Total Synthesis of γ-Hydroxy-α,β-Unsaturated Aldehydic Esters of Cholesterol and 2-Lysophosphatidylcholine

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Free radical-induced oxidation of polyunsaturated fatty esters in low-density lipoproteins (LDLs) generates 2-lysophosphatidylcholine (PC) and cholesterol esters of γ-hydroxy-α,β-unsaturated aldehydic acids that covalently modify LDL protein, and protein adducts of the corresponding acids are found in human blood. The chemistry and structures of these compounds resemble those of (*E*)-4-hydroxy-2-nonenal (HNE), previously considered the most cytotoxic aldehyde released during peroxidation of linoleate and arachidonate esters. The present report details total syntheses of 2-lyso-PC and cholesteryl esters of (*E*)-9-hydroxy-12-oxododec-10-enoic and (*E*)-5-hydroxy-8-oxooct-6-enoic acid that presumably are derived in vivo from linoleate and arachidonate esters, respectively. The syntheses depend on the use of a 3,3-dimethyl-2,4-dioxolanyl moiety as a latent aldehyde from which the chemically sensitive γ-hydroxy-α,β-unsaturated aldehyde array can be generated in the final step. For the cholesteryl esters, generation of the aldehyde group by oxidative cleavage of a vicinal diol could be accomplished in very good yields with periodate. However, for esters of 2-lyso-PC, the target aldehydes were not obtained upon treatment of vicinal diol precursors with periodate owing to a novel oxidative cleavage of the γ-hydroxy-α,β-unsaturated aldehydes by periodate. Fortunately, treatment of the vicinal diol precursors with $Pb(OAc)_4$ at −80 °C delivered good yields (82−85%) of the desired phospholipid aldehydes.

Introduction

The most abundant polyunsaturated fatty acids (PUFAs) in human low-density lipoprotein (LDL) are arachidonic acid (AA), linoleic acid (LA), and docosahexenoic acid, whose mean levels are 1100, 153, and 29 mol/mol LDL in healthy donors.[1] These PUFAs are present mainly as esters in phospholipid, cholesteryl ester, and triglyceride components of LDL. Aldehydes generated by oxidative cleavage of PUFA esters are the subject of intense study because their formation is a key event in pathological processes known collectively as oxidative stress,[2,3] and because some of the aldehydes are biologically active (vide infra). A subset of these aldehydes remain esterified to cholesterol, glycerol, or lysophosphatidylcholine (PC).[4] For example, the 5-oxovaleric acid ester of 2-lyso-PC (OV−PC) is generated in LDL by an oxidative cleavage of the AA ester of 2-lyso-PC. OV−PC activates endothelial cells to bind monocytes[5] and, consequently, may promote atherogenesis by fostering entry of monocytes into the vessel wall.

Covalent modification of LDL by reactions of lipid-derived electrophiles with protein-based nucleophiles[6−8] may also contribute to atherogenesis. Thus, recognition of the resulting protein modifications by macrophage scavenger receptors leads to endocytosis of the oxidized (ox) LDL[9−11] and accumulation of LDL components, such as cholesteryl esters which aggregate into droplets that resemble foam. The resulting bloated macrophages, called "foam cells", are progenitors of atherosclerotic plaques.[12] Nonenzymatic, free radical-induced oxidative cleavage of both AA and LA esters in LDL generates (*E*)-4-hydroxy-2-nonenal (HNE), a γ-hydroxy-α,β-unsaturated aldehyde. HNE forms protein adducts that include 2-pentylpyrrole derivatives (HNE-pyrrole) which incorporate the ϵ-amino group of protein lysyl residues (Scheme 1).[13]

Studies with LDL containing 2-[1-^{14}C]-arachidonyl PC show that, unlike HNE, a major fraction of the lipid-derived products that become bound to protein as a consequence of LDL oxidation retain the carbonyl carbon of their fatty ester precursor.[8] Recently, we found immunological evidence for the generation of protein-bound 2-(ω-carboxyalkyl)pyrroles (CAPs) during free radical-induced oxidative modification of LDL, and we found CAP immunoreactivity in human blood plasma.[14] In analogy with the chemistry of HNE, we postulated that CAPs are formed by reactions of γ-hydroxy-α,β-

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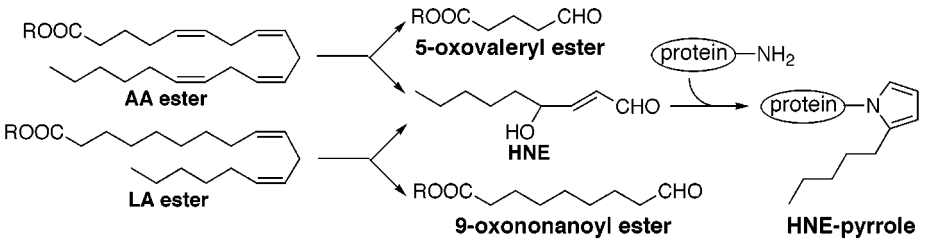
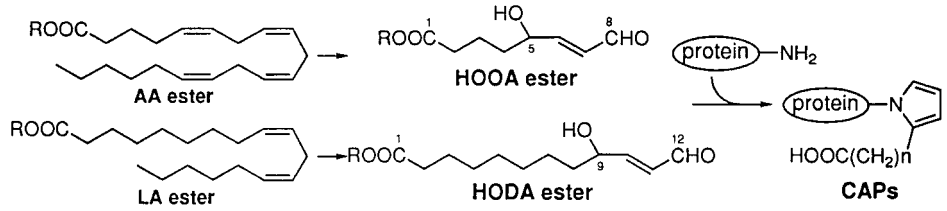
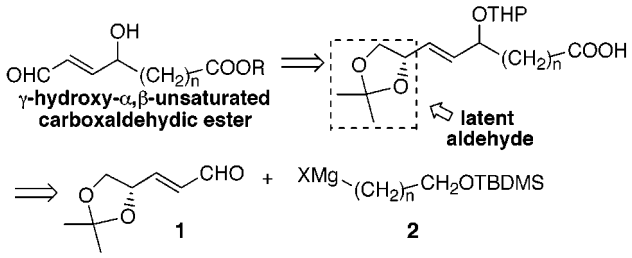
Scheme 1



