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Efficient synthesis of new butenolides by subsequent reactions: application for the synthesis of original iminolactones, bis-iminolactones and bis-lactones

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ABSTRACT

We have developed the synthesis of twenty four new iminolactones, bis-iminolactones and bis-lactones by subsequent esterification–condensation or addition–condensation reactions according to two strategies from α-hydroxyketones. The X-ray diffraction data of a bis-iminolactone is described and present an interesting helical column packing.

1. Introduction

Functionally substituted derivatives of 2,5-dihydrofurans (but-2-en-4-olides) constitute an important class of many natural and synthetic products.[1,2] They possess a wide range of biological activities, which include antibacterial,[3] antibiotic,[4] antifungal,[5] pesticides,[6] anti-inflammatory[7] and analgesic.[8] These properties have been responsible for considerable interest in the synthesis of substituted butenolides.[9,10]

Iminolactones are an important class of heterocyclic compounds due to their potential biological properties and were essentially known in coumarin series. They are precursor agents for the preparation of a wide spectrum of natural compounds.[11] However, there are only a few methods reported for the synthesis of iminolactones[12–16] compared to the butenolides.[9,10] Iminocoumarines are obtained by the reaction of a nitrile with salicylic aldehyde or 2-hydroxyacetophenones under acid–base conditions (Fig. 1).[13–15] The hydrolysis of iminolactones with aqueous hydrochloric acid produces butenolides.[16]

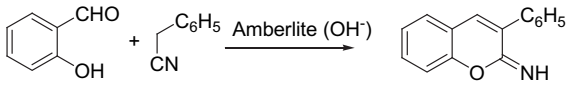

Fig. 1. An example of synthesis of iminocoumarins.[14]

In our laboratory, we have described the synthesis of iminoarylbutenolides (3-aryl-2-imino-4-methyl-2,5-dihydrofurans)[17,18] obtained by an one pot condensation reaction between different α-hydroxyketone and acetonitrile compounds, catalysed by sodium ethoxide in ethanol under classical conditions or microwave irradiation. The hydrolysis of these iminolactones afforded corresponding butenolides in good yields.

In the present work, we report in the first part a generic methodology for the synthesis of five-membered iminolactones (iminodihydrofurans) from various amines and their conversion into the corresponding butenolides (2,5-dihydrofurans) by a simple hydrolysis (Fig. 2).

In the second part, in view of synthesizing new heterocycles, we present simple protocols for preparing two series of bis-lactone derivatives (Fig. 3). These bis-lactone derivatives could be good candidates as chelating and bis-alkylating agents. Generally the butenolide cytotoxicity was attributed to their reactivity towards the cysteine residues of functional proteins forming covalent bond via

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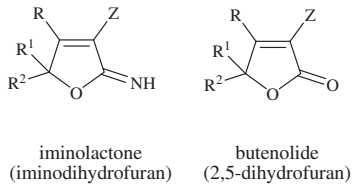


Fig. 2. Generic structures of butenolide, iminolactone.

reverse Michael type addition.[19] In the literature, bis-iminolactones have been the subject of only one report[20] for bis-iminocoumarins synthesis.

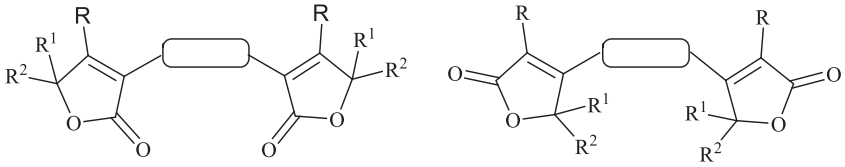
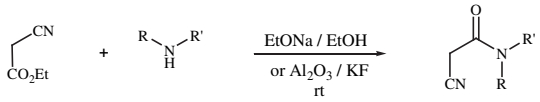


Fig. 3. Generic structures of bis-lactones.

2. Results and discussion

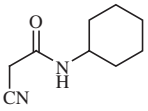
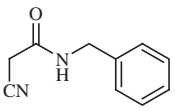
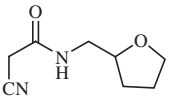
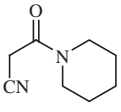
The simple and easy synthesis of iminolactones (*N*-alkyl-2,5-dihydro-2-iminofuran-3-carboxamides) **3a**–**d** begins with the preparation of *N*-substituted cyanoacetamide derivatives **2a**–**d**. The latter were easily obtained by direct condensation of ethyl cyanoacetate with primary amines at room temperature in the presence of a catalytic amount of sodium ethoxide in ethanol. The reaction was carried out also in solvent free conditions with KF-alumina (Al_2O_3/KF) for 1 h and gave similar isolated yields (85–90%) (Table 1).

Table 1
Synthesis of cyanoacetamide derivatives **2a**–**d**



2a-d

2a: R = H, R' = cyclohexyl
2b: R = H, R' = benzyl
2c: R = H, R' = tetrahydrofurfuryl
2d: R, R' = piperidinyl

Entry	R	R′	Product		Yield [%]
1	H	Cyclohexyl		**2a**	90[a]
2	H	Benzyl		**2b**	85[a]
3	H	Tetrahydrofurfuryl		**2c**	87[a]
4	Piperidinyl			**2d**	37[b]

[a] 1 h, rt.
[b] 24 h, rt.

However, secondary amine required longer reaction time (24 h) at room temperature and the reaction were incomplete. The cyanoacetamide **2d** was formed in 37% yield (Table 1).

Next, iminolactone compounds (*N*-alkyl-2,5-dihydro-2-iminofuran-3-carboxamides) **3a**–**d** were obtained, in cascade reaction, from α-hydroxyketone **1** and *N*-substituted cyanoacetamide derivatives **2a**–**d** in the presence of a catalytic amount of sodium ethoxide in ethanol at room temperature for 6–24 h (Table 2).

The spontaneous cyclisation between the hydroxyl group of compound **1** and the cyano group of intermediate **2** followed by a Knoevenagel[21] reaction led to iminolactone derivatives in good yields (75–96%). The ease of ring formation was probably due to the presence of a *gem*-diakyl moiety producing a Thorpe–Ingold conformational effect.[22,23] The supposed mechanism is described in Scheme 1.

The readily treatment of iminolactones **3a**–**d** with concentrated hydrochloric acid lead to the hydrolysis of the imino group affording the corresponding lactones **4a**–**d** in quantitative yields (Table 2). The structures of iminolactones **3a**–**d** and lactones **4a**–**d** were determined unambiguously by IR, ^{1}H NMR, ^{13}C NMR and mass spectra. Namely, the C=N absorptions of the imino group observed in IR (1674–1681 cm^{-1}) are lower than C=O absorptions of the lactone (1732–1748 cm^{-1}). This indicates clearly the formation of iminolactones. The different chemical shifts values in ^{13}C NMR spectra and the melting points also confirmed the formation of two different products.

In the second part of our work, we developed an easy and efficient method for preparation of various bis-lactone derivatives, which are new potential chelating compounds. We have investigated herein the synthesis of two types of new bis-lactones **7** and **9** (Fig. 4).

The bis-lactones **7** and **9** differ from the nature (amide or C=C bond, respectively) and the position (3 or 4, respectively) of the group, which binds to the spacer.

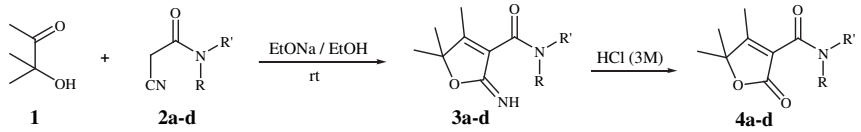
The synthesis of bis-lactones **7a**–**e** was based on the following procedure: a direct and simple condensation of different diamines with 2 equiv of ethyl cyanoacetate in the presence of a catalytic amount of basic catalyst afforded bis-cyanoacetamides **5a**–**d** in isolated yields (75–85%) at room temperature from primary amines. However with secondary amine, the reaction yield is lower (**5e** 39%) and needs higher temperature (80 °C) during a longer time (Table 3).

Then, the Knoevenagel condensation of bis-cyanoacetamides **5a**–**e** with 2 equiv of α-hydroxyketone **1** in the presence of the sodium ethoxide in ethanol afforded the bis-iminolactones **6a**–**e** in isolated yields (58–96%). The hydrolysis of the bis-iminolactones **6a**–**e** in the presence of hydrochloric acid (3 M) gave the bis-lactones **7a**–**d**. In the case of compound **6e** the bis-lactone was not obtained in this condition, a hydrolysis occurred followed by an esterification in ethanol to furnish the butenolide ester **8a**.

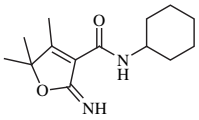
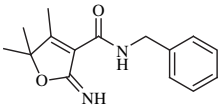
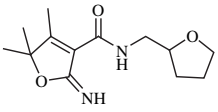
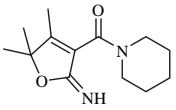
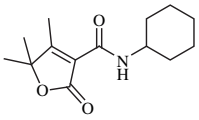
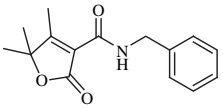
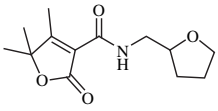
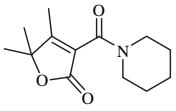
Following this successful synthesis, several substituted bis-imin olactones and bis-lactones were prepared (Table 4).

The new bis-iminolactone **6a** was obtained, crystallized and it was possible to carry out by the X-ray crystallography study. This

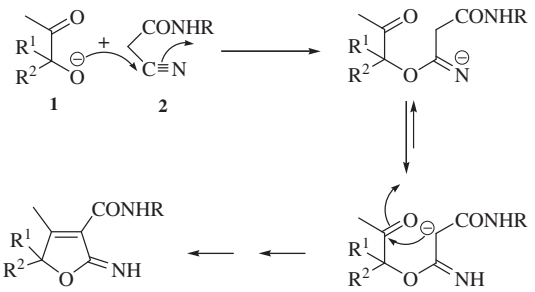
Table 2
Synthesis of iminolactones **3a**–**d** and their corresponding lactones **4a**–**d**



1 **2a-d** **3a-d** **4a-d**

Entry	R	R′	Product	Yield [%]
1	H	Cyclohexyl	 **3a**	96[a]
2	H	Benzyl	 **3b**	94[a]
3	H	Tetrahydrofurfuryl	 **3c**	75[a]
4	Piperidinyl		 **3d**	93[b]
5	H	Cyclohexyl	 **4a**	99[c]
6	H	Benzyl	 **4b**	98[c]
7	H	Tetrahydrofurfuryl	 **4c**	99[c]
8	Piperidinyl		 **4d**	95[c]

[a] 6 h, rt.
[b] 24 h, rt.
[c] : 5 h, reflux EtOH.



