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Synthesis of Photoactivatable Analogues of Lysophosphatidic Acid and Covalent Labeling of Plasma Proteins

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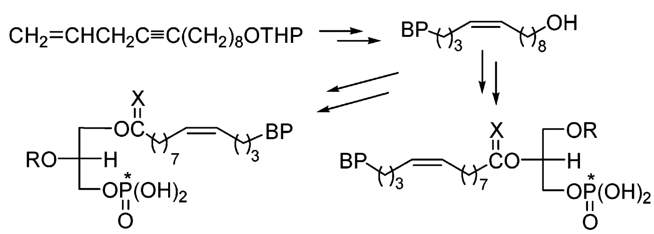

Lysophosphatidic acids bearing a benzophenone group in either the *sn*-1 or *sn*-2 chain of an oleoyl-type ester or oleyl-type ether chain and ^{32}P in the phosphate group were synthesized. The benzophenone moiety was introduced by selective hydroboration of the double bond of enyne **11** at low temperature, followed by a Suzuki reaction with 4-bromobenzophenone. The key intermediates for the preparation of ester-linked lysophosphatidic acid (LPA) **1** and **3** were obtained in one pot by a modified DIBAL-H reduction of orthoformate intermediate **22**. These probes were shown to covalently modify a single protein target in rat plasma containing albumin and several protein targets in rat plasma containing a low level of albumin.

Introduction

Lysophosphatidic acid (LPA) has the simplest structure of natural phospholipids, yet it has attracted significant attention because of the diversity and importance of its biological effects.[1−5] LPA is not a single compound; rather, it comprises a family of related mediators that differ in the length and degree of unsaturation of a hydrocarbon chain linked to a glycerol backbone via ester,[6] ether,[7] or vinyl ether[8] bonds at either the *sn*-1 or *sn*-2 position. Different LPA family members have distinct biological activities.[9] LPA plays a key role in a myriad of physiological processes, including Ca^{2+} flux, vascular and neuronal function, cell growth/death, and cell migration.[2,10] It is now appreciated that LPA has numerous intracellular, extracellular, and cell-surface targets. LPA exerts its activities mainly through several cell-surface G protein-coupled receptors (GPCR), including the widely reported LPA_1, LPA_2, and LPA_3

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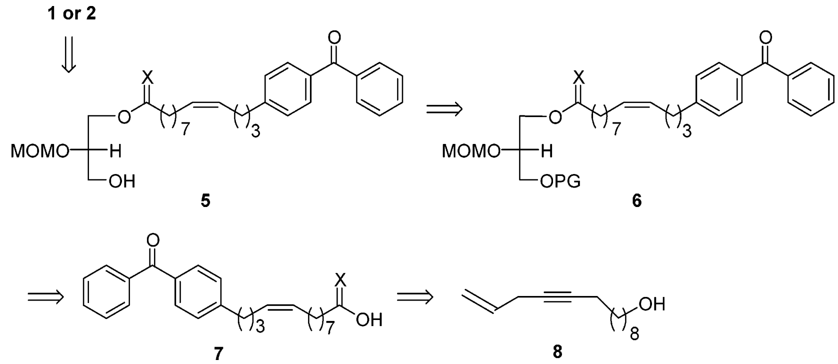
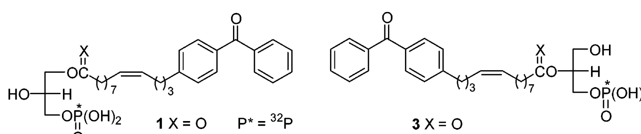
SCHEME 1. Retrosynthetic Strategy



receptor subtypes. Recently, the LPA_4/GPR23/P2Y9 receptor[11] and the nuclear transcription factor PPARγ[12] were identified as LPA receptors. LPA also interacts with numerous binding proteins, including albumin[13] and gelsolin.[14] It has been speculated that interactions with binding proteins may modulate the biological activity of LPA.

Despite recent progress elucidating many of the biological properties of LPA, a detailed understanding of the key roles of LPA in many disease processes has not yet been achieved. To gain insights into the protein targets of LPA, we have prepared photoreactive analogues of LPA. Photoactivatable lipid analogues have been widely employed to study hydrophobic binding sites of lipid targets.[15] Recently, we reported the first synthesis and characterization of two photoactivatable analogues of sphingosine 1-phosphate (S1P).[16] Likewise, photoactivatable analogues of bioactive glycerophospholipids[17] and lysosphingophospholipids[18] have been reported recently. One previous study reported the synthesis and characterization of a photoreactive LPA analogue containing a trifluoromethylphenyldiazirine group for labeling of fetal bovine serum and LPA responsive cells.[19] In this paper, we report the syntheses of additional photoactivatable analogues of acyl- and *O*-alkyl-linked LPAs in which the long chain resembles an oleoyl (ester) or oleyl (ether) chain, respectively. The rationale for this approach is that the oleoyl chain has been shown to represent the maximally effective fatty acyl chain of natural LPAs in previous structure−activity studies.[20] We have prepared both the 2-lyso (**1** and **2**) and 1-lyso (**3** and **4**) regioisomeric analogues of [^{32}P]-LPA, as well as the *O*-methoxymethyl (MOM)-protected photoreactive analogues of [^{32}P]-LPA (denoted as **20P** and **27P**). In the current analogues, benzophenone was employed as the photoprobe for labeling of proteins because it is readily activated with long-wavelength UV light, is stable in most of the chemical reactions used during the synthesis of the probe, and generally yields covalent products modified at a single site.[21] In the four probes reported herein, the benzophenone moiety is linked to the end of a Δ^9 cis hydrocarbon chain. These analogues were characterized via the covalent modification of rat plasma proteins.



1 X = O P* = ^{32}P **3** X = O
2 X = H$_2$ **4** X = H$_2$

Results and Discussion

Retrosynthetic Analysis. Our retrosynthetic strategy for the synthesis of **1** and **2** is outlined in Scheme 1. Analogues **1** and **2** were envisioned as being produced via enzymatic phosphorylation and deprotection of 2-MOM-protected 3-hydroxyglyceryl ester **5** (X = O) or ether (X = H$_2$), respectively. Compound **5** can be generated by the selective removal of the *sn*-3 protecting group (PG) from **6**, whereas intermediate **6** is accessible from carboxylic acid **7** (X = O) or from the corresponding alcohol (X = H$_2$). The introduction of the benzophenone probe into **7** may be achieved by the regioselective addition of 9-BBN to the double bond in **8**, provided that no reaction occurs at the internal triple bond, followed by Suzuki coupling with 4-bromobenzophenone. Compounds **3** and **4** can be prepared from the regioisomers of **5**−**8** using similar schemes.

