FORMATION AND REACTIONS OF IPSO ADDUCTS FROM CHLORINATION OF 2-METHYL-2-ARYLOXYPROPANOIC ACIDS

by

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

ACCEPTED
FACULTY OF GRADUATE STUDIES

DOCTOR OF PHILOSOPHY

_____ DEAN
DATE 1990-09-25

in the Department of Chemistry

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ABSTRACT

Chlorination of 2-methyl-2-aryloxypropanoic acids with aqueous hypochlorous acid gives spiro chloro adducts in moderate to high yields. In chlorination of 2-methyl-2-(2-methylphenoxy)propanoic acids, 1,2 adducts are formed, while in the case of 2-methyl-2-(4-methylphenoxy)propanoic acids, 1,4 adducts are obtained. In addition to the spiro adducts, 2-methyl-2-(4-chlorophenoxy)propanoic acids in the former case, and 2-methyl-2-(2-chlorophenoxy)propanoic acids in the latter case are formed, respectively. No 6-chlorosubstituted products are detected on chlorination of any of the substrates. Chlorination of 2-methyl-2-(2,4-dimethylphenoxy)propanoic acid affords only the 1,4-adduct. However, chlorination of 2-methyl-2-(5-chloro-2,4-dimethylphenoxy)propanoic acid gives both the 1,2- and the 1,4-adduct. 2-Methyl-2-(3,5-di-t-butylphenoxyl)propanoic acid on chlorination yields the diastereomeric secondary chloro adduct, 8-chloro-7,9-di-t-butyl-3,3-dimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one.

Under neutral and non-polar conditions, most of the 1,2 adducts undergo a thermal rearrangement of the chlorine which is shown to be a [1,5] sigmatropic chlorine shift. The rearrangement rates are highly dependent on the nature of the substituents in the diene systems.

Under acidic and non-nucleophilic conditions, most of the 1,4-adducts undergo an intramolecular 1,2 chlorine shift followed by aromatization to give the 3-chloro-substituted products. For the dienes in which the 3-position is originally substituted, successive 1,2 chlorine migrations and/or side chain substitution are observed. On the other hand, the 1,2-adducts under similar reaction conditions undergo an intermolecular 1,4 chlorine shift to give the 5-chlorosubstituted products. In the case that the

5-position is substituted by a methyl group, side chain substitution at the 5-methyl takes place. In the presence of added base, solvolyses of the 1,4-adducts in methanol affords simple solvolysis products and/or 1,2 carboxyl rearranged products.

The kinetic studies of the solvolyses of the 1,4-adducts have been carried out. The results reveal the substituent effects on both the simple solvolysis displacement and the rearrangement reactions.

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ACKNOWLEDGEMENTS

I wish to express my gratitude to Professor A. Fischer for his patient guidance and support throughout the course of this work.

I would like to thank Dr. T. Fyles and his group for their suggestion and permission to use the automatic titration devise in doing the kinetic study experiments. Special thanks to Katherine Kay for her help in computer programming for the kinetic studies.

I would also like to thank Dr. McGillivray and Mrs. C. Greenwood for their help throughout the course of the work.

Finally, I would like to express my appreciation to my husband, Dr. Pengzu Zhou, for his great support and encouragement.

Dedication

To my .....

Mom and Dad.

CHAPTER I

INTRODUCTION

1.1 OPENING REMARKS

Chlorination is one of the most widely used and extensively studied aromatic substitution reactions.[1-4] As in the case for aromatic electrophilic substitutions, the study of chlorination has significantly contributed to the development of theoretical organic chemistry, including the classification of substituents as *ortho-/para-* or *meta-*directing, the relationship between orientation and reactivity, as well as rules of substitution in multisubstituted aromatic systems.[5]

Many aromatic chloro compounds are important solvents, fine chemicals, and pharmaceuticals. They are also valuable intermediates for a large number of synthetic transformations such as the introduction of other functional groups by reaction with nucleophiles and preparation of a variety of organometallic compounds for further transformations. In addition to being widely used in the laboratory, many chloro aromatics have played an important role in industry as insecticides, herbicides, plastics etc. Chlorobenzene is an intermediate in the manufacture of phenol, aniline, DDT (1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane), and dyes; PCBs (polychlorinated biphenyls) have been used as dielectric materials in capacitors and transformers, and solvents in plastics and

printing inks.

