

Conformationally Constrained Analogues of Diacylglycerol. 30. An Investigation of Diacylglycerol-lactones Containing Heteroaryl Groups Reveals Compounds with High Selectivity for Ras Guanyl Nucleotide-Releasing Proteins

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Using a diacylglycerol-lactone (DAG-lactone) template previously developed in our laboratory as a scaffold with high binding affinity for C1 domains, we describe herein a series of novel DAG-lactones containing heterocyclic moieties (pyridines, quinolines, and indoles) as α -arylidene fragments. Some of the DAG-lactones obtained show selective binding to RasGRP3 as compared to PKC α by more than 2 orders of magnitude and possess subnanomolar affinities. Because activated C1 domains bound to their ligands (DAG or DAG-lactones) insert into membranes, the lipid composition of membranes (cellular, nuclear, and those of internal organelles) is an important determinant for specificity. Therefore, reaching a proper hydrophilic/lipophilic balance for these molecules is critical. This was achieved by carefully selecting partnering acyl fragments for the DAG-lactones with the appropriate lipophilicity. The results clearly show that the combination of chemical and physical properties in these molecules needs to be perfectly balanced to achieve the desired specificity.

Introduction

Protein kinase C (PKC) was the first enzyme identified as a receptor for the lipophilic second messenger diacylglycerol (DAG^a).¹ DAG is generated from the hydrolysis of phosphatidylinositol 4,5-bisphosphate catalyzed by phospholipase C isoforms, which become activated by G-protein-coupled receptors and by receptor tyrosine kinases.² DAG can also be generated indirectly from phosphatidylcholine via phospholipase D.³ PKCs have always been considered major players in cellular signal transduction involving numerous physiological and pathological processes, including proliferation, differentiation, apoptosis, angiogenesis, and drug resistance.⁴ However, the complexity of the different PKCs that are responsive to DAG, which include the conventional (α , β I, β II, and γ) and novel (δ , ϵ , η , and θ) isoforms, and their level of differential expression under physiological conditions make it difficult to assign a particular role to each isozyme. Furthermore, the discovery of other DAG-responsive proteins, such as the PKDs, RasGRPs, chimaerins, Munc13s, MRCKs, and DAGKs further complicates our understanding of the downstream roles of this widespread second messenger.^{5,6} The protein kinase D (PKD/PKC μ) family represents kinases superficially similar to PKC.

Interposed between the tandem C1/C2 domains and the catalytic domain of PKD is a PH domain present in many signal transduction proteins which is capable of binding to membrane lipids and other proteins.⁷ The Ras guanyl nucleotide-releasing protein family members (RasGRP1-4) function as guanine nucleotide exchange factors for Ras or Rap, leading to their activation, and are also substrates for PKC.^{8,9} The chimaerins are GTPase-activating proteins for Rac, leading to Rac inhibition.¹⁰ The Munc13 proteins are involved in the priming of vesicle fusion,¹¹ and the MRCKs (myotonic dystrophy kinase-related Cdc42-binding kinase) are downstream effectors of Cdc42, which are structurally related to the dystrophin myotonia kinase (DMPK) family, and are involved in actin cytoskeletal reorganization.¹² Finally, the DAGKs (DAG kinases) function to abrogate DAG signaling, thus providing a negative feedback regulatory loop for the DAG signaling pathway.¹³

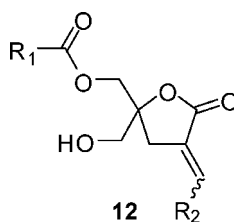
The major recognition motifs for DAG in PKC and other DAG-responsive proteins are zinc finger structures called C1 domains.¹⁴ These highly conserved structures of ~50 amino acids, which bind DAG or the DAG-mimicking phorbol esters, appear in tandem in the novel/classical PKCs and in the PKDs and as single domains in the chimaerins, RasGRPs, Munc13, and MRCK. X-ray crystallography and NMR analyses, together with molecular modeling, have provided a detailed understanding of the interaction of phorbol esters and DAG with C1 domains.^{15–19} The phorbol esters and DAG bind in a hydrophilic cleft in an otherwise hydrophobic surface atop the C1 domain, resulting in membrane translocation and a conformational change that in PKCs remove the pseudosubstrate domain from the catalytic site, thereby activating the enzyme.¹⁵ Strikingly, the affinity of C1 domains for DAG is approximately 3 orders of magnitude lower than that of the phorbol esters.²⁰ To help overcome this deficiency, we have developed a conformationally rigid DAG scaffold in the form of a DAG-lactone which, when substituted with an array of side chains

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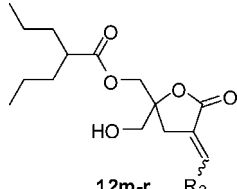
^a Abbreviations: CAN, ceric ammonium nitrate; DAG, diacylglycerol; DAGK, diacylglycerol kinase; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP, 4-dimethylaminopyridine; DMPK, dystrophin myotonia protein kinase; FAB-MS, fast atom bombardment mass spectrometry; GTP, guanosine triphosphate; IC₅₀, half maximal (50%) inhibitory concentration; LiHMDS, lithium hexamethyldisilazide; MRCK, myotonic dystrophy kinase-related Cdc42-binding kinase; MsCl, methanesulfonyl chloride; NMR, nuclear magnetic resonance; PDBu, [20-³H]phorbol 12,13-dibutyrate; PH, pleckstrin homology; PKC, protein kinase C; PKD, protein kinase D; RasGRP, Ras guanyl nucleotide-releasing protein; SAR, structure–activity relationship; TBAF, tetra-*n*-butylammonium fluoride; THF, tetrahydrofuran; TLC, thin layer chromatography.

Table 1. Binding Affinities (K_i , nM) for PKC α and RasGRP3 for Compounds **12a–l**

	R1	R2	SLog P	PKC α K_i (nM)	PKC α Z/E (K_i)	RasGRP3 K_i (nM)	RasGRP3 Z/E (K_i)
12a-E			2.0660	1020 $\pm$ 100	—	23.8 $\pm$ 2.6	—
12b-E			2.0660	790 $\pm$ 100	43	59 $\pm$ 13	33
12b-Z			2.0660	34100 $\pm$ 3300		1970 $\pm$ 360	
12c-E			2.0660	1110 $\pm$ 200	30	54 $\pm$ 13	44
12c-Z			2.0660	33200 $\pm$ 4300		2360 $\pm$ 150	
12d-E			3.2192	150 $\pm$ 21	105	11.0 $\pm$ 1.9	185
12d-Z			3.2192	15800 $\pm$ 5400		2040 $\pm$ 400	
12e-E			3.2192	755 $\pm$ 75	6.5	137 $\pm$ 16	10
12e-Z			3.2192	4880 $\pm$ 640		1410 $\pm$ 130	
12f-E			3.2192	174 $\pm$ 18	—	3.7 $\pm$ 0.8	—
12g-E			2.0086	1130 $\pm$ 390	24	35.8 $\pm$ 4.8	69
12g-Z			2.0086	27100 $\pm$ 3000		2470 $\pm$ 360	
12h-E			2.0086	810 $\pm$ 130	26	81 $\pm$ 12	68
12h-Z			2.0086	21200 $\pm$ 5600		5500 $\pm$ 1200	
12i-E			2.0086	1450 $\pm$ 150	18	54.2 $\pm$ 7.2	68
12i-Z			2.0086	25400 $\pm$ 1700		3660 $\pm$ 750	
12j-E			3.1618	132 $\pm$ 8.6	22	8.2 $\pm$ 1.1	170
12j-Z			3.1618	2940 $\pm$ 260		1390 $\pm$ 130	
12k-E			3.1618	144 $\pm$ 20	35	17.4 $\pm$ 1.7	52
12k-Z			3.1618	5100 $\pm$ 550		907 $\pm$ 98	
12l-E			3.4645	212 $\pm$ 35	—	3.3 $\pm$ 1.5	—

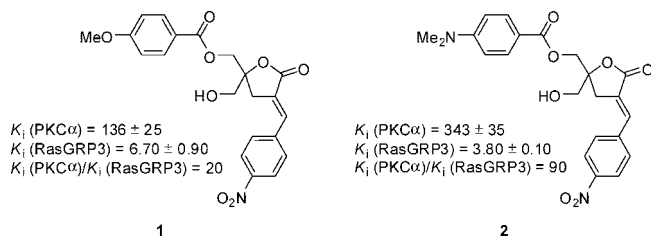
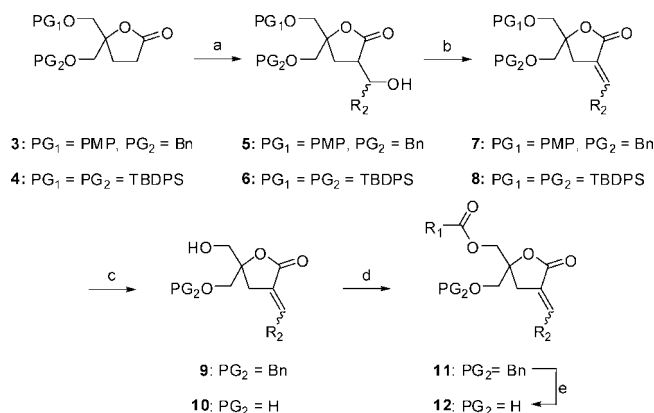
designed to achieve an appropriate hydrophobic/hydrophilic balance, provides ligands with strong binding affinities for PKCs.¹⁹ With this strategy, we have generated combinatorial libraries of DAG-lactones that function as potent surrogates of DAG. In these libraries, the nature of the R_1 and R_2 substituents

on the DAG-lactone template emerged as the principal determinant in controlling biological activity (see general structures in Tables 1 and 2). For example, switching from simple n -alkyl chains to branched alkyl chains or incorporating aromatic moieties at R_1 and/or R_2 produced compounds that in some cases

Table 2. Binding Affinities (K_i , nM) for PKC α and RasGRP3 for Compounds **12m-r**


	R ₂	Slog P	PKC α K_i (nM)	PKC α Z/E (K_i)	RasGRP3 K_i (nM)	RasGRP3 Z/E (K_i)
12m-E		2.9026	86.3 $\pm$ 0.7	16	0.72 $\pm$ 0.1	116
12m-Z		2.9026	1370 $\pm$ 120		83 $\pm$ 12	
12n-E		2.9026	76 $\pm$ 10	43	1.6 $\pm$ 0.1	419
12n-Z		2.9026	3270 $\pm$ 320		670 $\pm$ 70	
12o-E		2.9026	627 $\pm$ 22	1.4	13.8 $\pm$ 1.5	3
12o-Z		2.9026	870 $\pm$ 280		44 $\pm$ 14	
12p-E		4.0558	51.9 $\pm$ 8.8	1.5	1.7 $\pm$ 0.2	3
12p-Z		4.0558	78.8 $\pm$ 6		4.6 $\pm$ 0.6	
12q-E		4.0558	13.8 $\pm$ 1.7	13	0.52 $\pm$ 0.05	62
12q-Z		4.0558	177 $\pm$ 21		32.2 $\pm$ 4.2	
12r-E		4.3585	29.7 $\pm$ 1.1	—	0.18 $\pm$ 0.03	—

displayed significant degrees of specificity for PKC isozymes and other proteins containing DAG-responsive C1 domains.²¹ After the DAG-lactones bind to the C1 domain, these sets of side chains (R₁ and R₂) function as “chemical zip codes”, which are capable of interacting with the membrane in the chemical space outside the C1 domain of PKC and other C1-domain containing proteins.²¹ Owing to the different lipid compositions of plasma membranes, nuclear membranes and membranes of cellular organelles, such as lysosomes, peroxysomes, mitochondria, endoplasmic reticulum, lipid bodies, and Golgi, the interactions between the “chemical zip codes” and the characteristic lipid–water–protein microenvironment outside the C1-domain appear to direct the DAG-lactone–C1-domain complexes to distinct membrane locations producing unique biological responses.²¹ This sorting ability of the “chemical zip codes” was demonstrated with {2-(hydroxymethyl)-4-[(4-nitrophenyl)methylene]-5-oxo-2-(2,3-dihydrofurfuryl)}methyl 4-(dimethylamino)benzoate (**1**, aka 130C032) and {2-(hydroxymethyl)-4-[(4-nitrophenyl)methylene]-5-oxo-2-(2,3-dihydrofurfuryl)}methyl 4-methoxybenzoate (**2**, aka 130C037), which efficiently discriminated between PKC α and RasGRP (both isoforms RasGRP1 and RasGRP3).²² The selectivity for RasGRP3 over PKC α was 20-fold for **1** and 90-fold for **2** (Figure 1).²² Since according to the proposed binding mode for DAG-lactones²³ the α -arylidene moiety is oriented toward the C1 domain/lipid interface, we decided to explore changes in the *p*-nitrophenyl groups of **1** and **2**, beyond the *o*- and *p*-isomers already explored,²¹ to enhance even further the discrimination between PKC α and RasGRP. In order to search for different types of interactions, we decided to incorporate for the first time a set of α -heteroarylidene moieties while leaving the two acyl groups

**Figure 1.** Chemical structures of DAG-lactones **1** and **2**, K_i values for PKC α and RasGRP3, and K_i (PKC α)/ K_i (RasGRP3) ratios.**Scheme 1^a**

^a Conditions and reagents: (a) LiHMDS, R₂CHO, THF, –78 °C; (b) Et₃N, MsCl, DBU, CH₂Cl₂, 0 °C $\rightarrow$ room temp; (c) (7) CAN, CH₃CN, 0 °C; or (8) TBAF, THF; (d) (9) Et₃N, DMAP, R₁COCl; or (10) pyridine, CH₂Cl₂, then R₁COCl, 0 °C; (e) BCl₃, CH₂Cl₂, –78 °C.

constant as the *p*-dimethylaminophenyl and *p*-methoxyphenyl moieties, respectively (Table 1). Then, the α -heteroarylidene moieties were combined with lipophilic, branched acyl chains to replace the aromatic acyl moieties for optimal activity (Table 2).

Chemistry

As illustrated in Scheme 1, the syntheses of DAG-lactone analogues **12** were completed from racemic lactones (**3** and **4**)^{24–26} employing a well-established methodology developed in our laboratory.²⁶ This involves formation of the aldol intermediates (**5** and **6**) with different aldehydes, followed by elimination of the β -hydroxylactone intermediate to the corresponding olefin (**7** and **8**), which in most cases generated mixtures of *E*- and *Z*-isomers. Consistent with previously synthesized DAG-lactones, the *E/Z* geometry around the double bond was assigned by ¹H NMR; the vinyl proton for the *E*-isomers displayed a characteristic multiplet that was farther downfield from that of the corresponding *Z*-isomers. After separation of the geometric *E/Z*-isomers, the compounds were individually converted to the corresponding DAG-lactones with different R₁ acyl groups by conventional methods. When the protecting group was the benzyl ether (PG₂ = Bn), debenzilation of intermediates **11** afforded the desired compounds **12**. Because the methylindole moiety was labile to CAN, the syntheses of DAG-lactones where R₂ = methylindole were accomplished starting with **4**²⁶ with identical twin protecting groups (PG₁ = PG₂ = TBDPS). In this case, olefination of the aldol product (**6**) resulting from the reaction with 1-methylindole-3-carboxaldehyde afforded exclusively the *E*-isomer (**8**). The deprotection of the hydroxyl groups with TBAF (**10**) was followed by selective monoacylation to give directly the expected compounds **12**.

Table 3. Affinity Ratios of PKC α to RasGRP3 for Compounds **12a–r**

<i>E</i> -isomer	K_i ratio PKC α /RasGRP-3	<i>Z</i> -isomer	K_i ratio PKC α /RasGRP-3
12a-E	43		
12b-E	13	12b-Z	20
12c-E	19	12c-Z	14
12d-E	14	12d-Z	8
12e-E	6	12e-Z	3
12f-E	47		
12g-E	32	12g-Z	11
12h-E	10	12h-Z	4
12i-E	27	12i-Z	7
12j-E	16	12j-Z	2
12k-E	8	12k-Z	6
12l-E	64		
12m-E	119	12m-Z	16
12n-E	47	12n-Z	5
12o-E	45	12o-Z	20
12p-E	31	12p-Z	17
12q-E	27	12q-Z	5
12r-E	165		

The decision to prepare racemic DAG-lactones was mainly practical, especially when synthesizing a large number of compounds. These compounds are easier to synthesize, and in the case of the more potent analogues, which display subnanomolar binding affinities, the differences between enantiomers is minimal as we have shown previously.²⁷

Biological Results

The interaction of the target DAG-lactones with PKC α and RasGRP3 was assessed in terms of the ability of the ligands to displace bound [20-³H]phorbol 12,13-dibutyrate (PDBu) from recombinant PKC α and RasGRP3, respectively, in the presence of phosphatidylserine as previously described.²² The IC₅₀ values were determined by fitting the data points to the theoretical competition curve, and the K_i values for inhibition of binding were calculated from the corresponding IC₅₀ values (Tables 1, 2, and 4). For the biological studies, we selected PKC α as representative of the classical PKCs, which had previously shown the larger difference in SAR relative to the RasGRP isoforms.²² PKC α has the further advantage that it has been the standard PKC isoform against which all the DAG-lactones have routinely been characterized.¹⁹ RasGRP3 and RasGRP1 in previous studies have shown similar SAR.²² We picked RasGRP3 for the present comparisons because of its emerging role in solid tumors.

Table 1 displays DAG-lactones containing six different types of α -heteroarylidenes with either the *p*-dimethylaminophenyl (**12a–f**) or the *p*-methoxyphenyl (**12g–l**) acyl groups characteristic of **2** or **1**, respectively. In the majority of the cases, the geometric isomers were separated and studied individually except when only one isomer was obtained exclusively (compounds **12a-E**, **12f-E**, and **12l-E**). The K_i values in Table 1 for PKC α and RasGRP3 demonstrate, as expected, that none of the compounds had a very good affinity for PKC α whereas affinity for RasGRP3 was very good, particularly for compounds **12f-E** and **12l-E**. Another important observation was the large disparities in affinities shown by the two geometrical isomers for both enzymes. In previous studies with DAG-lactones having an α -alkylidene moiety the trend was different, almost always favoring the *Z*-isomer;¹⁹ however, the differences in binding affinities were small, less than 2-fold. Here, for the α -heteroarylidenes, not only was the trend reversed but the differences between geometrical isomers appeared as large as 100-fold (for PKC α) and 185-fold (for RasGRP3), always in favor of the *E*-isomer.

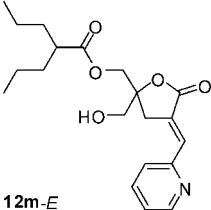
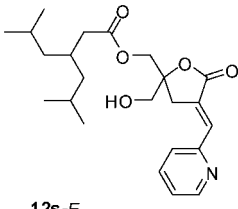
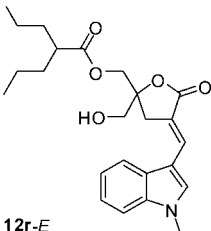
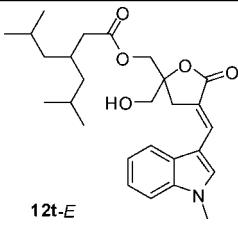
Because most of the compounds in Table 1 have log *P* values in the lower range of 2.0–3.5, we decided to replace the aromatic acyl moieties with the more lipophilic branched chain of valproic acid to improve membrane localization (Table 2). The preferred use of branched acyl chains, as opposed to linear *n*-alkyl chains, has been discussed previously.¹⁹ The changes resulting from the incorporation of valproic acid were very impressive, particularly for RasGRP3. Although affinity for PKC α improved somewhat for all the compounds relative to the values shown in Table 1, the changes were not as dramatic as those observed for RasGRP3 (Table 2) where the affinities were in the low nanomolar range and even reached subnanomolar values for compounds **12m-E**, **12q-E**, and **12r-E**. For PKC α , the preferred active isomers were again the *E*-isomers, but the differences were in general not as large as those observed in Table 1. On the contrary, for RasGRP3 the differences between geometrical isomers were equal to or even higher than those observed in Table 1, with the exception of two compounds (**12o** and **12p**) where the differences were only 3-fold.

To select the compounds with the highest selectivity for RasGRP3, the K_i ratios for PKC α /RasGRP3 were calculated for all the compounds in Tables 1 and 2. The results in Table 3 show that the two compounds with the highest selectivities for RasGRP3 are compounds **12m-E** and **12r-E** with ratios of 119 and 165, respectively. Both compounds were more selective for RasGRP3 than either **1** and **2**.

In earlier studies we have shown that a highly branched acyl chain endows the DAG-lactones with more stability and membrane affinity.¹⁹ Therefore, in an effort to expand even more the difference in affinities between PKC α and RasGRP3, the highly branched chain of 5-methyl-3-(2-methylpropyl)hexanoic acid was employed to modify compounds **12m-E** and **12r-E**. Unfortunately, despite the fact that the affinity for RasGRP3 remained in the subnanomolar range, the affinity for PKC α was also augmented. Thus, the ratio of 119 displayed by compound **12m-E** dropped to 23 for compound **12s-E** and the ratio of 165 for **12r-E** plummeted to 21 for compound **12t-E** (Table 4).

