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Versatile Synthesis of Acylfuranones by Reaction of Acylketenes with α-Hydroxy Ketones: Application to the One-Step Multicomponent Synthesis of Cadiolide B and Its Analogues

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Dedicated to Professor Kozo Shishido on the occasion of his retirement

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Functionalized acylfuranones have been prepared in a one-step procedure by thermal fragmentation of the corresponding dioxinones in the presence of hydroxy ketones in basic conditions. Multicomponent reactions also occur on addition of an aldehyde as a third reaction partner resulting in an expeditious access to cadiolide B and its analogues.

Introduction

Functionalized acylfuranones are present in many natural[1] and synthetic[2] products. Among them, cadiolides A–I (Figure 1), isolated from the Indonesian marine ascidians of the genus *Botryllus*,[3] present fascinating and similar antibacterial activities to vancomycin and platensimycin.[4] Moreover, they also share a common feature with refecoxib, a selective inhibitor of the COX-2 enzyme, promoting interesting anti-inflammatory activity.[5] Epicocconone is another example of an acylfuranone-containing natural product currently used as a fluorescent protein stain.[6]

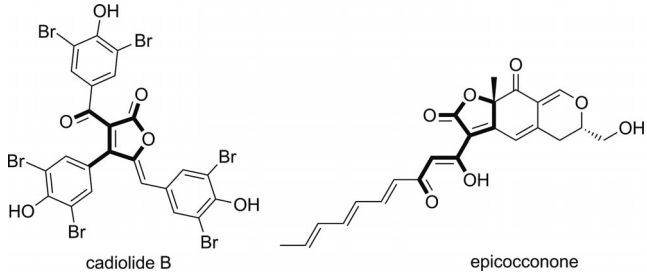

Figure 1. Acylfuranone moieties in cadiolide B and epicocconone.

The direct synthesis of acylfuranones is very little reported in literature. The first method was described by Lacey[7] in 1954 using diketene (Scheme 1). This methodology was later extended by other groups to the preparation of tetronic acid derivatives.[8] Unfortunately, this method suffers big limitations related to the scope of the R functional group. The majority of other methods used for the construction of the acylfuranone skeleton generally require two or three steps. Indeed, the most often described procedure remains the esterification reaction between an α-hydroxy ketone and a β-keto acid (or ester or malonate) followed by an intramolecular Knoevenagel cyclization reaction.[9] Acylfuranones can also be obtained by the direct acylation of furanones[10] or by an intramolecular lactonization/oxidation sequence.[11] Finally, one particular and limited method involves the photosensitive oxidation of furan derivatives.[12] In this article, we describe a new, easy and versatile access to acylfuranones by the reaction of α-hydroxy ketones **2** with acylketenes **3** in the presence of a base (Scheme 1). The interest in using acylketenes lies in their high reactivity towards hindered alcohols and their easy generation by thermal fragmentation of functionalized dioxinones **1**.[13]

Under these conditions, the fast trapping of the acylketene by the hydroxy moiety of a hydroxy ketone leads to an intermediate β-keto ester **4**. This intermediate then spontaneously cyclizes through an intramolecular Knoevenagel condensation to yield the desired furanone cycle. This synthetic strategy has already been employed by our group for the synthesis of epicocconone analogues[14] and we now wish to report the scope and limitations of this methodology in the reactions of various acylfuranones. Furthermore, an extension of the method to the expeditious synthesis of compounds of interest possessing the cadiolide framework is also described based on a multicomponent approach.

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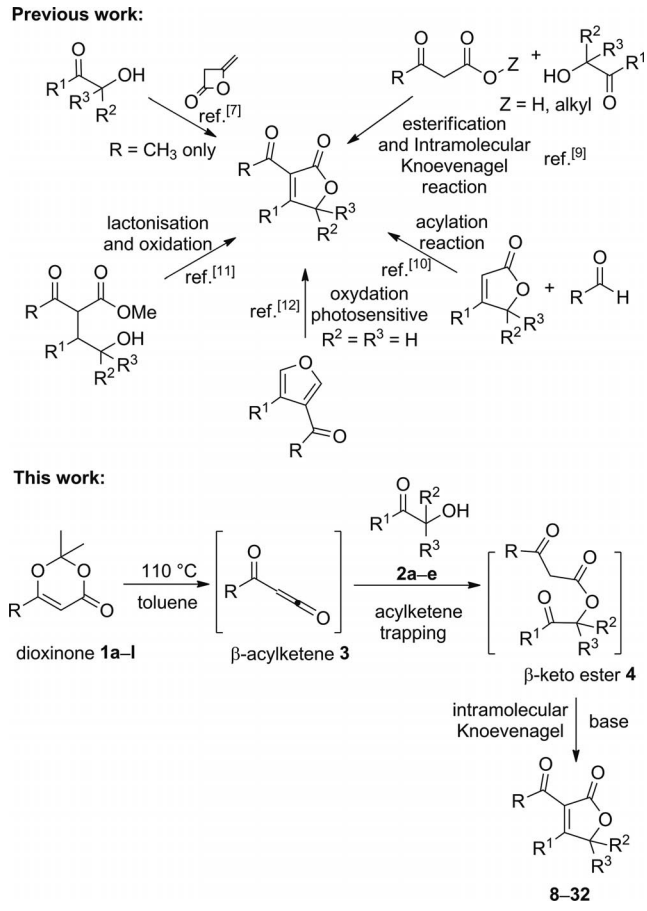
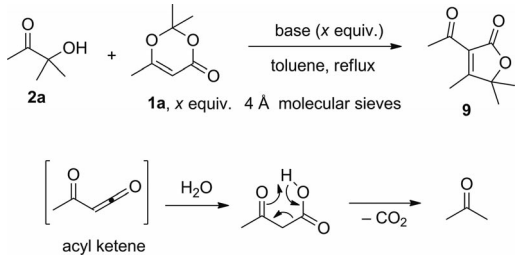


Scheme 1. Synthetic routes to acylfuranones.

Results and Discussion

The reaction conditions for the one-step synthesis of acylfuranones were determined for a simple model reaction between commercially available dioxinone **1a** with α-hydroxy ketone **2a** in toluene at reflux and in the presence of a base. Molecular sieves (4 Å) were also added to trap released water and prevent destruction of the ketene (Scheme 2, Table 1).



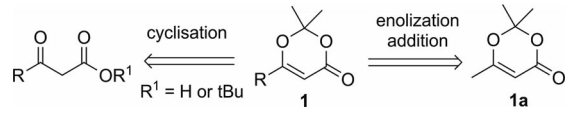
Scheme 2. Model reaction for the synthesis of acylfuranones.

Various parameters were considered, such as the amount of base or dioxinone **1a**, and the nature of the base. The results in Table 1 show that the amount of base and dioxinone has a significant effect on the yield of the cyclization reaction. Indeed, even though increasing the amount of base (*i*Pr$_2$NEt) from 0.5 to 2.0 resulted in an increase in the conversion (Table 1, entries 1–3), it also resulted in the appearance of side-products that were not observed with 0.5 equiv. of base (crude ^{1}H NMR spectra). Thus, in an attempt to prevent the formation of undesired products at a very low level, we used a sub-stoichiometric amount of base (0.5 equiv.) and increased the quantity of dioxinone from 1.05 to 2 equiv. (entries 1 and 4–6). The yield of acylfuranone **9** improved from 58% (1.05 equiv. dioxinone) to 87% (1.5 equiv. dioxinone). Increasing the amount of dioxinone to 2 equiv. resulted in no further increase in the conversion. Finally, the use of triethylamine instead of DIEA gave even higher yields (compare entries 5 and 7).

Table 1. Optimization of the reaction conditions for the synthesis of acylfuranone **9**.

Entry	Dioxinone **1a** [equiv.]	Base (amount [equiv.])	Yield of **9** [%]
1	1.05	DIEA (0.5)	58
2	1.05	DIEA (1.0)	64
3	1.05	DIEA (2.0)	71
4	1.20	DIEA (0.5)	74
5	1.50	DIEA (0.5)	87
6	2.00	DIEA (0.5)	83
7	1.50	Et_3N (0.5)	100

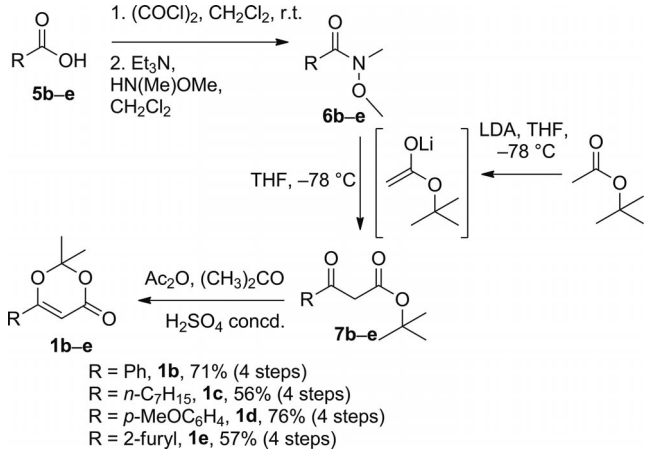
Having determined the optimal conditions for the one-step synthesis of furanone by using a simple model reaction, we turned our attention to more functionalized dioxinones and α-hydroxy ketones. The reactions of five α-hydroxy ketones (**2a**–**e**, either commercially available or synthesized by using a standard procedure[15]) and nine dioxinones (**1a**–**f**, **j**–**l**) were considered. Two different routes were used to prepare the functionalized dioxinones **1** (Scheme 3). The first involved a cyclization reaction between a β-keto acid or a β-keto ester and acetone under acidic conditions,[16] and the second involved the direct functionalization of the lithium enolate derived from the commercially available methyldioxinone.[17]



Scheme 3. Retrosynthetic routes to dioxinones **1**.

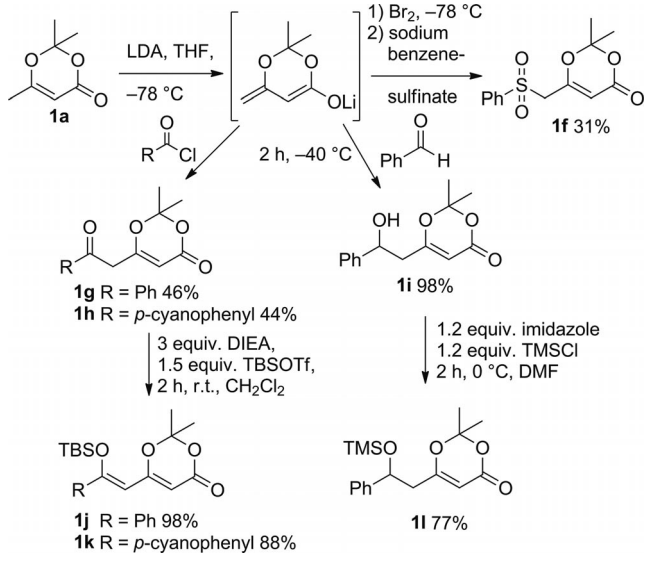
In the first case, β-keto esters **7b**–**e** were synthesized from the corresponding carboxylic acids **5b**–**e** via their Weinreb amides[18] (Scheme 4). Dioxinones **1b**–**e** bearing aromatic, heteroaromatic or alkyl groups were obtained in good yields by the reactions of **7b**–**e** with acetone in the presence of acetic anhydride and sulfuric acid by using a slight modification of the procedure of Gebauer and Blechert.[19]

