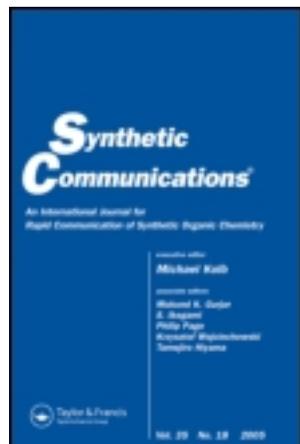


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### Synthesis of Novel Asymmetrical Single-Chain Phosphoglycol-Based Bolaamphiphiles

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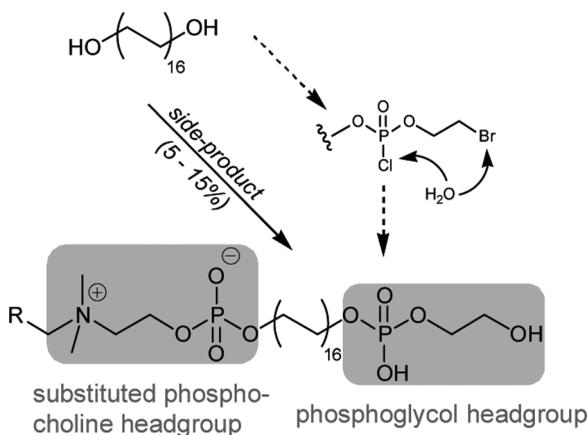
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## SYNTHESIS OF NOVEL ASYMMETRICAL SINGLE-CHAIN PHOSPHOGLYCOL-BASED BOLAAMPHIPHILES

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### GRAPHICAL ABSTRACT



**Abstract** The synthesis of long-chain 1,ω-diols with orthogonal cleavable protecting groups can be effectively performed with the use of the Grignard coupling reaction, successfully leading to the preparation of novel asymmetrical single-chain phosphoglycol-based bolaamphiphiles—a side-product that always occurred during the synthesis of symmetrical bolalipids.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications<sup>®</sup> for the following free supplemental resource(s): Full experimental and spectral details.]

**Keywords** Bipolar lipids; bolaamphiphiles; Grignard reaction; synthetic methods

## INTRODUCTION

Bipolar tetraether lipids (bolalipids or bolaamphiphiles<sup>[1]</sup>) are naturally found in the membranes of certain species of *Archaea*,<sup>[2,3]</sup> where they are responsible for the outstanding stability of these bacteria against extreme living conditions, such as high

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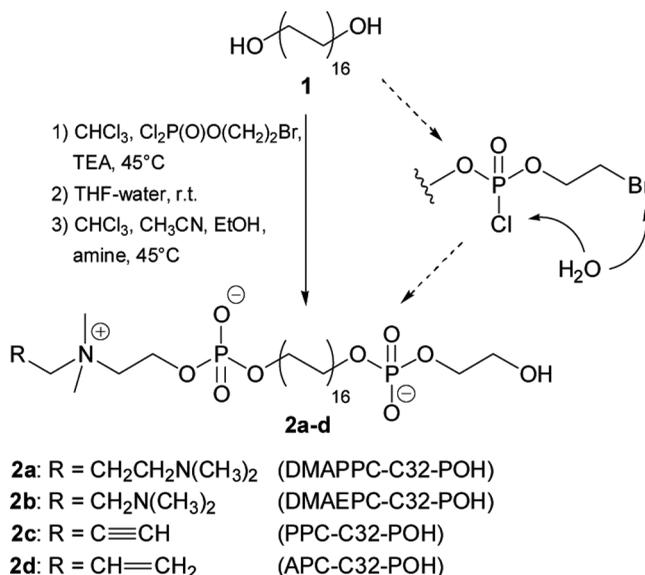
salt concentrations, high temperatures, and/or low pH values. The structural imitation of *Archaea* membrane lipids gave rise to the synthesis of bipolar archaeobacterial model lipids.<sup>[4,5]</sup> These model lipids are of great interest because their thermal and chemical stability as well as their capability to form closed vesicles make them applicable in fields of biotechnology, material science, and pharmacy.<sup>[6–11]</sup> For instance, thermally and chemically stable liposomes made from archaeobacterial bolalipids (archaeosomes) are an alternative to conventional liposomes in applications as drug delivery systems.<sup>[12]</sup> Beside the use of *symmetrical* archaeobacterial model lipids, *asymmetrical* bolalipids also attract attention.<sup>[13]</sup> The present work describes a novel approach to *asymmetrical* single-chain bolaamphiphiles.

