Total Synthesis of Oxidized Phospholipids. 3. The (11*E*)-9-Hydroxy-13-oxotridec-11-enoate Ester of 2-Lysophosphatidylcholine

Yijun Deng and Robert G. Salomon*

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-7078

rgs@po.cwru.edu.

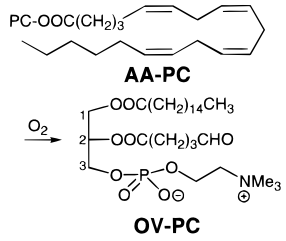
Received May 26, 2000

A total synthesis of (11*E*)-9-hydroxy-13-oxotridec-11-enoate ester of 2-lysophosphatidylcholine (HOT-PC) was devised to facilitate identification of this oxidized phospholipid. A lactone, 8-(3-oxo-1*H*,6*H*-2-oxinyl)octanoic acid (**1**), believed to be generated through an intermediate (11*E*)-9-hydroxy-13-oxotridec-11-enoic acid (HOT), is produced upon autoxidation of linoleic acid. A synthesis of lactone **1** methyl ester was accomplished from HOT involving a novel trans−cis isomerization that is driven to completion by cyclization to a hemiacetal. An alternative route to this carbon skeleton was also acheived that provides the lactone **1** itself.

Introduction

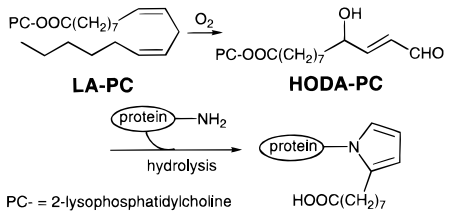
The study of lipid peroxidation is a rapidly growing field in medicine and biology, spurred by increasing evidence that lipid oxidation is involved in the pathogenesis of many chronic diseases, e.g., atherosclerosis, Alzheimer's disease, Parkinson disease, stroke, and aging.[1] In vivo, most fatty acids are present as esters of cholesterol or glycerol. Phospholipids, esters of glycerol-3-phosphate, are major components of biological membranes and lipoproteins, circulating micellelike particles solubilized with an outer shell of phospholipids. A vast array of aldehydes are produced by oxidative cleavage of polyunsaturated fatty acids and their phospholipid derivatives.[2] Many alkanals and alkenals, some containing hydroxyl or epoxy groups, have been isolated and fully characterized. Some covalently modify proteins, and this may be important for their biological activities, e.g., malondialdehyde, 2(*E*)-4-hydroxy-2-nonenal and 2(*E*)-4-hydroxy-2-hexenal. Less is known about aldehyde products of lipid peroxidation that remain esterified in phospholipids. To foster progress in this area, we are devising unambiguous chemical syntheses of oxidized phospholipids.[3] Recent studies showed that oxidative cleavage of the arachidonic acid (AA) ester AA-PC of 2-lyso-phosphatidylcholine (PC) generates a phospholipid ester of 5-oxovaleric (OV) acid.[4] OV-PC activates endothelial cells to bind monocytes. This may facilitate entry of monocytes into the vessel wall, an important event in atherogenesis. Our chemical synthesis of OV-PC facilitated its structural and biological characterization.

Some of the aldehydes generated by oxidative cleavage of phospholipids avidly bind covalently with proteins, leading to protein modifications that may interfere with biological functions. We previously identified lipid-



derived carboxyalkylpyrrole protein modifications in human blood proteins and oxidized low-density lipoproteins.[5] Carboxyalkylpyrroles are formed by the reaction of γ-hydroxy-α,β-unsaturated aldehydic esters of 2-lyso-PC with the primary amino groups of protein lysyl residues. For example, oxidative cleavage of linoleic acid-PC ester (LA-PC) generates protein-based carboxyheptylpyrroles by reaction of a 9-hydroxy-12-oxo-10-dodecenoic acid ester of lyso-PC (HODA-PC) with protein in conjunction with ester hydrolysis (Scheme 1).

Scheme 1



Very recently, the lactone **1** from (2*Z*)-5-hydroxy-2-tridecenedioate was identified as a product from the oxidative cleavage of LA. This lactone was postulated to arrise from 9-hydroxy-13-oxo-11-tridecenoic (HOT) acid, a δ-hydroxy-α,β-unsaturated aldehydic acid (Scheme 2).[1] To facilitate investigation of the formation of lactone **1** from LA and of various phospholipid derivatives from oxidative fragmentation of LA-PC in vivo, we devised total syntheses of lactone **1** and its putative precursor phospholipid, HOT-PC (**2**).

* To whom correspondence should be addressed. Telephone: 216-368-2592. FAX: 216-368-3006.

(1) Spiteller, G. *Chem. Phys. Lipids* **1998**, *95*, 105−62.

(2) Esterbauer, H.; Schaur, R. J.; Zollner, H. *Free Radic. Biol. Med.* **1991**, *11*, 81−128.

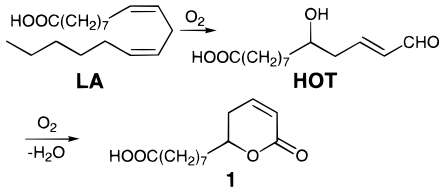
(3) , For previous papers in this series, see refs 4 and 6.

(4) Watson, A. D.; Leitinger, N.; Navab, M.; Faull, K. F.; Horkko, S.; Witztum, J. L.; Palinski, W.; Schwenke, D.; Salomon, R. G.; Sha, W.; Subbanagounder, G.; Fogelman, A. M.; Berliner, J. A. *J. Biol. Chem.* **1997**, *272*, 13597−607.

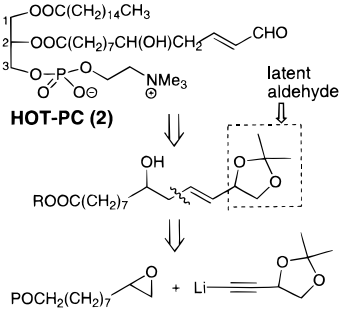
(5) Kaur, K.; Salomon, R. G.; O'Neil, J.; Hoff, H. F. *Chem. Res. Toxicol.* **1997**, *10*, 1387−96.

10.1021/jo000809u CCC: $19.00
Published on Web 08/31/2000

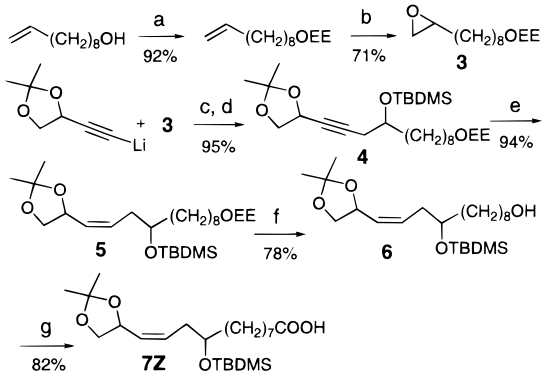
Scheme 2



Scheme 3



Scheme 4[a]



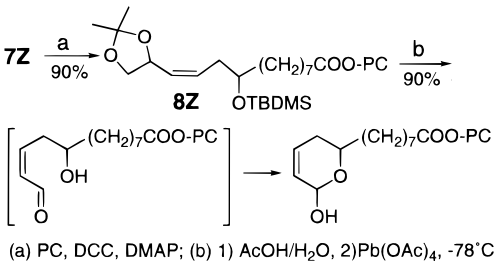
[a] (a) Ethyl vinyl ether, PPTS; (b) mCPBA; (c) BF_3-Et_2O, −78 °C; (d) TBDMSTf, 2,6-lutidine, −78 °C; (e) H_2/Pd, quinoline; (f) PPTS, MeOH; (g) PDC, DMF.

