Brief Articles

Conformationally Constrained Analogues of Diacylglycerol. 19. Synthesis and Protein Kinase C Binding Affinity of Diacylglycerol Lactones Bearing an *N*-Hydroxylamide Side Chain

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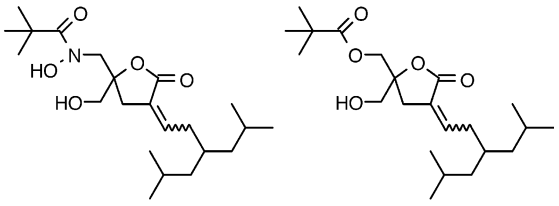
The structures of *N*-hydroxylamides **1a** and **1b**, previously reported by Lee et al. in *J. Med. Chem.* **2001**, *44*, 4309−4312 as strong protein kinase C (PK-C) ligands, were incorrect and correspond instead to esters **2a** and **2b**, respectively. Here, we report the synthesis and complete characterization of **1a** and **1b** together with the associated biological activity in terms of PK-C binding affinity.

With the intent of testing the limits of reducing the log *P* in diacylglycerol (DAG) lactones known for their high binding affinity toward protein kinase C (PK-C), isomeric compounds **1a** and **1b**, where the typical ester side chain was replaced by an *N*-hydroxylamide chain, were designed.[1] This structural change reduced the log *P* to an unprecedented calculated value of 3.58, almost matching the value of the prototypic phorbol ester phorbol 12,13-dibutyrate (PDBU, calculated log *P* = 3.43). The reported nanomolar binding affinities for compounds **1a** and **1b** were considered exceptional and informative regarding the precise mode of binding of DAG-lactones to the C1 domain of PK-C.[1] Unfortunately, the structures of **1a** and **1b** were incorrect and the PK-C binding affinities attributed to these compounds should correspond instead to those of the esters **2a** and **2b**, also reported in the same manuscript.[1] An erratum for this manuscript appears in the same issue as this manuscript.[2]



1a, Z-isomer
1b, E-isomer

2a, Z-isomer
2b, E-isomer

In the present manuscript, we correct this error and report on the synthesis of the intended *N*-hydroxylactam targets. The original synthesis of these compounds was based on the strategy that aldehydes **6a** and **6b** (Scheme 1) would generate the desired *N*-hydroxylamines **7a** and **7b** after treatment with $NH_2OH{\cdot}HCl$ followed by in situ reduction of the intermediate oximes with sodium cyanoborohydride. Unfortunately, either the intermediate oximes were never formed or they hydrolyzed backto aldehydes **6a** and **6b** under the reaction conditions, thus regenerating the starting alcohols **5a** and **5b** after hydride reduction. Consequently, the ensuing acylation with pivaloyl chloride produced instead esters **2a** and **2b**.

In this new approach, we employed a *tert*-butyldimethylsilyl-protected hydroxylamine reagent to form the intermediate oxime from the same aldehydes (**6a** and **6b**), and the resulting alkylhydroxylamines (**7a** and **7b**) obtained after sodium cyanoborohydride reduction were individually isolated and fully characterized. The *tert*-butyldimethylsilyl ether was removed during the hydride reduction step. Following the separation of *Z*- and *E*-isomers at the olefination stage (**4a** and **4b**), the reaction sequence was performed separately on each isomer. Acylation with pivaloyl chloride and final removal of the benzyl protective group with BCl_3 afforded the desired targets **1a** and **1b**.

