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Original article

Conformationally constrained diacylglycerol (DAG) analogs: 4-C-hydroxyethyl-5-*O*-acyl-2,3-dideoxy-D-glyceropentono-1,4-lactone analogs as protein kinase C (PKC) ligands

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Abstract

The (*R*)-DAG-lactones (**5** and **7E/Z**) are conformationally constrained diacylglycerol (DAG) analogs with high potency as protein kinase C (PKC) ligands. Here, we have prepared and characterized their one-carbon lengthened analogs (**6** and **8E/Z**). The target compounds were synthesized from 1,2-*O*-isopropylidene D-xylose through a key intermediate, 4-C-hydroxyethyl-2,3-dideoxy-D-glyceropentono-1,4-lactone (**13**); they were evaluated as competitive ligands to displace bound [^{3}H]phorbol 12,13-dibutyrate (PDBU) from a recombinant single isozyme (PKC-α). The binding affinities of the synthesized compounds were K_i = 2.623 μM for **6**, K_i = 1.080 μM for **8Z** and K_i = 0.92 μM for **8E**, which were ca. 27, 90, and 70 times less potent than the corresponding parent compounds (**5, 7Z** and **7E**). Molecular modeling indicated that the reduced binding affinity of the representative 3-alkylidene lactone **8Z**, as compared to **7Z**, may be explained by its poor fit in the sn-1 binding mode as well as by its entropic loss due to the relatively flexible hydroxyethyl group.

Keywords: Protein kinase C; DAG-lactone; Diacylglycerol; Phorbol ester

1. Introduction

The protein kinase C (PKC) family of phospholipid-dependent serine/threonine kinases is activated by diacylglycerol (DAG), which is released by the receptor-mediated hydrolysis of membrane-resident phosphatidylinositol 4,5-diphosphate (PIP_2) or by the hydrolysis of phosphatidyl choline (PC) [1–3]. DAG stereospecifically binds to the tandem C1a and C1b domains in the regulatory domain of PKC. The binding is competitive with respect to phorbol ester, a tumor promoting diterpene and ultrapotent DAG analog [4]. One reason for the lower binding affinity of DAG compared to phorbol ester is the conformational flexibility of the DAG, which results in an entropic penalty upon binding to the enzyme. Therefore, one aspect of our efforts to find ultrapotent PKC ligands has been to use conformationally constrained DAG analogs for the purpose of gaining an entropic advantage [5].

Over the past years, we have demonstrated that (*R*)-5-acyloxy-5-hydroxymethyltetrahydro-2-furanone analogs (**1** and **2**) are conformationally constrained DAG analogs with potent PKC binding affinities in the low nanomolar range, stereospecificity, and promising anti-tumor activities toward various tumor cell lines [6,7]. A pharmacophore-guided modeling study indicated that the SAR of these DAG-lactones matched well a three point pharmacophore model of the phorbol esters, comprising the C_3=O, C_9–OH and C_{20}–OH groups of the phorbol ester [8–10]. This binding model is somewhat different from the X-ray structure of the complex of the PKC-δ C1b domain and phorbol-13-acetate determined in the absence of phospholipid, in which only the C_3=O, C_4–OH and C_{20}–OH were interpreted as interacting with the enzyme [11]. On the other hand, the former pharmacophore model that we have used is consistent with experi-

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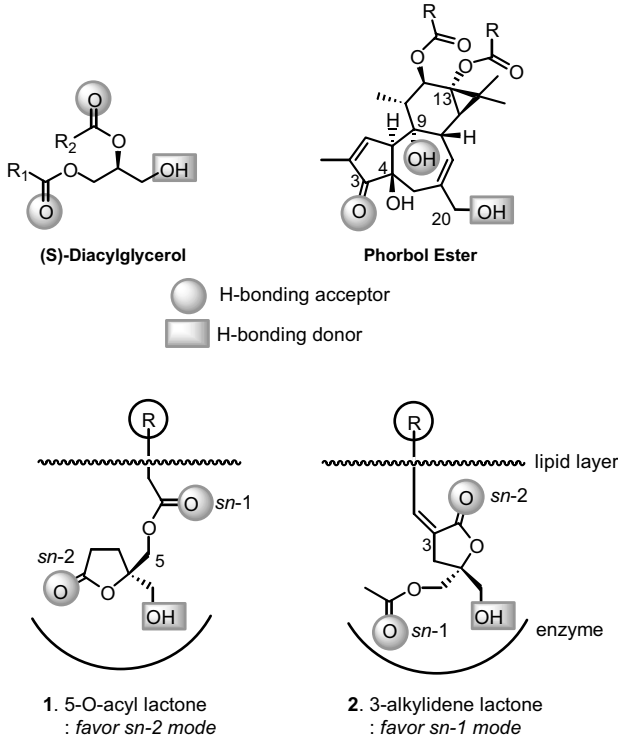


Fig. 1. sn-1 and sn-2 Binding mode of (*R*)-DAG-lactones.

mental results that were determined under more physiological conditions, which include phospholipid, which makes an important contribution to the binding affinity. For instance, Irie's group reported that 4β-deoxy-PDBu is functionally equipotent to PDBU [12], confirming the earlier conclusion from natural product derivatives that the C4 hydroxyl group is not necessary for PKC binding. Likewise, a role for the C_9–OH/C_{13}–C=O motif of phorbol esters in the binding to PKC is implied from the observation that both carbonyl groups of the DAG lactones are critical and one of these carbonyls corresponds to the C_9–OH/C_{13}–C=O motif [13]. The interpretation is that contribution of the second carbonyl to PKC binding is through the interaction with the phospholipid head groups associated with PKC in the active complex. Further support for the pharmacophoric importance of the C_{13}–C=O group (maybe related to the C_9–OH group through hydrogen bonding) comes from phorbol ester analogs lacking this functionality, as described by Sodeoka's group [14].