Results and Discussion

The Synthetic Design. The *δ*-hydroxy-α,*β*-unsaturated aldehyde array in HOT-PC (**2**) is a vinylogous aldol that was expected to be chemically sensitive. Therefore, a primary consideration of our synthetic design was to assemble a stable precursor from which HOT-PC could be generated conveniently and efficiently. As in our previous synthesis of HODA-PC,[6] a 3,3-dimethyl-2,4-dioxolanyl moiety was exploited as a latent aldehyde (Scheme 3). Addition of an alkylnyl nucleophile to an epoxide was chosen to provide the key carbon−carbon bond forming step in a convergent assembly of the requisite carbon skeleton.

A Cis Isomeric Carboxaldehydic Acid Precursor 7Z. Because *cis*-crotonaldehydes are converted rapidly with a trace of acid to corresponding trans isomers,[7] we expected that **7Z** (Scheme 4) could serve as a precursor for HOT-PC. The carbon skeleton of HOT-PC was assembled by the alkynylation of epoxide **3** with an alkynyl borane reagent that was prepared in situ at −78 °C in THF by the reaction of 4-ethynyl-2,2-dimethyl-1,3-dioxolane with *n*-butyllithium and boron trifluoride etherate.[8] The resulting secondary alcohol was protected as a TBDMS ether **4** with TBDMSOTf and 2,6-lutidine in quantitative yield.[9] A controlled Lindlar hydrogenation of alkyne **4** provided *cis*-alkene **5**. The acid **7Z** was prepared by PDC oxidation of the corresponding primary alcohol **6**.[10]

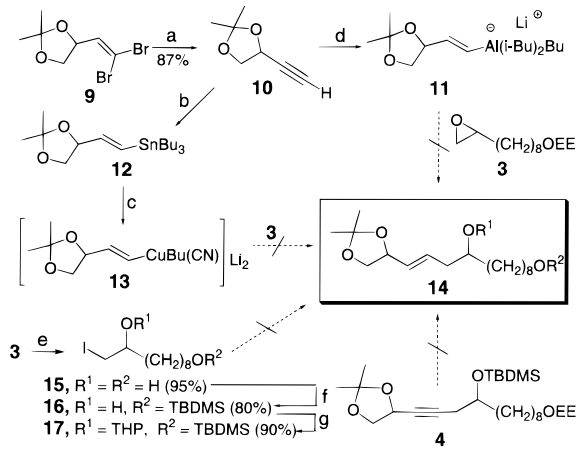
Scheme 5[a]



(a) PC, DCC, DMAP; (b) 1) AcOH/H_2O, 2)$Pb(OAc)_4$, -78°C

[a] (a) PC, DCC, DMAP; (b) (1) AcOH/H_2O, (2) $Pb(OAc)_4$, −78 °C.

Scheme 6[a]



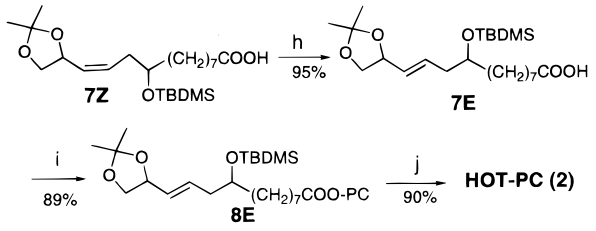
[a] (a) n-BuLi, H_2O; (b) Bu_3SnH, AlBN; (c) CuCN, n-BuLi; (d) $HAl(i\text{-}C_4H_9)_2$; n-BuLi; (e) PPh_3, I_2; (f) TBDMSCl, DMAP, Et_3N; (g) DHP, PPTS.

Attempts to convert phospholipid derivative **8Z** derived from acid **7Z** to HOT-PC through crotonaldehyde isomerization failed to give the desired product. Rather, a cyclic hemiacetal was produced (Scheme 5). Thus, interception of the aldehyde with an internal nucleophile apparently proceeded more rapidly than, and consequently prevented the desired cis−trans isomerization.

A Trans Isomeric Carboxaldehydic Acid Precursor 7E. We reasoned that cyclization to an unreactive hemiacetal could be avoided if the requisite *E*-alkenal was generated from the trans isomer of **8Z**. However, several C−C connective routes, outlined in Scheme 6, failed to deliver the target carbon skeleton with a trans C═C bond. Hydrometalation of alkyne **10** provided trans vinyl aluminum, tin, and copper nucleophiles. However, neither vinylalanate **11** nor vinylcuprate **13** reacted with epoxide **3** or iodide **17** to deliver trans alkenes of general structure **14**. Attempted reductions ($LiAlH_4$/diglyme/heat; Red-Al/THF; Na/liquid NH_3) of the alkyne **4** also failed to deliver the desired trans alkene **14**.

(6) Deng, Y.; Salomon, R. G. *J. Org. Chem.* **1998**, *63*, 7789−7794.
(7) McGreer, D. E.; Page, B. D. *Can. J. Chem.* **1969**, *47*, 866−867.
(8) Yamguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391−394.
(9) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399−402.
(10) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455−3458.

Scheme 7[a]



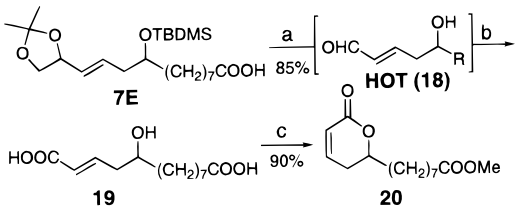
[a] (h) Ph_2S_2 (0.5 equiv), benzene, sunlamp, 6 h; (i) PC, DCC, DMAP; (j) (1) $AcOH/H_2O$, (2) $Pb(OAc)_4$, −78 °C.

Completion of the synthesis should be feasible if a cis−trans isomerization of the C=C bond preceded, rather than followed, generation of the aldehyde group. An excellent route to the trans alkene **7E** was ultimately acheived by photochemical isomerization of **7Z**. Of several methods examined for the isomerization (including thermal isomerization and photoisomerization, e.g., PhSH or Ph_2S_2/AIBN/benzene/reflux; I_2/benzene/sun lamp),[11−13] the most effective was diphenyl disulfide catalyzed photochemical isomerization. Compound **7Z** in benzene was irradiated in the presence of Ph_2S_2 (0.5 equiv) with a sun-lamp for 6 h to afford **7E** (*Z*:*E* = 4:96) in 95% yield (Scheme 7). Isomerization of alkene **5** under the same reaction conditions gave a 1:1 (*Z*:*E*) mixture.

