Novel Bioactive Phospholipids: Practical Total Syntheses of Products from the Oxidation of Arachidonic and Linoleic Esters of 2-Lysophosphatidylcholine[1]

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Total syntheses of nine novel phospholipids were accomplished to facilitate the identification and biological testing of compounds that are generated upon oxidative cleavage of arachidonate and linoleate esters of 2-lysophosphatidylcholine, the two most abundant polyunsaturated phospholipids in low-density lipoprotein. An efficient general synthesis exploiting 2-lithiofuran as a 4-oxo-2-butenoyl carbanion equivalent provided phospholipids containing γ-keto-α,β-unsaturated carbonyl functional arrays. By exploiting facile cis−trans isomerizations, two commercially available cis alkenes, (2*Z*)-2-butene-1,4-diol and 2,5-dihydrofuran, could be employed as starting materials for preparing the Horner−Wadsworth−Emmons reagent 4-(diethoxyphosphoryl)-2*E*-butenal, a valuable building block for the synthesis of 2,4-dienals. The reagent was exploited in a total synthesis of 13-oxotridec-9*E*,11*E*-dienoic acid, confirming the identity of this product that is generated upon autoxidation of linoleic acid and by decomposition of 13-hydroperoxy-9,11-octadecadienoate (13-HPODE), especially in the presence of redox active transition metal ions, cytochrome p-450, or hydroperoxide lyase.

Introduction

Oxidation of the arachidonic acid ester of 2-lysophosphatidylcholine (AA-PC) generates the 5-oxovaleric acid ester of 2-lysoPC (OV-PC), a biologically active oxidized phospholipid (oxPL). We assisted collaborators at UCLA in confirming the structure of OV-PC and facilitated exploration of the biological activities of this oxPL by providing samples through a convenient and unambiguous total synthesis.[2] A minor biologically active product generated during the synthesis was isolated and characterized as the monoester of glutaric acid with 2-lysoPC (G-PC). G-PC[2] is also generated upon oxidation of AA-PC (Scheme 1).

These studies piqued our interest in oxPL and their biological activities. They inspired a mechanism-based hypothesis (Scheme 1) that oxidation of AA-PC generates the 5-hydroxy-8-oxo-6-octenoic acid ester of 2-lysoPC (HOOA-PC) and oxidation of the linoleic acid ester of 2-lysoPC (LA-PC) generates the 9-hydroxy-12-oxo-10-dodecenoic acid ester of 2-lysoPC (HODA-PC). We developed immunoassays to detect protein adducts derived from HOOA-PC and HODA-PC and used them to obtain evidence for the formation of such γ-hydroxy-α,β-unsaturated aldehydic oxPL in vivo.[3] We also devised total syntheses of HOOA-PC and HODA-PC.[4] The synthetic HOOA-PC facilitated LC−MS experiments that confirmed the presence of this oxPL in oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine and demonstrated that HOOA-PC dose-dependently activates endothelial cells to bind monocytes and inhibits lipopolysaccharide-induced E-selectin expression by human aortic endothelial cells.[5]

We reported a total synthesis of the 9-hydroxy-13-oxotridec-11-enoic acid ester of 2-lysoPC (HOT-PC), a homologous δ-hydroxy-α,β-unsaturated aldehydic oxPL.[4] A mechanism suggested previously for generation of the corresponding free fatty acid from linoleic acid[6] leads to the expectation that HOT-PC is produced (Scheme 2) through hydration of the 13-oxo-9,11-tridecadienoic acid ester of 2-lysoPC (OTDE-PC, **6**).

Recently, our mechanistic hypothesis-driven quest to identify novel oxPL converged with an exploratory effort to isolate and identify biologically active components in the product mixture generated by myeloperoxidase-mediated oxidation of phospholipids. Guided by a bioassay that will be reported elsewhere,[7] we fractionated the oxidized lipids by reversed-phase HPLC and confirmed by LC−MS that HODA-PC and HOOA-PC are bioactive components in the oxPL mixtures generated by oxidation of LA-PC and AA-PC, respectively. Other more and less polar bioactive phospholipids were also detected. In view of the confirmed biological activities of the hydroxy aldehydes HODA-PC and HOOA-PC, we postulated that the less polar oxPL are keto aldehydes (Scheme 1) KOOA-PC (**3a**) and KODA-PC (**3b**). These might arise through

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(1) Total Synthesis of Oxidized Phospholipids. 4. For previous papers in this series, see refs 2, 4, and 10.

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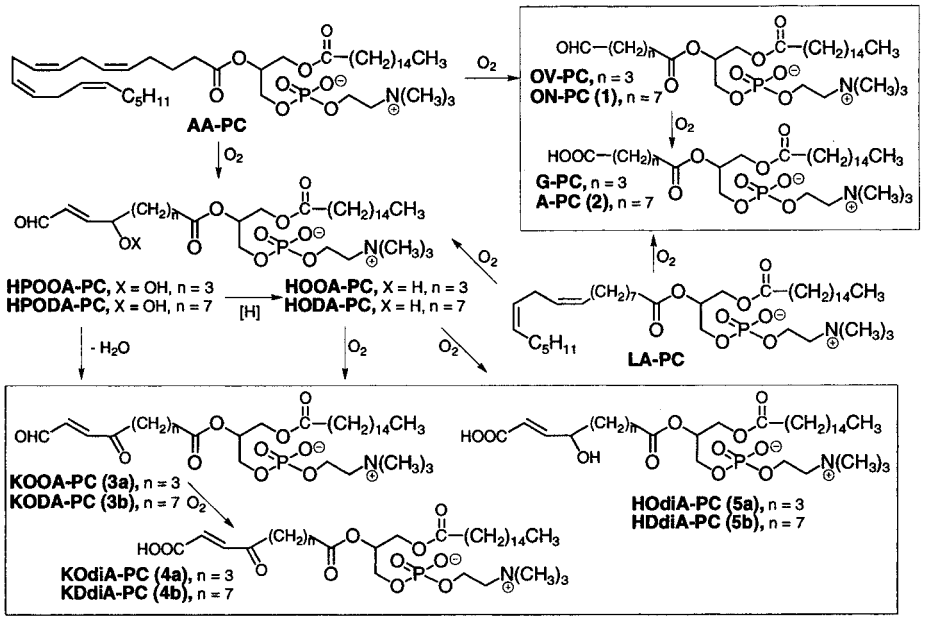
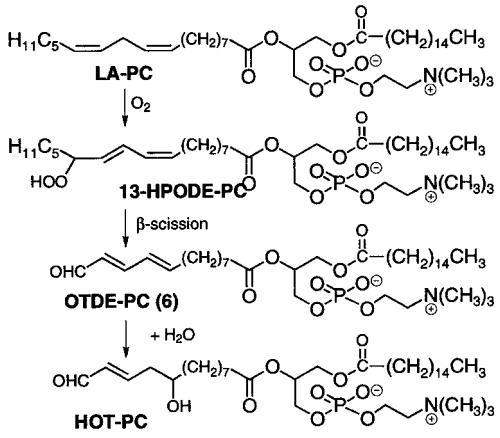
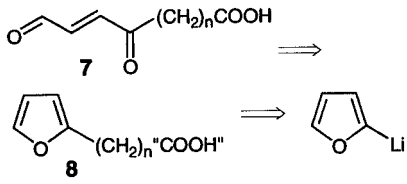
Scheme 1



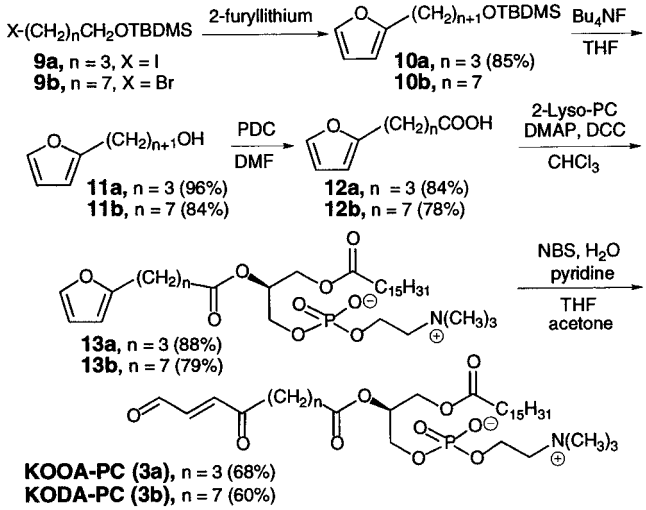
Scheme 2



Scheme 3



Scheme 4



oxidation of the corresponding alcohols or dehydration of the corresponding hydroperoxides, HPODA-PC and HPOOA-PC, respectively. The production of an analogous compound, 4-oxo-2-nonenal, by Fe^{2+}-mediated fragmentation of 13(*S*)-hydroperoxy-(*Z*,*E*)-9,11-octadecadienoic acid was reported recently.[8] The proclivity of aldehydes toward oxidation to carboxylic acids, e.g., the conversion of OV-PC into G-PC,[2] led us to postulate that the more polar oxPL are the corresponding hydroxy acids or keto acids (Scheme 1). We now report practical total syntheses of KOOA-PC (**3a**), KODA-PC (**3b**), KOdiA-PC (**4a**), KDdiA-PC (**4b**) HOdiA-PC (**5a**), HDdiA-PC (**5b**), as well as the 9-oxononanyl ester of 2-lysoPC (ON−PC, **1**), the monoester of azeleic acid with 2-lyso-PC (A-PC, **2**), and OTDE-PC (**6**) the putative precursor of HOT-PC (Scheme 2).

Results and Discussion

***γ*-Keto-α,*β*-Unsaturated Aldehydic Phospholipids KODA-PC and KOOA-PC.** Furans **8** bearing an *ω*-carboxyalkyl substituent at the 2-position are latent *ω*-carboxy-*γ*-keto-α,*β*-unsaturated aldehydes **7**. The requisite 2-substituted furans are readily available by alkylation of 2-furyllithium with appropriate masking of the carboxyl group (Scheme 3).

