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Using Singlet Oxygen to Synthesize Polyoxygenated Natural Products from Furans

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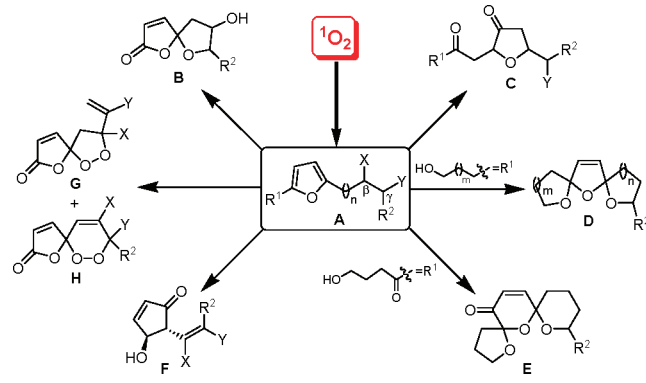

Singlet oxygen is a powerful tool in the armament of the synthetic organic chemist and possibly in that of nature itself. In this Account, we illustrate a small selection of the many ways singlet oxygen can be harnessed in the laboratory to aid in the construction of the complex molecular motifs found in natural products. A more philosophical question is also addressed: namely, how much do singlet oxygen oxidations influence the biogenesis of these natural products?

All the synthetic examples surveyed in this Account can be characterized as belonging to the same class because they all involve the oxidation of a substituted furan nucleus by singlet oxygen. Readily accessible and relatively simple furans can be transformed into a host of complex motifs present in a diverse range of natural products by the action of singlet-oxygen-mediated reaction sequences.

These reactions are highly advantageous because they frequently deliver a rapid and dramatic increase in molecular complexity in high yield. Furthermore, an unusually wide structural diversity is exhibited by the molecular motifs obtained from these reaction sequences. For example, relatively minor modifications to the starting substrate and to the reaction conditions may lead to products as variable as spiroketal lactones, 3-keto-tetrahydrofurans, various types of bis-spiroketals, 4-hydroxy cyclopentenones, or spiroperoxylactones. In addition, two more specialized examples are discussed in this Account. The core of the prunolide molecules and the chinensine family of natural products were rapidly synthesized using effective and short singlet oxygen mediated strategies; this adds weight to the assertion that singlet oxygen is a very effective moderator of complex cascade reaction sequences.

We also show how our synthetic investigations have provided evidence that these same strategies might be used in the biogenesis of these molecules. In the cases of the chinensines and the litseaverticillols, an entire and diverse family of natural products was synthesized beginning from known naturally occurring furan-bearing terpenes. Additionally, in several cases, intermediates in our syntheses have been isolated from natural sources, which suggests that we have followed the same synthetic paths as nature.

Certainly, the limit of the synthetic potential of singlet oxygen has not yet been reached, and we can look forward to seeing the boundaries expand in the future in a slew of new and interesting ways.

Introduction

Recent work emanating from our laboratories has sought to explore the scope and potential of two interwoven themes. In the first of these themes, the development and application of tandem and cascade reaction sequences mediated by singlet oxygen ($^1O_2$) to the synthesis of bioactive natural products has been targeted, and in the second, we have sought to verify the extent to which some of these sequences might be described as having

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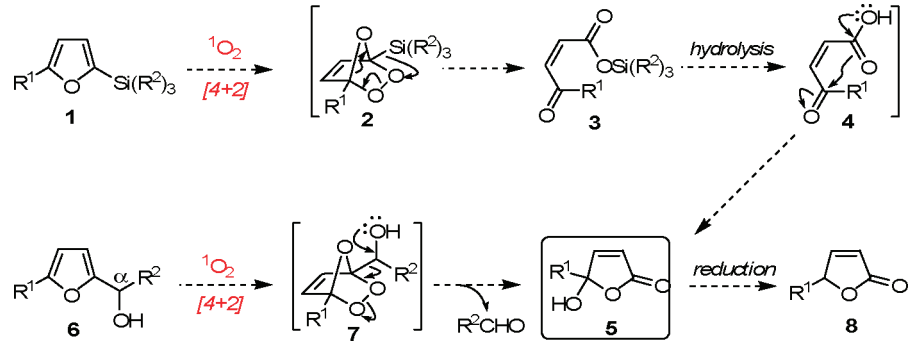
SCHEME 1



biomimetic roots. The goal in the first instance was to delineate highly efficient and rapid routes to the targeted natural products, which enhanced the synthetic scope of singlet oxygen, while in the second case a more philosophical hypothesis captured our interest. When it comes to the biogenesis of noncarbohydrate polyoxygenated natural products, the polyketide theory, where synthesis begins from acetyl coenzyme A, quite rightly dominates, but the question remains as to how much the influence of singlet oxygen oxidations in the latter stages of these biogenetic scenarios has been underestimated; after all, the right conditions for the generation and reaction of singlet oxygen abound in nature (particularly if we focus on phyto-environments). More specifically, there is an abundance of ground-state molecular dioxygen (~20% of atmospheric air is O_2), which in the presence of any one of the prolific natural photosensitizers (e.g., tannins, chlorophylls, and poryphrins, to name but a few) and natural sunlight can be excited into its singlet state—singlet oxygen ($^1O_2$). Furthermore, water is an ideal solvent for singlet oxygen chemistry, so the aqueous cellular environments of many plants and organisms support these reactions very well, especially since these solutions are also full of oxidizable substrates, such as terpenes. In this Account, a series of investigations will be discussed that reveal the progress that we have made in beginning to explore certain aspects of these dual concepts.

4-Hydroxybutenolides from Furans Using Singlet Oxygen

Even a cursory browse through the literature describing new isolates from nature reveals that 4-hydroxybutenolides (**5**, Scheme 1) and their derivatives (such as, lactones **8**) are ubiquitous, a fact that encouraged us to target the synthesis of selected exemplars, especially given that it also seems singlet oxygen is perfectly suited to the synthesis of this broad class of secondary metabolites. In the laboratory setting, the transformation of furans into 4-hydroxybutenolides mediated by $^1O_2$ has been well-studied,[1] and many significant improvements to the basic reaction have been uncovered. In its simplest form, it is possible for an unsubstituted furan to readily undergo the desired [4 + 2]-cycloaddition with photochemically generated singlet oxygen; however, the transformation of the resulting ozonide adduct into the corresponding 4-hydroxybutenolide by the action of base[2] has always incurred problems. A number of elegant solutions circumventing this obstacle have been published. As discovered by Adam and Rodriguez,[3] a silyl group can be used to stabilize the intermediates (**1** → **5**, Scheme 1), and this adaptation has seen many successful applications.[4] Alternatively, substitution of the 2-position of the starting furan with -CH(R)OH (as in **6** → **5**, Scheme 1),[5] -CHO,[1b] or -COOH[6] have all been employed to improve the transformation's outcome.

