Conformationally Constrained Analogues of Diacylglycerol. 13.[1] Protein Kinase C Ligands Based on Templates Derived from 2,3-Dideoxy-L-*erythro(threo)*-hexono-1,4-lactone and 2-Deoxyapiolactone

Jeewoo Lee,[†,‡] Nancy E. Lewin,[§] Peter Acs,[§] Peter M. Blumberg,[§] and Victor E. Marquez*[,†]

Laboratories of Medicinal Chemistry and of Cellular Carcinogenesis and Tumor Promotion, Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892

Received July 22, 1996[⊗]

In the present investigation, the last two possible modes of generating conformationally semirigid diacylglycerol (DAG) analogues embedded into five-membered ring lactones as templates **III** and **IV** are investigated. The first two templates studied in previous investigations corresponded to 2-deoxyribonolactone (template **I**) and 4,4-disubstituted γ-butyrolactone (template **II**), with the latter producing potent protein kinase C (PK-C) ligands with low nanomolar binding affinities. The templates reported in this work correspond to 2,3-dideoxy-L-*erythro*- or -*threo*-hexono-1,4-lactone (template **III**) and 2-deoxyapiolactone (template **IV**). Compounds constructed with the dideoxy-L-*erythro*- or -*threo*-hexono-1,4-lactone template were synthesized stereospecifically from tri-*O*-acetyl-L-glucal and L-galactono-1,4-lactone, respectively. Compounds constructed with the 2-deoxyapiolactone template were synthesized stereoselectively from di-*O*-isopropylidene-α-D-apiose. Inhibition of the binding of [^{3}H]phorbol-12,13-dibutyrate to PK-Cα showed that only the *threo*-isomer, 5-*O*-tetradecanoyl-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (**2**) was a good PK-C ligand ($K_i = 1\ \mu$M). The rest of the ligands had poorer affinities with K_i values between 10 and 28 μM. With these results, the order of importance of five-membered ring lactones as competent templates for the construction of semirigid DAG surrogates with effective PK-C binding affinity can be established as **II** ≫ **I** ∼ **III** > **IV**.

Introduction

Protein kinase C (PK-C) represents a family of at least 11 isozymes that are integrally coordinated with other important pathways in cell signal transduction.[2−5] The biological significance of this heterogeneity suggests that, in addition to their different tissue distribution, each isozyme might respond differently to various combinations of activating lipids present in the membrane.[6] With the exception of the atypical isozymes, the second messenger, diacylglycerol (DAG), appears to be the "common denominator" lipid required for PK-C activation.[2−6] Two important classes of DAG, differing in their fatty acid composition, can be identified as PK-C activators: (a) DAG derived from the receptor-activated hydrolysis of phosphatidylinositol 4,5-diphosphate (PIP_2) and (b) DAG derived from phosphatidyl choline (PC) hydrolysis. Although both forms of DAG appear capable of activating PK-C,[7] their involvement in cellular PK-C activation may differ.[6,7] Thus, DAG resulting from PIP_2 hydrolysis is rapidly inactivated to phosphatidic acid by DAG kinase, whereas DAG derived from PC appears to be involved in a more sustained activation of PK-C owing its poorer substrate affinity for DAG kinase.[8−10] All DAG-activated isozymes bind to DAG through a cysteine-rich, zinc finger-like motif present in the regulatory C1 domain of the protein.[11] In a similar manner, the phorbol esters can bind directly to the same site, causing a PK-C activation that bypasses the normal physiological, signal-mediated mechanism.[12] For this reason, the phorbol esters have become essential pharmacological tools for studying the involvement of PK-C in the regulation of cellular processes of growth and differentiation. However, despite being the paradigm of PK-C activators with binding affinities that are several orders of magnitude higher than any DAG, the phorbol esters may act supraphysiologically and could activate responses that are not normally elicited by DAG.[14] In an attempt to overcome this problem, we have recently synthesized a series of "super DAG" molecules that bind 2 orders of magnitude tighter to PK-C than DAG, by virtue of the smaller entropic penalty associated with their binding.[1,15,16] With these molecules, the affinity gap between phorbol esters and DAG has been narrowed, while still maintaining a desirable structural identity with the latter. The conformationally restricted DAG molecules have been derived by constraining the glycerol backbone to five-membered ring lactones, such as 2-deoxyribonolactone[17] (template **I**) and 5,5-disubstituted tetrahydro-2-furanone (template **II**, also known as 4,4-disubstituted γ-butyrolactone),[15,16] with the latter giving rise to the kind of super DAG molecules mentioned above. These templates resulted from two lactonization stragegies depicted in Scheme 1 as paths a and b, respectively. In the present paper, we report the results with the two remaining templates corresponding to lactonization options c and d (Scheme 1). With the inclusion of these templates, a comprehensive SAR analysis on the use of five-membered ring lactones as DAG surrogates can be completed. Such analysis is the subject of the present investigation.

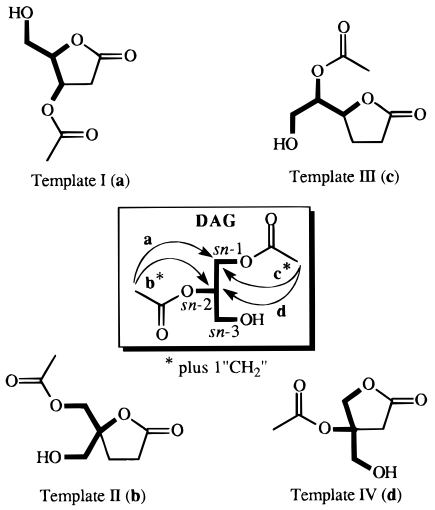
Chemistry

Construction of Compounds with Template III. Restriction of the glycerol backbone according to path c affords a 2,3-dideoxyhexono-1,4-lactone template. When

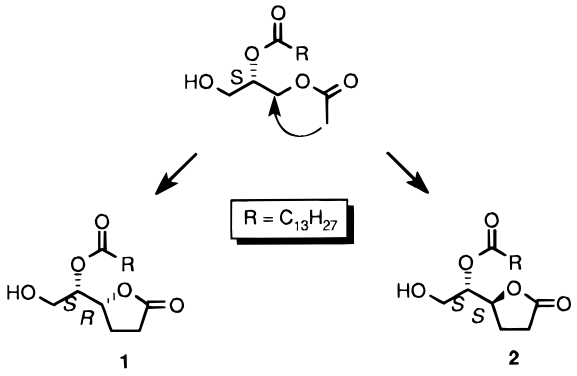
† Laboratory of Medicinal Chemistry.
‡ Present address: Laboratory of Medicinal Chemistry, College of Pharmacy, Seoul National University, Seoul, Korea.
§ Laboratory of Cellular Carcenogenesis and Tumor Promotion.
⊗ Abstract published in *Advance ACS Abstracts,* November 15, 1996.

S0022-2623(96)00525-0

Scheme 1



Scheme 2

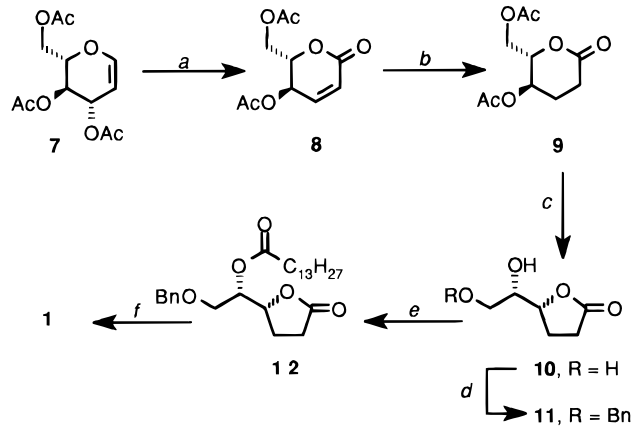


this process is performed on the active, chiral (*S*)-DAG, both *erythro* (**1**) and *threo* (**2**) isomers are possible, owing to the creation of a new chiral center (Scheme 2). As was the case with the other lactones,[1,15−17] the lipophilic side chain was initially maintained constant as the tetradecanoate ester for a preliminary investigation on the worthiness of the new template.

Synthesis of the *erythro* isomer **1** started with commercially available tri-*O*-acetyl-L-glucal (**7**), which was oxidized with pyridinium chlorochromate (PCC) to the α,β-unsaturated δ-lactone **8** as published[18] (Scheme 3). Catalytic hydrogenation of **8** gave the saturated lactone **9**, which after deacetylation under acidic conditions rearranged exclusively to the γ-lactone **10**. The IR absorption at 1762 cm^{-1} and the ^{13}C-NMR resonance at 180.25 ppm confirmed the γ-lactone structure. At this stage, the benzyl group was introduced selectively at the primary position via the dibutylstannylene intermediate to give the monobenzyl ether **11**, which was then acylated with tetradecanoyl chloride to give the penultimate intermediate **12**. Due to the ease with which acyl migration occurs with this type of compounds, removal of the benzyl group in **12** by BCl_3 at −78 °C was followed by a careful extraction of the product in a mixture of ether and a pH 7 buffer solution. For the same reason, compound **1** was not chromatographed on silica gel and was purified instead by recrystallization from hexane.