The carbon skeletons of the latent keto acids **8** were assembled by the coupling of furyl-lithium with the TBDMS ethers **9a** and **9b** of 4-iodobutanol or 8-bromooctanol, respectively (Scheme 4).[9] The requsite 4-iodobutanol TBDMS ether is readily available from tetrahydrofuran by reaction with NaI and TBDMSCl.[10] The TBDMS ether (**9b**) of 8-bromooctanol is obtained by

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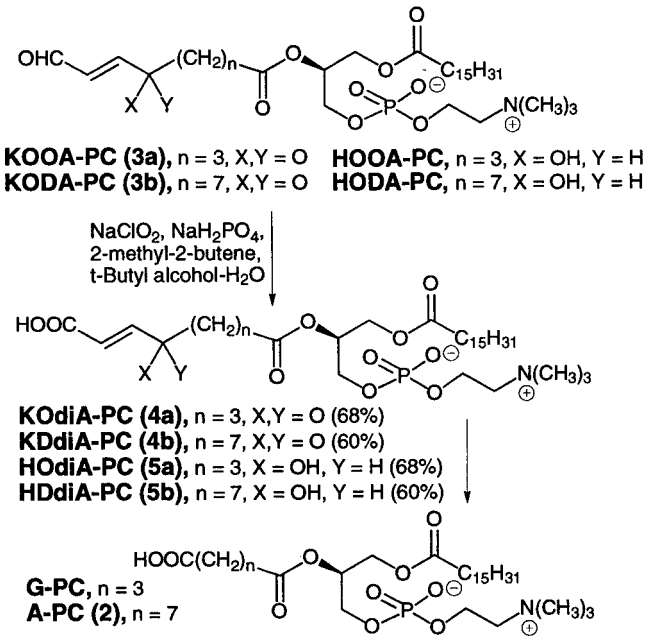
Scheme 5

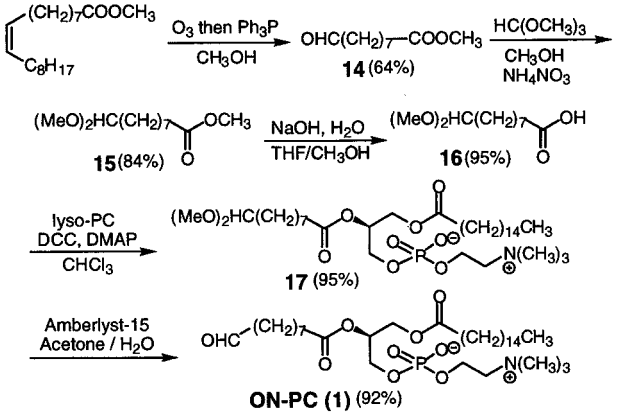


bromodehydroxylation of the corresponding monosilyl ether of 1,8-octanediol with DEAD, Ph_3P, and $ZnBr_2$. The requisite monosilyl ether was produced by the reaction of TBDMSCl with the sodium monoalkoxide of 1,8-octanediol.[10] The silyl ethers **10** were desilylated with fluoride affording primary alcohols **11**, from which furyl acids **8** were produced by oxidation with pyrdinium dichlorochromate (PDC). Esterification of the furyl acids **8** with L-α-lyso-phosphatidylcholine (lyso-PC) from egg albumin was accomplished in good yield with dicyclohexylcarbodiimide (DCC) and *N*,*N*-dimethylaminopyridine (DMAP). Aqueous *N*-bromosuccinamide (NBS)-promoted oxidative ring opening[9] of the furans produced the desired ketoalkenals, KOOA-PC (**3a**) and KODA-PC (**3b**) without oxidation of the sensitive aldehyde group. The yields were improved to 60−68% from 35% when the reaction time was increased from 3 to 6 h. In contrast, the aldehyde apparently did not survive oxidative ring opening with *m*-chloroperbenzoic acid at room temperature in chloroform.[11]

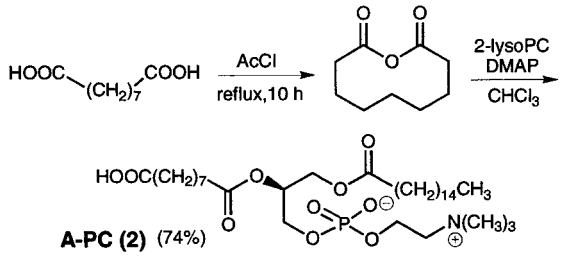
α,β-Unsaturated Dicarboxylic Phospholipids HDdiA-PC, HOdiA-PC, KDdiA-PC, and KOdiA-PC. The α,β-unsaturated dicarboxylic acid phospholipid monoesters HDdiA-PC (**5b**), HOdiA-PC (**5a**), KDdiA-PC (**4b**) and KOdiA-PC (**4a**) were obtained by selective oxidation of the corresponding aldehydes (Scheme 5) with sodium chlorite in the presence of 2-methyl-2-butene and NaH_2PO_4 in *tert*-butyl alcohol and water (5:1, v/v).[12] The reactions must be carefully monitored. If an inadequate amount of 2-methyl-2-butene is present, oxidative fragmentation ensues, delivering shorter chain carboxylic acids G-PC[2] and A-PC (**2**).

9-Oxononanoyl and Azeleyl Phospholipids. In view of its easy removal under mild conditions with an acidic resin, e.g., Amberlyst-15, a dimethyl acetal was exploited as the aldehyde protecting group in a synthesis (Scheme 6) of the 9-oxononanoyl ester of 2-lysoPC (ON-PC, **1**). Thus, 1-palmitoyl-2-(9-oxononanoyl)-*sn*-glycero-

Scheme 6



Scheme 7



3-phosphatidylcholine (ON-PC, **1**) is readily available by deprotection of a stable precursor, dimethyl acetyl **17**, that was prepared by esterification of 2-lysoPC with 9,9-dimethoxynonanoic acid (**16**). The acid **16** is readily obtained from methyl 9*Z*-octadecenoate in three steps: ozonolysis,[13,14] protection of the resulting aldehyde **14** as an acetal **15**,[15] and hydrolysis of the ester group in **15**. The oxidized phospholipid ON-PC undergoes gradual oxidation to form 1-palmitoyl-2-azeleyl-*sn*-glycero-3-phosphatidylcholine (A-PC, **2**). This monoester of azeleic acid with 2-lysoPC was also prepared by the reaction of 2-lysoPC and nonanedioic anhydride**,** which is readily obtained from azeleic acid and acetyl chloride according to the reported procedure,[16] catalyzed by DMAP (Scheme 7).

A 13-Oxotrideca-9,11-dienoic Acid Ester of 2-LysoPC (OTDE-PC, 6). The α,β,γ,δ-unsaturated aldehyde functional array is a common theme in oxidized lipids that are produced by peroxidation of polyunsaturated fatty acids. Thus, 2-*trans*-4-*cis*-2,4-decadienal is a major early oxidation product in the autoxidation of low-density lipoprotein (LDL), and its isomer, 2-*trans*-4-*trans*-2,4-decadienal becomes the main product within 2h.[17] Furthermore, 13-oxo-9,11-tridecadienoic acid (OTDEA, **18**) is a major product of both enzymatic and nonenzymatic oxidation of linoleic acid (LA).[18] Hydroperoxyoctadecadienoates (HPODEs) are the main primary peroxidation products from LA. One of the primary decomposition products from 13-HPODE is 13-OTDEA (**18**).[6] HPODEs are unstable, especially in the presence of redox active transition metal ions.[19,20] The formation of aldehydes

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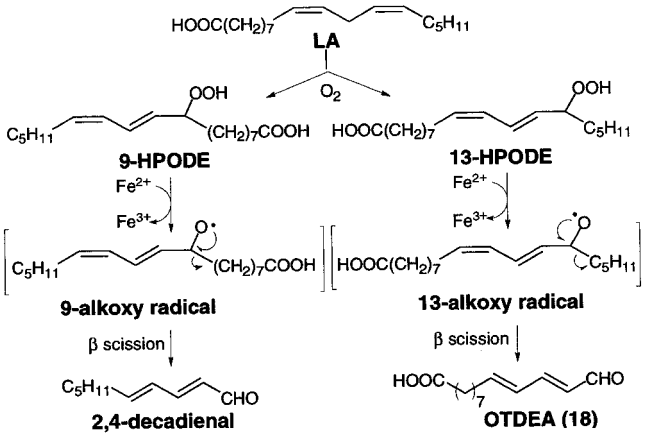
Scheme 8

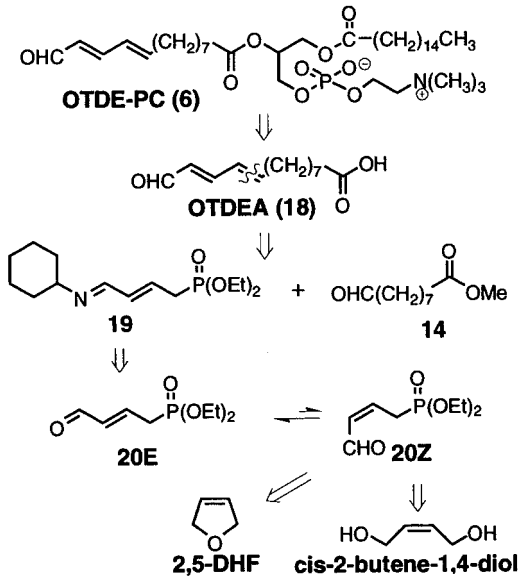


from HPODEs can occur by reaction with Fe^{2+} or Cu^{+} to produce alkoxy radicals that afford aldehydes upon β-scission. Such a mechanism would produce 2,4-decadienal[17] and OTDEA (**18**)[21] from 9-HPODE and 13-HPODE respectively (Scheme 8). Reductive β-scission of 13-HPODE catalyzed by cytochrome P-450 generates a 3:1 mixture of 9-*trans*-11-*trans*-13-OTDEA and 9-*trans*-11-*cis*-13-OTDEA.[3] The homolytic hydroperoxide lyase oxidation of 13-HPODE generates similar amounts of the 11-cis and 11-trans isomers.[22]

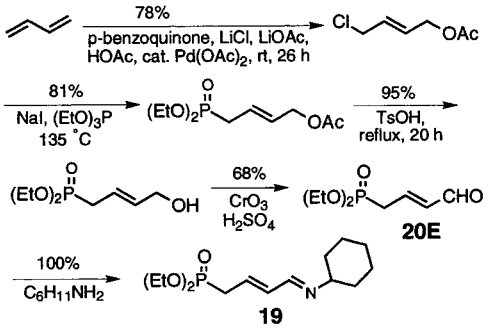
In vivo, fatty acids occur mainly as esters of cholesterol or glycerol. HPODE esters of 2-lysoPC are abundant in human blood plasma and oxidized LDL.[23,24] However, very little information is available about the secondary PC-containing products that are formed by decomposition of HPODE-PCs. To facilitate their structural and biological characterization, we devised total syntheses of OTDEA (**18**) and its 2-lysoPC ester, OTDE-PC (**6**). A convergent strategy for the synthesis of OTDE-PC (**6**) is outlined in Scheme 9. The carbon skeleton of the target should be readily accessible by the Horner-Wadsworth-Emmons condensation of a phosphoryl imine **19** derived from the trans crotonaldehyde **20E**.[25] The key intermediate in the synthesis, the phosphoryl unsaturated aldehyde **20E**, was prepared previously from 1,3-butadiene.[26] An alternative synthesis from commercially available *cis*-2-butene-1,4-diol seemed feasible in view of the likely facile isomerization of a cis-crotonaldehyde intermediate **20Z** to the trans isomer.[27] An especially efficient synthesis was ultimately devised that starts with 2,5-dihydrofuran (DHF).

