8b″)); 0.85 (*m*, Me(9a″,9b″)). ^{13}C-NMR (125.76 MHz, (D_6)DMSO): 161.55 (C(4)); 150.20 (C(2)); 140.18 (C(6)); 138.81 (C(3‴)); 134.45 (C(7‴)); 130.47 (C(11‴)); 124.01 (C(6‴)); 123.49 (C(10‴)); 118.69 (C(2‴)); 116.56 (C(ketal)); 100.87 (C(5)); 92.09 (C(1′)); 86.79 (C(4′)); 83.99 (C(3′)); 80.72 (C(2′)); 61.28 (C(5′)); 39.04 (C(8‴)); 38.74 (C(4‴)); 38.17 (C(1‴)); 36.36 (C(1a″)); 36.31 (C(1b″)); 31.19 (C(7a″));

31.16 (C(7b″)); 29.07 (C(3a″)); 29.02 (C(3b″)); 28.83 (C(4a″)); 28.78 (C(4b″)); 28.58 (C(5a″)); 28.56 (C(5b″)); 28.58 (C(6a″); 28.59 (C(6b″)); 26.09 (C(5‴)); 25.62 (C(9‴)); 25.34 (C(12‴)); 23.48 (C(2a″)); 22.83 (C(2b″)); 21.99 (C(8″)); 17.41 (C(15‴)); 16.06 (C(14‴)); 15.66 (C(13‴)); 13.81 (C(9″)). Anal. calc. for $C_{43}H_{72}N_2O_6$ (713.04): C 72.43, H 10.18, N 3.93; found: C 72.59, H 10.58, N 3.96.

*5′-O-[[Bis(1-methylethyl)amino](2-cyanoethoxy)phosphino]-2′,3′-O-(1-nonyldecylidene)-3-[(2*E*,6*E*)-3,7,11-trimethyl-2,6,10-dodecatrien-1-yl]uridine* (=*2-Cyanoethyl [(3a*R*,4*R*,6*R*,6a*R*)-6-[2,4-Dioxo-3-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]-3,4-dihydropyrimidin-1(2*H*)-yl}tetrahydro-2,2-dinonylfuro[3,4-*d*][1,3]dioxol-4-yl]methyl Bis(1-methylethyl)phosphoramidoite*; **5b**). Compound **4b** (0.214 g, 0.3 mmol) was converted to **5b** as described for **3a**. Yield: 0.253 g (0.26 mmol, 87%). Colorless oil stored at −20°. R_f (SiO_2 *60*; CH_2Cl_2/acetone 8:2) 0.97. ^{31}P-NMR (202.45 MHz, $CDCl_3$): 149.34 (P_R), 149.31 (P_S).

5-Methyl-2′,3′-O-(1-nonyldecylidene)uridine (=*1-[(3a*R*,4*R*,6*R*,6a*R*)-Tetrahydro-6-(hydroxymethyl)-2,2-dinonylfuro[3,4-*d*][1,3]dioxol-4-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione*; **7a**). Anh. *5-methyluridine* (**6**; 0.77 g, 3 mmol) was dissolved in dry DMF (10 ml). Then, nonadecan-10-one (1.13 g, 4 mmol), dissolved in CH_2Cl_2 (10 ml), $HC(OEt)_3$ (1 ml), and 4M HCl in 1,4-dioxane (4 ml) were added. The mixture was stirred at r.t. for 24 h. Subsequently, the mixture was partinioned between an aq. sat. Na_2CO_3 soln. (100 ml) and CH_2Cl_2 (100 ml). The org. phase was separated, dried (Na_2SO_4), filtered, and evaporated to dryness. Traces of DMF were removed by repeated evaporation from CH_2Cl_2. The residue was dried in high vacuum overnight. The resulting colorless foam was purified by CC (SiO_2 *60*, column: 6.5 × 10 cm; CH_2Cl_2/MeOH 95:5) to give one main zone which was pooled; the solvent was evaporated, and the residue was dried in high vacuum: **7a** (1.3 g, 83%). Colorless oil. R_f (SiO_2 *60*; CH_2Cl_2/MeOH 95:5) 0.31. UV (MeOH): 265 (10600). ^{1}H-NMR ((D$_6$)DMSO): 11.34 (*s*, H–N(3)); 7.63 (*s*, H–C(6)); 5.83 (*d*, $^3J(1',2') = 2.5$, H–C(1′)); 5.02 (*t*, ^3J(HO–C(5′),5′) = 5.0, HO–C(5′)); 4.88 (*dd*, $^3J(2',1') = 3.0$, $^3J(2',3') =$ 6.5, H–C(2′)); 4.75 (*dd*, $^3J(3',2') = 6.5$; $^3J(3',4') = 3.5$, H–C(3′)); 4.02 (*m*, $^3J(4',3') = 3.5$, $^3J(4',5') = 4.5$, H–C(4′)); 3.56 (*m*, CH_2(5′)); 1.76 (*s*, Me); 1.66 (*m*, CH_2(1a″)); 1.52 (*m*, CH_2(1b″)); 1.38 (*m*, CH_2(2a″)); 1.24 (*m*, CH_2(3a″–8a″, 2b″–8b″)); 0.85 (*m*, Me(9a″,9b″)). ^{13}C-NMR ((D$_6$)DMSO): 163.66 (C(4)); 150.27 (C(2)); 137.50 (C(6)); 116.77 (C(ketal)); 109.38 (C(5)); 90.52 (C(1′)); 86.24 (C(4′)); 83.50 (C(3′)); 80.58 (C(2′)); 61.31 (C(5′)); 36.33 (C(1a″)); 36.28 (C(1b″)); 31.17 (C(7a″)); 31.16 (C(7b″)); 29.06 (C(3a″)); 29.01 (C(3b″)); 28.83 (C(4a″)); 28.81 (C(4b″)); 28.80 (C(5″)); 28.77 (C(6a″)); 28.55 (C(6b″)); 23.48 (C(2a″)); 22.86 (C(2b″)); 21.97 (C(8a″)); 21.96 (C(8b″)); 13.82 (C(9a″)); 13.81 (C(9b″)); 11.94 (*Me*–C(5)). Anal. calc. for $C_{29}H_{50}N_2O_6$ (522.73): C 66.63, H 9.64, N 5.36; found: C 66.47, H 9.272, N 5.25.