Preparation of the Aldehydic Phospholipid, HOT-PC (2). The 2-lyso-phosphatidylcholine ester **8E**, which is a stable precursor of HOT-PC, was produced in 89% yield by the reaction of acid **7E** with 2-lyso-phosphatidylcholine in the presence of DCC and DMAP (Scheme 7). Exposure of the ester **8E** to aqueous acetic acid, which hydrolytically removed the TBDMS and acetonide protecting groups, and subsequent treatment of the resulting diol with lead tetraacetate in methylene chloride at −78 °C, delivered the target aldehyde HOT-PC in 90% yield.[6] A minor byproduct, presumably generated by cyclization of the minor *cis*-crotonaldehyde isomeric intermediate, was easily removed by reverse phase HPLC.

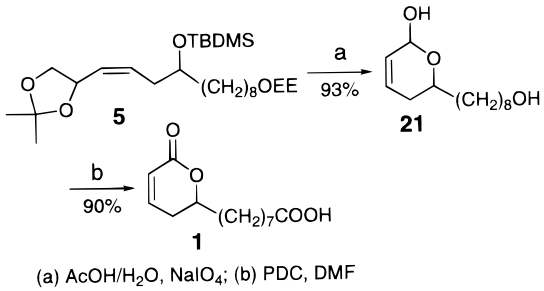
Lactone 1. Our first synthesis of the carbon skeleton of lactone **1** was accomplished from the *E* alkenal HOT (**18**) through a novel trans−cis isomerization of a crotonaldehyde intermediate that is driven to completion by cyclization to a hemiacetal. This pathway is reminiscent of that postulated for generation of lactone **1** during autoxidation of linoleic acid. Exposure of acid **7E** to aqueous acetic acid and treatment of the resulting diol with $NaIO_4$ at room-temperature delivered the δ-hydroxy-α,β-unsaturated aldehydic acid HOT (**18**) (Scheme 8).[6] Selective oxidation of the aldehyde group of **18** with $NaClO_2$ produced the dicarboxylic acid **19** in excellent yield.[14,15] Lewis acid-catalyzed photochemical isomerization[16] of **19** to its cis isomer not only was accompanied by cyclization to a δ-lactone, but also esterification producing **20**. Consequently, photochemical isomerization of **19** did not provide an optimal route to the lactone **1**

Scheme 8[a]



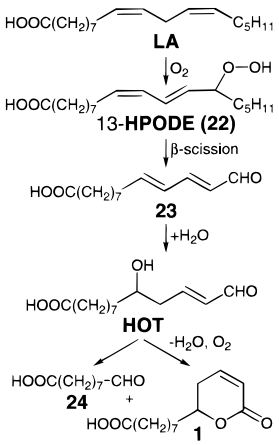
[a] (a) $AcOH/H_2O$, $NaIO_4$; (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; (c) t-$BuOH/H_2O$, Et_2AlCl, MeOH, UV 254 nm.

Scheme 9[a]



[a] (a) $AcOH/H_2O$, $NaIO_4$; (b) PDC, DMF.

Scheme 10



because an appropriate nonalcoholic solvent could not be found to accomplish isomerization without esterification.

An alternative approach, that generates a cis crotonaldehyde intermediate directly, was exploited to produce lactone **1** (Scheme 9). Treatment of cis alkene **5** with aqueous acetic acid and then oxidative cleavage of the corresponding diol with $NaIO_4$ afforded the cyclic acetal **21**. The acetal **21** was then oxidized by PDC to deliver lactone **1**.

Conclusion

Oxidation of LA produces a complex array of aldehydes by fragmentation of hydroperoxyoctadecadienoates, e.g., 13-HPODE (**22**). A cascade of reactions was recently proposed[1] (Scheme 10) to accommodate the early formation of 13-oxotrideca-9,11-dienoic acid (**23**) and ultimate generation of 9-oxononanoic acid (**24**) through Michael addition of water to **23**. The resulting HOT then gives **24** through retro aldol fragmentation and lactone **1**

(11) Moussebois, C.; Dale, J. *J. Chem. Soc. (C)* **1966**, 260−264.
(12) Sonnet, P. E. *Tetrahedron* **1980**, *36*, 557−604.
(13) Henrick, C. A.; Willy, W. E.; Baum, J. W.; Baer, T. A.; Garcia, B. A.; Mastre, T. A.; Chang, S. M. *J. Org. Chem.* **1975**, *40*, 1−7.
(14) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569.
(15) Kokayashi, Y.; Nakno, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505−7515.
(16) Lewis, F. D.; Howard, D. K.; Barancyk, S. V.; Oxman, J. D. *J. Am. Chem. Soc.* **1986**, *108*, 3016−3023.

through further oxidation and lactonization. With the completion of syntheses of HOT, HOT-PC, and lactone **1** reported above, as well as dienal **23** and the derived phospholipid (to be reported elsewhere), all of the compounds in the putative cascade as well as the corresponding phospholipids are now readily available. The results of ongoing studies to test the cascade hypothesis, to detect the formation of the various oxidized phospholipids upon oxidation of LA-PC, and determine their natural occurrence as well as to explore the biological activities of the oxidized phospholipids will be reported in due course.

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.[17] High-resolution mass spectra, solvent purification, and chromatography were performed as usual.[17] All reactions conducted in an inert atmosphere were in argon or N_2 unless otherwise specified.

1-(α-Ethoxyethoxy)dec-9-ene. Ethyl vinyl ether (9.2 g, 128 mmol) was added dropwise to an ice-cooled solution of 9-decen-1-ol (10 g, 64 mmol) and PPTS (64 mg, 0.26 mmol) in CH_2Cl_2 (100 mL) under an argon atmosphere.[18] The solution was stirred for 1.5 h at room temperature and then poured into a 1:1 mixture of hexanes and saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase was extracted with hexane. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography on a silica gel column afforded **1-(α-ethoxyethoxy)dec-9-ene** (13.5 g, 92%). TLC (ethyl acetate/hexanes, 1:23) $R_f = 0.25$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65 (m, 1 H), 4.85−5.05 (2 H), 4.65 (m, 1 H), 3.30−3.70 (4 H), 2.02 (m, 2 H), 1.55 (2 H), 1.2−1.4 (10 H), 1.26 (d, $J = 5.2$ Hz, 3 H), 1.17 (t, $J = 6.9$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.22, 114.14, 99.55, 65.30, 60.66, 33.82, 29.93, 29.45, 29.10, 28.94, 26.72, 19.91, 15.35; HRMS (EI) *m/z* calcd for $C_{14}H_{29}O_2$ (MH^+) 229.2170, found 229.2169; calcd for $C_{13}H_{25}O_2$ ($M^+ - CH_3$) 213.1855, found 213.1855.