1 **2**

Scheme 1. Mechanism of formation of 2-imino-4-methyl-2,5-dihydrofurans.

structure of **6a** confirms the formation of iminolactone with β-ketonitriles. To our knowledge, it is the first structure of a bis-iminolactone described in literature.

The ORTEP diagram is shown in Fig. 5:

The structure of the crystal is very original and shows a supramolecular arrangement in an infinite helical column (Fig. 6). The querying of the Cambridge Structural Database (CSD, Version 5.24, Allen & Kennard, 1993) showed that actually, there is not available structure of similar compounds. Furthermore, the arrangement of compound in an infinite helical column in the crystal is not common. These columns are connected between them along *a* axis by a weak C–H ···O interaction between H13A from C13 methyl group and O7. Two methyl hydrogen from two neighbouring molecules of one column interact with the same oxygen of the second column.

In the crystal structure N8 is situated in the proximity of hydrogen H9 of atom N9. The contact distance between N8 and H9 is 2.095–2.110Å, indicating formation of an intramolecular hydrogen bond. With this hydrogen bond, the six atoms N8, C2, C4, C6, N9 and H9 form a pseudo-six-membered ring. Formation of the pseudo-six-membered ring is accompanied by a delocalization of π electrons. So, in reality the compound behaves as a compound

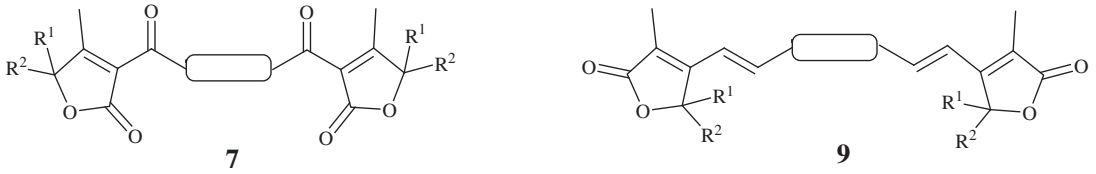
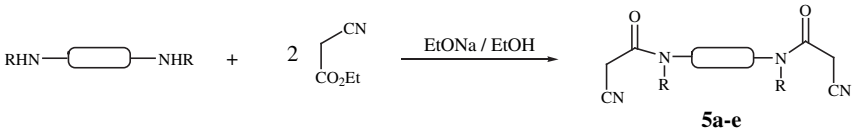
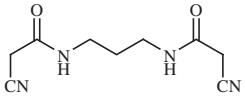
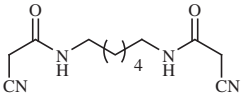
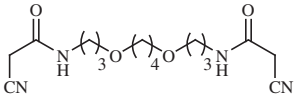
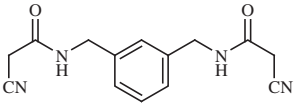
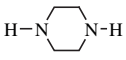
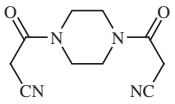


Fig. 4. Structures of bis-lactones **7** and **9**.

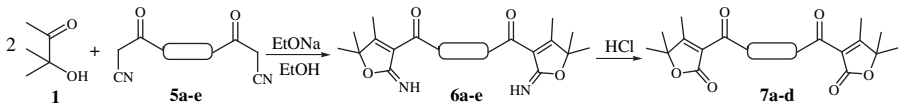
Table 3
Synthesis of bis-cyanoacetamide derivatives **5a**–**e**

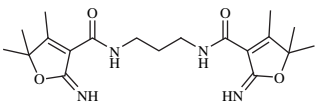
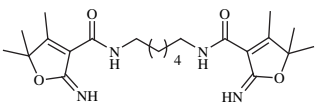
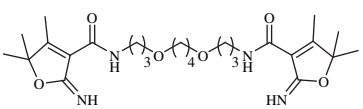


Entry	Diamine	Product		Yield [%]
1	$H_2N(CH_2)_3NH_2$		**5a**	85[a]
2	$H_2N(CH_2)_6NH_2$		**5b**	74[a]
3	$H_2N(CH_2)_3O(CH_2)_4O(CH_2)_3NH_2$		**5c**	78[a]
4	$1,3\text{-}H_2NCH_2C_6H_4CH_2NH_2$		**5d**	75[a]
5			**5e**	39[b]

[a] 2 h, rt.
[b] 12 h, reflux EtOH.

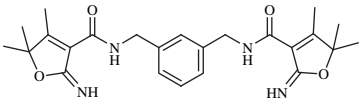
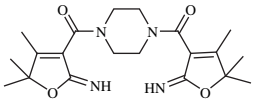
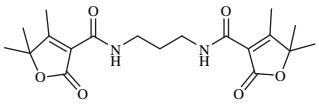
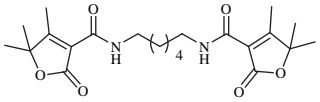
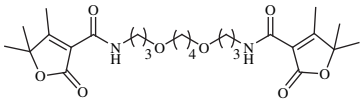
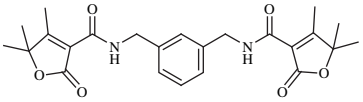
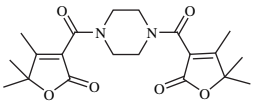
Table 4
Synthesis of bis-iminolactone and bis-lactone derivatives



Entry		Product		Yield [%]
1	$-HN(CH_2)_3NH-$		**6a**	96[a]
2	$-HN(CH_2)_6NH-$		**6b**	93[a]
3	$-HN(CH_2)_3O(CH_2)_4O(CH_2)_3NH-$		**6c**	80[a]

(*continued on next page*)

Table 4 (*continued*)

Entry		Product	Yield [%]
4	1,3-$HNCH_2C_6H_4CH_2NH$–	 **6d**	70[a]
5		 **6e**	58[b]
6	–$HN(CH_2)_3NH$–	 **7a**	94[c]
7	–$HN(CH_2)_6NH$–	 **7b**	98[c]
8	–$HN(CH_2)_3O(CH_2)_4O(CH_2)_3NH$–	 **7c**	88[c]
9	1,3-$HNCH_2C_6H_4CH_2NH$–	 **7d**	90[c]
10		 **7e**	0[c]

[a] 12 h, rt.
[b] 6 h, reflux EtOH.
[c] 5 h, reflux EtOH.

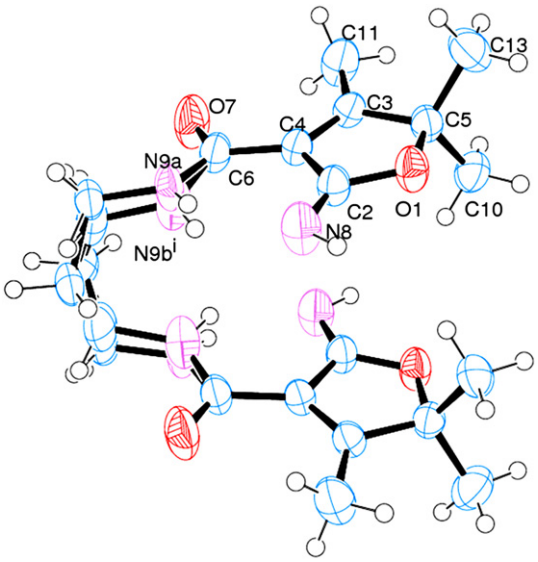


Fig. 5. ORTEP diagram of the X-ray crystal structure of compound **6a** with thermal ellipsoids at 50% probability.

with a bicycle on each extremity and the folded conformation of compound observed in the crystal is a result of π-stacking interaction occurring between the bicycles.

In the crystal, the packing is principally mediated by electrostatic interactions. The neighbouring molecules are linked by pair of two symmetry equivalent hydrogen bonds, N8–H8···O1 (symmetry code: $-x+1$, $-y$, $-z$) related by inversion centre. Thus, the intermolecular hydrogen-bonded molecules form infinite helical column along the *c* axis. These columns are connected between them by a weak C–H ···O interaction between H13A from C13 methyl group and O7. The disorder is situated on the aliphatic chain connecting the rings and it includes five atoms. The two conformations are the same probability of appearance, since this disorder is 50%.

Finally, we developed a synthesis of bis-lactones of type **9**. In this case, the methyl group in position 4 of 2,5-dihydrofurans is acid, vinylogue to the methylene of the malonate derivatives,[24] so it can easily be deprotonated and condensed with arylaldehyde.[17] In a similar manner, we report an efficient synthesis of bis-lactones of type **9** from readily available aromatic dialdehyde (*meta* or *para*).

As shown in Table 5, the bis-lactones **9a**–**g** were synthesized in two steps from different α-hydroxyketones **1a**–**c**. In the first step we prepared lactones **8a**–**d** according to a simple and easy method without solvent.[10] The condensation of 2 equiv of these lactones with an equivalent of terephtalaldehyde or isophtalaldehyde in the presence of 1 equiv of triethylamine in solvent free reaction conditions afforded the bis-lactones **9a**–**g** in good yields after heating at 80 °C during 5 h (Table 5).

