

Nucleosides with 5'-Fixed Lipid Groups – Synthesis and Anchoring in Lipid Membranes

Nicolai Brodersen,^[a] Jun Li,^[a] Oliver Kaczmarek,^[a] Andreas Bunge,^[b] Ludwig Löser,^[b] Daniel Huster,^[b] Andreas Herrmann,^[c] and Jürgen Liebscher*^[a]

Dedicated to Prof. Dr. Horst Hartmann on the occasion of his 70th birthday

Keywords: Nucleosides / Amphiphiles / Lipophilicity / Membrane anchoring / Synthesis

Nucleosides were synthesized bearing one or two lipophilic groups at the 5'-position. The lipophilic substituents can be fixed at a 5'-amino group or at the 5'-phosphate moiety. Selected examples of these lipophilic nucleosides are shown by

solid-state NMR spectroscopy to anchor in lipid double layers.

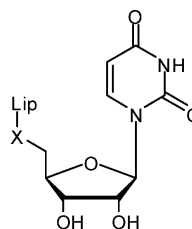
(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2007)

Introduction

Lipophilic nucleosides and oligonucleotides have received broad interest. Because of their amphiphilic properties they can form interesting supramolecular structures, such as monolayer films, micelles and/or vesicles,^[1–8] organogels^[5] or multilamellar layers.^[5,8] Normally their nucleobases are exposed to the aqueous phase, and they potentially can form complementary Watson–Crick base pairs.^[8–10] The lipophilic substituent can also act as an anchor for fixing lipophilic nucleosides or oligonucleotides in biocompatible lipid membranes, again by exposing the nucleotides to the aqueous phase.^[11–14] Recently we could show that nucleosides with lipid moieties linked to the nucleobase anchor in giant unilamellar vesicles (GUVs) and large unilamellar vesicles (LUVs) composed of unilamellar phospholipid bilayers.^[15] Oligonucleotides with two of such lipophilic nucleotides incorporated into the nucleotide chain anchor in both, GUVs and LUVs and were shown to form double-strand DNAs with complementary oligonucleotides in solution.^[16,17] For biotechnological applications, these lipophilic nucleosides can be enriched in lipid domains of distinct physical properties, for example, in liquid-disordered domains. The property of anchoring in li-

pid membranes has also been used in chip technology, when both the chip surface covered by a lipid double layer and a functionalized vesicle are established with complementary lipophilic oligonucleotide units.^[18] Lipophilic nucleosides and nucleotides exhibit antiviral activities^[4,19] and lipophilic nucleoside-5'-phosphate as diesters show antitumour activity^[20–23] (L1210 murine leukemia, murine ascitic carcinoma II) or can inhibit thymidine-5'-diphosphate-glucose-4,6-dehydratase.^[24] The lipophilic moiety is believed to improve the activity because of improved membrane passage and thus cellular uptake. Other very important features of lipophilic oligonucleotides are the ability to permeate cell membranes causing antiviral activity^[25] and the property of facilitating membrane passage of siRNA, which was achieved by the introduction of lipid anchors, such as cholesterol or dialkylaminophenyl groups into the 5' and 3'-end of the oligonucleotide chain.^[26,27]

In continuation of our studies on lipophilic nucleosides and oligonucleotides, we report here the synthesis of new lipophilic nucleosides **1**, where one or two lipophilic moieties are connected to the 5'-position as phosphate ($X = PO_4$) or as amine ($X = NR$).



1

[a] Institute of Chemistry, Humboldt University Berlin, Brook-Taylor-Str.2, 12489 Berlin, Germany
E-mail: liebscher@chemie.hu-berlin.de

[b] Junior Research Group "Structural Biology of Membrane Proteins", Institute of Biotechnology, Martin-Luther University Halle-Wittenberg, Kurt-Mothes-Str. 3, 06120 Halle, Germany

[c] Institute of Biology/Biophysics, Humboldt University Berlin, Invalidenstr. 42, 10115 Berlin, Germany

Supporting information for this article is available on the WWW under <http://www.eurjoc.org> or from the author.

Nucleoside-5'-phosphate triesters were rarely reported. *O,O*-Bis(*n*-butyl)thymidine 5'-phosphate contains only short alkyl groups at the phosphate.^[28] Nucleoside phosphates with two *O*-alkyl groups up to *n*-C₁₆H₃₃ were reported; however, only in the arabinose nucleoside series.^[29]

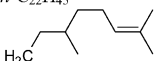
Results

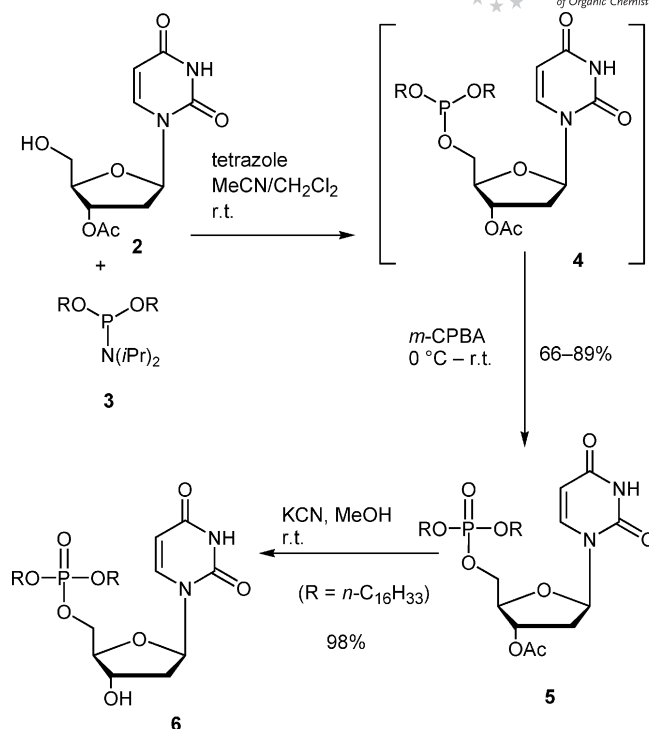
Synthesis of Lipophilic Nucleosides

Several methods were reported to synthesize phosphoric acid triester with one nucleoside as a constituent. Thus, 5-fluoro-2'-deoxyuridine was transformed into a phosphoric acid triester by reaction with a phosphoric acid diester chloride derived from a steroid and 2-chlorophenol.^[24] This method was also used in the synthesis of dinucleotide, wherein the bridging phosphate is a triester.^[30] The phosphoramidite method is a versatile method to introduce phosphates as diesters into alcohols to establish phosphoric acid triesters via intermediate phosphites. In this way, lipophilic phosphates like cholesteryl phosphates or long-chain glycerol ether phosphates were transferred as well. When nucleosides serve as substrates, the phosphate moiety can be introduced into several positions, position 5' included.^[19,31–33] This method seemed to provide promising access to lipophilic nucleoside 5'-phosphate triesters **6**.

The synthesis of starting phosphoramidites **3** was approached by adopting a procedure where *N,N*-diisopropylphosphoramidic dichloride derived from PCl₃ was treated with the corresponding alcohols in the presence of triethylamine in cyclohexane.^[34] It turned out that the reported procedure working at 0 °C was only useful for alcohols up to C₆, whereas alcohols between C₆ and C₁₂ or C₁₆ and C₂₂ required higher temperatures (50–60 or 80 °C, respectively) (Table 1). Because of the sensitivity of lipophilic products **3**, treatment with water was omitted during work up. Without prior purification, phosphoramidites **3** were treated with known 3'-acetyl-2'-deoxyuridine **2**^[35] in dichloromethane in the presence of tetrazole. Resulting phosphites **4** were oxidized in situ with *m*-chloroperbenzoic acid to afford high yields of lipophilic phosphates **5** (Scheme 1, Table 2). As shown for dihexadecyl ester **5e**, highly selective deprotection of the 3'-position to nucleotide diester **6** is possible by treatment with potassium cyanide in methanol at room temperature by adopting a procedure used for the deacetylation of sugars.^[36]

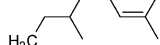
Table 1. *O,O*-Dialkyl-*N,N*-(diisopropyl)phosphoramidites **3**.

3	R	Reaction temp. [°C]	Yield [%]
a	<i>n</i> -C ₄ H ₉	–50 to 0	78
b	<i>n</i> -C ₆ H ₁₃	60	70
c	<i>n</i> -C ₈ H ₁₇	60	75
d	<i>n</i> -C ₁₂ H ₂₅	60	73
e	<i>n</i> -C ₁₆ H ₃₃	85	75
f	<i>n</i> -C ₁₈ H ₃₇	85	87
g	<i>n</i> -C ₂₂ H ₄₅	85	68
h		60	73



Scheme 1.

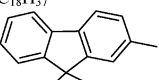
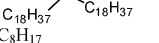
Table 2. Lipophilic nucleotide phosphate dialkyl esters **5**.

5	R	Yield [%]
a	<i>n</i> -C ₄ H ₉	87
b	<i>n</i> -C ₆ H ₁₃	77
c	<i>n</i> -C ₈ H ₁₇	83
d	<i>n</i> -C ₁₂ H ₂₅	66
e	<i>n</i> -C ₁₆ H ₃₃	75
f	<i>n</i> -C ₁₈ H ₃₇	87
g	<i>n</i> -C ₂₂ H ₄₅	89
h		76

