Mechanistic studies on the chemical oxidation of substituted tetrahydrobenzofurans
by Kirk Paul Manfredi

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University

Abstract:
here indicates that 15 does not undergo a NIH Shift but loses a proton to form the enol 109 which isomerizes to 81.

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MECHANISTIC STUDIES ON THE CHEMICAL OXIDATION OF SUBSTITUTED TETRAHYDROBENZOFURANS

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A thesis submitted in partial fulfillment
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APPROVAL

of a thesis submitted by

Kirk Paul Manfredi

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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INTRODUCTION

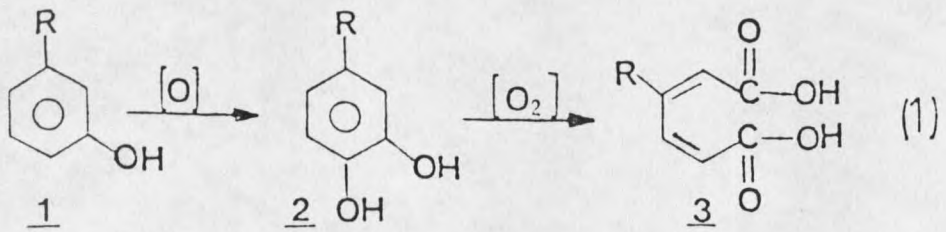
An increasing number of organic substrates that are either toxic or carcinogenic are now believed to have their effects enhanced (or even caused) by the products of their metabolic oxidation. The conversion of polyaromatic hydrocarbons to epoxides and diols and the conversion of nitrites to nitrosamines are just two examples. These oxidations are believed to occur in the liver of mammals and are catalyzed by a diverse class of hepatic enzymes known as mixed function oxidase enzymes (MFO). It is the purpose of this study to investigate a number of MFO chemical mimics and their subsequent reactions with alkyl substituted furans. It is appropriate, however, to define what is meant by the term mixed function oxidase and to examine the literature with regard to their mechanism of oxygen fixation, nature of the active oxygen species and evaluation of the various MFO mimics.

Xenobiotic substances in mammalian systems are oxidized in the liver by a diverse class of enzymes termed oxidases. In 1950, during a study on tryptophan metabolism, Hayaishi discovered a new type of oxidizing enzyme and gave it the classification of an

"oxygenase".[1,2]

Oxygenases are, therefore, a special class of oxidase. The term oxidase is given to an enzyme when the final acceptor of oxygen is a hydrogen. In an oxidase, either one, two or four electrons are transferred to a molecule of oxygen to form HO_2^-, H_2O_2, or $2H_2O$, respectively.[3]

Oxygenases which will be the focus of this introduction can be classified into two major categories. The first category is called dioxygenases. These are enzymes that catalyze reactions in which both atoms of a molecule of oxygen are transferred to a substrate. The second category is termed monooxygenase, these enzymes insert one atom of molecular oxygen into the substrate, while the other atom is made into H_2O. Since these enzymes appear to be bifunctional (i.e., hydrogen is the acceptor of an oxygen atom as in an oxidase) they are generally referred to as mixed function oxidases or MFOs. The functions of monooxygenases and dioxygenases can be coupled as shown in the hypothetical reaction scheme shown below (equation 1).



There are a number of known classes of MFOs that are based on the nature of the electron donor. Only the two classes that are known to be responsible for the oxidation of xenobiotic substances will be considered in this text. These two classes are termed flavoprotein monooxygenases and heme dependent microsomal cytochrome P-450 monooxygenase.

Flavin protein dependent monooxygenases require reduced purine as an electron donor. These enzymes are found in the liver microsomes of mammals and are known to hydroxylate aromatic substrates, epoxidize double bonds and oxidize sulfur and nitrogen containing compounds to sulfoxide and N-oxides respectively.[4,5] The second class is the cytochrome P-450 heme dependent MFOs. These are much less specific enzyme systems which hydroxylate alkanes as well as the same type of substrates as the flavin dependent MFOs. Flavoprotein monooxygenases are much more specific and better characterized than P-450 enzymes.[3a] Both of these enzyme systems appear to have different and unique methods of "fixing" atmospheric oxygen to a more reactive oxidizing agent.

Experiments with $^{18}O_2$ have shown that the oxygen incorporation in organic substrates during biological oxidations comes from atmospheric oxygen and not H_2O.[3] This may seem surprising since atmospheric oxygen is

relatively inert to organic substrates. Hamilton has proposed that the relative inertness of molecular oxygen is do to the fact that oxygen's ground state is a triplet.[6] A reaction between a triplet reagent and singlet substrate to give a singlet product is a spin forbidden process and requires a high activation energy. This is not to imply that free radical chemistry does not occur, just that the free radical chemistry of molecular oxygen is endothermic. What is then one of the intriguing properties of MFOs, is how they activate molecular oxygen.

It had been suggested that MFOs activate molecular oxygen by transforming it to a singlet state.[7,8] This, however, is now thought to be unlikely for a number of reasons.[6] For example, substrates which normally react with MFOs, such as olefins and aromatic compounds, give different products when reacted with singlet oxygen. Olefins give epoxides when reacted with MFOs but give allylic hydroperoxides when reacted with singlet oxygen. Secondly, the energy required to convert triplet oxygen to its lowest singlet excited state is 22 Kcal/mol. This energy barrier is close to the upper limit for many enzyme catalyzed reations. Finally, one must consider the incredible reactivity of singlet oxygen with some substrates such as alkenes which react extremely fast.

Alkanes, on the other hand, are inert to singlet oxygen but are substrates for MFO oxidations. Based on the above observations, singlet oxygen is probably not the reactive species in biological oxidations nor is it a good chemical mimic.

There appear to be two other pathways in which biological systems can activate molecular oxygen. The first pathway entails the reaction(s) between molecular oxygen and a transition metal. When oxygen interacts with a transition metal, the oxygen orbitals interact with the metal orbitals, in such a way that one can not speak of the number of unpaired electrons on either the oxygen or the metal, but only the number of unpaired electrons on the complex. Hamilton has suggested that when oxygen is in this environment it is neither a triplet or a singlet state and can react ionically with substrates to give singlet products.[6] When oxygen is complexed in this way, it is proposed to have low activation barriers.

The other proposed mechanism to activate oxygen can be achieved by having the initial reaction occur as a free radical process. A triplet molecule and a singlet molecule can react with each other to give two free radicals. These two radicals can then recombine to form an active singlet species. Oxygen does not normally

react with organic compounds at low temperature because free radical reactions with O_2 are normally very endothermic. There are, however, certain biological molecules that react with oxygen at low temperature. In particular they are the reduced flavins that are the prosthetic group of the flavin monooxygenases. The initial flavin free radicals that are formed are highly resonance stabilized and therefore decrease the activation energy required for the initial free radical reaction. The oxygen radical and flavin radical can then recombine to form an active oxygen donor.

It can be argued that the relative inertness of molecular oxygen is not related directly to the triplet ground state as Hamilton has suggested, just simply because of the energy of the oxygen-oxygen bond (e.g., the energy required to form a carbon-oxygen bond is greater than that required to break a O_2 bond). Regardless of how enzymes fix oxygen to oxidize organic substrates, it is the nature of the oxygen that is important when considering chemical mimics for MFOs.

When considering the chemical nature of the active oxygen species in MFOs, it was noticed that they catalyze reactions similar to carbene and nitrene reactions.[9] Carbenes will insert a methylene group into carbon-hydrogen bonds in alkanes, while MFOs will insert

oxygen to form alcohols. Carbenes will react with olefins to form cyclopropanes while MFOs give epoxides. MFOs will also react with aromatic substrates to give epoxides and diols while carbenes give alkyl benzenes and norocaradienes. These similarities have led researchers to postulate that the active oxygen donating species in MFOs donate an oxygen atom. This is now known as the oxenoid mechanism.[9]

The strongest evidence for the oxenoid mechanism comes from the experimental results obtained by the NIH group led by D.M. Jerina on what is now termed the NIH Shift[10-16] (Figure 1).

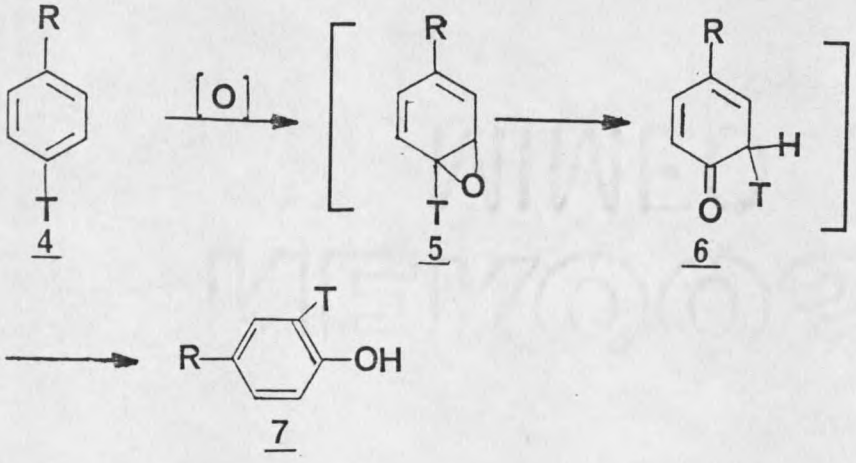


Figure 1. An example of an NIH Shift reaction.

During the enzyme catalyzed hydroxylation of an aromatic substrate, the intermediate arene oxide rearranges to form the ketone. During this transformation , a proton

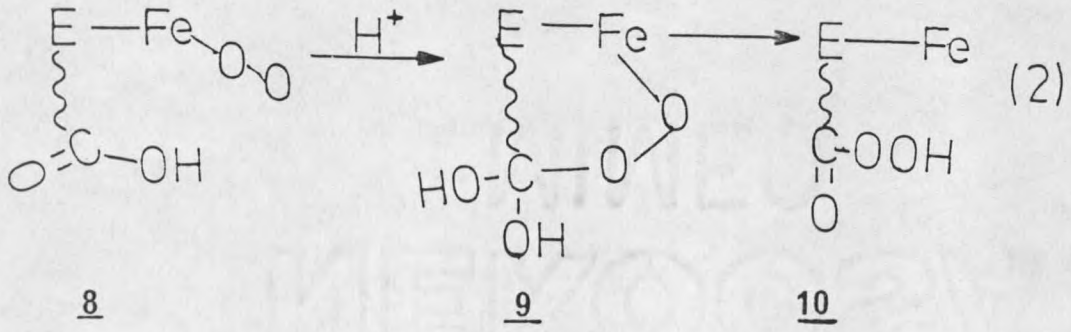
(T) isomerizes to the incipient carbonium ion and is referred to as the NIH Shift. A large portion of the label changes position relative to the R group at this time. This rearrangement causes more of the label to stay on the ring because of the primary isotope effect. The NIH Shift is observed with both liver microsomal suspension and isolated enzymes.[10,16] The importance of the NIH Shift to the oxenoid mechanism is that the intermediate arene oxide would be the product that one would expect from an oxene (carbene) type reaction. Sources of oxene such as m-chloroperbenzoic acid (mCPBA), peroxyacetic acid and trifluoroperacetic acid all give NIH Shift products when reacted with various aromatic substrates.[17]

Jerina has supported a loose set of criteria to determine the relevancy of chemical model systems to actual enzymes.[18] Chemical mimics for P-450 systems should display a broad spectrum of chemical reactivity. A chemical mimic should possess the ability to hydroxylate both aromatic and aliphatic compounds, epoxidize double bonds and oxidize nitrogen and sulfur containing compounds to N-oxides and sulfoxides, respectively. The most important criteria is that the reagent should give the NIH Shift product when oxidizing an aromatic substrate.

Over the years a number of investigators have attempted to develop chemical systems to mimic the P-450 microsomal MFO. The first of these systems was developed by Udenfriend and co-workers in 1954.[19] Udenfriend's reagent consists of O_2, Fe(II), EDTA, and ascorbic acid at neutral pH. This system is capable of converting aliphatic compounds to alcohols and carbonyl compounds, olefins to epoxides and aromatic substrates to phenols. The mechanism of this system has been studied extensively and it is unlikely that the reagent acts through an oxenoid pathway.[20] Further, the reagent does not give NIH Shift products. Finally, oxidation products in general are formed in very low yield.

A second system known as the Hamilton system consists of Fe(III) and catechol and uses H_2O_2 as its oxygen source.[21] This system hydroxylates aromatic substrates, but in much higher yield than Udenfriend's reagent. Although it gives low yields of NIH Shift products, it is still considered to be a model for the heme dependent P-450 systems. Recently Groves has developed a similar type system using Fe(II)-tetraphenyl-porphine chloride (FeTPPCl) and iodosylbenzene as an oxygen source.[22] This system undergoes many of the reactions that P-450 catalyzes. No work as yet has been done to determine if it gives NIH Shift products.

The above systems all use metals to activate some oxygen source. There are also chemical mimics that already have an active oxygen source. The photolysis of pyridine-N-oxide in the presence of aromatic substrates leads to high yields of NIH Shift phenolic compounds.[23] Peracetic acid, trifluoroperacetic acid and m-chloroperbenzoic acid all give NIH Shift products with various aromatic substrates.[17] In fact, Hamilton has proposed that the active oxygen in heme dependent P-450 systems is either a peracid or peramide.[6] He has proposed that the Fe(II) in P-450 first forms a complex with O_2. This complex then oxidizes an adjacent amide carbonyl or acid carbonyl to peramide or peracid with the concomitant loss of H_2O. The peracid or peramide is then the oxidizing agent (equation 2). More recent work, however, has



(2)

8 9 10

pointed to a sulfur-iron-oxene complex as the reactive intermediate.[24,25]

The uncertainty of the exact nature of the active

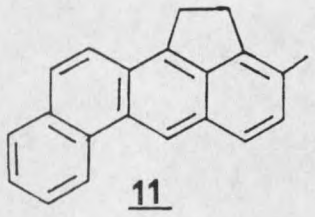
oxygen donor in P-450 enzymes has led to considerable difficulty in designing adequate chemical mimics to study oxidative metabolism. It has been possible to overcome this problem by using liver microsome preparations. These microsomal preparations have had considerable success in determining oxidation products of various organic substrates.

Liver microsomal preparations from rat and rabbit livers are good sources of MFOs. It is also known that by treating rabbits and rats with non lethal doses of Aroclor 1254, 3-methylcholanthrene or phenobarbital prior to microsome preparation, the P-450 activity can be greatly enhanced in in vitro studies. The induced P-450 enzymes show essentially no substrate specificity and oxidize a wide variety of substrates. Coon has isolated a number of P-450 enzymes from liver microsomes that are electrophoretically pure and show a wide range of substrate activity.[26,27]

Metabolism studies using induced liver microsomes as a source of P-450 MFO, have been examined extensively with polyaromatic hydrocarbons as substrates.[28] The oxidative metabolites of polyaromatic hydrocarbons (PAH) are known to be potent mutagens that function by binding to DNA.[29,30] Sims was the first to identify the oxidative metabolites of 3-methylcholanthrene.[31] In

this study, he isolated the microsomes from rat livers and incubated them with 3-methylcholanthrene. He then synthesized a number of potential metabolites and compared their thin layer chromatography R_f values and UV spectra to those of the 13 metabolites that he isolated from the microsomal reaction (Figure 2). Subsequent studies have identified the metabolites from benzanthracene and benzo [a] pyrene.[32] The metabolism of these compounds proved to be a variety of alcohols, phenols, diols, epoxides, and ketones. Extensive studies have also been done on the metabolism of aryl amines. Aryl amines are first acetylated, N-hydroxylated to give the hydroxamic acid derivatives which are known to be carcinogenic.[33,34]

PAHs and aromatic amines have received considerable attention because of their abundance in the environment. PAHs are produced from combustion of fossil fuels and wood products. Aryl amines are found in dyes and proteinaceous foods. There are probably a number of other toxic organic compounds whose metabolism increase their toxicity but they are less studied, perhaps because they are not as abundant in the environment as PAHs and aryl amines.



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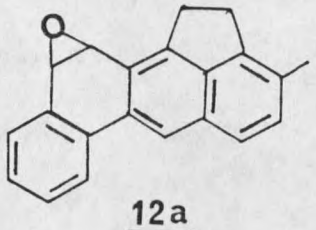
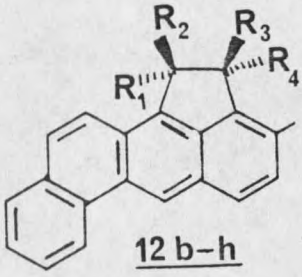
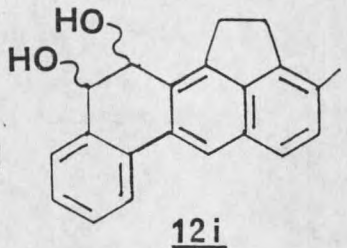


12a

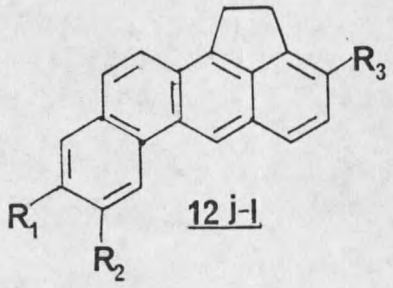


12 b–h

b $R_1=R_2=R_3=H$, $R_4=OH$
c $R_2=R_3=R_4=H$, $R_1=OH$
d $R_1=OH, R_2=R_3=H, R_4=OH$
e $R_1=OH, R_2=R_4=H, R_3=OH$
f $R_1==O, R_3=R_4=H$
g $R_1=R_2=H, R_{34}==O$
h $R_{12}=R_{34}==O$

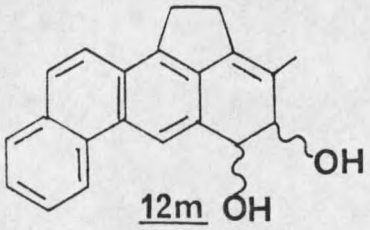


12 i



12 j-l

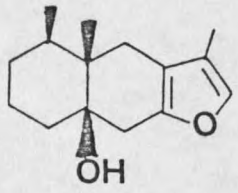
j $R_1=R_2=H, R_3=CH_2OH$
k $R_1=OH, R_2=H, R_3=CH_3$
l $R_1=H, R_2=OH, R_3=CH_3$



12m

Figure 2. Metabolites of 3-methylcholanthrene.

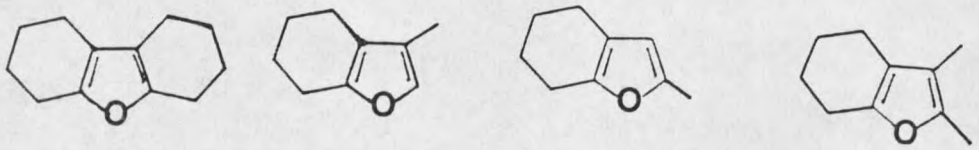
There is evidence that certain furan compounds are hepatotoxins and that their metabolic oxidation products are even more toxic to the animal. In 1974, Jennings and co-workers isolated toxic substances from the range plant Tetradymia glabrata.[35] This plant was responsible for the death of grazing sheep in central Utah. The major product isolated was a nonisoprenoid furanosesquiterpene given the name tetradymol 13. It



13

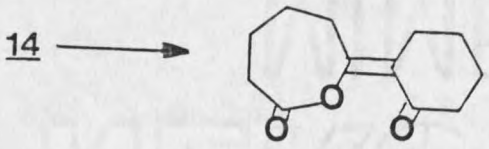
was subsequently shown that 13 was a hepatotoxin and that the product from its metabolism was the major cause of death to laboratory mice.[36] Studies on the liver microsomal metabolism of model furan compounds failed to yield any metabolites.[37] Subsequent to the microsomal work, a study also began using chemical mimics and alkyl substituted furans as models for the possible metabolism of 13 with microsomal P-450.[38-40] The researchers chose m-chloroperbenzoic acid (mCPBA) as a mimic for P-450; this had been previously suggested by other workers.[41]

Compounds 14 thru 17 were chosen as model compounds for alkyl furan oxidation. When compound 14 was reacted



14 15 16 17

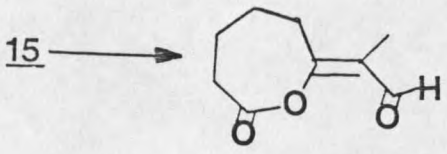
with 2 equivalents of mCPBA in CH_2Cl_2 at 0°C, it formed 18 quantitatively in 5 minutes (equation 3). Likewise,



(3)

18

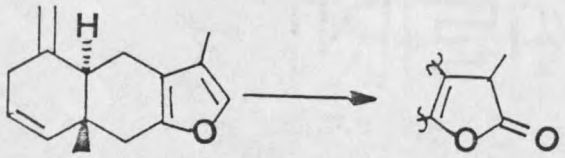
when 15 was reacted under identical conditions 19 was produced quantitatively (equation 4). Addition of only



(4)

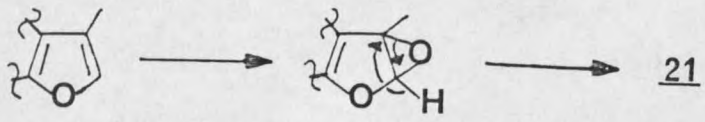
19

one equivalent of peracid to 15 led to the recovery of half of the starting furan. The product from 15 is in contrast to the only other peracid oxidation of a furanosesquiterpene reported by Takeda and co-workers in 1964.[42] In the degradation of lindestrene 20 it was shown to react with one mole of perbenzoic acid to give the lactone 21 (equation 5).



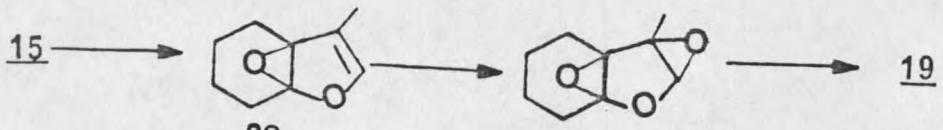
20 21 (5)

This lactone 21 can be rationalized as coming from the rearrangement of the intermediate epoxide 22 (equation 6).



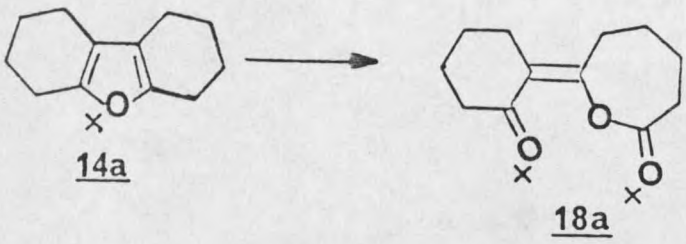
20 22 21 (6)

The results of the Jennings group initially led the workers to propose a diepoxide intermediate 24 (equation 7). Further investigation into the mechanism of the



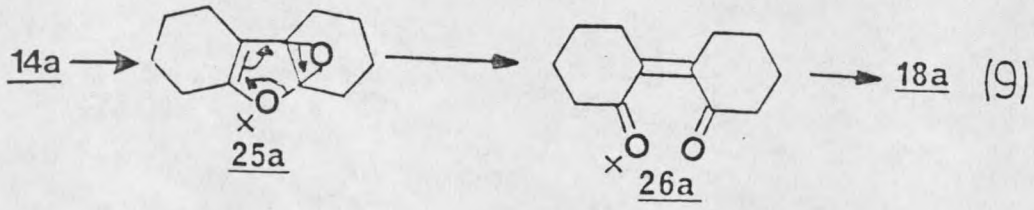
15 23 24 19 (7)

reactions using ^{18}O labeled furans (^{18}O labeled molecules are denoted with the letter "a") disproved the diepoxide intermediate for the reaction with 14 (equation 8). The diepoxide intermediate would predict that the



(8)

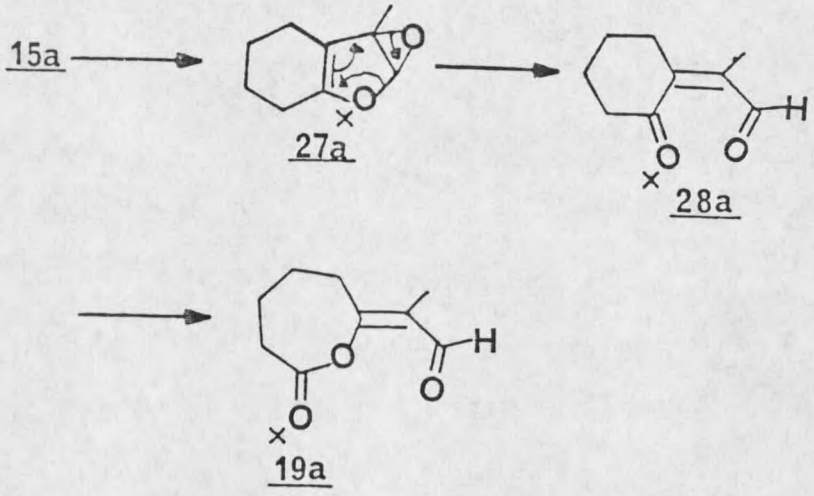
^{18}O would only be in the lactone carbonyl oxygen. In fact, the label was distributed equally in the carbonyls as shown in equation 8.[40] These results led the authors to propose a new mechanism (equation 9). In this scheme, the first equivalent of mCPBA is consumed in the epoxidation of one double bond which rearranges to the cis-1,4-enedicarbonyl 26a. Finally, 26a undergoes a Baeyer-Villiger oxidation to give the product. In the last



(9)

reaction, the peracid can attack either carbonyl which accounts for the label in both carbonyls of the product. In the analogous experiment with 15, the ^{18}O label was found to be entirely in the lactone carbonyl. This is also consistent with a dicarbonyl intermediate if the epoxidation occurs on the least substituted double bond

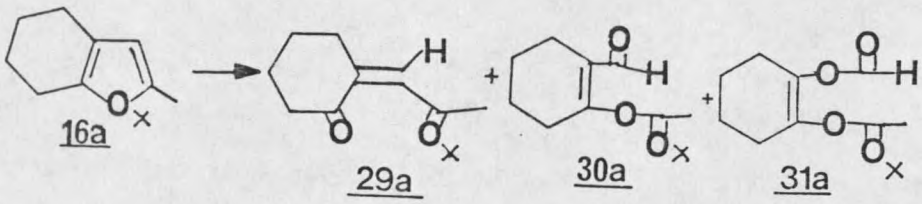
as shown in equation 10.



(10)

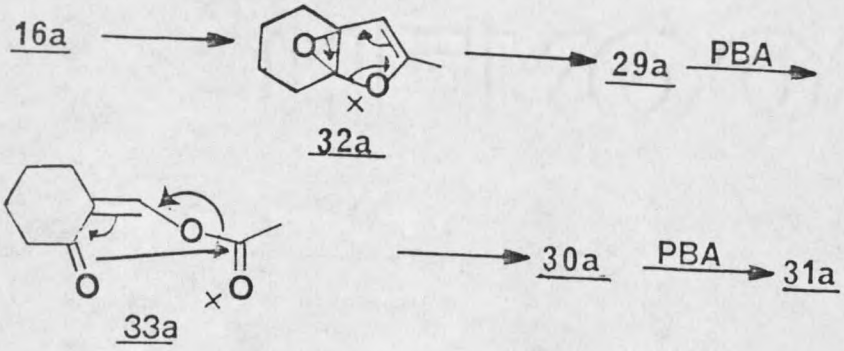
Attempts to synthesize the dicarbonyls 26 and 28 proved to be unsuccessful.[43] Cis-1,4-enedicarbonyls and cis- ene-one-als have been isolated by other workers in the peracid oxidation of substituted furans.[44,45] For example, LeGoff has reported that the reaction of one equivalent of mCPBA with 2,5-dimethylfuran produces the cis-1,4-enedicarbonyl in nearly quantitative yield.[46] Addition of a second equivalent does not lead to a Baeyer-Villiger oxidation product.

When the ^{18}O analogue of substrate 16 was reacted with 2 equivalents of mCPBA under the same conditions as 14 and 15, three different oxidation products were isolated (equation 11). The formation of 29 could be



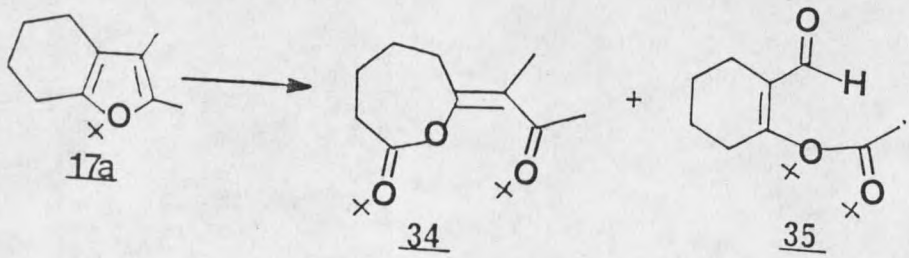
(11)

increased to 90% when only one equivalent of peracid was added. These results led the authors to propose the pathway shown in equation 12.



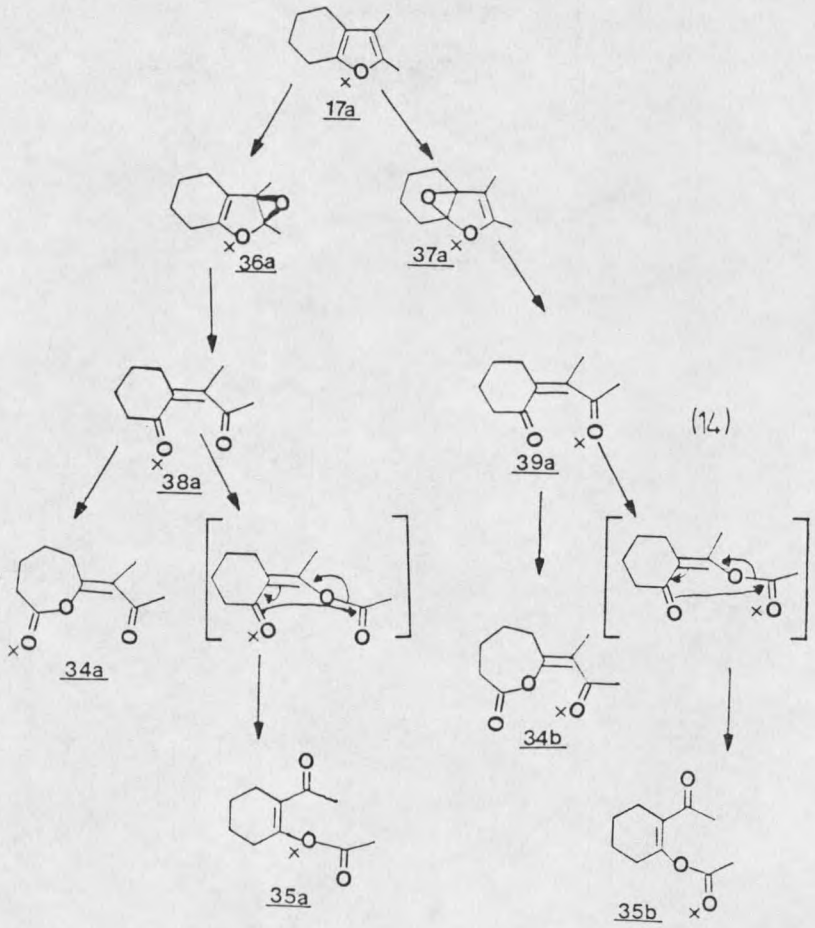
(12)

The ^{18}O analogue of 17 was synthesized and was expected to react as either 15 or 16 (e.g., epoxidize at both double bonds) or an entirely separate entity (equation 13). Both compounds 34 and 35 were formed in



(13)

nearly equal amounts. The ^{18}O labeling pattern could be explained, depending on which side the epoxidation took place (equation 14). These results then indicated that 17 behaved as both 15 and 16.



