Conformationally Constrained Analogues of Diacylglycerol. 12.[1] Ultrapotent Protein Kinase C Ligands Based on a Chiral 4,4-Disubstituted Heptono-1,4-lactone Template

Jeewoo Lee,[†] Rajiv Sharma,[†] Shaomeng Wang,[†] George W. A. Milne,[†] Nancy E. Lewin,[‡] Zoltan Szallasi,[‡] Peter M. Blumberg,[‡] Clifford George,[§] and Victor E. Marquez*,[†]

Laboratory of Medicinal Chemistry, Developmental Therapeutics Program, Division of Cancer Treatment, and Molecular Mechanisms of Tumor Promotion Section, Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, and Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D.C. 20375

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Conformationally constrained analogues of diacylglycerol (DAG) built on a 5-[(acyloxy)methyl]-5-(hydroxymethyl)tetrahydro-2-furanone template (**1**, Chart 1) were shown previously to bind tightly to protein kinase Cα (PK-Cα) in a stereospecific manner. These compounds, however, racemized readily through rapid acyl migration and lost biological potency. In order to circumvent this problem, the "reversed ester" analogues were designed as a new set of PK-C ligands. This reversal of the ester function produced some new DAG mimetics that are embedded in a C-4 doubly-branched heptono-1,4-lactone template. The reversed ester analogues were impervious to racemization, and their chemically distinct branches facilitated the enantiospecific syntheses of all targets. Compound **2**, the simplest reversed ester analogue of **1** (Chart 1), exhibited a 3.5-fold reduction in binding affinity toward PK-Cα which we attributed to the loss of a stabilizing *gauche* interaction that caused the ester branch in **2** to be more disordered than in the normal ester **1**. However, conversion of the propanoyl branch of **2** into a propenoyl branch restored binding affinity (**3** versus **5**). As expected, the compounds bound to the enzyme with strict enantioselectivity (**3** and **5** versus **4** and **6**). Functionalization of the propenoyl-branched compounds as α-alkylidene lactones, in a manner which proved successful with the 5-[(acyloxy)methyl]-5-(hydroxymethyl)tetrahydro-2-furanone template (**9** and **10**), produced stable compounds with equivalent ultrapotent binding affinities for PK-Cα (**7** and **8**). The additional incorporation of the propenoyl-branched carbonyl into a γ-lactone ring was performed (**11**−**14**) not only to derive a possible additional entropic advantage but also to confirm the spatial disposition of this carbonyl function in the ligand−enzyme complex. Although no additional entropic advantage was derived, the high binding affinities displayed by compounds **11** and **12** helped to establish the correct orientation of the equivalent carbonyl group in PK-C-bound DAG. As expected, these DAG analogues activated PK-Cα. The most potent agonist, compound **8**, stimulated phosphorylation of the α-pseudosubstrate peptide, and in primary mouse keratinocytes it caused inhibition of binding of epidermal growth factor with an ED_{50} of approximately 1 μM. In contrast to the phorbol esters, compound **8** did not induce acute edema or hyperplasia in skin of CD-1 mice, and its pattern of downregulation with several PK-C isozymes was different from that of phorbol 12-myristate 13-acetate (PMA).

Introduction

In the two previous papers we showed that semirigid diacylglycerol (DAG) analogues constructed on a 5-[(acyloxy)methyl]-5-(hydroxymethyl)tetrahydro-2-furanone template (**1**) possess unprecedented, high affinity levels for protein kinase Cα (PK-Cα).[1,2] It was also determined that potent binding affinity toward PK-Cα was associated with only one enantiomeric form of this lactone.[1] Unfortunately, a major limitation associated with the use of compounds built on this chiral template was their ease of racemization caused by the facile migration of the acyl group under very mild conditions.[1] Such a racemization was accompanied by a reduction in PK-C binding affinity.[1]

Our desire to prepare stable enantiomers using this newly discovered template led us to consider performing chemical changes to help differentiate both branches of the lactone. Since we have previously shown that the integrity of the ester function is critical for high PK-C binding affinity,[3] the reversal of the ester function was considered as a means of achieving the desired chemical differentiation between both branches of the lactone. Hence, compound **2**, which represents the simplest "reversed ester" analogue of **1**, was considered as a target (Chart 1). The impact of the reversal of the ester function on PK-C binding was promptly assessed first with racemic forms of **1** and **2** since such a seemingly subtle change, as ester reversal, was expected to have an important effect on the conformation of the molecule. For example, we were aware that an important and stabilizing interaction in compound **1**, represented by the attractive *gauche* interaction between the furan oxygen and the ether oxygen of the ester branch,[4] was

[†] Laboratory of Medicinal Chemistry, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.

[‡] Molecular Mechanisms of Tumor Promotion Section, Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, National Institutes of Health.

[§] Laboratory for the Structure of Matter, Naval Research Laboratory.

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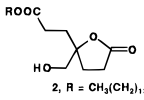
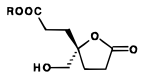
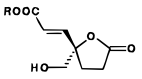
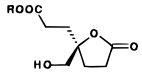
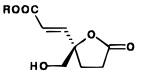
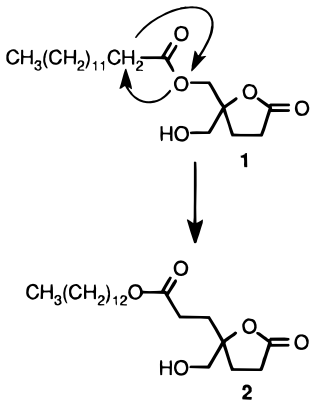
Table 1. Apparent K_i for Racemic and Enantiomeric Ligands as Inhibitors of PDBU Binding to PK-C

Racemate	K_i (nM)	Enantiomer	K_i (nM)	Enantiomer	K_i (nM)
 2, R = $CH_3(CH_2)_{13}$	489 ±87	 3, R = $CH_3(CH_2)_{13}$	260 ±41	 5, R = $CH_3(CH_2)_{13}$	109 ±6.7
		 4, R = $CH_3(CH_2)_{13}$	27,300 ±2,500	 6, R = $CH_3(CH_2)_{13}$	27,200 ±7,700

absent in compound **2**. Therefore, the reversed ester branch in **2**, which lacks the stabilizing *gauche* effect, was expected to be more disordered than the corresponding ester branch in **1**. This expectation was borne

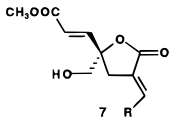
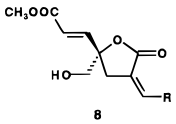
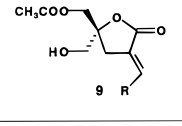
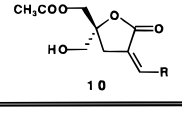
Chart 1



out by the 3.5-fold loss in affinity observed for the reversed ester **2** (*vide infra*). Supported by molecular modeling studies and with the aid of the phorbol ester pharmacophore model developed earlier,[5] we considered restoring some of the original conformational bias of the ester branch induced by the *gauche* interaction in **1**, by the addition of a double bond to compound **2**. On the basis of these considerations, four compounds with similar lipophilicities (**3**−**6**, Table 1) were selected as initial targets for enantioselective syntheses. On the basis of results obtained in our previous studies with the active (*R*)-enantiomer of **1**,[1] the chiral lactones **3** and **5** were predicted to behave as high-affinity ligands for PK-C, whereas lactones **4** and **6** were predicted to be either ineffective or weakly binding. In addition, the difference in binding affinity between lactones **3** and **5** was expected to reflect to what degree the double bond was indeed capable of compensating for the loss of the *gauche* effect.

An additional element that was contemplated in an attempt to transform these compounds into ultrapotent ligands consisted of downsizing the acyl function to a two carbon acetyl chain and relocating the alkyl chain to a more restricted position on the lactone ring. Therefore, α-alkylidine lactones **7** and **8** (Table 2) were selected as additional targets which feature an unsaturation in the middle of the alkyl chain. The anticipated "bend" caused by the *cis* double bond in the middle of the alkyl chain in these compounds was intended to mimic oleic acid, since oleoate esters of related lactone ligands have been shown to have enhanced PK-C binding affinities relative to the comparable saturated esters.[6] The new doubly-branched heptono-1,4-lactones

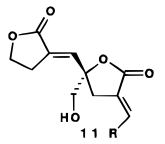
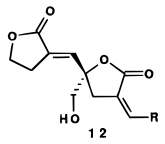
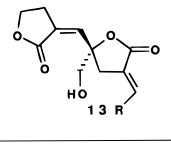
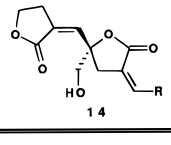
Table 2. Apparent K_i for Enantiomeric Ligands Having an α-Alkylidene Chain as Inhibitors of PDBU Binding to PK-C [R = (Z)-$CH_3(CH_2)_7CH{=}CH(CH_2)_7$]

