Synthesis of Functionalized Lipids, and Their Use for a Tunable Hydrophobization of Nucleosides and Nucleic Acids

by **Sergei Korneev** and **Helmut Rosemeyer***

Organic Chemistry I – Bioorganic Chemistry, Institute of Chemistry of New Materials, Fachbereich Biologie/Chemie, University of Osnabrück, Barbarastrasse 7, D-49076 Osnabrück (e-mail: helmut.rosemeyer@uos.de)

Dedicated to Prof. Dr. *Helmut Vorbrüggen*, Berlin, in admiration of his outstanding contributions to organic chemistry

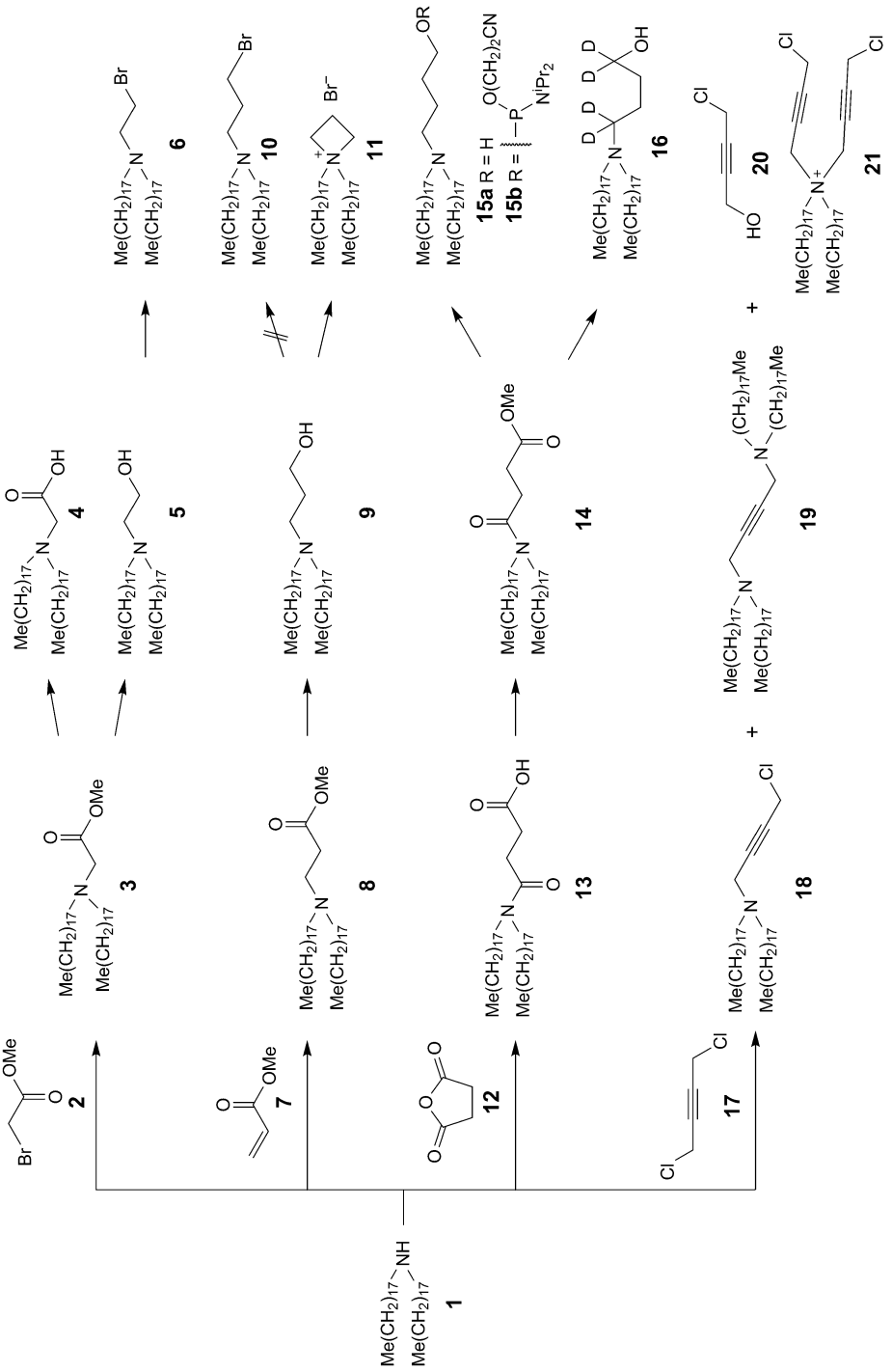
Two series of functionalized single and double side-chained lipid molecules (*Schemes 1* and *2*) were prepared. The compounds carry either terminal COOH, OH, or halogen substituents. Moreover, the double side-chained lipid **18** carries an internal alkyne functionality. The latter compound was used to hydrophobize thymidine at N(3) by base-catalyzed alkylation. Additionally, fully protected thymidine, **32**, was *N(3)*-alkylated with the double side-chained alcohol **9** applying *Mitsunobu* reaction conditions.

1. Introduction. – One of the major drawbacks of many chemotherapeutics is their insufficient penetration through cell membranes as well as the crossing of the blood–brain barrier due to their high hydrophilicity. This is particularly true for antisense and antigene oligonucleotides.

One method to overcome these problems is the introduction of lipophilic residues to the drug to render them hydrophobic and to improve their pharmacokinetics [1]. In the case of low-molecular-weight drugs, this kind of chemical modification is heading for the fulfilment of '*Lipinski*'s Rule of Five' [2]. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion, and is important for drug development where a pharmacologically active lead structure is optimized stepwise for increased activity and selectivity. One part of the rule is concerned with the drug's partition coefficient (log *P* between octan-1-ol and H_2O) within the range of -0.4 to $+5.5$. Herein, we describe the synthesis of a series of single and double side-chained lipids carrying different functional groups. *Via* these functional groups (halogene, COOR, COOH, OH, ammonium, and alkyne groups), the lipid residue can be introduced into chemotherapeutics such as nucleoside antimetabolites and others. Besides their synthesis, exemplary methods such as alkylation [3] and *Mitsunobu* reactions [4] for these introductions are presented.

2. Results and Discussion. – 2.1. *Syntheses of Double Side-Chained Lipids.* The first part of the manuscript describes the synthesis of a series of functionalized lipids carrying two octadecanyl chains. The syntheses are shown in *Scheme 1.*

Scheme 1


Me(CH2)17
Me(CH2)17
NH
1
Br
OMe
O
2
OMe
O
7
O
O
O
12
Cl
Cl
17
OMe
O
3
OH
O
4
OH
5
Br
6
OMe
8
OH
9
Br
10
Br−
11
OH
O
13
OMe
O
O
14
OR
15a R = H
15b R = P(O(CH2)2CN)(NiPr2)
D
D
D
D
OH
16
(CH2)17Me
(CH2)17Me
19
Cl
HO
20
Cl
Cl
21

Reaction of dioctadecylamine (**1**) with methyl 2-bromoacetate (**2**) in the presence of dibenzo-[18]-crown-6 gave the pure ester **3** in almost quantitative yield. This was either saponified to yield the acid **4** or reduced with $LiAlH_4$ to give the alcohol **5**. The latter was submitted to an *Appel* reaction with CBr_4 and Ph_3P to afford the bromo amine **6** in low yield. To extend the spacer between the OH group and the N-atom carrying the C-chains, the secondary amine **1** was reached with methyl acrylate (**7**) to furnish, in almost quantitative yield, the ester **8** which was further reduced with $LiAlH_4$ to give the lipophilic aminopropanol **9**. Subsequent *Appel* bromination to produce the 3-bromopropyl derivative **10**, however, was unsuccessful. NMR Spectroscopy revealed the formation of the quaternization product **11**, an *N*,*N*-dialkyl-azetidinium bromide[1]). This implies that the low yield in case of **6** is also due to the formation of a quaternization product, namely an *N*,*N*-dialkyl aziridinium bromide.

Next, the amine **1** was reacted with succinic anhydride (**12**) to give the acid **13**. This was converted to the ester **14** by reaction with Me_2SO_4 in the presence of K_2CO_3. Compound **14** was then reduced with $LiAlH_4$ to yield the further extended alcohol **15a**, or with $LiAlD_4$ to give the deuterated lipophilized 4-aminobutanol derivative **16**. It should be noted that this way of labelling of the molecule allows introduction of four isotope atoms of H in a single synthetic step, which is important for the introduction of low radioactivity labels, such as tritium ($^3H_1$). Moreover, compound **15a** was phosphitylated to the 2-cyanoethyl phosphoramidite **15b** ready to be used for a terminal hydrophobization of nucleic acids.

In a further reaction, the amine **1** was alkylated with 1,4-dichlorobut-2-yne (**17**) in the presence of Na_2CO_3 in benzene to afford, in 61% yield the alkynyl derivative **18**, besides the by-products **19**–**21**, each in low yield.

2.2. *Syntheses of Single Side-Chained Lipids.* Reaction of octadecylamine (**22**) with 3-bromoprop-1-yne (**23**) gave, in almost quantitative yield, the tertiary amine **24** (*Scheme 2*). Reaction of **22** with succinic anhydride (**12**) afforded the acid **25**, which was further esterified to give **26**. Treatment of the latter with $LiAlH_4$ (under the same conditions as for the reduction of **14** to **15**) yielded surprisingly the *N*-alkylated pyrrolidine **28** instead of the expected alcohol **27**. Reduction of the acid **25** with $LiAlH_4$ in THF at ambient temperature was attempted, however, it led to a reduction of COOH only, but not of the amide moiety, and gave the hydroxy amide **29** in 82% yield. Increasing of the reaction temperature to 65° furnished desired amino alcohol **27**, but only in moderate yield of 23%. Fortunately, replacement of THF by Et_2O gave compound **27** in a high yield of 84%. Subsequent reaction of **27** with **23** gave the alkynylamino alcohol **30** in 61% yield.

2.3. *Hydrophobization of Thymidine.* The regioselective introduction of lipophilic hydrocarbon chains in a nucleoside, particularly in a nucleoside with biological activity, is a difficult synthetic task. Such lipophilic groups can principally positioned either at the heterocyclic base or at the glyconic moiety, and can be introduced by various methods, *e.g.*, by base-catalyzed alkylation with alkyl halides; for an overview of such reactions on purines, see [3] and literature cited therein.

Some exemplary alkylation reactions of thymidine (**31**) with two of the functionalized lipids described above, namely with compounds **9** and **18**, are outlined

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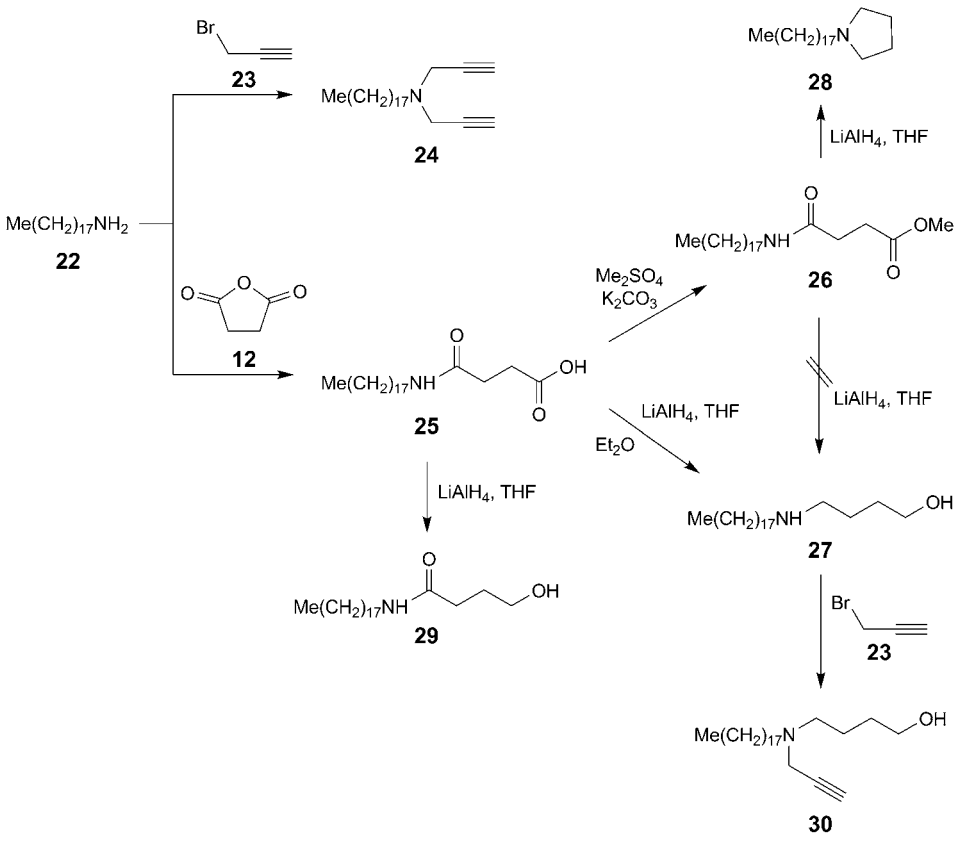
[1]) Spontaneous cyclization to azetidinium salt was also observed earlier [5].

