Mechanistic studies on the oxidation of alkyl substituted tetrahydrobenzofurans with m-chloroperbenzoic acid
by Samuel Beryl Gingerich

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University
© Copyright by Samuel Beryl Gingerich (1983)

Abstract:
The reaction of a series of alkyl substituted tetrahydrobenzo-furans with m-chloroperbenzoic acid has been explored. The furan substrates used included 3-methyl-4,5,6,7-tetrahydrobenzofuran, 1,2,3,4,5,6,7,8-octahydrodibenzofuran, 2-methy1-4,5,6,7-tetrahydro-benzofuran and 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran. The products arising from the oxidation of these substrates have been isolated and their structures determined. These substrates have also been prepared labeled with oxygen-18. These labeled substrates were also oxidized and the position of the label in the products determined by carbon-13 NMR spectroscopy. On the basis of the data obtained from these experiments, a detailed mechanistic scheme was developed. Initial attack of the furan moiety by m-chloroperbenzoic acid occurs to form an epoxide which subsequently undergoes ring openings to form a cis-enedione. These compounds are postulated as intermediates in all the reactions studied even though such a compound was isolated in only one case. These enediones undergo rapid Baeyer-Villiger oxidation with a second equivalent of m-chloroperbenzoic acid. In certain cases, the reaction with a third equivalent of m-chloroperbenzoic acid has been observed and, again, this is viewed as a Baeyer-Villiger oxidation.

MECHANISTIC STUDIES ON THE OXIDATION OF ALKYL SUBSTITUTED TETRAHYDROBENZOFURANS WITH m-CHLOROPERBENZOIC ACID

by

Samuel Beryl Gingerich

A thesis submitted in partial fulfillment
of the requirements for the degree

of

Doctor of Philosophy

in

Chemistry

MONTANA STATE UNIVERSITY
Bozeman, Montana

March 1983

Archives
D378
G433
cop. 1

APPROVAL

of a thesis submitted by

Samuel Beryl Gingerich

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.

3/18/83
Date

Da. P. W. Jennings
Chairperson, Graduate Committee

Approved for the Major Department

3/18/83
Date

Edwin H Abbott
Head, Major Department

Approved for the College of Graduate Studies

3-28-83
Date

Michael Malone
Graduate Dean

STATEMENT OF PERMISSION TO USE

In presenting this thesis in partial fulfillment of the requirements for a doctoral degree at Montana State University, I agree that the Library shall make it available to borrowers under rules of the Library. I further agree that copying of this thesis is allowable only for scholarly purposes, consistent with "fair use" as prescribed in the U.S. Copyright Law. Requests for extensive copying or reproduction of this thesis should be referred to University Microfilms International, 300 North Zeeb Road, Ann Arbor, Michigan 48106, to whom I have granted "the exclusive right to reproduce and distribute copies of the dissertation in and from microfilm and the right to reproduce and distribute by abstract in any format."

Signature Lowell B. Smith

Date March 25, 1983

ACKNOWLEDGEMENT

The author wishes to express his gratitude to Dr. P.W. Jennings for the direction given and the support offered during his sojourn here at Montana State University.

The author also wishes to thank the colleagues in his research group for the encouragement they offered professionally and personally during his graduate career. Gratitude is also expressed to the other members of the chemistry department for numerous helpful and stimulating discussions. A note of thanks to J.A. Campbell and Dr. C.F. Campana for their efforts on the x-ray crystallographic work.

Gratitude is expressed to Montana State University for financial support in the form of teaching and research assistantships.

The author thanks Joan Pribanic for the assistance freely given in so many aspects of this work.

And finally, the author wishes to thank his family for the love and the support they have offered over the years. Without their care, this project would have been so much more difficult.

TABLE OF CONTENTS

		Page
1.	VITA	iv
2.	ACKNOWLEDGEMENT	v
3.	TABLE OF CONTENTS	vi
4.	LIST OF TABLES	vii
5.	LIST OF FIGURES	viii
6.	ABSTRACT	ix
7.	INTRODUCTION	1
8.	STATEMENT OF THE PROBLEM	20
9.	DISCUSSION	23
	Oxidation of Furan	24
	Studies with 3-Methyl-4,5,6,7-tetrahydrobenzofuran	25
	Studies with 1,2,3,4,5,6,7,8-Octahydrodibenzofuran	34
	Studies with 3-Methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O and 1,2,3,4,5,6,7,8-Octohaydrodibenzofuran-^{18}O	39
	Attempted Synthesis of Enediones	57
	Studies with 2,5-Dimethylfuran	60
	Studies with 2-Methyl-4,5,6,7-tetrahydrobenzofuran	61
	Studies with 2,3-Dimethyl-4,5,6,7-tetrahydrobenzofuran	75
	Low Temperature ^{1}H NMR Studies with 3-Methyl-4,5,6,7-tetrahydroenzofuran	82
	Discussion of the Proposed Mechanism	85
10.	SUMMARY	93
11.	EXPERIMENTAL	95
12.	REFERENCES	134

LIST OF TABLES

		Page
Table 1.	^{18}O Content for Studies Involving 3-Methyl-4,5,6,7-tetrahydrobenzofuran.	46
Table 2.	^{18}O Content for Studies Involving Perhydrodibenzofuran.	52
Table 3.	^{18}O Content for Studies Involing 2-Methyl-4,5,6,7-tetrahydrobenzofuran.	73
Table 4.	^{18}O Content for Studies Involving 2,3-Dimethyl-4,5,6,7-tetrahydrobenzofuran.	81

LIST OF FIGURES

		Page
Figure 1.	Synthetic scheme followed for preparation of 3-methyl-4,5,6,7-tetrahydrobenzofuran	26
Figure 2.	Proposed mechanism for the oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran via a diepoxide intermediate.	32
Figure 3.	Synthetic scheme followed for preparation of perhydrodibenzofuran.	35
Figure 4.	Proposed mechanism for the oxidation of perhydrodibenzofuran via a diepoxide intermediate	37
Figure 5.	Perspective view of the molecular structure of 78	38
Figure 6.	Synthetic scheme followed for preparation of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O	44
Figure 7.	Proposed mechanism for the cyclization of β,γ-epoxy ketals to furans.	48
Figure 8.	Synthetic scheme followed for preparation of perhydrodibenzofuran-^{18}O.	50
Figure 9.	^{13}C NMR spectrum of 96a	51
Figure 10.	^{13}C NMR spectrum of 77a	53
Figure 11.	^{13}C NMR spectrum of 78a	54
Figure 12.	Proposed mechanism for the oxidation of perhydrodibenzofuran-^{18}O via an enedione intermediate.	55
Figure 13.	Proposed mechanism for the oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O via an enedione type intermediate	56

LIST OF FIGURES--Continued

		Page
Figure 14.	Synthetic scheme followed for preparation of 2-methyl-4,5,6,7-tetrahydrobenzofuran.	62
Figure 15.	^{13}C NMR analysis of carbonyl resonances of 110	64
Figure 16.	Initially proposed mechanism for the oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran . .	67
Figure 17.	Proposed mechanism for the oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran via an enedione intermediate.	75
Figure 18.	Proposed mechanism for the oxidation of 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran via an enedione intermediate.	83

ABSTRACT

The reaction of a series of alkyl substituted tetrahydrobenzofurans with m-chloroperbenzoic acid has been explored. The furan substrates used included 3-methyl-4,5,6,7-tetrahydrobenzofuran, 1,2,3,4,5,6,7,8-octahydrodibenzofuran, 2-methyl-4,5,6,7-tetrahydrobenzofuran and 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran. The products arising from the oxidation of these substrates have been isolated and their structures determined. These substrates have also been prepared labeled with oxygen-18. These labeled substrates were also oxidized and the position of the label in the products determined by carbon-13 NMR spectroscopy. On the basis of the data obtained from these experiments, a detailed mechanistic scheme was developed. Initial attack of the furan moiety by m-chloroperbenzoic acid occurs to form an epoxide which subsequently undergoes ring openings to form a cis-enedione. These compounds are postulated as intermediates in all the reactions studied even though such a compound was isolated in only one case. These enediones undergo rapid Baeyer-Villiger oxidation with a second equivalent of m-chloroperbenzoic acid. In certain cases, the reaction with a third equivalent of m-chloroperbenzoic acid has been observed and, again, this is viewed as a Baeyer-Villiger oxidation.

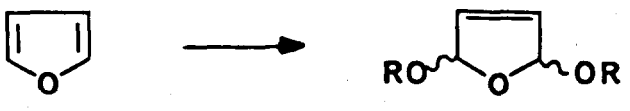
INTRODUCTION

The chemistry of furans has attracted the interest of many researchers over the years. However, of this work, little has centered on the oxidation of furans. In reviewing the literature, one finds that a few workers have carried out extensive studies in this area. A literature review also shows that most of the reports dealing with the oxidation of furans come from those whose research interests have impinged on this area of furan reactivity for other reasons. One example of this latter case would be reports stemming from the oxidation of furans with a specific reagent or procedure in which the primary interest of the author lies in the oxidative process used rather than in the furan moiety. In other cases, furans have appeared in synthetic schemes in which they have been transformed by oxidation into a desired product. Examples can also be found in which natural products containing the furan moiety have been oxidized to assist in structure elucidation.

A few techniques for the oxidation of furans have received repeated use over extended periods of time. Two of these will be discussed. Attention will then be turned to the use of organic peracids as oxidants and the results which have been obtained in these systems.

One method that has been extensively utilized since its development by Clauson-Kaas is the electrochemical oxidation.[1] In this

process, alcohols are used as solvents with ammonium bromide as a buffer and a platinum electrode is generally employed. Oxidations of this type can convert furan 1 into 2,5-dialkoxy-2,5-dihydrofurans 2 (equation 1). These compounds, which are useful as synthetic inter-

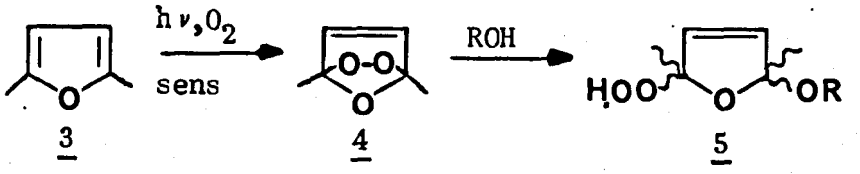


1 2 (1)

mediates, can be prepared in excellent yields. This electrochemical oxidation process was developed to replace the bromoalkoxylation reaction.[2] In these instances, bromine was used as the oxidant and similar products were obtained. However, yields were generally lower and the resulting products were often contaminated with a small amount of bromine. This greatly decreased their stability since these compounds are acid sensitive. Interest is still shown in the synthesis of these useful intermediates as evidenced by a recent report that cited use of vanadium(V) oxide to catalytically convert hydroperoxides formed from the photooxidation of furans to synthons of this type.[3]

A second type of furan oxidation which has received considerable attention has been the dye sensitized photooxidation.[4] This process results in the formation of endoperoxides 4 if the reaction is carried

out in aprotic solvents (equation 2). These products can be converted



3 4 5 (2)

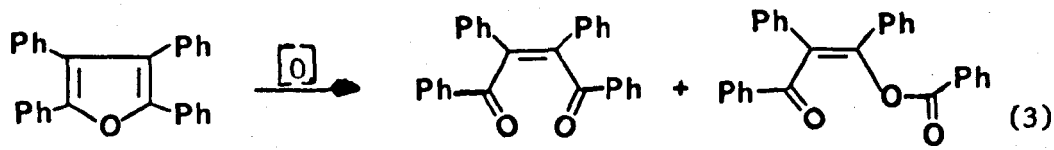
to hydroperoxides 5 by action of alcohol or the furan 3 can be converted directly to 5 by carrying out the oxidation using an alcohol as the solvent. Interest has been expressed in the endoperoxides 4 for a number of reasons. Initially, they were studied as stable ozonides.[5] These compounds can be considered as the ozonides of cyclobutadienes and the comment has been made that this is probably the only case where an ozonide was isolated before the parent compound.[6] Attention to the endoperoxides 4 has also persisted because of the interesting chemistry that they afford. Recent work by Adam has shown that these compounds are capable of epoxidizing olefins.[7] Work continues on the mechanism of this reaction.[8] Interest is also expressed in other conversions of these compounds as evidenced in the report noted above with vanadium(V) oxide.[3]

In reviewing the literature on the oxidation of furans with organic peracids, one notes discrepancies which seem to arise. As observed previously, some of these may occur since the stated purpose of the research relates to the peracid oxidation of a furan as a desired chemical transformation. Thus, details of the reaction are not reported that would be useful in a mechanistic study. Yet in

other cases, the results seem contradictory and obviously further studies are needed. Perhaps the most relevant observation is that there are very few references to research in this area.

Initially, attention will be directed to the oxidation of benzofurans or aryl substituted furans. This class of compounds is segragated in this way as a matter of convenience, rather than because they exhibit markedly different reactivities.

One of the earliest reports in this area is an article by Lutz.[9] One primary interest of his research group was the chemistry of substituted dibenzoylethylene. In this light, he reported that the oxidation of tetraphenylfuran 6 proceeds to give 7 and 8 (equation 3). A variety of oxidizing agents were used including, chromic acid,

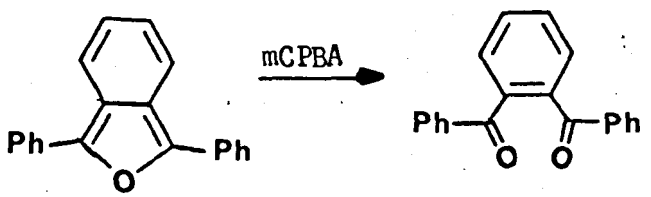


6 7 8 (3)

hydrogen peroxide, ozone and perbenzoic acid in acetic acid. Yields of 7 reportedly ranged between 40-80% and yields of 8 between 10-20%. It is inferred that under any of these conditions 7 can be oxidized to 8; but, given the brevity of this report, this point is not clear. Specific reaction conditions are also not noted and, therefore, yields with a given reagent are left in doubt. Because of the lack of experimental detail in this communication, its value is truly limited.

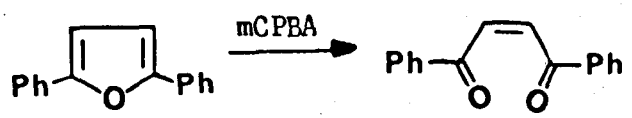
This area was approached next in an article by Boyer.[10] In this report attention was directed toward the oxidation of the singlet

oxygen acceptors 1,3-diphenylisobenzofuran 9 and 2,5-diphenylfuran 11. It was noted that the treatment of 9 with one equivalent of m-chloroperbenzoic acid (mCPBA) for two hours in refluxing methylene



9 10 (4)

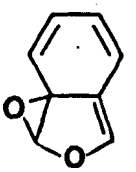
chloride in the dark gave o-dibenzoylbenzene 10 in 90% yield (equation 4). It was noted that the identical product was obtained by the photooxidation of 9. Similarly, 2,5-diphenylfuran 11 gave cis-dibenzoylethylene 12 in 85% yield when treated with one equivalent of mCPBA and reflux was continued for four hours (equation 5). Again,



11 12 (5)

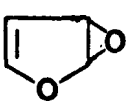
it was noted that the same product could be isolated by the singlet oxygen oxidation of 11. On the basis of further experimentation, the reaction with peracid was shown not to proceed through a singlet

oxygen mechanism and the epoxide 13 was suggested as the type of intermediate involved in the peracid oxidation.

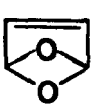


13

Considering the oxidation of furan itself with organic peracids, one again finds a progression of studies. The earliest reference dates from 1931.[11] In this case, it was noted that the oxidation of furan 1 with peracetic acid as a 6% solution in acetic acid proceeded slowly, requiring three days to go to completion as noted by the disappearance of the peracid. At the end of this time, attempts to isolate the product by removing the acetic acid by distillation afforded a resinous material whose molecular weight was found to be greater than 780. On the basis of this information, two intermediates

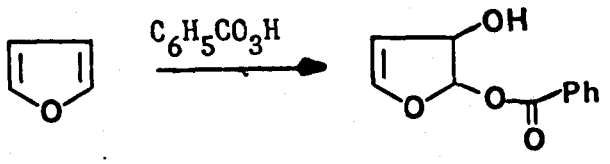


14



15

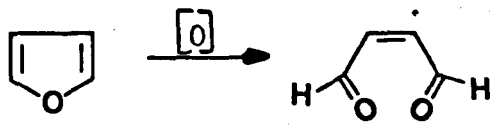
were proposed: 14 or 15. The oxidation was then carried out with perbenzoic acid in chloroform (equation 6). In this instance,



1 16 (6)

the product was determined to be 16 on the basis of carbon-hydrogen analysis and molecular weight determination. It was therefore concluded that epoxide 14 was the intermediate in both cases.

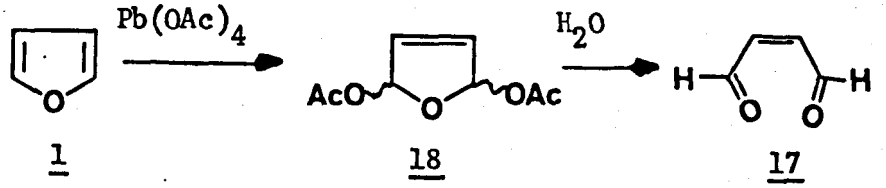
This reaction was reinvestigated by Clauson-Kaas in 1947.[12] Again peracetic acid and perbenzoic acid were used as the oxidants. In this case, the product was determined to be malealdehyde 17 on the basis of the bis-phenylhydrazone which was isolated (equation 7).



1 17 (7)

These reactions were run in a variety of solvents including chloroform, ether, acetic anhydride and water at temperatures ranging from 0-40°. Yields were reported to be less than 23% in all cases. No difference was noted between the two peracids. The authors proposed 15 to be the intermediate in these reactions. In a report by the same group five years later, they reported that oxidation of furan 1 with

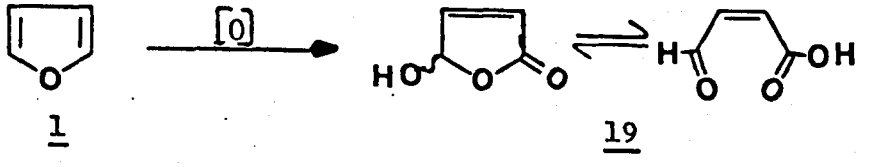
lead tetraacetate gave 18 in 70-80% yield (equation 8). Compound 18 was then hydrolyzed to give 17 which was isolated and identified as



1 18 17 (8)

the bis-phenylhydrazone.

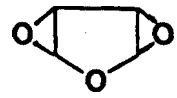
A final study on the oxidation of furan with peracids was reported in 1964.[14] The result noted with p-nitroperbenzoic acid as the oxidant was the isolation of aldehydomaleic acid 19 in 8% yield (equation 9). The reaction was carried out in ether using 2.2



1 19 (9)

equivalents of the peracid. Reaction time was reported as two days. The product 19 was identified on the basis of its ^1H NMR spectrum,

elemental analysis and the elemental analysis of a derived phenylhydrazone. In this case, diepoxide 20 was proposed as the inter-

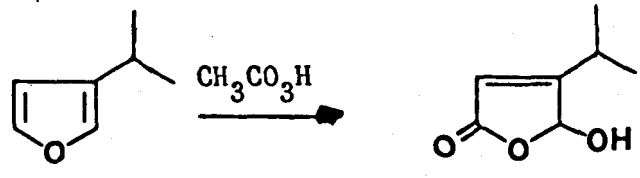


20

mediate in the reaction.

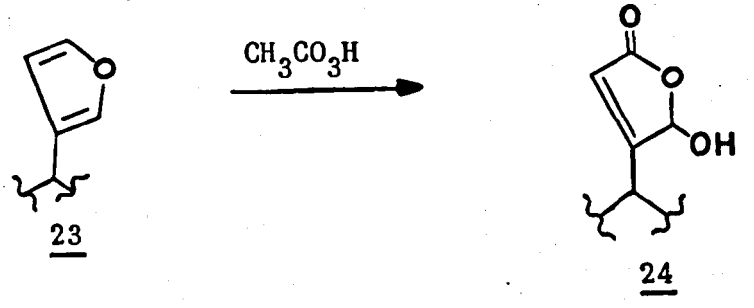
In analyzing the results from these three articles, it should be noted that p-nitroperbenzoic acid is a slightly stronger oxidant than perbenzoic acid which, in turn, is slightly stronger than peracetic acid. This ordering is based on the concept that stronger acids yield peracids with correspondingly stronger oxidizing ability.[15] The result obtained with p-nitroperbenzoic acid can therefore possibly be rationalized on the basis that a stronger oxidant was used. However, the earlier two reports are still conflicting and further studies in this area would be useful.

Turning attention to substituted furans, Lefbvre reported on the oxidation of 3-substituted furans with peracetic acid.[16] It was observed that 3-isopropylfuran 21 underwent oxidation with excess peracetic acid to give 22 (equation 10). The reaction was run in



21 22 (10)

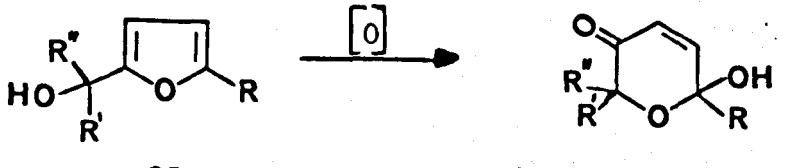
chloroform for two hours at 0-5°. Solid sodium acetate was added as a buffer. Even though no mechanism was proposed, this reaction seems to follow a pathway similar to that observed in the oxidation of furan with p-nitroperbenzoic acid. In this same article, the oxidation of a compound in the digitoxigenin series was reported (equation 11).



23 24 (11)

In this case the furan moiety is substituted on the D ring of a steroidal skeleton. The furan was found to oxidize again in two hours under similar conditions to form 24 in approximately 50% yield.

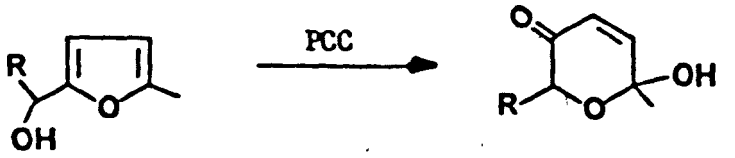
A second article by the same group followed in which they reported the transformation shown (equation 12).[17] In this case,



25 26 (12)

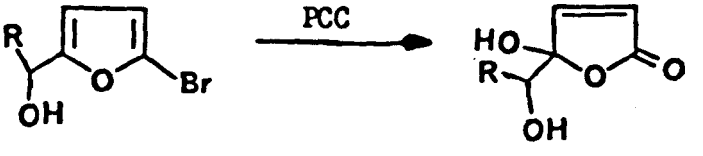
oxidation was carried out with mCPBA or peracetic acid. Reaction times were generally short and the products were isolated in varying yields, ranging between 50-90%, if the reaction proceeded at all. No mechanism was proposed in this report either.

It is interesting that a similar transformation was observed later by a group of Italian workers using pyridinium chlorochromate (PCC) as an oxidant (equation 13).[18] Methylene chloride was used as



27 28 (13)

the solvent and the products were generally isolated in greater than 90% yields. No oxidation of the secondary alcohol was noted. This work has recently been extended (equation 14).[19] These reactions were again carried out in methylene chloride using a 2:1 molar excess of

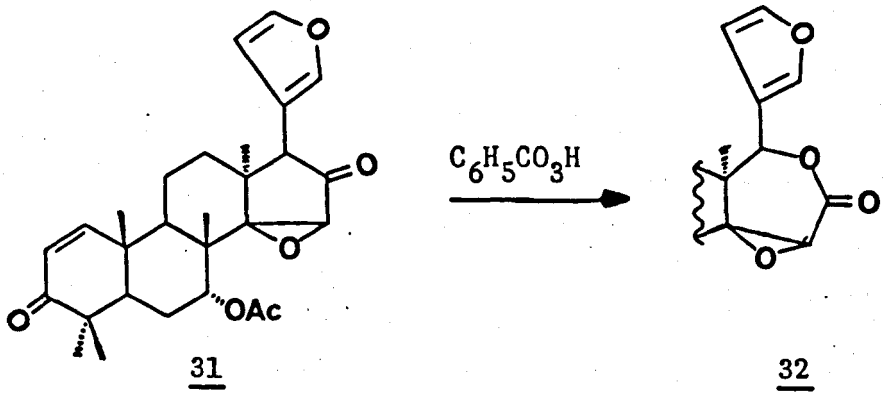


29 30 (14)

PCC. Reaction times were reported as approximately ninety minutes. It is noteworthy that the products 30, isolated in 60-75% yields, are of the same type one would expect from the peracid oxidation of the furan based on the report noted above on the oxidation of 3-substituted furans.

At this point, it may be interesting to discuss a couple of anomalies which have been reported. One case involved oxidation reactions of biogenetic interest.[20] When epoxyazadiradone 31 was treated with perbenzoic acid for two hours, gedunin 32 was isolated

in 90% yield (equation 15). No note was made of the quantity of

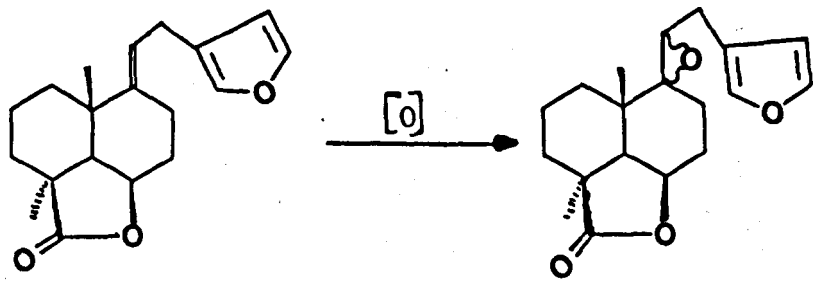


31 32 (15)

perbenzoic acid used. Similarly, 1,2-dihydroepoxyazadiradone was reported to react with perbenzoic acid to give two products: 1,2-dihydrogedunin and 1,2-dihydro-7α-obacunyl acetate. The latter product arises from Baeyer-Villiger oxidation in both the A and D rings of the steroidal nucleus. In this case reaction time was reported as nine hours; but, again, no comment was made on the quantity of perbenzoic acid used or on other conditions employed. No products in either instance were reported arising from oxidation of the furan moiety.

It should be noted that the furan in 31 is in a very similar environment to that of the furans discussed by Lefbvre (see equations 10 and 11). As observed previously, peracetic acid, as used by Lefbvre, is a weaker oxidant than perbenzoic acid, which was used above. With the longer reaction times used above, one would therefore predict some oxidation of the furan to occur. Since this was not observed, it is obvious that further studies are needed in this area to develop a more complete understanding of these systems.

Another paper which contained seemingly anomalous results outlined the synthesis of marubiin, a terrestrial natural product.[21] As one step in this scheme, 33 was oxidized with a 4% solution of monperphthalic acid to give the epoxide 34 as a mixture of diastereomers (equation 16). When this reaction was run for five



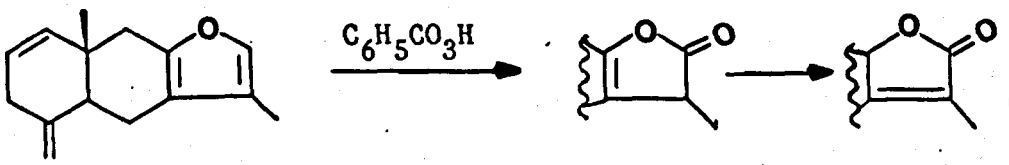
(16)

33 34

minutes at room temperature, 1.85 g of 33 reportedly gave 0.283 g of 34 and 1.475 g of 33 was recovered. Longer reaction times resulted in a mixture of products which was not easily separated. Again, this starting material is very similar to the 3-substituted furans noted above. Perphthallic acid is a much stronger oxidant than peracetic acid, yet, reaction was not reported to occur at the furan moiety. However, this reaction may occur to some extent since longer reaction times, as noted, led to a mixture of unidentified products.

Returning to reports in which the furan nucleus was involved in the oxidation, an article appearing in 1964 was noted.[22] In this instance, the oxidation was carried out as part of a degradation scheme in a structure proof of the compound lindestrene 35. It was observed that oxidation of this compound with 1.2 equivalents of perbenzoic acid gave 36 in nearly quantitative yield (equation 17).

The reaction was reportedly run for thirteen hours at 0°. However,

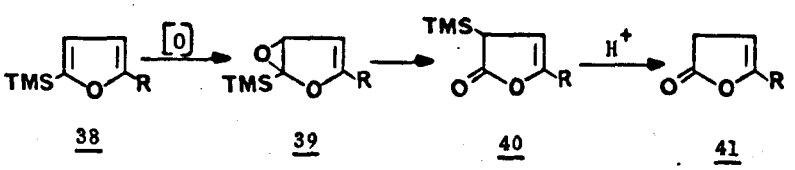


(17)

35 36 37

36 was identified solely on the basis of its IR spectrum (1790 cm^{-1}). It was converted to 37 by chromatography on alumina. Compound 37 was isolated in approximately 30% yield from lindestrene. It is therefore possible that materials other than 36 were in the reaction mixture. A more thorough investigation of this system would be warranted, especially in light of the work to be reported in this thesis.

In a recent report, Kuwajima detailed a synthetic scheme for the preparation of Δ^3-butenolides, compounds noted to be useful as synthetic intermediates but difficult to prepare given their propensity to rearrange.[23] This preparation involved the oxidation of 2-trimethylsilylfurans 38 with 40% peracetic acid (equation 18). The reaction conditions involved a fourfold excess of peracetic acid.



38 39 40 41

(18)

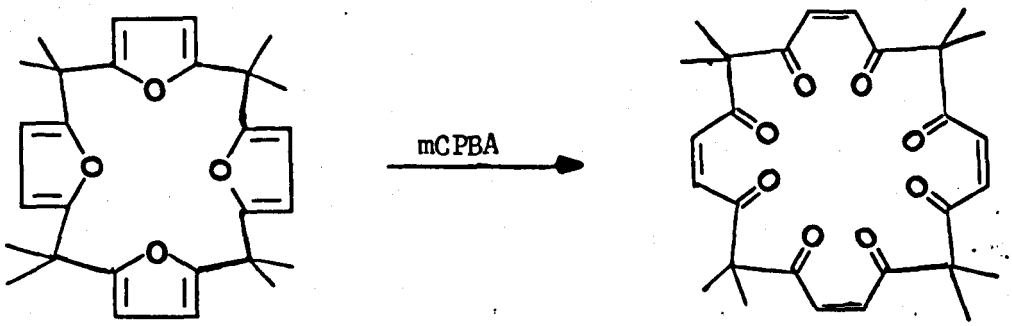
Solid sodium acetate was added as a buffer. Methylene chloride was used as the solvent and the reactions were run at 7°. The reaction

was proposed to proceed as shown from furan 38 to the butenolide 41. It was assumed that epoxide 39 was the initially formed intermediate. The trimethylsilyl group is electron releasing and will therefore direct the regioselectivity of the original attack. Compound 40 was seen by NMR spectroscopy but was too unstable to be isolated as the TMS derivative.

Two other points from this paper are also of interest. The authors found that mCPBA gave markedly lower yields than peracetic acid. This was ascribed to the fact that mCPBA is a stronger oxidant and therefore shows less regioselectivity in its attack on the furan moiety. Another possibility, not discussed in the article, is that mCPBA, as a stronger oxidant, carries out further chemistry on either the intermediates or the product of this reaction, thus lowering the yield. In this paper, it was also noted that the oxidation of 2-hexylfuran with peracetic acid or mCPBA resulted in the formation of an intractable mixture.

