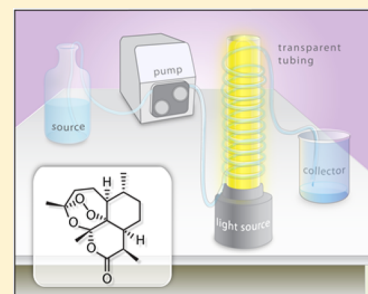


Using Singlet Oxygen to Synthesize Natural Products and Drugs

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ABSTRACT: This Review describes singlet oxygen ($^1\text{O}_2$) in the organic synthesis of targets on possible $^1\text{O}_2$ biosynthetic routes. The visible-light sensitized production of $^1\text{O}_2$ is not only useful for synthesis; it is extremely common in nature. This Review is intended to draw a logical link between flow and batch reactions—a combination that leads to the current state of $^1\text{O}_2$ in synthesis.



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1. INTRODUCTION

This Review discusses photogenerated singlet oxygen ($^1\text{O}_2$) in synthetic organic chemistry. Even though singlet oxygen is a short-lived metastable excited state of molecular oxygen, it is a practical reagent for compound oxidation and can form carbon–oxygen and heteroatom–oxygen bonds. The motivation for this Review is to encourage its further use in the synthesis of natural products and drugs.

2. BACKGROUND

Historically, $^1\text{O}_2$ showed diffusible properties with photosensitization as a convenient method for its production in the Foote–Wexler reaction 50 years ago.^{1,2} Since that time, $^1\text{O}_2$ has been established for its ability to oxidize organic and biological compounds^{3–11} or to be used in synthesis.

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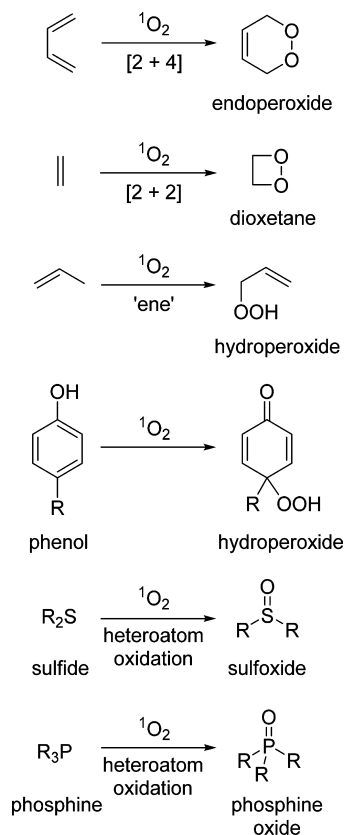
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In the 1980s, reports emerged on the use of singlet oxygen in the synthesis of natural products. The use of $^1\text{O}_2$ in organic synthesis was pioneered^{12–14} and routes to natural products by $^1\text{O}_2$ began to be classified as biomimetic. While singlet oxygen's frequency in the synthesis of natural products has increased in the past 10 years, it is still a relative newcomer.

Scheme 1 shows synthetically useful $^1\text{O}_2$ reactions for generating oxygenated compounds, including the formation of

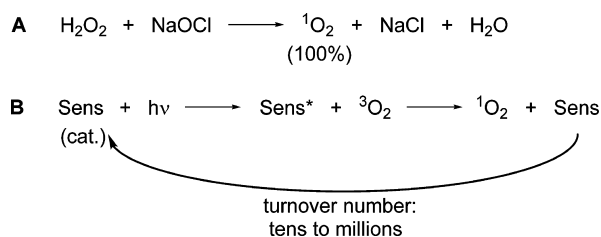
Scheme 1. Synthetic Utility of $^1\text{O}_2$ for Generating Oxygenated Hydrocarbons



endoperoxides from Diels–Alder reactions, dioxetanes from [2 + 2] cycloadditions, hydroperoxides from alkenes and phenols, sulfoxides from sulfides, and phosphine oxides from phosphines.^{15–22} Not only is the chemical trapping of $^1\text{O}_2$ easy (Scheme 1), its generation is also straightforward (Scheme 2).

Scheme 2 shows two methods that give rise to $^1\text{O}_2$, although this Review focuses exclusively on the second. The first route is a thermal process, i.e., dark singlet oxygenation (Scheme 2A), such as H_2O_2 with NaOCl ²³ or the use of peroxides [arene endoperoxides;^{24–27} hydrotrioxides;^{28–31} dihydroperoxides;^{32,33} potassium monoperoxysulfate (KHSO_5);^{34–36} dimethyldioxir-

Scheme 2. Generation of Singlet Oxygen



ane;³⁷ ozone/heterocycle adducts with pyrroles, oxazoles, and imidazoles;³⁸ or triphenylphosphite ozonide, cyclo-(PhO)₃ PO_3].^{39,40} Such peroxides are oxidants themselves that can react with the substrates directly or have poor functional group tolerance, which are synthetic concerns. However, these peroxide reagents can be eliminated in the second route.

The second route is the photosensitized production of $^1\text{O}_2$ (Scheme 2B).⁴¹ This oxygen-dependent photosensitization reaction is not only useful in organic synthesis, it is extremely common in nature. The route is appealing because it only requires visible light, oxygen, and a sensitizer to produce $^1\text{O}_2$. Light excites the sensitizer and not the substrate. Thus, the process is wavelength-selective, where narrow and broad-band light sources can be used.⁴² Furthermore, fabricated capillary reactors that run on miniature light-emitting diodes (LEDs) have advantages to batch reactors. Small reactors with low-energy long wavelengths are more appealing than large reactors with high-energy short wavelengths, as we will see.

3. SCOPE OF THE REVIEW

This Review is intended to be of interest to synthetic organic chemists. Only modest information is known for singlet oxygen's success in organic synthesis applied to complex targets or the use of $^1\text{O}_2$ in flow synthesis. No comprehensive coverage exists for $^1\text{O}_2$ in the organic synthesis of natural products and drugs. The rest of this Review has been organized into two sections (sections 4 and 5).

In section 4, natural products or related compounds are discussed where singlet oxygenation is a key step in their biomimetic synthesis. Because the synthesis of butenolides^{43–47} and trioxane antimalarial drugs^{48–59} using $^1\text{O}_2$ chemistry has been reviewed, our description of these topics will be confined to section 5. Similarly, because there are reviews on $^1\text{O}_2$ in physical-organic chemistry,^{60–63} this literature will not be explicitly covered. Physical and environmental chemistry aspects of $^1\text{O}_2$ will also not be covered due to preexisting reviews.^{64–67}

In section 5, $^1\text{O}_2$ flow photoreactors and their success in synthesis will be summarized in an effort to help validate them. Previous reviews on flow photoreactors that have selected coverage of $^1\text{O}_2$ in flow synthesis have been published.^{68–70} Our Review is up-to-date where section 5 exclusively covers $^1\text{O}_2$ flow photoreactors in synthesis. “Flowing” $^1\text{O}_2$ generators such as the chemical oxygen–iodine laser (COIL)^{71–75} with supersonic I_2/O_2 mixing will not be covered because there is no overlap with organic synthesis. Extensive studies have been carried out with direct substrate photolysis in flow reactions,^{76–83} which will also not be covered. Lastly, this Review will emphasize the interplay between basic (section 4) and applied research (section 5) to further establish $^1\text{O}_2$ in the synthesis of targets with industrial-scale syntheses in mind.

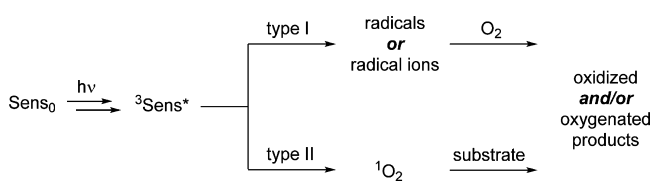
4. SINGLET OXYGEN IN SYNTHESIS

4.1. Background

In this section, we provide accounts of $^1\text{O}_2$ in batch reactions for the synthesis of natural products and drugs. Schemes 4–53 show the extent of complex targets synthesized to date using $^1\text{O}_2$. There are reports of tandem additions of $^1\text{O}_2$ molecules in the literature.^{84–96} Many studies formed peroxide cycloadducts as intermediates, which often rearranged or were reduced to more stable groups. Common reducing agents used are thiourea, dimethylsulfide, and triphenylphosphine. As we will see, tetraphenylporphyrin (TPP), rose bengal (RB), and methylene

blue (MB) are the most common sensitizers (Sens) in homogeneous solutions.^{97–101} Irradiation of Sens₀ causes Sens* to efficiently produce singlet oxygen (type II) and trace amounts of oxygen radicals (type I) (Scheme 3); the latter is

Scheme 3. Type I and II Photosensitized Oxidation



responsible for photobleaching over long irradiation times. Heterogeneous sensitizers are diphasic with two appeals (pun intended). They are generally less prone to photobleaching compared to homogeneous sensitizers,^{102–106} and they are easy to separate from solution after reaction; examples include polymer-supported RB, secoporphyrizine, and fullerenes.^{107–116} Self-sensitized photooxygenation reactions are also known,^{117–120} where the substrate absorbs visible light to generate ¹O₂, which reacts on itself; two examples are described in section 4.11 in the context of natural products and drug synthesis.

In the context of synthesis, there are caveats unique to singlet oxygen chemistry: (i) An inverse relationship exists between temperature and rate, where ¹O₂ often adds more rapidly at low temperature (many ¹O₂ reactions are under entropy control).^{121–124} (ii) Peroxide product stabilities vary, and low-temperature NMR spectroscopy is beneficial for detection in crude reaction mixtures. Furthermore, deuterated NMR solvents show duplicity with ¹O₂ in synthesis for in situ monitoring and faster reaction rates. (iii) The rate of ¹O₂ reactions is faster in deuterated solvents due to longer ¹O₂ lifetimes (τ_{Δ}); for example, compare toluene-*d*₈ (τ_{Δ} = 280 μ s) vs toluene (τ_{Δ} = 29 μ s) and CDCl₃ (τ_{Δ} = 7.0 ms) vs CHCl₃ (τ_{Δ} = 230 μ s).^{125,126} In contrast, protic solvents produce the shortest ¹O₂ lifetimes due to facile deactivation by O–H vibrational quenching to ground-state ³O₂.

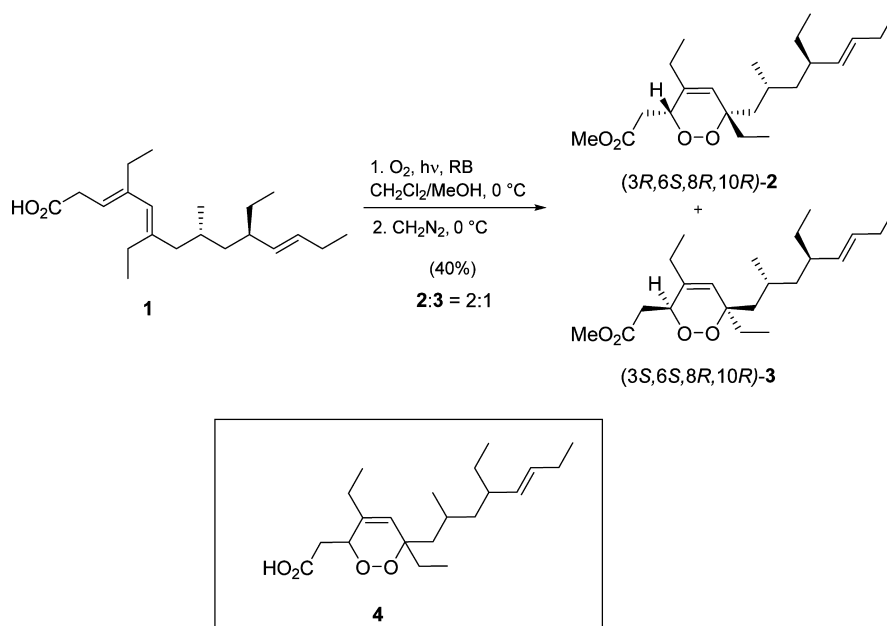
(iv) Some ¹O₂ is wasted through substrate physical quenching. The total rate constants (k_T) of ¹O₂ of a compound are known to be the sum of the chemical quenching rate constant (k_c) and the physical quenching rate constant (k_q), where reactions can be efficient ($k_c \approx k_T$) or inefficient ($k_q \approx k_T$). The latter case is observed with amines, which deactivate ¹O₂ by charge-transfer quenching (10^7 to 10^8 M⁻¹ s⁻¹).^{127–130} Additionally, amines can diverge the chemistry from type II (¹O₂) to type I, generating oxygen radicals.¹³¹ (v) In terms of selectivity, ¹O₂ reacts preferentially with compounds of higher nucleophilicity owing to singlet oxygen's electrophilicity.^{132–134} For example, the k_T of a tetrasubstituted diene (2,5-dimethyl-2,4-hexadiene)¹³⁵ is ~100-fold greater than a disubstituted diene [(*E,Z*)-2,4-hexadiene], so the former site is selectively reacted as is relevant in the first example in section 4.2, the synthesis of endoperoxide natural products.

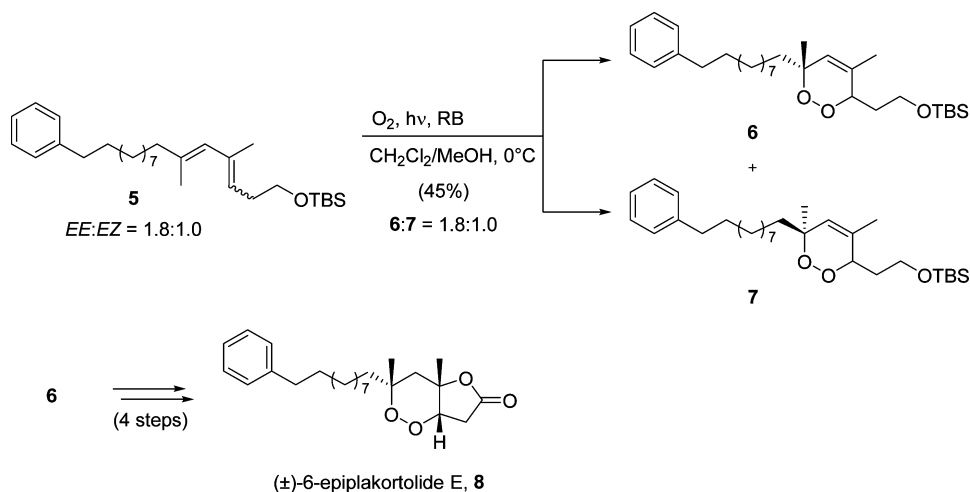
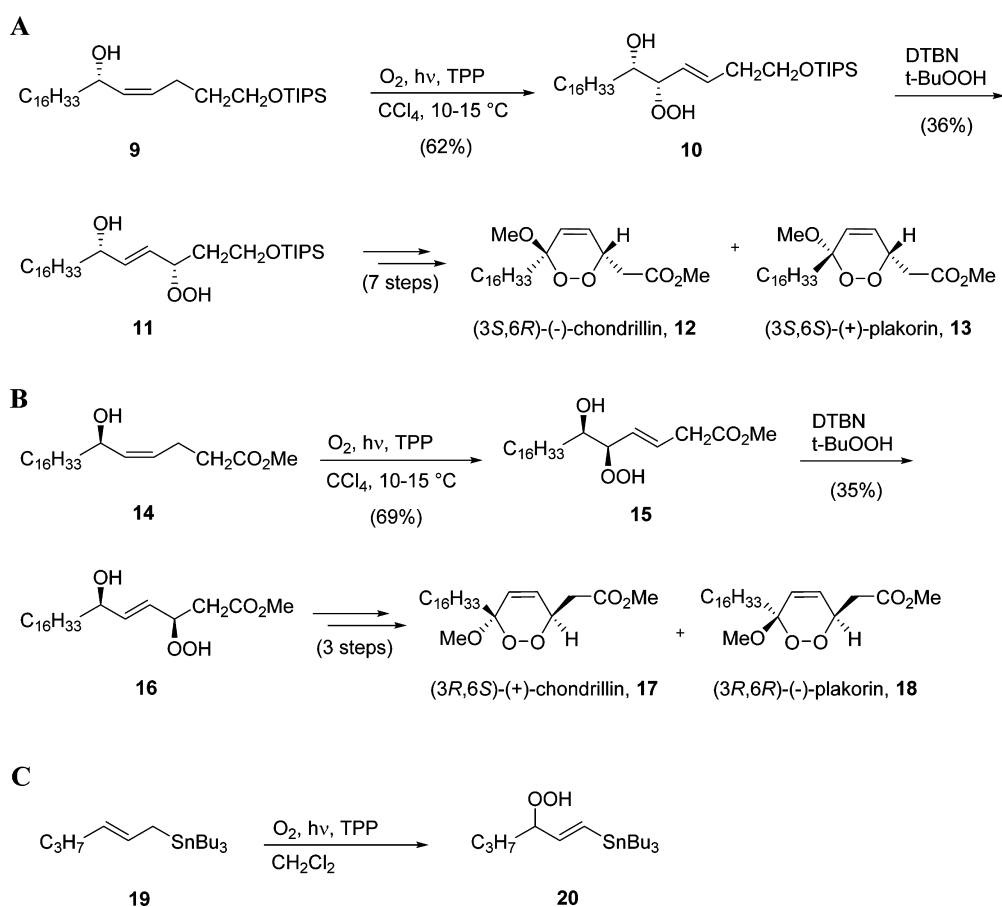
4.2. Endoperoxides

We have located 3 studies: first, a 2002 report describes the RB-sensitized photooxygenation of a trisubstituted diene selectively in the presence of a trisubstituted alkene to furnish a mixture of diastereomeric endoperoxides. The photooxidation of triene **1** was followed by a reaction with diazomethane, leading to endoperoxides **2** and **3** in 40% yield (Scheme 4).¹³⁶ To reach **2** and **3**, the synthesis was 18 steps in length with a total yield of 2.8%. On the basis of the assignment of diastereomeric (3*R*,6*S*,8*R*,10*R*)-**2** and (3*S*,6*R*,8*R*,10*R*)-**3**, the natural product **4** is tentatively assigned as 3*S*,6*R*,8*S*,10*R*. Carboxylic acid derivatives of **2** and **3** are known to have potent cytotoxic and antifungal activity.¹³⁷

Second, a 2002 report describes the RB-sensitized photooxidation of a 1.8:1.0 ratio of (3*E*,5*E*)/(3*Z*,5*E*) dienes **5** (Scheme 5),¹³⁸ to form diastereomeric endoperoxides **6** and **7** (also in a ratio of 1.8:1.0) in a 45% combined yield. Four additional steps furnished the natural product (±)-6-epiplakortolide **8**, which bears a flexible phenyl-terminated polymethylene chain. It is not obvious how **6** and **7** form in the same 1.8:1.0 ratio because it is expected that the ¹O₂ [2 + 4] cycloaddition is less feasible due to distortion of the 3*Z*,5*E* diene to reach the *s*-cis geometry. For

Scheme 4. Synthesis of Marine Sponge Endoperoxide Isomers



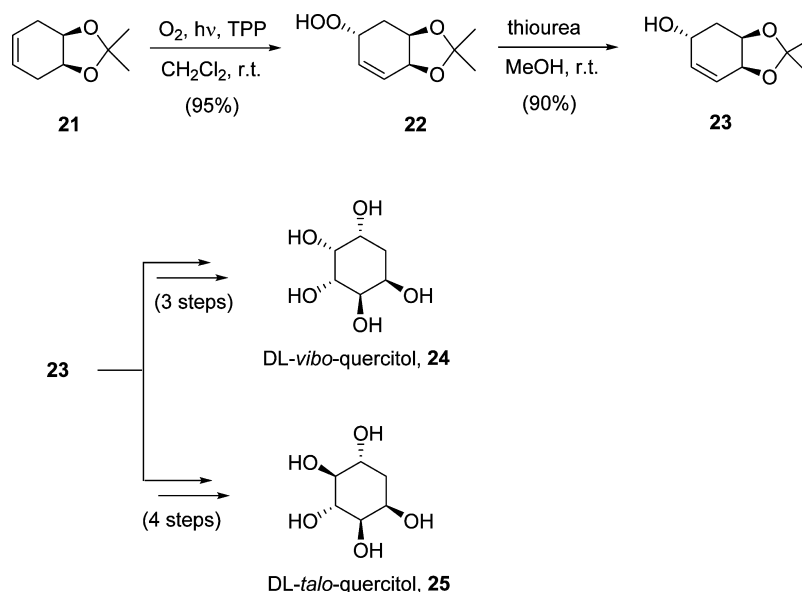
Scheme 5. Synthesis of (\pm)-6-Epiplakortolide EScheme 6. Synthesis of (\pm)-Chondrillin, (\pm)-Plakorin, and a Stannyl Alkenyl Hydroperoxide

example in 2,4-dimethyl-2,4-hexadienes, [2 + 4] addition is favored for *E,E*, but not *E,Z*, where the ene reaction and [2 + 2] addition also occur.¹³⁹

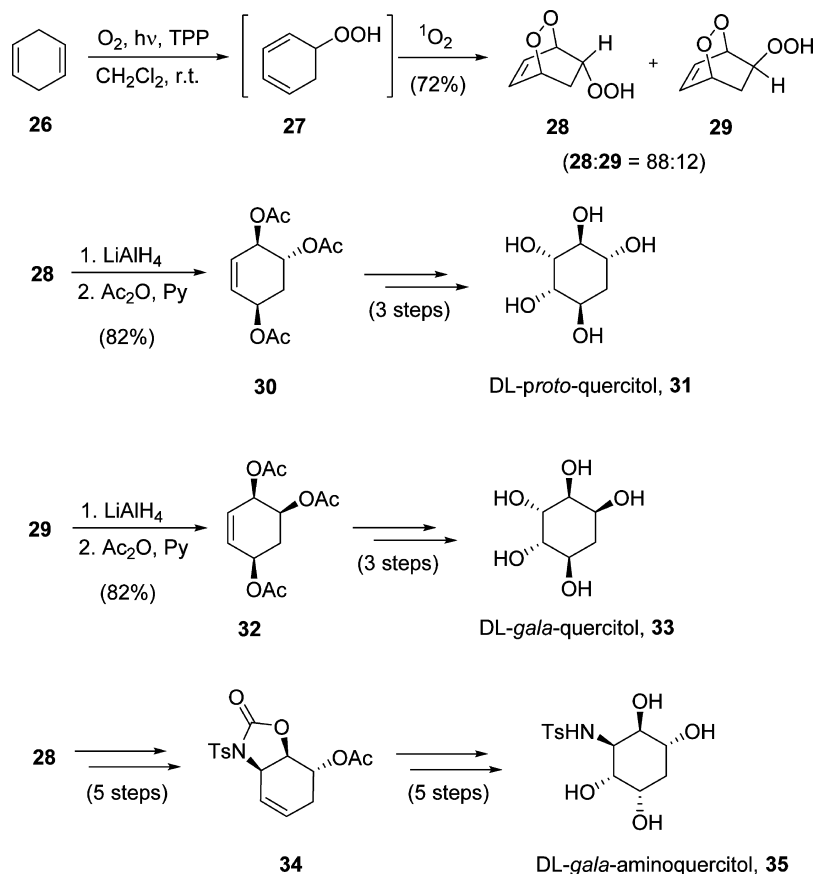
Third, an approach reported in 1999 features a TPP-sensitized photooxidation of **9** and **14** to give hydroperoxides **10** and **15** regioselectively in 62% and 69% yields, respectively (Scheme 6A and B).^{140,141} The regioselectivity was the result of ¹O₂ addition to the *Z*-allylic alcohol with H-bonding. The hydroperoxides reacted with DTBN, causing a peroxy radical Schenck rearrangement¹⁴² to hydroperoxides **11** and **16**. A series of

additional steps with hydroperoxide **11** and **16** afforded chondrillin (–)-**12** and (+)-**17**, and plakorin (+)-**13** and (–)-**18**. Chondrillin has shown antitumor activity against P388 leukemia cells, and plakorin is an activator of sarcoplasmic reticulum Ca(II)-ATPase.¹⁴³ We also note that stereoselective synthesis of (*Z*)-3-tributylstannyl-2-alkenyl hydroperoxides from the ¹O₂ “ene” reaction of allylstannanes^{144–147} have yielded synthons for peroxy natural products (Scheme 6C). Singlet oxygen chemistry is an efficient way to reach highly oxygenated

Scheme 7. Synthesis of DL-talo-Quercitol and DL-vibo-Quercitol



Scheme 8. Synthesis of DL-proto- and DL-gala-Quercitol and a gala-Aminoquercitol Derivative



compounds, such as carbasugars (polyhydroxy cyclohexanes), as we will see next.

4.3. Carbasugars

Singlet oxygen acts in some way as a liver enzyme (cytochrome P450) by processing hydrophobic compounds to increase their water solubility by introducing hydroxyl groups. A 1998 report described the TPP-sensitized photooxidation of dioxolane **21**,

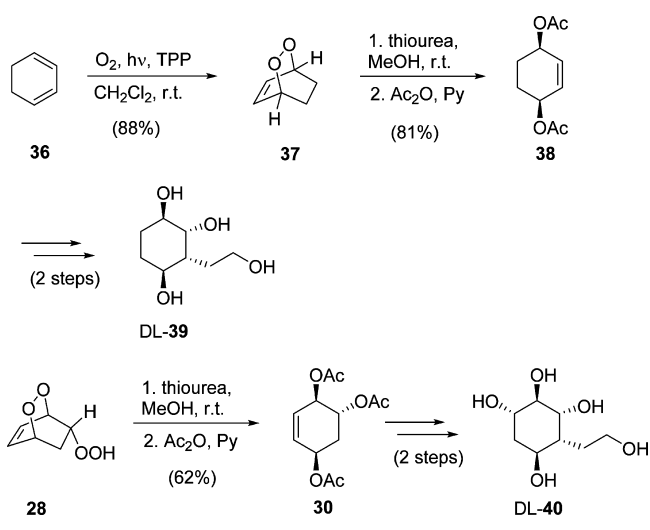
which gave hydroperoxide **22** in 95% yield (Scheme 7).¹⁴⁸ Hydroperoxide **22** was reduced with thiourea to form alcohol **23**, and subsequent reactions led to DL-vibo-quercitol **24** and DL-talo-quercitol **25**. There are literature examples of highly oxygenated compounds, such as pinitol, cyclitols, and polyols, synthesized by other oxidation methods, e.g., epoxidation, osmylation, and ozonolysis.^{148–150} Relatedly, ¹O₂ reactions have been previously

reported for the synthesis of condiritols,^{151–157} *proto*-quercitol, and *gala*-quercitol, as is discussed in the next example.¹⁵⁸

A synthesis reported in 1997 used the TPP-sensitized photooxidation of 1,4-cyclohexadiene **26** to give hydroperoxide **27**, which upon addition of a second ¹O₂ molecule led to hydroperoxy endoperoxides **28** and **29** in 72% yield (88:12 ratio) (Scheme 8).¹⁵⁸ The reduction of peroxides **28** and **29** with LiAlH₄ was followed by protection of the alcohol group with acetic anhydride affording triacetates **30** and **32**, respectively. Further reactions led to *DL*-*proto*-quercitol **31** and *DL*-*gala*-quercitol **33**. In a related report in 2010, hydroperoxide **28** was found to afford oxazolidinone **34**, leading to *DL*-*gala*-aminoquercitol **35**.¹⁵⁹

From 2014, a report described the TPP-sensitized photooxidation of cyclohexa-1,3-diene **36** (Scheme 9).¹⁶⁰ The addition

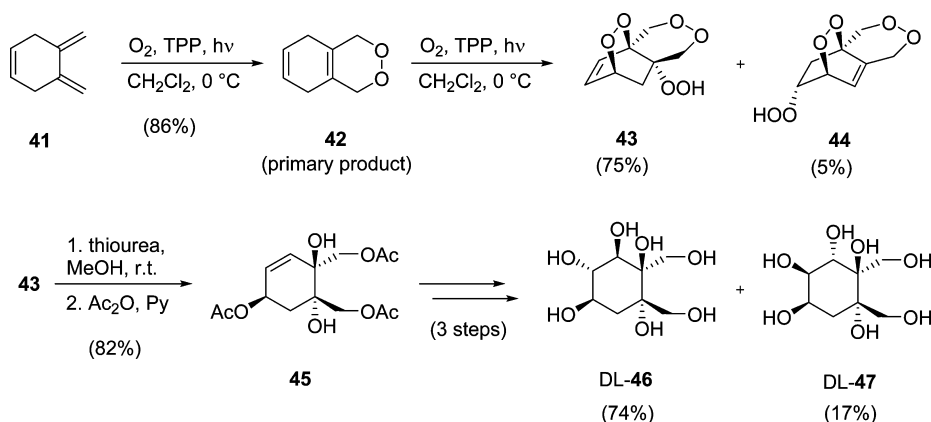
Scheme 9. Synthesis of a *DL*-Tetrol and a *DL*-Pentaol



of ¹O₂ to **36** occurred in the expected [2 + 4] pathway, leading to endoperoxide **37**, which was reduced and acetylated to afford diacetate **38**, and two additional steps led to *DL*-tetrol **39**. In a related report in 2014,¹⁶¹ other carbasugars such as *DL*-pentaol **40** arise from endoperoxide **28** following a similar strategy.

A 2013 paper describes the TPP-sensitized photooxidation of 4,5-dimethylenecyclohex-1-ene **41** (Scheme 10),¹⁶² where the tandem addition of three ¹O₂ molecules was observed. Singlet oxygen first added to **41** by a [2 + 4] cycloaddition to form

Scheme 10. Synthesis of Isomeric Heptols



endoperoxide **42** in 86% yield. A second equivalent of singlet oxygen added by an ene reaction, and a third singlet oxygen equivalent added by another [2 + 4] cycloaddition. As can be seen, resulting trisepoxides **43** and **44** contain a high degree of oxygenation. In addition to the evidence for **43** and **44** from NMR spectroscopy, X-ray crystal data were also obtained for **44**. The reduction of **43** was carried out with thiourea. The alcohol groups reacted with acetic anhydride in pyridine to form triacetate **45** in 82% yield. Isomeric heptols *DL*-**46** and *DL*-**47** were then formed in further reactions. Other reports also show that hydroperoxides are efficiently prepared by reacting cyclohexa-1,4-dienes with ¹O₂ in an ene reaction.^{163–165}

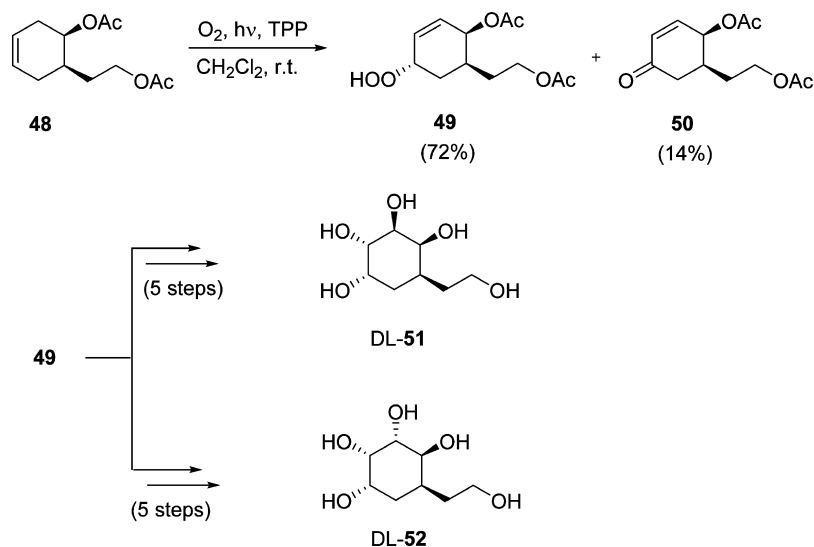
In 2011, a report appeared describing the TPP-sensitized photooxidation of 2-(6-acetoxycyclohex-3-en-1-yl)ethyl acetate **48** to form hydroperoxide **49** and enone **50** in 72% and 14% yields, respectively (Scheme 11).¹⁶⁶ Reduction and acetylation of hydroperoxide **49** followed by a series of reactions afforded Sa-carba-6-deoxy- α -*DL*-galactoheptopyranose (**51**) and Sa-carba-6-deoxy- α -*DL*-guloheptopyranose (**52**).

Lastly, a 2003 report described the TPP-sensitized photooxidation of *trans*-8-(acetyloxy)bicyclo[4.2.0]octa-2,4-dien-7-yl acetate **53**, which gave endoperoxide **54** in 70% yield (Scheme 12).¹⁶⁷ Reduction and acetylation of **54** led to tetraacetate **55** in 73% yield, and further reactions led to *DL*-bishomoinositol **56**. Leaving carbasugar synthesis, epoxides are described next.

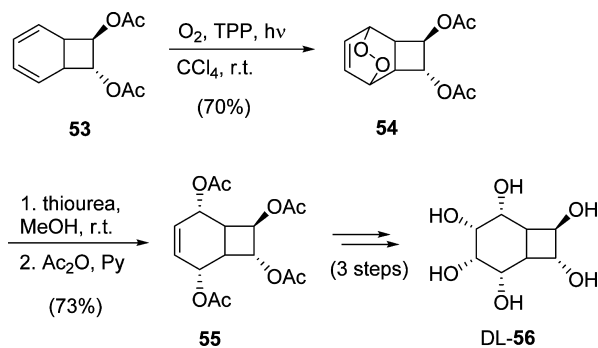
4.4. Epoxides

Even though ¹O₂ is a high-energy species, epoxide products are tolerant of it. Four preparative examples of ¹O₂ for reaching epoxide-containing natural products are described. First, a 2005 paper describes the MB-sensitized photooxidation of diastereomeric bicyclo[4.2.0]octanes **57** and **60**, which separately gave endoperoxides **58** and **61**, respectively, in 69% and 72% yield (Scheme 13).¹⁶⁸ Endoperoxides **58** and **61** were then isomerized with RuCl₂(PPh₃)₃ using Noyori's method to the diepoxides, elysiapyrones A **59** and elysiapyrones B **62**, in 68% and 50% yields, respectively. Additionally, (\pm)-ocellapyrone B has been used as a precursor to 14-methylelysiapyrone A.¹⁶⁹

Second, a 2015 paper describes the MB-sensitized photooxidation of diene **63**, which gave endoperoxide **64** selectively in 92% yield (Scheme 14).¹⁷⁰ Endoperoxide **64** was converted to diepoxide **65** by treatment with diisobutylaluminum hydride (DIBAL), followed by acetic anhydride and DMAP, and in a subsequent step by Noyori's ruthenium(II) catalytic method. Seven additional reactions then led to (\pm)-limonin **66**.

