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# An efficient synthesis of γ-hydroxy-α,β-unsaturated aldehydic esters of 2-lysophosphatidylcholine

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ABSTRACT

The diverse biological activities of γ-hydroxyalkenal phospholipids and their involvement in disease are the subject of intense study. Phospholipid aldehydes, such as the 4-hydroxy-7-oxohept-5-enoic acid ester of 2-lyso-phosphatidylcholine (HOHA-PC), the 5-hydroxy-8-oxo-6-octenoic acid ester of 2-lyso-PC (HOOA-PC), and the 9-hydroxy-12-oxododec-10-enoic acid ester of 2-lyso-PC (HODA-PC), are generated by oxidative cleavage of polyunsaturated fatty acyl phospholipids. To facilitate investigations of their chemistry and biology, we now report efficient total syntheses of HOOA, HODA, and HOHA phospholipids. Because the target γ-hydroxyalkenals readily decompose through oxidation of the aldehyde group to a carboxylic acid or through cyclization to furans, these syntheses generate the sensitive functional array of the target phospholipids under mild conditions from acetal derivatives that are suitable for long-term storage.



## 1. Introduction

Free radical-induced oxidative cleavage of phospholipids containing docosahexaenoate ($C_{22}$), arachidonate ($C_{20}$), or linoleate ($C_{18}$) generates truncated, biologically active aldehydes including γ-hydroxyalkenal phospholipids, that is, the 4-hydroxy-7-oxohept-5-enoic acid ester of 2-lyso-phosphatidylcholine (HOHA-PC), the 5-hydroxy-8-oxo-6-octenoic acid ester of 2-lyso-PC (HOOA-PC), and the 9-hydroxy-12-oxododec-10-enoic acid ester of 2-lyso-PC (HODA-PC), respectively (Scheme 1). These γ-hydroxyalkenals react with protein lysyl ε-amino residues to generate biologically active carboxyalkylpyrrole derivatives (Scheme 1).[1,2] HOHA-PC, HOOA-PC and HODA-PC, and the derived protein adducts 2-(ω-carboxyethyl)pyrroles (CEPs), 2-(ω-carboxypropyl)pyrroles (CPPs), and 2-(ω-carboxyheptyl)pyrroles (CHPs), are present in human atherosclerotic lesions.[3–5] The γ-hydroxyalkenal phospholipids contribute to the generation of atherosclerotic plaques. Thus, they promote the conversion of monocyte macrophages into foam cells by serving as ligands for the scavenger receptor CD36 that mediates endocytosis of oxidized low-density lipoprotein particles by macrophage cells.[6,7] Binding of these phospholipids, and their more oxidized derivatives, to platelet CD36 receptors induces aggregation leading to thrombosis.[8] Their binding to the macrophage scavenger receptor class B, type I (SR-BI) prevents binding of its physiological ligand, high-density lipoprotein, to SR-BI and consequently interferes with SR-BI-mediated selective uptake of cholesteryl esters in hepatocytes.[9] Thus, oxidative stress resulting in the accumulation of specific oxidized phospholipids in plasma may have an inhibitory effect on reverse cholesterol transport. HOOA-PC induces monocyte binding to endothelial cells[10–12] and this may promote infiltration of monocyte macrophages into the subendothelial space where they become foam cells through unregulated endocytosis of oxidized low-density lipoprotein. Also, HOOA-PC inhibits lipopolysaccharide-induced expression of E-selectin a major endothelial cell adhesion molecule involved in neutrophil binding.[10] Specifically, HOOA-PC induces expression of chemokines that promote interaction with monocytes.[13] Thus, HOOA-PC is important as a putative proinflammatory molecule regulating leukocyte endothelial interactions.[11,14] Furthermore, covalent modification of proteins by HOOA-PC and HODA-PC results, inter alia, in impaired proteolytic degradation of internalized macromolecules by mouse peritoneal macrophages and inhibition of cathepsin B, a lysosomal protease. HOHA-PC also inhibits posttranslational processing of the nascent 25 kDa membrane fusion protein Rab5a to produce the active 23 kDa 'mature' Rab5a in phagosomal membranes.[15] Most recently, proteins containing CEPs, that are generated in vivo from HOHA-PC, were shown to initiate destruction of the retina in age-related macular degeneration.[16] We previously reported total syntheses of HOHA-, HOOA-, and HODA-PC.[1,3] However, those syntheses were lengthy and involved reactions that are difficult to perform. Herein, we report superior syntheses of HOOA, HODA, and HOHA derivatives that will facilitate investigation of their biological involvements.

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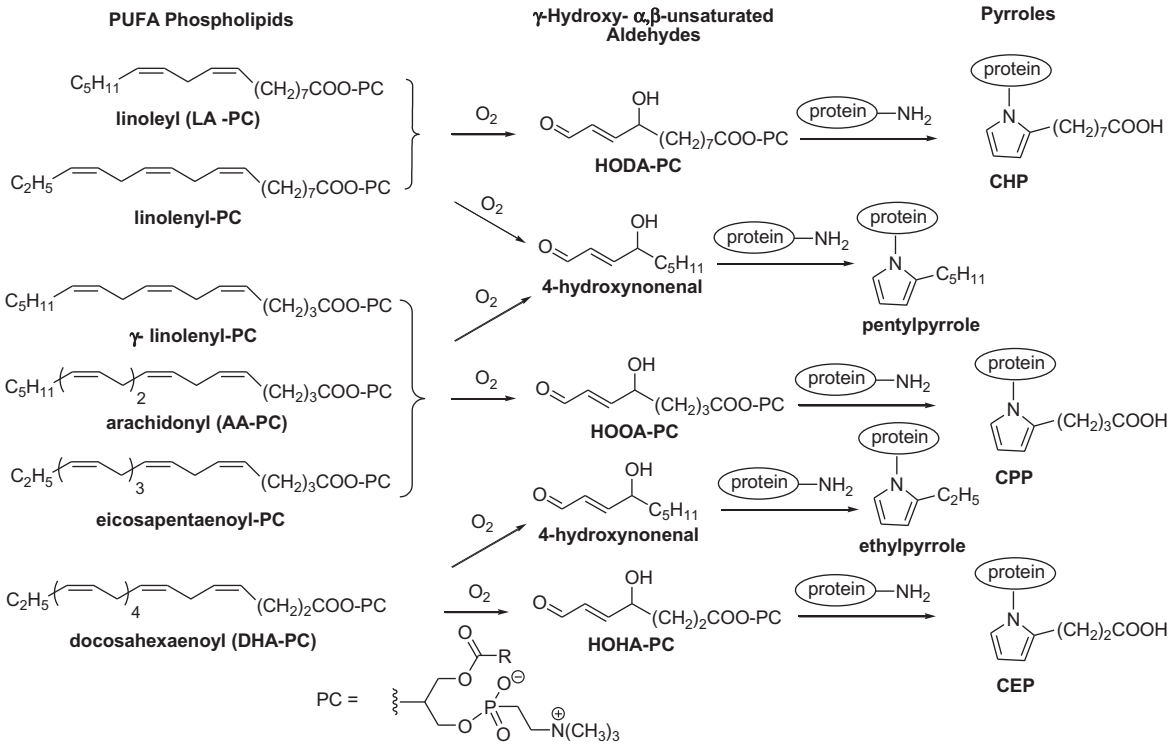
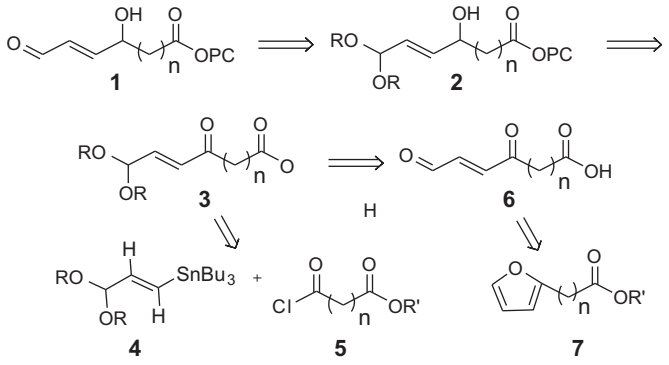



**Scheme 1.** Oxidation of polyunsaturated fatty acids generates γ-hydroxy-α,β-unsaturated aldehydes, that react with proteins and form 2-[ω-carboxylalkyl)pyrroles.