3. Conclusion

In conclusion, we have developed two simple and efficient routes for the synthesis of various iminolactone, bis-iminolactone and bis-lactone derivatives from simple and readily available starting materials. The bis-lactones were easily synthesized either by hydrolysis of bis-iminolactones or by solvent free cascade reaction between

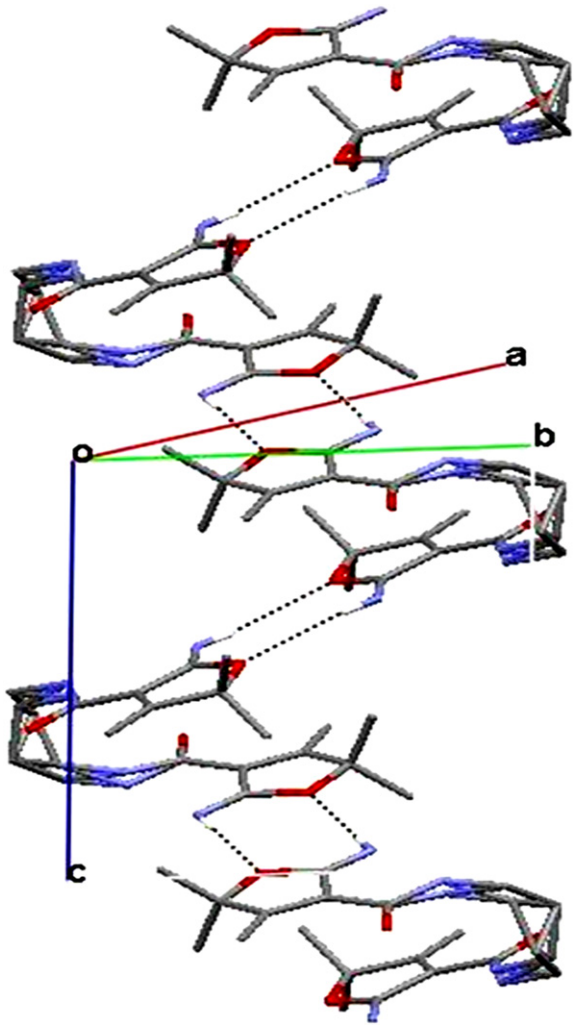


Fig. 6. A view of the electrostatic interactions in the crystal packing of **6a**.

dialdehyde and α,β-insaturated γ-lactones. Both methods are effective and allowed us to obtain twenty four new heterocyclic compounds, not described previously, with very good yields. Finally, we present herein the first X-ray diffraction data of a bis-imino-lactone, which shows an interesting helical column packing.

4. Experimental section

4.1. General methods

All commercial reagents were purchased from Acros, Aldrich and Sigma and were used as received without further purification. Reactions were monitored by TLC until no starting material remained. TLC was performed using Silica gel 60 F_{254} percolated aluminum sheets.

Melting points were recorded on a Kofler apparatus and are uncorrected. IR spectra were obtained with solids or neat liquids with a Fourier transform Perkin–Elmer Spectrum One with ATR accessory. Only significant absorptions are listed. NMR spectra were recorded at 250 MHz for ^{1}H NMR and 62.9 MHz for ^{13}C NMR with a 'Bruker AC 250' spectrophotometer in $CDCl_3$ and DMSO-d_6. Chemical shifts (δ) are expressed in parts per million (ppm) and are referenced to the internal deuterated solvents with tetramethylsilane as the internal standard. Data are reported as follows: multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qt=quintuplet, dd=doublet of doublet, dt=doublet of triplet, m=multiplet, br s=broad signal). Mass spectra were recorded on a QTOF Micro (Waters) spectrometer with electrospray ionization (ESI, positive mode), lockspray PEG, infusion introduction at 5 μL/min, a source temperature of 80 °C and desolvation temperature of 120 °C.

4.2. General procedure 1:synthesis of cyanoacetamides 2a–d

A mixture of a solution of sodium ethoxide (0.1 mmol) in ethanol (3 mL), ethyl cyanoacetate (10 mmol) and amine (10 mmol) was stirred at room temperature. The reaction time is 1 h for primary amines and 24 h for secondary amine **2d**. The precipitate obtained was separated by filtration, washed with diethylether and recrystallised in ethanol to provide a white solid of cyanoacetamides.

*4.2.1. 2-Cyano-N-cyclohexylacetamide **2a**.* The general procedure 1, using (1.13 g, 10 mmol) of ethyl cyanoacetate and (0.99 g, 10 mmol) of cyclohexylamine, gave the compound **2a** (1.49 g, 90%) as a white solid, mp 122–123 °C. ^{1}H NMR (DMSO-d_6) δ 8.13 (1H, qt, ^3J=7.5 Hz, NH), 3.58 (2H, s, CH_2CN), 3.48–3.56 (1H, m, CH), 1.09–1.79 (10H, m, $5CH_2$). ^{13}C NMR (DMSO-d_6) δ 160.9, 116.2, 48.4, 32.0, 25.0, 24.8, 24.3. EIMS m/z (% relative abundance): 167 (M+H, 52), 85 (100), 83 (56). HRMS (ES-QTOF) Calcd for $C_9H_{15}N_2O$ M+H 167.1184. Found 167.1186. IR ν_{max} (neat/cm^{-1}): 3276, 2261, 1646.

*4.2.2. 2-Cyano-N-benzylacetamide **2b**.* The general procedure 1, using (1.13 g, 10 mmol) of ethyl cyanoacetate and (1.07 g, 10 mmol) of benzylamine, gave the compound **2b** (1.47 g, 85%) as a white solid, mp 119–120 °C. ^{1}H NMR (DMSO-d_6) δ 8.81 (1H, t, ^3J=4.9 Hz, NH), 7.27–7.41 (5H, m, Harom), 4.35 (2H, d, ^3J=5.8 Hz, CH_2Ph), 3.76 (2H, s, CH_2CN). ^{13}C NMR (DMSO-d_6) δ 162.2, 138.5, 128.6, 127.3, 127.0, 116.2, 42.7, 25.3. EIMS m/z (% relative abundance): 175 (M+H, 12), 97 (18), 91 (100). HRMS (ES-QTOF) Calcd for $C_{10}H_{11}N_2O$ M+H 175.0871. Found 175.0873. IR ν_{max} (neat/cm^{-1}): 3302, 2255, 1644.

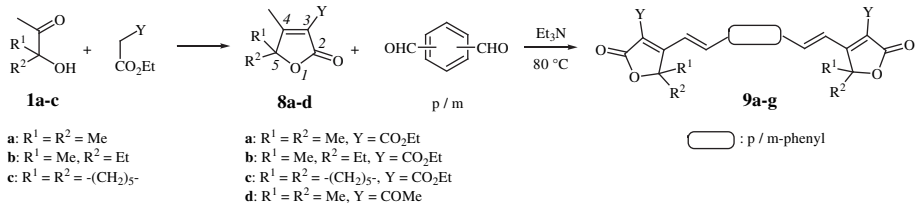
*4.2.3. 2-Cyano-N-((tetrahydrofuran-2-yl)methyl)acetamide **2c**.* The general procedure 1, using (1.13 g, 10 mmol) of ethyl cyanoacetate and (1.01 g, 10 mmol) of tetrahydrofurfurylamine, gave the compound **2c** (1.46 g, 87%) as a white solid, mp 89–90 °C. ^{1}H NMR (DMSO-d_6) δ 8.37 (1H, ^3J=7.0 Hz, NH), 3.66 (2H, s, CH_2CN), 3.55–3.60 (2H, m, CH_2), 3.64–3.69 (1H, m, CH), 3.13–3.23 (2H, m, CH_2NH), 1.47–1.93 (4H, m, $2CH_2$). ^{13}C NMR (DMSO-d_6) δ 162.2, 116.1, 76.8, 67.1, 43.1, 28.3, 25.3, 25.1. EIMS m/z (% relative abundance): 169 (M+H, 37), 151 (39), 97 (40), 85 (100). HRMS (ES-QTOF) Calcd for $C_8H_{13}N_2O_2$ M+H 169.0977. Found 169.0981. IR ν_{max} (neat/cm^{-1}): 3279, 2254, 1641.

*4.2.4. 3-Oxo-3-(piperidin-1-yl)propanenitrile **2d**.* The general procedure 1, using (1.13 g, 10 mmol) of ethyl cyanoacetate and (0.85 g, 10 mmol) of piperidine, gave the compound **2d** (0.56 g, 37%) as a white solid, mp 86–87 °C. ^{1}H NMR (DMSO-d_6) δ 4.02 (2H, s, CH_2CN), 3.45 (2H, t, ^3J=5.6 Hz, CH_2N), 3.32 (2H, t, ^3J=5.6 Hz, CH_2N), 1.44–1.63 (6H, m, $3CH_2$). ^{13}C NMR (DMSO-d_6) δ 160.9, 116.2, 46.4, 42.5, 25.6, 25.0, 24.7, 23.8. EIMS m/z (% relative abundance): 153 (M+H, 100), 112 (70), 85 (100). HRMS (ES-QTOF) Calcd for $C_8H_{13}N_2O$ M+H 153.1028. Found 153.1023. IR ν_{max} (neat/cm^{-1}): 2987, 2263, 1640.

4.3. General procedure 2:synthesis of *N*-alkyl-2,5-dihydro-2-imino-4,5,5-trialkylfuran-3-carboxamide 3a–d

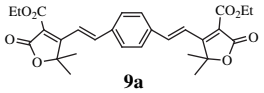
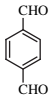
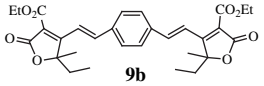
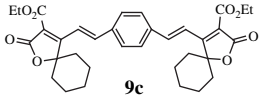
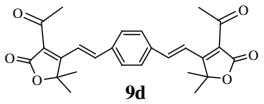
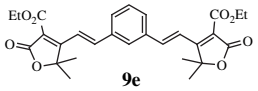
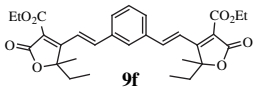
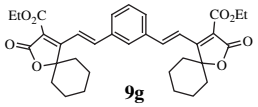
A mixture of 3-hydroxy-3-methylbutan-2-one **1** (10 mmol) and the substituted cyanoacetamides **2a–d** (10 mmol) with a solution of sodium ethoxide (0.5 mmol) in ethanol (10 mL) was stirred at room temperature. After evaporation of the solvent, the residue was acidified with 6 M aqueous HCl. The mixture was neutralised with a solution of potassium carbonate (10%), then extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried on

Table 5
Synthesis of bis-lactones **9**



a: $R^1 = R^2 = Me$
b: $R^1 = Me$, $R^2 = Et$
c: $R^1 = R^2 = -(CH_2)_5-$

a: $R^1 = R^2 = Me$, $Y = CO_2Et$
b: $R^1 = Me$, $R^2 = Et$, $Y = CO_2Et$
c: $R^1 = R^2 = -(CH_2)_5-$, $Y = CO_2Et$
d: $R^1 = R^2 = Me$, $Y = COMe$

Entry	Dialdehyde	Product	Yield [%]
1		 **9a**	48
2		 **9b**	40
3		 **9c**	35
4		 **9d**	67
5		 **9e**	81
6		 **9f**	73
7		 **9g**	70

$MgSO_4$, filtered and concentrated in vacuum. The recovered solid was recrystallised in ethanol to provide compounds **3a**–**d**.

