Macrocyclic Diacylglycerol-bis-lactones as Conformationally Constrained Analogues of Diacylglycerol-lactones. Interactions with Protein Kinase C

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Received March 23, 2004

A series of macrocyclic diacylglycerol (DAG)-bis-lactones were investigated as extreme conformationally constrained analogues of DAG-lactones in order to seek more potent protein kinase C (PKC) ligands with higher binding affinities and less lipophilicity than previous compounds. The additional constraint achieved the desired objective as exemplified by the macrocyclic DAG-bis-lactone **57**, which exhibited a 6-fold higher binding affinity for PKCα (K_i = 6.07 nM) than the corresponding nonmacrocyclic 3-alkylidene DAG-lactone **6**. A structure−activity relationship (SAR) analysis of the macrocyclic DAG-bis-lactones demonstrated a parabolic relationship between activity and lipophilicity, as well as a predilection for the *Z*-alkylidene isomers as the preferred ligands. Molecular docking studies revealed that macrocyclic DAG-bis-lactone **57** bound to the C1b domain of PKCα exclusively in the sn-1 binding mode in contrast to DAG-lactone **6**, which showed both sn-1 and sn-2 binding modes. It is proposed that the high potency displayed by these macrocyclic DAG-bis-lactones results from a set of more favorable hydrogen bonding and hydrophobic interactions with PKCα as well as from a reduced entropy penalty due to conformational restriction.

Introduction

Protein kinase C (PKC) comprises a family of serine/threonine kinases implicated in growth factor and G-protein-coupled receptor signaling and plays a key regulatory role in signal transduction events in response to specific hormonal, neuronal and growth factor stimuli.[1−3] The intrinsic function of PKC isozymes is regulated by three mechanisms: (1) phosphorylation, which primes the enzyme for catalysis, (2) cofactor binding, which allosterically activates the enzyme, and (3) interaction with targeting proteins that position PKC near its regulators and substrates.[4] The PKC family can be divided into three isozyme groups based on the differences in their structure and substrate requirements: conventional (α, βI, βII, and γ), novel (δ, ϵ, η, and θ), and atypical (ζ and ι/λ) groups.[4,5] Conventional and novel isozymes have twin diacylglycerol responsive C1 regions and become activated as a result of the association of the cytosolic enzyme with membranes containing acid phospholipids.[6] The physiological function of individual PKC isozymes has been identified using pharmacological approaches by PKC activators and inhibitors that display varying degrees of selectivity for the isozymes.[7]

Diacylglycerol (DAG) is an endogenous activator that binds to the Cl domain(s) of conventional and novel PKCs, where it allosterically activates the enzyme in the presence of phospholipid. Phorbol esters also bind to the DAG-binding site of the enzyme in a competitive manner and function as potent and metabolically stable DAG surrogates. The binding affinities of phorbol esters are 3−4 orders of magnitude greater than those of DAGs,[8] and their higher potencies are anticipated to be derived from a conformationally rigid orientation of hydrophilic pharmacophores unlike the less constrained orientation resulting from the flexible glycerol of DAG.

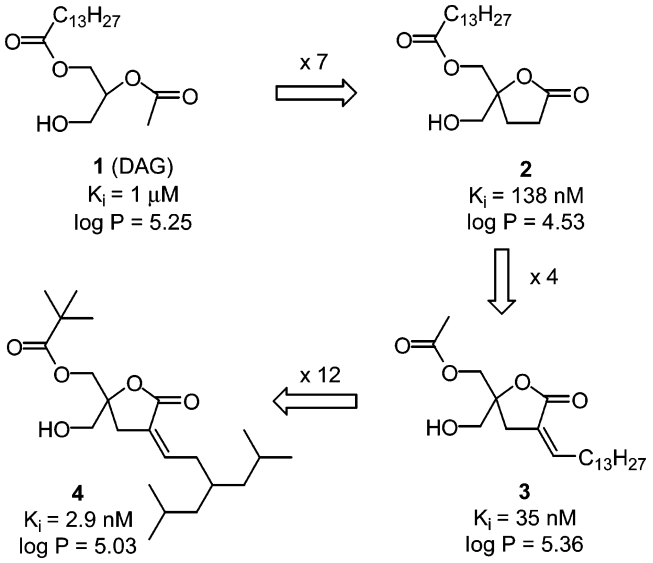

Figure 1. DAG-lactones as PKC ligands.

Over the past few years, we have explored conformationally constrained DAG analogues, so-called DAG-lactones, to bridge the affinity gap between phorbol

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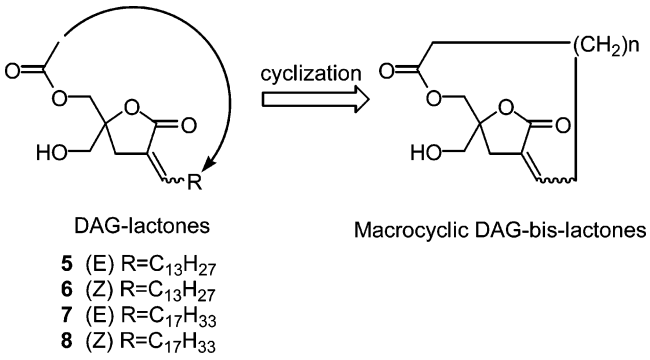
10.1021/jm0497747 CCC: $27.50
Published on Web 06/29/2004



5 (E) R=$C_{13}H_{27}$
6 (Z) R=$C_{13}H_{27}$
7 (E) R=$C_{17}H_{33}$
8 (Z) R=$C_{17}H_{33}$

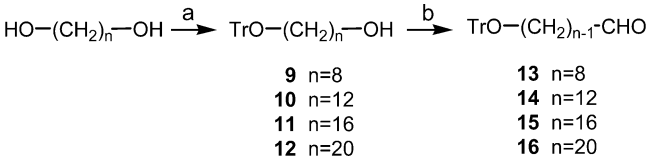
Figure 2. Conformational constraint of DAG-lactones.

esters and DAGs.[9,10] Pharmacophore-guided approaches following extensive SAR studies have led to a reduction in the potency gap between phorbol esters and DAGs by approximately 2 orders of magnitude (Figure 1). The first increase in binding affinity from DAG, e.g., glycerol-1-myristate-2-acetate (**1**, $K_i \approx 1$ μM), was achieved by cyclization to the 5-tetradecanoyl DAG-lactone (**2**, $K_i =$ 138 nM).[11] The second improvement in binding affinity was accomplished by shifting the hydrophobic alkyl chain from the 5-acyl to the 3-alkylidene position, resulting in the 3-tetradecylidene lactone (**3**, $K_i = 35$ nM).[11,12] These steps provided ca. 7- and 4-fold increases in binding affinity, respectively. Recently, more sophisticated receptor-guided approaches using the crystal coordinates of the C1b domain of PKCδ in complex with phorbol 13-acetate led to the design of highly branched alkyl chains capable of interacting with a cluster of conserved hydrophobic amino acids in the space between the two β-sheets of the C1 domain.[13] Eventually, these new DAG-lactones bearing branched alkyl chains were able to achieve low nanomolar binding affinities for PKCα. For example, DAG-lactone **4** ($K_i = 2.9$ nM) has 12-fold higher binding affinity than **3**, a linear DAG-lactone with similar lipophilicity.[14,15]

The high potency of DAG-lactones is basically derived from the loss of the entropic penalty of the flexible DAG glycerol backbone upon cyclization. Therefore, we envisaged that an additional conformational restriction of the remaining acyclic ester, the 5-acyl group, might likewise produce an entropic advantage in binding to the enzyme. One approach to achieve further conformational restriction was to link the two terminal alkyl ends of the 5-acyl and 3-alkylidene groups of the DAG-lactones to generate a macrocyclic ring. This would restrict the conformational mobility of the alkyl chain by allowing the ester to adopt the preferred s-trans configuration for ring sizes greater than 10. Following this approach, DAG-lactones **5**−**8** would generate the corresponding macrocyclic DAG-bis-lactones as depicted in Figure 2. These bis-lactones would contain a [*x*.2.1] bicyclic skeleton with $x = 18$ (for $n = 12$) in the case of macrocyclic DAG-bis-lactones generated from DAG-lactones **5** or **6**.