Scheme 11. Synthesis of 5a-Carba-6-deoxy- α -DL-galactoheptopyranose and 5a-Carba-6-deoxy- α -DL-guloheptopyranose

Scheme 12. Synthesis of DL-Bishomoinositol

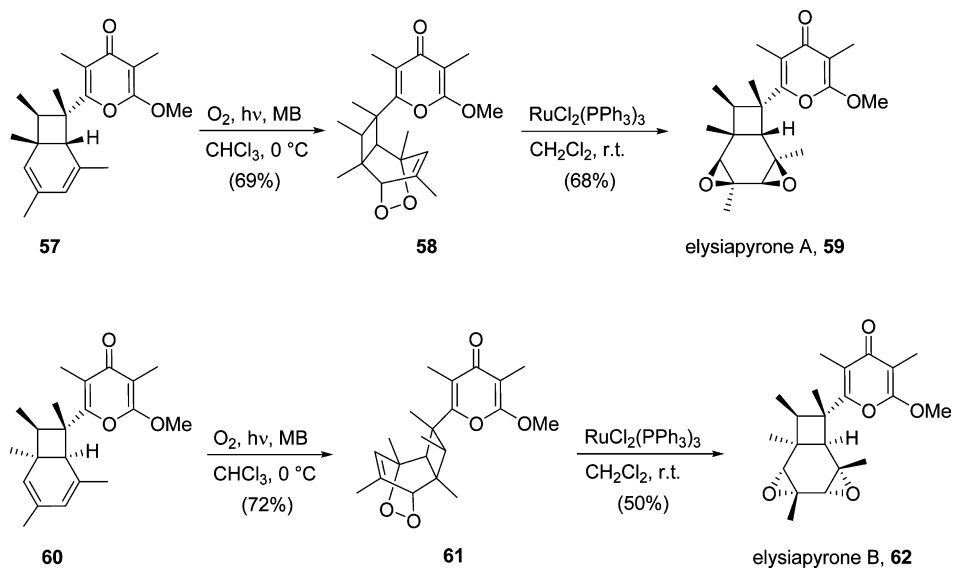


Third, a 1994 report described the TPP-sensitized photooxidation of a mixture of fusicocca-2(6)-3-diene **67** and fusicocca-2,5-diene **68** (ratio 2:3) (Scheme 15).¹⁷¹ Attack of singlet oxygen on the cyclopentadiene ring of **67** and **68** occurred, forming endoperoxides **69** and **70**. Upon warming,

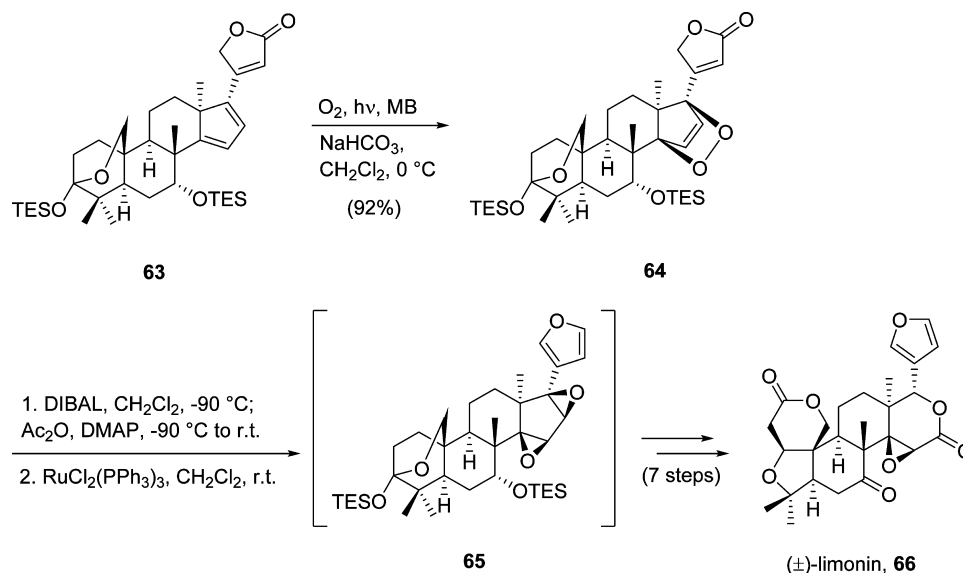
rearrangements of endoperoxides **69** and **70** proceed to diepoxide and epoxy ketone products. Namely, **69** led to fusicogigantepoxide **71** and fusicogigantone A **72**, while **70** led to 2 α ,3 α :5 α ,6 α -fusicogigantepoxide B **73** and 2 α ,3 α -fusicogigantone B **74**. NMR spectroscopy was used to help deduce the structures, and X-ray data were collected for **71**. Dienes **67** and **68** are plausible but not yet identified as natural precursors to reach **71**–**74** by singlet oxygenation. Studies of the rearrangement mechanism of 1,4-endoperoxides to 1,2:3,4-diepoxides have been reported.¹⁷² We point out that conversion of endoperoxides to *cis*-epoxides and epoxy ketones has also been successfully carried out with spiro[2,4]heptadiene.¹⁷³ Furthermore, a photooxidation strategy was successful in the synthesis of the natural product senepoxide.¹⁷⁴

Fourth, a 2014 paper describes the RB-sensitized photooxidation of furan **75** in the presence of diisopropylethylamine (DIPEA) (Scheme 16).¹⁷⁵ Preferential base abstraction of the left-hand bridgehead proton of the endoperoxide causes its decomposition by O–O bond heterolysis to butenolide **76**. The

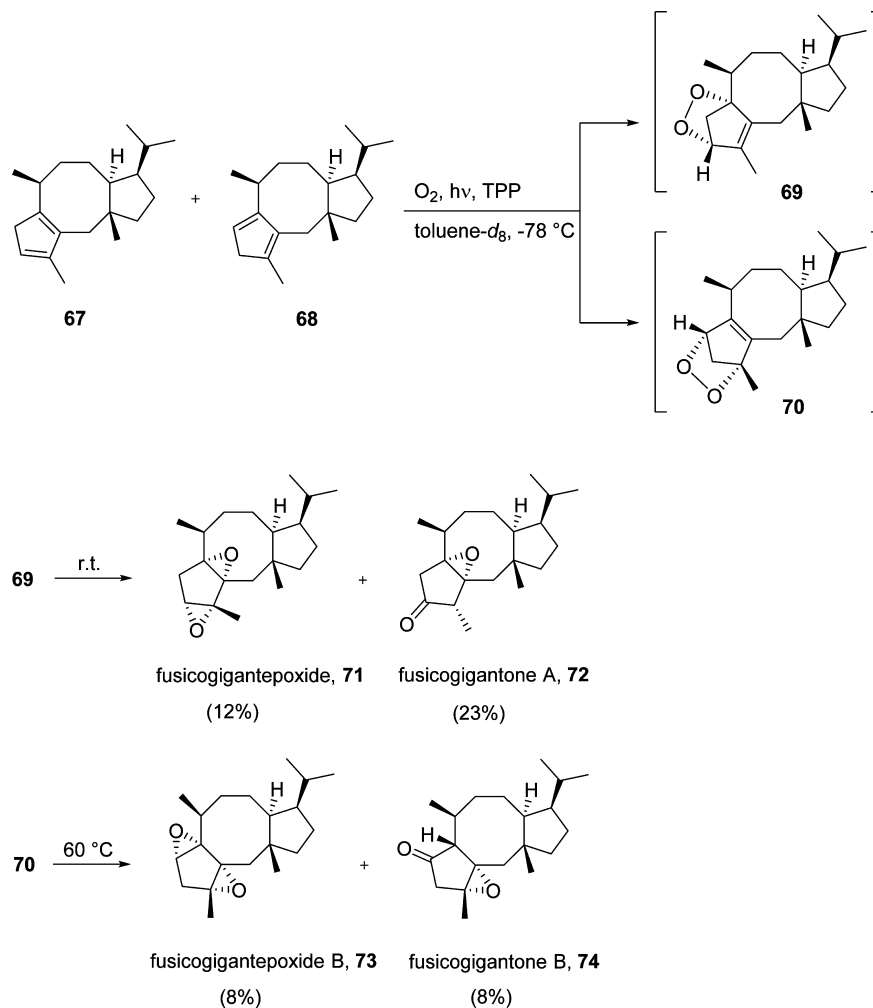
Scheme 13. Synthesis of Elysiapyrones A and B



Scheme 14. Synthesis of (±)-Limonin



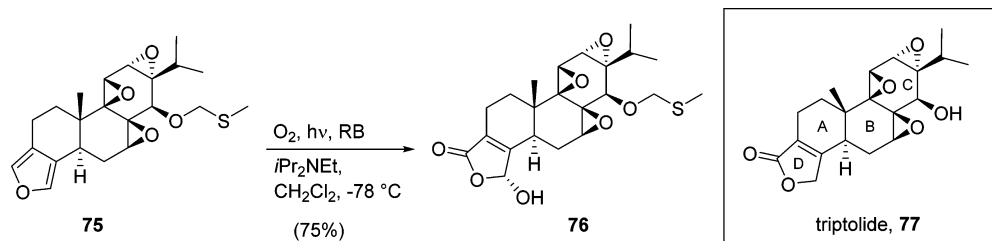
Scheme 15. Synthesis of Fusicogantepoxides and Fusicogantones



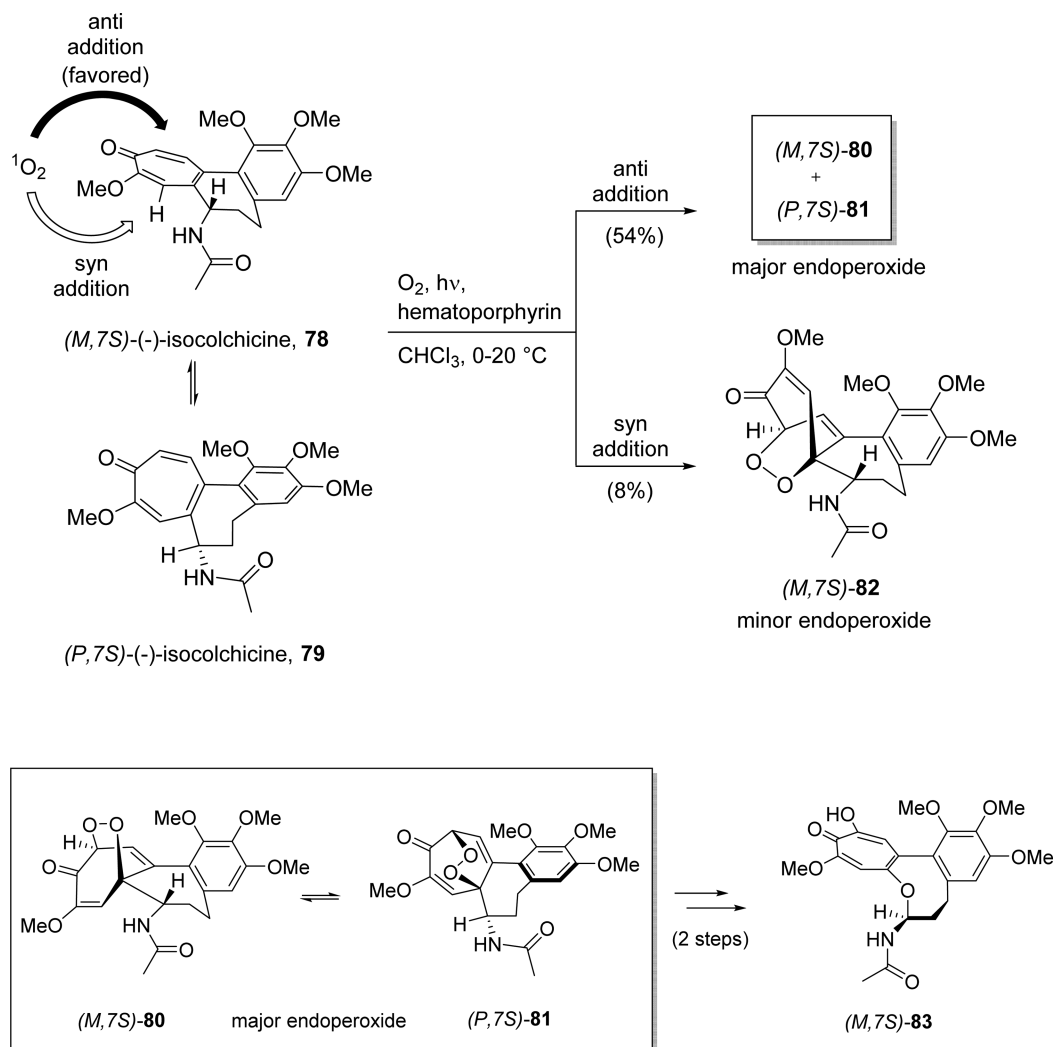
early finding on the furan mechanism of forming two C–O bonds and breaking of an O–O bond to reach butenolide is interesting,¹⁷⁶ and it has been exploited to reach other butenolide and spiroketal natural products (as mentioned in section 3).^{43–47}

Paradoxically, tertiary amines (such as DIPEA) physically quench $^1\text{O}_2$ yet are essential for the base-abstraction process. X-ray crystallographic data were also collected for 76. The preparation of four additional triptolide derivatives was

Scheme 16. Synthesis of a Triptolide Derivative



Scheme 17. Photooxidation of Isocolchicine Atropisomers



accomplished for an evaluation against ovarian (SKOV-3) and prostate (PC-3) cancer cells, showing that the activity depends critically on the D ring in these structures.

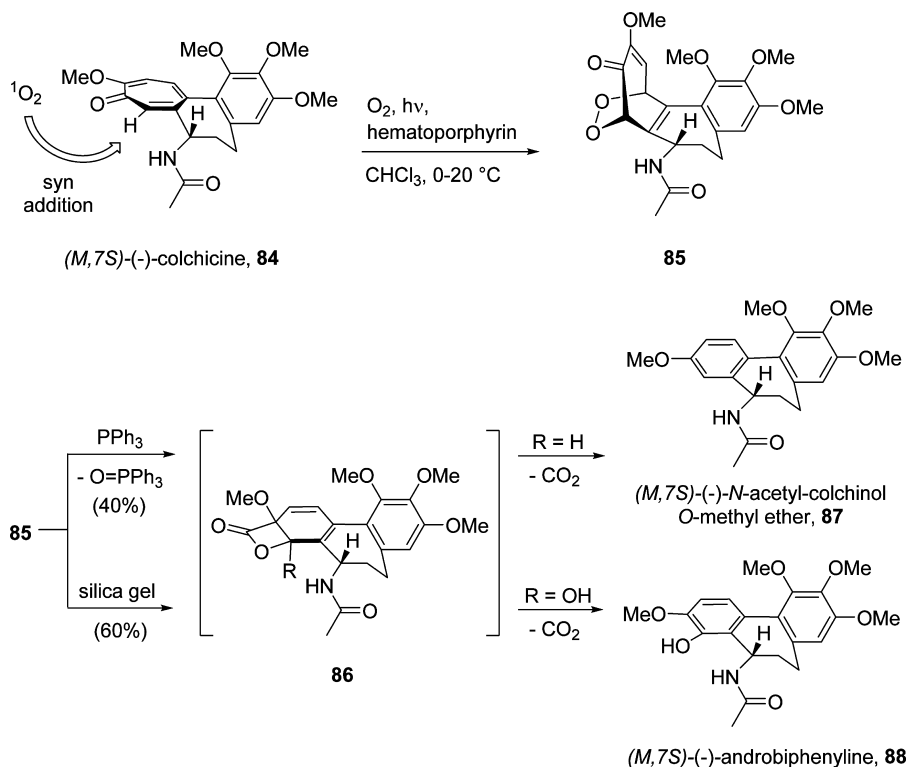
4.5. Tropones and Tropolones

Tropones and tropolones are widely seen in nature and represent highly oxygenated natural products. We have located four studies that use or form tropones and tropolones; first, a 2001 report described the hematoporphyrin-sensitized photooxidation of atropisomers of (–)-isocolchicine (78/79), which led to diastereomeric endoperoxides 80/81 and 82 in 54% and 8% yields, respectively (Scheme 17).¹⁷⁷ Preferential anti addition of $^1\text{O}_2$ to (*M*,7*S*)-(-)-78 atropisomer is due to molecule twisting negating the steric interactions from the benzenoid ring, leading

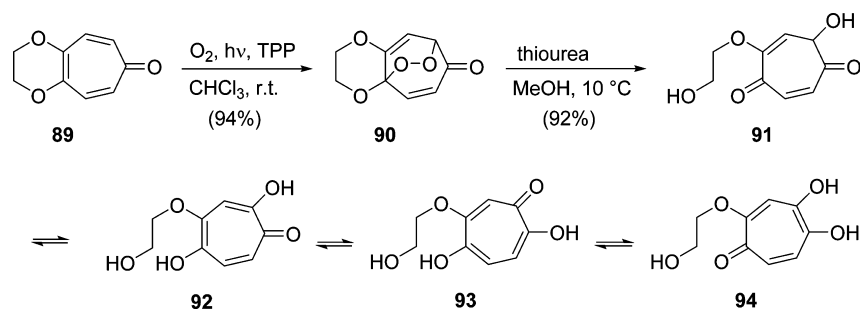
to 80/81 as major endoperoxide products. Endoperoxides 80/81 and 82 were separated by column chromatography, in which the latter was favored (ratio of 80/81:82 was 7:1). Further synthetic steps then led to 83.

Second, a 1997 paper described the reaction (–)-colchicine 84 with $^1\text{O}_2$ to reach endoperoxide 85 (Scheme 18).¹⁷⁸ This reaction has high regio- and facial selectivity due to the importance of sterics and hydrogen bonding of the acetamide N–H with $^1\text{O}_2$. Endoperoxide 85 was then treated with triphenylphosphine or silica gel to reach *N*-acetylcolchicol *O*-methyl ether (87) or androbiphenylene (88) via the 4-membered ring lactone 86. Alcolchicinoids, 87 and 88, are responsible for cell growth and tubulin polymerization inhibition,¹⁷⁹ but until this synthetic work, preparative photooxidations of helimers

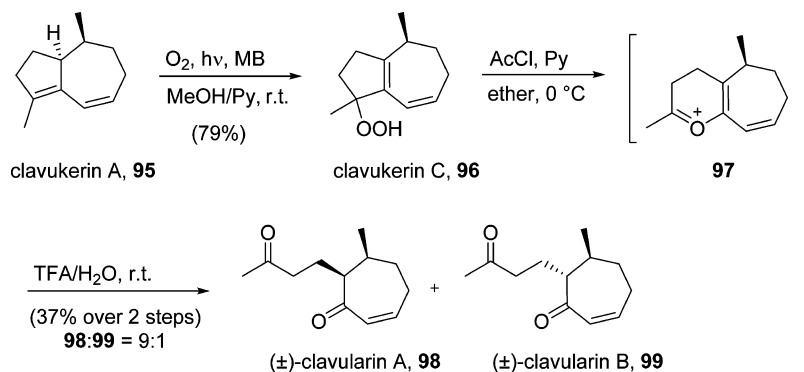
Scheme 18. Photooxidation of (–)-Colchicine



Scheme 19. Synthesis of Tropolone Compounds



Scheme 20. Synthesis of (±)-Clavularin A and B

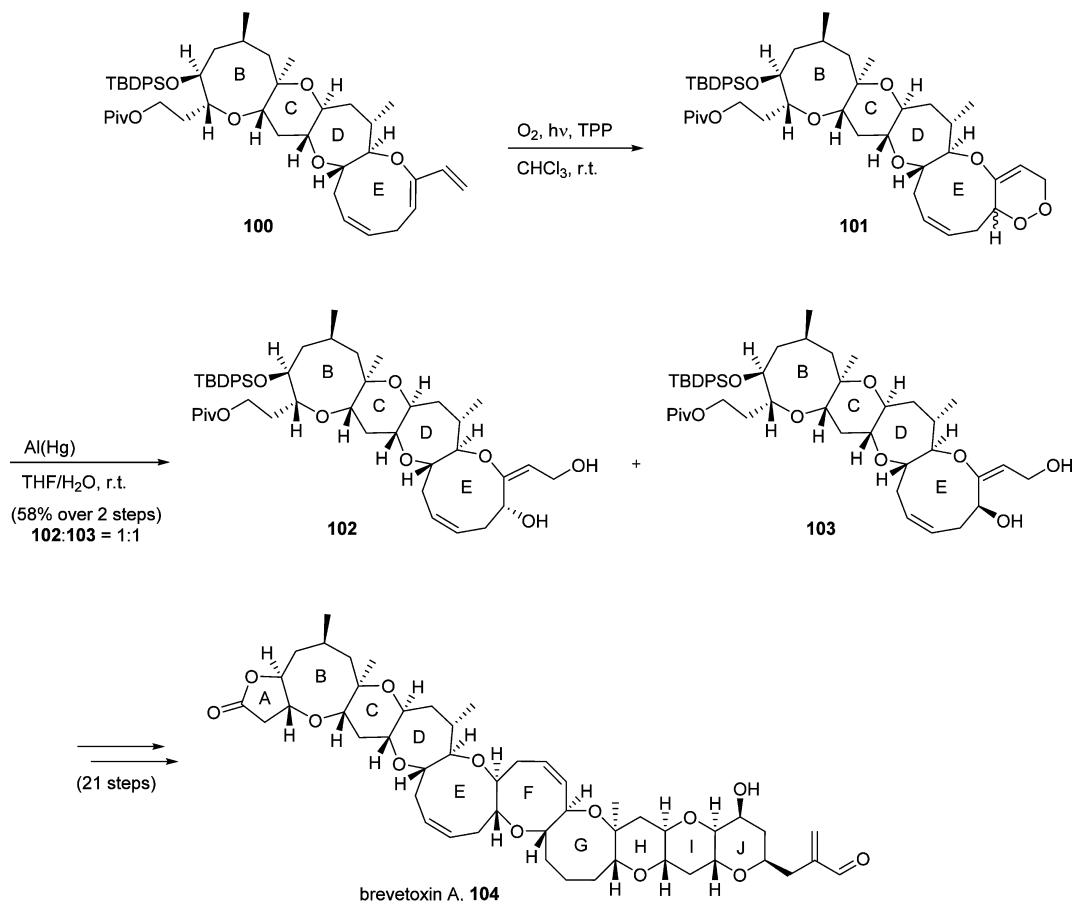


were largely neglected to reach natural product targets. Direct photolysis studies in the past few years have also shown the virtues of using helimers in synthetic applications.¹⁸⁰

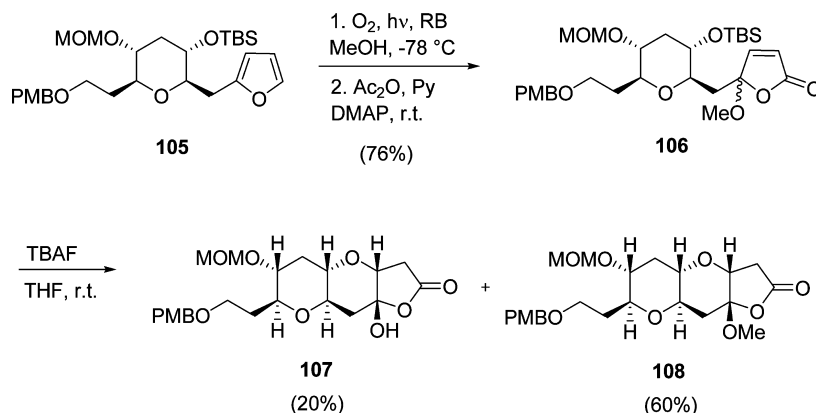
Third, a 2006 report on the TPP-sensitized photooxidation of a dioxin-fused cycloheptatriene (**89**) was found to produce tricyclic endoperoxide **90** in 94% yield (Scheme 19).¹⁸¹

Treatment of **90** with thiourea led to O–O bond reduction to tropolone **91** or other tautomers **92–94**, which bear some similarity to the natural product colchicine **84**. Tropone endoperoxide **90** releases $^1\text{O}_2$ in a reverse Diels–Alder reaction forming starting material **89**, in a similar fashion to naphthalene and anthracene endoperoxides, which are storage pools to get

Scheme 21. Singlet Oxygen Reaction in the Synthesis of Brevetoxin A



Scheme 22. Synthesis of Polycyclic Ethers



back $^1\text{O}_2$.^{182–184} Previous reports have also shown the photooxidations of benzotropones give endoperoxides that are stable at low temperatures.^{185–187} Encouragingly, benzotropones possess carbonic anhydrase isoenzyme inhibition properties.¹⁸⁸

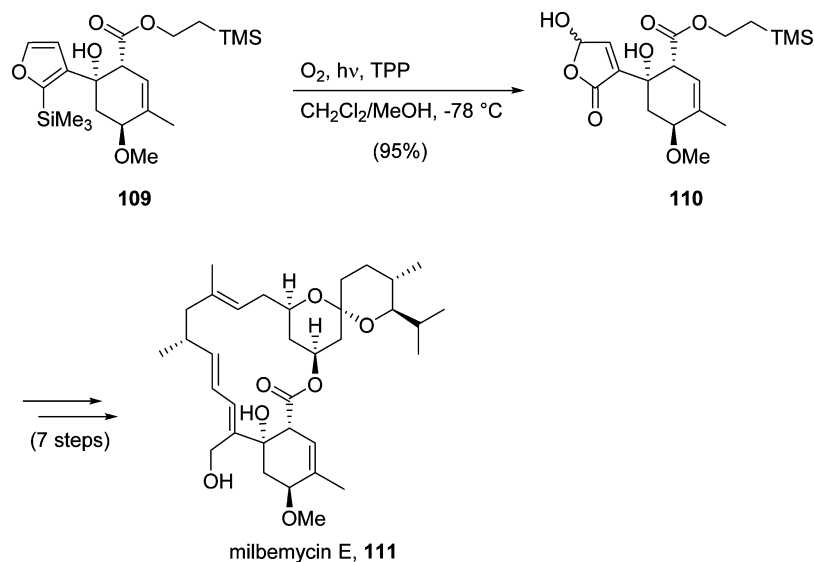
Fourth, a 1991 report described the MB-sensitized photooxidation of clavukerin A **95** with pyridine in methanol, which led to hydroperoxide **96** in 79% yield (Scheme 20).¹⁸⁹ Hydroperoxide **96** was treated with acetyl chloride in pyridine, giving the acetyl peroxide, which underwent a Hock-like 1,2-allyl shift to the oxonium ion **97**. Addition of TFA leads to a stereoselective protonation that can be explained by 1,2-neighboring group induction from the methyl center with ring-opening to the tetrahydrotropones, for (\pm)-clavularin A **98** and (\pm)-clavularin B

99 in a 9:1 mixture. Other than tropones and tropolones,¹⁹⁰ natural products containing multiple rings are common,¹⁹¹ as we will see next.

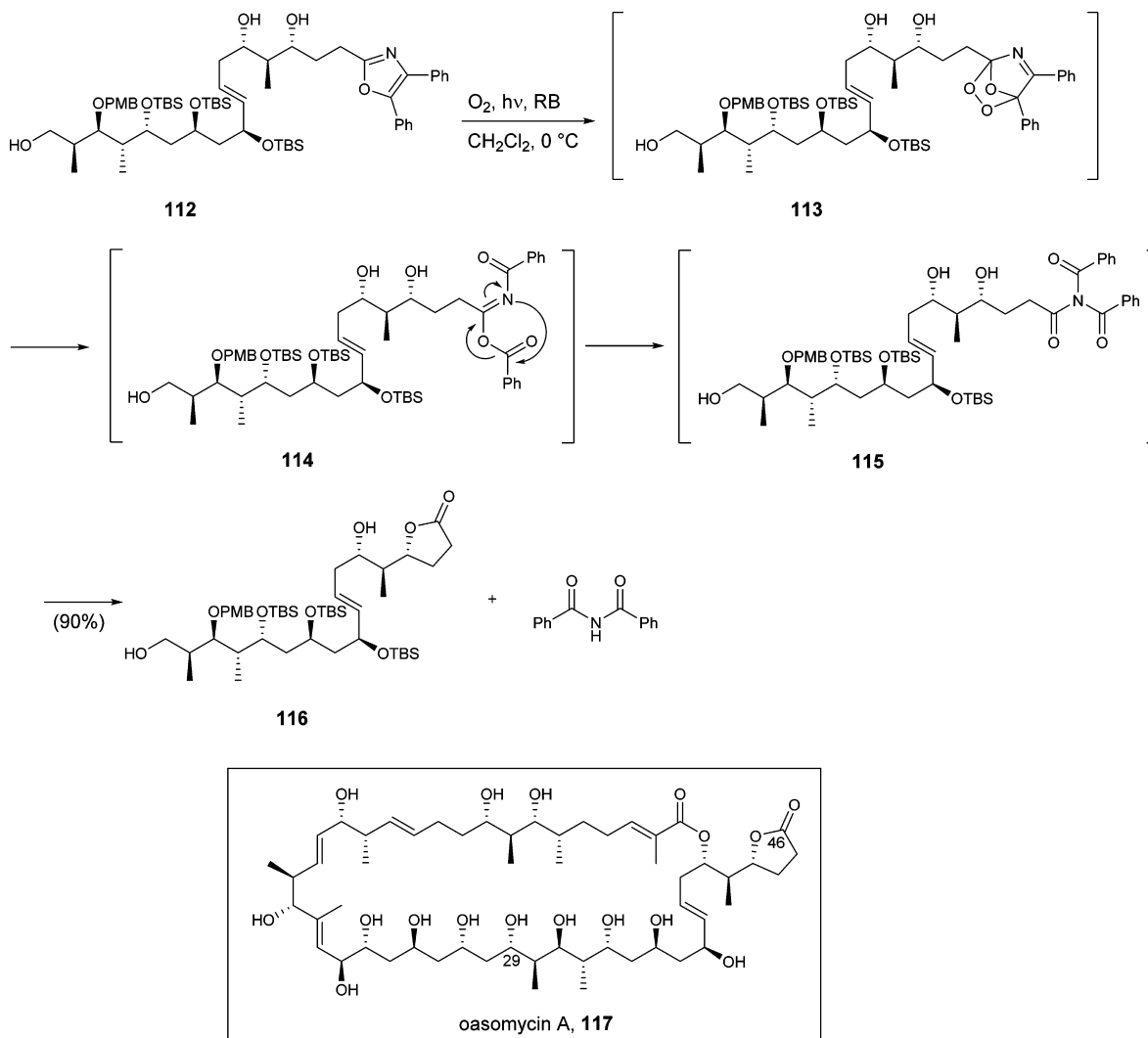
4.6. Polycyclic Ethers and Polyols

There have been reports in the synthesis of polycyclic ethers and polyols featuring $[2 + 4]^1\text{O}_2$ cycloaddition strategies. A 1999 report describes brevetoxin A **104** in which a key step was a TPP-sensitized photooxidation of the diene site of **100** (Scheme 21).¹⁹² This led to the formation of a diastereomeric endoperoxides **101**. Reduction of the O–O bond of **101** with aluminum amalgam in tetrahydrofuran (THF)/ H_2O led to the formation of diastereoisomeric diols **102** and **103** in a 1:1 ratio in 58% yield over 2 steps. Additional steps in the synthesis led to

Scheme 23. Synthesis of Milbemycin E



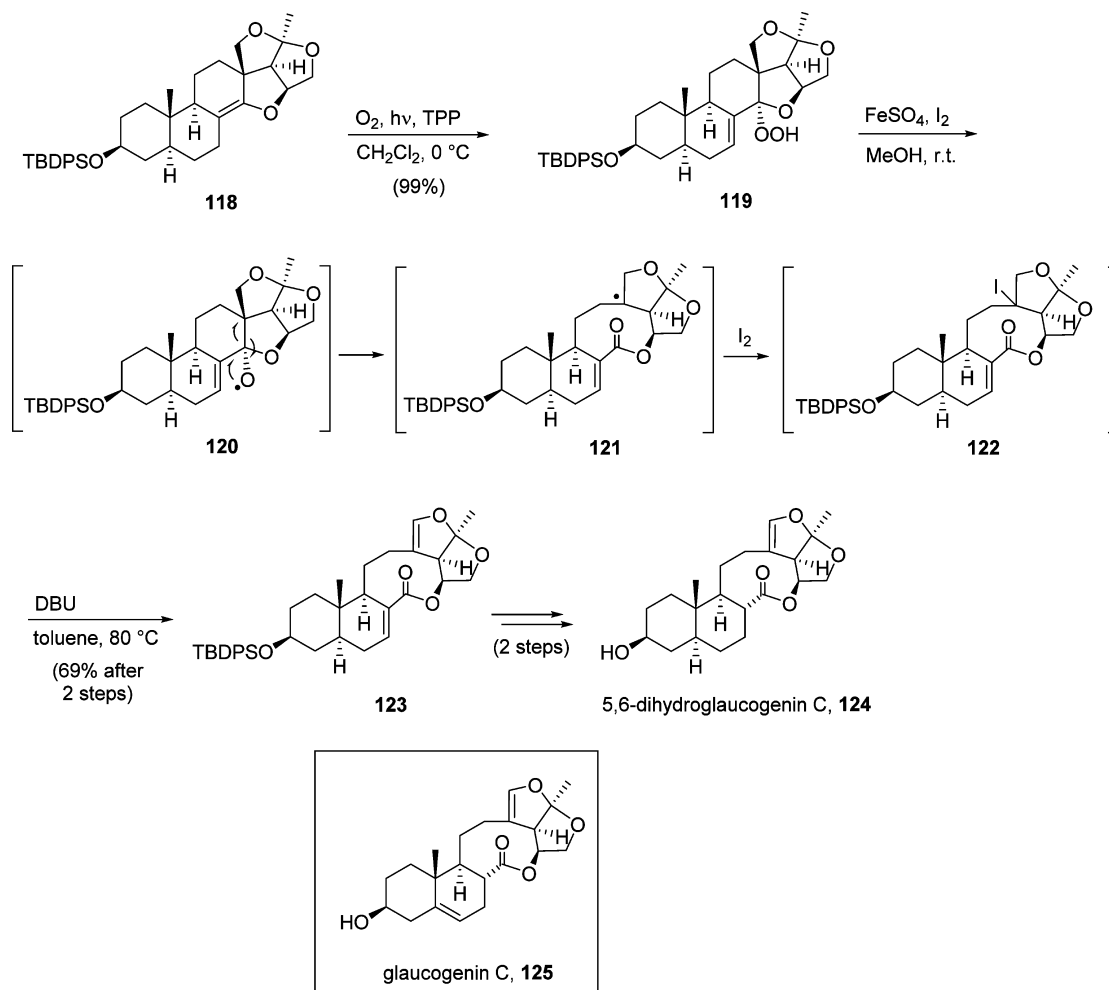
Scheme 24. Synthesis of the C29–C46 Subunit of Oasomycin A



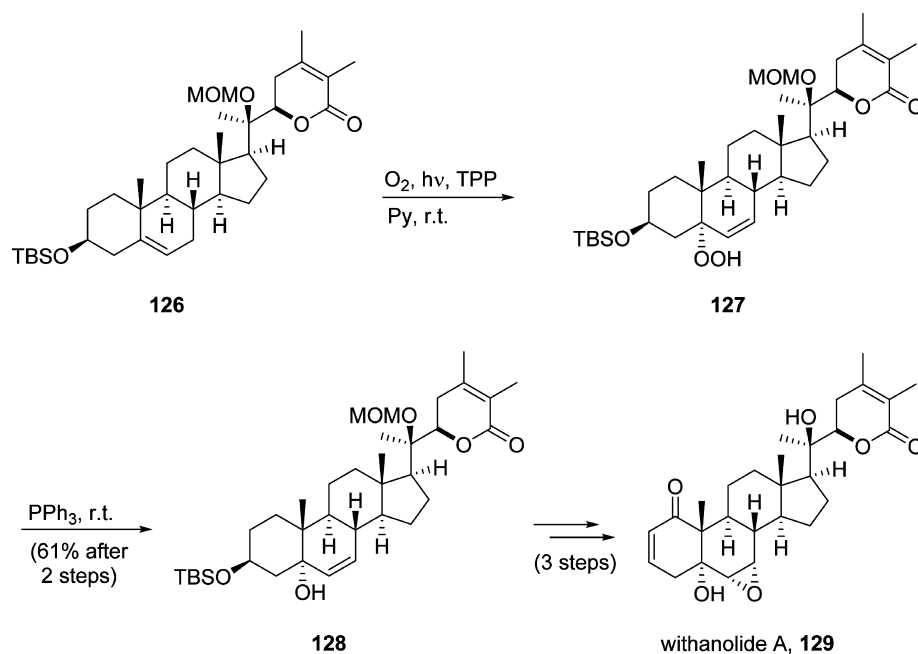
104. Such polycyclic ethers and biomimetic pathways to reach them have been of interest because of their therapeutic and toxic properties.^{193,194}

Recently, a 2014 report described the RB-sensitized photo-oxidation of furan **105** followed by reaction in pyridine with DMAP and acetic anhydride, which led to butenolide **106** in 76%

Scheme 25. Synthesis of 5,6-Dihydroglaucogenin C



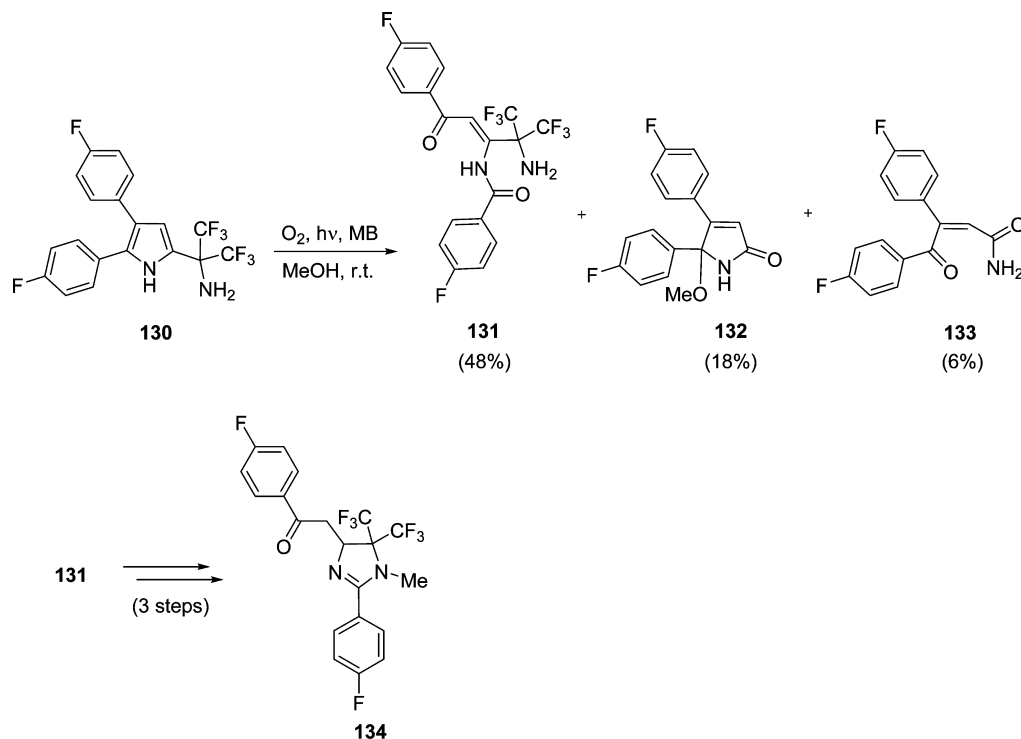
Scheme 26. Synthesis of Withanolide A



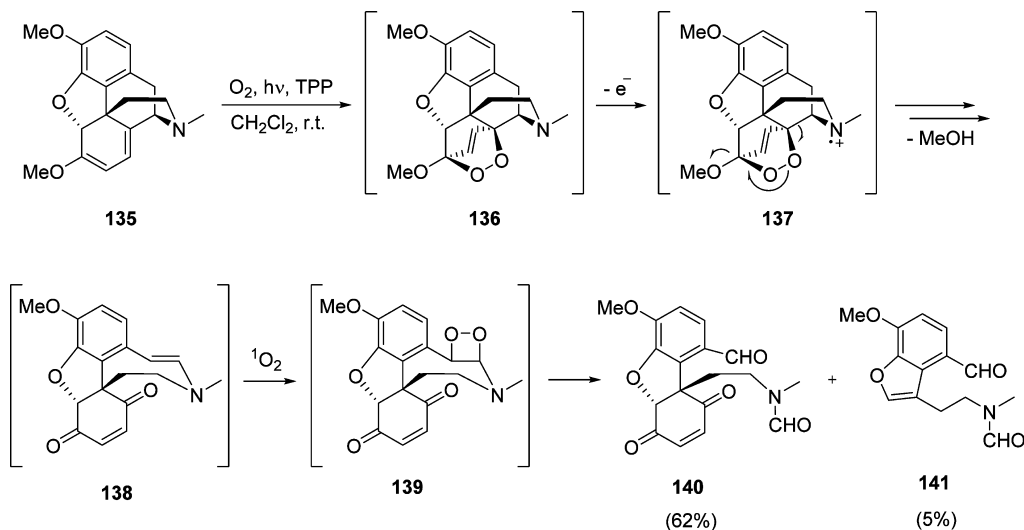
yield (Scheme 22).¹⁹⁵ Desilylation of butenolide **106** with tetrabutylammonium fluoride followed by a Michael addition/

cyclization led to (–)-(1S,3R,7R,9R,11S,12R)-furopyranopyranones **107** and **108** in 20% and 60% yields, respectively.

