Protein Kinase C Ligands Based on Tetrahydrofuran Templates Containing a New Set of Phorbol Ester Pharmacophores

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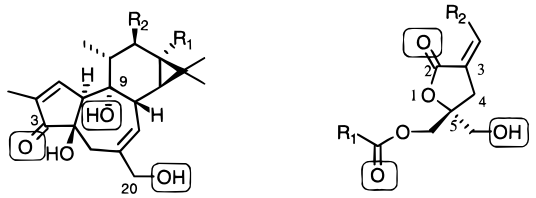
Received December 18, 1998

A series of substituted tetrahydrofurans with an embedded glycerol backbone carrying additional tetrahydrofuranylideneacetate or tetrahydrofuranylacetate motifs were grouped into four distinct templates (I−IV) according to stereochemistry. The compounds were designed to mimic three essential pharmacophores (C_3−C═O, C_{20}−OH and C_{13}−C═O) of the phorbol esters according to a new, revised model. The tetrahydrofuran ring was constructed from glycidyl 4-methoxyphenyl ether, and the structures of the isomeric templates were assigned by NMR spectroscopy, including NOE. The binding affinity for protein kinase C (PKC) was assessed in terms of the ability of the ligands to displace bound [^{3}H-20]phorbol 12,13-dibutyrate (PDBU) from a recombinant α isozyme of PKC. Geometric *Z*- and *E*-isomers (**1** and **3**, respectively) containing a tetrahydrofuranylideneacetate motif were the most potent ligands with identical K_i values of 0.35 μM. Molecular modeling studies of the four templates showed that the rms values when fitted to a prototypical phorbol 12,13-diacetate ester correlated inversely with affinities in the following order: I ≈ II > III > IV. These compounds represent the first generation of rigid glycerol templates seeking to mimic the binding of the C_{13}−C═O of the phorbol esters. The binding affinities of the most potent compounds are in the same range of the diacylglycerols (DAGs) despite the lack of a phorbol ester C_9−OH pharmacophore surrogate. This finding confirms that mimicking the binding of the C_{13}−C═O pharmacophore of phorbol is a useful strategy. However, since the C_9−OH and C_{13}−C═O in the phorbol esters appear to form an intramolecular hydrogen bond that functions as a combined pharmacophore, it is possible the lack of this combined motif in the target templates restricts the compounds from reaching higher binding affinities.

Introduction

Protein kinase C (PKC) represents a family of phospholipid-dependent, serine/threonine-specific protein kinases comprising 12 isozymes. These isozymes are believed to play important roles in cellular signal transduction pathways involved in cellular processes such as cell differentiation, proliferation, modulation of gene expression, and multiple-drug resistance (MDR).[1−5] Most PKC isozymes are activated endogenously by diacylglycerol (DAG) released from the receptor-activated hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) or from phosphatidylcholine (PC) hydrolysis.[6,7] PKC is also activated directly by several natural product tumor-promoting agents such as the phorbol esters.[8] The binding site of these ligands on PKC has been identified as a tandem repeat of two cysteine-rich zinc-finger motifs, so-called C1a and C1b, present in the regulatory C1 domain of the enzyme.[9] In general, the phorbol esters display binding affinities that are several orders of magnitude greater than those of the DAGs. This exceptional affinity can be explained in part by the relative conformational rigidity of the phorbol esters which confers on the molecule an entropic advantage during binding.

Chart 1



Phorbol Ester **Lactone Template**

Over the past few years, we have synthesized a series of conformationally constrained DAG analogues embedded in a variety of lactone templates designed to reduce part of the entropic penalty associated with the binding of the flexible glycerol backbone of DAG.[10−32] We have reported the benefits of this strategy which have culminated with a series of "ultrapotent" DAG analogues built on a 5-[(acyloxy)methyl]-5-(hydroxymethyl)-tetrahydro-2-furanone template. Depending on the type of hydrophobic substitution, some of the compounds built with this template displayed ca. 100-fold greater affinity for PKC-α than the equivalent DAGs (Chart 1).[24−26] A comprehensive molecular modeling study of this template in comparison to the phorbol esters indicated that the two C═O groups (acyloxy and lactone)

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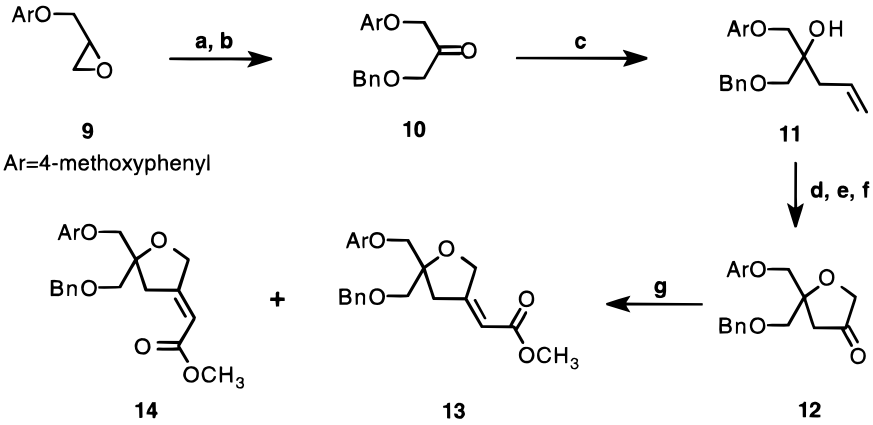
10.1021/jm980713g CCC: $18.00
Published on Web 09/16/1999

Scheme 1[a]



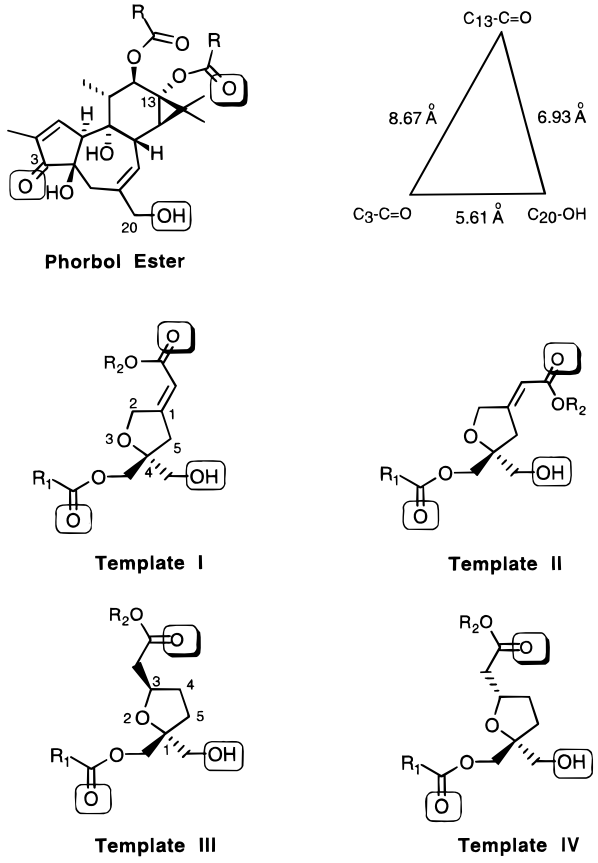
[a] Reagents and conditions: (a) BnOH, NaH, DMF, 80 °C; (b) PCC, 4 Å molecular sieve, CH_2Cl_2; (c) $CH_2{=}CHCH_2MgCl$, THF; (d) OsO_4, 4-NMO, acetone−H_2O, rt; (e) TsCl, pyridine; (f) PCC, molecular sieve, CH_2Cl_2; (g) $(MeO)_2P(=O)CH_2CO_2Me$, *t*-BuOK, THF, reflux.

and the primary OH overlapped almost perfectly with the C_3−C═O, C_{20}−OH, and C_9−OH of the diterpene.[25] This result supported a previous pharmacophore model in which the combined interaction of these three groups was considered essential for the strong binding of phorbol esters.[33−35] Other pharmacophore models emphasizing the importance of the adjacent C_4−OH group have been proposed.[36−38]

Recently, a new pharmacophore model was proposed by Hecker et al. who provided evidence in support of the importance of the C_{13}−C═O of the phorbol esters for irritant and tumor-promoting potency in mouse skin.[39] Similarly, the group of Shibasaki demonstrated indirectly the importance of the C_{13}−C═O with phorbol ester analogues lacking this functionality.[40] In a more direct fashion, photo-cross-linking experiments of a phorbol ester with a diazoacetyl group at C_{13} suggested that this group was indeed located in close proximity to the protein in the ligand−enzyme−phospholipid complex.[40] The Blumberg group also reported that the removal of the acyl group at C_{13} caused a significant drop in binding affinity when comparing phorbol 12- and 13-monoesters.[41]