In conclusion, this work demonstrates that α -heteroarylidenes are novel DAG-lactone constituents with the distinct ability to significantly discriminate between a conventional PKC isozyme, represented by the α -isozyme, and another C1 domain-containing protein, RasGRP3. Since this work describes only a minor fraction of a potentially sizable chemical space that could be explored further with larger sets of DAG-lactones, our findings bode well for the future discovery of compounds capable of differentiating between PKC isozymes and other C1 domain-containing proteins besides RasGRPs. The other significant finding of this work is the importance of the appropriate hydrophilic/lipophilic balance to achieve selectivity. Because the lipid composition of the cellular and nuclear membranes as well as membranes in other intracellular organelles is different, reaching a proper hydrophilic/lipophilic balance seems to be of paramount importance for achieving selectivity. Therefore, the combination of chemical and physical properties in these molecules has to be perfectly balanced. This was demonstrated by the loss of selectivity observed between compounds **12m-E** and **12s-E** and between compounds **12r-E** and **12t-E**, where an increase in 0.88 log *P* units brought about by enlarging the acyl group from valproate to 5-methyl-3-(2-methylpropyl)hexanoate abolished all selectivity. Presently, our laboratory is engaged in expanding the chemical and physical domains of novel DAG-

Table 4. Affinity Ratios of PKC α to RasGRP3 for Compounds **12m-E** versus **12s-E** and Compound **12r-E** versus **12t-E**

Compound	SlogP	PKC α K_i (nM)	RasGRP-3 K_i (nM)	Ratio PKC α /RasGRP-3
 12m-E	2.9026	86.3 $\pm$ 0.7	0.72 $\pm$ 0.1	119
 12s-E	3.7847	4.6 $\pm$ 0.5	0.20 $\pm$ 0.04	23
 12r-E	4.3585	29.7 $\pm$ 1.1	0.18 $\pm$ 0.03	165
 12t-E	5.2406	14.8 $\pm$ 1.0	0.70 $\pm$ 0.02	21

lactones with the intent of controlling the makeup of novel DAG-lactones that will show specificity and unique biology.

Experimental Section

General Procedures. All chemical reagents were commercially available. [20- ^3H]phorbol 12,13-dibutyrate (PDBu) was obtained from Perkin-Elmer, Waltham, MA. Melting points were determined on a MelTemp II apparatus, Laboratory Devices, and are uncorrected. Combi-flash column chromatography was performed on silica gel 60 (230–240 mesh) employing a Teledyne Isco instrument, and analytical TLC was performed on Analtech Uniplates silica gel GF. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity Inova instrument at 400 and 100 MHz, respectively. Spectra are referenced to the solvent in which they were run (7.26 ppm for CDCl_3). Positive-ion fast atom bombardment mass spectra were obtained on a VG 7070E-HF double-focusing mass spectrometer operating at an accelerating voltage of 6 kV under the control of a MASPEC-II data system for Windows (Mass Spectrometry Services, Ltd.). Either glycerol or 3-nitrobenzyl alcohol was used as the sample matrix, and ionization was effected by a beam of xenon atoms generated in a saddle-field ion gun at 8.0 ± 0.5 kV. Nominal mass spectra were obtained at a resolution of 1200, and matrix-derived ions were background-subtracted during data system processing. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Aldol Condensation (Procedure A). A solution of **3**^{24,25} (1 equiv) in THF (5 mL/mmol) at -78°C was treated dropwise with $[(\text{CH}_3)_3\text{Si}]_2\text{NLi}$ (LiHMDS, 1.5 equiv) and stirred at the same temperature for 2 h. A solution of R_2CHO (1.5 equiv) was added dropwise, and the mixture was stirred at -78°C (3–6 h). The reaction mixture was then quenched with a saturated aqueous solution of NH_4Cl and allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (3 $\times$). The combined organics were washed with H_2O (2 $\times$) and brine (1 $\times$), dried (MgSO_4), and concentrated in vacuo. Purification by silica gel flash column chromatography [hexanes and EtOAc (0% $\rightarrow$ 75%)] gave **5** as a mixture of diastereomers, which was used directly in the next step.

Olefination (Procedure B). A solution of **5** (1 equiv) and Et_3N (4 equiv) in CH_2Cl_2 (10 mL/mmol) was treated dropwise with $\text{CH}_3\text{SO}_2\text{Cl}$ (MsCl , 2 equiv) at 0°C and then stirred at room temperature for 1 h. The reaction mixture was then cooled again to 0°C and treated dropwise with 1,8-diazabicyclo[5.4.0]non-5-ene (DBU, 5 equiv). When the addition of DBU was completed, the reaction mixture was allowed to reach room temperature overnight. The volatiles were removed in vacuo, and the residue was treated with EtOAc followed by 1 N HCl . The layers were separated, and the aqueous layer was extracted with EtOAc (1 $\times$). The combined organics were washed with H_2O (2 $\times$) and brine (1 $\times$), dried (MgSO_4), and concentrated in vacuo. Purification by silica

gel flash column chromatography [hexanes and EtOAc (0% → 75%)] gave **7** as a mixture of *E*- and *Z*-isomers.

7-E (R₂ = 2-pyridyl): yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.70 (dm, 1H, *J* = 3.9 Hz, *H*₆-pyridine), 7.72 (irregular td, 1H, *J* ≈ 8.0, 2.0 Hz, *H*₃-pyridine), 7.51 (t, 2H, *J* = 2.9 Hz, CH=C), 7.43 (d, 1H, *J* = 7.7 Hz, *H*₄-pyridine), 7.21–7.31 (m, 6H, Ph, *H*₅-pyridine), 6.78–6.83 (m, 4H, CH₃OC₆H₄), 4.57–4.63 (AB m, 2H, PhCH₂OCH₂), 4.03–4.15 (AB m, 2H, CH₃OC₆H₄OCH₂), 3.68–3.77 (m, 5H, CH₃OC₆H₄, PhCH₂OCH₂), 3.58 (dd, 1H, *J* = 19.6, 2.8 Hz, CHH-lactone), 3.48 (dd, 1H, *J* = 19.6, 3.0 Hz, CHH-lactone); ¹³C NMR (100 MHz, CDCl₃) δ 171.45, 154.38, 154.06, 152.71, 150.08, 137.75, 136.59, 133.74, 130.02, 128.52, 127.86, 127.73, 126.95, 123.32, 115.90, 114.71, 84.14, 73.82, 72.29, 70.93, 55.82, 34.23; IR (neat) 1757 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 432.3 (MH⁺, 58%), 91.1 (100%). Anal. (C₂₆H₂₅NO₅) C, H, N.

7-Z (R₂ = 2-pyridyl): yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.53 (dm, 1H, *J* = 4.9 Hz, *H*₆-pyridine), 7.58 (dt, 1H, *J* = 7.6, 1.8 Hz, *H*₃ and *H*₅-pyridine), 7.23–7.33 (m, 6H, Ph, *H*₅-pyridine), 7.21 (t, 1H, *J* = 1.5 Hz, CH=C), 7.15 (dd, 1H, *J* = 4.9, 1.1 Hz, *H*₄-pyridine), 6.74–6.81 (m, 4H, CH₃OC₆H₄), 4.54 (AB q, 2H, *J* = 12.0 Hz, PhCH₂OCH₂), 4.21 (AB d, 1H, *J* = 10.4 Hz, CH₃OC₆H₄OCHH), 4.05 (AB d, 1H, *J* = 10.4 Hz, CH₃OC₆H₄OCH H), 3.82 (AB d, 1H, *J* = 1.4 Hz, PhCH₂OCH₂), 3.78 (d, 1H, *J* = 10 Hz, CHH-lactone), 3.75 (s, 3H, CH₃OC₆H₄), 3.72 (d, 1H, *J* = 10 Hz, CHH-lactone); ¹³C NMR (100 MHz, CDCl₃) δ 172.37, 157.26, 154.49, 152.45, 149.22, 137.52, 136.92, 134.04, 128.55, 127.95, 127.75, 123.46, 121.98, 115.92, 114.74, 87.25, 73.91, 70.61, 69.32, 55.81, 34.40; IR (neat) 1760 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 432.3 (MH⁺, 81%), 91.1 (100%). This material was used in the next step without further attempts to obtain an analytically pure sample.

7-E (R₂ = 3-pyridyl): yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.78 (d, 1H, *J* = 1.6 Hz, *H*₂-pyridine), 8.62 (dd, 1H, *J* = 1.2, 4.8 Hz, *H*₆-pyridine), 7.83 (dm, 1H, *J* = 8.0 Hz, *H*₄-pyridine), 7.53 (irregular t, 1H, *J* ≈ 2.8 Hz CH=C), 7.42 (dd, 1H, *J* = 7.9, 4.8 Hz, *H*₅-pyridine), 7.28–7.33 (m, 5H, Ph), 6.80 (s, 4H, CH₃OC₆H₄), 4.60 (s, 2H, PhCH₂OCH₂), 4.12 (AB d, 1H, *J* = 10.1 Hz, CH₃OC₆H₄OCHH), 4.06 (AB d, 1H, *J* = 10.1 Hz, CH₃OC₆H₄OCH H), 3.69–3.76 (m, 5H, CH₃OC₆H₄, PhCH₂OCH₂), 3.28 (dd, 1H, 17.9, 2.9 Hz, CHH-lactone), 3.21 (dd, 1H, 17.9, 2.9 Hz, CH H-lactone); ¹³C NMR (100 MHz, CDCl₃) δ 169.54, 153.58, 151.44, 149.28, 148.58, 136.44, 136.22, 131.36, 127.62, 127.15, 127.08, 126.82, 123.12, 114.88, 113.80, 82.52, 72.91, 70.97, 69.80, 54.84, 31.94; IR (neat) 1752 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 432.3 (MH⁺, 42%), 91.1 (100%). Anal. (C₂₆H₂₅NO₅•0.6H₂O) C, H, N.

7-Z (R₂ = 3-pyridyl): yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.50 (m, 2H, *H*₂ and *H*₆-pyridine), 7.55 (dt, 1H, *J* = 7.8, 2.1 Hz, *H*₄-pyridine), 7.18–7.34 (m, 6H, Ph, *H*₅-pyridine), 7.04 (t, 1H, *J* = 1.5 Hz, CH=C), 6.73–6.81 (m, 4H, CH₃OC₆H₄), 4.53 (AB q, 2H, *J* = 12.0 Hz, PhCH₂OCH₂), 4.19 (AB d, 1H, *J* = 11.8 Hz, CH₃OC₆H₄OCHH), 4.04 (AB d, 1H, *J* = 11.8 Hz, CH₃OC₆H₄OCHH), 3.77 (AB d, 1H, *J* = 12.2 Hz, PhCH₂OCHH), 3.75 (s, 3H, OCH₃), 3.68 (AB d, 1H, *J* = 12.2 Hz, PhCH₂OCH H), 3.63 (br s, 2H, CH₂-lactone); ¹³C NMR (100 MHz, CDCl₃) δ 171.93, 154.53, 152.29, 150.03, 148.93, 137.32, 136.53, 134.86, 132.91, 128.57, 128.03, 127.74, 123.71, 115.85, 114.76, 87.24, 73.90, 70.52, 69.22, 55.77, 29.15; IR (neat) 1758 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 432.3 (MH⁺, 100%). Anal. (C₂₆H₂₅NO₅•0.3H₂O) C, H, N.

7-E (R₂ = 4-pyridyl): Solid; mp 105–106 °C; ¹H NMR (400 MHz, CDCl₃) 8.66 (m, 2H, *H*₂ and *H*₆-pyridine), 7.43 (t, 1H, *J* = 2.9 Hz, CH=C), 7.29–7.31 (m, 2H, *H*₃ and *H*₅-pyridine), 7.22–7.28 (m, 5H, Ph), 6.76 (s, 4H, CH₃OC₆H₄), 4.55 (s, 2H, PhCH₂OCH₂), 4.07 (AB q, 2H, *J* = 9.9 Hz, CH₃OC₆H₄OCH₂), 3.70 (s, 3H, CH₃OC₆H₄), 3.71 (AB d, 1H, *J* = 10.2 Hz, PhCH₂OCHH), 3.67 (AB d, 1H, *J* = 10.2 Hz, PhCH₂OCH H), 3.27 (dd, 1H, *J* = 18.1, 2.9 Hz, CHH-lactone), 3.19 (dd, 1H, *J* = 18.1, 2.9 Hz, CH H-lactone); ¹³C NMR (100 MHz, CDCl₃) 170.24, 154.47, 152.30, 150.43, 141.79, 137.33, 133.13, 130.48, 128.51, 127.97, 127.70, 123.52, 115.77, 114.70, 73.76, 71.85, 70.68, 55.70, 32.85; IR (neat)

1751 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 432.2 (MH⁺, 100). Anal. (C₂₆H₂₅NO₅•0.3H₂O) C, H, N.

7-Z (R₂ = 4-pyridyl): yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.41 (m, 2H, *H*₂ and *H*₆-pyridine), 7.18–7.28 (m, 5H, Ph), 7.10 (m, 2H, *H*₃ and *H*₅-pyridine), 7.05 (t, 1H, *J* = 1.4 Hz, CH=C), 6.68–6.76 (m, 4H, CH₃OC₆H₄), 4.49 (AB q, 2H, *J* = 12.0 Hz, PhCH₂OCH₂), 4.16 (AB d, 1H, *J* = 9.9 Hz, CH₃OC₆H₄OCHH), 4.00 (AB d, 1H, *J* = 9.9 Hz, CH₃OC₆H₄OCH H), 3.76 (AB d, 1H, *J* = 9.9 Hz, PhCH₂OCHH), 3.70 (s, 3H, CH₃OC₆H₄), 3.66 (d, 1H, *J* = 9.9 Hz, PhCH₂OCH H), 3.58 (br s, 2H, CH₂-lactone); ¹³C NMR (100 MHz, CDCl₃) δ 171.88, 154.58, 152.25, 150.56, 149.50, 146.73, 137.26, 133.79, 128.61, 128.58, 128.12, 127.80, 127.77, 124.19, 123.56, 115.82, 114.79, 114.76, 113.58, 87.35, 73.98, 70.54, 69.26, 55.78, 31.17; IR (neat) 1758 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 432.1 (MH⁺, 100). Anal. (C₂₆H₂₅NO₅) C, H, N.

7-E (R₂ = 2-quinolyl): colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, 1H, *J* = 8.4 Hz, *H*₄-quinoline), 8.12 (d, 1H, *J* = 8.4 Hz, *H*₅-quinoline), 7.82 (dm, 1H, *J* = 8.2 Hz, *H*₈-quinoline), 7.73 (m, 2H, *H*₇-quinoline), 7.68 (t, 1H, *J* = 3.1 Hz, CH=C), 7.56 (dm, 1H, *H*₆-quinoline), 7.53 (d, 1H, *J* = 8.4 Hz, *H*₃-quinoline), 7.25–7.31 (m, 5H, Ph), 6.78–6.85 (m, 4H, CH₃OC₆H₄), 4.62 (AB m, 2H, PhCH₂OCH₂), 4.15 (AB m, 2H, CH₃OC₆H₄OCH₂), 3.78 (s, 2H, PhCH₂OCH₂), 3.69–3.74 (m, 4H, CH₃OC₆H₄, CHH-lactone), 3.66 (dd, 1H, *J* = 19.9, 3.1 Hz, CHH-lactone); ¹³C NMR (100 MHz, CDCl₃) δ 171.34, 154.40, 154.02, 152.75, 148.46, 137.75, 136.58, 133.73, 131.58, 130.09, 130.00, 128.54, 127.88, 127.76, 127.67, 127.47, 127.35, 123.96, 115.96, 114.73, 84.31, 73.85, 72.31, 71.01, 55.82, 34.55; IR (neat) 1755 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 482.5 (MH⁺, 100%). Anal. (C₃₀H₂₇NO₅) C, H, N.

7-Z (R₂ = 2-quinolyl): colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, 1H, *J* = 8.5 Hz, *H*₄-quinoline), 8.03 (d, 1H, *J* = 8.5 Hz, *H*₅-quinoline), 7.80 (d, 1H, *J* = 8.0 Hz, *H*₈-quinoline), 7.71 (m, 1H, *H*₇-quinoline), 7.52 (m, 1H, *H*₆-quinoline), 7.36 (d, 1H, *J* = 8.5 Hz, *H*₃-quinoline), 7.21–7.28 (m, 6H, Ph, CH=C), 6.72–6.78 (m, 4H, CH₃OC₆H₄), 4.54 (AB q, 2H, *J* = 12.0 Hz, PhCH₂OCH₂), 4.22 (dm, 1H, *J* = 9.8 Hz, CH₃OC₆H₄OCHH), 4.06 (dm, 1H, *J* = 9.8 Hz, CH₃OC₆H₄OCHH), 4.02 (br s, 2H, PhCH₂OCH₂), 3.79 (dm, 1H, *J* = 10.2 Hz, CHH-lactone), 3.74 (s, 3H, CH₃OC₆H₄), 3.72 (dm, 1H, *J* = 10.2 Hz, CHH-lactone); ¹³C NMR (100 MHz, CDCl₃) δ 172.26, 157.55, 154.32, 152.27, 149.44, 137.31, 136.96, 133.72, 129.67, 128.83, 128.37, 127.79, 127.59, 127.55, 126.94, 126.30, 121.40, 115.77, 114.56, 87.23, 73.75, 70.44, 69.18, 55.64, 34.88; IR (neat) 1758 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 482.7 (MH⁺, 100%). Anal. (C₃₀H₂₇NO₅) C, H, N.

7-E (R₂ = 3-quinolyl): yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 9.04 (d, 1H, *J* = 2.2 Hz, *H*₂-quinoline), 8.23 (br d, 1H, *J* = 1.9 Hz, *H*₄-quinoline), 8.13 (d, 1H, *J* = 8.4 Hz, *H*₅-quinoline), 7.88 (dm, 1H, *J* = 8.4 Hz, *H*₈-quinoline), 7.77 (m, 1H, *H*₇-quinoline), 7.71 (t, 1H, *J* = 2.9 Hz, CH=C), 7.60 (m, 1H, *H*₆-quinoline), 7.24–7.32 (m, 5H, Ph), 6.78–6.83 (m, 4H, CH₃OC₆H₄), 4.60 (s, 2H, PhCH₂OCH₂), 4.11 (AB q, 2H, *J* = 9.9 Hz, CH₃OC₆H₄OCH₂), 3.75 (AB q, 2H, *J* = 10.2 Hz, CH₃OC₆H₄OCH₂), 3.74 (s, 3H, CH₃OC₆H₄), 3.39 (dd, 1H, *J* = 17.8, 2.9 Hz, CHH-lactone), 3.31 (dd, 1H, *J* = 2.9, 17.8 Hz, CHH-lactone); ¹³C NMR (100 MHz, CDCl₃) δ 170.74, 154.52, 152.46, 151.14, 147.96, 137.44, 136.83, 132.90, 131.01, 129.45, 128.59, 128.51, 128.03, 127.28, 127.80, 127.64, 127.47, 115.87, 114.77, 83.47, 73.89, 71.99, 70.81, 55.79, 33.07, 31.63; IR (neat) 1751 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 482.1 (MH⁺, 100%). This material was used in the next step without further attempts to obtain an analytically pure sample.

7-Z (R₂ = 3-quinolyl): yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 9.00 (s, 2H, *H*₂ and *H*₄-quinoline), 8.08 (d, 1H, *J* = 8.4 Hz, *H*₅-quinoline), 7.89 (dd, 1H, *J* = 8.4, 1.1 Hz, *H*₈-quinoline), 7.74 (m, 1H, *H*₇-quinoline), 7.56 (m, 1H, *H*₆-quinoline), 7.27–7.32 (m, 5H, Ph), 7.09 (t, 1H, *J* = 2.4 Hz, CH=C), 6.75–6.82 (m, 4H, CH₃OC₆H₄), 4.62 (AB m, 2H, PhCH₂OCH₂), 4.11 (AB q, 2H, *J* = 9.9 Hz, CH₃OC₆H₄OCH₂), 3.70–3.83 (m, 5H, CH₃OC₆H₄OCH₂, CH₃OC₆H₄), 3.27 (dd, 1H, *J* = 17.2, 2.4 Hz, CHH-lactone), 3.21 (dd, 1H, *J* = 17.2, 2.4 Hz, CHH-lactone); ¹³C NMR (100 MHz,

CDCl_3) δ 167.84, 154.54, 152.58, 152.21, 147.93, 137.77, 137.62, 135.56, 130.59, 129.27, 129.00, 128.63, 128.05, 127.82, 127.80, 127.53, 127.07, 126.85, 115.86, 114.84, 82.87, 73.96, 72.13, 70.77, 55.87, 36.11; IR (neat) 1755 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 482.4 (MH^+ , 100%). Anal. ($\text{C}_{30}\text{H}_{27}\text{NO}_5$) C, H, N.

