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## SINGLET OXYGEN IN ORGANIC SYNTHESIS

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CONTENTS

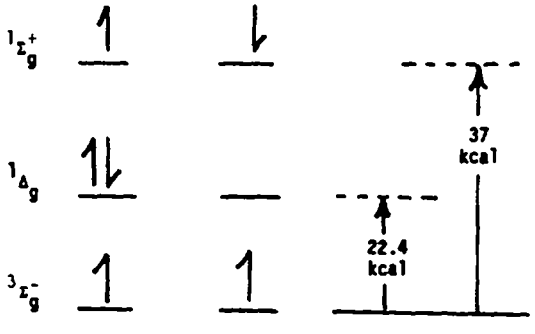


### I. INTRODUCTION

In recent years, there has been continuing widespread interest in the chemistry of singlet molecular oxygen following the demonstration that it is the active species in dye-sensitized photooxygenation. The large number of publications on this subject have been concerned with physical properties, chemical sources, studies on lifetimes, quenching effects, reactions with many different types of substrates and possible roles of singlet oxygen in biological processes.[2] In addition, the literature contains many accounts of the use of singlet oxygen as a reagent in organic synthesis.[3] These reports, starting with the early pioneering work of Schenck and Ziegler on the formation of (±)-ascaridole,[4] reflect the fact that singlet oxygen has served as an important preparative tool in the synthesis of many natural products and other compounds of special interest.

This review will illustrate the various uses of singlet oxygen in organic synthesis by selecting representative oxidations from among many examples, mostly in the natural product field. Through this presentation, we hope to show the possibilities available in the use of this versatile reagent for the preparation of many types of oxygenated intermediates. We have attempted to give as broad a coverage as is possible without providing an exhaustive compendium.

Singlet oxygen is the first excited electronic state of molecular oxygen ($^1\Delta g$) lying 22.4 kcal mol$^{-1}$ above the ground state triplet. The second singlet state ($^1\Sigma g^+$), 37 kcal mol$^{-1}$ above the ground state, is relatively short-lived ($10^{-12}$ sec) in solution due to a rapid spin-allowed transition to the longer-lived ($10^{-3}$–$10^{-6}$ sec) first excited state. The more stable singlet oxygen species ($^1\Delta g$) is considered to




HIGHEST OCCUPIED MOLECULAR ORBITALS OF $^1O_2$

Fig. 1

be the reactive intermediate in the photooxidation of organic compounds in solution. In the following discussion, we shall refer to the $^1\Delta g$ form of oxygen as "singlet oxygen" or $^1O_2$.

There are a number of methods for generating singlet oxygen in solution[2n] including the reaction of hydrogen peroxide with sodium hypochlorite,[5] the thermolysis of triaryl phosphite ozonides,[6] the decomposition of 9,10-diphenylanthracene peroxide,[7] and the dye-sensitized photochemical excitation of triplet oxygen.[8] The latter technique is, by far, the most efficient method and has been employed in the vast majority of synthetic applications of singlet oxygen. The mechanism for generating $^1O_2$ as proposed by Kautsky[8b] involves the excitation of an appropriate dye (such as Rose Bengal, methylene blue, bis-acenaphthalenethiophene or hematoporphyrin) with visible light to form the corresponding excited singlet state. Rapid intersystem crossing generates the excited triplet state of the sensitizer ($E_T \gg 22.4$ kcal mol$^{-1}$) which undergoes an energy transfer with triplet oxygen to form singlet oxygen ($^1O_2$), regenerating the ground state sensitizer.

Unlike the paramagnetic triplet oxygen, which takes part in free radical processes, the diamagnetic singlet oxygen undergoes two-electron reactions analogous to those of ethylene. The three most common modes of reaction of singlet oxygen with olefins are the ene reaction (A) leading to a hydroperoxide, the Diels–Alder type of cycloaddition (B) forming an endoperoxide, and the direct addition of $^1O_2$ to an activated double bond resulting in the formation of a 1,2-dioxetane (C) (Fig. 2).

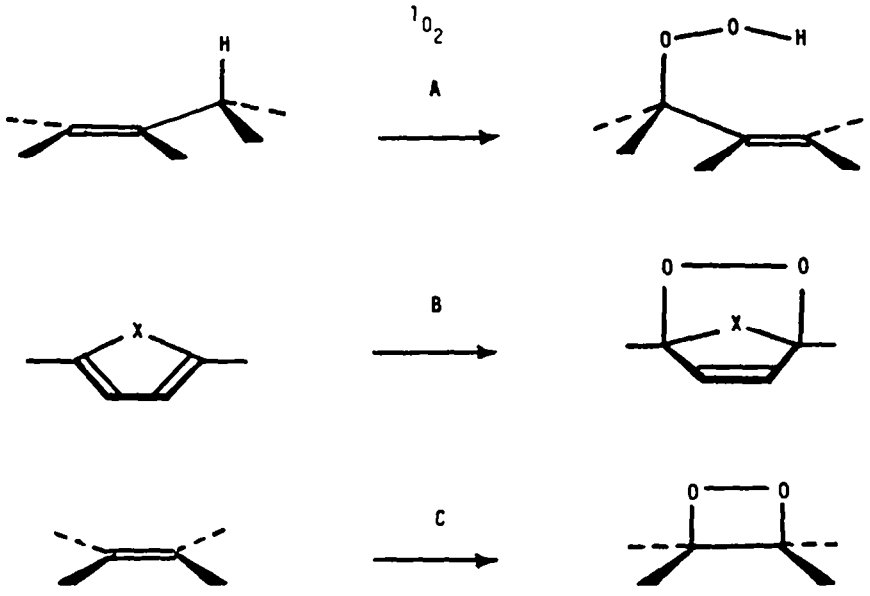



Fig. 2.

All three types of singlet oxygen reactions have been utilized in organic synthesis for the regiospecific and stereospecific oxidation of olefins. We will discuss each type separately using representative synthetic sequences and total syntheses.

## II. THE ENE REACTION

### (A) *General*

The ene reaction, by far the most widely investigated singlet oxygen reaction, involves the formation of an allylic hydroperoxide from an olefin by a process involving abstraction of an allylic proton along with migration of the carbon-carbon double bond. Reduction of the resulting allylic hydroperoxide (1) provides the corresponding allylic alcohol (Fig. 3, path a). In certain cases, the rearrangement of allylic alcohols has led to the regiospecific formation of olefins. Alternatively, allylic alcohols have been converted to *cis*-1,3-dienes for subsequent intramolecular Diels–Alder cycloadditions. In still other sequences allylic alcohols have been reduced to olefins or oxidized to $\alpha,\beta$-unsaturated ketones for subsequent Michael additions.

The initially formed allylic hydroperoxides have also been subjected to acid-catalyzed hydrolysis yielding dicarbonyl fragments, most probably through a Hock-type fragmentation[9] (path b) as will be

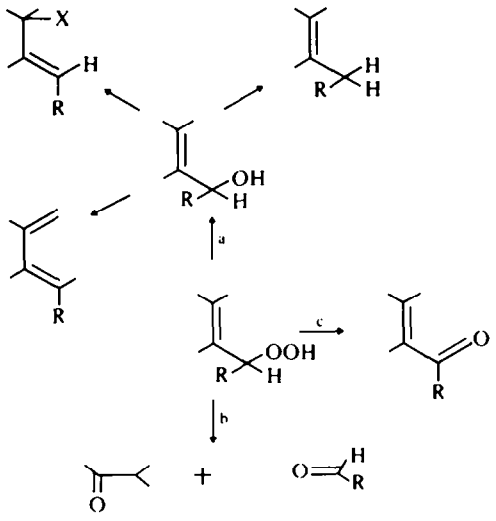


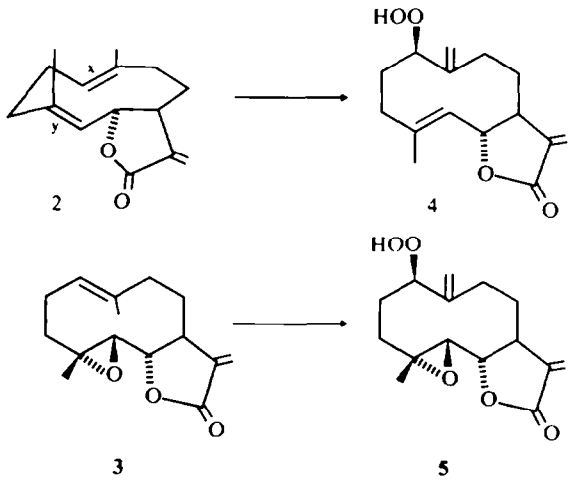
Fig. 3.

discussed later. The net effect of such a reaction is the oxidative cleavage of the starting C=C double bond. Alternatively, secondary allylic hydroperoxides have been converted directly to α,β-unsaturated ketones (path c).

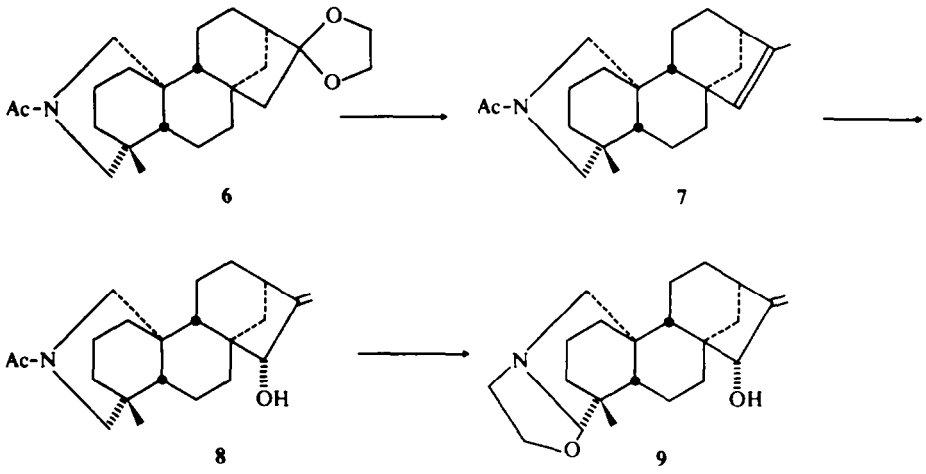
In some instances, the allylic hydroperoxides as naturally-occurring species have been primary targets of synthesis. Examples include the two novel cytotoxic germacranolides, peroxyconstunolide (**4**) and peroxyparthenolide (**5**)[10] (Scheme 1). These hydroperoxides were synthesized independently by the photooxygenation of the known germacranolides (**2** and **3**), respectively.[11] It is particularly interesting to observe the selectivity in the oxygenation of costunolide where only one of the trisubstituted double bonds (*x*) is affected. Presumably, the close proximity of the fused lactone ring represents an important steric factor inhibiting oxygen uptake at site *y*.

(B) *Naturally occurring allylic alcohols*

Naturally occurring allylic alcohols have also been prepared from olefin precursors utilizing a singlet oxygen ene reaction followed by reduction of the intermediate allylic hydroperoxide. As outlined below, the synthesis of garrya and atisine-type diterpene alkaloids utilized ene reactions for the introduction of the allylic alcohol functionality in the D-ring. Thus, Masamune's total synthesis of garryine (**9**) (Scheme 2) involved the formation of olefin (**7**) from the protected ketone (**6**). Photooxygenation of **7** gave, upon reduction, the allylic alcohol (**8**) as the single natural α-epimer.



Scheme 1.

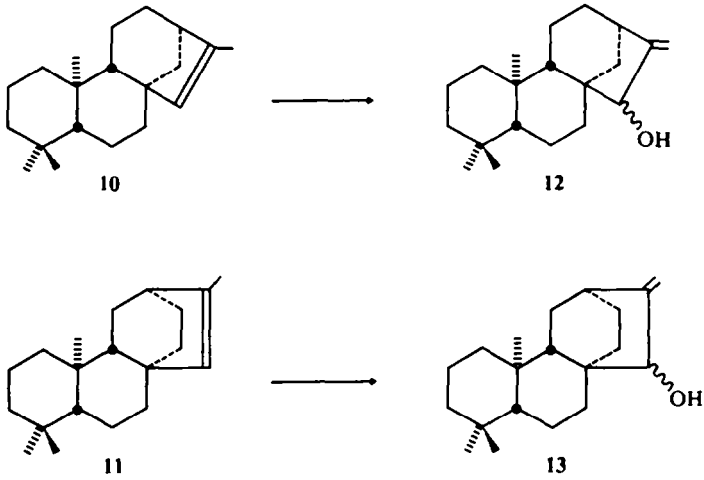



Scheme 2.

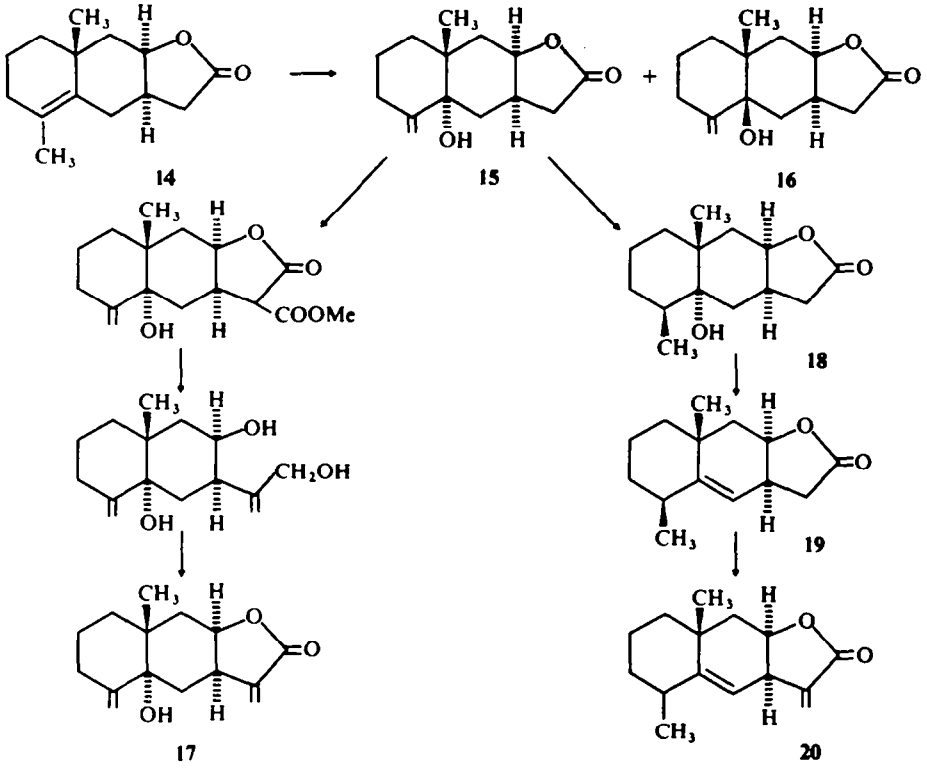
Further transformations leading to the construction of the oxazine ring completed the total synthesis of garryine (**9**).[12]

In similar studies in the field of diterpenoid alkaloids, Ireland *et al.*[13] utilized the photooxygenation of unsaturated olefin precursors in the synthesis of the C,D rings of garrya and atisine analogs (Scheme 3). In parallel sequences, the required endocyclic olefins (**10** and **11**) were prepared from D-ring ketones using standard reaction conditions. The formation of the desired allylic alcohols required a stereoselective method which would both preserve the bicyclic ring structure and yield a single, alcohol epimer. Photosensitized oxygenation was found to be the preferred method of oxidation. Contrary to the report by Masamune,[12] the photooxygenation of **10** and **11** proved to be nonstereoselective, affording both epimers of **12** and **13**. The lack of stereoselectivity was considered by the authors to be a minor complication since the undesired epimers could be sequentially oxidized to their corresponding ketones and selectively reduced to the desired natural isomers.[14]

The synthesis of eudesmane sesquiterpenes (±)-telekin and (±)-alantolactone by Marshall *et al.*[15] also employed an ene reaction as a method of introducing a bridgehead allylic alcohol (Scheme 4). The necessary unsaturated lactone (**14**), prepared in several steps from Hagemann's ester was photooxygenated and reduced to afford a mixture of epimeric allylic alcohols (**15** and **16**). Epimer **15** was converted to (±)-telekin (**17**) using the three-step methylenation sequence shown. Alternatively, **15** was stereoselectively hydrogenated to the hydroxylactone (**18**) which was subsequently converted




Scheme 3.



