Using singlet oxygen to synthesise a [6,6,5]-bis-spiroketal in one-pot from a simple 2,5-disubstituted furan†

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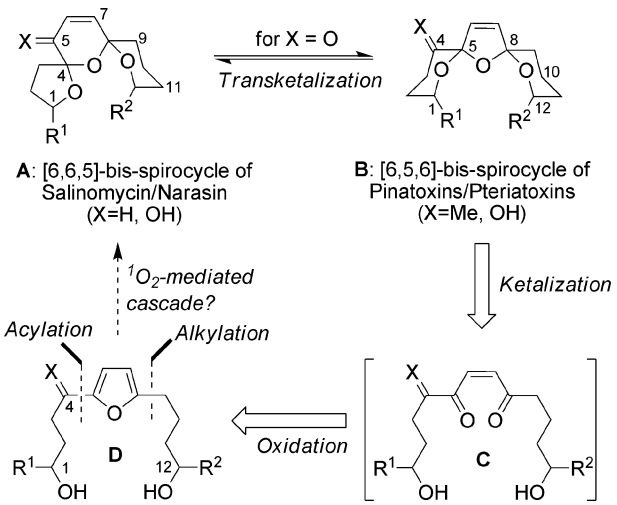
Singlet oxygen ($^1O_2$) proves to be a powerful tool in mediating the one-pot synthesis of a salinomycin-type [6,6,5]-bis-spiroketal unit starting from a suitably substituted furan nucleus.

Introduction

Bis-spiroketal motifs are found frequently in natural products originating from a host of sources. Structurally, we see that different biological sources produce spiroketals with subtle, but possibly interlinked, differences. These subtleties have profound implications for chemists striving to synthesise these biologically important and architecturally complex molecules. For example, if we examine and compare the bis-spiroketal unit present in two terrestrially derived ionophore antibiotics, salinomycin[1] and narasin,[2] with their marine counterparts, best exemplified by the pinnatoxins[3] and pteriatoxins,[4] we can reasonably propose that an oxidation level adjustment (at C-4 and C-5), combined with a simple transketalisation event, might effect interconversion of the two core structures (**A** ↔ **B**, Scheme 1). The most important corollary of this hypothesis is that a single precursor might give rise to two, apparently quite different, bis-spiroketal fragments. This postulate has informed our approach to the synthesis of these molecules.



Scheme 1 Retrosynthetic options and concepts for the [6,6,5]-bis-spirocycle **A** and the [6,5,6]-bis-spirocycle **B**.

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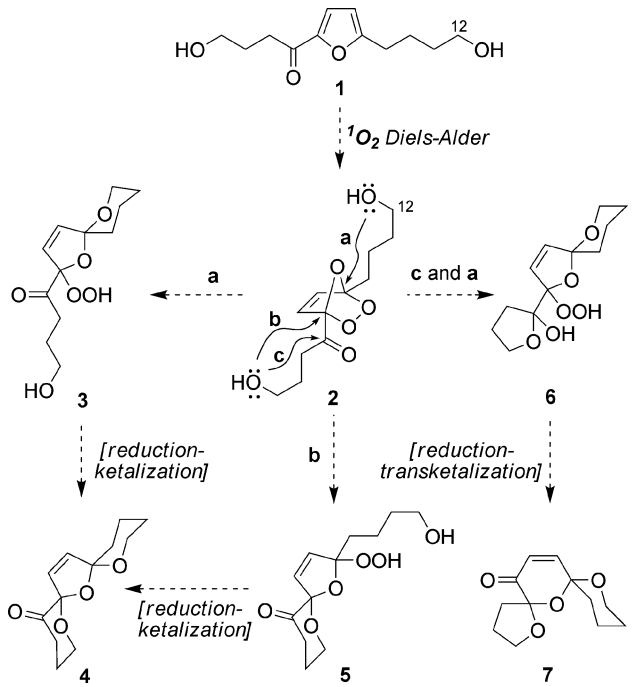
The majority of methods reported in the literature for bis-spiroketal synthesis target a linear precursor of type **C** (Scheme 1), which is, in general, assembled and cyclised using multiple independent steps.[5] Amongst the other reported approaches,[5] the oxidation of furans (employing Br_2,[6] NBS,[7] or electrochemical methods[8]) would appear to be particularly attractive, since this strategy offers the opportunity to use a cascade reaction sequence to yield the desired bis-spiroketal motifs by a one-pot procedure.[7b–d,8] Indeed, an NBS-mediated oxidation/bis-spiroketal formation of this type is at the heart of Kocieński's elegant total synthesis of salinomycin.[7b,c] Our experience in using singlet oxygen ($^1O_2$) as a powerful tool, with which cascade reaction sequences that transform furan-bearing precursors into important highly oxygenated motifs[9] (particularly spirocycles[10]) can be initiated, led us recently to investigate its use in the synthesis of bis-spiroketal units.[11] In this preliminary study, minimally functionalised furyl substrates were successfully zipped up to yield either [5,5,5]- or [6,5,6]-bis-spiroketal units upon treatment with $^1O_2$ followed by mild acid, through a domino reaction sequence in which the linear precursor of type **C** was replaced by an endoperoxide (similar to **2**, Scheme 2). However, before we could consider using such a sequence in the synthesis of bis-spiroketal-bearing natural products, the ramifications of including other functionality had to be deconvoluted, for it was far from clear how the complex reaction cascade would respond to such substrates. Of particular interest was the effect of introducing a new electrophilic centre, in the form of a furylic carbonyl group, as inclusion of this moiety would allow us to probe the aforementioned [6,6,5]-/[6,5,6]-bis-spiroketal equilibrium. Herein, we report the outcome of an investigation in which the desired [6,6,5]-bis-spiroketal motif was finally accessed from a substrate bearing a furylic carbonyl moiety, through a one-pot cascade reaction sequence, despite the fact that two competing fragmentation process were also uncovered.