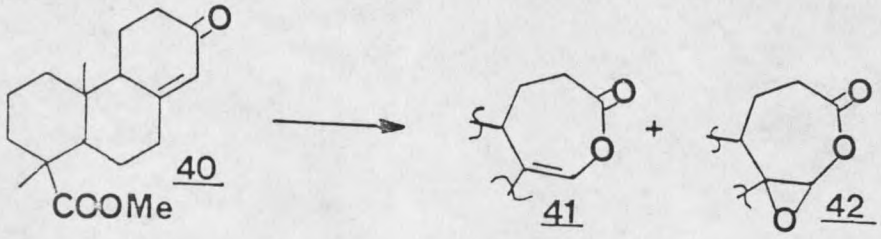
(14)

The conclusion of this work showed a general pathway for the peroxidation of alkylsubstituted furans. All furans were initially epoxidized followed by a rapid ring opening reaction to form a cis-1,4-enedicarbonyl. These dicarbonyls are then rapidly oxidized to give products that can be explained in terms of a

Baeyer-Villiger oxidation. Further, it was concluded that in all cases except one, the dicarbonyl was more reactive towards mCPBA than the parent furan. This led the researchers to propose that dicarbonyls might be the metabolites responsible for the toxicity of the parent furan compounds.

There are a number of features of the proposed mechanism which remain unclear. For example, the Baeyer-Villiger oxidation for these systems occurs in a higher yield and and at a faster rate than those reported for other Baeyer-Villiger oxidations.

Iyers and co-workers have reported on the mCPBA oxidation of the α,β-unsaturated ketone 40 (equation 15). Both the ϵ-lactone 41 and the ϵ-lactone-epoxide 42 were isolated in 30% yield after 7 hours[47]. The



(15)

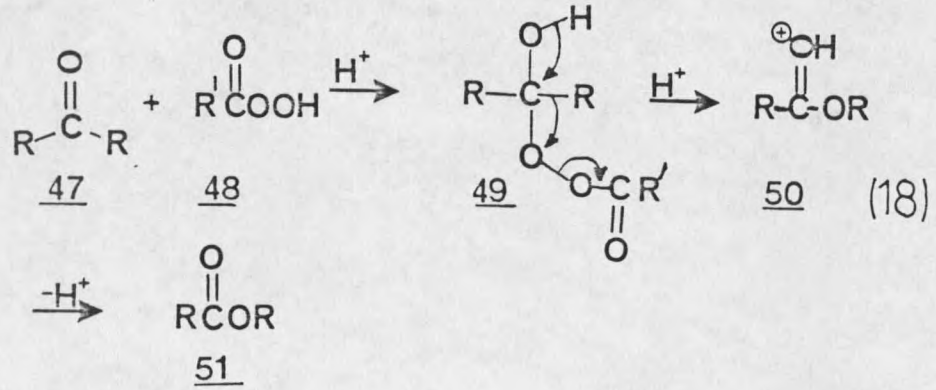
peroxidation of 2-methylcyclohexanone 43 with peracetic acid in ethyl acetate at 40°C gave the ϵ-lactone 44 in good yield, but after 8.5 hours (equation 16).[48]

43 44 (16)

Walton has reported on the peroxidation of the arylalkylidene 45.[49] This substrate is perhaps a better model for the dicarbonyls in question. In this reaction 45 gave the lactone 46 in 50% yield after 0.5 hours (equation 17).

45 46 (17)

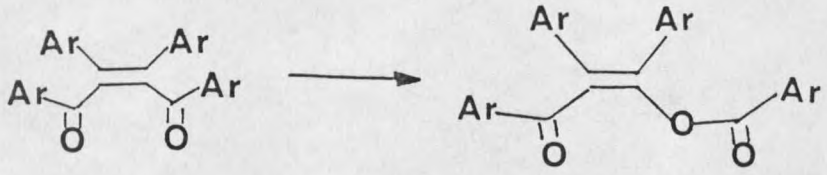
Finally, the current accepted mechanism for the Baeyer-Villiger oxidation of ketones is reported to be acid-catalyzed (equation 18). When $NaHCO_3$ was added to



47 48 49 50 51 (18)

the peroxidation of either 14 or 15, it appeared to have no effect on the reaction.[38] If the m-chlorobenzoic acid were facilitating the reaction, the $NaHCO_3$ would be expected to slow the reaction.

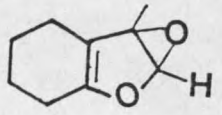
The examples therefore lead one to question why the Baeyer-Villiger oxidation of the 1,4-dicarbonyls is so fast. Further, LeGoff has previously reported that the addition of a second equivalent of mCPBA to the dicarbonyl from 2,5 dimethylfuran does not produce any ester products.[46] Moreover, the dicarbonyl 52 derived from tetraphenyl furan was reported to give ester products 53 in low yield (equation 19).[51] The authors gave no indication as to the rate of the reaction.



52 53 (19)

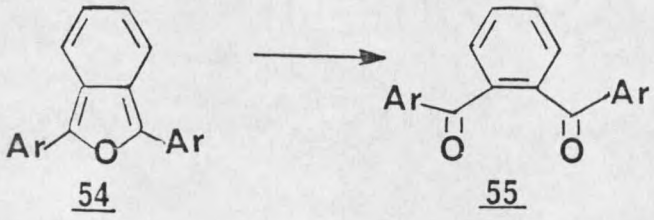
A second point in question on the proposed mechanism is whether an epoxide is first formed in the reaction. In the peracid oxidation of 15, low temperature NMR studies were done to help elucidate a general mechanism.[43] It was reported that at 240°K a peak was observed in the ^1H NMR spectra at 5.60 ppm. Upon raising the temperature the peak was seen to disappear with the

concomitant observation of a peak at 10.2 ppm that increased in intensity as the peak at 5.60 ppm decreased.[43] The peak at 5.60 ppm was therefore assigned to the acetal proton of the intermediate epoxy acetal 27 and the peak at 10.2 ppm was assigned to the aldehyde proton of product 19.



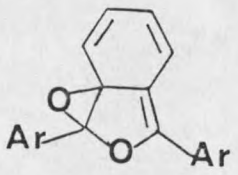
27

From what is known about the chemistry of peracids, the initial formation of an epoxide is a logical hypothesis and has been suggested as an intermediate in the peroxidation of 1,3 diphenylisobenzofuran (equation 20).[52] The authors proposed the intermediate epoxide 56



54 55 (20)

but it has never been observed. Isolation of epoxy acetals have been reported by Krause and co-workers from



56

the photooxygenation of 3-methyl furan 57 (equation 21).[53] The proton at C-2 of 58 is reported at 5.47 ppm

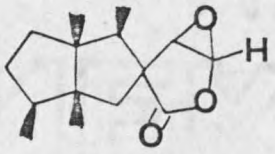
(21)

57 58

and the C-5 proton is reported at 5.30 ppm. These resonances are in accord with those observed in the low temperature spectra of the proposed epoxide 27.

No ^{13}C NMR data were reported for 58 or for 27. The expected chemical shifts for systems like 58 and 27 (e.g., acetals) would be between 90-105 ppm.[54] Examination into the reported ^{13}C NMR chemical shifts for epoxy acetals reveal that the acetal resonance is 20-25 ppm upfield from what would be expected for a normal acetal. For instance, Takeda and co-workers have recently isolated the natural product ptychanolide 59 and report the acetal carbon resonance at 76.1 ppm and the acetal proton at 5.52 ppm.[55] Based on the ptychanolide data it

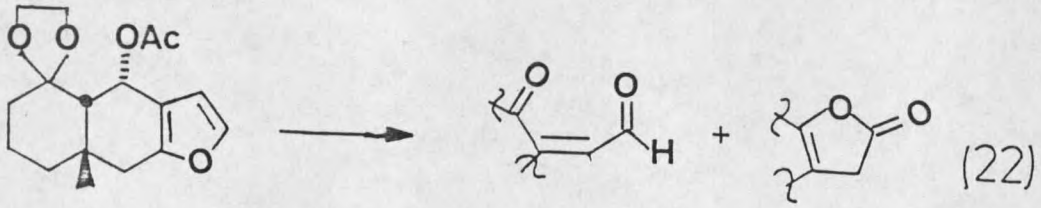
would appear that a low temperature ^{13}C NMR of the



59

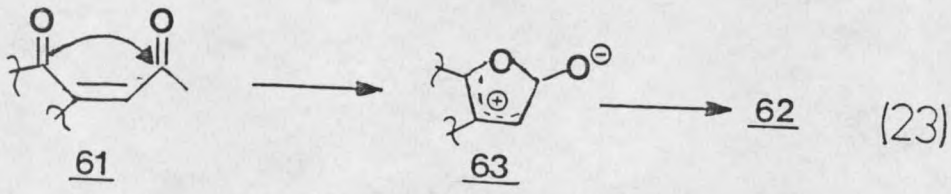
peracid oxidation of 15 could help support the existence of 27.

A final point of discrepancy in the peracid oxidation of alkyl substituted furans is that different workers investigating similar furan moieties report different products. Peroxidation of 15 (a 3,4,5 trialkyl substituted furan) leads to the quantitative yield of the ϵ-lactone 19.[43] The peroxidation of lindestrene 20 which is also a 3,4,5 trialkyl substituted furan consumes only 1 mole of peracid to give a γ-lactone 21. There is also the report by Tada on the peracid oxidation of a 2,3 substituted furan 60 that gave a mixture of dicarbonyl 61 and γ-lactone 62 (equation 22).[45]



60 61 62 (22)

The lactone 62 can be seen as arriving from the cyclization of the dicarbonyl 61, so it is possible that both lactones 21 and 62 arise from a dicarbonyl intermediate (equation 23).



(23)

Summary of Introduction

In reviewing the literature, it is apparent that there are no in vivo studies reported on the oxidative metabolism of alkyl furans. Initial studies with isolated liver microsomes appear to give no metabolism products with furans. Since the exact nature of the oxygen donating species is not known, it is difficult to design an ideal chemical mimic for P-450 enzymes. It is therefore pertinent to survey a number of P-450 mimics to identify potential biological oxidation products from alkyl furans. The reaction of alkyl substituted furans with mCPBA (a P-450 mimic) has been investigated and a mechanism has been proposed by Jennings and Gingerich. The proposed mechanism implies that the first step in the reaction is an epoxidation of one of the double bonds on

the furan. The only evidence for this is observation of a signal corresponding to an acetal in the ^1H NMR spectra of 15 with mCPBA at low temperature.

The second equivalent of peracid in the proposed mechanism is thought to be consumed in a Baeyer-Villiger reaction of a cis-1,4-enedicarbonyl intermediate. The reaction appears to be very fast which is in contrast to what is normally observed for Baeyer-Villiger oxidations. It is not clear why this oxidation should be much faster than other Baeyer-Villiger oxidations.

Lastly, two other investigators have reported that the peroxidation of alkyl substituted furans with an unsubstituted α-position give γ-lactones. This appears to be in contrast to the ϵ-lactones reported by Gingerich.

The goal of the research reported herein was to explore further the details of the Gingerich mechanism and to investigate the reaction of other mixed function oxidase mimics.

STATEMENT OF THE PROBLEM

In 1974, Jennings and co-workers isolated the hepatotoxin tetradymol 13 from Tetradymia glabrata.[35a] Subsequent studies showed that the metabolic oxidation of 13 led to a compound which had enhanced toxicity.[36] Identification of potential furan metabolic products from microsomal oxidation proved to be unsuccessful. Subsequent studies with the MFO mimic mCPBA on a series of alkyl substituted furans led to the conclusion that cis-1,4-enedicarbonyl compounds might be the metabolites responsible for the toxicity of furan compounds.

Since mCPBA might not be the most ideal MFO mimic, it was thought pertinent to investigate a number of other potential mimics.

The proposed mechanism for the peracid oxidation of alkyl substituted furans has some ambiguous points. Figure 3 depicts the general mechanism for the proposed oxidation pathway.[43] In step 1 the peracid is proposed to epoxidize one of the furan double bonds. Existence of the epoxide is based on the detection of a short lived intermediate by low temperature ^1H NMR spectroscopy.

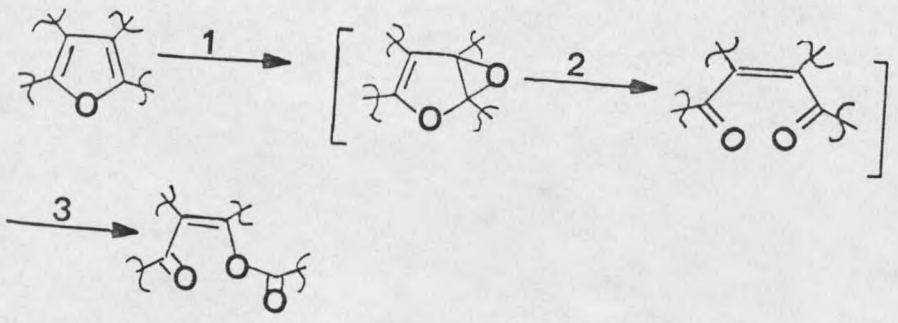


Figure 3. The proposed mechanism for the mCPBA oxidation of alkyl substituted furans.

Further evidence of the epoxide is anticipated with the use of low temperature ^{13}C NMR spectroscopy and will be elaborated in this thesis.

In step 3, a Baeyer-Villiger reaction is proposed to occur very rapidly with the intermediate 1,4 dicarbonyl compounds. In the literature, Baeyer-Villiger oxidations are reported to be acid catalyzed and occur at a much slower rate than is observed for the furan oxidation.

Lastly, conflicting reports on oxidation products occur when there is no substituent in the α position in alkyl substituted furans. Other workers have reported that these furans react with only one equivalent of peracid to form lactones in contrast to the Jennings report which shows that two equivalents are consumed with the formation of ϵ-lactones.

Based on these three discrepancies, it was thought

pertinent to reinvestigate some of the aspects of the proposed mechanism. During the course of the study reported herein, a novel ring expansion reaction has been discovered, more details of the oxidation scheme have been elaborated, and additional MFO mimics have been investigated.

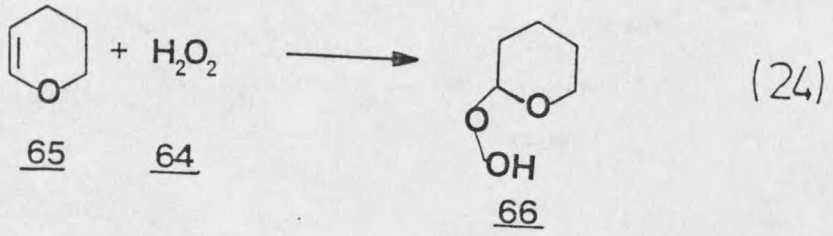
DISCUSSION

Oxidation of Tetrahydrobenzofuran Compounds with Mimics of Mixed Function Oxidase Enzymes

Studies with 2-Hydroperoxytetrahydropyran

Hamilton has shown that alkyl hydroperoxides will not epoxidize olefins without the presence of a transition metal.[56] Most certainly, then, alkylhydroperoxides without the presence of a transition metal would not be good mimics for P-450. However, Rebek has recently shown that α-hydroperoxy ethers are capable of olefin epoxidation.[57] Therefore, one α-hydroperoxy ether was investigated as a potential mimic for P-450 oxidations. Secondly, since these peroxides were probably not capable of Baeyer-Villiger oxidations, it was thought they might allow for the isolation of the dicarbonyl compounds from the oxidation of 14 and 15 as previously proposed by Gingerich.[43]

Synthesis of 2-hydroperoxytetrahydropyran 66. Following a modified procedure of Milas,[58] 66 was synthesized in 60% yield from dihydropyran (equation 24).



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Synthesis of octahydrodibenzofuran 14. Octahydrodibenzofuran was synthesized according to a modified adaption of Criese's procedure (Figure 4).[59]

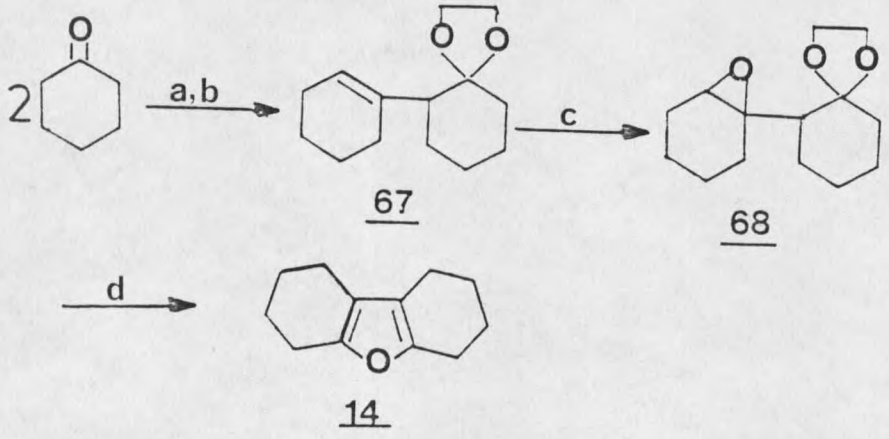
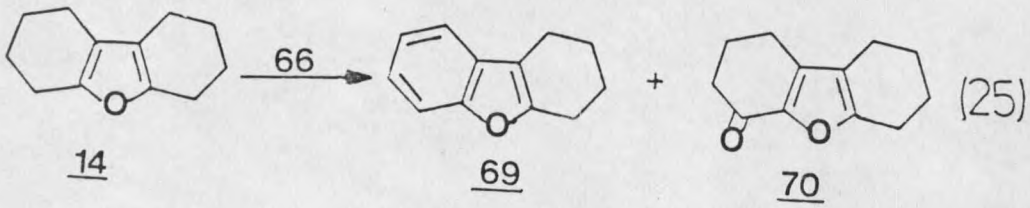


Figure 4. Synthetic scheme for the preparation of octahydrodibenzofuran 14.

a-HCl(g); b-$(HOCH_2)_2$, p-TsOH, C_6H_6 ; c-mCPBA; d-2MHCl, pentane.

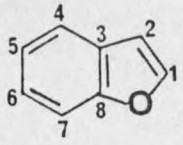
Oxidation of octahydrodibenzofuran 14. In a typical reaction, the furan 14 was dissolved in $CHCl_3$ that had been previously washed with H_2SO_4 and distilled to eliminate any EtOH that is present. The peroxide was then added dropwise and the reaction allowed to sit at room temperature for 48 hours. The reaction was monitored periodically by GC and TLC to measure the amount of furan remaining. After 48 hours, the reaction mixture was washed with 10% $Na_2S_2O_3$, brine and dried over $MgSO_4$. The crude material was then placed on silica gel and eluted with a gradient eluent system. The reaction gave the two products shown in equation 25.



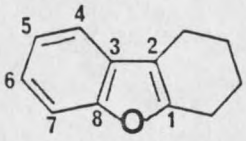
14 69 70

Product 69 was isolated in 27% yield and its structure was elucidated by spectral properties. The ^1H NMR spectrum showed 4 protons in the aromatic region between 7.0 and 7.4 ppm and an 8 proton multiplet between 2.70 and 1.90 ppm. An IR spectrum showed no carbonyl peak but exhibitited an intense peak at 744 cm^{-1} indicative of an ortho- disubstituted aromatic compound. The ^{13}C NMR spectrum showed 8 carbon resonances in the sp^2 region and

4 resonances in the sp^3 region. Table 1 gives the ^{13}C chemical shifts for the downfield carbons of 69 along with the chemical shifts for the model compound, benzofuran 71.



71

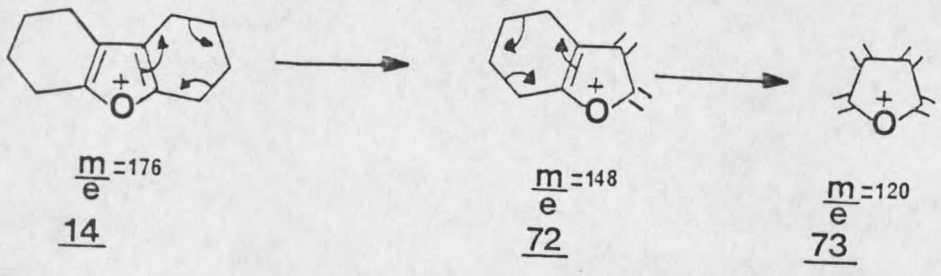


69

Table 1. ^{13}C chemical shifts for 71[54] and 69 (ppm) in $CDCl_3$.

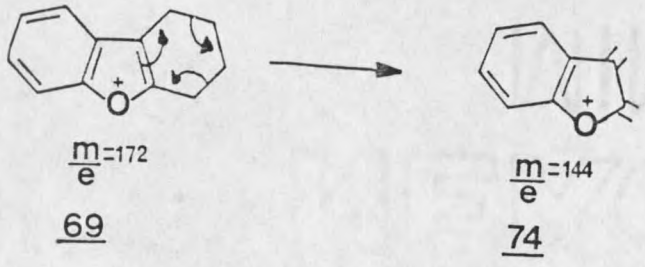
carbon #	71	69
1	144	154
2	111	112
3	127	128
4	121	118
5	122	122
6	124	123
7	106	110
8	155	154

Additional structure proof came from the mass spectrum of 69. It had been shown previously that the starting furan compound 14 gave a base peak at 148 m/e and a second most intense peak at 120 m/e.[59] Exact mass measurements showed that the two peaks were due to the loss of ethylene (equation 26). The mass spectrum of 69 showed a



(26)

molecular ion at 172 m/e and a base peak at 144 m/e. This was attributed to the loss of one ethylene as would be expected if the other ring was aromatized (equation 27). Attempts to synthesize nitroderivatives of 69 failed. Compound 69 was not very stable and decomposed in most solvents within one hour.



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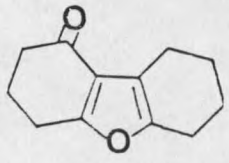
Compound 70 was isolated from the reaction mixture in 13% yield as a white solid (mp=61-62°C) and was quite stable in all solvents tested. The IR spectrum showed a strong carbonyl absorption at 1666 cm^{-1} which was assigned to an α,β-unsaturated ketone. It rapidly formed a 2,4-dinitrophenylhydrazone derivative whose elemental analysis corresponded to a molecular formula of $C_{18}H_{18}O_5N_4$. Accurate mass spectral analysis of 70 gave a

molecular ion corresponding to $C_{12}H_{14}O_2$. The ^{13}C NMR spectra of 70 showed 5 downfield resonances. The resonance at 185.5 ppm was assigned to the ketone carbonyl and those at 158.2, 146.0, 140.5, and 118.6 were assigned to the furan ring. Unfortunately, the position of the carbonyl could not be unambiguously established from this data. It was likely to be at the 1 position as shown in 70 or in the 4 position as is shown in 75. Attempts to obtain suitable crystals for X-ray analysis of the 2,4-DNP derivative or ketone proved unsuccessful.

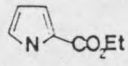
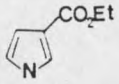
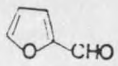


75

Investigation of the literature on UV spectral characteristics of pyrroles and furans showed that there is a significant difference when there is a carbonyl in the 2 position verses the 3 position.[60] As Table 2 indicates, a carbonyl in conjugation with pyrrole or furan gives rise to two UV absorbance maxima. When the carbonyl is in the 2 position the extinction coefficient for the longer wavelength maxima is greater than 10,000 and the shorter wavelength peak is less allowed ($\epsilon <$ 5,000). When the carbonyl is in the 3 position the shorter wavelength maxima has an extinction coefficient

that is usually greater than 10,000 and the extinction coefficient for the longer wavelength maxima is less than 5,000. As is evident in Table 2, the longer wavelength maxima for 70 has an extinction coefficient of 17,000,

Table 2. UV maxima for Pyrrole and Furan when in conjugation with a carbonyl.

Compound	λmax	ε
	233 265	4,500 15,900
	231 263	9,980 3,740
	227 272	3,000 13,200
70	242 292	1,860 17,000
75 [61]	231 280	20,000 3,980

which is in contrast to 75[61] in which the shorter wavelength maxima has the larger extinction coefficient. Based on the UV spectra it was concluded that the carbonyl moiety was in the 1 position as shown by structure 70.

The relative concentrations of 69 and 70 could be varied by changing the initial concentration of peroxide

66 (Table 3). The percent yield and product ratios were determined by quantitative ^{13}C NMR spectroscopy with CCl_4 and CH_2Cl_2 being used as internal standards. Reactions

Table 3. Effect of peroxide concentration reaction on products. ([14] = 9 X 10^{-2}M)

Equivalent(s) 66	%69	%70	Ratio 69/70
1	27	13	2.0
2	15	13	1.1
4	12	27	0.44
6	--	40	--

in either CH_2Cl_2 or benzene failed to show any products. Attempts at heating any of the reaction mixtures led to the rapid decomposition of 66 and reduced yields of products.

Maximum yield for the reaction was 40% and no other furan products could be isolated. No starting material or other identifiable material could be recovered. There was also no evidence for the formation of the cis-1,4-enedicarbonyl compound, 26. It is not readily apparent that epoxidation of the furan moiety of 14 would give products 69 and 70. A more reasonable explanation of their formation is an allylic oxidation. Since these reactions were low yield and slow, they were not pursued further.

Studies with 3-Methyl 4,5,6,7 Tetrahydrobenzofuran 15

Since the yield of the reaction with 14 was low and 60% of the furan could not be accounted for, a new substrate was selected. It was thought that the methyl group on 15 would help identify reaction products since methyl groups are relatively easy to identify in the ^{13}C and ^{1}H NMR spectra. Secondly, since 15 does not have an α-substituent it would be of interest to see if γ-lactone products would be produced as previously reported.[42,45]

Synthesis of 3-methyl-4,5,6,7-tetrahydrobenzofuran. The synthesis of 15 is outlined in Figure 5 and is the procedure used by Gingerich.[43]

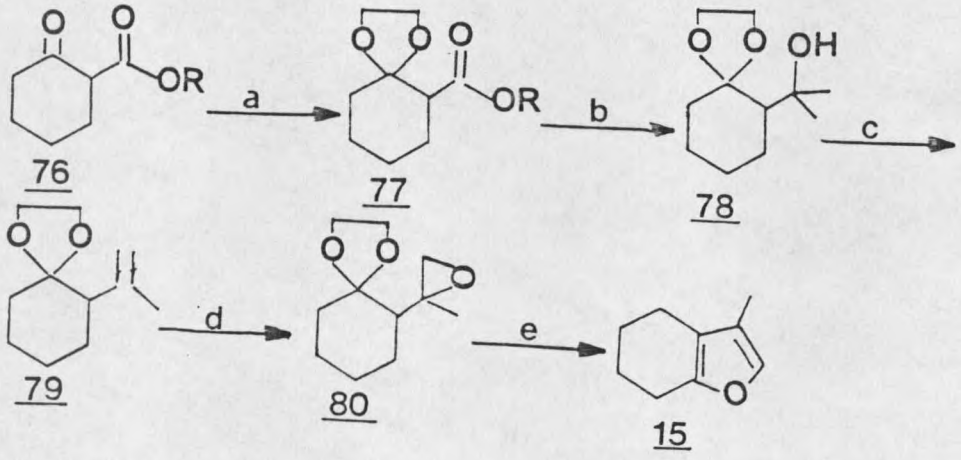


Figure 5. Synthesis of 3-Methyl-4,5,6,7 tetrahydobenzofuran 15.

a-$(HOCH_2)_2$, p-TsOH, C_6H_6, $\triangle$; b-MeMgI; c-p-TsOH, C_6H_6, d-mCPBA; e-2M HCl, pentane.

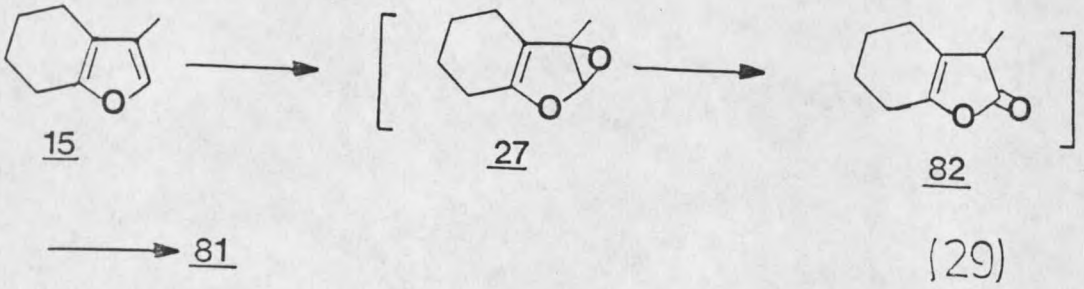
Oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran 15. When two equivalents of 66 were added dropwise to a $CHCl_3$ solution of 15, the solution slowly turned purple. After 12 hours no more furan could be seen by GLC analysis. After work-up as with 14 and column chromatography, lactone 81 was isolated as a clear oil in 20% yield (equation 28). No other products from 15 could be identified.

(28)

As with the products from the oxidation of 14, the product was identified on the basis of its spectral properties. The IR spectra showed a strong carbonyl peak at 1745 cm^{-1}, attributed to an α,β-unsaturated lactone carbonyl and a strong peak at 1690 cm^{-1} attributed to a double bond in conjugation with a carbonyl. The ^{13}C NMR spectra showed a peak at 172 ppm which was assigned to the lactone carbonyl. Resonances at 119 and 162 ppm were assigned to the α and β carbons, respectively. A doublet resonance at 80.1 ppm was assigned to the 7a carbon. The ^{1}H spectrum showed a multiplet at 4.56 ppm which was assigned to the 7a proton. The ^{1}H and IR spectra were

identical with those reported in the literature for 81.[62] As an additional proof, 81 was reduced with diisobutyl lithium aluminum hydride to give 15 in 80% yield.[63]

As in the case of the oxidation of 14, the yield of this reaction was very low. No other oxidation products of 15 could be identified. Since the reaction with 66 is so slow, decomposition of the furan is a serious competing reaction. Mechanistically lactone 81 can be seen as arising from an NIH Shift of an initially formed epoxide 27 (equation 29). β,γ-unsaturated-γ-lactones



(29)

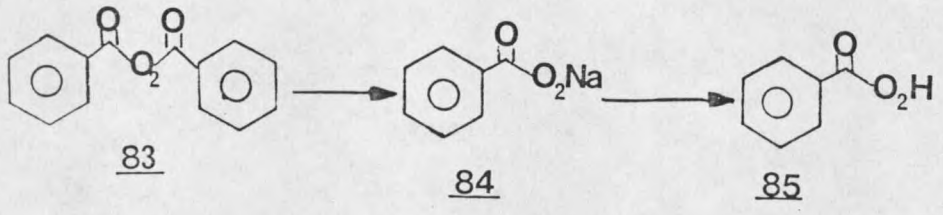
such as 82 have been previously shown to isomerize slowly to α,β-unsaturated-γ-lactones in many solvents or by heating.[64]

The results of the reaction of 66 with 14 indicate that 66 is not a good oxidizing reagent and most certainly is not a good MFO mimic. The results with 15 were a bit more encouraging but unfortunately the formation of 81 was in low yield and required long reaction times. At this point it was decided to pursue stronger oxidizing agents.