The ^1H NMR spectra of these compounds deserve some special comments. The variations in chemical shift and multiplicity for certain peaks when changing from $CDCl_3$ to DMSO-d_6 were remarkable and quite informative about the existence of an intramolecular H-bond pattern associated with these molecules. In the case of **1a**, the nonequivalent methylene protons on the CH_2N-(OH)$COC(CH_3)_3$ branch appeared as doublets (J = 15.4 Hz) separated from each other by 1.14 ppm when the solvent was $CDCl_3$. On the other hand, in DMSO-d_6 the same two doublets (J = 14.8 Hz) were just 0.31 ppm apart. In $CDCl_3$, the exchangeable primary alcohol

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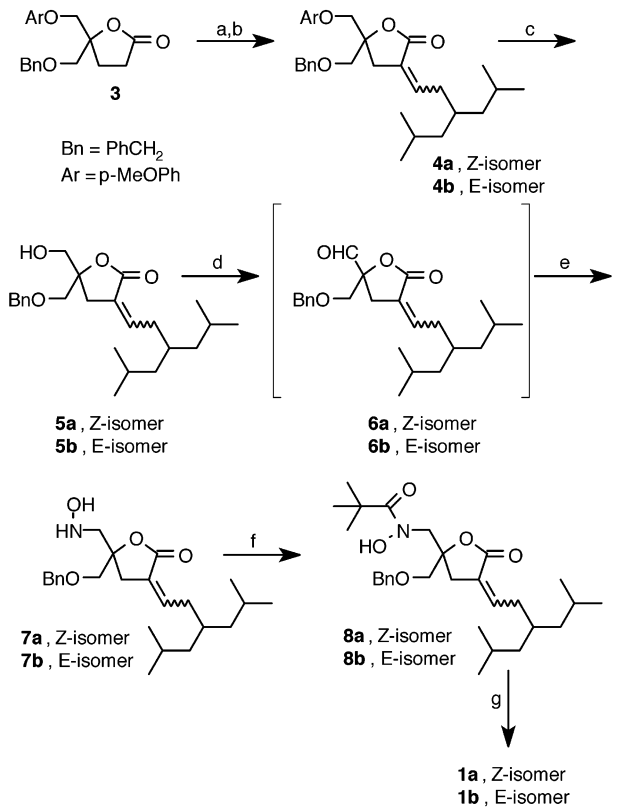
Scheme 1[a]



[a] (a) $[(CH_3)_3Si]_2NLi$ (2 equiv), $[(CH_3)_2CHCH_2]_2CHCH_2CHO$ (1 equiv), THF, −78 °C, 2 h; (b) (i) Et_3N (3 equiv), CH_3SO_2Cl (1.5 equiv), CH_2Cl_2, room temp, 10 min, (ii) DBU (3 equiv), room temp, 15 min; (c) $(NH_4)_2Ce(NO_3)_6$ (3 equiv), CH_3CN/H_2O (4:1), 0 °C, 30 min; (d) oxalyl chloride (1.5 equiv), DMSO (2.5 equiv), Et_3N (3 equiv), room temp, 15 min; (e) (i) $(CH_3)_3CSi(CH_3)_2ONH_2$ (1.5 equiv), pyridine, room temp, 3 h; (ii) $NaBH_3CN$ (1.7 equiv), AcOH, room temp, 1 h; (f) Et_3N (2 equiv), $(CH_3)CCOCl$ (1.2 equiv), CH_2Cl_2, 0 °C, 10 min; (g) BCl_3 (3 equiv), CH_2Cl_2, −78 °C, 30 min.

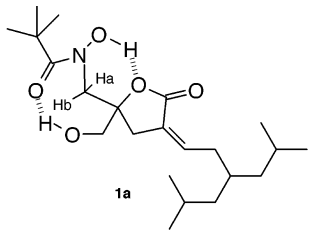


Figure 1. Proposed intramolecular H-bonding network for compound **1a**.

(CH_2OH) appeared as a doublet of doublets (J = 10.4, 4.6 Hz) at δ 3.97, whereas in DMSO-d_6 the same signal appeared as a triplet (J = 5.6 Hz) at δ 5.10. Finally, the signal for the NO*H* proton resonated at δ 6.68 in $CDCl_3$ and at δ 9.49 in DMSO-d_6. On the basis of these results, we propose the existence of two strong intramolecular H-bonds that keep the entire ensemble around the two side chains fixed and unable to rotate freely and that such a constrained system is more prevalent in $CDCl_3$ (Figure 1). The same changes were observed for the isomeric compound **1b**. These observations are important and could explain how these molecules behave in a lipid, nonpolar environment by adopting a similar conformation as in $CDCl_3$ that does not unfold to a conformation required for efficient binding. Indeed, this isosteric RC(O)O → RC(O)NOH replacement revealed a dramatic drop in binding affinity of more than 3 orders of magnitude relative to the esters, suggesting that the extra N−OH group is not directly involved in binding the C1 domain of PK-C (Table 1).