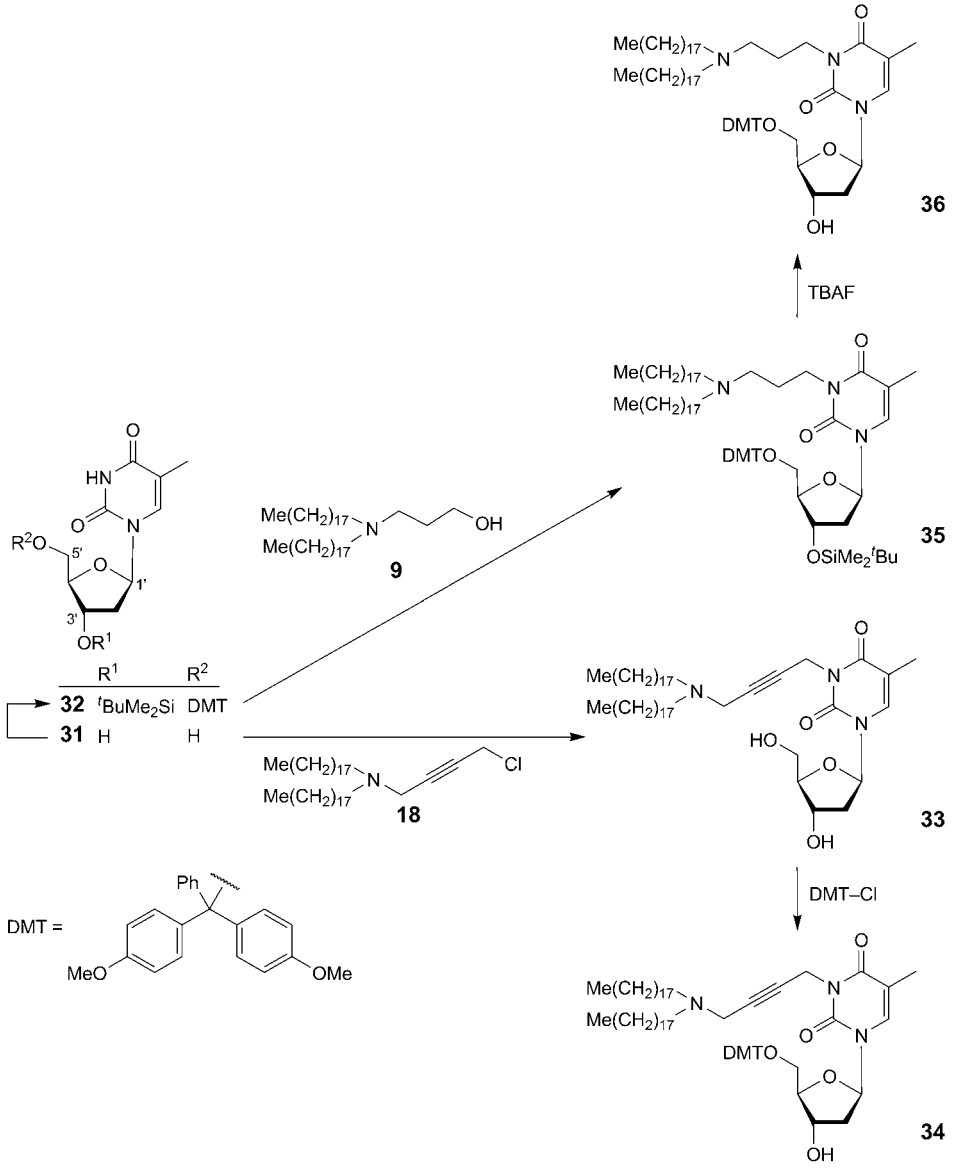
Scheme 2



in *Scheme 3*. The reaction of the unprotected thymidine with the alkyne **18** was performed in DMF/K_2CO_3 (direct alkylation) and gave the *N(3)*-alkylated compound **33**, which can be further reacted with an azide in a Ru-catalyzed variant of the azide–alkyne cycloaddition (RuAAC; *Huisgen–Sharpless–Meldal* [3 + 2] cycloaddition of azides with internal alkynes). Dimethoxytritylation of **33** afforded the derivative **34** for further 3′-*O*-phosphitylation.

Based on the finding that the direct alkylation of thymidine (**31**) with compound **18** gave only a moderate yield of **33** (46%), the 5′-*O*-DMT-protected thymidine derivative **37** – prepared from **31** – was subjected to the alkylation with **18** (*Scheme 4*). However, the yield of the alkylated product **34** was found to be nearly the same (51%). Therefore, the totally, orthogonally protected derivative **32** was prepared and subjected to alkylation. This reaction gave the product **38** in high yield (95%). It was then deprotected with Bu_4NF in THF to provide the desired compound **34** in high yield (95%). Compound **34** (which was, therefore, prepared in three different ways: from **37**, from **33**, and from **38**) was then reacted with 2-cyanoethyl *N,N*-diisopropylchlorophosphite in the presence of *Hünig*'s base to form the corresponding phosphoramidite

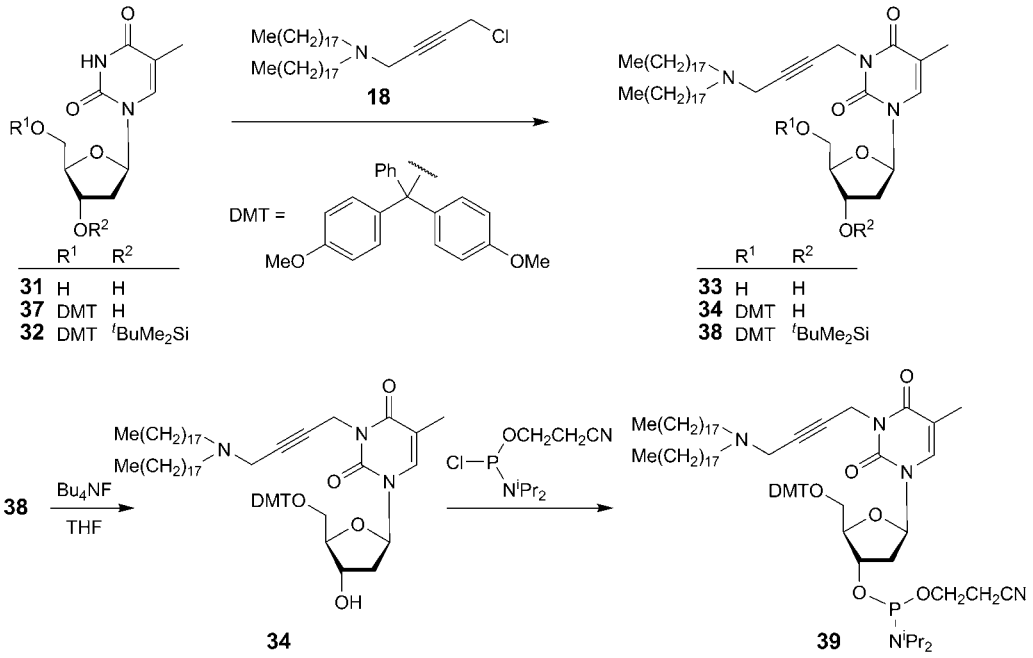
Scheme 3



39, which is ready to be used for the preparation of oligonucleotides lipophilized at any position within the sequence.

In a further approach, alkylation of thymidine (**31**) was performed by a *Mitsunobu* reaction [4]. This type of alkylation is somewhat more versatile, because alcohols which are precursors of halides can be used. However, a protection of the nucleoside OH

Scheme 4



groups is necessary. For this purpose, we first used also 5′-dimethoxytritylated thymidine **37** for a *Mitsunobu* reaction with the alcohol **9**, which led, however, to many by-products. Therefore, we also protected the 3′-OH group of **37** by a (*tert*-butyl)(dimethyl)silyl group (→ **32**). Reaction of compound **32** with the alcohol **9** in the presence of Ph_3P and diisopropyl azodicarboxylate (DIAD) gave in 70% yield the product **35**, which was subsequently desilylated with Bu_4NF to give compound **36**.

All compounds were characterized by ^{1}H- and ^{13}C-NMR spectroscopy, including the DEPT-135 pulse technique for assignment of ^{13}C resonances, as well as by elemental analyses or ESI mass spectrometry. An *N*-alkylation preferred over an *O*-alkylation during the *Mitsunobu* reaction [4] was established by comparison of the recorded ^{13}C-NMR chemical shifts with those of corresponding simulated spectra of both, the *N*- as well as *O*-alkylated compounds. However, an *O*-alkylation as side reaction is most probable.

In a forthcoming publication, the incorporation of the various phosphoramidites into oligonucleotides and applications thereof will be reported.

Experimental Part

General. Starting compounds and solvents were purchased from the appropriate suppliers and were used as obtained. *1,4-Dichlorobut-2-yne* (**17**) was prepared from but-2-yne-1,4-diol and $SOCl_2$ in pyridine as described in [6]. Reactions were carried out under Ar in a dry *Schlenk* flask. Column chromatography (CC): silica gel *60* (SiO_2; *Merck*, Germany). NMR Spectra: *AMX-500* spectrometer (*Bruker*, D-

Rheinstetten); ^{1}H: 500.14, ^{13}C: 125.76, and ^{31}P: 101.3 MHz; δ in ppm rel. to Me_4Si as internal standard for ^{1}H and ^{13}C nuclei, and external 85% H_3PO_4 for ^{31}P; J in Hz. ESI-MS: *Bruker Daltronics Esquire HCT* instrument (*Bruker Daltronics*, D-Leipzig); ionization was performed with a 2% aq. HCOOH soln. Elemental analyses (C, H, N): *VarioMICRO* instrument (Fa. *Elementar*, D-Hanau).

Methyl N,N-*(Dioctadecyl)glycinate* (**3**). N,N-*Dioctadecylamine* (**1**; 1.90 g, 3.65 mmol), *methyl 2-bromoacetate* (**2**; 1.62 g, 10.6 mmol), dibenzo-[18]-crown-6 (10 mg), and Na_2CO_3 (1.93 g, 18.3 mmol) were suspended in benzene (50 ml) at r.t., and the suspension was stirred overnight under reflux (20 h). A second portion of **2** (0.56 g, 3.65 mmol) was added, and stirring under reflux was continued for further 10 h, until the reaction was complete as monitored by ^{1}H-NMR analysis (amine **1**: 2.95 ppm, product **3**: 3.34 ppm). The white suspension was filtered through a SiO_2 layer (1 cm) to separate the unreacted amine **1**, washed with benzene (2×30 ml), and concentrated *in vacuo* to give **3** (2.10 g, 97%). Slightly yellow crystalline mass[2]). TLC (hexane/Et_2O 1:1): R_f 0.60. M.p. 60–61°. ^{1}H-NMR ($CDCl_3$): 3.71 (*s*, MeO); 3.34 (*s*, CH_2COO); 2.58–2.55 (*m*, 2 CH_2CH_2N); 1.48–1.42 (*m*, 2 CH_2CH_2N); 1.28 (br. *s*, 60 H); 0.90 (*t*, $J = 6.9$, 2 Me). ^{13}C-NMR ($CDCl_3$): 172.09 (C=O); 55.05 (NCH_2CH_2); 54.54 (NCH_2CO); 51.20, 51.16 (MeO); 31.90 (CH_2CH_2Me); 29.68, 29.61, 29.55, 29.31 ($CH_2(CH_2)_3N$); 27.47 (CH_2CH_2N); 27.37 ($CH_2(CH_2)_2N$); 22.65 ($MeCH_2$); 14.04, 14.03 ($MeCH_2$). ESI-MS: 594.7 ($[M+H]^+$). Anal. calc. for $C_{39}H_{79}NO_2$ (594.07): C 78.85, H 13.40, N 2.36; found: C 78.59, H 13.50, N 2.24.

