(Table III). Previous NMR[6] and computational[35] studies have indicated that 7 is conformationally heterogeneous, with N and S conformers having comparable stabilities. A computer analysis of the $^3J_{HH}$ values for 7 gave X_S = 0.65, which is significantly smaller than X_S determined for **1b**, **2b**, and **4b** (Table IV).[36] Thus, the conversion of the *O*-glycoside 7 to 1-**4b** significantly alters furanose ring conformation, as noted previously in the ribonucleosides.[8] The conformational heterogeneity observed in 7 is reduced in the erythronucleosides 1-**4b** by the selective stabilization of S conformers.

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Supplementary Material Available: 300-MHz ^{1}H NMR spectra of (1'-^{13}C)**1b**, **2b**, (1'-^{13}C)**2b**, **4b**, and (1'-^{13}C)**4b** and 75-MHz ^{1}H-decoupled ^{13}C NMR spectra of **3b** and **4b** (6 pages). Ordering information is given on any current masthead page.

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A New Reagent for the Removal of the 4-Methoxybenzyl Ether: Application to the Synthesis of Unusual Macrocyclic and Bolaform Phosphatidylcholines

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The total synthesis of two novel polymerizable phosphatidylcholines has been accomplished using 3-(4-methoxybenzyl)-*sn*-glycerol **10** as starting material. Diacylation of **10** with 13-tetradecynoic acid followed by oxidative coupling of the alkynes gives the 32-membered glycerol macrocycle **17**. Sequential acylation of **10** with palmitic acid and 15-hexadecynoic acid followed by oxidative coupling gives the bolaform **16**, tethered at the 2-position of the glycerol. A new method for the cleavage of 4-methoxybenzyl ethers using dimethylboron bromide at −78 °C in dichloromethane is described. 1,3-Diacetylenes, 1,4-dienes, and esters are stable under the experimental conditions, and the migration of acyl chains from secondary to primary positions is totally suppressed. The diacylglycerols are then efficiently converted into the corresponding phosphatidylcholines by tetrazole-catalyzed phosphitylation with 2-cyanoethyl 2-bromoethyl *N,N*-diisopropylamino phosphite, oxidation, and treatment with trimethylamine to simultaneously displace the bromide and eliminate the cyanoethyl group.

Introduction

Phospholipids constitute the main structural component of cell membranes. Due to their amphiphilic nature, they associate into aggregate structures such as vesicles, micelles, and bilayers. In biological phospholipid assemblies, the nature of the lipid components affects the function and dynamics of the membrane.[1] For example, the outer leaflet of plasma membranes is richer in phosphatidylcholines (PCs), while the inner leaflet is richer in phosphatidylethanolamines (PEs) and phosphatidylinositol (PIs).[2] In addition to differences in the polar portion, there is also a large difference in the length and degree of saturation of the lipid chains, both between monomers and between the primary and secondary positions on the glycerol backbone itself. Notably, unsaturated lipids, e.g., arachidonic acid, are almost exclusively esterified at the secondary position of the glycerol. A host of enzymes exist within the cell for the processing and turnover of membrane phospholipids.[3] Among the important members of this class is phospholipase A_2 (PLA_2), which releases arachidonate (and other fatty acids) at the 2-position of phosphatidylcholines for the production of eicosanoids, and phospholipase C, which cleaves PIs to release the important intracellular second messengers inositol triphosphate and diacylglycerol.

It is known that both the nature and the physical state of the phospholipids are important factors that determine the rate of enzymatic hydrolysis.[4] In order to gain understanding of this dependence at the molecular level with respect to the mechanism of PLA_2, we required a series of modified phospholipids with substituents on the 2-acyl chain. In a previous paper we described the synthesis of chain-substituted phosphatidylcholines by the coupling of a diacylglycerol with a 2-bromoethyl 2-cyanoethyl phosphoramidite with acid catalysis.[5] This strategy has several advantages over the standard methodology.[6] Firstly, the use of a mild acid catalyst prevents acyl migration in the diacylglycerol. Secondly, the intermediate phosphate triester is neutral and can be purified at this stage using

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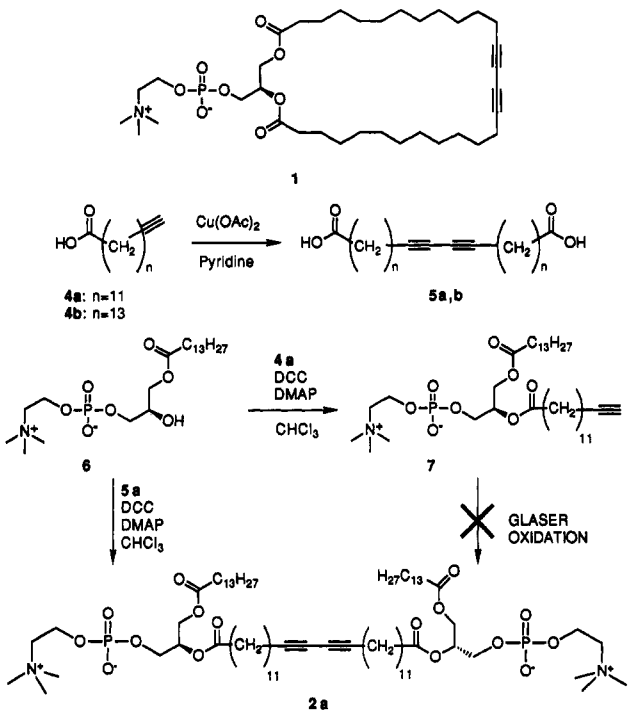
Scheme I



normal-phase flash chromatography. Thirdly, due to the appropriate choice of substituents on phosphorus, the zwitterionic phosphocholine is produced in the final step by elimination of the cyanoethyl group and displacement of the bromide with trimethylamine.[7] In this paper we describe the synthesis of the unusual macrocycle and bolaform phospholipids **1** and **2** bearing polymerizable fatty acids. The use of a new deprotection method for 4-methoxybenzyl ethers allowed the preparation of the requisite 1,2-diacylglycerols in high yield. At the same time we have extended the use of this protecting group and demonstrated the usefulness of our strategy for the synthesis of phosphatidylcholines bearing unsaturated acyl chains.

Results and Discussion

At the outset of this project we had planned the synthesis of the bolaform **2a** by the coupling of two phospholipids bearing an ω-acetylenic fatty acid at the 2-position of the glycerol to give a 1,3-diyne via oxidation of the alkyne functions.[8] The ω-alkynoic acids **4a** and **4b** (Scheme I) are accessible in two steps in 61% yield from commercially available acetylenic alcohols by "zipper" isomerization of the alkyne to the terminal position in superbase medium[9] followed by Jones oxidation of alcohols **3a** and **3b**. The acylation of commercially available 1-myristoyl-2-lysophosphatidylcholine **6** (lyso-PC) with 13-tetradecynoic acid **4a** using dicyclohexylcarbodiimide (DCC) and (dimethylamino)pyridine (DMAP) in dry chloroform gave a 91% yield of diacyl-PC **7**, but the coupling of the terminal acetylenes could not be effected under the various conditions of the Glaser oxidation. However, the ω-tetradecynoic acids **4** could be coupled in the presence of cupric acetate in aqueous pyridine to give the 13,15-diyne-1,28-dioic acid **5a** and 15,17-diyne-1,32-dioic acid **5b** in 89% yield. These light-sensitive diacids and 4 equiv of lyso-PC **6** were then treated with DCC and DMAP in chloroform in the usual way, but only a 10% yield of bolaform **2a** was obtained after purification. A saturated analogue of **1** has been obtained in 8% yield according to a recent report.[10] Since the yield of the hemisynthetic route to these compounds was so disappointing, we decided to explore a total synthesis.