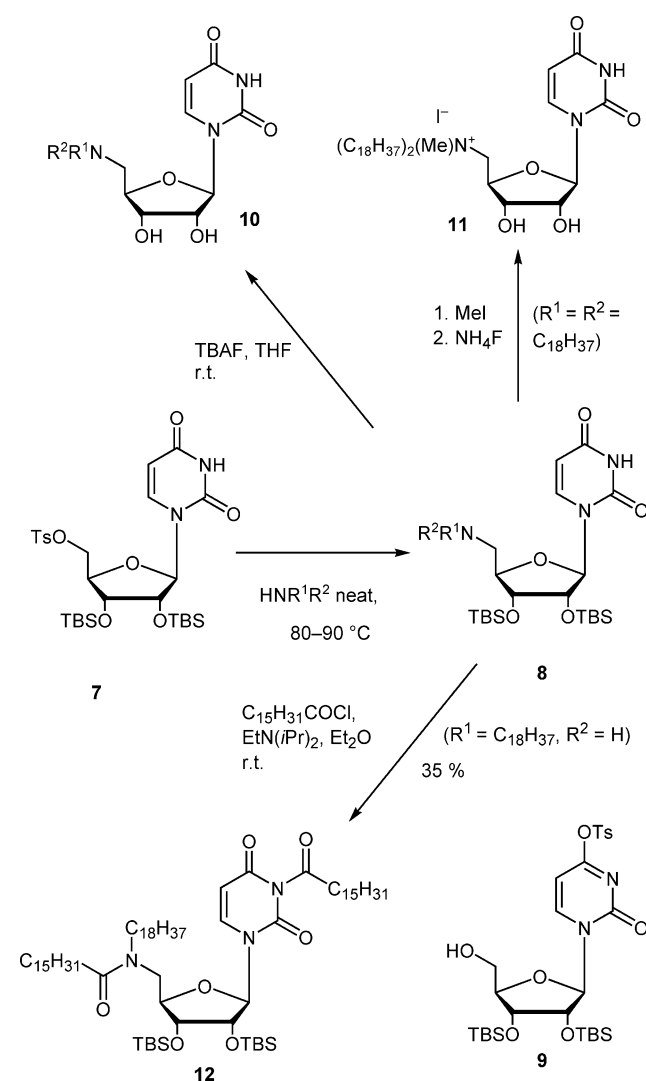
Nonlipophilic 5'-amino-5'-deoxynucleosides can be synthesized by various methods, such as the Mitsunobu reaction of nucleosides with phthalimides,^[37,38] nosylamides,^[39] phosphorazide,^[40] nitric acid^[41] and *N*-Boc-*O*-Cbz-hydroxyamine,^[42] Appel substitution of 5'-OH by azide in the presence of triphenylphosphane/tetrabromomethane^[43–45] and nucleophilic substitution at nucleoside 5-tosylates or mesylates with azide^[46–50] or amines.^[38,51–57] We used the latter method to synthesize lipophilic 5'-amino-5'-deoxynucleosides **8** by reaction with long-chain primary or secondary amines. Tosylate **7** is known and was obtained from uridine by threefold TBS-protection, selective 5'-deprotection^[58] and 5'-tosylation.^[59] Interestingly, during column chromatographic purification on silica, a small amount of unreacted **7** underwent transformation into the isomer **9**, where the tosyl group was found at the pyrimidine ring. Substitution of the tosyloxy group of uridine derivative **7** by primary or secondary long-chain amines in THF failed. However, by heating under neat conditions and by using an excess amount of amine as the solvent or in a melt was successful. Deprotection of resulting 5'-amino-5'-deoxyuri-

dines **8** to aminouridines **10** was possible by treatment with TBAF in THF. As shown in the synthesis of products **10c** and **10d**, a one-pot procedure starting from **7** is also possible by omitting the isolation of silylated substitution product **8**. The 5'-amino substituent in former product **10c** not only provides lipophilic properties but can serve as a fluorescence marker at the same time (Table 3).

Table 3. Lipophilic 5'-amino-5'-deoxyuridines **8** and **10**.

R ¹	R ²	Reaction temp. [°C] / time [h] / equiv. amine 6	Product 8 / Yield [%]	Deprotected product 10 / Yield [%]
C ₁₈ H ₃₇	H	80/10/30	a / 63	a / 22
C ₁₈ H ₃₇	C ₁₈ H ₃₇	80/12/14	b / 82	b / 40
	H	80/28/11		c / 42 ^[a]
	C ₈ H ₁₇	90/10/11		d / 31 ^[a]

[a] Over two steps.

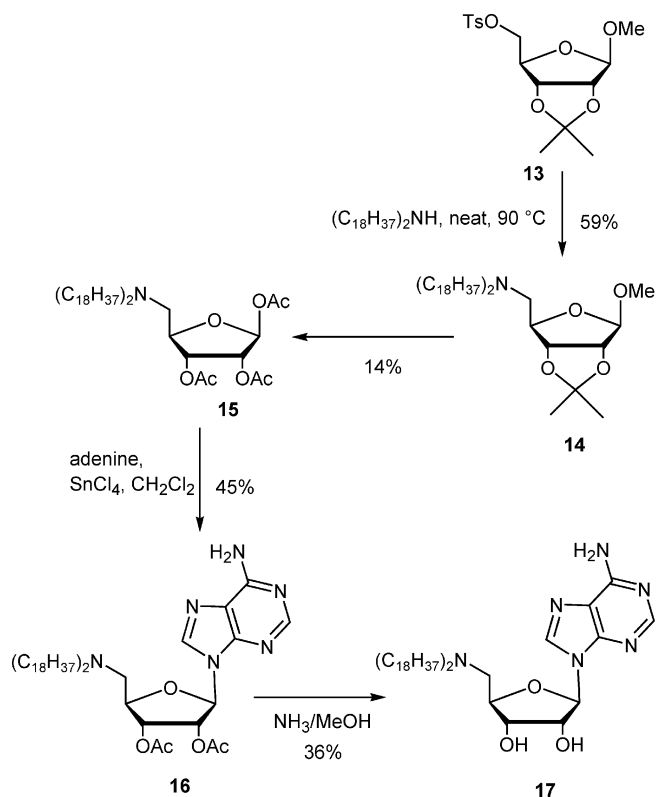


Scheme 2.

In general, the isolated yields of unprotected pure 5'-amino-5'-deoxyuridines **10** are low, because several chromatographic purifications of these amphiphilic materials were necessary.

In order to increase the hydrophilic property, 5'-dioctadecylamino-5'-deoxyuridine **8b** was methylated to afford amphiphilic quaternary ammonium salt **11** after deprotection. We also succeeded to synthesize 5'-amino-5'-deoxyuridine **12** with two lipophilic groups, where the 5'-amino group lacks basicity, by first introducing octadecylamine and then by acylating the resulting 5'-octadecylamino-5'-deoxyuridine with palmitoyl chloride (Scheme 2).

It can be expected that the extension of the methodology use to synthesize 5'-amino-5'-deoxynucleosides from 5'-sulfonated nucleosides and amines to nucleosides other than uridine will face problems, because such nucleoside-5'-sulfonates tend to undergo intramolecular substitution of the sulfonate by the nucleobase under basic conditions.^[60,61] Therefore, an alternative route was followed by first introducing the amino group into the sugar and finally establishing the nucleoside by *N*-glycoside formation as shown in Scheme 3. Known 1'-methyl-2',3'-isopropylidene-5'-tosylribose **13** was treated with neat *N,N*-dioctadecylamine at 90 °C to afford 5'-dioctadecylamino-5'-deoxyribose glycoside **14**. In order to obtain the β -anomer in the final *N*-glycoside formation, an acyl group had to be introduced into the 2'-position of glycoside **14**. Deprotection and acetylation with acetic anhydride gave 1',2',3'-triacetyl-5'-amino-5'-deoxyribose **15** in low yield. Transformation into 5'-amino-5'-deoxyadenosine **16** was achieved by treatment



Scheme 3.

with adenine in the presence of tin tetrachloride in dichloromethane. Final deacetylation with ammonia in methanol gave anticipated 5'-(*N,N*-dioctadecanylethyl)amino-5'-deoxyadenosine **17**. This methodology has not been applied to 5'-amino-5'-deoxyribosides before, but only to ribosides with the azido group masked as an amino functionality in the 5'-position.^[62–64]

Anchoring in Lipid Membranes

We used solid-state NMR spectroscopy to investigate the incorporation of lipophilic nucleosides **10b**, **11** and **17** into lipid membranes. The hydrophilic head groups of these nucleosides are uridine or adenine. The membrane anchorage of these units was achieved by lipophilic groups that are connected to the 5'-position of the ribose as amino moieties or as a quaternary ammonium salt.

To study the alterations in the general membrane morphology and structure after incorporation of lipophilic nucleosides **10b**, **11** and **17**, ³¹P and ²H NMR spectroscopic experiments were carried out.

The ³¹P NMR spectra of POPC membranes in the presence 20 mol-% of each of the three compounds are shown in Figure 1.^[65] From the shape of the NMR spectra, information about the structural and dynamic properties of the phospholipid head groups could be obtained. In the presence of the three lipophilic nucleosides, the POPC membranes remained in the lamellar liquid crystalline membrane phase, as indicated by the very similar spectra compared to the axially symmetric powder pattern for the pure lipid membrane. The chemical shift difference between the low- and the high-field edges of the ³¹P NMR spectra is termed chemical shift anisotropy and is related to the orientation and dynamics of the phosphate group of the lipid. A small decrease in the ³¹P NMR chemical shift anisotropy of the lipid head group can be observed in the presence of **10b** and **17**, whereas the spectrum of **11** is slightly broadened. The small deviations indicate only negligible changes in the chemical environment of the lipid phosphate groups. Quantitative values for the ³¹P NMR chemical shift anisotropy were obtained by using best-fit simulations and are listed in Table 4.

To investigate the influence of the lipophilic nucleosides on lipid chain packing properties in the membranes, ²H NMR spectra of chain-perdeuterated [D₃₁]POPC in the presence of substances **10b**, **11** and **17** were conducted.^[66] Figure 2 shows the smoothed order parameter profiles derived from the ²H NMR spectra as a function of the carbon atom position.

The carbon segments are numbered starting at the carbonyl group of the palmitoyl chain of the [D₃₁]POPC molecule. Small order parameter differences relative to pure lipid membranes are observed for **10b** and **17**, which indicates that the molecules are well incorporated into the membrane without large alterations in the phospholipids packing density. In contrast, the chain order of [D₃₁]POPC in the presence of positively charged ammonium compound **11** is sig-

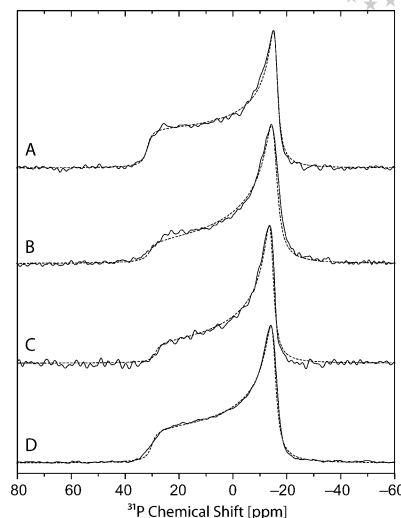


Figure 1. ³¹P NMR spectra of pure POPC membranes (D) and of POPC in the presence of **11** (20 mol-%) (A), **10b** (B) and **17** (C). All measurements were carried out at a water content of 40 wt.-% and a temperature of 30 °C. The dotted lines represent the best-fit simulations of the spectra.

Table 4. ³¹P NMR chemical shift anisotropy values, average order parameters and chain extent of POPC membranes in the presence of lipophilic nucleosides **10b**, **11** and **17**.