Studies with Perbenzoic Acid and p-Nitroperbenzoic Acid

As a general rule, the oxidizing ability of a peracid is related to its pKa.[65] Of the peracids commonly used in organic oxidations, trifluoroperacetic is therefore considered the strongest and peracetic the weakest. It was then decided to investigate peracids that have pKa's different from mCPBA. Perbenzoic acid (PBA) was chosen as an oxidizing agent. It would be predicted to be slightly weaker than mCPBA based on the pKa of the parent acids (pKa_{BA} = 4.2; pKa_{mCPBA} = 3.8).

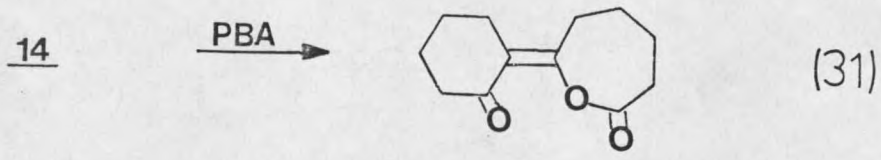
Synthesis of perbenzoic acid. PBA was synthesized according to the method of Braun.[66] Benzoyl peroxide was cleaved in MeOH/MeO^-Na^+ and the subsequent salt was acidified with H_2SO_4 (equation 30). PBA was recrystallized from pet ether:ether and stored at -5°C. The



83 84 85 (30)

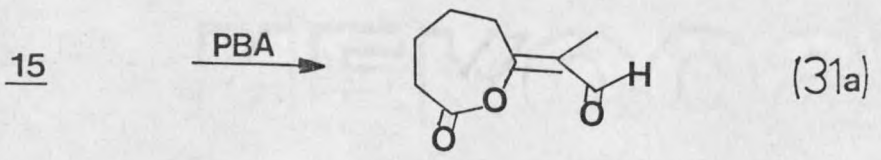
purity of the PBA was checked by standard iodometric titration.

Oxidation of 14 and 15 with PBA. When two equivalents of PBA were reacted with furan 14 in $CHCl_3$ at room temperature, the lactone-ketone 18 was produced quantitatively. Likewise, when PBA was reacted with 15, lactone 19 was produced quantitatively (equations 31 and 31a).



(31)

18



(31a)

19

As with mCPBA when only one equivalent of peracid was used, one half of the starting material was recovered with the other half accepting two moles of PBA and yielding 18 or 19. The rate of the reaction appeared to be similar to that for mCPBA.

When 15 was reacted with PBA under the identical conditions as reported by Takeda in the lindestrene 20 oxidation[42] (benzene, 0°C, 1.2 eq. PBA), 19 and starting furan 15 were identified. When the reaction was run in CH_2Cl_2, ether or THF, 19 was still the only product.

Thus, it was concluded that PBA reacts in the same manner as mCPBA.

Oxidation of 14 and 15 With p-Nitroperbenzoic Acid

Para-nitroperbenzoic acid (p-NBA) is a bit stronger oxidizing agent than mCPBA based on the pKa's of the parent acids (3.4 and 3.8, respectively). p-NPBA is also known to hydroxylate tertiary alkanes in high yields.[67] Reactions of 14 or 15 produced results which were identical to those using mCPBA and PBA. Thus, it appears that all aromatic peracids react in the same manner.

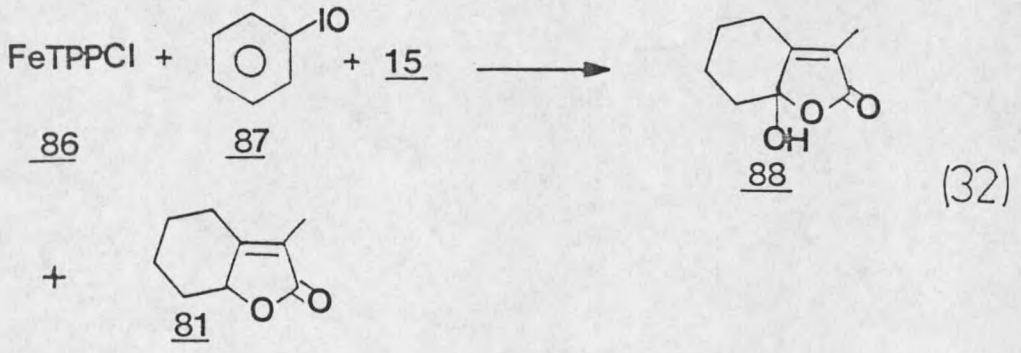
Studies with Chlorotetraphenylporphyrinato Iron III (FeTPPCl)

With the recent discoveries by Coon that P-450 enzymes can utilize H_2O_2 as an oxygen source[24], Groves developed a mimic using an iron III tetraphenylporphine complex and iodosobenzene as an oxygen source.[22] This system has been shown to epoxidize olefins in high yield and to form alcohols from unactivated alkanes.[68] Its reaction with aromatic substrates has not been reported.

Oxidation of 15 with FeTPPCl. FeTPPCl was

synthesized according to the literature procedure from tetraphenylporphine and $FeCl_2$ $4H_2O$.[69] In a typical experiment, one equivalent of FeTPPCl was dissolved in CH_2Cl_2 along with the furan, under N_2. The iodosobenzene (1.5 equivalents) was added slowly as a solid with a powder addition funnel. The furan was normally consumed within 20 minutes after the final addition. It was also noted that the FeTPPCl decomposed over this period as garnered by TLC. When the reaction was over, the CH_2Cl_2 was evaporated and the residue extracted with ether. The ether extract was then poured through activated charcoal and evaporated. The resultant residue was placed on silica gel and eluted with a polar gradient.

In the reaction of 15 with FeTPPCl, lactone 81 and the hydroxy-lactone 88 were isolated in 30% and 20% yield, respectively (equation 32). The hydroxy-lactone



(32)

was identified on the basis of its spectral properties. The ^{13}C NMR spectrum showed 4 down-field carbon resonances. The peak at 172 ppm was assigned to the

carbonyl. Peaks at 120 ppm and 160 ppm were assigned to the α and β carbons, respectively; and the peak at 103 ppm was assigned to the hemiketal carbon. The IR spectrum had a broad peak at 3430 cm^{-1}, which was assigned to the hydroxyl group and a carbonyl absorbance at 1745 cm^{-1}. The ^{1}H NMR spectrum exhibited a proton at 3.50 ppm that exchanged rapidly with D_2O, which is indicative of a hydroxyl proton. The mass spectrum gave a molecular ion at 168 m/e which indicated a compound with the addition of 2 oxygens more than the starting furan 15.

Studies with S-9

As a final survey of P-450 mimics, a commercial preparation of induced rat liver microsomes was reacted with 15 to see if any oxidation products could be observed.[70] For the preparation of S-9, rats are pretreated with either Aroclor 1254 or 3-methylcholanthrene to increase the P-450 activity. The rats are then sacrificed and their livers homogenized in a KCl buffer solution. After centrifugation, the supernatant is decanted and frozen. The supernatant's oxidation activity is then measured by its ability to form hydroxybenzopyrene from benzopyrene.[71] Based on substrate, the

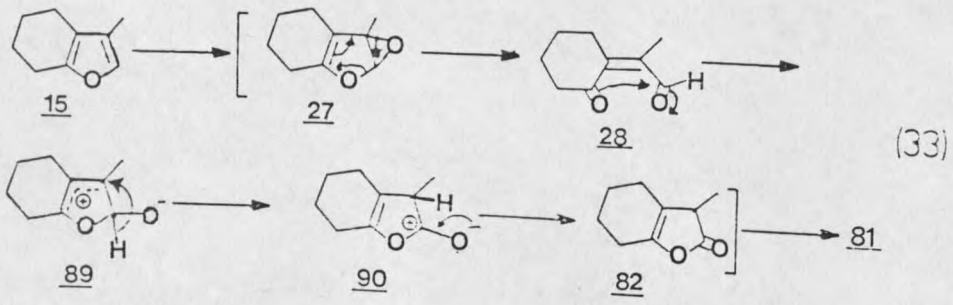
yield of hydroxybenzopyrene from benzopyrene is very low.

Oxidation of 15 with S-9. A preparation of S-9 was placed in an incubator at 37°C and furan 15 was added as a solution in DMSO. After 2 hours the mixture was extracted with CH_2Cl_2, dried over K_2CO_3, and filtered. The residue was then analyzed via GC/MS. The CH_2Cl_2 extract contained the starting furan, DMSO and a compound that gave the identical mass spectrum as 81. Purification of the lactone 81 on SiO_2 showed the yield to be 10%.

Summary of Chemical Mimic Investigations

The conclusions of previous work in this area stated that cis-1,4-enedicarbonyl compounds may be viable intermediates in the in vivo oxidation of furans.[43] The products observed from S-9, FeTPPCl and the hydroperoxyether 66 can be seen as arriving from a dicarbonyl intermediate (equation 33). Compounds similar to 88 have been previously reported as air oxidation products of β,γ-unsaturated-γ-lactones.[72] FeTPPCl might also oxidize 81 to 88 as it has been shown that FeTPPCl can form alcohols from tertiary alkanes.[68] An alternative to the

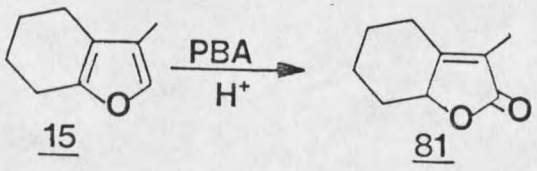
mechanism proposed in equation 33 is shown as equation 29 and follows an NIH Shift pathway. It is therefore possible that the peracids interact with epoxide 27 or dicarbonyl compound 28 to form 19, while S-9, 66, and FeTPPCl cannot add a second equivalent of oxygen, and either one of the intermediates rearrange to 81.



(33)

Effect of Acid on the Peracid Oxidation of Tetrahydrobenzofurans With an Unsubstituted Position

During the investigation of the reaction of PBA with 15, it was found that a catalytic amount of mineral acid had a profound effect on the reaction. When 15 was dissolved in ethanol free $CHCl_3$ that had been purified a month before, the solution turned pink. When PBA was added to this solution it turned colorless very rapidly. Spectroscopic analysis showed the product to be the unsaturated lactone 81 (equation 34). Since it is a well known fact that $CHCl_3$ will decompose to HCl when the



15 81 (34)

stabilizer is removed, it was reasonable to assume that mineral acid was affecting the reaction. When freshly purified $CHCl_3$ was used and a catalytic amount of concentrated HCl was incorporated into the reaction, the lactone 81 was again produced quantitatively. It was also found that p-NPBA or m-CPBA reacted in an identical manner.

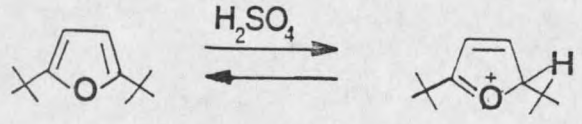
Effect of Various Acids and Solvents

In the solvents, THF, CH_2Cl_2, benzene and $CHCl_3$ furan 15 was converted to 81 when a catalytic amount of HCl was used in combination with PBA. If the acid was introduced to the reaction mixture (containing furan) prior to the addition of PBA, the solution turned pink. Presumably this is a result of the protonation of the furan. Gaseous HCl was also effective in facilitating reaction 34. The use of H_2SO_4 rather than HCl in $CHCl_3$ or ether appeared to reduce the rate of 81 formation. Finally, if one uses p-TsOH or acetic acid in $CHCl_3$, the yield of 81 is lowered and a number of other unidentified products are formed.

Thus, it appears that HCl is the acid of choice in any of the solvents investigated.

Role of H^+ In the Formation of 81 From PBA and HCl

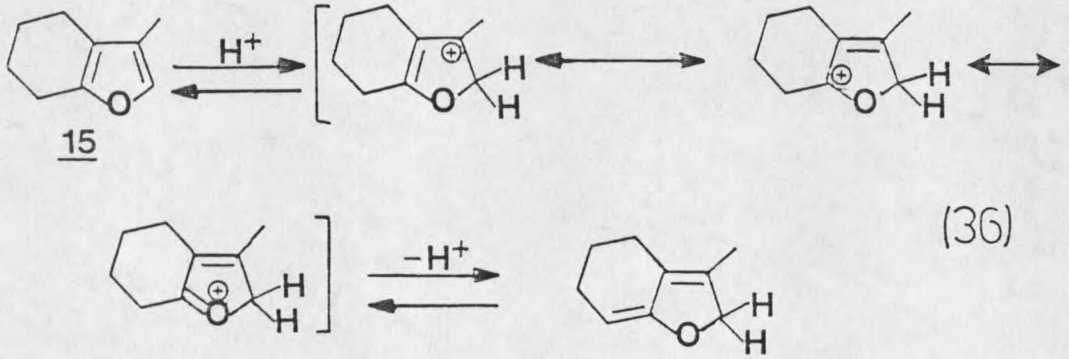
Effect of acid on furan. A reasonable assumption was that acid might effect the furan in some way before the reaction with peracid. It had been previously shown by NMR spectroscopy that 2,5 ditertiarybutyl furan formed a stable cation in neat sulfuric acid (equation 35).[73] The resultant cation was found to be stable in solution



91 92 (35)

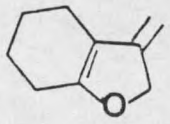
for a number of days and the furan could be recovered by the addition of H_2O. It is therefore conceivable that the pink color in the reaction of 15 with PBA and H^+ could be from a protonated form of 15. Unfortunately, the authors of the above reference gave no indication as to the color of the protonated species 92. The problem with invoking this type of an intermediate for the reaction of 15 is that peracid would be required to react with an electron deficient moiety. This seems unreasonable since PBA usually seeks out nucleophiles.

It does seem that the acid could react with the furan to form a protonated species, which in turn, loses a different proton to form a new more reactive substrate that reacts with PBA to form 81 (equation 36).



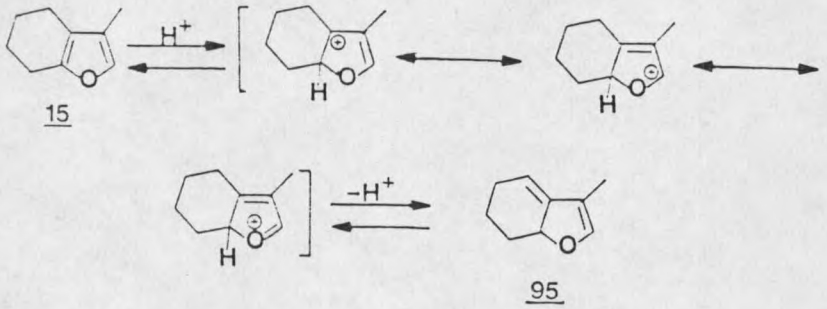
15 93 (36)

Protonation of 15 could occur at either the 2 position as shown in equation 36 or at the 7a position to give a number of possible products. Protonation at C-2 could give diene 93, but epoxidation of the resultant double bonds would not give product 81. Protonation of C-2 could also lead to the formation of diene 94, however, 94 could not lead to 81 via an epoxidation mechanism.



94

Protonation at C-7a and subsequent deprotonation leads to a different diene 95 as shown in equation 37.



(37)

95

Epoxidation of diene 95 could then lead to the formation of lactone 81 as shown in Figure 6. The enol 98 is

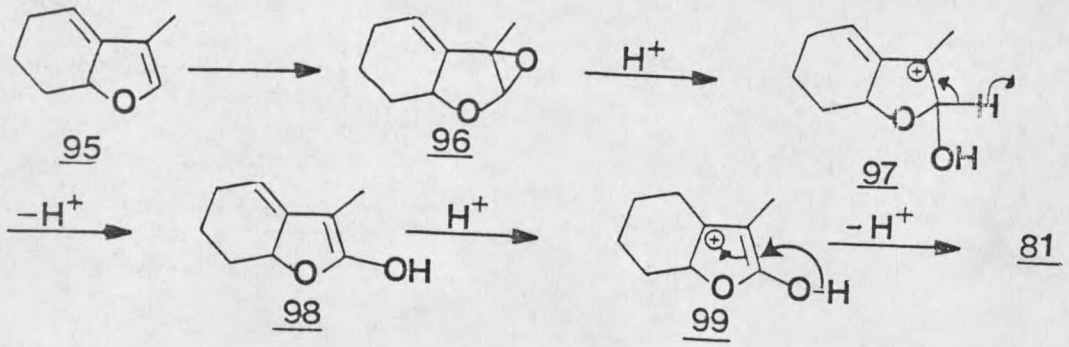
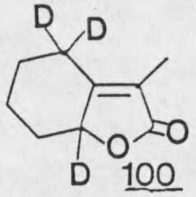


Figure 6. Formation of 81 from 95 with PBA and acid.

nothing more than one of the two possible enol forms of 81. Protonation of C-4 in 98 is then the initial step in the tautomerization to 81.

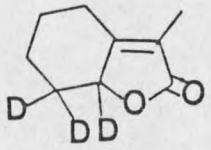
Investigation with deuterium. If the pathway shown in equation 37 and Figure 6 were operating in the conversion of 15 to 81, one would expect deuterium capture, as shown with structure 100. Deuterium at C-4 would result from the isomerization of 98 and deuterium at the 7a position would be from the initial protonation of



15. One problem with this test of mechanism is the fact that deuterium exchange at position 4 could occur with 15 prior to oxidation. However, exchange at C-4 in

15 can be easily tested for in the presence of acid without PBA.

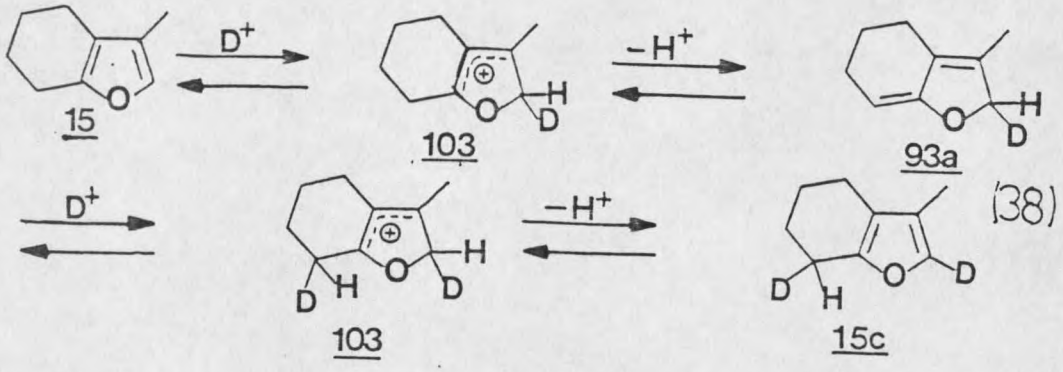
To test the validity of structure 100, the peroxidation of 15 was carried out with deutero-PBA and DCl. Deutero-PBA was synthesized by forming the sodium salt of PBA (NaOD in D_2O) and hydrolyzing it in DCl and D_2O. The furan 15 was subsequently dissolved in $CDCl_3$ along with a catalytic amount of DCl and deutero-PBA was added. The reaction was then worked up in the normal manner. The product isolated, 101 had deuterium on the 7 and 7a carbons.



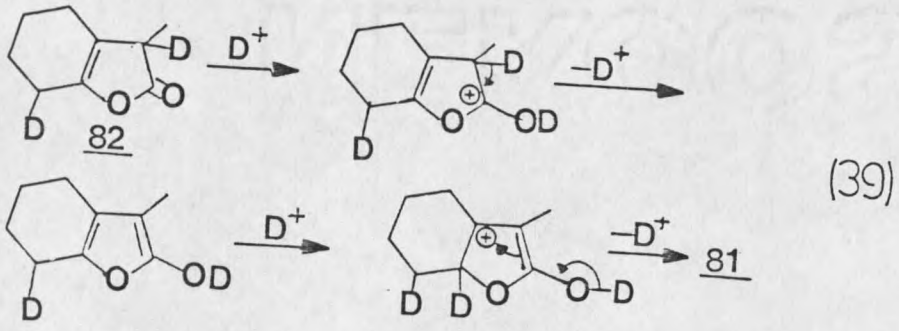
101

The positions of the deuterium were determined by noting the decrease in intensity of the signals in the ^1H spectra assigned to 7 and 7a. The ^2H spectrum showed 3 signals at the identical chemical shifts as the ^1H spectra relative to $CDCl_3$. From these results it was clear that 95 was not involved in the reaction.

The deuterium distribution of 101 can be explained by a rapid protonation at C-2 to form 15c, which then reacts with PBA to give 101 (equation 38). The

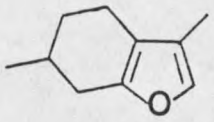


deuterium at 7a could be explained by an acid catalyzed rearrangement of 82 to 81 (equation 39). It should



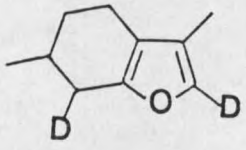
also be noted that there was no NMR spectral evidence for any deuterium in the methyl group.

To corroborate these results, menthofuran 102 was chosen for further studies. It has the advantage that the C-7 protons can be identified by relating them to the methyl group at C-6. The proton on C-6 was established



102

to be at 1.90 ppm by virtue of the fact that irradation of it collapsed the methyl doublet at 1.15 ppm to a singlet. At the same time the doublet of doublets at 2.88 ppm became a doublet. Further addition of 1 μl of DCl to a $CDCl_3$ solution of 102 rapidly caused a decrease in the signals at 7.05 ppm and 2.88 ppm. Thus, it was established that deuterium was in fact incorporated at C-7 and C-2 and that protonation occurs at C-2. The other C-7 proton could not be identified because it was buried under another multiplet. Menthofuran, reacts rapidly with DCl to give 102a which is an excellent model for 15c.



102a

In another experiment to corroborate that C-2 was protonated, 15 was dissolved in neat H_2SO_4 and its ^1H NMR and ^{13}C NMR spectra observed. Table 4 is a list of the ^{13}C NMR chemical shifts and multiplicities for 15 in neat

$CDCl_3$ and neat H_2SO_4. Thus, it appears from the multi-

Table 4. ^{13}C chemical shifts and multiplicities for 15 in $CDCl_3$ and H_2SO_4.

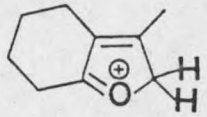
C#[c]	$CDCl_3$	m	H_2SO_4[a,b]	m
7a	150.8	s	210.4	s
2	136.6	d	92.3	t
3	119.7	s	138.6	s
4a	117.7	s	193.1	s
4	23.2	t	30.2	t
5	22.9	t	20.1	t
6	22.9	t	20.6	t
7	20.4	t	19.6	t
Me	7.9	q	14.0	q

a- Relative to $CDCl_3$. b- It is not certain if these chemical shifts correspond to the same carbons as in $CDCl_3$. c- Carbons 4,5,6,7 can be interchanged.

plicities of the carbons that there are 13 protons on the furan and the furan is in fact protonated.

The ^1H NMR spectrum of 15 in H_2SO_4 was similar to the spectrum in $CDCl_3$ except that the aromatic proton moved upfield 1.40 ppm from where it was in $CDCl_3$ and integrates to 2 protons. When the dark purple solution of 15 in H_2SO_4 was treated with H_2O and extracted, the furan was recovered in 80% yield. Addition of gaseous HCl to 15 in $CDCl_3$ had no effect on either the ^1H or ^{13}C NMR spectra. Since there are 13 protons in the furan based on the ^{13}C and ^1H NMR spectra, the structure of 15

in H_2SO_4 is probably cation 103.



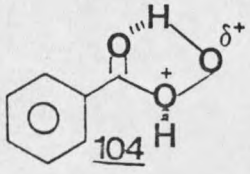
103 HSO_4^-

Competition between HCl and PBA. As a final test of the acid effect on furan, a competition experiment was carried out. It was thought that if the furan needed to interact with HCl before reaction with PBA, then addition of HCl at the same time PBA was added would result in a mixture of 81 and 19. This assumed that the PBA and H^+ react with the furan at a similar rate. When a solution of 1.2 equivalents of PBA and a catalytic amount of HCl was added to the furan, 81 was still the only product produced. If 2 equivalents of PBA were added the only product was again 81.

From the above experiments, it was apparent that the reaction of acid with furan to form a more reactive species did not occur in the peracid oxidation of 15 to 81. The results of the competition experiments also indicated that 15 did not have to interact with H^+ prior to oxidation with PBA to form 81.

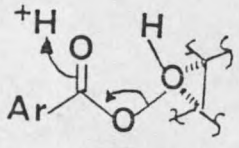
Effect of HCl on PBA

Since the work with DCl indicated that the interaction of acid with furan prior to oxidation was probably not responsible for the production of the lactone, the prospect of acid affecting the PBA to produce 81 was investigated. It has previously been shown that peracids form epoxides with olefins faster in the presence of mineral acid.[74] One possible explanation is that the acid protonates the oxygen closest to the carbonyl group to make the terminal oxygen more electropositive (104).



104

The other explanation is that during the epoxidation reaction the acid protonates the carbonyl oxygen to make the peracid a better leaving group (105). When PBA was



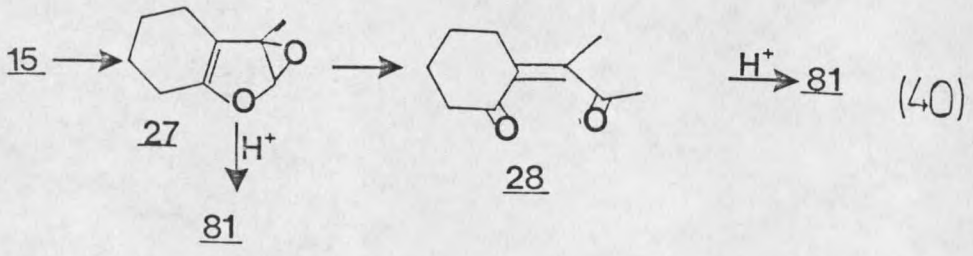
105

placed in $CDCl_3$ with DCl its ^{13}C NMR spectrum was identical to its spectrum without DCl. Its ^{1}H NMR spectrum in acid no longer showed the peroxide proton, which indicates that exchange is taking place. Thus, the

only perturbation caused by HCl on the peracid that could be detected by NMR spectroscopy was the exchange of the acid proton.

Studies with 3-Methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O In the Presence of Acid

At this point it was concluded that the acid did not affect the furan prior to its reaction with PBA to facilitate the γ-lactone formation. Acid affecting the PBA to facilitate the γ-lactone formation is a little less clear. Up to this point, it was assumed that 81 was formed by an acid modification on the standard epoxidation-dicarbonyl mechanism as shown in equation 40. The acid could either effect the epoxide 27 or the



(40)

dicarbonyl 28 to form 81. Thus, it was pertinent to do an ^{18}O labeling experiment to determine the fate of the furan oxygen in the acid catalyzed reaction. If the formation of 81 went through a 1,4 dicarbonyl

intermediate and/or an epoxide on the least substituted double bond, the furan oxygen would be found as the ester oxygen in the lactone ring. If the furan oxygen ended up in the carbonyl, then it would imply that epoxidation was occurring at the more substituted furan double bond or a completely different mechanism was operating.

The fate of the furan oxygen could be determined by synthesizing the ^{18}O analogue of 15 and oxidizing it with PBA in the presence of HCl. It had been previously shown that carbons bearing an ^{18}O or an ^{16}O could be distinguished from each other by the use of high resolution ^{13}C NMR spectroscopy.[43] Carbons bearing an ^{18}O resonate slightly upfield from their ^{16}O counterparts. By measuring the relative peak intensities, the amount of ^{18}O could also be established. This quantitation can also be correlated with the mass spectral measurement of the M^+ and M^++2 peak intensities.

Synthesis of 3-methyl-4,5,6,7-tetrahydrobenzofuran ^{18}O. The synthesis of the ^{18}O analogue of 15 (15a) was done following the procedure of Jennings and co-workers[75] and is outlined in Figure 7.

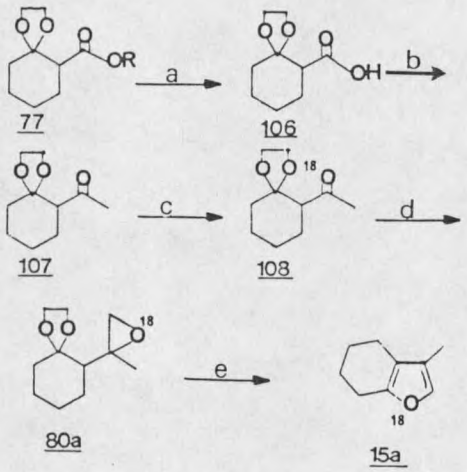


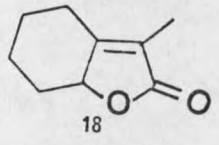
Figure 7. Synthetic outline of the synthesis of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O.

a-5M $NaOH/H_2O$; b-MeLi, EtOEt; c-$H_2{}^{18}O$, THF, H^+; d-$CH_2{=}S(CH_3)_2$; e-2M HCl pentane.

The ^{18}O was introduced in the ketone 107 by dissolving it in a minimal amount of THF and adding one equivalent of $H_2{}^{18}O$ along with 1 µl of HCl. After 1.5 hours, the reaction was quenched. Analysis of the ^{13}C NMR spectrum showed the carbonyl at 209.4 ppm to be resolved into two peaks with the upfield peak ($C{=}^{18}O$) 0.052 ppm upfield from the ^{16}O carbonyl. Measurements of the peak intensities showed 51% ^{18}O incorporation. Mass spectral analysis indicated 49% ^{18}O. Since the oxidation of 15a was to be conducted in aqueous HCl, and some label might be lost, the procedure was repeated to increase the amount of ^{18}O in the ketone. After the second exchange, ^{13}C NMR spectroscopy revealed 75% ^{18}O in the ketone.

Formation of the epoxide 80a from 108 proved to be a low yield reaction after work-up, with a significant amount of starting ketone left. This procedure was repeated a second time. Cyclization of 80a afforded the furan in 40% yield after column chromatography. ^{13}C NMR analysis of the peak at 150.9 ppm of the furan showed that it was 2 peaks. The C-^{18}O peak was 0.039 ppm upfield from the C-^{16}O peak. Intensity measurement showed there to be 39% ^{18}O incorporation. Analysis of the peak at 136.1 ppm showed that it was also two peaks. The C-^{18}O peak was 0.037 ppm upfield from the C-^{16}O peak. This peak also showed 39% incorporation.

Oxidation of 15a with PBA and aqueous HCl yielded 81a in 90% yield. High resolution ^{13}C NMR spectroscopy



81a

showed that the C-7a peak at 80.1 ppm was resolved into two peaks. The C-^{18}O peak was 0.024 ppm upfield from the C-^{16}O peak. Intensity measurements indicated 32% ^{18}O incorporation. Analysis of the carbonyl peak at 172 ppm also showed two peaks with the C=^{18}O peak shifted 0.011 ppm upfield from the C=^{16}O peak. Intensity measurements

showed 30% ^{18}O incorporation. Mass spectral analysis showed 30% ^{18}O incorporation.

Results of this experiment indicated that all of the ^{18}O is in the lactone ring oxygen. If any ^{18}O was in the carbonyl oxygen it would cause an upfield shift of the carbonyl carbons by about 0.04 ppm.[43] This was not detected. The loss of ^{18}O is attributed to the fact that the reaction was run in aqueous acid. It is unlikely that loss of ^{18}O occurs from exchange of the product because when 81a was allowed to stand in aqueous acid for 1 hour there was no change in the amount of ^{18}O. It is, therefore, possible to suggest that the loss of ^{18}O can be attributed to exchange with an intermediate 1,4 dicarbonyl compound shown in Figure 8.