5-Methyl-2′,3′-O-(1-pentadecylhexadecylidene)uridine (=*1-[(3a*R*,4*R*,6*R*,6a*R*)-Tetrahydro-6-(hydroxymethyl)-2,2-dipentadecylfuro[3,4-*d*][1,3]dioxol-4-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione*; **7b**). Hentriacontan-16-one (0.45 g, 1 mmol) was added to a soln. of **6** (1.29 g, 5 mmol), TsOH (0.19 g, 1 mmol), and $HC(OEt)_3$ (0.83 ml, 5 mmol) in THF (14 ml). This mixture was heated to 75° under reflux for 24 h. Then, Et_3N (0.6 ml) was added, and the resulting mixture was poured into an ice-cold aq. 4% $NaHCO_3$ soln. (50 ml). After stirring for 15 min at r.t., the mixture was partitioned between CH_2Cl_2 (100 ml) and H_2O (100 ml). The org. layer was separated, dried (Na_2SO_4), filtered, and the solvent was evaporated. The resulting oil was triturated with ice-cold MeOH on an ice bath, which led to precipitation of **7b** as a colorless solid. The latter was filtered off, and the filtrate was evaporated to yield another portion of solid **7b**. Total yield: 0.509 g (74%) as a yellowish solid. M.p. <70°. R_f (SiO_2 *60*; CH_2Cl_2/MeOH 95:5) 0.24. UV (CH_2Cl_2): 263 (12250). ^{1}H-NMR ((D$_6$)DMSO): 11.09 (*s*, H–N(3)); 7.58 (*s*, H–C(6)); 5.83 (*d*, $^3J(1',2') = 2.5$, H–C(1′)); 5.01 (*t*, ^3J(HO–C(5′),5′) = 5.0, HO–C(5′)); 4.89 (*dd*, $^3J(2',1') = 2.8$, $^3J(2',3') = 6.6$, H–C(2′)); 4.77 (*dd*, $^3J(3',2') = 6.6$, $^3J(3',4') = 3.5$, H–C(3′)); 4.05 (*Ψq*, $^3J(4',5') = {}^3J(4',3') = 4.4$, H–C(4′)); 3.60 (*m*, CH_2(5′)); 1.79 (*s*, Me–C(5)); 1.66 (*m*, CH_2(1a″)); 1.52 (*m*, CH_2(1b″)); 1.43–1.19 (*m*, CH_2(2a″–14a″, 2b″–14b″)); 0.85 (*m*, Me(15a″,15b″))). ^{13}C-NMR ((D$_6$)DMSO): 163.14 (C(4)); 149.91 (C(2)); 136.94 (C(6)); 116.59 (C(ketal)); 109.07 (C(5)); 90.50 (C(1′)); 86.03 (C(4′)); 83.31 (C(3′)); 80.38 (C(2′)); 61.12 (C(5′)); 36.32 (C(1a″)); 36.03 (C(1b″)); 30.74 (C(13″)); 28.63 (C(3a″)); 28.61 (C(3b″)); 28.44–28.10 (C(4″)–C(12″)); 23.02 (C(2a″)); 22.52 (C(2b″)); 21.48 (C(14″)); 13.24 (C(15″)); 11.33 (*Me*–C(5)). Anal. calc. for $C_{41}H_{74}N_2O_6$ (691.04): C 71.26, H 10.79, N 4.05; found: C 72.39, H 11.48, N 3.33.

2′,3′-O-(1-Heptadecyloctadecylidene)-5-methyluridine (=*1-[(3a*R*,4*R*,6*R*,6a*R*)-2,2-Diheptadecyltetrahydro-6-(hydroxymethyl)furo[3,4-*d*][1,3]dioxol-4-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione*; **7c**).