In our continuing effort to design conformationally constrained DAG analogues as potent PKC ligands able to compete efficiently with phorbol esters, we set out to investigate simple substituted tetrahydrofuran templates with an embedded glycerol backbone carrying an additional surrogate pharmacophore for the C_{13}−C═O of the phorbol esters. The four prototypes (templates I−IV) proposed were designed to retain the putative recognition domain of the phorbol ester: namely, the C_3−C═O and C_{20}−OH (Chart 2). Since from our previous work the C═O of the (acyloxy)methyl group and primary OH group of the potent lactone template overlaid nicely with the C_3−C═O and C_{20}−OH groups, respectively, these groups were retained. In the new templates I−IV the lactone C═O was removed and C═O groups at different positions were investigated as surrogate pharmacophores of the C_{13}−C═O of the phorbol esters. The position of the C_{13} ester-mimicking carbonyl in templates I−IV was derived from the spatial orientation of the C_{13}−C═O of phorbol 12,13-diacetate described in Hecker's molecular model (Chart 2). As in other conformationally constrained glycerol analogues, short and long alkyl chains were combined to optimize

Chart 2

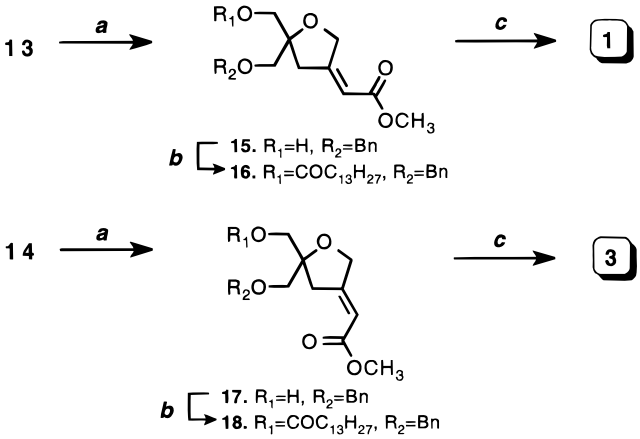


hydrophobic interactions at different ends of the template. The syntheses, binding affinities, and limited structure−activity relationship (SAR) analysis of the newly designed templates are reported herein.

Chemistry

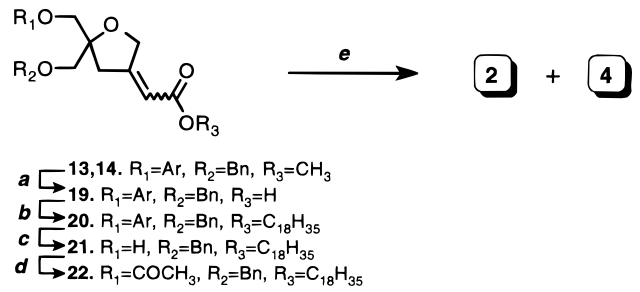
The key intermediate for the synthesis of targets **1**−**4** (Table 1) was compound **12**. This was prepared as shown in Scheme 1 from glycidyl 4-methoxyphenyl ether (**9**) in six steps that involved a 1,5-intramolecular cyclization and oxidation as penultimate and ultimate steps. Reaction of **12** with trimethyl phosphonoacetate provided both *E*- and *Z*-isomers which were separated with difficulty by column chromatography due to their close

Scheme 2[a]



[a] Reagents and conditions: (a) CAN, CH_3CN-H_2O; (b) $C_{13}H_{27}COCl$, NEt_3, DMAP, CH_2Cl_2; (c) BCl_3, CH_2Cl_2, −78 °C.

Scheme 3[a]



[a] Reagents and conditions: (a) LiOH, THF, H_2O; (b) $C_{18}H_{35}OH$, DCC, DMAP, CH_2Cl_2; (c) CAN, CH_3CN-H_2O; (d) Ac_2O, NEt_3, DMAP, CH_2Cl_2; (e) BCl_3, CH_2Cl_2, −78 °C.

R_f values. The geometric assignment of *E*/*Z*-isomers was based on the relative differences in chemical shift in H-2 and H-4 of the tetrahydrofuran ring. In each case, the chemical shift of the ring methylene closest to the carbonyl appeared downfield [**13** (*Z*-isomer) $\delta_{H-2} = 4.95$, $\delta_{H-5} = 2.86$; **14** (*E*-isomer) $\delta_{H-2} = 4.65$, $\delta_{H-5} = 3.17$].

Since initial syntheses of **1** and **3** directly from a mixture of **13** and **14** were unsuccessful due to the intractable separation of isomers at the final stage, the target compounds **1** and **3** were synthesized from pure samples of **13** and **14** after deprotection of the 4-methoxyphenyl group, acylation, and debenzylation (Scheme 2). For targets **2** and **4**, a mixture of **13** and **14** was used directly because the final compounds were readily separated by column chromatography (Scheme 3). As before, the structures of **2** and **4** were also assigned based on relative chemical shift differences between H-2 and H-5.

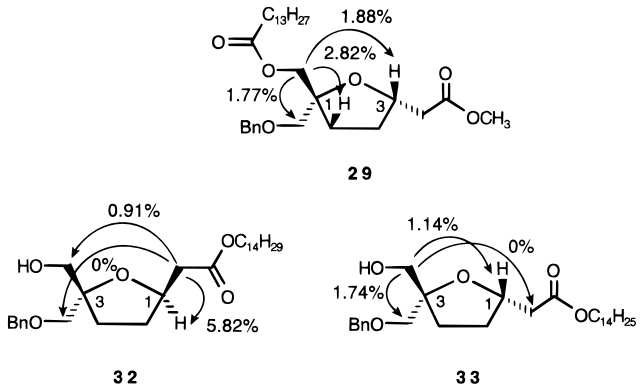
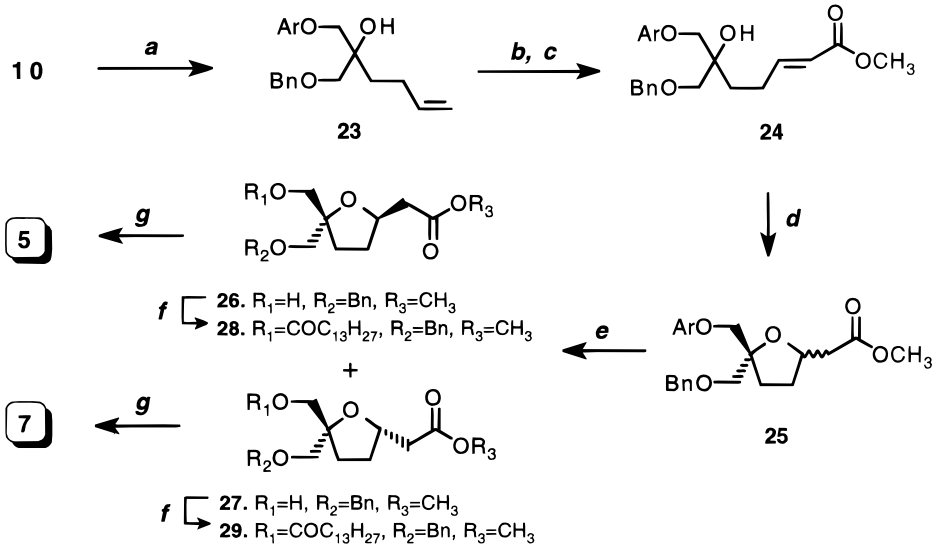


Figure 1. NOEs of compounds **29**, **32**, and **33**.

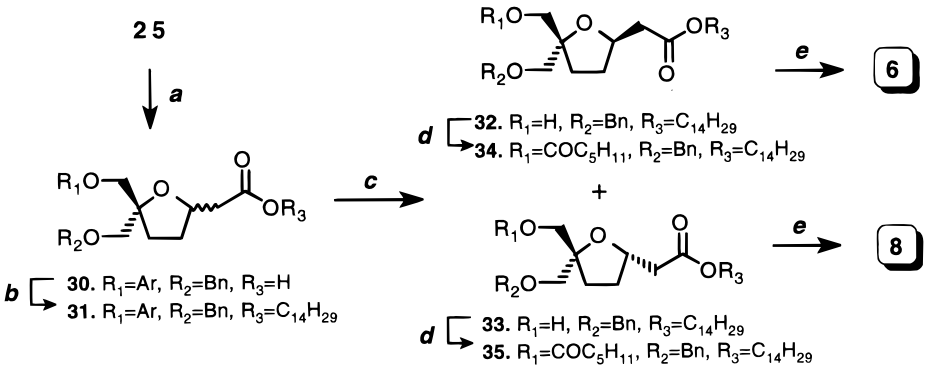
For the synthesis of targets **5**−**8** (Table 1), the key intermediate **25** was prepared by an intramolecular Michael-type reaction from α,β-unsaturated ester **24** which was obtained from ketone **10** in three steps (Scheme 4). Even though at the stage of **25** resolution of the two isomers was impossible, separation of isomers was possible by column chromatography at the stage of **26** and **27** after removal of the *p*-methoxyphenyl group. Acylation followed by debenzylation of each isomer produced the final target compounds **5** and **7**. The structures of the final compounds were assigned based on the results from NOE experiments performed at the stage of compound **29** (Figure 1). Compound **29** was ideal because it showed distinct chemical shifts for H-3 of the tetrahydrofuran ring and the 1′- and 1″-methyl-

Scheme 4[a]



[a] Reagents and conditions: (a) $CH_2{=}CHCH_2CH_2Br$, Mg, dibromoethane, THF; (b) OsO_4, 4-NMO, $NaIO_4$, acetone−H_2O; (c) $Ph_3P{=}CHCO_2CH_3$, toluene, reflux; (d) Bu_4NF, THF; (e) CAN, CH_3CN-H_2O; (f) $C_{13}H_{27}COCl$, NEt_3, DMAP, CH_2Cl_2; (g) H_2, Pd−C, EtOAc.