Scheme 27. Synthesis of an Imidazoline Steroid Mimic



Scheme 28. Photooxidation of Thebaine



Compounds **107** and **108** that arose from a furan precursor have potential synthetic utility as building blocks of polycyclic ether natural products.^{196–199}

In a different approach, one variation of the furan photooxidation topic is its substitution with a silyl group. A 1997 report described the TPP-sensitized photooxidation of trimethylsilyl-furan **109** (Scheme 23).²⁰⁰ Here, the reaction involved an intramolecular silyl migration,²⁰¹ leading to butenolide **110** in 95% yield. Further steps were then required to reach milbemycin E **111**.

A 2007 paper reported the synthesis of the C29–C46 subunit I (**116**) of oasomycin A **117**, in which one step included the RB-sensitized photooxidation of oxazole **112** (Scheme 24).²⁰² Here, singlet oxygen was taken up by the oxazole site in **112**. The reaction was a 1O_2 [2 + 4] cycloaddition and not a [2 + 2]

cycloaddition, as was previously deduced by singlet oxygen ^{18}O -tracer studies with oxazoles.²⁰³ The intermediate endoperoxide **113** underwent a Baeyer–Villiger-type rearrangement to form imino anhydride intermediate **114**, which upon *O*-acyl to *N*-acyl migration led to triamide intermediate **115**. The triamide **115** released *N*-benzoylbenzamide in a lactonization process to form **116** in 90% total yield. Such rearrangements of imino anhydrides to triamides are known and are highly useful.^{204–208} Next, we describe sterol natural products and mimics that are reachable by 1O_2 chemistry.

4.7. Sterols

Themes on the synthesis of sterols via 1O_2 chemistry have been reported.²⁰⁹ A 2011 report described the biomimetic synthesis of 5,6-dihydroglaucogenin C **124** (Scheme 25).²¹⁰ One step

involved the TPP-sensitized photooxidation of **118**, yielding the hydroperoxide **119** in 99% yield. The resultant hydroperoxide **119** reacted by a ferrous ion-catalyzed homolysis of the O–OH bond, forming an alkoxy radical and subsequently a 3° carbon radical as transient intermediates. Addition of I₂ led to an iodolactone, prior to a regioselective HI elimination affording **123** in 69% yield in 2 steps. Evidence for the existence of a 3° carbon radical was due to trapping with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), when used in place of I₂.

A 2013 report described the TPP-sensitized photooxidation of **126** in pyridine, which led to an ene reaction where treatment of the resulting hydroperoxide **127** with triphenylphosphine gave allylic alcohol **128** in 61% yield in 2 steps (Scheme 26).²¹¹ The synthesis of withanolide A **129** required three additional steps. An additional 15 unnatural analogues of **129** were prepared to probe their neuronal differentiation and neurite outgrowth activity.

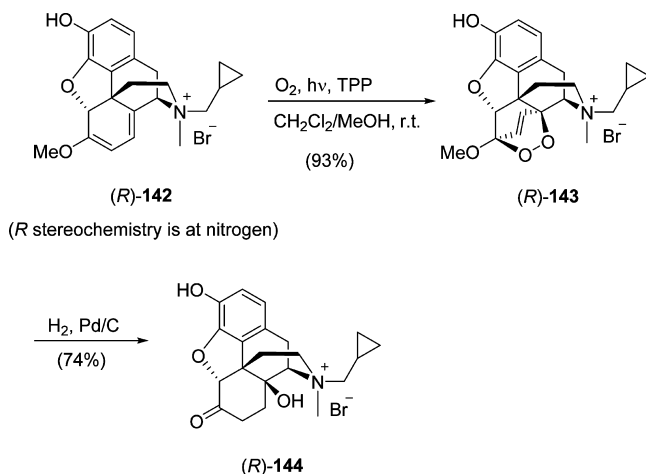
A 1996 report featured the synthesis of bis(trifluoromethyl)-imidazoline **134** from a MB-sensitized photooxidation of pyrrole **130** (Scheme 27).²¹² A [2 + 2] cycloaddition on **130** with ¹O₂ led to a dioxetane species in situ, which cleaved apart to the dicarbonyl compound, **131**. To a lesser extent, the photooxidation of pyrrole **130** proceeded by a Diels–Alder reaction with formation of a methanol adduct **132** and water adduct **133** in 18% and 6% yields, respectively. Further steps led to compound **134**, where an inhibition connection was found between **134** and active cholesterol acyltransferase (ACAT).

4.8. Opioids

Strategies have also been developed for accessing opioids via ¹O₂ chemistry, as the next two examples show. First, in 2000, a paper described the TPP-sensitized photooxidation of thebaine **135**, which led to an opioid endoperoxide **136** in the expected [2 + 4] fashion, which on loss of an electron led to cyclohexene-1,4-dione **138** (Scheme 28).²¹³ A second ¹O₂ molecule added by a [2 + 2] cycloaddition to form dioxetane **139** in situ. This di-singlet oxygenation process was followed by dioxetane ring-opening to formamide **140**. Benzofuran **141** was a minor product, and its origin was suggested from a double Norrish type I photocleavage of dione **140**.

Second, in 2015, a report described the TPP-sensitized photooxidation of diene (*R*)-**142**, in which the *R* stereochemistry is at nitrogen (Scheme 29).²¹⁴ Here, the singlet oxygenation of the diene quaternary salt led to the corresponding endoperoxide

Scheme 29. Synthesis of (*R*)-Methylnaltrexone

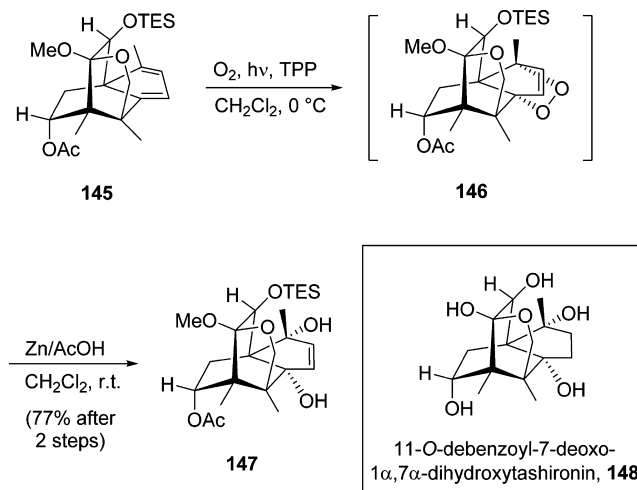


(*R*)-**143** in 93% yield. The formation of (*R*)-methylnaltrexone **144** occurred after the hydrogenation of (*R*)-**143**. Further examples of natural products bearing ring-fused structures are described next.

4.9. Ring-Fused Examples

Researchers have examined reactions of ring-fused compounds with ¹O₂, and four such examples are presented here. A 2011 report describes the TPP-sensitized photooxidation of cyclopentadienyl allocedrane **145**, where the *anti*-endoperoxide **146** arose from attack of ¹O₂ on the less-shielded bottom face of the diene (Scheme 30).²¹⁵ This was followed by addition of Zn and

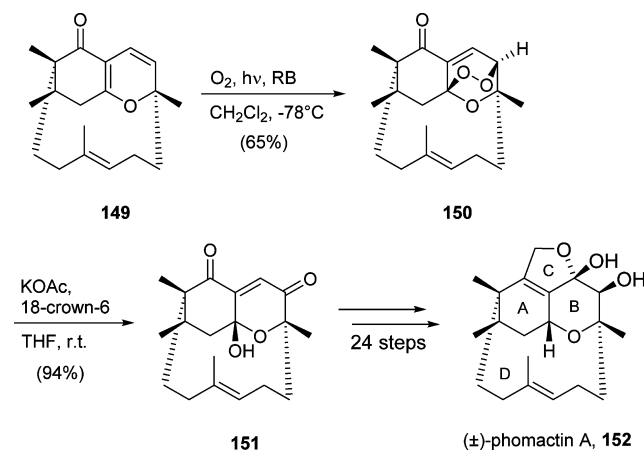
Scheme 30. Synthesis of a Tashironin-like Compound



acetic acid to furnish *cis*-1,4-enediol **147** in 77% yield after 2 steps, which contained a paddlane core similar to tashionin **148**. Other allocedrane derivatives were also examined in this 2011 paper.²¹⁵

Another intriguing example is from a 2009 report describing the synthesis of natural product (\pm)-phomactin A **152** (Scheme 31).^{216,217} One step in the synthesis involved a RB-sensitized photooxidation of diene **149** that led to endoperoxide **150** in 65% yield.²¹⁶ Singlet oxygen reacted from the more-exposed site above the diene to reach endoperoxide **150**, which reacted with KOAc and 18-crown-6 through a deprotonation reaction to give hydroxypyranone **151** in 94% yield. Attempts to reduce the

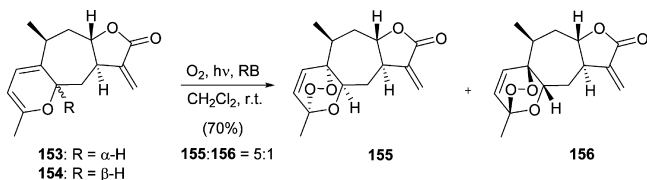
Scheme 31. Synthesis of (\pm)-Phomactin A



endoperoxide with Lindlar's catalyst, thiourea, or triphenylphosphine did not occur as would have been expected to reach enedione **151**.²¹⁸

A 2014 report describes the RB-sensitized photooxidation of **153** and **154**, which gave $4\beta,5\beta$ -epoxyxanthatin- $1\alpha,4\alpha$ -endoperoxide **155** and $4\alpha,5\alpha$ -epoxyxanthatin- $1\beta,4\beta$ -endoperoxide **156** as a mixture in 70% yield (Scheme 32).²¹⁹ Pure **155** and **156** were

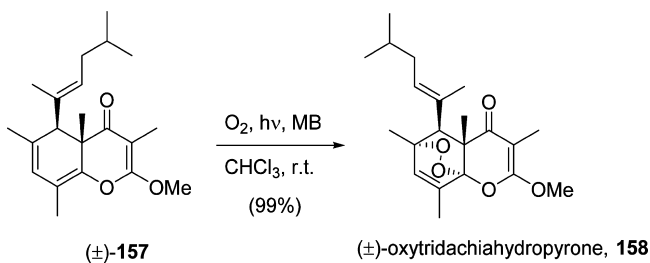
Scheme 32. Synthesis of Epoxyxanthatin Endoperoxides



isolated by preparative high-performance liquid chromatography (HPLC). The formation of endoperoxide **155** was favored (ratio of **155/156** was 5:1) as the result of $^1\text{O}_2$ addition to the diene anti to the methyl substituent.

A 2009 report describes the MB-sensitized photooxidation of tridachiahydropyrone (**157**), which gave (\pm)-**158** as a colorless oil in 99% yield (Scheme 33).²²⁰ In this work, the structure of

Scheme 33. Synthesis of (\pm)-Oxytridachiahydropyrone



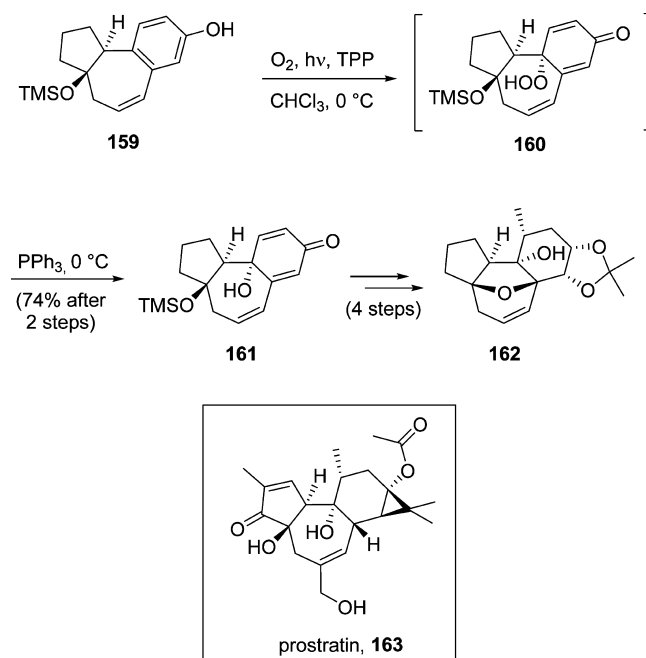
157 was revised, and (\pm)-**158** was named as (\pm)-oxytridachiahydropyrone. Heteronuclear multiple-bond correlation (HMBC), heteronuclear multiple-quantum correlation (HMQC), and correlation spectroscopy (COSY) data were collected, where $^1\text{O}_2$ reacts selectively via attack on the bottom face of **157** for the exclusive formation of the endo product (\pm)-**158**.

4.10. Phenols

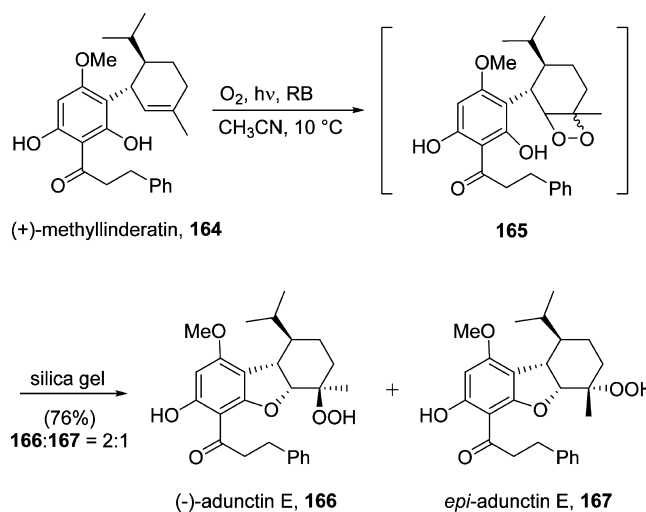
Strategies have been developed for accessing natural product phenols from $^1\text{O}_2$ reactions, as we will see in this subsection. An approach reported in 2014 uses the TPP-sensitized photooxidation of phenol **159**, which led to its dearomatization (Scheme 34).²²¹ Singlet oxygen added selectively to the opposite side of the shielding trimethylsilyl ether, furnishing the hydroperoxy quinol **160**. Quinol **161** was formed as a pink solid after the hydroperoxide group of **160** was reduced with triphenylphosphine in 74% yield in 2 steps. X-ray crystal data were obtained for **161**. Similar strategies on reduction of O–O bonds in peroxyquinols to form tertiary alcohols have been reported.²²² Tertiary alcohol **161** was a substrate for further reactions leading to model compound **162**, which has a [5–7–6] tricyclic core, similar to that for the natural product prostratin **163**.

A 2015 report described the RB-sensitized photooxidation of (+)-methylinderatin **164**, which led to dioxetane **165** by a $^1\text{O}_2$ [2 + 2] cycloaddition (Scheme 35).²²³ An adjacent phenol oxygen

Scheme 34. Synthesis of Tiglane and Daphnane-type Compounds



Scheme 35. Synthesis of (–)-Adunctin E

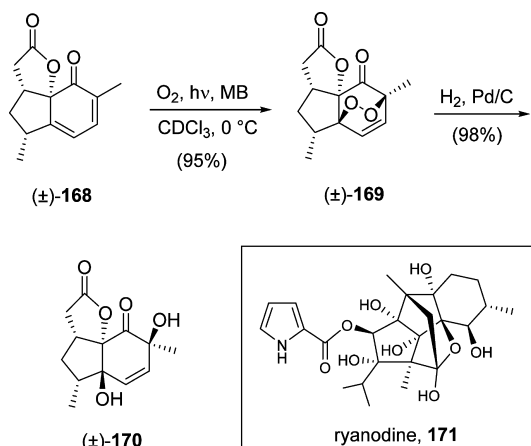


attacks the nearby dioxetane **165** carbon, which accounts for the C–O ring opening to a diastereomeric mixture of hydroperoxides **166** and **167** in a 2:1 ratio with 76% yield. X-ray data were collected for (–)-adunctin E **166** to help establish its absolute stereochemistry.

A 2003 report described the synthesis of a bicyclo[4.3.0] compound (\pm)-**170** to reach a BCE ring system similar to the natural product ryanodine **171** (Scheme 36).²²⁴ Introduction of the endoperoxide group in **169** was accomplished regioselectively by the MB-sensitized photooxidation of **168**. The hydrogenation of the endoperoxide O–O bond in **169** gave diol (\pm)-**170** in 98% yield, where X-ray crystallography was used to help establish its stereochemistry.

An approach reported in 2011 featured the MB-sensitized photooxidation of *trans*-resveratrol (**172**) (Scheme 37).²²⁵ Notably, the main pathways are a [2 + 2] cycloaddition of $^1\text{O}_2$ that led to aldehydes **175** and **176** and a [2 + 4] cycloaddition of

Scheme 36. Synthesis of the BCE Ring Structure of Ryanodine



$^1\text{O}_2$ that led initially to an endoperoxide, which upon heating rearranged to moracin M 177 and 2-hydroxyacetaldehyde. This study is a rare example in natural products synthesis where the reaction rate constants were quantitated. The chemical quenching rate constant (k_t) of $^1\text{O}_2$ with *trans*-resveratrol 172 was found to be $1.5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, where the k_t accounted for 25% of total rate constant (k_T).

A 2008 report describes the MB-sensitized photooxidation of isoeugenol (178) (Scheme 38).²²⁶ Here, a [2 + 2] cycloaddition of $^1\text{O}_2$ led initially to a dioxetane species, which cleaved apart to vanillin 179 and acetaldehyde. The reaction is a mixed photooxidized system because dehydroisoeugenol 180 and other products arise by a type I photosensitized oxidation⁴¹ forming oxygen radical intermediates. Compound 181 may form by phenolic hydrogen abstraction in 179 and radical addition to the aldehydic group of a second 179 molecule followed by hydrogen atom transfer. Mechanistically, condensation of 179 to furnish ester 181 likely involved a type I photosensitized oxidation to provide radicals for the ester coupling. Coniferyl alcohol also led to vanillin 179 (reaction not shown), although ferulic acid underwent a *trans*-*cis* C=C bond isomerization likely through zwitterionic peroxy intermediate analogous to (*E,Z*)-2,4-dimethyl-2,4-hexadiene^{139,227,228} and *trans*-propenyl anisole,²²⁹ which were also examined.

A 2014 report described the RB or $\text{Ru}(\text{bpy})_3^{2+}$ -sensitized photooxidation of triacetate 182, which was followed by reduction with triphenylphosphine, giving the tertiary alcohol 183 and secondary alcohol 184 in 62–71% yields (Scheme

39).²³⁰ The ratio of 183/184 was 2:1 for RB, but $\text{Ru}(\text{bpy})_3^{2+}$ produced an 8:1 ratio, suggesting not only $^1\text{O}_2$ but other oxygen species in the reaction. Three additional steps, including dehydration and a [2 + 4] cycloaddition, led to kuwanon I (185) and kuwanon J (186). Related natural products, brosimone A and B, were also synthesized in a similar manner to kuwanon I 185 and kuwanon J 186.²³¹

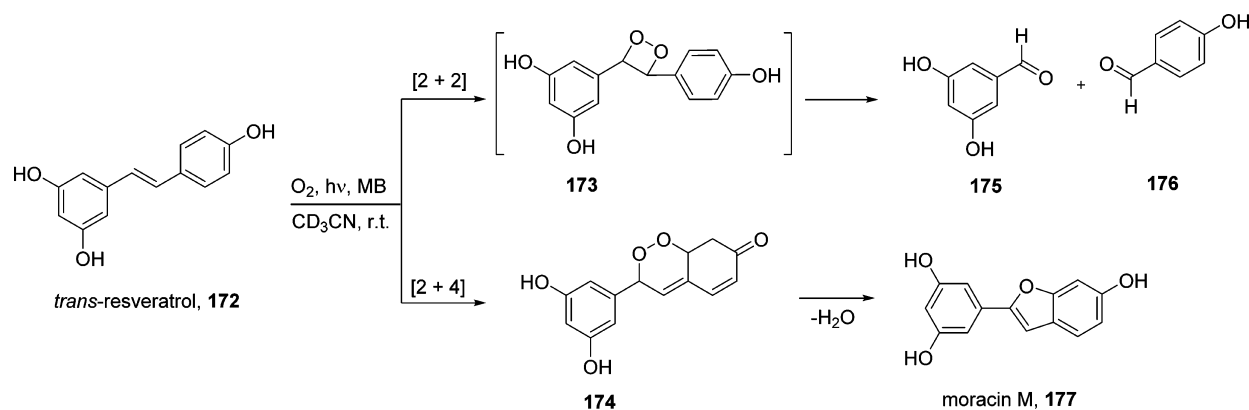
A 2004 report used a the TPP-sensitized photooxidation of natural prenylated coumarins mammea A/AA (187), mammea A/BA, and mammea B/AA followed by reduction with triphenylphosphine to get disparinol A 189, isodisparinol A, and disprorinol A in 60%, 63%, and 65% yields, respectively (Scheme 40).²³² In addition to the prenylcoumarins, the importance of natural prenylxanthone photooxidations was also realized. For example, xanthone 190 led to hydroperoxides 191 and 192, and after reduction with triphenylphosphine, to allylic alcohol 193 and a pyranoxanthone natural product 6-deoxyisojacareubine 194. A puzzling effect of regioselective formation of 188 but not in the case of 191 and 192 suggests to us the regioisomer of 188 was formed, but not isolated. The oxidations of prenylated natural products were of interest in terms of their bioactivity.²³³ While the vast majority of $^1\text{O}_2$ reactions use an external sensitizer as a strategy to synthesize natural products, this is not always necessary, as will be seen in the next section.

4.11. Self-Sensitized Examples

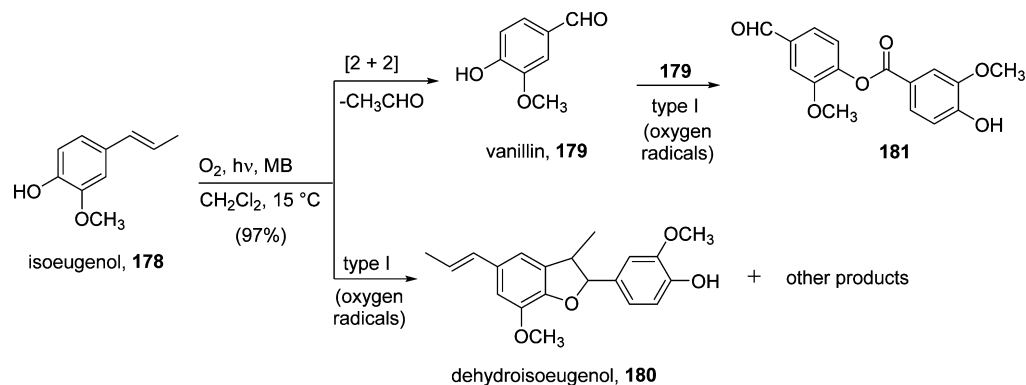
There are self-sensitized examples to reach natural products; a 1994 report described a self-sensitized photooxidation of anthracene 195 that was used in the synthesis of (–)-balanol 199 (Scheme 41).²³⁴ A $^1\text{O}_2$ [2 + 4] cycloaddition with 195 led to endoperoxide 196. Protonation of the peroxide oxygen destabilizes the C–OO bond toward heterolysis, where hydration and then methoxide ion attack and ring-opening led to benzophenone derivatives 197 and 198. Additional synthetic steps were carried out leading to (–)-balanol 199, which contains a benzophenone and a chiral hexahydroazepine. (–)-Balanol 199 is a potential inhibitor of protein kinase C.²³⁵

A paper in 1991 described a self-sensitized photooxidation of anthracene-1,5-diol 200 (Scheme 42).²³⁶ Singlet oxygen was captured by 200 regioselectively at the 9,10-positions, leading to cycloadduct 201, which was reduced with NaBH_4 and upon air oxidation led to anthraquinone 202. Additional steps were required to reach vineomycinone B2 methyl ester 203. Moving on from self-sensitized reactions, we now describe the synthesis of natural product indoles.

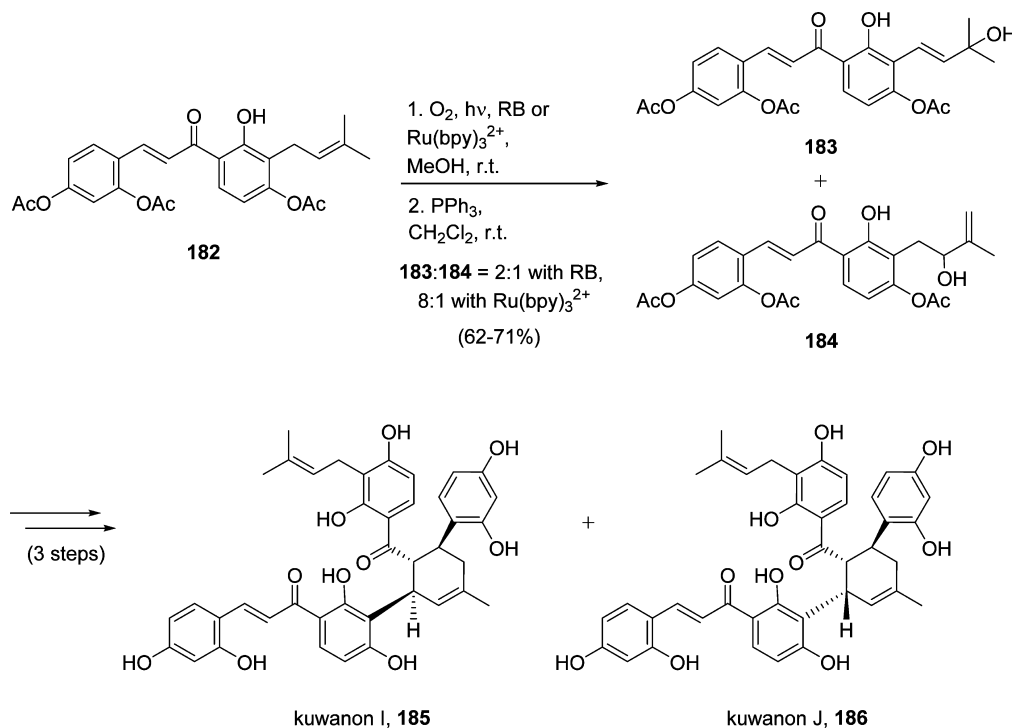
Scheme 37. Synthesis of Moracin M



Scheme 38. Synthesis of Vanillin, Dehydroisoeugenol, and Derivatives



Scheme 39. Synthesis of Kuwanons I and J



4.12. Indoles

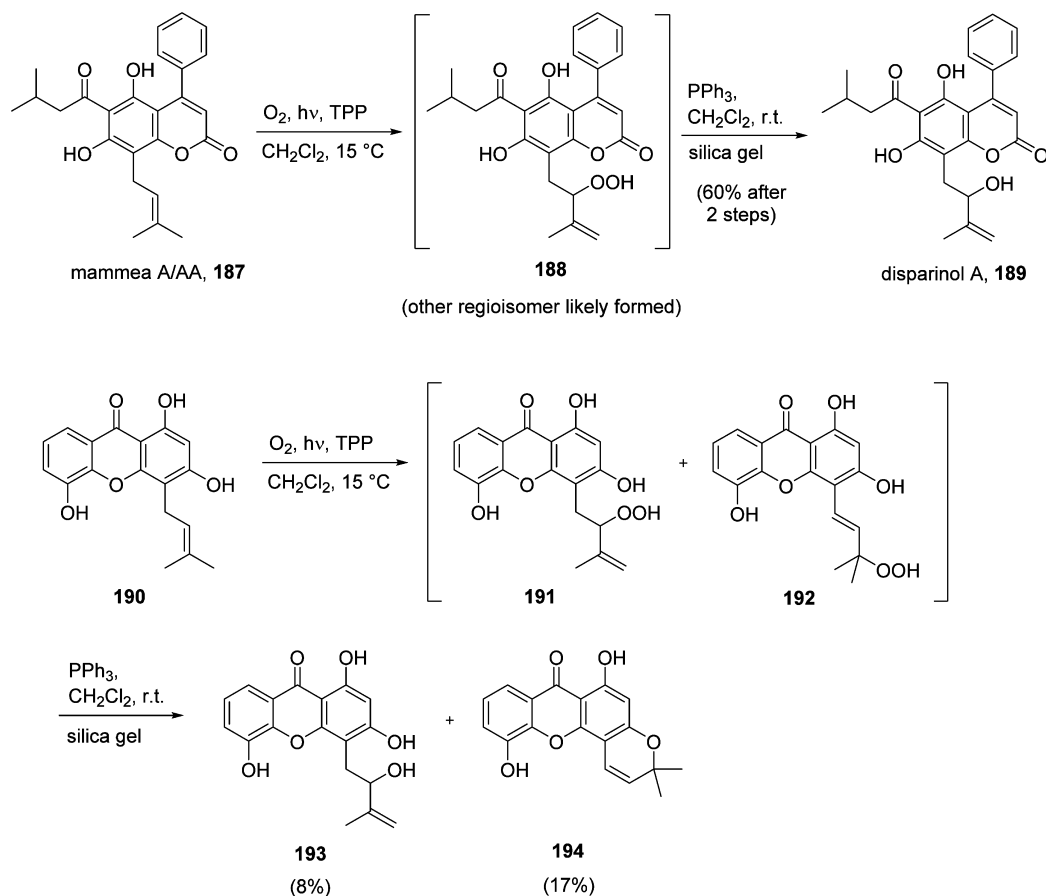
Strategies have been developed that use indole photooxidation in the synthesis of natural products and analogues. We have located four studies, including a report in 2009 that TPP-sensitized photooxidation of indole **204** led to hydroperoxide **205** (Scheme 43).²³⁷ Under acidic conditions, protonation of the hydroperoxide group in **205** causes water loss and carbonyl formation in oxindole **206** in 88% yield in 2 steps. Hydrogenation of **206** led to epimeric indoles **207** and **208** in a 1:2 ratio in 97% yield. Indoles **207** and **208** contained the [2.2.1]oxobicycloheptane core and thus are similar to the natural product welwistatin **209**. Further synthesis on a range of alkylated and acylated indole derivatives of **207** and **208** was conducted where the alkylated derivatives were furnished in higher yields.