## 2. Results and discussion

### 2.1. Synthetic design

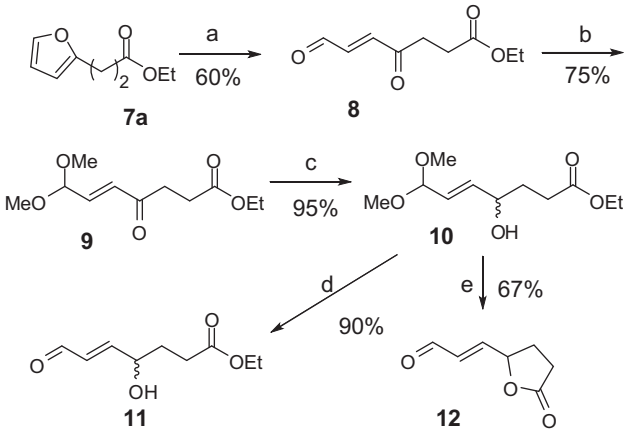
γ-Hydroxyalkenals readily decompose through oxidation of the aldehyde group to a carboxylic acid or cyclization to furans. Therefore, a synthetic strategy was designed that generates the sensitive functional array of the target phospholipids **1** under mild conditions from stable acetal precursors **2** that are suitable for long-term storage, and that might be readily converted to the target γ-hydroxyalkenal phospholipids under mild conditions (Scheme 2). Masking of the aldehyde carbonyl as an acetal also allows selective reduction of the ketone carbonyl in the ketoalkenal derivatives **3**. The precursors **3** might be assembled through cross-coupling of the known vinyl tin **4** and acid chlorides **5.** Alternatively, keto alkenal precursors **6** are readily available via oxidation of furans **7**.



**Scheme 2.** Retrosyntheses of γ-hydroxyalkenal phospholipids.

### 2.2. HOHA ethyl ester

To test the feasibility of generating the requisite γ-hydroxyalkenal functional array in two byselective reduction of a ketone from an ester of **3** ($n$ = 2, R = Me), we synthesized (*E*)-ethyl-4-hydroxy-7-oxohept-5-enoate (**11**) (Scheme 3). The furyl ester **7a** was oxidatively ring opened with *N*-bromosuccinimide (NBS).[17] The resulting keto aldehyde **8** was selectively protected using trimethyl orthoformate and Montmorillonite K10[18] to give **9**. Reduction of the ketone carbonyl in **9** was readily accomplished in excellent yield to provide the masked γ-hydroxyalkenal **10**. The target γ-hydroxyalkenal **11** could be generated by hydrolysis of the dimethyl acetal in **10** promoted by the weak acid, pyridinium




**Scheme 3.** Synthesis of HOHA ethyl ester. Reagents and conditions: (a) NBS, THF/acetone/$H_2O$ (5:4:1), pyridine; (b) K 10/$CH(OCH_3)_3$; (c) $NaBH_4$, MeOH; (d) PPTS, acetone/$H_2O$ (2:1); (e) Amberlyst-15, acetone/$H_2O$ (2:1), 67% or TFA/$H_2O$ (95:5), rt, 61%.

*p*-toluenesufonic acid (PPTs). However, concomitant transesterification delivered the lactone **12** in excellent yield when the hydrolysis was performed in the presence of stronger acid catalysts, such as Amberlyst-15 or TFA.

### 2.3. HOOA methyl ester

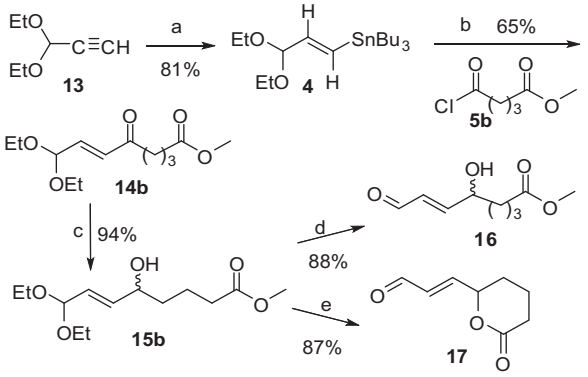
In an alternative approach (Scheme 4), the requisite carbon skeleton was assembled by regio- and stereoselective tributylstannylcupration of 3,3-diethoxyprop-1-yne (**13**) with the Lipshutz reagent,[19] $Bu_3SnCu(Bu)CNLi_2$, followed by $PdCl_2(CH_3CN)_2$ catalyzed acylation of the resulting vinyltin **4**[20] with glutaric acid monomethyl ester chloride (**5b**).[21] Reduction of the resulting ketone **14b** with sodium borohydride gave the stable masked γ-hydroxyalkenal **15b** in excellent yield. The target γ-hydroxyalkenal **16** could be generated by hydrolysis of **15b** promoted by a weak acid. However, as for the **10**→**11** conversion above, concomitant transesterification delivered the lactone **17** when the hydrolysis was performed in the presence of stronger acid catalysts.

### 2.4. HOHA-PC

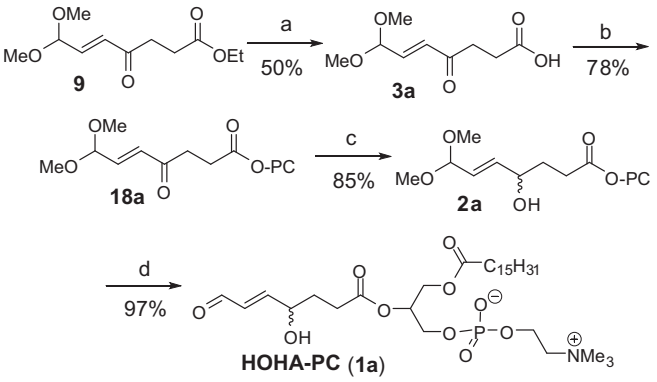
Enzymatic hydrolysis of ethyl ester **9** with porcine pancreatic lipase (PPL) in phosphate buffer saline (PBS) buffer afforded key intermediate **2** (Scheme 5), that is precursor for many oxidized phospholipids.[22] When lithium hydroxide was applied to hydrolyze methyl ester group, the diethyl acetal moiety was also deprotected. Therefore, selective enzymatic hydrolysis of the ester at pH 7 was considered. Synthesis of PC-ester **18** was efficiently accomplished using the coupling reagents 2,6-dichlorobenzoyl chloride and 1-methylimidazole,[23,24] resulting in 50% shorter reaction time and improved yield of the ester coupling product, as compared to using general coupling reagents such as dicyclohexylcarboimide and 4-*N*,*N*-dimethylaminopyridine, which adhere to silica gel resulting in laborious separation via chromatography. Selective reduction of ketone **18a** using $NaBH_4$ in methanol and subsequent mild deprotection of the dimethylacetal **2a** gave HOHA-PC **1a** in excellent yield.

