Pergamon

Tetrahedron 58 (2002) 5335–5345

TETRAHEDRON

Conformationally constrained analogues of diacylglycerol (DAG). Part 19: Asymmetric syntheses of (3*R*)- and (3*S*)-3-hydroxy-4,4-disubstituted heptono-1,4-lactones as protein kinase C (PK-C) ligands with increased hydrophilicity ☆

Kassoum Nacro,[a,†] Jeewoo Lee,[b] Joseph J. Barchi, Jr.,[a] Nancy E. Lewin,[c] Peter M. Blumberg[c] and Victor E. Marquez[a,*]

[a]*Laboratory of Medicinal Chemistry, Center for Cancer Research, National Cancer Institute at Frederick, Frederick, MD 21702, USA*
[b]*Laboratory of Medicinal Chemistry, College of Pharmacy, Seoul National University, Seoul 151-742, South Korea*
[c]*Laboratory of Cellular Carcinogenesis and Tumor Promotion, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892, USA*

Received 12 February 2002; revised 30 April 2002; accepted 2 May 2002

Abstract—The stereospecific introduction of (*R*)- and (*S*)-OH groups at position C-3 of two diacylglycerol γ-lactones (DAG-lactones) previously identified as strong protein kinase C (PK-C) ligands is presented. The compounds were designed to investigate whether the extra OH group in a specific orientation could establish an additional hydrogen bond with the C1 domain of PK-C, thus providing a DAG analogue with reduced lipophilicity. The OH groups were introduced following two different diastereoselective multistep syntheses starting from diacetone-D-glucose. The PK-C binding affinities for the new compounds were weaker in comparison to those of the parent compounds, suggesting that the extra OH does not engage efficiently in hydrogen bonding at the receptor.

1. Introduction and background

The 11 members of the protein kinase C (PK-C) family of isozymes have attracted much attention in recent years because of their individual involvement in cell growth, apoptosis, cell differentiation and malignant transformation. PK-C isozymes, which are functionally serine/threonine kinases, can be divided into three groups based on structural features and cofactor requirement. Both classical isoforms (α, βI, βII and γ) and novel isozymes (δ, ε, η, and θ) are responsive to diacylglycerol (DAG) and to the potent exogenous tumor promoter, the phorbol esters.[2,3] Physiologically, these PK-C isozymes become activated and translocate from the cytosol to the membrane in response to the lipophilic second-messenger DAG, which is generated as a product of receptor-coupled phosphoinositide metabolism and which binds stereospecifically to the C1 domain of the enzyme.[2,3] The third group of atypical isozymes (ζ and ι/λ) does not respond to DAG or to phorbol esters.[2,3]

Although non-specific hydrophobic interactions between the ligand (DAG/phorbol esters) and the phospholipids in the membrane are critical for efficient membrane insertion and activation, it is likely that distinct ligand–protein interactions, particularly those occurring within the C1 domain, can additionally control isozyme specificity. The combination of these specific and non-specific hydrophobic interactions appears to act in concert as a sub-cellular localization signal. Recently, we have synthesized a potent isozyme-selective DAG-lactone analogue (**1**)[1] containing a hydroxamate moiety that showed remarkable isozyme selectivity between PK-Cα and δ in various cellular assays.[4] We surmised that because of the compound's reduced lipophilicity (log *P*=3.58) relative to other DAG-lactones, such as **2** (log *P*=5.89),[5] specific protein-ligand interactions became dominant and allowed differences between isozymes to be revealed. This important change in the properties of compound **1** was probably due to the direct involvement of the additional OH group in hydrogen bonding at the receptor.[1] Such an interaction is a very important since a non-binding, free OH group would otherwise become solvated with water molecules and resist

☆ See Ref. 1.

Keywords: protein kinase C; diacylglycerol; DAG-lactones; carbohydrate chemistry; log *P*.

* Corresponding author. Address: Laboratory of Medicinal Chemistry, Center for Cancer Research, NCI-Frederick, 376 Boyles St., Bldg. 376 Rm 104, Frederick, MD 21702-1201, USA. Tel.: +1-301-846-5954; fax: +1-301-846-6033; e-mail: marquezv@dc37a.nci.nih.gov

† Present address: Albany Molecular Research Inc., 21 Corporate Circle, P.O. Box 15098, Albany, NY 12212-5098, USA.

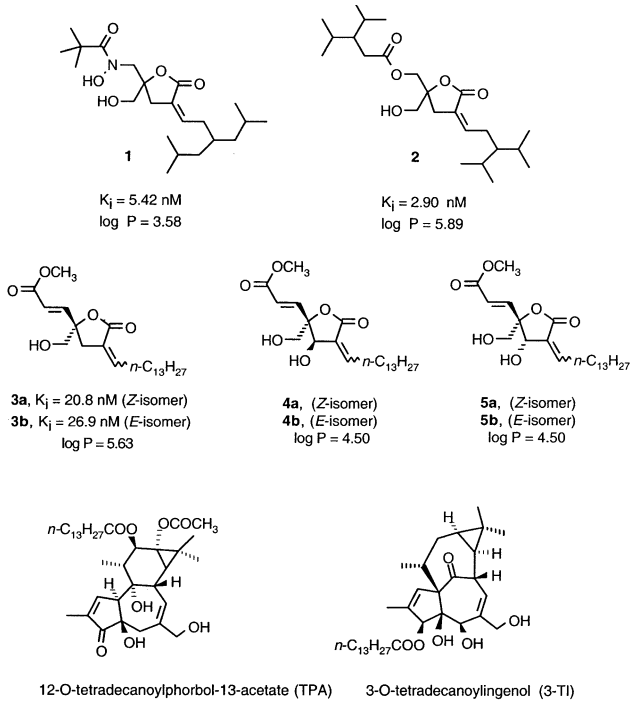
0040–4020/02/$ - see front matter
PII: S0040-4020(02)00477-5

Table 1. Apparent K_i and calculated log P values[15] for the new ligands assayed as inhibitors of PDBU binding to PK-Cα

Compounds	**3a**	**3b**	**4a**	**4b**	**5a**	**5b**
K_i (nM)[a]	20.80±2.1	26.90±3.7	273±12	290±20	5580±130	ND[b]
Log P	5.63	5.63	4.50	4.50	4.50	4.50

[a] K_i are mean±SEM, n=3 experiments.
[b] ND, not determined, 27.2±1.0% inhibition at 100 μM.

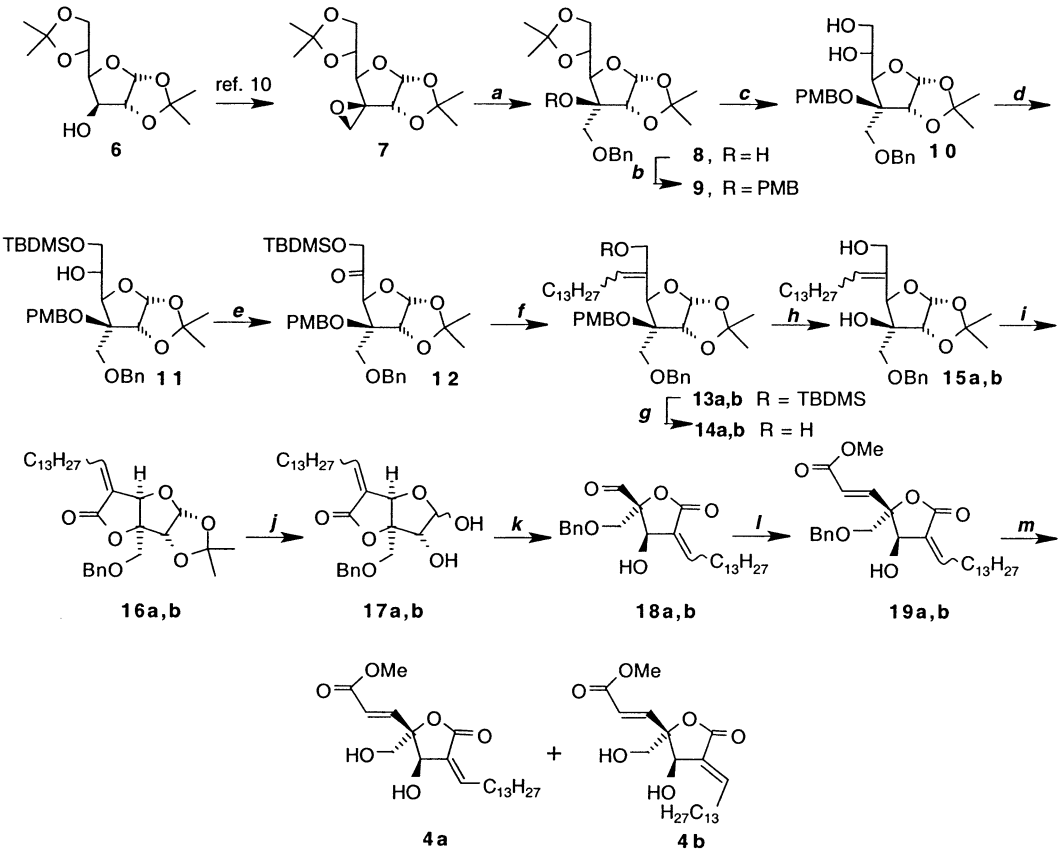
binding in a lipophilic environment. To further explore this concept, we set out to modify the structure of other known, high affinity DAG-lactone ligands (**3a**,**b**)[6] by introducing an extra OH group elsewhere in the molecule, viz. in the lactone ring (**4a**,**b** and **5a**,**b**). It was expected that these more hydrophilic DAG-lactones (Table 1) might also uncover additional isozyme-specific contacts similar to those observed with **1**. An additional structural consideration for incorporating the extra OH group to compounds **3a**,**b** came from examining the structure of the ingenol esters, which represent another important group of PK-C ligands.[7] Indeed, the potent ingenol ester 3-*O*-tetradecanoyl-ingenol (3-TI)[8] has an OH group in the southern poly-hydroxylated region of the molecule, which is in the same relative position to the hydroxymethyl group as in **4a**,**b** and **5a**,**b**. Such an extra OH group is lacking in **3a**,**b** and in the phorbol ester 12-tetradecanoylphorbol-13-acetate (TPA). Both stereochemical orientations (**4a**,**b** and **5a**,**b**) for the newly created center were explored utilizing two different synthetic approaches starting from cheap and plentiful acetone-D-glucose. The biological results indicate that the extra OH in the *S*-configuration (**5a** and **b**) produced a large decrease in binding affinity (ca. 200 fold) relative to the parent compounds (**3a** and **b**). However, the OH in the *R*-configuration resulted in only a 10-fold loss in binding affinity. Taken together these results indicate that the extra OH does not engage efficiently in binding at the receptor and contributes negatively to the partitioning of the compounds into the lipid milieu.