1-(8-(2-Oxiranyl)octyloxy)-1-ethoxyethane (3). To a solution of 1-(α-ethoxyethoxy)dec-9-ene (3.6 g, 15.8 mmol) in CH_2Cl_2 (30 mL) was added *m*-chloroperbenzoic acid (2.3 g, 17.3 mmol, 85% pure) in small quantities with constant stirring at room temperature. After the addition, the mixture was stirred for 60 h at room temperature. The resulting mixture was filtered, and the solvent was removed under reduced pressure. Flash chromatography on a silica gel column afforded **3** (2.4 g, 70%); TLC (ethyl acetate/hexanes, 1:20) $R_f = 0.26$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.65 (q, $J = 5.4$ Hz, 1 H), 3.32−3.68 (4 H), 2.88 (m, 1 H), 2.72 (dd, $J = 4.9$, 4.9 Hz, 1 H), 2.44(dd, $J = 4.9$, 2.7 Hz, 1 H), 1.28 (d, $J = 5.4$ Hz, 3 H), 1.18 (t, $J = 7.1$ Hz, 3 H). 1.2−1.6 (14 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT) δ 99.56 (CH), 65.29 (CH_2), 60.69 (CH_2), 52.40 (CH), 47.14 (CH_2), 32.51 (CH_2), 29.92 (CH_2), 29.52 (CH_2), 29.40 (CH_2), 26.26 (CH_2), 25.98 (CH_2), 19.92 (CH_3), 15.36 (CH_3); HRMS (EI) *m/z* calcd for $C_{14}H_{27}O_3$ ($M^+ - H$) 243.1957, found 243.1977; calcd for $C_{13}H_{25}O_2$ ($M^+ - CH_3$) 229.1804, found 229.1801.

12-(Ethoxyethoxy)-1-(3,3-dimethyl-2,4-dioxolanyl)dodec-1-yn-4-ol. Under a nitrogen atmosphere, a solution of *n*-butyllithium in hexane (0.52 mL of 1.6 M solution in hexanes, 0.83 mmol) was added to a THF (1 mL) solution of alkyne **10** (105 mg, 0.83 mmol) at −78 °C, and the mixture was stirred for 10 min. Then, boron trifluoride etherate (105 μL, 0.83 mmol) was added to the solution, and the stirring was continued for another 10 min at −78 °C. A solution of epoxide **3** (120 mg, 0.5 mmol) in THF (1 mL) was added and after being stirred for 30 min at −78 °C, the reaction mixture was quenched by adding aqueous $NaHCO_3$. Flash chromatography on a silica gel column provided the desired alcohol in 95% yield. TLC (ethyl acetate/hexanes, 1:4) $R_f = 0.23$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.68 (m, 1 H), 4.64 (t, $J = 5.3$ Hz, 1 H), 4.09 (m, 1 H), 3.83 (dd, $J = 7.7$, 5.5 Hz, 1 H), 3.30−3.75 (5 H), 2.43 (dd, $J = 16.7$, 4.8,1.5 Hz, 1 H), 2.32 (ddt, $J = 16.7$, 6.7, 2.0 Hz, 1 H), 1.4−1.6 (br, 2 H), 1.45 (s, 3 H), 1.34 (s, 3 H), 1.2−1.4 (10H), 1.27 (d, $J = 5.2$ Hz, 3 H), 1.17 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, APT) δ 110.11 (C), 99.56 (CH), 83.10 (C), 79.92 (C), 70.14 (CH_2), 69.96 (CH), 65.78, (CH), 65.54 (CH), 65.29 (CH_2), 60.67 (CH_2), 36.34 (CH_2), 29.91 (CH_2), 29.49 (CH_2), 27.80 (CH_2), 26.32 (CH_3), 26.25 (CH_2), 26.00 (CH_3), 25.59 (CH_2), 19.91 (CH_3), 15.35 (CH_3); HRMS (EI) *m/z* calcd for $C_{21}H_{39}O_5$ ($M^+ - CH_3$) 355.2484, found 355.2489; calcd for $C_{20}H_{37}O_5$ ($M^+ - C_2H_5$) 341.2328, found 341.2320.

12-(Ethoxyethoxy)-1-(3,3-dimethyl-2,4-dioxolanyl)-9-(1,1,2,2-tetramethyl-1-silapropoxy)dodec-11-yne (4). To a solution of the secondary alcohol (120 mg, 0.32 mmol) and 2,6-lutidine (93 μL, 0.8 mmol, freshly distilled from CaH_2) in CH_2Cl_2 (0.5 mL, 1 M of alcohol) was added TBDMSOTf (150 μL, 0.64 mmol) at −78 °C. After being stirred for 40 min at −78 °C, the reaction mixture was quenched by addition of saturated $NaHCO_3$ and diluted with ethyl ether, followed by extraction and concentration. Flash chromatography on a silica gel column (6% ethyl acetate in hexanes) gave **4** in a quantitative yield. TLC (8% ethyl acetate in hexanes) $R_f = 0.29$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.68 (m, 1 H), 4.66(q, $J = 5.4$ Hz, 1 H), 4.10 (dd, $J = 7.9$, 6.2 Hz, 1 H), 3.3−3.9 (5 H), 2.32 (dd, $J = 6.2$, 1.7, Hz 1 H), 1.4−1.6 (2 H), 1.45 (s, 3 H), 1.35 (s, 3 H), 1.2−1.4 (10 H), 1.28 (d, $J = 5.4$ Hz, 3 H), 1.18 (t, $J = 7.0$ Hz, 3 H), 0.85 (s, 9 H), 0.03 (s, 6 H); HRMS (EI) *m/z* calcd for $C_{26}H_{49}O_5Si$ ($M^+ - CH_3$) 469.3359, found 469.3349.