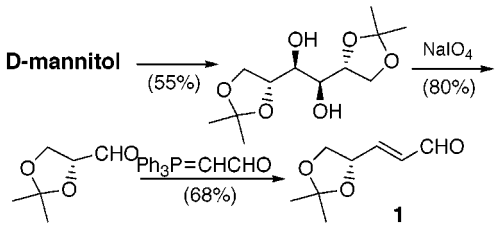
Scheme 2



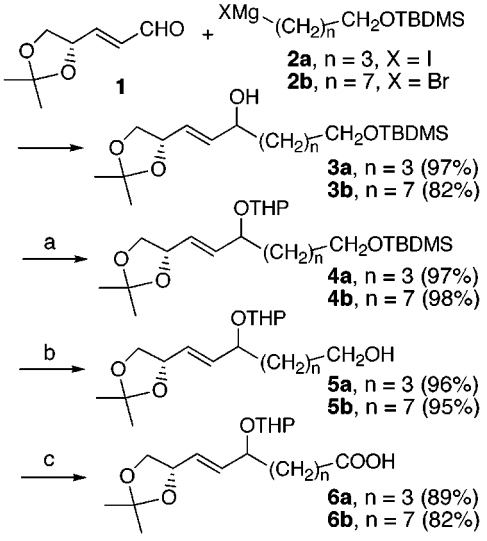
Scheme 3



Scheme 4



Scheme 5



(a) DHP, PPTS, CH_2Cl_2; (b) Bu_4NF, THF; (c) PDC, DMF

unsaturated aldehydic esters with the ϵ-amino group of lysyl residues in LDL protein. Thus, oxidative cleavage of AA and LA esters can give 5-hydroxy-8-oxooct-6-enoic acid (HOOA) and 9-hydroxy-12-oxododec-10-enoic acid (HODA) esters respectively (Scheme 2). To facilitate investigations on the chemistry and biology of HOOA and HODA derivatives, we now report total syntheses of their cholesterol and 2-lyso-PC esters.

Results and Discussion

Synthetic Design. A synthetic strategy was adopted that exploits a 3,3-dimethyl-2,4-dioxolanyl moiety in a common intermediate **1** as a latent aldehyde (Scheme 3).[15] Because the carboxyalkyl group in the target is introduced as a unit in a Grignard reagent precursor **2**, this convergent approach should be applicable to total syntheses of the entire family of γ-hydroxy-α,β-unsaturated carboxaldehydic esters that are derivable from PUFA esters.

Synthesis of Common Intermediate 1. A common intermediate **1** for the γ-hydroxy-α,β-unsaturated aldehyde portion of the target carboxaldehydic esters was assembled from D-mannitol as outlined in Scheme 4. D-Glyceraldehyde acetonide is readily available from D-mannitol by oxidative cleavage of an intermediate bis(acetonide).[16] Wittig olefination with triphenylphosphoranylidene acetaldehyde provides **1** in good yield.[17,18]

Synthesis of Latent Carboxaldehydic Acids 6. The carbon skeletons of the latent carboxyaldehydic acids **6a**,**b** were assembled by 1,2-addition of a Grignard reagent from the TBDMS ethers of 4-iodobutanol and 8-bromooctanol, respectively (Scheme 5). That the Grignard additions produce the allylic stereocenter in adducts **3** nonstereoselectively is especially evident from ^{13}C NMR spectra that show pairs of peaks of nearly equal intensity for several carbons in each of these secondary alcohols. The nonenzymatic, free radical-induced oxidations of PUFAs in vivo are also expected generate an allylic hydroxyl nonstereoselectively to produce esters of racemic HOOA and HODA. The secondary allylic alcohols **3** were protected as THP ethers **4** from which the primary

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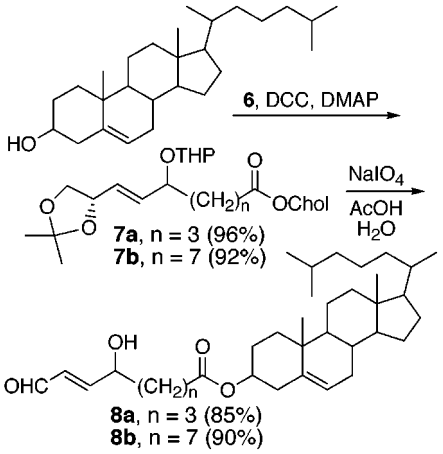
Scheme 6

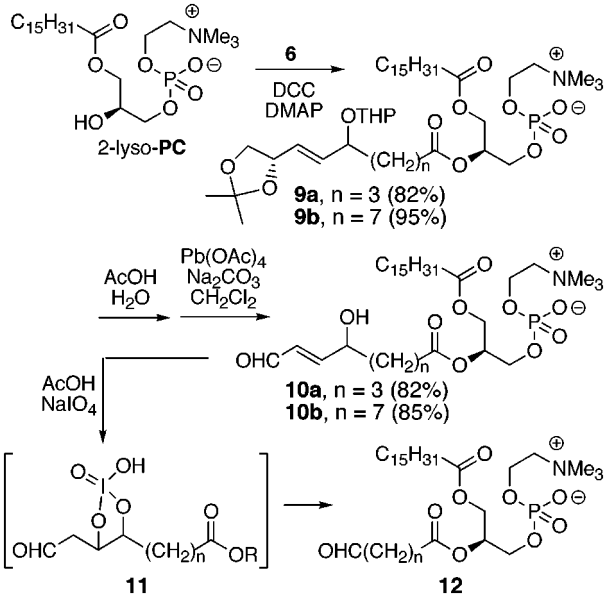


alcohols **5** were obtained upon desilylation with fluoride. Oxidation of these primary alcohols with PDC delivered the target latent carboxyaldehydic acids **6a**,**b** in 80% and 63% overall yields, respectively, in four steps. The starting 4-iodobutanol TBDMS ether is readily available in excellent yield (94%) in a single step from tetrahydrofuran by treatment with NaI and (TBDMS)Cl.[19] A more lengthy procedure afforded the requisite TBDMS ether of 8-bromooctanol. Thus, reaction of the sodium mono alkoxide from 1,8-octanediol with (TBDMS)Cl provides a mono TBDMS ether[20] in 69% yield after column chromatographic purification. Conversion of the remaining hydroxyl into a bromide was then accomplished in 81% yield by treatment with DEAD, Ph_3P, and $ZnBr_2$.[21]

Cholesteryl Esters. The γ-hydroxy-α,β-unsaturated aldehyde array is chemically sensitive, e.g. rearranging readily to generate furan derivatives.[22] Therefore, it is important to store the target carboxaldehydic esters as chemically stable precursors. The cholesterol esters **7**, obtained from the acids **6** in 92−96% yields, are excellent stable precursors that can be transformed readily into the corresponding aldehydes. Thus, a convenient one-pot hydrolysis of the THP and acetonide protecting groups and periodate cleavage of a vicinal diol intermediate delivers aldehydes **8** in 85−90% yield (Scheme 6).