A report in 2004 describes a secoporphyrazine-sensitized photooxidation of tryptophan **210** (Scheme 44).²³⁸ Afterward, hydroxypyrruloindole diastereoisomers **212** and **213** were formed in 1:1 ratio in 58% combined yield, where the anthelmintic natural compound (–)-CJ-12662 **214** was prepared in 4 further steps. Secoporphyrazine is less commonly used in

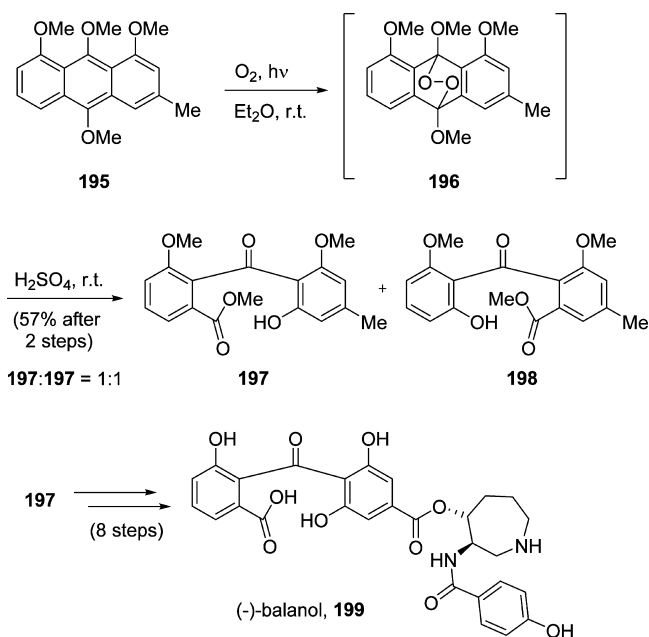
synthesis, but is a good sensitizer,²³⁹ which gave a high yield of a triplet state that is capable of efficient energy transfer to oxygen to form 1O_2 .^{240,241} The hydroxypyrruloindoles **212** and **213** originated from a 1O_2 [2 + 2] cycloaddition and deoxygenation of dioxetane by dimethylsulfide followed by nucleophilic attack at C2 by the amide nitrogen, and not through a 1O_2 ene reaction. Examples on tryptophan and indole photooxidations have been of interest.^{242–245}

A report from 2001 described the synthesis of (+)-okaramine N **218** (Scheme 45).²⁴⁶ Because the azocane-fused indole reacts readily with 1O_2 , it was protected with the enophile *N*-methyltriazolinedione (MTAD). The *N*-H allylic bond in diketopiperazine **215** reacted with MTAD by an ene reaction to reach urazole **216**, which enabled a regioselective photooxidation of the tethered indole in intermediate **216**. The RB-sensitized photooxidation of **216** was followed by deoxygenation with dimethylsulfide, and the intramolecular cyclization led to **217**. Additionally, the thermal release of MTAD in a retro-ene reaction led to okaramine N **218** in 70% yield in 4 steps. This reaction is unique because it protected the fused indole site and

Scheme 40. Photooxidation of Prenylated Coumarins and Xanthenes



Scheme 41. Synthesis of (–)-Balanol



more substituted C2–C3 indole bond,²⁴⁷ which capitalized on ene reactions with MTAD that have been characterized previously.^{248–257}

An approach reported in 2012 described the synthesis of (–)-meloheanine B (**223**) in 99% yield from the MB-sensitized photooxidation of epimers (±)-**219** and (±)-**220** (Scheme

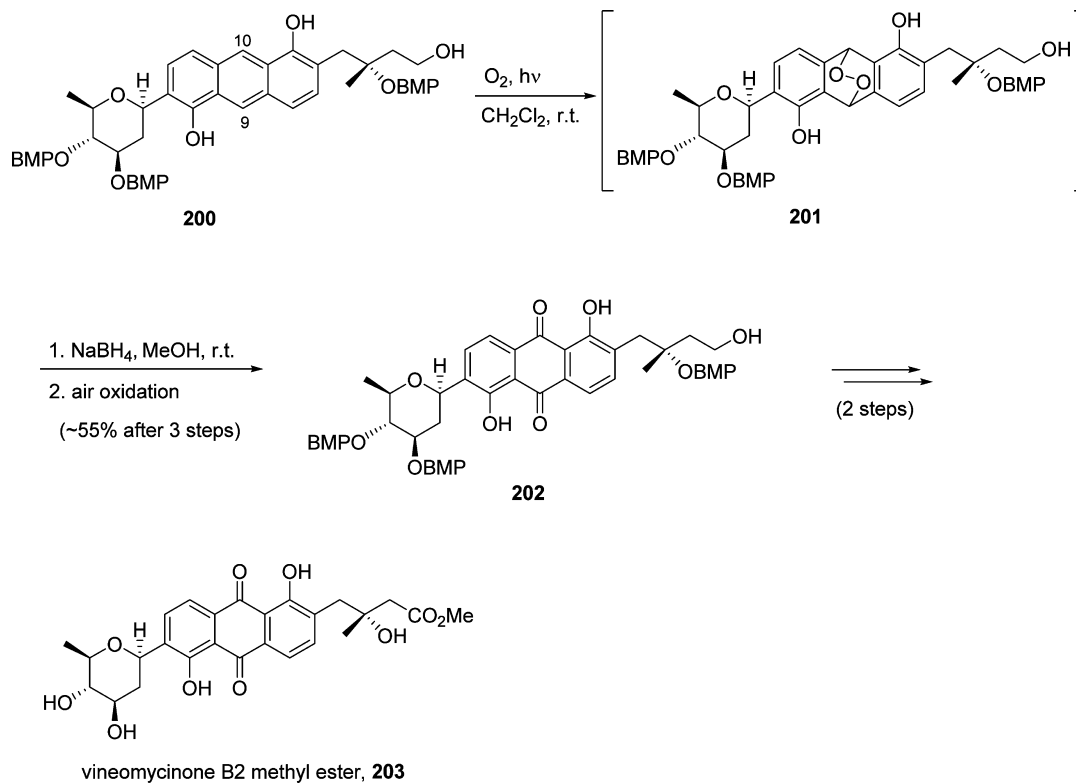
46).²⁵⁸ Notably, the ratio of epimers **219** and **220** was unimportant because the path sequence (dioxetane cleavage then hydroxypiperidine ring-opening or vice versa) ended with a stereospecific ring reclosure to reach (–)-**223**.^{259,260} Molecule curvature was of importance where singlet oxygen added regioselectively via the convex side of **219** and **220**. The dioxetane intermediates (**221** and **222**) were formed where C14 equilibration was through an aldehyde intermediate **226**, which also equilibrated with dioxetane **221**. The position of the hydroxyl group at C14 was assessed from X-ray data of (–)-**223**.

4.13. Lactams and Related Examples

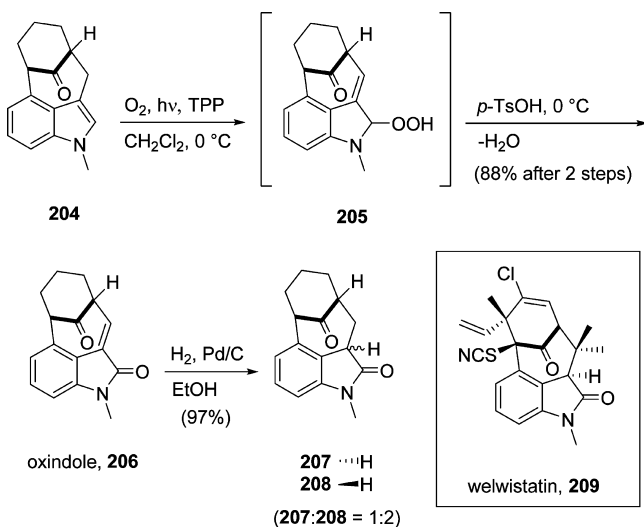
This subsection provides eight examples where singlet oxygen was used in the synthesis of natural product lactams. The first is a historical example with the synthesis of intermediate **229** reported in 1984 by an enamine–singlet oxygen reaction (Scheme 47).²⁶¹ A bisacenaphthalenethiophene (BANT)-sensitized photooxidation of **227** led to tricarbonyl **228** in 42% yield. The enamine site in **227** was cleaved by $^1\text{O}_2$ to form the vicinal tricarbonyl system in **228**. The facile cleavage of enamines by singlet oxygen to form carbonyl derivatives has utility in the synthesis not only of β -lactams but also of ketones, lactones, and esters.^{262–264} Desilylation and intramolecular cyclization by attack of the lactam nitrogen on the center carbonyl group of **228** followed by reaction with TMSI led to **229**. Compound **229** has served as a precursor in the synthesis of antibiotic (±)-PS-5 **230**.²⁶⁵

A 2015 report²⁶⁶ described the MB-sensitized photooxidation of difuran **231** where MB played a dual role, one as a sensitizer and the other as a redox catalyst (Scheme 48). After the

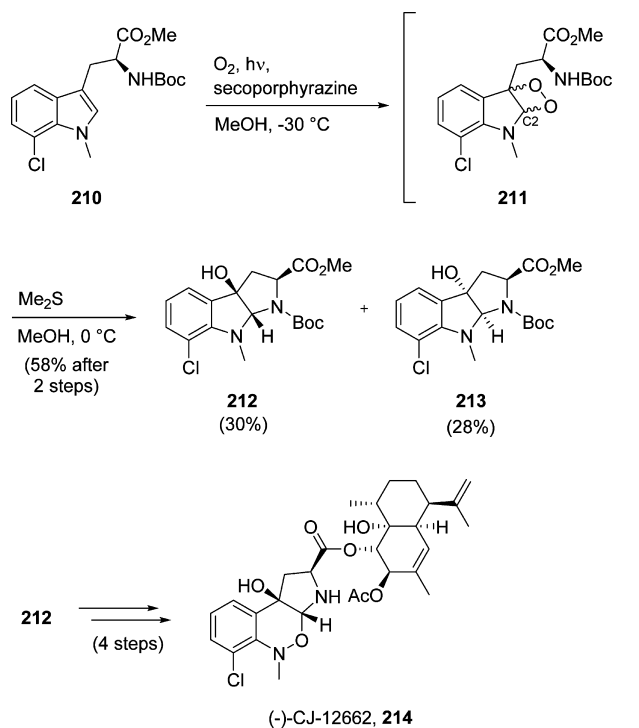
Scheme 42. Synthesis of Vineomycinone B2 Methyl Ester



Scheme 43. Synthesis of Oxindoles



Scheme 44. Synthesis of the Natural Product (-)-CJ-12662

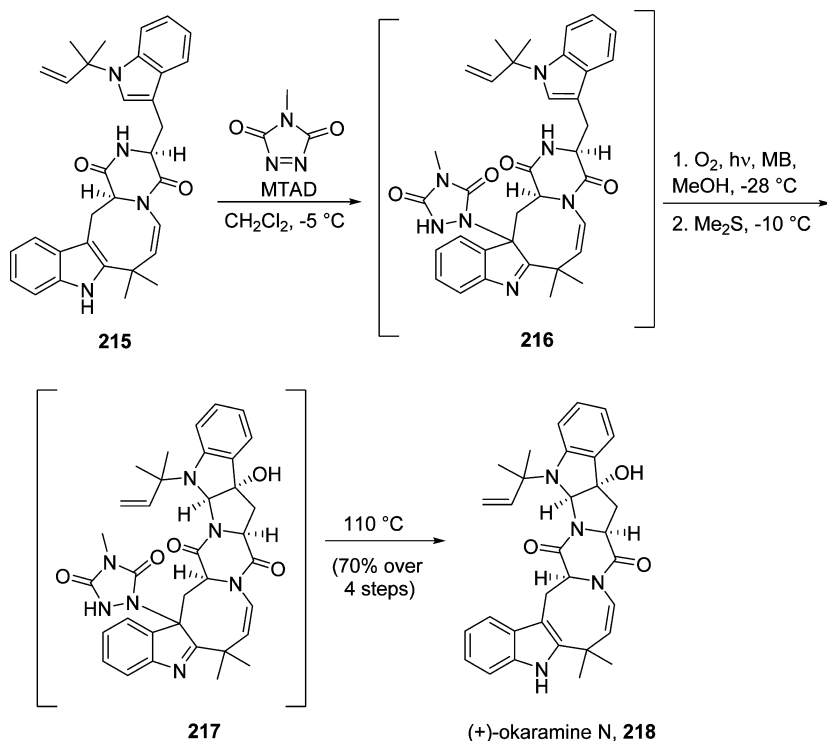


photoreaction, dimethylsulfide was added and subsequently ammonia, which led to the formation of 1,5-dihydropyrrol-2-one **232**. After concentrating the mixture, it was dissolved in chloroform containing molecular sieves (4 Å) and TFA to give pandamarine **233** in 30% overall yield. This MB sensitizer and redox catalyst approach^{266,267} has enabled the access to other units (diazaspiro[4,5] and 5-ylidenepyrrol-2(*SH*)-one) common in natural products and drugs.^{268–272}

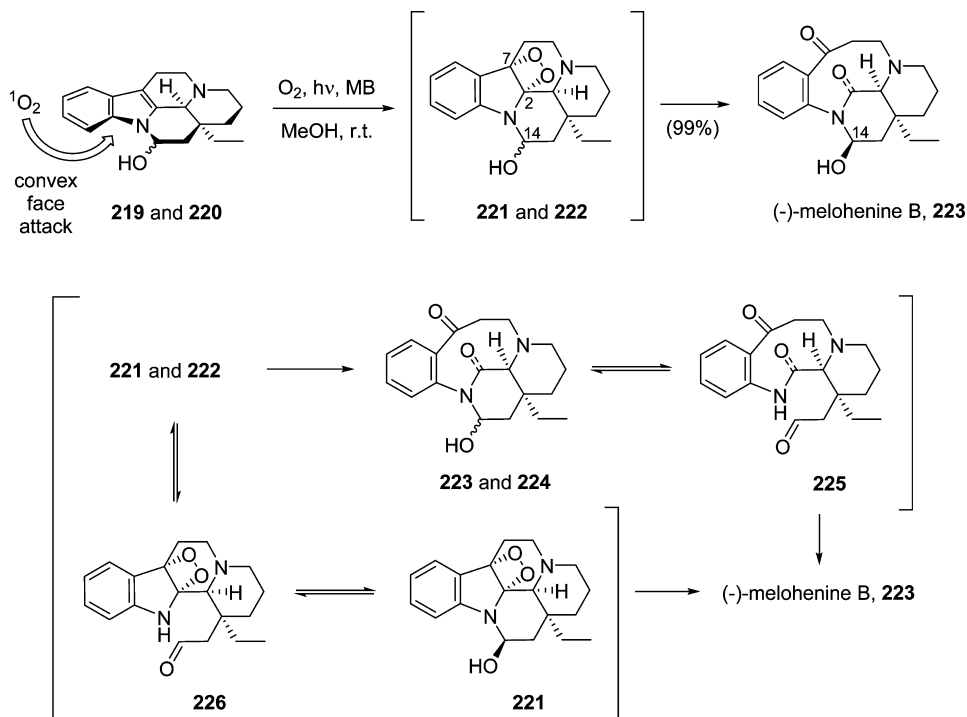
A 2014 report described the RB-sensitized photooxidation of difuran **234**, which led to a tandem addition of ¹O₂ (Scheme 49).²⁷³ After solvent removal, the residue was placed in pyridine with acetic anhydride, followed by the addition of TMSBr leading to methoxybutenolide **235** as a single diastereomer in 75% yield.

Addition of H₂SO₄ to a solution of butenolide **235** led to pandamarilactone-1 **236** in 12% yield, and pandamarilactonines A–D **237** in 48% yield with the latter in a dr ~ 55:30:10:5 ratio. While not lactam-forming, we thought it is logical for this example to be included in this subsection because a unique spiro-*N,O*-acetalization and elimination took place to form a

Scheme 45. Synthesis of (+)-Okaramine N

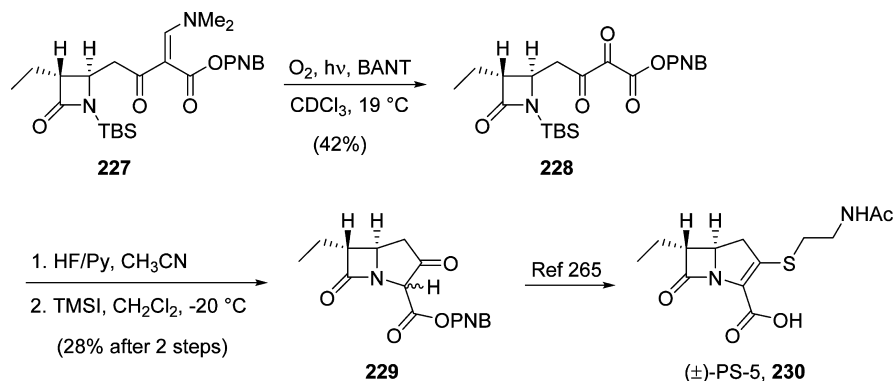


Scheme 46. Synthesis of (-)-Meloheanine B

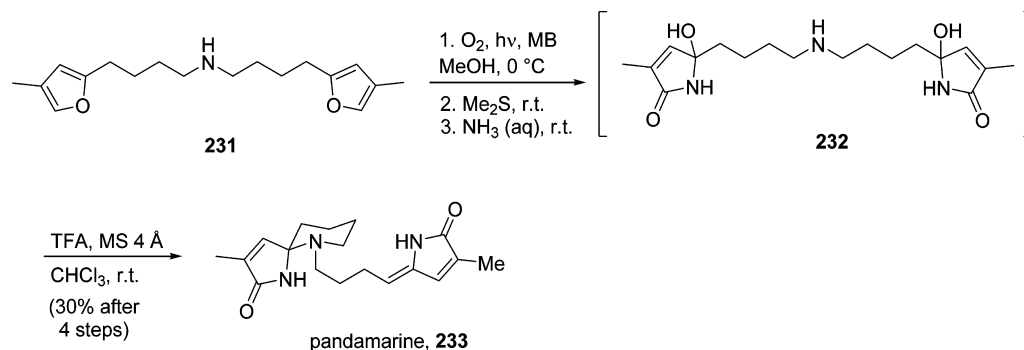


spirolactone piperidine structure in 236 and its rearranged lactone pyrrolidine structure in 237. Another example of the furan topic is a 1995 report on the RB-sensitized photooxidation of trimethylsilylfuran 238 in the presence of DIPEA, which led to 239 in 99% yield (Scheme 50).²⁷⁴ The presence of the trimethylsilyl group improved the yield of butenolide formation.^{201,275} Butenolide 239 underwent further reactions to reach (-)-PI-091 240, a platelet aggregation inhibitor.²⁷⁴

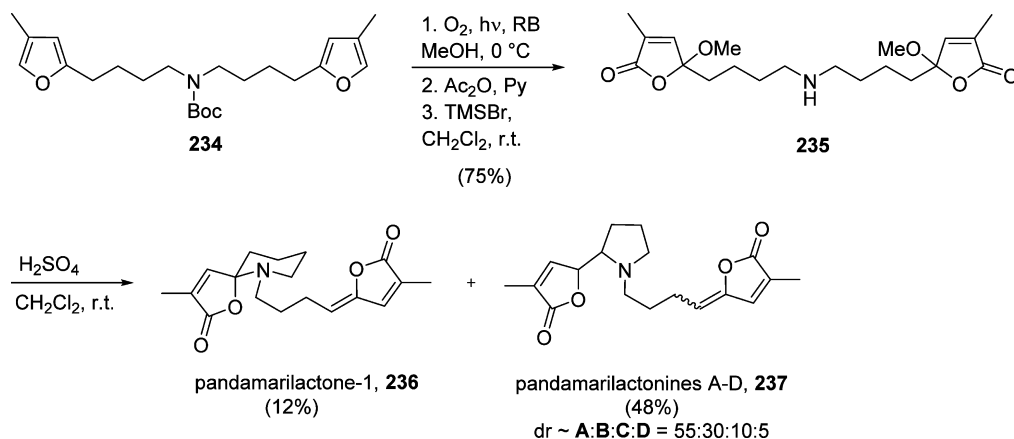
An approach reported in 2013 featured the RB-sensitized photooxidation of furan 241 followed by the addition of dimethylsulfide and then of 3,4-dimethoxyphenethylamine led to lactam 244 in 54% yield (Scheme 51).²⁷⁶ The cyclization process is rationalized by intermediate 242, where an additional step led to 1,5-dihydropyrrol-2-one 244. Compound 244 contains the bis-spiro structure similar to that seen in the natural product erysotramidine 245.

Scheme 47. Synthesis of Antibiotic (\pm)-PS-5

Scheme 48. Synthesis of Pandamarine



Scheme 49. Synthesis of Pandamarilactone-1



A 1993 report described the reaction of bipyrrrole **246** with $^1\text{O}_2$ by a [2 + 4] cycloaddition reaction (Scheme 52).²⁷⁷ This reaction led to the *D,L* and *meso* forms of isochrysohermidin (**248** and **249**) in 42% combined yield in a 1:1 ratio. The photooxidation of pyrroles have been shown to have utility in the synthesis of 1,5-dihydropyrrol-2-ones.²⁷⁸ An example is shown below. The singlet oxygenation of pyrrole **250**, in which RB was the photosensitizer, gave 1,5-dihydropyrrol-2-one **252** in 92% yield (Scheme 53).²⁷⁹ The reaction produced the endoperoxide **251** before the decarboxylation and formation of **252**. Pyrroles and related indolizines also tend to undergo type I photooxidation reactions.^{280–284}

In conclusion, section 4 described batch reactions that have been established using $^1\text{O}_2$ in the synthesis of natural products and analogues. There is continuity between batch photo-

oxygenations and reactions conducted in flow settings, as is discussed next.

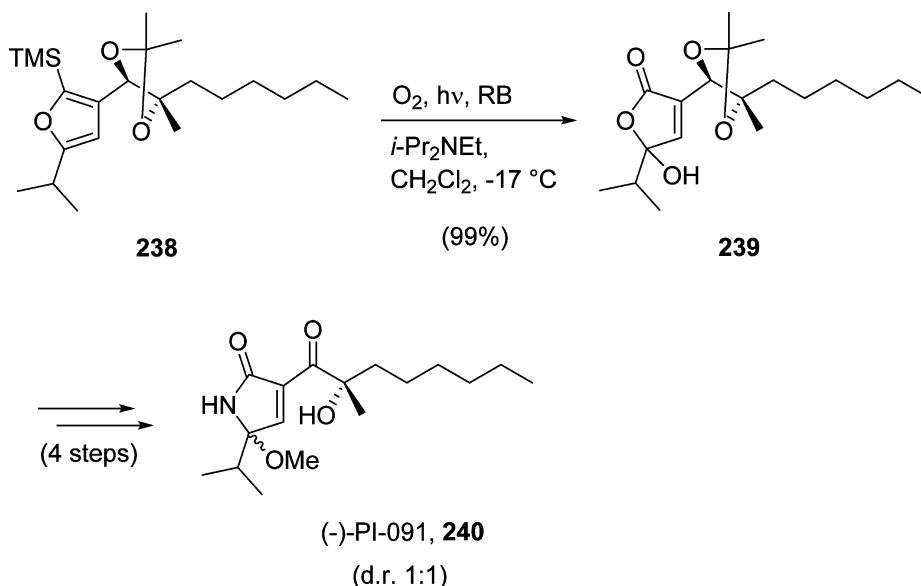
5. SINGLET OXYGEN IN FLOW SYNTHESIS

5.1. Background

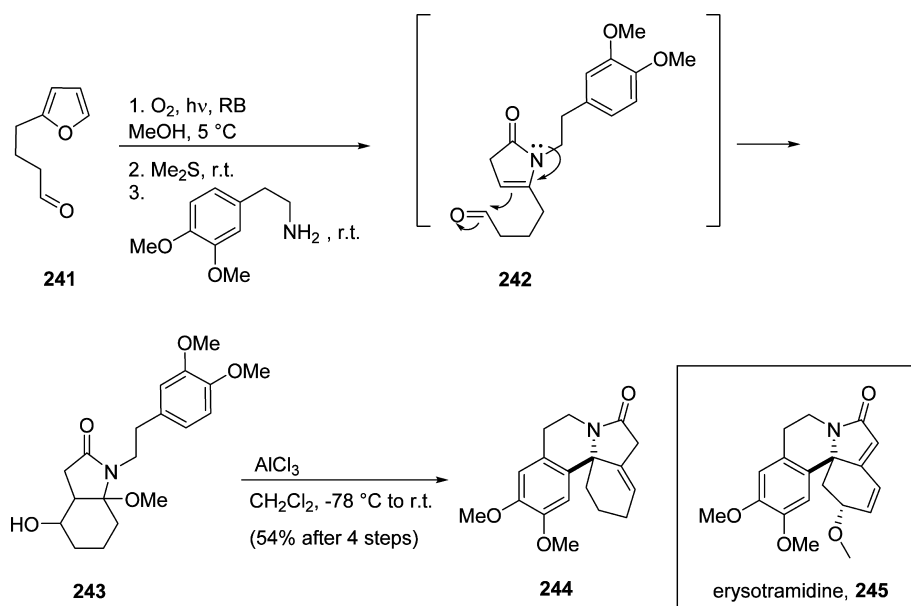
We now turn to $^1\text{O}_2$ flow photoreactors and discuss their success in synthesis to date. Schemes 54–66 show the extent of compounds synthesized thus far, including juglone, butenolides, rose oxide, and artemisinin. Flow experiments to synthesize compounds of high complexity as seen in section 4 have not yet emerged. Also, reports of tandem addition of singlet oxygen molecules in flow reactions are absent from the literature.

In what follows, $^1\text{O}_2$ microflow and macroflow photosystems are described, where Figures 1 and 2 provide illustrations, respectively. There are 20 studies that have used micro- or

Scheme 50. Synthesis of (-)-PI-091



Scheme 51. Synthesis of a Tetracyclic Compound Similar to the Natural Product Erysotramidine



macroflow $^1\text{O}_2$ photoreactors in synthesis. Photoreactors have also been used to produce airborne $^1\text{O}_2$ but will not be described.^{285–289} For example, a Pyrex-tube flowing $^1\text{O}_2$ was developed,²⁸⁵ where reaction rate data for $^1\text{O}_2$ with alkenes was reported in the gas phase (Figure 3), but this device is not compatible with organic synthesis because of a very rapid oxygen sparge rate, which would cause solvent evaporation.

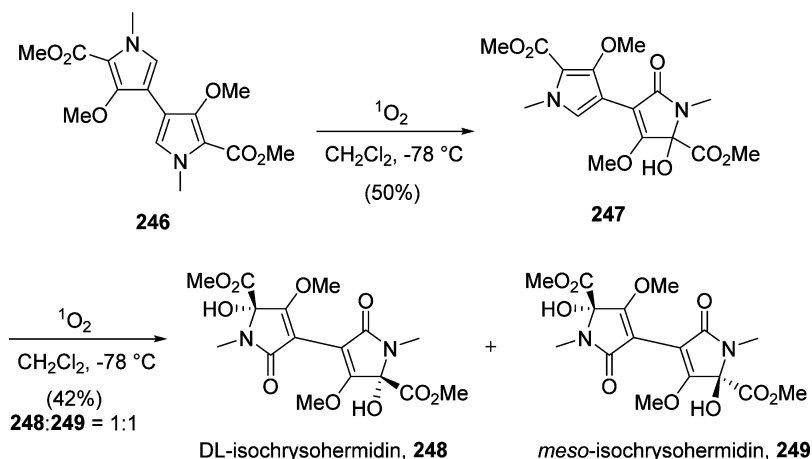
We provide accounts of four $^1\text{O}_2$ photoreactor geometries (i) microflow reactor, (ii) macroflow reactor, (iii) supercritical carbon dioxide reactor, and (iv) bubbling reactor in subsections 5.2 to 5.5. We start our discussion by presenting examples of $^1\text{O}_2$ microflow reactors that used dissolved sensitizers (section 5.2.1).

5.2. Singlet Oxygen Microphotoreactors

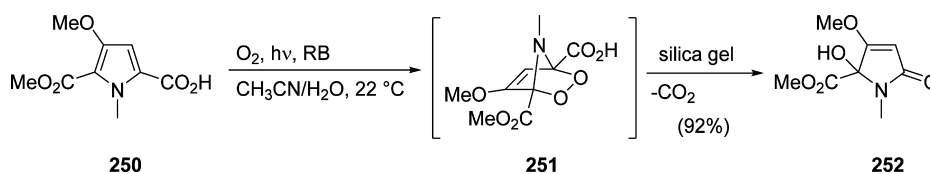
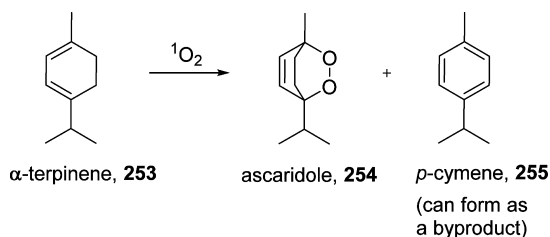
We have located 11 studies that use microflow photoreactors with solution-phase and immobilized sensitizers (sections 5.2.1 and 5.2.2).

5.2.1. Microphotoreactors with Solution-Phase Sensitizer. In 2013, a paper reported that ascaridole 254 and byproduct *p*-cymene 255 were formed in 90% total yield from a RB-sensitized microflow photooxidation of α -terpinene 253 (Scheme 54).²⁹⁰ Byproduct *p*-cymene 255 arises from a type I photosensitized oxidation process. The device consisted of a microcapillary film (MCF) with 10 parallel channels. Oxygen mass-transport was enhanced by using degassed solvent, where O_2 was transported through a fluorinated ethylene propylene (FEP) microcapillary film. Here, space-time yields were found to be 20 times greater compared to a batch reaction. A similar reaction was studied in 2002,²⁹¹ where ascaridole 254 (85% yield) was also formed from RB-sensitized flow photooxidation of α -terpinene 253 using a glass microchip device with etched channels.^{292,293}

A 2014 report described pinocarvone 257 that was synthesized from a TPP-sensitized microflow photooxidation of α -pinene

Scheme 52. Synthesis of DL and *meso*-Isochrysohermidin

Scheme 53. Synthesis of a 1,5-Dihydropyrrol-2-one

Scheme 54. Flow Reactor Photooxidation of α -Terpinene

256 (Scheme 55).²⁹⁴ The system was a microreactor-LED where the reaction led to pinocarvone 257 in pyridine with DMAP and acetic anhydride, as was previously established.²⁹⁵ Space-time yields for the microreactor were found to be 3–7 times higher than other reactors, including an immersed well and an annular flow system.

A report in 2007 focused on a Ru(bpy)₃²⁺-sensitized microflow photooxidation of (*S*)-(-)- β -citronellol 259 (Scheme 56).^{296,297} The device consisted of a blue LED light source and meandering channels where the solution came full circle, i.e., it was pumped in a loop while being irradiated for 60–70 h. The yield for 260 was 60% and for 261 was 40% by HPLC. The corresponding alcohols were formed after reduction with Na₂SO₃. Yields were found to be only slightly higher for the microflow reactor compared to the batch reactor, which used a Xe lamp.

A falling-film microreactor was reported in 2005 to synthesize 2-cyclopenten-1,4-diol 267 in 20% yield from RB-sensitized microflow photooxidation of cyclopentadiene 265 (Scheme 57).^{298,299} The reactor consisted of a plate with 32 parallel microchannels along with a Xe lamp. The film flowed downward simply as a consequence of gravity. After exiting the reactor, the endoperoxide 266 is reduced to *cis*-cyclopent-4-ene-1,3-diol 267 with thiourea. There was no optimization of this flow reaction.

In 2011, a paper described a dual microreactor to synthesize allylic alcohol 262 and 263 in 95% yield (262/263 = ratio

1.0:1.5) from a MB-sensitized microflow photooxidation of citronellol 259 (Schemes 56 and 58A).³⁰⁰ The products were analyzed after treatment of hydroperoxides 260 and 261 with NaBH₄ in methanol. The device used a white LED light source but was unique. It contained a polyvinylsilazane (PVSZ)-line dual-channel where liquid flow and oxygen flow channels were separated by a PDMS layer. The PDMS is gas-permeable and permitted rapid saturation of the solution with oxygen. Reaction times ranged from 2 to 3 min. Other substrates were photooxidized, including α -terpinene 253 that gave ascaridole 254 (91% yield), and allylic alcohols 268 (R = H or Me) to give hydroperoxides 269 (R = H or Me) in 99% yield. The relative efficiency of the dual-channel system was found to be greater than that of a monochannel system due to a more efficient oxygen mass transfer process. Furthermore, the efficiency of the dual-channel system was 2.6-fold higher compared to a batch reaction.

A 2014 report described a microreactor that was fabricated to synthesize ascaridole 254 in 92% yield from RB-sensitized microflow photooxidation of α -terpinene 253 (Scheme 54).³⁰¹ There are also data for the ¹O₂ microreaction with naphthalene-1,5-diol 272 to give juglone 273 in 92% yield (Scheme 59A) and also the ¹O₂ microreaction with citronellol 259 to give allylic hydroperoxides 260 and 261 in 92% yield. Ring-opening of an initially formed dioxetane can take place (Scheme 60). For example, the reaction of 2-(3-methoxyphenyl)-3-methyl-1-benzofuran 278 with ¹O₂ formed 2-acetylphenyl-3-methoxybenzoate 280 in 97% yield. The device consisted of borosilicate glass with channels and a serpentine section and used an OLED light source. This particular microphotoreactor did not outperform a batch reaction. However, the thinking was to wrap the flexible OLED white light source around the reactor, which seemed very reasonable.

Lastly, in 2012, a report described the sulfamidic Zn phthalocyanine-sensitized microflow photooxidation with 9,10-dimethylanthracene 281 in DMF (Scheme 61A).³⁰² In this case,

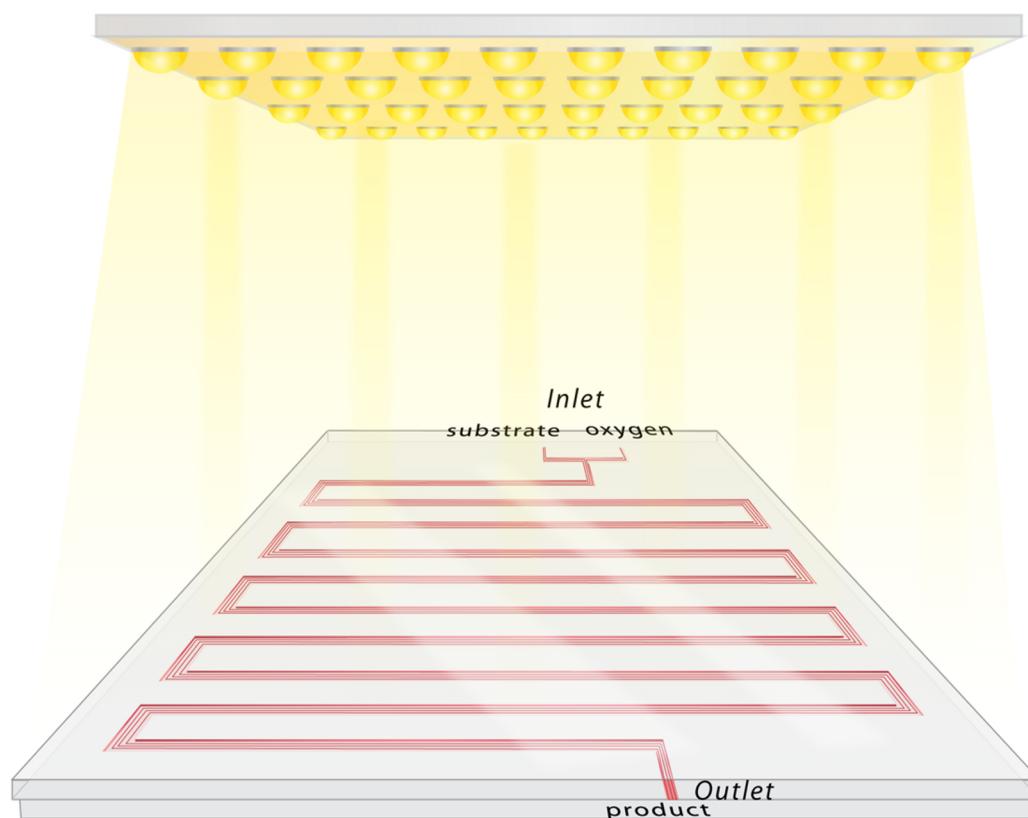


Figure 1. Microflow system capable of generating $^1\text{O}_2$ in micrometer-sized channels. LED or other light sources are often positioned above the plate.