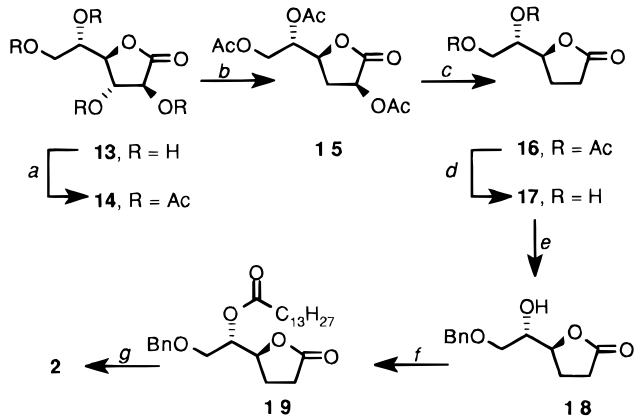
For the *threo* isomer **2**, commercially available L-galactono-1,4-lactone (**13**) was peracetylated to the tetra-*O*-acetyl derivative **14** and subjected to a tandem

Scheme 3[a]



[a] Reagents: (a) ref 18; (b) H_2, Pd/C, EtOAc (99%); (c) 2 N HCl, THF, Δ (93%); (d) (i) *n*-Bu_2SnO, $CHCl_3$−MeOH, (ii) CsF, BnBr, DMF (92%); (e) $C_{13}H_{27}COCl$, py, DMAP, CH_2Cl_2 (98%); (f) BCl_3, CH_2Cl_2, −78 °C (92%).

Scheme 4[a]

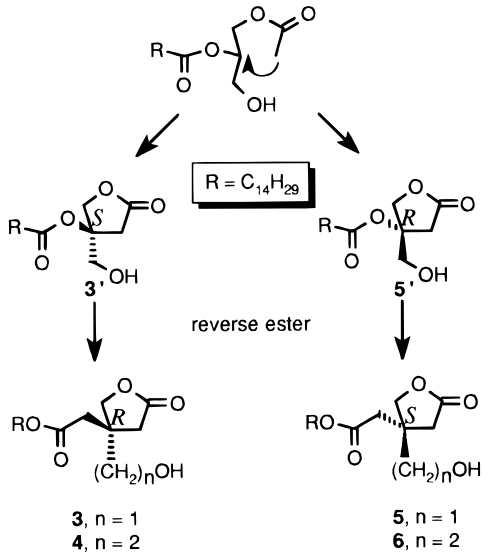


[a] Reagents: (a) ref 19; (b) H_2, Pd/C, Et_3N, EtOAc (98%); (c) SmI_2, HMPA, ethylene glycol−THF (62%); (d) 1 N HCl, THF, Δ (90%); (e) (i) *n*-Bu_2SnO, $CHCl_3$−MeOH, (ii) CsF, BnBr, DMF (94%); (f) $C_{13}H_{27}COCl$, py, DMAP, CH_2Cl_2 (97%); (g) BCl_3, CH_2Cl_2, −78 °C (92%).

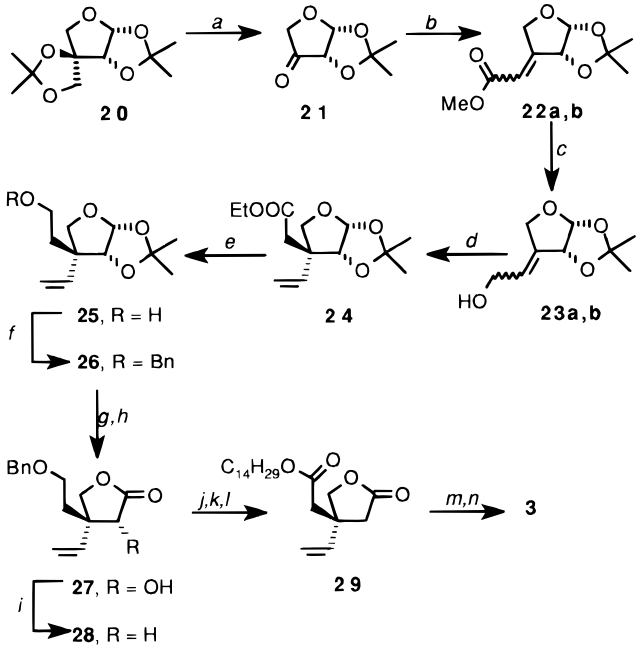
elimination−hydrogenolysis of the β-acetoxy group to give the triacetate **15** in same manner as reported for the D-form[19] (Scheme 4). The α-acetoxy group was then removed by a SmI_2-mediated radical reduction to afford the diacetate **16**. Deacetylation of **16** under acidic conditions gave the desired diol **17**. As before, the IR absorption at 1759 cm^{-1} and the ^{13}C-NMR resonance at 180.44 ppm confirmed the γ-lactone structure. From the diol **17**, an identical approach to the one used for the synthesis of **1** produced the desired *threo* isomer **2**.

Construction of Compounds with Template IV. The structure of template **IV** was very appealing due to its similarity to template **II**, which led to the construction of compounds with potencies in the nanomolar range.[15,16] As with the other templates, facile acyl migration from one alcohol function to the other was a potential problem. However, the situation was even more favorable in this case for rapid acyl migration between the tertiary and primary alcohol groups of targets **3′** and **5′** (Scheme 5). Hence, the strategy of reversing the ester function[1] was employed and targets **3** and **5** were proposed instead. Additional changes included a one-carbon extension of the primary alcohol chain to generate targets **4** and **6**, as suggested by the molecular superposition of this template onto the phor-

Scheme 5



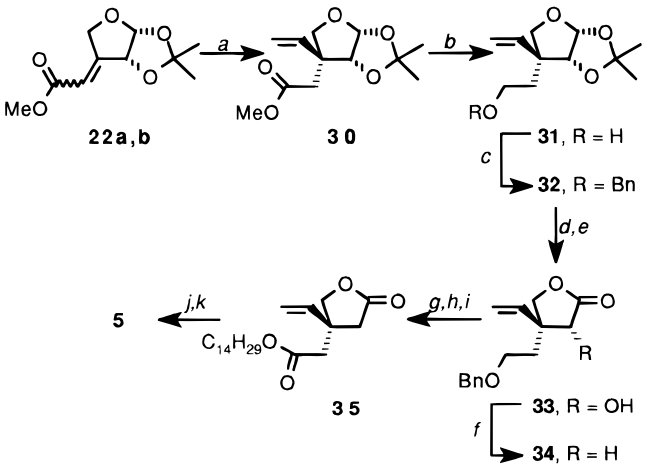
Scheme 6[a]



[a] Reagents: (a) ref 21; (b) Ph_3PCHCO_2Me, benzene, Δ (96%); (c) DIBAL, CH_2Cl_2, −30 °C (96%); (d) $Me(OEt)_3$, HCO_2Et, 135 °C, 14 h (79%); (e) $LiAlH_4$, THF; (f) NaH, BnBr, THF (79% from **24**); (g) AcOH−H_2O, 80 °C; (h) $AgCO_3$/Celite, benzene (76% from **26**); (i) SmI_2, HMPA, ethylene glycol−THF (98%); (j) BCl_3, CH_2Cl_2, −10 °C; (k) CrO_3, H_2SO_4, acetone; (l) $C_{14}H_{29}OH$, DCC, DMAP, CH_2Cl_2 (56% from **28**); (m) OsO_4, 4-NMO, $NaIO_4$, aqueous acetone, room temperature, 14 h; (n) $NaBH_4$, MeOH, −10 °C (72% from **29**).

bol esters.[20] The synthesis of all four target compounds (**3**−**6**) started from 1,2:3,5-di-*O*-isopropylidene-α-D-*threo*-apiofuranose (**20**). The synthesis of compound **3** is illustrated in Scheme 6. It commenced with the selective deprotection of **20** followed by diol cleavage to the 3-ulose **21**.[21] Wadsworth−Emmons reaction of **21** with methyl (triphenylphosphoranylidene)acetate produced a 4:1 mixture of *E*/*Z*-isomers (**22a,b**), which were separated and individually characterized. Selective reduction of the ester function with diisobutylaluminum hydride (DIBAL) gave the corresponding allylic alcohols (**23a,b**), setting the stage for the Claisen rearrangement of the intermediate enol ester. This was formed by reacting **23a,b** (as a mixture) with triethyl orthoacetate

Scheme 7[a]



[a] Reagents: (a) CH_2=CHMgBr, CuBr·SMe_2, THF−ether, −40 °C (68%); (b) $LiAlH_4$, THF; (c) NaH, BnBr, THF (79% from **30**); (d) AcOH−H_2O, 80 °C; (e) $AgCO_3$/Celite, benzene (76% from **32**); (f) SmI_2, HMPA, ethylene glycol−THF (98%); (g) BCl_3, CH_2Cl_2, −10 °C; (h) CrO_3, H_2SO_4, acetone; (i) $C_{14}H_{29}OH$, DCC, DMAP, CH_2Cl_2 (56% from **34**); (j) OsO_4, 4-NMO, $NaIO_4$, aqueous acetone, room temperature, 14 h; (k) $NaBH_4$, MeOH, −10 °C (72% from **35**).

in the presence of propionic acid to give intermediate **24** as the major product. The desired stereochemistry of C-3 resulted from the rearrangement occurring from the less hindered side of the molecule. However, this mixture of C-3 epimers was not well resolved by column chromatography until after reduction of the ester and benzyl ether protection of the resulting alcohol to give **26** (79%), together with 8% of its C-3 epimer. Lactonization was accomplished after removal of the 1,2-*O*-isopropylidene group with acid hydrolysis to give compound **27**, followed selective oxidation of the resulting hemiacetal. Subsequently, deoxygenation of the α-hydroxy lactone with SmI_2 gave the 2-deoxy lactone **28**. At this stage, the benzyl group was removed with BCl_3, and the resulting alcohol was oxidized to the acid via Jone's oxidation. The acid was then esterified with tetradecanol, thus completing the top, *β*-side of the target compound. Finally, oxidative cleavage of the terminal olefin with OsO_4/$NaIO_4$ gave the corresponding aldehyde, which was converted to the desired target **3** after sodium borohydride reduction.