A Previous Synthesis of the Phosphoryl Imine 19. The Horner−Wadsworth−Emmons reagent **19**, derived from 4-(diethoxyphosphoryl)-2*E*-butenal (**20E**), is a useful building block for synthesis of conjugated dienals. Previously, imine **19** was prepared from butadiene as outlined in Scheme 10.[26] The aldehyde **20E** was protected as an imine by treatment with cyclohexylamine in the presence of molecular sieves,[26] which serve as catalyst and dehydrating agent.[28]

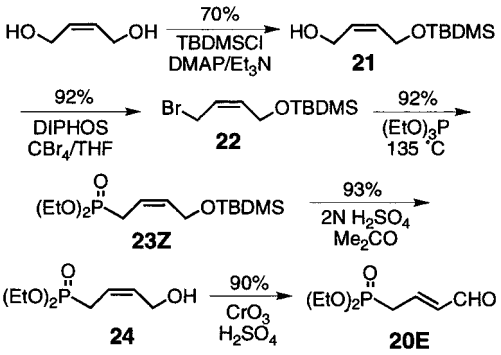
Scheme 9



Scheme 10



Scheme 11



Alternative Syntheses of Phosphoryl Alkenal 20E. We developed an alternative synthesis of *E*-aldehyde **20E** that relies upon cis−trans isomerization of a *cis*-crotonaldehyde intermediate **20Z** (Scheme 11).[27] Treatment of *cis*-2-butene-1,4-diol with TBDMSCl, DMAP, and Et_3N provides the monosilyl ether **21**.[29] Conversion of the

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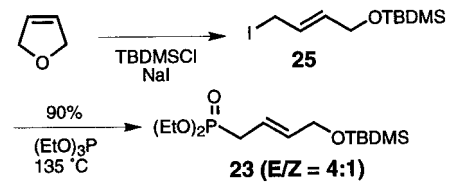
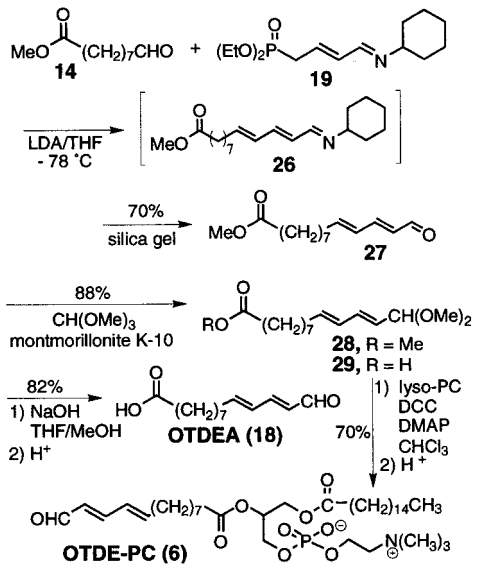
Scheme 12



Scheme 13



remaining hydroxyl group into the bromide **22** was accomplished in 92% yield by treatment with bis-(1,2-diphenylphosphino)ethane (DIPHOS) and CBr_4.[30] Reaction of the bromide **22** with triethyl phosphite under Arbuzov conditions provided the phosporyl TBDMS ether **23Z**.[26] Hydrolytic removal of the TBDMS protecting group with 2 N H_2SO_4, followed by oxidation of the corresponding alcohol **24** with Jones reagent[31] was accompanied by partial isomerization to give the phosphoryl aldehyde **20** as a 3:1 mixture of *E* and *Z* isomers. Isomerization of **20Z** to **20E** was completed with acid catalysis.[27] A solution of the cis/trans mixture in acetone was refluxed (60 °C) in the presence of a trace of 2 N H_2SO_4 for 30−60 min to afford **20E** in 90% yield (*E*/*Z* >99:1).

An even more concise synthesis that delivers the trans phosphonate **23** (*E*/*Z* = 4:1) was accomplished by the reaction of 2,5-DHF with TBDMSCl, NaI, and DMAP (Scheme 12). The resulting desymmetrization converts one ether linkage into an activated electrophile while protecting the remaining oxygen functionality as a silyl ether and the *cis* geometry of the C=C bond was isomerized (trans/cis = 95:5). This is an especially convenient route to the allylic iodide **25**. Phosphonate **23** was obtained in two steps and 90% yield.

A synthesis of 13-oxotridec-9*E*,11*E*-dienoic acid (OTDEA, **18**) was devised based on the Horner−Wadsworth−Emmons reagent **19** (Scheme 13). Condensation of aldehyde **14**[32] with phosphoryl imine **19** (LDA/THF/−78 °C) delivered the dienal imine **26**. The dienoate **27** was obtained in 70% overall yield by flash chromatography that was accompanied by hydrolysis of **26**.[26] The dienal was then protected as a dimethyl acetal **28** with Taylor reagent (Montmorillonite K-10/trimethyl orthoformate).[15] 13-Oxotridec-9*E*,11*E*-dienoic acid (OTDEA, **18**) was produced in 82% yield by hydrolysis of methyl ester **28** with NaOH, followed by acidification with 2 N HCl at room temperature.[33] The ^{1}H NMR spectrum of this authentic sample of OTDEA agreed well with that reported for a dienal acid obtained by lipid oxidation.[22,34]

A synthesis of OTDE-PC (**6**) was pursued by coupling OTDEA (**18**) with 2-lysoPC (Scheme 13). More carefully controlled hydrolysis of **28** delivered the dimethyl acetal **29**. Ice-cold 0.5 N HCl was added to the basic solution at 0 °C until pH 4 was reached to avoid the hydrolysis of the acetal. Both aldehydic acid (OTDEA, **18**) and acetal acid **29** were readily esterified with 2-lyso-PC in the presence of DCC and DMAP in $CHCl_3$ to deliver the desired phospholipid OTDE-PC after acidic work up. However, the esterification of **29** with lyso-PC generally provided a higher yield, 70−80% versus 50% from OTDEA (**18**). Owing to its reactivity as a Michael acceptor, *trans*,*trans*-2,4-decadienal (see Scheme 8) reacts with glutathione,[17] and is highly toxic to human diploid fibroblast cells.[35] Because its Michael adduction chemistry should be analogous to that of 2-*trans*-4-*trans*-2,4-decadienal, OTDEA (**18**) and the derived phospholipid OTDE-PC (**6**) are likely to exhibit similar biological activities. The total syntheses reported above will facilitate the examination of such questions as well as the detection and quantification of OTDE-PC (**6**) in vivo. Arachidonate and linoleate esters of 2-lysophosphatidylcholine are the two most abundant polyunsaturated phospholipids in low-density lipoprotein (LDL). Oxidation of LDL has been implicated in the etiology of atherosclerosis. Studies exploiting authentic samples of the novel oxPLs described above to examine their generation by oxidation of AA-PC and LA-PC, their presence in atherosclerotic plaques, and their biological activities will be reported elsewhere.[5,7]

Experimental Procedures

General Methods. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini spectrometer operating at 200, 300, or 600 MHz. Proton chemical shifts are reported in parts per million (ppm) on the δ scale relative to solvent. Carbon magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Gemini spectrometer operating at 75 MHz.

Thin-layer chromatography (TLC) was performed on glass plates precoated with silica gel (Kieselgel 60 F_{254}, E. Merck, Darmstadt, West Germany); R_f values are quoted for plates of thickness 0.25 mm. The plates were visualized by viewing under short-wavelength UV light or by treatment with iodine. Flash column chromatography was performed on 230−400 mesh silica gel supplied by E. Merck. High-performance liquid chromatography (HPLC) was performed with HPLC grade solvents using a Waters M600A solvent delivery system and a Waters U6K injector. The eluants were monitored using a SEDEX 55 evaporative light scattering detector and an ISCO V^4 UV−vis detector. Analytical RP-HPLC was performed on a Phenomenex LUNA C18 (2) column (4.6 mm i.d. × 25 cm).

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Semipreparative RP-HPLC was performed on a Phenomenex LUNA C18 (2) column (10 mm i.d. × 25 cm).

4-Iodo-1-(1,1,2,2-tetrmethyl-1-silapropoxy)butane (9a). This compound was prepared according to the procedure reported previously.[10] ^{1}H NMR (300 MHz): δ 3.61 (t, J = 6.1 Hz, 2H), 3.20 (t, J = 7.0 Hz, 2H), 1.8−1.9 (m, 2H), 1.4−1.6 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H).

8-Bromo-1-(1,1,2,2-tetrmethyl-1-silapropoxy)octane (9b). This compound was prepared according to the procedure reported previously.[10] ^{1}H NMR (300 MHz): δ 3.57 (t, J = 6.4 Hz, 2H), 3.38 (t, J = 6.8 Hz, 2H), 1.83 (4H), 1.35−1.55 (4H), 1.20−1.40 (4H), 0.89 (s, 9H), 0.02 (s, 6H).