Chlorination of phenols leads to the formation of chlorocyclohexadienones, useful intermediates in the synthesis of some herbicides, pesticides, as well as steroidal drugs.[6a,b] Polychlorocyclohexadienones are active promoters for the cross-linking of polymers.[6c]

1.2 CHLORINATING AGENTS

The most customarily used chlorinating agents fall into four general classes: 1) molecular chlorine; 2) molecular chlorine in the presence of a Lewis acid catalyst; 3) positive chlorine species such as Cl^+X^-; and 4) chlorine derived from reduction of a metal chloride. Normally, the reactivity of the reagent increases in the order of ClOH < ClOCl < ClOAc < Cl_2 < Cl_2 (catalysed) < $ClOR^+_2$ < Cl^+. This reflects the order of increasing positive charge on the chlorine in the reagent.

Chlorination by molecular chlorine is often carried out in solvents such as chlorinated hydrocarbons, nitro compounds, acetonitrile, and carboxylic acids. Increasing the polarity of the solvent increases the reactivity of molecular chlorine.[7,8] In addition to using molecular chlorine directly, chlorination can also be achieved by decomposition of certain types of compounds like iodobenzene dichloride,[7a,c] N-chloroamines, or N-chloroamides,[9,10] involving the formation of molecular chlorine.

The reactivity of molecular chlorine can be increased by using a Lewis acid as the catalyst. The most commonly used Lewis acids are tin chloride,[11] zinc chloride,[7a] and aluminum chloride.[12] These catalysts owe their catalytic effect to their abiiity to bring about polarization of the chlorine molecule, e.g., $Cl_2 + AlCl_3 \quad Cl\text{-}Cl\text{-}AlCl_3$.

The positive chlorinating agents include hypochlorous acid,[13] calcium hypochlorite,[14] t-butyl hypochlorite,[15] chlorine acetate,[16] and sulfonyl hypochlorite.[17]

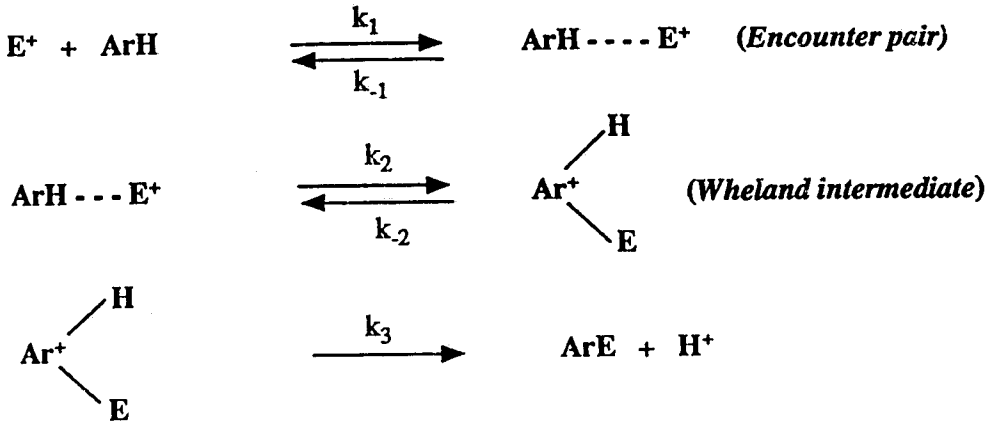
Recently, a number of regioselective chlorinating reagents have been reported in the literature. t-Butyl hypochlorite in the presence of zeolite X,[18] and benzeneselenenyl chloride in the presence of aluminum chloride[19] are found to be excellent *para* selective agents. N-chlorodialkylamines in the presence of silica are useful agents for *ortho* chlorination of phenols.[20]

1.3 MECHANISM OF CHLORINATION

1.3.1 The General Mechanism for Electrophilic Aromatic Substitution

The generally accepted mechanism for aromatic substitution is depicted in Scheme 1.1.

Scheme 1.1



The product forming intermediate, which is usually referred to as the Wheland intermediate or σ-complex, was first used by Wheland as a model for the transition state.[21a] It represents the intermediate in which the electrophile is localized at a particular carbon atom in the aromatic system.

