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EMERGING AREA

Green oxidations of furans—initiated by molecular oxygen—that give key natural product motifs

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In this article, we explore how changes in the positioning of pendant hydroxyl functionalities in the photooxygenation substrate dramatically alter the course of furan oxidations that are initiated by singlet oxygen; and, how these different reactivities can be harnessed through cascade reaction sequences to access, rapidly and effectively, a broad range of important natural product motifs.

Introduction

Not only is the furan nucleus commonly found in isolates from nature, but so are the many and varied products of its oxidation. It was this simple observation, combined with the knowledge that singlet oxygen (a remarkable, under-exploited, green, and atom-economic oxidant) might be able to affect the desired transformations, that originally spurred us to pursue the development of a set of new synthetic methods involving some ambitious cascade reaction sequences. The synthetic strategies that we have since deconvoluted and applied, have allowed us to rapidly and efficiently convert furan nuclei into a broad range of highly complex polyoxygenated scaffolds, and have, thereby, given us easy access to a host of bioactive natural products or key natural product motifs.

The reactivity of furans with the first excited state of molecular oxygen, known as singlet oxygen, was unearthed in 1967, in findings emanating from the pioneering groups of Professors Foote and Schenck.[1] Thus, reaction of singlet oxygen ($^1O_2$) with simple furans leads to the initial formation of an unstable ozonide (**2**, Scheme 1), which might then be the substrate for nucleophilic opening by MeOH to yield hydroperoxide **3** (only one of the two possible regioisomers is shown). Reduction of this hydroperoxide to the corresponding lactol **4** initiates elimination of MeOH and formation of the 1,4-enedione **5**. Alternatively, reaction of the fleeting ozonide **2** with a reducing agent (PPh_3 or Me_2S), at low temperatures, affords the same 1,4-enedione **5** *via* intermediate **6** (Scheme 1).[1,2]

It is this fundamental reactivity, albeit tempered, adjusted and manipulated, that we have repeatedly harnessed to be at the heart of carefully designed cascade reaction sequences targeting so many different, and, seemingly unrelated, polyoxygenated natural product motifs. In this article, the story is told of how this work began, of how it evolved, and, ultimately, of how with these emerging novel methods we provided some minor contributions towards achieving the synthetic chemist's Holy Grail; namely, attaining rapid increases in molecular complexity using efficient

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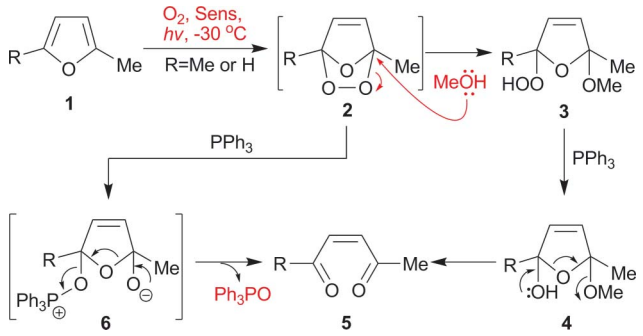
and gentle methods with low environmental impact and wide applicability.



Scheme 1 Photooxidations of simple furans.

Why use singlet oxygen?

Before we move onto specifics, it's worth briefly introducing singlet oxygen because it is a powerful reagent that has traditionally been under-exploited. Indeed, it is only recently that a significant body of work has emerged which has sought to extend the influence of this powerful oxidant into the cutting-edge realms of synthetic organic chemistry; previously, singlet oxygen was studied mostly in an attempt to understand fully its reactivity and kinetics. Much less attention was devoted to exploiting it in synthetic sequences. This fact is strange because singlet oxygen is endowed with a set of characteristics that clearly give it such potential in this arena. Firstly, it's generation is simple and cheap; trace quantities of a sensitizer (*e.g.* rose bengal, methylene blue, porphyrins, fullerenes *etc.*) are added to a reaction solution through which oxygen (or even air) is bubbled, a visible spectrum light source is then briefly applied and the subsequent reaction monitored using conventional means. Furthermore, these procedures in which oxygen from the air is excited to transiently generate singlet oxygen *in situ* are green, clean, and highly atom economic. Many standard laboratory oxidants use toxic heavy metals or reagents that require their own laborious synthesis. In contrast, when using singlet oxygen there is no waste either in terms of its generation (see above), or in its application wherein both oxygen atoms are transferred and incorporated into the oxidation substrate. Its environmental credentials are further fortified by the fact that singlet oxygen can be used in a range of solvents including water (although the nature of the substrates being investigated often deems this most environmentally benign of options untenable). It is also a highly specific oxidant unlike so many others in common use, which means that the need for protecting groups is essentially eliminated. Finally, as our work has proved, singlet oxygen's reactivity patterns (once properly deconvoluted with the relative rates of each reaction mode fully appreciated and understood) can be harnessed such that singlet oxygen becomes an invaluable collaborator in the orchestration of complex cascade reaction sequences. With the information now accumulated, these cascade reaction sequences can easily be designed to include more than one mode of $^1O_2$ reactivity; thus, simple and readily accessible substrates can be transformed with remarkable ease into complex polyoxygenated scaffolds.

