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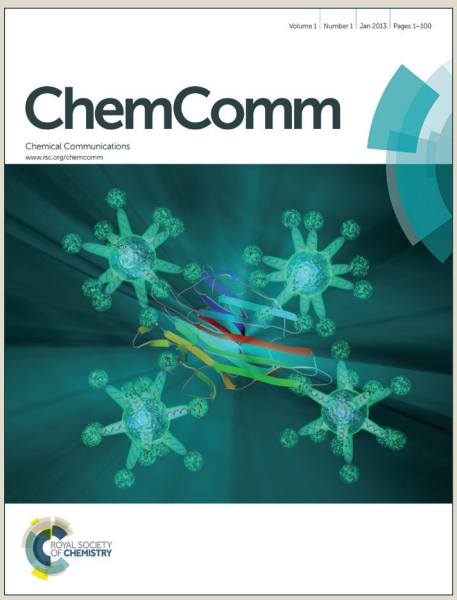

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ARTICLE TYPE

Furans and Singlet Oxygen – Why there is more to come from this powerful partnership.

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The purpose of this article is to give a taste of just how powerful the union between furans and photochemically-generated singlet oxygen is proving to be as a synthetic tool and to suggest that this chemistry is only now really coming of age. In attempting to achieve this goal, its progress from mechanistic curiosity to rapidly maturing applied science will be followed. It will be shown how the field has reached a point where the diversity of product structures attainable is expanding all the time at a tremendous pace and how this expansion allows for a wide variety of important developments from the discovery of new materials and methods for DNA-crosslinking, to the delineation of more sustainable synthetic technologies. To begin with, however, we look briefly at the investigations of the pioneers who laid all the necessary foundations by unravelling the reactions' key characteristics and then we will move on to show how their crucial work has been exploited and applied in increasingly creative ways over the years that have followed.

Part 1: Singlet Oxygen ($^1O_2$) – the reagent that has come in from the cold.

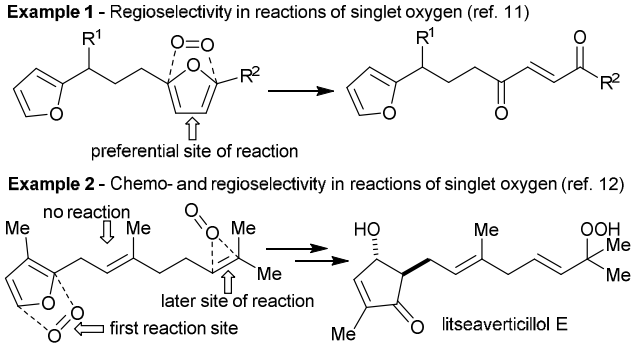
Singlet oxygen is the first excited state of molecular dioxygen and is photochemically generated from ground state triplet oxygen, in the presence of a suitable photosensitizer, by the action of visible spectrum light.[1] It has three important modes of reactivity;[2] the ene reaction with unactivated double bonds,[3] [2+2]-cycloadditions with electron rich double bonds bearing no allylic protons,[2,4] and [4+2]-cycloadditions with 1,3-dienes.[2,5] More specifically of interest to us as the subject of this review, is a major sub-group of this last category; namely, it's [4+2]-cycloadditions with furans.[6,7] In the first part of the review, we will set the context by taking a look at some of the important general characteristics of the reaction, the mechanisms involved and some key examples of synthetic work predating the year 2000; then, in the second and third parts of the review, we will step into the new millennium and look at the recent mushrooming of this field.

Furan and Singlet Oxygen – a compatible couple.

Before we examine the origins of this field more closely, it is worth taking a moment to highlight some of the basic features of the reaction between furans and photochemically-generated singlet oxygen ($^1O_2$) that explain why it is so flexible and versatile.

(1) Access to substrates: The first of these key characteristics is the ready accessibility of the substrate furans. It is fundamental chemistry. Furans, variably substituted at C2 and C5, are very easily synthesised through metalation of the furan core at the ortho-position followed by reaction of the so-formed furyl anion with an electrophile.[8] Furthermore, developments in transition metal-catalysed heterocycle synthesis,[9] especially, the recent efficient methods involving gold- and silver- catalysed cyclisations of various alkyne motifs,[10] have opened the door to new and facile ways of making furans substituted at the previously more challenging C3 and C4 positions.

(2) Reaction selectivity: The second point relates to the selectivity of the reagent. Singlet oxygen is remarkably specific in its choice of reaction site. Uniquely, for such a strong oxidant it shows little interest in reacting with C-O functionalities (such as, alcohols and aldehydes). This contrasts with many other metal/non-metallic oxidants and is a very important characteristic because it avoids the need to continually protect and deprotect these functionalities, or the need to shuttle back and forth between oxidation states (so-called redox-shuttling) – both of which have been common hindrances adversely effecting the efficiency of more traditional approaches to complex polyoxygenated molecules. This general feature has played an important role in promoting the rise of $^1O_2$ as a green reagent for use in sustainable chemistry – a topic that will be discussed in more detail further into this review as it is pivotal to the positive outlook for the future of the field. Furthermore, and, still regarding the selectivity issue, the rate at which singlet oxygen reacts with various unsaturated motifs is markedly different and makes chemoselectivity (and even regioselectivity) very easy to attain. Taking two illustrative examples, one from Ben Feringa's group[11] and one from our own work[12] we can see the high degree of selectivity that can be achieved (Scheme 1). In the first example, a dialkyl substituted furan reacts cleanly and in



Scheme 1 Examples of singlet oxygen's specificity.

preference to a monosubstituted furan that is also present in the substrate. Likewise, when synthesising the litseaverticillols (a family of natural products with anti-HIV activity), reaction of $^1O_2$ initially at the furan moiety of a substrate that also had isolated double bonds present in its side chains was easily and selectively undertaken.[12] Furthermore, later in the same synthesis, a $^1O_2$-ene reaction was carried out at just one of the two trisubstituted double bonds in the side chain – showing that both chemoselectivity and regioselectivity can be exceptionally high in these reactions.

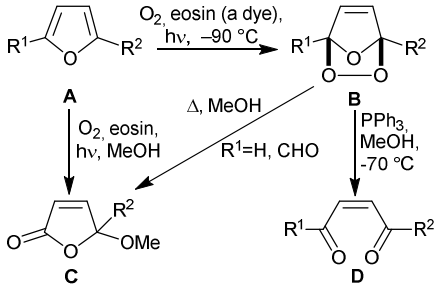
(3) Versatility of intermediates: Finally, the initial product of the reaction of a furan with singlet oxygen is always the endoperoxide **B** (Scheme 2). This motif is a highly versatile masked 1,4-enedione (**D**) and it is in the next steps of the reaction that the diversity begins to appear, as the fate of this intermediate can be tailored by addition of different additives, by choice of solvent, or through internal reactions with pendent substituents. There is great inherent flexibility with many highly controllable reaction pathways open to this intermediate.

Thus, we can see that the unique coming together of three key features have endowed the reaction of furans and singlet oxygen with enormous synthetic potential. We shall now look at how this potential first began to be uncovered.

Mechanistic milestones.

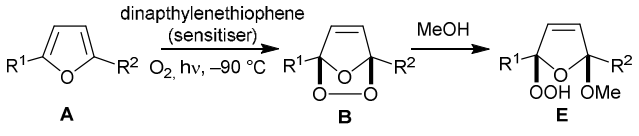
As war ravaged Europe, it was "explosives" of a very different nature that were occupying the mind of a brilliant and visionary young chemist named Günther Schenck.[13] In 1944, he not only postulated that it should be an unstable endoperoxide **B** that would be initially formed from the photosensitised reaction of a furan in air, but also that this intermediate might collapse to yield the all-important 1,4-enedione motif **D**.[14] His first assertion took just two years to be proven when, in 1946, Frenchmen, Dufraisse and Ecary, isolated the first of these explosive and fragile endoperoxides.[15] For many years afterwards, the isolation and characterisation of endoperoxides, as well as, mechanisms and characteristics of their reaction, or decomposition, continued to be a popular field of study.[2,6,16] In the midst of this work, Schenck[16f] once again broke new ground when he published the work shown in Scheme 2, and, in so doing, revealed reactivity patterns for the endoperoxides that we have been relying on and employing ever since.

The next important interventions come from another highly esteemed chemist to whom those who now apply singlet oxygen



Scheme 2 In 1953, Schenck unveils key reactivity patterns.

chemistry in their work owe a great debt, Christopher S. Foote.[17] Firstly, in two consecutive papers[1c,18] he clarified that the active species in all these photooxidations was singlet oxygen; until this point many had believed it was a sensitiser-oxygen complex that was operating. In addition, in one of these landmark papers,[1c] Foote also briefly introduced to the earlier key analysis of Schenck's (Scheme 2) a new intermediate, hydroperoxy-dihydrofuran **E** (Scheme 3). This intermediate, the product of solvent attack on the endoperoxide, was later discussed in more detail in a joint publication from Schenck and Foote on furan photooxidations.[19] It is important from a synthetic standpoint that this addition of an alcohol to the endoperoxide has proved in general to be highly regio- and stereo-selective,[6,16] usually favouring *syn*-addition (with respect to hydroperoxy group) of the alcohol molecule, at the more substituted position by reason of the enhanced stabilisation here of the intermediate which has oxonium ion charateristics.



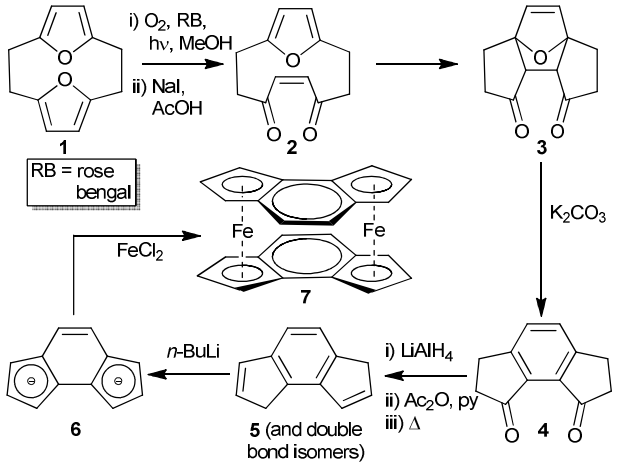
Scheme 3 Foote introduces another key intermediate.

In the end, Schenck became more famous for his work on the $^1O_2$-ene reaction to which he gave his name, but he continued to work on many other aspects of the photosensitised reactions of active oxygen species and we shall come across more of his visionary ideas later on in the article including the first large scale synthesis of a drug using singlet oxygen.[13]

The first synthetic applications for furan photooxygenations

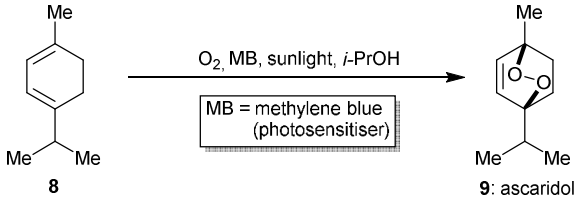
Chronologically, this is the place to describe a piece of work done by the Katz group[20] using an elegant photooxygenation sequence published a little earlier by Wasserman (Scheme 4).[21] It is a unique example of an application of this chemistry and its sophistication makes it seem somehow out-of-place in these early years (the 1960s). Wasserman had shown that the photooxygenation of furanophane **1** in methanol yielded tetracyclic **3**, which collapsed to aromatic tricycle **4** on treatment with either acid, or base. Katz improved and extended the initial sequence using it to synthesise the unusual *cis*-indacenyl dianion **6**, and, then, its corresponding bis(*as*-indacenyliron) **7**.

Singlet oxygen photochemistry continued to bloom over the next years and throughout the second half of the 20th century.



Scheme 4 Katz applies furan photooxidation developed by Wasserman to the synthesis of a new organometallic, bis(*as*-indacenyliron) **7**.

With each decade that passed new insight into the kinetics and mechanisms of its reactions was added to the growing body of knowledge (*vide infra*),[2,6,16] but another less widely broadcast development was occurring simultaneously and that was the recognition that $^1O_2$ had all the characteristics necessary to become a powerful tool in synthesis more generally.[6b,22] This progression signalled a tentative move away from the era of seeking to understand concepts towards an age of applications – the transition, however, would turn out to be a fairly lengthy one.

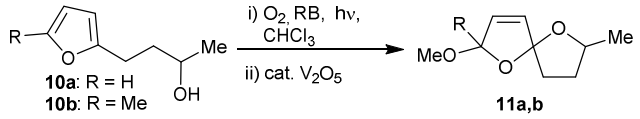


Scheme 5 Schenck's large scale production of the drug ascaridol.

It should come as no surprise that, once again, Schenck was the pioneer who linked photooxygenation reactions with the synthesis of useful natural products. It was just shortly after the war that he started to undertake quite large scale synthesis of ascaridol (a natural product and drug needed in large quantities to treat ascaris infections in humans, Scheme 5) in his garden![23] Despite the fact that we are in this case talking about a more general [4+2]-cycloaddition between $^1O_2$ and a diene unit of the terpene precursor (not a [4+2] between a furan and $^1O_2$) this work signalled to others where the future lay.

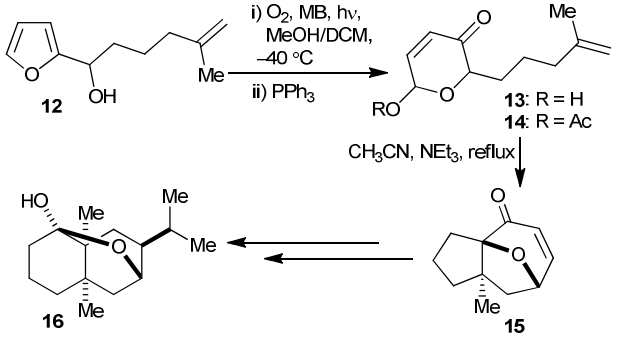
When it comes more specifically to furan [4+2]-cycloadditions, due credit must go to Ben Feringa who saw the broader potential and pursued early synthetic applications of this chemistry.[6b,11,24] For example, he noted in his 1987 review[6b] titled "Photo-oxidation of furans" that one of his stated goals was to give an account of "*the application of furan photo-oxidation in the formation of multifunctional synthons which has led to new approaches in natural product syntheses*" – with this statement he is giving us the strongest possible hint regarding the potential versatility of these reactions. From his work at this time, perhaps the most innovative example was one in the area of spirocycle formation (Scheme 6).[24b]

Other sporadic examples had began to appear in the literature,



Scheme 6 Feringa's synthesis of spiroketals.

like the use of a late stage furan photoxygenation to access the key 2-butene-1,4-diol motif in the total synthesis of portulal,[25] or the early stage photoxygenation in Sammes' elegant synthesis of cryptofauronol **16**.[26] (Scheme 7); however, most effort at this time was concentrated around the synthesis and use of γ-hydroxy- or γ-alkoxy-butenolide units (*vide infra*).



Scheme 7 Sammes' synthesis of cryptofauronol **16**.