Conversion of 2-Decyn-1-ol to Alcohol 14. Scheme 2 outlines the synthesis of Δ^9 alcohol **14**. The acetylene zipper reaction of commercially available 2-decyn-1-ol[22] gave terminal acetylide **9**. After the hydroxy group was protected as a THP ether to give **10** in nearly quantitative yield, addition of allyl bromide to the lithium anion of **9** provided enyne **11** in 79% yield. The benzophenone moiety was introduced by selective hydroboration of the double bond of **11** at low temperature, without reaction of the organoborane with the triple bond, followed by the Suzuki reaction of the terminal boronate with 4-bromobenzophenone. After the THP group of **12** was re-

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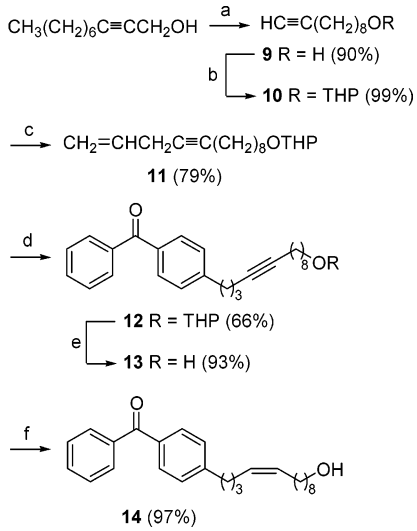
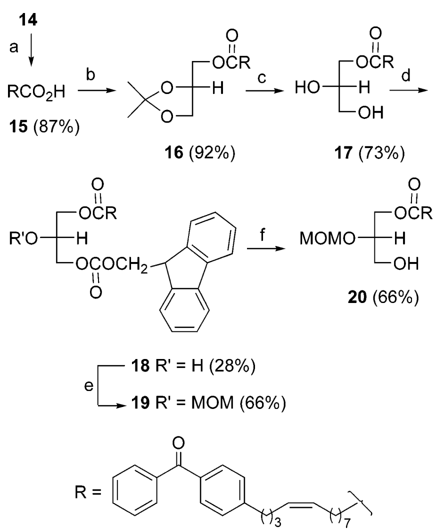
SCHEME 2. Synthesis of Long-Chain Alcohol 14[a]



[a] (a) $LiNH(CH_2)_3NH_2$, *t*-BuOK/$H_2N(CH_2)_3NH_2$; (b) DHP, PPTS, CH_2Cl_2; (c) (i) *n*-BuLi, THF, −78 °C to room temperature and (ii) allyl bromide, CuI, THF, −78 °C; (d) (i) 9-BBN, THF, −15 °C to room temperature and (ii) 4-bromobenzophenone, $Pd(PPh_3)_4$, K_3PO_4, THF/DMF, reflux, 2 h; (e) PPTS (cat.), MeOH; (f) H_2, Lindlar, MeOH.

SCHEME 3. Synthesis of Glyceride 20 via FMOC-Ester 18[a]



[a] (a) PDC/DMF, room temperature, 2 days; (b) (*R*)-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol, DCC, DMAP, CH_2Cl_2, room temperature; (c) 0.4 N HCl/90% dioxane, room temperature; (d) FMOC−chloroformate, DMAP, CH_2Cl_2, −10 °C; (e) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (f) piperidine, CH_2Cl_2.

moved, Lindlar-catalyzed hydrogenation of the triple bond in **13** afforded *Z* alcohol **14** in very high yield.

Synthesis of Ester-Linked LPA Probes 1 and 3. Conversion of Alcohol 14 to Glyceride 20. Oxidation of alcohol **14** with PDC gave acid **15**, which was converted to ester **16** by reaction with (*R*)-isopropylideneglycerol (Scheme 3). After removal of the acetonide protecting group in **16** afforded diol **17**, monoacylation of the resultant primary hydroxy group was accomplished according to a reported procedure[23] with 1 equiv of FMOC−chloroformate, providing secondary alcohol **18** in 28% yield based on diol **17**. This yield is comparable to that reported with a similar diol.[23] Treatment of **18** with MOM−Cl provided glyceride **19**, and removal of the FMOC group (10% piperidine in CH_2Cl_2) afforded **20**. Although this multistep synthesis is straightforward, the overall yield of ester **20** is low and the method does not allow for the preparation of the regioisomer of **20**. To overcome these deficiencies, an alternative synthetic strategy was designed (see Scheme 4).

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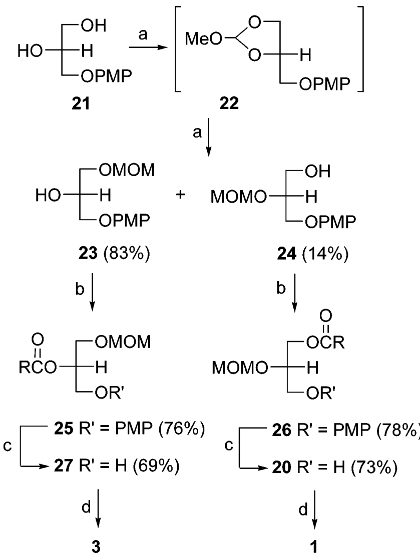
SCHEME 4. Synthesis of 1 and 3[a]



R is the same as in Scheme 3

[a] (a) (i) $HC(OMe)_3$, CSA (cat.), CH_2Cl_2, room temperature and (ii) DIBAL-H, 0 °C; (b) **15**, PPh_3, DIAD, THF, 0 °C to room temperature; (c) CAN, CH_3CN/H_2O (6:1); (d) (i) DGK, [^{32}P]ATP, pH 6.6, 37 °C, 2 h and (ii) TMSBr, CH_2Cl_2, 0 °C.

Syntheses of 1 and 3 via 3-*O*-PMP-*sn*-glycerol (21). Our revised synthetic scheme begins with the conversion of 3-*O*-PMP-*sn*-glycerol (**21**)[24] to glyceride **20** and its regioisomer **27** (Scheme 4). The MOM protecting group was introduced into diol **21** prior to ester formation by transesterification with trimethyl orthoformate using a modification of a previously reported procedure.[25] The key step in this scheme is the protection of one of the hydroxy groups of diol **21** as a MOM ether via orthoformate intermediate **22**, followed by reduction with DIBAL-H in toluene. When the reduction was conducted at −78 °C, regioisomers **23** and **24** were obtained in a ratio of 23:1 and an overall yield of 96% after chromatography. Thus, this methodology is a highly efficient route to the precursor of 1-lyso-LPA product **3** but not to the 2-lyso-LPA product **1**. We altered the reduction conditions to obtain an adequate amount of primary alcohol **24** for conversion to 1-acyl-LPA product **1**, which is needed in the photolabeling experiments. When the DIBAL-H reduction was carried out at 0 °C, compound **24** was obtained in 14% yield, which sufficed for the preparation of **1**. Esterification of **23** and **24** with acid **15** using Mitsunobu reaction conditions, followed by removal of the PMP group in **25** and **26** with CAN, provided **27** and **20**. Compounds **1** and **3** were obtained by phosphorylation of **27** and **20** with

