Conformationally Constrained Analogues of Diacylglycerol. 10. Ultrapotent Protein Kinase C Ligands Based on a Racemic 5-Disubstituted Tetrahydro-2-furanone Template[1]

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Received April 12, 1995[⊗]

5,5-Bis(hydroxymethyl)tetrahydro-2-furanone and its isomer 4,4-bis(hydroxymethyl)tetrahydro-2-furanone were investigated as possible templates for the construction of conformationally constrained analogues of the biologically important second messenger, diacylglycerol (DAG). The former lactone contains embedded within its structure an exact glycerol moiety, while in the latter the ring oxygen has been transposed to the other side of the carbonyl group. All target compounds were synthesized as racemates from 1,3-dihydroxy-2-propanone. The 5,5-bis(hydroxymethyl)tetrahydro-2-furanone proved to be the better template for the construction of DAG surrogates that were demonstrated to have high binding affinities for the biological target, protein kinase C (PK-C). The simplest target compounds derived from this template (**3e** and **3f**) have one of the hydroxyl moieties functionalized either as a myristate or as an oleate ester. The simplest target compound (**9c**) derived from the ineffective 4,4-bis-(hydroxymethyl)tetrahydro-2-furanone template was investigated only with a myristoyl acyl chain. Reducing the long acyl chain to an acetyl moiety and attaching a compensating lipophilic chain to the lactone ring as an α-alkylidene moiety produced compounds **10e** and **10f** (*Z*-isomers) and **11e** and **11f** (*E*-isomers), which were constructed on the more effective 5,5-bis(hydroxymethyl)tetrahydro-2-furanone template. Targets **14c** (*Z*-isomer) and **15c** (*E*-isomer) were derived, in turn, from 4,4-bis(hydroxymethyl)tetrahydro-2-furanone. The affinities of these ligands for PK-C were assessed in terms of their ability to displace bound [^{3}H-20]phorbol 12,13-dibutyrate (PDBU) from the single isozyme PK-Cα. The biological data support the hypothesis that the increase in binding affinity for PK-C shown by some of these constrained DAG mimetics appears to be entropic in nature. Two of the designed ligands (**10e** and **10f**) showed the highest affinities (34 and 24 nM, respectively) reported so far for a DAG analogue. Assuming that the interaction between these racemic compounds and PK-C is stereospecific, the potency of the active enantiomer is anticipated to double.

Introduction

Protein kinase C (PK-C) plays a pivotal role in cell signaling by functioning as a central signal transducing element. These signals are generated by a broad range of ligands which produce the lipid second messenger, diacylglycerol (DAG).[2,3] The identification of PK-C as the primary receptor for the phorbol esters,[4−7] and the demonstration that these esters bind to PK-C with extremely high affinities at a site used by DAG causing the activation of the enzyme,[8] has made the phorbol esters valuable tools for studying the role of PK-C in many cellular functions.[2] However, the phorbol esters may act supraphysiologically and activate responses that are not normally elicited by the physiologically relevant activator DAG.[9] This, combined with evidence for the existence of additional phorbol ester receptors with different biological functions,[10] suggests the utility of more specific and potent DAG agonists.

Since the phorbol esters bind to PK-C with affinities that are several orders of magnitude higher than those of any DAG, we have attempted to increase the potency of the latter by designing analogues which constrain the glycerol backbone in order to reduce the entropy penalty associated with binding. Although our original attempts suggested that this concept was plausible, the first conformationally constrained analogues—built on a 2-deoxy-L-ribonolactone template—were no more potent than the parent DAG molecule with an equivalent lipophilic acyl chain.[11] We later concluded that minor deviations in the orientation of important pharmacophore atoms, imposed by the structural constraints of the 2-deoxy-L-ribonolactone ring, canceled the entropic advantage.[12] In this paper, we describe a new lactone template which leads to compounds with a significant increase in binding affinity for PK-C relative to the equivalent linear DAG molecule. This new lactone template can be envisaged as resulting from an idealized intramolecular cyclization of DAG (path a, Chart 1) that requires an additional carbon atom to complete the five-membered ring structure (template **I**). Two additional modifications of template **I** were also considered. First, template **I** was transformed into template **II** (path b, Chart 1) to study the effects of a reversed lactone function. We have shown previously that a comparable reversal of the ester function on the acyl chain of 2-deoxy-L-ribonolactone analogues of DAG did not re-

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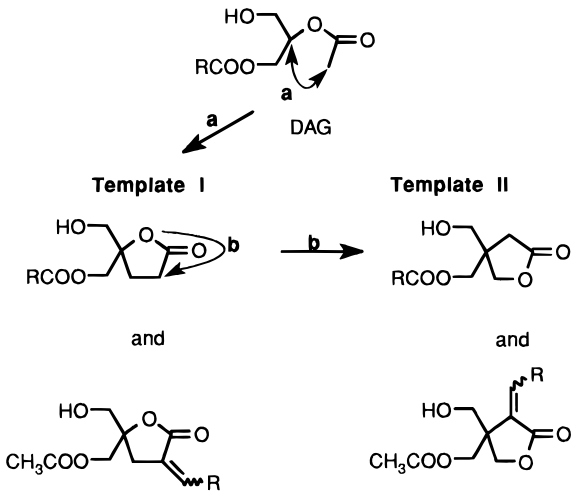
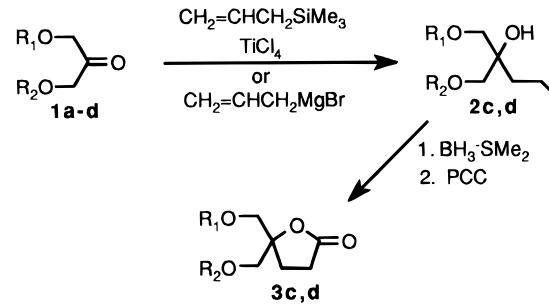
[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1995.

Chart 1



Scheme 1



1-3

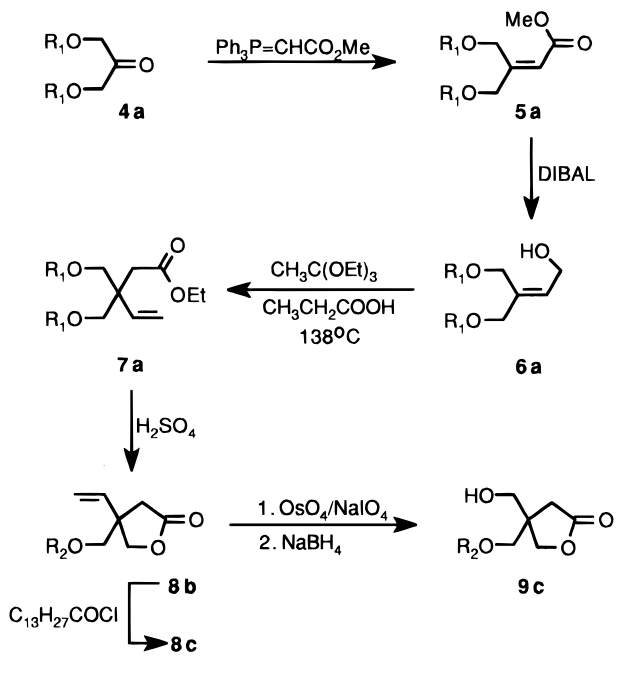
a, $R_1 = R_2 = H$
b, $R_1 = H$, $R_2 = Me_3CPh_2Si$
c, $R_1 = R_2 = Me_3CPh_2Si$
d, $R_1 = CH_3(CH_2)_{12}CO$, $R_2 = Me_3CPh_2Si$
e, $R_1 = CH_3(CH_2)_{12}CO$, $R_2 = H$
f, $R_1 = (Z)\text{-}CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$, $R_2 = H$

duce PK-C binding affinity.[13] Hence, placing the oxygen at the other side of the carbonyl, as in template **II**, maintains the carbonyl group in the same relative disposition (Chart 1). The second modification consisted of the abbreviation of the long acyl function in templates **I** and **II** to a simple acetyl function and the extension of the lipophilic chain from the lactone ring as an α-alkylidene appendage (Chart 1). Implementation of this change with the 2-deoxy-L-ribonolactone analogues of DAG investigated earlier led to compounds with a 10-fold increase in binding affinity for PK-C.[14] Initially, all the compounds constructed on templates **I** and **II** were investigated in racemic form.

Chemistry

Template **I** (Chart 1) was built from 1,3-dihydroxyacetone (**1a**) according to Scheme 1 where only the principal steps are shown. Two different approaches were followed. Initially, the monoprotected *tert*-butyldiphenylsilyl ether **1b** was treated with myristoyl chloride to give **1d**. Alternatively, **1a** was fully protected as **1c**. Conversion of **1c** and **1d** to the tertiary homoallylic alcohols **2c** and **2d** was achieved, respectively, with either allylmagnesium bromide or allyltrimethylsilane/$TiCl_4$.[15] Following the methodology of Mandal and Mahajan a "one-pot" synthesis of the

Scheme 2



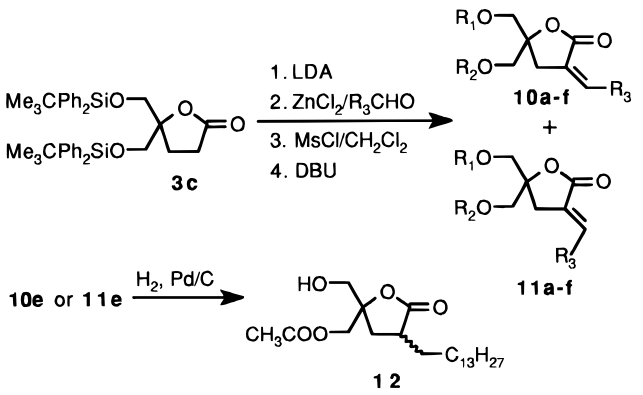
a, $R_1 = Me_3CMe_2Si$
b, $R_2 = H$
c, $R_2 = CH_3(CH_2)_{12}CO$

lactone was achieved by hydroboration of the double bond in **2c** and **2d** followed immediately by oxidation with pyridinium chlorochromate (PCC).[16] Under these reaction conditions, the ensuing cyclization to the lactol proceeded with further oxidation to give, respectively, the antepenultimate and penultimate intermediate lactones **3c** and **3d**. Removal of the silyl ether protection from **3d** with tetrabutylammonium fluoride (TBAF) afforded the target lactone **3e**, while **3c** was reacted with NH_4F[17] to give the free lactone **3a**. Monoacylation of lactone **3a** gave the oleate (**3f**).

Template **II** (Chart 1) required the same starting material, but this time protection was achieved with the less sterically demanding *tert*-butyldimethylsilyl chloride to give **4a** (Scheme 2). Wadsworth−Emmons reaction of **4a** with the stabilized ylide methyl (triphenylphosphoranylidene)acetate gave **5a**, which was reduced to the allylic alcohol **6a** with diisobutylaluminum hydride (DIBAL). Claisen rearrangement of the intermediate enol ester, formed by reacting **6a** with triethyl orthoacetate, produced the pivotal intermediate ester **7a** which cyclized to lactone **8b** under acidic conditions. Acylation of the primary alcohol function provided the myristate ester **8c**, and oxidation of the terminal olefin with $OsO_4/NaIO_4$ gave the corresponding aldehyde which was readily converted to the desired target lactone **9c** after borohydride reduction.