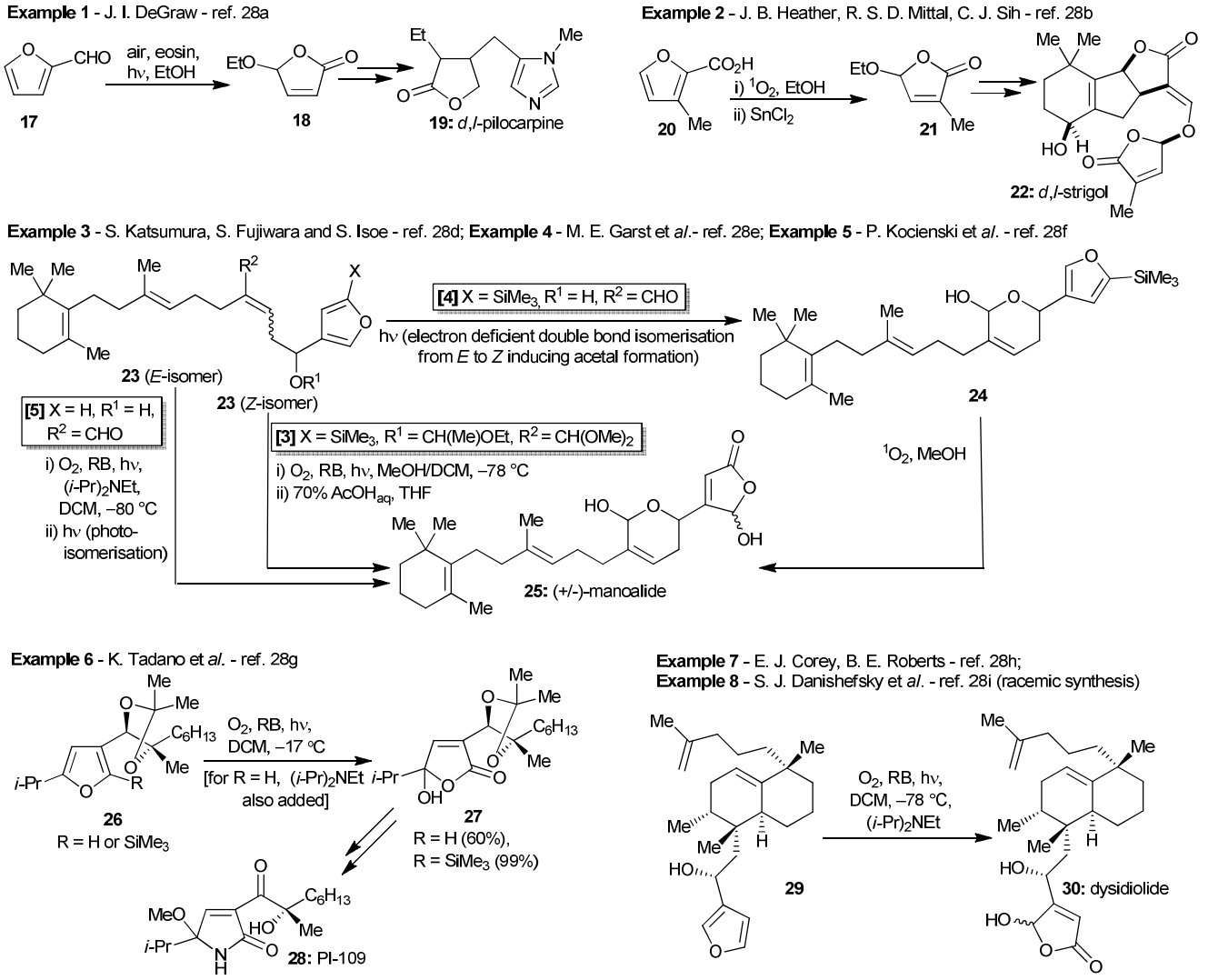
Ubiquitous γ-hydroxy- and γ-alkoxy-butenolides

γ-Hydroxy-butenolides (and γ-alkoxy-butenolides) are everywhere; they are both a common occurrence in bioactive natural products, and are useful building blocks in synthesis (Schemes 8 and 9).[27-31] For these two independent reasons, their production dominated literature examples of the applications of furan photooxygenations during the second half of the twentieth century.[28,29,30] Moreover, they continue to make very frequent appearances in publications today (as motifs themselves, or as stepping stones to other functionalities).[31] As a potential product of furan photooxidations, they were known about from the very beginning; indeed, the methoxy- variant appears in Schenck's original scheme (**C**, Scheme 2)[16f] as the product of thermal decomposition of the endoperoxide **B** in methanol. In the early days of the exploration of this chemistry, it was found that certain substituents (-CHROH,[23,32] -CHO,[16f,28a,29a,33] -COOH[29c,34])[6] at the 2-position of the furan induced fragmentations that could be harnessed in order to gain good regioselectivity (e.g. **20** → **21** Scheme 8, **42** → **43** Scheme 9) in the γ- hydroxyl/γ-alkoxy-butenolide formation. Regioselectivity is, of course, of relevance only in unsymmetric cases (for example; **23** → **25** and **29** → **30** Scheme 8 and **33** → **34** Scheme 9). Yields, however, although improved from the thermal decomposition[16f] route of Schenck's, were not always satisfactory when applying these fragmentation-based methods. In 1981, a key paper from Waldemar Adam was published.[35] Adam's paper revolutionized the synthesis of γ-hydroxyl-/γ-alkoxy-butenolides as he showed that by using a silyl group (at the 2- or 5-position of the furan) the regiochemistry could be controlled and high yields could be very consistently obtained (For example; **24** → **25**, Scheme 8). It should be mentioned that, also in 1981, Kuwajima published[1d] the same idea conceptually (using a silyl group to direct the regiochemistry

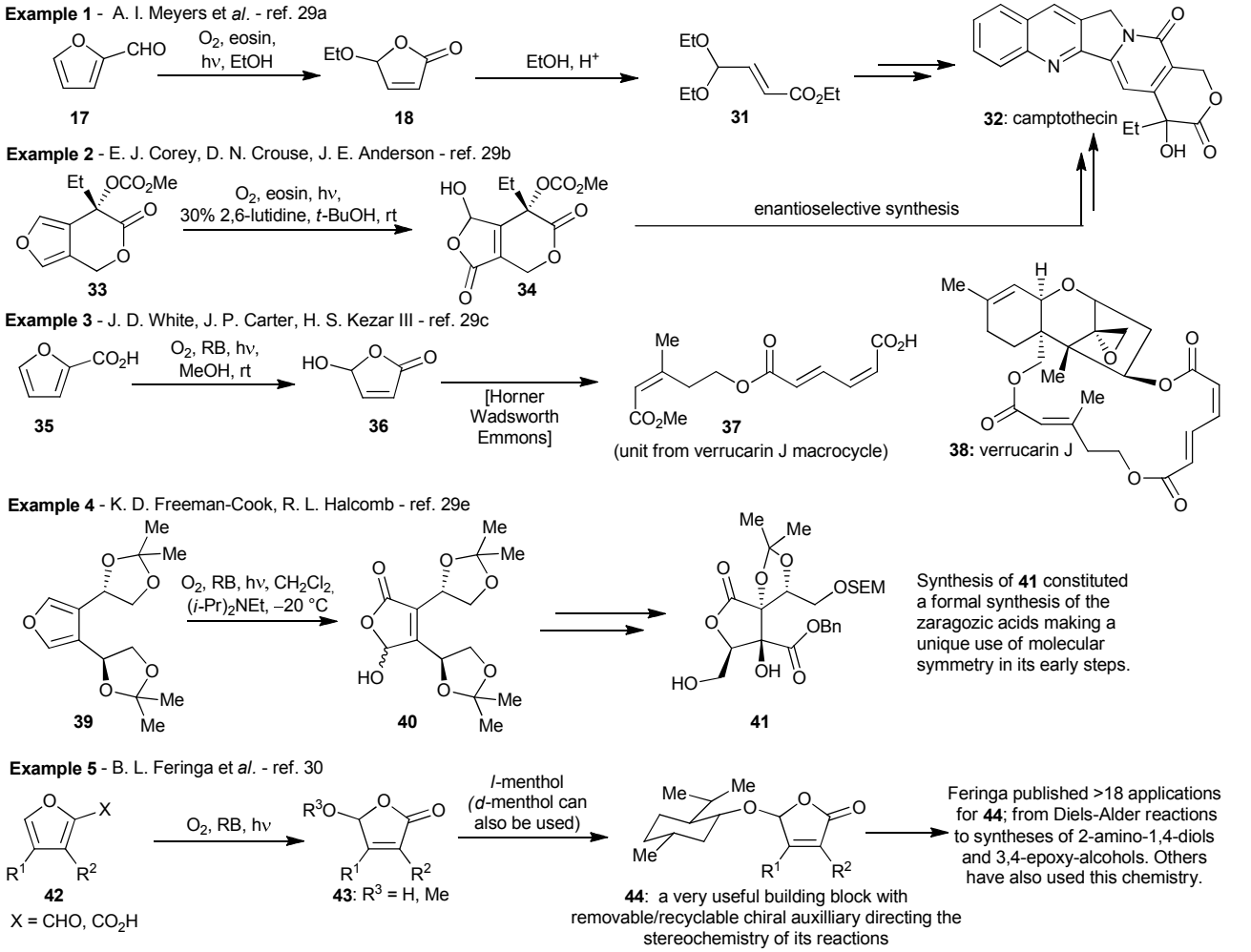
of γ-hydroxy-butenolide formation), but in his case using a less mild chemical source of singlet oxygen (CH_3CO_3H/NaOAc). Later, in 1988, Kernan and Faulkner[36] published the idea that by using a hindered base at low temperature the desired reaction (endoperoxide → γ-hydroxy-butenolide) could be regiospecifically promoted. For examples of this concept put into practice, see; **23** → **25** and **29** → **30** (Scheme 8). Here, it should be noted that Corey et *al*. had used this concept earlier (1975, **33** → **34**, Scheme 9) in their synthesis of camptothecin,[29b] but had conducted the reaction at room temperature resulting in relatively poor selectivity. Kernan and Faulkner improved the strategy by conducting the reactions at low temperatures and commented on its generality; hence the reason why the latter are usually credited with introducing the idea. The hindered base method continues to be used as an alternative to Adam's silyl group-directed approach, although, generally, the latter remains the method of choice due to its higher yields.[32b] For a direct comparison of the hindered base- versus the Adam- method, see; **26** → **27** where yields of 60 and 99% were obtained, respectively.[28g] It is important to remember that γ-hydroxy-butenolides are by oxidation a source of anhydride units,[31h] or by reduction a source of butenolides[31a,c,e] and since these interconversions yield important functionalities they are frequently used.

Concluding Part 1; the tale of these early years.

We have now placed the reactions of photochemically-generated singlet oxygen with furans in context, and described where the state-of-the-art was as we approached the new millennium. We have highlighted the work of some really visionary pioneers to whom a great debt is owed because it is on their strong foundations that this field with all its great promise rests today. To summarise; up to the year 2000, progress in the field can be described as having consisted of mostly intensive pursuit of mechanistic detail and understanding accompanied by fairly sporadic applications for the singlet oxygen-mediated oxidation of a furan nucleus mostly, but not exclusively, concentrated on the synthesis of γ-hydroxyl/alkoxy-butenolides. Furthermore, whilst highly successful in many cases, the applications tended to be just one step in a synthesis in which they were looking to achieve one fairly obvious transformation in a sequence of many transformations. The ability of singlet



Scheme 8 Selected syntheses of natural products containing the (γ-hydroxy/alkoxy) butenolide unit either intact or only slightly modified, using furan photooxidations, prior to 2000.



Scheme 9 Selected syntheses of γ-hydroxy/alkoxy-butenolide building blocks using furan photooxidations, prior to 2000.

oxygen to participate in a more central role in building large frameworks, or structurally complex motifs, had barely been touched upon.

Part 2: The new millennia and how we are responding to a change in perspectives.

With the dawning of the new millennium has come an evolution in the goals being pursued in organic synthesis that has mirrored what is happening across science and society.[37] Having proven in the preceding decades that even very large and/or complex natural products could be made,[38] chemists have now shifted their emphasis, recognising that the future prosperity of their science lies in the twin goals of attaining greater efficiency and sustainability. These two apparently simple to define goals are of course intricately linked, and, in addition, have many different component tasks. For example, efficiency is not just about making target molecules in shorter sequences (step economy[39]) with higher yielding reactions, but it encompasses atom economy[40] and the minimisation of all forms of waste (from time and labour, to solvents and residues). Sustainability encompasses all the same ideas (inefficiency is by definition unsustainable), but also has the added constraints that relate to countering our current trend towards depletion of resources and achieving minimal negative environmental impact. Many of these ideas are drawn together in the concept of "*the ideal synthesis*" which was first described by Hendrickson,[41] but which has, more recently, been fully elaborated on within a modern context by Baran et *al.* with Hoffmann.[42] But why is this global perspective relevant to this article? The answer is because singlet oxygen and its reactions with furans conscribe to all aspects of this new paradigm beautifully,[43] and it is on how it achieves this new role as a truly modern reagent that we will be focusing on now. The developments, despite still being in their infancy, hold so much promise especially since previously envisaged obstacles to progress (such as, for example; scalability, or the inclusion of basic nitrogen functionalities) are beginning to tumble.

Sustainability; first and foremost.