We decided to assemble a protected 1,2-diacylglycerol with the required acyl chains, proceed with the Glaser coupling of the acetylenes, and introduce the phosphocholine moiety in the last step using our previously developed methodology.[5] We reported earlier that a 1,2-diacyl-3-*O*-allyl-*sn*-glycerol is easily deprotected in two steps by isomerization of the allyl to the 1-propenyl ether, followed by hydrolysis of the enol ether with *N*-bromosuccinimide in moist tetrahydrofuran. The isomerically pure 1,2-diacyl-*sn*-glycerol is then further transformed into the corresponding phospholipid by a modified phosphite triester method. However, the use of the allyl protecting group prevented the incorporation of unsaturated fatty acids (e.g., linoleic acid) because the cis double bonds in the acyl chains did not survive the rhodium-catalyzed isomerization of the allyl ether.[11] We were therefore faced with the problem of finding a glycerol protecting group which could withstand the assembly of the bolaform, but could be removed without affecting the alkynes, under nonbasic conditions to avoid acyl migration.

Martin and Josey have described the use of a 4-methoxybenzyl ether (PMB group) in their synthesis of phospholipids, but they removed it before introducing unsaturated fatty acids.[12] Presumably they were unable to remove it efficiently without affecting the olefinic side chains. More recently, in the synthesis of the ubraculumins,[13] a PMB ether was used as protecting group. In the final step, dichlorodicyanoquinone oxidation of the PMB group produced the desired diacylglycerol in 29% yield. Several groups have reported the use of 3-*O*-benzyl-*sn*-glycerol derivatives as intermediates in the synthesis of various phospholipids[6,14] and diacylglycerols.[15] The benzyl ether can be removed by catalytic hydrogenation and also with dimethylboron bromide[16] (Me_2BBr) at −10 °C. When we attempted to deprotect 1,2-dilinoleoyl-3-*O*-benzyl glycerol with this reagent, the reaction would not go to completion and was accompanied by varying amounts of decomposition. We reasoned, however, that since the reaction proceeds by coordination to the ether oxygen, followed by displacement by bromide ion, the hydrolysis of the more electron-rich 4-methoxybenzyl (PMB) ether should proceed more rapidly and at lower temperature than for the unsubstituted benzyl group. We were concerned that the use of a Lewis acid could cause some acyl migration, but the use of low temperatures would help minimize this. In order to test the hypothesis, we treated 1,2-dilinoleoyl-3-*O*-(4-methoxybenzyl)-*sn*-glycerol (**14**) (vide infra) with 3 equiv of dimethylboron bromide at −78 °C in dichloromethane. After 5 min, the reaction was quenched by diluting with diethyl ether and washing with water until the

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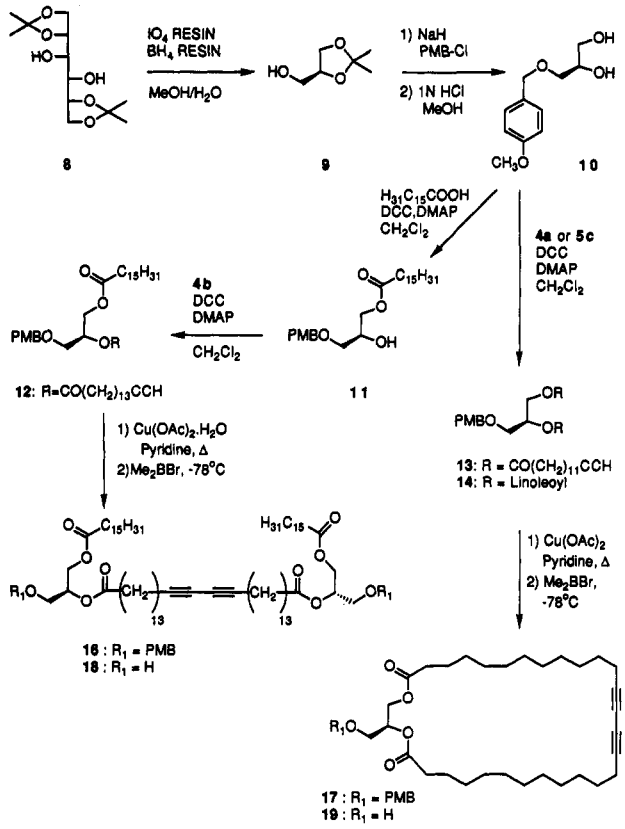
Scheme II



extracts were neutral. We obtained a quantitative yield of diacylglycerol without any detectable isomerization of the 1,4-diene portion of the linoleate chain. Moreover, no 1,3-diacylglycerol isomer was observed after workup in the absence of base.[17] Having established to our satisfaction that the alcohol function required for coupling with the dialkylphosphoramidite could be obtained in the presence of olefinic groups by the cleavage of a PMB ether without any 1,2-acyl migration, we set out to synthesize the bolaform and macrocyclic glycerol PMB ethers.

The starting material for the elaboration of our strategy was obtained by the following sequence: 1,2,5,6-diisopropylidene mannitol (Scheme II) was converted to 1,2-isopropylidene-*sn*-glycerol (**9**) in one step by treatment with a mixture of periodate and borohydride anion exchange resins in 9:1 methanol/water.[18] After filtration of the spent resins and removal of the solvents, the crude alcohol was alkylated with 4-methoxybenzyl chloride and the acetonide group hydrolyzed by the method of Manley et al.[19] As Martin and Josey first described, it was then possible to acylate diol **10** regioselectively at the primary hydroxyl. Treatment of **10** with 0.95 equiv of palmitic acid and 1.2 equiv DCC and DMAP in CH_2Cl_2 at 0 °C gave **11** in 65% yield after chromatography, along with a small amount of diester and 2-acyl isomer. When the reaction was carried out at room temperature, the ratio of primary to secondary isomer decreased and the proportion of diester increased. The second acylation of **11** with 15-hexadecynoic acid **4b** proceeded smoothly in the presence of excess DCC and DMAP in CH_2Cl_2 at room temperature to give a 99% yield of diacyl glycerol **12** after chromatography. It was previously shown that chain migration did not occur under these conditions during the acylation of the more labile lyso-PEs.[20] Diesters bearing identical acyl chains such as **13** and **14** could also be obtained in 77 and 85% yield, respectively, with 2.3 equiv of an acid (e.g., 15-hexadecynoic acid **4b** or linoleic acid **5c**) in the presence of excess DCC and DMAP in methylene chloride.

After a number of attempts with several catalysts, solvents, and temperatures,[8] a 68% yield of bolaform **16** was obtained by warming a solution of the acetylene monomer and 10 equiv of cupric acetate to 80 °C in freshly distilled pyridine in an inert atmosphere. Temperatures in excess of 80 °C, prolonged reaction times, and "old" pyridine were found to cause extensive decomposition of the product. At this point the bolaform could be easily separated from a small amount of unreactive diacylglycerol which was found to contain an ω-allenic chain at the *sn*-2 position.[9] This material, which arises in the zipper isomerization, is difficult to separate from the alkyne by recrystallization and is inseparable by chromatography at an earlier step. In an alternative experiment, the bolaform was assembled in 69% yield by the acylation of monoacylglycerol **11** with 15,17-diyne-1,32-dioic acid **5b** (0.5 equiv) in the presence of excess DCC and DMAP. The assembly of the diacylglycerol prior to the Glaser coupling is preferable due to the propensity of the light-sensitive diacids **5** to polymerize during their preparation.