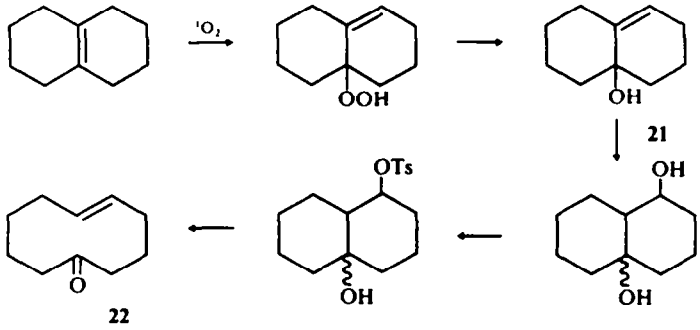
Scheme 4.

to its corresponding chloride and dehydrohalogenated to afford the unsaturated lactone (**19**). Using the same three-step methylenation sequence, **19** was converted to (±)-alantolactone (**20**).

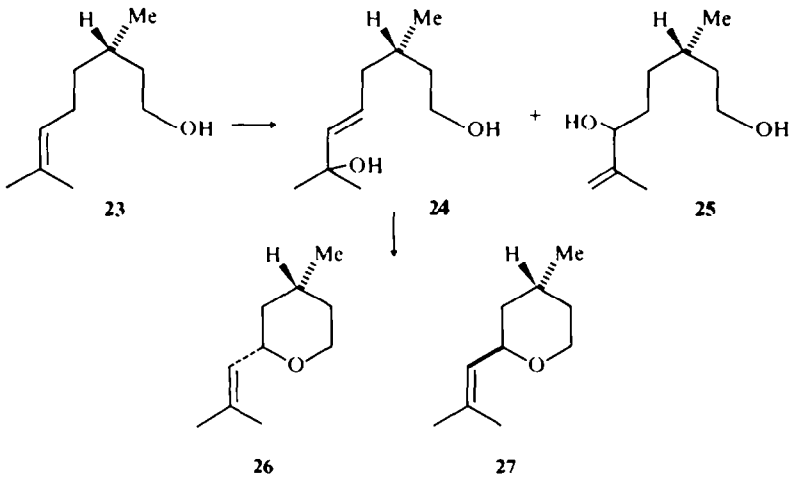
(C) *Allylic alcohols as intermediates*

Allylic alcohols, formed from singlet oxygen ene reactions, have also served as important intermediates for other types of synthesis. A classic example is provided by the synthesis of *trans*-5-cyclodecenone by Wharton *et al.*[16] (Scheme 5). Photooxygenation of $\Delta^9$-octalin provided, upon reduction with hydrazine, the desired $\Delta^{1(9)}$-10-octalol (**21**). Treatment with diborane followed by tosylation of the secondary alcohol provided 1,3-monotosylates which underwent stereoselective cleavage with base to form the *trans*-cyclodecenone (**22**).

Allylic alcohols formed by ene reactions may undergo rearrangement to afford a variety of regiospecific olefins. In an early example, the synthesis of the diastereomers of (−)-rose oxide (**26** and **27**) from (−)-citronellol (**23**) by Schenck *et al.*[17] utilized an $S_N2'$ displacement to differentiate a mixture of isomeric allylic alcohols (Scheme 6). Photooxygenation of **23** gave, upon reduction, a 3:2



Scheme 5.



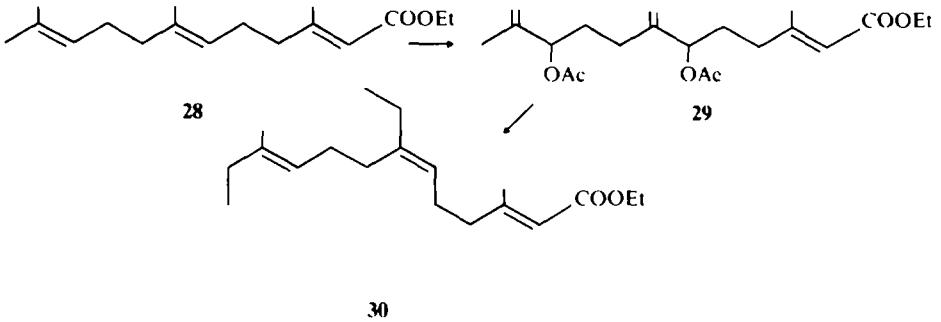

Scheme 6.

mixture of allylic alcohols (**24** and **25**) in nearly quantitative yield. Acidification resulted in selective cyclization of tertiary allylic alcohol (**24**) to the desired (−)-rose oxide (**26** and **27**) in 60% overall yield. The isolation of **23**, **26** and **27** and allylic alcohol (**25**) from Bulgarian rose oil suggests that the biogenetic pathway may be similar to the synthetic route employed by Schenck *et al.*[3a]

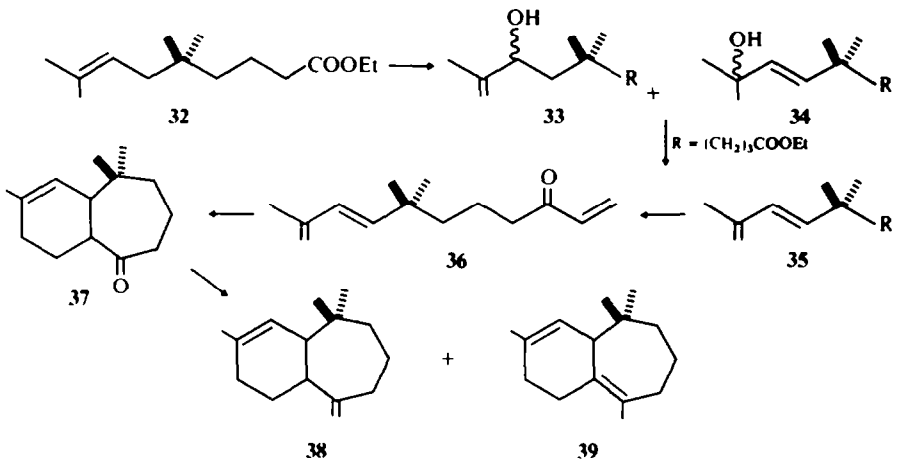
In a similar fashion, allylic alcohols have provided sites for nucleophilic substitution. Thus, Anderson *et al.*,[18] in their stereoselective synthesis of olefins from allylic acetates, prepared the insect juvenile hormone skeleton (**30**) from ethyl farnesoate (**28**) using a double ene reaction (Scheme 7). Photooxygenation of **28** afforded a diallylic hydroperoxide which could be reduced and acylated to form **29**. Introduction of methyl groups with lithium dimethylcuprate took place with $S_N2'$ displacement of the acetate residues, yielding a mixture of trienes containing 76% of the desired *trans,cis,trans*-isomer (**30**).

Allylic alcohols generated from ene reactions have also been employed in the regiospecific formation of 1,3-dienes. Wenkert *et al.*[19], in a synthesis of α- and β-himachalene, employed an ene reaction to construct an acyclic triene which could be cyclized by an intramolecular Diels–Alder cycloaddition (Scheme 8). The trisubstituted olefin (**32**) was photooxygenated to afford the allylic alcohols (**33** and **34**) after the usual reduction. Dehydration gave the desired diene (**35**) which was further transformed to the trieneone (**36**). A Lewis acid-catalyzed Diels–Alder reaction gave the *cis*-fused bicyclic ketone (**37**) which was converted to α- and β-himachalene (**38** and **39**) respectively.

Another potentially useful application of the ene reaction is found in the oxidation of *trans*-1,3-dienes. The initial uptake of singlet oxygen yields an intermediate hydroperoxy *cis*-1,3-diene which may then react with a second equivalent of $^1O_2$ in a Diels–Alder-type reaction to form the peroxide (**40**; Fig. 4).[2k,2m]




Scheme 7.




Scheme 8.

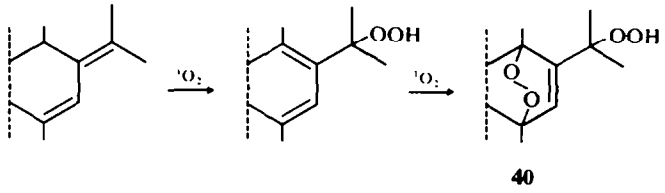
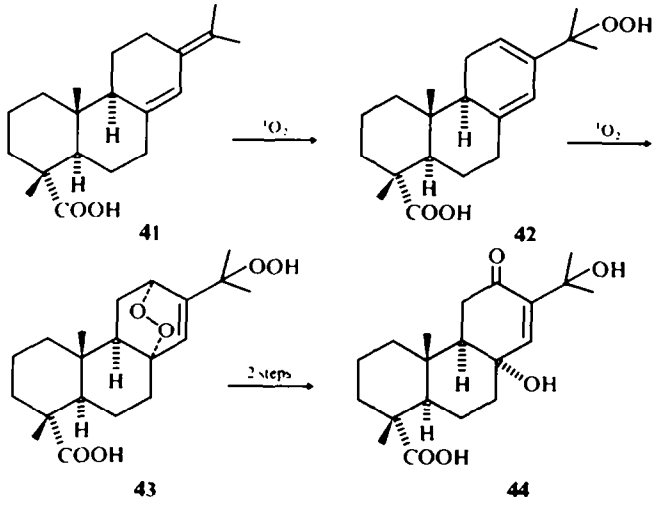



Fig. 4

Schuller and Lawrence[20] made use of this type of two-step oxidation in their work on the photooxygenation of the pine gum resin constituent, neoabietic acid (**41**) (Scheme 9). Initial reaction of **41** with singlet oxygen occurred exclusively at the tetrasubstituted olefin to form the allylic hydroperoxide (**42**) containing a *cis*-1,3-diene. Further oxidation at the site of the diene afforded the peroxide (**43**) which was selectively reduced and hydrolyzed to the highly functionalized $\gamma$-hydroxy-$\alpha,\beta$-unsaturated ketone (**44**).




Scheme 9.

In addition to the preparation of 1,3-dienes, the singlet oxygen ene reaction has also been utilized for the regiospecific synthesis of *mono* olefins.[21] For example, in a total synthesis of (±)-khusimone (**48**),[21a] Büchi *et al.*[21a] employed the ene reaction as a method for the contrathermodynamic isomerization of an olefin (Scheme 10). The required zizaene skeleton was constructed from triene (**45**) by a Diels–Alder cycloaddition followed by an acid-catalyzed Wagner–Meerwein rearrangement. The key tetrasubstituted olefin (**46**) was converted to the desired exocyclic, disubstituted olefins khusimone (**48**) and epikhusimone (**47**) by an ene reaction with $^1O_2$ followed by an interesting reduction[21b] of the epimeric allylic alcohols.

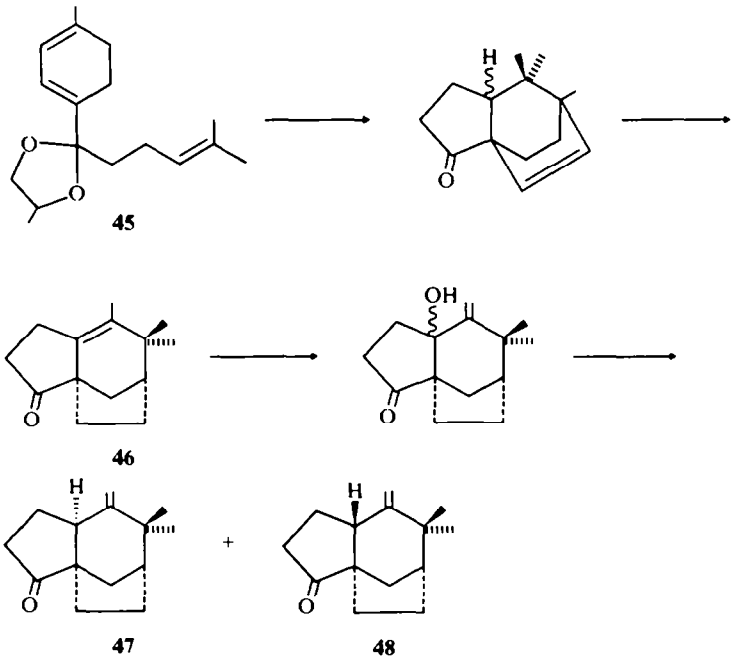
The ene reaction has also served in several natural product syntheses as a method of generating allylic alcohols which could then be oxidized further to reactive α′,β-unsaturated ketones. Ireland and Johnson[22] collaborated on synthesizing *dl*-germanicol (**53**) from the pentacyclic ketone (**52**) (Scheme 11). Olefin (**49**) gave, upon photooxygenation and reduction, the α-methylene allylic alcohol (**50**) which was then oxidized to the Michael acceptor (**50a**). This α,β-unsaturated ketone underwent conjugate addition to form **51** which was cyclized to **52** and converted to **53** in a further series of reactions.

In continued studies directed towards the total synthesis of pentacyclic triterpenes, Ireland *et al.*[23] again utilized an α-methylene ketone (**54**) formed by oxidation of the epimeric allylic alcohols resulting from a $^1O_2$ ene reaction (Scheme 12). Michael addition to the enone (**54**) and further steps leading to ketone (**55**) provided routes to frieldelin and β-amyrin-type triterpenes.