### 2.5. HOOA and HODA-PCs

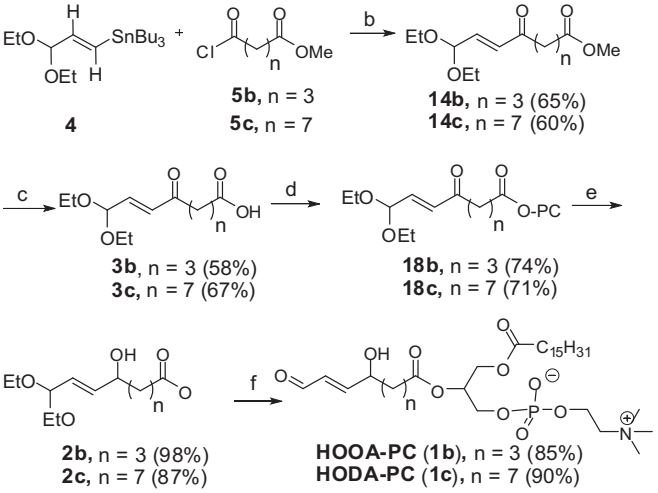
HOOA-PC (**1b**) and HODA-PC (**1c**) were assembled by $PdCl_2(CH_3CN)_2$-catalyzed acylation of vinylstannane **4**[20] with glutaric acid monomethyl ester chloride (**5b**) or azelaeic acid monomethyl ester chloride (**5c**)[25–27] to generate ketones **14b** or **14c**, respectively (Scheme 6). Acylation of L-α-lysophosphatidylcholine (HO-PC) with the carboxylic acids produced by hydrolysis of the



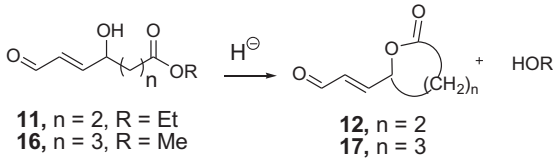

**Scheme 4.** Synthesis of HOOA methyl ester. Reagents and conditions: (a) $Bu_3SnCu(Bu)CNLi_2$, THF, −78 °C, then $H_2O$; (b) $PdCl_2(MeCN)_2$ (1 mol %), DMF, 0 °C; (c) $NaBH_4$, EtOH, 0 °C; (d) PPTS, acetone/$H_2O$ (2:1), rt; (e) Amberlyst-15, TFA/$H_2O$ (95:5), rt.




**Scheme 5.** Synthesis of HOHA-PC. Reagents and conditions: (a) porcine pancreatic lipase, phosphate buffer; (b) L-α-lysophosphatidylcholine (HO-PC), 2,6-dichlorobenzoyl chloride, 1-methylimidazole, $CH_2Cl_2$; (c) $NaBH_4$, MeOH, (d) PPTS, THF/acetone/$H_2O$ (5:4:1).




**Scheme 6.** Syntheses of HOOA and HODA-PCs. Reagents and conditions: (a) oxalyl chloride, benzene; (b) $PdCl_2(MeCN)_2$ (1 mol %), DMF, 0 °C; (c) porcine pancreatic lipase, PBS; (d) L-α-lysophosphatidylcholine (HO-PC), 2,6-dichlorobenzoyl chloride, 1-methylimidazole, $CH_2Cl_2$; (e) $NaBH_4$, MeOH; (f) PPTS, THF/acetone/$H_2O$ (5:4:1).




**Scheme 7.** Lactone formation is promoted by strong acid.

methyl esters **3** followed by selective reduction of the ketone carbonyl delivered stable precursors **2** of the γ-hydroxyalkenal phospholipids **1**.

## 3. Conclusion

New total syntheses readily deliver the γ-hydroxy-α,β-unsaturated aldehydic esters HOHA-PC (**1a**), HOOA-PC (**1b**), and HODA-PC (**1c**) of 2-lysophosphatidylcholine from the corresponding acetals **2**. These relatively stable precursors are protected against oxidative degradation of the aldehyde and cyclization to furans. However, our model studies with **11** and **16** revealed a potential pitfall, acid-catalyzed lactonization to **12** or **17**, respectively (Scheme 7). Since L-α-lysophosphatidylcholine (HO-PC)—that

would be released by such lactonization of HOHA-PC (**1a**) or HOOA-PC (**1b**)—is biologically active, it is important to avoid strongly acidic conditions during the generation of these oxidatively truncated phospholipids from the stable acetal precursors.

## 4. Experimental section

### 4.1. Ethyl (*E*)-4,7-dioxohept-5-enoate (8)

*N*-Bromosuccinimide (NBS, 1.59 g, 8.9 mmol) was dissolved in tetrahydrofuran/acetone/$H_2O$ (5:4:1, 12 mL) and slowly added to a solution of ethyl-(3-(2-furyl)propanoate (**7a**, 1 g, 5.9 mmol) and pyridine (962 μL, 11.9 mmol) in tetrahydrofuran/acetone/$H_2O$ (5:4:1, 8 mL) at −20 °C. The solution was stirred for 1 h at −20 °C and 3 h at room temperature. The solvents were then evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (30% ethyl acetate/hexanes, TLC: $R_f$ = 0.3) to give **8** (653 mg, 60%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.76 (d, *J* = 7.1 Hz, 1H), 6.89 (d, *J* = 16.2 Hz, 1H), 6.79 (dd, *J* = 16.9, 7.0 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.99 (t, *J* = 6.2 Hz, 2H), 2.65 (t, *J* = 6.1 Hz, 2H), 1.22 (t, *J* = 6.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) 198.2, 193.4, 172.3, 144.5, 137.7, 60.9, 35.8, 27.9, 14.2. HRMS (FAB): *m/z* calcd for $C_9H_{13}O_4$ ($MH^+$), 185.0814; found, 185.0818.

### 4.2. Ethyl (*E*)-7,7-dimethoxy-4-oxohept-5-enoate (9)

Aldehyde **8** (299 mg, 1.6 mmol) was stirred with suspension of the Montmorillonite K-10 (500 mg) and trimethyl orthoformate (500 μL) in dry dichloromethane (3 mL) at room temperature for 1 h. The mixture was then filtered through a pad of Celite 521, followed by washing the residue with dichloromethane (10 mL). The solvents were evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (10% ethyl acetate/hexanes) to give **9** (280 mg, 75%). TLC (30% ethyl acetate/hexanes, $R_f$ = 0.32): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.62 (dd, *J* = 19.5, 3.9 Hz, 1H), 6.37 (dd, *J* = 16.2, 1.1 Hz, 1H), 4.93 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.32 (s, 6H), 2.89 (t, *J* = 6.6 Hz, 2H), 2.60 (t, *J* = 6.6 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) 198.1, 172.8, 140.8, 131.9, 101.1, 60.8, 53.1, 35.3, 28.1, 14.4. HRMS (FAB): *m/z* calcd for $C_{11}H_{19}O_5$ ($MH^+$), 231.1232; found, 231.1235.