Enantiomer	K_i (nM)
 7 R	20 ±2.9
 8	11 ±0.7
 9 R	13 ±1.3
 10	12 ±0.4

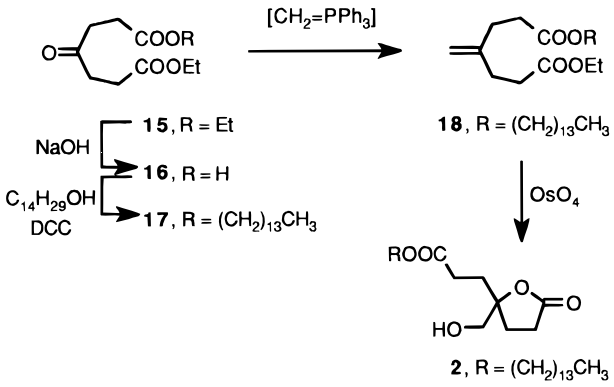
7 and **8** (Table 2) with an α,β-unsaturated methyl ester branch represent the two most *potent and stable* semirigid DAG analogues synthesized to date (*vide infra*). The PK-C binding affinities of these compounds essentially reproduced the values obtained previously for the chiral 5-[(acyloxy)methyl]-5-(hydroxymethyl)tetrahydro-2-furanones **9** and **10**[1] (Table 2) and confirmed the bioisosteric equivalence of both templates.[7]

With the aid of the phorbol ester pharmacophore,[5] a conformational analysis of compounds **7** and **8** raised the possibility of restricting even further the orientation of the ester carbonyl group. This exercise was not only intended to derive the possible benefits of an additional entropic advantage, but it was additionally expected to confirm the correct orientation of this carbonyl group in the ligand−enzyme complex. To achieve this goal, this ester function was incorporated into a second lactone ring which provided two possible orientations for the carbonyl relative to the double bond. Of the four target compounds (**11**−**14**, Table 3) containing two γ-lactone pharmacophores, compounds **11** and **12** were predicted to have the two lactones in the correct orientation in agreement with the phorbol ester pharmacophore model.[5] PK-C binding studies indicated that although no additional entropic advantage was derived, the high binding affinities displayed by compounds **11** and **12** helped to establish the correct orientation of the equivalent carbonyl group in PKC-bound DAG.

Table 3. Apparent K_i for Enantiomeric Ligands with Two γ-Lactone Pharmacophores as Inhibitors of PDBU Binding to PK-C [R = (Z)-$CH_3(CH_2)_7CH{=}CH(CH_2)_7$]

Enantiomer	K_i (nM)
 11 R	26 ±4.8
 12	19 ±1.9
 13 R	2,020 ±340
 14	746 ±25

Scheme 1

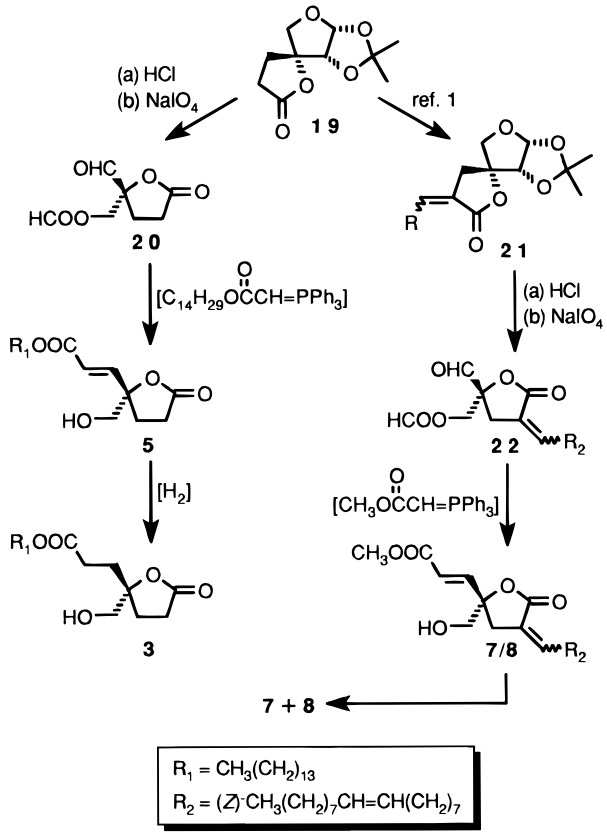


Chemistry

Synthesis of the racemic reverse ester lactone **2** was straightforward and was performed according to Scheme 1. Partial hydrolysis of diethyl 4-oxopimelate (**15**) with NaOH gave the half-ester **16** which was condensed with myristyl alcohol to give the mixed diester **17**. A Wittig olefination reaction of **15** with methyltriphenylphosphonium bromide/t-BuOK gave the expected olefin **18** which after *cis*-hydroxylation with OsO_4 cyclized unidirectionally to the desired target lactone **2**.

The enantioselective synthesis of lactones **3**, **5**, **7** and **8**, all containing the "active" chiral template, started with the same intermediate **19**[1] that was used in the preceding paper for the synthesis of the active enantiomer of **1** (Scheme 2). Conversion of **19** to **20**, which was also reported in the previous paper,[1] was followed by a reaction of the resulting aldehyde with myristyl (triphenylphosphoranylidene)acetate to give the corresponding target α,β-unsaturated ester **5**. This Wittig reagent, myristyl (triphenylphosphoranylidene)acetate, was prepared in three steps from α-bromoacetic acid.[8] Catalytic hydrogenation of the double bond in **5** produced the saturated branched target **3**.

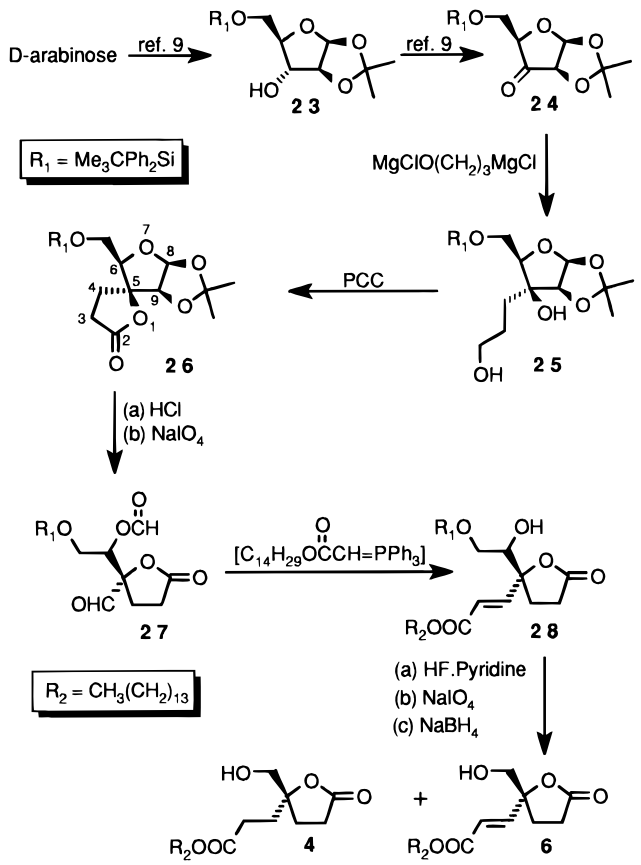
Scheme 2



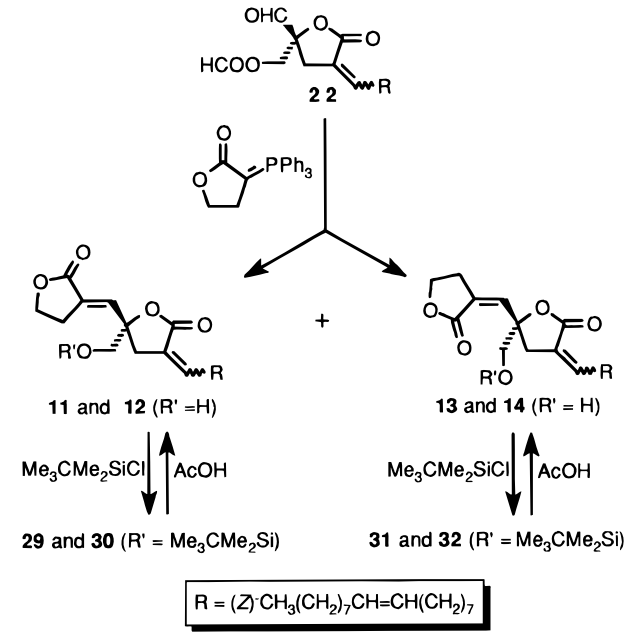
The two α-alkylidene targets **7** and **8** were also prepared from intermediate **19**[1] which reacted with oleoyl aldehyde to give a mixture of geometric isomers (**21**) after dehydration. A similar sequence of steps to those employed for the transformation of **19** to **20** was used to convert **21** to **22**, which was isolated as a mixture of geometric isomers. Reaction **22** with methyl (triphenylphosphoranylidene)acetate gave the corresponding final targets which were chromatographically separated as the *E*-(**7**) and *Z*-(**8**) isomers, respectively.

Since building of compounds with the "inactive" template was intended merely to corroborate the identity of the "active" template, our synthetic effort toward this objective was limited to the preparation of the simpler analogues **4** and **6** (Table 1), which correspond, respectively, to the optical antipodes of lactones **3** and **5**. For this synthesis, a similar strategy to that used for the construction of chiral lactone **19**[1] was performed starting from D-arabinose (Scheme 3). Protection of this sugar as the 5−*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidene-β-D-arabinofuranose (**23**) was followed by chromium trioxide oxidation to the keto sugar **24**.[9] Spirolactonization via the diol **25** was performed using PCC oxidation, as reported previously,[1] to give the 2-keto-1,7-dioxaspiro[4.4]nonane intermediate **26**. In this instance, the addition of the Grignard reagent to give **25** occurred stereospecifically from the less hindered α-side, thus ensuring the desired stereochemical outcome. As before, removal of the acetonide and metaperiodate cleavage of the resulting glycol moiety provided lactone **27**. Wittig olefination of **27** with myristyl (triphenylphosphoranylidene)acetate gave the α,β-unsaturated ester **28** which required shortening of one of the branches by one carbon atom. This one-carbon

Scheme 3



Scheme 4



shortening was accomplished, after removal of the silyl ether protection, by a second metaperiodate cleavage of the glycol moiety in **28**, followed by sodium borohydride reduction to give the target compounds **4** and **6**.