The Glaser coupling to give the 32-membered ring was surprisingly easy when compared to the previously reported diacylation of glycerophosphatidylcholine.[10] The macrocyclic lactone **17** was obtained, in 50–60% yield after chromatography, by the slow addition (syringe pump over 3 h) of bis-acetylene **13** to a refluxing solution of 10 equiv of cupric acetate in dry pyridine. The protected glycerols **16** and **17** were then demethoxybenzylated by exposure to a 2-fold excess of dimethylboron bromide in anhydrous CH_2Cl_2 at −78 °C for 5 min. Solutions of bolaform **16** needed to be warmed slightly because of the low solubility of the starting material at that temperature. Workup in the absence of base gave a quantitative yield of the corresponding alcohols **18** and **19**, free of any isomerization products. The alcohols were used immediately in the next step without purification since the side products were not found to interfere with subsequent reactions. In fact, we have noticed a drastic lowering of the yield of phosphotriester and some formation of 1,3-isomer after chromatography of the alcohol.

The basis of our strategy for the assembly of phospholipids lies in the realization that the formation of P–O bonds can be accomplished under acidic conditions.[21] For example, the formation of internucleosidic linkages is routinely performed in vitro by the coupling of a nucleoside 3′-phosphoramidite and the 5′-hydroxyl of the growing DNA or RNA chain in the presence of tetrazole. The use of this type of methodology for the synthesis of phospholipids has so far been limited,[22] and examples described involve the *base*-catalyzed coupling of a glycerol and a

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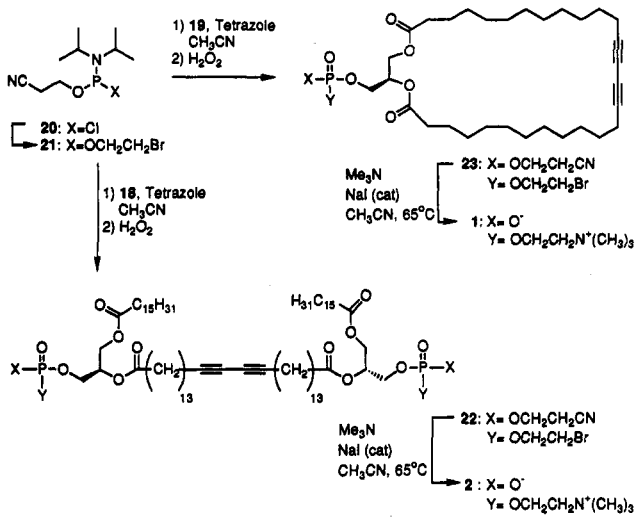
Scheme III



phosphonamidic chloride. A more commonly used approach to introduce the phosphocholine headgroup is based on the use of various phosphoryl chlorides in the presence of an amine base.[4,6,7] We became concerned about these methods when we noticed severe isomerization of 1,2-diacylglycerols during the course of a Hg^{II}-catalyzed hydrolysis of a 1-propenyl ether: simply washing the ethereal extracts with a bicarbonate solution was sufficient to produce a 1:1 mixture of 1,2- and 1,3-isomers.[5] Acyl migration was not apparent during extraction from slightly acidic solutions, however; nor was it as rapid in organic solvents containing acids. We therefore investigated the possibility of forming the glycerol phosphate ester in acidic conditions. The appropriately substituted phosphate triester could then be converted to a phosphatidylcholine by treatment with trimethylamine: the bromoethyl group is known to be easily converted with trimethylamine to the choline function,[23] and from previous work in this laboratory we knew that the cyanoethyl group could be removed by elimination with an amine base. Dialkylphosphoramidite **21** was made by the reaction of 2-bromoethanol with the commercially available chlorophosphite **20** and triethylamine in CH_2Cl_2 (Scheme III). The purification of **21** by Kugelrohr distillation in vacuo was attempted, but only intractable products were obtained. It was found that crude **21**, after precipitation of the amine hydrochloride, was sufficiently pure to be used immediately in the following step. The use of excess bromoethanol is not recommended because it leads to the formation of side products in subsequent transformations.

Deprotected glycerols **18** or **19**, obtained from Me_2BBr treatment of the corresponding PMB ethers, and phosphoramidite **21** (4 equiv per mol of **18**, 2 equiv per mol of **19**) were therefore treated with tetrazole in anhydrous acetonitrile. The intermediate phosphites were oxidized in situ with hydrogen peroxide giving phosphotriesters **22** and **23** in 65 and 81% yield, respectively, after purification, based on the protected precursors **16** and **17**. From a practical standpoint, it was found that the best yields of **22** and **23** were obtained when the preparation of **21**, the deprotection of **16** and **17**, and the phosphitylation of the resulting alcohols were performed on the same day.

Treatment of the phosphate triesters **22** and **23** with trimethylamine and a catalytic amount of sodium iodide in acetonitrile in a pressure bottle at 65 °C overnight simultaneously removed the cyanoethyl groups and displaced the bromides to give the product phosphatidylcholines **1** (85%, 69% from **17**) and **2** (56%, 35% from **16**) in excellent yield.

In summary, we have developed a highly efficient total synthesis of unsaturated and polymerizable phospholipids based on a novel method for cleavage of the 4-methoxybenzyl ether of a suitably substituted diacyl glycerol. The alcohol is transformed in high yield into its phosphocholine derivative using a three-step, two-pot protocol: acid-catalyzed phosphitylation, oxidation, and deprotection/substitution. Two previously unknown phospholipids were synthesized using this approach: the macrocycle **1** and the bolaform **2**. We are currently investigating the properties of these new compounds, their behavior at air/water interfaces, their polymerizability in the aggregated state, and their ability to serve as substrates for PLA_2. Results in these areas will be reported elsewhere.

Experimental Section

General Procedures. Chemicals were obtained from Aldrich Chemical Corporation and Farchan Ltd and were used without prior purification. Solvents used were of reagent grade and were distilled before use: THF from sodium benzophenone ketyl, CH_2Cl_2 from P_2O_5, and acetonitrile, pyridine, and triethylamine from calcium hydride. $CHCl_3$ was washed with water, dried with $CaCl_2$, distilled from P_2O_5, and stored in the dark. Reactions were performed under an inert atmosphere (N_2 or Ar) unless otherwise indicated. Thin-layer chromatography was done using Merck Kieselgel 60 F_{254} aluminum-backed plates and visualized by dipping in a solution of $(NH_4)_2MoO_4$ and Ce_2SO_4 in dilute H_2SO_4 and charring. Water was removed from solvent extracts by swirling over anhyd $MgSO_4$ and filtering. Chromatography was done on Merck silica gel 60 (230–400 mesh). Melting points were determined on a Gallenkamp Block and are uncorrected. NMR spectra were recorded using the residual ^1H or ^{13}C solvent peak as internal reference (e.g., 7.24 ppm for $CHCl_3$ and the $CDCl_3$ triplet at 77.00 ppm). Fast atom bombardment mass spectra were measured at the McGill Biomedical Mass Spectrometry Unit using *m*-nitrobenzyl alcohol (NBA) as the matrix with a Xenon gun ionization source (8 kV, 1 mA beam current). Chemical ionization mass spectra were obtained by direct inlet using NH_3 as ionization gas (5×10^{-4} Torr). Elemental analyses were performed at Guelph Chemical Laboratories Ltd.