***cis*-1-(Ethoxyethoxy)-12-(3,3-dimethyl-2,4-dioxolanyl)-9-(1,1,2,2-tetramethyl-1-silapropoxy)dodec-11-ene (5).** To a suspension of Lindlar catalyst ($Pd/CaCO_3$, 50 mg) and synthetic quinoline (5 drops), after being evacuated and flushed with hydrogen alternatively several times, was added **4** (630 mg, 1.3 mmol) in methanol (25 mL) via syringe. The reaction was monitored by the uptake of hydrogen and was stopped when the desired amount of hydrogen was consumed (29.1 mL, 1 equiv) in about 1 h. The reaction mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was dissolved in diethyl ether and washed with saturated aqueous NH_4Cl, water, and brine. The ether phase was dried ($MgSO_4$), concentrated, and purified by flash chromatography on a silica gel column (8% ethyl acetate in hexanes) to afford **5** (672 mg, 94%). TLC (10% ethyl acetate in hexanes) $R_f = 0.28$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.62 (m, 1 H), 5.44 (dd, $J = 10.5$, 8.7 Hz, 1 H), 4.78 (dd, $J = 14.0$, 8.0 Hz, 1 H), 4.64 (q, $J = 5.4$ Hz, 1 H), 4.01 (dd, $J = 8.0$, 6.0 Hz, 1 H), 3.2−3.7 (6 H), 2.22 (t, $J = 7.6$ Hz, 2 H), 1.4−1.6 (2 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.27 (d, $J = 5.4$ Hz, 3 H), 1.2−1.4 (12 H), 1.17 (t, $J = 7.0$ Hz, 3 H), 0.84 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT), δ 131.60, 131.22 (CH), 128.64, 128.54 (CH), 109.07 (C), 99.55 (CH), 72.20, 72.14 (CH), 71.94, 71.88 (CH), 69.46 (CH_2), 65.30 (CH_2), 60.66 (CH_2), 37.05 (CH_2), 36.79 (CH_2), 35.63 (CH_2), 29.93 (CH_2), 29.73 (CH_2), 29.61 (CH_2), 29.47 (CH_2), 26.81 (CH_3), 26.27 (CH_2), 25.92 (CH_3), 25.39,25.27 (CH_2), 19.91 (CH_3), 18.13 (C), 15.36 (CH_3), −4.52 (CH_3); HRMS (EI) *m/z* calcd for $C_{26}H_{54}O_5Si$ ($M^+ - H$) 485.3660, found 485.3636; calcd for $C_{25}H_{51}O_5Si$ ($M^+ - CH_3$) 471.3495, found 471.3490.

***cis*-12-(3,3-Dimethyl-2,4-dioxolanyl)-9-(1,1,2,2-tetramethyl-1-silapropoxy)dodec-11-en-1-ol (6).** A mixture of ethoxyethyl ether **5** (540 mg, 1.11 mmol) and PPTS (28 mg, 0.11 mmol) in methanol (8 mL) was stirred for 4 h at room temperature under argon. Then, the volatiles were removed under reduced pressure. Saturated aqueous $NaHCO_3$ was added to the residue. The resulting mixture was extracted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), and filtered. Solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on a silica gel column (20% ethyl acetate in hexanes) to provide **6** (322 mg, 78%). TLC (25% ethyl acetate in hexanes) $R_f = 0.31$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.64 (m, 1 H), 5.44 (m, 1 H), 4.77 (dd, $J = 14.7$, 7.8 Hz, 1 H), 4.01 (dd, $J = 8.0$, 6.1, 1 H), 3.62 (m, 1 H), 3.58 (t, $J = 6.6$ Hz, 3 H), 3.47 (dd, $J = 8.0$, 8.0 Hz, 1 H), 2.22 (m, 2 H), 1.51 (m, 2 H), 1.38 (s, 3 H), 1.35 (s, 3 H), 1.1−1.4 (1 0H), 0.84 (s, 9 H), 0.01 (s, 6 H);

(17) Miller, D. B.; Raychaudhuri, S. R.; Avasthi, K.; Lal, K.; Levison, B.; Salomon, R. G. *J. Org. Chem.* **1990**, *55*, 3164−3175.

(18) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1993**, *72*, 6−13.

^{13}C NMR ($CDCl_3$, 75 MHz, APT) δ 99.56 (CH), 65.29 (CH_2), 60.69 (CH_2), 52.40 (CH), 47.14 (CH_2), 32.51 (CH_2), 29.92 (CH_2), 29.52 (CH_2), 29.40 (CH_2), 26.26 (CH_2), 25.98 (CH_2), 19.92 (CH_3), 15.36 (CH_3); HRMS (EI) *m/z* calcd for $C_{23}H_{46}O_4Si$ (M^+) 414.3165, found 414. 3164; calcd for $C_{22}H_{43}O_4Si$ ($M^+ - CH_3$) 399.2930 found 399.2894, calcd for $C_{23}H_{44}O_3Si$ ($M^+ - H_2O$) 396.3059 found 396.3220.

***cis*-12-(3,3-Dimethyl-2,4-dioxolanyl)-9-(1,1,2,2-tetramethyl-1-silapropoxy)dodec-11-enoic Acid (7Z).** A solution of alcohol **6** (250 mg, 0.6 mmol) and pyridinium dichromate (PDC) (1.35 g, 3.6 mmol) in DMF (5 mL) was stirred at room temperature for 20 h, diluted with saturated aqueous NH_4Cl (50 mL), and extracted with diethyl ether. The combined ether phases were dried over $MgSO_4$ and concentrated by rotary evaporation. Flash chromatography on a silica gel column (28% ethyl acetate in hexanes) afforded **7Z** (210 mg, 82%); TLC (ethyl acetate/hexanes, 2:3): $R_f = 0.40$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.5−5.7 (m, 1 H), 5.44 (dd, J = 11.0, 8.5 Hz, 1 H), 4.78 (dd, J = 14.2, 8.0 Hz, 1 H), 4.01 (dd, J = 8.0, 5.8 Hz, 1 H), 3.63 (m, 1 H), 3.58 (tt, J = 6.5, 6.5 Hz, 1 H), 3.47 (ddd, J = 8.0, 8.0, 1.8 Hz, 1 H), 2.22 (t, J = 6.2 Hz, 3 H), 1.4−1.6 (2 H), 1.38 (s, 3 H), 1.35 (s, 3 H), 1.2−1.4 (12 H), 0.84 (s, 9 H), 0.00 (s, 6 H); HRMS (EI) *m/z* calcd for $C_{23}H_{44}O_5Si$ (M^+) 428.2958, found 428.2948; calcd for $C_{22}H_{43}O_5Si$ ($M^+ - H$) 427.2878 found 427.2870.

***trans*-12-(3,3-Dimethyl-2,4-dioxolanyl)-9-(1,1,2,2-tetramethyl-1-silapropoxy)dodec-11-enoic Acid (7E).** Cis-olefin **7Z** (40 mg. 0.093 mmol) and Ph_2S_2 (10 mg, 0.046 mmol) were dissolved in benzene-d_6 (0.8 mL) in a NMR tube. The resulting solution was exposed to a GE, sun-lamp (275 W) at 1−1.5 feet for 5−6 h. The isomerization was monitored conveniently by NMR. After equilibration (E:Z = 96:4, characterized by NMR), the solvent was removed, and the crude product was purified by flash chromatography on a silica gel column (20% ethyl acetate in hexanes) to afford trans-isomer **7E** in 95% yield (38 mg, E:Z = 96:4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65−5.85 (m, 1 H), 5.42 (dd, J = 15.4, 8.0 Hz, 1 H), 4.45 (dd, J = 14.1, 7.6 Hz, 1 H), 4.03 (dd, J = 7.6, 7.0 Hz, 1 H), 3.63 (m, 1 H), 3.53 (dd, J = 8.0, 8.0 Hz, 1 H), 2.31 (t, J = 7.3 Hz, 3 H), 2.16 (m, 2 H), 1.5−1.7 (2 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.1−1.4 (12 H), 0.85 (s, 9 H), 0.00(s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.83 132.44, 132.07, 129.46, 109.14, 76.43, 71.92, 71.79, 40.32, 40.20, 36.93, 36.71, 34, 29.51, 29.20, 29.00, 26.43, 25.92, 25.27, 25.21, 24.67, 24.61, 18.14, −4.44; HRMS (EI) *m/z* calcd for $C_{23}H_{44}O_5Si$ (M^+) 428.2958, found 428.3048; calcd for $C_{22}H_{43}O_5Si$ ($M^+ - H$) 427.2878 found 427.2862.