General Procedure for the Synthesis of 9. Ceric ammonium nitrate (CAN, 3 equiv) was added to a stirring solution of **7** (1 equiv) in acetonitrile (8 mL/mmol of **7**) and water (2 mL/mmol of **7**) at 0 °C. The reaction was monitored by TLC and quenched after 30 min with a saturated aqueous NaHCO_3 solution, and the mixture was warmed to room temperature. The resulting aqueous solution was extracted with EtOAc ($3\times$), dried (MgSO_4), and concentrated in vacuo. Purification by silica gel flash column chromatography [CH_2Cl_2 – MeOH (0% $\rightarrow$ 10%)] gave intermediate **9**.

9-E ($\text{R}_2 = 2\text{-pyridyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.67 (dm, 1H, $J = 4.3$ Hz, H_6 -pyridine), 7.70 (td, 1H, $J = 7.7$, 1.8 Hz, H_4 -pyridine), 7.46 (t, 1H, $J = 3.0$ Hz, $\text{CH}=\text{C}$), 7.40 (d, 1H, $J = 7.8$ Hz, H_5 -pyridine), 7.20–7.31 (m, 6H, Ph, H_3 -pyridine), 4.55 (s, 2H, $\text{PhCH}_2\text{OCH}_2$), 3.84 (AB d, 1H, $J = 12.1$ Hz, HOCHH), 3.72 (AB d, 1H, $J = 12.1$ Hz, HOCHH), 3.63 (s, 2H, $\text{PhCH}_2\text{OCH}_2$), 3.40 (dd, 1H, $J = 19.6$, 3.0 Hz, CHH -lactone), 3.36 (dd, 1H, $J = 19.6$, 3.0 Hz, CHH -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 171.70, 153.95, 150.02, 137.69, 136.58, 133.85, 130.22, 128.49, 127.85, 127.69, 126.85, 123.33, 85.56, 73.77, 72.17, 65.65, 33.57; IR (neat) 3412 (OH), 1746 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 326.2 (MH^+ , 97%), 91.1 (100%). Anal. ($\text{C}_{19}\text{H}_{19}\text{NO}_4$) C, H, N.

9-Z ($\text{R}_2 = 2\text{-pyridyl}$): colorless oil; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 8.55 (d, 1H, $J = 4.8$ Hz, H_6 -pyridine), 7.88 (t, 1H, $J = 7.8$ Hz, H_4 -pyridine), 7.56 (d, 1H, $J = 7.8$ Hz, H_3 -pyridine), 7.50 (irregular t, 1H, $J \approx 6.3$ Hz, H_5 -pyridine), 7.34 (s, 1H, $\text{CH}=\text{C}$), 7.16–7.26 (m, 5H, Ph), 4.42 (AB s, 2H, $\text{PhCH}_2\text{OCH}_2$), 3.95 (s, 2H, CH_2OH), 3.74 (AB q, 2H, $J = 12.0$ Hz, $\text{PhCH}_2\text{OCH}_2$), 3.66 (AB q, 2H, $J = 10.4$ Hz, CH_2 -lactone); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 172.58, 153.98, 152.61, 144.12, 143.44, 137.33, 130.40, 128.43, 127.88, 127.76, 126.39, 124.23, 90.29, 73.80, 70.06, 62.64, 30.81; IR (neat) 3420 (OH), 1751 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 326.1 (MH^+ , 100%). Anal. ($\text{C}_{19}\text{H}_{19}\text{NO}_4$) C, H, N.

9-E ($\text{R}_2 = 3\text{-pyridyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.71 (d, 1H, $J = 1.7$ Hz, H_2 -pyridine), 8.56 (dd, 1H, $J = 4.8$, 1.3 Hz, H_6 -pyridine), 7.77 (dt, 1H, $J = 8.0$, 1.8 Hz, H_4 -pyridine), 7.44 (t, 1H, $J = 2.9$ Hz, $\text{CH}=\text{C}$), 7.34 (dd, 1H, $J = 8.0$, 4.8 Hz, H_5 -pyridine), 7.21–7.30 (m, 5H, Ph), 4.53 (s, 2H, $\text{PhCH}_2\text{OCH}_2$), 3.84 (AB d, 1H, $J = 12.2$ Hz, HOCHH), 3.72 (AB d, 1H, $J = 12.2$ Hz, HOCHH), 3.60 (s, 2H, $\text{PhCH}_2\text{OCH}_2$), 3.20 (dd, 1H, $J = 17.8$, 2.9 Hz, CHH -lactone), 3.12 (dd, 1H, $J = 17.8$, 2.9 Hz, CHH -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 171.10, 150.81, 150.02, 137.47, 136.75, 132.47, 130.82, 128.54, 128.27, 127.97, 127.70, 123.88, 85.22, 73.77, 71.89, 65.09, 32.27; IR (neat) 3060 (OH), 1745 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 326.2 (MH^+ , 100%). Anal. ($\text{C}_{19}\text{H}_{19}\text{NO}_4$) C, H, N.

9-Z ($\text{R}_2 = 3\text{-pyridyl}$): white solid; mp 146–147 °C; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 8.54–8.66 (br doublets, 2H, H_2 and H_6 -pyridine), 8.02 (d, 1H, $J = 7.9$ Hz, H_4 -pyridine), 7.50 (br s, 1H, H_5 -pyridine), 7.20–7.31 (m, 6H, Ph, $\text{CH}=\text{C}$), 4.48 (AB q, $J = 12.0$ Hz, 1H, $\text{PhCH}_2\text{OCH}_2$), 3.71–3.81 (m, 4H, HOCH_2 , $\text{PhCH}_2\text{OCH}_2$), 3.66 (AB q, 2H, $J = 10.3$ Hz, CH_2 -lactone); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 172.71, 151.89, 145.06, 142.77, 141.00, 137.30, 131.90, 128.42, 127.88, 127.68, 126.50, 126.48, 90.21, 73.74, 70.17, 62.46, 28.49; IR (neat) 3376 (OH), 1752 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 326.1 (MH^+ , 100%). Anal. ($\text{C}_{19}\text{H}_{19}\text{NO}_4 \cdot 0.2\text{H}_2\text{O}$) C, H, N.

9-E ($\text{R}_2 = 4\text{-pyridyl}$): white solid; mp 144–145 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.67 (m, 2H, H_2 and H_6 -pyridine), 7.56 (m, 2H, H_3 and H_5 -pyridine), 7.34 (t, 1H, $J = 2.9$ Hz, $\text{CH}=\text{C}$), 7.23–7.31 (m, 5H, Ph), 5.25 (t, 1H, $J = 5.8$ Hz, HOCH_2), 4.52 (s, 2H, $\text{PhCH}_2\text{OCH}_2$), 3.52–3.66 (m, 4H, $\text{PhCH}_2\text{OCH}_2$, HOCH_2), 3.20 (dd, 1H, $J = 18.4$, 2.9 Hz, CHH -lactone), 3.12 (dd, 1H, $J = 18.4$, 2.9 Hz, CHH -lactone); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 170.33, 150.29, 150.26, 141.52, 137.97, 132.34, 130.91, 130.85, 128.24, 127.48, 127.25, 123.58, 123.55, 85.73, 72.53, 71.75, 63.43, 31.90;

IR (neat) 3144 (OH), 1745 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 326.2 (MH^+ , 100%). Anal. ($\text{C}_{19}\text{H}_{19}\text{NO}_4 \cdot 0.3\text{H}_2\text{O}$) C, H, N.

9-Z ($\text{R}_2 = 4\text{-pyridyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.40 (m, 2H, H_2 and H_6 -pyridine), 7.23–7.34 (m, 5H, Ph), 7.14 (m, 2H, H_3 and H_5 -pyridine), 7.04 (t, 1H, $J = 1.4$ Hz, $\text{CH}=\text{C}$), 4.51 (AB q, 2H, $J = 11.9$ Hz, $\text{PhCH}_2\text{OCH}_2$), 3.82 (AB q, 2H, $J = 12.0$ Hz, HOCH_2), 3.74 (d, 1H, $J = 10.0$ Hz, PhCH_2OCHH), 3.60–3.63 (overlapped d and br s, 3H, PhCH_2OCHH , CH_2 -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 172.36, 150.22, 149.54, 147.06, 137.34, 133.50, 128.61, 128.11, 127.78, 124.32, 89.23, 73.96, 70.48, 63.63, 31.17; IR (neat) 3316 (OH), 1754 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 326.1 (MH^+ , 100%). Anal. ($\text{C}_{19}\text{H}_{19}\text{NO}_4 \cdot 0.2\text{H}_2\text{O}$) C, H, N.

9-E ($\text{R}_2 = 2\text{-quinolyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, 1H, $J = 8.4$ Hz, H_4 -quinoline), 8.11 (d, 1H, $J = 8.4$ Hz, H_5 -quinoline), 7.82 (dm, 1H, $J = 8.4$ Hz, H_8 -quinoline), 7.73 (m, 1H, H_7 -quinoline), 7.65 (t, 1H, $J = 3.1$ Hz, $\text{CH}=\text{C}$), 7.55 (m, 1H, H_6 -quinoline), 7.51 (d, 1H, $J = 8.4$ Hz, H_3 -quinoline), 7.25–7.30 (m, 5H, Ph), 4.59 (s, 2H, $\text{PhCH}_2\text{OCH}_2$), 3.90 (AB d, 1H, $J = 12.2$ Hz, HOCHH), 3.79 (AB d, 1H, $J = 12.2$ Hz, HOCHH), 3.67 (s, 2H, $\text{PhCH}_2\text{OCH}_2$), 3.65 (dd, 1H, $J = 19.8$, 3.1 Hz, CHH -lactone), 3.55 (dd, 1H, $J = 19.8$, 3.1 Hz, CHH -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 171.39, 153.81, 137.68, 137.42, 130.27, 129.80, 128.61, 128.57, 127.95, 127.83, 127.78, 127.70, 127.65, 127.40, 123.86, 85.66, 73.97, 73.86, 72.17, 65.83, 33.07; ^{13}C NMR (100 MHz, CDCl_3) δ 171.39, 153.81, 137.68, 137.42, 130.27, 129.80, 128.61, 128.57, 127.95, 127.83, 127.78, 127.70, 127.65, 127.40, 123.86, 85.66, 73.97, 73.86, 72.17, 65.83, 33.95; IR (neat) 3348 (OH), 1754 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 376.1 (MH^+ , 100%). This material was used in the next step without further attempts to obtain an analytically pure sample.

9-Z ($\text{R}_2 = 2\text{-quinolyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.47 (d, 1H, $J = 8.4$ Hz, H_4 -quinoline), 8.36 (d, 1H, $J = 8.4$ Hz, H_5 -quinoline), 7.96 (d, 1H, $J = 8.3$ Hz, H_8 -quinoline), 7.92 (irregular t, 1H, $J \approx 7.7$ Hz, H_7 -quinoline), 7.81 (d, 1H, $J = 8.4$ Hz, H_6 -quinoline), 7.74 (t, 1H, $J = 7.6$ Hz, H_3 -quinoline), 7.61 (br s, 1H, $\text{CH}=\text{C}$), 7.19–7.27 (m, 5H, Ph), 4.45 (s, 2H, $\text{PhCH}_2\text{OCH}_2$), 4.32 (AB q, 2H, $J = 15.8$ Hz, HOCH_2), 3.83 (AB q, 2H, $J = 12.0$ Hz, $\text{PhCH}_2\text{OCH}_2$), 3.73 (AB q, 2H, $J = 10.5$ Hz, CH_2 -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 172.26, 155.98, 154.00, 146.01, 138.58, 137.51, 134.81, 129.26, 128.57, 128.55, 128.53, 127.92, 127.90, 127.51, 122.93, 121.51, 90.66, 73.89, 70.21, 62.96, 30.69; FAB-MS (m/z , relative intensity) 376.1 (MH^+ , 100%). This material decomposed on standing and was not analyzed.

9-E ($\text{R}_2 = 3\text{-quinolyl}$): with solid; mp 138–139 °C; ^1H NMR (400 MHz, CDCl_3) δ 9.02 (d, 1H, $J = 2.2$ Hz, H_2 -quinoline), 8.23 (d, 1H, $J = 2.0$ Hz, H_4 -quinoline), 8.11 (d, 1H, $J = 8.4$ Hz, H_5 -quinoline), 7.85 (dm, 1H, $J = 8.2$ Hz, H_8 -quinoline), 7.76 (m, 1H, H_7 -quinoline), 7.64 (t, 1H, $J = 2.9$ Hz, $\text{CH}=\text{C}$), 7.59 (m, 1H, H_6 -quinoline), 7.22–7.31 (m, 5H, Ph), 4.56 (s, 2H, $\text{PhCH}_2\text{OCH}_2$), 3.91 (AB d, 1H, $J = 12.2$ Hz, HOCHH), 3.81 (AB d, 1H, $J = 12.2$ Hz, HOCHH), 3.68 (AB q, 2H, $J = 10.2$ Hz, $\text{PhCH}_2\text{OCH}_2$), 3.33 (dd, 1H, $J = 17.8$, 2.9 Hz, CHH -lactone), 3.33 (dd, 1H, $J = 17.8$, 2.9 Hz, CHH -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 171.18, 151.08, 147.76, 137.46, 137.00, 132.84, 132.85, 131.06, 129.25, 128.58, 128.50, 128.02, 127.94, 127.78, 127.66, 85.15, 73.85, 71.96, 65.26, 32.49; IR (neat) 3420 (OH), 1745 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 376.4 (MH^+ , 100%). Anal. ($\text{C}_{23}\text{H}_{21}\text{NO}_4 \cdot 0.3\text{H}_2\text{O}$) C, H, N.

9-Z ($\text{R}_2 = 3\text{-quinolyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.82 (d, 1H, $J = 1.7$ Hz, H_2 -quinoline), 8.12 (d, 1H, $J = 8.4$ Hz, H_5 -quinoline), 8.08 (d, 1H, $J = 1.7$ Hz, H_4 -quinoline), 7.68–7.74 (m, 2H, H_7 and H_8 -quinoline), 7.54 (m, 1H, H_6 -quinoline), 7.22–7.31 (m, 5H, Ph), 7.07 (t, 1H, $J = 1.4$ Hz, $\text{CH}=\text{C}$), 4.52 (AB q, 2H, $J = 12.0$ Hz, $\text{PhCH}_2\text{OCH}_2$), 3.83 (AB q, 2H, $J = 12.0$ Hz, HOCH_2), 3.80 (br s, 2H, $\text{PhCH}_2\text{OCH}_2$), 3.73 (AB d, 1H, $J = 10.0$ Hz, CH_2 -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 172.37, 150.56, 150.04, 145.70, 137.35, 137.02, 134.33, 130.41, 130.20, 130.16, 128.63, 128.22, 128.10, 127.81, 127.77, 127.54, 89.11, 73.97, 70.53, 63.78, 29.39; IR (neat) 3450 (OH), 1738 (CO) cm^{-1} ;

FAB-MS (m/z , relative intensity) 376.1 (MH^+ , 100%). Anal. ($C_{23}H_{21}NO_4 \cdot 0.8H_2O$) C, H, N.

General Procedure for the Synthesis of 11. A solution of **9** (1 equiv) in CH_2Cl_2 (12 mL/mmol) was treated with Et_3N (3 equiv), R_1COCl (1.5 equiv), and a catalytic amount of DMAP (0.1 equiv). The mixture was stirred at room temperature and monitored by TLC. Upon completion, the mixture was concentrated in vacuo and purified by silica gel flash column chromatography [hexanes– $EtOAc$ (0% $\rightarrow$ 75%)] to give **11**.

11-E ($R_1 = 4-(CH_3)_2NC_6H_4$, $R_2 = 2$ -pyridyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.68 (dm, 1H, $J = 4.8$ Hz, H_6 -pyridine), 7.79 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 7.70 (td, 1H, $J = 7.7$, 1.9 Hz, H_4 -pyridine), 7.50 (t, 1H, $J = 3.0$ Hz, $CH=C$), 7.40 (d, 1H, $J = 7.8$ Hz, H_3 -pyridine), 7.20–7.30 (m, 6H, Ph, H_5 -pyridine), 6.57 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.62 (s, 2H, $PhCH_2O$), 4.48 (AB m, 2H, CO_2CH_2), 3.72 (AB m, 2H, $PhCH_2OCH_2$), 3.56 (dd, 1H, $J = 19.6$, 3.0 Hz, CHH -lactone), 3.52 (dd, 1H, $J = 19.6$, 3.0 Hz, CHH -lactone), 3.01 (s, 6H, $(CH_3)_2NC_6H_4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.43, 166.39, 153.95, 153.55, 150.11, 137.63, 136.53, 133.70, 131.58, 129.95, 128.52, 127.87, 127.73, 126.87, 123.32, 116.11, 110.77, 83.87, 73.85, 72.23, 66.00, 40.13, 34.29; IR (neat) 1754 (CO), 1701 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 473.2 (MH^+ , 41%), 148.1 (MH^+ , 100%). Anal. ($C_{28}H_{28}N_2O_5$) C, H, N.

11-E ($R_1 = 4-(CH_3)_2NC_6H_4$, $R_2 = 3$ -pyridyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, 1H, $J = 2.0$ Hz, H_2 -pyridine), 8.58 (dd, 1H, $J = 4.8$, 1.4 Hz, H_6 -pyridine), 7.72–7.77 (m, 3H, H_4 -pyridine, $(CH_3)_2NC_6H_4CO_2$), 7.51 (t, 1H, $J = 2.9$ Hz, $CH=C$), 7.34 (dd, 1H, $J = 8.0$, 4.8 Hz, H_5 -pyridine), 7.26–7.30 (m, 5H, Ph), 6.56 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.59 (AB q, 2H, $J = 12.1$ Hz, $PhCH_2O$), 4.52 (AB d, $J = 12.1$ Hz, 1H, CO_2CHH), 4.42 (AB d, $J = 12.1$ Hz, 1H, CO_2CHH), 3.73 (AB d, 1H, $J = 10.2$ Hz, $PhCH_2OCHH$), 3.71 (AB q, 2H, $J = 10.2$ Hz, $PhCH_2OCH_2$), 3.24 (dd, 1H, $J = 17.8$, 2.9 Hz, CHH -lactone), 3.14 (dd, 1H, $J = 17.8$, 2.9 Hz, CHH -lactone), 3.01 (s, 6H, $(CH_3)_2NC_6H_4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.56, 166.24, 153.63, 151.15, 150.33, 137.32, 136.23, 132.62, 131.54, 130.56, 128.58, 128.04, 127.79, 127.63, 123.78, 115.64, 110.75, 83.26, 73.88, 71.83, 65.75, 40.09, 33.03; IR (neat) 1753 (CO), 1700 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 473.3 (MH^+ , 36%), 148.1 (MH^+ , 100%). Anal. ($C_{28}H_{28}N_2O_5 \cdot 0.3H_2O$) C, H, N.

11-Z ($R_1 = 4-(CH_3)_2NC_6H_4$, $R_2 = 3$ -pyridyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.40–8.42 (m, 2H, H_2 and H_6 -pyridine), 7.71 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 7.37 (dt, 1H, $J = 6.1$, ~ 1.9 Hz, H_4 -pyridine), 7.21–7.31 (m, 5H, Ph), 7.04 (ddd, 1H, $J = 4.9$, 3.0, ~ 0.7 Hz, H_5 -pyridine), 6.90 (t, 1H, $J = 1.5$ Hz, $CH=C$), 6.56 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.65 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 4.51 (AB q, 2H, $J = 12.0$ Hz, $PhCH_2O$), 4.36 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 3.71 (AB d, 1H, $J = 10.1$ Hz, $PhCH_2OCHH$), 3.60 (AB d, 1H, $J = 10.1$ Hz, $PhCH_2OCHH$), 3.51 (br s, 2H, CCH_2 -lactone), 3.01 (s, 3H, $(CH_3)_2NC_6H_4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.93, 166.12, 153.69, 149.89, 148.27, 148.13, 137.19, 136.54, 135.00, 132.77, 131.51, 128.62, 128.09, 127.81, 123.72, 115.63, 110.85, 87.45, 73.97, 70.69, 63.01, 40.13, 29.11; IR (neat) 1755 (CO), 1702 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 473.2 (MH^+ , 95%), 148.1 (MH^+ , 100%). Anal. ($C_{28}H_{28}N_2O_5 \cdot 0.1H_2O$) C, H, N.

