# Conformationally Constrained Analogues of Diacylglycerol. 21. A Solid-Phase Method of Synthesis of Diacylglycerol Lactones as a Prelude to a Combinatorial Approach for the Synthesis of Protein Kinase C Isozyme-Specific Ligands

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A solid-phase method for the synthesis of diacylglycerol lactones as protein kinase C ligands was developed, and a small array of nine compounds were selected with the idea of testing this methodology and forecasting the reliability of the biological data as a preamble for the construction of large chemical libraries to be synthesized under the same conditions. The process started with the loading of 5-(hydroxymethyl)-5-[(4-methoxyphenoxy)methyl]-3,4,5-trihydrofuran-2-one (**1**) to a 3,4-dihydro-2*H*-pyran resin packed inside IRORI MacroKan reactors. The elements of diversity were introduced at the α-alkylidene ($R^1$) and acyl ($R^2$) positions using a set of three different aldehydes and three different acid chlorides, respectively. An LDA-mediated aldol condensation with $R^1CHO$ in the presence of $ZnCl_2$ followed by a DBU-catalyzed elimination of the triflate of the resulting aldol gave the α-alkylidene intermediates as mixtures of geometric isomers. Removal of the aryl-protecting group followed by acylation with $R^2COCl$ introduced the second element of diversity. Acid-assisted cleavage of the compounds from the resin afforded the final targets. The biological results obtained using the crude samples directly obtained from the resin compared well with those from pure materials, as the $K_i$ values between the two sets varied only by a factor between 1.5 and 3.7.

## Introduction

The central role of protein kinase C (PK-C) in cellular signal transduction has established it as an important therapeutic target for cancer and other diseases.[1] PK-C isozymes, a family of related serine/threonine kinases, contain in their regulatory domain one or two copies of cysteine-rich motifs (C1 domains) about 50 amino acids long, which bind to phorbol ester tumor promoters and the second messenger diacylglycerol (DAG) exclusively in the classic (α, $\beta$1, $\beta$2, and $\gamma$) and novel isoforms ($\delta$, $\epsilon$, $\eta$, and $\theta$), resulting in their translocation and activation.[2] The atypical isoforms ($\zeta$ and $\iota/\lambda$) contain a single nonfunctional C1 domain that fails to bind either phorbol esters or DAG.[2]

It is now well established that there are other families of proteins that contain C1 domains that are similarly responsive to phorbol esters and DAG.[3−8] The PKD/PKC $\mu$ family represents kinases superficially similar to PK-C; however, the kinase domains are not homologous and show different selectivity. Other "non-kinase" proteins that have a single copy of a functional C1 domain and bind phorbol esters or DAG include the Rac GTPase activating proteins (GAPs) α- and $\beta$-chimaerins, the Ras exchange factor RasGRP, the Unc-13/Munc-13 family of scaffolding proteins, and DAG kinases that abrogate DAG signaling.

During the past years, we have synthesized a number of compounds built on a constrained glycerol scaffold (DAG-lactone, **7**) where, depending on the nature of the groups present at $R^1$ or $R^2$, the compounds appear to have some degree of isozyme specificity.[9] Since among the kinase and non-kinase C1 domains there are important amino acid variations along the top rim of the two $\beta$-loops that conform the area of the domain thought to interact with the membrane, we surmised that by employing a more extensive approach of exploring chemical diversity at $R^1$ and $R^2$, we could improve the chances of discovering specific C1-domain ligands for each class of these multifaceted receptors.

To reach this goal, it was first necessary to develop a robust solid-phase method of synthesis as a prelude to the synthesis of a large number of compounds by a combinatorial approach. The methodology that was elaborated is presented in this manuscript, together with the synthesis of a small, nine-member array of compounds designed to test both the synthetic procedure and the suitability for biological testing of the crude materials directly obtained after cleavage from the resin. For this purpose, each compound in the array was purified and PK-C binding affinities for the α-isozyme were compared with those obtained for the crude products. Because phorbol esters and DAG-lactones compete for the same site on the enzyme (the C1 domain), displacement of PK-C-bound [20-$^3$H]phorbol-12,13-dibutyrate (PDBU) by a DAG-lactone, expressed as $K_i$, provides a convenient assay for binding affinity. The results described herein show that the method is chemically sound and that the biological data obtained from the crude samples provide valuable information, as evidenced by the less than 4-fold variance in $K_i$ between purified and crude products.

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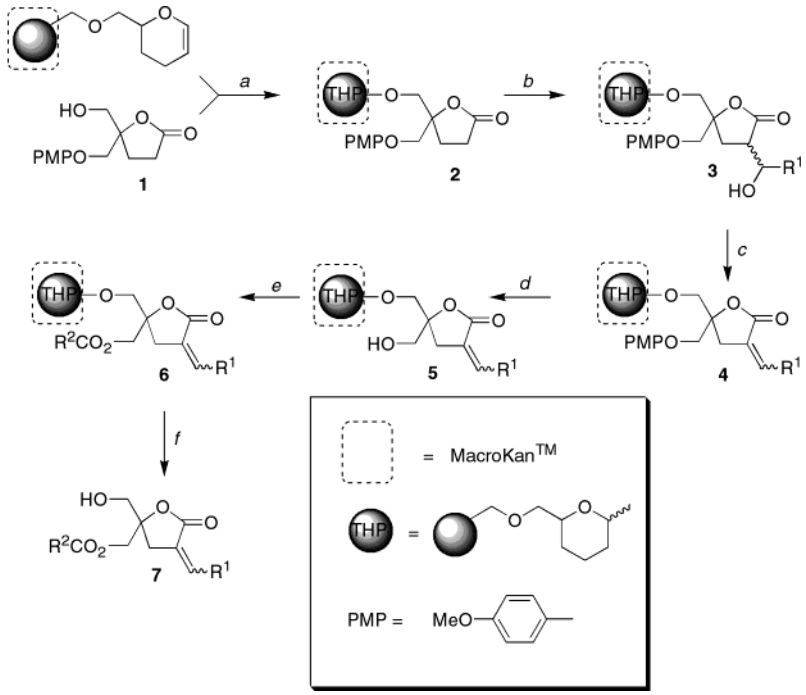
**Scheme 1**[a]



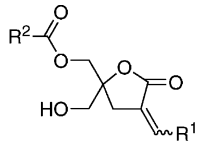

[a] Reagents and conditions: (a) lactone **1** (5 equiv), PPTS (4 equiv), 1,2-dichloroethane, 60 °C, 24 h (93%); (b) (i) LDA (10 equiv), THF, −78 °C, 6 h, (ii) $ZnCl_2$ (12 equiv), −45 °C, 30 min, (iii) $R^1CHO$ (12 equiv), −45 °C, 3 h, (iv) saturated $NH_4Cl$ solution, 90% (i → iv); (c) (i) pyridine (20 equiv), $(CF_3SO_2)_2O$ (10 equiv), $CH_2Cl_2$, −20 °C, 20 h, (ii) DBU (20 equiv), toluene, −78 °C → room temp, 16 h, 75% (i → ii); (d) CAN (20 equiv), $THF/H_2O$ (4:1), 0 °C → room temp, 16 h, 100%; (e) $R^2COCl$ (10 equiv), $Et_3N$ (20 equiv), 4-DMAP (1 equiv), $CH_2Cl_2$, room temp, 20 h; (f) PPTS (10 equiv), *n*-butanol/1,2-dichloroethane (1:1), 60 °C, 16 h.