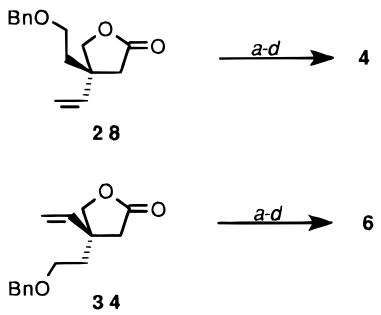
Synthesis of the optical antipode of **3** (compound **5**, Scheme 7) started with compound **22a,b** (mixture of isomers). Addition of vinylmagnesium bromide to the α,*β*-unsaturated ester from the less hindered side of the molecule gave exclusively compound **30** with the desired stereochemistry at C-3. As before, the ester function was reduced to the alcohol and protected as the benzyl ether to give compound **32**. From this point onward, the synthetic steps leading to the enantiomeric target **5** were identical to those used in the previous scheme.

Compounds **4** and **6**, corresponding to the one-carbon homologues of **3** and **5**, were easily accessed from compounds **28** and **34**, respectively (Scheme 8). Separately, compounds **4** and **6** were obtained in four steps comprising hydroboration of the terminal olefin to the alcohol, oxidation, esterification of the acid with tetradecanol, and removal of the benzyl ether protection.

Biological Results

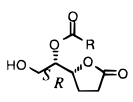
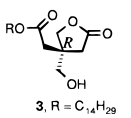
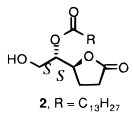
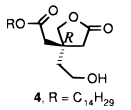
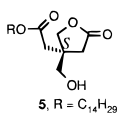
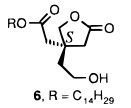
The affinity of these ligands for PK-C was assessed in terms of their ability to displace bound [^{3}H-20]phorbol

Scheme 8[a]



[a] Reagents: (a) (i) BH_3·SMe_2, THF, 0 °C, (ii) $NaBO_3$, H_2O (35%); (b) CrO_3, H_2SO_4, acetone; (c) $C_{14}H_{29}OH$, DCC, DMAP, CH_2Cl_2 (76% for two steps); (d) H_2, Pd/C, EtOH, AcOH (98%).

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

Template III		Template IV	
Compound	K_i	Compound	K_i
 **1**, R = $C_{13}H_{27}$	28.0±2.8	 **3**, R = $C_{14}H_{29}$	16.9±2.2
 **2**, R = $C_{13}H_{27}$	1.07±0.02	 **4**, R = $C_{14}H_{29}$	24.1±4.9
		 **5**, R = $C_{14}H_{29}$	18.4±0.6
		 **6**, R = $C_{14}H_{29}$	10.4±0.6

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.[1,15−17] The K_i values for inhibition of binding were calculated from the ID_{50} values. With this preliminary assay one can compare the efficiency of the various templates before pursuing further biological evaluation of the most potent compounds. The results from this type of assay will constitute the basis for the structure−activity analysis of this work. A comparison of the K_i values for **1**, **2**, and **3**−**6** (Table 1), derived from templates **III** and **IV**, respectively, suggests that these templates are not very good for the construction of potent DAG surrogates, since even the best ligand (compound **1**) has an affinity for PK-C in the same range as the structurally equivalent DAG analogue, glycerol 1-myristate 2-acetate.[17] The difference between compounds **1** and **2** shows that introduction of a new asymmetric center at the *sn*-1 position of DAG is important for the stereospecific interaction of the glycerol backbone with PK-C. Although both compounds have the same absolute stereochemistry as natural (*S*)-DAG at the *sn*-2 position, only diastereoisomer **1** with the *S*,*R*-configuration (Scheme 2) shows good binding affinity for the enzyme. These results contrast with those in which a single methyl substituent at the *sn*-1 position of DAG resulted in a decrease of PK-C agonist activity that was independent of the stereochemistry.[22] All the compounds built with template **IV** were disappointingly weak ligands. Even factoring a 4-fold increase in the K_i value (4-fold reduction in binding affinity) that results from the transposition of the oxygen in the ester function,[1] the values for the "normal esters" would not have even approached 1 μM. Interestingly, in these "reversed esters" the stereochemistry of the only asymmetric carbon in the molecule is of little relevance, since *R*-isomer **3** and *S*-isomer **5** have nearly the same affinity for the enzyme. Finally, a one-carbon extension of the hydroxymethyl chain resulted in only a slight affinity improvement for compound **6** with the *S*-configuration.

With these results, and those from our previous investigations with templates **I** and **II**, the following structure−activity summary can be assembled:

1. The creation of an additional asymmetric center by the intramolecular folding of DAG at *sn*-1 (Scheme 1, paths a and c), which leads to templates **I**[17] and **III**, offers little or no entropic advantage over the open chain DAG. The most potent compounds constructed with this template have equal affinity for PK-C as DAG.

2. The maintenance of just one asymmetric center by the intramolecular folding of DAG at *sn*-2, according to path b (Scheme 1), results in a large entropic advantage of 100-fold over the open chain DAG molecule.[16] The most potent compounds constructed with this template have affinities for PK-C in the 10−20 nM range.[16] The use of this template alters the stereochemical preference from *R* to *S*, relative to DAG.[16]

3. The maintenance of just one asymmetric center by the intramolecular folding of DAG at *sn*-2, according to path d (Scheme 1), results in compounds with indistinct stereochemical preference, no entropic advantage, and loss of binding affinity.

4. From the three previous observations, it is concluded that the importance of five-membered ring lactones for the construction of semirigid DAG surrogates follows the sequence **II** ≫ **I** ∼ **III** > **IV**.

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 Nonradioactive Ligands. Enzyme−ligand interactions were analyzed by competition with [^{3}H]PDBU binding essentially as described in our previous work,[15] 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 23. 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.[1,15−17,23] Values represent the mean ± standard error (three determinations).

4,6-Di-*O*-acetyl-2,3-dideoxy-L-*erythro*-hex-2-enono-1,5-lactone (8). This compound was prepared from tri-*O*-acetyl-L-glucal (**7**) according to the literature.[18]

4,6-Di-*O*-acetyl-2,3-dideoxy-L-*erythro*-hexono-1,5-lactone (9). A solution of **8** (1.60 g, 7 mmol) in EtOAc (100 mL) was hydrogenated under a balloon of hydrogen for 2 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc:hexanes (3:1) as eluant to give **9** as a colorless oil (1.60 g, 99%): $[\alpha]_D = -22.15$ (*c* 2.19, $CHCl_3$); IR (neat) 1741 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.04 (q, 1 H, $J = 5.9$ Hz, H-4), 4.53 (m, 1 H, H-5), 4.25 (AB d, 2 H, $J = 4.3$ Hz, H-6), 2.51−2.78 (m, 2 H, H-2), 2.08 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 1.90−2.30 (m, 2 H, H-3); ^{13}C NMR δ 170.26, 169.73, 169.16, 78.25, 65.41, 62.83, 26.31, 23.67, 20.80, 20.53. Anal. ($C_{10}H_{14}O_6$) C, H.

2,3-Dideoxy-L-*erythro*-hexono-1,4-lactone (10). A solution of **9** (1.60 g, 6.95 mmol) in 1 N HCl (50 mL) and THF (50 mL) was refluxed for 4 h and then cooled over an ice bath. The reaction mixture was neutralized with solid $NaHCO_3$ and concentrated under reduced pressure. The semisolid mixture was dissolved in THF, filtered, and reconcentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with $CHCl_3$:MeOH (9:1 to 7:1) as eluant to give **10** as a colorless oil (0.94 g, 93%): $[\alpha]_D = -5.36$ (*c* 5.19, MeOH); IR (neat) 3384 (OH), 1762 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.10 (d, 1 H, $J = 5.3$ Hz, OH), 4.68 (t, 1 H, $J = 5.6$ Hz, OH), 4.53 (ddd sextet, 1 H, $J = 7.1$, 7.1, 3.8 Hz, H-4), 3.65 (m, 1 H, H-5), 3.25−3.42 (m, 2 H, H-6), 2.37−2.50 (m, 2 H, H-2), 2.00−2.20 (m, 2 H, H-3); ^{13}C NMR (CD_3OD) δ 180.25, 82.14, 73.54, 63.73, 29.30, 23.03. Anal. ($C_6H_{10}O_4$) C, H.