One form of interaction between the electrophile and the substrate which has been postulated to occur in the encounter pair prior to the formation of the Wheland intermediate is the formation of a π-complex. In the π-complex the electrophile is, instead of being located on a particular carbon, held near to the π-electron clouds. It was Olah[21b] who first introduced the concept of a π-complex in the mechanism for aromatic electrophilic substitution. He observed that in a competitive experiment of nitration

of benzene and toluene with nitronium salts, while the positional selectivity was conserved, the substrate selectivity was lost. This contradicts Brown's selectivity-reactivity principle,[22] i.e., the loss of the substrate selectivity should lead to the loss of positional selectivity. Olah rationalized the result by postulating that the substrate selectivity was lost in the formation of the π-complex prior to the formation of the Wheland intermediate, with the retention of the positional selectivity. Although Olah's experimental observations were subsequently shown to result from incomplete mixing of the reagents,[23] the π-complex concept is still useful to explain certain features of the mechanisms of electrophilic aromatic substitution reactions.[24]

A number of kinetic studies[2,25-27] has revealed that most aromatic chlorinations and brominations involve a rate-determining transition state that closely resembles the Wheland intermediate, as judged by structure reactivity effects, and that the observed effects are different from those that would be expected for a π-complex. This indicates that in aromatic chlorination the formation step of the Wheland intermediate is rate determining.

1.3.2 Chlorination by Molecular Chlorine

There are a number of reports in the literature[7,8,9] that uncatalysed aromatic chlorination by molecular

chlorine in acetic acid exhibits second order kinetics, first order in each of the reactants (eq.1.1). Studies[28-35] have also shown that the reaction is neither strongly

$$\text{rate} = k[ArH][Cl_2] \qquad (1.1)$$

catalysed by acids nor strongly inhibited by chloride or acetate ions. Therefore it is unlikely that a species such as Cl^+, $ClHOAc^+$, or ClOAc is the reactive electrophile. Molecular chlorine must be the attacking species.

Chlorination in solvents other than acetic acid also follows second order kinetics (eq 1.1). Solvent effects on chlorination rates of alkylbenzenes have been examined by Andrews and Keefer.[7a] They found that the rates increase with increasing polarity of the solvents in the order 1,2-$C_2H_4Cl_2$ << Ac_2O ≈ MeCN ≈ HOAc < $PhNO_2$ < $MeNO_2$ << TFA.[7,8] This order can be attributed to the activation energy for the uncatalysed reaction diminishing appreciably as the dielectric constant of the solvent increases, as would be expected for a reaction with a polar transition state.

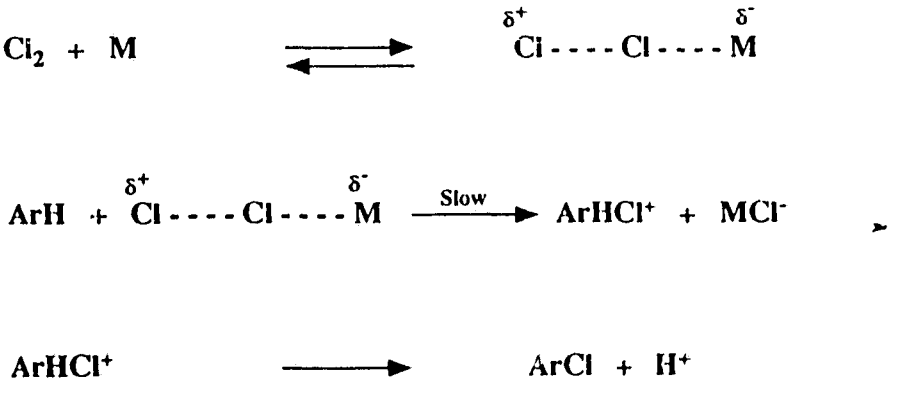
Chlorination in the least polar solvents such as dichloroethane and carbon tetrachloride is very slow and the reaction is subject to catalysis by acids and by other polar substances such as ICl_2, $ZnCl_2$, etc. A series of quantitative measurements for the chlorination of toluene

in the presence of hydrochloric acid has been carried out[35b] and this revealed kinetics which were first order in chlorine, aromatic, and the catalyst M (eq. 1.2). There are

$$\text{rate} = k\,[\text{ArH}][\text{Cl}_2][\text{M}] \qquad (1.2)$$

two possible mechanisms in this case: either the catalyst interacts with chlorine in a preliminary fast step to form a complex which is the active electrophile, or the Cl-Cl bond in such a complex is broken to give Cl^+ as the electrophile. Since there is no evidence of a prior dissociation of the chlorine to Cl^+,[7a], it is likely that the first mechanism applies, as illustrated in Scheme 1.2.

