Monatsh Chem (2010) 141:339–349
DOI 10.1007/s00706-010-0255-y

ORIGINAL PAPER

Synthesis of novel symmetrical, single-chain, diacetylene-modified bolaamphiphiles with different alkyl chain lengths

Simon Drescher · Katrin Helmis · Andreas Langner · Bodo Dobner

Received: 24 September 2009 / Accepted: 15 January 2010 / Published online: 13 February 2010

Abstract General syntheses of novel symmetrical, single-chain, diacetylene-modified bolaphospholipids have been carried out in five steps. For the ω-alkynols, which have an important role as key intermediates, three different synthetic approaches were comprehensively investigated. For the final synthesis it is suggested that (1) alkylation of lithium (trimethylsilyl)acetylide with tetrahydropyranyl-protected ω-bromoalcohols, followed by (2) cleavage of the trimethylsilyl moiety and the tetrahydropyranyl protecting group, and (3) copper(II)-catalyzed Eglinton coupling is the best strategy for obtaining diacetylene-modified alkane-1,ω-diols, because higher yields were obtained while avoiding the formation of by-products. Moreover, conversion of the diols into bipolar phospholipids was achieved by bis-phosphorylation with β-bromoethyl-phosphoric acid dichloride and subsequent quaternization with trimethylamine or dimethylamine. Finally, spectral data are presented for novel single-chain, diacetylene-modified bolaphospholipids with promising potential as starting molecules in the formation of polymerizable and, thus, thermostable nanofibers.

Keywords Alkynes · Diacetylenes · Lipids · Nanostructures · Phosphates · Phospholipids

S. Drescher (✉) · K. Helmis · A. Langner · B. Dobner
Department of Biochemical Pharmacy, Institute of Pharmacy, Martin-Luther-University Halle-Wittenberg, Wolfgang-Langenbeck-Str. 4, 06120 Halle (Saale), Germany
e-mail: simon.drescher@pharmazie.uni-halle.de

Introduction

In recent years, many symmetrical and unsymmetrical bipolar amphiphiles (bolaamphiphiles, BAs) have been synthesized, enabling the study of their outstanding self-assembly properties in aqueous media [1, 2]. BAs were originally observed in the membrane lipids of some species of *Archaea* [1]. Those bipolar molecules are composed of two polar headgroups attached to one or two long hydrophobic spacers, often alkyl chains. The membrane-spanning and thus membrane-stabilizing properties of these BAs are responsible for the outstanding stability of the *Archaea*—even under hostile conditions, for example anaerobic milieu or high temperatures (hot springs) in combination with low pH. The qualities summarized above make the BAs attractive candidates for use in vesicular drug-delivery systems or for the stabilization of supported biosensor devices [3, 4]. Because well characterized complex BAs are difficult to isolate from natural *Archaea* membranes, much effort has been devoted to their synthesis, and that of novel and simplified bipolar amphiphiles [2, 5]. Unexpectedly, simplification of the *Archaea* model compounds to bipolar lipids with only one long alkyl chain resulted in the formation of novel aggregate structures, e.g. nanofibers and nanoparticles of self-assembled BAs [6, 7].

Recently, we reported the synthesis and aggregation behavior of symmetrical single-chain polymethylene-1,ω-bis(phosphocholines) with alkyl chain lengths of 22–32 carbon atoms and two phosphocholine headgroups attached at each end [8]. The simplified archaeal model lipids resulting from that work self-assemble at room temperature into long and flexible nanofibers, forming a dense network, which gels water very efficiently [9, 10]. Within these fibers, the bola molecules are arranged side by side, but twisted relative to each other, because of the bulky

headgroups, leading to a helical superstructure of the nanofibers [11]. Thereby, the self-assembly process is exclusively driven by van-der-Waals interactions between the long alkyl chains, because the phosphocholine headgroups are not able to form intermolecular hydrogen bonds. Above a certain transition temperature, which is solely dependent on the lengths of the alkyl spacers, the nanofibers reversibly transform into smaller aggregates—for example spherical micelles or discs. However, the gel character of the aqueous suspension is completely lost after this transformation.

Stabilization can be achieved by changing the headgroup structure from a phosphocholine to a phosphodimethylethanolamine one while implementing a stabilization process performed by hydrogen bonds [12]. Insertion of dissociable H-atoms furnished pH-sensitive bolaform hydrogelators, which are important for drug-delivery systems. Nevertheless, the heat stability of these nanofibers is also limited to a fiber–micelle transformation in which the nanofibers are completely destroyed and a liquefaction of the hydrogel is observed [12, 13].

One possible means of overcoming this temperature-dependent fiber–micelle transformation and associated gel liquefaction is covalent bonding among the bola molecules within the fiber. Therefore, the insertion of diacetylene groups, which can be polymerized to polydiacetylenes (PDA) by UV irradiation, is seen to be the predestined strategy. The formation of PDAs is well described in the literature and the applications of this conjugated polymer widely range from materials science [14–16] to a huge number of various biosensing devices [17–21]. Hence, the combination of nanofiber-forming BAs and PDAs might be one promising approach to novel aggregates, e.g. thermostable nanofibers forming a hydrogel with adjustable gel strength.

In this work, we examined synthetic approaches to novel symmetrical, single-chain, diacetylene-modified BAs with an overall chain length of 30–36 carbon atoms and phosphocholine or phosphodimethylethanolamine headgroups.

Results and discussion

In general, the synthesis of covalently bridged single-chain BAs can be achieved by insertion of polymerizable functionality either in the headgroup region or within the long alkyl chain. However, since modifications of the headgroups have a distinct effect on the aggregation behavior of bipolar amphiphiles [22], the choline moieties of the BAs should be unmodified and, hence, polymerizable diacetylenic groups were inserted in the middle of the alkyl spacer leading to target molecules as shown in Fig. 1.

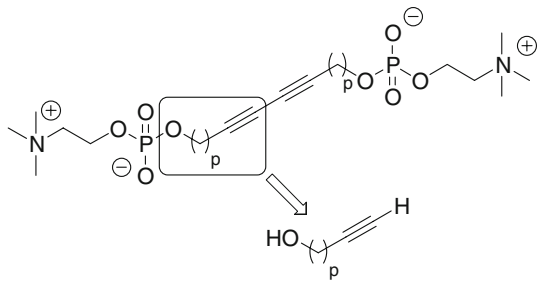


Fig. 1 Diacetylene-modified bolaamphiphiles as target molecules and ω-alkynols as key intermediates ($p = 13$–16)

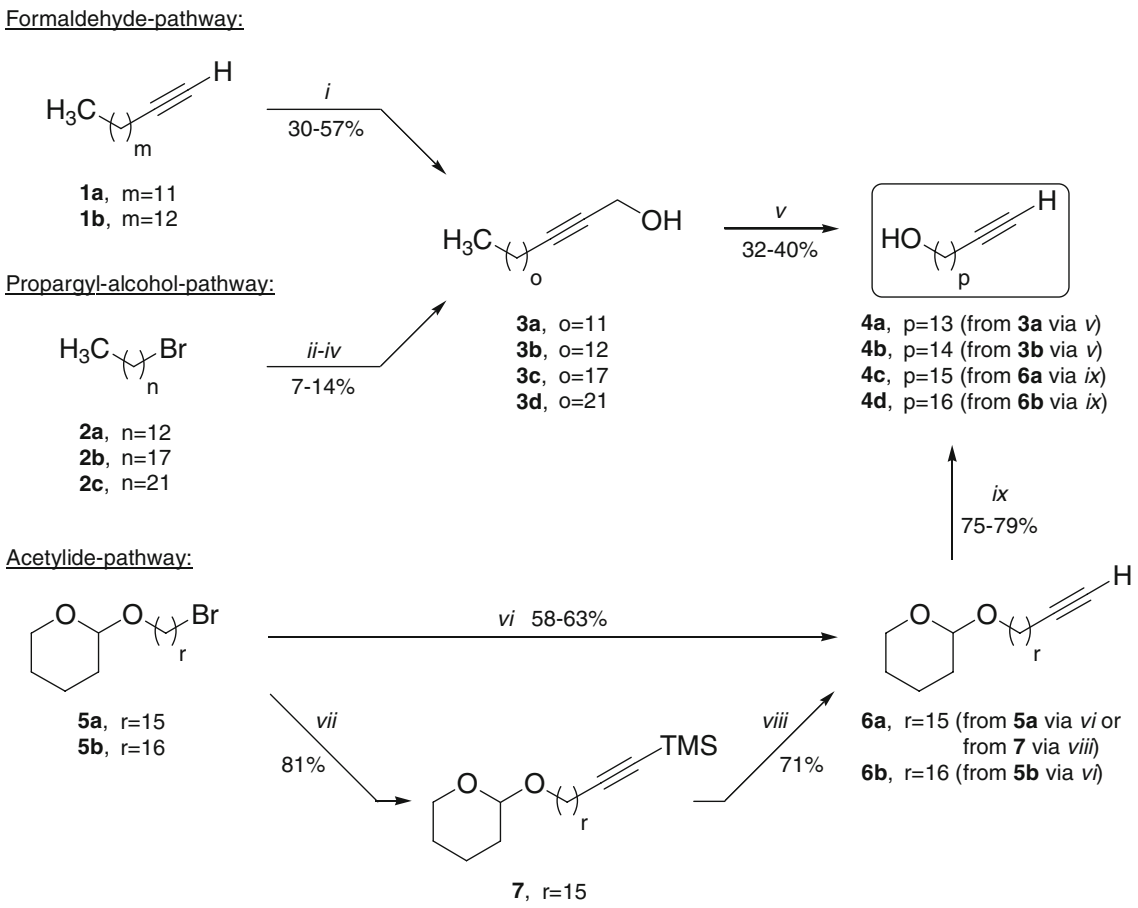
Retro-synthetic analysis of the target BA arrived at the conclusion that alkyn-1-ols with a terminal triple bond could be regarded as the key intermediates for synthesis of symmetrical and polymerizable BAs. Herein, three different approaches for the synthesis of terminal alkyn-1-ols will be discussed:

1. the formaldehyde pathway starting from terminal, long-chain alkynes and paraformaldehyde;
2. the propargyl alcohol pathway using tetrahydropyranyl (THP)-protected propargyl alcohol which was alkylated with different alkyl bromides; and
3. the acetylide pathway, the direct alkylation of lithium acetylide or lithium (trimethylsilyl)acetylide with THP-protected ω-bromoalcohols.