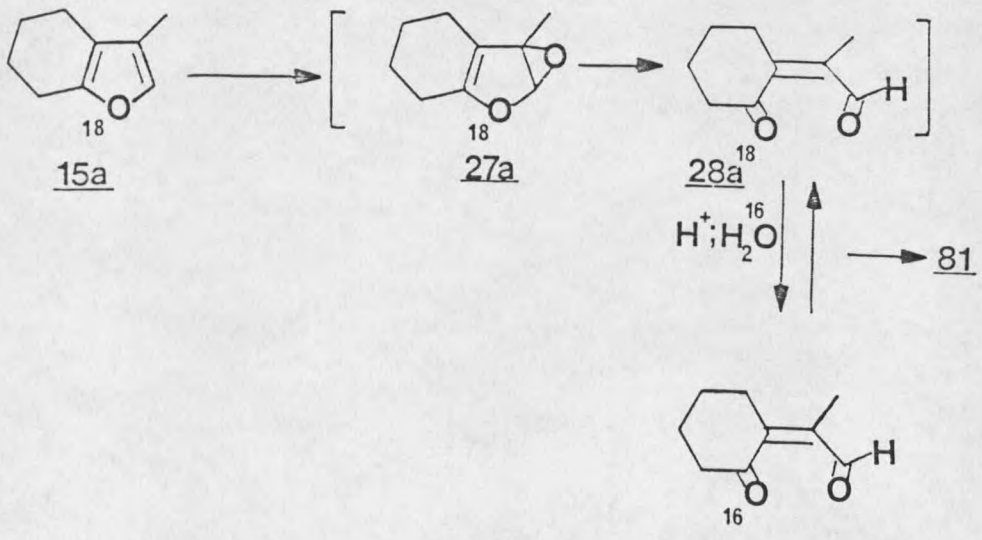


Figure 8. Possible pathway to account for loss of ^{18}O in oxidation of 15a.

The results of the ^{18}O labeling experiment indicate that if the first step of the reaction is epoxidation, it occurs on the least substituted double bond, which is the same as in the non acid catalyzed case. At this point, it appeared that there were two reasonable pathways for the formation of 81. The first pathway, depicted in Figure 9, is referred to as the "non" NIH Shift pathway. The second pathway which will be discussed shortly is shown in Figure 11 and it is referred to as the dicarbonyl pathway.

The pathway depicted in Figure 9 assumes the acid reacts with the epoxide 27 to give the ion 89. It can then lose a proton to give the enol 109, which isomerizes

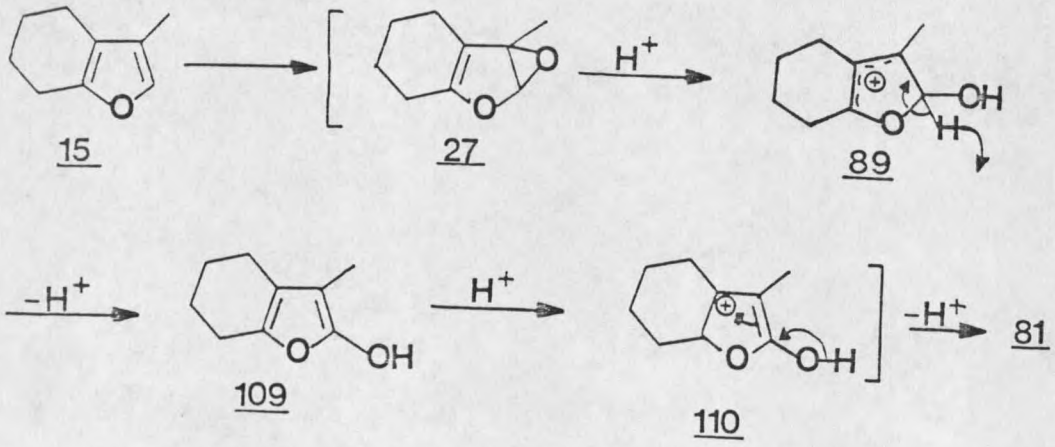
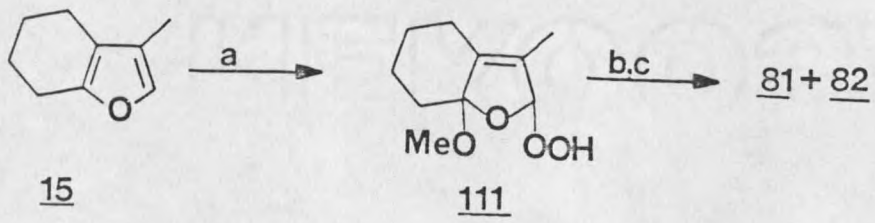


Figure 9. Non NIH Shift pathway for the formation of 81.

to 81. This mechanism can also account for the fact that the NIH Shift product, the β,γ-unsaturated-γ-

lactone, 82 is not observed.

To confirm that the NIH Shift product 82, is not produced in the reaction, 82 was synthesized via a modified procedure of Foote[64] (Figure 10). After 111 was treated with $P\phi_3$ in refluxing ether, the solvent was evaporated at reduced pressure. The residue was then dissolved in benzene and refluxed for 2 hours. Evaporation of solvent afforded a 90:10 mixture of 82 to 81.



15 111

Figure 10. Synthesis of the β,γ -unsaturated- γ -lactone 82.

a- rose bengal, O_2, hv, MeOH; b-$P\phi_3$, EtOEt,A; c- Δ, C_6H_6

Addition of HCl to a $CDCl_3$ solution of 82 and 81 did not cause a rapid isomerization of 82 to 81. After 2 hours the amount of 82 had decreased by 20% while the amount of 81 had increased by 20%. After 24 hours the only product present was 81 and its concentration had increased greatly relative to an internal standard indicating that it

was derived from 82.

The results of the above experiment indicate that the conversion of 82 to 81 does occur in $CDCl_3$ and acid (equation 41), but it is a slow process compared to the formation of 81 from the peroxidation of 15. The conversion of the menthofuran analogues of 82 and 81 has been

82 81 (41)

reported to occur thermally at 155°C in 48 hours.[72] Treatment of a mixture of 82 and 81 to the identical conditions as the peracid oxidation of 15 to 81 still afforded a mixture of 82 and 81.

The non-NIH Shift mechanism (Figure 9) cannot account for the loss of ^{18}O in the labeling experiments. So a second possible mechanism (termed the cis-1,4-enedicarbonyl mechanism) is proposed to account for the loss (Figure 11). In this mechanism the H^+ interacts with the

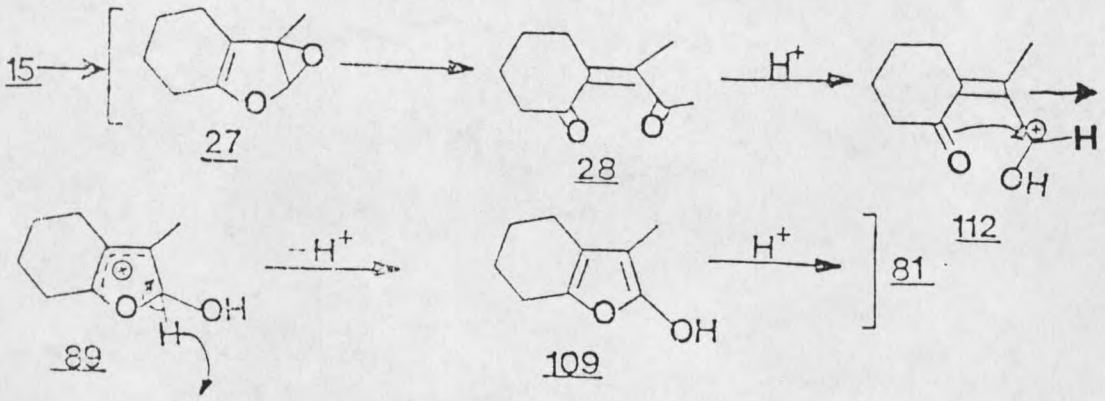
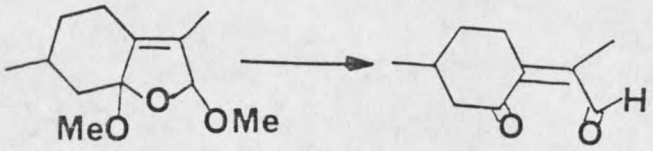


Figure 11. Dicarbonyl mechanism for the formation of 81.

dicarbonyl compound 28 which cyclizes to 89, which then loses a proton to form 109. Note that both proposed mechanisms form the same intermediate ion 89, but through different routes. Protonation at the ketone carbonyl probably also occurs, but does not lead to the observed product.

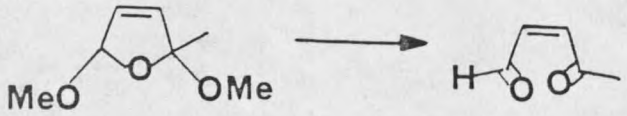
Effect of Acid on Cis-1,4-Enedicarbonyls

At this point it was decided to investigate the fate of cis-1,4-enedicarbonyl compounds in acid. Foote had previously reported the preparation of the dicarbonyl compound 114 from the hydrolysis of the ketal 113 (equation 42).[76] The workers, however, did not totally characterize the molecule, but simply determined its



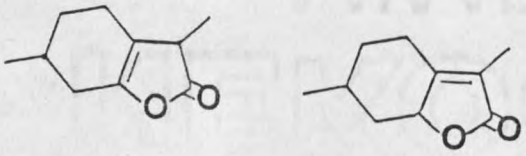
113 114 (42)

molecular formula and characterized its structure based on the analogy of the formation of β-acetylacrolein 116 from the hydrolysis of 2,5 dimethoxy-2,5-dihydrosylvan 115 (equation 42a).[72] In an attempt to confirm or deny



115 116 (42a)

the proposed structure of 114, Eastman and Hirsch repeated the hydrolysis of 113 and isolated lactones 117 and 118.[72] There was never any evidence for the formation of 114. Attempted synthesis of the cis-1,4-



117 118

enedicarbonyl 28 in this laboratory proved to be unsuccessful.[43]

It was then apparent that the synthesis of 28 would

be very difficult if at all possible. Hence, it was decided to synthesize a good model dicarbonyl compound that could readily form a lactone (e.g., a cis-1,4-enedicarbonyl). It was previously noted in the literature that Tada had synthesized a mixture of lactone 62 and the dicarbonyl compound 61 from the peracid oxidation of a 2,3-unsub-stituted furan 60 (equation 22).[45] It was then decided to synthesize tetrahydrobenzofuran, and

60 61 62 (22)

attempt to synthesize a 1,4 dicarbonyl compound and investigate its fate in acid.

Synthesis of tetrahydrobenzofuran 119. Following the procedure of Scharf and Wolters,[77] tetrahydrobenzofuran was synthesized in 40% yield from cyclohexanone (Figure 12).

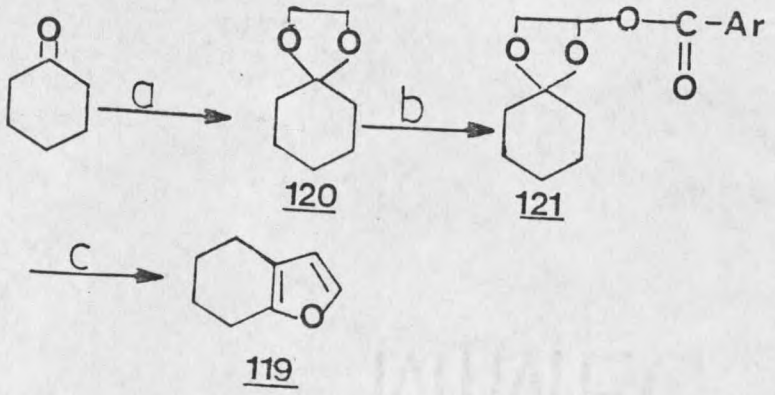
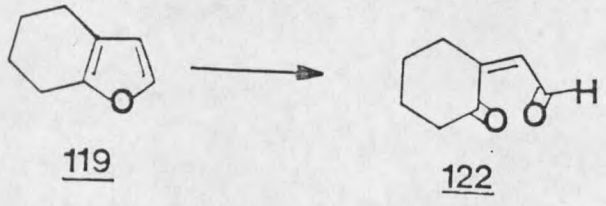


Figure 12. Synthesis of tetrahydrobenzofuran.

a-$(HOCH_2)_2$, pTsOH, C_6H_6, Δ ; b-t-butylperbenzoate, CuCl, C_6H_6, Δ ; c-H^+, Δ .

Oxidation of 119 with PBA. When one equivalent of PBA was reacted with a CH_2Cl_2 solution of 119, the dicarbonyl compound 122 was produced quantitatively (equation 43). The dicarbonyl compound was identified on

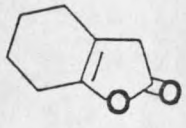


(43)

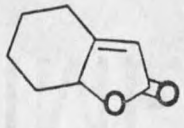
the basis of its spectral properties. The ^1H NMR spectrum showed two downfield doublets. The one at 9.78 ppm was assigned to the aldehyde proton and the other peak at 5.92 ppm was assigned to the olefin. The protons

were coupled to one another by 8 Hz. The ^{13}C NMR spectra showed a downfield singlet at 202 ppm which was assigned to the ketone and a downfield doublet at 192 ppm which was assigned to the aldehyde. A singlet at 157 ppm was assigned to the olefinic carbon in the ring. A doublet at 131 ppm was assigned to the other olefin carbon. The IR spectrum showed a broad carbonyl peak centered at 1675 cm^{-1} and a sharp peak at 1612 cm^{-1} assigned to the double bond. The mass spectrum showed a molecular ion at 138 m/e which indicated the addition of one oxygen to the original furan. The compound was a yellow oil which decomposed on standing at room temperature.

Treatment of 122 with aqueous HCl and $CHCl_3$. When HCl was added to a dilute solution of 122 in $CHCl_3$, it was no longer detectable after 3.5 hours. After work-up, the ^1H NMR spectra showed the products to be a 70:30 mixture of lactones 123 and 124, respectively. After 2 weeks in $CDCl_3$ (with no H^+ present), 50% of 123 had



123



124

isomerized to 124. Addition of aqueous HCl to this solution caused complete conversion of 123 to 124 in 24 hours.

When aqueous acid was added to the furan prior to adding PBA, 122 was still produced quantitatively. Addition of a second equivalent of either peracid to 122 resulted in the recovery of 40% of material by weight after work-up. Over 90% of this material was the starting dicarbonyl compound. The other 60% of material was lost in the water phase during work-up. It is very possible that the peracid oxidized 122 to the corresponding acid which could be water soluble.

Mechanistically, 123 could arise from the cyclization of 122 (Figure 13). The α,β-unsaturated lactone 124 could arise either directly from 122 or from the isomerization of 123.

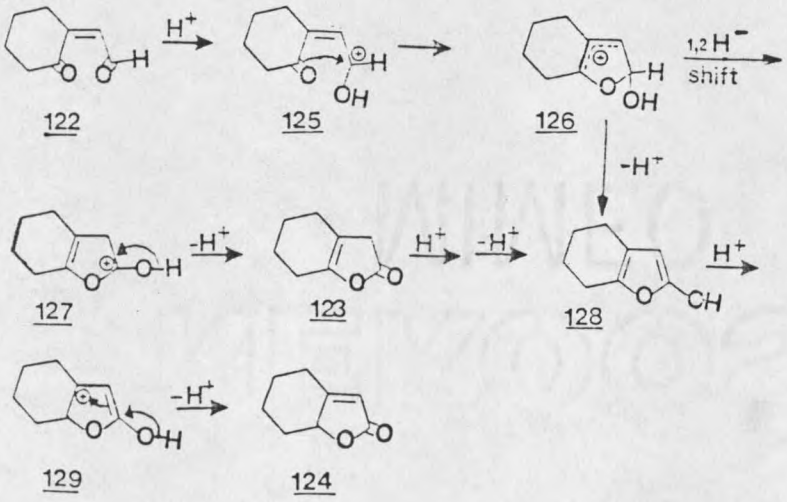
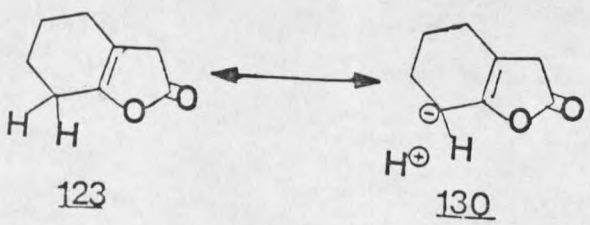


Figure 13. Formation of lactone 123 and 124 from 122.

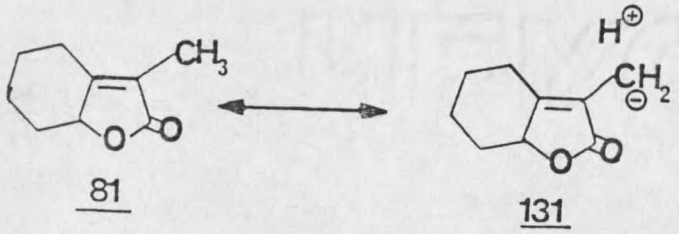
The results of this experiment indicate that cis-1,4-enedicarbonyl compounds in which one of the carbonyls is an aldehyde functionality will cyclize to lactones in acid. So, this does lend credence to the initial dicarbonyl mechanism for the formation of 81 as shown in Figure 11. However, one piece of evidence which remains dubious is that 122 forms both lactones 123 and 124 in acid. In the actual oxidation reaction of 15, which may proceed via the dicarbonyl it forms only the α,β-unsaturated lactone 81. One would have anticipated both isomers in analogy to compound 122.

The lack of formation of the β,γ-isomer 82 may be explained in terms of the substitution on furan and subsequently on the stability of the lactone. It has been previously shown that a substituent in the γ position of an unsaturated carbonyl compound greatly effects the position of the double bond.[78] A γ-group with protons (particularly a methyl group) greatly favors the double bond in the β-γ position. This can be explained in terms of hyperconjugation of the alkyl group with the double bond (equation 44). The situation is quite



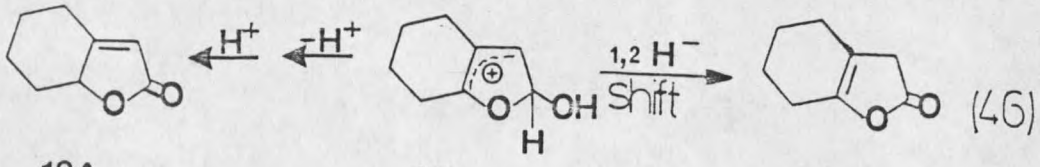
123 130 (44)

different when there is an α substituent with protons. It was shown that an α -methyl group greatly favors the α, β isomer.[78] This again can be attributed to additional conjugation of the double bond due to hyperconjugation with the methyl group (equation 45).



81 131 (45)

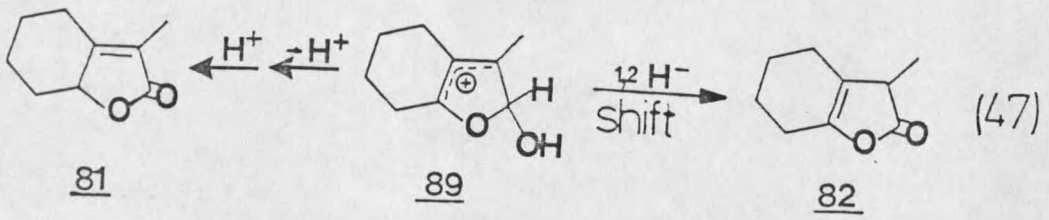
It is then reasonable to justify the products from the cyclization of 28 and 122 on the basis of their thermodynamic stability. In the case of 122, the intermediate ion 126 can form either 123 or 124 (equation 46).



124 126 123 (46)

Products 123 and 124 are both formed because of their apparently similar thermodynamic stability.

In the proposed dicarbonyl 28, the subsequent intermediate ion 89 can form either 81 or 82 (equation 47). In this case, however, the lactone 81 is probably

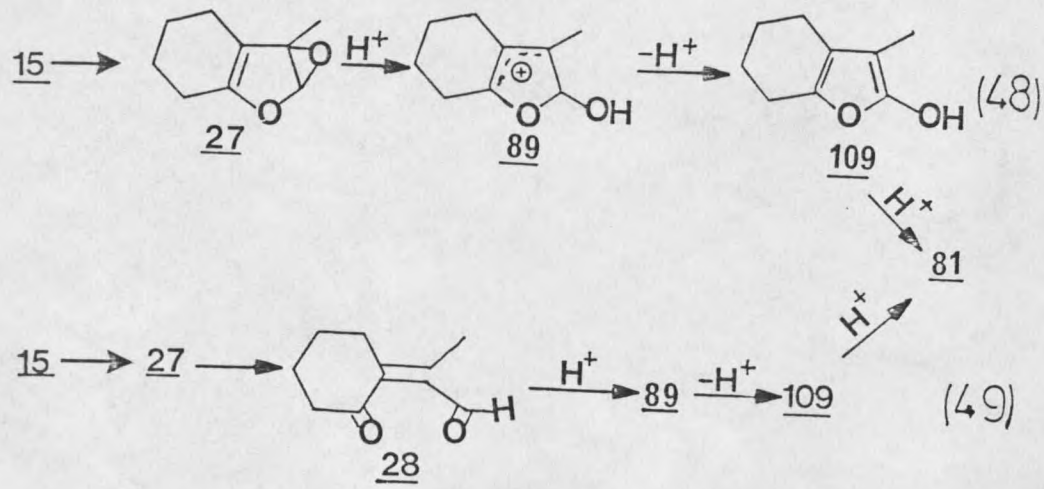


81 89 82 (47)

much more thermodynamically stable than 82 because of the α-methyl group.

Investigation of the Low Temperature Oxidation of Tetrahydrobenzofuran Compounds Using ^{13}C and ^{1}H NMR Spectroscopy

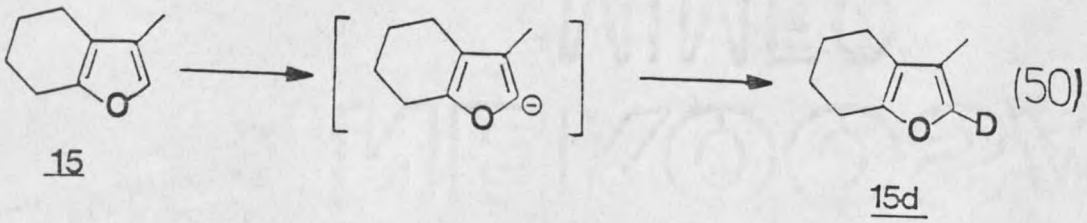
Up to this point, the non-NIH Shift mechanism (equation 48) and the dicarbonyl mechanism (equation 49) seemed to be the most reasonable mechanistic pathways to account for the formation of 81. The dicarbonyl mechanism seemed more viable because acid had no effect



on the formation of 122 when it was added to 119 prior to the addition of PBA. Therefore, it was decided to try to generate the proposed epoxide 27 at low temperature and then add acid to see if it would generate lactone 81. It had been previously shown (see introduction) that the oxidation of 15 at low temperature (240°K) would generate a strong signal at 5.60 ppm in the ^{1}H NMR spectra.[43] This signal was assumed to be the epoxy-acetal proton of 27. It was assigned to 27 because of its chemical shift and because it disappeared with the concomitant appearance of the aldehyde signal at 10.2 ppm for 19 upon heating.

Before attempting low temperature experiments, it was necessary to confirm that the proton resonance at 5.60 ppm in the ^{1}H NMR spectrum was due to 27 and that it was the signal due to a proton on C-2.

Synthesis of 3-methyl-4,5,6,7-tetrahydrobenzofuran-2-^{2}H. The C-2 deuterium analogue of 15 was synthesized by generating the anion of 15 with n-butylithium and then adding D_2O (equation 50). This process was repeated with 15 until the 2 position showed 95% incorporation of deuterium. Measurement of the amount of the deuterium

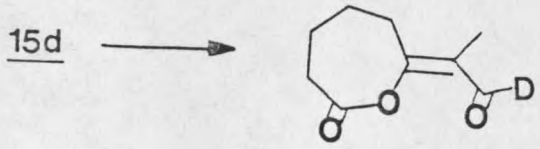


(50)

was done by integrating the area for the proton at 7.1 ppm and comparing it to the area for the C-4 and C-7 protons.

Low temperature oxidation of 15 and 15d. In this experiment, two equivalents of PBA were dissolved in $CDCl_3$ in a NMR tube and cooled to 210°K in the NMR magnet. Furan 15 was subsequently added and the temperature raised (235°K) until the furan had reacted completely (via ^{1}H NMR analysis at 7.1 ppm). There was a considerable ^{1}H NMR signal at 5.60 ppm. Upon heating (245°-250°K), this peak slowly disappeared and a peak at 10.2 ppm slowly increased in intensity. Thus, the previous work by Gingerich was corroborated.[43]

The procedure was then repeated with 15d. Since the proton on C-2 was 95% deuterium, only a small peak at 5.60 ppm was anticipated. Thus, the temperature was raised in an identical manner as with 15, a small peak at 5.60 ppm was in fact observed. After warming the reaction to room temperature to produce 19, the signal at 10.2 ppm integrated for 5% of the area it should have been for 19. This, then, established that the proton at 5.60 ppm was in fact on C-2 of the furan and that it ended up as the aldehyde proton on 19 (equation 51). However, this did not establish the structure of 27.



(51)

19d

Low Temperature Oxidation of 15d Monitored By ^{13}C NMR Spectroscopy

To establish further evidence for the structure of 27, the same procedure was repeated as for the ^{1}H experiment, but this time it was monitored via ^{13}C NMR spectroscopy. It was anticipated that the two epoxide carbons of 27 would be readily distinguished due to unique chemical shifts.

Figure 14 exhibits the broad band decoupled ^{13}C spectra for the resonance at 136 ppm for furan 15d. The 3 larger peaks are due to 15d and the coupling is 30 Hz. The smaller peak between the 2 downfield resonances is due to a small amount of the non deuterated furan 15. If

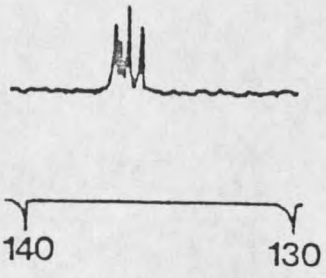


Figure 14. The ^{1}H decouple ^{13}C NMR spectra of the carbon at 136 ppm of 15d.

27 is the observed low temperature intermediate, one would expect to see a resonance between 50-60 ppm for C-3 and a resonance between 70-85 ppm for C-2.[54,55] Further, these two signals would be the only peaks in that region of the ^{13}C NMR spectra except for the $CDCl_3$ resonances.

When the reaction was run as for the previously noted procedure, no peaks were seen between 50-90 ppm (aside from the $CDCl_3$ peaks). However, a very broad resonance was seen at 103 ppm (Figure 14a). The

broadness of this resonance was thought to be due to deuterium coupling, but further efforts to resolve it into three peaks were not successful. The experiment was then repeated with 15 and a gated ^{13}C NMR spectra was

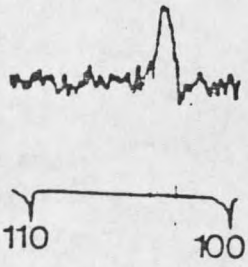


Figure 14a. Low temperature ^{13}C NMR spectrum of the peak at 103 ppm from the oxidation of 15d.

ran. This revealed that the peak at 103 ppm was a doublet. Moreover, when the proton at 5.60 ppm was selectively decoupled while observing the ^{13}C NMR spectrum, the peak at 103 ppm was observed to be a singlet. This established that the proton at 5.60 ppm was attached to the carbon that resonated at 103 ppm.

Based on the literature[54,55], 103 ppm is too far downfield for the carbon to be an epoxy-acetal. In addition, there was also no evidence for any peak in the ^{13}C spectrum that could be assigned to the other epoxide carbon. This assumes that it was not buried under the $CDCl_3$ resonance. This also established that the proton

at 5.60 ppm was not an epoxy-acetal. Therefore, the structure for the epoxide 27 appeared to be in doubt. Thus, it became necessary to establish the nature of this intermediate. An in-depth study of the low temperature NMR spectrum was initiated.

In a typical experiment, 70 mg of 15 were dissolved in $CDCl_3$ in a 10 mm NMR tube which was put into the NMR cavity and the temperature reduced to 200°K. The sample was then taken out of the cavity and a cold $CDCl_3$ solution of PBA (2.1 equivalents) was rapidly injected. After shaking, the sample was rapidly placed back in the magnet. The temperature was slowly raised and ^{13}C NMR spectra were recorded at various temperatures (normally 100 scans were acquired/spectrum). After 0.5 hours at 210°K, the furan 15, PBA, benzoic acid and the intermediate were still in solution. At 240°K the furan resonances were no longer visible in the spectrum and only a minute amount of PBA remained. At 260°K the two major products were benzoic acid and the intermediate (there was no evidence for the lactone-aldehyde 19). Figure 15 is the ^{13}C spectrum of the reaction mixture at 265°K and Table 5 is a list of the chemical shifts and multiplicities for the intermediate. Upon warming to

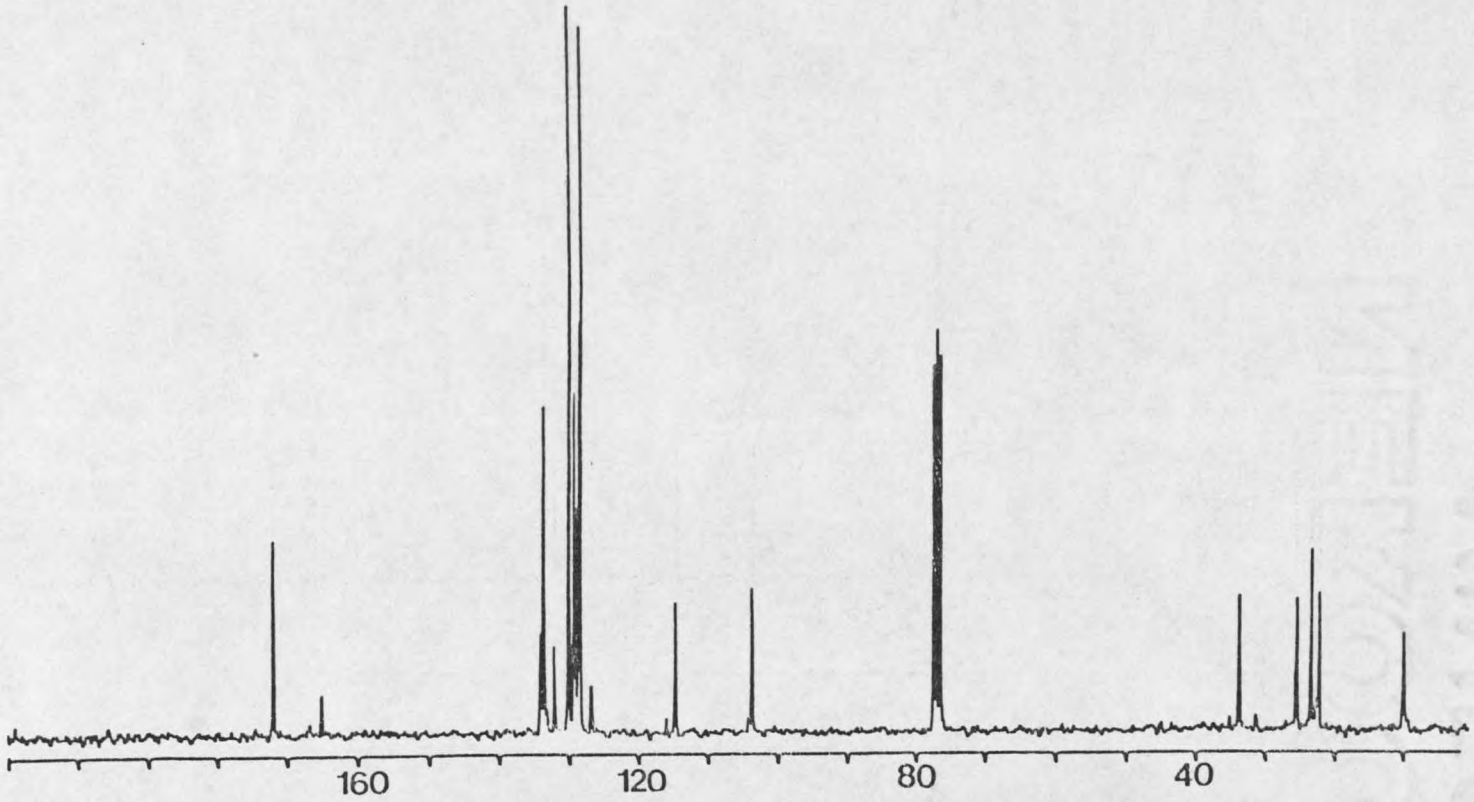


Figure 15. Low temperature ^{13}C NMR spectrum of the proposed intermediate 132.

room temperature, the resonances for this product disappeared and only those for benzoic acid and lactone-aldehyde 19 were observed.