More functionalized dioxinone derivatives like sulfone **1f**, silyl enol ethers **1j**–**k** or silyl ether **1l** were synthesized by the second method (Scheme 5). Indeed, the reaction of the lithium enolate prepared from the commercially available methyldioxinone **1a** with electrophiles such as bromine (followed by displacement of the bromine atom by sodium benzenesulfinate), acid chlorides or benzaldehyde gave rise to the corresponding dioxinone **1f**, β-keto-dioxinones **1g**,**h** and β-hydroxy-dioxinone **1i**. Note that dioxinones **1j**–**k**

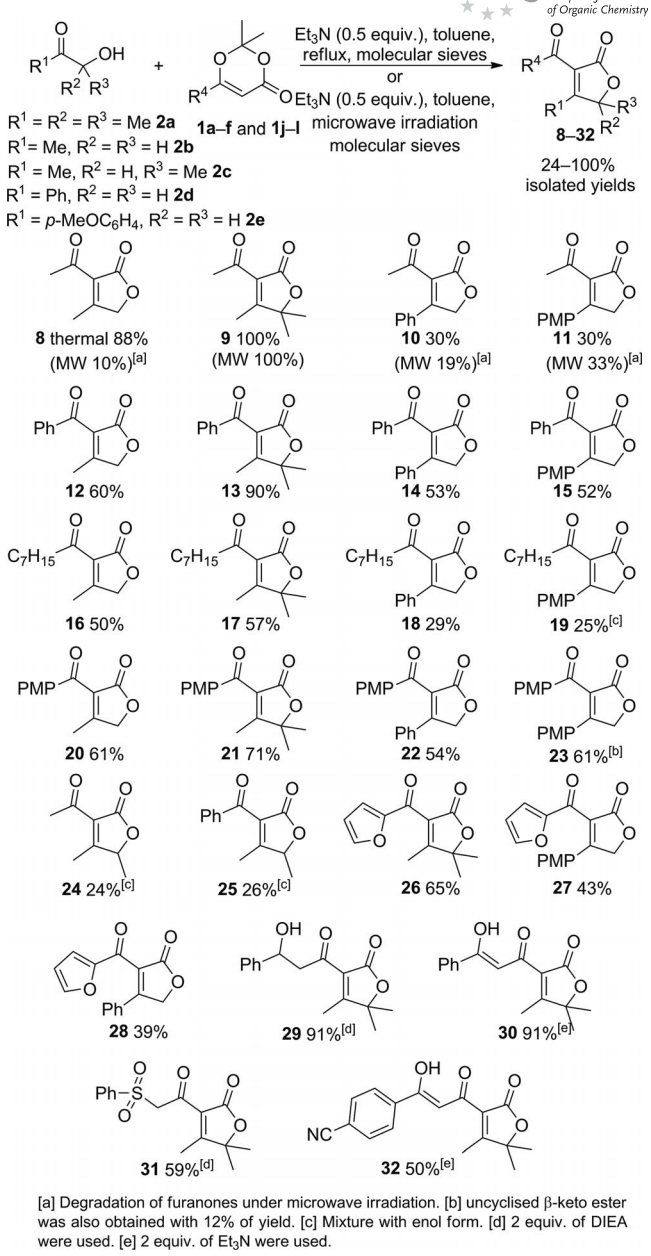


Scheme 4. Synthetic route to dioxinones **1a**–**e**.

(bearing a silyl enol ether) were prepared from the corresponding ketones and used directly because of their instability with time.



Scheme 5. Synthetic route to dioxinones **1f**–**l**.



[a] Degradation of furanones under microwave irradiation. [b] uncyclised β-keto ester was also obtained with 12% of yield. [c] Mixture with enol form. [d] 2 equiv. of DIEA were used. [e] 2 equiv. of Et_3N were used.

Scheme 6. Various acylfuranones obtained from the reactions of **1** with **2a**–**e**.

To study the scope and limitations of this reaction, we first looked at the influence of the degree of the substitution (R^2 and R^3) on the hydroxy ketones **2a**–**c**. As can be seen in Scheme 6, good to excellent yields were obtained when tertiary hydroxy ketone **2a** was used, whereas moderate yields were usually obtained when primary hydroxy ketone **2b** was engaged. These results can be explained by either the Thorpe–Ingold effect in the case of tertiary hydroxy groups or a possible enolization of the lactone leading to degradation in the case of primary hydroxy groups. In the case of secondary hydroxy groups (R^2 = H, R^3 = Me), the yields remained low (24% for **24**, 26% for **25**). This can be explained by the fact that the starting hydroxy ketone **2c** is sold as a mixture of monomer and dimer.

Microwave irradiation (110 °C, 5 min) instead of conventional heating was used with the aim of improving the yield of the condensation reaction with **2b**. Unfortunately, the yields dropped dramatically from 88 to 10% in the case of acylfuranone **8** (by using hydroxy ketone **2b**) but remained the same for acylfuranone **9** (by using hydroxy ketone **2a**). These results suggest a thermal degradation of the less substituted acylfuranones arising from hydroxy ketone **2b**. The nature of R^1 and R^4 showed little influence on reaction outcomes as the Me, Ph and *p*-MeOPh substituents gave similar yields of furanones when R^4 was an aromatic group (compare **12/14/15**, **20/22/23**). A drop in yield was noted by switching R^1 from an aliphatic to an aromatic group with R^4 aliphatic (compare **16/18/19**). This reduction in yield

suggests a higher tendency of the furanone to be enolized in the case of **18** and **19** compared with **16**, leading to polymerization-type side products. Finally, for the more functionalized dioxinones **1j**,**k**, two equiv. of base were required to achieve satisfactory yields. For example, dioxinones **1j** and **1k** bearing a silyl enol ether gave rise to furanones **30** and **32** bearing a 1,3-diketo side-chain in which one ketone is present in its enol form. Dioxinone **1l** bearing a β-silyloxy group provided furanone **29** bearing an hydroxylated side-chain in 91% yield with no β-elimination. Dioxinone **1f** with the sulfonyl group yielded the furanone **31** in 59% yield.

Thus, acylfuranones **8**–**32** have been prepared in good to excellent yields from the reactions of hydroxy ketones **2a**–**e** with **1**, with yields ranging from 50–100% for ketones bearing tertiary hydroxys, 29–88% for primary hydroxys, and 24–26% for secondary hydroxys.

Application to the Synthesis of Cadiolide B and Its Analogues

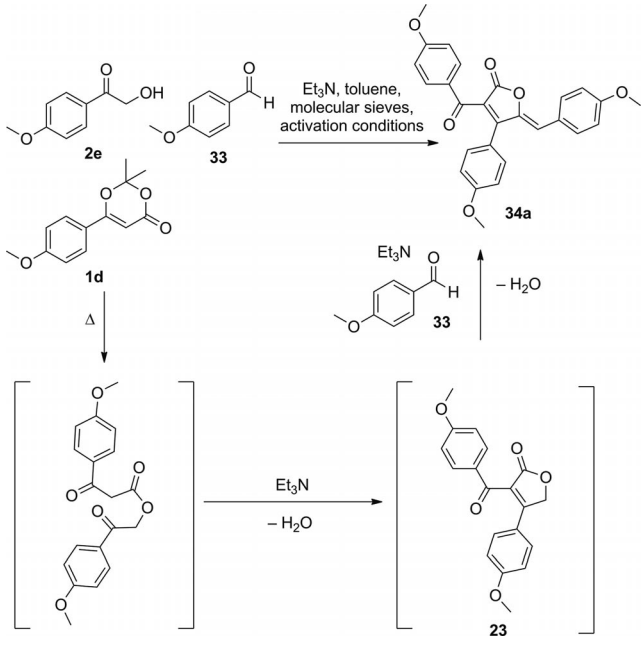
The methodology developed above was then extended to the synthesis of analogues of cadiolide B by a one-step multicomponent reaction involving dioxinone derivatives and α-hydroxy ketones in the presence of an aldehyde as the third reaction partner. To date, only one total synthesis of cadiolide B has been reported,[20] which gave an overall yield of 42% in six steps from commercially available 4-bromo-2,5-dihydro-2-oxofuran. Our strategy allowed us to obtain in only one step the skeleton of cadiolide B **34a** as well as analogues **34b**–**e** of the natural product.

Thus, by taking advantage of the previously observed facile enolization of unsubstituted aromatic acylfuranones such as **14**, **15**, **22** and **23**, we envisioned that they would further react in situ with an aldehyde by an aldolization/crotonization sequence (Scheme 7). This idea was evaluated with dioxinone **1d** and hydroxy ketone **2e** in the presence of *p*-MeOPhCHO (**33**). Unfortunately, by using this approach with the previous reaction conditions, only 12% of acylfuranone **23** was obtained with no trace of the desired addition compound **34a** (Table 2, entry 1). Increasing the amount of base from 0.5 equiv. to 2 equiv. proved to be effective and allowed us to increase the yield of **23** to 49% and **34a** was obtained in 23% yield (entry 2). The addition of more base and aldehyde did not increase the yield of either the furanone or the addition product (entry 3). In an attempt to promote the formation of **34a**, we performed the reaction with microwave irradiation. This proved to be successful as we obtained **34a** in a one-pot sequence in a yield of 77% (300 W, 150 °C during 5 min).

Table 2. Optimization parameters.

Entry	**1d** [equiv.][a]	**33** [equiv.][a]	Et_3N [equiv.][a]	Activation conditions	Yield [%] **23**	Yield [%] **34a**
1	1.2	1.5	0.5	thermal	12	0
2	1.5	1.2	2	thermal	49	23
3	1.5	2	4	thermal	43	21
4	2	1.2	2	MW[b]	0	77

[a] Relative to **2e**. [b] In the absence of molecular sieves.



Scheme 7. One-pot multicomponent sequence.

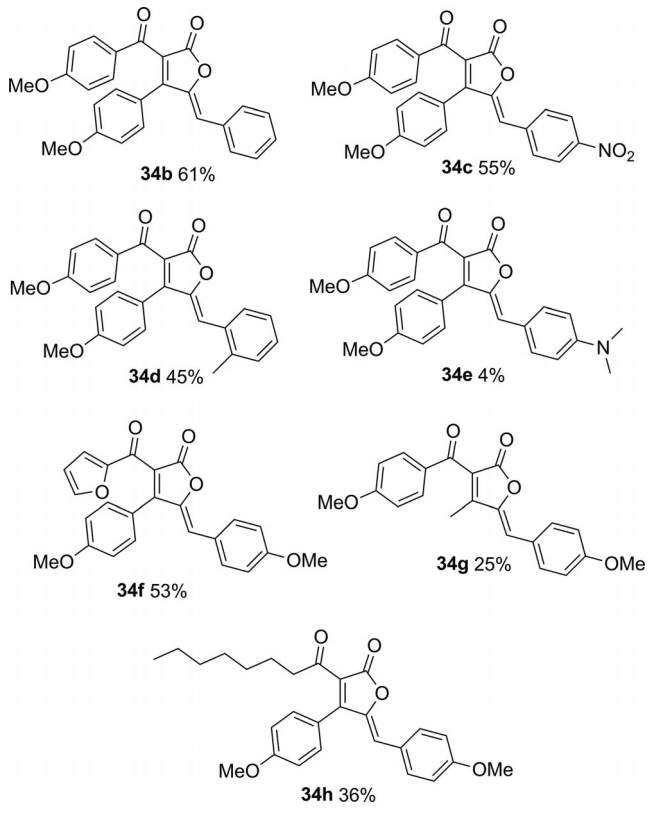
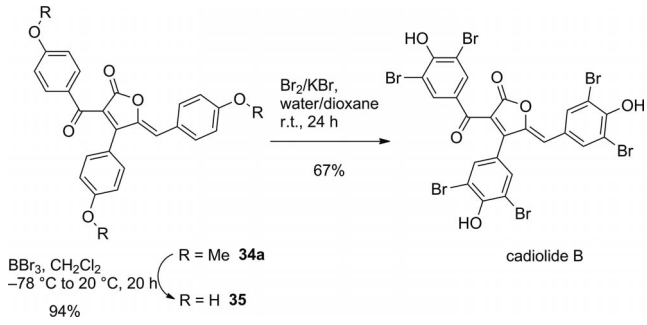


Figure 2. Analogues of cadiolide prepared by the multicomponent approach.