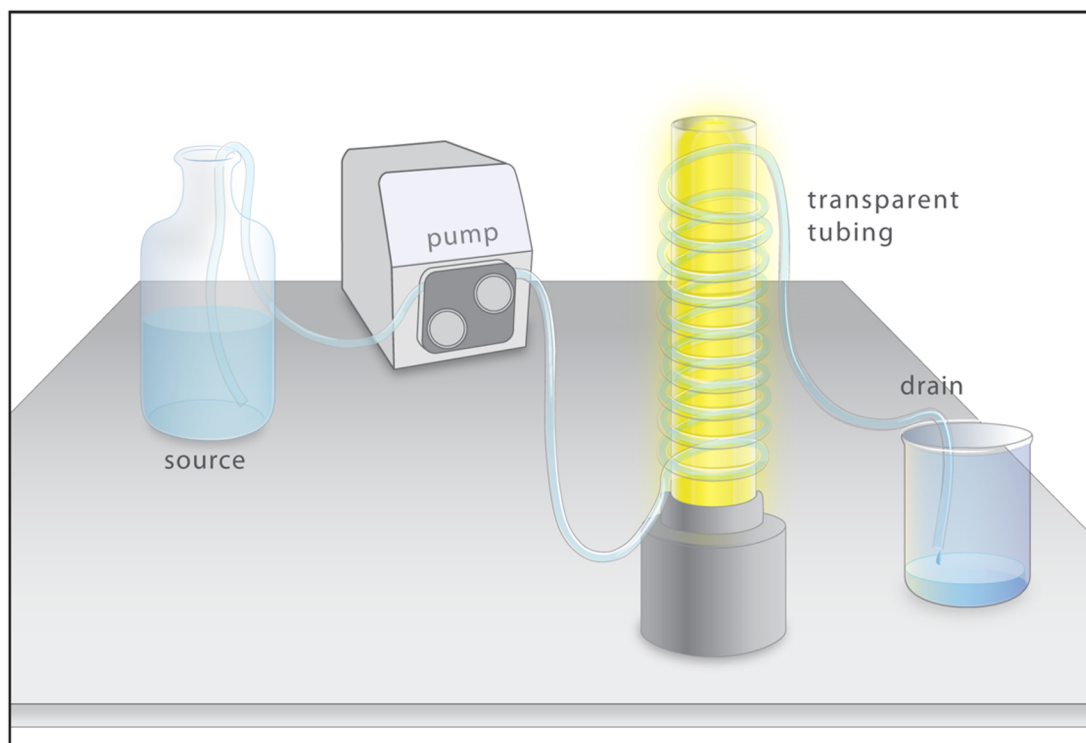


Figure 2. Macroflow system capable of generating $^1\text{O}_2$ in a millimeter-sized channel. Optical energy is delivered from a light source with transparent tubing coiled around it. Reagents are conveyed through the tube, and products drain out the end.

a high-pressure mercury lamp was the light source, and samples were followed by HPLC. The data showed that the microreactor

could photooxidize the anthracene **281** more rapidly than in a batch reactor.

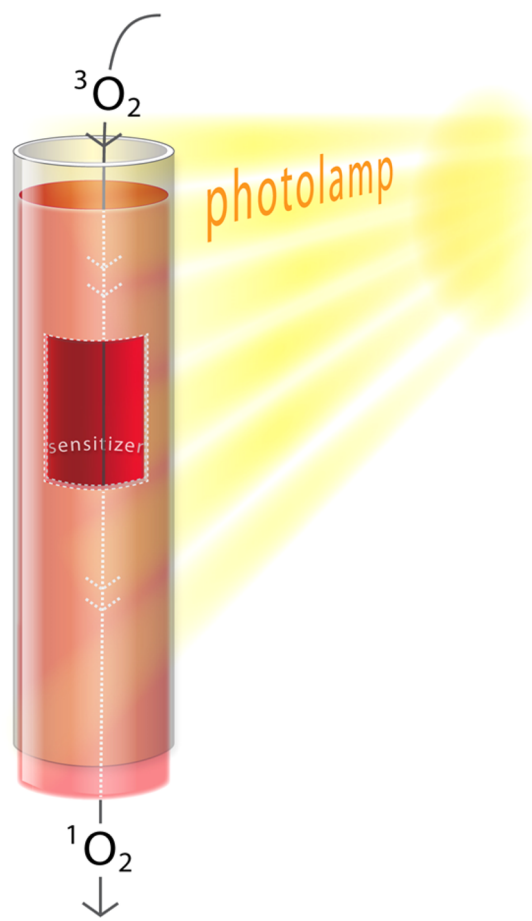
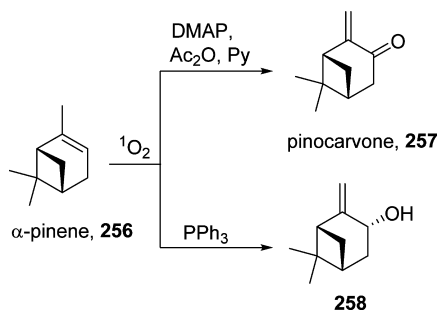


Figure 3. Murray's gaseous $^1\text{O}_2$ photoreactor device. A Pyrex tube was coated on the inside with rose bengal. Oxygen gas flowing through the illuminated tube exits enriched with $^1\text{O}_2$.

Scheme 55. Flow Reactor Photooxidation of α -Pinene



5.2.2. Microphotoreactors with Immobilized Sensitizers. Heterogeneous $^1\text{O}_2$ sensitizers have been used in flow, although they are few in number. We have located three studies that use microflow photoreactors with immobilized sensitizers, i.e., the solution is devoid of any sensitizer. It is expected that sensitizers such as porphyrins and fullerenes would remain powerful sensitizers for the production of $^1\text{O}_2$ when immobilized in the photoreactor. However, restoring of photobleached sensitizer sites has not yet been accomplished.

A 2012 paper reported on immobilized tri(*N*-methyl-4-pyridyl)porphyrin-sensitized microflow photooxidations of α -terpinene **253**, citronellol **259**, cholesterol **285**, and other compounds that were carried out in 30 s in methanol/ CH_2Cl_2 (Schemes 56, 62, and 67).³⁰³ The device consisted of a glass

microfluidic system with 16 parallel channels that had tetraaryl porphyrin covalently attached through a thiourea bridge to photogenerate $^1\text{O}_2$. Samples collected from the α -terpinene **253** and citronellol **259** experiments were monitored by HPLC and liquid chromatography–mass spectrometry (LCMS). The singlet oxygenation of cholesterol **285** led to 5*R*-hydroperoxycholesterol **286**, where the reaction also provides a route to 7*R*/7 β -hydroperoxy and 6*R*/6 β -hydroperoxy cholesterol byproducts by oxygen radicals and not a $^1\text{O}_2$ reaction. The product-forming efficiency of the microfluidic system was higher than that in a batch reaction. Other reports also describe cholesterol hydroperoxides and epoxides that are carcinogenic or mutagenic³⁰⁴ and their formation by photosensitized production of singlet oxygen (type II) and oxygen radicals (type I).

A 2006 paper described the generation of *p*-benzoquinone **276** from a silica bead-supported tetraaryl porphyrin-sensitized microflow photooxidation of phenol **274** after 42 s in buffer solution (pH 10) (Schemes 59B and 68).³⁰⁵ There was evidence for the existence of the endoperoxide intermediate, but the *p*-benzoquinone oxidatively processed to CO_2 and maleic or fumaric acid. *p*-Catechol is also a known product of phenol photooxidation.³⁰⁶ The device consisted of PTFE microchannels with silica beads bearing a covalently bound porphyrin through a pyridinium ion bridge to photochemically generate $^1\text{O}_2$. The silica beads were stationary and resided at the bottom of the microchannels. The activity of this microflow system was higher than the silica beads in suspension based on the photooxidative decomposition of phenol.

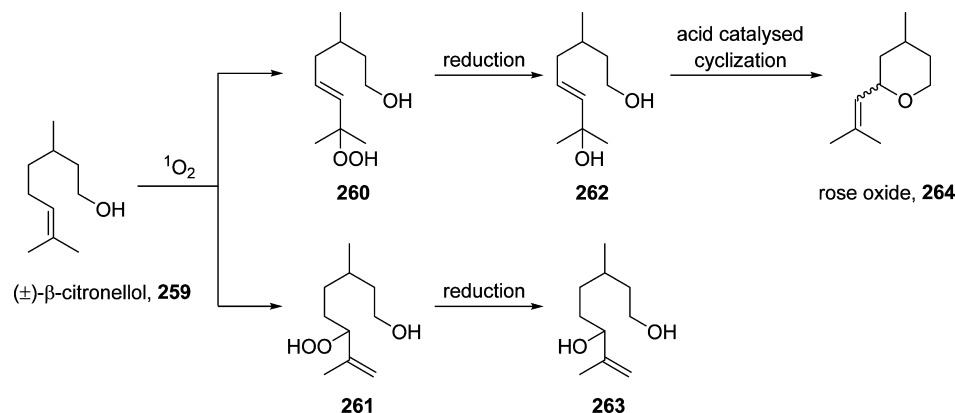
In 2008, a report appeared on a microreactor to synthesize ascaridole **254** in 94–97% yields in 40–50 s from [60]fullerene-sensitized microflow photooxidation of α -terpinene **253** in toluene (Schemes 54 and 69).³⁰⁷ *L*-Methoinine methyl ester **288** was also photooxidized in D_2O , which gave the corresponding sulfoxide nearly quantitatively (Scheme 63). The device consisted of thiolene microfluidic channels and a white LED light source. Tentagel-supported or silica gel-supported [60]-fullerene beads were packed into the microchannels and held in by a filter. The microreactor led to higher product yields compared to a batch reactor that used a tungsten halogen lamp. In the past, fullerene-containing polymers in $^1\text{O}_2$ jet-type generators pumped by LEDs have also been used.³⁰⁸

In conclusion, some 11 $^1\text{O}_2$ microflow reactions have been reported in the literature.^{290–303,305,307} As we will see below, relative to microflow about half of this number has been reported for $^1\text{O}_2$ macroflow reactions.

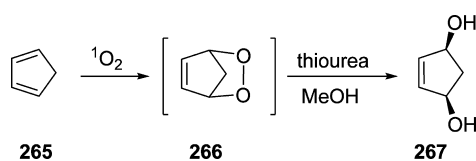
5.3. Singlet Oxygen Macrophotoreactors

There have been five reports of $^1\text{O}_2$ macroflow reactors that feature dissolved sensitizers in solution (section 5.3.1).

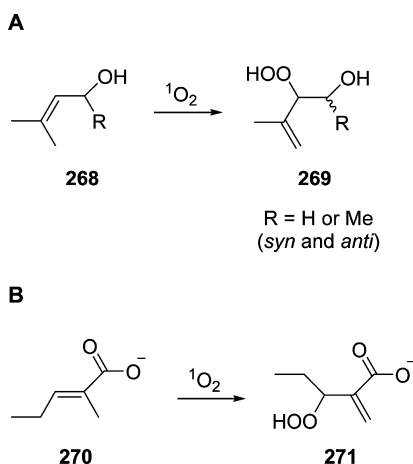
5.3.1. Macrophotoreactors with a Solution-Phase Sensitizer. A 2012 report described the synthesis of artemisinin **301** in a 1.36 g quantity (39% yield) from a TPP-sensitized macroflow photooxidation of dihydroartemisinic acid **297** (Scheme 64).³⁰⁹ The device was a macro-FEP tubing system coiled around an Hg lamp. Flowing dihydroartemisinic acid **297** in an acidic solution of CH_2Cl_2 led to formation of hydroperoxide **298** in 91% conversion and 75% yield. Through a protonated hydroperoxide, Hock cleavage of **298** led to **299**, which added to $^3\text{O}_2$ and followed by condensation steps reaches artemisinin **301**.³¹⁰ Only minor quantities of other hydroperoxides were formed, where byproducts included a 5-membered and 6-membered lactone. Because of therapeutic interest, there are additional reports on synthetic artemisinins as

Scheme 56. Flow Reactor Photooxidation of (\pm)- β -Citronellol

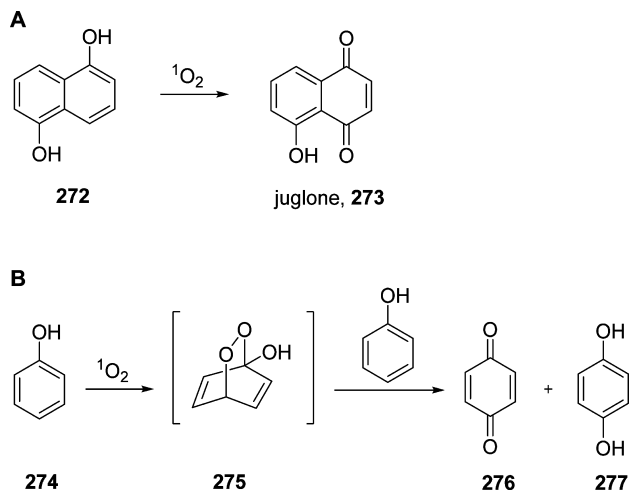
Scheme 57. Flow Reactor Photooxidation of Cyclopentadiene



Scheme 58. Flow Reactor Photooxidation of Alkenes



Scheme 59. Flow Reactor Photooxidation of 1,5-Dihydroxynaphthalene and Phenol



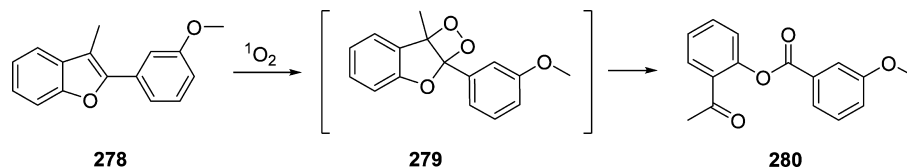
powerful antimalarial APIs.³¹¹ Also, it may be noted that the 2015 Nobel Prize in Physiology or Medicine was for the antimalarial drug artemisinin where $^1\text{O}_2$ was used in its total synthesis.^{312–314}

In 2014, a paper appeared where α -aminonitriles were synthesized in 71–99% yields from TPP-sensitized macroflow photooxidation of primary and secondary amines followed by the addition of TMSCN in CH_2Cl_2 (Scheme 65).³¹⁵ Oxidative cyanation could be accomplished over oxidative coupling. For example, **302** was converted to its corresponding nitrile **304**. The device consisted of macro-FEP tubing and a 420 nm LED light source and had variable-temperature control. The oxidative cyanation was favored at $-50\text{ }^\circ\text{C}$, whereas at higher temperature ($25\text{ }^\circ\text{C}$), the dimer formed from oxidative coupling and cyanide addition. The product percent yield was high and only depended slightly on the amine structure, as was studied in detail. This macroflow method may be useful for $^1\text{O}_2$ -based syntheses of unprotected amino acids on an industrial scale, which could in turn serve as templates for peptide synthesis.³¹⁶ Previous synthetic batch reactions have been carried out on the $^1\text{O}_2$ oxidation of amines to imines.^{317,318}

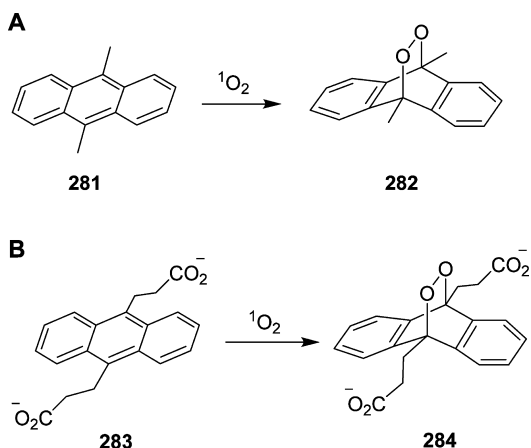
We have only located one study that provided a macroflow reaction of $^1\text{O}_2$ with sulfides. In 2011, a paper described the formation of sulfoxide **295** and sulfone **296** (95% yield, **295/296** ratio 3:1) in a TPP-sensitized macroflow photooxidation of 2-(ethylmercapto)ethanol **294** in a biphasic mixture (Scheme 63).³¹⁹ The device consisted of a macro-FEP tubing that was coiled around an Hg lamp. Further evidence for the utility of the flow system was the photooxidation of other substrates, α -pinene **256** (alcohol product **258**, 63% yield), α -terpinene **253** (ascaridole **254**, 85% yield), 2-methylfuran **306** (to reach ketoacid **309**, 68% yield), and citronellol **259** (after reduction with sodium sulfite to reach diols **262** and **263**, in a ratio of 1.1:1.0, 22.8 g, 88% yield) (Schemes 55 and 66). In the case of 2-methylfuran **306**,³¹⁹ the approach features the presence of 1.25 equiv of DIPEA followed by addition of pyridine in THF and acetone to reach ketoacid **309** in 68% yield. As noted in sections 4.1 and 4.13, $^1\text{O}_2$ reaction efficiencies can be reduced in the presence of amines such as DIPEA. The flow photooxidation of methionine was less productive (4.5 mg/h) compared to the photooxidation of α -terpinene (10 mg/h),³⁰⁷ which may not be unexpected. For some sulfide–singlet oxygen reactions, cleavage occurs through a hydroperoxysulfonium ylide that affords aldehydes or disulfides.^{320–322}

A 2008 report found that 1,3-diphenylisobenzofuran **320** reacted with $^1\text{O}_2$ and formed **322** in 34% yield from a porous silicon nanocrystal-sensitized macroflow photooxidation in

Scheme 60. Flow Reactor Photooxidation of 2-(3-Methoxyphenyl)-3-methyl-1-benzofuran



Scheme 61. Flow Reactor Photooxidation of 9,10-Dimethylanthracene and 9,10-Anthracene Diproponate Dianion

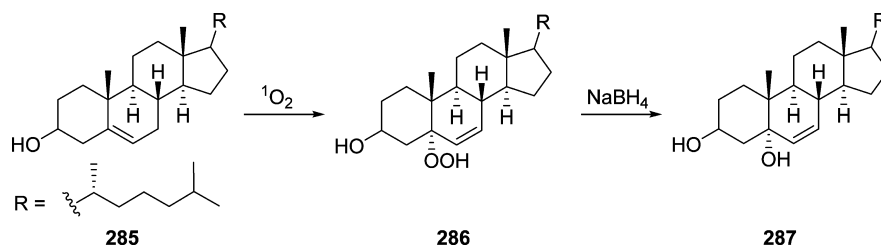


CH_2Cl_2 (Scheme 66).³²³ The device consisted of an annular flow reactor with either an Ar^+ laser (488 nm) or a green LED (524 nm) light source, although evidence was not provided on whether the silicon nanocrystal was functioning as a sensitizer.

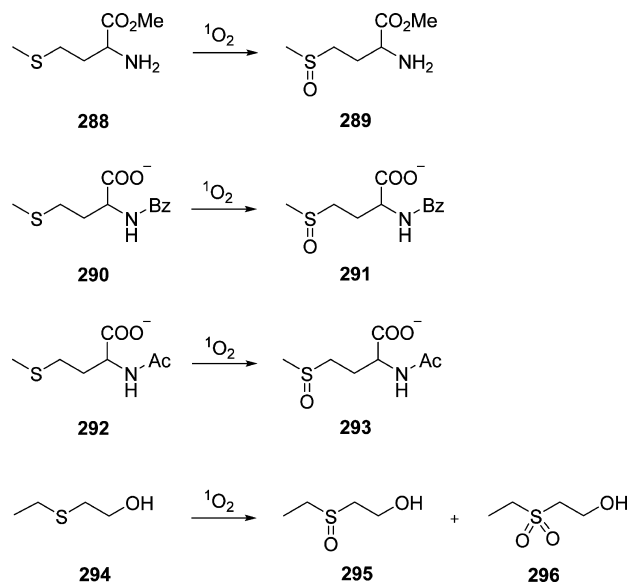
A 2015 report described a RB-sensitized macroflow photooxidation of 5-hydroxymethylfurfural **310** in aqueous alcohol mixtures that formed intermediate **311**, which led to products **312–314** (Scheme 66).³²⁴ The device consisted of a perfluoroether (PFA) tubing, which was coiled around a fluorescent lamp. One optimized condition used a solution of 5-(hydroxymethyl)furan-2-carbaldehyde **310** in *i*-PrOH/ H_2O (1:1), which led first to the corresponding endoperoxide **311** and then to butenolide **312** (93% yield). As desired, trace amounts of **313** and **314** were formed with *i*-PrOH/ H_2O , whereas greater amounts were formed with methanol or ethanol. A thermal isomerization of butenolide **312** led to oligomers of **315**. Previously, the syntheses of butenolide **312** from endoperoxide **311** has been reported.^{325–327}

Butenolides have been extensively studied in batch reactions of 1O_2 . For example, observations that singlet oxygen reacts with furans to produce butenolides and spiroketal natural products was an important discovery.^{328–342} Much synthetic utility has been found; one example of a batch reaction is shown in Scheme

Scheme 62. Flow Reactor Photooxidation of Cholesterol



Scheme 63. Flow Reactor Photooxidation of Methionine Derivatives and an Organic Sulfide



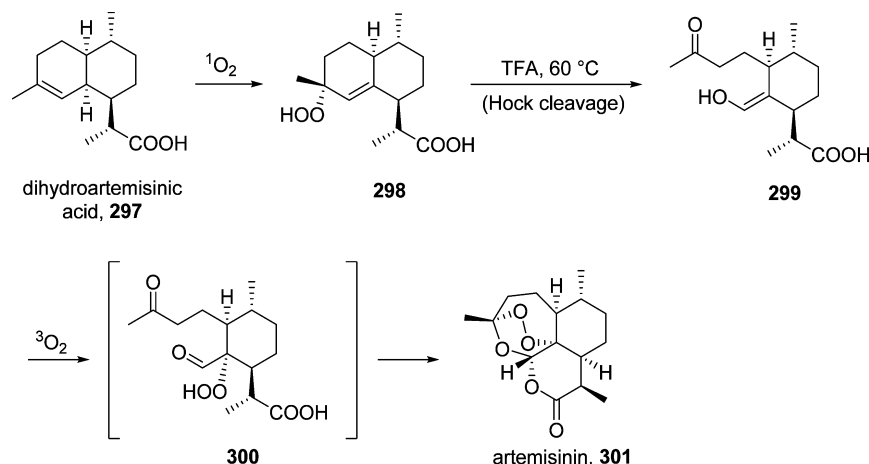
70.³²⁸ Here, the synthesis of a tetraquinane oxa-cage bislactone structure in (\pm)-parasecolide **325** occurred from the MB-sensitized photooxidation of furan **323** at 0 °C.³²⁸ Afterward, 5-hydroxybutenolide **324** was heated to 110 °C for a [2 + 4] dimerization of **324** to reach paracaseolide A **325** in 59% yield.

In conclusion, section 5.3 describes macrophotoreactors that have been established for using 1O_2 in synthesis. Singlet oxygen macrophotoreactors with immobilized sensitizers with conventional solvents have so far not been reported.

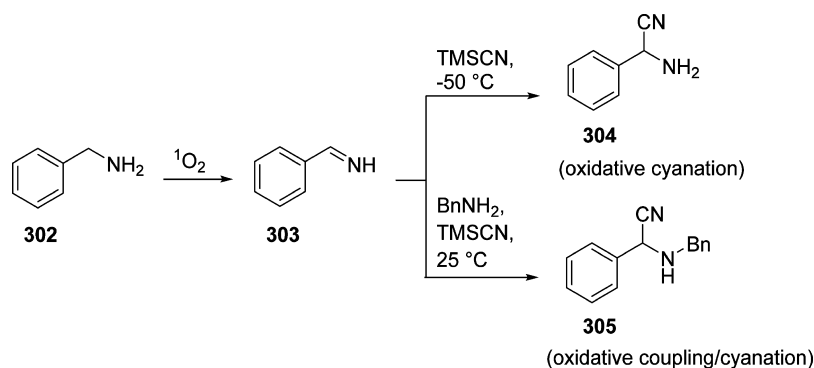
5.4. Supercritical Carbon Dioxide 1O_2 Photoreactor

Next, we describe examples of 1O_2 flow reactors that used supercritical CO_2 with sensitizer in the liquid phase (section 5.4.1) and immobilized (section 5.4.2). There are advantages in using supercritical CO_2 such as safety (it is nonflammable) and enhanced O_2 solubility, as well as the fact that the reactions give higher product yields, due to longer 1O_2 lifetimes (5.1 ms under the conditions) to overcome mass-transfer limitations of conventional solvents. O_2 solubility in CO_2 is higher than

Scheme 64. Flow Reactor Photooxidation of Dihydroartemisinic Acid



Scheme 65. Flow Reactor Photooxidation of Amines



those in perfluorinated solvents, which are higher than those in organic solvents.

5.4.1. Supercritical Carbon Dioxide Photoreactors Using Dissolved Sensitizer. A 5,10,15,20-tetrakis-(pentafluorophenyl)porphyrin (TPFPF)-sensitized macroflow photooxidation in supercritical CO_2 was reported in 2009 to generate hydroperoxides **260** and **261** in 52% and 48% yields, respectively, from citronellol **259** after 4 h (Scheme 56).³⁴³ The TPFPF sensitizer was dissolved in the liquid. The device was tubular in shape with a sapphire cell mounted in a flow system where the light source was a white LED. The product hydroperoxides **260** and **261** were reduced after exiting the apparatus in an aqueous solution of Na_2SO_3 . Space-time yields were ~ 9 times higher in this macroreactor compared to a batch reaction.

5.4.2. Supercritical Carbon Dioxide Photoreactor Using an Immobilized Sensitizer. A macroflow photooxidation in supercritical CO_2 was reported in 2011 to convert citronellol **259** to hydroperoxides **260** and **261** in 88% yield, and α -terpinene **253** to ascaridole **254** in 85% yield (Schemes 56 and 71).³⁴⁴ The device was a packed sapphire flow system, in which 4 immobilized sensitizers were examined (Scheme 71A–D). For example, 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin (TDCPP) was tethered through an amide bridge to polyvinyl chloride (PVC) and loaded in the device with glass wool. Under the conditions, the $^1\text{O}_2$ lifetime was found to be 5.1 ms, which far surpasses typical tens of microsecond lifetimes in organic solvents. Previously, supercritical CO_2 reactions have been used with $^1\text{O}_2$.^{345–348} Other photochemical reactors have been reported for the synthesis of organometallic compounds in

supercritical CO_2 or other supercritical solvents and are the subject of recent interest.^{349–351}

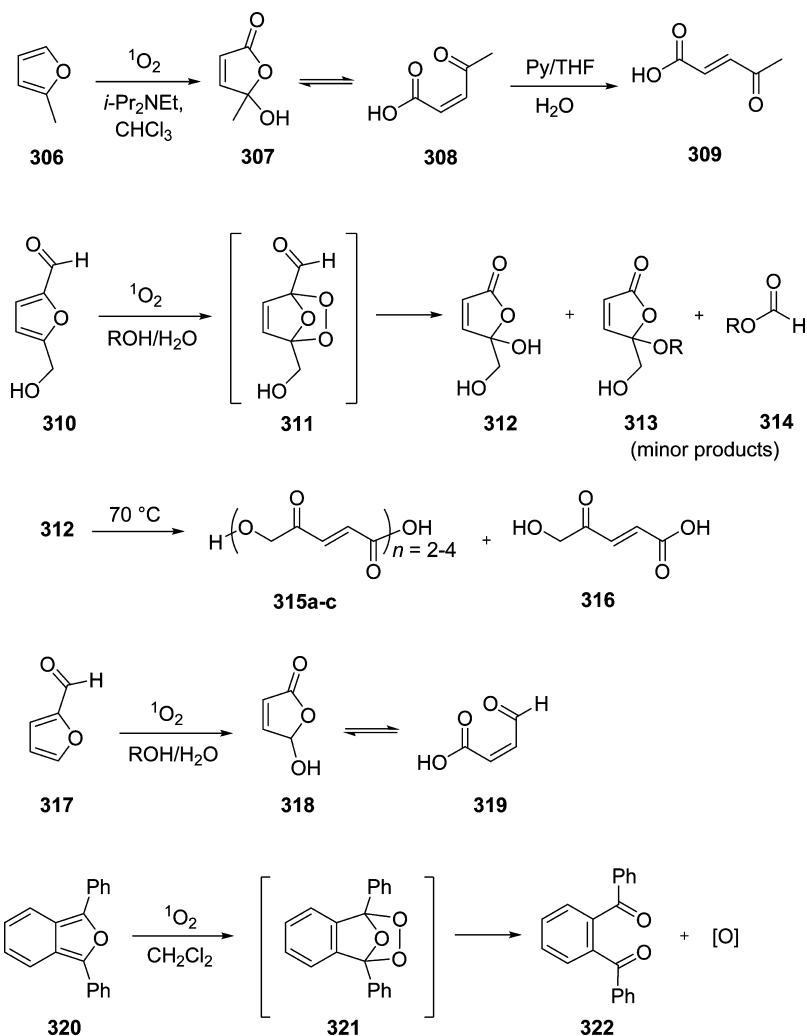
5.5. Bubbling Photoreactors

Singlet oxygen bubbling reactors have been scarcely studied. In this section we describe examples of two $^1\text{O}_2$ bubbling reactors. One used a dissolved sensitizer in solution (section 5.5.1), and the other used a heterogeneous sensitizer shielded from solution behind a membrane (section 5.5.2).

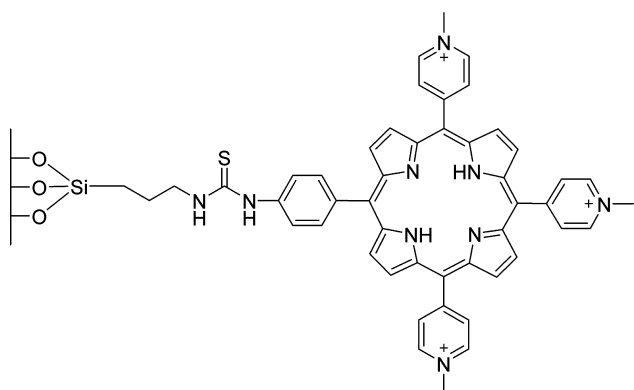
5.5.1. Bubbling Photoreactor Using a Dissolved Sensitizer. A 2012 report described juglone **273** synthesized in 70% yield in a RB-sensitized bubbling photooxidation of 1,5-dihydroxynaphthalene **272** in *t*-AmOH/ H_2O (9:1) (Scheme 59A).³⁵² The apparatus consisted of a Pyrex glass tube that was situated between two fluorescent lamps. This bubbling reactor is unique and is somewhat similar to a batch system, but with a rising airflow. Bubble diameters were ~ 50 – $100\text{ }\mu\text{m}$, where water-poor media flowed gas via bullet-shaped bubbles. Various solvents were used, such as *i*-PrOH, *i*-PrOH/ H_2O (9:1), *t*-AmOH/ H_2O (9:1), EtOH/ H_2O (9:1), and MeOH/ H_2O (9:1). High product yields were observed for the conversion of α -terpinene **253** to ascaridole **254** (71% yield), citronellol **259** to hydroperoxides **261** and **262** (88% yield, ratio 1.1:1.0), and furfural **317** to 5-hydroxyfuran-2(*SH*)-one (γ -hydroxybutenolide) **318** ($>95\%$ yield).

5.5.2. Bubbling Photoreactor Using a “Shielded” Heterogeneous Sensitizer. An SMA-modified device with dry Si-phthalocyanine particles was reported in 2012 in a bubbling photooxidation of *trans*-2-methyl-2-pentenoic acid **270**, 9,10-anthracene dipropionate dianion **283**, *N*-benzoyl-D,L-

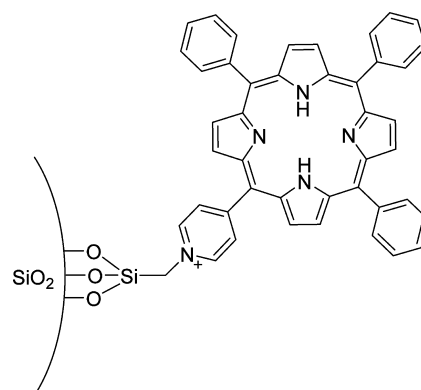
Scheme 66. Flow Reactor Photooxidation of Furan Derivatives



Scheme 67. Structure of the Glass-Attached Porphyrin



Scheme 68. Structure of a Silica-Attached Porphyrin

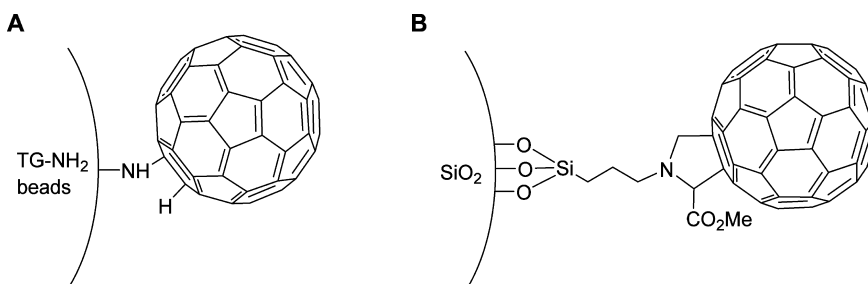
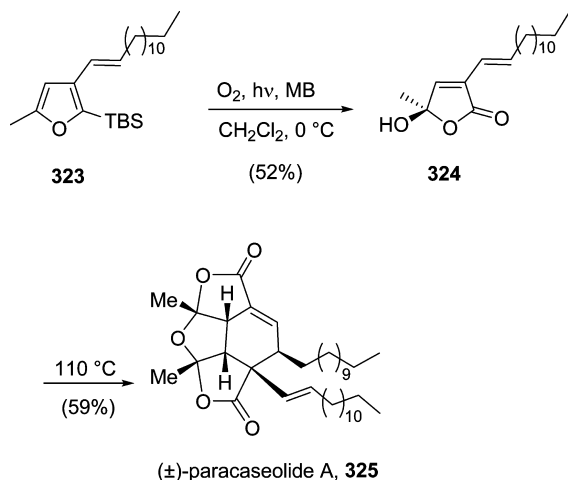


methionine **290**, and *N*-acetyl-*D,L*-methionine **292** in D_2O and H_2O (26–46% yields) (Schemes 51 and 63).^{353,354} The device chamber was loaded with Si-phthalocyanine glass sensitizer particles, which resided behind a microporous membrane with pores that excluded water. An O_2 gas feed tube and a red diode laser via a fiber optic were coupled to the SMA device. Bubbles were generated enriched with $^1\text{O}_2$, which left behind no waste or byproducts other than $^3\text{O}_2$. The photooxidation reaction rate was shown to increase in O_2 -poor more than in O_2 -saturated

solutions where mass transfer was facilitated in an important way.^{354,355}

In conclusion, there are several $^1\text{O}_2$ photoreactor types that have been developed. These include micro- and macroreactors. We have seen that (i) high product yields were achieved for flow systems in short periods of time, (ii) sensitizers immobilized in the reactor itself were 2 times less studied than homogeneous sensitizers, and (iii) about half of the studies reported $^1\text{O}_2$ flow relative to batch conditions with an improved efficiency for flow.