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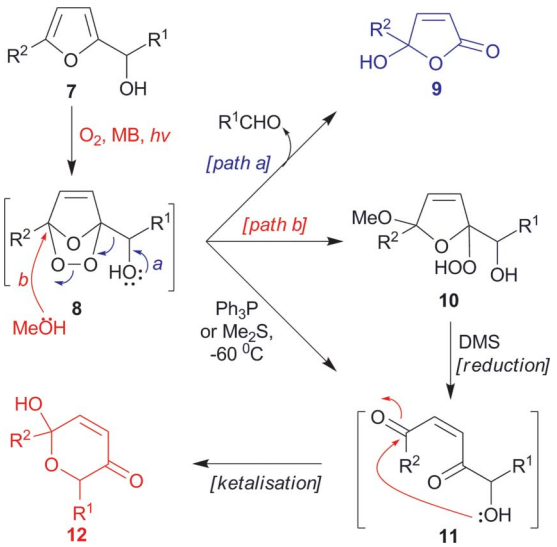
Singlet oxygen reactions of furans containing hydroxyl(s) only on the 2-alkyl substituent

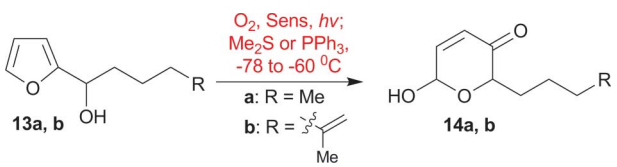
Photooxidation of 2-(α-hydroxyalkyl) furans in MeOH

It is well known that, with multifarious advantages and disadvantages to each discrete method, 2-(α-hydroxyalkyl) furans can be oxidised to afford the corresponding 6-hydroxy-3(2*H*)-pyranones (**7** → **12**, Scheme 2) under a variety of conditions including; Br_2/MeOH,[3] peracids (*e.g.* *m*-CPBA,[4] magnesium monoperoxyphthalate[5]), NBS,[6] dioxiranes (DMDO[7]), metal based oxidations (PCC,[8] $VO(acac)_2$/*t*-BuOOH,[9] titanium(IV) silicalite 1/H_2O_2[10]), as well as electrochemical oxidation.[11]



Scheme 2 Photooxidation of 2-(α-hydroxyalkyl) furans.

Harking back to the initial key findings regarding the reactivity of simple furans with singlet oxygen,[1] it was very reasonable to assume that 6-hydroxy-3(2*H*)-pyranone **12** (Scheme 2) might be the final product of the $^1O_2$ photooxidation of 2-(α-hydroxyalkyl) furans of type **7** *via* intermediate formation of enedione **11**. There exists, however, a competing fragmentation pathway (see path **a**, Scheme 2).[12] Indeed, $^1O_2$ photooxidation of 2-(α-hydroxyalkyl) furans of type **7** is known to be one of the most efficient ways to synthesise the 5-hydroxy-2(5*H*)-furanone nucleus **9**[12] (*via* path **a**, Scheme 2); however, when the same photooxidations were performed at low temperature and the intermediate ozonides **8** were also reduced at low temperature by dimethyl sulfide (DMS) or PPh_3 the formation of 6-hydroxy-3(2*H*)-pyranone **12** was observed.[12,13] This adapted $^1O_2$ technology was successfully applied as one of the key steps in the synthesis of secodolastanes,[13a] cyathin,[13b] and taxane[13c] diterpene skeletons, as well as, as the key step (**13b** → **14b**, Scheme 3) in the total synthesis of cryptofauronol.[13d] In the later case the problem of the concurrent



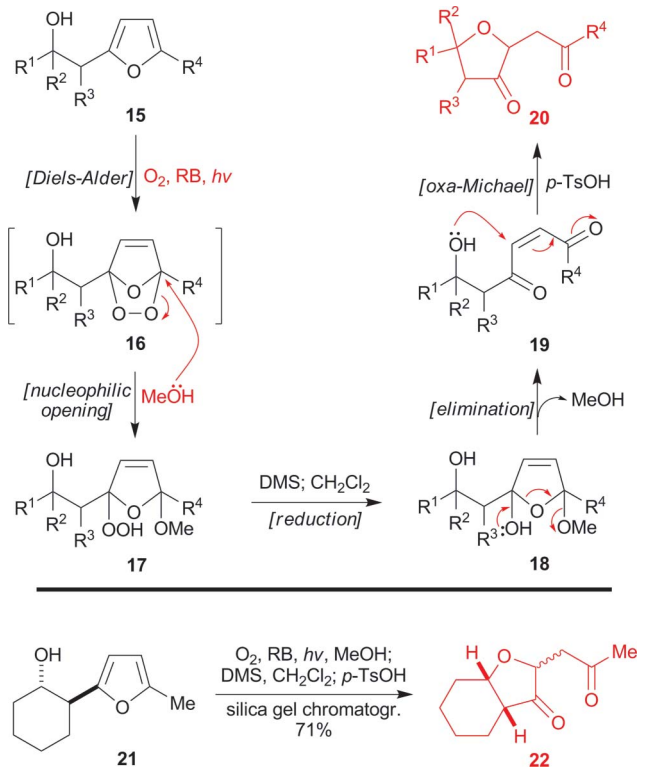
Scheme 3 Synthesis of 6-hydroxy-3(2*H*)-pyranones.

oxidation of the disubstituted double bond when either *m*-CPBA or Br_2/MeOH were used as oxidant was eliminated.[13d] Similarly, the highly chemoselective singlet oxygen-oxidation of a furan nucleus to yield the desired corresponding intermediate 1,4-enedione, in the presence of two trisubstituted double bonds on the 2-alkyl side chain, was achieved in the total synthesis of litseaverticillols.[14] Application of the literature protocols for the direct oxidation of furans to 1,4-enediones, involving treatment with either Br_2/MeOH,[3] *m*-CPBA,[4] or magnesium monoperoxyphthalate (MMPP),[5] had led to rapid bromination, or epoxidation of the side chain double bonds.