6-*O*-Benzyl-2,3-dideoxy-L-*erythro*-hexono-1,4-lactone (11). A solution of **10** (0.94 g, 6.43 mmol) in chloroform (90 mL) and MeOH (10 mL) was treated with dibutyltin oxide (1.6 g, 6.43 mmol) and refluxed for 3 h until a clear solution was obtained. The solution was concentrated under reduced pressure, and the residue was treated with cesium fluoride (1.95 g, 12.86 mmol) and dried overnight under high vaccum. The mixture was dissolved in DMF (20 mL) and treated with benzyl bromide (1.21 g, 7.07 mmol). The reaction mixture was stirred for 48 h at room temperature, quenched with EtOAc (50 mL) and water (1 mL), and stirred for 30 min. The mixture was filtered through a short pad of silica gel and eluted with EtOAc. The organic filtrate was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc:hexanes (2:1) as eluant to give **11** as a colorless oil (1.40 g, 92%): $[\alpha]_D = -11.96$ (*c* 3.27, $CHCl_3$); IR (neat) 3440 (OH), 1770 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−7.40 (m, 5 H, phenyl), 4.44−4.60 (m, 3 H, H-4 and $PhCH_2O$), 3.91 (m, 1 H, H-5), 3.50−3.65 (m, 2 H, H-6), 2.40−2.64 (m, 2 H, H-2), 2.16−2.30 (m, 2 H, H-3); ^{13}C NMR ($CDCl_3$) δ 177.36, 137.42, 128.39, 127.83, 127.69, 79.81, 73.46, 70.84, 70.35, 28.12, 22.67. Anal. ($C_{13}H_{16}O_4$) C, H.

6-*O*-Benzyl-5-*O*-tetradecanoyl-2,3-dideoxy-L-*erythro*-hexono-1,4-lactone (12). A solution of **11** (0.47 g, 2.0 mmol) in CH_2Cl_2 (40 mL) was treated with pyridine (0.65 mL, 8.0 mmol), a catalytic amount of DMAP, and tetradecanoyl chloride (1.1 mL, 4.0 mmol). After 3 h of stirring at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ether, filtered, and reduced to dryness under vacuum. The residue was purified by flash column chromatography on silica gel with EtOAc:hexanes (1:2) as eluant to give **12** as a colorless oil (0.87 g, 98%): $[\alpha]_D = +3.93$ (*c* 3.74, $CHCl_3$); IR (neat) 1785 and 1742 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−7.40 (m, 5 H, phenyl), 5.18 (ddd quartet, 1 H, $J = 5.0$ Hz, H-5), 4.74 (ddd sextet, $J = 7.0$, 5.0, 5.0 Hz, 1 H, H-4), 4.51 (s, 2 H, $PhCH_2O$), 3.64 (m, 2 H, H-6), 2.46−2.56 (m, 2 H, H-2), 2.12−2.35 (m, 4 H, H-3 and $OC(O)CH_2C_{12}H_{25}$), 1.60 (m, 2 H, $OC(O)CH_2CH_2C_{11}H_{23}$), 1.10−1.65 (m, 20 H, $OC(O)CH_2CH_2(C_{10}H_{20})CH_3$), 0.86 (distorted t, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 176.51, 172.79, 137.52, 128.43, 127.84, 127.61, 77.98, 73.44, 72.03, 67.88, 34.24, 31.89, 29.64, 29.62, 29.58, 29.41, 29.33, 29.21, 29.03, 27.96, 24.88, 23.21, 22.66, 14.10. Anal. ($C_{27}H_{42}O_5$) C, H.

5-*O*-Tetradecanoyl-2,3-dideoxy-L-*erythro*-hexono-1,4-lactone (1). A solution of **12** (0.45 g, 1.0 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C and treated dropwise with boron trichloride in CH_2Cl_2 (1 M, 3 mL, 3 mmol). After being stirred for 2.5 h at −78 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution (3 mL) and immediately partitioned between ether and a pH 7 buffer solution. The organic layer was washed with the pH 7 buffer five times, dried ($MgSO_4$), and concentrated under reduced pressure to give **1** as a solid. The solid was dissolved in ether (3 mL), cooled over an ice bath, and crystallized by adding cold hexanes. The deposited solid was filtered to give pure **1** as a white solid: mp 52.5 °C; $[\alpha]_D = -7.44$ (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 3481 (OH), 1778 and 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.04 (ddd quartet, 1 H, $J = 4.6$ Hz, H-5), 4.71 (ddd, quartet, 1 H, $J = 7.0$ Hz, H-4), 3.82 (AB d, 2 H, $J = 4.5$ Hz, H-6), 2.50−2.60 (m, 2 H, H-2), 2.05−2.40 (m, 4 H, H-3 and $OC(O)CH_2C_{12}H_{25}$), 1.60 (m, 2 H, $OC(O)CH_2CH_2C_{11}H_{23}$), 1.15−1.35 (m, 20 H, $OC(O)CH_2CH_2(C_{10}H_{20})CH_3$), 0.86 (distorted t, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 176.41, 173.40, 77.52, 74.36, 61.43, 34.23, 31.89, 29.64, 29.60, 29.56, 29.40, 29.32, 29.19, 29.05, 27.92, 24.86, 23.54, 22.65, 14.09; FAB MS *m/z* (relative intensity) 357 (MH^+, 100). Anal. ($C_{20}H_{36}O_5$) C, H.

2,5,6-Tri-*O*-acetyl-3-deoxy-L-*xylo*-hexono-1,4-lactone (15). This compound was prepared from L-galactono-1,4-lactone in two steps according to the published literature.[19]

5,6-Di-*O*-acetyl-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (16). Hexamethylphosphoramide (9.6 mL, 55.18 mmol) and ethylene glycol (4.28 mL, 76.8 mmol) were added to a solution of **15** (1.85 g, 6.4 mmol) in THF (64 mL) at room temperature. A solution of samarium iodide in THF (0.1 M, 200 mL, 20 mmol) was added dropwise while the mixture was stirred. After 1 h, the reaction was quenched with saturated $NaHCO_3$ solution, and then the mixture was reduced to dryness under reduced pressure. The residue was partitioned between EtOAc and water, and the organic layer was washed with sodium thiosulfate solution and water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc:hexanes (2:1) as eluant to give **16** as a colorless oil (0.9 g, 62%): $[\alpha]_D = -2.83$ (*c* 2.30, $CHCl_3$); IR (neat) 1781 and 1746 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.17 (dt, 1 H, $J = 6.6$, 4.2 Hz, H-5), 4.70 (ddd sextet, 1 H, $J = 6.8$, 3.7 Hz, H-4), 4.35 (dd, 1 H, $J = 11.8$, 4.5 Hz, H-6a), 4.15 (dd, 1 H, $J = 11.8$, 6.8 Hz, H-6b), 2.52 (irregular t, 2 H, H-2), 2.10 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 1.90−2.40 (m, 2 H, H-3); ^{13}C NMR δ 176.09, 170.29, 169.96, 77.47, 71.57, 62.12, 27.78, 23.58, 20.63, 20.50. Anal. ($C_{10}H_{14}O_6$) C, H.

2,3-Dideoxy-L-*threo*-hexono-1,4-lactone (17). This compound was obtained from **16** by acid hydrolysis similar to the procedure used for the synthesis of **10**. The compound was obtained as a colorless oil in 90% yield: $[\alpha]_D = +58.18$ (*c* 2.03, MeOH); IR (neat) 3384 (OH), 1759 (C=O) cm^{-1}; ^1H NMR (CD_3OD) δ 4.68 (distorted t, 1 H, H-4), 3.55−3.65 (m, 3 H, H-5 and H-6), 2.43−2.64 (m, 2 H, H-2), 2.10−2.40 (m, 2 H, H-3); ^{13}C NMR (CD_3OD) δ 180.44, 81.79, 74.53, 63.77, 29.34, 24.68. Anal. ($C_6H_{10}O_4$) C, H.

6-*O*-Benzyl-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (18). This compound was obtained from **17** by the same procedure used for the synthesis of **11**. The compound was obtained as a white solid in 94% yield: mp 103 °C; $[\alpha]_D = +45.96$ (*c* 1.88, $CHCl_3$); IR ($CHCl_3$) 3440 (OH), 1769 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−7.40 (m, 5 H, phenyl), 4.50−4.60 (m, 3 H, H-4 and $PhCH_2O$), 3.82 (m, 1 H, H-5), 3.58 (AB d, 2 H, $J = 5.9$ Hz, H-6), 2.40−2.62 (m, 2 H, H-2), 2.16−2.30 (m, 2 H, H-3); ^{13}C NMR ($CDCl_3$) δ 177.49, 137.51, 128.40, 127.83, 127.74, 79.76, 73.49, 72.00, 70.73, 28.27, 23.72. Anal. ($C_{13}H_{16}O_4$) C, H.

6-*O*-Benzyl-5-*O*-tetradecanoyl-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (19). This compound was obtained from **18** by the same procedure used for the synthesis of **12**. The compound was obtained as a colorless oil in 97% yield: $[\alpha]_D = +16.17$ (*c* 3.76, $CHCl_3$); IR (neat) 1783 and 1741 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−7.40 (m, 5 H, phenyl), 5.11 (ddd sextet, 1 H, $J = 5.8$, 3.7 Hz, H-5), 4.82 (ddd, 1 H, $J = 7.6$, 6.7, 3.7 Hz, 1 H, H-4), 4.55 (d, 1 H, $J = 11.8$ Hz, $PhCHHO$), 4.48 (d, 1 H, $J = 11.8$ Hz, $PhCHHO$), 3.65 (dd, 1 H, $J = 10.0$, 6.1, 10.05 Hz, H-6a), 3.60 (dd, 1 H, $J = 10.0$, 5.8 Hz, H-6b), 2.50 (irregular t, 2 H, H-2), 2.20−2.37 (m, 3 H, H-3a, $OC(O)CH_2C_{12}H_{25}$), 1.98 (m, 1 H, H-3b), 1.60 (m, 2 H, OC(O)-

$CH_2CH_2C_{11}H_{23}$), 1.15−1.40 (m, 20 H, OC(O)$CH_2CH_2C_{10}H_{20}$-CH_3), 0.86 (distorted t, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 176.41, 172.82, 137.40, 128.25, 127.66, 127.47, 77.68, 73.24, 72.36, 67.81, 34.03, 31.73, 29.48, 29.46, 29.41, 29.26, 29.17, 29.06, 28.89, 27.93, 24.72, 23.48, 22.51, 13.95. Anal. ($C_{27}H_{42}O_5$) C, H.