## Chemistry

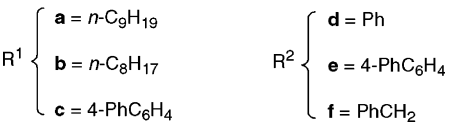
The parent DAG-lactone **1** [5-(hydroxymethyl)-5-[(4-methoxyphenoxy)methyl]-3,4,5-trihydrofuran-2-one] was dissolved in 1,2-dichloroethane and loaded onto a PL-DHP (3,4-dihydro-2*H*-pyran) resin in the presence of pyridinium *p*-toluenesulfonate (PPTS) (Scheme 1).[10] This operation was performed with the resin inside IRORI MacroKan reactors in preparation for a future large-scale combinatorial operation. The larger MacroKan reactors were chosen with the purpose of obtaining useful quantities of material suitable for purification by column chromatography. A loading yield of 93% was calculated from a single MacroKan by comparing the integration of $^1H$ NMR signals of the cleaved product (**1**) with those of dibromomethane used as an internal standard. PPTS-assisted cleavage of **2** (Scheme 1) was performed in a 1:1 *n*-butanol/1,2-dichloroethane solution.[10] Yields for the rest of the intermediate steps were similarly determined after cleaving the product from a portion of the resin using the same PPTS-assisted method. The first element of diversity ($R^1$) was introduced in two steps: (1) an LDA-mediated aldol condensation with $R^1CHO$, which was facilitated by metal exchange with $ZnCl_2$, and (2) a DBU-catalyzed elimination of the triflate of the aldol product (**3**) to give mixtures of both *E*- and *Z*-α-alkylidene isomers (**4**). The presence of $ZnCl_2$ was critical to minimize the retro-aldol reaction in the solid phase.[11] Indeed, the aldol reaction of the polymer-bound lactone **2** gave an increase of 20% conversion when performed in the presence of the Lewis acid. A one-pot mesylation of the polymer-bound aldol product **3** followed by a DBU-catalyzed elimination as reported in solution did not work well.[12] Rather, two individual steps consisting of triflation in dichloromethane followed by a DBU-mediated elimination in toluene were necessary to obtain the polymer-bound α-alkylidene lactone **4** in 75%. The quantitative removal of the *p*-methoxyphenyl **(**PMP) group with ammonium cerium(IV) nitrate (CAN) was successful in THF/water (4:1), while the standard literature method using acetonitrile/water (4:1) failed,[13] possibly because of poor swelling of the cross-linked polystyrene resin in this solvent system. Final removal of the aryl (PMP) protection was followed by acylation with $R^2COCl$, thus introducing the second element of diversity. PPTS-assisted cleavage of the fully assembled DAG-lactone from the resin afforded the final target compounds (**7**, Table 1). During the entire process the MacroKan reactors performed as filters. Hence, the solid-phase reaction and its workup could be finished inside these reactors, resulting in a simple operation without loss of resin. This augured well for our future plans to use this strategy in a radiofrequency (rf) tag-encoded combinatorial synthesis.[14]

The final compounds were obtained in sufficient quantities to allow purification and full characterization of each of the constituents of the nine-member set. As far as the ratio of geometric isomers, the *E*-isomer was major. Compounds **7ad**, **7ae**, **7bd**, and **7be** were purified as inseparable *E*/*Z*-mixtures with the *E*-isomer predominating, whereas compounds **7af**, **7bf**, **7cd**, **7ce**, and **7cf** were purified exclusively as *E*-isomers because the amounts of the separable *Z*-isomers were negligible. As we have previously observed, the vinyl proton for the *E*-isomer appeared consistently ca. 0.5 ppm downfield relative to the same signal for the *Z*-isomer.[12] In cases

**Table 1.** Chemical and Biological Parameters of Compounds



**7**




| compd | crude yield (%)[a] | *E*-isomer (%) | $K_i$ (nM), pure | $K_i$ (nM), crude | $K_i$-based % purity of crude | % HPLC purity of crude at 254/210 nm | calcd log *P* [b] |
|---|---|---|---|---|---|---|---|
| **7ad** | 62 | 70 | 20.3 ± 4.8 | 37.0 ± 6.8 | 54.86 | 66.77/90.22 | 4.85 |
| **7ae** | 56 | 80 | 19.1 ± 0.6 | 52.4 ± 2.1 | 36.45 | 67.34/74.94 | 6.61 |
| **7af** | 60 | 100 | 43.8 ± 1.2 | 92.5 ± 2.4 | 47.35 | 8.25/40.71 | 5.10 |
| **7bd** | 62 | 80 | 25.7 ± 2.9 | 45.6 ± 2.7 | 56.35 | 69.29/89.49 | 4.36 |
| **7be** | 62 | 80 | 28.0 ± 2.0 | 41.8 ± 4.7 | 66.98 | 53.26/53.19 | 6.12 |
| **7bf** | 53 | 100 | 43.3 ± 2.9 | 145.0 ± 7.3 | 29.86 | 14.33/62.49 | 4.61 |
| **7cd** | 38 | 100 | 14.1 ± 1.8 | 41.0 ± 2.7 | 34.39 | 14.47/28.14 | 3.90 |
| **7ce** | 42 | 100 | 22.7 ± 0.8 | 83.9 ± 5.2 | 27.05 | 19.60/25.50 | 5.66 |
| **7cf** | 43 | 100 | 48.0 ± 2.1 | 152.3 ± 4.1 | 31.51 | 12.31/19.92 | 4.15 |

[a] [(Molar weight of crude product obtained from the resin)/(initial molar weight of DHP resin lactone **4** (0.25 mmol))] × 100. [b] Calculated log *P* values with the program KOWWIN 1.67.[15]

where $R^1$ was the bulky (4-phenylphenyl)methylene chain, the normally preferred *E*-isomer became even more dominant.