## RESULTS AND DISCUSSION

The crucial factors in the preparation of bipolar archaeobacterial model phospholipids are on the one hand an effective, high-yielding synthesis of 1, $\omega$ -diols and on the other hand an efficient insertion of the phosphate moiety. In our group, we use the Sonogashira cross-coupling reaction<sup>[14]</sup> and the Grignard reaction for the synthesis of long-chain 1, $\omega$ -diols. This dilithium tetrachlorocuprate(II)<sup>[15]</sup>–catalyzed Grignard reaction can be designed as a homo-coupling<sup>[16–19]</sup> or a bis-coupling reaction.<sup>[18,20–22]</sup> For the insertion of the phosphate headgroup we use the well-established 2-bromoethylphosphoric acid dichloride as phosphorylation reagent. According to other studies on bolaphospholipid synthesis,<sup>[23,24]</sup> this classic reagent was more efficient than other methods, such as the use of 2-chloro-2-oxo-1,3,2-dioxaphospholane.

However, during the syntheses of *symmetrical*, single-chain bolalipids with modified chain and headgroup structures,<sup>[25]</sup> we could isolate an *asymmetrical* bolaamphiphile as side-product (in 5–15% yield) at nearly *all* times while using the 2-bromoethylphosphoric acid dichloride. Low-resolution mass spectrometry (MS) indicated the existence of one hydroxy(2-hydroxyethoxy)phosphoryl (POH) headgroup—which also can be termed as phosphoglycol group—beside the other phosphocholine (PC) moiety within one bolalipid molecule. The chemical structures of these novel *asymmetrical* bolaamphiphiles could be initially verified by high-resolution mass spectrometry (HRMS), <sup>1</sup>H NMR, and correlation spectrometry (H,H-COSY NMR) measurements (see the Supplementary Information). The occurrence of this side-product is explained as follows: The phosphorylation reaction, which is performed in dry CHCl<sub>3</sub>, is followed by a hydrolysis in a tetrahydrofuran (THF) / water mixture to replace the remaining chlorine atom. During this hydrolysis, a substitution of the bromine atom with a hydroxy moiety could occur, which led to the formation of the POH headgroup (see dashed arrows in Scheme 1). The existence of this POH group and, hence, the formation of *asymmetrical* bolalipids, could be shown for various syntheses, namely the synthesis of 3-dimethylaminopropyl-PC (DMAPP), 2-dimethylaminoethyl-PC (DMAEPC), propynyl-PC (PPC), and allyl-PC (APC) modified bolaamphiphiles<sup>[25]</sup> (**2a–d**, Scheme 1, and Supplementary Information). However, the formation of a bolalipid with two POH headgroups could not be detected.

To verify the chemical structure of this side-product, a synthetic strategy for the preparation of *asymmetrical* single-chain bolaamphiphiles was developed, which