An important question arose and remained unanswered from this work, and that was: which one of the two possible paths (fragmentation **a** or intermolecular nucleophilic opening **b**, Scheme 2) would prevail if the reaction was run in a nucleophilic solvent such as MeOH at ambient temperature? In other words, there was a need to explore the scope and the limitations of the photooxygenation of 2-(α-hydroxyalkyl) furans in MeOH, in order to understand the final product distribution, (5-hydroxy-2(5*H*)-furanone of type **9** *vs.* 6-hydroxy-3(2*H*)-pyranones of type **12**). Both of these moieties are of interest because they are found in myriad biologically active natural products. A very recent study,[15] undertaken by our group, has deconvoluted this issue by clearly showing that the substitution of the starting 2-(α-hydroxyalkyl) furan **7**, at position-5 (R^2), is crucial in determining the reaction outcome, and, to a lesser extent the nature of R^1 may also play a part. Thus, when R^2 = H almost exclusive formation of the fragmentation product 4-hydroxybutenolide **9** was observed; whilst, when R^2 = alkyl formation of 6-hydroxy-3(2*H*)-pyranone **12** dominates. These results are consistent with the substituent stabilising a positive charge that develops during the nucleophilic attack of MeOH onto the intermediate ozonide **8** (Scheme 2). This stabilisation makes nucleophilic opening (path **b**) kinetically favoured in comparison to the alternative fragmentation pathway (path **a**). The same mechanistic explanation had been used previously to explain the regioselective attack of MeOH, EtOH and *i*-PrOH onto the more sterically hindered 2-position of a 2-alkylfuran endoperoxide.[2a] These results are encouraging not only because pyranone systems are motifs seen in many natural products, but also because 6-hydroxy-3(2*H*)-pyranones are extremely useful synthetic intermediates by virtue of the fact that they contain at least three reactive sites for further synthetic elaboration. In summary, the singlet oxygen-oxidation of readily accessible 2-(α-hydroxyalkyl) furans is one of the most efficient methods, and is, by far, the most environmentally friendly, for the synthesis of an important class of oxocycles, the 6-hydroxy-3(2*H*)-pyranones.

Photooxidation of 2-(β-hydroxyalkyl) furans in MeOH

Simply by modifying the photooxidation substrate from an 2-(α-hydroxyalkyl) to a 2-(β-hydroxyalkyl) furan (**15**, Scheme 4), it is possible to synthesise a completely different, but equally interesting, new set of natural product motifs. This distancing of the hydroxyl functionality away from the furan nucleus eliminates any possibility of fragmentation (path **a**, Scheme 2) and leaves nucleophilic opening of the intermediate ozonide **16** as the only remaining option (only one of the two possible nucleophilic attacks is shown since both regiochemistries ultimately give the



Scheme 4 Photooxidation of 2-(β-hydroxyalkyl) furans in MeOH.

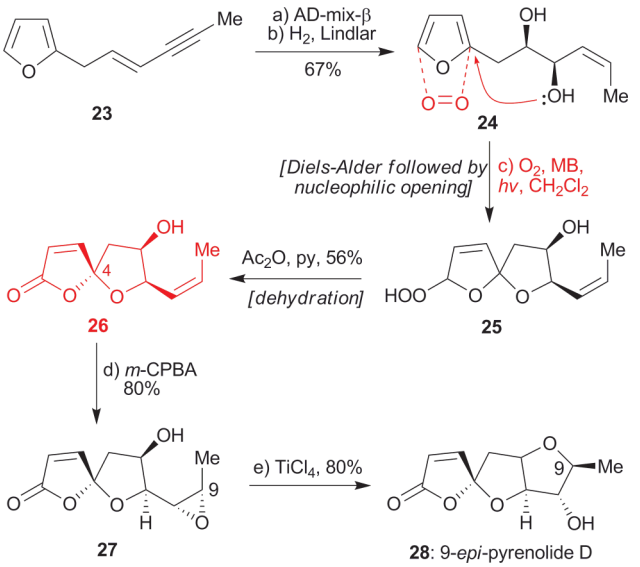
same enedione **19**, Scheme 4). More precisely, treatment of hydroperoxide **17** with a reducing agent (Me_2S or PPh_3), after MeOH has been replaced with an inert solvent, results in the formation of a 1,4-enedione of type **19**, which is in turn the subject of an intramolecular 5-*exo*-Michael addition to afford the final product, a 3-keto-tetrahydrofuran of type **20** (Scheme 4).[16] Once again, such a motif is of interest because it exists in a diverse range of natural products including the scabrolides,[17] and pectenotoxins[18] (PTXs, our work towards the PTXs is further elaborated on in a later section of this article).