Table 1. PK-Cα Binding Affinity and Calculated log P [5] for *N*-Hydroxylamides (**1a** and **1b**) and Esters (**2a** and **2b**)

	Z/*E*	log *P*	K_i (nM)
1a	*Z*	3.58	6980 ± 110
1b	*E*	3.58	6790 ± 190
2a	*Z*	5.03	2.90 ± 0.4
2b	*E*	5.03	4.51 ± 0.5

Experimental Section

(*Z*)-5-[(4-Methoxyphenoxy)methyl]-3-[5-methyl-3-(2-methylpropyl)hexilidene]-5-[(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (4a) and (*E*)-5-[(4-Methoxyphenoxy)methyl]-3-[5-methyl-3-(2-methylpropyl)hexilidene]-5-[(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (4b). A stirred solution of **3**[3,4] (4 g, 12 mmol) in THF (30 mL) was cooled to −78 °C and treated dropwise with lithium bis-(trimethylsilyl)amide (1 M in THF, 24 mL, 24 mmol). After being stirred for 30 min at −78 °C, the mixture was treated with a solution of aldehyde $[(CH_3)_2CHCH_2]_2CHCH_2CHO$ (2 g, 12 mmol) in THF (20 mL) and stirred for 2 h at the same temperature. The reaction was quenched by the slow addition of a saturated aqueous solution of NH_4Cl and extracted several times with ether. The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:4) as eluant to give the intermediate β-hydroxylactone as an oil (5.6 g, 11 mmol). A solution of the above compound in CH_2Cl_2 (30 mL) was cooled to 0 °C and treated with Et_3N (4.5 mL, 33 mmol) and CH_3SO_2Cl (1.3 mL, 17 mmol). The mixture was stirred at ambient temperature for 10 min and then treated with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 4.9 mL, 33 mmol). After additional stirring for 15 min, the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:10) as eluant to give **4a** (*Z*-isomer, 2.0 g, 4.2 mmol, 35%) and **4b** (*E*-isomer, 2.0 g, 35%) as oils.

4a: ^{1}H NMR ($CDCl_3$) δ 7.25−7.32 (m, 5 H, Ph), 6.80 (s, 4 H, *Ph*OCH_3), 6.18−6.23 (m, 1 H, >C═CH), 4.58 (AB q, 2 H, J = 12.3, 14.5 Hz, O*C*H_2Ph), 4.02 (AB q, 2 H, J = 9.7, 28.4 Hz, *C*H_2OPhOCH$_3$), 3.76 (s, 3 H, OCH_3), 3.66 (AB q, 2 H, J = 10.1, 22.4 Hz, *C*H_2OCH$_2$Ph), 2.82−2.98 (m, 2 H, H-4), 2.62−2.76 (m, 2 H, >CH═CHC*H*$_2$), 1.58−1.69 (m, 3 H, 2 × C*H*Me$_2$, C*H*(*i*-Bu)$_2$), 1.06−1.13 (m, 4 H, 2 × CHC*H*$_2$CHMe$_2$), 0.79−0.93 (m, 12 H, 4 × CH_3); FABMS *m*/*z* (relative intensity) 494 (MH^+, 35). Anal. ($C_{31}H_{42}O_5$) C, H.

