Conformationally Constrained Analogues of Diacylglycerol. 20. The Search for an Elusive Binding Site on Protein Kinase C through Relocation of the Carbonyl Pharmacophore Along the *sn*-1 Side Chain of 1,2-Diacylglycerol Lactones

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Previous studies with 1,2-diacylglycerol (DAG) lactones, which behave as high-affinity ligands for protein kinase C (PK-C), have established the importance of maintaining intact the pharmacophore triad of two carbonyl moieties (*sn*-1 and *sn*-2) and the primary alcohol. In addition, docking studies of DAG-lactones into an empty C1b receptor of PK-Cδ (as it appears in complex with phorbol 13-*O*-acetate) have revealed that in either of the two possible binding alternatives (*sn*-1 or *sn*-2) only one carbonyl group of the DAG-lactone is involved in binding. Therefore, the unknown receptor for the orphaned carbonyl appears to lie outside the boundaries of this binary complex, possibly residing at the membrane or near the membrane−protein interface. A strategy to locate the optimal location of the unengaged carbonyl was conceived by utilizing a small group of DAG-lactones (**1**−**4**) with a highly branched chain adjacent to the *sn*-2 carbonyl such that *sn*-2 binding is favored. With these compounds, various locations of the *sn*-1 carbonyl along the side chain were tested for their binding affinity for PK-C. The results indicate that the location of the side chain *sn*-1 carbonyl in a DAG-lactone must have perfect mimicry to the *sn*-1 carbonyl of the parent DAG for it to display high binding affinity. A proposed model from this work is that the missing pharmacophore in the ternary complex, which includes the membrane, is close to the membrane−protein interface.

Introduction and Background

Protein kinase C (PK-C) is a family of serine/threonine-specific isozymes that are regulated by phosphorylation, by calcium, and by association with phospholipids and *sn*-1,2-diacylglycerol (DAG).[1−3] The PK-C family comprises 10 isozymes grouped into three classes: conventional (α, β, γ), novel (δ, ϵ, η, θ), and atypical (ζ, ι/λ). In addition, PK-C μ and ν are considered by some to constitute a fourth class and by others to comprise a distinct family called protein kinase D.[4] All members contain a C-terminal kinase domain with serine/threonine specific kinase activity and an N-terminal regulatory domain. The regulatory domain contains two key functionalities: an autoinhibitory sequence and one or two membrane-targeting domains (C1 and C2).

The central role of PK-C in cell signal transduction has been well established over the past 2 decades since its discovery[5] with the lipophilic second messenger, DAG, playing a prominent role in this cellular signal transduction.[6] Both the classical (α, β, and γ) and novel (δ, ϵ, η, θ) PK-C isozymes are thought to become activated as a result of association of the cytosolic enzyme with membranes containing acid phospholipids.[7,8] This association is strongly facilitated by DAG, which is generated as a result of a stimulus-initiated activation of phospholipase C.[9] The accepted dogma has been that these isozymes are cytosolic in the inactive state and, as part of the activation process, translocate to the inner leaflet of the cellular membrane.[10,11] The binding of PK-C to the plasma membrane is transient and regulated by the association of its C1 domain with DAG in the membrane.[12]

The classical and novel PK-C isozymes each contain two small (~50 residues) zinc-finger-like domains (C1a and C1b) consisting of two β-sheets and a small α-helix. The crystal structure of an isolated C1 domain from PK-Cδ in complex with phorbol 13-*O*-acetate[13] showed that when the ligand is bound in the pocket between the β-sheets, a continuous hydrophobic surface is created over the top third of the domain, which in turn promotes its insertion into the membrane. This binary complex structure confirmed the importance of hydrogen bonding of the main phorbol ester pharmacophores, C3 (C=O), C4 (OH), and C20 (OH), in agreement with previous SAR studies showing that any modification to these key functional groups abrogated or reduced the activity of the phorbol esters (Figure 1).[14,15] The structure also revealed that the C12 hydroxyl and C13 acetate moieties were not hydrogen-bonded to any residue on the C1 domain. However, SAR studies have also shown that lipophilic acyl chains at these positions are important for activity because they bind to membrane lipids in the ternary complex.[16,17] The C9 (OH), although originally

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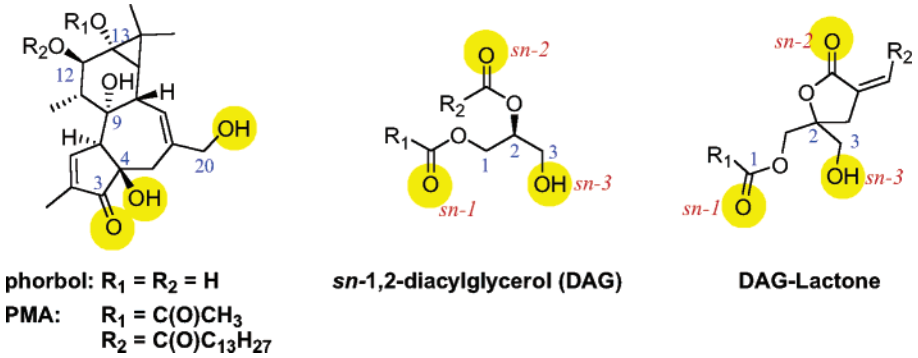


Figure 1. Pharmacophores (yellow) of phorbol, PMA, DAG, and DAG-lactone.

believed to be involved in binding, appeared intramolecularly hydrogen-bonded to the C13 carbonyl ester. While it has been suggested that such an intramolecular arrangement prevents these polar groups from residing in the lipid phase with unsatisfied hydrogen bonds,[13] it is also possible that this motif could interact at the protein−lipid interface as an additional pharmacophore not revealed in the binary complex. Corresponding to the phorbol ester pharmacophores are C1 (C═O), C2 (C═O), and C3 (CH_2OH) in DAG, although a substantial difference in binding affinity (≥3 orders of magnitude) is found favoring the phorbol esters (Figure 1).[18,19] On the basis of the spatial correspondence between the key oxygen atoms in phorbol and DAG, a pharmacophore-guided approach was used to design highly potent PK-C ligands based on the DAG structure where the glycerol backbone is constrained into a five-member lactone ring (DAG-lactone, Figure 1).[20−22]

Modeling studies using the crystal coordinates of the C1b domain of PK-Cδ in complex with phorbol 13-*O*-acetate revealed two possible binding modes (*sn*-1 and *sn*-2) when a DAG-lactone was docked into the empty C1b domain.[20] Although the carbonyl moieties are not equivalent, they display a similar hydrogen-bonding network in two distinct orientations with participation from the primary OH and only one of the carbonyl groups, to Thr242, Leu251, and Gly253, akin to that seen with phorbol 13-*O*-acetate. The *sn*-1 binding mode in either DAG or DAG-lactones is defined as that in which only the *sn*-1 carbonyl is directly bound to the protein, while the *sn*-2 binding mode is defined as that in which only the *sn*-2 carbonyl is directly bound to the protein. Since the DAG-lactones compete with phorbol esters for the same binding site,[23] a common binding mode between these two classes of ligands would require *at least one C═O group of the DAG-lactone to be involved in binding to the C1 domain of the enzyme.*

While we observe that in terms of hydrogen bonding both the *sn*-1 and *sn*-2 binding modes are allowed, the disposition and nature of the acyl chain, particularly if it is highly branched, can have a direct influence on the binding orientation of the DAGs.[24] Indeed, we found that in general DAG-lactones prefer to bind *sn*-2, and this *sn*-2 binding predilection can be enhanced by placing larger bulky groups α to the lactone carbonyl.[21] It is in this binding mode (Figure 2) that DAG-lactones exhibit a large increase in binding affinity when compared to their open-chain counterparts.[21] While in this binding mode the *sn*-1 carbonyl appears to be unengaged with the C1 domain in the binary complex, its presence is

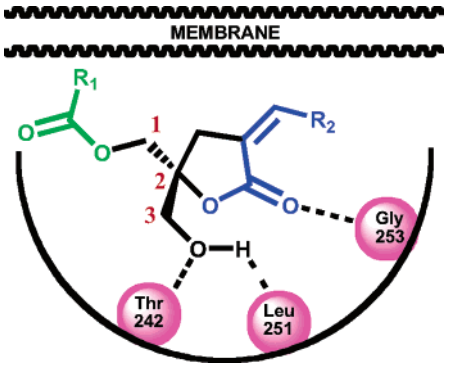


Figure 2. Hydrogen-bonding interaction of DAG-lactone at the C1 domain of PK-Cδ in the *sn*-2 binding mode.

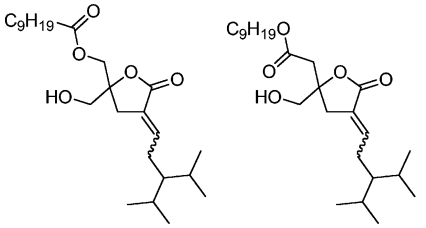
absolutely essential;[25] thus, it is probable that this key pharmacophore interacts with phospholipid headgroups, other structural elements outside the C1 domain to which the DAG-lactone is bound, and even amino acid residues on the adjacent, unoccupied C1 domain. Therefore, in the absence of a solved ternary complex structure, which involves the DAG-lactone, the C1 domain(s) and the membrane, the optimal location of this orphan *sn*-1 pharmacophore cannot be determined with confidence. A small number of DAG-lactones, which are described in the present work, were designed and synthesized to find the optimal location of this elusive pharmacophore.

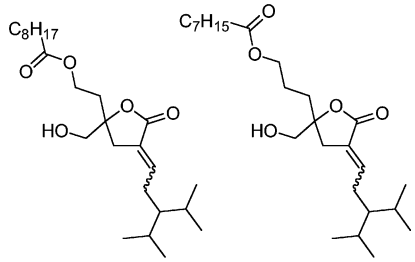
Design and Synthesis

To better understand the more subtle details of the interaction of the *sn*-1 carbonyl, we undertook the task to explore the preferred location of this pharmacophore to complement its unidentified receptor. By placement of a large bulky group next to the *sn*-2 carbonyl and a slimmer, linear chain in the *sn*-1 position, lactones (**1**−**4**) were designed to favor *sn*-2 binding to the protein, thus leaving the *sn*-1 carbonyl free to bind to the unspecified receptor. In this series of compounds, the *sn*-1 carbonyl is "moved" through the side chain in an attempt to identify its optimal position for interacting with its unidentified receptor.

Relative to the position of the *sn*-1 carbonyl in **1**, targets were selected with a one-carbon reduction (**2**), achieved by reversing the ester functionality and thus moving the carbonyl one position closer to the lactone ring, and with a one-carbon elongation (**3**) and two-carbon elongation (**4**), achieved by moving the carbonyl

one and two positions, respectively, further away from the lactone ring. It is noteworthy that since all the

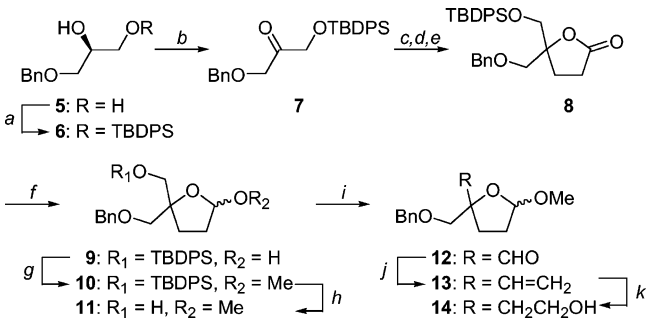




compounds have the same empirical formula and identical calculated log *P* values (log *P* = 6.61), they would be expected to have similar hydrophobicities, at least to a first approximation. However, since the compounds can form different intramolecular H-bonding networks, their movement into a lipid environment would involve different desolvation energy penalties that could additionally influence their binding affinity to some degree.

A common intermediate, **14**, was synthesized starting from commercially available 3-benzyloxy-1,2-propanediol (**5**), as outlined in Scheme 1. Protection of the primary alcohol (**6**) followed by oxidation gave the requisite ketone intermediate **7**. Grignard reaction with allylmagnesium bromide followed by hydroboration and PCC oxidation gave lactone **8**. DIBAL reduction of the carbonyl followed by conversion of the resulting lactol (**9**) to the methyl glycoside (**10**) and silyl deprotection gave **11**. Oxidation of the primary alcohol to an aldehyde (**12**), followed by reaction under Wittig conditions, elongated the chain by one carbon (**13**). Final hydroboration and oxidation gave **14**.

Scheme 1[a]



[a] (a) TBDPSCl, imidazole, CH_2Cl_2, DMF; (b) PCC, 4 Å molecular sieves, CH_2Cl_2; (c) allylmagnesium bromide, THF, 0 °C to room temperature; (d) BH_3·SMe_2, THF, −78 °C to room temperature; (e) PCC, 4 Å molecular sieves, CH_2Cl_2; (f) DIBAL, PhMe, −78 °C; (g) Dowex 50WX8-200, AcOH, MeOH, THF; (h) TBAF, THF, 0 °C to room temperature; (i) DCC, DCAA, DMSO; then oxalic acid, Et_2O, −78 °C; (j) $MePPh_3Br$, $KOC(CH_3)_3$, THF; (k) BH_3·SMe_2, THF, −78 to 0 °C, then $NaBO_3$·H_2O, 0 °C to room temperature.