Membrane system	$\Delta\sigma$ [ppm]	S_{av}	$\langle L^*c \rangle$ [Å]
POPC	45.2	0.154	11.48
POPC/ 10b	46.5	0.165	11.84
POPC/ 11	47.7	0.209	13.04
POPC/ 17	42.9	0.157	11.60

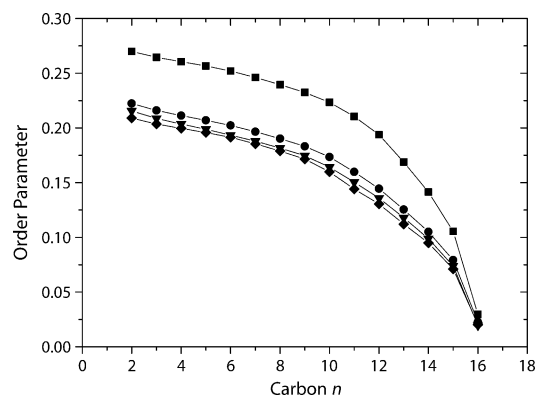


Figure 2. Smoothed order parameter profiles determined from solid-state ²H NMR experiments of *sn*-1 chain perdeuterated [D₃₁]POPC (◆) and 1:4 (mol/mol) mixtures of **10b**/[D₃₁]POPC (●), **11**/[D₃₁]POPC (■) and **17**/[D₃₁]POPC membranes (▼) at a temperature of 303 K and a water content of 40 wt.-%.

nificantly increased, which indicates that the large perturbation of the membrane packing properties may be due to the electrostatic interaction of the positive charge with the negatively charged phosphate group of the phospholipids or a by a change in the lipid head group orientation. Further,

because of the Born repulsion of the charge from the hydrophobic membrane surface, the head group of the nucleoside is likely to be repelled from this surface. This can also be seen from the average order parameter, which is largest for the mixture of POPC/11 and translates into the longest chain length of the lipid matrix (Table 4).

The preferential location of the lipophilic nucleosides within the membrane was investigated by two dimensional ^1H NOESY NMR spectroscopy under magic-angle spinning conditions.^[67] This technique further allowed the de-

termination of the distribution of the sugar/base moiety in the membrane. To this end, intermolecular cross peaks between the phospholipids and the nucleoside were analyzed. The intermolecular cross peak volumes were calculated at various mixing times, and the corresponding NOE build-up curves were fitted to the standard spin pair model to obtain cross relaxation rates σ_{ij} .

Because the intermolecular σ_{ij} values are proportional to contact probabilities between interacting molecular segments,^[67] spatial information can be obtained to find the localization of the lipophilic nucleosides in the lipid membrane.

The nucleoside moieties of **10b**, **11** and **17** were broadly distributed along the bilayer as illustrated in Figure 3 due to the thermal disorder within the membrane. The highest probability of contacts (highest cross relaxation rate) and therefore the most probable localization of the hydrophilic nucleoside moieties could be observed in the lipid–water interface region of the membranes. The probability distribution of localization of the 6-H, 5-H and 1'-H protons of positively charged **11** is significantly shifted to the head-group region of the phospholipids relative to **10b**, which may also explain the more ordered membrane seen by ^2H NMR spectroscopy. This effect is more pronounced for the polar sugar moiety where the localization of the less-polar uracil base indicates a backfolding of the nucleobase towards the hydrophobic core of the membrane.

Conclusions

A number of new amphiphilic nucleosides bearing one or two lipophilic groups at the 5'-position were synthesized. Reaction of 3'-acetyl-2'-deoxyuridine with various long-chain dialkyl phosphoramidites and subsequent oxidation with *m*-chloroperbenzoic acid afforded 2'-deoxyuridine-5'-phosphate triesters **5** and **6**, whereas the reaction of 2',3'-diprotected uridine-5'-tosylate with long-chain alkylamines afforded 5'-amino-5'-deoxyuridines **10**. In an alternative way, dioctadecylamine was first introduced into a protected ribose 5'-tosylate and finally *N*-glycosylated with adenine. Two lipophilic groups could be introduced into uridine by reaction of the 5'-tosylate with *N*-octadecylamine and subsequent acylation with palmitoyl chloride. 5'-*N,N'*-Dioctadecylamino-5'-deoxyuridine could be quaternized by methyl iodide to afford an amphiphilic nucleotide with more pronounced polar properties. The latter as well as nonquaternized 5'-amino-5'-deoxynucleosides anchor in the phospholipid membranes with their lipophilic alkyl chains. As determined by ^2H -, ^{31}P - and ^1H MAS NMR spectroscopy, this anchoring does not disturb the structure of the membrane, and the polar sugar moieties are oriented in the interphase between the polar choline phosphate head groups of the membrane and water. The sugar/base moiety of the nucleosides is localized in the lipid water interface of the membrane, whereas the lipophilic chains insert into the hydrophobic membrane interior.

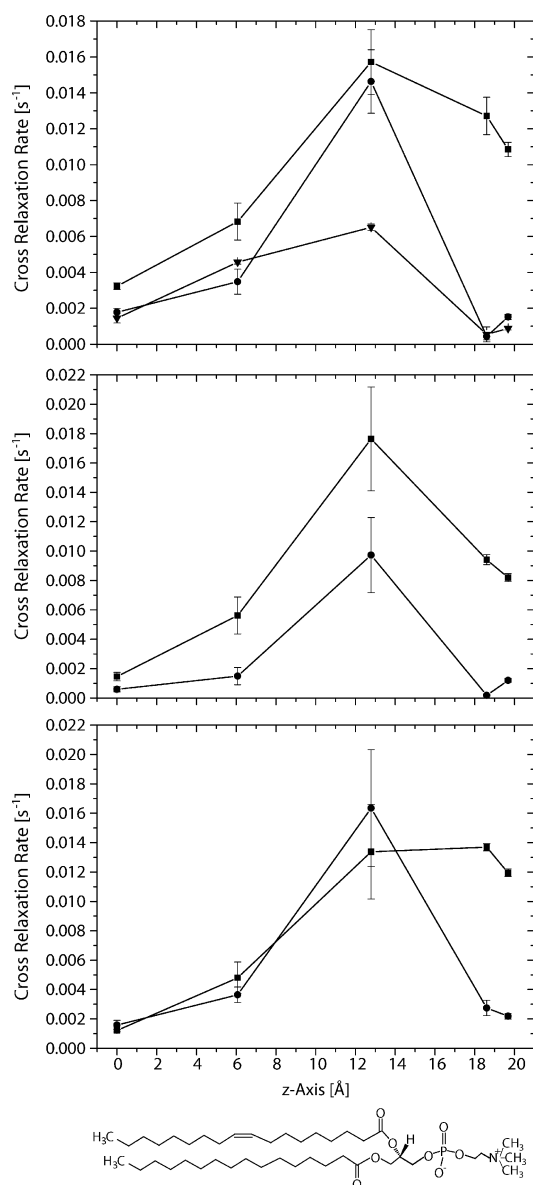


Figure 3. ^1H NOESY NMR cross-relaxation rates (s^{-1}) between molecular segments of the lipophilic nucleosides and segments of POPC molecules in the membrane as a function of the coordinates obtained from a molecular dynamics simulation of pure POPC membranes.^[68] Top: Distribution of the 6-H proton of the uracil moiety of **10b** (●) and **11** (■) and the 8-H proton of the adenine nucleobase of **17** (▼) with respect to the membrane normal; middle: localization of the 5-H proton of the uracil nucleobase of **10b** (●) and **11** (■) and bottom: distribution of the 1'-H proton of the ribose moiety of **10b** (●) and **11** (■) within the POPC matrix.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, with a Bruker AC 300 in CDCl_3 with TMS as an internal standard. POPC (1-[D_{31}]palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine) and [D_{31}]POPC were purchased from Avanti Polar Lipids (Alabaster, AL) and used without further purification. For ^2H -, ^{31}P - and ^1H NOESY NMR measurements, mixtures of phospholipids and lipophilic nucleosides were prepared in a chloroform/methanol mixture (1/1). The solvent was removed by rotary evaporation, and the resulting lipid film was redissolved in cyclohexane and lyophilized overnight to obtain a fluffy powder. Samples were hydrated with 40 wt.-% water and equilibrated by 10 freeze–thaw cycles and gentle centrifugation. The liposome dispersion was transferred into 4-mm high-resolution MAS rotors fitted with spherical Kel-F inserts for liquid samples or into 5-mm glass vials for static ^2H NMR experiments. ^{31}P NMR spectra were recorded with a Bruker DRX 600 NMR spectrometer at a resonance frequency of 242.8 MHz for ^{31}P by using a Hahn-echo pulse sequence with a 90° pulse length of 7 μs , a Hahn-echo delay of 50 μs , a spectral width of 100 kHz, and a recycle delay of 4 s. Continuous-wave proton decoupling was applied during signal acquisition. Spectral simulations of the ^{31}P NMR line shape were carried out to obtain the chemical shift anisotropy ($\Delta\sigma$) by using a program written in *Mathcad 2001* (MathSoft Engineering & Education Inc., Cambridge, MA). ^2H NMR spectra were recorded with a Bruker Avance400 NMR spectrometer at a resonance frequency of 61.5 MHz for ^2H by using a solids probe with a 5 mm solenoid coil. The ^2H NMR spectra were accumulated by using the quadrupolar echo sequence and a relaxation delay of 1 s. The two 3.1 μs $\pi/2$ pulses were separated by a 60 μs delay. ^2H NMR spectra were depaked and order parameters for each methylene group in the chain were determined as described.^[68] ^1H MAS NMR spectra were acquired at a spinning speed of 6009 Hz with a Bruker DRX 600 NMR spectrometer by using a 4-mm HR MAS probe. Typical $\pi/2$ pulse lengths were 9 μs . A ^2H lock was used for field stability. Two-dimensional ^1H MAS NOESY spectra were acquired at various mixing times (between 1 and 600 ms). The dwell time of the indirect dimension was set equal to one rotor period to avoid folding of spinning sidebands into the centre band region of the 2D NOESY spectra. Typically, between 400 and 500 data points were acquired in the indirect dimension with 32 scans per increment at a relaxation delay of 3.5 s. The volumes of the diagonal and cross peaks were integrated by using the Bruker *XWINNMR* software package. NOE build-up curves were fitted to the spin-pair model obtaining cross relaxation rates. All spectra were acquired at a temperature of 30 $^\circ\text{C}$. Silica gel (0.04–0.063 mm, Merck) was used for preparative column chromatography. Starting materials **3**,^[34] **7**^[58,59] and **13**^[26] were synthesized according to literature procedures. All the other materials were purchased from commercial suppliers.