### 4.3. Ethyl (*E*)-4-hydroxy-7,7-dimethoxyhept-5-enoate (10)

Sodium borohydride (9.4 mg, 0.25 mmol) was added in small portions over 5 min at 0 °C to a stirred solution of ester **9** (47.7 mg, 0.2 mmol) in ethanol (1.5 mL). The reaction mixture was stirred for 4 h and then quenched by addition of methanol to destroy excess sodium borohydride. The mixture was neutralized to pH 7 by addition of saturated sodium bicarbonate solution, followed by addition of brine. The aqueous layer was extracted with ethyl acetate. Solvents were evaporated from the combined organic extracts under reduced pressure, and the residue purified by flash chromatography on a silica gel column (20% ethyl acetate/hexanes) to give **10** (45.7 mg, 95%). TLC (45% ethyl acetate/hexanes, $R_f$ = 0.21): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.88 (ddd, *J* = 15.8, 5.7, 1.0 Hz, 1H), 5.69 (ddd, *J* = 15.8, 4.7, 1.3 Hz, 1H), 4.79 (d, *J* = 4.8 Hz, 1H), 4.22 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.31 (s, 6H), 2.45 (t, *J* = 6.6 Hz, 2H), 2.06 (s, –OH), 2.00–1.74 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). HRMS (FAB): *m/z* calcd for $C_{11}H_{20}NaO_5$ ($MNa^+$), 255.1209; found, 255.1206.

### 4.4. Ethyl (*E*)-4-hydroxy-7-oxohept-5-enoate (11)

Acetal **10** (5 mg, 0.02 mmol) was dissolved in acetone/water = 2:1 (0.5 mL) and pyridinium *p*-toluenesulfonate (PPTS, 5.9 mg, 0.022 mmol) was added and the mixture was stirred at room temperature for 2 h. Solvents were then evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (20% ethyl acetate/hexanes) to give **11** (3.6 mg, 90%). TLC (45% ethyl acetate/hexanes, $R_f$ = 0.20): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.60 (d, *J* = 7.8 Hz, 1H), 6.80 (dd, *J* = 15.7, 4.4 Hz, 1H), 6.35 (ddd, *J* = 15.7, 7.8, 1.7 Hz, 1H), 4.54 (m,1H), 4.15 (q, *J* = 7.1 Hz, 3H), 2.59 (d, *J* = 4.8 Hz, 1H), 2.50 (ddd, *J* = 1 7.1, 10.4, 7.6 Hz, 3H), 2.14–1.98 (m, 1H), 1.89 (dt, *J* = 14.4, 6.6 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 6H). HRMS (FAB): *m/z* calcd for $C_9H_{13}O_3$ ($MH^+-H_2O$), 169.0865; found, 169.0867.

### 4.5. (*E*)-3-(5-Oxotetrahydrofuran-2-yl)acrylaldehyde (12)

*Method (A)*: Amberlyst-15 (15 mg) was added in small portions to a stirred solution of acetal **10** (15 mg, 0.06 mmol) in acetone/water = 3:1 (1.5 mL) and the mixture was stirred at room temperature for 2 h. Solvents were then evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (40% ethyl acetate/hexanes) to give lactone **12** (6 mg, 67%). TLC (50% ethyl acetate/hexanes, $R_f$ = 0.15).

*Method (B)*: Acetal **10** was dissolved in TFA/$H_2O$ = 95:5 (1 mL) and stirred for 1.5 h. Solvents were then evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (40% ethyl acetate/hexanes) to give lactone **12** (5.5 mg, 61%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.60 (d, *J* = 7.6 Hz, 1H), 6.80 (dd, *J* = 15.8, 4.7 Hz, 1H), 6.32 (ddd, *J* = 15.8, 7.6, 1.6 Hz, 1H), 5.31–5.10 (m, 1H), 2.69–2.43 (3H), 2.20–1.97 (m, 1H). HRMS (FAB): *m/z* calcd for $C_7H_9O_3$ ($MH^+$), 141.0551; found, 141.0473. The $^1$H NMR spectral data for **12** is in agreement with that reported previously.[28,29]

### 4.6. (*E*)-7,7-Dimethoxy-4-oxohept-5-enoic acid (3a)

To increase solubility at room temperature ester **9** (205 mg, 0.89 mmol) was dissolved in PBS (pH 7.4, 50 mM, 7 mL) and methanol (1 mL). To this rapidly stirred solution, was then added porcine pancreatic lipase (type II, crude, 50 mg), sodium chloride (5 mg), and calcium chloride (10 mg). The pH of the reaction mixture was maintained at 7.0–7.2 by addition of sodium hydroxide solution (0.1 N). Upon completion, the solution was evaporated under reduced pressure, the residue extracted with chloroform/methanol (2:1, v/v), filtered, and dried with anhydrous magnesium sulfate. Solvents were then evaporated from the combined organic extracts under reduced pressure and the residue purified by flash chromatography on a silica gel column (chloroform/methanol = 20:1) to give **3a** (90 mg, 50%). TLC (chloroform/methanol/$H_2O$ = 80:19:1, $R_f$ = 0.44): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.63 (dd, *J* = 16.4, 4 Hz, 1H), 6.38 (dd, *J* = 16.4, 1.2 Hz, 1H), 4.95 (dd, *J* = 4.0, 1.6 Hz, 1H), 3.33 (s, 6H), 2.90 (t, *J* = 6.4 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) 198.2, 178.4, 140.1, 131.8, 101.1, 53.2, 35.3, 28.1. HRMS (FAB): *m/z* calcd for $C_9H_{14}NaO_5$ ($MNa^+$), 225.0740; found, 225.0746.

### 4.7. (*E*)-(7,7-Dimethoxy-4-oxohept-5-enoyl)-1-palmitoyl-*sn*-glycero-3-phosphatidylcholine (18a)

1-Methylimidazole (18.7 μL, 0.23 mmol) and 2,6-dichlorobenzoyl chloride (37 μL, 0.26 mmol) were added to a solution of acid **3a** (31.7 mg, 0.16 mmol) and L-α-lysophosphatidylcholine (38.8 mg, 78 μmol) in dry methylene chloride (4 mL). The resulting mixture was stirred for 20 h at room temperature and monitored by TLC for disappearance of starting material. Solvents were then evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (chloroform/methanol/$H_2O$ = 16:9:1, TLC: $R_f$ = 0.23) to give **18a** (41.5 mg, 78%). $^1$H

NMR (400 MHz, $CD_3OD/CDCl_3$ = 1:2) $\delta$ 6.61 (dd, $J$ = 16.2, 3.9 Hz, 1H), 6.36 (d, $J$ = 16.2 Hz, 1H), 5.19 (m, 1H), 4.93 (m, 1H), 4.37 (m, 1H), 4.34 (m, 1H), 4.14 (dd, $J$ = 11.9, 6.4 Hz, 2H), 3.98 (m, 2H), 3.83 (m, 2H), 3.37 (br s, 9H), 3.34 (s, 6H), 2.89 (m, 2H), 2.62 (m, 2H), 2.27 (t, $J$ = 7.6 Hz, 2H), 1.56 (m, 2H), 1.24 (24H), 0.87 (t, $J$ = 7.0 Hz, 3H). $^{13}C$ NMR (100 MHz, $CD_3OD/CDCl_3$ = 1:2) 198.1, 173.8, 172.3, 141.0, 131.8, 101.1, 76.9, 71.7, 71.6, 66.7, 63.7, 62.9, 59.5, 54.7, 53.3, 35.1, 34.3, 32.2, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 28.1, 25.1, 22.3, 14.4. HRMS (FAB): $m/z$ calcd for $C_{33}H_{63}NO_{11}P$ ($M^+$), 680.4139; found, 680.4131.