Phospholipids. In view of the successful one-pot generation of analogous cholesterol esters outlined above and our effective use of this chemistry for a synthesis of radiolabeled HNE,[23] synthesis of phospholipid γ-hydroxy-α,β-unsaturated aldehydes **10** from esters **9** of 2-lyso-PC with the acids **6** proved unexpectedly elusive. Thus, exposure of the esters **9** to aqueous acetic acid and periodate failed to give any of the desired γ-hydroxy-α,β-unsaturated carboxaldehydic esters **10**. Rather, shorter chain aldehydes **12** were produced, presumably by Michael addition of periodate to the target α,β-unsaturated aldehydes **10** and oxidative fragmentation of intermediate periodate esters **11** (Scheme 7). Some of the target aldehyde was obtained upon hydrolytic removal of the THP and acetonide protecting groups with aqueous acetic acid, followed by evaporation of the aqueous acetic acid

Scheme 7



and treatment of the resulting diol with lead tetraacetate in methylene chloride in the presence of a suspension of sodium carbonate at room temperature (22% yield of **9b** from **8b**). The yield was improved to 37% when the oxidative cleavage was conducted at 0 °C and was improved further (82%) by performing the oxidative cleavage at −80 °C.

Owing to its reactive electrophilic γ-hydroxy-α,β-unsaturated aldehyde functional array, HNE readily forms covalent adducts with protein-based nucleophiles. This results, inter alia, in the inactivation of enzymes[24−27] and is undoubtedly the chemical basis for the view that HNE is the "most cytotoxic aldehyde" released during peroxidation of AA and LA esters.[28] The succinct total syntheses detailed above provide ready access to authentic samples of carboxaldehydic esters that incorporate the same reactive γ-hydroxy-α,β-unsaturated aldehyde functional array as that in HNE. Studies on the biological activities and biologically important chemistry of these lipid oxidation products are now feasible.

Experimental Procedures

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and are reported as described previously.[15] High-resolution mass spectroscopy, solvent purification, and chromatography was performed as usual.[15] All reactions conducted in an inert atmosphere were in argon unless otherwise specified.

4-Iodo-1-(1,1,2,2-tetramethyl-1-silapropoxy)butane. This iodide was prepared as described previously.[19] The ^{1}H NMR spectrum agreed with that reported.[19] The ^{13}C NMR (75 MHz, APT, $CDCl_3$) showed δ 61.99 (CH_2), 46.59 (CH_2), 33.57 (CH_2), 30.23 (CH_2), 25.97(CH_3), 7.17 (C), and −5.28 (CH_3).

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8-(1,1,2,2-Tetramethyl-1-silapropoxy)octan-1-ol. Sodium hydride (900 mg, 37.5 mmol) was suspended in THF (50 mL) after being washed with hexanes.[20] 1,8-Octanediol (5 g, 34.2 mmol) was added to the suspension at room temperature, and the mixture was stirred for 20 h. (TBDMS)Cl (5.2 g, 34.5 mmol) was then added, and vigorous stirring was continued for 4 h. After filtration, the solvent was removed on a rotary evaporator. Flash chromatography of the residue with 15% ethyl acetate in hexanes gave the title monosilyl ether (6.1 g, 69%); TLC (ethyl acetate/hexanes, 3:17) $R_f = 0.31$; ^{1}H NMR ($CDCl_3$) δ 3.62 (t, $J = 6.6$ Hz, 2 H), 3.57 (t, $J = 6.6$ Hz, 2 H), 1.4−1.6 (4 H), 1.25−1.35 (8 H), 0.89 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (APT, $CDCl_3$) 63.32 (CH_2), 62.92 (CH_2), 32.83 (CH_2), 32.78 (CH_2), 32.77 (CH_2), 29.42 (CH_2), 26.0 (CH_3), 25.74 (CH_2), 18.38 (C), −5.25 (CH_3). HRMS (EI) (*m*/*z*) calcd for $C_{10}H_{23}O_2Si$ ($M^+ - CMe_3$) 203.1467, found 203.1468.

8-Bromo-1-(1,1,2,2-tetramethyl-1-silapropoxy)octane. To a magnetically stirred solution of 8-(1,1,2,2-tetramethyl-1-silapropoxy)octan-1-ol (62.5 mg, 0.24 mmol) and Ph_3P (189 mg, 0.72 mmol) in THF (3 mL) under argon,[21] $ZnBr_2$ (54 mg, 0.24 mmol) in THF (2.5 mL) was added. After the solution was stirred for 10 min, diethyl azodicarboxylate (DEAD, 167 mg, 0.96 mmol) in THF (1 mL) was added dropwise with a syringe. The resulting mixture was stirred at room temperature for another 40 min. The solution was filtered and the solvent removed with a rotary evaporator. The crude product was purified by flash chromatography on a silica gel column with 1.5% ethyl acetate in hexanes to afford the title bromide (63 mg, 81%): TLC (ethyl acetate/hexanes, 1:24) $R_f = 0.30$; ^{1}H NMR ($CDCl_3$) δ 3.57 (t, $J = 6.4$ Hz, 2 H), 3.38 (t, $J = 6.8$ Hz, 2 H), 2.83 (m, 2 H), 1.35−1.55 (4 H), 1.2−1.4 (6 H), 0.89 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (APT, $CDCl_3$) δ 63.20 (CH_2), 33.92 (CH_2), 32.80 (CH_2), 29.21 (CH_2), 28.74 (CH_2), 28.10 (CH_2), 25.97 (CH_3), 25.69 (CH_2), 18.35 (C), −5.27 (CH_3); HRMS (EI) (*m*/*z*) calcd for $C_{10}H_{22}BrOSi$ ($M^+ - CMe_3$) 265.0610, found 265.0620.