For the syntheses of the bis-γ-lactones (Scheme 4), aldehyde **22** was reacted with α-(triphenylphosphoranylidene)-γ-butyrolactone[10] to give a mixture of all four isomers (**11**−**14**). Chromatographic separation of these isomers was possible only after protection of the primary alcohol function as the *tert*-butyldimethylsilyl ether (compounds **29**−**32**). Removal of the silyl ether group from each individual isomer provided the desired target compounds.

Biological Results

The affinities of ligands **2** (racemic) and **3**−**14** (enantiomeric) for PK-Cα, expressed in terms of their abilities to displace bound [^{3}H-20]phorbol 12,13-dibutyrate (PDBU), were measured in the same manner as described in the preceding papers.[1,2] Analysis of the data indicated that the reversed ester racemic ligand **2** (K_i = 489 nM, Table 1) suffered a 3.5-fold loss in binding affinity relative to racemate **1** (K_i = 138 nM).[1,2] This loss in binding affinity was consistent with the presence of a more disordered side chain in **2** and the associated entropic penalty that had to be paid during its binding to PK-C. Relative to the enantiomeric compounds (Table 1), the predicted active ligands **3** (K_i = 260 nM) and **5** (K_i = 109 nM) showed a direct structural correspondence[7] to the active (*R*)-enantiomer of **1** (K_i = 96 nM)[1] that was built on a 5-[(acyloxy)methyl]-5-(hydroxymethyl)tetrahydro-2-furanone template. Consistent with our predictions, the corresponding optical antipodes **4** and **6** were respectively 100−200-fold less potent. A direct comparison between compound **5** (K_i = 109 nM) and the active enantiomer of **1** reported earlier (K_i = 96 nM)[1] demonstrated that within experimental error, the more rigid α,β-unsaturated ester branch in **5** was able to recover the loss in binding affinity that resulted from the reversal of the ester function. As we shall see in the molecular modeling section, compounds built on a 5-[(acyloxy)methyl]-5-(hydroxymethyl)tetrahydro-2-furanone template (e.g., compounds **1**, **9**, and **10**) show, in their presumed bound conformation, the furan oxygen and the ether oxygen of the ester function in a *gauche* disposition. This relative disposition of oxygens happens to correspond to the most energetically favored rotamer in these molecules. Rather fortuitously, the double bond in **5** appears capable of steering the carbonyl ester pharmacophore in the same direction (*vide infra*) as in the stable *gauche* rotamer of 5-[(acyloxy)methyl]-5-(hydroxymethyl)tetrahydro-2-furanones. The same phenomenon was observed for the more potent α-alkylidene analogues **7** (K_i = 20 nM) and **8** (K_i = 11 nM) which proved to be equivalent to the corresponding α-alkylidenes **9**[1] and **10**[1] built on a chiral 5-[(acyloxy)methyl]-5-(hydroxymethyl)tetrahydro-2-furanone template (Table 2). Compounds **7** and **8** are to date the most *potent and stable* DAG mimics.

The incorporation of the methyl ester group of compounds **7** and **8** into a γ-lactone ring allowed us to predict the correct relative disposition of both carbonyl pharmacophores in the ligand−enzyme complex. Indeed, compounds **11** (K_i = 26 nM) and **12** (19 nM) were, respectively, 30−100-fold more potent than their isomers **13** and **14** (Table 3). The fact that **11** and **12** did not show an increase in binding, relative to the more flexible analogues **7** and **8**, is probably indicative of a slight deviation from the ideal conformation that results from unfavorable steric contacts between the two γ-lactone rings (see molecular modeling section).

The biological activity of compound **8** was evaluated further. First, we sought to determine whether the binding of compound **8** to PK-Cα led to activation of the enzyme. We found that, as expected for a DAG ana-

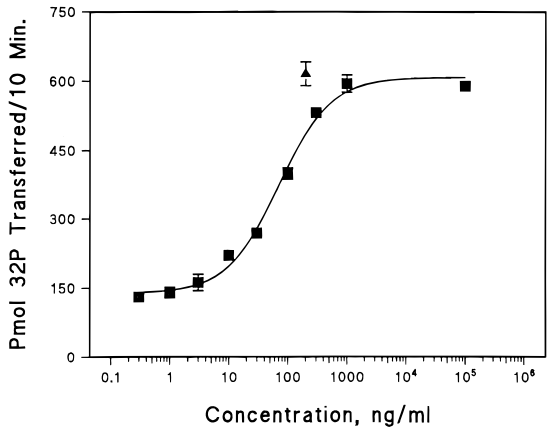


Figure 1. Stimulation of PK-Cα by compound **8**. Points represent the mean ± range of duplicate measurements in a single experiment. A second experiment gave similar results.

logue, compound **8** stimulated phosphorylation of the α-pseudosubstrate peptide (a standard substrate for assay of PK-C) with an ED_{50} of 163 ± 17 nM (Figure 1). This finding suggests that **8** would function in the intact cell or organism as either an agonist or a partial antagonist. In primary mouse keratinocytes, compound **8** caused inhibition of binding of epidermal growth factor with an ED_{50} of approximately 1 μM (data not shown), which is a typical response to PK-C activation.[11] In contrast to the phorbol esters, compound **8** did not induce acute edema (10−100 μg, 6 h) or hyperplasia (10−100 μg, 72 h) in skin of CD-1 mice. Finally, the ability of compound **8** to down-regulate PK-Cα and PK-Cδ in primary mouse keratinocytes after 24 h was examined. We found that compound **8** down-regulated the levels of PK-Cα and -δ with an ED_{50} of approximately 300 nM, whereas it did not down-regulate the levels of PK-Cϵ or PK-Cη. It is well-known that the pattern of down regulation differs for PK-C ligands that induce different sets of biological responses.[12] The pattern of down regulation of compound **8** thus distinguishes it from the typical phorbol ester, phorbol 12-myristate 13-acetate (PMA), which has greater potency for the down regulation of PK-Cδ than PK-Cα (0.8 versus 40 nM at 6 h),[11] or from 12-deoxyphorbol 13-(phenyl acetate), which down regulates PK-Cϵ.[13] These results are of further interest in that activity of PMA is lost by 24 h, reflecting metabolism. This is not found for compound **8**. We conclude that compound **8** has a different pattern of behavior from the typical phorbol esters and may thus have unique utility.

X-ray Analysis and Molecular Modeling. The critical functional pharmacophores in the phorbol esters that are responsible for PK-C recognition are thought to be the C-20 hydroxyl, the C-3 carbonyl, and the C-9 hydroxyl (PDBU, Chart 2).[5] The latter two appear to function as hydrogen bond acceptors, while the primary alcohol at C-20 functions as a hydrogen bond donor. Correspondingly in DAG, as well as in the lactone surrogates, the two carbonyls behave as hydrogen bond acceptors and the primary alcohol as a hydrogen bond donor (Chart 2).[5] The superposition of PDBU on the lowest energy conformer of the potent α-alkylidene *Z*-isomer **10**,[1] which was constructed earlier on a 5-[(acyloxy)methyl]-5-(hydroxymethyl)tetrahydro-2-furanone template, produced in an excellent fit (Figure 2, rms = 0.390 Å) of the critical pharmacophores. Such

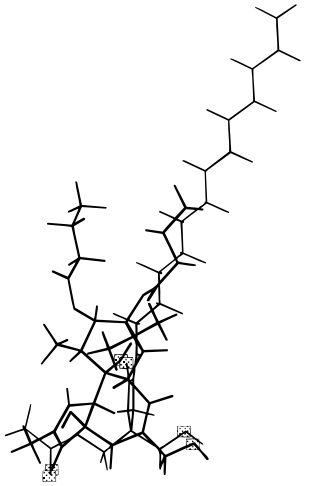
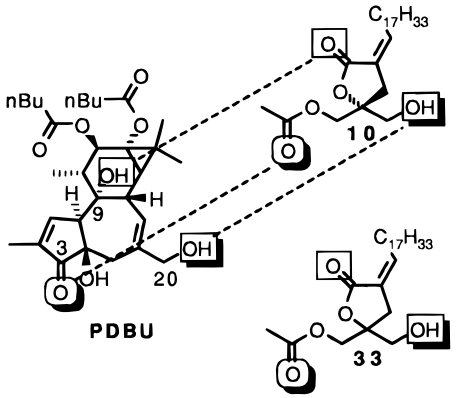


Figure 2. Superposition of a low-energy conformer of **10** on PDBU. The critical pharmacophore atoms (see text) are highlighted in boxes.

an optimal fit can be reached only when the lactone carbonyl is made to correspond directly to the C-9 hydroxyl of phorbol, and the side chain ester carbonyl overlays the C-3 carbonyl of phorbol (Chart 2). In this