4-(2-Furyl)-1-(1,1,2,2-tetrmethyl-1-silapropoxy)butane (10a). *n*-Butyllithium (9.5 mL, 1.2 M in hexane, 11.4 mmol) was added dropwise to an ice-cold solution of furan (1.5 mL, 15.6 mmol) and bipyridine (10 mg) in dry THF (20 mL) under argon. The resulting brown solution was stirred for 1 h to generate 2-furyllithium. Then 4-iodo-1-(1,1,2,2-tetrmethyl-1-silapropoxy)butane (**9a**, 1.19 g, 3.8 mmol) in THF (2 mL) was added. The solution was kept at 0 °C for 1 h and then warmed to room temperature. After 3 h, the reaction was quenched by the addition of saturated NH_4Cl. The mixture was extracted with hexane. The organic extract was dried with $MgSO_4$ and concentrated with a rotary evaporator to give a residue that was purified by flash chromatography on a silica gel column (2% ethyl acetate in hexanes, R_f = 0.35) to afford **10a** (819 mg, 85%) as a colorless oil. ^{1}H NMR (200 MHz): δ 7.28 (d, J = 2 Hz, 1 H) 6.27 (dd, J = 3.2, 2 Hz, 1 H), 5.98 (d, J = 3.2 Hz, 1 H), 3.64 (t, J = 6.2 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2 H), 1.5−1.7 (4 H), 0.91 (s, 9 H). 0.06 (s, 6 H). C NMR (75 MHz): δ 156.2, 140.6, 109.9, 104.6, 62.7, 32.2, 32.2., 27.7, 25.9, 24.36, 18.3, −5.3.

4-(2-Furyl)butan-1-ol (11a). *n*-Bu_4NF (6.9 mL, 1 M in THF, 6.9 mmol) was added dropwise to a stirred solution of the silyl ether **10a** (659 mg, 2.73 mmol) in dry THF (5 mL). The resulting solution was stirred overnight under nitrogen. Water (4 mL) was then added. The suspension was extracted with ethyl ether. The organic extract was dried with sodium sulfate and concentrated. The residue was then purified by flash chromatography on a silica gel column (20% ethyl acetate in hexanes; TLC, R_f = 0.4) to afford **5a** (366 mg, 96%). ^{1}H NMR (200 MHz): δ 7.27 (dd, J = 1.9, 0.8 Hz, 1H), 6.25 (dd, J = 3.1, 0.9 Hz, 1H), 3.64 (t, J = 6.4, 2H), 2.64 (t, J = 7.3, 2H), 1.4−1.8 (4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.9, 140.7, 110.0, 104.7, 62.3, 32.0, 27.6, 24.2. HRMS (EI): m/z calcd for $C_8H_{12}O_2$ (M^+) 140.0837, found 140.0837.

8-(2-Furyl)octan-1-ol (11b). *n*-Butyllithium (3.9 mL, 1.2 M in hexane, 4.7 mmol) was added dropwise to the ice-cold solution of furan (0.6 mL, 15.6 mmol) and bipyridine (5 mg) in dried THF (10 mL) under argon. The resulting brown solution was stirred for 1 h to generate 2-furyllithium. 8-Bromo-1-(1,1,2,2-tetrmethyl-1-silapropoxy)octane (**9b**, 0.5 g, 1.55 mmol) in THF (2 mL) was added to the solution. The solution was kept at 0 °C for 1 h and then warmed to room temperature. After 7 h, the reaction was quenched by the addition of saturated NH_4Cl. The mixture was extracted with hexane. The combined organic layer was dried with $MgSO_4$ and concentrated with a rotary evaporator to give a residue (**10b**). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.29 (d, J = 2 Hz, 1 H), 6.27 (dd, J = 3.2, 2 Hz, 1 H), 5.96 (d, J = 3.2 Hz, 1 H), 3.60 (t, J = 6.2 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2 H), 1.5−1.7 (12 H), 0.91 (s, 9 H). 0.06 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7, 140.7, 110.1, 104.6, 63.4, 32.9, 29.4, 29.2, 28.1, 28.0, 26.1, 25.8, 18.5, −5.2. Without further purification, THF (5 mL) and Bu_4NF (6 mL, 1 M in THF, 6 mmol) were sequentially added to the residue. After 5 h, aqueous NH_4Cl (10 mL) was added to quench the reaction. The resulting mixture was extracted with ethyl ether. The combined organic layer was concentrated and purified on a silica gel column (25% ethyl acetate in hexanes; TLC, R_f = 0.24) to give furyl alcohol (**11b**, 257 mg, 84%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.27 (dd, J = 1.9, 0.8 Hz, 1H), 6.25 (dd, J = 3.1, 1.8 Hz, 1H), 5.94 (dd, J = 3.1, 0.8 Hz, 1H), 3.61 (t, J = 6.6, 2H), 2.59 (t, J = 7.5, 2H), 1.45−1.71 (4H), 1.30−1.34 (12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.5, 140.6, 110.0, 104.5, 63.0, 32.7, 29.3, 29.1, 28.0, 27.9, 25.7. HRMS (EI): m/z calcd for $C_{12}H_{20}O_2$ (M^+) 196.1463, found 194.1462.

4-(2-Furyl)butanoic Acid (12a). PDC (316 mg, 0.84 mmol) was added to the solution of alcohol **11a** (20 mg, 0.14 mmol) in DMF (0.5 mL). The resulting mixture was stirred for 20 h. The solution was diluted by saturated NH_4Cl aqueous solution (5 mL) and extracted with ethyl ether. The organic extract was washed with water (pH 3) and dried with $MgSO_4$. The solvent was removed on a rotary evaporator. The residue was chromatographed on a on a silica gel column (50% ethyl acetate in hexanes; TLC, R_f = 0.2) to give acid **12a** (18 mg, 84%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.29 (dd, J = 1.9, 0.7 Hz, 1H), 6.26 (dd, J = 3.1, 1.9 Hz, 1H), 6.00 (dd, J = 3.1, 0.8 Hz, 1H), 2.68 (t, J = 7.3, 2H), 2.39 (t, J = 7.4, 2H), 1.89−2.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 180.0, 154.8, 110.0, 141.1, 110.1, 105.5, 33.2, 27.1, 23.0. HRMS (EI): m/z calcd for $C_8H_{10}O_3$ (M^+) 154.0630, found 154.0631.

8-(2-Furyl)octanoic Acid (12b). PDC (2.19 g, 6.3 mmol) was added to a solution of alcohol **11b** (206 mg, 1.05 mmol) in DMF (3 mL). The resulting mixture was stirred for 18 h. The solution was diluted by saturated NH_4Cl aqueous solution (30 mL) and extracted with ethyl ether. The organic extract was washed with water (pH 3) and dried with $MgSO_4$. The solvent was removed on a rotary evaporator. The residue was chromatographed on a on a silica gel column (45% ethyl acetate in hexanes; TLC, R_f = 0.32) to give acid **12b** (172 mg, 78%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.28 (dd, J = 1.9, 0.8 Hz, 1H), 6.26 (dd, J = 3.1, 1.9 Hz, 1H), 5.95 (d, J = 3.1, 1H), 2.59 (t, J = 7.5, 2H), 2.33 (t, J = 7.6, 2H), (4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 180.4, 156.4, 140.6, 110.0, 104.6, 34.0, 28.9, 27.9, 27.8, 24.6. HRMS (EI): m/z calcd for $C_{12}H_{18}O_3$ (M^+) 210.1256, found 210.1259.

1-Palmitoyl-2-(4-(2-furyl)butanoyl)-*sn*-glycero-3-phosphatidylcholine (13a). A mixture of furyl acid **12a** (30 mg, 0.19 mmol) and 1-palmitoyl-2-lyso-*sn*-glycero-3-phosphatidylcholine (50 mg,0.1 mmol), which was dried on a vacuum pump (0.1 mmHg) equipped with a dry ice−acetone trap for 10 h at room temperature, was dissolved in dry $CHCl_3$ (2 mL, shaken with P_2O_5 for 0.5 h and distilled). Dicyclohexylcarbodiimide (DCC, 120 mg, 0.6 mmol) and *N*,*N*-dimethylaminopyridine (DMAP, 12 mg, 0.1 mmol) were added. The mixture was stirred for 96 h under nitrogen. The mixture was concentrated, and the residue was chromatographed on silica with $CHCl_3$/MeOH/H_2O (16/9/1) to produce the furyl phospholipid **13a** (56 mg, 88%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (d, J = 1.9, Hz, 1H), 6.25 (dd, J = 3.1, 1.9 Hz, 1H), 5.99 (dd, J = 3.1, 1H), 5.18 (m, 1H), 4.36 (dd, J = 12.2, 2.8 Hz, 1H), 4.25 (bm, 2H), 4.10 (dd, J = 12.2, 7.4, 1H), 3.91 (t, J = 6 Hz, 2H), 3.76 (bm, 2H); 3.33 (bs, 9H), 2.64 (t, J = 7.4 Hz, 2H), 2.34 (t, J = 7.3 Hz, 2H), 1.8−2.1 (m, 2H), 1.4−1.6 (m, 2H), 1.23 (24H), 0.86 (t, J = 6.7 Hz, 3H). HRMS (FAB): m/z 632.3927 (MH^+) calcd for $C_{32}H_{59}NO_9P$, found 632.3934.