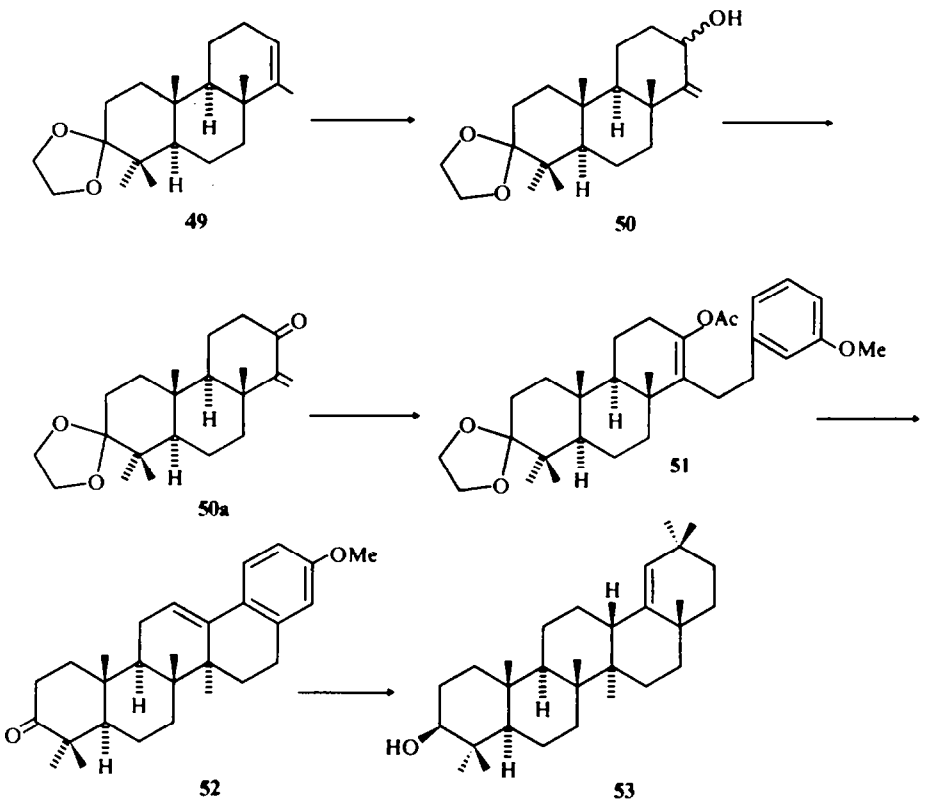
Heathcock *et al.*[24] employed similar chemistry in the synthesis of optically pure AB ring precursors to pentacyclic triterpenes (Scheme 13). The required bicyclic enone (**57**) was prepared from the olefin (**56**) using the same type of ene reaction, reduction, and reoxidation sequence employed previously by Ireland's and Johnson's groups.[22]

A more direct route to α,β-unsaturated ketones can take place by β-elimination of water from allylic hydroperoxides. Ireland *et al.*,[25] in their investigation of α-methylene ketones, studied the photooxygenation of the model systems (**58–60**) (Scheme 14) and the subsequent reactions of the intermediate allylic hydroperoxides with acetic anhydride. Decomposition of the intermediate allylic peracetates yielded the desired α-methylene ketones along with ring-expanded divinyl ethers. The elimination of acetic acid from the peracetates to form the desired α-methylene ketones (Scheme 15, path a) was accompanied by a Hock fragmentation[9] (path b) leading to the observed cyclic ethers.

Thomas[26] applied the above Hock-type fragmentation in his synthesis of (−)-geijerone (Scheme 16). The starting triene, (+)-γ-elemene contained three double bonds of varying reactivity towards the



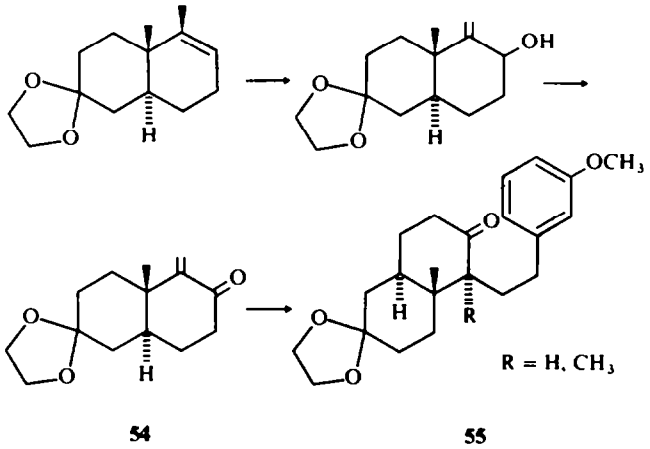

Scheme 10.



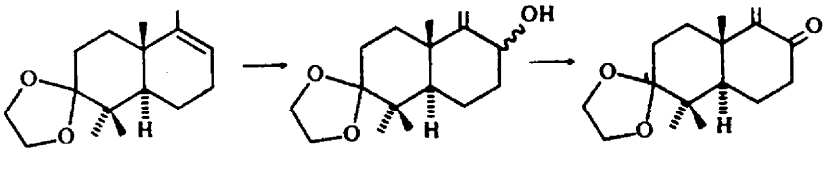

Scheme 11.

electrophilic singlet oxygen. Selective oxidation of the more electron-rich tetrasubstituted olefin with singlet oxygen gave a mixture of the three possible allylic hydroperoxides as shown. Acid hydrolysis of the mixture afforded the single product, (−)-geijerone (**61**), presumably by way of Hock fragmentations of the three different hydroperoxides.[27]

In special cases, the decomposition of intermediate allylic hydroperoxides yielded α,β-unsaturated ketones without competing Hock-type fragmentations.[28] Thus, in their total synthesis of α- and β-santonin, Marshall and Wuts[28a] employed such an ene reaction sequence for the introduction of the required dienone system (Scheme 17). Reaction of the *cis*-fused diene (**62**) with singlet oxygen proceeded by two pathways as might be predicted. A selective ene reaction at the site of the

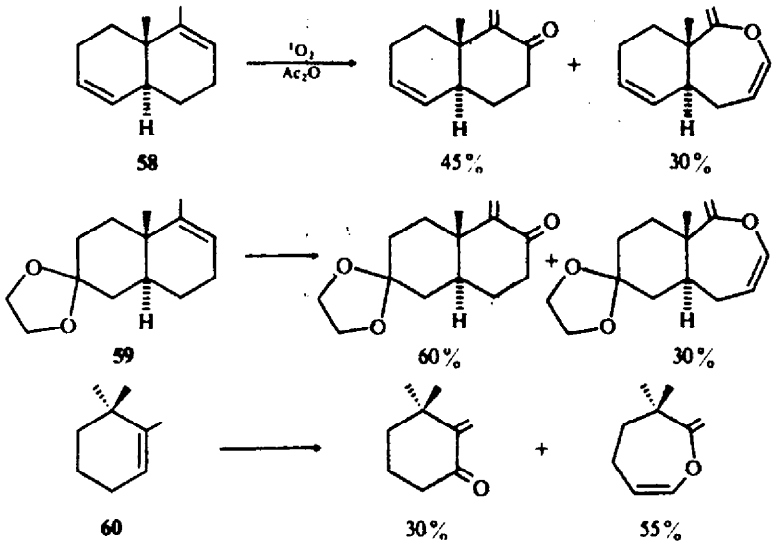



Scheme 12.



56 57

Scheme 13.

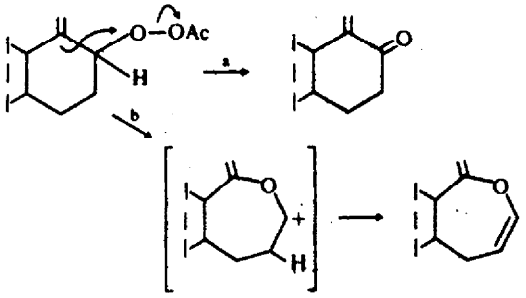


58 45% 30%

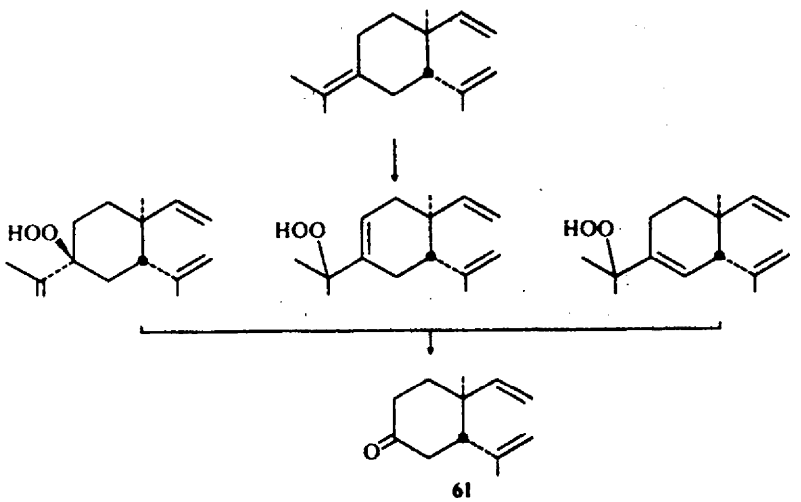
59 60% 30%

60 30% 55%

Scheme 14.



Scheme 15.



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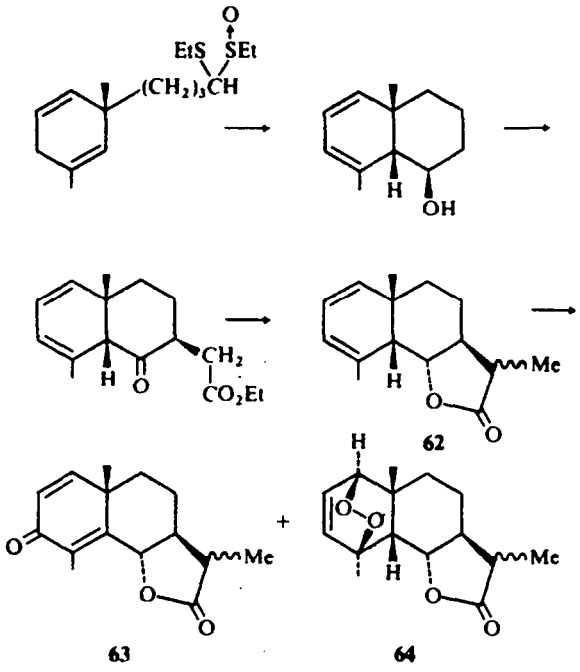
Scheme 16.



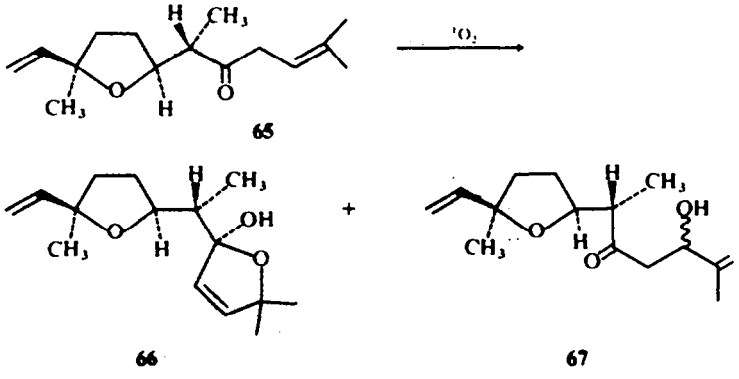
Scheme 17.

trisubstituted bond followed by loss of water from the diallylic hydroperoxide provided the desired α- and β-santonins (**63**) in 19% yield. Oxygenation of the diene in a Diels–Alder fashion provided the 1,4-endoperoxide (**64**) as a by-product.

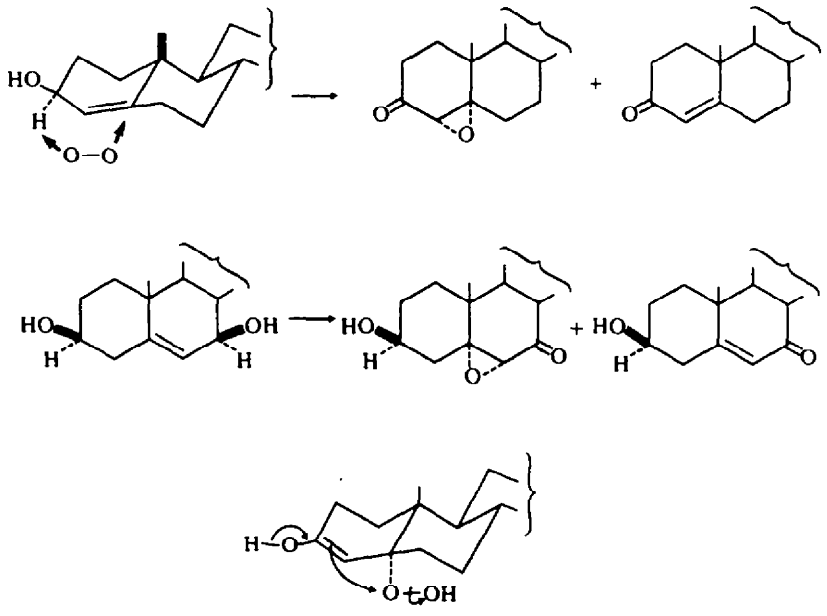
Thomas and Dubini,[29] in their investigation of the photooxygenation of davanone (**65**) (Scheme 18) obtained a mixture of two unstable hydroperoxides resulting from the two possible ene reactions. Reduction *in situ* with triphenylphosphine provided the allylic alcohol (**67**) and the hemiketal (**66**).

Allylic hydroperoxides have also served as key intermediates in the stereospecific conversion of allylic alcohols to α,β-epoxy ketones.[2k, 2m, 28] Nickon and Mendelson[30] found that the photooxygenation of allylic alcohols in $\Delta^4$- and $\Delta^5$-steroid systems yielded epoxy ketones stereospecifically, along with the corresponding α,β-unsaturated ketones (Scheme 19). Addition of $^1O_2$ to the double bond in a direction *cis* to the allylic hydrogen generated the corresponding enolic hydroperoxides. Fragmentation as shown (**68**) afforded the α,β-epoxy ketone, while loss of hydrogen peroxide gave the enone.

There has been special interest in the possibility that singlet oxygen-like oxidations may be involved in biogenetic processes.[31] In this regard, a report by Scott and Bedford[32] on the synthesis of 7-chlorodehydrotetracycline (**71**) is of interest in considering a possible biogenetic pathway for the



Scheme 18.