Total Synthesis of Chinensines A–E

The chinensine family of natural products, isolated from the aerial parts of a perennial shrub (*Alpina chinensis*) native to Hong Kong[7] and from a Southeast Asian plant species *Etlingera elatior*,[8] presented an ideal opportunity to showcase singlet oxygen's synthetic scope. The synthetic attraction of the compounds themselves was significantly enhanced by novel biological activities noted for the plant extracts, which already had a long history of use in Chinese traditional medicine for treatment of conditions as diverse as asthma and generalized pain. Among the newly reported biological properties, cytotoxicity against the HeLa tumor cell line[9] and certain antitumor promoting activities[10] stand out as being of particular interest.

Naturally occurring furan coronarin E (**9**, Scheme 2), which was also isolated from *Alpina chinensis*,[7] might first be the substrate for a [4 + 2]-cycloaddition with $^1O_2$, after which the resulting ozonide adduct might collapse in the presence of natural amine bases to yield the first chinensine family members, chinensines A and B (**12** and **13**). In the laboratory, this sequence was emulated, after a simple and rapid route to coronarin E (**9**) had been deconvoluted, using

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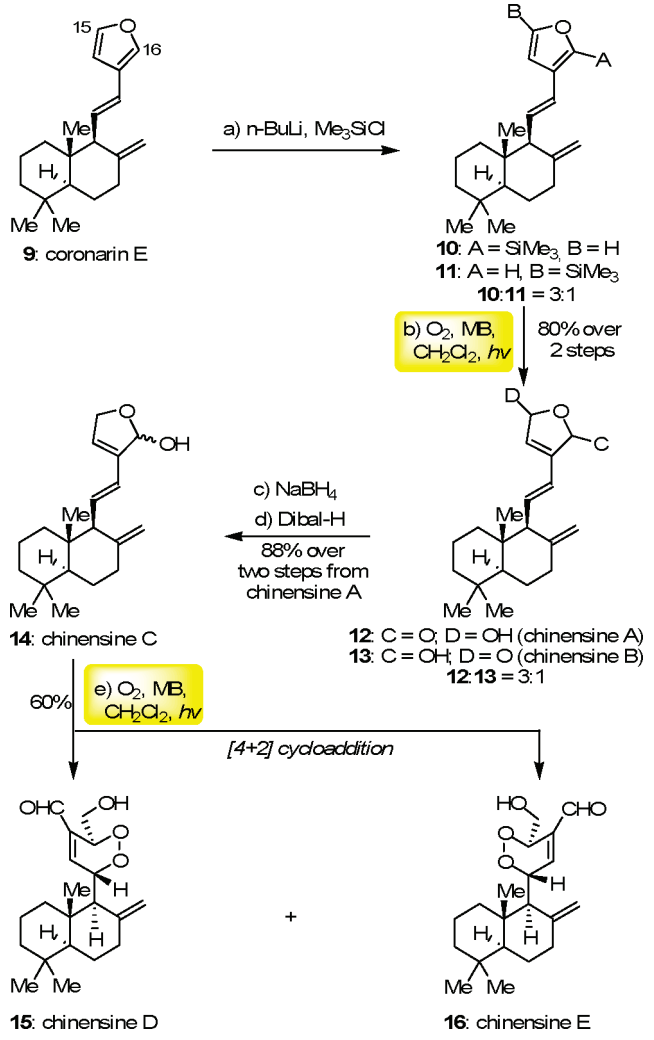

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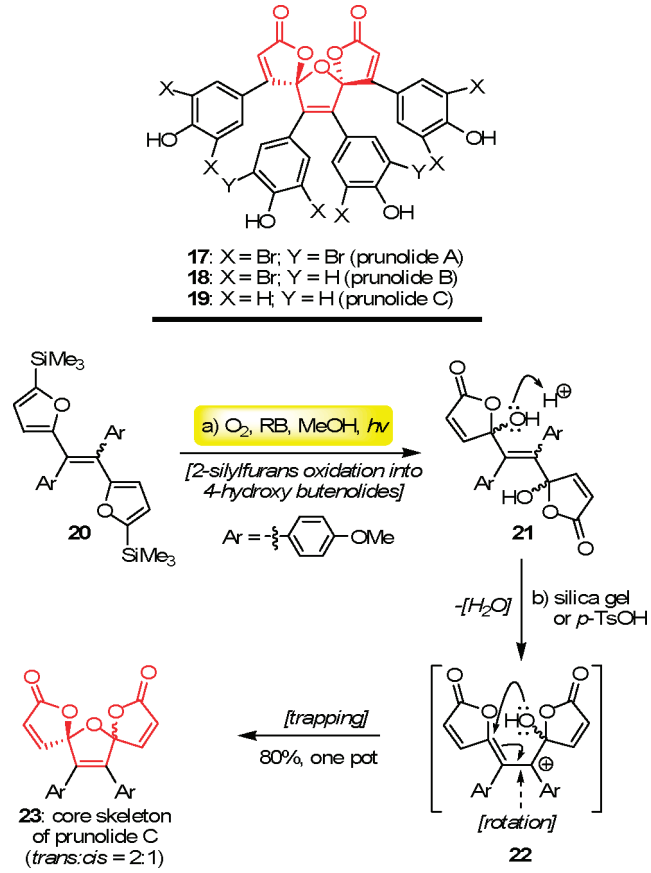
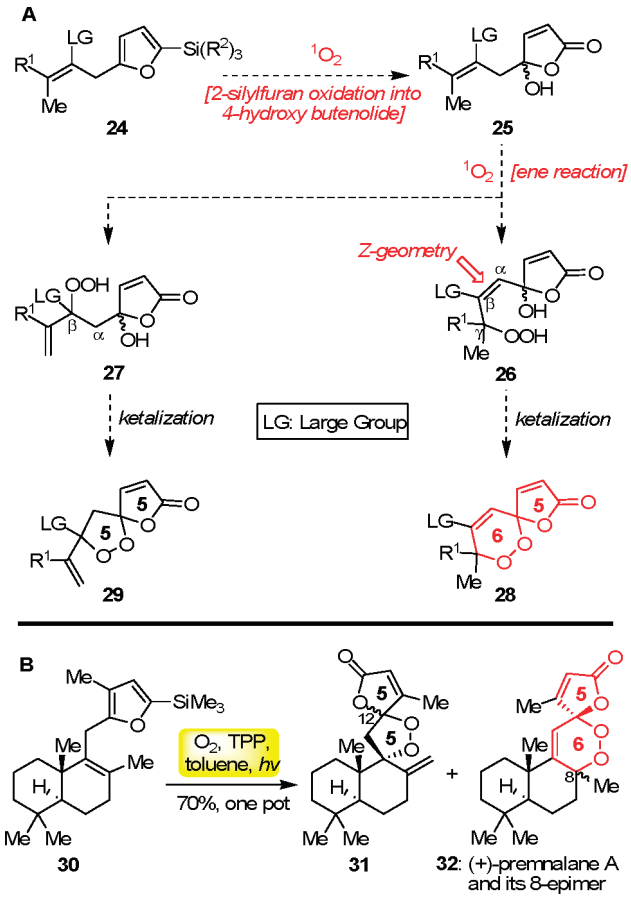