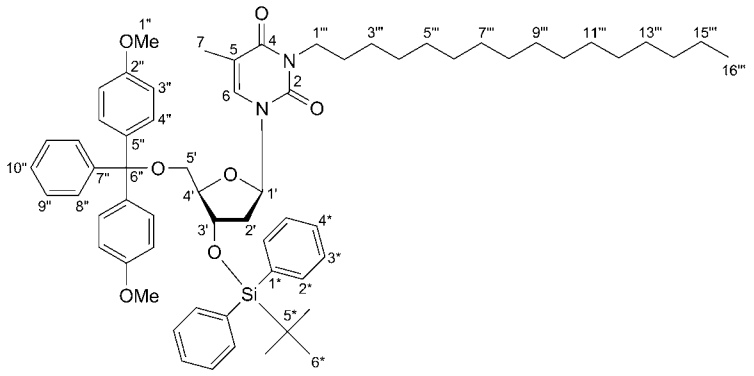
Pentatriacontan-18-one (0.50 g, 1 mmol) was added to a soln. of **6** (1.29 g, 5 mmol), TsOH (0.19 g, 1 mmol), and $HC(OEt)_3$ (0.83 ml, 5 mmol) in THF (10 ml). This mixture was heated to 75° under reflux for 24 h. Then, Et_3N (0.6 ml) was added, and the mixture was poured into an ice-cold aq. 4% $NaHCO_3$ soln. (50 ml). After stirring for 15 min at r.t., the mixture was partitioned between CH_2Cl_2 (100 ml) and H_2O (100 ml). The org. layer was separated, dried (Na_2SO_4), filtered, and the solvent was evaporated. The resulting oil was triturated with cold MeOH which led to precipitation of raw **7c**. The product was filtered off, and the filtrate was evaporated to yield a further crop of **7c**. Total yield: 0.5 g (68%). M.p. 72°. R_f (SiO_2 *60*; CH_2Cl_2/MeOH 95:5) 0.19. UV (CH_2Cl_2): 263 (14380). ^{1}H-NMR ((D$_6$)DMSO): 11.31 (*s*, H–N(3)); 7.62 (*s*, H–C(6)); 5.84 (*d*, ^3J(1′,2′) = 2.5, H–C(1′)); 5.02 (*t*, ^3J(HO–C(5′),5′) = 6.5, HO–C(5′)); 4.88 (*dd*, ^3J(2′,1′) = 2.5, ^3J(2′,3′) = 6.6, H–C(2′)); 4.75 (*dd*, ^3J(3′,2′) = 6.6, ^3J(3′,4′) = 3.5, H–C(3′)); 4.02 (*dd*, ^3J(4′,5′) = 4.2, ^3J(4′,3′) = 4.2, H–C(4′)); 3.57 (*m*, CH_2(5′)); 1.76 (*s*, Me–C(5)); 1.66 (*m*, CH_2(1a″)); 1.51 (*m*, CH_2(1b″)); 1.37 (*m*, CH_2(2a″)); 1.24 (*m*, CH_2(3a″–16a″, 2b″–16b″)); 0.85 (*m*, CH_2(17a″,17b″)). ^{13}C-NMR ((D$_6$)DMSO): 163.33 (C(4)); 150.04 (C(2)); 137.14 (C(6)); 116.64 (C(ketal)); 109.18 (C(5)); 90.48 (C(1′)); 86.09 (C(4′)); 83.38 (C(3′)); 80.44 (C(2′)); 61.18 (C(5′)); 36.31 (C(1a″)); 36.06 (C(1b″)); 30.90 (C(15″)); 28.75 (C(3a″)); 28.71 (C(3b″)); 28.59–28.27 (C(4″)–C(14″)); 23.17 (C(2a″)); 22.63 (C(2b″)); 21.66 (C(16″)); 13.46 (C(17″)); 11.56 (*Me*–C(5)). Anal. calc. for $C_{45}H_{82}N_2O_6$ (747.14): C 72.34, H 11.06, N 3.75; found: C 72.39, H 11.48, N 3.33.

5′-O-{[Bis(1-methylethyl)amino](2-cyanoethoxy)phosphino}-5-methyl-2′,3′-O-(1-nonyldecylidene)uridine (=*2-Cyanoethyl [(3a*R,*4*R,*6*R,*6a*R)*-Tetrahydro-6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H)*-yl)-2,2-dinonylfuro[3,4-*d*][1,3]dioxol-4-yl]methyl Bis(1-methylethyl)phosphoramidoite*; **8a**). Compound **7a** (0.157 g, 0.3 mmol) was converted to **8a** as described for **3a** (0.155 g, 71%). Colorless oil stored at −20°. R_f (SiO_2 *60*; CH_2Cl_2/acetone 8:2) 0.88. ^{31}P-NMR (202.45 MHz, $CDCl_3$): 149.36 (P_R), 149.22 (P_S).

5′-O-{[Bis(1-methylethyl)amino](2-cyanoethoxy)phosphino}-2′,3′-O-(1-heptadecyloctadecylidene)-5-methyluridine (=*2-Cyanoethyl [(3a*R,*4*R,*6*R,*6a*R)*-2,2-Diheptadecyltetrahydro-6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H)*-yl)furo[3,4-*d*][1,3]dioxol-4-yl]methyl Bis(1-methylethyl)phosphoramidoite*; **8c**). Compound **7c** (0.214 g, 0.3 mmol) was converted to **8c** as described for **3a** (0.20 g, 0.21 mmol, 70%). Colorless oil stored at −20°. R_f (silica *60*; CH_2Cl_2/acetone 8:2) 0.87. ^{31}P-NMR (101.25 MHz, $CDCl_3$): 149.31 (P_R), 149.17 (P_S).