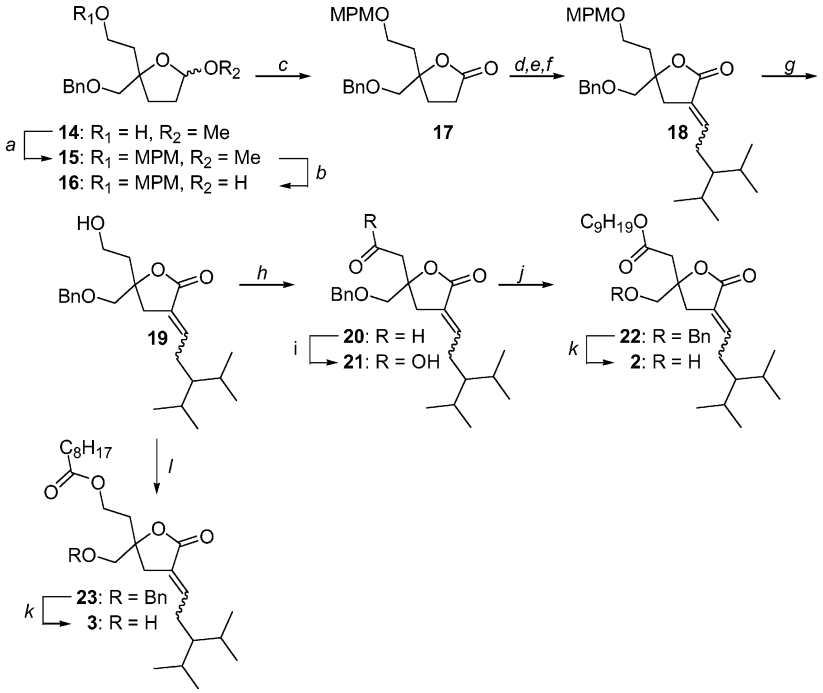
As shown in Scheme 2, protection of the primary hydroxyl group of **14** as its MPM ether (**15**), followed by hydrolysis of the methyl glycoside and subsequent oxidation, gave **17**. α-Alkylation of lactone **17** followed by dehydration gave **18** as a mixture of *E* and *Z* α-alkylidene isomers, which were easily separated by silica gel column chromatography. The MPM ether of each isomer was then separately deprotected to give **19**, the common late-stage intermediate for the syntheses of **2** and **3**. For each isomer of **19** (*E*/*Z*), the primary alcohol was subjected to Swern oxidation to the aldehyde (**20**) and further oxidation to the carboxylic acid to give **21** (*E*/*Z*). DCC coupling with 1-nonanol and final removal of the benzyl group gave the desired one-carbon reduction reverse ester compounds **2E** and **2Z**. Alternatively, direct acylation of the primary alcohol of **19** (*E*/*Z*) followed by removal of the protecting group gave **3E** and **3Z**, the one-carbon elongated analogues.

To synthesize the longer two-carbon extension lactone **4**, intermediate **14** underwent further transformations to give the elongated chain (**26**, Scheme 3). The primary alcohol of **26** was then protected as its MPM ether (**27**), the methyl glycoside was hydrolyzed, and the resultant secondary alcohol (**28**) was oxidized to give DAG-lactone **29**. Successive α-alkylation followed by dehydration gave **30** as a mixture of *E* and *Z* isomers, which were separated by silica gel column chromatography. The MPM ether of each isomer was then separately deprotected and acylated using octanoyl chloride. Final removal of the benzyl group of **32E** and **32Z** gave, respectively, **4E** and **4Z** as shown in Scheme 3.

Biological Results and Discussion

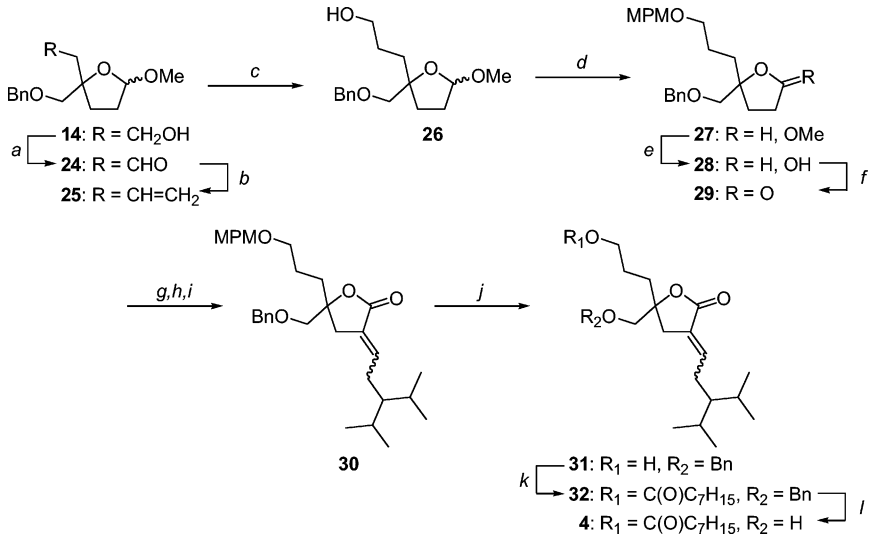
On the basis of our understanding that a DAG-lactone like **1** with a large, branched α-alkylidene chain preferentially binds in an *sn*-2 mode[21] with the *sn*-1 carbonyl devoid of a tangible contact with the C1 domain in the binary complex, isomeric compounds **2**−**4** were designed with the intent of finding the best location for this pharmacophore in a phospholipid-containing ternary complex. Compound **1** was identified in a previous study as a very potent ligand with the characteristic activity profile showing ca. 2-fold difference in binding affinity favoring the *Z* isomer (K_i = 2.3 versus 6.6 nM for the *E* isomer).[20] Because **1**−**4** are structurally similar and have identical empirical formulas and calculated log *P* values, their hydrophobicities should be similar; thus, the only variable that remains is the displacement of the *sn*-1 carbonyl along the fixed-length arm of a DAG-lactone relative to the prototype compound **1**. As already mentioned, the displacement of the *sn*-1 carbonyl along the chain is also accompanied by changes in the intramolecular web of H-bonding, which could facilitate or hinder the molecule's movement into a lipid environment and influence the binding affinity. The transposition of the ester oxygen and carbonyl in compound **2**, which brings the position of the carbonyl closer to the lactone ring, resulted in ca. 10-fold loss in binding affinity for both the *Z* and *E* isomers (Table 1). Going in the other direction, increasing the distance between the lactone and the carbonyl of the side chain by one (**3**) or two (**4**) carbons resulted in a 100- to 300-fold decrease in binding affinity. The reproducible and superior binding affinity in favor of the *Z* isomers in

Scheme 2[a]



[a] (a) NaH, THF, 0 °C, then MPMCl, Bu_4NI, Δ; (b) HCl, THF, H_2O, 0 °C to room temperature; (c) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2/CH_3CN, 0 °C to room temperature; (d) LDA, THF, $((CH_3)_2CH)_2CHCH_2CHO$, −78 °C; (e) MsCl, Et_3N, 0 °C to room temperature; (f) DBU, 0 °C to room temperature; (g) DDQ, H_2O, CH_2Cl_2; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C; (i) 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4, $(CH_3)_3COH$, H_2O; (j) *n*-$C_9H_{19}OH$, DMAP, DCC, pyridine, 0 °C to room temperature; (k) BCl_3, CH_2Cl_2, −78 °C; (l) *n*-$C_8H_{17}C(O)Cl$, pyridine, CH_2Cl_2, 0 °C.

Scheme 3[a]



[a] (a) DCC, DCAA, DMSO; then oxalic acid, Et_2O, −78 °C; (b) $MePPh_3Br$, $KOC(CH_3)_3$, THF; (c) $BH_3{\cdot}SMe_2$, THF, −78 to 0 °C, then $NaBO_3{\cdot}H_2O$, 0 °C to room temperature; (d) NaH, MPMCl, Bu_4NI, THF, Δ; (e) HCl, THF, H_2O 0 °C to room temperature; (f) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2/CH_3CN, 0 °C to room temperature; (g) $((CH_3)_2CH)_2CHCH_2CHO$, LDA, THF, −78 °C; (h) MsCl, Et_3N, 0 °C to room temperature; (i) DBU, 0 °C to room temperature; (j) DDQ, H_2O, CH_2Cl_2; (k) $CH_3(CH_2)_6C(O)Cl$, pyridine, CH_2Cl_2, 0 °C; (l) BCl_3, CH_2Cl_2, −78 °C.

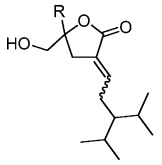
these compounds supports a common binding mode where the only variable is the displacement of the *sn*-1 carbonyl.

Although the modeling was performed with the isolated C1b domain of the δ-isozyme, the measured K_i values reflect the binding affinity of the compounds for the complete α-isozyme. In principle, both the C1a and C1b domains contain a binding pocket for phorbol/DAG. However, studies with isolated domains have shown that, with the exception of PK-Cγ, only the C1b domains of the conventional and novel PK-C isozymes bind PDBU (phorbol 12,13-dibutyrate) with comparable affinities to those of the native isozymes.[26]

Conclusions

Complementing previous work from our laboratory where we conclusively showed that each carbonyl on the DAG-lactone is an indispensable pharmacophore,[25] the present findings confirm that the location of the side

Table 1. Binding Affinities of Compounds **1**−**4**



Log P = 6.61

compd	R	K_i (nM) (*Z*-isomer)	K_i (nM) (*E* isomer)
1	$CH_2OC(O)C_9H_{19}$	2.3 ± 0.1[a]	6.6 ± 1.0[a]
2	$CH_2C(O)OC_9H_{19}$	55.7 ± 2.9	62.2 ± 7.2
3	$CH_2CH_2OC(O)C_8H_{17}$	208 ± 27	459 ± 69
4	$CH_2CH_2CH_2OC(O)C_7H_{15}$	736 ± 83	1430 ± 140

[a] From ref 20.

chain carbonyl in a DAG-lactone has to have perfect mimicry to the *sn*-1 carbonyl of the parent DAG for it to display high binding affinity. A proposed model from this work is that the missing pharmacophore in the ternary complex, which includes the membrane, is close to the membrane−protein interface. This is in agreement with the recent proposal of Newton et al. suggesting that the two C1 domains are likely to be oriented with their ligand-binding pockets facing the membrane.[27]

Experimental Section

Biological Activity. Enzyme-ligand interactions were assessed in terms of the ability of the ligand to displace bound [20-^{3}H]phorbol 12,13-dibutyrate (PDBU) from a recombinant single isozyme (PKC-α) in the presence of phosphatidylserine.[28−31] The octanol/water partition coefficients (log *P*) were calculated according to the fragment-based program KOWWIN 1.67 (http://www.epa.gov/oppt/exposure/docs/episuitedl.htm).

General Procedures. All chemical reagents were commercially available. DCAA = dichloroacetic acid; DCC = 1,3-dicyclohexylcarbodiimide; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DIBAL = diisobutylaluminum hydride; MPM = methoxyphenylmethyl; MsCl = methanesulfonyl chloride; PCC = pyridinium chlorochromate; NMO = 4-methylmorpholine *N*-oxide; TBDPSCl = *tert*-butyldiphenylsilyl chloride; TPAP = tetrapropylammonium perruthenate. Column 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 $CDCl_3$). Infrared spectra were recorded on a Perkin-Elmer 1600 series FT-IR. 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.

3-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-1-(phenylmethoxy)propan-2-ol (6). Under argon, a solution of commercially available 3-benzyloxy-1,2-propanediol (**5**, 32.5 g, 178 mmol) in CH_2Cl_2 (557 mL) was treated with imidazole (27.9 g, 410 mmol) and stirred for 85 min at room temperature. The mixture was then diluted sequentially with CH_2Cl_2 (279 mL) and DMF (279 mL), treated with *tert*-butyldiphenylsilyl chloride (53.7 mL, 207 mmol) and stirred at room temperature overnight. The reaction mixture was then diluted with Et_2O (1 L) and quenched with saturated aqueous NH_4Cl (200 mL). The organic layer was washed sequentially with H_2O and brine, dried over $MgSO_4$, and concentrated to give **6**, which was used without further purification.

3-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-1-(phenylmethoxy)acetone (7). Under argon, a solution of **6** (178 mmol) in CH_2Cl_2 (1 L) was successively treated with 4 Å molecular sieves (89 g) and PCC (154 g, 714 mmol), stirred at room temperature overnight, then heated to reflux for 2 h, cooled to room temperature, filtered through silica gel eluting with hexane/EtOAc (3:2), and concentrated. Purification by silica gel column chromatography gave **7** (46.9 g, 63% from **5**). IR (neat) 2947 (CH), 2868 (CH), 1739 (C=O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.17 (s, 9 H, $(CH_3)_3CPh_2SiOCH_2C(O)CH_2OCH_2Ph$), 4.43 (s, 4 H, $(CH_3)_3CPh_2SiOCH_2C(O)CH_2OCH_2Ph$), 4.64 (s, 2 H, $(CH_3)_3CPh_2SiOCH_2C(O)CH_2OCH_2Ph$), 7.41−7.72 (m, 15 H, $(CH_3)_3CPh_2SiOCH_2C(O)CH_2OCH_2Ph$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.22, 26.76, 68.64, 73.18, 73.34, 127.82, 127.94, 128.40, 129.96, 132.33, 134.73, 135.40, 136.97, 206.51. Anal. ($C_{26}H_{30}O_3Si\cdot0.9H_2O$) C, H.