Scheme 69. Structures of the Tentagel-Supported (A) and Silica Gel-Supported (B) [60]Fullerene

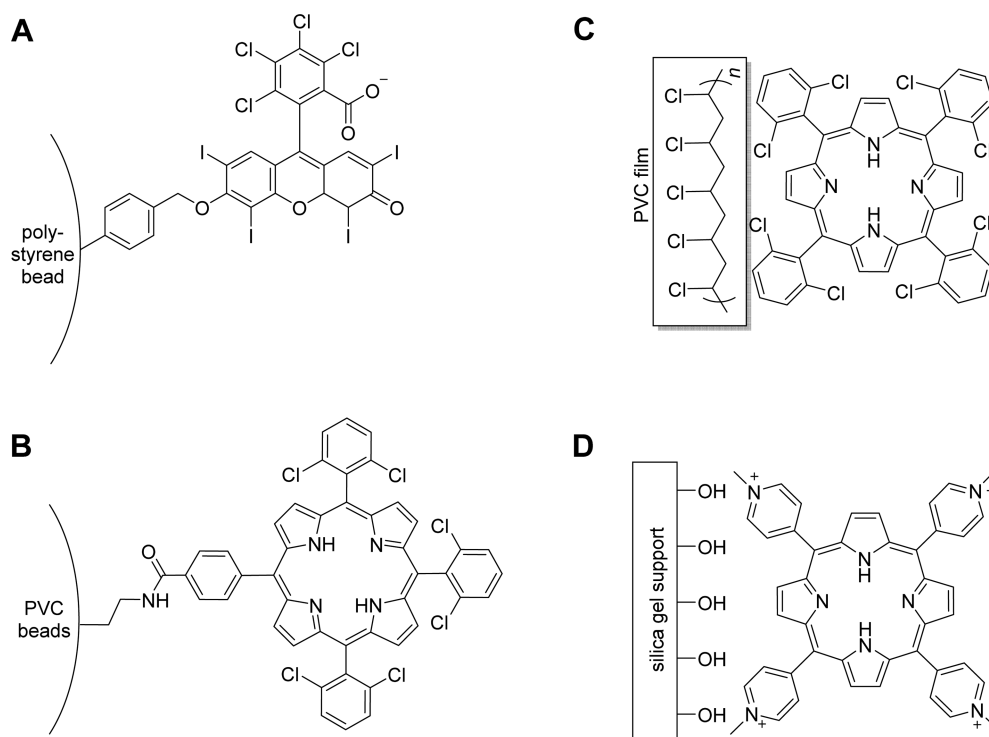
Scheme 70. Synthesis of (\pm)-Paracaseolide A

6. PROSPECTIVES

6.1. State of $^1\text{O}_2$ Synthetic Science

Sections 4 and 5 present the interplay of basic and applied reactions of $^1\text{O}_2$ in synthesis, respectively. Batch photooxidations in section 4 have been used with success for decades but are subject to fundamental limitations. Problems emerge when batch reactions are scaled up, including (i) long reaction times, (ii) sensitizer photobleaching, (iii) mass transfer limitations between oxygen and the substrate, and (iv) inner filter effects (large volumes increase the optical path length where light can be blocked from reaching the sensitizer).

Even though fewer publications exist for $^1\text{O}_2$ flow reactions compared to batch reactions, the former has advantages, including (i) short reaction times when scaling up, (ii) reduced sensitizer photobleaching, (iii) high surface-to-volume ratios for high $^1\text{O}_2$ -substrate mixing, (iv) lack of inner filter effect problems, (v) high sensitizer concentrations that can be used concurrent with high transmittance and photon flux, and (vi) O_2 -depleted solutions that enhance $^1\text{O}_2$ delivery by mass transfer

Scheme 71. Structures of the Immobilized Sensitizers in Flow Devices: (A) Rose Bengal Covalently Bound to Polystyrene, (B) TDCPP Derivative Covalently Bound to PVC, and (C) TDCPP Adhered to PVC, and (D) Tetracation Porphyrin Immobilized on SiO_2 Gel

assistance (while paradoxical, less oxygen in solution leads to greater oxygenation).

The utility of singlet oxygen photoreactors in synthetic organic chemistry has emerged. Disappointingly, $^1\text{O}_2$ flow reactions are not as popular as batch reactions, leading us to ask: *Why are $^1\text{O}_2$ photoreactors underutilized by synthetic chemists?* Some answers may be suggested: (i) assembly of the photoreactor is required, (ii) there are questions about interchangeability of parts and system configurations, and (iii) flow reactors cannot commonly be purchased “off the shelf”.

7. SUMMARY AND OUTLOOK

Progress has been made regarding $^1\text{O}_2$ in the organic synthesis of complex targets. Synthesis of natural products is often modeled on possible $^1\text{O}_2$ biosynthetic routes. Thus, biomimetic $^1\text{O}_2$ reactions that use alkene and diene precursors are common; however, fewer examples are known with polyenes, di- and polysulfides, and amines due to their facile physical quenching of singlet oxygen ($^1\text{O}_2 \rightarrow ^3\text{O}_2$).^{356–361} Singlet oxygen can be used widely, but except for artemisinin^{362–365} and rose oxide,³⁶⁶ no $^1\text{O}_2$ reactions have yet been used in the pharmaceutical industry. Consequently, one may look forward to estimate what is likely to happen in the field.

What are the future prospects of $^1\text{O}_2$ in synthetic chemistry? It seems the combination of fundamental and applied research is beneficial in a reciprocal manner (compare sections 4 and 5). The connection between flow technology and synthesis of simple natural products was noticed. It was recognized that the ongoing use of batch reactions for large quantities has drawbacks; therefore, new flow options can provide answers.

In closing, we look back to pioneers of $^1\text{O}_2$ in synthetic and natural products chemistry.^{12–14} This brings organic chemistry to the front, in reminding us of the first efforts of Foote and Wexler some 50 years ago.^{1,2} Here, the success of research was not only assured but also reaffirmed by the notion to look backward *and* forward as the field of $^1\text{O}_2$ evolves.

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Notes

The authors declare no competing financial interest.

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Alec Greer received his Ph.D. degree from the University of Wyoming under Edward L. Clennan. He was a postdoctoral fellow at the UCLA with Christopher S. Foote and then moved to Brooklyn College of CUNY in 1999. He cofounded the company Singlet O_2 Therapeutics LLC. His research interests are in photochemistry, singlet oxygen, peroxides, and photodynamic therapy.

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ABBREVIATIONS

Ac	acetyl
ACAT	active cholesterol acyltransferase
AIBN	azobis(isobutyronitrile)
API	active pharmaceutical ingredient
BANT	bisacenaphthalenethiophene
BMP	<i>p</i> -biphenylmethyl
Bn	benzyl
Boc	<i>t</i> -butyloxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMC	dimethyl carbonate
DMF	<i>N,N</i> -dimethylformamide
DPBF	1,3-diphenylisobenzofuran
DTBN	di- <i>t</i> -butyl hyponitrite
FEP	fluorinated ethylene propylene
GPTMS	3-glycidyoxypropyltrimethoxysilane
i.d.	inner diameter
LDA	lithium diisopropylamide
LED	light-emitting diode
<i>m</i> -CPBA	<i>m</i> -chlorobenzoic acid
MB	methylene blue
MCF	microcapillary film
MOM	methoxymethyl
MTAD	<i>N</i> -methyltriazolinedione
Ms	methanesulfonyl
$^1\text{O}_2$	excited state $^1\text{O}_2$ ($^1\Delta_g$)
$^3\text{O}_2$	ground-state $^3\text{O}_2$ ($^3\Sigma_g^-$) (the negative sign refers to two electrons with the same spin but occupying different orbitals)
OLED	organic light-emitting diode
o.d.	outer diameter
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
Pc	phthalocyanine
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PDMS	polydimethylsiloxane
PDT	photodynamic therapy
PFA	perfluoroether
PMB	<i>p</i> -methoxybenzyl
PNB	<i>p</i> -nitrobenzylester
PPTS	pyridinium <i>p</i> -toluenesulfonate
PTFE	polytetrafluoroethylene
PVC	polyvinyl chloride
Py	pyridine
PTAD	<i>N</i> -phenyltriazolinedione
PVSZ	polyvinylsilazane
RB	rose bengal
scCO ₂	supercritical CO ₂
SMA	shape memory alloy
STY	space-time yield
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>t</i> -butyldimethylsilyl
TBDPS	<i>t</i> -butyldiphenylsilyl
TDCPP	5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TG	Tentagel

TIPS	triisopropylsilyl ether
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
TPFPP	5,10,15,20-tetrakis(pentafluorophenyl)porphyrin
TPP	tetraphenylporphyrin

REFERENCES

- (1) Foote, C. S.; Wexler, S. Olefin Oxidations with Excited Singlet Molecular Oxygen. *J. Am. Chem. Soc.* **1964**, *86*, 3879–3880.
- (2) Foote, C. S.; Wexler, S. Singlet Oxygen. A Probable Intermediate in Photosensitized Autoxidations. *J. Am. Chem. Soc.* **1964**, *86*, 3880–3881.
- (3) Foote, C. S.; Clennan, E. L. Properties and Reactions of Singlet Oxygen. In *Active Oxygen in Chemistry*; Foote, C. S., Valentine, J. S., Greenberg, A., Liebman, J. F., Eds.; Springer: Netherlands, 1995; pp 105–140.
- (4) Turro, N. J.; Ramamurthy, V.; Scaiano, J. C. *Modern Molecular Photochemistry of Organic Molecules*; University Science Books: Sausalito, CA, 2010; pp 1001–1040.
- (5) Greer, A.; Balaban, A. T.; Liebman, J. F. An Introduction to the Consequences of Spin and Bond Strength in the Chemistry of Diatomic Oxygen, Peroxides and Related Species. In *The Chemistry of Peroxides*, Vol. 3; Greer, A., Liebman, J. F., Eds.; John Wiley & Sons, Ltd: Chichester, U.K., 2014; pp 1–20.
- (6) Redmond, R. W.; Gamlin, J. N. A Compilation of Singlet Oxygen Yields from Biologically Relevant Molecules. *Photochem. Photobiol.* **1999**, *70*, 391–475.
- (7) Protti, S.; Manzini, S.; Fagnoni, M.; Albini, A. The Contribution of Photochemistry to Green Chemistry. In *Eco-Friendly Synthesis of Fine Chemicals*; Ballini, R., Ed.; The Royal Society of Chemistry: London, 2009; pp 80–111.
- (8) Hoffmann, N. Photochemical Reactions as Key Steps in Organic Synthesis. *Chem. Rev.* **2008**, *108*, 1052–1103.
- (9) Matsumoto, M. Synthesis with Singlet Oxygen. In *Singlet O₂*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; pp 205–274.
- (10) Balci, M. Bicyclic Endoperoxides and Synthetic Applications. *Chem. Rev.* **1981**, *81*, 91–108.
- (11) Ohloff, G. Singlet Oxygen: a Reagent in Organic Synthesis. *Pure Appl. Chem.* **1975**, *43*, 481–502.
- (12) Wasserman, H. H.; DeSimone, R. W.; Chia, K. R. X.; Banwell, M. G. Singlet Oxygen. In *Encyclopedia of Reagents for Organic Synthesis*; Charette, A., Ed.; John Wiley & Sons, Ltd: Chichester, U.K., 2001; pp 1–11.
- (13) Wasserman, H. H. Recent Applications of the Use of Singlet Oxygen in the Synthesis of Compounds of Biological Interest. In *Studies in Organic Chemistry*; Ando, W., Moro-oka, Y., Eds.; Elsevier Science Publishers: Amsterdam, Netherlands, 1988; Chapter 33, pp 3–11.
- (14) Wasserman, H. H.; Ives, J. L. Singlet Oxygen in Organic Synthesis. *Tetrahedron* **1981**, *37*, 1825–1852.
- (15) Iesce, M. R.; Cermola, F. Photooxygenation, [2 + 2] and [4 + 2]. In *CRC Handbook of Organic Photochemistry and Photobiology*, 3rd ed.; Griesbeck, A., Oelgemöller, M., Ghetti, F., Eds.; CRC Press: Boca Raton, FL, 2012; pp 727–764.
- (16) Iesce, M. R.; Cermola, F.; Rubino, M. Photooxygenation of Non-Aromatic Heterocycles. *Curr. Org. Chem.* **2007**, *11*, 1053–1075.
- (17) Sawwan, N.; Greer, A. Rather Exotic Types of Cyclic Peroxides: Heteroatom Dioxiranes. *Chem. Rev.* **2007**, *107*, 3247–3285.
- (18) Clennan, E. L.; Pace, A. Advances in Singlet Oxygen Chemistry. *Tetrahedron* **2005**, *61*, 6665–6691.
- (19) Waldemar, A.; Bosio, S.; Bartoschek, A.; Griesbeck, A. G. Photooxygenation of 1,3-Dienes. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W., Francesco, L., Eds.; CRC Press: Boca Raton, FL, 2004; pp 25/1–25/19.
- (20) Clennan, E. L. Persulfoxide: Key Intermediate in Reactions of Singlet Oxygen with Sulfides. *Acc. Chem. Res.* **2001**, *34*, 875–884.
- (21) Stephenson, L. M.; Grdina, M. B.; Orfanopoulos, M. Mechanism of the Ene Reaction Between Singlet Oxygen and Olefins. *Acc. Chem. Res.* **1980**, *13*, 419–425.
- (22) Saito, I.; Matsuura, T. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; Vol. 40, pp 511–574.
- (23) Adam, W.; Kazakov, D. V.; Kazakov, V. P. Singlet-oxygen Chemiluminescence in Peroxide Reactions. *Chem. Rev.* **2005**, *105*, 3371–3387.
- (24) Fudickar, W.; Linker, T. Intermediates in the Formation and Thermolysis of Peroxides from Oxidations with Singlet Oxygen. *Aust. J. Chem.* **2014**, *67*, 320–327.
- (25) Fudickar, W.; Linker, T. Applications of Endoperoxides Derived from Acenes and Singlet Oxygen. In *Patai's Chemistry of Functional Groups—The Chemistry of Peroxides*; Greer, A., Liebman, J. F., Eds.; John Wiley & Sons Ltd.: Chichester, U.K., 2014; Vol. 3, pp 21–86.
- (26) Clennan, E. L.; Foote, C. S. Endoperoxides. In *Organic Peroxides*; Ando, W., Ed.; Wiley: Chichester: U.K., 1992; pp 255–318.
- (27) Martinez, G. R.; Ravanat, J.-L.; Cadet, J.; Miyamoto, S.; Medeiros, M. H. G.; Di Mascio, P. Energy Transfer Between Singlet (¹Δ_g) and Triplet (³Σ_g⁻) Molecular Oxygen in Aqueous Solution. *J. Am. Chem. Soc.* **2004**, *126*, 3056–3057.
- (28) Voukides, A. C.; Konrad, K. M.; Johnson, R. P. Competing Mechanistic Channels in the Oxidation of Aldehydes by Ozone. *J. Org. Chem.* **2009**, *74*, 2108–2113.
- (29) Cerkovnik, J.; Plesnicar, B.; Koller, J.; Tuttle, T. Hydrotrioxides Rather than Cyclic Tetraoxides (Tetraoxolanes) as the Primary Reaction Intermediates in the Low-Temperature Ozonation of Aldehydes. The Case of Benzaldehyde. *J. Org. Chem.* **2009**, *74*, 96–101.
- (30) Tuttle, T.; Cerkovnik, J.; Plesnicar, B.; Cremer, D. Hemiotho Esters and Hydrotrioxides as the Primary Products in the Low-Temperature Ozonation of Cyclic Acetals: An Experimental and Theoretical Investigation. *J. Am. Chem. Soc.* **2004**, *126*, 16093–16104.
- (31) Stary, F. E.; Emge, D. E.; Murray, R. W. Ozonation of Organic Substrates. Hydroperoxide Formation and Decomposition to Give Singlet Oxygen. *J. Am. Chem. Soc.* **1976**, *98*, 1880–1884.
- (32) Hang, J.; Ghorai, P.; Finkenstaedt-Quinn, S. A.; Findik, I.; Sliz, E.; Kuwata, K. T.; Dussault, P. H. Generation of Singlet Oxygen from Fragmentation of Monoactivated 1,1-Dihydroperoxides. *J. Org. Chem.* **2012**, *77*, 1233–1243.
- (33) Ghorai, P.; Dussault, P. H. A New Peroxide Fragmentation: Efficient Chemical Generation of ¹O₂ in Organic Media. *Org. Lett.* **2009**, *11*, 4572–4575.
- (34) De Vietro, N.; Annese, C.; D'Accolti, L.; Fanelli, F.; Fusco, C.; Fracassi, F. A New Synthetic Approach to Oxidation Organocatalysis Supported on Merrifield Resin Using Plasma-enhanced Chemical Vapor Deposition. *Appl. Catal., A* **2014**, *470*, 132–139.
- (35) Kazakov, D. V.; Kazakov, V. P.; Maistrenko, G. Y.; Mal'zev, D. V.; Schmidt, R. On the Effect of 1,4-Diazobicyclo[2.2.2]octane on the Singlet-oxygen Dimol Emission: Chemical Generation of (¹O₂)₂ in Peroxide Reactions. *J. Phys. Chem. A* **2007**, *111*, 4267–4273.
- (36) Carreno, M. C.; Gonzalez-Lopez, M.; Urbano, A. Oxidative De-aromatization of Para-alkyl Phenols into Para-peroxyquinols and Para-quinols Mediated by Oxone as a Source of Singlet Oxygen. *Angew. Chem., Int. Ed.* **2006**, *45*, 2737–2741.
- (37) Ovchinnikov, M. Y.; Kazakov, D. V.; Khursan, S. L. Kinetics and Mechanism of the Highly Efficient Generation of Singlet Oxygen in Dimethyldioxirane Decomposition Induced by Chloride Ion. *Kinet. Catal.* **2012**, *53*, 42–53.
- (38) Wasserman, H. H.; Yoo, J. U.; DeSimone, R. W. Singlet Oxygen Reactions from the Adducts of Ozone with Heterocycle Substrates. *J. Am. Chem. Soc.* **1995**, *117*, 9772–9773.
- (39) Bartlett, P. D.; Mendenhall, G. D. Evidence for a Duality of Mechanism in the Oxidation Reactions of Triphenyl Phosphite Ozonide. *J. Am. Chem. Soc.* **1970**, *92*, 210–211.
- (40) Kopecky, K. R.; van de Sande, J. H. Deuterium Isotope Effects in the Oxidation of 2,3-Dimethyl-2-butene via the Bromohydroperoxide, by Singlet Oxygen and by Triphenylphosphite Ozonide. *Can. J. Chem.* **1972**, *50*, 4034–4049.
- (41) Greer, A. Christopher Foote's Discovery of the Role of Singlet Oxygen [¹O₂ (¹Δ_g)] in Photosensitized Oxidation Reactions. *Acc. Chem. Res.* **2006**, *39*, 797–804.

- (42) Albini, A.; Germani, L. Photochemical Methods. In *Handbook of Synthetic Photochemistry*; Albini, A., Fagnoni, M., Eds.; Wiley-VCH: Weinheim, Germany, 2010; pp 2–10.
- (43) Montagnon, T.; Kalaitzakis, D.; Triantafyllakis, M.; Stratakis, M.; Vassilikogiannakis, G. Furans and Singlet Oxygen—Why There is More to Come from This Powerful Partnership. *Chem. Commun.* **2014**, *50*, 15480–15498.
- (44) Montagnon, T.; Noutsias, D.; Alexopoulou, I.; Tofi, M.; Vassilikogiannakis, G. Green Oxidations of Furans-Initiated by Molecular Oxygen That Give Key Natural Product Motifs. *Org. Biomol. Chem.* **2011**, *9*, 2031–2039.
- (45) Zamadar, M.; Greer, A. In *Handbook of Synthetic Photochemistry*; Albini, A., Fagnoni, M., Eds.; Wiley-VCH: Weinheim, Germany, 2010; pp 353–386.
- (46) Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. Using Singlet Oxygen to Synthesize Polyoxygenated Natural Products from Furans. *Acc. Chem. Res.* **2008**, *41*, 1001–1011.
- (47) Margaros, I.; Montagnon, T.; Tofi, M.; Pavlakos, E.; Vassilikogiannakis, G. The Power of Singlet Oxygen Chemistry in Biomimetic Syntheses. *Tetrahedron* **2006**, *62*, 5308–5317.
- (48) Paddon, C. J.; Keasling, J. D. Semi-synthetic Artemisinin: A Model for the Use of Synthetic Biology in Pharmaceutical Development. *Nat. Rev. Microbiol.* **2014**, *12*, 355–367.
- (49) Slack, R. D.; Jacobine, A. M.; Posner, G. H. Antimalarial Peroxides: Advances in Drug Discovery and Design. *MedChemComm* **2012**, *3*, 281–297.
- (50) Baader, W. J.; Bastos, E. L. Product Subclass 6: Six-membered Cyclic Peroxides with One Further Oxygen Atom in the Ring (1,2,4-Trioxanes). In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations. Vol. 38: Peroxides*; Berkessel, A., Ed.; Georg Thieme Verlag KG: Stuttgart, Germany, 2014; pp 421–448.
- (51) Corsello, M. A.; Garg, N. K. Synthetic Chemistry Fuels Interdisciplinary Approaches to the Production of Artemisinin. *Nat. Prod. Rep.* **2015**, *32*, 359–366.
- (52) Malik, S.; Khan, S. A.; Ahuja, P.; Arya, S. K.; Sahu, S.; Sahu, K. Singlet Oxygen-mediated Synthesis of Malarial Chemotherapeutic Agents. *Med. Chem. Res.* **2013**, *22*, 5633–5653.
- (53) Booker-Milburn, K. Flow Chemistry: A Light Touch to a Deadly Problem. *Nat. Chem.* **2012**, *4*, 433–435.
- (54) Chen, H.-J.; Han, W.-B.; Hao, H.-D.; Wu, Y. A Facile and Scalable Synthesis of Qinghaosu (Artemisinin). *Tetrahedron* **2013**, *69*, 1112–1114.
- (55) Griesbeck, A. G.; Raabe, A. Peroxide Dyads from Natural Artemisinin and Synthetic Perorthoesters and Endoperoxides. *Synlett* **2009**, *9*, 1514–1516.
- (56) Griesbeck, A. G.; Neudörfl, J.; Hörauf, A.; Specht, S.; Raabe, A. Antimalarial Peroxide Dyads from Natural Artemisinin and Hydroxyalkylated 1,2,4-Trioxanes. *J. Med. Chem.* **2009**, *52*, 3420–3423.
- (57) Griesbeck, A. G.; Blunk, D.; El-Idreesy, T. T.; Raabe, A. Bicyclic Peroxides and Perorthoesters with 1,2,4-Trioxane Structures. *Angew. Chem., Int. Ed.* **2007**, *46*, 8883–8886.
- (58) Griesbeck, A. G.; Bartoschek, A.; El-Idreesy, T. T.; Hoeinck, O.; Miara, C. Type II Photooxygenation in Polymer Matrices for the Synthesis of New Antimalarial Peroxides. *J. Mol. Catal. A: Chem.* **2006**, *251*, 41–48.
- (59) Griesbeck, A. G.; de Kiff, A.; Neudörfl, J. M.; Sillner, S. Singlet Oxygen Addition to Cyclo-1,3-hexadienes from Natural Sources and from Organocatalytic Enal Dimerization. *ARKIVOC* **2015**, *3*, 101–110.
- (60) Orfanopoulos, M.; Vougioukalakis, G. C.; Stratakis, M. Selective Formation of Allylic Hydroperoxides via Singlet Oxygen Ene Reaction. In *Chemistry of Peroxides*; Rappoport, Z., Ed.; John Wiley & Sons, Ltd: Chichester, U.K., 2006; Vol. 2 (Pt. 2), pp 831–898.
- (61) Clennan, E. L. Photo-oxygenation of the Ene-Type. In *Synthetic Organic Photochemistry*; Griesbeck, A. G., Mattay, J., Eds.; Molecular and Supramolecular Photochemistry; CRC Press: Boca Raton, FL, 2004; Vol. 12, pp 365–390.
- (62) Griesbeck, A. G.; Mattay, J. Synthetic Organic Photochemistry. In *Synthetic Organic Photochemistry*; Griesbeck, A. G., Mattay, J., Eds.; Molecular and Supramolecular Photochemistry; CRC Press: Boca Raton, FL, 2004; Vol. 12, pp 1–9.
- (63) Orfanopoulos, M. Singlet-oxygen Ene-sensitized Photo-oxygenations: Stereochemistry and Mechanisms. In *Understanding and Manipulating Excited-State Processes*; Ramamurthy, V., Schanze, K. S., Eds.; Molecular and Supramolecular Photochemistry; CRC Press: Boca Raton, FL, 2001; Vol. 8, pp 243–285.
- (64) Lundeen, R. A.; Janssen, E. M. L.; Chu, C. H.; McNeill, K. Environmental Photochemistry of Amino Acids, Peptides and Proteins. *Chimia* **2014**, *68*, 812–817.
- (65) Ogilby, P. R. Singlet Oxygen: There Is Indeed Something New Under the Sun. *Chem. Soc. Rev.* **2010**, *39*, 3181–3209.
- (66) Jimenez-Banzo, A.; Ragas, X.; Kapusta, P.; Nonell, S. Time-resolved Methods in Biophysics. 7. Photon Counting vs. Analog Time-resolved Singlet Oxygen Phosphorescence Detection. *Photochem. Photobiol. Sci.* **2008**, *7*, 1003–1010.
- (67) Schweitzer, C.; Schmidt, R. Physical Mechanisms of Generation and Deactivation of Singlet Oxygen. *Chem. Rev.* **2003**, *103*, 1685–1757.
- (68) Coyle, E. E.; Oelgemöller, M. Micro-photochemistry: Photochemistry in Microstructured Reactors. The New Photochemistry of the Future? *Photochem. Photobiol. Sci.* **2008**, *7*, 1313–1322.
- (69) Knowles, J. P.; Elliott, L. D.; Booker-Milburn, K. I. Flow Photochemistry: Old Light Through New Windows. *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052.
- (70) Gilmore, K.; Seeberger, P. H. Continuous Flow Photochemistry. *Chem. Record* **2014**, *14*, 410–418.
- (71) Pichugin, S. Y.; Heaven, M. C. A Pared-down Gas-phase Kinetics for the Chemical Oxygen-iodine Laser Medium. *Chem. Phys.* **2013**, *425*, 80–90.
- (72) Heaven, M. C. Recent Advances in the Development of Discharge-pumped Oxygen-iodine Lasers. *Laser Photon. Rev.* **2010**, *4*, 671–683.
- (73) Lee, S.; Rawlins, W. T.; Davis, S. J. Surface-catalyzed Singlet Oxygen Production on Iodine Oxide Films. *Chem. Phys. Lett.* **2009**, *469*, 68–70.
- (74) Davis, S. J.; McDermott, W. E.; Heaven, M. C. Atomic Iodine Lasers. *Opt. Sci. Eng.* **2007**, *121*, 413–448.
- (75) Ionin, A. A.; Kochetov, I. V.; Napartovich, A. P.; Yuryshv, N. N. Physics and Engineering of Singlet Delta Oxygen Production in Low-temperature Plasma. *J. Phys. D: Appl. Phys.* **2007**, *40*, R25–R61.
- (76) Hook, B. D. A.; Dohle, W.; Hirst, P. R.; Pickworth, M.; Berry, M. B.; Booker-Milburn, K. I. A Practical Flow Reactor For Continuous Organic Photochemistry. *J. Org. Chem.* **2005**, *70*, 7558–7564.
- (77) Yoon, T. P.; Ischay, M. A.; Du, J. Visible Light Photocatalysis as a Greener Approach to Photochemical Synthesis. *Nat. Chem.* **2010**, *2*, 527–532.
- (78) Pimparkar, K.; Yen, B.; Goodell, J. R.; Martin, V. I.; Lee, W.-H.; Porco, J. A., Jr.; Beeler, A. B.; Jensen, K. F. Development of a Photochemical Microfluidics Platform. *J. Flow Chem.* **2011**, *1*, 53–55.
- (79) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. Visible-Light Photoredox Catalysis in Flow. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144–4147.
- (80) Wang, X.; Cuny, G. D.; Noël, T. A Mild, One-Pot Stadler-Ziegler Synthesis of Arylsulfides Facilitated by Photoredox Catalysis in Batch and Continuous-Flow. *Angew. Chem., Int. Ed.* **2013**, *52*, 7860–7864.
- (81) Schuster, E. M.; Wipf, P. Photochemical Flow Reactions. *Isr. J. Chem.* **2014**, *54*, 361–370.
- (82) Martin, V. I.; Goodell, J. R.; Ingham, O. J.; Porco, J. A.; Beeler, A. B. Multidimensional Reaction Screening for Photochemical Transformations as a Tool for Discovering New Chemotypes. *J. Org. Chem.* **2014**, *79*, 3838–3846.
- (83) Gemoets, H. P. L.; Su, Y.; Shang, M.; Hessel, V.; Luque, R.; Noël, T. Liquid Phase Oxidation Chemistry in Continuous-Flow Microreactors. *Chem. Soc. Rev.* **2016**, *45*, 83–117.
- (84) Kouridaki, A.; Sofiadis, M.; Montagnon, T.; Vassilikogiannakis, G. Pectenotoxin's ABCDE Ring System: A Complex Target to Test the Potential for Singlet Oxygen Super Cascades as Tools for Synthesis. *Eur. J. Org. Chem.* **2015**, *2015*, 7240–7243.

- (85) Griesbeck, A. G.; de Kiff, A.; Kleczka, M. Tetraphenylporphyrin-catalyzed Tandem Photooxygenation of Polyenes and 1,4-Dienes: Multiple and Diverse Oxyfunctionalizations. *Adv. Synth. Catal.* **2014**, *356*, 2839–2845.
- (86) Griesbeck, A. G.; de Kiff, A. A New Directing Mode for Singlet Oxygen Ene Reactions: The Vinylogous Gem Effect Enables a $^1\text{O}_2$ Domino Ene/[4 + 2] Process. *Org. Lett.* **2013**, *15*, 2073–2075.
- (87) Tofi, M.; Koltsida, K.; Vassilikogiannakis, G. Singlet-oxygen-mediated One-Pot Synthesis of 3-Keto-tetrahydrofurans from 2-(Beta-hydroxyalkyl) Furans. *Org. Lett.* **2009**, *11*, 313–316.
- (88) Sofikiti, N.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G.; Stratakis, M. Synthesis of the Spirocyclic Core of the Prunolides Using a Singlet Oxygen-Mediated Cascade Sequence. *Org. Lett.* **2005**, *7*, 2357–2359.
- (89) Margaros, I.; Vassilikogiannakis, G. Synthesis of Chinensines A-E. *J. Org. Chem.* **2007**, *72*, 4826–4831.
- (90) Margaros, I.; Montagnon, T.; Vassilikogiannakis, G. Spiroperoxy Lactones from Furans in One Pot: Synthesis of (+)-Premnalane A. *Org. Lett.* **2007**, *9*, 5585–5588.
- (91) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T.; Stratakis, M. Illustrating the Power of Singlet Oxygen Chemistry in a Synthetic Context: Biomimetic Syntheses of Litseaverticillols A-G, I and J and the Structural Reassignment of Litseaverticillol E. *Chem. - Eur. J.* **2005**, *11*, 5899–5907.
- (92) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T. Biomimetic Total Synthesis of Litseaverticillols B, E, I, and J and Structural Reassignment of Litseaverticillol E. *Org. Lett.* **2004**, *6*, 2039–2042.
- (93) Vassilikogiannakis, G.; Stratakis, M. Biomimetic Total Synthesis of Litseaverticillols A, C, D, F, and G: Singlet-oxygen-Initiated Cascades. *Angew. Chem., Int. Ed.* **2003**, *42*, 5465–5468.
- (94) Zhang, X.; Lin, F.; Foote, C. S. Sensitized Photooxygenation of 6-Heteroatom-substituted Fulvenes: Primary Products and Their Chemical Transformations. *J. Org. Chem.* **1995**, *60*, 1333–1338.
- (95) Burns, P. A.; Foote, C. S.; Mazur, S. Chemistry of Singlet Oxygen. XXIII. Low Temperature Photooxygenation of Indenes in Aprotic Solvent. *J. Org. Chem.* **1976**, *41*, 899–907.
- (96) Gollnick, K. Type II Photooxygenation Reactions in Solution. *Adv. Photochem.* **1968**, *6*, 1–122.
- (97) Chesneau, E.; Neckers, D. C. Electron Transfer Sensitized Photobleaching of Rose Bengal Induced by Triplet Benzophenones. *J. Photochem. Photobiol., A* **1988**, *42*, 269–281.
- (98) Linden, S. M.; Neckers, D. C. Type I and Type II Sensitizers Based on Rose Bengal Onium Salts. *Photochem. Photobiol.* **1988**, *47*, 543–550.
- (99) Bonnett, R. Photosensitizers of the Porphyrin and Phthalocyanine Series for Photodynamic Therapy. *Chem. Soc. Rev.* **1995**, *24*, 19–33.
- (100) DeRosa, M. C.; Crutchley, R. J. Photosensitized Singlet Oxygen and Its Applications. *Coord. Chem. Rev.* **2002**, *233–234*, 351–371.
- (101) Krufft, B. I.; Greer, A. Photosensitization Reactions In Vitro and In Vivo. *Photochem. Photobiol.* **2011**, *87*, 1204–1213.
- (102) Schaap, A. P.; Thayer, A. L.; Blossey, E. C.; Neckers, D. C. Polymer-Based Sensitizers for Photooxidations. II. *J. Am. Chem. Soc.* **1975**, *97*, 3741–3745.
- (103) Ding, X.; Han, B.-H. Metallophthalocyanine-Based Conjugated Microporous Polymers as Highly Efficient Photosensitizers for Singlet Oxygen Generation. *Angew. Chem., Int. Ed.* **2015**, *54*, 6536–6539.
- (104) Spada, R. M.; Cepeda-Plaza, M.; Gómez, M. L.; Günther, G.; Jaque, P.; Pizarro, N.; Palacios, R. E.; Vega, A. Clean Singlet Oxygen Production by a Rei Complex Embedded in a Flexible Self-standing Polymeric Silsesquioxane Film. *J. Phys. Chem. C* **2015**, *119*, 10148–10159.
- (105) Le Behec, M.; Costarramone, N.; Pigot, T.; Lacombe, S. Gas-phase Photooxidation: Reactors and Materials. *Chem. Eng. Technol.* **2016**, *39*, 26–38.
- (106) Shailaja, J.; Sivaguru, J.; Ramamurthy, V. Zeolite Matrix Assisted Decomposition of Singlet Oxygen Sensitizers During Photooxidation. *J. Photochem. Photobiol., A* **2016**, DOI: 10.1016/j.jphotochem.2016.02.010.
- (107) Neckers, D. C.; Valdes-Aguilera, O. M. Photochemistry of the Xanthene Dyes. *Adv. Photochem.* **1993**, *18*, 315–394.
- (108) Lissi, E. A.; Encinas, M. V.; Lemp, E.; Rubio, M. A. Singlet Oxygen $\text{O}_2(^1\Delta_g)$ Bimolecular Processes. Solvent and Compartmentalization Effects. *Chem. Rev.* **1993**, *93*, 699–723.
- (109) Foote, C. S. Photophysical, Photochemical, and Chemical Reactions of Fullerenes and Dihydrofullerene Derivatives. In *Physics and Chemistry of the Fullerenes*; Prassides, K., Ed.; Springer: Netherlands, 1994; Vol. 443, pp 79–96.
- (110) Iliev, V.; Ileva, A.; Bilyarska, L. Oxidation and Photooxidation of Sulfur-Containing Compounds in the Presence of Immobilized Phthalocyanine Complexes. *J. Mol. Catal. A: Chem.* **1997**, *126*, 99–108.
- (111) Bourdelande, J. L.; Font, J.; Marques, G.; Abdel-Shafi, A. A.; Wilkinson, F.; Worrall, D. R. On the Efficiency of the Photosensitized Production of Singlet Oxygen in Water Suspensions of a Tris-(bipyridyl)Ruthenium(II) Complex Covalently Bound to an Insoluble Hydrophilic Polymer. *J. Photochem. Photobiol., A* **2001**, *138*, 65–68.
- (112) Griesbeck, A. G.; Bartoschek, A. Sustainable Photochemistry: Solvent-free Singlet Oxygen-photooxygenation of Organic Substrates Embedded in Porphyrin-Loaded Polystyrene Beads. *Chem. Commun.* **2002**, 1594–1595.
- (113) Li, W.; Gandra, N.; Ellis, E. D.; Courtney, S.; Li, S.; Butler, E.; Gao, R. pH-Responsive, TiO_2 -attached Porphyrin for Singlet Oxygen Production in an Aqueous Solution. *ACS Appl. Mater. Interfaces* **2009**, *1*, 1778–1784.
- (114) Lacombe, S.; Pigot, T. New Materials for Sensitized Photooxygenation. In *Photochemistry*, Vol. 38; Albini, A., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 2010; pp 307–329.
- (115) Zhao, M.; Ou, S.; Wu, C.-D. Porous Metal–Organic Frameworks for Heterogeneous Biomimetic Catalysis. *Acc. Chem. Res.* **2014**, *47*, 1199–1207.
- (116) Appiani, E.; McNeill, K. Photochemical Production of Singlet Oxygen from Particulate Organic Matter. *Environ. Sci. Technol.* **2015**, *49*, 3514–3522.
- (117) Nani, R. R.; Kelley, J. A.; Ivanic, J.; Schnermann, M. J. Reactive Species Involved in the Regioselective Photooxidation of Heptamethine Cyanines. *Chem. Sci.* **2015**, *6*, 6556–6563.
- (118) Griesbeck, A. G.; Kleczka, M.; de Kiff, A.; Vollmer, M.; Eske, A.; Sillner, S. Singlet Oxygen and Natural Substrates: Functional Polyunsaturated Models for the Photooxidative Degradation of Carotenoids. *Pure Appl. Chem.* **2015**, *87*, 639–647.
- (119) Changtong, C.; Carney, D. W.; Luo, L.; Zoto, C. A.; Lombardi, J. L.; Connors, R. E. A Porphyrin Molecule That Generates, Traps, Stores, and Releases Singlet Oxygen. *J. Photochem. Photobiol., A* **2013**, *260*, 9–13.
- (120) Manju, T.; Manoj, N.; Braun, A. M.; Oliveros, E. Self Sensitized Photooxidation of N-Methyl Phenothiazine: Acidity Control of the Competition between Electron and Energy Transfer Mechanisms. *Photochem. Photobiol. Sci.* **2012**, *11*, 1744–1755.
- (121) Gorman, A. A.; Lovering, G.; Rodgers, M. A. J. The Entropy-controlled Reactivity of Singlet Oxygen ($^1\Delta_g$) Toward Furans and Indoles in Toluene. A Variable-temperature Study by Pulse Radiolysis. *J. Am. Chem. Soc.* **1979**, *101*, 3050–3055.
- (122) Hurst, J. R.; Schuster, G. B. Ene Reaction of Singlet Oxygen: An Entropy-controlled Process Determines the Reaction Rate. *J. Am. Chem. Soc.* **1982**, *104*, 6854–6856.
- (123) Clennan, E. L.; Chen, X. Temperature, Solvent, and Substituent Effects on the Singlet Oxidations of Allylic Phenyl Sulfoxides, Sulfones, and Sulfides. *J. Am. Chem. Soc.* **1989**, *111*, 8212–8218.
- (124) Erden, I.; Alscher, P. E.; Keeffe, J. R.; Mercer, C. Dye-sensitized Photooxygenation of the C=N Bond. 5. Substituent Effects on the Cleavage of the C=N Bond of C-Aryl-N-methylhydrazones. *J. Org. Chem.* **2005**, *70*, 4389–4392.
- (125) Wilkinson, F.; Helman, W. P.; Ross, A. B. Quantum Yields for the Photosensitized Formation of the Lowest Electronically Excited Singlet State of Molecular Oxygen in Solution. *J. Phys. Chem. Ref. Data* **1995**, *24*, 663–1021.
- (126) Schmidt, R.; Afshari, E. Collisional Deactivation of $\text{O}_2(^1\Delta_g)$ by Solvent Molecules. Comparative Experiments with $^{16}\text{O}_2$ and $^{18}\text{O}_2$. *Ber. Bunsenges. Phys. Chem.* **1992**, *96*, 788–794.