4b: ^{1}H NMR ($CDCl_3$) δ 7.25−7.35 (m, 5 H, Ph), 6.81 (s, 4 H, *Ph*OCH_3), 6.76−6.81 (m, 1 H, >C═CH), 4.58 (AB q, 2 H, J = 12.4, 14.0 Hz, O*C*H_2Ph), 4.02 (AB q, 2 H, J = 9.7, 26.8 Hz, *C*H_2OPhOCH$_3$), 3.76 (s, 3 H, OCH_3), 3.66 (AB q, 2 H, J = 10.4, 25.3 Hz, *C*H_2OCH$_2$Ph), 2.81−2.93 (m, 2 H, H-4), 2.11−2.14 (m, 2 H, >CH═CHC*H*$_2$), 1.60−1.74 (m, 3 H, 2 × C*H*Me$_2$, C*H*(*i*-Bu)$_2$), 1.04−1.15 (m, 4 H, 2 × CHC*H*$_2$CHMe$_2$), 0.81−0.93 (m, 12 H, 4 × CH_3); FABMS *m*/*z* (relative intensity) 494 (MH^+, 23). Anal. ($C_{31}H_{42}O_5 \cdot 0.1H_2O$) C, H.

(*Z*)-5-(Hydroxymethyl)-3-[5-methyl-3-(2-methylpropyl)-hexylidene]-5-(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (5a). A solution of **4a** (2.07 g, 4.2 mmol) in CH_3CN/H_2O (4:1, 10 mL) was cooled to 0 °C and treated with ammonium cerium(IV) nitrate (6.9 g, 12.6 mmol). After being stirred for 30 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:2) as eluant to give **5a** as an oil (1.25 g, 76%): ^{1}H NMR ($CDCl_3$) δ 7.26−7.36 (m, 5 H, Ph), 6.17−6.21

(m, 1 H, >C=CH), 4.56 (AB q, 2 H, J = 12.1, 13.8 Hz, OCH_2-Ph), 3.64−3.76 (m, 2 H, CH_2OH), 3.58 (AB q, 2 H, J = 9.8, 17.6 Hz, CH_2OCH_2Ph), 2.81−2.82 (m, 2 H, H-4), 2.64−2.68 (m, 2 H, >CH=CHCH_2), 1.57−1.68 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.06−1.10 (m, 4 H, 2 × CHCH_2CHMe$_2$), 0.81−0.88 (m, 12 H, 4 × CH_3); ^{13}C NMR ($CDCl_3$) δ 169.3, 144.2, 137.7, 128.6, 128.0, 127.8, 125.2, 83.4, 73.90, 72.00, 65.70, 44.1, 33.6, 33.4, 32.2, 25.3, 23.2, 22.9, 22.8; FABMS m/z (relative intensity) 389 (MH^+, 48.7). Anal. ($C_{24}H_{36}O_4$) C, H.

(*Z*)-5-Carbonyl-3-[5-methyl-3-(2-methylpropyl)hexylidene]-5-(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (6a). A cooled solution of DMSO (0.34 mL, 4.8 mmol) in CH_2Cl_2 (5 mL) at −78 °C was treated with oxalyl chloride (0.25 mL, 2.9 mmol). After the mixture was stirred for 30 min at −78 °C, a solution of **5a** (728 mg, 1.9 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred for 2 h at the same temperature. The reaction was quenched by the slow addition of Et_3N (0.79 mL, 5.7 mmol) followed by 30 min of stirring at room temperature. After the addition of CH_2Cl_2 (20 mL), the solution was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:4) as eluant to give **6a** as an oil (537 mg, 74%): ^{1}H NMR ($CDCl_3$) δ 9.73 (s, 1 H, CHO), 7.26−7.36 (m, 5 H, Ph), 6.11−6.28 (m, 1 H, >C=CH), 4.49−4.63 (m, 2 H, OCH_2Ph), 3.61−3.75 (AB m, 2 H, CH_2OCH_2Ph), 2.74−3.02 (m, 2 H, H-4), 2.64−2.69 (m, 2 H, >CH=CHCH_2), 1.57−1.67 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.03−1.11 (m, 4 H, 2 × CHCH_2CHMe$_2$), 0.83−0.88 (m, 12 H, 4 × CH_3). This compound was used immediately in the following step without further purification.