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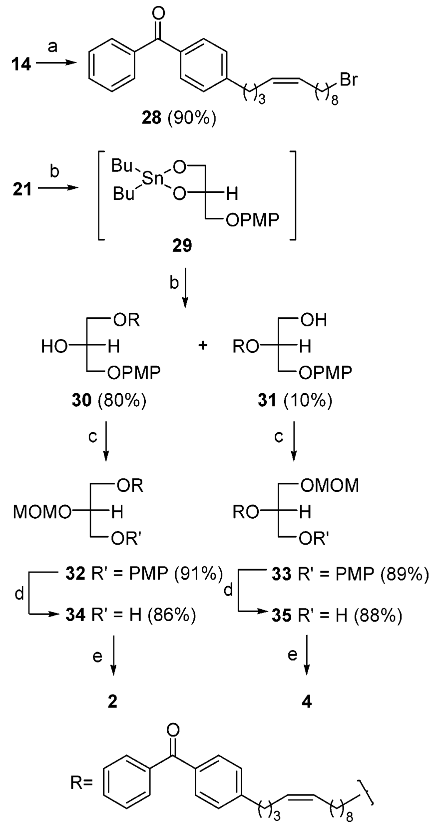
SCHEME 5. Synthesis of Ether-Linked Probes 2 and 4[a]



[a] (a) (i) CH_3SO_2Cl, Et_3N, 0 °C to room temperature and (ii) LiBr, THF, reflux; (b) (i) $(n\text{-}Bu)_2SnO$, $CHCl_3$/MeOH (10:1), reflux and (ii) **28**, CsF, 18-crown-6, DMF, room temperature, 1 day; (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (d) CAN, CH_3CN/H_2O (6:1); (e) (i) DGK, [^{32}P]ATP and (ii) TMSBr, CH_2Cl_2, 0 °C.

diacylglycerol kinase (DGK) and [^{32}P]ATP.[26] The final step, deprotection of the MOM group of **20P** and **27P**, was accomplished in quantitative yield with trimethylsilyl bromide in dry CH_2Cl_2 at 0 °C.

Synthesis of Ether-Linked LPA Probes 2 and 4. Scheme 5 depicts the strategy we used to introduce an *O*-alkyl chain bearing a benzophenone probe into the *sn*-1 or *sn*-2 position of glycerol. Reaction of diol **21** with dibutyltin oxide afforded cyclic tin intermediate **29**,[27] which was used without purification. Ethers **30** and **31** were obtained in 80 and 10% yields, respectively, by nucleophilic substitution of bromide **28** with intermediate **29**. After the hydroxy group in **30** or **31** was protected as a MOM ether, the PMP group was removed with CAN to give precursor **34** or **35** in high yield. Ether-linked probes **2** and **4** were obtained from **34** and **35** using the same phosphorylation and deprotection methodology as that described for the preparation of **1** and **3**.

Plasma Protein Photolabeling. The goal of this research was to generate tools that can be used to distinguish targets of individual LPA family members, i.e., acyl vs *O*-alkyl and *sn*-1 vs *sn*-2 linked aliphatic benzophenones. To that end, we tested five of the synthesized target compounds and intermediates for the ability to photolabel plasma proteins. Probes **1** and **2** allow for a comparison of the *sn*-1 acyl vs *O*-alkyl analogues, whereas **2** and **4** allow for a comparison of the *sn*-1 vs *sn*-2 regioisomers. Comparisons between compounds **1** and **3** were not made because of facile acyl migration inherent in probe **3**.[28] However, the *sn*-3 phosphorylation products (**20P** and **27P**) of synthetic intermediates **20** and **27** afford an additional comparison between the acyl regioisomers of LPA without the risk of acyl migration. Plasma from the Sprague−Dawley rat ("normal rat plasma" (NRP)) contains 19.4 mg of albumin per milliliter[29] and was used as a surrogate for normal human plasma. Conversely, plasma from the Nagase analbuminemic rat ("analbuminemic rat plasma" (ARP)) contains only 0.4 mg of albumin per milliliter.[29] This material was used as a tool to examine binding to plasma proteins other than albumin.

Benzophenone-containing LPA probes were characterized by UV-dependent labeling of plasma proteins (Figure 1). Probes **1**, **2**, **4**, **20P**, and **27P** all showed time- (Figure 1A) and concentration-dependent (data not shown) labeling of predominantly one protein band in NRP. On the basis of the fact that LPA was initially purified from serum as biological activity associated with albumin[13] and the size of the labeled band in this study (∼70 kDa), we conclude that this protein is likely albumin. In contrast, four or five targets were identified on photolabeling of plasma with a low content of albumin (ARP) with the same probes (Figure 1B). Once again, labeling for all probes was time (Figure 1B) and dose (data not shown) dependent. The intensity of the individual labeled bands varied among the probes, but all of the probes modify similar targets in both NRP and ARP. This was expected because these targets are presumed to be transport proteins in which the interactions are based more on hydrophobicity than on stereochemistry or regiochemistry. Further identification and characterization of plasma protein targets of LPA-containing benzophenones, as well as examination of the pharmacology of these reagents at individual LPA GPCR and cellular targets, is currently underway in our laboratories.

Experimental Section

Tetrahydro-2-(tridec-12-en-9-ynyloxy)-2*H*-pyran (11). To a solution of alkyne **10** (2.00 g, 8.40 mmol) in 20 mL of dry THF was added *n*-BuLi (3.5 mL, 10.1 mmol, a 2.89 M solution in hexane) at −78 °C under N_2. After being stirred for 1 h at −78 °C, the reaction mixture was warmed to room temperature and stirred for an additional 1.5 h. The mixture was then slowly added to a solution of allyl bromide (1.22 g, 10.1 mmol) and CuI (100 mg, 0.50 mmol) in 20 mL of THF at −78 °C. After the reaction mixture was stirred overnight at room temperature, the mixture was filtered through a short silica gel column. The solvent was removed, and the residue was purified by chromatography (hexane/EtOAc 20:1) to afford **11** (1.85 g, 79%) as a colorless oil: ^{1}H NMR δ 1.24−1.90 (m, 18H), 2.14−2.22 (m, 2H), 2.90−2.97 (m, 2H), 3.34−3.41 (m, 1H), 3.48−3.52 (m, 1H), 3.69−3.76 (m, 1H), 3.84−3.89 (m, 1H), 4.55−4.59 (m, 1H), 5.06−5.11 (m, 1H), 5.27−5.36 (m, 1H), 5.77−5.84 (m, 1H); ^{13}C NMR δ 18.7, 19.6, 23.1, 25.4, 26.1, 28.8, 29.0, 29.0, 29.3, 29.7, 30.7, 62.2, 67.6, 76.4, 82.8, 98.8, 115.5, 133.3; HR-MS [MNa$^+$] m/z calcd for $C_{18}H_{30}O_2Na$ 301.2138, found 301.2107.