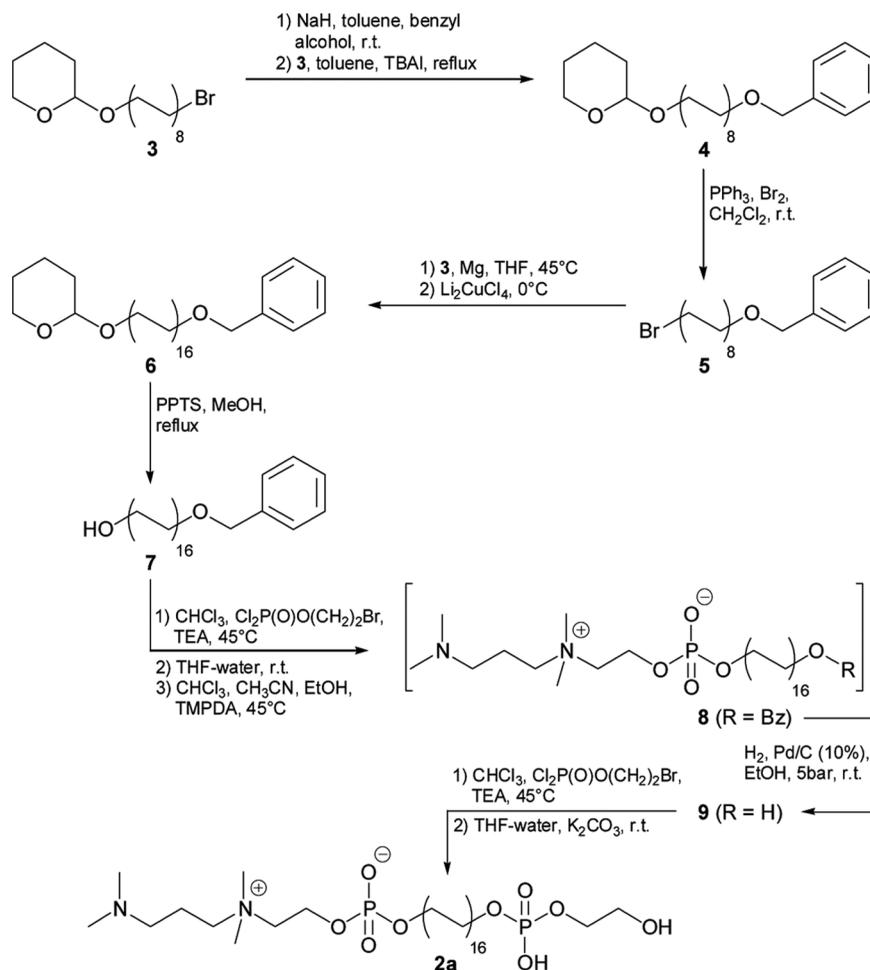


**Scheme 1.** Proposed mechanism for the formation of the asymmetrical side-product including a phosphoglycol headgroup (dashed arrows) during the preparation of bolaamphiphiles.<sup>[25]</sup>

is shown for the synthesis of compound **2a**. As starting point we chose the copper(II)-catalyzed Grignard homo-coupling of tetrahydropyranyl (THP)-protected 16-bromohexadecan-1-ol (THPO-C16-Br, **3**), published previously.<sup>[18]</sup> To introduce orthogonally cleavable protection groups, the THP moiety was replaced by the benzyl (Bn) group, which is stable under most acidic and basic conditions and can be easily cleaved by hydrogenation. Therefore, the sodium salt of benzyl alcohol was alkylated with THPO-C16-Br (**3**), in toluene and in the presence of *n*-tetrabutylammonium iodide (TBAI). The use of toluene and higher temperatures (reflux) is recommended in this step because the use of other solvents (e.g., THF) resulted in lower yields. The THP group of the resulting 2-[(16-benzyloxyhexadec-1-yl)oxy]tetrahydro-2*H*-pyran (THPO-C16-OBn, **4**) was nearly quantitatively transformed into the corresponding bromide (Br-C16-OBn, **5**) while using the procedure described by Schwarz et al.<sup>[26]</sup>

In the next step, the same THPO-C16-Br (**3**) was converted into the Grignard reagent<sup>[18]</sup> and subsequently coupled with Br-C16-OBn (**5**) under catalysis with dilithium tetrachlorocuprate(II),<sup>[15]</sup> yielding the 2-[(32-benzyloxydotriacont-1-yl)oxy]tetrahydro-2*H*-pyran (THPO-C32-OBn, **6**), a long-chain 1, $\omega$ -diol with orthogonally cleavable protection moieties. For the purification of compound **6** it is useful to recrystallize the raw product prior to the column chromatography from acetone to remove the short-chain side-products. The THP group was subsequently removed by heating compound **6** in methanol with catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS), finally resulting in the formation of 32-benzyloxydotriacontan-1-ol (HO-C32-OBn, **7**; see Scheme 2).

The insertion of the first headgroup was carried out using the phosphorylation reaction with 2-bromoethylphosphoric acid dichloride and the subsequent



**Scheme 2.** Synthetic pathway for the preparation of asymmetrical bolaamphiphiles.

quarternisation with tetramethylpropylenediamine (TMPDA) as described previously.<sup>[25]</sup> Because the size of the amine used has a great impact on the yields—leading to very marginal, detectable amounts of product only in mass spectrometry in the synthesis of the symmetrical DMAPPC-C32-DMAPPC<sup>[25]</sup>—poor yields of DMAPPC-C32-OBn (**8**) are unfortunately unavoidable. The synthesis of 32-benzylhydroxydtriacontane-1-yl- $\{2-[N-(3\text{-dimethylaminopropyl})-N,N\text{-di-methylammonio}]ethylphosphate\}$  (DMAPPC-C32-OH, **9**) was completed after the cleavage of the benzyl protection group using hydrogenation (5 atm) in ethanol and palladium on carbon as catalyst (see Scheme 2).

For the conversion of the free hydroxy moiety of compound **9** into the POH headgroup, various synthetic methods are feasible: Eibl<sup>[27]</sup> and de Jongh and de Kruijff<sup>[28]</sup> have used POCl<sub>3</sub> as phosphorylating agent combined with a subsequently performed reaction with ethylene glycol / TEA and an acidic dioxaphospholane ring

opening. On the other hand, Dijkman et al.<sup>[29]</sup> and Campins et al.<sup>[30]</sup> have used the 2-chloro-2-oxo-1,3,2-dioxaphospholane methodology. In contrast to these procedures described, we performed this conversion using a comparable phosphorylation reaction as shown previously. Instead of the final quarternization with tertiary amines, the bromine atom was exchanged for the hydroxy group in a mixture of THF/water, alkaline conditions ( $K_2CO_3$ ), prolonged reaction time, and slightly increased temperature. Mass spectrometric analyses of the 32-{[hydroxy(2-hydroxyethoxy)phosphoryl]oxy}dotriacontane-1-yl-2-[*N*-(3-dimethylaminopropyl)-*N,N*-dimethylammonio]ethylphosphate} (DMAPPC-C32-POH, **2a**) achieved from this *asymmetrical* synthetic pathway (Scheme 2) are in accordance with those obtained from the side-product of the *symmetrical* way (Scheme 1) described previously.