Singlet oxygen is a reagent with a very strong set of efficiency/sustainability credentials; it's generated from air in the presence of a sensitiser (which can be natural; for example, tannins, chlorophyll, porphyrins or spirulina[43a]) and visible

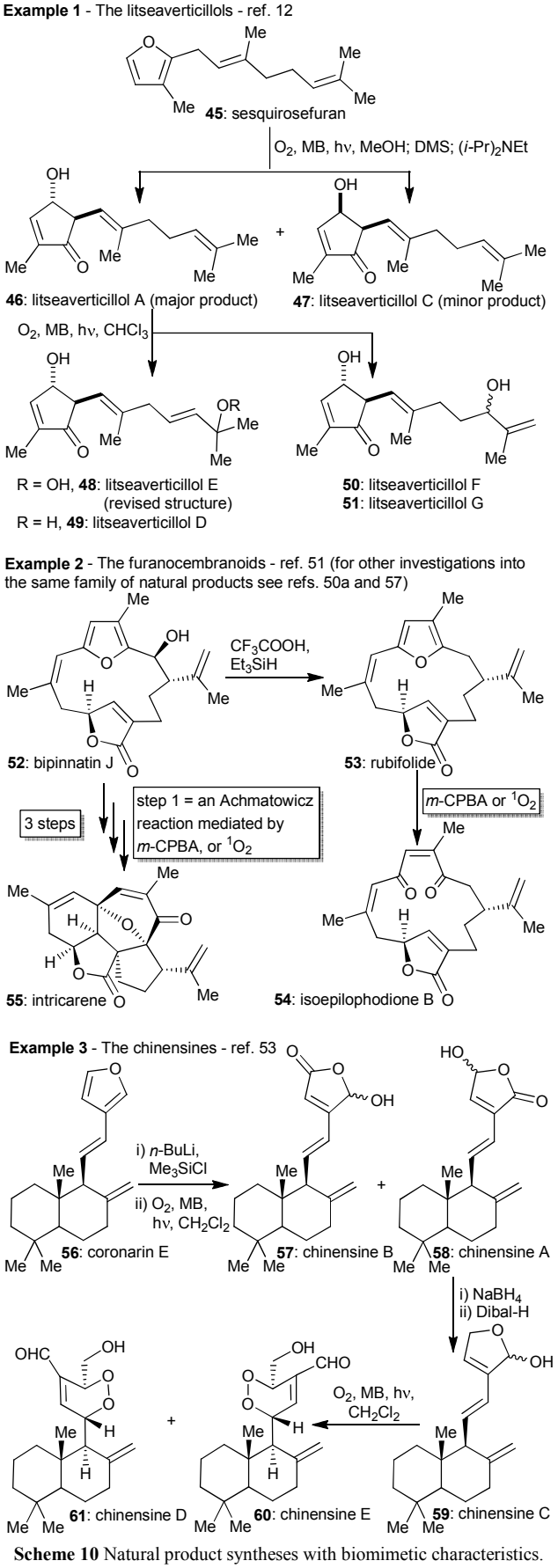
spectrum light (sunlight), it can be used in reactions that have water as the solvent[43a,c] and by itself it generates minimal waste, toxic or otherwise, (unlike a majority of other oxidants) because it is atom economic delivering all its constituent atoms to the substrate. Additionally, a survey of the literature will quickly underline just how many oxidising species there are that can react with a furan substrate to give results in some ways similar to those achieved with singlet oxygen (from *m*-CPBA, Selectfluor™, NBS and Br_2 through to Jones' reagent), but, they leave a variety of residues, and, almost without exception, they are harsh and suffer from a lack of compatibility with other functional groups. Singlet oxygen's inherent selectivity reduces, if not eliminates, the need for protecting groups[44] and for redox-shuttling[45] (two commonly employed tactics to avoid unwanted reactions in the synthesis of polyoxygenated skeletons, *vide infra*); and, it can initiate complex cascade reaction sequences[46] that lead to rapid increases in molecular complexity. Even the final hurdle, the reactions' energy efficiency is an issue that is being successfully tackled using LED technologies.[47]

As a small personal aside; in our group, we had been very excited to discover that we could use the water-soluble food supplement spirulina as a sensitiser in a range of highly sustainable water-based operations[43a] – for us it represented the culmination of investigations during which we had even tested chopped spinach (it works, but not as well as spirulina). Only later did we learn that the spinach idea was very old; in 1944, Schenck had used spinach and sunlight when synthesising ascaridol (Scheme 5)[48] – another reminder that he was a true pioneer in every sense of the word.

Returning to singlet oxygen's use today, it's indeed hard to find other reagents and reactions that embrace the new model so completely; to illustrate this point, it is no accident that when the group of the leading organic chemist, Alois Fürstner, sets about undertaking a new age catalysis-based total synthesis (of the marine oxylipins – hybridalactone and ecklonialactones A, B, and C) which is devoid of protecting groups, singlet oxygen (reacting with a furan) plays a role as the oxidant of choice in a key section of the synthesis.[49]

Natural Biomimetic Chemistry.

The first indicators of the potential for $^1O_2$ to step into the role of an environmentally benign oxidant may have come as people began to realise that under certain circumstances singlet oxygen is acting in the natural environment[50] and selected molecules can be synthesised using singlet oxygen via biomimetic strategies (Scheme 10).[12,31c,51-54] Obviously, in many natural environments the four essential prerequisites for singlet oxygen reactions occur together; namely, (i) the presence of sunlight providing visible spectrum radiation, (ii) the proliferation of natural sensitisers (tannins, chlorophylls, porphyrins etc.), (iii) molecular dioxygen (≈20% of atmospheric air, or variable amounts dissolved in sea water), and (iv) an abundance of oxidisable substrates such as terpenes (of particular relevance here are furan containing natural products, such as, coronarin E (**56**),[55] sesquirosefuran (**45**),[56] and some furanocembranoids (e.g. **52** and **53**),[50a,57] to name but a few. Of course, there are also plenty of natural molecules that quench singlet oxygen, but it might be said that these merely act to



Scheme 10 Natural product syntheses with biomimetic characteristics.

regulate a natural process.

The full extent of singlet oxygen's influence in Nature is a matter of debate and one in which researchers tend to be surprisingly non-committal in their proposals. However, the ease and precision with which singlet oxygen can be employed to make complex motifs and whole families of natural products, combined with the relationships between certain natural products that it appears to clarify (Scheme 10),[12,51,53] might suggest it is a more common tool in Nature than it has previously been credited with being.

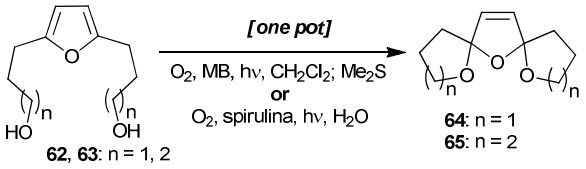
The synthesis of polyoxygenated motifs.

A significant proportion of the effort dedicated to synthesis in organic chemistry is directed towards building up polycyclic polyoxygenated scaffolds. This broad group of structures in addition to its popularity as a source of target structures, also provides the most demanding testing ground for strategies targeting ideal synthesis[42] and sustainability because of the intrinsic characteristics related to the reactivity profiles of molecules rich in C-O functionalities. To date, building up oxygen-rich organic molecules has almost inevitably meant the use of many non-constructive, and, therefore inefficient steps (concessionary steps[42]); such as, protections, deprotections and redox-shuttling (non-strategic redox manipulations[42,45]). Furthermore, in these syntheses we have traditionally relied upon oxidants that are not atom economic (such as, hypervalent iodine reagents), harsh/non-selective (such as, Anelli's catalytic TEMPO with excess bleach) and/or leave toxic residues (such as, chromium-based oxidants). Therefore, substantial progress in synthetic chemistry will come in the form of strategies and reagent systems that tackle head-on these apparently intransigent hindrances to efficiency and sustainability in broadly applicable ways. Cascade reaction sequences initiated by a reaction between singlet oxygen and a simple furan substrate can begin to answer this need[43a,b] as we shall try to show below; starting with, new routes to complex oxygen-containing spirocyclic systems.

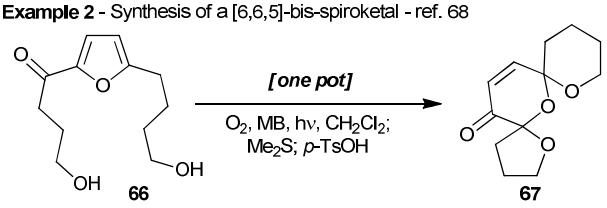
Bis-spiroketals and bicyclic ketals.

Lots of natural products contain bis-spiroketal motifs; such as, the ionophore antibiotics - salinomycin and narasin,[58] or the marine toxins - the pinnatoxins/pteriatoxins,[59] spirolides[60] and azaspiracids.[61] These have become increasingly popular as synthetic targets due to the combination of their potent cytotoxicity, and, as a consequence, their promise as new cancer therapies, and the fact that they posses wonderful, yet fragile, 3D-architectures which offer an irresistible challenge to synthetic chemists. The traditional approach to these structures has the stepwise construction of a linear precursor precede an acid-catalysed ketalisation-cyclisation event (or several events) and many syntheses have been accomplished in this manner.[62] Others have sought to design new methods to make bis-spiroketals that avoid some of the efficiency pitfalls of the more traditional chemistry (*vide supra*).[62] Amongst these other ideas, we were inspired by the use of furan oxidations as a starting point for the synthesis of bis-spiroketals;[63-66] however, application of this approach was frequently limited to simple substrates in response

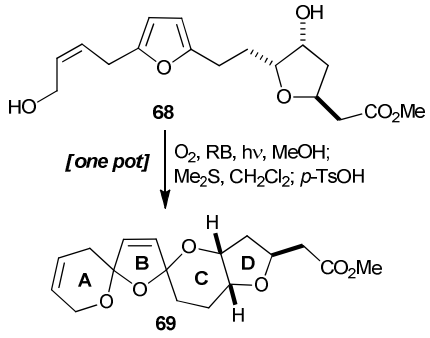
Example 1 - Synthesis of [5,5,5]- and [6,5,6]-bis-spiroketals - ref. 67a & 43a



Example 2 - Synthesis of a [6,6,5]-bis-spiroketal - ref. 68



Example 3 - Synthesis of the ABCD-ring skeleton of azspiracids - ref. 67b

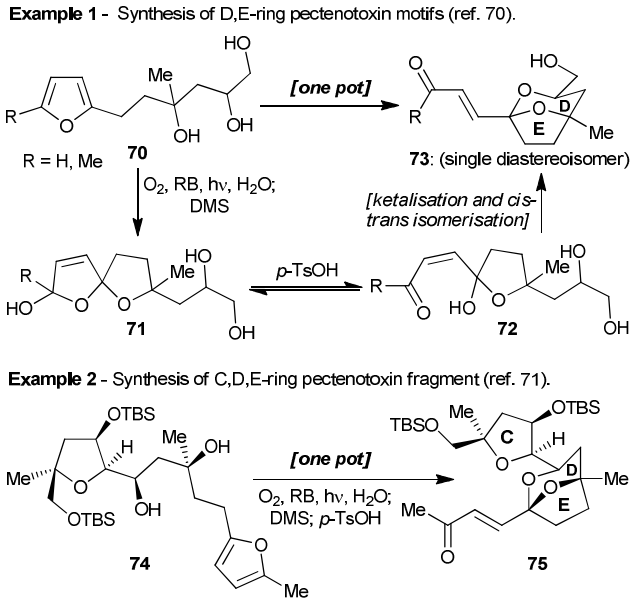


Scheme 11 Using singlet oxygen-mediated furan oxidations to make bis-spiroketals.

to the harsh/non-selective oxidants employed (Br_2,[63] NBS,[64] electrochemical oxidation[65]). A noteworthy exception to the "simple substrate"-limitation is to be found within the investigations that culminated in several elegant total syntheses of salinomycin by Kocieński's group published in the 1990s.[64b,66]

We believed we could use $^1O_2$ as a clean and selective oxidant to synthesise this key motif, and, furthermore, that we could do it in a way that formed all three rings of the bis-spiroketal in one operation – an efficiency feat only once achieved previously by Stockman (with NBS).[64c] Indeed, this turned out to be the case so that, starting from simple and readily accessible furan substrates, either [5,5,5]- or [6,5,6]-bis-spiroketals could be obtained directly in high yield (Scheme 11).[67a] Furthermore, these reactions could also be undertaken in water using the natural sensitiser, spirulina, and no reductant (no Me_2S) in a highly sustainable set of protocols.[43a] The method was then successfully adapted to include a further rearrangement during the course of the reaction sequence such that it now gave access to a [6,6,5]-bis-spiroketal motif of the type found in salinomycin (Scheme 11).[68] As proof that this strategy could readily be applied to the more elaborate molecules we frequently target, the ABCD-ring skeleton of the azaspiracids was recently synthesised (**68** → **69**, Scheme 11).[67b]

These ideas were further expanded in syntheses, first, of motifs from the D,E-ring sections of various pectenotoxins,[69] and, later, of the complete C,D,E-fragment of these challenging natural products (Scheme 12, **70** → **73**[70] and **74** → **75**,[71] respectively). In this case, after its formation, a spiroketal intermediate (**71**, not isolated) was opened and rearranged under acid catalysis to afford the desired bicycles.[70,71]

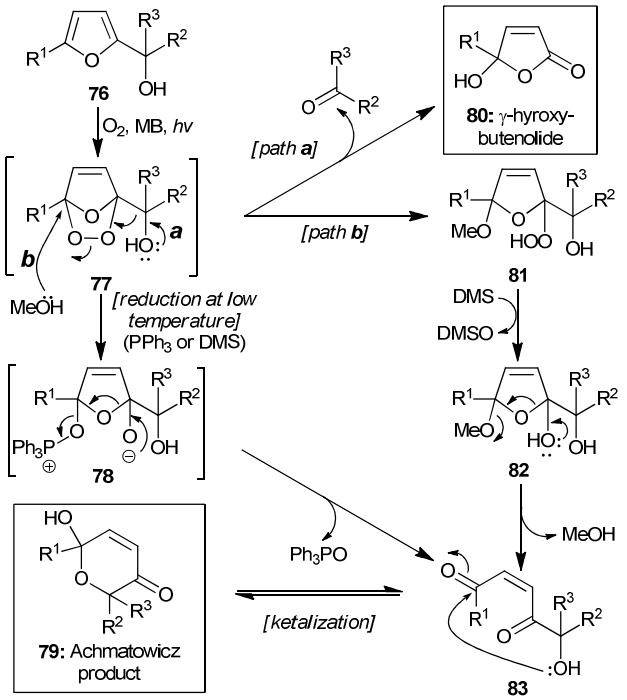


Scheme 12 Using singlet oxygen-mediated furan oxidations to make pectenotoxin fragments.

All these syntheses are particularly noteworthy, in comparison with other approaches to the same motifs, for the minimal use of protecting groups, their particularly rapid increase in 3D-complexity and because they can be undertaken in water [43a,70,71] – all these characteristics being in line with the goals of ideal synthesis.[42]

The Achmatowicz Reaction.

In 1971, the Polish chemist, Osman Achmatowicz Jr (his father who had exactly the same name was also a renowned chemist) described what was set to become an extremely versatile and much-used reaction in which a 2-(α-hydroxyalkyl) furan, could undergo oxidative rearrangement to furnish a 6-hydroxy-3(2*H*)-pyranones (**76** → **79**, Scheme 13).[72] He had envisioned the reaction as a means to transform furans back into sugars; thus, reversing the well-known dehydration of sugars to furfurals (or other furan derivatives), but it has turned out to be much more broadly applicable. This is due to the rich and easily differentiable substitution pattern of the 6-hydroxy-3(2*H*)-pyranone product that makes it a synthetically very versatile motif bearing many handles for further elaboration. Over the next 35 years, the method was thoroughly explored and a variety of different oxidants were shown to facilitate the Achmatowicz reaction from the original Br_2-based reagent system[72] through NBS,[73] peracid- (*m*-CPBA,[74] magnesium monoperoxypthalate[75]), dioxirane,[76] metal-based oxidant (PCC,[77] $VO(acac)_2$/*t*-BuOOH,[78] titanium(IV) silicalite/H_2O_2[79]) systems to an electrochemical variant.[80] As with the bis-spiroketal precedent that we discussed previously, the major limitation defeating many attempts to employ the Achmatowicz reaction in more advanced synthetic situations related to the harsh and unselective nature of the oxidants; for example, few of these reagent systems could tolerate the presence of other C-C double bonds within the reaction substrate. In the early 1980s, frustrated by exactly this last problem when trying to synthesise the natural product,

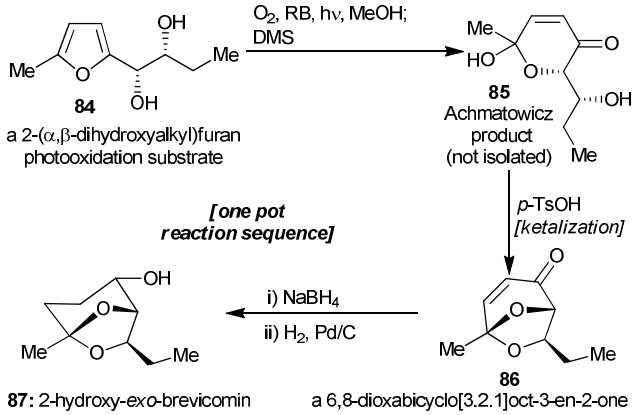


Scheme 13 Mechanistic analysis of the singlet oxygen-facilitated Achmatowicz reaction and competing fragmentation.

cryptofauronol, Peter Sammes hit upon the singlet oxygen Achmatowicz solution (Scheme 7, **12** → **13**).[26] Elegant applications would follow,[81,82] but problems persisted – the reaction appeared to be fragile requiring low temperatures in order to achieve the desired outcome[32b,82] and conducting low temperature photochemistry turned out to be a bit too tricky for the method to attain wide appeal. The root of the problem lay in the competing fragmentation reaction that affords γ-hydroxy-butenolides (**76** → **80**, Scheme 13) – a reaction that is under different circumstances, of course, synthetically useful itself (*vide supra*).