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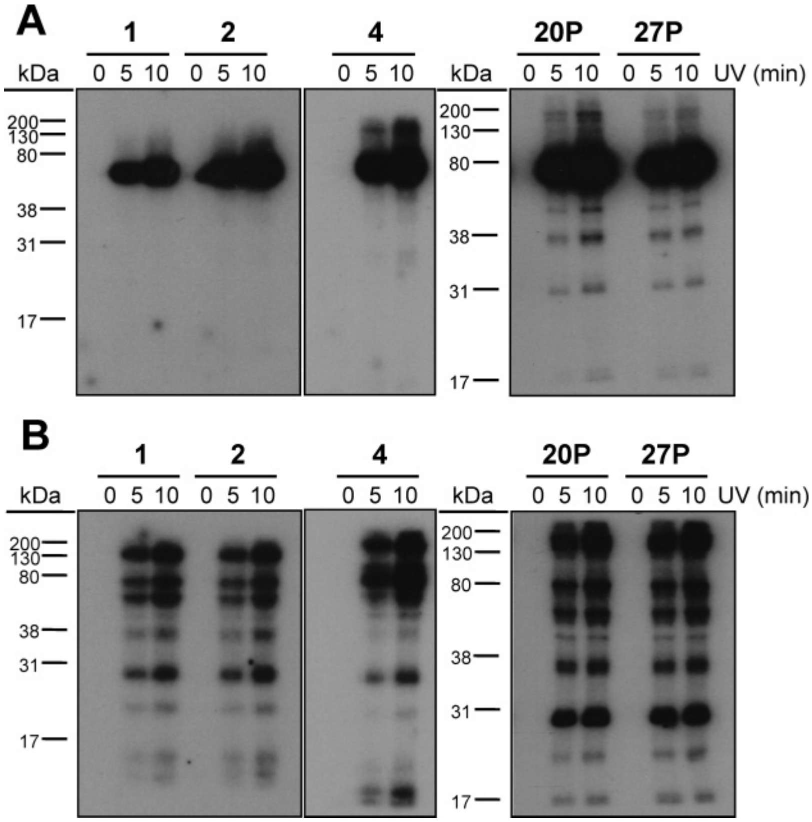

FIGURE 1. Covalent modification of plasma proteins by benzophenone-containing LPA analogues. Plasma (5% in PBS) from Sprague−Dawley (19.4 mg albumin/mL) (**A**) or Nagase rats (0.4 mg albumin/mL) (**B**) was incubated with compounds **1**, **2**, **4**, **20P**, and **27P** (50 nM, DMSO 10% final concentration) in the dark for 30 min prior to UV irradiation for up to 10 min on ice. Samples were diluted with 2 × sample loading buffer and separated by SDS−PAGE. Gels were subsequently dried, and radioactive bands were visualized by autoradiography.

4-(13-(Tetrahydro-2*H*-pyran-2-yloxy)tridec-4-ynyl)benzophenone (12). A flask charged with **11** (1.11 g, 4.00 mmol) and 15 mL of THF was cooled to −15 °C in a salt−ice bath, and 9-BBN (12 mL, 6.0 mmol, a 0.5 M solution in THF) was added dropwise under N_2. After the addition, the reaction mixture was warmed to room temperature and stirred for 5 h. 4-Bromobenzophenone (1.04 g, 4.00 mmol), $Pd(PPh_3)_4$ (230 mg, 0.20 mmol), DMF (15 mL), and anhydrous K_3PO_4 (1.57 g, 8.00 mmol) were added, and the resulting mixture was heated at reflux for 2 h. The reaction mixture was poured into 100 mL of water and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were washed with 100 mL of water and dried (Na_2SO_4). The solvent was removed under vacuum, and the residue was purified by chromatography (hexane/EtOAc 8:1) to provide **12** (1.21 g, 66%) as a colorless oil: ^{1}H NMR δ 1.28−1.90 (m, 20H), 2.12−2.22 (m, 4H), 2.80 (t, 2H, J = 7.6 Hz), 3.32−3.40 (m, 1H), 3.43−3.50 (m, 1H), 3.68−3.74 (m, 1H), 3.82−3.87 (m, 1H), 4.53−4.58 (m, 1H), 7.28−7.80 (m, 9H). ^{13}C NMR δ 18.0, 18.5, 19.5, 25.3, 26.0, 28.6, 28.9, 29.2, 29.5, 30.2, 30.6, 34.6, 62.1, 67.4, 77.2, 79.1, 80.9, 98.6, 128.0, 128.3, 129.7, 130.1, 132.0, 135.1, 137.7, 146.9, 196.1; HR-MS [MNa^+] m/z calcd for $C_{31}H_{40}O_3Na$ 483.2870, found 483.2880.

4-(13-Hydroxytridec-4-ynyl)benzophenone (13). A solution of **12** (370 mg, 0.80 mmol) and a catalytic amount of PPTS in MeOH was heated at reflux for 3 h. Concentration, followed by purification of the residue by chromatography (hexane/EtOAc 4:1), provided **13** (282 mg, 93%): ^{1}H NMR δ 1.25−1.60 (m, 12H), 1.80−1.85 (m, 2H), 2.14−2.21 (m, 4H), 2.75 (s, 1H), 2.80 (t, 2H, J = 7.6 Hz), 3.58 (t, 2H, J = 6.8 Hz), 7.27−7.79 (m, 9H); ^{13}C NMR δ 17.9, 18.5, 25.5, 28.5, 28.8, 28.9, 29.1, 30.0, 32.4, 34.5, 62.3, 79.1, 80.9, 127.9, 128.2, 129.6, 130.1, 132.0, 134.9, 137.5, 146.9, 196.2; HR-MS [MNa^+] m/z calcd for $C_{26}H_{32}O_2Na$ 399.2294, found 399.2285.

4-((*Z*)-13-Hydroxytridec-4-enyl)benzophenone (14). Lindlar catalyst (15 mg, 5.5 wt %) was added to a solution of **13** (270 mg, 0.72 mmol) in 10 mL of MeOH. The mixture was stirred under a hydrogen balloon until the starting alkyne was consumed (monitored by thin-layer chromatography (TLC), hexane/EtOAc 2:1). The solvent was removed under vacuum, and the residue was purified by chromatography (hexane/EtOAc 4:1) to give **14** (262 mg, 97%) as an oil: ^{1}H NMR δ 1.25−1.48 (m, 10H), 1.50−1.56 (m, 2H), 1.68−1.74 (m, 2H), 1.96−2.13 (m, 4H), 2.45 (s, 1H), 2.69 (t, 2H, J = 7.6 Hz), 3.59 (t, 2H, J = 6.8 Hz), 5.33−5.40 (m, 2H), 7.25−7.77 (m, 9H); ^{13}C NMR δ 25.6, 26.5, 27.1, 29.0, 29.2, 29.3, 29.5, 30.9, 32.5, 35.2, 62.5, 128.0, 128.2, 128.7, 129.7, 130.1, 130.5, 132.0, 134.9, 137.6, 147.7, 196.4; HR-MS [MNa^+] m/z calcd for $C_{26}H_{34}O_2Na$ 401.2451, found 401.2454.