5-[(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)methyl]-5-[(phenylmethoxy)methyl]-3,4,5-trihydrofuran-2-one (8). Under argon, allylmagnesium bromide (205 mL, 1 M solution) was added slowly to a solution of **7** (43 g, 107.7 mmol) in THF (700 mL) at 0 °C, and the mixture was stirred overnight, warming to room temperature. The resulting mixture was quenched with 1 N aqueous HCl (100 mL), and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was then taken up in THF (105 mL) under argon, cooled to −78 °C, and treated with $BH_3\cdot SMe_2$ (105 mL, 2 M solution). After 1 h, the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was concentrated and then sequentially treated with CH_2Cl_2 (1.1 L), 4 Å molecular sieves (53 g), and PCC (226 g, 1050 mmol), which was added in portions. The resulting mixture was then stirred for 2 days, after which it was filtered through silica gel eluting with hexane/EtOAc (3:2) and concentrated. Purification by silica gel column chromatography gave **8** (31.7 g, 62% for three steps). IR (neat) 3058 (CH), 2936 (CH), 2861 (CH), 1777 (C=O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.16 (s, 9 H, $(CH_3)_3CPh_2SiOCH_2C$), 2.27 (app t, J = 8.7 Hz, 2 H, lactone β-CH_2), 2.65−2.80 (m, 2 H, lactone α-CH_2), 3.66 (AB quartet, J = 10.4 Hz, 2 H, $PhCH_2OCH_2C$), 3.81 (AB quartet, J = 10.9 Hz, 2 H, $(CH_3)_3CPh_2SiOCH_2C$), 4.63 (s, 2 H, $PhCH_2OCH_2C$), 7.34−7.75 (m, 15 H, $PhCH_2OCH_2C$ and $(CH_3)_3CPh_2SiOCH_2C$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.20, 26.01, 26.72, 29.20, 66.55, 72.34, 73.61, 87.36, 127.47, 127.65, 127.72, 128.31, 129.79, 132.41, 132.64, 135.44, 135.50, 137.53, 176.93; FAB-MS (*m*/*z*, relative intensity) 475 (MH^+, 5), 91 (100). Anal. ($C_{29}H_{34}O_4Si\cdot0.25H_2O$) C, H.

5-[(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)methyl]-5-[(phenylmethoxy)methyl]oxolan-2-ol (9). Under argon, DIBAL (4.6 mL, 4.59 mmol, 1 M in THF) was added to a mixture of **8** (1.81 g, 3.82 mmol) in toluene (25 mL) at −78 °C, and the mixture was stirred for 2 h. An additional equivalent of DIBAL was added to push the reaction to completion, after which it was quenched with methanol (493 μL). The reaction mixture was diluted with CH_2Cl_2 (50 mL), and then Celite was added followed by a saturated solution of aqueous ammonium chloride (3 mL). The mixture was dried over $MgSO_4$, filtered, and concentrated to give **9** as an oil (1.6 g, 88%), which was used in the next step without further purification.

(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy){5-methoxy-2-[(phenylmethoxy)methyl]oxolan-2-yl}methane (10). Dowex 50WX8-200 (13.4 g), methanol (34 mL), and AcOH (63 mL, 80%) were added in portions to a stirring solution of **9** (crude, 1.6 g, 3.27 mmol) in THF (15 mL), and the reaction was monitored by TLC. Upon completion, the mixture was filtered, diluted with toluene, and concentrated. The resulting mixture was neutralized with $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel column chromatography (5% EtOAc in hexane) gave an anomeric mixture of **10A** (376 mg, 23%) and **10B** (406 mg, 25%) as oils. When feasible, the anomers were separated for characterization.

10A: IR (neat) 3018 (CH), 2932 (CH), 2859 (CH) 1104 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (s, 9 H, $(CH_3)_3CPh_2SiOCH_2C$), 1.86−2.15 (m, 4 H, ring-CH_2CH_2), 3.41 (s, 3 H, >$CHOCH_3$), 3.57−3.92 (m, 4 H, $PhCH_2OCH_2C$ and $(CH_3)_3CPh_2SiOCH_2C$), 4.68 (s, 2 H, $PhCH_2OCH_2C$), 5.07 (d, J = 2.9 Hz, 1 H, >$CHOCH_3$), 7.34−7.51 (m, 10 H, $(CH_3)_3CPh_2$-

SiOCH$_2$C), 7.75−7.80 (m, 5 H, *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 19.27, 26.79, 28.15, 32.11, 54.27, 65.42, 73.41, 74.24, 86.46, 105.66, 127.26, 127.46, 127.49, 128.11, 129.42, 133.35, 133.45, 135.50, 135.53, 138.36; FAB-MS (*m*/*z*, relative intensity) 459 (MH$^+$ − CH$_3$OH, 4), 91 (100). Anal. (C$_{30}$H$_{38}$O$_4$Si) C, H.

10B: IR (neat) 3017 (CH), 2932 (CH), 2860 (CH), 1102 (CO) cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 1.16 (s, 9 H, (C*H*$_3$)$_3$CPh$_2$SiOCH$_2$C), 1.95−2.10 (m, 4 H, ring-C*H*$_2$C*H*$_2$), 3.33 (s, 3 H, >CHOC*H*$_3$), 3.61−3.91 (m, 4 H, PhCH$_2$OC*H*$_2$C and (CH$_3$)$_3$CPh$_2$SiOC*H*$_2$C), 4.68 (s, 2 H, PhC*H*$_2$OCH$_2$C), 5.13 (d, J = 4.2 Hz, 1 H, >C*H*OCH$_3$), 7.37−7.51 (m, 10 H, (CH$_3$)$_3$CP*h*$_2$SiOCH$_2$C), 7.74−7.81 (m, 5 H, *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 19.31, 26.81, 28.55, 32.35, 54.32, 67.59, 72.38, 73.52, 86.44, 105.68, 127.29, 127.40, 127.47, 128.15, 129.44, 133.43, 133.45, 135.49, 135.54, 138.37; FAB-MS (*m*/*z*, relative intensity): 459 (MH$^+$ − CH$_3$OH, 7), 91 (100). Anal. (C$_{30}$H$_{38}$O$_4$Si) C, H.

{5-Methoxy-2-[(phenylmethoxy)methyl]oxolan-2-yl}methan-1-ol (11). A solution of **10** (742 mg, 1.5 mmol, mixture of anomers) in THF (15 mL) was treated with TBAF (2.3 mmol, 1.5 equiv, 1 M in THF) at 0 °C for 1 h, after which additional TBAF (2.3 mmol, 1.5 equiv, 1 M in THF) was added. After a total time of 2 h, the reaction mixture was warmed to room temperature and stirred for 1 h more. The crude reaction mixture was then concentrated in vacuo and purified by silica gel column chromatography to give an anomeric mixture of **11A** (46%) and **11B** (53%) as colorless oils. When feasible, the anomers were separated for characterization.

11A: IR (neat) 3467 (OH), 3009 (CH), 2930 (CH) 2865 (CH), 1095 (CO), 1034 (CO) cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 1.89−2.17 (m, 4 H, ring-C*H*$_2$C*H*$_2$), 3.45−3.80 (m, 4 H, PhCH$_2$OC*H*$_2$C and HOC*H*$_2$C), 3.46 (s, 3 H, >CHOC*H*$_3$), 4.63 (AB quartet, J = 12.3 Hz, 2 H, PhC*H*$_2$OCH$_2$C), 5.10 (d, J = 3.7 Hz, 1 H, >C*H*OCH$_3$), 7.34−7.43 (m, 5 H, *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 26.92, 32.61, 54.97, 66.53, 73.10, 73.49, 87.12, 105.90, 127.41, 127.53, 128.25, 137.91; FAB-MS (*m*/*z*, relative intensity): 221 (MH$^+$ − CH$_3$OH, 56), 91 (100). Anal. (C$_{14}$H$_{20}$O$_4$) C, H.

11B: IR (neat) 3587 (OH), 3016 (CH), 2925 (CH) 2867 (CH), 1098 (CO), 1035 (CO) cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 1.92−2.10 (m, 4 H, ring-C*H*$_2$C*H*$_2$), 3.38 (s, 3 H, >CHOC*H*$_3$), 3.56−3.79 (2 overlapping AB quartets, 4 H, PhCH$_2$OC*H*$_2$C and HOC*H*$_2$C), 4.65 (AB quartet, J = 12.2 Hz, 2 H, PhC*H*$_2$OCH$_2$C), 5.11 (t, J = 1.7 Hz, 1 H, >C*H*OCH$_3$), 7.34−7.43 (m, 5 H, *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 28.70, 32.46, 54.43, 66.27, 73.51, 75.09, 85.46, 105.80, 127.48, 127.54, 128.25, 137.93; FAB-MS (*m*/*z*, relative intensity) 221 (MH$^+$ − CH$_3$OH, 54), 91 (100). Anal. (C$_{14}$H$_{20}$O$_4$) C, H.

{5-Methoxy-2-[(phenylmethoxy)methyl]oxolan-2-yl}formaldehyde (12). DCC (1.10 g, 5.33 mmol) and DCAA (54.9 μL, 0.67 mmol) were added to a solution of **11** (336 mg, 1.33 mmol) in DMSO (2.7 mL) and stirred overnight. After 16 h the reaction was quenched with portions of oxalic acid (480 mg, 5.3 mmol), diluted with Et$_2$O (20 mL), and cooled to −78 °C. The resulting mixture was filtered and washed with cold Et$_2$O to remove excess DCU. The organic solution was then washed with water and brine, dried over MgSO$_4$, and concentrated to give **12** as a mixture of anomers that was used directly without further purification.

(5-Methoxy-2-vinyloxolan-2-yl)(phenylmethoxy)methane (13). According to the literature,[29,32] potassium *tert*-butoxide (2.66 mL, 2.66 mmol, 1.0 M in THF) was combined with MePPh$_3$Br (952 mg, 2.66 mmol) and stirred. After 30 min the mixture was added slowly to a solution of **12** (1.33 mmol) in THF (3.3 mL), and the resulting mixture was stirred overnight. The reaction was quenched with AcOH (0.2 mL), and the mixture was filtered and concentrated. Purification by silica gel column chromatography (EtOAc/hexane) gave an anomeric mixture of **13** (240 mg, 73%) as a colorless oil. When feasible, the anomers were separated for characterization.

One Anomer: IR (neat) 3017 (CH), 2919 (CH), 2859 (CH), 1645 (C═C), 1097 (CO), 1033 (CO) cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 1.81−2.16 (m, 4 H, ring-C*H*$_2$C*H*$_2$), 3.43 (s, 3 H, >CHOC*H*$_3$), 3.56−3.64 (m, 2 H, PhCH$_2$OC*H*$_2$C), 4.63−4.74 (m, 2 H, PhC*H*$_2$OCH$_2$C), 5.16−5.41 (m, 3 H, CCH═C*H*$_2$ and >C*H*OCH$_3$), 6.03 (dd, J = 17.1, 10.7 Hz, 1 H, CC*H*═CH$_2$), 7.35−7.43 (m, 5 H, *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 31.17, 31.37, 54.37, 73.37, 76.63, 86.14, 105.48, 113.00, 127.32, 127.45, 128.13, 138.31, 140.17; FAB-MS (*m*/*z*, relative intensity) 217 (MH$^+$ − CH$_3$OH, 19), 91 (100). Anal. (C$_{15}$H$_{20}$O$_3$) C, H.

2-{5-Methoxy-2-[(phenylmethoxy)methyl]oxolan-2-yl}ethan-1-ol (14). A solution of BH$_3$·SMe$_2$ in THF (812 μL, 1.63 mmol, 2 M solution) was added dropwise to a −78 °C solution of **13** (202 mg, 0.81 mmol) in THF (3 mL). The reaction mixture was then slowly allowed to reach 0 °C and stirred. After 17 h the reaction mixture was treated with NaBO$_3$·H$_2$O (250 mg, 1.63 mmol) at 0 °C and then stirred for 2 h, warming to room temperature. The reaction mixture was diluted with EtOAc, the organic layer was washed with water and brine, dried over MgSO$_4$, and concentrated. Purification by silica gel column chromatography (EtOAc/hexanes) gave an anomeric mixture of **14** (121 mg, 56%) as a colorless oil. IR (neat) 3504 (OH), 3017 (CH), 2931 (CH), 1097 (CO) 1034 (CO) cm^{-1}; FAB-MS (*m*/*z*, relative intensity) 235 (MH$^+$ − CH$_3$OH, 20), 91 (100). Anal. (C$_{15}$H$_{22}$O$_4$) C, H.