(*Z*)-5-(Hydroxylamino)methyl)-3-[5-methyl-3-(2-methylpropyl)hexylidene]-5-(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (7a). A solution of **6a** (537 mg, 1.4 mmol) in pyridine (5 mL) was treated with *O*-*tert*-(butyldimethylsilyl)-hydroxylamine (265 mg, 1.8 mmol). After being stirred for 3 h at ambient temperature, the reaction mixture was concentrated in vacuo. Following the complete removal of pyridine, acetic acid (15 mL) was added and the resulting solution was stirred for 1 h at room temperature. After treatment of this solution with $NaBH_3CN$ (128 mg, 2.0 mmol) for 1 h, the mixture was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:2) as eluant to give **7a** as a white solid: mp 90−91 °C (300 mg, 54%); ^{1}H NMR ($CDCl_3$) δ 7.26−7.36 (m, 5 H, Ph), 6.17−6.20 (m, 1 H, >C=CH), 4.59 (s, 2 H, OCH_2Ph), 3.57 (AB q, 2 H, J = 9.9, 18.9 Hz, CH_2OCH_2Ph), 3.20 (AB q, 2 H, J = 13.7, 25.6 Hz, CH_2NHOH), 2.86−2.90 (m, 2 H, H-4), 2.65−2.69 (m, 2 H, >CH=CHCH_2), 1.57−1.69 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.04−1.10 (m, 4 H, 2 × CHCH_2CHMe$_2$), 0.83−0.88 (m, 12 H, 4 × CH_3); ^{13}C NMR ($CDCl_3$) δ 169.1, 143.7, 137.8, 128.6, 128.0, 127.8, 125.4, 82.7, 73.8, 73.0, 58.6, 44.1, 35.6, 33.4, 32.1, 25.3, 23.2, 22.8; FABMS m/z (relative intensity) 404 (MH^+, 2.4). Anal. ($C_{24}H_{37}NO_4$) C, H, N.

(*Z*)-*N*-Hydroxy-2,2-dimethyl-*N*-({4-[5-methyl-3-(2-methoxypropyl)hexylidene]-5-oxo-2-[(phenylmethoxy)methyl]-(2−2,3-dihydrofuryl)}methyl)propanamide (8a). A cooled solution of **7a** (200 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) at 0 °C was stirred with Et_3N (0.14 mL, 1.0 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) for 10 min at 0 °C. The reaction mixture was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:10) as eluant to give **8a** as an oil (187 mg, 78%): ^{1}H NMR ($CDCl_3$) δ 7.26−7.36 (m, 5 H, Ph), 6.18−6.22 (m, 1 H, >C=CH), 4.48 (AB q, 2 H, J = 11.7, 18.2 Hz, OCH_2-Ph), 3.99 (AB q, 2 H, J = 15.0, 146.2 Hz, CH_2N(OH)CO), 3.55 (AB q, 2 H, J = 10.3, 25.4 Hz, CH_2OCH_2Ph), 2.80−2.91 (m, 2 H, H-4), 2.56−2.72 (m, 2 H, >CH=CHCH_2), 1.56−1.68 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.23 (s, 9 H, NCO(CH_3)$_3$), 1.06−1.09 (m, 4 H, 2 × CHCH_2CHMe$_2$), 0.83−0.86 (m, 12 H, 4 × CH_3); ^{13}C NMR ($CDCl_3$) δ 178.7, 169.1, 144.6, 137.1, 128.7, 128.3, 127.9, 124.7, 83.6, 74.2, 73.4, 55.2, 44.1, 44.0, 39.2, 35.0, 33.4, 32.2, 27.2, 27.1, 25.3, 23.2, 22.9, 22.8; FABMS m/z (relative intensity) 488 (MH^+, 37). Anal. ($C_{29}H_{45}NO_5$) C, H, N.