Results showed that the first and second strategies involved a base-induced acetylene zipper reaction which turned out to be the limiting factor in the synthesis of long-chain alkynols above 18 carbon atoms. The above mentioned synthetic approaches are summarized in Scheme 1.

Formaldehyde pathway

The formaldehyde pathway started with commercially available terminal, long-chain alkynes, e.g., tetradec-1-yne (**1a**) and pentadec-1-yne (**1b**), which were transformed into the corresponding pentadec-2-yn-1-ol (**3a**) or hexadec-2-yn-1-ol (**3b**) by applying a Grignard-analogue reaction using ethyl magnesium chloride and paraformaldehyde [23–25]. In contrast with the work of Takano et al., the mixtures had to be heated for at least for 3 h to 45 °C in order to obtain moderate yields (30–57%). The alkynols **3a** and **3b** were then converted by means of an acetylene zipper reaction—a base-induced alkene–alkyne rearrangement [26]—affording the analogous pentadec-14-yn-1-ol (**4a**) and hexadec-15-yn-1-ol (**4b**) in isolated yields of 32–40%. The sodium salt of 1,3-diaminopropane (DAP), suggested by Macaulay [27], and the lithium potassium salt of DAP, employed by Oppolzer et al. [28], were applied as base. However, both syntheses showed no differences concerning reaction procedures and resulted in comparable yields.



i) EtMgCl, THF, 0°C; then paraformaldehyde, rt, 24 h; *ii*) propargyl alcohol, DHP, CH_2Cl_2, PPTS, rt, 24 h; *iii*) *n*-BuLi, THF, **2**, DMPU, 40°C, 24 h; *iv*) PPTS, MeOH, 40°C, 12 h; *v*) NaH, DAP, 55°C, 5 h; *vi*) Li-acetylide·$H_2NCH_2CH_2NH_2$, DMSO, 65°C, 24 h; *vii*) Li(trimethylsilyl)acetylide, THF, -35°C, DMPU, 12 h; *viii*) TBAF, THF, rt, 48 h; *ix*) PPTS, MeOH, reflux, 12 h.

Scheme 1

Propargyl alcohol pathway

A second strategy for synthesis of terminal alkyn-1-ols was the alkylation of THP-protected propargyl alcohols with long-chain alkyl bromides, e.g., tridecyl bromide (**2a**), octadecyl bromide (**2b**), and docosyl bromide (**2c**). In accordance with the work of Schwarz and Waters [29] and Oppolzer et al. [28], the alcohol moiety of the propargyl alcohol was protected with 3,4-dihydro-2*H*-pyran (DHP) in the presence of pyridinium *p*-toluene sulfonate (PPTS). The alkyne group was deprotonated with *n*-BuLi. Alkylation with the above mentioned alkyl bromides in dry 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) and tetrahydrofuran (THF) at 40 °C, and subsequent deprotection of the THP group with catalytic amounts of PPTS in MeOH led to the formation of hexadec-2-yn-1-ol (**3b**), heneicos-2-yn-1-ol (**3c**), and pentacos-2-yn-1-ol (**3d**) in 7–14% isolated yields. The low solubility of the long-chain alkyl bromides in DMPU–THF could be a plausible reason for the marginal yields. Extension of the reaction time and an increase of the reaction temperature had no positive effect on product composition. In fact, high temperatures induced the formation of by-products. The final conversion of the alkynols **3b**–**3d** into the ω-alkynols was realized using the acetylene zipper reaction described above. However, only **3b** could be transferred to the hexadec-15-yn-1-ol (**4b**), whereas formation of heneicos-20-yn-1-ol and pentacos-24-yn-1-ol failed. In our hands and in contrast with the work of Godt et al. [30], the base-induced alkene–alkyne rearrangement was limited by the length of the alkyl chain while using the procedures employed by Macaulay [27] or Oppolzer et al. [28].

Acetylide pathway

The third procedure for preparation of terminal alkyn-1-ols was the direct alkylation of lithium acetylene implementing THP-protected ω-bromoalcohols. The lithium acetylide–ethylenediamine complex was dissolved in THF under argon atmosphere. Subsequent addition of 2-(15-bromopentadec-1-yloxy)tetrahydro-2*H*-pyran (**5a**) or 2-(16-bromohexadec-1-yloxy)tetrahydro-2*H*-pyran (**5b**), diluted in THF, and stirring for 48 h at 25 °C yielded in no observable formation of the product. However, after this reaction we could isolate small amounts (3–5%) of the bis-alkylated 1,ω-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]alkyne. When the solvent was changed to DMSO and the reaction temperature increased to 65 °C, 2-(heptadec-16-yn-1-yloxy)tetrahydro-2*H*-pyran (**6a**) and 2-(octadec-17-yn-1-yloxy)tetrahydro-2*H*-pyran (**6b**) were obtained in 58–63% isolated yields. In this reaction procedure we also observed formation of the bis-alkylated by-product, which could be separated by column chromatography. In contrast, use of the versatile reagent lithium (trimethylsilyl)acetylide in THF [31] avoided this side reaction and resulted in efficient formation of 2-(17-trimethylsilylheptadec-16-yn-1-yloxy) tetrahydro-2*H*-pyran (**7**) in 81% yield. Deprotection of the terminal trimethylsilyl group with tetrabutylammonium fluoride (TBAF) afforded **6a** in 71% yield. Finally, deprotection of the THP group with PPTS in MeOH under reflux for 12 h provided heptadec-16-yn-1-ol (**4c**) and octadec-17-yn-1-ol (**4d**) in 75–79% isolated yield.

Comparing all three approaches for the synthesis of terminal alkyn-1-ols **4**, the acetylide pathway using lithium (trimethylsilyl)acetylide is the most efficient synthetic strategy, because higher yields were obtained while avoiding the formation of by-products.

Oxidative coupling

Several reaction conditions were studied for oxidative coupling of the terminal alkyn-1-ols **4** to the corresponding compounds **8** (Scheme 2) using reaction procedures employed by Menger et al. [32] or Eglinton and Galbraith [33]. In a first attempt, the alkyn-1-ols **4a** and **4b** were dissolved in xylene containing CuCl and tetramethylethylenediamine (TMEDA). While heating to 140 °C, oxygen was gently passed into the mixture through a gas inlet tube [32]. This reaction conditions led to numerous by-products associated with the complete decomposition of the molecule. In a second approach, an excess of copper(II) acetate monohydrate dissolved in pyridine was utilized [33], affording triaconta-14,16-diyn-1,30-diol (**8a**) and dotriaconta-15,17-diyn-1,32-diol (**8b**) in 14–30% isolated yields. Because of problems during the work-up, the pyridine was replaced by a mixture of triethylamine (TEA) and toluene (2:1, *v*/*v*) for oxidative coupling of the alkyn-1-ols **4c** and **4d**, respectively. This change of solvent resulted in the formation of tetratriaconta-16,18-diyn-1,34-diol (**8c**) and hexatriaconta-17,19-diyn-1,36-diol (**8d**) in elevated isolated yields (55–60%).

Phosphorylation and quaternization

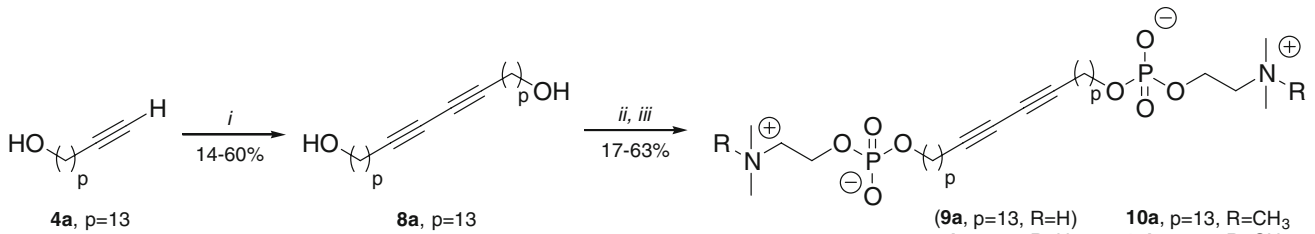
The final conversion of **8** to the respective bis(phosphodimethylethanolamines) **9** or bis(phosphocholines) **10** was achieved using a bis-phosphorylation reaction with β-bromoethylphosphoric acid dichloride in TEA–$CHCl_3$ and subsequent quaternization with an ethanolic solution of Me_2NH or Me_3N, respectively (Scheme 2). In contrast with the procedures described previously [8] excess phosphorylating reagent was minimized because of the susceptibility of the diacetylenic groups. Moreover, the reaction was carried out avoiding light irradiation. This final reaction resulted in the formation of the desired alkadiyn-1,ω-diylbis[2-(dimethylammonio)ethylphosphates] **9b–9d** and the alkadiyn-1,ω-diylbis[2-(trimethylammonio)ethylphosphates] **10a–10d** in 17–63% isolated yields.