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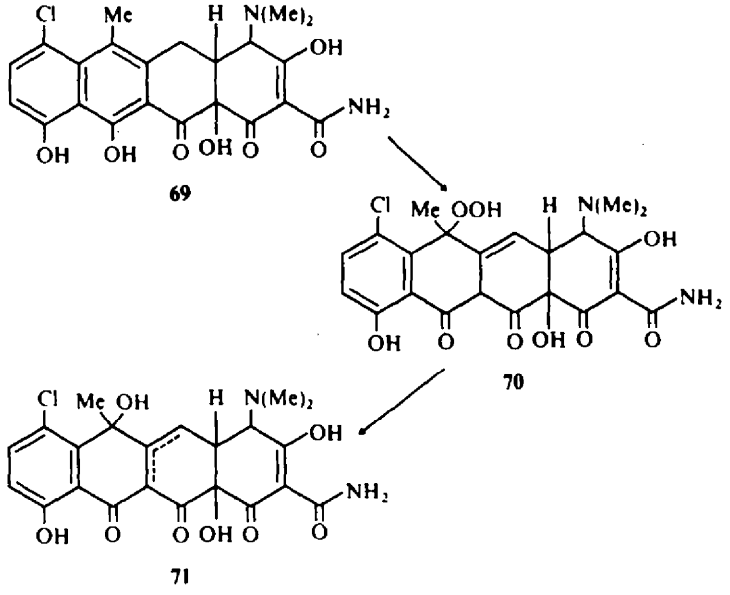
Scheme 19.



69 70 71

Scheme 20.

formation of tetracyclines (Scheme 20). Self-sensitized photooxygenation of 7-chloroanhydrotetracycline (**69**) resulted in the selective oxygenation of the C-6 position to form the hydroperoxide (**70**) having the naturally-occurring stereochemistry. Catalytic reduction of **70** provided the proposed biogenetic precursor (**71**) in quantitative yield.[33]

## III. THE DIELS–ALDER REACTION

The reactions of singlet oxygen with 1,3-dienes to form 1,4-endoperoxides have been widely investigated in both carbocyclic and heterocyclic systems.[33] This selective and stereospecific oxygenation of the terminal carbons of a 1,3-diene system has received wide application in synthesis.

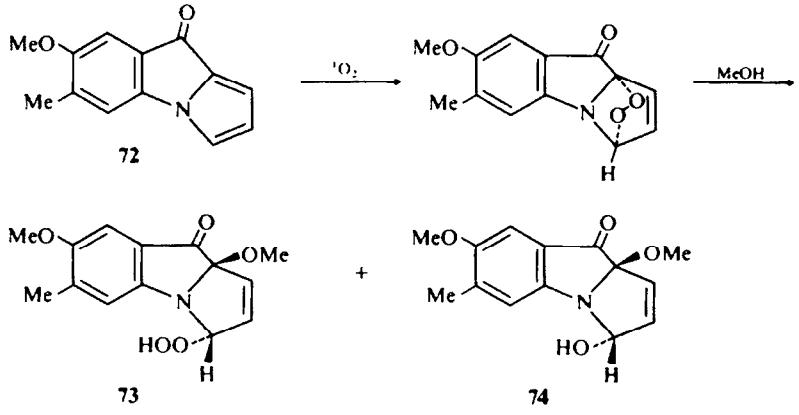
(A) *Heterocyclic dienes*[34]

The photooxygenation of pyrroles affords the corresponding 1,4-endoperoxides which can be further transformed into a variety of 2,5-oxygenated pyrrole derivatives depending on the choice of solvent, temperature and concentration. Both Franck[35] and Kametani[36] have employed this type of pyrrole oxidation in their studies on the synthesis of systems related to mitomycin (Scheme 21).

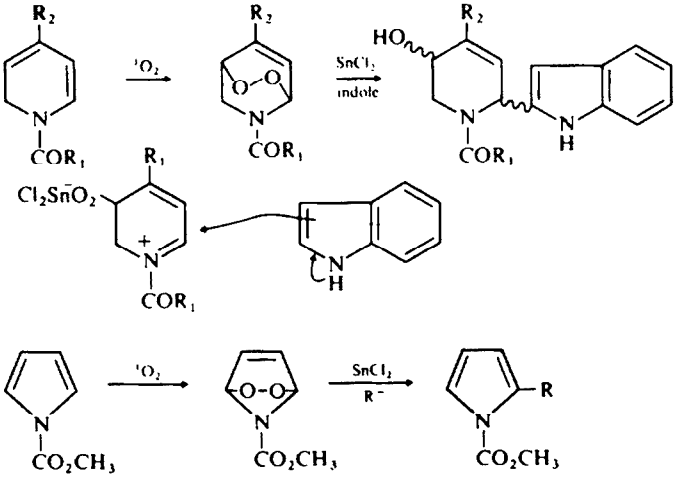
Dye-sensitized photooxygenation of the tricyclic pyrrole (**72**) gave the hydroperoxide (**73**) and the carbinolamine (**74**) most probably through the methanolysis of the intermediate endoperoxide.[36] It is possible that **74** could have formed by reaction of **73** with water.

Recent investigations by Natsume *et al.*[37] on the photooxygenation of pyrroles and dihydropyridines have provided new routes to pyrrole and pyridine derivatives. In particular, endoperoxides of 1,2-dihydropyridines[37a] reacted with nucleophiles in the presence of stannous chloride to give 2-substituted derivatives as shown in Scheme 22. Likewise,[37b] N-carbomethoxypyrrole reacted with singlet oxygen to give the corresponding 1,4-endoperoxide which was reacted with stannous chloride and a variety of carbon nucleophiles to give 2-substituted pyrroles as the major products.

The oxidation of furans with singlet oxygen has had widespread application in organic synthesis. This oxidation which takes place through an initial 1,4-endoperoxide, leads to many different types of



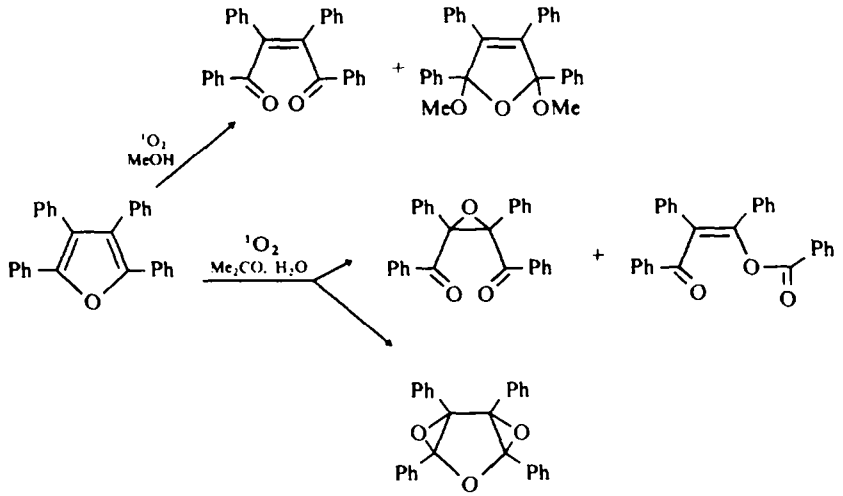

Scheme 21.



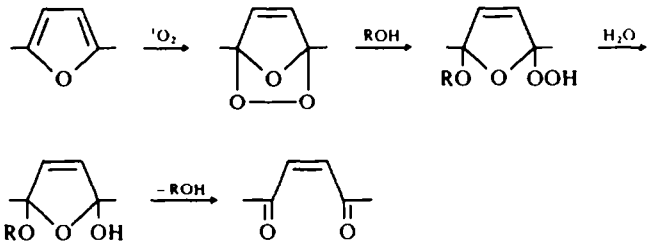

R = indole, N-methylpyrrole, silyl enol ethers

Scheme 22.

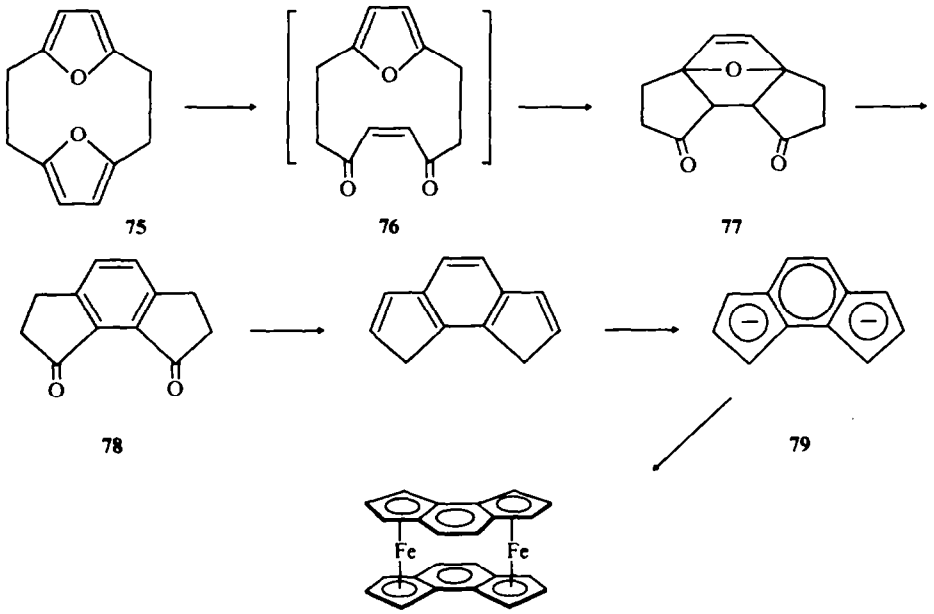
products depending on the reaction conditions. Thus, the intermediate peroxide may undergo solvolysis or rearrangement to yield 1,4-endiones, epoxy-1,4-diones, vinylic esters, *bis*-epoxides or cyclic ketals.[2k, 2m, 3] Scheme 23 illustrates the variety of oxidized products resulting from the reaction of $^1O_2$ with tetraphenylfuran.[38] In particular, the formation of enediones by the reaction of furans with singlet oxygen in alcoholic solvents appears to occur by the solvolysis of initially formed endoperoxides to yield alkoxy hydroperoxides which may be hydrolyzed to the corresponding enediones as shown in Scheme 24.[39]




Scheme 23.

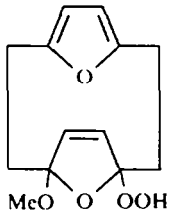



Scheme 24.

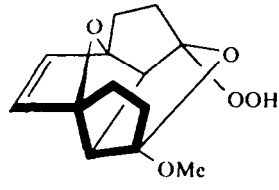



Scheme 25.

Thus, photooxygenation of the furanophane (**75**) in methanol appeared to take place through a mono-enedione (**76**) which underwent an intramolecular Diels–Alder reaction to form the polycyclic system (**77**). Treatment of **77** in either acid or base afforded the aromatic diketone (**78**) (Scheme 25).[40] Katz *et al.*[41] applied this sequence to a synthesis of the *cis*-indacenyl dianion (**79**) and its corresponding ferrocene (**80**) as shown in Scheme 25. The intermediacy of the methoxy hydroperoxide (**81**) was shown by the isolation of the Diels–Alder adduct (**82**).



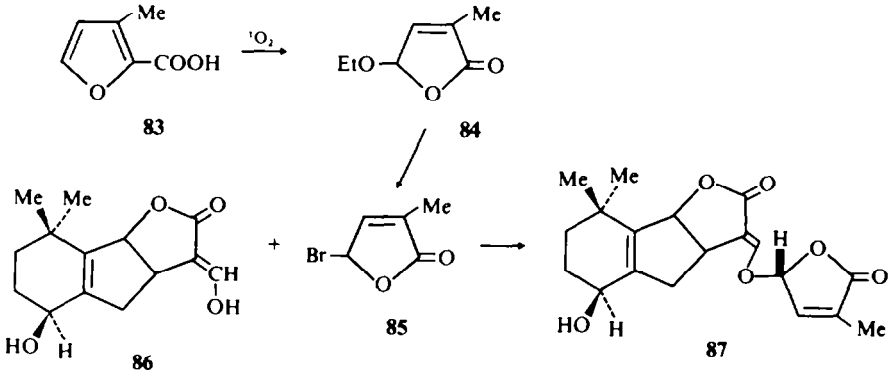

**81**




**82**

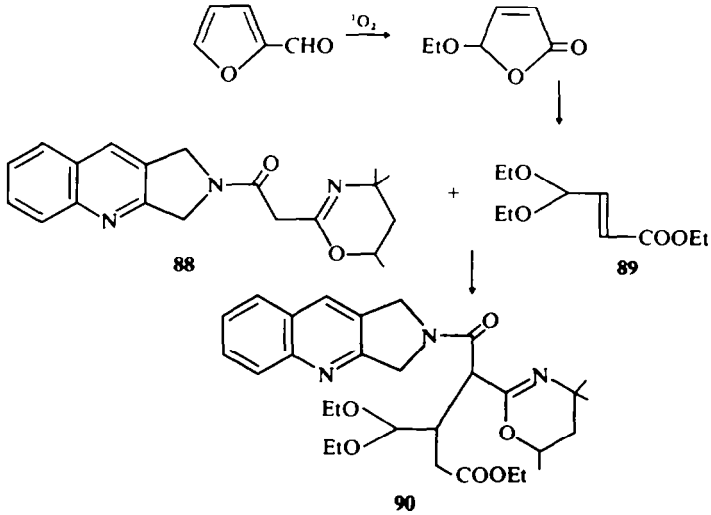
The conversion of furan endoperoxides to γ-alkoxy-α,β-unsaturated butyrolactones has been utilized by Sih *et al.*[42] in the total synthesis of *dl*-strigol (Scheme 26). Photooxygenation of 3-methyl-2-furoic acid (**83**) in ethanol yielded the lactone acetal (**84**) which was hydrolyzed to the corresponding lactol. Subsequent treatment with triphenylphosphine and carbon tetrabromide afforded bromobutenolide (**85**) which was used in the O-alkylation of the formylated lactone (**86**) to yield *dl*-strigol (**87**) and its epimeric (C-4′) 1,4′-epistrigol.

In a related furan oxidation, Meyers *et al.*[43] utilized the photooxygenation of 2-furfural to prepare **90**, a key intermediate in their synthesis of camptothecin (Scheme 27). Oxygenation of furfural in




**83** **84** **85** **86** **87**

Scheme 26.

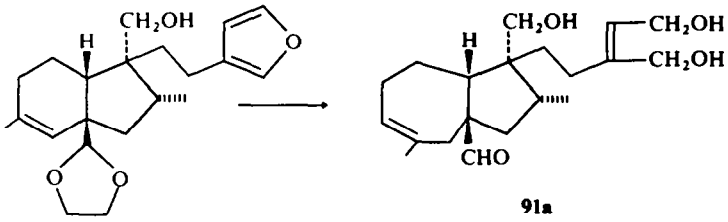



**88** **89** **90**

Scheme 27.

ethanol afforded a butenolide which underwent ethanolysis to the acetal ester (**89**). Reaction of **89** and **88** provided the Michael addition product (**90**) which was converted to campothecin.