A report by LeGoff in 1981 dealt with the synthesis of enedione functionalized macrocycles by oxidative ring opening of furans.[24] The macrocyclic furans used were tetramers 42 or hexamers synthesized by the condensation of acetone and furan. When these were treated with a slight molar excess of mCPBA (4.2 equivalents for the tetramer or 6.3 equivalents for the hexammer) the furans underwent oxidative ring opening to form the macrocycles as shown (equation 19). These reactions were run overnight at room temperature and yields were reported as 85% in both cases. The reaction was also attempted utilizing bromine in methanol, as described above, followed by

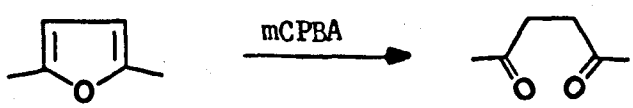
hydrolysis. However, yields were significantly lower than with



(19)

42 43

mCPBA, all the furans did not undergo ring opening, and the cis-enediones generally underwent isomerization to the trans isomer. It was reported that 2,5-dimethylfuran 3, studied as a model, underwent a similar reaction to give cis-hexene-2,5-dione 44 (equation 20). In this case, 1.1 equivalent 5 of mCPBA were added in one portion to a



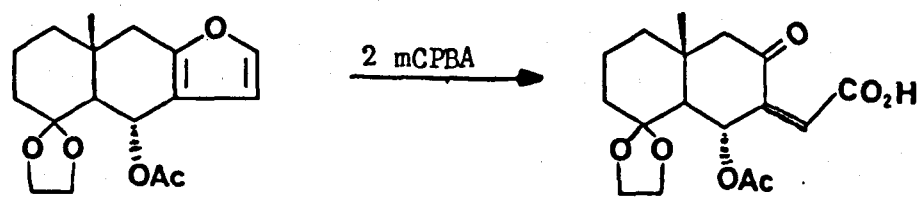
(20)

3 44

solution of the furan at -10°. The solution was allowed to warm to room temperature and stirred overnight. Work-up led to the isolation of 44 in 99% yield.

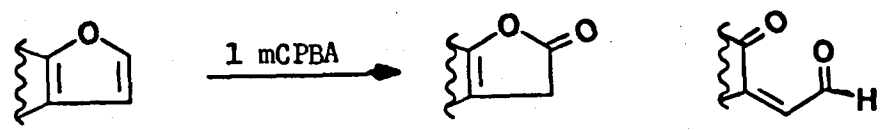
A report by Tada appeared in 1982 in which the oxidation of compound 45 with two equivalents of mCPBA proceeded to give product

46 which was isolated in high yield (equation 21).[25] The interesting note about this reaction is that addition of one equivalent of mCPBA



45 46 (21)

to 45 resulted in the formation of two products: the lactone 47 and the aldehyde 48 (equation 22). The author had hoped lactone 47 would

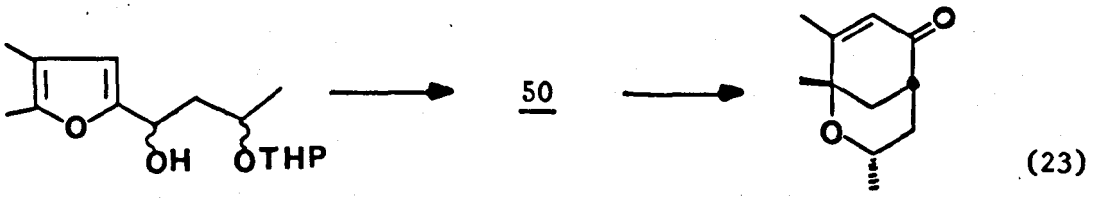


45 47 48 (22)

be the sole product of this reaction. This prediction was based on the oxidation of lindestrene which was discussed above.

Finally, a report by DeShong is most enlightening.[26] This paper dealt with the synthesis of substituted 2,9-dioxabicyclo[3.3]nonanes as models for tirandamycin, an antibiotic. The key step in this transformation was oxidation of the furan derivative 49 to yield intermediates 50. Treatment of the intermediates with dilute acid gave 51 in 25% yield (equation 23). Since 49 would generate 50 as a mixture of diastereomers, only one half of which would react to give the desired product, this yield was found to be acceptable. The

oxidizing reagent for which this yield was reported was bromine in methanol. However, it was noted that this oxidation could also be carried out with pyridinium chlorochromate at 0°, with singlet oxygen in methanol at -20° and with mCPBA in methylene chloride at 0°. It



49 50 51 (23)

is interesting to observe that, even though these reactions probably generate different intermediates, although this is not noted in the article, all lie on a pathway from the furan 49 to the desired product 51.

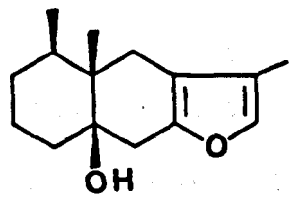
In reviewing these references, it is observed that there are some unifying themes in this area as well as some discrepancies. It is difficult to draw any real conclusions since, as stated, in many of these cases the oxidation was not of primary importance to the author. One can attempt to make mechanistic comparisons by analyzing reaction conditions, but this is fraught with pitfalls. It is sufficient to say that there have been no mechanistic studies on the oxidation of alkyl substituted furans with peracids.

The research reported in this thesis was begun in 1979. The last four references discussed above were published after this date. These

reports were noted as they appeared in the literature to determine how they fit in with this ongoing research project. In this light, one can see that relatively little was known concerning the oxidation of alkyl substituted furans.

STATEMENT OF THE PROBLEM

In the first half of this century, it was reported that the plant Tetradymia glabrata, when ingested by sheep, caused numerous fatalities.[27] This fact led to a study by previous workers in Dr. Jennings' laboratory in an attempt to isolate and identify toxic constituents of this plant. This work resulted in the characterization of tetradymol 52 as a major toxic component of T. glabrata.[28, 29] Further studies carried out with this furanosesquiterpene indicated



52

that it was oxidized by the mixed function oxidase system to form a metabolite even more toxic than the parent compound.[30]

Interest was then directed toward possible metabolites of alkyl substituted furans in an attempt to rationalize this enhanced toxicity. In this light, in vitro metabolic studies were begun using liver microsomal suspensions and model furan compounds. It was hoped that this work would lead to the isolation and characterization of metabolites that could be shown to cause effects similar to those of the furan substrates.

With this as background, it was decided to pursue chemical modeling studies using mimics for the mixed function oxidases. These studies were planned to parallel the in vitro experiments by using the same model compounds. It was hoped that the chemical studies might indicate the types of products to be expected from the in vitro counterparts.

A literature search was then undertaken to determine the types of chemical oxidants which have been used as mimics for the mixed function oxidases. It was found that a wide range of compounds have been utilized including Undenfriends reagent,[31] oxotransition metal complexes,[32] aromatic-N-oxides,[33] hydroperoxyflavins[34] and organic peracids.[35] A number of oxidants developed in recent years, such as 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3H-pyrazole,[36] 2-hydroperoxyhexafluoro-2-propanol[37] and triphenylsilyl hydroperoxide,[38] have also been shown to afford similar reactivity with certain systems as those reagents noted above which have been touted as mimics.

An organic peracid, m-chloroperbenzoic acid, was selected as a mimicking reagent in our model studies.[39] This choice was made largely on the basis of the fact that the chemistry of this oxidant is fairly well understood. It is also available as a solid which is easily purified and is stable for extended periods of time.

With this choice made we therefore proposed to study the oxidation of alkyl substituted furans which were models for naturally occurring compounds with m-chloroperbenzoic acid. It was hoped that

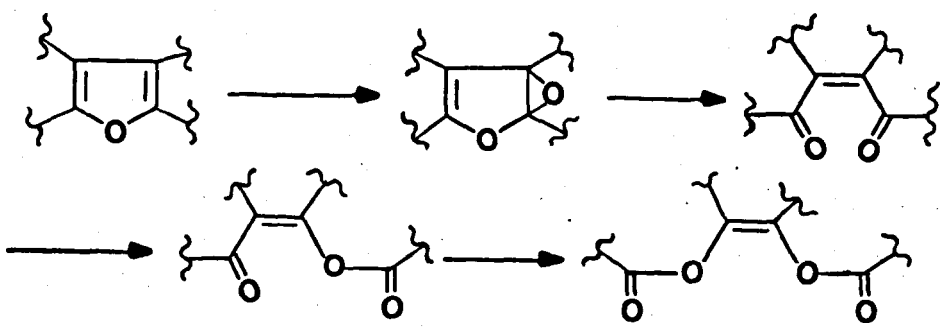
this work would shed light on the enhanced toxicity shown when furans were oxidized *in vivo*.

As will be noted in the following section, initial studies led to some rather unexpected results. The goal of further research then shifted to understanding the mechanism of this observed reaction. A series of alkyl substituted tetrahydrobenzofurans were prepared and the mechanism of their oxidation with *m*-chloroperbenzoic acid was investigated. However, this work resulted in an understanding of these systems which may, in fact, be related to the question of metabolites of furans responsible for the toxicity evidenced in the *in vivo* studies.

DISCUSSION

The work presented in this thesis was directed toward elucidating the mechanism of the oxidation of furans with m-chloroperbenzoic acid (mCPBA). As studies were conducted, the mechanistic implications were reviewed and new experimental approaches were proposed and carried out. The results of these studies will be presented and discussed from a historical perspective.

The results fit into the simplified scheme shown (equation 24).



(24)

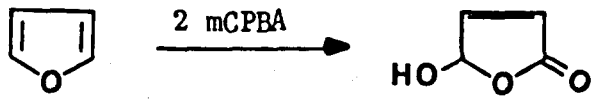
Initial attack is proposed to occur on the furan moiety to form an epoxide. This intermediate subsequently undergoes ring opening to yield a cis-enedione. In all cases these compounds react very rapidly with a second equivalent of mCPBA and undergo a Baeyer-Villiger oxidation. Reaction with a third equivalent of mCPBA can occur, again as a Baeyer-Villiger oxidation. The fine points of this mechanism will be discussed as data are presented.

Oxidation of Furan

Initially, studies were carried out on the oxidation of furan 1 with mCPBA. This series of reactions was run in a variety of nonpolar solvents including carbon tetrachloride, chloroform, methylene chloride and benzene. The progress of the reaction was monitored by gas chromatography. Reactions were run at 0° or room temperature. Reaction times ranged from two to 24 hours.

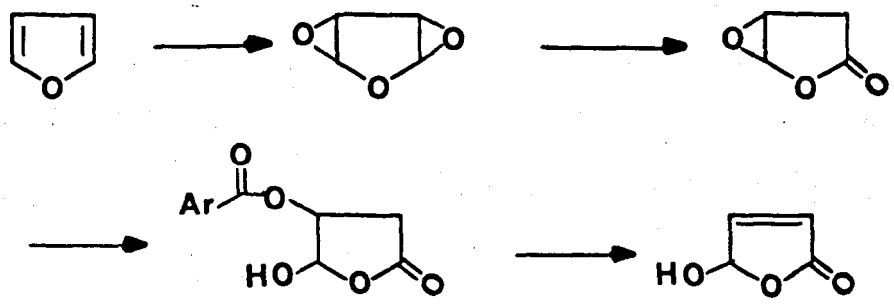
It was observed in all these cases that addition of one equivalent of mCPBA consumed approximately 50% of the furan. Addition of a second equivalent of mCPBA carried the reaction to completion as shown by GC analysis. Attempts to isolate products from this reaction mixture were uniformly unsuccessful. m-Chlorobenzoic acid, formed as a side product, was typically removed by extracting the reaction mixture with base. When the organic layers from these reactions were subjected to this procedure, the basic aqueous layer turned brown-black. Further work-up of the organic layer led to no isolatable product.

It was noted that a procedure had been developed by Camps which utilized activated potassium fluoride to complex with m-chlorobenzoic acid and quantitatively form an insoluable precipitate.[40] Using this technique, it was possible to oxidize furan 1 with two equivalents of mCPBA and isolate aldehydomaleic acid 19 in 52% yield (equation 25). This product was identical to that prepared by Catala, who used p-nitroperbenzoic acid as an oxidant.[14] In this article, the authors



1 19 (25)

proposed the mechanism shown (equation 26). This mechanism may be



(26)

operative in our experiments with mCPBA. The only comment to be added is that the addition of the second equivalent of mCPBA must be much faster than initial attack of the furan by this reagent.

Since isolation of products in this instance was difficult and because of their hydrophilic nature, it was decided to extend the studies to substituted furans. It was hoped that products in these cases would be more lipophilic and more easily isolated.

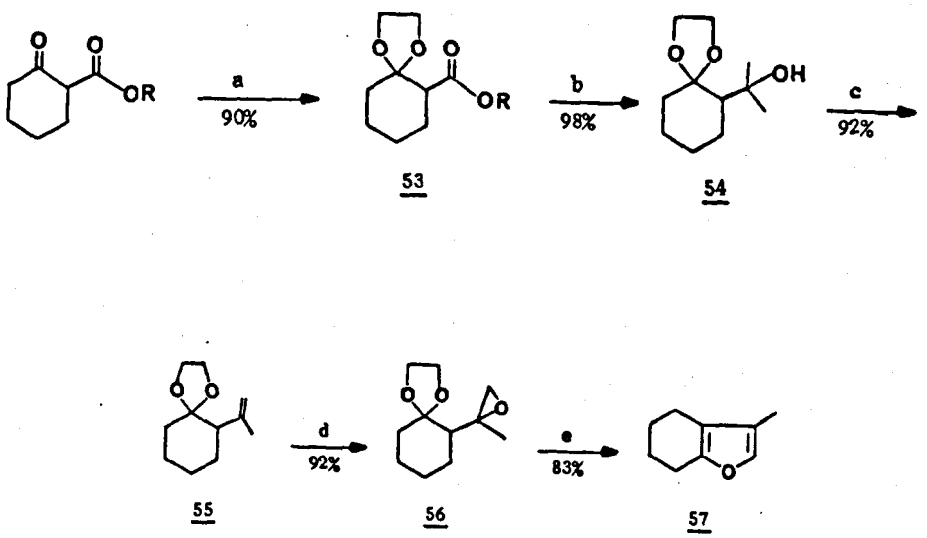
Studies with 3-Methyl-4,5,6,7-tetrahydrobenzofuran

When this work commenced, concurrent studies were under way utilizing liver microsomal suspensions for *in vitro* oxidations of model furan compounds. One of these model compounds was 3-methyl-4,5,6,7-tetrahydrobenzofuran 57. It was decided to extend our studies to this substrate since it met the requirement of being more lipophilic than furan. Furthermore, this substituted furan is also a good model

for naturally-occurring furans and, in this sense, it tied in well with our chemical modeling studies.

Synthesis of 3-methyl-4,5,6,7-tetrahydrobenzofuran 57. The synthetic scheme utilized to prepare this compound is shown (Figure 1). The key step is the cyclization of ketal epoxide 56 to the desired furan 57. A recent report by Takahashi had been noted in which menthofuran was prepared from 9-methyl-6-(2-methyloxirane)-1,4-dioxaspiro[4.5]decane.[41] In an analogous fashion, the goal of this synthesis was 6-(2-methyloxirane)-1,4-dioxaspiro[4.5]decane 56 which could be cyclized in high yield to the furan 57.

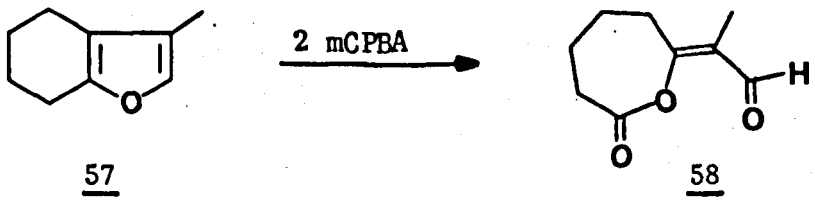
Figure 1. Synthetic scheme followed for preparation of 3-methyl-4,5,6,7-tetrahydrobenzofuran.



a-$(HOCH_2)_2$, p-TsOH, C_6H_6, Δ; b-MeMgI; c-p-TsOH, C_6H_6, Δ; d-mCPBA; e-1M HCl, pentane

The synthesis began with ethyl 2-oxocyclohexanone carboxylate (approximately 40% corresponding methyl ester) which was ketalized. The ketal ester 53 was converted to the alcohol 54 with methyl magnesium iodide. Elimination proceeded to form the terminal alkene 55.[42] This compound was converted to the epoxide 56 with mCPBA and then this material was cyclized to the furan 57 as desired.

Oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran 57. Oxidation of this compound occurred with the consumption of two equivalents of mCPBA to afford ε-lactone 58 in nearly quantitative yield (equation 27). The structure of 58 was deduced from its spectral



57 58 (27)

properties. The ^{1}H-decoupled ^{13}C NMR spectrum showed nine resonances, four of which appeared at 189.8, 170.7, 164.8 and 123.9 ppm. The resonance at 189.8 ppm was found to be a doublet in the gated decoupled spectrum and was assigned to the aldehydic carbon. The other three downfield resonances noted above appeared as singlets in the gated decoupled spectrum. The resonance at 170.7 ppm was assigned to the carbonyl carbon of the lactone functionality. The resonance at 123.9 ppm was assigned to the olefinic carbon adjacent to the aldehyde and the resonance at 164.8 ppm to the other olefinic carbon. The ^{1}H

NMR spectrum showed a resonance for a single proton at 10.2 ppm which was assigned to the aldehydic hydrogen. A methyl singlet was observed at 1.8 ppm. The IR spectrum showed a weak band at 2750 cm^{-1} which resulted from the carbon-hydrogen stretch of the aldehyde group. There were strong absorptions observed at 1755 and 1680 cm^{-1} assigned as the carbonyl stretching frequencies of the lactone and aldehyde groups, respectively. A moderate absorption was observed at 1640 cm^{-1} which was assigned to the carbon-carbon double bond stretching. The mass spectrum showed a molecular ion at m/e 168 indicating that two oxygens had been added to the furan substrate. This material was isolated as a clear oil which was easily converted to a 2,4-dinitrophenylhydrazone for further characterization.

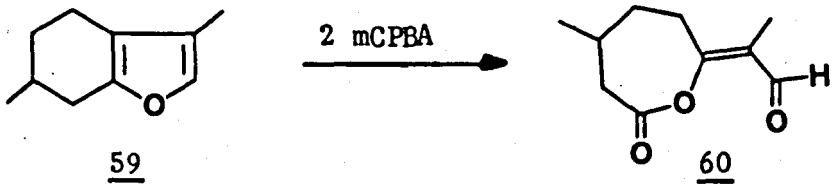
When one equivalent of mCPBA was added to a solution of 57 in methylene chloride, only 50% of the substrate reacted as shown by gas chromatography and ^1H NMR spectroscopy. Thus, in the NMR spectrum of a sample of this reaction mixture, a resonance occurred at 1.90 ppm which was assigned to the methyl group of the furan 57 and a second resonance of equal intensity appeared at 1.80 ppm which was assigned to the methyl group of the product 58. Addition of a second equivalent of mCPBA consumed the rest of the starting furan 57.

The reaction of this substrate with two equivalents of mCPBA occurred extremely rapidly. When a solution of the furan was added to a solution of mCPBA at 0°, the reaction mixture became cloudy within seconds. After one minute, a flocculent precipitate of m-chlorobenzoic acid appeared. Analysis of the reaction mixture after five minutes showed no remaining furan.

A number of experiments were performed to determine what variables affected the course of this reaction. Addition of the furan to a solution of two equivalents of mCPBA gave 58 in identical yield as the addition of two equivalents of mCPBA in one portion to a solution of the furan.

The reaction was run with or without solid sodium bicarbonate added to determine if acid catalysis resulted because of the liberation of m-chlorobenzoic acid. In both cases the yields of 58 were identical, so this aspect was eliminated from further consideration. A question could still be raised as to the effectiveness of solid sodium bicarbonate as a buffer in methylene chloride. An analogy could be drawn to the use of sodium dihydrogen phosphate as a buffer in Baeyer-Villiger oxidations carried out with trifluoroperacetic acid.[43] This added salt, which is an insoluble solid, was able to suppress transesterification of the product of the oxidation and was therefore assumed to be effective.

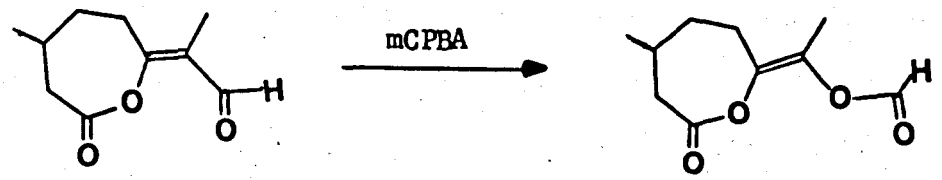
Oxidation of menthofuran 59. This reaction was also explored with menthofuran 59, a close analog of 3-methyl-4,5,6,7-tetrahydrobenzofuran 57. It was found that this reaction proceeded similarly to that of 57 to yield ε-lactone 60 (equation 28). Again this structure



59 60 (28)

assignment was based on its spectral properties. These properties coincided very well with those for 58 with the exception of the perturbations introduced by the methyl group.

It was also found that lactone aldehyde 60 reacted with a third equivalent of mCPBA to yield formate 61 (equation 29). This reaction



60 61 (29)

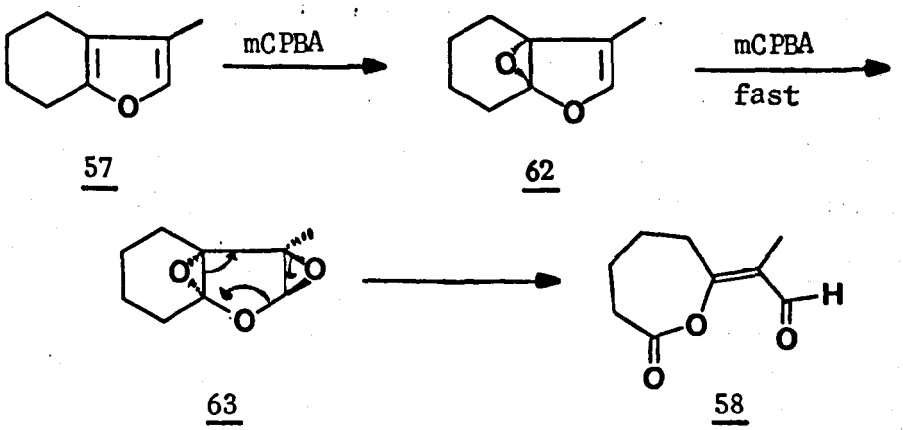
was viewed as a Baeyer-Villiger oxidation of 60 and went to completion in four hours. The structure proposed for 61 was based on its spectral properties. The ^{13}C NMR spectrum showed resonances at 171.5, 158.1, 139.0 and 133.1 ppm. The resonance at 171.5 ppm was assigned to the carbonyl carbon of the lactone functionality. The resonance at 158.1 ppm appeared as a doublet in the gated decoupled spectrum with a carbon-hydrogen coupling constant of 233 Hz. This was, therefore, assigned to the formate carbon. The resonances at 139.0 and 133.1 ppm, both singlets in the gated decoupled spectrum, were assigned to the olefinic carbons. The ^{1}H NMR spectrum showed a resonance for one proton at 7.95 ppm which was attributed to the formate proton. A methyl singlet appeared at 1.9 ppm and a methyl doublet at 1.1 ppm. The IR spectrum showed an intense broad absorption at 1760 cm^{-1} assigned to the carbonyl stretches of the lactone and formate groups.

Mass spectral analysis showed a molecular ion at m/e 198 indicating addition of three oxygens to menthofuran.

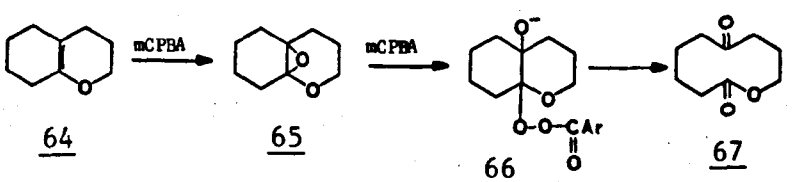
The reaction of menthofuran 59 with two equivalents of mCPBA was run in solvents of varying polarity. In nonpolar solvents (chloroform, methylene chloride and benzene), the course of the reaction was the same and the product 60 was isolated in uniformly high yields. However, as the polarity of the solvents was increased (ether, ethyl acetate, acetone and dimethyl formamide), side product formation became predominant even though 60 could be identified in the crude reaction mixtures by NMR spectroscopy.

Proposed mechanism for the oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran 57 with a diepoxide intermediate. A mechanism for the oxidation of this substrate with two equivalents of mCPBA was proposed (Figure 2). Initial oxidation would be expected to occur at the more substituted double bond of the furan moiety to form 62.[44] Addition of the second equivalent of mCPBA would occur rapidly to form diepoxide 63. This intermediate was proposed to be a trans-diepoxide because of the repulsion between the initially formed epoxide and the approaching second equivalent of mCPBA.[45] Diepoxide 63 would then rearrange as shown to form 58.

Figure 2. Proposed mechanism for the oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran via a diepoxide intermediate.



A second possible pathway considered at this point was derived from reports by Borowitz on the oxidation of enol ethers with mCPBA.[46, 47] This reaction was proposed to proceed to consume two equivalents of peracid and resulted in the ring expanded product (equation 30). However, several features of this reaction contrast

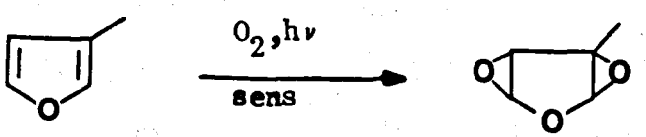


(30)

with the reaction of two equivalents of mCPBA with the furan substrate. First, Borowitz' reaction reportedly required several hours at room temperature to go to completion. Next, yields reported (approximately 50%) are significantly lower than those seen with the furan substrate. Moreover, it would be difficult to justify the product observed in the furan case by following this mechanistic

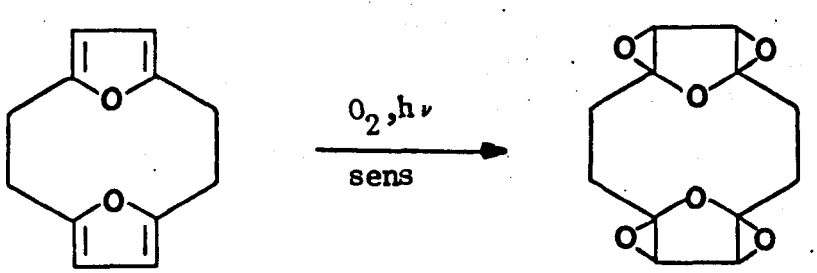
scheme. For these reasons, it was felt that this mechanism was not operative in the furan case and the mechanism with a diepoxide intermediate was, therefore, advanced.

The inclusion of a diepoxide intermediate in the proposed mechanism should cause no concern because diepoxides derived from furans are known to exist. These compounds are generally formed from the endoperoxides which result from the singlet oxygen oxidation of furans. One example reported by Kraus utilized 3-methylfuran 68 (equation 31).[48] The photooxidation of 68 in methylene chloride



68 69 (31)

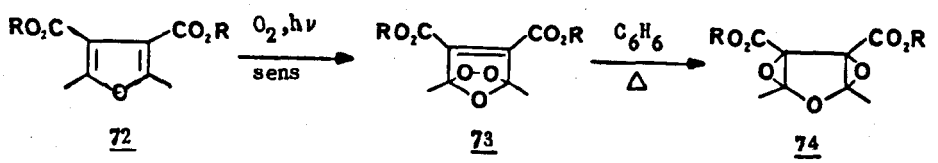
resulted in diepoxide 69 which was isolated from a mixture of products in 23% yield. A second example was reported by Wasserman (equation 32).[49] The sensitized photoxidation of [2.2](2.5)furan-



70 71 (32)

ophane 70 in methylene chloride resulted in the tetraepoxide 71, which was isolated in high yield. Still another example showed the

endoperoxide to indeed be the intermediate of this reaction (equation 33).[55] Sensitized photooxidation of 72 afforded 73. When this



72 73 74 (33)

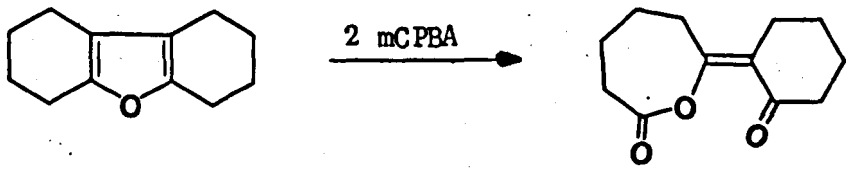
endoperoxide was heated in refluxing benzene, the diepoxide 74 was isolated, reportedly in quantitative yield.

Studies with 1,2,3,4,5,6,7,8 - Octahydrodibenzofuran

Synthesis of 1,2,3,4,5,6,7,8 - octahydrodibenzofuran 77. At this point it was decided to extend our studies to other furan substrates to see how general the reaction that we had observed was. The next substrate chosen was perhydrodibenzofuran 77. This compound was synthesized by modifying a procedure reported by Creese in the literature (Figure 3).[51] Following the procedure of Wenkert, dry hydrogen chloride gas was bubbled through cyclohexanone to effect coupling.[52] The crude ketochloride which resulted was ketalized to yield ketal alkene 75. This was converted to the epoxide 76 with mCPBA. Cyclization was carried out to yield furan 77 using a biphasic mixture of 2 M HCl and pentane.

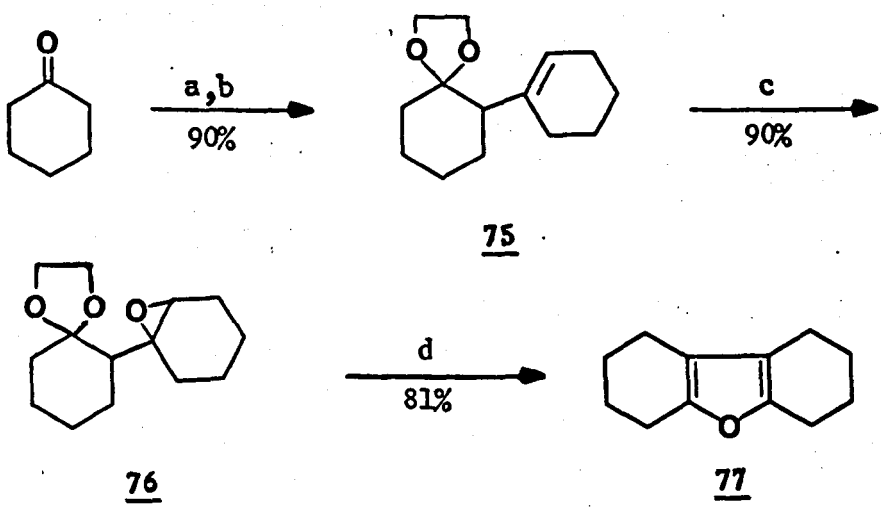
Oxidation of perhydrodibenzofuran 77. As in the previous examples, this substrate reacted to consume two equivalents of mCPBA to give 78 as a white solid in nearly quantitative yield (equation 34).

As before, the structure of this product was elucidated from its spectral properties. The ^{13}C NMR spectrum exhibited resonances at 201.5,



77 78 (34)

Figure 3. Synthetic scheme followed for preparation of perhydrodibenzofuran 77.