Results and discussion

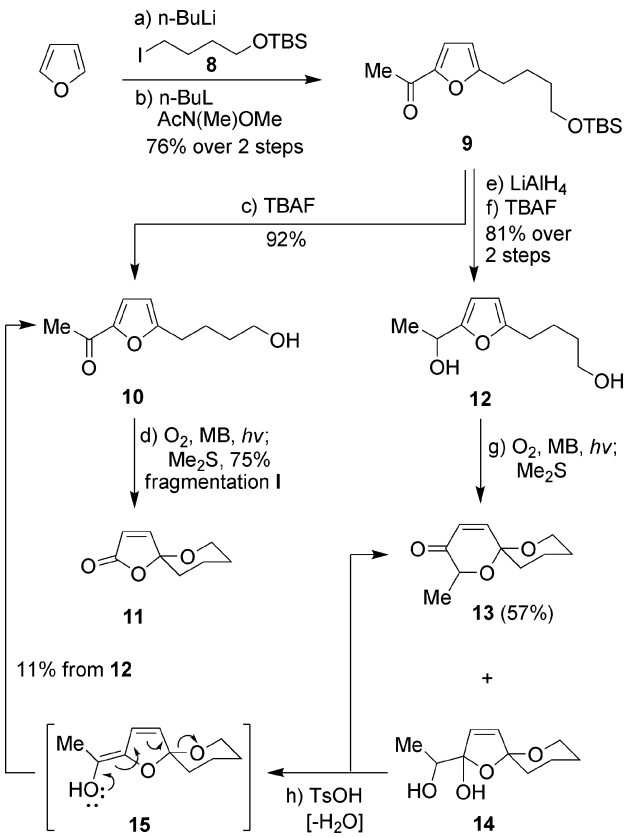
At the outset of our investigation we deemed that the first task must be to assess whether the naked unprotected substrate, bearing the desired furylic carbonyl functionality, could be induced to participate in the previously designed cascade reaction sequence without recourse to any oxygen functionality protection. Several different fates could be envisioned for even the simplest substate, furan **1** (Scheme 2), and which one of these pathways would dominate was an important question requiring an answer. If the endoperoxide **2**, obtained from furan **1**, followed the pattern set



Scheme 2 Possible nucleophilic openings of the transient endoperoxide **2**.