2. Results and discussion

2.1. Synthesis of (3*R*)-3-hydroxy-4,4-disubstituted heptono-1,4-lactones

The approach to the synthesis of **4a**,**b** relied on accessing the key intermediates **16a**,**b** where the requisite lactone's stereogenic centers are embedded in a tricyclic ring system (Scheme 1). Commercially available acetone-D-glucose was used as the starting material. The first three steps of the synthesis leading to compound **7** have already been described,[10] and the success of the approach was based on the regioselective opening of the epoxide ring of **7** with sodium benzylate to give intermediate **8**. The ensuing protection of the newly created tertiary alcohol with *p*-methoxybenzyl (PMB) chloride proceeded well to give compound **9** in excellent yield. Mono-deprotection of bis-ketal **9** to diol **10** was smoothly achieved under mild hydrolytic conditions, which selectively removed the more labile 5,6-*O*-isopropylidene group. Silyl-ether protection of the newly generated primary alcohol gave compound **11**, which after PCC oxidation produced the expected ketone **12**. Wittig reaction of ketone **12** with $C_{14}H_{29}PPh_3Br$ and *n*-BuLi in THF gave the expected mixture of *Z*- and *E*-olefins (**13a**,**b**) in low yield (34%). This is the only low-yielding step of the synthesis, which is attributed to the sterically congested ketone and the bulky phosphonium salt. The protective silyl and *p*-methoxybenzyl groups were sequentially removed to give first **14a**,**b** as a mixture of isomers, and then **15a** and **b** which were separated chromatographically as individual *Z*- and *E*-isomers in 55 and 43% yields, respectively. At this stage of the synthesis, complete characterization of both geometric isomers was not possible, but it could be later established unequivocally by association with the correct geometric isomer identified after lactonization (vide infra). The remaining steps of the synthesis were performed separately for each individual isomer. The primary hydroxyl group in **15a** and **b** was first oxidized into an aldehyde and allowed to react intramolecularly with the tertiary alcohol to give the expected lactol intermediate, which was oxidized in situ to afford **16a** or **b** in excellent yield. As in previous cases with this class of lactones, the geometry of the exocyclic double bond was assigned by ^{1}H NMR.[9] For these cisoid enone systems, the β-*cis* vinyl proton (*E*-isomer **16b**, δ=6.85) normally resonates in a 0.3–0.9 ppm range downfield from the corresponding β-*trans* proton (*Z*-isomer **16a**, δ=6.47).[9] Such a difference was consistently maintained throughout the rest of the synthesis. The remaining 2,3-*O*-isopropylidene group was hydrolyzed under acidic conditions with 2N HCl in THF to give diols **17a** and **b**, respectively, which upon oxidative cleavage with sodium metaperiodate afforded compounds **18a** and **b**. Wittig coupling of **18a** and **b** with triphenylphosphoranylidene acetate provided exclusively

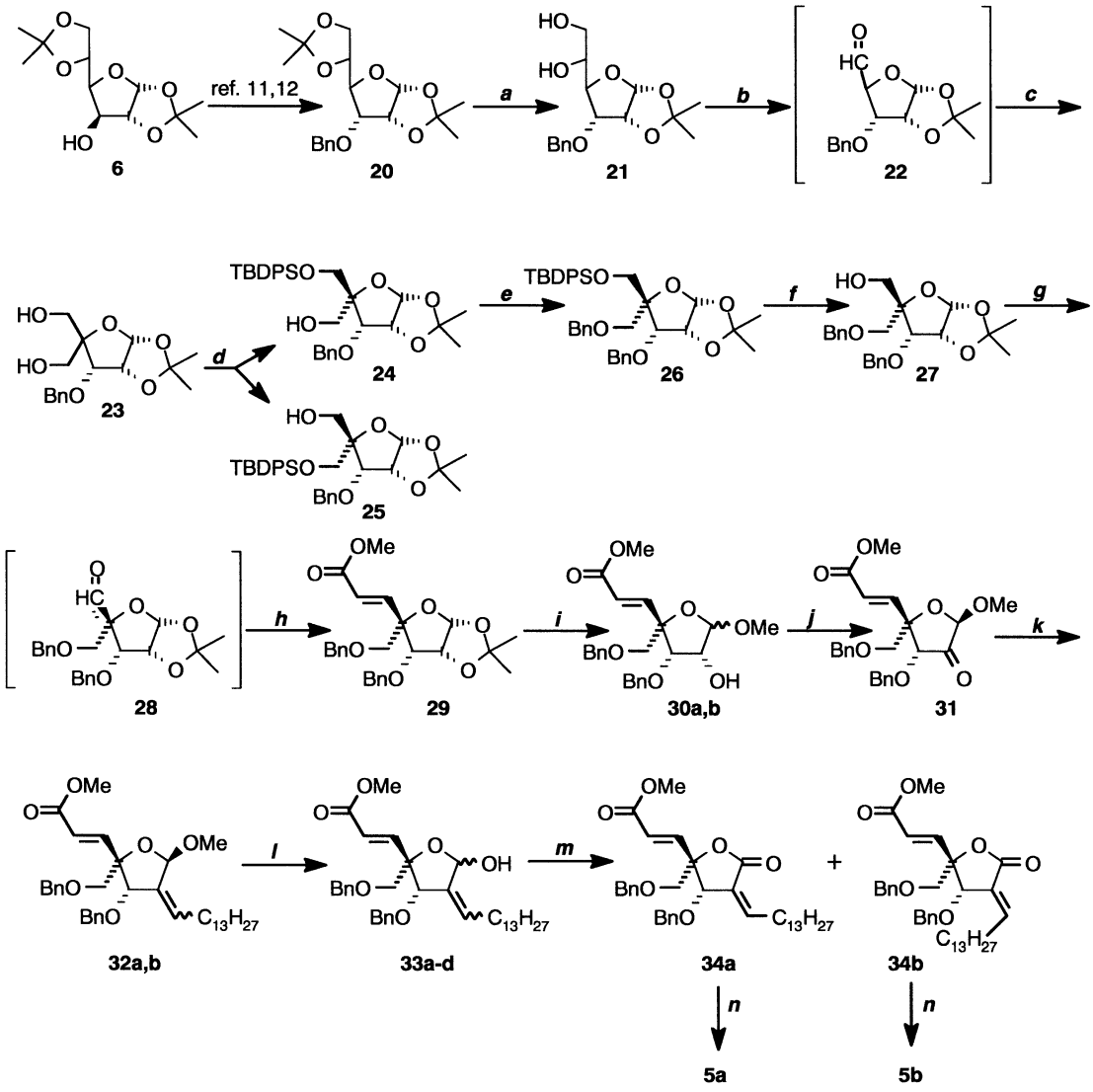


Scheme 1. (a) $PhCH_2OH$, NaH, THF, 98%; (b) *p*-$MeOPhCH_2Cl$ (PMBCl), NaH, Bu_4NI, THF, 96%; (c) 2N HCl, EtOH, 95%; (d) *t*-$BuSiMe_2Cl$ (TBDMSCl), imidazole, CH_2Cl_2–DMF, 99%; (e) PCC, 4 Å molecular sieves, CH_2Cl_2, 80%; (f) $C_{14}H_{29}PPh_3Br$, *n*-BuLi, THF, 34%; (g) *n*-Bu_4NF, THF; (h) DDQ, CH_2Cl_2–H_2O, 98% two steps; (i) MnO_2, CH_2Cl_2, 94%; (j) 2N HCl, THF, 75°C; (k) $NaIO_4$, MeOH–H_2O; (l) $PPh_3{=}CHCO_2CH_3$, CH_2Cl_2, 56–60%, three steps; (m) BCl_3, CH_2Cl_2, −78°C, 46–87%.

compounds **19a** (*Z*,*E*-isomer) and **19b** (*E*,*E*-isomer) in 60% overall yield for the last three steps. Finally, removal of the benzyl group afforded the desired targets **4a** and **b**. During the final deblocking step of **19a** with BCl_3 some of the desired *Z*,*E*-isomer **4a** isomerized to the more stable *E*,*E*-isomer **4b**, even when the reaction was quenched with $NaHCO_3$ and a neutral buffer was used during work up. The results were the same when MeOH was employed to quench the reaction.