Chart 2



low-energy conformation, presumably the conformation of **10** most likely to bind PK-C, the furan oxygen and the ether oxygen of the ester branch are in a stable +*sc gauche* disposition (Figure 3a). The fact that this energetically preferred rotamer shows an excellent fit to phorbol may explain the compound's exceptional affinity for PK-C (Table 2). Although we were unable to crystallize **10**, we succeeded in solving the X-ray crystal structure of a related α-alkylidene racemate (±)-**33** (Chart 2) synthesized earlier.[2] This compound differs from **10** in that it has a tetradecanylidene alkyl chain instead of a (*Z*)-9-octadecenylidene alkyl chain. From the unit cell, which contained both enantiomers, the (*R*)-enantiomer was selected and its structure was compared with that of the already described minimized structure of **10** (Figure 3a,b). The crystal structure of the (*R*)-isomer of **33** shows an analogous attractive *gauche* interaction for the ester side chain, but corresponding, instead, to that of the alternate *ap gauche* rotamer, which was probably favored by crystal packing forces. The rest of the atoms in both lactone rings remained virtually unchanged. This comparison suggests that for these molecules there is a definitive preference for either one of these *gauche* rotamers, one of which directs the essential pharmacophores in the correct orientation. The

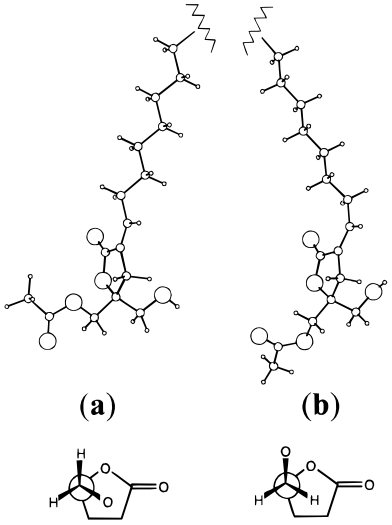


Figure 3. (a) Low energy conformer of **10** as in Figure 2 showing the +*sc gauche* disposition of the oxygens at the C-5 branch. (b) X-ray structure of **10** as it exists in the unit cell of a racemic crystal showing the *ap gauche* disposition of the oxygens at the C-5 branch.

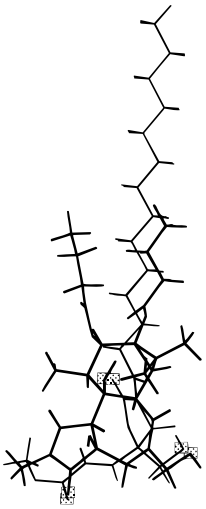


Figure 4. Superposition of a low energy conformer of **8** on PDBU. The critical pharmacophore atoms (see text) are highlighted in boxes.

energy difference *in vacuo* between the two *gauche* conformers was 1.37 kcal/mol in favor of the rotamer with the correct orientation.

The biological equivalence between compounds **8** and **10** (K_i ca. 11 nM, Table 2) suggests that the double bond in compound **8** is indeed capable of directing its side chain ester into the equivalent space occupied by the side chain ester of the +*sc gauche* rotamer of **10**. This can be appreciated in Figure 4, where the most stable conformer of **8** shows an excellent fit to PDBU (rms = 0.350 Å). Also, the superposition of compound **12** and PDBU (Figure 5, rms = 0.710 Å) confirms the model's prediction regarding the correct position of the side chain ester carbonyl required for effective binding.

An interesting qualitative observation regarding the orientation of the alkyl chain in compounds **8**, **10** and **12** (Figures 2, 4, and 5) is how well they match the general direction of the acyl chains in PDBU. Although the acyl chains in the phorbol esters and DAG are not part of the pharmacophore units usually defined for PK-C recognition, they are essential for PK-C binding

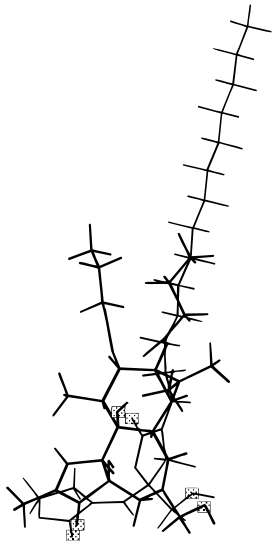


Figure 5. Superposition of a low energy conformer of **12** on PDBU. The critial pharmacophore atoms (see text) are highlighted in boxes.

and probably help orient the hydrophilic part of the molecule once the molecule becomes inserted into the lipid bilayer. When the simpler compounds that lack the α-alkylidene moiety (e.g., compounds **3** and **5**) were modeled and superimposed on PDBU (data not shown), the different location of the lipophilic chain changes the manner in which the pharmacophores relate to one another. Assuming that the side chain's role is indeed to orient the molecule into the lipid bilayer, and assuming that the orientation of the acyl chains in PDBU is the correct one, the superposition of **3** and **5** onto PDBU would force the long acyl ester carbonyl to correspond to the C-9 hydroxyl of phorbol and the lactone carbonyl to correspond to the C-3 carbonyl of phorbol. This alternative correspondence leads to a poorer fit when compared to the fit described above for compounds **8** and **10**. Hence, the aliphatic and hydrophobic portion of the molecule, when attached to the lactone ring, constrains the lactone carbonyl to match exclusively with the C-9 hydroxyl group of phorbol producing a better fit (*vide supra*). This may explain the 10-fold increase in binding affinity observed with the α-alkylidene lactones. These observations also underscore the important role of the side chain not in only providing the required lipophilicity, but also in steering the compound into the lipid bilayer and thus contributing with an additional entropic advantage during the binding process.

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 and specific rotations were measured in a Perkin-Elmer Model 241 polarimeter. 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,[14] 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 15. 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.[14,15] Values represent the mean ± standard error (three determinations).

Molecular Modeling. The methods used in the conformational search and analysis for compounds **2**−**6** were the same as those described in the preceding paper. However, for compounds **7**−**14**, which have fewer rotatable bonds within their designated pharmacophore, a systematic conformational search approach was applied with an angular increment of 60° in order to better access the conformational space for these compounds. The same program described in the preceding paper[1] was used to automatically determine the fit of each resulting conformation to phorbol and to identify the low-energy conformations with the best fit. The low-energy conformations with the best fit were further minimized by a a semiempirical quantum mechanics method, AM1 in MOPAC6.0 with a precision specified keyword GNORM = 0.01 running on a host mainframe Convex C240 supercomputer, in order to validate the molecular mechanics results obtained with CHARMm. The results obtained with CHARMm and AM1 for compounds **8**, **10**, and **12** were also validated by *ab initio* quantum mechanics, in the level HF/3-21G, using GAUSSIAN 90 running on a Cray-YMP supercomputer of the NCI Biomedical Supercomputing Center. The results from semiempirical and *ab initio* methods essentially agreed with the CHARMm results.

X-ray Analysis. Crystal data for (±)-**33**: $C_{22}H_{38}O_5$, FW = 382.52, mp 58−59 °C. Triclinic space group, $P\bar{1}$, a = 5.301(2) Å, b = 5.506(1) Å, c = 43.520(9) Å, α = 92.62(2)°, β = 90.94(2)°, γ = 113.67(2)°, V = 1161.3 (5) Å^3, Z = 2, D_c = 1.094 mg mm^{-3}, λ(Cu Kα) = 1.541 78 Å, μ = 0.61 mm^{-1}, $F(000)$ = 420, T = 293 K. Final residuals were R = 0.080 for 2040 reflections $I > 2\sigma(I_0)$. Tables of atomic coordinates, bond distances and angles, and anisotropic thermal parameters have been deposited.

4-Oxoheptanedioic Acid, Monoethyl Ester (16). A stirred solution of diethyl 4-oxopimelate (4.81 g, 20.9 mmol) in 95% EtOH (100 mL) was treated with a solution of NaOH (0.835 g, 20.9 mmol) in water (30 mL) at room temperature. After stirring for 4 h, the reaction mixture was concentrated under suction, acidified to pH ≈ 2 with 1 N HCl, and extracted with EtOAc (3 × 30 mL). The combined organic extract was washed with water (2 × 50 mL), dried (Na_2SO_4), and concentrated. The oil obtained was purified by flash column chromatography over silica gel using EtOAc/hexane (1:1) as eluant which provided 1.35 g of recovered starting material (**15**). Upon further elution with EtOAc, the title compound **16** was isolated as a white solid (1.44 g, 47%, based on recovered starting material): mp 68.5−69.5 °C (EtOAc/hexane); IR (CH_2Cl_2) 1731 (C═O) and 1704 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3 H, CH_3), 2.60 and 2.75 (multiplets, 8 H, HOOC(CH_2)$_2$CO(CH_2)$_2$COOCH_2CH$_3$), 4.10 (q, J = 7.1 Hz, 2 H, COOCH_2CH$_3$); ^{13}C NMR ($CDCl_3$) δ 14.11, 27.65, 27.96, 36.80, 36.97, 37.05, 60.70, 172.71, 178.07, 206.80. Anal. ($C_9H_{14}O_5$) C, H.