1-[(4-Methoxyphenyl)methoxy]-2-{5-methoxy-2-[(phenylmethoxy)methyl]oxolan-2-yl}ethane (15). According to the literature,[33] a solution of **14** (110 mg, 0.41 mmol) in THF (2 mL) was added dropwise to a 0 °C slurry of NaH (33 mg, 0.82 mmol, 60% in oil) in THF (2 mL). The reaction mixture was then heated to reflux, and *p*-methoxybenzyl chloride (141 μL) and Bu$_4$NI (30 mg) were added in sequential portions over the course of 3 days as the reaction was monitored by TLC. The reaction mixture was then cooled to 0 °C, and quenched with methanol (500 μL) followed by saturated aqueous NH$_4$Cl (10 mL). The aqueous solution was then extracted with CH$_2$Cl$_2$, dried over MgSO$_4$, and concentrated. Purification by silica gel column chromatography (hexanes/EtOAc) gave an anomeric mixture of **15** (122 mg, 77%) as an oil. IR (neat) 3017 (CH), 2931 (CH), 2862 (CH), 1097 (CO) 1036 (CO) cm^{-1}; FAB-MS (*m*/*z*, relative intensity) 387 (MH$^+$, 2), 121 (100). Anal. (C$_{23}$H$_{30}$O$_5$) C, H.

5-{2-[(4-Methoxyphenyl)methoxy]ethyl}-5-[(phenylmethoxy)methyl]oxolan-2-ol (16). According to the literature,[33] HCl (350 μL, 2 N) was added to a 0 °C solution of **15** in THF (4.7 mL) and H$_2$O (1.8 mL). After the mixture was allowed to warm to room temperature over a 5 h period, additional HCl (400 μL, 2 N) was added and the reaction mixture was stirred overnight. The reaction was then quenched with solid NaHCO$_3$ followed by H$_2$O (10 mL). The aqueous solution was extracted with CH$_2$Cl$_2$, dried over MgSO$_4$, and concentrated. Purification by silica gel column chromatography (hexane/EtOAc) gave an anomeric mixture of **16** (69 mg, 74%) as a colorless oil. IR (neat) 3419 (OH), 3010 (CH), 2956 (CH), 2865 (CH), 1093 (CO) 1035 (CO) cm^{-1}; FAB-MS (*m*/*z*, relative intensity) 371 (MH$^+$ − H$_2$, 3), 355 (MH$^+$ − H$_2$O, 6), 121 (100). Anal. (C$_{22}$H$_{28}$O$_5$) C, H.

5-{2-[(4-Methoxyphenyl)methoxy]ethyl}-5-[(phenylmethoxy)methyl]-3,4,5-trihydrofuran-2-one (17). According to the literature,[34] solid TPAP (2.2 mg, 0.006 mmol, 5 mol %) was added in one portion to a stirring mixture of **16** (46.5 mg, 0.125 mmol), NMO (21.0 mg, 0.19 mmol), and powdered 4 Å molecular sieves (55 mg heat-dried under vacuum) in CH$_2$Cl$_2$/CH$_3$CN (0.23 mL, 10% CH$_3$CN in CH$_2$Cl$_2$) at 0 °C under argon. The reaction mixture was stirred overnight and allowed to reach room temperature. The crude reaction mixture was then concentrated in vacuo, filtered through Celite (eluting with CH$_2$Cl$_2$) followed by filtration through silica gel (eluting with EtOAc), and concentrated to give **17** (38.9 mg, 84%). IR (neat) 3020 (CH), 2928 (CH), 2862 (CH), 1766 (C═O) cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 2.05−2.10 (m, 2 H, OCH$_2$C*H*$_2$C), 2.23−2.78 (m, 4 H, lactone-C*H*$_2$C*H*$_2$), 3.59−3.68 (m, 4 H, OC*H*$_2$CH$_2$C and PhCH$_2$OC*H*$_2$C), 3.89 (s, 3 H, C*H*$_3$OC$_6$H$_4$CH$_2$O), 4.47 (s, 2 H, CH$_3$OC$_6$H$_4$C*H*$_2$O), 4.55−4.67 (m, 2 H, PhC*H*$_2$OCH$_2$C), 6.92−6.97 (m, 2 H, CH$_3$OC$_6$*H*$_4$CH$_2$O), 7.26−7.43 (m, 7 H, CH$_3$OC$_6$*H*$_4$CH$_2$O and *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, CDCl$_3$)

δ 29.26, 29.41, 36.86, 55.19, 65.05, 72.77, 73.50, 74.98, 86.60, 113.70, 127.40, 127.61, 128.30, 129.16, 129.91, 137.63, 159.08, 177.11; FAB-MS (*m/z*, relative intensity) 371 (MH^+, 4), 121 (100). Anal. ($C_{22}H_{26}O_5$) C, H.

5-{2-[(4-Methoxyphenyl)methoxy]ethyl}-3-[4-methyl-3-(methylethyl)pentylidene]-5-[(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (18E/Z). Under argon, a −78 °C solution of **17** (1.0 g, 2.81 mmol) in THF (10 mL) was treated dropwise with LDA (2.0 mL, 3.93 mmol, 2 M solution in heptane/THF/ethylbenzene) and stirred for 2 h. A solution of 4-methyl-3-(methylethyl)pentanal (719 mg, 5.1 mmol) in THF (10 mL) was added dropwise maintaining the same temperature, and the reaction was monitored by TLC. The reaction was quenched with saturated aqueous NH_4Cl and then warmed to room temperature. The aqueous layer was extracted with Et_2O, washed with water, dried, and concentrated to give an oil that was then taken up in CH_2Cl_2 (20 mL) under argon and treated with MsCl (0.44 mL, 5.62 mmol) and Et_3N (1.57 mL, 11.23 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h. The reaction mixture was then cooled to 0 °C, DBU (2.1 mL, 14.0 mmol) was added, and the resultant solution was stirred at room temperature for 3 h. The crude reaction mixture was filtered through a pad of silica gel and concentrated. Purification by silica gel column chromatography gave **18E** (600 mg, 43%) and **18Z** (407 mg, 29%).

18E: IR (neat) 3022 (CH), 2961 (CH), 2873 (CH), 1746 (C=O), 1676 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90, (d, J = 6.8 Hz, 6 H, C=CHCH$_2$CH(CH(CH_3)$_2$)$_2$), 0.95 and 0.96 (d, J = 6.8 Hz, 3 H, C=CHCH$_2$CH(CH(CH_3)$_2$)$_2$), 1.29−1.32 (m, 1 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 1.75−1.93 (m, 2 H, C=CHCH$_2$-CH(CH(CH$_3$)$_2$)$_2$), 2.02−2.20 (m, 2 H, OCH$_2$CH_2C), 2.75−3.02 (m, 2 H, C=CHCH_2CH(CH(CH$_3$)$_2$)$_2$), 2.94 (s, 2 H, lactone-CH_2), 3.57 (s, 2 H, PhCH$_2$OCH_2C), 3.62−3.67 (m, 2 H, OCH_2CH$_2$C), 3.87 (s, 3 H, CH_3OC$_6$H$_4$CH$_2$O), 4.44 (s, 2 H, CH$_3$OC$_6$H$_4$CH_2O), 4.60 (app d, J = 1.7 Hz, 2 H, PhCH_2OCH$_2$C), 6.76−6.85 (m, 1 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 6.91−6.95 (m, 2 H, *Ph*CH$_2$-OCH$_2$C), 7.23−7.45 (m, 7 H, *Ph*CH$_2$OCH$_2$C and CH$_3$OC$_6$*H*$_4$-CH$_2$O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.22, 19.32, 21.47, 21.57, 28.48, 29.10, 29.15, 33.39, 36.91, 50.17, 55.16, 65.00, 72.74, 73.43, 74.39, 83.48, 113.64, 126.13, 127.37, 127.51, 128.20, 129.11, 129.98, 137.65, 141.95, 159.02, 170.42; FAB-MS (*m/z*, relative intensity) 495 (MH^+, 4), 121 (100). Anal. ($C_{31}H_{45}O_5$·H_2O) C, H.

18Z: IR (neat) 3019 (CH), 2960 (CH), 2870 (CH), 1746 (C=O), 1666 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94, 0.95, 0.98, and 0.99 (d, J = 6.8 Hz, 3 H, C=CHCH$_2$CH(CH-(CH_3)$_2$)$_2$), 1.17 (pentet, J = 5.4 Hz, 1 H, C=CHCH$_2$CH(CH-(CH$_3$)$_2$)$_2$), 1.75−1.95 (m, 2 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 2.08−2.13 (m, 2 H, OCH$_2$CH_2C), 2.78−2.86 (m, 2 H, lactone-CH_2), 2.90−2.96 (m, 2 H, C=CHCH_2CH(CH(CH$_3$)$_2$)$_2$), 3.56 (s, 2 H, PhCH$_2$OCH_2C), 3.65 (t, J = 6.3 Hz, 2 H, OCH_2CH$_2$C), 3.88 (s, 3 H, CH_3OC$_6$H$_4$CH$_2$O), 4.45 (s, 2 H, CH$_3$OC$_6$H$_4$CH_2O), 4.61 (s, 2 H, CCH$_2$OCH_2Ph), 6.22 (tt, J = 7.3, 2.0 Hz, 1 H, C=CHCH$_2$-CH(CH(CH$_3$)$_2$)$_2$), 6.88−7.00 (m, 2 H, CH$_3$OC$_6$*H*$_4$CH$_2$O), 7.25−7.48 (m, 7 H, CH$_3$OC$_6$*H*$_4$CH$_2$O and *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.38, 19.41, 21.60, 21.63, 26.13, 29.30, 36.72, 36.81, 51.13, 55.17, 65.06, 72.71, 73.42, 74.21, 82.80, 113.66, 124.09, 127.41, 127.52, 128.22, 129.09, 130.05, 137.74, 145.66, 159.03, 169.24; FAB-MS (*m/z*, relative intensity) 493 ($MH^+ - H_2$, 4), 121 (100). Anal. ($C_{31}H_{45}O_5$) C, H.

(*E*)-5-(2-Hydroxyethyl)-3-[4-methyl-3-(methylethyl)-pentylidene]-5-[(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (19E). According to the literature,[29,32] DDQ (122 mg, 0.54 mmol) was added to a stirring solution of **18E** (177 mg, 0.36 mmol) in CH_2Cl_2 (2.5 mL) and H_2O (0.50 mL). After 2.5 h, the mixture was filtered through Celite and washed with CH_2Cl_2. The organic phase was washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. Purification by chromatography gave **19E** (101 mg, 76%) as an oil. IR (neat) 3466 (OH), 3017 (CH), 2961 (CH), 2873 (CH), 1748 (C=O), 1675 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91, 0.92, 0.97, and 0.98 (d, J = 6.8 Hz, 3 H, C=CHCH$_2$CH(CH(CH_3)$_2$)$_2$), 1.25−1.35 (m, 1 H, C=CHCH$_2$CH-(CH(CH$_3$)$_2$)$_2$), 1.80−1.95 (m, 2 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 1.95 (br s, 1 H, *H*OCH$_2$CH$_2$C), 2.07−2.20 (m, 4 H, HOCH$_2$CH_2C and C=CHCH_2CH(CH(CH$_3$)$_2$)$_2$), 2.71−3.02 (m, 2 H, lactone-CH_2), 3.56 (AB quartet, J = 10.2 Hz, 2 H, PhCH$_2$OCH_2C), 3.87 (t, J = 6.0 Hz, 2 H, HOCH_2CH$_2$C), 4.64 (s, 2 H, PhCH_2OCH$_2$C), 6.80−6.90 (m, 1 H, C=CHCH$_2$CH(CHMe$_2$)$_2$), 7.34−7.44 (m, 5 H, *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.25, 19.31 21.51, 21.57, 28.58, 29.12, 29.15, 33.87 39.94, 50.20, 57.91, 73.62, 74.10, 83.49, 125.40, 127.52, 127.73, 128.32, 137.24, 142.87, 170.10; FAB-MS (*m/z*, relative intensity) 375 (MH^+, 44), 91 (100). Anal. ($C_{23}H_{34}O_4$) C, H.

(*Z*)-5-(2-Hydroxyethyl)-3-[4-methyl-3-(methylethyl)-pentylidene]-5-[(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (19Z). According to the literature,[32] DDQ (187 mg, 0.83 mmol) was added to a stirring solution of **18Z** (271 mg, 0.55 mmol) in CH_2Cl_2 (3.8 mL) and H_2O (0.77 mL). After 2 h, the mixture was filtered through Celite and washed with CH_2Cl_2. The organic phase was washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. Purification by chromatography gave **19Z** (1.88 mg, 92%) as an oil. IR (neat) 3608 (OH), 3022 (CH), 2960 (CH), 2872 (CH), 1749 (C=O), 1666 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92, 0.93, 0.97, and 0.98 (d, J = 6.8 Hz, 3 H, C=CHCH$_2$CH(CH-(CH_3)$_2$)$_2$), 1.16 (pentet, J = 5.4 Hz, 1 H, C=CHCH$_2$CH(CH-(CH$_3$)$_2$)$_2$), 1.75−1.93 (m, 2 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 2.05 (t, J = 6.1 Hz, 2 H, HOCH$_2$CH_2C), 2.43 (s, 1 H, *H*OCH$_2$CH$_2$C), 2.75−3.05 (m, 4 H, lactone-CH_2 and C=CHCH_2CH(CH-(CH$_3$)$_2$)$_2$), 3.58 (s, 2 H, PhCH$_2$OCH_2C), 3.83 (t, J = 6.1 Hz, 2 H, HOCH_2CH$_2$C), 4.63 (s, 2 H, PhCH_2OCH$_2$C), 6.15−6.30 (m, 1 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 7.35−7.41 (m, 5 H, *Ph*CH$_2$-OCH$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.36, 19.39, 21.59, 21.62, 26.18, 29.29, 37.23, 39.73, 51.10, 57.78, 73.55, 73.95, 82.92, 123.49, 127.51, 127.70, 128.30, 137.34, 146.43, 169.05; FAB-MS (*m/z*, relative intensity) 375 (MH^+, 22), 91 (100). Anal. ($C_{23}H_{34}O_4$) C, H.