Phospholipid (8E). Dicyclohexylcarbodiimide (DCC, 37 mg, 0.18 mmol) and *N*,*N*-dimethylaminopyridine (DMAP, 16 mg, 0.13 mmol) were added to the solution of the acid **7E** (50 mg, 0.12 mmol) and L-α-lysophosphatidylcholine (38 mg, 0.076 mmol) in dry $CHCl_3$ (2 mL, freshly distilled over P_2O_5). The resulting mixture was stirred for 48 h at room temperature. After filtration, the solvent was removed. Flash chromatography of the residue on a silica gel column ($CHCl_3$/MeOH/H_2O, 35:14:1) gave phospholipid **8E** (59.5 mg, 89%); TLC ($CHCl_3$/MeOH/H_2O, 35:14:1) $R_f = 0.23$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.5−5.8 (m, 1 H), 5.41 (dd, J = 15.2, 8.0 Hz, 1 H), 5.16 (m, 1 H), 4.1−4.5 (4 H), 4.2 (m, 2 H), 3.88 (m, 2 H), 3.6−3.8 (2 H), 3.4−3.6 (m, 2 H), 3.29 (s, 9 H), 2.1−2.3 (6 H), 1.4−1.6 (2 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.3−1.3 (38 H), 0.85(bs, 12 H), 0.00-(s, 6 H). HRMS (FAB, CsI/NaI/glycerol) *m/z* calcd for $C_{47}H_{92}NO_{11}PSiNa$ (MNa^+) 928.6075, found 928.6081; calcd for $C_{47}H_{93}NO_{11}PSiNa$ ($MNa^+ + H$) 906.6255 found 906.6241.

HOT-PC (2). A solution of the compound **8E** (15 mg, 0.017 mmol) in acetic acid/water (2:1, v/v, 1 mL) was stirred magnetically for 4 h at 40 °C, then the solvent was removed via rotary evaporator under reduced pressure. The trace of acetic acid was removed by azeotropic distillation with *n*-heptane (3 × 1 mL) under high vacuum. Dry methylene chloride (1 mL) was added to the residue. The resulting solution was added to $Pb(OAc)_4$ (8.4 mg, 0.019 mmol) in dry CH_2Cl_2 (1 mL) in a dropwise manner at −78 °C under an argon atmosphere. The reaction mixture was stirred for 10 min, the solvent was removed via rotary evaporator, and the residue was purified by flash chromatography on a silica gel column ($CHCl_3$/MeOH/H_2O, 15:9:1) to give **HOT-PC** (10 mg, 82%) as a diastereomeric mixture of epimers at the allylic hydroxyl; TLC ($CHCl_3$/MeOH/H_2O, 15:9:1) R_f = 0.21; ^{1}H NMR (300, $CDCl_3$, 300 MHz) δ 9.49 (d, J = 8.2 Hz, 1 H), 6.96 (dt, J = 15.6, 6.9 Hz, 1 H), 6.15 (dd, J = 15.6, 8.2 Hz, 1 H), 5.18 (b, 1 H), 4.2−4.4 (3 H), 4.12(m, 1 H), 3.84−4.0 (2 H), 3.68−3.82 (3 H), 3.32 (s, 9 H), 2.45 (m, 2 H), 2.28(m, 2 H), 2.25 (t, J = 7.7 Hz, 2 H),1.5−1.6 (4 H), 1.35−1.5 (2 H), 1.1−1.4 (32 H), 0.85 (t, J = 7.0 Hz, 3 H).HRMS (FAB, CsI/NaI/glycerol) *m/z* calcd for $C_{37}H_{70}NO_{11}PCs$ (MCs^+) 852.3791, found 852.3802.

4-(2,2-Dibromovinyl)-2,2-dimethyl-1,3-dioxolane (9). Triphenylphosphine (8.1 g, 30.9 mol) was slowly added to a magnetically stirred solution of CBr_4 (10.3 g, 31 mmol) in dry methylene chloride (100 mL). To the resulting orange solution, zinc dust (2.1 g. 33 mmol) was added slowly at 0 °C (green to light tan), and then the reaction mixture was stirred at room temperature for 48 h. Glyceraldehyde acetonide (2.2 g, 16.9 mmol, freshly prepared from 1,2,5,6-di-*O*-isopropylidene-D-mannitol[18]) in CH_2Cl_2 (10 mL) was added dropwise to the above mixture. After being stirred for 2 h, the reaction mixture was transferred to a Erlenmeyer flask and extracted with pentane. Solvent was removed on a rotary evaporator. Compound **9** (4.5 g, 94%) was obtained by distillation under reduced pressure (55 °C, 30 mmHg). TLC (ethyl acetate/hexanes, 3:97) R_f = 0.23; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.51 (d, J = 7.6 Hz, 1 H), 4.70 (ddd, J = 10.2, 7.6 Hz, 1 H), 4.17 (ddd, J = 10.2, 8.4, 6.5 Hz, 1 H), 3.66 (dd, J = 8.4, 6.5 Hz, 1 H), 1.40 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.13 (CH), 110.01 (C), 92.61-(C), 76.17 (CH), 68.02 (CH_2), 26.60 (CH_3), 25.63(CH_3).

4-Ethynyl-2,2-dimethyl-1,3-dioxolane (10). A solution of **9** (7 g, 24.5 mmol) in 20 mL of dry THF at −78 °C under nitrogen was treated with *n*-butyllithium in hexane (33.6 mL of a 1.6 M solution in hexane, 53.8 mmol). After being stirred for 1 h at −78 °C, the reaction mixture was warmed to 25 °C, stirred for another 1 h, and then quenched with water. Extraction with pentane and distillation (85 °C, 110 mmHg) afforded **10** (2.7 g, 87%). TLC (ethyl acetate/hexanes, 5:95) R_f = 0.27; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.69 (ddd, J = 6.3, 6.3, 2.1 Hz, 1 H), 4.15 (dd, J = 8.1, 6.3 Hz, 1 H), 3.93 (dd, J = 8.1, 6.3 Hz, 1 H), 2.47 (d, J = 1.8 Hz, 1 H), 1.48 (s, 3 H), 1.36 (s, 3 H).