The purity of the crude samples obtained after cleavage from the resin was estimated by normal-phase HPLC chromatography (Table 1). Because of the extreme nonpolar nature of the compounds, reverse-phase HPLC was not practical, and although normal-phase HPLC is not ideal, purity could be effectively calculated at two different wavelengths (210 and 254 nm) by integration. Relative to the purity calculated on the basis of $K_i$ ratios for crude and pure samples (vide infra), the HPLC purity determined at 254 nm approximated the biological-based purity for compounds **7ad**, **7bd**, **7be**, and **7bf** (±12−16%). Better matches were obtained at 210 nm for compounds **7af**, **7cd**, **7ce**, and **7cf** (±2−12%). For compound **7ae**, the HPLC estimated purity exceeded by more than 30% the biologically estimated purity. Naturally, these numbers are to be used only as a guide in determining problems with the synthesis and, in the context of a larger library, to help in the selection of potential targets to be resynthesized by conventional solution techniques.

## Biological Results

Binding affinity assays were done with intact recombinant PK-Cα, an isozyme where both the C1a and C1b domains are involved in ligand binding and membrane translocation. The activity of the DAG-lactones was 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 (PK-Cα) in the presence of phosphatidylserine.[12] The inhibition curves obtained for all ligands were of the type expected for competitive inhibition, and the $K_i$ values were calculated from the $ID_{50}$ values (see Experimental Section). For each compound two sets of $K_i$ values were obtained, one from the pure fully characterized material and one from the same target obtained in crude form directly after cleavage from the resin (Table 1). It is important to note that some compounds were purified as inseparable mixtures of geometric *E*- and *Z*-isomers (vide supra). However, since the same ratio of isomers also exists in the crude samples, the biological comparisons between the two sets are valid. The results show that the data obtained from the crude samples provide valuable information because the difference in $K_i$ between the crude product and purified compound was only a factor between 1.5 and 3.7 (Table 1). Finally, as a guide to interpreting the biological data, the octanol/water partition coefficient (log *P*) was also calculated for all target compounds according to the fragment-based program KOWWIN 1.67.[15]

Although the intent of this work was to develop a solid-phase synthesis method, the introduction of the biphenyl moiety in the context of the DAG-lactone template was also explored for the first time. The strong preference for protein binding of the biphenyl moiety, one of the most "privileged" substructures, has been recognized in the literature.[16] The most potent member of this small matrix is compound **7cd** ($K_i$ = 14.1 nM), which does contain the biphenyl moiety as part of the α-alkylidene group ($R^1$). The most remarkable property of **7cd** is not only its potency, but also the fact that it is the ligand with the lowest lipophilicity (log *P* = 3.90). Next in potency is **7ae** ($K_i$ = 19.1 nM, log *P* = 6.61), but in this case the compound is nearly 3 orders of magnitude more lipophilic! Although the biphenyl moiety seems to work well both as acyl and α-alkylidene groups, the latter seems to be the preferred location, especially in combination with the phenyl moiety as $R^2$ **(7cd)**. Combining both biphenyl moieties as acyl and α-alkylidene groups did not improve binding affinity and produced instead a weaker ligand (**7ce**, $K_i$ = 22.7 nM). Another interesting observation is the difference a methylene group makes at the $R^2$ position as one compares the benzoyl and phenylacetyl moieties. In all the cases where the phenylacetyl moiety is present (**7af**, **7bf**, and **7cf**), the compounds are the weakest ligands, whereas compounds with the benzoyl group (**7ad**, **7bd**,

and **7cd**) are among the most potent. One important point regarding the relationship between the *E*- and *Z*-geometry of the α-alkylidene group is the generally observed trend that the *Z*-isomers are ca. 2-fold more potent than the *E*-isomers. This means that for those cases where the *Z*-isomer is 20−30% of the mixtures, the $K_i$ values for the pure Z-isomer could be as low as 4−6 nM.

In comparison with the best DAG-lactones reported to date,[9] the compounds in Table 1 exhibit comparable potencies in binding to PK-Cα. However, a compound such as **7cd** is an attractive molecule for possible future drug development because of its lower log *P* value compared to most DAG-lactones. It is important to point out that all the compounds made in this set are potential "hits" in their own right. With a DAG-lactone as an invariant scaffold, it is very likely that the all compounds will bind to PK-Cα with varying degrees of affinities. Our intent is that future tests with other PK-C isozymes, as well as other families of proteins that contain C1 domains, will reveal important individual specificities.

## Conclusion

We have developed a robust solid-phase method using a PL-DHP resin for the synthesis of DAG-lactones using an exploratory set of $R^1$ and $R^2$ groups at the α-alkylidene and acyl positions, respectively. The use of MacroKan reactors simplified the operation and provided good reproducibility. The method was tested with the synthesis of a small, nine-member array with the idea of forecasting the reliability of the biological data that could be obtained when using larger chemical libraries synthesized under the same conditions. We conclude that the biological results obtained using crude samples directly obtained from the resin provide valuable information because the difference in $K_i$ between pure and crude materials varied only by a factor between 1.5 and 3.7. Although the intent of this effort was not drug discovery, a potentially interesting compound (**7cd**) combining high affinity for PK-C with low lipophilicity and bearing the "privileged" biphenyl moiety at the α-alkylidene position was identified.

## Experimental Section

**General Techniques.** All reagents and solvents purchased were of the highest commercial quality and used without further purification unless otherwise stated. MacroKan (IRORI) reactors were purchased from Discovery Partners International, San Diego, CA. PL-DHP (3,4-dihydro-2*H*-pyran) resin (1.7 mmol/g, 150−300 μm) was purchased from Polymer Laboratories, Ltd., Amherst, MA. All solid-phase reactions were performed in MacroKan reactors filled with 147.1 mg (0.25 mmol) of PL-DHP resin. The loading yield on the resin was determined from an aliquot by comparing the integration of $^1$H NMR signals of the cleaved product with those of an internal standard ($CH_2Br_2$). Yields for intermediate steps of the synthesis were similarly determined after cleavage of a portion of the resin and calculation of the percent conversion by integration of $^1$H NMR signals. Final crude products were obtained after cleavage from the resin and evaporation of the solvent. Purities of the crude products were determined by normal-phase HPLC (see Table 1) under various conditions: **7ad**, **7ae**, **7bd**, **7be** (1% 2-propanol/*n*-hexane, isocratic, 1.5 mL/min); **7af,** (1% 2-propanol/*n*-hexane, isocratic, 1.7 mL/min); **7bf** (2% → 10% 2-propanol/*n*-hexane, 1.7 mL/min, 45 min); **7cd**, **7ce**, **7cf** (2% → 50% 2-propanol/*n*-hexane, 1.7 mL/min, 40 min). Samples of all nine compounds were further purified by column chromatography on silica gel and fully characterized by FT-IR, $^1$H NMR, $^{13}$C NMR, MS, and elemental analysis.