(*E*)-3-[4-Methyl-3-(methylethyl)pentylidene]-5-(2-oxoethyl)-5-[(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (20E). Under argon, a solution of DMSO (107 μL) in CH_2Cl_2 (0.20 mL) was added dropwise to a −78 °C solution of oxalyl chloride (60 μL) in CH_2Cl_2 (0.70 mL). After 20 min, a solution of **19E** (172 mg, 0.46 mmol) in CH_2Cl_2 (0.20 mL) was added and the mixture was stirred at −78 °C for 1 h. Triethylamine (0.38 mL) was added dropwise, and the resulting mixture was stirred for 2 h warming to 0 °C. The reaction mixture was then again cooled to −78 °C, quenched with saturated aqueous NH_4Cl, warmed to room temperature, and extracted with Et_2O. The organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated to give **20E**, which was used directly in the next step without further purification.

(*Z*)-3-[4-Methyl-3-(methylethyl)pentylidene]-5-(2-oxoethyl)-5-[(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (20Z). Under argon, a solution of DMSO (64 μL) in CH_2Cl_2 (0.12 mL) was added dropwise to a −78 °C solution of oxalyl chloride (36 μL) in CH_2Cl_2 (0.42 mL). After 20 min, a solution of **19Z** (103 mg, 0.27 mmol) in CH_2Cl_2 (0.12 mL) was added and the mixture was stirred at −78 °C for 1 h. Triethylamine (0.23 mL) was added dropwise, and the resulting mixture was stirred for 2 h warming to 0 °C. The reaction mixture was then again cooled to −78 °C, quenched with saturated aqueous NH_4Cl, warmed to room temperature, and extracted with Et_2O. The organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated to give **20Z**, which was used directly in the next step without further purification.

(*E*)-2-{4-[4-Methyl-3-(methylethyl)pentylidene]-5-oxo-2-[(phenylmethoxy)methyl]-2-2,3-dihydrofuryl}acetic Acid (21E). Under argon, 2-methyl-2-butene (320 μL), $NaClO_2$ (67 mg, 80%), and a solution of NaH_2PO_4 (71 mg) in H_2O (460 μL) were added to a solution of **20E** (0.46 mmol) in *tert*-butyl alcohol (580 μL), and the mixture was stirred overnight at room temperature. The mixture was then concentrated, diluted with H_2O, acidified to pH 2, and extracted three times with Et_2O. The combined ethereal layers were dried over $MgSO_4$ and concentrated to give **21E**, which was used directly in the next step without further purification.

(*Z*)-2-{4-[4-Methyl-3-(methylethyl)pentylidene]-5-oxo-2-[(phenylmethoxy)methyl]-2-2,3-dihydrofuryl}acetic Acid (21Z). Under argon, 2-methyl-2-butene (192 μL), $NaClO_2$ (40 mg, 80%), and a solution of NaH_2PO_4 (43 mg) in H_2O (367 μL) were added to a solution of **20Z** (0.27 mmol) in *tert*-butyl alcohol (347 μL), and the mixture was stirred overnight at room temperature. The mixture was then concentrated, diluted with H_2O, acidified to pH 2, and extracted three times with Et_2O. The combined ethereal layers were dried over $MgSO_4$ and concentrated to give **21Z**, which was used directly in the next step without further purification.

(*E*)-Nonyl 2-{4-[4-Methyl-3-(methylethyl)pentylidene]-5-oxo-2-[(phenylmethoxy)methyl]-2-2,3-dihydrofuryl}-acetate (22E). Under argon, 1-nonanol (400 μL), DMAP (5.60 mg), and DCC (472 mg) were added to a 0 °C solution of **21E** (0.458 mmol) in pyridine (1 mL), and the mixture was stirred overnight warming to room temperature. The crude reaction mixture was filtered through Celite and concentrated. Purification by silica gel column chromatography gave **22E** (110 mg, 47% for three steps from **19E**) as a colorless oil. IR (neat) 3020 (CH), 2959 (CH), 2930 (CH), 2858 (CH), 1751 (C=O), 1676 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90−0.99 (m, 15 H, C=CHCH$_2$CH(CH(CH_3)$_2$)$_2$ and CH_3(CH$_2$)$_6$CH$_2$CH$_2$OC(O)CH$_2$C), 1.23−1.45 (m, 13 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$ and CH$_3$(CH_2)$_6$CH$_2$CH$_2$OC(O)CH$_2$C), 1.58−1.74 (m, 2 H, CH$_3$(CH$_2$)$_6$CH_2CH$_2$OC(O)CH$_2$C), 1.75−1.94 (m, 2 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 2.15−2.20 (m, 2 H, C=CHCH_2CH(CH(CH$_3$)$_2$)$_2$), 2.88 (AB quartet, J = 15.9 Hz, 2 H, CH$_3$(CH$_2$)$_6$CH$_2$CH$_2$OC(O)CH_2C, 2.98 (br s, 2 H, lactone-CH_2), 3.65 (s, 2 H, PhCH$_2$OCH_2C), 4.12 (t, J = 6.8 Hz, 2 H, CH$_3$(CH$_2$)$_6$CH$_2$CH_2OC(O)CH$_2$C), 4.63 (s, 2 H, PhCH_2OCH$_2$C), 6.80−6.89 (m, 1 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 7.35−7.41 (m, 5 H, *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.06, 19.23 19.33, 21.49, 21.58, 22.60, 25.81, 28.40, 28.55, 29.10, 29.17, 29.39, 31.77, 32.89, 41.03, 50.19, 65.00, 73.52, 74.21, 81.49, 125.46, 127.41, 127.61, 128.24, 137.43, 142.56, 169.13, 169.78; FAB-MS (*m*/*z*, relative intensity) 515 (MH^+, 18), 91 (100). Anal. ($C_{32}H_{50}O_5$) C, H.

(*Z*)-Nonyl 2-{4-[4-Methyl-3-(methylethyl)pentylidene]-5-oxo-2-[(phenylmethoxy)methyl]-2-2,3-dihydrofuryl}-acetate (22Z). Under argon, 1-nonanol (239 μL), DMAP (3.35 mg), and DCC (283 mg) were added to a 0 °C solution of **21Z** (0.274 mmol) in pyridine (0.6 mL), and the mixture was stirred overnight warming to room temperature. The crude reaction mixture was filtered through Celite and concentrated. Purification by silica gel column chromatography gave **22Z** (79 mg, 56% for three steps from **19Z**) as a colorless oil. IR (neat) 3024 (CH), 2959 (CH), 2929 (CH), 2858 (CH), 1750 (C=O), 1666 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92−1.00 (m, 15 H, C=CHCH$_2$CH(CH(CH_3)$_2$)$_2$ and CH_3(CH$_2$)$_6$CH$_2$CH$_2$OC(O)CH$_2$C), 1.12−1.24 (m, 1 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 1.30−1.45 (br s, 14 H, CH$_3$(CH_2)$_6$CH_2CH$_2$OC(O)CH$_2$C), 1.60−1.75 (m, 2 H, C=CHCH_2CH(CH(CH$_3$)$_2$)$_2$), 1.77−1.94 (m, 2 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 2.63−3.17 (m, 4 H, CH$_3$(CH$_2$)$_6$CH$_2$CH$_2$OC(O)CH_2C and lactone-CH_2), 3.64 (s, 2 H, PhCH$_2$OCH_2C), 4.12 (t, J = 6.7 Hz, 2 H, CH$_3$(CH$_2$)$_6$CH$_2$CH_2OC(O)CH$_2$C), 4.64 (s, 2 H, PhCH_2OCH$_2$C), 6.22−6.31 (m, 1 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 7.35−7.41 (m, 5 H, *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.06, 19.34 19.42, 21.56, 21.64, 22.61, 25.81, 26.16, 28.41, 29.17, 29.27, 29.31, 29.40, 31.78, 36.25, 40.89, 51.11, 64.94, 73.50, 74.00, 80.92, 123.30, 127.42, 127.59, 128.24, 137.51, 146.40, 168.58, 169.19; FAB-MS (*m*/*z*, relative intensity) 515 (MH^+, 29), 91 (100). Anal. ($C_{32}H_{50}O_5$) C, H.

(*E*)-Nonyl 2-{2-(Hydroxymethyl)-4-[4-methyl-3-(methylethyl)pentylidene]-5-oxo-2-2,3-dihydrofuryl}acetate (2E). Under argon, BCl_3 (132 μL, 1 M in CH_2Cl_2) was added slowly to a −78 °C solution of **22E** (34.0 mg, 0.07 mmol) in CH_2Cl_2 (1.3 mL), and the mixture was stirred for 2 h. Buffer solution (pH 7.2) was then added slowly, and the reaction mixture was diluted with Et_2O. The layers were separated, the aqueous layer was further extracted twice with $CHCl_3$, and the combined organics were dried over $MgSO_4$. Purification by silica gel column chromatography gave **2E** (26.2 mg, 93%). IR (neat) 3422 (OH), 3021 (CH), 2960 (CH), 2929 (CH), 2857 (CH), 1751 (C=O), 1674 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91−1.00 (m, 15 H, C=CHCH$_2$CH(CH(CH_3)$_2$)$_2$ and CH_3(CH$_2$)$_6$CH$_2$CH$_2$OC(O)CH$_2$C), 1.24−1.45 (m, 13 H, C=CH-CH$_2$CH(CH(CH$_3$)$_2$)$_2$ and CH$_3$(CH_2)$_6$CH$_2$CH$_2$OC(O)CH$_2$C), 1.61−1.76 (m, 2 H, CH$_3$(CH$_2$)$_6$CH_2CH$_2$OC(O)CH$_2$C), 1.77−1.96 (m, 2 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 2.14−2.26 (m, 2 H, lactone-CH_2), 2.40 (br s, 1 H, *H*OCH$_2$C), 2.84 (d, J = 15.9 Hz, 2 H, C=CHCH_2CH(CH(CH$_3$)$_2$)$_2$), 2.90−3.00 (m, 2 H, CH$_3$(CH$_2$)$_6$CH$_2$-CH$_2$OC(O)CH_2C), 3.79 (AB quartet, J = 12.2 Hz, 2 H, HOCH_2C), 4.15 (t, J = 6.8 Hz, 2 H, CH$_3$(CH$_2$)$_6$CH$_2$CH_2OC(O)-CH$_2$C), 6.83−6.92 (m, 1 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.05, 19.26 19.30, 21.55, 22.59, 25.80, 28.39, 28.62, 29.15, 29.38, 31.77, 32.16, 40.47, 50.22, 65.18, 67.23, 82.52, 125.14, 143.56, 169.32, 169.82; FAB-MS (*m*/*z*, relative intensity) 425 (MH^+, 100). Anal. ($C_{25}H_{44}O_5$) C, H.

(*Z*)-Nonyl 2-{2-(Hydroxymethyl)-4-[4-methyl-3-(methylethyl)pentylidene]-5-oxo-2-2,3-dihydrofuryl}acetate (2Z). Under argon, BCl_3 (223 μL, 1 M in CH_2Cl_2) was added slowly to a −78 °C solution of **22Z** (57.4 mg, 0.11 mmol) in CH_2Cl_2 (2.0 mL), and the mixture was stirred for 2 h. Buffer solution (pH 7.2) was then added slowly, and the reaction mixture was diluted with Et_2O. The layers were separated, the aqueous layer was further extracted twice with $CHCl_3$, and the combined organics were dried over $MgSO_4$. Purification by silica gel column chromatography gave **2Z** (42.1 mg, 89%). IR (neat) 3432 (OH), 3022 (CH), 2959 (CH), 2929 (CH), 2857 (CH), 1749 (C=O), 1665 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92−0.99 (m, 15 H, C=CHCH$_2$CH(CH(CH_3)$_2$)$_2$ and CH_3(CH$_2$)$_6$CH$_2$CH$_2$OC(O)CH$_2$C), 1.14−1.23 (m, 1 H, C=CHCH$_2$-CH(CH(CH$_3$)$_2$)$_2$), 1.27−1.45 (m, 12 H, CH$_3$(CH_2)$_6$CH$_2$CH$_2$OC-(O)CH$_2$C), 1.61−1.75 (m, 2 H, CH$_3$(CH$_2$)$_6$CH_2CH$_2$OC(O)CH$_2$C), 1.76−1.94 (m, 2 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 2.37 (br s, 1 H, *H*OCH$_2$C), 2.74−2.94 (m, 4 H, C=CHCH_2CH(CH(CH$_3$)$_2$)$_2$ and lactone-CH_2), 2.99−3.00 (m, 2H, CH$_3$(CH$_2$)$_6$CH$_2$CH$_2$OC-(O)CH_2C), 3.77 (AB quartet, J = 12.1 Hz, 2 H, HOCH_2C), 4.14 (t, J = 6.7 Hz, 2 H, CH$_3$(CH$_2$)$_6$CH$_2$CH_2OC(O)CH$_2$C), 6.31 (tt, J = 7.4, 2.2 Hz, 1 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.03, 19.34 19.39, 21.55, 21.60, 22.59, 25.78, 26.25, 28.40, 29.14, 29.26, 29.30, 29.38, 31.76, 35.48, 40.39, 51.09, 65.13, 67.00, 81.88, 123.01, 147.34, 168.57, 169.38; FAB-MS (*m*/*z*, relative intensity) 425 (MH^+, 100). Anal. ($C_{25}H_{44}O_5$) C, H.