13-Tetradecyn-1-ol (3a).[9a] A suspension of lithium wire (1.05 g, 150 mmol) in 75 mL of 1,3-diaminopropane (distilled under nitrogen from barium oxide and stored over 4 Å molecular sieve) was heated at 70 °C until the blue color discharged (2 h). The reaction mixture was cooled at rt, and potassium *tert*-butoxide (11.2 g, 100 mmol) was added. The resultant mixture was stirred for 30 min, and then 3-tetradecyn-1-ol (5.25 g, 25 mmol in 5 mL of diaminopropane) was injected via syringe. After 45 min, the mixture was carefully hydrolyzed with ice-cold H_2O, acidified with an aqueous solution of 10% HCl, and extracted with hexane (3 × 200 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. The crude product was chromatographed (CH_2Cl_2, then hexane/EtOAc (8:2)) and recrystallized at −18 °C (hexane) to yield the product (4.472 g, 75%, mp 37–40 °C (lit.[9a] mp 40–41°C)). TLC (hexane/EtOAc (8:2)): R_f 0.28. ^1H NMR (200 MHz, $CDCl_3$): δ 3.36 (t, 2 H, CH_2OH, J = 7 Hz), 2.20 (dt, 2 H, $C{\equiv}CCH_2$, J = 7, 4 Hz), 1.95 (t, 1 H, $HC{\equiv}C-$, J = 4 Hz), 1.6–1.2 (m, 20 H, CH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 84.8, 68.0, 63.0, 32.8, 29.6, 29.6, 29.4, 29.1, 28.7, 28.5, 25.7, 18.4. Anal. Calcd for $C_{14}H_{26}O$: C, 79.9; H, 12.5. Found: C, 79.7; H, 12.7.

15-Hexadecyn-1-ol (3b). The procedure for **3a** was followed using 7-hexadecyn-1-ol as starting material. The product was converted directly to **4b** by oxidation with Jones reagent as described below.

13-Tetradecyn-1-oic Acid (4a).[9b] To a solution of 13-tetradecyn-1-ol (**3a**, 3 g, 14.3 mmol) in 150 mL of acetone was added dropwise a solution of Jones' reagent until the characteristic orange color of the reagent persisted. 2-Propanol was added to neutralize

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the excess reagent. The chromium salts were filtered, the acetone was evaporated, and the residue was dissolved in EtOAc, washed three times with 0.01 N HCl, dried, and evaporated. The crude product was recrystallized in hexane at −18 °C to yield **4a** (2.614 g, 82%). TLC (hexane/EtOAc (1:1)): R_f 0.5. Mp 45–47 °C. ^{1}NMR (200 MHz, $CDCl_3$): δ 2.35 (t, 2 H, CH_2CO, J = 7 Hz), 2.20 (dt, 2 H, $C{\equiv}CCH_2$, J = 7, 4 Hz), 1.95 (t, 1 H, $HC{\equiv}C$, J = 4 Hz), 1.7–1.3 (m, 4 H, CH_2CH_2COO and $CH_2CH_2C{\equiv}C$), 1.25 (s, 14 H, CH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 179.6, 84.8, 68.0, 33.9, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 28.5, 24.7, 18.4. MS (CI): m/z 242 (M + NH_4^+, 100).

15-Hexadecyn-1-oic Acid (4b). The procedure for **4a** was followed. Mp 53–55 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (t, 2 H, CH_2CO, J = 7 Hz), 2.20 (dt, 2 H, $C{\equiv}CCH_2$, J = 7, 4 Hz), 1.95 (t, 1 H, $HC{\equiv}C$, J = 4 Hz), 1.7–1.3 (m, 4 H, CH_2CH_2COO and $CH_2CH_2C{\equiv}C$), 1.25 (s, 18 H, CH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 180.0, 84.8, 68.0, 34.0, 29.6, 29.5, 29.4, 29.2, 29.1, 29.0, 28.7, 28.5, 24.7, 18.4. MS (CI): m/z 270 (M + NH_4^+, 100).

13,15-Octacosadiyne-1,28-dioic Acid (5a). To a solution of $Cu(OAc)_2{\cdot}H_2O$ (10 g, 50 mmol) in 40 mL of freshly distilled pyridine and 20 mL of H_2O was added **4a** (800 mg, 3.56 mmol). The mixture was heated at 45 °C overnight, then a further 5 g of $Cu(OAc)_2{\cdot}H_2O$ was added and heating continued 24 h. After completion of the reaction, the mixture was acidified with aqueous 10% HCl to pH 2, extracted with $CHCl_3$/MeOH 2:1 (3 × 200 mL), and washed with pH 2 MeOH/H_2O (1:1). The organic phase was evaporated and dried by azeotropic distillation of toluene (3 × 25 mL). Trituration in EtOAc yielded, after filtration, white crystals of diacid **5a** (718 mg, 89%). The product is light sensitive and gradually turns blue. TLC (hexane/EtOAc (6:4)): R_f 0.24. Mp 105–108 °C. ^{1}H NMR (200 MHz, $CDCl_3/CD_3OD$ (2:1)): δ 2.20 (t, 4 H, CH_2CO, J = 7 Hz), 2.12 (t, 4 H, $C{\equiv}CCH_2$, J = 7 Hz), 1.6–1.3 (m, 8 H, CH_2CH_2COO, $CH_2CH_2C{\equiv}C$), 1.25 (s broad, 28 H, CH_2). ^{13}C NMR (75.4 MHz, DMSO): δ 174.4, 77.9, 65.3, 33.6, 28.9, 28.7, 28.5, 28.4, 28.2, 27.7, 24.5, 18.3. MS (CI): m/z 464 (M + NH_4^+, 100), 447 (M + H^+, 60.3), 429 (M + H^+ − H_2O, 27.0).

1-Myristoyl-2-(13-tetradecyn-1-oyl)-*sn*-glycero-3-phosphatidylcholine (7). The acid **4a** (336 mg, 1.5 mmoles) and 1-myristoyl-2-lyso-*sn*-glycero-3-phosphatidylcholine (**6**, 0.5 mmol, 240 mg) were dried by azeotropic distillation with toluene (3 × 10 mL) under reduced pressure at rt, then at 30 °C overnight (1 mmHg). The flask was then filled with argon, and 30 mL of dry $CHCl_3$ was injected. DCC (1.5 mmol, 309 mg) and DMAP (1.5 mmol; 183 mg) were added to the mixture. After 24 h, the mixture was acidified to pH 2 with aqueous 10% HCl, extracted with $CHCl_3$/MeOH (2:1) (3 × 150 mL), and washed with pH 2 MeOH/H_2O (1:1). The organic phase was evaporated, dried by azeotropic distillation of toluene, and chromatographed using $CHCl_3$/MeOH (9:1) to elute the unreacted fatty acid and urea then $CHCl_3$/MeOH/H_2O (70:26:4) to elute the phospholipid (308 mg; 91%). TLC ($CHCl_3$/MeOH/H_2O (70:26:4)): R_f 0.56. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.21 (m, 1 H, H 2), 4.5–4.1 (m, 4 H, H1, NCH_2CH_2OP, J = 7 Hz), 4.00 (t, 2 H, H3), 3.84 (m, 2 H, NCH_2CH_2OP), 3.40 (s, 9 H, $N(CH_3)_3$), 2.4–2.0 (m, 6 H, $CH_2C{\equiv}C$, C_1OCOCH_2, C_2OCOCH_2), 1.94 (t, 1 H, $C{\equiv}CH$, J = 4 Hz), 1.7–1.4 (m, 6 H, $C_1OCOCH_2CH_2$, $C_2OCOCH_2CH_2$, $CH_2CH_2C{\equiv}C$), 1.25 (s broad, 34 H, CH_2), 0.88 (t, 3 H, CH_3, J = 7 Hz).