(*Z*)-13-(4-Benzoylphenyl)-9-tridecenoic Acid (15). A solution of **14** (730 mg, 1.93 mmol) and PDC (7.3 g, 19.3 mmol) in DMF (20 mL) was stirred at room temperature for 2 days. Water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (100 mL) and dried (Na_2SO_4). The solvent was removed under vacuum, and the residue was purified by chromatography (hexane/EtOAc 2:1) to give **15** (657 mg, 87%) as a viscous oil: ^{1}H NMR δ 1.24−1.40 (m, 8H), 1.58−1.75 (m, 4H), 1.96−2.12 (m, 4H), 2.33 (t, 2H, J = 7.2 Hz), 2.70 (t, 2H, J = 7.6 Hz), 5.33−5.44 (m, 2H), 7.26−7.79 (m, 9H); ^{13}C NMR δ 24.6, 26.7, 27.2, 28.9, 29.0, 29.1, 29.5, 31.0, 34.0, 35.4, 128.1, 128.3, 128.9, 129.9, 130.3, 130.6, 132.1, 135.0, 137.8, 147.8, 179.9, 196.5; HR-MS [MNa^+] m/z calcd for $C_{26}H_{32}O_3Na$ 415.2244, found 415.2255.

1-*O*-(13-(4-Benzoylphenyl)-9-(*Z*)-tridecenoyl)-3-*O*-FMOC-*sn*-glycerol (18). DCC (6.3 mg, 0.031 mmol) and DMAP (1.0 mg, 8.1 μmol) were added to a solution of **15** (10.0 mg, 0.025 mmol) and (*R*)-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol (4.0 mg, 0.031 mmol) in 1 mL of CH_2Cl_2. After the mixture was stirred at room temperature for 40 h, the solvent was removed under vacuum, and the residue was purified by chromatography (hexane/EtOAc 4:1) to provide (*Z*)-13-benzoylphenyl-9-tridecenoic acid (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl ester (**16**) (11.9 mg, 92%): ^{1}H NMR δ 1.23−1.37 (m, 8H), 1.37 (s, 3H), 1.43 (s, 3H), 1.60−1.75 (m, 4H), 1.96−2.12 (m, 4H), 2.34 (t, 2H, J = 7.6 Hz), 2.70 (t, 2H, J = 7.6 Hz), 3.71−3.75 (m, 1H), 4.05−4.18 (m, 3H), 4.28−4.33 (m, 1H), 5.33−5.42 (m, 2H), 7.26−7.80 (m, 9H); ^{13}C NMR δ 24.8, 25.3, 26.6, 26.7, 27.1, 29.0, 19.0, 29.0, 29.5, 31.0, 34.0, 35.4, 64.4, 66.2, 73.5, 109.7, 128.1, 128.4, 128.9, 129.8, 130.2, 130.5, 132.1, 135.0, 137.8, 147.7, 173.5, 196.3.

One drop of concentrated HCl was added to a solution of **16** (90 mg, 0.18 mmol) in 90% dioxane (3 mL). After the mixture was stirred at room temperature for 4 h, the solvent was removed under vacuum and the residue was purified by chromatography (hexane/EtOAc 1:1) to give 1-((*Z*)-13-(4-benzoylphenyl)-9-tridecenoyl))-*sn*-glycerol (**17**) (60 mg, 73%): ^{1}H NMR δ 1.23−1.38 (m, 8H), 1.55−1.68 (m, 4H), 1.95−2.12 (m, 4H), 2.33 (t, 2H, J = 7.6 Hz), 2.70 (t, 2H, J = 7.6 Hz), 2.75 (br s, 2H), 3.55−3.68 (m, 2H), 3.88−3.94 (m, 1H), 4.15 (t, 2H, J = 4.8 Hz), 5.34−5.43 (m, 2H), 7.25−7.79 (m, 9H); ^{13}C NMR δ 24.8, 26.6, 27.1, 29.0, 29.0, 29.0, 29.5, 31.0, 34.0, 35.4, 63.3, 65.0, 70.1, 128.2, 128.3, 128.9, 129.9, 130.3, 130.6, 132.2, 135.0, 137.8, 147.9, 174.2, 196.7.

A solution of **17** (58 mg, 0.12 mmol) and DMAP (15 mg, 0.12 mmol) in 1 mL of dry CH_2Cl_2 was cooled to −10 °C in a salt−ice bath. A solution of FMOC−chloroformate (32 mg, 0.12 mmol) in 2 mL of dry CH_2Cl_2 was added dropwise. After the reaction mixture was stirred for 30 min, the solution was washed with water (5 mL) and dried (Na_2SO_4). A small amount (12 mg) of starting material **17** was recovered after chromatography, and **18** (19 mg, 28%) was also obtained after chromatography (hexane/EtOAc 1:3): ^{1}H NMR δ 1.22−1.76 (m, 12H), 1.95−2.21 (m, 5H), 2.35 (t, 2H, J = 7.6 Hz), 2.70 (t, 2H, J = 7.6 Hz), 4.10−4.28 (m, 5H), 4.41 (d, 2H, J = 7.2 Hz), 5.33−5.42 (m, 2H), 7.24−7.80 (m, 17H); ^{13}C NMR δ 24.8, 26.7, 27.2, 29.1, 29.1, 29.6, 30.9, 31.1, 34.1, 35.5, 46.7, 64.8, 68.1, 68.5, 70.1, 120.1, 125.1, 127.2, 127.9, 128.2, 129.0, 129.9, 130.3, 130.6, 132.2, 135.1, 137.9, 141.3, 143.2, 147.8, 155.2, 173.8, 196.6, 207.0; HR-MS [MNa$^+$] m/z calcd for $C_{44}H_{48}O_7Na$ 711.3292, found 711.3302.

1-*O*-(13-(4-Benzoylphenyl)-9-(*Z*)-tridecenoyl)-2-*O*-methoxymethyl-3-*O*-FMOC-*sn*-glycerol (19). Chloromethyl methyl ether (7 mg, 87 μmol) was added to a stirred solution of **18** (6 mg, 8.7 μmol) and *i*-Pr_2NEt (11 mg, 87 μmol) in dry CH_2Cl_2 (1 mL) under N_2 at 0 °C. After the mixture was stirred at 0 °C for 2 h and at room temperature for 2 days, water (5 mL) and CH_2Cl_2 (5 mL) were added. The organic layer was washed with brine (5 mL) and water (5 mL) and then dried (Na_2SO_4). Product **19** (4.2 mg, 66% yield) was obtained after removal of the solvent and purification by chromatography (hexane/EtOAc 4:1): ^{1}H NMR δ 1.21−1.39 (m, 12H), 1.57−1.75 (m, 4H), 1.95−2.12 (m, 4H), 2.34 (t, 2H, J = 7.6 Hz), 2.70 (t, 2H, J = 7.6 Hz), 3.40 (s, 3H), 4.03−4.33 (m, 5H), 4.41 (d, 2H, J = 7.1 Hz), 4.73 (s, 2H), 5.33−5.44 (m, 2H), 7.24−7.83 (m, 17H); ^{13}C NMR δ 24.9, 26.8, 27.3, 29.1, 29.6, 31.1, 34.1, 35.5, 46.7, 55.7, 63.0, 67.0, 70.0, 72.4, 96.0, 100.0, 120.1, 125.1, 127.2, 127.9, 128.2, 128.4, 129.0, 130.0, 130.3, 130.7, 132.2, 135.1, 137.9, 141.3, 143.3, 147.8, 155.0, 173.4, 196.5; HR-MS [MNa$^+$] m/z calcd for $C_{46}H_{52}O_8Na$ 755.3560, found 755.3598.