(*E*)-2-{4-[4-Methyl-3-(methylethyl)pentylidene]-5-oxo-2-[(phenylmethoxy)methyl]-2-2,3-dihydrofuryl}ethyl Nonanoate (23E). According to the literature,[20] nonanoyl chloride (166 mg, 0.94 mmol) was added to a 0 °C stirring solution of **19E** (87.7 mg, 0.23 mmol) and pyridine (76 μL, 0.94 mmol) in CH_2Cl_2 (5 mL) under argon. The reaction was monitored by TLC, and then the mixture was concentrated in vacuo. Purification by silica gel column chromatography gave **23E** (54 mg, 45%). IR (neat) 3026 (CH), 2959 (CH), 2929 (CH), 2858 (CH), 1747 (C=O), 1676 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90−0.99 (m, 15 H, C=CHCH$_2$CH(CH(CH_3)$_2$)$_2$ and CH_3(CH$_2$)$_5$CH$_2$CH$_2$C(O)), 1.20−1.48 (m, 11 H, C=CHCH$_2$-CH(CH(CH$_3$)$_2$)$_2$ and CH$_3$(CH_2)$_5$CH$_2$CH$_2$C(O)), 1.60−1.77 (m, 2 H, CH$_3$(CH$_2$)$_5$CH_2CH$_2$C(O)), 1.78−1.93 (m, 1 H, C=CHCH$_2$-CH(CH(CH$_3$)$_2$)$_2$), 2.05−2.25 (m, 3 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$ and OCH$_2$CH_2C), 2.30−2.37 (m, 2 H, C=CHCH_2CH(CH-(CH$_3$)$_2$)$_2$), 2.43 (t, J = 7.6 Hz, 2 H, CH$_3$(CH$_2$)$_5$CH$_2$CH_2C(O)), 2.86 (br AB quartet, J = 17.0 Hz, 2 H lactone-CH_2), 3.56 (s, 2 H, PhCH$_2$OCH_2C), 4.28 (t, J = 6.8 Hz, 2 H, OCH_2CH$_2$C), 4.63 (s, 2 H, PhCH_2OCH$_2$C), 6.80−6.89 (m, 1 H, C=CHCH$_2$CH(CH-(CH$_3$)$_2$)$_2$), 7.34−7.43 (m, 5 H, *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.03, 19.24, 19.32, 21.49, 21.57, 22.57, 24.80, 28.57, 29.05, 29.07, 29.11, 29.14, 31.73, 33.29, 34.20, 35.82, 50.19, 59.33, 73.55, 74.02, 82.69, 125.45, 127.44, 127.66, 128.28, 137.38, 142.70, 169.98, 173.39; FAB-MS (*m*/*z*, relative intensity) 515 (MH^+, 22), 91 (100). Anal. ($C_{32}H_{50}O_5 \cdot 0.2H_2O$) C, H.

(*Z*)-2-{4-[4-Methyl-3-(methylethyl)pentylidene]-5-oxo-2-[(phenylmethoxy)methyl]-2-2,3-dihydrofuryl}ethyl Nonanoate (23Z). According to the literature,[20] nonanoyl chloride (141 mg, 0.80 mmol) was added to a 0 °C stirring

solution of **19Z** (75 mg, 0.20 mmol) and pyridine (65 μL, 0.80 mmol) in CH_2Cl_2 (4 mL) under argon. The reaction was monitored by TLC, and then the mixture was concentrated in vacuo. Purification by silica gel column chromatography gave **23Z** (76 mg, 74%). IR (neat) 3021 (CH), 2959 (CH), 2929 (CH), 2859 (CH), 1745 (C═O), 1666 (C═C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91−1.00 (m, 15 H, C═CHCH$_2$CH(CH(CH_3)$_2$)$_2$ and CH_3(CH$_2$)$_5$CH$_2$CH$_2$C(O)), 1.14−1.19 (m, 1 H, C═CHCH$_2$C*H*(CH-(CH$_3$)$_2$)$_2$), 1.35 (br s, 10 H, CH$_3$(CH_2)$_5$CH$_2$CH$_2$C(O)), 1.57−1.75 (m, 2 H, CH$_3$(CH$_2$)$_5$CH_2CH$_2$C(O)), 1.76−1.94 (m, 2 H, C═CH-CH$_2$CH(C*H*(CH$_3$)$_2$)$_2$), 2.0−2.25 (m, 2 H, OCH$_2$CH_2C), 2.30−2.36 (m, 2 H, CH$_3$(CH$_2$)$_5$CH$_2$CH_2C(O)), 2.77−3.05 (m, 4 H, lactone-CH_2 and C═CHCH_2CH(CH(CH$_3$)$_2$)$_2$), 3.54 (s, 2 H, PhCH$_2$-OCH_2C), 4.24−4.30 (m, 2 H, OCH_2CH$_2$C), 4.62 (s, 2 H, PhCH_2OCH$_2$C), 6.29−6.40 (m, 1 H, C═C*H*CH$_2$CH(CH(CH$_3$)$_2$)$_2$), 7.36−7.41 (m, 5 H, *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.03, 19.34, 19.38, 21.57, 21.60, 22.57, 24.79, 26.17, 29.04, 29.06, 29.14, 29.29, 31.73, 34.19, 35.61, 36.72, 51.12, 59.38, 73.50, 73.86, 82.02, 123.46, 127.44, 127.64, 128.27, 137.45, 146.34, 168.80, 173.38; FAB-MS (*m*/*z*, relative intensity) 515 (MH^+, 23), 91 (100). Anal. ($C_{32}H_{50}O_5$·0.3H_2O) C, H.

(*E*)-2-{2-(Hydroxymethyl)-4-[4-methyl-3-(methylethyl)-pentylidene]-5-oxo-2,3-dihydrofuryl}ethyl Nonanoate (3E). Under argon, a solution of BCl_3 (0.21 mL, 0.21 mmol, 1 M in CH_2Cl_2) was added slowly to a −78 °C solution of **23E** (54 mg, 0.11 mmol) in CH_2Cl_2 (2 mL). The reaction was monitored by TLC and quenched slowly at −78 °C with pH 7.2 buffer solution, and the mixture was then diluted with Et_2O. The organic layer was washed with pH 7.2 buffer, dried, and concentrated. Purification by chromatography gave **3E** (33 mg, 73%). IR (neat) 3595 (OH), 3432 (OH), 3023 (CH), 2960 (CH), 2930 (CH), 2872 (CH), 1746 (C═O), 1674 (C═C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92−1.00 (m, 15 H, C═CHCH$_2$-CH(CH(CH_3)$_2$)$_2$ and CH_3(CH$_2$)$_5$CH$_2$CH$_2$C(O)), 1.25−1.35 (m, 11 H, CH$_3$(CH_2)$_5$CH$_2$CH$_2$C(O) and C═CHCH$_2$C*H*(CH(CH$_3$)$_2$)$_2$), 1.62−1.71 (m, 2 H, CH$_3$(CH$_2$)$_5$CH_2CH$_2$C(O)), 1.80−1.93 (m, 2 H, C═CHCH$_2$CH(C*H*(CH$_3$)$_2$)$_2$), 2.05−2.26 (m, 5 H, OCH$_2$CH_2C, C═CHCH_2CH(CH(CH$_3$)$_2$)$_2$ and *H*OCH$_2$C), 2.36 (t, J = 7.6 Hz, 2 H, CH$_3$(CH$_2$)$_5$CH$_2$CH_2C(O)), 2.86 (br AB quartet, J = 17.3 Hz, 2 H lactone-CH_2), 3.72 (AB quartet, J = 12.1 Hz, 2 H, HOCH_2C), 4.29 (t, J = 6.6 Hz, 2 H, OCH_2CH$_2$C), 6.84−6.93 (m, 1 H, C═C*H*CH$_2$CH(CH(CH$_3$)$_2$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.03, 19.27, 19.30, 21.55, 22.57, 24.79, 28.65, 29.04, 29.07, 29.14, 29.17, 31.73, 32.35, 34.19, 35.22, 50.24, 59.29, 67.09, 83.73, 125.21, 143.56, 169.93, 173.37; FAB-MS (*m*/*z*, relative intensity) 425 (MH^+, 55), 57 (100). Anal. ($C_{25}H_{44}O_5$) C, H.

(*Z*)-2-{2-(Hydroxymethyl)-4-[4-methyl-3-(methylethyl)-pentylidene]-5-oxo-2,3-dihydrofuryl}ethyl Nonanoate (3Z). Under argon, a solution of BCl_3 (0.30 mL, 0.30 mmol, 1 M in CH_2Cl_2) was added slowly to a −78 °C solution of **23Z** (76 mg, 0.15 mmol) in CH_2Cl_2 (3 mL). The reaction was monitored by TLC and quenched slowly at −78 °C with pH 7.2 buffer solution, and then the mixture was diluted with Et_2O. The organic layer was washed with pH 7.2 buffer, dried, and concentrated. Purification by chromatography gave **3Z** (42 mg, 66%). IR (neat) 3594 (OH), 3432 (OH), 3025 (CH), 2959 (CH), 2929 (CH), 2858 (CH), 1744 (C═O), 1664 (C═C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92−0.99 (m, 15 H, C═CHCH$_2$-CH(CH(CH_3)$_2$)$_2$ and CH_3(CH$_2$)$_5$CH$_2$CH$_2$C(O)), 1.13−1.22 (m, 1 H, C═CHCH$_2$C*H*(CH(CH$_3$)$_2$)$_2$), 1.33−1.35 (m, 10 H, CH$_3$(CH_2)$_5$-CH$_2$CH$_2$C(O)), 1.62−1.73 (m, 2 H, CH$_3$(CH$_2$)$_5$CH_2CH$_2$C(O)), 1.76−1.94 (m, 2 H, C═CHCH$_2$CH(C*H*(CH$_3$)$_2$)$_2$), 2.02−2.22 (m, 3 H, OCH$_2$CH_2C and *H*OCH$_2$C), 2.33−2.38 (m, 2 H, CH$_3$(CH$_2$)$_5$-CH$_2$CH_2C(O)), 2.76−3.03 (m, 4 H, C═CHCH_2CH(CH(CH$_3$)$_2$)$_2$ and lactone-CH_2), 3.69 (AB quartet, J = 12.2 Hz, 2 H, HOCH_2C), 4.28 (t, J = 6.6 Hz, 2 H, OCH_2CH$_2$C), 6.28−6.34 (m, 1 H, C═C*H*CH$_2$CH(CH(CH$_3$)$_2$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.01, 19.36, 21.57, 22.55, 24.78, 26.26, 29.03, 29.05, 29.12, 29.29, 31.72, 34.19, 34.99, 35.70, 51.12, 59.34, 66.86, 83.10, 123.24, 147.21, 168.82, 173.39; FAB-MS (*m*/*z*, relative intensity) 425 (MH^+, 46), 57 (100). Anal. ($C_{25}H_{44}O_5$) C, H.

2-{5-Methoxy-2-[(phenylmethoxy)methyl]oxolan-2-yl}-ethanal (24). DCC (1.02 g, 4.96 mmol) and DCAA (51.1 μL, 0.62 mmol) were added to a solution of **14** (330 mg, 1.24 mmol) in DMSO (2.5 mL), and the mixture was stirred overnight. After 16 h, the reaction was quenched with portions of oxalic acid (447 mg, 4.96 mmol) and the mixture was diluted with Et_2O (20 mL) and cooled to −78 °C. The resulting mixture was filtered and washed with cold Et_2O to remove excess DCU. The organic solution was then washed with water and brine, dried over $MgSO_4$, and concentrated to give crude **24**, which was used directly without further purification.

(5-Methoxy-2-prop-2-enyloxolan-2-yl)(phenylmethoxy)-methane (25). According to the literature,[29] $MePPh_3Br$ (886 mg, 2.48 mmol) was added to potassium *tert*-butoxide (2.48 mL, 2.48 mmol, 1.0 M in THF). After 30 min, the mixture was added slowly to a solution of **24** (1.24 mmol) in THF (3.1 mL), and the resulting mixture was stirred overnight. The reaction was quenched with AcOH (0.2 mL), filtered and concentrated. Purification by silica gel column chromatography (EtOAc/hexane) gave an anomeric mixture of **25** (150 mg, 46%). When feasible, the anomers were separated for characterization.