1-Palmitoyl-2-(8-(2-furyl)octanoyl)-*sn*-glycero-3-phosphatidylcholine (13b). A mixture of furyl acid **12b** (84 mg, 0.4 mmol) and 1-palmitoyl-2-lyso-*sn*-glycero-3-phosphatidylcholine (100 mg, 0.2 mmol), which was dried on a vacuum pump (0.1 mmHg) equipped with a dry ice−acetone trap for 6 h at room temperature, was dissolved in dry $CHCl_3$ (4 mL, shaken with P_2O_5 for 0.5 h and distilled). Dicyclohexylcarbodiimide (DCC, 240 mg, 1.2 mmol) and *N*,*N*-dimethylaminopyridine (DMAP, 24 mg, 0.2 mmol) were added. The mixture was stirred for 96 h under nitrogen. The mixture was concentrated, and the residue was purified by flash chromatography on silica with $CHCl_3$/MeOH/H_2O (16/9/1) to produce the furyl phospholipid **13b** (110 mg, 79%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, J = 1.9, Hz, 1H), 6.20 (dd, J = 3, 1.9 Hz, 1H), 5.92 (d, J = 3, 1H), 5.14 (m, 1H), 4.34 (dd, J = 12.2, 2.8 Hz, 1H), 4.25 (bm, 2H), 4.10 (dd, J = 12.2, 7.4, 1H), 3.91 (m, 2H), 3.76 (bm, 2H), 3.35 (bs, 9H), 2.54 (t, J = 7.4 Hz, 2H), 2.2−2.4 (4H), 1.5−1.6 (6H), 1.1−1.3 (30H), 0.83 (t, J = 6.30 Hz, 3H). HRMS (FAB): m/z 688.4553 (MH^+) calcd for $C_{36}H_{67}NO_9P$, found 688.4532.

1-Palmitoyl-2-(5-oxo-8-oxooct-6-enoyl)-*sn*-glycero-3-phosphatidylcholine (KOOA-PC, 3a). *N*-Bromosuccinimide (10 mg, 0.05 mmol) and pyridine (5.8 mL, 0.07 mmol) were

sequentially added to a solution of furyl phosphatidylcholine **13a** (22 mg, 0.035 mmol) in THF/acetone/water (5:4:2) at −20 °C. The resulting mixture was stirred for 1 h at this temperature and then kept at room temperature for 3 h. The solvent was then removed quickly by rotary evaporation, and the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH/H_2O = 16/9/1) affording a mixture (24 mg) that contained about 80% **KOOA-PC (3a)** as determined by reversed-phase HPLC. A second flash chromatography was necessary to produce pure **KOOA-PC** (**3a**,17 mg, 68%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.77 (d, J = 7.2 Hz, 1H), 6.91 (d, J = 16.8 Hz, 1H), 6.81 (dd, J = 16.8, 7.2 Hz, 1H), 5.21 (m, 1H), 4.32 (3H), 4.12 (m, 1H), 3.98 (m, 2H), 3.79 (m, 2H), 3.13 (bs, 9H), 2.85 (2H, d, J = 7.1 Hz), 2.2−2.5 (4H), 1.9−2.0 (m, 2H), 1.5−1.6 (2H), 1.1−1.3 (24H), 0.83 (t, J = 6.3 Hz, 3H). HRMS (FAB): m/z 648.3876 (MH^+) calcd for $C_{32}H_{59}NO_{10}P$, found 648.3856.

1-Palmitoyl-2-(9-oxo-12-oxododec-10-enoyl)-*sn*-glycero-3-phosphatidylcholine (KODA-PC, 3b). NBS (16 mg, 0.09 mmol) and pyridine (10 mL, 0.12 mmol) were sequentially added to a solution of furyl phosphatidylcholine **13b** (42 mg, 0.06 mmol) in THF/acetone/water (5/4/2) at −20 °C. The resulting mixture was stirred for 1 h at this temperature and then kept at room temperature for 5 h. The solvent was then removed quickly by rotary evaporation, and the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH/H_2O = 16/9/1) affording a mixture (30 mg) that contained about 80% **KODA-PC (3b)** as determined by reversed-phase HPLC analysis described elswhere.[7] A second flash chromatography was necessary to obtain pure **KODA-PC** (**3b**, 20 mg, 50%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.77 (d, J = 7.8 Hz, 1H), 6.87 (d, J = 16.2 Hz, 1H), 6.76 (dd, J = 16.2, 7.8, 1H), 5.18 (m, 1H), 4.37 (m, 1H), 4.30 (bm, 2H), 4.10 (dd, J = 11.4, 7.2, 1H), 3.92 (m, 2H), 3.80 (bm, 2H), 3.35 (bs, 9H), 2.68 (t, J = 7.2 Hz, 2H), 2.2−2.4 (4H), 1.5−1.7 (6H), 1.1−1.4 (30H), 0.86 (t, J = 6.9 Hz, 3H). HRMS (FAB): m/z 704.4502 (MH^+) calcd for $C_{36}H_{67}NO_{10}P$, found 704.4502.

1-Palmitoyl-2-(7-carboxy-5-oxohept-6-enoyl)-*sn*-glycero-3-phosphatidylcholine (KOdiA-PC, 4a). To a magnetically stirred solution of KOOA-PC (**3a**) (5.3 mg, 0.008 mmol) in t-BuOH−H_2O (5:1, v/v, 0.3 mL) were added NaH_2PO_4 (1.66 mg, 0.012 mmol), 2-methyl-2-butene (40 μL, 0.085 mmol, 2 M solution in THF), and $NaClO_2$ (2.2 mg, 0.024 mmol). The resulting mixture was stirred for 2 h at room temperature under Ar. The solvent was removed. The residue was extracted with 4:1 $CHCl_3$/MeOH. The crude product was purified by flash chromatography on a silica gel column ($CHCl_3$/MeOH/H_2O, 15: 9:1; TLC, R_f = 0.23) to give KOOA-acid-PC (3.4 mg, 64%). ^{1}H NMR (CD_3OD, 600 MHz): δ 6.87 (d, J = 14.4 Hz, 1H), 6.74 (d, J = 14.4 Hz, 1H), 5.23 (m, 1H), 4.38 (dd, J_1 = 12.3 Hz, J_2 = 3 Hz1H), 4.27 (m, 2H), 4.16 (dd, J_1 = 12, J_2 = 6.6, 1H), 4.00 (m, 2H), 3.64 (m, 2H), 3.22 (s, 9H), 2.77 (2H), 2.39 (t, J = 6.6 Hz, 2H), 2.30 (t, J = 7.2 Hz, 2H), 1.91 (m, 2H), 1.57 (m, 2 H), 1.3−1.2 (24 H), 0.88 (t, J = 7.2 Hz, 3H). HRMS (MALDI-TOF): m/z calcd for $C_{32}H_{61}NO_{11}P^+$ (MH^+) 664.3826, found 664.3914.

1-Palmitoyl-2-(11-carboxy-9-oxoundec-10-enoyl)-*sn*-glycero-3-phosphatidylcholine (KDdiA-PC, 4b). To a magnetically stirred solution of KODA-PC (**3b**) (10 mg, 0.014 mmol) in t-BuOH−H_2O (5:1, v/v, 0.6 mL) was added NaH_2PO_4 (2.8 mg, 0.021 mmol), 2-methyl-2-butene (80 μL, 0.16 mmol, 2 M solution in THF), and $NaClO_2$ (3.8 mg, 0.042 mmol). The resulting mixture was stirred for 2 h at room temperature under Ar. The solvent was removed. The residue was extracted with 4:1 $CHCl_3$/MeOH. The crude product was purified by flash chromatography on a silica gel column ($CHCl_3$/MeOH/H_2O, 11: 9:1; TLC, R_f = 0.29) to give KODA-acid-PC (6.2 mg, 62%). ^{1}H NMR (CD_3OD, 600 MHz): δ 6.81 (d, J = 15 Hz, 1H), 6.75 (d, J = 15 Hz, 1H), 5.22 (m, 1H), 4.28 (dd, J_1 = 12 Hz, J_2 = 3 Hz, 1H), 4.28 (m, 2H), 4.14 (dd, J_1 = 12 Hz, J_2 = 7.2 Hz, 1H), 3.99 (m, 2H), 3.64 (m, 2H), 3.22 (s, 9H), 2.65 (t, J = 7.2 Hz, 2H), 2.0.25−2.35 (4H), 1.5−1.7 (6H), 1.32−1.26 (30 H), 0.88 (t, J = 7.2 Hz, 3H). HRMS (MALDI-TOF): m/z calcd for $C_{36}H_{69}NO_{11}P^+$ (MH^+) 720.4452, found 720.4699.

1-Palmitoyl-2-(5-hydroxy-7-carboxyhept-6-enoyl)-*sn*-glycero-3-phosphatidylcholine (HOdiA-PC, 5a). To a magnetically stirred solution of HOOA-PC (7.4 mg, 0.011 mmol) in t-BuOH−H_2O (5:1, v/v, 0.3 mL) was added a solution containing NaH_2PO_4 (4.5 mg, 0.017 mmol), 2-methyl-2-butene (33 μL, 0.07 mmol, 2 M solution in THF), and $NaClO_2$ (3.1 mg, 0.034 mmol) in t-BuOH−H_2O (5:1, v/v, 0.3 mL). The resulting mixture was stirred for 2 h at room temperature under argon. The solvent was then removed by rotary evaporation. The residue was extracted with 4:1 $CHCl_3$/MeOH. The crude product was purified by flash chromatography on a silica gel column ($CHCl_3$/MeOH/H_2O, 15:9:1; TLC, R_f = 0.15) to give HOdiA-PC (**5a**, 5.2 mg, 71%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.88 (d, J = 15 Hz, 1H), 6.01 (m,1H), 5.24 (m, 1H), 4.15−4.25 (4H), 4.14 (m, 1H), 4.07 (m, 1H), 3.94 (m, 1H), 3.76 (m, 2H), 3.29 (s, 9H), 2.20−2.50 (m, 4H), 1.77 (m, 1H), 1.0.67 (m, 1H), 1.56 (m, 4 H),1.1−1.3 (24 H), 0.86 (t, J = 6 Hz, 3H). HRMS (FAB): m/z calcd for $C_{32}H_{61}NO_{11}P^+$ (MH^+) 666.39816, found 666.39934.