N,N-*Dioctadecylglycine* (**4**). Powder of **3** (2.97 g, 5 mmol) was added at once to a freshly prepared soln. of NaOH (0.40 g, 10 mmol) in H_2O (50 ml), and the resulting suspension was stirred at 95° overnight. White precipitate was removed by filtration, washed with Et_2O (3×5 ml), suspended in H_2O (20 ml), and carefully made acidic (pH 6) by addition of 5% HCl. The precipitate was collected, washed with H_2O, pressed, and dried in vacuum to furnish **4** (2.84 g, 98%). TLC (CH_2Cl_2/MeOH 10:1): R_f 0.43. M.p. 102–103° ([7]: 102–103°). ^{1}H-NMR ($CDCl_3$): 8.63 (br. *s*, 0.5 H, COOH); 8.15 (br. *s*, 0.5 H, COOH); 3.46 (*s*, CH_2CO); 3.06–3.03 (*m*, 2 CH_2N); 1.70–1.65 (*m*, 2 CH_2CH_2N); 1.25 (br. *s*, 60 H); 0.88 (*t*, $J = 6.8$, 2 Me). ^{13}C-NMR ($CDCl_3$): 168.69 (COO); 54.17 (NCH_2); 31.94 ($MeCH_2CH_2$); 29.77, 29.70, 29.52, 29.38, 27.32 (CH_2CH_2N); 26.64 ($CH_2(CH_2)_2N$); 24.89, 22.69 ($MeCH_2$); 14.08 (Me) (^{1}H- and ^{13}C-NMR are in agreement with those reported in [7]).

2-(Dioctadecylamino)ethanol (**5**). Ester **3** (2.24 g, 3.77 mmol) was dissolved in THF (150 ml), cooled in an ice-bath, and $LiAlH_4$ (0.57 g, 15 mmol) was added in portions under stirring within 3 min (gas evolution). The cooling bath was removed, and stirring was continued overnight at r.t. The mixture was cooled in an ice-bath, and MeOH (2.5 ml) was added dropwise to destroy the excess of $LiAlH_4$. The mixture obtained was concentrated *in vacuo* (25 Torr), suspended in CH_2Cl_2 (100 ml), and carefully treated with H_2O (40 ml) until the formation of a precipitate. The org. layer was separated, washed with H_2O (50 ml), dried (Na_2SO_4), and concentrated to afford **5** (2.0 g, 94%). Off-white solid[2])[3]). TLC (SiO_2, Et_2O): R_f 0.26. M.p. 43–44°. ^{1}H-NMR ($CDCl_3$): 3.52 (*t*, $J = 5.4$, CH_2O); 3.1 (br. *s*, OH); 2.57 (*t*, $J = 5.4$, OCH_2CH_2N); 2.44 (*t*, $J = 7.2$, 2 $CH_2CH_2CH_2N$); 1.43 (*m*, $CH_2CH_2CH_2N$); 1.26 (br. *s*, 60 H); 0.89 (*t*, $J = 6.9$, 2 Me). ^{13}C-NMR ($CDCl_3$): 58.28 (CH_2O); 55.54 (CH_2CH_2O); 53.90 ($NCH_2(CH_2)_{16}$); 31.93 ($MeCH_2CH_2$); 29.70, 29.66, 29.60, 29.36 ($CH_2(CH_2)_3N$); 27.45 ($CH_2CH_2CH_2N$); 27.24 ($CH_2(CH_2)_2N$); 22.68 ($MeCH_2$); 14.08 (Me). ESI-MS: 566.7 ($[M+H]^+$).

(2-Bromoethyl)dioctadecylamine (**6**). PPh_3 (8.80 g, 33.6 mmol) was dissolved in a pre-cooled soln. of **5** (3.80 g, 6.71 mmol) in CH_2Cl_2 (180 ml) at 5°, followed by addition of CBr_4 (11.15 g, 33.6 mmol) in portions within 3 min. The resulting orange soln. was stirred at r.t. for 30 h. The mixture was concentrated, and **6** was isolated by CC (SiO_2 (100 g); hexane/CH_2Cl_2 1:1 to 0:1) in low yield (0.43 g, 10%). TLC (SiO_2; hexane/CH_2Cl_2 1:1): R_f 0.58. M.p. 69–71°. ^{1}H-NMR ($CDCl_3$): 3.38 (*t*, $J = 7.5$, CH_2Br); 2.88 (*t*, $J = 7.5$, $BrCH_2CH_2N$); 2.50 (*t*, $J = 7.2$, 2 $(CH_2)_{16}CH_2N$); 1.49–1.41 (*m*, 2 $CH_2CH_2CH_2N$); 1.27 (br. *s*, 60 H); 0.90 (*t*, $J = 6.9$, 2 Me). ^{13}C-NMR ($CDCl_3$): 56.16 ($BrCH_2CH_2$); 54.48 ($NCH_2(CH_2)_{16}$); 31.91 ($MeCH_2CH_2$); 29.68, 29.64, 29.61, 29.52 (CH_2Br); 29.33, 27.35 ($NCH_2CH_2CH_2$) 27.21, 22.65 ($MeCH_2$); 14.05 (Me). ESI-MS (calc. 627(^{79}Br)): 548.7 ($[M-HBr+H]^+$), 628.7 ($[M(^{79}Br)+H]^+$), 630.6

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[2]) The crude product was pure enough to be used in the next step without further purification, however, it could be purified for anal. purpose by recrystallization from the appropriate solvent or by chromatography over SiO_2.

[3]) The alcohol **5** was only poorly characterized [8].

([M(^{81}Br) + H]$^+$). Anal. calc. for $C_{38}H_{78}BrN$ (628.96): C 72.57, H 12.50, N 2.23; found: C 72.18, H 12.38, N 2.04.

Methyl N,N-*Dioctadecyl-3-aminopropanoate* (**8**). Compound **1** (0.93 g, 1.78 mmol) was added to a soln. of **7** (1.75 g, 20.3 mmol) in a mixture i-PrOH (14 ml)/CH_2Cl_2 (6 ml), and the resulting white suspension was stirred at 45° overnight. The mixture was filtered through a paper filter and concentrated *in vacuo* (10 Torr) to afford **8** (1.04 g, 96%). White solid mass[2])[4]). TLC (SiO_2, hexane/Et_2O 1:1): R_f 0.58. M.p. 44–45°. ^{1}H-NMR ($CDCl_3$): 3.67 (*s*, MeO); 2.78 (*t*, J = 5.4, CH_2CO); 2.47–2.36 (*m*, 3 CH_2N); 1.48–1.36 (*m*, 2 $CH_2CH_2CH_2N$); 1.26 (br. *s.*, 60 H); 0.89 (*t*, J = 6.9, 2 Me) (in a good agreement with those reported in [10]). ^{13}C-NMR ($CDCl_3$): 173.35 (C=O); 54.00 ($NCH_2(CH_2)_{16}$); 51.42 (MeO); 49.42 (CH_2CH_2CO); 32.30 (CH_2CO); 31.90 ($MeCH_2CH_2$); 29.68, 29.64, 29.60, 29.33 ($N(CH_2)_3CH_2$); 27.50 ($NCH_2CH_2CH_2$); 27.19 ($N(CH_2)_2CH_2$); 22.66 ($MeCH_2$); 14.07 ($MeCH_2$). ESI-MS: 608.7 ([M + H]$^+$). Anal. calc. for $C_{40}H_{81}NO_2$ (608.10): C 79.01, H 13.43, N 2.30; found: C 78.86, H 13.39, N 2.12.

3-(Dioctadecylamino)propanol (**9**). $LiAlH_4$ (0.26 g, 6.84 mmol) was added in portions within 2 min to a soln. of **8** (1.04 g, 1.71 mmol) in THF (45 ml), cooled in an ice-bath. The bath was removed, and stirring was continued overnight. The mixture was carefully treated with a soln. of MeOH (0.6 ml) in Et_2O (2 ml) with cooling in an ice-bath, until the gas evolution ceased. Org. solvents were removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 (70 ml), washed with H_2O (3 × 30 ml), dried (Na_2SO_4), and concentrated to give **9** (0.98 g, 98%). White solid mass[2])[5]). TLC (SiO_2, Et_2O): R_f 0.23. M.p. 48–49° ^{1}H-NMR ($CDCl_3$): 5.68 (*s*, OH); 3.79 (*t*, J = 5.3, CH_2OH); 2.63 (*t*, J = 5.3, $CH_2CH_2CH_2OH$); 2.38–2.43 (*m*, 2 $(CH_2)_{16}CH_2N$); 1.67 (*quint.*, J = 5.3, $CH_2CH_2CH_2OH$); 1.53–1.40 (*m*, 2 $(CH_2)_{15}CH_2CH_2N$); 1.26 (br. *s*, 60 H); 0.89 (*t*, J = 6.5, 2 Me). ^{13}C-NMR ($CDCl_3$): 64.82 (CH_2O); 55.36 ($CH_2(CH_2)_2O$); 54.22 ($NCH_2(CH_2)_{16}$); 31.90 ($MeCH_2CH_2$); 29.68, 29.64, 29.60, 29.33, 27.83 (CH_2CH_2O); 27.51 ($NCH_2CH_2(CH_2)_{15}$); 26.82 ($N(CH_2)_2CH_2(CH_2)_{14}$); 22.66 ($MeCH_2$); 14.06 (Me). ESI-MS: 580.7 ([M + H]$^+$).

1,1-Dioctadecylazetidinium Bromide (**11**). Crystals of CBr_4 (320 mg, 1 mmol) were added to a pre-cooled (ice-bath) soln. of **9** (116 mg, 0.2 mmol) and PPh_3 (260 mg, 1 mmol) in CH_2Cl_2 (13 ml), and the resulting mixture was stirred at the same temp. overnight. The yellow suspension was filtered through a SiO_2 layer (4 cm), and washed consecutively by CH_2Cl_2 (100 ml) and Et_2O (100 ml) to give in the second fraction light-yellow crystalline **11** (16 mg, 13%). TLC (SiO_2; CH_2Cl_2/Et_2O 4:1): R_f 0.64. ^{1}H-NMR ($CDCl_3$): 4.52–4.49 (*m*, NCH_2); 3.57–3.54 (*m*, NCH_2); 3.51–3.48 (*m*, 2 H); 2.87–2.79 (*m*, 2 H); 1.56 (br. *s*, 2 H); 1.34–1.26 (*m*, 60 H); 1.89 (*t*, J = 6.8, 2 Me). ESI-MS (calc. 641(^{79}Br)): 562.7 ([M − HBr + H]$^+$), 642.6 ([M(^{79}Br) + H]$^+$), 644.6 ([M(^{81}Br) + H]$^+$).