One Anomer: IR (neat) 3010 (CH), 2913 (CH), 2860 (CH), 1640 (C═C), 1098 (CO), 1037 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.84−2.13 (m, 4 H, lactone-CH_2CH_2), 2.45−2.49 (m, 2 H, CH$_2$═CHCH_2C), 3.38 (s, 3 H, >CHOCH_3), 3.51 (AB quartet, J = 9.3 Hz, 2 H, PhCH$_2$OCH_2C), 4.61−4.72 (m, 2 H, PhCH_2OCH$_2$C), 5.07−5.21 (m, 3 H, >C*H*OCH$_3$ and CH_2═CH-CH$_2$C), 5.82−5.93 (m, 1 H, CH$_2$═C*H*CH$_2$C), 7.35−7.44 (m, 5 H, *Ph*CH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.98, 32.38, 41.34, 54.25, 73.35, 76.54, 85.70, 105.59, 117.76, 127.33, 127.49, 128.13, 134.02, 138.36; FAB-MS (*m*/*z*, relative intensity) 231 (MH^+ − CH_3OH, 51), 91 (100). Anal. ($C_{16}H_{22}O_3$) C, H.

3-{5-Methoxy-2-[phenylmethoxy)methyl]oxolan-2-yl}-propan-1-ol (26). According to the literature,[29] a solution of BH_3·SMe_2 in THF (482 μL, 0.96 mmol, 2 M solution) was added dropwise to a −78 °C stirring solution of **25** (127 mg, 0.48 mmol) in THF (1.5 mL). The reaction mixture was slowly allowed to reach 0 °C, and after 17 h, it was treated with $NaBO_3$·H_2O (148 mg, 0.96 mmol) at 0 °C. The reaction mixture then stirred for 2 h warming to room temperature and was diluted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. Purification by silica gel column chromatography (EtOAc/hexane) gave an anomeric mixture of **26** (89 mg, 66%). IR (neat) 3446 (OH), 3012 (CH), 2952 (CH), 1098 (CO), 1037 (CO) cm^{-1}; FAB-MS (*m*/*z*, relative intensity) 249 (MH^+ − CH_3OH, 27), 91 (100). Anal. ($C_{16}H_{24}O_4$) C, H.

1-[(4-Methoxyphenyl)methoxy]-3-{5-methoxy-2-[(phenylmethoxy)methyl]oxolan-2-yl}propane (27). According to the literature,[33] a solution of **26** (79 mg, 0.28 mmol) in THF (3 mL) was added dropwise to a 0 °C slurry of NaH (23 mg, 0.56 mmol, 60% in oil) in THF (2 mL), followed by addition of *p*-methoxybenzyl chloride (42 μL, 0.31 mmol) and Bu_4NI (10 mg). The reaction mixture was then heated to reflux and monitored by TLC. Upon completion, the reaction was cooled to 0 °C and quenched with methanol (500 μL), followed by saturated aqueous NH_4Cl (10 mL). The aqueous solution was then extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. Purification by silica gel column chromatography (hexanes/EtOAc) gave an anomeric mixture of **27** (90 mg, 80%). IR (neat) 3015 (CH), 2954 (CH), 2861 (CH), 1097 (CO), 1036 (CO) cm^{-1}; FAB-MS (*m*/*z*, relative intensity) 369 (MH^+ − CH_3OH, 9), 121 (100). Anal. ($C_{24}H_{32}O_5$) C, H.

5-{3-[(4-Methoxyphenyl)methoxy]propyl}-5-[(phenylmethoxy)methyl]oxolan-2-ol{5-methoxy-2-[(phenylmethoxy)methyl]oxolan-2-yl}propane (28). According to the literature,[33] HCl (1.4 mL, 2 N) was added to a solution of **27** (389 mg, 0.97 mmol) in THF (18.3 mL) and H_2O (7.03 mL) at 0 °C. After the mixture was allowed to warm to room temperature over a 5 h period, additional HCl (1.5 mL) was added and the reaction mixture was stirred overnight. The reaction was quenched with solid $NaHCO_3$ followed by H_2O. The aqueous solution was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. Silica gel column chromatography

(hexane/EtOAc) gave an anomeric mixture of **28** (173 mg, 46%), which was used without further purification.

5-{3-[(4-Methoxyphenyl)methoxy]propyl}-5-[(phenylmethoxy)methyl]-3,4,5-trihydrofuran-2-one (29). According to the literature,[34] solid TPAP (7.6 mg, 0.022 mmol, 5 mol %) was added in one portion to a stirring mixture of **28** (167 mg, 0.43 mmol), NMO (75.7 mg, 0.65 mmol), and powdered 4 Å molecular sieves (190 mg heat-dried under vacuum) in CH_2Cl_2/CH_3CN (0.8 mL, 10% CH_3CN in CH_2Cl_2) at 0 °C under argon. The reaction mixture was stirred overnight and allowed to reach room temperature. The crude reaction mixture was then concentrated in vacuo, filtered through Celite (eluting with CH_2Cl_2) followed by filtration through silica gel (eluting with EtOAc), and concentrated to give **29** (147 mg, 89%). IR (neat) 3020 (CH), 2931 (CH), 2861 (CH), 1766 (C=O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.71−1.89 (m, 3 H, OCH_2CH_2-$CHHC$), 1.99−2.12 (m, 2 H, OCH_2CH_2CHHC and lactone-$CHHCH_2$), 2.30−2.39 (m, 1 H, lactone-$CHHCH_2$), 2.51−2.62 (m, 1 H, lactone-CH_2CHH), 2.72−2.84 (m, 1 H, lactone-CH_2-CHH), 3.50−3.64 (m, 4 H, $OCH_2CH_2CH_2C$ and $PhCH_2OCH_2C$), 3.87 (s, 3 H, $CH_3OC_6H_4CH_2O$), 4.50 (s, 2 H, $CH_3OC_6H_4CH_2O$), 4.61 (br AB quartet, J = 12.0 Hz, 2 H, $PhCH_2OCH_2C$), 6.94−6.98 (d, J = 8.8 Hz, 2 H, $CH_3OC_6H_4CH_2O$), 7.31−7.45 (m, 7 H, $PhCH_2OCH_2C$ and $CH_3OC_6H_4CH_2O$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 23.64, 28.78, 29.52, 33.76, 55.18, 69.56, 72.48, 73.51, 74.66, 87.23, 113.67, 127.40, 127.64, 128.32, 129.09, 130.32, 137.61, 159.02, 177.02; FAB-MS (*m*/*z*, relative intensity) 385 (MH^+, 7), 121 (100). Anal. ($C_{23}H_{28}O_5$) C, H.

5-{3-[(4-Methoxyphenyl)methoxy]propyl}-3-[4-methyl-3-(methylethyl)pentylidene]-5-[(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (30E/Z). Under argon, a −78 °C solution of **29** (142 mg, 0.37 mmol) in THF (1.4 mL) was treated dropwise with LDA (0.26 mL, 0.52 mmol, 2 M solution in heptane/THF/ethylbenzene) and stirred for 2 h. A solution of 4-methyl-3-(methylethyl)pentanal (95 mg, 0.67 mmol) in THF (0.3 mL) was added dropwise maintaining the same temperature and the reaction was monitored by TLC. The reaction mixture was quenched with saturated aqueous NH_4Cl, and then warmed to room temperature. The aqueous layer was extracted with Et_2O, washed with water, dried, and concentrated. The residue was then taken up in CH_2Cl_2 (3.5 mL) under argon, cooled to 0 °C, treated sequentially with MsCl (0.57 μL, 0.74 mmol) and Et_3N (206 μL, 1.48 mmol), and stirred at 0 °C for 30 min and then at room temperature for 2 h. The reaction was then cooled again to 0 °C, DBU (277 μL, 1.85 mmol) was added, and the resultant solution was stirred at room temperature for 3 h. The crude reaction mixture was filtered through a pad of silica gel and concentrated. Purification by silica gel column chromatography gave **30E** (58 mg, 31%) and **30Z** (58 mg, 31%).

30E: IR (neat) 3020 (CH), 2959 (CH), 2930 (CH), 2870 (CH), 1745 (C=O), 1675 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90−0.99 (m, 12 H, $C=CHCH_2CH(CH(CH_3)_2)_2$), 1.25−1.42 (m, 1 H, $C=CHCH_2CH(CH(CH_3)_2)_2$), 1.64−1.89 (m, 6 H, $C=CHCH_2$-$CH(CH(CH_3)_2)_2$ and $OCH_2CH_2CH_2C$), 2.13−2.19 (m, 2 H, $C=CHCH_2CH(CH(CH_3)_2)_2$), 2.80 (br AB quartet, J = 17.0 Hz, 2 H, lactone-CH_2), 3.50−3.55 (m, 2 H, $OCH_2CH_2CH_2C$), 3.55 (s, 2 H, $PhCH_2OCH_2C$), 3.89 (s, 3 H, $CH_3OC_6H_4CH_2O$), 4.49 (s, 2 H, $CH_3OC_6H_4CH_2O$), 4.56−4.70 (m, 2 H, $PhCH_2OCH_2C$), 6.78−6.86 (m, 1 H, $C=CHCH_2CH(CH(CH_3)_2)_2$), 6.95 (d, J = 8.8 Hz, 2 H, $CH_3OC_6H_4CH_2O$), 7.34−4.41 (m, 7 H, $PhCH_2$-OCH_2C and $CH_3OC_6H_4CH_2O$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.25, 19.32, 21.50, 21.57, 23.31, 28.51, 29.12, 29.14, 32.90, 33.92, 50.18, 55.19, 69.57, 72.43, 73.49, 74.09, 84.11, 113.64, 126.12, 127.40, 127.56, 128.23, 129.06, 130.32, 137.61, 142.11, 158.99, 170.42; FAB-MS (*m*/*z*, relative intensity) 509.5 (MH^+, 3), 121 (100). Anal. ($C_{32}H_{44}O_5 \cdot 0.3H_2O$) C, H.

30Z: IR (neat) 3015 (CH), 2959 (CH), 2931 (CH), 2870 (CH), 1745 (C=O), 1665 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92−1.0 (m, 12 H, $C=CHCH_2CH(CH(CH_3)_2)_2$), 1.09−1.23 (m, 1 H $C=CHCH_2CH(CH(CH_3)_2)_2$), 1.65−1.94 (m, 6 H, $C=CHCH_2$-$CH(CH(CH_3)_2)_2$ and $OCH_2CH_2CH_2C$), 2.62−3.03 (m, 4 H, $C=CHCH_2CH(CH(CH_3)_2)_2$ and lactone-CH_2), 3.49−3.54 (m, 4 H, $PhCH_2OCH_2C$ and $OCH_2CH_2CH_2C$), 3.89 (s, 3 H, CH_3-$OC_6H_4CH_2O$), 4.49 (s, 2 H, $CH_3OC_6H_4CH_2O$), 4.62 (s, 2 H, $PhCH_2OCH_2C$), 6.16−6.26 (m, 1 H, $C=CHCH_2CH(CH(CH_3)_2)_2$), 6.95 (d, J = 8.5 Hz, 2 H, $CH_3OC_6H_4CH_2O$), 7.30−7.41 (m, 7 H, $PhCH_2OCH_2C$ and $CH_3OC_6H_4CH_2O$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.37, 21.59, 23.38, 26.13, 29.29, 33.68, 36.31, 51.15, 55.19, 69.65, 72.43, 73.46, 73.95, 83.37, 113.63, 124.10, 127.42, 127.54, 128.23, 129.06, 130.43, 137.69, 145.80, 158.97, 169.27; FAB-MS (*m*/*z*, relative intensity) 507.5 ($MH^+ - H_2$, 3), 121 (100). Anal. ($C_{32}H_{44}O_5$) C, H.

(*E*)-5-(3-Hydroxypropyl)-3-[4-methyl-3-(methylethyl)-pentylidene]-5-[(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (31E). According to the literature procedure,[32] DDQ (31 mg, 0.14 mmol) was added to a stirring solution of **30E** (47 mg, 0.09 mmol) in CH_2Cl_2 (0.64 mL) and H_2O (0.13 mL). After 2.5 h, the mixture was filtered through Celite rinsing with CH_2Cl_2. The organic phase was washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. Purification by silica gel column chromatography gave **31E** (31 mg, 88%). IR (neat) 3464 (OH), 3021 (CH), 2959 (CH), 2928 (CH), 2856 (CH), 1746 (C=O), 1675 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91, 0.92, 0.97, and 0.98 (d, J = 6.8 Hz, 3 H, $C=CHCH_2CH(CH(CH_3)_2)_2$), 1.21−1.40 (m, 1 H, $C=CHCH_2$-$CH(CH(CH_3)_2)_2$), 1.60−2.02 (m, 6 H, $C=CHCH_2CH(CH(CH_3)_2)_2$ and $HOCH_2CH_2CH_2C$), 2.12−2.23 (m, 2 H, $C=CHCH_2CH(CH$-$(CH_3)_2)_2$), 2.80 (br AB quartet, J = 17.0 Hz, 2 H, lactone-CH_2), 3.56 (s, 2 H, $PhCH_2OCH_2C$), 3.73 (t, J = 6.2 Hz, 2 H, $CHOCH_2$-CH_2CH_2C), 4.62 (AB quartet, J = 12.2 Hz, 2 H, $PhCH_2OCH_2C$), 6.79−6.88 (m, 1 H, $C=CHCH_2CH(CH(CH_3)_2)_2$), 7.31−7.48 (m, 5 H, $PhCH_2OCH_2C$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.25, 19.32, 21.51, 21.58, 26.07, 28.55, 29.12, 29.15, 33.06, 33.45, 50.19, 62.49, 73.50, 73.98, 84.04, 125.96, 127.45, 127.61, 128.26, 137.53, 142.39, 170.42; FAB-MS (*m*/*z*, relative intensity) 389 (MH^+, 20), 91 (100). Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.17; H, 10.11.