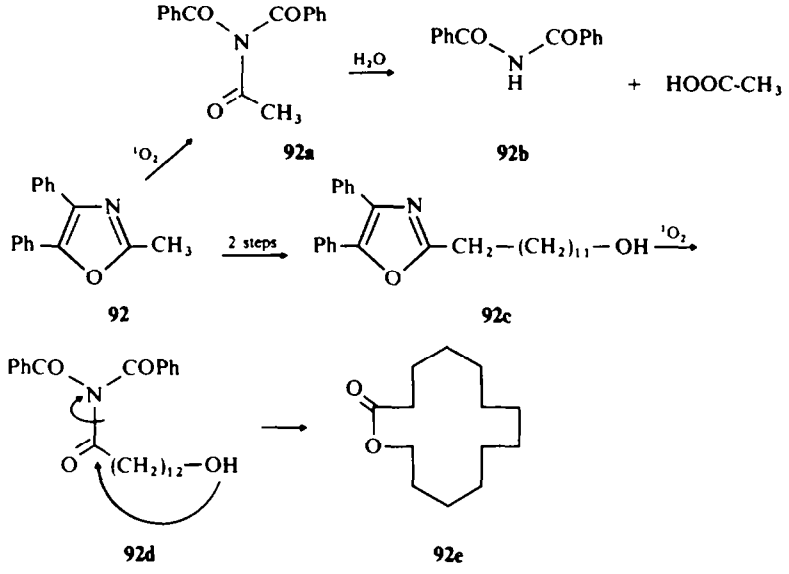
The photooxygenation of furans has also been employed as a route to 1,4-enediols, as illustrated in the work of Tokoroyama *et al.*[44] leading to the synthesis of portulal (**91a**).




**91** **91a**

Oxidation of the intermediate furan derivative (**91**) afforded the endoperoxide which was reduced with vitride to the corresponding 1,4-enediol. Removal of the protecting group gave portulal (**91a**).

While the reactions of oxazoles with singlet oxygen can lead to varied products, depending on solvent and substituents, the oxidation most generally results in formation of triamides.[34a-e] This rearrangement thus provides a means of generating a latent carboxyl group. In the case of 2-methyl-4,5-diphenyloxazole (**92**) the reaction leads to the triamide (**92a**) which can undergo hydrolysis to the diamide (**92b**) by selective attack at the less-hindered acetyl CO. The oxazole photooxidation has been adapted to the synthesis of lactones by the sequence shown in Scheme 28.[45]



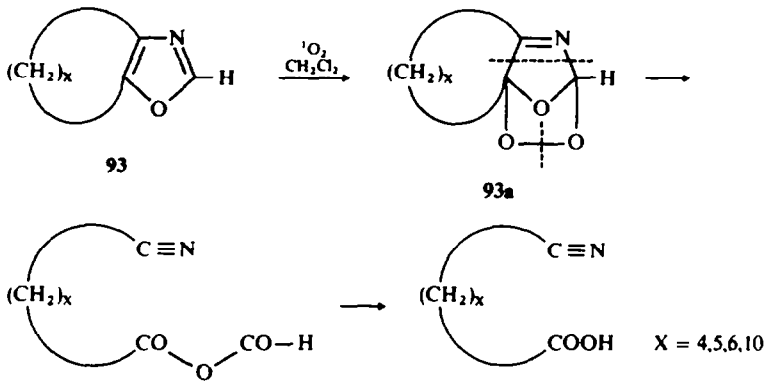

**92a** **92b** **92** **92c** **92d** **92e**

Scheme 28.

Alkylation of **92**, using LDA at $-78°$, with the THP ether of 11-iodo-1-undecanol followed by deprotection of the alcohol, yielded the $\omega$-hydroxy oxazole (**92c**). Reaction of **92c** with singlet oxygen in methylene chloride yielded the triamide (**92d**) which, on warming in benzene under acid catalysis gave a high yield of tridecanolide (**92d**). The ready participation of oxazoles in Diels–Alder reactions with singlet oxygen (and possibly other reactive dienophiles) thus permits their use for the protection of the carboxyl function. The advantage of this method lies in the mild, selective nature of the photooxidation step for deprotection and in the fact that the carboxyl function which is unmasked is in a highly activated (triamide) form.

Fused ring oxazoles of type **93** undergo a different type of oxidative breakdown in nonpolar solvents. The initially formed endoperoxide (**93a**) undergoes cleavage at the 2–3 and 4–5 positions of

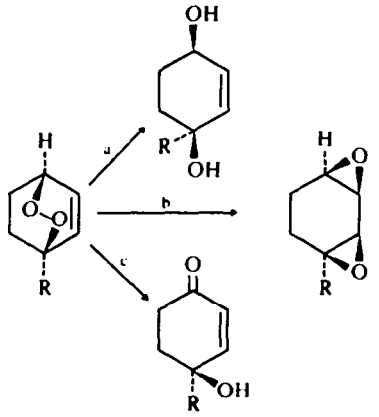
the oxazole ring forming cyano-anhydrides,[4,5] which may undergo hydrolysis or loss of CO. This sequence has been adapted to a synthesis of ω-cyano carboxylic acids in high yields (70–90%) as shown in Scheme 29.[34c]



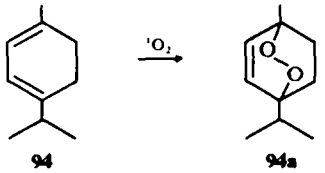

Scheme 29.

(B) *Carbocyclic and acyclic* 1,3-*dienes*

The reactions of 1,3-dienes and their carbocyclic analogues with singlet oxygen have been extensively investigated in organic synthesis.[2,3] The formation of intermediate 1,4-endoperoxides provides a general route to 1,4-oxygenated systems (Fig. 5). In path a, for example, reduction of the O–O bond of these endoperoxides provides *cis*-1,4-enediols which may be further reduced to saturated *cis*-1,4-diol derivatives. Alternatively (path b), the 1,4-endoperoxides may be thermally rearranged to *cis*-diepoxides. In path c, certain endoperoxides can be transformed to regio- or stereospecific 4-hydroxyenone systems which, in the case of acyclic dienes, can be dehydrated to furans.




The synthesis of (±)-ascaridole by Schenck and Zielger,[4] one of the first examples of the use of singlet oxygen in organic synthesis, is a classic application of the Diels–Alder-singlet oxygen reaction. The photooxygenation of α-terpene (**94**) afforded the naturally-occurring endoperoxide, (±)-ascaridole (**94a**) in nearly quantitative yield.




**94** **94a**

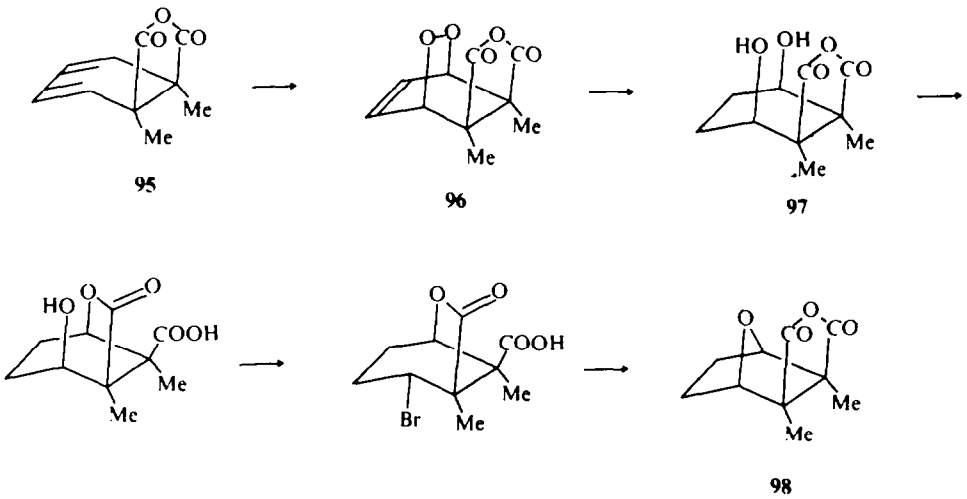
(C) *Reduction of endoperoxides to* 1,4-*diols*

Schenck also employed the Diels–Alder singlet oxygen reaction as a method for introducing a 1,4-diol system stereospecifically in his synthesis of cantharidin (**98**) (Scheme 30).[46] Photooxygenation of **95** afforded **96** containing an endoperoxide bridge in the desired *cis*-relationship to the anhydride ring. Catalytic hydrogenation provided the 1,4-diol (**97**) which was then transformed to the ether-anhydride (**98**).

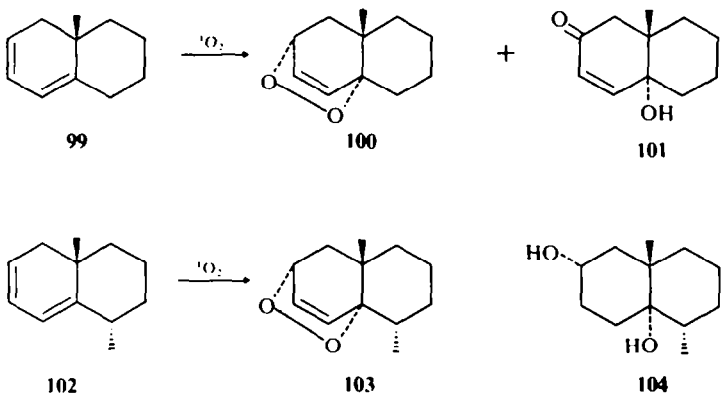
The more recent stereoselective synthesis of (±)-cybullol (**104**) by Ayer and co-workers[47a] also utilized this Diels–Alder reaction to generate the required *cis*-diol in a *trans*-fused octalin system (Scheme 31). Photooxygenation of the model 10-methyl hexalin (**99**) gave stereoselectively the endoperoxide (**100**) and the hydroxy enone (**101**). This steric effect of the angular 10-Me group was also observed in the photooxygenation of the hexalin (**102**), forming the endoperoxide (**103**) with the required *trans* ring juncture. This peroxide was then reduced to give (±)-cybullol (**104**).[47b]

(D) *Rearrangement of endoperoxides to diepoxides*

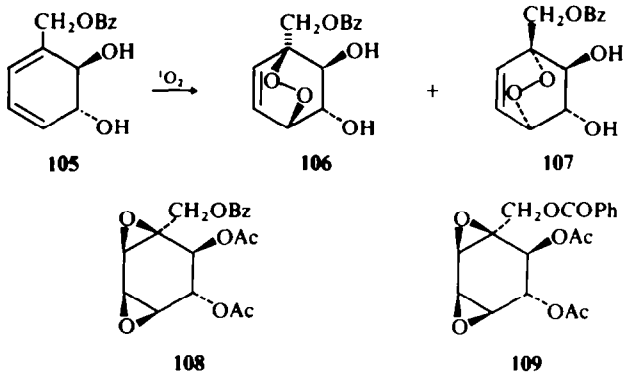
The thermal rearrangement of 1,4-endoperoxides to *cis*-1,3-diepoxides has had direct application in the synthesis of the (±)-crotepoxide family of naturally occurring 1,3-diepoxides which exhibit tumor-inhibiting, antileukemic, and/or antibiotic activity. One of the first examples of the use of this reaction is found in the synthesis of (±)-crotepoxide (**109**) by White *et al.*[48] (Scheme 32). The cyclohexadiene (**105**) was photooxygenated to give a mixture of unstable endoperoxides (**106** and **107**). Acetylation and




Scheme 30.



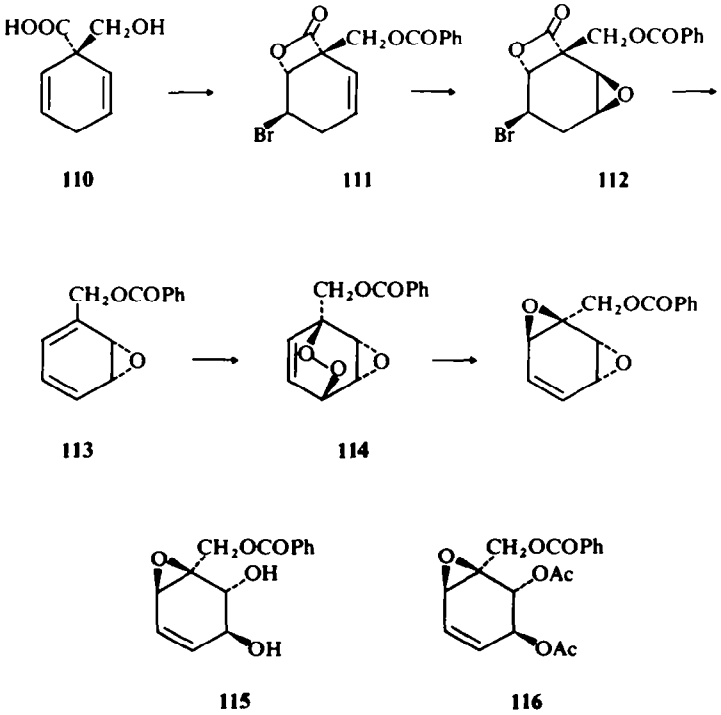

Scheme 31.



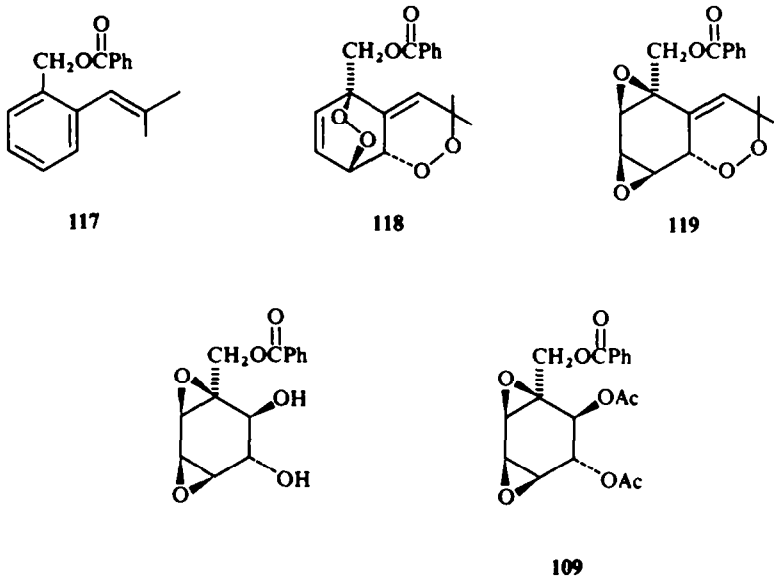

Scheme 32.

heating afforded the diepoxide (**108**), resulting from thermal rearrangement of (**106**). (The endoperoxide (**107**) was reputed to yield only an undesired aromatic system, rather than the corresponding diepoxide). Hydrogenolysis and benzoylation of **108** gave the desired (±)-crotepoxide (**109**). In a related investigation by Ganem *et al.*[49] on the synthesis of senepoxide (**116**), the required *cis*-1,3-diepoxide was introduced through a $^1O_2$-Diels–Alder reaction. (Scheme 33). The arene oxide (**113**) was prepared by a four-step sequence from the cyclohexadiene (**110**) *via* the β-lactones (**111**) and (**112**). Photooxygenation of **113** afforded a single crystalline *trans*-endoperoxyepoxide (**114**) which was reduced regioselectively and then hydrolyzed to afford a mixture of isomeric diols. Separation of the diols and acetylation of isomer **115** gave *dl*-senepoxide (**116**).