- (127) Matheson, I. B. C.; Lee, J. Quenching of Photophysically Formed Singlet ($^1\Delta_g$) Oxygen in Solution by Amines. *J. Am. Chem. Soc.* **1972**, *94*, 3310–3313.
- (128) Monroe, B. M. Quenching of Singlet Oxygen by Aliphatic Amines. *J. Phys. Chem.* **1977**, *81*, 1861–1864.
- (129) Clennan, E. L.; Noe, L. J.; Wen, T.; Szneler, E. Solvent Effects on the Ability of Amines to Physically Quench Singlet Oxygen as Determined by Time-resolved Infrared Emission Studies. *J. Org. Chem.* **1989**, *54*, 3581–3584.
- (130) Darmanyan, A. P.; Jenks, W. S.; Jardon, P. Charge-transfer Quenching of Singlet Oxygen $O_2(^1\Delta_g)$ by Amines and Aromatic Hydrocarbons. *J. Phys. Chem. A* **1998**, *102*, 7420–7426.
- (131) Bartholomew, R. F.; Davidson, R. S. The Photosensitized Oxidation of Amines. Part II. The Use of Dyes as Photosensitizers: Evidence that Singlet Oxygen is Not Involved. *J. Chem. Soc. C* **1971**, 2347–2351.
- (132) Paquette, L. A.; Carr, R. V. C.; Arnold, E.; Clardy, J. Electronic Control of Stereoselectivity. 5. Stereochemistry of Singlet Oxygen Capture by Cyclopentadiene Rings Fused to Norbornyl and Norbornenyl Frameworks. *J. Org. Chem.* **1980**, *45*, 4907–4913.
- (133) Murray, R. W.; Agarwal, S. K. Singlet Oxygen Oxidation of Substituted Thiobenzamides. *J. Photochem.* **1984**, *25*, 335–343.
- (134) Lemp, E.; Günther, G.; Castro, R.; Curitol, M.; Zanicco, A. L. Reaction of Singlet Molecular Oxygen, $O_2(^1\Delta_g)$, with the Cinchona Tree Alkaloids. *J. Photochem. Photobiol., A* **2005**, *175*, 146–153.
- (135) Manning, L. E.; Foote, C. S. Chemistry of Singlet Oxygen. 44. Mechanism of Photooxidation of 2,5-Dimethylhexa-2,4-diene and 2-Methyl-2-pentene. *J. Am. Chem. Soc.* **1983**, *105*, 4710–4717.
- (136) Yao, G.; Steliou, K. Synthetic Studies toward Bioactive Cyclic Peroxides from the Marine Sponge *Plakortis angulospiculatus*. *Org. Lett.* **2002**, *4*, 485–488.
- (137) Gunasekera, S. P.; Gunasekera, M.; Gunawardana, G. P.; McCarthy, P.; Burres, N. Two New Bioactive Cyclic Peroxides from the Marine Sponge *Plakortis Angulospiculatus*. *J. Nat. Prod.* **1990**, *53*, 669–674.
- (138) Jung, M.; Ham, J.; Song, J. First Total Synthesis of Natural 6-Epiplakortolide E. *Org. Lett.* **2002**, *4*, 2763–2765.
- (139) O'Shea, K. E.; Foote, C. S. Chemistry of Singlet Oxygen. 51. Zwitterionic Intermediates from 2,4-Hexadienes. *J. Am. Chem. Soc.* **1988**, *110*, 7167–7170.
- (140) Dussault, P. H.; Eary, C. T.; Woller, K. R. Total Synthesis of the Alkoxydioxines (+)- and (–)-Chondrillin and (+)- and (–)-Plakorin via Singlet Oxygenation/Radical Rearrangement. *J. Org. Chem.* **1999**, *64*, 1789–1797.
- (141) Dussault, P. H.; Woller, K. R. Singlet Oxygenation/Radical Rearrangement as an Approach to 1,4-Dioxygenated Peroxides: Asymmetric Total Synthesis of Plakorin and Enantio-Chondrillin. *J. Am. Chem. Soc.* **1997**, *119*, 3824–3825.
- (142) Davies, A. G. The Schenck Rearrangement of Allylic Hydroperoxides. *J. Chem. Res.* **2009**, 2009, 533–544.
- (143) Casteel, D. A. Peroxy Natural Products. *Nat. Prod. Rep.* **1992**, *9*, 289–312.
- (144) Dussault, P. H.; Zope, U. R. Reaction of 1O_2 with Alkoxyallylstannanes: Synthesis of 1,2-Dioxolanes and Allyl Hydroperoxides. *Tetrahedron Lett.* **1995**, *36*, 2187–2190.
- (145) Dussault, P. H.; Lee, R. J. Stereoselective Dioxygenation of Allylstannanes: Synthesis of Enantiomerically Enriched Allyl Hydroperoxides. *J. Am. Chem. Soc.* **1994**, *116*, 4485–4486.
- (146) Dussault, P. H.; Eary, C. T. Palladium-Mediated Carbon–Carbon Bond Forming Reactions as a New Method for the Synthesis of Peroxides and Hydroperoxides. *J. Am. Chem. Soc.* **1998**, *120*, 7133–7134.
- (147) Dussault, P. H.; Schultz, J. A. Diastereoselective Addition of Singlet Oxygen to Highly Functionalized Z-Allylic Alcohols: Effect of Neighboring Functional Groups. *J. Org. Chem.* **1999**, *64*, 8419–8422.
- (148) Maraş, A.; Seçen, H.; Sütbeyaz, Y.; Balci, M. A Convenient Synthesis of (\pm)-Talo-Quercitol (1-Deoxy-neo-inositol) and (\pm)-Vibo-queritol (1-Deoxy-myo-inositol) via Ene Reaction of Singlet Oxygen. *J. Org. Chem.* **1998**, *63*, 2039–2041.
- (149) Adam, W.; Balci, M.; Kiliç, H. Oxyfunctionalization of Biphenylene by Singlet Oxygen, Hydrogen Peroxide/Methyltrioxorhenium, and Dimethyldioxirane. *J. Org. Chem.* **1998**, *63*, 8544–8546.
- (150) Adam, W.; Cueto, O.; De Lucchi, O. Oxygen Functionalization of Cyclooctatetraene via Singlet Oxygenation: Synthesis and Transformations of *Anti*-7,8-dioxatricyclo[4.2.2.0_{2,5}]deca-3,9-Diene, the Endoperoxide of the Bicyclic Valence Tautomer of Cyclooctatetraene. *J. Org. Chem.* **1980**, *45*, 5220–5221.
- (151) Sütbeyaz, Y.; Secen, H.; Balci, M. A Novel and Stereospecific Synthesis of Conduritol-A. *J. Chem. Soc., Chem. Commun.* **1988**, 1330–1331.
- (152) Seçen, H.; Sütbeyaz, Y.; Balci, M. A New and Stereospecific Synthesis of Conduritol-F and Conduritol-Bs. *Tetrahedron Lett.* **1990**, *31*, 1323–1326.
- (153) Balci, M.; Sütbeyaz, Y.; Secen, H. Conduritols and Related Compounds. *Tetrahedron* **1990**, *46*, 3715–3742.
- (154) Seçen, H.; Gültekin, S.; Sütbeyaz, Y.; Balci, M. Stereospecific Synthesis of Conduramine-F4 and Conduritol-F (Leucantheimitol). *Synth. Commun.* **1994**, *24*, 2103–2108.
- (155) Gueltekin, M. S.; Celik, M.; Balci, M. Cyclitols. Conduritols and Related Compounds. *Curr. Org. Chem.* **2004**, *8*, 1159–1186.
- (156) Balci, M. Synthesis of Conduritols and Related Compounds. *Pure Appl. Chem.* **1997**, *69*, 97–104.
- (157) Aydin, G.; Savran, T.; Aktas, F.; Baran, A.; Balci, M. Stereoselective Syntheses of Racemic Quercitols and Bromoquercitols Starting from Cyclohexa-1,4-diene: Gala-, Epi-, Muco-, and Neo-queritol. *Org. Biomol. Chem.* **2013**, *11*, 1511–1524.
- (158) Salamci, E.; Secen, H.; Sütbeyaz, Y.; Balci, M. A Concise and Convenient Synthesis of DL-*proto*-Quercitol and DL-*gala*-Quercitol via Ene Reaction of Singlet Oxygen Combined with [2 + 4] Cycloaddition to Cyclohexadiene. *J. Org. Chem.* **1997**, *62*, 2453–2457.
- (159) Kurbanoğlu, N. I.; Çelik, M.; Kiliç, H.; Alp, C.; Şahin, E.; Balci, M. Stereospecific Synthesis of a DL-*gala*-Aminoquercitol Derivative. *Tetrahedron* **2010**, *66*, 3485–3489.
- (160) Baran, A.; Aydin, G.; Savran, T.; Sahin, E.; Balci, M. Trisequential Photooxygenation Reaction: Application to the Synthesis of Carbasugars. *Org. Lett.* **2013**, *15*, 4350–4353.
- (161) Altun, Y.; Dogan, S. D.; Balci, M. Synthesis of Branched Carbasugars via Photooxygenation and Manganese(III) Acetate Free Radical Cyclization. *Tetrahedron* **2014**, *70*, 4884–4890.
- (162) Baran, A.; Aydin, G.; Savran, T.; Sahin, E.; Balci, M. Trisequential Photooxygenation Reaction: Application to the Synthesis of Carbasugars. *Org. Lett.* **2013**, *15*, 4350–4353.
- (163) Griesbeck, A. G.; Goldfuss, B.; Leven, M.; de Kiff, A. Comparison of the Singlet Oxygen Ene Reactions of Cyclic Versus Acyclic β,γ -Unsaturated Ketones: An Experimental and Computational Study. *Tetrahedron Lett.* **2013**, *54*, 2938–2941.
- (164) Stratakis, M.; Orfanopoulos, M. Regioselectivity in the Ene Reaction of Singlet Oxygen with Alkenes. *Tetrahedron* **2000**, *56*, 1595–1615.
- (165) Yardımcı, Ş. D.; Kaya, N.; Balci, M. Regioselectivity in the Ene-Reaction of Singlet Oxygen with Cyclic alkenes: Photooxygenation of Methyl-substituted 1,4-Cyclohexadiene Derivatives. *Tetrahedron* **2006**, *62*, 10633–10638.
- (166) Kishali, N. H.; Dogan, D.; Sahin, E.; Gunel, A.; Kara, Y.; Balci, M. Stereoselective Synthesis of Deoxycarbaheptopyranose Derivatives: Sa-Carba-6-deoxy- α -DL-galacto-heptopyranose and Sa-Carba-6-deoxy- α -DL-gulo-heptopyranose. *Tetrahedron* **2011**, *67*, 1193–1200.
- (167) Kara, Y.; Balci, M. A New and Stereospecific Synthesis of an Inositol Analogue: Bis-Homoinositol. *Tetrahedron* **2003**, *59*, 2063–2066.
- (168) Barbarow, J. E.; Miller, A. K.; Trauner, D. Biomimetic Synthesis of Elysiapyrones a and B. *Org. Lett.* **2005**, *7*, 2901–2903.
- (169) Miller, A. K.; Trauner, D. Mining the Tetraene Manifold: Total Synthesis of Complex Pyrones from *Placobranchus Ocellatus*. *Angew. Chem., Int. Ed.* **2005**, *44*, 4602–4606.
- (170) Yamashita, S.; Naruko, A.; Nakazawa, Y.; Zhao, L.; Hayashi, Y.; Hiram, M. Total Synthesis of Limonin. *Angew. Chem., Int. Ed.* **2015**, *54*, 8538–8541.

- (171) Kato, N.; Nakanishi, K.; Wu, X.; Nishikawa, H.; Takeshita, H. Total Synthesis of Fusicogigantones A and B and Fusicogigantepoxide Via the Singlet Oxygen-oxidation of Fusicoccadienes. "Fusicogigantepoxide B", a Missing Congener Metabolite. *Tetrahedron Lett.* **1994**, *35*, 8205–8208.
- (172) Boyd, J. D.; Foote, C. S.; Imagawa, D. K. Synthesis of 1,2:3,4-Diepoxides by Catalyzed Rearrangement of 1,4-Endoperoxides. *J. Am. Chem. Soc.* **1980**, *102*, 3641–3642.
- (173) Takeshita, H.; Kanamori, H.; Hatsui, T. Sensitized Photooxidation of Spiro[2,4]hepta-4,6-diene. *Tetrahedron Lett.* **1973**, *14*, 3139–3140.
- (174) Holbert, G. W.; Ganem, B. Shikimate-derived Metabolites. 3. Total Synthesis of Senepoxide and Senelol According to a Biogenetic Proposal. *J. Am. Chem. Soc.* **1978**, *100*, 352–353.
- (175) Xu, H.; Tang, H.; Feng, H.; Li, Y. Design, Synthesis and Structure–Activity Relationships Studies on the D Ring of the Natural Product Triptolide. *ChemMedChem* **2014**, *9*, 290–295.
- (176) Kernan, M. R.; Faulkner, D. J. Regioselective Oxidation of 3-Alkylfurans to 3-Alkyl-4-hydroxybutenolides. *J. Org. Chem.* **1988**, *53*, 2773–2776.
- (177) Brecht, R.; Buttner, F.; Bohm, M.; Seitz, G.; Frenzen, G.; Pilz, A.; Massa, W. Photooxygenation of the Helimers of (–)-Isocolchicine: Regio- and Facial Selectivity of the [4 + 2] Cycloaddition with Singlet Oxygen and Surprising Endoperoxide Transformations. *J. Org. Chem.* **2001**, *66*, 2911–2917.
- (178) Brecht, R.; Haenel, F.; Seitz, G.; Frenzen, G.; Pilz, A.; Massa, W.; Wocadlo, S. Positional and Facial Selectivity in Diels-Alder Reactions of (–)-(a*S*,7*S*)-Colchicine: Synthesis of Novel Analogues of the Alkaloid. *Liebigs Ann.* **1997**, *1997*, 851–857.
- (179) Brecht, R.; Haenel, F.; Seitz, G. Dihydrocolchicine 8,12-Endoperoxide: A Novel Starting Material for Convenient Syntheses of the Alcolchicinoids *N*-Acetylcolchinol *O*-Methyl Ether and Androphenylene. *Liebigs Ann.* **1997**, *1997*, 2275–2279.
- (180) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atropselective Chemical Transformations. *Chem. Rev.* **2015**, *115*, 11239–11300.
- (181) Daştan, A.; Balci, M. Chemistry of Dioxine-annelated Cycloheptatriene Endoperoxides and Their Conversion into Tropolone Derivatives: An Unusual Non-Benzenoid Singlet Oxygen Source. *Tetrahedron* **2006**, *62*, 4003–4010.
- (182) Aubry, J.-M.; Pierlot, C.; Rigaudy, J.; Schmidt, R. Reversible Binding of Oxygen to Aromatic Compounds. *Acc. Chem. Res.* **2003**, *36*, 668–675.
- (183) Martinez, G. R.; Ravanat, J.-L.; Medeiros, M. H. G.; Cadet, J.; Di Mascio, P. Synthesis of a Naphthalene Endoperoxide as a Source of ¹⁸O-labeled Singlet Oxygen for Mechanistic Studies. *J. Am. Chem. Soc.* **2000**, *122*, 10212–10213.
- (184) Eisenthal, K. B.; Turro, N. J.; Dupuy, C. G.; Hrovat, D. A.; Langan, J.; Jenny, T. A.; Sitzmann, E. V. State-selective Photochemistry of Singlet Oxygen Precursors: Kinetics and Wavelength Dependence of the Photodissociation of Anthracene Endoperoxides. *J. Phys. Chem.* **1986**, *90*, 5168–5173.
- (185) Liu, N.; Song, W.; Schienebeck, C. M.; Zhang, M.; Tang, W. Synthesis of Naturally Occurring Tropones and Tropolones. *Tetrahedron* **2014**, *70*, 9281–9305.
- (186) Coşkun, A.; Güney, M.; Daştan, A.; Balci, M. Oxidation of Some Alkoxy-Cycloheptatriene Derivatives: Unusual Formation of Furan and Furanoids from Cycloheptatrienes. *Tetrahedron* **2007**, *63*, 4944–4950.
- (187) Güney, M.; Dastan, A.; Balci, M. Chemistry of the Benzotropone Endoperoxides and their Conversion into Tropolone Derivatives: Unusual Endoperoxide Rearrangements. *Helv. Chim. Acta* **2005**, *88*, 830–838.
- (188) Güney, M.; Coşkun, A.; Topal, F.; Daştan, A.; Gülçin, İ.; Supuran, C. T. Oxidation of Cyanobenzocycloheptatrienes: Synthesis, Photooxygenation Reaction and Carbonic Anhydrase Isoenzymes Inhibition Properties of Some New Benzotropone Derivatives. *Bioorg. Med. Chem.* **2014**, *22*, 3537–3543.
- (189) Kim, S. K.; Pak, C. S. Total Synthesis of (±)-Clavukerin-A. A New Trinorgauiene Sesquiterpene—Biomimetic Synthesis of (±)-Clavularin-A from (±)-Clavukerin-A. *J. Org. Chem.* **1991**, *56*, 6829–6832.
- (190) Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. The Cycloaddition Strategy for the Synthesis of Natural Products Containing Carbocyclic Seven-membered Rings. *Chem. - Eur. J.* **2006**, *12*, 3438–3447.
- (191) Martí-Centelles, V.; Pandey, M. D.; Burguete, M. I.; Luis, S. V. Macrocyclization Reactions: The Importance of Conformational, Configurational, and Template-induced Preorganization. *Chem. Rev.* **2015**, *115*, 8736–8834.
- (192) Nicolaou, K. C.; Gunzner, J. L.; Shi, G.-Q.; Agrios, K. A.; Gärtner, P.; Yang, Z. Total Synthesis of Brevetoxin A: Part 4: Final Stages and Completion. *Chem. - Eur. J.* **1999**, *5*, 646–658.
- (193) Vilotijevic, I.; Jamison, T. F. Synthesis of Marine Polycyclic Polyethers via Endo-selective Epoxide-opening Cascades. *Mar. Drugs* **2010**, *8*, 763–809.
- (194) Nakata, T. Total Synthesis of Marine Polycyclic Ethers. *Chem. Rev.* **2005**, *105*, 4314–4347.
- (195) Pazos, G.; Perez, M.; Gandara, Z.; Gomez, G.; Fall, Y. Synthesis of a Chiral Building Block for Highly Functionalized Polycyclic Ethers. *Org. Biomol. Chem.* **2014**, *12*, 7750–7757.
- (196) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. Total Synthesis of Brevetoxin B. 3. Final Strategy and Completion. *J. Am. Chem. Soc.* **1995**, *117*, 10252–10263.
- (197) Nicolaou, K. C. The Total Synthesis of Brevetoxin B: A Twelve-Year Odyssey in Organic Synthesis. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 588–607.
- (198) Nicolaou, K. C.; Yang, Z.; Shi, G.-Q.; Gunzner, J. L.; Agrios, K. A.; Gärtner, P. Total Synthesis of Brevetoxin A. *Nature* **1998**, *392*, 264–269.
- (199) Nicolaou, K. C.; Gunzner, J. L.; Shi, G.-Q.; Agrios, K. A.; Gärtner, P.; Yang, Z. Total Synthesis of Brevetoxin A: Part 4: Final Stages and Completion. *Chem. - Eur. J.* **1999**, *5*, 646–658.
- (200) Steel, P. G.; Mills, O. S.; Parmee, E. R.; Thomas, E. J. Total Synthesis of Milbemycin E: Resolution of the C1-C10 Fragment and Final Assembly. *J. Chem. Soc., Perkin Trans. 1* **1997**, 391–400.
- (201) Adam, W.; Rodriguez, A. Intramolecular Silyl Migration in the Singlet Oxygenation of 2-Methyl-5-trimethylsilylfuran. *Tetrahedron Lett.* **1981**, *22*, 3505–3508.
- (202) Evans, D. A.; Nagorny, P.; Reynolds, D. J.; McRae, K. J. Enantioselective Synthesis of Oasomycin A, Part II: Synthesis of the C29–C46 Subunit. *Angew. Chem., Int. Ed.* **2007**, *46*, 541–544.
- (203) Wasserman, H. H.; Vinick, F. J.; Chang, Y. C. Reaction of Oxazoles with Singlet Oxygen. Mechanism of the Rearrangement of Triamides. *J. Am. Chem. Soc.* **1972**, *94*, 7180–7182.
- (204) Wasserman, H. H.; Gambale, R. J.; Pulver, M. J. Activated Carboxylates from the Photooxygenation of Oxazoles: Application to the Synthesis of Recifeiolide, Curvularin and other Macrolides. *Tetrahedron* **1981**, *37*, 4059–4067.
- (205) Wasserman, H. H.; Gambale, R. J. Oxazoles as Masked Activated Carboxylates. Synthesis of (±)-Di-*O*-methylcurvularin. *Tetrahedron Lett.* **1981**, *22*, 4849–4852.
- (206) Wasserman, H. H.; Gambale, R. J.; Pulver, M. J. Activated Carboxylates from the Photooxygenation of Oxazoles. Application to the Synthesis of Recifeiolide and Other Macrocylic Lactones. *Tetrahedron Lett.* **1981**, *22*, 1737–1740.
- (207) Wasserman, H. H.; Gambale, R. J. Synthesis of (+)-Antimycin A3. Use of the Oxazole Ring in Protecting and Activating Functions. *J. Am. Chem. Soc.* **1985**, *107*, 1423–1424.
- (208) Wasserman, H. H.; DeSimone, R. W.; Ho, W.-B.; McCarthy, K. E.; Prowse, K. S.; Spada, A. P. Singlet Oxygen in Synthesis. Oxazoles as Carbonyl 1,1-Dipole Synthons. *Tetrahedron Lett.* **1992**, *33*, 7207–7210.
- (209) Lagunes, I.; Trigos, A. Photooxidation of Ergosterol: Indirect Detection of Antioxidant Photosensitizers or Quenchers of Singlet Oxygen. *J. Photochem. Photobiol., B* **2015**, *145*, 30–34.
- (210) Gui, J.-H.; Wang, D.-H.; Tian, W.-S. Biomimetic Synthesis of 5,6-Dihydro-glaucogenin C: Construction of the Discopregnane Skeleton by Iron (II)-Promoted Fragmentation of an α -Alkoxy Hydroperoxide. *Angew. Chem., Int. Ed.* **2011**, *50*, 7093–7096.

- (211) Liffert, R.; Hoecker, J.; Jana, C. K.; Woods, T. M.; Burch, P.; Jessen, H. J.; Neuburger, M.; Gademann, K. Withanolide A: Synthesis and Structural Requirements for Neurite Outgrowth. *Chem. Sci.* **2013**, *4*, 2851–2857.
- (212) Li, H. Y.; Drummond, S.; DeLucca, I.; Boswell, G. A. Singlet Oxygen Oxidation of Pyrroles: Synthesis and Chemical Transformations of Novel 4,4-Bis(trifluoromethyl)imidazoline Analogs. *Tetrahedron* **1996**, *52*, 11153–11162.
- (213) Lopez, D.; Quinoa, E.; Riguera, R. The [4 + 2] Addition of Singlet Oxygen to Thebaine: New Access to Highly Functionalized Morphine Derivatives Via Opioid Endoperoxides. *J. Org. Chem.* **2000**, *65*, 4671–4678.
- (214) Machara, A.; Werner, L.; Leisch, H.; Carroll, R. J.; Adams, D. R.; Haque, D. M.; Cox, D. P.; Hudlicky, T. Synthesis of Naltrexone and (R)-Methylnaltrexone from Oripavine via Direct Oxidation of its Quaternary Salts. *Synlett* **2015**, *26*, 2101–2108.
- (215) Mehta, G.; Maity, P. Explorations En Route to Synthesis of Tashironins: Singlet Oxygen Cycloaddition to 1,3-Cyclopentadienes Embedded within Allo-Cedrane Framework. *Tetrahedron Lett.* **2011**, *52*, 5161–5165.
- (216) Tang, Y.; Cole, K. P.; Buchanan, G. S.; Li, G.; Hsung, R. P. Total Synthesis of Phomactin A. *Org. Lett.* **2009**, *11*, 1591–1594.
- (217) Deng, J.; Wang, X.-N.; Hsung, R. P. A Formal [3 + 3] Cycloaddition Approach to Natural Product Synthesis. In *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*; Nishiwaki, N., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2014; Chapter 12, pp 283–354.
- (218) Buchanan, G. S.; Cole, K. P.; Tang, Y.; Hsung, R. P. Total Synthesis of (±)-Phomactin A. Lessons Learned from Respecting a Challenging Structural Topology. *J. Org. Chem.* **2011**, *76*, 7027–7039.
- (219) Shang, H.; Liu, J. H.; Bao, R. Y.; Cao, Y.; Zhao, K.; Xiao, C. Q.; Zhou, B.; Hu, L. H.; Tang, Y. F. Biomimetic Synthesis: Discovery of Xanthanolide Dimers. *Angew. Chem., Int. Ed.* **2014**, *53*, 14494–14498.
- (220) Sharma, P.; Lygo, B.; Lewis, W.; Moses, J. E. Biomimetic Synthesis and Structural Reassignment of the Tridachiahydropyrone. *J. Am. Chem. Soc.* **2009**, *131*, 5966–5972.
- (221) Tong, G. H.; Liu, Z.; Li, P. F. Stereocontrolled Construction of the Tricyclic Framework of Tiglanes and Daphnanes by an Oxidative Dearomatization Approach. *Org. Lett.* **2014**, *16*, 2288–2291.
- (222) Prein, M.; Maurer, M.; Peters, E. M.; Peters, K.; von Schnering, H. G.; Adam, W. Diastereoselective Synthesis of 4-Hydroperoxy-3,5-cyclohexadienones in the Photooxygenation of Hydroxyethyl-Substituted Phenols. *Chem. - Eur. J.* **1995**, *1*, 89–94.
- (223) Dethe, D. H.; Dherange, B. D. Enantioselective Total Syntheses of (+)-Hostmanin A, (–)-Linderol A, (+)-Methylinderatin and Structural Reassignment of Aduncin E. *J. Org. Chem.* **2015**, *80*, 4526–4531.
- (224) Wood, J. L.; Graeber, J. K.; Njardarson, J. T. Application of Phenolic Oxidation Chemistry in Synthesis: Preparation of the BCE Ring System of Ryanodine. *Tetrahedron* **2003**, *59*, 8855–8858.
- (225) Celaje, J. A.; Zhang, D.; Guerrero, A. M.; Selke, M. Chemistry of *trans*-Resveratrol with Singlet Oxygen: [2 + 2] Addition, [4 + 2] Addition, and Formation of the Phytoalexin Moracin M. *Org. Lett.* **2011**, *13*, 4846–4849.
- (226) DellaGreca, M.; Iesce, M. R.; Previtera, L.; Purcaro, R.; Rubino, M.; Zarrelli, A. Lignans by Photo-oxidation of Propenyl Phenols. *Photochem. Photobiol. Sci.* **2008**, *7*, 28–32.
- (227) Motoyoshiya, J.; Okuda, Y.; Matsuoka, I.; Hayashi, S.; Takaguchi, Y.; Aoyama, H. Tetraphenylporphine-Sensitized Photooxygenation of (E,E)- and (E,Z)-1-Aryl-1,3-pentadienes Generating *cis*-Endoperoxides. *J. Org. Chem.* **1999**, *64*, 493–497.
- (228) Vassilikogiannakis, G.; Stratakis, M.; Orfanopoulos, M. Primary and Secondary Isotope Effects in the Photooxidation of 2,5-Dimethyl-2,4-hexadiene. Elucidation of the Reaction Energy Profile. *J. Org. Chem.* **1998**, *63*, 6390–6393.
- (229) Greer, A.; Vassilikogiannakis, G.; Lee, K.-C.; Koffas, T. S.; Nahm, K.; Foote, C. S. Reaction of Singlet Oxygen with *Trans*-4-Propenylanisole. Formation of [2 + 2] Products with Added Acid. *J. Org. Chem.* **2000**, *65*, 6876–6878.
- (230) Han, J.; Li, X.; Guan, Y.; Zhao, W.; Wulff, W. D.; Lei, X. Enantioselective Biomimetic Total Syntheses of Kuwanons I and J and Brosimones A and B. *Angew. Chem., Int. Ed.* **2014**, *53*, 9257–9261.
- (231) Helesbeux, J. J.; Duval, O.; Guilet, D.; Séraphin, D.; Rondeau, D.; Richomme, P. Regioselectivity in the Ene Reaction of Singlet Oxygen with *Ortho*-prenylphenol Derivatives. *Tetrahedron* **2003**, *59*, 5091–5104.
- (232) Helesbeux, J. J.; Duval, O.; Dartiguelongue, C.; Seraphin, D.; Oger, J. M.; Richomme, P. Synthesis of 2-Hydroxy-3-methylbut-3-enyl Substituted Coumarins and Xanthenes as Natural Products. Application of the Schenck Ene Reaction of Singlet Oxygen with *Ortho*-prenylphenol Precursors. *Tetrahedron* **2004**, *60*, 2293–2300.
- (233) Pinto, M. M. M.; Castanheiro, R. Natural Prenylated Xanthenes: Chemistry and Biological Activities. In *Natural Products: Chemistry, Biochemistry and Pharmacology*; Brahmachari, G., Ed.; Alpha Science International: Oxford, U.K., 2009; Chapter 17, pp 520–675.
- (234) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. Total Synthesis of (–)-Balanol. *J. Org. Chem.* **1994**, *59*, 5147–5148.
- (235) Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B.; Katz, B. Balanol: A Novel and Potent Inhibitor of Protein Kinase C from the Fungus *Verticillium Balanoides*. *J. Am. Chem. Soc.* **1993**, *115*, 6452–6453.
- (236) Bolitt, V.; Mioskowski, C.; Kollah, R. O.; Manna, S.; Rajapaksa, D.; Falck, J. R. Total Synthesis of Vineomycinone-B2Methyl-Ester Via Double Bradsher Cyclization. *J. Am. Chem. Soc.* **1991**, *113*, 6320–6321.
- (237) Boissel, V.; Simpkins, N. S.; Bhalay, G. Singlet Oxygen Conversion of Indoles into α,β -Unsaturated Oxindoles in Model Compounds Related to the Welwitindolinone Alkaloids. *Tetrahedron Lett.* **2009**, *50*, 3283–3286.
- (238) Didier, C.; Critcher, D. J.; Walshe, N. D.; Kojima, Y.; Yamauchi, Y.; Barrett, A. G. M. Full Stereochemical Assignment and Synthesis of the Potent Anthelmintic Pyrrolobenzoxazine Natural Product CJ-12662. *J. Org. Chem.* **2004**, *69*, 7875–7879.
- (239) Trabanco, A. A.; Montalban, A. G.; Rumbles, G.; Barrett, A. G. M.; Hoffman, B. M. A Seco-porphyrazine: Superb Sensitizer for Singlet Oxygen Generation and Endoperoxide Synthesis. *Synlett* **2000**, *7*, 1010–1012.
- (240) Sakellariou, E.; Montalban, A. G.; Meunier, H. G.; Rumbles, G.; Phillips, D.; Ostler, R. B.; Suhling, K.; Barrett, A. G. M.; Hoffman, B. M. Peripherally Metalated Secoporphyrazines: A New Generation of Photoactive Pigments. *Inorg. Chem.* **2002**, *41*, 2182–2187.
- (241) Lee, S.; Stackow, R.; Foote, C. S.; Barrett, A. G. M.; Hoffman, B. M. Tuning the Singlet Oxygen Quantum Yield of Near-IR-absorbing Porphyrazines. *Photochem. Photobiol.* **2003**, *77*, 18–21.
- (242) Nakagawa, M.; Kato, S.; Kataoka, S.; Kodato, S.; Watanabe, H.; Okajima, H.; Hino, T.; Witkop, B. Dye-sensitized Photooxygenation of Tryptophan : 3a-Hydroperoxytryptolindole as a Labile Precursor of Formylkynurenine. *Chem. Pharm. Bull.* **1981**, *29*, 1013–1026.
- (243) Nakagawa, M.; Yokoyama, Y.; Kato, S.; Hino, T. Dye-sensitized Photo-oxygenation of Tryptophan. *Tetrahedron* **1985**, *41*, 2125–2132.
- (244) Zhang, X.; Foote, C. S. 1,2-Dioxetane Formation in Photooxygenation of *N*-Acylylated Indole Derivatives. *J. Org. Chem.* **1993**, *58*, 5524–5527.
- (245) Huvaere, K.; Skibsted, L. H. Light-induced Oxidation of Tryptophan and Histidine. Reactivity of Aromatic *N*-Heterocycles Towards Triplet-excited Flavins. *J. Am. Chem. Soc.* **2009**, *131*, 8049–8060.
- (246) Baran, P. S.; Guerrero, C. A.; Corey, E. J. Short, Enantioselective Total Synthesis of Okaramine N. *J. Am. Chem. Soc.* **2003**, *125*, 5628–5629.
- (247) Baran, P. S.; Guerrero, C. A.; Corey, E. J. The First Method for Protection–Deprotection of the Indole 2,3- π Bond. *Org. Lett.* **2003**, *5*, 1999–2001.
- (248) Nakamura, T.; Takegami, A.; Abe, M. Generation and Intermolecular Trapping of 1,2-Diaza-4-silacyclopentane-3,5-diyls in the Denitrogenation of 2,3,5,6-Tetraaza-7-Silabicyclo[2.2.1]hept-2-ene: An Experimental and Computational Study. *J. Org. Chem.* **2010**, *75*, 1956–1960.