5-*O*-Tetradecaonyl-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (2). This compound was obtained from **19** by the same procedure used for the synthesis of **1**. It was obtained as a white solid in 92% yield: mp 61 °C; $[\alpha]_D$ = +7.40 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3487 (OH), 1777 and 1737 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.98 (ddd sextet, 1 H, *J* = 5.4, 3.8 Hz, H-5), 4.80 (m, 2 H, H-4), 3.85 (dd, 1 H, *J* = 11.8, 5.3 Hz, H-6a), 3.78 (dd, 1 H, *J* = 11.8, 5.7 Hz, H-6b), 2.48−2.58 (m, 2 H, H-2), 2.25−2.42 (m, 3 H, H-3a, OC(O)$CH_2C_{12}H_{25}$), 1.90−2.10 (m, 1 H, H-3b), 1.60 (m, 2 H, OC(O)$CH_2CH_2C_{11}H_{23}$), 1.15−1.35 (m, 20 H, OC(O)$CH_2CH_2C_{10}H_{20}CH_3$), 0.86 (distorted t, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 176.44, 173.54, 77.88, 74.70, 61.51, 34.21, 31.89, 29.60, 29.56, 29.42, 29.32, 29.20, 29.06, 28.05, 24.88, 23.80, 22.65, 14.09; FAB MS *m/z* (relative intensity) 357 (MH^+, 100). Anal. ($C_{20}H_{36}O_5$) C, H.

1,2-*O*-Isopropylidene-α-D-*glycero*-tetrose-3-ulose (21). This compound was prepared from 1,2:3,5-di-*O*-isopropylidene-α-D-*threo*-apiofuranose (**20**) in two steps according to the method of Carey et al.[21]

(*E*)-3-Deoxy-3-*C*-[(methoxycarbonyl)methylidene]-1,2-*O*-isopropylidene-α-D-*erythro*-furanose (22a) and (*Z*)-3-Deoxy-3-C-[(methoxycarbonyl)methylidene]-1,2-*O*-isopropylidene-α-D-*erythro*-furanose (22b). A solution of **20** (2.56 g, 16.2 mmol) in benzene (100 mL) was treated with methyl (triphenylphosphoranylidene)acetate (8.12 g, 24.3 mmol) and a catalytic amount of benzoic acid. After 1 h of reflux, the reaction mixture was cooled and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography with EtOAc:hexanes (1:3) as eluant to give both *E*- and *Z*-isomers as a colorless oils in 77% and 19% yield, respectively.

22a: *E*-isomer, R_f = 0.52 (EtOAc:Hex = 1:2); $[\alpha]_D$ = +149.05 (*c* 6.02, $CHCl_3$); IR (neat) 1716 (C=O) and 1678 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.09 (m, 1 H, HC=), 5.88 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1), 4.94−5.00 (m, 3 H, H-2 and H-4); 3.72 (s, 3 H, $COOCH_3$), 1.45 (s, 3 H, $C(CH_3)$), 1.38 (s, 3 H, $C(CH_3)$); ^{13}C NMR δ 165.85 (s), 157.61 (s), 116.28 (d), 112.72 (s), 104.57 (d), 81.04 (d), 69.90 (t), 51.55 (q), 27.43 (q), 27.32 (q). Anal. ($C_{10}H_{14}O_5$) C, H.

22b: *Z*-isomer, R_f = 0.44 (EtOAc:Hex = 1:2); $[\alpha]_D$ = +220.68 (*c* 4.10, $CHCl_3$); IR (neat) 1725 (C=O) and 1684 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.88−5.94 (m, 2 H, HC= and H-1), 5.66 (m, 1 H, H-2), 4.76 (dq, 1 H, *J* = 14.3, 2.1, 1.3 Hz, H-4a), 4.42 (dd, 1 H, *J* = 14.3, 1.5 Hz, H-4b), 3.76 (s, 3 H, $COOCH_3$), 1.49 (s, 3 H, $C(CH_3)$), 1.41 (s, 3 H, $C(CH_3)$); ^{13}C NMR δ 165.28 (s), 155.17 (s), 115.28 (d), 112.71 (s), 106.13 (d), 77.05 (d), 70.00 (t), 51.70 (q), 27.17 (q), 26.94 (q). Anal. ($C_{10}H_{14}O_5$) C, H.

(*E*)-3-Deoxy-3-*C*-(hydroxyethylidene)-1,2-*O*-isopropylidene-α-D-*erythro*-furanose (23a) and (*Z*)-3-Deoxy-3-*C*-(hydroxyethylidene)-1,2-*O*-isopropylidene-α-D-*erythro*-furanose (23b). A cooled solution of each ester **22a** or **22b** (1.07 g, 5.0 mmol) in CH_2Cl_2 (200 mL) at −40 °C was treated with a solution of DIBAL in toluene (1.5 M, 12 mL, 18 mmol) which was added slowly via syringe. After 2 h, the reaction mixture was carefully quenched with a solution of potassium sodium tartrate (0.5 M, 100 mL) and stirred at room temperature until a clear solution was obtained. The organic layer was separated, washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with EtOAc:hexanes (2:1) as eluant to give allylic alcohols **23a** and **23b** as a colorless oils (90%).

23a: *E*-isomer; $[\alpha]_D$ = +129.87 (*c* 3.07, $CHCl_3$); IR (neat) 3432 (C=O) and 1654 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.90 (m, 1 H, HC=), 5.82 (d, 1 H, *J* = 3.9 Hz, H-1), 4.85 (d, 1 H, *J* = 3.9 Hz, H-2), 4.54 (m, 2 H, CH_2OH), 4.15 (AB d, 2 H, H-4), 1.49 (s, 3 H, $C(CH_3)$), 1.35 (s, 3 H, $C(CH_3)$); ^{13}C NMR δ 138.10 (s), 126.57 (d), 112.31 (s), 104.87 (d), 81.70 (d), 66.94 (t), 59.93 (t), 27.25 (q), 26.88 (q). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.90; H, 7.56.

23b: *Z*-isomer; $[\alpha]_D$ = +176.2 (*c* 2.00, $CHCl_3$); IR (neat) 3440 (OH) and 1656 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.88 (d, 1 H, *J* = 4.2 Hz, H-1), 5.77 (m, 1 H, HC=), 5.14 (d, 1 H, *J* = 4.2 Hz, H-2), 4.65 (dm, *J* = 12.5 Hz, 1 H, H-4a), 4.27−4.38 (m, 3 H, H-4b and CH_2OH), 1.48 (s, 3 H, $C(CH_3)$), 1.36 (s, 3 H, $C(CH_3)$); ^{13}C NMR δ 139.10 (s), 125.17 (d), 112.21 (s), 106.02 (d), 77.14 (d), 70.05 (t), 60.00 (t), 27.20 (q), 27.04 (q). Anal. ($C_9H_{14}O_4$) C, H.

(3*R*)-3-*C*-[(Benzyloxy)ethyl]-3-*C*-vinyl-1,2-*O*-isopropylidene-α-D-*erythro*-furanose (26). A mixture of **23a** and **23b** (2.0 g, 10.8 mmol), triethyl orthoacetate (14 mL, 75.6 mmol), and propionic acid (0.27 mL, 3.6 mmol) was heated at 135 °C for 16 h with removal of ethanol. After concentration under reduced pressure, the residue was purified by flash column chromatography over silica gel with EtOAc:hexanes (1:4 to 4:1) as eluant to give an inseparable mixture of **24** and the undesirable regioisomer as a colorless oil (10:1, 1.76 g, 64%), along with starting material (0.413 g, 15%). The above crude ester **24** (1.90 g, 7.41 mmol) was dissolved in THF (80 mL), cooled to −10 °C, and treated dropwise with $LiAlH_4$ in THF (1 M, 10 mL, 10 mmol). After 30 min of stirring, the reaction mixture was quenched with water and 15% NaOH solution (total volume 2 mL), followed by the slow addition of water. The reaction mixture was stirred overnight at room temperature and filtered, and the filtrate was concentrated under reduced pressure to give alcohol **25**, which was further dried under high vacuum. This crude alcohol was used for the next step without further purification. Hence, **25** was dissolved in THF (100 mL) and treated with NaH (60% dispersion, 0.568 g, 14.2 mmol) at 0 °C. After 20 min of stirring at room temperature, the reaction mixture was treated with benzyl bromide (1.26 mL, 10.64 mmol) and tetrabutylammonium iodide (0.13 g, 0.355 mmol). The resulting solution was stirred overnight at room temperature, quenched with acetic acid (1 mL), and diluted with ether. The suspension was filtered through a short pad of silica gel by eluting with ether. The combined filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography over silica gel with EtOAc:hexanes (1:3) as eluant to give **26** (2.0 g, 79%, combined yield of 2 steps) and its C-3 epimer (0.2 g) as colorless oils.