(*Z*)-5-(3-Hydroxypropyl)-3-[4-methyl-3-(methylethyl)-pentylidene]-5-[(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (31Z). According to the literature procedure,[32] DDQ (33 mg, 0.14 mmol) was added to a stirring solution of **30Z** (49 mg, 0.10 mmol) in CH_2Cl_2 (0.67 mL) and H_2O (0.13 mL). After 2.5 h, the mixture was filtered through Celite rinsing with CH_2Cl_2. The organic phase was washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. Purification by silica gel column chromatography gave **31Z** (22 mg, 58%) as an oil. IR (neat) 3021 (CH), 2957 (CH), 2929 (CH), 2856 (CH), 1746 (C=O), 1666 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93, 0.94, 0.97, and 0.98 (d, J = 6.8 Hz, 3 H, $C=CHCH_2CH(CH(CH_3)_2)_2$), 1.10−1.23 (m, 1 H, $C=CHCH_2$-$CH(CH(CH_3)_2)_2$), 1.55−1.95 (m, 6 H, $C=CHCH_2CH(CH(CH_3)_2)_2$ and $HOCH_2CH_2CH_2C$), 2.66−3.06 (m, 4 H, $C=CHCH_2CH(CH$-$(CH_3)_2)_2$ and lactone-CH_2), 3.54 (s, 2 H, $PhCH_2OCH_2C$), 3.73 (t, J = 6.2 Hz, 2 H, $HOCH_2CH_2CH_2C$), 4.63 (app s, 2 H, $PhCH_2$-OCH_2C), 6.20−6.28 (m, 1 H, $C=CHCH_2CH(CH(CH_3)_2)_2$), 7.36−7.42 (m, 5 H, $PhCH_2OCH_2C$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.37, 21.60, 21.61, 26.16, 29.30, 29.64, 33.21, 36.50, 51.15, 62.59, 73.48, 73.82, 83.26, 123.93, 127.47, 127.60, 128.26, 137.60, 146.05, 169.22; FAB-MS (*m*/*z*, relative intensity) 389 (MH^+, 14), 91 (100). Anal. ($C_{24}H_{36}O_4$) C, H.

(*E*)-3-{4-[4-Methyl-3-(methylethyl)pentylidene]-5-oxo-2-[(phenylmethoxy)methyl]-2-2,3-dihydrofuryl}propyl Octanoate (32E). According to the literature,[20] octanoyl chloride (44 μL, 0.26 mmol) was added to a 0 °C stirring solution of **31E** (24.9 mg, 0.06 mmol) and pyridine (21 μL, 0.26 mmol) in CH_2Cl_2 (1.5 mL) under argon. The reaction was monitored by TLC, and upon completion, the mixture was concentrated in vacuo. Purification by silica gel column chromatography gave **32E** (28 mg, 86%). IR (neat) 3021 (CH), 2959 (CH), 2930 (CH), 2859 (CH), 1744 (C=O), 1675 (C=C) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90−1.00 (m, 3 H, $CH_3(CH_2)_4CH_2CH_2C(O)$), 0.91, 0.92, 0.97, and 0.98 (d, J = 6.8 Hz, 3 H, $C=CHCH_2CH(CH$-$(CH_3)_2)_2$), 1.24−1.45 (m, 9 H, $C=CHCH_2CH(CH(CH_3)_2)_2$ and $CH_3(CH_2)_4CH_2CH_2C(O)$), 1.60−1.98 (m, 8 H, $C=CHCH_2CH$-$(CH(CH_3)_2)_2$, $OCH_2CH_2CH_2C$ and $CH_3(CH_2)_4CH_2CH_2C(O)$), 2.15−2.20 (m, 2 H, $C=CHCH_2CH(CH(CH_3)_2)_2$), 2.36 (t, J = 7.6 Hz, 2 H, $CH_3(CH_2)_4CH_2CH_2C(O)$), 2.80 (br AB quartet, J =

17.0 Hz, 2 H, lactone-CH_2), 3.55 (AB quartet, J = 10.0 Hz, 2 H, PhCH_2OCH_2C), 4.13 (t, J = 6.0 Hz, 2 H, OCH_2CH_2CH_2C), 4.62 (AB quartet, J = 12.1 Hz, 2 H, PhCH_2OCH_2C), 6.80−6.89 (m, 1 H, C=CHCH_2CH(CH(CH_3)$_2$)$_2$), 7.36−7.45 (m, 5 H, PhCH_2OCH_2C); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.02, 19.25, 19.30, 21.51, 21.57, 22.37, 22.54, 24.90, 28.56, 28.85, 29.05, 29.12, 29.14, 31.59, 33.09, 33.65, 34.21, 50.19, 63.76, 73.51, 73.83, 83.61, 125.77, 127.45, 127.65, 128.28, 137.48, 142.53, 170.24, 173.63; FAB-MS (*m*/*z*, relative intensity) 515 (MH^+, 49), 91 (100). Anal. ($C_{32}H_{50}O_5$) C, H.

(*Z*)-3-{4-[4-Methyl-3-(methylethyl)pentylidene]-5-oxo-2-[(phenylmethoxy)methyl]-2-2,3-dihydrofuryl}propyl Octanoate (32Z). According to the literature,[20] octanoyl chloride (38 μL, 0.20 mmol) was added to a 0 °C stirring solution of **31Z** (19.2 mg, 0.05 mmol) and pyridine (16 μL, 0.20 mmol) in CH_2Cl_2 (1.2 mL) under argon. The reaction was monitored by TLC, and upon completion, the mixture was concentrated in vacuo. Purification by silica gel column chromatography gave **32Z** (23 mg, 91%). IR (neat) 3022 (CH), 2958 (CH), 2929 (CH), 2857 (CH), 1741 (C=O), 1666 (C=C) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.91−1.00 (m, 15 H, CH_3(CH$_2$)$_4$CH$_2$CH$_2$C(O) and C=CHCH$_2$CH(CH(CH_3)$_2$)$_2$), 1.12−1.23 (m, 1 H, C=CHCH$_2$-CH(CH(CH$_3$)$_2$)$_2$), 1.30−1.45 (m, 10 H, OCH$_2$CH$_2$CH_2C and CH$_3$-(CH_2)$_4$CH$_2$CH$_2$C(O)), 1.60−1.97 (m, 6 H, C=CHCH$_2$CH-(CH(CH$_3$)$_2$)$_2$, OCH$_2$CH_2CH$_2$C and CH$_3$(CH$_2$)$_4$CH_2CH$_2$C(O)), 2.36 (t, J = 7.5 Hz, 2 H, CH$_3$(CH$_2$)$_4$CH$_2$CH_2C(O)), 2.66−3.02 (m, 4 H, lactone-CH_2 and C=CHCH_2CH(CH(CH$_3$)$_2$)$_2$), 3.52 (s, 2 H, PhCH$_2$OCH_2C), 4.13 (t, J = 5.8 Hz, 2 H, OCH_2CH$_2$CH$_2$C), 4.63 (app s, 2 H, PhCH_2OCH$_2$C), 6.20−6.29 (m, 1 H, C=CHCH$_2$-CH(CH(CH$_3$)$_2$)$_2$), 7.35−7.42 (m, 5 H, PhCH$_2$OCH$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.00, 19.36, 21.60, 22.43, 22.53, 24.90, 26.18, 28.84, 29.04, 29.30, 29.31, 31.59, 33.40, 34.21, 36.49, 51.15, 63.83, 73.48, 73.69, 82.90, 123.78, 127.45, 127.62, 128.26, 137.56, 146.19, 169.07, 173.63; FAB-MS (*m*/*z*, relative intensity) 515 (MH^+, 27), 91 (100). Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 75.47; H, 10.06.

(*E*)-3-{2-(Hydroxymethyl)-4-[4-methyl-3-(methylethyl)-pentylidene]-5-oxo-2-2,3-dihydrofuryl}propyl Octanoate (4E). Under argon, BCl_3 (94 μL, 0.094 mmol, 1 M in CH_2Cl_2) was added slowly to a −78 °C solution of **32E** (24.3 mg, 0.047 mmol) in CH_2Cl_2 (1.0 mL) and stirred for 2 h. Buffer solution (pH 7.2) was added slowly, and the reaction mixture was diluted with Et_2O and warmed to room temperature. The layers were separated, the aqueous layer was further extracted with $CHCl_3$ (2×), and the combined organics were dried over $MgSO_4$. Purification by silica gel column chromatography gave **4E** (19 mg, 93%). IR (neat) 3596 (OH), 3023 (CH), 2960 (CH), 2829 (CH), 2872 (CH), 1742 (C=O), 1674 (C=C) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92−1.00 (m, 15 H, CH_3(CH$_2$)$_4$CH$_2$-CH$_2$C(O) and C=CHCH$_2$CH(CH(CH_3)$_2$)$_2$), 1.24−1.45 (m, 9 H, CH$_3$(CH_2)$_4$CH$_2$CH$_2$C(O) and C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 1.60−1.95 (m, 8 H, CH$_3$(CH$_2$)$_4$CH_2CH$_2$C(O), OCH$_2$CH_2CH_2C and C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$), 2.08 (br s, 1 H, HOCH$_2$C), 2.15−2.25 (m, 2 H, C=CHCH_2CH(CH(CH$_3$)$_2$)$_2$), 2.36 (t, J = 7.4 Hz, 2 H, CH$_3$(CH$_2$)$_4$CH$_2$CH_2C(O)), 2.80 (br AB quartet, J = 17.1 Hz, 2 H, lactone-CH_2), 3.71 (AB quartet, J = 12.0 Hz, 2 H, HOCH_2C), 4.13−4.17 (m, 2 H, OCH_2CH$_2$CH$_2$C), 6.82−6.91 (m, 1 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.00, 19.27, 19.29, 21.53, 21.57, 22.35, 22.52, 24.89, 28.64, 28.84, 29.04, 29.14, 29.18, 31.58, 32.83, 33.01, 34.20, 50.23, 63.68, 67.12, 84.74, 125.62, 143.28, 170.27, 173.64; FAB-MS (*m*/*z*, relative intensity) 425 (MH^+, 66), 57 (100). Anal. ($C_{25}H_{44}O_5$) C, H.

(*Z*)-3-{2-(Hydroxymethyl)-4-[4-methyl-3-(methylethyl)-pentylidene]-5-oxo-2-2,3-dihydrofuryl}propyl Octanoate (4Z). Under argon, BCl_3 (79 μL, 0.08 mmol, 1 M in CH_2Cl_2) was added slowly to a −78 °C solution of **32Z** (20.4 mg, 0.04 mmol) in CH_2Cl_2 (1.0 mL) and stirred for 2 h. Buffer solution (pH 7.2) was added slowly, and the reaction mixture was diluted with Et_2O and warmed to room temperature. The layers were separated, the aqueous layer was further extracted with $CHCl_3$ (2×), and the combined organics were dried over $MgSO_4$. Purification by silica gel column chromatography gave **4Z** (16 mg, 93%). IR (neat) 3591 (OH), 2959 (CH), 2929 (CH), 2857 (CH), 1739 (C=O), 1664 (C=C) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.93−1.00 (m, 15 H, C=CHCH$_2$CH(CH(CH_3)$_2$)$_2$ and CH_3(CH$_2$)$_4$CH$_2$CH$_2$C(O)), 1.13−1.24 (m, 1 H, C=CHCH$_2$CH(CH-(CH$_3$)$_2$)$_2$), 1.28−1.44 (m, 8 H, CH$_3$(CH_2)$_4$CH$_2$CH$_2$C(O)), 1.60−1.95 (m, 8 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$, CH$_3$(CH$_2$)$_4$CH_2CH$_2$C-(O) and OCH$_2$CH_2CH_2C), 2.02 (br s, 1 H, HOCH$_2$C), 2.37 (t, J = 7.6 Hz, 2 H, CH$_3$(CH$_2$)$_4$CH$_2$CH_2C(O)), 2.67−3.03 (m, 4 H, C=CHCH_2CH(CH(CH$_3$)$_2$)$_2$ and lactone-CH_2), 3.69 (AB quartet, J = 12.1 Hz, 2 H, HOCH_2C), 4.13−4.17 (m, 2 H, OCH_2CH$_2$-CH$_2$C), 6.27−6.35 (m, 1 H, C=CHCH$_2$CH(CH(CH$_3$)$_2$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.01, 19.33, 19.39, 21.57, 21.60, 22.43, 22.53, 24.89, 26.27, 28.84, 29.04, 29.29, 29.32, 31.59, 32.77, 34.20, 35.12, 51.15, 63.74, 66.97, 83.98, 123.58, 147.05, 169.07, 173.64; FAB-MS (*m*/*z*, relative intensity) 425 (MH^+, 48), 57 (100). Anal. Calcd for $C_{25}H_{44}O_5$: C, 70.72; H, 10.44. Found: C, 71.27; H, 10.73.

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