11-E ($R_1 = 4-(CH_3)_2NC_6H_4$, $R_2 = 4$ -pyridyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.62 (br d, 2H, $J = 6.0$ Hz, H_2 and H_6 -pyridine), 7.70 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 7.38 (t, 1H, $J = 2.9$ Hz, $CH=C$), 7.22–7.25 (m, 7H, Ph, H_3 and H_5 -pyridine), 6.52 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.53 (AB q, 2H, $J = 11.8$ Hz, $PhCH_2O$), 4.50 (AB d, 1H, $J = 12.0$ Hz, CO_2CHH), 4.37 (AB d, 1H, $J = 12.0$ Hz, CO_2CHH), 3.67 (AB m, 2H, $J = PhCH_2OCH_2$), 3.21 (dd, 1H, $J = 18.0$, 2.9 Hz, CHH -lactone), 3.12 (dd, 1H, $J = 18.0$, 2.9 Hz, CHH -lactone), 2.98 (s, 6H, $(CH_3)_2NC_6H_4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.17, 166.19, 153.65, 149.90, 142.31, 137.24, 132.88, 131.55, 130.90, 128.59, 128.07, 127.80, 123.65, 115.52, 110.74, 83.59, 73.89, 71.72, 65.62, 40.09, 33.03; IR (neat)

1762 (CO), 1703 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 473.2 (MH^+ , 73%), 148.1 (MH^+ , 100%). Anal. ($C_{28}H_{28}N_2O_5 \cdot 0.5H_2O$).

11-Z ($R_1 = 4-(CH_3)_2NC_6H_4$, $R_2 = 4$ -pyridyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.32 (br d, $J = 6.0$ Hz, 2H, H_2 and H_6 -pyridine), 7.74 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 7.27–7.36 (m, 5H, Ph), 7.07 (br d, 2H, $J = 6.0$ Hz, H_3 and H_5 -pyridine), 7.05 (t, 1H, $J = 1.4$ Hz, $CH=C$), 6.59 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.78 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 4.55 (AB q, 2H, $J = 11.9$ Hz, $PhCH_2O$), 4.38 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 3.77 (AB d, 1H, $J = 10.1$ Hz, $PhCH_2OCHH$), 3.67 (AB d, 1H, $J = 10.1$ Hz, $PhCH_2OCHH$), 3.58 (br s, 2H, CH_2 -lactone), 2.98 (s, 6H, $(CH_3)_2NC_6H_4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.85, 166.21, 153.81, 149.17, 148.66, 137.15, 133.54, 131.58, 128.70, 128.24, 127.91, 124.43, 115.40, 110.91, 110.85, 87.76, 74.11, 70.79, 62.88, 40.20, 31.29; IR (neat) 1759 (CO), 1698 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 473.2 (MH^+ , 100%). Anal. ($C_{28}H_{28}N_2O_5$) C, H, N.

11-E ($R_1 = 4-(CH_3)_2NC_6H_4$, $R_2 = 2$ -quinolyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1H, $J = 8.4$ Hz, H_4 -quinoline), 8.07 (d, 1H, $J = 8.4$ Hz, H_5 -quinoline), 7.80 (m, 3H, $(CH_3)_2NC_6H_4CO_2$, H_8 -quinoline), 7.69 (m, 1H, H_7 -quinoline), 7.64 (t, 1H, $J = 3.0$ Hz, $CH=C$), 7.52 (m, 1H, H_6 -quinoline), 7.47 (d, 1H, $J = 8.4$ Hz, H_3 -quinoline), 7.20–7.28 (m, 5H, Ph), 6.53 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.58 (s, 2H, $PhCH_2O$), 4.49 (AB q, 2H, $J = 12.00$ Hz, CO_2CH_2), 3.61–3.78 (overlapping AB q and dd, 3H, $J = 10.2$ and 19.8, 3.0 Hz, $PhCH_2OCH_2$ and CHH -lactone), 3.60 (dd, 1H, $J = 19.8$, 3.0 Hz, CHH -lactone), 3.01 (s, 6H, $(CH_3)_2NC_6H_4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.35, 166.45, 153.93, 153.59, 148.48, 137.64, 136.55, 133.70, 131.62, 131.53, 130.17, 130.03, 128.56, 127.91, 127.79, 127.63, 127.49, 127.35, 123.86, 116.12, 110.80, 84.08, 73.89, 72.23, 66.08, 40.15, 34.62; IR (neat) 1759 (CO), 1701 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 523.3 (MH^+ , 40%), 148.1 (MH^+ , 100%). Anal. ($C_{32}H_{30}N_2O_5 \cdot 0.1H_2O$) C, H, N.

11-Z ($R_1 = 4-(CH_3)_2NC_6H_4$, $R_2 = 2$ -quinolyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.02 (br d, 1H, $J = 8.4$ Hz, H_4 -quinoline), 7.94 (d, 1H, $J = 8.4$ Hz, H_5 -quinoline), 7.73–7.77 (m, 4H, $(CH_3)_2NC_6H_4CO_2$, H_7 and H_8 -quinoline), 7.51 (m, 1H, $J = H_6$ -quinoline), 7.20–7.31 (m, 7H, Ph, H_3 -quinoline, $CH=C$), 6.50 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.66 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 4.56 (AB q, 2H, $J = 12.0$ Hz, $PhCH_2O$), 4.45 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 3.98 (br s, 2H, $PhCH_2OCH_2$), 3.77 (AB d, 1H, $J = 10.1$ Hz, $C_6H_5CH_2OCHH$), 3.66 (AB d, 1H, $J = 10.1$ Hz, $C_6H_5CH_2OCHH$), 3.02 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.39, 166.09, 157.44, 153.57, 149.35, 149.33, 137.30, 133.74, 131.50, 130.02, 128.62, 128.57, 128.00, 127.84, 127.80, 127.66, 127.07, 126.57, 121.50, 115.81, 110.74, 87.50, 73.78, 70.86, 63.18, 40.14, 34.69; IR (neat) 1762 (CO), 1703 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 523.2 (MH^+ , 87%), 148.1 (MH^+ , 100%). This material was used in the next step without further attempts to obtain an analytically pure sample.

11-E ($R_1 = 4-(CH_3)_2NC_6H_4$, $R_2 = 3$ -quinolyl): yellow solid; mp 146–147 $^{\circ}C$; 1H NMR (400 MHz, $CDCl_3$) δ 8.94 (br d, 1H, $J = 1.7$ Hz, H_2 -quinoline), 8.14 (br d, 1H, $J = 1.8$ Hz, H_4 -quinoline), 8.07 (d, 1H, $J = 8.4$ Hz, H_5 -quinoline), 7.82 (dm, 1H, $J = 8.4$ Hz, H_8 -quinoline), 7.71–7.75 (m, 3H, H_7 -quinoline, $(CH_3)_2NC_6H_4CO_2$), 7.64 (br t, 1H, $J = 2.9$ Hz, $CH=C$), 7.56 (m, 1H, H_6 -quinoline), 7.20–7.29 (m, 5H, Ph), 6.51 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.57 (AB m, 2H, $PhCH_2OCH_2$), 4.53 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 4.41 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 3.78 (AB q, 2H, $J = 10.1$ Hz, $C_6H_5CH_2OCH_2$), 3.32 (dd, 1H, $J = 17.8$, 2.9 Hz, CHH -lactone), 3.22 (dd, 1H, $J = 17.8$, 2.9 Hz, CHH -lactone), 2.96 (s, 3H, $(CH_3)_2NC_6H_4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.68, 166.26, 153.60, 151.19, 147.98, 137.32, 136.58, 132.74, 131.53, 130.95, 129.43, 128.59, 128.50, 128.03, 127.82, 127.58, 127.49, 115.63, 110.73, 83.33, 73.91, 71.86, 65.79, 40.07, 33.20; IR (neat) 1752 (CO), 1699 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 523.5 (MH^+ , 75%), 148.2 (MH^+ , 100%). Anal. ($C_{32}H_{30}N_2O_5 \cdot 0.5H_2O$) C, H, N.

11-Z ($R_1 = 4-(CH_3)_2NC_6H_4$, $R_2 = 3$ -quinolyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, 1H, $J = 2.2$ Hz, H_2 -quinoline), 8.07 (d, 1H, $J = 8.4$ Hz, H_8 -quinoline), 7.92 (br d, 1H, $J = 1.8$ Hz, H_4 -quinoline), 7.64–7.70 (m, 3H, $(CH_3)_2NC_6H_4CO_2$, H_5 -quinoline), 7.49 (br dm, 1H, $J = 8.0$ Hz, H_7 -quinoline), 7.48 (m, 1H, H_6 -quinoline), 7.24–7.32 (m, 5H, Ph), 7.03 (t, 1H, $J = 1.4$ Hz, $CH=C$), 6.46 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.69 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 4.54 (AB q, 2H, $J = 12.0$ Hz, $PhCH_2OCH_2$), 4.41 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 3.74–3.76 (m, 3H, $C_6H_5CH_2OCH_2$, CHH -lactone), 3.64 (AB d, 1H, $J = 10.1$ Hz, CHH -lactone), 2.99 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.00, 166.14, 153.56, 151.23, 148.43, 137.18, 135.74, 134.90, 131.40, 129.93, 129.41, 129.00, 128.98, 128.62, 128.09, 128.06, 127.80, 127.77, 126.93, 115.51, 110.74, 87.48, 74.00, 70.75, 63.01, 40.09, 29.32; IR (neat) 1762 (CO), 1702 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 523.2 (MH^+ , 100%). This material was used in the next step without further attempts to obtain an analytically pure sample.

11-E ($R_1 = 4-CH_3OC_6H_4$, $R_2 = 2$ -pyridyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.69 (dm, 2H, $J = 4.8$ Hz, H_6 -pyridine), 7.87 (m, 2H, $CH_3OC_6H_4CO_2$), 7.72 (td, 1H, $J = 7.7$, 1.8 Hz, H_4 -pyridine), 7.51 (t, 1H, $J = 3.0$ Hz, $CH=C$), 7.40 (d, 1H, $J = 7.7$ Hz, H_3 -pyridine), 7.21–7.30 (m, 6H, Ph, H_5 -pyridine), 6.85 (m, 2H, $CH_3OC_6H_4CO_2$), 4.60 (AB m, 2H, CO_2CH_2), 4.51 (AB q, 2H, $J = 11.9$ Hz, $C_6H_5CH_2OCH_2$), 3.83 (s, 3H, $CH_3OC_6H_4$), 3.71 (AB q, 2H, $J = 10.1$ Hz, $C_6H_5CH_2OCH_2$), 3.54 (dd, H, $J = 19.6$, 3.0 Hz, CHH -lactone), 3.47 (dd, 1H, $J = 19.6$, 3.0 Hz, CHH -lactone); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.31, 165.79, 163.69, 153.84, 150.09, 137.54, 136.65, 133.79, 131.90, 129.77, 128.55, 127.94, 127.79, 126.97, 123.43, 121.89, 113.77, 83.64, 73.87, 72.10, 66.46, 55.55, 34.35; IR (neat) 1755 (CO), 1714 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 460.2 (MH^+ , 95%), 135.1 (MH^+ , 100%). Anal. ($C_{27}H_{25}NO_6$) C, H, N.

11-Z ($R_1 = 4-CH_3OC_6H_4$, $R_2 = 2$ -pyridyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, $J = 4.6$ Hz, 1H, H_6 -pyridine), 7.78 (m, 2H, $CH_3OC_6H_4CO_2$), 7.49 (td, 1H, $J = 7.7$, 1.8 Hz, H_4 -pyridine), 7.24–7.31 (m, 5H, Ph), 7.17 (irregular br t, 1H, $CH=C$), 7.13 (d, 1H, $J = 7.7$ Hz, H_3 -pyridine), 7.11 (br dd, 1H, $J \approx 7.6$, 5.1 Hz, H_5 -pyridine), 6.85 (m, 2H, $CH_3OC_6H_4CO_2$), 4.63 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 4.56 (AB q, 2H, $J = 12.0$ Hz, $PhCH_2O$), 4.48 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 3.84 (s, 3H, $CH_3OC_6H_4$), 3.74–3.77 (m, 3H, $PhCH_2OCH_2$, CHH -lactone), 6.63 (AB d, 1H, $J = 10$ Hz, CHH -lactone); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.19, 165.52, 163.75, 156.05, 149.05, 148.82, 137.37, 137.24, 134.02, 131.86, 128.59, 128.05, 127.82, 123.60, 122.12, 121.71, 113.82, 87.05, 73.96, 70.78, 63.65, 55.58, 33.94; IR (neat) 1769 (CO), 1709 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 460.2 (MH^+ , 100%). Anal. ($C_{27}H_{25}NO_6 \cdot 0.5H_2O$) C, H, N.

11-E ($R_1 = 4-CH_3OC_6H_4$, $R_2 = 3$ -pyridyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, 1H, $J = 2.1$ Hz, H_2 -pyridine), 8.59 (dd, 1H, $J = 4.8$, 1.6 Hz, H_6 -pyridine), 7.84 (m, 2H, $CH_3OC_6H_4CO_2$), 7.73 (br dt, 1H, $J = 8.0$ Hz, H_4 -pyridine), 7.51 (t, 1H, $J = 2.9$ Hz, $CH=C$), 7.34 (br dd, 1H, $J \approx 8.0$, 4.5 Hz, H_5 -pyridine), 7.23–7.31 (m, 5H, Ph), 6.84 (m, 2H, $CH_3OC_6H_4CO_2$), 4.58 (AB q, $J = 12.1$ Hz, $PhCH_2O$), 4.53 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 4.46 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 3.82 (s, 3H, $CH_3OC_6H_4$), 3.69 (AB q, 2H, $J = 10.0$ Hz, $PhCH_2O$), 3.26 (dd, 1H, $J = 17.8$, 2.9 Hz, CHH -lactone), 3.12 (dd, 1H, $J = 17.8$, 2.9 Hz, CHH -lactone); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.40, 165.61, 163.78, 150.98, 150.36, 137.21, 136.35, 132.83, 131.82, 130.46, 128.58, 128.06, 127.80, 127.31, 123.81, 121.50, 113.81, 82.94, 73.86, 71.64, 66.18, 55.53, 33.08; IR (neat) 1757 (CO), 1715 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 135.1 (100%), 460.2 (MH^+ , 96%). Anal. ($C_{27}H_{25}NO_6$) C, H, N.

11-Z ($R_1 = 4-CH_3OC_6H_4$, $R_2 = 3$ -pyridyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.45 (br s, 2H, H_2 and H_6 -pyridine), 7.81 (m, 2H, $CH_3OC_6H_4CO_2$), 7.43 (br dt, 1H, $J = 8.0$ Hz, H_4 -pyridine), 7.24–7.35 (m, 5H, Ph), 7.10 (br dd, 1H, $J \approx 7.8$, 4.8 Hz, H_5 -pyridine), 6.96 (br t, 1H, $J \approx 1.5$ Hz, $CH=C$), 6.87 (m, 2H, $CH_3OC_6H_4CO_2$), 4.68 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 4.54 (AB q, 2H, $J = 12.0$ Hz, $C_6H_5CH_2O$), 4.45 (AB d, 1H, $J =$

11.8 Hz, CO_2CHH), 3.86 (s, 3H, $CH_3OC_6H_4$), 3.75 (AB d, 1H, $J = 10$ Hz, $C_6H_5CH_2OCHH$), 3.61 (AB d, 1H, $J = 10$ Hz, $PhCH_2OCHH$), 3.56 (AB m, 2H, CH_2 -lactone); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.79, 165.56, 163.89, 149.80, 148.13, 137.10, 136.61, 135.18, 132.92, 131.83, 128.67, 128.18, 127.87, 123.80, 121.50, 114.26, 113.95, 87.14, 74.01, 70.66, 63.49, 55.62, 29.16; IR (neat) 1763 (CO), 1716 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 460.2 (MH^+ , 100%). Anal. ($C_{27}H_{25}NO_6 \cdot 0.5H_2O$) C, H, N.

11-E ($R_1 = 4CH_3OC_6H_4$, $R_2 = 4$ -pyridyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.69 (irregular d, 2H, $J \approx 6.0$ Hz, H_2 and H_6 -pyridine), 7.83 (m, 2H, $CH_3OC_6H_4CO_2$), 7.45 (br t, 1H, $J = 3.0$ Hz, $CH=C$), 7.34 (br d, 2H, $J \approx 6.0$ Hz, H_3 and H_5 -pyridine), 7.26–7.30 (m, 5H, Ph), 6.86 (m, 2H, $CH_3OC_6H_4CO_2$), 4.58 (AB q, 2H, $J = 12.0$ Hz, $C_6H_5CH_2O$), 4.55 (AB d, 1H, $J = 12.0$ Hz, CO_2CHH), 4.46 (AB d, 1H, $J = 12.0$ Hz, CO_2CHH), 3.81 (s, 3H, $CH_3OC_6H_4$), 3.74 (AB q, 2H, $J = 10.1$ Hz, $C_6H_5CH_2OCH_2$), 3.69 (AB d, 1H, $J = 10.1$ Hz, $C_6H_5CH_2OCHH$), 3.28 (dd, 1H, $J = 18.1$, 3.0 Hz, CHH -lactone), 3.15 (dd, 1H, $J = 18.1$, 3.0 Hz, CHH -lactone); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.04, 165.66, 163.91, 149.89, 149.87, 137.17, 133.11, 131.90, 128.67, 128.20, 127.90, 123.71, 121.46, 113.89, 83.34, 73.97, 71.61, 66.12, 55.61, 33.15, 31.71, 22.78; IR (neat) 1760 (CO), 1715 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 460.2 (MH^+ , 100%). Anal. ($C_{27}H_{25}NO_6$) C, H, N.

11-Z ($R_1 = 4-CH_3OC_6H_4$, $R_2 = 4$ -pyridyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.35 (br d, 2H, $J = 6.0$ Hz, H_2 and H_6 -pyridine), 7.82 (m, 2H, $CH_3OC_6H_4CO_2$), 7.26–7.34 (m, 5H, Ph), 7.07 (m, 2H, H_3 and H_5 -pyridine), 7.05 (br t, 1H, $J = 1.4$ Hz, $CH=C$), 6.88 (m, 2H, $CH_3OC_6H_4CO_2$), 4.74 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 4.55 (AB q, $J = 12.0$ Hz, $C_6H_5CH_2O$), 4.45 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 3.88 (s, 3H, $CH_3OC_6H_4$), 3.79 (AB d, 1H, $J = 10.0$ Hz, $C_6H_5CH_2OCHH$), 3.65 (AB d, 1H, $J = 10$ Hz, $PhCH_2OCHH$), 3.58 (br s, 2H CH_2 -lactone); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.71, 165.62, 164.04, 149.07, 148.85, 147.25, 137.06, 133.92, 131.86, 128.73, 128.31, 127.95, 124.32, 121.39, 114.02, 87.36, 74.13, 70.71, 63.43, 55.70, 31.27; IR (neat) 1761 (CO), 1702 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 460.3 (MH^+ , 100%). Anal. ($C_{27}H_{25}NO_6$) C, H, N.

11-E ($R_1 = 4-CH_3OC_6H_4$, $R_2 = 2$ -quinolyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, 1H, $J = 8.4$ Hz, H_4 -quinoline), 8.17 (d, 1H, $J = 8.4$ Hz, H_5 -quinoline), 7.87 (m, 2H, $CH_3OC_6H_4CO_2$), 7.80 (br d, 1H, $J = 8.4$ Hz, H_8 -quinoline), 7.73 (m, 1H, H_6 -quinoline), 7.68 (t, 1H, $J = 3.0$ Hz, $CH=C$), 7.56 (m, 1H, H_7 -quinoline), 7.49 (d, 1H, $J = 8.4$ Hz, H_3 -quinoline), 7.24–7.32 (m, 5H, Ph), 6.84 (m, 2H, $CH_3OC_6H_4CO_2$), 4.62 (s, 2H, $C_6H_5CH_2OCH_2$), 4.55 (AB q, 2H, $J = 11.9$ Hz, CO_2CH_2), 3.81 (s, 3H, $CH_3OC_6H_4$), 3.71–3.79 (m, 3H, $C_6H_5CH_2OCH_2$, CHH -lactone), 3.66 (dd, 1H, $J = 19.8$, 3.0 Hz, CHH -lactone); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.18, 165.78, 163.64, 153.78, 148.41, 137.51, 136.57, 133.79, 131.86, 131.22, 130.07, 130.03, 128.54, 127.92, 127.78, 127.63, 127.51, 127.32, 123.89, 121.84, 113.75, 83.78, 73.84, 72.05, 66.47, 55.51, 34.63; IR (neat) 1761 (CO), 1715 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 510.3 (MH^+ , 81%), 135.1 (MH^+ , 100%). Anal. ($C_{31}H_{27}NO_6 \cdot 0.1H_2O$) C, H, N.