26: $[\alpha]_D$ = +53.30 (*c* 3.85, $CHCl_3$); IR (neat) 1637 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.20−7.40 (m, 5 H, phenyl), 5.92 (dd, 1 H, *J* = 11.0, 17.8 Hz, CH=CH_2), 5.84 (d, 1 H, *J* = 3.52 Hz, H-1), 5.21 (d, 1 H, *J* = 11.0 Hz, CH=C*H*H), 4.98 (d, 1 H, *J* = 17.8 Hz, CH=CH*H*), 4.46 (s, 2 H, PhCH_2O), 4.38 (d, 1 H, *J* = 3.5 Hz, H-2), 3.95 (d, 1 H, *J* = 8.5 Hz, H-4a), 3.77 (d, 1 H, *J* = 8.5 Hz, H-4b), 3.55 (t, 2 H, *J* = 6.65 Hz, BnOCH_2), 1.78 (m, 2 H, BnOCH_2CH_2), 1.48 (s, 3 H, $C(CH_3)$), 1.39 (s, 3 H, $C(CH_3)$); ^{13}C NMR δ 138.09, 136.04, 128.26, 127.47, 127.43, 116.10, 111.59, 105.70, 85.38, 72.90, 72.33, 66.61, 51.62, 33.68, 26.55, 26.13. Anal. ($C_{18}H_{24}O_4$) C, H.

(3*R*)-3-*C*-[(Benzyloxy)ethyl]-3-*C*-vinyl-D-erythronic γ-Lactone (27). A solution of **26** (2.0 g, 6.57 mmol) in aqueous acetic acid (60%, 100 mL) was heated at 80 °C for 6 h and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with EtOAc:hexanes (2:1) as eluant to give the corresponding hemiacetal, which was immediately dissolved in benzene (80 mL) and treated with silver carbonate over Celite (50% w/w, 5.44 g, 9.86 mmol) at reflux for 1 h. The reaction mixture was cooled, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with EtOAc:hexanes (1:1) as eluant to give **27** as a colorless oil (1.3 g, 76% combined yield of 2 steps): $[\alpha]_D$ = −36.24 (*c* 2.93, $CHCl_3$); IR (neat) 3422 (OH), 1785 (C=O), 1638 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.20−7.40 (m, 5 H, phenyl), 5.84 (dd, 1 H, *J* = 17.8, 11.1 Hz, CH=CH_2), 5.38 (d, 1 H, *J* = 11.1 Hz, CH=C*H*H), 5.30 (d, 1 H, *J* = 17.8 Hz, CH=CH*H*), 4.47 (s, 2 H, PhCH_2O), 4.42 (d, 1 H, *J* = 9.8 Hz, H-4a), 4.28 (d, 1 H, *J* = 4.2 Hz, H-2), 4.02 (d, 1 H, *J* = 9.8 Hz, H-4b), 3.58 (m, 2 H, BnOCH_2), 3.15 (d, 1 H, *J* = 4.2 Hz, OH), 1.80−2.10 (m, 2 H, BnOCH_2CH_2); ^{13}C NMR δ 175.73, 137.33, 133.74, 128.44, 127.84, 127.67, 117.83, 75.58, 73.34, 72.44, 66.36, 49.35, 36.02. Anal. ($C_{15}H_{18}O_4$) C, H.

(3*R*)-3-*C*-[(Benzyloxy)ethyl]-3-*C*-vinyl-γ-butyrolactone (28). A solution of **27** (1.31 g, 5 mmol) in THF (50 mL) was treated with hexamethylphosphoramide (7.5 mL, 43.1 mmol) and ethylene glycol (3.25 mL, 60 mmol). This solution was treated dropwise with a solution of SmI_2 in THF (0.1 M, 150 mL, 15 mmol) and stirred for 30 min at room temperature. The reaction was quenched with saturated $NaHCO_3$ solution (20 mL), and the mixture was concentrated to a small volume. The solution was diluted with EtOAc, and the organic layer was washed with sodium thiosulfate solution, water, and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with EtOAc:hexanes (2:3) as eluant to give **28** as a colorless oil (1.21 g, 98%): $[\alpha]_D = -41.55$ (*c* 2.84, $CHCl_3$); IR (neat) 1781 (C=O), 1638 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−7.40 (m, 5 H, phenyl), 5.78 (dd, 1 H, *J* = 17.5, 10.8 Hz, C*H*=CH_2), 5.21 (d, 1 H, *J* = 10.8 Hz, CH=C*H*H), 5.12 (d, 1 H, *J* = 17.5 Hz, CH=CH*H*), 4.43 (s, 2 H, PhCH_2O), 4.25 (d, 1 H, *J* = 9.3 Hz, H-4a), 4.15 (d, 1 H, *J* = 9.3 Hz, H-4b), 3.49 (t, 2 H, *J* = 6.0 Hz, BnOCH_2), 2.55 (AB t, 2 H, *J* = 18.2 Hz, H-2), 1.88 (t, 2 H, *J* = 6.0 Hz, BnOCH$_2$CH_2); ^{13}C NMR δ 175.82, 139.30, 137.77, 128.10, 127.35, 127.28, 114.93, 76.02, 72.81, 66.29, 44.96, 39.43, 36.91. Anal. ($C_{15}H_{18}O_3$) C, H.

(3*R*)-3-*C*-[(Tetradecanoxycarbonyl)methyl]-3-*C*-vinyl-γ-butyrolactone (29). A solution of **28** (0.493 g, 2.0 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C and treated dropwise with BCl_3 in CH_2Cl_2 (1 M, 6 mL, 6 mmol). The reaction mixture was warmed to −10 °C and stirred for 1 h. The mixture was quenched with saturated $NaHCO_3$ solution (6 mL) and partitioned between CH_2Cl_2 and water. The organic layer was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give the intermediate crude alcohol, which was used for the next step without further purification. The alcohol was dissolved in acetone (20 mL), cooled to 0 °C, and treated dropwise with Jone's reagent (8 N, 2.0 mL, 16 mmol). After the mixture was stirred for 30 min at 0 °C, a small amount of 2-propanol was added to destroy the excess oxidizing reagent. The reaction mixture was partitioned between chloroform and water, and the aqueous layer was extracted twice with chloroform. The combined organic extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to the crude acid. The above acid was dissolved in CH_2Cl_2 (15 mL), and the solution was treated with tetradecanol (0.514 g, 2.0 mmol) and 4-(dimethylamino)-pyridine (0.048 g, 0.4 mmol). A solution of dicyclohexylcarbodiimide in CH_2Cl_2 (1 M, 4 mL, 4 mmol) was added dropwise, and after stirring for 1 h at room temperature, the reaction mixture was quenched with acetic acid (0.35 mL, 6 mmol) and further stirred for 1 h. The mixture was concentrated under reduced pressure, dissolved in cold hexane, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with EtOAc:hexanes (1:5) as eluant to give ester **29** as a white solid (0.41 g, 56% for 3 steps): mp 41 °C; $[\alpha]_D = -15.58$ (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 1762 and 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.92 (dd, 1 H, *J* = 17.5, 10.8 Hz, C*H*=CH_2), 5.21 (d, 1 H, *J* = 10.8 Hz, CH=C*H*H), 5.17 (d, 1 H, *J* = 17.5 Hz, CH=CH*H*), 4.30 (AB d, 2 H, *J* = 9.5 Hz, H-4), 4.05 (t, 2 H, *J* = 6.7 Hz, COOCH_2(CH$_2$)$_{12}$-CH$_3$), 2.65 (s, 2 H, CH_2COO), 2.60 (AB d, *J* = 15.5 Hz, H-2), 1.60 (m, 2 H, COOCH$_2$CH_2(CH$_2$)$_{11}$CH$_3$), 1.15−1.40 (m, 22 H, COOCH$_2$CH$_2$(CH_2)$_{11}$CH$_3$), 0.87 (distorted t, 3 H, CH$_3$); ^{13}C NMR δ 175.29, 170.05, 138.74, 115.45, 75.71, 65.07, 44.10, 41.56, 39.47, 31.87, 29.60, 29.51, 29.45, 29.37, 29.30, 29.14, 28.47, 25.85, 22.64, 14.06. Anal. ($C_{22}H_{38}O_4$) C, H.