1-Palmitoyl-2-(9-hydroxy-11-carboxyundec-10-enoyl)-*sn*-glycero-3-phosphatidylcholine (HDdiA-PC, 5b). To a magnetically stirred solution of HODA-PC (15.3 mg, 0.022 mmol) in t-BuOH−H_2O (5:1, v/v, 0.3 mL) was added solution containing NaH_2PO_4 (4.5 mg, 0.033 mmol), 2-methyl-2-butene (65 μL, 0.13 mmol, 2 M solution in THF), and $NaClO_2$ (6 mg, 0.066 mmol) in t-BuOH−H_2O (5:1, v/v, 0.3 mL). The resulting mixture was stirred for 2 h at room temperature under Argon. The solvent was then removed by rotary evaporation. The residue was extracted with 4:1 $CHCl_3$−MeOH. The crude product was purified by flash chromatography on a silica gel column ($CHCl_3$/MeOH/H_2O, 11:9:1; TLC, R_f = 0.26) to give HDdiA-PC (**5b**, 11 mg, 70%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.86 (d, J = 7.2 Hz, 1H), 6.01 (d, J = 7.2 Hz, 1H), 5.20 (m, 1H), 4.31 (3H), 4.22 (m, 1H), 4.121 (m, 1H), 3.96 (m, 2H), 3.73 (m, 2H), 3.28 (s, 9H), 2.1−2.3 (4H), 1.55 (4H), 1.4−1.6 (6H), 1.1−1.3 (32H), 0.86 (t, J = 6 Hz, 3H). HRMS (FAB): m/z calcd for $C_{36}H_{69}NO_{11}P^+$ (MH^+) 722.46077, found 722.46139.

Methyl 9-Oxononanoate (14). With stirring below −65 °C, ozone was bubbled through a solution of methyl 9Z-octadecenoate (10 g, 0.0338 mmol, 1.0 equiv) in dry methanol (55 mL) that had been flushed with N_2. After 3.5 h of continuous bubbling, the reaction was stopped after the total consumption of methyl 9Z-octadecenoate as indicated by the appearance of light blue color in the solution. The reaction mixture was flushed with N_2 again. Then triphenylphosphine (9.2 g, 0.0350 mmol, 1.04 equiv) was added. The resulting reaction mixture was allowed to warm to −20 °C over 2 h and then was left overnight at room temperature. The solvent was removed under reduced pressure, and the crude product was distilled under reduced pressure (105−108 °C, 1.0 mmHg) to provide the desired methyl 9-oxononanoate (**14**, 4.0 g, 64%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.78 (s, 1H), 3.78 (s, 3H), 2.42 (t, 2H, J = 8.2 Hz), 2.30 (t, 2H, J = 8.2 Hz), 1.55−1.68 (4H), 1.25−1.38 (6H). This spectrum agrees with that reported previously.[32]

Methyl 9,9-Dimethoxynonanoate (15). To a magnetically stirred solution containing ammonium nitrate (38 mg, 0.1 mmol) in dry methanol (10 mL) were added trimethyl orthoformate (2.00 g, 19.0 mmol, 4 equiv) and methyl 9-oxononanoate (**14**, 883 mg, 4.75 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature and monitored by TLC. After being stirred for 36 h, the reaction was stopped and solvent was removed completely by rotary evaporation. The residue was triturated with diethyl ether (30 mL). The ether solution was filtered through Celite to remove ammonium nitrate. The filtrate was again concentrated under reduced pressure. The crude product was subjected to flash chromatography on silica gel with 25% ethyl acetate in hexanes (R_f = 0.37) to afford **15** (926 mg, 84%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.35 (t, 1H, J = 6.8 Hz), 3.66 (s, 3H), 3.31 (s, 6H), 2.30 (t, 2H, J = 8.2 Hz), 1.55−1.68 (4H), 1.28−1.30 (8H). This spectrum agrees with that reported previously.[36]

9,9-Dimethoxynonanoic Acid (16). Methyl 9,9-dimethoxynonanoate (**15**, 142 mg, 0.612 mmol, 1.0 equiv) was stirred

with a solution of sodium hydroxide (122.4 mg, 3.06 mmol, 5.0 equiv) in water/methanol/tetrahydrofuran (2:5:3, v/v/v, 3.06 mL) at room temperature. The reaction was monitored by TLC for the disappearance of the starting ester. After being stirred for 1.5 h, the reaction was stopped, the reaction mixture was acidified to pH 3 with ice-cold 2 N HCl, and then the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed once with brine (10 mL), dried over $MgSO_4$, and filtered, and solvent was removed under reduced pressure to provide pure 9,9-dimethoxynonanoic acid (**16**, 127 mg, 95% yield). The acid was used immediately for the next step without further purification. ^{1}H NMR (acetone-d_6, 200 MHz): δ 4.38 (t, 1H, J = 7.5 Hz), 3.25 (s, 6H), 2.28 (t, 2H, J = 8.8 Hz), 1.45−1.70 (4H), 1.25−1.45 (8H). ^{13}C (aceton-d_6, 75 MHz): δ 174.8, 105.3, 52.8, 34.3, 33.4, 30.2, 30.1, 29.9, 25.7, 25.4. HRMS (20 eV): m/z calcd for $C_{10}H_{19}O_3$ ($M^+ - OCH_3$) 187.1334, m/z found 187.1365.

1-Palmitoyl-2-(9,9-dimethoxynonanoyl)-*sn*-glycero-3-phosphatidylcholine (17). Esterification of 2-lysophosphatidylcholine with 9,9-dimethoxynonaoic acid (**16**) was accomplished by a general method reported previously.[4] Traces of moisture were removed from a mixture of acid **9** (219 mg, 1.00 mmol, 2.9 equiv) and 1-palmitoyl-2-lyso-*sn*-glycero-3-phosphatidylcholine (169 mg, 0.34 mmol, 1.0 equiv) by azeotropic distillation with toluene (3 × 10 mL) under reduced pressure at room temperature, and the mixture was attached to a high vacuum pump (0.1 mmHg) and evacuated through a dry ice−acetone cooled trap for 5 h. Anhydrous $CHCl_3$ (20 mL) freshly distilled from P_2O_5, dicyclohexylcarbodiimide (207 mg, 1.0 mmol, 3.0 equiv), and *N*,*N*-dimethylaminopyridine (134 mg, 1.1 mmol, 3.3 equiv) were added. Then the flask was flushed with nitrogen and protected from light. The reaction mixture was stirred at room temperature and was monitored by TLC for the disappearance of lysophosphatidylcholine. The reaction was stopped after stirring for 48 h, and the solvent was removed completely under reduced pressure. The resulting residue was flash chromatographed on silica gel with $CHCl_3$/MeOH/H_2O (40:50:10, v/v/v, R_f = 0.35) as eluant to afford **17** (225 mg, 95% based on lyso-PC). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.18−5.24 (m, 1H), 4.33−4.40 (4H), 4.10−4.17 (dd, 1H, J = 4.2 Hz, 7.4 Hz), 3.91−3.95 (m, 2H), 3.63−3.67 (m, 2H), 3.30 (s, 9H), 3.23 (s, 6H), 2.18−2.35 (4H), 1.51−1.59 (6H), 1.28−1.38 (8H), 1.22−1.28 (24H), 0.88 (t, 3H, J = 8.0 Hz). HRMS (20 eV): m/z calcd for $C_{34}H_{67}NO_9P$ ($M^+ - OCH_3$) 664.4553, m/z found 664.4560.

1-Palmitoyl-2-(9-oxononanoyl)-*sn*-glycero-3-phosphatidylcholine (ON−PC, 1). Hydrolysis of 1-palmitoyl-2-(9,9-dimethoxynonanoyl)-*sn*-glycero-3-phosphatidylcholine **17** was catalyzed by an acidic resin.[6] Thus, phospholipid acetal **17** (28 mg, 0.040 mmol) was dissolved in acetone−water (5:1, v/v, 6 mL) and stirred magnetically with Amberlyst-15 resin (15 mg). The reaction was monitored by TLC for the total disappearance of acetal. After the mixture was stirred at room temperature for 6 h, the reaction was stopped, the mixture was filtered, and the solvent was removed under reduced pressure. The crude product was flash chromatographed on a silica gel column with $CHCl_3$/MeOH/H_2O (40:50:10, v/v/v, R_f = 0.29) as eluant to yield the desired 1-palmitoyl-2-(9-oxononanoyl)-*sn*-glycero-3-phosphatidylcholine (26 mg, 92%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.76 (s, 1H), 5.18−5.22 (1H), 4.2−4.4 (3H), 4.0−4.2 (1H), 3.77−3.93 (m, 2H), 3.62−3.72 (3H), 3.34 (s, 9H), 2.40−2.45 (t, 2H, J = 8.2 Hz), 2.22−2.33 (4H), 1.48−1.57 (6H), 1.18−1.32 (30H), 0.88 (t, 3H, J = 7.6 Hz). HRMS (20 eV): m/z calcd for $C_{33}H_{64}NO_9P$ (M^+) 649.4318, m/z found 649.4325.

1-Palmitoyl-2-azeleyl-*sn*-glycero-3-phosphatidylcholine (A-PC, 2). Azeleic acid anhydride was prepared from azeleic acid according to the reported procedure.[16] The anhydride was recrystallized twice from dry benzene. The anhydride (102 mg, 0.6 mmol) and DMAP (12 mg, 0.1 mmol) were added under argon to a solution of 2-lysoPC (50 mg, 0.1 mmol) in dry $CHCl_3$ freshly distilled from P_2O_5. The mixture was stirred for 2 days. The solvent was then removed by rotary evaporation. The residue was flash chromatographed on a silica gel column ($CHCl_3$/MeOH/H_2O = 16:9:1), producing **A-PC** (**2**, 50 mg, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.20 (m, 1H), 4.30−4.37 (3H), 4.13 (dd, J = 11.2, 7.0, 1H), 3.96 (m, 2H), 3.79 (bm, 2H); 3.33 (bs, 9H), 2.22−2.29 (6H), 1.5−1.7 (6H), 1.2−1.4 (32H), 0.86 (t, J = 6.8 Hz, 3H). HRMS (FAB): m/z 666.4346 (MH^+) calcd for $C_{33}H_{65}NO_{10}P$, found 666.4336.