75 76 77

a-HCl(g); b-$(HOCH_2)_2$, p-TsOH, $C_6H_5CH_3$, Δ; C-mCPBA; d-2M HCl, pentane

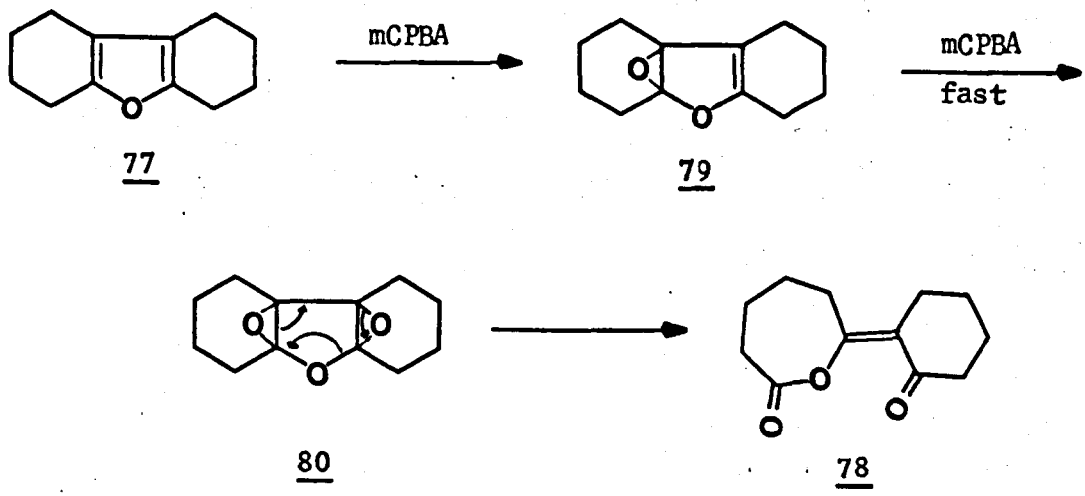
172.3, 150.6, and 125.7 ppm, all of which appeared as singlets in the gated decoupled spectrum. The resonance at 201.5 ppm was assigned to the carbonyl carbon of the ketone and that at 172.3 ppm to the

carbonyl carbon of the lactone functionality. The resonances at 150.6 and 125.7 ppm were assigned to the olefinic carbons; the upfield one to the olefinic carbon adjacent to the ketone group and the downfield resonance to the olefinic carbon adjacent to the oxygen of the lactone functionality. The IR spectrum showed strong absorptions at 1750 and 1690 cm^{-1} which were assigned as the carbonyl stretching frequencies of the lactone and ketone, respectively. A weaker band was observed at 1660 cm^{-1} and this was attributed to the carbon-carbon double bond stretching. The mass spectrum showed a molecular ion at m/e 208, again indicating addition of two oxygens.

This reaction exhibited characteristics similar to those observed for 3-methyl-4,5,6,7-tetrahydrobenzofuran 57. The reaction was rapid, going to completion in approximately five minutes at 0°. Again, addition of one equivalent of mCPBA consumed only 50% of the substrate 77 as shown by gas chromatography and NMR spectroscopy.

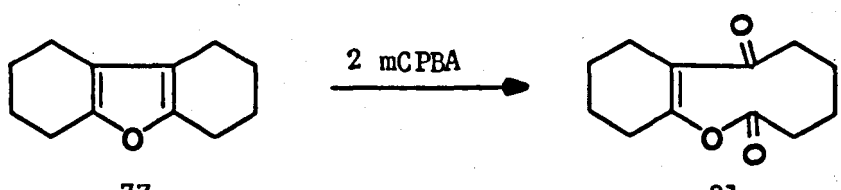
Since the pattern exhibited by this reaction was similar to that shown by 3-methyl-4,5,6,7-tetrahydrobenzofuran 57, a similar mechanistic scheme was proposed (Figure 4). Initial attack would occur on either side of the furan moiety in this symmetrical molecule. Subsequent attack of this monoepoxide 79 would occur rapidly to yield diepoxide 80. This diepoxide would then rearrange to the observed product 78.

Figure 4. Proposed mechanism for the oxidation of perhydrodibenzofuran 77 via a diepoxide intermediate.



77 79 80 78

However, it was noted that in this case, if the furan reacted as an enol ether, the product would have been 81 (equation 35). Structurally, this compound is very similar to 78 and would be expected to



77 81 (35)

have closely related spectral properties. In order to differentiate between these possibilities, it was elected to have a crystal structure determined.

The result of this single crystal X-ray analysis is shown (Figure 5). Not only did this analysis demonstrate the product to have the structure predicted, but also it determined that the stereochemistry about the double bond is that of the Z-isomer, as shown.

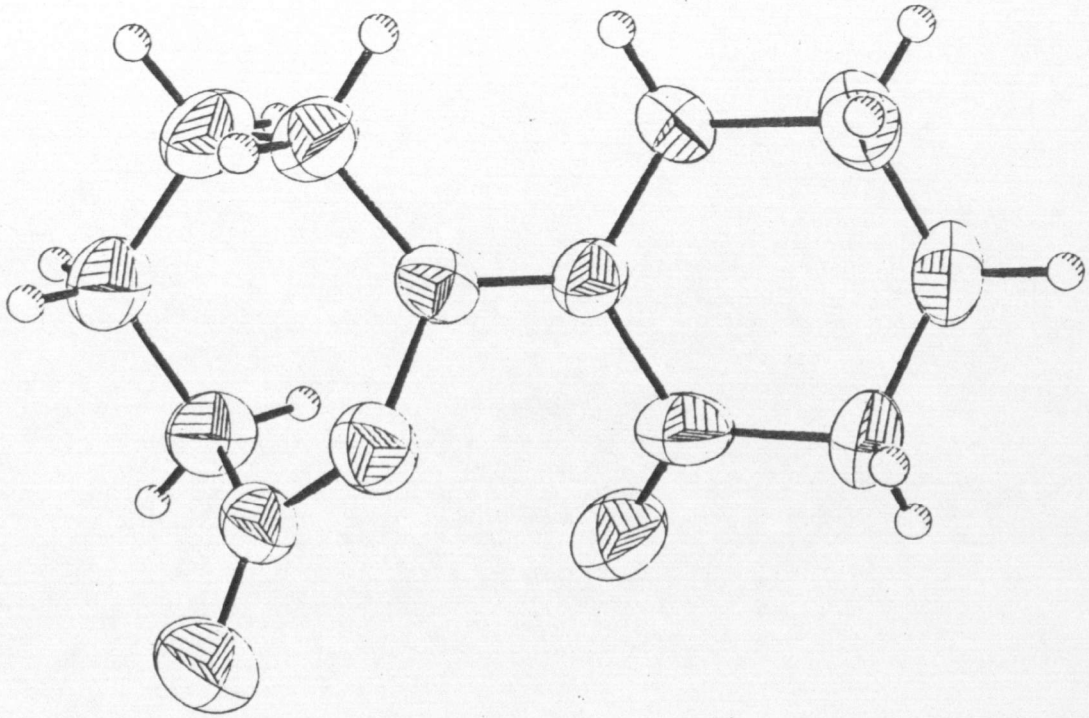
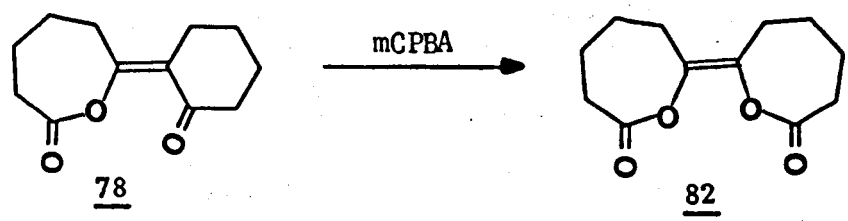


Figure 5. Perspective view of the molecular structure of 78

It was again found that a third equivalent of mCPBA would react in this system resulting in a Baeyer-Villiger oxidation to afford 82 (equation 36). The structure assigned to this product followed



78 82 (36)

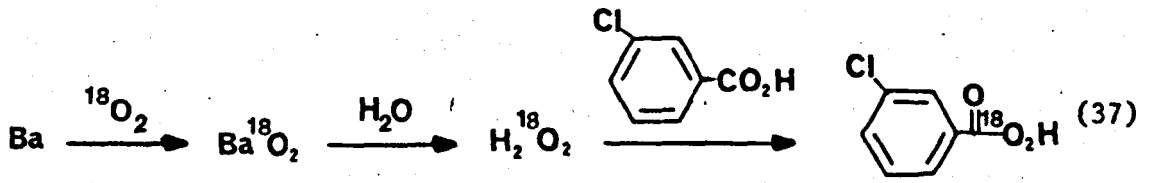
directly from its spectral properties. The ^{13}C NMR spectrum showed six resonances which included one at 171.9 ppm and another at 138.7 ppm. These were assigned to the carbonyl carbons of the lactone groups and the olefinic carbons, respectively. The IR spectrum showed a strong absorption at 1750 cm^{-1} attributed to the carbonyl stretching of the lactone functionalities. The mass spectrum showed the molecular ion at m/e 224, indicating that three oxygens had been added to the original furan 77. This solid product was not characterized further.

Studies with 3-Methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O and 1,2,3,4,5,6,7,8-Octahydrodibenzofuran-^{18}O

Preliminary considerations. While considering possible mechanisms for the reactions discussed above with 3-methyl-4,5,6,7-tetrahydrobenzofuran 57 and perhydrodibenzofuran 77, it was noted that there were three oxygen atoms in the products 58 and 78. Two of these oxygens were delivered by the mCPBA and the third arose from the furan moiety. If the origin of the oxygen atoms in the products could be

determined, a much better understanding of the reaction pathway would result. Therefore, it was decided to pursue labeling experiments with ^{18}O.

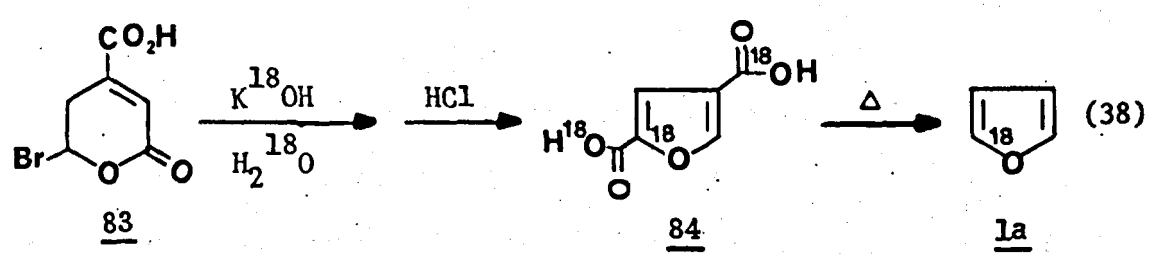
Initially, thought was given to synthesizing ^{18}O labeled mCPBA. There were no reports found in the literature dealing with ^{18}O labeled peracids. A tentative scheme was developed (equation 37).



(37)

Barium peroxide with ^{18}O incorporated could be produced by burning barium in an atmosphere of $^{18}O_2$. Treatment of this product with water would yield $H_2{}^{18}O_2$. This could then be used to synthesize the labeled peracid following standard procedures. However, this scheme seemed rather tedious. Furthermore, it should be noted that 50% of the ^{18}O incorporated in the peracid would be lost when using it as an oxidant.

Attention was therefore directed toward the synthesis of ^{18}O labeled furans. A literature search revealed three reports on the synthesis of compounds of this type. The earliest reference involved the synthesis of furan 1a (equation 38).[53] In this scheme the overall

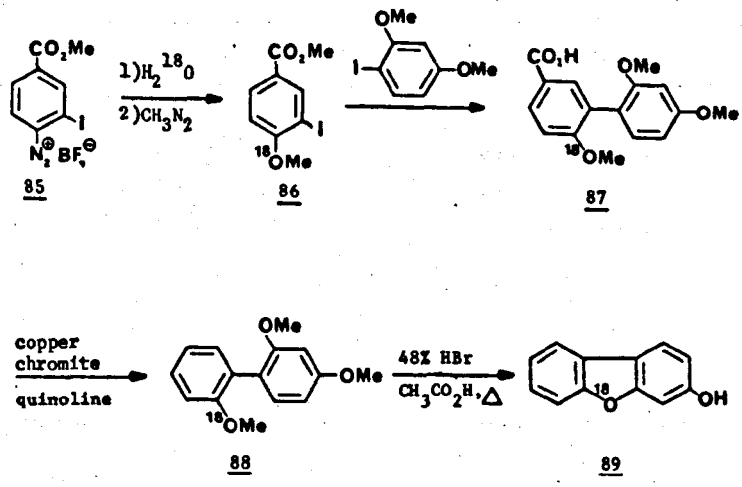


83 84 1a

(38)

yield of 1a was reported as 26% based on 83. The furan 1a synthesized by this method contained 25% ^{18}O as shown by mass spectrometry. It should be noted that at least two-thirds of the originally incorporated ^{18}O is lost as this synthesis proceeds, thus detracting considerably from its merits. Also, functionalization of the furan moiety to arrive at desired substrates would be difficult.

A second scheme detailed the synthesis of a labeled diaryl furan (equation 39).[54] The overall yield of this sequence was 4%. This procedure was not attractive for a number of additional reasons. The ^{18}O is incorporated in the first step and subsequently, a large amount is lost due to the poor overall yield. The final product of this scheme is a diaryl furan and modification to gain systems of interest would be problematical.



(39)

A third method used the process of incubating 15-hydroperoxy-5,8,11,13-eicosatetraeneoate (PPG_2) in an atmosphere of $^{18}O_2$ with prostaglandin synthetase.[55] This resulted in the preparation of

dibenzofuran with high incorporation of label. Again, this sequence was not attractive since we required non-aryl furans.

However, it was felt that the synthetic methodologies for preparing furan containing compounds have been well developed. These sequences were reviewed to find examples in which ketones are intermediates. Exchange between the carbonyl oxygen of such ketonic compounds and ^{18}O enriched water could easily be effected. With ^{18}O incorporated in this way, the synthesis could be continued to yield the desired labeled furan.

With this process in mind, methods which could be used to analyze compounds labeled with ^{18}O were considered. Classically, mass spectrometry has been the method of choice for analysis of stable isotopes. However, in our examples, the fragmentation patterns were rather complex. Unambiguous identification of these fragments seemed rather doubtful and, therefore, the exact position of the label could not be ascertained. Nevertheless, mass spectrometry has been used to determine the amount of ^{18}O in a given sample by comparison of the intensities of the molecular ions of the labeled and unlabeled materials.

On occasion, infrared spectroscopy has been used for analysis of ^{18}O labeled ketones.[56] This technique seemed rather dubious because data were available only for ketones. Use of this technique in the compounds of interest would require some model studies to be carried out to extend the data to other functional groups. Because the resolution of the available infrared spectrometers is rather poor, it would be difficult to measure peak intensities accurately enough to

quantitate the amount of ^{18}O incorporated in any given position. However, IR spectroscopy was used to give a qualitative picture of ^{18}O incorporation.

Recent reports were noted in which ^{13}C NMR spectroscopy was used as a technique for the determination of ^{18}O incorporation.[57, 58] This was carried out by measuring the ^{13}C NMR spectrum of labeled compounds at high resolution. The resonances for those ^{13}C nuclei bonded to ^{18}O appear slightly upfield compared to those bonded to ^{16}O. The magnitude of this upfield shift varies between 0.01 and 0.05 ppm. Apparently, the magnitude of the shift can also be correlated with the functionality within which the ^{18}O is contained. Ketones show the largest perturbations, and these decrease to alcohols, which show the smallest.

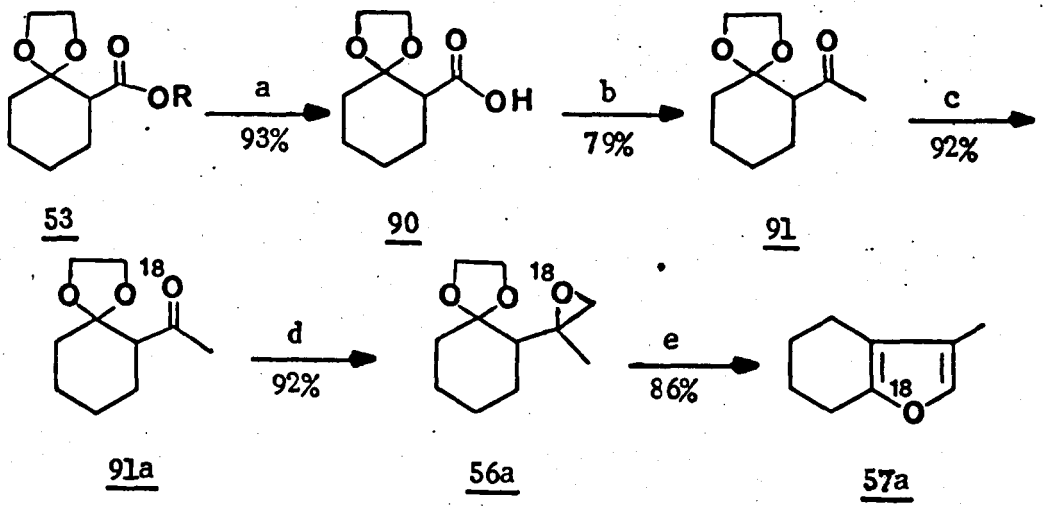
This phenomenon can be explained in the following manner.[59] With the heavier isotope, the carbon-oxygen bond of interest sits lower in its potential well and, therefore, its mean displacement from equilibrium is reduced. Since the stretching of bonds generally leads to a reduction in shielding, the effect of the substitution of a heavier isotope is to cause the shielding to increase.

It was decided to use ^{13}C NMR spectroscopy as the principal tool for determination of ^{18}O incorporation. By observing the resonances which were perturbed in the labeled compounds, the position of the ^{18}O could be determined. The magnitude of the shift difference between the two resonances could be correlated with model compounds as a check on the isotope position. It is also possible to determine the extent of ^{18}O incorporation by ^{13}C NMR spectroscopy. In the

studies conducted in this research, the ^{13}C NMR spectra typically had a signal to noise (S/N) ratio of 100:1. Therefore, these measurements should be accurate to approximately 1%.

Synthesis and oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 57a. A scheme was developed to prepare this compound labeled with ^{18}O (Figure 6). As stated earlier, the goal of this synthesis was to isolate a ketonic intermediate in which exchange between the carbonyl oxygen and ^{18}O enriched water could be carried out. This was effected as shown by preparing 6-acetyl-1,4-dioxaspiro[4.5]decane 91. The synthesis began by hydrolyzing ketal ester 53 to give acid 90. Following the procedure of Jorgenson, this ketal acid 90 was converted to the desired ketal ketone 91.[60]

Figure 6. Synthetic scheme followed for preparation of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 57a.



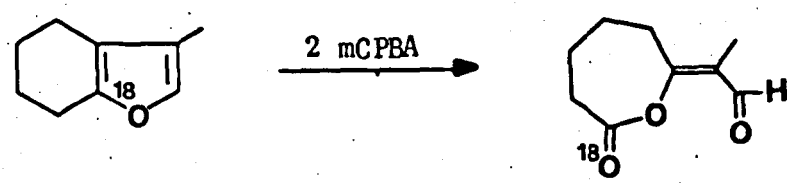
a-5M NaOH, Δ; b-2 CH_3LLi; c-$H_2{}^{18}O$, THF, H^+; d-$CH_2{=}S(CH_3)_2$; e-1M HCl, pentane

In all cases, exchange was accomplished by adding 97-99% enriched $H_2{}^{18}O$ to the ketone of interest and then adding sufficient tetrahydrofuran to solubilize these materials.[61] Finally, concentrated hydrochloric acid was added to bring the concentration of H^+ to approximately 1×10^{-3} M. The progress of incorporation of ^{18}O was monitored by mass spectrometry. Using the technique outlined above it would be possible to incorporate high concentrations of ^{18}O into a sample by repeated exchanges. However, for these mechanistic studies, it was felt optimum results could be obtained with approximately a 1:1 ratio of ^{16}O to ^{18}O in our substrates.

In this case, exchange was carried out within 1.5 hours to yield 91a. Following the procedure of Corey, this compound was then converted to the labeled epoxide 56a utilizing dimethylsulfonium methylide.[62] This epoxide was cyclized using the same procedure developed for the unlabeled material. Thus, the synthesis of labeled furan 57a was carried out in 73% yield in the steps involving ^{18}O labeled materials. There was some small loss of label during this sequence; but, overall, this process appears to be excellent for incorporating ^{18}O into the furan moiety.

The extent of ^{18}O incorporation in these compounds was determined by NMR and mass spectrometry. The agreement between these techniques was generally excellent and problems arose only in cases in which the mass spectrum showed only a weak molecular ion. The results for this series are summarized in Table 1.

Oxidation of 57a with two equivalents of mCPBA resulted in the formation of 58a (equation 40). In the ^{13}C NMR spectrum of 58a, the



57a 58a (40)

Table 1. ^{18}O Content for Studies Involving 3-Methyl-4,5,6,7-tetrahydrobenzofuran.

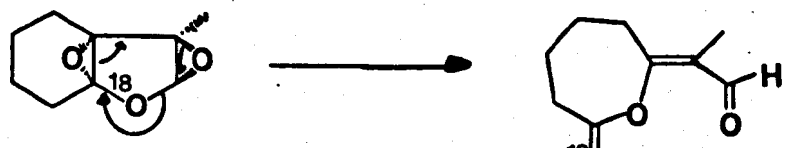
Compound	^{13}C NMR Data δ^a (ppm)	$\Delta\delta$ (ppm)	% ^{18}O	Mass Spectral Data (% ^{18}O)
91a	209.4(s)	0.051	54	55[b]
56a	56.4(s)	0.042	48	55[b]
	55.8(t)	0.030	48	
57a	150.9(s)	0.039	46	48
	136.7(d)	0.036	47	
58a	170.7(s)	0.040	41	42

[a]Chemical shift and multiplicity of carbons showing isotope induced shift.
[b]Molecular ion not intense enough to accurately determine.

resonances at 189.9 and 164.3 ppm, assigned to the aldehydic carbon and the olefinic carbon of interest, both appeared as single lines. The resonance at 170.6 ppm was resolved into two lines with the upfield resonance shifted by 0.040 ppm. This is the resonance assigned to the carbonyl carbon of the lactone. The magnitude of the chemical shift difference between the two resonances indicates that

it is the carbonyl oxygen which is partially substituted with ^{18}O. This was also supported by the IR spectrum which showed two bands for the carbonyl stretch of the lactone, one at 1755 cm^{-1} ($C^{16}O$), the other at 1710 cm^{-1} ($C^{18}O$).

The result of this experiment was consistent with our proposed mechanism with a diepoxide intermediate. The label ends up solely in the position predicted by collapse of the diepoxide intermediate 63a into the product 58a (equation 41). However, on the basis of this



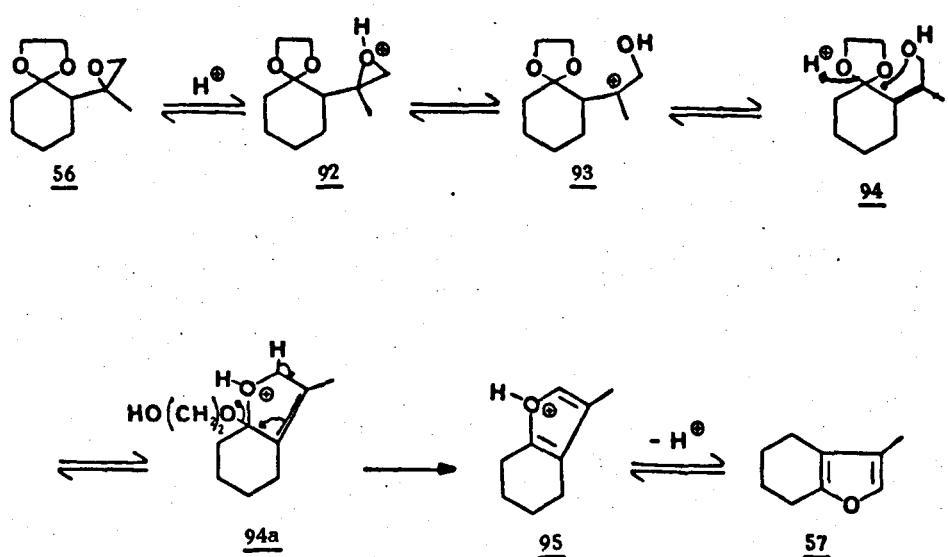
63a 58a (41)

data, no insight can be gained as to the site of initial attack on the furan moiety by mCPBA.

Mechanism of the cyclizations of β,γ-epoxy ketals to furans. As a sidelight, the synthesis of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 57a allows further elucidation of the mechanism of cyclization of β,γ-epoxy ketals to furans. This cyclization has been utilized in a number of synthetic schemes but comments concerning the mechanism of this reaction have been uniformly open-ended.[63, 64] Most of the ^{18}O which was incorporated in epoxide 56a was found in furan 57a. Using this as a basis, the following mechanism is proposed (Figure 7). Ring opening of the protonated epoxide 92 to form 93 is followed quickly by cyclization. This cyclization to 94 must occur soon after the epoxide

opens since very little (1-2%) ^{18}O is lost by exchange in this reaction. If intermediate 93, or other related species, had a long lifetime it would be expected that more ^{18}O would be lost by exchange in this acidic medium. The cyclization of 93 to 94 is shown as an S_N2 process. This is assumed to be the case since formation of the furan occurs faster than deketalization under similar circumstances. The driving force for the final elimination to form 95 is aromatization of the furan moiety.

Figure 7. Proposed mechanism for the cyclization of β,γ-epoxy ketals to furans.



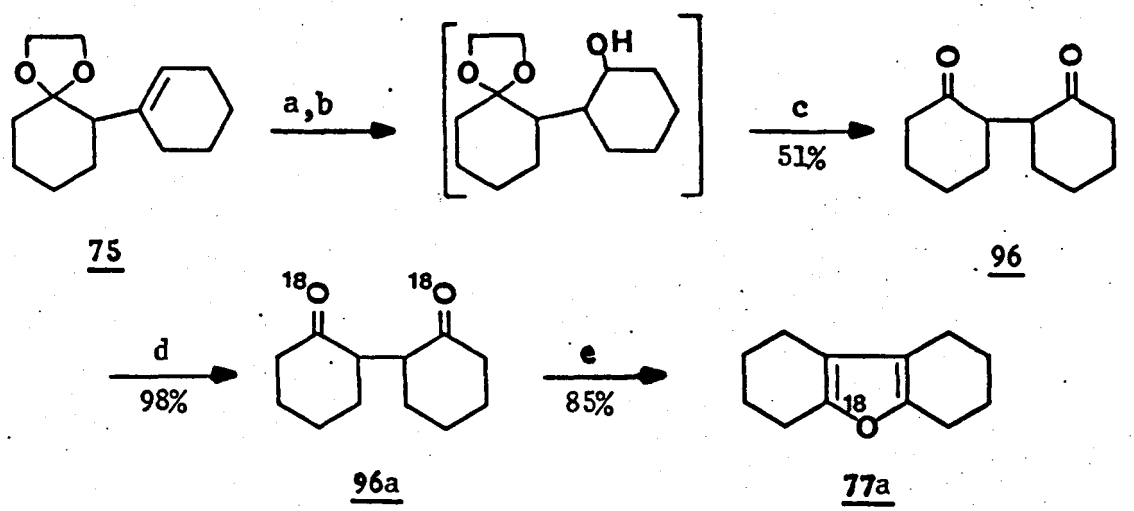
This reaction occurs in a biphasic mixture. Initially, an equilibrium is established with a certain portion of the epoxy ketal in the acidic aqueous layer. The reaction occurs in this layer and the furan product is then extracted back into the pentane layer.

Observation of the reaction mixture supports this. The initial aqueous layer is clear, but within a few minutes, after the beginning of stirring, it becomes cloudy. The aqueous layer maintains this opaque quality for two-thirds of the reaction time. It then slowly clears and reaction is complete when the bottom layer returns almost to its original clear state.

Synthesis and oxidation of 1,2,3,4,5,6,7,8-octahydrodibenzofuran-^{18}O 77a. The synthesis of perhydrodibenzofuran-^{18}O 77a was initiated with ketal alkene 23 (Figure 8). This was converted to the alcohol by hydroboration-oxidation. This alcohol was not purified and the crude material was converted directly into the diketone 96 by oxidation with three equivalents of Jones reagent. Initially, attempts were made to oxidize this crude ketal alcohol to the ketal ketone. However, oxidation with one equivalent of Jones reagent gave a mixture of materials, some of which was found to be the desired diketone 96. Utilization of Sarett reagent for the oxidation was no more successful. Since one equivalent of Jones reagent gave some of the desired diketone, the oxidation was carried out using three equivalents in a controlled manner. The diketone 96 was isolated as a mixture of diastereomers as reported in the literature.[65]

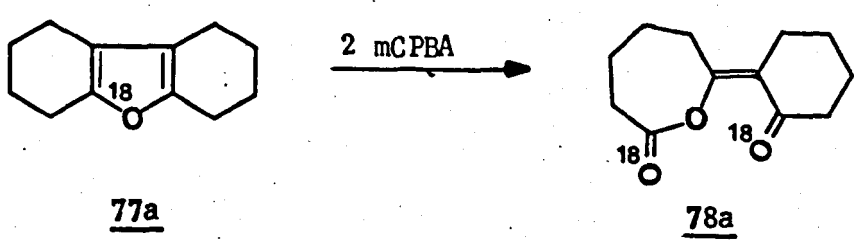
The synthesis was continued with the incorporation of ^{18}O. Again exchange was effected by preparing a solution of diketone 96 and 99% enriched $H_2{}^{18}O$ in tetrahydrofuran and adding sufficient concentrated aqueous hydrochloric acid to make the solution approximately one

Figure 8. Synthetic scheme followed for preparation of perhydrodibenzofuran-^{18}O 77a.



a-$NaBH_4$, BF_3, THF; b- ^-OH, H_2O_2; c-Jones oxidation (CrO_3, H_2SO_4, CH_3COCH_3); d-$H_2{}^{18}O$, THF, H^+; e-H_2SO_4, Δ

This compound was then oxidized with two equivalents of mCPBA to yield 78a (equation 42). The position of the label in the product



(42)

millimolar in H^+. Exchange was complete within 22 hours. Analysis by ^{13}C NMR spectroscopy showed 52% incorporation of ^{18}O (Figure 9).

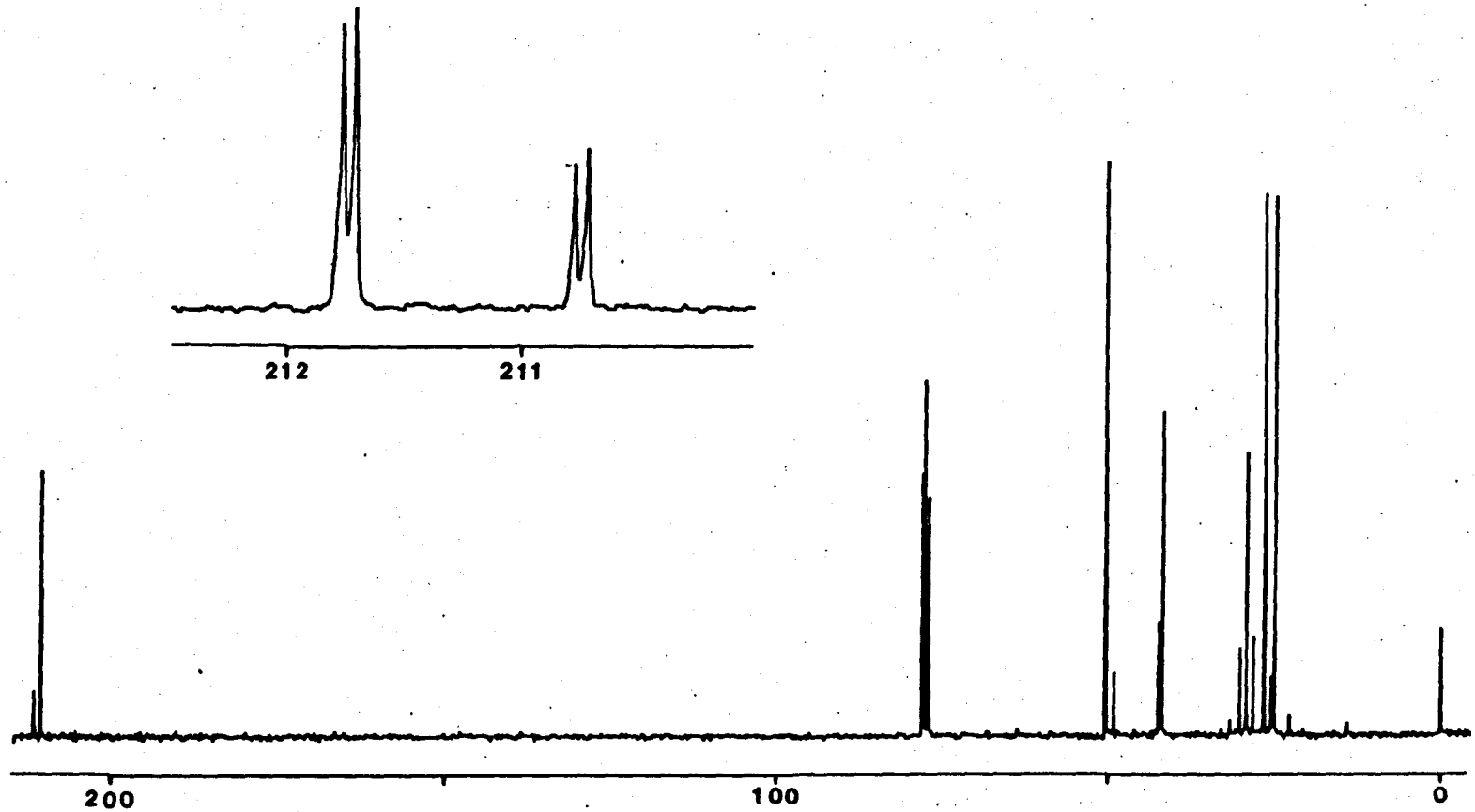


Figure 9. ^{13}C NMR spectrum of 96a

Cyclization in this case was carried out by treating labeled diketone with a small amount of concentrated sulfuric acid and heating this mixture under aspirator vacuum. Furan 77a was collected as it distilled. Analysis by ^{13}C NMR spectroscopy showed 39% incorporation of ^{18}O (Figure 10). Mass spectral analysis, again in excellent agreement with the NMR data, showed 40% label incorporation. was determined by ^{13}C NMR spectroscopy (Figure 11). The resonance at 201.5 ppm was resolved into two peaks with the upfield resonance shifted by 0.050 ppm. This resonance, assigned to the ketone functionality, showed 20% incorporation of ^{18}O. The resonance at 172.3 ppm was also resolved into two lines with the upfield resonance shifted by 0.040 ppm. This resonance, assigned to the lactone functionality, showed 20% incorporation of ^{18}O. The magnitude of the chemical shift difference indicates that it is the carbonyl oxygen partially substituted with ^{18}O.