We believed that by using just methanol (with no co-solvent) as solvent for the photooxidation at normal reaction temperatures (usually meaning the use of an ice bath to prevent heating of the reaction by the lamp), the fragmentation pathway (path a, **76** → **77** → **80** Scheme 13) could be disrupted forcing the reaction towards the desired product (**79**) using path b (Scheme 13); this solution was dependent on the assumption that the solvent methanol would react faster with endoperoxide **77** (path b, Scheme 13) than its unimolecular fragmentation would occur. In the end, this rationale was proven correct provided generally that R^1 was not H and when R^2, or R^3, was not a group such as a phenyl, or allyl, that promoted fragmentation (**77** → **80**).[83] It was later proven that water was an even better solvent than methanol for achieving the desired transformation being accompanied by even less fragmentation.[43a] Thus, by using methanol[83] or water[43a] as solvent, the singlet-oxygen mediated Achmatowitcz reaction had become much more amenable to general use in synthesis; and, because of its mild conditions and selectivity should be applicable to more complex situations than those in which the other known reagents could participate.

Wishing to prove the versatility of this newly adapted method, we sought to add another reaction to the one-pot sequence in an

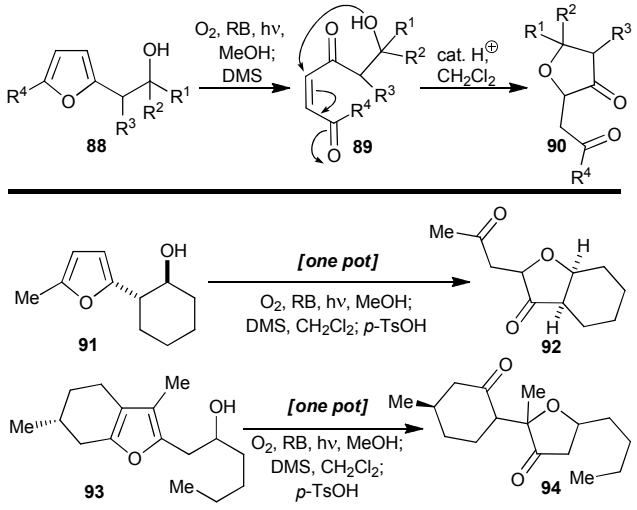


Scheme 14 Application of the singlet oxygen-mediated Achmatowicz reaction to the synthesis of 2-hydroxy-*exo*-brevicomin.

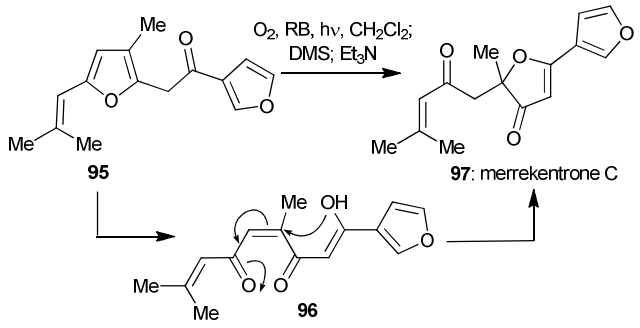
attempt to target a new motif; namely, the 6,8-dioxabicyclo[3.2.1]oct-3-en-2-ones (like **86**, Scheme 14) present in many natural products (e.g. pteriatoxins/pinnatoxins[59] and the didemniserinolipids[84]). To make this motif, it was hoped that the photooxidation of a 2-(α,β-dihydroxyalkyl)furans would initially furnish the Achmatowicz product (**84** → **85**) which could then be encouraged to undergo an internal ketalisation step if catalytic acid was added to the reaction solution prior to work-up. The plan was successfully implemented and the method applied to the synthesis of a natural product, 2-hydroxy-*exo*-brevicomin **87**.[83,85] Once again, the same outcome could be achieved if the photooxidation reaction of a similar 2-(α,β-dihydroxyalkyl) furan was run in water without a reductant (Me_2S).[43a]

Intramolecular Oxa-Michael or Aldol Reactions.

Stimulated by the Achmatowicz chemistry (in particular intermediate **83**), we began to consider whether, if the pendent hydroxyl was shifted one carbon further away from the ene-1,4-dione unit (**89**, Scheme 15), an *oxa*-Michael reaction might be encouraged to occur as part of a new one pot reaction sequence that would furnish 3-keto-tetrahydrofurans **90**, a common natural product motif. This idea was successfully implemented[86] to add yet another set of polyoxygenated motifs to those that could be



Scheme 15 Synthesis of 3-keto-tetrahydrofurans.

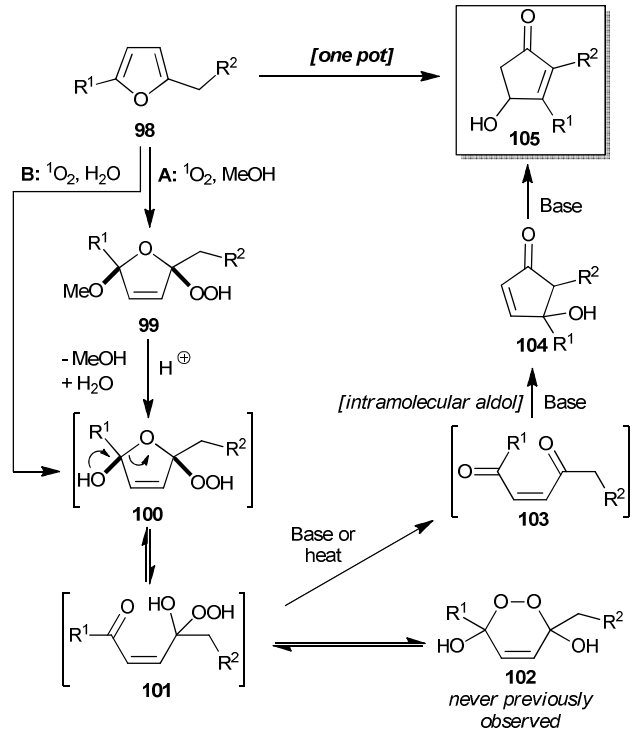


Scheme 16 Synthesis of merrekentrone C.

attained using $^1O_2$-mediated furan photooxidation reaction sequences.

Furthermore, it was also shown in work from Stratakis' group that an enol-oxygen could also act as the nucleophile, a concept that was applied to a synthesis of the natural product merrekentrone C (**97**, Scheme 16).[87]

It should be noted here, that the group of Fall has worked extensively for some time implementing 1,4-additions to γ-hydroxy-/γ-alkoxy-butenolides (the products of furan photoxidations) in a stepwise manner, to synthesise natural products and motifs of interest.[88]



Scheme 17 Synthesis of 4-hydroxy-2-cyclopentenones.

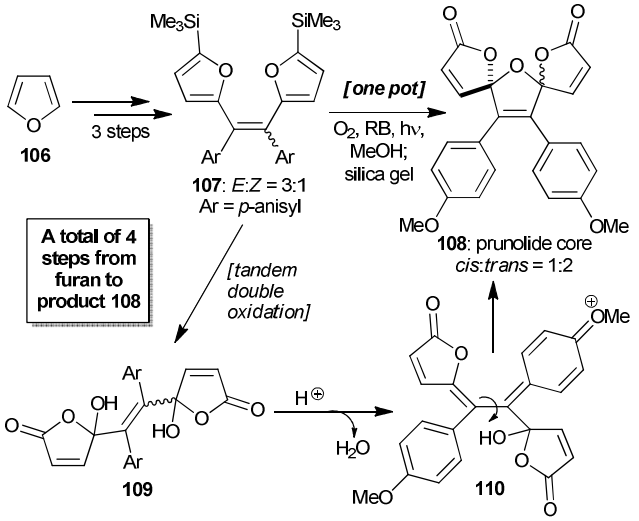
As an indication of how readily these reaction sequences can be tailored to follow just one desired pathway out of many options when small changes to the additives, or reaction conditions, are made, we were also able to develop very recently a methodology for the one pot transformation of a wide variety of furans into 4-hydroxy- (or 4-methoxy-) 2-cyclopentenones (Scheme 17).[89] In its most refined form this transformation could be achieved in water and without the use of a reductant (like Me_2S) in a protocol that scores very highly on the

green/sustainable chemistry scales.

Double oxidations and super cascades.

The previous examples have shown the ease with which $^1O_2$ can be used to insert oxygen functionalities into molecules at the same time as orchestrating the rearrangement of substrates from more liner, flatter morphologies to much more complex 3D-architectures; but, the real power of this reagent lies in its ability to do these things at different positions in parallel through so-called double events, or super cascades, wherein the increases in molecular complexity and the efficacies of the oxidations are maximised.

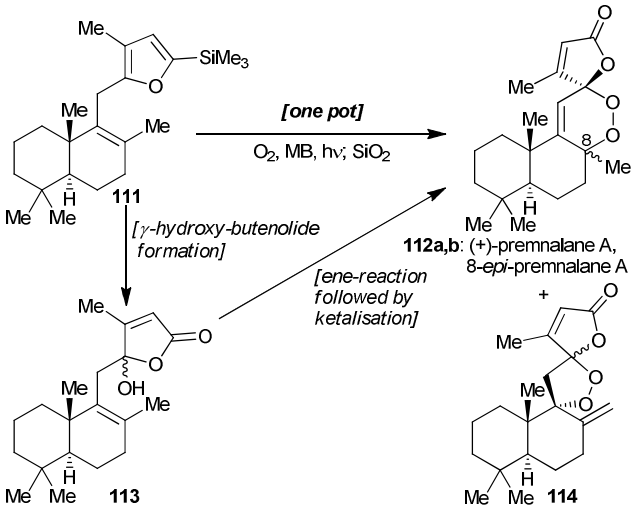
Our first example of this type of double oxidation event involves the synthesis of a complex molecule representing the core of the prunolides (a family of cytotoxic natural products) in just 4 steps starting from furan itself and using a tandem double oxidation sequence (**107** → **108**, Scheme 18).[90] The first 3 steps assembled the singlet oxygen precursor **107** as a 1:3 (*Z*:*E*) mixture. These isomers were separable; however, this was irrelevant as when either isomer was subjected to the $^1O_2$-cascade reaction sequence conditions the same product mix was afforded - predominantly the desired *trans*-isomer accompanied by smaller amounts of its meso *cis*-isomer (**108**, *trans*:*cis* = 2:1). In this cascade sequence, both furans present in the substrate had undergone oxidation to give intermediate **109** which loses a molecule of water to give cationic intermediate **110** about whose



Scheme 18 Synthesis of the prunolide core using a singlet oxygen-mediated cascade reaction sequence.

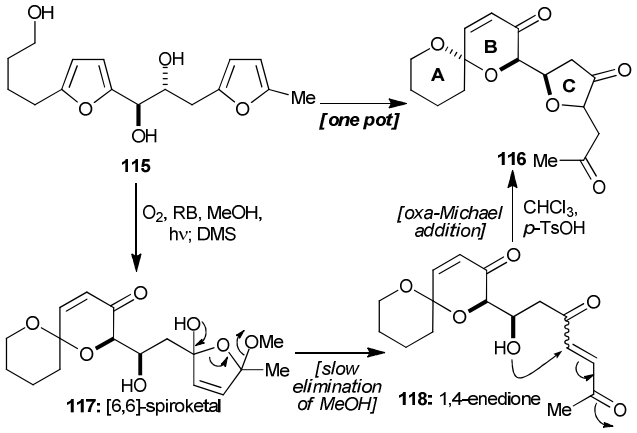
central bond rotation is possible before the final cyclisation gives the prunolide core **108**. Because the gain in 3D-molecular complexity is so great, it should be reiterated that the transformation of **107** into **108** was achieved as a one pot process with no isolation of intermediates, expect in the first proof of principle studies.

Our second example involves a cascade reaction sequence which utilises two modes of reaction for $^1O_2$ (γ-hydroxy-butenolide formation and an ene reaction) in the same one pot process (**111** → **112a**, Scheme 19), and, which following a final acid-catalysed cyclisation step, furnished the enantiomer of the



Scheme 19 Total synthesis of premnalane A using two modes of singlet oxygen reaction in a single one pot sequence.

antibacterial natural product, premnalane A **112a**.[54] NMR studies showed that, as predicted, the γ-hydroxy-butenolide formed first within seconds with the subsequent ene-reaction occurring as the irradiation period was extended to several minutes. Of note in this sequence is the unprecedented *Z*-geometry of the double bond that arose from the ene reaction.



Scheme 20 Synthesis of the ABC-ring motif from certain pectenotoxins using a singlet oxygen-mediated super cascade.

In our final example, a simple, readily accessible, difuran precursor (**115**, Scheme 20) was transformed into the ABC-ring motif (**116**) from certain of the pectenotoxins[69] in a one pot, super cascade, mediated by $^1O_2$ (Scheme 19).[91] In this case, the spiroketal forming method (**115** → **117**) was combined with that of the 3-ketotetrahydrofuran synthesis (**118** → **116**), with these two transformations remarkably occurring simultaneously in the same molecule.

Part 3: The missing elements and the future.

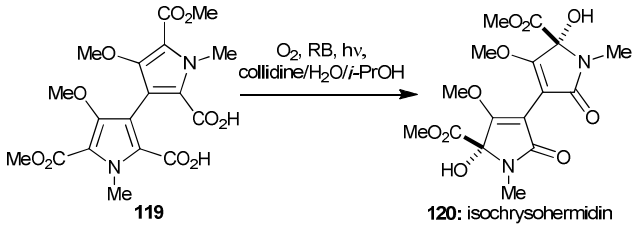
It has been shown how from the outset singlet oxygen, in its reaction with furans, was found to be a very powerful tool for synthesising certain motifs with selectivity and precision. We have also shown how adept singlet oxygen-mediated cascade reaction sequences are, not only at inserting oxygen

functionalities into molecules, but also at stitching up these molecules to give complex polyoxygenated polycyclic structures – very rapidly going from flatter more linear substrates to three dimensionally complex products. And finally, it has been shown how it was recognised that this chemistry could form a key part of highly efficient (from many different perspectives) strategies that use sustainable (green) chemistry. As if these features alone are not enough to give this chemistry a bright future with broad applications, there are more new developments.