**5-(Hydroxymethyl)-5-[(4-methoxyphenoxy)methyl]-3,4,5-trihydrofuran-2-one (1).** A solution of 5-[(4-methoxyphenoxy)methyl]-5-[(phenylmethoxy)methyl]-3,4,5-trihydrofuran-2-one[17] (3.4 g, 10.0 mmol) in dichloromethane (200 mL) was cooled to −78 °C and treated with boron trichloride (1.0 M in dichloromethane, 40 mL). After being stirred at −78 °C for 2 h, the reaction mixture was quenched with a saturated solution of sodium bicarbonate and immediately partitioned. The water layer was extracted with diethyl ether (200 mL, 1×), and the combined organic phase was washed with water (1×), dried ($Na_2SO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with ethyl acetate/hexane (1:1) as eluant to give **1** (2.3 g, 91%) as a white solid: mp 60−62 °C (hexane/ethyl acetate); IR (neat) 3445 (OH), 1771 (C=O) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 6.80 (s, 4 H, $CH_3OC_6H_4OCH_2C$), 4.04 (d, $J$ = 10.0 Hz, 1 H, $CH_3OC_6H_4OCHHC$), 3.99 (d, $J$ = 10.0 Hz, 1 H, $CH_3OC_6H_4OCHHC$), 3.84 (dd, $J$ = 12.1, 6.8 Hz, 1 H, HOC*H*HC), 3.68−3.78 (m, 4 H, HOCH*H*C and C$H_3OC_6H_4OCH_2$C), 2.59−2.82 (m, 2 H, H-$3_{a,b}$), 2.15−2.34 (m, 2 H, H-$4_{a,b}$), 1.93 (t, $J$ = 6.8 Hz, 1 H, *H*OCH$_2$C); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.13, 154.64, 152.58, 115.86, 114.92, 87.05, 71.13, 65.77, 55.92, 29.31, 25.88; FAB MS (*m*/*z*, relative intensity) 253 ($MH^+$, 46), 252 ($M^{+\bullet}$, 100). Anal. ($C_{13}H_{16}O_5$) C, H.

**Procedure for Loading 1 on the PL-DHP Resin.** Ten MacroKan reactors, each containing 0.147 g (0.25 mmol) of DHP resin, were placed in a 250 mL round-bottom flask equipped with a stirring bar. Lactone **1** (3.2 g, 12.5 mmol, 5 equiv), pyridinium *p*-toluenesulfonate (PPTS, 2.5 g, 10 mmol, 4 equiv), and 1,2-dichloroethane (100 mL) were introduced into the flask. The MacroKan reactors were degassed in the solution by lowering the temperature to −30 °C in vacuo for 5 min. The temperature was then raised to 60 °C, and the solution was stirred for 24 h. After reaching room temperature, the solution was decanted into another flask to recover excess unreacted lactone. The MacroKan reactors containing polymer-bound lactone (**2**) were washed subsequently with dichloromethane (1×), 1:1 DMF/water (4×), DMF (3×), dichloromethane (3×) and finally dried in vacuo.

**Procedure for Standard PPTS-Assisted Cleavage.** One MacroKan containing polymer-bound lactone (**2**, 0.25 mmol, 1.0 equiv) was treated with PPTS (0.628 g, 2.5 mmol, 10.0 equiv) in 1:1 *n*-butanol/1,2-dichloroethane (25 mL). After being stirred at 60 °C for 16 h and cooling to room temperature, the solution was transferred to a separatory funnel. The MacroKan was washed with dichloromethane (3 × 20 mL), and the combined organic phase was washed with a saturated aqueous sodium bicarbonate solution (2×) and water (2×). The solution was then dried over $Na_2SO_4$ and concentrated in vacuo to give **1** as colorless oil. A 93% loading yield was calculated from the integration of the $^1$H NMR ($CDCl_3$) signals of **1** compared to a known amount of dibromomethane added as an internal standard.

**Procedure for the Aldol Reaction of Polymer-Bound Lactone 2 with Decyl Aldehyde.** MacroKan reactors containing polymer-bound lactone **2** (9 MacroKan reactors, 2.25 mmol, 1 equiv) were suspended in THF (225 mL) in a round-bottom flask equipped with a stirring bar. After the mixture was degassed at −78 °C in vacuo for 5 min, LDA (2.0 M in heptane/THF/ethylbenzene, 11.3 mL, 10 equiv) was added while the temperature was maintained at −78 °C. After being stirred for 6 h at −78 °C, the solution was treated with $ZnCl_2$ (0.5 M in THF, 54 mL, 12 equiv) and the reaction was allowed to warm to −45 °C for 30 min. A solution of decyl aldehyde (5.4 mL, 27 mmol, 12.0 equiv) in THF (18 mL) was then added, and stirring continued at −45 °C for 3 h. The reaction was quenched with a saturated solution of ammonium chloride, and the mixture was allowed to reach room temperature. The MacroKan reactors containing polymer-bound aldol product **3** were washed with 1:1 DMF/water (4×), DMF (3×), dichloromethane (3×) and dried in vacuo. Standard PPTS-assisted

cleavage of a single MacroKan afforded the free aldol product as a colorless solid (0.077 g, 87% yield). The crude product was purified by flash column chromatography on silica gel with ethyl acetate/hexane (2:3) as eluant to afford pure 3-(hydroxydecyl)-5-(hydroxylmethyl)-5-[(4-methoxyphenoxy)methyl]-3,4,5-trihydrofuran-2-one as a white solid: mp 107−109 °C (hexane/ethyl acetate); IR (neat) 3432 (OH), 1715 (C═O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.79 (s, 4 H, $CH_3OC_6H_4OCH_2C$), 3.95−4.05 (m, 2 H, $CH_3OC_6H_4OCH_2C$), 3.78−3.85 (m, 1 H, HOC*H*HC), 3.65−3.75 (m, 5 H, HOCH*H*C, $CH_3OC_6H_4OCH_2C$ and C*H*(OH)$C_8H_{16}CH_3$), 2.83−3.01 (m, 1 H, H-3), 2.34−2.42 (m, 1 H, H-$4_a$), 1.95−2.06 (m, 1 H, H-$4_b$), 1.15−1.55 (m, 16 H, CH(OH)$C_8H_{16}CH_3$), 0.84 (t, $J$ = 7.2 Hz, 3 H, CH(OH)$C_8H_{16}CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 179.23, 154.67, 152.48, 115.86, 114.93, 85.51, 72.45, 70.96, 65.62, 55.91, 45.83, 34.97, 32.08, 29.78, 25.30, 22.87, 14.31; FAB MS ($m/z$, relative intensity) 409 ($MH^+$, 77) 408 ($M^{+\bullet}$, 100). Anal. ($C_{23}H_{36}O_6$) C, H.