silyl stabilization at the 2-position of coronarin E's furan moiety as the only modification (**9** → **10** + **11** → **12** × **13**).[11] It is worthy of note that the silylation of coronarin E (**9**) afforded both of the two possible regioisomers, **10** and **11**. As desired for the synthesis' continuation, the major product was chinensine A's precursor, silyl furan **10** (**10**/**11** = 3:1). The desired bias for the more sterically hindered position had been accomplished due to the unsaturated nature of the substituent at the 3-position of the coronarin E's furan.[12] The photooxygenation was facilitated by the sensitizer methylene blue and took just 2 min of irradiation with a visible spectrum lamp in combination with the administration of a stream of oxygen bubbling gently through the solution. The reaction rates of singlet oxygen with furans are exceedingly high, and thus very short reaction times are necessary. Overoxidation should be avoided by careful analysis of the substrate conversion. Next a two-step reduction (using first $NaBH_4$ followed by Dibal-H) of chinensine A (**12**) furnished the lactol chinensine C (**14**, 88% over two steps). The final two family members, chinensine D (**15**) and chinensine E (**16**), were prepared by invoking a second classical [4 + 2]-cycloaddition between $^1O_2$ and, in this case, the *E*,*E*-diene moiety of chinensine C (**14**). An alternate sequence of events had been proposed in the isolation paper,[7] including a different [4 + 2]-cycloaddition between $^1O_2$ and a more electron-deficient *E*,*Z*-diene that would have had trouble adopting the requisite *s-cis* configuration. All the spectroscopic data for synthetically obtained chinensine D (**15**) and E (**16**) matched that for the natural products exactly. In this way, it was possible to establish the relative stereochemistry of the endoperoxides of **15** and **16** as being *cis* for the first time, since they had arisen from a concerted [4 + 2]-cycloaddition between $^1O_2$ and an *E*,*E*-diene. The synthesis, thereby, also confirmed the natural product's absolute stereochemistry and validated our refined biogenetic proposal. Furthermore, a rapid and efficient synthesis of the chinensine family members A–E (**12**–**16**), employing two different modes of singlet oxygen reactivity had been accomplished.

SCHEME 4



Synthesis of the [5,5,5]-Bis-spiroketal Core of the Prunolides

In a more ambitious application of the silyl-stabilization method for 4-hydroxybutenolide synthesis using singlet oxygen, we sought to employ an intricate cascade reaction sequence to synthesize the core structure of an exciting new class of potent cytotoxic compounds, the prunolides[13] (Scheme 3).

The task was successfully accomplished when the architecturally beautiful core of the prunolide molecules was synthesized in just four steps starting from furan itself.[14] The last step and crescendo of the synthesis involved subjecting 1,2-difuryl alkene **20** (*Z*/*E* ≈ 1:3) to a set of standard $^1O_2$ photooxygenation conditions (10^{-4} M Rose Bengal as sensitizer and oxygen bubbling through the reaction solution, accompanied by visible spectrum light irradiation for 2 min, Scheme 3). Regardless of the starting olefin's geometry, the reaction's product, obtained in high yield (80%), was the spirocyclic core of the prunolides (**23**). This remarkable cascade began with the transformation of both 2-silylfurans into their corresponding 4-hydroxybutenolides following a double [4 + 2]-cycloaddition with two molecules of $^1O_2$ (**20** → **21**); addition of a mild acid (either silica gel or *p*-TsOH) was then enough to effect a dehydration and cation trapping sequence that furnished the intact spirocyclic core of the prunolides (**21** → **23**).