It might be said that there were two holes in the arguments presented by those who believed singlet oxygen (particularly, in its reaction with furan) could answer many important challenges in modern organic synthesis, and, thus, become a widely used and indispensible tool; and those were, (a) nitrogen is sparsely represented in protocols and (b) scale issues in photochemistry have tended to limit its applications to small research problems rather than industrial production, or even larger scale synthetic situations. In this section, we will show how these two hindrances no longer restrict the use of $^1O_2$ in synthesis.

Adding a little blue to the palette.

Nitrogen is generally depicted using the colour blue and it was with blue that we and others have sought to enrich our palettes more recently. The inclusion of nitrogen in substrates is by no means unknown in $^1O_2$ chemistry[92] - it is just that with its own intrinsic reactivity towards this electrophile it can complicate matters[93] and has often been avoided. In fact, one of the best examples of the use of singlet oxygen in total synthesis comes in

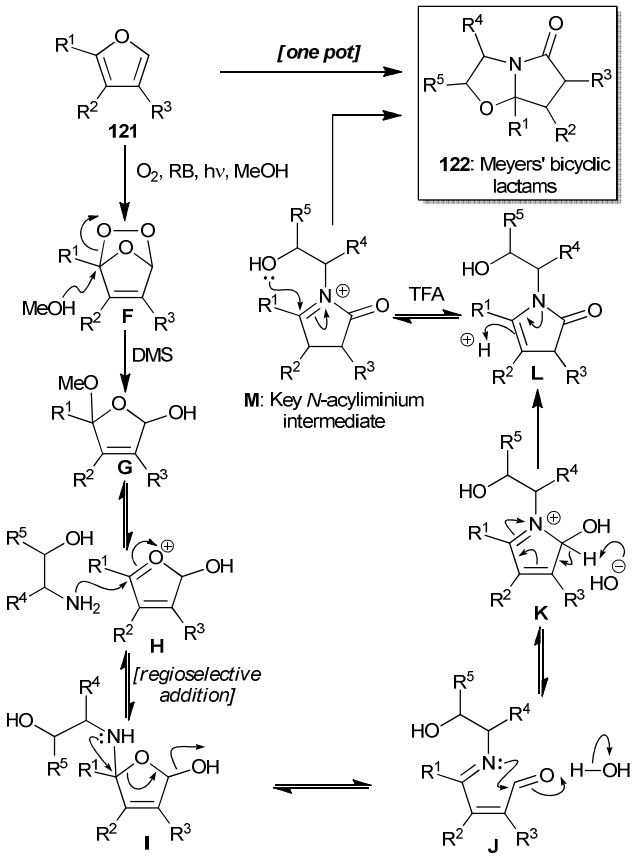


Scheme 21 Synthesis of isochrysohermidin.

the form of Boger and Baldino's elegant synthesis of isochrysohermidin **120**;[94] wherein, two pyrrole units are concomitantly reacted with singlet oxygen in a double oxidation-decarboxylation event (Scheme 21).

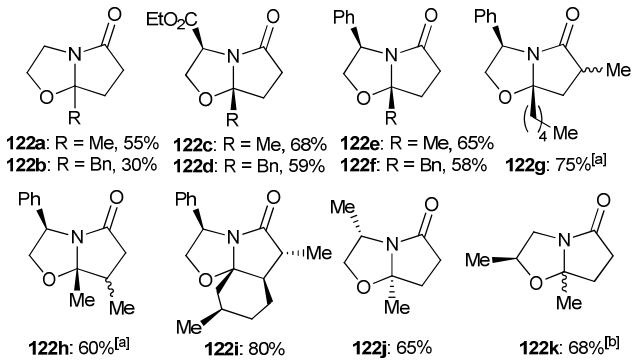
The isochrysohermidin example involves an aromatic nitrogen, what we hoped to do was to include much more basic alkyl-nitrogen functionalities within cascade reaction sequences. In our previous reaction sequences, we had already become accustomed to adding the reductant dimethylsulphide (DMS), or a catalytic amount of an acid, once the reaction tlc indicated a certain stage in the sequence had been attained. We, therefore, reasoned that basic nitrogen could be introduced in the same way; thus, avoiding its presence during the photooxidation initiation phase of the sequence.

Applying this logic, it was hoped that the 1,4-enedione (or its equivalent), formed via photooxidation of an appropriate furan, could be intercepted with amines. It should be noted that Cermola and co-workers have published an example wherein one such intermediate in the photooxidation of a furan bearing sugar unit



Scheme 22 Cascade reaction sequence for the synthesis of Meyers' bicyclic lactams.

was intercepted by hydrazine to afford a pyridazine.[95] In our first investigation aminoalcohols were targeted, with the hope that the resulting intermediate could be rearranged under acidic conditions to furnish the extremely versatile Meyers' bicyclic lactams (Scheme 22). These homochiral motifs have, ever since they were pioneered by Meyers,[96a] been exceedingly popular and flexible scaffolds for the enantioselective construction of new stereogenic centres.[96] Furthermore, the existing syntheses generally either required high temperature (and acidic) condensation reactions and/or stepwise construction of the template. It was hoped that a mild one pot synthesis of these compounds could be developed starting from furans and using a singlet oxygen-mediated cascade reaction sequence with all its



[a] separable diastereoisomers. [b] inseparable diasetereoisomers.

Table 1 Examples of Meyers' bicyclic lactams formed using the singlet oxygen-mediated cascade reaction sequence.

inherent advantages (selectivity, broad functional group tolerance, lack of protecting groups, mild reaction conditions etc.) that adhered to the principles of sustainable chemistry.

Despite the extraordinary complexity of the design for the proposed cascade on paper (Scheme 22), the idea was implemented in an operationally very simple manner, whereby the photooxidation was followed by serial addition of the requisite reagents at the appropriate time as indicated by tlc (Table 1).[97] The one pot reaction yields were high, especially when the degree of structural complexity enhancement is taken into account. There was excellent transfer of chirality (Table 1) when monosubstituted (at R^1, Scheme 22) furans were reacted with aminoalcohols substituted (with Me, Ph, or CO_2Et) adjacent to the amino group (R^4 in Scheme 22). Overall, a highly competitive method had been developed.

With this work we had achieved what we set out to do; namely another important and useful motif had been made using a singlet oxygen cascade reaction sequence, but crucially this time the method included the use of unprotected basic nitrogen participants. Furthermore, 2-pyrrolidinone **L** (Scheme 22) had been isolated and spectroscopically identified, this is a very exciting intermediate with the potential to react via its protonated form **M** (the *N*-acyliminium ion) in many other ways; so immediately there were promising new avenues to explore.

The first new investigation initiated was to see if a Pictet-Spengler reaction[98] could be included in such a cascade reaction sequence. In other words, could an intermediate *N*-acyliminium ion (similar to **M**, Scheme 22) be made and reacted with a pendent aromatic group using an acid (Brønsted, or Lewis), all as part of a single one pot process creating a range of complex nitrogen-bearing polycyclic motifs? The answer was that it was indeed possible and Table 2 illustrates some representative examples.[99] It should be noted that both activated aromatics (dimethoxyphenyl, or indole) and unactivated (unsubstituted phenyl) could participate in the reaction, although the latter did present some limitations, as long as an appropriate choice of acid

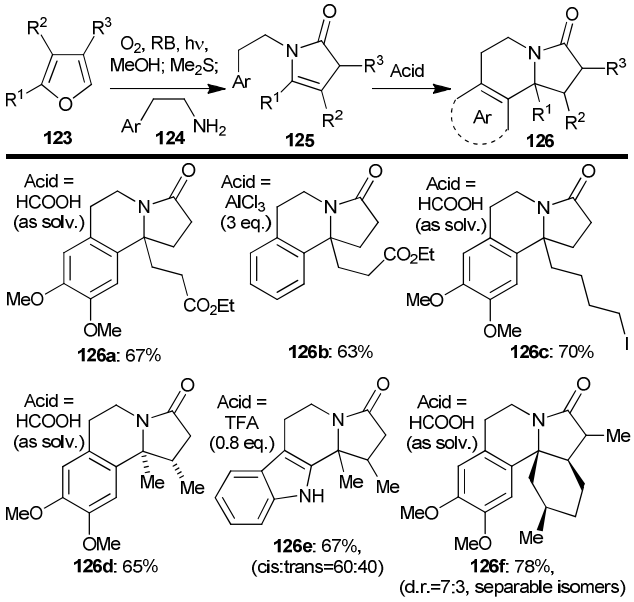
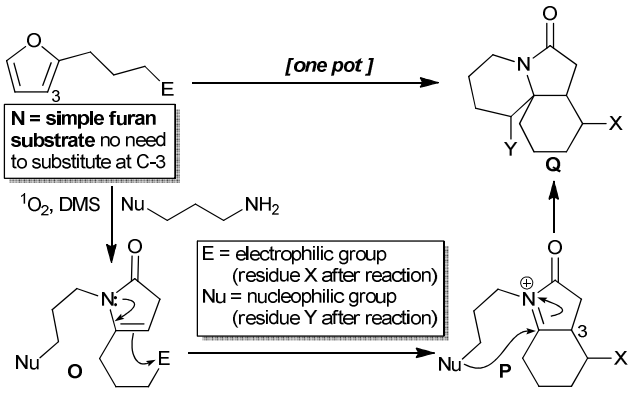


Table 2 Selected Pictet-Spengler products from the singlet oxygen-initiated cascade reaction sequence.

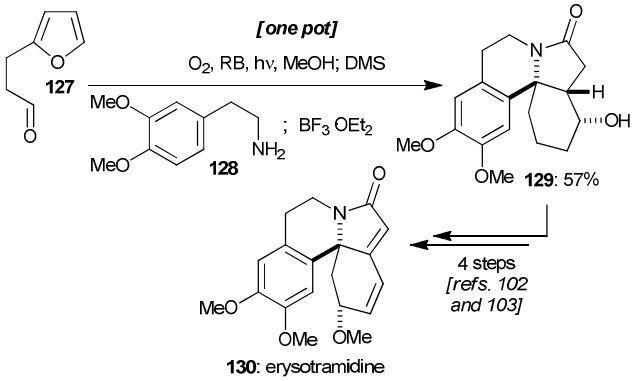
was made. The reaction of *N*-acyliminium ions with aromatic rings is well-known, but what is remarkable here is its inclusion in such an intricate, yet mild and efficient, cascade reaction sequence that transforms a simple furan substrate into a complex polycyclic product in a one pot procedure.

The Pictet-Spengler work afforded some products that were tantalisingly close to members of the aromatic erythrina family of bioactive alkaloids.[100] Indeed, when menthofuran and 2-(3,4-dimethoxyphenyl)ethan-1-amine were used the intact skeleton of this family of natural products was synthesised (**126f**, Table 2).



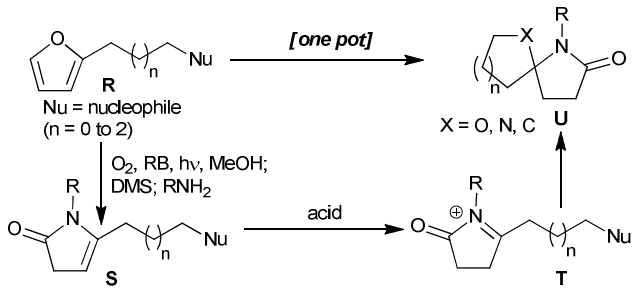
Scheme 23 Rationale illustrating the dual reactivity of *N*-acylenamine intermediate from the cascade reaction sequences.

The synthesis of an erythrina family member would also help to reveal another hidden beauty of these cascade reaction sequences working via intermediates of type **L** and **M** (Scheme 22). This would involve showing how the *N*-acylenamine could react first as a nucleophile (**O** → **P**, Scheme 23), and, then, as an electrophile (**P** → **Q**), in such a way that the starting furan substrate could be kept very simple (there is no need to substitute at the tricky C-3 position of the furan as a C-C bond can be formed as part of the cascade reaction sequence).



Scheme 24 Formal synthesis of erysotramidine.

To this end, an aldehyde was included as the electrophile (E, Scheme 23) and a dimethoxyphenyl-group as the nucleophile (Nu). Appending an aldehyde to the initial furan substrate would also reinforce the message regarding the broad functional group tolerance and mild nature of the cascade reaction sequence as a whole. The proposed cascade sequence was successfully undertaken (**127** + **128** → **129**, Scheme 24)[101] and by itself constituted a formal synthesis of erysotramidine **130** as it intersected with the chemistry of Simpkins[102] and Padwa.[103] The



Scheme 25 Mechanistic rationale for synthesis of 1-azaspiro frameworks.

increase in molecular complexity seen in this one pot process is exceptional.

A recent endeavour, again working within this still underexplored reactivity mode, involved the development of a flexible method for the synthesis of, 1-azaspirocycles (X = C), spiroaminals (X = O) and 1,6-diazaspirocycles (X = N, **U** Scheme 25). These types of motif are ubiquitous, appearing in a slew of natural products and pharmaceuticals. Methods exist for their synthesis with some of the reported examples occurring via *N*-acyliminium ion formation and reaction; however, very rarely is this undertaken as part of a one pot method and there are no reports of a widely applicable method for accessing all three motif types.[104]

The simplest of these three new cascade reaction sequences to implement was the case in which X = O wherein, both five- and six-membered rings were readily accessed (**131** → **132**, Table 3).[104] Furthermore, it was shown that by tailoring the conditions used for a substrate where both the Pictet-Spengler type reaction and spirocycle formation were possible, the mode of reaction could be completely controlled and selectivity for one or the other reaction readily achieved (e.g. **132f** or **133**, **132g** or **134**, Table 3). Next a selection 1-azaspirocycles was also made using this technology (Scheme 25);[104] once again the choice of acid tailored the result with Lewis acids being more powerful in this C-C bond forming scenario (**T** → **U** with X = C, Scheme 25).