Representative Procedure for the Preparation of Phosphoramidites 3. ***O,O*-Dibutyl-*N,N*-diisopropylphosphoramidite (3a):** *N,N*-diisopropylphosphoramidite dichloride^[34] (1.01 g, 5.00 mmol) was dissolved in hexane (6 mL) under an atmosphere of argon. The solution was cooled to -50°C and a solution of *n*-BuOH (740 mg, 10.0 mmol) and DIPEA (1.9 g, 15.0 mmol) in hexane (4 mL) was added. The solution was stirred and the temperature slowly rose to 20 $^\circ\text{C}$. Further stirring at room temperature for 2 h led to the completion of the reaction. The precipitate was filtered off, and the filtrate was concentrated in vacuo. Compound **3a** was obtained as a colourless oil. Yield: 1.08 g (78%). ^1H NMR (300 MHz, CDCl_3): δ = 0.84 (t, J = 7.4 Hz, 6 H, CH_3), 1.09, 1.11 (d, J = 6.0 Hz, 12 H, CH_3), 1.30 (m, 4 H, CH_2), 1.53 (m, 4 H, CH_2), 3.50 (m, 6 H, CH_2O

+ CH) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): δ = 13.8 (CH_3), 19.1 (CH_2), 24.5 (CH_3), 24.6 (CH_3), 33.3 (CH_2), 33.4 (CH_2), 42.6 (CH), 42.7 (CH), 63.0 (CH_2O) ppm. ^{31}P NMR (242.8 MHz, CDCl_3): δ = 145.54, 139.79 ppm.

General Procedure for the Synthesis of *O,O*-Dialkyl-*O*-(3'-*O*-acetyl-2'-deoxyuridin-5'-yl)phosphates 5a–h: *O,O*-Dialkyl-*N,N*-diisopropylphosphoramidite **3a–h** (0.40 mmol) and 3'-*O*-acetyl-2'-deoxyuridine **2** (0.20 mmol) were dissolved in a tetrazole solution (~ 0.45 M in MeCN, 2 mL) and dry DCM (2 mL). The suspension was stirred at room temperature for 24 h. The mixture was cooled to 0 $^\circ\text{C}$ and *m*-CPBA (138 mg, 0.80 mmol) was added. After stirring for 1 h at 0 $^\circ\text{C}$ and 2 h at room temperature, the precipitate was filtered off and washed with DCM (5×5 mL). The combined filtrates were concentrated and dried in vacuo, and crude materials **5a–h** were submitted to silica gel column chromatography (DCM/EtOAc, 5:3).

***O,O*-Dibutyl-*O*-(3'-*O*-acetyl-2'-deoxyuridin-5'-yl)phosphate (5a):** Yield: 80 mg (87%). ^1H NMR (300 MHz, [D_6]DMSO): δ = 0.68 (m, 6 H, CH_3), 1.12 (m, 4 H, CH_2), 1.37 (m, 4 H, CH_2), 1.87 (s, 3 H, CH_3), 2.15 (m, 2 H, CH_2'), 3.76 (q, J = 6.0 Hz, 4 H, CH_2), 3.96 (m, 3 H, CH_4' , CH_25'), 5.00 (s, 1 H, CH_3'), 5.44, 5.47 (d, J = 9.0 Hz, 1 H, CH_5), 5.96 (t, J = 7.2 Hz, 1 H, CH_1'), 7.47, 7.50 (d, J = 9.0 Hz, 1 H, CH_6), 11.23 (s, 1 H, NH) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): δ = 13.5 (CH_3), 18.2 (CH_2), 20.9 (CH_3), 31.7 (CH_2), 31.8 (CH_2), 35.9 (C_2'), 66.6, 66.7 (C_5'), 67.1 (CH_2O), 67.2 (CH_2O), 73.6 (C_3'), 82.0, 82.1 (C_1'), 84.6 (C_4'), 103.0 (C_5), 139.6 (C_6), 150.4 (C_2), 163.3 (C_4), 170.5 ($\text{O}=\text{CCH}_3$) ppm. ^{31}P NMR (242.8 MHz, CDCl_3): δ = 0.26 ppm. MS (ESI): m/z = 462.31.

***O,O*-Dihexadecyl-*O*-(3'-*O*-acetyl-2'-deoxyuridin-5'-yl)phosphate (5e):** Yield: 120 mg (75%). ^1H NMR (300 MHz, CDCl_3): δ = 0.76 (t, J = 6.8 Hz, 6 H, CH_3), 1.13 (m, 52 H, CH_2), 1.56 (m, 4 H, CH_2), 1.99 (s, 3 H, CH_3O), 2.01–2.37 (m, 2 H, CH_2'), 3.94 (q, J = 6.9 Hz, 4 H, CH_2O), 4.06 (m, 1 H, CH_4'), 4.17 (m, 2 H, CH_25'), 5.16, 5.18 (d, J = 6.0 Hz, 1 H, CH_3'), 5.66 (dd, J = 9.0 Hz, J = 3.0 Hz, 1 H, CH_5), 6.26 (q, J = 4.9 Hz, 1 H, CH_1'), 7.58, 7.60 (d, J = 6.0 Hz, 1 H, CH_6), 9.24 (s, 1 H, NH) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): δ = 14.1 (CH_3), 20.9 (CH_3), 22.7 (CH_2), 25.4 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 30.3 (CH_2), 30.3 (CH_2), 31.9 (CH_2), 37.6 (C_2'), 66.8, 66.9 (C_5'), 68.3 (CH_2O), 68.4 (CH_2O), 74.5 (C_3'), 83.1, 83.2 (C_1'), 84.8 (C_4'), 103.1 (C_5), 139.4 (C_6), 150.4 (C_2), 163.0 (C_4), 170.5 ($\text{O}=\text{CCH}_3$) ppm. ^{31}P NMR (242.8 MHz, CDCl_3): δ = -0.15 ppm. HRMS: calcd. for $\text{C}_{43}\text{H}_{79}\text{N}_2\text{O}_9\text{P}$ 799.55 [$\text{M} + \text{H}$] $^+$; found 799.67.

***O,O*-Dihexadecyl-*O*-(2'-deoxyuridin-5'-yl)phosphate (6):** Nucleoside-5'-phosphate **5e** (130 mg, 0.16 mmol) and KCN (20 mg, 0.31 mmol) were dissolved in MeOH (5 mL) at room temperature and stirred for 4 h. After evaporation of the solvent, the residue was submitted to silica gel column chromatography (DCM/MeOH, 20:1; R_f = 0.4). Product **6** was obtained as a white solid. Yield: 121 mg (98%). ^1H NMR (300 MHz, CDCl_3): δ = 0.85 (t, J = 6.8 Hz, 6 H, CH_3), 1.23 (m, 52 H, CH_2), 1.65 (m, 4 H, CH_2), 2.13, 2.41 (m, 2 H, CH_2'), 3.91 (m, 1 H, CH_4'), 4.03 (q, J = 7.2 Hz, 4 H, CH_2O), 4.23 (m, 2 H, CH_25'), 4.47 (m, 1 H, CH_3'), 5.70, 5.73 (d, J = 9.0 Hz, 1 H, CH_5), 6.28 (t, J = 6.3 Hz, 1 H, CH_1'), 7.58, 7.61 (d, J = 9.0 Hz, 1 H, CH_6), 9.36 (s, 1 H, NH) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): δ = 14.1 (CH_3), 22.7 (CH_2), 25.4 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 30.2 (CH_2), 30.3 (CH_2), 31.9 (CH_2), 40.4 (C_2'), 66.4 (C_5'), 68.4 (CH_2O), 68.5 (CH_2O), 70.7 (C_3'), 84.8, 84.9 (C_4'), 85.1 (C_1'), 102.6 (C_5), 139.7 (C_6), 150.4 (C_2), 163.2 (C_4) ppm. ^{31}P NMR (242.8 MHz, CDCl_3): δ = 0.19 ppm.

General Procedure for the Synthesis of 5'-Amino-2',3'-[Bis(*tert*-butyldimethylsilyl)]-5'-deoxyuridines **8 and 5'-Amino-5'-deoxyuridines **10a–d**:** 5'-Tosyl-2',3'-[bis(*tert*-butyldimethylsilyl)]uridine **7** (1 equiv.) was dissolved in neat amine HNR^1R^2 (11–30 equiv.) at 80–90 °C under an atmosphere of argon. The solution was kept at that temperature for 3.5–28 h under vigorous stirring. As TLC indicated the final progress of the reaction, the melt was solidified at room temperature and pulverized (except **8d**). The material was suspended in Et_2O and stored at –20 °C for 1 h. The solid material was filtered off and washed with cold Et_2O . The filtrates were combined, and the solvent evaporated. The residue was submitted to silica gel column chromatography. In the case of **8c,d** the filtrates were evaporated, and the residues treated with TBAF (1 M in THF) without purification. Compounds **8a,b** were isolated, characterized and deprotected with TBAF afterwards (r.t., 30 min). Raw materials **10a–d** were purified by silica gel column chromatography.

5'-Octadecylamino-2',3'-[bis(*tert*-butyldimethylsilyl)]-5'-deoxyuridine (8a**):** Starting material **7** (150 mg, 0.24 mmol), octadecylamine (1.90 g, 7.0 mmol, 29 equiv.), 80 °C, 3.5 h. Column chromatography EtOAc, $R_f = 0.3$. Yield: 110 mg (63%). Colourless oil. ^1H NMR (300 MHz, CDCl_3): $\delta = 0.06$ (s, 9 H, Si- CH_3), 0.09 (s, 3 H, Si- CH_3), 0.86 (s, 3 H, $-\text{CH}_2-\text{CH}_3$), 0.87 [s, 9 H, Si- $\text{C}(\text{CH}_3)_3$], 0.89 [s, 9 H, Si- $\text{C}(\text{CH}_3)_3$], 1.23 (s, 30 H, $-\text{CH}_2-$), 1.47 (s, 2 H, $-\text{NH}-\text{CH}_2-\text{CH}_2-$), 2.63 (t, $J = 6.8$ Hz, 2 H, $-\text{NH}-\text{CH}_2-\text{CH}_2-$), 2.86 (m, 2 H, $-\text{CH}_2\text{S}'$), 3.88 (m, 1 H, $-\text{CH}-\text{OH}$, 4'), 4.13 (m, 1 H, $-\text{CH}-\text{OH}$, 2'), 4.21 (t, $J = 3.8$ Hz, 1 H, $-\text{CH}-\text{OH}$, 3'), 5.65 (d, $J = 3.4$ Hz, 1 H, $-\text{CH}-$, 1'), 5.70 (d, $J = 8.3$ Hz, 1 H, CH5), 7.74 (d, $J = 8.3$ Hz, 1 H, CH6) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = -4.75$ (Si- CH_3), -4.73 (Si- CH_3), -4.43 (Si- CH_3), -4.11 (Si- CH_3), 14.23 ($-\text{CH}_2-\text{CH}_3$), 18.08 [$-\text{C}(\text{CH}_3)_3$], 18.15 [$-\text{C}(\text{CH}_3)_3$], 22.79 ($-\text{CH}_2-$), 25.88 [$-\text{C}(\text{CH}_3)_3$], 25.93 [$-\text{C}(\text{CH}_3)_3$], 27.43 ($-\text{CH}_2-$), 29.49 ($-\text{CH}_2-$), 29.69 ($-\text{CH}_2-$), 29.75 ($-\text{CH}_2-$), 29.77 ($-\text{CH}_2-$), 29.80 ($-\text{CH}_2-$), 30.25 ($-\text{CH}_2-$), 32.02 ($-\text{CH}_2-$), 50.56 ($\text{CH}_2\text{S}'$), 72.51 (CH_3'), 75.26 (CH_2'), 83.15 (CH_4'), 91.37 (CH_1'), 102.04 (CH5), 141.11 (CH6), 150.38 (C2), 163.87 (C4) ppm. HRMS: calcd. for $\text{C}_{39}\text{H}_{78}\text{N}_3\text{O}_5\text{Si}_2^+$ 724.5475; found 724.5475.