In summary, the synthesis of long-chain 1, $\omega$ -diols with orthogonally cleavable protection moieties we have developed in this work offers the possibility for the preparation of a huge variety of *asymmetrical* single-chain bolaamphiphiles. In addition, the synthesis of phosphocholines while using the 2-bromoethylphosphoric acid dichloride is connected with the formation of side-products, namely a hydroxy(2-hydroxyethoxy)phosphoryl (POH) or phosphoglycol headgroup. But how to explain the importance of these side-products? Because the self-assembly properties of symmetrical, single-chain bolaamphiphiles also depends on the protonation state and, hence, electrostatic interactions of the headgroup,<sup>[22,31–34]</sup> the combination of both an amine-modified and, hence, protonable PC headgroup (e.g., DMAPPC) and an acidic phosphor ester headgroup (POH) in one bolalipid molecule should force new aggregate structures, such as lamellar sheets, rods, vesicles, or nanotubes. A detailed comparative physicochemical study of different *asymmetrical* bolaamphiphiles, such as DMAPPC-C32-POH (**2a**) and DMAPPC-C32-OH (**9**), has been published elsewhere.<sup>[13]</sup>

## EXPERIMENTAL

All chemicals were purchased from Sigma Aldrich Co. and were used without further purification. All solvents for synthetic purpose were dried and distilled before use. The purity of all compounds was checked by thin-layer chromatography (TLC) using silica gel 60 F<sub>254</sub> plates. Silica gel (0.063–0.200 mm) was used for column chromatography of the products. Melting points were determined with a Boetius apparatus. <sup>1</sup>H, <sup>13</sup>C, and <sup>31</sup>P NMR spectra were recorded on a VNMRS 400-MHz spectrometer or an Inova 500-MHz spectrometer with the use of CDCl<sub>3</sub> or CD<sub>3</sub>OD as internal standard. Mass spectrometric data were obtained with a Finnigan MAT SSQ 710 C (ESI-MS) or were recorded on an AMD 402 (70 eV) spectrometer (EI-MS). High-resolution mass spectra (HRMS) were recorded on a Thermo Fisher Scientific LTQ-Orbitrap mass spectrometer with static nano-electrospray ionization. Elemental analyses were conducted using a Leco CHNS-932.

### General Procedure for the Phosphorylation and Quarternization Reaction

2-Bromoethylphosphoric acid dichloride (0.48 g, 2 mmol) was poured into dry CHCl<sub>3</sub> (10 mL) under cooling with ice water. A solution of 0.5 mL TEA in 10 mL CHCl<sub>3</sub> was added slowly, and the resulting mixture was stirred for 30 min at 0 °C.

Subsequently, 0.5 mmol of dotriacontane-1,32-diol (for the synthesis of **2a–d**), 1 mmol of HO-C32-OBn (**7**; for the synthesis of **8**), and 1 mmol of DMAPPC-C32-OH (**9**; for the synthesis of **2a**), respectively, were added in one portion, and the mixture was gently heated until the alcohol had completely dissolved. The stirring was continued for 24 h at 25 °C. Afterward, crushed ice was added to the solution, and the mixture was stirred vigorously for another 2 h. The organic layer was separated and the aqueous phase was extracted with CHCl<sub>3</sub> (3 × 15 mL). The combined organic layers were evaporated, and the crude bromoethyl ester was dissolved in 10 mL THF/H<sub>2</sub>O (9/1, v/v) and stirred for a further 1.5 h.

For the subsequently performed quarternization reaction (products **2a–d**, **8**), the solvent was evaporated and the oily residue was transferred into a mixture of CHCl<sub>3</sub> (15 mL), acetonitrile (15 mL), and ethanol (5 mL). The pure amine (20 mmol) was added slowly, and the mixture was kept in a close tube at 45 °C for 48 h. For the alternative alkaline substitution of the bromine atom (synthesis of **2a** via **9**), equimolar amounts of K<sub>2</sub>CO<sub>3</sub> were added to the THF/H<sub>2</sub>O mixture, which was stirred for 10 h at room temperature.

For workup, the complete mixture was concentrated by evaporation of the solvent, and the residue was purified by column chromatography using CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O as eluent and gradient technique to give products as white substances.