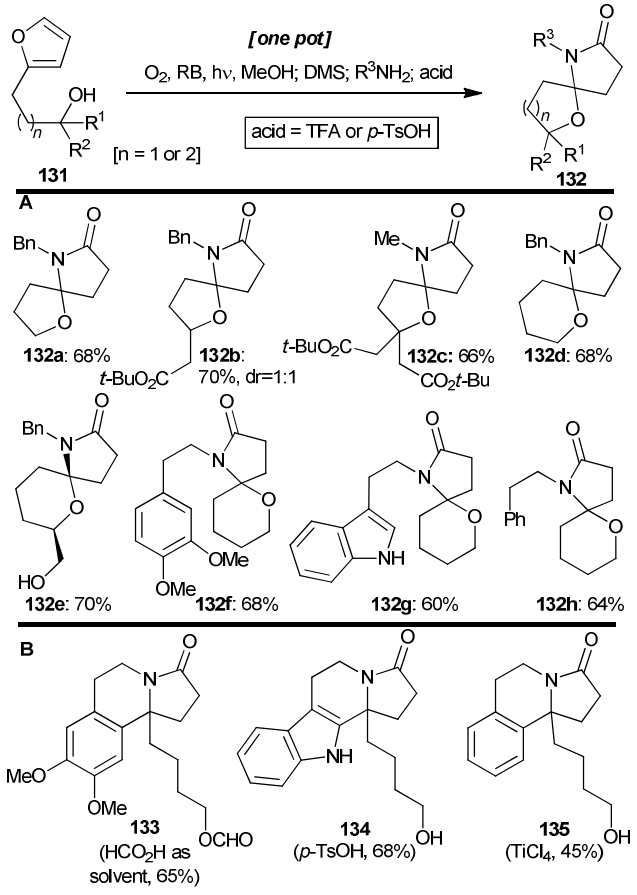
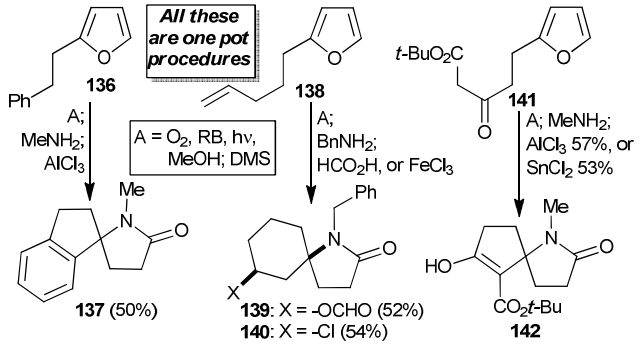
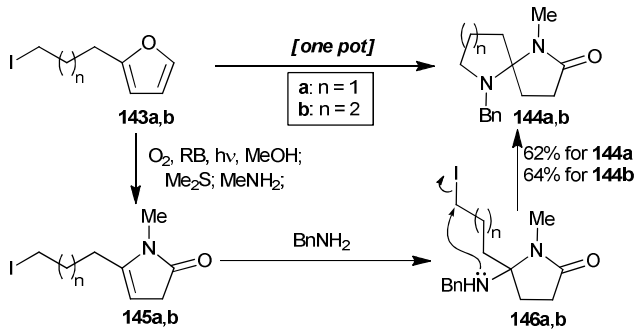


Table 3 A: Synthesis of spiroaminals. **B**: Conditions for preferential Pictet-Spengler reaction.



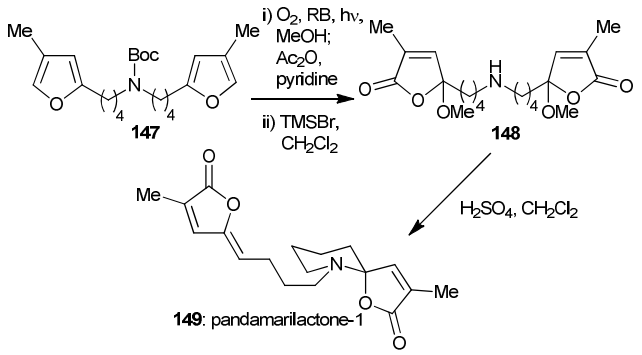
Scheme 26 One pot preparation of 1-azaspirocycles.

Synthesis of the diazaspirocycles (X = N, **U**, Scheme 25) was accomplished as a one pot procedure (Scheme 26),[104] but required the use of a small trick to avoid the complicating presence of an unprotected basic nitrogen functionality in the photooxidation step. We had previously shown that an alkyl iodide functionality could be carried through the reaction sequence untouched (Table 2, **126c**) so this was once again used as the initial furan substrate (**143**, Scheme 27). Two different amines were added during the sequence, the first acted in the formation of the *N*-acylenamine **145** and the second reacted with the *N*-acyliminium ion intermediate. This second amine was then intramolecularly alkylated (**146** → **144**) as part of the same one pot reaction sequence by the iodide residue, thus furnishing the desired diazaspirocycles.



Scheme 27 One pot synthesis of diazaspirocycles.

Just as we were completing the writing of this manuscript a nice example with relevance to this topic was published by Robertson's group.[105] Therein, a symmetric difuran substrate **147** (containing a Boc-protected nitrogen) was photooxidised with the resultant di-γ-methoxy-butenolide **148** affording the natural product pandamarilactone-1 **149** after reaction under acid conditions (Scheme 28).



Scheme 28 Synthesis of pandamarilactone-1.

Cumulatively, we[97,99,101,104] and others[92,95,105] have shown that nitrogen (either in its basic, protected or a masked form) can be introduced into sequences that initially harness the reaction of $^1O_2$ and furan and that furnish a diverse range of complex polycycles whilst tolerating fragile functionalities (such as iodides and aldehydes). Many possibilities for further study still remain in this area.

Scaling up.

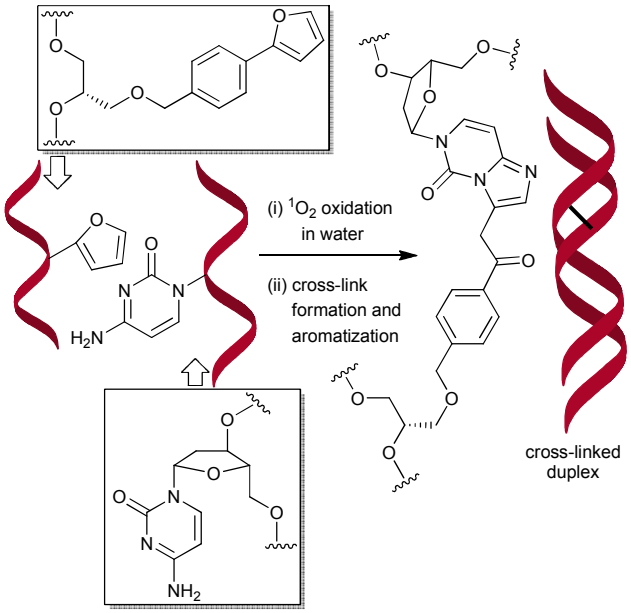
The second and, until recently, contentious area relates to the scaling up photochemical reactions. The problems typically associated with scaling up photochemical reactions (for example; cooling systems for the lamps and light penetration) had severely limited their application in different settings and had, therefore, prevented the broader uptake of these methods. Industry has traditionally shunned photochemistry and its implementation was mostly restricted to small scale research problems. However, recent advances in technology (for example; lamps requiring less cooling[47]) and new reactor designs (namely; the use of Continuous Flow Reactors) have gone a substantial way towards reversing this negative outlook.

The things we are talking of in this section are considered by many to be part of a "hot" current topic in synthetic organic chemistry, but it is worth remembering however that some have always believed in the potential of large scale singlet oxygen photochemistry;[106] indeed, Schenck, our original hero of the subject, was making ascaridol on large scales using natural sunlight 60 years ago in his garden (*vide supra*, Scheme 5).[13,23] What is making a difference today, however, is not this post-war precedent, but the movement embracing new reactor technologies which began almost in unison with the new millennium. Continuous Flow Reactors (CFRs) have solved so many problems (in comparison to the traditional fixed volume batch reactors) in a host of different synthetic scenarios, and, critically, are proving to be relatively easy to construct within ordinary synthetic laboratory settings that their use is blossoming. It is beyond our remit to comprehensively cover this field, even within the realms of photochemical applications so instead, we will highlight a few key papers and instances where simple, effective and easily reproducible apparatus/protocols have been employed. An early innovation came in the form of Falling Film Reactors,[107] but these were quickly superseded by the more efficient CFR prototypes. A key publication came from the mainstream synthetic organic laboratory of Kevin Booker-Milburn (in 2005) in which it was described how a CFR had been simply constructed and applied to several preparative photochemical reactions (not involving $^1O_2$, scales from 178g/24h to 685g/24h).[108] When we talk specifically about singlet oxygen reactions, it might be said that Peter Seeberger has more systematically begun to explore the field, although some examples had already been reported.[109] In 2011, he with his co-worker, Lévesque, published a simple CFR system applied to a range of singlet oxygen-mediated reactions.[110] More recently, they have published a CFR synthesis of the anti-malarial drug artemisinin (including a $^1O_2$-mediated step)[111] and a small review covering this topic.[112] Other flow devices are also beginning to be reported such as a bubble reactor,[113] or glass microfluidic device functionalised with photoactive porphyrins.[114] It is still early days, but the future of benign large scale photochemical technologies is looking very bright!

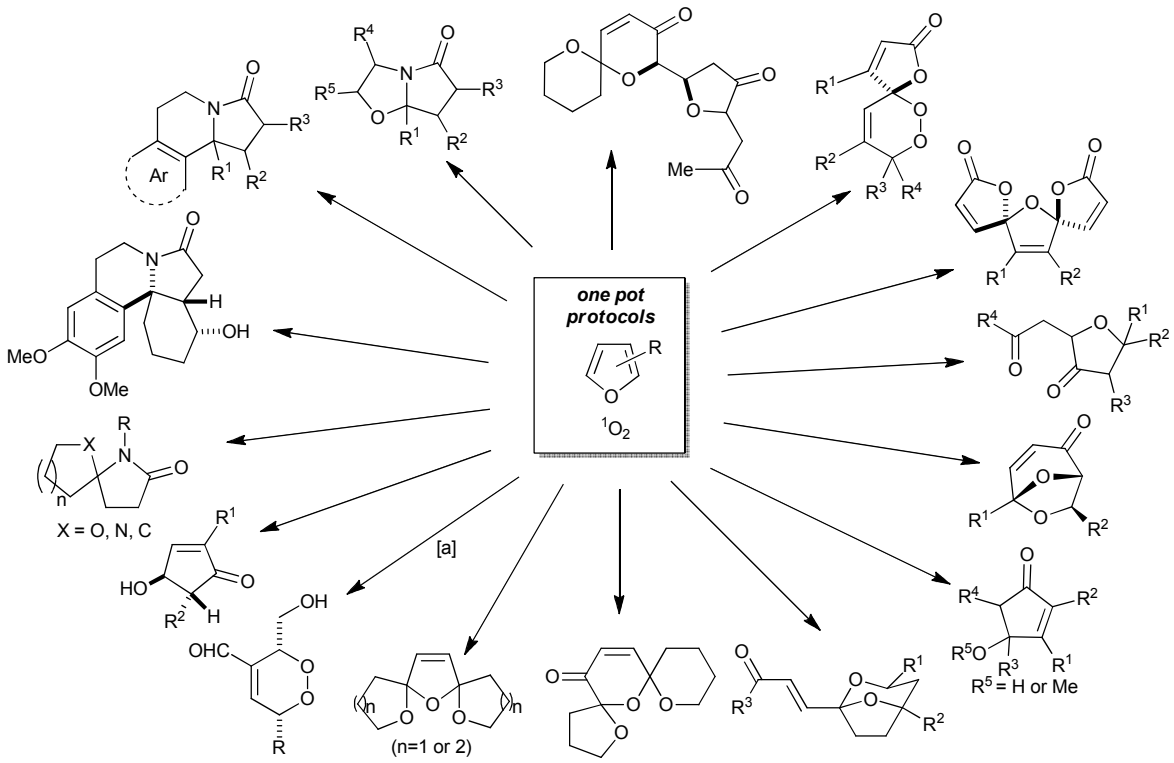
Furthermore, over the years there have been instances where industry has used large scale photochemistry, but they have been not only rare but somewhat reluctant. This too, however, may be changing. For example, Sanofi (Sisteron Plant, France) is undertaking the industrial scale semi-synthesis of the important anti-malarial drug artemisinin, in a bid to meet the world's ever-increasing need for this drug, using, as one of their four steps, a singlet oxygen-mediated photooxidation reaction.[115]

Other Applications.

There is always a section with miscellany in every review and this is ours; however, we think here it is a very important section because when ideas spread beyond the field in which they were originally conceived it is a sign of their real usefulness and from there the trend is generally upwards. This is turning out to be true for $^1O_2$ reactions with furan which are now starting to pop up all over the place - used in entirely novel ways in a diverse range of new research fields. For example; in sequence specific



Scheme 29 Furan photooxidation for DNA cross linking by Madder and co-workers



[a] - not one pot procedure

Scheme 30 A diverse set of motifs that have been accessed by singlet oxygen-mediated furan oxidations in our group.

DNA/RNA cross-linking triggered by light (for achieving artificial control of gene expression, Scheme 29),[116] protein-RNA cross-linking,[117] $^1O_2$-responsive conjugated polymers (new materials),[118] fluorescent probes for detection of intracellular oxygen,[119] the sustainable synthesis of herbicides,[120] and the sustainable synthesis of new surfactants.[121]

Conclusions

We have shown that today the range of chemistry that can be done based around the reaction of $^1O_2$ with furan, and the diversity of product motifs attainable from these protocols, is huge, and, furthermore, it's still expanding at a very fast rate (for selected examples from our work only, see: Scheme 30). We have shown that $^1O_2$-mediated cascade reaction sequences are extremely versatile and flexible and can be used to attain rapid increases in three dimensional molecular complexity. They can also include a broad range of different sensitive functionalities (from unprotected alcohols, iodides and aldehydes to basic nitrogen groups). Furthermore, we have shown how $^1O_2$ is a green and highly efficient reagent that can be readily used in procedures that conform to many of the criteria relating to the ideal of achieving scalable sustainable chemistry.

All that now remains is for more readers to give it a try in their own research and in order for the probability of success to be maximised we will close with a few practical tips. Firstly, the examples above show that small changes in reaction conditions (for example; a switch from an organic solvent to MeOH, or to water) can alter the course of the reaction sequence quite dramatically – so the conditions required must be considered and carefully tailored to the problem-in-hand. Secondly, and depending very much on the light source, reaction times can be very short – in our laboratory we have a powerful lamp and reaction times are measured with a stopwatch not a wall-mounted clock. Thirdly, excluding the lamp (that may be virtually any source of visible light, as long as the reaction times are adjusted appropriately), no special apparatus is required; we use nothing but standard laboratory glassware, needles etc. Perhaps the only extra consideration required is to ensure that the path of the light from lamp to substrate is not hindered (for example, we use a glass ice bath and place the reaction vessel right at its edge so that neither bath, nor ice, stop light passing to the substrate). Further details can be found in the Supporting Information section of any of our papers (*vide supra*).

Photochemistry, in general, and, singlet oxygen-mediated photooxidations in particular, are coming of age. Give them a try; for the rewards can be very big.

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Notes and references

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1 In this review, we will focus on photochemically-generated singlet oxygen because of its broader functional group tolerance. Singlet oxygen can also be generated by non-photochemical means (for example, by reaction of H_2O_2/NaOCl,[1c] or RCO_3H/NaOAc,[1d] or ozone/triphenyl phosphite,[1e,1f] or H_2O_2/sodium molybdate[1g]), see: (*a*) M. C. DeRosa, R. J. Crutchley, *Coord. Chem. Rev*., 2002, **233-234**, 351; (*b*) R. W. Murray, In *Singlet Oxygen*, H. H. Wasserman and R. W. Murray Ed. Academic Press: New York, 1979, pp 59-114; (*c*) C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, 1964, **86**, 3879; (*d*) I. Kuwajima and H. Urabe, *Tetrahedron Lett.*, 1981, **22**, 5191; (*e*) R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, 1969, **91**, 5358; (*f*) P. D. Bartlett, G. D. Medenhall and D. L. Durham, *J. Org. Chem*., 1980, **45**, 4269; (*g*) J. M. Aubry, B. Cazin and F. Duprat, *J. Org. Chem*., 1989, **54**, 726.