By using microwave irradiation and different aldehydes, dioxinones and hydroxy ketones, a set of cadiolide analogues were prepared in yields ranging from 25 to 61% (except when *p*-(dimethylamino)benzaldehyde was used, which gave only 4% of **34e**, Figure 2).[20] This reaction worked well for aromatic dioxinones and hydroxy ketones. When aliphatic substituents were used, the yields were moderate, but still satisfactory bearing in mind the six consecutive transformations involved (thermal fragmentation of dioxinone/acylketene trapping/cyclization/dehydration/aldol/dehydration).

Finally, cadiolide B was synthesized in an overall yield of 48% from dioxinone **1d** after removal of the methyl groups with BBr_3 and bromination[21] of the phenolic groups (Scheme 8).



Scheme 8. Synthesis of cadiolide B.

Conclusions

We have developed an efficient method for the one-pot synthesis of acylfuranones from easily available starting materials such as dioxinones and hydroxy ketones. The methodology was extended to the one-pot multicomponent synthesis of densely functionalized furanone cores. This diversity-oriented approach gave expeditious access to various small-ring compounds with potentially high antimicrobial activities and will most certainly find a broad range of applications in medicinal chemistry.

Experimental Section

General: ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ with a Bruker DPX 300 spectrometer. ^1H and ^{13}C NMR chemical shifts (δ) are quoted in ppm with $CHCl_3$ as reference. Mass spectra were recorded with a Finnigan LCQ Advantage MAX (ion trap) spectrometer equipped with an electropray (ESI) source. IR spectra were recorded with a Perkin–Elmer FT-IR Spectrum 100 spectrometer equipped with an ATR accessory.

General Procedure for the Synthesis of Weinreb Amides 6b–e (Procedure A): Oxalyl chloride [$(COCl)_2$; 1.25 equiv.] and DMF (0.004 equiv.) were added at room temperature to a CH_2Cl_2 solution (for a solution of 0.1 mol L^{-1}) containing acid **5b–e** (1 equiv.) in a round-bottomed flask flushed with argon. After 1.5 h, the solvent and the excess oxalyl chloride were removed by evaporation under vacuum. CH_2Cl_2 (for a solution of 0.1 mol L^{-1}), *N*,*O*-dimethylhydroxylamine (1.4 equiv.), and Et_3N (3 equiv.) were then successively added at room temperature. After 2 h, the reaction was quenched at room temperature with a saturated solution of $NaHCO_3$ and the mixture extracted twice with CH_2Cl_2. The combined organic layers were then washed with a saturated solution of NH_4Cl and brine. The organic layer was then dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was then purified by flash chromatography on silica gel by using an appropriate gradient of a cyclohexane/EtOAc mixture as eluent to give the desired Weinreb amide **6b–e**.

***N*-Methoxy-*N*-methylbenzamide (6b):** Following procedure A, benzoic acid (2.44 g, 20 mmol) was used to afford **6b** as a yellow oil in 98% yield (2.93 g, 19.6 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20). Analyses are similar to those described in the literature.[22] ^1H NMR (300 MHz, $CDCl_3$): δ = 3.29 (s, 3 H), 3.48 (s, 3 H), 7.21–7.40 (m, 3 H), 7.53–7.64 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.8, 61.0, 128.05, 128.13, 130.6, 134.2, 169.9 ppm.

***N*-Methoxy-*N*-methyloctanamide (6c):** Following procedure A, octanoic acid (3.2 mL, 20 mmol) was used to afford **6c** as a yellow oil in 86% yield (3.23 g, 17.2 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20). Analyses are similar to those described in the literature.[23] ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, J = 6.8 Hz, 3 H), 1.26–1.33 (m, 8 H), 1.58–1.63 (m, 2 H), 2.38 (t, J = 7.7 Hz, 2 H), 3.16 (s, 3 H), 3.66 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 22.9, 25.0, 29.4, 29.7, 32.0, 32.5, 33.0, 61.5, 175.1 ppm. IR (neat): $\tilde{\nu}$ = 2929, 2856, 1670, 1466, 1414, 1388, 1177, 998 cm^{-1}. MS (ESI): m/z = 188 $[M + H]^+$.

***N*,4-Dimethoxy-*N*-methylbenzamide (6d):** Following procedure A, *p*-methoxybenzoic acid (3.41 g, 20 mmol) was used to afford **6d** as a white solid in 95% yield (3.71 g, 19 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 60:40). Analyses are similar to those described in the literature.[22] M.p. 70 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.35 (s, 3 H), 3.56 (s, 3 H), 3.84 (s, 3 H), 6.89 (d, J = 8.9 Hz, 2 H), 7.71 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.2, 55.6, 61.2, 113.6, 126.3, 130.9, 161.8, 169.7 ppm. IR (neat): $\tilde{\nu}$ = 2935, 1637, 1608, 1512, 1459, 1421, 1375, 1305, 1254, 1173, 1029, 842 cm^{-1}. MS (ESI): m/z = 196 $[M + H]^+$.

***N*-Methoxy-*N*-methylfuran-2-carboxamide (6e):** Following procedure A, 2-furoic acid (2.24 g, 20 mmol) was used to afford **6e** as a yellow oil in 94% yield (2.72 g, 18.8 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30). Analyses are similar to those described in the literature.[22] ^1H NMR (300 MHz, $CDCl_3$): δ = 3.34 (s, 3 H), 3.76 (s, 3 H), 6.50 (dd, J = 1.7, 3.6 Hz, 2 H), 7.02 (d, J = 3.4 Hz, 1 H), 7.47 (d, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.1, 61.4, 111.7, 117.4, 145.3, 145.6, 159.1 ppm. MS (ESI): m/z = 156 $[M + H]^+$. IR (neat): $\tilde{\nu}$ = 2938, 1705, 1618, 1392, 1228, 1178, 977, 756 cm^{-1}.

General Procedure for the Synthesis of *tert*-Butyl Esters 7b–e (Procedure B): *n*-Butyllithium (*n*BuLi, 1.2 M in hexane, 3.1 equiv.) was added at –78 °C to a THF solution (for a solution of 0.1 mol L^{-1}) containing diisopropylamine (DIPA; 3 equiv.) in a round-bottomed flask flushed with argon. After 30 min at 0 °C, the medium was recooled to –78 °C and freshly distilled *t*Bu acetate (3 equiv.) was added. After 30 min at –78 °C, Weinreb amide **6b–e** (1 equiv.) was added at this temperature. After 1 h, the reaction was quenched at room temperature with a saturated solution of $NaHCO_3$ and the mixture extracted twice with EtOAc. The combined organic layers were then washed with a saturated solution of NH_4Cl. The organic layer was then dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was then purified by flash

chromatography on silica gel by using an appropriate gradient of a cyclohexane/EtOAc mixture as eluent to give the desired *tert*-butyl ester **7b–e**.

***tert*-Butyl 3-Oxo-3-phenylpropanoate and *tert*-Butyl (*Z*)-3-Hydroxy-3-phenylacrylate (7b):** Following procedure B, Weinreb amide **6b** (2.93 g, 19.6 mmol) was used to afford **7b** as a colourless oil in 99% yield (4.27 g, 19.4 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20). A mixture of the keto ester and enol forms (78:22) were obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 7 H), 1.42 (s, 2 H), 3.77 (s, 1.6 H), 5.48 (s, 0.2 H), 7.25–7.46 (m, 3 H), 7.63 (d, J = 7.0 Hz, 0.4 H), 7.81 (d, J = 7.5 Hz, 1.6 H), 12.67 (s, 0.2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.7, 28.2, 47.2, 81.0, 81.7, 88.7, 125.8, 128.3, 128.4, 128.6, 130.9, 133.4, 133.6, 136.1, 166.6, 170.7, 173.0, 192.9 ppm. IR (neat): $\tilde{\nu}$ = 3062, 2980, 2933, 1732, 1688, 1637, 1599, 1450, 1408, 1369, 1326, 1326, 1278, 1154, 690 cm^{-1}. MS (ESI): m/z = 221 [M + H]$^+$.

***tert*-Butyl 3-Oxodecanoate (7c):** Following procedure B, Weinreb amide **6c** (3.23 g, 17.2 mmol) was used to afford **7c** as a colourless oil in 91% yield (3.79 g, 15.7 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 75:25). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, J = 6.8 Hz, 3 H), 1.21–1.22 (m, 8 H), 1.41 (s, 9 H), 1.50–1.55 (m, 2 H), 2.14 (t, J = 7.3 Hz, 2 H), 3.28 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 22.8, 23.7, 28.2, 29.2, 29.3, 31.9, 43.1, 50.9, 82.0, 166.7, 203.7 ppm. IR (neat): $\tilde{\nu}$ = 2930, 2857, 1716, 1457, 1410, 1369, 1318, 1252, 1149 cm^{-1}. MS (ESI): m/z = 243 [M + H]$^+$.

***tert*-Butyl 3-(4-Methoxyphenyl)-3-oxopropanoate (7d):** Following procedure B, Weinreb amide **6d** (3.71 g, 19 mmol) was used to afford **7d** as a yellow oil in 98% yield (4.66 g, 18.6 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 60:40). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 3.79 (s, 2 H), 3.80 (s, 3 H), 6.87 (d, J = 9.0 Hz, 2 H), 7.71 (d, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9, 47.1, 55.5, 81.7, 113.8, 129.2, 130.8, 163.8, 167.0, 191.5 ppm. IR (neat): $\tilde{\nu}$ = 2978, 2935, 2841, 1732, 1678, 1602, 1512, 1326, 1260, 1171, 1028, 841 cm^{-1}. MS (ESI): m/z = 251 [M + H]$^+$.

***tert*-Butyl 3-(Furan-2-yl)-3-oxopropanoate (7e):** Following procedure B, Weinreb amide **6e** (2.72 g, 18.8 mmol) was used to afford **7e** as a white solid in 94% yield (3.72 g, 17.7 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30), m.p. 76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 3.73 (s, 2 H), 6.53 (dd, J = 1.7, 3.6 Hz, 2 H), 7.23 (d, J = 3.6 Hz, 1 H), 7.58 (d, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2, 47.2, 82.4, 112.9, 118.3, 147.1, 152.4, 166.5, 181.9 ppm. IR (neat): $\tilde{\nu}$ = 1732, 1681, 1469, 1154, 762 cm^{-1}. MS (ESI): m/z = 211 [M + H]$^+$.

General Procedure for the Synthesis of Dioxinones 1b–e (Procedure C): Acetic anhydride (15 equiv.) and sulfuric acid (1 equiv.) were added at 0 °C to an acetone solution (10 equiv.) containing *tert*-butyl ester **7b–e** (1 equiv.) in a round-bottomed flask flushed with argon. The medium was then warmed slowly to room temperature over 10 min. After 45 min, the reaction was quenched at room temperature with an aqueous solution containing sodium carbonate (30 equiv.) and EtOAc (100 mL) was added. The biphasic medium was then stirred for 40 min (hydrolysis of the remaining acetic anhydride) and the aqueous layer was extracted twice with EtOAc. The combined organic layers were then washed with a saturated solution of NH_4Cl. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude residue was finally purified by flash chromatography on silica gel using an appropriate gradient of a cyclohexane/EtOAc mixture as eluent to give the desired dioxinone **1b–e**.