in the simple substrates which we had previously investigated,[11] one of the pendant alcohols would attack the endoperoxide, giving either hydroperoxide **3** or **5** (by pathway **a** or **b**, Scheme 2). It is hard on paper to assess which pathway might dominate, since pathway **b** is likely to be favoured stereochemically due to the Thorpe–Ingold-type effect exerted by the furylic carbonyl group, whilst, on the other hand, pathway **a** would be electronically favoured because pathway **b** suffers from having an electron-withdrawing substituent attached to the carbon on which a positive charge must develop in the transition state. It was anticipated that hydroperoxides **3** and **5** would both be readily reduced upon treatment with dimethyl sulfide to afford the corresponding labile hemiketals. In turn, these intermediates might cyclise to yield the desired bis-spiroketal **4**, on contact with traces of acid. The synthesis of the pinnatoxin and pteriatoxin families requires access to bis-spiroketal **4**. However, we postulated that endoperoxide **2** could also succumb to an entirely different fate. On losing the stabilising influence of the furan ring, the carbonyl would become more electrophilic, and, therefore, susceptible to attack from the hydroxyl most proximal to it (pathway **c**). With this hydroxyl now tied up as a hemiketal, the remaining C-12 hydroxyl is left to open up the endoperoxide **2** (pathway **a**), thus furnishing hydroperoxide **6**. If hydroperoxide **6** were then to be subjected to the established reduction and ketalisation conditions, it is reasonable to suggest that it may rearrange to afford bis-spiroketal **7**, or, in other words, the bis-spiroketal motif required for the synthesis of salinomycin.

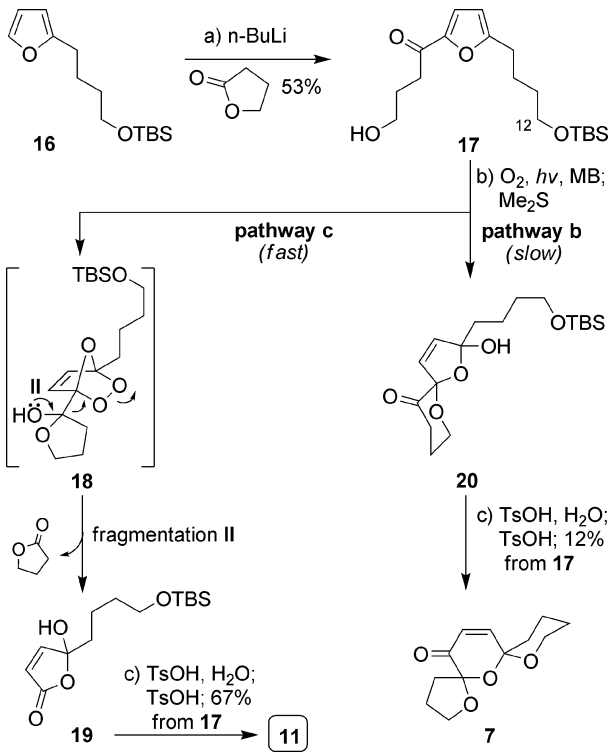
In order to begin delineating which pathway would dominate upon inclusion of a furylic carbonyl in the oxidation substrate, furan **10** was rapidly synthesised using a series of standard reactions (3 steps, overall yield 70%). This model compound was then subjected to our recently established $^1O_2$ cascade reaction sequence conditions,[11] namely 10^{-4} M Methylene Blue as sensitizer, with O_2 bubbling through the reaction solution and exposure to visible light (Scheme 3). Unfortunately, the major product isolated from this reaction was lactone **11** (75% yield), formed by fragmentation of the intermediate hydroperoxide (fragmentation **I**). A mechanistically similar fragmentation, occurring when a furylic aldehyde was included in an oxidation precursor, has been reported.[12] In an attempt to circumvent this undesirable outcome, the furylic carbonyl of furan **9** was reduced to the corresponding alcohol using $LiAlH_4$. Following a TBAF-mediated desilylation, a new oxidation substrate **12** was obtained (81% two steps). When furan **12** was subjected to the $^1O_2$ cascade reaction conditions, we were gratified to see that the major product was the salinomycin-type spiroketal **13** (formed as a 5 : 1 mixture of anomers) accompanied by spiroketal **14** (**13** : **14** ≈ 2 : 1). When this crude reaction mixture was treated with mild acid, spiroketal **14** was transformed to the desired lactone **13** and furanone **10** (1 : 1). The total yield after column chromatographic purification was 57% for **13** and 11% for **10**.



Scheme 3 Successful one-pot formation of the [6,5,6]-bis-spiroketal **13** from dihydroxyfuran **12**.