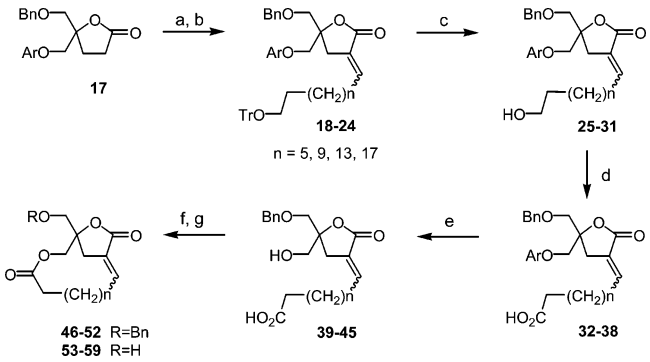
Since the role of the alkyl chains in DAGs and DAG-lactones is to facilitate partitioning into the lipid-rich membrane environment, the lipophilicities of the compounds have been correlated with their binding affinities in a parabolic manner.[14] It is desirable that nonspecific interactions be minimized not only to allow the protein−ligand interaction to become dominant but also to render the ligands physicochemically suitable as drug

Scheme 1. Syntheses of Aldehydes[a]



[a] Reagents and conditions: (a) TrCl, pyridine, 60−70%; (b) PCC, 4 Å molecular sieves, CH_2Cl_2, 70−80%.

Scheme 2. Syntheses of DAG-bis-macrolactones[a]



[a] Reagents and conditions: (a) (i) LiHMDS, THF, −78 °C; (ii) RCHO (**13**−**16**); (b) (i) MsCl, NEt_3, CH_2Cl_2; (ii) DBU, 45−52% for two steps; (c) HCO_2H, ether, 100%; (d) PDC, DMF, 80−88%; (e) CAN, CH_3CN/H_2O, 75−82%; (f) DMAP, DMAP/HCl, DCC, CH_2Cl_2, 60−70%; (g) BCl_3, CH_2Cl_2, 80−92%.

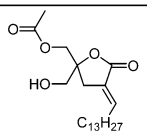
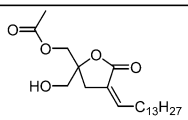
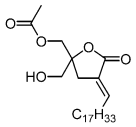
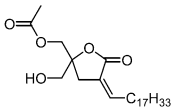
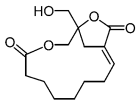
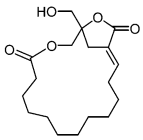
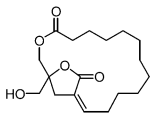
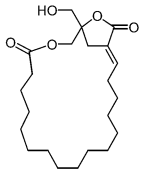
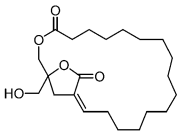
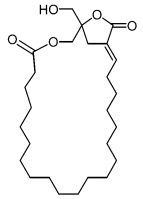
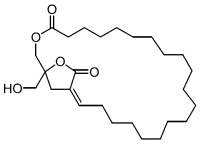
candidates. Another advantage from the second lactonization is the reduction in lipophilicity resulting from cyclization, something known as the "cyclic ester correction", which can reduce the log *P* value by as much as 1.5 units.[16] This reduction is equivalent to the effect of excising three carbons (ca. 0.5 unit each) from the fatty chain. Therefore, we envisaged that the conformational restriction of the acyclic ester (5-acyl group) would result in both an increase in binding affinity, by reducing the entropy penalty, and a lowering of lipophilicity.

In this study, a series of macrocyclic DAG-bis-lactones having a [*x*.2.1] bicyclic skeleton were synthesized and evaluated as PKCα ligands. Their binding mode with the enzyme was also investigated by molecular modeling.

Chemistry

Aldehydes **13**−**16** used for the condensation with γ-lactone (**17**) were prepared starting from the corresponding commercially available diols after two consecutive steps involving monotritylation and oxidation as shown in Scheme 1. The synthesis of the macrocyclic DAG-bis-lactones (**53**−**59**) is illustrated in Scheme 2. 5-Benzyloxymethyl-5-(4-methoxyphenoxy)methyl-γ-lactone (**17**), synthesized according to the previously published procedure,[17] was condensed with the aldehydes (**13**−**16**), and the intermediate β-hydroxylactones obtained were converted (by elimination) into 3-alkylidene γ-lactones (**18**−**24**) as mixtures of *E*/*Z* isomers. In the case of $n = 5$ in Scheme 2, only the *E* isomer (**18**) was isolated. After the separation of *E*/*Z* isomers, the trityl group in **18**−**24** was removed under acidic conditions to provide the corresponding alcohols (**25**−**31**), which were oxidized to the corresponding carboxylic acids (**32**−**38**) by pyridinium dichromate in DMF. After deprotection of the 4-methoxyphenyl group in **32**−**38**,

Table 1. Apparent K_i (nM) Values and log P of Synthesized DAG-bis-macrolactones

E-isomer	Cpd #	Log P	K_i (nM)	Z-isomer	Cpd #	Log P	K_i (nM)
	**5**	5.36	77.85[a]		**6**	5.36	35.09[a]
	**7**	7.11	28[a]		**8**	7.11	24[a]
	**53**	-0.08	1,800 (±250)				
	**54**	1.88	107.2 (±8.1)		**55**	1.88	52.7 (±3.5)
	**56**	3.85	12.16 (±0.41)		**57**	3.85	6.07 (±0.72)
	**58**	5.81	22.0 (±2.6)		**59**	5.81	10.29 (±0.76)

[a] Reference 11.

the corresponding hydroxy acids (**39**−**45**) were cyclized using Keck and Boden's macrocyclization method[18] to produce 13-, 17-, 21-, and 25-membered macrolactones (**46**−**52**), respectively. Finally, debenzylation of **46**−**52** afforded the target macrocyclic DAG-bis-lactones (**53**−**59**).