2,2-Dimethyl-6-phenyl-4*H*-1,3-dioxin-4-one (1b): Following procedure C, *tert*-butyl ester **7b** (4.27 g, 19.4 mmol) was used to afford **1b** as a white solid in 73% yield (2.89 g, 14.2 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20), m.p. 66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78 (s, 6 H), 5.87 (s, 1 H), 7.40–7.66 (m, 3 H), 7.67 (d, J = 7.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 91.4, 106.8, 126.5, 129.0, 131.2, 132.3, 162.1, 165.2 ppm. IR (neat): $\tilde{\nu}$ = 2998, 1727, 1450, 1389, 1363, 1279, 1225, 1204, 990, 770, 691 cm^{-1}. HRMS (ESI): calcd. for $[C_{12}H_{12}O_3 + H]^+$ 205.0865; found 205.0869.

6-Heptyl-2,2-dimethyl-4*H*-1,3-dioxin-4-one (1c): Following procedure C, *tert*-butyl ester **7c** (3.79 g, 15.7 mmol) was used to afford **1c** as a yellow oil in 71% yield (2.52 g, 11.1 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80–0.84 (m, 3 H), 1.22–1.23 (m, 8 H), 1.45–1.50 (m, 2 H), 1.62 (s, 6 H), 2.14 (t, J = 7.5 Hz, 2 H), 5.16 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.1, 25.8, 28.98, 29.01, 31.7, 33.7, 93.2, 106.3, 161.5, 172.3 ppm. IR (neat): $\tilde{\nu}$ = 2999, 2929, 2858, 1732, 1634, 1463, 1392, 1463, 1392, 1271, 1205, 1013, 901, 806 cm^{-1}. MS (ESI): m/z = 227 [M + H]$^+$.

6-(4-Methoxyphenyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (1d): Following procedure C, *tert*-butyl ester **7d** (4.66 g, 18.6 mmol) was used to afford **1d** as a yellow solid in 82% yield (3.57 g, 15.3 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20), m.p. 68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (s, 6 H), 3.84 (s, 3 H), 5.77 (s, 1 H), 6.92 (d, J = 9.0 Hz, 2 H), 7.71 (d, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 55.7, 89.5, 106.5, 114.4, 123.5, 128.4, 162.4, 163.0, 165.1 ppm. IR (neat): $\tilde{\nu}$ = 2999, 2940, 2842, 1721, 1607, 1513, 1363, 1252, 1179, 1027, 804 cm^{-1}. MS (ESI): m/z = 235 [M + H]$^+$. HRMS (ESI): calcd. for $[C_{13}H_{14}O_4 + H]^+$ 235.0970; found 235.0976.

6-(Furan-2-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (1e): Following procedure C, *tert*-butyl ester **7e** (3.72 g, 17.7 mmol) was used to afford **1e** as a red oil in 64% yield (2.20 g, 11.3 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71 (s, 6 H), 5.74 (s, 1 H), 6.49 (dd, J = 1.7, 3.6 Hz, 1 H), 6.86 (d, J = 3.6 Hz, 1 H), 7.53 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 89.6, 107.0, 112.5, 114.2, 146.2, 146.3, 156.4, 161.6 ppm. IR (neat): $\tilde{\nu}$ = 3134, 3000, 2945, 1727, 1679, 1641, 1470, 1361, 1278, 1205, 1017 cm^{-1}. MS (ESI): m/z = 195 [M + H]$^+$.

2,2-Dimethyl-6-(phenylsulfonylmethyl)-4*H*-1,3-dioxin-4-one (1f): *n*BuLi (7.9 mL, 11 mmol, 1.4 M in hexane) was added at –78 °C to a THF solution (100 mL) of DIPA (1.6 mL, 11 mmol) in a round-bottomed flask flushed with argon. After 30 min at 0 °C, the solution was recooled to –78 °C and 2,2,6-trimethyl-2,4-dihydro-1,3-dioxin-4-one (**1a**; 1.4 mL, 10 mmol) was added. After 30 min at –78 °C, bromine (0.6 mL, 11 mmol) was added at this temperature. After 2 h at –40 °C, the reaction was quenched at 0 °C with H_2O and the mixture extracted twice with EtOAc. The combined organic layers were washed with $Na_2S_2O_3$ and then with 1 N HCl. The combined organic layers were then dried with $MgSO_4$, filtered and concentrated under vacuum. The crude residue was dissolved in a DMF (50 mL) containing sodium benzenesulfinate (2.0 g, 12 mmol). After 0.5 h at room temp., the reaction was quenched at 0 °C with brine and the mixture extracted twice with EtOAc. The organic layer was then washed three times with brine. The combined organic layers were dried with $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using cyclohexane/EtOAc (60:40) as

eluent to give the dioxinone **1f** as a brown solid in 31% yield (885 mg, 3.1 mmol), m.p. 110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (s, 6 H), 3.98 (s, 2 H), 5.29 (s, 1 H), 7.62 (t, J = 7.0 Hz, 2 H), 7.73 (t, J = 7.0 Hz, 1 H), 7.92 (d, J = 7.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 60.2, 99.3, 107.8, 128.4, 129.6, 134.7, 138.5, 158.5, 159.9 ppm. IR (neat): $\tilde{\nu}$ = 1705, 1639, 1375, 1313, 1278, 1204, 1154, 1082, 1017, 911, 799, 740, 725, 687 cm^{-1}. MS (ESI): m/z = 283 $[M + H]^+$, 300 $[M + H_2O]^+$.

General Procedure for the Synthesis of Dioxinones 1g,h (Procedure D): *n*BuLi (1.2 M in hexane, 2.0 equiv.) was added at –78 °C to a THF solution (0.1 mol L^{-1}) of DIPA (2 equiv.) in a round-bottomed flask flushed with argon. After 30 min at 0 °C, the solution was recooled to –78 °C and 2,2,6-trimethyl-2,4-dihydro-1,3-dioxin-4-one (**1a**; 2 equiv.) was added. After 30 min at –78 °C, benzoyl chloride (1 equiv.) was finally added at this temperature. After 2 h at –40 °C, the reaction was quenched at 0 °C with 1 N HCl and the mixture extracted twice with EtOAc. The combined organic layers were then dried with $MgSO_4$, filtered and concentrated under vacuum. The desired product was finally precipitated by using a 1:10 mixture of Et_2O/pentane (first Et_2O and then pentane) to give the desired dioxinone **1g**,**h**.

2,2-Dimethyl-6-(2-oxo-2-phenylethyl)-4*H*-1,3-dioxin-4-one (1g): Following procedure D, benzoyl chloride (2.3 mL, 20 mmol) was used to afford **1g** as a white solid in 46% yield (2.26 g, 9.2 mmol), m.p. 114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (s, 6 H), 3.90 (s, 2 H), 5.41 (s, 1 H), 7.49 (t, J = 7.7 Hz, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.93 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 43.4, 97.1, 107.4, 128.4, 129.0, 134.2, 136.0, 160.9, 165.3, 193.2 ppm. IR (neat): $\tilde{\nu}$ = 3098, 2999, 2962, 2930, 1716, 1687, 1644, 1392, 1377, 1222, 1019, 822 cm^{-1}. MS (ESI): m/z = 247 $[M + H]^+$.

4-[2-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetyl]benzonitrile (1h): Following procedure D, *p*-cyanobenzoyl chloride (1.82 g, 11 mmol) was used to afford **1h** as a red solid in 44% yield (1.30 g, 4.8 mmol), m.p. 77 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71 (s, 6 H), 3.91 (s, 2 H), 5.43 (s, 1 H), 7.81 (d, J = 8.5 Hz, 2 H), 8.03 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 43.5, 97.5, 107.6, 117.7, 127.5, 128.8, 132.5, 132.9, 138.7, 160.6, 193.4 ppm. IR (neat): $\tilde{\nu}$ = 2234, 1724, 1691, 1636, 1375, 1270, 1204, 1015, 838 cm^{-1}. MS (ESI): m/z = 270 $[M – H]^+$.

6-(2-Hydroxy-2-phenylethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (1i): *n*BuLi (32.3 mL, 42 mmol, 1.3 M in hexane) was added at –78 °C to a THF solution (200 mL) containing DIPA (5.9 mL, 42 mmol) in a round-bottomed flask flushed with argon. After 30 min at 0 °C, the solution was recooled to –78 °C and 2,2,6-trimethyl-2,4-dihydro-1,3-dioxin-4-one (**1a**; 5.8 mL, 42 mmol) was added. Finally, after 30 min at –78 °C, benzaldehyde (3.6 mL, 35 mmol) was added. After 2 h at –40 °C, the reaction was quenched at 0 °C with 1 N HCl and the mixture extracted twice with EtOAc. The combined organic layers were then dried with $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using cyclohexane/EtOAc (70:30) as eluent to give the dioxinone **1i** as a yellow solid in 98% yield (8.5 g, 34 mmol), m.p. 75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (s, 3 H), 1.64 (s, 3 H), 2.57 [A(ABX), J_{AB} = 21.9, J_{AX} = 7.5 Hz, 1 H], 2.62 (br. s, 1 H), 2.68 [B(ABX), J_{AB} = 21.9, J_{BX} = 12.3 Hz, 1 H], 4.95 [X(ABX), J_{AX} = 7.5, J_{BX} = 12.3 Hz, 1 H], 5.27 (s, 1 H), 7.28–7.36 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7, 25.4, 43.2, 71.2, 95.3, 106.8, 125.8, 128.3, 128.8, 142.9, 161.4, 168.6 ppm. IR (neat): $\tilde{\nu}$ = 3424, 1691, 1641, 1375, 1281, 1204, 1015, 805, 750, 700 cm^{-1}. MS (ESI): m/z = 249 $[M + H]^+$.

General Procedure for the Synthesis of Silylated Dioxinones 1j,k (Procedure E): DIEA (3 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf; 1.5 equiv.) were added at room temp. to a CH_2Cl_2 solution (0.1 mol L^{-1}) containing dioxinone **1g**,**h** (1 equiv.) in a round-bottomed flask flushed with argon. After 2 h, the reaction was quenched at room temp. with a saturated solution of $NaHCO_3$ and the mixture extracted twice with of CH_2Cl_2. The combined organic layers were washed with a saturated solution of NH_4Cl and then dried with $MgSO_4$, filtered and concentrated under vacuum. The crude product (100% conversion) was quickly purified by flash chromatography on silica gel with a mixture of cyclohexane/EtOAc (9:1) as eluent to give the silylated dioxinones **1j**,**k**, which were directly engaged in the next step.

6-[(*Z*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-phenylvinyl]-2,2-dimethyl-4*H*-1,3-dioxin-4-one (1j): Following procedure E, dioxinone **1g** (1.23 g, 5 mmol) was used to afford **1j** as a yellow oil in 98% yield (1.77 g, 4.9 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.06 (s, 6 H), 0.97 (s, 9 H), 1.69 (s, 6 H), 5.41 (s, 1 H), 5.85 (s, 1 H), 7.30–7.36 (m, 3 H), 7.44–7.47 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –3.5, 18.4, 25.1, 25.9, 93.7, 103.5, 105.6, 126.8, 128.4, 129.9, 138.5, 161.8, 162.4, 163.6 ppm.