2.2. Synthesis of (3*S*)-3-hydroxy-4,4-disubstituted heptono-1,4-lactones

Diacetone-D-glucose (**6**) was readily converted to 1,2:5,6-di-*O*-isopropylidene-3-*O*-benzyl-α-D-allofuranose (**20**) and 1,2-*O*-ispropylidene-3-*O*-benzyl-α-D-allofuranose (**21**) according to published methods (Scheme 2).[11,12] Oxidation of **21** with sodium metaperiodate gave the corresponding aldehyde **22**, which was condensed as a crude product with formaldehyde and aqueous NaOH to give crystalline **23** identical to the material described by Moffatt et al.[13] The Cannizzaro reaction was modified slightly to give almost quantitative yields of **23**, by allowing the reaction to take place in the presence of an excess of formaldehyde (2–4 equiv.) and adding the 1 M NaOH solution last. One of the primary hydroxyl groups in **23** was singly protected with *t*-butyldiphenylsilyl (TBDPS) chloride to give a combined quantitative yield of diastereoisomers **24** (38%) and **25** (62%). One-dimensional NOE spectroscopy was used to assign the position of the TBDPS protecting group in **24** and **25**. Spectra in $CDCl_3$ were well dispersed for **24**, but the methyl groups in **25** overlapped in this solvent, prompting us to reexamine the spectrum of **25** in benzene-d_6. Several shifts in resonance position were observed in this solvent, including a large separation of the methyl singlets that permitted selective irradiation of each signal for assignment purposes. The relatively rigid nature of the bicyclic ring system in compounds **24** and **25** aided in the assignments. Highly diagnostic was the enhancement of only one of the methyl signals of the isopropylidene group after irradiation of either H-1 or H-2 (carbohydrate numbering). For this reason, this methyl signal was assigned to the methyl group oriented toward the *exo* face of the bicyclic system (Fig. 1). Observed NOEs to the remaining methyl group included those from the CH_2 group at C-4 oriented toward the *endo* side of the ring system. Since the assignment of the methylene bearing the free OH group was also obvious from the observed coupling to the hydroxyl proton (and sharpening of these signals after D_2O exchange), it remained a simple matter to distinguish which CH_2O functional group was on the 'bottom' (*endo*) half of the molecule. All other NOEs (Fig. 1) were in agreement with the assigned structures. The observed NOEs were also corroborated by limited molecular modeling using the INSIGHT/DISCOVER package (Accelerys, Inc., San Diego, CA). Energy minimization of compound **24** revealed



Scheme 2. (a) 2N HCl/EtOH; (b) $NaIO_4$, MeOH/H_2O, 72% (two steps); (c) H_2CO, 1N NaOH, Dioxane, 94%; (d) *t*-BuSiPh$_2$Cl (TBDPSCl), *n*-BuLi, THF, 100%; (e) $PhCH_2Br$ (BnBr), NaH, THF, 76%; (f) *n*-Bu_4NF, THF, 94%; (g) DMSO, DCC, $CHCl_2CO_2H$; (h) Ph_3PCHCO_2Me, CH_2Cl_2 85% (two steps); (i) 0.2N HCl, MeOH, 75%; (j) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2; (k) $BrPh_3PC_{14}H_{29}$, *n*-BuLi, THF 31% (two steps); (l) 0.1N HCl, THF/H_2O, 87%; (m) MnO_2, CH_2Cl_2, 64%; (n) BCl_3, CH_2Cl_2, −78°C, 96%.

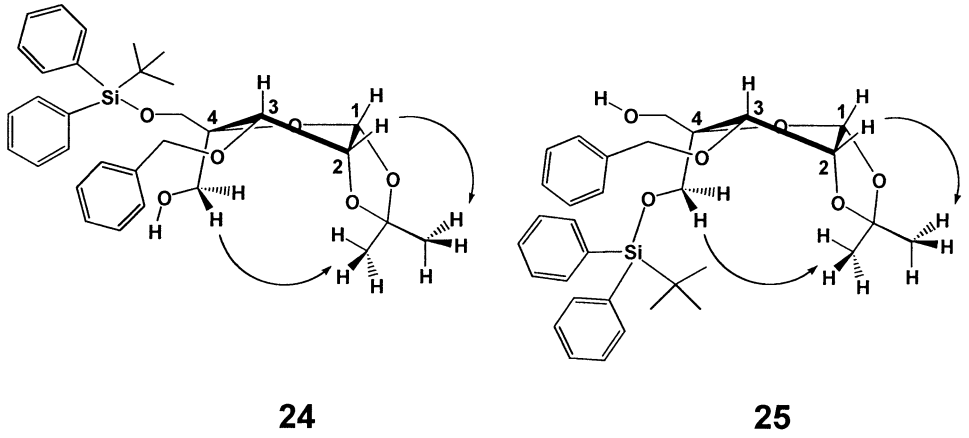


Figure 1. Diagnostic NOEs in compounds **24** and **25**.

that the protons of the *endo*-oriented methyl group and those on the methylene unit of the *endo*-oriented CH_2 at C-4 may be as little as 3.2–3.5 Å apart. The remaining free hydroxyl group in **24** was then protected as a benzyl ether to give **26**, and the TBDPS protective group was removed to give **27**. This was the preferred strategy, rather than using compound **25** directly, based on the robustness of the benzyl group relative to the TBDPS group. The primary alcohol in **27** was oxidized under mild conditions to aldehyde **28**, which was immediately reacted with triphenylphosphoranylidene acetate to give olefin **29** (85% two steps). The ensuing acid-catalyzed methanolysis of **29** proceeded smoothly to give **30a**,**b** (75%) as a mixture of α,β-anomers. Although it was possible to pursue the synthesis with the mixture, it proved more convenient to separate the anomers at this stage and to carry out the oxidation separately. The pure β-anomer (singlet at δ 5.03) was oxidized to give ketone **31**, which upon treatment with tetradecyltriphenylphosphonium bromide and *n*-BuLi gave a mixture of geometric isomers **32a**,**b** (31% two steps). Hydrolysis of the methyl glycoside gave a mixture of four compounds (**33a**,**b**), which after Swern oxidation gave the expected mixture of geometric isomers (**34a** and **b**), which were then separated by column chromatography. Finally, removal of the benzyl protective group with BCl_3 gave the desired target compounds **5a** and **b**. During this last step, a similar isomerization to the one reported during the deprotection of **19a** into mixtures of **4a** and **b** led to the isomerization of the less stable *E*,*Z*-isomer **5a** into the more stable *EE*-isomer **5b** regardless of the method used for quenching the reaction. These compounds are separable by column chromatography, and, as before, the β-*cis* vinyl proton of the *E*,*E*-isomer **5b** (δ=7.08) resonates ca. 0.5 ppm downfield from the corresponding β-*trans* proton in the *E*,*Z*-isomer **5a** (δ=6.60).[9]

2.3. Biological results

The binding affinities of **4a**,**b** and **5a**,**b** relative to **3a**,**b** were measured in terms of the ability of the ligands to displace bound [20-^{3}H]phorbol 12,13-dibutyrate (PDBU) from a recombinant PK-C α-isozyme as previously described (Table 1).[14] 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 non-cooperative competition curve. The K_i's for inhibition of binding were calculated from the ID_{50} values. A comparison between compounds **4a**,**b** and the parent DAG-lactones **3a**,**b** revealed a 10-fold reduction in binding affinity which is indicative of the lack of involvement of the extra OH group in effectively hydrogen bonding with the receptor. A comparison between **5a** and **3a** revealed an even greater drop in affinity, ca. 268-fold. This means that the 'down', 3-(*S*)-OH in **5a** is in a worse disposition to engage in effective H-bonding with the receptor than the 'up', 3-(*R*)-OH in either **4a** or **4b**, which experienced only 10-fold reductions in binding affinity relative to the parent DAG-lactones (**3a** and **b**).

3. Conclusion

We have described the enantiospecific synthesis of four highly functionalized DAG-lactones (**4a**,**b**, **5a**, and **b**) from the abundant chiral template, diacetone-D-glucose. Relative to the parent DAG-lactones (**3a** and **b**), the new compounds bind to PK-C with poorer binding affinities. Although the extra OH group reduced lipophilicity (log *P*) by ca. 10-fold, it also lowered the binding affinity for PK-Cα suggesting that the additional polar group does not contribute to the overall binding. Rather, the extra OH group hinders the effectual partitioning of the molecules into the lipid environment of the enzyme. These results strongly support the concept that the addition of extra polar groups to an otherwise strong ligand leads to a severe penalty of desolvation—especially in a hydrophobic pocket—if the group does not engage in effective interactions with the receptor.

4. Experimental

4.1. General procedures

All chemical reagents were commercially available. Melting points were determined on a MelTemp II apparatus, Laboratory Devices, USA, and are uncorrected. Silica gel chromatography was performed on silica gel 60, 230–400 mesh (E. Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-250 instrument at 250 and 62.9 MHz, respectively. Spectra are referenced to the solvent in which they were run (7.24 ppm for ^{1}H $CDCl_3$). One-dimensional NOE spectra were collected on a Varian spectrometer with a three channel INOVA console at 500 MHz using an inverse detection H-X probe (Nalorac corp., Martinez, CA.) with an actively shielded *Z*-axis gradient. NOE's were obtained using the excitation sculpting of selective pulses (Double Pulsed Field Gradient Spin Echo NOE, DPFGSE-NOE) method of Scott et al.,[16] employing a homospoil gradient pulse for randomization of magnetization prior to the relaxation delay (Varian pulse sequence NOESY1D from the CHEMPACK suite of programs, provided by Krish Krishnamurthy, Eli Lilly and Company, Indianapolis, IN). The probehead temperature was maintained at 25°C and no attempt was made to deoxygenate the samples. Sech180 shaped pulses were used for selective excitation of specific resonances. For 1D experiments, 128 increments were collected and the FIDs were Fourier transformed using no apodization or special processing functions. Distances were not quantified since qualitative measurements were sufficient for assignment purposes. Infrared spectra were recorded on a Perkin–Elmer 1600 series FT-IR. Optical rotations were recorded on a Perkin–Elmer model 241 polarimeter at room temperature with a path length=1 dm. Positive ion fast-atom bombardment mass spectra (FAB-MS) were obtained on a VG 7070E mass spectrometer at an accelerating voltage of 6 kV and a resolution of 2000. Glycerol was used as the sample matrix and ionization was effected by a beam of xenon atoms. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

4.1.1. Methyl (2*Z*)-3-[(2*S*)-2-(hydroxymethyl)-5-oxo-4-tetradecylidene(2-2,3-dihydrofuryl)]prop-2-enoate (3a) and methyl (2*E*)-3-[(2*S*)-2-(hydroxymethyl)-5-oxo-4-tetradecylidene(2-2,3-dihydrofuryl)]prop-2-enoate (3b). These compounds were prepared essentially as described

in Ref. 9 except that myristyl aldehyde was used instead of oleyl aldehyde. Anal. calcd for $C_{23}H_{38}O_5$: C, 70.01; H, 9.71. Found (**3a**): C, 70.13; H, 9.80. Found (**3b**): C, 70.11; H, 9.76.