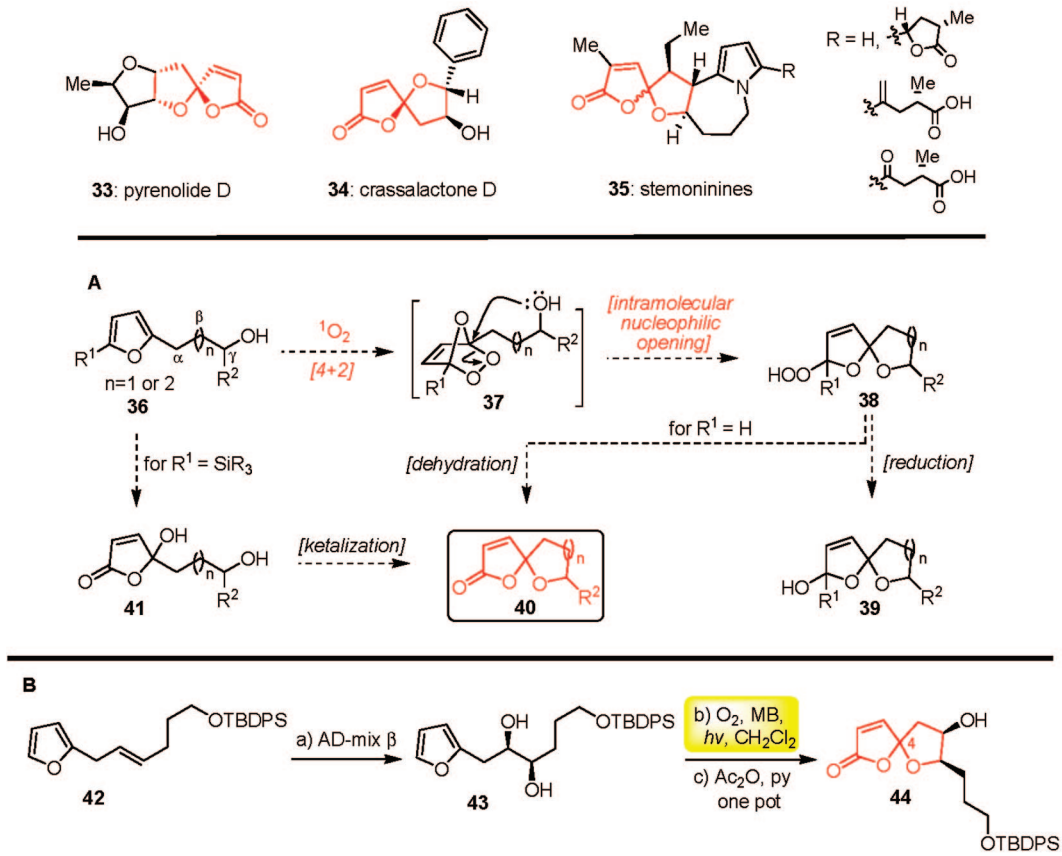
Total Synthesis of (+)-Premnalane A

The success of the spirocyclization sequence in the prunolide synthesis led to speculation about whether other spirocycles might be accessible using a similar concept. The unusual γ-spiroperoxy-γ-lactone portion of the antibacterial natural product premnalane A[15] attracted immediate attention, not only because it might allow for extension of the spirocyclization strategy, this time to include ketalization with a pendant hydroperoxide moiety instead of the previously used hydroxyl group, but also because a tandem reaction sequence employing two different modes of singlet oxygen might be used to access the γ-spiroperoxy-γ-lactone portion in a one-pot operation beginning from a simple furan precursor (Scheme 4).[16] The concept, outlined in Scheme 4A, involved once again employing a silyl-substituted furan to 4-hydroxybutenolide transformation, mediated by $^1O_2$, as the kick-off reaction (**24** → **25**). By appending an allyl group to the 5-position of the starting furan, we hoped that an ene reaction might follow thus placing a hydroperoxide moiety either β or γ to the 4-hydroxybutenolide (**25** → **27** or **25** → **26**). These hydroperoxides might, in turn, cyclize under the influence of a mild acid (e.g., *p*-toluenesulfonic acid (PTSA) or SiO_2) to yield the [5,5]- or the desired [5,6]-spiroperoxylactone motifs (**27** → **29** or **26** → **28**). This proposed tandem reaction sequence is not as simple as it first appears due to a number of mechanistic hurdles that needed to be negotiated.[16] The plan was realized, and (+)-premnalane A was rapidly synthesized (Scheme 4B) in one pot starting from 2-silyl-furan **30**.[16] Furan **30** had itself been synthesized in a short and straightforward sequence (6 steps, 53% overall yield), beginning from (+)-sclareolide, which made use of a very efficient allenone to furan methodology.[17] Interestingly, the tandem reaction sequence's intrinsic bias toward the [5,5]-peroxylactone, rather than premnalane A's [5,6]-spiroperoxylactone, could be minimized by simply changing the reaction solvent from a polar variant (such as MeOH, which gave **31**/**32** = 4:1) to a nonpolar variant (such as toluene, which gave **31**/**32** = 1.2:1). As had been predicted, premnalane A's unique steric environment afforded exclusively the *Z*-geometry in the newly formed double bond from the ene reaction.

Synthesis of γ-Spiroketal-γ-lactones

The premnalane A synthesis illustrated that an ene reaction could be used to install a nucleophile (a hydroperoxide), which