Scheme 1.2



Brown and Stock[36] have reported that chlorination of aromatics in acetic acid has a large negative ρ value (-9 to -10). Since the ρ value, the reaction constant in the Hammett equation,[37a] reflects the sensitivity of the

reaction to substituent effects, and a large negative ρ indicates that the rate-determining transition state is strongly favored by electron donating substituents, the transition state can thus be regarded as being similar to the Wheland intermediate. Furthermore, study of the isotope effect, k_H/k_D[37b], shows that the formation of the Wheland intermediate is rate-determining, e.g., molecular chlorination in a polar solvent gives values of k_H/k_D = 0.92 for 3-bromo-1,2,4,5-tetramethylbenzene[38] and 0.85 for naphthalene,[39] which indicate the C-H bond breaking step is not rate determining.

1.3.3 Chlorination with Chlorine in the Presence of a Catalyst

Zinc chloride-catalysed chlorination of alkylbenzene in acetic acid follows a rate law expressed in eq. 1.3.[7a]

$$\text{rate} = k\,[ArH][Cl_2] + k_o[ArH][Cl_2][ZnCl_2] \quad (1.3)$$

The first term in the rate law represents the kinetics of the chlorination in the absence of the catalyst, while the second term reflects the catalyst effect on the reaction rate. In comparison with bromination and iodination, the second term appears relatively insignificant for

chlorination. Similar kinetics have been observed for chlorination catalysed by aluminum chloride in nitro-compound solvents.[12] In contrast to zinc chloride, aluminum chloride has a great influence on the rate of the reaction. Olah and his coworkers[40] used a competition method to investigate the kinetics of the chlorination of benzene and toluene, and observed low substrate selectivities, but at the same time high positional selectivities. They attributed this to a rate determining formation of the π-complex intermediate. However, a similar study carried out later by Caille et al[12] by a direct method gave substrate selectivities $k_{toluene}/k_{benzene}$ at 0 °C of 247 in $PhNO_2$ and 215 in $MeNO_2$, much larger than the values obtained by Olah.[40] It seems that the competition method is unsuitable for determining the large reactivity differences and that Olah's evidence for the π-complex mechanism is invalid.

Chlorination catalysed by tin chloride exhibits second order kinetics, first order in both chlorine and the catalyst[11] (eq. 1.4). The absence of the aromatic in the rate law indicates that the formation of the complex of chlorine-catalyst as the electrophile is likely to be the rate-determining step.

$$\text{rate} = k\,[Cl_2][SnCl_4] \qquad (1.4)$$

One piece of evidence for the formation of the chlorine-catalyst complex as the electrophile is that when the size of the complex, $Cl^{+}MX_nCl^{-}$, is increased, the positional selectivity, the *ortho/para* ratio, is decreased. Kovacic and Sparks[41] investigated the reaction of antimony pentachloride ($SbCl_5$) with benzene and toluene, and observed a substantially lower *ortho/para* ratio than those observed in chlorination catalysed by some other catalysts such as $FeCl_3$.[11,40]

1.3.4 Chlorination by Chlorine from Decomposition of Other Reagents

Iodobenzene dichloride can be used as a chlorinating agent. Chlorination occurs by a prior dissociation to give free chlorine, as demonstrated in eq.1.5. The dissociation

$$PhICl_2 \rightleftharpoons PhI + Cl_2 \qquad (1.5)$$

is subject to catalysis by polar substances such as trifluoroacetic acid. Kinetic evidence[7a,7c] has shown that in acetic acid chlorination of some reactive polymethylbenzenes involves the dissociation of iodobenzene dichloride (eq. 1.5) as the rate-determining step. However, in a less polar solvent, such as carbon tetrachloride, the dissociation does not occur unless there is a polar catalyst present. In this case iodobenzene dichloride

itself may act as the electrophile to attack the aromatic.[42] Evidence for this has been found in chlorination of unsaturated compounds by iodobenzene dichloride, in which the stereochemistry of the adducts is different from that obtained by molecular chlorine chlorination.[43]

N-chloroamines, in a polar solvent and in the presence of HCl, can also serve as chlorinating agents by producing molecular chlorine via a prior dissociation equilibrium (eq. 1.6).[9a] Since HCl is produced as the byproduct during the chlorination, the reaction is auto catalysed, and the concentration of chlorine can be maintained

$$R_2NCl + HCl \rightleftharpoons R_2NH + Cl_2 \qquad (1.6)$$

stoichiometrically by initially adding a certain amount of HCl. If other acids are used with acetic acid as the solvent, then ClOAc becomes the reactive electrophile.