### General Procedure for the Grignard Coupling Reaction

A solution of 12.7 g 2-[(16-bromohexadec-1-yl)oxy]tetrahydro-2H-pyran<sup>[18]</sup> (THPO-C16-Br, **3**, 31.2 mmol) in dry THF (75 mL) was added dropwise with stirring to magnesium turnings (1.22 g, 50 mmol) under an argon atmosphere. After the exothermic reaction had subsided, the mixture was stirred at 45 °C for 3 h. The excess magnesium was removed under argon and the Grignard solution was cooled to –5 °C. A freshly prepared solution of Li<sub>2</sub>CuCl<sub>4</sub> (0.1 M in THF, 3.0 mL) was added with stirring. After a solution of 9.94 g Br-C16-OBn (**5**, 24.2 mmol) in dry THF (70 mL) was added in one portion, stirring was continued for further 3 h at about 0 °C. For workup Et<sub>2</sub>O (150 mL) was added and the resulting mixture was poured into a cold saturated solution of NH<sub>4</sub>Cl (150 mL). The organic layer was separated and the aqueous phase was extracted with Et<sub>2</sub>O (2 × 50 mL). The combined organic phases were washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to dryness under reduced pressure. The crude product was recrystallized from acetone to remove the short-chain by-products. The final purification was carried out by chromatography using a heptane/CHCl<sub>3</sub> gradient (+0.5% TEA) as eluent to obtain 8.7 g (55%) of THPO-C32-OBn (**6**).

### Spectral Data for Selected Compounds

**32-[[Hydroxy(2-hydroxyethoxy)phosphoryl]oxy]dotriacontane-1-yl-[[N-(3-dimethylaminopropyl)-N,N-dimethylammonio]ethylphosphate}** (DMAPPC-C32-POH, **2a**). White, waxy solid; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD): δ = 1.15–1.28 [m, 56H, (CH<sub>2</sub>)<sub>28</sub>], 1.48–1.54 [m, 4H, OCH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>28</sub>CH<sub>2</sub>CH<sub>2</sub>O], 2.09–2.16 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.62 [s, 6H, (H<sub>3</sub>C)<sub>2</sub>NCH<sub>2</sub>], 2.83–2.91 [m, 2H, (H<sub>3</sub>C)<sub>2</sub>NCH<sub>2</sub>], 3.08 [s, 6H, CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 3.29–3.43 [m, 2H, (H<sub>3</sub>C)<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N], 3.49–3.51 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>O), 3.60–3.62 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>OH),

3.72–3.77 [m, 4H,  $\text{OCH}_2(\text{CH}_2)_{30}\text{CH}_2\text{O}$ ], 3.80–3.85 (m, 2H,  $\text{OCH}_2\text{CH}_2\text{OH}$ ), 4.08–4.12 ppm (m, 2H,  $\text{NCH}_2\text{CH}_2\text{O}$ );  $^{31}\text{P}$  NMR (161.9 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD}$ ):  $\delta = 1.455, 0.012$  ppm; ESI-MS:  $m/z = 842.1$   $[\text{M} - \text{H}]^-$ , 844.8  $[\text{M} + \text{H}]^+$ , 866.1  $[\text{M} + \text{Na}]^+$ . Anal. calcd. (%) for  $\text{C}_{43}\text{H}_{92}\text{N}_2\text{O}_9\text{P}_2 \cdot 2\text{H}_2\text{O}$ : C, 58.74; H, 11.00; N, 3.19. Found: C, 58.45; H, 10.83; N, 3.01. HRMS: calcd for  $\text{C}_{43}\text{H}_{93}\text{N}_2\text{O}_9\text{P}_2$   $[\text{M} + \text{H}]^+$  843.6351; found 843.6356;  $\text{C}_{43}\text{H}_{92}\text{N}_2\text{O}_9\text{NaP}_2$   $[\text{M} + \text{Na}]^+$  865.6170; found 865.6176.