4.1.2. 1,2:5,6-Di-*O*-isopropylidene-3-*C*-hydroxymethyl-3,3′-anhydro-α-D glucofuranose or 7-[(4*R*)-2,2-dimethyl(1,3-dioxolan-4-yl)]-(1*R*,5*S*,7*R*,8*R*)-3,3-dimethyl-2,4,6-trioxaspiro[bicyclo[3.3.0]octane-8,2′-oxirane (7). This compound was prepared from diacetone-D-glucose (**6**) following the procedure described by Funabashi et al.[10]

4.1.3. 3-[(4*R*)-2,2-Dimethyl(1,3-dioxolan-4-yl)]-(1*R*,2*R*,3*R*,5*S*)-7,7-dimethyl-4,6,8-trioxa-2-[(phenylmethoxy)-methyl]bicyclo[3.3.0]octan-2-ol (8). A solution of benzyl alcohol (7.94 g, 73.46 mmol) in THF (147 ml) was treated with sodium hydride (60%, 2.94 g, 73.46 mmol) and stirred for 30 min at room temperature. To this mixture, a solution of **7** (10.00 g, 36.73 mmol) in THF (147 ml) was added dropwise and then refluxed for 36 h. The reaction was cooled to room temperature and quenched with acetic acid (4.21 ml). The mixture was filtered and concentrated under vacuum, and the remaining benzyl alcohol was removed by distillation in a Kugelrohr apparatus under high vacuum. The residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate mixtures of 3/1 and 2/1 as eluants to give pure **8** (13.72 g, 36.07 mmol, 98%) as a white solid: mp 85–86°C; $[\alpha]_D^{22}=+22.30°$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3386 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5H), 5.85 (d, 1H, *J*=3.5 Hz), 4.63 (AB d, 1H, *J*=12.0 Hz), 4.58 (AB d, 1H, *J*=12.0 Hz), 4.40 (d, 1H, *J*=3.5 Hz), 4.33 (m, 1H), 4.07 (dd, 1H, *J*=8.7, 6.2 Hz), 3.99 (dd, 1H, *J*=8.7, 5.3 Hz), 3.77 (m, 3H), 2.83 (br s, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.32 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.72, 128.28, 127.70, 127.61, 112.39, 109.04, 104.72, 85.40, 81.22, 80.66, 73.47, 72.52, 68.93, 67.26, 27.16, 26.66, 26.51, 25.18. Anal. calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 63.32; H, 7.45.

4.1.4. {3-[(4*R*)-2,2-Dimethyl(1,3-dioxolan-4-yl)]-(1*R*,2*R*,3*R*,5*S*)-2-[(4-methoxyphenyl)methoxy]-7,7-dimethyl-4,6,8-trioxabicyclo[3.3.0]oct-2-yl}(phenylmethoxy)methane (9). A solution of **8** (5.84 g, 15.35 mmol) in THF (150 ml) was treated with sodium hydride (60%, 2.46 g, 61.4 mmol) and stirred for 20 min at room temperature. 4-Methoxybenzyl chloride (4.16 ml, 30.7 mmol) and tetrabutylammonium iodide (2.83 g, 7.68 mmol) were added to this mixture, which was then refluxed for 3 h. After cooling to room temperature, the reaction mixture was filtered through a short pad of silica gel and further eluted with ether. The combined filtrate was concentrated under vacuum and the residue was purified by silica gel flash column with hexanes/ethyl acetate mixtures of 5/1–3/1 as eluants to give **9** (7.38 g, 96%) as an oil: $[\alpha]_D^{22}=+14.60°$ (*c* 2.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5H), 7.19 (d, 2H), 6.83 (d, 2H), 5.82 (d, 1H, *J*=3.5 Hz), 4.50–4.77 (m, 5H), 4.40 (q, 1H), 3.80–4.06 (m, 5H), 3.78 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H), 1.31 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 158.87, 138.09, 131.02, 128.40, 128.23, 127.55, 113.63, 112.24, 108.51, 104.92, 86.21, 83.39, 82.42, 73.54, 73.31, 68.83, 66.88, 66.17, 55.19, 27.18, 26.59, 26.53, 25.34. Anal. calcd for $C_{28}H_{36}O_8$: C, 67.18; H, 7.25. Found: C, 67.22; H, 7.25.

4.1.5. 1-{(1*R*,2*R*,3*R*,5*S*)-4-[(4-Methoxyphenyl)methoxy]-7,7-dimethyl-2,6,8-trioxa-4-[(phenylmethoxy)methyl]bicyclo[3.3.0]-3-yl}(1*R*)-ethane-1,2-diol (10). A solution of **9** (2.0 g, 4 mmol) in ethanol (90 ml) was treated with 2N HCl solution (10 ml) and stirred for 16 h at room temperature. The reaction mixture was neutralized with solid $NaHCO_3$ and concentrated under vacuum. The residue was dissolved in EtOAc, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate mixtures of 1/1–1/2 as eluants to give **10** (1.74 g, 95%) as an oil: $[\alpha]_D^{22}=+17.52°$ (*c* 1.33, $CHCl_3$); IR (neat) 3418 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5H), 7.19 (d, 2H), 6.83 (d, 2H), 5.81 (d, 1H, *J*=3.7 Hz), 4.42–4.72 (m, 5H), 3.98–4.15 (m, 3H), 3.65–3.85 (m, 6H), 1.49 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.81, 136.25, 130.03, 128.34, 128.22, 127.90, 113.53, 112.29, 104.15, 84.91, 84.43, 81.95, 73.66, 73.31, 67.38, 64.86, 64.01, 54.97, 26.77, 26.23. Anal. calcd for $C_{25}H_{32}O_8$: C, 65.20; H, 7.01. Found: C, 65.08; H, 7.03.

4.1.6. 1-{(1*R*,2*R*,3*R*,5*S*)-4-[(4-Methoxyphenyl)methoxy]-7,7-dimethyl-2,6,8-trioxa-4-[(phenylmethoxy)methyl]bicyclo[3.3.0]-3-yl}-(1*R*)-2-(1,1,2,2-tetramethyl-1-silapropoxy)ethan-1-ol (11). *Procedure 1*. A solution of **10** (5.53 g, 12 mmol) in CH_2Cl_2 (160 ml) was treated with triethylamine (10.04 ml, 72 mmol) and 4-dimethylaminopyridine (0.146 g, 1.2 mmol) followed by *tert*-butyldimethylsilyl chloride (2.71 g, 18 mmol). The solution was stirred at room temperature for 48 h, concentrated under vacuum, and the residue was purified by silica gel flash column chromatography with a mixture of hexanes/ethyl acetate (3/1) as eluant to give **11** (6.07 g, 88%) as an oil: $[\alpha]_D^{22}=+17.06°$ (*c* 1.87, $CHCl_3$); IR (neat) 3448 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5H), 7.19 (d, 2H), 6.83 (d, 2H), 5.79 (d, 1H, *J*=3.6 Hz), 4.50–4.76 (m, 5H), 3.62–4.02 (m, 9H), 1.47 (s, 3H), 1.30 (s, 3H), 0.87 (s, 9H), 0.51 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 158.89, 137.54, 130.96, 128.41, 128.32, 127.75, 113.65, 112.16, 104.43, 86.04, 82.54, 82.49, 73.62, 68.61, 68.12, 65.84, 64.76, 55.21, 27.02, 26.58, 25.94, 18.38, −5.33, −5.37. Anal. calcd for $C_{31}H_{46}O_8Si$: C, 64.78; H, 8.07. Found: C, 64.68; H, 8.06.

Procedure 2. A solution of **10** (11.31 g, 25.56 mmol) in CH_2Cl_2 (76.8 ml) was treated with imidazole (3.85 g, 56.49 mmol) and stirred for 1 h at room temperature. Then, CH_2Cl_2 (38.4 ml), DMF (38.4 ml) and *tert*-butyldimethylsilyl chloride (4.29 g, 28.49 mmol) were added successively, and the resulting solution was stirred at room temperature for 19 h. Following the addition of diethyl ether (300 ml), the solution was extracted with water (3×30 ml), dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by silica gel flash chromatography with hexanes/ethyl acetate mixtures of 9/1–4/1 as eluants to afford **11** (13.99 g, 99%) as an oil identical to the material obtained under procedure 1.

4.1.7. 1-{(1*R*,2*R*,3*R*,5*S*)-4-[(4-Methoxyphenyl)methoxy]-7,7-dimethyl-2,6,8-trioxa-4-[(phenylmethoxy)methyl]bicyclo[3.3.0]-3-yl}-(1*R*)-2-(1,1,2,2-tetramethyl-1-silapropoxy)ethan-1-one (12). A solution of **11** (5.00 g, 8.70 mmol) in CH_2Cl_2 (87 ml) was cooled to 0°C and treated

with 4 Å molecular sieves (10 g) and pyridinium chlorochromate (5.63 g, 26.10 mmol). After stirring for 40 min at room temperature, the reaction mixture was diluted with ether (300 ml) and treated with a mixture of celite and silica. After stirring for a short time, the suspension was filtered through a short pad of silica gel and further eluted with ether. The combined filtrate was concentrated under vacuum and the residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate (9/1) as eluant to give **12** (4.00 g, 80%) as a white solid: mp 55.4–56.7°C; $[\alpha]_D^{22}=+22.69°$ (*c* 1.08, $CHCl_3$); IR (neat) 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5H), 7.12 (d, 2H), 6.81 (d, 2H), 5.93 (d, 1H, *J*=3.2 Hz), 4.77 (d, 1H, *J*=3.2 Hz), 4.50–4.75 (m, 6H), 4.35 (s, 1H), 4.02 (AB d, 1H, *J*=10.9 Hz), 3.93 (AB d, 1H, *J*=10.9 Hz), 3.78 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 0.84 (s, 9H), −0.04 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 206.47, 158.95, 137.83, 130.58, 128.63, 128.20, 127.52, 113.61, 112.81, 105.59, 88.62, 86.09, 81.18, 73.54, 68.97, 68.87, 67.19, 55.10, 27.15, 26.49, 25.73, 18.35, −5.50, −5.54. Anal. calcd for $C_{31}H_{44}O_8Si$: C, 65.00; H, 7.74. Found: C, 65.09; H, 7.75.