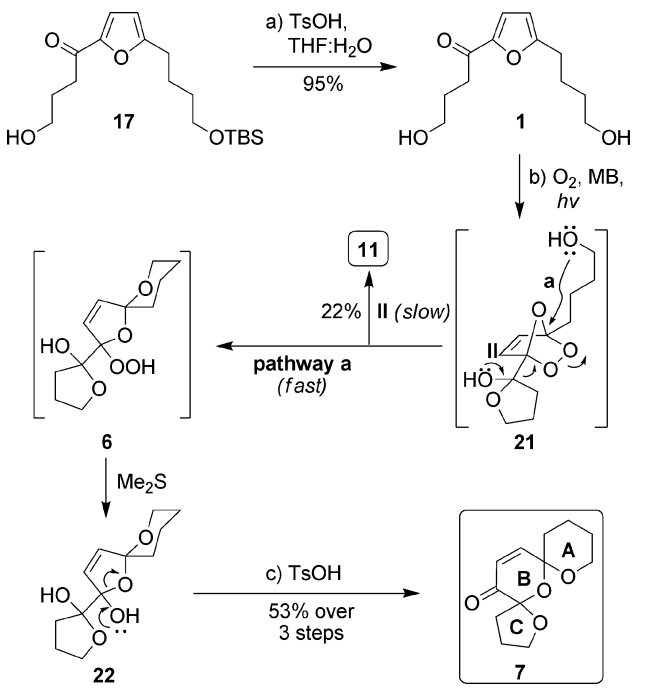
Encouraged by this positive result, we next sought to examine a fully functionalised system from which the desired bis-spiroketal might be derived. We reasoned that it would not be necessary to take the extra protective step of reducing the furylic carbonyl if the hydroperoxide functionality of the intermediate, formed upon opening of the endoperoxide, could be generated regioselectively at the position most distal to the carbonyl group (akin to hydroperoxide **5** rather than hydroperoxide **3**, Scheme 2). Practically, this result could be achieved by selectively protecting the appropriate hydroxyl group, thereby blocking a pathway-**a**-type

attack on the endoperoxide **2** (Scheme 2). Once the hydroperoxide placement had been acheived, the resulting intermediate **5** would not be susceptible to decomposition by a type-**I** fragmentation mechanism. To this end, furan **17** was synthesised in short order by acylation of the anion of furan **16**[11] with butyrolactone (yield 53%, Scheme 4).[7a] Furan **17** was then subjected to the established $^1O_2$ reaction conditions, followed by reduction with Me_2S, but, instead of exclusively forming the desired hemiketal **20**, the major product of this reaction was 4-hydroxybutenolide **19**, presumably formed by the loss of butyrolactone from intermediate endoperoxide **18** (type-**II** fragmentation[13]). Treatment of the mixture of **19** and **20** with *p*-TsOH, first in the presence of water (-OTBS deprotection) and then in its absence (ketalization), furnished lactone **11** in an overall yield of 67%, accompanied by the desired bis-spiroketal **7**, albeit in low yield (12%).



Scheme 4 Obtaining spirolactone **7** from furan **17** provides us with the missing pieces of the jigsaw puzzle.

Despite the disappointing identification of a new and unwanted fragmentation process, the results of this reaction were highly didactic and pleasing. Since pathway **a** was blocked by the TBS protection of the C-12 hydroxyl group, the only means by which furan **17** could have given rise to bis-spiroketal **7** was through the intermediacy of a hydroperoxide analogous to **5** (by pathway **b**, Scheme 2), thus validating certain aspects of our original retrosynthetic proposal. However, no evidence of bis-spiroketal **4** was seen, suggesting that although the equilibrium between the pinnatoxin/pteriatoxin core and the salinomycin core does indeed exist, it strongly favours the latter structure under these conditions. Perhaps most crucially, the reaction sequence also revealed that pathway **c** is faster than pathway **b**, so that in the fully functionalised systems there will always be a natural and in-built protection against fragmentation **I**. It was, therefore, unnecessary to expend any effort in trying to place the hydroperoxide moiety using selective hydroxyl protection. Indeed, we now felt confident that by utilising a complete and unprotected substrate we might be able to synthesise the desired salinomycin core precursor in one-pot, as originally hoped, using this beautiful $^1O_2$-mediated cascade sequence, the only caveat being that the rate of the pathway **a** reaction must be faster than the undesired type-**II** fragmentation (Schemes 2 and 4). If successful, this final investigation would not only synthesise the sought-after [5,6,6]-bis-spiroketal unit in a most efficient and elegant manner, but it would also complete the deciphering of the relative rates of all the competing pathways open to initially formed endoperoxide intermediate **2** (Scheme 2). Anxious to test the final hypothesis, furan **1** was rapidly synthesised by deprotecting furan **17** (TsOH, THF–H_2O, 95%, Scheme 5). Furan **1** was then subjected to the tandem reaction sequence conditions and we were gratified to observe the formation of the desired bis-spiroketal **7** (as a separable 2 : 1 mixture of anomers) and in 53% overall yield. The major anomer was identified as being the *cis*-[5,6,6]-bis-spiroketal after a conclusive NOE was seen between one of the two C-3 protons and one of the C-9 protons (in the other anomer no such NOE was observed). Further retrospective study of the cascade sequence allowed us to isolate and fully characterise the hemiketal product **22** (as the predicted mixture of 4 diastereoisomers, but with one diastereomer dominating as seen by ^{13}C NMR) of the reduction step, thus confirming its intermediacy in this multifaceted transformation of **1** → **7**. The isolation of 22% of lactone **11** from this reaction proved that, although pathway **a** dominated just as we had anticipated, type-**II** fragmentation was still a reaction competing with the desired alternative, albeit at a more minor level.