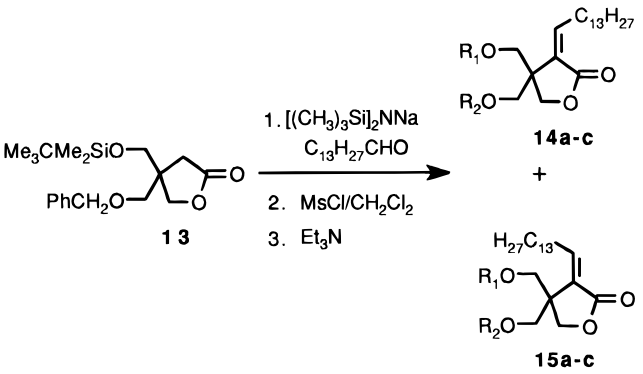
The abbreviation of the acyl function and extension of the lipophilic chain from the lactone ring was performed in a similar manner for templates **I** and **II** (Chart 1). Following our reported methodology,[14] lactones **3c** (Scheme 3) and **13** (Scheme 4) were treated with the corresponding aldehydes (myristoyl or oleoyl aldehyde) to give ca. 70% of the intermediate alcohol which was readily dehydrated to a separable mixture of the corresponding *Z*- (**10a**,**b** and **14a**) and *E*-isomers (**11a**,**b** and **15a**). The geometry of the exocyclic double

Scheme 3



a, $R_1 = R_2 = Me_3CPh_2Si$, $R_3 = CH_3(CH_2)_{12}$
b, $R_1 = R_2 = Me_3CPh_2Si$, $R_3 = (Z)\text{-}CH_3(CH_2)_7CH{=}CH(CH_2)_7$
c, $R_1 = R_2 = H$, $R_3 = CH_3(CH_2)_{12}$
d, $R_1 = R_2 = H$, $R_3 = (Z)\text{-}CH_3(CH_2)_7CH{=}CH(CH_2)_7$
e, $R_1 = CH_3CO$, $R_2 = H$, $R_3 = CH_3(CH_2)_{12}$
f, $R_1 = CH_3CO$, $R_2 = H$, $R_3 = (Z)\text{-}CH_3(CH_2)_7CH{=}CH(CH_2)_7$

Scheme 4



a, $R_1 = Me_3CMe_2Si$, $R_2 = PhCH_2$
b, $R_1 = CH_3CO$, $R_2 = PhCH_2$
c, $R_1 = CH_3CO$, $R_2 = H$

bond in these isomers was assigned by ^{1}H NMR spectroscopy which showed the *β-cis* vinyl protons ca. 0.5 ppm downfield from the corresponding *β-trans* protons.[14] Removal of the protective ether groups from these compounds, followed by formation of the corresponding monoacetates, gave the desired targets **10e**,**f** and **11e**,**f** (template **I**), and **14c** and **15c** (template **II**). Catalytic hydrogenation of either **10e** or **11e** afforded compound **12** as a mixture of epimers.

Biological Results

The affinity of these ligands for PK-C was assessed in terms of their ability to displace bound [^{3}H-20]phorbol 12,13-dibutyrate (PDBU) from a recombinant single isozyme PK-Cα. The inhibition curves obtained for these ligands were of the type expected for competitive inhibition, and the ID_{50} values were determined by fit of the data points to the theoretical noncooperative competition curve.[11] The K_i's for inhibition of binding were calculated from the ID_{50} values. A comparison between the simplest compound derived from template **I** (**3e**) and the equivalent lactone derived from our previous 2-deoxy-L-ribonolactone template (**16**)[11] revealed an order of magnitude difference in affinity in favor of the new template **I** (Chart 2). On the other hand, the equivalent isolactone **9c** constructed with template **II** displayed very poor affinity for PK-C (Table 1). For the active template **I**, changes in the constitution of the acyl chain were also accompanied by increases in affinities consistent with the previously observed trend with the 2-deoxy-L-ribonolactones.[18] Hence, the oleate analogue (**3f**) was ca. 1.5 times more potent than the myristate **3e** (Table 1).

Chart 2

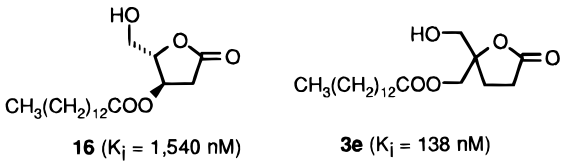
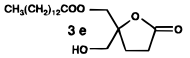
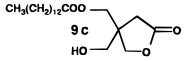
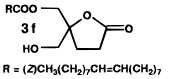
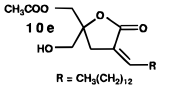
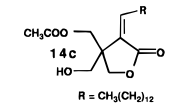
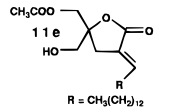
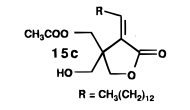
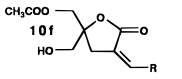
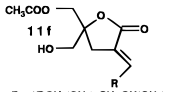


Table 1. Apparent K_i (nM) Values for Ligands as Inhibitors of PDBU Binding to PK-Cα

Template **I**		Template **II**	
Compound	K_i	Compound	K_i
	138±24		9,810±900
	96±7.5		
	35±1.3		6,510±450
	78±4.7		6,500±450
	24±2.9		
	28±2.2		

With either template **I** or **II**, where the acyl function had been abbreviated to a simple acetyl and the lipophilic component incorporated in the form of an α-alkylidene chain (Chart 1), PK-C binding affinities increased in each case (Table 1). However, the corresponding increases observed for template **II** were minimal, suggesting that it was indeed a poor template for a rigid diacylglycerol backbone. On the other hand, the increases observed for template **I** were quite impressive. The simplest of the compounds with a $CH_3(CH_2)_{12}$ alkyl chain (**10e**) displayed unprecedented potency for a DAG analogue (K_i = 35 nM). This suggests that the spatial disposition of pharmacophores achieved with this template is probably very close to that present in PK-C-bound DAG. Also, a 2-fold difference in affinity was confirmed for the *Z*-isomer (**10e**) relative to the corresponding *E*-isomer (**11e**). The magnitude of this difference was similar to that observed for the equivalent α-alkylidene isomers built with our previous 2-deoxy-

L-ribonolactone template[14] and supports our view that the orientation of the alkyl chain is a key factor for the optimization of binding. The incorporation of an additional midpoint unsaturation to mimic the oleate side chain in compounds **10f** and **11f** resulted in a slight, but definitive, increase in affinity. However, in these compounds, the difference favoring the *Z*-isomer almost disappeared. It is possible that for these compounds the midpoint *cis* double bond further along the alkyl chain compensates for the less favorable orientation of the *E*-isomer. Ultimately, removal of the unsaturation gave the corresponding α-alkyl analogue as an inseparable mixture of epimers (**12**) which showed a reduced level of affinity for PK-C ($K_i = 75 \pm 2.5$ nM) similar to that shown by the less effective *E*-isomer **11e** (78 ± 4.7 nM).

These investigations have produced a conformationally restricted DAG molecule (**10f**) with the highest affinity ($K_i = 24$ nM) reported to date for a DAG analogue. Structurally, **10f** represents a constrained form of the lipophilically equivalent 1-oleoyl-2-acetyl-*sn*-glycerol (OAG), which under the same experimental conditions was 10-fold less potent ($K_i = 230$ nM)[19] than **10f**. It is proposed that the 10-fold increase in binding affinity for **10f** is derived from the highly complementary binding of this preorganized OAG analogue where the conformational entropic penalty associated with the binding of the linear and more flexible molecule is reduced.[20] Finally, assuming that the interaction between **10f** and PK-C is stereospecific, as is the case with DAGs,[21] one can anticipate a two-fold increase in binding affinity for the active enantiomer. The realization of such a goal through the chiral synthesis of the active enantiomer is the subject of the following paper.

Molecular Modeling

The dramatic difference in binding affinities between the isosteric lactones **3e** (138 nM) and **9c** (9810 nM) was at first intriguing since the only structural difference between the two compounds was the transposed lactone oxygen from one side of the carbonyl to the other. This enormous variance, which was not observed when the same transposition was performed on the acyl chain of DAG analogues built with the 2-deoxy-L-ribonolactone template,[13] suggested that such an operation in the cyclic system had caused a significant change in the conformation of the lactone ring. Indeed, a search in the Cambridge Structural Database[22] for the unconstrained "Core Templates" identified four compounds corresponding to template **I** (present in compound **3e**, Figure 1) and three compounds corresponding to template **II** (present in compound **9c**, Figure 1) which showed significant differences in ring puckering. Not surprisingly, the X-ray structures within each group showed a virtually identical form of ring puckering. When these isolated templates (**I** and **II**) were energy minimized and compared, it could be seen that the different forms of puckering could cause a severe mistmach of pharmacophores, although the conformational barrier to force one conformation into the other was not very large (3.0 kcal/mol) according to QUANTA CHARMm. In order to visualize the displacement of pharmacophores, template **I** and template **II** were superimposed on each other using the quaternary carbon on the ring as the anchor point. When this was done, the ring carbonyl pharmacophores appeared severely displaced from each other by 1.620 Å (Figure 1).

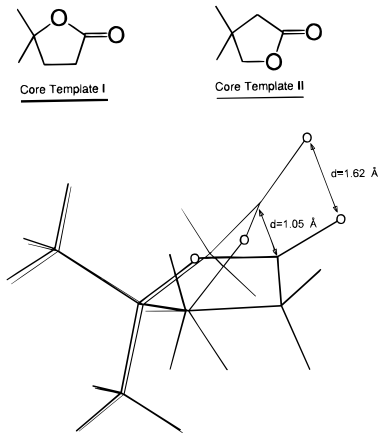


Figure 1. Superposition of core template **I** and core template **II**.

The reason for selecting this quaternary carbon as the anchor point is that it allows the superposition of the hydroxymethyl pharmacophore in both lactones. Although we have no proof that this pharmacophore binds first to the receptor, a recent X-ray study of the Cys2 domain of PK-Cδ complexed to phorbol 13-acetate showed that hydrogen bonding of the equivalent hydroxymethyl pharmacophore in phorbol was the most important interaction in the complex.[23] Therefore, if in this hypothetical model we assume that the spatial disposition achieved with template **I** approximates the ideal conformation of bound DAG, our comparison would explain the inadequacy of template **II** (Figure 1). When the same conformational analysis was extended to compounds **10e** and **10f** (template **I**), which have the additional α-alkylidene chain, the molecules superimposed nicely on **3e** with a root mean square (rms) deviation of 0.0580 Å for all non-hydrogen atoms on the lactone rings. This means that introduction of an sp^2 carbon adjacent to the carbonyl function did not have a major conformational effect, and the ring puckering of the potent ligands **3e**, **10e**, and **10f** remained virtually identical. Similarly, the lactone rings of the inactive compounds **9c**, **14c** and **15c**, superimposed nicely with each other (rms = 0.0510 Å).

Experimental Section

General Experimental. All chemical reagents were commercially available. Melting points were determined on a Mel-Temp II apparatus, Laboratory Devices, USA, and are uncorrected. Silica gel column chromatography was performed on silica gel 60, 230−400 mesh (E. Merck). Proton and ^{13}C NMR spectra were recorded on a Bruker AC-250 instrument at 250 and 62.9 MHz, respectively. Spectra were referenced to the solvent in which they were run (7.24 ppm for $CDCl_3$). Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

Analysis of Inhibition of [^{3}H]PDBU Binding by Non-radioactive Ligands. Enzyme−ligand interactions were analyzed by competition with [^{3}H]PDBU binding essentially as described in our previous work,[11] except that the PK-C preparation used here was the single isozyme PK-Cα. This recombinant PK-Cα was expressed in the baculovirus system and was isolated as described in ref 19. 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 as described before.[11,19] Values represent the mean ± standard error (three determinations).