Scheme 5[a]



[a] Reagents and conditions: (a) LiOH, THF, H_2O; (b) $C_{14}H_{29}OH$, DCC, DMAP, CH_2Cl_2; (c) CAN, CH_3CN-H_2O; (d) $C_5H_{11}COCl$, NEt_3, DMAP, CH_2Cl_2; (e) H_2, Pd−C, EtOAc.

ene groups located above and below the plane of the five-membered ring.

For the synthesis of **6** and **8**, the methyl ester of **25** was exchanged by a tetradecyl group in two steps (Scheme 5). Following deprotection of the 4-methoxyphenyl group of **31**, the two isomers **32** and **33** were separated and their structures assigned by NOE (Figure 1). Acylation of each isomer was performed with hexanoyl chloride instead of acetyl chloride to avoid possible acyl migration which would have caused epimerization at C-5. Removal of the benzyl group afforded the desired final compounds **6** and **8** without signs of acyl migration.

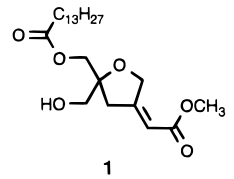
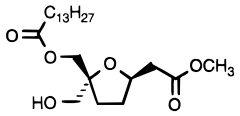
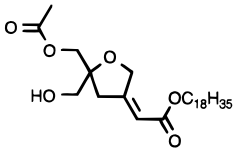
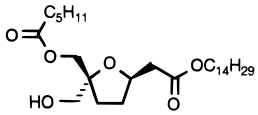
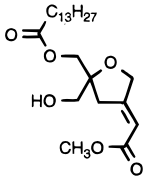
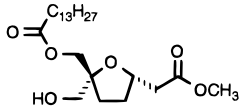
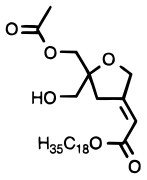
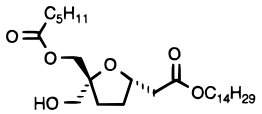
Results and Discussion

The binding affinities of the target compounds **1**−**8** (Table 1) were assessed in terms of their ability to displace bound [^{3}H-20]phorbol 12,13-dibutyrate (PDBU) from a single recombinant PKC-α.[10] The ID_{50} values (concentration yielding 50% inhibition of [^{3}H]PDBU binding) were determined by fit of the data points to the equation for noncooperative competition. The K_i values for inhibition of binding were calculated from the ID_{50} values. With this preliminary assay, one can compare the efficiency of the new templates (I−IV) relative to 14 previously synthesized templates[10−32] before pursuing further biological evaluation on the most promising compounds. Therefore, the results of this work (Table 1) must be viewed in the context of a larger universe that includes all the previous templates investigated, but with particular reference to the most potent lactone template shown in Chart 1. Relative to this potent template, two of the critical recognition elements of the template were left intact and only the position of the third pharmacophore was changed to a limited range of distances from the ring to best match the C_{13} carbonyl of phorbol (Chart 2). To complement the strategy alkyl chains of suitable length were appended at opposite sites of the templates in order to steer these molecules into the lipid milieu in two possible orientations. This strategy has proven successful with previous templates, and the present work represents an extension of this approach. From our previous studies, we have also learned that these molecules required a critical lipophilic character to be active and to partition appropriately into the membrane.[18] We have determined that for this purpose the required alkyl chains have to be between 13 and 18 carbons long,[18] which puts limits on the number of compounds that one can generate. Hence, for target compounds **1**−**4**, alkyl chains of 13 and18 carbons were studied (Table 1). In the case of target compounds **5**−**8**, however, a smaller 5-carbon acyl chain was required at one end of the molecule to avoid the racemization that is normally observed when acetyl groups are used. Such a change demanded the use of a reduced size alkyl chain at the other end of the molecule to approximate closely the lipophilicity provided by an 18-carbon chain. Following our standard approach, the larger lipophilic groups were switched from one carbonyl group to the other.

Compounds **1** and **3** had basically the same binding affinity with a $K_i = 0.35\ \mu$M. This binding affinity was superior to that shown by the corresponding DAG analogue, *rac*-glycerol 1-myristate 2-acetate (GMA) with a reported K_i of 0.7 μM.[42] On the other hand, in compounds **2** and **4**, where the relative disposition of the hydrophobic chain was inverted relative to 1 and 3, the binding affinities were only comparable to that of GMA. Compounds **5**−**8** were significantly less potent than GMA but showed modest discrimination between cis and trans isomers.

From the standpoint of ligands having equivalent lipophilic parameters to compare the effects of the different location of the ester side chains, compounds **1**, **3**, **5**, and **7** were selected for a structural analysis. These compounds differed in terms of the spatial disposition of the C═O group that was designed to mimic the $C_{13}-C{=}O$ ester of phorbol. Their relative binding affinities followed the order: **1** (template I) ≈ **3** (template II) > **5** (template III) > **7** (template IV). Correlating their biological potency with the spatial orientations of this critical ester group was examined by molecular modeling. Compounds **1**, **3**, **5**, and **7** were selected as representatives of each of the different templates. Molecular modeling was performed using the program Sybyl 6.4 from Tripos. The lowest energy conformers obtained after a full conformational search are shown in Figures 2 and 3. The internal distances between the carbonyls and hydroxyl pharmacophores are also depicted as forming a triangle. The three pharmacophores in each template were superimposed onto the $C_3-C{=}O$, $C_{20}-OH$, and $C_{13}-C{=}O$ of phorbol diacetate whose coordinates were derived from Hecker's study.[39] The resulting rms values relative to phorbol with ligands **1** and **3** (Figure 2) were very low: 0.002 for compound **1** and 0.009 for compound **3**. These

Table 1. Apparent K_i Values for Ligands **1**−**8** as Inhibitors of PDBU Binding to PKC-α

Template I	K_i (μM)	Template III	K_i (μM)
 **1**	0.35±0.011	 **5**	2.72±0.75
 **2**	0.85±0.097	 **6**	2.38±0.41
Template II	K_i (μM)	**Template IV**	K_i (μM)
 **3**	0.35±0.026	 **7**	10.80±0.3
 **4**	1.86±0.080	 **8**	12.78±1.73

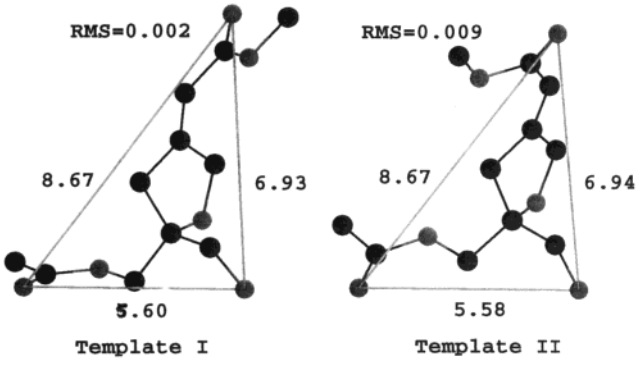


Figure 2. Lowest energy conformers of **1** (template I) and **3** (template II) and their rms values after fitting to phorbol 12,13-diacetate.

compounds showed a very similar triangular disposition of pharmacophores in both preferred geometrical orientations of the α,β-unsaturated esters which would explain why they have similar binding affinities. The higher rms values for **5** and **7** (0.603 and 1.34, respectively) are in keeping with their poorer binding affinities.

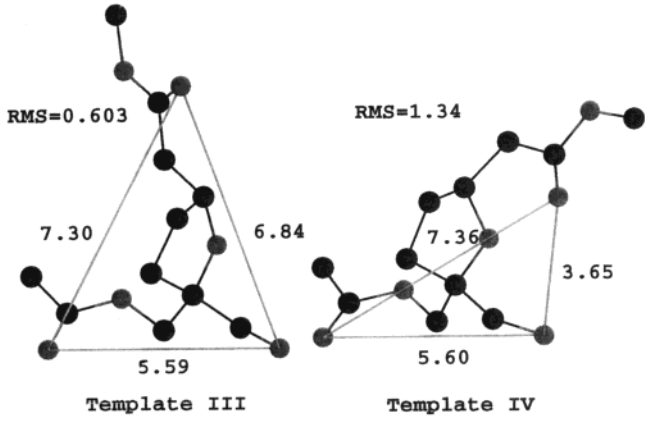


Figure 3. Lowest energy conformers of **5** (template III) and **7** (template IV) and their rms values after fitting to phorbol 12,13-diacetate.