The potential of this approach as a versatile method for accessing a wide variety of the 3-keto-tetrahydrofurans found in natural products is further highlighted by the one-pot synthesis of [6,5]-fused bicyclic motifs[16] of type **22** starting from a very simple and easily accessible substrate (**21**, Scheme 4). Bicyclic motifs similar to **22**, are to be found in a variety of natural products, including; (+)-phyllanthocin,[19] (+)-phyllanthocindiol,[19] (+)-phyllantoside,[20] and the phyllantostatins.[21]

Photooxidations of 2-(β,γ-dihydroxyalkyl) furans: synthesis of 9-*epi*-pyrenolide D and crassalactone D

The only difference between these photooxidation precursors and the previously described 2-(β-hydroxyalkyl) furans is the presence of an extra hydroxy group at the γ-position of the 2-alkyl side chain. How does this extra hydroxyl group change the substrates' reactivity patterns and how can we use this modification to expand the set of natural products (or natural product motifs) that can be obtained *via* singlet oxygen-mediated oxidation of simple furans?

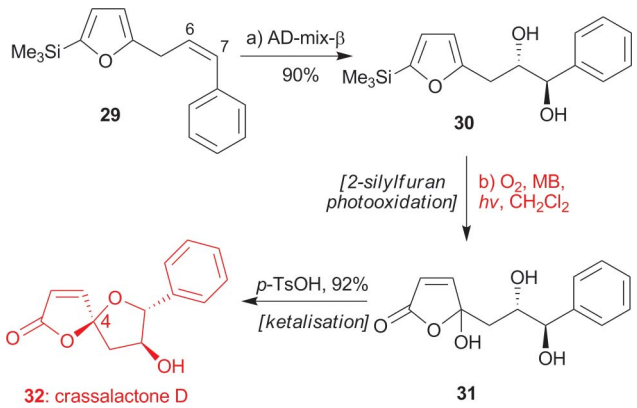
We find the answers to these questions in our work targeting the natural products pyrenolide D[22] and crassalactone D,[23] chosen as worthy targets of a synthetic project due to their potent activity against a number of human tumour cell lines. In this instance, the requisite photooxidation precursor **24** (Scheme 5) was easily prepared by *ortho*-alkylation of furan with an allylic bromide, followed by Sharpless Asymmetric Dihydroxylation (SAD),[24] and finally by Lindlar partial hydrogenation of the triple bond. The photooxidation was performed in a non-nucleophilic solvent (CH_2Cl_2), in order to promote intramolecular attack on the ozonide, as opposed to the intermolecular variant which could dominate in the presence of a nucleophilic solvent, such as, MeOH.



Scheme 5 Synthesis of 9-*epi*-pyrenolide D.

As predicted,[25] formation of spiro-hydroperoxide **25** was observed. Treatment of the crude hydroperoxides **25** with acetic anhydride in pyridine[26] gave the desired γ-spiroketal γ-lactone **26**, accompanied by 15% of its chromatographically separable 4-epimer. *m*-CPBA epoxidation of the side chain double bond, followed by a demanding 5-*endo* epoxide opening, using $TiCl_4$, afforded 9-*epi*-pyrenolide D (**28**).[27] The unexpected stereochemical scrambling resulting in the formation of the 9-epimer in the final cyclisation step is consistent with the intermediacy of a C9 carbocation at this stage.[27]

A similar synthetic strategy was designed and applied in order to achieve the synthesis of crassalactone D **32** and its 4-epimer (Scheme 6).[27] In this later case, the required C6═C7 double bond geometry was *cis* (in contrast to the *trans* geometry required in the pyrenolide D precursors). In the crassalactone D project, a further neat adaptation was employed[28] in order to promote the desired reaction progression during the photooxidation sequence; namely, a trimethylsilyl (TMS) group was introduced at the *ortho* position of the furan (see **30**, Scheme 6). This small extra modification resulted in significant improvement to the overall cascade reaction sequence yield. In this case, the photooxygenation gave rise to the 4-hydroxybutenolide **31**[28] which was then easily coaxed into ketalising to give the final product, crassalactone D (**32**) and its 4-epimer.[27] A similar synthetic protocol might easily be applied to the synthesis of the γ-spiroketal γ-lactone moiety of other



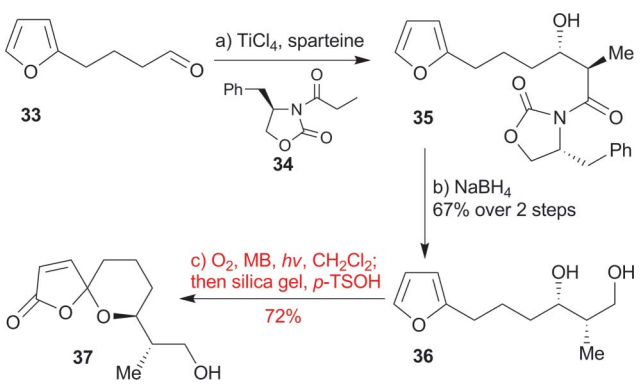
Scheme 6 Synthesis of crassalactone D.

biologically active natural products, such as, the stemoninine family.[29]

Overall, the whole procedure for the synthesis of the important γ-spiroketal γ-lactone motifs, starting with a simple furan alkylation used to begin construction of the photooxygenation substrate and proceeding through double bond asymmetric dihydroxylation to end with a singlet oxygen furan oxidation, is extremely rapid and highly efficient.