In the modeling study comparing (*R*)-DAG-lactone and phorbol ester, two hydrogen bonding acceptors in the lactone template, represented by the two carbonyls of the 5-acyloxymethyl and the lactone, could be overlapped with the C_3=O and C_9–OH groups of the phorbol ester in two different ways (Fig. 1). This resulted in two predicted binding modes, a sn-1 and a sn-2 mode, in which the sn-1 or sn-2 carbonyls, respectively, in the DAG-lactone matched the C_3=O of the phorbol [5]. Our extensive analysis of these two binding modes in DAG-lactones suggested a general principle determining the binding mode: the carbonyl bearing the larger lipid chain, mimicking the C_9–OH of the phorbol ester, will not be involved in binding to the enzyme but rather in

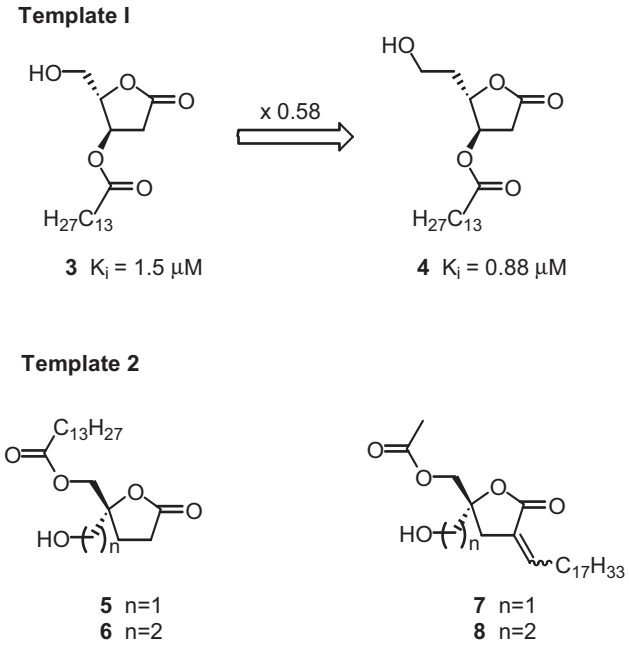


Fig. 2. The design of target lactones **6** and **8**.

binding to the protein–lipid interface. This principle has been useful for predicting the binding modes of DAG-lactones. For instance, the 3-alkylidene lactone (**2**) favors the sn-1 binding mode because the sn-2 carbonyl interacts with the phospholipids. Conversely, the 5-acyl lactones (**1**) bind to the enzyme in the sn-2 mode, because the sn-1 position interacts with the phospholipids [15].

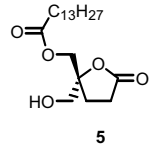
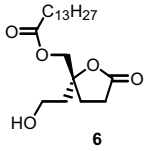
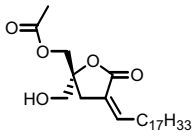
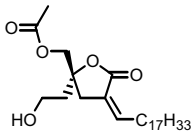
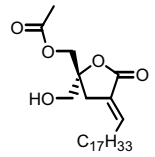
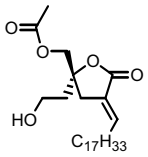
We previously reported that 2-deoxy-3-*O*-tetradecyl-L-ribonolactone (**3**), a conformationally constrained DAG surrogate [16], bound stereospecifically with an affinity of 1.5 μM and its one-carbon lengthened homolog, 2,5-dideoxy-3-*O*-tetradecanoyl-D-galactono-1,4-lactone (**4**) [17], showed a slightly better affinity of 0.88 μM (Fig. 2). This result was explained by the fact that, since **3** and **4** would have a preference for the sn-2 mode, the improved fit, in the sn-2 mode, of **4** to the phorbol ester more than compensated for the entropic penalty due to the hydroxyethyl group [17].

In the present study, we decided to investigate one-carbon elongated homologs (**6** and **8**) of potent (*R*)-DAG-lactones **5** and **7** as PKC ligands (Fig. 2). One advantage of the elongated homologs is that they would be resistant to the racemization that occurred at the final stage in the synthesis of chiral **7**, in which the chiral purity of **7** was readily destroyed by facile 5′-*O*-acyl migration during purification [6]. Here, we describe the syntheses, binding affinities, and the interaction of chiral (*R*)-5-acyloxy-5-hydroxyethyltetrahydro-3-furanone analogs with the enzyme.

2. Chemistry

The synthesis of the 5-acyl lactone analog (**6**) is outlined in Fig. 3. Starting from 1,2-*O*-isopropylidene D-xylose, spirolactone **9** was prepared in four steps according to a

Table 1
PKC-α binding affinities for one-carbon elongated analogues

	K_i (μM)		K_i (μM)
 **5**	0.096	 **6**	2.623 ± 0.082
 **7Z**	0.012	 **8Z**	1.080 ± 0.087
 **7E**	0.013	 **8E**	0.92 ± 0.14

previous report [18]. The isopropylidene group of **9** was deprotected under acidic conditions to afford the corresponding diol, which was then cleaved to the aldehyde **10** by sodium periodate. The ensuing reduction of **10** with sodium borohydride produced the alcohol **11** concomitant with the deprotection of the *O*-formyl group. The primary alcohol of **11** was selectively protected by a *tert*-butyldimethylsilyl (TBS) group, and then the secondary alcohol was deoxygenated by Barton's procedure to produce **13**. Deprotection of the TBS group in **13** and acylation with tetradecanoyl chloride followed by benzyl deprotection with boron trichloride produced the final compound **6**.

For the synthesis of the 3-alkylidene lactone analogs, the lactone **13** was initially employed for the condensation with the branched aldehyde. However, problems in deprotection of the benzyl group at the final stage forced us to replace it with the 4-methoxyphenyl protected **17**. The synthesis of the 3-alkylidene lactone is represented in Fig. 4. The condensation of lactone **17** with oleyl aldehyde, followed by elimination of the corresponding β-hydroxy lactone, afforded a separable mixture of geometric Z/E isomers (**18Z/18E** = 1:1.5). After separation at this stage, each isomer was hydrolyzed to deprotect the TBS group, acetylated, and finally deprotected to afford the final compounds, **8Z** and **8E**, respectively.

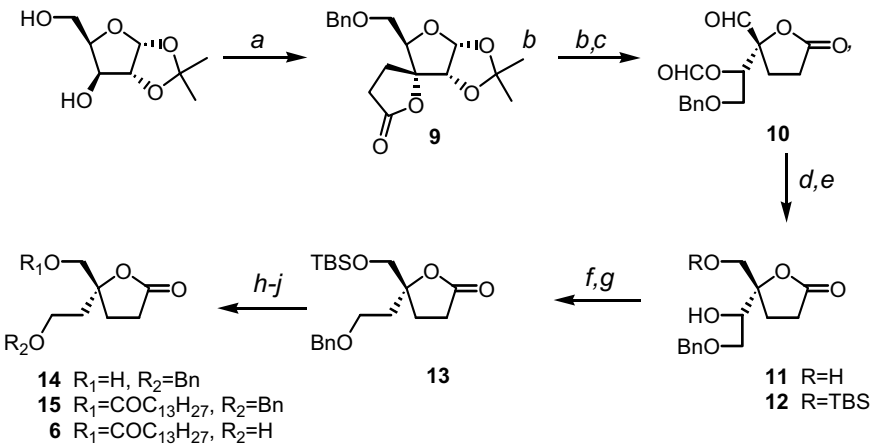


Fig. 3. The synthesis of lactone **6**. Reagents and conditions: (a) Ref. [15]; (b) 2 N HCl, THF; (c) $NaIO_4$, MeOH, H_2O; (d) $NaBH_4$, MeOH, 54% in three steps; (e) TBDMSCl, imidazole, DMAP, CH_2Cl_2, 84%; (f) PhOC(=S)Cl, DMAP, CH_2Cl_2, 99%; (g) Bu_3SnH, AIBN, toluene, 95%; (h) Bu_4NF, THF, 95%; (i) $C_{13}H_{27}COCl$, pyridine, DMAP, CH_2Cl_2, 95%; (j) BCl_3, CH_2Cl_2, –78 °C, 92%.