1-(3,3-Dimethyl-2,4-dioxolanyl)-7-(1,1,2,2-tetramethyl-1-silapropoxy)hept-1-en-3-ol (3a). Magnesium turnings (926 mg, 38.1 mmol) and dry diethyl ether (3.0 mL) were placed in a 200 mL, flame dried, three-necked flask with a mechanical stirrer and condenser under an argon atmosphere at room temperature. A few drops of a solution of 4-iodo-1-(1,1,2,2-tetramethyl-1-silapropoxy)butane (4.0 g, 12.7 mmol) in dry diethyl ether (2 mL) were added. After formation of the Grignard reagent began, another 45 mL of dry diethyl ether was added, the remaining iodide was then added dropwise, and the reaction mixture was then stirred overnight. After chilling of the mixture to 0 °C, (4,5-(isopropylidenedioxy)-2-pentenal[17,18,29] (**1**, 700 mg, 4.5 mmol) was added dropwise. After being stirred for another 30 min, the reaction was quenched by addition of saturated aqueous NH_4Cl, extracted with diethyl ether, and the extract dried with magnesium sulfate. The solvent was removed with a rotary evaporator. The residue was flash chromatographed on a silica gel column (30% ethyl acetate in hexanes) to give **3a** (1.5 g, 97%, based on **1**): TLC (ethyl acetate/hexanes, 3:7) $R_f = 0.25$; ^{1}H NMR ($CDCl_3$, **3a***S* + **3a***R*) δ 5.81 (ddd, $J = 15.4$ Hz, 5.8 Hz, 2.7 Hz, 1 H), 5.648, 5.644 (ddd, $J = 15.4$ Hz, 6.9 Hz, 3.3 Hz, 1 H), 4.49 (dd, $J = 6.8$ Hz, 7.5 Hz, 1 H), 4.12 (m, 1 H), 4.075, 4.082 (td, $J = 8.1$ Hz, 6.2 Hz, 1 H), 3.5−3.65 (3 H), 1.4−1.6 (12 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 0.89 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (APT, $CDCl_3$) δ 137.39 (CH), 127.84, 127.65 (CH, two diastereomers), 109.39 (C), 76.58 (CH), 71.96, 71.75 (CH), 69.44 (CH_2), 63.07 (CH_2), 36.82, 36.70 (CH_2), 32.58 (CH_2), 26.69 (CH_3), 26.00 (CH_3), 25.91 (CH_3), 21.74, 21.67 (CH_2), 18.38 (C), −5.25 (CH_3); HRMS (EI) (*m*/*z*) calcd for $C_{17}H_{33}O_4Si$ ($M^+ - CH_3$) 329.2144, found 329.2163.

1-(3,3-Dimethyl-2,4-dioxolanyl)-11-(1,1,2,2-tetramethyl-1-silapropoxy)undec-1-en-3-ol (3b). Magnesium turnings (301 mg, 12.4 mmol) and dry THF (10 mL) were placed in a 200 mL, flame-dried, three-necked flask with a mechanical stirrer and condenser under an argon atmosphere at room temperature. A few drops of a solution of 8-bromo-1-(1,1,2,2-tetramethyl-1-silapropoxy)octane (2.0 g, 6.2 mmol) in dry THF (2 mL) were added. After formation of the Grignard reagent commenced, another 30 mL of dried THF were added followed by dropwise addition of the remaining bromide. The reaction mixture was stirred overnight and then chilled to 0 °C, followed by slow addition of 4,5-(isopropylidenedioxy)-2-pentenal (**1**, 450 mg, 2.88 mmol). After the mixture was stirred for another 30 min, saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with diethyl ether and dried with magnesium sulfate. The solvent was removed with a rotary evaporator. The residue was flash chromatographed on a silica gel column (20% ethyl acetate in hexanes) to give **3b** (950 mg, 82%, based on **1**): TLC (ethyl acetate/hexanes, 1:4): $R_f = 0.23$; ^{1}H NMR ($CDCl_3$) δ 5.81 (dd, $J = 15.3$ Hz, 5.9 Hz, 1 H), 5.64 (m, 1 H), 4.49 (dd, $J = 13.8$ Hz, 7.4 Hz, 1 H), 4.00−4.15 (2 H), 3.57 (t, $J = 6.5$ Hz, 2 H), 3.57 (dd. $J = 6.5$ Hz, 6.7 Hz, 1 H), 1.4−1.6 (6 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.18−1.30 (8 H), 0.89 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (APT, $CDCl_3$, **3b***S* + **3b***R*) δ 137.50, 137.42 (CH), 127.79, 127.72 (CH), 109.37 (−C−), 76.62, 76.58 (CH), 72.07, 71.95 (CH), 69.49 (CH_2), 63.33 (CH_2), 37.17, 37.06 (CH_2), 32.88 (CH_2), 29.56, 29.50 (CH_2), 29.39 (CH_2), 26.71 (CH_3), 26.02 (CH_3), 25.93 (CH_3), 25.80 (CH_2), 25.41 (CH_2), 25.35 (CH_2), 18.41 (−C−), −5.22 (CH_3); HRMS (EI) (*m*/*z*) calcd for $(C_{21}H_{41}O_4Si)$ ($M^+ - Me$) 385.2774, found 385.2772, calcd for $C_{22}H_{42}O_3Si$ ($M^+ - H_2O$) 382.2902, found 382.2897.