Table 5. The ^{13}C NMR chemical shifts and multiplicities for the low temperature intermediate from the peroxidation of 15.

ppm ($CDCl_3$)	m	ppm ($CDCl_3$)	m
165.3	s	114.5	s
134.0	s	103.5	d
133.8	d	33.4	t
131.8	s	25.2	t
129.3	d	23.2	t
128.5	d	22.0	t
126.5	s	10.1	t

Since the data in Figure 15 and Table 5 indicate that the intermediate has at least 14 carbons and two equivalents of PBA were consumed, it is reasonable to suggest that the intermediate could be a perbenzoate ester. With this assumption in mind, the peak at 165.3 ppm was assigned to the perester carbonyl. The peaks at 129.3 ppm and 128.5 ppm were assigned to the aromatic ring of the perbenzoic ester because of their intensities and typical long range coupling in the gated ^{13}C spectrum. Likewise, the peaks at 138.8 ppm and 126.5 ppm

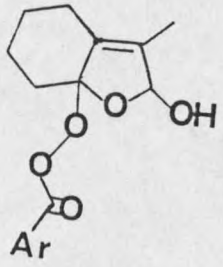
were also assigned to the aromatic carbons based on their long range coupling in the gated ^{13}C spectra. Table 6 lists the ^{13}C chemical shifts for benzoic acid, methyl benzoate, PBA, t-butyl perbenzoate and the shifts for the aromatic portion of the proposed perester intermediate.

Table 6. ^{13}C NMR chemical shifts for benzoic acid (BA), methylbenzoate (MB), perbenzoic acid (PBA), t-butylperbenzoate (t-BPB),and the benzene ring carbons for the proposed intermediate.

Carbon	BA	MB	PBA	t-BPB	Intermediate
carbonyl	172.6	167.0	168.0	164.3	165.3
ipso	129.4	129.8	124.9	127.6	126.5
ortho	130.2	128.0	129.3	129.0	129.3
meta	128.2	128.0	128.8	128.5	128.5
para	133.7	132.0	134.5	133.2	133.8

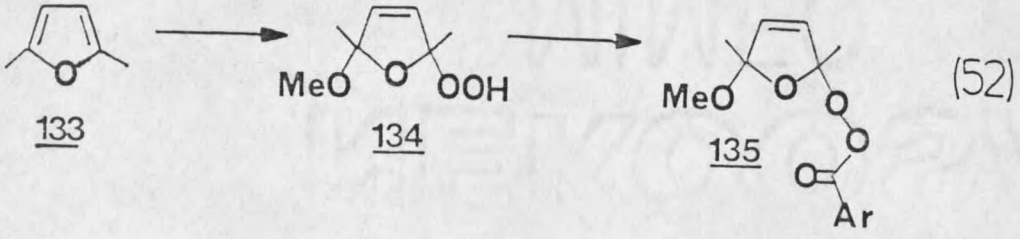
The data in Table 6 indicates that a perester carbonyl at 165.3 ppm is a reasonable assignment for the intermediate when compared to the perester carbonyl of t-BPB at 164.3 ppm. The table also indicates that the ipso carbons of aromatic peresters and peracids are at higher field than the corresponding esters or acid ipso carbons. Thus, this also lends support to a perester intermediate rather than an ester intermediate. Proceeding with other resonance assignments for the perester intermediate, the peaks at 134.0 ppm and

131.8 ppm were assigned to a tetrasubstituted olefin. The peak at 114.5 ppm was assigned to peroxyketal and the peak at 103.5 was assigned to a hemiacetal. Based on these assignments, structure 132 is proposed as the low temperature intermediate.



132

To further support the proposed structure of 132 and the NMR assignments, a model compound was synthesized following a procedure of Foote (equation 52).[64] Photooxygenation of 2,5 dimethylfuran with singlet oxygen in methanol led to the hydroperoxy ketal 134 which was



(52)

then esterified to give the perester 135.[79] Table 7 lists the ^{13}C NMR chemical shifts for these two products.

Table 7. ^{13}C NMR chemical shifts of 134 and 135.

Carbon	134	135
C-2	114.0	115.7
*C-3	134.6	133.0
*C-4	131.7	129.6
C-5	111.7	112.
$-OCH_3$	50.9	50.6
$-CH_3$	25.4	22.3
$-CH_3$	22.5	24.1
$-\overset{O}{\overset{\|}{C}}-O-O$		162.5

*These shifts can be interchanged.

As can be seen from Table 7, a ketal carbon where one of the oxygen functionalities is the terminal oxygen on a perester, resonates at 115.7 ppm. This is in agreement with the analogous ketal carbon in 132 which was assigned at 114.5 ppm. The table also indicates that a peroxy-hemiketal carbon resonates farther downfield (114.0 ppm) than a ketal carbon (111.7 ppm).

The proposed structure 132 leads to some interesting conclusions on the general mechanism of furan oxidation which was previously proposed by Gingerich.[43] First of all, the low temperature NMR data does not support the proposed epoxide intermediate 27 (though it still may be formed). While the peak at 5.60 ppm may be reasonable for an epoxy-acetal, in this case it appears to be a hemi-acetal. Secondly, these data seems to indicate that

the addition of both equivalents of peracid is fast, since the observable intermediate has already consumed both equivalents. It can be suggested that the rate determining step in the reaction could be the rearrangement of 132 to 19. The formation of 132 can be rationalized as a Baeyer-Villiger oxidation of the 1,4 dicarbonyl compound 28 (Figure 16).

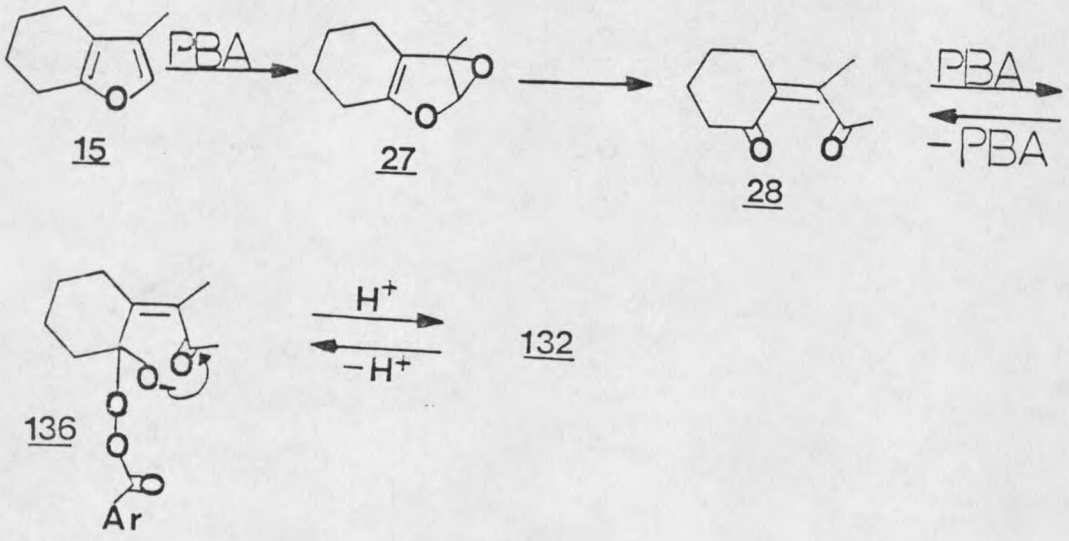
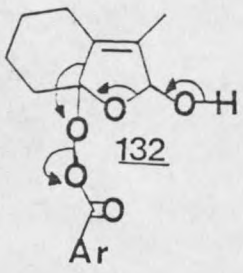


Figure 16. Proposed mechanism for the formation of perester 132.

The intermediate 132 may be viewed as a trapped intermediate in the Baeyer-Villiger oxidation of 28, which subsequently rearranges to 19 (equation 53).



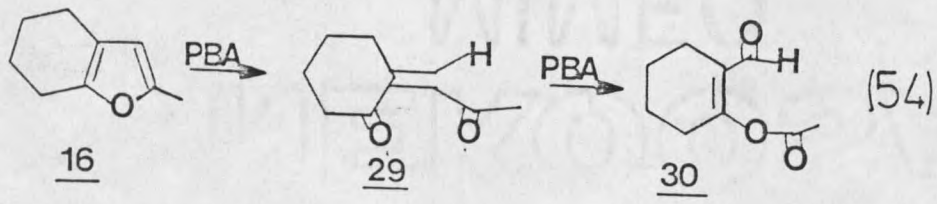
(53)

If one views 132 as a Baeyer-Villiger reaction intermediate, it supports the suggestion that the rearrangement of 132 to 19 might be the rate determining step because it has been shown in many cases that the rearrangement of the peroxy adduct is the rate determining step (RDS) in Baeyer-Villiger oxidations.[85]

It may be possible to explain the rate of the rearrangement of 132 on the bases of its geometry. If it is assumed that the perester group occupies an axial position on the six membered ring, then the acid leaving group is in a sterically hindered position and remains in a fixed geometry relative to the migrating carbon. This favorable geometry may then allow for facile electron migration. In a Baeyer-Villiger oxidation of cyclohexanone for example, the acid leaving group can be allowed to rotate freely, which may slow down migration.

Low Temperature ^{13}C NMR Analysis of the Peroxidation of 2-Methyl 4,5,6,7,-tetrahydrobenzofuran

Since the 1,4 dicarbonyl compound of 16 is stable and has been isolated, it was decided to see if an intermediate similar to 132 could be observed for the peroxidation of 16. If such a compound were observed, it would be reasonable to assume that it arises from the Baeyer-Villiger oxidation of the dicarbonyl compound 29 (equation 54). The formation of such an intermediate would support the hypothesis that 132 also arises from the 1,4 dicarbonyl compound, 28.



(54)

Synthesis and low temperature peroxidation of 16. The furan 16 was synthesized according to the method of Nienhouse[80] (Figure 17). When two equivalents of PBA were reacted with 16 in a manner identical to the low

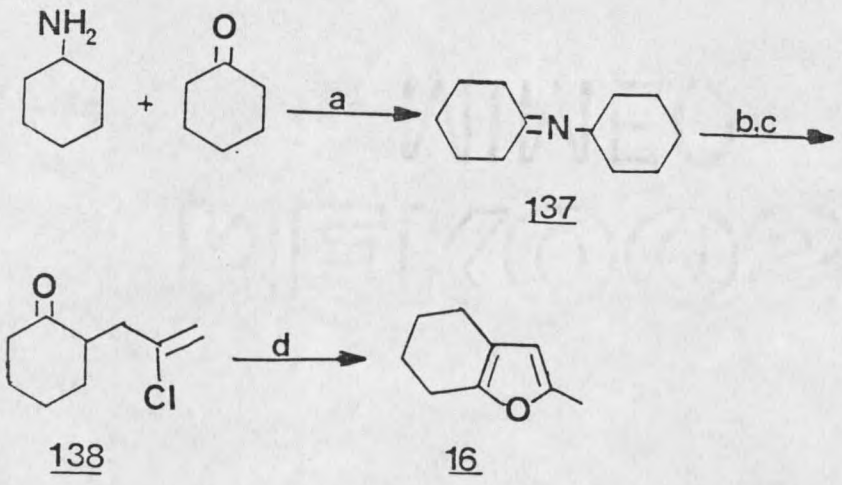


Figure 17. Synthesis of 2-methyl-4,5,6,7 tetrahydro-benzofuran.

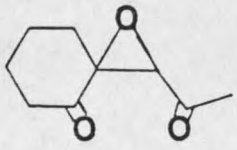
a-4 A molecular sieves, ether; b-EtMgBr; c-2,3 dichloro-propene; d-H_2SO_4.

temperature reaction of 15, 4 compounds could be ascertained by ^{13}C NMR analysis at 245°K: the 1,4-dicarbonyl compound 29, benzoic acid, starting furan and an unknown intermediate whose ^{13}C chemical shifts and multiplicities are given in Table 8. Upon warming the reaction to room temperature, the ^{13}C NMR spectrum showed

Table 8. ^{13}C NMR chemical shifts for the intermediate from the low temperature peroxidation of 16.

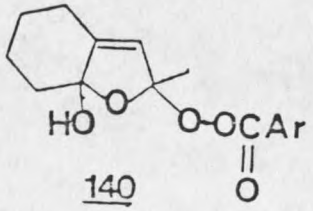
ppm	m	ppm	m	ppm	m
165.4	s	126.3	s	26.0	t
152.0	s	117.3	d	25.5	t
133.9	d	114.3	s	22.0	t
129.3	d	107.2	s	21.3	q
128.6	d	38.0	t	--	-

a mixture of 29 and 30 along with a small amount of the proposed epoxide 139.[43] The proposed structure for the unknown intermediate 140 is in accord with the results



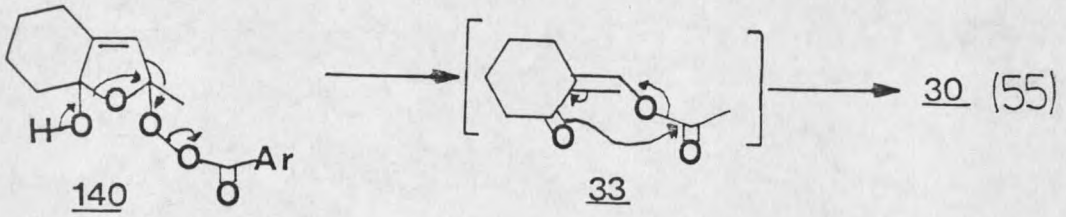
139

from the low temperature peroxidation of 15. The resonance at 165.4 ppm was assigned to the perester carbonyl. The resonance at 114.3 ppm was assigned to the peroxy-ketal and the resonance at 107.2 ppm was assigned to the hemiketal. This intermediate can rearrange in



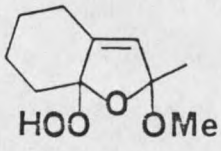
140

an analogous manner as 132 to give the aldehyde-ester 30 (equation 55). One further conclusion can be made, based on the following logic and observations. At 245°K, the



reaction mixture showed no PBA left in the reaction. At the same temperature however, the furan was still present. When the reaction mixture was warmed to room temperature, all the furan was consumed. This then shows that the reaction between 29 and PBA is freely reversible or that compound 140 is capable of oxidizing 16.

In an attempt to produce a model compound for 140, 16 was photooxygenated in methanol to give the hydroperoxide 141. The monosubstituted carbon on the



141

double bond showed a doublet at 124 ppm while the other double bond carbon resonated at 143.0 ppm. The two ketal carbons resonated at 112.8 and 110.5 ppm. The peak at 110.5 is next to the methyl group as evidenced by the observed quartet in the gated spectrum. The coupling

constant for the quartet is 4 Hz which is what would be expected for $^{2}J_{C-H}$ coupling.[80] An -OH would be expected to bring a ketal carbon further downfield than a methyl group so the hydroperoxide is placed at the ring juncture and the methoxy group at C-2. Attempts to esterify the hydroperoxy group failed to produce any perester.

Low Temperature Peroxidation of 29

In order to confirm that 140 arises from 29, it was isolated and reacted with one equivalent of PBA at low temperature. At 230°K, the major peaks corresponded to the intermediate 140 (Figure 18). As can be seen in Figure 18, these ^{13}C resonances all correspond with those presented in Table 8. Upon warming to room temperature aldehyde-ester 30 was produced along with a very small amount of the epoxide 139 (assumed to arise from the epoxidation of 29).

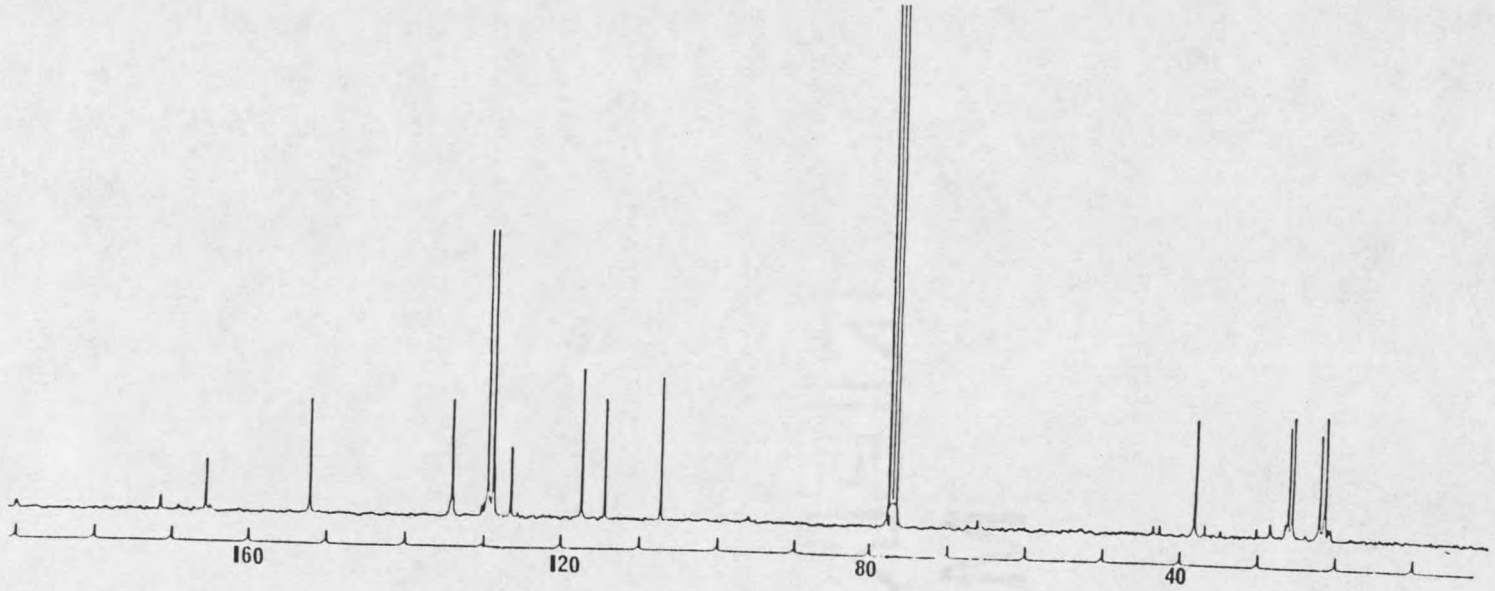
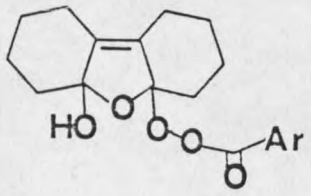


Figure 18. Low temperature ^{13}C NMR spectrum for the intermediate 140.

Low Temperature Peroxidation of Octahydrodibenzofuran 14

In an attempt to see if peroxy-ketal intermediates, like 132 and 140 were common to other furans, 14 was treated with two equivalents of PBA at 210°K and the reaction was monitored by ^{13}C NMR spectroscopy. When the temperature was raised to 225°K, resonances corresponding to an intermediate similar to 132 and 140 were seen as the only major product (Figure 19). In Figure 19, the peak at 202 ppm represents the ketone carbonyl in the product 18. In Table 9, the ^{13}C chemical shifts are listed and appear to correspond nicely to the proposed intermediate 142. The resonance at 165.0 ppm was assigned to the perester carbonyl. The peaks at 113.4 ppm and 107.1 ppm were assigned to the peroxy-ketal and hemiketal, respectively. These chemical shifts correspond to those seen for 132 and 140. Upon



142

warming, the only product produced was keto-lactone 18.

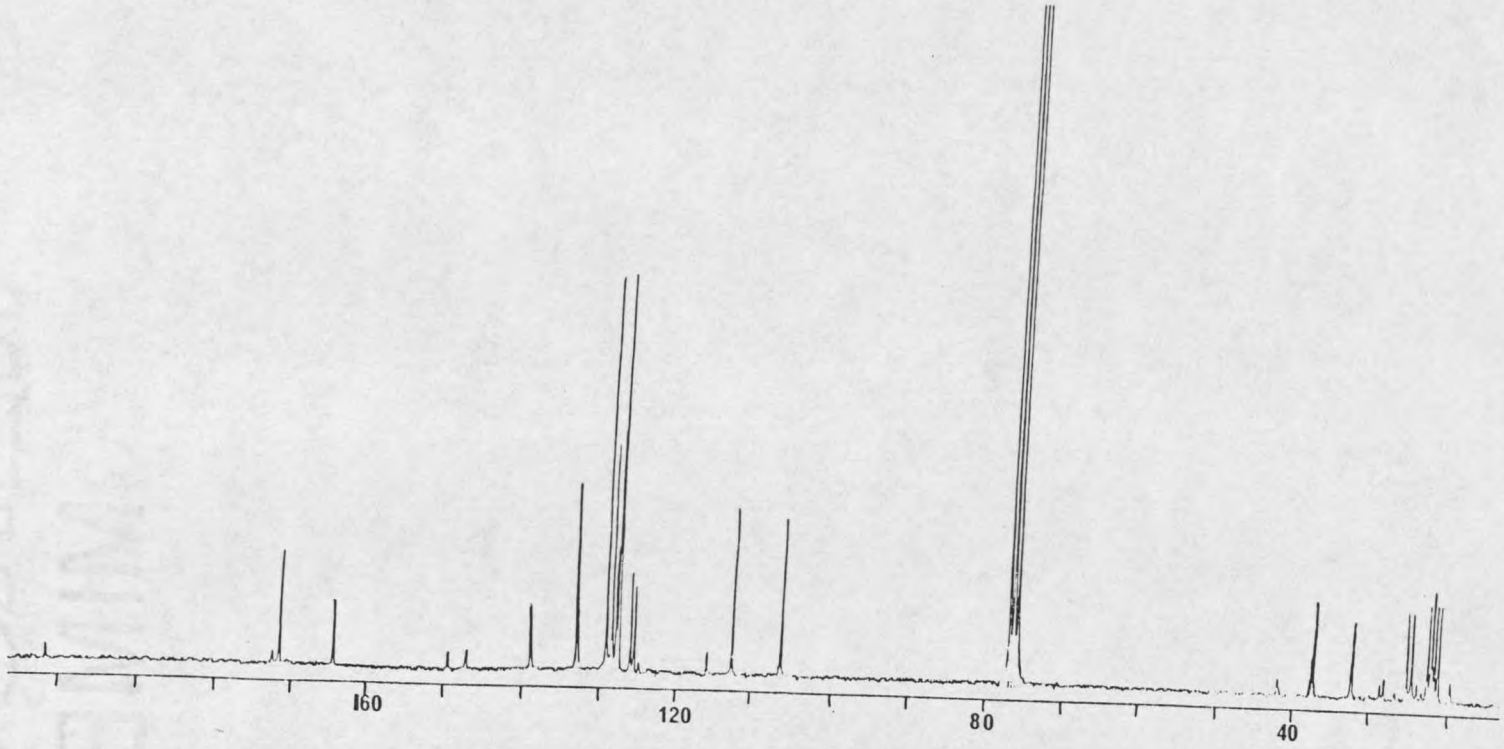


Figure 19. Low temperature ^{13}C NMR spectrum for 142.

Table 9. ^{13}C chemical shifts and multiplicities for 142.

ppm	m	ppm	m	ppm	m
165.0	s	126.8	s	26.0	t
139.7	s	126.3	s	25.3	t
133.8	d	113.4	s	23.3	t
129.3	d	107.1	s	22.9	t
128.5	d	38.2	t	22.5	t
--	-	33.1	t	21.9	t

Synthesis of Keto-Lactone 18 Via Synthesis of 142

If a separate and unique route to 18 could be achieved in which 142 was an actual or implied intermediate, it would lend evidence for the postulate of these new ketal intermediates.

Following a procedure similar to that used by Foote, 18 was brought to fruition (Figure 20).[64]

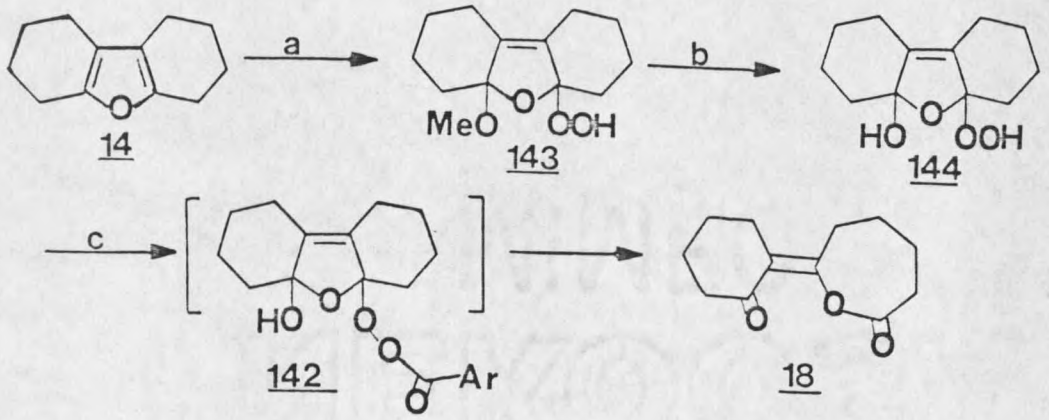
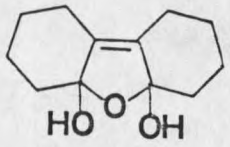


Figure 20. Synthesis of 18.

a-MeOH, rose bengal, hv, O_2; b-H_2O, THF; c-BSCl, pNBA, pyridine.

Photooxygenation of 14 produced 144 in 90% yield. It was then hydrolyzed in a 10:1 mixture of H_2O:THF to produce a 70:30 mixture of 144 and 145, respectively, as ascertained by ^{13}C NMR spectroscopy. Attempts to separate 144 from 145 on silica gel resulted in the transformation



145

of 144 to 145. Thus, the mixture was subsequently esterified with p-nitrobenzoic acid and benzenesulfonyl-chloride in pyridine to form intermediate 142. After work-up, the ^{13}C spectrum showed the two major products to be diol 145 and keto-lactone 18 in a ratio of 40 to 60, respectively. The expected ratio of 145 to 18 should have been 20:70, but under conditions used, 144 probably reacts to form 145 in competition with esterification to 142. Thus, the yield of 18 is slightly lower than expected.

The formation of 18 is attributed to the formation of the intermediate perester 142. It is assumed that the hydroperoxide esterifies before the 3^{o} alcohol. Evidence for this is from the fact that the diol 145 produced no ester when the purified diol was reacted under identical conditions.

The results of the low temperature oxidation of 14,

15 and 16 clearly indicate that the three oxidation products arise from similar peroxy-ketal intermediates. These intermediates all appear to arise during the Baeyer-Villiger oxidation of a cis-1,4-enedicarbonyl intermediate; they subsequently cyclize to give the observed peroxy-ketal intermediates 132, 140 and 142. These results also suggest that the RDS of the reaction is the rearrangement of these intermediates to products. Finally, these results give no indication as to what the product of the first oxidation is (e.g., an epoxide as previously suggested), except for the fact that the byproduct is benzoic acid.

Low Temperature Peracid Oxidation of Tetrahydrobenzofuran 119

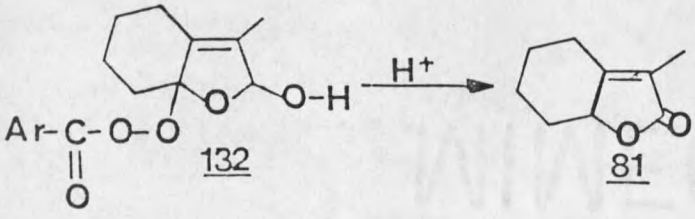
In a final experiment, compound 119 oxidized at low temperature and monitored via NMR spectroscopy. When one equivalent of PBA was reacted with 119 at 200°K, no reaction occurred. As the temperature was slowly raised, the dicarbonyl compound 122 began to appear. At 230°K only the dicarbonyl compound and benzoic acid were observed. There was no indication of an epoxide or a peroxy-ketal at any temperature. If an epoxide is formed it must rearrange to the dicarbonyl compound 122 very

fast. As expected, no peroxy-ketal intermediate was observed since 122 has already been shown to be unreactive towards PBA.

119 122

Effect of Acid on the Low Temperature Oxidation of 15

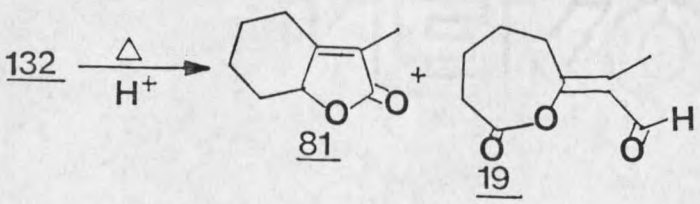
With the identification of the "new" ketal-perester intermediates 132, 140 and 142, research was pursued to see if this type of intermediate was an integral part of the acid catalyzed oxidation scheme. Two experiments were then undertaken. In first experiment, furan would be added to a cold solution of PBA and HCl to see if an intermediate was generated and observable. In the second experiment, the ketal-perester intermediate would be generated and then HCl added to see if lactone 81 was produced from it (equation 56).