11-Z ($R_1 = 4-CH_3OC_6H_4$, $R_2 = 2$ -quinolyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.00 (br d, 1H, $J = 8.5$ Hz, H_4 -quinoline), 7.95 (d, 1H, $J = 8.3$ Hz, H_5 -quinoline), 7.73–7.77 (m, 3H, $CH_3OC_6H_4CO_2$, H_8 -quinoline), 7.68 (m, 1H, H_7 -quinoline), 7.51 (m, 1H, H_6 -quinoline), 7.24–7.29 (m, 7H, Ph, H_3 -quinoline, $CH=C$), 6.74 (m, 2H, $CH_3OC_6H_4CO_2$), 4.66 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 4.55 (AB q, 2H, $J = 12.0$ Hz, $C_6H_5CH_2O$), 4.53 (AB d, 1H, $J = 11.8$ Hz, C_6H_5CHHO), 4.50 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 3.98 (br AB d, 2H, $J = 1.4$ Hz, $C_6H_5CH_2OCH_2$), 3.81 (s, 3H, $CH_3OC_6H_4$), 3.78 (AB d, 1H, $J = 10.0$ Hz, CHH -lactone), 3.64 (AB d, 1H, $J = 10.0$ Hz, CHH -lactone); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.27, 165.47, 163.65, 157.39, 148.99, 137.19, 133.99, 131.72, 129.85, 128.84, 128.56, 128.03, 127.79, 127.64, 127.01, 126.47, 121.56, 121.43, 113.71, 87.14, 73.94, 70.80, 63.57, 55.52, 34.82; IR (neat) 1762 (CO), 1715

(CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 510.1 (MH^+ , 100%). Anal. ($\text{C}_{31}\text{H}_{27}\text{NO}_5$) C, H, N.

11-E ($\text{R}_1 = 4\text{-CH}_3\text{OC}_6\text{H}_4$, $\text{R}_2 = 3\text{-quinolyl}$): This intermediate was used directly in the next step without further purification or characterization.

11-Z ($\text{R}_1 = 4\text{-CH}_3\text{OC}_6\text{H}_4$, $\text{R}_2 = 3\text{-quinolyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.75 (d, 1H, $J = 2.0$ Hz, H_2 -quinoline), 8.07 (d, 1H, $J = 8.4$ Hz, H_8 -quinoline), 7.93 (d, 1H, $J = 2.0$ Hz, H_4 -quinoline), 7.74 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 7.66 (m, 1H, H_7 -quinoline), 7.62 (br dd, 1H, $J \approx 8.0$, 1.5 Hz, H_5 -quinoline), 7.51 (m, 1H, H_6 -quinoline), 7.24–7.32 (m, 5H, Ph), 7.04 (t, 1H, $J = 1.4$ Hz, $\text{CH}=\text{C}$), 6.72 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 4.68 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 4.57 (AB q, 2H, $J = 12.0$ Hz, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$), 4.45 (AB d, 1H, $J = 11.8$ Hz, CO_2CHH), 3.79 (s, 3H, OCH_3), 3.71–3.74 (m, 3H, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$, CHH -lactone), 3.62 (AB d, 1H, $J = 10.0$ Hz, CHH -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 171.85, 165.54, 163.72, 151.19, 148.19, 146.95, 137.07, 135.63, 135.12, 131.65, 129.87, 129.47, 129.06, 128.64, 128.15, 128.00, 127.83, 127.70, 127.01, 121.33, 113.80, 87.14, 74.00, 70.69, 63.45, 55.51, 29.32; IR (neat) 1763 (CO), 1714 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 510.2 (MH^+ , 100%). Anal. ($\text{C}_{31}\text{H}_{27}\text{NO}_6 \cdot 0.5\text{H}_2\text{O}$) C, H, N.

11-E ($\text{R}_1 = \text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, $\text{R}_2 = 2\text{-pyridyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.69 (dm, 1H, $J = 4.7$ Hz, H_6 -pyridine), 7.72 (td, 1H, $J = 7.7$, 1.8 Hz, H_4 -pyridine), 7.48 (t, 1H, $J = 3.0$ Hz, $\text{C}=\text{CH}$), 7.42 (d, 1H, $J = 7.7$ Hz, H_3 -pyridine), 7.21–7.34 (m, 6H, Ph, H_5 -pyridine), 4.58 (s, 2H, $\text{PhCH}_2\text{OCH}_2$), 4.30 (s, 2H, CO_2CH_2), 3.65 (AB q, 2H, $J = 10.1$ Hz, $\text{PhCH}_2\text{OCH}_2$), 3.41 (m, 2H, CH_2 -lactone), 2.29–3.36 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.46–1.52 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.29–1.35 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.11–1.23 (m, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.74 and 0.78 (t, 6H, $J = 7.3$ Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 176.02, 171.24, 153.95, 150.09, 137.55, 136.63, 133.57, 129.88, 128.58, 127.98, 127.78, 127.01, 123.37, 83.44, 73.91, 72.30, 65.98, 45.37, 34.95, 34.57, 34.30, 20.69, 14.02, 13.98; IR (neat) 1733 (CO), 1756 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 452.3 (MH^+ , 93%), 91.1 (100%). Anal. ($\text{C}_{27}\text{H}_{33}\text{NO}_5$) C, H, N.

11-E ($\text{R}_1 = \text{CH}_2\text{CH}[\text{CH}_2\text{CH}(\text{CH}_3)_2]_2$, $\text{R}_2 = 2\text{-pyridyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.69 (dm, 1H, $J = 4.8$ Hz, H_6 -pyridine), 7.72 (td, 1H, $J = 7.7$, 1.8 Hz, H_4 -pyridine), 7.47 (t, 1H, $J = 3.0$ Hz, $\text{C}=\text{CH}$), 7.41 (dm, 1H, $J = 7.7$ Hz, H_3 -pyridine), 7.21–7.34 (m, 6H, Ph, H_5 -pyridine), 4.54 (s, 2H, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$), 4.25 (s, 2H, CO_2CH_2), 3.59 (AB q, 2H, $J = 10.0$ Hz, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$), 3.46 (dd, 1H, $J = 19.7$, 3.0 Hz, CHH -lactone), 3.33 (dd, 1H, $J = 19.7$, 3.0 Hz, CHH -lactone), 2.18 (d, 2H, $J = 6.5$ Hz, $\text{CH}_2\text{CH}[\text{CH}_2\text{CH}(\text{CH}_3)_2]_2$), 1.84–1.91 (m, 1H, $\text{CH}_2\text{CH}[\text{CH}_2\text{CH}(\text{CH}_3)_2]_2$), 1.51–1.57 (m, 2H, $\text{CH}_2\text{CH}[\text{CH}_2\text{CH}(\text{CH}_3)_2]_2$), 0.99–1.12 (m, 4H, $\text{CH}_2\text{CH}[\text{CH}_2\text{CH}(\text{CH}_3)_2]_2$), 0.77–0.82 (m, 12H, $\text{CH}_2\text{CH}[\text{CH}_2\text{CH}(\text{CH}_3)_2]_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 186.59, 173.03, 171.17, 153.92, 150.09, 137.56, 136.62, 133.71, 129.74, 128.55, 127.94, 127.75, 127.01, 123.37, 83.28, 73.85, 72.20, 65.98, 44.11, 39.46, 34.23, 30.68, 25.20, 22.65, 22.92, 22.67, 22.63; IR (neat) 1758 (CO), 1741 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 494.2 (MH^+ , 88%), 91.1 (100%). Anal. ($\text{C}_{30}\text{H}_{39}\text{NO}_5$) C, H, N.

11-Z ($\text{R}_1 = \text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, $\text{R}_2 = 2\text{-pyridyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.53 (dm, 1H, $J = 4.9$ Hz, H_6 -pyridine), 7.60 (td, 1H, $J = 7.7$, 1.8 Hz, H_4 -pyridine), 7.23–7.34 (m, 6H, Ph, H_5 -pyridine), 7.17 (m, 1H, H_5 -pyridine), 7.12 (t, 1H, $J = 1.4$ Hz, $\text{C}=\text{CH}$), 4.53 (AB q, 2H, $J = 12.0$ Hz, CO_2CH_2), 4.33 (s, 2H, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$), 3.81 (s, 2H, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$), 3.70 (AB d, 1H, $J = 10.0$ Hz, CH -lactone), 3.57 (AB d, 1H, $J = 10.0$ Hz, CH -lactone), 2.26–3.33 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.44–1.54 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.30–1.39 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.17–1.26 (m, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.83–0.87 (2 t, 6H, $J = 7.2$ Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 175.77, 172.14, 148.73, 137.29, 128.61, 128.07, 127.78, 123.71, 123.70, 123.67, 122.17, 86.63, 73.99, 70.89, 63.31, 45.18, 34.50, 34.46, 20.68, 20.65, 14.11, 14.09; IR (neat) 1764 (CO), 1765 (CO) cm^{-1} ; FAB-

MS (m/z , relative intensity) 452.2 (MH^+ , 100%). Anal. ($\text{C}_{27}\text{H}_{33}\text{NO}_5 \cdot 0.6\text{H}_2\text{O}$) C, H, N.

11-E ($\text{R}_1 = \text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, $\text{R}_2 = 3\text{-pyridyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.74 (s, 1H, H_2 -pyridine), 8.61 (br d, 1H, $J = 4.0$ Hz, H_6 -pyridine), 7.75 (dm, 1H, $J = 8.0$ Hz, H_4 -pyridine), 7.75 (t, 1H, $J = 2.9$ Hz, $\text{C}=\text{CH}$), 7.37 (dd, 1H, $J = 8.0$, 4.8 Hz, H_5 -pyridine), 7.25–7.33 (m, 5H, Ph), 4.56 (s, 2H, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$), 4.28 (AB q, 2H, $J = 11.9$ Hz, $\text{CH}_2\text{CO}_2\text{CH}_2$), 3.61 (AB q, 2H, $J = 10$ Hz, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$), 3.20 (dd, 1H, $J = 17.9$, 2.9 Hz, CHH -lactone), 3.02 (dd, 1H, $J = 17.9$, 2.9 Hz, CHH -lactone), 2.29–3.36 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.43–1.52 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.29–1.38 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.10–1.24 (m, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.73–0.80 (overlapping t, 6H, $J = 7.3$ Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 175.85, 170.30, 151.08, 150.45, 137.19, 136.37, 132.76, 130.52, 128.61, 128.12, 127.81, 127.26, 123.83, 82.61, 73.90, 71.79, 65.72, 45.25, 34.52, 34.48, 33.02, 20.69, 20.64, 13.98, 13.94; IR (neat) 1757 (CO), 1734 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 452.3 (MH^+ , 91%), 91.1 (100%). Anal. ($\text{C}_{27}\text{H}_{33}\text{NO}_5$) C, H, N.

11-Z ($\text{R}_1 = \text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, $\text{R}_2 = 3\text{-pyridyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.52 (s, 2H, H_2 and H_6 -pyridine), 7.60 (dm, 1H, $J = 7.8$ Hz, H_5 -pyridine), 7.23–7.34 (m, 6H, Ph, H_4 -pyridine), 6.92 (t, 1H, $J = 1.5$ Hz, $\text{C}=\text{CH}$), 4.51 (AB q, 2H, $J = 11.9$ Hz, CO_2CH_2), 4.32 (s, 2H, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$), 3.68 (AB d, 1H, $J = 10.0$ Hz, CHH -lactone), 3.62 (br s, 2H, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$), 3.53 (AB d, 1H, $J = 10.0$ Hz, CHH -lactone), 2.26–3.33 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.44–1.54 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.30–1.39 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.17–1.26 (m, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.83–0.87 (overlapping t, 6H, $J = 7.3$ Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 175.76, 171.63, 149.43, 148.33, 147.78, 137.18, 137.09, 135.00, 128.66, 128.19, 127.83, 86.62, 74.02, 70.71, 63.20, 45.16, 34.50, 34.48, 29.18, 20.70, 20.65, 14.09, 14.07; IR (neat) 1768 (CO), 1734 (CO) cm^{-1} ; 452.3 (MH^+ , 100%); FAB-MS (m/z , relative intensity). Anal. ($\text{C}_{27}\text{H}_{33}\text{NO}_5$) C, H, N.

11-E ($\text{R}_1 = \text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, $\text{R}_2 = 4\text{-pyridyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.71 (d, 2H, $J = 6.1$ Hz, H_2 and H_6 -pyridine), 7.46 (t, 1H, $J = 2.9$ Hz, $\text{C}=\text{CH}$), 7.35 (br d, 2H, $J = 6.1$ Hz, H_3 and H_5 -pyridine), 7.24–7.34 (m, 4H, Ph), 4.56 (s, 2H, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$), 4.29 (s, 2H, CO_2CH_2), 3.62 (AB q, 2H, $J = 10.1$ Hz, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$), 3.22 (dd, 1H, $J = 18.2$, 2.9 Hz, CHH -lactone), 3.05 (dd, 1H, $J = 18.2$, 2.9 Hz, CHH -lactone), 2.30–3.33 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.46–1.52 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.32–1.37 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.15–1.25 (m, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.75–0.82 (overlapping t, 6H, $J = 7.3$ Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 174.87, 168.87, 148.75, 136.13, 131.92, 127.68, 127.24, 126.89, 122.81, 81.97, 72.99, 70.73, 64.65, 52.56, 44.29, 33.57, 33.52, 32.08, 19.74, 19.69, 13.03, 12.99; IR (neat) 1765 (CO), 1735 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 452.3 (MH^+ , 100%). Anal. ($\text{C}_{27}\text{H}_{33}\text{NO}_5 \cdot \text{H}_2\text{O}$) C, H, N.

11-Z ($\text{R}_1 = \text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, $\text{R}_2 = 4\text{-pyridyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.48 (d, 2H, $J = 6.0$ Hz, H_2 and H_6 -pyridine), 7.23–7.36 (m, 5H, Ph), 7.16 (d, 2H, $J = 6.0$ Hz, H_3 and H_5 -pyridine), 6.97 (t, 1H, $J = 1.4$ Hz, $\text{C}=\text{CH}$), 4.51 (AB q, 2H, $J = 11.8$ Hz, CO_2CH_2), 4.33 (s, 2H, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$), 3.72 (AB d, 1H, $J = 10.0$ Hz, CHH -lactone), 3.62 (s, 2H, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$), 3.57 (AB d, 1H, $J = 10.0$ Hz, CHH -lactone), 2.27–3.34 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.45–1.54 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.32–1.41 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.16–1.27 (m, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.84–0.88 (overlapping t, 6H, $J = 7.3$ Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 175.80, 171.61, 149.62, 148.77, 137.06, 134.10, 128.72, 128.32, 127.90, 124.29, 86.72, 74.12, 70.70, 63.23, 45.22, 34.54, 34.50, 31.27, 20.74, 20.68, 14.12, 14.10; IR (neat) 1764 (CO), 1718 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 452.3 (MH^+ , 100%). Anal. ($\text{C}_{27}\text{H}_{33}\text{NO}_5 \cdot 0.6\text{H}_2\text{O}$) C, H, N.

11-E ($\text{R}_1 = \text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$, $\text{R}_2 = 2\text{-quinolyl}$): colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, 1H, $J = 8.4$ Hz, H_4 -quinoline), 8.09 (d, 1H, $J = 8.4$ Hz, H_5 -quinoline), 7.81 (d, 1H, J

= 8.4 Hz, H_8 -quinoline), 7.73 (m, 1H, H_6 -quinoline), 7.65 (t, 1H, J = 3.0, Hz, $CH=C$), 7.57 (m, 1H, H_7 -quinoline), 7.51 (d, 1H, J = 8.4 Hz, H_3 -quinoline), 7.24–7.31 (m, 5H, Ph), 4.60 (s, 2H, $PhCH_2OCH_2$), 4.35 (s, 2H, CO_2CH_2), 3.67 (AB q, 2H, J = 10.0 Hz, $PhCH_2OCH_2$), 3.54–3.61 (m, 2H, CH_2 -lactone), 2.30–3.37 (m, 1H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.45–1.55 (m, 2H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.28–1.36 (m, 2H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.11–1.23 (m, 4H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 0.68 and 0.76 (t, 6H, J = 7.3 Hz, $(CH_3CH_2CH_2)_2CHCO_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.05, 171.13, 153.88, 148.48, 137.55, 136.59, 133.60, 131.36, 130.09, 130.05, 128.59, 127.98, 127.80, 127.67, 127.54, 127.33, 124.00, 83.61, 73.91, 72.29, 65.96, 45.36, 34.60, 34.56, 20.69, 14.00, 13.94; IR (neat) 1763 (CO), 1735 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 502.3 (MH^+ , 100%). Anal. ($C_{31}H_{35}NO_5 \cdot 0.5H_2O$) C, H, N.

11-Z ($R_1 = CH(CH_2CH_2CH_3)_2$, $R_2 = 2$ -quinolyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.03–8.07 (irregular t, 2H, J $\approx$ 9 Hz, H_4 and H_5 -quinoline), 7.79 (dm, 1H, J = 8.2 Hz, H_8 -quinoline), 7.70 (m, 1H, H_6 -quinoline), 7.52 (m, 1H, H_7 -quinoline), 7.36 (d, 1H, J = 8.4 Hz, H_3 -quinoline), 7.20–7.23 (m, 5H, Ph), 7.17 (br t, 1H, J = 1.4 Hz, $CH=C$), 4.50 (AB q, 2H, J = 12.0 Hz, CO_2CH_2), 4.33 (s, 2H, $C_6H_5CH_2OCH_2$), 4.00 (s, 2H, $C_6H_5CH_2OCH_2$), 3.69 (AB d, 1H, J = 10.0 Hz, CHH -lactone), 3.56 (AB d, 1H, J = 10.0 Hz, CHH -lactone), 2.22–3.29 (m, 1H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.40–1.50 (m, 2H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.24–1.34 (m, 2H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.13–1.22 (m, 4H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 0.81 (t, 6H, J = 7.2 Hz, $(CH_3CH_2CH_2)_2CHCO_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.68, 172.16, 157.46, 148.92, 137.20, 137.16, 133.99, 129.87, 128.88, 128.86, 128.53, 128.00, 127.71, 127.66, 127.06, 126.50, 121.54, 121.52, 86.65, 73.91, 70.82, 63.26, 45.11, 34.80, 34.65, 34.42, 34.39, 20.60, 20.57, 14.02, 14.00; IR (neat) 1766 (CO), 1735 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 502.2 (MH^+ , 82%), 91.1 (MH^+ , 100%). Anal. ($C_{31}H_{35}NO_5 \cdot 0.2H_2O$) C, H, N.

11-E ($R_1 = CH(CH_2CH_2CH_3)_2$, $R_2 = 3$ -quinolyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, 1H, J = 2.1 Hz, H_2 -quinoline), 8.22 (d, 1H, J = 1.8 Hz, H_4 -quinoline), 8.13 (d, 1H, J = 8.4 Hz, H_5 -quinoline), 7.87 (d, 1H, J = 8.4 Hz, H_8 -quinoline), 7.79 (m, 1H, H_7 -quinoline), 7.70 (t, 1H, J = 2.9 Hz, $CH=C$), 7.62 (m, 1H, H_6 -quinoline), 7.26–7.33 (m, 5H, Ph), 4.58 (s, 2H, $C_6H_5CH_2OCH_2$), 4.33 (AB q, 2H, J = 12.0 Hz, CO_2CH_2), 3.60 (AB q, 2H, J = 10.0 Hz, $C_6H_5CH_2OCH_2$), 3.32 (dd, 1H, J = 17.9, 2.9 Hz, CHH -lactone), 3.14 (dd, 1H, J = 17.9, 2.9 Hz, CHH -lactone), 2.32–3.36 (m, 1H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.39–1.52 (m, 2H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.31–1.39 (m, 2H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.10–1.25 (m, 4H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 0.73 and 0.78 (t, 6H, J = 7.3 Hz, $(CH_3CH_2CH_2)_2CHCO_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.94, 170.45, 151.05, 148.02, 137.22, 136.86, 132.98, 131.16, 129.50, 128.66, 128.50, 128.17, 127.89, 127.86, 127.77, 127.65, 127.15, 82.69, 73.99, 71.86, 65.78, 45.29, 34.57, 34.52, 33.21, 20.74, 20.69, 14.02, 13.97; IR (neat) 1752 (CO), 1735 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 502.5 (MH^+ , 100%). This material was used in the next step without further attempts to obtain an analytically pure sample.

11-Z ($R_1 = CH(CH_2CH_2CH_3)_2$, $R_2 = 3$ -quinolyl): colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, 1H, J = 2.2 Hz, H_2 -quinoline), 8.07 (d, 1H, J = 8.4 Hz, H_5 -quinoline), 7.98 (d, 1H, J = 1.9 Hz, H_4 -quinoline), 7.64–7.70 (m, 2H, H_7 and H_8 -quinoline), 7.50 (m, 1H, J = 1.2, 8.1, 8.4 Hz, H_6 -quinoline), 7.18–7.29 (m, 5H, Ph), 6.94 (t, 1H, J = 1.5 Hz, $CH=C$), 4.47 (AB q, 2H, J = 12.0 Hz, $C_6H_5CH_2OCH_2$), 4.30 (AB q, 2H, J = 11.8 Hz, CO_2CH_2), 3.80 (br s, 2H, $C_6H_5CH_2OCH_2$), 3.65 (AB d, 1H, J = 10.0 Hz, CHH -lactone), 3.52 (AB d, 1H, J = 10.0 Hz, CHH -lactone), 2.20–3.27 (m, 1H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.37–1.47 (m, 2H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.23–1.31 (m, 2H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 1.10–1.20 (m, 4H, $(CH_3CH_2CH_2)_2CHCO_2CH_2$), 0.78 and 0.81 (t, 6H, J = 7.2 Hz, $(CH_3CH_2CH_2)_2CHCO_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.50, 171.55, 151.25, 148.10, 147.09, 136.96, 135.34, 135.07, 129.81, 129.31, 129.11, 128.45, 127.96, 127.91, 127.58, 127.50, 126.93, 86.47, 73.79, 70.55, 63.02, 44.97,

34.28, 34.26, 29.20, 20.49, 20.20, 13.93, 13.88; IR (neat) 1764 (CO), 1735 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 91.1 (MH^+ , 100%), 502.2 (MH^+ , 82%). Anal. ($C_{31}H_{35}NO_5 \cdot 0.2H_2O$) C, H, N.