Summary and outlook

In conclusion, we have examined a general synthetic approach for synthesis of novel symmetrical, single-chain, diacetylenic BAs with an over-all chain length of 30–36 carbon atoms. For the ω-alkynols, which have an essential role as key intermediates, the acetylide pathway using the alkylation of lithium (trimethylsilyl)acetylide with THP-protected ω-bromoalcohols followed by cleavage of the trimethylsilyl group and the THP protecting group is the best synthetic strategy among the other approaches investigated in this work. The synthetic methodology presented herein is also well transferrable to the preparation of symmetrical, diacetylenic BAs with shorter or longer alkyl chains. These novel single-chain bipolar amphiphiles have promising potential as starting molecules for the design of polymerizable nanofibers which form thermostable hydrogels with adjustable gel strength. Further investigations including differential scanning calorimetry, transmission electron microscopy, and rheology measurements are under way.

Experimental

All substances were purchased from Sigma–Aldrich and were used without further purification. 2-(ω-Bromoalkane-1-yloxy)tetrahydro-2*H*-pyrans **5a** and **5b** [8] and β-bromoethylphosphoric acid dichloride [34] were prepared according to the literature. All organic solvents used were



4a, p=13
4b, p=14
4c, p=15
4d, p=16

8a, p=13
8b, p=14
8c, p=15
8d, p=16

(**9a**, p=13, R=H)
9b, p=14, R=H
9c, p=15, R=H
9d, p=16, R=H

10a, p=13, R=CH_3
10b, p=14, R=CH_3
10c, p=15, R=CH_3
10d, p=16, R=CH_3

i) $Cu(OAc)_2$, pyridine or triethylamine/toluene (2/1, v/v), MeOH, 70 °C, 12 h; *ii*) $CHCl_3$, *β*-bromoethylphosphoric acid dichloride, 40 °C; then THF/H_2O, rt, 2 h; *iii*) $CHCl_3$, CH_3CN, EtOH, $N(CH_3)_2R$, 50 °C, 72 h

Scheme 2

purified and dried. The purity of all compounds was checked by thin-layer chromatography (TLC, plates obtained from Merck) using the following mobile phases: A = $CHCl_3$–heptane (3:2, *v/v*), B = $CHCl_3$, C = $CHCl_3$–Et_2O (1:1, *v/v*), D = $CHCl_3$–MeOH–NH_3 (10:10:1, *v/v/v*), E = $CHCl_3$–MeOH–NH_3 (10:10:2, *v/v/v*), F = $CHCl_3$–MeOH–NH_3 (10:10:3, *v/v/v*). Purification of the final BAs was carried out by medium-pressure liquid chromatography (MPLC, Büchi) using silica gel (Merck, 0.032–0.060 mm). Melting points were determined with a Boetius apparatus. ^{1}H NMR and ^{13}C NMR analysis was performed on a Varian Inova 500 or Gemini 2000 NMR spectrometer using $CDCl_3$ or CD_3OD as internal standard. Mass spectrometric data were obtained with a Finnigan MAT model SSQ 710 C mass spectrometer (ESI–MS) or were recorded on an AMD 402 (70 eV) spectrometer. Elemental analysis (C, H, N) was conducted using a Leco CHNS-932; results were in good agreement (±0.4%) with calculated values.

Formaldehyde pathway: general procedure for reaction of long-chain alkynes with formaldehyde

A solution of ethyl magnesium chloride in THF (12 cm^3, 2 M) was added dropwise to a cold solution of either **1a** or **1b** (24 mmol) in 30 cm^3 dry THF, adjusting the rate so the temperature remained below 0 °C. After addition the mixture was kept at 45 °C for 3 h. After cooling to 25 °C 1.44 g solid paraformaldehyde (48 mmol) was added stepwise and the mixture was stirred for 24 h at this temperature. For work-up the resulting mixture was diluted with 60 cm^3 H_2O, acidified with HCl, and then extracted with 100 cm^3 Et_2O (4×). The combined organic phases were washed with 100 cm^3 brine and 100 cm^3 H_2O, dried over Na_2SO_4, and concentrated to dryness in vacuo, affording 1.62–3.26 g (30–57% yield) of either **3a** or **3b**. The final purification of **3a** and **3b** was carried out by flash chromatography on silica gel (0.032–0.060 mm) using gradient elution and heptane–Et_2O as eluent.

Pentadec-2-yn-1-ol (**3a**)

Compound **3a** was obtained as a white solid in 30% yield (1.62 g) from reaction of 4.66 g **1a** (24 mmol) with 1.44 g paraformaldehyde (48 mmol) according to the general procedure described above. M.p.: 41 °C (Ref. [35] 38–41 °C, Ref. [28] 43–45 °C); $R_f = 0.13$ (solvent A), 0.54 (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $^3J = 6.6$ Hz, 3H, $-CH_3$), 1.20–1.54 (m, 20H, $-(CH_2)_{10}CH_3$), 2.19 (tt, $^3J = 7.1$ Hz, $^5J = 2.1$ Hz, 2H, $-C\equiv CCH_2CH_2-$), 4.31 (t, $^5J = 2.1$ Hz, 2H, $HOCH_2-$) ppm; MS (70 eV): *m/z* (%) = 224 (1) [M^+], 206 (4) [$M^+ - H_2O$].

Hexadec-2-yn-1-ol (**3b**)

Compound **3b** was obtained as a white solid in 57% yield (3.26 g) from reaction of 5.00 g **1b** (24 mmol) with 1.44 g paraformaldehyde (48 mmol) according to the general procedure described above. M.p.: 52 °C (Ref. [36] 49.5–50.0 °C, Ref. [37] 54.2–55.0 °C); $R_f = 0.13$ (solvent A), 0.57 (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $^3J = 6.6$ Hz, 3H, $-CH_3$), 1.24–1.37 (m, 20H, $-(CH_2)_{10}CH_3$), 1.51–1.54 (m, 2H, $-C\equiv CCH_2CH_2-$), 2.19 (tt, $^3J = 7.1$ Hz, $^5J = 2.1$ Hz, 2H, $-C\equiv CCH_2CH_2-$), 4.23 (t, $^5J = 2.1$ Hz, 2H, $HOCH_2-$) ppm; MS (70 eV): *m/z* (%) = 237 (2) [M^+], 220 (2) [$M^+ - H_2O$].

Propargyl alcohol pathway: general procedure for reaction of long-chain alkyl bromides with propargyl alcohol

A solution of 5.6 g propargyl alcohol (0.1 mol), 15.1 g freshly distilled DHP (0.18 mol), and catalytic amounts of PPTS in 50 cm^3 dry CH_2Cl_2 was stirred at 25 °C. After 24 h 100 cm^3 H_2O was added to the mixture and the organic layer was separated. The aqueous residue was extracted with 25 cm^3 CH_2Cl_2 (2×). The combined organic layers were washed with H_2O, dried over Na_2SO_4, and concentrated to dryness in vacuo. The crude

residue was passed through a silica gel column using gradient elution with heptane–Et_2O as eluent to obtain 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran as a colorless oil. A solution of *n*-BuLi in hexane (5.5 cm^3, 1.6 M) was added slowly to a solution of 2.94 g 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (20 mmol) in 20 cm^3 dry THF at 0 °C. After 2 h a solution of **2a**, **2b**, or **2c** (23 mmol) in dry DMPU was introduced dropwise and the mixture was stirred for 24 h at 40 °C. For work-up 50 cm^3 of a cold saturated solution of NH_4Cl was added and the organic layer was separated. The aqueous residue was extracted with 25 cm^3 heptane (2×). The combined organic phases were washed with H_2O, dried over Na_2SO_4, and concentrated to dryness in vacuo. For cleavage of the THP protecting groups the crude alkyne THP ethers were dissolved in 50 cm^3 dry MeOH and stirred at 40 °C with catalytic amounts of PPTS. After 12 h the solution was poured into ice water and the mixture obtained was extracted with 50 cm^3 $CHCl_3$ (3×). The organic layers were dried over Na_2SO_4 and concentrated to dryness in vacuo, affording 0.33–0.86 g **3b**, **3c**, or **3d**, respectively, in 8–14% isolated yields. The final purification of **3b**–**3d** was carried out by flash chromatography on silica gel (0.032–0.060 mm) using gradient elution with heptane–Et_2O as eluent.

Hexadec-2-yn-1-ol (**3b**)
Compound **3b** was obtained as a white solid in 7% yield (0.33 g) from reaction of 6.05 g **2a** (23 mmol) with 2.94 g THP-protected propargyl alcohol (20 mmol) according to the general procedure described above. For spectral data see section above.