Scheme 5 Successful one-pot formation of the [6,6,5]-bis-spiroketal motif **7** from unprotected furan **1**.

Conclusions

A cascade sequence orchestrated by singlet oxygen was successfully employed to transform the simple furan **1**, bearing a furylic ketone, into the desired [5,6,6]-bis-spiroketal **7** in high yield and one-pot, and despite the fact that two competing fragmentation pathways were unveiled during the investigation.

Experimental

tert-Butyl(dimethyl)silyl 4-(2-furyl)butyl ether (16)

A solution of furan (300 mg, 4.4 mmol) in anhydrous THF (2 mL) was added dropwise to a solution of *n*-BuLi (3.14 mL of a 1.4 M solution in hexane, 4.4 mmol) in anhydrous THF (2 mL) at −25 °C. After 4 h at −15 °C, a solution of iodide **8**[14] (690 mg, 2.2 mmol) in anhydrous THF (3 mL) was added dropwise and the reaction mixture stirred for 1 h at −15 °C. The reaction was warmed to room temperature and stirred for a further 4 h, after which it was partitioned between Et_2O (15 mL) and H_2O (15 mL). The layers were separated and the organic layer was washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*.The residue was purified by column chromatography (silica gel, hexane–EtOAc = 20 : 1) to afford the desired monosubstitued furan **16** (505 mg, 90%). **16**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, J = 1.7 Hz, 1H), 6.28 (dd, J_1 = 2.9 Hz, J_2 = 1.7 Hz, 1H), 5.98 (d, J = 2.9 Hz, 1H), 3.63 (t, J = 6.5 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 1.69 (m, 2H), 1.57 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.3, 140.7, 110.0, 104.7, 62.8, 32.3, 27.7, 25.9 (3C), 24.4, 18.3, −5.3 (2C) ppm; HRMS(TOF ES+): calcd for $C_{14}H_{26}O_2NaSi$: 277.1600 [M + Na]$^+$; found: 277.1591.

1-[5-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}butyl)-2-furyl]-1-ethanone (9)

A soluition of *n*-BuLi (2.13 mL of 1.4 M solution in hexane, 2.98 mmol) was added dropwise to a solution of monosubstituted furan **16** (505 mg, 1.99 mmol) in anhydrous THF (7 mL) at 0 °C. After 20 min stirring at the same temperature, a solution of *N*-methoxy-*N*-methylacetamide (307 mg, 2.98 mmol) in anhydrous THF (5 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for a further 3 h, after which it was partitioned between Et_2O (15 mL) and NH_4Cl (15 mL). The layers were separated and the organic layer was washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane–EtOAc = 20 : 1 → 10 : 1) to afford the desired methyl furylketone **9** (490 mg, 84%). **9**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 (d, J = 3.5 Hz, 1H), 6.16 (d, J = 3.5 Hz, 1H), 3.62 (t, J = 6.2 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.42 (s, 3H), 1.74 (m, 2H), 1.56 (m, 2H), 0.89 (s, 9H), 0.03 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.0, 161.8, 151.4, 119.0, 108.1, 62.6, 32.1, 28.0, 25.9 (3C), 25.6, 24.1, 18.3, −5.4 (2C) ppm; HRMS (TOF ES+): calcd for $C_{16}H_{29}O_3Si$: 297.1886 [M + H]$^+$; found: 297.1896.