1-*O*-(13-(4-Benzoylphenyl)-9-(*Z*)-tridecenoyl)-2-*O*-methoxymethyl-*sn*-glycerol (20) from 19. Piperidine (0.2 mL) was added to a solution of **19** (1.3 mg, 1.7 μmol) in dry CH_2Cl_2 (2 mL) under nitrogen. The mixture was stirred at room temperature until the starting material was consumed (TLC, hexane/EtOAc 4:1). Concentration and purification by chromatography (hexane/EtOAc 2:1) afforded **20** (0.6 mg, 66%). The R_f value and the ^{1}H NMR spectrum were identical with data obtained for the same compound prepared from **26** (see below).

1-(4-Methoxyphenoxy)-3-(methoxymethoxy)propan-(2*R*)-2-ol (23) and 3-(4-Methoxyphenoxy)-(2*R*)-2-(methoxymethoxy)-propan-1-ol (24). Trimethyl orthoformate (0.66 mL, 6.0 mmol) was added to a stirred suspension of diol **21** (594 mg, 3.0 mmol) and D-10-camphorsulfonic acid (12 mg, 50 μmol) in 36 mL of dry CH_2Cl_2 at room temperature under nitrogen. The reaction mixture was stirred at room temperature until diol **21** was fully consumed (TLC, hexane/EtOAc 1:1). The mixture was cooled to 0 °C, and 12 mL of DIBAL-H (18 mmol, a 1.5 M solution in toluene) was added slowly. Stirring was continued at 0 °C until the ortho ester intermediate disappeared (TLC, hexane/EtOAc 4:1). A solution of potassium sodium tartrate (10.2 g, 36.0 mmol) in water (40 mL) was added cautiously to quench the reaction, and the resulting mixture was stirred at room temperature overnight. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with water (50 mL) and dried (Na_2SO_4 and a small amount of K_2CO_3). The solvent was removed under vacuum, and the residue was purified by chromatography (a gradient of hexane/EtOAc from 10:1 to 1:1) to provide 603 mg (83%) of **23** and 99 mg (14%) of **24**. Data for compound **23**: ^{1}H NMR δ 3.31 (s, 1H), 3.35 (s, 3H), 3.65−3.77 (m, 5H), 3.96 (d, 2H, J = 5.8 Hz), 4.08−4.15 (m, 1H), 4.65 (s, 2H), 6.77−6.86 (m, 4H); ^{13}C NMR δ 55.0, 55.3, 68.9, 69.2, 69.4, 96.6, 114.4, 115.3, 152.5, 153.8; HR-MS [MNa$^+$] m/z calcd for $C_{12}H_{18}O_5Na$ 265.1046, found 265.1049. Data for compound **24**: ^{1}H NMR δ 2.69 (s, 1H), 3.43 (s, 3H), 3.71−3.86 (m, 5H), 3.93−4.04 (m, 3H), 4.79 (s, 2H), 6.78−6.87 (m, 4H); ^{13}C NMR δ 55.6, 62.9, 68.3, 78.0, 96.7, 114.6, 115.4, 152.6, 154.0; HR-MS [MNa$^+$] m/z calcd for $C_{26}H_{34}O_2Na$ 265.1046, found 265.1037.

1-*O*-Methoxymethyl-2-*O*-(13-(4-benzoylphenyl)-9-(*Z*)-tridecenoyl)-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (25). DIAD (10 mg, 49.5 μmol) was added to a solution of acid **15** (16 mg, 41.3 μmol), alcohol **23** (10 mg, 41.3 μmol), and PPh_3 (13 mg, 49.5 μmol) in dry THF (2 mL) at 0 °C. After the mixture was warmed to room temperature and stirred for 24 h, water (5 mL) and CH_2Cl_2 (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed twice with water (5 mL) and dried (Na_2SO_4). After the solvents were removed under vacuum, the residue was purified by chromatography (hexane/EtOAc 4:1) to give **25** (19 mg, 76%): ^{1}H NMR δ 1.24−1.36 (m, 8H), 1.58−1.76 (m, 4H), 1.95−2.12 (m, 4H), 2.35 (t, 2H, J = 7.6 Hz), 2.70 (t, 2H, J = 7.6 Hz), 3.34 (s, 3H), 3.76 (s, 3H), 3.79 (d, 2H), 4.06−4.13 (m, 2H), 4.64 (s, 2H), 5.29−5.35 (m, 1H), 5.36−5.44 (m, 2H), 6.80−6.87 (m, 4H), 7.27−7.82 (m, 9H); ^{13}C NMR δ 24.9, 26.8, 27.3, 29.0, 29.1, 29.2, 29.6, 31.1, 34.3, 35.5, 55.3, 55.7, 65.8, 67.0, 70.8, 96.5, 114.6, 115.6, 128.2, 128.4, 129.0, 130.0, 130.4, 130.7, 132.2, 135.1, 137.9, 147.8, 152.7, 154.1, 173.3, 196.5; HR-MS [MNa$^+$] m/z calcd for $C_{38}H_{48}O_7Na$ 639.3292, found 639.3298.

1-*O*-(13-(4-Benzoylphenyl)-9-(*Z*)-tridecenoyl)-2-*O*-methoxymethyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (26). Compound **26** was prepared in 78% yield according to the procedure used to prepare compound **25**: ^{1}H NMR δ 1.24−1.35 (m, 8H), 1.58−1.78 (m, 4H), 1.95−2.13 (m, 4H), 2.30−2.35 (m, 2H), 2.68−2.73 (m, 2H), 3.41 (s, 3H), 3.76 (s, 3H), 4.02 (d, 2H, J = 5.3 Hz), 4.11−4.17 (m, 1H), 4.22−4.28 (m, 1H), 4.33−4.38 (m, 1H), 4.77 (s, 2H), 5.36−5.42 (m, 2H), 6.80−6.86 (m, 4H), 7.26−7.82 (m, 9H); ^{13}C NMR δ 24.9, 26.8, 27.2, 29.1, 29.1, 29.2, 29.6, 31.1, 34.1, 35.5, 55.6, 55.7, 63.6, 68.2, 73.3, 96.1, 114.6, 115.5, 128.2, 128.3, 129.0, 129.9, 130.3, 130.6, 132.1, 135.1, 137.9, 147.8, 152.7, 154.1, 173.5, 196.5; HR-MS [MNa$^+$] m/z calcd for $C_{38}H_{48}O_7Na$ 639.3292, found 639.3297.