4-(Dioctadecylamino)-4-oxobutanoic Acid (**13**). Compound **1** (522 mg, 1 mmol) and Et_3N (202 mg, 2 mmol) were added consecutively to a stirred soln. of *succinic anhydride* (**12**; 150 mg, 1.5 mmol) in CH_2Cl_2 (10 ml), and the white suspension formed was stirred at 35° overnight. The resulting clear soln. was concentrated *in vacuo* and recrystallized from acetone (3 ml) to give **13** (600 mg, 96%). White powder. TLC (SiO_2; CH_2Cl_2/AcOEt 1:1): R_f 0.62. M.p. 68–69° (acetone; [7]: 63–64° (Et_2O)). ^{1}H-NMR ($CDCl_3$): 3.36–3.33 (*m*, NCH_2); 3.26–3.23 (*m*, NCH_2); 2.70 (*s*, $COCH_2CH_2CO$); 1.62–1.52 (*m*, 2 NCH_2CH_2); 1.28 (br. *s*, 60 H); 0.90 (*t*, J = 6.9, 2 Me). ^{13}C-NMR ($CDCl_3$): 173.88 (COO); 172.55 (CON); 48.42, 46.80 (NCH_2); 31.90 ($MeCH_2CH_2$); 30.69 ($NCOCH_2$); 29.67, 29.63, 29.59, 29.57, 29.54, 29.52, 29.49, 29.33, 29.28, 28.81, 28.08, 27.61, 26.99, 26.87 ($NCH_2CH_2CH_2$); 22.65 ($MeCH_2$); 14.06 (Me) (^{1}H- and ^{13}C-NMR are in agreement to those partly reported in [12]). ESI-MS: 622.7 ([M + H]$^+$). Anal. calc. for $C_{40}H_{79}NO_3$ (622.08): C 77.23, H 12.80, N 2.25; found: C 77.12, H 12.89, N 2.08.

Methyl 4-(dioctadecylamino)-4-oxobutanoate (**14**). Me_2SO_4 (126 mg, 1 mmol) and K_2CO_3 (198 mg, 1.43 mmol) were added consecutively to a suspension of **13** (311 mg, 0.5 mmol) in acetone (4 ml), and the mixture was stirred at 55° overnight. The resulting white suspension was cooled to r.t., the precipitate was filtered off, washed with acetone (3 ml), and the filtrate was concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (5 ml), washed with aq. NH_3 (2 ml), to destroy the excess of Me_2SO_4, and H_2O (2 × 3 ml), dried (Na_2SO_4), and concentrated to yield **14** (291 mg, 91%). Colorless oil, which solidified upon

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[4]) Ester **8** was obtained in 42% yield, when the reaction was conducted in only CH_2Cl_2 according to [9].

[5]) No spectral data for the propanol **9** were reported in [11].

standing[2]). TLC (SiO_2; hexane/Et_2O 1:1): R_f 0.55. M.p. 29–30°. ^{1}H-NMR ($CDCl_3$): 3.70 (*s*, MeO); 3.31–3.29 (*m*, NCH_2); 3.26–3.23 (*m*, NCH_2); 2.70–2.67 (*m*, 2 H, $COCH_2CH_2CO$); 2.64–2.61 (*m*, 2 H, $COCH_2CH_2CO$); 1.61–1.48 (*m*, 2 NCH_2CH_2); 1.27 (br. *s*, 60 H); 0.90 (*t*, $J = 6.9$, 2 Me). ^{13}C-NMR ($CDCl_3$): 173.72 (COO); 170.49 (CON); 51.62 (MeO); 47.85, 46.18 (NCH_2); 31.90, 29.67, 29.63, 29.58, 29.54, 29.42, 29.32, 28.94, 27.99, 27.79, 27.06, 26.92 ($NCH_2CH_2CH_2$); 22.65 ($MeCH_2$); 14.06 (Me). ESI-MS (calc. 635): 1294.2 ($[2M + Na]^+$), 658.7 ($[M + Na]^+$), 636.7 ($[M + H]^+$).

4-(Dioctadecylamino)butan-1-ol (**15a**). Powdered $LiAlH_4$ (106 mg, 2.8 mmol) was added in portions during 2 min to a pre-cooled (ice-bath) soln. of **14** (222 mg, 0.35 mmol) in THF (4 ml), and the resulting suspension was stirred at r.t. overnight. The mixture was cooled on an ice-bath, and MeOH (1 ml) was added dropwise to destroy the excess of $LiAlH_4$. Stirring was continued, until the gas evolution had ceased. The precipitate formed was filtered off, washed with Et_2O (5 × 5 ml), the filtrate was concentrated, and the crude product was purified by chromatography (prep. TLC (CH_2Cl_2/MeOH 15:1)) to afford **15a** (122 mg, 76%). Colorless solid. TLC (SiO_2, CH_2Cl_2/MeOH 15:1): R_f 0.30. M.p. 57–58°. ^{1}H-NMR ($CDCl_3$): 3.56 (br. *s*, CH_2O); 2.49–2.43 (*m*, 6 H, $(CH_2)_2NCH_2$); 1.68–1.64 (*m*, 4 H); 1.54–1.43 (*m*, 4 H); 1.26 (br. *s*, 60 H); 0.88 (*t*, $J = 6.9$, 2 Me). ^{13}C-NMR ($CDCl_3$): 62.56 (OCH_2); 54.58 (NCH_2); 53.61 ($NCH_2(CH_2)_{16}$); 32.54 (br. *s*, CH_2CH_2OH); 31.30 ($MeCH_2CH_2$); 29.67, 29.63, 29.60, 29.50, 29.33, 27.62 ($NCH_2CH_2(CH_2)_{15}$); 26.05 (br. *s*, NCH_2CH_2); 25.71 ($N(CH_2)_2CH_2(CH_2)_{14}$); 22.65 ($MeCH_2$); 14.05 (Me). ESI-MS: 522.7 ($[M - C_4H_8 + H]^+$), 594.8 ($[M + H]^+$).

2-Cyanoethyl 4-(Dioctadecylamino)butyl N,N-*Diisopropylphosphoramidite* (**15b**). A soln. of **15a** (154 mg, 0.26 mmol) in CH_2Cl_2 (5 ml) under Ar was treated with *Hünig*'s base (101 mg, 0.78 mmol). The resulting mixture was cooled in an ice-bath, and (chloro)(2-cyanoethoxy)(diisopropylamino)phosphine (123 mg, 0.56 mmol) was added, and the mixture was stirred for 20 min with cooling and then for 1 h at r.t. The resulting colorless clear soln. was diluted with CH_2Cl_2 (40 ml), washed with an ice-cold aq. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4) and concentrated. The resulting oil was chromatographed (SiO_2; eluted with benzene/Et_2O/Et_3N 80:10:1) to give **2** (191 mg, 93%) from the first three fractions upon evaporation. Colorless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): 3.91–3.79 (*m*, OCH_2); 3.72–3.58 (*m*, OCH_2, 2 NC*H*); 2.65 (*t*, $J = 6.55$, $NCCH_2$); 2.44–2.41 (*m*, NCH_2); 2.40–2.37 (*m*, 2 NCH_2); 1.65–1.60 (*m*, OCH_2CH_2); 1.54–1.48 (*m*, NCH_2CH_2); 1.45–1.39 (*m*, 2 NCH_2CH_2); 1.35–1.1.27 (*m*, CH_2); 1.27 (br. *s*, CH_2); 1.20 (*d*, $J = 6.65$, $CH(Me)_2$); 1.19 (*d*, $J = 6.65$, $CH(Me)_2$); 0.90 (*t*, $J = 6.65$, 2 $MeCH_2$). ^{13}C-NMR ($CDCl_3$,125 MHz): 117.53 (C≡N); 63.72 (*d*, ^2J(C,P) = 17.1, CH_2OP); 58.32 (*d*, ^2J(C,P) = 19.0, CH_2OP); 54.25 (2 CH_2N); 53.91 (CH_2N); 43.51 (*d*, ^2J(C,P) = 12.4, 2 CHNP); 31.90 (2 CH_2CH2 Me); 29.68, 29.37, 29.33, 27.66 (2 CH_2CH_2N); 27.16 (2 $CH_2(CH_2)_2N$); 24.65 (CHMe); 24.59 (2 CHMe); 24.52 (CHMe); 23.59 (CH_2CH_2N); 22.66 (2 $MeCH_2$); 20.34 (*d*, ^3J(C,P) = 6.7, CH_2CH_2OP); 14.06 (2 Me). ^{31}P-NMR ($CDCl_3$, 202.5 MHz): 147.42. ESI-MS (calc. 793): 711.7 ($[M - N^iPr_2 + OH + H]^+$), 741.8 ($[M - O(CH_2)_2CN + OH + H]^+$), 810.8 ($[M + O + H]^+$).

4-(Dioctadecylamino)[1,1,4,4-$^2H_4$]butan-1-ol (**16**). Powdered $LiAlD_4$ (109 mg, 2.6 mmol) was added portionwise during 2 min to a pre-cooled (ice-bath) soln. of **14** (206 mg, 0.32 mmol) in THF (4 ml), and the resulting suspension was stirred at r.t. overnight. The mixture was cooled in an ice-bath, diluted with Et_2O (10 ml), and MeOH (1 ml) was added dropwise to destroy an excess of $LiAlD_4$. Stirring was continued, until gas evolution had ceased (10 min). The precipitate formed was filtered off, washed with Et_2O (5 × 5 ml), the filtrate was concentrated, and the crude product was suspended in CH_2Cl_2. The resulting precipitate was filtered off and washed with CH_2Cl_2 (5 × 1 ml). The filtrate was concentrated resulting in the formation of **16** (145 mg, 75%). White solid[2]). TLC (SiO_2; CH_2Cl_2/MeOH 8:1): R_f 0.60. M.p. 59–60°. ^{1}H-NMR ($CDCl_3$): 2.46–2.42 (*m*, $(CH_2)_2NCD_2$); 1.66–1.62 (*m*, 4 H); 1.51–1.46 (*m*, 4 H); 1.27 (br. *s*, 60 H); 0.89(*t*, $J = 6.9$, 2 Me). ^{13}C-NMR ($CDCl_3$): 61.89 (*quint.*, J(C,D) = 20.5, OCD_2); 53.98 (*quint.*, J(C,D) = 21.1, NCD_2); 53.71 (NCH_2); 32.51 (br. *s*, CH_2CD_2OH); 31.90 ($MeCH_2CH_2$); 29.67, 29.63, 29.61, 29.53, 29.33, 27.66 (NCH_2CH_2); 26.13 (br. *s*, NCD_2CH_2); 25.93 ($N(CH_2)_2CH_2(CH_2)_{14}$); 22.66 ($MeCH_2$); 14.05 (Me). ESI-MS: 522.7 ($[M - C_4H_4D_4 + H]^+$), 598.8 ($[M + H]^+$).

N-*(4-Chlorobut-2-yn-1-yl)*-N-*octadecyloctadecan-1-amine* (**18**). Compound **1** (2.08 g, 4.0 mmol), 1,4-dichlorobut-2-yne **17**, 1.48 g, 12 mmol), and Na_2CO_3 (1.69 g, 16 mmol) were suspended in benzene (40 ml) and stirred at 65–70° (bath) overnight (16 h), until the reaction was completed (NMR analysis: amine **1**: 2.66 ppm, product **18**: 2.44 ppm). The light-brown mixture was concentrated, diluted with Et_2O, inorganic salts and residual starting amine **1** were filtered off and washed with pre-cooled Et_2O (+5°,

20 ml). The filtrate was concentrated resulting in the formation of 2.1 g of a beige solid mass. The product **18** was isolated by CC (SiO_2; (100 g); CH_2Cl_2/Et_2O 4:1; 400 ml) as a light beige mass (1.57 g, 60.5%), followed by other products (in order of their elution from the column): N,N,N′,N′-*tetraoctadecylbut-2-yne-1,4-diamine* (**19**), *4-chlorobut-2-yn-1-ol* (**20**), and bis(*4-chlorobut-2-ynyl*)*dioctadecylammonium chloride* (**21**).

Data of **18**. TLC (SiO_2; CH_2Cl_2): R_f 0.45. M.p. 51–52°. ^{1}H-NMR ($CDCl_3$): 4.18 (*t*, *J* = 1.83, CH_2Cl); 3.44 (*t*, *J* = 1.83, $NCH_2C\equiv$); 2.47–2.44 (*m*, 2 CH_2CH_2N); 1.48–1.41 (*m*, 2 CH_2CH_2N); 1.28 (br. *s*, 60 H); 0.90 (*t*, *J* = 6.9, 2 Me). ^{13}C-NMR ($CDCl_3$): 82.45 (ClC–*C*≡); 79.31 (ClC–C≡*C*); 53.83 (NCH_2CH_2); 42.19 ($NCH_2C\equiv$); 31.92 (CH_2CH2 Me); 30.60 (CH_2Cl); 29.70, 29.65, 29.56 (CH_2CH_2CH2 Me); 29.35 ($CH_2(CH_2)_3N$); 27.52 (CH_2CH_2N); 27.46 ($CH_2(CH_2)_2N$); 22.66 (MeCH_2); 14.03 (Me). ESI-MS (calc. 607(^{35}Cl)): 608.7 ([*M*(^{35}Cl) + H]$^+$), 609.7, 610.7 ([*M*(^{37}Cl) + H]$^+$), 611.7. Anal. calc. for $C_{40}H_{78}ClN$ (608.53): C 78.95, H 12.92, N 2.30; found: C 78.73, H 12.97, N 2.15.