Heneicos-2-yn-1-ol (**3c**)
Compound **3c** was obtained as a white solid in 14% yield (0.86 g) from reaction of 7.67 g **2b** (23 mmol) with 2.94 g THP-protected propargyl alcohol (20 mmol) according to the general procedure described above. M.p.: 62 °C (Ref. [38] 65–66 °C); $R_f = 0.17$ (solvent A), 0.59 (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $^3J = 6.6$ Hz, 3H, –CH_3), 1.19–1.52 (m, 32H, –(CH_2)$_{16}$CH$_3$), 2.19 (tt, $^3J = 7.1$ Hz, $^5J = 2.1$ Hz, 2H, –C≡CCH_2CH$_2$–), 4.23 (t, $^5J = 2.1$ Hz, 2H, HOCH_2–) ppm; MS (70 eV): *m*/*z* (%) = 308 (2) [M^+].

Pentacos-2-yn-1-ol (**3d**)
Compound **3d** was obtained a as white solid in 8% yield (0.58 g) from reaction of 8.96 g **2c** (23 mmol) with 2.94 g THP-protected propargyl alcohol (20 mmol) according to the general procedure described above. M.p.: 70 °C (Ref. [30] 77–79 °C); $R_f = 0.18$ (solvent A), 0.60 (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $^3J = 6.6$ Hz, 3H, –CH_3), 1.24–1.52 (m, 40H, –(CH_2)$_{20}$CH$_3$), 2.19 (tt, $^3J = 7.1$ Hz, $^5J = 2.1$ Hz, 2H, –C≡CCH_2CH$_2$–), 4.23 (t, $^5J = 2.1$ Hz, 2H, HOCH_2–) ppm; MS (70 eV): *m*/*z* (%) = 364 (1) [M^+], 346 (9) [$M^+ - H_2O$].

General procedure for the acetylene zipper reaction

NaH (0.41 g, 17 mmol) was suspended in 15 cm^3 dry DAP under argon atmosphere and the mixture was kept at 70 °C for 2 h. After cooling to 25 °C a solution of either **3a** or **3b** (2.1 mmol) in 8 cm^3 dry DAP was added and the mixture obtained was stirred for further 3–5 h at 55 °C. For work-up the solution was poured into ice water and extracted several times with Et_2O. The organic layers were washed with H_2O, dilute HCl, and cold saturated brine, dried over Na_2SO_4, and concentrated to dryness in vacuo, affording 0.16–0.19 g of either **4a** or **4b** in 32–40% isolated yields. The final purification was carried out by MPLC using $CHCl_3$ as eluent.

Pentadec-14-yn-1-ol (**4a**)
Compound **4a** was obtained in 40% yield (0.19 g) from the acetylene zipper reaction of 0.47 g **3a** (2.1 mmol) following the general procedure described above. M.p.: 39 °C (Ref. [39] 35–36 °C); $R_f = 0.42$ (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.17$–1.58 (m, 22H, –(CH_2)$_{11}$CH$_2$C≡CH), 1.92 (t, $^4J = 2.5$ Hz, 1H, –C≡CH), 2.16 (td, $^3J = 7.1$ Hz, $^4J = 2.5$ Hz, 2H, –CH_2C≡CH), 3.62 (t, $^3J = 6.6$ Hz, 2H, HOCH_2–) ppm; MS (70 eV): *m*/*z* (%) = 224 (1) [M^+].

Hexadec-15-yn-1-ol (**4b**)
Compound **4b** was obtained in 32% yield (0.16 g) from the acetylene zipper reaction of 0.50 g **3b** (2.1 mmol) following the general procedure described above. M.p.: 48 °C (Ref. [32] 49.5–50.5 °C); $R_f = 0.10$ (solvent A), 0.43 (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.15$–1.58 (m, 24H, –(CH_2)$_{12}$CH$_2$C≡CH), 1.92 (t, $^4J = 2.5$ Hz, 1H, –C≡CH), 2.16 (td, $^3J = 7.1$ Hz, $^4J = 2.5$ Hz, 2H, –CH_2C≡CH), 3.62 (t, $^3J = 6.6$ Hz, 2H, HOCH_2–) ppm; MS (70 eV): *m*/*z* (%) = 238 (1) [M^+].

Acetylide pathway: general procedure for alkylation of lithium acetylide with long-chain THP-protected ω-bromoalcohols

A solution of 0.92–5.0 g lithium acetylide–ethylenediamine complex (90%, 9.0–48.9 mmol) in 5–10 cm^3 DMSO (freshly distilled over CaH_2) was stirred under argon atmosphere at 0 °C for 10 min. After this time, 3.66–19.11 g **5a** or **5b** (9.0–48.9 mmol) in 5–10 cm^3 DMSO was added slowly and the mixture was heated to 65 °C for a further 24 h. For work-up the reaction was quenched with 50 cm^3 H_2O and the resulting mixture was extracted with 50 cm^3 heptane (2×), washed with 50 cm^3 H_2O, dried over Na_2SO_4, and concentrated to dryness in vacuo, affording

1.84–10.33 g of either **6a** or **6b** in 58–63% isolated yields. The final purification was carried out by chromatography using a heptane–Et_2O gradient (+0.5% TEA) as eluent.

2-(Heptadec-16-yn-1-yloxy)tetrahydo-2H-pyran (**6a**, $C_{22}H_{40}O_2$)

Compound **6a** was obtained as a white waxy solid in 63% yield (10.33 g) from the reaction of 19.11 g **5a** (48.9 mmol) with a solution of 5.0 g lithium acetylide–ethylenediamine complex (90%, 48.9 mmol) in 10 cm^3 DMSO following the general procedure described above. $R_f = 0.51$ (solvent B); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.23$–1.38 (m, 22H, –CH_2–), 1.46–1.60 (m, 8H, –CH_2–), 1.65–1.72 (m, 1H, –OCH$_2$CH_2(CH$_2$)$_{13}$–), 1.75–1.84 (m, 1H, –OCH$_2$CH_2(CH$_2$)$_{13}$–), 1.90 (t, $^4J = 2.5$ Hz, 1H, –C≡CH), 2.15 (td, $^3J = 7.1$ Hz, $^4J = 2.5$ Hz, 2H, –CH_2C≡CH), 3.35 (dt, $^2J = 9.5$ Hz, $^3J = 6.6$ Hz, 1H, –OCH_2(CH$_2$)$_{14}$–), 3.44–3.49 (m, 1H, –OCH_2(CH$_2$)$_3$CH–), 3.70 (dt, $^2J = 9.5$ Hz, $^3J = 6.8$ Hz, 1H, –OCH_2(CH$_2$)$_{14}$–), 3.81–3.87 (m, 1H, –OCH_2(CH$_2$)$_3$CH–), 4.53–4.55 (m, 1H, –CH–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.42$ and 19.71 (–CH$_2$C≡CH and –O(CH$_2$)$_2$$CH_2CH_2$CH–), 25.56 and 26.27 (–O(CH$_2$)$_2$$CH_2$(CH$_2$)$_{12}$C≡CH and –OCH$_2$$CH_2$(CH$_2$)$_2$CH–), 28.52, 28.77, 29.12, 29.51, 29.61, 29.66, and 29.79 (–CH$_2$–), 30.82 (–CH$_2$CH–), 62.27 (–OCH$_2$(CH$_2$)$_3$CH–), 67.66 (–OCH$_2$(CH$_2$)$_{14}$–), 67.99 (–C≡CH), 84.72 (–C≡CH), 98.76 (–CH–) ppm; MS (70 eV): m/z (%) = 335 (10) [M^+ – H], 311 (5) [M^+ – C≡CH], 101 (95) [THPO], 85 (100) [THP].

2-(Octadec-17-yn-1-yloxy)tetrahydro-2H-pyran (**6b**, $C_{23}H_{42}O_2$)

Compound **6b** was obtained as a white waxy solid in 58% yield (1.84 g) from the reaction of 3.66 g **5b** (9.0 mmol) with a solution of 0.92 g lithium acetylide–ethylenediamine complex (90%, 9.0 mmol) in 5 cm^3 DMSO following the general procedure described above. $R_f = 0.57$ (solvent B); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.23$–1.37 (m, 24H, –CH_2–), 1.46–1.58 (m, 8H, –CH_2–), 1.66–1.72 (m, 1H, –OCH$_2$CH_2(CH$_2$)$_{14}$–), 1.76–1.83 (m, 1H, –OCH$_2$CH_2(CH$_2$)$_{14}$–), 1.90 (t, $^4J = 2.5$ Hz, 1H, –C≡CH), 2.15 (td, $^3J = 7.1$ Hz, $^4J = 2.5$ Hz, 2H, –CH_2C≡CH), 3.35 (dt, $^2J = 9.5$ Hz, $^3J = 6.6$ Hz, 1H, –OCH_2(CH$_2$)$_{15}$–), 3.44–3.49 (m, 1H, –OCH_2(CH$_2$)$_3$CH–), 3.70 (dt, $^2J = 9.5$ Hz, $^3J = 7.1$ Hz, 1H, –OCH_2(CH$_2$)$_{15}$–), 3.81–3.86 (m, 1H, –OCH_2(CH$_2$)$_3$CH–), 4.54–4.55 (m, 1H, –CH–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.49$ and 19.78 (–CH$_2$C≡CH and –O(CH$_2$)$_2$$CH_2CH_2$CH–), 25.62 and 26.33 (–O(CH$_2$)$_2$$CH_2$(CH$_2$)$_{13}$C≡CH and –OCH$_2$$CH_2$(CH$_2$)$_2$CH–), 28.59, 28.84, 29.18, 29.57, 29.67, 29.72, and 29.85 (–CH$_2$–), 30.88 (–CH$_2$CH–), 62.29 (–OCH$_2$(CH$_2$)$_3$CH–), 67.68 (–OCH$_2$(CH$_2$)$_{15}$–), 68.00 (–C≡CH), 84.72 (–C≡CH), 98.76 (–CH–) ppm; MS (70 eV): m/z (%) = 349 (2) [M^+ – H], 101 (98) [THPO], 85 (100) [THP].