### 4.8. (*E*)-2-(4-Hydroxy-7,7-dimethoxyhept-5-enoyl)-1-palmitoyl-*sn*-glycero-3-phosphatidylcholine (2a)

Sodium borohydride (1.7 mg, 45.8 μmol) was slowly added at 4 °C to a stirred solution of ester **18a** (26 mg, 38 μmol) in dry methylene chloride (0.5 mL) and methanol (1 mL). Once complete, the reaction mixture was neutralized with acetic acid, solvents were evaporated under reduced pressure, and the residue purified by flash chromatography on a silica gel column (chloroform/methanol/$H_2O$ = 11:9:1, TLC: $R_f$ = 0.27) to give **2a** (22.1 mg, 85%). $^1H$ NMR (400 MHz, $CD_3OD/CDCl_3$ = 1:2) $\delta$ 5.99 (dd, $J$ = 16, 6 Hz, 1H), 5.76 (dd, $J$ = 16.4, 4.8 Hz, 1H), 5.34 (m, 1H), 4.89 (d, 1H), 4.51 (m, 1H), 4.42 (m, 2H), 4.27 (dd, $J$ = 12, 6.8 Hz, 2H), 4.12 (m, 2H), 3.82 (m, 2H), 3.48 (s, 1H), 3.44 (br s, 9H), 3.37 (s, 6H), 2.56 (m, 2H), 2.43 (m, 2H), 1.93 (m, 2H), 1.70 (m, 2H), 1.41 (24H), 0.98 (t, $J$ = 6.8 Hz, 3H). $^{13}C$ NMR (100 MHz, $CD_3OD/CDCl_3$ = 1:2) 173.8, 173.0, 137.8, 128.6, 101.0, 76.9, 71.8, 71.6, 70.2, 66.4, 63.6, 62.9, 59.4, 54.7, 53.4, 35.1, 34.3, 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 28.3, 25.2, 22.3, 14.4. HRMS (FAB): $m/z$ calcd for $C_{33}H_{63}NNaO_{11}P$ ($(M-H)Na^+$), 704.4115; found, 704.4119.

### 4.9. (*E*)-2-(4-Hydroxy-7-oxohept-5-enoyl)-1-palmitoyl-*sn*-glycero-3-phosphatidylcholine (HOHA-PC, 1a)

PPTS (1.3 mg, 5.1 μmol) was added to a stirred solution of ester **2a** (3.2 mg, 4.6 μmol) in tetrahydrofuran/acetone/$H_2O$ = 5:4:1 (1 mL). The resulting mixture was stirred for 2 h at room temperature and monitored by TLC for disappearance of starting material. Upon completion, the solvents were evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (chloroform/methanol/$H_2O$ = 11:9:1, TLC: $R_f$ = 0.2) to give **1a** (2.9 mg, 97%). $^1H$ NMR (400 MHz, $CD_3OD/CDCl_3$ = 1:2) $\delta$ 9.54 (d, $J$ = 8 Hz, 1H), 6.92 (dd, $J$ = 15.6, 4.4 Hz, 1H), 6.29 (dd, $J$ = 16, 8 Hz, 1H), 5.21 (m, 1H), 4.35 (m, 1H), 4.28 (m, 2H), 4.13 (m, 2H), 3.98 (m, 2H), 3.65 (m, 2H), 3.30 (s, 9H), 2.43–2.62 (m, 2H), 2.27–2.34 (m, 2H), 1.80–1.97 (m, 2H), 1.57 (m, 2H), 1.23 (24H), 0.85 (t, $J$ = 6.8 Hz, 3H). HRMS (FAB): $m/z$ calcd for $C_{31}H_{59}NNaO_{10}P$ ($M+H^+$), 636.3876; found, 636.3850.

### 4.10. 1-Tributylstannyl-3,3-diethoxy-prop-1-ene (4)

According to the published procedure,[21] 3,3-diethoxy-1-propyne (0.97 mL, 6.8 mmol) was added dropwise via syringe to a THF solution of $Bu_3SnCu(Bu)CNLi_2$, and the reaction mixture was stirred for 2 h under −78 °C before quenching with water. The dark solution was extracted with ether (3 × 20 mL), followed by drying of the combined extracts over anhydrous sodium sulfate. The solvents were evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (ethyl acetate/hexanes = 3:97, TLC: $R_f$ = 0.28) to give **4** (2.56 g, 81%). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.40–6.26 (m, 1H), 6.03–5.88 (m, 1H), 4.89–4.72 (m, 1H), 3.63 (dq, $J$ = 9.5, 7.1 Hz, 3H), 3.49 (dq, $J$ = 9.5, 7.1 Hz, 3H), 1.57–1.40 (9H), 1.36–1.25 (9H), 1.24–1.14 (6H), 0.93–0.80 (9H). The $^1H$ NMR spectral data for stannane **4** is in agreement with that reported previously.[30]

### 4.11. Methyl (*E*)-8,8-diethoxy-5-oxooct-6-enoate (14b)

The procedure was modified from that reported.[21] Glutaric acid monomethyl ester chloride (371 μL, 2.68 mmol) was added dropwise via syringe to a solution of stannane **4** (1.12 g, 2.68 mmol) and $PdCl_2(MeCN)_2$ (6.9 mg, 26.8 μmol) in DMF (3 mL). The reaction mixture was then cooled in an ice bath and stirred for 1 h, and then for 4 h at room temperature. Saturated aqueous sodium fluoride and acetone were added to the brown-red reaction mixture to remove tributyltin chloride. The mixture was extracted with ethyl acetate (3 × 20 mL), followed by drying of the combined extracts over anhydrous sodium sulfate. Solvent was evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (ethyl acetate/hexanes = 7:93) to give **14b** (450 mg, 65%). TLC: (30% ethyl acetate/hexanes; $R_f$ = 0.38). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.62 (dd, $J$ = 16, 4.4 Hz, 1H), 6.32 (dd, $J$ = 16.4, 1.2 Hz, 1H), 5.02 (m, 1H), 3.64 (s, 3H), 3.59–3.64 (m, 2H), 3.48–3.54 (m, 2H), 2.64 (t, $J$ = 6.6 Hz, 2H), 2.34 (t, $J$ = 7.2 Hz, 2H), 1.92 (tt, $J$ = 7.2, 7.2 Hz, 2H), 1.20 (t, $J$ = 7.2 Hz, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$) 199.6, 173.8, 141.5, 131.6, 99.7, 61.7, 51.8, 39.4, 33.2, 19.1, 15.4. HRMS (FAB): $m/z$ calcd for $C_{13}H_{23}O_5$ ($MH^+$), 259.1545; found, 259.1504.