Results and Discussion

Biological Activitiy. The interaction of macrocyclic DAG-bis-lactones **53**−**59** with PKC was assessed in terms of the ability of the ligand to displace bound [20-^{3}H]phorbol 12,13-dibutyrate (PDBU) from the recombinant PKCα isozyme in the presence of phosphatidylserine as previously described.[14] IC_{50} values were determined by fitting the data points to the theoretical noncooperative competitive inhibition curve. The K_i values for inhibition of binding were calculated from the corresponding IC_{50} values and are listed in Table 1. The log *P* values of the lactones were calculated by the fragment-based program KowWin 1.63.[16] The binding affinities of the macrocyclic DAG-bis-lactones were compared with those reported for the parent DAG-lactones (**5**−**8**), which were used as reference.[11]

The macrocyclic DAG-bis-lactones **56** and **57**, bearing a [18.2.1] bicyclic skeleton, were generated by connecting the two terminal carbons at the 3 and 5 positions of DAG-lactones **5** and **6**, respectively. The resulting **56** (K_i = 12.16 nM) and **57** (K_i = 6.07 nM) showed ca. 6-fold enhancement compared to **5** (K_i = 77.85 nM) and **6** (K_i = 35.09 nM), respectively. It is of interest to note that macrocyclization resulted in a comparable entropic advantage for both *E*- and *Z*-DAG-bis-lactone isomers as reflected by the similar increase in binding affinity. Furthermore, the log *P* values for **56** and **57** (log *P* = 3.85) are lower than parent lactones **5** and **6** (log *P* = 5.36) by 1.51 units. In a similar way, the macrocyclization of **7** and **8** produced [22.2.1] bicyclic systems **58** and **59**, respectively. The *Z* isomer **59** (K_i = 10.29 nM) displayed only a modest ca. 2-fold increase in binding affinity compared to **8** (K_i = 24 nM), while the binding affinity of the *E* isomer **58** (K_i = 22.0 nM) was only a little better than that of **7** (K_i = 28 nM). These results demonstrate that macrocyclization of DAG-lactones provides PKC ligands with higher binding affinities and lower lipophilicities.

The size of the macrolactone seems to be a critical parameter. While the binding affinities for the larger macrocyclic DAG-bis-lactones **58** and **59** were ca. 2-fold weaker than the affinities for **56** and **57**, four-carbon smaller macrolactones also produced deficient ligands

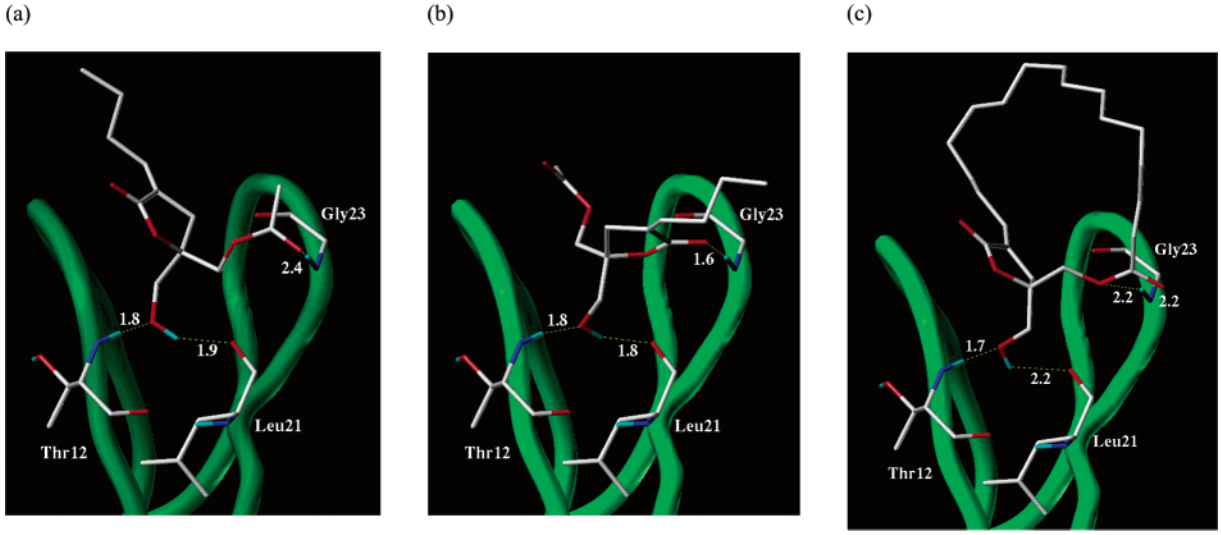


Figure 3. Proposed models of PKCα−ligand complexes. Acyclic DAG-lactone **6** in sn-1 (a) and sn-2 (b) binding modes. Macrocyclic DAG-bis-lactone **57** in sn-1 binding mode (c).

(**54**, K_i = 107.2 nM; **55**, K_i = 52.7 nM**)** ca. 9-fold weaker than **56** and **57**. The macrolactone reduced by an additional four carbons, **53**, displayed very low affinity (K_i = 1,800 nM). This result indicates that the size and lipophilicity of macrocyclic DAG-bis-lactones **56** and **57** appear to be optimal for membrane partitioning and PKC activation. Previously, a parabolic dependence between log(1/K_i) and log *P* had been reported for the set of DAG-lactones bearing acyl or 3-alkylidene chains, with an optimal log *P* for DAG-lactones between 5 and 6.[14] In a similar manner, this macrocyclic DAG-bis-lactone series showed a parabolic relationship between binding affinity and lipophilicity with a maximum log(1/K_i) in the same range. The macrocyclic DAG-bis-lactones also showed a geometric preference similar to that described for DAG-lactones. The *Z* isomers of the macrocyclic DAG-bis-lactones (**55**, **57**, **59**) consistently exhibited about 2-fold greater potency than the corresponding *E* isomers (**54**, **56**, **58**). Thus, the relationship between binding affinity, lipophilicity, and geometry in our series of macrocyclic DAG-bis-lactones shows a pattern similar to that of the parent DAG-lactones.

Molecular Modeling. Previously, the molecular modeling studies revealed that DAG-lactones have two possible binding orientations when they were docked into the empty C1b domain derived from the crystal coordinates of PKCδ in complex with phorbol 13-acetate. These two apparently equivalent binding modes, sn-1 and sn-2, form a network of hydrogen bonds with amino acids Thr242, Leu251, and Gly253 identical to those formed by phorbol 13-acetate in the crystal structure of the complex. The sn-1 (or sn-2) binding mode is defined when the sn-1 (or sn-2) carbonyl, corresponding to the carbonyl of the 5-acyloxymethyl (or the lactone), and the hydroxyl group in the DAG-lactone are directly bound to the protein by hydrogen bonding.[9,10] In the two binding alternatives, one of the two carbonyls of the DAG lactone remained unengaged with the protein. It has been hypothesized that this orphan pharmacophore functions equivalently to the C-9(OH)/C-13(C=O) motif in phorbol esters, which also appears to be free of interactions in the phorbol ester/C1b complex, and is presumably involved in interacting with phospholipid headgroups, or with other hydrophilic elements, required for high-affinity binding under the conditions of the biological assays.