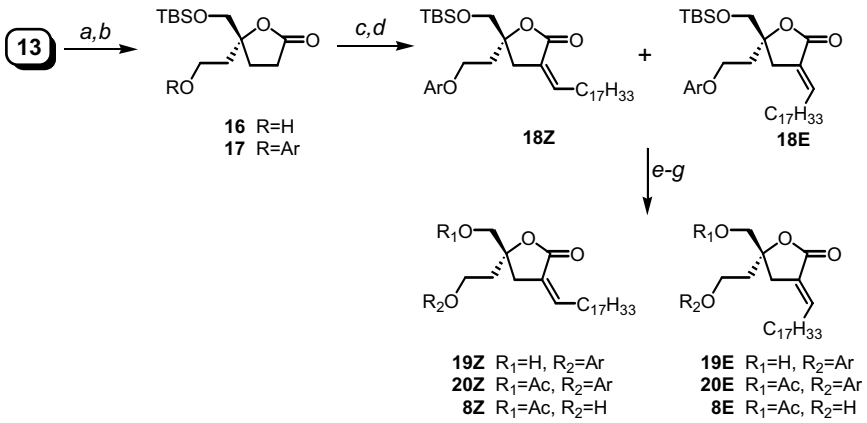


Fig. 4. The synthesis of lactone **8**. Reagents and conditions: (a) H_2, Pd–C, EtOAc, 95%; (b) 4-methoxyphenol, PPh_3, DEAD, THF, 90%; (c) LiHMDS, THF, –78 °C; $C_{17}H_{33}CHO$, HMPA, 76%; (d) MsCl, NEt_3, CH_2Cl_2; DBU, 58% for **18E**, 38% for **18Z**; (e) AcOH–H_2O–THF, 60 °C, 90%; (f) Ac_2O, pyridine, DMAP, CH_2Cl_2, 99%; (g) CAN, CH_3CN–H_2O, 0 °C, 92%.

3. Results and discussion

The interaction of the target compounds (**6, 8Z** and **8E**) with PKC was assessed in terms of the ability of the ligand to displace bound [^{3}H]phorbol 12,13-dibutyrate (PDBU) from the recombinant single isozyme (PKC-α) in the presence of phosphatidylserine, as previously described [6]. The inhibition curves obtained for all ligands were of the type expected for competitive inhibition, and the ID_{50} values were determined by fitting the data points to the theoretical non-cooperative competition curve. The K_is for inhibition of binding were calculated from the ID_{50} values. As shown in Table 1, the binding affinities of the synthesized compounds were K_i = 2.623 μM for **6**, K_i = 1.080 μM for **8Z** and K_i = 0.92 μM for **8E**. Their affinities were estimated to be ca. 27, 90, and 70 times less potent than the corresponding parent compounds, which were reported as K_i = 0.096 μM for **5**, K_i = 0.012 μM for **7Z** and K_i = 0.013 μM for **7E**, respectively [6]. However, the order of their binding affinities represented the same pattern as the parent compounds (**8Z** =**8E** >**6**), and the Z- and E-isomers showed similar potencies.

Since the binding mode of DAG-lactones depends on the principle that "the carbonyl bearing the larger lipid chain, corresponding to C_9–OH in the phorbol ester–PKC-δ complex, will not be involved in binding to the receptor, but rather it will bind to the protein–lipid interface" [13,15], **3** and **4** are predicted to bind to the enzyme in the sn-2 binding mode because the lipid is attached to the sn-1 carbonyl placed in the 3-*O*-acyl group. The computer-generated molecular superposition of **3** and **4** on phorbol-12-myristate-13-acetate (PMA) in the sn-2 mode indicated that the three-point fit for the elongated homolog **4** to PMA was significantly better than that of **3** on PMA (rms 0.391 vs. 1.237) and the distance between the lactone carbonyl (sn-2 carbonyl) and the hydroxyl in **3** appeared to be too short to match the C_{20}–OH and the C_3=O in PMA [17]. In the same way, the 3-alkylidene DAG-lactones **7** and **8** would favor the sn-1 binding mode because the fatty chain is close to the lactone carbonyl (sn-2 carbonyl) which presumably interacts with the protein–lipid interface.

In order to investigate the comparison by modeling between phorbol, the sn-2 mode of **3** and **4**, and the sn-1 mode of **7** and **8** for comparison with their binding affinities, energy minimized conformers of **3, 4, 7Z** and **8Z**, were obtained by a conformational search based on a previous report, respectively [11]. The pharmacophoric comparisons were examined only for the distance (5.348 Å) between the C_3=O and the C_{20}–OH in phorbol 13-acetate obtained from the X-ray structure of its complex with the C1b domain of PKC-δ [11] because the C_9–OH of phorbol is assumed to bind to the protein–lipid interface rather than to the enzyme as evidenced by the X-ray complex (Fig. 5). In the 2-deoxy-L-ribonolactone analogs, whereas the distance (3.93 Å) between the lactone carbonyl (sn-2 carbonyl) and the hydroxyl in the sn-2 mode of **3** was shorter than the 5.348 Å of phorbol, the distance in **4** (5.38 Å) was very close to that of phorbol. This improved matching of **4** overcame the entropic penalty due to the one carbon extension and led to the enhancement of its binding affinity. On the other hand, the distances between the acyloxy carbonyl (sn-1 carbonyl) and the hydroxyl group in the (*R*)-lactone analogs were calculated as 5.06 Å in **7Z** and 5.80 Å in **8Z**, and in its sn-1 mode, were compared with that of phorbol (5.348 Å) (Fig. 5). Contrary to the 2-deoxy-L-ribonolactone template, the one-carbon elongation in the (*R*)-lactone template caused relatively poor pharmacophoric matching and resulted in weaker binding to the enzyme. Although the relative difference to phorbol is not significant (0.288 vs. 0.452 Å), the extra carbon in **8Z** may force the chain to coil somewhat into a less favorable conformation, which costs an additional entropic penalty to reach the binding site appropriately, and therefore, affords more loss of binding affinity (Figs. 4 and 5).