Photooxidation of 2-(δ-hydroxyalkyl) furans

The logical extension to our previous studies now becomes the investigation into what happens when you conduct the photoxygenation of a 2-(δ-hydroxyalkyl) furan; is the efficient preparation of δ-spiroketal γ-lactones possible? The answer is resoundingly affirmative and a very characteristic example is shown in Scheme 7. Homochiral 2-(δ-hydroxyalkyl) furan **36** was prepared by Evans[30] asymmetric aldol condensation between aldehyde **33** and the *N*-acyl oxazolidinone **34** assisted by sparteine and $TiCl_4$.[31] The reaction of furan **36** with photochemically generated singlet oxygen was then performed using the previously developed conditions,[27] and, subsequently, dehydration of the intermediate spiro-hydroperoxide (not shown in this case) was achieved upon treatment with silica gel/*p*-TsOH. The final product, a [6,5]-spiroketal, is very similar to the AB-spiroketal motif of pectenotoxins 1–7 (PTXs 1–7).[18]

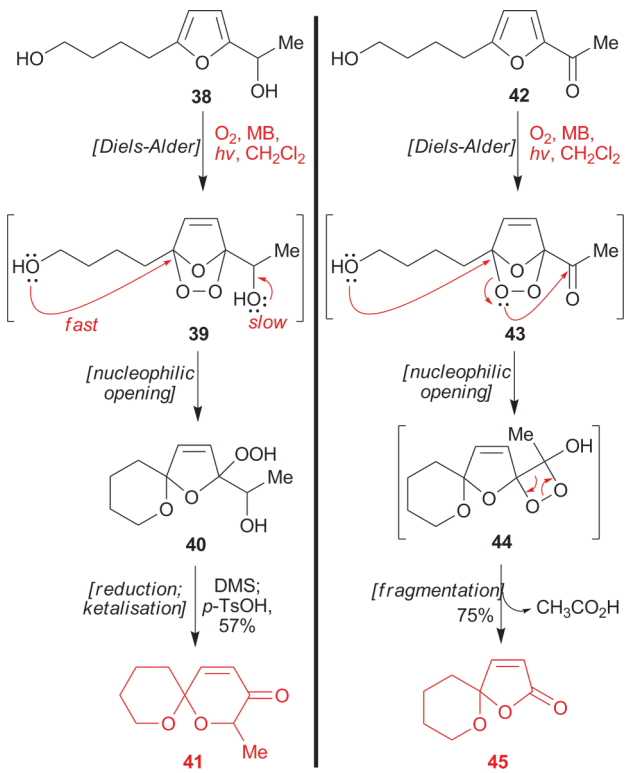


Scheme 7 Photooxidation of 2-(δ-hydroxyalkyl) furans.

Singlet oxygen reactions of furans containing hydroxyls on both the 2- and 5-alkyl substituents

Photooxidation of 2-(α-hydroxyalkyl)-5-(δ-hydroxyalkyl), as well as 2-(α-oxoalkyl)-5-(δ-hydroxyalkyl) furans

Furan **38** (Scheme 8) was chosen as a very simple and easily accessible substrate for the investigation into the outcome of the singlet oxygen interaction with 2-(α-hydroxyalkyl)-5-(δ-hydroxyalkyl) furans. The previous results and discussion have clearly shown that two types of reactivity are possible for the intermediate fleeting ozonide **39**. What remained ambiguous was if the nucleophilic opening of the ozonide by the appended δ-hydroxyl was going to be faster than the fragmentation pathway initiated by the hydroxyl at the α position of the furan's alkyl side chain. Indeed, when furan **38** was subjected to the $^1O_2$ reaction conditions[32] followed by *in situ* treatment of the intermediate spiro-hydroperoxide **40** with Me_2S and subsequently *p*-TsOH, we were gratified to see that the major product was the [6,6]-spiroketal **41** (5 : 1 mixture of anomers). Such spiroketal units are present in many biologically active natural products; such as, the terrestrially derived ionophore antibiotics salinomycin[33] and narasin,[34] as well as, the marine derived cytotoxic compounds PTX2c, PTX8-10, and PTX11c.[18]



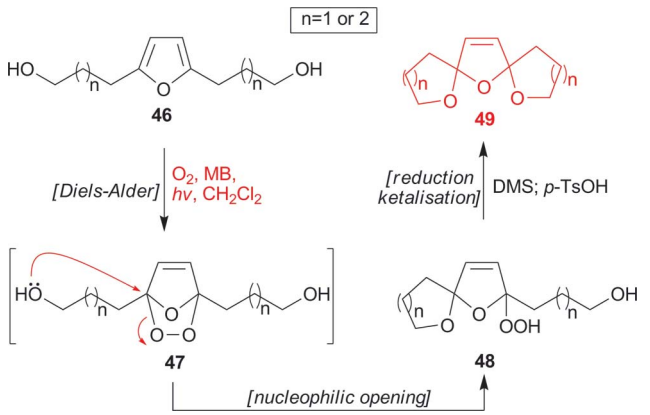
Scheme 8 Photooxidation of 2-(α-hydroxyalkyl)-5-(δ-hydroxyalkyl), as well as 2-(α-oxoalkyl)-5-(δ-hydroxyalkyl) furans.