1-*O*-Methoxymethyl-2-*O*-(13-(4-benzoylphenyl)-9-(*Z*)-tridecenoyl)-*sn*-glycerol (27). CAN (181 mg, 0.33 mmol) was added to a solution of **25** (85 mg, 0.14 mmol) in 7 mL of CH_3CN/water (6:1) at room temperature. The mixture was stirred until compound **25** was consumed (∼1 h, TLC, hexane/EtOAc 1:1) and was then diluted with water (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 6 mL), and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (hexane/EtOAc 2:1) to furnish **27** (49 mg, 69%): ^{1}H NMR δ 1.23−1.38 (m, 8H), 1.57−1.77 (m, 4H), 1.96−2.13 (m, 4H), 2.35 (t, 2H, J = 7.6 Hz), 2.70 (t, 2H, J = 7.6 Hz), 3.36 (s, 3H), 3.70−3.83 (m, 4H), 4.63 (s, 2H), 5.01−5.07 (m, 1H), 5.34−5.45 (m, 2H), 7.27−7.81 (m, 9H); ^{13}C NMR δ 24.9, 26.7, 27.2, 29.1, 29.1, 29.2, 29.6, 31.1, 34.3, 35.5, 55.4, 62.3, 66.3, 73.1, 96.6, 128.2, 128.4, 129.0, 130.0, 130.4, 130.6, 132.2, 135.1, 137.9, 147.9, 173.6, 196.6; HR-MS [MNa$^+$] *m*/*z* calcd for $C_{31}H_{42}O_6Na$ 533.2874, found 533.2865.

1-*O*-(13-(4-Benzoylphenyl)-9-(*Z*)-tridecenoyl)-2-*O*-methoxymethyl-*sn*-glycerol (20) from Compound 26. Compound **20** was prepared in 73% yield by the same procedure used to prepare compound **27**: ^{1}H NMR δ 1.24−1.38 (m, 8H), 1.56−1.76 (m, 4H), 1.95−2.17 (m, 4H), 2.33 (t, 2H, J = 7.6 Hz), 2.71 (t, 2H, J = 7.6 Hz), 3.42 (s, 3H), 3.58−3.71 (m, 2H), 3.80−3.85 (m, 1H), 4.14−4.24 (m, 2H), 4.74 (s, 2H), 5.35−5.44 (m, 2H), 7.24−7.82 (m, 9H); ^{13}C NMR δ 24.9, 26.7, 27.2, 29.1, 29.1, 29.6, 31.1, 34.1, 35.5, 55.7, 62.6, 63.2, 77.7, 96.6, 128.2, 128.3, 129.0, 129.9, 130.3, 130.6, 132.2, 135.1, 137.9, 147.8, 173.7, 196.5; HR-MS [MNa$^+$] *m*/*z* calcd for $C_{31}H_{42}O_6Na$ 533.2874, found 533.2863.

4-((*Z*)-Bromotridec-4-enyl)benzophenone (28). To 3 mL of CH_2Cl_2 under N_2 were added alcohol **14** (108 mg, 0.29 mmol) and Et_3N (43 mg, 0.43 mmol) at 0 °C. After the mixture was stirred for 5 min, methanesulfonyl chloride (49 mg, 0.43 mmol) was added, and the resulting reaction mixture was stirred at room temperature overnight, quenched with 5 mL of water, and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude mesylate was dissolved in dry THF (5 mL), and lithium bromide (50 mg, 0.57 mmol) was added. The reaction mixture was heated at reflux overnight and then cooled to room temperature and poured into water (5 mL) and CH_2Cl_2 (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with water (10 mL), dried (Na_2SO_4), and concentrated. The resulting yellow oil was purified by chromatography (hexane/EtOAc 10:1) to provide **28** (113 mg, 90%) as a colorless oil: ^{1}H NMR δ 1.22−1.45 (m, 10H), 1.68−1.86 (m, 4H), 1.96−2.12 (m, 4H), 2.70 (t, 2H, J = 7.8 Hz), 3.37 (t, 2H, J = 6.8 Hz), 5.35−5.44 (m, 2H), 7.25−7.82 (m, 9H); ^{13}C NMR δ 26.6, 27.1, 28.0, 28.6, 29.1, 29.2, 29.5, 31.0, 32.7, 33.9, 35.4, 128.1, 128.2, 128.9, 129.8, 130.2, 130.5, 132.0, 135.0, 137.8, 147.7, 196.2; HR-MS [MNa$^+$] *m*/*z* calcd for $C_{26}H_{33}BrONa$ 463.1607, found 463.1600.

1-*O*-(13-(4-Benzoylphenyl)-9-(*Z*)-tridecenyl)-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (30) and 2-*O*-(13-(4-Benzoylphenyl)-9-(*Z*)-tridecenyl)-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (31). Di-*n*-butyltin oxide (64 mg, 0.26 mmol) was added to a solution of diol **21** (51 mg, 0.26 mmol) in 3 mL of $CHCl_3$/MeOH (10:1). After the resulting suspension was heated at reflux for 3 h to give a clear solution, the solvents were evaporated to give cyclic stannoxane intermediate **29** as a white solid. Cesium fluoride (78 mg, 0.51 mmol) and 18-crown-6 (8 mg, 26 μmol) were added, and the solid mixture was dried overnight under high vacuum. After DMF (3 mL) and bromide **28** (71 mg, 0.16 mmol) were added, the reaction mixture was stirred at room temperature for 1 day. Water (0.5 mL) and EtOAc (10 mL) were added, and the mixture was stirred for an additional 1 h and was subsequently filtered through a pad of silica gel to remove an insoluble byproduct. The filtrate was washed with water (5 mL), dried (Na_2SO_4), and concentrated. The residue was purified by chromatography (hexane/EtOAc 2:1) to provide **30** (72 mg, 80%) and **31** (8.7 mg, 10%). Data for compound **30**: ^{1}H NMR δ 1.21−1.38 (m, 8H), 1.52−1.76 (m, 4H), 1.94−2.12 (m, 4H), 2.54 (br s, 1H), 2.70 (t, 2H, J = 7.6 Hz), 3.43−3.64 (m, 4H), 3.75 (s, 3H), 3.93−4.01 (m, 2H), 4.09−4.16 (m, 1H), 5.33−5.45 (m, 2H), 6.79−6.88 (m, 4H), 7.25−7.82 (m, 9H); ^{13}C NMR δ 26.0, 26.7, 27.2, 29.2, 29.4, 29.4, 29.5, 29.6, 31.0, 35.4, 55.6, 69.1, 69.7, 71.5, 71.7, 114.6, 115.5, 128.1, 128.3, 128.9, 129.9, 130.3, 130.7, 132.1, 135.1, 137.9, 147.8, 152.7, 154.0, 196.4; HR-MS [MNa$^+$] *m*/*z* calcd for $C_{36}H_{46}O_5Na$ 581.3237, found 581.3249. Data for compound **31**: ^{1}H NMR δ 1.22−1.38 (m, 8H), 1.52−1.77 (m, 4H), 1.95−2.14 (m, 4H), 2.68 (t, 2H, J = 7.8 Hz), 3.52−3.86 (m, 5H), 3.76 (s, 3H), 3.94−4.04 (m, 2H), 5.34−5.45 (m, 2H), 6.79−6.91 (m, 4H), 7.25−7.81 (m, 9H); ^{13}C NMR δ 26.1, 26.8, 27.3, 29.3, 29.5, 29.5, 29.7, 30.1, 31.1, 35.5, 55.7, 62.5, 68.1, 70.7, 78.2, 114.7, 115.5, 128.2, 128.4, 129.0, 130.0, 130.4, 130.8, 132.2, 135.1, 138.0, 147.9, 152.8, 154.0, 196.6; HR-MS [MNa$^+$] *m*/*z* calcd for $C_{36}H_{46}O_5Na$ 581.3237, found 581.3252.