The SAR results of **5** and **6** were hard to explain. We initially expected an improvement in binding affinity of the elongated homolog **6** since its binding would be in the sn-2 mode as a 2-deoxy-L-ribonolactone analogs. Unfortunately, the binding affinity of **6** was weaker than that of the parent

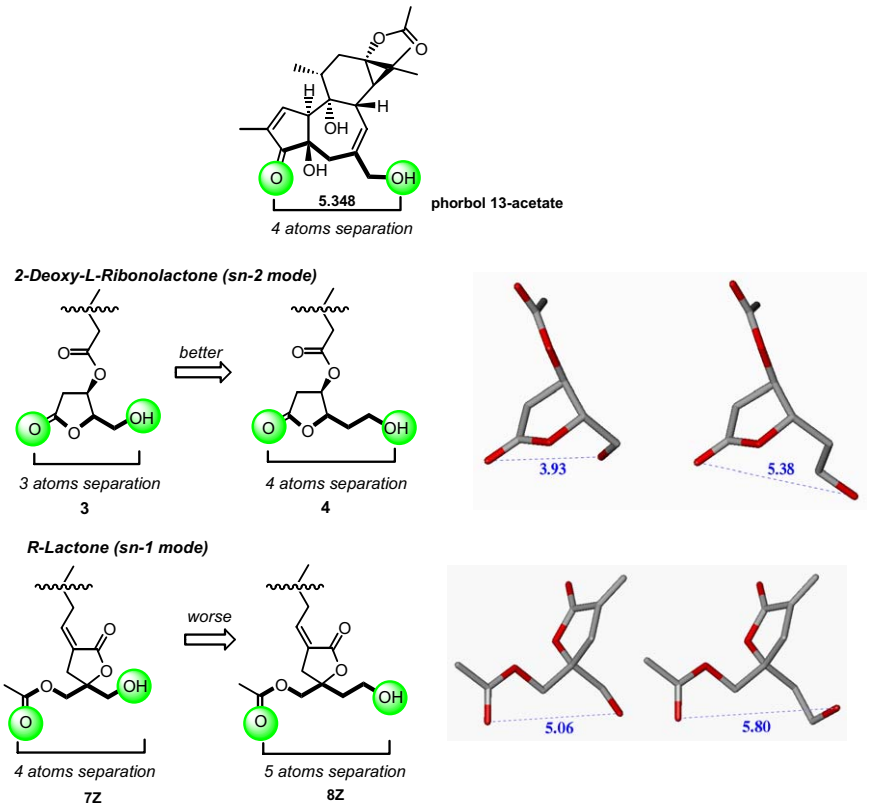


Fig. 5. The overlay matching of DAG-lactones with C_3=O and C_{20}–OH in phorbol 13-acetate.

lactone **5**. This template cannot be compared directly with 2-deoxy-L-ribonolactone analogs because the sn-1 carbonyls in **4** and **6** are placed on different positions of the lactone. We, therefore, reason that in this case, entropic loss due to the one carbon extension is more significant than pharmacophoric matching for enzyme binding. Nevertheless, the penalty incurred by lengthening the OH tether in the sn-2 mode in **6** is less severe (×27 loss) than that in the sn-1 binding mode (×90 and ×70 loss) found in **8Z** and **8E** because of improved pharmacophoric matching in the sn-2 mode.

In summary, we synthesized one-carbon elongated analogs (**6, 8Z** and **8E**) of the ultrapotent DAG (*R*)-lactones (**5, 7Z** and **7E**) reported previously and found that they exhibited lower binding affinities to PKC-α than did the parent compounds. The weaker binding of **8Z/8E** was a consequence of their poor fit on the phorbol ester in the sn-1 mode, as revealed by pharmacophore-guided molecular modeling, and the entropic penalty for enzyme binding due to the relatively flexible hydroxyethyl group. However, improved matching of **6** in the sn-2 mode was overwhelmed by the entropic loss upon elongation resulting in weaker binding although its magnitude of loss is less severe than that of **8**.

4. Experimental protocols

4.1. Chemistry

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). Proton and ^{13}C NMR spectra were recorded on a Bruker AC-250 instrument at 250 and 62.9 MHz, respectively. Spectra were referenced to the solvent in which they were run (7.24 ppm for $CDCl_3$). Infrared spectra were recorded on a Perkin–Elmer 1600 Series FTIR and specific rotations were measured in a Perkin–Elmer Model 241 polarimeter. Positive-ion fast-atom bombardment mass spectra (FABMS) were obtained on a VG 7070E mass spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Analyses indicated by the symbols of the elements or functions were within ±0.4% of the theoretical values.

*4.1.1. 5-O-Benzyl-3-C-hydroxypropyl-α-lactone-1,2-O-isopropylidene-α-D-ribofuranose (**9**)*

The compound was prepared from 1,2-*O*-isopropylidene-D-xylose by following the procedure of a previous report [18].

*4.1.2. 6-O-Benzyl-4-C-hydroxymethyl-2,3-dideoxy-D-threo-hexono-1,4-lactone (**11**)*

A solution of **9** (8.36 g, 25 mmol) in THF (150 ml) and H_2O (150 ml) was treated with Dowex H^+ resin (15 g, prewashed with MeOH) and refluxed for 24 h. The reaction mixture was filtered and concentrated in vacuo. The residue was dissolved with EtOAc and treated with $NaHCO_3$ and $MgSO_4$. The mixture was filtered and concentrated in vacuo

to give the corresponding hemiacetal, which was used for the next step without further purification. The hemiacetal was dissolved in MeOH (150 ml) and H_2O (75 ml) and treated with sodium periodate (10.7 g, 50 mmol). After stirring for 1 h at room temperature, the reaction mixture was filtered and concentrated in vacuo. The residue was dissolved with EtOAc, dried over $MgSO_4$ and concentrated in vacuo to give aldehyde **10**, which was used for the next step without further purification. The aldehyde **10** was dissolved in MeOH (200 ml) and cooled to 0 °C. The solution was treated with sodium borohydride portionwise until the starting material was consumed on TLC. The reaction mixture was quenched with acetone and, after 20 min, acetic acid, and then concentrated in vacuo. The residue was diluted with EtOAc, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (3:1) to EtOAc/MeOH (9:1) as eluant to give **11** (5.0 g, 75% in three steps) as a syrup: $[\alpha]_D = +8.56$ (c 1.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2–7.4 (m, 5H, Ph), 4.52 (s, 2H, $PhCH_2O$), 3.93 (dd, 1H, J = 4.2, 6.7 Hz, H-5), 3.75 (d of AB, 1H, J = 12.2 Hz, H-6a), 3.61 (d of AB, 1H, J = 12.2 Hz, H-6b), 3.50–3.66 (m, 2H, H-4′), 2.88 (bs, 2H, OH), 2.5–2.63 (m, 2H, H-2), 2.08–2.35 (m, 2H, H-3); ^{13}C NMR ($CDCl_3$) δ 177.73, 137.25, 128.47, 127.94, 127.77, 88.64, 73.61, 72.37, 69.78, 64.84, 29.00, 25.08; IR (neat) 3418 (OH), 1760 (C=O) cm^{-1}. Anal. $C_{14}H_{18}O_5$ (C, H).