4.1.8. 3-{(1*E*)-1-[(1,1,2,2-Tetramethyl-1-silapropoxy)-methyl]pentadec-1-enyl}-(1*R*,2*R*,3*R*,5*S*)-2-[(4-methoxyphenyl)methoxy]-7,7-dimethyl-4,6,8-trioxabicyclo[3.3.0]-oct-2-yl)(phenylmethoxy)methane and 3-{(1*Z*)-1-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]pentadec-1-enyl}-(1*R*,2*R*,3*R*,5*S*)-2-[(4-methoxyphenyl)methoxy]-7,7-dimethyl-4,6,8-trioxabicyclo[3.3.0]oct-2-yl)(phenylmethoxy)methane (13a and 13b). A solution of tetradecylphosphonium bromide (7.54 g, 13.97 mmol) in THF (87.3 ml) was cooled to −25°C and treated with *n*-butyllithium (1.6 M in hexanes, 8.1 ml, 12.9 mmol). After stirring for 1.5 h, the temperature reached −10°C. The reaction mixture was then cooled to −30°C before proceeding to add dropwise a solution of **12** (2.00 g, 3.71 mmol) in toluene (40 ml). While stirring for 2.5 h, the reaction mixture temperature was allowed to warm up to 0°C, and 15 h later to reach room temperature. The reaction mixture was diluted with toluene (200 ml) and treated with a saturated solution of aqueous ammonium chloride (35 ml) and brine (5 ml). The aqueous layer was extracted with diethyl ether and the combined organic phases were washed successively with a saturated solution of aqueous sodium bicarbonate (60 ml), brine (2×60 ml), dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate (9/1) as eluant to give a mixture of **13a** and **b** (0.94 g, 34%) as an oil.

4.1.9. (1*R*,2*R*,3*R*,5*S*)-3-[(1*E*)-2-Hydroxy-1-tetradecylideneethyl]-7,7-dimethyl-4,6,8-trioxa-2-[(phenylmethoxy)-methyl]bicyclo[3.3.0]octan-2-ol (15a) and (1*R*,2*R*,3*R*,5*S*)-3-[(1*Z*)-2-Hydroxy-1-tetradecylideneethyl]-7,7-dimethyl-4,6,8-trioxa-2-[(phenylmethoxy)methyl]bicyclo[3.3.0]-octan-2-ol (15b). A solution of **13a**,**b** (1.8 g, 2.39 mmol) in THF (100 ml) was treated with tetra-*n*-butylammonium fluoride (1.0 M in THF, 4.78 ml, 4.78 mmol). After stirring for 5 h at room temperature, the reaction mixture was concentrated under vacuum. The residue was dissolved in diethyl ether, filtered through a short pad of silica gel and further eluted with ether. The filtrate was concentrated under vacuum to afford a mixture of **14a**,**b** as a crude oil (1.62 g), which was used directly in the next step.

The above mixture of products (1.62 g, ~2.39 mmol) was dissolved in CH_2Cl_2/H_2O (120 ml/6.5 ml) and treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.814 g, 3.59 mmol). After stirring overnight at room temperature, the reaction mixture was dried ($MgSO_4$), filtered through a short pad of silica gel using hexanes/ethyl acetate (1/2) as eluant, and the filtrate was concentrated under vacuum. The residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate mixtures of 3/1–2/1 as eluants to give **15a** (*E*-isomer, 0.533 g, 43%) and **15b** (*Z*-isomer, 0.684 g, 55%) as oils.

*Compound **15a***. $[\alpha]_D^{22}=+4.42°$ (*c* 0.86, $CHCl_3$); IR (neat) 3355 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5H), 5.94 (d, 1H, *J*=3.6 Hz), 5.58 (t, 1H, *J*=7.4 Hz), 4.57 (s, 2H), 4.41 (d, 1H, *J*=3.6 Hz), 4.34 (s, 1H), 4.13 (s, 2H), 3.79 (AB d, 1H, *J*=9.5 Hz), 3.42 (AB d, 1H, *J*=9.5 Hz), 3.11 (br s, 2H), 2.00–2.25 (m, 2H), 1.49 (s, 3H), 1.32 (s, 3H), 1.15–1.40 (m, 22H), 0.86 (irregular t, 3H); ^{13}C NMR ($CDCl_3$) δ 137.57, 137.46, 133.02, 128.38, 127.83, 127.63, 112.23, 104.25, 85.21, 84.79, 81.49, 73.76, 69.67, 56.10, 31.87, 29.63, 29.56, 29.44, 29.30, 29.25, 27.58, 27.03, 26.42, 22.64, 14.07. Anal. calcd for $C_{31}H_{50}O_6$: C, 71.78; H, 9.72. Found: C, 71.89; H, 9.68.

*Compound **15b***. $[\alpha]_D^{22}=-27.5°$ (*c* 0.16, $CHCl_3$); IR (neat) 3336 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5H), 5.95 (d, 1H, *J*=3.6 Hz), 5.75 (br t, 1H), 4.89 (s, 1H), 4.59 (AB d, 1H, *J*=12.2 Hz), 4.54 (AB d, 1H, *J*=12.2 Hz), 4.43 (d, 1H, *J*=3.6 Hz), 4.25 (AB d, 1H, *J*=11.4 Hz), 3.95 (AB d, 1H, *J*=11.4 Hz), 3.79 (AB d, 1H, *J*=9.3 Hz), 3.40 (AB d, 1H, *J*=9.3 Hz), 2.86 (br s, 2H), 1.80–2.10 (m, 2H), 1.52 (s, 3H), 1.34 (s, 3H), 1.15–1.40 (m, 22H), 0.86 (irregular t, 3H); ^{13}C NMR ($CDCl_3$) δ 137.66, 137.55, 132.81, 128.36, 127.76, 127.60, 112.25, 104.33, 84.80, 82.25, 77.72, 73.81, 69.88, 64.29, 31.87, 29.61, 29.52, 29.42, 29.30, 29.26, 27.91, 27.10, 26.44, 22.64, 14.07. Anal. calcd for $C_{31}H_{50}O_6$: C, 71.78; H, 9.72. Found: C, 71.66; H, 9.78.

4.1.10. (1*R*,2*R*,6*R*,8*S*)-10,10-Dimethyl-3,7,9,11-tetraoxa-2-[(phenylmethoxy)methyl]-5(*Z*)-tetradecylidenetricyclo-[6.3.0.0⟨2,6⟩]undecan-4-one (16a). A solution of **15a** (0.16 g, 0.308 mmol) in CH_2Cl_2 (20 ml) was treated with activated MnO_2 (1.6 g, 18.5 mmol) and stirred at room temperature for 36 h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate (4/1) as eluant to give the *Z*-isomer **16a** (0.15 g, 94%) as an oil: $[\alpha]_D^{22}=+8.70°$ (*c* 0.23, $CHCl_3$); IR (neat) 1770 (C=O), 1679 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5H), 6.47 (t, 1H, *J*=7.7 Hz), 5.96 (d, 1H, *J*=3.7 Hz), 4.89 (s, 1H), 4.67 (d, 1H, *J*=3.7 Hz), 4.55 (AB d, 1H, *J*=12.0 Hz), 4.49 (AB d, 1H, *J*=12.0 Hz), 3.87 (AB d, 1H, *J*=11.0 Hz), 3.82 (AB d, 1H, *J*=11.0 Hz), 2.55–2.80 (m, 2H), 1.48 (s, 3H), 1.32 (s, 3H), 1.15–1.45 (m, 22H), 0.86 (irregular t, 3H); ^{13}C NMR ($CDCl_3$) δ 167.59, 149.33, 137.45, 128.30, 127.69, 127.32, 127.03, 113.61, 106.50, 90.32, 83.49, 83.30, 73.76, 69.20, 31.88, 29.62, 29.49, 29.36, 29.32, 29.19, 28.58, 27.89,

27.28, 26.83, 22.65, 14.09. Anal. calcd for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 72.46; H, 8.99.

4.1.11. (1*R*,2*R*,6*R*,8*S*)-10,10-Dimethyl-3,7,9,11-tetraoxa-2-[(phenylmethoxy)methyl]-5(*E*)-tetradecylidenetricyclo-[6.3.0.0⟨2,6⟩]undecan-4-one (16b). A solution of **15b** (0.14 g, 0.27 mmol) in CH_2Cl_2 (20 ml) was treated with manganese dioxide (0.94 g, 10.8 mmol) and reacted in the same manner as for **16a** to give **16b** (0.13 g, 94%) as an oil: $[\alpha]_D^{22}$=+28.82° (*c* 0.17, $CHCl_3$); IR (neat) 1775 (C=O), 1686 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5H), 6.85 (ddd, 1H, *J*=7.96, 7.96, 1.0 Hz), 5.96 (d, 1H, *J*=3.7 Hz), 5.20 (d, 1H, *J*=0.9 Hz), 4.68 (d, 1H, *J*=3.7 Hz), 4.55 (AB d, 1H, *J*=12.2 Hz), 4.47 (AB d, 1H, *J*=12.2 Hz), 3.86 (AB d, 1H, *J*=10.9 Hz), 3.81 (AB d, 1H, *J*=10.9 Hz), 2.20–2.40 (m, 2H), 1.49 (s, 3H), 1.33 (s, 3H), 1.15–1.45 (m, 22H), 0.86 (irregular t, 3H); ^{13}C NMR ($CDCl_3$) δ 168.73, 146.13, 137.38, 128.34, 127.69, 127.64, 127.27, 113.60, 106.67, 90.82, 83.49, 79.36, 73.60, 69.23, 31.84, 29.99, 29.56, 29.40, 29.28, 29.15, 28.26, 27.25, 26.70, 22.61, 14.04. Anal. calcd for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 72.09; H, 8.96.