2,2′-(13,15-Octacosadiyn-1,28-dioyl)bis(1-myristoyl-*sn*-glycero-3-phosphatidylcholine) (2a). Bolaform Phosphatidylcholine. Hemisynthesis. The diacid **5a** (446 mg, 1 mmol) and 1-myristoyl-2-lyso-*sn*-glycero-3-phosphatidylcholine (**6**, 2 mmoles, 934 mg) were dried by azeotropic distillation with toluene (3 × 10 mL) under reduced pressure at rt then at 30 °C overnight (1 mmHg). The flask was then filled with argon, and 30 mL of dry $CHCl_3$ was injected. DDC (2 mmol, 412 mg) and DMAP (2 mmol, 244 mg) were added to the mixture. After being stirred for 3 days, the mixture was acidified to pH 2 with aqueous 10% HCl, extracted with $CHCl_3$/MeOH (2:1) (3 × 200 mL), and washed with pH2 MeOH/H_2O (1:1). The organic phase was evaporated, dried by azeotropic distillation of toluene, and chromatographed using $CHCl_3$/MeOH/H_2O (70:26:4) to elute the unreacted fatty diacid, dicyclohexylurea, and monocoupled phospholipid then $CHCl_3$/MeOH/H_2O (40:50:10) to elute excess lysophospholipid and then the bolaform phospholipid **2a** (136 mg; 10%). TLC ($CHCl_3$/MeOH/H_2O (70:26:4)): R_f 0.08. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.21 (m, 2 H, H_2), 4.5–4.1 (m, 8 H, H1, $POCH_2CH_2N$), 4.00 (t, 4 H, H_3, J = 7 Hz), 3.84 (m, 4 H, $POCH_2CH_2N$), 3.40 (s, 18 H, $N(CH_3)_3$), 2.2–2.0 (m, 12 H, $CH_2C{\equiv}C$, C_1OCOCH_2, C_2OCOCH_2), 1.5–1.3 (m, 12 H, $C_1OCOCH_2CH_2$, $C_2OCOCH_2CH_2$, $CH_2CH_2C{\equiv}C$), 1.25 (s broad, 68 H, CH_2), 0.88 (t, 6 H, CH_3, J = 7 Hz). FAB-MS (NBA): m/z 1346 (M + H^+), 897, 469.

3-(4-Methoxybenzyl)-*sn*-glycerol (10). A solution of 3.00 g (12 mmol) of 1,2:5,6-di-*O*-isopropylidene-D-mannitol **8** in 10 mL of MeOH was added to a suspension of 36 mL of Amberlite A27 borohydride form and 40 mL of Amberlite A27 periodate form in 150 mL of MeOH/M_2O (9:1). After being stirred for 2 h, the starting material had been consumed (GC monitoring), and the spent resins were filtered off. The solvent was evaporated under reduced pressure, 100 mL of brine was added, and the emulsion was extracted with CH_2Cl_2 (2 × 150 mL), dried, and evaporated. Crude isopropylidene glycerol **9** was azeotroped twice with toluene, dissolved in anhyd THF (10 mL), and added dropwise to a suspension of sodium hydride (0.80 g, 80% dispersion in mineral oil, 26 mmol) in 120 mL of THF. After the mixture was stirred for 45 min, 4.07 g (3.52 mL, 26 mmol) of 4-methoxybenzyl chloride was added in two portions, and stirring continued for 16 h. After the careful addition of 10 mL of H_2O, the solvent was stripped off and the product was extracted with EtOAc (3 × 100 mL), and washed with portions of 0.05 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine. The combined organic layers were dried and evaporated. The product was redissolved in 15 mL of MeOH and 10 mL of 1 N HCl and stirred for 1 h. After extraction with EtOAc and removal of the solvent, the residual oil was purified by flash chromatography using 2% MeOH in $CHCl_3$ as eluant. A clear oil which solidified on standing was obtained (3.04 g, 14.3 mmol, mp 40–41 °C) in 60% yield. TLC (hexane/EtOAc (3:1)): R_f 0.20. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 159.4, 129.7, 129.4, 113.9, 73.2, 71.5, 70.5, 64.1, 55.3. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.05; H, 8.01.

1-Palmitoyl-3-(4-methoxybenzyl)-*sn*-glycerol (11). To a solution of 1.013 g (4.78 mmol) of diol **10** and 1.18 g (4.6 mmol) of palmitic acid in 35 mL of dry CH_2Cl_2 at 0 °C was added dropwise a solution of 1.14 g (5.5 mmol) of DCC and 0.60 g (5.5 mmol) of DMAP in 15 mL of dry CH_2Cl_2. The solution was stirred at 0 °C for 16 h and filtered, the solvent removed, and the residue purified by flash chromatography with 1:3 EtOAc/hexane. Pure product was isolated as a white solid (1.40 g, 3.1 mmol, 65%, mp 40–41 °C, R_f 0.33), along with 15% of a mixture of product and its more polar 2-*O*-palmitoyl isomer (R_f 0.25). This mixture could be equilibrated to a 5:1 mixture of primary to secondary esters by refluxing in toluene in the presence of triethylamine. TLC (hexane/EtOAc (3:1)): R_f 0.33. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24 (d, 2 H, ArH, J = 8.6 Hz), 6.87 (d, 2 H, ArH, J = 8.6 Hz), 4.48 (s, 2 H, $ArCH_2$), 4.14 (m, 2 H, H_1), 4.03 (m, 1 H, H_2), 3.80 (s, 3 H, $ArOCH_3$), 3.48 (m, 2 H, H_3), 2.31 (t, 2 H, $OCOCH_2$, J = 7.8 Hz), 1.58 (m, 2 H, $OCOCH_2CH_2$), 1.24 (s, 26 H, CH_2), 0.87 (t, 3 H, CH_3, J = 6.6 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 174.0, 159.4, 129.8, 129.5, 113.9, 73.2, 70.6, 68.8, 65.4, 55.2, 35.2, 32.0, 29.7, 29.5, 29.4, 29.3, 29.2, 26.0, 22.7, 14.2. MS (CI): m/z 468 (M + NH_4^+, 4.5), 313 (0.31), 121 (100). Anal. Calcd for $C_{27}H_{46}O_5$: C, 71.96; H, 10.29. Found: C, 71.65; H, 10.46.