*4.3.1. N-Cyclohexyl-2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide **3a**.* The general procedure 2, using (1.02 g, 10 mmol) of 3-hydroxy-3-methylbutan-2-one and (1.66 g, 10 mmol) of 2-cyano-*N*-cyclohexylacetamide **2a** in the presence of sodium ethoxide (0.01 g, 0.5 mmol), gave, in 6 h, compound **3a** (2.40 g, 96%) as yellow solid, mp<50 °C. ^{1}H NMR ($CDCl_3$) δ 9.51 (1H, d, ^3J=5.0 Hz, CONH), 6.80 (1H, s, C=NH), 3.82–3.89 (1H, m, NHCH), 2.36 (3H, s, CH_3), 1.84–1.89 (2H, m, CH_2), 1.65–1.66 (2H, m, CH_2), 1.50–1.52 (2H, m, CH_2), 1.37 (6H, s, $2CH_3$), 1.26–1.35 (4H, m, $2CH_2$). ^{13}C NMR ($CDCl_3$) δ 171.4, 167.8, 161.1, 119.0, 88.4, 47.3, 32.6, 29.2, 25.7, 24.6, 12.5. EIMS *m*/*z* (% relative abundance): 251 (M+H, 100), 234 (23), 169 (28), 152 (73), 151 (79). HRMS (ES-QTOF) Calcd for $C_{14}H_{23}N_2O_2$ M+H 251.1760. Found 251.1761. IR ν_{max} (neat/cm^{-1}): 2978, 2854, 1674, 1640, 1552.

*4.3.2. N-Benzyl-2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide **3b**.* The general procedure 2, using (1.02 g, 10 mmol) of 3-hydroxy-3-methylbutan-2-one and (1.74 g, 10 mmol) of 2-cyano-*N*-benzylacetamide **2b** in the presence of sodium ethoxide (0.01 g, 0.5 mmol), gave, in 6 h, compound **3b** (2.42 g, 94%) as yellow solid, mp 56–58 °C. ^{1}H NMR ($CDCl_3$) δ 9.93 (1H, s, CONH), 7.16–7.26 (5H, m, Harom), 6.87 (1H, s, C=NH), 4.47 (2H, d, ^3J=5.8 Hz, CH_2Ph), 2.33 (3H, s, CH_3), 1.32 (6H, s, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 172.1, 167.6, 162.0, 138.5, 128.7, 127.5, 127.1, 119.0, 88.6, 42.7, 24.9, 12.6. EIMS *m*/*z* (% relative abundance): 259 (M+H, 54), 241 (14), 224 (10), 214 (20), 199 (43), 196 (25), 185 (16), 181 (14), 157 (22), 152 (26), 135 (27), 106 (32), 91 (100). HRMS (ES-QTOF) Calcd for $C_{15}H_{19}N_2O_2$ M+H 259.1447. Found 259.1447. IR ν_{max} (neat/cm^{-1}): 3256, 3063, 2850, 1674, 1644, 1552.

*4.3.3. N-((Tetrahydrofuran-2-yl)methyl)-2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide **3c**.* The general procedure 2, using (1.02 g, 10 mmol) of 3-hydroxy-3-methylbutan-2-one and (1.68 g, 10 mmol) of 2-cyano-*N*-((tetrahydrofuran-2-yl)methyl)acetamide **2c** in the presence of sodium ethoxide (0.01 g, 0.5 mmol), gave, in 6 h, compound **3c** (1.89 g, 75%) as yellow solid, mp 64–65 °C. ^{1}H NMR ($CDCl_3$) δ 9.76 (1H, s, CONH), 6.96 (1H, s, C=NH), 4.02–4.09 (1H, m, CH), 3.74–3.91 (2H, m, CH_2), 3.33–3.56 (2H, m, $NHCH_2$), 2.38 (3H, s, CH_3), 1.84–1.94 (4H, m, $2CH_2$), 1.38 (6H, s, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 175.7, 168.1, 159.2, 119.8, 98.5, 76.6, 67.1, 42.9, 28.6, 25.1, 23.0, 13.3. EIMS *m*/*z* (% relative abundance): 253 (M+H, 48), 236 (15), 235 (10), 153 (31), 152 (100), 135 (35). HRMS (ES-QTOF) Calcd for $C_{13}H_{21}N_2O_3$ M+H 253.1552. Found 253.1554. IR ν_{max} (neat/cm^{-1}): 3181, 3049, 2668, 1681, 1627, 1551.

*4.3.4. (5-Ethyl-2-imino-4,5-dimethyl-2,5-dihydrofuran-3-yl)(piperidin-1-yl)methanone **3d**.* The general procedure 2, using (1.02 g,

10 mmol) of 3-hydroxy-3-methylpentan-2-one and (1.52 g, 10 mmol) of 3-oxo-3-(piperidin-1-yl)propanenitrile **2d** in the presence of sodium ethoxide (0.01 g, 0.5 mmol) gave, in 24 h, compound **3d** (2.19 g, 93%) as viscous liquid. ^{1}H NMR ($CDCl_3$) δ 5.29 (1H, s, C=NH), 3.56 (4H, t, ^3J=5.2 Hz, $2CH_2$), 2.20 (3H, s, CH_3), 1.80 (6H, s, $2CH_3$), 1.56–1.60 (6H, m, $3CH_2$). ^{13}C NMR ($CDCl_3$) δ 168.4, 162.3, 159.9, 114.1, 91.3, 48.1, 32.2, 25.0, 18.4, 11.6. EIMS *m*/*z* (% relative abundance): 237 (M+H, 100). HRMS (ES-QTOF) Calcd for $C_{13}H_{21}N_2O_2$ M+H 237.1598. Found 237.1591. IR ν_{max} (neat/cm^{-1}): 3322, 2987, 2901, 1676, 1641.

4.4. General procedure 3: hydrolysis of iminolactones 3a–d in butenolides 4a–d

To a solution of HCl (3 M, 2 mL) was added *N*-alkyl-2,5-dihydro-2-imino-4,5,5-trialkylfuran-3-carboxamide **3a**–**d** (2 mmol) in ethanol (5 mL). After being refluxed for 5 h, the mixture was evaporated and the obtained residue was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried on $MgSO_4$, filtered and concentrated in vacuum to give butenolides **4a**–**d**, after recrystallisation in ethanol.

*4.4.1. N-Cyclohexyl-2,5-dihydro-4,5,5-trimethyl-2-oxofuran-3-carboxamide **4a**.* The general procedure 3, using (0.50 g, 2 mmol) of *N*-cyclohexyl-2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide **3a**, yielded **4a** (0.49 g, 99%) as yellow solid, mp 80–81 °C. ^{1}H NMR ($CDCl_3$) δ 8.12 (1H, d, ^3J=5.7 Hz, CONH), 3.81–3.93 (1H, m, CH), 2.47 (3H, s, CH_3), 1.69–1.92 (4H, m, $2CH_2$), 1.55–1.59 (2H, m, CH_2), 1.47 (6H, s, $2CH_3$), 1.24–1.40 (4H, m, $2CH_2$). ^{13}C NMR ($CDCl_3$) δ 174.3, 169.9, 154.5, 111.8, 81.1, 42.0, 27.2, 20.0, 19.1, 18.7, 7.4. EIMS *m*/*z* (% relative abundance): 252 (M+H, 57), 171 (10), 170 (100). HRMS (ES-QTOF) Calcd for $C_{14}H_{22}NO_3$ M+H 252.1607. Found 252.1600. IR ν_{max} (neat/cm^{-1}): 3334, 2981, 2854, 1733, 1666, 1641.

*4.4.2. N-Benzyl-2,5-dihydro-4,5,5-trimethyl-2-oxofuran-3-carboxamide **4b**.* The general procedure 3, using (0.52 g, 2 mmol) of *N*-benzyl-2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide **3b**, yielded **4b** (0.50 g, 98%) as yellow solid, mp 83–84 °C. ^{1}H NMR ($CDCl_3$) δ 8.55 (1H, s, NH), 7.20–7.34 (5H, m, Harom), 4.53 (2H, d, ^3J=5.9 Hz, CH_2), 2.48 (3H, s, CH_3), 1.46 (6H, s, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 180.5, 171.3, 160.9, 137.9, 128.8, 127.7, 127.4, 117.1, 86.8, 42.8, 24.2, 13.0. EIMS *m*/*z* (% relative abundance): 260 (M+H, 46), 91 (100). HRMS (ES-QTOF) Calcd for $C_{15}H_{18}NO_3$ M+H 260.1287. Found 260.1285. IR ν_{max} (neat/cm^{-1}): 3348, 3031, 2931, 1732, 1659, 1644.

*4.4.3. 2,5-Dihydro-N-((tetrahydrofuran-2-yl)methyl)-4,5,5-trimethyl-2-oxofuran-3-carboxamide **4c**.* The general procedure 3, using *N*-((tetrahydrofuran-2-yl)methyl)-2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide **3c** (0.50 g, 2 mmol), yielded **4c** (0.50 g, 99%) as yellow solid, mp 90–92 °C. ^{1}H NMR ($CDCl_3$) δ 8.38 (1H, s, NH), 4.01–4.05 (1H, m, CH), 3.72–3.90 (2H, m, CH_2), 3.33–3.53 (2H, m, CH_2NH), 2.46 (3H, s, CH_3), 1.53–1.95 (4H, m, $2CH_2$), 1.46 (6H, s, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 179.0, 170.2, 160.2, 116.3, 85.7, 75.6, 67.3, 41.6, 27.8, 24.9, 23.1, 11.9. EIMS *m*/*z* (% relative abundance): 254 (M+H, 65), 236 (19), 182 (20), 171 (70), 170 (100), 153 (46), 152 (12). HRMS (ES-QTOF) Calcd for $C_{13}H_{20}NO_4$ M+H 254.1392. Found 254.1391. IR ν_{max} (neat/cm^{-1}): 3342, 2979, 2872, 1735, 1666, 1648.