Acetylide pathway: general procedure for the alkylation of lithium (trimethylsilyl)acetylide with long-chain THP-protected ω-bromoalcohols

2-(17-Trimethylsilylheptadec-16-yn-1-yloxy)tetrahydro-2H-pyran (**7**, $C_{25}H_{48}O_2Si$)

A 250-cm^3 round-bottomed flask was filled with 0.5 M lithium (trimethylsilyl)acetylide solution in 50 cm^3 THF under argon atmosphere and cooled to −35 °C. Dry DMPU was added, and the mixture was stirred at this temperature. After 30 min a solution of **5a** (15 mmol) in 30 cm^3 dry THF was added at such a rate that the temperature remained below −15 °C and stirring was continued for a further 12 h at 25 °C. For work-up the reaction was quenched by slowly adding of 30 cm^3 H_2O, and the organic product obtained was extracted with 50 cm^3 Et_2O (2×). The organic layer was dried over Na_2SO_4 and concentrated to dryness in vacuo, affording 4.98 g (81% yield) of **7**. The final purification was carried out by chromatography using a heptane–Et_2O gradient (+0.5% TEA) as eluent. $R_f = 0.52$ (solvent B); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.11$ (s, 9H, 3× –CH_3), 1.23–1.35 (m, 22H, –CH_2–), 1.44–1.60 (m, 8H, –CH_2–), 1.65–1.72 (m, 1H, –OCH$_2$CH_2(CH$_2$)$_{13}$–), 1.76–1.84 (m, 1H, –OCH$_2$CH_2(CH$_2$)$_{13}$–), 2.17 (t, $^3J = 7.1$ Hz, 2H, –CH_2C≡C–), 3.35 (dt, $^2J = 9.5$ Hz, $^3J = 6.6$ Hz, 1H, –OCH_2(CH$_2$)$_{14}$–), 3.44–3.49 (m, 1H, –OCH_2(CH$_2$)$_3$CH–), 3.70 (dt, $^2J = 9.5$ Hz, $^3J = 6.8$ Hz, 1H, –OCH_2(CH$_2$)$_{14}$–), 3.81–3.87 (m, 1H, –OCH_2(CH$_2$)$_3$CH–), 4.53–4.55 (m, 1H, –CH–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 0.30$ (3× –CH$_3$), 19.78 and 19.99 (–CH$_2$C≡C– and –O(CH$_2$)$_2$ CH$_2$CH$_2$CH–), 25.63 and 26.34 (–O(CH$_2$)$_2$$CH_2$(CH$_2$)$_{12}$ C≡C– and –OCH$_2$$CH_2$(CH$_2$)$_2$CH–), 28.72, 28.87, 29.15, 29.56, 29.66, 29.67, 29.69, 29.72, 29.74, and 29.85 (–CH$_2$–), 30.88 (–CH$_2$CH–), 62.29 (–OCH$_2$(CH$_2$)$_3$CH–), 67.67 (–OCH$_2$(CH$_2$)$_{14}$–), 84.17 (–CH$_2$C≡C–Si), 98.76 (–CH–), 107.68 (–CH$_2$$C$≡C–Si) ppm; MS (70 eV): m/z (%) = 408 (5) [M^+], 393 (6) [M^+ – CH_3], 335 (6) [M^+ – Si(CH$_3$)$_3$], 307 (5) [M^+ – OTHP], 234 (4) [M^+ – Si(CH$_3$)$_3$ – OTHP], 128 (18) [THPOCH$_2$CH$_2$], 101 (23) [THPO], 85 (100) [THP], 73 (34) [Si(CH$_3$)$_3$].

Acetylide pathway: general procedure for the removal of the trimethylsilyl protecting group

2-(Heptadec-16-yn-1yloxy)tetrahydro-2H-pyran (**6a**)

To a solution of 3.93 g **7** (9.6 mmol) in 30 cm^3 dry THF was added dropwise 10 cm^3 TBAF solution in THF (1 M) at −5 °C. After 48 h at 25 °C the reaction was quenched with HCl (2 M), and the resulting mixture was extracted with 50 cm^3 heptane (2×). The organic layer was washed with 50 cm^3 brine, dried over Na_2SO_4, and concentrated to dryness in vacuo, affording 2.29 g (71% yield) of **6a**. The

product was used for the next reaction without further purification. For spectral data see section above.

Acetylide pathway: general procedure for the removal of the THP protecting group

THP ethers **6** (0.91–6.21 g, 2.6–18.5 mmol) were heated under reflux in 15–30 cm^3 dry MeOH with catalytic amounts of PPTS. After 12 h, the solvent was removed in vacuo, and the crude product was recrystallized from petroleum ether (50–70), affording 0.52–3.68 g of either **4c** or **4d** in 75–79% isolated yield.

Heptadec-16-yn-1-ol (**4c,** $C_{17}H_{32}O$)
Compound **4c** was obtained as white crystals in 79% yield (3.68 g) from the deprotecting reaction of 6.21 g **6a** (18.5 mmol) following the general procedure described above. M.p.: 54.5–56.0 °C; $R_f = 0.27$ (solvent B), 0.47 (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.24$–1.38 (m, 22H, $HO(CH_2)_2(CH_2)_{11}(CH_2)_2C{\equiv}CH$), 1.46–1.58 (m, 4H, $HOCH_2CH_2(CH_2)_{11}CH_2CH_2C{\equiv}CH$), 1.91 (t, $^4J =$ 2.7 Hz, 1H, $-C{\equiv}CH$), 2.15 (td, $^3J = 7.1$ Hz, $^4J = 2.7$ Hz, 2H, $-CH_2C{\equiv}CH$), 3.61 (t, $^3J = 6.6$ Hz, 2H, $HOCH_2$–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.43$ ($-CH_2C{\equiv}$ CH), 25.77 ($HO(CH_2)_2CH_2$–), 28.53, 28.79, 29.13, 29.46, 29.51, 29.62, and 29.66 (–CH_2–), 32.83 ($HOCH_2CH_2$–), 63.08 ($HOCH_2$–), 68.00 (–C≡*C*H), 84.78 (–*C*≡CH) ppm; MS (70 eV): *m*/*z* (%) = 252 (1) [M^+].

Octadec-17-yn-1-ol (**4d**)
Compound **4d** was obtained as white crystals in 75% yield (0.52 g) from the deprotecting reaction of 0.91 g **6b** (2.6 mmol) following the general procedure described above. M.p.: 58.0–58.5 °C (Ref. [32] 59.0–60.5 °C); $R_f = 0.28$ (solvent B), 0.51 (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.24$–1.39 (m, 24H, $HO(CH_2)_2(CH_2)_{12}(CH_2)_2C{\equiv}CH$), 1.47–1.57 (m, 4H, $HOCH_2CH_2(CH_2)_{12}CH_2CH_2C{\equiv}CH$), 1.92 (t, $^4J = 2.3$ Hz, 1H, –C≡*C*H), 2.16 (td, $^3J = 6.9$ Hz, $^4J = 2.3$ Hz, 2H, $-CH_2C{\equiv}$CH), 3.62 (t, $^3J = 6.6$ Hz, 2H, $HOCH_2$–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.51$ ($-CH_2C{\equiv}CH$), 25.85 ($HO(CH_2)_2CH_2$–), 28.61, 28.86, 29.19, 29.52, 29.58, 29.69, and 29.73 (–CH_2–), 32.92 ($HOCH_2CH_2$–), 63.13 ($HOCH_2$–), 68.01 (–C≡*C*H), 84.80 (–*C*≡CH) ppm; MS (70 eV): *m*/*z* (%) = 266 (1) [M^+].

Eglinton coupling: general procedure for the copper-catalyzed dimerization of alkynols to alkadiyndiols

To a solution of 0.9–15.0 g copper(II) acetate monohydrate (4.5–75 mmol) in 50 cm^3 pyridine or 7–15 cm^3 TEA–toluene (2:1, *v*/*v*) was added the corresponding ω-alkynol **4a**–**4d** (1.5–20.5 mmol) dissolved in 2–30 cm^3 MeOH. The mixture was kept at 70 °C while stirring. After 12 h, the mixture was cooled to 25 °C and the reaction was quenched with 50 cm^3 half-concentrated HCl. The organic product was extracted with 50 cm^3 $CHCl_3$ (2×); the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness in vacuo. The crude product was recrystallized from petroleum ether (50–70), affording 0.22–1.38 g of **8a**-**d** in 14–60% isolated yields.

Triaconta-14,16-diyn-1,30-diol (**8a**, $C_{30}H_{54}O_2$)
Compound **8a** was obtained as white crystals in 30% yield (1.38 g) from the dimerization reaction of 4.60 g **4a** (20.5 mmol) using a solution of 15.0 g copper(II) acetate monohydrate (75 mmol) in 50 cm^3 pyridine, following the general procedure described above. M.p.: 93 °C; $R_f = 0.19$ (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.24$–1.58 (m, 44H, 2× $HOCH_2(CH_2)_{11}CH_2C{\equiv}C$–), 2.22 (t, $^3J = 7.1$ Hz, 4H, 2× $-CH_2C{\equiv}C$–), 3.62 (t, $^3J = 6.6$ Hz, 4H, 2× $HOCH_2$–) ppm; MS (70 eV): *m*/*z* (%) = 446 (10) [M^+].