(*Z*)-*N*-Hydroxy-*N*-({2-(hydroxymethyl)-4-[5-methyl-3-(2-methylpropyl)hexylidene]-5-oxo(2-2,3-dihydrofuryl)}-methyl)-2,2-dimethylpropanamide (1a). A stirred solution of **8a** (175 mg, 0.36 mmol) in CH_2Cl_2 (4 mL) was cooled to −78 °C and treated dropwise with BCl_3 (1 M CH_2Cl_2, 1.1 mL). After the mixture was stirred for 30 min at − 78 °C, the reaction was quenched with saturated $NaHCO_3$ and the mixture was immediately partitioned between ether and the $NaHCO_3$ solution. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:2) as eluant to give **1a** as a white solid: mp 100−101 °C (101 mg, 69%); ^{1}H NMR ($CDCl_3$) δ 6.68 (s, 1 H, N(OH)CO, D_2O exchangeable), 6.30−6.35 (m, 1 H, >C=CH), 4.54 (d, 1 H, J = 15.4 Hz, CHHNCO), 3.97 (dd, 1H, J = 4.6, 10.4 Hz, CH_2OH, D_2O exchangeable), 3.51 (dd, 1 H, J = 4.4, 12.1 Hz, CHHOH), 3.41 (d, 1 H, J = 15.4 Hz, CHHNCO), 3.34 (distorted triplet, 1 H, J = 10.9, 11.3 Hz, CHHOH), 3.00−3.05 (dm, 1 H, J = 16.4 Hz, 4-H$_a$), 2.58−2.75 (m, 3 H, 4-H$_b$, >CH=CHCH_2), 1.59−1.66 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.31 (s, 9 H, NCO(CH_3)$_3$), 1.04−1.14 (m, 4 H, 2 × CHCH_2CHMe$_2$), 0.85−0.87 (2 br doublets, 12 H, 4 × CH_3); ^{1}H NMR (DMSO-d_6) δ 9.49 (s, 1 H, N(OH)CO, D_2O exchangeable), 6.11−6.13 (m, 1 H, >C=CH), 5.10 (t, 1 H, J = 5.6 Hz, CH_2OH, D_2O exchangeable), 3.72 (d, 1 H, J = 14.8 Hz, CHHNCO), 3.51 (d, 1 H, J = 14.8 Hz, CHHNCO), 3.31−3.41 (m, 2 H, CH_2OH), 2.64−2.75 (m, 2 H, 4-H$_{a,b}$), 2.48−2.52 (m, 2 H, >CH=CHCH_2), 1.47−1.61 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.11 (s, 9 H, NCO-(CH_3)$_3$), 0.94−1.06 (m, 4 H, 2 × CHCH_2CHMe$_2$), 0.77−0.78 (br d, 12 H, 4 × CH_3); ^{13}C NMR ($CDCl_3$) δ 179.9, 168.7, 146.6, 123.6, 84.3, 63.6, 55.2, 44.1, 39.3, 35.4, 33.4, 32.4, 27.0, 25.3, 23.2, 23.1, 22.9, 22.8; ^{13}C NMR (DMSO-d_6) δ 182.3, 174.1, 145.8, 132.1, 89.6, 70.0, 58.0, 48.8, 43.8, 38.1, 36.5, 32.4, 30.1, 28.3, 28.0; FABMS m/z (relative intensity) 398 (MH^+, 100). Anal. ($C_{22}H_{39}NO_5$) C, H, N.

(*E*)-5-(Hydroxymethyl)-3-[5-methyl-3-(2-methylpropyl)-hexylidene]-5-(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (5b). A solution of **4b** (2.0 g, 4.0 mmol) in CH_3CN/H_2O (4:1, 6 mL) was cooled to 0 °C and treated with ammonium cerium(IV) nitrate (6.5 g, 12 mmol). Following a similar procedure as for **5a**, the *E*-isomer (**5b**) was obtained as an oil (1.4 g, 92%): ^{1}H NMR ($CDCl_3$) δ 7.26−7.36 (m, 5 H, Ph), 6.73−6.78 (m, 1 H, >C=CH), 4.56 (AB q, 2 H, J = 12.1, 13.8 Hz, OCH_2Ph), 3.61−3.78 (m, 2 H, CH_2OH), 3.58 (AB q, 2 H, J = 9.9, 27.3 Hz, CH_2OCH_2Ph), 2.68−2.79 (m, 2 H, H-4), 2.20 (t, 1 H, CH_2OH), 2.09−2.13 (m, 2 H, >CH=CHCH_2), 1.56−1.69 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.06−1.11 (m, 4 H, 2 × CHCH_2-CHMe$_2$), 0.84−0.86 (m, 12 H, 4 × CH_3); ^{13}C NMR ($CDCl_3$) δ 170.3, 140.6, 137.7, 128.6, 128.0, 127.8, 127.4, 84.3, 73.9, 72.1, 65.7, 44.0 34.9, 33.0, 30.3, 25.4, 23.1, 22.8; FABMS m/z (relative intensity) 389 (MH^+, 68). Anal. ($C_{24}H_{36}O_4$) C, H.