4.1.12. Methyl (2*E*)-3-{(2*S*,3*R*)-3-hydroxy-5-oxo-2-[(phenylmethoxy)methyl]-4(*Z*)-tetradecylidene(2-2,3-dihydrofuryl)}prop-2-enoate (19a). A solution of *Z*-isomer **16a** (0.12 g, 0.23 mmol) in THF (10 ml) was treated with 2N HCl solution (9.3 ml) and heated overnight at 75°C. After cooling, the reaction mixture was neutralized with solid $NaHCO_3$ (1.68 g) and concentrated under vacuum. The residue was dissolved in ethyl acetate, dried, ($MgSO_4$) and concentrated under vacuum to give crude diol **17a** (156 mg) as an oil.

The above diol was dissolved in a mixture of MeOH (14 ml) and H_2O (7.1 ml) and cooled to 0°C. The solution was treated with sodium metaperiodate (0.39 g, 1.84 mmol) and stirred at room temperature for 4 h. The reaction mixture was concentrated, diluted with ethyl acetate, filtered, and concentrated to give intermediate aldehyde **18a** as an oil.

The above aldehyde was dissolved in CH_2Cl_2 (20 ml) and the solution was treated with methyl (triphenylphosphoranylidene)acetate (0.31 g, 0.93 mmol). After stirring at room temperature for 24 h, the reaction mixture was concentrated and the residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate (3/1) as eluant to give **19a** as an oil (0.062 g, 0.124 mmol, 53%) and a small amount of the *E*,*E*-isomer **19b** (0.008 g, 0.016 mmol, 7.8%). Compound **19a**: ^1H NMR ($CDCl_3$) δ 7.24–7.30 (m, 5H), 7.02 (d, 1H, *J*=15.8 Hz), 6.47 (dt, 1H, *J*=8.0, 1.7 Hz), 6.21 (d, 1H, *J*=15.8 Hz), 4.87 (dd, 1H, *J*=7.3, 1.11 Hz), 4.53 (s, 2H), 3.72 (s, 3H), 3.65 (AB d, 1H, *J*=10.1 Hz), 3.51 (AB d, 1H, *J*=10.1 Hz), 2.65–2.80 (m, 2H), 2.1 (d, 1H, *J*=7.3 Hz), 1.16–1.40 (m, 22H), 0.86 (irregular t, 3H).

4.1.13. Methyl (2*E*)-3-{(2*S*,3*R*)-3-hydroxy-5-oxo-2-[(phenylmethoxy)methyl]-4(*E*)-tetradecylidene(2-2,3-dihydrofuryl)}prop-2-enoate (19b). A solution of *E*-isomer **16b** (0.12 g, 0.23 mmol) in THF (10 ml) was treated with 2N HCl solution (10 ml) and heated at 75°C for 48 h. After cooling, the reaction mixture was neutralized with solid $NaHCO_3$ (1.68 g) and concentrated under vacuum. The residue was dissolved in ethyl acetate, dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate mixtures of 1/1–2/1 as eluants to give diol **17b** as an oil.

The above diol was dissolved in a mixture of MeOH (16 ml) and H_2O (8 ml) and cooled to 0°C. The solution was treated with sodium metaperiodate (0.2 g, 0.93 mmol) and stirred for 4 h at room temperature. The reaction mixture was concentrated, diluted with ethyl acetate, filtered, and concentrated. The residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate mixtures of 1/1–3/2 as eluants to give aldehyde **18b** as an oil.

The above aldehyde was dissolved in CH_2Cl_2 (20 ml) and the solution was treated with methyl (triphenylphosphoranylidene)acetate (0.31 g, 0.93 mmol). After stirring at room temperature for 24 h, the reaction mixture was concentrated and the residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate (3/1) as eluant to give **19b** as an oil (0.070 g, 60% from **15b**): ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5H), 7.02 (d, 1H, *J*=15.8 Hz), 6.95 (m, 1H), 6.26 (d, 1H, *J*=15.8 Hz), 5.00 (d, 1H, *J*=1.1 Hz), 4.53 (AB d, 1H, *J*=12.1 Hz), 4.47 (AB d, 1H, *J*=12.1 Hz), 3.73 (s, 3H), 3.62 (AB d, 1H, *J*=10.0 Hz), 3.41 (AB d, 1H, *J*=10.0 Hz), 2.25–2.45 (m, 2H), 1.15–1.50 (m, 22H), 0.86 (irregular t, 3H).

4.1.14. Methyl (2*E*)-3-{(2*S*,3*R*)-3-hydroxy-2-(hydroxymethyl)-5-oxo-4(*Z*)-tetradecylidene(2-2,3-dihydrofuryl)}-prop-2-enoate (4a). A solution of **19a** (0.029 g, 0.058 mmol) in CH_2Cl_2 (2.76 ml) was cooled to −78°C and treated dropwise with boron trichloride (1.0 M, 0.28 ml, 0.28 mmol). After stirring for 2 h at −78°C, the reaction mixture was quenched with saturated $NaHCO_3$ solution (0.28 ml) and immediately partitioned between ether and a pH 7 buffer solution. The organic layer was washed with pH 7 buffer (3×5 ml), dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate (2/1) as eluant to give the *E*,*Z*-isomer **4a** (0.011 g, 46%) and the *E*,*E*-isomer **4b** (0.013 g, 54%) both as white solids. **4a**: mp 71.8–73.3°C; $[\alpha]_D^{22}$=+28.6° (*c* 0.21, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.01 (d, 1H, *J*=15.9 Hz), 6.49 (m, 1H), 6.15 (d, 1H, *J*=15.9 Hz), 4.98 (br s, 1H), 3.72–3.77 (m, 5H), 3.35 (m, 2H), 2.65 (irregular q, 2H), 1.22–1.42 (m, 22H), 0.85 (irregular t, 3H); ^{13}C NMR ($CDCl_3$) δ 167.62, 166.10, 149.71, 142.00, 127.24, 123.47, 87.44, 71.55, 64.40, 51.94, 31.89, 29.64, 29.51, 29.39, 29.32, 29.25, 28.78, 27.90, 22.65, 14.08; FAB MS (*m*/*z*, relative intensity) 411 (MH^+, 100), 393 (MH^+-H_2O, 38.8), 369 (MH^+-42, 18.0). Anal. calcd for $C_{23}H_{38}O_6$: C, 67.29; H, 9.33. Found: C, 67.13; H, 9.34.

4.1.15. Methyl (2*E*)-3-{(2*S*,3*R*)-3-hydroxy-2-(hydroxymethyl)-5-oxo-4(*E*)-tetradecylidene(2-2,3-dihydrofuryl)}-prop-2-enoate (4b). A solution of **19b** (0.063 g, 0.126 mmol) in CH_2Cl_2 (6 ml) was cooled to −78°C and treated with boron trichloride (1.0 M, 0.6 ml, 0.6 mmol). After stirring for 90 min at −78°C, the reaction mixture

was quenched with saturated $NaHCO_3$ solution (0.6 ml) and immediately partitioned between ether and a pH 7 buffer solution. The organic layer was washed with pH 7 buffer several times, dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate (3/2) as eluant to give *E*,*E*-isomer **4b** (0.045 g, 87%) as a white solid: mp 59.4–60.6°C; $[\alpha]_D^{22}=+66.07°$ (*c* 0.28, $CHCl_3$); IR (neat) 3485 and 3352 (OH), 1757 and 1724 (C=O), 1671 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02 (d, 1H, *J*=15.8 Hz), 7.00 (m, 1H), 6.26 (d, 1H, *J*=15.8 Hz), 5.05 (br s, 1H), 3.74 (s, 3H), 3.72 (m, 2H), 2.30–2.50 (m, 2H), 2.03 (br s, 1H), 1.50 (m, 2H), 1.10–1.40 (m, 20H), 0.86 (irregular t, 3H); ^{13}C NMR ($CDCl_3$) δ 168.82, 166.36, 149.63, 141.63, 128.78, 123.22, 88.48, 69.99, 66.03, 51.98, 31.90, 29.63, 29.50, 29.38, 28.38, 22.67, 14.10; FAB MS (*m/z*, relative intensity) 411.4 (MH^+, 50.6), 393.4 (MH^+-H_2O, 11.0). Anal. calcd for $C_{23}H_{38}O_6$: C, 67.29; H, 9.33. Found: C, 67.20; H, 9.29.

4.1.16. {3-[(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-methyl]-(1*S*,3*R*,4*S*,5*R*)-7,7-dimethyl-2,6,8-trioxa-4-(phenylmethoxy)bicyclo[3.3.0]oct-3-yl}methan-1-ol (24) and {3-[(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)-methyl]-(1*S*,3*S*,4*S*,5*R*)-7,7-dimethyl-2,6,8-trioxa-4-(phenylmethoxy)-bicyclo[3.3.0]oct-3-yl}methan-1-ol (25). A solution of *n*-BuLi (2.5 M solution in hexane, 6 ml) was added dropwise to a solution of **23** (4.42 g, 14.2 mmol) in 25 ml of THF at −78°C, followed by the addition of *t*-$BuPh_2SiCl$ (4 g, 14.5 mmol). The resulting mixture was stirred at −78°C for 30 min. After allowing it to warm to room temperature, it was stirred for an additional 30 min and then heated to reflux for 1 h. After the removal of the volatiles under vacuum, the residue was purified by silica gel flash chromatography with hexanes/ethyl acetate mixtures of 4/1 and 2/1 as eluants to give a quantitative yield of the two monoprotected diastereoisomers **24** (3.06 g, 5.58 mmol, 38%) and **25** (4.96 g, 9.04 mmol, 62%).