5'-Diocadecylamino-2',3'-[bis(*tert*-butyldimethylsilyl)]-5'-deoxyuridine (8b**):** Starting material **7** (180 mg, 0.29 mmol), dioctadecylamine (2.10 g, 4.0 mmol, 14 equiv.), 80 °C, 12 h. Column chromatography EtOAc/cyclohexane, 1:4; $R_f = 0.3$. Yield: 230 mg (82%). Colourless oil. ^1H NMR (300 MHz, CDCl_3): $\delta = 0.06$ (s, 3 H, Si- CH_3), 0.07 (s, 6 H, Si- CH_3), 0.09 (s, 3 H, Si- CH_3), 0.87 [s, 9 H, Si- $\text{C}(\text{CH}_3)_3$], 0.88 [s, 9 H, Si- $\text{C}(\text{CH}_3)_3$], 0.90 [s, 9 H, Si- $\text{C}(\text{CH}_3)_3$], 1.24 (s, 60 H, $-\text{CH}_2-$), 1.42 (s, 4 H, $-\text{N}-\text{CH}_2-\text{CH}_2-$), 2.47 (m, 4 H, $-\text{N}-\text{CH}_2-\text{CH}_2-$), 2.64 (m, 2 H, $-\text{CH}_2\text{S}'$), 3.81 (m, 1 H, $-\text{CH}-\text{OH}$, 4'), 4.10 (m, 1 H, $-\text{CH}-\text{OH}$, 2'), 4.21 (t, $J = 3.8$ Hz, 1 H, $-\text{CH}-\text{OH}$, 3'), 5.68 (d, $J = 3.8$ Hz, 1 H, $-\text{CH}-$, 1'), 5.72 (d, $J = 8.3$ Hz, 1 H, CH5), 7.56 (d, $J = 8.3$ Hz, 1 H, CH6) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = -4.67$ (Si- CH_3), -4.34 (Si- CH_3), -4.00 (Si- CH_3), 14.25 ($-\text{CH}_2-\text{CH}_3$), 18.12 [$-\text{C}(\text{CH}_3)_3$], 22.82 ($-\text{CH}_2-$), 25.94 [$-\text{C}(\text{CH}_3)_3$], 27.07 ($-\text{CH}_2-$), 27.66 ($-\text{CH}_2-$), 29.79 ($-\text{CH}_2-$), 29.84 ($-\text{CH}_2-$), 32.05 ($-\text{CH}_2-$), 55.11 ($-\text{CH}_2-$), 56.39 ($\text{CH}_2\text{S}'$), 73.41 (CH_3'), 74.64 (CH_2'), 83.08 (CH_4'), 91.08 (CH_1'), 102.05 (CH5), 140.87 (CH6), 150.23 (C2), 163.63 (C4) ppm.

5'-Octadecylamino-5'-deoxyuridine (10a**):** Compound **8a** (267 mg, 0.37 mmol), THF (2 mL), TBAF (1 M in THF; 1 mL, 1 mmol, 2.7 equiv.). Column chromatography MeOH/ CHCl_3 , 1:30 to 1:10; $R_f = 0.1$. Yield: 41 mg (22%). Colourless oil. ^1H NMR (300 MHz, CDCl_3): $\delta = 0.85$ (t, $J = 6.8$ Hz, 3 H, $-\text{CH}_2-\text{CH}_3$), 1.23 (s, 30 H, $-\text{CH}_2-$), 1.56 (s, 2 H, $-\text{NH}-\text{CH}_2-\text{CH}_2-$), 2.76 (s, 2 H, $-\text{NH}-\text{CH}_2-\text{CH}_2-$), 3.08 (m, 2 H, $-\text{CH}_2\text{S}'$), 4.16 (m, 2 H, $-\text{CH}-\text{OH}$, 2'4'), 4.27

(m, 1 H, $-\text{CH}-\text{OH}$, 3'), 5.69 (d, $J = 7.5$ Hz, 1 H, CH5), 5.77 (s, 1 H, $-\text{CH}-$, 1'), 7.62 (d, $J = 7.5$ Hz, 1 H, CH6) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 14.19$ ($-\text{CH}_2-\text{CH}_3$), 22.74 ($-\text{CH}_2-$), 27.07 ($-\text{CH}_2-$), 29.36 ($-\text{CH}_2-$), 29.41 ($-\text{CH}_2-$), 29.64 ($-\text{CH}_2-$), 29.71 ($-\text{CH}_2-$), 29.76 ($-\text{CH}_2-$), 31.98 ($-\text{CH}_2-$), 49.33 ($-\text{CH}_2-$), 49.74 ($\text{CH}_2\text{S}'$), 71.27 (CH_3'), 73.97 (CH_2'), 80.54 (CH_4'), 91.3795 (CH_1'), 102.49 (CH5), 142.03 (CH6), 150.35 (C2), 163.16 (C4) ppm. HRMS: calcd. for $\text{C}_{27}\text{H}_{50}\text{N}_3\text{O}_5^+$ 496.3745; found 496.3751.

5'-Diocadecylamino-5'-deoxyuridine (10b**):** Compound **8b** (130 mg, 0.13 mmol), THF (2 mL), TBAF (1 M in THF; 1 mL, 1 mmol). Column chromatography MeOH/ CHCl_3 , 1:7; $R_f = 0.2$. Yield: 40 mg (40%). Colourless solid, m.p. 53–55 °C. ^1H NMR (300 MHz, CDCl_3): $\delta = 0.87$ (t, $J = 6.8$ Hz, 6 H, $-\text{CH}_2-\text{CH}_3$), 1.25 (s, 60 H, $-\text{CH}_2-$), 1.45 (s, 4 H, $-\text{NH}-\text{CH}_2-\text{CH}_2-$), 2.56 (s, 4 H, $-\text{NH}-\text{CH}_2-\text{CH}_2-$), 2.82 (m, 2 H, $-\text{CH}_2\text{S}'$), 4.00 (m, $J = 6.0$ Hz, 1 H, $-\text{CH}-\text{OH}$, 4'), 4.10 (m, $J = 6.0$ Hz, 1 H, $-\text{CH}-\text{OH}$, 2'), 4.21 (s, 1 H, $-\text{CH}-\text{OH}$, 3'), 5.71 (d, $J = 8.3$ Hz, 1 H, CH5), 5.75 (d, $J = 1.8$ Hz, 1 H, $-\text{CH}-$, 1'), 7.71 (d, $J = 8.3$ Hz, 1 H, CH6) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 14.27$ ($-\text{CH}_2-\text{CH}_3$), 22.83 ($-\text{CH}_2-$), 26.37 ($-\text{CH}_2-$), 27.62 ($-\text{CH}_2-$), 29.40 ($-\text{CH}_2-$), 29.51 ($-\text{CH}_2-$), 29.76 ($-\text{CH}_2-$), 29.81 ($-\text{CH}_2-$), 29.87 ($-\text{CH}_2-$), 32.02 ($-\text{CH}_2-$), 54.82 ($-\text{CH}_2-$), 56.06 ($\text{CH}_2\text{S}'$), 72.21 (CH_3'), 74.85 (CH_2'), 81.59 (CH_4'), 92.05 (CH_1'), 102.40 (CH5), 140.84 (CH6), 151.06 (C2), 163.94 (C4) ppm. HRMS: calcd. for $\text{C}_{45}\text{H}_{86}\text{N}_3\text{O}_5^+$ 748.6562; found 748.6563.

5'-(9,9-Dioctadecyl-9H-fluorene-2-ylamino)-5'-deoxyuridine (10c**):** Compound **7** (200 mg, 0.32 mmol), 2-amino-9,9-dioctadecyl-9H-fluorene (2.4 g, 3.5 mmol, 11 equiv.), 80–90 °C, 28 h. One-pot procedure: for deprotection THF (18 mL) and TBAF (1 M in THF; 9 mL, 9 mmol) was added, and the mixture was kept at room temperature for 50 min. Column chromatography EtOAc/cyclohexane, 1:9; $R_f = 0.1$. Yield: 123 mg (42%). Yellow oil. ^1H NMR (300 MHz, CDCl_3): $\delta = 0.61$ (s, 4 H, $-\text{CH}_2-$), 0.86 (t, $J = 6.8$ Hz, 6 H, $-\text{CH}_2-\text{CH}_3$), 1.33–0.93 (m, 60 H, $-\text{CH}_2-$), 1.86 (m, 4 H, $-\text{N}-\text{CH}_2-\text{CH}_2-$), 3.76–3.38 (m, 2 H, $-\text{CH}_2\text{S}'$), 4.19 (m, 1 H, $-\text{CH}-\text{OH}$, 4'), 4.23 (m, 1 H, $-\text{CH}-\text{OH}$, 2'), 4.28 (m, 1 H, $-\text{CH}-\text{OH}$, 3'), 5.47 (s, 1 H, $-\text{CH}-$, 1'), 5.80 (s, 1 H, CH5), 6.63 (m, 2 H, CH_{ar}), 7.28–7.10 (m, 3 H, CH_{ar}), 7.46 (d, $J = 8.0$ Hz, 1 H, CH_{ar}), 7.47 (d, $J = 8.3$ Hz, 1 H, CH_{ar}), 7.52 (d, $J = 7.3$ Hz, 1 H, CH_{ar}) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 14.27$ ($-\text{CH}_2-\text{CH}_3$), 22.84 ($-\text{CH}_2-$), 23.97 ($-\text{CH}_2-$), 29.52 ($-\text{CH}_2-$), 29.77 ($-\text{CH}_2-$), 29.83 ($-\text{CH}_2-$), 29.88 ($-\text{CH}_2-$), 30.28 ($-\text{CH}_2-$), 32.07 ($-\text{CH}_2-$), 40.72 ($-\text{CH}_2-$), 46.09 ($\text{CH}_2\text{S}'$), 54.95 ($-\text{CH}_{\text{ar}}$), 70.78 (CH_3'), 74.71 (CH_2'), 83.30 (CH_4'), 91.41 (CH_1'), 102.41 (CH5), 107.55 ($-\text{C}_{\text{ar}}$), 112.18 ($-\text{C}_{\text{ar}}$), 118.44 ($-\text{C}_{\text{ar}}$), 120.62 ($-\text{C}_{\text{ar}}$), 122.73 ($-\text{C}_{\text{ar}}$), 125.43 ($-\text{C}_{\text{ar}}$), 126.75 ($-\text{C}_{\text{ar}}$), 132.21 ($-\text{C}_{\text{ar}}$), 140.52 (CH6), 141.53 ($-\text{C}_{\text{ar}}$), 147.82 ($-\text{C}_{\text{ar}}$), 149.76 ($-\text{C}_{\text{ar}}$), 151.36 (C2), 152.89 ($-\text{C}_{\text{ar}}$), 163.92 (C4) ppm. UV (0.13 mmol L^{-1} in CHCl_3): λ (ε, $\text{L mol}^{-1} \text{cm}^{-1}$) = 300 (26970). HRMS: calcd. for $\text{C}_{58}\text{H}_{94}\text{N}_3\text{O}_5^+$ 912.7188; found 912.7188.