To investigate the binding mode of the most potent macrocyclic DAG-bis-lactone **57** and by comparison of it to the corresponding acyclic DAG-lactone **6**, both compounds were docked into the C1b domain of PKCα derived through homology modeling.[19] By use of the program Autodock 3.0, as previously described,[20] compounds **6** and **57** were evaluated with the number of dockings set to 100. DAG-lactone **6** appears to bind favoring the sn-2 binding mode [44% for sn-2 binding (Figure 3a) versus 36% for sn-1 binding (Figure 3b)] relative to the macrocyclic DAG-bis-lactone **57**, which seems to bind exclusively in a variant of the typical sn-1 binding mode (Figure 3c). Compounds **6** and **57** interact with Thr12, Leu21, and Gly23 in the C1b domain of PKCα, which correspond to Thr242, Leu251, and Gly253 in the full length protein. In the sn-1 mode of compound **6**, the hydroxyl group engages in a bifurcated hydrogen bond to the amide proton of Thr12 (1.8 Å) and the carbonyl of Leu21 (1.9 Å), while the sn-1 carbonyl acts as a hydrogen bond acceptor for the backbone nitrogen of Gly23 (2.4 Å). (Note that the numbers should correspond to the ones in the figure.) The sn-2 binding mode for compound **6** shows a network of hydrogen bonds similar to these amino acids. The hydroxyl group makes equivalent hydrogen bonds to Thr12 (1.8 Å) and Leu21 (1.8 Å), but it is the sn-2 carbonyl of the lactone ring that now forms a hydrogen bond with Gly23 (1.6 Å). The preference of **6** for the sn-2 binding mode correlates with the better quality of hydrogen bonds formed in this modality. In the case of compound **57**, the hydroxyl group engages in an identical pattern of hydrogen bonds to Thr12 (1.7 Å) and Leu21 (2.2 Å). However, in this unique sn-1 binding mode the amide proton of Gly23 makes a bifurcated hydrogen bond to the sn-1 carbonyl (2.2 Å) and the sp^3 oxygen (2.2 Å) of the ester. In addition, this single sn-1 binding mode reveals that the hydrophobic alkyl chain is fitted to the highly conserved hydrophobic residues in PKCα, such as Pro11, Phe13, Leu20, Tyr22, and Leu24. In particular, the alkyl chain of the macrolactone contacts closely

the hydrophobic side chains of Leu20, Tyr22, and Leu24. The role of hydrophobic residues in the C1b domain of PKCα on ligand recognition has been investigated by site-directed mutagenesis.[21] Three hydrophobic residues, Leu250, Trp252, and Leu254, were identified as essential residues for binding, and since these amino acids correspond to Leu20, Tyr22, and Leu24 (Figure 3c), the hydrophobic interactions between the macrocyclic side chain and these amino acids may contribute to the observed high binding affinity. Therefore, the higher potency of compound **57** (K_i = 6.07 nM) relative to compound **6** (K_i = 35.09 nM) may be explained by extra hydrogen bonding and hydrophobic interactions in addition to the entropy gain due to conformational restriction.

Conclusion

An additional conformational restriction imposed on DAG-lactones provided a new set of macrocyclic DAG-bis-lactones, some of which displayed greater binding affinities for PKC than conventional DAG-lactones with reduced lipophilicity. Specifically, compound **57** exhibited a high binding affinity for PKCα (K_i = 6.07 nM), which was 6-fold higher than the corresponding acyclic 3-alkylidene DAG-lactone **6**. The SAR analysis demonstrated a parabolic relationship between activity and lipophilicity, as well as a predilection for the *Z*-alkylidene isomers as the preferred ligands. Molecular docking studies revealed that the highly potent DAG-bis-macrolactone **57** binds exclusively in the sn-1 binding mode to the C1b domain of PKCα. The combination of a highly favorable pattern of hydrogen bonding and hydrophobic interactions with the expected entropy gain due to conformational restriction appears to contribute to its high binding affinity.

Experimental Section

All chemical reagents were commercially available. Melting points were determined on a melting point Büchi B-540 apparatus and are uncorrected. Silica gel column chromatography was performed on silica gel 60, 230−400 mesh, Merck. Proton NMR spectra were recorded on a JEOL JNM-LA 300 at 300 MHz. Chemical shifts are reported in ppm units with Me_4Si as a reference standard. Infrared spectra were recorded on a Perkin-Elmer 1710 series FTIR. Mass spectra were recorded on a VG Trio-2 GC−MS instrument. Elemental analyses were performed with an EA 1110 automatic elemental analyzer, CE Instruments.

General Procedure for the Synthesis of 9−12. A solution of diol (10 mmol) in DMF (10 mL) was treated with pyridine (1.6 mL, 20 mmol) and trityl chloride (2.78 g, 10 mmol) and stirred for 1 h at room temperature. The mixture was diluted with H_2O and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:4) as eluant to afford **9**−**12** as colorless oils in 60−70% yield.

8-(Trityloxy)-1-octanol (9): ^{1}H NMR ($CDCl_3$) δ 7.0−7.5 (m, 15 H, CPh_3), 3.59 (t, 2 H, J = 6.6 Hz, CH_2OH), 3.04 (t, 2 H, J = 6.6 Hz, CH_2OTr), 1.2−1.7 (m, 12 H, $(CH_2)_6$).

12-(Trityloxy)-1-dodecanol (10): ^{1}H NMR ($CDCl_3$) δ 7.0−7.5 (m, 15 H, CPh_3), 3.62 (t, 2 H, J = 6.6 Hz, CH_2OH), 3.03 (t, 2 H, J = 6.6 Hz, CH_2OTr), 1.2−1.7 (m, 20 H, $(CH_2)_{10}$).

16-(Trityloxy)-1-hexadecanol (11): ^{1}H NMR ($CDCl_3$) δ 7.0−7.5 (m, 15 H, CPh_3), 3.59 (t, 2 H, J = 6.6 Hz, CH_2OH), 3.04 (t, 2 H, J = 6.6 Hz, CH_2OTr), 1.2−1.7 (m, 28 H, $(CH_2)_{14}$).

20-(Trityloxy)-1-eicosanol (12): ^{1}H NMR ($CDCl_3$) δ 7.0−7.5 (m, 15 H, CPh_3), 3.59 (t, 2 H, J = 6.6 Hz, CH_2OH), 3.04 (t, 2 H, J = 6.6 Hz, CH_2OTr), 1.2−1.7 (m, 36 H, $(CH_2)_{18}$).

General Procedure for the Synthesis of 13−16. A suspension of **9**−**12** (6 mmol) and 4 Å molecular sieves (3.88 g) in CH_2Cl_2 (40 mL) was treated with pyridinium chlorochromate (3.88 g, 18 mmol) and stirred for 1 h at room temperature. The mixture was treated with ether and Celite and stirred for 30 min. The suspension was filtered through a short pad of silica gel, and the combined filtrates were concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:10) as eluant to afford **13**−**16** as colorless oils in 70−80% yield.

8-(Trityloxy)-1-octanal (13): ^{1}H NMR ($CDCl_3$) δ 9.76 (t, 1 H, J = 2.0 Hz, CHO), 7.15−7.5 (m, 15 H, CPh_3), 3.04 (t, 2 H, J = 6.6 Hz, CH_2OTr), 2.41 (dt, 2 H, J = 2.0, 7.3 Hz, CH_2CHO), 1.2−1.7 (m, 10 H, $(CH_2)_5$).

12-(Trityloxy)-1-dodecanal (14): ^{1}H NMR ($CDCl_3$) δ 9.75 (t, 1 H, J = 2.0 Hz, CHO), 7.15−7.5 (m, 15 H, CPh_3), 3.04 (t, 2 H, J = 6.6 Hz, CH_2OTr), 2.40 (dt, 2 H, J = 2.0, 7.3 Hz, CH_2-CHO), 1.2−1.7 (m, 18 H, $(CH_2)_9$).

16-(Trityloxy)-1-hexadecanal (15): ^{1}H NMR ($CDCl_3$) δ 9.74 (t, 1 H, J = 2.0 Hz, CHO), 7.15−7.5 (m, 15 H, CPh_3), 3.04 (t, 2 H, J = 6.6 Hz, CH_2OTr), 2.40 (dt, 2 H, J = 2.0, 7.3 Hz, CH_2CHO), 1.2−1.7 (m, 26 H, $(CH_2)_{13}$).