Compound ***24***. Oil, $[\alpha]_D^{22}=+44.95°$ (*c* 1.01, $CHCl_3$); IR (neat) 3508 (OH), 2951–2855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22–7.42 (m, 15H), 5.91 (d, 1H, *J*=3.5 Hz), 4.90 (AB d, 1H, *J*=11.9 Hz), 4.78 (irregular t, 1H, *J*~4.3 Hz), 4.60 (AB d, 1H, *J*=11.9 Hz), 4.52 (d, 1H, *J*=5.1 Hz), 3.95–3.75 (2 overlapping quartets, 4H), 2.45 (broad s, 1H), 1.74 and 1.46 (singlets, 6H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 137.16, 135.45, 135.41, 133.05, 132.85, 129.60, 129.54, 128.42, 127.94, 127.64, 127.59, 127.54, 113.66, 104.38, 87.38, 79.05, 76.42, 72.50, 65.38, 63.01, 26.83, 26.78, 26.25, 19.18. Anal. calcd for $C_{32}H_{40}O_6Si$: C, 70.04; H, 7.35. Found: C, 69.82; H, 7.37.

Compound ***25***. Oil, $[\alpha]_D^{22}=+3.72°$ (*c* 1.36, $CHCl_3$); IR (neat) 3408 (OH), 3070–2857 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81–7.40 (m, 15H), 5.81 (d, 1H, *J*=3.9 Hz), 4.75 (AB q, 2H, *J*=11.9 Hz), 4.62 (br d, 1H, *J*=2.9 Hz), 4.29–4.08 (m, 4H), 3.68 (br m, d after D_2O exchange, 1H, *J*=11.9 Hz), 2.05 (broad d, 1H), 1.34 (s, 6H), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 137.58, 135.70, 135.61, 133.14, 133.04, 129.49, 128.21, 127.70, 113.01, 103.92, 87.27, 78.74, 77.71, 72.46, 65.06, 64.22, 26.95, 26.28, 25.86, 19.25. Anal. calcd for $C_{32}H_{40}O_6Si$: C, 70.04; H, 7.35. Found: C, 70.28; H, 7.32.

4.1.17. 1-({(1*S*,3*R*,4*S*,5*R*)-7,7-Dimethyl-2,6,8-trioxa-4-(phenylmethoxy)-3-[(phenylmethoxy)-methyl]bicyclo-[3.3.0]oct-3-yl}methoxy)-2,2-dimethyl-1,1-diphenyl-1-silapropane (26). A solution of **24** (3.18 g, 5.79 mmol) in 24 ml of THF at 0°C was treated with 60% NaH suspended in mineral oil (0.46 g, 11.6 mmol). The solution was stirred at 0°C for 1 h, and following the addition of benzyl bromide (0.76 ml, 6.37 mmol) and *n*-Bu_4NI (0.21 g, 0.58 mmol), the reaction mixture was allowed to reach room temperature and was stirred for 3 h. The entire mixture was filtered through a short pad of silica gel and the collected filtrate was dried under reduced pressure and purified by silica gel flash chromatography with hexanes/ethyl acetate mixtures of 9/1, 7/1 and 4/1 as eluants to give three products. The first, minor product corresponded to the benzylated ether of diastereoisomer **25**, which probably arose through rearrangement of the silyl group prior to benzylation. The second product was the desired compound **26** (2.82 g, 76%), and the third product (0.79 g) was the tribenzylated analogue resulting from NaH-catalyzed desilylation of **24** followed by complete benzylation.

Compound ***26***. Oil, $[\alpha]_D^{22}=+6.45°$ (*c* 0.89, $CHCl_3$); IR (neat) 2934–2858 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80–7.33 (m, 20H), 5.85 (d, 1H, *J*=3.9 Hz), 4.79–4.53 (m, 5H), 4.29 (d, 1H, *J*=5.3 Hz), 4.16 (AB d, 2H, *J*=1.7 Hz), 3.80 (AB q, 2H, *J*=10.2 Hz), 1.39 and 1.37 (singlets, 6H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 138.07, 137.84, 135.74, 135.59, 133.47, 133.24, 129.34, 128.18, 128.11, 127.57, 127.43, 113.19, 104.15, 87.62, 79.60, 78.18, 73.63, 72.38, 72.01, 64.67, 26.85, 26.59, 26.34, 19.29. Anal. calcd for $C_{39}H_{46}O_6Si$: C, 73.32; H, 7.26. Found: C, 73.42; H, 7.33.

4.1.18. {(1*S*,3*S*,4*S*,5*R*)-7,7-Dimethyl-2,6,8-trioxa-4-(phenylmethoxy)-3-[(phenylmethoxy)methyl]-bicyclo[3.3.0]oct-3-yl}methan-1-ol (27). A solution of *n*-Bu_4NF (1 M, 7 ml) was added dropwise to a solution of **26** (2.12 g, 3.32 mmol) in 15 ml of THF at 0°C. The reaction mixture was stirred at room temperature overnight, concentrated under vacuum and filtered through a short pad of silica gel. It was further eluted with hexanes/ethyl acetate (1/1) and the filtrate was concentrated under vacuum. The residual syrup was purified by silica gel flash chromatography using hexanes/ethyl acetate mixtures of 4/1 and 2/1 as eluants to afford **27** (1.23 g, 93%) as an oil: $[\alpha]_D^{22}=+76.62°$ (*c* 1.42, $CHCl_3$); IR (neat), 3530 (OH), 2937–2362 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42–7.36 (m, 10H), 5.87 (d, 1H, *J*=3.9 Hz), 4.87 (AB d, 1H, *J*=11.7 Hz,), 4.73 (dd, 1H, *J*=5.1, 3.9 Hz), 4.59 (m, 3H), 4.36 (d, 1H, *J*=5.1 Hz), 4.01 (ABX dd, 1H, *J*~11.7, ~5.5 Hz), 3.92 (ABX dd, 1H, *J*~11.7, 7.5 Hz), 3.68 (AB q, 2H, *J*=10.6 Hz), 2.47 (broad ABX t, 1H, *J*~6.7 Hz), 1.72 and 1.43 (singlets, 6H); ^{13}C NMR ($CDCl_3$) δ 137.95, 137.32, 128.36, 128.23, 127.91, 127.71, 127.50, 113.43, 104.34, 86.43,78.79, 78.52, 73.54, 72.51, 71.57, 63.11, 26.71, 26.14. Anal. calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.98; H, 7.13.

4.1.19. Methyl(2*E*)-3-{(1*S*,3*R*,4*S*,5*R*)-7,7-dimethyl-2,6,8-trioxa-4-(phenylmethoxy)-3-[(phenylmethoxy)methyl]-bicyclo[3.3.0]oct-3-yl}prop-2-enoate (29). A solution of **27** (1.1 g, 2.72 mmol) in 6 ml of DMSO was treated at room temperature with dicyclohexylcarbodiimide (DCC,

2.25 g, 10.9 mmol) and dichloroacetic acid (0.11 ml, 1.36 mmol). The reaction mixture was stirred overnight, diluted with Et_2O and quenched by the careful addition of oxalic acid (0.98 g, 2.72 mmol). The mixture was cooled to −78°C and the solids removed by filtration. The filtrate was concentrated under vacuum to give **28** as a crude product (1.5 g, ca. 2.72 mmol) which was used without further purification in the next step. Compound **28** was dissolved in CH_2Cl_2 (30 ml) and the solution was cooled to 0°C before it was treated with triphenylphosphoralydene acetate (3.64 g, 10.84 mmol). The cooling bath was removed and the mixture was then stirred at room temperature overnight. The solution was filtered through a short pad of silica gel and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography using hexanes/ethyl acetate 4/1 as eluant to give **29** (1.05 g, 85%) as an oil: $[\alpha]_D^{22}=+2.25°$ (*c* 0.91, $CHCl_3$); IR (neat) 2944, 1720 (C=O), 1656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46–7.27 (m, 11H), 6.34 (dd, 1H, *J*=16.0, 0.6 Hz), 5.84 (d, 1H, *J*=3.6 Hz), 4.83 (AB d, 1H, *J*=12.4 Hz), 4.71–4.59 (m, 2H), 4.65 (AB q, 2H, *J*=12.2 Hz), 4.35 (d, 1H, *J*=4.8 Hz), 3.81 (s, 3H), 3.42 (s, 2H), 1.55 and 1.36 (singlets, 6H); ^{13}C NMR ($CDCl_3$) δ 166.49, 145.64, 137.60, 137.41, 128.31, 128.23, 127.87, 127.85, 127.59, 127.52, 122.13, 113.28, 103.90, 85.79, 77.70, 77.52, 77.26, 73.50, 72.45, 71.66, 51.43, 25.92, 25.47. Anal. calcd for $C_{26}H_{30}O_7$: C, 68.71; H, 6.65. Found: C, 68.56; H, 6.60.

4.1.20. Compound 30 (mixture of anomers). A solution of **29** (3.95 g, 8.69 mmol) in MeOH (54 ml) was treated with 0.09N methanolic HCl (14.8 ml) and heated at 85°C for 30 min. After cooling, the reaction mixture was neutralized with solid $NaHCO_3$, filtered and concentrated under vacuum. The residue was purified by silica gel flash column chromatography with ethyl acetate/hexanes mixtures of 1/1 and 2/1 as eluants to give **30** as a mixture of anomers. One anomer was obtained pure (1.95 g, 52%), while the other was isolated as an enriched mixture, still contaminated with the more abundant anomer (0.85 g, 23%). The pure β-anomer was fully characterized: oil, $[\alpha]_D^{22}=-52.71°$ ($CHCl_3$, *c* 1.77); IR (neat) 3485 (OH), 3030–2930, 1720 (C=O), 1659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (m, 10H), 7.24 (d, 1H, *J*=15.6 Hz), 5.67 (d, 1H, *J*=15.6 Hz), 5.03 (s, 1H), 4.70 and 4.62 (singlets, 4H), 4.35 (d, 1H, *J*=4.8 Hz), 4.10 (d, 1H, *J*=4.8 Hz), 3.83 (s, 3H), 3.52 (s, 2H), 3.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.75, 147.11, 137.65, 136.86, 128.42, 128.25, 128.04, 127.83, 127.59, 127.51, 120.87, 107.37, 85.05, 81.52, 74.81, 74.12, 73.53, 72.93, 55.01, 51.46. Anal. calcd for: $C_{24}H_{28}O_7$: C, 67.28; H, 6.59. Found: C, 67.23; H, 6.50.