A representative fitting between Z-isomer **1** and phorbol diacetate is shown in Figure 4. Although this figure shows a perfect superposition of the C_{13}−C═O and C═O ester mimic in **1**, the rest of the ester moieties do not match well and are disposed like mirror images

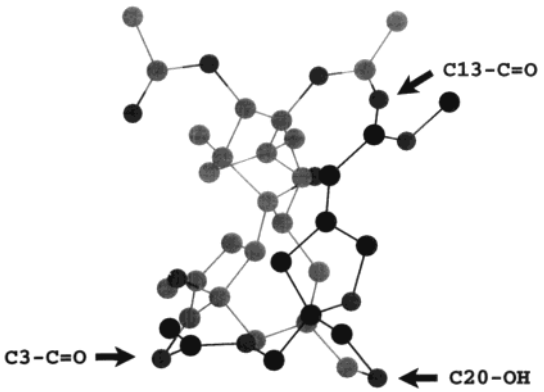


Figure 4. Superposition of **1** on phorbol 12,13-diacetate.

of each other. This may explain, in part, the difference in biological potency between the phorbol esters and **1**. The results obtained from molecular modeling agree with the biological data and confirmed the already established order of potency for templates I−IV (I ≈ II > III > IV). Equivalent template ligands to **1**, **3**, **5**, and **7** (**2**, **4**, **6**, and **8**) having long alkyl chains at alternative positions showed similar or slightly less binding affinities than the parent structures. The term relative potency among templates has to be taken with a word of caution. As already mentioned, most of these compounds have to be designed with a required lipophilic/hydrophilic balance, and hence they share a common affinity to localize into lipids. From our experience with other templates, we have learned that the majority of these templates generate rather modest ligands with similar binding affinities despite their structural diversity. Only with the best templates (Chart 1)[25,26] do the K_i values move to submicromolar and low-nanomolar values. The reason for such a phenomenon is that with these amphiphilic molecules there is always a nonspecific binding effect resulting from their presence in the lipid environment which produces a sort of "background" effect regardless of the structure of the template. It is only when the hydrophilic groups on the lactone template are additionally capable of fitting well into the binding site of PKC that a significant increase in binding affinity is observed. We can conclude that in the present study such a significant increase was not realized. Certainly in relation to our best reference template (Chart 1) binding affinity was diminished with the changes implemented. However, based on past record, templates I and II in the present paper fall into the category of better templates because of their submicromolar K_i's, whereas templates III and IV are in the category of poor templates. Indeed, ligands **1** and **3** showed better binding affinity than the structurally equivalent DAG analogue, although they are still about 10 times less potent than the equivalent lactone template (Chart 1, K_i = 35−77 nM) whose three hydrogen-bond-forming pharmacophores overlay the three classical phorbol pharmacophores shown in Chart 1 (C_3−C═O, C_{20}−OH, and C_9−OH).[24] This may lead to the conclusion that in terms of binding affinity to PKC, the C_{13}−C═O group is less critical than the C_9−OH group in phorbol ester binding. However, it may be difficult to separate the individual function of these two groups and evaluate their relative importance to binding, since in phorbols these groups are aligned very closely by intramolecular hydrogen bonding. Probably the presence of both groups may be necessary for high binding affinity. However, the observed differences in binding affinities of our four prototype templates suggest that indeed the C_{13}−C═O of phorbol is very likely involved in interacting with PKC at the same DAG binding site. Although the X-ray structure of the phorbol ester 13-acetate/C1b complex of PKC-δ showed that the C_{13}−C═O of phorbol was outside the binding pocket and formed no contact with the protein,[37b] the C_{13}−C═O has been shown to be crucial for bioactivity in recent SAR studies by Hecker and Shibasaki.[39,40] Additional molecular modeling studies and site-directed mutagenesis experiments also support the involvement of the C_{13}−C═O group in PKC binding.[43]

It is possible that the intramolecularly hydrogen-bonded C_9−OH/C_{13}−C═O motif in phorbol 13-*O*-acetate—the missing pharmacophore!—may be interacting at the membrane interface, and since the crystal structure of the phorbol 13-*O*-acetate/C1b complex does not contain lipid, this pharmacophore appears uninvolved. We might conclude from this work that future templates that contain all four pharmacophores (C_3−C═O, C_{20}−OH, C_9−OH, and C_{13}−C═O) would probably produce better ligands and help resolve the issue of the missing pharmacophore.

Experimental Section

General Experimental. 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 and carbon NMR spectra were recorded on a JEOL JNM-LA 300 at 300 MHz and JEOL JNM-GCX 400 at 100 MHz, respectively. Chemical shifts are reported in ppm units with Me_4Si as reference standard. Infrared spectra were recorded on a Perkin-Elmer 1710 series FTIR. Mass spectra were recorded on a VG Trio-2 GC−MS. Elemental analyses were performed with an EA 1110 automatic elemental analyzer, CE Instruments.

Analysis of Inhibition of [^{3}H-20]PDBU Binding by Nonradioactive Ligands. Enzyme−ligand interactions toward the single PKC isozyme (PKC-α) were analyzed by competition of [^{3}H-20]PDBU binding essentially as described in our previous work.[10] The ID_{50} values were determined from the competition curves, and the corresponding K_i values for the ligands were calculated from the ID_{50} values. Values represent the mean ± standard error (three experiments).

Molecular Modeling. The structures of the four templates were built and optimized using SYBYL 6.4, Tripos. All calculations including the conformational search were performed on a Silicon Graphics O_2 R10000 workstation. The structure of phorbol 12,13-diacetate was constructed based on a previous reference.[39]

1-(Benzyloxy)-3-(4-methoxyphenoxy)acetone (10). A solution of benzyl alcohol (8.6 mL, 83.2 mmol) in DMF (40 mL) was treated portionwise with NaH (60%, 3.33 g, 83.2 mmol) while maintained at 0 °C. After 30 min of stirring at room temperature, the mixture was treated with **9** (10 g, 55.5 mmol) portionwise. The reaction mixture was heated at 80 °C for 4 h and cooled to room temperature. The mixture was diluted with H_2O and extracted with EtOAc several times. The combined organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexane (1:2) as eluant to give the correponding alcohol as an oil (14.46 g, 90%): ^{1}H NMR ($CDCl_3$) δ 7.27−7.37 (m, 5 H, phenyl), 6.80−6.86 (m, 4 H, 4-methoxyphenyl), 4.58 (s, 2 H, $PhCH_2O$), 4.17 (m, 1 H, CHOH), 4.00 (dd of AB, 1 H, CH_2OAr, J = 4.8 and 10 Hz), 3.96 (dd of AB, 1 H, CH_2OAr, J = 6.0 and 10 Hz), 3.76 (s,

3 H, OCH_3), 3.67 (dd of AB, 1 H, $BnOCH_2$, J = 4.4 and 10 Hz), 3.61 (dd of AB, 1 H, $BnOCH_2$, J = 6.0 and 10 Hz), 2.60 (bs, 1 H, OH).

A suspension of 4-Å molecular sieves (32.3 g) and pyridinium chloroformate (32.3 g, 150 mmol) in CH_2Cl_2 (150 mL) was slowly treated with alcohol (14.46 g, 50 mmol) in CH_2Cl_2 (50 mL) via syringe. After 24 h of stirring at room temperature, the reaction mixture was quenched with ether and Celite and stirred for 30 min. The mixture was filtered through a short pad of silica gel, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel with EtOAc/hexane (1:2) as eluant to give **10** as a white solid (13.26 g, 92%): mp 58.8 °C; IR (neat) 1753 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30−7.40 (m, 5 H, phenyl), 6.83 (bs, 4 H, 4-methoxyphenyl), 4.71 (s, 2 H, CH_2OAr), 4.62 (s, 2 H, $PhCH_2O$), 4.36 (s, 2 H, CH_2OBn), 3.77 (s, 3 H, OCH_3).

1-(Benzyloxy)-2-[(4-methoxyphenoxy)methyl]-4-penten-2-ol (11). Allylmagnesium chloride (2 M in THF, 30 mL, 60 mmol) was slowly added to a cooled solution of **10** (5.76 g, 20 mmol) in THF (20 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The mixture was quenched with 1 N HCl and concentrated to a small volume which was diluted with H_2O and extracted with ether several times. The combined organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexane (1:4) as eluant to give **11** as an oil (5.76 g, 88%): IR (neat) 3468 (OH), 1641 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.75−6.86 (m, 4 H, 4-methoxyphenyl), 5.89 (m, 1 H, C*H*=CH_2), 5.10−5.20 (m, 2 H, CH=C*H*$_2$), 4.55 (s, 2 H, $PhCH_2O$), 3.87 (s, 2 H, CH_2OAr), 3.76 (s, 3 H, OCH_3), 3.57 (d, 1 H, $BnOCH_2$, J = 9.2 Hz), 3.48 (d, 1 H, $BnOCH_2$, J = 9.2 Hz), 2.60 (bs, 1 H, OH), 2.44 (d, 2 H, C*H*$_2$CH=CH_2, J = 7.3 Hz).