*5-Methyl-2′,3′-O-(1-nonyldecylidene)-3-[(2*E,*6*E*)-3,7,11-trimethyl-2,6,10-dodecatrien-1-yl]uridine* (=*1-[(3a*R,*4*R,*6*R,*6a*R)*-Tetrahydro-6-(hydroxymethyl)-2,2-dinonylfuro[3,4-*d*][1,3]dioxol-4-yl]-5-methyl-3-[(2*E,*6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]pyrimidine-2,4(1*H,*3*H*)-dione*; **9a**). Compound **7a** (0.52 g, 1 mmol) was dissolved in dry DMF (14 ml), and anh. K_2CO_3 (1 g, 7.24 mmol) was added. Then, (*E*,*E*)-farnesyl bromide (0.35 ml, 1.1 mmol) was added dropwise, and the mixture was stirred under Ar for 24 h under the exclusion of light. Then, the mixture was partitioned between H_2O (200 ml) and CH_2Cl_2 (100 ml). The org. layer was separated, dried (Na_2SO_4), filtered, and the solvent was evaporated. Traces of DMF were removed by drying in high vacuum overnight. CC (SiO_2 *60*, column: 2 × 21 cm; CH_2Cl_2/MeOH, 99:1) gave one main zone which was pooled and evaporated to dryness. Further drying in high vacuum gave **9a** (0.5 g, 68%). Colorless oil. R_f (SiO_2 *60*; CH_2Cl_2/MeOH 95:5) 0.66. UV (MeOH): 266 (8700). ^{1}H-NMR ((D$_6$)DMSO): 7.68 (*s*, H–C(6)); 5.89 (*d*, ^3J(1′,2′) = 2.5, H–C(1′))); 5.12 (*t*, ^3J(HO–C(5′),5′) = 5.0, HO–C(5′)); 5.07–5.00 (*m*, H–C(2‴,6‴,10‴)); 4.85 (*dd*, ^3J(2′,1′) = 2.8, ^3J(2′,3′) = 6.6, H–C(2′)); 4.76 (*dd*, ^3J(3′,2′) = 6.6, ^3J(3′,4′) = 3.5, H–C(3′)); 4,39 (*m*, CH_2(1‴)); 4.06 (*m*, H–C(4′)); 3.62–3.52 (*m*, CH_2(5′)); 2.03 (*m*, CH_2(5‴)); 1.99–1.92 (*m*, CH_2(8‴,9‴)); 1.92–1.86 (*m*, CH_2(4‴)); 1.81 (*s*, Me–C(5)); 1.74 (*s*, Me(13‴)); 1.69–1.64 (*m*, CH_2(1a″)); 1.63 (*s*, Me(12‴)); 1.54 (*s*, Me(14‴)); 1.52 (*m*, CH_2(1b″)); 1.43–1.17 (*m*, CH_2(2a″–8a″, 2b″–8b″)); 0.85 (*m*, Me(9a″,9b″)). ^{13}C-NMR ((D$_6$)DMSO): 162.27 (C(4)); 150.09 (C(2)); 138.71 (C(6)); 135.71 (C(3‴)); 134.42 (C(7‴)); 130.45 (C(11‴)); 123.98 (C(6‴)); 123.46 (C(10‴)); 118.75 (C(2‴)); 116.74 (C(ketal)); 108.57 (C(5)); 91.42 (C(1′)); 86.34 (C(4′)); 83.64 (C(3′)); 80.61 (C(2′)); 61.25 (C(5′)); 38.98 (C(8‴)); 38.76 (C(4‴)); 38.52 (C(1‴)); 36.30 (C(1″)); 31.15 (C(7a″)); 31.13 (C(7b″)); 29.03 (C(3a″)); 28.97 (C(3b″)); 28.80 (C(4a″)); 28.74 (C(4b″)); 28.55 (C(5a″)); 28.52 (C(5b″)); 26.06 (C(6a″)); 25.55 (C(6b″)); 25.32 (C(5‴)); 23.44 (C(9‴)); 22.80 (C(12‴)); 21.95 (C(2a″)); 21.93 (C(2b″)); 17.37 (C(8″)); 16.03 (C(15‴)); 15.64 (C(14″)); 13.79 (C(13‴)); 13.78 (C(9″)); 12.59 (*Me*–C(5)). Anal. calc. for $C_{44}H_{74}N_2O_6$ (727.07): C 72.69, H 10.26, N 3.85; found: C 72.67, H 9.925, N 3.76.

5′-O-*{[Bis(1-methylethyl)amino](2-cyanoethoxy)phosphino}-5-methyl-2′,3′*-O-*(1-nonyldecylidene)-3-[(2*E*,6*E*)-3,7,11-trimethyl-2,6,10-dodecatrien-1-yl]uridine* (=*2-Cyanoethyl [(3a*R*,4*R*,6*R*,6a*R*)-Tetrahydro-6-{5-methyl-2,4-dioxo-3-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]-3,4-dihydropyrimidin-1(2*H*)-yl}-2,2-dinonylfuro[3,4-*d*][1,3]dioxol-4-yl]methyl Bis(1-methylethyl)phosphoramidoite*; **10a**). Compound **9a** (0.22 g, 0.3 mmol) was converted to **10a** as described for **3a** (0.2 g, 0.22 mmol, 77.9%). Colorless oil stored at −20°. R_f (SiO_2 *60*; CH_2Cl_2/acetone 8:2) 0.97. ^{31}P-NMR (202.45 MHz, $CDCl_3$): 149.28 (P_R), 149.26 (P_S).



2′-Deoxy-3-hexadecyl-3,4-dihydrothymidine (=*3-Hexadecyl-1-[(2*R*,4*S*,5*R*)-tetrahydro-4-hydroxy-5-(hydroxymethyl)furan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione*; **12**). *2′-Deoxythymidine* (**11**, 0.98 g, 4.05 mmol) was dissolved in anh. DMF (24 ml). After heating to 48° on a water bath, K_2CO_3 (1.465 g, 10.6 mmol) was added under N_2. After stirring for 10 min, 1-bromohexadecane (1.1 ml, 4.5 mmol) was added portionwise during 5 h. Stirring was continued for further 23 h. Then, the mixture was filtered, and the residue was washed with CH_2Cl_2. The filtrate was dried (Na_2SO_4), filtered, and evaporated to dryness. CC (SiO_2 *60*, 6.5 × 13 cm; stepwise elution with *i*) CH_2Cl_2/MeOH 98:2, *ii*) CH_2Cl_2/MeOH 96:4, *iii*) CH_2Cl_2/MeOH 95:5) gave one main zone which was evaporated and then dried in high vacuum to give **12** (1.03 g, 2.67 mmol, 66%). Amorphous foam. $T_{glass\,transition}$ 106–112°. R_f (SiO_2; CH_2Cl_2/MeOH 9:1): 0.26. log *P:* 8.60 ± 0.56. ^{1}H-NMR ((D_6)DMSO): 1.484 (*Ψq*, ^3J(H,H) = 7.2, CH_2(2‴)); 1.235 (*m*, CH_2(3‴–15‴)); 0.851 (*t*, ^3J(16‴,15‴) = 6.9, Me(16‴)); 7.745 (*s*, H–C(6)); 1.816 (*s*, Me(7)); 6.201 (*Ψt*, ^3J(1′,H_α–C(2′)) = 6.9, ^3J(1′,H_β–C(2′)) = 6.8, H–C(1′)); 2.094 (*ddd*, ^2J(H_α–C(2′),H_β–C(2′)) = −11.6, ^3J(H_α–C(2′),1′) = 6.7, ^3J(H_β–C(2′),1′) = 6.6, ^3J(H_α–C(2′),3′) = 4.9, ^3J(H_β–C(2′),3′) = 5.0, CH_2(2′)); 4.240 (*Ψq*, H–C(3′)); 5.218 (*d*, ^3J(HO–C(3′),3′) = 3.4, HO–C(3′)); 3.538–3.623 (*m*, ^2J(H_a–C(5′),H_b–C(5′)) = −15.0, CH_2(5′)); 5.005 (*t*, ^3J(OH–C(5′),5′) = 3.9, HO–C(5′)); 3.744–3.799 (*m*, H–C(4′), CH_2(1‴)). ^{13}C-NMR ((D_6)DMSO): 40.92 ((C(1‴)); 26.939 (C(2‴)); 26.251 (C(3‴)); 28.5967 (C(4‴)); 28.767–28.928 (C(5‴–12‴)); 28.560 (C(13‴)); 31.200 (C(14‴)); 21.992 (C(15‴)); 13.846 (C(16‴)); 150.289 (C(2)); 162.532 (C(4)); 108.386 (C(5)); 134.605 (C(6)); 12.820 (C(7)); 84.697 (C(1′)); 135 40.08 (C(2′)); 70.230 (C(3′)); 87.311 (C(4′)); 61.188 (C(5′)). Anal. calc. for $C_{26}H_{46}N_2O_5$ (466.654): C 66.92, H 9.94, N 6.00; found: C 66.70, H 10.01, N 5.77.