Molecular Modeling. All structures were modeled using QUANTA 3.1 on a Silicon Graphics Indigo with CHARMm 2.2

force field parameters. Semi-empirical quantum mechanics studies using AM1 Hamiltonian parameters within Mopac 6.0, performed on a Convex mini-supercomputer, confirmed the results obtained using CHARMm.

1-*O*-(*tert*-Butyldiphenylsilyl)-1,3-dihydroxy-2-propanone (1b). *tert*-Butylchlorodiphenylsilane (0.76 g, 2.7 mmol) was added over a period of 10 min to a chilled (0 °C) solution of 1,3-dihydroxyacetone (**1a**, 0.5 g, 2.7 mmol) and (dimethylamino)pyridine (DMAP, 0.085 g, 0.7 mmol) in dry pyridine (20 mL). The reaction mixture was allowed to reach room temperature, and stirring was continued for a total of 16 h. After the addition of ice-cold water (100 mL), the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extract was washed with 1 N HCl solution (3 × 10 mL) and water (15 mL) and dried over Na_2SO_4. The residue obtained after removing the organic solvent was purified by flash column chromatography over silica gel with mixtures of hexane/EtOAc (95:5 followed by 85:15) as eluants to give **1b** (0.472 g, 52%) as an oil: IR (neat) 3444 and 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 9 H, $C(CH_3)_3$), 4.30 (s, 2 H, CH_2OSi), 4.60 (s, 2 H, CH_2OH), 7.30−7.70 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 19.20, 26.71, 66.76, 68.30, 128.03, 130.23, 132.00, 135.44, 210.28. Anal. ($C_{19}H_{24}O_3Si$) C, H.

1,3-Bis-*O*-(*tert*-butyldiphenylsilyl)-1,3-dihydroxy-2-propanone (1c). *tert*-Butylchlorodiphenylsilane (50 g, 181.9 mmol) was added over a period of 30 min to a chilled (0 °C) solution of 1,3-dihydroxyacetone (**1a**, 7.28 g, 0.42 mmol) and DMAP (2.47 g, 20.2 mmol) in dry pyridine (100 mL). The reaction mixture was allowed to reach room temperature, and stirring was continued for a total of 4 days. The reaction mixture was poured over crushed ice (500 g) and left overnight. The precipitated solid was filtered and washed with water (ca. 500 mL). The filtrate was extracted with EtOAc (3 × 150 mL), and the combined organic extract was washed with 1 N HCl (3 × 100 mL) and water (2 × 100 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give a white solid. The solid was recrystallized from EtOAc/hexane to a give **1c** (41.7 g, 91%) as a white solid: mp 100−101 °C; IR (KBr) 1749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 18 H, $C(CH_3)_3$), 4.40 (s, 4 H, CH_2OSi), 7.30−7.60 (m, 20 H, Ph); ^{13}C NMR ($CDCl_3$) δ 19.17, 26.68, 68.53, 127.81, 129.91, 132.58, 135.46, 207.10. Anal. ($C_{35}H_{42}O_3Si_2$) C, H.

3-*O*-Tetradecanoyl-1-*O*-(*tert*-butyldiphenylsilyl)-1,3-dihydroxy-2-propanone (1d). A solution of **1b** (0.170 g, 0.52 mmol), dry pyridine (0.204 g, 2.6 mmol), and DMAP (0.010 g, 0.08 mmol) in dry CH_2Cl_2 (12 mL) was treated with myristoyl chloride (0.255 g, 1.03 mmol), and the resulting mixture was stirred under argon for 24 h. After volatiles were removed, the residue was partitioned in a mixture of ether (20 mL) and 1 N HCl (10 mL). The ether layer was washed consecutively with 1 N HCl (10 mL) and water (10 mL) and dried (Na_2SO_4). The solvent was removed, and the residue obtained was purified by flash column chromatography over silica gel with hexane/EtOAc (96:4) as eluant to provide **1d** (0.215 g, 77%) as an oil: IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (distorted t, 3 H, CH_3), 1.10 (s, 9 H, $C(CH_3)_3$), 1.20−1.40 (m, 20 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 1.65 (m, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.40 (t, J = 7.5 Hz, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 4.25 (s, 2 H, CH_2OSi), 5.02 (s, 2 H, CH_2OCO), 7.45−7.65 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.10, 19.17, 22.67, 24.85, 26.71, 29.07, 29.25, 29.33, 29.43, 29.59, 29.63, 29.65, 31.90, 33.82, 66.76, 68.78, 127.99, 130.16, 132.04, 135.44, 173.07, 203.31. Anal. ($C_{33}H_{50}O_4Si$) C, H.

2-Hydroxy-2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1-[(*tert*-butyldiphenylsilyl)oxy]-4-pentene (2c). A stirred solution of **1c** (1.0 g, 1.76 mmol) in THF (12 mL) at 0 °C was treated with a solution of allylmagnesium bromide (2 M, 1.76 mL), which was added dropwise over a period of 5 min. The reaction mixture was stirred at 0 °C for 1 h, the reaction was quenched with 1 N HCl (5 mL), and the mixture was concentrated under reduced pressure. The residue was extracted with EtOAc (2 × 20 mL), and the organic extract was washed with water (10 mL), dried ($NaSO_4$), and concentrated under vacuum. The residue obtained was purified by flash column chromatography using silica gel and hexane/EtOAc (98:2) to give the title compound **2c** (0.99 g, 93%) as a colorless liquid: IR (neat) 3565, 1427 cm^1; ^1H NMR ($CDCl_3$) δ 1.05 (s, 18 H, $C(CH_3)_3$), 2.35 (d, J = 7.2 Hz, 2 H, $CH_2CH{=}CH_2$), 2.50 (s, 1 H, OH), 3.65 (AB q, J = 9.8 Hz, 4 H, CH_2OSi), 5.00 (m, 2 H, $CH{=}CH_2$), 5.75 (m, 1 H, $CH{=}CH_2$), 7.30−7.70 (m, 20 H, Ph); ^{13}C NMR ($CDCl_3$) δ 19.28, 26.88, 38.40, 66.05, 74.39, 117.97, 127.70, 129.71, 133.08, 133.29, 135.62. Anal. ($C_{38}H_{48}O_3Si_2$) C, H.

2-Hydroxy-2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1-(tetradecanoyloxy)-4-pentene (2d). A solution of $TiCl_4$ in CH_2Cl_2 (1 M, 6.3 mL) was added to a stirred solution of **1d** (2.25 g, 4.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. After 5 min, neat allyltrimethylsilane (1.43 g, 12.5 mmol) was rapidly added, and stirring was continued for 40 min. The reaction was quenched with ice-cold water (50 mL) and extracted with ether (3 × 50 mL). The combined ether extract was washed with water (3 × 25 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed by flash column chromatography over silica gel. The appropriate fractions, eluted with hexane containing increasing proportions of EtOAc (3−4%), were combined and evaporated under reduced pressure to give **2d** (1.87 g, 77%) as an oil: IR (neat) 3486, 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (distorted t, 3 H, CH_3), 1.10 (s, 9 H, $C(CH_3)_3$), 1.30 (m, 20 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 1.60 (m, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.25 (t, J = 7.4 Hz, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.35 (br d, J = 8.3 Hz, 2 H, $CH_2CH{=}CH_2$), 2.50 (s, 1 H, OH), 3.52 (s, 2 H, CH_2OSi), 4.10 (AB q, J = 13.4 Hz, 2 H, CH_2OCO), 5.00−5.10 (m, 2 H, $CH{=}CH_2$), 5.70−5.90 (m, 1 H, $CH{=}CH_2$), 7.30−7.70 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.10, 19.26, 22.67, 24.88, 26.84, 29.15, 29.25, 29.34, 29.45, 29.59, 29.63, 29.66, 31.90, 34.18, 38.88, 66.08, 66.12, 73.23, 118.91, 127.77, 129.87, 132.38, 135.58, 173.64. Anal. ($C_{36}H_{56}O_4Si$) C, H.

5-Bis[[(*tert*-butyldiphenylsilyl)oxy]methyl]tetrahydro-2-furanone (3c). A stirred solution of **2c** (1.92g, 3.15 mmol) in dry THF (30 mL) at −78 °C was treated dropwise with a THF solution of $BH_3{\cdot}SMe_2$ (2 M, 3.15 mL) while being maintained under a blanket of argon. The reaction mixture was allowed to reach room temperature during the course of 24 h, and then it was concentrated under reduced pressure. The residue obtained was dissolved in dry CH_2Cl_2 (100 mL) and treated with pyridinium chlorochromate (PCC,15 g, 69.5 mmol). The dark reaction mixture was stirred at room temperature for 36 h and was diluted with dry ether (200 mL) before being filtered through a short silica gel column. The solution obtained was dried (Na_2SO_4) and evaporated, and the residue was purified by flash column chromatography over silica gel using hexane/EtOAc (94:6) as eluant to give the title compound **3c** (1.28 g, 65%) as a white solid: mp 125.5−126.5 °C (EtOAc/hexane); IR (KBr) 1784 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 18 H, 2 × $C(CH_3)_3$), 2.20 (distorted t, 2 H, H-$4_{a,b}$), 2.65 (distorted t, 2 H, H-$3_{a,b}$), 3.70 (AB q, J = 10.9 Hz, 4 H, CH_2OSi), 7.30−7.70 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 19.19, 25.69, 26.73, 29.41, 66.46, 88.23, 127.72, 127.82, 129.88, 132.52, 132.77, 135.55, 135.61, 177.14. Anal. ($C_{38}H_{46}O_4Si_2$) C, H.

5-Bis(hydroxymethyl)tetrahydro-2-furanone (3a). A solution of **3c** (0.62 g, 1 mmol) and ammonium fluoride (0.37 g, 10 mmol) in MeOH (30 mL) was stirred at room temperature for 4 days. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using EtOAc/MeOH (95:5) as eluant to give the title compound **3a** (0.058 g, 40%) as a clear liquid: IR (neat) 3415.9, 1760.1 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (distorted t, 2 H, H-$4_{a,b}$), 2.65 (m, 4 H, H-$3_{a,b}$, 2 × OH), 3.65 (dd, J = 12.1, 6.0 Hz, 2 H, CH_2OH), 3.80 (dd, J = 12.1, 6.2 Hz, 2 H, CH_2OH); ^{13}C NMR ($CDCl_3$) δ 25.10, 29.17, 65.24, 88.48, 177.57. Anal. ($C_6H_{10}O_4$) C, H.