1-*O*-(13-(4-Benzoylphenyl)-9-(*Z*)-tridecenyl)-2-*O*-methoxymethyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (32). Chloromethyl methyl ether (40 mg, 497 μmol) was added under N_2 to a stirred solution of **30** (56 mg, 99 μmol) and *i*-Pr_2NEt (64 mg, 497 μmol) in dry CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 days. The solvent was removed, and the residue was purified by chromatography (hexane/EtOAc 4:1) to afford unreacted **30** (10 mg) and **32** (45 mg, 91%): ^{1}H NMR δ 1.22−1.38 (m, 8H), 1.52−1.76 (m, 4H), 1.96−2.15 (m, 4H), 2.70 (t, 2H, J = 7.8 Hz), 3.41 (s, 3H), 3.41−3.50 (m, 2H), 3.56−3.65 (m, 2H), 3.75 (s, 3H), 3.99−4.11 (m, 3H), 4.79 (s, 3H), 5.34−5.45 (m, 2H), 6.79−6.87 (m, 4H), 7.28 (d, 2H, J = 8.3 Hz), 7.47 (t, 2H, J = 7.8 Hz), 7.57 (t, 1H, J = 7.3 Hz), 7.72−7.81 (m, 4H); ^{13}C NMR δ 26.0, 26.7, 27.2, 29.2, 29.4, 29.4, 29.6, 29.6, 31.1, 35.4, 55.4, 55.6, 68.7, 70.4, 71.7, 84.5, 96.2, 114.5, 115.4, 128.1, 128.3, 128.9, 129.9, 130.3, 130.7, 132.1, 135.1, 137.9, 147.8, 152.9, 153.8, 196.4; HR-MS [MNa$^+$] *m*/*z* calcd for $C_{38}H_{50}O_6Na$ 625.3500, found 625.3519.

1-*O*-Methoxymethyl-2-*O*-(13-(4-benzoylphenyl)-9-(*Z*)-tridecenyl)-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (33). Compound **33** was prepared in 89% yield from **31** by the same procedure used to prepare **32**: ^{1}H NMR δ 1.22−1.39 (m, 8H), 1.55−1.62 (m, 2H), 1.68−1.76 (m, 2H), 1.97−2.04 (m, 2H), 2.07−2.13 (m, 2H), 2.70 (t, 2H, J = 7.8 Hz), 3.34 (s, 3H), 3.58−3.80 (m, 5H), 3.76 (s, 3H), 3.97−4.08 (m, 2H), 4.65 (s, 2H), 5.34−5.44 (m, 2H), 6.80−6.88 (m, 2H), 7.26−7.81 (m, 9H); ^{13}C NMR δ 26.0, 26.7, 27.3, 29.3, 29.4, 29.5, 29.7, 30.0, 31.1, 35.5, 55.2, 55.7, 66.9, 68.2, 70.7, 77.1, 96.7, 114.6, 115.5, 128.2, 128.3, 128.9, 129.9, 130.3, 130.8, 132.1, 135.1, 137.9, 147.8, 153.0, 153.9, 196.5; HR-MS [MNa$^+$] *m*/*z* calcd for $C_{38}H_{50}O_6Na$ 625.3500, found 625.3497.

1-*O*-(13-(4-Benzoylphenyl)-9-(*Z*)-tridecenyl)-2-*O*-methoxymethyl-*sn*-glycerol (34). Compound **34** was prepared in 86% yield using the procedure described to prepare compound **27**: ^{1}H NMR δ 1.24−1.39 (m, 8H), 1.52−1.60 (m, 2H), 1.68−1.77 (m, 2H), 1.97−2.04 (m, 2H), 2.06−2.13 (m, 2H), 2.70 (t, 2H, J = 7.6 Hz), 3.42 (s, 3H), 3.40−3.80 (m, 7H), 4.75 (s, 2H), 5.34−5.45 (m, 2H), 7.27−7.82 (m, 9H); ^{13}C NMR δ 26.0, 26.7, 27.3, 29.2, 29.4, 29.4, 29.6, 29.7, 31.1, 35.5, 55.6, 63.7, 71.1, 71.8, 78.5, 96.6, 128.2, 128.3, 128.9, 129.9, 130.3, 130.7, 132.1, 135.1, 137.9, 147.8, 196.5; HR-MS [MNa$^+$] *m*/*z* calcd for $C_{31}H_{44}O_5Na$ 519.3081, found 519.3079.

1-*O*-Methoxymethyl-2-*O*-(13-(4-benzoylphenyl)-9-(*Z*)-tridecenyl)-*sn*-glycerol (35). The same method used to prepare **34** was used to prepare **35** in 88% yield: ^{1}H NMR δ 1.22−1.40 (m, 8H), 1.52−1.77 (m, 4H), 1.95−2.13 (m, 4H), 2.70 (t, 2H, J = 7.6 Hz), 3.37 (s, 3H), 3.46−3.77 (m, 7H), 4.63 (s, 2H), 5.34−5.45 (m, 2H), 7.27−7.82 (m, 9H); ^{13}C NMR δ 26.1, 26.7, 27.3, 29.2, 29.4, 29.5, 29.7, 30.0, 31.1, 35.5, 55.3, 62.6, 67.0, 70.3, 78.5, 96.7, 128.2, 128.3, 128.9, 129.9, 130.3, 130.7, 132.2, 135.1, 137.9, 147.8, 196.5; HR-MS [MNa$^+$] *m*/*z* calcd for $C_{31}H_{44}O_5Na$ 519.3081, found 519.3095.

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Supporting Information Available: Procedures for enzymatic incorporation of [^{32}P]-phosphate into the benzophenone-containing analogues, for covalent modification of plasma proteins, and for the preparation of compounds **9** and **10** and ^{1}H and ^{13}C NMR spectra for all new compounds and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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