Tetradecyl Ethyl 4-Oxopimelate (17). A stirred solution of **16** (0.784 g, 3.88 mmol), 1-tetradecanol (1.00 g, 4.66 mmol), and DMAP (50 mg) in dry CH_2Cl_2 (25 mL) was kept under argon at room temperature and treated with dicyclohexylcarbodiimide (5.82 mL, 1M solution in CH_2Cl_2). After stirring for 24 h, the reaction mixture was quenched with a few drops of CH_3COOH and MeOH, stirred for a few more minutes, and then concentrated under vacuum. The residue was diluted with ether (50 mL), filtered, and concentrated. The residue was purified by flash column chromatography over silica gel using a gradient of 3−12% EtOAc in hexane, to give **17** (0.304 g, 60%) as a colorless solid: mp 42−43 °C (EtOAc/hexane); IR (KBr) 1731 (C═O) and 1705 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (distorted t, 3H, CH_3(CH_2)$_{13}$), 1.20−1.40 (m, 25 H, CH_3(CH_2)$_{11}$CH_2CH_2OCO, CH_3CH_2OCO), 1.55 (m, 2 H, CH_3-(CH_2)$_{11}$CH_2CH_2OCO), 2.55 (distorted t, 4 H, OCCH_2CH_2-COCH_2CH_2CO), 2.73 (distorted t, 4 H, OCCH_2CH_2COCH_2CH_2-CO), 3.95−4.10 (m, 4H, CH_3(CH_2)$_{11}$CH_2CH_2OCO, CH_3CH_2O); ^{13}C NMR ($CDCl_3$) δ 14.05, 14.10, 22.63, 25.83, 27.92, 28.53, 29.19, 29.30, 29.46, 29.52, 29.59, 31.87, 37.04, 60.55, 64.81, 172.61, 172.69, 206.92. Anal. ($C_{23}H_{42}O_5$) C, H.

Tetradecyl 4-[(Ethoxycarbonyl)ethyl]-4-pentenoate (18). Potassium *tert*-butoxide (0.195 g, 1.73 mmol) was added to a stirred suspension of methyl triphenylphosphonium bromide (0.618 g, 1.73 mmol) in dry benzene (8 mL), which was maintained under argon at room temperature. After stirring for 30 min, the reaction mixture was cooled to 0 °C and a solution of ketone **17** (0.46 g, 1.16 mmol) in dry THF was added rapidly. The reaction was quenched after 60 min at 0 °C with brine (∼10 mL), the mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layer was washed with water (1 × 10 mL) and dried (Na_2SO_4). The residue obtained after concentration was purified by flash column chromatography over silica gel using hexane/EtOAc (95:5), giving **18** as a liquid (0.72 g, 71.5%): IR (neat) 1738 (C═O) and 1647 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (distorted t, 3H, CH_3(CH_2)$_{13}$), 1.20−1.40 (m, 25 H, CH_3(CH_2)$_{11}$CH_2CH_2OCO, CH_3CH_2OCO), 1.60 (m, 2 H, CH_3(CH_2)$_{11}$CH_2CH_2OCO), 2.35 (m, 4 H, OCCH_2CH_2-(C═CH_2)CH_2CH_2CO), 2.45 (m, 4 H, OCCH_2CH_2(C═CH_2)CH_2-CH_2CO),4.00−4.15 (m, 4H, CH_3(CH_2)$_{11}$CH_2CH_2OCO, CH_3CH_2O), 4.75 (s, 2 H, ═CH_2); ^{13}C NMR ($CDCl_3$) δ 14.09, 14.20, 22.66, 25.89, 28.60, 29.23, 29.33, 29.50, 29.56, 29.62, 31.00, 31.03, 31.89, 32.64, 60.35, 64.61, 109.75, 146.37, 173.08, 173.18. Anal. ($C_{24}H_{44}O_4$) C, H.

(±)-5-(Hydroxymethyl)-5-[2-(tetradecanoxycarbonyl)-ethyl]tetrahydro-2-furanone (2). A stirred solution of olefin **18** (0.117 g, 0.29 mmol) in *t*-BuOH (3 mL) and water (1 mL) at 0 °C, containing *N*-methylmorpholine *N*-oxide (0.069 g, 0.59 mmol), was treated with 2.5% aqueous OsO_4 solution (0.16 mL). The reaction mixture was brought to room temperature slowly and stirred for 12 h; Na_2SO_3 (0.20 g) was added, and after stirring for a few more minutes it was concentrated under vacuum. The residue was extracted with EtOAc (3 × 10 mL), and the combined extract was washed with water (10 mL) and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was purified by flash column chromatography over silica gel using hexane/EtOAc (3:2) as eluant to give the title compound **2** (0.072 g, 65%) as white solid: mp 60−61 °C (EtOAc/hexane); IR (KBr) 3380 (OH) and 1728 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (distorted t, 3H, CH_3(CH_2)$_{13}$), 1.10−1.40 (m, 22 H, CH_3(CH_2)$_{11}$CH_2CH_2OCO), 1.60 (m, 2 H, CH_3(CH_2)$_{11}$CH_2CH_2OCO), 1.86−2.12 (m, 4 H, H-4$_{a,b}$, CH_2CH$_2$-COOC$_{14}$H$_{29}$), 2.25−2.78 (multiplets, 4 H, H-3$_{a,b}$, CH$_2$CH_2-COOC$_{14}$H$_{29}$), 2.90 (t, J = 6.5 Hz, 1 H, OH), 3.50 (dd, J = 12.1, 6.5 Hz, 1 H, CHHOH), 3.65 (dd, J = 12.1, 6.5 Hz, 1 H, CHHOH), 4.05 (t, J = 6.7 Hz, 2 H, CH_3(CH_2)$_{11}$CH_2CH_2OCO); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.65, 25.85, 28.05, 28.33, 28.51, 29.15, 29.21, 29.32, 29.48, 29.55, 29.61, 30.97, 31.88, 65.16, 66.41, 87.54, 173.28, 177.03; FAB MS m/z (relative intensity) 385 (38, MH$^+$), 171 (100, MH − $C_{14}H_{29}OH$). Anal. ($C_{22}H_{40}O_5$) C, H.

(*S*)-5-(Hydroxymethyl)-5-[2-(tetradecanoxycarbonyl)-(*E*)-ethenyl]tetrahydro-2-furanone (5). A solution of **19**[1] (0.214 g, 1 mmol) in THF (5 mL) was treated with 1 N HCl solution (5 mL) and stirred at room temperature for 20 h. The reaction mixture was neutralized with solid $NaHCO_3$ and diluted with EtOAc. The mixture was dried ($MgSO_4$) and concentrated to give the crude hemiacetal which was used for the next step without further purification. This compound was dissolved in a mixture of MeOH (10 mL) and water (5 mL), and the solution was stirred with sodium metaperiodate (0.428 g, 2 mmol) for 2 h at room temperature. The reaction mixture was filtered, and the filtrate was concentrated to dryness. The residue was dissolved in EtOAc, dried (Na_2SO_4), and concentrated to give aldehyde **20**, which was used for the next step without further purification. Aldehyde **20** was dissolved in benzene (30 mL) and treated with tetradecanyl (triphenylphosphoranylidene)acetate[8] (0.775 g, 1.5 mmol). The reaction mixture was refluxed for 2 h and concentrated. The residue was filtered through a short pad of silica gel and washed with ether, and the filtrate was concentrated to give a mixture of formate ester and the free alcohol. The mixture was dissolved in methanol (10 mL), cooled to 0 °C, and treated with

ammonium hydroxide solution (0.1 mL) with stirring for 20 min. The reaction mixture was quenched with acetic acid (0.1 mL) and concentrated. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (3:2) as eluant to give **5** (0.250 g, 65% from **19**) as a white solid: mp 58−59 °C; $[\alpha]^{22}_D$ −25.8° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3449 (OH), 1778 and 1752 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3(CH$_2$)$_{13}$), 1.10−1.40 (m, 22 H, CH$_3$(CH_2)$_{11}$CH$_2$CH$_2$OCO), 1.65 (m, 2 H, CH$_3$(CH$_2$)$_{11}$CH_2CH$_2$-OCO), 2.08 (m, 2 H, H-4$_a$, OH), 2.42−2.74 (m, 3 H, H-4$_b$, H-3$_{a,b}$), 3.64 (dd, *J* = 12.2, 7.1 Hz, 1 H, C*H*HOH), 3.79 (dd, *J* = 12.2, 5.3 Hz, 1 H, CH*H*OH), 4.12 (t, *J* = 6.7 Hz, 2 H, CH$_3$(CH$_2$)$_{11}$-CH$_2$CH_2OCO), 6.13 (d, *J* = 15.7 Hz, 1 H, C*H*=CHCO), 6.85 (d, *J* = 15.7 Hz, 1 H, CH=C*H*CO); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.67, 25.88, 28.15, 28.40, 28.56, 29.23, 29.33, 29.49, 29.56, 29.63, 31.90, 65.16, 66.48, 86.98, 122.32, 144.47, 165.71, 176.11; FAB MS *m*/*z* (relative intensity) 383 (MH^+,18), 169 (100, MH − $C_{14}H_{29}$). Anal. ($C_{22}H_{38}O_5$) C, H.

(*R*)-5-(Hydroxymethyl)-5-[2-(tetradecanoxycarbonyl)-ethyl]tetrahydro-2-furanone (3). A solution of **5** (0.154 g, 0.4 mmol) in EtOAc (20 mL) was treated with 10% Pd−C (0.4 g) and hydrogenated under a hydrogen balloon for 2 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (2:1) as eluant to give the title compound **3** (0.151 g, 98%) as white solid: mp 60−61 °C; $[\alpha]^{22}_D$ +7.90° (*c* 1.0, $CHCl_3$). The IR, ^1H NMR, and ^{13}C NMR were identical to those reported for the racemate **2**.[1] Anal. ($C_{22}H_{40}O_5$) C, H.