(*Z*)-4-{1-[*tert*-Butyl(dimethyl)silyloxy]-2-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)vinyl}benzonitrile (1k): Following procedure E, dioxinone **1h** (1.1 g, 4.0 mmol) was used to afford **1k** as a red oil in 88% yield (1.38 g, 3.5 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.03 (s, 6 H), 1.00 (s, 9 H), 1.72 (s, 6 H), 5.52 (s, 1 H), 5.87 (s, 1 H), 7.00 (d, J = 8.5 Hz, 2 H), 7.68 (d, J = 8.5 Hz, 2 H) ppm.

2,2-Dimethyl-6-[2-(trimethylsilyloxy)-2-phenylethyl]-4*H*-1,3-dioxin-4-one (1l): Imidazole (413 mg, 6 mmol) and trimethylsilyl chloride (0.76 mL, 6 mmol) were added at 0 °C to a DMF solution (50 mL) of dioxinone **1i** (1.24 g, 5 mmol) in a round-bottomed flask flushed with argon. After 2 h at 0 °C, the reaction was quenched with water and the mixture extracted twice with CH_2Cl_2. The organic layer was then washed three times with brine. The combined organic layers were then dried with $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using cyclohexane/EtOAc (95:5) as eluent to give the silylated dioxinone **1l** as a yellow oil in 77% yield (1.23 g, 3.85 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 9 H), 1.64 (s, 3 H), 1.67 (s, 3 H), 2.49 [A(ABX), J_{AB} = 21.0, J_{AX} = 6.6 Hz, 1 H], 2.64 [B(ABX), J_{AB} = 21.0, J_{BX} = 12.6 Hz, 1 H], 4.92 [X(ABX), J_{AX} = 6.6, J_{BX} = 12.6 Hz, 1 H], 5.25 (s, 1 H), 7.29–7.34 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.2, 25.0, 25.5, 45.1, 72.0, 95.4, 106.5, 126.0, 128.0, 128.6, 143.4, 161.3, 168.7 ppm. IR (neat): $\tilde{\nu}$ = 1727, 1632, 1385, 1374, 1272, 1250, 1207, 1087, 1068, 1010, 941, 836, 806, 752, 701 cm^{-1}. MS (ESI): m/z = 321 $[M + H]^+$.

General Procedure for the Synthesis of α-Hydroxy Ketones 2d,e (Procedure F):[15] Sodium formate (3 equiv.) was stirred in ethanol (0.1 mol L^{-1}) for 15 min in a round-bottomed flask and the relevant acetophenone (1 equiv.) was then added. The mixture was stirred at 70 °C overnight. The solution was filtered hot and concentrated under vacuum. The crude residue was then purified by flash chromatography on silica gel using an appropriate gradient of cyclohexane/EtOAc as eluent to give the desired α-hydroxy ketone **2d**,**e**.

2-Hydroxy-1-phenylethanone (2d): Following procedure F, 2-bromoacetophenone (4.02 g, 20 mmol) was used to afford **2d** as a white solid in 44% yield (1.20 g, 8.8 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20), m.p. 82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.58 (br. s, 1 H), 4.86 (s, 2 H), 7.46 (t, J = 7.4 Hz, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.88 (d, J = 7.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.7,

127.9, 129.2, 133.6, 134.5, 198.7 ppm. IR (neat): $\tilde{\nu}$ = 3420, 3389, 1682, 1598, 1583, 1447, 1407, 1292, 1231, 1104, 971, 752 cm^{-1}.

2-Hydroxy-1-(4-methoxyphenyl)ethanone (2e): Following procedure F, 2-bromo-4-methoxyacetophenone (4.68 g, 20 mmol) was used to afford **2e** as a white solid in 90% yield (2.99 g, 18 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20), m.p. 112 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.58 (br. s, 1 H), 3.89 (s, 3 H), 4.83 (s, 2 H), 6.97 (d, J = 8.9 Hz, 2 H), 7.91 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7, 65.1, 114.3, 126.4, 130.2, 164.5, 196.8 ppm. IR (neat): $\tilde{\nu}$ = 3419, 3376, 1683, 1670, 1605, 1577, 1512, 1226, 1185, 1104, 1030, 977, 834, 821 cm^{-1}.

General Procedure for the Synthesis of Acyfuranones 8–28 (Procedure G): Et_3N (0.5 equiv.), dioxinone **1a**–**e** (1.5 equiv.) and molecular sieves (4 Å, 200 mg mol^{-1}) were added at room temp. to a toluene solution (0.1 mol L^{-1}) of α-hydroxy ketone **2a**–**e** (1 equiv.) in a round-bottomed flask flushed with argon. The mixture was then heated to 110 °C. After 3 h, the reaction was quenched at room temp. with 1 N HCl and the mixture extracted with EtOAc. The aqueous layer was then extracted twice with ethyl acetate. The combined organic layers were then dried with $MgSO_4$, filtered and concentrated under vacuum. The crude residue was purified by flash chromatography on silica gel using an appropriate gradient of cyclohexane/EtOAc as eluent to give the desired acylfuranone **8**–**28**.

3-Acetyl-4-methylfuran-2(5*H*)-one (8): Following procedure G, hydroxyacetone **2b** (0.07 mL, 1 mmol) and 2,2,6-trimethyl-2,4-dihydro-1,3-dioxin-4-one (**1a**; 0.20 mL, 1.5 mmol) were used to afford **8** as a yellow oil in 88% yield (123 mg, 0.88 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 2.52 (s, 3 H), 4.74 (s 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9, 30.3, 72.7, 125.3, 171.4, 174.6, 194.9 ppm. IR (neat): $\tilde{\nu}$ = 1754, 1714, 1362, 1210, 1163, 1020 cm^{-1}. MS (ESI): m/z = 139 $[M - H]^+$.

3-Acetyl-4,5,5-trimethylfuran-2(5*H*)-one (9): Following procedure G, 3-hydroxy-3-methylbutan-2-one (**2a**; 0.11 mL, 1 mmol) and 2,2,6-trimethyl-2,4-dihydro-1,3-dioxin-4-one (**1a**; 0.20 mL, 1.5 mmol) were used to afford **9** as a white solid in 100% yield (168 mg, 1 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 50:50), m.p. 47 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 6 H), 2.34 (s, 3 H), 2.56 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.3, 24.4, 30.2, 85.7, 123.6, 169.4, 180.9, 195.4 ppm. IR (neat): $\tilde{\nu}$ = 1760, 1691, 1288, 1030 cm^{-1}. MS (ESI): m/z = 167 $[M - H]^+$. $C_9H_{12}O_3$ (168.19): calcd. C 64.27, H 7.19; found C 64.23, H 7.21.

3-Acetyl-4-phenylfuran-2(5*H*)-one (10): Following procedure G, α-hydroxy ketone **2d** (136 mg, 1 mmol) and 2,2,6-trimethyl-2,4-dihydro-1,3-dioxin-4-one (**1a**; 0.20 mL, 1.5 mmol) were used to afford **10** as a colourless oil in 30% yield (61 mg, 0.30 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.55 (s, 3 H), 5.15 (s, 2 H), 7.43–7.56 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.0, 71.1, 126.3, 128.4, 129.4, 129.7, 132.5, 165.2, 171.2, 196.4 ppm. IR (neat): $\tilde{\nu}$ = 1744, 1693, 1623, 1447, 1332, 1220, 1175, 1047, 999, 762, 692 cm^{-1}. MS (ESI): m/z = 203 $[M + H]^+$.

3-Acetyl-4-(4-methoxyphenyl)furan-2(5*H*)-one (11): Following procedure G, α-hydroxy ketone **2e** (166 mg, 1 mmol) and 2,2,6-trimethyl-2,4-dihydro-1,3-dioxin-4-one (**1a**; 0.20 mL, 1.5 mmol) were used to afford **11** as a yellow oil in 30% yield (70 mg, 0.30 mmol, 30%) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.59 (s, 3 H), 3.87 (s, 3 H), 5.16 (s, 2 H), 6.95 (d, J = 9.0 Hz, 2 H), 7.62 (d, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.9, 55.7, 70.6, 114.6, 121.8, 123.6, 130.6, 163.1, 164.5, 171.7, 196.8 ppm. IR (neat): $\tilde{\nu}$ = 1745, 1686, 1602, 1512, 1254, 1176, 1023, 830 cm^{-1}. MS (ESI): m/z = 231 $[M - H]^+$.

3-Benzoyl-4-methylfuran-2(5*H*)-one (12): Following procedure G, hydroxyacetone **2b** (0.07 mL, 1 mmol) and dioxinone **1b** (306 mg, 1.5 mmol) were used to afford **12** as a yellow oil in 60% yield (121 mg, 0.6 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3 H), 4.88 (s, 2 H), 7.48 (t, J = 10.5 Hz, 2 H), 7.63 (t, J = 10.5 Hz, 1 H), 7.87 (d, J = 10.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 73.0, 127.7, 128.8, 129.7, 134.3, 136.2, 169.2, 170.6, 189.8 ppm. IR (neat): $\tilde{\nu}$ = 1752, 1658, 1598, 1447, 1320, 1242, 888 cm^{-1}. MS (ESI): m/z = 203 $[M + H]^+$.

3-Benzoyl-4,5,5-trimethylfuran-2(5*H*)-one (13): Following procedure G, 3-hydroxy-3-methylbutan-2-one (**2a**; 0.11 mL, 1 mmol) and dioxinone **1b** (306 mg, 1.5 mmol) were used to afford **13** as a white solid in 90% yield (207 mg, 0.9 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30), m.p. 126 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.57 (s, 6 H), 2.11 (s, 3 H), 7.47 (t, J = 7.4 Hz, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.84 (d, J = 7.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.6, 24.8, 86.6, 126.4, 128.8, 129.6, 134.2, 136.4, 168.8, 175.8, 190.2 ppm. IR (neat): $\tilde{\nu}$ = 1742, 1655, 1345, 1289, 925, 894, 767, 693, 670 cm^{-1}. MS (ESI): m/z = 229 $[M - H]^+$.

3-Benzoyl-4-phenylfuran-2(5*H*)-one (14): Following procedure G, α-hydroxy ketone **2d** (136 mg, 1 mmol) and dioxinone **1b** (306 mg, 1.5 mmol) were used to afford **14** as a colourless oil in 53% yield (140 mg, 0.53 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.35 (s, 2 H), 7.32–7.44 (m, 7 H), 7.57–7.62 (m, 1 H), 7.91–7.94 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 70.7, 125.8, 127.9, 129.0, 129.1, 129.4, 129.7, 132.2, 134.7, 135.5, 161.2, 170.8, 191.5 ppm. IR (neat): $\tilde{\nu}$ = 1730, 1664, 1636, 1596, 1453, 1331, 1241, 1039, 921, 877, 759, 678 cm^{-1}. MS (ESI): m/z = 263 $[M - H]^+$.

3-Benzoyl-4-(4-methoxyphenyl)furan-2(5*H*)-one (15): Following procedure G, α-hydroxy ketone **2e** (166 mg, 1 mmol) and dioxinone **1b** (306 mg, 1.5 mmol) were used to afford **15** as a yellow solid in 52% yield (153 mg, 0.52 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30), m.p. 120 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 5.32 (s, 2 H), 6.85 (d, J = 9.0 Hz, 2 H), 7.36 (d, J = 9.0 Hz, 2 H), 7.46 (t, J = 7.5 Hz, 2 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.94 (d, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4, 70.5, 114.7, 121.3, 123.0, 128.9, 129.6, 129.8, 134.5, 135.6, 160.8, 162.6, 171.2, 192.0 ppm. IR (neat): $\tilde{\nu}$ = 2926, 2855, 1734, 1662, 1597, 1514, 1333, 1261, 1240, 1179, 1024, 830, 674 cm^{-1}. MS (ESI): m/z = 293 $[M - H]^+$.