5′-O-*[Bis(4-methoxyphenyl)phenylmethyl]-2′-deoxy-3,4-dihydrothymidine* (=*1-[(2*R*,4*S*,5*R*)-5-{[Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}tetrahydro-4-hydroxyfuran-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione*; **13**) [15]. Anh. **11** (1.94 g, 8 mmol) was evaporated from dry pyridine and then dissolved in dry pyridine (40 ml). Then, 4,4′-dimethoxytrityl chloride (3.52 g, 10.4 mmol) was added, and the mixture was stirred under N_2 for 24 h. After subsequent addition of MeOH, stirring was continued for 30 min. After addition of an ice-cold 5% aq. $NaHCO_3$ soln. and further stirring for 30 min, the mixture was extracted three times with H_2O, followed by extraction with CH_2Cl_2. The org. layer was dried (Na_2SO_4, 30 min), filtered, evaporated, and dried in high vacuum. The residue was chromatographed (SiO_2 *60*, column: 4 × 24 cm; stepwise elution with CH_2Cl_2/MeOH 99:1, 97:3, and 95:5). After removal of the solvent, **13** (3.36 g, 6.2 mmol, 77%) was isolated as a slightly yellowish foam. $T_{glass\,transition}$ 80–87°. R_f

(SiO_2; CH_2Cl_2/MeOH 96:4) 0.28. log *P:* 4.88 ± 0.51. ^{1}H-NMR ((D_6)DMSO): 11.299 (*s*, H–N(3)); 7.500 (*s*, H–C(6)); 1.462 (*s*, Me(7)); 6.209 (*Ψt*, ^3J(1′,H_α–C(2′)) = 7.0, ^3J(1′,H_β–C(2′)) = 6.7, H–C(1′)); 2.162 (*ddd*, ^2J(H_α–C(2′),H_β–C(2′)) = – 13.4, ^3J(H_α–C(2′),1′) = 6.3, ^3J(H_α–C(2′),3′) = 3.6, H_α–C(2′)); 2.241 (*ddd*, ^2J(H_β–C(2′),H_α–C(2′)) = – 13.5, ^3J(H_β–C(2′),1′) = 6.8, H_β–C(2′)); 4.305 – 4.341 (*m*, H–C(3′)); 5.298 (*d*, ^3J(HO–C(3′),3′) = 4.3, HO–C(3′)); 3.890 (*dd*, ^3J(4′,3′) = 3.4, H–C(4′)); 3.173 – 3.237 (*m*, ^2J(H_a–C(5′),H_b–C(5′)) = – 10.7, CH_2(5′)); 3.736 (*s*, 2 Me(1″)); 6.893 (*d*, ^3J(3″,4″) = 7.5, H–C(3″), 4 H); 7.391 (*d*, ^3J(8″,9″) = 7.6, H–C(8″), 2 H); 7.217 – 7.325 (*m*, 4 H–C(4″), 2 H–C(9″), H–C(10″)). ^{13}C-NMR ((D_6)DMSO): 150.271 (C(2)); 163.546 (C(4)); 109.470 (C(5)); 135.229 (C(6)); 11.595 (C(7)); 83.717 (C(1′)); 39.41 (C(2′)); 70.463 (C(3′)); 85.561 (C(4′)); 63.696 (C(5′)); 54.962 (C(1″)); 158.078 (C(2″)); 113.160 (C(3″)); 129.634 (C(4″)); 135.570 (C(5″)); 85.769 (C(6″)); 144.622 (C(7″)); 127.346 (C(8″)); 127.778 (C(9″)); 126.681 (C(10″)). Anal. calc. for $C_{31}H_{32}N_2O_7$ (544.595): C 68.35, H 5.92, N 5.14; found: C 68.02, H 5.91, N 4.99.