**32-{[Hydroxy(2-hydroxyethoxy)phosphoryl]oxy}dotriacontane-1-yl-[2-[N-(2-dimethyl-aminoethyl)-N,N-dimethylammonio]ethylphosphate} (DMAEPC-C32-POH, 2b).** White, waxy solid;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD}$ ):  $\delta = 1.14\text{--}1.26$  [m, 56H,  $(\text{CH}_2)_{28}$ ], 1.47–1.53 [m, 4H,  $\text{OCH}_2\text{CH}_2(\text{CH}_2)_{28}\text{CH}_2\text{CH}_2\text{O}$ ], 2.47 [s, 6H,  $(\text{H}_3\text{C})_2\text{NCH}_2$ ], 3.04–3.12 [bm, 2H,  $(\text{H}_3\text{C})_2\text{NCH}_2$ ], 3.13 [s, 6H,  $\text{CH}_2\text{N}(\text{CH}_3)_2\text{CH}_2$ ], 3.50–3.52 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 3.58–3.63 [m, 4H,  $\text{OCH}_2\text{CH}_2\text{OH}$ ,  $(\text{H}_3\text{C})_2\text{NCH}_2\text{CH}_2\text{N}$ ], 3.71–3.76 [m, 4H,  $\text{OCH}_2(\text{CH}_2)_{30}\text{CH}_2\text{O}$ ], 3.79–3.82 (m, 2H,  $\text{OCH}_2\text{CH}_2\text{OH}$ ), 4.09–4.13 ppm (m, 2H,  $\text{NCH}_2\text{CH}_2\text{O}$ );  $^{31}\text{P}$  NMR (161.9 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD}$ ):  $\delta = -0.315, -0.562$  ppm; ESI-MS:  $m/z = 828.0$   $[\text{M} - \text{H}]^-$ , 830.0  $[\text{M} + \text{H}]^+$ , 852.0  $[\text{M} + \text{Na}]^+$ . Anal. calcd (%) for  $\text{C}_{42}\text{H}_{90}\text{N}_2\text{O}_9\text{P}_2 \cdot 2\text{H}_2\text{O}$ : C, 58.31; H, 10.95; N, 3.24. Found: C, 58.37; H, 10.56; N, 3.41. HRMS: calcd. for  $\text{C}_{42}\text{H}_{91}\text{N}_2\text{O}_9\text{P}_2$   $[\text{M} + \text{H}]^+$  829.6194; found 829.6208.

**32-{[Hydroxy(2-hydroxyethoxy)phosphoryl]oxy}dotriacontane-1-yl-[2-(N,N-dimethyl-N-prop-2-yn-1-ylammonio)ethylphosphate] (PPC-C32-POH, 2c).** White, waxy solid;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD}$ ):  $\delta = 1.08\text{--}1.17$  [m, 56H,  $(\text{CH}_2)_{28}$ ], 1.40–1.47 [m, 4H,  $\text{OCH}_2\text{CH}_2(\text{CH}_2)_{28}\text{CH}_2\text{CH}_2\text{O}$ ], 2.92 (t,  $^4J = 2.5$  Hz, 1H,  $\text{HC}\equiv\text{CCH}_2\text{N}$ ), 3.09 (s, 6H,  $2 \times \text{CH}_3$ ), 3.49–3.54 (m, 4H,  $\text{NCH}_2\text{CH}_2\text{O}$ ,  $\text{OCH}_2\text{CH}_2\text{OH}$ ), 3.64–3.70 [m, 4H,  $\text{OCH}_2(\text{CH}_2)_{30}\text{CH}_2\text{O}$ ], 3.72–3.76 (m, 2H,  $\text{OCH}_2\text{CH}_2\text{OH}$ ), 4.04–4.08 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 4.21 ppm (d,  $^4J = 2.5$  Hz, 2H,  $\text{HC}\equiv\text{CCH}_2\text{N}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD}$ ):  $\delta = 25.0, 25.2, 28.7, 28.8, 29.0$  (2 signals), 29.1 (3 signals), 29.8 (d,  $\text{POCH}_2\text{CH}_2\text{CH}_2$ ), 30.2 (d,  $\text{POCH}_2\text{CH}_2\text{CH}_2$ ), 50.6 ( $\text{CH}_3$ ), 54.80 (b,  $\text{HC}\equiv\text{CCH}_2$ ), 58.2 (d,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 60.9 (d,  $\text{OCH}_2\text{CH}_2\text{OH}$ ), 63.7 (d,  $\text{OCH}_2\text{CH}_2\text{OH}$ ), 65.5 [d,  $\text{POCH}_2(\text{CH}_2)_{31}\text{O}$ ], 66.4 [d,  $\text{POCH}_2(\text{CH}_2)_{31}\text{O}$ ], 67.4 (d,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 70.4 ( $\text{HC}\equiv\text{C}$ ), 81.4 ppm ( $\text{HC}\equiv\text{C}$ );  $^{31}\text{P}$  NMR (161.9 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD}$ ):  $\delta = 0.127, -0.156$  ppm; ESI-MS:  $m/z = 794.5$   $[\text{M} - \text{H}]^-$ , 818.6  $[\text{M} + \text{Na}]^+$ . Anal. calcd. (%) for  $\text{C}_{41}\text{H}_{83}\text{NO}_9\text{P}_2 \cdot 2\text{H}_2\text{O}$ : C, 59.18; H, 10.58; N, 1.68. Found: C, 59.35; H, 10.71; N, 1.87. HRMS: calcd for  $\text{C}_{41}\text{H}_{84}\text{NO}_9\text{P}_2\text{Na}$   $[\text{M} + \text{H} + \text{Na}]^{2+}$  409.7754; found 409.7754;  $\text{C}_{41}\text{H}_{84}\text{NO}_9\text{P}_2$   $[\text{M} + \text{H}]^+$  796.5616; found 796.5619.