General Procedure for the Synthesis of 12 ($R_2 \neq 1$ -Methylindole). BCl_3 (3 equiv) was added slowly to a stirring solution of **11** (1 equiv) in CH_2Cl_2 (20 mL/mmol of **11**) at $-78^\circ C$. The reaction was monitored by TLC and quenched upon completion by the slow addition of a saturated aqueous $NaHCO_3$ solution, diluted with CH_2Cl_2 (20 mL/mmol of **11**), and warmed to room temperature. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 $\times$). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification by silica gel flash column chromatography [CH_2Cl_2 -MeOH (0% $\rightarrow$ 10%)] gave **12**.

12a-E: colorless oil; 1H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 8.67 (br d, 1H, J = 3.8 Hz, H_6 -pyridine), 7.80 (d, 2H, J = 9.0 Hz, $(CH_3)_2NC_6H_4CO_2$), 7.72 (br t, 1H, J = 7.3, 7.6 Hz, H_4 -pyridine), 7.50 (irregular t, 1H, J $\approx$ 2.9 Hz, $CH=C$), 7.41 (d, 1H, J = 7.6 Hz, H_3 -pyridine), 7.22 (m, 1H, H_5 -pyridine), 6.57 (d, 2H, J = 9.0 Hz, $(CH_3)_2NC_6H_4CO_2$), 4.51 (AB d, 1H, J = 12.0 Hz, CO_2CHH), 4.39 (AB d, 1H, J = 12.0 Hz, CO_2CHH), 3.82 (AB d, 1H, J = 12.3 Hz, $HOCHH$), 3.75 (AB d, 1H, J = 12.3 Hz, $HOCHH$), 3.52 (dd, 1H, J = 19.8, 2.9 Hz, CHH -lactone), 3.40 (dd, 1H, J = 19.8, 2.9 Hz, CHH -lactone), 3.00 (s, 6H, $(CH_3)_2NC_6H_4$); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$) δ 171.76, 166.88, 153.70, 153.68, 150.03, 136.77, 134.11, 131.67, 129.90, 126.95, 123.55, 115.75, 110.83, 85.06, 65.56, 64.83, 40.13, 33.54; IR (neat) 3370 (OH), 1719 (CO), 1626 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 383.1 (MH^+ , 84%), 148.1 (100%); HRMS (FAB) calc for $C_{21}H_{22}N_2O_5$, 383.1607; found, 383.1640.

12b-E: white solid; mp 158–159 $^\circ C$; 1H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 8.63 (s, 1H, H_2 -pyridine), 8.50 (d, 1H, J = 4.2 Hz, H_6 -pyridine), 7.78 (d, 1H, J = 8.0 Hz, H_4 -pyridine), 7.69 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 7.45 (t, 1H, J = 2.8 Hz, $CH=C$), 7.35 (dd, 1H, J = 8.0, 4.8 Hz, H_5 -pyridine), 6.52 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.39 (AB q, 2H, J = 12.0 Hz, CO_2CH_2), 3.80 (AB d, 1H, J = 12.2 Hz, $HOCHH$), 3.70 (AB d, 1H, J = 12.2 Hz, $HOCHH$), 3.27 (dd, 1H, J = 17.8, 2.8 Hz, CHH -lactone), 3.08 (dd, 1H, J = 17.8, 2.8 Hz, CHH -lactone), 2.97 (s, 6H, $(CH_3)_2NC_6H_4$); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$) δ 171.19, 166.70, 153.73, 150.66, 149.88, 136.75, 132.63, 131.53, 130.75, 128.06, 124.04, 115.27, 110.74, 84.78, 65.48, 64.31, 40.02, 32.20; IR (neat) 3402 (OH), 1702 (CO), 1654 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 383.2 (MH^+ , 57%), 148.1 (100%). Anal. ($C_{21}H_{22}N_2O_5 \cdot 0.1H_2O$) C, H, N.

12b-Z: colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 9.19 (m, 1H, H_2 -pyridine), 9.10 (m, 1H, H_6 -pyridine), 8.00 (br d, 1H, J = 8.0 Hz, H_4 -pyridine), 7.74 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 7.46 (dd, 1H, J = 8.0, 6.1 Hz, H_5 -pyridine), 7.05 (t, 1H, J = 1.2 Hz, $CH=C$), 6.62 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.72 (AB d, 1H, J = 11.9 Hz, CO_2CHH), 4.46 (AB d, 1H, J = 11.9 Hz, CO_2CHH), 3.88 (s, 2H, $HOCH_2$), 3.79 (AB q, 2H, J = 16.0 Hz, CH_2 -lactone), 3.07 (s, 6H, $(CH_3)_2NC_6H_4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.61, 166.50, 150.00, 144.63, 144.05, 143.19, 132.65, 131.68, 125.91, 125.89, 111.30, 111.28, 89.28, 63.48, 62.43, 40.41, 29.17; IR (neat) 3412 (OH), 1715 (CO), 1637 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 383.1 (MH^+ , 60%), 148.1 (100%); HRMS (FAB) calc for $C_{21}H_{22}N_2O_5$, 383.1607; found, 383.1590.

12c-E: yellow solid; mp 130–133 $^\circ C$; 1H NMR (400 MHz, $DMSO-d_6$) δ 8.75 (d, J = 6.2 Hz, 2H, H_2 and H_6 -pyridine), 7.72 (d, 2H, J = 6.2 Hz, H_3 and H_5 -pyridine), 7.63 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 7.46 (t, 1H, J = 2.9 Hz, $CH=C$), 6.67 (m, 2H, $(CH_3)_2NC_6H_4CO_2$), 4.40 (AB q, 2H, J = 11.9 Hz, CO_2CH_2), 3.69 (AB q, 2H, J = 11.9 Hz, $HOCH_2$), 3.32 (dd, 1H, J = 18.7, 2.9 Hz, CHH -lactone), 3.26 (dd, 1H, J = 18.7, 2.9 Hz, CHH -lactone), 2.99 (s, 6H, $(CH_3)_2NC_6H_4$); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ 170.00, 165.29, 153.38, 148.38, 133.31, 130.80, 130.73, 124.36, 124.35, 124.33, 124.32, 114.89, 110.82, 110.78, 84.95, 65.56, 63.20, 32.01; IR (neat) 3176 (OH), 1750 (CO), 1713 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 383.2 (MH^+ , 100%). Anal. ($C_{21}H_{22}N_2O_5 \cdot 0.9H_2O$) C, H, N.

12c-Z: white solid; mp 142–143 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.39 (v br d, J = 4.7 Hz, 2H, H_2 and H_6 -pyridine), 7.78 (m, 2H, $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CO}_2$), 7.19 (br d, 2H, J = 5.6 Hz, H_3 and H_5 -pyridine), 7.09 (br s, 1H, $\text{CH}=\text{C}$), 6.61 (m, 2H, $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CO}_2$), 4.67 (AB d, 1H, J = 12.0 Hz, CO_2CHH), 4.48 (AB d, 1H, J = 12.0 Hz, CO_2CHH), 3.81–3.88 (AB m, 2H, HOCH_2), 3.63 (s, 2H, CH_2 -lactone), 3.08 (s, 6H, $(\text{CH}_3)_2\text{NC}_6\text{H}_4$); ^{13}C NMR (100 MHz, CDCl_3) δ 171.81, 166.52, 153.97, 150.24, 144.76, 132.75, 131.68, 129.34, 126.04, 118.84, 114.93, 110.87, 89.37, 63.43, 62.48, 43.21, 40.26, 31.70; IR (neat) 3175 (OH), 1755 (CO), 1715.41 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 383.1 (MH^+ , 40%), 176 (MH^+ , 100%). Anal. ($\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_5 \cdot 0.4\text{H}_2\text{O}$) C, H, N.

12d-E: yellow solid; mp 120–122 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, 1H, J = 8.4 Hz, H_4 -quinoline), 8.05 (d, 1H, J = 8.4 Hz, H_5 -quinoline), 7.66 (dm, 1H, J = 8.4 Hz, H_8 -quinoline), 7.65–7.69 (m, 3H, $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CO}_2$, H_7 -quinoline), 7.61 (t, 1H, J = 3.0 Hz, $\text{CH}=\text{C}$), 7.48–7.53 (m, 2H, H_3 , and H_6 -quinoline), 6.49 (m, 2H, $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CO}_2$), 4.40 (AB q, 2H, J = 12.00 Hz, CO_2CH_2), 3.80 (AB d, 1H, J = 12.2 Hz, HOCHH), 3.72 (AB d, 1H, J = 12.2 Hz, HOCHH), 3.61 (dd, 1H, J = 19.6, 3.0 Hz, CHH -lactone), 3.50 (dd, 1H, J = 19.6, 3.0 Hz, CHH -lactone), 2.92 (s, 6H, $(\text{CH}_3)_2\text{NC}_6\text{H}_4$); ^{13}C NMR (100 MHz, CDCl_3) δ 172.10, 167.40, 154.21, 153.39, 139.00, 132.79, 132.76, 131.85, 131.58, 128.60, 128.37, 128.12, 123.43, 115.87, 111.26, 110.62, 86.14, 66.25, 64.75, 43.29, 40.17, 33.88; IR (neat) 3378 (OH), 1752 (CO), 1698 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 433.3 (MH^+ , 61%), 148.1 (MH^+ , 100%). Anal. ($\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_5 \cdot 0.1\text{H}_2\text{O}$) C, H, N.

12d-Z: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.96 (v br d, 2H, J = 8.4 Hz, H_4 and H_5 -quinoline), 7.66–7.70 (m, 3H, $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CO}_2$, H_8 -quinoline), 7.60 (m, 1H, H_7 -quinoline), 7.42 (m, 1H, H_6 -quinoline), 7.23 (d, 1H, J = 8.4 Hz, H_3 -quinoline), 7.15 (br s, 1H, $\text{CH}=\text{C}$), 6.44 (m, 2H, $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CO}_2$), 4.45 (s, 2H, CO_2CH_2), 3.92 (AB d, 2H, J = 1.3 Hz, HOCH_2), 3.75 (AB q, 2H, J = 12.0 Hz, CH_2 -lactone), 2.93 (s, 6H, $\text{N}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 172.41, 166.67, 157.21, 153.75, 149.38, 137.85, 133.88, 131.69, 130.27, 128.39, 127.71, 127.16, 126.76, 121.75, 115.48, 110.79, 110.17, 88.63, 63.52, 62.99, 40.16, 34.56; IR (neat) 3392 (OH), 1760 (CO), 1703 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 433.2 (MH^+ , 100%). Anal. ($\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_5 \cdot 0.1\text{H}_2\text{O}$) C, H, N.

12e-E: white solid; mp 135–137 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.12 (d, 1H, J = 2.2 Hz, H_2 -quinoline), 8.65 (br d, 1H, J = 1.7 Hz, H_4 -quinoline), 8.10 (dm, 1H, J = 8.4 Hz, H_5 -quinoline), 8.04 (d, 1H, J = 8.4 Hz, H_8 -quinoline), 7.82 (m, 1H, H_7 -quinoline), 7.62–7.69 (m, 4H, H_6 -quinoline, $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CO}_2$, $\text{CH}=\text{C}$), 6.65 (m, $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CO}_2$), 4.41 (AB q, 2H, J = 11.9 Hz, CO_2CH_2), 3.71 (AB q, 2H, J = 11.9 Hz, HOCH_2), 3.37–3.39 (m, 2H, CH_2 -lactone), 2.97 (s, 6H, $(\text{CH}_3)_2\text{NC}_6\text{H}_4$); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 170.48, 165.35, 153.35, 151.67, 147.18, 136.28, 130.80, 130.77, 129.27, 128.81, 128.71, 127.82, 127.37, 127.23, 114.95, 110.77, 84.62, 65.76, 63.36, 32.04; IR (neat) 3424 (OH), 1749 (CO), 1677 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 433.2 (MH^+ , 89%), 148.1 (MH^+ , 100%). Anal. ($\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_5 \cdot 0.8\text{H}_2\text{O}$) C, H, N.

12e-Z: colorless oil; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 8.68 (d, 1H, J = 1.9 Hz, H_2 -quinoline), 7.96 (d, 1H, J = 8.4 Hz, H_8 -quinoline), 7.94 (d, 1H, J = 1.9 Hz, H_4 -quinoline), 7.57–7.63 (m, 4H, $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CO}_2$, H_5 and H_7 -quinoline), 7.49 (m, 1H, H_6 -quinoline), 7.07 (t, 1H, J = 1.3 Hz, $\text{CH}=\text{C}$), 6.38 (m, 2H, $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CO}_2$), 4.59 (AB d, 1H, J = 11.8 Hz, CO_2CHH), 4.38 (AB d, 1H, J = 11.8 Hz, CO_2CHH), 3.77 (AB q, 2H, J = 12.0 Hz, HOCH_2), 3.71 (br s, 2H, CH_2 -lactone), 2.92 (s, 6H, $\text{N}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 172.66, 166.48, 153.50, 150.66, 148.95, 145.93, 136.20, 134.46, 131.12, 130.07, 129.65, 127.99, 127.75, 127.71, 127.01, 114.90, 110.52, 89.00, 63.01, 62.54, 39.75, 28.96; IR (neat) 3428 (OH), 1759 (CO), 1684 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 433.2 (MH^+ , 100%). Anal. ($\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_5 \cdot 0.6\text{H}_2\text{O}$) C, H, N.

12g-E: white solid; mp 92–94 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.70 (dm, 1H, J = 4.8 Hz, H_6 -pyridine), 7.92 (m, 2H, J = 2.1, 9.0 Hz, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 7.73 (td, 1H, J = 7.7, 1.8 Hz, H_4 -pyridine),

7.52 (t, 1H, J = 3.0 Hz, $\text{CH}=\text{C}$), 7.42 (d, 1H, J = 7.7 Hz, H_3 -pyridine), 7.24 (ddd, J = 7.7, 4.7, 1.1 Hz, H_5 -pyridine), 6.87 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 4.59 (AB d, 1H, J = 12.0 Hz, CO_2CHH), 4.44 (AB d, 1H, J = 12.0 Hz, CO_2CHH), 3.84–3.88 (m, 4H, $\text{CH}_3\text{OC}_6\text{H}_4$, HOCHH), 3.79 (AB d, 1H, J = 12.2 Hz, HOCHH), 3.55 (dd, 1H, J = 19.7, 3.0 Hz, CHH -lactone), 3.47 (dd, 1H, J = 19.7, 3.0 Hz, CHH -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 171.32, 166.21, 163.88, 153.71, 150.13, 136.74, 134.37, 132.04, 129.46, 127.13, 123.59, 121.66, 113.88, 84.54, 65.98, 65.11, 55.61, 33.71; IR (neat) 3421 (OH), 1751 (CO), 1714 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 370.1 (MH^+ , 75%), 135.1 (MH^+ , 100%). Anal. ($\text{C}_{20}\text{H}_{19}\text{NO}_6 \cdot 0.1\text{H}_2\text{O}$) C, H, N.

12g-Z: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.47 (br d, 1H, J = 3.7 Hz, H_6 -pyridine), 7.89 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 7.59 (td, 1H, J = 7.7, 1.7 Hz, H_4 -pyridine), 7.14–7.23 (m, 3H, $\text{CH}=\text{C}$, H_3 and H_5 -pyridine), 6.89 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 3.57 (AB q, 2H, J = 12.0 Hz, CO_2CH_2), 2.81–2.89 (m, 5H, HOCH_2 , $\text{CH}_3\text{OC}_6\text{H}_4$), 2.81 (br s, 2H, CH_2 -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 172.25, 165.98, 163.94, 149.04, 148.81, 137.74, 134.20, 132.01, 124.00, 122.39, 121.51, 113.93, 110.18, 88.30, 63.61, 63.44, 55.63, 33.91; IR (neat) 3343 (OH), 1760 (CO), 1714 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 370.1 (MH^+ , 100%). Anal. ($\text{C}_{20}\text{H}_{19}\text{NO}_6 \cdot 0.1\text{H}_2\text{O}$) C, H, N.

12h-E: white solid; mp 139–140 °C; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 8.67 (br d, 1H, J = 1.2 Hz, H_2 -pyridine), 8.53 (dd, 1H, J = 4.8, 1.4 Hz, H_6 -pyridine), 7.80–7.83 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 7.77 (dm, 1H, J = 8.0 Hz, H_4 -pyridine), 7.47 (t, 1H, J = 2.9 Hz, $\text{CH}=\text{C}$), 7.38 (dd, 1H, J = 8.0, 4.8 Hz, H_5 -pyridine), 6.83 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 4.44 (s, 2H, CO_2CH_2), 3.83 (AB d, J = 12.2 Hz, HOCHH), 3.80 (s, 2H, $\text{CH}_3\text{OC}_6\text{H}_4$), 3.74 (AB d, J = 12.2 Hz, HOCHH), 3.30 (dd, 1H, J = 17.9, 2.9 Hz, CHH -lactone), 3.09 (dd, 1H, J = 17.9, 2.9 Hz, CHH -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 171.10, 165.94, 163.82, 150.02, 149.39, 137.18, 132.27, 131.67, 130.84, 128.24, 124.22, 121.21, 113.75, 84.59, 65.93, 64.04, 55.38, 32.08; IR (neat) 3401 (OH), 1709 (CO), 1652 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 370.1 (100%). Anal. ($\text{C}_{20}\text{H}_{19}\text{NO}_6 \cdot 0.1\text{H}_2\text{O}$) C, H, N.

12h-Z: yellow solid; mp 155–157 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.49 (br s, 1H, H_2 -pyridine), 8.43 (br d, 1H, J = 4.9 Hz, H_6 -pyridine), 7.84 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 7.55 (br d, 1H, J = 7.8 Hz, H_4 -pyridine), 7.18 (dd, 1H, J = 7.7, 5.0 Hz, H_5 -pyridine), 7.02 (br s, 1H, $\text{CH}=\text{C}$), 6.87 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 4.53 (AB d, 1H, J = 12.0 Hz, CO_2CHH), 4.49 (AB d, 1H, J = 12.0 Hz, CO_2CHH), 3.84 (s, 3H, $\text{CH}_3\text{OC}_6\text{H}_4$), 3.80 (AB q, 2H, J = 12.0 Hz, HOCH_2), 3.59 (br s, 2H, CH_2 -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 171.89, 165.98, 164.07, 148.89, 148.41, 147.06, 137.96, 135.08, 133.47, 131.98, 124.20, 121.30, 114.05, 88.47, 63.59, 63.25, 55.68, 29.26; IR (neat) 3094 (OH), 1756 (CO), 1607 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 370.1 (MH^+ , 100%). Anal. ($\text{C}_{20}\text{H}_{19}\text{NO}_6$) C, H, N.

12i-E: white solid; mp 164–166 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.68 (m, 2H, H_2 and H_6 -pyridine), 7.78 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 7.57 (m, 2H, H_3 and H_5 -pyridine), 7.42 (t, 1H, J = 2.9 Hz, $\text{CH}=\text{C}$), 7.00 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 5.40 (br s, 1H, HOCH_2), 4.44 (AB q, 2H, J = 11.9 Hz, CO_2CH_2), 3.82 (s, 3H, $\text{CH}_3\text{OC}_6\text{H}_4$), 3.68–3.70 (m, 2H, HOCH_2), 3.28–3.29 (m, 2H, CH_2 -lactone); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 170.14, 164.84, 163.34, 150.27, 150.22, 141.45, 131.82, 131.47, 131.37, 131.27, 131.20, 123.65, 123.56, 121.21, 114.12, 114.08, 84.65, 66.14, 63.24, 31.94; IR (neat) 3164 (OH), 1750 (CO), 1710 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 370.1 (MH^+ , 100%). Anal. ($\text{C}_{20}\text{H}_{19}\text{NO}_6 \cdot 0.4\text{H}_2\text{O}$) C, H, N.

12i-Z: yellow solid; mp 156–158 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.38 (br d, 2H, J = 6.0 Hz, H_2 and H_6 -pyridine), 7.86 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 7.09 (m, 2H, H_3 and H_5 -pyridine), 7.05 (t, 1H, J = 1.4 Hz, $\text{CH}=\text{C}$), 6.89 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 4.67 (AB d, 1H, J = 11.9 Hz, CO_2CHH), 4.51 (AB d, 1H, J = 11.9 Hz, CO_2CHH), 3.86 (overlapping s and AB q, 5H, J $\approx$ 12 Hz, $\text{CH}_3\text{OC}_6\text{H}_4$, HOCH_2), 3.58 (br s, 2H, CH_2 -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 171.93, 165.94, 164.09, 149.64, 148.64, 146.64, 134.40, 131.92, 124.30, 121.28, 114.04, 88.62, 63.63, 63.20, 55.67, 31.30;

IR (neat) 3095 (OH), 1758 (CO), 1705 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 370.1 (MH^+ , 100%). Anal. ($\text{C}_{20}\text{H}_{19}\text{NO}_6$) C, H, N.