20-(Trityloxy)-1-eicosanal (16): ^{1}H NMR ($CDCl_3$) δ 9.76 (t, 1 H, J = 2.0 Hz, CHO), 7.15−7.5 (m, 15 H, CPh_3), 3.04 (t, 2 H, J = 6.6 Hz, CH_2OTr), 2.41 (dt, 2 H, J = 2.0, 7.3 Hz, CH_2-CHO), 1.2−1.7 (m, 34 H, $(CH_2)_{17}$).

General Procedure for the Synthesis 18−24. A stirred solution of **17** (1.03 g, 3.0 mmol) in THF (6 mL) was cooled to −78 °C and treated dropwise with lithium bis(trimethylsilyl)-amide (1 M in THF, 4.5 mL, 4.5 mmol). After being stirred for 30 min at −78 °C, the mixture was treated with a solution of the aldehyde (**13**−**16**, 3.6 mmol) in THF (3.6 mL) and stirred for 2 h at the same temperature. The reaction was quenched by the slow addition of a saturated aqueous solution of ammonium chloride, and the mixture was extracted with ether several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:4) as eluant to give the intermediate β-hydroxylactones as an oil. A solution of the above compound in CH_2Cl_2 (6 mL) was cooled to 0 °C and treated with triethylamine (1.1 mL, 8 mmol) and methanesulfonyl chloride (0.3 mL, 4.0 mmol). The mixture was stirred at 0 °C for 30 min and then for 2 h at room temperature. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 1.2 mL, 8.0 mmol) was added at 0 °C, and the resulting solution was stirred for 30 min. The reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:10) as eluant to afford a mixture of *E* and *Z* isomers (**18**−**24**) as colorless oils in 45−52% yield.

5-(Benzyloxy)methyl-5-(4-methoxyphenoxy)methyl-3-[(*E*)-8-trityloxyoctylidene]tetrahydro-2-furanone (18): ^{1}H NMR ($CDCl_3$) δ 7.2−7.5 (m, 20 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.58 (s, 2 H, $PhCH_2O$), 4.02 (AB q, 2 H, J = 9.5 Hz, CH_2Ar), 3.74 (s, 3 H, OCH_3), 3.66 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.03 (t, 2 H, J = 6.6 Hz, CH_2OTr), 2.83 (m, 2 H, H-4), 2.14 (q, 2 H, >C=CH−CH_2), 1.25−1.65 (m, 10 H, $(CH_2)_5$).

5-(Benzyloxy)methyl-5-(4-methoxyphenoxy)methyl-3-[(*E*)-12-trityloxydodecylidene]tetrahydro-2-furanone (19): ^{1}H NMR ($CDCl_3$) δ 7.2−7.5 (m, 20 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.58 (s, 2 H, $PhCH_2O$), 4.02 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.75 (s, 3 H, OCH_3), 3.67 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.03 (t, 2 H, J = 6.6 Hz, CH_2OTr), 2.83 (m, 2 H, H-4), 2.16 (q, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 18 H, $(CH_2)_9$).

5-(Benzyloxy)methyl-5-(4-methoxyphenoxy)methyl-3-[(*Z*)-12-trityloxydodecylidene]tetrahydro-2-furanone (20): ^{1}H NMR ($CDCl_3$) δ 7.15−7.5 (m, 20 H, phenyl), 6.80 (s, 4 H, Ar), 6.18 (m, 1 H, >C=CH), 4.57 (m, 2 H, $PhCH_2O$), 4.00 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.73 (s, 3 H, OCH_3), 3.64 (AB q, 2

H, J = 10.2 Hz, $BnCH_2O$), 3.04 (t, 2 H, J = 6.6 Hz, CH_2OTr), 2.88 (m, 2 H, H-4), 2.72 (m, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 18 H, $(CH_2)_9$).

5-(Benzyloxy)methyl-5-(4-methoxyphenoxy)methyl-3-[(*E*)-16-trityloxyhexadecylidene]tetrahydro-2-furanone (21): ^{1}H NMR ($CDCl_3$) δ 7.2−7.5 (m, 20 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.58 (s, 2 H, $PhCH_2O$), 4.02 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.75 (s, 3 H, OCH_3), 3.67 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.03 (t, 2 H, J = 6.6 Hz, CH_2OTr), 2.84 (m, 2 H, H-4), 2.16 (q, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 26 H, $(CH_2)_{13}$).

5-(Benzyloxy)methyl-5-(4-methoxyphenoxy)methyl-3-[(*Z*)-16-trityloxyhexadecylidene]tetrahydro-2-furanone (22): ^{1}H NMR ($CDCl_3$) δ 7.15−7.5 (m, 20 H, phenyl), 6.80 (s, 4 H, Ar), 6.19 (m, 1 H, >C=CH), 4.57 (m, 2 H, $PhCH_2O$), 4.01 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.65 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.03 (t, 2 H, J = 6.6 Hz, CH_2OTr), 2.88 (m, 2 H, H-4), 2.72 (m, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 26 H, $(CH_2)_{13}$).

5-(Benzyloxy)methyl-5-(4-methoxyphenoxy)methyl-3-[(*E*)-20-trityloxyeicosylidene]tetrahydro-2-furanone (23): ^{1}H NMR ($CDCl_3$) δ 7.2−7.5 (m, 20 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.58 (s, 2 H, $PhCH_2O$), 4.02 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.67 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.03 (t, 2 H, J = 6.6 Hz, CH_2OTr), 2.84 (m, 2 H, H-4), 2.16 (q, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 34 H, $(CH_2)_{17}$).

5-(Benzyloxy)methyl-5-(4-methoxyphenoxy)methyl-3-[(*Z*)-20-trityloxyeicosylidene]tetrahydro-2-furanone (24): ^{1}H NMR ($CDCl_3$) δ 7.15−7.5 (m, 20 H, phenyl), 6.80 (s, 4 H, Ar), 6.20 (m, 1 H, >C=CH), 4.58 (AB q, 2 H, J = 11.9 Hz, $PhCH_2O$), 4.01 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.65 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.03 (t, 2 H, J = 6.6 Hz, CH_2OTr), 2.90 (m, 2 H, H-4), 2.72 (m, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 34 H, $(CH_2)_{17}$).

General Procedure for the Synthesis 25−31. A solution of **18**−**24** (0.5 mmol) in ether (3 mL) was treated with formic acid (3 mL) and stirred for 1 h at room temperature. The mixture was neutralized with solid sodium bicarbonate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:4) as eluant to afford **25**−**31** as colorless oils in almost quantitative yield.

5-(Benzyloxy)methyl-3-[(*E*)-8-hydroxyoctylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (25): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.58 (s, 2 H, $PhCH_2O$), 4.03 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.6−3.7 (m, 4 H, $BnCH_2O$ and CH_2OH), 2.84 (m, 2 H, H-4), 2.16 (q, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 10 H, $(CH_2)_5$).

5-(Benzyloxy)methyl-3-[(*E*)-12-hydroxydodecylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (26): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.58 (s, 2 H, $PhCH_2O$), 4.03 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.6−3.7 (m, 4 H, $BnCH_2O$ and CH_2OH), 2.84 (m, 2 H, H-4), 2.16 (q, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 18 H, $(CH_2)_9$).