*4.4.4. 5-Ethyl-4,5-dimethyl-3-(piperidine-1-carbonyl)furan-2(5H)-one **4d**.* The general procedure 3, using (5-ethyl-2-imino-4,5-dimethyl-2,5-dihydrofuran-3-yl)(piperidin-1-yl)methanone **3d** (0.50 g, 2 mmol), yielded **4d** (0.46 g, 97%) as yellow solid, mp 60–61 °C. ^{1}H NMR ($CDCl_3$) δ 3.59 (4H, t, ^3J=5.3 Hz, $2CH_2$), 2.22 (3H, s, CH_3), 1.78 (6H, s, $2CH_3$), 1.56–1.60 (6H, m, $3CH_2$). ^{13}C NMR ($CDCl_3$) δ 170.3, 168.8, 161.0, 115.5, 89.0, 48.1, 32.2, 25.3, 23.1, 12.1. EIMS *m*/*z* (% relative abundance): 238 (M+H, 82). HRMS (ES-QTOF) Calcd for $C_{13}H_{20}NO_3$ M+H 238.1438. Found 238.1440. IR ν_{max} (neat/cm^{-1}): 2972, 1748, 1629.

4.5. General procedure 4: synthesis of bis-cyanoacetamides 5a–e

A mixture of a solution of sodium ethoxide (1 mmol) in ethanol (3 mL), ethyl cyanoacetate (10 mmol) and the diamine (5 mmol) was stirred. The white precipitate obtained was separated by filtration, rinsed with diethylether and recrystallised in ethanol to provide bis-cyanoacetamides **5a**–**e**.

*4.5.1. Bis-(2-cyanoacetamide)-N,N′-propylidene **5a**.* The general procedure 4, using ethyl cyanoacetate (1.13 g, 10 mmol) and propanediamine (0.37 g, 5 mmol), gave in 2 h at room temperature, compound **5a** (0.88 g, 85%) as white solid, mp 159–160 °C. ^{1}H NMR (DMSO-d_6) δ 8.25 (2H, s, 2NH), 3.64 (4H, s, $2CH_2CN$), 3.11 (4H, q, ^3J=6.7 Hz, $CH_2CH_2CH_2$), 1.59 (2H, m, ^3J=6.9 Hz, $CH_2CH_2CH_2$). ^{13}C NMR (DMSO-d_6) δ 162.6, 116.2, 36.9, 28.5, 25.2. EIMS *m*/*z* (% relative abundance): 209 (M+H, 100), 142 (90), 125 (62). HRMS (ES-QTOF) Calcd for $C_9H_{13}N_4O_2$ M+H 209.1039. Found 209.1040. IR ν_{max} (neat/cm^{-1}): 3287, 3092, 2927, 2257, 1649, 1561.

*4.5.2. Bis-(2-cyanoacetamide)-N,N′-hexylidene **5b**.* The general procedure 4, using ethyl cyanoacetate (1.13 g, 10 mmol) and 1,6-hexanediamine (0.58 g, 5 mmol), gave in 2 h at room temperature, compound **5b** (0.92 g, 74%) as white solid, mp 149–150 °C. ^{1}H NMR (DMSO-d_6) δ 8.25 (2H, s, 2NH), 3.63 (4H, s, $2CH_2CN$), 3.08 (4H, q, ^3J=6.6 Hz, $2CH_2$), 1.28–1.45 (8H, m, $4CH_2$). ^{13}C NMR (DMSO-d_6) δ 161.8, 116.2, 38.9, 28.6, 25.9, 25.2. EIMS *m*/*z* (% relative abundance): 251 (M+H, 100), 184 (90), 167 (18). HRMS (ES-QTOF) Calcd for $C_{12}H_{19}N_4O_2$ M+H 251.1508. Found 251.1511. IR ν_{max} (neat/cm^{-1}): 3287, 3066, 2868, 2259, 1648, 1544.

*4.5.3. 1,4-Bis-(2-cyanoacetamido)-N-bis-(propyloxy)butane **5c**.* The general procedure 4, using ethyl cyanoacetate (1.13 g, 10 mmol) and 4,9-dioxa-1,12-dodecanediamine (1.02 g, 5 mmol), gave in 2 h at room temperature, compound **5c** (1.31 g, 78%) as white solid, mp 100–102 °C. ^{1}H NMR (DMSO-d_6) δ 8.29 (2H, s, 2NH), 3.63 (4H, s, $2CH_2CN$), 3.30–3.46 (8H, m, $4CH_2$), 3.14 (4H, q, ^3J=6.6 Hz, $2CH_2NH$), 1.66 (4H, m, ^3J=6.5 Hz, $2CH_2$), 1.55 (4H, m, $2CH_2$). ^{13}C NMR (DMSO-d_6) δ 161.9, 116.2, 69.8, 67.3, 36.4, 29.0, 26.0, 25.2. EIMS *m*/*z* (% relative abundance): 339 (M+H, 83), 125 (100). HRMS (ES-QTOF) Calcd for $C_{16}H_{27}N_4O_4$ M+H 339.2032. Found 339.2034. IR ν_{max} (neat/cm^{-1}): 3262, 3096, 2804, 2255, 1651, 1571.

*4.5.4. 1,3-Bis-((2-cyanoacetamido)-N-methyl)benzene **5d**.* The general procedure 4, using ethyl cyanoacetate (1.13 g, 10 mmol) and *m*-xylylenediamine (0.68 g, 5 mmol), gave in 2 h at room temperature, compound **5d** (1.01 g, 75%) as white solid, mp 170–172 °C. ^{1}H NMR (DMSO-d_6) δ 8.81 (2H, t, ^3J=5.4 Hz, 2NH), 7.18–7.37 (4H, m, Harom), 4.31 (4H, d, ^3J=5.7 Hz, $2CH_2Ph$), 3.73 (4H, s, $2CH_2CN$). ^{13}C NMR (DMSO-d_6) δ 162.1, 138.7, 128.4, 126.3, 126.0, 116.2, 42.5, 25.2. EIMS *m*/*z* (% relative abundance): 271 (M+H, 87), 205 (13), 187 (100). HRMS (ES-QTOF) Calcd for $C_{14}H_{15}N_4O_2$ M+H 271.1195. Found 271.1198. IR ν_{max} (neat/cm^{-1}): 3288, 3080, 2800, 2258, 1647, 1549.

*4.5.5. 3-(4-(3-oxopropanenitrile)piperazin-1-yl)-3-oxopropanenitrile **5e**.* The general procedure 4, is used with ethyl cyanoacetate (1.13 g, 10 mmol) and piperazine (0.43 g, 5 mmol). The mixture was refluxed during 12 h to obtain **5e** (0.43g, 39%) as white solid, mp 240–241 °C. ^{1}H NMR (DMSO-d_6) δ 4.09 (4H, s, $2CH_2CN$), 3.43 (8H, s, $4CH_2$). ^{13}C NMR (DMSO-d_6) δ 161.8, 116.0, 45.0, 24.8. EIMS *m*/*z* (% relative abundance): 221 (M+H, 100), 180 (14), 154 (28). HRMS (ES-

QTOF) Calcd for $C_{10}H_{13}N_4O_2$ M+H 221.1039. Found 221.1038. IR ν_{max} (neat/cm^{-1}): 2975, 2900, 2260, 1646, 1465.

4.6. General procedure 5: synthesis of bis-iminolactones 6a–e

A mixture of 3-hydroxy-3-methylbutan-2-one **1** (20 mmol) and the substituted bis-cyanoacetamides (10 mmol) with a solution of sodium ethoxide (1 mmol) in ethanol (10 mL) was stirred. After evaporation of the solvent, the residue was acidified with 6 M aqueous HCl. The mixture was neutralised with potassium carbonate, then extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried on $MgSO_4$, filtered and concentrated in vacuum. The obtained solid was recrystallised in ethanol to provide bis-iminolactones **6a**–**e**.

4.6.1. N,N′-Propan-1′,3′-bis-(2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide) ***6a***. The general procedure 5, using 3-hydroxy-3-methylbutan-2-one **1** (2.04 g, 20 mmol) and bis-(2-cyanoacetamide)-*N*,*N*′-propylidene **5a** (2.08 g, 10 mmol) in the presence of sodium ethoxide (0.02 g, 1 mmol), gave in 12 h at room temperature, **6a** (3.61 g, 96%) as yellow solid, mp 128–129 °C. ^{1}H NMR ($CDCl_3$) δ 9.61 (2H, s, 2CONH), 6.91 (2H, s, 2C=NH), 3.41 (4H, q, ^3J=6.8 Hz, $CH_2CH_2CH_2$), 2.38 (6H, s, $2CH_3$), 1.85 (2H, m, ^3J=6.9 Hz, $CH_2CH_2CH_2$), 1.39 (12H, s, $4CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.7, 167.7, 162.2, 118.9, 88.5, 36.5, 29.3, 24.6, 12.5. EIMS *m*/*z* (% relative abundance): 377 (M+H, 40), 360 (08), 252 (14), 226 (69), 209 (24), 208 (100). HRMS (ES-QTOF) Calcd for $C_{19}H_{29}N_4O_4$ M+H 377.2189. Found 377.2196. IR ν_{max} (neat/cm^{-1}): 3307, 3190, 1677, 1643, 1552.