(*E*)-5-Carbonyl-3-[5-methyl-3-(2-methylpropyl)hexylidene]-5-(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (6b). Following a similar method of oxidation as before, **6b** was obtained as an oil (525 mg, 85%): ^{1}H NMR ($CDCl_3$) δ 9.73 (s, 1 H, CHO), 7.26−7.36 (m, 5 H, Ph), 6.73−6.78 (m, 1 H, >C=CH), 4.49−4.63 (m, 2 H, OCH_2Ph), 3.61−3.75 (AB m, 2 H, CH_2OCH_2Ph), 2.74−3.02 (m, 2 H, H-4), 2.09−2.13 (m, 2 H, >CH=CHCH_2), 1.57−1.67 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.03−1.11 (m, 4 H, 2 × CHCH_2CHMe$_2$), 0.83−0.88 (m, 12 H, 4 × CH_3). This compound was used immediately in the following step.

(*E*)-5-(Hydroxylamino)methyl)-3-[5-methyl-3-(2-methylpropyl)hexylidene]-5-(phenylmethoxy)methyl]-4,5-dihydrofuran-2-one (7b). The reaction of aldehyde **6b** with *O*-*tert*-(butyldimethylsilyl)hydroxylamine was performed in the same manner as with **6a** to give, after workup, **7b** as a white solid: mp 86−87 °C (283 mg, 54%); ^{1}H NMR ($CDCl_3$) δ 7.26−7.35 (m, 5 H, Ph), 6.72−6.77 (m, 1 H, >C=CH), 4.59 (s, 2 H, OCH_2Ph), 3.57 (AB q, 2 H, J = 10.1, 19.0 Hz, CH_2OCH_2-Ph), 3.20 (AB q, 2 H, J = 13.6, 32.2 Hz, CH_2NHOH), 2.77−2.87 (m, 2 H, H-4), 2.08−2.12 (m, 2 H, >CH=CHCH_2), 1.58−1.66 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.04−1.12 (m, 4 H, 2 × CHCH_2CHMe$_2$), 0.80−0.88 (m, 12 H, 4 × CH_3); ^{13}C NMR

($CDCl_3$) δ 170.2, 140.3, 137.7, 128.6, 128.0, 127.8, 127.4, 83.4, 73.8, 73.2, 58.7, 44.0, 34.8, 33.0, 32.4, 25.4, 23.1, 22.8; FABMS *m*/*z* (relative intensity) 404 (MH^+, 19.2). Anal. ($C_{24}H_{37}NO_4$) C, H, N.