Some bulky N-chloroamines such as N-chloropiperidine appear to be highly selective chlorinating agents. McKeer and his coworkers[44] have reported that in the presence of trifluoroacetic acid chlorination of anisole and phenol with these bulky N-chloroamines exhibits a remarkable para selectivity (para product ratio > 90%). A kinetic study[45] has revealed that the reaction is catalysed by acids but the rate is not influenced by the concentration of chloride

ion. This indicates that the protonated N-chloroamine is formed as the attacking species by a fast protonation equilibrium (eq. 1.7). Smith and coworkers[46] have also

$$R_2NCl + H^+ \rightleftharpoons R_2HN^+Cl \qquad (1.7)$$

found that the high para selectivity of the reaction is unlikely to result from a steric effect, since blocking the 4-position of anisole or phenol with a substituent leads to only poor or moderate yields of the 2-chlorinated products. Some evidence[46] implies that there might be a radical or radical cation intermediate involved in the reaction.

1.3.5 Chlorination by Positive Chlorine Species

a) Hypochlorous acid

Hypochlorous acid itself is a weak chlorinating agent. However it can become a much more reactive species under catalysis by acids.[13] Chlorination by hypochlorous acid is also subject to the catalysis by Cl^- and ClO^-, presumably due to the formation of Cl_2 (eq. 1.8)[47] and Cl_2O (eq. 1.9)[48] respectively. Early mechanistic and kinetic

$$HOCl + H^+ + Cl^- \longrightarrow Cl_2 + H_2O \qquad (1.8)$$

$$HOCl + ClO^- \longrightarrow Cl_2O + OH^- \qquad (1.9)$$

studies[49] on the chlorination of reactive aromatics led to

the rate laws shown in eq. 1.10 for the reactions with a low aromatic concentration, and eq. 1.11 for reactions with a high aromatic concentration. The first two terms in both

$$\text{rate} = k_1[\text{HOCl}] + k_2[\text{HOCl}][\text{H}^+] \quad (1.10)$$

$$\text{rate} = k_1[\text{HOCl}]+k_2[\text{HOCl}][\text{H}^+]+k_3[\text{HOCl}][\text{H}^+][\text{ArH}] \quad (1.11)$$

equations suggest the formation of Cl^+ as the attacking species, whilst the last term in eq. 1.11 implies the attack of H_2OCl^+ on the aromatics, which should become significant at high aromatic concentrations. Although some evidence[50] supports the above Cl^+ mechanism, thermodynamic calculation[51] of the equilibrium constants for the formation of Cl^+ and H_2OCl^+ argues strongly against the possibility: the estimated equilibrium concentration of $Cl^+ = 10^{-40}$ M is far too low to account for the observed rate.

More recently, the mechanism has been reinvestigated by Swain and his coworkers[52], using anisole as the substrate. A rather complex rate expression has been obtained, as shown in eq. 1.12. The terms of second order

$$\text{rate} = k_1[\text{HOCl}]^2+k_2[\text{H}^+][\text{HOCl}]^2+k_3[\text{HOCl}][\text{H}^+][\text{ArH}] \quad (1.12)$$

in HOCl imply a rate-determining formation of Cl_2O as the reactive electrophile, via either of the pathways shown in eq. 1.13 and eq. 1.14. The latter equation represents an

$$2HOCl \longrightarrow Cl_2O + H_2O \qquad (1.13)$$

$$2HOCl + H^+ \longrightarrow Cl_2O + H_3O^+ \qquad (1.14)$$

acid catalysed dehydration process. The third term in eq. 1.12 is in accord with two mechanisms, via a termolecular rate-determining process as shown in eq. 1.15, or the formation of H_2OCl^+ as the electrophile in a fast prior equilibrium mentioned above for eq. 1.11. Some experimental