132 81 (56)

In the first experiment, furan 15 was added to a

$CDCl_3$ solution containing 1.4 equivalents of PBA and a catalytic amount of aqueous HCl at 205°K. The temperature was then raised to 220°K, after 25 minutes at 220°K, all the furan was consumed. The ^1H NMR spectra showed peaks at 6.10 and 5.60 ppm which were singlets. The low temperature ^{13}C NMR spectra showed a peak at 103.5 ppm for the hemiacetal of 132. There was also a peak of similar intensity at 104.0 ppm. The ketal carbon resonance at 114.5 ppm was present but there was also a peak at 115.6 ppm of similar intensity. Similar "doublets" were also observed for the methyl group at 10.1 ppm (9.9 ppm), the methylene at 33.4 ppm (34.8 ppm), the carbonyl at 165.4 ppm (164.4 ppm) and the other methylene groups. Upon warming to 255°K, both the lactone 81 and ∈-lactone 19 were observed. After warming the mixture to room temperature, the two lactones were the only products present in a ratio of 80:20, with the lactone 81 being the major product (equation 57). When the reaction was repeated with only one equivalent



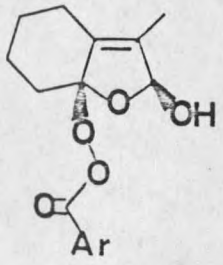
(57)

of PBA, the same intermediates were formed. There was some furan remaining in the reaction mixture at 250°K but

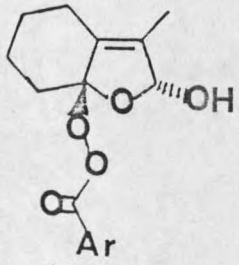
no PBA. When this reaction mixture was warmed to room temperature, only lactone 81 was observed and no furan remained.

From the "doublets" observed in the ^{13}C NMR spectra from the experiments above, it appeared that there was a new intermediate generated from 15 along with 132 in the presence of acid. From the experiment with only one equivalent of PBA, it also appeared that both intermediates produced the same lactone 81.

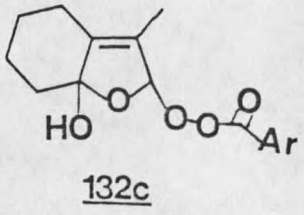
The chemical shifts of the new intermediate are very similar to those for 132 (e.g., a peroxy-ketal) and since they appear to produce the same product upon rearrangement, it is reasonable to suggest that they are cis and trans isomers 132a and 132b. It is unlikely that they



132a



132b



132c

are regioisomers because the hemiketal in 132c would result in a ^{13}C resonance occurring between 106-110 ppm.

The results of the above experiments suggest that acid may affect the stereochemistry of 132. However, when the experiment with 1.4 equivalents of PBA and HCl

was repeated, but the furan added at 220°K instead of 205°K and then the temperature raised to 240°K, only one stereoisomer of 132 was observed. It was subsequently shown that both isomers of 132 could be produced without HCl, if the temperature was not allowed to rise above 220°K during the course of the reaction.

It can then be concluded that the stereochemistry of 132 can be affected by temperature at which the reaction is run. It also appeared that lactone 81 and 19 came from the same intermediates since during the reaction with 1.4 equivalents of PBA and HCl, only the intermediates 132a and 132b were present and upon warming a mixture of 81 and 19 were produced. To show that both stereoisomers produce the same product, the reaction was run with only one equivalent of PBA and acid and the temperature kept below 220°K. Both isomers 132a and 132b were produced and upon warming only 81 was formed. When both isomers of 132 were produced without acid, only 19 was found upon warming.

To confirm that the intermediate 132 formed lactone 81, the second proposed experiment was run in which acid was added to a solution containing the intermediate and benzoic acid. Thus, equivalents of PBA were added to a $CDCl_3$ solution of furan at 220°K. The reaction was subsequently kept at 235°K until no more furan was

observable by ^1H NMR spectroscopy. The temperature was then reduced to 210°K and acid added. When the temperature was slowly raised to room temperature a 65:35 ratio of the γ-lactone 19 to the ϵ-lactone 81 was produced.

In a final experiment, one equivalent of PBA was added to the furan and the reaction kept at 220°K until no more PBA was observed. Acid was then added and the reaction slowly raised to room temperature. At room temperature, the reaction mixture showed 60% γ-lactone 81, 25% ϵ-lactone 19, 10% lactone 82 (β,γ-unsaturated isomer of 81) and 5% starting furan.

Conclusion of Mechanistic Study of the Acid Catalyzed Oxidation of 15

The results of the low temperature reactions of 15 with HCl indicate that both lactone 19 and lactone 81 come from the same intermediate. It is also evident that at low temperature the formation of 19 can compete with 81. The proposed overall reaction pathway for the H^+ catalyzed oxidation of 15 is shown in Figure 21. It is evident from the low temperature experiment with one equivalent of PBA and acid that the intermediate regenerates PBA (or 132 acts as an oxidixing agent) because during the reaction there is a point when only

furan and intermediate are present, but when the reaction is warmed the furan is consumed. In the proposed mechanism, two equivalents of PBA react with 15 to form 132. Acid then cleaves 132 to give the ion 89 and PBA. The ion 89 subsequently loses the proton on C-2 to give 109 which then isomerizes to 81.

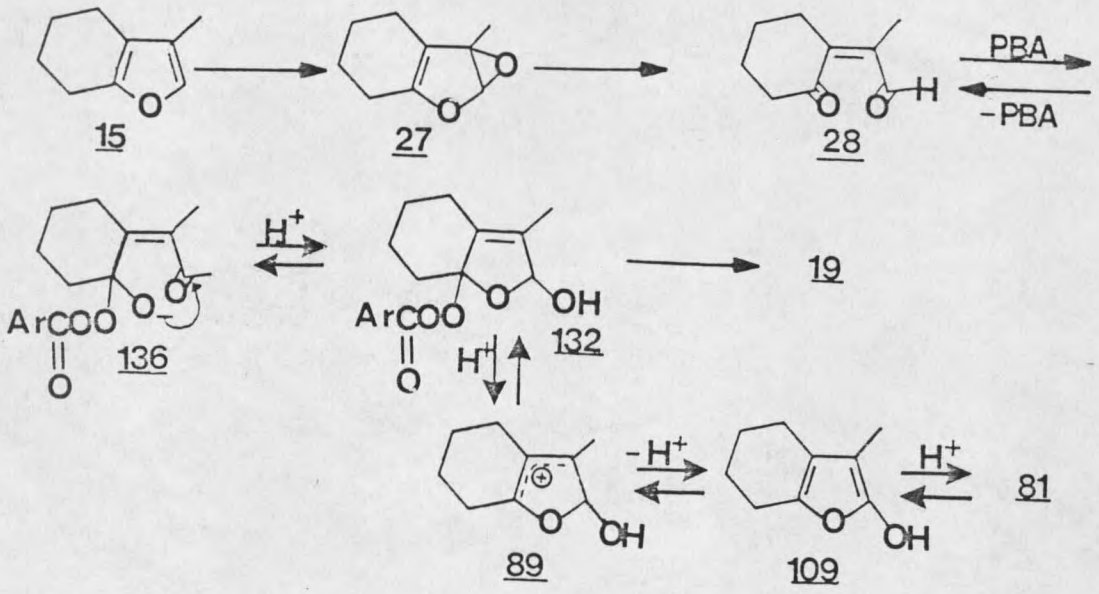


Figure 21. Pathway for the "acid" effect in the peroxidation of 15.

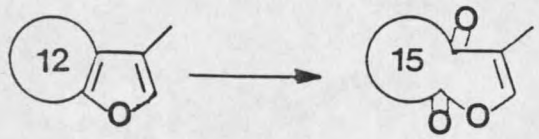
The pathway depicted above is deduced from the low temperature ^{13}C NMR data. It appears that the reaction runs slightly different at room temperature than at low temperature. At room temperature, the cleavage of 132 to 89 must be significantly faster than the rearrangement to 19 because in the presence of H^+ at room temperature, the

reaction with PBA produces only 81. At low temperature however, both 19 and 81 are produced so the rearrangement of 132 to 19 is able to compete with the cleavage of 132 to 89. It may be possible to explain this in terms of the nature of the added acid. Since the HCl is ad to 89. It may be possible to explain this in terms of the nature of the added acid. Since the HCl is added as an aqueous solution, it may be bound in solid H_2O and thus, its affective (catalytic) concentration is lowered. Thus, the rate of the cleavage reaction is lowered.

Finally, comment should be directed towards the two mechanisms previously proposed in this thesis on the acid effect in the oxidation of 15. It appears that at low temperature, neither the non-NIH Shift or the dicarbonyl mechanism is operative. Acid does not appear to effect either the epoxide 27 or the dicarbonyl 28 as previously proposed. The acid appears to be involved in the cleavage of 132 and the isomerization of 109 to form 81. The possibility of acid reacting with either 27 or 28 at room temperature cannot be ruled out, since it is not known if 132 is formed in the presence of acid at room temperature.

Details of a Novel Ring Expansion of 3,4,5-Trialkyl Substituted Furans

Gingerich[43], had observed the reaction shown in equation 58. It is interesting for three reasons:



146 147 (58)

(1) the product appears to be a novel route to large membered ring lactones with useful functionality; (2) the yield is quite respectable; (3) the mechanistic possibilities for the production of 147 are interesting and might relate to the oxidation of 15.

Mechanistically, it was proposed that 147 arose in a manner analogous to the formation of 30 from 16 (Figure 22). Products similar to 147 had been previously made

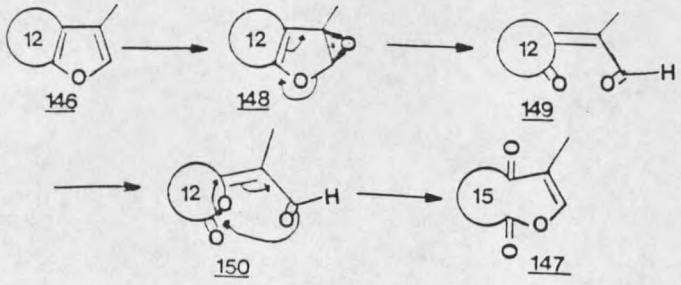
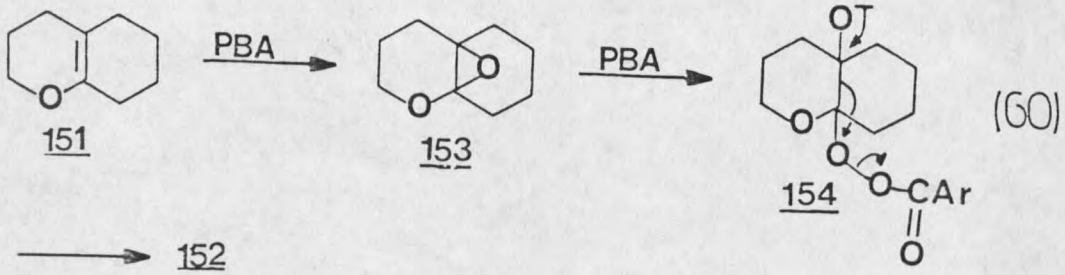


Figure 22. Formation of lactone-ketone 147.

from the reaction of cyclic vinyl ethers with mCPBA by Borowitz[82] (equation 59).

151 152 (59)

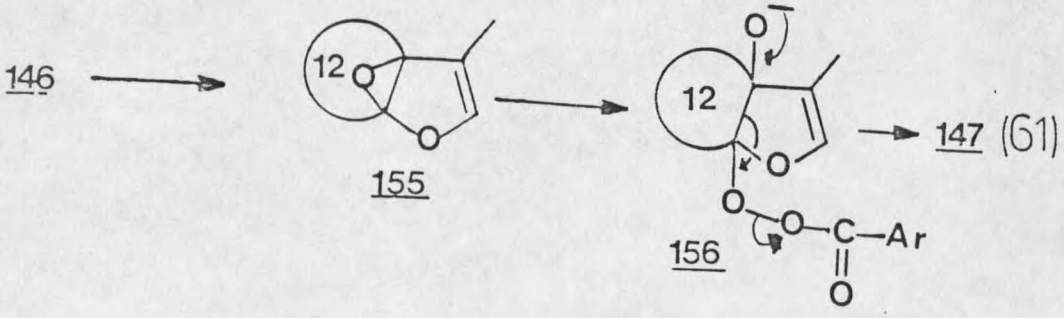
The formation of 152 was proposed to occur from the nucleophillic attack of a second mole of mCPBA on the initially formed epoxide 153 (equation 60). The



(60)

152

Borowitz mechanism for the formation of 152 could also be operative for the formation of 147 if the furan is viewed as a vinyl ether (equation 61). According to the



(61)

original work by Borowitz, the reaction was reported to take 16 hours and three equivalents of mCPBA.[83] This is

in contrast to the reaction for 146 which requires only two equivalents and goes rapidly at 0°C.

The two mechanistic sequences can easily be distinguished by an ^{18}O labeling experiment. If the Borowitz mechanism is operating, the furan oxygen of 146 would be found as the ester oxygen in the lactone ring of 147. If the Gingerich mechanism is operating, the furan oxygen would be found in the lactone carbonyl of 147. In order to distinguish between these two pathways the ^{18}O analogue of 146 was synthesized.

Synthesis of 3-methyl-perhydrocyclododeca [b] furan ^{18}O. The scheme for synthesizing 146a, which is shown in Figure 23, is similar to methodologies previously developed for the incorporation of ^{18}O into other furan compounds.[75] In contrast to earlier labeling of ketones with $H_2{}^{18}O$, which normally takes 1-2 hours, the reaction with 161 took 14 hours to achieve 52% incorporation of ^{18}O. After epoxidation and cyclization, the furan showed 51% ^{18}O incorporation.

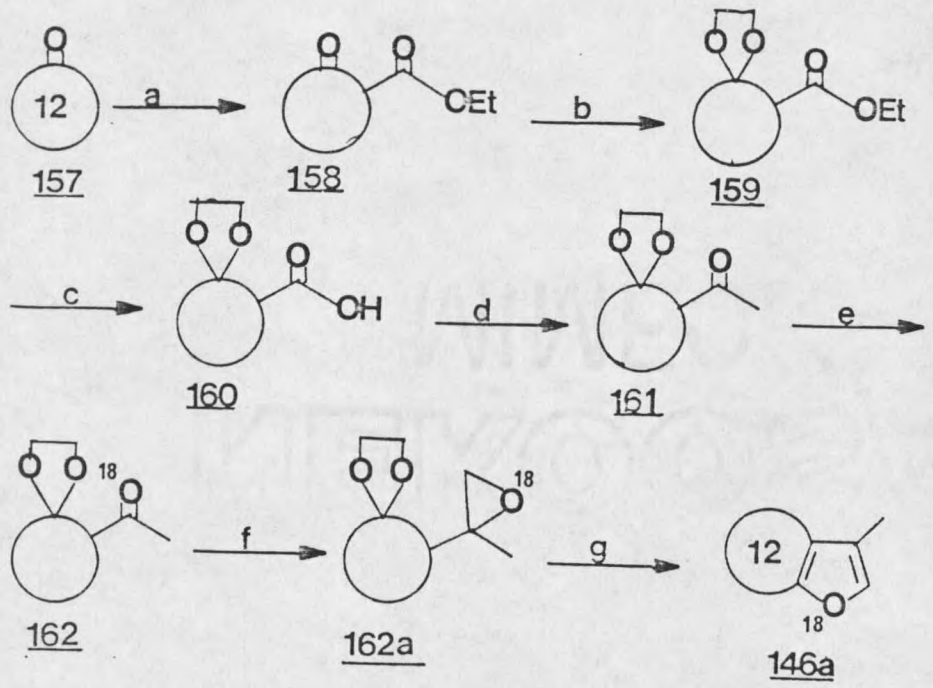


Figure 23. Synthetic outline of 146a.

a-NaH, EtOCOEt, △ ; b-$(OHCH_2)_2$, pTsOH, C_6H_6,△ ; c-THF, 6M NaOH; d-MeLi, EtOEt, e-THF, $H_2{}^{18}O$, HCl; f-$CH_2{=}S(CH_3)_2$ g-5M HCl, pentane.

Oxidation of 113a with mCPBA. The labeled furan 146a was dissolved in CH_2Cl_2 and two equivalents of mCPBA were added dropwise over a period of five minutes. The reaction was then quenched by adding 10% $Na_2S_2O_3$ and worked up in the normal manner. The keto-lactone 147a was isolateed in 85% yield. Mass spectral analysis of the product showed 51% ^{18}O incorporation into the product. High resolution ^{13}C NMR analysis of the lactone carbonyl at 169 ppm showed it to be resolved into 2 peaks

separated by 0.04 ppm. Measurements of the relative intensities of the 2 peaks showed 50% ^{18}O.

The conclusion that can be drawn from this ^{18}O work is that the Borowitz mechanism is not operating in the case of 146. It is important to note that the intramolecular rearrangement that occurs for the proposed 150 does not occur in 19. This is probably because the large ring in 150 allows the lactone carbonyl to become perpendicular to the aldehyde oxygen and nucleophilic attack can readily occur. The confirmation of the seven membered ring in 19 probably does not allow for the lactone carbonyl to become perpendicular to the aldehyde. A similar but reverse nucleophilic reaction is observable in the case of 30. In this case (equation 12) the ester is free to rotate, so nucleophilic attack by the cyclohexanone carbonyl occurs easily.

It is possible that the ring expansion reaction could be applied to other large rings of trialkyl furans. This would depend on the geometry of the aldehyde carbonyl relative to the lactone oxygen. A lactone containing eight or nine carbons may allow for a geometry favorable for rearrangement, whereas a ring containing only seven carbons might not. Further experiments are warranted to utilize fully the synthetic potential of this reaction.

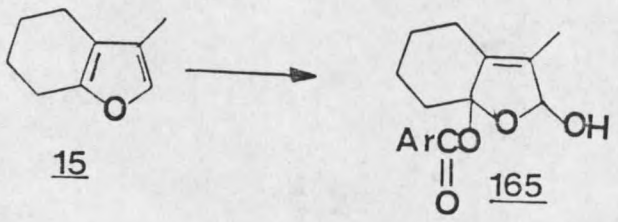
Discussion of the Proposed Mechanism For the Oxidation of Tetrahydrobenzofurans In the Absence of Acid

Formation of Epoxide

Since there is no direct evidence for the formation of an epoxide, the validity of referring to it as the first step of the mechanism should be addressed. Aside from epoxidation there are probably two other reasonable ways in which a peracid could react with a furan. First of all, it could be adding in a 1,4 manner as shown in equation 62. If it was to add this way, however, both oxygens would be equivalent and it would not explain the ^{18}O experiments for the oxidation of 15 and 16.

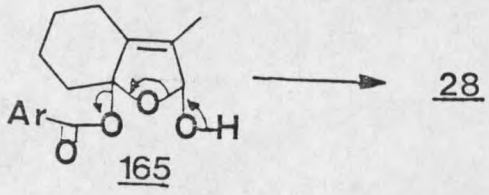
15 164 (62)

Secondly, it is possible to have a peracid adding in a 1,4 manner to a furan to put on -OH group on one carbon and an ester group on the other (equation 63). If this



15 165 (63)

type of addition was to occur it would explain the ^{18}O experiments for 14, 15, and 16. In all three furans investigated these ketal intermediates can rearrange to cis-1,4-enedicarbonyl compounds (equation 64). Thus, rearrangements of these intermediates and subsequent



165 28 (64)

addition of another oxygen to the 1,4 dicarbonyl compound could account for the ^{18}O labeling experiments in all three furans.

The main difficulty with this mechanism is that there is no low temperature NMR evidence for molecules like 165 in the reaction. It would seem probable that 165 would be more stable than its perester counterpart 132 which is observable at low temperature in the NMR spectra. Epoxides would be less stable than esters like 165 because of ring strain and would be expected to rearrange faster. Since the epoxides would be less

stable than the ester (165), they would be less likely to be seen in the low temperature NMR experiments.

The most convincing evidence for the formation of an epoxide is from the results observed from the peracid oxidation of cyclopentadiene.[84] Furan can be considered as a butadiene with the 1 and 4 carbons held together by an oxygen. Likewise, cyclopentadiene can be viewed as a butadiene with the terminal carbons held together by a carbon atom. When cyclopentadiene 166 is reacted with peracetic acid, epoxide 167 is the only product observed (equation 65). Therefore, using cyclopentadiene as a model, epoxidation is a reasonable assumption for the

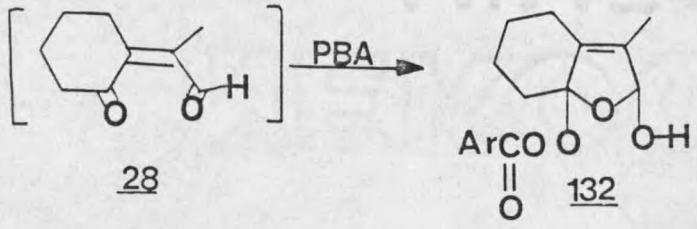
166 167 (65)

reaction of 14, 15, and 16 with the first equivalent of PBA.

Formation of 1,4 Dicarbonyl Compounds

The results of this work and others [39,40] clearly show that a stable cis-1,4-enedicarbonyl compound is formed from the reaction of 16 with PBA. Further, it has been shown that the dicarbonyl compound 29 reacts rapidly

with one equivalent of PBA to form the peroxy-ketal 140. Thus, the results of this work do not prove the formation of the 1,4 dicarbonyl compound 28 from the oxidation of 15, but only infer its existence from the formation of 132 (equation 66).

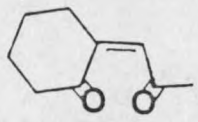


28 132 (66)

Aside from the formation of 140 from 29 (equation 54) the results from the ^{18}O studies with 15 also support the intermediate 28. As was shown earlier, the loss of ^{18}O in the lactone 81 can be explained by an acid catalyzed exchange of $H_2{}^{16}O$ with the intermediate 28a (Figure 8).

Alternative Pathways to the Formation of 132

Based on the inherent stability of cis-1,4-enedicarbonyl compounds such as 29, 116[72], and 122, it is not clear why 28 would not be stable. Therefore, it is very possible that 132 is not formed. Thus, it is pertinent to look at alternative pathways to 132.



29

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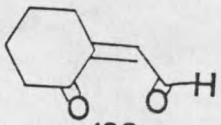
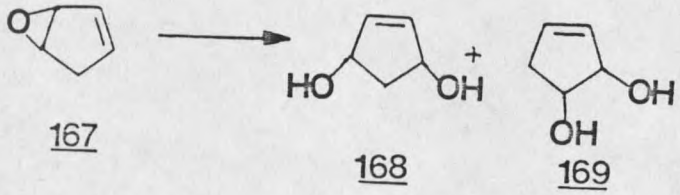


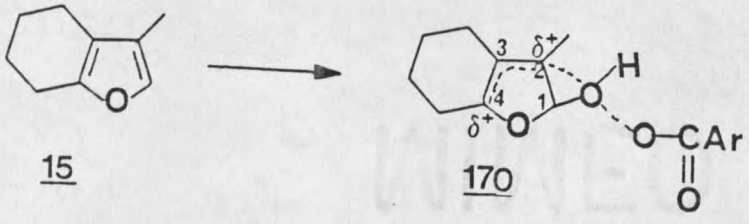
122

The H_2O catalyzed hydrolysis of the epoxide from cyclopentadiene (166) produces two different diols 168 and 169 (equation 67).[84] The formation of 168 is interesting in that it gives a 1,4 addition product very



167 168 169 (67)

similar to what is seen in 132. Based on these results it is possible to see how 132 might be produced without going through 28. A transition state in the epoxidation of 15 can be viewed as shown in equation 68. During the



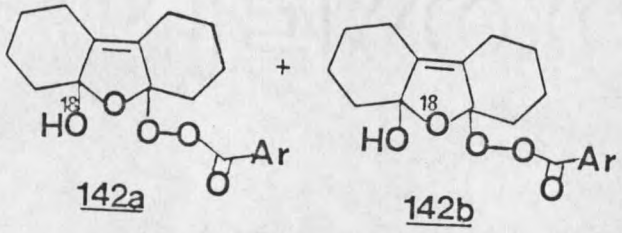
15 170 (68)

course of epoxidation, the bond to C-1 and C-2 are not formed at the same rate with the bond to C-1 forming faster. This then develops a slight positive charge on the C-2 carbon which is allylic and allows for the positive charge to be distributed throughout the allylic π-system. Since the furan C-4 carbon is next to an

oxygen it can better stabilize the positive charge than C-2. Nucleophilic attack at the C-4 carbon by PBA could then readily form 132. The transition state in 170 could also explain why no epoxide is ever seen. This mechanism, however, would not explain the loss of ^{18}O in the acid catalyzed experiment.

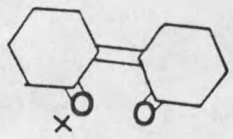
Alternative Pathways to 142

In the oxidation of 14 the dicarbonyl compound 26 is not seen and its existence is based on 142 and the ^{18}O experiments.[43] Recall that in the ^{18}O experiment with 14a that half of the label is in the ketone and half of the label is in the lactone. So if the ^{18}O experiment were run again and the intermediate trapped there would be two compounds 142a and 142b. The compound with the



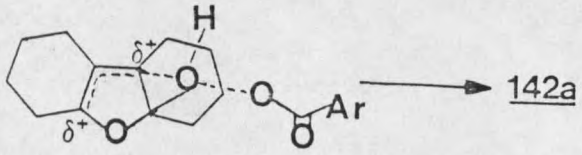
^{18}O in the alcohol 142a would lead to the label in the ketone and the compound with the ^{18}O in the ring (142b) would lead to the ^{18}O in the lactone. Currently, the most reasonable explanation to the formation of 142a and 142b

is through nucleophilic attack on either of the ketone carbonyl groups by PBA on 26a followed by cyclization.



26a

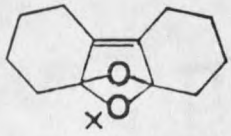
If the same argument is used here as was used for 132, the ^{18}O results would not be justified. Attack at C-4 on 171 will lead to the ^{18}O only in the ring and hence, only in the lactone carbonyl (equation 69). Therefore, nucleophilic attack by PBA on the transition state of epoxidation (e.g., 171) would not account for the observed ^{18}O results in the oxidation of 14.



171

142a (69)

A second alternative is also envisioned. If only the oxygen were to add 1,4, then the intermediate would be symmetrical and 142a and 142b would be formed in equal amounts (equation 70). As stated earlier there is no evidence in the literature that peracids ever add 1,4 so



172

PBA → 142a + 142b (70)

the existence of 172 is doubtful.

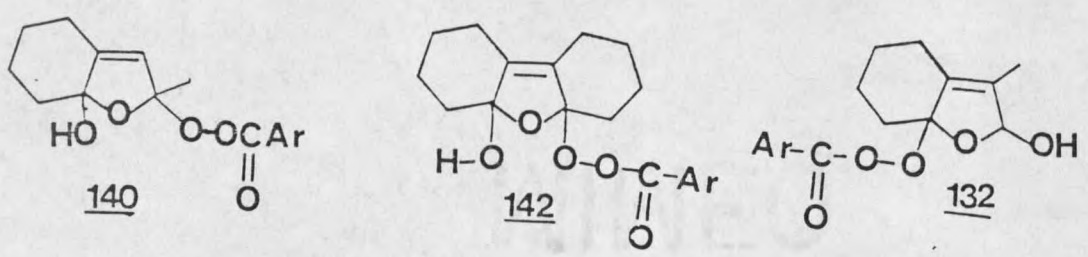
Lastly, it appears that the rates of all three oxidations are about the same. Up to 210 ^{o}K the reaction between PBA and all the furans is slow. At 230^{o}K all the furan is consumed and only intermediate is seen. At 240^{o}K, all three intermediates rearrange to products within an hour. At temperatures above 260^{o}K, the intermediates rearrange fairly rapidly to products in $CDCl_3$.

Thus, it also appears that the rate determining step in the reaction at low temperature, and presumably at room temperature, is the rearrangement of the intermediate peroxy-ketal to products. This is in accord with other reports on the RDS of Baeyer-Villiger reactions.[85] The addition of both equivalents of peracid is very fast, but which one is faster is not known.

Based on the above results and results presented previously [43], it is the belief of this author that the mechanistic sequence of epoxidation, rearrangement to a 1,4 dicarbonyl compound, followed by a Baeyer-Villiger oxidation is the mechanism that best fits the current data.

SUMMARY

The peracid oxidation of three alkyl substituted furans was examined by low temperature ^{13}C NMR spectroscopy and three low temperature intermediates 132, 140, and 142 were identified. The formation of these

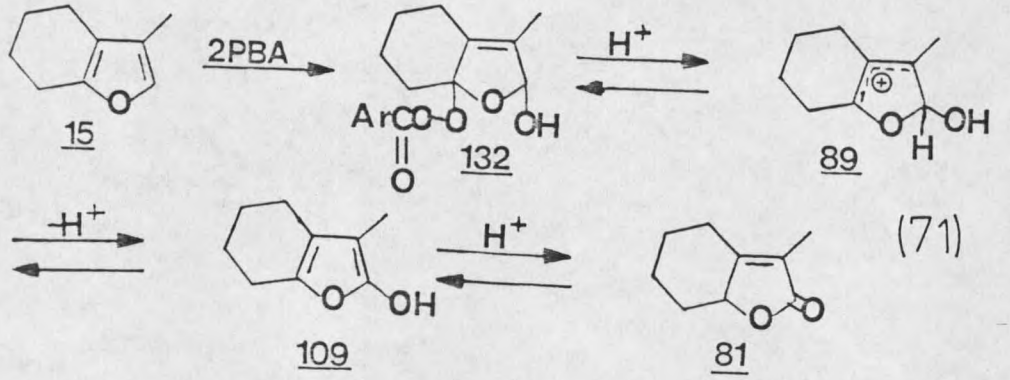


peroxy-ketals is proposed to result from the Baeyer-Villiger oxidation of their respective cis-1,4-enedicarbonyl compounds. In the case of 140 there is direct evidence for its formation from the 1,4 dicarbonyl compound, while for 132 and 142 the evidence is indirect. These compounds represent the very first Baeyer-Villiger oxidation intermediates ever observed and lend evidence to the currently accepted mechanism for the Baeyer-Villiger oxidation.[85]

Low temperature NMR investigations showed no evidence for epoxidation of the furans studied. The existence of epoxides is based mainly on the reaction of peracids with other dienes. Epoxides also represent

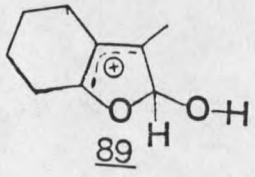
viable precursors to the proposed cis-1,4-enedicarbonyl intermediates.

The effect of acid on the peracid oxidation of 15 to give 81 was explained by the cleavage of the peroxy-ketal to yield the carbonium ion 89 which loses a proton to give enol 109 which rapidly isomerizes to 81 (equation 71).

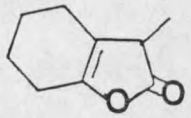


(71)

Three different peracids: PBA, mCPBA and pNPBA were all found to react with 15 to produce the lactone ketone 19. In contrast, S-9, FeTPPCl and 2-hydroperoxy-tetrahydropyran oxidations of 15 yielded 81 as the main product. Lactone 81 is believed to arise from the carbonium ion 89. This carbonium ion has the possibility



to undergo an NIH Shift reaction to form lactone 82 or to lose a proton to form the enol 109. Evidence presented



82

here indicates that 15 does not undergo a NIH Shift but loses a proton to form the enol 109 which isomerizes to 81.

EXPERIMENTAL SECTION

General

Proton NMR spectra were either obtained on a Varian T-60 or a Bruker WM 250 spectrometer operating at 60 MHz and 250 MHz, respectively. ^{13}C NMR spectra were run on a Bruker WM 250 operating at 63.83 MHz. Multiplicities of carbon resonances were determined by gated decoupled spectra. In the determination of ^{18}O by ^{13}C NMR spectroscopy, sweep widths of 500 Hz were typically used. Data were acquired as a 4K block and transformed as an 8K block. IR spectra were run on a Beckman IR5A spectrometer and calibrated using polystyrene. Mass spectra were obtain on a VGMM16 mass spectrometer operating at 70eV. Accurate mass was determined on a VG7070E mass spectrometer. Melting points were determined on a Fischer-Johns melting point apparatus and are uncorrected.