(3*R*)-3-*C*-[(Tetradecanoxycarbonyl)methyl]-3-*C*-(hydroxymethyl)-γ-butyrolactone (3). A solution of **29** (0.073 g, 0.2 mmol) in aqueous acetone (50%, 10 mL) was treated with 4-methylmorpholine *N*-oxide (0.047 g, 0.4 mmol), sodium metaperiodate (0.086 g, 0.4 mmol), and OsO_4 (2.5% solution in 2-methyl-2-propanol, 0.05 mL, 0.004 mmol). After 14 h of stirring at room temperature, the reaction mixture was diluted with EtOAc (100 mL). The organic layer was washed with a solution of sodium thiosulfate solution, water, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc:hexanes (2:3) as eluant to give the intermediate aldehyde as an oil. The aldehyde was dissolved in MeOH (10 mL), cooled to −10 °C, and treated with sodium borohydride portionwise until the starting material was consumed. The reaction was quenched with acetone followed by acetic acid, and the mixture was concentrated. The residue was partitioned between ether and water, and the aqueous layer was extracted with ether. The combined organic layer was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc:hexanes (2:3) as eluant to give **3** as a white solid (0.053 g, 72% for two steps): mp 41 °C; $[\alpha]_D = -3.75$ (*c* 0.64, $CHCl_3$); IR ($CHCl_3$) 3482 (OH), 1764 and 1728 (C=O); ^1H NMR ($CDCl_3$) δ 4.31 (d, 1 H, *J* = 9.6 Hz, H-4a), 4.15 (d, 1 H, *J* = 9.6 Hz, H-4b), 4.07 (t, 2 H, *J* = 6.8 Hz, COOCH_2(CH$_2$)$_{12}$CH$_3$), 3.67 (s, 2 H, CH_2OH), 2.60 (s, 2 H, CH_2-COO), 2.58 (d, 1 H, *J* = 17.7 Hz, H-2a), 2.50 (d, 1 H, *J* = 17.7 Hz, H-2b), 1.60 (m, 2 H, COOCH$_2$CH_2(CH$_2$)$_{11}$CH$_3$), 1.10−1.70 (m, 22 H, COOCH$_2$CH$_2$(CH_2)$_{11}$CH$_3$), 0.86 (distorted t, 3 H, CH$_3$); ^{13}C NMR ($CDCl_3$) δ 175.90, 170.90, 74.03, 65.62, 65.31, 42.23, 38.85, 36.81, 31.89, 29.62, 29.53, 29.46, 29.32, 29.17, 28.48, 25.86, 22.65, 14.08; FAB MS *m/e* (relative intensity) 371 (MH^+, 23), 175 (MH − $C_{14}H_{28}$, 100). Anal. ($C_{21}H_{38}O_5$) C, H.

(3*S*)-3-*C*-[(Methoxycarbonyl)methyl]-3-*C*-vinyl-1,2-*O*-isopropylidene-α-D-*erythro*-furanose (30). A solution of vinylmagnesium bromide (1 M in THF, 36 mL, 36 mmol) was cooled to −40 °C, treated with copper(I) bromide−dimethyl sulfide complex (0.74 g, 3.6 mmol), and stirred for 10 min. A solution of **22a,b** (2.58 g, 12.0 mmol) in ether (36 mL) was then slowly added during the course of 1 h and stirred for an additional hour. The reaction mixture was quenched with a saturated NH_4Cl solution and allowed to warm up to room temperature. The mixture was diluted with ether, and the organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc:hexanes (1:3 to 1:2) as eluant to give **30** as a colorless oil (1.97, 68%): $[\alpha]_D = +20.0$ (*c* 3.40, $CHCl_3$); IR (neat) 1740 (C=O), 1639 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.83 (dd, 1 H, *J* = 17.6, 10.9 Hz, C*H*=CH_2), 5.78 (d, 1 H, *J* = 3.5 Hz, H-1), 5.23 (d, 1 H, *J* = 17.6 Hz, CH=C*H*H), 5.21 (d, 1 H, *J* = 10.9 Hz, CH=CH*H*), 4.46 (d, 1 H, *J* = 3.5 Hz, H-2), 4.06 (d, 1 H, *J* = 8.8 Hz, H-4a), 3.89 (d, 1 H, *J* = 8.8 Hz, H-4b), 3.64 (s, 3 H, $COOCH_3$), 2.70 (AB q, *J* = 16.0 Hz, CH_2COOCH$_3$), 1.50 (s, 3 H, C(CH$_3$)), 1.31 (s, 3 H, C(CH$_3$)); ^{13}C NMR δ 171.65 (s), 138.52 (d), 116.36 (t), 111.94 (s), 105.47 (d), 84.95 (d), 73.78 (t), 51.55 (q), 50.39 (s), 36.40 (t), 26.82 (q), 26.40 (q). Anal. ($C_{12}H_{18}O_5$) C, H.

(3*S*)-3-*C*-[(Benzyloxy)ethyl]-3-*C*-vinyl-1,2-*O*-isopropylidene-α-D-*erythro*-furanose (32). This compound was obtained from **30** by following the same procedure used for the synthesis of **26**: $[\alpha]_D = +25.28$ (*c* 2.35, $CHCl_3$); IR (neat) 1637 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−7.40 (m, 5 H, phenyl), 5.72 (d, 1 H, *J* = 3.4 Hz, H-1), 5.71 (dd, 1 H, *J* = 17.6, 10.9 Hz, C*H*=CH_2), 5.21 (d, 1 H, *J* = 10.9 Hz, CH=C*H*H), 5.18 (d, 1 H, *J* = 17.6 Hz, CH=CH*H*), 4.45 (s, 2 H, PhCH_2O), 4.35 (d, 1 H, *J* = 3.4 Hz, H-2), 3.93 (d, 1 H, *J* = 8.7 Hz, H-4a), 3.85 (d, 1 H, *J* = 8.7 Hz, H-4b), 3.50 (m, 2 H, BnOCH_2), 1.95 (m, 2 H, BnOCH$_2$CH_2), 1.51 (s, 3 H, C(CH$_3$)), 1.30 (s, 3 H, C(CH$_3$)); ^{13}C NMR δ 139.31, 138.27, 128.19, 127.34, 127.31, 116.08, 111.66, 105.35, 85.17, 73.83, 72.77, 66.61, 51.31, 30.97, 26.83, 26.29. Anal. ($C_{18}H_{24}O_4$) C, H.

(3*S*)-3-*C*-[(Benzyloxy)ethyl]-3-*C*-vinyl-D-erythronic γ-Lactone (33). This compound was obtained from **32** by following the same procedure for the synthesis of **27**: $[\alpha]_D = -4.77$ (*c* 3.84, $CHCl_3$); IR (neat) 3421 (OH), 1788 (C=O), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−7.40 (m, 5 H, phenyl), 5.88 (dd, 1 H, *J* = 17.5, 10.9, C*H*=CH_2), 5.23 (d, 1 H, *J* = 10.9 Hz, CH=C*H*H), 5.19 (d, 1 H, *J* = 17.5 Hz, CH=CH*H*), 4.57 (d, 1 H, *J* = 11.6 Hz, PhC*H*HO), 4.31 (d, 1 H, *J* = 11.6 Hz, PhCH*H*O), 4.10−4.30 (m, 3 H, H-4 and H-2), 3.62 (m, 1 H, BnOC*H*H), 3.50 (td, 1 H, *J* = 12.3, 2.3 Hz, BnOCH*H*), 2.05 (m, 1 H, BnOCH$_2$C*H*H), 1.75 (ddd, 1 H, *J* = 15.3, 5.3, 2.3 Hz, BnOCH$_2$CH*H*); ^{13}C NMR δ 176.02 (s), 139.20 (d), 136.79 (s), 128.55 (d), 128.28 (d), 128.09 (d), 116.00 (t), 73.85 (d), 73.25 (t), 72.65 (t), 65.91 (t), 49.67 (s), 32.26 (t). Anal. ($C_{15}H_{18}O_4$) C, H.

(3*S*)-3-*C*-[(Benzyloxy)ethyl]-3-*C*-vinyl-γ-butyrolactone (34). This compound was obtained from **33** by following the procedure for the synthesis of its optical antipode **28**: $[\alpha]_D = +41.35$ (*c* 4.0, $CHCl_3$); the IR, ^1H NMR, and ^{13}C NMR spectra were identical to those of **28**. Anal. ($C_{15}H_{18}O_3$) C, H.

(3*S*)-3-*C*-[(Tetradecanoxycarbonyl)methyl]-3-*C*-vinyl-γ-butyrolactone (35). This compound was obtained from **34** by following the procedure for the synthesis of its optical antipode **29**: white solid; mp 41 °C; $[\alpha]_D = +15.08$ (*c* 1.26, $CHCl_3$); the IR, ^1H NMR, and ^{13}C NMR spectra were identical to those of **29**. Anal. ($C_{22}H_{38}O_4$) C, H.

(3*S*)-3-*C*-[(Tetradecanoxycarbonyl)methyl]-3-*C*-(hydroxymethyl)-γ-butyrolactone (5). This compound was obtained from **35** by following the procedure for the synthesis of its optical antipode **3**: white solid: mp 42 °C; $[\alpha]_D = +4.12$ (*c* 0.97, $CHCl_3$); the IR, ^1H NMR, ^{13}C NMR, and FAB MS spectra were identical to those of **1**. Anal. ($C_{21}H_{38}O_5$) C, H.