1-(5-(2-Oxanyloxy)-7-(3,3-dimethyl-2,4-dioxolanyl)hept-6-enyloxy)-1,1,2,2-tetramethyl-1-silapropane (4a). Pyridinium *p*-toluenesulfonate (PPTS, 11 mg, 0.044 mmol) was added to a solution of alcohol **3a** (150 mg, 0.44 mmol) and dihydropyran (55 mg, 0.65 mmol, freshly distilled) in dry methylene chloride (4 mL).[30] The resulting solution was stirred overnight at room temperature and then diluted with water and extracted with diethyl ether and washed with brine. Solvent was removed with a rotary evaporator. The crude product was purified by flash chromatography on a silica gel column (8% EtOAc in hexanes) to afford the THP ether **4a** (180 mg, 97%). TLC (ethyl acetate/hexanes, 2:23): $R_f = 0.25$; ^{1}H NMR ($CDCl_3$) δ 5.50−5.86 (m, 2 H), 4.55−4.68 (m, 1 H), 4.45−4.55 (m, 1 H), 4.0−4.12 (m, 2 H), 3.82 (m, 1 H), 3.56 (m, 3 H), 3.45 (m, 1 H), 1.3−1.9 (12 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 0.86 (s, 9 H), 0.02 (s, 6 H); HRMS (EI) (*m*/*z*) calcd for $C_{22}H_{41}O_5Si$ ($M^+ - CH_3$) 414.2719, found 414.2734.

1-(9-(2-Oxanyloxy)-11-(3,3-dimethyl-2,4-dioxolanyl)undec-10-enyloxy)-1,1,2,2-tetramethyl-1-silapropane (4b). This THP ether was prepared similarly to **4a** using PPTS (25.0 mg, 0.1 mmol) alcohol **3b** (460 mg, 1.15 mmol) and dihydropyran (145.3 mg, 1.73 mmol, freshly distilled) in dry methylene chloride (15 mL). The crude product was purified by flash chromatography on a silica gel column (10% ethyl acetate in hexanes) to afford the THP ether **4b** (450 mg, 98%). TLC (ethyl acetate/hexanes, 3:22): $R_f = 0.31$; ^{1}H NMR ($CDCl_3$) δ 5.55−5.88 (m, 2 H), 4.56−4.68 (m, 1 H), 4.50 (m, 1 H), 4.00−4.12 (2 H), 3.84 (m, 1 H), 3.57 (t, $J = 6.6$ Hz, 2 H), 3.55 (m, 1 H), 3.45 (m, 1 H), 1.4−1.9 (12H), 1.40 (s, 3 H), 1.37 (s, 3 H), 1.15−1.35 (8 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 0.87 (s, 9 H), 0.02 (s, 6 H); HRMS (EI) (*m*/*z*) calcd for $C_{26}H_{49}O_5Si$ ($M^+ - CH_3$) 469.3349, found 469.3374, calcd for $C_{23}H_{43}O_5Si$ ($M^+ - CMe_3$) 427.2880, found 427.2889.

5-(2-Oxanyloxy)-7-(3,3-dimethyl-2,4-dioxolanyl)hept-6-en-1-ol (5a). *n*-Bu_4NF (0.55 mL, 1 M in THF) was added dropwise to a stirred solution of the silyl ether **4a** (78 mg, 0.82 mmol) at room temperature.[31] The resulting mixture was stirred overnight, and then 2.0 mL of water was added. The resulting mixture was extracted with diethyl ether (3 × 10 mL), washed with brine, and dried ($MgSO_4$), and solvents were removed with a rotary evaporator. The resulting residue was flash chromatographed on a silica gel column (40% ethyl

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acetate in hexanes) to afford the primary alcohol **5a** (55 mg, 96%): TLC (ethyl acetate/hexanes, 3:7) $R_f = 0.17$; ^{1}H NMR ($CDCl_3$) δ 5.50−5.85 (m, 2 H), 4.42−4.66 (m, 2 H), 3.88−4.14 (m, 2 H), 3.80 (m, 1 H), 3.48−3.64 (m, 3 H), 3.42 (m, 1 H), 1.3−1.9 (12 H), 1.39 (s, 3 H), 1.35 (s, 3 H); HRMS (EI) (*m*/*z*) calcd for $C_{16}H_{27}O_5$ ($M^+ - CH_3$) 299.1854, found 299.1866.

9-(2-Oxanyloxy)-11-(3,3-dimethyl-2,4-dioxolanyl)undec-10-en-1-ol (5b). This primary alcohol was prepared similarly to **5a** using *n*-Bu_4NF (2.3 mL, 1 M in THF) and the silyl ether **4b** (440 mg, 0.91 mmol) in THF (2 mL) at room temperature. The crude product was flash chromatographed on a silica gel column (40% ethyl acetate in hexanes) to give primary alcohol **5b** (320 mg, 95%): TLC (ethyl acetate/hexanes, 2:3) $R_f = 0.26$; ^{1}H NMR ($CDCl_3$) δ 5.50−5.85 (m, 2 H), 4.64 (m, 1 H), 4.50 (m, 1 H), 4.06 (dd, J = 8.1 Hz, 6.3 Hz, 1 H), 4.06 (m. 1 H), 3.84 (m, 1 H), 3.61 (t, J = 6.6 Hz, 2 H), 3.55 (m, 1 H), 3.45 (m, 1 H), 1.4−1.9 (12 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 1.15−1.35 (8 H); HRMS (EI) (*m*/*z*) calcd for $C_{20}H_{35}O_5$ ($M^+ - CH_3$) 355.2484, found 355.2466, calcd for $C_{16}H_{29}O_3$ ($M^+ - C_5H_9O_2$) 269.2117, found 269.2107.

5-(2-Oxanyloxy)-7-(3,3-dimethyl-2,4-dioxolanyl)hept-6-enoic Acid (6a). A solution of alcohol **5a** (44 mg, 0.14 mmol) and pyridinium dichromate (PDC, 316 mg, 0.84 mmol) in DMF (0.5 mL) was stirred for 20 h at room temperature[32] and then diluted with aqueous acetic acid to pH = 4 and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were dried over $MgSO_4$ and concentrated with a rotary evaporator. Flash chromatography on a silica gel column (55% ethyl acetate in hexanes) afforded the acid **6a** (40.7 mg, 88.5%): TLC (ethyl acetate/hexanes, 11:9) $R_f = 0.26$; ^{1}H NMR ($CDCl_3$) δ 5.50−5.86 (m, 2 H), 4.55−4.68 (m,1 H), 4.49 (m, 1H), 3.88−4.18 (m, 2 H), 3.82 (m, 1 H), 3.55 (m, 1 H), 3.45 (m, 1 H), 2.35 (2t, J = 6.6 Hz, 7.5 Hz, 2H), 1.4−1.8 (10 H), 1.40 (s, 3 H), 1.36 (s, 3 H); HRMS (EI) *m*/*z* 328.1886 (M^+) calcd for $C_{17}H_{28}O_6$ found 328.1895, calcd for $C_{16}H_{24}O_6$ ($M^+ - CH_3$) 313.1647, found 313.1650.