**Procedure for Trifylation of Polymer-Bound Aldol Product 3 Followed by DBU-Assisted Elimination.** MacroKan reactors containing polymer-bound aldol product **3** (3 MacroKan reactors, 0.75 mmol, 1.0 equiv) were placed in a round-bottom flask equipped with a stirring bar and suspended in dichloromethane (75 mL). After the mixture was degassed at −78 °C in vacuo for 5 min, pyridine (1.2 mL, 15 mmol, 20 equiv) and trifluoromethylsulfonic anhydride (1.3 mL, 7.5 mmol, 10 equiv) were subsequently introduced into the flask at the same temperature. The resulting mixture was stirred at −20 °C for 20 h. The reaction was then quenched with a saturated solution of sodium bicarbonate, and the mixture was allowed to reach room temperature. The MacroKan reactors were washed with dichloromethane (1×), 1:1 DMF/water (4×), DMF (3×), dichloromethane (3×) and dried in vacuo. The MacroKan reactors were then immediately suspended in toluene (75 mL), and after degassing at −78 °C for 5 min, DBU (2.25 mL, 15 mmol, 20 equiv) was added at the same temperature. The MacroKan reactors were stirred at room temperature for 16 h, after which time the reaction was quenched with a saturated solution of ammonium chloride. The MacroKan reactors containing polymer-bound α-alkylidene lactone **4** were washed with dichloromethane (1×), 1:1 DMF/water (4×), DMF (3×), dichloromethane (3×) and dried in vacuo. Standard PPTS-assisted cleavage of one MacroKan afforded the free α-alkylidene lactone as a yellow oil (0.071 g, 80% yield). The crude product was purified by flash column chromatography on silica gel with ethyl acetate/hexane (2:3) as eluant to afford pure 3-decylidene-5-(hydroxylmethyl)-5-[(4-methoxyphenoxyl)methyl]-4,5-dihydrofuran-2-one as a white solid: mp 67−68 °C (hexane); IR (neat) 3441 (OH), 1755 (C═O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.79 (s, 4 H, $CH_3OC_6H_4OCH_2C$), 6.71−6.78 (m, 0.9 H, (*E*)-C═C*H*), 6.18 (t, $J$ = 7.6 Hz, 0.1 H, (*Z*)-C═C*H*), 4.04 (d, $J$ = 9.6 Hz, 1 H, $CH_3OC_6H_4OCHHC$), 3.95 (d, $J$ = 9.6 Hz, 1 H, $CH_3OC_6H_4OCHHC$), 3.84 (d, $J$ = 12.2 Hz, 1 H, HOC*H*HC), 3.75 (d, $J$ = 12.2 Hz, 1 H, HOCH*H*C), 3.73 (s, 3 H, $CH_3OC_6H_4OCH_2C$), 2.89 (d, $J$ = 17.2 Hz, 1 H, H-$4_a$), 2.76 (d, $J$ = 17.2 Hz, 1 H, H-$4_b$), 2.16 (irregular q, 2 H, $CH_2C_7H_{14}CH_3$), 1.16−1.55 (m, 14 H, $CH_2C_7H_{14}CH_3$), 0.85 (t, $J$ = 6.8 Hz, 3 H, $CH_2C_7H_{14}CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.40, 154.59, 152.62, 142.23, 126.29, 115.81, 114.89, 83.85, 70.47, 65.64, 55.91, 32.05, 30.48, 29.67, 28.28, 22.84, 14.29; FAB MS ($m/z$, relative intensity) 390 ($MH^+$, 100%). Anal. ($C_{23}H_{36}O_6$) C, H.

A similar procedure was used to obtain and purify 5-(hydroxymethyl)-5-[(4-methoxyphenoxy)methyl]-3-[(4-phenylphenyl)methylene]-4,5-dihydrofuran-2-one, which was obtained as a white solid: mp 151−153 °C (hexane/ethyl acetate); IR (neat) 3371 (OH), 1729 (C═O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.91 (d, $J$ = 8.2 Hz, 0.4 H, Ar), 7.64 (d, $J$ = 8.4 Hz, 1.6 H, Ar), 7.58−7.62 (m, 4.8 H, Ar and (*E*)-C═C*H*), 7.36−7.46 (m, 3 H, Ar), 7.05 (m, 0.2 H, (*Z*)-C═C*H*), 6.77−6.82 (m, 4 H, $CH_3OC_6H_4OCH_2C$), 4.10 (d, $J$ = 9.6 Hz, 1 H, $CH_3OC_6H_4OCHHC$), 4.02 (d, $J$ = 9.6 Hz, 1 H, $CH_3OC_6H_4OCHHC$), 3.80−3.97 (m, 2 H, HOC$H_2$C), 3.72 (s, 3 H, $CH_3OC_6H_4OCH_2C$), 3.15−3.35 (m, 2 H, H-$4_{a,b}$), 2.02 (t, $J$ = 6.8 Hz, 1 H, *H*OCH$_2$C); $^{13}C$ NMR ($CDCl_3$) $\delta$ 171.49, 154.67, 152.54, 142.971, 140.16, 137.17, 133.63, 131.51, 130.87, 129.16, 129.03, 128.20, 127.77, 127.30, 126.99, 124.30, 115.88, 115.83, 113.91, 83.99, 70.52, 65.69, 55.91, 32.59; FAB MS ($m/z$, relative intensity) 417 ($MH^+$, 100%) 416 ($M^{+\bullet}$, 93). Anal. ($C_{26}H_{24}O_5$) C, H.

**Procedure for Removal of the *p*-Methoxyphenyl (PMP) Group from Polymer-Bound α-Alkylidene Lactone 4.** MacroKan reactors containing polymer-bound α-alkylidene lactone **4** (8 MacroKan reactors, 2 mmol, 1.0 equiv) were suspended in a 4:1 THF/$H_2O$ mixture (200 mL) inside a round-bottom flask equipped with a stirring bar. After the mixture was cooled to 0 °C, ammonium cerium(IV) nitrate (CAN, 21.9 g, 40 mmol, 20 equiv) was introduced into the flask and stirring continued at room temperature for 20 h. Finally, the MacroKan reactors containing polymer-bound diol-α-alkylidene lactone **5** were washed with a 5% solution of sodium thiosulfate (3×), THF (1×), 1:1 DMF/water (4×), DMF (3×), dichloromethane (3×) and dried in vacuo. Standard PPTS-assisted cleavage of one MacroKan afforded the free diol-α-alkylidene lactone as a yellow oil (0.039 g, 100% yield). The crude product was purified by flash column chromatography on silica gel with ethyl acetate/methanol (100:1) as eluant to afford pure 5,5-bis-(hydroxymethyl)-3-decylidene-4,5-dihydrofuran-2-one as a white solid: mp 57−58 °C (hexane); IR (neat) 3393 (OH), 1746 (C═O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.64−6.73 (m, 0.9 H, (*E*)-C═C*H*), 6.17 (t, $J$ = 7.6 Hz, 0.1 H, (*Z*)-C═C*H*), 3.72 (d, $J$ = 12.1 Hz, 2 H, C$H_2$OH), 3.62 (d, $J$ = 12.1 Hz, 2 H, C$H_2$OH), 2.70 (s, 0.2 H, (*Z*)-H-$4_{a,b}$), 2.65 (s, 1.8 H, (*E*)-H-$4_{a,b}$), 2.57 (br s, 2 H, *H*OCH$_2$C), 2.10 (irregular q, 2 H, $CH_2C_7H_{14}CH_3$), 1.12−1.46 (m, 14 H, $CH_2C_7H_{14}CH_3$), 0.81 (t, $J$ = 6.8 Hz, 3 H, $CH_2C_7H_{14}CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.99, 142.45, 126.43, 85.52, 65.29, 32.04, 30.50, 29.58, 28.25, 22.85, 14.29; FAB MS ($m/z$, relative intensity) 285 ($MH^+$, 100%). Anal. ($C_{16}H_{28}O_4 \cdot 0.2H_2O$) C, H.