*5′-*O*-[Bis(4-methoxyphenyl)phenylmethyl]-2′-deoxy-3′-*O*-[(1,1-dimethylethyl)diphenylsilyl]-3,4-dihydrothymidine* (*=1-[(2*R*,4*S*,5*R*)-5-{[Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-{[(1,1-dimethylethyl)diphenylsilyl]oxy}tetrahydrofuran-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione*; **14**). Compound **13** (0.47 g, 0.88 mmol) was dissolved in anh. DMF (7 ml). Then, 1*H*-imidazole (0.18 g, 2.64 mmol) was added. To the mixture, (*tert*-butyl)(diphenyl)silyl chloride (TBDPSiCl; 1.32 mmol, 0.35 ml) was added dropwise under cooling in an ice bath (N_2 atm.). After 22 h, the reaction was quenched by addition of MeOH (4 ml). After stirring for 30 min at r.t., to the mixture was added a 5% aq. $NaHCO_3$ soln., and the mixture was extracted twice with AcOEt. After washing with H_2O, the org. layer was dried (Na_2SO_4, 30 min), filtered, evaporated, and then dried in high vacuum. The residue was purified by CC (SiO_2 *60*, column: 4 × 15 cm; equilibrated with petroleum ether (PE)/AcOEt 2.1, containing 3% of Et_3N). Elution with PE/AcOEt 2.1, followed by PE/AcOEt 1.1, gave one main zone, from which **14** (514 mg, 76%) was isolated. Colorless amorphous solid. R_f (SiO_2, PE/AcOEt 1:1) 0.54. $T_{glass\,transition}$ 61.7 – 70.2°. log *P:* 11.54 + / – 0.75. ^{1}H-NMR ((D_6)DMSO): 11.287 (*s*, H–N(3)); 1.410 (*s*, Me(7)); 6.249 (*Ψt*, ^3J(1′,H_β–C(2′)) = 7.0, ^3J(1′,H_α–C(2′)) = 6.8, H–C(1′)); 2.203 (*ddd*, ^2J(H_α–C(2′),H_β–C(2′)) = – 13.4, ^3J(H_α–C(2′),1′) = 6.0, ^3J(H_α–C(2′),3′) = 2.9, H_β–C(2′)); 2.126 (*ddd*, ^2J(H_β–C(2′),H_α–C(2′)) = – 13.7, ^3J(H_β–C(2′),1′) = 6.7, H_β–C(2′)); 4.443 (*Ψq*, H–C(3′)); 4.010 (*m*, (H–C(4′)); 2.912 (*dd*, ^2J(H_a–C(5′),H_b–C(5′)) = – 14.9, H_a–C(5′)); 3.027 (*dd*, ^2J(H_b–C(5′),H_a–C(5′)) = 13.4, H_b–C(5′)); 3.719 (*s*, 2 Me(1″)); 6.8 (*dd*, ^3J(3″,4″) = 4.3, 4 H–C(3″)); 7.096 (*Ψq*, ^3J(H,H) = 8.3, 4 H–C(4″)); 7.322 – 7.408 (*m*, 2 H–C(8″), 2 H–C(9″), H–C(10″)); 7.194 – 7.221 (*m*, H–C(6), 4 H–C(2*)); 7.507, 7.562 (2*d*, ^3J(H,H) = 6.9, H–C(3*), 2 × 2 H); 7.471 – 7.485 (*m*, 2 H–C(4*)); 0.980 (*s*, 3 Me(6*)). ^{13}C-NMR ((D_6)DMSO): 150.787 (C(2)); 164.026 (C(4)); 110.070 (C(5)); 135.639 (C(6)); 12.132 (C(7)); 84.377 (C(1′)); 39.33 (C(2′)); 73.801 (C(3′)); 85.903 (C(4′)); 63.717 (C(5′)); 55.540 (C(1″)); 158.630 (C(2″)); 113.664 (C(3″)); 130.080 (C(4″)); 135.970 (C(5″)); 86.392 (C(6″)); 144.995 (C(7″)); 128.019 (C(8″)); 128.201 (C(9″)); 127.214 (C(10″)); 133.150 (C(1*)); 135.715 (C(2*)); 128.397 (C(3*)); 130.542 (C(4*)); 19.059 (C(5*)); 27.148 (C(6*)). Anal. calc. for $C_{47}H_{50}N_2O_7Si \cdot 0.5\ H_2O$ (782.995): C 71.21, H 6.44, N 3.54; found: C 71.48, H 6.41, N 3.35.

*5′-*O*-[Bis(4-methoxyphenyl)phenylmethyl]-2′-deoxy-3′-*O*-[(1,1-dimethylethyl)diphenylsilyl]-3-hexadecyl-3,4-dihydrothymidine* (*=1-[(2*R*,4*S*,5*R*)-5-{[Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-{[(1,1-dimethylethyl)diphenylsilyl]oxy}tetrahydrofuran-2-yl]-3-hexadecyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione*; **15**). The fully protected **14** (1.1 g, 1.4 mmol) was dissolved in THF (12 ml). At r.t., cetyl alcohol (0.34 g, 1.4 mmol), Ph_3P (0.55 g, 2.1 mmol), and diisopropyl azodicarboxylate (DIAD; 0.6 ml, 2.1 mmol) were added. Stirring was continued overnight under N_2 and under exclusion of light. Then, the mixture was evaporated to dryness, and the residue was purified by CC (SiO_2 *60*, column: 4 × 20 cm; PE/AcOEt 6:1, containing 5% of Et_3N). Evaporation of the main zone afforded a material which was redissolved in cold AcOEt and extracted with H_2O to remove traces of Et_3N. After evaporation of the org. layer, the residue was dried for several days in high vacuum to give **15** (1.03 g, 50%). Colorless foam. R_f (SiO_2, PE/AcOEt 6:1) 0.45. log *P:* 20.82 + / – 0.78. ^{1}H-NMR ((D_6)DMSO): 3.767 (*t*, ^3J(1‴,2‴) = 7.3, CH_2(1‴)); 1.239 (*m*, CH_2(2‴ – 15‴)); 0.854 (*t*, ^3J(16‴,15‴) = 6.7, Me(16‴)); 1.470 (*s*, Me(7)); 6.306 (*Ψt*, ^3J(1′,H_α–C(2′)) = 7.0, ^3J(1′,H_β–C(2′)) = 6.7, H–C(1′)); 2.249 (*ddd*, ^2J(H_α–C(2′),H_β–C(2′)) = – 13.4, ^3J(H_α–C(2′),1′) = 6.0, ^3J(H_α–C(2′),3′) = 3.0, H_α–C(2′)); 2.132 (*ddd*, ^2J(H_β–C(2′),H_α–C(2′)) = – 13.8, ^3J(H_β–C(2′),1′) = 6.6, H_β–C(2′)); 4.465 (*Ψq*, H–C(3′)); 4.049 (*dd*, ^3J(4′,3′) = 3.4, H–C(4′)); 2.947 (*dd*,