Along similar lines, Matsumoto *et al* found that derivatives of β,β-dimethylstyrene undergo dye-sensitized photooxygenation to yield *bis*-endoperoxides resulting from addition of two molecules of singlet oxygen.[50,51] The observation that these systems isomerize easily on heating to the corresponding diepoxy endoperoxides provided a basis for a synthesis of (±)-crotepoxide (**109**) (Scheme 34).[51] The styrene derivative (**117**) consumed two equivalents of singlet oxygen in successive 1,4-additions to yield a mixture containing **118** and its epimer. On heating the peroxide **118**, it was




Scheme 33.




117 118 119

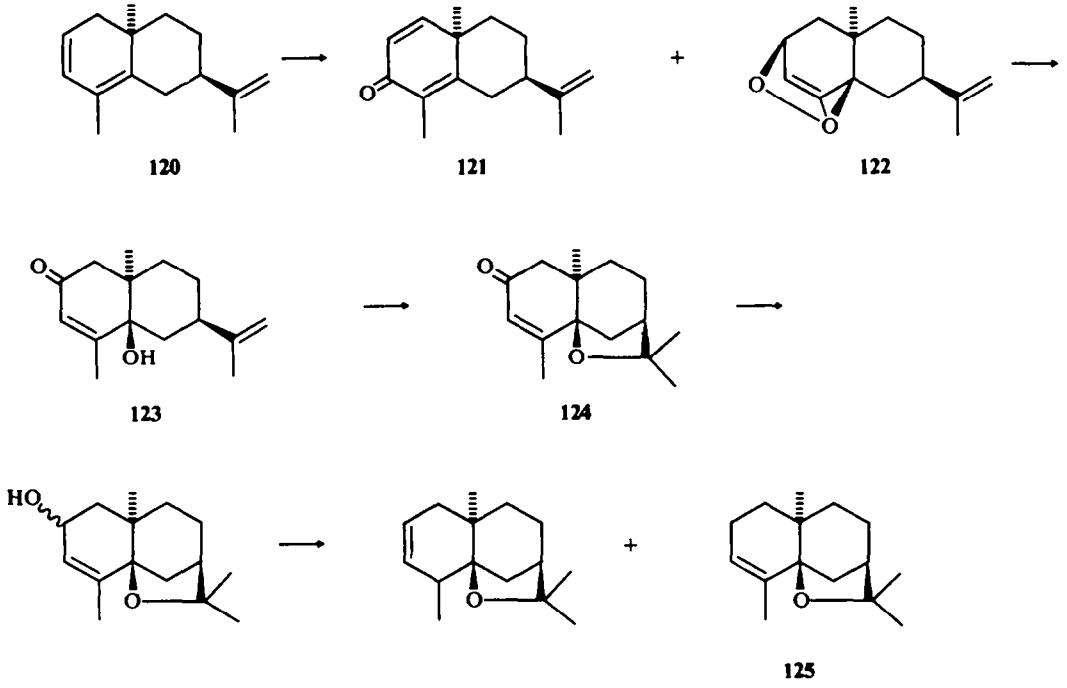
109

Scheme 34.

converted to the diepoxide (**119**) which was then converted to **109** by ozonolysis, reduction and acetylation.

(E) *Formation of Hydroxy Enones*

In addition to the synthesis of 1,4-diols and 1,3-diepoxides the photooxygenation of dienes provides a route to 4-hydroxy enone systems by $\beta$-elimination of intermediate endoperoxides.[52,53] The synthesis of $\alpha$-agarofuran by Barrett and Büchi[52] employed such a photooxygenation of a homoannular diene as a means of introducing a bridgehead hydroxyl group stereoselectively (Scheme 35). The required triene **120**, derived from (−)-epi-$\alpha$-cyperone, was reacted with singlet oxygen to afford the endoperoxide (**122**) as the major product. The minor product, trienone (**121**) resulted from a competing ene reaction. On treatment with basic alumina, the endoperoxide (**122**) was converted to hydroxy ketone (**123**)




120 121 122

123 124

125

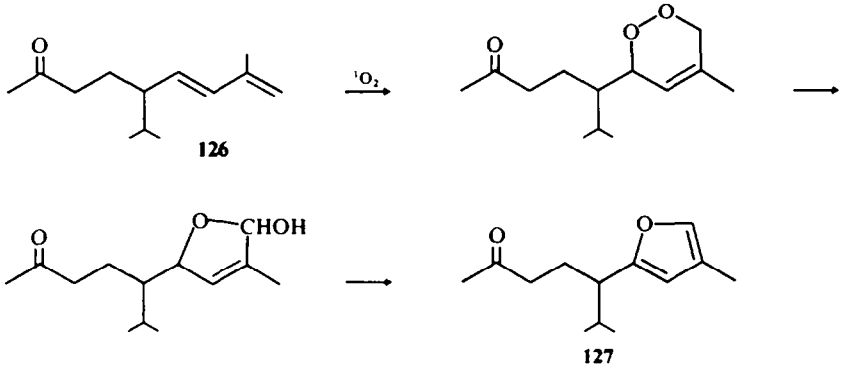
Scheme 35.

bearing the desired hydroxyl group in the α-configuration. Subsequent cyclization to **124** and reduction gave α-agarofuran (**125**).

(F) *Formation of furans*

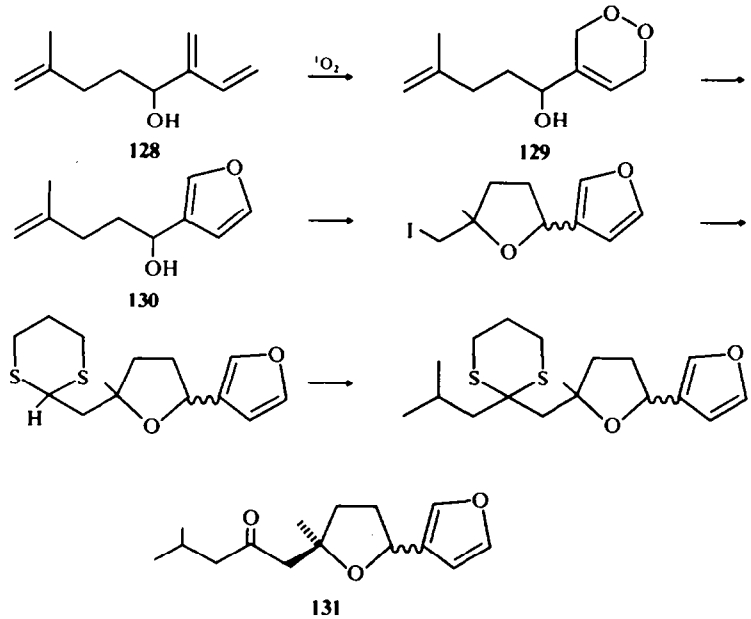
Unlike cyclic 1,3-dienes, simple acyclic 1,3-dienes react with singlet oxygen to afford endoperoxides which can be rearranged and dehydrated to furans. The usefulness of this procedure has been demonstrated in a number of furanoterpene syntheses. Demole *et al.*[54] first illustrated the application of this photooxygenation-dehydration sequence in their biomimetic conversion of solanone (**126**) to solanofuran (**127**), a flavor constituent of *Burley* tobacco (Scheme 36). The endoperoxide resulting from the oxygenation of **126** undergoes a β-elimination on treatment with alumina to form a hydroxy aldehyde, which undergoes dehydration thermally or with silica gel forming **127**.

More recently, Kondon and Matsumoto[55] have utilized this method for converting dienes to furans in the synthesis of a variety of furanoterpenes. The synthesis of the phytoalexin (±)-ipomeamarone and its epimer is representative of the preparation of compounds of this type (Scheme 37).[55c] Dye-sensitized photooxygenation of the monoterpene alcohol (**128**) afforded the cyclic peroxide (**129**) (70%). Decomposition of the endoperoxide followed by cyclization and dehydration gave the furan intermediate (**130**). Subsequent elaboration of the cyclic ether and ketone side chain




**126** **127**

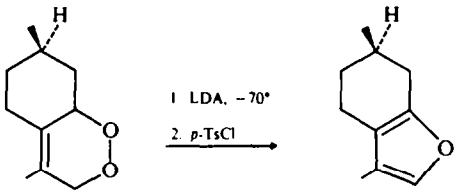
Scheme 36.




**128** **129** **130** **131**

Scheme 37.

gave (±)-ipomeamarone and epiipomeamarone (**131**). Harirchian and Magnus[56] in related studies have reported the synthesis of fused furanoterpenes such as *p*-menthofuran (**132**) from the corresponding endoperoxide using a mild, non-acidic dehydration sequence (Scheme 38).




**132**

Scheme 38.

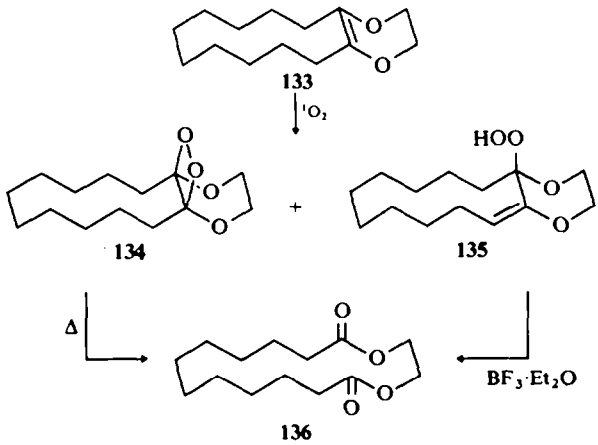
## IV. ADDITIONS TO ACTIVATED DOUBLE BONDS

### 1,2-*Dioxetanes*

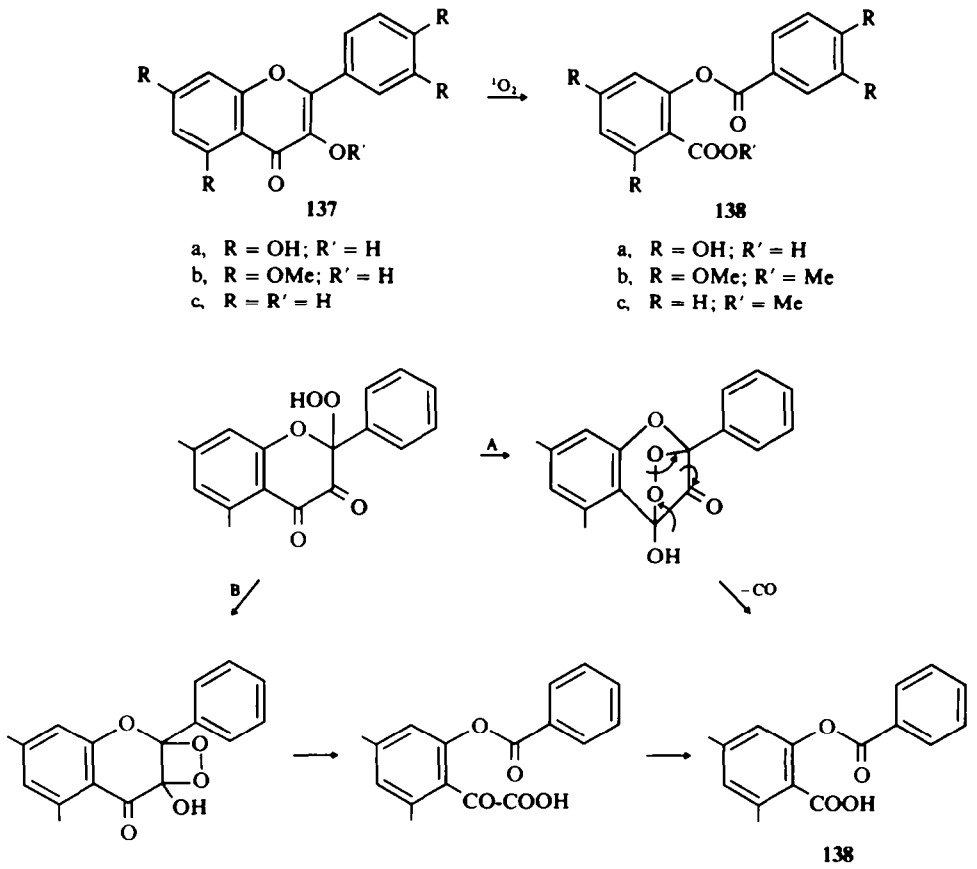
The formation of 1,2-dioxetanes by singlet oxygen addition to double bonds is usually limited to highly strained or electron-rich olefins such as vinyl sulfides, enol ethers, enamines or alkyl-substituted alkenes which do not take part in an "ene" reaction. These unstable peroxides normally decompose on warming to form carbonyl products resulting from the oxidative cleavage of the original C=C double bond.[57] Because of the restriction of this type of oxygenation to specific types of olefinic systems, applications of the dioxetane-singlet oxygen reaction in synthesis have been limited.

The oxidation of enol ethers with singlet oxygen has been investigated by Foote, Schaap and others[2] and has been reported to yield a mixture of 1,2-dioxetanes and allylic hydroperoxides resulting from competing 1,2-addition and ene reaction, respectively. An imaginative use of this reaction was reported by Becker and Ohloff[58] as a method for introducing a *bis*-lactone functionality in a synthesis of a macrocyclic musk fragrance (Scheme 39). Cyclododecanone was converted in several steps to the dihydropyran (**133**). Subsequent photooxygenation gave the expected mixture of dioxetane (**133**) and allylic hydroperoxide. Conversion of both components of this mixture to the desired *bis*-lactone (**136**) involved the thermolysis of **134** and the $BF_3$·etherate-promoted Hock fragmentation[9] of **135**.

In other investigations by Matsuura *et al.*[59] on the photooxygenation of 3-hydroxyflavanones, products were obtained which appeared to have resulted from dioxetane intermediates (Scheme 40). Irradiation of flavanones (**137**) in the presence of a sensitizer gave depsides (**138**) resulting from the addition of one mole of oxygen and the loss of one mole of carbon monoxide. Formation of **138** could result from cyclization of an intermediate hydroperoxide followed by decomposition of the cyclized




Scheme 39.