**Procedure for Acylation of Polymer-Bound Diol Lactone 5 with Benzoyl Chloride.** A MacroKan containing polymer-bound diol-α-alkylidene lactone **5** (1 MacroKan, 0.25 mmol, 1.0 equiv) was suspended in $CH_2Cl_2$ (25 mL) in a round-bottom flask equipped with a stirring bar. After the mixture was degassed at −78 °C for 5 min, triethylamine (0.7 mL, 5 mmol, 20 equiv), 4-DMAP (30.5 mg, 0.25 mmol, 1 equiv), and benzoyl chloride (0.29 mL, 2.5 mmol, 10 equiv) were subsequently introduced into the flask. The mixture was stirred at room temperature for 20 h, after which time the MacroKan was washed with dichloromethane (1×), 1:1 DMF/water (4×), DMF (3×), dichloromethane (3×) and dried in vacuo. The polymer-bound target DAG-lactone **6** was treated with the standard PPTS-assisted cleavage protocol to provide the final crude DAG-lactone as a yellow oil (60 mg, 90%). The crude product was purified by flash column chromatography on silica gel with ethyl acetate/hexane (2:3) as eluant to afford pure [4-decylidene-2-(hydroxymethyl)-5-oxo-2-2,3-dihydrofuryl]-methyl benzoate (**7ad**) as a colorless solid: mp 77−81 °C (hexane); IR (neat) 3426 (OH), 1759 (C═O), 1724 (C═O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.94 (d, $J$ = 7.5 Hz, 2 H, *Ph*CO$_2$CH$_2$C), 7.54 (t, $J$ = 7.5 Hz, 1 H, *Ph*CO$_2$CH$_2$C), 7.40 (t, $J$ = 7.5 Hz, 2 H, *Ph*CO$_2$CH$_2$C), 6.72−6.81 (m, 0.7 H, (*E*)-C═C*H*CH$_2$), 6.21 (t, $J$ = 7.6 Hz, 0.3 H, (*Z*)-C═C*H*CH$_2$), 4.45 (AB q, $J$ = 11.9 Hz, 2 H, PhCO$_2$C*H*$_2$C), 3.75 (AB q, $J$ = 12.1 Hz, 2 H, HOC$H_2$C), 2.71−2.99 (m, 2 H, H-$4_{a,b}$), 2.60−2.69 (m, 0.6 H, (*Z*)-C═CHC$H_2$), 2.34 (br s, 1 H, *H*OCH$_2$C), 2.07−2.19 (m, 1.4 H, (*E*)-C═CHC$H_2$), 1.12−1.46 (m, 14 H, C$_7H_{14}$CH$_3$), 0.84 (t, $J$ = 6.9 Hz, 3 H, C$_7$H$_{14}$C$H_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.19, 166.50, 145.88, 142.40, 133.72, 129.99, 129.30, 128.72, 126.00, 83.50, 66.31, 65.01, 32.03, 30.50, 30.12, 29.50, 28.22, 22.84, 14.30; FAB MS ($m/z$, relative intensity) 389 ($MH^+$, 89%), 105 (100%). Anal. ($C_{23}H_{32}O_5$) C, H.

**Final PPTS-Assisted Cleavage.** The rest of the target DAG-lactones were obtained after following the same standard PPTS-assisted cleavage method described above.

**[4-Decylidene-2-(hydroxymethyl)-5-oxo-2-2,3-dihydrofuryl]methyl 4-Phenylbenzoate (7ae).** Colorless solid, mp 116−120 °C (hexane/ethyl acetate); IR (neat) 3409 (OH), 1729 (C═O), 1714 (C═O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.97 (d, $J$ = 8.2 Hz, 2 H, Ar*H*), 7.48−7.65 (m, 4 H, Ar*H*), 7.26−7.45 (m, 3 H,

Ar*H*), 6.70−6.78 (m, 0.8 H, (*E*)-C=C*H*CH$_2$), 6.17 (t, *J* = 7.6 Hz, 0.2 H, (*Z*)-C=C*H*CH$_2$), 4.43 (AB q, *J* = 11.8 Hz, 2 H, ArCO$_2$C*H*$_2$C), 3.71 (AB q, *J* = 12.1 Hz, 2 H, HOC*H*$_2$C), 2.68−2.96 (m, 2 H, H-4$_{a,b}$), 2.48−2.65 (m, 0.4H, (*Z*)-C=CHC*H*$_2$), 2.27 (br s, 1 H, *H*OCH$_2$C), 2.02−2.18 (m, 1.6 H, (*E*)-C=CHC*H*$_2$), 1.05−1.44 (m, 14 H, C$_7$*H*$_{14}$CH$_3$), 0.79 (t, *J* = 6.9 Hz, 3 H, C$_7$H$_{14}$C*H*$_3$); $^{13}$C NMR (CDCl$_3$) $\delta$ 170.19, 166.41, 146.50, 145.89, 142.41, 139.95, 130.53, 129.18, 128.51, 127.47, 126.03, 83.53, 66.33, 65.03, 32.01, 30.51, 30.16, 29.47, 28.25, 22.84, 14.29; FAB MS (*m*/*z*, relative intensity) 465 (MH$^+$, 32%), 181 (100%). Anal. (C$_{29}$H$_{36}$O$_5$) C, H.