Data of **19**. TLC (SiO_2; CH_2Cl_2): R_f 0.40. M.p. 55–56°. ^{1}H-NMR ($CDCl_3$): 3.43 (*s*, 2 $NCH_2C\equiv$); 2.47–2.44 (*m*, 4 CH_2CH_2N); 1.48–1.41 (*m*, 4 CH_2CH_2N); 1.27 (br. *s*, 120 H); 0.90 (*t*, *J* = 6.9, 4 Me). ^{13}C-NMR ($CDCl_3$): 79.36 (C≡C); 53.95 (NCH_2CH_2); 41.97 ($NCH_2C\equiv$); 31.91 (CH_2CH2 Me); 29.70, 29.66, 29.64, 29.34, 27.61, 27.52, 22.66 (MeCH_2); 14.06 (Me). ESI-MS (calc. 1092): 548.7 ([*M* + 2 H]$^{2+}$).

Data of **20**[6]). TLC (SiO_2, CH_2Cl_2/Et_2O 1:1): R_f 0.31. ^{1}H-NMR ($CDCl_3$): 4.34 (*t*, *J* = 1.75, CH_2O); 4.19 (*t*, *J* = 1.75, CH_2Cl).

Data of **21**. ^{1}H-NMR ($CDCl_3$): 4.97 (*s*, 2 $\equiv CCH_2N^+$); 4.21 (*s*, 2 CH_2Cl); 3.60–3.56 (*m*, 2 $CH_2CH_2N^+$); 1.91–1.86 (*m*, 2 $CH_2CH_2N^+$); 1.27 (br. *s*, 120 H); 0.90 (*t*, *J* = 6.9, 4 Me).

N-*Octadecyl*-N,N-*diprop-2-yn-1-ylamine* (= N,N-*Di(prop-2-yn-1-yl)octadecan-1-amine*; **24**). 3-Bromoprop-1-yne (**23**; 3.57 g, 30 mmol) and K_2CO_3 (4.14 g, 30 mmol) were added consecutively to a stirred suspension of *octadecylamine* (**22**; 2.69 g, 10 mmol) in MeOH (20 ml) in a bottle with a screw stopper. The resulting mixture was stirred at r.t. overnight. The brown suspension was filtered through a SiO_2 layer (1 cm), washed with AcOEt (100 ml), and the filtrate was concentrated to give **24** (3.34 g, 96%). Viscous mass, which solidified upon standing. The product is pure enough for further reactions, however, it could be easily purified for anal. purpose by filtration through a SiO_2 (5 cm; with hexane/AcOEt 15:1). TLC (hexane/AcOEt, 2:2): R_f 0.85. M.p. 43–44° (MeOH). ^{1}H-NMR ($CDCl_3$): 3.45 (*d*, *J* = 2.3, $NCH_2C\equiv$); 2.54–2.51 (*m*, $NCH_2(CH_2)_{16}$); 2.22 (*t*, *J* = 2.3, CH≡); 1.51–1.44 (*m*, 2 H); 1.27 (br. *s*, 30 H); 0.90 (*t*, *J* = 6.5, Me). ^{13}C-NMR ($CDCl_3$): 78.91 (CH≡*C*); 72.72 (CH≡); 53.05 ($NCH_2(CH_2)_{16}$); 42.08 ($NCH_2C\equiv$); 31.90, 29.66, 29.59, 29.55, 29.48, 29.32, 27.45, 27.32, 22.65 (MeCH_2); 14.05 (Me). ESI-MS: 384.4 ([*M* + K]$^+$), 346.4 ([*M* + H]$^+$), 318.3 ([*M* – C_2H_4 + H]$^+$), 270.3 ([*M* – C_6H_4 + H]$^+$).

4-(Octadecylamino)-4-oxobutanoic acid (**25**). Powdered **12** (0.440 g, 4.4 mmol) was added in portions to a stirred soln. of **22** (1.076 g, 4 mmol) in CH_2Cl_2 (20 ml) at r.t., followed by Et_3N (0.808 g, 8 mmol). The resulting white suspension was stirred for 3 h until dissolution of the precipitate. The clear colorless soln. was concentrated *in vacuo*, and the residue was crystallized from acetone to afford **25** (1.277 g, 87%). White crystals. Chromatographic separation of the concentrated mother liquid (SiO_2 (10 g)); CH_2Cl_2/MeOH 1:1) gave a further amount of **25** (0.088 g, 6%). TLC (SiO_2, CH_2Cl_2/MeOH 8:1): R_f 0.64. M.p. 124–125°. ^{1}H-NMR ($CDCl_3$): 5.69 (br. *s*, NH); 3.31–3.27 (*m*, NCH_2); 2.73–2.71 (*m*, NCH_2); 2.56–2.54 (*m*, O=CCH_2); 1.56–1.51 (*m*, $NCH_2CH_2(CH_2)_{15}$); 1.31 (br. *s*, 2 H); 1.28 (br. *s*, 28 H); 0.90 (*t*, *J* = 6.9, Me). ^{13}C-NMR: 173.02 (COO); 170,90 (CON); 40.05 (NCH_2); 31.90 ($MeCH_2CH_2$); 30.75, 30.08, 29.66, 29.63, 29.59, 29.54, 29.49, 29.39, 29.32, 29.21, 26.83 ($NCH_2CH_2CH_2$); 22.65 (MeCH_2); 14.05 (Me). ESI-MS: 370.4 ([*M* + H]$^+$).

Methyl 4-(Octadecylamino)-4-oxobutanoate (**26**). Me_2SO_4 (0.454 g, 3.6 mmol) and K_2CO_3 (1.01 g, 7.4 mmol) were added consecutively to a stirred soln. of **25** (0.680 mg, 1.8 mmol) in acetone (4 ml) at r.t., and the resulting suspension was heated at 55° overnight. The mixture was cooled to r.t., all solids were filtered off, washed with acetone (5 ml), the filtrate was concentrated, and the residue was dissolved in CH_2Cl_2 (5 ml). The soln. was washed with H_2O (2 × 5 ml), dried (Na_2SO_4), and concentrated to give **26** (0.502 mg, 72%). Light-cream crystals. TLC (hexane/AcOEt 1:1): R_f 0.50. M.p. 86–87° ([14]: 86.5–87.5°). ^{1}H-NMR ($CDCl_3$): 5.60 (br. *s*, 0.8 H, NH); 5.35 (br. *s*, 0.2 H, NH); 3.69 (*s*, MeO); 3.23 (*q*, *J* = 6.75, NCH_2); 2.68 (*t*, *J* = 6.75, $COCH_2$); 2.46 (*t*, *J* = 6.75, $COCH_2$); 1.59 (br. *s*, 2 H); 1.54–1.44 (*m*,

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6) The ^{1}H- and ^{13}C-NMR spectra are in agreement with those reported [13].

2 H); 1.26 (br. *s*, 28 H); 0.88 (*t*, $J = 6.8$, *Me*CH_2). ^{13}C-NMR ($CDCl_3$): 173.54 (COO); 171.28 (CON); 51.79 (MeO); 39.72 (NCH_2); 31.92, 31.14 ($NCOCH_2$); 29.69, 29.65, 29.59, 29.54, 29.48, 29.34, 29.28, 26.88 ($NCH_2CH_2CH_2$); 22.67 (MeCH_2); 14.08 (Me). ESI-MS: 406.3 ($[M + Na]^+$), 384.4 ($[M + H]^+$).

1-Octadecylpyrrolidine (**28**). Powdered $LiAlH_4$ (80 mg, 2.08 mmol) was added portionswise to a pre-cooled (ice-bath) soln. of **26** (100 mg, 0.26 mmol) in THF (3 ml), and the resulting suspension was stirred at r.t. during 5 h. The resulting grey suspension was cooled on an ice-bath, diluted with Et_2O (6 ml), and MeOH (1 ml) was added dropwise. The resulting mixture was stirred for 30 min until the formation of a crystalline precipitate was completed. Solids were separated, washed with Et_2O (2×5 ml), and the filtrate was concentrated *in vacuo* to yield **28** (60 mg, 71%). Yellowish solid mass. TLC (CH_2Cl_2/MeOH 10:1): R_f 0.46. M.p. 25–27° ([15]: 26–27°). ^{1}H-NMR ($CDCl_3$): 2.49 (br. *s*, 2 $N(CH_2CH_2)_2$); 2.43–2.40 (*m*, $NCH_2(CH_2)_{16}$); 1.78 (br. *s*, $N(CH_2CH_2)_2$); 1.54–1.46 (*m*, $NCH_2CH_2(CH_2)_{15}$); 1.30–1.26 (*m*, 30 H); 0.89 (*t*, $J = 6.8$, Me). ^{13}C-NMR ($CDCl_3$): 56.72 ($NCH_2(CH_2)_{16}$); 54.21 ($N(CH_2CH_2)_2$); 31.89 ($MeCH_2CH_2$); 29.66, 29.59, 29.32, 29.02, 27.72, 23.38 ($N(CH_2CH_2)_2$); 22.65 (MeCH_2); 14.05 (Me). ESI-MS: 324.4 ($[M + H]^+$), 296.3 ($[M - C_2H_4 + H]^+$).

4-Hydroxy-N-*octadecylbutanamide* (**29**). Powdered $LiAlH_4$ (182 mg, 4.8 mmol) was added in portions during 3 min to a pre-cooled (ice-bath) stirred suspension of **25** (222 mg, 0.6 mmol), dissolved in THF (10 ml). After 15 min, the cooling bath was removed, and stirring was continued at r.t. for another 5 h. The mixture was cooled on an ice-bath, diluted with Et_2O (20 ml), and MeOH (1 ml) and H_2O (1 ml) were added dropwise until the gas evolution had ceased, and the violet suspension turned into a white precipitate. It was filtered off, washed with Et_2O, filtrates were concentrated, and the residue was separated by prep. TLC (SiO_2; CH_2Cl_2/MeOH 8:1) to give **29** (175 mg, 82%). Colorless crystals. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.42. M.p. 86–87° ([16] 86–87°). ^{1}H-NMR ($CDCl_3$): 5.73 (br. *s*, NH); 3.72–3.70 (*m*, CH_2O); 3.25 (*q*, $J = 6.7$, NCH_2); 2.37–2.34 (*m*, $CH_2C{=}O$); 1.81 (*quint.*, $J = 6.2$, $CH_2CH_2C{=}O$); 1.51 (*quint.*, $J = 6.8$, NCH_2CH_2); 1.27 (br. *s*, 30 H); 0.89 (*t*, $J = 6.8$, Me). ^{13}C-NMR ($CDCl_3$): 173.03 (C=O); 62.37 (COH); 39.71 (NCH_2); 34.06 ($COCH_2$); 31.89, 29.66, 29.62, 29.57, 29.52, 29.32, 29.26, 28.17 (NCH_2CH_2); 26.91 ($N(CH_2)_2CH_2$); 22.64 (MeCH_2); 14.06 (Me). ESI-MS: 356.3 ($[M + H]^+$).