$^2J(H_a–C(5'),H_b–C(5')) = -10.6$, $H_a–C(5')$); 3.063 (*dd*, $^2J(H_b–C(5'),H_a–C(5')) = -10.6$, $H_b–C(5')$); 3.729 (*s*, 2 Me(1″)); 6.805 (*d*, $^3J(3'',4'') = 4.4$, 4 H–C(3″)); 7.112 (*Ψt*, $^3J(H,H) = 8.3$, 4 H–C(4″)); 7.334–7.420 (*m*, 2 H–C(8″), 2 H–C(9″), H–C(10″)); 7.206–7.233 (*m*, H–C(6), 4 H–C(2*)); 7.521, 7.579 (2*d*, $^3J(H,H) = 6.9$, 2 × 2 H–C(3*)); 7.445–7.481 (*m*, 2 H–C(4*)); 0.996 (*s*, 3 Me(6*)). ^{13}C-NMR ((D$_6$)DMSO): 40.17 (C(1‴)); 26.54 (C(2‴)); 26.23 (C(3‴)); 28.55 (C(4‴)); 28.77–28.87 (C(5‴–12‴)); 28.48 (C(13‴)); 31.149 (C(14‴)); 21.941 (C(15‴)); 13.790 (C(16‴)); 150.102 (C(2)); 162.340 (C(4)); 108.599 (C(5)); 134.967 (C(6)); 12.229 (C(7)); 84.802 (C(1′)); 39.32 (C(2′)); 73.149 (C(3′)); 85.448 (C(4′)); 63.059 (C(5′)); 54.939 (C(1″)); 113.062 (C(3″)); 129.493 (C(4″)); 135.042 (C(5″)); 85.832 (C(6″)); 144.388 (C(7″)); 127.430 (C(8″)); 127.690 (C(9″)); 126.626 (C(10″)); 133.937 (C(1*)); 135.121 (C(2*)); 127.802 (C(3*)); 129.948 (C(4*)); 18.467 (C(5*)); 26.32 (C(6*)). Anal. calc. for $C_{63}H_{82}N_2O_7Si$ (1007.420): C 75.11, H 8.20, N 2.78; found: C 74.71, H 8.16, N 2.66.

5′-O-[Bis(4-methoxyphenyl)(phenyl)methyl]-2′-deoxy-3-hexadecyl-3,4-dihydrothymidine (*=1-[(2*R*,4*S*,5*R*)-5-{[Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}tetrahydro-4-hydroxyfuran-2-yl]-3-hexadecyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione*; **16**). Compound **15** (0.56 g, 0.56 mmol) was dissolved in THF (7 ml). To this soln., Bu_4NF (TBAF; 5.5 ml), dissolved in THF, was added. The mixture was stirred for 30 min at r.t. and evaporated to dryness. Purification was performed by CC (SiO_2, column: 4 × 24 cm; PE/AcOEt 2:1, containing 3% of Et_3N, followed by PE/AcOEt 1:1). Evaporation of the main zone gave a material which was redissolved in cold AcOEt and extracted with H_2O to remove traces of Et_3N. Evaporation of the org. phase in high vacuum gave **16** (0.336 g, 79%). Slightly orange foam. R_f (SiO_2, PE/AcOEt 2:1) 0.43. log *P:* 14.17 +/− 0.56. ^{1}H-NMR ((D$_6$)DMSO): 3.778 (*t*, $^3J(1''',2''') = 7.3$, $CH_2(1''')$); 1.226 (*m*, $CH_2(2'''–15''')$); 0.841 (*t*, $^3J(16''',15''') = 6.8$, Me(16‴)); 7.546 (*s*, H–C(6)); 1.504 (*s*, Me(7)); 6.241 (*Ψt*, $^3J(1',H_\alpha–C(2')) = 6.8$, $^3J(1',H_\beta–C(2')) = 6.6$, H–C(1′)); 2.200 (*ddd*, $^2J(H_\alpha–C(2'),H_\beta–C(2')) = -13.4$, $^3J(H_\alpha–C(2'),1') = 6.2$, $^3J(H_\alpha–C(2'),3') = 4.0$, $H_\alpha–C(2')$); 2.243 (*ddd*, $^2J(H_\beta–C(2'),H_\alpha–C(2')) = -13.5$, $^3J(H_\beta–C(2'),1') = 6.7$, $H_\beta–C(2')$); 4.314–4.349 (*m*, H–C(3′)); 5.296 (*d*, $^3J(HO–C(3'),3') = 3.7$, HO–C(3′)); 3.908 (*dd*, $^3J(4',3') = 3.4$, H–C(4′)); 3.189–3.250 (*m*, $^2J(H_a–C(5'),H_b–C(5')) = -10.1$, $CH_2(5')$); 3.730 (*s*, 2 Me(1″)); 6.878 (*d*, $^3J(3'',4'') = 7.5$, 4 H–C(3″)); 7.391 (*d*, $^3J(8'',9'') = 7.6$, 2 H–C(8″)); 7.217–7.325 (*m*, 4 H–C(4″), 2 H–C(9″), H–C(10″)). ^{13}C-NMR ((D$_6$)DMSO): 40.54 (C(1‴)); 26.901 (C(2‴)); 26.238 (C(3‴)); 28.585 (C(4‴)); 28.740–28.990 (C(5‴–12‴)); 28.550 (C(13‴)); 31.1872 (C(14‴)); 21.981 (C(15‴)); 13.836 (C(16‴)); 150.194 (C(2)); 162.450 (C(4)); 108.630 (C(5)); 134.252 (C(6)); 12.298 (C(7)); 84.812 (C(1′)); 39.63 (C(2′)); 70.351 (C(3′)); 85.555 (C(4′)); 60.654 (C(5′)); 113.173 (C(3″)); 129.651 (C(4″)); 135.389 (C(5″)); 85.793 (C(6″)); 144.632 (C(7″)); 127.624 (C(8″)); 127.792 (C(9″)); 126.701 (C(10″)). Anal. calc. for $C_{47}H_{64}N_2O_7 \cdot 1.5$ AcOEt (769.020): C 70.45, H 8.42, N 3.10; found: C 70.53, H 8.72, N 2.97.