(3*R*)-3-*C*-[(Tetradecanoxycarbonyl)methyl]-3-*C*-(hydroxyethyl)-γ-butyrolactone (4). A solution of **28** (0.12 g, 0.5 mmol) in THF (10 mL) was cooled to −78 °C and treated dropwise with a borane−methyl sulfide complex in THF (2 M, 0.5 mL, 1.0 mmol). The reaction mixture was gradually allowed to reach 0 °C and stirred for 14 h. The mixture was quenched with a sodium perborate solution (2 equiv) which was added slowly at 0 °C. The cooling bath was removed and stirring continued for 3 h. The mixture was diluted with EtOAc, and the organic layer was washed with water and brine. The solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc:hexanes (3:1) as eluant to give the corresponding alcohol as a colorless oil (0.05 g, 35%). The alcohol (0.05 g, 0.19 mmol) was dissolved in acetone (5 mL), cooled to 0 °C, and treated with Jone's reagent (8 N, 0.1 mL). After being stirred for 30 min at 0 °C, the reaction mixture was treated with 2-propanol to destroy the excess oxidizing reagent and partitioned between chloroform and water. The aqueous layer was extracted twice with chloroform, and the combined organic layer was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to the crude acid. The acid was dissolved in CH_2Cl_2, and the solution was treated with tetradecanol (0.1 g, 0.5 mmol) and a catalytic amount of 4-(dimethylamino)pyridine. A solution of dicyclohexylcarbodiimide in CH_2Cl_2 (1 M, 1 mL, 1 mmol) was then added dropwise, and stirring was continued for 2 h at room temperature. The reaction mixture was quenched with acetic acid (0.05 mL) and stirred for 1 h. The mixture was concentrated, dissolved in cold hexane, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with EtOAc:hexanes (1:4) as eluant to give the corresponding ester. Finally, the ester (0.047, 0.1 mmol) was dissolved in ethanol (10 mL) containing 2 drops of acetic acid and treated with 10% palladium on carbon (0.05 g). The mixture was hydrogenated under a balloon of hydrogen for 2 h and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel with EtOAc:hexanes (1:1) as eluant to give **4** as a white solid: mp 53 °C; $[\alpha]_D = +6.06$ (*c* 0.66, $CHCl_3$); IR ($CHCl_3$) 3496 (OH), 1762 and 1732 (C=O); ^1H NMR ($CDCl_3$) δ 4.27 (AB d, 1 H, $J = 9.6$ Hz, H-4a), 4.22 (AB d, 1 H, $J = 9.6$ Hz, H-4b), 4.06 (t, 2 H, $J = 6.7$ Hz, $C_{13}H_{27}CH_2OC(O)$), 3.78 (t, 2 H, $J = 6$ Hz, CH_2CH_2OH), 2.50−2.70 (m, 4 H, H-2 and $CH_2COOC_{14}H_{29}$), 1.88 (t, 2 H, $J = 6.0$ Hz, CH_2CH_2OH), 1.60 (m, 2 H, $C_{12}H_{25}CH_2$-$CH_2OC(O)$), 1.1−1.7 (m, 22 H, $CH_3(C_{11}H_{22})CH_2CH_2OC(O)$), 0.86 (distorted t, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 175.94, 170.62, 76.24, 64.88, 58.74, 40.66, 40.32, 40.28, 38.18, 31.64, 29.37, 29.29, 29.23, 29.08, 28.93, 28.25, 25.63, 22.41, 13.84; FAB MS *m/e* (relative intensity) 385 (MH^+, 33), 171 ($MH^+ - HOC_{14}H_{29}$, 100). Anal. ($C_{22}H_{40}O_5$) C, H.

(3*S*)-3-*C*-[(Tetradecanoxycarbonyl)methyl]-3-*C*-(hydroxyethyl)-γ-butyrolactone (6). This compound was obtained from **34** by following the procedure for the synthesis of its optical antipode **4**: white solid; mp 53 °C; $[\alpha]_D = -6.67$ (*c* 0.90, $CHCl_3$); the IR, ^1H NMR, ^{13}C NMR and FAB MS spectra were identical to those of **2**. Anal. Calcd for $C_{22}H_{40}O_5$: C, 68.71; H, 10.49. Found: C, 68.64; H, 10.43.

References

(1) Previous reference in the sequence: Lee, J.; Sharma, R.; Wang, S.; Milne, G. W. A.; Lewin, N. E.; Szallazi, Z.; Blumberg, P. M.; George, C.; Marquez, V. E. Conformationally Constrained Analogues of Diacylglycerol. 12. Ultrapotent Protein Kinase C Ligands Based on a Chiral 4,4-Disubstituted Heptono-1,4-lactone Template. *J. Med. Chem.* **1996**, *39*, 36−45.

(2) Pears, C. Structure and Function of the Protein Kinase C Gene Family. *J. Biosci.* **1995**, *20*, 311−332.

(3) Lord, J. M.; Pongracz, J. Protein Kinase C: a Family of Isozymes with Distinct Roles in Pathogenesis. *Clin. Mol. Pathol.* **1995**, *48*, M57−M64.

(4) Dekker, L. V.; Parker, P. J. Protein Kinase C. A Question of Specificity. *Trends Biochem. Sci.* **1994**, *19*, 73−77.

(5) Liu, J.-P. Protein Kinase C and its Substrates. *Mol. Cell Endocrinol.* **1996**, *116*, 1−29.

(6) Nishizuka, Y. Protein Kinase C and Lipid Signaling for Sustained Cellular Responses. *FASEB J.* **1995**, *9*, 484−496.

(7) Zeisel, S. H. Choline Phospholipids: Signal Transduction and Carcinogenesis. *FASEB J.* **1993**, *7*, 551−557.

(8) Lee, C.; Fisher, S. K.; Agranoff, B. W.; Hajra, A. K. Quantitative Analysis of Molecular Species of Diacylglycerol and Phosphatidate Formed Upon Muscarinic Receptor Activation of Human SK-N-SH Neuroblastome Cells. *J. Biol. Chem.* **1991**, *266*, 22837−22846.

(9) Ford, D. A.; Gross, R. W. Differential Metabolism of Diradyl Glycerol Molecular Subclasses and Molecular Species by Rabbit Brain Diglyceride Kinase. *J. Biol. Chem.* **1990**, *265*, 12280−12286.

(10) Florin-Christensen, J.; Florin-Christensen, M.; Delfino, J. M.; Stegmann, T.; Rasmussen, H. Metabolic Fate of Plasma Membrane Diacylglycerols in NIH 3T3 Fibroblasts. *J. Biol. Chem.* **1992**, *267*, 14783−14789.

(11) Kaibuchi, K.; Fukumoto, Y.; Oku, N.; Takai, Y. Molecular Genetic Analysis of the Regulatory and Catalytic Domains of Protein Kinase-C. *J. Biol. Chem.* **1989**, *264*, 13489−13496.

(12) Ono, Y.; Fujii, T.; Igarashi, K.; Kuno, T.; Tanaka, C.; Kikkawa, U.; Nishizuka, Y. Phorbol Ester Binding to Protein Kinase C Requires a Cysteine-Rich Zinc-Finger-Like Sequence. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 4868−4871.

(13) Blumberg, P. M. Complexities of the Protein Kinase C Pathway. *Mol. Carcinog.* **1991**, *4*, 339−344.

(14) Wilkinson, S. E.; Hallaman, T. J. Protein Kinase C: Is It Pivotal Role in Cellular Activation Overstated? *Trends Pharmacol. Sci.* **1994**, *15*, 53−57.

(15) Sharma, R.; Lee, J.; Wang, S.; Milne, G. W. A.; Lewin, N. E.; Blumberg, P. M.; Marquez, V. E. Conformationally Constrained Analogues of Diacylglycerol. 10. Ultrapotent Protein Kinase C Ligands Based on a Racemic 5-Disubstituted Tetrahydro-2-furanone Template. *J. Med. Chem.* **1996**, *39*, 19−28.

(16) Lee, J.; Wang, S.; Milne, G. W. A.; Sharma, R.; Lewin, N. E.; Blumberg, P. M.; Marquez, V. E. Conformationally Constrained Analogues of Diacylglycerol. 11. Ultrapotent Protein Kinase C Ligands Based on a Chiral 5-Disubstituted Tetrahydro-2-furanone Template. *J. Med. Chem.* **1996**, *39*, 29−35.

(17) Teng, K.; Marquez, V. E.; Milne, G. W. A.; Barchi, J. J., Jr.; Kazanietz, M. G.; Lewin, N. E.; Blumberg, P. M.; Abushanab, E. Conformationally Constrained Analogues of Diacylglycerol. Interaction of γ-Lactones with the Phorbol Ester Receptor of Protein Kinase C. *J. Am. Chem. Soc.* **1992**, *114*, 1059−1070.

(18) Rollin, P.; Sinay, P. A Convenient, One-step Oxidation of Glycals to Lactones Using Pyridinium Chlorochromate. *Carbohydr. Res.* **1981**, *98*, 139−142.

(19) Bock, K.; Lundt, I.; Pedersen, C. Preparation of 3-Deoxy-aldonolactones by Hydrogenolysis of Acylated Aldonolactones. *Acta Chem. Scand.* **1981**, *B35*, 155−162.

(20) The same homologation stragegy when employed with a lactone built on template I produced a more potent compound. Sharma, R.; Marquez, V. E.; Milne, G. W. A.; Lewin, N. E.; Blumberg, P. M. *BioMed. Chem. Lett.* **1993**, *3*, 1993−1998.

(21) Carey, F. A.; Ball, D. H.; Long, L., Jr. 1,2:3,5-Di-O-Isopropylidene-α-D-apio-L-Furanose. *Carbohydr. Res.* **1996**, *3*, 205−213.

(22) Molleyres, L. P.; Rando, R. R. Structural Studies on the Diglyceride-mediated Activation of Protein Kinase C. *J. Biol. Chem.* **1988**, *263*, 14832−14838.

(23) Kazanietz, M. G.; Areres, L. B.; Bahador, A.; Mischak, H.; Goodnight, J.; Mushinski, J. F.; Blumberg, P. M. Characterization of Ligand and Substrate Specificity for the Calcium-Dependent and Calcium-Independent Protein Kinase C Isozymes. *Mol. Pharmacol.* **1993**, *44*, 298−307.

JM960525V