4.6.2. N,N′-Hexan-1′,6′-bis-(2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide) ***6b***. The general procedure 5, using 3-hydroxy-3-methylbutan-2-one **1** (2.04 g, 20 mmol) and bis-(2-cyanoacetamide) *N*,*N*′-hexylidene **5b** (2.50 g, 10 mmol) in the presence of sodium ethoxide (0.02 g, 1 mmol), gave in 12 h at room temperature, **6b** (3.88 g, 93%) as white solid, mp 119–120 °C. ^{1}H NMR ($CDCl_3$) δ 9.66 (2H, s, 2CONH), 8.03 (2H, s, 2C=NH), 3.21 (4H, q, ^3J=6.5 Hz, $2CH_2$), 2.36 (6H, s, $2CH_3$), 1.47–1.52 (4H, m, $2CH_2$), 1.41 (12H, s, $4CH_3$), 1.21–1.26 (4H, m, $2CH_2$). ^{13}C NMR ($CDCl_3$) δ 171.4, 166.1, 161.0, 118.0, 88.0, 37.8, 28.8, 26.1, 24.1, 12.0. EIMS *m*/*z* (% relative abundance): 419 (M+H, 35), 402 (16), 268 (100). HRMS (ES-QTOF) Calcd for $C_{22}H_{35}N_4O_4$ M+H 419.2658. Found 419.2673. IR ν_{max} (neat/cm^{-1}): 3256, 1674, 1641, 1554.

4.6.3. N,N′-Bis-(propyloxy)butan-bis-(2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide) ***6c***. The general procedure 5, using 3-hydroxy-3-methylbutan-2-one **1** (2.04 g, 20 mmol) and 1,4-bis-(2-cyanoacetamido)-*N*-bis-(propyloxy)butane **5c** (3.38 g, 10 mmol) in the presence of sodium ethoxide (0.02 g, 1 mmol), gave in 2 h at room temperature, **6c** (4.05 g, 80%) as viscous liquid. ^{1}H NMR ($CDCl_3$) δ 9,66 (2H, s, 2NH), 8.03 (2H, s, 2C=NH), 2.35 (6H, s, $2CH_3$), 1.70 (6H, m, ^3J=6.2 Hz, $3CH_2$), 1.55 (8H, m, $4CH_2$), 1.40 (12H, s, $4CH_3$), 1.18–1.20 (6H, m, $3CH_2$). ^{13}C NMR ($CDCl_3$) δ 171.4, 166.0, 161.1, 118.1, 88.0, 69.8, 67.5, 35.2, 29.1, 25.9, 24.3, 12.0. EIMS *m*/*z* (% relative abundance): 507 (M+H, 80), 490 (15), 356 (100), 339 (29), 209 (60). HRMS (ES-QTOF) Calcd for $C_{26}H_{43}N_4O_6$ M+H 507.3183. Found 507.3182. IR ν_{max} (neat/cm^{-1}): 3260, 3070, 2863, 1675, 1642, 1561.

4.6.4. N,N′-Metaxylyl-bis-(2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide) ***6d***. The general procedure 5, using 3-hydroxy-3-methylbutan-2-one **1** (2.04 g, 20 mmol) and 1,3-bis-((2-cyanoacetamido)-*N*-methyl)benzene **5d** (2.70 g, 10 mmol) in the presence of sodium ethoxide (0.02 g, 1 mmol), gave in 2 h at room temperature, **6d** (3.06 g, 70%) as white solid, mp 125–126 °C. ^{1}H NMR ($CDCl_3$) δ 10.07 (2H, t, ^3J=5.4 Hz, 2CONH), 8.12 (2H, s, 2C=NH), 7.28–7.41 (4H, m, Harom), 4.50 (4H, d, ^3J=5.8 Hz, $2CH_2$), 2.42 (6H, s, $2CH_3$), 1.46 (12H, s, $4CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.8, 166.1, 161.2, 139.1, 128.6, 126.4, 126.0, 118.0, 88.3, 41.6, 24.3, 12.1. EIMS *m*/*z* (% relative abundance): 439 (M+H, 47), 422 (13), 288 (100), 271 (15). HRMS (ES-QTOF) Calcd for $C_{24}H_{31}N_4O_4$ M+H 439.2345. Found 439.2362. IR ν_{max} (neat/cm^{-1}): 3259, 1674, 1643, 1552.

4.6.5. 3,4-Bis-(5-ethyl-2-imino-4,5-dimethyl-2,5dihydrofuran-3-yl) (piperazin-1-yl)methanone ***6e***. The general procedure 5, is used with 3-hydroxy-3-methylpentan-2-one (2.04 g, 20 mmol) and 3-(4-(3-oxopropanenitrile)piperazin-1-yl)-3-oxopropanenitrile **5e** (2.20 g, 10 mmol) in the presence of sodium ethoxide (0.02 g, 1 mmol). The mixture was refluxed during 6 h to give compound **6e** (2.17 g, 58%) as yellow solid, mp 188–189 °C. ^{1}H NMR ($CDCl_3$) δ 5.28 (2H, s, 2C=NH), 3.20 (8H, s, $4CH_2$), 2.19 (6H, s, $2CH_3$), 1.28 (12H, s, $4CH_3$). ^{13}C NMR ($CDCl_3$) δ 170.6, 166.7, 161.2, 117.8, 82.0, 44.5, 23.6, 13.8. EIMS *m*/*z* (% relative abundance): 389 (M+H, 100). HRMS (ES-QTOF) Calcd for $C_{20}H_{29}N_4O_4$ M+H 389.2184. Found 389.2165. IR ν_{max} (neat/cm^{-1}): 3318, 2987, 2901, 1678, 1643.

4.7. General procedure 6: hydrolysis of bis-iminolactones 6a–d to bis-butenolides 7a–d

To a solution of HCl (3 M, 2 mL) was added bis-iminolactone **6a**–**d** (1 mmol) in ethanol (5 mL). After being refluxed for 5 h, the mixture was evaporated and the residue obtained was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried on $MgSO_4$, filtered and concentrated in vacuum to give after recrystallisation in ethanol, bis-butenolides **7a**–**d**.

4.7.1. N,N′-Propan-1′,3′-bis-(2,5-dihydro-4,5,5-trimethyl-2-oxofuran-3-carboxamide) ***7a***. The general procedure 6, using *N*,*N*′-propan-1′,3′-bis-(2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide) **6a** (0.37 g, 1 mmol), yielded **7a** (0.35 g, 94%) as white solid, mp 145–146 °C. ^{1}H NMR ($CDCl_3$) δ 8.31 (2H, s, 2NH), 3.42 (4H, q, ^3J=6.5 Hz, $2CH_2$), 2.48 (6H, s, $2CH_3$), 1.85 (2H, m, ^3J=6,6 Hz, CH_2), 1.48 (12H, s, $4CH_3$). ^{13}C NMR ($CDCl_3$) δ 180.1, 171.3, 161.2, 117.2, 86.7, 36.7, 29.4, 24.2, 12.9. EIMS *m*/*z* (% relative abundance): 379 (M+H, 90), 361 (25), 210 (100). HRMS (ES-QTOF) Calcd for $C_{19}H_{27}N_2O_4$ M+H 379.1855. Found 379.1869. IR ν_{max} (neat/cm^{-1}): 3340, 2982, 2875, 1729, 1662, 1647, 1531.

4.7.2. N,N′-Hexan-1′,6′-bis-(2,5-dihydro-4,5,5-trimethyl-2-oxofuran-3-carboxamide) ***7b***. The general procedure 6, using *N*,-*N*′hexan-1′,6′-bis(2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide) **6b** (0.42 g, 1 mmol), yielded **7b** (0.41 g, 98%) as white solid, mp 130–131 °C. ^{1}H NMR (DMSO-d_6) δ 8.17 (2H, t, ^3J=5.5 Hz, 2CONH), 3.24 (4H, q, ^3J=6.5 Hz, $2CH_2NH$), 2.38 (6H, s, $2CH_3$), 1.49–1.54 (4H, m, $2CH_2$), 1.46 (12H, s, $4CH_3$), 1.20–1.32 (4H, m, $2CH_2$). ^{13}C NMR (DMSO-d_6) δ 178.7, 170.2, 160.2, 117.6, 86.5, 38.0, 28.8, 26.0, 23.7, 12.4. EIMS *m*/*z* (% relative abundance): 421 (M+H, 100), 403 (14), 252 (94), 182 (14). HRMS (ES-QTOF) Calcd for $C_{22}H_{33}N_2O_6$ M+H 421.2339. Found 421.2318. IR ν_{max} (neat/cm^{-1}): 3343, 2982, 2859, 1730, 1664, 1647, 1536.

4.7.3. N,N′-Bis-(propyloxy)butan-bis-(2,5-dihydro-4,5,5-trimethyl-2-oxofuran-3-carboxamide) ***7c***. The general procedure 6, using of *N*,*N*′-bis-(propyloxy)butan-bis-(2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide) **6c** (0.51 g, 1 mmol), yielded **7c** (0.45 g, 88%) as viscous liquid. ^{1}H NMR ($CDCl_3$) δ 8.24 (2H, t, ^3J=5.4 Hz, 2NH), 2.39 (6H, s, $2CH_3$), 1.70–1.78 (6H, m, $3CH_2$), 1.52–1.58 (8H, m, $4CH_2$), 1.47 (12H, s, $4CH_3$), 0.88–1.21 (6H, m, $3CH_2$). ^{13}C NMR ($CDCl_3$) δ 178.9, 170.2, 160.3, 117.5, 86.5, 69.9, 67.8, 35.9, 29.0, 25.9, 23.7, 12.4. EIMS *m*/*z* (% relative abundance): 509 (M+H, 98), 210 (100). HRMS (ES-QTOF) Calcd for $C_{26}H_{41}N_2O_8$ M+H 509.2863.

Found 509.2875. IR ν_{max} (neat/cm^{-1}): 3340, 3070, 2863, 1733, 1664, 1650, 1537.