[5'-(N-Methyl)diocadecylammonio-5'-deoxyuridine]iodide (11**):** Compound **8b** (182 mg, 0.19 mmol) was dissolved in dry Et_2O (1 mL) and MeI (160 μL , 2.57 mmol) was added under an atmosphere of argon. The solution was stirred at room temperature for 72 h. For deprotection, Et_2O (17 mL), MeOH (6 mL) and ammonium fluoride (500 mg, 13.5 mmol) were added, and the suspension was stirred at 45 °C for 3 h and at room temperature for 48 h. After TLC indicated the final progress of the deprotection, MeOH (10 mL), Et_2O (3 mL) and water (20 mL) were added, and the resulting white precipitate was filtered off, washed with water and submitted to silica gel chromatography (MeOH/ CHCl_3 , 1:9; $R_f = 0.2$). Product **11** was obtained as a pale-yellow oil. Yield: 51 mg

(30%). ^1H NMR (300 MHz, CDCl_3): δ = 0.88 (t, J = 6.8 Hz, 6 H, $-\text{CH}_2-\text{CH}_3$), 1.25 (s, 60 H, $-\text{CH}_2-$), 1.74 (s, 4 H, $-\text{N}-\text{CH}_2-\text{CH}_2-$), 3.31 (s, 3 H, $-\text{N}-\text{CH}_3$), 3.46 (s, 4 H, $-\text{N}-\text{CH}_2-\text{CH}_2-$), 4.23 (m, 2 H, $-\text{CH}_25'$), 4.45 (s, 1 H, $-\text{CH}-\text{OH}$, 4'), 4.67 (s, 1 H, $-\text{CH}-\text{OH}$, 2'), 4.83 (s, 1 H, $-\text{CH}-\text{OH}$, 3'), 5.79 (s, 1 H, CH5), 5.88 (s, 1 H, $-\text{CH}-$, 1'), 7.91 (s, 1 H, CH6), 10.26 (s, 1 H, $-\text{NH}-$, 3) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): δ = 14.12 ($-\text{CH}_2-\text{CH}_3$), 22.69 ($-\text{CH}_2-$), 26.32 ($-\text{CH}_2-$), 29.24 ($-\text{CH}_2-$), 29.38 ($-\text{CH}_2-$), 29.52 ($-\text{CH}_2-$), 29.62 ($-\text{CH}_2-$), 29.69 ($-\text{CH}_2-$), 29.78 ($-\text{CH}_2-$), 31.93 ($-\text{CH}_2-$), 46.31 ($-\text{CH}_25'$), 50.11 ($-\text{N}-\text{CH}_3$), 71.20 ($\text{CH3}'$), 72.53 ($\text{CH2}'$), 72.62 ($\text{CH4}'$), 77.28 ($\text{CH1}'$), 102.82 (CH5), 130.92 (CH6) ppm. HRMS: calcd. for $\text{C}_{46}\text{H}_{88}\text{N}_3\text{O}_5^+$ 762.6719; found 762.6719.

2',3'-[Bis(*tert*-butyldimethylsilyl)]-5'-deoxy-3-(*N*-palmitoyl)-5'-(*N*-palmitoyl-*N*-octylamino)uridine (12**):** Compound **8a** (178 mg, 0.25 mmol) was dissolved in dry Et_2O (10 mL) and DIPEA (60 μL , 0.35 mmol) was added. Under vigorous stirring, palmitoyl chloride (100 μL , 0.33 mmol) was slowly added to the solution. TLC indicated the final progress of the reaction after 10 min. The white precipitate was filtered off, and the filtrate was concentrated in vacuo. The resulting residue was submitted to silica gel column chromatography ($\text{EtOAc}/\text{cyclohexane}$, 1:12; R_f = 0.1). The product was obtained as a colourless oil. Yield: 103 mg (35%). ^1H NMR (300 MHz, CDCl_3): δ = 0.02 (s, 3 H, $-\text{Si}-\text{CH}_3$), 0.05 (s, 3 H, $-\text{Si}-\text{CH}_3$), 0.06 (s, 3 H, $-\text{Si}-\text{CH}_3$), 0.07 (s, 3 H, $-\text{Si}-\text{CH}_3$), 0.92–0.81 [m, 27 H, $-\text{C}(\text{CH}_3)_3$ and $-\text{CH}_2-\text{CH}_3$], 1.24 (s, 78 H, $-\text{CH}_2-$), 1.58 (m, 4 H, $-\text{CO}-\text{CH}_2-\text{CH}_2-$ and $-\text{NH}-\text{CH}_2-\text{CH}_2-$), 1.71 (m, 2 H, $-\text{CO}-\text{CH}_2-\text{CH}_2-$), 2.29 (t, J = 7.2 Hz, 2 H, $-\text{CO}-\text{CH}_2-$), 2.77 (t, J = 7.2 Hz, 2 H, $-\text{CO}-\text{CH}_2-$), 3.26 (t, J = 6.8 Hz, 2 H, $-\text{NH}-\text{CH}_2-$), 3.81–3.35 (m, 2 H, CH_25'), 3.89 (m, 1 H, $-\text{CH}-\text{OH}$, 4'), 4.09 (m, 1 H, $-\text{CH}-\text{OH}$, 2'), 4.27 (m, 1 H, $-\text{CH}-\text{OH}$, 3'), 5.76 (d, J = 6.0 Hz, 1 H, $-\text{CH}-$, 1'), 5.79 (d, J = 8.3 Hz, 1 H, CH5), 7.64 (d, J = 8.3 Hz, 1 H, CH6) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): δ = -4.75 ($-\text{Si}-\text{CH}_3$), -4.68 ($-\text{Si}-\text{CH}_3$), -4.55 ($-\text{Si}-\text{CH}_3$), -4.36 ($-\text{Si}-\text{CH}_3$), 14.22 ($-\text{CH}_2-\text{CH}_3$), 18.01 [$-\text{C}(\text{CH}_3)_3$], 18.10 [$-\text{C}(\text{CH}_3)_3$], 22.79 ($-\text{CH}_2-$), 23.50 ($-\text{CH}_2-$), 25.63 ($-\text{CH}_2-$), 25.81 [$-\text{C}(\text{CH}_3)_3$], 25.84 [$-\text{C}(\text{CH}_3)_3$], 26.92 ($-\text{CH}_2-$), 28.72 ($-\text{CH}_2-$), 28.92 ($-\text{CH}_2-$), 29.38 ($-\text{CH}_2-$), 29.47 ($-\text{CH}_2-$), 29.53 ($-\text{CH}_2-$), 29.57 ($-\text{CH}_2-$), 29.63 ($-\text{CH}_2-$), 29.70 ($-\text{CH}_2-$), 32.03 ($-\text{CH}_2-$), 33.12 ($-\text{CH}_2-$), 40.67 ($-\text{CH}_2-$), 46.81 ($-\text{CH}_2-$), 47.81 (CH_25'), 73.74 ($\text{CH3}'$), 74.17 ($\text{CH2}'$), 82.47 ($\text{CH4}'$), 90.22 ($\text{CH1}'$), 102.66 (CH5), 140.81 (CH6), 149.03 (C2), 161.71 (C4), 173.97 ($-\text{CH}_2-\text{CO}-\text{N}-$), 176.03 ($-\text{CH}_2-\text{CO}-\text{N}-$) ppm. HRMS: calcd. for $\text{C}_{71}\text{H}_{138}\text{N}_3\text{O}_7\text{Si}_2^+$ 1201.0068; found 1201.0085.

5'-Diioctadecyl-5'-deoxy-2',3'-*O*-isopropylidene-1-*O*-methyl- β -D-ribofuranose (14**):** Starting material **13** (400 mg, 1.10 mmol) was dissolved in a melt of dioctadecylamine (1.26 g, 2.4 mmol) and stirred at 90 °C for 2 d and 5 h. When TLC indicated the final progress of the reaction, CHCl_3 (40 mL) was added, and the solution was quickly cooled to room temperature. Silica gel was added, and the solvent was evaporated. The powder was submitted to silica gel column chromatography ($\text{EtOAc}/\text{cyclohexane}$, 1:4; R_f = 0.8). Product **14** was obtained as a yellow oil. Yield: 500 mg (59%). ^1H NMR (300 MHz, CDCl_3): δ = 0.87 (t, J = 6.6 Hz, 6 H, $-\text{CH}_2-\text{CH}_3$), 1.26 (s, 60 H, $-\text{CH}_2-$), 1.30 [s, 3 H, $\text{C}(\text{CH}_3)_2$], 1.40 (s, 4 H, $-\text{N}-\text{CH}_2-\text{CH}_2-$), 1.47 [s, 3 H, $\text{C}(\text{CH}_3)_2$], 2.39 (m, J = 6.4 Hz, 4 H, $-\text{N}-\text{CH}_2-\text{CH}_2-$), 2.47 (m, J = 7.5 Hz, 2 H, $-\text{CH}_25'$), 3.30 (s, 3 H, $-\text{O}-\text{CH}_3$), 4.20 (t, J = 8.1 Hz, 1 H, $-\text{CH}-\text{OH}$, 4'), 4.55 (d, J = 6.0 Hz, 1 H, $-\text{CH}-\text{OH}$, 2'), 4.67 (d, J = 5.9 Hz, 1 H, $-\text{CH}-\text{OH}$, 3'), 4.92 (s, 1 H, $-\text{CH}-$, 1') ppm. ^{13}C NMR (75.5 MHz, CDCl_3): δ = 14.08 ($-\text{CH}_2-\text{CH}_3$), 22.68 ($-\text{CH}_2-$), 24.95 [$\text{C}(\text{CH}_3)_2$], 26.45 [$\text{C}(\text{CH}_3)_2$], 27.03 ($-\text{CH}_2-$), 27.45 ($-\text{CH}_2-$), 29.39 ($-\text{CH}_2-$), 29.73 ($-\text{CH}_2-$), 31.94 ($-\text{CH}_2-$), 54.58 ($-\text{CH}_2-$), 54.72 ($\text{O}-\text{CH}_3$), 57.55 (CH_25'), 83.20 ($\text{CH3}'$), 85.24 ($\text{CH2}'$), 109.55 ($\text{CH1}'$), 111.90 [$\text{C}(\text{CH}_3)_2$] ppm.