137

a, R = OH; R′ = H
b, R = OMe; R′ = H
c, R = R′ = H

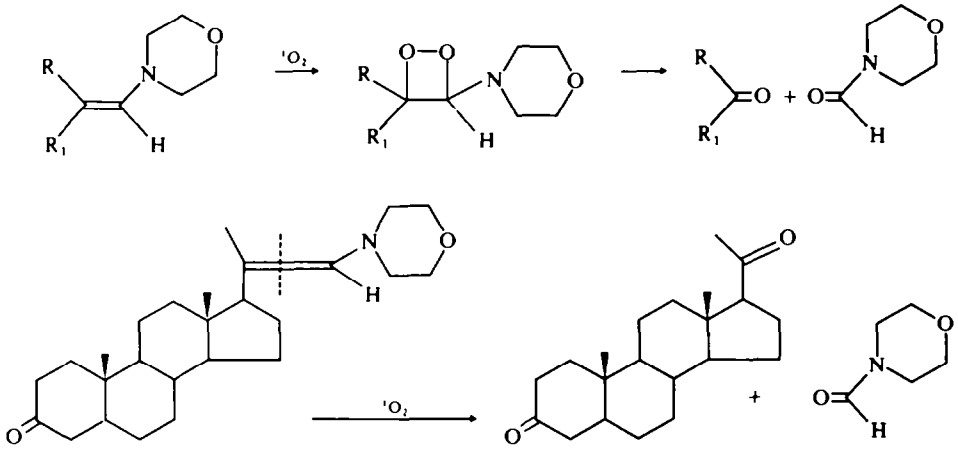
138

a, R = OH; R′ = H
b, R = OMe; R′ = Me
c, R = H; R′ = Me

Scheme 40.

peroxide with loss of carbon monoxide as shown (path A). Alternatively (path B), a dioxetane formed by addition of $^1O_2$ to the carbon–carbon double bond could cleave to form an α-keto acid which, after loss of carbon dioxide and oxidation of the intermediate aldehyde, would yield **138**. Such a mechanism has been proposed as a nonenzymatic pathway for the biological oxidation of quercetin (**137a**).[31]

The oxidation of enamines by singlet oxygen has also had application in synthesis. Early reports by Foote *et al.*[60a] and by Huber[60b] demonstrated that enamines of aldehydes react with singlet oxygen, presumably through dioxetane intermediates, to give high yields of amide and carbonyl fragments resulting from the oxidative cleavage of the enamine carbon–carbon double bond (Scheme 41).[60]



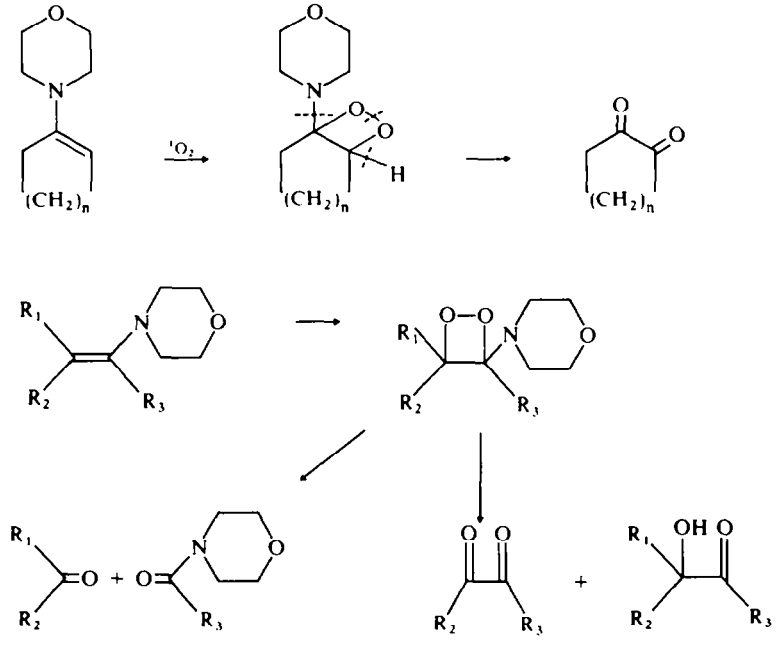
139

Scheme 41.

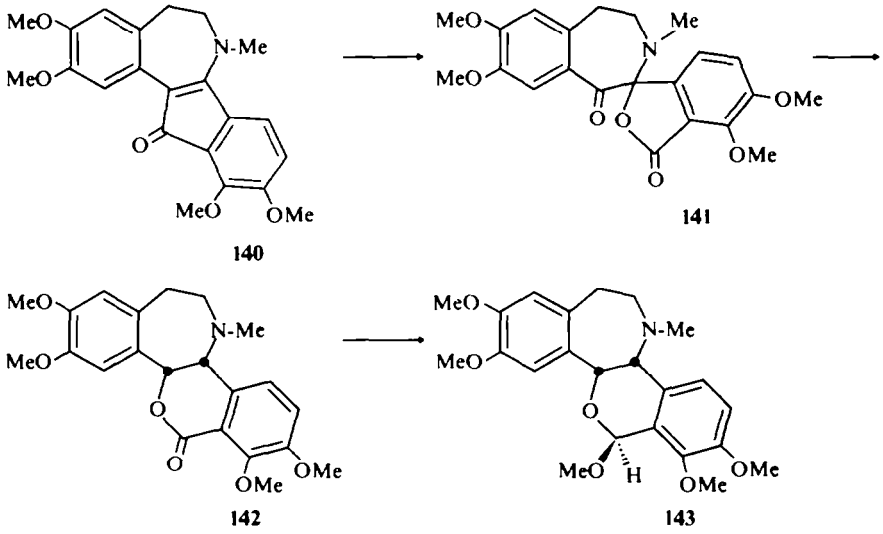
Huber demonstrated the usefulness of this reaction in the formation of testosterone (**139**) from an enamine precursor.[60b]

Subsequent studies by Wasserman and Terao[61] demonstrated that enamines of cyclic ketones also formed dioxetane intermediates when reacted with singlet oxygen. However, these dioxetanes were found to decompose, not to cleavage products as observed in the open-chain cases, but to α-diketones. More recently, Ando *et al.*[62] as well as Wasserman and Ives have found that enamines derived from acyclic ketones react with singlet oxygen to form mixtures containing both cleavage products and α-diketones (Scheme 42).[63]

Orito *et al.*[64] employed an enamine photooxygenation in their elegant synthesis of the rhoeadine alkaloid, (±)-*cis*-alpinine (**143**) (Scheme 43). Photooxygenation of **140** gave not the expected cleavage or α-oxygenated products previously observed but, instead, the novel spiro-ketolactone (**141**) as



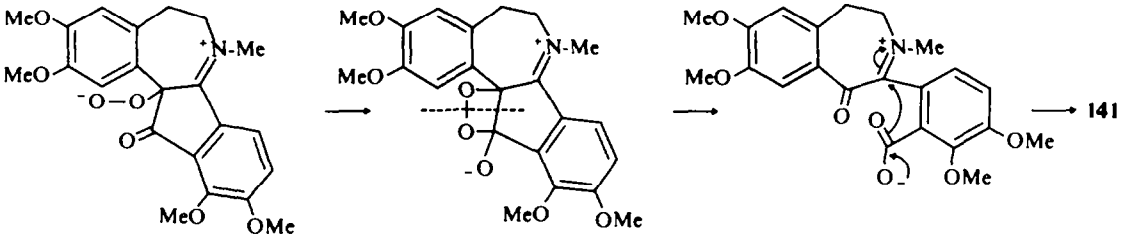
Scheme 42.



Scheme 43.

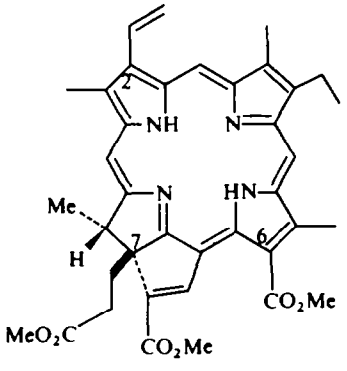
shown in Scheme 44. This reaction outcome can be explained by picturing initial addition of singlet oxygen to the enamine double bond followed by closure of the zwitterionic intermediate (**140a**) to the alkoxy dioxetane. Cleavage of the dioxetane and addition of the carboxylate anion to the iminium salt would produce **141**. Subsequent reduction and rearrangement of **141** gave the fused $\delta$-valerolactone (**142**) which was further transformed to (±)-*cis*-alpinine **143**.

A related, interesting photooxidation played an important role in Woodward's[65] total synthesis of chlorophyll-a (Scheme 45). Irradiation of the chlorin (**144**) in the presence of oxygen resulted in the oxidative cleavage of the cyclopentene ring to give the desired cleavage product (**145**). A possible mechanism involves the initial addition of singlet oxygen (formed in a self-sensitized process) to the dienamine to form a transient dioxetane which could undergo decomposition as shown to form **145**.

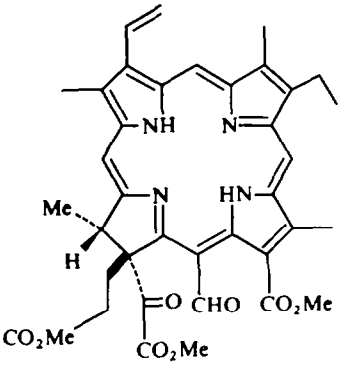



**140**

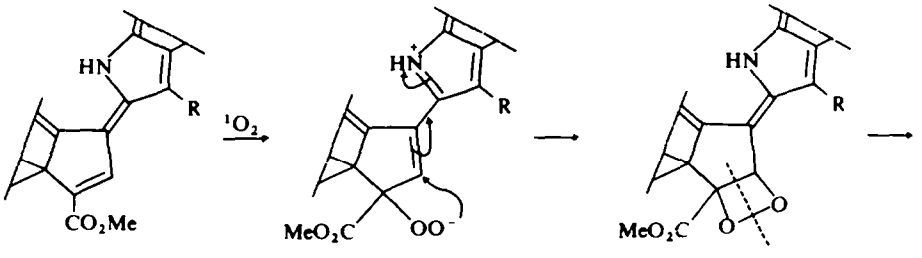
Scheme 44.




**144**



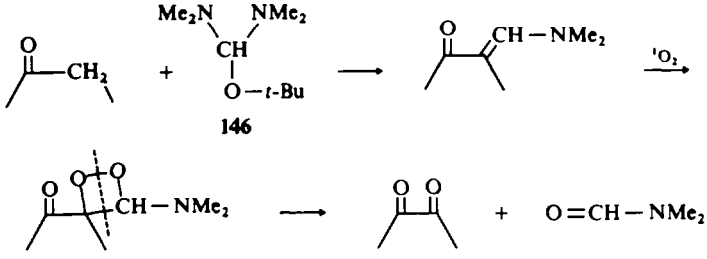

**145**



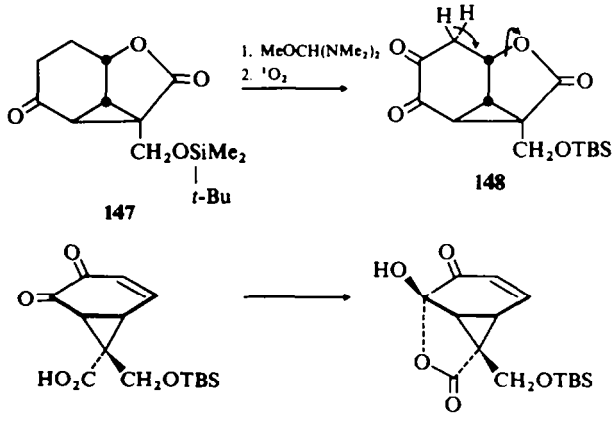

Scheme 45.

The oxidation of enamino ketones with singlet oxygen has been developed by Wasserman and Ives[66] as a general method for the preparation of α-diketones. α-Enamino ketones react with singlet oxygen to provide the corresponding α-diketones in high yield. The overall conversion can be accomplished in two steps (Scheme 46) by treating the starting ketone with an alkoxy *bis*(dimethylamino)methane (Bredereck's Reagent (**146**)) to form the corresponding enamino ketone which is then oxidized *in situ* with singlet oxygen to yield the dicarbonyl-containing product.

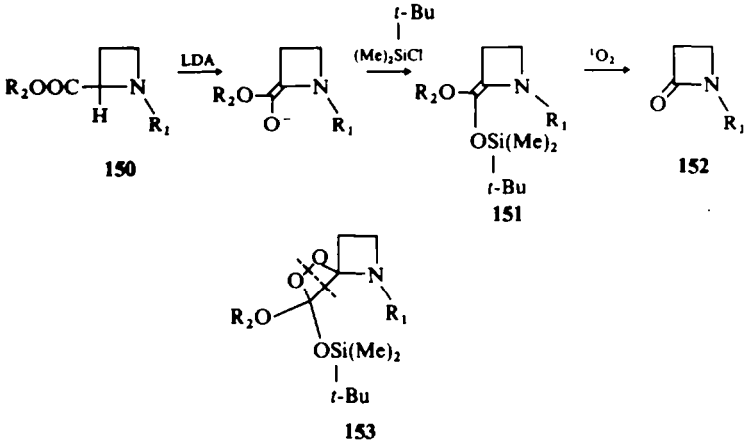
Ziegler *et al.*[67] utilized this procedure in the synthesis of a transient α-diketone (**148**) which subsequently underwent rearrangement to **149** (Scheme 47). Reaction of methoxy*bis*(dimethylamino)methane with the tricyclic ketone (**147**) yielded the corresponding enamino ketone which was then photooxygenated to form the intermediate (**148**). Further studies by Wasserman and Ives[68,69] on the synthesis and photooxygenation of other enamino carbonyl systems have provided new synthetic routes to α-keto esters, α-keto lactones,[68] α-keto amides, and α-keto lactams.




Scheme 46.




Scheme 47.




Scheme 48.

An interesting example of an enamine photooxygenation was developed by Wasserman *et al.*[70] in the synthesis of β-lactams from 2-azetidine carboxylic esters (Scheme 48). Reaction of readily available azetidine esters (**150**) with lithium diisopropylamide at −78° generated the corresponding enolates which were trapped with trialkylsilyl chlorides to form the novel amino silyl ketene acetals (**151**). Photooxygenation of **150** gave the desired β-lactams (**152**) most probably by the decomposition of intermediate dioxetanes (**153**).

## REFERENCES


[1]Current address: Smith, Kline & French Laboratories, 1500 Spring Garden Street, Philadelphia, Pennsylvania.

[2]For reviews on this subject see: [a]R. M. Hochstrasser and G. B. Porter, *Quart. Rev.* **14**, 146 (1960); [b]R. Livingston, *Autoxidation and Antioxidants* (Edited by W. O. Lundberg) Vol. 1, p. 249, Interscience, N.Y., (1961); [c]E. T. Bowen, *Adv. Photochem.* **1**, 23 (1963); [d]K. Gollnick and G. O. Schenck, *Pure Appl. Chem.* **9**, 507 (1964); [e]Y. A. Arbuzov, *Press. Chem. Rev.* **34**, 558 (1965); [f]K. Gollnick and G. O. Schenck, *1,4-Cycloaddition Reactions*, (Edited by T. Hamer) p. 255, Academic Press, New York (1967); [g]K. Gollnick, *Adv. Photochem.* **6**, 1 (1968); [h]C. S. Foote, *Accts. Chem. Res.* **1**, 104 (1968); [i]A. Schönberg, *Preparative Organic Photochemistry*, Springer, New York (1968); [j]*International Conference on Singlet Molecular Oxygen and Its Role in Environmental Sciences* (Edited by A. M. Trozzolo) Ann. N.Y. Acad. Sci. No. 171, New York Acad. Sci., New York (1979); [k]D. R. Kearns, *Chem. Rev.* **71**, 395 (1971); [l]R. W. Denny and A. Nickon, *Org. React.* **20**, 133 (1973); [m]*Singlet Molecular Oxygen* (Edited by A. P. Schaap) Dowden, Hutchinson and Ross, Stroudesburg, Pennsylvania (1976); [n]*Singlet Oxygen* (Edited by H. H. Wasserman and R. W. Murray) Academic Press, New York (1979).