5′-O-[Bis(4-methoxyphenyl)phenylmethyl]-3′-O-[[bis(1-methylethyl)amino](2-cyanoethoxy)phosphino]-2′-deoxy-3-hexadecyl-3,4-dihydrothymidine (*=(2*R*,3*S*,5*R*)-2-{[Bis(4-methoxyphenyl)(phenyl)-methoxy]methyl}-5-(3-hexadecyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl 2-Cyanoethyl Bis(1-methylethyl)phosphoramidite*; **17**). Compound **16** (0.23 g, 3 mmol) was three times co-evaporated from CH_2Cl_2 and subsequently dissolved in CH_2Cl_2 (15 ml). Then, *Hünig*'s base (126 µl, 0.72 mmol) and (chloro)(2-cyanoethoxy)(diisopropylamino)phosphine (156 µl, 0.6 mmol) were added under Ar. After stirring for 15 at r.t., a 5% aq. $NaHCO_3$ soln. (12 ml) was added. The mixture was extracted three times with CH_2Cl_2. The combined org. phases were dried (Na_2SO_4; 1 min!), filtered, and evaporated to dryness (bath temp. ≤25°). The raw product was then subjected to flash chromatography in a water-cooled column (SiO_2, column: 2 × 10.5 cm, 0.5 bar N_2 pressure). Elution with CH_2Cl_2/acetone 8:2 gave a main zone which was evaporated and dried for 5 min in high vacuum to give **17** (119 mg, 41%). Colorless glass (which can be stored under N_2 at −40°) for months. R_f (SiO_2; CH_2Cl_2/acetone 8:2) 0.85/0.93. ^{31}P-NMR ((D$_6$)DMSO): 147.413, 147.734.

Oligonucleotides. The oligonucleotides **20** and **21**, and their MS analysis were performed by *Eurogentec S. A.*, Liege Science Park, Belgium.

REFERENCES

[1] E. Werz, S. Korneev, M. Montilla-Martinez, R. Wagner, R. Hemmler, C. Walter, J. Eisfeld, K. Gall, H. Rosemeyer, *Chem. Biodiversity* **2012**, *9*, 272.
[2] K. Köstler, E. Werz, E. Malecki, M. Montilla-Martinez, H. Rosemeyer, *Chem. Biodiversity* **2013**, *10*, 39.
[3] E. Malecki, H. Rosemeyer, *Helv. Chim. Acta* **2010**, *93*, 1500.
[4] S. Korneev, H. Rosemeyer, *Helv. Chim. Acta* **2013**, *96*, 201.
[5] E. Malecki, V. Ottenhaus, E. Werz, M. Montilla-Martinez, C. Knies, H. Rosemeyer, *Chem. Biodiversity* **2013**, submitted.
[6] H. Rosemeyer, E. Malecki, S. Korneev, E. Werz, K. Gall, Reactive, 'Lipophilic Nucleoside Building Blocks for the Synthesis of Hydrophobic Nucleic Acids', Europäische Patentanmeldung, 28.09. 2012, EP12186576.0.
[7] C. Wolfrum, S. Shi, K. N. Jayaprakash, M. Jayaraman, G. Wang, R. K. Pandey, K. G. Rjeev, T. Nakayama, K. Charrise, E. M. Ndungo, T. Zimmermann, V. Koteliansky, M. Manoharan, M. Stoffel, *Nat. Biotechnol.* **2007**, *25*, 1149; M. Anaya, M. Kwak, A. J. Musser, K. Müllen, A. Herrmann, *Chem. – Eur. J.* **2010**, *16*, 12852.
[8] L. Moreau, M. Camplo, M. Wathier, N. Taib, M. Laguerre, I. Bestel, M. W. Grinstaff, P. Barthélémy, *J. Am. Chem. Soc.* **2008**, *130*, 14454.
[9] E. Breitmaier, W. Voelter, '^{13}C-NMR Spectroscopy; Monographs in Modern Chemistry', Verlag Chemie, Weinheim, New York, 1978, Vol. 5, pp. 72, 74.
[10] M. Karplus, J. A. Pople, *J. Chem. Phys.* **1963**, *38*, 2803.
[11] D. M. Grant, B. V. Cheney, *J. Am. Chem. Soc.* **1967**, *89*, 5315.
[12] K. C. Kumara Swamy, N. N. Bhuwan Kumar, E. Balaraman, K. V. P. Pavan Kumar, *Chem. Rev.* **2009**, *109*, 2551; T. Brossette, E. Klein, C. Creminon, J. Grassi, C. Mioskowski, L. Lebeau, *Tetrahedron* **2001**, *57*, 8129; F. Himmelsbach, B. S. Schulz, T. Trichtinger, R. Charubala, W. Pfleiderer, *Tetrahedron* **1984**, *40*, 59; E. Quezada, D. Viña, G. Delogu, F. Borges, L. Santana, E. Uriarte, *Helv. Chim. Acta* **2010**, *93*, 309; O. R. Ludek, C. Meier, *Synlett* **2005**, 3145; O. R. Ludek, C. Meier, *Synlett* **2006**, 324.
[13] C. Taylor Clelland, V. Risca, C. Bancroft, *Nature* **1999**, *399*, 533.
[14] H. Rosemeyer, United States Patent US 7914991, 'Nucleolipids and Use thereof and Devices for Nucleic Acid Analysis', 29.03.2011.
[15] P. S. Pallan, P. von Matt, C. J. Wilds, K.-H. Altmann, M. Egli, *Biochemistry* **2006**, *45*, 8048; C. Bleasdale, S. B. Ellwood, B. T. Golding, *J. Chem. Soc., Perkin Trans. 1* **1990**, 803.

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