9-(2-Oxanyloxy)-11-(3,3-dimethyl-2,4-dioxolanyl)undec-10-enoic Acid (6b). This carboxylic acid was prepared similarly to **6a** using a solution of alcohol **5b** (271 mg, 0.73 mmol) and PDC (1.65 g, 4.38 mmol) in DMF (4 mL). Flash chromatography of the crude product on silica gel column (50% ethyl acetate in hexanes) afforded the acid **6b** (320 mg, 82%): TLC (ethyl acetate/hexanes, 1:1) $R_f = 0.28$; ^{1}H NMR ($CDCl_3$) δ 5.50−5.88 (m, 2 H), 4.62 (m, 1 H), 4.49 (m, 1H), 4.0−4.1 (2 H), 3.83 (m, 1 H), 3.54 (m, 1 H), 3.44 (m, 1 H), 2.35 (t, J = 7.4 Hz, 2H), 1.4−1.9 (10 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.15−1.35 (8 H); HRMS (EI) (*m*/*z*) calcd for $C_{21}H_{36}O_6$ (M^+) 384.2512, found 384.2465, calcd for $C_{20}H_{33}O_6$ (M^+ − Me) 369.2277, found 369.2235, and calcd for $C_{16}H_{25}O_3$ ($M^+ - C_5H_9O_2 - H_2O$) 265.1802, found 265.1806.

Cholesteryl 5-(2-Oxanyloxy)-7-(3,3-dimethyl-2,4-dioxolanyl)hept-6-enoate (7a). Dicyclohexylcarbodiimide (DCC) (114 mg, 0.54 mmol) and *N*,*N*-dimethylaminopyridine (DMAP, 26 mg, 0.21 mmol) were added to a solution of the acid **6a** (88.0 mg, 0.27 mmol) and cholesterol (69.5 mg, 0.18 mmol) in dry CH_2Cl_2 (2.0 mL).[33] The resulting mixture was stirred at room temperature for 48 h. The solution was then filtered, and solvent was removed with a rotary evaporator. The residue was purified by flash chromatography on a silica gel column (12% ethyl acetate in hexanes) to afford the ester **7a** (120 mg, 96%): TLC (ethyl acetate/hexanes, 3:22) $R_f = 0.22$; ^{1}H NMR ($CDCl_3$) δ 5.54−5.89 (m, 2 H), 5.37 (bd, J = 4.5 Hz, 1 H), 4.67 (m, 1 H), 4.61 (m, 1H), 4.52 (td, J = 6.6 Hz, 7.4 Hz, 1 H), 4.10 (m, 2 H), 3.85 (m, 1 H), 3.58 (m, 1 H), 3.47 (m, 1 H), 2.30 (4 H), 0.8−2.2 (35 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.02 (s, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 6 H), 0.68 (s, 3 H); HRMS (EI) (*m*/*z*) calcd for $C_{43}H_{69}O_6$ ($M^+ - CH_3$) 681.5094, found 681.5119, and calcd for $C_{39}H_{63}O_4$ ($M^+ - C_5H_9O_2$) 595.4726, found 595.4737.

Cholesteryl 9-(2-Oxanyloxy)-11-(3,3-dimethyl-2,4-dioxolanyl)undec-10-enoate (7b). This carboxylic ester was prepared similarly to **7a** using a mixture of the acid **6b** (18.5 mg, 0.048 mmol), cholesterol (12.4 mg, 0.032 mmol), DCC (20.0 mg, 0.096 mmol), and DMAP (5 mg, 0.04 mmol) in dry CH_2Cl_2 (1.0 mL). The crude product was purified by flash chromatography on a silica gel column (12% ethyl acetate in hexanes) to afford the ester **7b** (22 mg, 92%): TLC (ethyl acetate/hexanes, 3:17): $R_f = 0.32$; ^{1}H NMR ($CDCl_3$) δ 5.5−5.86 (m, 2 H), 5.35 (bd, J = 4.0 Hz, 1 H), 4.55−4.70 (m, 2 H), 4.48 (m, 1H), 4.06 (m, 2 H), 3.83 (m, 1H), 3.55 (m, 1 H), 3.45 (m, 1 H), 2.23 (t, J = 7.6 Hz, 2 H), 2.26 (d, J = 7.6 Hz, 2H), 0.8−2.2 (43 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 0.99 (s, 3 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.840 (d, J = 6.6 Hz, 3 H), 0.836 (d, J = 6.7 Hz, 3 H), 0.65 (s, 3 H).