The results of synthesis of this series of compounds are summarized in Table 2.

Table 2. ^{18}O Content for Studies Involving Perhydrodibenzofuran.

	^{13}C NMR Data			Mass Spectral
Compound	δ^a (ppm)	$\Delta\ \delta$ (ppm)	% ^{18}O	Data (% ^{18}O)
96a[b]	211.8(s)	.053	52	54
	210.8(s)	.053	52	
77a	148.4(s)	.039	39	41
78a	201.5(s)	.050	20	41
	172.3(s)	.040	20	

[a]Chemical shift and multiplicity of carbons showing isotope induced shift.
[b]Data available from both diastereomers.

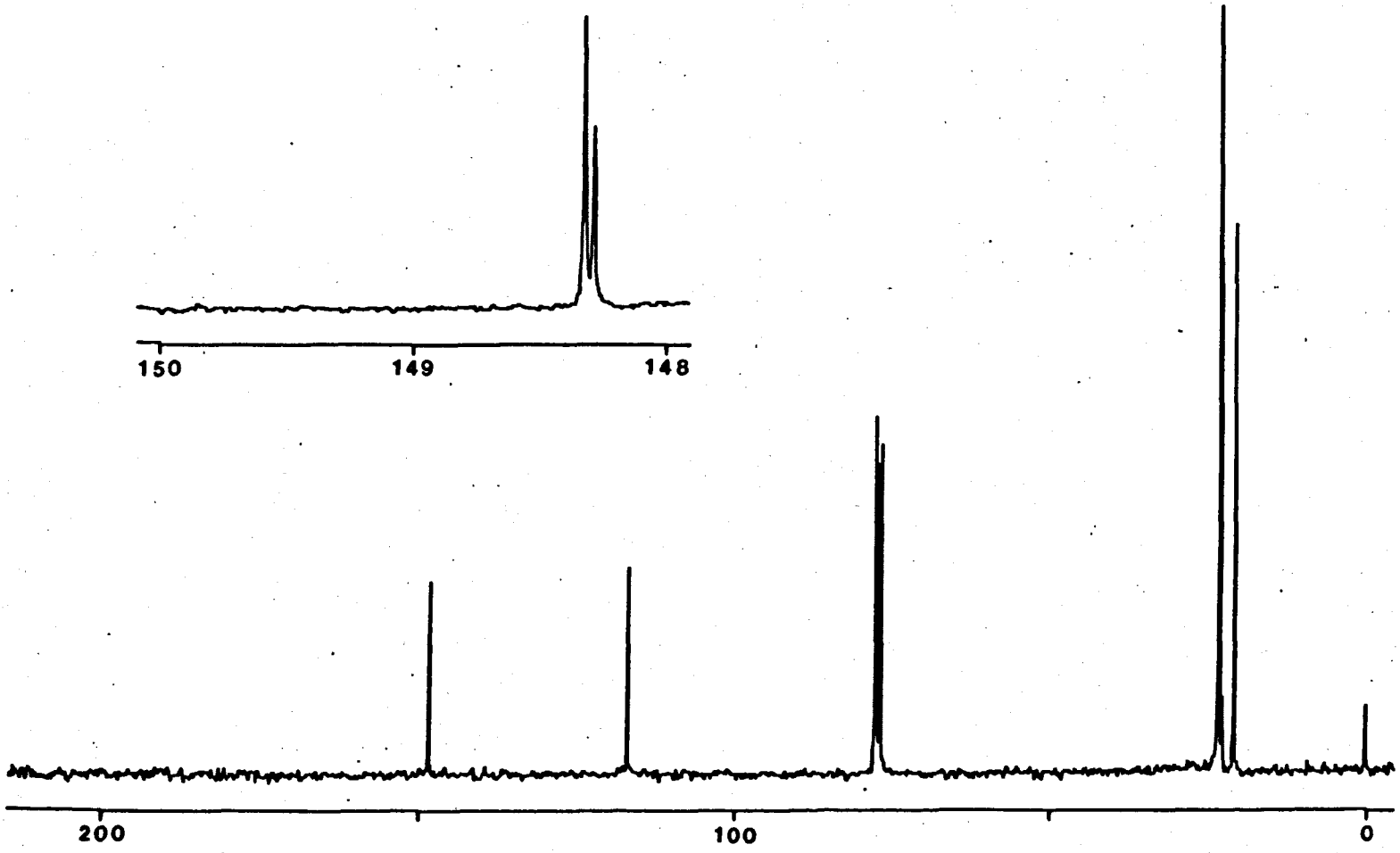


Figure 10. ^{13}C NMR spectrum of 77a.

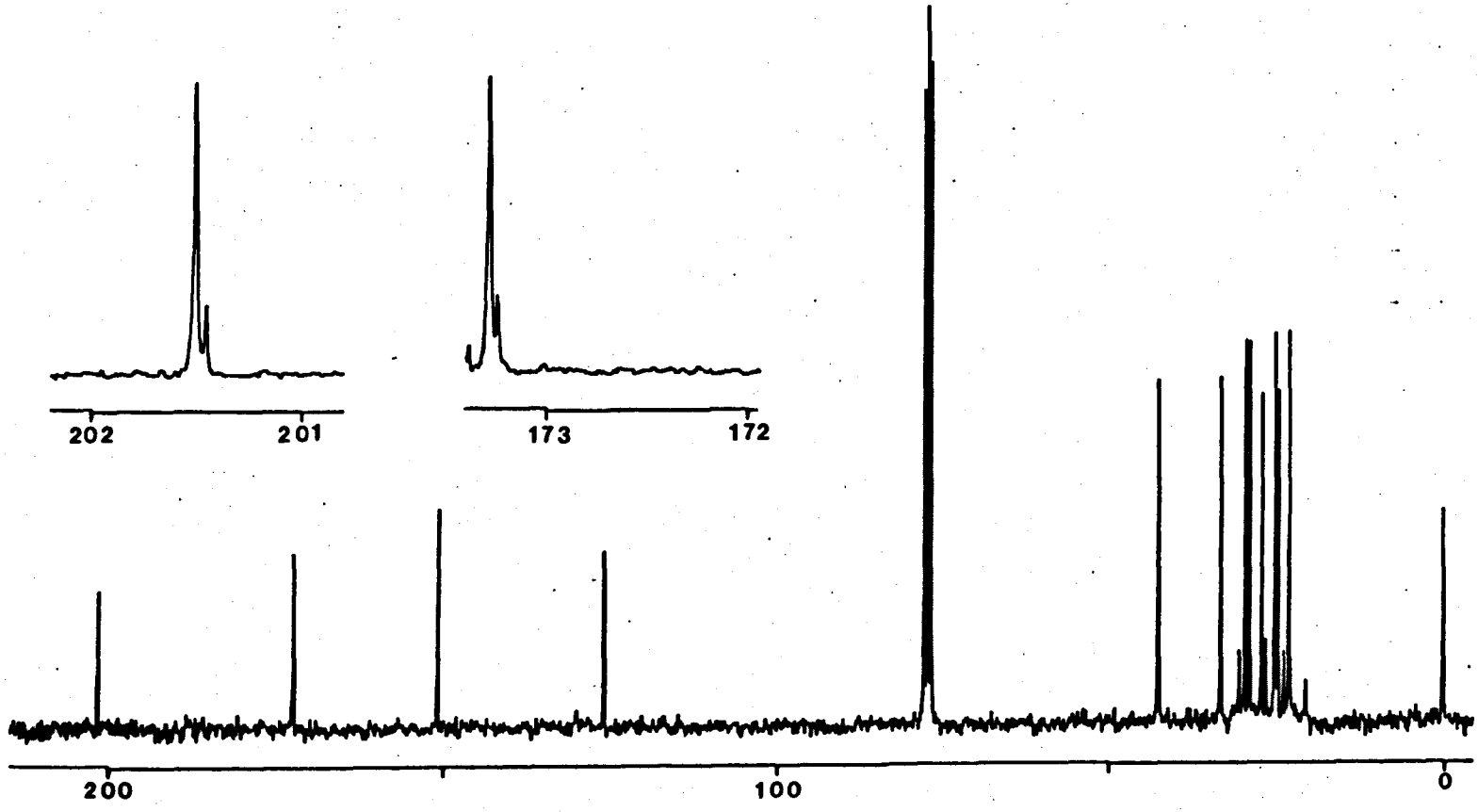
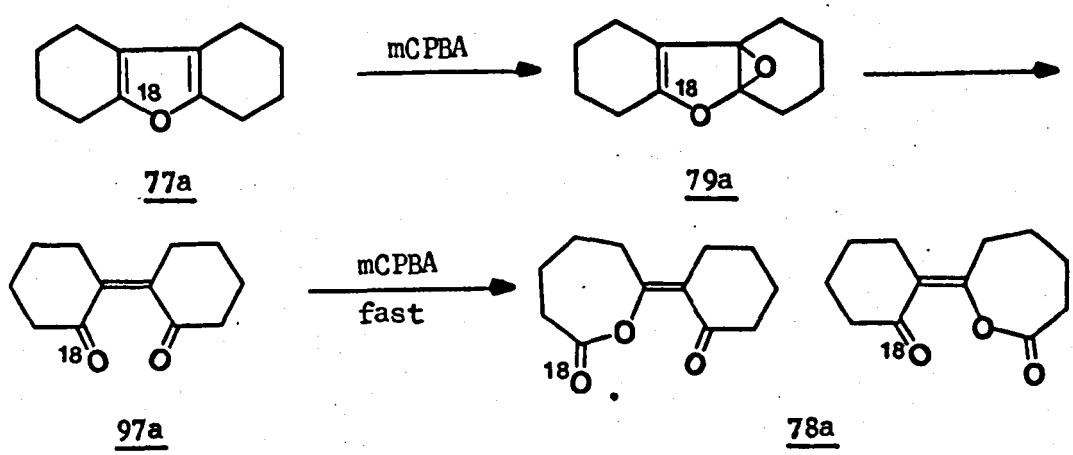


Figure 11. ^{13}C NMR spectrum of 78a.

The mechanism proposed earlier, which postulated that the reaction proceeded via a diepoxide intermediate, would predict that all of the ^{18}O should be in the carbonyl oxygen of the lactone functionality. Because the ^{18}O was found to be evenly distributed between two sites in the product, a major revision of the mechanism appeared necessary. A new mechanism was, therefore, proposed (Figure 12). Initial attack would occur to yield monoepoxide 79a. This intermediate would subsequently open to give cis-enedione 97a, a symmetrical intermediate. A Baeyer-Villiger oxidation would then occur to yield the observed product with the label scrambled as indicated.

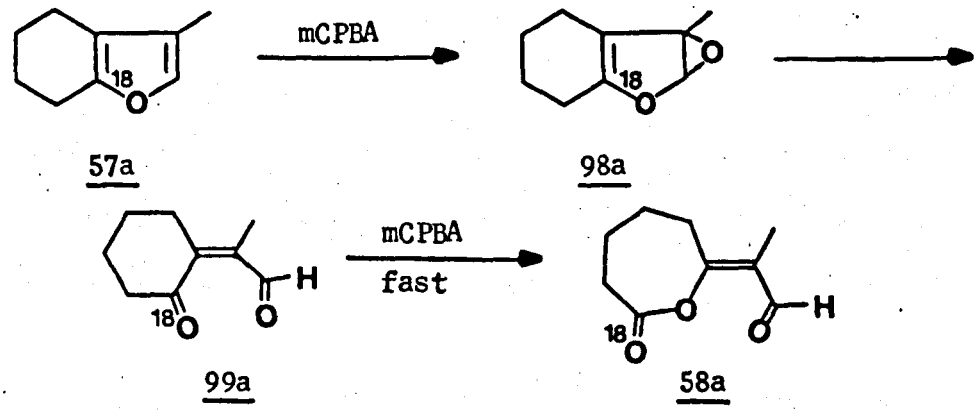
Figure 12. Proposed mechanism for the oxidation of perhydrobidenzofuran-^{18}O 77a via an enedione intermediate.



Furthermore, these results caused us to reinvestigate our proposed mechanism for the oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran. As it appeared, an analogous mechanism could be postulated for this substrate which also would involve an enedione type intermediate. Thus, the following mechanism was proposed, taking

into account the results of the ^{18}O labeling studies with this substrate (Figure 13). Initial attack would occur on the least substituted side of the furan moiety to form epoxide 98a. This would undergo ring opening to yield 99a with label in the position indicated. Subsequent rapid Baeyer-Villiger oxidation would lead to 58a, the product observed in the labeling studies.

Figure 13. Proposed mechanism for the oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 57a via an enedione type intermediate.



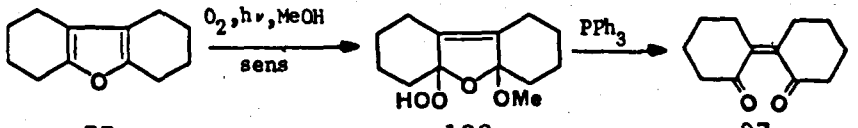
At this point two questions were raised concerning the proposed mechanisms. In the mechanism just discussed, initial attack of the furan moiety is predicted to occur on the lesser substituted side. Usually, when studying oxidations with mCPBA, it is observed that the more substituted positions are attacked.[44] This divergence from the norm raised some questions. A second problem arose concerning the rate of the proposed Baeyer-Villiger oxidations. These reactions tend to show a limited range of reaction rates.[66] For some reason, in the

cases studied above, the reactions occurred one to two orders of magnitude faster than normal. Further studies were undertaken to answer these questions.

Attempted Syntheses of Enediones

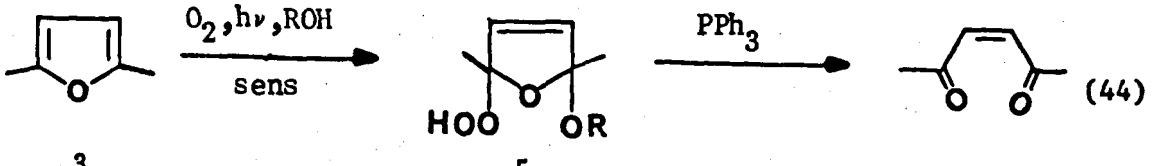
Attempt to prepare enedione derived from perhydrodibenzofuran. Since enediones derived from ring opening of the substrates studied were proposed as intermediates, efforts were made to synthesize these compounds. It was felt that, if they could be isolated, further experimental work could be carried out to determine if they were indeed intermediates in the reaction pathway.

Initially, attempts were directed toward the synthesis of the enedione derived from perhydrodibenzofuran. One method tried was derived from earlier work reported by Foote on the photooxidation of furans (equation 43).[4] In this paper, it was reported that the



77 100 97 (43)

initial product formed upon the photosensitized oxidation of 77 was 100. In this same paper, a similar sequence was carried out with 2,5-dimethylfuran 3 (equation 44). In this case, the initial adduct



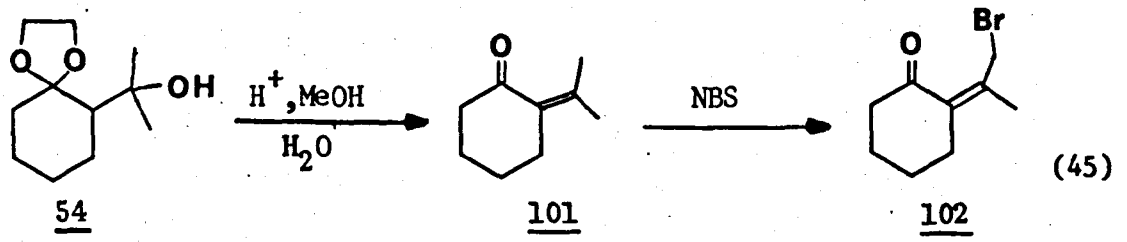
3 5 44 (44)

was opened with triphenylphosphine to yield cis-2,5-hexenedione 44. In our laboratory, intermediate 100 was easily prepared when perhydrodibenzofuran 77 was photooxidized in methanol with rose bengal added as a sensitizer. Treatment of 100 with triphenylphosphine resulted in the formation of triphenylphosphine oxide but no discernable enedione 97.

A second attempt to prepare enedione 97 was carried out using selenium dioxide to oxidize diketone 96. This follows a number of reports on the oxidation of ketones with selenium dioxide to yield α,β-unsaturated ketones.[67] Initially, ethanol was used as a solvent but no reaction was observed. The reaction was then run in acetic acid and a veritable plethora of products were produced. This mixture was chromatographed on silica gel to yield a small amount of furan 77, but no enedione 97 was identified. A number of the fractions showed olefinic resonances in their ^{13}C NMR spectra, indicating that oxidation had occurred, but not at the desired position. Work in this area was not pursued further.

Attempt to prepare enedione derived from 3-methyl-4,5,6,7-tetrahydrobenzofuran 57. Thought was also given to the synthesis of 98, the proposed intermediate in the reaction of 3-methyl-4,5,6,7-tetrahydrobenzofuran. A scheme was designed, the first steps of which are

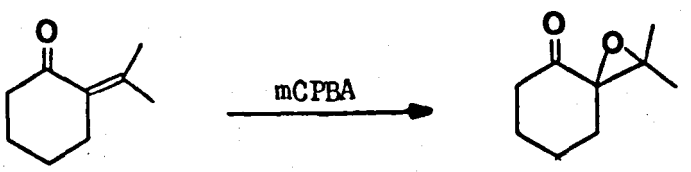
shown (equation 45). Following a procedure of Mukherji, α,β-unsatur-



54 101 102 (45)

ated ketone 101 was prepared from 54.[68] Attempts to brominate this compound with NBS led to a gross mixture of products from which the desired ketobromide could not be isolated. It was hoped that 102 could be isolated in reasonable yield. The proposed scheme called for the conversion of 102 to the corresponding alcohol followed by oxidation to give 98. This scheme was abandoned.

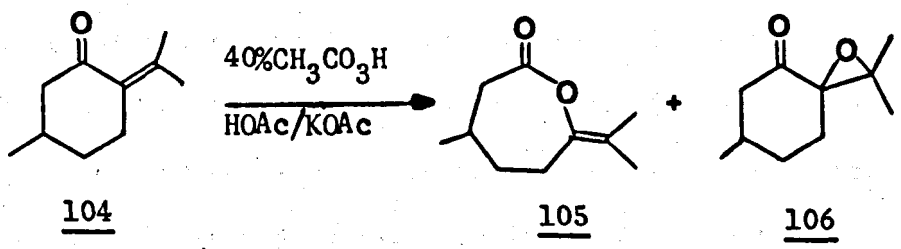
Studies were carried out on the oxidation of 101 with mCPBA. It was found that this compound reacted with one equivalent of mCPBA to quantitatively yield, the epoxide 103 (equation 46). This was at a



101 103 (46)

slight variance with a report by Silverstein.[69] In this article, it was reported that the oxidation of pulegone 104, the 5-methyl derivative of 101, gave lactone 105 in 40% yield and epoxide 106 in

unspecified yield when the oxidation was carried out with peracetic acid (equation 47).



104 105 106 (47)

A competition experiment was carried out by adding one equivalent of mCPBA to a solution containing one equivalent of furan 57 and one equivalent of 101. Analysis showed that one-half of the furan had been oxidized to 58 but that none of the 101 had reacted. It was therefore concluded that the extreme rate of the second addition did not relate solely to the strain induced by the exocyclic double bond.

Studies with 2,5-Dimethylfuran

At this point in the research program, a report appeared by LeGoff on the oxidation of 2,5-disubstituted furans with mCPBA to yield cis-enediones.[24] It was reported that these oxidations were carried out with an excess of mCPBA, yet no further oxidation of the initially formed cis-enediones was noted. As an example, 2,5-dimethylfuran 3 reacted to give cis-2,5-hexenedione in 99% yield when oxidized with 1.1 equivalents of mCPBA. It was decided to further explore the chemistry of this system.

As reported, 2,5-dimethylfuran reacted with one equivalent of mCPBA to form cis-2,5-hexenedione. Addition of two equivalents of

mCPBA and reaction times of 24 hours at room temperature still afforded this product in quantitative yield.

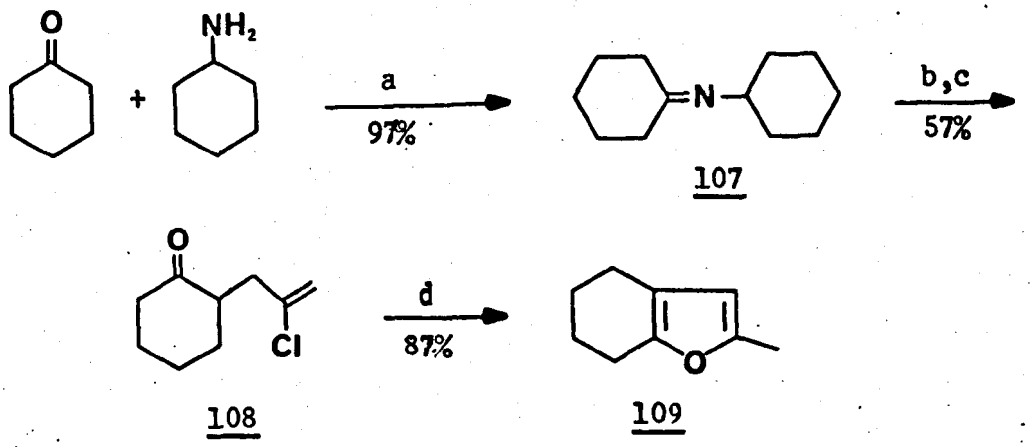
The reaction was then run with two equivalents of mCPBA in refluxing chloroform for 24 hours. Work-up of the reaction followed by spectral analysis revealed two products. These were identified as trans-2,5-hexenedione and the epoxide of either cis- or trans-2,5-hexenedione. There was no evidence in the ^{13}C NMR data for resonances near 170 ppm which would be indicative of the product formed by Baeyer-Villiger oxidation of the initially formed enedione. On the basis of these studies, it was concluded that the extreme ease of the second addition of mCPBA in the systems studied was not inherent in all cis-enedione systems.

Studies with 2-Methyl-4,5,6,7-tetrahydrobenzofuran

Synthesis of 2-methyl-4,5,6,7-tetrahydrobenzofuran 109. It was decided to expand our studies to a different substrate. 2-methyl-4,5,6,7-tetrahydrobenzofuran 109 was chosen as a logical molecule to explore next.

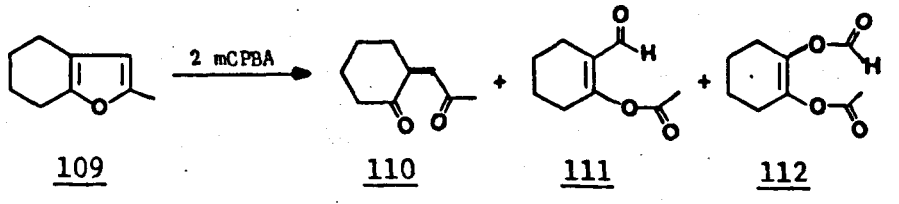
This compound was synthesized by a compilation of reactions previously reported in the literature (Figure 14). N-cyclohexylidenecyclohexylamine 107 was prepared by treatment of an ethereal solution of cyclohexanone and cyclohexylamine with 4Å molecular sieves. Alkylation of the imine salt was performed to yield chloroketone 108.[70] Following the procedure of Nienhouse, this was cyclized with 90% sulfuric acid to yield 2-methyl-4,5,6,7-tetrahydrobenzofuran 109.[71]

Figure 14. Synthetic scheme followed for preparation of 2-methyl-4,5,6,7-tetrahydrobenzofuran 109



a-4Å molecular sieves, ether; b-EtMgBr; c-2,3-dichloropropene; d-90% H_2SO_4

Oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran 109. Oxidation of 109, which was added in one portion to a solution of two equivalents of mCPBA, gave a mixture of products (equation 48).



(48)

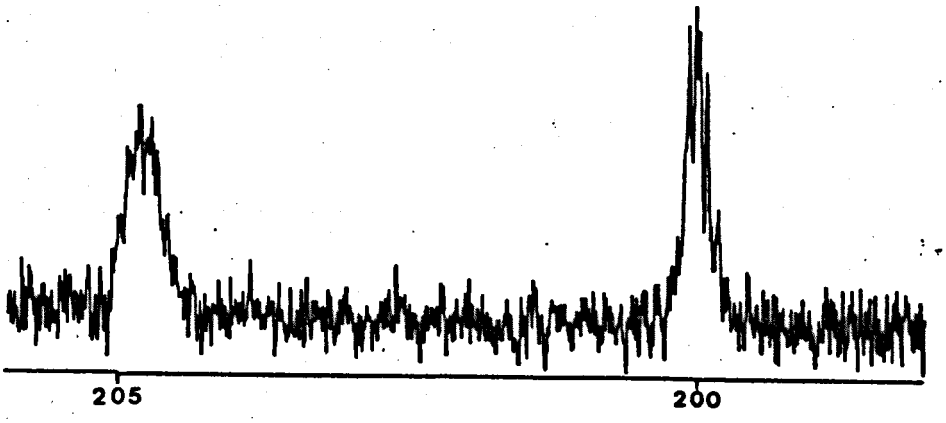
The approximate yields of these products was 20%:45%:20% for 110, 111, and 112, respectively.

The structures of these compounds were elucidated from their spectral properties. Compound 110 showed a molecular ion at m/e 152 in the mass spectrum indicating addition of one oxygen. The ^{13}C NMR spectrum showed resonances at 204.6, 200.1, 150.1 and 129.6 ppm. The first three resonances all appeared as singlets in the gated decoupled spectrum whereas that at 126.9 ppm appeared as a doublet. Further

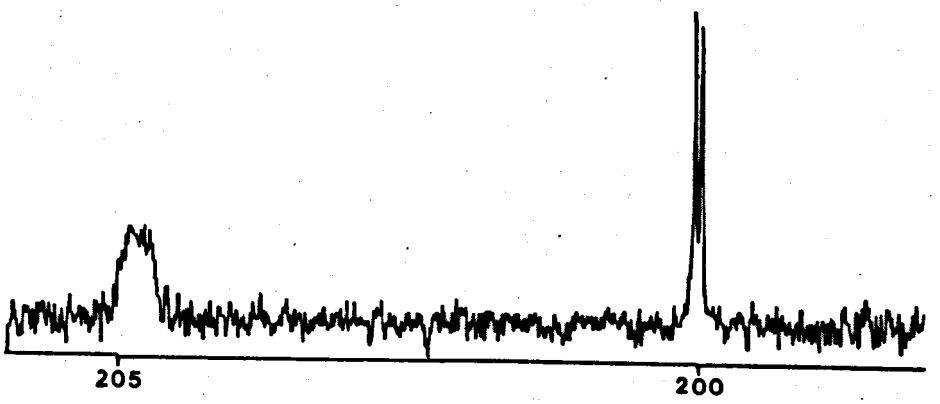
analysis of this compound by ^{13}C NMR spectrometry showed the resonance at 200.1 ppm to be coupled to the protons of the methyl group ($^{2}J_{C-H}$ = 6Hz) and the olefinic proton ($^{2}J_{C-H}$ = 4Hz) (Figure 15). This was determined by obtaining a ^{1}H-coupled ^{13}C NMR spectrum of the resonances at 204.6 and 200.1 ppm. Specific proton decoupling of the protons of the methyl group collapsed the multiplet centered at 200.1 ppm into a doublet. Similarly, decoupling the olefinic proton collapsed this multiplet into a quartet. On the basis of this information, the resonance at 204.6 ppm was assigned to the carbonyl carbon of the cyclohexanone moiety and the resonance at 200.1 ppm was assigned to the carbonyl carbon of the acetyl moiety. The resonances at 150.1 and 129.6 ppm were assigned to the olefinic carbon in the cyclohexanone moiety and the olefinic carbon with the proton, respectively. The ^{1}H NMR spectrum showed a broad singlet for one proton at 5.97 ppm and a methyl singlet at 2.22 ppm. The IR spectrum showed a strong, broad absorption of 1690 cm^{-1} assigned to the carbonyl stretch of the ketone functionalities and a weaker band at 1630 cm^{-1} assigned to the olefinic stretching frequency.

Compound 111 showed a molecular ion at m/e 168 in the mass spectrum indicating addition of two oxygens. The ^{13}C NMR spectrum of this compound showed resonances at 189.2, 168.6, 164.2 and 126.7 ppm. The resonance at 189.2 appeared as a doublet in the gated decoupled spectrum with a carbon-hydrogen coupling constant of 178 Hz. This resonance was assigned to the aldehydic carbon. The other resonances all appeared as singlets in the gated decoupled spectrum and were assigned to the carbonyl carbon of the acetate group, the olefinic carbon

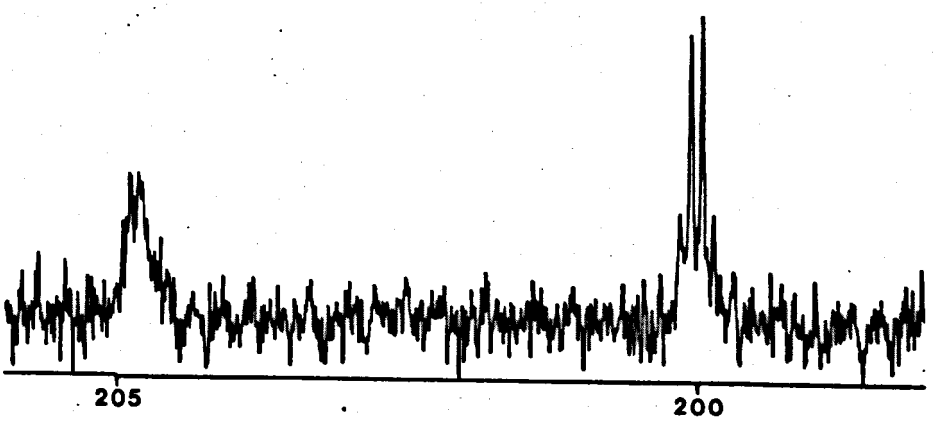
Figure 15. ^{13}C NMR analysis of carbonyl resonances of 110.



a.) ^{1}H-coupled spectra.



b.) Methyl protons decoupled.