[3]For earlier reviews of the application of singlet oxygen in synthesis see: [a]G. Ohloff, *Pure Appl. Chem.* **43**, 481 (1975); [b]M. Matsumoto and K. Kondo, *J. Syn. Org. Chem. Japan* **35**, 188 (1977).

[4a]G. O. Schenck and K. Ziegler, *Naturwissenschaften*, **32**, 157 (1954); [b]G. O. Schenck, *Angew. Chem.* **64**, 12 (1952).

[5a]C. S. Foote and S. Wexler, *J. Am. Chem. Soc.* **86**, 3879 (1964); [b]*Ibid.* **86**, 3880 (1964); [c]E. McKeown and W. A. Waters, *J. Chem. Soc.* (**B**), 1040 (1966); [d]C. S. Foote, S. Wexler, W. Ando and R. Higgins, *J. Am. Chem. Soc.* **90**, 975 (1968).

[6]R. W. Murray and M. L. Kaplan, *Ibid.* **91**, 5358 (1969).

[7a]H. H. Wasserman and J. F. Scheffer, *Ibid.* **89**, 3073 (1967); [b]H. H. Wasserman, J. R. Scheffer and J. L. Cooper, *Ibid.* **94**, 4991 (1972).

[8a]G. O. Schenck, *Angew. Chem.* **69**, 579 (1957); [b]H. Kautsky, *Biochem. Z.* **291**, 271 (1937).

[9a]H. Hock and S. Lang, *Ber. Dtsch. Chem. Ges.* **75**, 300 (1942); [b]*Ibid.* **77**, 257 (1944); [c]H. Hock and H. Kropf, *Angew. Chem.* **69**, 313 (1957); [d]R. Criegee, *Liebigs Ann.* **560**, 127 (1948).

[10]F. S. El-Feraly, Y.-M. Chan, E. Fairchild and R. W. Doskotch, *Tetrahedron Letters* 1973 (1977).

[11]For other naturally-occurring peroxides, see, for example: [a]Y. Kashman and M. Rotem, *Tetrahedron Letters* 1707 (1979); [b]M. D. Higgs and D. J. Faulkner, *J. Org. Chem.* **43**, 3454 (1978); [c]B. M. Howard, W. Fenical, J. Finer, K. Hirotsu and J. Clardy, *J. Am. Chem. Soc.* **99**, 6440 (1977); [d]F. G. Fisher and H. Mägerlein, *Liebigs Ann.* **636**, 88 (1960).

[12]S. Masamune, *J. Am. Chem. Soc.* **86**, 290 (1964).

[13a]R. A. Bell, R. E. Ireland L. N. Mander, *J. Org. Chem.* **31**, 2536 (1966); [b]R. A. Bell and R. E. Ireland, *Tetrahedron Letters* 269 (1963).

[14]For the syntheses of other naturally-occurring allylic alcohols see, for example: [a]A. F. Thomas and W. Pawlak, *Helv. Chim. Acta* **54**, 1822 (1971); [b]B. Willholm and A. F. Thomas, *J. Chem. Soc.* Chem. Comm. 1380 (1969); and refs 2*k*, 2*m* and 3.

[15a]J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Am. Chem. Soc.* **88**, 3408 (1966); [b]J. A. Marshall and W. I. Fanta, *J. Org. Chem.* **29**, 2501 (1964).

[16a]P. S. Wharton, G. A. Hiegel and R. V. Coombs, *Ibid.* **28**, 3217 (1963).

[17]G. Ohloff, E. Klein and G. O. Schenck, *Angew. Chem.* **73**, 578 (1961).

[18]R. J. Anderson, C. A. Henrick and J. B. Siddall, *J. Am. Chem. Soc.* **92**, 735 (1970).

[19]E. Wenkert and K. Naemura, *Synthetic Comm.* **3**, 45 (1973).

[20]W. H. Schuller and R. V. Lawrence, *J. Am. Chem. Soc.* **83**, 2563 (1961).

[21a]G. Büchi, A. Hauser and J. Limacher, *J. Org. Chem.* **42**, 3323 (1977); [b]S. Murayama, D. Chan and M. Brown, *Tetrahedron Letters* 3715 (1968).

[22]R. E. Ireland, S. W. Baldwin, D. J. Dawson, M. I. Dawson, J. E. Dolfini, J. Newbould, W. S. Johnson, M. Brown, R. J. Crawford, P. F. Hudrlik, G. H. Rasmussen and K. K. Schmiegel, *J. Am. Chem. Soc.* **92**, 5743 (1970).

[23]R. E. Ireland, S. W. Baldwin and S. C. Welch, *Ibid.* **94**, 2056 (1972).

[24a]J. S. Dutcher, J. G. Macmillan and C. H. Heathcock, *J. Org. Chem.* **41**, 2663 (1976); [b]J. S. Dutcher, J. G. Macmillan and C. H. Heathcock, *Tetrahedron Letters* 929 (1974); [c]J. S. Dutcher and C. H. Heathcock, *Ibid.* 933 (1974).

[25]R. E. Ireland, K. Huthmacher, P. A. Aristoff and R. Farr, unpublished results.

[26]A. F. Thomas, *Helv. Chim. Acta.* **55**, 2429 (1972).

[27]For other examples of the Hock fragmentation of allylic hydroperoxides, see: [a]G. Ohloff, H. Strickler, B. Willholm, C. Borer and M. Hinder, *Helv. Chim. Acta* **53**, 623 (1970); [b]B. Maurer, H. Fracheboud, A. Grieder and G. Ohloff, *Helv. Chim. Acta* **55**, 2371 (1970).

[28a]J. A. Marshall and P. G. M. Wuts, *J. Org. Chem.* **43**, 1086 (1978); [b]J. W. Huffmann, *Ibid.* **41**, 3847 (1976).

[29]A. F. Thomas and R. Dubini, *Helv. Chim. Acta* **57**, 2076 (1974).

[30a]A. Nickon and W. L. Mendelson, *J. Am. Chem. Soc.* **85**, 1894 (1963); [b]*Ibid.* **87**, 3921 (1965).

[31]For a review on biomimetic oxygenations, see: T. Matsuura, *Tetrahedron* **33**, 2869 (1977).

[32]A. I. Scott and C. T. Bedford, *J. Am. Chem. Soc.* **84**, 2271 (1962).

[33]For a later report on the photooxygenation of tetracyclines, see: M. S. von Wittenau, *J. Org. Chem.* **29**, 2746 (1964).

[34a]For a recent review on the photooxygenation of heterocycles, see: H. H. Wasserman and B. Lipshutz, *Singlet Oxygen*, in Ref. 2*n*; [b]H. H. Wasserman and M. B. Floyd, *Tetrahedron Suppl.* **7**, 441 (1966); [c]H. H. Wasserman and E. Druckrey, *J. Am. Chem. Soc.* **90**, 2440 (1968); [d]H. H. Wasserman, F. J. Vinick and Y. C. Chang, *J. Am. Chem. Soc.* **94**, 7180 (1972); [e]H. H. Wasserman and G. Lenz, *Heterocycles* **5**, 409 (1976).

[35a]R. W. Franck and J. Auerbach, *J. Org. Chem.* **36**, 31 (1971); [b]G. J. Sinta, R. W. Franck and R. J. Kempton, *Ibid.* **39**, 3739 (1974).

[36a] T. Kametani, T. Ohsawa, K. Takahashi, N. Ihara and K. Fukamoto, *Heterocycles* **4**, 1637 (1976); [b] T. Kametani, T. Ohsawa, M. Ihara and K. Fukamoto, *J. Chem. Soc.* Perkin Trans. I, 389 (1976).
[37a] M. Natsume, Y. Sekine, M. Ogawa, H. Soyagimi and Y. Kitagawa, *Tetrahedron Letters* 3473 (1979); [b] M. Natsume and H. Muratake, *Ibid.* 3477 (1979); [c] M. Natsume, Y. Sekine and H. Soyagimi, *Chem. Pharm. Bull. Tokyo* **26**, 2188 (1978); M. Natsume, M. Wada and M. Ogawa, *Ibid.* **26**, 3364 (1978).
[38a] H. H. Wasserman and A. Liberles, *J. Am. Chem. Soc.* **82**, 2086 (1960); [b] R. E. Lutz, W. J. Welstead, Jr., R. G. Bass and J. I. Dale, *J. Org. Chem.* **27**, 1111 (1962).
[39] C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. G. O. Schenck and K.-J. Schulte-Elte, *Tetrahedron* **23**, 2583 (1967).
[40] H. H. Wasserman and A. R. Doumaux, Jr., *J. Am. Chem. Soc.* **84**, 4611 (1962).
[41] T. J. Katz, V. Balogh and J. Schulman, *Ibid.* **90**, 734 (1968).
[42] J. B. Heather, R. S. D. Mittal and C. J. Sih, *Ibid.* **96**, 1976 (1974).
[43] A. I. Meyers, R. L. Nolen, E. W. Collington, T. A. Narwid and R. C. Strickland, *J. Org. Chem.* **38**, 1974 (1973).
[44a] R. Kanazawa, H. Kotsuki and T. Tokoroyama, *Tetrahedron Letters* 3651 (1975); [b] T. Tokoroyama, K. Matsuo, R. Kanazawa, H. Kotsuki and T. Kubota, *Ibid.* 3093 (1974).
[45] H. H. Wasserman and R. J. Gambale, to be published. *Abstr.* 180*th Am. Chem. Soc.*, San Francisco, California (1980).
[46] G. O. Schenck, *Angew. Chem.* **69**, 579 (1957).
[47a] W. A. Ayer, L. M. Browne, and S. Fung, *Can. J. Chem.* **54**, 3276 (1976). [b] A similar use of reduction of a 1,4-endoperoxide is described in Y. Honwa and Y. Ban, *Heterocycles* **6**, 129 (1977).
[48] M. R. Demuth, P. E. Garrett and J. D. White, *J. Am. Chem. Soc.* **98**, 634 (1976).
[49a] G. W. Holbert and B. Ganem, *J. Am. Chem. Soc.* **100**, 352 (1978); [b] B. Ganem, G. W. Holbert, L. B. Weiss and K. Ishizumi, *Ibid.* **100**, 6483 (1978); [c] B. Gamem and G. Holbert, *Bioorganic Chem.* **6**, 393 (1977).
[50] For the reaction of singlet oxygen with styrenes to form 1:2 styrene-$O_2$ adducts, see: [a] C. S. Foote, S. Mazur, P. A. Burns and D. Lerdal, *J. Am. Chem. Soc.* **95**, 586 (1973); [b] G. Rio, D. Bricout and J. Lacomb, *Tetrahecron* **29**, 3553 (1973); [c] P. A. Burns, C. S. Foote and S. Mazur, *J. Org. Chem.* **41**, 899 (1976); [d] P. A. Burns and C. S. Foote, *Ibid.* **41**, 908 (1976); [e] M. Matsumoto, S. Dobashi and K. Kondo, *Tetrahedron Letters* 2329 (1977).
[51] M. Matsumoto, S. Dobashi and K. Kuroda, *Ibid.* 3361 (1977).
[52] H. C. Barrett and G. Büchi, *J. Am. Chem. Soc.* **89**, 5665 (1967).
[53a] T. G. Halsall, W. R. Rodewald and D. Willis, *Proc. Chem. Soc. London* 231 (1958); [b] R. N. Moore and R. V. Lawrence, *J. Am. Chem. Soc.* **81**, 458 (1959).
[54] E. Demole, C. Demole and D. Berthet, *Helv. Chim. Acta* **56**, 265 (1973).
[55a] M. Matsumoto and K. Kondo, *J. Org. Chem.* **40**, 2259 (1975); [b] K. Kondo and M. Matsumoto, *Tetrahedron Letters* 391 (1976); [c] *Ibid.* 4363 (1976); [d] K. Kondo and M. Matsumoto, *Chem. Lett.* 701 (1974).
[56] B. Harirchian and P. D. Magnus, *Synth. Comm.* **7**, 119 (1977).
[57] For a review of dioxetane chemistry, see: P. Bartlett and M. Landis, *The Dioxetanes* in Ref. 2*n*.
[58] J. Becker and G. Ohloff as described in Ref. 3*a*.
[59a] T. Matsuura, H. Matsushima and R. Nakashima, *Tetrahedron* **26**, 435 (1970); [b] T. Matsuura, H. Matsushima and H. Sakamoto, *J. Am. Chem. Soc.* **89**, 6370 (1967).
[60a] C. S. Foote and J. W.-P. Lin, *Tetrahedron Letters* 3267 (1968); [b] J. E. Huber, *Ibid.* 3271 (1968); [c] C. S. Foote, A. A. Dzakpasu and J. W.-P. Lin, *Ibid.* 1247 (1975); [d] K. Pfoertner and K. Bernauer, *Helv. Chim. Acta* **51**, 1787 (1968); [e] W. Ando and K. Watanabe, *Chem. Letters* 947 (1977).
[61] H. H. Wasserman and S. Terao, *Tetrahedron Letters* 1735 (1975).
[62] W. Ando, T. Saiki and T. Migita, *J. Am. Chem. Soc.* **97**, 5028 (1975).
[63] H. H. Wasserman and J. L. Ives, unpublished results.
[64] K. Orito, R. H. Manske and R. Rodrigo, *J. Am. Chem. Soc.* **96**, 1944 (1974).
[65a] R. B. Woodward, *Pure Appl. Chem.* **2**, 383 (1961); [b] R. B. Woodward, W. A. Ayer, J. M. Beaton, F. Bickelhaupt, R. Bonnett, P. Buchschacher, G. L. Closs, H. Dutler, J. Hannah, F. P. Hauck, S. Ito, A. Langemann, E. LeGoff, W. Leimgruber, W. Lwowski, J. Sauer, Z. Valenta and H. Volz, *J. Am. Chem. Soc.* **82**, 3800 (1960).
[66] H. H. Wasserman and J. L. Ives, *Ibid.* **98**, 7868 (1976).
[67] F. E. Ziegler, M. A. Cady, R. V. Nelson and J. M. Photis, *Tetrahedron Letters* 2741 (1979).
[68] H. H. Wasserman and J. L. Ives, *J. Org. Chem.* **43**, 3238 (1978).
[69] J. L. Ives, Ph.D. Thesis, Yale University (1978).
[70] H. H. Wasserman, B. H. Lipshutz and J. S. Wu, *Heterocycles* **7**, 321 (1977).