### 4.12. Methyl (*E*)-8,8-diethoxy-5-hydroxyoct-6-enoate (15b)

Sodium borohydride (1.5 mg, 0.03 mmol) was added in small portions over 2 min at 0 °C to a stirred solution of ester **14b** (10 mg, 0.03 mmol) in ethanol (1 mL). The reaction mixture was stirred for 4 h and then quenched by addition of methanol to destroy excess sodium borohydride. The mixture was neutralized to pH 7 by addition of saturated sodium bicarbonate solution, followed by addition of brine. The aqueous layer was extracted with ethyl acetate, solvents were evaporated from the combined organic extracts under reduced pressure, and the residue purified by flash chromatography on a silica gel column (20% ethyl acetate/hexanes) to give **15b** (9.4 mg, 94%). TLC (45% ethyl acetate/hexanes, $R_f$ = 0.24): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.86 (dd, $J$ = 15.7, 6.0 Hz, 1H), 5.70 (ddd, $J$ = 15.7, 5.0, 1.2 Hz, 1H), 4.89 (d, $J$ = 5.0 Hz, 1H), 4.12 (m, 1H), 3.68–3.58 (5H), 3.55–3.41 (m, 2H), 2.34 (m, 2H), 1.77–1.62 (3H), 1.62–1.50 (2H), 1.29–1.13 (6H). HRMS (FAB): $m/z$ calcd for $C_{13}H_{24}NaO_5$ ($MNa^+$), 283.1522; found, 283.1523.

### 4.13. Methyl (*E*)-5-hydroxy-8-oxooct-6-enoate (16)

Acetal **15b** (9.4 mg, 0.03 mmol) was dissolved in acetone/water = 2:1 (1 mL), PPTS (10 mg, 0.033 mmol) was added, and the mixture stirred at room temperature for 2 h. After completion, solvents were evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (20% ethyl acetate/hexanes) to give **16** (5.9 mg, 88%). TLC (45% ethyl acetate/hexanes, $R_f$ = 0.20): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.58 (d, $J$ = 7.8 Hz, 1H), 6.81 (dd, $J$ = 15.7, 4.5 Hz, 1H), 6.32 (ddd, $J$ = 15.7, 7.8, 1.6 Hz, 1H), 4.45 (br s, –OH), 4.13 (q, $J$ = 7.1 Hz, 1H), 3.67 (s, 3H), 2.47–2.26 (2H), 1.86–1.51 (2H), 1.35–1.08 (2H). HRMS (FAB): $m/z$ calcd for $C_9H_{13}O_3$ ($MH^+-H_2O$), 167.0709; found, 167.0722.

### 4.14. (*E*)-3-(6-Oxotetrahydro-2H-pyran-2-yl)acrylaldehyde (17)

Amberlyst-15 (10 mg) was added in small portions to a stirred solution of acetal **15b** (16 mg, 0.06 mmol) in TFA/water = 95:5 (1.5 mL) and the mixture was stirred at room temperature for 1.5 h. Solvents were then evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (45% ethyl acetate/hexanes) to give lactone **17** (8.2 mg, 87%). TLC (50% ethyl acetate/hexanes, $R_f$ = 0.1): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$

9.61 (d, $J$ = 7.5 Hz, 1H), 6.76 (dd, $J$ = 15.8, 4.3 Hz, 1H), 6.37 (ddd, $J$ = 15.8, 7.6, 1.7 Hz, 1H), 5.19–5.04 (m, 1H), 2.76–2.62 (m, 1H), 2.55 (m, 1H), 2.18–2.05 (m, 1H), 2.06–1.87 (m, 2H), 1.83–1.64 (m, 1H). HRMS (TOF-MS/ESI): *m/z* calcd for $C_8H_{10}NaO_3$ ($MNa^+$), 177.0528; found, 177.0529. $^1$H NMR spectral data for **17** is in agreement with that reported previously.[28]

### 4.15. (*E*)-8,8-Diethoxy-5-oxooct-6-enoic acid (3b)

The acid **3b** was prepared using a solution of ester **14b** (118.5 mg, 0.45 mmol) in PBS (pH 7.4, 50 mM, 8 mL) and methanol (1 mL) to increase solubility at room temperature. Porcine pancreatic lipase (PPL, type II, crude, 100 mg), then sodium chloride (20 mg) and calcium chloride (40 mg) were added. The pH of the reaction mixture was maintained at 7.0–7.2 by addition of sodium hydroxide solution (0.1 N). After completion, solvents were evaporated under reduced pressure, the residue extracted with chloroform/methanol (2:1, v/v), filtered, and dried using anhydrous magnesium sulfate. Solvents were evaporated from the combined organic extracts under reduced pressure and the residue purified by flash chromatography on a silica gel column (chloroform/methanol = 20:1) to give **3b** (65 mg, 58%). TLC (chloroform/methanol/$H_2O$ = 80:19:1, $R_f$ = 0.51): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.65 (dd, $J$ = 16.2, 4 Hz, 1H), 6.34 (dd, $J$ = 16, 1.2 Hz, 1H), 5.05 (dd, $J$ = 4.2, 1.6 Hz, 1H), 3.63–3.69 (m, 2H), 3.50–3.56 (m, 2H), 2.69 (t, $J$ = 7.2 Hz, 2H), 2.43 (t, $J$ = 6.8 Hz, 2H), 1.95 (tt, $J$ = 7.2, 7.2 Hz, 2H), 1.24 (t, $J$ = 7.2 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) 199.7, 179.2, 141.6, 131.6, 99.7, 61.8, 39.3, 33.2, 18.8, 15.4. HRMS (FAB): *m/z* calcd for $C_{12}H_{21}O_5$ ($MH^+$), 245.1389; found, 245.1382.

### 4.16. (*E*)-2-(8,8-Diethoxy-5-oxooct-6-enoyl)-1-palmitoyl-*sn*-glycero-3-phosphatidylcholine (18b)

1-Methylimidazole (11.5 μL, 0.14 mmol) and 2,6-dichlorobenzoyl chloride (22.7 μL, 0.16 mmol) were added to a solution of acid **3b** (31.7 mg, 0.16 mmol) and L-2-lysophophatidylcholine (23.5 mg, 96 μmol) in dry methylene chloride (4 mL). The resulting mixture was stirred for 17 h at room temperature and monitored by TLC for disappearance of the starting material. Solvents were then evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (chloroform/methanol/$H_2O$ = 16:9:1, TLC: $R_f$ = 0.34) to give **18b** (25.6 mg, 74%). $^1$H NMR (400 MHz, $CD_3OD/CDCl_3$ = 1:2) $\delta$ 6.64 (dd, $J$ = 16.2, 4.0 Hz, 1H), 6.33 (dd, $J$ = 16.0, 1.2, 1H), 5.21 (m, 1H), 5.04 (m, 1H), 4.39 (m, 1H), 4.25 (m, 2H), 4.13 (dd, $J$ = 12.0, 5.2 Hz, 2H), 4.00 (m, 2H), 3.61–3.69 (4H), 3.49–3.57 (m, 2H), 3.30 (br s, 9H), 2.70 (t, $J$ = 6.8 Hz, 2H), 2.37 (t, $J$ = 6.8 Hz,2H), 2.29 (t, $J$ = 7.2 Hz, 2H), 1.89 (m, 2H), 1.57 (m, 2H), 1.22 (30H), 0.85 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CD_3OD/CDCl_3$ = 1:2) 200.5, 174.1, 172.9, 141.8, 131.3, 99.8, 70.8, 66.5, 63.9, 62.6, 61.9, 59.3, 54.0, 39.2, 34.1, 33.2, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 24.9, 22.7, 18.9, 14.9, 13.8. HRMS (FAB): *m/z* calcd for $C_{33}H_{69}NO_{11}P$ ($MH^+$), 722.4608; found, 722.4589.