**(*E*)-[4-Decylidene-2-(hydroxymethyl)-5-oxo-2-2,3-dihydrofuryl]methyl 2-Phenylacetate (7af).** Colorless solid, mp 68−70 °C (hexane); IR (neat) 3383 (OH), 1730 cm$^{-1}$ (C=O); $^1$H NMR (CDCl$_3$) $\delta$ 7.18−7.31 (m, 5 H, *Ph*CH$_2$CO$_2$CH$_2$C), 6.65−6.75 (m, 1 H, C=C*H*CH$_2$), 4.27 (d, *J* = 11.9 Hz, 1 H, C$_6$H$_5$-CH$_2$CO$_2$C*H*HC), 4.16 (d, *J* = 11.9 Hz, 1 H, *Ph*CH$_2$CO$_2$CH*H*C), 3.62 (d, *J* = 12.1 Hz, 1 H, HOC*H*HC), 3.61 (s, 2 H, *Ph*C*H*$_2$-CO$_2$CH$_2$C), 3.54 (d, *J* = 12.1 Hz, 1 H, HOCH*H*C), 2.70 (d, *J* = 17.0 Hz, 1 H, H-4$_a$), 2.52 (d, *J* = 17.0 Hz, 1 H, H-4$_b$), 2.08 (irregular q, 2 H, C=CHC*H*$_2$), 1.92 (br s, 1 H, *H*OCH$_2$C), 1.12−1.46 (m, 14 H, C$_7$*H*$_{14}$CH$_3$), 0.85 (t, *J* = 6.8 Hz, 3 H, C$_7$H$_{14}$C*H*$_3$); $^{13}$C NMR (CDCl$_3$) $\delta$ 171.52, 169.99, 146.10, 142.51, 133.56, 129.44, 128.91, 127.55, 125.74, 83.06, 65.89, 65.02, 41.56, 32.06, 30.48, 29.59, 28.26, 22.86, 14.30; FAB MS (*m*/*z*, relative intensity) 403 (MH$^+$, 100%). Anal. (C$_{24}$H$_{34}$O$_5$) C, H.

**[4-Nonylidene-2-(hydroxymethyl)-5-oxo-2-2,3-dihydrofuryl]methyl Benzoate (7bd).** Colorless solid, mp 80−81 °C (hexane); IR (neat) 3420 (OH), 1765 (C=O), 1730 (C=O); $^1$H NMR (CDCl$_3$) $\delta$ 7.94 (d, *J* = 7.5 Hz, 2 H, *Ph*CO$_2$CH$_2$C), 7.54 (t, *J* = 7.5 Hz, 1 H, *Ph*CO$_2$CH$_2$C), 7.39 (t, *J* = 7.5 Hz, 2 H, *Ph*CO$_2$CH$_2$C), 6.71−6.79 (m, 0.8 H, (*E*)-C=C*H*CH$_2$), 6.21 (t, *J* = 7.6 Hz, 0.2 H, (*Z*)-C=C*H*CH$_2$), 4.45 (AB q, *J* = 11.9 Hz, 2 H, PhCO$_2$C*H*$_2$C), 3.75 (AB q, *J* = 12.1 Hz, 2 H, HOC*H*$_2$C), 2.66−2.99 (m, 2 H, H-4$_{a,b}$), 2.60−2.64 (m, 0.4 H, (*Z*)-C=CHC*H*$_2$), 2.40 (br s, 1 H, *H*OCH$_2$C), 2.04−2.19 (m, 1.6 H, (*E*)-C=CHC*H*$_2$), 1.14−1.44 (m, 12 H, C$_6$*H*$_{12}$CH$_3$), 0.84 (t, *J* = 6.9 Hz, 3 H, C$_6$H$_{12}$C*H*$_3$); $^{13}$C NMR (CDCl$_3$) $\delta$ 170.20, 166.50, 142.39, 133.72, 129.98, 129.30, 128.72, 126.01, 83.51, 66.31, 65.01, 32.00, 30.49, 30.11, 29.49, 29.31, 28.22, 22.81, 14.27; FAB MS (*m*/*z*, relative intensity) 375 (MH$^+$, 100). Anal. (C$_{22}$H$_{30}$O$_5$) C, H.

**[4-Nonylidene-2-(hydroxymethyl)-5-oxo-2-2,3-dihydrofuryl]methyl 4-Phenylbenzoate (7be).** Colorless solid, mp 121−123 °C (hexane/ethyl acetate); IR (neat) 3409 (OH), 1729 (C=O), 1714 (C=O) cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 8.01 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 7.30−7.68 (m, 7 H, Ar*H*), 6.72−6.81 (m, 0.8 H, (*E*)-C=C*H*CH$_2$, 6.22 (t, *J* = 7.6 Hz, 0.2 H, (*Z*)-C=C*H*CH$_2$), 4.48 (AB q, *J* = 11.9 Hz, 2 H, ArCO$_2$C*H*$_2$C), 3.80 (dd, *J* = 12.1, 6.5 Hz, 1H, HOC*H*HC), 3.75 (dd, *J* = 12.1, 6.5 Hz, 1 H, HOCH*H*C), 2.66−2.99 (m, 2 H, H-4$_{a,b}$), 2.48−2.65 (m, 0.4 H, (*Z*)-C=CHC*H*$_2$), 2.37 (t, *J* = 6.5 Hz, 1 H, *H*OCH$_2$C), 2.05−2.21 (m, 1.6 H, (*E*)-C=CHC*H*$_2$), 1.05−1.45 (m, 12 H, C$_6$*H*$_{12}$CH$_3$), 0.82 (t, *J* = 6.9 Hz, 3 H, C$_6$H$_{12}$C*H*$_3$); $^{13}$C NMR (CDCl$_3$) $\delta$ 170.21, 166.41, 146.49, 142.39, 139.95, 130.53, 129.16, 128.51, 127.97, 127.47, 126.05, 83.55, 66.34, 65.03, 32.00, 30.51, 30.15, 29.54, 29.52, 28.25, 22.80, 14.26; FAB MS (*m*/*z*, relative intensity) 451 (MH$^+$, 54%), 181 (100%). Anal. (C$_{28}$H$_{34}$O$_5$) C, H.

**(*E*)-[4-Nonylidene-2-(hydroxymethyl)-5-oxo-2-2,3-dihydrofuryl]methyl 2-Phenylacetate (7bf).** Colorless solid, mp 54−57 °C (hexane); IR (neat) 3384 (OH), 1757 (C=O), 1730 cm$^{-1}$ (C=O); $^1$H NMR (CDCl$_3$) $\delta$ 7.08−7.38 (m, 5 H, *Ph*CH$_2$-CO$_2$CH$_2$C), 6.65−6.75 (m, 1 H, C=C*H*CH$_2$), 4.26 (d, *J* = 11.9 Hz, 1 H, PhCH$_2$CO$_2$C*H*HC), 4.16 (d, *J* = 11.9 Hz, 1 H, PhCH$_2$-CO$_2$CH*H*C), 3.61 (s, 2 H, PhC*H*$_2$CO$_2$CH$_2$C), 3.59 (dd, *J* = 12.1, 6.5 Hz, 1 H, HOC*H*HC), 3.54 (dd, *J* = 12.1, 6.5 Hz, 1 H, HOCH*H*C), 2.69 (dd, *J* = 17.0, 2.8 Hz, 1 H, H-4$_a$), 2.51 (dd, *J* = 17.0, 2.8 Hz, 1H, H-4$_b$), 1.97−2.14 (m, 3 H, *H*OCH$_2$C and C=CHC*H*$_2$), 1.08−1.49 (m, 12 H, C$_6$*H*$_{12}$CH$_3$), 0.85 (t, *J* = 6.8 Hz, 3 H, C$_6$H$_{12}$C*H*$_3$); $^{13}$C NMR (CDCl$_3$) $\delta$ 171.49, 169.92, 142.49, 133.54, 129.41, 128.89, 127.53, 125.70, 83.01, 65.86, 65.00, 41.35, 32.01, 30.47, 29.88, 29.53, 28.25, 22.83, 14.28; FAB MS (*m*/*z*, relative intensity) 389 (MH$^+$, 86%), 91 (100%). Anal. (C$_{23}$H$_{32}$O$_5$).