12j-E: white solid; mp 90–91 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, 1H, $J = 8.4$ Hz, H_4 -quinoline), 8.17 (d, 1H, $J = 8.5$ Hz, H_5 -quinoline), 7.72–7.78 (m, 3H, H_8 -quinoline, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 7.65 (m, 1H, H_7 -quinoline), 7.59 (t, 1H, $J = 3.0$ Hz, $\text{CH}=\text{C}$), 7.49 (m, 1H, H_6 -quinoline), 7.47 (d, 1H, $J = 8.4$ Hz, H_3 -quinoline), 6.75 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 4.46 (AB d, 1H, $J = 12.0$ Hz, CO_2CHH), 4.40 (AB d, 1H, $J = 12.0$ Hz, CO_2CHH), 3.80 (AB d, 1H, $J = 12.2$ Hz, HOCHH), 3.73 (AB d, 1H, $J = 12.2$ Hz, HOCHH), 3.72 (s, 3H, $\text{OCH}_3\text{C}_6\text{H}_4$), 3.67 (br s, 1H, HOCH_2), 3.60 (dd, 1H, $J = 19.7$, 3.0 Hz, CHH -lactone), 3.53 (dd, 1H, $J = 19.7$, 3.0 Hz, CHH -lactone); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 171.75, 166.07, 163.68, 153.33, 147.79, 137.07, 133.63, 131.68, 130.29, 129.29, 127.64, 127.57, 127.32, 123.39, 121.41, 113.69, 85.24, 66.13, 64.45, 55.34, 33.47; IR (neat) 3381 (OH), 1731 (CO), 1715 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 420.2 (MH^+ , 73%), 135.1 (MH^+ , 100%). Anal. ($\text{C}_{24}\text{H}_{21}\text{NO}_6 \cdot \text{H}_2\text{O}$) C, H, N.

12j-Z: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.99 (irregular t, 2H, $J \approx 8$ Hz, H_4 and H_5 -quinoline), 7.79 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 7.74 (dd, 1H, $J = 8.4$, 1.3 Hz, H_8 -quinoline), 7.66 (m, 1H, H_7 -quinoline), 7.49 (m, 1H, H_6 -quinoline), 7.29 (d, 1H, $J = 8.4$ Hz, H_3 -quinoline), 7.24 (t, 1H, $J = 1.3$ Hz, $\text{CH}=\text{C}$), 6.76 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 4.62 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 4.54 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 3.98 (br AB d, 2H, HOCH_2), 3.89 (br AB q, 2H, CH_2 -lactone), 3.81 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 172.45, 165.86, 163.79, 157.32, 148.94, 147.56, 137.39, 134.17, 131.83, 130.00, 128.61, 127.68, 127.06, 126.56, 121.60, 121.38, 113.76, 88.49, 63.51, 63.33, 55.55, 34.70; IR (neat) 3354 (OH), 1759 (CO), 1713 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 420.1 (MH^+ , 100%). Anal. ($\text{C}_{21}\text{H}_{21}\text{NO}_6 \cdot 0.5\text{H}_2\text{O}$) C, H, N.

12k-E: white solid; mp 161–162 °C; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 9.00 (v br s, 1H, H_2 -quinoline), 8.22 (s, 1H, H_4 -quinoline), 8.06 (m, 1H, H_8 -quinoline), 7.88 (br d, 1H, $J = 7.7$ Hz, H_5 -quinoline), 7.80 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 7.74 (br t, 1H, $J = 6.8$ Hz, H_6 -quinoline), 7.64 (t, 1H, $J = 2.5$ Hz, $\text{CH}=\text{C}$), 7.57 (dd, 1H, $J = 8.1$, 6.9 Hz, H_7 -quinoline), 6.83 (m, 2H, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 4.45 (s, 2H, CO_2CH_2), 3.84 (AB d, 1H, $J = 12.2$ Hz, HOCHH), 3.73–3.77 (overlapping s and AB d, 4H, HOCHH , OCH_3), 3.41 (AB d, $J = 17.8$, 2.5 Hz, CHH -lactone), 3.18 (AB d, $J = 17.8$, 2.5 Hz, CHH -lactone); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 171.15, 166.03, 163.94, 163.91, 137.60, 132.89, 131.87, 131.56, 128.79, 128.77, 128.75, 128.71, 128.66, 128.03, 127.78, 121.35, 113.88, 84.60, 66.00, 64.38, 55.55, 32.45; IR (neat) 3393 (OH), 1748 (CO), 1714 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 420.1 (MH^+ , 100%). Anal. ($\text{C}_{24}\text{H}_{21}\text{NO}_6$) C, H, N.

12k-Z: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.76 (d, 1H, $J = 1.7$ Hz, H_2 -quinoline), 8.04 (d, 1H, $J = 8.4$ Hz, H_5 -quinoline), 7.97 (s, 1H, H_4 -quinoline), 7.74 (d, 2H, $J = 9.1$ Hz, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 7.63–7.67 (m, 2H, H_8 -quinoline, H_7 -quinoline), 7.48 (irregular t, 1H, $J \approx 7$ Hz, H_6 -quinoline), 7.12 (s, 1H, $\text{CH}=\text{C}$), 6.71 (d, 2H, $J = 9.1$ Hz, $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}_2$), 4.63 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 4.49 (AB d, 1H, $J = 11.9$ Hz, CO_2CHH), 3.88 (br s, 2H, HOCH_2), 3.78 (s, 3H, $\text{CH}_3\text{OC}_6\text{H}_4$), 3.74 (br s, 2H, CH_2 -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 172.54, 165.77, 163.65, 150.58, 148.76, 145.90, 136.40, 134.65, 131.42, 130.09, 129.81, 127.98, 127.82, 127.68, 127.18, 121.00, 113.66, 88.79, 63.05, 63.00, 55.31, 28.99; IR (neat) 3396 (OH), 1758 (CO), 1715 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 420.1 (MH^+ , 100%). Anal. ($\text{C}_{24}\text{H}_{21}\text{NO}_6$) C, H, N.

12m-E: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.67 (dm, 1H, $J = 4.8$ Hz, H_6 -pyridine), 7.72 (td, 1H, $J = 7.7$, 1.9 Hz, H_4 -pyridine), 7.48 (t, 1H, $J = 3.0$ Hz, $\text{CH}=\text{C}$), 7.42 (br d, 1H, $J = 7.7$ Hz, H_3 -pyridine), 7.23 (ddd, 1H, $J = 7.7$, 4.8, 1.0 Hz, H_5 -pyridine), 4.29 (AB q, 2H, $J = 11.9$ Hz, CO_2CH_2), 3.80 (AB d, 1H, $J = 12.2$ Hz, HOCHH), 3.72 (AB d, 1H, $J = 12.2$ Hz, HOCHH), 3.44 (dd, 1H, $J = 19.7$, 3.0 Hz, CHH -lactone), 3.38 (dd, 1H, $J = 19.7$, 3.0 Hz, CHH -lactone), 2.31–2.38 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.46–1.55 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2$);

CHCO_2CH_2), 1.32–1.37 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.15–1.24 (m, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.79 and 0.75 (t, 3H, $J = 7.3$ Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 176.33, 171.32, 153.79, 150.09, 136.65, 134.09, 129.61, 127.10, 123.48, 84.42, 65.47, 65.23, 45.34, 34.55, 33.55, 20.69, 14.01, 13.97; IR (neat) 3458 (OH), 1752 (CO), 1734 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 362.2 (MH^+ , 100%). Anal. ($\text{C}_{20}\text{H}_{27}\text{NO}_5 \cdot 0.2\text{H}_2\text{O}$) C, H, N.

12m-Z: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.53 (d, 1H, $J = 4.1$ Hz, H_6 -pyridine), 7.69 (td, 1H, $J = 7.6$, 1.0 Hz, H_4 -pyridine), 7.32 (d, 1H, $J = 7.6$ Hz, H_3 -pyridine), 7.22 (m, 1H, H_5 -pyridine), 7.12 (d, 1H, $J = 1.1$ Hz, $\text{C}=\text{CH}$), 4.33 (AB q, 2H, $J = 11.6$ Hz, CO_2CH_2), 3.77 (s, 2H, HOCH_2), 3.82 (s, 2H, CH_2 -lactone), 3.18 (br s, 1H, HOCH_2), 2.31–3.38 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.47–1.57 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.33–1.42 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.22 (sextuplet, 4H, $J \approx 7.4$ Hz, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.86 (overlapping t, 6H, $J = 7.3$ Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 176.22, 172.10, 156.39, 148.84, 137.98, 134.05, 124.24, 122.52, 87.94, 63.56, 63.00, 45.20, 34.52, 33.84, 20.72, 20.70, 14.11; IR (neat) 3357 (OH), 1761 (CO), 1735 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 362.2 (MH^+ , 100%). Anal. ($\text{C}_{20}\text{H}_{27}\text{NO}_5 \cdot 0.5\text{H}_2\text{O}$) C, H, N.

12n-E: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.77 (br s, 1H, H_2 -pyridine), 8.61 (br s, 1H, H_6 -pyridine), 7.47 (d, 1H, $J = 7.6$ Hz, H_4 -pyridine), 7.53 (br irregular t, 1H, $\text{CH}=\text{C}$), 7.40 (br dd, 1H, $J = 7.6$, 4.7 Hz, H_5 -pyridine), 4.28 (AB q, 2H, $J = 12.0$ Hz, CO_2CH_2), 3.82 (AB d, 1H, $J = 12.1$ Hz, HOCHH), 3.73 (AB d, 1H, $J = 12.1$ Hz, HOCHH), 3.29 (dd, 1H, $J = 17.9$, 2.9 Hz, CHH -lactone), 3.03 (dd, 1H, $J = 17.9$, 2.9 Hz, CHH -lactone), 2.32–2.38 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.46–1.56 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.32–1.41 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.14–1.26 (m, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.77 and 0.81 (t, 6H, $J = 7.3$ Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 176.26, 170.54, 150.89, 150.39, 136.77, 133.18, 127.35, 124.01, 83.88, 65.37, 64.77, 45.31, 34.55, 34.53, 32.33, 20.76, 20.72, 14.03, 14.00; IR (neat) 3459 (OH), 1735 (CO), 1655 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 362.3 (MH^+ , 100%). Anal. ($\text{C}_{20}\text{H}_{27}\text{NO}_5$) C, H, N.

12n-Z: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.84 (br s, 1H, H_2 -pyridine), 8.56 (br s, 1H, H_6 -pyridine), 7.97 (d, 1H, $J = 7.9$ Hz, H_4 -pyridine), 7.53 (dm, 1H, $J = 7.9$ Hz, H_5 -pyridine), 7.19 (s, 1H, $\text{C}=\text{CH}$), 4.35 (AB q, 2H, $J = 11.9$, CO_2CH_2), 3.82 (AB d, 1H, $J = 11.8$ Hz, HOCHH), 3.70–3.79 (m, 3H, HOCHH , CH_2 -lactone), 2.32–3.39 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.49–1.58 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.35–1.43 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.19–1.29 (m, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.87 and 0.88 (t, 3H, $J = 7.2$ Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 176.13, 171.76, 149.74, 146.47, 144.04, 141.38, 133.66, 110.19, 88.34, 63.22, 62.94, 45.20, 34.54, 29.30, 20.75, 20.72, 14.12; IR (neat) 3495 (OH), 1735 (CO), 1662 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 362.3 (MH^+ , 100%). Anal. ($\text{C}_{20}\text{H}_{27}\text{NO}_5$) C, H, N.

12o-E: yellow solid; mp 83–86 °C; ^1H NMR (400 MHz, CD_3OD) δ 8.67 (m, 2H, H_2 and H_6 -pyridine), 7.66 (m, 2H, H_3 and H_5 -pyridine), 7.47 (t, 1H, $J = 3.0$ Hz, $\text{CH}=\text{C}$), 4.31 (AB q, 2H, $J = 12.0$ Hz, CO_2CH_2), 3.80 (AB d, 1H, $J = 12.0$ Hz, HOCHH), 3.72 (AB d, 1H, $J = 12.0$ Hz, HOCHH), 3.34 (AB dd, 1H, $J = 18.6$, 3.0 Hz, CHH -lactone), 3.18 (AB d, 1H, $J = 18.6$, 3.0 Hz, CHH -lactone), 2.29–2.36 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.43–1.50 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.30–1.41 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.14–1.24 (m, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.77 and 0.79 (overlapping t, 6H, $J = 7.2$ Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 177.05, 172.01, 150.19, 145.06, 134.12, 132.78, 132.71, 125.65, 125.61, 86.08, 66.85, 65.03, 46.62, 35.73, 35.70, 33.25, 21.66, 21.58, 14.20, 14.19; IR (neat) 3164 (OH), 1759 (CO), 1722 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 362.2 (MH^+ , 100%). Anal. ($\text{C}_{20}\text{H}_{27}\text{NO}_5 \cdot 0.7\text{H}_2\text{O}$) C, H, N.

12o-Z: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.52 (d, 2H, $J \approx 6.0$ Hz, H_2 and H_6 -pyridine), 7.23 (d, 2H, $J \approx 6.0$ Hz, H_3

and *H*₅-pyridine), 6.99 (irregular t, 1H, *J* < 1 Hz, CH=C), 4.38 (AB d, 1H, *J* = 11.9 Hz, CO₂CHH), 4.30 (AB d, 1H, *J* = 11.9 Hz, CO₂CHH), 3.79 (s, 2H, HOCH₂), 3.64 (s, 2H, CH₂-lactone), 2.78 (br s, 1H, HOCH₂), 2.31–3.38 (m, 1H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.47–1.55 (m, 2H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.34–1.43 (m, 2H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.19–1.28 (m, 4H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 0.87 and 0.88 (t, 6H, *J* = 7.3 Hz, (CH₃CH₂CH₂)₂CHCO₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 176.21, 171.72, 149.27, 148.74, 147.34, 134.32, 124.58, 110.18, 87.99, 63.56, 62.96, 45.22, 34.52, 31.40, 20.75, 20.72, 14.11, 14.10; IR (neat) 3179 (OH), 1761 (CO), 1735 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 362.2 (MH⁺, 100%). Anal. (C₂₀H₂₇NO₅·0.2H₂O) C, H, N.

12p-E: colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, 1H, *J* = 8.2 Hz, *H*₄-quinoline), 8.09 (d, 1H, *J* = 8.4 Hz, *H*₅-quinoline), 7.81 (dd, 1H, *J* = 8.4, 1.2 Hz, *H*₈-quinoline), 7.73 (m, 1H, *H*₇-quinoline), 7.65 (t, 1H, *J* = 3.1 Hz, CH=C), 7.56 (m, 1H, *H*₆-quinoline), 7.51 (d, 1H, *J* = 8.4 Hz, *H*₃-quinoline), 4.34 (AB q, 2H, *J* = 12.0 Hz, CO₂CH₂), 3.86 (AB d, 1H, *J* = 12.2 Hz, HOCHH), 3.77 (AB d, 1H, *J* = 12.2 Hz, HOCHH), 3.64 (dd, 1H, *J* = 20.0, 3.1 Hz, CHH-lactone), 3.03 (dd, 1H, *J* = 20.0, 3.1 Hz, CHH-lactone), 2.50 (br s, 1H, HOCH₂), 2.32–3.39 (m, 1H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.47–1.56 (m, 2H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.29–1.39 (m, 2H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.09–1.26 (m, 4H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 0.71 and 0.77 (t, 6H, *J* = 7.3 Hz, (CH₃CH₂CH₂)₂CHCO₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 176.37, 171.19, 153.68, 148.39, 136.69, 134.06, 131.12, 130.13, 130.00, 127.67, 127.63, 127.36, 124.00, 84.59, 65.48, 65.27, 45.53, 34.58, 34.55, 33.87, 20.70, 14.00, 13.94; IR (neat) 3364 (OH), 1757 (CO), 1734 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 412.3 (MH⁺, 98%), 57.1 (MH⁺, 100%). Anal. (C₂₄H₂₉NO₅·0.2H₂O) C, H, N.

12p-Z: colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, 1H, *J* = 8.4 Hz, *H*₄-quinoline), 8.02 (d, 2H, *J* = 8.4 Hz, *H*₅-quinoline), 7.80 (dd, 1H, *J* = 8.4, 1.3 Hz, *H*₈-quinoline), 7.70 (m, 1H, *H*₇-quinoline), 7.52 (m, 1H, *H*₆-quinoline), 7.39 (d, 1H, *J* = 8.4 Hz, *H*₃-quinoline), 7.15 (irregular t, 1H, *J* ≈ 1.5 Hz, CH=C), 4.34 (AB q, 1H, *J* = 12.1 Hz, CO₂CH₂), 4.03 (dd, 1H, *J* = 16.3, 1.5 Hz, C HH-lactone), 3.98 (dd, 1H, *J* = 16.3, 1.5 Hz, CHH-lactone), 3.80 (s, 2H, HOCH₂), 2.28–3.35 (m, 1H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.44–1.54 (m, 2H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.29–1.38 (m, 2H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.15–1.25 (m, 4H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 0.83 and 0.85 (t, 6H, *J* = 7.3 Hz, (CH₃CH₂CH₂)₂CHCO₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 176.20, 172.24, 157.22, 148.80, 137.53, 134.20, 130.15, 128.60, 127.73, 127.16, 126.71, 121.74, 88.00, 63.52, 62.97, 45.18, 34.61, 34.47, 20.67, 14.06, 14.05; IR (neat) 3460 (CO), 1762 (CO), 1736 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 412.2 (MH⁺, 100%). Anal. (C₂₄H₂₉NO₅·0.4H₂O) C, H, N.

12q-E: yellow solid; mp 113–114 °C; ¹H NMR (400 MHz, CDCl₃) δ 9.04 (br s, 1H, *H*₂-quinoline), 8.24 (br d, 1H, *J* = 1.6 Hz, *H*₄-quinoline), 8.12 (d, 1H, *J* = 8.4 Hz, *H*₅-quinoline), 7.86 (br d, 1H, *J* = 8.4 Hz, *H*₈-quinoline), 7.78 (m, 1H, *H*₇-quinoline), 7.70 (t, 1H, *J* = 3.0 Hz, CH=C), 7.61 (m, 1H, *H*₆-quinoline), 4.36 (AB d, 1H, *J* = 12.0 Hz, CO₂CHH), 4.30 (AB d, 1H, *J* = 12.0 Hz, CO₂CHH), 3.88 (AB d, 1H, *J* = 12.2 Hz, HOCHH), 3.78 (AB d, 1H, *J* = 12.2 Hz, HOCHH), 3.42 (dd, 1H, *J* = 17.8, 3.0 Hz, CHH-lactone), 3.15 (dd, 1H, *J* = 17.8, 3.0 Hz, CHH-lactone), 2.32–3.39 (m, 1H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.46–1.56 (m, 2H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.31–1.40 (m, 2H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.12–1.26 (m, 4H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 0.74 and 0.79 (t, 6H, *J* = 7.3 Hz, (CH₃CH₂CH₂)₂CHCO₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 176.30, 170.71, 150.92, 150.89, 147.92, 137.20, 133.39, 131.29, 129.35, 128.53, 127.84, 127.65, 127.09, 83.93, 65.41, 64.79, 45.29, 34.55, 34.51, 32.50, 20.75, 20.71, 14.03, 13.97; IR (neat) 3367 (OH), 1734 (CO), 1655 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 412.2 (MH⁺, 100%). Anal. (C₂₄H₂₉NO₅·0.8H₂O) C, H, N.

12q-Z: colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 8.84 (br d, 1H, *J* = 2.0 Hz, *H*₂-quinoline), 8.10–8.12 (m, 2H, *H*₅ and *H*₄-quinoline), 7.79 (br dd, 1H, *J* = 8.2, 1.2 Hz, *H*₈-quinoline), 7.71

(m, *H*₆-quinoline), 7.56 (m, 1H, *H*₇-quinoline), 7.02 (t, 1H, *J* = 1.5 Hz, CH=C), 4.37 (AB d, 1H, *J* = 11.9 Hz, CO₂CHH), 4.29 (AB d, 1H, *J* = 11.9 Hz, CO₂CHH), 3.81 (br s, 2H, CH₂-lactone), 3.78 (s, 2H, HOCH₂), 2.27–3.34 (m, 1H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.44–1.54 (m, 2H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.29–1.38 (m, 2H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 1.14–1.25 (m, 4H, (CH₃CH₂CH₂)₂CHCO₂CH₂), 0.83 and 0.84 (overlapping t, 6H, *J* = 7.3 Hz, (CH₃CH₂CH₂)₂CHCO₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 176.16, 171.94, 150.78, 148.52, 146.19, 136.71, 135.20, 130.08, 128.39, 128.16, 127.76, 127.51, 88.07, 63.51, 62.96, 45.18, 34.47, 29.46, 20.71, 20.67, 14.09, 14.06; IR (neat) 3298 (OH), 1757 (CO), 1735 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 412.2 (MH⁺, 100%). Anal. (C₂₄H₂₉NO₅·0.3H₂O) C, H, N.