(*E*)-*N*-Hydroxy-2,2-dimethyl-*N*-({4-[5-methyl-3-(2-methoxypropyl)hexylidene]-5-oxo-2-[(phenylmethoxy)methyl]-(2−2,3-dihydrofuryl)}methyl)propanamide (8b). Acylation of **7b** with pivaloyl chloride was performed in the same manner as with **7a** to give, after workup, **8b** as an oil (130 mg, 71%): ^{1}H NMR ($CDCl_3$) δ 7.25−7.36 (m, 5 H, Ph), 6.72−6.78 (m, 1 H, >C═CH), 4.58 (AB q, 2 H, J = 11.9, 15.6 Hz, OCH_2Ph), 4.00 (AB q, 2 H, J = 14.8, 100.6 Hz, CH_2NCO), 3.54 (AB q, 2 H, J = 10.1, 21.1 Hz, CH_2OCH_2Ph), 2.77 (s, 2 H, H-4), 2.08−2.12 (m, 2 H, >CH═CHCH_2), 1.56−1.68 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.23 (s, 9 H, NCO(CH_3)$_3$), 1.06−1.11 (m, 4 H, 2 × CHCH_2CHMe$_2$), 0.84−0.86 (m, 12 H, 4 × CH_3); ^{13}C NMR ($CDCl_3$) δ 178.8, 170.2, 141.0, 137.1, 128.7, 128.2, 127.9, 126.9, 84.6, 74.1, 73.3, 55.3, 44.0, 39.2, 34.9, 32.9, 31.7, 27.2, 27.1, 25.4, 23.1, 22.8, 22.7; FABMS *m*/*z* (relative intensity) 488 (MH^+, 46.3). Anal. ($C_{29}H_{45}NO_5$) C, H, N.

(*Z*)-*N*-Hydroxy-*N*-({2-(hydroxymethyl)-4-[5-methyl-3-(2-methylpropyl)hexylidene]-5-oxo(2-2,3-dihydrofuryl)}-methyl)2,2-dimethylpropanamide (1b). Following an identical deprotection procedure, **1b** was obtained as a white solid: mp 95−96 °C (75 mg, 79%); ^{1}H NMR ($CDCl_3$) δ 7.05 (s, 1 H, NCO(OH), D2O exchangeable), 6.81−6.87 (m, 1 H, >C═CH), 4.50 (d, 1 H, J = 15.2 Hz, CHHNCO), 4.04−4.07 (m, 1H, CH_2OH, D_2O exchangeable), 3.56 (dd, 1 H, J = 4.8, 9.3 Hz, CHHOH), 3.48 (d, 1 H, J = 15.4 Hz, CHHNCO), 3.30−3.35 (m, 1 H, CHHOH), 2.52−2.98 (m, 1 H, 4-H), 2.12−2.16 (m, 3 H, 4-H, >CH═CHCH_2), 1.57−1.69 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.31 (s, 9 H, NCO(CH_3)$_3$), 1.01−1.16 (m, 4 H, 2 × CHCH_2CHMe$_2$), 0.82−0.87 (m, 12 H, 4 × CH_3); ^{1}H NMR (DMSO-d_6) δ 9.49 (s, 1 H, NCO(OH), D_2O exchangeable), 6.38−6.45 (m, 1 H, >C═CH), 5.12 (t, 1H, CH_2OH, D_2O exchangeable), 3.90 (dd, 1 H, J = 14.8 Hz, CHHNCO), 3.51 (d, 1 H, J = 14.8 Hz, CHHNCO), 3.39−3.45 (m, 2 H, CH_2OH), 2.64 (s, 2 H, 4-H), 1.94−2.01 (m, 2 H, >CH═CHCH_2), 1.55−1.58 (m, 3 H, 2 × CHMe$_2$, CH(i-Bu)$_2$), 1.11 (s, 9 H, NCO(CH_3)$_3$), 1.01−1.06 (m, 4 H, 2 × CHCH_2CHMe$_2$), 0.79−0.81 (m, 12 H, 4 × CH_3); ^{13}C NMR ($CDCl_3$) δ 180.0, 169.8, 143.1, 125.7, 85.0, 64.0, 55.4, 44.0, 39.3, 35.1, 32.9, 32.1, 27.0, 25.4, 23.2, 23.1, 22.8, 22.7; ^{13}C NMR (DMSO-d_6) δ 177.5, 170.0, 137.3, 129.7, 85.6, 65.3, 55.5, 44.1, 39.1, 34.6, 32.9, 30.2, 27.6, 25.4, 23.5, 23.2; FABMS *m*/*z* (relative intensity) 398 (MH^+, 100). Anal. ($C_{22}H_{39}NO_5$) C, H, N.

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