*4.7.4. N,N′-Metaxylyl-bis-(2,5-dihydro-4,5,5-trimethyl-2-oxofuran-3-carboxamide) **7d**.* The general procedure 6, using *N,N′*-metaxylyl-bis-(2,5-dihydro-2-imino-4,5,5-trimethylfuran-3-carboxamide) **6d** (0.44 g, 1 mmol), yielded **7d** (0.39 g, 90%) as white solid, mp 140–141 °C. ^{1}H NMR ($CDCl_3$) δ 8.66 (2H, t, ^3J=2.5 Hz, 2NH), 7.24–7.33 (4H, m, Harom), 4.50 (4H, d, ^3J=6.0 Hz, $2CH_2$), 2.42 (6H, s, $2CH_3$), 1.50 (12H, s, $4CH_3$). ^{13}C NMR ($CDCl_3$) δ 179.2, 170.1, 160.4, 139.0, 128.4, 126.2, 126.0, 117.5, 86.6, 41.7, 23.7, 12.5. EIMS *m/z* (% relative abundance): 441 (M+H, 82), 272 (100). HRMS (ES-QTOF) Calcd for $C_{24}H_{29}N_2O_6$ M+H 441.2026. Found 441.2021. IR ν_{max} (neat/cm^{-1}): 3339, 2978, 2868, 1731, 1666, 1650, 1531.

4.8. General procedure 7: synthesis of ethyl 4-methyl-5,5-dialkyl-2-oxo-2,5-dihydrofuran-3-carboxylate 8a–c

A mixture of α-hydroxyketone (20 mmol) and ethyl malonate (4 mmol) was adsorbed on KF-alumina (3 g) and then stirred at room temperature without solvent for 3 h. The mixture was extracted with diethylether (3×20 mL). The combined organic layers were subsequently washed with water, dried on $MgSO_4$, filtered and concentrated in vacuum.

*4.8.1. Ethyl 2,5-dihydro-4,5,5-trimethyl-2-oxofuran-3-carboxylate **8a**.* The general procedure 7, using 3-hydroxy-3-methylbutan-2-one (2.04 g, 20 mmol), ethyl malonate (3.20 g, 20 mmol) and 3 g of Al_2O_3/KF, yielded **8a** (3.25 g, 82%) as colourless needles, mp<50 °C. ^{1}H NMR ($CDCl_3$) δ 4.34 (2H, q, ^3J=7.1 Hz, CH_2), 2.35 (3H, s, C=C–CH_3), 1.50 (6H, s, $2CH_3$), 1.37 (3H, t, ^3J=7.1 Hz, $CO_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 180.4, 167.4, 161.8, 118.4, 85.4, 61.4, 24.4, 14.2, 13.2. EIMS *m/z* M$^+$ 198 (12), 183(8), 155 (100). HRMS (ES-QTOF) Calcd for $C_{10}H_{15}O_4$ M+H 199.0970. Found 199.0972. IR ν_{max} (neat/cm^{-1}): 1774, 1718, 1654.

*4.8.2. Ethyl 5-ethyl-2,5-dihydro-4,5-dimethyl-2-oxofuran-3-carboxylate **8b**.* The general procedure 7, using 3-hydroxy-3-methylpentan-2-one (2.32 g, 20 mmol), ethyl malonate (3.20 g, 20 mmol) and 3 g of Al_2O_3/KF, yielded **8b** (3.18 g, 75%) as colourless liquid, bp 128 °C/5 mtorr. ^{1}H NMR ($CDCl_3$) δ 4.36 (2H, q, ^3J=7.1 Hz, $CO_2CH_2CH_3$), 2.31 (3H, s, C=C–CH_3), 1.96 (1H, dq, ^2J=14.8 Hz, ^3J=7.4 Hz, C(Me)CHaHbCH$_3$), 1.75 (1H, dq, $^2J_{HH}$=14.8 Hz, ^3J=7.4 Hz, C(Me)CHaHbCH$_3$), 1.48 (3H, s, C–CH_3), 1.38 (3H, t, ^3J=7.1 Hz, $CO_2CH_2CH_3$), 0.81 (3H, t, ^3J=7.4 Hz, CCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 179.3, 167.5, 161.4, 119.1, 87.7, 61.1, 23.0, 22.9, 14.00, 13.6, 7.1. EIMS *m/z* M$^+$ 212 (4), 183(33), 169 (55), 137 (100). HRMS (ES-QTOF) Calcd for $C_{11}H_{17}O_4$ M+H 213.1127. Found 213.1126. IR ν_{max} (neat/cm^{-1}): 1772, 1716, 1652.

*4.8.3. Ethyl 4-methyl-2,5-dihydro-5,5-pentamethylene-2-oxofuran-3-carboxylate **8c**.* The general procedure 7, using 1-(1-hydroxycyclohexyl)ethanone (2.84 g, 20 mmol), ethyl malonate (3.20 g, 20 mmol) and 3 g of Al_2O_3/KF, yielded **8c** (4.09 g, 86%) as white solid, mp 67–68 °C. ^{1}H NMR ($CDCl_3$) δ 4.35 (2H, q, ^3J=7.2 Hz, OCH_2CH_3), 2.32 (3H, s, C=C–CH_3), 1.65–1.85 (8H, m, 4 CH_2), 1.50–1.54 (2H, m, CH_2), 1.37 (3H, t, ^3J=7.2 Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 180.3, 167.6, 161.8, 118.4, 87.1, 61.9, 32.9, 24.4, 21.5, 14.1, 13.4. EIMS *m/z* M$^+$ 238 (40), 193(36), 192 (39), 181 (49), 137 (100). HRMS (ES-QTOF) Calcd for $C_{13}H_{19}O_4$ M+H 239.1283. Found 239.1280. IR ν_{max} (neat/cm^{-1}): 1756, 1708, 1636.

*4.8.4. Synthesis of 3-acetyl-4,5,5-trimethyl-5H-furan-2-one **8d**.* 3-Hydroxy-3-methylbutan-2-one (2.04 g, 20 mmol) and *tert*-butyl acetylacetonate (3.16 g, 20 mmol) was added to a mixture of sodium ethoxide (2 mmol) in ethanol (2 mL). The whole was refluxed for 4 h. The solvent was removed by evaporation and aqueous HCl (18%) was added. The mixture was extracted with diethylether (3×30 mL). The combined organic layers were washed with water, dried on $MgSO_4$, filtered and concentrated. The obtained residue was distilled to provide 3-acetyl-4,5,5-trimethyl-5*H*-furan-2-one **8d** (1.01 g, 30% yield) as colourless liquid, bp: 94 °C/5 mtorr. ^{1}H NMR ($CDCl_3$) δ 2.56 (3H, s, $COCH_3$), 2.35 (3H, s, C=C–CH_3), 1.50 (6H, s, 2 CH_3). ^{13}C NMR ($CDCl_3$) δ 195.2, 180.1, 169.2, 123.5, 85.5, 27.9, 24.0, 12.5. HRMS (ES-QTOF) Calcd for $C_9H_{13}O_3$ M+H 169.0865. Found 169.0864. IR ν_{max} (neat/cm^{-1}): 1755, 1688, 1627.

4.9. General procedure 8: synthesis of the bis-lactones from the bis-aldehydes 9a–g

A mixture of ethyl 4,5,5-trialkyl-2-oxo-2,5-dihydrofuran-3-carboxylate (4 mmol), dialdehyde (2 mmol) and triethylamine (4 mmol) was heated to 80 °C for 5 h. The solid obtained was washed several times with diethylether and some drops of methanol to provide yellow solid **9a–g**.

*4.9.1. Ethyl 4-(4-(2-(4-(ethoxycarbonyl)-2,5-dihydro-2,2-dimethyl-5-oxofuran-3yl)vinyl)styryl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carboxylate **9a**.* The general procedure 8, using ethyl 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate **8a** (0.79 g, 4 mmol), teraphtalaldehyde (0.27 g, 2 mmol) and triethylamine (0.40 g, 4 mmol), gave **9a** (0.47 g, 48%) as yellow solid, mp decomposed around 267 °C. ^{1}H NMR ($CDCl_3$) δ 7.95 (2H, d, ^3J=17.0 Hz, 2CH=CH–Ph), 7.63 (4H, s, Harom), 7.20 (2H, d, ^3J=17.0 Hz, 2CH=CH–Ph), 4.42 (4H, q, ^3J=7.1 Hz, $2CH_2CH_3$), 1.74 (12H, s, $4CH_3$), 1.42 (6H, t, ^3J=7.1 Hz, $2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.6, 166.9, 162.3, 141.0, 137.2, 128.7, 128.5, 119.2, 84.1, 61.6, 27.0, 14.2. EIMS *m/z* (% relative abundance): 495 (M+H, 94), 467 (100), 449 (47). HRMS (ES-QTOF) Calcd for $C_{28}H_{31}O_8$ M+H 495.2019. Found 495.2000. IR ν_{max} (neat/cm^{-1}): 1747, 1702, 1610, 1574.

*4.9.2. Ethyl 4-(4-(2-(4-(ethoxycarbonyl)-2-ethyl-2,5-dihydro-2-methyl-5-oxofuran-3-yl)vinyl)styryl)-5-ethyl-2,5-dihydro-5-methyl-2-oxofuran-3-carboxylate **9b**.* The general procedure 8, using ethyl 5-ethyl-4,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate **8b** (0.85 g, 4 mmol), teraphtalaldehyde (0.27 g, 2 mmol) and triethylamine (0.40 g, 4 mmol), gave **9b** (0.42 g, 40%) as yellow solid, mp 220–222 °C. ^{1}H NMR ($CDCl_3$) δ 7.98 (2H, d, ^3J=16,9 Hz, 2CH=CH–Ph), 7.63 (4H, s, Harom), 7.19 (2H, d, ^3J=16.9 Hz, 2CH=CH–Ph), 4.42 (4H, q, ^3J=7.1 Hz, $2OCH_2CH_3$), 1.96–2.17 (4H, m, $2CH_2CH_3$), 1.71 (6H, s, $2CCH_3$), 1.43 (6H, t, ^3J=7.1 Hz, $2OCH_2CH_3$), 0.85 (6H, t, ^3J=7.3 Hz, $2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 170.5, 167.3, 162.1, 140.5, 137.2, 128.7, 119.3, 118.6, 86.9, 61.6, 32.6, 25.9, 14.2, 7.6. EIMS *m/z* (% relative abundance): 523 (M+H, 55), 495 (100), 477 (77), 449 (14), 431 (18). HRMS (ES-QTOF) Calcd for $C_{30}H_{35}O_8$ M+H 523.2332. Found 523.2308. IR ν_{max} (neat/cm^{-1}): 1746, 1702, 1607, 1574.