4-(Octadecylamino)butan-1-ol (**27**). Powdered $LiAlH_4$ (340 mg, 8 mmol) was added in portions during 10 min to a pre-cooled (ice-bath) stirred suspension of **24** (371 mg, 1 mmol) in Et_2O (20 ml). After 5 min, the cooling bath was removed, and stirring was continued at r.t. for another 1 h and then at 35° overnight. The mixture was cooled on an ice-bath, diluted with Et_2O (20 ml), and H_2O (0.5 ml) was added dropwise until the gas evolution had ceased; the grey suspension turned into a white precipitate. It was filtered off and washed with Et_2O. The filtrates were concentrated, and the white residue was separated by prep. TLC (SiO_2; CH_2Cl_2/MeOH 8:1) to give **27** (288 mg, 84%) as colorless crystals, followed by **29** (22 mg, 6%). TLC (CH_2Cl_2/Et_2O 1:1): R_f 0.42. M.p. 68–69° ([17]: 68–70°). ^{1}H-NMR ($CDCl_3$): 3.60–3.58 (*m*, CH_2O); 2.67–2.65 (*m*, NCH_2); 2.63–2.60 (*m*, NCH_2); 1.72–1.67 (*m*, CH_2); 1.65–1.58 (*m*, CH_2, OH); 1.52–1.48 (*m*, CH_2); 1.26 (br. *s*, 30 H); 0.88 (*t*, $J = 6.8$, Me). ^{13}C-NMR ($CDCl_3$): 61.53 (COH); 47.90, 47.80 (NCH_2); 31.90 ($MeCH_2CH_2$); 29.68, 29.63, 29.60, 29.53, 29.44, 29.33, 29.07, 26.80, 25.96 (NCH_2CH_2); 23.66 ($OCH_2CH_2CH_2$); 22.65 (MeCH_2); 14.06 (Me). ESI-MS: 270.4 ($H_3C(CH_2)_{17}NH_3^+$), 314.4 ($[M - 28 + H]^+$), 342.7 ($[M + H]^+$).

4-[Octadecyl(prop-2-yn-1-yl)amino]butan-1-ol (**30**). Compound **23** (21 mg, 0.18 mmol) was added to a stirred suspension of K_2CO_3 (25 mg, 0.18 mmol) of a soln. of **27** (30 mg, 0.09 mmol) in MeOH (1 ml) at r.t. The resulting mixture was stirred overnight. The resulting precipitate was filtered off, washed with AcOEt (3 ml), the filtrate was concentrated *in vacuo*, and CC (SiO_2; CH_2Cl_2/Et_2O 1:1) gave **30** (20 mg, 61%). Colorless crystals. TLC (CH_2Cl_2/Et_2O 1:1): R_f 0.32. M.p. 33–34°. ^{1}H-NMR ($CDCl_3$): 3.59 (br. *s*, CH_2O); 3.48 (br. *s*, $CH_2C{\equiv}$); 2.61–2.59 (*m*, NCH_2); 2.58–2.55 (*m*, 2 H, $NCH_2(CH_2)_{15}$); 2.21 (br. *s*, $CH{\equiv}$); 1.66 (br. *s*, $CH_2CH_2CH_2O$); 1.56–1.46 (*m*, NCH_2CH_2); 1.26 (br. *s*, 30 H); 0.88 (*t*, $J = 6.7$, Me). ^{13}C-NMR ($CDCl_3$): 73.80 ($CH{\equiv}$); 62.63 (CH_2OH); 53.87, 53.61 (NCH_2); 40.94 ($NCH_2C{\equiv}$); 31.90, 30.32 (OCH_2CH_2); 29.66, 29.62, 29.59, 29.53, 29.43, 29.32, 27.40, 26.83, 25.25 ($OCH_2CH_2CH_2$); 22.65 (MeCH_2); 14.06 (Me). ^{13}C-NMR (C_6D_6): 78.88 ($CH{\equiv}C$); 73.97 ($CH{\equiv}$); 63.25 (CH_2OH); 54.65, 54.49 (NCH_2); 41.87 ($NCH_2C{\equiv}$); 32.93, 32.76 (OCH_2CH_2); 32.79, 30.72, 30.58, 30.41, 28.40, 28.29, 26.00, 23.70 (MeCH_2); 14.94 (Me). ESI-MS: 308.4 ($[M - C_4H_8O + H]^+$), 362.4 ($[M - H_2O + H]^+$), 380.4 ($[M + H]^+$).

5′-O-[Bis(4-methoxyphenyl)(phenyl)methyl]-2′-deoxy-3,4-dihydrothymidine (**37**). *2′-Deoxythymidine* (**31**; 0.726 g, 3.0 mmol) was added portionwise at r.t. to a yellowish clear soln. of 4,4′-dimethoxytrityl chloride (1.220 g, 3.6 mmol) in pyridine (15 ml), and the resulting orange mixture was stirred overnight. It was diluted with AcOEt (80 ml), washed with H_2O (3 × 25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give an orange viscose mass (2.0 g). The product **37** was isolated by CC (SiO_2, 120 g; hexane/AcOEt 2 :1 to 0 :1; 120 ml) as a light-yellow oil (1.52 g, 93.8%), which solidified on standing at r.t. TLC (SiO_2, AcOEt): R_f 0.5. M.p. 123–125° ([18a]: 122–124°). ^{1}H-NMR ($CDCl_3$): 9.67 (br. *s*, NH); 7.60 (*s*, H–C(6)); 7.41 (*d*, *J* = 7.9, 2 arom. CH); 7.31–7.28 (*m*, 6 H); 7.21 (*t*, *J* = 7.2, 1 arom. CH); 6.83 (*d*, *J* = 8.7, 4 arom. CH); 6.45–6.41 (*m*, H–C(1′)); 4.58–4.56 (*m*, H–C(3′)); 4.11–4.07 (*m*, H–C(4′)); 3.77 (*s*, 2 MeO); 3.47–3.35 (q_{AB}, $\delta(H_A)$ 3.46, $\delta(H_B)$ 3.37, $J_{AB} = -10.5$, $J_{AX} = J_{BX} = 2.6$, CH_2(5′)); 2.47–2.43 (*m*, 1 H of CH_2(2′)); 2.33–2.28 (*m*, 1 H of CH_2(2′)); 1.47 (*s*, Me(7)). ^{13}C-NMR ($CDCl_3$): 164.15 (C(4)); 158.69 (MeO–C(arom.)); 150.72 (C(2)); 144.38, 135.78 (C(6)); 135.48, 135.42, 130.08, 128.14, 127.95, 127.08, 113.27, 111.24 (C(5)); 86.88 (CH_2OC); 86.37 (C(4′)); 84.85 (C(1′)); 72.38 (C(3′)); 63.67 (C(5′)); 55.21 (MeO); 40.94 (C(2′)); 11.78 (C(7)) (^{1}H- and ^{13}C-NMR spectra are in a good agreement with those reported in [18]). ESI-MS: 567.3 ($[M + Na]^+$), 583.3 ($[M + K]^+$), 1111.5 ($[2M + Na]^+$).

*5′-O-[Bis(4-methoxyphenyl)(phenyl)methyl]-3′-O-[(*tert*-butyl)(dimethyl)silyl]-2′-deoxy-3,4-dihydrothymidine* (**32**). 1*H*-Imidazole (0.52 g, 7.6 mmol) was dissolved in a soln. of 5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxythymidine (1.36 g, 2.5 mmol) in DMF (20 ml) at r.t. The resulting mixture was cooled in an ice-bath, and a soln. of ^{t}BuMe$_2$SiCl (0.57 g, 3.8 mmol) in DMF (3 ml) was added dropwise during 5 min. The cooling bath was removed, and the mixture was stirred at r.t. overnight. MeOH (10 ml) was added to destroy the excess of ^{t}BuMe$_2$SiCl, and the resulting mixture was stirred for 30 min, diluted with AcOEt (200 ml), washed consecutively with aq. $NaHCO_3$ and H_2O, and dried (Na_2SO_4) and concentrated to give crude **32** (1.95 g) as a colorless viscous oil[2]), which was purified by CC (SiO_2 (200 g); hexane/AcOEt/Et_3N 15 :15 :1), to give pure **32** (1.45 g, 88%) as a colorless viscose oil, which turned to a solid foam on drying in high vacuum[7]). TLC (SiO_2; hexane/AcOEt 2 :1): R_f 0.29. M.p. 87–88°. ^{1}H-NMR ($CDCl_3$): 8.46 (*s*, NH); 7.64 (*s*, H–C(6)); 7.43 (*d*, *J* = 7.9, 2 arom. CH); 7.33–7.29 (*m*, 6 arom. CH); 7.27–7.24 (*m*, 1 arom. H); 6.85 (*d*, *J* = 8.8, arom. CH); 6.37–6.34 (*m*, H–C(1′)); 4.54–4.52 (*m*, H–C(3′)); 3.98–3.95 (*m*, H–C(4′)); 3.79 (*s*, 2 MeO); 3.50–3.24 (q_{AB}, H_A = 3.46, H_B = 3.27, $J_{AB} = -10.6$, $J_{AX} = J_{BX} = 2.8$, CH_2(5′)); 2.37–2.32 (*m*, CH_2(2′)); 2.25–2.21 (*m*, CH_2(2′)); 1.51 (*s*, Me(7)); 0.84 (*s*, $SiCMe_3$); 0.03 (*s*, SiMe); −0.03 (*s*, SiMe). ^{13}C-NMR ($CDCl_3$): 163.61 (C(4)); 158.76 (MeO*C*(arom.)); 150.18 (C(2)); 144.35, 135.58 (C(6)); 135.50, 135.46, 130.06, 130.04, 128.14, 127.95, 127.11, 113.28, 113.27, 110.98 (C(5)); 86.84 (CH_2OC); 86.80 (C(4′)); 84.90 (C(1′)); 72.11 (C(3′)); 62.94 (C(5′)); 55.23 (MeO); 41.54 (C(2′)); 25.70 (Si*CMe*); 17.92 (SiC); 11.86 (C(7)); −4.69, −4.88 (SiMe) (^{1}H- and ^{13}C-NMR spectra are in a good agreement with those reported in [19]). ESI-MS: 681.4 ($[M + Na]^+$), 697.4 ($[M + K]^+$).

2′-Deoxy-3-[4-(dioctadecylamino)but-2-yn-1-yl]-3,4-dihydrothymidine (**33**). Compound **31** (32 mg, 0.132 mmol), DMSO (0.1 ml), and K_2CO_3 (36 mg, 0.264 mmol) were consecutively added to a stirred soln. of **18** (80 mg, 0.132 mmol) in THF (0.5 ml) at r.t. in a bottle with a screw stopper, and the mixture was stirred at 70° during 48 h. The resulting brown mixture was cooled to r.t., treated with H_2O (4 ml) and Et_2O (4 ml), the org. phase was separated, and the H_2O phase was extracted with Et_2O (4 ml). Combined org. phases were washed with H_2O, dried (Na_2SO_4), concentrated, and prep. TLC (SiO_2; AcOEt) afforded **33** (49 mg, 46%). Yellow oil. TLC (AcOEt): R_f 0.33. M.p. 49–50°. ^{1}H-NMR ($CDCl_3$): 7.49 (*s*, H–C(6)); 6.24 (*t*, *J* = 6.7, H–C(1′)); 4.72 (*s*, $CONCH_2C{\equiv}$); 4.58–4.56 (*m*, H–C(3′)); 4.00–3.98 (*m*, H–C(4′)); 3.92–3.83 (q_{AB}, $\delta(H_A)$ 3.91, $\delta(H_B)$ 3.84, $J_{AB} = -11.8$, $J_{AX} = J_{BX} = 2.8$, CH_2(5′)); 3.33 (*s*, $CH_2NCH_2C{\equiv}$); 2.47–2.41 (*m*, $N(CH_2)_2$); 2.34–2.32 (*m*, CH_2(2′)); 1.99 (*s*, Me(7)); 1.44–1.40 (*m*, 4 H); 1.27 (br. *s*, 60 H); 0.89 (*t*, *J* = 6.9, 2 *Me*CH_2). ^{13}C-NMR ($CDCl_3$): 162.36 (C(4)); 150.24 (C(2)); 134.92 (C(6)); 110.30 (C(5)); 87.26 (C(4′)); 86.86 (C(1′)); 71.43 (C(3′)); 62.33 (C(5′)); 53.68 ($NCH_2(CH_2)_{16}$); 42.25 ($NCH_2C{\equiv}$); 40.25 ($CHCH_2CH$); 31.90 ($MeCH_2CH_2$); 30.74 ($CONCH_2$); 29.68, 29.63, 29.55, 29.33, 27.48 (NCH_2CH_2); 27.07 ($N(CH_2)_2CH_2$); 22.65 ($MeCH_2$); 14.06 (*Me*CH_2); 13.22 (C(7)). ^{13}C-NMR (CD_3OD): 164.36 (C(4)); 151.64 (C(2)); 136.73 (C(6)); 110.69 (C(5)); 89.06 (C(4′)); 87.28 (C(1′)); 81.09 (C≡); 77.77 (C≡); 72.11 (C(3′)); 62.77 (C(5′)); 54.82 ($NCH_2(CH_2)_{16}$); 42.76 ($NCH_2C{\equiv}$); 41.49

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[7]) The compound **32** is sensitive to acids including SiO_2, and addition of Et_3N into the elution mixture improves the isolated yield.