4-Methyl-3-octanoylfuran-2(5*H*)-one (16): Following procedure G, hydroxyacetone **2b** (0.07 mL,1 mmol) and dioxinone **1c** (339 mg, 1.5 mmol) were used to afford **16** as a colourless oil in 50% yield (112 mg, 0.5 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.79–0.84 (m, 3 H), 1.22–1.24 (m, 8 H), 1.53–1.58 (m, 2 H), 2.36 (s, 3 H), 2.88 (t, J = 7.4 Hz, 2 H), 4.71 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.6, 22.6, 23.3, 29.1, 29.2, 31.7, 42.2, 72.4, 125.1, 171.0, 173.4, 197.4 ppm. IR (neat): $\tilde{\nu}$ = 2921, 2859, 1758, 1692, 1627, 1375, 1020, 933 cm^{-1}. MS (ESI): m/z = 223 $[M - H]^+$.

4,5,5-Trimethyl-3-octanoylfuran-2(5*H*)-one (17): Following procedure G, 3-hydroxy-3-methylbutan-2-one (**2a**; 0.11 mL, 1 mmol) and dioxinone **1c** (339 mg, 1.5 mmol) were used to afford **17** as a colourless oil in 57% yield (144 mg, 0.57 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77–0.81 (m, 3 H), 1.19–1.23 (m, 8 H), 1.41 (s, 6 H), 1.48–1.55 (m, 2 H), 2.25 (s, 3 H), 2.87 (t, J = 16.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2, 14.2, 22.7, 23.4, 24.4, 29.1, 29.2, 31.8, 42.3, 85.7, 123.8, 169.3, 180.4, 198.2 ppm. IR (neat): $\tilde{\nu}$ = 2934, 2853, 1751, 1689, 1624, 1282, 1039, 967, 921 cm^{-1}. MS (ESI): m/z = 251 [M – H]$^+$.

3-Octanoyl-4-phenylfuran-2(5*H*)-one (18): Following procedure G, α-hydroxy ketone **2d** (136 mg, 1 mmol) and dioxinone **1c** (339 mg, 1.5 mmol) were used to afford **18** as a colourless oil in 29% yield (83 mg, 0.29 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.88 (m, 3 H), 1.24–1.27 (m, 8 H), 1.58–1.67 (m, 2 H), 2.88 (t, J = 7.5 Hz, 2 H), 5.16 (s, 2 H), 7.44–7.54 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 23.3, 29.0, 29.1, 31.7, 43.0, 70.8, 126.3, 128.0, 129.2, 129.4, 132.1, 164.0, 171.1, 199.6 ppm. IR (neat): $\tilde{\nu}$ = 2928, 2853, 1764, 1705, 1618, 1450, 1241, 1157, 977, 765, 690 cm^{-1}. MS (ESI): m/z = 285 [M – H]$^+$.

4-(4-Methoxyphenyl)-3-octanoylfuran-2(5*H*)-one and (*Z*)-3-(1-Hydroxyoctylidene)-4-(4-methoxyphenyl)furan-2(3*H*)-one (19): Following procedure G, α-hydroxy ketone **2e** (166 mg, 1 mmol) and dioxinone **1c** (339 mg, 1.5 mmol) were used to afford **19** as a colourless oil in 25% yield (79 mg, 0.25 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30). A mixture of the ketone and its enol form (60:40) was formed. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.88 (m, 3 H), 1.25–1.28 (m, 8 H), 1.62–1.67 (m, 2 H), 2.64 (t, J = 7.4 Hz, 0.8 H), 2.92 (t, J = 7.4 Hz, 1.2 H), 3.62 (s, 0.4 H), 3.87 (s, 1.8 H), 3.88 (s, 1.2 H), 5.15 (s, 1.2 H), 5.36 (s, 0.4 H), 6.93–6.97 (m, 2 H), 7.56 (d, J = 9.0 Hz, 1.2 H), 7.89 (d, J = 9.0 Hz, 0.8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.7, 23.6, 29.0, 29.1, 29.2, 31.7, 43.1, 49.0, 55.6, 55.7, 66.5, 70.6, 114.2, 114.6, 121.9, 123.9, 127.0, 130.2, 130.3, 162.9, 163.4, 164.2, 166.9, 171.6, 190.1, 200.2, 202.9 ppm. IR (neat): $\tilde{\nu}$ = 2921, 2853, 1745, 1692, 1602, 1515, 1260, 1182, 1064, 1030, 973, 830 cm^{-1}. MS (ESI): m/z = 287 [M – H]$^+$.

3-(4-Methoxybenzoyl)-4-methylfuran-2(5*H*)-one (20): Following procedure G, hydroxyacetone **2b** (0.07 mL, 1 mmol) and dioxinone **1d** (351 mg, 1.5 mmol) were used to afford **20** as a white solid in 61% yield (142 mg, 0.61 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 60:40), m.p. 102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 3.88 (s, 3 H), 4.86 (s, 2 H), 6.95 (d, J = 8.1 Hz, 2 H), 7.85 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 55.7, 72.9, 114.1, 127.9, 129.3, 132.2, 164.6, 168.0, 170.8, 188.1 ppm. IR (neat): $\tilde{\nu}$ = 1746, 1602, 1575, 1259, 1181, 1015, 838, 788 cm^{-1}. MS (ESI): m/z = 231 [M – H]$^+$.

3-(4-Methoxybenzoyl)-4,5,5-trimethylfuran-2(5*H*)-one (21): Following procedure G, 3-hydroxy-3-methylbutan-2-one (**2a**; 0.11 mL, 1 mmol) and dioxinone **1d** (351 mg, 1.5 mmol) were used to afford **21** as a yellow solid in 71% yield (185 mg, 0.71 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30), m.p. 67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 6 H), 2.08 (s, 3 H), 3.86 (s, 3 H), 6.93 (d, J = 8.5 Hz, 2 H), 7.82 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.5, 24.8, 55.7, 86.5, 114.0, 126.6, 129.4, 132.1, 164.5, 169.0, 174.8, 188.5 ppm. IR (neat): $\tilde{\nu}$ = 1746, 1597, 1569, 1253, 1176, 1071, 1021, 921, 905 cm^{-1}. MS (ESI): m/z = 259 [M – H]$^+$.

3-(4-Methoxybenzoyl)-4-phenylfuran-2(5*H*)-one (22): Following procedure G, α-hydroxy ketone **2d** (136 mg, 1 mmol) and dioxinone **1d** (351 mg, 1.5 mmol) were used to afford **22** as a white solid in 54% yield (158 mg, 0.54 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30), m.p. 98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 5.33 (s, 2 H), 6.92 (d, J = 9.0 Hz, 2 H), 7.35–7.44 (m, 5 H), 7.91 (d, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7, 70.7, 114.4, 126.1, 127.8, 128.7, 129.2, 129.4, 132.0, 132.2, 160.4, 164.9, 171.1, 189.8 ppm. IR (neat): $\tilde{\nu}$ = 1748, 1596, 1571, 1254, 1173, 1026, 846, 768, 690 cm^{-1}. MS (ESI): m/z = 293 [M – H]$^+$.

3-(4-Methoxybenzoyl)-4-(4-methoxyphenyl)furan-2(5*H*)-one (23): Following procedure G, α-hydroxy ketone **2e** (166 mg, 1 mmol) and dioxinone **1d** (351 mg, 1.5 mmol) were used to afford **23** as a yellow solid in 61% yield (198 mg, 0.61 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30), m.p. 170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 3.86 (s, 3 H), 5.30 (s, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 6.93 (d, J = 8.7 Hz, 2 H), 7.36 (d, J = 8.7 Hz, 2 H), 7.91 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 55.6, 70.5, 114.3, 114.8, 121.5, 123.3, 128.8, 129.8, 132.2, 160.0, 162.5, 164.8, 171.5, 190.4 ppm. IR (neat): $\tilde{\nu}$ = 1735, 1597, 1508, 1248, 1159, 1021, 833 cm^{-1}. MS (ESI): m/z = 325 [M + H]$^+$.

3-Acetyl-4,5-dimethylfuran-2(5*H*)-one and (*Z*)-3-(1-Hydroxyethylidene)-4,5-dimethylfuran-2(3*H*)-one (24): Following procedure G, 3-hydroxybutan-2-one (**2c**; 0.09 mL, 1 mmol) and 2,2,6-trimethyl-2,4-dihydro-1,3-dioxin-4-one (**1a**; 0.20 mL, 1.5 mmol) were used to afford **24** as a colourless oil in 24% yield (37 mg, 0.24 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30). A mixture of the ketone and its enol form (25:75) was formed. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, J = 7.0 Hz, 0.75 H), 1.69 (s, 2.25 H), 2.37 (s, 0.75 H), 2.38 (s, 2.25 H), 2.55 (s, 2.25 H), 2.56 (s, 0.75 H), 3.65 (br. s, 0.75 H), 4.91 (q, J = 6.8, 14.0 Hz, 0.25 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 14.3, 17.7, 23.3, 30.3, 30.5, 79.7, 105.0, 124.7, 125.0, 168.3, 170.6, 174.8, 178.3, 195.5, 195.6 ppm. IR (neat): $\tilde{\nu}$ = 1754, 1677, 1630, 1362, 1325, 1232, 1185, 1011, 908 cm^{-1}. MS (ESI): m/z = 153 [M – H]$^+$.

3-Benzoyl-4,5-dimethylfuran-2(5*H*)-one and (*Z*)-3-[Hydroxy(phenyl)methylene]-4,5-dimethylfuran-2(3*H*)-one (25): Following procedure G, 3-hydroxybutan-2-one (**2c**; 0.09 mL, 1 mmol) and dioxinone **1b** (306 mg, 1.5 mmol) were used to afford **25** as a white solid in 26% yield (56 mg, 0.26 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30), m.p. 98 °C. A mixture of the ketone and its enol form (75:25) was formed. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (d, J = 7.0 Hz, 2.25 H), 1.75 (s, 0.75 H), 2.10 (s, 0.75 H), 2.14 (s, 2.25 H), 4.47 (br. s, 0.25 H), 5.04 (q, J = 6.8, 13.6 Hz, 0.75 H), 7.44–7.50 (m, 2 H), 7.58–7.63 (m, 1 H), 7.82–7.86 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.4, 13.5, 18.1, 23.6, 80.2, 105.9, 127.2, 127.5, 128.8, 128.9, 129.6, 129.7, 134.3, 134.5, 136.1, 136.2, 167.6, 169.2, 169.9, 172.9, 190.1 ppm. IR (neat): $\tilde{\nu}$ = 3427, 3062, 1754, 1652, 1595, 1351, 1246, 1061, 901, 769, 693, 672 cm^{-1}. MS (ESI): m/z = 217 [M – H]$^+$.

3-(Furan-2-ylcarbonyl)-4,5,5-trimethylfuran-2(5*H*)-one (26): Following procedure G, 3-hydroxy-3-methylbutan-2-one (**2a**; 0.11 mL, 1 mmol) and dioxinone **1e** (291 mg, 1.5 mmol) were used to afford **26** as a yellow solid in 65% yield (143 mg, 0.65 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30), m.p. 103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 6 H), 2.19 (s, 3 H), 6.59 (br. s, 1 H), 7.36 (d, J = 3.6 Hz, 1 H), 7.68 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.6, 24.6, 86.5, 112.8, 121.6, 125.4, 148.0, 151.9, 168.4, 176.3, 177.4 ppm. IR

(neat): $\tilde{\nu}$ = 3133, 2986, 1728, 1639, 1464, 1395, 1338, 1273, 1079, 1028, 944, 772 cm^{-1}. MS (ESI): *m*/*z* = 219 $[M - H]^+$.