5-{[(4-Methoxyphenyl)methoxy]methyl}-5-[(phenylmethoxy)methyl]oxolan-3-one (12). A solution of **11** (3.28 g, 10 mmol) in acetone (10 mL) and H_2O (10 mL) was treated with 4-methylmorpholine *N*-oxide (2.35 g, 20 mmol) and osmium tetraoxide (0.1 mL, 2.5 wt % in 2-methyl-2-propanol, 0.05 mmol) and stirred for 2 h at room temperature. The reaction mixture was quenched with sodium thiosulfate solution and concentrated to a small volume, which was diluted with H_2O and extracted with EtOAc several times. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexane (1:1) as eluant to give the corresponding triol as an oil (3.44 g). The triol was dissolved in pyridine (15 mL) and treated with *p*-toluenesulfonyl chloride (2.67 g, 14 mmol) at 0 °C. After 2 h of stirring at room temperature, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2 several times. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexane (1:4) as eluant to give the alcohol as an oil (2.74 g). The alcohol in CH_2Cl_2 (10 mL) was slowly added via syringe to a suspension of 4-Å molecular sieves (5.17 g) and pyridinium chloroformate (5.17 g, 24 mmol) in CH_2Cl_2 (20 mL). After 4 h of stirring at room temperature, the reaction mixture was quenched with ether and Celite and stirred for 30 min. The mixture was filtered through a short pad of silica gel, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexane (1:5) as eluant to give **12** as an oil (1.71 g, 50%): IR (neat) 1763 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2−7.3 (m, 5 H, phenyl), 6.75 (m, 4 H, 4-methoxyphenyl), 4.52 (s, 2 H, $PhCH_2O$), 4.10 (s, 2 H, H-2), 3.98 (dd of AB, 2 H, $ArOCH_2$), 3.69 (s, 3 H, OCH_3), 3.65 (dd of AB, 2 H, $BnOCH_2$), 2.57 (dd of AB, 2 H, H-4); ^{13}C NMR ($CDCl_3$) δ 213.80, 154.20, 152.50, 137.56, 128.46, 127.82, 127.54, 115.46, 114.60, 83.30, 73.68, 73.28, 72.21, 71.98, 55.67, 41.50. Anal. ($C_{20}H_{22}O_5$) C, H.

(*Z*)- and (*E*)-Methyl 2-{4-{[(4-Methoxyphenyl)methoxy]methyl}-4-[(phenylmethoxy)methyl]-3-oxolanylidene}acetate (13 and 14). Potassium *tert*-butoxide (5.8 mL, 1.0 M in THF, 5.8 mmol) was added to a stirred solution of trimethyl phosphonoacetate (1.6 g, 8.7 mmol) in THF (8 mL). After 1 h of stirring at room temperature, the mixture was cooled to 0 °C and a solution of **12** (1.0 g, 2.9 mmol) in THF (4 mL) was added. The resulting solution was refluxed for 10 h, cooled to room temperature, and concentratred in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc/hexane (1:4) as eluant to afford **13** (0.404 g, 35%) and **14** (0.452 g, 39%) as colorless oils, respectively.

13: *Z*-isomer, R_f = 0.50 (EtOAc:Hex = 1:4); IR (neat) 1714 (C=O), 1508 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.82 (s, 4 H, 4-methoxyphenyl), 5.85 (m, 1 H, C=$CHCO_2Me$), 4.95 (m, 2 H, H-2), 4.57 (dd of AB, 2 H, $PhCH_2O$), 3.98 (dd of AB, 2 H, $ArOCH_2$), 3.77 (s, 3 H, OCH_3), 3.71 (s, 3 H, CO_2CH_3), 3.60 (dd of AB, 2 H, $BnOCH_2$), 2.86 (m, 2 H, H-5); ^{13}C NMR ($CDCl_3$) δ 166.3, 162.7, 154.0, 152.8, 137.9, 128.3, 127.6, 127.5, 115.5, 114.5, 111.2, 83.2, 73.5, 71.8, 71.4, 70.0, 55.6, 51.2, 38.6. Anal. ($C_{23}H_{26}O_6$) C, H.

14: *E*-isomer, R_f = 0.43 (EtOAc:Hex = 1:4); IR (neat) 1715 (C=O), 1509 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, phenyl), 6.82 (s, 4 H, 4-methoxyphenyl), 5.78 (m, 1 H, C=$CHCO_2Me$), 4.65 (m, 2 H, H-2), 4.57 (dd of AB, 2 H, $PhCH_2O$), 3.98 (dd of AB, 2 H, $ArOCH_2$), 3.76 (s, 3 H, OCH_3), 3.73 (s, 3 H, CO_2CH_3), 3.61 (dd of AB, 2 H, $BnOCH_2$), 3.17 (m, 2 H, H-5); ^{13}C NMR ($CDCl_3$) δ 166.6, 161.8, 154.0, 152.9, 138.0, 128.3, 127.6, 127.5, 115.6, 114.5, 110.1, 85.5, 73.6, 72.5, 72.0, 70.64, 55.7, 51.2, 37.2. Anal. ($C_{23}H_{26}O_6$) C, H.

(*Z*)-Methyl 2-[4-(Hydroxymethyl)-4-(tetradecanoyloxymethyl)-3-oxolanylidene]acetate (1). A solution of **13** (0.232 g, 0.6 mmol) in CH_3CN-H_2O (4:1, 10 mL) was cooled to 0 °C and treated with ammonium cerium(IV) nitrate (0.656 g, 1.2 mmol). After 30 min of stirring 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 EtOAc/hexane (1:2) as eluant to give **15** as an oil (0.168 g, 93%): ^1H NMR ($CDCl_3$) δ 7.25−7.38 (m, 5 H, phenyl), 5.84 (m, 1 H, C=$CHCO_2Me$), 4.89 (m, 2 H, H-2), 4.54 (dd of AB, 2 H, $PhCH_2O$), 3.70 (s, 3 H, CO_2CH_3), 3.63 (dd of AB, 2 H, CH_2OH), 3.48 (dd of AB, 2 H, CH_2OBn), 2.78 (m, 2 H, H-5), 2.06 (t, 1 H, OH).

A solution of **15** (0.168 g, 0.48 mmol) in CH_2Cl_2 (10 mL) was treated with triethylamine (0.268 mL, 1.92 mmol), a catalytic amount of DMAP, and tetradecanoyl chloride (0.24 g, 0.96 mmol) at 0 °C. After 6 h of stirring at room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:4) as eluant to give **16** as an oil (0.196 g, 82%): ^1H NMR ($CDCl_3$) δ 7.25−7.38 (m, 5 H, phenyl), 5.83 (m, 1 H, C=$CHCO_2Me$), 4.89 (m, 2 H, H-2), 4.54 (s, 2 H, $PhCH_2O$), 4.17 (dd of AB, 2 H, $OCOCH_2$), 3.70 (s, 3 H, CO_2CH_3), 3.48 (dd of AB, 2 H, CH_2OBn), 2.75 (m, 2 H, H-5), 2.27 (t, 2 H, CH_2COO), 1.2−1.65 (m, 22 H, $CH_3(CH_2)_{11}CH_2COO$), 0.88 (distorted t, 3 H, $CH_3(CH_2)_{12}$).

A solution of **16** (0.162 g, 0.32 mmol) in CH_2Cl_2 (8 mL) was cooled to −78 °C and treated with boron trichloride in CH_2Cl_2 (1.28 mL, 1.0 M, 1.28 mmol). After 2 h of stirring at −78 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution and immediately partitioned between ether and $NaHCO_3$ solution. The organic layer was washed with H_2O, dried, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:2) as eluant to give **1** as an oil (0.112 g, 84%): IR (neat) 3443 (OH), 1730 and 1716 (C=O), 1671 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.86 (m, 1 H, C=$CHCO_2Me$), 4.91 (m, 2 H, H-2), 4.13 (s, 2 H, $OCOCH_2$), 3.71 (s, 3 H, CO_2CH_3), 3.58 (dd of AB, 2 H, CH_2OH), 2.75 (m, 2 H, H-5), 2.33 (t, 2 H, CH_2COO), 2.16 (bs, 1 H, OH), 1.2−1.7 (m, 22 H, $CH_3(CH_2)_{11}CH_2COO$), 0.88 (distorted t, 3 H, $CH_3(CH_2)_{12}$); ^{13}C NMR ($CDCl_3$) δ 173.8, 166.2, 161.8, 111.7, 83.2, 71.7, 64.8, 63.6. 51.3, 37.6, 34.1, 31.9. 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.8, 22.7, 14.1; MS *m/e* 413 ($M^+ + 1$). Anal. ($C_{23}H_{40}O_6$) C, H.

(*E*)-Methyl 2-[4-(Hydroxymethyl)-4-(tetradecanoyloxymethyl)-3-oxolanylidene]acetate (3). This compound was

obtained from **14** by following the same procedure used for the synthesis of **1**.

17: oil; ^{1}H NMR ($CDCl_3$) δ 7.25−7.38 (m, 5 H, phenyl), 5.76 (m, 1 H, C=CHCO_2Me), 4.59 (m, 2 H, H-2), 4.55 (m, 2 H, PhCH_2O), 3.72 (s, 3 H, CO_2CH_3), 3.65 (ddd of AB, 2H, CH_2-OH), 3.51 (dd of AB, 2 H, CH_2OBn), 3.06 (m, 2 H, H-5), 2.06 (t, 1 H, OH).

18: oil; ^{1}H NMR ($CDCl_3$) δ 7.25−7.38 (m, 5 H, phenyl), 5.77 (m, 1 H, C=CHCO_2Me), 4.60 (m, 2 H, H-2), 4.56 (s, 2 H, PhCH_2O), 4.17 (dd of AB, 2 H, OCOCH_2), 3.73 (s, 3 H, CO_2-CH_3), 3.50 (dd of AB, 2 H, CH_2OBn), 3.07 (m, 2 H, H-5), 2.28 (t, 2 H, CH_2COO), 1.2−1.65 (m, 22 H, CH_3(CH_2)$_{11}$CH_2COO), 0.88 (distorted t, 3 H, CH_3(CH_2)$_{12}$).