**(*E*)-{2-(Hydroxymethyl)-5-oxo-4-[(4-phenylphenyl)-methylene]-2-2,3-dihydrofuryl}methyl Benzoate (7cd).** Colorless solid, mp 140−143 °C (hexane/ethyl acetate); IR (neat) 3382 (OH), 1714 (C=O) cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.89 (d, *J* = 8.4 Hz, 2 H, Ar), 7.46−7.65 (m, 8 H, Ar and C=C*H*), 7.28−7.44 (m, 5 H, Ar), 4.54 (d, *J* = 11.9 Hz, 1 H, PhCO$_2$C*H*HC), 4.41 (d, *J* = 11.9 Hz, 1 H, PhCO$_2$CH*H*C), 3.83 (dd, *J* = 12.3, 6.9 Hz, 1 H, HOC*H*HC), 3.76 (dd, *J* = 12.3, 6.9 Hz, 1H, HOCH*H*C), 3.28 (dd, *J* = 17.6, 3.1 Hz, 1 H, H-4$_a$), 3.11 (dd, *J* = 17.6, 3.1 Hz, 1H, H-4$_b$), 2.21 (t, *J* = 6.9 Hz, 1 H, *H*OCH$_2$C); $^{13}$C NMR (CDCl$_3$) $\delta$ 171.31, 166.52, 143.08, 140.09, 137.32, 133.74, 133.43, 130.81, 130.00, 129.25, 129.17, 128.73, 128.24, 127.79, 127.29, 123.98, 83.64, 66.27, 64.98, 32.68; FAB MS (*m*/*z*, relative intensity) 415 (MH$^+$, 100%). Anal. (C$_{26}$H$_{22}$O$_5$·0.2H$_2$O) C, H.

**(*E*)-{2-(Hydroxymethyl)-5-oxo-4-[(4-phenylphenyl)-methylene]-2-2,3-dihydrofuryl}methyl 4-Phenylbenzoate (7ce).** Colorless solid, mp 234−236 °C (hexane/ethyl acetate); IR (neat) 3390 (OH), 1765 (C=O), 1716 (C=O) cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.96 (d, *J* = 8.4 Hz, 2 H, Ar), 7.46−7.65 (m, 11 H, Ar and C=C*H*), 7.28−7.44 (m, 6 H, Ar), 4.57 (d, *J* = 11.9 Hz, 1 H, ArCO$_2$C*H*H), 4.44 (d, *J* = 11.9 Hz, 1 H, ArCO$_2$CH*H*), 3.84 (dd, *J* = 12.3, 6.9 Hz, 1 H, HOC*H*HC), 3.77 (dd, *J* = 12.3, 6.9 Hz, 1 H, HOCH*H*C), 3.29 (dd, *J* = 17.8, 2.9 Hz, 1 H, H-4$_a$), 3.13 (dd, *J* = 17.8, 2.9 Hz, 1H, H-4$_b$), 2.22 (t, *J* = 6.9 Hz, 1 H, *H*OCH$_2$C); $^{13}$C NMR (CDCl$_3$) $\delta$ 171.33, 166.42, 146.51, 143.08, 140.09, 137.33, 133.44, 130.82, 130.54, 129.16, 128.51, 128.24, 127.90, 127.81, 127.48, 127.39, 127.29, 123.98, 83.67, 66.28, 64.98, 32.70; FAB MS (*m*/*z*, relative intensity) 491 (MH$^+$, 49), 181 (100). Anal. (C$_{32}$H$_{26}$O$_5$·0.3H$_2$O) C, H.

**(*E*)-{2-(Hydroxymethyl)-5-oxo-4-[(4-phenylphenyl)-methylene]-2-2,3-dihydrofuryl}methyl 2-Phenylacetate (7cf).** Colorless solid, mp 110−114 °C (hexane/ethyl acetate); IR (neat) 3364 (OH), 1735 (C=O) cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.65 (d, *J* = 8.2 Hz, 2 H, Ar), 7.60 (d, *J* = 8.2 Hz, 2 H, Ar), 7.54 (t, *J* = 2.9 Hz, 1 H, C=C*H*), 7.34−7.52 (m, 5 H, Ar), 7.13−7.19 (m, 5 H, Ar), 4.32 (d, *J* = 11.9 Hz, 1 H, PhCH$_2$CO$_2$C*H*HC), 4.24 (d, *J* = 11.9 Hz, 1H, PhCH$_2$CO$_2$CH*H*C), 3.66 (dd, *J* = 12.1, 7.0 Hz, 1 H, HOC*H*HC), 3.58 (dd, *J* = 12.1, 7.0 Hz, 1H, HOCH*H*C), 3.56 (s, 2 H, PhC*H*$_2$CO$_2$CH$_2$C), 3.06 (dd, *J* = 17.8, 2.9 Hz, 1 H, H-4$_a$), 2.88 (dd, *J* = 17.8, 2.9 Hz, 1 H, H-4$_b$), 2.01 (t, *J* = 6.7 Hz, 1 H, *H*OCH$_2$C); $^{13}$C NMR (CDCl$_3$) $\delta$ 171.45, 171.17, 143.08, 140.11, 137.20, 133.50, 130.89, 129.35, 129.20, 128.87, 128.27, 127.77, 127.49, 127.31, 123.78, 83.35, 65.89, 65.10, 41.42, 32.30; FAB MS (*m*/*z*, relative intensity) 429 (MH$^+$, 100). Anal. (C$_{27}$H$_{24}$O$_5$·0.7H$_2$O) C, H.

**Analysis of Inhibition of [$^3$H]PDBU Binding by Nonradioactive Ligands.** Enzyme−ligand interactions were analyzed by competition with [$^3$H]PDBU binding for the single isozyme PK-C$\alpha$ essentially as described previously.[12] The ID$_{50}$ values were determined by least-squares fitting of the theoretical sigmoidal competition curve to the binding data. The $K_i$ was calculated from the ID$_{50}$ values according to the relationship

$$K_i = \frac{ID_{50}}{1 + L/K_d}$$

where *L* is the concentration of free [$^3$H]PDBU at the ID$_{50}$ and $K_d$ is the dissociation constant for [$^3$H]PDBU under the assay conditions.[18] Values represent the mean ± standard error (three determinations).

**Supporting Information Available:** Elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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