β -D-1',2',3'-Tri-*O*-acetyl-5'-deoxy-5'-dioctadecylribofuranose (15**):** 14 (950 mg, 1.3 mmol) was dissolved in acetic anhydride (8.5 mL, 90 mmol), AcOH (6.5 mL) and CHCl_3 (1.5 mL). Sulfuric acid (concentrated, 0.67 mL) was added, and the suspension was stirred at room temperature for 3.5 h. The orange solution was kept in the refrigerator at -24 °C overnight and then brought to room temperature after 16 h. The reaction mixture was quenched with NaOAc (1.8 g, 22 mmol). EtOH (25 mL) was added and evaporated, and the cycle was repeated three times. The residue was dried at 10 mbar (45 °C) for 50 min. CHCl_3 (20 mL) was added, and the organic phase was washed with tris buffer solution (1 M, 3 mL) and brine (30 mL). The organic phase was separated and dried with MgSO_4 . The filtrate was concentrated and purified by silica gel chromatography (MeOH/DCM , 1:50; R_f = 0.3). Product **15** was obtained as a yellow oil. Yield: 140 mg (14%). The major fractions gave *N*-acetyldioctadecylamine as a fragmentation product (30%). ^1H NMR (300 MHz, CDCl_3): δ = 0.88 (t, J = 6.8 Hz, 6 H, $-\text{CH}_2-\text{CH}_3$), 1.25 (s, 60 H, $-\text{CH}_2-$), 1.39 (m, 4 H, $-\text{N}-\text{CH}_2-\text{CH}_2-$), 2.05 (s, 3 H, $-\text{CO}-\text{CH}_3$), 2.08 (s, 3 H, $-\text{CO}-\text{CH}_3$), 2.11 (s, 3 H, $-\text{CO}-\text{CH}_3$), 2.45 (m, 4 H, $-\text{N}-\text{CH}_2-\text{CH}_2-$), 2.66 (m, J = 7.4 Hz, 2 H, $-\text{CH}_25'$), 4.29 (t, J = 6.6 Hz, 1 H, $-\text{CH}-\text{OH}$, 4'), 5.26 (m, 2 H, $-\text{CH}-\text{OH}$, 2'3'), 6.13 (s, 1 H, $-\text{CH}-$, 1') ppm. ^{13}C NMR (75.5 MHz, CDCl_3): δ = 14.10 ($-\text{CH}_2-\text{CH}_3$), 20.50 ($-\text{CO}-\text{CH}_3$), 21.05 ($-\text{CO}-\text{CH}_3$), 22.68 ($-\text{CH}_2-$), 27.39 ($-\text{CH}_2-$), 29.36 ($-\text{CH}_2-$), 29.70 ($-\text{CH}_2-$), 31.92 ($-\text{CH}_2-$), 54.69 ($-\text{CH}_2-$), 57.09 (CH_25'), 72.73 ($\text{CH2}'$), 74.19 ($\text{CH3}'$), 80.57 ($\text{CH4}'$), 98.45 ($\text{CH1}'$), 169.08 ($\text{CO}-\text{CH}_3$), 169.46 ($\text{CO}-\text{CH}_3$), 169.70 ($\text{CO}-\text{CH}_3$) ppm.

2',3'-Di-*O*-Acetyl-5'-deoxy-5'-dioctadecyladenosine (16**):** Compound **15** (140 mg, 0.18 mmol) and adenine (190 mg, 1.44 mmol, 8 equiv.) were dissolved in dry MeCN (6 mL) and dry DCM (5 mL). SnCl_4 (0.36 mL, 3.1 mmol, 17 equiv.) was added to the suspension, and the mixture was stirred under an atmosphere of argon at room temperature for 20 h. The solvent was evaporated and DCM (20 mL), water (20 mL) and triethylamine (2 mL) were added. The organic phase was separated and washed with brine (10 mL). The aqueous phases were extracted with DCM, and the combined organic phase was evaporated to dryness. The residue was treated with toluene and evaporated, and the cycle was repeated three times. The crude material was purified by silica gel chromatography (MeOH/DCM , 1:14 + Et_3N , 1%; R_f = 0.3). Product **16** was obtained as a brown oil. Yield: 70 mg (45%). ^1H NMR (300 MHz, CDCl_3): δ = 0.89 (t, J = 6.9 Hz, 6 H, $-\text{CH}_2-\text{CH}_3$), 1.26 (s, 60 H, $-\text{CH}_2-$), 1.42 (m, 4 H, $-\text{N}-\text{CH}_2-\text{CH}_2-$), 2.07 (s, 3 H, $-\text{CO}-\text{CH}_3$), 2.14 (s, 3 H, $-\text{CO}-\text{CH}_3$), 2.48 (m, 4 H, $-\text{N}-\text{CH}_2-\text{CH}_2-$), 2.84 (m, 2 H, $-\text{CH}_25'$), 4.30 (m, 1 H, $-\text{CH}-\text{OH}$, 4'), 5.57 (m, J = 5.1 Hz, 1 H, $-\text{CH}-\text{OH}$, 3'), 5.92 (m, J = 5.5 Hz, 1 H, $-\text{CH}-\text{OH}$, 2'), 6.14 (d, J = 5.5 Hz, 1 H, $-\text{CH}-$, 1'), 8.01 (s, 1 H, CH2), 8.36 (s, 1 H, CH8) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): δ = 14.12 ($-\text{CH}_2-\text{CH}_3$), 20.45 ($-\text{CO}-\text{CH}_3$), 20.61 ($-\text{CO}-\text{CH}_3$), 22.69 ($-\text{CH}_2-$), 27.45 ($-\text{CH}_2-$), 29.37 ($-\text{CH}_2-$), 29.71 ($-\text{CH}_2-$), 31.93 ($-\text{CH}_2-$), 55.05 ($-\text{CH}_2-$), 55.96 (CH_25'), 72.06 ($\text{CH3}'$), 72.92 ($\text{CH2}'$), 81.69 ($\text{CH4}'$), 85.99 ($\text{CH1}'$), 120.04 (C5), 149.79 (C4), 153.27 (CH2), 155.49 (C6), 169.43 ($\text{CO}-\text{CH}_3$), 169.64 ($\text{CO}-\text{CH}_3$) ppm. HRMS: calcd. for $\text{C}_{50}\text{H}_{91}\text{N}_6\text{O}_5^+$ 855.7045; found 855.7037.

5'-Diioctadecyl-5'-deoxyadenosine (17**):** Compound **16** (300 mg, 0.35 mmol) was dissolved in DCM (12 mL) and MeOH (15 mL). The solution was cooled under an atmosphere of argon to -72 °C and gaseous ammonia was condensed (approximately 40 mL). The solution was kept at -70 °C for 1 h and then the temperature was gradually raised to 20 °C overnight. When ammonia finally disappeared, argon was led through the equipment and the solvent was evaporated. The crude material was purified by silica gel chromatography ($\text{MeOH}/\text{CHCl}_3$, 1:5; R_f = 0.3). Product **17** was

obtained as a colourless solid. M.p. 60–61 °C. Yield: 98 mg (36%). ¹H NMR (300 MHz, CDCl₃): δ = 0.89 (t, *J* = 6.8 Hz, 6 H, -CH₂-CH₃), 1.26 (s, 60 H, -CH₂-), 1.45 (m, *J* = 6.2 Hz, 4 H, -N-CH₂-CH₂-), 2.52 (m, *J* = 7.9 Hz, 4 H, -N-CH₂-CH₂-), 2.81 (m, *J* = 6.2 Hz, 2 H, -CH₂5'), 4.26 (m, *J* = 5.1 Hz, 1 H, -CH-OH, 4'), 4.37 (m, *J* = 5.1 Hz, 1 H, -CH-OH, 3'), 4.62 (m, *J* = 4.5 Hz, 1 H, -CH-OH, 2'), 5.97 (d, *J* = 4.0 Hz, 1 H, -CH-, 1'), 6.21 (s, 2 H, NH₂), 8.00 (s, 1 H, CH₂), 8.25 (s, 1 H, CH₈) ppm. ¹³C NMR (75.5 MHz, CDCl₃): δ = 14.13 (-CH₂-CH₃), 22.70 (-CH₂-), 26.77 (-CH₂-), 27.45 (-CH₂-), 29.38 (-CH₂-), 29.73 (-CH₂-), 31.94 (-CH₂-), 55.08 (-CH₂-), 56.77 (CH₂5'), 73.46 (CH₃'), 74.90 (CH₂'), 82.51 (CH₄'), 90.23 (CH₁'), 119.90 (C₅), 149.00 (C₄), 152.64 (CH₂), 155.55 (C₆) ppm. HRMS: calcd. for C₄₆H₈₇N₆O₃⁺ 771.6834; found 771.6833.

Supporting Information (see footnote on the first page of this article): Experimental and spectroscopic data for products **3b–g**, **5b–h**, **10d** and 2-amino-9,9-dioctadecyl-9H-fluorene.

Acknowledgments

Financial support by the Bundesministerium für Bildung und Forschung (BMBF) is gratefully acknowledged. We thank Dr. Burkhard Ziemer, Institute of Chemistry, Humboldt University Berlin for X-ray crystal analyses and Bayer Services GmbH & Co. OHG, BASF AG, Sasol GmbH for donation of chemicals.