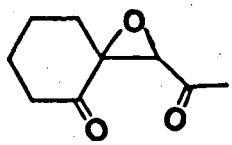
c.) Olefinic proton decoupled.

adjacent to the acetate group and the olefinic carbon adjacent to the aldehyde group, respectively. The ^{1}H NMR spectrum showed a resonance at 9.93 ppm, assigned to the aldehydic hydrogen, and a methyl singlet at 2.24 ppm. The IR spectrum showed a weak band at 2750 cm^{-1} assigned to the carbon-hydrogen stretch of the aldehyde functionality. Strong absorptions appeared at 1760 and 1675 cm^{-1} and were assigned to the carbonyl stretches of the ester and aldehyde functionalities, respectively. Another absorption was apparent at 1650 cm^{-1} and was assigned to the carbon-carbon double bond stretch.

Compound 112 showed a molecular ion at m/e 184 in the mass spectrum indicating that three oxygens had been added to the furan substrate. The ^{13}C NMR spectrum showed resonances at 168.3, 158.6, 137.2 and 136.1 ppm. The resonance at 158.6 ppm appeared as a doublet in the gated decoupled spectrum and showed a carbon-hydrogen coupling constant of 229 Hz. The position of this resonance and the magnitude of the coupling constant indicated the formate functionality. The resonance at 168.3 appeared as a singlet in the gated decoupled spectrum and was assigned to the carbonyl carbon of the acetate group. The other two resonances were also singlets and these were assigned to the olefinic carbons. The ^{1}H NMR spectrum showed a singlet at 8.01 ppm assigned to the hydrogen of the formate group. A resonance assigned to the methyl group appeared as a singlet at 2.13 ppm. The IR spectrum showed a broad band at 1760 cm^{-1} which was assigned to the carbonyl stretches of both the acetate and formate groups.

A fourth product was seen by NMR spectroscopy but was never isolated in sufficient purity to allow unambiguous identification.

It was tentatively assigned structure 113, the epoxide of enedione 110. The ^{13}C NMR spectrum showed resonances at 204.1, 204.1, 67.2,



113

and 66.4 ppm. The two resonances at 204.1 both appeared as singlets in the gated decoupled spectrum and were assigned to the carbonyl carbons. The resonance at 66.4 ppm appeared as a doublet in the gated decoupled spectrum and was assigned to the methine group of the oxirane. The resonance at 67.2, a singlet in the gated decoupled spectrum, was assigned to the other carbon in the oxirane. The ^{1}H NMR spectrum showed a singlet at 3.4 ppm. As stated, this compound was never isolated. The data referred to above was arrived at by analysis of spectra of mixtures which contained this compound. Further work needs to be carried out to allow verification of the structure of this compound.

The results detailed above on the 2-methyl derivative led to the development of the mechanistic scheme outlined (Figure 16). Initial attack by mCPBA would occur on either side of the furan moiety to form monoepoxides 114 or 115. Either of these would undergo ring opening to give enedione 110. However, epoxide 115 would also undergo nucleophilic attack to form 116 which would subsequently collapse to form aldehyde 111. This part of the scheme relates to work carried out by

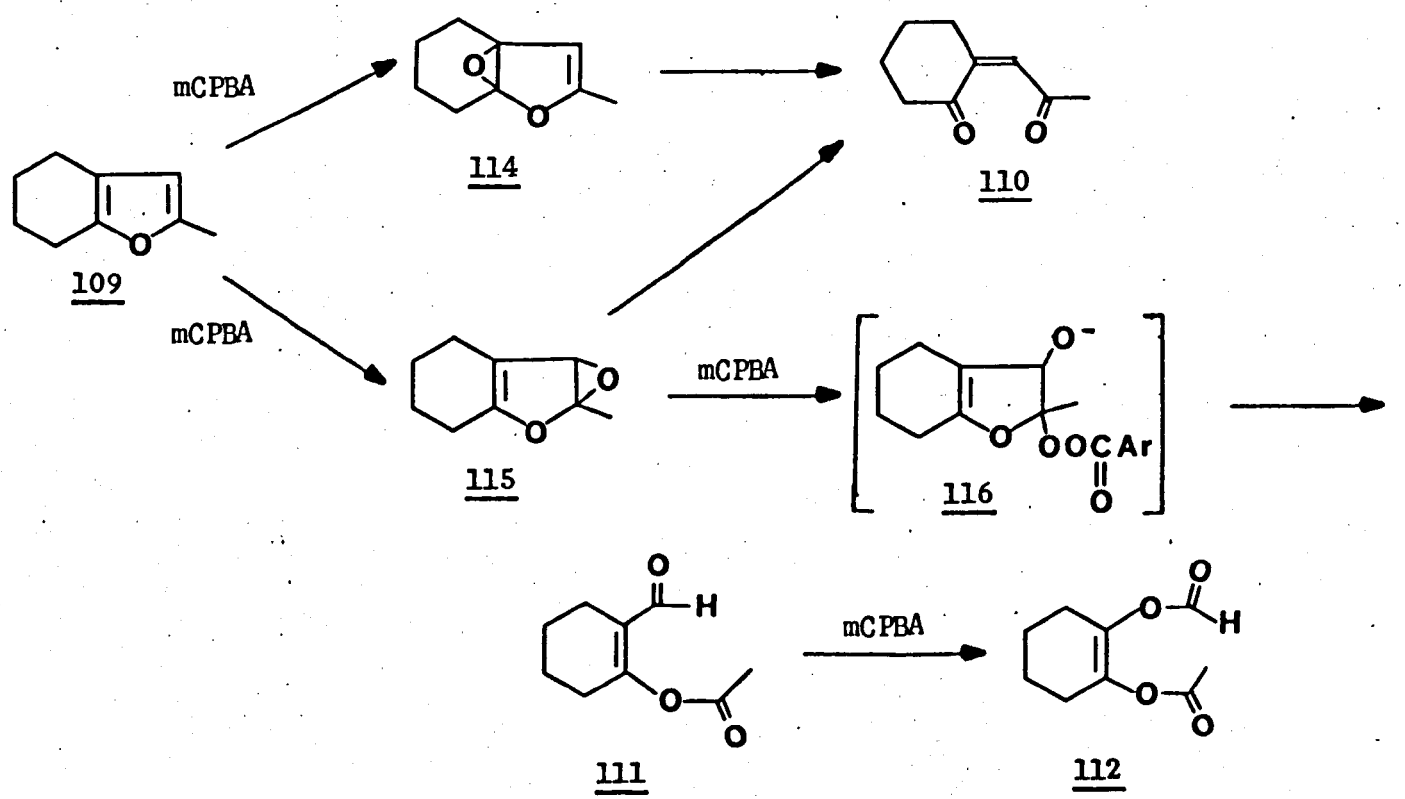


Figure 16. Initially proposed mechanism for the oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran

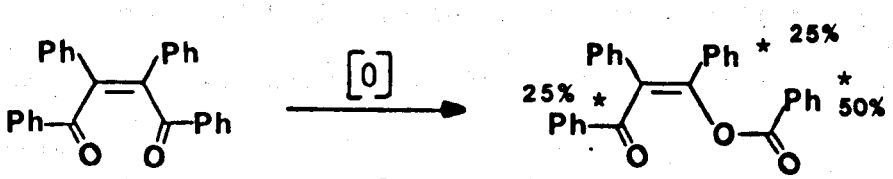
Borowitz on enol ethers referred to earlier.[46, 47] Finally, the aldehyde 111 would undergo Baeyer-Villiger oxidation to yield formate 112.

As stated above, this mixture of products arose from adding the furan in one portion to two equivalents of mCPBA. Qualitatively, this reaction was the most exothermic of all the furan substrates studied. When the furan 109 was added to a solution of mCPBA cooled to 0°, the methylene chloride began mild refluxing within seconds. This reaction also went to completion in a short time, as had been observed with the other substrates.

It was decided to see if the yield of enedione 110 could be increased. In the proposed scheme, this product could arise from either of the two epoxides. However, the one monoepoxide 115 could also react with a second equivalent of mCPBA to decrease the amount of enedione which could form. It was therefore decided to slowly add a solution of one equivalent of mCPBA to a solution of the furan to minimize the concentration of mCPBA at any one moment. This proposed reaction was carried out in methylene chloride. Typically, one gram of furan 109 was dissolved in 100 mL methylene chloride and a solution of one equivalent of mCPBA was added dropwise over a period of two to three hours. Upon work-up of these reaction mixtures, NMR spectroscopy showed that three components were present. These were identified as the starting furan 109, the enedione 110 and the aldehyde 111 in ratios of 1:8:1, respectively. Chromatography on silica gel allowed isolation of enedione 110 in 70-80% yield based on starting furan.

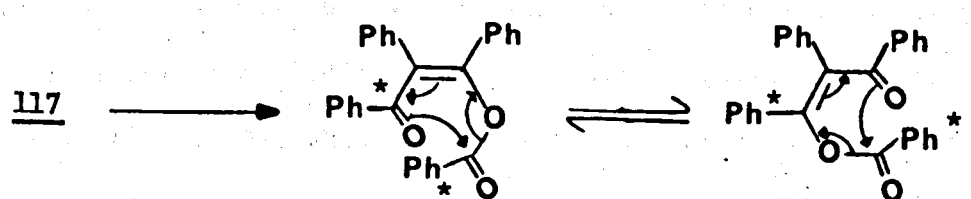
Exploration of the oxidation of enedione 110 with mCPBA was pursued next. As mentioned, a fourth product had been observed in our initial reaction mixture and it had been tentatively identified as the epoxide formed by further oxidation of enedione 110. It was hoped this work would permit access to more of this material for further characterization.

However, oxidation of enedione 110 was found to give aldehyde 111 in high yields. After some thought, a paper by Lutz was recalled in which an interesting oxidation was reported (equation 49).[9] When



117 118 (49)

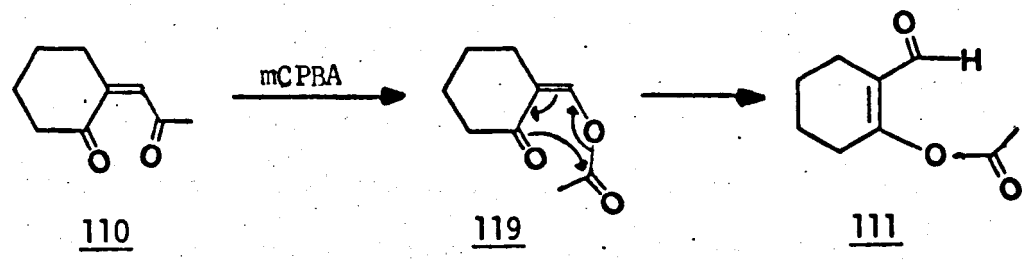
117 was oxidized with chromic acid or hydrogen peroxide, 118 was isolated with the ^{14}C scrambled to the extent indicated. This was rationalized in the following manner (equation 50). The initially



(50)

formed product can rearrange as shown until an equilibrium is established. In this instance, the use of ^{14}C label was the tool which allowed determination of this rearrangement. An analogous pathway could be proposed in the observed oxidation of enedione 110 to

aldehyde 111 (equation 51). The intermediate 119, formed by



110 119 111 (51)

Baeyer-Villiger oxidation of enedione 110, would undergo acetyl transfer as shown to yield the aldehyde 111. Needless to say, none of the epoxide 113, derived from enedione 110, was found.

To continue our studies on the mechanism of this reaction, the aldehyde 111 was oxidized with mCPBA and found to yield formate 112 as expected.

Not only can these reactions be carried out in a stepwise manner as described above but the furan 109 can be oxidized directly to the aldehyde 111 or the formate 112. Oxidation of 109 with two equivalents of mCPBA added slowly yields aldehyde 111 in 80% yield. Similarly, addition of three equivalents of mCPBA in one portion to a solution of the furan allows isolation of formate 112 in 65% yield.

It should be noted that in this case addition of the third equivalent of mCPBA, which oxidizes the aldehyde to the formate, occurs readily. In the cases discussed earlier, this final Baeyer-Villiger oxidation occurred very slowly and did not interfere with the products formed from the oxidation of the furan substrates if reaction times were kept short. However, in this case, oxidation of the furan with two equivalents of mCPBA added in one portion, the formate was found to be approximately 20% of the product mixture. It

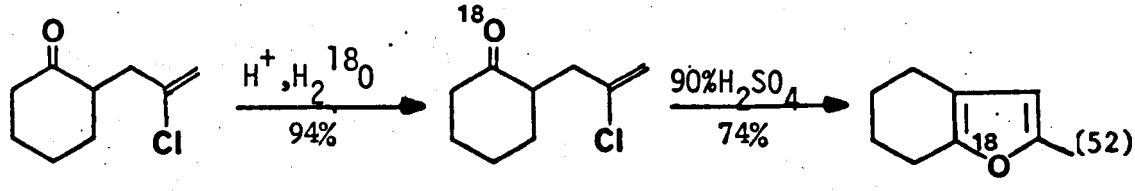
was also noted that, in trying to prepare the aldehyde 111 from either the furan 109 or the enedione 110, care had to be taken to prevent further oxidation of this to the formate 112. If the reaction was maintained at low temperatures (0-20°) and the mCPBA was added slowly, only a minimal amount of the formate was observed.

The results outlined above led to some simplification of our mechanistic scheme. It was now known that initial attack on the furan moiety led to an epoxide which subsequently underwent ring opening to give the enedione. This compound, when oxidized with a second equivalent of mCPBA, was proposed to undergo a Baeyer-Villiger oxidation and then rearrangement to give the aldehyde. Addition of a third equivalent of mCPBA resulted in another Baeyer-Villiger oxidation to form the formate.

Two questions still remained to be answered. It was not known on which side of the furan moiety attack occurred or if there was a preference. Also, the oxidation of the enedione to the aldehyde was proposed to follow the pathway shown, but it was not certain this was operative. To answer these questions, it was again decided to carry out ^{18}O labeling studies.

Synthesis and oxidation of 2-methyl-4,5,6,7,-tetrahydrobenzofuran-^{18}O 109a. This substrate labeled with ^{18}O was prepared as shown

(equation 52). The exchange conditions were the same as before and

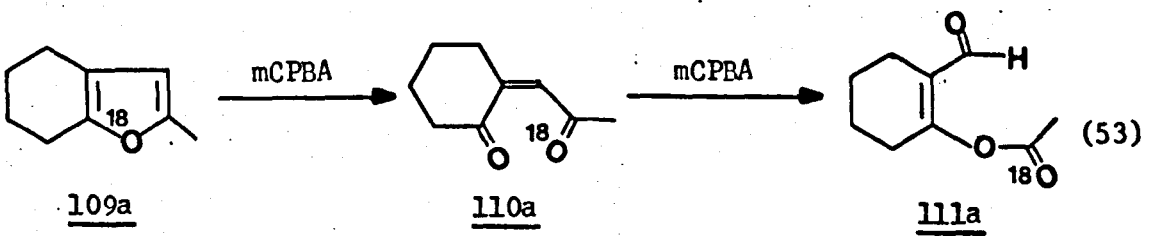


108 108a 109a

incorporation of ^{18}O occurred readily to yield 108a. However, the cyclization to the furan 109a was problematical in that substantial amounts of label were lost. An initial experiment was carried out cyclizing 108a with 47% incorporated ^{18}O in 90% sulfuric acid. This led to isolation of the furan 109a with only 9% incorporated ^{18}O. A second cyclization was carried out using 108a with 38% incorporated ^{18}O and 90% sulfuric acid prepared using 97% enriched $H_2{}^{18}O$. In this case, furan 109a with 12% ^{18}O label resulted. Apparently exchange is occurring with the oxygens of the sulfate group. One possible way to avoid this would be to treat the labeled chloroketone 108a with a trace of concentrated sulfuric acid (1-2 drops) and then heat the mixture under aspirator vacuum to distill the furan 109a as it formed. However, since the amount of ^{18}O incorporated was felt to be sufficient for mechanistic studies, this was not pursued.

The oxidation of the labeled furan was carried out to yield the labeled enedione 110a. After analysis, this was oxidized further to

the labeled aldehyde 111a (equation 53). The results are summarized



109a 110a 111a

in Table 3. As noted above, this series of reactions was run with furan containing small amounts of ^{18}O. Oxidation of 109a resulted in loss of 2-3% of the ^{18}O as shown by NMR spectroscopy in both cases. It was assumed that this was lost by exchange during work-up of the reaction mixtures. The methylene chloride used as a solvent had been rigorously purified and dried prior to use.

Table 3. ^{18}O Content for Studies Involving 2-Methyl-4,5,6,7-tetrahydrobenzofuran.

	^{13}C NMR Data			Mass Spectral
Compound	δ^a (ppm)	$\Delta\ \delta$ (ppm)	% ^{18}O	Data
108a	210.8(s)	.053	38	37
109a	149.8(s)	.041	12	14
	149.0(s)	.039	12	
110a	200.1(s)	.050	10	b
111a	168.6(s)	.037	9	10

[a]Chemical shift and multiplicity of carbons showing isotope induced shift.
[b]Not determined (see text).

The ^{13}C NMR spectrum of enedione 110a showed the resonance at 200.1 ppm to be resolvable into two lines with the upfield line shifted by 0.050 ppm. Comparison of peak intensities showed 10% ^{18}O

incorporation. Further oxidation of this material to the aldehyde 111a indicated the label to be in the position shown. The resonance at 168.6 ppm, assigned to the carbonyl carbon of the acetate group, was resolved into two peaks with the upfield peak shifted by 0.037 ppm. Comparison of the intensities of these lines showed 9% ^{18}O incorporation, which was in good agreement with the mass spectral value of 10%.

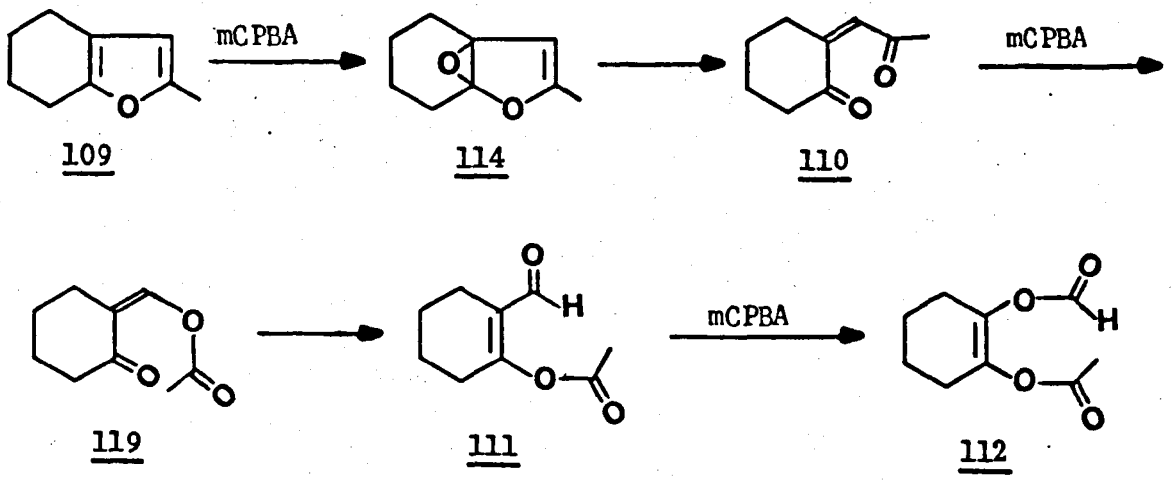
As noted, 2-3% of the ^{18}O was lost during the course of these oxidations. It was considered that in enedione 110a, the ^{18}O could be in the carbonyl of the cyclohexanone moiety. In the NMR spectrum of this material, the resonance at 204.6 ppm was very broad and it was impossible to determine if there was an isotope induced shift. Mass spectral analysis was carried out on the crude reaction mixture which contained some of the aldehyde 111a. Unfortunately, it was found that this compound fragmented to produce ions whose mass fell into the area of the molecular ion for 110a. Thus, it was not possible to determine the amount of ^{18}O incorporated in enedione 110a in this manner.

However, oxidation of enedione 110a resulted in the isolation of aldehyde 111a. This was shown to contain 9% ^{18}O by NMR spectroscopy and 10% ^{18}O by mass spectral analysis. If 2-3% of the ^{18}O had been incorporated in the other ketone in enedione 110a, this would have ended up as the alkoxy oxygen of the acetate group in 111a and therefore not been exchangeable. This would have been easily determined by mass spectral analysis. Since the mass spectral analysis of 111a agreed well with the extent of ^{18}O incorporation shown by ^{13}C NMR

spectroscopy, it was assumed that this also substantiated the proposition that the remaining ^{18}O was lost by exchange from the enedione 110a.

The following mechanism was therefore proposed for the oxidation of this substrate with mCPBA. Initial attack by mCPBA would occur on the more substituted side of the furan as predicted.[44] This monoepoxide 114 would undergo ring opening to yield 110. This enedione would undergo a Baeyer-Villiger oxidation to lead to 119 which would rearrange to yield aldehyde 111. A final Baeyer-Villiger oxidation would follow affording formate 112.

Figure 17. Proposed mechanism for the oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran via an enedione intermediate.

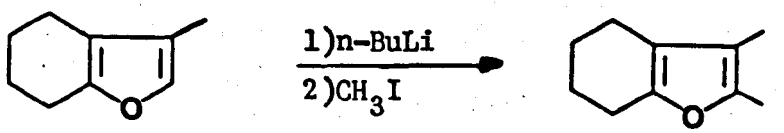


Studies with 2,3-Dimethyl-4,5,6,7-tetrahydrobenzofuran

The studies discussed above with the 2-methyl derivative fit well into our earlier proposed mechanistic scheme. The initial attack

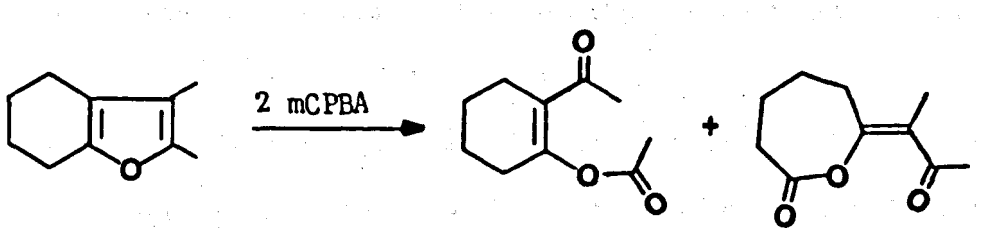
by mCPBA occurred on the more substituted side of the furan moiety. The enedione formed by subsequent ring opening underwent rapid Baeyer-Villiger oxidation to lead to the other products observed. However, as mentioned previously, 3-methyl-4,5,6,7-tetrahydrobenzofuran 57 did not appear to fit into this scheme. Labeling studies suggested a pathway in which initial attack by mCPBA occurred on the least substituted side of the furan moiety or possibly a different mechanism with a diepoxide intermediate was involved. It was therefore decided to investigate a different system in hope that this point could be clarified.

Synthesis and oxidation of 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran 120. Following the procedure of Cohen,[72] this substrate was synthesized in one step from 57 (equation 54).



57 120 (54)

The oxidation of furan 120 with two equivalents of mCPBA proceeded to give two products, 121 and 122 (equation 55). The ratio



120 121 122 (55)

of compound 121 to compound 122 in these reaction mixtures varied between 60:40 and 50:50 as demonstrated by NMR spectroscopy. These products were identified by spectral means.

Compound 121 showed a molecular ion at m/e 182 in the mass spectrum indicating addition of two oxygens to the furan substrate. The ^{13}C NMR spectrum showed resonances at 198.4, 168.5, 155.0 and 126.1 ppm, all of which appeared as singlets in the gated decoupled spectrum. The resonances at 198.4 and 168.5 ppm were assigned to the carbonyl carbons of the acetyl and acetate groups, respectively. The other two resonances were assigned to the olefinic carbons with the resonance at 155.0 ppm being assigned to the carbon adjacent to the acetate group and the resonance at 126.1 ppm to the carbon adjacent to the acetyl group. Perhaps more helpful in this case was the ^{1}H NMR spectrum which showed methyl singlets at 2.27 and 2.21 ppm. Exact assignments of these two resonances were not made. However, it was noted that the position of these two resonances confirmed that the methyl groups were in deshielding environments, adjacent to the carbonyls in this case. The IR spectrum showed bands at 1760, 1690, 1650 and 1215 cm^{-1}. The absorptions at 1760 and 1215 cm^{-1} were assigned to the vinyl acetate group. The band at 1690 cm^{-1} was assigned to the carbonyl stretching of the ketone functionality and that at 1650 cm^{-1} to the olefinic stretching.

Compound 122 also showed a molecular ion at m/e 182 in the mass spectrum. The ^{13}C NMR spectrum showed resonances at 200.2, 171.2, 154.2 and 124.5 ppm, all of which appeared as singlets in the gated decoupled spectrum. The resonances at 200.2 and 171.2 ppm were

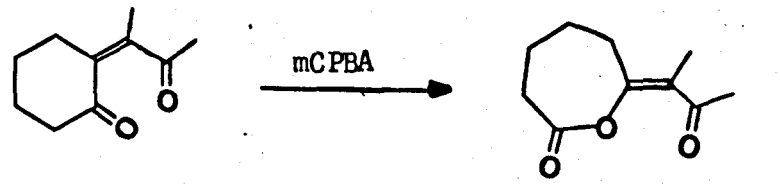
assigned to the carbonyl carbons of the acetyl and lactone functionalities, respectively. The other two resonances were assigned to the olefinic carbons with the resonance at 154.2 ppm attributed to the one adjacent to the lactone functionality and the peak at 124.5 ppm to the one adjacent to the acetyl group. It should be noted that these resonances correspond closely to those of 78, the product from the oxidation of perhydrodibenzofuran 77. The ^{1}H NMR spectrum of 122 showed a singlet at 2.37 ppm which was assigned to the methyl group of the acetyl functionality and another singlet at 1.85 ppm was assigned to the methyl group substituted on the olefin. The IR spectrum showed absorptions at 1760, 1680, 1640 and 1160 cm^{-1}. The bands at 1760 and 1160 cm^{-1} were assigned to the ester group of the lactone functionality. The band at 1680 cm^{-1} was assigned to the carbonyl stretching of the acetyl group. The weaker absorption at 1640 was assigned to the olefinic stretch.

The result of this oxidaton was intriguing from a mechanistic standpoint. Compound 121 was felt to arise from a pathway analogous to that proposed for the oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran 109. Initial attack on the furan moiety would yield a monoepoxide which would subsequently ring open to give a cis-enedione. This enedione would undergo Baeyer-Villiger oxidation followed by rearrangement to yield the observed product 121. It is also possible that this product 121 would arise from the cleavage of the 2,3-bond by a Borowitz type mechanism.

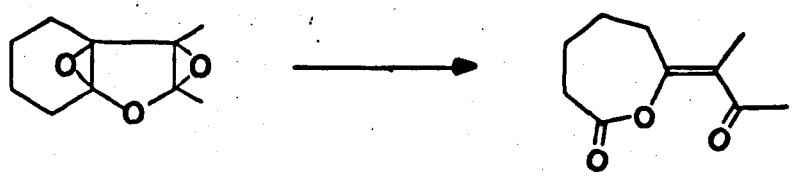
The other product 122 was of greater interest from a mechanistic point of view since it could be formed via two pathways. It could

arise from the Baeyer-Villiger oxidation of the intermediate enedione (equation 56). Another possibility would be its formation from a diepoxide intermediate (equation 57).

This product 122 was of interest because it is analogous to the ε-lactone 58, formed upon oxidation of the 3-methyl derivative 57. As noted earlier in this section, there were still questions concerning the reaction pathway which led to the formation of 58 from 57. Labeling studies were therefore planned with 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran 120 to determine the pathway by which ε-lactone 122 was formed.



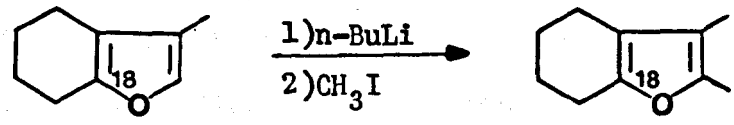
123 122 (56)



124 122 (57)

Synthesis and oxidation of 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 120a. The substrate labeled with ^{18}O was prepared in the

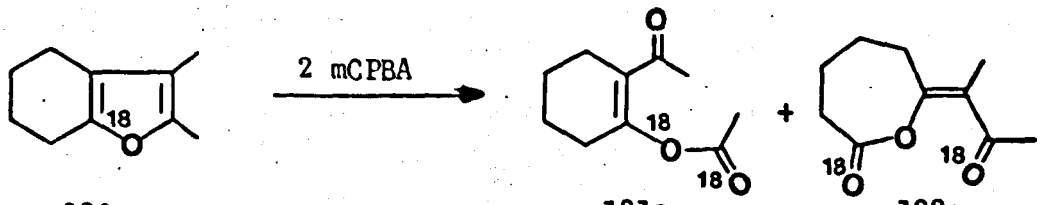
same fashion as the unlabeled material (equation 58). Analysis



57a 120a (58)

by ^{13}C NMR spectroscopy showed 43% incorporation of ^{18}O and mass spectroscopy showed 45% ^{18}O.

Oxidation of 120a with two equivalents of mCPBA gave 121a and 122a in an approximately 1:1 ratio (equation 59). The position of



120a 121a 122a (59)

the label was determined by ^{13}C NMR spectroscopy and is summarized in Table 4.

For compound 121a the resonance at 168.5 ppm was resolved into three lines. One of the resonances was shifted upfield by 0.010 ppm and the third resonance was shifted by 0.037 ppm. Analysis of the relative intensities of these lines indicated that 26% of the ^{18}O was associated with the resonance shifted by 0.010 ppm and 15% with the resonance shifted by 0.037 ppm. This showed that 15% of the carbonyl oxygen of the acetate group was ^{18}O and, similarly, 26% of the alkoxy oxygen of this same group was ^{18}O. Unfortunately, the resonance at

155.0 ppm could not be resolved into a sharp line so no useful information could be obtained from this peak. Mass spectral analysis showed 40% ^{18}O incorporation in this compound. The IR spectrum showed a strong absorption at 1760 cm^{-1} and a weaker one at 1720 cm^{-1}. These were assigned to the $C^{16}O$ and $C^{18}O$ stretches of the carbonyl group in the acetate functionality, respectively.

Table 4. ^{18}O Content for Studies Involving 2,3-Dimethyl-4,5,6,7-tetrahydrobenzofuran.

	^{13}C NMR Data			Mass Spectral
Compound	δ^a (ppm)	$\Delta\delta$ (ppm)	% ^{18}O	Data (% ^{18}O)
57a	150.9(s)	.039	43%	44
	136.7(d)	.036	43%	
120a	147.8(s)	.040	44%	45
	144.7(s)	.040	44%	
121a	168.5(s)	.010	26%	40
		.037	15%	
	155.0(s)	b		
122a	200.2(s)	.049	15%	41
	171.2(s)	.040	26%	

[a]Chemical shift and multiplicity of carbons showing isotope induced shift.
[b]Not determined (see text).

Analysis of 122a was carried out in the same way. The resonance at 200.2 ppm was resolved into two peaks with the upfield line shifted by 0.050 ppm. Comparison of the relative intensities of these lines showed 15% ^{18}O to be incorporated as the carbonyl oxygen of the acetyl group. The resonance at 171.2 ppm was similarly resolved into two lines with the upfield resonance shifted by 0.040 ppm. Analysis showed 26% incorporation of ^{18}O at this position, the carbonyl of the

lactone functionality. Mass spectral analysis showed 41% incorporation of label in this compound. The IR spectrum showed a band at 1760 cm^{-1} and a second at 1730 cm^{-1}. These were assigned respectively to the $C^{16}O$ and $C^{18}O$ stretches of the carbonyl group of the lactone functionality. A second band could not be identified for the $C^{18}O$ stretching of the ketone because of the band arising from the olefin at 1640 cm^{-1}.

These results led to the following proposed mechanism (Figure 18). Initial attack by mCPBA would occur preferentially on the side of the furan substituted with the two methyl groups. These monoepoxides would undergo ring opening to form the two enediones 123a differentiated by the position of the ^{18}O. These enediones would subsequently react with a second equivalent of mCPBA in a Baeyer-Villiger oxidation to yield the ε-lactone product 122a or the enol acetate 125a. The enol acetate would then rearrange to give 121a. There appears to be little regioselectivity in this final Baeyer-Villiger oxidation.