5-(Benzyloxy)methyl-3-[(*Z*)-12-hydroxydodecylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (27): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.81 (s, 4 H, Ar), 6.17 (m, 1 H, >C=CH), 4.58 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.01 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.6−3.7 (m, 4 H, $BnCH_2O$ and CH_2OH), 2.90 (m, 2 H, H-4), 2.72 (m, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 18 H, $(CH_2)_9$).

5-(Benzyloxy)methyl-3-[(*E*)-16-hydroxyhexadecylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (28): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.59 (s, 2 H, $PhCH_2O$), 4.03 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.6−3.7 (m, 4 H, $BnCH_2O$ and CH_2OH), 2.84 (m, 2 H, H-4), 2.16 (q, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 26 H, $(CH_2)_{13}$).

5-(Benzyloxy)methyl-3-[(*Z*)-16-hydroxyhexadecylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (29): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.81 (s, 4 H, Ar), 6.20 (m, 1 H, >C=CH), 4.58 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.01 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.6−3.7 (m, 4 H, $BnCH_2O$ and CH_2OH), 2.90 (m, 2 H, H-4), 2.72 (m, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 26 H, $(CH_2)_{13}$).

5-(Benzyloxy)methyl-3-[(*E*)-20-hydroxyeicosylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (30): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.59 (s, 2 H, $PhCH_2O$), 4.03 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.6−3.7 (m, 4 H, $BnCH_2O$ and CH_2OH), 2.84 (m, 2 H, H-4), 2.16 (q, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 34 H, $(CH_2)_{17}$).

5-(Benzyloxy)methyl-3-[(*Z*)-20-hydroxyeicosylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (31): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.81 (s, 4 H, Ar), 6.20 (m, 1 H, >C=CH), 4.58 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.01 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.6−3.7 (m, 4 H, $BnCH_2O$ and CH_2OH), 2.90 (m, 2 H, H-4), 2.72 (m, 2 H, >C=CH−CH_2), 1.2−1.65 (m, 34 H, $(CH_2)_{17}$).

General Procedure for the Synthesis of 32−38. A solution of **25**−**31** (0.5 mmol) in DMF (4 mL) was treated with pyridinium dichromate (1.13 g, 3.0 mmol) and stirred for 24 h at room temperature. The mixture was diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:1) as eluant to afford **32**−**38** as colorless oils in 80−88% yield.

5-(Benzyloxy)methyl-3-[(*E*)-8-carboxyheptylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (32): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.58 (s, 2 H, $PhCH_2O$), 4.03 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.67 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 2.84 (m, 2 H, H-4), 2.27 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 2.14 (q, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 8 H, $(CH_2)_4$).

5-(Benzyloxy)methyl-3-[(*E*)-12-carboxyundecylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (33): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.58 (s, 2 H, $PhCH_2O$), 4.03 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.67 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 2.84 (m, 2 H, H-4), 2.27 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 2.14 (q, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 16 H, $(CH_2)_8$).

5-(Benzyloxy)methyl-3-[(*Z*)-12-carboxyundecylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (34): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.80 (s, 4 H, Ar), 6.20 (m, 1 H, >C=CH), 4.58 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.01 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.75 (s, 3 H, OCH_3), 3.66 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 2.90 (m, 2 H, H-4), 2.71 (m, 2 H, >C=CH−CH_2), 2.33 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 1.25−1.7 (m, 16 H, $(CH_2)_8$).

5-(Benzyloxy)methyl-3-[(*E*)-16-carboxypentadecylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (35): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.58 (s, 2 H, $PhCH_2O$), 4.02 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.67 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 2.84 (m, 2 H, H-4), 2.34 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 2.14 (q, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 24 H, $(CH_2)_{12}$).

5-(Benzyloxy)methyl-3-[(*Z*)-16-carboxypentadecylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (36): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.80 (s, 4 H, Ar), 6.20 (m, 1 H, >C=CH), 4.59 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.01 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.66 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 2.90 (m, 2 H, H-4), 2.72 (m, 2 H, >C=CH−CH_2), 2.34 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 1.25−1.7 (m, 24 H, $(CH_2)_{12}$).

5-(Benzyloxy)methyl-3-[(*E*)-20-carboxynonadecylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (37): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.80 (s, 4 H, Ar), 6.75 (m, 1 H, >C=CH), 4.58 (s, 2 H, $PhCH_2O$), 4.03 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.67 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 2.84 (m, 2 H, H-4), 2.34 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 2.16 (q, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 32 H, $(CH_2)_{16}$).

5-(Benzyloxy)methyl-3-[(*Z*)-20-carboxynonadecylidene]-5-(4-methoxyphenoxy)methyltetrahydro-2-furanone (38): ^{1}H NMR ($CDCl_3$) δ 7.2−7.35 (m, 5 H, phenyl), 6.81 (s, 4 H, Ar), 6.20 (m, 1 H, >C=CH), 4.59 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.01 (AB q, 2 H, J = 9.7 Hz, CH_2Ar), 3.76 (s, 3 H, OCH_3), 3.66 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 2.90 (m, 2 H, H-4), 2.72 (m, 2 H, >C=CH−CH_2), 2.35 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 1.25−1.7 (m, 32 H, $(CH_2)_{16}$).

General Procedure for the Synthesis of 39−45. A solution of **32−38** (0.4 mmol) in CH_3CN/H_2O (4:1, 5 mL) was cooled to 0 °C and treated with ammonium cerium(IV) nitrate (438 mg, 0.8 mmol). After being stirred for 30 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with only EtOAc as eluant to afford **39−45** as colorless oils in 75−82% yield.

5-(Benzyloxy)methyl-3-[(*E*)-8-carboxyheptylidene]-5-hyroxymethyltetrahydro-2-furanone (39): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.69 (m, 1 H, >C=CH), 4.55 (s, 2 H, $PhCH_2O$), 3.72 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.56 (AB q, 2 H, J = 10.2 Hz, CH_2OH), 2.75 (m, 2 H, H-4), 2.30 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 2.14 (q, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 8 H, $(CH_2)_4$).

5-(Benzyloxy)methyl-3-[(*E*)-12-carboxyundecylidene]-5-hydroxymethyltetrahydro-2-furanone (40): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.73 (m, 1 H, >C=CH), 4.56 (s, 2 H, $PhCH_2O$), 3.72 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.58 (AB q, 2 H, J = 10.2 Hz, CH_2OH), 2.74 (m, 2 H, H-4), 2.34 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 2.15 (q, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 16 H, $(CH_2)_8$).

5-(Benzyloxy)methyl-3-[(*Z*)-12-carboxyundecylidene]-5-hydroxymethyltetrahydro-2-furanone (41): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.20 (m, 1 H, >C=CH), 4.56 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 3.70 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.56 (AB q, 2 H, J = 10.2 Hz, CH_2OH), 2.80 (m, 2 H, H-4), 2.68 (m, 2 H, >C=CH−CH_2), 2.33 (t, 2 H, J = 7.3 Hz, CH_2CO_2H), 1.2−1.7 (m, 16 H, $(CH_2)_8$).