1-(3,3-Dimethyl(2,4-dioxolanyl))-3,3-dibutyl-3-stannahept-1-ene (12). Tri-*n*-butylstannane (770 mg, 2.64 mmol) was added to a stirred mixture of 5-ethynyl-2,2-dimethyl-1,3-dioxolane **10** (230 mg, 1.82 mmol) and azobis(isobutyronitrile) (AIBN, 8 mg).[19] The stirred solution was heated at 130 °C for 2 h and then cooled to room temperature. The residue was purified by flash chromatography on silica gel (2% ethyl acetate in hexanes R_f = 0.16) to afford tin compound **12** (530 mg, 70%).^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.29 (d, J = 12.6 Hz, 1 H), 5.93 (dd, J = 12.6, 4.5 Hz, 1 H), 4.45 (dd, J = 9.3, 4.9 Hz, 1 H), 4.07 (dd, J = 5.3, 4.1 Hz, 1 H), 3.58 (dd, J = 5.3, 5.3 Hz, 1 H), 1.4−1.6 (6 H), 1.42 (s, 3 H), 1.37 (s, 3 H), 1.2−1.4 (6 H), 0.7−1.0 (15 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT) δ 145.23 (CH), 133.23 (CH), 109.30 (C), 80.04 (CH), 69.38 (CH_2), 29.06 (CH_2), 27.27 (CH_2), 26.72 (CH_3), 25.96 (CH_3), 13.70 (CH_3), 9.48 (CH_2); HRMS (EI) *m/z* calcd for $C_{19}H_{38}O_2Sn$ (M^+) 418.1890, found 418.1847; calcd for $C_{19}H_{37}O_2Sn$ ($M^+ - H$) 417.1810 found 417.1803.

10-Iododececane-1,9-diol (15). To a magnetically stirred solution of iodine (150 mg, 0.58 mmol) in dry CH_2Cl_2 (2 mL) was added triphenylphosphine (153.5 mg, 0.58 mmol). The brown solution turned immediately to a pale yellow color, and then 1-(8-(2-oxiranyl)octyloxy)-1-ethoxyethane **3** (130 mg, 0.53 mmol) in CH_2Cl_2 (1 mL) was added at room temperature. After 5−10 min, the reaction mixture was poured into iced aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with ethyl ether. The combined organic layers were washed with 6% NaS_2O_3, water, and brine and then dried over $MgSO_4$. The crude product was purified by flash chromatography on a silica gel column (50% ethyl acetate in hexanes, TLC R_f = 0.3) to afford the product **15** (140 mg, 95%); ^{1}H NMR ($CDCl_3$, 300

(19) Roy, S. C.; Nagarajan, L.; Salomon, R. G. *J. Org. Chem.* **1999**, *64*, 1218−1224.

MHz) δ 3.59 (t, J = 6.6 Hz, 2 H), 3.47 (m, 1 H), 3.34 (dd, J = 10.2, 3.7 Hz, 1 H) 3.19 (dd, J = 10.2, 6.7 Hz, 1 H), 1.4−1.6 (4 H), 1.2−1.4 (10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.96, 62.99, 36.60, 32.73, 29.46, 29.38, 29.32, 25.72, 25.65, 16.68.

1-Iodo-10-(1,1,2,2-tetramethyl-1-silapropoxy)decan-2-ol (16). To a solution of 10-iododececane-1,9-diol (175 mg, 0.58 mmol) and TBDMSCl (97 mg, 0.64 mmol) in CH_2Cl_2 (3 mL) were added DMAP (7 mg, 0.06 mmol) and Et_3N (70 mg, 0.7 mmol) at room temperature. The reaction mixture was stirred under N_2 overnight, washed with water, aqueous NH_4Cl, and brine, and dried over $MgSO_4$. Flash chromatography on a silica gel column (10% ethyl acetate in hexanes, R_f = 0.35) afforded **16** (193 mg, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.56 (t, J = 6.6 Hz, 2 H), 3.47 (m, 1 H), 3.36 (dd, J = 10.2, 3.7 Hz, 1 H), 3.20 (dd, J = 10.2, 6.7 Hz, 1 H), 1.4−1.6 ((4 H), 1.2−1.3 (10 H), 0.86 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT), δ 71.01 (CH), 63.34 (CH_2), 36.64 (CH_2), 32.89 (CH_2), 29.52 (CH_2), 29.44 (CH_2), 29.38 (CH_2), 26.04 (CH_3), 25.80 (CH_2), 25.71 (CH_2), 18.43 (C), 16.86 (CH_2), −5.19 (CH_3).

10-Iodo-9-(2-oxanyloxy)-1-(1,1,2,2,-tetramethyl-1-silapropoxy)decane (17). A small amount of pyridinium *p*-toluenesulfonate (PPTS) (12 mg, 0.048 mmol) was added to a solution of **16** (190 mg, 0.46 mmol) and dihydropyran (DHP) (58 mg, 0.69 mmol, freshly distilled) in 5 mL of dry methylene chloride. The resulting solution was stirred overnight at room temperature, diluted and extracted with diethyl ether, and washed with water and brine. The solvent was removed with a rotary evaporator. The crude product was purified by flash chromatography on a silica gel column (4% ethyl acetate in hexanes) to afford **17** (203 mg, 89%). TLC (6% ethyl acetate in hexanes, R_f = 0.5); ^{1}H NMR ($CDCl_3$, 300 MHz, four isomers) δ 4.67 (dt, J = 11.5, 4.1 Hz, 1 H), 3.89 (m, 1 H), 3.55 (t, J = 6.6 Hz, 2 H), 3.47 (m, 1 H), 3.38 (m, 1 H), 3.28 (dd, J = 10.4, 5.8 Hz, 1 H), 3.18 (dd, J = 10.4, 4.3 Hz, 1 H), 1.4−1.8 (8 H), 1.2−1.3 (12 H), 0.85 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT), δ 99.42 (CH), 96.78 (CH), 77.53 (CH), 73.92 (CH), 63.33 (CH_2), 62.95 (CH_2), 62.66 (CH_2), 35.46 (CH_2), 34.36 (CH_2), 32.90 (CH_2), 31.00 (CH_2), 29.53 (CH_2), 29.48 (CH_2), 25.41 (CH_2), 26.03 (CH_3), 25.81 (CH_2), 25.47 (CH_2), 25.25 (CH_2), 25.04 (CH_2), 19.65 (CH_2), 18.41 (C), 12.15 (CH_2), 10.64 (CH_2), −5.20 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{34}IO_3Si$ ($M^+ - CMe_3$) 441.1281 found 441.1318.