($CHCH_2CH$); 33.06 ($MeCH_2CH_2$); 31.52 ($CONCH_2$); 30.75, 30.66, 30.64, 30.51, 30.44, 28.53 (NCH_2CH_2); 27.81 ($N(CH_2)_2CH_2$); 23.71 ($MeCH_2$); 14.41 ($MeCH_2$); 13.13 (C(7)). ESI-MS: 814.7 ($[M+H]^+$).

5′-O-[Bis(4-methoxyphenyl)(phenyl)methyl]-2′-deoxy-3-[4-(dioctadecylamino)but-2-yn-1-yl]-3,4-dihydrothymidine (**34**) *from* **33**. A soln. of 4,4′-dimethoxytrityl chloride (13.4 mg, 0.039 mmol) in pyridine (0.1 ml) was added to a pre-cooled (ice-bath) soln. of **33** (28 mg, 0.034 mmol), and the resulting orange soln. was stirred at r.t. 48 h. The mixture was diluted with CH_2Cl_2 (2 ml), concentrated in vacuum (0.05 Torr), and the residue was separated by prep. TLC (20 × 20 cm, SiO_2; CH_2Cl_2/AcOEt/Et_3N 40 : 9 : 1) to give in the 3rd fraction **34** (28 mg, 73%). Yellowish oil. TLC (SiO_2, CH_2Cl_2/AcOEt/Et_3N 40 : 9 : 1): R_f 0.44. ^{1}H-NMR ($CDCl_3$): 7.55 (*s*, H–C(6)); 7.42 – 7.41 (*m*, 2 arom. H); 7.32 – 7.30 (*m*, 6 arom. H); 7.26 – 7.24 (*m*, 1 arom. H); 6.86 – 6.84 (*m*, 2 arom. H); 6.43 (*t*, $J = 6.6$, H–C(1′)); 4.74 (*s*, $CONCH_2C\equiv$); 4.58 – 4.55 (*m*, H–C(3′)); 4.05 – 4.03 (*m*, H–C(4′)); 3.81 (*s*, 2 MeO); 3.52 – 3.39 (q_{AB}, $\delta(H_A)$ 3.45, $\delta(H_B)$ 3.40, $J_{AB} = -10.5$, $J_{AX} = 3.3$, $J_{BX} = 3.1$, CH_2(5′)); 3.36 (*s*, $CH_2NCH_2C\equiv$); 2.47 – 2.41 (*m*, $N(CH_2)_2$); 2.34 – 2.29 (*m*, $NCHCH_2$); 1.57 (*s*, Me(7)); 1.46 – 1.40 (*m*, 4 H); 1.27 (br. *s*, 60 H); 0.89 (*t*, $J = 6.9$, 2 $MeCH_2$). ^{13}C-NMR ($CDCl_3$): 162.46 (C(4)); 158.78 (*C*OMe); 150.21 (C(2)); 144.32 (OC*C*(arom.)); 135.40 (OC*C*(arom.)); 133.69 (C(6)); 130.06 (arom. CH); 128.12 (arom. CH); 127.14 (arom. CH); 113.31 (arom. CH); 110.38 (C(5)); 86.99 (O*C*C(arom.)); 85.84 (C(4′)); 85.30 (C(1′)); 72.36 (C(3′)); 63.43 (C(5′)); 55.23 ($NCH_2(CH_2)_{16}$); 53.72 (MeO); 42.35 ($NCH_2C\equiv$); 41.03 (C(2′)); 31.90 ($MeCH_2CH_2$); 30.76 ($CONCH_2$); 29.69, 29.65, 29.60, 29.33, 27.52 (NCH_2CH_2); 27.41, 22.66 ($MeCH_2$); 14.07 ($MeCH_2$); 12.60 (C(7)). ^{13}C-NMR (C_6D_6): 161.89 (C4)); 159.03 (*C*OMe); 150.11 (C(2)); 144.88 (OC*C*(arom.)); 135.63 (OC*C*(arom.)); 133.40 (C(6)); 130.21 (arom. CH); 128.30 (arom. CH); 126.99 (arom. CH); 113.30 (arom. CH); 109.93 (C(5)); 86.87 (O*C*C(arom.)); 85.89 (C(4′)); 85.45 (C(1′)); 79.78 (C≡); 77.59 (C≡); 71.90 (C(3′)); 63.64 (C(5′)); 54.48 ($NCH_2(CH_2)_{16}$); 53.70 (MeO); 42.12 ($NCH_2C\equiv$); 40.72 ($CHCH_2CH$); 31.96 ($MeCH_2CH_2$); 30.64 ($CONCH_2$); 29.84, 29.75, 29.72, 29.44, 27.75 (NCH_2CH_2); 27.49, 22.72 ($MeCH_2$); 13.96 ($MeCH_2$); 12.56 (C(7)). ESI-MS: 1116.9 ($[M+H]^+$).

5′-O-[Bis(4-methoxyphenyl)(phenyl)methyl]-2′-deoxy-3-[4-(dioctadecylamino)but-2-yn-1-yl]-3,4-dihydrothymidine (**34**) *from* **37**. *A* clear soln. of **37** (72 mg, 0.132 mmol) and **18** (80 mg, 0.132 mmol) in THF (0.5 ml) was diluted with DMSO (0.2 ml), then K_2CO_3 (36 mg, 0.264 mmol) was added, and the resulting mixture was stirred at 70° during 2 d. The resulting brownish mixture was cooled and treated with H_2O (5 ml), extracted with Et_2O (2 × 5 ml), washed with H_2O (2 × 2 ml), dried (Na_2SO_4), and evaporated. The crude product was purified by CC (SiO_2 *60*, gradient CH_2Cl_2/MeOH 500 – 30 : 1) to give **34** (75 mg, 51 %) and starting **37** (28 mg, 39%; in order of their elution from the column). TLC (SiO_2; CH_2Cl_2/AcOEt/Et_3N 40 : 9 : 1): R_f 0.46. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.55 (*s*, H–C(6)); 7.41 (*d*, $J = 7.65$, 2 arom. CH); 7.32 – 7.30 (*m*, 6 arom. CH); 7.25 (*t*, $J = 7.3$, 1 arom. CH); 6.85 (*d*, $J = 8.55$, 4 arom. CH); 6.43 (*t*, $J = 6.6$, H–C(1′)); 4.77 – 4.70 (*m*, $\equiv CCH_2$); 4.58 – 4.54 (*m*, H–C(3′)); 4.05 – 4.02 (*m*, H–C(4′)); 3.81 (*s*, 2 MeO); 3.52 – 3.38 (q_{AB}, $H_A = 3.50$, $H_B = 3.40$, $J_{AB} = -10.5$, $J_{AX} = J_{BX} = 3.3$, CH_2(5′)); 3.43 (*s*, OH); 3.36 (*s*, $\equiv CCH_2$); 2.47 – 2.40 (*m*, CH_2NCH_2, 1 H of CH_2(2′)); 2.35 – 2.28 (*m*, 1 H of CH_2(2′)); 1.57 (*s*, Me(7)); 1.47 – 1.40 (*m*, 2 $NCH_2CH_2(CH_2)_{15}$); 1.28 (br. *s*, 60 H); 0.90 (*t*, $J = 6.8$, $MeCH_2$).

*5′-O-[Bis(4-methoxyphenyl)(phenyl)methyl]-3′-O-[(*tert*-butyl)(dimethyl)silyl]-2′-deoxy-3-[4-(dioctadecylamino)but-2-yn-1-yl]-3,4-dihydrothymidine* (**38**). A soln. of **32** (329 mg, 0.50 mmol) and **18** (304 mg, 0.50 mmol) in THF (4.0 ml) was diluted with DMF (5 ml); K_2CO_3 (276 mg, 2.0 mmol) and dibenzo-[18]-crown-6 (30 mg, 0.08 mmol) were added, and the resulting mixture was stirred at 60° for 2 d. The cooled brown mixture was treated with Et_2O (100 ml), washed with H_2O (4 × 15 ml) and brine, dried (Na_2SO_4), and concentrated to give **38** (589 mg, 95%). TLC (SiO_2; hexane/CH_2Cl_2/acetone/Et_3N 20 : 5 : 5 : 1): R_f 0.75. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.65 (*s*, H–C(6)); 7.43 (*d*, $J = 7.65$, 2 arom. CH); 7.33 – 7.29 (*m*, 6 arom. CH); 7.25 (*t*, $J = 7.3$, 1 arom. CH); 6.85 (*d*, $J = 8.55$, 4 arom. CH); 6.40 (*t*, $J = 6.5$, H–C(1′)); 4.79 – 4.71 (*m*, $\equiv CCH_2$); 4.53 – 4.51 (*m*, H–C(3′)); 4.00 – 3.98 (*m*, H–C(4′)); 3.81 (*s*, 2 MeO); 3.50 – 3.27 (q_{AB}, $H_A = 3.49$, $H_B = 3.29$, $J_{AB} = -10.6$, $J_{AX} = J_{BX} = 2.6$, CH_2(5′)); 3.37 (*s*, $\equiv CCH_2$); 2.45 – 2.42 (*m*, CH_2NCH_2); 2.38 – 2.34 (*m*, 1 H of CH_2(2′)); 2.24 – 2.18 (*m*, 1 H of CH_2(2′)); 1.57 (*s*, Me(7)); 1.45 – 1.39 (*m*, 2 $NCH_2CH_2(CH_2)_{15}$); 1.28 (br. *s*, 60 H); 0.90 (*t*, $J = 6.5$, $MeCH_2$); 0.86 (*s*, $SiCMe_3$); 0.04 (*s*, SiMe); – 0.02 (*s*, SiMe). ^{13}C-NMR ($CDCl_3$, 125 MHz): 162.52 (C(4)); 158.75 (2 O*C*(arom.)); 150.21 (C(2)); 144.36 (OC*C*(arom.)); 135.49 (2 OC*C*(arom.)); 133.73 (C(6)); 130.06, 130.05 (4 arom. CH); 128.14 (2 arom. CH); 127.93 (2 arom. CH); 127.09 (arom. CH); 113.27, 113.26 (4 arom. CH); 110.22

(C(5)); 86.83 (O*C*C(arom.)); 86.74 (C(1′)); 85.58 (C(4′)); 78.94 (≡C); 77.56 (≡C); 72.06 (C(3′)); 62.92 (C(5′)); 55.22 (2 MeO); 53.74 (CH_2NCH_2); 42.42 (CH_2C≡); 41.64 (C(2′)); 31.91 (CH_2C≡); 30.71, 29.69, 29.64, 29.33, 27.52, 25.69 (CMe_3); 22.66 (2 MeCH_2); 17.90 (SiC); 14.07 (2 $MeCH_2$); 12.62 (C(7)); −4.69, −4.89 (2 SiMe). ESI-MS: 1230.9 ($[M+H]^+$).

5′-O-[Bis(4-methoxyphenyl)(phenyl)methyl]-2′-deoxy-3-[4-(dioctadecylamino)but-2-yn-1-yl]-3,4-dihydrothymidine (**34**) *from* **38**. A soln. of **38** (192 mg, 0.156 mmol) in THF (0.4 ml) was diluted with H_2O (0.05 ml), and a soln. of Bu_4NF (0.17ml, 0.156 mmol) in THF was added in one portion. The resulting clear mixture was stirred at 50° overnight. It was cooled and diluted with CH_2Cl_2 (10 ml). The aq. phase was separated, and the soln. was dried (Na_2SO_4) and concentrated. Pure **34** (135 mg, 78%) was isolated by CC (SiO_2; hexane/CH_2Cl_2/acetone/Et_3N 40 : 10 : 5 : 1). Beige mass TLC (SiO_2, hexane/AcOEt 2 : 1): R_f 0.69.