5-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-[(tetradecanoyloxy)methyl]tetrahydro-2-furanone (3d). A stirred solution of **2d** (1.04 g, 1.8 mmol) in dry THF (35 mL) at −78 °C was treated dropwise with a THF solution of $BH_3{\cdot}SMe_2$ (2 M, 1.8 mL) while being maintained under a blanket of argon. The reaction mixture was allowed to reach room temperature during the course of 3 h and was stirred further for 12 h. Evaporation of the solvent under reduced pressure gave a residue that was dissolved in dry CH_2Cl_2 (100 mL) and treated with pyridinium chlorochromate (PCC, 15 g, 69.5 mmol). The

dark reaction mixture was stirred at room temperature for 3 days and was diluted with dry ether (500 mL) before being filtered through a short silica gel column. The solution obtained was dried (Na_2SO_4) and reduced to dryness. The residue was purified by flash column chromatography over silica gel using 10% EtOAc in hexane as eluant to give **3d** (0.758 g, 71%) as a pale yellow oil: IR (neat) 1785, 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (distorted t, 3 H, CH_3), 1.05 (s, 9 H, $C(CH_3)_3$), 1.25 (m, 20 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 1.55 (m, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.00−2.40 (m, 4 H, H-$4_{a,b}$, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.60 (m, 2 H, H-$3_{a,b}$), 3.70 (AB q, J = 10.8 Hz, 2 H, CH_2OSi), 4.20 (AB q, J = 12.0 Hz, 2 H, CH_2-OCO), 7.30−7.70 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.10, 19.17, 22.67, 24.78, 25.91, 26.72, 28.87, 29.08, 29.20, 29.33, 29.41, 29.57, 29.62, 31.90, 34.03, 65.64, 66.15, 85.77, 127.88, 130.01, 132.25, 132.50, 135.52, 135.59, 173.15, 176.28. Anal. ($C_{36}H_{54}O_5Si$) C, H.

5-[(Tetradecanoyloxy)methyl]-5-(hydroxymethyl)tetrahydro-2-furanone (3e). A solution of **3d** (0.118 g, 0.2 mmol) in THF (3 mL) at room temperature was stirred with a solution of *n*-tetrabutylammonium fluoride in THF (1 M, 0.3 mL) for 40 min. The solution was evaporated under vacuum, dissolved in EtOAc (20 mL), dried (Na_2SO_4), and concentrated. The residue obtained was purified by flash column chromatography over silica gel using hexane/EtOAc (7:3) as eluant to give **3e** (0.051 g, 72%) as a white solid: mp 65−66 °C (EtOAc/hexane); IR (KBr) 3448, 1763, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (distorted t, 3 H, CH_3), 1.30 (m, 20 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 1.60 (m, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.00−2.12 (m, 1 H, H-$4_a$), 2.20−2.30 (m, 1 H, H-$4_b$), 2.33 (t, J = 7.6 Hz, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.45 (t, J = 6.4 Hz, 1 H, OH), 2.65 (m, 2 H, H-$3_{a,b}$), 3.60 (dd, J = 12.1, 5.9 Hz, 1 H, CHOH), 3.75 (dd, J = 12.1, 6.1 Hz, CHOH), 4.10 (d, J = 12.0 Hz, 1 H, CHOCO), 4.30 (d, J = 12.0 Hz, 1 H, CHOCO); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.65, 24.81, 25.47, 28.79, 29.07, 29.19, 29.32, 29.41, 29.56, 29.60, 31.89, 34.03, 64.82, 65.45, 86.02, 173.48, 176.47; FAB MS (m/z, relative intensity) 357 (MH^+, 100), 211 ($C_{13}H_{27}CO^+$, 35). Anal. ($C_{20}H_{36}O_5$) C, H.

5-{[(*Z*)-9-Octadecenoyloxy]methyl}-5-(hydroxymethyl)-tetrahydro-2-furanone (3f). A stirred solution of **3a** (0.025 g, 0.17 mmol), dry pyridine (68 mg), and DMAP (2 mg) in dry CH_2Cl_2 (5 mL) at 0 °C was treated with oleoyl chloride (0.051 g, 0.17 mmol). After 1 h, the reaction was quenched with water (3 mL), and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (1 × 5 mL), and the combined organic extract was washed with 1 N HCl (5 mL) and water (5 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue obtained was purified by flash column chromatography over silica gel using hexane/EtOAc (65:35) as eluant to give the title compound **3f** (0.046 g, 66%) as a white solid: mp 38.5−39.5 °C (EtOAc/hexane); IR (KBr) 3447, 1780, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.30 (m, 20 H, $CH_3(CH_2)_6CH_2CH{=}CHCH_2(CH_2)_4CH_2$-$CH_2CO$), 1.60 (m, 2 H, $CH_3(CH_2)_6CH_2CH{=}CHCH_2(CH_2)_4CH_2$-$CH_2CO$),1.90−2.10 (m, 5 H, $CH_2CH{=}CHCH_2$, H-4_a), 2.20−2.40 (m, 3 H, $CH_3(CH_2)_6CH_2CH{=}CHCH_2(CH_2)_4CH_2CH_2CO$, H-$4_b$), 2.65 (m, 2 H, H-$3_{a,b}$), 3.61 (d, J = 12.1 Hz, 1 H, CHOH), 3.75 (d, J = 12.1 Hz, CHOH), 4.12 (d, J = 12.0 Hz, 1 H, CHOCO), 4.30 (d, J = 12.0 Hz, 1 H, CHOCO), 5.32 (m, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.65, 24.80, 25.48, 27.13, 27.19, 28.76, 29.05, 29.10, 29.29, 29.50, 29.66, 29.73, 31.87, 34.02, 64.82, 65.44, 85.93, 129.67, 130.01, 173.45, 176.36; FAB MS (m/z, relative intensity) 411 (MH^+, 37), 265 ($C_{17}H_{33}CO^+$, 11). Anal. ($C_{24}H_{42}O_5$) C, H.

(*Z*)-5-Bis[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-tetradecanylidenetetrahydro-2-furanone (10a) and (*E*)-5-Bis[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-tetradecanylidenetetrahydro-2-furanone (11a). A solution of **3c** (0.685 g, 1.10 mmol) in anhydrous THF (10 mL) at −78 °C was treated with lithium diisopropylamide (2 M in heptane/THF/ethylbenzene, 1.37 mL) and stirred for 1 h. A solution of $ZnCl_2$ (0.5 M in THF, 2.3 mL) was added, and after 5 min a solution of 1-tetradecanal (0.280 g, 1.32 mmol) in THF (9 mL) was introduced into the reaction mixture dropwise. After 1.3 h, the reaction was quenched with a saturated NH_4Cl solution (10 mL), and the temperature was allowed to reach ambient conditions. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extract was washed with water (15 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by flash column chromatography over silica gel using hexane/EtOAc (95:5) as eluant to give the corresponding β-hydroxy lactone intermediate (0.641 g, 70%) as a clear liquid: IR (neat) 3510, 1752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (distorted t, 3 H, CH_3), 1.10 (s, 18 H, 2 × $C(CH_3)_3$), 1.20−1.50 (m, 24 H, $(CH_2)_{12}CH_3$), 1.90 (distorted t, 1 H, H-4_a), 2.20 (dd, J = 12.7, 10.1 Hz, 1 H, H-4_b), 2.85 (dd, J = 19.5, 10.1 Hz, 1 H, H-3), 3.60−3.80 (m, 4 H, CH_2OSi), 4.00 (s, 1 H, CHOH), 7.30−7.70 (m, 20 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.13, 19.15, 19.21, 22.69, 24.86, 26.56, 26.73, 26.77, 28.99, 29.36, 29.66, 29.69, 31.92, 34.83, 45.87, 65.76, 66.40, 72.16, 86.84, 127.70, 127.80, 127.90, 129.62, 129.90, 129.99, 132.24, 132.54, 132.62, 132.68, 134.79, 135.52, 135.57, 135.61, 179.56. Anal. ($C_{52}H_{74}O_5Si_2$) C, H.

A solution of this compound (0.583 g, 0.68 mmol) and triethylamine (0.343 g, 3.4 mmol) in dry CH_2Cl_2 (12 mL) was treated with methanesulfonyl chloride (0.196 g, 1.7 mmol), and the resulting mixture was stirred for 75 min. The reaction mixture was cooled to 0 °C, treated with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU, 0.624 g, 4 mmol), and allowed to reach room temperature. Stirring continued for a total of 4 h. The volatiles were removed under vacuum, and the residue was treated with 1 N HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extract was washed with 1 N HCl (2 × 20 mL) and water (5 mL) and dried (Na_2SO_4). The residue was purified by flash column chromatography over silica gel using hexane/EtOAc (98:2) to give **10a** (0.172 g, 30%) as the less polar compound, followed by **11a** (0.345 g, 60.5%). Both compounds were isolated as oils. **10a**: IR (neat) 1759, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (distorted t, 3 H, CH_3), 1.05 (s, 18 H, 2 × $C(CH_3)_3$), 1.20−1.60 (m, 22 H, $(CH_2)_{11}CH_3$), 2.70 (m, 2 H, $=CHCH_2$), 2.80 (br s, 2 H, H-$4_{a,b}$), 3.70 (AB q, J = 10.7 Hz, 2 H, CH_2OSi), 6.10 (distorted t, 1 H, =CH), 7.30−7.70 (m, 20 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.12, 19.22, 22.68, 26.68, 27.01, 29.18, 29.34, 29.51, 29.59, 29.66, 31.91, 33.15, 66.05, 84.37, 125.34, 127.75, 129.78, 132.70, 132.89, 135.57, 135.61, 143.35, 169.35. Anal. ($C_{52}H_{72}O_4Si_2$) C, H.

11a: IR (neat) 1763 and 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (distorted t, 3 H, CH_3), 1.00 (s, 18 H, 2 × $C(CH_3)_3$), 1.30−1.50 (m, 22 H, $(CH_2)_{11}CH_3$), 2.15 (m, 2 H, $=CHCH_2$), 2.75 (s, 2 H, H-$4_{a,b}$), 3.70 (AB q, J = 10.7 Hz, 2 H, CH_2OSi), 6.70 (m, 1 H, =CH), 7.30−7.60 (m, 20 H, Ph); ^{13}C NMR δ 14.12, 19.20, 22.68, 26.67, 28.14, 29.35, 29.41, 29.46, 29.53, 29.66, 30.18, 31.91, 66.16, 85.22, 127.47, 127.76, 129.81, 132.62, 132.87, 135.56, 135.61, 139.79, 170.60. Anal. ($C_{52}H_{72}O_4Si_2$) C, H.

(*Z*)-5-Bis[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-[(*Z*)-9-octadecenylidene]tetrahydro-2-furanone (10b) and (*E*)-5-Bis[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-[(*Z*)-9-octadecenylidene]tetrahydro-2-furanone (11b). These compounds were obtained as oils in a fashion similar to **10a** and **11a** starting from **3c** and oleyl aldehyde.

β-Hydroxy lactone intermediate (74%): IR (neat) 3510, 1750, 1589 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.00 and 1.05 (singlets, 18 H, $C(CH_3)_3$), 1.20−1.50 (m, 24 H, $CHOH(CH_2)_6CH_2CH{=}CHCH_2(CH_2)_6CH_3$), 1.90 (dd, J = 12.6, 10.9 Hz, 1 H, H-4_a), 2.00 (m, 4 H, $CH_2CH{=}CHCH_2$), 2.20 (dd, J = 12.6, 10.1 Hz, 1 H, H-4_b), 2.80 (m, 1 H, H-3), 3.50−3.80 (m, 4 H, CH_2OSi), 3.97 (s, 1 H, CHOH), 5.45 (m, 2 H, CH=CH), 7.30−7.60 (m, 20 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.10, 19.14, 19.20, 22.67, 24.88, 26.71, 26.75, 27.21, 28.97, 29.30, 29.51, 29.56, 29.60, 29.76, 31.88, 34.84, 45.87, 65.72, 66.38, 72.14, 86.82, 127.79, 127.88, 129.80, 129.89, 129.94, 129.98, 132.21, 132.51, 132.61, 132.65, 135.51, 135.55, 135.59, 179.54. Anal. ($C_{56}H_{80}O_5Si_2$) C, H.