3: oil; IR (neat) 3461 (OH), 1730 and 1720 (C=O), 1671 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.80 (m, 1 H, C=CHCO_2Me), 4.60 (m, 2 H, H-2), 4.15 (dd of AB, 2 H, OCOCH_2), 3.73 (s, 3 H, CO_2CH_3), 3.60 (ddd of AB, 2 H, CH_2OH), 3.07 (m, 2 H, H-5), 2.33 (t, 2 H, CH_2COO), 2.13 (t, 1 H, OH), 1.2−1.7 (m, 22 H, CH_3(CH_2)$_{11}$CH_2COO), 0.88 (distorted t, 3 H, CH_3(CH_2)$_{12}$); ^{13}C NMR ($CDCl_3$) δ 173.8, 166.4, 160.7, 110.8, 85.5, 72.1, 64.8, 64.1. 51.3, 36.2, 34.2, 31.9. 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 22.7, 14.1; MS *m/e* 413 ($M^+ + 1$). Anal. ($C_{23}H_{40}O_6$) C, H.

(*Z*)- and (*E*)-Octadec-9-enyl 2-[4-(Acetoxymethyl)-4-(hydroxymethyl)-3-oxolanylidene]acetate (2 and 4). A solution of **13** and **14** (0.48 g, 1.2 mmol) mixture in THF (10 mL) and H_2O (10 mL) was treated with LiOH (0.058 g, 2.4 mmol) and stirred for 12 h at room temperature. The reaction mixture was concentrated to a small volume, acidified to pH 3 by adding 1 N HCl, and extracted with EtOAc several times. The combined organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo to give **19** as an oil (0.456 g, 1.2 mmol, 99%). Acid **19** in CH_2Cl_2 (20 mL) was treated with oleyl alcohol (85%, 0.28 mL, 1.44 mmol), (dimethylamino)-pyridine (0.015 g, 0.12 mmol), and DCC (1.0 M in CH_2Cl_2, 1.4 mL, 1.4 mmol) and stirred for 12 h at room temperature. The reaction mixture was treated with several drops of acetic acid, stirred for 2 h, and concentrated. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:6) as eluant to give **20** as an oil (0.6 g, 0.94 mmol, 79%). Ester **20** in CH_3CN-H_2O (4:1, 15 mL) was cooled to 0 °C and treated with ammonium cerium(IV) nitrate (1.038 g, 1.88 mmol). After 1 h of stirring 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 EtOAc/hexane (2:3) as eluant to give **21** as an oil (0.3 g, 0.58 mmol, 62%). Alcohol **21** in CH_2Cl_2 (10 mL) was treated with triethylamine (0.32 mL, 2.28 mmol) and acetic anhydride (0.16 mL, 1.72 mmol) at 0 °C. After 8 h of stirring at room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:6) as eluant to give **22** (0.280 g, 0.5 mmol, 86%). Ester **22** in CH_2Cl_2 (10 mL) was cooled to −78 °C and treated with boron trichloride in CH_2Cl_2 (1.0 M, 2 mL, 2 mmol). After 2 h of stirring at −78 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution and immediately partitioned between ether and $NaHCO_3$ solution. The organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:2) as eluant to give **2** (0.072 g, 30%) and **4** (0.132 g, 55%) as oils, respectively.

2: *Z*-isomer, R_f = 0.32 (EtOAc:Hex = 1:2); IR (neat) 3469 (OH), 1740 and 1715 (C=O), 1668 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.79 (m, 1 H, C=CHCO_2R), 5.3−5.4 (m, 2 H, CH=CH), 4.60 (m, 2 H, H-2), 4.07−4.21 (m, 4 H, CH_2OAc and CO_2-CH_2), 3.60 (m, 2 H, CH_2OH), 3.06 (m, 2 H, H-5), 2.09 (s, 3 H, OCOCH_3), 1.95−2.1 (m, 4 H, CH_2CH=CHCH_2), 1.2−1.7 (m, 24 H), 0.88 (distorted t, 3 H,CH_3(CH_2)$_7$CH=CH); ^{13}C NMR ($CDCl_3$) δ 170.94, 165.94, 160.17, 136.66, 124.57, 85.43, 65.01, 64.38, 64.15, 63.67, 38.55, 33.39, 31.88, 29.54, 29.48, 29.41, 29.36, 29.30, 29.24, 29.20, 29.18, 29.12, 28.54, 26.51, 25.87, 22.68, 20.82, 14.10; MS *m/e* 480 (M^+). Anal. ($C_{28}H_{48}O_6$) C, H.

4: *E*-isomer, R_f = 0.26 (EtOAc:Hex = 1:2); IR (neat) 3466 (OH), 1741 and 1722 (C=O), 1668 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.59 (m, 1 H, C=CHCO_2R), 5.3−5.4 (m, 2 H, CH=CH), 4.70 (m, 2 H, H-2), 4.18 (dd of AB, 2 H, CH_2OAc), 4.09 (t, 2 H, CO_2CH_2), 3.62 (m, 2 H, CH_2OH), 3.20 (m, 2 H, H-5), 2.08 (s, 3 H, OCOCH_3), 1.95−2.1 (m, 4 H, CH_2CH=CHCH_2), 1.2−1.7 (m, 24 H), 0.88 (distorted t, 3 H,CH_3(CH_2)$_7$CH=CH); ^{13}C NMR ($CDCl_3$) δ 171.02, 169.81, 158.12, 136.66, 124.57, 92.18, 65.56, 65.29, 64.89, 64.37, 38.55, 33.39, 31.88, 29.54, 29.48, 29.41, 29.36, 29.30, 29.24, 29.20, 29.18, 29.12, 28.54, 26.51, 25.87, 22.68, 20.82, 14.10; MS *m/e* 480 (M^+). Anal. ($C_{28}H_{48}O_6$) C, H.

1-(Benzyloxy)-2-[(4-methoxyphenoxy)methyl]-5-hexen-2-ol (23). A round-bottomed flask containing magnesium turnings (0.74 g, 26 mmol) was dried under vacuum and treated with 4-bromo-1-butene (2.0 mL, 19.5 mmol) in THF (40 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature and treated with **10** (1.76 g, 6.5 mmol) in THF (20 mL) dropwise. After overnight stirring at room temperature, the mixture was filtered through Celite and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:2) as eluant to give **23** as an oil (1.91 g, 82%): IR (neat) 3478 (OH), 1640 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.24−7.35 (m, 5 H, phenyl), 6.83 (s, 4 H, 4-methoxyphenyl), 5.83 (m, 1 H, CH=CH_2), 5.03 (d, 1 H, J = 17 Hz, CH=CH_2), 4.94 (d, 1 H, J = 10 Hz, CH=CH_2), 4.54 (s, 2 H, PhCH_2O), 3.87 (s, 2 H, CH_2-OAr), 3.77 (s, 3 H, OCH_3), 3.52 (dd of AB, 2 H, BnOCH_2), 2.60 (s, 1 H, OH), 2.14−2.22 (m, 2 H, CH_2CH=CH_2), 1.70−1.78 (m, 2 H, (HO)CCH_2); ^{13}C NMR ($CDCl_3$) δ 154.02, 152.89, 138.80, 137.97, 128.40, 127.71, 127.62, 115.60, 114.62, 114.45, 73.42, 73.19, 72.62, 71.01, 55.74, 33.71, 27.12; MS *m/e* 342 (M^+). Anal. ($C_{21}H_{26}O_4$) C, H.

Methyl (*E*)-7-(Benzyloxy)-6-hydroxy-6-[(4-methoxyphenoxy)methyl]-2-heptenoate (24). A solution of **23** (1.9 g, 5.32 mmol) in acetone (10 mL) and H_2O (10 mL) was treated with 4-methylmorpholine *N*-oxide (1.25 g, 10.64 mmol), sodium periodate (2.28 g, 10.64 mmol), and osmium tetraoxide (0.1 mL, 2.5 wt % in 2-methyl-2-propanol, 0.05 mmol). After 20 h of stirring at room temperature, the reaction mixture was diluted with EtOAc and filtered. The filtrate was washed sequentially with a solution of sodium thiosulfate, 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/hexane (1:2) as eluant to give a lactol as an oil (1.05 g, 3.2 mmol, 60%). The lactol in toluene (20 mL) was treated with methyl (triphenylphosphoranylidene)acetate (1.6 g, 4.8 mmol), refluxed for 2 h, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (2:3) as eluant to give **24** as an oil (1.059 g, 87%): IR (neat) 3478 (OH), 1722 (C=O), 1656 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.24−7.35 (m, 5 H, phenyl), 6.99 (dt, 1 H, J = 15.7 and 6.84 Hz, CH=CHCO_2Me), 6.82 (s, 4 H, 4-methoxyphenyl), 5.83 (dt, 1 H, J = 15.7 and 1.44 Hz, CH=CHCO_2Me), 4.54 (s, 2 H, PhCH_2O), 3.86 (s, 2 H, CH_2OAr), 3.77 (s, 3 H, OCH_3), 3.71 (s, 3 H, CO_2CH_3), 3.51 (dd of AB, 2 H, BnOCH_2), 2.64 (s, 1 H, OH), 2.29−2.38 (m, 2 H, CH_2CH_2CH=CH), 1.75−1.82 (m, 2 H, C$H_2$$CH_2$CH=CH); ^{13}C NMR ($CDCl_3$) δ 167.05, 154.13, 152.72, 149.41, 137.79, 128.44, 127.80, 127.66, 120.90, 115.60, 114.66, 73.44, 72.92, 72.44, 70.88, 55.74, 51.40, 32.70, 25.71; MS *m/e* 400 (M^+). Anal. ($C_{23}H_{28}O_6$) C, H.