(*S*)-5-(Hydroxymethyl)-5-[2-(methoxycarbonyl)-(*E*)-ethenyl]-3-{(*E*)-[(*Z*)-9-octadecenylidene]}tetrahydro-2-furanone (7) and (*S*)-5-(Hydroxymethyl)-5-[2-(methoxycarbonyl)-(*E*)-ethenyl]-3-{(*Z*)-[(*Z*)-9-octadecenylidene]}-tetrahydro-2-furanone (8). A solution of **21**[1] (0.463 g, 1 mmol) in THF (15 mL) was treated with 2 N HCl solution and stirred for 5 days at room temperature. The reaction mixture was then neutralized with solid $NaHCO_3$ while being chilled over ice, filtered, and concentrated. The residue was diluted with EtOAc, dried (Na_2SO_4), and concentrated to give the corresponding hemiacetal as an oil, which was used for the next step without further purification. This compound was dissolved in a mixture of MeOH (20 mL) and H_2O (10 mL) and treated with sodium metaperiodate (0.428 g, 2 mmol). After stirring at room temperature for 4 h, the reaction mixture was filtered and concentrated. The residue was dissolved in ether, dried (Na_2SO_4), and concentrated to give aldehyde **22**, which was used for the next step without further purification. Aldehyde **22** was dissolved in benzene (20 mL) and stirred with methyl (triphenylphosphoranylidene)acetate (0.067 g, 2.0 mmol) for 4 h. The solvent was evaporated, and the residue was dissolved in ether and filtered through a short pad of silica gel with additional ether. The filtrate was concentrated to give a mixture of four products: the formate esters and free alcohols of both *E*/*Z* isomers. The mixture was dissolved in methanol (5 mL), cooled to 0 °C, and treated with ammonium hydroxide solution (0.05 mL) with stirring for 20 min. The reaction mixture was quenched with acetic acid (0.05 mL) and concentrated. The residue was purified by flash column chromatography over silica gel with hexanes/EtOAc (2:1) as eluant to give first *E*-isomer **7**, followed by *Z*-isomer **8**. The combined yield was 0.316 g (70.5% from **21**).

***E*-Isomer 7:** white solid; mp 53−54 °C; $[\alpha]^{22}_D$ +20.32° (*c* 0.62, $CHCl_3$); IR ($CHCl_3$) 3447 (OH), 1755 and 1722 (C=O), and 1676 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3(CH$_2$)$_7$CH=CH(CH$_2$)$_7$CH=C<), 1.10−1.50 (m, 22 H, CH$_3$(CH_2)$_6$CH$_2$CH=CHCH$_2$(CH_2)$_5$CH$_2$CH=C<), 2.00 (m, 4 H, CH$_3$(CH$_2$)$_6$CH_2CH=CHCH_2(CH$_2$)$_5$CH$_2$CH=C<), 2.15 (m, 2 H, CH$_3$(CH$_2$)$_6$CH$_2$CH=CHCH$_2$(CH$_2$)$_5$CH_2CH=C<), 2.68 (dm, *J* = 16.7 Hz, 1 H, H-4$_a$), 3.05 (dm, *J* = 16.7 Hz, 1 H, H-4$_b$), 3.62 (AB d, *J* = 12.0 Hz, 1 H, C*H*HOH), 3.74 (s, 3 H, CH$_3$O), 3.78 (AB d, *J* = 12.0 Hz, 1 H, CH*H*OH), 5.33 (m, 2 H, CH$_3$(CH$_2$)$_6$-CH$_2$C*H*=C*H*CH$_2$(CH$_2$)$_5$CH$_2$CH=C<), 6.13 (d, *J* = 15.7 Hz, 1 H, CH$_3$OCOCH=C*H*), 6.76 (m, 1 H, CH=C<), 6.89 (d, *J* = 15.7 Hz, CH$_3$OCOC*H*=CH); ^{13}C NMR ($CDCl_3$) δ 14.07, 22.64, 27.12, 27.19, 28.00, 29.10, 29.25, 29.28, 29.48, 29.66, 29.72, 30.30, 31.87, 32.25, 32.56, 51.89, 66.65, 83.83, 121.75, 125.03, 129.66, 130.01, 142.68, 145.24, 166.14, 169.73; FAB MS *m*/*z* (relative intensity) 449 (MH^+, 26). Anal. ($C_{27}H_{44}O_5$) C, H.

***Z*-Isomer 8:** oil; $[\alpha]^{22}_D$ −5.56° (*c* 0.36, $CHCl_3$); IR (neat) 3440 (OH), 1761 and 1729 (C=O), 1666 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, CH_3(CH$_2$)$_7$CH=CH(CH$_2$)$_7$-CH=C<), 1.10−1.50 (m, 22 H, CH$_3$(CH_2)$_6$CH$_2$CH=CHCH$_2$-(CH_2)$_5$CH$_2$CH=C<), 1.55 (br s, 1 H, OH), 2.00 (m, 4 H, CH$_3$(CH$_2$)$_6$CH_2CH=CHCH_2(CH$_2$)$_5$CH$_2$CH=C<), 2.6−2.78 (m, 3 H, CH$_3$(CH$_2$)$_6$CH$_2$CH=CHCH$_2$(CH$_2$)$_5$CH_2CH=C<, H-4$_a$), 3.12 (dm, *J* = 16.0 Hz, 1 H, H-4$_b$), 3.55−3.80 (m, 5 H, OCH$_3$ and CH$_2$OH), 5.33 (m, 2 H, CH$_3$(CH$_2$)$_6$CH$_2$C*H*=C*H*CH$_2$(CH$_2$)$_5$CH$_2$-CH=C<), 6.13 (d, *J* = 15.6 Hz, 1 H, CH$_3$OCOCH=C*H*), 6.22 (m, 1 H, CH=C<), 6.86 (d, *J* = 15.7 Hz, CH$_3$OCOC*H*=CH); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.66, 27.19, 27.79, 28.98, 29.18, 29.30, 29.40, 29.50, 29.72, 29.74, 31.88, 32.58, 35.51, 51.88, 66.48, 83.30, 121.83, 123.03, 129.77, 129.95, 145.34, 146.20, 166.17, 168.44; FAB MS *m*/*z* 449 (MH^+, 10). Anal. ($C_{27}H_{44}O_5$) C, H.

5-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-*β*-D-*threo*-pentofuranose-3-ulose (24). This compound was prepared in three steps from D-arabinose by the method of Dahlman et al.[9]

5-*O*-(*tert*-Butyldiphenylsilyl)-3-*C*-(3-hydroxypropyl)-1,2-*O*-isopropylidene-*β*-D-lyxofuranose (25). A stirred solution of 3-chloropropanol (2.127 g, 22.5 mmol) in dry THF (20 mL) at −20 °C was treated dropwise with a solution of methylmagnesium chloride (3M in THF, 7.5 mL) and stirred for 20 min at the same temperature. The reaction mixture was warmed to room temperature, and magnesium (0.82 g, 33.8 mmol) was added. The reaction mixture was refluxed for 2 h with periodic addition of dibromomethane (0.025 mL each) at 0, 1, and 1.3 h intervals. After cooling to 0 °C, a solution of ketone **24** (3.20 g, 7.5 mmol) in THF (25 mL) was added dropwise. The reaction was quenched at 0 °C after 1 h by the addition of saturated NH_4Cl solution (25 mL). The layers were separated, and the aqueous portion was extracted with EtOAc (2 × 25 mL). The combined organic layer was dried (Na_2SO_4) and concentrated. The residue obtained was purified by flash chromatography over silica gel using EtOAc/hexane (1:1) to give the title compound **25** as a liquid (3.0 g, 82%): $[\alpha]^D_{25}$ = +15.16° (*c* 0.89, $CHCl_3$); IR (neat) 3499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H, C(CH_3)$_3$), 1.30 and 1.40 (singlets, 6 H, CH$_3$), 1.50−1.80 (m, 4 H, (CH_2)$_2$CH$_2$OH), 2.5 (br s, 2 H, OH), 3.60 (m, 2 H, CH_2OH),3.80−4.10 (m, 3 H, H-5$_{a,b}$, H-4), 4.20 (d, *J* = 4.1 Hz, 1 H, H-2), 5.68 (d, *J* = 4.1 Hz, 1 H, H-1), 7.30−7.40 (m, 6 H, Ph), 7.60−7.80 (m, 4 H, Ph); ^{13}C NMR ($CDCl_3$) δ 19.13, 26.56, 26.67, 26.81, 26.89, 35.01, 62.74, 63.62, 78.04, 84.17, 85.30, 104.45, 113.91, 127.70, 129.70, 133.04, 133.27, 135.62, 135.68. Anal. ($C_{27}H_{38}O_6Si$) C, H.

(5*S*,6*R*,8*S*,9*S*)-6-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-8,9-*O*-isopropylidene-2-keto-1,7-dioxaspiro[4.4]nonane (26). A stirred suspension of powdered molecular sieves (4 Å, 7.5 g) and **25** (3.67g, 7.54 mmol) in anhydrous CH_2Cl_2 (100 mL) was treated with pyridinium chlorochromate (5.69 g, 26.4 mmol) at room temperature. After stirring for 1 h, the reaction mixture was diluted with ether (200 mL) and filtered through a short pad of silica gel. The silica gel pad was washed with ether (ca. 100 mL), and the filtrate was concentrated and purified by flash chromatography over silica gel using hexane/EtOAc (7:3) to give the title compound **26** (3.12 g, 85.7%) as a solid: mp 122−123 °C (EtOAc/hexane); $[\alpha]^D_{25}$ = −9.72° (*c* 1.07, $CHCl_3$); IR (KBr) 1793 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 9 H, C(CH_3)$_3$), 1.30 and 1.48 (singlets, 6 H, CH$_3$), 2.10−2.22 (m, 1 H, H-4$_a$), 2.30−2.70 (m, 3 H, H-4$_b$, H-3$_{a,b}$), 3.80−4.10 (m, 3 H, (CH$_3$)$_3$SiOCH_2, H-6), 4.48 (d, *J* = 4.5 Hz, 1 H, H-9), 5.72 (d, *J* = 4.5 Hz, 1 H, H-8), 7.30−7.50 (m, 6 H, Ph), 7.60−7.70 (m, 4 H, Ph); ^{13}C NMR ($CDCl_3$) δ 19.08, 26.46, 26.77, 27.50, 27.75, 30.93, 62.20, 83.82, 86.17, 86.51, 104.12, 115.81, 127.77, 127.81, 129.82, 132.89, 135.53, 175.18. Anal. ($C_{27}H_{34}O_6Si$) C, H.