(11*E*)-9-Hydroxy-13-oxotridec-11-enoic Acid (HOT, 18). A solution of the compound **7E** (40 mg, 0.093 mmol) in acetic acid/water (2:1, v/v, 1 mL) was stirred magnetically for 3.5 h at 40 °C, and then sodium metaperiodate (42 mg, 0.2 mmol) was added at room temperature. The resulting mixture was stirred for another 1.5 h at room temperature, followed by removal of the solvent under reduced pressure. The residue was extracted with ethyl acetate. The extract was washed with water and brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. The trace of acetic acid was removed by azeotropic distillation with *n*-heptane (3 × 3 mL) under high vacuum (0.1 mmHg) to afford the title acid **18** (20 mg, 89%); TLC (ethyl acetate: hexanes: acetic acid = 60:40:0.5, v/v/v, R_f = 0.28); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.49 (d, J = 7.8 Hz, 1 H), 6.90 (dt, J = 15.6, 7.1 Hz, 1 H), 6.16 (dd, J = 15.6, 7.8 Hz, 1 H), 3.80 (m, 1 H), 2.50 (m, 2 H), 2.32 (t, J = 7.4 Hz, 2 H), 1.55−1.60 (2 H), 1.40−1.50 (2 H), 1.20−1.40 (8 H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 194.12 (CHO), 179.52 (COOH), 154.99 (CH =), 134.92 (CH =), 70.57 (CHOH), 40.49 (CH_2), 37.30 (CH_2), 29.23 (CH_2), 29.11 (CH_2), 28.90 (CH_2), 25.43 (CH_2), 24.62 (CH_2); HRMS (EI) m/z calcd for $C_{13}H_{22}O_4$ (M^+) 242.1518 found 242.1520.

(2*E*)-5-Hydroxytridec-2-enedioic Acid (19). To a magnetically stirred solution of (11*E*)-9-hydroxy-13-oxotridec-11-enoic acid (**18**, 20 mg, 0.08 mmol) in *tert*-butyl alcohol/water (5:1, v/v, 1 mL) were added successively NaH_2PO_4 (17 mg, 0.12 mmol), 2-methyl-2-butene (250 mL, 2 M solution in THF, 0.5 mmol), and $NaClO_2$ (23 mg, 0.25 mmol). The resulting mixture was stirred for 2.5 h until the yellow solution turned colorless. The solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate, washed with water and brine, and dried over $MgSO_4$. Removal of the solvent gave the dicarboxylic acid **19** (20 mg, 95%) without further purification; ^{1}H NMR ($CD_3)_2CO$, 300 MHz) δ 7.03 (dt, J = 15.7, 7.3 Hz, 1 H), 6.02 (dt, J = 15.7, 1.44 Hz, 1 H), 3.72 (m, 1 H), 2.35 (m, 2 H), 2.29 (t, J = 7.3 Hz, 2 H), 1.5−1.7 (2 H), 1.4−1.5 (4 H), 1.3−1.4 (6 H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz), δ 174.81 (COOH), 167.57 (=CHCOOH), 147.80 (CH=). 123.75 (CH=), 70.70 (CHOH), 41.16 (CH_2), 38.25 (CH_2), 34.27 (CH_2), 30.15 (CH_2), 26.41 (CH_2),25.74 (CH_2); HRMS (EI) m/z calcd for $C_{13}H_{22}O_5$ (M^+) 258.1467, found 258.1460.

Methyl 8-(3-Oxo-1*H*,6*H*-2-oxinyl)octanoate (20). Ethylaluminum dichloride (0.016 mmol, 16 mL, 1 M solution in hexane) was added to a solution of (2*E*)-5-hydroxytridec-2-enedioic acid (**19**, 10 mg, 0.041 mmol) in MeOH (0.5 mL) under an argon atmosphere. The resulting solution was transferred to a small quartz tube and irradiated with 254 nm light in a Rayonet photoreactor for 2−3 h. The irradiated solution was quenched with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated, and subjected to flash chromatography on silica gel with 50% ethyl acetate in hexanes to provide the lactone methyl ester **20** (7 mg, 70%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.85 (dt, J = 14.5, 5.6 Hz, 1 H), 6.00 (dt, J = 14.5, 2.8 Hz, 1 H), 4.3−4.5 (m, 1 H), 3.65 (s, 3 H), 2.26−2.33 (m, 2 H), 2.28 (t, J = 7.6 Hz, 2 H), 1.7−1.9 (m, 2 H), 1.5−1.7 (4 H), 1.2−1.4 (6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.31, 164.62, 145.03, 121.51, 77.26, 51.52, 34.88, 34.09, 29.45, 29.18, 29.11, 29.04, 24.91, 24.78; HRMS (EI) m/z calcd for $C_{14}H_{22}O_4$ (M^+) 254.1518 found 254.1546; calcd for $C_{14}H_{23}O_5$ (MH^+) 255.1597 found 255.1597.

2-(8-Hydroxyoctyl)-2*H*,3*H*,6*H*-oxin-6-ol (21). A solution of the compound **5** (40 mg, 0.08 mmol) in acetic acid/water (2:1, v/v, 1 mL) was stirred magnetically for 3.5 h at 40 °C, and then sodium metaperiodate (26 mg, 0.12 mmol) was added at room temperature. The resulting mixture was stirred at room temperature for another 1.5 h, followed by removal of the solvent under reduced pressure. The residue was extracted with ethyl acetate. The extract was washed with water and brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. The trace of acetic acid was removed by azeotropic distillation with *n*-heptane (3 × 3 mL) under high vacuum (0.1 mmHg). The crude product was purified by flash chromatography on a silica gel column (50% ethyl acetate in hexanes, R_f = 0.2) to afford cyclic acetal **21** (18 mg, 93%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92−6.05 (m, 1 H), 5.55−5.75 (m, 1 H), 4.92 (m, 1 H), 3.75(m, 1 H), 3.61 (t, J = 6.5 Hz, 2 H), 1.92 (m, 2 H), 1.4−1.7 (4 H), 1.2−1.4 (8 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 129.11, 125.67, 94.78, 67.88, 66.30, 63.07, 35.59, 32.82, 30.82, 29.90, 29.64, 29.56, 29.45, 26.42, 25.64; HRMS (EI) m/z calcd for $C_{13}H_{20}O_3$ (M^+) 228.1725 found 228.1712.

8-(3-Oxo-1*H*,6*H*-2-oxinyl)octanoic Acid (1). A solution of alcohol **21** (4 mg, 0.018 mmol) and pyridinium dichromate (PDC) (68 mg, 0.18 mmol) in DMF (0.3 mL) was stirred at room temperature for 20 h, diluted with saturated aqueous NH_4Cl (1 mL), and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated with a rotary evaporator. Flash chromatography on a silica gel column (55% ethyl acetate in hexanes, TLC R_f = 0.2) afforded racemic lactone **1** (3.2 mg, 73%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.86 (dt, J = 9.6, 3.8 Hz, 1 H), 6.50 (dt, J = 9.6, 1.9 Hz, 1 H), 4.49 (m, 1 H), 2.33 (t, 7.2 Hz, 2 H), 2.25−2.35 (m, 2 H), 1.5−1.7 (4 H), 1.2−1.4 (8 H); HRMS (EI) m/z calcd for $C_{13}H_{20}O_4$ (M^+) 240.1362 found 240.1392; calcd for $C_{13}H_{21}O_4$ (MH^+) 241.1441 found 241.1438; calcd for $C_{13}H_{18}O_3$ ($M^+ - H_2O$) 222.1255 found 222.1257.

Acknowledgment. We thank the National Institute of General Medical Sciences of the National Institutes of Health for support of this research by grant GM21249 (to R.G.S.).

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

JO000809U