***cis*-4-(1,1,2,2-Tetramethyl-1-silapropoxy)but-2-en-1-ol (21).** To a solution of but-2-ene-1,4-diol (5 g, 56.7 mmol), DMAP (350 mg, 1.4 mmol), and Et_3N (4.8 mL, 34 mmol) in CH_2Cl_2 (150 mL) was added TBDMSCl (4.2 g, 27.8 mmol) in CH_2Cl_2 (10 mL) over 4 h with a syringe pump at room temperature. The reaction mixture was stirred under N_2 overnight, washed with water, aqueous NH_4Cl, and brine, and dried over $MgSO_4$. Flash chromatography on a silica gel column (25% ethyl acetate in hexanes, R_f = 0.3) afforded the silyl ether **21** (4 g, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.55−5.75 (2 H), 4.21 (m, 2 H), 4.14 (m, 2 H), 2.45 (br, 1 H), 0.86 (s, 9 H), 0.04 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz, APT): δ 131.20 (CH), 130.12 (CH), 59.57 (CH_2), 58.70 (CH_2), 25.91 (CH_3), 18.33 (C), −5.32 (CH_3). HRMS (EI): m/z calcd for $C_{10}H_{22}O_2Si$ (M^+) 202.1324, found 202.1389; calcd for $C_{10}H_{23}O_2Si$ (MH^+) 203.1468, found 203.1464; calcd for $C_{10}H_{21}OSi$ ($M^+ - OH$) 185.1362, found 185.1329.

4-Bromo-1-(1,1,2,2-tetramethyl-1-silapropoxy)but-2-ene (22). To a solution of the alcohol **21** (3.2 g, 15.8 mmol) in CH_2Cl_2 (200 mL) at 0 °C were added tetrabromomethane (5.8 g, 17.5 mmol) and bis(1,2-diphenylphosphino)ethane (DIPHOS) (7.5 g, 18.8 mmol). The resulting mixture was stirred at room temperature for 45 min. The solvent was removed by rotary evaporation. The residue was extracted with hexane. The organic extracts were concentrated and purified by flash chromatography on a silica gel column (2% ethyl acetate in hexanes, R_f = 0.3) to afford the desired bromide **22** (7.8 g, E/Z = 1:4, 92%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.55−5.84 (2 H), 4.32 (d, J = 5.4 Hz, 2 H), 4.03 (d, J = 7.7 Hz, 2 H), 0.88 (s, 9 H), 0.06 (s, 6 H). ^{13}C ($CDCl_3$, 75 MHz, APT): δ 134.52 (CH), 125.90 (CH), 59.03 (CH_2), 26.86 (CH_2), 26.04 (CH_3), 18.33 (C), −5.25 (CH_3). HRMS (EI): m/z calcd for $C_{10}H_{21}BrOSi$ (M^+) 264.0545, found 264.0546; calcd for $C_9H_{18}BrOSi$ ($M^+ - Me$) 249.0310, found 249.0329.

Diethoxyphosphino(4-(1,1,2,2-tetramethyl-1-silapropoxy)but-2-enyl)-1-one (*E*/*Z* = 4:1) (23). Method A. A mixture of the bromide **22** (1.6 g, 6.0 mmol) and $(EtO)_3P$ (1.53 mL, 9 mmol) was heated to 130−135 °C for 6 h. The low boiling point fraction was removed by distillation under reduced pressure (50−60 °C, 15 mmHg). The residue was purified by flash chromatography on a silica gel column to give the desired compound **23** (1.6 g, 84%). TLC: R_f = 0.26 (2% methanol in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.67 (m, 1 H), 5.42 (m, 1 H), 4.18 (m, 2 H), 4.03 (qd, J = 7.4, 7.1 Hz, 4 H), 2.56 (dd, J = 22.3, 7.9 Hz, 2 H), 1.25 (t, J = 7.1 Hz, 6 H), 0.83 (s, 9 H), 0.00 (s, 6 H). ^{13}C ($CDCl_3$, 75 MHz, APT): δ 134.17 (d, J_{PC} = 9.8 Hz, CH), 118.69 (d, J_{PC} = 8.6 Hz, CH), 61.91 (d, J_{PC} = 4.9 Hz, CH_2), 59.34 (d, J_{PC} = 2.3 Hz, CH_2), 26.23 (d, J_{PC} = 104.6 Hz), 25.89 (CH_3), 18.30 (C), 16.45 (d, J_{PC} = 4.5 Hz), −5.21 (CH_3). HRMS (EI): m/z calcd for $C_{14}H_{32}O_4PSi$ (MH^+) 323.1808, found 323.1792; calcd for $C_{13}H_{28}O_4PSi$ ($M^+ - Me$) 307.1494, found 307.1490.

Method B. *tert*-Butyl dimethylsilyl chloride (1 g, 6.6 mmol) was added to a stirred suspension of $CaCO_3$ (70 mg, 0.7 mmol), NaI (990 mg, 6.6 mmol), and DMAP (320 mg, 2.6 mmol) in 2,5-dihyrofuran (2,5-DHF, 8 mL). The mixture was refluxed for 48 h, and then the excess 2,5-DHF was removed with a rotary evaporator to give a residue that was purified by flash chromatography on a silica gel column (1.5% ethyl acetate in hexanes) to afford **4-iodo-1-(1,1,2,2-tetramethyl-1-silapropoxy)but-2-ene** (**25**, 1 g, 52%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.9−6.0 (m, 1 H), 5.79 (dt, J = 4.6,J = 15.8 Hz, 1H) 4.16 (d, J = 4.6 Hz, 2 H), 3.89 (d, J = 7.8 Hz, 2 H), 0.91 (s, 9 H), 0.07 (s, 6 H). ^{13}C ($CDCl_3$, 75 MHz): δ 133.31 (CH), 127.54 (CH), 62.70 (CH_2), 26.01 (CH_3), 25.90 (CH_2), 18.44 (C), 5.38 (CH_2), −5.12 (CH_3). This iodide was characterized further by conversion to **23**. A mixture of the iodide (400 mg, 1.28 mmol)

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and $(EtO)_3P$ (0.5 mL, 3 mmol) was heated to 120 °C for 6 h. The low boiling point fraction was removed by distillation under reduced pressure (50−60 °C, 15 mmHg). The residue was purified by flash chromatography on a silica gel column (2% methanol in CH_2Cl_2, TLC $R_f = 0.26$) to give the desired compound **15** (*E*/*Z* = 4:1, 380 mg, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.77−5.66 (2H), 4.17−4.06 (6 H), 2.60 (dd, $J = 21.3$, 6.9 Hz, 2 H), 1.32 (t, $J = 7.1$ Hz, 6 H), 0.81 (s, 9 H), 0.07 (s, 6 H). ^{13}C ($CDCl_3$, 75 MHz): δ 134.6 (d, $J_{PC} = 10.7$ Hz), 119.4 (d, $J_{PC} = 7.9$ Hz), 63.4 (d, $J_{PC} = 1.9$ Hz), 61.9 (d, $J_{PC} = 5.0$ Hz), 30.2 (d, $J_{PC} = 104.2$), 26.0, 18.4 (C), 16.5 (d, $J_{PC} = 4.5$ Hz), −5.2 (CH_3). HRMS (EI): *m*/*z* calcd for $C_{14}H_{32}O_4PSi$ (MH^+) 323.1808, found 323.1792; calcd for $C_{13}H_{28}O_4PSi$ ($M^+ - Me$) 307.1494, found 307.1495.

Diethoxy(4-hydroxybut-2-enyl)phosphino-1-one (*E*/*Z* = 4:1) (24). To the solution of TBDMS ether **15** (100 mg, 0.31 mmol) in Me_2CO (2 mL) was added 2 N H_2SO_4 (1 mL). The resulting mixture was stirred for 3 h at room temperature and then extracted with CH_2Cl_2 (3 × 5 mL). The solvent was removed, and the residue was purified by flash chromatography on a silica gel column with 3% methanol in CH_2Cl_2 (TLC, $R_f = 0.25$) to afford phosphoryl alcohol **24** (60 mg, 93%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.75 (m, 1 H), 5.45 (m, 1 H), 3.8−4.0 (4 H), 2.52 (dd, $J = 22.6$, 8.1 Hz, 2 H), 1.15 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.26 (d, $J_{PC} = 9.9$ Hz), 119.66 (d, $J_{PC} = 8.9$ Hz), 62.28 (d, $J_{PC} = 5.1$ Hz), 57.71 (d, $J_{PC} = 2.2$ Hz), 25.54 (d, $J_{PC} = 103.6$ Hz), 16.34 (d, $J_{PC} = 4.4$ Hz). HRMS (EI) *m*/*z* calcd for $C_8H_{17}O_4P$ (M^+) 208.0864, found 208.0873; calcd for $C_8H_{16}O_3P$ ($M^+ - OH$) 191.0837, found 191.0842.

4-(Diethoxyphosphoryl)-2*E*-butenal (20E). To a solution of alcohol **24** (430 mg, 2.06 mmol) in acetone (10 mL) was added dropwise CrO_3 in 2 N H_2SO_4 (210 mg, 2.07 mmol, 2.1 mL of 100 mg/mL CrO_3 solution) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C, and another 15 min at room temperature, then quenched by addition of 1 mL of 2-propanol. After the mixture was stirred for another 10−15 min, solid $NaHCO_3$ (1 g) was added, and the mixture was stirred for a few minutes and then filtered. The filtrate was refluxed (60 °C) for 30−60 min for isomerization (before isomerization, *E*/*Z* = 4:1). After the mixture was cooled to room temperature, acetone was removed with a rotary evaporator. The aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The organic extract was washed with water and brine, dried ($MgSO_4$), and concentrated. TLC (4% MeOH in CH_2Cl_2, $R_f = 0.27$) and ^{1}H NMR showed that the product (380 mg, 90%) was suitable for the next reaction without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.49 (d, $J = 7.8$ Hz, 1 H), 6.75 (ddd, $J = 15.5$, 15.4, 7.9 Hz, 1 H), 6.18 (m, 1 H), 4.0−4.2 (4 H), 2.84 (dd, $J = 22.5$, 7.7 Hz, 2 H), 1.28 (t, $J = 7.1$ Hz, 6 H). The NMR spectrum is consistent with that reported previously.[26]

(5-Aza-5-cyclohexylpenta-2,4-dienyl)diethoxyphosphin-1-one (19). To a solution of the phosphoryl aldehyde **20E** (160 mg, 0.78 mmol) in dry THF (1.5 mL) was added dropwise cyclohexylamine (77.5 mg, 0.78 mmol) at room temperature under argon atmosphere. After 1 h, freshly activated 4 Å molecular sieves (ca. 0.1 g/0.1 g of the aldehyde) were added, and the reaction mixture was stirred gently overnight to provide intermediate **19** in situ. The ^{1}H NMR spectrum of **11** is in agreement with that reported previously.[26]