1-[5-(4-Hydroxybutyl)-2-furyl]-1-ethanone (10)

A solution of TBAF (920 μL of a 1.0 M solution in THF, 0.92 mmol) was added dropwise to a solution of TBS-protected hydroxyfuran **9** (179 mg, 0.60 mmol) in anhydrous THF (8 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 3 h, after which it was partitioned between EtOAc (10 mL) and H_2O (10 mL). The layers were separated and the organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane–EtOAc = 3 : 1 → 1 : 1 → 1 : 2) to afford hydroxyfuran **10** (100 mg, 92%). **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (d, J = 3.3 Hz, 1H), 6.16 (d, J = 3.3 Hz, 1H), 3.64 (t, J = 6.3 Hz, 2H), 2.86 (brs, 1-OH), 2.71 (t, J = 7.5 Hz, 2H), 2.40 (s, 3H), 1.77 (m, 2H), 1.65 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.1, 161.8, 151.3, 119.3, 108.1, 61.9, 31.9, 28.0, 25.5, 23.9 ppm; HRMS (ESI+): calcd for $C_{10}H_{14}O_3Na$ [M + Na$^+$]: 205.0835, found: 205.0835.

1,6-Dioxaspiro[4.5]dec-3-en-2-one (11)

Hydroxyfuran **10** (25 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (5 mL) containing a catalytic amount (10^{-4} M) of Methylene Blue. The solution was cooled to 0 °C. Oxygen was gently bubbled through the solution while it was irradiated with a xenon Variac Eimac Cermax 300 W lamp for 8 min. An excess of dimethyl sulfide was added and the solution was warmed to room temperature and stirred for a further 12 h. The solvent was removed *in vacuo* and the residue passed through a short pad of silica (hexane–EtOAc = 6 : 1 → 4 : 1) to afford **11** (16 mg, 75%). **11**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12 (d, J = 5.6 Hz, 1H), 6.09 (d, J = 5.6 Hz, 1H), 4.02 (dt, J_1 = 11.4 Hz, J_2 = 3.3 Hz, 1H), 3.91 (dd, J_1 = 11.4 Hz, J_2 = 4.7 Hz, 1H), 1.95 (m, 1H), 1.85 (m, 2H), 1.70 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.5, 154.2, 123.0, 106.8, 65.0, 32.1, 24.0, 19.0 ppm; HRMS (ESI+): calcd for $C_{16}H_{28}O_6$ [2M + Na$^+$]: 331.1152, found: 331.1148.

4-[5-(1-Hydroxyethyl)-2-furyl]-1-butanol (12)

$LiAlH_4$ (58 mg, 1.52 mmol) was added to a solution of ketone **9** (226 mg, 0.76 mmol) in anhydrous Et_2O (10 mL) under an argon atmosphere at 0 °C. The reaction was then warmed to room temperature and stirred for 30 min, after which it was partitioned between EtOAc (10 mL) and a saturated solution of sodium potassium tartate (10 mL). The layers were separated and the organic phase dried (Na_2SO_4) and concentrated *in vacuo* to afford the corresponding hydroxyfuran (215 mg, 95%). To a solution of this TBS-protected hydroxyfuran (215 mg, 0.72 mmol) in anhydrous THF (10 mL) at 0 °C, TBAF (870 μL of 1.0 M solution in THF, 0.87 mmol) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 2 h, after which it was partitioned between EtOAc (10 mL) and brine (10 mL). The layers were separated, and the organic phase was dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane–EtOAc = 1 : 1 + Et_3N) to afford hydroxyfuran **12** (113 mg, 85%). **12**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.08 (d, J = 3.0 Hz, 1H), 5.90 (d, J = 3.0 Hz, 1H), 4.80 (q, J = 6.5 Hz, 1H), 3.62 (t, J = 6.5 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 2.03 (brs, 1-OH), 1.72 (m, 2H), 1.67 (brs, 1-OH), 1.60 (m, 2H), 1.50 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.8, 155.5, 105.7, 105.4, 63.5, 62.4, 32.1, 27.7, 24.2, 21.1 ppm.