- (249) Acevedo, O.; Squillacote, M. E. A New Solvent-dependent Mechanism for a Triazolinedione Ene Reaction. *J. Org. Chem.* **2008**, *73*, 912–922.
- (250) Pastor, A.; Adam, W.; Wirth, T.; Tóth, G. Diastereoselective Reactions of the Tiglic Acid Functionality Mediated by Oxazolidine Chiral Auxiliaries: A Mechanistic Comparison of DMD and *m*-CPBA Epoxidations Versus Singlet Oxygen and PTAD Ene Reactions. *Eur. J. Org. Chem.* **2005**, *2005*, 3075–3084.
- (251) Alberti, M. N.; Vougioukalakis, G. C.; Orfanopoulos, M. Electronic Effects in the Regioselectivity of the Singlet Oxygen and 4-Methyl-1,2,4-Triazoline-3,5-Dione Ene Reactions with Isobutenylarenes. *Tetrahedron Lett.* **2003**, *44*, 903–905.
- (252) Sheu, C.; Kang, P.; Khan, S.; Foote, C. S. Low-Temperature Photosensitized Oxidation of a Guanosine Derivative and Formation of an Imidazole Ring-opened Product. *J. Am. Chem. Soc.* **2002**, *124*, 3905–3913.
- (253) Adam, W.; Bottke, N.; Krebs, O.; Lykakis, I.; Orfanopoulos, M.; Stratakis, M. Ene Reaction of Singlet Oxygen, Triazolinedione, and Nitrosoarene with Chiral Deuterium-Labeled Allylic Alcohols: The Interdependence of Diastereoselectivity and Regioselectivity Discloses Mechanistic Insights into the Hydroxy-group Directivity. *J. Am. Chem. Soc.* **2002**, *124*, 14403–14409.
- (254) Stratakis, M.; Hatzimariniaki, M.; Froudakis, G. E.; Orfanopoulos, M. Stereochemistry in the Reaction of 4-Methyl-1,2,4-Triazoline-3,5-Dione (MTAD) with β,β -Dimethyl-*p*-Methoxystyrene. Are Open Biradicals the Reaction Intermediates? *J. Org. Chem.* **2001**, *66*, 3682–3687.
- (255) Vassilikogiannakis, G.; Stratakis, M.; Orfanopoulos, M. Isotope Effects and Syn Selectivity in the Ene Reaction of Triazolinedione with Conjugated Enones: Aziridinium Imide or an Open Intermediate Mechanism? *Org. Lett.* **2000**, *2*, 2245–2248.
- (256) Vassilikogiannakis, G.; Stratakis, M.; Orfanopoulos, M.; Foote, C. S. Stereochemistry in the Ene Reactions of Singlet Oxygen and Triazolinediones with Allylic Alcohols. A Mechanistic Comparison. *J. Org. Chem.* **1999**, *64*, 4130–4139.
- (257) Stratakis, M.; Orfanopoulos, M.; Foote, C. S. Reactions of Singlet Oxygen and N-Methyltriazolinediones with β,β -Dimethylstyrene. Exceptional Syn Selectivity in the Ene Products. *J. Org. Chem.* **1998**, *63*, 1315–1318.
- (258) Lancefield, C. S.; Zhou, L. N.; Lebl, T.; Slawin, A. M. Z.; Westwood, N. J. The Synthesis of Melohenine B and a Related Natural Product. *Org. Lett.* **2012**, *14*, 6166–6169.
- (259) Liu, G.; Lancefield, C. S.; Lorion, M. M.; Slawin, A. M. Z.; Westwood, N. J. Synthesis and Oxidative Cleavage of Oxazinocarbazoles: Atropselective Access to Medium-Sized Rings. *Synthesis* **2014**, *46*, 2808–2814.
- (260) Jones, A. M.; Liu, G.; Lorion, M. M.; Patterson, S.; Lébl, T.; Slawin, A. M. Z.; Westwood, N. J. Asymmetric Catalytic Oxidative Cleavage of Polycyclic Systems: The Synthesis of Atropisomeric Diazonanes and Diazecanes. *Chem. - Eur. J.* **2011**, *17*, 5714–5718.
- (261) Wasserman, H. H.; Han, W. T. A Synthesis of Antibiotic (\pm)-PS-5. *Tetrahedron Lett.* **1984**, *25*, 3747–3750.
- (262) Wasserman, H. H.; Ives, J. L. A Novel Method for Converting Ketones to α -Diketones. The Reaction of Enamino Ketones with Singlet Oxygen. *J. Am. Chem. Soc.* **1976**, *98*, 7868–7869.
- (263) Wasserman, H. H.; Ives, J. L. Reaction of Singlet Oxygen with Enamino Lactones. Conversion of Lactones to α -Keto Lactones. *J. Org. Chem.* **1978**, *43*, 3238–3240.
- (264) Wasserman, H. H.; Han, W. T. Vicinal Tricarbonyl Products from Singlet Oxygen Reactions—Application to the Synthesis of Carbacephams. *Tetrahedron Lett.* **1984**, *25*, 3743–3746.
- (265) Kametani, T.; Honda, T.; Nakayama, A.; Sasakai, Y.; Mochizuki, T.; Fukumoto, K. A Short and Stereoselective Synthesis of the Carpapem Antibiotic PS-5. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2228–2232.
- (266) Kalaitzakis, D.; Noutsias, D.; Vassilikogiannakis, G. First Total Synthesis of Pandamarine. *Org. Lett.* **2015**, *17*, 3596–3599.
- (267) Kalaitzakis, D.; Kouridaki, A.; Noutsias, D.; Montagnon, T.; Vassilikogiannakis, G. Methylene Blue as a Photosensitizer and Redox Agent: Synthesis of 5-Hydroxy-1*H*-pyrrol-2(*5H*)-ones from Furans. *Angew. Chem., Int. Ed.* **2015**, *54*, 6283–6287.
- (268) Feng, T.; Cai, X.-H.; Liu, Y.-P.; Li, Y.; Wang, Y.-Y.; Luo, X.-D. Melodines A–G, Monoterpenoid Indole Alkaloids from *Melodinus Henryi*. *J. Nat. Prod.* **2010**, *73*, 22–26.
- (269) Nay, B.; Riache, N.; Evanno, L. Chemistry and Biology of Non-Tetramic γ -Hydroxy- γ -Lactams and γ -Alkylidene- γ -Lactams from Natural Sources. *Nat. Prod. Rep.* **2009**, *26*, 1044–1062.
- (270) Kumar, M. M. K.; Naik, J. D.; Satyavathi, K.; Ramana, H.; Varma, P. R.; Nagasree, K. P.; Smitha, D.; Rao, D. V. Denigrins A–C: New Antitubercular 3,4-Diarylpyrrole Alkaloids from *Dendrilla Nigra*. *Nat. Prod. Res.* **2014**, *28*, 888–894.
- (271) Miyazaki, H.; Miyake, T.; Terakawa, Y.; Ohmizu, H.; Ogiku, T.; Ohtani, A. Evaluation of Pyrrolin-2-one Derivatives Synthesized by a New Practical Method as Inhibitors of Plasminogen Activator Inhibitor-1 (PAI-1). *Bioorg. Med. Chem. Lett.* **2010**, *20*, 546–548.
- (272) Chatzimpaloglou, A.; Kolosov, M.; Eckols, T. K.; Twardy, D. J.; Sarli, V. Synthetic and Biological Studies of Phaeosphaerides. *J. Org. Chem.* **2014**, *79*, 4043–4054.
- (273) Seah, K. Y.; Macnaughton, S. J.; Dallimore, J. W.; Robertson, J. Synthesis of Pandamarilactone-1. *Org. Lett.* **2014**, *16*, 884–887.
- (274) Shiraki, R.; Sumino, A.; Tadano, K.-I.; Ogawa, S. Total Synthesis of PI-091. *Tetrahedron Lett.* **1995**, *36*, 5551–5554.
- (275) Katsumura, S.; Hori, K.; Fujiwara, S.; Ise, S. Regiospecific Synthesis of γ -Hydroxybutenolide. Photosensitized Oxygenation of Substituted 2-Trimethylsilylfuran. *Tetrahedron Lett.* **1985**, *26*, 4625–4628.
- (276) Kalaitzakis, D.; Montagnon, T.; Antonatou, E.; Vassilikogiannakis, G. One-pot Synthesis of the Tetracyclic Framework of the Aromatic Erythrina Alkaloids from Simple Furans. *Org. Lett.* **2013**, *15*, 3714–3717.
- (277) Wasserman, H. H.; DeSimone, R. W.; Boger, D. L.; Baldino, C. M. Singlet Oxygen Oxidation of Bipyroles: Total Synthesis of D,L- and Meso-Isochrysohermidin. *J. Am. Chem. Soc.* **1993**, *115*, 8457–8458.
- (278) Wasserman, H. H.; Rotello, V. M.; Frechette, R.; DeSimone, R. W.; Yoo, J. U.; Baldino, C. M. Singlet Oxygen in Synthesis. Formation of D,L- and Meso-isochrysohermidin from a 3,3'-Bipyrrrole Precursor. *Tetrahedron* **1997**, *53*, 8731–8738.
- (279) Boger, D. L.; Baldino, C. M. Singlet Oxygen Mediated Oxidative Decarboxylation of Pyrrole-2-carboxylic Acids. *J. Org. Chem.* **1991**, *56*, 6942–6944.
- (280) de Mayo, P.; Reid, S. T. The Photooxidation of Pyrrole: A Simple Synthesis of Maleimide. *Chem. Ind.* **1962**, *35*, 1576–1577.
- (281) Foote, C. S. Mechanisms of Photosensitized Oxidation. There are Several Different Types of Photosensitized Oxidation Which May be Important in Biological Systems. *Science* **1968**, *162*, 963–970.
- (282) Grunewald, J. O.; Walker, J. C.; Strobe, E. R. Photooxidation of Xanthobilirubin Acid in Aqueous Solution: Product and Mechanism Studies. *Photochem. Photobiol.* **1976**, *24*, 29–40.
- (283) Li, Y.; Hu, H.-Y.; Ye, J.-P.; Fun, H.-K.; Hu, H.-W.; Xu, J.-H. Reaction Modes and Mechanism in Indolizine Photooxygenation Reactions. *J. Org. Chem.* **2004**, *69*, 2332–2339.
- (284) Alberti, M. N.; Vougioukalakis, G. C.; Orfanopoulos, M. Photosensitized Oxidations of Substituted Pyrroles: Unanticipated Radical-Derived Oxygenated Products. *J. Org. Chem.* **2009**, *74*, 7274–7282.
- (285) Eisenberg, W. C.; Taylor, K.; Murray, R. W. Gas-Phase Kinetics of the Reaction of Singlet Oxygen with Olefins at Atmospheric Pressure. *J. Phys. Chem.* **1986**, *90*, 1945–1948.
- (286) Naito, K.; Tachikawa, T.; Cui, S.-C.; Sugimoto, A.; Fujitsuka, M.; Majima, T. Single-molecule Detection of Airborne Singlet Oxygen. *J. Am. Chem. Soc.* **2006**, *128*, 16430–16431.
- (287) Naito, K.; Tachikawa, T.; Fujitsuka, M.; Majima, T. Real-time Single-molecule Imaging of the Spatial and Temporal Distribution of Reactive Oxygen Species with Fluorescent Probes: Applications to TiO₂ Photocatalysts. *J. Phys. Chem. C* **2008**, *112*, 1048–1059.
- (288) Fudickar, W.; Fery, A.; Linker, T. Reversible Light and Air-driven Lithography by Singlet Oxygen. *J. Am. Chem. Soc.* **2005**, *127*, 9386–9387.

- (289) Malek, B.; Ghogare, A. A.; Choudhury, R.; Greer, A. Air-water Interface Effects on the Regioselectivity of Singlet Oxygenations of a Trisubstituted Alkene. *Tetrahedron Lett.* **2015**, *56*, 4505–4508.
- (290) Elvira, K. S.; Wootton, R. C. R.; Reis, N. M.; Mackley, M. R.; deMello, A. J. Through-Wall Mass Transport as a Modality for Safe Generation of Singlet Oxygen in Continuous Flows. *ACS Sustainable Chem. Eng.* **2013**, *1*, 209–213.
- (291) Wootton, R. C. R.; Fortt, R.; deMello, A. J. A Microfabricated Nanoreactor for Safe, Continuous Generation and Use of Singlet Oxygen. *Org. Process Res. Dev.* **2002**, *6*, 187–189.
- (292) Mitchell, M. C.; Spikmans, V.; Mello, A. J. Microchip-Based Synthesis and Analysis: Control of Multicomponent Reaction Products and Intermediates. *Analyst* **2001**, *126*, 24–27.
- (293) Sirichai, S.; de Mello, A. J. A Capillary Electrophoresis Microchip for the Analysis of Photographic Developer Solutions Using Indirect Fluorescence Detection. *Analyst* **2000**, *125*, 133–137.
- (294) Loponov, K. N.; Lopes, J.; Barlog, M.; Astrova, E. V.; Malkov, A. V.; Lapkin, A. A. Optimization of a Scalable Photochemical Reactor for Reactions with Singlet Oxygen. *Org. Process Res. Dev.* **2014**, *18*, 1443–1454.
- (295) Mihelich, E. D.; Eickhoff, D. J. One-pot Conversion of Olefins to α,β -unsaturated Carbonyl Compounds. An Easy Synthesis of 2-Cyclopentenone and Related Compounds. *J. Org. Chem.* **1983**, *48*, 4135–4137.
- (296) Meyer, S.; Tietze, D.; Rau, S.; Schäfer, B.; Kreisel, G. Photosensitized Oxidation of Citronellol in Microreactors. *J. Photochem. Photobiol., A* **2007**, *186*, 248–253.
- (297) Kreisel, G.; Meyer, S.; Tietze, D.; Fidler, T.; Gorges, R.; Kirsch, A.; Schäfer, B.; Rau, S. Leuchtdioden in der Chemie. Eine Hochzeit verschiedener Technologien. *Chem. Ing. Tech.* **2007**, *79*, 153–159.
- (298) Jähnisch, K.; Dingerdissen, U. Photochemical Generation and [4 + 2]-cycloaddition of Singlet Oxygen in a Falling-film Microreactor. *Chem. Eng. Technol.* **2005**, *28*, 426–427.
- (299) Jähnisch, K. Photochemische Erzeugung und [4 + 2] Cycloaddition von Singulett-Sauerstoff im Mikrofallfilmreaktor. *Chem. Ing. Tech.* **2004**, *76*, 630–632.
- (300) Park, C. P.; Maurya, R. A.; Lee, J. H.; Kim, D. P. Efficient Photosensitized Oxygenations in Phase Contact Enhanced Microreactors. *Lab Chip* **2011**, *11*, 1941–1945.
- (301) Ziegenbalg, D.; Kreisel, G.; Weiss, D.; Kralisch, D. OLEDs as Prospective Light Sources for Microstructured Photoreactors. *Photochem. Photobiol. Sci.* **2014**, *13*, 1005–1015.
- (302) Drhova, M.; Hejda, S.; Kristal, J.; Kluson, P. Performance of Continuous Micro Photo Reactor – Comparison with Batch Process. *Procedia Eng.* **2012**, *42*, 1365–1372.
- (303) Lumley, E. K.; Dyer, C. E.; Pamme, N.; Boyle, R. W. Comparison of Photo-oxidation Reactions in Batch and a New Photosensitizer-Immobilized Microfluidic Device. *Org. Lett.* **2012**, *14*, 5724–5727.
- (304) Foote, C. S. Chemistry of Reactive Oxygen Species. In *Chemical Changes in Food During Processing*; Richardson, T., Finley, J. W., Eds.; AVI Publishing Co.: SpringerWestport, CT, 1985; pp 17–32.
- (305) Kitamura, N.; Yamada, K.; Ueno, K.; Iwata, S. Photodecomposition of Phenol by Silica-Supported Porphyrin Derivative in Polymer Microchannel Chips. *J. Photochem. Photobiol., A* **2006**, *184*, 170–176.
- (306) Briviba, K.; Devasagayam, T. P. A.; Sies, H.; Steenken, S. Selective Para-Hydroxylation of Phenol and Aniline by Singlet Molecular Oxygen. *Chem. Res. Toxicol.* **1993**, *6*, 548–553.
- (307) Carofiglio, T.; Donnola, P.; Maggini, M.; Rossetto, M.; Rossi, E. Fullerene-promoted Singlet-oxygen Photochemical Oxygenations in Glass-polymer Microstructured Reactors. *Adv. Synth. Catal.* **2008**, *350*, 2815–2822.
- (308) Bagrov, I. V.; Belousova, I. M.; Grenishin, A. S.; Kiselev, V. M.; Kislyakov, I. M.; Sosnov, E. N. A Jet-type Singlet Oxygen Generator Based on Porous Fullerene-containing Structures. *Opt. Spectrosc.* **2012**, *112*, 935–942.
- (309) Lévesque, F.; Seeberger, P. H. Continuous-flow Synthesis of the Anti-malaria Drug Artemisinin. *Angew. Chem., Int. Ed.* **2012**, *51*, 1706–1709.
- (310) Kopetzki, D.; Lévesque, F.; Seeberger, P. H. A Continuous-Flow Process for the Synthesis of Artemisinin. *Chem. - Eur. J.* **2013**, *19*, 5450–5456.
- (311) Gilmore, K.; Kopetzki, D.; Lee, J. W.; Horvath, Z.; McQuade, D. T.; Seidel-Morgenstern, A.; Seeberger, P. H. Continuous Synthesis of Artemisinin-derived Medicines. *Chem. Commun.* **2014**, *50*, 12652–12655.
- (312) Kong, L. Y.; Tan, R. X. Artemisinin, A Miracle of Traditional Chinese Medicine. *Nat. Prod. Rep.* **2015**, *32*, 1617–1621.
- (313) Tu, Y. The Discovery of Artemisinin (Qinghaosu) and Gifts from Chinese Medicine. *Nat. Med.* **2011**, *17*, 1217–1220.
- (314) Shen, B. A New Golden Age of Natural Products Drug Discovery. *Cell* **2015**, *163*, 1297–1300.
- (315) Ushakov, D. B.; Gilmore, K.; Kopetzki, D.; McQuade, D. T.; Seeberger, P. H. Continuous-Flow Oxidative Cyanation of Primary and Secondary Amines Using Singlet Oxygen. *Angew. Chem., Int. Ed.* **2014**, *53*, 557–561.
- (316) Vukelić, S.; Ushakov, D. B.; Gilmore, K.; Kokschi, B.; Seeberger, P. H. Flow Synthesis of Fluorinated α -Amino Acids. *Eur. J. Org. Chem.* **2015**, *2015*, 3036–3039.
- (317) Jiang, G.; Chen, J.; Huang, J.-S.; Che, C.-M. Highly Efficient Oxidation of Amines to Imines by Singlet Oxygen and its Application in Ugi-Type Reactions. *Org. Lett.* **2009**, *11*, 4568–4571.
- (318) Enders, D.; Shilcock, J. P. Some Recent Applications of α -Amino Nitrile Chemistry. *Chem. Soc. Rev.* **2000**, *29*, 359–373.
- (319) Lévesque, F.; Seeberger, P. H. Highly Efficient Continuous Flow Reactions Using Singlet Oxygen as a “Green” Reagent. *Org. Lett.* **2011**, *13*, 5008–5011.
- (320) Baciocchi, E.; Del Giacco, T.; Lanzalunga, O.; Lapi, A. Singlet Oxygen Promoted Carbon-heteroatom Bond Cleavage in Dibenzyl Sulfides and Tertiary Dibenzylamines: Structural Effects and the Role of Exciplexes. *J. Org. Chem.* **2007**, *72*, 9582–9589.
- (321) Greer, A.; Chen, M.-F.; Jensen, F.; Clennan, E. L. Experimental and *ab Initio* Computational Evidence for New Peroxidic Intermediates (Iminopersulfonic Acids). Substituent Effects in the Photooxidations of Sulfenic Acid Derivatives. *J. Am. Chem. Soc.* **1997**, *119*, 4380–4387.
- (322) Ishiguro, K.; Hayashi, M.; Sawaki, Y. Mechanism of Sulfone Formation in the Reaction of Sulfides and Singlet Oxygen: Intermediacy of S-Hydroperoxysulfonium Ylide. *J. Am. Chem. Soc.* **1996**, *118*, 7265–7271.
- (323) Lapkin, A. A.; Boddu, V. M.; Aliev, G. N.; Goller, B.; Polisski, S.; Kovalev, D. Photo-Oxidation by Singlet Oxygen Generated on Nanoporous Silicon in a LED-Powered Reactor. *Chem. Eng. J.* **2008**, *136*, 331–336.
- (324) Heugebaert, T. S.; Stevens, C. V.; Kappe, C. O. Singlet-oxygen Oxidation of 5-Hydroxymethylfurfural in Continuous Flow. *ChemSusChem* **2015**, *8*, 1648–1651.
- (325) Cottier, L.; Descotes, G.; Nigay, H.; Parron, J.-C.; Gregoire, V. Photo-oxygenation des Derives de L’hydroxymethyl-5 Furfural-2. *Bull. Soc. Chim. Fr.* **1986**, *5*, 844–850.
- (326) Cottier, L.; Descotes, G.; Eymard, L.; Rapp, K. Syntheses of γ -Oxo Acids or γ -Oxo Esters by Photooxygenation of Furanic Compounds and Reduction Under Ultrasound: Application to the Synthesis of 5-Aminolevulinic Acid Hydrochloride. *Synthesis* **1995**, *1995*, 303–306.
- (327) Marisa, C.; Ilaria, D. S.; Marotta, R.; Roberto, A.; Vincenzo, C. Production of 5-Hydroxy-4-Keto-2-Pentenoic Acid by Photo-Oxidation of 5-Hydroxymethylfurfural with Singlet Oxygen: A Kinetic Investigation. *J. Photochem. Photobiol., A* **2010**, *210*, 69–76.
- (328) Noutsias, D.; Vassilikogiannakis, G. First Total Synthesis of Paracaseolide A. *Org. Lett.* **2012**, *14*, 3565–3567.
- (329) González, M.; Gándara, Z.; Martínez, A.; Gómez, G.; Fall, Y. Synthesis of (4S,5S,11R) and (4S,5S,11S)-Iso-Cladospolide B. *Tetrahedron Lett.* **2013**, *54*, 3647–3650.
- (330) González, M.; Gándara, Z.; Martínez, A.; Gómez, G.; Fall, Y. Synthesis of (+)-Muricatacin and a Formal Synthesis of CMI-977 from L-Malic Acid. *Synthesis* **2013**, *45*, 1693–1700.
- (331) González, M.; Gándara, Z.; Pazos, G.; Gómez, G.; Fall, Y. Synthesis of (–)-Muricatacin from Tri-O-acetyl-D-glucal. *Synthesis* **2013**, *45*, 625–632.

- (332) García, I.; Gómez, G.; Teijeira, M.; Terán, C.; Fall, Y. The Furan Approach to Oxacycles. Part 4: A Synthesis of (+)-Decarestrictine L. *Tetrahedron Lett.* **2006**, *47*, 1333–1335.
- (333) Hugelshofer, C. L.; Magauer, T. Total Synthesis of the Leucosceptroid Family of Natural Products. *J. Am. Chem. Soc.* **2015**, *137*, 3807–3810.
- (334) Dong, J. Q.; Wong, H. N. Biomimetic Total Synthesis of (\pm)-Pallavicinonide A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2351–2354.
- (335) Vlad, P. F.; Ciocarlan, A.; Edu, C.; Aricu, A.; Biriic, A.; Coltsa, M.; D'Ambrosio, M.; Deleanu, C.; Nicolescu, A.; Shova, S.; et al. Regio- and Stereoselective Synthesis of (+)-6-Ketoeuryfuran, (+)-6-Ketowinterin, and (–)-7-Ketoeuryfuran from Accessible Labdane Diterpenoids (+)-Larixol and (–)-Sclareol. *Tetrahedron* **2013**, *69*, 918–926.
- (336) Ciocarlan, A.; Edu, C.; Biriic, A.; Lungu, L.; Aricu, A.; D'Ambrosio, M.; Shova, S.; Nicolescu, A.; Deleanu, C.; Vornicu, N. Synthesis of Polyfunctional Drimanes from Drim-7,9(11)-diene and Drim-8-en-7-one. *Synth. Commun.* **2013**, *43*, 3020–3033.
- (337) Urones, J. G.; Diez, D.; Gomez, P. M.; Marcos, I. S.; Basabe, P.; Moro, R. F. Chemistry of Zamoranic Acid, Part 10: Homochiral Hemisynthesis of Pereniporin A. *J. Chem. Soc., Perkin Trans. 1* **1997**, *11*, 1815–1818.
- (338) Pavlakos, E.; Georgiou, T.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G. γ -Spiroketal γ -Lactones from 2-(γ -Hydroxyalkyl)-furans: Syntheses of Epi-pyrenolide D and Crassalactone D. *Org. Lett.* **2009**, *11*, 4556–4559.
- (339) Triantafyllakis, M.; Tofi, M.; Montagnon, T.; Kouridaki, A.; Vassilikogiannakis, G. Singlet Oxygen-mediated Synthesis of Bis-spiroketal Found in Azaspiracids. *Org. Lett.* **2014**, *16*, 3150–3153.
- (340) Noutsias, D.; Kouridaki, A.; Vassilikogiannakis, G. Scope and Limitations of the Photooxidations of 2-(α -Hydroxyalkyl)furans: Synthesis of 2-Hydroxy-Exo-Brevicomine. *Org. Lett.* **2011**, *13*, 1166–1169.
- (341) Margaros, I.; Vassilikogiannakis, G. Synthesis of (+)-Zerumin B Using a Regioselective Singlet Oxygen Furan Oxidation. *J. Org. Chem.* **2008**, *73*, 2021–2023.
- (342) Demeke, D.; Forsyth, C. J. Novel Total Synthesis of the Anticancer Natural Product Dysidiolide. *Org. Lett.* **2000**, *2*, 3177–3179.
- (343) Bourne, R. A.; Han, X.; Poliakov, M.; George, M. W. Cleaner Continuous Photo-Oxidation Using Singlet Oxygen in Supercritical Carbon Dioxide. *Angew. Chem., Int. Ed.* **2009**, *48*, 5322–5325.
- (344) Han, X.; Bourne, R. A.; Poliakov, M.; George, M. W. Immobilised Photosensitisers for Continuous Flow Reactions of Singlet Oxygen in Supercritical Carbon Dioxide. *Chem. Sci.* **2011**, *2*, 1059–1067.
- (345) Abdel-Shafi, A. A.; Wilkinson, F.; Worrall, D. R. Photosensitized Production of Singlet Oxygen, O_2 ($a^1\Delta_g$), in the Unique 'Heavy-Atom' Solvent, Supercritical Fluid Xenon. Pressure Dependence of Electronic to Vibrational Energy Conversion During Quenching of O_2 ($a^1\Delta_g$) by Xenon and by Ground State Oxygen. *Chem. Phys. Lett.* **2001**, *343*, 273–280.
- (346) Abdel-Shafi, A. A.; Worrall, D. R. Photosensitized Production of Singlet Oxygen and Factors Governing Its Decay in Xenon and Carbon Dioxide Supercritical Fluids. *J. Photochem. Photobiol., A* **2007**, *186*, 263–269.
- (347) Worrall, D. R.; Abdel-Shafi, A. A.; Wilkinson, F. Factors Affecting the Rate of Decay of the First Excited Singlet State of Molecular Oxygen O_2 ($a^1\Delta_g$) in Supercritical Fluid Carbon Dioxide. *J. Phys. Chem. A* **2001**, *105*, 1270–1276.
- (348) Bourne, R. A.; Han, X.; Chapman, A. O.; Arrowsmith, N. J.; Kawanami, H.; Poliakov, M.; George, M. W. Homogeneous Photochemical Oxidation via Singlet O_2 in Supercritical CO_2 . *Chem. Commun.* **2008**, 4457–4459.
- (349) Darr, J. A.; Poliakov, M. New Directions in Inorganic and Metal-Organic Coordination Chemistry in Supercritical Fluids. *Chem. Rev.* **1999**, *99*, 495–541.
- (350) Licence, P.; Ke, J.; Sokolova, M.; Ross, S. K.; Poliakov, M. Chemical Reactions in Supercritical Carbon Dioxide: From Laboratory to Commercial Plant. *Green Chem.* **2003**, *5*, 99–104.
- (351) Amara, Z.; Bellamy, J. F. B.; Horvath, R.; Miller, S. J.; Beeby, A.; Burgard, A.; Rossen, K.; Poliakov, M.; George, M. W. Applying Green Chemistry to the Photochemical Route to Artemisinin. *Nat. Chem.* **2015**, *7*, 489–495.
- (352) Yavorsky, A.; Shvydkiv, O.; Limburg, C.; Nolan, K.; Delauré, Y. M. C.; Oelgemöller, M. Photooxygenations in a Bubble Column Reactor. *Green Chem.* **2012**, *14*, 888–892.
- (353) Bartusik, D.; Aebischer, D.; Ghafari, B.; Lyons, A. M.; Greer, A. Generating Singlet Oxygen Bubbles: A New Mechanism for Gas-liquid Oxidations in Water. *Langmuir* **2012**, *28*, 3053–3060.
- (354) Bartusik, D.; Aebischer, D.; Lyons, A. M.; Greer, A. Bacterial Inactivation by a Singlet Oxygen Bubbler: Identifying Factors Controlling the Toxicity of 1O_2 Bubbles. *Environ. Sci. Technol.* **2012**, *46*, 12098–12104.
- (355) Davidovits, P.; Kolb, C. E.; Williams, L. R.; Jayne, J. T.; Worsnop, D. R. Mass Accommodation and Chemical Reactions at Gas-liquid Interfaces. *Chem. Rev.* **2006**, *106*, 1323–1354.
- (356) Lambert, C.; Redmond, R. W. Triplet Energy Level of β -Carotene. *Chem. Phys. Lett.* **1994**, *228*, 495–498.
- (357) Clennan, E. L.; Wang, D.; Clifton, C. C.; Chen, M.-F. Geometry-dependent Quenching of Singlet Oxygen by Dialkyl Disulfides. *J. Am. Chem. Soc.* **1997**, *119*, 9081–9082.
- (358) Fu, Y.; Krasnovsky, A. A., Jr.; Foote, C. S. Quenching of Singlet Oxygen and Sensitized Delayed Phthalocyanine Fluorescence. *J. Phys. Chem. A* **1997**, *101*, 2552–2554.
- (359) Clennan, E. L.; Noe, L. J.; Wen, T.; Szneler, E. Solvent Effects on the Ability to Physically Quench Singlet Oxygen as Determined by Time-resolved Infrared Emission Studies. *J. Org. Chem.* **1989**, *54*, 3581–3584.
- (360) Foote, C. S.; Chang, Y. C.; Denny, R. W. Chemistry of Singlet Oxygen. XI. *Cis-trans* Isomerization by Singlet Oxygen and a Probable Quenching Mechanism. *J. Am. Chem. Soc.* **1970**, *92*, 5218–5219.
- (361) Foote, C. S.; Denny, R. W.; Weaver, L.; Chang, Y. C.; Peters, J. Quenching of Singlet Oxygen. *Ann. N. Y. Acad. Sci.* **1970**, *171*, 139–148.
- (362) Paddon, C. J.; Westfall, P. J.; Pitera, D. J.; Benjamin, K.; Fisher, K.; McPhee, D.; Leavell, M. D.; Tai, A.; Main, A.; Eng, D.; et al. High-level Semi-synthetic Production of the Potent Antimalarial Artemisinin. *Nature* **2013**, *496*, 528–532.
- (363) Schmid, G.; Hofheinz, W. Total Synthesis of Qinghaosu. *J. Am. Chem. Soc.* **1983**, *105*, 624–625.
- (364) Turconi, J.; Griolo, F.; Guevel, R.; Oddon, G.; Villa, R.; Geatti, A.; Hvala, M.; Rossen, K.; Göller, R.; Burgard, A. Semisynthetic Artemisinin, the Chemical Path to Industrial Production. *Org. Process Res. Dev.* **2014**, *18*, 417–422.
- (365) Baumann, M.; Baxendale, I. R. The Synthesis of Active Pharmaceutical Ingredients (APIs) Using Continuous Flow Chemistry. *Beilstein J. Org. Chem.* **2015**, *11*, 1194–1219.
- (366) Ravelli, D.; Protti, S.; Neri, P.; Fagnoni, M.; Albin, A. A. Photochemical Technologies Assessed: The Case of Rose Oxide. *Green Chem.* **2011**, *13*, 1876–1884.