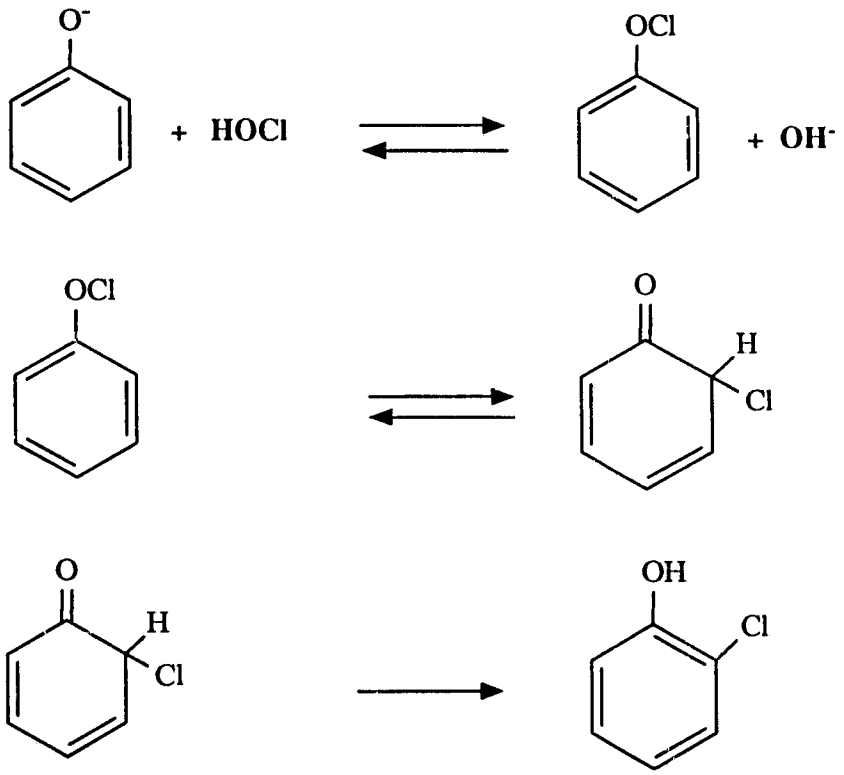
$$HOCl + H^+ + ArH \longrightarrow ArCl + H_3O^+ \qquad (1.15)$$

results[53] have demonstrated that the termolecular mechanism (eq. 1.15) is more likely to be the case.

Recently, Kimura and coworkers[54] studied the chlorination of phenol and anisole with aqueous sodium hypochlorite over a range of pH. They found that the *ortho/para* ratio for the reaction of phenol was strongly influenced by the pH value, e.g., *ortho/para* = 0.64 at pH 4.0, and 4.3 at pH 10. In contrast to this, the ratio for the reaction of anisole was almost pH independent (0.63 - 0.66 at pH 4 - 10). The high *ortho* orientation at high pH in the chlorination of phenol was attributed to the formation of phenyl hypochlorite, which gave the *ortho* chlorinated product by migration of the chlorine group from the oxygen atom to the neighboring *ortho* position (Scheme

1.3). This mechanism is also in accordance with the unchanged *ortho/para* ratio under various pH conditions

Scheme 1.3



observed for the chlorination of anisole, since anisole is unable to form phenyl hypochlorite. In addition, the migration of chlorine from oxygen to the ring carbon has been supported by similar rearrangements known in the acylation of phenol via an intermediate of phenyl ester,[55] the chlorination of aniline,[56] etc. Finally, some of the intermediates such as 2,4,6-tribromophenyl hypochlorite

have been isolated from the reaction of the phenol with hypochlorous acid[57].

Nwaukwa and Keehn[14] have reported that calcium hypochlorite in aqueous acetone/acetic acid is an efficient chlorinating agent for activated aromatics such as toluene, xylene, and anisoles. Furthermore, the reaction conditions is very mild, and the operating procedure is very straightforward.

b) Esters of hypochlorous acid

As the most stable ester of hypochlorous acid, t-butyl hypochlorite can be isolated by distillation. Studies on chlorination of anisole, phenol, and chlorobenzene with t-butyl hypochlorite[15] have shown that in non-acidic conditions, the reaction gives almost the same *ortho/para* ratios as those obtained from chlorination with molecular chlorine, e.g., with t-butyl hypochlorite, chlorination of anisole has *ortho/para* = 0.30; with molecular chlorine, *ortho/para* = 0.26, indicating that in both cases molecular chlorine is the reactive electrophile. On the other hand, under acid catalysed conditions t-butylhypochlorite gives an *ortho/para* ratio which is similar to that obtained with hypochlorous acid. For example, the ratio for chlorination of anisole with t-butyl hypochlorite in acetic acid and sulfuric acid mixture is 0.55, and with aqueous hypochlorous acid the ratio is also 0.55. It turns out that under acid-catalysed conditions, chlorination by t-butyl

hypochlorite involves the same attacking entity as that with the one by hypochlorous acid, i.e., Cl_2O.