***rel*-(1*R*,3*S*)- and *rel*-(1*S*,3*S*)-Methyl 2-{3-{[(4-Methoxyphenyl)methoxy]methyl}-3-[(phenylmethoxy)methyl]-2-oxolanyl}acetate (26 and 27).** A solution of **24** (1.0 g, 2.6 mmol) in THF (20 mL) was treated with tetrabutylammonium fluoride (5.2 mL, 1.0 M in THF, 5.2 mmol) and stirred overnight. The reaction mixture was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:3) as eluant to give **25** as an oil (0.99 g, 2.57 mmol, 99%). A solution of **25** in CH_3CN-H_2O (4:1, 15 mL) was cooled to 0 °C and treated with ammonium cerium(IV) nitrate (2.74 g, 5 mmol). After 4 h of stirring at 0 °C, the reaction mixture was diluted with CH_2-

Cl_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 EtOAc/hexane (1:2 to 1:1) as eluant to give **26** and **27** as oils, respectively (0.484 g, 64%).

26: $R_f = 0.36$ (EtOAc:Hex = 1:1); IR (neat) 3445 (OH), 1732 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22−7.37 (m, 5 H, phenyl), 4.54 (dd of AB, 2 H, $PhCH_2O$), 4.38 (m, 1 H, H-1), 3.68 (s, 3 H, CO_2CH_3), 3.56 (dd of AB, 2 H, $HOCH_2$), 3.39 (dd of AB, 2 H, $BnOCH_2$), 2.78 (s, 1 H, OH), 2.56 (ddd of AB, 2 H, CH_2CO_2-Me), 1.83−2.16 (m, 3 H), 1.70 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.79, 138.07, 128.34, 127.58, 127.52, 85.46, 75.92, 73.45, 73.14, 66.01, 51.73, 40.16, 31.33, 29.48; MS *m/e* 295 ($M^+ + 1$). Anal. ($C_{26}H_{22}O_5$) C, H.

27: $R_f = 0.29$ (EtOAc:Hex = 1:1); IR (neat) 3458 (OH), 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22−7.37 (m, 5 H, phenyl), 4.54 (dd of AB, 2 H, $PhCH_2O$), 4.37 (m, 1 H, H-1), 3.67 (s, 3 H, CO_2CH_3), 3.56 (dd of AB, 2 H, $HOCH_2$), 3.41 (dd of AB, 2 H, $BnOCH_2$), 2.55 (ddd of AB, 2 H, CH_2CO_2Me), 2.43 (s, 1 H, OH), 1.60−2.16 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.54, 138.11, 128.29, 127.52, 127.45, 84.91, 75.94, 73.43, 73.33, 65.95, 51.54, 40.58, 31.36, 30.03; MS *m/e* 295 ($M^+ + 1$). Anal. ($C_{26}H_{22}O_5$) C, H.

***rel*-(1*R*,3*R*)-{3-[(Methoxycarbonyl)methyl]-1-[(phenylmethoxy)methyl]-2-oxolanyl}methyl Tetradecanoate (28).** This compound was obtained from **26** by following the same procedure used for the synthesis of **16**: oil; ^1H NMR ($CDCl_3$) δ 7.22−7.37 (m, 5 H, phenyl), 4.55 (dd of AB, 2 H, $PhCH_2O$), 4.39 (m, 1 H, H-3), 4.08 (dd of AB, 2 H, $OCOCH_2$), 3.67 (s, 3 H, CO_2CH_3), 3.41 (dd of AB, 2 H, $BnOCH_2$), 2.70 (dd of AB, 1 H, CH_2CO_2Me), 2.45 (dd of AB, 1 H, CH_2CO_2Me), 2.29 (t, 2 H, CH_2COO), 2.12 (m, 1 H), 1.86−1.93 (m, 2 H), 1.55−1.73 (m, 3 H), 1.2−1.4 (m, 20 H), 0.88 (distorted t, 3 H).

***rel*-(1*R*,3*S*)-{3-[(Methoxycarbonyl)methyl]-1-[(phenylmethoxy)methyl]-2-oxolanyl}methyl Tetradecanoate (29).** This compound was obtained from **27** by following the same procedure used for the synthesis of **16**: oil; ^1H NMR ($CDCl_3$) δ 7.22−7.37 (m, 5 H, phenyl), 4.54 (s, 2 H, $PhCH_2O$), 4.39 (m, 1 H, H-3), 4.10 (s, 2 H, $OCOCH_2$), 3.66 (s, 3 H, CO_2CH_3), 3.40 (dd of AB, 2 H, $BnOCH_2$), 2.70 (dd of AB, 1 H, CH_2CO_2Me), 2.45 (dd of AB, 1 H, CH_2CO_2Me), 2.31 (t, 2 H, CH_2COO), 1.95−2.10 (m, 2 H), 1.55−1.85 (m, 4 H), 1.2−1.4 (m, 20 H), 0.88 (distorted t, 3 H).

***rel*-(1*R*,3*R*)-{1-(Hydroxymethyl)-3-[(methoxycarbonyl)methyl]-2-oxolanyl}methyl Tetradecanoate (5).** A solution of **28** (0.12 g, 0.24 mmol) in EtOAc (10 mL) was treated with 10% Pd−C (0.12 g) and hydrogenated under a hydrogen-filled balloon. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel with EtOAc/hexane (1:1) as eluant to give **5** as a white solid (0.09 g, 90%): mp 52 °C; IR (neat) 3459 (OH), 1731 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.40 (m, 1 H, H-3), 4.05 (dd of AB, 2 H, $OCOCH_2$), 3.69 (s, 3 H, CO_2CH_3), 3.51 (dd of AB, 2 H, $HOCH_2$), 2.66 (dd of AB, 1 H, *J* = 6.8 and 15.4 Hz, CH_2CO_2Me), 2.50 (dd of AB, 1 H, *J* = 6.1 and 15.4 Hz, CH_2CO_2Me), 2.33 (t, 2 H, CH_2COO), 2.15 (m, 1 H), 1.55−1.9 (m, 5 H), 1.2−1.4 (m, 20 H), 0.88 (distorted t, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.78, 171.45, 84.23, 76.31, 65.77, 65.14, 51.67, 40.51, 34.21, 31.87, 31.40, 29.91, 29.63, 29.61, 29.56, 29.42, 29.32, 29.22, 29.11, 24.90, 22.65, 14.08; MS *m/e* 415 ($M^+ + 1$). Anal. ($C_{23}H_{42}O_6$) C, H.

***rel*-(1*R*,3*S*)-{1-(Hydroxymethyl)-3-[(methoxycarbonyl)methyl]-2-oxolanyl}methyl Tetradecanoate (7).** This compound was obtained from **29** by following the same procedure used for the synthesis of **5**: white solid; mp 40.5 °C; IR (neat) 3459 (OH), 1731 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.41 (m, 1 H, H-3), 4.04 (dd of AB, 2 H, $OCOCH_2$), 3.70 (s, 3 H, CO_2CH_3), 3.52 (dd of AB, 2 H, $HOCH_2$), 2.63 (dd of AB, 1 H, *J* = 6.6 and 14.9 Hz, CH_2CO_2Me), 2.54 (dd of AB, 1 H, *J* = 5.6 and 14.9 Hz, CH_2CO_2Me), 2.33 (t, 2 H, CH_2COO), 2.15 (m, 1 H), 1.55−1.9 (m, 5 H), 1.2−1.4 (m, 20 H), 0.88 (distorted t, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.80, 171.64, 84.70, 76.11, 65.87, 65.13, 51.76, 39.95, 34.18, 31.86, 31.19, 29.62, 29.58, 29.55, 29.39, 29.35, 29.30, 29.21, 29.08, 24.88, 22.63, 14.05; MS *m/e* 415 ($M^+ + 1$). Anal. ($C_{23}H_{42}O_6$) C, H.