Low Temperature ^1H NMR Studies With 3-Methyl-4,5,6,7-tetrahydrobenzofuran

The results from the above study strongly suggested that the ε-lactone product was formed by Baeyer-Villiger oxidation of an intermediate enedione. In the case of 3-methyl-4,5,6,7-tetrahydrobenzofuran 57, if this is the reaction pathway, initial epoxidation must occur exclusively on the lesser substituted side of the furan moiety.

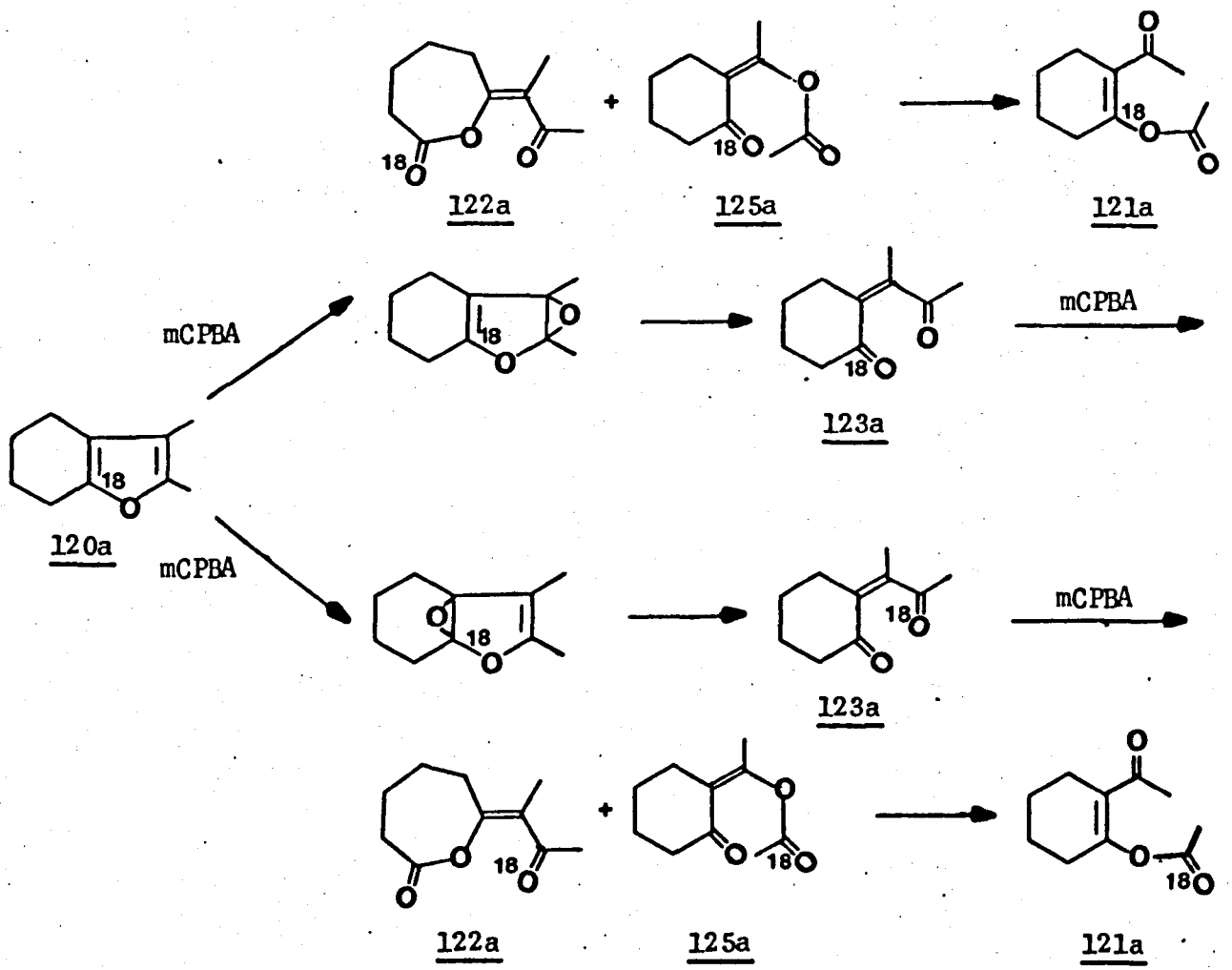


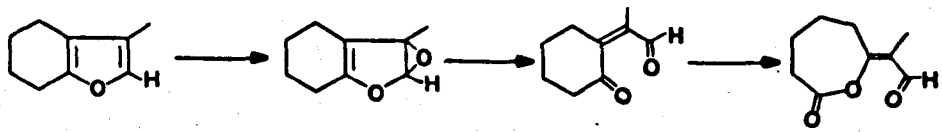
Figure 18. Proposed mechanism for the oxidation of 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran via an enedione intermediate.

To test this hypothesis, low temperature ^1H NMR experiments were carried out. Exploratory studies showed that the reaction proceeded slowly at 230°K and at 240°K it was found that the reaction would go to completion in approximately three hours. The progress of the reaction could be monitored by following the proton at the α-position in furan moiety which ended up as the aldehydic proton.

In carrying out these studies, a solution of mCPBA was prepared in deuterochloroform and this solution was cooled in the probe to 240°K. The tube was removed and an aliquot of furan 57 was injected. The tube was inverted to insure mixing and then quickly returned to the probe. The sample was pulsed at one minute intervals. In these experiments, twelve pulses were accumulated per file. A set of sequential files were generated which were then transformed to yield the spectra which were analyzed.

In the initial spectrum, the resonance at 7.0 ppm, assigned to the α-hydrogen on the furan, had decreased in intensity and a second signal had appeared at 5.6 ppm. In the next spectrum, these resonances were still apparent and two others appeared at 9.66 and 10.14 ppm. Throughout the course of this reaction from this point on, the resonance at 7.0 ppm decreased in intensity and the one at 10.14 increased. The resonance at 5.6 ppm remained constant at approximately 15% of the total area for these four resonances and the one at 9.66 at approximately 5% of this total. As the reaction approached completion, the resonances at 5.6 and 9.66 ppm decreased in intensity until they were barely evident.

This data fits the mechanism proposed with an enedione intermediate (equation 60). The α-proton in furan 57 is assigned to the



57 98 99 58 (60)

signal at 7.0 ppm. In the monepoxide intermediate 98, the signal for this proton appears at 5.6 ppm. Ring opening leads to 99 with the same proton giving rise to the signal at 9.66 ppm. Finally, Baeyer-Villiger oxidation leads to 58 with the proton resonance at 10.14 ppm. Therefore, this system is in mechanistic agreement with the other systems studied. Initial epoxidation occurs to yield a monoepoxide which undergoes ring opening to give a cis-enedione type intermediate. Subsequent rapid Baeyer-Villiger oxidation of the cyclohexanone moiety gives the observed ε-lactone.

Discussion of the Proposed Mechanism

The proposed mechanism for oxidation of the furans used in this study can be viewed as occurring in two separate steps. Initially, the furan moiety is attacked by one equivalent of mCPBA to form an epoxide which undergoes subsequent ring opening to yield an enedione. In the second step, another equivalent of mCPBA carries out a Baeyer-Villiger oxidation of this enedione to lead to the observed products.

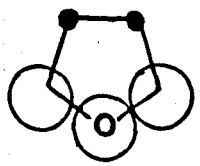
As noted throughout the discussion of these reactions, there is some regioselectivity exhibited by mCPBA in both the steps. It is also of interest to note that the Baeyer-Villiger oxidation occurs at

an extremely fast rate. These points will be discussed here, and some thoughts will be put forth which may be the basis for further studies in this area.

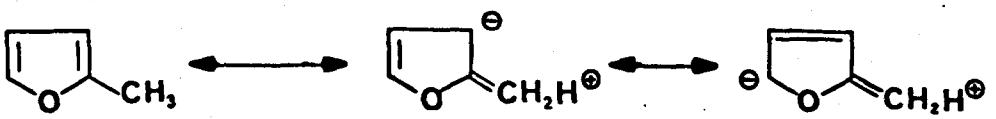
The first point to be considered is the regioselectivity exhibited in the initial attack by mCPBA on the furan moiety. This will be discussed in light of the results obtained with 3-methyl-4,5,6,7-tetrahydrobenzofuran 57 and 2-methyl-4,5,6,7-tetrahydrobenzofuran 109. It is assumed in these cases that mCPBA is reacting as it usually does and no unusual aspects will be considered. mCPBA is known to act as an electrophile. Epoxidations performed with this reagent have been carried out selectively with reaction occurring at the site of greatest electron density. Therefore, it seemed necessary to develop a rationale for the selectivity observed in these studies with a basis in the electronic structure of the furan moiety.

It was found that, even though furan itself has been the subject of several molecular orbital studies, few have dealt with substituted furans.[73] A set of publications by a group of Czechoslovakian workers was noted in which calculational results were related to observed NMR spectral properties and some selected reactivities.[74, 75] However, the results of the calculations reported were not broad enough to encompass the needs of our studies. A study was recently reported by Radom.[76] In this case, ab initio calculations were carried out using the STO-3G basis set. The results for a broad series of substituted furans were then related to a valence bond model of these systems. The concepts developed here seemed to be applicable to our question.

The furan molecule, as a zeroth order approximation, can be thought of as arising from a butadiene entity and an oxygen atom. Granted, there is some delocalization which gives rise to the aromaticity of furan, but, for simplicities sake, this will not be considered. In this case, where only the π electrons are of interest, this allows the following picture to be put forth for the highest occupied molecular orbital (HOMO) of furan. Note that the electron density is



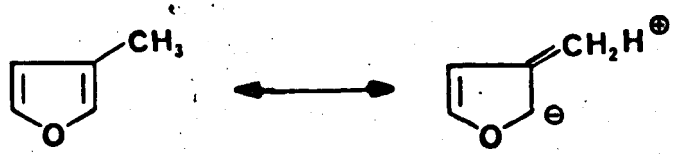
greatest at the oxygen and carbons two and five. In analyzing substituent effects on this basic framework, the following concepts can be developed. Electron releasing substituents in the two position of furan lead to perturbations in the electronic structure as explained by the resonance forms shown (equation 61). Note, the increase in



(61)

electron densities is at carbons three and five. For the 3-methyl case, on the other hand, there is only one resonance form which makes

a major contribution (equation 62). This shows an increase in elec-



(62)

tron density at the two position.

The two furans considered in this section can be viewed as a 3,4,5-trialkylfuran and a 2,4,5-trialkylfuran. A summation of the substitutent effects leads to the concept that, in the 3,4,5-trialkylfurans, the greatest perturbation occurs at the two carbon and, in the 2,4,5-trialkyl system, at the five position.

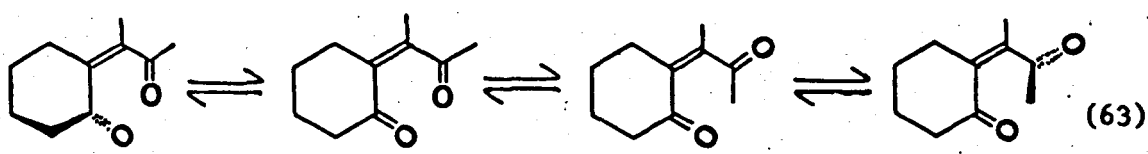
This picture may then be extended to predict the regioselectivity observed. In the 2-methyl case, the mCPBA approaches the furan moiety and sees the greatest electron density at the oxygen end of the furan. It then "slides" to the 4-5 double bond since greater electron density is felt in that direction. The mCPBA then reacts, epoxidizing that double bond. In the 3-methyl case, the approach of the mCPBA is similar but greater electron density is seen on the 2-3 double bond. Thus, the reagent moves that way, epoxidizing the less substituted double bond.

On the basis of this explanation, it would be interesting to determine the mechanism of this reaction with substituents with varying electronic effects. This would suggest itself as a logical way to carry out further studies in any event.

Attention will now be turned to the Baeyer-Villiger oxidation of the intermediate enedione. Initial considerations will be focused on

the regioselectivity shown by this reaction again exemplified by 3-methyl-4,5,6,7-tetrahydrobenzofuran 57 and 2-methyl-4,5,6,7-tetrahydrobenzofuran 109. It will be assumed that this reaction is proceeding in the manner determined for Baeyer-Villiger oxidations. This mechanism can be viewed as initial nucleophilic attack on the carbon of the carbonyl group by the peracid followed by rearrangement of this intermediate with migration of the substituent which can best stabilize positive charge. The question of the regioselectivity observed in these reactions therefore can be redefined as a question of why the attack by mCPBA occurs with such regioselectivity.

An obvious place to begin is with consideration of the structure of the enediones proposed as intermediates. It should be realized that all of these enediones, except that derived from perhydrodibenzofuran 77, can exist in four forms which are labeled as s-cis, s-trans and skewed forms (equation 63). The cyclohexanone moiety in all cases



(63)

is assumed to be most rigid in respect to the substituent even though enough distortion is possible to allow this carbonyl a skewed relationship with respect to a planar substituent. The reader should realize that these models are presented as a grossly simplified scheme. A detailed discussion could ensue as to the amount of distortion required to define a system as being skewed, other possible

conformations and other considerations. However, this is beyond the scope of this discussion.

The distortions envisioned may have rather dramatic effects on the electronic structure of these molecules. One possible result could be that these enediones actually consist of an α,β-unsaturated carbonyl and a localized carbonyl. Effects similar to this have been noted by Lutz in studies of the spectroscopic properties of substituted cis-dibenzoylethylenes.[77] If similar studies were carried out on the enediones in this study, perhaps similar effects could be noted. Differentiation of the carbonyls in this way could possibly be used to explain the regioselectivity observed in this Baeyer-Villiger oxidation. In the 2-methyl case, it is the acetyl group which acts as a localized carbonyl group and attack by the mCPBA preferentially occurs at this position. On the other hand, with the 3-methyl case, the exocyclic group is planar and the carbonyl group of the cyclohexanone acts as the localized group. Thus, nucleophilic attack by mCPBA occurs here.

On the basis of these thoughts, it also might be interesting to study the regioselectivity of a variety of nucleophiles with these enediones to see if similar results are evidenced throughout. It should be realized that the approach discussed above is only one way of dissecting this problem. Since the chemistry of cis-enediones has really not been explored to a great extent, further work in any aspect of their chemistry will generate information which will allow new insight into their reactivity.

The third question which persisted throughout the course of this research arose from the extremely fast rate at which these Baeyer-Villiger oxidations proceeded. It has been noted that Baeyer-Villiger oxidations exhibit rates which do not vary widely, most falling within a range of two orders of magnitude.[66] The rate constants reported for this reaction extrapolate to reaction times on the order of hours to days. In a qualitative sense, the reactions reported in this thesis are inordinately faster, in one case proceeding at 240°K.

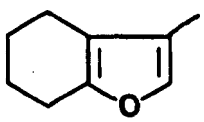
A closer look at the mechanism of this reaction may again provide insight. It has been noted that in cases where a system is studied with a variety of organic peracids the faster rates are observed with the stronger acids suggesting that rearrangement is rate determining. If addition were rate determining, one would expect the weaker peracid, being more nucleophilic, to show the faster rates. It should be noted that m-chlorobenzoic acid is not a very strong acid (pK=3.82).

However, certain compounds have been found to exhibt faster rates. For instance, cyclohexanone was found to oxidize approximately twenty times faster than other cyclanones of ring sizes between four and eight.[78] In this case, the increased rate has been attributed to a greater concentration of the initially formed adduct of the peracid and the carbonyl.[66] This may be related to the increased rates observed in these systems. Perhaps the carbonyl of interest readily undergoes nucleophilic attack leading to a high concentration of the peroxide intermediate. This then rearranges to give the observed product.

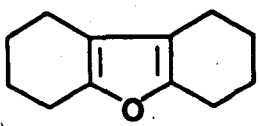
In essence, the studies proposed previously with a variety of nucleophiles also ties in here. If increased rates are observed in such studies, this proposal may have some validity. Obviously, a detailed kinetic study would be in order. Not only would this be useful in quantitating the reaction rate, it could also be useful in confirming that the pathway followed by this reaction is indeed consistent with that proposed for Baeyer-Villiger oxidations.

SUMMARY

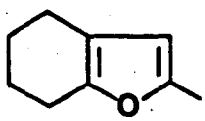
A series of four furans were prepared including 3-methyl-4,5,6,7-tetrahydrobenzofuran 57, 1,2,3,4,5,6,7,8-octahydrodibenzofuran 77, 2-methyl-4,5,6,7-tetrahydrobenzofuran 109 and 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran 120. The products arising from the



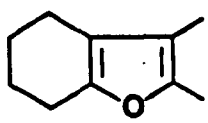
57



77



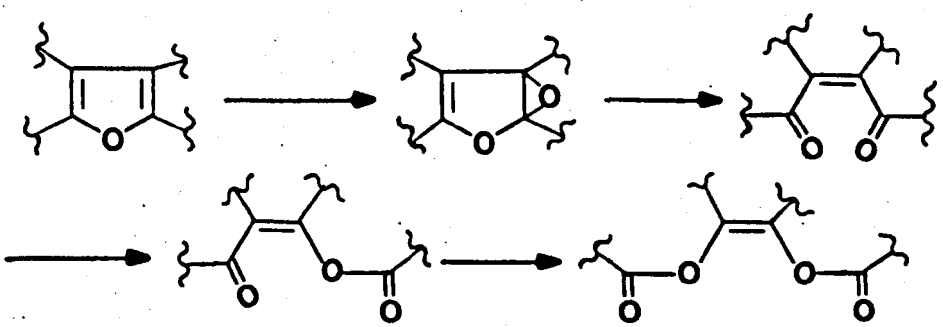
109



120

oxidation of these substrates with mCPBA were isolated and their structures determined by spectral means. In one case, a single crystal x-ray analysis was performed. These reactions were explored under a variety of conditions to determine what effect was observed on the progress of the reaction. These four substrates were also prepared labeled with ^{18}O. This is the first report of a synthesis of alkyl substituted furans labeled in this way. The oxidation of the labeled materials was also carried out with mCPBA and the position of the ^{18}O in the products determined by ^{13}C NMR spectroscopy. On the basis of these studies, it is possible to propose a detailed mechanism for the oxidation of these furans (equation 64).

The furan moiety is initially attacked by peracid to form an



(64)

epoxide which subsequently undergoes ring opening to form a cis-enedione. This enedione reacts rapidly in all cases with a second equivalent of mCPBA to effect a Baeyer-Villiger oxidation. In certain cases, where regioselectivity was observed, it was commented on.

Finally, it may be possible to advance the understanding of the toxicity evidenced by certain furans in vivo. In all these model cases studied, cis-enediones are thought to be one of the intermediates formed. It has been observed in all cases but one that these enediones show enhanced reactivity to mCPBA relative to the furan from which they were derived. On the basis of this greater reactivity, it could be proposed that cis-enediones are the metabolities more toxic than the parent furans.

EXPERIMENTAL

General

^{1}H NMR spectra were recorded on either a Varian A-60 or a Bruker WM 250 spectrometer at 60 or 250 MHz respectively. ^{13}C NMR spectra were recorded on a Bruker WM 250 spectrometer at 62.83 MHz. Both ^{1}H-decoupled and gated decoupled spectra were determined. The spectra were measured in deuteriochloroform, unless otherwise stated, and tetramethylsilane was used as an internal standard. In the determination of ^{18}O incorporation by ^{13}C NMR spectroscopy, sweep widths of 500 Hz were typically used. Data was acquired as a 4K block and transformed as an 8K block following 0.3 Hz exponential multiplication. IR spectra were determined on a Beckman IR5A spectrometer and these were calibrated using polystyrene. Mass spectra were obtained from a Varian Mat CH-5 spectrometer operating at 70 ev. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analysis was performed by Gailbraith Laboratories or the University of Idaho.

Analytical gas chromatography was carried out using a Varian Aerograph Model 1700 equipped with a flame ionization detector or a Varian Aerograph Model 1400 equipped with a thermal conductivity detector. Columns used were either a 13' x ¼" column packed with 5% SE-30 on 100/120 Chromosorb Z or a 6' x ¼" column packed with 5% Carbowax on 100/120 Chromosorb WHP. Preparative gas chromatography

was performed using a Varian Aerograph Model 2700 equipped with either a 5' x ¼" column packed with 20% SE-30 on 60/80 Chromosorb W, a 10' x ¼" column packed with 15% Carbowax on base washed Chromosorb W or a 6' x ¼" column packed with 15% OV-101 on 100/120 Chromosorb G. In all cases helium was used as the carrier gas. 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.

Reagent grade solvents were purchased from Baker and used as obtained unless otherwise noted. Tetrahydrofuran and diethyl ether were routinely distilled from calcium hydride prior to use. Technical grade m-chloroperbenzoic acid was purchased from Aldrich and either used as obtained, assuming 85% purity, or purified by the procedure of Schwartz.[79] The purity of this material was checked by ^{1}H NMR spectroscopy and found to be greater than 98% peracid. Other reagents were purchased as noted and used without further purification. Gases were obtained from Matheson and used directly with the exception of nitrogen which was purchased as dry grade and then run through an anhydrous calcium chloride column prior to use.

Studies With Furan

Reaction of furan with mCPBA in different solvents. To a stirred solution of mCPBA (3.11 g, 16 mmol, technical grade) in 100 mL of benzene at 0° was added a solution of furan 1 (1.02 g, 15 mmol, Aldrich) in benzene (10 mL). The progress of the reaction was monitored by analytical gas chromatography (carbowax column).

After a twelve hour period it was observed that the concentration of furan was no longer decreasing and approximately one-half of it still remained. A second portion of mCPBA (3.11 g, 15 mmol, technical grade) was added. Analysis showed the concentration of furan to again decrease and after a second twelve hour period only a trace remained in the yellow solution.

A portion of this reaction mixture was washed with 5% NaOH, water and brine and dried over $MgSO_4$. The solvent was removed and no material was found remaining in the flask. Another portion was concentrated and then filtered to remove m-chlorobenzoic acid. Removal of the remaining solvent led to an intractable material.

The reaction was also attempted in carbon tetrachloride, chloroform and methylene chloride. The reaction was found to follow a similar course in all of these cases, yet no products could be isolated by any means tried.

Oxidation of furan with mCPBA using activated potassium fluoride. Following the procedure of Camps, to a solution of furan 1 (0.50 g, 7.4 mmol, Aldrich) in 50 mL of methylene chloride was added, in one portion, mCPBA (3.18 g, 16 mmol, technical grade).[40] The flask was swirled and then allowed to stand for 18 hours. At this time potassium fluoride (2.18 g, 38 mmol, activated by heating at 100° and 0.1 mmHg for one hour) was added. The mixture was slowly stirred for 24 hours. Filtration, followed by removal of solvent gave a white solid. Recrystalization from 30% chloroform in petroleum ether (60-110°) afforded 0.38 g of aldehydomaleic acid 19 (52%): mp 55.5-57°

[lit[14] mp 55°]; ^{1}H NMR[14] 7.31 (1H, d), 6.24 (2H, m), 4.70 (1H, br s) ppm; ^{13}C NMR 171.3(s), 152.0(d), 124.9(d), 98.7(d) ppm; IR ($CHCl_3$) 3300, 1745, 1340, 1130, 1080, 1000, 915, 830 cm^{-1}.

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

Preparation of ethyl and methyl 1,4-dioxaspiro[4.5]decane-6-carboxylate 53. A solution of ethyl and methyl 2-cyclohexanonecarboxylate (22.0 g, 134 mmol, Aldrich), ethylene glycol (14.4 g, 233 mmol, Baker) and 0.5g p-toluenesulfonic acid in 125 mL benzene was refluxed with a Dean-Stark water trap for 12 hours. The reaction mixture was washed with water, twice with 10% $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of solvent gave a yellow oil which was distilled to yield 26.0 g of 53 (93%) as a clear liquid: bp 131-136° (10 mmHg) [lit[68] bp 120-124° (8 mmHg)]; IR (neat) 1740 cm^{-1}.

Preparation of 6-(1-hydroxy-1-methylethyl)-1,4-dioxaspiro[4.5]-decane 54. A solution of MeMgI in ether was prepared under nitrogen by dropwise addition of a solution of methyl iodide (43.01 g, 300 mmol, Baker) in ether (150 mL) to magnesium turnings (7.29 g, 300 mmol). After addition was complete (approximately 30 minutes), the reaction mixture was refluxed for an additional 30 minutes. To this, a solution of ketal ester 53 (30.0 g, 145 mmol) in ether (150 mL) was added dropwise over a period of 30 minutes and the resulting mixture was stirred an additional 1.5 hours. Hydrolysis was performed by adding 100 mL of 3.5M acetic acid. The layers were separated and the aqueous portion extracted several times with ether. The combined organic layers were washed twice with 10% $NaHCO_3$ and brine and dried

over K_2CO_3. Removal of solvent followed by distillation gave 27.3 g of 54 (95%) as a clear liquid: bp135-137° (16 mmHg) [lit[68] bp 160-162° (20 mmHg); ^{1}H NMR 4.60 (1H, s), 3.95 (4H, s), 2.35-2.15 (1H, m), 2.0-1.2 (8H, m), 1.15 (3H, s), 1.05 (3H, s) ppm; IR (neat) 3450 cm^{-1}.

Preparation of 6-(1-methylethenyl)-1,4-dioxaspiro[4.5]decane 55. A solution of ketal alcohol 54 (5.01 g, 25 mmol) and 0.22 g p-toluenesulfonic acid was refluxed in benzene with a Dean-Stark water trap until no more water separated (approximately eight hours). The reaction mixture was washed with 10% $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of solvent gave a yellow oil which was chromatographed on silica gel. Elution with 5% ether in hexane afforded 4.25 g of 55 (92%) as a colorless liquid: bp 94-95° (11 mmHg); ^{1}H NMR 4.90-4.80 (2H, d), 3.94-3.80 (4H, m), 2.30-2.20 (1H, m), 1.81 (3H, s), 1.80-1.20 (8H, 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 57. To a stirred solution of mCPBA (3.03 g, 15 mmol, technical grade) in 100mL methylene chloride at 0° was added $NaHCO_3$ (2.0 g) and a solution of ketal alkene 55 (1.94 g, 11 mmol) in methylene chloride (10 mL). Stirring was continued for one hour at 0°. The reaction

mixture was then 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 1.96g of 56 (92%) 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 (4H, m), 2.83 (1H, d), 2.65 (1H, d), 2.0-1.1 (9H, m), 1.28 (3H, 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 (4H, m), 1.69 (1H, d), 1.47 (1H, d), 1.9-1.1 (9H, m), 1.41 (3H, s). Diastereomeric mixture: IR (neat) 1720, 1225, 1160, 1095, 1045, 930, 870, 815, 735 cm^{-1}; mass spectrum 198 (M^+) m/e.

Preparation of 3-methyl-4,5,6,7-tetrahydrobenzofuran 57. Following the procedure of Takahashi, to a vigorously stirred solution of ketal oxirane 56 (3.45 g, 17.4 mmol) in 50 mL pentane was added 25 mL of aqueous 2M HCl.[41] Stirring was continued for 2.5 hours and the layers were then separated. The aqueous layer was extracted several times with pentane. The combined pentane layers were washed with 10% $NaHCO_3$ and brine and dried over K_2CO_3. The solvent was removed and the yellow oil chromatographed on silica gel. Elution with pentane gave 1.97g of 57 (83%) as a clear liquid: bp 69-71° (10 mmHg) [lit[80] bp 110° (13 mmHg)]; ^{1}H NMR[80] 7.0 (1H, br s), 2.75-2.20 (4H, m), 1.90 (3H, d), 2.0-1.5 (4H, m) ppm; ^{13}C NMR 151.0(s), 136.8(d), 126.1(s), 118.0(s), 23.4(t), 23.1(t), 23.1(t), 20.6(t), 8.1(q) ppm; IR[81] (neat) 1760, 1640, 1560, 1450, 1100, 1080, 895, 880, 730 cm^{-1}; mass spectrum 136 (M^+) m/e.

Oxidation of 3-Methyl-4,5,6,7-tetrahydrobenzofuran with mCPBA

Stepwise oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran 57 with mCPBA. To a stirred solution of mCPBA (1.18 g, 6.84 mmol) in 20 mL methylene chloride was added $NaHCO_3$ (0.5g) and then a solution of 57 (0.93 g, 6.84 mmol) in methylene chloride (5 mL). After 15 minutes an aliquot was removed, filtered and analyzed by ^1H NMR spectroscopy. The spectrum showed two resonances of equal intensity at 1.90 and 1.80 ppm. The former belonged to 57 and the latter to 58. Analysis by gas chromatography (SE-30 column) confirmed that one-half of the furan 57 had reacted. A second addition of mCPBA (1.18 g, 6.84 mmol) was performed on the cooled mixture and stirring was continued for 15 minutes. The reaction mixture was washed with 10% $Na_2S_2O_3$, 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent yielded 0.93 g of 58 (81%) as a clear oil: ^1H NMR 10.2 (1H, s), 2.7(4H, m), 1.9 (4H, m), 1.8 (3H, s) ppm; ^{13}C NMR 189.8(d), 170.7(s), 164.8(s), 123.9(s), 33.7(t), 31.2(t), 25.5(t), 23.4(t), 9.0(q) ppm; IR (neat) 2750, 1755, 1680, 1640, 1170, 1120, 1095, 995, 735 cm^{-1}; mass spectrum 168 (M^+), 85 (100) m/e.

Preparation of 2,4-dinitrophenylhydrazone derivative. To an acidic solution of 2,4-dinitrophenylhydrazine (0.20 g, 1.0 mmol) in methanol was added a solution of ε-lactone 58 (0.17 g, 1.0 mmol) in methanol. An orange precipitate formed immediately. The flask was stoppered and placed in a refrigerator overnight. The product was collected by filtration and repeated recrystallizations from ethyl acetate, ethanol and water gave an orange solid: mp 220-221.5°; ^{13}C

NMR 171.7, 157.6, 154.3, 145.0, 138.5, 130.1, 129.7, 123.6, 119.5, 116.8, 33.9, 30.6, 26.6, 23.4, 11.5 ppm. Anal. Calcd for $C_{15}H_{16}N_4O_6$: C, 51.73; H, 4.63; N, 16.09. Found: C, 51.33; H, 4.62; N, 15.55.

Oxidation without added solution bicarbonate. To a stirred solution of 57 (0.12 g, 0.86 mmol) in 20 mL methylene chloride at 0° was added, in one portion, mCPBA (0.30 g, 1.74 mmol). After a ten minute period, the reaction was worked-up as before to yield 0.12 g of 58 (82%). This material showed identical spectral properties to that prepared above.

Studies with Menthofuran

Purification of menthofuran 59. Menthofuran was purchased from Eastman Organic Chemicals. Prior to use this material was chromatographed on silica gel. Elution with pentane afforded 59 as a clear oil: ^{1}H NMR 6.95 (1H, br s), 1.90 (3H,s), 1.07 (3H, d) ppm; ^{13}C NMR 150.9, 137.0, 119.7, 117.5, 31.6, 31.4, 29.7, 21.5, 19.9, 8.1 ppm.

Oxidation of menthofuran 59 with two equivalents of mCPBA. To a stirred solution of mCPBA (4.17 g, 24 mmol) in 60 mL methylene chloride at 0° was added $NaHCO_3$ (2.3 g) and then menthofuran 59 (1.81 g, 12 mmol). Within one minute a flocculent precipitate of m-chlorobenzoic acid formed. After 15 minutes, the reaction mixture was washed with 10% $Na_2S_2O_3$, twice with 5% NaOH, water and brine and dried over $MgSO_4$. Removal of solvent gave 1.85 g of 60 (84%) as a clear oil: ^{1}H NMR 10.16 (1H, s), 2.95-0.8 (7H, m), 1.78 (3H, s), 1.11 (3H, d) ppm; ^{13}C NMR 189.9 (d, J_{C-H} = 181 Hz), 169.6(s), 164.4(s), 123.7(s),

40.8(t), 33.1(t), 29.9(t), 29.7(d), 21.7(q), 9.1(q) ppm; IR (neat) 1760, 1675, 1645, 1460, 1300, 1210, 1070 cm^{-1}.