Smith and Butters[18] have recently reported that a highly *para* selective aromatic chlorination can be achieved by using t-butyl hypochlorite in the presence of zeolites. In their work, well defined, crystalline aluminosilicate zeolites have been employed as the inorganic supports. Since the major active sites in these microporous solids are embedded with pores or cavities of molecular dimensions, the orientation of the reactants is controlled by the lattice structure. The reagent has been applied to chlorination of a series of monosubstituted benzenes such as alkylbenzenes and halobenzenes. High yields (82%-97%) of *para* chlorinated products have been observed.

c) Chlorine acetate (ClOAc)

Chlorine acetate can either be prepared from reaction of mercury (II) acetate with chlorine in acetic acid, or be formed in the solution of hypochlorous acid in acetic acid (eq.1.16). Since the equilibrium constant for the formation

$$HOAc + HOCl \rightleftharpoons ClOAc + H_2O \qquad (1.16)$$

of chlorine acetate (eq.1.16) is about 2.5×10^{-3}, chlorine acetate is readily hydrolysed by water.[16] Thus the reactive electrophile in chlorination by chlorine acetate in aqueous solution is actually hypochlorous acid. A detailed kinetic

study of the chlorination carried out by de la Mare and his coworkers[16] has revealed that in acetic acid in the absence of catalysts, the reaction exhibits a total second order rate law as shown in 1.17, while in the presence of strong acids at high concentrations, the rate law becomes acid dependent (eq.1.18). In addition, the rate of

$$\text{rate} = k\,[\text{ArH}]\,[\text{HOCl}] \qquad (1.17)$$

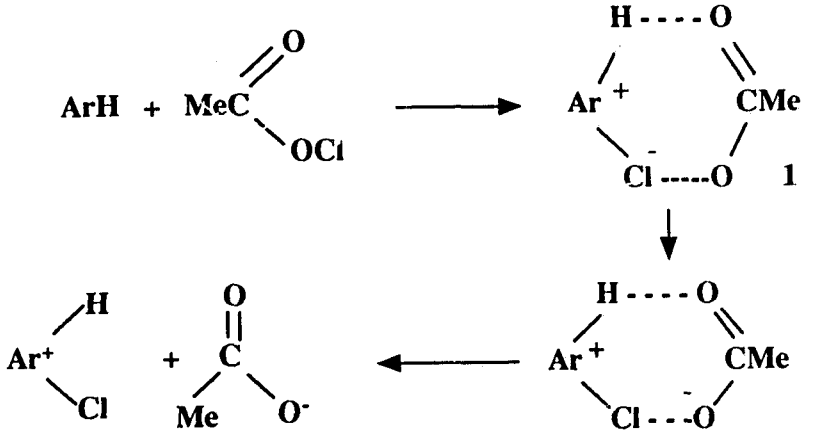
$$\text{rate} = k_1[\text{ArH}][\text{HOCl}] + k_2 f[\text{H}^+][\text{ArH}][\text{HOCl}] \qquad (1.18)$$

chlorination is also influenced by the solvent composition or the percentage of acetic acid. One instance is that the rate of chlorination of nitroaniline passes through a maximum in the region of 50% aqueous acetic acid and then falls to a minimum when the concentration of acetic acid is increased to 90%. This result indicates that the reactive electrophile involving the reaction is likely to be the solvated species, $ClOAcH^+$. In the region of 0-50% acetic acid, the reaction rate increases due to the increasing concentration of $ClOAcH^+$, while in the region of 50-90%, even though the concentration of ClOAc increases, the solvation degree of the species declines.[16]

de la Mare and coworkers[16] have also noticed that the reactivity of the chlorinating agent towards toluene decreases in the following order: ClOAc > Cl-Cl > ClOH. This is quite surprising. Considering electron affinities,

the order Cl-Cl > ClOAc > ClOH would be expected. In order to explain this, they proposed a six-center cyclic transition state (**1**) for chlorination by chlorine acetate, in which fission of the Cl-O bond is facilitated by an intramolecular hydrogen bond (Scheme 1.4).