### 4.17. (*E*)-2-(5-Hydroxy-8,8-diethoxyoct-6-enoyl)-1-palmitoyl-*sn*-glycero-3-phosphatidylcholine (2b)

Sodium borohydride (1.9 mg, 50 μmol) was slowly added at 4 °C to a stirred solution of ester **18b** (33.4 mg, 46 μmol) in dry methylene chloride (1 mL) and methanol (2 mL). Once complete, the reaction mixture was neutralized with acetic acid, solvents were evaporated under reduced pressure, and the residue purified by flash chromatography on a silica gel column (chloroform/methanol/$H_2O$ = 11:9:1, TLC: $R_f$ = 0.22) to give **2b** (32.8 mg, 98%). $^1$H NMR (400 MHz, $CD_3OD/CDCl_3$ = 1:2) $\delta$ 5.81 (dd, $J$ = 15.6, 6 Hz, 1H), 5.62 (dd, $J$ = 15.6, 6 Hz, 1H), 5.21 (m, 1H), 4.86 (d, 1H), 4.37 (m, 1H), 4.22 (m, 2H), 4.13 (dd, $J$ = 12.4, 7.2 Hz, 2H), 4.07 (m, 1H), 3.64 (m, 2H), 3.47–3.59 (4H), 3.16 (br s, 9H), 2.27–2.36 (4H), 1.68 (m, 2H), 1.52–1.57 (4H), 1.16–1.26 (30H), 0.85 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CD_3OD/CDCl_3$ = 1:2) 174.1, 173.4, 137.1, 127.3, 101.6, 70.8, 70.6, 66.5, 63.8, 62.6, 61.5, 59.2, 54.0, 36.3, 36.2, 34.0, 33.9, 32.0, 29.7, 29.5, 29.4, 29.3, 29.2, 24.9, 22.7, 20.9, 14.9, 13.9. HRMS (FAB): *m/z* calcd for $C_{36}H_{70}NNaO_{11}P$ ($MNa^+$), 746.4584; found, 746.4584

### 4.18. (*E*)-2-(5-Hydroxy-8-oxooct-6-enoyl)-1-palmitoyl-*sn*-glycero-3-phosphatidylcholine (HOOA-PC, 1b)

PPTS (4.6 mg, 18.4 μmol) was added to a stirred solution of ester **2b** (11.1 mg, 15.3 μmol) in tetrahydrofuran/acetone/$H_2O$ = 5:4:1 (2 mL), the resulting mixture was stirred for 4 h at room temperature, and monitored by TLC for disappearance of starting material. Upon completion, solvents were evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (chloroform/methanol/$H_2O$ = 11:9:1, TLC: $R_f$ = 0.18) to give **1b** (8.4 mg, 85%). $^1$H NMR (400 MHz, $CD_3OD/CDCl_3$ = 1:2) $\delta$ 9.53 (d, $J$ = 8 Hz, 1H), $\delta$ 6.93 (dd, $J$ = 15.6, 4.4 Hz, 1H). 6.29 (ddd, $J$ = 15.6, 8, 1.6 Hz, 1H), 5.21 (m, 1H), 4.36 (m, 2H), 4.11–4.26 (4H), 3.99 (m, 2H), 3.58 (m, 2H), 3.30 (s, 9H), 2.39 (m, 2H), 2.31 (m, 2H), 1.57–1.77 (6H), 1.57 (m, 2H), 1.26 (24H), 0.85 (t, $J$ = 6.8 Hz, 3H). HRMS (FAB): *m/z* calcd for $C_{32}H_{61}NO_{10}P$ ($MH^+$), 650.4033; found, 650.4030.

### 4.19. Methyl 9-(chlorocarbonyl)octanoate (5c)

Monomethyl azelate (500 mg, 2.4 mmol) was added dropwise via syringe to a solution of oxalyl chloride (300 mg, 3.5 mmol, 1.5 equiv) in benzene (3 mL). The reaction mixture was stirred for 30 min at room temperature and then refluxed for 2 h, after which time no acid starting material was detected by IR. Upon completion, the solvent was evaporated under reduced pressure and the residue purified by vacuum distillation to give **5c** (491 mg, 90%). IR (film, $cm^{-1}$) 2943, 2861, 1811, 1733, 1462, 1434, 1251, 1205. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.66 (s, 3H), $\delta$ 2.87 (m, 2H), 2.30 (m, 2H), 1.65 (m, 2H), 1.60 (m, 2H), 1.35 (6H).

### 4.20. Methyl (*E*)-12,12-diethoxy-9-oxododec-10-enoate (14c)

The procedure was modified from that reported.[21] 1-Tributylstannyl-3,3-diethoxy-prop-1-ene (**4**, 380 mg, 0.9 mmol) was added dropwise via syringe to a solution of acyl chloride **5c** (200 mg, 0.9 mmol) and $PdCl_2(MeCN)_2$ (2.3 mg, 9 μmol) in DMF (1.5 mL) and the reaction mixture stirred first for 1 h in an ice bath and then 3 h at room temperature. Saturated aqueous sodium fluoride and acetone were added to the brown-red reaction mixture to remove tributyltin chloride. The mixture was extracted with ethyl acetate (3 × 20 mL), followed by drying of the combined extracts over anhydrous sodium sulfate. Solvents were evaporated from the organic extracts under reduced pressure and the residue purified by flash chromatography on a silica gel column (ethyl acetate/hexanes = 7:93) to give **14c** (171 mg, 60%). TLC (30% ethyl acetate/hexanes; $R_f$ = 0.51). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.62 (dd, $J$ = 16.1, 4.3 Hz, 1H), 6.33 (dd, $J$ = 16.1, 1.3 Hz, 1H), 5.04 (dd, $J$ = 4.3, 1.3 Hz, 1H), 3.76–3.59 (m, 5H), 3.59–3.43 (m, 2H), 2.64 (t, $J$ = 6.6 Hz, 2H), 2.34 (t, $J$ = 7.2 Hz, 2H), 1.92 (p, $J$ = 7.2 Hz, 2H), 1.20 (t, $J$ = 7.2 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) 200.8, 174.5, 141.1, 131.8, 99.8, 61.7, 51.7, 40.6, 34.3, 29.2, 25.09, 24.06, 15.54, 15.43. HRMS (FAB): *m/z* calcd for $C_{17}H_{31}O_5$ ($MH^+$), 315.2171; found, 315.2175.