It is of note that when singlet oxygen was reacted with the oxidised analogue of furanol **38**, furanone **42**, δ-spiroketal γ-lactone **45** was isolated.[32] The reaction mechanism for this spiroketalisation/fragmentation is described in Scheme 8. Similar results have been previously observed for a furfural derivative of compound **42** by Feringa and Butselaar.[35]

With this branch of investigation, we have added yet more commonly found bioactive motifs to the list of those that can be made by oxidising simply substituted furan substrates using singlet oxygen, but it does not end here; the line of investigation is not yet exhausted, but can be pursued further still to develop even more new methods and produce more useful motifs.

Photooxidation of 2-(γ-hydroxyalkyl)-5-(γ-hydroxyalkyl), as well as 2-(δ-hydroxyalkyl)-5-(δ-hydroxyalkyl) furans

Based on experience, it was very reasonable to assume that the transformation of a 2-(γ-hydroxyalkyl) or 2-(δ-hydroxyalkyl) furan into spiro-hydroperoxides of type **48** (Scheme 9) using singlet oxygen would be a straightforward process. However, what we now hoped to achieve, by the inclusion of an extra hydroxyl at the γ- or δ-position of the 5-alkyl substituent, was to expand the scope of the developed technology to the synthesis of *bis*-spiroketals of type **49**. Satisfyingly, *in situ* reduction of the intermediate hydroperoxide **48** followed by *in situ* ketalisation with *p*-TsOH did provide, very efficiently, and in a single synthetic operation, the sought after [6,5,6], or when desired, [5,5,5]-*bis*-spiroketals **49** (as almost 1 : 1 mixtures of diastereoisomers).[36]



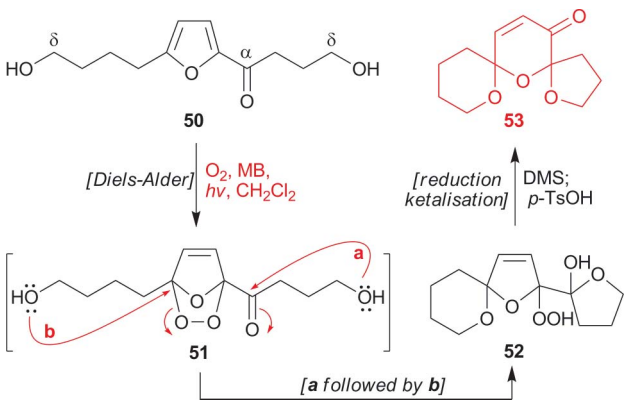
Scheme 9 Photooxidation of 2-(γ-hydroxyalkyl)-5-(γ-hydroxyalkyl) as well as 2-(δ-hydroxyalkyl)-5-(δ-hydroxyalkyl) furans.

This new technology should have broad applications because Nature has seen fit to include the delicate *bis*-spiroketal functionality in a wide range of interesting natural products. Several different classes of marine toxin, including the spirolides,[37] pinnatoxins,[38] pteriatoxins[39] and the azaspiracids,[40] contain such a motif. It is also a common subunit present in terrestrially derived ionophore antibiotics.[41]

A number of strategies for the synthesis of *bis*-spiroketals, reliant on the oxidation of a furan nucleus have sporadically appeared in the literature over the last four decades. Indeed, electrochemistry has been used for the transformation of a simple furan bearing pendant hydroxyl groups to the corresponding *bis*-spiroketal in one step.[42] Later Albizati and Perron,[43] Kocienski *et al.*,[44] and Stockman and McDermott[45] all deployed electrophilic bromine as the oxidant to transform various furans into the corresponding *bis*-spiroketal moiety. However, only in the latter of these cases,[45] the electrochemical procedure,[42] and in our photooxidation method[36] were both spiroketals formed in a single synthetic step. Furthermore, the specificity of singlet oxygen means that it might be said that the photooxygenation method tolerates other functionality better and is milder than any given source of electrophilic bromine, and, it is certainly easier to conduct than an electrochemical transformation, suggesting that it is the method which holds most synthetic promise.