Analytical gas chromatography was done on a Varian Model 1700 equipped with a flame ionization detector. Columns were 10' x 1/4" and packed with 3% SE 30 on chromasorb W. Thin layer chromatography (TLC) was carried out on Baker-flex silica gel plates with fluorescent indicator. Column chromatography was

performed using Baker reagent grade silica gel 60-200 mesh.

Solvents were purchased from either Baker or Fisher and were purified according to standard literature procedures prior to use. Deuterated solvents were purchased from either Stohler or Wilmad and TMS was added as an internal standard when spectra were run. Elemental analyses were performed by Galbraith Laboratories.

Synthesis of Octahydrodibenzofuran

Preparation of 6-cyclohexenyl-1,4-dioxaspiro [4.5] decane. Following the procedure of Wenkert[86], 150 ml of reagent cyclohexanone (1.44 moles, Baker) were placed in a flask and gaseous HCl was bubbled through for 14 hours. A saturated $NaHCO_3$ solution was added until effervescence was no longer observed. The solution was then placed in a ice bath for 1 hour. The white crystals that precipitated were washed and filtered. The crude crystals were then ketalized without further purification. The coupled product (170 g, 0.79 moles) was dissolved in 500 ml of benzene. To this solution 87 g of ethylene glycol (Baker) and 5 g of p-TsOH were added.

The solution was then refluxed for 15 hours, and a Dean-Stark trap removed water as formed. After cooling, the solution was washed with H_2O, 10% $NaHCO_3$ and brine, dried over $MgSO_4$ and the benzene removed at reduced pressure. Distillation of the product afforded 130 g of the ketal-alkene as a clear colorless liquid (74%): bp 90-92° (0.5mm Hg) [Lit[59] bp 85°-89°(0.2mm Hg]; ^1H NMR[59] 5.52(1H, brs), 3.95-3.75(4H,m), 2.2-1.9(5H,m), 1.8-1.1(12H,m)ppm; ^{13}C NMR 137.9(s), 124.4(d), 111.2(s), 65.1(t), 65.0(t), 53.1(d), 37.1(t), 29.6(t), 29.2(t), 25.9(t), 25.8(t), 24.3(t) 23.8(t), 22.8(t) ppm; IR (neat) 1450, 1220, 1175, 1155, 1140, 1090, 930cm^{-1}; mass spectrum 222(M^+), 99 (100)m/e.

Preparation of 2-(1, 2-epoxycyclohex-1-yl) cyclohexanone ketal 121. To a stirred solution of mCPBA (5.9 g, 34.5 mmol, tech grade, Aldrich) in 150 ml of CH_2Cl_2 was added $NaHCO_3$ (3.0 g) and the ketal-alkene 67 (5.0 g). The flask was capped and placed in the refrigerator overnight. The reaction was then washed with 10% $Na_2S_2O_2$, 5% NaOH, brine and then dried over $MgSO_4$. Removal of solvent gave 5.3 g of ketal-epoxide 68 (95%) as a colorless oil: ^1H NMR[59] 4.0-3.8 (4H, m), 3.2-3.0 (1H, m), 2.0-1.0 (17H, m).

Preparation of octahydrodibenzofuran 14. To a vigorously stirred solution of ketal-epoxide 68 (3.3 g, 18 mmol) in 50 ml of pentane was added 27ml of 2N HCL. Stirring was continued for 4 hours and the layers were then separated. The aqueous layer was extracted with pentane several times. The combined pentane layers were washed with 10% $NaHCO_3$ and brine and dried over K_2CO_3. Removal of solvent afforded 1.9 g of a yellow oil which was placed on silica gel. Elution with pentane gave 1.4 g (45%) of the furan as a colorless oil: ^1H NMR[59] 2.60-2.50(4H, m), 2.35-2.26 (4H, m), 1.87-1.65 (8H, m) ppm; ^{13}C NMR 147.9 (s), 116.4 (s), 23.9 (t), 23.0(t), 22.7(t), 20.4 (t), ppm; mass spectrum m/e (relative intensity) 176 (100) M^+, 148, 120; IR[58](neat) 1600, 1445, 1150, 1130, 955, 900, 860 cm^{-1}.

Synthesis of 3-Methyl-4,5,6,7-tetrahydrobenzofuran

Preparation of ethyl and methyl 1,4-dioxaspiro [4.5] decane-6-carboxylate 77. A solution of ethyl and methyl-2 cyclohexanone-carboxylate 76 (22.9 g, 140 mmol, Aldrich), ethylene glycol (15.1 g 240 mmol, Baker) and 0.5 g p-toluenesulfonic acid in 125 ml of benzene was refluxed with a Dean-Stark water trap for 12 hours. After cooling, the reaction mixture was washed with H_2O, twice

with 10% $NaHCO_3$ and brine and dried over $MgSO_4$. The resultant yellow oil was distilled to give 23 g of the ketal (96%) as a colorless oil: bp 120-124 (8 mm Hg) [Lit[87] 80-85 (1 mm Hg)].

Preparation of 6-(1-hydroxy-1-methylethyl)-1,4-dioxaspiro [4.5]-decane: A solution of MeMgI in ether was prepared under N_2 by the addition of a solution of methyl iodide (40.0 g, 270 mmol, Baker) in 150 ml of ether to magnesium turning (60.5 g, 270 mmol) in 100 m of ether. After 30 minutes the addition was complete and the solution was refluxed for as additional hour. To this, a solution of ketal 77 (2.80 g, 134 mmol) in 150 ml of ether was added dropwise over a period of 0.5 hour and allowed to stir another 1.5 hours. The solution was hydrolyzed by the slow addition of 100 ml of 3.5 M acetic acid. The layers were separated and the aqueous layer extracted several times with ether. The combined layers were washed twice with 10% $NaHCO_3$, brine and dried over K_2CO_3. Removal of solvent followed by distillation gave 23.0 g of the desired alcohol (86%) as a colorless oil: bp 135-137 (16 mm Hg) [Lit[87] bp 160-162 °C (20 mm Hg)]. H^1 NMR 4.60 (1H, s), 3.95 (4 H, s), 2.35-2.15 (1 H, m), 2.0-1.2 (8 H, m), 1.15 (3H, s), 1.05 (3 H, s) ppm; IR (neat) 3450 cm^{-1}.

Preparation of 6-(1-methylethenyl)-1,4-dioxaspiro [4.5] decane 79. A solution of ketal-alcohol 78 (23.0 g, 11.6 mmol) and 0.5 g of p-toluenesulfonic acid in 250 ml of benzene was refluxed for 12 hour with a Dean-Stark water trap. After cooling the solution was washed with 10% $NaHCO_3$ and brine and dried over $MgSO_4$. Evaporation of the solvent at reduced pressure afforded 18.9 g of a yellow oil. Chromatography on silica gel (SiO_2) with 5% EtOAc in hexane as the eluent gave the alkene 79 (85%) as a colorless liquid: bp 94-95 (11 mm Hg); ^1H NMR 4.90-4.80 (2 H, d), 3.94-3.80 (4 H, m), 2.30-2.20 (1 H, m), 1.81 (3 H, s), 1.80-1.20 (8 H, m) ppm; ^{13}C NMR 146.1 (s), 113.4 (t), 111.1 (s), 65.1 (t), 65.0 (t), 52.5 (d), 37.0 (t), 30.2 (t), 25.9 (t), 24.3 (t), 23.7 (q) ppm; IR (neat) 3020, 1650, 1445, 1155, 1090, 1045, 885 cm^{-1}; mass spectrum 182 (M^+) m/e. A sample for analysis was prepared by preparative gas chromatography (OV-101 column). Anal Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.56; H, 10.04.

Preparation of 6-(2-methyloxirane)-1,4-dioxaspiro [4.5] decane 80. To a stirred solution of mCPBA (4.14 g, 24 mmol technical grade, Aldrich) in 150 ml of CH_2Cl_2 at 0°C was added $NaHCO_3$ (2.0 g) and a solution of ketal alkene 79 (3.13 g, 17.0 mmol) in 10 ml of CH_2Cl_2.

Stirring was continued for 1 hour at 0°C. The reaction was washed with 10% $Na_2S_2O_3$, 5% NaOH and brine and dried over $MgSO_4$. After the solvent was removed, the yellow oil was chromatographed on silica gel. Elution with 10% ether in hexane gave 3.29 g (97%) of the epoxide 80 as a clear liquid. This material was found to be a mixture of diastereomers by NMR spectroscopy. Major diastereomer 60%: ^{1}H NMR 4.05-3.80 (4 H, m), 2.83 (1 H, d), 2.65 (1 H, d), (2.0-1.1) (9 H, m), 1.28 (3 H, s) ppm; ^{13}C NMR 110.0, 64.7, 64.4, 56.4, 55.8 ppm. Minor diastereomer: ^{1}H NMR 4.1-3.9 (4 H, m), 1.69 (1 H, d), 1.47 (1 H, d), 1.9-1.1 (9 H, m), 1.41 (3 H, s). Diastereomeric mixture: IR (neat) 1225, 1160, 1095, 930, 870, 815, 735 cm^{-1}; mass spectrum m/e 198 (M^+).

Preparation of 3-methyl-4,5,6,7-tetrahydrobenzofuran 15. Following the procedure of Takahashi, 25 ml of 2N HCl was added to a vigorously stirred solution of ketal-epoxide 80 (3.2 g, 16 mmol) in pentane.[88] The solution was allowed to stir for an additional 2 hours. The layers were separated and the aqueous layer extracted several times with pentane. The combined pentane fractions were washed with 10% $NaHCO_3$ and brine and dried over K_2CO_3. Evaporation of the solvent at reduced pressure afforded a pale yellow liquid. The liquid was

chromatogramed on silica gel with pentane to yield 1.5 g of the desired furan (70%) as a colorless oil: bp 69-71° (10 mmol Hg) [Lit[62] bp 110° (13 mm Hg)]; ^{1}H NMR[62] 7.0 (1 H, s), 2.75-2.20 (4 H, m), 1.90 (3 H, d), 2.0-1.5 (4 H, m) ppm; ^{13}C 151.0 (s), 136.8 (d), 120.0 (s), 118.0 (s), 23.4 (t), 23.1 (t), 23.1 (t), 20.6 (t), 8.1 (q) ppm; IR[62] (neat) 1640, 1560, 1450, 1100, 1080, 895, 880, 730 cm^{-1}; mass spectrum m/e 136 (M^+).

Preparation of 2-Methyl-4,5,6,7-tetrahydrobenzofuran 16[80]

Preparation of N-cyclohexlidenecyclohexylamine. A solution of cyclohexanone (20.0 g, 204 mmol, Baker) and cyclohexylamine (20.2 g, 204 mmol, Aldrich) in ether was allowed to stand over 4A molecular sieves for 12 hours. Filtration and removal of solvent followed by distillation afforded 29.2 g of imine (80%) 137 as a white solid: bp 113-115° (8.8 mm Hg) [Lit [89] bp 121-123.4° (10 mm Hg)]; mp 23-25°, ^{1}H NMR[89] 3.4-3.2 (1 H, m), 2.4-2.2 (4 H, m), 1.9-1.0 (16 H, m) ppm; ^{13}C NMR 170.7 (s), 58.0 (d), 40.4 (t), 34.3 (t), 34.3 (t), 29.1 (t), 28.1 (t), 27.8 (t), 26.4 (t), 26.0 (t), 25.2 (t), 25.2 (t) ppm; IR[89] (neat) 1660, 1450, 1350, 1230, 1000, 955, 890 cm^{-1}; mass spectrum m/e 193 (M^+), 98 (100).

Preparation of 2-(2-chloroprop-2-enyl)-cyclohexanone.

Following the procedure of Stork, a solution of EtMgBr was prepared under N_2 by dropwise addition of a solution of ethyl bromide (17.6 g, 16 mmol, Baker) in 100 ml of THF to magnesium turnings (3.93 g, 161 mmol)[90]. The addition was complete in 30 minutes and the reaction mixture was refluxed an additional 1 hour. The resulting yellow grey solution was allowed to cool to room temperature and a solution of the imine 137 (28.8 g, 149 mmol) in 100 ml of THF was added with stirring over a period of 15 minutes. The solution was again refluxed for 1 hour. The resulting burgundy colored reaction mixture was allowed to cool and to this stirred mixture was added a solution of 2,3-dichloropropene (17.9 g, 161 mmol) in 50 ml of THF over a 15 minute period. The solution was then refluxed for 12 hours. The yellow solution was cooled to room temperature and hydrolyzed by the addition of 100 ml of 2M aqueous HCl. The aqueous layer was extracted several times with ether. The combined ether extracts were washed with 10% $NaHCO_3$, water and brine and dried over K_2CO_3. Removal of solid followed by distillation yielded 15.8 g of the vinyl halide[138](57%) as a clear oil: bp 104-106 (10 mm Hg) [Lit[80] bp 86(4 mm Hg)]; ^1H NMR 5.18 (2 H, d), 2.91 (1 H, dd), 2.7 (1 H, d), 2.5-2.3 (2 H, m), 2.3-2.05 (3 H, m),

1.95-1.8 (1 H, m), 1.8-1.55 (2 H, m), 1.38-1.20 (1 H, m) ppm; ^{13}C NMR 210.8 (s), 140.3 (s), 113.8 (t), 47.4 (d), 41.8 (t), 38.7 (t), 32.7 (t), 27.6 (t), 24.8 (t) ppm; IR (neat) 1715, 1640, 1450, 1435, 1150, 1125, 890 cm^{-1}; mass spectrum m/e 137 (M^+-Cl, 100), 93, 67, 55, 41, 39.

Preparation of 2-methyl-4,5,6,7-tetrahydrobenzofuran 16. Following the procedure of Nienhouse[80], to 15 ml of vigorously stirred 90% H_2SO_4 with nitrogen bubbled through at 0°C was added dropwise to the vinyl chloride 138 (6.58 g, 38 mmol). The addition was complete in 30 minutes, and the reaction was stirred an additional 30 minutes. The mixture was then poured into 150 ml of ice water which was extracted several times with hexane. The combined extracts were washed with 10% $NaHCO_3$ and brine and dried over K_2CO_3. Removal of solvent afforded a yellow liquid which was chromatographed on silica gel. Elution with pentane gave 4.5 g of the furan (87%) as a colorless oil: bp 67-68° (10 mm Hg) [Lit[80] 77-79° (17 mm Hg)]; ^1H NMR 5.78 (1 H, s), 2.6-2.5 (2 H, m), 2.45-2.3 (2 H, m), 2.27 (3 H, s), 1.9-1.65 (4 H, m); ^{13}C NMR 149.8 (s), 149.0 (s), 117.6 (s), 106.5 (s), 23.4 (t), 23.4 (t), 23.2 (t), 22.3 (t), 13.5 (q) ppm. The ^{13}C gated spectra of the furan showed the peak at 149.8 to be a finely coupled quartet (^2J=10 Hz). Irradiation of the methyl

signal in the ^{1}H NMR collapses the 149.8 peak into a doublet ($^{2}J_{C-H}$ Hz); IR[80] (neat) 1580, 1450, 1260, 1225, 1130, 960, 915, 790 cm^{-1}; mass spectrum (relative intensity) m/e 136 (M^{+}), 108 (100).

Preparation of 4,5,6,7-Tetrahydrobenzofuran 119

Preparation of 1,4 dioxaspiro[4.5]octane 120. Following the procedure of Wolters[77], a solution of cyclohexanone (31.9 g, 326 mmol, Baker) and ethylene glycol (34.4 g, 550 mmol, Baker), and 1.4 g of p-toluenesulfonic acid in 250 ml of benzene was refluxed for 12 hours with a Dean-Stark water trap. After cooling the solution was washed with H_2O, twice with 10% $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of solvent yielded 40.0 g of the desired ketal (86%) as a clear colorless oil: IR (neat) 1450, 1375, 1285, 1110, 1040, 930, 850, 835 cm^{-1}; ^{1}H NMR 3.75 (4H, s), 1.7-1.3 (10H, m) ppm.

Preparation of 3-benzoate-1,4-dioxaspiro[4.5]octane 121. A mixture of ketal 120 (33.7 g, 237 mmol) and CuBr (120 mg) were heated to boiling in 265 ml of benzene under N_2. Tertiary butyl perbenzoate (36.7 g, 194 mmol,

Aldrich) was added dropwise to the solution over a period of 2 hours. The solution was then cooled to room temperature and washed with 10% $NaHCO_3$. The aqueous phases were then washed several times with ether. The organic phases were combined, washed with brine, dried over K_2CO_3 and the solvent evaporated. Distillation of the crude reaction mixture afforded 29.6 g of product (50%) as a colorless liquid: bp 133-136 (0.3 mm Hg) [Lit[91] 97° 0.01 mm Hg)]; IR[91] (neat) 1710, 1450, 1360, 1280, 980, 915 cm^{-1}; ^1H NMR[91] 8.05 (2 H, d), 7.55 (1 H, t), 7.40 (2 H, d), 6.55 (1 H, t), 4.2 (2 H, d), 1.7-1.4 (10 H, m) ppm; mass spectrum (relative intensity) m/e 262 (M^+), 141, 105 (100), 77.

Preparation of 4,5,6,7-tetrahydrobenzofuran 117. A 25 ml 2-neck round bottom flask with a Vigreux column attached to it containing 0.5 g of p-tertiary butyl benzoic acid was heated to 230°C in an oil bath. The ester (12.0 g) was added to the stirred molten acid over a period of 1.5 hours. After one more hour the furan and H_2O were co-distilled and collected. Pentane was added to the distillate along with K_2CO_3. The solution was filtered and the solvent removed to give 3 g of furan 119 (51%) as a colorless oil: ^1H NMR[77] 7.3 (1H, d), 6.59 (1H, d), 2.65-2.6 (2H, m), 2.45-2.60 (2H, m), 1.90-1.65

(4H, m) ppm; ^{13}C 150.6 (s), 139.9 (d), 116.4 (s), 22.8 (t), 22.6 (t), 22.6 (t), 21.7 (t) ppm; IR[77] (neat) 1510, 1450, 1300, 1225, 1170, 1110, 1040, 895, 724 cm^{-1} mass spectrum 122 (M^+).

Preparation of 3-Methyl-perhydrocyclododeca[b]furan 146

Preparation of keto ester 158 and ketal ester 159. To a 500 ml roundbottom flask containing pet. ether and washed NaH (15.85 g, 50% oil dispersion, Baker) was added 300 ml of dry diethylcarbonate. The flask was flushed with N_2 for 0.5 hours prior to NaH addition. A solution of cylododecanone (30.97 g, Aldrich) in 50 ml of diethyl-carbonate was then added over a 2 hour period. After the addition was complete, the solution was allowed to reflux overnight, poured into an ice cold solution of 20 ml acetic acid in 100 ml of H_2O and then extracted 5 times with ether. The ether layer was washed with H_2O, brine, and dried over anhydrous K_2CO_3. Removal of solvent under reduced pressure gave 40 g of yellow oil which was chromatographed on SiO_2 to give a 75% yield of ethyl-2-cyclododecanonecarboxylate 158: IR (neat) 1711 cm^{-1}; ^1H NMR ($CDCl_3$) 4.18 (2 H, q), 3.82 1 H, dd), 1.2-2.8 (23 H, m) ppm; ^{13}C NMR 206.6, 170.0, 61.2, 57.6, 38.6, 26.9, 25.6, 25.3, 24.5, 24.3 (2), 23.3, 22.6, 22.0, 14.0 ppm;

mass spectrum m/e (relative intensity) 254 (M^+), 209. 98 (100); Anal. (accurate mass) calcd for $C_{15}H_{26}O_3$, 254.1875; found, 254.1876. The ketoester 158 was then ketalyzed using standard procedure to give the ketal ester 159 which was distilled (bp 134.0-136.0, 0.2 mm Hg) to give a 85% yield of product. ^{13}C NMR ($CDCl_3$) 172.9 (s), 112.0 (s), 64.8 (t), 59.9 (d), 47.2 (d), 32.4 (t), 25.9 (t), 25.6 (t), 24.5 (t), 24.3 (t), 24.2 (t), 22.4 (t), 22.2 (t), 21.9 (t), 19.7 (t), and 14.1 (q) ppm; Mass spectrum M^+ 298; IR (neat) 1754 cm^{-1}.

Preparation of carboxylic acid 160. To a solution of ketal-ester 159 (11.6 g in 35 ml of THF) was added 60 ml of 5N NaOH and the solution refluxed for 20 hours. After the mixture sat in an ice bath for 2 hours, the crystals which formed were filtered and washed with ether. The ether soluble crystals were identified as starting cyclododecanone. The insoluble material was acidified in EtOH and the crystals that formed were filtered to give 4.15 g (42% yield) of 1,4 dioxaspiro [4.11] pentadecane-12-carboxylic acid 160: mp 98.5-100.0°C (benzene); IR (KBr) 2850, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) 10.5 (1 H, brs), 3.9-4.1 (4 H, m), 3.1 (1 H, dd), 1.25-2.05 (20 H, m) ppm; ^{13}C NMR 174.9, 112.9, 64.89, 64.81, 47.4, 31.6, 26.2, 26.0, 25.0, 24.4, 22.6 (2),

22.5, 22.2, 20.0 ppm; mass spectrum, m/e (relative intensity) 270 (M^+), 143, 99(100); Anal. (accurate mass) calcd for $C_{15}H_{26}O_4$ 270.1830; found, 270.1833.

Preparation of methylketone 161. A solution of 160 (2.24 g in 50 ml of dry ether) was placed in a 2 neck roundbottom flask cooled to 0°C and purged with N_2. Two equivalents of MeLi (1.55 M Alfa) in 20 ml of ether were added dropwise to the stirred solution over a period of 2 hours. The solution was stirred for an additional hour at 0°C and then overnight at room temperature. The reaction was hydrolyzed by adding it, in small portions, to a rigorously stirred ice-water solution which was extracted several times with ether. The combined ether fractions were dried over anhydrous $MgSO_4$ and evaporated at reduced pressure to give 1.60 g (72% yield) of the desired 12-acetyl-1,4 dioxaspiro [4.11] pentadecane 161 as a white solid (mp 85-87): IR ($CHCl_3$) 1718 cm^{-1}; ^1H NMR ($CDCl_3$) 4.8-4.0 (4 H, m), 3.2 (1 H, d), 2.08 (3 H, s), 1.1-2.0 (16 H, m) ppm; ^{13}C NMR 209.7, 112.9, 64.3, 64.2, 52.8, 32.0, 31.8, 26.1, 25.7, 24.7, 23.4, 23.3, 22.4, 22.1, 22.0, 19.9 ppm; mass spectrum, (relative intensity) m/e 268 (M^+) 225, 141, 99(100); Anal. (accurate mass) calcd for $C_{16}H_{28}O_3$, 268.2039; found 268.2037.

Preparation of epoxide 163. To a solution of finely ground $(CH_3)_3S^+I^-$ (2.38 g in 20 ml of THF) at -15°C was added 4.5 ml of a solution of n-BuLi (2.6 M ether solution, Aldrich) with stirring for 15 minutes. The ketal-ketone 161 (1.06 g in 1.5 ml of THF) was then added over a period 10 minutes with stirring continued at 0°C for 2 hours and then for an additional 2 hours at room temperature. The reaction mixture was then poured into water and extracted several times with ether which was separated, washed with H_2O, and dried over anhydrous K_2CO_3. Since GC analysis of the ether extract showed that 70% of the ketone still remained, the procedure was repeated 2 more times until no ketone was observable. Evaporation of the ether gave 700 mg of 12- (2-methyloxirane)-1,4 dioxaspirane[4.11]pentadecane 163 as an oil mixture of diastereomers: (major isomer) ^1H NMR 3.90 (4 H, m), 2.68 (1 H, d, J = 5.7), 2.18 (1 H, d, J = 5.7), 1.27 (3 H, s), 1.2-1.9 (21 H, m) ppm; ^{13}C NMR 114.0, 64.6, 63.8, 56.7, 54.6, 45.6, 32.2, 26.8, 25.9, 24.6, 23.2, 22.8, 22.6, 22.4, 22.3, 19.9, 19.0 ppm; mass spectrum, m/e (relative intensity) 282 (M^+), 253 (100), 197, 155.

Preparation of furan 146. The ketal-epoxide was then cyclized to the furan, by treating a stirred

solution of ketal epoxide 163 (700 mg) in 25 ml of pentane with 7 ml of 5 N HCl for 2 hours. The reaction mixture was then extracted several times with pentane, washed with 10% $NaHCO_3$ and dried over anhydrous K_2CO_3. Evaporation of the solvent afforded a yellow oil which was placed on SiO_2 and eluted with pentane to give 400 mg of the desired furan 146 as a colorless oil: IR (neat) 1550, 1475, 1140, 975, 900, 740 cm^{-1}; ^1H NMR[91] ($CDCl_3$) 7.04 (1 H, q, J = 1.5), 2.55 (2 H, m,) 2.36 (2 H, m), 1.94 (3 H, d, J = 1.5), 1.2-1.8 (16 H, m) ppm; ^{13}C NMR 151.9, 137.0, 120.5, 119.5, 27.0, 26.1, 25.1, 24.7, 24.6, 24.5, 23.3, 22.6, 22.5, 20.7, 8.7 ppm; mass spectrum m/e (relative intensities) 220 (M^+, 100), 105; Anal. (accurate mass) calcd for $C_{15}H_{24}O$, 220.1827; found 220.1827.

Synthesis of Oxidants

Synthesis of peroxybenzoic acid (PBA) 85. PBA was synthesized according to the method of Braun.[66] Benzoylperoxide 83 (24.75 g, 102 mmol, Eastman) was dissolved in 80 ml of $CHCl_3$ and cooled to 0°C. A solution of MeO^-Na^+ in MeOH was prepared by dissolving 2.5 g of sodium in 40 ml of MeOH and cooled to -5°C. The

MeO^-Na^+ solution was then added to the benzoyl peroxide solution making sure the temperature did not rise above 5°C. Stirring was continued for 5 minutes and the milky white solution was extracted with 250 ml of water containing chopped ice. The water solution was then extracted twice with cold $CHCl_3$ to get rid of anymore methylbenzoate. The sodium perbenzoate 84 was then hydrolyzed by adding 120 ml of cold 1N H_2SO_4 and extracted three times with cold $CHCl_3$. The $CHCl_3$ was then washed twice with H_2O and dried over Na_2SO_4. After removal of solvent at reduced pressure, the white solid was recrystallized from petroleum ether-ether (mp 39°). The purity of the PBA was periodically checked by adding a measured quantity to a solution of KI in acetic acid, H_2O and $CHCl_3$ and then titrating the liberated I_2 with standard $Na_2S_2O_3$. The PBA used was normally greater than 95% pure.

Synthesis of tetraphenylporphenatoiron (III) chloride (FeTPPCl) 86. Tetraphenylporphine (Aldrich) was purified according to the procedure of Smith.[92] Following the procedure of Kobayashi [69] H_2TPP (1.43 g) and $FeCl_2$ 4 H_2O (7.12 g) were dissolved in 700 ml DMF and refluxed for 3 hours. After cooling, dilute HCl was added until purple crystals no longer precipitated. The crystals were then

recrystallized in hexane-1,2 dichloroethane.

Synthesis of iodosobenzene 87. Iodobenzene diacetate was hydrolyzed according to the method of Saltzman.[93] Iodobenzene diacetate (3.2 g) was placed in a 50 ml beaker and 15 ml of 3N NaOH was added over a period of 15 minutes with vigorous stirring. The solid that formed was macerated for 15 minutes and allowed to stand for another 45 minutes. After addition of 10 ml of H_2O and filtration, the solid was macerated in $CHCl_3$ and filtered again. The pale yellow solid was then dried in vacuum overnight.

Synthesis of 2-hydroperoxytetrahydropyran 66. Following the procedure of Milas[58], 22 ml of 30% H_2O_2 (0.2 mol, Baker), and 0.1 ml of H_2SO_4 were placed in a beaker and cooled to 0°C. Dihydropyran (8 g, 0.1 mol, Aldrich) 65 was added dropwise to the stirred solution over a period of 20 minutes and the temperature was not allowed to rise over 10°C. After 1 hour the mixture was put into ether and shaken with saturated $(NH_4)SO_4$. The layers were separated and the ether layer was washed with brine and dried over $MgSO_4$. The ether was evaporated at reduced pressure and the resultant colorless oil was chromatogramed on SiO_2 and eluted with 2% EToAc in hexane

to give 6.71 g (60% yield) of 2-hydroperoxytetrahyropyran 66 as a clear colorless viscous oil: IR (neat) 3330, 1219, 1110, 1050, 980cm^{-1} g. ^{1}H NMR ($CDCl_3$) 9.65 (1H, s) 5.05 (1H, t), 4.0 (1H, m), 3.65 (1H, m), 1.90-1.40 (6H, m) ppm; ^{13}C NMR 102.2 (d), 62.4 (t), 27.1 (t), 24.7 (t), 19.2 (t) ppm. The compound rapidly liberated iodine in a KI/AcOH/$CHCl_3$ test confirming the presence of a peroxide.

mCPBA and pNPBA were purchased from Aldrich and were of technical grade. mCPBA was recrystallized according to the method of Schwartz[94] and its purity assayed by titration with standard $Na_2S_2O_3$.

Oxidation Furan Substrates

Oxidation of 15 with PBA. Addition of two equivalents of PBA to a CH_2Cl_2 solution of 3 produced the previously seen lactone aldehyde 19.[38]

Oxidation of 15 with PBA in the presence of a catalytic amount of aqueous HCl. To a stirred solution of furan 15 (233 mg) in 20 ml of EtOH free $CHCl_3$ was added 10 µl of concentrated aqueous HCl (Baker). The solution immediately turned light pink. PBA was added as a solid (1.4 equivalents) and the solution first turned

yellow, then colorless within one minute. The reaction was then washed with 10% $Na_2S_2O_3$, twice with saturated $NaHCO_3$, brine and dried over K_2CO_3. Removal of solvent yielded 232 mg of lactone 81 (93%) as a clear oil: ^{13}C NMR ($CDCl_3$) 174.8 (s), 162.5 (s), 119.6 (s), 80.1 (d), 34.2 (s), 26.2 (s), 26.2 (s), 22.7 (s), 8.0 (q) ppm; ^1H NMR[62] 4.55 (1H, m), 2.79 (1H, m), 2.47 (1H, m), 2.2-1.8 (3H, m), 1.78 (3H, t, J=1.5 Hz), 165-1.0 (3H, m) ppm; IR[62] (neat) 1750 cm^{-1}, 1690 cm^{-1}; mass spectrum, m/e (relative intensity) 152 (M^+), 123 (61), 95 (100); Anal. (Accurate mass) calcd for $C_9H_{12}O_2$, 152.0834; found 152.0841.

Reduction of 81 to 15. Following the procedure of Nagasaki[63], to a solution of lactone 81 (224 mg) in dry THF was added 1.1 equivalent of DIBAL (1.62 ml, Alfa, 1M in hexane) over a period of 15 minutes at -20°C under N_2. The solution was then allowed to stir an additional 1 hour. The reaction was quenched by adding it to a 10% solution of H_2SO_4 and extracted several times with pentane. The pentane extracts were washed with $NaHCO_3$ and dried over K_2CO_3. Removal of the solvent afforded 180 mg (92%) of furan 15.