Dotriaconta-15,17-diyn-1,32-diol (**8b**, $C_{32}H_{58}O_2$)
Compound **8b** was obtained as white crystals in 14% yield (0.68 g) from the dimerization reaction of 4.89 g **4b** (20.5 mmol) using a solution of 15.0 g copper(II) acetate monohydrate (75 mmol) in 50 cm^3 pyridine, following the general procedure described above. M.p.: 92 °C; $R_f = 0.23$ (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.24$–1.57 (m, 48H, 2× $HOCH_2(CH_2)_{12}CH_2C{\equiv}C$–), 2.22 (t, $^3J = 7.1$ Hz, 4H, 2× $-CH_2C{\equiv}C$–), 3.62 (t, $^3J = 6.6$ Hz, 4H, 2× $HOCH_2$–) ppm; MS (70 eV): *m*/*z* (%) = 474 (10) [M^+].

Tetratriaconta-16,18-diyn-1,34-diol (**8c,** $C_{34}H_{62}O_2$)
Compound **8c** was obtained as white crystals in 60% yield (0.59 g) from the dimerization reaction of 1.0 g **4c** (3.96 mmol) using a solution of 2.34 g copper(II) acetate monohydrate (11.9 mmol) in 15 cm^3 TEA–toluene (2:1, *v*/*v*), following the general procedure described above. M.p.: 95 °C; $R_f = 0.22$ (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.22$–1.57 (m, 52H, 2× $HOCH_2(CH_2)_{13}CH_2C{\equiv}C$–) 2.22 (t, $^3J = 7.1$ Hz, 4H, 2× $-CH_2C{\equiv}C$–), 3.63 (t, $^3J = 6.6$ Hz, 4H, 2× $HOCH_2$–) ppm; ^{13}C NMR: (100 MHz, $CDCl_3$): $\delta = 19.27$ (2× $-CH_2C{\equiv}C$–), 25.79 (2× $HO(CH_2)_2CH_2$–), 28.41, 28.90, 29.13, 29.47, 29.51, 29.62, 29.65, 29.66, and 29.67 ($HO(CH_2)_3(CH_2)_{11}CH_2C{\equiv}C$–), 32.89 (2× $HOCH_2CH_2$–), 63.12 (2× $HOCH_2$–), 65.29 (2× $-CH_2C{\equiv}C$–), 77.56 (2× $-CH_2C{\equiv}$ C–) ppm; MS (70 eV): *m*/*z* (%) = 502 (63) [M^+].

Hexatriaconta-17,19-diyn-1,36-diol (**8d**)
Compound **8d** was obtained as white crystals in 55% yield (0.22 g) from the dimerization reaction of 0.4 g **4d** (1.5 mmol) using a solution of 0.9 g copper(II) acetate monohydrate (4.5 mmol) in 7 cm^3 TEA–toluene (2:1, *v*/*v*),

following the general procedure described above. M.p.: 96 °C (Ref. [40] 94 °C); $R_f = 0.31$ (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.24$–1.57 (m, 56H, 2× $HOCH_2(CH_2)_{14}CH_2C\equiv C$–), 2.22 (t, $^3J = 7.1$ Hz, 4H, 2× $-CH_2C\equiv C$–), 3.62 (t, $^3J = 6.6$ Hz, 4H, 2× $HOCH_2$–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.26$ (2× $-CH_2C\equiv C$–), 25.79 (2× $HO(CH_2)_2CH_2$–), 28.40, 28.90, 29.13, 29.47, 29.50, 29.62, and 29.67 (2× $HO(CH_2)_3(CH_2)_{12}CH_2C\equiv C$–), 32.87 (2× $HOCH_2CH_2$–), 63.11 (2× $HOCH_2$–), 65.28 (2× $-CH_2C\equiv C$–), 77.56 (2× $-CH_2C\equiv C$–) ppm; MS (70 eV): m/z (%) = 530 (16) [M^+].

General procedure for phosphorylation and quaternization reaction

The reaction procedure is based on the general synthesis of polymethylene-1,ω-diylbis(phosphocholines) described previously [8]. β-Bromoethylphosphoric acid dichloride (0.24–0.97 g, 1–4 mmol) was poured into 5–15 cm^3 dry $CHCl_3$ under argon atmosphere and cooling with ice–water. A solution of 0.20–0.81 g dry TEA (2–8 mmol) in 5–15 cm^3 $CHCl_3$ was added slowly with stirring, which was continued for further 30 min at 0 °C. After this time, the corresponding diacetylene-modified 1,ω-diol **8a**–**8d** (0.25–1.0 mmol) was added as solid substance in one portion, avoiding light irradiation. The suspension was heated for 10 min to 40 °C (until the solid was completely dissolved), then rapidly cooled to 25 °C, and stirring was continued for a further 24–48 h at this temperature. After TLC showed complete conversion of the 1,ω-diol **8a**–**8d**, 5–15 cm^3 crushed ice was added to the solution and the mixture was stirred vigorously for 2 h. The organic layer was separated, and the aqueous phase was diluted with 25 cm^3 of a cold saturated solution of NaCl and extracted with 30 cm^3 $CHCl_3$ (2×). The combined organic phases were concentrated in vacuo, the oily residue was dissolved in 10–30 cm^3 THF–H_2O (9:1, *v*/*v*), and the mixture was stirred for 1 h. After this time, the solvent was evaporated and the residue was added to a mixture of 15 cm^3 dry $CHCl_3$, 15 cm^3 CH_3CN, and an ethanolic solution of Me_2NH (5.6 M, 4 cm^3) for synthesis of the bis(phosphodimethylethanolamines) **9** or Me_3N (4.2 M, 5 cm^3) for the synthesis of the corresponding bis(phosphocholines) **10**. The mixture was kept in a closed tube at 50 °C for 72 h, avoiding light irradiation. Afterwards, the mixture was concentrated by evaporation of the solvent, and the residue was purified by MPLC using a gradient and $CHCl_3$–MeOH–H_2O as eluent, affording 0.07–0.48 g of the diacetylene-modified BAs **9b**–**9d** and **10a**–**10d** in 17–63% isolated yields.

Triaconta-14,16-diyn-1,30-diylbis[2-(dimethylammonio)ethylphosphate] (**9a**)

Compound **9a** was obtained from the phosphorylation reaction of **8a** and subsequent quaternization with an ethanolic solution of Me_2NH following the general procedure described above. ESI–MS: $m/z = 747.6$ [M^+ – H], 749.5 [M^+ + H], 776.5 [M^+ + Na]. Because of problems during the purification procedures no additional spectral data could be obtained.

Dotriaconta-15,17-diyn-1,32-diylbis[2-(dimethylammonio)ethylphosphate] (**9b**, $C_{40}H_{78}N_2O_8P_2$)

Compound **9b** was obtained as a white solid in 35% yield (136 mg) from the phosphorylation reaction of 0.24 g **8b** (0.5 mmol) and subsequent quaternization with an ethanolic solution of Me_2NH following the general procedure described above. $R_f = 0.43$ (solvent D); ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): $\delta = 1.24$–1.39 (m, 40H, 2× $-O(CH_2)_2(CH_2)_{10}(CH_2)_2C\equiv C$–), 1.46–1.53 (m, 4H, 2× $-CH_2CH_2C\equiv C$–), 1.57–1.64 (m, 4H, 2× $-OCH_2CH_2(CH_2)_{12}C\equiv C$–), 2.24 (t, $^3J = 7.1$ Hz, 4H, 2× $-CH_2C\equiv C$–), 2.82 (s, 12H, 4× $-CH_3$), 3.12–3.14 (m, 4H, 2× NCH_2CH_2O–), 3.89 (q, $J = 6.6$ Hz, 4H, 2× $-OCH_2(CH_2)_{13}C\equiv C$–), 4.22–4.26 (m, 4H, 2× NCH_2CH_2O–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD): $\delta = 18.97$ (2× $-CH_2C\equiv C$–), 25.59 (2× $-O(CH_2)_2CH_2(CH_2)_{11}C\equiv C$–), 28.18, 28.64, 28.89, 29.19, 29.27, and 29.43 (2× $-O(CH_2)_3(CH_2)_{10}CH_2C\equiv C$–), 30.55 (d, $^3J_{C,P} = 6.9$ Hz, 2× $-OCH_2CH_2(CH_2)_{12}C\equiv C$–), 43.19 (4× $-CH_3$), 58.62 and 59.07 (2d, $J_{C,P} = 5.0$ Hz, 2× NCH_2CH_2O–), 65.05 (2× $-CH_2C\equiv C$–), 66.01 (d, $^2J_{C,P} = 6.1$ Hz, 2× $-OCH_2(CH_2)_{13}C\equiv C$–), 77.25 (2× $-CH_2C\equiv C$–) ppm; ESI–MS: $m/z = 775.6$ [M^+ – H], 778.4 [M^+ + H], 799.6 [M^+ + Na].