5-(Benzyloxy)methyl-3-[(*E*)-16-carboxypentadecylidene]-5-hydroxymethyltetrahydro-2-furanone (42): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.74 (m, 1 H, >C=CH), 4.58 (s, 2 H, $PhCH_2O$), 3.72 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.58 (AB q, 2 H, CH_2OH), 2.74 (m, 2 H, H-4), 2.33 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 2.15 (q, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 24 H, $(CH_2)_{12}$).

5-(Benzyloxy)methyl-3-[(*Z*)-16-carboxypentadecylidene]-5-hydroxymethyltetrahydro-2-furanone (43): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.20 (m, 1 H, >C=CH), 4.56 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 3.70 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.56 (AB q, 2 H, J = 10.2 Hz, CH_2OH), 2.81 (m, 2 H, H-4), 2.68 (m, 2 H, >C=CH−CH_2), 2.34 (t, 2 H, J = 7.3 Hz, CH_2CO_2H), 1.2−1.7 (m, 24 H, $(CH_2)_{12}$).

5-(Benzyloxy)methyl-3-[(*E*)-20-carboxynonadecylidene]-5-hydroxymethyltetrahydro-2-furanone (44): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.75 (m, 1 H, >C=CH), 4.56 (s, 2 H, $PhCH_2O$), 3.73 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.58 (AB q, 2 H, CH_2OH), 2.75 (m, 2 H, H-4), 2.34 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 2.15 (q, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 32 H, $(CH_2)_{16}$).

5-(Benzyloxy)methyl-3-[(*Z*)-20-carboxynonadecylidene]-5-hydroxymethyltetrahydro-2-furanone (45): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.20 (m, 1 H, >C=CH), 4.56 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 3.71 (AB q, 2 H, J = 10.2 Hz, $BnCH_2O$), 3.57 (AB q, 2 H, J = 10.2 Hz, CH_2OH), 2.81 (m, 2 H, H-4), 2.69 (m, 2 H, >C=CH−CH_2), 2.35 (t, 2 H, J = 7.3 Hz, CH_2CO_2H), 1.2−1.7 (m, 32 H, $(CH_2)_{16}$).

General Procedure for the Synthesis of 46−52. To a stirred suspension of 4-(dimethylamino)pyridine (183 mg, 1.5 mmol), 4-(dimethylamino)pyridine hydrochloride (237 mg, 1.5 mmol), and dicyclohexylcarbodiimide (1 M, 1.5 mL, 1.5 mmol) in refluxing CH_2Cl_2 (30 mL) was added dropwise a solution of **39−45** (0.3 mmol) in CH_2Cl_2 (5 mL) via syringe pump. After being refluxed for 16 h, the reaction mixture was cooled and quenched with methanol (2 mL) and acetic acid (0.2 mL). The mixture was rapidly stirred at room temperature and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:10) as eluant to afford **46−52** as colorless oils in 60−70% yield.

1-(Benzyloxy)methyl-3,14-dioxabicyclo[10.2.1]pentadec-11(*E*)-ene-4,13-dione (46): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.55 (m, 1 H, >C=CH), 4.98 (d, 1 H, J = 12.2 Hz, $OCOCH_2$), 4.55 (AB q, 2 H, J = 12 Hz, $PhCH_2O$), 3.88 (d, 1 H, J = 12.2 Hz, $OCOCH_2$), 3.60 (s, 2 H, $BnCH_2O$), 2.70 (m, 2 H, H-4), 2.28 (t, 2 H, J = 7.5 Hz, CH_2CO_2), 2.15 (m, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 8 H, $(CH_2)_4$).

1-(Benzyloxy)methyl-3,18-dioxabicyclo[14.2.1]nonadec-15(*E*)-ene-4,17-dione (47): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.75 (m, 1 H, >C=CH), 4.58 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.24 (s, 2 H, $OCOCH_2$), 3.55 (s, 2 H, $BnCH_2O$), 2.80 (m, 2 H, H-4), 2.28 (t, 2 H, J = 7.5 Hz, CH_2CO_2), 2.15 (m, 2 H, >C=CH−CH_2), 1.2−1.7 (m, 16 H, $(CH_2)_8$).

1-(Benzyloxy)methyl-3,18-dioxabicyclo[14.2.1]nonadec-15(*Z*)-ene-4,17-dione (48): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.24 (m, 1 H, >C=CH), 4.57 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.25 (AB q, 2 H, $OCOCH_2$), 3.53 (AB q, 2 H, J = 10 Hz, $BnCH_2O$), 2.8−3.0 (m, 3 H, H-4 and >C=CH−CH_2), 2.2−2.4 (m, 3 H, CH_2CO_2 and >C=CH−CH_2), 1.2−1.7 (m, 16 H, $(CH_2)_8$).

1-(Benzyloxy)methyl-3,22-dioxabicyclo[18.2.1]trieicos-19(*E*)-ene-4,21-dione (49): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.74 (m, 1 H, >C=CH), 4.58 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.25 (AB q, 2 H, J = 12 Hz, $OCOCH_2$), 3.56 (s, 2 H, $BnCH_2O$), 2.78 (m, 2 H, H-4), 2.28 (t, 2 H, J = 7.5 Hz, CH_2CO_2), 2.15 (m, 2 H, >C=CH−CH_2), 1.2−1.7 (m, 24 H, $(CH_2)_{12}$).

1-(Benzyloxy)methyl-3,22-dioxabicyclo[18.2.1]trieicos-19(*Z*)-ene-4,21-dione (50): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.20 (m, 1 H, >C=CH), 4.57 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.25 (s, 2 H, $OCOCH_2$), 3.53 (AB q, 2 H, J = 10 Hz, $BnCH_2O$), 3.12 (m, 1 H, >C=CH−CH_2), 2.80 (m, 2 H, H-4), 2.2−2.4 (m, 3 H, CH_2CO_2 and >C=CH−CH_2), 1.2−1.7 (m, 24 H, $(CH_2)_{12}$).

1-(Benzyloxy)methyl-3,26-dioxabicyclo[22.2.1]heptaeicos-23(*E*)-ene-4,25-dione (51): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.73 (m, 1 H, >C=CH), 4.58 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.25 (AB q, 2 H, J = 12 Hz, $OCOCH_2$), 3.56 (s, 2 H, $BnCH_2O$), 2.76 (m, 2 H, H-4), 2.28 (t, 2 H, J = 7.5 Hz, CH_2CO_2), 2.16 (m, 2 H, >C=CH−CH_2), 1.2−1.7 (m, 32 H, $(CH_2)_{16}$).

1-(Benzyloxy)methyl-3,26-dioxabicyclo[22.2.1]heptaeicos-23(*Z*)-ene-4,25-dione (52): ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.19 (m, 1 H, >C=CH), 4.57 (AB q, 2 H, J = 12.2 Hz, $PhCH_2O$), 4.25 (s, 2 H, $OCOCH_2$), 3.54 (AB q, 2 H, J = 10 Hz, $BnCH_2O$), 2.95 (m, 1 H, >C=CH−CH_2), 2.82 (m, 2 H, H-4), 2.48 (m, 1 H, >C=CH−CH_2), 2.29 (m, 3 H, J = 7.3 Hz, CH_2CO_2), 1.2−1.7 (m, 32 H, $(CH_2)_{16}$).