**32-{[Hydroxy(2-hydroxyethoxy)phosphoryl]oxy}dotriacontane-1-yl-[2-(N-allyl-N,N-di-methylammonio)ethylphosphate] (APC-C32-POH, 2d).** White, waxy solid;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD}$ ):  $\delta = 1.15\text{--}1.27$  [m, 56H,  $(\text{CH}_2)_{28}$ ], 1.48–1.58 [m, 4H,  $\text{OCH}_2\text{CH}_2(\text{CH}_2)_{28}\text{CH}_2\text{CH}_2\text{O}$ ], 3.03 (s, 6H,  $2 \times \text{CH}_3$ ), 3.45–3.46 (m, 2H,  $\text{OCH}_2\text{CH}_2\text{OH}$ ), 3.62–3.65 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 3.75–3.80 and 3.83–3.88 [2 m, 4H,  $\text{OCH}_2(\text{CH}_2)_{30}\text{CH}_2\text{O}$ ], 3.91 (d,  $^2J = 7.3$  Hz, 2H,  $\text{NCH}_2\text{CH}=\text{CH}_2$ ), 3.92–3.94 (m, 2H,  $\text{OCH}_2\text{CH}_2\text{OH}$ ), 4.13–4.19 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 5.60–5.67 (m, 2H,  $\text{NCH}_2\text{CH}=\text{CH}_2$ ), 5.89 ppm (ddt,  $^3J[E] = 17.3$  Hz,  $^3J[Z] = 10.3$  Hz,  $^3J = 7.3$  Hz, 1H,  $\text{NCH}_2\text{CH}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD}$ ):  $\delta = 25.0, 25.2, 28.7, 28.9, 29.0, 29.1$  (4 signals), 29.2, 29.9 (d,  $\text{POCH}_2\text{CH}_2\text{CH}_2$ ), 30.2

(d, POCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 50.3 (CH<sub>3</sub>), 58.2 (d, NCH<sub>2</sub>CH<sub>2</sub>O), 60.9 (d, OCH<sub>2</sub>CH<sub>2</sub>OH), 63.5 (b, OCH<sub>2</sub>CH<sub>2</sub>OH), 65.6 [d, POCH<sub>2</sub>(CH<sub>2</sub>)<sub>31</sub>O], 66.7 [d, POCH<sub>2</sub>(CH<sub>2</sub>)<sub>31</sub>O], 67.4 (b, NCH<sub>2</sub>CH=CH<sub>2</sub>), 67.6 (d, NCH<sub>2</sub>CH<sub>2</sub>O), 123.9 (CH=CH<sub>2</sub>), 129.1 ppm (CH=CH<sub>2</sub>); <sup>31</sup>P NMR (161.9 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD): δ = -0.181, -0.199 ppm; ESI-MS: *m/z* = 796.9 [M - H]<sup>-</sup>, 799.6 [M + H]<sup>+</sup>, 821.2 [M + Na]<sup>+</sup>. Anal. calcd. (%) for C<sub>41</sub>H<sub>85</sub>NO<sub>9</sub>P<sub>2</sub> · 2H<sub>2</sub>O: C, 59.04; H, 10.76; N, 1.68. Found: C, 59.40, H, 10.90; N, 1.96. HRMS: calcd. for C<sub>41</sub>H<sub>86</sub>NO<sub>9</sub>P<sub>2</sub>Na [M + H + Na]<sup>2+</sup> 410.7832; found 410.7831, C<sub>41</sub>H<sub>86</sub>NO<sub>9</sub>P<sub>2</sub> [M + H]<sup>+</sup> 798.5772; found 798.5773.