Methyl 13-Oxotrideca-9*E*,11*E*-dienoate (27). The resulting bright orange solution of imine **19** was added dropwise to a solution of LDA (0.66 mmol, 380 μL of 2 M solution in hexane, 0.97 equiv) at −78 °C under an argon atmosphere via a airtight syringe. The color of the solution changed instantaneously to deep red. After the mixture was stirred for 1 h at −78 °C, methyl 9-oxononanoate **14** (115 mg, 0.62 mmol) in dry THF (1 mL) was added. The resulting mixture was stirred at −78 °C for 1 h and then warmed to 0 °C for 2 h and room temperature for another 1 h. Then water (3 mL) was added, and the mixture was stirred for a few minutes and then extracted with ethyl ether (3 × 5 mL). The organic extract was dried over $MgSO_4$. Rotary evaporation of the solvent provided the crude cyclohexyl imine as an orange-red oil. The crude product was hydrolyzed[37] and purified via flash chromatography on a silica gel column (10% ethyl acetate in hexanes, TLC, $R_f = 0.25$, with a depth of 8−9 in. of silica gel, instead of the 5−6 in. recommended,[38] to improve the hydrolysis of the imines) to afford methyl 13-oxotrideca-9,11-dienoate (**27**, 70 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.51 (d, $J = 8$ Hz, 1 H), 7.05 (m, br dd, $J = 15.3$, 9.8 Hz, 1 H), 6.25 (m, 2 H), 6.04 (dd, $J = 15.3$, 8.0 Hz, 1 H), 3.63 (s, 3H), 2.27 (t, $J = 7.3$ Hz, 2 H), 2.22 (m, 2 H), 1.5−1.7 (2 H), 1.3−1.5 (2 H), 1.15−1.35 (6 H). HRMS (EI): *m*/*z* calcd for $C_{14}H_{22}O_3$ (M^+) 238.1569, found 238.1573; calcd for $C_{14}H_{23}O_3$ (MH^+) 239.1649, found 1239.1654.

Methyl 13,13-Dimethoxytrideca-9*E*,11*E*-dienoate (28). K-10 montmorillonite clay (2 g) was mixed with trimethyl orthoformate (1.5 mL) and methanol (1.5 mL). The resulting mixture was stirred for a few minutes and then filtred. The wet filter cake (Taylor reagent for acetalization[15]) was used directly without any further treatment. Methyl 13-oxotrideca-9*E*,11*E*-dienoate (**27**, 57 mg, 0.24 mmol) was stirred with a suspension of the K-10 montmorillonite/trimethyl orthoformate reagent (200 mg) in dichloromethane (1 mL) at room temperature for 2 h, with monitoring by TLC until complete conversion. The mixture was filtered through a Celite 521 bed, followed by washing the filtrate with saturated $NaHCO_3$ solution, water, and brine and drying over $MgSO_4$. The solvent was removed by rotary evaporation. The last traces of solvent were transferred into a dry ice−acetone cooled trap under high vacuum (0.1 mmHg) for 1 h to afford the desired product **28** (60 mg, 88%). Because the compound partially decomposed on the silica gel column, the product was used immediately for next step without further purification (>95% pure by NMR, TLC 10% ethyl acetate in hexanes, $R_f = 0.17$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.26 (ddd, $J = 15.4$, 10.3, 1.0 Hz, 1 H), 5.99 (bdd, $J = 15.0$, 10.3 Hz, 1 H), 5.70 (dt, $J = 14.8$, 8.3 Hz, 1 H), 5.45 (dd, $J = 15.4$, 5.2 Hz, 1 H), 4.76 (d, $J = 5.2$ Hz, 1 H), 3.61 (s, 3 H), 3.26 (s, 6 H), 2.25 (t, $J = 7.5$ Hz, 2 H), 2.03 (td $J = 6.9$, 6.5 Hz, 2 H), 1.45−1.65 (2 H), 1.10−1.40 (8 H). ^{13}C NMR ($CDCl_3$, 75 MHz, APT): δ 174.29 (C), 137.13 (CH), 134.13 (CH), 129.08 (CH), 126.44 (CH), 102.87 (CH), 52.59 (CH_3), 51.46 (CH_3), 34.07 (CH_2), 32.61 (CH_2), 32.44 (CH_2), 29.07 (CH_2), 24.92 (CH_2), 24.53 (CH_2). HRMS (EI): *m*/*z* calcd for $C_{16}H_{28}O_4$ (M^+) 284.1987, found 284.1993; calcd for $C_{16}H_{27}O_4$ ($M^+ - H$) 283.1907, found 283.1907; calcd for $C_{15}H_{25}O_3$ ($M^+ - HOMe$) 252.1724, found 252.1734.

13-Oxotrideca-9*E*,11*E*-dienoic Acid (OTDEA, 18). Methyl 13,13-dimethoxytrideca-9*E*,11*E*-dienoate (**28**, 50 mg, 0.176 mmol) was stirred with a solution of sodium hydroxide (35 mg, 0.875 mmol) in water/methanol/THF (2:5:3, v/v/v, 1 mL) at room temperature. The reaction was monitored by TLC until complete disappearance of the starting material. After being stirred for 2.5 h, the reaction mixture was acidified to pH 3 with ice-cold 1 N HCl. The resulting acidic solution was stirred for 30 min under a N_2 atmosphere at room temperature and then extracted with ethyl acetate (3 × 5 mL). The organic extract was washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation. Flash chromatography on a silica gel column afforded the hydrolyzed dienoic acid **OTDEA** (**18**, 32 mg, 82%), TLC (ethyl acetate/hexanes/acetic acid, 45:55:0.5, v/v/v, $R_f = 0.35$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.48 (d, $J = 8.0$ Hz, 1 H), 7.05 (dd, $J = 15.4$, 9.9 Hz, 1 H), 6.20−6.30 (2 H), 6.04 (dd, $J = 15.4$, 8.0 Hz, 1 H), 2.30 (t, $J = 7.4$ Hz, 2 H), 2.17 (td, $J = 6.8$, 6.6 Hz, 2 H), 1.55−1.65 (2 H), 1.15−1.55 (8 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.18 (CHO), 179.98 (COOH), 153.06, 147.37, 130.05, 128.76, 34.03, 33.18, 29.02, 28.96, 28.48, 24.62. HRMS (EI): *m*/*z* calcd for $C_{13}H_{20}O_3$ (M^+) 224.1412, found 224.1413. The NMR spectrum is consistent with that reported (isolated from lipid oxidation).[22,34]

13,13-Dimethoxytrideca-9*E*,11*E*-dienoic Acid (29). Methyl 13,13-dimethoxytrideca-9*E*,11*E*-dienoate (**28**, 30 mg,

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0.105 mmol) was stirred with a solution of sodium hydroxide (25 mg, 0.625 mmol) in water/methanol/THF (2:5:3, v/v/v, 1 mL) at room temperature. The reaction was monitored by TLC until complete disappearance of the starting material. After being stirred for 2.5 h, the reaction mixture was acidified to pH 4 with ice-cold 0.5 N HCl and then extracted with ethyl acetate (3 × 5 mL) at 0 °C. The organic extract was washed with water and brine and then dried over $MgSO_4$. The solvent was removed by rotary evaporation. The last traces of solvent were transferred into a dry ice−acetone cooled trap under high vacuum (0.1 mmHg) for 3 h to give the acetal acid **29** in 80% yield. This product was used for next reaction without further purification, TLC (ethyl acetate/hexanes/acetic acid, 45:55:0.1, v/v/v, $R_f = 0.3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.27 (dd, J = 14.5, 10.5 Hz, 1 H), 6.00 (dd, J = 14.5, 10.2 Hz, 1 H), 5.71 (J = 15.0, 6.8 Hz, 1 H), 5.46 (dd, J = 15.0, 5.1 Hz, 1 H), 4.77 (d, J = 5.2 Hz, 1 H), 3.27 (s, 6 H), 2.26 (t, J = 7.5 Hz, 2 H), 2.04 (td, J = 6.6, 5.1 Hz, 2 H), 1.45−1.65 (2 H), 1.15−1.45 (8 H). HRMS (EI): m/z calcd for $C_{16}H_{28}O_4$ (M^+) 270.1831, found 270.1830.

Dienal Phospholipid (OTDE-PC, 6). A mixture of the dienoic acid **29** (24 mg, 0.107 mmol) and 1-palmitoyl-2-lyso-*sn*-glycero-3-phosphatidylcholine (25 mg, 0.05 mmol) was dried by transfer of moisture into a dry ice−acetone-cooled trap under high vacuum (0.1 mmHg) for 5 h at room temperature and then dissolved in dry $CHCl_3$ (2 mL, freshly distilled from P_2O_5). Dicyclohexylcarbodiimide (DCC, 33 mg, 0.16 mmol) and *N*,*N*-dimethylaminopyridine (DMAP, 7 mg, 0 .06 mmol) were added. The resulting mixture was stirred for 48 h, washed with 1N HCl (1 mL), and extracted with $CHCl_3$/MeOH (2:1, v/v) solution (4 × 5 mL). The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel with $CHCl_3$/MeOH/H_2O (55:40:5, v/v/v, $R_f = 0.23$) to deliver the dienal phospholipid **OTDE-PC** (**6**, 27 mg, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.51 (d, J = 8.0 Hz, 1 H), 7.06 (m, 1 H), 6.15−6.35 (2 H), 6.05 (dd, J = 15.4, 8.0 Hz, 1 H), 5.17 (bs, 1 H), 4.25−4.45 (3 H), 4.10 (m, 1 H), 3.94 (m, 2 H), 3.80 (m, 2 H), 3.36 (bs, 9 H), 2.12−2.35 (6 H), 1.5−1.65 (6 H), 1.40−1.50 (2 H), 1.10−1.40 (30 H), 0.85 (t, J = 6.9 Hz, 3 H). HRMS (FAB, NaI/mNBA/PEG_{246}): m/z calcd for $C_{37}H_{68}NNaO_9P^+$ (MNa^+) 724.4529, found 724.4544.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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