SCHEME 5

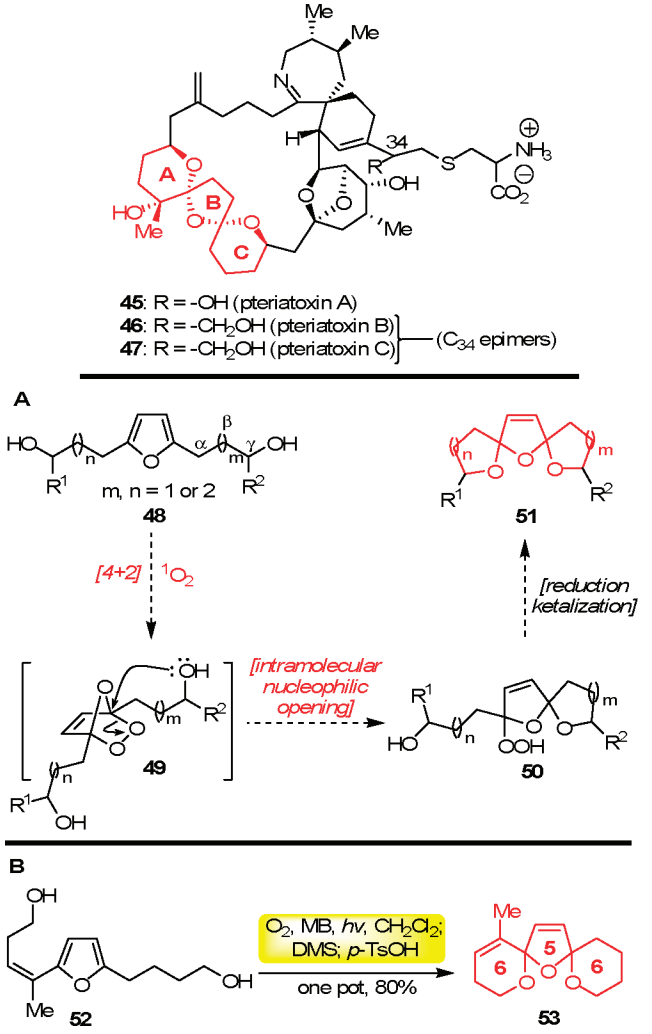


may then be used in a spiroketalization reaction with an already present 4-hydrobutenolide moiety. The question for the investigation now became whether the nucleophile (for example, a hydroxyl group) could be included prior to the construction of the 4-hydroxybutenolide, thus opening up a potential synthetic route toward a slew of exciting and bioactive natural products such as pyrenolide D (**33**),[18] crassalactone D (**34**),[19] and the stemoninines (**35**).[20] It is known that substitution with an α-hydroxyl group on the 2-alkyl substituent of the furan precursor leads to rapid fragmentation of the ozonide adduct obtained from the [4 + 2]-cycloaddition between this furan and $^1O_2$ (**6** → **5**, Scheme 1). But what fate awaits the corresponding 2-(γ- or δ-)hydroxyalkyl) substituted furans upon treatment with singlet oxygen? It was postulated that if a furan bearing no stabilizing substituents (such as **36** where R^1 = H, Scheme 5A) was subjected to the standard set of $^1O_2$ oxygenation conditions, the ozonide adduct of the [4 + 2]-cycloaddition might be attacked by the pendant hydroxyl to yield a spirocyclic hydroperoxide (e.g., **37** → **38**), which would dehydrate to give a spirolactone (such as **40**) of the sort needed for the synthesis of the aforementioned natural products. Alternatively, if a silyl group at the 2-position of the furan were included from the outset (such as **36** where R^1 = SiR$_3$, Scheme 5A), the pendant hydroxyl might cyclize to form again the desired spirolactone, but this time it would be through ketalization with the 4-hydroxybutenolide that would be produced upon reaction of the furan with singlet oxygen (**36** → **41** → **40**). Proof of principle was very recently obtained for this new synthetic strategy (Scheme 5B). The required pendant hydroxyl was installed enantioselectively into the furan precursor **42** using a Sharpless asymmetric dihydroxylation. The resulting diol **43** was subjected to a standard set of $^1O_2$ reaction conditions (methylene blue as sensitizer, oxygen bubbling through the solution, and visible spectrum light irradiation for 3 min), and then acetic anhydride and pyridine were added into the same pot to afford spirolactone **44** (in good yield, 57% over two steps). Work to complete the synthesis of pyrenolide D (**33**), crassalactone D (**34**), and selected stemoninines (**35**) using this one-pot transformation is ongoing.

Synthesis of [5,5,5]- and [6,5,6]-Bis-spiroketals

The above example illustrates how one pendant hydroxyl can readily be encouraged to cyclize after singlet oxygen oxidation of a furan nucleus. Can this concept be extended so that two pendant hydroxyls might be included at the γ or δ posi-