(5*R*)-5-[(1*R*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-1-hydroxyethyl]-5-[2-(tetradecanoxycarbonyl)-(*E*)-ethenyl]tetrahydro-2-furanone (28). A solution of **26** (3.07g, 6.36 mmol) in THF (125 mL) was treated with a 1 N HCl solution (57 mL) and stirred for 11 h at room temperature. The reaction

mixture was neutralized by the careful addition of solid $NaHCO_3$, after which it was concentrated and extracted with EtOAc (3 × 40 mL). The combined organic extract was washed with water (2 × 50 mL) and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was flash chromatographed over silica gel using EtOAc/hexane (3:2), giving the corresponding deprotected hemiacetal intermediate as a liquid (1.92 g, 68%) mixture of anomers. Anal. ($C_{24}H_{30}O_6Si$) C, H. This hemiacetal intermediate (0.31 g, 0.7 mmol) was dissolved in a mixture of MeOH (20 mL) and water (8 mL) and stirred with sodium metaperiodate (0.599 g, 2.8 mmol) at room temperature for 3.5 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was dissolved in EtOAc (30 mL), dried (Na_2SO_4), and concentrated to give the intermediate aldehyde **27** which was used for the next reaction without further purification. The above aldehyde was dissolved in benzene (15 mL) and stirred with tetradecanyl (triphenylphosphoranylidene)acetate[8] (0.726 g, 1.4 mmol) for 18 h at room temperature. The reaction mixture was filtered through a short pad of silica gel and washed with ether (ca. 50 mL). The filtrate was concentrated, dissolved in MeOH (10 mL), and cooled to 0 °C. The solution was stirred and treated with concentrated NH_4OH (0.1 mL) for 12 h. The reaction mixture was quenched with acetic acid (0.1 mL) and concentrated. The residue was purified by flash column chromatography over silica gel using a gradient of 20−40% EtOAc in hexane, to give the title compound **28** (0.359 g, 80.3%) as an oil: $[\alpha]^D_{25} = +2.25°$ (*c* 1.51, $CHCl_3$); IR (neat) 3473 (OH), 1786 and 1722 (C=O), and 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (distorted t, 3 H, C*H*$_3$(CH$_2$)$_{13}$), 1.02 (s, 9 H, C(C*H*$_3$)$_3$), 1.20−1.40 (m, 22 H, CH$_3$(C*H*$_2$)$_{11}$CH$_2$CH$_2$OCO), 1.60 (m, 2 H, CH$_3$(CH$_2$)$_{11}$C*H*$_2$CH$_2$OCO), 2.10−2.22 (m, 1 H, H-4$_a$), 2.40−2.60 (m, 3 H, H-4$_b$, H-3$_{a,b}$), 2.85 (br, 1H, OH), 3.62 (dd, *J* = 11.7, 7.5 Hz, 1 H, SiOC*H*HOCH(OH)), 3.78 (m, 2 H, SiOCH*H*OC*H*(OH)), 4.08 (t, *J* = 6.7 Hz, 2 H, CH$_3$(CH$_2$)$_{11}$CH$_2$C*H*$_2$OCO), 6.02 (d, *J* = 15.8 Hz, 1 H, C*H*=CHCO),7.00 (d, *J* = 15.7 Hz, 1 H, CH=C*H*CO), 7.30−7.50 (m, 6 H, Ph), 7.60−7.70 (m, 4 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.10, 19.14, 22.67, 25.88, 26.79, 27.51, 28.55, 29.25, 29.34, 29.40, 29.49, 29.58, 29.63, 29.67, 31.90, 63.44, 65.00, 75.08, 86.84, 121.43, 127.91, 130.03, 130.05, 132.38, 135.47, 144.16, 165.63, 175.71. Anal. ($C_{39}H_{58}O_6Si$) C, H.

(*R*)-5-(Hydroxymethyl)-5-[2-(tetradecanoxycarbonyl)-(*E*)-ethenyl]tetrahydro-2-furanone (6) and (*R*)-5-(Hydroxymethyl)-5-[2-(tetradecanoxycarbonyl)ethyl]tetrahydro-2-furanone (4). A stirred solution of **28** (0.25 g, 0.39 mmol) in THF (7 mL) at 0 °C was treated with HF−pyridine (1.5 mL). The reaction mixture was brought to room temperature during the course of 1 h and stirred further for 15 h. The reaction mixture was then diluted with a mixture of ice and ether, and the layers were separated. The aqueous layer was extracted with ether (3 × 15 mL), and the combine organic extract was washed with water (2 × 10 mL) and dried (Na_2SO_4). The residue obtained after evaporation was purified by flash column chromatography over silica gel using a gradient from 60% to 100% EtOAc in hexane to give the intermediate, (5*R*)-5-[(1*R*)-1,2-hydroxyethyl]-5-[2-(tetradecanoxycarbonyl)-ethenyl]tetrahydro-2-furanone, as a white solid (0.115 g, 73%): mp 47−48 °C (EtOAc/hexane); $[\alpha]^D_{25} = +21.78°$ (*c* 1.01, $CHCl_3$); IR (CH_2Cl_2) 3453 (OH), 1779 and 1707 (CO), and 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (distorted t, 3 H, C*H*$_3$(CH$_2$)$_{13}$), 1.10−1.40 (m, 22 H, CH$_3$(C*H*$_2$)$_{11}$CH$_2$CH$_2$OCO), 1.65 (m, 2 H, CH$_3$(CH$_2$)$_{11}$C*H*$_2$CH$_2$OCO), 2.00−2.22 (m, 1 H, H-4$_a$), 2.40−2.70 (m, 3 H, H-4$_b$, H-3$_{a,b}$), 3.60 (dd, *J* = 11.2, 7.0 Hz, 1 H, C*H*HOCH(OH)), 3.72−3.90 (m, 2 H, CH*H*OC*H*(OH)), 4.10 (t, *J* = 6.7 Hz, 2 H, CH$_3$(CH$_2$)$_{11}$CH$_2$C*H*$_2$OCO), 6.10 (d, *J* = 15.7 Hz, 1 H, C*H*=CHCO), 6.95 (d, *J* = 15.7 Hz, 1 H, CH=C*H*CO); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.67, 25.88, 27.70, 28.49, 28.53, 29.24, 29.33, 29.49, 29.57, 29.63, 31.90, 62.27, 65.23, 75.21, 87.26, 122.04, 144.12, 165.75, 175.88. Anal. ($C_{23}H_{40}O_6$) C, H.

A stirred solution of this intermediate (0.112 g, 0.28 mmol) and $NaHCO_3$ (0.047 g, 0.56 mmol) in ethanol (5 mL) and water (2 mL) was treated with sodium metaperiodate (0.180 g, 0.84 mmol) at room temperature for 3.5 h. The reaction mixture was cooled to 0 °C and treated with $NaBH_4$ (0.0 21 g, 0.56 mmol) for 1.5 h. The reaction mixture was then concentrated and extracted with EtOAc (3 × 20 mL). The combined organic extract was washed with water (2 × 10 mL) and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was purified by flash column chromatography over silica gel using hexane/EtOAc (65:35) as eluant to give compound **6** (0.035 g, 34%), followed by **4** (0.024 g, 23%). Compound **6**: mp 59−60 °C (EtOAc/hexane); $[\alpha]^D_{25} = +24.56°$ (*c* 0.81, $CHCl_3$). All the spectral properties were identical to the optical antipode **5**. Anal. ($C_{22}H_{38}O_5$) C, H. Compound **4**: mp 49−50 °C (EtOAc/hexane); $[\alpha]^D_{25} = -7.92°$ (*c* 1.06, $CHCl_3$). All the spectral properties were identical to the optical antipode **3** and the racemate **2**. Anal. ($C_{22}H_{40}O_5$) C, H.