Cholesteryl 5-Hydroxy-8-oxooct-6-enoate (8a). A solution of **7a** (21.0 mg, 0.03 mmol) in acetic acid/water (2:1, v/v, 1.2 mL) was stirred for 4 h at 40 °C,[15] and then sodium metaperiodate (9.7 mg, 0.045 mmol) was added. After being stirred another 1.5 h at room temperature, the solution was neutralized by the portionwise addition of saturated aqueous sodium bicarbonate and then extracted with diethyl ether. The ether phase was dried over $MgSO_4$, and solvents were removed with a rotary evaporator. The residue was flash chromatographed on a silica gel column (25% ethyl acetate in hexanes) to provide aldehyde **8a** (13.8 mg, 85%): TLC (ethyl acetate/hexanes, 2:3): $R_f = 0.26$; ^{1}H NMR ($CDCl_3$) δ 9.57 (d, J = 7.75 Hz, 1 H), 6.79 (dd, J = 15.6 Hz, 4.5 Hz, 1 H), 6.30 (ddd, J = 15.6 Hz, 6.6 Hz, 1.5 Hz, 1 H), 5.35 (bd, J = 4.3 Hz, 1 H), 4.59 (m, 1 H), 4.43 (m, 1H), 2.34 (t, J = 6.4 Hz, 2 H) 2.30 (dd, J = 9.7 Hz, 7.8 Hz, 2 H), 0.8−2.2 (30 H), 0.99 (s, 3 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 6 H), 0.65 (s, 3 H); ^{13}C NMR (APT, $CDCl_3$) δ 193.43 (CHO), 173.01 (C═O), 158.35 (CH), 139.54 (C), 130.91 (CH), 122.82 (CH), 74.27 (CH), 70.52 (CH), 56.71 (−), 56.17 (−), 50.05 (+), 42.35 (+), 39.75 (+), 39.55 (+), 38.17 (+), 37.00 (+), 36.63 (+), 36.22 (+), 35.83 (−), 35.72 (+), 34.03 (+), 31.95 (+), 31.88 (−), 28.27 (+), 28.05 (−), 27.85 (+), 24.32 (+), 23.87 (+), 22.86 (−), 22.61 (−), 21.07 (+), 20.42 (+), 19.35 (−), 18.76 (−), 11.90 (−); HRMS (EI) (*m*/*z*) calcd for $C_{35}H_{54}O_5$ ($M^+ - H_2O$) 522.4071, found 522.4099.

Cholesteryl 9-Hydroxy-12-oxododec-10-enoate (8b). This aldehyde was prepared similarly to **8a** using a solution of **7b** (20 mg, 0.0265 mmol) in acetic acid/water (2:1, v/v, 1.2 mL) and sodium metaperiodate (8.5 mg, 0.040 mmol). The crude product was flash chromatographed (20% ethyl acetate in hexanes) to afford the aldehyde **8b** (14 mg, 90%): TLC (ethyl acetate/hexanes, 1:4) $R_f = 0.21$; ^{1}H NMR ($CDCl_3$) δ 9.57 (d, J = 7.8 Hz, 1 H), 6.80 (dd, J = 15.6 Hz, 4.51 Hz, 1 H), 6.29 (ddd, J = 15.6 Hz, 7.7 Hz, 1.7 Hz, 1 H), 5.35 (d, J = 4.3 Hz, 1 H), 4.59 (m, 1 H), 4.41 (m, 1H), 2.27 (t, J = 7.8 Hz, 2 H) 2.26 (dd, J = 15.0 Hz, 7.4 Hz, 2 H), 0.8−2.2 (38 H), 0.99 (s, 3 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.84 (d, J = 5.6 Hz, 6 H), 0.65 (s, 3 H); ^{13}C NMR (APT, $CDCl_3$) δ 193.50 (CHO), 173.31 (−CO−), 158.80 (CH), 139.73 (C), 130.74 (CH), 122.67 (CH), 73.79 (CH), 71.11 (CH), 56.72 (−), 56.17 (−), 50.05 (+), 42.34 (+), 39.76 (+), 39.55 (+), 38.20 (+), 37.03 (+), 36.64 (+), 36.51 (+), 36.21 (+), 35.83 (−), 34.66 (+), 31.95 (+), 31.89 (−), 29.20 (+), 29.09 (+), 28.97 (+), 28.26 (+), 28.05 (−), 27.85 (+),25.12 (+), 24.96 (+), 24.32 (+), 23.86 (+), 22.86 (−), 22.60 (−), 21.07 (+), 19.36 (−), 18.75 (−), 11.89 (−); HRMS (EI) (*m*/*z*) calcd for $C_{39}H_{62}O_3$ ($M^+ - H_2O$) 578.4651, found 578.4705.

Phospholipid 9a. Dicyclohexylcarbodiimide (DCC, 101 mg, 0.49 mmol) and *N*,*N*-dimethylaminopyridine (DMAP) (26 mg, 0.21 mmol) were added to a solution of the acid **6a** (107 mg, 0.32 mmol) and L-α-lysophosphatidylcholine (104 mg, 0.21 mmol) in dry $CHCl_3$ (5 mL).[33] The resulting mixture was stirred for 48 h at room temperature. The solution was filtered, and the solvent was removed by rotary evaporation. Flash chromatography of the residue ($CHCl_3$/MeOH/H_2O, 30:19:1) gave phospholipid **9a** (210 mg, 82%): TLC ($CHCl_3$/MeOH/H_2O, 30:19:1) $R_f = 0.16$; ^{1}H NMR ($CDCl_3$) δ 5.5−5.85 (m, 2 H), 5.18 (m, 1 H), 4.5−4.65 (m, 1 H), 4.48 (td, J = 6.8 Hz, 6.4 Hz, 1 H), 4.15−4.42 (m, 3 H), 4.0−4.1 (3 H), 3.92 (m, 2 H), 3.65−3.85 (3 H), 3.55 (m, 1 H), 3.43 (m, 1 H), 3.35 (s, 9 H), 2.24 (t, J = 7.6 Hz, 2 H), 2.27 (m, 2 H), 1.4−1.9 (12 H), 1.39 (s, 3H), 1.35 (s, 3H), 1.22 (24H), 0.85 (t, J = 6.8 Hz, 3 H); HRMS

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(FAB, CsI/NaI/glycerol) (*m*/*z*) calcd for $C_{41}H_{76}NO_{12}PCs$ (MCs^+) 938.4155, found 938.4154.

Phospholipid 9b. This phospholipid was prepared similarly to **9a** using the acid **6b** (74 mg, 0.19 mmol), L-α-lysophosphatidylcholine (47 mg, 0.095 mmol), dry $CHCl_3$ (2 mL),DCC (60 mg, 0.29 mmol), and DMAP (12 mg, 0.095 mmol). Flash chromatography of the crude product on a silica gel column ($CHCl_3$/MeOH/H_2O, 30:19:1) gave **9b** (78 mg, 95%): TLC ($CHCl_3$/MeOH/H_2O, 30:19:1) $R_f = 0.28$; ^{1}H NMR ($CDCl_3$) δ 5.5−5.85 (m, 2 H), 5.17 (m, 1 H),4.54−4.67 (m, 1 H), 4.48 (m, 1 H), 4.18−4.42 (3 H), 3.96−4.14 (3 H), 3.92 (3 H), 3.72−3.98 (3 H), 3.53 (m, 1 H), 3.43 (m, 1 H), 3.35 (s, 9 H), 2.25 (4 H), 1.4−1.9 (13 H), 1.39 (s, 3 H), 1.37 (s, 3H), 1.22 (33 H), 0.85 (t, $J = 6.4$ Hz, 3 H); HRMS (FAB, CsI/NaI/Gly) (*m*/*z*) calcd for $C_{45}H_{84}NO_{12}PCs$ (MCs^+) 994.4781, found 994.4773.