*4.1.3. 6-*O*-Benzyl-4-C-*tert*-butyldimethylsilyloxymethyl-2,3-dideoxy-D-threo-hexono-1,4-lactone (**12**)*

A solution of **11** (0.466 g, 1.75 mmol) in CH_2Cl_2 (30 ml) was treated with TBS chloride (0.316 g, 2.10 mmol), imidazole (0.48 g, 7 mmol) and 4-dimethylaminopyridine (0.02 g, 0.175 mmol). After stirring for 14 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with 0.5 N HCl solution, saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (2:3) as eluant to give **12** (0.56 g, 84%) as a colorless oil: $[\alpha]_D = +1.60$ (c 1.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2–7.4 (m, 5H, Ph), 4.53 (t, 2H, J = 12.5 Hz, $PhCH_2O$), 3.92 (dd, 1H, J = 3.7, 7.5 Hz, H-5), 3.71 (d of AB, 1H, J = 10.7 Hz, H-6a), 3.66 (d of AB, 1H, J = 10.7 Hz, H-6b), 3.50–3.65 (m, 2H, H-4′), 2.88 (bs, 2H, OH), 2.5–2.65 (m, 2H, H-2), 2.08–2.40 (m, 2H, H-3), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 177.12, 137.44, 128.50, 127.94, 127.76, 88.05, 73.60, 72.47, 69.65, 66.20, 29.18, 25.72, 25.45, 18.12, –5.60, –5.69; IR (neat) 3448 (OH), 1776 (C=O) cm^{-1}. Anal. $C_{20}H_{32}O_5Si$ (C, H).

*4.1.4. 4-C-Benzyloxyethyl-5-*O*-tert-butyldimethylsilyl-2,3-dideoxy-D-glyceropentono-1,4-lactone (**13**)*

A solution of **12** (0.52 g, 1.37 mmol) in CH_2Cl_2 (30 ml) was treated with 4-dimethylaminopyridine (0.668 g, 5.46 mmol) and phenyl chlorothionoformate (0.38 ml, 2.73 mmol). After stirring for 3 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in ether, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (2:3) as eluant to give the corresponding thionoester (0.70 g, 99%) as an oil.

The thionoester (0.7 g, 1.35 mmol) was dissolved in toluene (30 ml) and treated with AIBN (0.12 g, 0.677 mmol) and tributyltin hydride (0.72 ml, 2.71 mmol). After heating at 90 °C for 1 h, the reaction mixture was cooled and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (1:5) as eluant to give **13** (0.47 g, 95%) as an oil: $[\alpha]_D = +2.23$ (c 2.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2–7.4 (m, 5H, Ph), 4.46 (s, 2H, $PhCH_2O$), 3.54–3.71 (m, 4H, J = 3.7 Hz, H-5 and $BnOCH_2$), 2.39–2.72 (m, 2H, H-2), 2.0–2.31 (m, 2H, H-3), 1.95 (t, 2H, J = 6.2 Hz, $BnOCH_2CH_2$), 0.86 (s, 9H), 0.03 (d, 6H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 177.26, 137.93, 128.38, 127.66, 127.61, 87.37, 73.19, 68.61, 65.48, 36.58, 29.70, 28.70, 25.74, 23.37, 18.15, –5.60, –5.69; IR (neat) 1774 (C=O) cm^{-1}. Anal. $C_{20}H_{32}O_4Si$ (C, H).

*4.1.5. 4-C-Benzyloxyethyl-2,3-dideoxy-D-glyceropentono-1,4-lactone (**14**)*

A solution of **13** (0.092 g, 0.25 mmol) in THF (5 ml) was treated dropwise with tetrabutylammonium fluoride (1 M, 0.5 ml, 0.5 mmol) and stirred for 30 min at room temperature. The reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (3:1) as eluant to give **14** (0.60 g, 95%) as an oil: $[\alpha]_D = -6.67$ (c 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2–7.4 (m, 5H, Ph), 4.48 (s, 2H, $PhCH_2O$), 3.52–3.70 (m, 4H, J = 3.7 Hz, H-5 and $BnOCH_2$), 1.9–2.7 (m, 6H, H-2, H-3 and $BnOCH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 176.96, 137.40, 128.50, 127.91, 127.77, 87.47, 73.44, 66.62, 65.51, 36.60, 28.78, 28.72; IR (neat) 3441 (OH), 1769 (C=O) cm^{-1}. Anal. $C_{14}H_{18}O_4$ (C, H).

*4.1.6. 4-C-Benzyloxyethyl-5-*O*-tetradecanoyl-2,3-dideoxy-D-glyceropentono-1,4-lactone (**15**)*

A solution of **13** (0.056 g, 0.224 mmol) in CH_2Cl_2 (10 ml) was treated with pyridine (0.073 ml, 0.898 mmol), a catalytic amount of 4-dimethylaminopyridine and tetradecanoyl chloride (0.122 ml, 0.449 mmol). After stirring for 2 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in cold ether, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (1:2) as eluant to give **15** (0.098 g, 95%) as an oil: $[\alpha]_D = +3.33$ (c 1.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2–7.4 (m, 5H, Ph), 4.46 (s, 2H, $PhCH_2O$), 4.20 (d of AB, 1H, J = 12.0 Hz, H-5a), 4.11 (d of AB, 1H, J = 12.0 Hz, H-5b), 3.61 (t, 2H, J = 6.0 Hz, $BnOCH_2$), 2.45–2.7 (m, 2H, H-2), 2.30 (t, 2H, J = 7.4 Hz, CH_2CO_2), 2.08–2.28 (m, 2H, H-3), 2.03 (t, 2H, J = 6.0 Hz, $BnOCH_2CH_2$), 1.1–1.7 (m, 22H), 0.86 (distorted t, 3H); ^{13}C NMR ($CDCl_3$) δ 176.36, 173.14, 137.72, 128.44, 127.76, 127.67, 85.07, 73.33, 68.17, 65.15, 36.80, 34.08, 31.88, 29.63, 29.60, 29.55, 29.40, 29.31,

29.19, 29.07, 28.97, 28.93, 24.81, 22.65, 14.08. IR (neat) 1780 and 1741 (C=O) cm^{-1}. Anal. $C_{28}H_{44}O_5$ (C, H).