(*S*)-5-(Hydroxymethyl)-5-[(3,4-dihydro-2-oxo-5*H*-furan-3(*E*)-ylidene)methyl]-3-{(*E*)-[(*Z*)-9-octadecenylidene]}-tetrahydro-2-furanone (11), (*S*)-5-(Hydroxymethyl)-5-[(3,4-dihydro-2-oxo-5*H*-furan-3(*E*)-ylidene)methyl]-3-{(*Z*)-[(*Z*)-9-octadecenylidene]}tetrahydro-2-furanone (12), (*S*)-5-(Hydroxymethyl)-5-[(3,4-dihydro-2-oxo-5*H*-furan-3(*Z*)-ylidene)methyl]-3-{(*E*)-[(*Z*)-9-octadecenylidene]}tetrahydro-2-furanone (13), and (*S*)-5-(Hydroxymethyl)-5-[(3,4-dihydro-2-oxo-5*H*-furan-3(*Z*)-ylidene)methyl]-3-{(*Z*)-[(*Z*)-9-octadecenylidene]}tetrahydro-2-furanone (14). Aldehyde **22** (1.0 mmol) was dissolved in a mixture of benzene (20 mL) and dichloromethane (10 mL) and treated with α-(triphenylphosphoranylidene)-γ-butyrolactone[10] (0.070 g, 2.0 mmol). The reaction mixture was stirred for 14 h and concentrated. The residue was passed through a short pad of silica gel and eluted with ether. The filtrate was concentrated under reduce pressure to give a mixture of formate esters and free alcohols. The products were dissolved in methanol (5 mL), and the solution was cooled to 0 °C and treated with ammonium hydroxide solution (0.05 mL) with stirring for 10 min at 0 °C. The reaction mixture was quenched with acetic acid (0.05 mL) and concentrated to give four products of different *E*/*Z* geometries (**11**−**14**) with very close R_f values on TLC. The mixture of four products was dissolved in dichloromethane (40 mL), treated with *tert*-butyldimethylsilyl chloride (0.226 g, 1.5 mmol) and imidazole (0.272 g, 4.0 mmol), and stirred for 14 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (5:1 to 3:1) as eluant. The order of elution of products was as follows: **30** (protected **12**), **29** (protected **11**), **32** (protected **14**), and **31** (protected **13**). Each isomer was dissolved in a mixture of acetic acid, water, and THF (3:1:1) and heated to 60 °C for 48 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography with EtOAc/hexanes (1:1) to give the final targets. The combined yield of products from **22** was 0.322 (70%).

Compound **12**: oil; $[\alpha]^{22}_D$ −5.71° (*c* 0.14, $CHCl_3$); IR (neat) 3421 (OH), 1756 (C=O), 1670 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, C*H*$_3$(CH$_2$)$_7$CH=CH(CH$_2$)$_7$CH=C<), 1.10−1.50 (m, 22 H, CH$_3$(C*H*$_2$)$_6$CH$_2$CH=CHCH$_2$(C*H*$_2$)$_5$CH$_2$-CH=C<), 1.85 (br s, 1 H, OH), 2.00 (m, 4 H, CH$_3$(CH$_2$)$_6$C*H*$_2$-CH=CHC*H*$_2$(CH$_2$)$_5$CH$_2$CH=C<), 2.60−2.85 (m, 3 H, CH$_3$(CH$_2$)$_6$-CH$_2$CH=CHCH$_2$(CH$_2$)$_5$C*H*$_2$CH=C<, H-4$_a$), 3.00−3.30 (m, 3 H, H-4$_b$, H-4′$_{a,b}$), 3.70 (AB q, *J* = 12.5 Hz, 2 H, C*H*$_2$OH), 4.36 (t, *J* = 7.3 Hz, 2 H, H-5′$_{a,b}$), 5.32 (m, 2 H, CH$_3$(CH$_2$)$_6$CH$_2$C*H*=C*H*-(CH$_2$)$_7$CH=C<), 6.26 (m, 1 H, C$_{17}$H$_{33}$C*H*=C<), 6.61 (t, *J* = 2.9 Hz, 1 H, >C=CHC); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.66, 25.86, 27.16, 27.19, 27.86, 28.95, 29.18, 29.22, 29.29, 29.40, 29.50, 29.70, 29.73, 31.88, 36.23, 65.95, 66.38, 83.95, 123.02, 128.11, 129.72, 129.98, 136.35, 146.44, 168.47, 171.2; FAB MS *m*/*z* (relative intensity) 461 (MH^+, 10). Anal. ($C_{28}H_{44}O_5$) C, H.

Compound **11**: oil; $[\alpha]^{22}_D$ +26.85° (*c* 0.54, $CHCl_3$); IR (neat) 3422 (OH), 1756 (C=O), 1680 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, C*H*$_3$(CH$_2$)$_7$CH=CH-(CH$_2$)$_7$CH=C<), 1.10−1.50 (m, 22 H, CH$_3$(C*H*$_2$)$_6$CH$_2$CH=CH-CH$_2$(C*H*$_2$)$_5$CH$_2$CH=C<), 2.00 (m, 4 H, CH$_3$(CH$_2$)$_6$C*H*$_2$CH=CH-C*H*$_2$(CH$_2$)$_5$CH$_2$CH=C<), 2.18 (m, 2 H, CH$_3$(CH$_2$)$_6$CH$_2$-CH=CHCH$_2$(CH$_2$)$_5$C*H*$_2$CH=C<), 2.72 (dm, *J* = 16.9 Hz, 1 H, H-4$_a$), 2.95−3.30 (m, 3 H, H-4$_b$, H-4′$_{a,b}$), 3.73 (AB q, *J* = 12.1 Hz, 2 H, C*H*$_2$OH), 4.35 (t, *J* = 7.3 Hz, 2 H, H-5′$_{a,b}$), 5.32 (m, 2 H, CH$_3$(CH$_2$)$_7$C*H*=C*H*(CH$_2$)$_7$CH=C<), 6.64 (t, *J* = 2.9 Hz, 1 H, >C=CHC), 6.77 (m, 1 H, C$_{17}$H$_{33}$C*H*=C<); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.58, 25.79, 27.05, 27.12, 27.95, 29.05, 29.22, 29.25,

29.42, 29.60, 29.66, 30.33, 31.80, 32.87, 66.00, 66.42, 84.62, 125.09, 127.86, 129.57, 129.95, 136.42, 142.74, 169.91, 171.33; FAB MS *m/z* (relative intensity) 461 (MH^+, 19). Anal. ($C_{28}H_{44}O_5$) C, H.

Compound **14**: semisolid gum; $[\alpha]^{22}_D$ −30.00° (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3423 (OH), 1753 and 1720 (C═O), 1675 cm^{-1} (C═C); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, $CH_3(CH_2)_7CH$═CH-$(CH_2)_7CH$═C<), 1.10−1.50 (m, 22 H, $CH_3(CH_2)_6CH_2CH$═CH-$CH_2(CH_2)_5CH_2CH$═C<), 1.85 (br s, 1 H, OH), 2.00 (m, 4 H, $CH_3(CH_2)_6CH_2CH$═$CHCH_2(CH_2)_5CH_2CH$═C<), 2.65 (m, 2 H, $CH_3(CH_2)_6CH_2CH$═$CHCH_2(CH_2)_5CH_2CH$═C<), 3.00 (m, 3 H, H-4_a, H-$4'_{a,b}$), 3.42 (dm, J = 16.9 Hz, 1 H, H-4_b), 3.90 (AB q, J = 11.9 Hz, 2 H, CH_2OH), 4.38 (m, 2 H-$5'_{a,b}$), 5.32 (m, 2 H, $CH_3(CH_2)_6CH_2CH$═$CH(CH_2)_7CH$═C<), 6.18 (m, 1 H, $C_{17}H_{33}$-CH═C<), 6.47 (t, J = 2.4 Hz, 1 H, >C═CH-C); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.67, 27.20, 27.69, 29.03, 29.20, 29.23, 29.30, 29.50, 29.56, 29.69, 29.71, 31.89, 37.68, 65.71, 66.71, 85.63, 124.47, 126.49, 129.79, 129.95, 143.20, 145.05, 168.31, 168.67; FAB MS *m/z* (relative intensity) 461 (MH^+, 22). Anal. ($C_{28}H_{44}O_5$) C, H.

Compound **13**: semisolid gum; $[\alpha]^{22}_D$ −16.19° (*c* 0.42, $CHCl_3$); IR (neat) 3407 (OH), 1746 and 1722 (C═O), 1678 cm^{-1} (C═C); ^1H NMR ($CDCl_3$) δ 0.86 (distorted t, 3 H, $CH_3(CH_2)_7CH$═CH-$(CH_2)_7CH$═C<), 1.10−1.50 (m, 22 H, $CH_3(CH_2)_6CH_2CH$═CH-$CH_2(CH_2)_5CH_2CH$═C<), 2.00 (m, 4 H, $CH_3(CH_2)_6CH_2CH$═CH-$CH_2(CH_2)_5CH_2CH$═C<), 2.18 (m, 2 H, $CH_3(CH_2)_6CH_2$-CH═$CHCH_2(CH_2)_5CH_2CH$═C<), 2.88 (dm, J = 17.9 Hz, 1 H, H-4_a), 3.00 (m, 2 H, H-$4'_{a,b}$), 3.40 (dm, J = 17.9 Hz, 1 H, H-4_b), 3.92 (AB q, J = 12.0 Hz, 2 H, CH_2OH), 4.38 (m, 2 H, H-$5'_{a,b}$), 5.32 (m, 2 H, $CH_3(CH_2)_6CH_2CH$═$CH(CH_2)_7CH$═C<), 6.49 (t, J = 2.4 Hz, 1 H, >C═CH-C), 6.69 (m, 1 H, $C_{17}H_{33}CH$═C<); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.67, 27.16, 27.21, 28.09, 29.16, 29.30, 29.51, 29.69, 29.74, 30.21, 31.89, 32.59, 34.64, 65.74, 66.75, 86.27, 126.45, 126.54, 129.71, 130.01, 141.66, 143.14, 168.33, 169.90; FAB MS *m/z* (relative intensity) 461 (MH^+, 26). Anal. ($C_{28}H_{44}O_5$) C, H.

Supporting Information Available: Tables of atomic coordinates, bond distances and angles, and anisotropic thermal parameters for compound (±)-**33** (Tables 4−8) (5 pages). Ordering information is given on any current masthead page.

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(7) The relative stereochemistry at C-5 is the same in both templates; however, the presence of the double bond in **5** (as well as in **7** and **8**) causes the chiral center to change from "*R*" to "*S*".

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