*5′-O-[Bis(4-methoxyphenyl)(phenyl)methyl]-3′-O-{(2-cyanoethoxy)[*N,N*-(diisopropyl)amino]phosphanyl}-2′-deoxy-3-[4-(dioctadecylamino)but-2-yn-1-yl]-3,4-dihydrothymidine* (**39**). *Hünig*'s base (47 mg, 0.36 mmol) was added to a soln. of **34** (135 mg, 0.12 mmol) in CH_2Cl_2 (3 ml) under Ar; the resulting mixture was cooled in an ice-bath, (chloro)(2-cyanoethoxy)(diisopropylamino)phosphine was added, and the mixture was stirred for 10 min with cooling, and 1 h at r.t. The resulting light yellow clear soln. was diluted with CH_2Cl_2 (30 ml), washed with a cold aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and concentrated. The resulting yellowish oil was subjected to CC (SiO_2; CH_2Cl_2/acetone/Et_3N 85 : 14 : 1) to give, from the first four fractions **39**, upon evaporation as a colorless oil (142 mg, 90%) as a mixture of non-assigned (R_P) and (S_P) diastereoisomers. ^{1}H-NMR ($CDCl_3$, 500 MHz; mixture of diastereoisomers **X** and **Y** in a ratio of 2.6: 1): 7.64 (*s*, 0.72 H, H–C(6), **X**); 7.59 (*s*, 0.28 H, H–C(6), **Y**); 7.43–7.41 (*m*, 2 arom. H, **X**, **Y**); 7.33–7.28 (*m*, 6 arom. CH, **X**, **Y**); 7.27–7.23 (*m*, 1 arom. H, **X**, **Y**); 6.86–6.83 (*m*, 4 arom. CH, **X**, **Y**); 6.48–6.46 (*m*, 0.28 H, H–C(1′), **X**); 6.46–6.43 (*m*, 0.72 H, H–C(1′), **Y**); 4.79–4.71 (*m*, ≡CCH_2, **X**, **Y**); 4.69–4.63 (*m*, H–C(3′), **X**, **Y**); 4.20–4.18 (*m*, 0.72 H, H–C(4′), **X**); 4.17–4.15 (*m*, 0.28 H, H–C(4′), **Y**); 3.81 (*s*, 4.3 H, 2 MeO, **X**); 3.80 (*s*, 1.68 H, 2 MeO, **Y**); 3.69–3.55 (*m*, $POCH_2$, 2 NCH, **X**, **Y**); 3.56–3.33 (q_{AB}, 0.72 H, $\delta(H_A)$ 3.55, $\delta(H_B)$ 3.34, $J_{AB}=-10.6$, $J_{AX}=J_{BX}=2.6$, CH_2(5′), **X**); 3.51–3.31 (q_{AB}, 0.28 H, $\delta(H_A)$ 3.49, (δH_B) 3.33, $J_{AB}=10.6$, $J_{AX}=J_{BX}=2.6$, CH_2(5′), **Y**); 3.36 (br. *s*, ≡CCH_2, **X**, **Y**); 2.65–2.61 (*m*, CH_2CN, **X**, **Y**); 2.60–2.55 (*m*, 0.28 H, CH_2(2′), **Y**); 2.53–2.48 (*m*, 0.72 H, CH_2(2′), **X**); 2.45–2.41 (*m*, CH_2NCH_2, **X**, **Y**); 2.35–2.29 (*m*, 1 H of CH_2(2′), **X**, **Y**); 1.51 (*s*, Me(7), **X**, **Y**); 1.45–1.39 (*m*, 2 $NCH_2CH_2(CH_2)_{15}$, **X**, **Y**); 1.28 (br. *s*, 60 H); 1.20–1.18 (*m*, 2 $CHMe_2$, **X**, **Y**); 0.91–0.88 (*m*, $MeCH_2$, **X**, **Y**). ^{31}P-NMR ($CDCl_3$, 202.5 MHz): 149.17, 148.54.

*5′-O-[Bis(4-methoxyphenyl)(phenyl)methyl]-3′-O-[(*tert*-butyl)(dimethyl)silyl]-2′-deoxy-3-[3-(dioctadecylamino)propyl]-3,4-dihydrothymidine* (**35**). Powdered Ph_3P (48 mg, 0.182 mmol) was added in one portion to a stirred clear soln. of **32** (80 mg, 0.121 mmol) and **9** (70 mg, 0.121 mmol) in benzene (2 ml) at r.t. The mixture was stirred for 5 min until dissolution of all the precipitate. Then, the mixture was cooled on an ice-bath, and diisopropyl azodicarboxylate (DIAD; 37 mg, 0.182 mmol) in benzene (0.5 ml) was added dropwise within 1 min. After 5 min, the cooling bath was removed, and the mixture was stirred at r.t. overnight. The solvent was removed *in vacuo*, and the light-yellow solid residue was subjected to CC (SiO_2; hexane/AcOEt/Et_3N 12 : 6 : 1) to yield **34** (71 mg, 48%). Viscous yellowish mass. TLC (SiO_2; hexane/AcOEt/Et_3N 120 : 60 : 1): R_f 0.53. ^{1}H-NMR ($CDCl_3$): 7.61 (*s*, H–C(6)); 7.41 (*d*, $J=$ 7.65, 2 arom. CH); 7.32–7.29 (*m*, 6 arom. CH); 7.23 (*t*, $J=7.3$, 1 arom. CH); 6.83 (*d*, $J=8.55$, 4 arom. CH); 6.39–6.37 (*m*, H–C(1′)); 4.51–4.49 (*m*, H–C(3′)); 3.97–3.92 (*m*, H–C(4′); $CONCH_2$); 3.79 (*s*, 2 MeO); 3.48–3.26 (q_{AB}, $\delta(H_A)$ 3.46, $\delta(H_B)$ 3.27, $J_{AB}=-10.6$, $J_{AX}=J_{BX}=2.6$, CH_2(5′)); 2.54–2.51 (*m*, $NCH_2(CH_2)_2N$); 2.42–2.39 (*m*, 2 $NCH_2(CH_2)_{16}$); 2.36–2.31 (*m*, 1 H of CH_2(2′)); 2.21–2.17 (*m*, 1 H of CH_2(2′)); 1.80–1.76 (*m*, $NCH_2CH_2CH_2N$); 1.55 (*s*, Me(7)); 1.45–1.39 (*m*, 2 $NCH_2CH_2(CH_2)_{15}$); 1.26 (br. *s*, 60 H); 0.88 (*t*, $J=6.5$, $MeCH_2$); 0.84 (*s*, $SiCMe_3$); 0.03 (*s*, SiMe); −0.03 (*s*, SiMe). ^{13}C-NMR ($CDCl_3$): 163.40 (C(4)); 158.70 (MeO*C*(arom.)); 150.79 (C(2)); 144.36 (OC*C*(arom.)); 135.50 (C(6)); 133.34 (OC*C*(arom.)); 130.03 (OCC=CH(arom.)); 128.11 (arom. CH); 127.91 (arom. CH); 127.04 (arom. CH); 113.22 (MeOCCH(arom.)); 110.11 (C(5)); 86.76 (C(4′)); 86.62 (C(1′)); 85.41 (CH_2OC); 72.03 (C(3′)); 62.89 (C(5′)); 55.18 (MeO); 53.83 ($NCH_2(CH_2)_{16}$); 51.55 ($NCH_2(CH_2)_2N$); 41.58 (C(2′)); 40.04 ($CONCH_2$); 31.88 ($MeCH_2CH_2$); 29.66 ($(CH_2)_{11}$); 29.31 ($N(CH_2)_3CH_2$); 27.58 ($N(CH_2)_2CH_2CH_2$); 26.95 ($NCH_2CH_2(CH_2)_{15}$); 25.66 ($SiCMe$); 24.84 ($NCH_2CH_2CH_2N$); 22.64 ($MeCH_2$); 17.87 (SiC); 14.04 ($MeCH_2$); 12.67 (C(7)); −4.72 (SiMe); −4.94 (SiMe). ESI-MS: 522.7 ($(C_{18})_2NH_2^+$), 1221.1 ($[M+H]^+$).

5′-O-[Bis(4-methoxyphenyl)(phenyl)methyl]-2′-deoxy-3-[3-(dioctadecylamino)propyl]-3,4-dihydrothymidine (**36**). A soln. of Bu_4NF (0.05 ml, 1M in THF) was added to a soln. of **35** (65 mg, 0.05 mmol) and H_2O (20 mg, 1 mmol) in THF (0.1 ml) at r.t., and the resulting mixture was stirred at 50° overnight. The solvent was removed, the residue was dissolved in CH_2Cl_2 (1 ml) and filtered through a SiO_2 layer (2 cm), washed consecutively with CH_2Cl_2 (40 ml), CH_2Cl_2/AcOEt 10:1 (40ml), and AcOEt (40 ml) to yield **36** (54 mg, 90%) from the 3rd fraction as a colorless glassy mass. TLC (SiO_2, AcOEt): R_f 0.4. ^{1}H-NMR ($CDCl_3$): 7.55 (*s*, H–C(6)); 7.41 (*d*, $J = 7.65$, 2 arom. CH); 7.32–7.29 (*m*, 6 arom. CH); 7.24 (*t*, $J = 7.3$, 1 arom. CH); 6.84 (*d*, $J = 8.55$, 4 arom. CH); 6.45–6.43 (*m*, H–C(1′)); 4.57–4.54 (*m*, H–C(3′)); 4.06–4.03 (*m*, H–C(4′)); 3.98–3.90 (*m*, $CONCH_2$); 3.80 (*s*, 2 MeO); 3.50–3.37 (q_{AB}, $\delta(H_A) = 3.49$, $\delta(H_B)$ 3.39, $J_{AB} = -10.5$, $J_{AX} = J_{BX} = 2.9$, $CH_2(5')$); 2.53–2.50 (*m*, $NCH_2(CH_2)_2N$); 2.44–2.39 (*m*, 5 H, 2 $NCH_2(CH_2)_{16}$, $CH_2(2')$); 2.33–2.27 (*m*, 1 H of $CH_2(2')$); 1.77 (*quint.*, $J = 7.3$, $NCH_2CH_2CH_2N$); 1.54 (*s*, Me(7)); 1.45–1.39 (*m*, 2 $NCH_2CH_2(CH_2)_{15}$); 1.27 (br. *s*, 60 H); 0.90 (*t*, $J = 6.9$, $MeCH_2$). ^{13}C-NMR ($CDCl_3$): 163.39 (C4)); 158.75 (MeO*C*(arom.)); 150.84 (C(2)); 144.38 (OC*C*(arom.)); 135.49 (OC-*C*(arom.)); 133.34 (C(6)); 130.07 (OCC=CH(arom.)); 128.14 (arom. CH); 127.96 (arom. CH); 127.10 (arom. CH); 113.29 (MeOCCH(arom.)); 110.27 (C(5)); 86.92 (CH_2OC); 85.91 (C(4′)); 85.25 (C(1′)); 72.21 (3′)); 63.52 (C(5′)); 55.21 (MeO); 53.88 ($NCH_2(CH_2)_{16}$); 51.61 ($NCH_2(CH_2)_2N$); 41.06 (C(2′)); 40.10 ($CONCH_2$); 31.90 ($MeCH_2CH_2$); 29.69 (CH_2); 29.64 (CH_2); 29.33 ($N(CH_2)_3CH_2$); 27.62 ($N(CH_2)_2CH_2CH_2$); 26.92 ($NCH_2CH_2(CH_2)_{15}$); 24.90 ($NCH_2CH_2CH_2N$); 22.66 ($MeCH_2$); 14.07 ($MeCH_2$); 12.65 (C(7)). ESI-MS: 1106.9 ($[M+H]^+$).

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