2-Methyl-1,7-dioxaspiro[5.5]undec-4-en-3-one (13)

Hydroxyfuran **12** (50 mg, 0.27 mmol) was dissolved in CH_2Cl_2 (5 mL) containing a catalytic amount (10^{-4} M) of Methylene Blue. The solution was cooled to 0 °C. Oxygen was bubbled gently through the solution while it was irradiated with light from a xenon Variac Eimac Cermax 300 W lamp for 2 min. An excess of dimethyl sulfide (50 μL) was added and the solution was warmed to room temperature, after which it was stirred for a further 17 h. The solvent was removed *in vacuo* and the residue passed through a short pad of silica (hexane–EtOAc = 1 : 2) to afford a mixture of **13** and **14**. To a solution of **13** and **14** in CH_2Cl_2 (5 mL) at room temperature was added catalytic amounts of *p*-TsOH (5 mg). The reaction mixture was stirred for 12 h, after which it was partitioned between CH_2Cl_2 (5 mL) and $NaHCO_3$ (5 mL). The layers were separated and the organic phase was washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford **13** (28 mg, 57%) as a 5 : 1 mixture of diastereoisomers, and **10** (5 mg, 11%). **13**: ^{1}H NMR (500 MHz, $CDCl_3$, major): $\delta = 6.67$ (d, $J = 10.1$ Hz, 1H), 6.00 (d, $J = 10.1$ Hz, 1H), 4.46 (q, $J = 6.8$ Hz, 1H), 3.79 (m, 2H), 1.91 (m, 2H), 1.67 (m, 4H), 1.40 (d, $J = 6.8$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 176.6$, 148.4, 126.8, 93.2, 70.0, 62.6, 34.3, 24.7, 17.8, 15.3 ppm; HRMS (ESI+): calcd for $C_{10}H_{14}O_3Na$ [M + Na^+]: 205.0835, found: 205.0835.

1-[5-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}butyl)-2-furyl]-4-hydroxy-1-butanone (17)

n-BuLi (787 μL of a 1.5 M solution in hexane, 1.18 mmol) was added dropwise to a solution of **16** (200 mg, 0.79 mmol) and TMEDA (238 μL, 1.57 mmol) in anhydrous THF (4 mL) at −15 °C. After 5 min at 0 °C, the mixture was added dropwise to a solution of butyrolactone (90 μL, 1.18 mmol) in anhydrous THF (2 mL) at −15 °C and the reaction mixture stirred for a further 2 h at −15 °C, after which it was quenched with MeOH at the same temperature. The reaction mixture was partitioned between Et_2O (10 mL) and NH_4Cl (10 mL). The layers were separated, and the organic layer was washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane–EtOAc = 5 : 1 → 4 : 1 → 3 : 1 → 2 : 1 → 1 : 1) to afford **17** (142 mg, 53%). **17**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.12$ (d, $J = 3.3$ Hz, 1H), 6.15 (d, $J = 3.3$ Hz, 1H), 3.69 (t, $J = 6.1$ Hz, 2H), 3.61 (t, $J = 6.1$ Hz, 2H), 2.90 (t, $J = 7.2$ Hz, 2H), 2.70 (t, $J = 7.5$ Hz, 2H), 2.22 (brs, 1-OH), 1.95 (m, 2H), 1.73 (m, 2H), 1.55 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 188.8$, 161.7, 151.1, 118.8, 107.9, 62.4, 62.0, 34.6, 31.9, 27.9, 26.9, 25.7 (3C), 23.9, 18.1, −5.6 (2C) ppm; HRMS (ESI+): calcd for $C_{18}H_{32}O_4NaSi$ [M + Na^+]: 363.1962, found: 363.1962.

4-Hydroxy-1-[5-(4-hydroxybutyl)-2-furyl]-1-butanone (1)

A catalytic amount of *p*-TsOH was added to a solution of **17** (116 mg, 0.34 mmol) in THF–H_2O (20 : 1) at room temperature. The reaction mixture was stirred for 3.5 h, after which it was partitioned between EtOAc (10 mL) and $NaHCO_3$ (10 mL). The layers were separated and the organic phase was washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford the desired diol **1** (73 mg, 95%). **1**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.12$ (d, $J = 3.6$ Hz, 1H), 6.15 (d, $J = 3.6$ Hz, 1H), 3.67 (t, $J = 5.8$ Hz, 2H), 3.64 (t, $J = 5.8$ Hz, 2H), 2.89 (t, $J = 7.0$ Hz, 2H), 2.71 (t, $J = 7.3$ Hz, 2H), 2.36 (brs, 2-OH), 1.94 (m, 2H), 1.76 (m, 2H), 1.61 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 189.1$, 161.7, 151.3, 119.1, 108.3, 62.2, 62.1, 34.8, 32.0, 28.0, 27.2, 24.0 ppm; HRMS (ESI+): calcd for $C_{12}H_{18}O_4Na$ [M + Na^+]: 249.1097, found: 249.1100.