Hydrolysis and Periodate Oxidation of 9b. Treatment of a solution of **9b** in acetic acid/water (2:1, v/v), and sodium metaperiodate as described for **7b** above, did not deliver the expected γ-hydroxy-α,β-unsaturated aldehyde **10b**. Rather, 1-palmitoyl-2-(9-oxononanoyl)-*sn*-glycero-3-phosphocholine (**12**, $n = 7$) was obtained (75−80%): HRMS (FAB, CsI/NaI/Gly) (*m*/*z*) calcd for $C_{33}H_{64}NO_9PCs$ (MCs^+) 782.3368, found 782.3391. The ^{1}H NMR spectrum of the phospholipid was identical with that reported previously for **12** ($n = 7$).[5]

Phospholipid Aldehyde 10a. A solution of the compound **9a** (22 mg, 0.027 mmol) in acetic acid/water (2:1, v/v, 1.2 mL) was stirred magnetically for 4 h at 40 °C, and then the solvent was removed with a rotary evaporator. Traces of residual HOAc were removed by azeotropic distillation with *n*-heptane (2 × 1 mL) under high vacuum. Dry methylene chloride (1 mL) and Na_2CO_3 (5.7 mg, 0.054 mmol) were added to the residue. The solution was stirred magnetically at −78 °C under argon. $Pb(OAc)_4$ (13.3 mg, 0.03 mmol) in dry methylene chloride (1 mL)[34] was added dropwise with a syringe. The resulting solution was stirred for 10 min, and then the solvent was removed by rotary evaporation and the residue was flash chromatographed on a silica gel column ($CHCl_3$/MeOH/H_2O, 15:9:1) to give phospholipid aldehyde **10a** (14.3 mg, 82%): TLC ($CHCl_3$/MeOH/H_2O, 15:9:1) $R_f = 0.17$; ^{1}H NMR ($CDCl_3$) δ 9.53 (d, $J = 7.7$ Hz, 1 H), 6.85 (dd, $J = 15.3$ Hz, 3.7 Hz, 1 H), 6.28 (dd, $J = 15.3$ Hz, 8.2 Hz, 1 H), 5.22 (m, 1 H), 4.37 (m, 1 H), 4.1−4.35 (4 H), 3.99 (m, 1 H), 3.91 (m, 1 H), 3.75 (m, 2 H), 3.30 (s, 9 H), 2.36 (m, 2 H), 2.26 (t, $J = 6.2$ Hz), 1.5−1.9 (6 H), 1.22 (24 H), 0.85 (t, $J = 6.4$ Hz); ^{13}C NMR (APT, $CDCl_3$) δ 194.18 (CHO), 173.56 (−CO−), 173.15 (−CO−), 161.06 (CH), 130.52 (CH), 70.79 (CH), 70.31 (CH), 66.40 (CH_2), 62.56 (CH_2), 59.41 (CH_2), 59.32 (CH_2), 54.51 (CH_3), 34.10 (CH_2), 31.95 (CH_2), 29.73 (CH_2), 29.55 (CH_2), 29.37 (CH_2), 29.19 (CH_2), 24.90 (CH_2), 14.14 (CH_3).

Phospholipid Aldehyde (10b). This aldehyde was prepared similarly to **10a** using a solution of the compound **9b** (28 mg, 0.032 mmol) in acetic acid/water (2:1, v/v, 1.5 mL) followed by treating a solution of the vicinal diol intermediate in dry methylene chloride (1.2 mL) with Na_2CO_3 (6.8 mg, 0.064 mmol) and then $Pb(OAc)_4$ (15.5 mg, 0.035 mmol) in dry CH_2Cl_2 (1 mL). The crude product was flash chromatographed on a silica gel column ($CHCl_3$/MeOH/H_2O, 15:9:1) to give the phospholipid aldehyde **10b** (19.2 mg, 85%): TLC ($CHCl_3$/MeOH/H_2O, 15:9:1) $R_f = 0.18$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (d, $J = 8.0$ Hz, 1 H), 6.86 (dd, $J = 15.5$ Hz, 4.1 Hz, 1 H), 6.28 (ddd, $J = 15.5$ Hz, 8.1 Hz, 1.3 Hz, 1 H), 5.19 (m, 1 H), 4.37 (m, 1 H), 4.32 (dd, $J = 12.1$ Hz, 3.2 Hz, 1 H), 4.27 (m, 2 H), 4.11 (dd, $J = 12.0$ Hz, 7.3 Hz, 1 H), 3.92 (dd, $J = 6.1$ Hz, 6.0 Hz, 2 H), 3.76 (m, 2 H), 3.32 (s, 9 H), 2.28 (m, 2 H), 2.25 (t, $J = 7.5$ Hz, 2 H), 1.45−1.70 (7 H), 1.3−1.5 (12 H), 1.22 (19 H), 0.85 (t, $J = 6.5$ Hz); ^{13}C NMR (300 MHz, APT, $CDCl_3$) δ 194.21 (CHO), 173.62 (−CO−), 173.32 (−CO−), 161.77 (CH), 130.21 (CH), 70.74, 70.65 (CH), 70.16, 70.11 (CH), 66.53, 66.48, (CH_2), 63.56, (CH_2), 62.89 (CH_2), 59.28, 59.23 (CH_2), 54.54 (CH_3), 36.40, (CH_2), 34.16 (CH_2), 31.96 (CH_2), 29.96 (CH_2), 29.74 (CH_2), 29.65 (CH_2), 29.39 (CH_2), 29.20 (CH_2), 28.77 (CH_2), 28.56 (CH_2), 28.19 (CH_2), 24.93 (CH_2), 24.72 (CH_2), 22.73 (CH_2), 14.16 (CH_3).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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