Photooxidation of 2-(α-oxo-δ-hydroxyalkyl)-5-(δ-hydroxyalkyl) furan 50

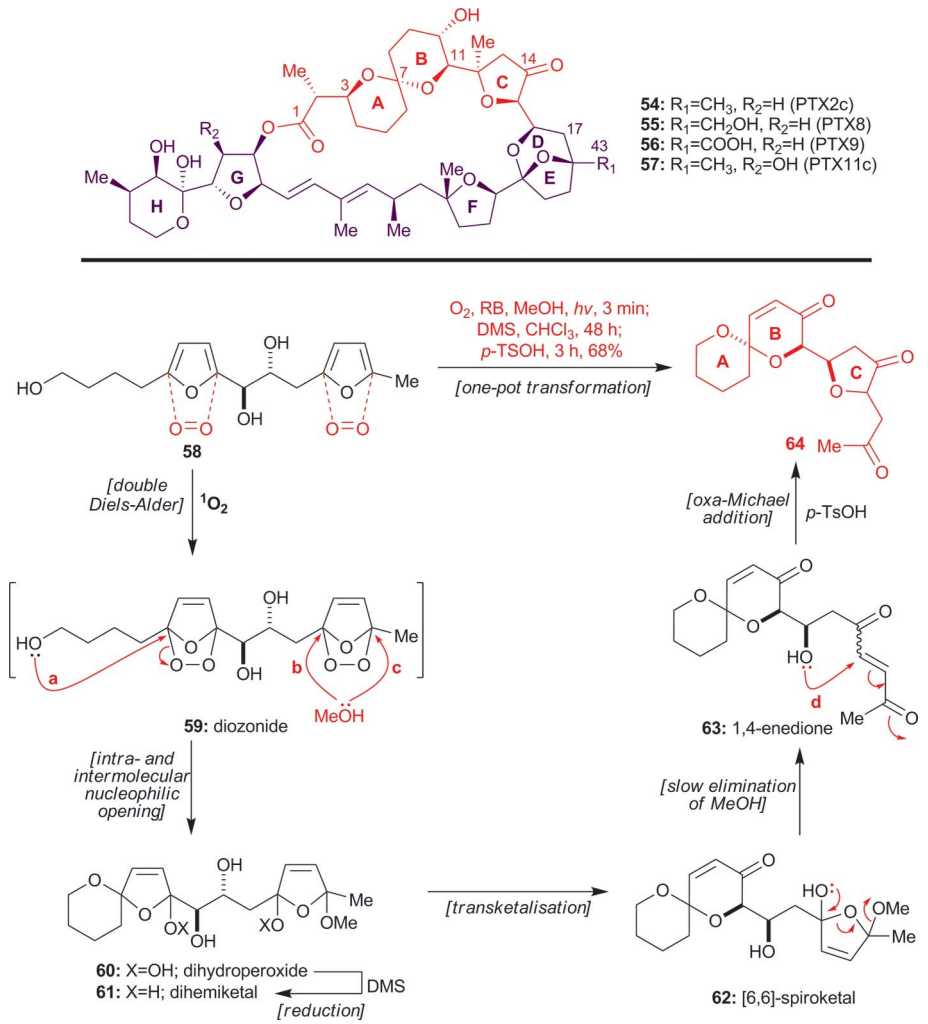
Furan **50** is very similar to furan **42**, and, therefore, its reaction with singlet oxygen might be expected to afford the δ-spiroketal γ-lactone **45** based on the fragmentation mechanism described in Scheme 8. However, the presence of an extra δ-hydroxyl on the 2-alkyl side chain deviates the cascade reaction sequence in a very useful and interesting way, as shown in Scheme 10. Ketalisation of the carbonyl group (importantly, now no longer in conjugation with a furan ring, path **a**) is kinetically faster than the dioxetane formation; thus, leading to the intermediate spiro-hydroperoxide **52** (Scheme 10) in which the carbonyl is masked as a lactol. *In situ* reduction of this intermediate hydroperoxide followed by *in situ* transketalisation of the resulting *bis*-lactol (not shown), results in the formation of the final product a [6,6,5]-*bis*-spiroketal **53** (formed as a separable 2 : 1 mixture of diastereoisomers with the *cis*-isomer being the major one).[32] This discovery is exciting not only because yet another different motif has been produced by singlet oxygen oxidation of a furan, but because it may also prove useful as a method to access the [6,6,5]-*bis*-spiroketals that are present in the terrestrially derived ionophore antibiotics, salinomycin[33] and narasin.[34]



Scheme 10 Photooxidation of 2-(α-oxo-δ-hydroxyalkyl)-5-(δ-hydroxyalkyl) furan **50**.

Introducing the "super cascade" concept: a means to synthesise the pectenotoxins' ABC-ring motif in one operation

With so much information gathered on exactly how hydroxy-substituted furans react, and with the proliferation of target molecules bearing more than one of our product motifs, we wondered whether it would be possible to take the cascade reaction sequence idea even further and design ambitious double sequences to be undertaken concurrently. In our first attempt, we sought to combine the methodology for the synthesis of [6,6]-spiroketals,[32] with that for the preparation of 3-keto-tetrahydrofurans[16] in what we would call a $^1O_2$-mediated "super cascade" sequence. The target of this super cascade being the key ABC-ring motif (**64**, Scheme 11)