2-(2-Hydroperoxy-1,6-dioxaspiro[4.5]dec-3-en-2-yl)tetrahydro-2-furanol (22)

Diol **1** (50 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (5 mL) containing a catalytic amount (10^{-4} M) of Methylene Blue. The solution was cooled to 0 °C. Oxygen was bubbled gently through the solution while it was irradiated with light from a xenon Variac Eimac Cermax 300 W lamp for 5 min. An excess of dimethyl sufide was added (100 μL) and the solution was warmed to room temperature, after which it was stirred for a further 12 h. The solvent was removed *in vacuo* and the residue passed through a short pad of silica (hexane–EtOAc = 2 : 1 → 1 : 1 → 1 : 2) to afford **22** (36 mg, 68%) as a mixture of 4 diastereoisomers and **11** (7 mg, 22%). **22**: ^{1}H NMR (500 MHz, $CDCl_3$, major): $\delta = 6.04$ (d, $J = 5.3$ Hz, 1H), 5.95 (d, $J = 5.3$ Hz, 1H), 3.95 (m, 3H), 3.80 (m, 2H), 2.14 (m, 2H), 1.95 (m, 4H), 1.75 (m, 2H), 1.60 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, major): $\delta = 135.9$, 130.2, 111.4, 110.3, 105.2, 68.8, 63.8, 34.5, 33.2, 24.8, 24.5, 19.0 ppm; HRMS (ESI+): calcd for $C_{12}H_{18}O_5Na$ [M + Na^+]: 265.1046, found: 265.1049.

1,6,8-Trioxadispiro[4.1.5.3]pentadec-13-en-15-one (7)

A catalytic amount of *p*-TsOH (5 mg) was added to a solution of **22** (36 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was stirred for 30 min, after which it was partitioned between CH_2Cl_2 (5 mL) and $NaHCO_3$ (5 mL). The layers were separated, and the organic phase was washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford **7** (26 mg, 78%) as a mixture of two stereoisomers in a 2 : 1 ratio. The isomers were separated by flash column chromatography (silica gel, hexane–EtOAc = 10 : 1 → 5 : 1 → 2 : 1). *Trans* isomer: ^{1}H NMR (500 MHz, C_6D_6): $\delta = 6.30$ (d, $J = 10.4$ Hz, 1H), 5.88 (d, $J = 10.4$ Hz, 1H), 3.95 (m, 1H), 3.75 (m, 1H), 3.66 (q, $J = 7.3$ Hz, 1H), 3.54 (m, 1H), 2.53 (td, $J_1 = 12.8$ Hz, $J_2 = 8.5$ Hz, 1H), 2.14 (brd, $J = 12.8$ Hz, 1H), 1.91 (ddd, $J_1 = 12.8$ Hz, $J_2 = 7.9$ Hz, $J_3 = 5.0$ Hz, 1H), 1.73 (m, 2H), 1.60 (m, 1H), 1.40–1.28 (m, 3H), 1.14 (m, 1H) ppm; ^{13}C NMR (125 MHz, C_6D_6): $\delta = 190.2$, 149.9, 125.9, 105.9, 95.3, 69.8, 61.6, 35.1, 34.9, 25.3, 25.0, 18.9 ppm; HRMS (ESI+): calcd for $C_{12}H_{16}O_4Na$ [M + Na^+]: 247.0941, found: 247.0942. *Cis* isomer: ^{1}H NMR (500 MHz, C_6D_6,): $\delta = 6.22$ (d, $J = 10.5$ Hz, 1H), 5.90 (d, $J = 10.5$ Hz, 1H), 3.87 (m, 2H), 3.72 (m, 1H), 3.61 (m, 1H), 2.66 (td, $J_1 = 12.6$ Hz, $J_2 = 8.3$ Hz, 1H), 1.81 (m, 2H), 1.74 (m, 1H), 1.65 (m, 1H), 1.44 (brd, $J = 12.6$ Hz, 1H), 1.34 (m, 2H), 1.23 (dt, $J_1 = 13.1$ Hz, $J_2 = 4.3$ Hz, 1H), 1.18 (m, 2H) ppm; ^{13}C NMR (125 MHz, C_6D_6): $\delta = 190.5$, 148.7, 125.7, 105.0, 93.5, 70.3, 61.6, 35.8, 34.8, 25.5, 25.1, 18.3 ppm; HRMS (ESI+): calcd for $C_{12}H_{16}O_4Na$ [M + Na^+]: 247.0941, found: 247.0942.

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