Preparation of 2,4-dinitrophenylhydrazone derivative. To an acidic solution of 2,4-dinitrophenylhydrazine (0.40 g, 2.0 mmol) in methanol was added a solution of 60 (0.36 g, 2.1 mmol) in methanol. The flask was stoppered and placed in a refrigerator overnight. The product was collected and recrystallized from ethyl acetate to yield an orange solid: mp 213-215°; ^{13}C NMR 170.9(s), 154.5(s), 145.4(d), 145.0(s), 138.4(s), 130.0(d), 129.6(s), 123.6(d), 119.1(s), 116.7(d), 41.0(t), 34.4(t), 29.9(q), 29.1(t), 22.0(d), 11.5(q) ppm.

Oxidation of aldehyde 60 to formate 61. To a stirred solution of mCPBA (0.30 g, 1.7 mmol) in 20 mL methylene chloride at 0° was added a solution of 60 (0.25 g, 1.4 mmol) in methylene chloride (5 mL). The reaction mixture was maintained at 0° for three hours. The solution was washed with 10% $Na_2S_2O_3$, 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent gave 0.26 g of 61 (96%) as a clear liquid: ^1H NMR 7.95 (1H, s), 2.75-0.85 (7H, m), 1.97 (3H, s), 1.05 (3H, d) ppm; ^{13}C NMR 171.5(s), 158.2(d, J_{C-H} = 233 Hz), 139.0(s) 133.1(s), 41.1(t), 35.4(t), 29.4(d), 27.3(t), 22.0(q), 15.2(q); IR (neat) 1760, 1745, 1210, 1180, 1120, 1070 cm^{-1}; mass spectrum 198 (M^+), 43 (100) m/e.

Oxidation of menthofuran 59 in different solvents. Menthofuran 59 (0.47 g, 3.1 mmol) in 30 mL benzene was oxidized with mCPBA (1.06 g, 6.2 mmol). The reaction mixture was worked up as above to

yield 0.49 g of 60 (86%). The spectral properties were identical to those reported above.

Menthofuran 59 (0.42 g, 2.8 mmol) in 20 mL ether was oxidized with mCPBA (.98 g, 5.7 mmol, technical grade). The reaction mixture was worked-up to yield 0.30g of a light yellow oil found to be ~85% 60 by NMR spectroscopy.

Menthofuran 59 (0.43 g, 2.8 mmol) in 20 mL acetone was oxidized with mCPBA (0.98 g, 5.7 mmol). The reaction mixture was worked up to yield 0.41 g of a yellow oil found to be approximately 60% 60 by NMR spectroscopy.

Menthofuran 59 (0.45 g, 3.0 mmol) 15 mL dimethylformamide was oxidized with mCPBA (1.04 g, 6.0 mmol). The reaction mixture was worked-up to yield 0.36 g of a bright yellow oil found to be approximately 5% 60 by NMR spectroscopy.

Synthesis of 1,2,3,4,5,6,7,8-Octahydrodibenzofuran

Preparation of 6-cyclohexenyl-1,4-dioxaspiro[4.5]decane 23. Following the procedure of Wenkert, cyclohexanone (94.2 g, 960 mmol, Baker) was placed in a flask and HCl(g) was bubbled through for 15 hours.[52] The solid product was collected on a filter, washed with 10% $NaHCO_3$ and water and then dried. This crude product was ketalized in 20 g batches without further purification. A solution of the ketochloride (20 g, 90 mmol), ethylene glycol (10 g, 160 mmol) and 0.2 g p-toluenesulfonic acid in toluene was refluxed with a Dean-Stark water trap for 15 hours. The reaction mixture was washed with water, 10% $NaHCO_3$, and brine and dried over $MgSO_4$. Removal of solvent

followed by distillation afforded 96.0g of 75 (90%) as a clear liquid: bp 90-92° (0.5 mmHg) [lit[51] bp 85-89° (0.2mm Hg)]; ^{1}H NMR[51] 5.52 (1H, br s), 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, 930 cm^{-1}; mass spectrum 222 (M^{+}), 99 (100) m/e.

Preparation of 6-(1,2-epoxycyclohexyl)-1,4-dioxaspiro[4.5]-decane 76. To a stirred solution of mCPBA (10.1 g, 50 mmol, technical grade) in 275 mL methylene chloride at 0° was added $NaHCO_3$ (6.0 g) and then ketal alkene 75 (7.1 g, 32 mmol). The reaction mixture was placed in a refrigerator overnight. It was then washed with 10% $Na_2S_2O_3$, 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent gave 6.9g of 76 (95%) as a clear oil: ^{1}H NMR[51] 4.0-3.8 (4H, m), 3.2-3.0 (1H, m), 2.0-1.0 (17H, m) ppm.

Preparation of 1,2,3,4,5,6,7,8-octahydrodibenzofuran 77. To a vigorously stirred solution of ketal epoxide 76 in 100 mL pentane was added 50 mL 2M HCl. Stirring was continued for four hours and the layers were then separated. The aqueous layer was extracted several times with pentane. The combined pentane layers were washed with 10% $NaHCO_3$ and brine and dried over K_2CO_3. Removal of solvent gave a yellow oil whch was chromatographed on silica gel. Elution with pentane gave 2.10g of 77 (69%) as a clear oil: ^{1}H NMR[51] 2.60-2.50 (4H, m), 2.35-2.26(4H, m), 1.87-1.65 (8H, m) ppm; IR[51] 1600, 1445, 1150, 1130, 955, 900, 860 cm^{-1}.

Oxidation of 1,2,3,4,5,6,7,8-Octahydrodibenzofuran

Oxidation of perhydrobidenzofuran 77 with two equivalents of mCPBA. To a stirred solution of mCPBA (0.95g, 5.5mmol) in 25 mL methylene chloride at 0° was added $NaHCO_3$ (0.7 g) and then a solution of 77 (0.48 g, 2.7 mmol) in methylene chloride (10 mL). The reaction mixture was stirred for 15 minutes. The mixture was washed with 10% $Na_2S_2O_3$, twice with 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent afforded a white solid which was recrystallized from 10% hexane in methylene chloride to yield 0.53 g of 78 (92%) as a white solid: mp 111.5-112.5°; ^1H NMR 2.66-2.58 (2H, m), 2.59-2.51 (2H, m), 2.48-2.38 (4H, m), 2.0-1.5 (8H, m) ppm; ^{13}C NMR 201.5(s), 172.3(s), 150.6(s), 125.7(s), 42.6(t), 33.2(t), 29.6(t), 28.8(t), 27.1(t), 25.2(t), 24.7(t), 23.1(t) ppm; IR (KBr pellet) 1750, 1690, 1660, 1190, 1130, 1020, 680 cm^{-1}; mass spectrum 208 (M^+), 125 (100) m/e. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.11; H,7.67.

X-ray structural determination of 78. Crystals of 78 were obtained by slow evaporation of a 10% hexane in methylene chloride solution. The density of the crystals was determined by suspending a sample in a mixture of carbon tetrachloride-hexane and determining the density of the solution. The value measured by this method was 1.27 g/cm^3. A specimen suitable for analysis was mounted in a capillary. The structure was determined at Nicolet XRD Corporation, Cupertino, California.

X-ray data collection was carried out on a Nicolet R3m automated diffractometer equipped with a Cu target X-ray tube (λ = 1.548 Å) and a graphite crystal monochromator. Unit cell constants were determined to be a = 6.717(1), b = 14.963(2) and c = 10.923(2)Å and β = 95.46(1)° for a cell of monoclinic symmetry. Systematic absences of 0k0 (h = 2n+1) and h01 (h+1 = 2n+1) indicated the space group to be $P2_1/n$ (nonstandard $P2_1/c$) which was confirmed by the successful solution and refinement of the structure. X-ray intensity data were measured for a total of 1117 independent reflections for $2\sigma \leq 100°$, of which 1077 were observed with $I \geq 3\sigma(I)$. The structure was solved by direct methods which revealed the location of all nonhydrogen atoms on the initial E map. The structure was refined to a final R value of 4.14% by full-matrix least-squares techniques with anisotropic thermal parameters for all nonhydrogen atoms. Hydrogen atoms were placed in idealized positions with isotropic thermal parameters. All structural determinations and refinements were carried out with the SHLXTL package on the Nicolet R3m crystallographic system. An experimental density measurement of 1.26 g/cm^3 agrees well with a calculated density of 1.27 g/cm^3 based on four molecules of $C_{12}H_{16}O_3$ in a unit cell with a volume of 1092.9 Å^3. The final difference map revealed no abnormal features. The crystal structure of 78 consists of discrete molecules with the geometry shown in Figure 5.

Oxidation of 77 with one equivalent of mCPBA. To a stirred solution of mCPBA (0.54 g, 3.1 mmol) in 20 mL methylene chloride at

0° was added a solution of 77 (0.55 g, 3.1 mmol) in methylene chloride. Stirring was continued for 15 minutes and the reaction mixture was then washed with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent gave 0.56 g of a yellow oil. Gas chromatographic (SE-30 column) analysis showed approximately 50% of the furan remained. ^{13}C NMR spectroscopy confirmed this and showed the predominant product to be 78 along with a small amount of side products.

Oxidation of 78 to 82. To a solution of mCPBA (0.09 g, 0.4 mmol, technical grade) in 10 mL methylene chloride at 0° was added $NaHCO_3$ (0.2 g) and then 78 (0.081 g, 0.4 mmol). The reaction mixture was maintained at 0° for four hours. The mixture was then washed with 10% $Na_2S_2O_3$, 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent afforded 0.085 g of 82 (97%) as a white solid: ^1H NMR 2.7-2.2 (8H, m); 2.1-1.6 (8H, m); ^{13}C NMR 171.9, 138.7, 33.8, 28.3, 27.7, 23.0 ppm; IR ($CHCl_3$) 1755, 1685, 1205, 1170, 1125, 1090, 1030 cm^{-1}; mass spectrum 224 (M^+), 125 (100).

Synthesis and Oxidation of 3-Methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O

Preparation of 1,4-dioxaspiro[4.5]decane-6-carboxylic acid 90. A solution of ketal esters 53 (5.02 g, 24 mmol) in 25 mL 5M NaOH was refluxed for six hours. The solution was cooled, acidified with aqueous HCl (pH~2) and extracted several times with ether. The combined extracts were dried over $MgSO_4$. Removal of solvent followed by recrystallization from benzene gave 4.17g of 90 (93%) as a white solid: mp 99.5-100.5 [lit[82] mp 73° (ethanol-water)]; ^1H NMR 10.7 (1H, br s), 4.1-4.0 (4H, m), 2.7 (1H, dd), 2.05-1.2 (8H, m) ppm; ^{13}C

NMR 176.3(s), 108.9(s), 64.9(t), 64.5(t), 49.6(d), 34.2(t), 27.1(t), 23.3(t), 23.0(t) ppm; IR[82] ($CHCl_3$) 3050(br), 1750, 1720, 1210, 1165, 1145, 1090, 1050, 930 cm^{-1}; mass spectrum 186 (M^+), 99 (100) m/e.

Preparation of 6-acetyl-1,4-dioxaspiro[4.5]decane 91. To a vigorously stirred solution of ketal acid 90 in 250 mL ether at 0° under a nitrogen atmosphere was added dropwise a solution of CH_3Li 38 mL, 59 mmol, Aldrich 1.55 M in ether) in ether (70 mL).[60] The addition was complete in two hours, the ice bath was then removed and stirring was continued for ten hours. The reaction mixture was hydrolyzed in 50 mL aliquots by dropwise addition to vigorously stirred 25 mL portions of ice-water. The layers were separated and the aqueous portion extracted several times with ether. The combined ether layers were washed with brine and dried over $MgSO_4$. (The aqueous layer was acidified and extracted to reclaim 1.16 g of unreacted acid.) Removal of solvent afforded a light yellow oil which was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane gave 3.04 g of 91 (79% based on recovered acid) as a clear oil: ^1H NMR 4.0-3.8 (4H, m), 2.81 (1H, dd), 2.23 (3H, s), 2.0-1.2 (8H, m) ppm; ^{13}C NMR 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) 1710, 1450, 1360, 1230, 1155, 1090, 1040, 955, 930 cm^{-1}; mass spectrum 184 (M^+), 99 (100) m/e. A sample for elemental analysis was prepared by preparative gas chromatography (SE-30 column). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.10; H, 8.66.

Preparation of 6-acetyl-^{18}O-1,4-dioxaspiro[4.5]decane 91a. A solution of ketal ketone 91 (0.56 g, 3.0 mmol), 60 μL H_2O (99% ^{18}O, Stohler Isotope Chemicals) and 1μL concentrated aqueous HCl in 1.3 mL of tetrahydrofuran (sufficient to solubilize) was allowed to stand for 1.25 hours. The reaction was quenched by pouring into 30 mL of methylene chloride and washing with 10% $NaHCO_3$ and brine and drying over K_2CO_3. Removal of solvent afforded 0.51 g of 91a (92%) as a clear oil: ^{13}C NMR as above. The carbonyl carbon resonance at 209.4 was resolved into two lines with the upfield resonance ($C^{18}O$) shifted by 0.051 ppm. Comparison of the relative intensities of these lines showed 54% incorporation of ^{18}O. IR (neat) 1710 ($C^{16}O$), 1685 ($C^{18}O$) cm^{-1}. Mass spectral analysis showed 55% incorporation of ^{18}O.

Preparation of 6-(2-methyloxirane-^{18}O)-1,4-dioxaspiro[4.5]decane 56a. Following the procedure of Corey, NaH (0.26 g, 5.4 mmol, 50% dispersion in mineral oil, Baker) was placed in a two necked flask and washed three times with petroleum ether (30-60°).[62] The final traces of petroleum ether were removed under aspirator vacuum, the flask flushed with nitrogen and then maintained under a nitrogen atmosphere. Dimethylsulfoxide (3.3 mL, freshly distilled from CaH_2) was added and the reaction mixture was heated to 70-75° until the evolution of hydrogen ceased (approximately 30 minutes). The flask was cooled to room temperature and tetrahydrofuran (3.3 mL) was added. The stirred reaction mixture was then cooled to -10° and a solution of trimethylsulfonium iodide (1.11 g, 5.4 mmol) in dimethylsulfoxide (5 mL) was added over a period of 2.5 minutes. After an additional

minute at -10°, a solution of labeled ketal ketone 91a (0.50 g, 2.7 mmol) in THF (0.4 mL) was added. The reaction mixture was then stirred at -10° for ten minutes and room temperature for one hour. The reaction mixture was poured into water and extracted several times with ether. The combined extracts were washed with brine and dried over K_2CO_3. Removal of solvent afforded 0.50 g of 56a (92%) as a light yellow oil which was found to be a mixture of diastereomers: ^1H NMR spectroscopy showed this mixture to be approximately 85% of the major diastercomer as reported for 56. ^{13}C NMR: the major diastereomer showed resonances at 56.4(s) and 55.8(t) ppm. The resonance at 56.4 ppm was resolved into two lines with the upfield ($C^{18}O$) line shifted by .042 ppm (48% ^{18}O). The resonance at 55.8 ppm was also resolved with the $C^{18}O$ line shifted by .030 ppm (48% ^{18}O). The minor diastereomer showed resonances at 56.7(s) and 52.1(t) ppm which exhibited similar chemical shifts for the labeled material and similar values for isotope incorporation. IR as above.

Preparation of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 57a. To a vigorously stirred solution of labeled ketal oxirane 56a (0.50 g, 2.5 mmol) in 40 mL pentane was added 20 mL 1M aqueous HCl. Stirring was continued for 2.25 hours and the layers were then separated. The aqueous layer was extracted four times with pentane. The combined pentane layers were washed with 10% $NaHCO_3$ and brine and dried over K_2CO_3. Removal of solvent and chromatography on silica gel yielded 0.30 g of 57a (87%) as clear oil: ^1H NMR and ^{13}C NMR as above. In the ^{13}C NMR analysis, the resonance at 150.9 ppm was resolved into two

peaks with the upfield peak shifted by 0.039 ppm (46% ^{18}O). The resonance at 136.7 ppm was resolved similarly with the upfield line shifted by 0.036 ppm (47% ^{18}O). Mass spectral analysis showed 48% ^{18}O incorporation.

Oxidation of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 57a. To a stirred solution of 57a (0.144 g, 1.1 mmol) in 20 mL methylene chloride was added $NaHCO_3$ (0.2 g). The mixture was cooled to 0° and then was added, in one portion, mCPBA (0.456 g, 2.2 mmol, technical grade). Stirring was continued ten minutes at 0°. The reaction mixture was washed with 10% $Na_2S_2O_3$, 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent afforded 0.152 g of 58a (85%) as a clear oil: ^1H NMR as above; ^{13}C NMR as above. High resolution ^{13}C NMR analysis of the resonances at 189.8, 164.8 and 123.9 ppm showed them all to be single lines in the ^1H decoupled spectrum. However, the resonance at 170.7 ppm was resolved into two lines with the upfield resonance ($C^{18}O$) shifted by 0.040 ppm (41% ^{18}O). IR (neat) 1755 ($C^{16}O$), 1715 ($C^{18}O$) cm^{-1}. Mass spectral analysis showed 42% isotope incorporation.

Synthesis and Oxidation of 1,2,3,4,5,6,7,8-Octahydrodibenzofuran-^{18}O

Preparation of 2-(2-oxocyclohexyl)-cyclohexanone 96. Following the procedure of Brown, to a stirred suspension of $NaBH_4$ (1.72 g, 45 mmol, pulverized prior to use) in 50 mL tetrahydrofuran containing ketal alkene 75 (22.21 g, 100 mmol) at room temperature was added dropwise a solution of boron triflouride etherate (8.72 g, 61 mmol, freshly distilled from calcium hydride, Baker) in tetrahydrofuran

(10 mL).[83] The addition was complete in one hour and the reaction mixture was then stirred an additional hour. At this point 16 mL of 3M NaOH was added and the product then oxidized by dropwise addition of 16 mL 30% H_2O_2 over a period of one hour. The reaction mixture was poured into water and extracted several times with ether. The combined extracts were washed with water and brine and dried over K_2CO_3. Removal of solvent gave 24.95 g of a crude yellow oil: ^{13}C NMR 110.3, 70.2, 64.7, 64.3 ppm; IR (neat) 3400 cm^{-1}. The alcohol was oxidized without further purification.[84] The crude alcohol was dissolved in 150 ml of acetone and cooled to 0°. A solution of Jones reagent (350 mmol, prepared by dissolving 35 g CrO_3 in 250 mL of water and adding 30 mL concentrated H_2SO_4) was added dropwise with stirring over a period three hours keeping the temperature below 5°. After the addition was complete, the reaction mixture was stirred two hours at room temperature. A small amount of sodium bisulfite was added to discharge the brown color of chromic acid from the upper layer. The layers were separated and the lower (aqueous) layer extracted three times with petroleum ether (35-60°). These extracts were combined with the original upper layer and they were washed twice with 10% $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed to yield a yellow oil which was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane afforded 9.89 g of 96 (51%) as a clear oil. This material was found to be a mixture of diasteromers as noted in the literature.[65] Initially this material was composed of 90% of the material reported as an oil: ^{13}C NMR 210.8(s), 50.3(d), 41.9(t), 29.1(t), 26.5(t), 25.0(t) ppm; TLC on silica gel, R_f = 0.22

[hexane-ether (1:1)]. Upon standing at 0°, the material slowly isomerized to the material reported as a solid: ^{13}C NMR 211.8(s), 49.0(d), 42.4(t), 30.2(t), 28.1(t), 25.5(t) ppm; TLC on silica gel R_f = 0.27 [hexane-ether (1:1)]. Mixture of diastereomers: IR (neat) 1705, 1450, 1310, 1220, 1130, 1025, 835 cm^{-1}; mass spectrum 194 (M^+), 98 (100) m/e.

Preparation of 2-(2-oxocyclohexyl-^{18}O)-cyclohexanone-^{18}O 96a. A solution of diketone 96 (0.57 g, 2.9 mmol), 117 μL of H_2O (99% ^{18}O, Stohler Isotope Chemicals) and 2μL of concentrated aqueous HCl in 2 mL tetrahydrofuran (sufficient to soluibilize) was allowed to stand for 22 hours. The solution was poured into 10 mL water and extracted several times with hexane. The combined extracts were washed with 10% $HaHCO_3$ and brine and dried over K_2CO_3. Removal of solvent afforded 0.56 g of 96a (98%) as a clear oil: ^1H NMR (mixture of diastereomers) 2.98-2.82(m), 2.7-2.6(m), 2.5-2.3(m), 2.2-1.2(m); ^{13}C NMR as above. The resonances at 211.8 and 210.8 ppm were both resolved into two lines with the upfield resonance in each case shifted by .053 ppm (52% ^{18}O). IR 1705 ($C^{16}O$), 1670 ($C^{18}O$) cm^{-1}. Mass spectral analysis showed 54% incorporation of ^{18}O.

Preparation of perhydrodibenzofuran-^{18}O 77a. Labeled diketone 96a (0.40 g, 2.0 mmol) was placed in a one mL flask. Two drops of concentrated H_2SO_4 were added and the flask heated to 130° under aspirator vacuum for ten minutes. The product was collected at 0° as it distilled. The reaction mixture was then washed with hexane and

the distilled product was dissolved in hexane. These combined solutions were washed with 10% $HaHCO_3$ and brine and dried over K_2CO_3. Removal of solvent yielded 0.31 g of 77a (85%) as a light yellow oil: ^1H NMR and IR as above; ^{13}C NMR 148.4(s), 116.9(s), 23.4(t), 23.3(t), 23.2(t), 20.7(t) ppm. The resonance at 148.4 ppm was resolved into two peaks with the upfield peak shifted by 0.039 ppm. Comparison of relative intensities of these resonances showed 39% ^{18}O incorporation. Mass spectral analysis showed 41% incorporation of ^{18}O.

Oxidation of perhydrodibenzofuran-^{18}O 77a. To a stirred solution of mCPBA (0.76 g, 4.4 mmol) in 20 mL methylene chloride at 0° was added a solution of 77a (0.38 g, 2.2 mmol) in methylene chloride (10 mL). After stirring for an additional ten minutes, the reaction mixture was washed with 10% $Na_2S_2O_3$, twice with 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent gave 0.37 g of 78a (82%) as a white solid: ^{13}C NMR as above. The resonance at 201.5 ppm was resolved into two lines with the upfield resonance shifted by 0.050 ppm. Comparison of the intensities of these lines showed 20% ^{18}O incorporation at this point. In a similar manner the resonance at 172.3 ppm was resolved with the upfield resonance shifted by 0.040 ppm. Analysis showed 20% ^{18}O incorporaton at this site also. Mass spectral analysis showed 39% ^{18}O incorporation.

Attempted Syntheses of Enediones

Attempt to prepare enedione dervied from perhydrodibenzofuran 77 by photooxidation of 77. Following the procedure of Foote, a solution of 77 (1.00 g, 5.7 mmol) and 35 mg rose bengal in 35 mL methanol

was photolysed while oxygen was bubbled through the system.[4] After 30 minutes, analysis by TLC showed no remaining furan. The methanol was removed and the residue was recrystallized from petroleum ether (35-60°). Filtration afforded 1.21 g of 100 (89%) as a white solid: mp 98-100° [lit[4] mp 101°]; ^{1}H NMR 8.38 (1H, br s), 3.26 (3H, s), 2.6-1.0 (16H, m) ppm; ^{13}C NMR 134.8(s), 131.4(s), 113.1(s), 109.7(s), 50.3(q), 37.1(t), 35.0(t), 26.9(t), 26.7(t), 23.8(t), 23.6(t), 23.0(t), 22.9(t) ppm; IR ($CHCl_3$) 3400, 1460, 1170, 1120, 1040, 1000, 965, 940, 905 cm^{-1}. An attempt was made to reduce this compound with triphenylphosphine. To a stirred solution of 100 (1.20 g, 5.0 mmol) in 20 mL ether was added slowly a solution of triphenylphosphine (1.30 g, 5.3 mmol) in 30 mL ether. After standing one hour the solution was concentrated. Analysis of the mixture by ^{13}C NMR spectroscopy showed only one small resonance in the carbonyl region (207 ppm). This material was chromatographed on silica gel. Triphenylphosphine oxide was isolated but no compounds of interest were recovered.

Attempt to prepare enedione derived from perhydrodibenzofuran 77 by selenium dioxide oxidation of diketone 96 in ethanol. A solution of diketone 96 (0.25 g, 1.3 mmol) and SeO_2 (0.40 g, 3.6 mmol) in 75 mL absolute ethanol was refluxed for seven hours.[67] The reaction mixture was concentrated to approximately 10 mL, poured into water, and extracted several times with ether. The combined extracts were washed with 10% $NaHCO_3$ and brine and dried over K_2CO_3. Removal of solvent

gave 0.24 g of a white solid shown to be unreacted starting material 96 by ^{13}C NMR spectroscopy.

Attempt to prepare enedione derived from perhydrodibenzofuran 77 by selenium dioxide oxidation of diketone 96 in acetic acid. A solution of diketone 96 (0.49 g, 2.5 mmol) and SeO_2 (0.29 g, 2.6 mmol) in 30 mL acetic acid was refluxed for 30 minutes.[67] The mixture turned a bright red during this reflux period. The solution was cooled and then poured into water. The aqueous solution was extracted several times with methylene chloride and the combined extracts were washed with 10% $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of solvent gave 0.50 g of a red oil. This material was chromatographed on silica gel and elution with hexane-ethyl acetate in varying proportions afforded several fractions. Material eluted with hexane was found to contain perhydrodibenzofuran 77 by NMR spectroscopy. No other material appeared to account for more than 5% of the reaction mixture. This was not pursued further.

Attempt to prepare enedione derived from 3-Methyl-4,5,6,7-tetrahydrobenzofuran. Preparation of 2-(1-methylethylidene)-cyclohexanone 101. Following the procedure of Mukherji, a solution of ketal-alcohol 54 (14.59 g, 73 mmol) and five drops concentrated aqueous HCl in 20 mL methanol and 150 mL water was refluxed for two hours.[68] The solution was cooled, poured into water and extracted several times with ether. The combined extracts were washed with 10% $NaHCO_3$ and brine and dried over K_2CO_3. Removal of solvent followed by distillation from a crystal of iodine gave 9.95 g of 101 (89%) as a clear liquid: bp 78-80°

(10 mmHg) [lit[84] bp 120-125° (20 mmHg); ^{1}H NMR 2.52-2.42 (2H, m), 2.42-2.35 (2H, m), 1.97 (3H, s), 1.90-1.65 (4H, m), 1.75 (3H, s) ppm; ^{13}C NMR 204.3(s), 142.1(s), 132.6(s), 42.5(t), 29.9(t), 24.6(t), 24.6(t), 23.0(q), 22.0(q) ppm; IR (neat) 1680, 1610, 1445, 1370, 1290, 1220, 1140, 1070, 990, 830 cm^{-1}. An attempt was made to brominate this compound using N-bromosuccinimide. A solution of ketoalkene 101 (1.00 g, 7.2 mmol) and NBS (1.34 g, 7.5 mmol, Eastman Organic Chemicals) in 200 mL carbon tetrachloride was allowed to stand for one week. During this time the solution turned light orange and a white precipitate formed. The solution was filtered and the solvent removed. A ^{13}C NMR spectrum of the reaction mixture showed it to consist of numerous products. These were not isolated or further identified.

Oxidation of ketoalkene 101 to epoxide 103. To a solution of mCPBA (0.78 g, 3.8 mmol technical grade) in 30 mL methylene chloride at 0° was added ketoalkene 101 (0.50 g, 3.6 mmol). The reaction mixture was maintained at 0° for 30 minutes. At this point, only a faint precipitate of m-chlorobenzoic acid was observed. The reaction mixture was therefore allowed to warm. After five hours at room temperature, the reaction was worked-up by washing with 10% $Na_2S_2O_3$, twice with 5% NaOH and brine and drying over $MgSO_4$. Removal of solvent afforded 0.55 g of 103 (98%) as a clear liquid: ^{1}H NMR 2.70-2.58 (2H, m), 2.32-1.70 (6H, m), 1.44 (3H, s), 1.22 (3H, s) ppm; ^{13}C NMR 207.2(s), 70.6(s), 63.2(s), 43.4(t), 31.5(t), 26.3(t), 24.6(t), 19.8(q), 19.5(q) ppm; IR (neat) 1715, 1360, 1115, 885, 785 cm^{-1}.

Oxidation of ketoalkene 101 and menthofuran 59 with one equivalent of mCPBA. To a stirred solution of ketoalkene 101 (0.50 g, 3.6 mmol) and menthofuran 59 (0.54 g, 3.6 mmol) in 30 mL methylene chloride at 0° was added, in one portion, mCPBA (0.78 g, 3.8 mmol, technical grade). Stirring was continued for ten minutes. The reaction mixture was washed twice with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent gave 1.02 g of a clear liquid. Analysis by gas chromatography (SE-30 column) showed a substantial amount of menthofuran had reacted but there was no evidence for epoxide 103. ^{13}C NMR spectroscopy showed resonances for menthofuran 59, the ε-lactone 60 and ketoalkene 101.

Studies With 2,5-Dimethylfuran

Oxidation of 2,5-dimethylfuran 3 with one equivalent of mCPBA. Following the procedure of LeGoff, to a solution of 2,5-dimethylfuran 3 (1.01 g, 11 mmol) in 55 mL methylene chloride at 0° was added, in one portion, mCPBA (2.34 g, 11 mmol, technical grade).[24] The flask was swirled and allowed to warm to room temperature. After standing for 11 hours, the reaction mixture was washed three times with 10% $NaHCO_3$ and brine and dried over Na_2SO_4. Removal of solvent afforded 1.10 g of cis-hexene-2,5-dione 44 (93%) as a light yellow liquid: ^{13}C NMR 200.8, 135.9, 29.8 ppm.

Oxidation of 2,5-dimethylfuran 3 with two equivalents of mCPBA. To a solution of 2,5-dimethylfuran (0.20 g, 2.1 mmol, Aldrich) in 12 mL methylene chloride at 0° was added, in one portion, mCPBA (0.93 g, 4.6 mmol technical grade). The flask was swirled and allowed

to warm to room temperature. After 11 hours, the reaction mixture was worked-up as above to yield 0.22 g of cis-hexene-2,5-dione 44 (94%) as a light yellow oil: ^{13}C NMR 200.6, 135.9 and 29.8 ppm.

Oxidation of 2,5-dimethylfuran 3 with two equivalents of mCPBA in refluxing chloroform. A solution of 2,5-dimethylfuran 3 (0.20 g, 2.1 mmol, Aldrich) and mCPBA (0.93 g, 4.6 mmol, technical grade) in 25 mL chloroform was refluxed for 24 hours. The solution was cooled, washed three times with 10% $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of solvent gave 0.25 g of a viscous oil. Analysis by NMR spectroscopy showed this to be a mixture of two products. Approximately 80% was identified as trans-hexene-2,5-dione: ^1H NMR 6.80 (1H, s), 2.38 (3H, s) ppm; ^{13}C NMR 198.6, 138.0, 28.0 ppm. The other product (20%) was identified as an epoxide: ^1H NMR 2.38 (1H, s), 2.13 (3H, s) ppm; ^{13}C NMR 202.4, 57.6, 24.2 ppm.

Synthesis of 2-Methyl-4,5,6,7-tetrahydrobenzofuran

Preparation of N-cyclohexylidenecyclohexylamine 107. A solution of cyclohexanone (20.0 g, 204 mmol, Baker) and cyclohexylamine (20.2 g, 204 mmol, Aldrich) in 150 mL ether was allowed to stand over 4 Å molecular sieves for 12 hours. Filtration and removal of solvent followed by distillation afforded 35.4 g of 107 (97%) as a white solid: bp 113-115° (8 mmHg) [lit[85] bp 121-123.4° (10 mmHg)]; mp 23-24°, ^1H NMR[85] 3.4-3.2 (1H, m), 2.4-2.2 (4H, m), 1.9-1.0 (16H, 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[85] (neat)

1660, 1450, 1350, 1230, 1000, 955, 890 cm^{-1}; mass spectrum[85] 193 (M^+), 98 (100) m/e.