SCHEME 6

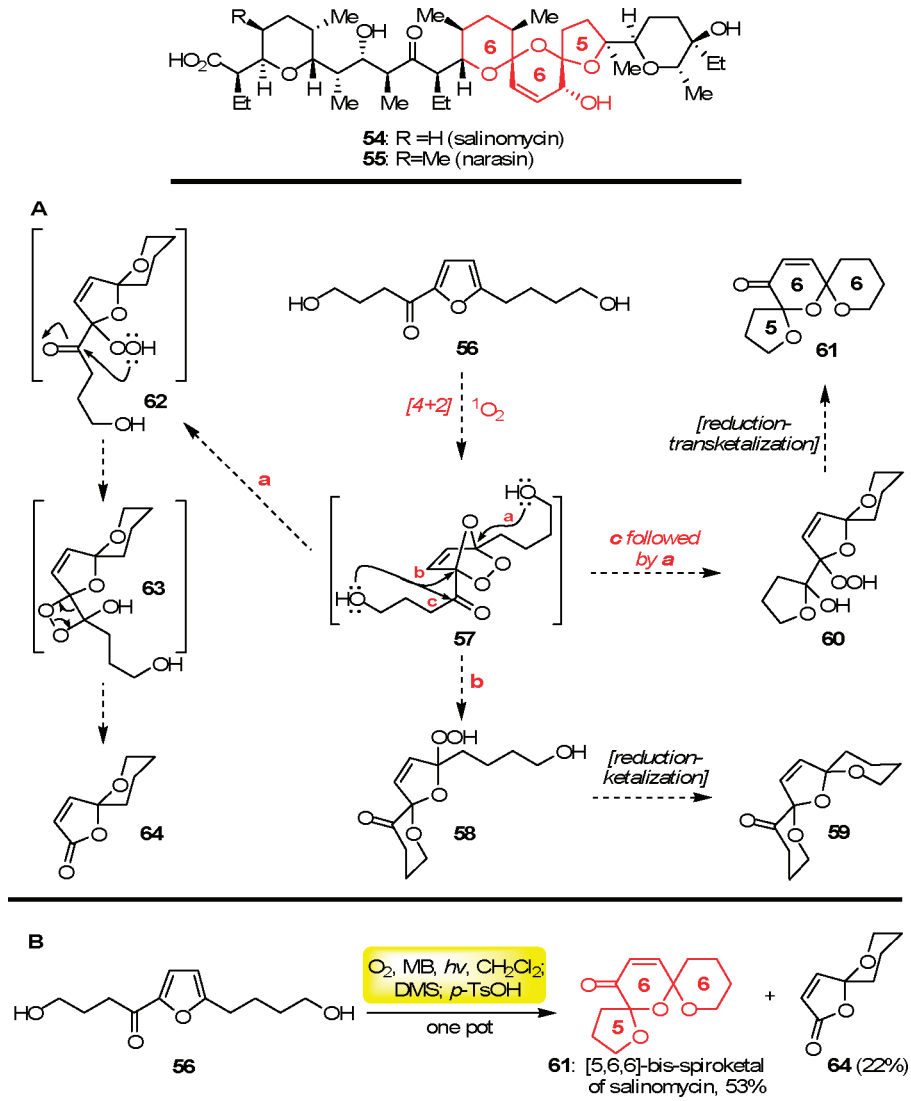


tion of the alkyl substituents of a 2,5-disubstituted furan in order that they might subsequently be encouraged to sequentially cyclize, thus forming a bis-spiroketal moiety (as found in a host of important natural products, such as the pteriatoxins,[21] pinnatoxins,[22] or spirolides,[23] Scheme 6)? It should be noted that the concept of oxidizing a furan nucleus with the ultimate goal of synthesizing a bis-spiroketal motif, is not in itself new.[24] Indeed, the synthesis of a bis-spiroketal ring system was first reported using electrochemical methods to oxidize a simple furan bearing the requisite hydroxyl substituents in a one-pot procedure.[25] Later Albizati,[26] Kocienski,[27] and Stockman[28] all deployed electrophilic bromine as an oxidant to transform various furans into bis-spiroketals. In the last of these cases, a one-pot operation was also employed. The advantages of using a singlet oxygen based approach are multiple; first, $^1O_2$ is highly selective and requires little by the way of protection for other functional groups, and second, the whole transformation is easily performed in one pot with all the inherent advantages of efficiency that such an approach holds. The concept is outlined in Scheme 6A. To test the hypothesis, a model precursor to the pteriatoxin and pinnatoxin bis-spiroketal systems was synthesized using simple alkylation, acylation, and Wittig technologies.[29] A double bond was included to allow for the introduction of the requisite tertiary alcohol at a later stage. This diol **52** was then subjected to a standard set of $^1O_2$ photooxygenation conditions (methylene blue as sensitizer, oxygen bubbling through the reaction mixture, and visible spectrum light irradiation for 5 min, Scheme 6B). The hydroperoxide (analogous to **50**) that resulted was reduced *in situ* using dimethyl sulfide (DMS), after which, addition of catalytic TsOH promoted the final desired cyclization event, such that the one-pot procedure furnished bis-spiroketal **53** in excellent yield (80%). The same protocol could be applied to other systems;[29] thus, a general and versatile method for making [5,5,5]- or [6,5,6]-bis-spiroketal units (depending on the hydroxyl's positioning in the precursor) in one pot had been developed.

Synthesis of [6,6,5]-Bis-spiroketals

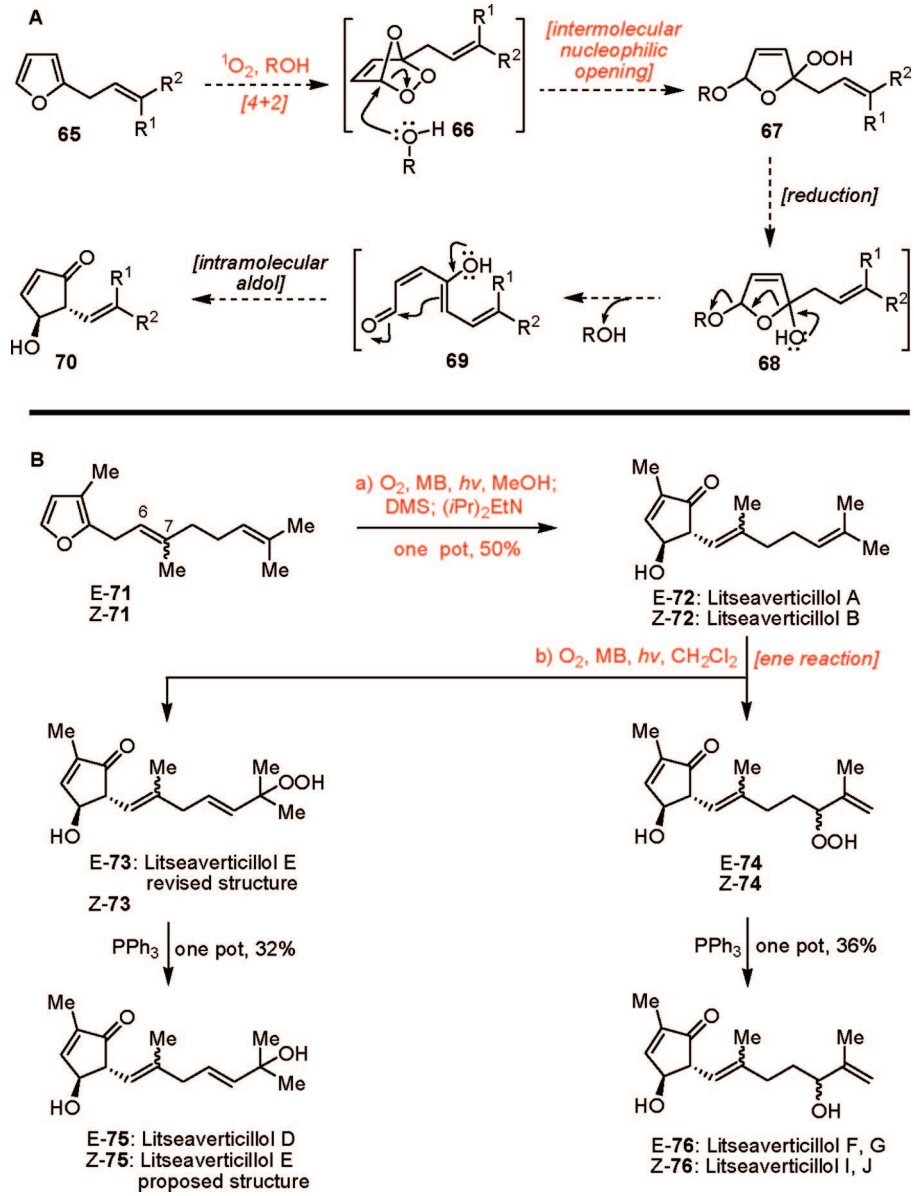
With the previous method in mind, if one examines the structure of the bis-spiroketal unit of the pteriatoxins, pinatoxins, or spirolides, it is obvious that if an α-ketone can be placed on the alkyl substituent at the 2-position of the furan precursor, a handle (see structure **59**, Scheme 7A) would then be provided for the introduction of the requisite tertiary alcohol present on a flanking six-membered ring of the bis-spiroketal unit. It was of interest, therefore, to pursue this idea; however, the effect of such a substitution on the photooxygenation−spirocyclization sequence was far from clear for it also appears that if a transketalization event occurred during this process, it might instead deliver a [5,6,6]-bis-spiroketal unit (see structure **61**, Scheme 7A). Far from yielding an unwanted dead-end, this result would in turn be exciting, because the [5,6,6]-bis-spiroketal motif present in such natural products as salinomycin[30] and narasin[31] (Scheme 7) is of exactly this type. Indeed, a reasonable hypothesis might propose a biogenetic link among all these natural products with transketalization being responsible for the interconversion between the two types of bis-spiroketal (i.e., [5,6,6]-bis-spiroketal → [6,5,6]-bis-spiroketal). It should be noted here that an elegant synthesis of salinomycin was published by Kocieński and co-workers in the 1990s that had an *N*-bromosuccinimide (NBS)-mediated furan oxidation/bis-spiroketal formation sequence at its heart.[27b,c] Upon initiation of the investigation designed to deconvolute these issues, the syn-