10b (32%): IR (neat) 1759 and 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.00 (s, 18 H, 2 × $C(CH_3)_3$), 1.20−1.50 (m, 22 H, $CH_2(CH_2)_5CH_2CH{=}CHCH_2(CH_2)_6CH_3$), 2.00 (m, 4 H, $CH_2CH{=}CHCH_2$), 2.65 (m, 2 H, $>C{=}CHCH_2$), 2.80 (br s, 2 H, H-$4_{a,b}$), 3.70 (AB q, J = 10.7 Hz, 2 H, CH_2OSi), 5.35 (m, 2 H, CH=CH), 6.10 (distorted t, 1 H, $>C{=}CH$), 7.30−7.70 (m, 20 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.11, 19.21, 22.67, 26.68, 27.21, 27.59, 29.17, 29.23, 29.30, 29.41, 29.51, 29.76, 31.89, 33.15,

66.05, 84.37, 125.37, 127.74, 129.77, 129.82, 129.91, 132.69, 132.88, 135.56, 135.60, 143.27, 169.36. Anal. ($C_{56}H_{78}O_4Si_2$) C, H.

11b (60%): IR (neat) 1763 and 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (distorted t, 3 H, CH_3), 1.03 (s, 18 H, 2 × $C(CH_3)_3$), 1.20−1.50 (m, 22 H, $CH_2(CH_2)_5CH_2CH{=}CHCH_2(CH_2)_6CH_3$), 2.00 (m, 4 H, $CH_2CH{=}CHCH_2$), 2.15 (m, 2 H, >C=CHCH_2), 2.75 (br s, 2 H, H-$4_{a,b}$), 3.70 (AB q, J = 10.7 Hz, 2 H, CH_2OSi), 5.35 (m, 2 H, CH=CH), 6.70 (m, 1 H, >C=CH), 7.30−7.65 (m, 20 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.13, 19.22, 22.69, 26.69, 27.19, 27.23, 28.16, 29.18, 29.33, 29.39, 29.53, 29.69, 29.76, 30.18, 31.91, 66.19, 85.23, 127.52, 127.78, 129.73, 129.83, 130.02, 132.62, 132.88, 135.58, 135.62, 139.72, 170.59. Anal. ($C_{56}H_{78}O_4Si_2$) C, H.

General Desilylation Procedure for the Synthesis of 10c,d and 11c,d. A stirred solution of **10a**,**b**/**11a**,**b** (0.28 mmol) in THF (8 mL) at room temperature was treated with a THF solution of tetrabutylammonium fluoride (1 M, 0.85 mL) for the course of 1 h. After the volatiles were removed under reduced pressure, the residue was partitioned between EtOAc (20 mL) and water (10 mL). The organic layer was separated and dried (Na_2SO_4). After evaporation of the solvent, the residue obtained was purified by flash column chromatography over silica gel using a 0%−25% gradient of EtOAc in hexane as eluant. The compounds were isolated as colorless oils or solids:

***(Z)*-5-Bis(hydroxymethyl)-3-tetradecanylidenetetrahydro-2-furanone (10c):** solid (80% yield from **10a**): mp 63−64 °C (EtOAc/hexane); IR (KBr) 3316, 1750, and 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (distorted t, 3 H, CH_3), 1.10−1.50 (m, 22 H, $(CH_2)_{11}CH_3$), 2.65 (m, 2 H, >C=CHCH_2), 2.75 (br s, 2 H, H-$4_{a,b}$), 3.00 (t, J = 6.2 Hz, 2 H, OH), 3.70 (m, 2 H, CH_2OH), 6.20 (m, 1 H, >C=CH); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.67, 27.78, 29.05, 29.28, 29.33, 29.45, 29.56, 29.63, 29.66, 31.90, 32.66, 64.92, 84.49, 124.09, 145.84, 169.58. Anal. ($C_{20}H_{36}O_4$) C, H.

***(Z)*-5-Bis(hydroxymethyl)-3-[(*Z*)-9-octadecenylidene]-tetrahydro-2-furanone (10d):** oil (81% yield from **10b**); IR (neat) 3416, 1759, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.20−1.50 (m, 22 H, $CH_2(CH_2)_5CH_2CH{=}CHCH_2(CH_2)_6CH_3$), 2.00 (m, 4 H, $CH_2CH{=}CHCH_2$), 2.15 (t, J = 6.5 Hz, 2 H, OH), 2.68 (m, 2 H, >C=CHCH_2), 2.80 (br s, 2 H, H-$4_{a,b}$), 3.70 (m, 2 H, CH_2OH), 5.35 (m, 2 H, CH=CH), 6.22 (m, 1 H, >C=CH); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.65, 27.19, 27.76, 29.04, 29.19, 29.25, 29.29, 29.35, 29.49, 29.63, 29.73, 31.87, 32.67, 64.82, 84.60, 124.16, 129.77, 129.94, 145.74, 169.71. Anal. ($C_{24}H_{42}O_4$) C, H.

***(E)*-5-Bis(hydroxymethyl)-3-tetradecanylidenetetrahydro-2-furanone (11c):** solid (80% yield from **11a**): mp 76.5−77.5 °C (EtOAc/hexane); IR (KBr) 3414, 1715, 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.10−1.50 (m, 22 H, $(CH_2)_{11}CH_3$), 2.15 (m, 2 H, =CHCH_2), 2.68 (br s, 2 H, H-$4_{a,b}$), 3.05 (br, 2 H, OH), 3.70 (AB q, J = 12.1 Hz, 2 H, CH_2OH), 6.70 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.66, 28.05, 29.34, 29.36, 29.38, 29.52, 29.62, 30.29, 31.89, 64.93, 85.55, 126.29, 142.20, 171.03. Anal. ($C_{20}H_{36}O_4$) C, H.

***(E)*-5-Bis(hydroxymethyl)-3-[(*Z*)-9-octadecenylidene]-tetrahydro-2-furanone (11d):** oil (76% yield from **11b**); IR (neat) 3411, 1714, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (distorted t, 3 H, CH_3), 1.20−1.50 (m, 22 H, $CH_2(CH_2)_5CH_2CH{=}CHCH_2(CH_2)_6CH_3$), 2.00 (m, 4 H, $CH_2CH{=}CHCH_2$), 2.15 (m, 2 H, >C=CHCH_2), 2.70 (br s, 2 H, H-$4_{a,b}$), 2.85 (br s, 2 H, OH, D_2O exchanged), 3.70 (AB q, J = 12.0 Hz, 2 H, CH_2OH), 5.35 (m, 2 H, CH=CH), 6.72 (m, 1 H, >C=CH); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.65, 27.14, 27.20, 28.03, 29.14, 29.29, 29.34, 29.50, 29.69, 29.73, 30.27, 31.88, 65.05, 85.33, 126.23, 129.68, 130.01, 142.20, 170.78. Anal. ($C_{24}H_{42}O_4$) C, H.

General Procedure for the Monoacetylation of Diols 10c,d and 11c,d. Syntheses of 10e,f and 11e,f. A stirred solution of diol **10c**,**d**/**11c**,**d** (0.14 mmol), pyridine (0.7 mmol), and DMAP (1 mg) in dry CH_2Cl_2 (4 mL) at 0 °C was treated with acetic anhydride (0.14 mmol) for 1 h. The reaction was quenched by the addition of water (2 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL), and the combined organic extract was washed with 1 N HCl (5 mL) and water (5 mL) and dried (Na_2SO_4). The residue obtained after evaporation was purified by flash column chromatography over silica gel using 25−30% EtOAc in hexane. The compounds were isolated as colorless oils or solids:

***rac*-(*Z*)-5-[(Acetyloxy)methyl]-5-(hydroxymethyl)-3-tetradecanylidenetetrahydro-2-furanone (10e):** solid (67% yield from **10c**): mp 58−59 °C (EtOAc/hexane); IR (KBr) 3387, 1728.0, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.20−1.50 (m, 22 H, $(CH_2)_{11}CH_3$), 2.05 (s, 3 H, CH_3CO), 2.34 (br s, 1 H, OH), 2.65 (m, 3 H, H-4_a, =CHCH_2), 2.88 (m, 1 H, H-4_b), 3.62 (br AB q, J = 12.1 Hz, 2 H, CH_2OH), 4.20 (AB q, J = 11.8 Hz, 2 H, CH_2OAc), 6.20 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.09, 20.65, 22.65, 27.73, 29.05, 29.26, 29.32, 29.42, 29.53, 29.62, 29.64, 31.89, 33.05, 64.53, 65.28, 82.22, 123.58, 145.77, 168.65, 170.81; FAB MS (*m*/*z*, relative intensity) 383 (MH^+, 100). Anal. ($C_{22}H_{38}O_5$) C, H.

***rac*-(*Z*)-5-[(Acetyloxy)methyl]-5-(hydroxymethyl)-3-[(*Z*)-9-octadecenylidene]tetrahydro-2-furanone (10f):** semisolid gum (62% yield from **10d**): IR (neat) 3433, 1747, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (distorted t, 3 H, CH_3), 1.20−1.50 (m, 22 H, $CH_2(CH_2)_5CH_2CH{=}CHCH_2(CH_2)_6CH_3$), 2.00 (m, 4 H, $CH_2CH{=}CHCH_2$), 2.10 (s, 3 H, CH_3CO), 2.70 (m, 3 H, H-4_a, >C=CHCH_2), 2.88 (m, 1 H, H-4_b), 3.62 (m, 2 H, CH_2-OH), 4.20 (AB q, J = 11.8 Hz, 2 H, CH_2OAc), 5.32 (m, 2 H, CH=CH), 6.22 (m, 1 H, >C=CH); ^{13}C NMR ($CDCl_3$) δ 14.09, 20.66, 22.66, 27.19, 27.72, 29.04, 29.18, 29.23, 29.30, 29.50, 29.71, 29.74, 31.88, 33.08, 64.56, 65.23, 82.11, 123.52, 129.76, 129.96, 145.80, 168.50, 170.80; FAB MS (*m*/*z*, relative intensity) 437 (MH^+, 36). Anal. ($C_{26}H_{44}O_5$) C, H.

***rac*-(*E*)-5-[(Acetyloxy)methyl]-5-(hydroxymethyl)-3-tetradecanylidenetetrahydro-2-furanone (11e):** solid (54% yield from **11c**): mp 77.5−78.5 °C: IR (KBr) 3384, 1733, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (distorted t, 3 H, CH_3), 1.20−1.50 (m, 22 H, $(CH_2)_{11}CH_3$), 2.05 (s, 3 H, CH_3CO), 2.15 (m, 2 H, =CHCH_2), 2.40 (t, J = 6.7 Hz, 1 H, OH), 2.60 (dd, J = 17.1, 2.6 Hz, 1 H, H-4_a), 2.80 (dd, J = 17.1, 2.8 Hz, H-4_b), 3.65 (m, 2 H, CH_2OH), 4.20 (AB q, J = 11.8 Hz, 2 H, CH_2OAc), 6.72 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.09, 20.63, 22.66, 28.05, 29.32, 29.37, 29.50, 29.61, 29.79, 30.28, 31.89, 64.71, 65.43, 82.90, 125.64, 142.22, 169.89, 170.77; FAB MS (*m*/*z*, relative intensity) 383 (MH^+, 100). Anal. ($C_{22}H_{38}O_5$) C, H.