Preparation of 2-(2-chloroprop-2-enyl)-cyclohexanone 108. Following the procedure of Stork, a solution of EtMgBr in tetrahydrofuran was prepared under nitrogen by dropwise addition of a solution of ethyl bromide (17.60 g, 161 mmol, Baker) in tetrahydrofuran (100 mL) to magnesium turnings (3.93 g, 161 mmol).[70] The addition was complete in 30 minutes and the reaction mixture was refluxed an additional hour. The resulting yellow-grey solution was allowed to cool to room temperature and a solution of the imine 107 (28.88 g, 149 mmol) in tetrahydrofuran (100 mL) was added with stirring over a 15 minute period. The solution was again refluxed for one hour. The resulting burgundy reaction mixture was again allowed to cool and to this stirred mixture was added a solution of 2,3-dichloropropene (17.91 g, 161 mmol, Aldrich) in tetrahydrofuran (50 mL) over a 15 minute period. The reaction mixture was then refluxed for 12 hours. The resulting yellow solution was cooled and then hydrolyzed by addition of 100 mL of 2M aqueous HCl. The mixture was extracted several times with ether. The combined extracts were washed with 10% $NaHCO_3$, water and brine and dried over K_2CO_3. Removal of solvent followed by distillation yielded 15.83 g of 108 (57%) as a clear liquid: bp 104-106° (10 mmHg) [lit[71] bp 86° (4 mmHg)]; ^1H NMR 5.18 (2H, d), 2.91 (1H, dd), 2.7 (1H, d), 2.5-2.3 (2H, m), 2.3-2.05 (3H, m), 1.95-1.8 (1H, m), 1.8-1.55 (2H, m), 1.38-1.20 (1H, m) ppm; ^{13}C NMR 210.8(s), 140.5(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 137 (M^+-Cl, 100), 93, 67, 55, 41, 39 m/e.

Preparation of 2-methyl-4,5,6,7-tetrahydrobenzofuran 109. Following the procedure of Nienhouse, to 15 mL vigorously stirred 90% H_2SO_4 with nitrogen bubbled through at 0° was added dropwise chloroketone 108 (6.58 g, 38 mmol).[71] The addition was complete in 30 minutes and the reaction mixture was stirred an additional hour. The reaction mixture was then poured into 150 mL ice-water and this was extracted several times with hexane. The comined extracts were washed with 10% $NaHCO_3$ and brine and dried over K_2CO_3. Removal of solvent afforded a crude yellow liquid which was chromatographed on silica gel. Elution with pentane gave 4.50 g of 109 (87%) as a clear oil: bp 67-69° (10 mmHg) [lit bp 77-79° (17 mmHg); ^1H NMR 5.78 (1H, br S), 2.6-2.5 (2H, m), 2.45-2.3 (2H, m), 2.27 (3H, s), 1.9-1.65 (4H, m) ppm; ^{13}C NMR 149.8(s), 149.0(s), 117.6(s), 106.5(d), 23.4(t), 23.4(t), 23.2(t), 22.3(t), 13.5(q) ppm. In a ^1H coupled ^{13}C NMR spectrum at high resolution the resonances at 149.8 and 149.0 ppm both appear as multiplets. Specific proton decoupling of the resonance at 5.78 ppm collapses the peak at 149.8 ppm into a quartet ($^2J_{C-H}$ = 10 Hz). Similarly, irradiation of the methyl resonance at 2.27 ppm collapses the signals at 149.8 ppm into a doublet ($^2J_{C-H}$ = 7Hz); IR[71] (neat) 1580, 1450, 1260, 1225, 1130, 960, 915, 790 cm^{-1}; mass spectrum 136 (M^+), 108 (100) m/e.

Oxidation of 2-Methyl-4,5,6,7-tetrahydrobenzofuran

Oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran 109 with two equivalents of mCPBA. To a stirred solution of mCPBA (3.69 g, 21.4 mmol) in 50 mL methylene chloride was added $NaHCO_3$ (0.5 g) and then a solution of 109 (1.5 g, 10.7 mmol) in methylene chloride (10 mL). The reaction mixture began a gently reflux within seconds and a flocculent precipitate of m-chlorobenzoic acid formed within one minute. Stirring was continued for ten minutes at 0°. The reaction mixture was then washed with 10% $Na_2S_2O_3$, 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent gave 1.74 g of a yellow oil found to be a mixture by NMR spectroscopy. Further analysis of the mixture in conjunction with these spectra showed the products of this reaction to be enedione 110 (20%), aldehyde 111 (45%), formate 112 (20%) and another product tentatively identified as epoxide 113 (15%). Chromatography on silica gel allowed separation of this mixture.

The product arising from oxidation with one equivalent of mCPBA was identified as enedione 110: ^1H NMR 5.97 (1H, br s), 2.65-2.50 (4H, m), 2.22 (3H, s), 2.00-1.80 (4H, m) ppm; ^{13}C NMR 204.6(s), 200.1(s), 150.1(s), 129.6(d), 43.2(t), 36.3(t), 29.7(q), 26.2(t), 26.2(t) ppm. Further analysis showed the ^{13}C resonance at 200.1 ppm was coupled to the methyl hydrogens by 6Hz and to the olefinic proton by 4Hz and this resonance was therefore assigned to the carbonyl carbon of the acetyl group: IR (neat) 1690 (br), 1630, 1450, 1420, 1360, 1225, 1200, 1140, 1115, 1070, 1020, 980, 915, 825 cm^{-1}; mass spectrum 152(M^+), 109 (100) m/e. A sample for elemental analysis was

prepared by bulb-to-bulb distillation: bp 93-99° (0.75 mmHg). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.89; H, 7.88. The product arising from the oxidation with two equivalents of mCPBA was identified as the aldehyde 111: bp 100-107° (0.8 mmHg); ^{1}H NMR 9.93 (1H, s), 2.50-2.35 (2H, m), 2.35-2.15 (2H, m); 2.24 (3H, s), 1.85-1.60 (4H, m) ppm; ^{13}C NMR 189.2 (d, J_{C-H} = 178 Hz), 168.6(s), 164.2(s), 126.7(s), 28.8(t), 22.1(t), 21.2(t), 21.1(t), 20.7(q) ppm; IR (neat) 2750, 1760, 1675, 1650, 1365, 1275, 1235, 1205, 1180, 1125, 1100, 1070, 1020, 920 cm^{-1}; mass spectrum 168 (M^+), 126 (100) m/e. The product arising from the oxidation with three equivalents of mCPBA was identified as the formate 112: ^{1}H NMR 8.01 (1H, s), 2.35-2.25 (4H, m), 2.13 (3H, s), 1.85-1.70 (4H, m) ppm; ^{13}C NMR 168.3(s), 158.6 (d, J_{C-H} = 229 Hz), 137.2(s), 136.1(s), 26.8(t), 26.6(t), 22.3(t), 22.3(t), 20.7(q) ppm; IR (neat) 1760 (br), 1450, 1435, 1370, 1220, 1200, 1170, 1120, 1090, 1075, 1015, 925, 915, 880 cm^{-1}; mass spectrum 184 (M^+), 43 (100). A sample for elemental analysis was prepared by preparative gas chromatography (Carbowax column). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.53; H, 6.77. A fourth product was tentatively identified formed from enedione 110 and having the structure of epoxide 113 ^{1}H NMR 3.4(s) ppm; ^{13}C NMR 204.2(s), 204.1(s), 67.2(s), 66.4(d), 42.6(t), 35.0(t), 27.6(q), 25.5(t), 23.9(t) ppm. This material was not obtained pure enough to allow further characterization.

Oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran 109 with one equivalent of mCPBA. To a stirred solution of 109 (1.03 g, 7.6 mmol) in 100 ml methylene chloride was added dropwise a solution of mCPBA (1.28 g, 7.6 mmol) in methylene chloride (40 mL). The addition required three hours. The reaction mixture was washed twice with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent yielded 1.13 g of a yellow oil which was chromatographed on silica gel. Elution with 1% ethyl acetate in hexane gave an oil shown by NMR spectroscopy to be a mixture of starting furan 109 and aldehyde 111. Elution with ethyl acetate afforded 0.89 g of enedione 110 (77%) as a yellow oil: spectral properties as above.

Oxidation of enedione 110 to aldehyde 111. To a stirred solution of mCPBA (0.61 g, 3.0 mmol technical grade) in 10 mL methylene chloride at 0° was added dropwise a solution of enedione 110 (0.45 g, 3.0 mmol) in methylene chloride (5 mL). Addition was complete in five minutes and the reaction mixture was then stirred for 15 minutes. The mixture was then washed twice with 5% NaOH and brine and dried over $MgSO_4$. The solvent was removed and the yellow oil chromatographed on silica gel. Elution with 1% ethyl acetate in hexane afforded 0.41 g of aldehyde 111 (82%) as a clear oil: spectral properties as above.

Oxidation of aldehyde 111 to formate 112. To a solution of aldehyde 111 (0.29 g, 1.7 mmol) in 10 mL methylene chloride was added in one portion mCPBA (0.30 g, 0.17 mmol). The flask was swirled and allowed to stand at room temperature for two hours. The reaction

mixture was washed twice with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent gave 0.28 g of formate 112 (91%) as a clear oil: spectral properties as above.

Oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran 109 with two equivalents of mCPBA added slowly. To a stirred solution of 109 in 20 mL methylene chlorie at 0° was added dropwise a solution of mCPBA (1.31 g, 7.6 mmol) in methylene chloride (30 mL). Addition was complete in 1.5 hours. The reaction mixture was washed twice with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent yielded a crude oil which was chromatographed on silica gel. Elution with 1% ethyl acetate in hexane gave 0.52 g of aldehyde 111 (80%) as a clear oil: spectral properties as above.

Oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran 108 with three equivalents of mCPBA. To a solution of 109 (0.30 g, 2.2 mmol) in 20 mL methylene chloride was added, in small portions, mCPBA (1.30 g, 7.5 mmol). The flask was swirled between additions and stored at 0° for 12 hours. The reaction mixture was washed twice with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent afforded 0.26 g of formate 112 (64%) as a clear oil: spectral properties as above.

Synthesis and Oxidation of 2-Methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O.

Preparation of 2-(2-chloroprop-2-enyl)-cyclohexanone-^{18}O 108a. A solution of chloroketone 108 (0.69 g, 4.0 mmol), 75 μL H_2O (99% ^{18}O, Stohler Isotope Company) and 2 μL concentrated aqueous HCl in

3 mL tetrahydrofuran (sufficient to solubilize) was allowed to stand at room temperature for 12 hours. The reaction mixture was poured into water and 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 yielded 0.65 g of 108a (94%) as a clear oil: ^1H NMR as above; ^{13}C NMR as above. The resonance at 210.8 ppm was resolved into two peaks with the upfield peak shifted by 0.053 ppm. Comparison of the intensities of these resonances showed 38% incorporaton of label. IR (neat) 1705 ($C^{16}O$), 1675 ($C^{18}O$) cm^{-1}. Mass spectral analysis showed 37% incorporation of ^{18}O.

Preparation of 2-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 109a. To the stirred labeled chloroketone 59a (.64 g, 3.7 mmol) at 0° under a nitrogen atmosphere was added 1.2 mL 90% H_2SO_4 (prepared using 120 μL of 97% ^{18}O H_2O, MSD Isotopes). The mixture was stirred for one hour at 0° and then poured into 15 mL of water. The aqueous mixture 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 followed by chromatography gave 0.37 g of 109a (74%) as a clear oil: ^1H NMR and IR as above; ^{13}C NMR as above. The resonance at 149.8 ppm was resolved into two lines with the upfield peak shifted by 0.041 ppm (12% ^{18}O). Similarly, the resonance at 149.0 ppm was resolved into two lines with the upfield line shifted by 0.039 ppm and again analysis showed 12% ^{18}O. Mass spectral analysis showed 14% incorporation of ^{18}O.

Oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 109a with one equivalent of mCPBA. To a stirred solution of 109a (0.37 g, 2.7 mmol) in 100 mL methylene chloride (dried by distillation from P_2O_5) was added dropwise a solution of mCPBA (0.46 g, 2.7 mmol) in methylene chloride (45 mL). After a three hour addition period, the reaction mixture was washed twice with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent yielded 0.37 g of a yellow oil. ^{13}C NMR spectroscopy showed the oil to consist of a mixture as before. The resonance at 200.1 ppm was resolved into two lines with the upfield resonance shifted by 0.050 ppm. Analysis showed 9% ^{18}O.

Oxidation of labeled enedione 110a to labeled aldehyde 111a. To a solution of labeled enedione 110a (0.35 g, 2.3 mmol) in 20 mL methylene chloride was added, in one portion, mCPBA (0.44 g, 2.6 mmol). The flask was swirled and then allowed to stand for 15 minutes. The reaction mixture was washed with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent afforded 0.37 g of a yellow oil. ^{13}C NMR as above. The resonance at 168.6 ppm was resolved into two lines with the upfield line shifted by 0.037 ppm (9% ^{18}O). Mass spectral analysis showed 10% incorporation of ^{18}O.

Synthesis and Oxidation of 2,3-Dimethyl-4,5,6,7-tetrahydrobenzofuran

Preparation of 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran 120. Following the procedure of Cohen, to a stirred solution of 3-methyl-4,5,6,7-tetrahydrobenzofuran 57 (1.58 g, 12 mmol) in 50 mL tetrahydrofuran at -20° (ice-$CaCl_2$ slush) under a nitrogen atmosphere was added, in one portion, a solution of n-butyl lithium (7.3 mL, 12 mmol, 1.6 M

in hexane, Aldrich).[72] The reaction mixture was stirred at -20° to -10° for 2.25 hours. To this yellow solution was added methyl iodide (1.80 g, 13 mmol, Baker). The reaction mixture was allowed to warm to room temperature and stirred for four hours. At this point, 25 mL of water was added and the mixture extracted three times with pentane-ether (1:1). The combined extracts were washed with 5% $NaHSO_3$, three times with water and brine and dried over K_2CO_3. Removal of solvent gave a yellow liquid which was chromatographed on silica gel. Elution with pentane afforded 1.67 g of a clear oil. Analysis by gas chromatography (SE-30 column) and ^1H NMR spectroscopy showed this material to contain 10% unreacted 3-methyl-4,5,6,7-tetrahydrobenzofuran 57 as well as the dimethylfuran 120. The yield of 69 was therefore 96%: ^1H NMR[87] 2.59-2.47 (2H, m), 2.37-2.25 (2H, m), 2.17 (3H, s), 1.83 (3H, s), 1.86-1.65 (4H, m) ppm; ^{13}C NMR 147.8(s), 144.8(s), 118.3(s), 113.7(s), 23.3(t), 23.3(t), 23.2(t), 20.8(t), 11.3(q), 8.0(q) ppm; IR[87] (neat) 1605, 1450, 1390, 1370, 1270, 1255, 1230, 1165, 1150, 1100, 905 cm^{-1}; mass spectrum[87] 150 (M^+), 122 (100) m/e.

Oxidation of 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran 120 with two equivalents of mCPBA. To a stirred solution of 120 (0.78 g, 5.2 mmol) in 50 mL methylene chloride at 0° was added dropwise a solution of mCPBA (1.78 g, 10.4 mmol) in methylene chloride (50 mL). This addition required 15 minutes and the reaction mixture was then stirred for ten minutes. The mixture was washed with 10% $Na_2S_2O_3$, twice with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent yielded 0.865 g of a clear oil. Analysis by NMR spectroscopy showed this

material to be 60% enol acetate 121 and 40% ε-lactone 122. This material was chromatographed on silica gel. Elution with hexane afforded 121 as a clear oil: ^{1}H NMR 2.40-2.25 (4H, m), 2.27 (3H, s), 2.21 (3H, s), 1.80-1.58 (4H, m) ppm; ^{13}C NMR 198.4(s), 168.5(s), 155.0(s), 126.1(s), 30.5(q), 28.8(t), 25.0(t), 22.3(t), 21.8(t), 21.3(q) ppm; IR (neat) 1760, 1695, 1600, 1430, 1370, 1285, 1260, 1215, 1160, 1110, 1075, 920, 735 cm^{-1}; mass spectrum 182 (M^{+}), 140, 125 43 (100) m/e; TLC on silica gel, R_f = 0.29 [hexane-ether (1:1)]. A sample for elemental analysis was prepared by preparative gas chromatography (SE-30 column). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.74; H, 7.69. Elution with 10% ethyl acetate in hexane afforded 122 as a clear liquid: ^{1}H NMR 2.65-2.58 (2H, m), 2.58-2.51 (2H, m), 2.37 (3H, s), 1.86 (3H, s), 2.00-1.77 (4H, m) ppm; ^{13}C NMR 200.2(s), 171.2(s), 154.5(s), 124.5(s), 33.7(t), 31.8(q), 31.1(t), 26.0(t), 23.3(t), 13.3(q) ppm; IR (neat) 1755, 1670, 1580, 1450, 1365, 1300, 1225, 1175, 1130, 1105, 1000, 915, 735 cm^{-1}; mass spectrum 182 (M^{+}), 140, 99 (100), 43 m/e; TLC on silica gel, R_f = 0.15 [hexane - ether (1:1)]. A sample for elemental analysis was prepared by chromatography on silica gel. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.76; H, 7.78.

Synthesis and Oxidation of 2,3-Dimethyl-4,5,6,7-tetrahydrobenzofuran-^{18}O

Preparation of 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 120a. To a stirred solution of 3-methyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 57a (0.50 g, 3.7 mmol, 44% ^{18}O) in 15 mL tetrahydrofuran at

-22° (carbon tetrachloride - dry ice slush) under a nitrogen atmosphere was added, in one portion, a solution of n-butyl lithium (3.3 mL, 5.3 mmol, 1.6M in hexane, Aldrich). The solution was stirred for four hours at -22° and then was added methyl iodide (1.14 g, 8.0 mmol, Baker). The reacton mixture was stirred an additional hour at -22° and then six hours at room temperature. The solution was poured into water and extracted several times with pentane-ether (1:1). The combined extracts were washed with 5% $NaHSO_3$, water and brine and dried over K_2CO_3. Removal of solvent followed by chromatography on silica gel yielded 0.42 g of 120a (75%) as a clear oil: ^1H NMR as above; ^{13}C NMR as above. The resonances at 147.8 and 144.8 ppm were both resolved into two lines with the upfield line shifted by 0.04 ppm. Comparison of the intensities of these resonances revealed 44% incorporation of label. Mass spectral analysis showed 45% incorporation of ^{18}O.

Oxidation of 2,3-dimethyl-4,5,6,7-tetrahydrobenzofuran-^{18}O 120a with two equivalents of mCPBA. To a stirred solution of 120a (0.39 g, 2.6 mmol) in 20 mL methylene chloride at 0° was added dropwise a solution of mCPBA (1.20 g, 5.9 mmol, technical grade) in methylene chloride (30 mL). The addition was complete in 30 minutes. The reaction mixture was then washed with 10% $Na_2S_2O_3$, twice with 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent gave a clear oil shown by analysis by NMR spectroscopy to be 50% 121a and 50% 122a. This material was then chromatographed on silica gel. Elution with hexane afforded 0.14 g of 121a as a clear oil: ^1H NMR as above; ^{13}C NMR as

above. The resonance at 168.5 ppm was resolved into three lines with one resonance shifted upfield by 0.010 ppm and the third resonance shifted upfield by 0.037 ppm. Comparison of the intensities of these lines showed 26% of the material to be associated with the resonance shifted by 0.010 ppm and 16% with the resonance shifted by 0.037 ppm. IR (neat) 1760 ($C^{16}O$), 1730 ($C^{18}O$) cm^{-1}. Mass spectral analysis showed 41% incorporation of ^{18}O. Elution with 10% ethyl acetate in hexane afforded 0.13 g of 122a as a clear oil: ^{1}H NMR as above; ^{13}C NMR as above. The resonance at 200.2 ppm was resolved into two lines with the upfield resonance shifted by 0.049 ppm (15% ^{18}O). Similarly the resonance at 171.2 ppm was resolved into two lines with the upfield resonance shifted by 0.040 ppm (26% ^{18}O). IR (neat) 1755 ($C^{16}O$), 1730 ($C^{18}O$) cm^{-1}. Mass spectral analysis showed 40% incorporation of ^{18}O.

Low Temperature ^{1}H NMR Experiment Monitoring the Reaction of 3-Methyl-4,5,6,7-tetrahydrobenzofuran with mCPBA

A solution of mCPBA (4.5 mg, 0.026 mmol) in 0.3 mL deuteriochloroform was placed in a 5 mm NMR tube and cooled in the probe to 230°K. The tube was removed and 3-methyl-4,5,6,7-tetrahydrobenzofuran 57 (2.2 μL, 0.015 mmol) was added. The tube was inverted and returned immediately to the probe. Sets of 12 acquisitions were accumulated per file with a delay of one minute between pulses. The first five sets of scans were acquired at 230° and the probe was warmed to 240° where two more sets were acquired. After this, a final set of 12

scans was acquired at 260°. These files were then trasformed to yield the set of spectra which were analyzed.

The first spectrum showed a substantial resonance at 5.60 ppm and another very small peak at 9.66 ppm as well as a diminished resonance for the furan proton at 7.0 ppm. In the second spectrum the resonances at 5.60 and 9.66 ppm were both larger and another resonance had appeared at 10.14 ppm. Again the resonance for the proton on the furan moiety was less intense. In the following spectra, the resonances at 5.60 and 9.66 ppm remained at relatively constant intensity and the resonance at 7.0 ppm decreased in intensity while that at 10.14 increased. When 80% of the mCPBA had reacted, as seen in the first spectrum at 240°, the resonance at 5.60 ppm began to decrease markedly in intensity. The next spectrum showed the resonance at 9.66 ppm to also be less intense. The resonance at 10.14 ppm continued to grow throughout the experiment.

REFERENCES

1. Weinberg, N. L.; Weinberg, R. H. Chem. Rev. 1968, 68, 449.

2. Elming, N. Advn. Org. Chem. 1960, 2, 67.

3. Feringa, B. L.; Butselaar, R. J. Tetrahedron Lett. 1982, 1941.

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

5. Wasserman, H. H.; Lipshutz, B. H. In "Singlet Oxygen"; Wasserman, H. H.; Murray, R. W., Eds.; Academic Press: New York, 1979; p. 429.

6. Dean, F. M. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Ed.; Academic Press: New York, 1982; Vol. 30, p. 167.

7. Adam, W.; Rodriguez, A. J. Am. Chem. Soc. 1980, 102, 404.

8. Adam, W.; Rodriguez, A. Tetrahedron Lett. 1981, 3509.

9. Lutz, R. E.; Welstead, W. J., Jr.; Bass, R. G.; Dale, J. I. J. Org. Chem. 1962, 27, 1111.

10. Boyer, R. F.; Lindstrom, C. G.; Darby, B.; Hylarides, M. Tetrahedron Lett. 1975, 4111.

11. Boeseken, J.; Vermij, C. O. G.; Bunge, H.; Van Meeuwen, C. Rec. Trav. Chim. 1931, 50, 1023.

12. Clauson-Kaas, N.; Fakstorp, J. Acta Chem. Scand. 1947, 1, 415.

13. Elming, N.; Clauson-Kaas, N. Acta Chem. Scand. 1952, 6, 535.

14. Catala, F.; Defaye, J. Compt. Rend. 1964, 258, 4094.

15. Plesnicar, B. In "Oxidation in Organic Chemistry. Part C"; Trahanovsky, W. S., Ed.; Academic Press: New York, 1978; p. 211.

16. Ferland, J. M.; Lefebvre, Y.; Deghenghi, R.; Wiesner, K. Tetrahedron Lett. 1966, 3617.

17. Lefebvre, Y. Tetrahedron Lett. 1972, 133.

18. Piancatelli, G.; Scettri, A.; D'Auria, M. Tetrahedron Lett. 1977, 2199.

19. Piancatelli, G.; Scettri, A.; D'Auria, M. Tetrahedron Lett. 1979, 1507.

20. Lavie, D.; Levy, E. C. Tetrahedron Lett. 1970, 1315.

21. Mangoni, L.; Adinolfi, M.; Laonigro, G.; Caputo, R. Tetrahedron 1972, 28, 611.

22. Takeda, K.; Minato, H.; Ishikawa, M.; Miyawaki, M. Tetrahedron 1964, 20, 2655.

23. Kuwajima, I.; Urabe, H. Tetrahedron Lett. 1981, 5191.

24. Williams, P. D.; LeGoff, E. J. Org. Chem. 1981, 46, 4143.

25. Tada, M. Chem. Lett. 1982, 441.

26. DeShong, P.; Ramesh, S.; Perez, J. J.; Bodish, C. Tetrahedron Lett. 1982, 2243.

27. Kingsbury, J. M. "Poisonous Plants of the United States and Canada"; Prentice-Hall: Englewood Cliffs, New Jersey, 1964.

28. Jennings, D. W.; Reeder, S. K.; Hurley, J. C.; Caughlan, C. N.; Smith, G. D. J. Org. Chem. 1974, 39, 3392.

29. Jennings, P. W.; Hurley, J. C.; Reeder, S. K.; Holian, A.; Lee, P.; Caughlan, C. N.; Larsen, R. D. J. Org. Chem. 1976, 41, 4078.

30. Holian, S. K.: M.S. Thesis, Montana State University, 1975.

31. Undenfriend, S.; Clark, C. T.; Axelrod, J.; Brodie, B. B. J. Biol. Chem. 1954, 208, 731.

32. Sharpless, K. B.; Flood, T. C. J. Am. Chem. Soc. 1971, 93, 2316.

33. Jerina, D. M.; Boyd, D. R.; Daly, J. W. Tetrahedron Lett. 1970, 457.

34. Kemal, C.; Bruice, T. C. Proc. Nat. Acad. Sci. USA 1976, 73, 995.

35. Jerina, D.; Daly, J.; Landis, W.; Witkop, B.; Undenfriend, S. J. Am. Chem. Soc. 1967, 89, 3347.

36. Baumstark, A. L.; Chrisope, D. R.; Landis, M. E. J. Org. Chem. 1981, 46, 1964.

37. Heggs, R. P.; Ganem, B. J. Am. Chem. Soc. 1979, 101, 2484.

38. Rebek, J.; McCready, R. Tetrahedron Lett. 1979, 4337.

39. Hanzlik, R. P.; Westkaemper, R. B. J. Am. Chem. Soc. 1980, 102, 2465.

40. Camps, F.; Coll, J.; Messeguer, A.; Pericas, M. A. Tetrahedron Lett. 1981, 3895.

41. Sato, T.; Tada, M.; Takahashi, T. Bull. Chem. Soc. Jpn. 1979, 52, 3129.

42. Peterson, Q. R.; Sowers, E. E. J. Org. Chen. 1964, 29, 1627.

43. Emmons, W. D.; Lucas, G. B. J. Am. Chem. Soc. 1955, 77, 2787.

44. House, J. O. "Modern Synthetic Reactions", 2nd Ed.; W. A. Benjamin, Inc.: New York, 1972; Chapter 6.

45. Foote, C. S.; Boyd, J. D.; Imagawa, D. K. J. Am. Chem. Soc. 1980, 102, 3641.

46. Borowitz, I. J.; Gonis, G.; Kelsey, R.; Rapp, R.; Williams, G. J. J. Org. Chem. 1966, 31, 3032.

47. Borowitz, I. J.; Williams, G. J.; Gross, L.; Rapp, R. J. Org. Chem. 1968, 33, 2013.

48. Grimminger, W.; Kraus, K. Liebigs Ann. Chem. 1979, 1571.

49. Wasserman, H. H.; Kitzing, R. Tetrahedron Lett. 1969, 5315.

50. Graziano, M. L.; Iesce, M. R.; Scarpat, R. J. Chem. Soc. Chem Comm. 1981, 720.

51. Creese, M. W.; Smissman, E. E. J. Org. Chem. 1976, 41, 169.

52. Wenkert, E.; Bhattacharya, S. K.; Wilson, E. M. J. Chem. Soc. 1964, 5617.

53. Bak, B.; Nielsen, J. T.; Schottlander, M. Acta Chem. Scand. 1962, 16, 771.

54. Pring, B. G.; Stjernstrom, N. E. Acta Chem. Scand. 1968, 538.

55. Marnett, L. J.; Bienkowski, M. J.; Pagels, W. R. J. Biol. Chem. 1979, 254, 5077.

56. Byrn, M.; Calvin, M. J. Am. Chem. Soc. 1966, 88, 1916.

57. Risley, J. M.; Van Etten, R. L. J. Am. Chem. Soc. 1979, 101, 252.

58. Vederas, J. C. J. Am. Chem. Soc. 1980, 102, 374.

59. Raines, W. T. "Nuclear Magnetic Resonance", Abraham, R. J., Ed.; Alden Press: Oxford, 1978; Vol. 7, p. 21.

60. Jorgenson, M. J. In "Organic Reactions"; Dauben, W. G., Ed.; Wiley: New York, 1970; Vol. 18, p. 1.

61. Benner, S. A.; Maggio, J. E.; Simmons, H. E., III. J. Am. Chem. Soc. 1981, 103, 1581.

62. Corey, E. J.; Chaykovsky, M. J. Am. Chem. Soc. 1965, 87, 1353.

63. Cornforth, J. W. J. Chem. Soc. 1958, 1310.

64. Bell, R. A.; Fetizon, M. Can. J. Chem. 1976, 54, 141.

65. Hawkins, E. G. E.; Large, R. J. Chem. Soc. Perkins I 1974, 280.

66. Smith, P. A. S. In "Molecular Rearrangements", De Mayo, P., Ed.; Wiley: New York, 1963; Part I, p. 457.

67. Barnes, C. S.; Barton, D. H. R. J. Chem. Soc. 1953, 1419.

68. Mukherji, S. M.; Gandhi, R. P.; Vig, O. P.; J. Indian Chem. Soc. 1956, 33, 853.

69. Handley, J. R.; Swigar, A.A.; Silverstein, R. M. J. Org. Chem. 1979, 44, 2954.

70. Stork, G.; Dowd, S. R. J. Am. Chem. Soc. 1963, 85, 2178.

71. Nienhouse, E. J.; Irwin, R. M.; Finni, G. R. J. Am. Chem. Soc. 1967, 89, 4557.

72. Nolan, S. M.; Cohen, T. J. Org. Chem. 1981, 46, 2473.

73. Dean, F. M. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Ed.; Academic Press: New York, 1982; Vol. 31, p. 237.

74. Srogl, J.; Janda, M.; Stibor, I.; Skala, V.; Trska, P.; Ryska, M. Collection Czechoslov. Chem. Commun. 1974, 39, 3109.

75. Stibor, I.; Trska, P.; Srogl, J.; Janda, M. Collection Czechoslov. Chem. Commun. 1978, 43, 2170.

76. John, I. G.; Radom, L. J. Am. Chem. Soc. 1978, 100, 3981.

77. Kuhn, L. P.; Lutz, R. E.; Bauer, C. R. J. Am. Chem. Soc. 1950, 72, 5058.

78. Friess, S. L.; Frankenburg, P. E. J. Am. Chem. Soc. 1952, 74, 2679.

79. Schwartz, N. N.; Blumbergs, J. H. J. Org. Chem. 1964, 29, 1976.

80. Tsuboi, S.; Shimozuma, K.; Takeda, A. J. Org. Chem. 1980, 45, 1517.

81. Minato, H.; Nagasaki, T. J. Chem. Soc. C. 1966, 377.

82. Plieninger, H.; Zeltner, M. Chem. Ber. 1975, 108, 3286.

83. Brown, H. C.; Murray, K. J.; Murray, L. J.; Snover, J. A.; Zweifel, G. J. Am. Chem. Soc. 1960, 82, 4233.

84. Meinwald, J.; Crandall, J.; Hymans, W. E. Org. Syn. 1965, 45, 77.

85. Jacobson, R. M.; Raths, R. A.; McDonald, J. H. III. J. Org. Chem. 1977, 42, 2545.

86. Morel, T.; Verkade, P. E. Rec. Trav. Chim. 1951, 70, 35.

87. Jacobson, R. M.; Abbaspour, A.; Lahn, G. P. J. Org. Chem. 1978, 43, 4650.

MONTANA STATE UNIVERSITY LIBRARIES
3 1762 10200123 5