**2-[(32-Benzyloxydotriacont-1-yl)oxy]tetrahydro-2H-pyran. (THPO-C32-OBn, 6).** White solid, mp 62–64 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.24–1.37 [m, 56H, (CH<sub>2</sub>)<sub>28</sub>], 1.47–1.63 (m, 8H, 4 × CH<sub>2</sub>CH<sub>2</sub>O), 1.66–1.73 [m, 1H, CHOCH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>30</sub>O], 1.77–1.85 [m, 1H, CHOCH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>30</sub>O], 3.36 [dt, <sup>2</sup>*J* = 9.6 Hz, <sup>3</sup>*J* = 6.7 Hz, 1H, CHOCH<sub>2</sub>(CH<sub>2</sub>)<sub>31</sub>O], 3.44 [t, <sup>3</sup>*J* = 6.7 Hz, 2H, CHO(CH<sub>2</sub>)<sub>31</sub>CH<sub>2</sub>O], 3.45–3.51 [m, 1H, OCH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH], 3.71 (dt, <sup>2</sup>*J* = 9.6 Hz, <sup>3</sup>*J* = 6.8 Hz, 1H, CHOCH<sub>2</sub>(CH<sub>2</sub>)<sub>31</sub>O), 3.83–3.88 [m, 1H, OCH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH], 4.48 (s, 2H, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 4.55–4.57 (m, 1H, OCHO), 7.23–7.33 ppm (m, 5H, C<sub>6</sub>H<sub>5</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 19.7, 25.5, 26.2, 26.3, 29.5, 29.6 (2 signals), 29.7 (2 signals), 29.8 (2 signals), 30.8 (CH<sub>2</sub>CH), 62.3 [OCH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH], 67.7 [CHOCH<sub>2</sub>(CH<sub>2</sub>)<sub>15</sub>], 70.6 (OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 72.9 (CH<sub>2</sub>OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 98.8 (CH), 127.4, 127.6, 128.3, 138.8 ppm; EI-MS (70 eV): *m/z* (%) = 657 (12) [M]<sup>+</sup>. Anal. calcd (%) for C<sub>44</sub>H<sub>80</sub>O<sub>3</sub> (657.10): C, 80.42; H, 12.27. Found: C, 80.81; H, 12.15.

**32-Hydroxydotriacontane-1-yl-{2-[N-(3-dimethylaminopropyl)-N,N-dimethylammonio]ethyl-phosphate} (DMAPPC-C32-OH, 9).** White solid, mp 115–118 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD): δ = 1.23–1.35 [m, 56H, (CH<sub>2</sub>)<sub>28</sub>], 1.47–1.54 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 1.56–1.64 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 2.13–2.21 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.70 [s, 6H, (H<sub>3</sub>C)<sub>2</sub>N], 2.93 [t, *J* = 7.4 Hz, 2H, (H<sub>3</sub>C)<sub>2</sub>NCH<sub>2</sub>], 3.17 [s, 6H, CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 3.46–3.51 [m, 2H, (H<sub>3</sub>C)<sub>2</sub>NCH<sub>2</sub>-CH<sub>2</sub>CH<sub>2</sub>N], 3.52 (t, *J* = 6.8 Hz, 2H, CH<sub>2</sub>OH), 3.59–3.62 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>O), 3.83 [“quar,” *J* = 6.6 Hz, 2H, OCH<sub>2</sub>(CH<sub>2</sub>)<sub>31</sub>OH], 4.17–4.22 ppm (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>O); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD): δ = 18.9, 25.3 (d, POCH<sub>2</sub>-CH<sub>2</sub>CH<sub>2</sub>), 28.9, 29.0, 29.1 (2 signals), 29.2 (6 signals), 30.3 [d, POCH<sub>2</sub>-CH<sub>2</sub>(CH<sub>2</sub>)<sub>30</sub>OH], 32.0 (CH<sub>2</sub>CH<sub>2</sub>OH), 36.6, 42.9 [(H<sub>3</sub>C)<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>], 51.7 [t, CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 53.9 [b, (H<sub>3</sub>C)<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>], 58.4 (d, NCH<sub>2</sub>CH<sub>2</sub>O), 61.4 (b, NCH<sub>2</sub>CH<sub>2</sub>O), 61.8 [(H<sub>3</sub>C)<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>], 62.8 (b, CH<sub>2</sub>OH), 65.6 ppm [d, POCH<sub>2</sub>(CH<sub>2</sub>)<sub>31</sub>OH]; <sup>31</sup>P NMR (161.9 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD): δ = -0.233 ppm; ESI-MS: *m/z* = 719.53 [M + H]<sup>+</sup>, 742.57 [M + Na]<sup>+</sup>, 1438.07 [2M + H]<sup>+</sup>. Anal. calcd, (%) for C<sub>41</sub>H<sub>87</sub>N<sub>2</sub>O<sub>5</sub>P · 2H<sub>2</sub>O: C, 65.21; H, 12.15; N, 3.71. Found: C, 65.46; H, 12.31; N, 3.85. HRMS: calcd. for C<sub>41</sub>H<sub>88</sub>N<sub>2</sub>O<sub>5</sub>P [M + H]<sup>+</sup> 719.6425; found 719.6411.

## SUPPORTING INFORMATION

Full experimental detail; <sup>1</sup>H, <sup>13</sup>C, and <sup>31</sup>P NMR; MS; and HRMS spectra can be found via the Supplementary Content section of this article's Web page.

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