Oxidation of 119 with PBA. To a stirred solution of

93 (150 mg) in 10 ml of CH_2Cl_2 was added 1.1 equivalents of PBA (169 mg). The furan was consumed in 5 minutes. The reaction was worked up by first washing with 10% $Na_2S_2O_3$ then twice with 10% $NaHCO_3$, brine and dried over K_2CO_3. Evaporation of the solvent yielded 150 mg (90%) of the cis-1,4-enedicarbonyl compound.[122] ^{13}C NMR ($CDCl_3$) 202.2 (s), 191.9 (d), 157.5 (s), 131.3 (d), 43.4 (t), 36.5 (t), 25.3 (t), 25.3 (t) ppm; ^1H NMR ($CDCl_3$) 9.78 (1H, d, J=8 Hz), 5.90 (1H, d, J= 8 Hz), 2.60 (4H, m), 1.95 (4H, m) ppm; IR (neat) 1670 cm^{-1} (broad), 1610 cm^{-1}; mass spectrum, m/e 138 (M^+), 110, 67: Anal (accurate mass) calcd for $C_8H_{10}O_2$, 138.0681; found 138.0682.

Oxidation of 119 with mCPBA or pNPBA produced 122. If aqueous HCl was added prior to oxidation and the reaction was worked up rapidly, 140 was still the only product.

Oxidation of 122 with PBA. To a solution of 122 (96 mg) in 10 ml of CH_2Cl_2 was added 1 equivalent of PBA (96 mg). The reaction was stirred for 1.5 hours and worked up with 10% $Na_2S_2O_3$, brine and dried over K_2CO_3. After removal of solvent at reduced pressure, 44 mg of a yellow oil were recovered that was identified as starting material. No attempt was made to account for the

starting material that was lost in the water phase during work-up.

Oxidations Using FeTPPCl

Oxidation of 15 with FeTPPCl/iodosobenzene. FeTPPCl (1.20 g) and 15 (0.138 g) were dissolved 15 ml of dry CH_2Cl_2 in a two neck roundbottom flask. The mixture was purged with N_2 for 5 minutes. Iodosobenzene (0.600 g) was then added to the reaction mixture using a powder addition funnel over a period of 10 minutes. After addition was complete, a 1 μl sample of the reaction mixture was injected into the GC and showed no furan. Pentane was then added to the reaction mixture to precipitate the FeTPPCl and the solution was filtered. The solvent was evaporated and the residue extracted with ether. The ether solution was then poured through activated charoal and evaporated at reduced pressure. The residue was placed on silica gel and eluted with a hexane-EtOAc eluent grading. Elution with 30% EtOAc in hexane afforded 30 mg (20%) of the lactone 81. Elution with 50% EtoAc in hexane afforded 15 mg (10%) of the lactone- alcohol[88]: ^{13}C NMR ($CDCl_3$) 172.0 (s), 160.4 (s), 121.4 (s), 103.1 (s), 38.3 (t), 26.7 (t), 25.0 (t),

22.2 (t), 8.1 (q) ppm; ^1H NMR ($CDCl_3$) 3.5 (1H, s), 2.7 (1H, m), 2.35 (2H, m), 2.05 (1H, m), 1.9-1.1 (4H, m), 1.8 (3H, s) ppm; IR (neat) 1740 cm^{-1}, 3330 cm^{-1}; mass spectrum m/e (relative intensity) 168(M^+). 140 (100), 95 (825). The ^1H at 3.5 was found to disappear in the ^1H NMR in $CDCl_3$ upon addition of D_2O.

Oxidation of 119 with FeTPPCl. FeTPPCl (1.2 g) was dissolved in CH_2Cl_2 under N_2. To this solution was added 100 mg of furan 119 and 600 mg of iodosobenzene. After 10 minutes, the CH_2Cl_2 was evaporated and the residue extracted with EtoEt and filtered through activated charcoal. The ^{13}C NMR spectrum revealed the only product to be the cis-1,4-enedicarbonyl compound 122.

Oxidation of octahydrodibenzofuran 14 with 2-hydroperoxy-tetrahydropyran 66. To a solution of 14 (158 mg) in 10 ml of EtOH free $CHCl_3$ was added 2 equivalents of 66 (211 mg). The solution sat at room temperature for 48 hours and slowly turned purple. The reaction was then added to a solution of 10% $Na_2S_2O_3$, washed with $NaHCO_3$, brine and dried over $MgSO_4$. After evaporation of solvent, the dark oil was placed on SiO_2 and eluted with a hexane-EtOAc eluent system. Elution with hexane yielded 23 mg of 5,6,7,8 tetrahydrodibenzofuran 69 (15%):

^{13}C NMR ($CDCl_3$) 154.5 (s), 154.1 (s), 128.9 (s), 123.0 (d), 122.2 (d), 118.4 (d), 112.9 (s), 110.8 (d), 23.4 (t), 22.9 (t), 22.7 (t), 20.5 (t) ppm; ^1H NMR (CCl_4) 7.3 (2H, m), 7.05 (2H, m), 2.75 (2H, t), 2.61 (2H, t), 1.9 (4H, m) ppm; mass spectrum, m/e (relative intensity) 172 (M^+), 144 (100); IR (neat) 1630 cm^{-1}, 743 cm^{-1}. This compound slowly decomposed in $CHCl_3$ and attempts to make a nitro derivative failed.

Elution with 15% EtOAc in hexane yielded the ketone 70 in 13% yield (22 mg): ^{13}C NMR ($CDCl_3$) 185.5 (s), 158.2 (s), 146.0 (s), 140.5 (s), 118.6 (s), 38.0 (t), 24.2 (t), 23.5 (t), 22.5 (t), 22.5 (t), 21.5 (t), 20.3 (t), ppm; ^1H NMR ($CDCl_3$) 2.60 (2H, t), 2.55 (2H, t), 2.45 (2H, t), 2.30 (2H, t), 2.05 (2H, p), 1.72 (4H, m) ppm; IR ($CHCl_3$) 1662 cm^{-1}, mass spectrum, m/e 190 (M+), 134: Anal. (accurate mass) calcd for $C_{12}H_{14}O_2$ 190.0994; found 190.1018. U.V. (EtOH) 294 (17,000), 242 (1800). DNP derivative mp 271-272°C. (The other 72% of starting material could not be accounted for).

It was found that the ratio of 69 to 70 could be varied according to the number of equivalents of 66 used. This ratio was determined by quantitative ^{13}C NMR spectroscopy using CCl_4 and CH_2Cl_2 as internal standards. A delay time of 200 seconds was used in an inverse gated spectra and the absolute amounts of product were

determined by the average integrations of their peaks and comparing them to the internal standards. Table 1 shows the results.

Oxidation of 15 with 66. When 2 equivalents of 66 (165 mg, 1.40 mmol) were added to a $CHCl_3$ (10 ml) solution of 15 (100 mg, 7mmol), the furan was consumed in 12 hours. The reaction was worked up by addition of 10% $Na_2S_2O_3$, washed with 10% $NaHCO_3$ and dried over K_2CO_3. After evaporation of the solvent, the viscous oil was placed on SiO_2. Elution with 30% EtoAc in hexane afforded 23 mg (20%) of lactone 81. (As with 14 the rest of the starting material could not be accounted for).

Reaction with S-9 microsomal preparation. A 5 ml vial of S-9 purchased from Litton Bionetics (Charleston, NC 29405), induced with Aroclor 1254 (assay; 25 mg protein/ml) was warmed to 37°C in an incubator. To this solution was added 10 mg of 15 in 100 ul of DMSO. After 2 hours the reaction was poured into CH_2Cl_2 and extracted. After drying the CH_2Cl_2 over K_2CO_3 and removing the solvent, 13 mg of residue showed it containing starting furan, DMSO and lactone 81. Partial purification of the residue on SiO_2, yielded approximately 1 mg of 81 based on the ^1H NMR spectrum.

Experiments with Deuterium

Synthesis of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{2}H 15d. To a solution of 15 (782 mg, 5.7 mmol) in 10 ml of THF at -20°C (CO_2/CCl_4) under N_2 was added 6.6 ml of n-BuLi (2.6 M in hexane, Aldrich). D_2O (115 ul, 5.7 mM, 99.5% D, Stohler) was then added to the yellow solution and stirring was continued for 1 hour. The reaction was quenched by adding D_2O and extracted several times with pentane. The pentane extracts were combined and washed with 5% $NaHSO_3$, H_2O, brine and dried over K_2CO_3. The ^{1}H NMR spectrum showed that there was 65% incorporation of deuterium in the 2 position based on the loss of the ^{1}H intensity at 7.1 ppm. The procedure was then repeated again and 3 now showed 93% incorporation. The ^{13}C NMR spectrum of 15d showed the peak at 136.2 to be resolved into three peaks of fairly equal intensity, coupled by 30 Hz ($^{1}J_{C-D}$).

Low temperature oxidation of 15d with PBA. A $CDCl_3$ solution of 15d (60 mg, 0.4 mmol) was placed in a 10 mm NMR tube and cooled to 210°K in the NMR magnet. The tube was rapidly removed, 2 equivalents of PBA were added in a solution of $CDCl_3$ (1 ml), the sample shaken and replaced in the magnet. The temperature was raised to 240°K at which point no furan was left and no product 19 was yet

observable. The ^{13}C NMR spectrum of the intermediate showed a very broad signal centered at 103 ppm which could not be resolved into three lines. The ^{1}H spectrum showed no peak at 5.60 ppm, thus indicating that the proton previously seen at 5.60 in the low temperature ^{1}H NMR was in fact the proton at C-2. After raising the temperature to room temperature, the lactone-aldehyde 19 was the only product and the deuterium was on the aldehyde carbon.

Reactions of 15 with d-mCPBA and DCl

Synthesis of d-m-chloroperbenzoic acid. d-mCPBA was synthesized by dissolving mCPBA in $CDCl_3$ and adding a cold solution of NaOD in D_2O (30% NaOD in 99% D_2O, Aldrich) to form the perbenzoate salt. The $CDCl_3$ was removed and DCl in D_2O was added (38% DCl in 99% D_2O, Stohler) until the pH was acidic (= 2). The solution which was milky white was extracted several times with $CDCl_3$. After drying over K_2CO_3, the ^{1}H spectrum showed no -O-O-H proton, which is normally visible in a ^{1}H spectrum of PBA.

Oxidation of 15 with d-mCPBA and DCl. The furan 15 was added to a solution of DCl in $CDCl_3$. The resultant

pink solution was allowed to stir for 1 minute. After the addition of 1.2 equivalents of d-mCPBA, the reaction was worked up in the normal way. The ^{1}H spectrum showed deuterium at 4.57 ppm (C-7a), 2.45 ppm (C-7), and 1.17 ppm (C-7). This is determined by the loss of signal at these shifts due to deuterium in these positions. The position of these protons were established by hetero decoupling ^{1}H NMR. Irradiation at either 2.45 ppm or 1.17 ppm changed the C-7a proton to a doubled. Irradiation at 4.57 changed the multiplet at 2.45 to a doublet (with other fine coupling) and drastically changed the coupling pattern at 1.17 ppm. Since it was subsequently shown that the furan rapidly exchanges with DCl, the reaction was repeated with 15d to increase the amount of deuterium in the product. When this was done, the peak at 4.57 ppm showed 37% ^{2}H and the peaks at 1.17 and 2.45 showed 45% incorporation. The carbon at 34.2 ppm of the lactone could be resolved into two triplets of equal intensity, thus indicating the position of the C-7 carbon. The ^{2}H NMR spectrum showed three ^{2}H signals at the identical chemical shifts as the ^{1}H spectrum relative to $CDCl_3$; thus indicating three deuterium atoms also.

Reaction of DCl with 15. When DCl was added to 15 in $CDCl_3$, the peak at 7.1 ppm and the multipletat 2.65

ppm began to broaden and lose intensity. It was assumed that the protons at 2.65 ppm were on the C-7 carbon, based on the results from the lactone experiment. To verify this, the same reaction was run with menthofuran (Eastman).[102] One of the protons at C-7 was easily resolved into a doublet of doublets at 2.85 ppm. This was determined by irradiating the multiplet at 1.90 ppm, which changed the doublet of doublets at 2.85 ppm into a doublet and the methyl group at (1.07) C-6 into a singlet. Thus the multiplet at 1.9 ppm contained the sole C-6 proton, establishing that the signal at 2.85 ppm was infact on C-7. When DCl was added to menthofuran in $CDCl_3$, the solution instantly turned pink. The ^1H NMR spectra showed the peak at 7.1 ppm and 2.85 ppm to rapidly lose intensity, thus indicating acid catalyzed exchange at C-7 and C-2.

Reactions with ^{18}O

Preparation of 3-Methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 15a

Preparation of 1,4-dioxaspiro[4.5]decane-6-carboxylic acid 107. A solution of ketal esters 77 (5.02 g, 24 mmol) was hydrolyzed for 6 hours in 25 ml of 6N NaOH. The solution was acidified (pH = 2) and extracted

several times with ether. The ether layers were combined and dried over $MgSO_4$. Removal of solvent followed by recyrstalization from benzene gave 4.17 g (93%) of the acid 106 as a white crystalline material: mp 99-100.5 [Lit[95], mp 73 (ethanol-water)]; ^1H NMR 10.7 (1H, br., s), 4.1-4.0 (4H, m), 2.7 (1H, d), 2.05-1.2 (8H, m) ppm; ^{13}C NMR 176.3 (s), 108.9 (s), 62.9 (t), 64.5 (t), 49.6 (d), 34.2 (t), 27.1 (t), 23.3 (t), 23.0 (t) ppm; IR[95] ($CHCl_3$) 3050 (br), 1750, 1720, 1210, 1165, 1145, 1090, 1050, 930 cm^{-1}; mass spectrum (relative intensity) m/e 186 (M^+), 99(100).

Preparation of 6-acetyl-1,4-dioxaspiro[4.5]decane 107. To a vigorously stirred solution of ketal acid 106 in 250 ml of ether at 0°C under N_2, was added dropwise a solution of MeLi (38.0 ml, 59.0 mmol, 1.55 M in ether, Aldrich) in 70 ml of ether.[13] The addition was complete in two hours, the ice bath was then removed and stirring was contained for 10 hours. The reaction mixture was hydrolyzed in 50 ml aliquots by dropwise addition to vigorously stirred 25 ml portions of ice-water. The aqueous portion was then extracted several times with ether. The combined layers were washed with brine and dried over $MgSO_4$. (The aqueous layer was acidified and extracted with ether to recover 1.6 g of unreacted acid.)

Removal of solvent afforded a yellow solid which was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane gave 30.4 g (79%) of the ketone 107 as a clear oil: ^{1}H NMR[95] 4.0-3.8 (4H, m), 2.81 (1H, dd), 2.23 (3H, s), 2.0-1.2 (8H, m) ppm; ^{13}C NMR[12] 209.4 (s), 109.5 (s), 64.7 (t), 64.3 (t), 57.0 (d), 35.1 (t), 31.5 (q), 26.6 (t), 23.6 (t), 23.5 (t) ppm; IR (neat)[95] 1710, 1450, 1360, 1230, 1155, 1090, 1040, 955, 930 cm^{-1}; mass spectrum (relative intensity) m/e 184 (M^{+}), 99(100).

Preparation of 6-acetal-^{18}O-1,4-dioxaspiro[4.5]decane 108. A solution of ketal-ketone 107 (0.90 g, 4.9 mmol), 98 ml of $H_2{}^{18}O$ (4.3 mmol, Stohler, 99%), 1 ml THF and 1 ul of concentrated HCl was stirred at room temperature for one hour. The reaction was quenched by pouring it into 30 ml of CH_2Cl_2, washing with 10% $NaHCO_3$, brine and drying over K_2CO_3. Mass spectral analysis showed 51% ^{18}O incorporation. The above procedure was then repeated to yield 0.8 g (88%) of the ketone 108 after work-up. ^{13}C NMR analysis showed the ketone carbonyl at 209.4 ppm to be a doublet. The upfield peak corresponding to the ^{18}O carbonyl was 0.050 ppm upfield from the ^{16}O carbonyl. Comparison of the intensities showed 75% ^{18}O incorporation.

Preparation of 6-(2-methyloxirane-^{18}O-1,4 dioxaspiro [4.5] decane 80a. Following the method of Corey[96], NaH 91 g, 8.6 mmol, 50% oil dispersion, Baker) was placed in a two neck flask and washed three times with pet. ether. The final traces of ether were removed under aspiration and the system was flushed with N_2 for 0.5 hours. DMSO (freshly distilled from CaH_2, 3.5 ml) was added and the reaction mixture was heated to 70°C for 0.5 hours until H_2 gas ceased to evolve. The flask was then cooled to room temperature and 3.3 ml of THF was added. The stirred reaction mixture was then cooled to -10°C and a solution of trimethyl-sulfonium iodide (1.7 g, 8.6 mmol) in DMSO (5 ml) was added over a period of 2.5 minutes. After an additional minute at -10°C, a solution of ketal-ketone 108 (0.80 g, 4.3 mmol) in THF (0.4 ml was added. The reaction was then stirred at 10°C for 10 minutes and 1 hour at room temperature. The reaction mixture was then poured into H_2O and extracted several times with ether. The ether layer was then washed with brine and dried over K_2CO_3. GC analysis showed that only 65% of the ketone was converted to the epoxide, so the procedure was repeated again. After work-up 752 mg (88%) of the epoxide 80a was obtained.

Preparation of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 15a. To a vigorously stirred solution of ketal-oxirane 80a (0.70 g, 3.5 mmol) in 40 ml of pentane was added 29 ml of 1N HCl. The solution was then allowed to stir for 2.5 hours. The aqueous phase was then separated and extracted several times with pentane. The pentane layers were combined, washed with 10% $NaHCO_3$, brine and dried over K_2CO_3. Removal of solid followed by column chromatography of SiO_2 afforded 208 mg of the furan 15a (44%). In the ^{13}C NMR analysis, the resonance at 150.9 was resolved into 2 peaks with the upfield peak shifted by 0.039 ppm (39% ^{18}O). The resonance at 136.7 was similarly resolved with the upfield peak shifted by 0.036 ppm (39% ^{18}O). GC/MS analysis also showed 39% ^{18}O incorporation.

Oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O with PBA and HCl. To a stirred solution of 15a (208 mg, 1.5 mmol) in 20 ml of $CHCl_3$ (EtOH free) was added 10 ul of concentrated HCl and 1.2 equivalents of PBA. The reaction was worked up as before and 210 mg (90%) of the lactone 81a were isolated. GC-MS analysis showed 32% ^{18}O incorporation. The high resolution ^{13}C NMR spectra of the peak at 80.1 ppm showed 2 peaks with the ^{18}O peak being 0.024 ppm upfield from the ^{16}O peak. Measurement

of the peak intensity showed 33% ^{18}O. High resolution ^{13}C NMR of the lactone carbonyl carbon at 172.3 showed two peaks with the ^{18}O peak upfield by 0.011 ppm. Measurement of the intensities showed 30% incorporation. If any ^{18}O was in the lactone carbonyl oxygen, it would be shifted by 0.04-0.05 ppm. Thus, the two peaks for the lactone carbonyl are due to ^{18}O in the ring and not the carbonyl oxygen.

Preparation of the ^{18}O analog of 146. To a solution containing ketal-ketone 161 (884 mg) in 2 ml of dry THF, was added 1 ul of concentrated HCl and 67 mg of $H_2{}^{18}O$ (99%, Stohler). The mixture was stirred for 4 hours, quenched by adding 30 ml of CH_2Cl_2 and washed with 10% $NaHCO_3$, brine and dried over K_2CO_3. Mass spectral analysis showed only 12% ^{18}O incorporated so the procedure was repeated and allowed to stir overnight. Removal of solvent after the same work-up procedure gave 788 mg (89%) of the ketone 162. Mass spectral analysis showed 51% ^{18}O incorporation. ^{13}C NMR analysis of the carbonyl peak at 209.7 ppm showed two lines with the upfield resonance shifted by 0.052 ppm also showing 51% incorporation. The ^{18}O furan 146a was then prepared in the identical manner as that previously stated. Mass

spectral analysis of the furan showed 50% ^{18}O incorporation. ^{13}C NMR analysis showed the peaks at 151.9 and 137.0 ppm to give 2 lines each. The isotope peak for the 151.9 carbon shifted 0.041 ppm upfield, while the isotope peak for the 137.0 resonance was shifted 0.036 ppm.

Oxidation of 3-methyl-perhydrocyclododeca[b]furan with m-CPBA. To a stirred solution of furan (100 mg) in 10 ml of CH_2Cl_2 at 0°C was added dropwise 2 equivalents of mCPBA in 5 ml of CH_2Cl_2. After stirring for 15 minutes, the reaction was washed with 5% $Na_2S_2O_3$, 10% $NaHCO_3$, brine and dried over K_2CO_3. Removal of solvent gave the keto-lactone 147a in 75% yield: IR (neat) 1760, 1666, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) 7.6 (1H, s), 2.8 (2H, m), 2.5 (2H, m), 1.78 (3H, s), 1.1-1.6 (16H, m) ppm; ^{13}C NMR 202.1 (s), 169.9 (s), 138.5 (d), 120.1 (s), 43.4 (t), 34.2 (t), 29.6 (t), 27.2 (t), 26.7 (t), 26.2 (t), 26.0(t), 25.8 (t), 24.4 (t), 22.9 (t), 14.9 (q) ppm; Mass spectrum, m/e (relative intensity) 252 (M^+), 224, 73 (100): Anal. (accurate mass) calcd for $C_{15}H_{24}O_3$, 252.1719; found 252.1749.

Oxidation of the ^{18}O analogue of 146. In an analogous experiment, the ^{18}O labeled furan 146a was oxidized and separated from its reaction as noted above

for compound 147. Mass spectral analysis of the product showed 50% ^{18}O incorporation. A ^{13}C NMR spectrum of 147a showed 2 lines at 169.9 ppm with the upfield resonance shifted by 0.043 ppm which correlated the 50% ^{18}O incorporation. Similar analysis of the vinyl carbon at 138.5 failed to show any isotope resonance.

Preparation of Lactones

Synthesis of lactones 123 and 124. To the dicarbonyl compound 122 (560 mg, 4.1 mmol) in 300 ml of CH_2Cl_2 was added 40 μl of concentrated HCl. After stirring for 3.0 hours the reaction was worked up by washing with 10% $NaHCO_3$, brine and dried over K_2CO_3. ^1H NMR spectroscopy showed the products to be a 70:30 mixture of the β,γ-unsaturated lactone 123 and the α,β-unsaturated lactone 124, respectively.

The two lactones were separated on silica gel, using 30% EtOAc in hexane as an eluent. The β,γ-unsaturated lactone 123 was identified on the basis of its spectral properties: ^{13}C NMR ($CDCl_3$) 176.5 (s), 150.4 (s), 110.6 (s), 36.0 (t), 22.5 (t), 22.3 (t), 22.3 (t), 22.2 (t) ppm; ^1H NMR 3.1 (2H, m), 2.25 (2H, m), 2.1 (2H, m), 1.8 (4H, m) ppm; IR (neat) 1792 cm^{-1}, 1700 cm^{-1}; mass spectra m/e (relative intensity) 138(M^+), 110 (22), 82 (31), 67

(100): Anal. (accurate mass) calcd for $C_8H_{10}O_2$, 138.0681; found 138.0681.

The α,β-unsaturated lactone 124 was also identified via to its spectral properties: ^{13}C NMR ($CDCl_3$) 171.9 (s), 151.6 (s), 112.5 (d), 81.4 (d), 34.4 (t), 28.1 (t), 26.6 (t), 22.5 (t) ppm; ^1H NMR ($CDCl_3$) 5.7 (1H, s), 4.65 (1H, m), 2.95 (1H, m), 2.65 (1H, m), 2.3 (1H, m), 1.95 (2H, m), 1.35 (2H, m) ppm; IR (neat) 1750 cm^{-1}, 1970 cm^{-1}; mass spectrum, m/e (relative intensity) 138 (M^+), 109 (100), 81 (30): Anal. (accurate mass) calcd for $C_8H_{10}O_2$ 138.0681 found 138.0687.

The β,γ-unsaturated lactone 123 isomerized to the α,β-unsaturated isomer 124 in the GC. It slowly isomerized to 123 in $CDCl_3$ over a period of two weeks. Addition of acid to a $CDCl_3$ solution of 123 caused isomerization to 124 in 24 hours.

Synthesis of lactone 81 and 82 from the photosensitized oxygenation of 15. Following the procedure of Foote[64], the peroxide 111 (300 mg, 1.5 mmol) was dissolved in 5 ml of ether. This solution was then added dropwise over a period of 1.5 hours to a solution of triphenylphosphine (440 mg, 1.6 mmol, Baker) in 30 ml of boiling ether. After refluxing for an additional

hour, the solution was chilled to -5°C and filtered to remove the triphenylphosphine oxide. An IR of the crude mixture showed no peaks in the carbonyl region. The mixture was then dissolved in benzene and refluxed for 1 hour. After 1 hour, the IR showed a significant peak at 1795 cm^{-1}. The ^{1}H NMR spectra revealed the products to be a mixture of lactones 81 and 82. The lactone 82 was identified by the methyl doublet at 1.28 ppm and the quartet at 3.08 ppm. These are the same chemical shifts reported by Hirsh in the analogous experiment with menthofuran.[72] Addition of 1 ul of HCl to this mixture caused a slight increase in 81 after 2 hours. Measurement of the two products were carried out by monitoring the peak at 4.65 ppm in 81 and comparing it to an internal standard. After 24 hours, all of 82 had isomerized to 81. The ^{13}C NMR chemical shifts for 82 were: ($CDCl_3$) 180.2 (s), 148.7 (s), 115.6 (s), 40.9 (d), 22.3 (t), 22.3 (t), 22.0 (t), 20.9 (t), 14.1 (q) ppm.

Photosensitized Oxidation of 14 and 16

Photooxidation of octahydrodibenzofuran 14. Following the procedure of Foote[64], 100 mg of 14 was dissolved in 8 ml of MeOH containing 1 mg of rose bengal. The solution was placed in a large test tube with a

steady stream of oxygen. The tube was then placed in front of a 300 watt tungsten light source and irradiated for 5 minutes. After 5 minutes, the MeOH was removed at reduced pressure and the residue was dissolved in ether and rapidly poured through activated alumina. Evaporation of solvent gave 95 mg of 144 as a white solid (mp 100°C) [Lit[64] 101m°C]; ^{13}C NMR (D-6 benzene) 134.8 (s), 131.8 (s), 112.8 (s), 109.8 (s), 49.9 (t), 38.1 (t), 35.3 (t), 27.0 (t), 26.9 (t), 26.9 (t), 23.8 (t), 23.7 (t), 23.1 (t), 23.0 (t) ppm; IR[72] ($CDCl_4$) 3333 cm^{-1}. Mass spectral analysis failed to give a molecular ion in the 70eV electron impact ionization source. The compound rapidly liberates I_2 in a KI/$CHCl_3$/AcOH test.[66]

Photooxidation of 2-methyl tetrahydrobenzofuran 16. As with 14, 16 was treated in the same way to yield the hydroperoxide 141 in 90% yield as a white solid (mp 73-75°C): ^{13}C NMR (D-6-benzene) 143.0 (s), 124.7 (d), 112.8 (s), 110.5 (s), 50.9 (q), 35.4 (t), 29.6 (t), 26.0 (t), 25.4 (t), 22.8 (q) ppm; ^{1}H NMR (D-6-benzene) 8.9 (1H, brs), 5.3 (1H, s), 3.3 (3H, s), 2.83 (1H, m), 2.28 (2H, m), 1.9-1.2 (5H, m), 1.65 (3H, s) ppm. The compound rapidly liberated I_2 in a KI/$CHCl_3$/AcOH test.

Photosensitized Oxidation of 2,5 Dimethylfuran 133

Photooxidation of 133. As for the other furans the same procedure was followed for 133, but after evaporation of the MeOH, the crude product was sublimed (65°C, 0.7 mm Hg) to give 62% of the hydroperoxide 134 as a white solid (mp 75-77°C) [Lit[64] 75-76]. ^{13}C NMR (D-6-benzene) 134.6 (d), 134.9 (d), 114.3 (s), 111.7 (s), 50.9 (q), 25.4 (q), 22.5 (q) ppm; ^{1}H NMR (D-6-benzene) 8.7 (1H, brs), 5.68 (1H, d), 5.60 (1H, d), 3.3 (3H, s), 1.60 (3H, s), 1.48 (3H, s) ppm; IR ($CDCl_4$) 3330 cm^{-1} (br.). The compound rapidly liberated I_2 in a KI/$CHCl_3$/AcOH test.

Esterfication of 134. Following the procedure of Brewster and Ciotte[79], 605 mg of benzenesulfonyl chloride was added to a pyridine solution of p-Nitrobenzoic acid (283 mg) and cooled to 0°C. The hydroperoxide was added as a solid (275 mg) and the solution was allowed to stir for three hours. The reaction mixture was then added to 4 volumes of ice water. The crystals that precipitated were filtered and dried to give 217 mg of perester 135 (43%) (mp 89-90) [Lit[64] 90-91°C]: ^{13}C NMR ($CDCl_3$) 162.5 (s), 150.7 (s), 136.9 (d), 133.0 (s), 130.6 (s), 129.6

(d), 123.7 (d), 115.7 (s), 112.1 (s), 50.6 (q), 24.1 (q), 22.3 (q) ppm; ^{1}H NMR ($CDCl_3$) 8.28 (2H, d), 8.14 (2H, d), 6.10 (1H, d), 6.00 (1H, d), 3.25 (3H, s), 1.7 (3H, s), 1.5 (3H, s) ppm; IR ($CHCl_3$) 1776 cm^{-1}.

Synthesis of Lactone-Ketone 18 Via the Formation of a Peroxyester

Formation of hydroperoxy-alcohol 144. To 20 ml of H_2O was added 255 mg of the hydroperoxy-ketal 143. THF was added dropwise until the solid dissolved. Stirring was continued for an additional 6 hours. The reaction mixture was extracted several times with pet. ether to give 210 mg of a clear oily material. ^{13}C NMR analysis revealed the product to be a 70:20 mixture of the desired hydroperoxy-alcohol 144 and diol 145. The hydroperoxy-alcohol was identified based on its ^{13}C NMR spectrum: 135.8 (s), 129.8 (s), 112.8 (s), 106.3 (s), 39.2 (t), 35.9 (t), 26.9 (t), 26.8 (t), 23.7 (t), 23.4 (t), 23.4 (t), 23.2 (t). The mixture showed a broad -OH peak in the IR at 3400 cm^{-1} and rapidly discharged I_2 from KI indicating the presence of a peroxide. Attempted isolation of 144 on silica gel led to its conversion to diol 145: ^{13}C NMR ($CDCl_3$) 130.4 (s), 97.4 (s), 34.3 (s), 26.5 (s), 24.4 (s), 22.0 (s) ppm; IR (KBr) 3300 cm^{-1}; (mp

165-170°C). This product did not liberate I_2 in a KI/$CHCl_3$/AcOH test. The other 10% of product was not identified.

Formation of 18 from 144. Following the same procedure as for the formation of perester 135, 73 mg of pNBA and 154 mg benzenesulfonyl were dissolved in pyridine and 100 mg of the alcohol mixture was added as a pyridine solution. After 1 hour, the reaction was poured into 10% $NaHCO_3$ and extracted with ether several times. The ether was evaporated and the residue dissolved in $CDCl_3$. The ^{13}C NMR spectrum revealed the products to be the diol 145 and the keto-lactone 18 in a ratio of 2:3.

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