***rac*-(*E*)-5-[(Acetyloxy)methyl]-5-(hydroxymethyl)-3-[(*Z*)-9-octadecaenylidene]tetrahydro-2-furanone (11f):** solid (62% yield from **11d**): mp 45.5−46.5 °C: IR (KBr) 3383, 1732, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (distorted t, 3 H, CH_3), 1.20−1.50 (m, 22 H, $CH_2(CH_2)_5CH_2CH{=}CHCH_2(CH_2)_6CH_3$), 2.00 (m, 4 H, $CH_2CH{=}CHCH_2$), 2.10 (s, 3 H, CH_3CO), 2.15 (m, 2 H, >C=CHCH_2), 2.35 (t, J = 6.8 Hz, 1 H, OH), 2.62 (dd, J = 17.1, 2.6 Hz, 1 H, H-4_a), 2.80 (dd, J = 17.1, 2.8 Hz, 1 H, H-4_b), 3.61 (m, 2 H, CH_2OH), 4.26 (AB q, J = 11.8 Hz, 2 H, CH_2OAc), 5.32 (m, 2 H, CH=CH), 6.75 (m, 1 H, >C=CH); ^{13}C NMR ($CDCl_3$) δ 14.09, 20.63, 22.65, 27.12, 27.19, 28.05, 29.13, 29.29, 29.49, 29.68, 29.73, 29.78, 30.27, 31.87, 64.70, 65.42, 82.89, 125.66, 129.64, 130.04, 142.17, 169.80, 170.77; FAB MS (*m*/*z*, relative intensity) 437 (MH^+, 68). Anal. ($C_{26}H_{44}O_5$) C, H.

5-[(Acetyloxy)methyl]-5-(hydroxymethyl)-3-tetradecanyltetrahydro-2-furanone (Mixture of Diastereoisomers, 12). A solution of **11e** (0.006 g) in EtOAc (5 mL) was hydrogenated in the presence of 10% Pd/C (0.003 g) at 45 psi for 1.3 h. The reaction mixture was filtered through a small pad of silica gel which was washed with additonal EtOAc (10 mL). The collected filtrate was concentrated under vaccum to give the title compound as a white solid in nearly quantitative yield: mp 79−81 °C (EtOAc/hexane); IR (KBr) 3415, 1741 cm^{-1}; FAB MS (*m*/*z*, relative intensity) 385 (MH^+, 100). Anal. ($C_{22}H_{40}O_5$) C, H.

1,3-Bis-*O*-(*tert*-butyldimethylsilyl)-1,3-dihydroxy-2-propanone (4a). This compound was prepared in the same fashion as **1c** according to the method of Kinder et al.[24]

Methyl 3,3-Bis[(*tert*-butyldimethylsiloxy)methyl]acrylate (5a). A solution of **4a** (12.74 g, 40 mmol) in benzene (200 mL) was treated with methyl (triphenylphosphoranylidene)acetate (16.05 g, 48 mmol) and refluxed for 8 h. The reaction mixture was cooled and concentrated under reduced pressure. The residue was dissolved in hexane and filtered, and the filtrate was concentrated. The residue was purified

by flash column chromatography over silica gel with hexane/EtOAc (19:1) as eluant to give the title compound **5a** (13.48 g, 90%) as an oil: IR (neat) 1719, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 and 0.06 (s, 6 H, $Si(CH_3)_2$), 0.87 and 0.91 (s, 9 H, $C(CH_3)_3$), 3.67 (s, 3 H, CO_2CH_3), 4.42 (m, 2 H, CH_2OSi), 4.85 (m, 2 H, CH_2OSi), 5.98 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ −2.14, 18.15, 18.37, 25.76, 25.88, 50.99, 61.55, 63.17, 111.33, 162.07, 166.96. Anal. ($C_{18}H_{38}O_4Si_2$) C, H.

3,3-Bis[(*tert*-butyldimethylsiloxy)methyl]-2-propen-1-ol (6a). A solution of **5a** (11.24 g, 30 mmol) in CH_2Cl_2 (100 mL) was cooled to −60 °C and treated dropwise with a solution of diisobutylaluminum hydride in CH_2Cl_2 (1.0 M, 40 mL). The reaction was quenched with saturated potassium sodium tartrate tetrahydrate, and the mixture was warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was washed with water and brine. The organic layer was dried ($NaSO_4$) and concentrated. The residue was purified by flash column chromatography over silica gel with hexane/EtOAc (5:1) as eluant to give the title compound **6a** (9.77 g, 94%) as an oil: IR (neat) 3357, 1471 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 and 0.06 (s, 12 H, $Si(CH_3)_2$), 0.88 and 0.89 (s,18 H, $C(CH_3)_3$), 1.86 (br s, 1 H, OH), 4.14 (br s, 2 H, CH_2OH), 4.20 (m, 4 H, 2 × CH_2OSi), 5.80 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ −1.95, 18.19, 18.33, 25.62, 25.79, 25.88, 58.50, 59.24, 64.75, 125.47, 140.81. Anal. ($C_{17}H_{38}O_3Si_2$) C, H.

Ethyl 3,3-Bis[(*tert*-butyldimethylsiloxy)methyl]-4-pentenoate (7a). A mixture of **6a** (9.36 g, 27 mmol), triethyl orthoacetate (34.75 mL, 189 mmol), and propionic acid (0.2 mL, 2.7 mmol) was heated at 138 °C for 20 h with removal of ethanol. The reaction mixture was cooled and concentrated under vacuum, and the residue was purified by flash column chromatography over silica gel with hexane/EtOAc (19:1) as eluant to give the title compound **7a** (8.77 g, 78%) as an oil: IR (neat) 1737, 1471 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (br s, 12 H, 2 × $Si(CH_3)_2$), 0.85 (br s, 18 H, 2 × $C(CH_3)_3$), 1.21 (t, 3 H, CH_3CH_2), 2.42 (s, 2 H, CH_2COEt), 3.61 (AB q, J = 9.3 Hz, 4 H, 2 × CH_2OSi), 4.06 (q, 2 H, CH_2CH_3), 5.06 (m, 2 H, $CH{=}CH_2$), 5.84 (dd, J = 19.9, 11.3, 1 H, $CH{=}CH_2$); ^{13}C NMR ($CDCl_3$) δ −5.58, 14.24, 18.23, 25.84, 36.81, 45.97, 59.84, 64.63, 114.47, 139.73, 171.87. Anal. ($C_{21}H_{44}O_4Si_2$) C, H.

4-(Hydroxymethyl)-4-vinyltetrahydro-2-furanone (8b). A solution of **7a** (8.34 g, 20 mmol) in aqueous THF (60 mL, 1:1) was treated with concentrated H_2SO_4 (10 mL) and stirred at room temperature for 24 h. The mixture was concentrated under vacuum and diluted with water, and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with H_2O, dried ($NaSO_4$), and concentrated. The residue was purified by flash column chromatography over silica gel with EtOAc/hexane (2:1) as eluant to give the title compound **8b** (2.50 g, 88%) as an oil: IR (neat) 3452 (OH), 1777 (C=O), 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (d of AB, J = 17.4 Hz, 1 H, H-3_a), 2.63 (d of AB, J = 17.4 Hz, 1 H, H-3_b), 3.62 (s, 2 H, CH_2OH), 4.16 (d of AB, J = 9.2 Hz, 1 H, H-5_a), 4.32 (d of AB, J = 9.2 Hz, 1 H, H-5_b), 5.19 (d, J = 17.5 Hz, 1 H, CH=CH*H*), 5.29 (d, J = 10.8 Hz, 1 H, CH=CH*H*), 5.85 (dd, J = 17.5, 10.8 Hz, 1 H, $CH{=}CH_2$); ^{13}C NMR ($CDCl_3$) δ 35.94, 47.61, 65.56, 73.33, 116.18, 137.55, 176.97. Anal. ($C_7H_{10}O_3$) C, H.

4-[(Tetradecanoyloxy)methyl]-4-vinyltetrahydro-2-furanone (8c). A solution of **8b** (0.2 g, 1.4 mmol) in CH_2Cl_2 (20 mL) was treated with pyridine (0.45 mL, 5.6 mmol), (dimethylamino)pyridine (0.034 g, 0.28 mmol), and tetradecanoyl chloride (0.76 mL, 2.8 mmol). After stirring for 2 h at room temperature, the reaction mixture was concentrated, and the residue was purified by flash column chromatography over silica gel with hexane/EtOAc (3:1) as eluant to give the title compound **8c** (0.49 g, 99%) as an oil: IR (neat) 1788 and 1741 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.25 (m, 20 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 1.60 (m, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.31 (t, J = 7.4 Hz, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.60 (s, 2 H, H-$3_{a,b}$), 4.12 (AB q, J = 11.3 Hz, 2 H, $CH_2OCOC_{13}H_{27}$), 4.20 (AB q, J = 9.3 Hz, 2 H, H-$5_{a,b}$), 5.19 (d, J = 17.6 Hz, 1 H, CH=CH*H*), 5.28 (d, J = 10.9 Hz, 1 H, CH=CH*H*), 5.84 (dd, J = 10.9, 17.6 Hz, $CH{=}CH_2$); ^{13}C NMR ($CDCl_3$) δ 14.02, 22.58, 24.69, 28.99, 29.11, 29.24, 29.34, 29.48, 29.53, 29.56, 31.81, 33.93, 36.57, 45.76, 66.63, 73.60, 116.63, 136.81, 173.27, 175.03. Anal. ($C_{21}H_{36}O_4$) C, H.