### 4.21. (*E*)-12,12-Diethoxy-9-oxododec-10-enoic acid (3c)

The acid was prepared using a solution of ester **14c** (88.7 mg, 0.28 mmol) in PBS (pH 7.4, 50 mM, 8 mL) and methanol (1 mL) to increase solubility at room temperature. Porcine pancreatic lipase (type II, crude, 100 mg), sodium chloride (20 mg), and calcium chloride (40 mg) were added. The pH of the reaction mixture was maintained at 7.0–7.2 by addition of sodium hydroxide solution (0.1 N). Upon completion, solvents were evaporated under reduced pressure, the residue extracted with chloroform/methanol (2:1, v/v), filtered, and dried with anhydrous magnesium sulfate. Solvents were evaporated from the combined organic extracts under reduced pressure and the residue purified by flash chromatography on a silica gel column (chloroform/methanol = 15:1) to give **3c** (56 mg, 67%). TLC (chloroform/methanol/$H_2O$ = 80:19:1, $R_f$ = 0.70): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.61 (dd, $J$ = 16, 4.4 Hz, 1H), 6.33 (dd, $J$ = 16, 1.2 Hz, 1H), 5.04 (dd, $J$ = 4.4, 1.2 Hz, 1H), 3.65–3.66 (m, 2H), 3.50–3.56 (m, 2H), 2.56 (t, $J$ = 7.6 Hz, 2H), 2.33 (t, $J$ = 7.2 Hz, 2H), 1.60 (m, 2H), 1.30 (6H), 1.22 (6H). $^{13}$C NMR (100 MHz, $CDCl_3$) 200.9, 179.8, 141.2, 131.8, 99.8, 61.7, 40.5, 34.2, 29.2, 29.1, 29.0, 24.8, 24.1, 15.4. HRMS (FAB): *m/z* calcd for $C_{16}H_{28}O_5$ ($M^+$), 300.1937; found, 300.1930.

### 4.22. (*E*)-2-(12,12-Diethoxy-9-oxododec-10-enoyl)-1-palmitoyl-*sn*-glycero-3-phosphatidylcholine (18c)

1-Methylimidazole (10.6 μL, 0.13 mmol) and 2,6-dichlorobenzoyl chloride (20.9 μL, 0.14 mmol) were added to a solution of acid **3c** (20 mg, 0.06 mmol) and L-α-lysophophatidylcholine (22 mg, 0.04 mmol) in dry methylene chloride (4 mL). The resulting mixture was stirred for 24 h at room temperature and monitored by TLC for disappearance of starting material. The mixture was evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (chloroform/methanol/$H_2O$ = 16:9:1, TLC: $R_f$ = 0.34) to give **18c** (24.5 mg, 71%). $^1$H NMR (400 MHz, $CD_3OD$/$CDCl_3$ = 1:2) $\delta$ 6.61 (dd, $J$ = 16.1, 4.4 Hz, 1H), 6.32 (dd, $J$ = 16.1, 1.2 Hz, 1H), 5.20 (m, 1H), 5.04 (m, 1H), 4.39 (m, 1H), 4.23 (dt, $J$ = 11.8, 6.0 Hz, 2H), 4.13 (dd, $J$ = 11.9, 6.8 Hz, 1H), 3.95 (m, 2H), 3.72–3.46 (6H), 3.26 (br s, 9H), 2.59 (t, $J$ = 7.4 Hz, 2H), 2.30 (4H), 1.58 (6H), 1.33–1.09 (36H), 0.85 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CD_3OD$/$CDCl_3$ = 1:2) 200.9, 174.1, 173.6, 141.5, 141.1, 131.9, 99.8, 68.3, 67.0, 62.6, 62.1, 61.9, 57.5, 54.0, 40.5, 35.6, 34.2, 34.1, 32.0, 29.7, 29.6, 29.4, 29.3, 29.1, 29.0, 28.9, 24.9, 24.8, 23.9, 22.7, 17.7, 14.9, 13.9. HRMS (FAB): *m/z* calcd for $C_{40}H_{77}NO_{11}P$ ($M^+$), 778.5229; found, 778.5124.

### 4.23. (*E*)-2-(9-Hydroxy-12,12-diethoxydodec-10-enoyl)-1-palmitoyl-*sn*-glycero-3-phosphatidylcholine (2c)

Sodium borohydride (1.4 mg, 37 μmol) was slowly added at 4 °C to a stirred solution of ester **18c** (24.5 mg, 31.4 μmol) in dry methylene chloride (1 mL) and methanol (2 mL). Upon completion, the reaction mixture was neutralized with glacial acetic acid. Solvents were evaporated under reduced pressure, and residue purified by flash chromatography on a silica gel column (chloroform/methanol/$H_2O$ = 11:9:1, TLC: $R_f$ = 0.30) to give **2c** (20.5 mg, 87%). $^1$H NMR (400 MHz, $CD_3OD$/$CDCl_3$ = 1:2) $\delta$ 5.80 (dd, $J$ = 15.6, 6.4 Hz, 1H), 5.60 (dd, $J$ = 15.6, 6.4 Hz, 1H), 5.21 (m, 1H), 4.86 (m, 1H), 4.41 (m, 1H), 4.26 (m, 2H), 4.13 (dd, $J$ = 12, 6.8 Hz, 1H), 4.04 (m, 1H), 3.96 (m, 2H), 3.71–3.41 (6H), 3.18 (br s, 9H), 2.27–2.33 (4H), 1.58 (8H), 1.16–1.29 (36H), 0.85 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CD_3OD$/$CDCl_3$ = 1:2) 174.1, 173.6, 137.6 127.0, 101.7, 71.4, 70.5, 66.5, 63.8, 62.7, 61.4, 59.2, 54.0, 40.3, 37.1, 34,2, 34.1, 32.0, 29.7, 29.6, 29.4, 29.3, 29.1, 29.0, 28.9, 24.9, 24.8, 22.7, 15.0, 14.9, 13.9. HRMS (FAB): *m/z* calcd for $C_{40}H_{78}NNaO_{11}P$ ($MNa^+$), 802.5210; found, 802.5217.

### 4.24. (*E*)-(9-Hydroxy-12-oxodec-10-enoyl)-1-palmitoyl-*sn*-glycero-3-phosphatidylcholine (HODA-PC, 1c)

PPTS (5.6 mg, 22.2 μmol) was added to a stirred solution of ester **2c** (14.5 mg, 18.6 μmol) in tetrahydrofuran/acetone/$H_2O$ = 5:4:1 (2 mL). The resulting mixture was stirred for 5 h at room temperature and monitored by TLC for disappearance of starting material. Upon completion, solvents were evaporated under reduced pressure and the residue purified by flash chromatography on a silica gel column (chloroform/methanol/$H_2O$ = 11:9:1, TLC: $R_f$ = 0.4) to give **1c** (11.8 mg, 90%). $^1$H NMR (400 MHz, $CD_3OD$ + $CDCl_3$) $\delta$ 9.52 (d, $J$ = 8 Hz, 1H), 6.91 (dd, $J$ = 15.6, 4.8 Hz, 1H), 6.26 (ddd, $J$ = 15.6, 8, 1.6 Hz, 1H), 5.20 (m, 1H), 4.38 (m, 1H), 4.31 (m, 1H), 4.22 (m, 2H), 4.14 (m, 1H), 3.97 (m, 2H), 3.58 (m, 2H), 3.30 (s, 9H), 2.27–2.33 (4H), 1.57 (7H), 1.23–1.31 (31H), 0.85 (t, $J$ = 6.8 Hz, 3H). HRMS (FAB): *m/z* calcd for $C_{36}H_{67}NO_9P$ ($MH^+-H_2O$), 688.4548; found, 688.4583.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.10.058.

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