General Procedure for the Synthesis of 53−59. A stirred solution of **46−52** (0.2 mmol) in CH_2Cl_2 (4 mL) was cooled to −78 °C and treated dropwise with boron trichloride (1 M, 0.6 mL, 0.6 mmol). After being stirred for 2 h at − 78 °C, the reaction mixture was quenched with the addition of saturated $NaHCO_3$ solution and immediately partitioned between ether and $NaHCO_3$ solution. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:1) as eluant to afford **53−59** as colorless oils in 80−92% yield.

1-Hydroxymethyl-3,14-dioxabicyclo[10.2.1]pentadec-11(*E*)-ene-4,13-dione (53): ^{1}H NMR ($CDCl_3$) δ 6.58 (m, 1 H, >C=CH), 4.92 (d, 1 H, J = 12.2 Hz, $OCOCH_2$), 3.90 (d, 1 H, J = 12.2 Hz, $OCOCH_2$), 3.75 (AB q, 2 H, J = 12.5 Hz, CH_2OH), 2.70 (m, 2 H, H-4), 2.30 (t, 2 H, J = 7.5 Hz, CH_2CO_2), 2.15 (m, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 8 H, $(CH_2)_4$); IR (neat) 3445, 1732, 1682 cm^{-1}; MS (FAB) m/z 269 (MH^+). Anal. ($C_{14}H_{20}O_5$) C, H.

1-Hydroxymethyl-3,18-dioxabicyclo[14.2.1]nonadec-15(*E*)-ene-4,17-dione (54): ^{1}H NMR ($CDCl_3$) δ 6.78 (m, 1 H, >C=CH), 4.22 (AB q, 2 H, J = 11.8 Hz, $OCOCH_2$), 3.72 (AB q,

2 H, J = 12.4 Hz, CH_2OH), 2.79 (m, 2 H, H-4), 2.31 (t, 2 H, J = 7.5 Hz, CH_2CO_2), 2.15 (m, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 16 H, $(CH_2)_8$); IR (neat) 3441, 1743, 1679 cm^{-1}; MS (FAB) m/z 325 (MH^+). Anal. ($C_{18}H_{28}O_5$) C, H.

1-Hydroxymethyl-3,18-dioxabicyclo[14.2.1]nonadec-15(*Z*)-ene-4,17-dione (55): ^{1}H NMR ($CDCl_3$) δ 6.24 (m, 1 H, >C=CH), 4.24 (dt, 2 H, J = 11.9 Hz, $OCOCH_2$), 3.67 (m, 2 H, CH_2OH), 3.08 (m, 1 H, >C=CH−CH_2), 2.82 (m, 2 H, H-4), 2.25−2.45 (m, 3 H, CH_2CO_2 and >C=CH−CH_2), 1.2−1.7 (m, 16 H, $(CH_2)_8$); IR (neat) 3443, 1746, 1679 cm^{-1}; MS (FAB) m/z 325 (MH^+). Anal. ($C_{18}H_{28}O_5$) C, H.

1-Hydroxymethyl-3,22-dioxabicyclo[18.2.1]trieicos-19-(*E*)-ene-4,21-dione (56): ^{1}H NMR ($CDCl_3$) δ 6.76 (m, 1 H, >C=CH), 4.24 (AB q, 2 H, J = 11.8 Hz, $OCOCH_2$), 3.70 (AB q, 2 H, J = 12.2 Hz, CH_2OH), 2.76 (m, 2 H, H-4), 2.31 (t, 2 H, J = 7.5 Hz, CH_2CO_2), 2.15 (m, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 24 H, $(CH_2)_{12}$); IR (neat) 3445, 1747, 1683 cm^{-1}; MS (FAB) m/z 381 (MH^+). Anal. ($C_{22}H_{36}O_5$) C, H.

1-Hydroxymethyl-3,22-dioxabicyclo[18.2.1]trieicos-19-(*Z*)-ene-4,21-dione (57): ^{1}H NMR ($CDCl_3$) δ 6.24 (m, 1 H, >C=CH), 4.24 (dt, 2 H, J = 11.9 Hz, $OCOCH_2$), 3.67 (m, 2 H, CH_2OH), 3.08 (m, 1 H, >C=CH−CH_2), 2.82 (m, 2 H, H-4), 2.25−2.45 (m, 3 H, CH_2CO_2 and >C=CH−CH_2), 1.2−1.7 (m, 24 H, $(CH_2)_{12}$); IR (neat) 3445, 1748, 1683 cm^{-1}; MS (FAB) m/z 381 (MH^+). Anal. ($C_{22}H_{36}O_5$) C, H.

1-Hydroxymethyl-3,26-dioxabicyclo[22.2.1]heptaeicos-23(*E*)-ene-4,25-dione (58): ^{1}H NMR ($CDCl_3$) δ 6.76 (m, 1 H, >C=CH), 4.24 (AB q, 2 H, J = 11.8 Hz, $OCOCH_2$), 3.70 (AB q, 2 H, J = 12.2 Hz, CH_2OH), 2.75 (m, 2 H, H-4), 2.32 (t, 2 H, J = 7.5 Hz, CH_2CO_2), 2.17 (m, 2 H, >C=CH−CH_2), 1.25−1.7 (m, 32 H, $(CH_2)_{16}$); IR (neat) 3446, 1741, 1683 cm^{-1}; MS m/z 437 (MH^+). Anal. ($C_{26}H_{44}O_5$) C, H.

1-Hydroxymethyl-3,26-dioxabicyclo[22.2.1]heptaeicos-23(*Z*)-ene-4,25-dione (59): ^{1}H NMR ($CDCl_3$) δ 6.23 (m, 1 H, >C=CH), 4.22 (AB q, 2 H, J = 12 Hz, $OCOCH_2$), 3.66 (AB q, 2 H, J = 11.8 Hz, CH_2OH), 3.08 (m, 1 H, >C=CH−CH_2), 2.82 (m, 2 H, H-4), 2.53 (m, 1 H, >C=CH−CH_2), 2.29 (m, 3 H, J = 7.3 Hz, CH_2CO_2), 1.2−1.7 (m, 32 H, $(CH_2)_{16}$); IR (neat) 3446, 1741, 1683 cm^{-1}; MS (FAB) m/z 437 (MH^+). Anal. ($C_{26}H_{44}O_5$) C, H.

Molecular Modeling. The structures of compounds **6** and **57** were built using the Sybyl molecular modeling program (Tripos, Inc.), and then the geometry was fully optimized using the Tripos force field with the following nondefault options: (method) conjugate gradient; (termination) gradient 0.01 kcal mol^{-1} $Å^{-1}$; (max iterations) 10,000. The partial atomic charges were calculated by the Gasteiger−Hückel method in the Sybyl program. The theoretical structure of the C1b domain of PKCα, which was constructed through homology modeling by Marquez and colleagues,[19] was used in the docking study. Only polar hydrogens were added, and then the Kollman united-atom partial atomic charges were assigned to the macromolecule. Each compound was docked into the C1b domain of PKCα using the program Autodock 3.0 with 100 genetic algorithm (GA) runs. The long alkyl chain ($-C_{13}H_{27}$) of compound **6** was shortened to three methylene groups ($-C_3H_7$) in order to reduced the number of degrees of freedom during docking simulation. The torsions of each compound were defined to fully consider conformational flexibility while the C1b domain of PKCα remained rigid. All computational work was done on a Silicon Graphics O_2 R10000 workstation.

Acknowledgment. This work was supported by Korea Research Foundation Grant KRF-2003-015-E00229.

Supporting Information Available: Elemental analysis data for final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM0497747