4-(Hydroxymethyl)-4-[(tetradecanoyloxy)methyl]-4-vinyltetrahydro-2-furanone (9c). A stirring solution of **8c** (0.49 g, 1.4 mmol) in aqueous acetone (1:1, 20 mL) was treated with 4-methylmorpholine *N*-oxide (0.33 g, 2.8 mmol), sodium metaperiodate (0.6 g, 2.8 mmol), and osmium tetroxide (2.5 wt % solution in *tert*-butyl alcohol, 1.75 mL, 0.14 mmol) for 20 h at room temperature. The reaction mixture was quenched with saturated sodium thiosulfate solution (10 mL), stirred for 10 min, and extracted with EtOAc. The combined organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography over silica gel with EtOAc/hexane (1:1) as eluant to give the corresponding aldehyde (0.432 g, 88%) as a white solid: mp 63 °C; IR (KBr) 1784, 1767, and 1735 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.25 (m, 20 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 1.60 (m, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.30 (t, J = 7.4 Hz, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.54 (d of AB, J = 17.9 Hz, 1 H, H-3_a), 2.92 (d of AB, J = 17.9 Hz, 1 H, H-3_b), 4.21 (d of AB, J = 9.9 Hz, 1 H, H-5_a), 4.38 (AB q, J = 11.65 Hz, 2 H, $CH_2OCOC_{13}H_{27}$), 4.55 (d of AB, J = 9.9 Hz, 1 H, H-5_b), 9.66 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 14.05, 22.62, 24.67, 28.98, 29.12, 29.28, 29.36, 29.51, 29.56, 31.84, 32.11, 33.76, 54.27, 63.49, 68.66, 173.10, 173.30, 196.71, 196.86. Anal. ($C_{20}H_{34}O_5$) C, H. This aldehyde (0.425 g, 1.2 mmol) was dissolved in MeOH (15 mL), cooled to −10 °C, and treated with sodium borohydride (0.09 g, 2.4 mmol). After stirring for 30 min, the reaction mixture was quenched by the slow addition of a phosphate buffer solution (pH 4, 5 mL) and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography over silica gel with EtOAc/hexane (1:1) as eluant to give the title compound **9c** (0.35 g, 82%) as a white solid: mp 50 °C; IR (KBr) 3461 (OH), 1764, and 1739 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.25 (m, 20 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 1.60 (m, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.33 (t, J = 7.4 Hz, 2 H, $CH_3(CH_2)_{10}CH_2CH_2CO$), 2.50 (AB q, J = 17.8 Hz, 2 H, H-3 $_{a,b}$), 3.58 (bs, 2 H, CH_2OH), 4.15 (AB q, J = 9.6 Hz, 2 H, H-$5_{a,b}$), 4.17 (s, 2 H, $CH_2OCOC_{13}H_{27}$); ^{13}C NMR ($CDCl_3$) δ 13.99, 22.56, 24.73, 29.00, 29.10, 29.22, 29.33, 29.48, 29.52, 29.54, 31.79, 33.94, 34.04, 45.17, 63.47, 64.78, 72.05, 173.93, 176.19; FAB MS m/z (relative intensitiy) 357 (MH^+, 59), 211 ($C_{13}H_{27}CO^+$, 55). Anal. ($C_{20}H_{36}O_5$) C, H.

4-[(Benzyloxy)methyl]-4-[(*tert*-butyldimethylsiloxy)-methyl]tetrahydro-2-furanone (13). A solution of **8b** (1.28 g, 9.0 mmol) in THF (60 mL) was cooled to 0 °C, treated with sodium hydride (60% dispersion in mineral oil, 0.72 g, 18 mmol), and stirred for 30 min. The reaction mixture was warmed to room temperature and treated with benzyl bromide (1.6 mL, 13.5 mmol) followed by tetrabutylammonium iodide (0.33 g, 0.9 mmol). The reaction mixture was stirred for 8 h at room temperature, cooled with an ice bath, and quenched with acetic acid (1 mL). The mixture was filtered through a short pad of silica gel, and the filtrate was concentrated. The residue was purified by flash column chromatography over silica gel with hexane/EtOAc (2:1) as eluant to give the corresponding benzyl ether (2.0 g, 96%) as an oil: IR (neat) 1780 (C=O) and 1641 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 2.49 (d of AB, J = 17.3 Hz, 1 H, H-3_a), 2.65 (d of AB, J = 17.3 Hz, 1 H, H-3_b), 3.42 (s, 2 H, CH_2OCH_2Ph), 4.14 (d of AB, J = 9.05 Hz, 1 H, H-5_a), 4.32 (d of AB, J = 9.05 Hz, 1 H, H-5_b), 4.54 (s, 2 H, CH_2OCH_2Ph), 5.16 (d, J = 17.6 Hz, 1 H, CH=CH*H*), 5.22 (d, J = 10.8 Hz, CH=CH*H*), 5.87 (dd, J = 17.6, 10.9 Hz, 1 H, $CH{=}CH_2$), 7.20−7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 36.50, 46.55, 73.03, 73.35, 73.87, 115.71, 127.49, 127.79, 128.41, 137.45, 137.99, 175.91. Anal. ($C_{14}H_{16}O_3$) C, H.

The above compound (2.0 g, 8.6 mmol) was dissolved in aqueous acetone (1:1, 80 mL) and treated with 4-methylmorpholine *N*-oxide (2.02 g, 17.22 mmol), sodium metaperiodate (3.68 g, 17.22 mmol), and osmium tetroxide (2.5 wt % in *tert*-butyl alcohol, 2.16 mL, 0.17 mmol). After stirring for 20 h at room temperature, the reaction mixture was quenched with a saturated sodium thiosulfate solution (40 mL), stirred for 10 min, and extracted with EtOAc. The organic layer was washed

with water, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography over silica gel with EtOAc/hexane (2:1) as eluant to give the corresponding aldehyde (1.90 g, 94%) as an oil: IR (neat) 1781 and 1728 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) δ 2.51 (d of AB, J = 17.9 Hz, 1 H, H-3_a), 2.84 (d of AB, J = 17.9 Hz, 1 H, H-3_b), 3.69 (AB m, 2 H, CH_2OCH_2Ph), 4.23 (d of AB, J = 9.8 Hz, 1 H, H-5_a), 4.51 (d of AB, J = 9.8 Hz, 1 H, H-5_b), 4.54 (s, 2 H, CH_2OCH_2Ph), 7.20−7.40 (m, 5 H, Ph), 9.67 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 32.05, 54.75, 69.14, 69.95, 73.49, 127.62, 128.03, 128.47, 136.73, 174.08, 198.66, 198.82. Anal. ($C_{13}H_{14}O_4$) C, H.

The above aldehyde (1.08 g, 4.6 mmol) was dissolved in aqueous THF (1:9, 100 mL) and cooled to −15 °C. The solution was treated with sodium borohydride (0.348 g, 9.2 mmol) and stirred for 30 min. The reaction mixture was acidified with 1 N HCl solution to pH 2−3 and concentrated to small volume. The mixture was diluted with water and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography over silica gel with EtOAc/hexane (3:2) as eluant to give the corresponding alcohol (1.07 g, 98%) as an oil: IR (neat) 3456 (OH), 1775 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) δ 2.14 (bs, 1 H, OH), 2.45 (AB q, J = 17.9 Hz, 2 H, H-$3_{a,b}$), 3.51 (s, 2 H, CH_2OH), 3.68 (AB m, 2 H, CH_2OCH_2Ph), 4.16 (d of AB, J = 9.45 Hz, 1 H, H-5_a), 4.22 (d of AB, J = 9.45 Hz, 1 H, H-5_b), 4.52 (s, 2 H, CH_2OCH_2Ph), 7.20−7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 34.23, 45.54, 64.96, 72.17, 72.37, 73.48, 127.57, 127.94, 128.49, 137.29, 176.69. Anal. ($C_{13}H_{16}O_4$) C, O.

The above alcohol (1.07 g, 4.5 mmol) was dissolved in DMF (20 mL) and treated with *tert*-butyldimethylsilyl chloride (1.02 g, 6.75 mmol) and imidazole (1.23 g, 18 mmol). The reaction mixture was stirred for 14 h and then diluted with water. The aqueous phase was extracted with CH_2Cl_2, and the organic layer was washed with water and brine. The organic phase was then dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography over silica gel with hexane/EtOAc (5:1) as eluant to give the title compound **13** (1.51 g, 96%) as an oil: IR (neat) 1781 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, Si(CH_3)$_2$), 0.85 (s, 9 H, C(CH_3)$_3$), 2.44 (s, 2 H, H-$3_{a,b}$), 3.41 (s, 2 H, CH_2OSi), 3.57 (s, 2 H, CH_2OCH_2-Ph), 4.13 (s, 2 H, H-$5_{a,b}$), 4.49 (s, 2 H, CH_2OCH_2Ph), 7.20−7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ −5.66, 18.09, 25.68, 34.05, 46.07, 64.35, 71.08, 72.32, 73.42, 127.55, 127.80, 128.43, 137.60, 176.56. Anal. ($C_{19}H_{30}O_4Si$) C, H.

(*Z*)-4-[(Benzyloxy)methyl]-4-[(*tert*-butyldimethylsiloxy)-methyl]-3-tetradecanylidenetetrahydro-2-furanone (14a) and (*E*)-4-[(Benzyloxy)methyl]-4-[(*tert*-butyldimethylsiloxy)methyl]-3-tetradecanylidenetetrahydro-2-furanone (15a). A solution of **13** (1.563 g, 4.46 mmol) in THF (9 mL) was cooled to −78 °C, treated with sodium bis(trimethylsilyl) amide (1.0 M in tetrahydrofuran, 5.35 mL, 5.35 mmol), and stirred for 1 h. A mixture of tetradecyl aldehyde (80%, 1.42 g, 5.35 mmol) and hexamethylphosphoramide (0.96 g, 5.35 mmol) was added, and the reaction mixture was stirred at −78 °C for 1 h and at −48 °C for another hour. The mixture was quenched with a saturated NH_4Cl solution and diluted with ether. The organic layer was washed with water, dried (Na_2-SO_4), and concentrated. The residue was purified by flash column chromatography over silica gel with hexane/EtOAc (from 10:1 to 5:1) as eluant to give the β-hydroxy lactone intermediate. This compound was dissolved in CH_2Cl_2 (100 mL), cooled to 0 °C, and stirred with triethylamine (3.0 mL, 21.5 mmol) and methanesulfonyl chloride (0.66 mL, 8.53 mmol) for 30 min. The reaction mixture was warmed to room temperature, stirred for 30 min extra, and additional triethylamine (12.0 mL, 86 mmol) was added. After stirring for 24 h at room temperature, the mixture was concentrated and diluted with ether. The ethereal solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography over silica gel with hexane/EtOAc (19:1) as eluant to give the *Z*-isomer **14a** (1.26 g, 52%) as the first fraction, followed by the *E*-isomer **15a** (0.63 g, 26%). Compound **14a**: oil; IR (neat) 1757 (C═O), 1658 cm^{-1} (C═C); ^1H NMR ($CDCl_3$) δ 0.01 (s, 6 H, Si(CH_3)$_2$), 0.85 (m, 12 H, C(CH_3)$_3$, (CH_2)$_{12}$CH_3), 1.10−1.50 (m, 22 H, ═CHCH_2(CH_2)$_{11}$$CH_3$), 2.72 (m, 2 H, ═CHC$H_2$), 3.41 (d of AB, J = 8.8 Hz, 1 H, CHHOSi), 3.49 (d of AB, J = 8.8 Hz, 1 H, CHHOSi), 3.60 (s, 2 H, CH_2-OCH_2Ph), 4.13 (AB q, J = 9.5 Hz, 2 H, H-5), 4.50 (AB q, J = 12.2 Hz, 2 H, CH_2OCH_2Ph), 6.22 (t, J = 7.6 Hz, 1 H, ═CH), 7.20−7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ −5.65, −5.57, 14.11, 18.15, 22.67, 25.74, 27.53, 29.16, 29.23, 29.34, 29.45, 29.54, 29.64, 29.66, 31.90, 48.24, 65.04, 70.37, 71.62, 73.46, 127.24, 127.51, 127.71, 128.39, 137.85, 146.55, 170.28. Anal. ($C_{33}H_{56}O_4Si$) C, H.