3-(Furan-2-ylcarbonyl)-4-(4-methoxyphenyl)furan-2(5*H*)-one (27): Following procedure G, α-hydroxy ketone **2e** (166 mg, 1 mmol) and dioxinone **1e** (291 mg, 1.5 mmol) were used to afford **27** as a yellow oil in 43% yield (122 mg, 0.43 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 5.28 (s, 2 H), 6.54–6.56 (m, 1 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 7.24–7.26 (m, 2 H), 7.43 (d, *J* = 9.0 Hz, 1 H), 7.62 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 70.6, 113.0, 114.7, 121.4, 121.6, 122.0, 129.9, 148.4, 151.9, 162.1, 162.7, 171.0, 178.2 ppm. IR (neat): $\tilde{\nu}$ = 1747, 1647, 1604, 1516, 1461, 1261, 1184, 1061, 1023 cm^{-1}. MS (ESI): *m*/*z* = 283 $[M - H]^+$.

3-(Furan-2-ylcarbonyl)-4-phenylfuran-2(5*H*)-one (28): Following procedure G, α-hydroxy ketone **2d** (136 mg, 1 mmol) and dioxinone **1e** (291 mg, 1.5 mmol) were used to afford **28** as a yellow solid in 39% yield (99 mg, 0.39 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30), m.p. 128 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.31 (s, 2 H), 6.54–6.56 (m, 1 H), 7.40–7.48 (m, 6 H), 7.61 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 70.8, 113.1, 121.5, 124.9, 127.9, 129.2, 129.4, 132.3, 148.4, 151.9, 162.6, 170.6, 177.7 ppm. IR (neat): $\tilde{\nu}$ = 1733, 1633, 1459, 1332, 1201, 1082, 1059, 1024, 939, 843, 762, 689, 589 cm^{-1}. MS (ESI): *m*/*z* = 253 $[M - H]^+$.

General Procedure for the Synthesis of Acylfuranones 29–32 (Procedure H): Et_3N or DIEA (2 equiv.) as base and the appropriate dioxinone (1.5 equiv.) were added at room temp. to a toluene solution (0.1 mol L^{-1}) of 3-hydroxy-3-methylbutan-2-one (**2a**; 1 equiv.) and molecular sieves (4 Å, 200 mg per mmol) in a round-bottomed flask flushed with argon. The mixture was then heated to 110 °C. After 3 h, the reaction was quenched at room temp. with 1 N HCl and the mixture extracted with EtOAc. The combined organic layers were then dried with $MgSO_4$, filtered and concentrated under vacuum. The crude residue was dissolved in a mixture of THF/1 N HCl (10:1). After 2 h, the aqueous layer was extracted with EtOAc. The combined organic layers were then dried with $MgSO_4$, filtered and concentrated under vacuum (except for the sulfone derivative **31**). The crude was then purified by flash chromatography on silica gel using an appropriate gradient of cyclohexane/EtOAc as eluent to give the desired acylfuranones **29**–**32**.

3-(3-Hydroxy-3-phenylpropanoyl)-4,5,5-trimethylfuran-2(5*H*)-one (29): Following procedure H, 3-hydroxy-3-methylbutan-2-one (**2a**; 0.08 mL, 0.7 mmol), dioxinone **1l** (332 mg, 1.0 mmol) and DIEA (0.24 mL, 1.4 mmol) were used to afford **29** as a yellow solid in 91% yield (175 mg, 0.64 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 50:50), m.p. 90 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 6 H), 2.36 (s, 3 H), 3.20 (d, *J* = 4.0 Hz, 1 H), 3.41 (d, *J* = 6.0 Hz, 2 H), 5.21–5.26 (m, 1 H), 7.25–7.42 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 24.4, 24.5, 50.7, 70.3, 86.1, 123.5, 125.9, 127.8, 128.6, 142.9, 169.4, 182.1, 197.5 ppm. IR (neat): $\tilde{\nu}$ = 3441, 1724, 1696, 1630, 1370, 1287, 1198, 1065, 1015, 921, 744, 700 cm^{-1}. MS (ESI): *m*/*z* = 273 $[M - H]^+$.

(*Z*)-3-(3-Hydroxy-3-phenylacryloyl)-4,5,5-trimethylfuran-2(5*H*)-one (30): Following procedure H, 3-hydroxy-3-methylbutan-2-one (**2a**; 0.11 mL, 1.0 mmol), dioxinone **1j** (541 mg, 1.5 mmol) and Et_3N (0.28 mL, 2 mmol) were used to afford **30** as a white solid in 91% yield (248 mg, 0.9 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20), m.p. 127 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 6 H), 2.44 (s, 3 H), 7.41–7.52 (m, 4 H), 7.97 (d, *J* = 7.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 24.4, 85.6, 97.2, 120.1, 127.6, 128.7, 133.0, 135.5, 168.9, 176.4, 178.3, 189.2 ppm. IR (neat): $\tilde{\nu}$ = 2909, 1742, 1633, 1596, 1524, 1462, 1369, 1254, 1036, 827, 793, 781, 694 cm^{-1}. MS (ESI): *m*/*z* = 273 $[M + H]^+$.

4,5,5-Trimethyl-3-[2-(phenylsulfonyl)acetyl]furan-2(5*H*)-one (31): Following procedure H, 3-hydroxy-3-methylbutan-2-one (**2a**; 0.11 mL, 1.0 mmol), dioxinone **1f** (423 mg, 1.5 mmol) and DIEA (0.35 mL, 2 mmol) were used to afford **32** as a white solid in 59% yield (183 mg, 0.59 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30), m.p. 100 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 6 H), 2.31 (s, 3 H), 4.90 (s, 2 H), 7.54 (t, *J* = 7.7 Hz, 2 H), 7.65 (t, *J* = 7.7 Hz, 1 H), 7.90 (d, *J* = 7.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 24.2, 64.7, 86.3, 123.0, 128.4, 129.3, 134.3, 139.6, 168.9, 183.8, 184.7 ppm. IR (neat): $\tilde{\nu}$ = 2915, 1748, 1695, 1624, 1446, 1334, 1306, 1297, 1269, 1157, 1123, 1058, 980, 886, 759, 687 cm^{-1}. MS (ESI): *m*/*z* = 307 $[M - H]^+$.

(*Z*)-4-[1-Hydroxy-3-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)-3-oxoprop-1-enyl]benzonitrile (32): Following procedure H, 3-hydroxy-3-methylbutan-2-one (**2a**; 0.11 mL, 1.0 mmol), dioxinone **1k** (278 mg, 1.5 mmol) and Et_3N (0.28 mL, 2 mmol) were used to afford **32** as a yellow solid in 50% yield (149 mg, 0.5 mmol) after precipitation in EtOAc. Decomp. 200 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1 53 (s, 6 H), 2.49 (s, 3 H), 7.47 (s, 1 H), 7.77 (d, *J* = 8.7 Hz, 2 H), 8.08 (d, *J* = 8.7 Hz, 2 H), 16.1 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 24.6, 86.0, 97.8, 116.0, 118.2, 120.1, 128.1, 132.6, 139.2, 168.9, 178.8, 180.0, 185.8 ppm. IR (neat): $\tilde{\nu}$ = 2224, 1758, 1636, 1515, 1487, 1328, 1291, 1257, 1210, 1061, 1036, 967, 843, 818, 687 cm^{-1}. MS (ESI): *m*/*z* = 296 $[M - H]^+$.

General Procedure for the Synthesis of Acylfuranones 34a–h (Procedure I): Toluene (for a solution of 1.0 mol L^{-1}), Et_3N (2.0 equiv.) and the appropriate α-hydroxy ketone (1 equiv.), dioxinone (2 equiv.) and aldehyde (1 equiv.) were added to a 15 mL tube flushed with argon. The tube was sealed and then heated in a microwave reactor. Over 1.5 min, the temperature was raised to 150 °C, held for 5 min, and then cooled for 10 min. The reaction was quenched at room temperature with 1 N HCl and the mixture extracted with EtOAc. The combined organic layers were then dried with $MgSO_4$, filtered and concentrated under vacuum. The crude was then purified by flash chromatography on silica gel using an appropriate gradient of cyclohexane/EtOAc as eluent to give the desired acylfuranones **34a**–**h**.

(5*Z*)-3-(4-Methoxybenzoyl)-5-(4-methoxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one (34a): Following procedure I, α-hydroxy ketone **2e** (83 mg, 0.5 mmol), dioxinone **1d** (234 mg, 1.0 mmol) and *p*-methoxybenzaldehyde (**33**; 0.06 mL, 0.5 mmol) were used to afford **34a** as a yellow solid in 77% yield (170 mg, 0.77 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 60:40). Analyses are similar to those described in the literature.[21] M.p. 188 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 3.82 (s, 3 H), 3.85 (s, 3 H), 6.23 (s, 1 H), 6.84 (d, *J* = 8.9 Hz, 2 H), 6.90 (d, *J* = 7.9 Hz, 2 H), 6.93 (d, *J* = 7.9 Hz, 2 H), 7.36 (d, *J* = 8.9 Hz, 2 H), 7.80 (d, *J* = 7.9 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.8, 55.8, 55.9, 114.2, 114.7, 114.9, 117.4, 121.8, 123.1, 126.1, 129.6, 131.2, 132.5, 133.4, 146.1, 157.4, 161.4, 161.7, 164.6, 167.2, 188.7 ppm. IR (neat): $\tilde{\nu}$ = 2934, 2840, 1755, 1655, 1639, 1600, 1511, 1460, 1425, 1377, 1305, 1259, 1175, 1028, 973, 919, 838, 732 cm^{-1}. MS (ESI): *m*/*z* = 443 $[M + H]^+$.

(*Z*)-5-Benzylidene-3-(4-methoxybenzoyl)-4-(4-methoxyphenyl)furan-2(5*H*)-one (34b): Following procedure I, α-hydroxy ketone **2e** (50 mg, 0.3 mmol), dioxinone **1d** (141 mg, 0.6 mmol) and benzalde-

hyde (0.03 mL, 0.3 mmol) were used to afford **34b** as a yellow oil in 61% yield (76 mg, 0.18 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 3.84 (s, 3 H), 6.27 (s, 1 H), 6.87 (d, J = 8.7 Hz, 2 H), 6.92 (d, J = 8.7 Hz, 2 H), 7.37–7.44 (m, 5 H), 7.80–7.85 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 55.7, 114.1, 114.6, 116.8, 121.3, 124.1, 129.1, 129.3, 130.0, 131.0, 131.2, 132.3, 133.0, 147.5, 156.9, 161.6, 164.5, 166.6, 188.2 ppm. IR (neat): $\tilde{\nu}$ = 1754, 1730, 1655, 1593, 1571, 1506, 1372, 1250, 1166, 1026, 970, 837 cm^{-1}. MS (ESI): m/z = 413 [M + H]$^+$.