Tetratriaconta-16,18-diyn-1,34-diylbis[2-(dimethylammonio)ethylphosphate] (**9c**, $C_{42}H_{82}N_2O_8P_2$)

Compound **9c** was obtained as a white solid in 63% yield (0.48 g) from the phosphorylation reaction 0.48 g **8c** (0.95 mmol) and subsequent quaternization with an ethanolic solution of Me_2NH following the general procedure described above. $R_f = 0.53$ (solvent E); ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): $\delta = 1.23$–1.39 (m, 44H, 2× $-O(CH_2)_2(CH_2)_{11}(CH_2)_2C\equiv C$–), 1.45–1.52 (m, 4H, 2× $-CH_2CH_2C\equiv C$–), 1.56–1.63 (m, 4H, 2× $-OCH_2CH_2(CH_2)_{13}C\equiv C$–), 2.22 (t, $^3J = 7.1$ Hz, 4H, 2× $-CH_2C\equiv C$–), 2.87 (s, 12H, 4× $-CH_3$), 3.18–3.22 (m, 4H, 2× NCH_2CH_2O–), 3.86 (q, $J = 6.6$ Hz, 4H, 2× $-OCH_2(CH_2)_{14}C\equiv C$–), 4.19–4.24 (m, 4H, 2× NCH_2CH_2O–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD): $\delta = 18.99$ (2× $-CH_2C\equiv C$–), 25.61 (2× $-O(CH_2)_2CH_2(CH_2)_{12}C\equiv C$–), 28.18, 28.66, 28.91, 29.20, 29.30, and 29.46 (2× $-O(CH_2)_3(CH_2)_{11}CH_2C\equiv C$–), 30.54 (d, $^3J_{C,P} = 6.9$ Hz, 2× $-OCH_2CH_2(CH_2)_{13}C\equiv C$–), 43.14 (4× $-CH_3$), 58.78

(d, $^{3}J_{C,P}$ = 4.6 Hz, 2× NCH_2CH$_2$O–), 58.86 (d, $^{2}J_{C,P}$ = 5.4 Hz, 2× NCH$_2$CH_2O–), 65.06 (2× –CH$_2$C≡C–), 66.07 (d, $^{2}J_{C,P}$ = 5.4 Hz, 2× –OCH_2(CH$_2$)$_{14}$C≡C–), 77.19 (2× –CH$_2$C≡C–) ppm; ESI–MS: *m/z* = 804.1 [M$^+$ – H], 806.6 [M$^+$ + H], 828.5 [M$^+$ + Na], 1,631.9 [2M$^+$ + Na].

Hexatriaconta-17,19-diyn-1,36-diylbis[2-(dimethylammonio)ethylphosphate] (**9d**, $C_{44}H_{86}N_2O_8P_2$)

Compound **9d** was obtained as a white solid in 61% yield (127 mg) from the phosphorylation reaction of 0.13 g **8d** (0.25 mmol) and subsequent quaternization with an ethanolic solution of Me_2NH following the general procedure described above. R_f = 0.55 (solvent E); ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): δ = 1.14–1.25 (m, 48H, 2× –O(CH$_2$)$_2$(CH_2)$_{12}$(CH$_2$)$_2$C≡C–), 1.36–1.43 (m, 4H, 2× –CH_2CH$_2$C≡C–), 1.48–1.55 (m, 4H, 2× –OCH$_2$CH_2(CH$_2$)$_{14}$C≡C–), 2.12 (t, ^{3}J = 7.1 Hz, 4H, 2× –CH_2C≡C–), 2.77 (s, 12H, 4× –CH_3), 3.14–3.16 (m, 4H, 2× NCH_2CH$_2$O–), 3.77 (q, *J* = 6.6 Hz, 4H, 2× –OCH_2(CH$_2$)$_{15}$C≡C–), 4.01–4.06 (m, 4H, 2× NCH$_2$CH_2O–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD): δ = 19.04 (2× –CH$_2$C≡C–), 25.63 (2× –O(CH$_2$)$_2$CH$_2$(CH$_2$)$_{13}$C≡C–), 28.21, 28.69, 28.94, 29.23, 29.32, 29.50, and 29.53 (2× –O(CH$_2$)$_3$(CH$_2$)$_{12}$CH$_2$C≡C–), 30.57 (d, $^{3}J_{C,P}$ = 7.7 Hz, 2× –OCH$_2$CH$_2$(CH$_2$)$_{14}$C≡C–), 43.25 (4× –CH$_3$), 58.83 (d, $^{3}J_{C,P}$ = 6.1 Hz, 2× NCH$_2$CH$_2$O–), 59.01 (d, $^{2}J_{C,P}$ = 3.8 Hz, 2× NCH$_2$CH$_2$O–), 65.09 (2× –CH$_2$C≡C–), 66.19 (d, $^{2}J_{C,P}$ = 5.4 Hz, 2× –OCH$_2$(CH$_2$)$_{15}$C≡C–), 77.22 (2× –CH$_2$C≡C–) ppm; ESI–MS: *m/z* = 832.0 [M$^+$ – H], 835.1 [M$^+$ + H], 856.1 [M$^+$ + Na]

Triaconta-14,16-diyn-1,30-diylbis[2-(trimethylammonio)ethylphosphate] (**10a**, $C_{40}H_{78}N_2O_8P_2$)

Compound **10a** was obtained as a white solid in 20% yield (78 mg) from the phosphorylation reaction of 0.22 g **8a** (0.5 mmol) and subsequent quaternization with an ethanolic solution of Me_3N following the general procedure described above. R_f = 0.12 (solvent F); ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): δ = 1.17–1.55 (m, 44H, 2× –OCH$_2$(CH_2)$_{11}$CH$_2$C≡C–), 2.16 (t, ^{3}J = 7.1 Hz, 4H, 2× –CH_2C≡C–), 3.13 (s, 18H, 6× –CH_3), 3.50–3.55 (m, 4H, 2× NCH_2CH$_2$O–), 3.77 (q, *J* = 6.6 Hz, 4H, 2× –OCH_2(CH$_2$)$_{12}$C≡C–), 4.11–4.17 (m, 4H, 2× NCH$_2$CH_2O–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD): δ = 19.03 (2× –CH$_2$C≡C–), 25.68 (2× –O(CH$_2$)$_2$CH$_2$(CH$_2$)$_{10}$C≡C–), 28.22, 28.69, 28.95, 29.27, 29.34, 29.46, and 29.49 (2× –O(CH$_2$)$_3$(CH$_2$)$_9$CH$_2$C≡C–), 30.68 (d, $^{3}J_{C,P}$ = 6.9 Hz, 2× –OCH$_2$CH$_2$(CH$_2$)$_{11}$C≡C–), 54.14 (t, *J* = 3.7 Hz, 6× –CH$_3$), 58.66 (d, $^{2}J_{C,P}$ = 5.2 Hz, 2× NCH$_2$CH$_2$O–), 65.12 (2× –CH$_2$C≡C–), 65.77 (d, $^{2}J_{C,P}$ = 6.1 Hz, 2× –OCH$_2$(CH$_2$)$_{12}$C≡C–), 66.43 (b, 2× NCH$_2$CH$_2$O–), 77.20 (2× –CH$_2$C≡C–) ppm; ESI–MS: *m/z* = 777.6 [M$^+$ + H], 799.5 [M$^+$ + Na].

Dotriaconta-15,17-diyn-1,32-diylbis[2-(trimethylammonio)ethylphosphate] (**10b**, $C_{42}H_{82}N_2O_8P_2$)

Compound **10b** was obtained as a white solid in 17% yield (70 mg) from the phosphorylation reaction of 0.24 g **8b** (0.5 mmol) and subsequent quaternization with an ethanolic solution of Me_3N following the general procedure described above. R_f = 0.13 (solvent F); ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): δ = 1.10–1.14 (m, 48H, 2× –OCH$_2$(CH_2)$_{12}$CH$_2$C≡C–), 1.95 (t, ^{3}J = 7.1 Hz, 4H, 2× –CH_2C≡C–), 2.97 (s, 18H, 6× –CH_3), 3.33–3.36 (m, 4H, 2× NCH_2CH$_2$O–), 3.62 (q, *J* = 6.6 Hz, 4H, 2× –OCH_2(CH$_2$)$_{13}$C≡C–), 3.97–4.00 (m, 4H, 2× NCH$_2$CH_2O–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD): δ = 19.01 (2× –CH$_2$C≡C–), 25.65 (2× –O(CH$_2$)$_2$CH$_2$(CH$_2$)$_{11}$C≡C–), 28.21, 28.68, 28.93, 29.26, 29.31, and 29.48 (2× –O(CH$_2$)$_3$(CH$_2$)$_{10}$CH$_2$C≡C–), 30.65 (d, $^{3}J_{C,P}$ = 6.9 Hz, 2× –OCH$_2$CH$_2$(CH$_2$)$_{12}$C≡C–), 54.12 (t, *J* = 3.8 Hz, 6× –CH$_3$), 58.60 (d, $^{2}J_{C,P}$ = 5.0 Hz, 2× NCH$_2$CH$_2$O–), 65.09 (2× –CH$_2$C≡C–), 65.74 (d, $^{2}J_{C,P}$ = 6.0 Hz, 2× –OCH$_2$(CH$_2$)$_{13}$C≡C–), 66.48 (b, 2× NCH$_2$CH$_2$O–), 77.26 (2× –CH$_2$C≡C–) ppm; ESI–MS: *m/z* = 805.5 [M$^+$ + H], 828.5 [M$^+$ + Na].