SCHEME 7



thesis of selected model compounds soon revealed two competing fragmentation processes that clouded matters.[32] A mechanistically similar fragmentation to one of the two we observed (see **62** → **63** → **64**) had been previously reported in furylic aldehydes subjected to singlet oxygen photooxygenation.[1b] Fortunately, further experimentation revealed that the kinetics of these reactions worked in our favor, and, when diol **56** was treated to the established $^1O_2$ reaction conditions (10^{-4} M methylene blue as sensitizer, oxygen bubbling through a cooled solution, and visible spectrum light irradiation for 5 min), followed by DMS-mediated reduction and subsequent addition of mild acid (*p*-TsOH) to assist the final cyclization, the formation of salinomycin-type [5,6,6]-bis-spiroketal **61** as the major product (53%) was observed. The product of an unwanted fragmentation, spirolactone **64**, was also observed but in a much reduced percentage (22%) compared with the earlier model studies. A simplified explanation of the outcome is as follows: from diol **56**, an ozonide adduct (**57**) is initially formed that may suffer any one of three different fates (see pathways a, b, and c, Scheme 7A). The product distribution would suggest that pathway c attack is the fastest (thus, suppressing pathway b altogether) of these alternatives, but that pathway a does still compete to a small extent. In this way, the reaction is funneled down two distinct avenues; first, the dominant pathway converts the ozonide **57** into spirocycle **60** through sequential pathway c and a attacks in quick succession, the resultant hydroperoxide **60** is then reduced (by DMS) and subject to transketalization (upon addition of TsOH) to furnish the desired [5,6,6]-bis-spiroketal **61**. The minor pathway sees a type a attack on the ozonide **57** to yield spirocycle **62**, which then fragments to give spirolactone **64**. Thus, a model for the [5,6,6]-bis-spiroketal motif of salinomycin had been synthesized in one pot from a readily accessible acyl furan.

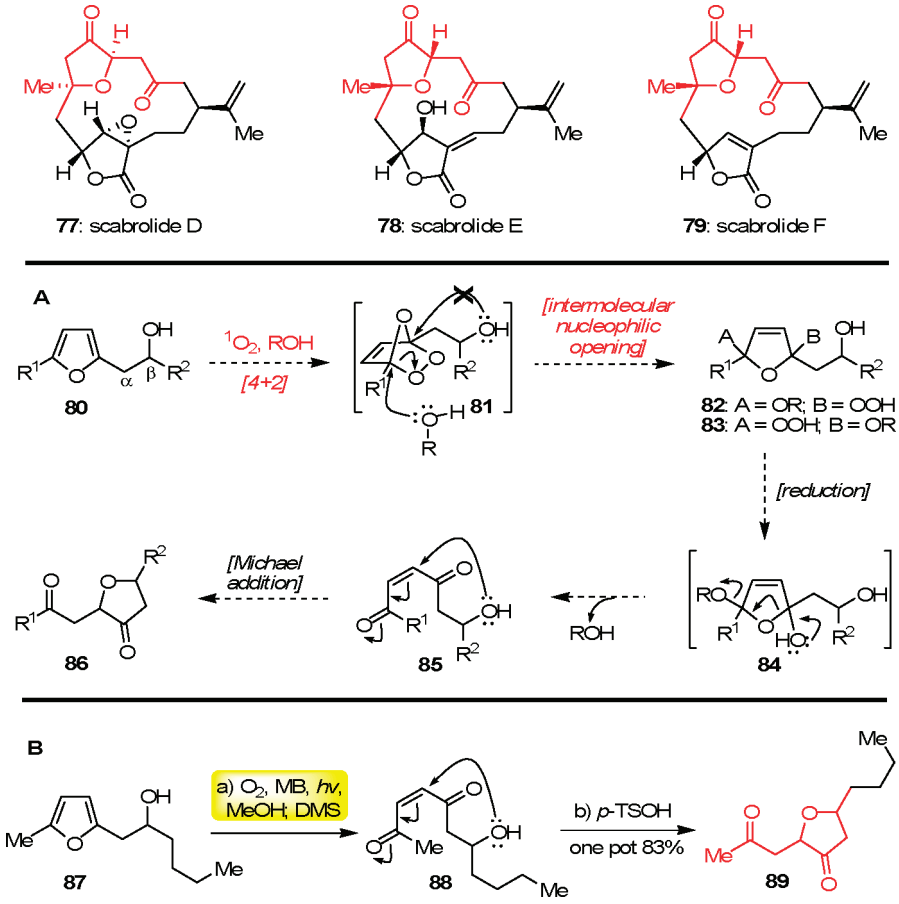
SCHEME 8



Total Synthesis of Litseaverticillols A−G, I, and J

In the previous three schemes, we have delineated how intramolecular ozonide trappings can be productively employed in synthesis. The next example of singlet oxygen's prowess as a synthetic tool illustrates how intermolecular nucleophilic attacks can also be successfully applied to the synthesis of interesting natural products. The litseaverticillols were isolated after bioassay guided fractionation of extracts taken from the leaves and twigs of a perennial shrub (*Litsea verticillata*) found growing in Vietnam's Cuc Phuong National Park.[33] This series of eight new natural products all exhibited inhibitory activity against HIV-1 replication in specialized HOG.R5 cells.[33c] Crucially their antiviral activity was selective and did not affect the growth of the host cell. In the synthetic plans, two highly efficient one-pot singlet oxygen oxidation sequences were envisaged that would furnish the litseaverticillols rapidly from a simple furan precursor. The first ambitious cascade sequence would target the natural product's hydroxy enone core and would deliver the so-called first generation litseaverticillols. Further singlet oxygen mediated functionalization of the side chains would then furnish the second generation natural products. Our strategy began from a naturally occurring furan, sesquirosefuran (*E*-**71**, Scheme 8), and was designed to be biomimetic, an assertion later proved correct through a structural reassignment[34b] and via several other critical observations.[34] The proposal for the synthesis of the first generation litseaverticillols is outlined in Scheme 8A and