2 E. L. Clennan and A. Pace, *Tetrahedron*, 2005, **61**, 6665.

3 (*a*) E. L. Clennan, *Tetrahedron*, 2000, **56**, 9151; (*b*) M. Stratakis and M. Orfanopoulos, *Tetrahedron*, 2000, **56**, 1595; (*c*) M. Prein and W. Adam, *Angew. Chem. Int. Ed.*, 1996, **35**, 477.

4 A. L. Baumstark, In *Organic Peroxides*, A. A. Frimer Ed. CRC Press: Boca Raton, FL, 1985, Vol II, pp 1-35.

5 E. L. Clennan and C. S. Foote, In *Organic Peroxides*, W. Ando Ed. John Wiley & Sons Ltd.: New York, 1992, pp 255-318.

6 (*a*) K. Gollnick and A. Griesbeck, *Tetrahedron*, 1985, **41**, 2057; (*b*) B. L. Feringa, *Recl. Trav. Chim. Pays-Bas*, 1987, **106**, 469.

7 T. Montagnon, M. Tofi and G. Vassilikogiannakis, *Acc. Chem. Res.*, 2008, **41**, 1001.

8 B. König, *Sci. Synth.*, 2000, **9**, 183.

9 For reviews, see: (*a*) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395; (*b*) S. F. Kirsch, *Org. Biomol. Chem*., 2006, **4**, 2076; (*c*) R. C. D. Brown, *Angew. Chem. Int. Ed.*, 2005, **44**, 850.

10 For leading references, see: (*a*) A. N. Butkevich, L. Meerpoel, I. Stansfield, P. Angibaud, A. Corbu, J. Cossy, *Org. Lett*., 2013, **15**, 3840; (*b*) E. Li, W. Yao, X. Xie, C. Wang, Y. Shao and Y. Li, *Org. Biomol. Chem*., 2012, **10**, 2960; (*c*) M. Egi, K. Azechi and S. Akai, *Org. Lett*., 2009, **11**, 5002; (*d*) A. Aponick, C.-Y. Li, J. Malinge and E. F. Marques, *Org. Lett*., 2009, **11**, 4624.

11 B. L. Feringa, O. J. Gelling and L. Meesters, *Tetrahedron Lett*., 1990, **31**, 7201.

12 (*a*) G. Vassilikogiannakis and M. Stratakis, *Angew. Chem. Int. Ed.*, 2003, **42**, 5465; (*b*) G. Vassilikogiannakis, I. Margaros and T. Montagnon, *Org. Lett*., 2004, **6**, 2039; (*c*) G. Vassilikogiannakis, I. Margaros, T. Montagnon and M. Stratakis, *Chem. Eur. J.*, 2005, **11**, 5899.

13 K. Schaffner, *Angew. Chem. Int. Ed.*, 2003, **42**, 2932.

14 G. O. Schenck, *Angew. Chem.*, 1944, **56**, 101.

15 C. Dufraisse and S. Ecary, *C. R. Acad. Sci. Paris*, 1946, **233**, 735.

16 For selected leading references, see: (*a*) M. R. Iesce, F. Cermola, M. L. Graziano, G. Cimminiello and R. Scarpati, *J. Chem. Soc. Perkin Trans. 1*, 1992, 1855; (*b*) M. L. Graziano, M. R. Iesce, F. Cermola, G. Cimminiello and R. Scarpati, *J. Chem. Soc. Perkin Trans. 1*, 1991, 1479; (*c*) M. I. Graziano, M. R. Iesce, *Synthesis*, 1985, 1151; (*d*) E. L. Clennan and M. E. Mehrsheikh-Mohammadi, *J. Am. Chem. Soc.*, 1984, **106**, 7112; (*e*) K. Gollnick and A. Griesbeck, *Angew. Chem. Int. Ed.*, 1983, **22**, 726; (*f*) G. O. Schenck, *Liebigs Ann. Chem*., 1953, **584**, 156.

17 A. Greer, *Acc. Chem. Res.*, 2006, **39**, 797.

18 C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, 1964, **86**, 3880.

19 C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denny, G. O. Schenck and K.-H. Schulte-Elte, *Tetrahedron*, 1967, **23**, 2583.

20 T. J. Katz, V. Balogh and J. M. Schulman, *J. Am. Chem. Soc.*, 1968, **90**, 734.

21 H. H. Wasserman and A. R. Doumaux, Jr., *J. Am. Chem. Soc.*, 1962, **84**, 4611.

22 H. H. Wasserman and J. L. Ives, *Tetrahedron*, 1981, **37**, 1825.

23 G. O. Schenck, *Angew. Chem.*, 1952, **64**, 12.

24 (*a*) B. L. Feringa, *Tetrahedron Lett*., 1981, **22**, 1443; (*b*) B. L. Feringa and R. J. Butselaar, *Tetrahedron Lett*., 1982, **23**, 1941; (*c*) B. L. Feringa and B. de Lange, *Tetrahedron Lett*., 1988, **29**, 1303.

25 R. Kanazawa, H. Kotsuki and T. Tokoroyama, *Tetrahedron Lett.*, 1975, **16**, 3651.

26 (*a*) P. G. Sammes and L. J. Street, *J. Chem. Soc. Chem. Commun.*, 1983, 666; (*b*) P. G. Sammes, L. J. Street and R. J. Whitby, *J. Chem. Soc. Perkin Trans. 1*, 1986, 281.

27 For selected leading references and reviews, see: (*a*) Y. S. Rao, *Chem. Rev.*, 1976, **76**, 625; (*b*) D. W. Knight, *Contemp. Org. Synth.*, 1994, **1**, 287; (*c*) N. B. Carter, A. E. Nadany and J. B. Sweeney, *J. Chem. Soc., Perkin Trans. 1*, 2002, **1**, 2324; (*d*) S. N. Patil and F. Liu, *Org. Lett.*, 2007, **9**, 195; (*e*) A. Munoz and R. P. Murelli, *Tetrahedron Lett.*, 2012, **53**, 6779. See also ref. 31.

28 For selected examples (from prior to 2000) of furan photooxidations used to make natural products containing γ-hydroxy/alkoxy-butenolides (or close modifications thereof), see: (*a*) J. I. DeGraw, *Tetrahedron*, 1972, **28**, 967; (*b*) J. B. Heather, R. S. D. Mittal and C. J. Sih, *J. Am. Chem. Soc.*, 1974, **96**, 1976; (*c*) K. Naya, R. Kanazawa and M. Sawada, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 3220; (*d*) S. Katsumura, S. Fujiwara and S. Isoe, *Tetrahedron Lett.*, 1985, **26**, 5827; (*e*) M. E. Garst, E. A. Tallman, J. N. Bonfiglio, D. Harcourt, E. B. Ljungwe and A. Tran, *Tetrahedron Lett.*, 1986, **27**, 4533; (*f*) P. Bury, G. Hareau, P. Kocieński and D. Dhanak, *Tetrahedron*, 1994, **50**, 8793; (*g*) R. Shiraki, A. Sumino, K. Tadano and S. Ogawa, *J. Org. Chem.*, 1996, **61**, 2845; (*h*) E. J. Corey and B. E. Roberts, *J. Am. Chem. Soc.*, 1997, **119**, 12425; (*i*) S. R. Magnuson, L. Sepp-Lorenzino, N. Rosen and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1998, **120**, 1615.

29 For selected examples (from prior to 2000) of furan photooxidations used to make butenolide building blocks, see: (*a*) A. I. Meyers, R. L. Nolen, E. W. Collington, T. A. Narwid and R. C. Strickland, *J. Org. Chem*., 1973, **38**, 1974; (*b*) E. J. Corey, D. N. Crouse and J. E. Anderson, *J. Org. Chem*., 1975, **40**, 2140; (*c*) J. D. White, J. P. Carter and H. S. Kezar III, *J. Org. Chem*., 1982, **47**, 929; (*d*) P. Magnus, P. M. Cairns and C. S. Kim, *Tetrahedron Lett.*, 1985, **26**, 1963; (*e*) K. D. Freeman-Cook and R. L. Halcomb, *J. Org. Chem*., 2000, **65**, 6153.

30 For selected leading references, see: (*a*) B. L. Feringa and J. C. De Jong, *J. Org. Chem*., 1988, **53**, 1125; (*b*) B. L. Feringa and B. De Lange, *Tetrahedron*, 1988, **44**, 7213; (*c*) B. L. Feringa, B. De Lange and J. C. De Jong, *J. Org. Chem*., 1989, **54**, 2471; (*d*) B. De Lange, F. van Bolhuis and B. L. Feringa, *Tetrahedron*, 1989, **45**, 6799; (*e*) B. L. Feringa, B. De Lange, J. F. G. A. Jansen, J. C. De Jong, M. Lubben, W. Faber and E. P. Schudde, *Pure Appl. Chem.*, 1992, **64**, 1865. See also ref. 24c.

31 For selected examples from a large field post 2000, see: (*a*) I. T. Chen, I. Baitinger, L. Schreyer and D. Trauner, *Org. Lett*., 2014, **16**, 166; (*b*) E. E. Anagnostaki and A. L. Zografos, *Org. Lett.*, 2013, **15**, 152; (*c*) J.-Q. Dong and H. N. C. Wong, *Angew. Chem. Int. Ed*., 2009, **48**, 2351; (*d*) F. Yoshimura, M. Sasaki, I. Hattori, K. Komatsu, M. Sakai, K. Tanino and M. Miyashita, *Chem. Eur. J*., 2009, **15**, 6626; (*e*) Y. Hayashi, M. Shoji, H. Ishikawa, J. Yamaguchi, T. Tamura, H. Imai, Y. Nishigaya, K. Takabe, H. Kakeya and H. Osada, *Angew. Chem. Int. Ed*., 2008, **47**, 6657; (*f*) I. Margaros and G. Vassilikogiannakis, *J. Org. Chem.*, 2008, **73**, 2021; (*g*) S. N. Patil and F. Liu, *J. Org. Chem*., 2008, **73**, 4476; (*h*) J. S. Clark, J. M. Northall, F. Marlin, B. Nay, C. Wilson, A. J. Blake and M. J. Waring, *Org. Biomol. Chem*., 2008, **6**, 4012; (*i*) M. Helliwell, S. Karim, E. R. Parmee and E. J. Thomas, *Org. Biomol. Chem*., 2005, **3**, 3636; (*j*) B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 2003, **125**, 3090; (*k*) L. H. Mace, M. S. Shanmugham, J. D. White and M. G. B. Drew, *Org. Biomol. Chem*., 2006, **4**, 1020; (*l*) I. T. Chen, I. Baitinger, L. Schreyer, D. Trauner, *Org. Lett*., 2014, **16**, 166.

32 (*a*) B. L. Feringa and R. J. Butselaar, *Tetrahedron Lett.*, 1981, **22**, 1447; (*b*) G. C. M. Lee, E. T. Syage, D. A. Harcourt, J. M. Holmes and M. E. Garst, *J. Org. Chem*., 1991, **56**, 7007.

33 B. L. Feringa and R. J. Butselaar, *Tetrahedron Lett.*, 1983, **24**, 1193. See also ref. 16f.

34 F. Perez and F. Ramso, M. Victoria, Spanish Patent 431 794; *Chem Abstr.*, 1972, **87**, 22418.

35 W. Adam and A. Rodriguez, *Tetrahedron Lett.*, 1981, **22**, 3505.

36 M. R. Kernan and D. J. Faulkner, *J. Org. Chem*., 1988, **53**, 2773.

37 P. T. Anastas and J. C. Warner, In Green Chemistry: Theory and Practice, Oxford University Press: USA, 2000.

38 (*a*) K. C. Nicolaou and T. Montagnon, In Molecules that Changed the World, Wiley-VCH: Weinheim, 2008; (*b*) K. C. Nicolaou and E. J. Sorensen, In Classics in Total Synthesis I, Wiley-VCH: Weinheim, 1996; (*c*) K. C. Nicolaou and S. A. Snyder, In Classics in Total Synthesis II, Wiley-VCH: Weinheim, 2003.

39 (*a*) P. A. Wender, *Tetrahedron*, 2013, **69**, 7529; (*b*) P. A. Wender, V. A. Verma, T. J. Paxton and T. H. Pillow, *Acc. Chem. Res.*, 2008, **41**, 40; (*c*) P. A. Wender and B. L. Miller, In *Organic Synthesis: Theory and Applications*, T. Hudlicky Ed. JAI: Greenwich, 1993, pp 27-66.

40 B. M. Trost, *Science*, 1991, **254**, 1471.

41 J. B. Hendrickson, *J. Am. Chem. Soc.*, 1975, **97**, 5784.

42 (*a*) T. Newhouse, P. S. Baran and R. W. Hoffmann, *Chem. Soc. Rev.*, 2009, **38**, 3010; (*b*) T. Gaich and P. S. Baran, *J. Org. Chem*., 2010, **75**, 4657.

43 (*a*) For a range of different highly efficient and sustainable reactions all carried out in water, see: D. Noutsias, I. Alexopoulou, T. Montagnon and G. Vassilikogiannakis, *Green Chemistry*, 2012, **14**, 601; (*b*) T. Montagnon, D. Noutsias, I. Alexopoulou, M. Tofi and G. Vassilikogiannakis, *Org. Biomol. Chem*., 2011, **9**, 2031; (*c*) A. Astarita, F. Cermola, M. DellaGreca, M. R. Iesce, L. Previtera, M. Rubino, *Green Chem*, 2009, **11**, 2030.

44 (*a*) R. W. Hoffmann, *Synthesis*, 2006, 3531; (*b*) I. S. Young and P. S. Baran, *Nat. Chem.*, 2009, **1**, 193.

45 N. Z. Burns, P. S. Baran and R. W. Hoffmann, *Angew. Chem. Int. Ed.*, 2009, **48**, 2854.

46 (*a*) E. A. Anderson, *Org. Biomol. Chem*., 2011, **9**, 3997; (*b*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem. Int. Ed.*, 2006, **45**, 7134; (*c*) L. F. Tietze, *Chem. Rev*. 1996, **96**, 115; (*d*) H. Pellissier, *Chem. Rev*., 2013, **113**, 442.

47 J. M. Carney, R. J. Hammer, M. Hulce, C. M. Lomas and D. Miyashiro, *Synthesis*, 2012, **44**, 2560.

48 G. O. Schenck and K. Ziegler, *Naturwiss*, 1944, **32**, 157.

49 V. Hickmann, A. Kondoh, B. Gabor, M. Alcarazo and A. Fürstner, *J. Am. Chem. Soc.*, 2011, **133**, 13471.

50 For selected early examples of biogenetic hypotheses involving singlet oxygen, see: (*a*) S. A. Look, M. T. Burch, W. Fenical, Q. Zheng and J. Clardy, *J. Org. Chem*. 1985, **50**, 5741; (*b*) B. Carté, M. R. Kernan, E. B. Barrabee, D. J. Faulkner, G. K. Matsumoto and J. Clardy, *J. Org. Chem*. 1986, **51**, 3528.