(*Z*)-3-(4-Methoxybenzoyl)-4-(4-methoxyphenyl)-5-(4-nitrobenzylidene)furan-2(5*H*)-one (34c): Following procedure I, α-hydroxy ketone **2e** (50 mg, 0.3 mmol), dioxinone **1d** (141 mg, 0.6 mmol) and *p*-nitrobenzaldehyde (46 mg, 0.3 mmol) were used to afford **34c** as a yellow oil in 55% yield (75 mg, 0.16 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 70:30). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 3.83 (s, 3 H), 6.30 (s, 1 H), 6.86 (d, J = 13.2 Hz, 2 H), 6.93 (d, J = 12.9 Hz, 2 H), 7.38 (d, J = 12.9 Hz, 2 H), 7.80 (d, J = 13.2 Hz, 2 H), 7.96 (d, J = 13.2 Hz, 2 H), 8.23 (d, J = 13.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 55.7, 113.0, 114.2, 114.7, 120.6, 124.1, 125.5, 128.9, 130.9, 131.5, 132.2, 139.1, 147.6, 149.9, 156.1, 161.9, 164.7, 165.8, 187.6 ppm. IR (neat): $\tilde{\nu}$ = 1770, 1590, 1512, 1341, 1257, 1166, 1017, 827, 793 cm^{-1}. MS (ESI): m/z = 458 [M + H]$^+$.

(*Z*)-3-(4-Methoxybenzoyl)-4-(4-methoxyphenyl)-5-(2-methylbenzylidene)furan-2(5*H*)-one (34d): Following procedure I, α-hydroxy ketone **2e** (166 mg, 1.0 mmol), dioxinone **1d** (469 mg, 2.0 mmol) and *o*-tolualdehyde (0.12 mL, 1.0 mmol) were used to afford **34d** as a yellow solid in 45% yield (192 mg, 0.45 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20), m.p. 174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.92 (s, 3 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 6.52 (s, 1 H), 6.87 (d, J = 8.7 Hz, 2 H), 6.93 (d, J = 8.7 Hz, 2 H), 7.19–7.31 (m, 3 H), 7.41 (d, J = 8.7 Hz, 2 H), 7.83 (d, J = 8.7 Hz, 2 H), 8.22 (d, J = 7.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 55.7, 55.9, 114.0, 114.3, 114.7, 121.7, 124.3, 127.0, 129.5, 130.1, 130.8, 131.2, 131.4, 131.7, 132.5, 138.3, 147.7, 157.1, 161.8, 164.7, 167.0, 188.5 ppm. IR (neat): $\tilde{\nu}$ = 1754, 1594, 1565, 1511, 1376, 1255, 1168, 1024, 973, 839, 756 cm^{-1}. MS (ESI): m/z = 427 [M + H]$^+$.

(*Z*)-5-[4-(Dimethylamino)benzylidene]-3-(4-methoxybenzoyl)-4-(4-methoxyphenyl)furan-2(5*H*)-one (34e): Following procedure I, α-hydroxy ketone **2e** (50 mg, 0.3 mmol), dioxinone **1d** (141 mg, 0.6 mmol) and *p*-dimethylaminobenzaldehyde (46 mg, 0.3 mmol) were used to afford **34e** as a red oil in 4% yield (5 mg, 0.01 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.06 (s, 6 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 6.21 (s, 1 H), 6.69 (d, J = 8.9 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 6.90 (d, J = 8.6 Hz, 2 H), 7.36 (d, J = 8.9 Hz, 2 H), 7.77 (d, J = 8.9 Hz, 2 H), 7.83 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.2, 55.5, 55.6, 112.0, 113.9, 114.3, 119.0, 121.0, 121.2, 122.2, 129.9, 131.0, 132.3, 133.5, 144.5, 151.5, 157.4, 161.2, 164.2, 167.4, 188.7 ppm. MS (ESI): m/z = 456 [M + H]$^+$.

(*Z*)-3-(Furan-2-ylcarbonyl)-5-(4-methoxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one (34f): Following procedure I, α-hydroxy ketone **2e** (166 mg, 1.0 mmol), dioxinone **1e** (388 mg, 2.0 mmol) and *p*-methoxybenzaldehyde (**33**; 0.11 mL, 1.0 mmol) were used to afford **34f** as a red solid in 53% yield (212 mg, 0.53 mmol) after purification by flash chromatography on silica gel (cyclohexane/DCM, 20:80), m.p. 54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 3.83 (s, 3 H), 6.24 (s, 1 H), 6.46 (dd, J = 2.4, 5.4 Hz, 1 H), 6.90 (d, J = 13.2 Hz, 2 H), 6.94 (d, J = 13.2 Hz, 2 H), 7.15 (d, J = 5.4 Hz, 1 H), 7.39 (d, J = 13.2 Hz, 2 H), 7.50 (d, J = 2.4 Hz, 1 H), 7.78 (d, J = 13.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 112.7, 114.4, 114.6, 118.1, 121.0, 121.2, 121.3, 125.7, 131.0, 133.3, 145.7, 147.7, 152.0, 158.4, 161.3, 161.5, 166.4, 176.1 ppm. IR (neat): $\tilde{\nu}$ = 1744, 1639, 1600, 1562, 1507, 1456, 1392, 1303, 1252, 1175, 1021, 823 cm^{-1}. MS (ESI): m/z = 403 [M + H]$^+$.

(*Z*)-3-(4-Methoxybenzoyl)-5-(4-methoxybenzylidene)-4-methylfuran-2(5*H*)-one (34g): Following procedure I, hydroxyacetone **2b** (0.07 mL, 1.0 mmol), dioxinone **1d** (468 mg, 2.0 mmol) and *p*-methoxybenzaldehyde (**33**; 0.11 mL, 1.0 mmol) were used to afford **34g** as a yellow solid in 25% yield (87 mg, 0.25 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20), m.p. 176 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 3.86 (s, 3 H), 3.88 (s, 3 H), 6.28 (s, 1 H), 6.95 (d, J = 9.0 Hz, 2 H), 6.96 (d, J = 9.0 Hz, 2 H), 7.83 (d, J = 9.0 Hz, 2 H), 7.87 (d, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.5, 55.6, 55.7, 113.8, 114.0, 114.7, 124.2, 125.5, 129.9, 132.3, 133.2, 146.7, 158.3, 161.2, 164.4, 167.2, 188.2 ppm. IR (neat): $\tilde{\nu}$ = 1751, 1639, 1600, 1568, 1514, 1357, 1306, 1258, 1172, 1024, 948, 826, 784 cm^{-1}. MS (ESI): m/z = 351 [M + H]$^+$.

(*Z*)-5-(4-Methoxybenzylidene)-4-(4-methoxyphenyl)-3-octanoylfuran-2(5*H*)-one (34h): Following procedure I, α-hydroxy ketone **2e** (166 mg, 1.0 mmol), dioxinone **1c** (453 mg, 2.0 mmol) and *p*-methoxybenzaldehyde (**33**; 0.11 mL, 1.0 mmol) were used to afford **34h** as a yellow oil in 36% yield (156 mg, 0.36 mmol) after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83–0.88 (m, 3 H), 1.25–1.30 (m, 8 H), 1.53–1.58 (m, 2 H), 2.89 (t, J = 7.5 Hz, 2 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 6.11 (s, 1 H), 6.92 (d, J = 6.9 Hz, 2 H), 7.01 (d, J = 6.9 Hz, 2 H), 7.39 (d, J = 6.9 Hz, 2 H), 7.78 (d, J = 6.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 22.9, 23.9, 29.4, 29.4, 32.0, 42.9, 55.7, 55.7, 114.1, 114.9, 119.6, 120.7, 121.7, 126.1, 131.5, 133.7, 146.6, 160.4, 161.8, 167.6, 196.9 ppm. IR (neat): $\tilde{\nu}$ = 1751, 1683, 1600, 1549, 1507, 1376, 1303, 1252, 1175, 1028, 983, 829 cm^{-1}. MS (ESI): m/z = 435 [M + H]$^+$.

(*Z*)-3-(4-Hydroxybenzoyl)-5-(4-hydroxybenzylidene)-4-(4-hydroxyphenyl)furan-2(5*H*)-one (35): BBr_3 (0.37 mL, 2.15 mmol) was added at –78 °C to a CH_2Cl_2 solution (2 mL) of acylfuranone **34a** (95 mg, 0.21 mmol) in a round-bottomed flask flushed with argon. The medium was then warmed slowly to room temp. over 20 h. The reaction was quenched at –78 °C with MeOH then at room temp. with H_2O and the mixture extracted twice with EtOAc. The combined organic layers were then dried with $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by chromatography on silica gel by using cyclohexane/EtOAc (40:60) as eluent to give the acylfuranone **35** as a yellow solid in 94% yield (79 mg, 0.20 mmol). Analyses are similar to those described in the literature.[21] M.p. 262 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.33 (s, 1 H), 6.78 (d, J = 8.7 Hz, 2 H), 6.82 (d, J = 8.7 Hz, 2 H), 6.89 (d, J = 8.7 Hz, 2 H), 7.22 (d, J = 8.7 Hz, 2 H), 7.68 (d, J = 8.7 Hz, 2 H), 7.74 (d, J = 8.7 Hz, 2 H), 10.15 (br. s, 1 H), 10.28 (br. s, 1 H), 10.69 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 115.5, 115.8, 116.1, 116.4, 119.3, 121.4, 124.0, 127.4, 130.8, 132.1, 133.0, 144.6, 155.9, 159.5, 159.6, 163.2, 166.1, 188.0 ppm. MS (ESI): m/z = 399 [M – H]$^+$.

Cadiolide B: A brominating agent (0.69 mL) prepared from Br_2 (0.03 mL) and KBr (150 mg) in H_2O (1 mL) was added dropwise to a solution of acylfuranone **35** (26 mg, 0.065 mmol) in dioxane/H_2O (2 mL, 1:1). The mixture was stirred for 24 h, treated with brine and the mixture extracted with Et_2O. The organic layer was washed with brine and then with $Na_2S_2O_3$. The combined organic layers were then dried with Na_2SO_4, filtered and concentrated un-

der vacuum. The crude product was purified by chromatography on silica gel using a gradient of EtOAc/MeOH (100:0 to 90:10) to give Cadiolide B as a black solid in 67% yield (38 mg, 0.044 mmol). Analyses are similar to those described in the literature.[3,4a] ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.40 (s, 1 H), 7.55 (s, 2 H), 7.91 (s, 2 H), 8.12 (s, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 109.7, 111.8, 112.0, 112.2, 114.0, 122.3, 122.8, 127.1, 130.2, 133.0, 133.7, 134.8, 146.2, 152.6, 154.8, 156.2, 165.3, 184.3 ppm. MS (ESI): *m/z* (%) = 879 (8), 878 (14), 877 (30), 874 (78), 873 (100), 871 (84), 868 (30), 867 (6).

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for **1b**–**1k**, and **8**–**35**.

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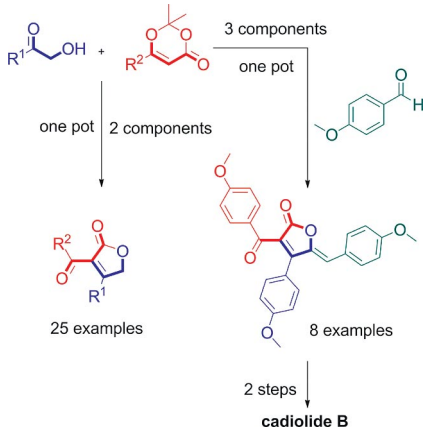
Multicomponent Reaction

A new method for the synthesis of acylfuranones is described based on the fragmentation of dioxinones to acylketenes followed by trapping with hydroxy ketones. Addition of an aldehyde as a third reaction partner leads to a supplementary aldolization/crotonization sequence resulting in an expeditious synthesis of cadiolide B and its analogues.



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Versatile Synthesis of Acylfuranones by Reaction of Acylketenes with α-Hydroxy Ketones: Application to the One-Step Multicomponent Synthesis of Cadiolide B and Its Analogues

Keywords: Synthetic methods / Multicomponent reactions / Oxygen heterocycles / Natural products / Ketenes