*4.1.7. 4-C-Hydroxyethyl-5-*O*-tetradecanoyl-2,3-dideoxy-D-glyceropentono-1,4-lactone (**6**)*

A solution of **15** (0.083 g, 0.18 mmol) in CH_2Cl_2 (10 ml) was cooled to –78 °C and treated dropwise with boron trichloride in CH_2Cl_2 (1 M, 0.9 ml, 0.9 mmol). After stirring for 6 h at –78 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution (1 ml) and immediately partitioned between ether and pH 7 buffer solution. The organic layer was washed with pH 7 buffer solution five times, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (2:1) as eluant to give **6** (0.061 g, 92%) as a white solid: m.p. 39 °C; $[\alpha]_D$ = –3.75 (c 0.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.23 (d of AB, 1H, J = 11.9 Hz, H-5a), 4.13 (d of AB, 1H, J = 11.9 Hz, H-5b), 3.83 (t, 2H, J = 6.1 Hz, $HOCH_2$), 2.5–2.76 (m, 2H, H-2), 2.32 (t, 2H, J = 7.4 Hz, CH_2CO_2), 2.21 (t, 2H, J = 8.5 Hz, H-3), 1.99 (t, 2H, J = 6.1 Hz, $BnOCH_2CH_2$), 1.18–1.65 (m, 22H), 0.86 (distorted t, 3H); ^{13}C NMR ($CDCl_3$) δ 176.28, 173.23, 85.23, 67.96, 57.86, 39.15, 34.09, 31.88, 29.64, 29.60, 29.56, 29.42, 29.32, 29.20, 29.15, 29.07, 28.89, 24.81, 22.65, 14.09. IR (KBr) 3543 (OH), 1752 and 1739 (C=O) cm^{-1}. Anal. $C_{21}H_{38}O_5$ (C, H), MS(FAB) m/z 371 (MH^+).

*4.1.8. 5-*O*-tert-Butyldimethylsilyl-4-C-hydroxyethyl-2,3-dideoxy-D-glyceropentono-1,4-lactone (**16**)*

A solution of **13** (0.5 g, 1.37 mmol) in ethylacetate (30 ml) was treated with 10% palladium on carbon (1.0 g) and acetic acid (four drops). The suspension was hydrogenated under a balloon of hydrogen for 6 h, filtered and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (2:1) as eluant to give **16** (0.358 g, 95%) as an oil: $[\alpha]_D$ = –0.92 (c 2.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.78 (t, 2H, J = 6.1 Hz, $HOCH_2$), 3.70 (d of AB, 1H, J = 10.8 Hz, H-5a), 3.59 (d of AB, 1H, J = 10.8 Hz, H-5b), 2.43–2.74 (m, 2H, H-2), 1.98–2.32 (m, 2H, H-3), 1.93 (t, 2H, J = 6.1 Hz, $BnOCH_2CH_2$), 0.86 (s, 9H), 0.03 (d, 6H, J = 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 177.23, 87.57, 68.29, 57.86, 39.18, 29.38, 28.89, 25.70, 18.12, –5.60, –5.69; IR (neat) 3445 (OH), 1770 (C=O) cm^{-1}. Anal. $C_{13}H_{26}O_4Si$ (C, H).

*4.1.9. 5-*O*-tert-Butyldimethylsilyl-4-C-4-methoxyphenoxyethyl-2,3-dideoxy-D-glyceropentono-1,4-lactone (**17**)*

To a stirred solution of **16** (0.32 g, 1.166 mmol) and triphenylphosphine (0.428 g, 1.63 mmol) in THF (4 ml) was slowly added over a period of 20 min a solution of diethyl azodicarboxylate (0.284 g, 1.63 mmol) and 4-methoxyphenol (0.434 g, 3.5 mmol) in THF (4 ml). The reaction mixture was stirred for 2 h at room temperature and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:2) as eluant to give **17** along with inseparable 4-methoxyphenol. To remove 4-methoxyphenol, the crude **17** was dissolved in CH_2Cl_2 (20 ml) and treated with acetic anhydride (0.5 ml) and pyridine (0.5 ml). After stirring for 1 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (1:3) as eluant to give pure **17** (0.4 g, 90%) as an oil: $[\alpha]_D$ = +2.80 (c 1.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.7–6.9 (m, 4H, aromatic), 4.05 (t, 2H, J = 6.2 Hz, $ArOCH_2$), 3.75 (s, 3H, CH_3O), 3.74 (d of AB, 1H, J = 10.8 Hz, H-5a), 3.63 (d of AB, 1H, J = 10.8 Hz, H-5b), 2.4–2.76 (m, 2H, H-2), 2.0–2.38 (m, 2H, H-3 and $ArOCH_2CH_2$), 0.86 (s, 9H), 0.03 (d, 6H, J = 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 177.01, 153.92, 152.35, 115.23, 114.59, 87.07, 68.45, 63.65, 55.57, 36.02, 29.54, 28.65, 25.67, 18.08, –5.66, –5.73; IR (neat) 1774 (C=O), 1508 and 1472 cm^{-1}. Anal. $C_{20}H_{32}O_5Si$ (C, H).

*4.1.10. 5-*O*-tert-Butyldimethylsilyl-4-C-4-methoxyphenoxyethyl-2-C-[(Z)-9-octadecaenylidene]-2,3-dideoxy-D-glyceropentono-1,4-lactone (**18Z**) and 5-*O*-tert-butyldimethylsilyl-4-C-4-methoxyphenoxyethyl-2-C-[(E)-9-octadecaenylidene]-2,3-dideoxy-D-glyceropentono-1,4-lactone (**18E**)*

A stirred solution of **17** (0.38 g, 1.0 mmol) in THF (4 ml) was cooled to –78 °C and treated slowly with lithium *bis*(trimethylsilyl)amide (1 M in THF, 1.2 ml, 1.2 mmol). After stirring for 1 h, the reaction mixture was treated with a mixture of oleyl aldehyde (0.32 g, 1.2 mmol) and hexamethylphosphoramide (0.215 g, 1.2 mmol) and stirring was continued for 1 h at –78 °C and for 1 h at –40 °C. The mixture was quenched with a solution of saturated ammonium chloride and diluted with ether. The organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (1:5) as eluant to give the intermediate β-hydroxy lactone (0.478 g, 74%). This compound was dissolved in CH_2Cl_2 (20 ml) and cooled to 0 °C. The solution was then stirred with triethylamine (0.41 ml, 3 mmol) and methanesulfonyl chloride (0.12 ml, 1.48 mmol) for 30 min. The reaction mixture was warmed to room temperature and stirred for 1 h before the addition of 1,8-diazabicyclo[5,4,0]undec-7-ene (0.66 ml, 3 mmol). After further stirring for 6 h at room temperature, the mixture was concentrated and diluted with ether. The ethereal solution was washed with diluted HCl, H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (1:8) as eluant to give **18Z** (Z-isomer, 0.20 g, 38%) and **18E** (E-isomer: 0.27 g, 58%) as colorless oils, respectively.