12s-E: colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 8.68 (br d, 1H, *J* = 4.6 Hz, *H*₆-pyridine), 7.72 (m, 1H, *H*₄-pyridine), 7.47 (irregular t, 1H, *J* ≈ 3.0 Hz, C=CH-), 7.41 (br d, 1H, *J* = 7.8 Hz, *H*₃-pyridine), 7.22–7.25 (m, 1H, *H*₅-pyridine), 4.32 (dd, 1H, *J* = 11.9, <1.0 Hz, CO₂CHH), 4.23 (dd, 1H, *J* = 11.9, <1.0 Hz, CO₂CHH), 3.80 (AB d, 1H, *J* = 12.2 Hz, HOCHH), 3.72 (AB d, 1H, *J* = 12.2 Hz, HOCHH), 3.47 (dd, 1H, *J* = 19.8, 3.0 Hz, CHH-lactone), 2.84 (dd, 1H, *J* = 19.8, 3.0 Hz, CHH-lactone), 2.20 (irregular d, 2H, *J* ≈ 6.4 Hz, CH₂CH[CH₂CH(CH₃)₂]₂), 1.85–1.92 (septuplet, 1H, *J* ≈ 6.7 Hz, CH₂CH[CH₂CH(CH₃)₂]₂), 1.51–1.58 (m, 2H, CH₂CH[CH₂CH(CH₃)₂]₂), 0.98–1.13 (m, 4H, CH₂CH[CH₂CH(CH₃)₂]₂), 0.79–0.83 (m, 12H, CH₂CH[CH₂CH(CH₃)₂]₂); ¹³C NMR (100 MHz, CDCl₃) δ 173.36, 171.21, 153.69, 149.98, 136.82, 134.07, 129.59, 127.14, 123.56, 84.28, 65.48, 65.19, 44.13, 39.47, 33.54, 30.73, 25.23, 22.95, 22.93, 22.68, 22.64; IR (neat) 3450 (OH), 1737 (CO), 1663 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 404.2 (MH⁺, 100%). Anal. (C₂₃H₃₃NO₅) C, H, N.

12t-E: yellow solid; mp 111–112 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.94 (t, 1H, *J* = 2.6 Hz, CH=C), 7.82 (dm, 1H, *J* = 7.8 Hz, *H*₄-indole), 7.24–7.37 (m, 4H, *H*₂, *H*₅, *H*₆, and *H*₇-indole), 4.34 (AB d, 1H, *J* = 11.9 Hz, CO₂CHH), 4.28 (AB d, 1H, *J* = 11.9 Hz, CO₂CHH), 3.85 (s, 3H, CH₃N), 3.77 (AB d, 1H, *J* = 12.1 Hz, HOCHH), 3.74 (AB d, 1H, *J* = 12.1 Hz, HOCHH), 3.05 (dd, 1H, *J* = 17.2, 2.6 Hz, CHH-lactone), 2.84 (dd, 1H, *J* = 17.2, 2.6 Hz, CHH-lactone), 2.22 (irregular d, 2H, *J* = 6.5 Hz, CH₂CH[CH₂CH(CH₃)₂]₂), 1.87–1.93 (septuplet, 1H, *J* ≈ 6.8 Hz, CH₂CH[CH₂CH(CH₃)₂]₂), 1.50–1.59 (m, 2H, CH₂CH[CH₂CH(CH₃)₂]₂), 1.00–1.11 (m, 4H, CH₂CH[CH₂CH(CH₃)₂]₂), 0.77–0.83 (m, 12H, CH₂CH[CH₂CH(CH₃)₂]₂); ¹³C NMR (100 MHz, CDCl₃) δ 173.68, 171.73, 136.89, 130.66, 128.84, 128.04, 123.44, 121.44, 119.06, 119.00, 117.00, 111.95, 109.86, 82.85, 65.63, 65.09, 44.15, 44.12, 39.44, 33.55, 33.32, 30.71, 25.24, 25.21, 22.96, 22.70, 22.62; IR (neat) 3449 (OH), 1737 (CO), 1635 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 456.3 (MH⁺, 97%), 455.2 (M⁺⁺, 100). Anal. (C₂₇H₃₇NO₅·0.1H₂O) C, H, N.

General Procedure for the Synthesis of 8 (R₂ = 1-Methylindole). This compound was prepared from **4**²⁶ following a similar protocol described in procedures A and B.

8-E: white solid; mp 196–197 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.91 (t, 1H, *J* = 2.5 Hz, CH=C), 7.86 (d, 1H, *J* = 7.9 Hz, *H*₅-indole), 7.59–7.62 (m, 8H, *H*₆-*H*₈-indole, Ph), 7.27–7.42 (m, 15H, Ph), 7.14 (s, 1H, *H*₂-indole), 3.87 (s, 3H, NCH₃), 3.83 (AB q, 4H, 2 × SiOCH₂), 2.89 (AB m, 2H, CH₂-lactone), 0.99 (s, 18H, 2 × SiC (H₃)); ¹³C NMR (100 MHz, CDCl₃) δ 172.31, 136.85, 135.77, 135.74, 133.12, 132.96, 130.09, 129.89, 129.88, 128.14, 127.85, 127.05, 123.23, 121.15, 119.46, 119.22, 112.31, 109.73, 85.05, 66.41, 33.58, 33.26, 26.84, 19.38; IR (neat) 1747 (CO) cm⁻¹; FAB-MS (*m/z*, relative intensity) 764.5 (MH⁺, 37%), 763 (M⁺⁺, 15%), 135.1 (100%). This material was used in the next step without further attempts to obtain an analytically pure sample.

General Procedure for the Synthesis of 10 (R₂ = 1-Methylindole). A solution of **8** (1 equiv) in tetrahydrofuran (THF, 10 mL/mmol) was treated with [(CH₃(CH₂)₃)₄F (TBAF, 3 equiv). The mixture was stirred at room temperature for 1 h and concentrated in vacuo. Purification by silica gel flash column chromatography [CH₂Cl₂–MeOH (0% → 10%)] gave **10** as a yellow solid in 62% yield.

10-E: white solid; mp 211–212 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 7.84 (d, 1H, J = 7.9 Hz, H_5 -indole), 7.81 (s, 1H, H_2 -indole), 7.64 (t, 1H, J = 2.7 Hz, $\text{CH}=\text{C}$), 7.53 (d, 1H, J = 8.0 Hz, H_8 -indole), 7.28 (m, 1H, H_6 -indole), 7.20 (m, 1H, H_7 -indole), 5.10 (t, 2H, J = 5.7 Hz, $2 \times \text{HOCH}_2$), 3.90 (s, 3H, CH_3N), 3.48–3.57 (m, 4H, $2 \times \text{HOCH}_2$), 2.91 (br AB d, J = 2.7 Hz, 2H, CH_2 -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 171.49, 136.48, 131.73, 127.30, 125.26, 122.55, 120.66, 120.10, 118.28, 110.53, 110.41, 85.53, 63.63, 32.98, 31.94; IR (neat) 3259 (OH), 1724 (CO) cm^{-1} , FAB-MS (m/z , relative intensity) 288.2 (MH^+ , 10%). This material was used in the next step without further attempt to obtain an analytically pure sample.

General Procedure for the Synthesis of 12 (R_2 = 1-Methylindole). A solution of **10** (1 equiv) in CH_2Cl_2 (16 mL/mmole) was treated with anhydrous pyridine (2 equiv) at room temperature and stirred for 2 h. The reaction temperature was then lowered to 0 °C, and the acid chloride (R_1COCl , 1.1 equiv) was added dropwise. The resulting solution was stirred at 0 °C for 30 min to 1 h and then at room temperature until the reaction was considered complete by TLC. The crude solution was then concentrated in vacuo and purified by silica gel flash column chromatography [CH_2Cl_2 –MeOH (0% $\rightarrow$ 10%)] to give **12** and variable amounts of the diacylated product, which was not characterized.

12f-E: yellow solid; mp 160–162 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (br t, 1H, J = 2.6 Hz, $\text{CH}=\text{C}$), 7.83 (m, 2H, $(\text{CH}_3)_2\text{NC}$ $\delta\text{H}_4\text{CO}_2$), 7.27–7.35 (m, 5H, indole), 6.55 (m, 2H, $(\text{CH}_3)_2\text{NC}$ $\delta\text{H}_4\text{CO}_2$), 4.63 (AB d, 1H, J = 12.0, Hz, CO_2CHH), 4.39 (AB d, 1H, J = 12.0, Hz, CO_2CHH), 3.86 (s, 3H, NCH_3), 3.80 (s, 2H, HOCH_2), 2.87–3.17 (m, 8H, $(\text{CH}_3)_2\text{NC}$ δH_4 , CH_2 -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 171.92, 167.31, 153.71, 136.91, 131.80, 130.74, 128.87, 128.10, 123.38, 121.37, 119.06, 117.27, 115.67, 111.95, 110.87, 110.17, 109.89, 83.35, 65.67, 64.91, 40.16, 33.62, 33.51; IR (neat) 3396 (OH), 1738 (CO), 1698 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 435.2 (MH^+ , 15%), 148.1 (100%). Anal. ($\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5 \cdot 0.9\text{H}_2\text{O}$) C, H, N.

12l-E: white solid; mp 120–122 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (t, J = 2.6 Hz, 1H, $\text{CH}=\text{C}$), 7.81 (m, 2H, CH_3OC $\delta\text{H}_4\text{CO}_2$), 7.78 (dm, 1H, J = 8.0 Hz, H_4 -indole), 7.19–7.32 (m, 4H, indole), 6.75 (m, 2H, CH_3OC $\delta\text{H}_4\text{CO}_2$), 4.59 (AB d, 1H, J = 11.9 Hz, CO_2CHH), 4.41 (AB d, 1H, J = 11.9 Hz, CO_2CHH), 3.81 (s, 3H, NCH_3), 3.77 (AB q, 2H, J = 11.9 Hz, HOCH_2), 3.73 (s, 3H, CH_3OC δH_4), 3.05 (dd, 1H, J = 17.1, 2.6 Hz, CHH -lactone), 2.93 (dd, J = 17.1, 2.6 Hz, CHH -lactone); ^{13}C NMR (100 MHz, CDCl_3) δ 172.76, 166.31, 163.73, 136.84, 131.80, 130.90, 128.70, 127.96, 123.31, 121.49, 121.29, 118.81, 117.36, 113.78, 111.71, 109.85, 83.80, 66.36, 64.68, 55.43, 33.46, 33.17; IR (neat) 3366 (OH), 1706 (CO), 1636 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 422.2 (MH^+ , 91%), 135.1 (100%). Anal. ($\text{C}_{24}\text{H}_{23}\text{NO}_6$) C, H, N.

12r-E: yellow solid; mp 125–127 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.96 (t, J = 2.7 Hz, 1H, $\text{CH}=\text{C}$), 7.84 (irregular d, J $\approx$ 7.9 Hz, 2H, H_4 -indole), 7.27–7.37 (m, 4H, H_2 , H_5 , H_6 , and H_7 -indole), 4.39 (AB d, 1H, J = 11.9 Hz, CO_2CHH), 4.27 (AB d, 1H, J = 11.9 Hz, CO_2CHH), 3.87 (s, 3H, NCH_3), 3.79 (AB d, 1H, J = 12.1 Hz, HOCHH), 3.73 (AB d, 1H, J = 12.1 Hz, HOCHH), 3.05 (dd, 1H, J = 17.1, 2.7 Hz, CHH -lactone), 2.84 (dd, 1H, J = 17.1, 2.7 Hz, CHH -lactone), 2.35–2.42 (m, 1H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.49–1.57 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.36–1.40 (m, 2H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 1.19–1.27 (m, 4H, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$), 0.78 and 0.83 (t, 6H, J = 7.3 Hz, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 176.73, 171.68, 136.92, 130.57, 128.89, 128.06, 123.49, 121.48, 119.80, 117.04, 112.04, 109.88, 82.87, 65.50, 65.18, 45.37, 34.56, 33.63, 33.37, 20.76, 14.07, 14.02; IR (neat) 3437 (OH), 1735 (CO), 1637 (CO) cm^{-1} ; FAB-MS (m/z , relative intensity) 414.3 (MH^+ , 100%) 413.3 (M^{++} , 94.5). Anal. ($\text{C}_{24}\text{H}_{31}\text{NO}_5 \cdot 0.6\text{H}_2\text{O}$) C, H, N.

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Supporting Information Available: Combustion analysis results and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Takai, Y.; Kishimoto, A.; Kikkawa, U.; Mori, T.; Nishizuka, Y. Unsaturated diacylglycerol as a possible messenger for the activation of calcium-activated, phospholipid-dependent protein kinase system. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 1218–1224.
- (2) Rhee, S. G. Regulation of phosphoinositide-specific phospholipase C. *Annu. Rev. Biochem.* **2001**, *70*, 281–312.
- (3) Nishizuka, Y. Intracellular signaling by hydrolysis of phospholipids and activation of protein kinase C. *Science* **1992**, *258*, 607–614.
- (4) Hofmann, J. Protein kinase C isozymes as potential targets for anticancer therapy. *Curr. Cancer Drug Targets* **2004**, *4*, 125–146.
- (5) Ron, D.; Kazanietz, M. G. New insights into the regulation of protein kinase C and novel phorbol ester receptors. *FASEB J.* **1999**, *13*, 1658–1676.
- (6) Brose, N.; Rosenmund, C. Move over protein kinase C, you've got company: alternative cellular effectors of diacylglycerol and phorbol esters. *J. Cell Sci.* **2002**, *115*, 4399–4411.
- (7) Rozengurt, E.; Sinnett-Smith, J.; Zugaza, J. Protein kinase D: a novel target for diacylglycerol and phorbol esters. *Biochem. Soc. Trans.* **1997**, *25*, 565–571.
- (8) Ebinu, J. O.; Bottorff, D. A.; Chan, E. Y. W.; Stang, S. L.; Dunn, R. J.; Stone, J. C. RasGRP, a Ras guanyl nucleotide-releasing protein with calcium and diacylglycerol-binding motifs. *Science* **1998**, *280*, 1082–1086.
- (9) Kawasaki, H.; Spright, G. M.; Toki, S.; Canales, J. J.; Harlan, P.; Blumenstiel, J. P.; Chen, E. J.; Bany, I. A.; Mochizuki, N.; Ashbacher, A.; Matsuda, M.; Housman, D. E.; Graybiel, A. M. A Rap guanine nucleotide exchange factor enriched highly in the basal ganglia. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 13278–13283.
- (10) Ahmed, S.; Lee, J.; Kozma, R.; Best, A.; Monfries, C.; Lim, L. A novel functional target for tumor-promoting phorbol esters and lysophosphatidic acid—the P21rac-Gtpase activating protein n-Chimaerin. *J. Biol. Chem.* **1993**, *268*, 10709–10712.
- (11) Brose, N.; Rosenmund, C.; Rettig, J. Regulation of transmitter release by Unc-13 and its homologues. *Curr. Opin. Neurobiol.* **2000**, *10*, 303–311.
- (12) Choi, S. H.; Czifra, G.; Kedei, N.; Lewin, N. E.; Lazar, J.; Pu, Y.; Marquez, V. E.; Blumberg, P. M. Characterization of the interaction of phorbol esters with the C1 domain of MRCK (myotonic dystrophy kinase-related Cdc42-binding kinase) α/β . *J. Biol. Chem.* **2008**, *283*, 10543–10549.
- (13) Luo, B.; Regier, D. S.; Prescott, S. M.; Topham, M. K. Diacylglycerol kinases. *Cell. Signalling* **2004**, *16*, 983–989.
- (14) Geiger, M.; Wrulich, O. A.; Jenny, M.; Schwaiger, W.; Grunicke, H. H.; Uberall, F. Defining the human targets of phorbol ester and diacylglycerol. *Curr. Opin. Mol. Ther.* **2003**, *5*, 631–641.
- (15) Zhang, G. G.; Kazanietz, M. G.; Blumberg, P. M.; Hurley, J. H. Crystal-structure of the Cys2 activator-binding domain of protein-kinase C- δ in complex with phorbol ester. *Cell* **1995**, *81*, 917–924.
- (16) Hommel, U.; Zurini, M.; Luyten, M. Solution structure of a cysteine rich domain of rat protein kinase C. *Nat. Struct. Biol.* **1994**, *1*, 383–387.
- (17) Xu, R. X.; Pawelczyk, T.; Xia, T. H.; Brown, S. C. NMR structure of a protein kinase C- γ phorbol-binding domain and study of protein–lipid micelle interactions. *Biochemistry* **1997**, *36*, 10709–10717.
- (18) Shen, N.; Guryev, O.; Rizo, J. Intramolecular occlusion of the diacylglycerol-binding site in the C1 domain of Munc13-1. *Biochemistry* **2005**, *44*, 1089–1096.
- (19) Marquez, V. E.; Blumberg, P. M. Synthetic diacylglycerols (DAG) and DAG-lactones as activators of protein kinase C (PK-C). *Acc. Chem. Res.* **2003**, *36*, 434–443.
- (20) Sharkey, N. A.; Blumberg, P. M. Comparison of the activity of phorbol 12-myristate 13-acetate and the diglyceride glycerol 1-myristate 2-acetate. *Carcinogenesis* **1986**, *7*, 677–679.
- (21) Duan, D.; Sigano, D. M.; Kelley, J. A.; Lai, C.; Lewin, N. E.; Kedei, N.; Peach, M. L.; Lee, J.; Abeyweera, T. P.; Rotenberg, S. A.; Kim, H.; Kim, Y. H.; El Kazouli, S.; Chung, J.-U.; Young, H. A.; Young, M.; Baker, A.; Colburn, N. H.; Haimovitz-Friedman, A.; Truman, J. P.; Parrish, D. A.; Deschamps, J. R.; Perry, N. A.; Surawski, R. J.; Blumberg, P. M.; Marquez, V. E. Conformationally constrained

- analogues of diacylglycerol (DAG). 29. Cells sort DAG-lactone chemical zip codes to produce diverse and selective biological activities. *J. Med. Chem.* **2008**, *51*, 5198–5220.
- (22) Pu, Y.; Perry, N. A.; Yang, D.; Lewin, N. E.; Keddi, N.; Braun, D. C.; Choi, S. H.; Blumberg, P. M.; Garfield, S. H.; Stone, J. C.; Duan, D.; Marquez, V. E. A novel diacylglycerol-lactone shows marked selectivity in vitro among C1 domains of protein kinase C (PKC) isoforms α and δ as well as selectivity for RasGRP compared with PKC α . *J. Biol. Chem.* **2005**, *280*, 27329–27338.
- (23) Kang, J. H.; Benzaria, S.; Sigano, D. M.; Lewin, N. E.; Pu, Y. M.; Peach, M. L.; Blumberg, P. M.; Marquez, V. E. Conformationally constrained analogues of diacylglycerol. 26. Exploring the chemical space surrounding the C1 domain of protein kinase C with DAG-lactones containing aryl groups at the sn-1 and sn-2 positions. *J. Med. Chem.* **2006**, *49*, 3185–3203.
- (24) Lee, J. Design and synthesis of bioisosteres of ultrapotent protein kinase C (PKC) ligand, 5-acetoxymethyl-5-hydroxymethyl-3-alkylidene tetrahydro-2-furanone. *Arch. Pharmacol. Res.* **1998**, *21*, 452–457.
- (25) Choi, Y.; Kang, J. H.; Lewin, N. E.; Blumberg, P. M.; Lee, J.; Marquez, V. E. Conformationally constrained analogues of diacylglycerol. 19. Synthesis and protein kinase C binding affinity of diacylglycerol lactones bearing an *N*-hydroxylamide side chain. *J. Med. Chem.* **2003**, *46*, 2790–2793.
- (26) Nacro, K.; Bienfait, B.; Lee, J.; Han, K. C.; Kang, J. H.; Benzaria, S.; Lewin, N. E.; Bhattacharyya, D. K.; Blumberg, P. M.; Marquez, V. E. Conformationally constrained analogues of diacylglycerol (DAG). 16. How much structural complexity is necessary for recognition and high binding affinity to protein kinase C? *J. Med. Chem.* **2000**, *43*, 921–944.
- (27) Kang, J.-H.; Siddiqui, M. A.; Lewin, N. E.; Sigano, D. M.; Blumberg, P. M.; Lee, J.; Marquez, V. E. Conformationally constrained analogues of diacylglycerol. 24. Asymmetric synthesis of a chiral *R*-DAG-lactone template as a versatile precursor for highly functionalized DAG-lactones. *Org. Lett.* **2004**, *6*, 2413–2416.

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