4.1.21. Compounds 32a,b (mixture of geometric isomers). Starting with the pure anomer **30** (1.82 g, 4.25 mmol), Swern oxidation performed according to the exact protocol of Yoshikawa et al.[11] afforded the crude keto compound **31** (1.81 g, IR (neat) 1724 cm^{-1}), which was used directly for the next step without further purification. Separately, a stirred solution of strictly anhydrous tetradecyl phosphonium bromide (4.58 g, 8.49 mmol) in THF (106 ml) was cooled to −78°C and treated dropwise with *n*-BuLi (2.5 M in hexanes, 3.06 ml). Stirring continued for 1.5 h and a solution of **31** (ca. 4.25 mmol) in THF (10 ml) was transferred slowly to the solution of the ylide. The resulting solution was stirred overnight while allowing the cooling bath to reach room temperature. The next day, the solution was filtered through a pad of silica gel with hexanes/ethyl acetate (2/1) as eluant. The filtrate was concentrated under vacuum and the residue was purified by silica gel flash column chromatography with hexanes/ethyl acetate mixtures of 95/5, 9/1 and 4/1 as eluants to give an inseparable mixture of compounds **32a** and **b** (0.797 g, 31%).

4.1.22. Compound 33a–d (mixture of anomers and geometric isomers). A stirred solution of compounds **32a**,**b** (0.79 g, 1.30 mmol) in a mixture of THF (25 ml) and water (10 ml) was cooled to 0°C and treated dropwise with concentrated HCl (0.32 ml). The solution was stirred overnight while allowing the temperature to reach 10°C. Additional concentrated HCl (0.2 ml) was added and stirring was continued at room temperature for 3 h. Solid $NaHCO_3$ was added until neutrality was achieved and the mixture was filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel flash chromatography with hexanes/ethyl acetate mixtures of 9/1, 4/1 and 3/1 as eluants to give a mixture of **33a–d** (0.67 g, 87%).

4.1.23. Methyl (2*E*)-3-{(2*S*,3*S*)-5-oxo-3-(phenylmethoxy)-2-[(phenylmethoxy)methyl]-(*Z*)-4-tetradecylidene(2-2,3-dihydrofuryl)}prop-2-enoate (24a) and Methyl (2*E*)-3-{(2*S*,3*S*)-5-oxo-3-(phenylmethoxy)-2-[(phenylmethoxy)methyl]-(*E*)-4-tetradecylidene(2-2,3-dihydrofuryl)}prop-2-enoate (24b). A solution of **33a–d** (0.66 g, 1.11 mmol) in CH_2Cl_2 (30 ml) was treated with activated MnO_2 (4.53 g, 44.29 mmol). The mixture was stirred at room temperature overnight, filtered, and the filtrate concentrated under vacuum. The residue was purified by silica gel flash chromatography with hexanes/ethyl acetate (9/1) as eluant to give pure *E*,*Z*-isomer **34a** (0.133 g, 21%), a mixture **34a** and **b** (0.04 g, 6%), and pure *E*,*E*-isomer **34b** (0.243 g, 37%) as oils.

*Compounds **34a***. Oil, $[\alpha]_D^{22}=-2.57°$ ($CHCl_3$, *c* 0.51); IR (neat) 3422–2854, 1766 and 1726 (C=O), 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41–7.31 (m, 10H), 7.17 (d, 1H, *J*=15.7 Hz), 6.43 (broad t, 1H. *J*~8.03 Hz), 6.32 (d, 1H, *J*=15.75 Hz), 4.75 (broad s, 1H), 4.65 (AB q, 2H, *J*=11.9 Hz), 4.59 (s, 2H), 3.83 (s, 3H), 3.55 (AB q, 2H, *J*=10.2 Hz), 2.79 (irregular q, 2H, *J*~7.08 Hz), 1.34 (broad s, 22H), 0.97 (irregular t, 3H, *J*~6.35 Hz); ^{13}C NMR ($CDCl_3$) δ 166.70, 166.00, 149.78, 141.96, 136.99, 136.94, 128.42, 128.32, 128.26, 127.92, 127.84, 127.76, 127.61, 125.47, 122.45, 85.72, 78.61, 73.69, 72.24, 71.18, 51.67, 31.86, 29.62, 29.60, 29.48, 29.34, 29.30, 29.19, 28.76, 27.84, 22.64, 14.07. Anal. calcd for $C_{38}H_{53}O_6$: C, 75.22; H, 8.53. Found: C, 75.18; H, 8.60.

*Compounds **34b***. Oil, $[\alpha]_D^{22}=-36.98°$ ($CHCl_3$, *c* 0.53); IR (neat): 2924–2855, 1767 and 1726 (C=O), 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.33 (m, 10H), 7.25 (d, 1H, *J*=15.8 Hz), 7.08 (irregular t, 1H, *J*~7.69 Hz), 6.39 (d, 1H, *J*=15.8 Hz), 4.95 (s, 1H), 4.61 (s, 2H), 4.55 (AB q, 2H, *J*=11.2 Hz), 3.84 (s, 3H), 3.68 (AB d, 1H, *J*=9.9 Hz), 3.48 (AB d, 1H, *J*=9.9 Hz), 2.40–2.10 (m, 1H), 1.34 (br s, 22H), 0.97 (irregular t, 3H, *J*~6.25 Hz); ^{13}C NMR

($CDCl_3$) δ 168.24, 166.00, 148.66, 141.37, 136.85, 136.67, 128.37, 128.35, 128.01, 127.97, 127.91, 127.60, 126.72, 122.71, 86.43, 76.39, 73.74, 72.73, 71.51, 51.69, 31.86, 30.00, 29.60, 29.45, 29.32, 28.19, 22.64, 14.08. Anal. calcd for $C_{38}H_{53}O_6$: C, 75.22; H, 8.53. Found: C, 75.24; H, 8.54

4.1.24. Methyl (2*E*)-3-[(2*S*,3*S*)-3-hydroxy-2-(hydroxymethyl)-5-oxo-(*Z*)-4-tetradecylidene(2-2,3-dihydrofuryl)]-prop-2-enoate (5a). A stirred solution of **34a** (112.2 mg, 0.199 mmol) in CH_2Cl_2 (9 ml) at −78°C was treated with a solution of BCl_3 (1 M in CH_2Cl_2, 904 μl) and maintained at that temperature for 2 h. The reaction was quenched with 1 ml of MeOH and allowed to reach room temperature. Volatiles were removed under reduced pressure and the residue was purified by silica gel flash chromatography with hexanes/ethyl acetate mixtures of 2/1 and 1/1 as eluants to afford the *E*,*E*-isomer **5b** (28 mg, 34%), a mixture of **5a** and **b** (35 mg, 43%) an the desired *E*,*Z*-isomer **5a** (12 mg, 15%) as white solids. Overall yield 92%.

Compound ***5a***. Mp 69.9–71.9°C; $[\alpha]_D^{22}=-30.45°$ ($CHCl_3$, *c* 0.22); IR ($CHCl_3$) 3592 and 3406 (OH), 3021–2855, 1760 and 1721 (C=O), 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14 (d, 1H, *J*=15.8 Hz), 6.60 (dt, 1H, *J*~7.8, 1.7 Hz), 6.26 (d, 1H, *J*=15.8 Hz), 5.09 (d, 1H, *J*=6.3 Hz), 3.89–3.83 (m, 5H), 3.21 (d, 1H, *J*=7.5 Hz, D_2O exchanged), 3.13 (m, 1H, D_2O exchanged), 2.79 (irregular q, 2H, *J*~7.24 Hz) 1.53–1.33 (m, 22H), 0.96 (irregular t, 3H, *J*~6.35 Hz); ^{13}C NMR ($CDCl_3$) δ 167.17, 165.86, 149.64, 141.67, 127.20, 123.49, 87.19, 71.66, 64.54, 51.87, 31.85, 29.58, 29.47, 29.34, 29.29, 29.19, 28.73, 27.86, 22.62, 14.05; FAB MS (*m*/*z*, relative intensity) 411 (MH^+, 100), 393 (MH^+-H_2O, 38.7). Anal. calcd for $C_{23}H_{38}O_6$: C, 67.29; H, 9.33. Found: C, 67.64; H, 9.43.

4.1.24. Methyl (2*E*)-3-[(2*S*,3*S*)-3-hydroxy-2-(hydroxymethyl)-5-oxo-(*E*)-4-tetradecylidene(2-2,3-dihydrofuryl)]-prop-2-enoate (5b). A stirred solution of **34b** (215.3 mg, 0.364 mmol) in CH_2Cl_2 (17 ml) at −78°C was treated with a solution of BCl_3 (1 M in CH_2Cl_2, 1.73 ml) in the same manner as for **5a**. Purification by silica gel flash chromatography with the same solvent system afforded **5b** (129 mg, 85%) and a mixture of **5a** and **b** (27 mg, 18%).

Compound ***5b***. Mp 55.6–57.8°C; $[\alpha]_D^{22}=-64.26°$ ($CHCl_3$, *c* 0.31); IR ($CHCl_3$) 3587 and 3430 (OH), 3020–2855, 1757 and 1721 (C=O), 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (d, 1H, *J*=7.6 Hz), 7.08 (m, 1H), 6.34 (d, 1H, *J*=15.6 Hz), 5.15 (d, 1H, *J*=8.0 Hz), 3.83–3.74 (m, 5H), 2.56–2.45 (m, 4H), 1.59–1.34 (m, 22H), 0.96 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 168.98, 166.36, 149.37, 141.81, 128.66, 122.81, 88.64, 69.83, 65.81, 51.90, 31.84, 29.57, 29.51, 29.46, 29.34, 29.28, 28.33, 22.61, 14.04; FAB MS (*m*/*z*, relative intensity) 411 (MH^+, 85.6), 393 (MH^+-H_2O, 19.1). Anal. calcd for $C_{23}H_{38}O_6$: C, 67.29; H, 9.33. Found: C, 67.40; H 9.36.

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