Compound **18Z**: R_f = 0.56 (EtOAc/hexanes = 1:5); $[\alpha]_D$ = –0.57 (c 1.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.73–6.85 (m, 4H, aromatic), 6.09 (m, 1H, >C=CH), 5.33 (m, 2H, CH_2CH=$CHCH_2$), 4.04 (t, 2H, J = 6.3 Hz, $ArOCH_2$), 3.75 (s, 3H, CH_3O), 3.67 (d of AB, 1H, J = 10.7 Hz, H-5a), 3.59 (d of AB, 1H, J = 10.7 Hz, H-5b), 2.55–3.0 (m, 4H, >C=CHCH_2- and H-3a,b), 1.9–2.2 (m, 6H, $ArOCH_2CH_2$,

$CH_2CH{=}CHCH_2$), 1.1–1.4 (m, 22H), 0.75–0.9 (m, 12H, CH_3 and $(CH_3)_3Si$), 0.03 (s, 6H, J = 3.0 Hz); ^{13}C NMR ($CDCl_3$) δ 169.36, 153.96, 152.56, 143.46, 129.93, 129.82, 125.44, 115.36, 114.65, 83.32, 67.87, 63.70, 55.70, 36.16, 36.00, 31.90, 29.75, 29.65, 29.52, 29.38, 29.31, 29.22, 29.13, 27.61, 27.21, 25.72, 22.67, 18.15, 14.11, –5.56; IR (neat) 1757 (C=O), 1670 (C=C), 1508 and 1464 cm^{-1}. Anal. $C_{38}H_{64}O_5Si$ (C, H).

Compound **18E**: R_f = 0.50 (EtOAc/hexanes = 1:5); $[\alpha]_D$ = –1.28 (c 1.56, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.73–6.85 (m, 4H, aromatic), 6.63 (m, 1H, >C=CH), 5.33 (m, 2H, $CH_2CH{=}CHCH_2$), 4.04 (m, 2H, $ArOCH_2$), 3.75 (s, 3H, CH_3O), 3.69 (d of AB, 1H, J = 10.7 Hz, H-5a), 3.60 (d of AB, 1H, J = 10.7 Hz, H-5b), 2.65–2.97 (m, 2H, H-3a,b), 1.9–2.25 (m, 8H, >C=CHCH_2–, $ArOCH_2CH_2$ and $CH_2CH{=}CHCH_2$), 1.15–1.5 (m, 22H), 0.75–0.9 (m, 12H, CH_3 and $(CH_3)_3Si$), 0.03 (s, 6H, J = 3.3 Hz); ^{13}C NMR ($CDCl_3$) δ 170.53, 153.99, 152.50, 139.84, 129.99, 129.70, 127.52, 115.36, 114.65, 84.05, 67.97, 63.69, 55.68, 36.13, 32.64, 31.89, 30.12, 29.74, 29.71, 29.51, 29.31, 29.13, 28.10, 27.20, 27.14, 25.67, 22.66, 18.15, 14.09, –5.56; IR (neat) 1759 (C=O), 1683 (C=C), 1508 and 1464 cm^{-1}. Anal. $C_{38}H_{64}O_5Si$ (C, H).

*4.1.11. C-4-Methoxyphenoxyethyl-2-C-[(Z)-9-octadecaenylidene]-2,3-dideoxy-D-glyceropentono-1,4-lactone (**19Z**) and 4-C-4-methoxyphenoxyethyl-2-C-[(E)-9-octadecaenylidene]-2,3-dideoxy-D-glyceropentono-1,4-lactone (**19E**)*

A solution of **18Z** (0.2 g, 0.318 mmol) in acetic acid (9 ml), H_2O (3 ml) and THF (3 ml) was heated at 60 °C for 48 h and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (1:1) as eluant to give **19Z** (0.147 g, 90%) as an oil: $[\alpha]_D$ = –0.64 (c 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.7–6.9 (m, 4H, aromatic), 6.18 (m, 1H, >C=CH), 5.33 (m, 2H, $CH_2CH{=}CHCH_2$), 4.05 (m, 2H, $ArOCH_2$), 3.75 (s, 3H, CH_3O), 3.65 (dd of AB, 2H, H-5a,b), 2.57–3.0 (m, 4H, >C=CHCH_2- and H-3a,b), 1.9–2.3 (m, 6H, $ArOCH_2CH_2$, $CH_2CH{=}CHCH_2$), 1.15–1.44 (m, 22H), 0.86 (distorted t, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.18, 154.08, 152.19, 145.07, 129.86, 129.72, 124.52, 115.27, 114.61, 83.63, 66.76, 63.75, 55.60, 36.20, 35.85, 32.53, 31.83, 29.68, 29.58, 29.45, 29.28, 29.24, 29.17, 29.14, 29.00, 27.65, 27.13, 22.61, 14.05. IR (neat) 3421 (OH), 1752 (C=O), 1670 (C=C), 1508 and 1465 cm^{-1}. Anal. $C_{32}H_{50}O_5$ (C, H).

Compound **19E** was obtained from **18E**, by following the above procedure, as a low-melting solid in 90% yield: m.p. 40 °C; $[\alpha]_D$ = –7.85 (c 1.86, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.7–6.9 (m, 4H, aromatic), 6.71 (m, 1H, >C=CH), 5.33 (m, 2H, $CH_2CH{=}CHCH_2$), 4.05 (m, 2H, $ArOCH_2$), 3.75 (s, 3H, CH_3O), 3.66 (dd of AB, 2H, H-5a,b), 2.7–2.95 (m, 2H, H-3a,b), 1.9–2.3 (m, 8H, $ArOCH_2CH_2$, >C=CHCH_2– and $CH_2CH{=}CHCH_2$), 1.15–1.5 (m, 22H), 0.86 (distorted t, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.48, 154.07, 152.19, 141.50, 129.94, 129.63, 126.60, 115.29, 114.61, 84.39, 67.01, 63.75, 55.60, 36.04, 32.68, 32.53, 31.82, 30.16, 29.67, 29.65, 29.57, 29.44, 29.23, 29.08, 28.01, 27.13, 27.08, 22.60, 14.05. IR ($CHCl_3$) 3371 (OH), 1727 (C=O), 1681 (C=C), 1511 and 1466 cm^{-1}. Anal. $C_{32}H_{50}O_5$ (C, H).