51 P. A. Roethle, P. T. Hernandez and D. Trauner, *Org. Lett.*, 2006, **8**, 5901.

52 For a review of the subject, see: I. Margaros, T. Montagnon, M. Tofi, E. Pavlakos and G. Vassilikogiannakis, *Tetrahedron*, 2006, **62**, 5308.

53 I. Margaros and G. Vassilikogiannakis, *J. Org. Chem.*, 2007, **72**, 4826.

54 I. Margaros, T. Montagnon and G. Vassilikogiannakis, *Org. Lett*. 2007, **9**, 5585.

55 (*a*) S. Singh, A. I. Gray, B. W. Skelton, P. G. Waterman and A. H. White, *Aust. J. Chem.*, 1991, **44**, 1789; (*b*) H. M. Sirat, D. Masri and A. A. Rahman, *Phytochemistry*, 1994, **36**, 699; (*c*) L.-K. Sy and G. D. Brown, *J. Nat. Prod*., 1997, **60**, 904.

56 E. Breitmaier, In *Terpenes: Flavours, Fragrances, Pharmaca, Pheromones*, Wiley-VCH: Weinheim, 2006, pp 24.

57 For a leading reference, see: J. Marrero, A. D. Rodríguez and C. L. Barnes, *Org. Lett.*, 2005, **7**, 1877.

58 (*a*) Y. Miyazaki, M. Shibuya, H. Sugawara, O. Kawaguchi, C. Hirose, J. Nagatsu and S. Esumi, *J. Antibiot.*, 1974, **27**, 814; (*b*) J. L. Occolowitz, D. H. Berg, M. Debono and R. L. Hamill, *Biomed. Mass Spectrom*., 1976, **3**, 272; (*c*) H. Seto, T. Yahagi, Y. Miyazaki and N. Otake, *J. Antibiot.*, 1977, **30**, 530.

59 For a review of the isolation investigations, see: M. Kita and D. Uemura, *Chem. Lett*., 2005, **34**, 454.

60 For the original isolation paper, see: T. Hu, J. M. Curtis, Y. Oshima, M. A. Quilliam, J. A. Walter, W. M. Watson-Wright and J. L. C. Wright, *J. Chem. Soc., Chem. Commun.*, 1995, 2159.

61 For a leading reference, see: K. C. Nicolaou, M. O. Frederick, E. Z. Loizidou, G. Petrovic, K. P. Cole, T. V. Koftis and Y. M. A. Yamada, *Chem. Asian J*., 2006, **1**, 245.

62 For a leading review, see: M. A. Brimble and F. A. Farès, *Tetrahedron*, 1999, **55**, 7661.

63 (*a*) R. Whitby and P. Kocieński, *J. Chem. Soc., Chem. Commun.*, 1987, 906; (*b*) P. Kocieński, Y. Fall and R. Whitby, *J. Chem. Soc., Perkin Trans. 1*, 1989, 841.

64 (*a*) F. Perron and K. F. Albizati, *J. Org. Chem*., 1989, **54**, 2044; (*b*) R. C. D. Brown and P. J. Kocieński, *Synlett*, 1994, 417; (*c*) P. J. McDermott and R. A. Stockman, *Org. Lett*. 2005, **7**, 27.

65 A. A. Ponomarev and I. A. Markushina, *Zh. Obshch. Khim*., 1963, **33**, 3955.

66 P. J. Kocieński, R. C. D. Brown, A. Pommier, M. Procter and B. Schmidt, *J. Chem. Soc., Perkin Trans. 1*, 1998, 9.

67 (*a*) T. Georgiou, M. Tofi, T. Montagnon and G. Vassilikogiannakis, *Org. Lett.*, 2006, **8**, 1945; (*b*) M. Triantafyllakis, M. Tofi, T. Montagnon, A. Kouridaki, G. Vassilikogiannakis, *Org. Lett*., 2014, **16**, 3150.

68 M. Tofi, T. Montagnon, T. Georgiou and G. Vassilikogiannakis, *Org. Biomol. Chem.*, 2007, **5**, 772.

69 For original isolation, see: (*a*) T. Yasumoto, M. Murata, Y. Oshima, M. Sano, G. K. Matsumoto and J. Clardy, *Tetrahedron*, 1985, **41**, 1019; For the only total synthesis to date, see: (*b*) D. A. Evans, H. A. Rajapakse and D. Stenkamp, *Angew. Chem. Int. Ed*., 2002, **41**, 4569; (*c*) D. A. Evans, H. A. Rajapakse, A. Chiu and D. Stenkamp, *Angew. Chem. Int. Ed*., 2002, **41**, 4573.

70 A. Kouridaki, T. Montagnon, M. Tofi and G. Vassilikogiannakis, *Org. Lett.*, 2012, **14**, 2374.

71 A. Kouridaki, T. Montagnon, D. Kalaitzakis and G. Vassilikogiannakis, *Org. Biomol. Chem*., 2013, **11**, 537.

72 O. Achmatowicz Jr., P. Bukowski, B. Szechner, Z. Zwierzchowska and A. Zamojski, *Tetrahedron*, 1971, **27**, 1973.

73 M. P. Georgiadis and E. A. Couladouros, *J. Org. Chem*., 1986, **51**, 2725.

74 (*a*) R. Laliberté, G. Médawar and Y. Lefebvre, *J. Med. Chem*., 1973, **16**, 1084; (*b*) O. Achmatowicz Jr. and R. Bielski, *Carbohydr. Res*. 1977, **55**, 165.

75 C. Domínguez, A. G. Csáky and J. Plumet, *Tetrahedron Lett.*, 1990, **31**, 7669.

76 B. M. Adger, C. Barrett, J. Brennan, M. A. McKervey and R. W. Murray, *J. Chem. Soc., Chem. Commun.*, 1991, 1553.

77 G. Piancatelli, A. Scettri and M. D'Auria, *Tetrahedron Lett.*, 1977, **18**, 2199.

78 T.-L. Ho and S. G. Sapp, *Synth. Commun.*, 1983, **13**, 207.

79 J. Wahlen, B. Moens, D. E. De Vos, P. L. Alsters and P. A. Jacobs, *Adv. Synth. Catal.*, 2004, **346**, 333.

80 T. Shono and Y. Matsumura, *Tetrahedron Lett.*, 1976, **17**, 1363.

81 (*a*) D. R. Williams, J. W. Benbow and E. E. Allen, *Tetrahedron Lett*., 1990, **31**, 6769; (*b*) P. Magnus and L. Shen, *Tetrahedron*, 1999, **55**, 3553.

82 For examples of the use in syntheses of low temperature $^1O_2$-mediated Achmatowitcz reactions, see: (*a*) D. R. Williams, J. W. Benbow, J. G. McNutt and E. E. Allen, *J. Org. Chem*., **60**, 1995, 833; (*b*) W. E. Bauta, J. Booth, M. E. Bos, M. DeLuca, L. Diorazio, T. J. Donohoe, C. Frost, N. Magnus, P. Magnus, J. Mendoza, P. Pye, J. G. Tarrant, S. Thom and F. Ujjainwalla, *Tetrahedron*, 1996, **52**, 14081; (*c*) P. Magnus, L. Diorazio, T. J. Donohoe, M. Giles, P. Pye, J. Tarrant and S. Thom, *Tetrahedron*, 1996, **52**, 14147; (*d*) F. Cermola, R. Sferruzza and M. R. Iesce, *Tetrahedron Lett*., 2014, **55**, 737.

83 D. Noutsias, A. Kouridaki and G. Vassilikogiannakis, *Org. Lett*., 2011, **13**, 1166.

84 N. González, J. Rodríguez and C. Jiménez, *J. Org. Chem.*, 1999, **64**, 5705.

85 For a leading reference regarding 2-hydroxy-*exo*-brevicomin and a synthesis, see: B. Cheng and L. S. Liebeskind, *Org. Lett*., 2009, **11**, 3682.

86 M. Tofi, K. Koltsida and G. Vassilikogiannakis, *Org. Lett*., 2009, **11**, 313.

87 C. Gryparis, I. N. Lykakis, C. Efe, I.-P. Zaravinos, T. Vidali, E. Kladou and M. Stratakis, *Org. Biomol. Chem*., 2011, **9**, 5655.

88 For leading examples, see: (*a*) A. Zúñiga, G. Pazos, P. Besada and Y. Fall, *Tetrahedron Lett*., 2012, **53**, 4293; (*b*) I. García, M. Pérez, P. Besada, G. Gómez and Y. Fall, *Tetrahedron Lett*., 2008, **49**, 1344; (*c*) D. Alonso, M. Pérez, G. Gómez, B. Covelo and Y. Fall, *Tetrahedron*, 2005, **61**, 2021.

89 D. Kalaitzakis, M. Triantafyllakis, I. Alexopoulou, M. Sofiadis, G. Vassilikogiannakis, *Angew. Chem. Int. Ed*., 2014, just accepted.

90 N. Sofikiti, M. Tofi, T. Montagnon, G. Vassilikogiannakis and M. Stratakis, *Org. Lett*., 2005, **7**, 2357.

91 G. Vassilikogiannakis, I. Alexopoulou, M. Tofi and T. Montagnon, *Chem. Commun.*, 2011, **47**, 259.

92 For selected examples using an azide group as a masked basic amine in furan photooxidations, see: (*a*) I. García, M. Pérez, Z. Gándara, G. Gómez and Y. Fall, *Tetrahedron Lett*., 2008, **49**, 3609; (*b*) E. A. Kazancioglu, M. Z. Kazancioglu, M. Fistikci, H. Secen and R. Altundas, *Org. Lett*., 2013, **15**, 4790. Ref 92a also reports photooxidation of a substrate containg a Boc-protected amine.

93 (*a*) E. Baciocchi, T. Del Giaco, O. Lanzalunga, and A. Lapi, *J. Org. Chem*., 2007, **72**, 9582; (*b*) G. Jiang, J. Chen, J.-S. Huang, and C.-M. Che, *Org. Lett*., 2009, **11**, 4568.

94 (*a*) D. L. Boger and C. M. Baldino, *J. Org. Chem.*, 1991, **56**, 6942; (*b*) D. L. Boger and C. M. Baldino, *J. Am. Chem. Soc*., 1993, **115**, 11418.

95 F. Cermola, M. R. Iesce and G. Buonerba, *J. Org. Chem*., 2005, **70**, 6503.

96 For the first report, see: (*a*) A. I. Meyers, M. Harre and R. Garland, *J. Am. Chem. Soc*., 1984, **106**, 1146; For selected reviews of the field, see: (*b*) D. Romo and A. I. Meyers, *Tetrahedron*, 1991, **47**, 9503; (*c*) M. D. Groaning and A. I. Meyers, *Tetrahedron*, 2000, **56**, 9843.

97 D. Kalaitzakis, T. Montagnon, I. Alexopoulou and G. Vassilikogiannakis, *Angew. Chem. Int. Ed*., 2012, **51**, 8868.

98 (*a*) A. Pictet and T. Spengler, *Ber. Dtsch. Che. Ges*., 1911, **44**, 2030; (*b*) E. D. Cox and J. M. Cook, *Chem. Rev*., 1995, **95**, 1797.

99 D. Kalaitzakis, T. Montagnon, E. Antonatou, N. Bardají and G. Vassilikogiannakis, *Chem. Eur. J*., 2013, **19**, 10119.

100 (*a*) S. F. Dyke and S. N. Quessy, In *The Alkaloids*, R. G. A. Rodrigo Ed., Academic Press: New York, 1981, Vol. 18, pp 1-98; (*b*) T. Sano and Y. Tsuda, In *The Alkaloids*, G. A. Cordell Ed.; Academic Press: New York, 1996, Vol. 48, pp 249-337; see, also ref. 98 as a leading reference for other work in this field.

101 D. Kalaitzakis, T. Montagnon, E. Antonatou and G. Vassilikogiannakis, *Org. Lett*., 2013, **15**, 3714.

102 (*a*) F. Zhang, N. S. Simpkins and A. J. Blake, *Org. Biomol. Chem*., 2009, **7**, 1963; (*b*) A. J. Blake, C. Gill, D. A. Greenhalgh, N. S. Simpkins and F. Zhang, *Synthesis*, 2005, 3287.

103 H. I. Lee, M. P. Cassidy, P. Rashatasakhon and A. Padwa, *Org. Lett*., 2003, **5**, 5067.

104 For details of our method, and, as a lead reference for other work in relevant fields, see: D. Kalaitzakis, E. Antonatou and G. Vassilikogiannakis, *Chem. Commun*. 2014, **50**, 400.

105 K. Y. Seah, S. J. Macnaughton, J. W. P. Dallimore and J. Robertson, *Org. Lett.*, 2014, **16**, 884.

106 P. Esser, B. Pohlmann and H.-D. Scharf, *Angew. Chem. Int. Ed.*, 1994, **33**, 2009.

107 A. G. Griesbeck, N. Mapture, S. Bondock, and M. Oelgemöller, *Photochem. Photobiol. Sci*., 2003, **2**, 450.

108 B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry, K. I. Booker-Milburn, *J. Org. Chem*., 2005, **70**, 7558.

109 For selected early examples, see: (*a*) R. C. R. Wootton, R. Fortt and A. J. de Mello, *Org. Proc. Res. Dev*. 2002, **6**, 187; (*b*) K. Jähnisch and U. Dingerdissen, *Chem. Eng. Technol*., 2005, **28**, 426.

110 F. Lévesque and P. H. Seeberger, *Org. Lett*. 2011, **13**, 5008.

111 F. Lévesque and P. H. Seeberger, *Angew. Chem. Int. Ed.*, 2012, **51**, 1706.

112 D. T. McQuade and P. H. Seeberger, *J. Org. Chem*., 2013, **78**, 6384.

113 A. Yavorskyy, O. Shvydkiv, C. Limburg, K. Nolan, Y. M. C. Delauré and M. Oelgemöller, *Green Chem*., 2012, **14**, 888.

114 E. K. Lumley, C. E. Dyer, N. Pamme and R. W. Boyle, *Org. Lett*., 2012, **14**, 5724.

115 (*a*) J. Turconi, In *Semisynthetic artemisinin: path to industrial production*, the Sanofi Lecture at ESOC 2013 conf., Marseille, July 7-12 2013; (*b*) J. Dhainaut, A. Dlubala, R. Guevel, A. Medard, G. Oddon, N. Raymond and J. Turconi, patent publication WO2011026865 (02.03.2011).

116 (a) M. Op de Beeck and A. Madder, *J. Am. Chem. Soc*., 2012, **134**, 10737; (b) L. L. G. Carrette, E. Gyssels, J. Loncke and A. Madder, *Org. Biomol. Chem*., 2014, **12**, 931.

117 M. J. Schmidt, D. Summerer, *Angew. Chem. Int. Ed*., 2013, **52**, 4690.

118 E. Altınok, S. Friedle and S. W. Thomas III, *Macromolecules*, 2013, **46**, 756.

119 D. Song, S. Cho, Y. Han, Y. You and W. Nam, *Org. Lett*. 2013, **15**, 3582.

120 M. Mascal and S. Dutta, *Green Chem*., 2011, **13**, 40.

121 A. Gassama, C. Ernenwein, A. Youssef, M. Agach, E. Riguet, S. Marinković, B. Estrine and N. Hoffmann, *Green Chem*., 2013, **15**, 1558.