1-Palmitoyl-2-(15-hexadecyn-1-oyl)-3-(4-methoxybenzyl)-*sn*-glycerol (12). A solution of DCC (0.250 g, 1.2 mmol) and DMAP (0.060 g, 0.5 mmol) in 5 mL of dry CH_2Cl_2 was added to a solution of acid **4b** (0.255 g, 1.0 mmol) and **11** (0.410 g, 0.91 mmol) in 5 mL of CH_2Cl_2 at rt. Stirring was continued for 5 h until the starting material had disappeared. The solution was filtered and the solvent removed. Flash chromatography of the residue (hexane/EtOAc (9:1)) gave 0.617 g (99%) of the product as a waxy solid. TLC (hexane/EtOAc (3:1)): R_f 0.78. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22 (d, 2 H, ArH, J = 8.6 Hz), 6.86 (d, 2 H, ArH, J = 8.6 Hz), 5.21 (ddd, 1 H, H_2, J_{23} = 5.2 Hz, J_{12} = 3.7, 6.5 Hz), 4.46 (ABq, 2 H, $ArCH_2$), 4.32 (dd, 1 H, H_{1a}, J_{ab} = 11.8 Hz, J_{12} = 3.7 Hz), 4.17 (dd, 1 H, H_{1b}, J_{ab} = 11.8 Hz, J_{12} = 6.5 Hz), 3.80 (s, 3 H, $ArOCH_3$), 3.54 (d, 2 H, H_3, J = 5.2 Hz), 2.24 (m 4 H, C_1OCOCH_2, C_2OCOCH_2), 2.17 (dt, 2 H, $CH_2C{\equiv}CH$, J = 2.7, 7.0 Hz), 1.93 (t, 1 H, $CH_2C{\equiv}CH$, J = 2.7 Hz), 1.8–1.4 (m, 6 H, $C_1OCOCH_2CH_2$, $C_2OCOCH_2CH_2$, $CH_2CH_2C{\equiv}C$), 1.25 (s, 42 H, CH_2), 0.87 (t, 3 H, CH_3, J = 6.7 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.4, 173.1, 159.2, 129.7, 129.2, 113.8, 72.9, 70.0, 68.0, 67.8, 62.6, 55.2, 34.3, 34.1, 31.9, 29.7, 29.6, 29.4, 29.3, 29.2, 29.1, 28.7, 28.4, 24.9, 23.8, 22.6, 18.3, 14.1. FABMS (NBA): m/z 685 (M + H^+,

4.9), 548 (50), 313 (48), 121 (100). Anal. Calcd for $C_{43}H_{72}O_6$: C, 75.17; H, 10.86. Found: C, 74.95; H, 10.87.

1,2-Di-13-tetradecyn-1-oyl-3-(4-methoxybenzyl)-*sn*-glycerol (13). DCC (0.94 g, 4.6 mmol) and DMAP (0.52 g, 4.3 mmol) in 5 mL of dry CH_2Cl_2 were added to a solution of diol **10** (0.40 g, 1.9 mmol) and acid **4a** (0.965 g, 4.3 mmol) in 15 mL of CH_2Cl_2 at rt in an inert atmosphere. After 2 h the precipitate was filtered, the solvent evaporated, and the residue purified by flash chromatography to give 0.917 g (1.47 mmol, 77%) of **13** as a waxy solid. TLC (hexane/EtOAc (9:1)): R_f 0.34. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22 (d, 2 H, ArH, J = 8.6 Hz), 6.86 (d, 2 H, ArH, J = 8.6 Hz), 5.21 (m, 1 H, H_2, J_{23} = 5.1 Hz, J_{1a2} = 3.8 Hz, J_{1b2} = 6.4 Hz), 4.46 (ABq, 2 H, ArCH2), 4.31 (q, 1 H, H_{1a}, J_{ab} = 11.9 Hz, J_{1a2} = 3.8 Hz), 4.17 (q, 1 H, H_{1b}, J_{ab} = 11.9 Hz, J_{1b2} = 6.4 Hz), 3.78 (s, 3 H, $ArOCH_3$), 3.54 (d, 2 H, H_3, J_{23} = 5.1 Hz), 2.29 (m, 4 H, C_1OCOCH_2, C_2OCOCH_2), 2.17 (dt, 4 H, CH_2CCH, ^3J = 6.8 Hz, ^4J = 2.7 Hz), 1.93 (t, 2 H, CH_2CCH, ^4J = 2.7 Hz), 1.8–1.2 (36 H, CH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.4, 173.1, 159.3, 129.7, 129.3, 113.8, 84.8, 72.9, 70.0, 68.0, 67.9, 62.7, 55.2, 34.3, 34.1, 29.6, 29.5, 29.4, 29.3, 29.1, 28.9, 28.7, 28.6, 28.5, 24.9, 24.8, 18.4. MS (CI): m/z 642 (M + NH_4^+, 100), 625 (M + H^+, 42). HRMS (CI): calcd for $C_{39}H_{61}O_6$ 625.44681, found 625.44651. Anal. Calcd for $C_{39}H_{60}O_6$: C, 74.96; H, 9.68. Found: C, 74.82; H, 9.96.

1,2-Dilinoleoyl-3-(4-methoxybenzyl)-*sn*-glycerol (14). The same procedure as for **13** was followed using linoleic acid **5c** and gave 85% yield of product.

2,2′-(15,17-Dotriacontadiyne-1,32-dioyl)bis(1-palmitoyl-3-(4-methoxybenzyl)-*sn*-glycerol) (16). PMB-Bolaform. Protected diacylglycerol **12** (0.446 g, 0.65 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (1.30 g, 6.5 mmol) were dissolved in 5 mL of freshly distilled pyridine under argon. The blue solution was warmed to 80 °C in an oil bath for 2 h. The now green solution was acidified to pH 2 with 1 N HCl. The aqueous layer was extracted with EtOAc (3 × 100 mL), washed with 1% HCl, saturated aqueous $NaHCO_3$, and brine, dried, and evaporated. Flash chromatography using 10% EtOAc in hexanes as eluant gave 0.297 g (0.22 mmol, 68%) of product as a white waxy solid. TLC (hexane/EtOAc (3:1)): R_f 0.66. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22 (d, 2 H, ArH, J = 8.6 Hz), 6.85 (d, 2 H, ArH, J = 8.6 Hz), 5.21 (m, 2 H, H_2, J_{23} = 5.2 Hz, J_{1a2} = 3.7 Hz, J_{1b2} = 6.6 Hz), 4.45 (s, 4 H, $ArCH_2$), 4.31 (dd, 2 H, H_{1a}, J_{ab} = 11.8 Hz, J_{1a2} = 3.7 Hz), 4.16 (dd, 2 H, H_{1b}, J_{ab} = 11.8 Hz, J_{1b2} = 6.6 Hz), 3.79 (s, 6 H, $ArOCH_3$), 3.54 (d, 4 H, H_3, J_{23} = 5.2 Hz), 2.4–2.1 (m, 12 H, C_1OCOCH_2, C_2OCOCH_2, $CH_2C{\equiv}C$), 1.8–1.4 (m, 12 H, $C_1OCOCH_2CH_2$, $C_2OCOCH_2CH_2$, $CH_2CH_2C{\equiv}C$), 1.24 (s, 96 H, CH_2), 0.87 (t, 6 H, CH3, J = 6.7 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.3, 173.0, 159.2, 129.7, 129.2, 113.7, 72.9, 69.4, 67.8, 65.2, 62.6, 55.2, 34.3, 34.2, 31.9, 29.6, 29.4, 29.3, 29.2, 29.1, 28.8, 28.3, 24.9, 24.8, 22.6, 19.2, 14.1. FABMS (NBA): m/z 1369 (M + H^+, 0.6), 1367 (0.7), 1230 (0.9), 1110 (2.3), 313 (11.4).

2,2′-(15,17-Dotriacontadiyne-1,32-dioyl)bis(1-palmitoyl-*sn*-glycerol) (18). Bolaform Alcohol. A solution of bis-PMB ether **16** (0.567 g, 0.414 mmol) in 5 mL of dry CH_2Cl_2 was cooled to −78 °C under Ar. Dimethylboron bromide (0.150 mL, 1.5 mmol), was added neat and the cooling bath removed. As soon as the suspension of bolaform dissolved (5 min), it was quenched with 50 mL of diethyl ether. The ether layer was washed with distilled H_2O until the washings were neutral (4 × 50 mL). After drying and evaporation under reduced pressure, the crude bis-alcohol **18** was used immediately without purification in the phosphitylation reaction. TLC (hexane/EtOAc (1:1)): R_f 0.55.