*4.1.12. 5-O-Acetyl-C-4-methoxyphenoxyethyl-2-C-[(Z)-9-octadecaenylidene]-2,3-dideoxy-D-glyceropentono-1,4-lactone (**20Z**) and 5-O-acetyl-C-4-methoxyphenoxyethyl-2-C-[(E)-9-octadecaenylidene]-2,3-dideoxy-D-glyceropentono1,4-lactone (**20E**)*

A solution of **19Z** (0.098 g, 0.19 mmol) in CH_2Cl_2 (12 ml) was cooled to –10 °C and treated with pyridine (0.092 ml, 1.14 mmol), acetic anhydride (0.072 ml, 0.76 mmol) and a catalytic amount of 4-dimethylaminopyridine. After stirring for 30 min at 0 °C, the reaction mixture was concentrated in vacuo at 0 °C. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (1:1) as eluant to give **20Z** (0.105 g, 99%) as an oil: $[\alpha]_D$ = +5.81 (c 0.86, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.73–6.85 (m, 4H, aromatic), 6.16 (m, 1H, >C=CH), 5.33 (m, 2H, $CH_2CH{=}CHCH_2$), 4.22 (d of AB, 1H, J = 11.9 Hz, H-5a), 4.15 (d of AB, 1H, J = 11.9 Hz, H-5b), 4.05 (m, 2H, $ArOCH_2$), 3.74 (s, 3H, CH_3O), 2.58–3.0 (m, 4H, >C=CHCH_2- and H-3a,b), 2.03 (s, 3H, CH_3COO), 1.9–2.3 (m, 6H, $ArOCH_2CH_2$, $CH_2CH{=}CHCH_2$), 1.15–1.4 (m, 22H), 0.86 (distorted t, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.38, 168.62, 154.03, 152.27, 144.70, 129.88, 129.71, 124.19, 115.24, 114.61, 81.24, 67.78, 63.27, 55.62, 36.58, 36.19, 31.83, 29.70, 29.67, 29.63, 29.59, 29.46, 29.29, 29.24, 29.20, 29.13, 29.03, 27.62, 27.15, 27.12, 22.61, 20.61, 14.05. IR (neat) 1753 (C=O), 1670 (C=C), 1509 and 1466 cm^{-1}. Anal. $C_{34}H_{52}O_6$ (C, H).

Compound **20E** was obtained from **19E**, by following the above procedure, as an oil in 99% yield: $[\alpha]_D$ = +0.83 (c 0.84, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.73–6.85 (m, 4H, aromatic), 6.71 (m, 1H, >C=CH), 5.33 (m, 2H, $CH_2CH{=}CHCH_2$), 4.24 (d of AB, 1H, J = 11.9 Hz, H-5a), 4.18 (d of AB, 1H, J = 11.9 Hz, H-5b), 4.05 (m, 2H, $ArOCH_2$), 3.74 (s, 3H, CH_3O), 2.7–2.94 (m, 2H, H-3a,b), 2.03 (s, 3H, CH_3COO), 1.9–2.3 (m, 8H, $ArOCH_2CH_2$, >C=CHCH_2 and $CH_2CH{=}CHCH_2$), 1.15–1.55 (m, 22H), 0.86 (distorted t, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.31, 169.79, 154.04, 152.22, 141.15, 129.95, 129.57, 126.20, 115.26, 114.60, 81.85, 67.96, 63.29, 55.59, 36.40, 33.10, 31.81, 30.15, 29.67, 29.63, 29.56, 29.43, 29.23, 29.06, 28.02, 27.13, 27.06, 22.60, 20.55, 14.03. IR (neat) 1754 (C=O), 1680 (C=C), 1509 and 1466 cm^{-1}. Anal. $C_{34}H_{52}O_6$ (C, H).

*4.1.13. 5-O-Acetyl-C-4-hydroxyethyl-2-C-[(Z)-9-octadecaenylidene]-2,3-dideoxy-D-glyceropentono-1,4-lactone (**8Z**) and 5-O-acetyl-C-4-hydroxyethyl-2-C-[(E)-9-octadecaenylidene]-2,3-dideoxy-D-glyceropentono-1,4-lactone (**8E**)*

A solution of **20Z** (0.09 g, 0.16 mmol) in acetonitrile (4 ml) and H_2O (1 ml) was cooled to 0 °C and treated with ammonium cerium(IV) nitrate (0.18 g, 0.32 mmol) in one portion. After stirring for 10 min at 0 °C, the reaction mixture was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2, and the combined organic

layer was washed with H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (1:1) as eluant to give **8Z** (0.067 g, 92%) as an oil: $[\alpha]_D$ = +4.65 (c 0.86, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.18 (m, 1H, >C=CH), 5.33 (m, 2H, CH_2CH=C$H$$CH_2$), 4.19 (d of AB, 1H, J = 12.0 Hz, H-5a), 4.13 (d of AB, 1H, J = 12.0 Hz, H-5b), 3.81 (t, 2H, J = 6.1 Hz, $HOCH_2$), 2.6–2.9 (m, 4H, >C=CHCH_2- and H-3a,b), 2.04 (s, 3H, CH_3COO), 1.9–2.1 (m, 6H, $ArOCH_2CH_2$, CH_2CH=CHCH_2), 1.15–1.5 (m, 22H), 0.86 (distorted t, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.48, 168.71, 144.72, 129.88, 129.69, 124.21, 81.66, 67.69, 57.61, 39.02, 36.67, 32.52, 31.82, 29.67, 29.43, 29.27, 29.23, 29.19, 29.12, 29.05, 27.62, 27.13, 22.60, 20.61, 14.03. IR (neat) 3462 (OH), 1750 (C=O), 1670 (C=C) cm^{-1}. Anal. $C_{27}H_{46}O_5$ (C, H), MS(FAB) *m/z* 451 (MH^+).

Compound **8E** was obtained from **20E**, by following the above procedure, as an oil in 92% yield: $[\alpha]_D$ = +11.62 (c 0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.72 (m, 1H, >C=CH), 5.33 (m, 2H, CH_2CH=C$H$$CH_2$), 4.18 (s, 2H, H-5a,b), 3.82 (t, 2H, J = 6.2 Hz, $HOCH_2$), 2.78 (m, 2H, H-3a,b), 2.04 (s, 3H, CH_3COO), 1.9–2.2 (m, 8H, $ArOCH_2CH_2$, >C=CHCH_2– and CH_2CH=CHCH_2), 1.15–1.5 (m, 22H), 0.86 (distorted t, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.43, 170.02, 141.13, 129.92, 129.54, 126.29, 82.38, 67.89, 57.42, 39.19, 33.19, 32.47, 31.77, 30.12, 29.62, 29.59, 29.52, 29.39, 29.28, 29.19, 29.03, 28.00, 27.09, 27.02, 22.55, 20.51, 13.99. IR (neat) 3448 (OH), 1748 (C=O), 1679 (C=C) cm^{-1}. Anal. $C_{27}H_{46}O_5$ (C, H), MS(FAB) *m/z* 451 (MH^+).

4.2. Molecular modeling

The structures of **3, 4, 7Z** and **8Z** were built using the Sybyl molecular modeling program (Tripos, Inc., St. Louis), and then the geometries were fully optimized using the Tripos force field with the following non-default options (method: conjugate gradient, termination: gradient 0.01 kcal mol Å, and max iterations: 10,000). The partial atomic charges were calculated by the Gasteiger–Hückel method in the Sybyl program. The Grid search method was used to evaluate the conformational properties of these compounds. Torsion angles for the hydroxyalkyl and acetate groups were driven from –180° to 180° in steps of 30° and fully minimized structures were obtained at each point. All calculations were performed on a Silicon Graphics O_2 R10000 workstation.

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