SCHEME 9



involves a five step cascade reaction sequence beginning from sesquirosefuran (*E*-**71**) and its geometrical isomer, both of which may be synthesized in short order from citraconic anhydride.[34] A classic [4 + 2]-cycloaddition between the starting furan **65** and singlet oxygen would serve to initiate the sequence; this reaction would be followed immediately by nucleophilic attack of the solvent (MeOH), thus opening the resulting ozonide **66** to yield a hydroperoxide **67**, which would, in turn, be reduced *in situ* to furnish hemiketal **68**. It was hoped that this hemiketal **68** would collapse by eliminating MeOH to furnish the achiral 1,4-enedicarbonyl **69**, which would then succumb to an intramolecular aldol reaction thereby furnishing the first generation litseaverticillols (represented here by 4-hydroxy cyclopentenone **70**). That the litseaverticillols were isolated as racemates supports the idea of intermediacy for a common conjugated achiral precursor such as **69** (furthermore, we suspected that the $\Delta^{6,7}$ geometry of the starting furan might prove irrelevant due to facile isomerization catalyzed by mild base at this stage). This blueprint was executed when sesquirosefuran *E*-**71** (or its geometric isomer, *Z*-**71**) was treated with singlet oxygen. As had been predicted, singlet oxygen proved to be highly selective, reacting, at this stage, only with the furan moiety leaving the distal double bonds intact. Thus, litseaverticillols A (*E*-**72**) and B (*Z*-**72**) were synthesized in a one-pot operation from the corresponding furans. Following a change of solvent to CH_2Cl_2, a second subjection to $^1O_2$ reaction conditions afforded the hydroperoxide products of ene reactions *E*-**73**, *E*-**74** and *Z*-**73**, *Z*-**74**; these were reduced *in situ* upon the addition of triphenylphosphine to furnish litseaverticillols D, the proposed structure for litseaverticillol E, litseaverticillols F and G, and litseaverticillols I and J. Isolation of the intermediary hydroperoxides combined with careful analysis of NMR data led to reassignment of the structure for litseaverticillol E as being that of hydroperoxide *E*-**73**, a feature which lent credence to our suggested biogenesis for these compounds. Furthermore, minor amounts of scrambling at the $\Delta^{6,7}$ double bond were observed indicating that sesquirosefuran (*E*-**71**) might indeed be the common precursor to all the litseaverticillols as had been originally proposed. Overall an extremely efficient synthesis of this family of compounds had been delineated, which allowed samples of scarce or, as yet, not isolated cogeners (litseaverticillols I and J) to be supplied for further biological testing.

Synthesis of 3-Keto-tetrahydrofurans

In the explorations described thus far, we have seen what happens if a furan oxidation substrate has an α-hydroxyl at the 2-alkyl substituent (leads to fragmentation, Scheme 1) or a γ/δ-hydroxyl (affords intramolecular trapping to give a spiroketal, Schemes 5–7), but the effect of placing the hydroxyl at the β-position has not yet been probed. Obviously, an intramolecular nucleophilic ozonide opening of the sort seen with γ/δ-hydroxyls is unlikely because it represents an unfavored 4-*exo*-cyclization. Drawing on the litseaverticillols experience, however, it was interesting to wonder whether, when MeOH is employed as the photooxygenation solvent, the analogous 1,4-enedione (see **80** → **85**, Scheme 9) might be obtained. This unsaturated 1,4-enedione might then be the subject of an intramolecular Michael-type addition to yield the cyclized motif seen in **86**. As one might suspect from the general themes of this Account, such a motif is of interest because it can be found in a diverse range of interesting natural products, such as the scabrolides,[35] and one might, once again, ask whether nature uses this type of reaction sequence to create the motif. To explore this notion, the model substrate, furan **87**, was synthesized via a short sequence and then subjected to a standard set of $^1O_2$ reaction conditions for 3 min. Following a change of solvent (removal of the MeOH in vacuo and replacement with $CDCl_3$), an *in situ* reduction using dimethylsulfide afforded the desired enedione (**88**, as seen by ^1H NMR), which could be coaxed to cyclize in the desired manner upon addition of catalytic amounts of TsOH. Thus, spiroketone **89** was obtained in good yield (83%). Application of an analogous one-pot operation to the synthesis of the scabrolides is feasible.

Conclusion

In this Account, we have described a selection of furan nucleus transformations mediated by singlet oxygen driven reaction sequences. In general, the furan substrates are simple and readily accessible, while the product motifs accessed are diverse and complex. These highly efficient synthetic methods and strategies have targeted bioactive natural products (or key motifs from such molecules). It is hoped that the transformations described herein will attest to the power of singlet oxygen as a synthetic tool and persuade others to explore its, as yet, mostly untapped potential.

In addition, the investigations have uncovered some evidence that these strategies might be biomimetic.[36] Once again, more research can and will be done to investigate the hypothesis that singlet oxygen is a major player in late stage synthesis and manipulation of polyoxygenated terpenoid natural products. Until then, this idea remains attractive but without definitive proof.

All the students who have been involved in these projects are thanked for their contributions.

BIOGRAPHICAL INFORMATION

Tamsyn Montagnon obtained her Ph.D. from Sussex University (U.K.) in 2000, the result of work undertaken in the laboratory of Professor P. J. Parsons. She then joined the group of Professor K. C. Nicolaou at The Scripps Research Institute (San Diego, California) as a Glaxo-Wellcome Postdoctoral Fellow where she stayed until 2004. Since leaving the U.S., she has been a Marie-Curie Fellow at The University of Crete conducting research in the field that is the topic of this Account. She is also the coauthor of the recently published book entitled "Molecules that Changed the World".

Maria Tofi completed her Bachelor's degree at The University of Crete in 2003. She went on to obtain a Master's degree from the same institution in 2005 and is currently continuing work towards her Ph.D. Her research career thus far has taken place in the laboratory of Professor G. Vassilikogiannakis.

Georgios Vassilikogiannakis obtained his Ph.D in 1998 from the University of Crete (Greece). His doctoral studies focused on electrophilic additions to fullerenes and were conducted in the laboratories of Professor M. Orfanopoulos. From 1999 to 2002, he was a postdoctoral fellow at The Scripps Research Institute (San Diego, California) in the group of Professor K. C. Nicolaou. Here he participated in the completion of a number of natural product total syntheses and in the development of several new synthetic methodologies. He then returned to Crete to begin his independent career as an Assistant Professor. Today, the focus of work emanating from his laboratory is the development of new strategies for the synthesis of bioactive natural products. He was recently promoted to Associate Professor.

FOOTNOTES

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