1,2-(13,15-Octacosadiyne-1,28-dioyl)-3-(4-methoxybenzyl)-*sn*-glycerol (17). PMB-Macrocycle. A solution of diacylglycerol **13** (0.55 g, 0.88 mmol) in 10 mL of freshly distilled pyridine was added over a period of 4 h via syringe pump to a gently refluxing solution of $Cu(OAc)_2{\cdot}H_2O$ in 60 mL of pyridine. Heating was continued 1 h after the addition was complete, at which time most of the pyridine was distilled in vacuo at rt. The residue was diluted with H_2O (50 mL), acidified to pH 2 with 1 N HCl, and extracted with EtOAc (3 × 100 mL). The organic layers were washed with successive portions of 0.05 N HCl, saturated $NaHCO_3$, and brine, and the combined organic phases were dried and evaporated. After flash chromatography (hexanes/EtOAc (9:1)) 0.30 g (0.48 mmol, 54%) cyclic product was obtained. TLC (hexane/EtOAc (9:1)): R_f 0.29. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22 (d, 2 H, ArH, J = 8.7 Hz), 6.86 (d, 2 H, ArH, J = 8.7 Hz), 5.21 (m, 1 H, H_2, J_{12} = 3.7, 6.6 Hz, J_{23} = 5.3 Hz), 4.46 (s, 2 H, $ArCH_2$), 4.32 (dd, 1 H, H_{1a}, J_{ab} = 11.8 Hz, J_{12} = 3.7 Hz), 4.16 (dd, 1 H, H_{1b}, J_{ab} = 11.8 Hz, J_{12} = 6.6 Hz), 3.79 (s, 3 H, OCH_3), 3.54 (d, 2 H, H_3, J_{23} = 5.3 Hz), 2.4–2.1 (m, 8 H, C_1OCOCH_2, C_2OCOCH_2, $CH_2C{\equiv}CC{\equiv}CCH_2$), 1.8–1.2 (m, 36 H, CH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.3, 173.0, 159.2, 129.7, 129.2, 113.8, 72.9, 70.0, 67.9, 65.5, 62.8, 55.2, 34.3, 34.1, 29.3, 29.2, 29.1, 29.0, 28.8, 28.7, 28.3, 28.2, 27.8, 25.8, 25.7, 19.0. MS (CI): m/z 640 (M + NH_4^+, 100), 623 (M + H^+, 69%). HRMS (CI): calcd for $C_{39}H_{59}O_6$ 623.43116, found 623.43089.

1,2-(13,15-Octacosadiyne-1,28-dioyl)-*sn*-glycerol (19). Macrocycle Glycerol. Dimethylboron bromide (0.068 mL, 0.7 mmol) was added to a solution of PMB ether **17** (0.30 g, 0.48 mmol) in 5 mL of anhyd CH_2Cl_2 at −78 °C. After 5 min, the solution was quenched with 100 mL of diethyl ether and washed with distilled H_2O until neutral. The organic phase was dried, the solvent removed in vacuo, and the product used immediately in the next step. TLC (hexane/EtOAc (3:1)): R_f 0.28.

2-Cyanoethyl 2-Bromoethyl *N*,*N*-Diisopropylamino Phosphite (21). To a solution of 0.390 mL (1.75 mmol) of 2-cyanoethyl *N*,*N*-diisopropylamino chlorophosphite (**20**) in 10 mL of dry CH_2Cl_2 was added dropwise 0.25 mL (1.78 mmol) of triethylamine, followed by 0.125 mL (1.75 mmol) of 2-bromoethanol at rt. Stirring was continued for 1 h and the solvent pumped off at low temperature. The residue was redissolved in diethyl ether and filtered under an inert atmosphere to remove the amine hydrochloride. Removal of the ether at low temperature gave the crude product, which was used in the next step directly.

2,2′-(15,17-Dotriacontadiyne-1,32-dioyl)bis[1-palmitoyl-*sn*-glycero-3-(2-bromoethyl 3-(2-bromoethyl 2-cyanoethyl phosphate)]. (22). Bolaform Bis(phosphate triester). The crude bolaform diol **18** (0.414 mmol) was dissolved in 10 mL of 1:1 acetonitrile/THF, and a solution of freshly prepared phosphoramidite **21** (1.75 mmol) in 5 mL of THF was added. Solid tetrazole (0.14 g, 2.0 mmol) was then added and the solution stirred for 1 h until the starting material had disappeared. The solution was treated with 0.25 mL of 30% H_2O_2 (8.2 mmol) and stirring continued for a further 1 h. When the oxidation was judged complete by TLC, 100 mL of H_2O was added, and the solution was extracted with CH_2Cl_2 (2 × 200 mL), washed with 0.05 N HCl, saturated $NaHCO_3$, and brine, and dried. Evaporation of the solvent and flash chromatography of the residue using EtOAc/hexane (3:1) gave 0.432 g (2.7 mmol, 65%) of the bis-phosphate triester as a hygroscopic gum. TLC (EtOAc): R_f 0.60. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.25 (m, 2 H, H_2), 4.5–4.1 (m, 16 H, $POCH_2CH_2Br$, $POCH_2CH_2CN$, H_3, H_1), 3.55 (t, 4 H, CH_2Br), 2.87 (t, 4 H, CH_2CN), 2.4–2.2 (m, 12 H, C_1OCOCH_2, C_2OCOCH_2, $CH_2C{\equiv}C$), 1.7–1.5 (m, 12 H, $C_1OCOCH_2CH_2$, $C_2OCOCH_2CH_2$, $CH_2CH_2C{\equiv}C$), 1.30 (s, 96 H, CH_2), 0.85 (t, 6 H, CH_3, J = 6.6 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.2, 172.8, 116.2, 69.2 ($^3J_{PC}$ = 7 Hz), 67.4 ($^2J_{PC}$ = 6 Hz), 66.1 ($^2J_{PC}$ = 6 Hz), 65.2, 62.3 ($^2J_{PC}$ = 5 Hz), 61.4, 34.1, 34.0, 31.9, 30.4, 30.3, 29.6, 29.5, 29.4, 29.3, 29.1, 28.9, 28.6, 28.5, 28.4, 24.8, 22.7, 22.5, 22.4, 19.7 ($^4J_{PC}$ = 7 Hz), 19.2, 14.1.

2,2′-(15,17-Dotriacontadiyne-1,32-dioyl)bis(1-palmitoyl-*sn*-glycero-3-phosphatidylcholine) (2). Bolaform Phosphatidylcholine. Trimethylamine[24] (10 mL) was condensed in a pressure vessel at −78 °C, and a solution of phosphate triester **22** (0.364 g, 0.225 mmol) in 5 mL of toluene was added followed by sodium iodide (0.041 g, 0.27 mmol) in 6 mL of dry acetonitrile. The bottle was sealed and the solution stirred at 65 °C overnight. The excess trimethylamine was distilled off, the solution was acidified to pH 2 with 1 N HCl and extracted with 2:1 $CHCl_3$/MeOH (3 × 200 mL). The combined organic layers were washed once with pH 2 MeOH/H_2O (1:1) (200 mL) and evaporated, and the H_2O was removed from the residue by azeotropic distillation with toluene under reduced pressure. The product was purified by flash chromatography with $CHCl_3$/MeOH/H_2O (65:25:4 then 65:35:6), yielding 0.185 g (0.127 mmol, 56%) of bolaform **2** as a hygroscopic tan solid, from which the last traces of water were impossible to remove. Overall yield from **16** was 36%. TLC ($CHCl_3$/MeOH/H_2O (65:25:4)): R_f 0.08. ^{1}H NMR (200 MHz,

(24) **Caution! Stench!** Although no problems were ever encountered, adequate precautions should be used in the handling of this gas. Venting into a trap containing a large volume of dilute acid is recommended.