***rel*-(1*R*,3*S*)- and *rel*-(1*S*,3*S*)-Tetradecyl 2-[3-(Hydroxymethyl)-3-[(phenylmethoxy)methyl]-2-oxolanyl]acetate (32 and 33).** A solution of **25** (0.384 g, 1.0 mmol) in a mixture of THF (10 mL) and H_2O (10 mL) was treated with LiOH (0.048 g, 2.0 mmol) and stirred for 16 h at room temperature. The reaction mixture was concentrated to a small volume, acidified to pH 3 with 1 N HCl, and extracted with EtOAc several times. The combined organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo to give **30** as an oil (0.348 g, 0.94 mmol, 94%). Acid **30** in CH_2Cl_2 (12 mL) was treated with 1-tetradecanol (0.242 g, 1.13 mmol), (dimethylamino)pyridine (0.013 g, 0.1 mmol), and DCC (1.0 M in CH_2Cl_2, 1.9 mL, 1.9 mmol) and stirred for 16 h at room temperature. The reaction mixture was treated with several drops of acetic acid, stirred for 2 h, and concentrated. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:7) as eluant to give **31** as an oil (0.384 g, 0.68 mmol, 72%). Ester **31** in CH_3CN-H_2O (4:1, 10 mL) was cooled to 0 °C and treated with ammonium cerium(IV) nitrate (0.746 g, 1.36 mmol). After 4 h of stirring 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 EtOAc/hexane (1:3 to 1:2) as eluant to give **32** and **33** as oils (0.204 g, 0.43 mmol, 63%).

32: $R_f = 0.24$ (EtOAc:Hex = 1:3); IR (neat) 3460 (OH), 1732 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25−7.37 (m, 5 H, phenyl), 4.54 (dd of AB, 2 H, $PhCH_2O$), 4.39 (m, 1 H, H-1), 4.08 (t, 2 H, $COOCH_2$), 3.56 (dd of AB, 2 H, $HOCH_2$), 3.40 (dd of AB, 2 H, $BnOCH_2$), 2.65 (s, 1 H, OH), 2.60 (dd of AB, 1 H, *J* = 7.1 and 14.6 Hz, $CH_2CO_2C_{14}H_{29}$), 2.51 (dd of AB, 1 H, *J* = 5.6 and 14.6 Hz, $CH_2CO_2C_{14}H_{29}$), 1.55−2.2 (m, 6 H), 1.2−1.4 (m, 22 H), 0.88 (distorted t, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.40, 138.10, 128.31, 127.56, 127.51, 85.44, 76.03, 73.48, 73.21, 66.06, 64.82, 40.47, 31.84, 31.33, 29.57, 29.50, 29.45, 29.28, 29.17, 28.50, 25.81, 22.63, 14.05; MS *m/e* 477 ($M^+ + 1$). Anal. ($C_{29}H_{48}O_5$) C, H.

33: $R_f = 0.15$ (EtOAc:Hex = 1:3); IR (neat) 3460 (OH), 1732 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25−7.37 (m, 5 H, phenyl), 4.54 (dd of AB, 2 H, $PhCH_2O$), 4.37 (m, 1 H, H-1), 4.06 (t, 2 H, $COOCH_2$), 3.56 (dd of AB, 2 H, $HOCH_2$), 3.42 (dd of AB, 2 H, $BnOCH_2$), 2.63 (dd of AB, 1 H, *J* = 6.8 and 15.3 Hz, $CH_2CO_2C_{14}H_{29}$), 2.45 (dd of AB, 1 H, *J* = 6.3 and 15.3 Hz, $CH_2CO_2C_{14}H_{29}$), 1.55−2.2 (m, 6 H), 1.2−1.4 (m, 22 H), 0.88 (distorted t, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.22, 138.15, 128.38, 127.63, 127.54, 84.80, 77.20, 76.10, 73.54, 66.17, 64.71, 40.97, 31.92, 31.44, 29.63, 29.57, 29.50, 29.34, 29.23, 28.57, 25.88, 22.68, 14.10; MS *m/e* 477 ($M^+ + 1$). Anal. ($C_{29}H_{48}O_5$) C, H.

***rel*-(1*R*,3*R*)-{1-[(Phenylmethoxy)methyl]-3-[(tetradecyloxycarbonyl)methyl]-2-oxolanyl}methyl Hexanoate (34).** A solution of **32** (0.072 g, 0.15 mmol) in CH_2Cl_2 (5 mL) was treated at 0 °C with triethylamine (0.084 mL, 0.6 mmol), a catalytic amount of DMAP, and hexanoyl chloride (0.042 mL, 0.3 mmol). After 12 h of stirring at room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:3) as eluant to give **34** (0.082 g, 95%) as an oil: ^1H NMR ($CDCl_3$) δ 7.25−7.37 (m, 5 H, phenyl), 4.55 (dd of AB, 2 H, $PhCH_2O$), 4.39 (m, 1 H, H-3), 4.0−4.12 (m, 4 H, $COOCH_2CH_2$ and $H_{11}C_5COOCH_2$), 3.42 (dd of AB, 2 H, $BnOCH_2$), 2.71 (dd of AB, 1 H, *J* = 6.1 and 15.4 Hz, $CH_2CO_2C_{14}H_{29}$), 2.43 (dd of AB, 1 H, *J* = 7.1 and 15.4 Hz, $CH_2CO_2C_{14}H_{29}$), 2.29 (t, 2 H, CH_2COO), 1.5−2.2 (m, 8 H), 1.2−1.4 (m, 26 H), 0.8−1.0 (m, 6 H).

***rel*-(1*R*,3*R*)- and *rel*-(1*R*,3*S*)-{1-[(Phenylmethoxy)methyl]-3-[(tetradecyloxycarbonyl)methyl]-2-oxolanyl}methyl Hexanoate (35).** This compound was obtained from **33** by following the same procedure used for the synthesis of **34** as an oil: ^1H NMR ($CDCl_3$) δ 7.25−7.37 (m, 5 H, phenyl), 4.54 (dd of AB, 2 H, $PhCH_2O$), 4.38 (m, 1 H, H-3), 4.0−4.12 (m, 4 H, $COOCH_2CH_2$ and $H_{11}C_5COOCH_2$), 3.40 (dd of AB, 2 H, $BnOCH_2$), 2.70 (dd of AB, 1 H, *J* = 6.1 and 15.4 Hz, $CH_2CO_2C_{14}H_{29}$), 2.42 (dd of AB, 1 H, *J* = 7.6 and 15.4 Hz, CH_2-

$CO_2C_{14}H_{29}$), 2.29 (t, 2 H, CH_2COO), 1.55−2.2 (m, 8 H), 1.2−1.4 (m, 26 H), 0.8−0.95 (m, 6 H).

***rel*-(1*R*,3*R*)-[1-(Hydroxymethyl)-3-[(tetradecyloxycarbonyl)methyl]-2-oxolanyl]methyl Hexanoate (6).** This compound was obtained from **34** by following the same procedure used for the synthesis of **5** as an oil: IR (neat) 3461 (OH), 1731 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.39 (m, 1 H, H-3), 4.0−4.12 (m, 4 H, $COOCH_2CH_2$ and $H_{11}C_5COOCH_2$), 3.51 (dd of AB, 2 H, $HOCH_2$), 2.65 (dd of AB, 1 H, J = 6.8 and 15.6 Hz, $CH_2CO_2C_{14}H_{29}$), 2.47 (dd of AB, 1 H, J = 6.6 and 15.6 Hz, $CH_2CO_2C_{14}H_{29}$), 2.33 (t, 2 H, CH_2COO), 2.15 (m, 1 H), 1.5−1.9 (m, 7 H), 1.2−1.4 (m, 26 H), 0.85−0.95 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 173.78, 171.11, 84.18, 76.41, 65.82, 65.16, 64.76, 40.82, 34.20, 31.90, 31.44, 31.26, 29.96, 29.63, 29.56, 29.50, 29.34, 29.23, 28.55, 25.88, 24.60, 22.66, 22.28, 14.08, 13.87; MS *m/e* 485 ($M^+ + 1$). Anal. ($C_{28}H_{52}O_6$) C, H.

***rel*-(1*R*,3*S*)-[1-(Hydroxymethyl)-3-[(tetradecyloxycarbonyl)methyl]-2-oxolanyl]methyl Hexanoate (8).** This compound was obtained from **35** by following the same procedure used for the synthesis of **5** as an oil: IR (neat) 3462 (OH), 1731 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.41 (m, 1 H, H-3), 4.09 (t, 2 H, $COOCH_2CH_2$), 4.01 (t, 2 H, $H_{11}C_5COOCH_2$), 3.52 (dd of AB, 2 H, $HOCH_2$), 2.64 (dd of AB, 1 H, J = 6.6 and 14.7 Hz, $CH_2CO_2C_{14}H_{29}$), 2.52 (dd of AB, 1 H, J = 5.9 and 14.7 Hz, $CH_2CO_2C_{14}H_{29}$), 2.33 (t, 2 H, CH_2COO), 2.0−2.2 (m, 2 H), 1.5−1.85 (m, 6 H), 1.2−1.4 (m, 26 H), 0.85−0.95 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 173.79, 171.31, 84.68, 76.23, 65.95, 65.20, 64.94, 40.31, 34.18, 31.90, 31.26, 29.63, 29.56, 29.50, 29.34, 29.21, 28.53, 25.84, 24.58, 22.61, 22.28, 14.08, 13.87; MS *m/e* 485 ($M^+ + 1$). Anal. ($C_{28}H_{52}O_6$) C, H.

Acknowledgment. This work was supported in part by Grant No. KOSEF 96-0403-01-01-3 from the Korea Science and Engineering Foundation and by 99 S.N.U. Research Fund.

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JM980713G