*4.9.3. Ethyl 4-(4-(2-(4-(ethoxycarbonyl)-2,5-dihydro-2,2-pentamethylene-5-oxofuran-3yl)vinyl)styryl)-2,5-dihydro-5,5-pentamethylene-2-oxofuran-3-carboxylate **9c**.* The general procedure 8, using ethyl 4-methyl-2-oxo-1-oxa-spiro[4,5]dec-3-ene-3-carboxylate **8c** (0.95 g, 4 mmol), teraphtalaldehyde (0.27 g, 2 mmol) and triethylamine (0.40 g, 4 mmol), gave **9c** (0.40 g, 35%) as yellow solid, mp 209–210 °C. ^{1}H NMR ($CDCl_3$) δ 7.82 (2H, d, ^3J=16.9 Hz, 2CH=CH–Ph), 7.68 (4H, s, Harom), 7.34 (2H, d, ^3J=16.9 Hz, 2CH=CH–Ph), 4.41 (4H, q, ^3J=7.1 Hz, $2CH_2CH_3$), 1.74–2.09 (20H, m, $10CH_2$), 1.41 (6H, t, ^3J=7.1 Hz, $2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.2, 167.3, 162.5, 140.9, 137.2, 128.6, 128.5, 119.2, 86.3, 61.6, 35.6, 24.6, 22.0, 14.2. EIMS *m/z* (% relative abundance): 575 (M+H, 64), 547 (100), 529 (84). HRMS (ES-QTOF) Calcd for $C_{34}H_{39}O_8$ M+H 575.2645. Found 575.2632. IR ν_{max} (neat/cm^{-1}): 1745, 1709, 1612, 1574.

*4.9.4. 4-(4-(2-(4-Acetyl-2,5-dihydro-5,5-dimethyl-2-oxofuran-3yl)vinyl)styryl)-4-acetyl-5,5-dimethylfuran-2(5H)-one **9d**.* The general

procedure 8, using 3-acetyl-4,5,5-trimethyl-5*H*-furan-2-one **8d** (0.67 g, 4 mmol), teraphtalaldehyde (0.27 g, 2 mmol) and triethylamine (0.40 g, 4 mmol), gave **9d** (0.58 g, 67%) as yellow solid, mp 213–214 °C. ^{1}H NMR ($CDCl_3$) δ 8.08 (2H, d, ^3J=17.0 Hz, 2CH=CHPh), 7.65 (4H, s, Harom), 7.26 (2H, d, ^3J=17.0 Hz, 2CH=CHPh), 2.66 (6H, s, $2COCH_3$), 1.76 (12H, s, $4CH_3$). ^{13}C NMR ($CDCl_3$) δ 196.0, 171.3, 162.6, 142.3, 137.6, 128.9, 128.6, 119.8, 85.2, 30.9, 27.3. EIMS *m*/*z* (% relative abundance): 435 (M+H, 100), 417 (84), 399 (16), 375 (37). HRMS (ES-QTOF) Calcd for $C_{26}H_{27}O_6$ M+H 435.1808. Found 435.1803. IR ν_{max} (neat/cm^{-1}): 1742, 1681, 1607, 1564.

4.9.5. Ethyl 4-(3-(2-(4-ethoxycarbonyl-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-yl)vinyl)styryl)-2,5-dihydro-2,2-dimethyl-5-oxofuran-3-carboxylate ***9e***. The general procedure 8, using ethyl 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate **8a** (0.79 g, 4 mmol), isophtalaldehyde (0.27 g, 2 mmol) and triethylamine (0.40 g, 4 mmol), gave **9e** (0.80 g, 81%) as white solid, mp 130–132 °C. ^{1}H NMR ($CDCl_3$) δ 7.92 (2H, d, ^3J=17.0 Hz, 2CH=CHPh), 7.49–7.85 (4H, m, Harom), 7.19 (2H, d, ^3J=17.0 Hz, 2CH=CHPh), 4.37 (4H, q, ^3J=7.1 Hz, $2CH_2CH_3$), 1.69 (12H, s, $4CH_3$), 1.36 (6H, t, ^3J=7.1 Hz, $2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.4, 166.9, 162.2, 140.7, 137.1, 133.0, 131.6, 129.9, 128.9, 119.4, 84.2, 61.7, 27.0, 14.2. EIMS *m*/*z* (% relative abundance): 495 (M+H, 84), 467 (100), 449 (57), 421 (15). HRMS (ES-QTOF) Calcd for $C_{28}H_{31}O_8$ M+H 495.2019. Found 495.2004. IR ν_{max} (neat/cm^{-1}): 1747, 1702, 1610, 1574.

4.9.6. Ethyl 4-(3-(2-(4-ethoxycarbonyl-2,5-dihydro-5-methyl-2-oxofuran-3-yl)vinyl)styryl)-2-ethyl-2,5-dihydro-2-methyl-5-oxofuran-3-carboxylate ***9f***. The general procedure 8, using ethyl 5-ethyl-4,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate **8b** (0.85 g, 4 mmol), isophtalaldehyde (0.27 g, 2 mmol) and triethylamine (0.40 g, 4 mmol), gave **9f** (0.76 g, 73%) as white solid, mp 110–112 °C. ^{1}H NMR ($CDCl_3$) δ 7.95 (2H, d, ^3J=16.9 Hz, 2CH=CHPh), 7.45–7.70 (4H, m, Harom), 7.23 (2H, d, ^3J=16.9 Hz, 2CH=CHPh), 4.42 (4H, q, ^3J=7.1 Hz, $2OCH_2CH_3$), 1.98–2.20 (4H, m, $2CH_2CH_3$), 1.71 (6H, s, $2CCH_3$), 1.44 (6H, t, ^3J=7.1 Hz, $2OCH_2CH_3$), 0.87 (6H, t, ^3J=7.2 Hz, $2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 170.7, 167.3, 162.2, 140.8, 136.1, 129.8, 129.5, 128.1, 119.0, 118.6, 86.9, 61.6, 32.6, 26.0, 14.2, 7.6. EIMS *m*/*z* (% relative abundance): 523 (M+H, 72), 495 (100), 477 (54), 431 (17). HRMS (ES-QTOF) Calcd for $C_{30}H_{35}O_8$ M+H 523.2332. Found 523.2312. IR ν_{max} (neat/cm^{-1}): 1748, 1705, 1608, 1574.

4.9.7. Ethyl 4-(3-(2-(4-(ethoxycarbonyl)-2,5-dihydro-2,2-pentamethylene-5-oxofuran-3yl)vinyl)styryl)-2,5-dihydro-5,5-pentamethylene-2-oxofuran-3-carboxylate ***9g***. The general procedure 8, using ethyl 4-methyl-2-oxo-1-oxa-spiro[4,5]dec-3-ene-3-carboxylate **8c** (0.95 g, 4 mmol), isophtalaldehyde (0.27 g, 2 mmol) and triethylamine (0.40 g, 4 mmol), gave **9g** (0.80 g, 70%) as white solid, mp 99–101 °C. ^{1}H NMR ($CDCl_3$) δ 7.90 (2H, d, ^3J=16.9 Hz, 2CH=CHPh), 7.50–7.86 (4H, m, Harom), 7.33 (2H, d, ^3J=16.9 Hz, 2CH=CHPh), 4.36 (4H, q, ^3J=7.1 Hz, $2CH_2CH_3$), 1.68–2.04 (20H, m, $10CH_2$), 1.35 (6H, t, ^3J=7.1 Hz, $2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.0, 167.3, 162.4, 140.8, 137.1, 132.9, 130.0, 129.8, 128.9, 119.4, 86.4, 61.7, 35.6, 24.6, 21.9, 14.2. EIMS *m*/*z* (% relative abundance): 575 (M+H, 76), 547 (100), 529 (86). HRMS (ES-QTOF) Calcd for $C_{34}H_{39}O_8$ M+H 575.2644. Found 575.2634. IR ν_{max} (neat/cm^{-1}): 1745, 1709, 1612, 1574.

Supplementary data

Data for crystal structure analysis were collected at 293 K with a Bruker–Nonius Kappa CCD area detector diffractometer with graphite–monochromatized Mo Kα radiation (λ=0.71073 Å). The structure was solved using direct methods and refined by full-matrix least-squares analysis on F^2. Single crystals of bis-iminolactone **6a** suitable for X-ray crystallographic analysis were obtained by slow evaporation of methanol. Crystallographic data: Crystal size: 0.47×0.39×0.28 mm Formula $C_{19}H_{28}N_4O_4$, formula weight 376.45, crystal system monoclinic, space group *C* 2/*c*, *a*=16.9302(4) Å, *b*=10.9054(4) Å, *c*=11.3432(3) Å, α=90°, β=103.316(2)°, γ=90°, V=2038.00(10) Å^3, *Z*=4, calculated density=1.227 g/cm^3, μ=0.087 mm^{-1}, R_{int}=0.042, $R[F^2>2\sigma(F^2)]$=0.051, $wR(F^2)$=0.151. Selected bond lengths (Å), angles (deg) and dihedral angles (deg): N8–C2 1.2626(13), C6-O7 1.2216(12), C10–C5–C13 111.67(9) N8–C2-O1 124.23(9). Program(s) used to solve structure: SHELXS–97. Program(s) used to refine structure: SHELXL–97. Software used to prepare material for publication: SHELXTL–97 (G. M. Sheldrick, Bruker ACS Inc.: Madison, WI, 2004). Crystallographic data for compound **6a** have been deposited at the Cambridge Crystallographic Data Centre, CCDC No 769499. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (+44 1223 336408; E-mail:deposit@ccdc.cam.ac.ukor http://www.ccdc.cam.ac.uk). Deposited Data-CCDC 769499.

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21. **8a** was formed by the reaction of diethyle malonate and **1**. The replacement of **1** by 3-methoxy-3-methyl-2-butanone in the same conditions gave no butenolide or Knoevenagel product (L. Liao, Ph.D. thesis, University of Caen **1999**). From this result we think the transesterification of **1** by malonate takes place before the cyclisation by Knoevenagel reaction favoured by Thorpe–Ingold effect.
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