$CDCl_3/CD_3OD$ (2:1)): δ 5.00 (m, 2 H, H_2), 4.20 (dd, 2 H, H_{1a}), 4.02 (m, 4 H, $POCH_2CH_2N$), 3.90 (dd, 2 H, H_{1b}), 3.78 (t, 4 H, H_3), 3.38 (t, 4 H, $POCH_2CH_2N$), 3.00 (s, 18 H, $N(CH_3)_3$), 2.2–1.9 (m, 12 H, C_1OCOCH_2, C_2OCOCH_2, $CH_2C{\equiv}C$), 1.5–1.2 (m, 12 H, $C_1OCOCH_2CH_2$, $C_2OCOCH_2CH_2$, $CH_2CH_2C{\equiv}C$), 1.05 (s, 96 H, CH_2), 0.68 (t, 6 H, CH3). ^{13}C NMR (75.4 MHz, $CDCl_3/CD_3OD$ (2:1)): δ 173.6, 173.2, 70.0 ($^3J_{PC}$ = 9 Hz), 66.0 ($^3J_{PC}$ = 6 Hz), 65.2, 63.2 ($^2J_{PC}$ = 4 Hz), 62.3, 58.7 ($^2J_{PC}$ = 5 Hz), 53.6, 33.8, 33.7, 31.5, 29.2, 29.1, 28.9, 28.8, 28.7, 28.4, 28.2, 28.1, 28.0, 27.9, 27.8, 24.5, 24.4, 22.2, 18.7, 13.5. FABMS (NBA): m/z 1458 (M + H^+, 1.3), 224 (100). Anal. Calcd for $C_{80}H_{150}N_2O_{16}P_2$: C, 65.90; H, 10.37; N, 1.92; P, 4.25. Found:[25] C, 58.28; H, 10.33; N, 1.60; P, 4.23.

1,2-(13,15-Octacosadiyne-1,28-dioyl)-*sn*-glycero-3-(2-bromoethyl 2-cyanoethyl phosphate) (23). Macrocycle Phosphate Triester. To a solution of diacylglycerol **19** (0.48 mmol) and dialkyl phosphoramidite **21** (1.0 mmol) in 5 mL of anhyd acetonitrile at rt was added a solution of tetrazole (0.105 g, 1.5 mmol) in 5 mL of acetonitrile. After 15 min, TLC showed complete disappearance of the starting material. Aqueous hydrogen peroxide (0.2 mL 30% H_2O_2, 6.5 mmol) was then added and stirring continued for 1 h. After completion of the oxidation, 100 mL H_2O was added, and the solution was extracted with CH_2Cl_2 (2 × 200 mL), washed with 0.05 N HCl, saturated $NaHCO_3$, and brine, and dried. Evaporation of the solvent and flash chromatography of the residue using EtOAc/hexane (3:1) gave 0.288 g (0.39 mmol, 81%) phosphate triester as a hygroscopic white gum. TLC (hexane/EtOAc (1:1)): R_f 0.14. ^1H NMR (200 MHz, $CDCl_3$): δ 5.28 (m, 1 H, H_2), 4.5–4.0 (m, 8 H, $2H_1$, $2H_3$, $POCH_2CH_2Br$, $POCH_2CH_2CN$), 3.55 (t, 2 H, CH_2Br, J = 6.0 Hz), 2.78 (t, 2 H, CH_2CN, J = 6.0 Hz), 2.4–2.2 (m, 8 H, C_1OCOCH_2, C_2OCOCH_2, $CH_2C{\equiv}CC{\equiv}CCH_2$), 1.7–1.2 (m, 36 H, CH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.2, 172.8, 116.2, 69.2 ($^3J_{PC}$ = 8 Hz), 67.4 ($^2J_{PC}$ = 6 Hz), 66.1 ($^2J_{PC}$ = 6 Hz), 65.5, 62.3 ($^2J_{PC}$ = 5 Hz), 61.6, 34.2, 34.0, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.8, 28.4, 28.3, 27.9, 24.8, 19.7 ($^3J_{PC}$ = 7 Hz), 19.1. FABMS (NBA): m/z 745 (M + H^+, 3.6), 743 (M + H^+, 4.0), 486 (100). Anal. Calcd for $C_{36}H_{57}NO_8PBr$: C, 58.22; H, 7.74; N, 1.89; P, 4.17. Found:[25] C, 57.68; H, 7.75; N, 1.67; P, 4.24.

(25) No accurate microanalytic results could be obtained for these compounds due to their hygroscopicity.

1,2-(13,15-Octacosadiyne-1,28-dioyl)-*sn*-glycero-3-phosphatidylcholine (1). Macrocycle Phosphatidylcholine. A solution of phosphate triester **23** (288 mg, 0.39 mmol) in 5 mL of dry acetonitrile was added to 10 mL of anhyd trimethylamine[24] at −78 °C in a pressure bottle followed by a solution of sodium iodide (0.080 g, 0.53 mmol) in 5 mL of acetonitrile. The bottle was sealed and the solution stirred at 65 °C overnight. The excess trimethylamine was distilled off, and the solution was acidified to pH 2 with 1 N HCl and extracted with 2:1 $CHCl_3$/MeOH (3 × 200 mL). The combined organic layers were washed once with pH 2 MeOH/H_2O (1:1) (200 mL) and evaporated, and the H_2O was removed from the residue by azeotropic distillation with toluene under reduced pressure. The product was purified by flash chromatography with $CHCl_3$/MeOH/H_2O (65:25:4), giving 0.221 g (0.33 mmol, 85%) of the title product as a hygroscopic solid from which the last traces of water were impossible to remove. The overall yield from **17** was 69%. TLC ($CHCl_3$/MeOH/H_2O (65:25:4)): R_f 0.5. ^1H NMR (200 MHz, $CDCl_3$): δ 5.22 (m, 1 H, H_2), 4.5–4.2 (br m, 3 H, H_{1a}, $POCH_2$), 4.12 (br dd, 1 H, H_{1b}), 3.93 (br t, 2 H, H_3), 3.80 (br s, 2 H, CH_2N), 3.35 (s, 9 H, $N(CH_3)_3$), 2.4–2.2 (m, 8 H, C_1OCOCH_2, C_2OCOCH_2, $CH_2C{\equiv}CC{\equiv}CCH_2$), 1.7–1.2 (m, 36 H, CH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.5, 173.2, 70.5 ($^3J_{PC}$ = 8 Hz), 66.3, 65.6, 63.4 ($^2J_{PC}$ = 5 Hz), 63.0, 59.3 ($^2J_{PC}$ = 4 Hz), 54.4, 34.4, 34.2, 29.5, 29.3, 29.1, 29.0, 28.9, 28.8, 28.7, 28.3, 28.2, 27.9, 27.8, 24.9, 24.8, 19.1, 19.0. FABMS (NBA): m/z 669 (M + H^+, 35.6), 184 (100). Anal. Calcd for $C_{36}H_{62}NO_8P$: C, 64.74; H, 9.36; N, 2.10; P, 4.64. Found:[25] C, 62.80; H, 9.47; N, 2.18; P, 5.41.

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Supplementary Material Available: ^1H and ^{13}C spectra for compounds **1**, **2**, **16**, **17**, and **23** (10 pages). Ordering information is given on any current masthead page.