- [1] S. Bonaccio, D. Capitani, A. L. Segre, P. Walde, P. L. Luisi, *Langmuir* **1997**, *13*, 1952.
- [2] S. Bonaccio, P. Walde, P. L. Luisi, *J. Phys. Chem.* **1994**, *98*, 10376.
- [3] S. K. Choi, T. K. Vu, J. M. Jung, S. J. Kim, H. R. Jung, T. Y. Chang, B. H. Kim, *ChemBioChem* **2005**, *6*, 432.
- [4] S. Bonaccio, P. Walde, P. L. Luisi, *J. Phys. Chem.* **1994**, *98*, 6661.
- [5] B. Moreau, P. Barthélemy, M. El Maataoui, M. W. Grinstaff, *J. Am. Chem. Soc.* **2004**, *126*, 7533.
- [6] G. Zandomenighi, P. L. Luisi, L. Mannina, A. Segre, *Helv. Chim. Acta* **2001**, 3710.
- [7] L. Moreau, M. W. Grinstaff, P. Barthélemy, *Tetrahedron Lett.* **2005**, *46*, 1593.
- [8] C. Gosse, A. Boutorine, I. Aujard, M. Chami, A. Kononov, E. Cogne-Laage, J. F. Allemand, J. Li, L. Jullien, *J. Phys. Chem. B* **2004**, *108*, 6485.
- [9] C. Li, J. Huang, Y. Liang, *Langmuir* **2000**, *16*, 7701.
- [10] W. G. Miao, X. Z. Du, Y. Q. Liang, *Langmuir* **2003**, *19*, 5389.
- [11] F. Pincet, L. Lebeau, S. Cribier, *Eur. Biophys. J. Biophys. Lett.* **2001**, *30*, 91.
- [12] O. Cruciani, L. Mannina, A. P. Sobolev, A. Segre, P. Luisi, *Langmuir* **2004**, *20*, 1144.
- [13] C. Yoshina-Ishii, G. P. Miller, M. L. Kraft, E. T. Kool, S. G. Boxer, *J. Am. Chem. Soc.* **2005**, *127*, 1356.
- [14] C. Yoshina-Ishii, S. G. Boxer, *J. Am. Chem. Soc.* **2003**, *125*, 3696.
- [15] H. A. Scheidt, W. Flasche, C. Cismas, M. Rost, A. Herrmann, J. Liebscher, D. Huster, *J. Phys. Chem. B* **2004**, *108*, 16279.
- [16] A. Kurz, A. Bunge, A. K. Windeck, M. Rost, W. Flasche, A. Arbuzova, D. Strohbach, S. Mueller, J. Liebscher, D. Huster, A. Herrmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 4440.
- [17] A. Bunge, A. Kurz, A.-K. Windeck, T. Korte, W. Flasche, J. Liebscher, A. Herrmann, D. Huster, *Langmuir* **2007**, *23*, 4455.
- [18] I. Pfeiffer, F. Höök, *J. Am. Chem. Soc.* **2004**, *126*, 10224.
- [19] C. MacKellar, D. Graham, D. W. Will, S. Burgess, T. Brown, *Nucl. Acids Res.* **1992**, *20*, 3411.
- [20] Y. H. Ji, C. Moog, G. Schmitt, P. Bischoff, B. Luu, *J. Med. Chem.* **1990**, *33*, 2264.
- [21] H. Schott, R. A. Schwendener, *Liebigs Ann.* **1996**, 365.
- [22] R. A. Schwendener, H. Schott, *J. Cancer Res. Clin. Oncol.* **1996**, *122*, 723.
- [23] M. Christ, Y. H. Ji, C. Moog, X. Pannecoucke, G. Schmitt, P. Bischoff, B. Luu, *Anticancer Res.* **1991**, *11*, 359.
- [24] A. Naundorf, W. Klaffke, *Carbohydr. Res.* **1999**, *318*, 38.
- [25] R. Chillemi, D. Aleo, G. Granata, S. Sciuto, *Bioconj. Chem.* **2006**, *17*, 1022.
- [26] J. Soutschek, A. Akinc, B. Bramlage, K. Charisse, R. Constien, M. Donoghue, S. Elbashir, A. Geick, P. Hadwiger, J. Harborth, M. John, V. Kesavan, G. Lavine, R. K. Pandey, T. Racie, K. G. Rajeev, I. Rohl, I. Toudjarska, G. Wang, S. Wuschko, D. Bumcrot, V. Kotliansky, S. Limmer, M. Manoharan, H. P. Vornlocher, *Nature* **2004**, *432*, 173.
- [27] C. Lorenz, P. Hadwiger, M. John, H. P. Vornlocher, C. Unverzagt, *Bioorg. & Med. Chem. Lett.* **2004**, *14*, 4975.
- [28] C. McGuigan, S. R. Nicholls, T. J. O'Connor, D. Kinchington, *Antiviral Chem. Chemother.* **1990**, *1*, 25.
- [29] C. McGuigan, A. Perry, C. J. Yarnold, P. W. Sutton, D. Lowe, W. Miller, S. G. Rahim, M. J. Slater, *Antiviral Chem. Chemother.* **1998**, *9*, 233.
- [30] A. M. Michelson, A. R. Todd, *J. Chem. Soc.* **1955**, 2632.
- [31] S. L. Beaucage, R. P. Iyer, *Tetrahedron* **1993**, *49*, 1925.
- [32] S. L. Beaucage, R. P. Iyer, *Tetrahedron* **1993**, *49*, 6123.
- [33] D. W. Will, T. Brown, *Tetrahedron Lett.* **1992**, *33*, 2729.
- [34] M. V. de Almeida, D. Dubreuil, J. Cleophax, C. Verre-Sebrie, M. Pipelier, G. Prestat, G. Vass, S. D. Gero, *Tetrahedron* **1999**, *55*, 7251.
- [35] J. Butenandt, A. P. M. Eker, T. Carell, *Chem. Eur. J.* **1998**, *4*, 642.
- [36] J. J. Herzig, A. Nudelman, H. E. Gottlieb, B. Fischer, *J. Org. Chem.* **1986**, *51*, 727.
- [37] C. Richert, P. Grünefeld, *Synlett* **2007**, 1.
- [38] M. Kolb, C. Danzin, J. Barth, N. Clavierie, *J. Med. Chem.* **1982**, *25*, 550.
- [39] J. J. Turner, D. V. Filippov, M. Overhand, G. A. van der Marel, J. H. van Boom, *Tetrahedron Lett.* **2001**, *42*, 5763.
- [40] H. Homma, Y. Watanabe, T. Abiru, T. Murayama, Y. Nomura, A. Matsuda, *J. Med. Chem.* **1992**, *35*, 2881.
- [41] A. R. Yeager, N. S. Finney, *J. Org. Chem.* **2004**, *69*, 613.
- [42] H. Li, M. J. Miller, *J. Org. Chem.* **1999**, *64*, 9289.
- [43] I. Yamamoto, M. Sekine, T. Hata, *J. Chem. Soc. Perkin Trans. 1* **1980**, 306.
- [44] R. Kierzek, Y. Li, D. H. Turner, P. C. Bevilacqua, *J. Am. Chem. Soc.* **1993**, *115*, 4985.
- [45] J. B. Behr, T. Gurlain, A. Helimi, G. Guillermin, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1713.
- [46] A. Rosowsky, S.-H. Kim, D. Trites, M. Wick, *J. Med. Chem.* **1982**, *25*, 1034.
- [47] M. Maccoss, E. K. Ryu, R. S. White, R. L. Last, *J. Org. Chem.* **1980**, *45*, 788.
- [48] S. Ajmera, P. V. Danenberg, *J. Med. Chem.* **1982**, *25*, 999.
- [49] V. Skaric, D. Katalenic, D. Skaric, I. Salaj, *J. Chem. Soc. Perkin Trans. 1* **1982**, 2091.
- [50] E. I. Kvasnyuk, T. I. Kulak, I. A. Mikhailopulo, R. Charubala, W. Pfeiderer, *Helv. Chim. Acta* **1995**, *78*, 1777.
- [51] B. G. Ugarkar, A. J. Castellino, J. S. DaRe, M. Ramirez-Weinhouse, J. J. Kopcho, S. Rosengren, M. D. Erion, *J. Med. Chem.* **2003**, *46*, 4750.
- [52] M. Pignot, C. Siethoff, M. Linscheid, E. Weinhold, *Angew. Chem. Int. Ed.* **1998**, *37*, 2888.
- [53] N. Elloumi, B. Moreau, L. Aguiar, N. Jaziri, M. Sauvage, C. Hulen, M. L. Capmau, *Eur. J. Med. Chem.* **1992**, *27*, 149.
- [54] M. Pankaskie, M. M. Abdel-Monem, *J. Med. Chem.* **1980**, *23*, 121.
- [55] A. A. Minnick, G. L. Kenyon, *J. Org. Chem.* **1988**, *53*, 4952.
- [56] E. M. van der Wenden, M. Carnielli, H. C. P. F. Roelen, A. Lorenzen, J. K. von Frijtag, D. Kunzel, A. P. IJzerman, *J. Med. Chem.* **1998**, *41*, 102.
- [57] M. J. Thompson, A. Mekhafia, D. P. Hornby, G. M. Blackburn, *J. Org. Chem.* **1999**, *64*, 7467.
- [58] M. Nomura, S. Shuto, M. Tanaka, T. Sasaki, S. Mori, S. Shigeta, A. Matsuda, *J. Med. Chem.* **1999**, *42*, 2901.

- [59] S. Manfredini, P. G. Baraldi, E. Durini, S. Vertuani, J. Balzarini, E. De Clercq, A. Karlsson, V. Buzzoni, L. Thelander, *J. Med. Chem.* **1999**, 42, 3243.
- [60] M. Ikehara, K. Muneyama, *J. Org. Chem.* **1967**, 32, 3039.
- [61] M. Ikehara, K. Muneyama, *J. Org. Chem.* **1967**, 32, 3042.
- [62] H. B. Cottam, D. B. Wasson, H. C. Shih, A. Raychaudhuri, G. Dipasquale, D. A. Carson, *J. Med. Chem.* **1993**, 36, 3424.
- [63] L. Schmidt, E. B. Pedersen, C. Nielsen, *Acta Chem. Scand.* **1994**, 48, 215.
- [64] M. Sharma, Y. X. Li, M. Ledvina, M. Bobek, *Nucleosides Nucleotides* **1995**, 14, 1831.
- [65] J. Seelig, *Biochim. Biophys. Acta* **1978**, 515, 105.
- [66] J. H. Davis, *Biochim. Biophys. Acta* **1983**, 737, 117.
- [67] D. Huster, K. Arnold, K. Gawrisch, *J. Phys. Chem. B* **1999**, 103, 243.
- [68] S. Feller, personal communication.

Received: June 6, 2007

Published Online: October 23, 2007