Compound **15a**: oil; IR (neat) 1760 (C═O) and 1672 cm^{-1} (C═C); ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H, Si(CH_3)$_2$), 0.85 (m, 12 H, C(CH_3)$_3$, (CH_2)$_{12}$CH_3), 1.10−1.50 (m, 22 H, ═CHCH_2(CH_2)$_{11}$-CH_3), 2.25 (m, 2 H, ═CHCH_2), 3.60 (AB q, J = 8.8 Hz, CH_2-OSi), 3.70 (d of AB, J = 9.7 Hz, 1 H, CHHOCH_2Ph), 3.80 (d of AB, J = 9.7 Hz, 1 H, CHHOCH_2Ph), 4.13 (AB q, J = 9.4 Hz, 2 H, H-5), 4.50 (AB q, J = 12.0 Hz, 2 H, CH_2OCH_2Ph), 6.83 (t, J = 7.8 Hz, 1 H, ═CH), 7.20−7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ −5.62, −5.59, 14.11, 18.18, 22.67, 25.74, 28.93, 28.99, 29.35, 29.42, 29.53, 29.64, 31.90, 49.20, 64.65, 70.94, 71.03, 73.55, 127.47, 127.43, 127.79, 128.40, 137.62, 144.79, 171.85. Anal. ($C_{33}H_{56}O_4Si$) C, H.

(*Z*)-4-(Acetoxymethyl)-4-[(Benzyloxy)methyl]-3-tetradecanylidenetetrahydro-2-furanone (14b). A solution of **14a** (0.80 g, 1.47 mmol) in THF (20 mL) was cooled to 0 °C, treated dropwise with tetrabutylammonium fluoride (1.0 M, 3.0 mL, 3 mmol), and stirred for 30 min. The reaction mixture was diluted with ether, and the organic phase was washed with water. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography over silica gel with hexane/EtOA (2:1) as eluant to give the intermediate alcohol (0.63 g, 99.6%) as an oil: IR (neat) 3447 (OH), 1754 (C═O) and 1662 cm^{-1} (C═C); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.10−1.50 (m, 22 H, ═CHCH_2(CH_2)$_{11}$$CH_3$), 2.10 (br s, OH), 2.70 (m, 2 H, ═CHCH_2), 3.51 (AB q, J = 9.0 Hz, 2 H, CH_2OH), 3.64 (d of AB, J = 11.0 Hz, 1 H, CHHOCH_2Ph), 3.74 (d of AB, J = 11.0 Hz, 1 H, CHHOCH_2Ph), 4.18 (d of AB, J = 9.5 Hz, H-5_a), 4.27 (d of AB, J = 9.5 Hz, 1 H, H-5_b), 4.51 (AB q, J = 12.1 Hz, 1 H, CH_2-OCH_2Ph), 6.16 (t, J = 7.6 Hz, 1 H, ═CH), 7.20−7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.67, 27.54, 29.09, 29.23, 29.34, 29.41, 29.53, 29.63, 29.65, 31.90, 47.98, 66.50, 70.44, 73.69, 73.91, 126.84, 127.63, 128.04, 128.57, 137.27, 146.65, 169.93. Anal. ($C_{27}H_{42}O_4$) C, H. This compound (0.63 g, 1.46 mmol) was dissolved in CH_2Cl_2 (30 mL) and treated with pyridine (0.5 mL, 6.2 mmol) and acetic anhydride (0.3 mL, 3.2 mmol). After stirring for 1 h at room temperature, the reaction mixture was concentrated and the residue was purified by flash column chromatography over silica gel with hexane/EtOAc (3:1) as eluant to give the title compound **14b** (0.684 g, 99%) as an oil: IR (neat) 1750 (C═O) and 1662 cm^{-1} (C═C); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.10−1.50 (m, 22 H, ═CHCH_2(CH_2)$_{11}$$CH_3$), 1.99 (s, 3 H, C$H_3$CO), 2.72 (m, 2 H, ═CHC$H_2$), 3.42 (s, 2 H, C$H_2OCH_2$Ph), 4.10−4.24 (m, 4 H, CH_2OAc, H-5), 4.51 (AB q, J = 12.2 Hz, 2 H, CH_2OCH_2Ph), 6.22 (t, 1 H, J = 7.6 Hz, 1 H, ═CH), 7.20−7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.10, 20.64, 22.67, 27.47, 29.00, 29.16, 29.33, 29.40, 29.53, 29.62, 31.90, 46.51, 65.78, 70.15, 72.02, 73.45, 126.19, 127.57, 127.88, 128.45, 137.43, 147.23, 169.48, 170.51. Anal. ($C_{29}H_{44}O_5$) C, H.

(*E*)-4-(Acetoxymethyl)-4-[(Benzyloxy)methyl]-3-tetradecanylidenetetrahydro-2-furanone (15b). Starting with **15a**, the same procedure described for the synthesis of **14b** afforded the corresponding intermediate alcohol in 99% yield: oil; IR (neat) 3446 (OH), 1757 (C═O) and 1676 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.10−1.50 (m, 22 H, ═CHCH_2(CH_2)$_{11}$$CH_3$), 2.23 (m, 2 H, ═CHC$H_2$), 3.57 (d of AB, J = 9.0 Hz, 1 H, CHHOH), 3.72 (d of AB, J = 11.0 Hz, 1 H, CHHOCH_2Ph), 3.76 (d of AB, J =9.0 Hz, 1 H, CHHOH), 4.01 (d of AB, J = 11.0 Hz, 1 H, CHHOCH_2Ph), 4.25 (d of AB, J = 9.5 Hz, 1 H, H-5_a), 4.34 (d of AB, J = 9.5 Hz, 1 H, H-5_b), 4.51 (AB q, J = 11.9 Hz, 2 H, CH_2OCH_2Ph), 6.83 (t, J = 8.0 Hz, 1 H, ═CH), 7.20−7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.67, 28.78, 29.00, 29.16, 29.34, 29.39, 29.50, 29.63, 31.90, 32.26, 32.31, 48.63, 50.55, 63.36, 65.82, 70.96, 72.94, 73.89, 127.68, 127.75, 128.15, 128.50, 128.60, 135.02, 145.45, 171.32. Anal. ($C_{27}H_{42}O_4$) C, H. This compound was

acetylated as described for the synthesis of **14b** to afford the *E*-isomer **15b** in 99% yield: oil; IR (neat) 1750 (C=O) and 1672 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.10−1.50 (m, 22 H, $=CHCH_2(CH_2)_{11}CH_3$), 2.00 (s, 3 H, CH_3CO), 2.24 (m, 2 H, $=CHCH_2$), 3.53 (d of AB, J = 9.0 Hz, 1H, $CHHOCH_2Ph$), 3.63 (d of AB, J = 9.0 Hz, 1 H, $CHHOCH_2Ph$), 4.15 (d of AB, J = 9.5 Hz, 1 H, $CHHOAc$), 4.23 (d of AB, J = 9.5 Hz, 1 H, $CHHOAc$), 4.30 (AB q, J = 11.2 Hz, 2 H, H-$5_{a,b}$), 4.50 (AB q, J = 12.0 Hz, 2 H, CH_2OCH_2Ph), 6.88 (t, J = 7.9 Hz, 1 H, =CH), 7.20−7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.10, 20.70, 22.67, 28.86, 29.17, 29.33, 29.36, 29.42, 29.51, 29.63, 31.90, 46.86, 65.26, 70.73, 71.18, 73.57, 126.20, 127.68, 127.97, 128.48, 137.23, 145.94, 170.57, 171.08. Anal. ($C_{29}H_{44}O_5$) C, H.

***(Z)*-4-(Acetoxymethyl)-4-(hydroxymethyl)-3-tetradecanylidenetetrahydro-2-furanone (14c).** A solution of **14b** (0.324 g, 0.685 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C, treated with boron trichloride (1.0 M in dichloromethane, 2.74 mL, 2.74 mmol) and stirred for 1 h at that temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (3.0 mL) and immediately partitioned between chloroform and a pH 7 phosphate buffer solution. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography over silica gel with EtOAc/hexane (1:1) as eluant to give the title compound **14c** (0.252 g, 96%) as a white solid: mp 48 °C; IR (KBr) 3489 (OH), 1735 (C=O), and 1667 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.10−1.50 (m, 22 H, $=CHCH_2(CH_2)_{11}CH_3$), 2.08 (s, 3 H, CH_3CO), 2.60−2.90 (m, 2 H, $=CHCH_2$), 3.59 (AB m, 2 H, CH_2OH), 4.18 (2 AB multiplets, 4 H, H-$5_{a,b}$, CH_2OAc), 6.28 (t, 1 H, J = 7.6 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.11, 20.72, 22.68, 27.61, 29.06, 29.24, 29.35, 29.41, 29.55, 29.64, 31.91, 47.58, 64.42, 65.34, 69.86, 126.06, 147.72, 169.69, 171.19; FAB MS m/z 383 (MH^+, 100). Anal. ($C_{22}H_{38}O_5$) C, H.

***(E)*-4-(Acetoxymethyl)-4-(hydroxymethyl)-3-tetradecanylidenetetrahydro-2-furanone (15c).** The identical deblocking procedure described for the preparation of **14c** was applied to **15b** to yield the title compound **15c** in 96% yield: solid; mp 52 °C; IR (neat) 3545 (OH), 1757 and 1724 (C=O), and 1672 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3), 1.10−1.50 (m, 22 H, $=CHCH_2(CH_2)_{11}CH_3$), 1.90 (br s, 1 H, OH), 2.07 (s, 3 H, CH_3CO), 2.32 (m, 2 H, $=CHCH_2$), 3.75 (d of AB, J = 11.1 Hz, 1 H, $CHHOH$), 3.82 (d of AB, J = 11.1 Hz, 1H, $CHHOH$), 4.15 (d of AB, J = 9.6 Hz, 1 H, H-5_a), 4.25 (d of AB, J = 9.6 Hz, 1 H, H-5_b), 4.37 (AB q, J = 11.3 Hz, 2 H, CH_2OAc), 6.94 (t, 1 H, J = 7.9 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.10, 20.73, 22.67, 28.95, 29.01, 29.34, 29.44, 29.52, 29.63, 31.90, 48.16, 63.94, 65.03, 70.51, 126.18, 146.37, 170.97, 171.51; FAB MS m/z 383 (MH^+, 100). Anal. ($C_{22}H_{38}O_5$) C, H.

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(20) Based on the 10-fold difference in K_i values between compound **10f** and OAG, the following equation

$$-2.303RT\Delta(\log K_i)_{\mathrm{OAG-10f}} = \Delta(\Delta G)_{\mathrm{OAG-10f}} = \Delta(\Delta H)_{\mathrm{OAG-10f}} - \Delta(T\Delta S)_{\mathrm{OAG-10f}}$$

helps us calculate what the entropic advantage is for the binding of **10f** relative to OAG. $\Delta(\log K_i)_{\mathrm{OAG-10f}}$ is the binding affinity difference between OAG and **10f** in a log scale; $\Delta(\Delta G)_{\mathrm{OAG-10f}}$ is the difference in free energy change between OAG and **10f** associated with the binding process; $\Delta(\Delta H)_{\mathrm{OAG-10f}}$ is the difference in the enthalpic energy change between OAG and **10f** associated with the binding process; and $\Delta(T\Delta S)_{\mathrm{OAG-10f}}$ is the difference in the entropic energy change between OAG and **10f** associated with the binding process. The enthalpic energy associated with the binding of OAG and **10f** should be the same, thus $\Delta(\Delta H)_{\mathrm{OAG-10f}}$ becomes zero. Therefore, the above equation is reduced to

$$\Delta(T\Delta S)_{\mathrm{OAG-10f}} = 2.303RT\Delta(\log K_i)_{\mathrm{OAG-10f}}$$

Since $\Delta(\log K_i)$ equals one, the corresponding entropic advantage for the binding of **10f** at 25 °C is 5.70 kJ/mol or 1.36 kcal/mol. For additional details, see ref 12.

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JM950276V