Tetratriaconta-16,18-diyn-1,34-diylbis[2-(trimethylammonio)ethylphosphate] (**10c**, $C_{44}H_{86}N_2O_8P_2$)

Compound **10c** was obtained as a white solid in 50% yield (105 mg) from the phosphorylation reaction of 0.13 g **8c** (0.25 mmol) and subsequent quaternization with an ethanolic solution of Me_3N following the general procedure described above. R_f = 0.19 (solvent F); ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): δ = 0.98–1.10 (m, 44H, 2× –O(CH$_2$)$_2$(CH_2)$_{11}$(CH$_2$)$_2$C≡C–), 1.20–1.27 (m, 4H, 2× –CH_2CH$_2$C≡C–), 1.31–1.38 (m, 4H, 2× –OCH$_2$CH_2(CH$_2$)$_{13}$C≡C–), 1.96 (t, ^{3}J = 7.1 Hz, 4H, 2× –CH_2C≡C–), 2.93 (s, 18H, 6× –CH_3), 3.32–3.34 (m, 4H, 2× NCH_2CH$_2$O–), 3.59 (q, *J* = 6.6 Hz, 4H, 2× –OCH_2(CH$_2$)$_{14}$C≡C–), 3.94–3.99 (m, 4H, 2× NCH$_2$CH_2O–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD): δ = 18.57 (2× –CH$_2$C≡C–), 25.26 (2× –O(CH$_2$)$_2$CH$_2$(CH$_2$)$_{12}$C≡C–), 27.87, 28.31, 28.58, 28.91, 28.97, and 29.16 (2× –O(CH$_2$)$_3$(CH$_2$)$_{11}$CH$_2$C≡C–), 30.24 (d, $^{3}J_{C,P}$ = 7.4 Hz, 2× –OCH$_2$CH$_2$(CH$_2$)$_{13}$C≡C–), 53.61 (t, *J* = 3.7 Hz, 6× –CH$_3$), 58.60 (d, $^{2}J_{C,P}$ = 5.9 Hz, 2× NCH$_2$CH$_2$O–), 65.77 (d, $^{2}J_{C,P}$ = 5.2 Hz, 2× –OCH$_2$(CH$_2$)$_{14}$C≡C–), 77.19 (2× –CH$_2$C≡C–) ppm; ESI–MS: *m/z* = 868.0 [M$^+$ + Cl], 834.0 [M$^+$ + H], 867.7 [M$^+$ + Na].

Hexatriaconta-17,19-diyn-1,36-diylbis[2-(trimethylammonio)ethylphosphate] (**10d**, $C_{46}H_{90}N_2O_8P_2$)

Compound **10d** was obtained as a white solid in 56% yield (120 mg) from the phosphorylation reaction of 0.13 g **8d** (0.25 mmol) and subsequent quaternization with an ethanolic solution of Me_3N following the general

procedure described above. $R_f = 0.20$ (solvent F); ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): $\delta = 1.18$–1.32 (m, 48H, 2× –O(CH_2)$_2$(CH_2)$_{12}$(CH_2)$_2$C≡C–), 1.40–1.47 (m, 4H, 2× –$CH_2$$CH_2$C≡C–), 1.51–1.58 (m, 4H, 2× –O$CH_2$$CH_2$($CH_2$)$_{14}$C≡C–), 2.17 (t, $^3J = 7.1$ Hz, 4H, 2× –CH_2C≡C–), 3.17 (s, 18H, 6× –CH_3), 3.57–3.59 (m, 4H, 2× N$CH_2$$CH_2$O–), 3.80 (q, $J = 6.6$ Hz, 4H, 2× –OCH_2(CH_2)$_{15}$C≡C–), 4.16–4.22 (m, 4H, 2× N$CH_2$$CH_2$O–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD): $\delta = 19.07$ (2× –CH_2C≡C–), 25.66 (2× –O(CH_2)$_2$$CH_2$($CH_2$)$_{13}$C≡C–), 28.19, 28.66, 28.96, 29.29, 29.33, 29.45, and 29.54 (2× –O(CH_2)$_3$(CH_2)$_{12}$$CH_2$C≡C–), 30.66 (d, $^3J_{C,P} = 7.4$ Hz, 2× –O$CH_2$$CH_2$($CH_2$)$_{14}$C≡C–), 54.29 (t, $J = 3.7$ Hz, 6× –CH_3), 58.95 (d, $^2J_{C,P} = 4.4$ Hz, 2× N$CH_2$$CH_2$O–), 65.21 (2× –$CH_2$C≡C–), 66.07 (d, $^2J_{C,P} = 5.9$ Hz, 2× –OCH_2(CH_2)$_{15}$C≡C–), 66.36 (b, 2× N$CH_2$$CH_2$O–), 77.20 (2× –$CH_2$C≡C–) ppm; ESI–MS: $m/z = 862.3$ [$M^+ + H$], 884.3 [$M^+ + Na$], 1,744.0 [$2M^+ + Na$].

Acknowledgments We are grateful to the Deutsche Forschungsgemeinschaft (DFG) for financial support.

References

1. Fuhrhop JH, Wang T (2004) Chem Rev 104:2901
2. Meister A, Blume A (2007) Curr Opin Colloid Interface Sci 12:138
3. Sprott GD, Tolson DL, Patel GB (1997) FEMS Microbiol Lett 154:17
4. Cornell BA, Braach-Maksvytis VBL, King GL, Osman PDJ, Raguse B, Wieczorek L (1997) Nature 387:580
5. Benvegnu T, Brard M, Plusquellec D (2004) Curr Opin Colloid Interface Sci 8:469
6. Newkome GR, Baker GR, Arai S, Saunders MJ, Russo PS, Theriot KJ, Moorefield CN, Rogers LE, Miller JE, Lieux TR, Murray ME, Phillips B, Pascal L (1990) J Am Chem Soc 112:8458
7. Iwaura R, Yoshida K, Masuda M, Yase K, Shimizu T (2002) Chem Mater 14:3047
8. Drescher S, Meister A, Blume A, Karlsson G, Almgren M, Dobner B (2007) Chem Eur J 13:5300
9. Köhler K, Förster G, Hauser A, Dobner B, Heiser UF, Ziethe F, Richter W, Steiniger F, Drechsler M, Stettin H, Blume A (2004) Angew Chem Int Ed 43:245
10. Köhler K, Forster G, Hauser A, Dobner B, Heiser UF, Ziethe F, Richter W, Steiniger F, Drechsler M, Stettin H, Blume A (2004) J Am Chem Soc 126:16804
11. Meister A, Drescher S, Mey I, Wahab M, Graf G, Garamus VM, Hause G, Mogel HJ, Janshoff A, Dobner B, Blume A (2008) J Phys Chem B 112:4506
12. Köhler K, Meister A, Förster G, Dobner B, Drescher S, Ziethe F, Richter W, Steiniger F, Drechsler M, Hause G, Blume A (2006) Soft Matter 2:77
13. Meister A, Drescher S, Garamus VM, Karlsson G, Graf G, Dobner B, Blume A (2008) Langmuir 24:6238
14. Inoue K, One Y, Kanekiyo Y, Hanabusa K, Shinkai S (1999) Chem Lett 28:429
15. George M, Weiss RG (2003) Chem Mater 15:2879
16. Shirakawa M, Fujita N, Shinkai S (2005) J Am Chem Soc 127:4164
17. Charych D, Cheng Q, Reichert A, Kuziemko G, Stroh M, Nagy JO, Spevak W, Stevens RC (1996) Chem Biol 3:113
18. Song J, Cheng Q, Zhu S, Stevens RC (2002) Biomed Microdevices 4:213
19. Song J, Cisar JS, Bertozzi CR (2004) J Am Chem Soc 126:8459
20. Reppy MA, Pindzola BA (2007) Chem Commun 4317
21. Ahn DJ, Kim JM (2008) Acc Chem Res 41:805
22. Drescher S, Meister A, Graf G, Hause G, Blume A, Dobner B (2008) Chem Eur J 14:6796
23. Corey EJ, Katzenellenbogen JA, Gilman NW, Roman SA, Erickson BW (1968) J Am Chem Soc 90:5618
24. Corey EJ, Katzenellenbogen JA, Roman SA, Gilman NW (1971) Tetrahedron Lett 12:1821
25. Takano S, Sugihara T, Ogasawara K (1991) Synlett 279
26. Brown CA, Yamashita A (1975) J Am Chem Soc 97:891
27. Macaulay SR (1980) J Org Chem 45:734
28. Oppolzer W, Radinov RN, El-Sayed E (2001) J Org Chem 66:4766
29. Schwarz M, Waters RM (1972) Synthesis 567
30. Godt A, Duda S, Ünsal Ö, Thiel J, Härter A, Roos M, Tschierske C, Diele S (2002) Chem Eur J 8:5094
31. Carballeira NM, Montano N, Padilla LF (2007) Chem Phys Lipids 145:37
32. Menger FM, Chen XY, Brocchini S, Hopkins HP, Hamilton D (1993) J Am Chem Soc 115:6600
33. Eglinton G, Galbraith AR (1959) J Chem Soc 889
34. Hirt G, Berechthold R (1958) Pharm Acta Helv 33:349
35. van Aar MPM, Thijs L, Zwanenburg B (1995) Tetrahedron 51:11223
36. Kinsho T, Mori K (1989) Agric Biol Chem 53:2785
37. Grimmer G, Hildebrandt A (1965) Justus Liebigs Ann Chem 685:154
38. Sammul OR, Hollingsworth CA, Wotiz JH (1953) J Am Chem Soc 75:4856
39. Christie WW, Holman RT (1967) Chem Phys Lipids 1:407
40. Augustin KE, Schäfer HJ (1991) Liebigs Ann Chem 1037