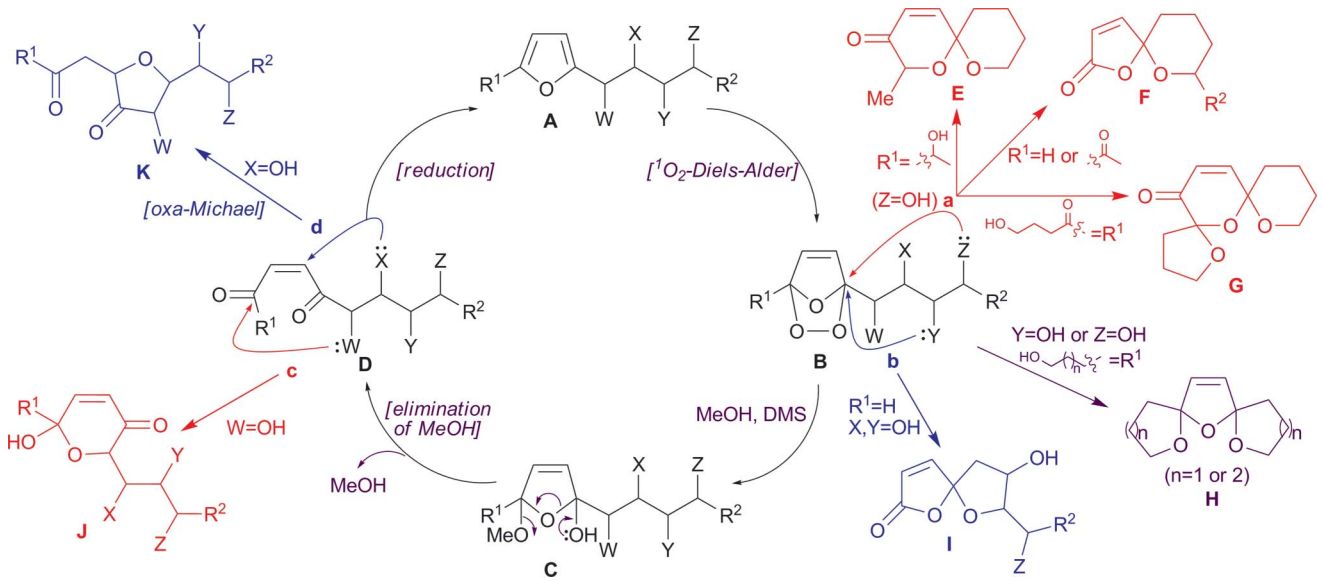


Scheme 11 Phootooxidation of difuran-triol **58** into the ABC motif of PTXs 2c, 8, 9 and 11c.

of PTXs 2c, 8, 9 and 11c and its substrate being relatively simple difuran **58**.

A solution of **58** (the *erythro*-diol), contaminated with 28% of the *threo* diastereoisomer, in MeOH, containing rose bengal as photosensitizer, was irradiated for three minutes with visible spectrum light whilst oxygen was bubbled gently through the solution. Very careful replacement of MeOH with either $CHCl_3$ or CH_2Cl_2, followed by treatment for 72 h with an excess of dimethyl sulfide (DMS) and then with *p*-TsOH for 3 h, resulted in the remarkable formation of compound **64** (68% based on the purity of the starting material, mixture of two diastereoisomers in 7 : 3 ratio).[46] Thus, we achieved the super cascade reaction sequence, in which, molecular complexity was enhanced by unprecedented amounts for a single synthetic operation by taking a simple difuran precursor and transforming it into a large and complex PTX-fragment using concurrent $^1O_2$ cascade reaction sequences.

The synthetic strategy that we had developed for this large PTX fragment had been predicated on our combined previous experience in the field of developing synthetic $^1O_2$ methodologies[16,32] and this prior intelligence gathering would also support the following mechanistic rationale (Scheme 11) for the transformation of **58** into **64**. First of all, the formation of dihydroperoxide **60** (Scheme 11) is expected to occur *via* one intra- and one intermolecular nucleophilic opening of fleeting diozonide **59** (N.B. only one of the two possible regioisomers, arising from nucleophilic openings **b** and **c**, is shown). It is always possible that the cycloaddition to one of the furan nucleus of difuran **58**, followed by nucleophilic opening could be faster than the cycloaddition to the other furan nucleus. The replacement of MeOH with CH_2Cl_2 and the subsequent reduction of the mixture of dihydroperoxides **60**, by treatment with an excess of dimethyl sulfide, affords the corresponding dihemiketal **61**. A transketalisation reaction[32] leads to the transformation of the [6,5]-spiroketal of **61** into the [6,6]-spiroketal **62**. Under these same reaction conditions the remaining hemiketal moiety of this intermediate slowly eliminates a molecule of MeOH,[14,16] thus, revealing the 1,4-enedione moiety of intermediate **63**. In the final step of this remarkable cascade sequence, *p*-TsOH catalyses an *oxa*-Michael cyclisation[16] between the -OH group and the 1,4-enedione moiety resulting in the formation of the sought after ABC-ring motif of PTXs in the form of compound **64**.



Scheme 12 A summary of the natural product motifs prepared by photooxidation of differently substituted furans.

Conclusions

In this article, we have shown how, simply by altering the position of a pendant hydroxyl group(s) in the furan substrate, a broad range of interesting products can be obtained from the photooxygenations we have developed (Scheme 12). This happens because the position of the hydroxyl group(s) can dramatically alter the course of the cascade reaction sequence that is initiated when the readily accessible linear furan substrate is treated with singlet oxygen; this feature is positive as it leads to diversity in the products that can be accessed using this chemistry and it means that these cascade reaction sequences are powerful and manipulatable tools with which to gain rapid enhancement in molecular complexity and with which many different types of polyoxygenated and common natural product motifs can be accessed.

Furthermore, the chemistry that has been developed herein meets the criteria for it to be described as "green chemistry". The oxidant is non-toxic, leaves no toxic residues, and the reactions are atom efficient (both $^1O_2$'s oxygen atoms are transferred to the product). With all these positive characteristics $^1O_2$-mediated cascade reaction sequences should continue to prove a rich source of new and powerful synthetic methods.

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