Scheme 1.4



A notable feature of chlorination by ClOAc is that it shows little steric hindrance, which is also true for HOCl. Similar *ortho/para* ratios have been obtained for both reagents.

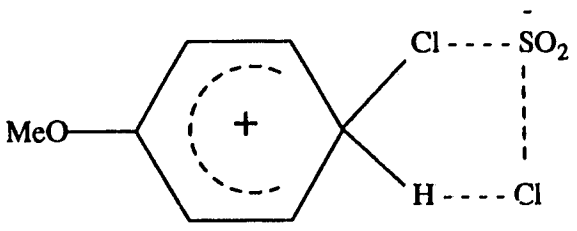
1.3.6 Chlorination by Sulphuryl Chloride

Although aliphatic chlorination by sulphuryl chloride often involves a radical process, reaction of sulphuryl chloride with some aromatics exhibits an electrophilic mechanism.[58-59] Evidence for the mechanism includes: a) the reaction rate increases with increasing polarity of the solvent in the order of benzene < chlorobenzene < o-

dichlorobenzene << nitrobenzene; b) the reaction rate is strongly influenced by the electronic effects of substituents in the substrates. Second order kinetics for the chlorination, first order with respect to both sulphuryl chloride and aromatic, have been observed by de la Mare and his coworkers (eq. 1.19).[59] Since the reaction

$$\text{rate} = k\,[\text{ArH}]\,[SO_2Cl_2] \qquad (1.19)$$

is neither retarded by the presence of chloride ion, nor affected by addition of sulfur dioxide, neither chlorinium ion, Cl^+, nor chlorosulphinium ion, $ClSO_2^+$, are likely to be the effective electrophile. Based on the reaction kinetics, de la Mare and coworkers proposed molecular sulphuryl chloride as the electrophile, which reacts with the aromatic ether via a cyclic transition state (**2**).[59] In addition to being in agreement with the rate law



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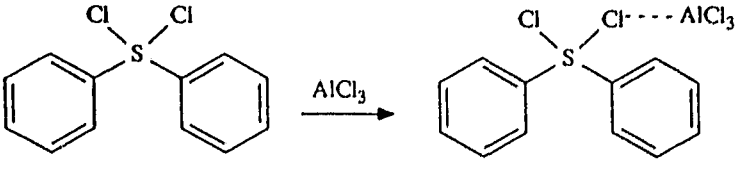
(eq. 1.19), the proposed transition state also accounts for the lack of effect of sulfur dioxide and chloride ion upon the rate of the reaction, since the liberation of both of

these entities would occur at or after the transition state.

Evidence for the electrophilic mechanism has been provided by Bolton,[60] who reported that the Hammett correlation for the chlorination of substituted anisoles fits best with σ^+ substituent constants, and gives a ρ value of -7.2, while for chlorination of substituted 1,3-dimethoxybenzenes the correlation affords a ρ value of -4.0. Obviously, the lower ρ value in the latter case is commensurate with the high reactivity of the substrates which produces an earlier transition state.

In comparison with molecular chlorine, sulphuryl chloride is a relatively weak electrophile. Thus it produces a low *ortho/para* ratio of the products: high regioselectivity with substantial monochlorination. Especially when diphenyl sulfide and aluminum chloride are used as the catalysts, the chlorinating reagent is very efficient for *para* chlorination of activated aromatics.[61] It is likely that in this case sulphuryl chloride reacts with Ph_2S to give diphenylsulfur dichloride (**3**) which forms a complex (**4**) with aluminum chloride as the bulky attacking electrophile.



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1.3.7 Chlorination by Metal Chlorides

A number of metal chlorides such as antimony pentachloride, copper(II) chloride, thallium(III) chloride, and titanium(IV) chloride have been used as electrophilic chlorinating agents. The kinetic study of chlorination by antimony pentachloride has been investigated by Corriu and Coste[62] and a rate law for the reaction has been obtained as shown in eq. 1.20. The term of second order in $SbCl_5$ in

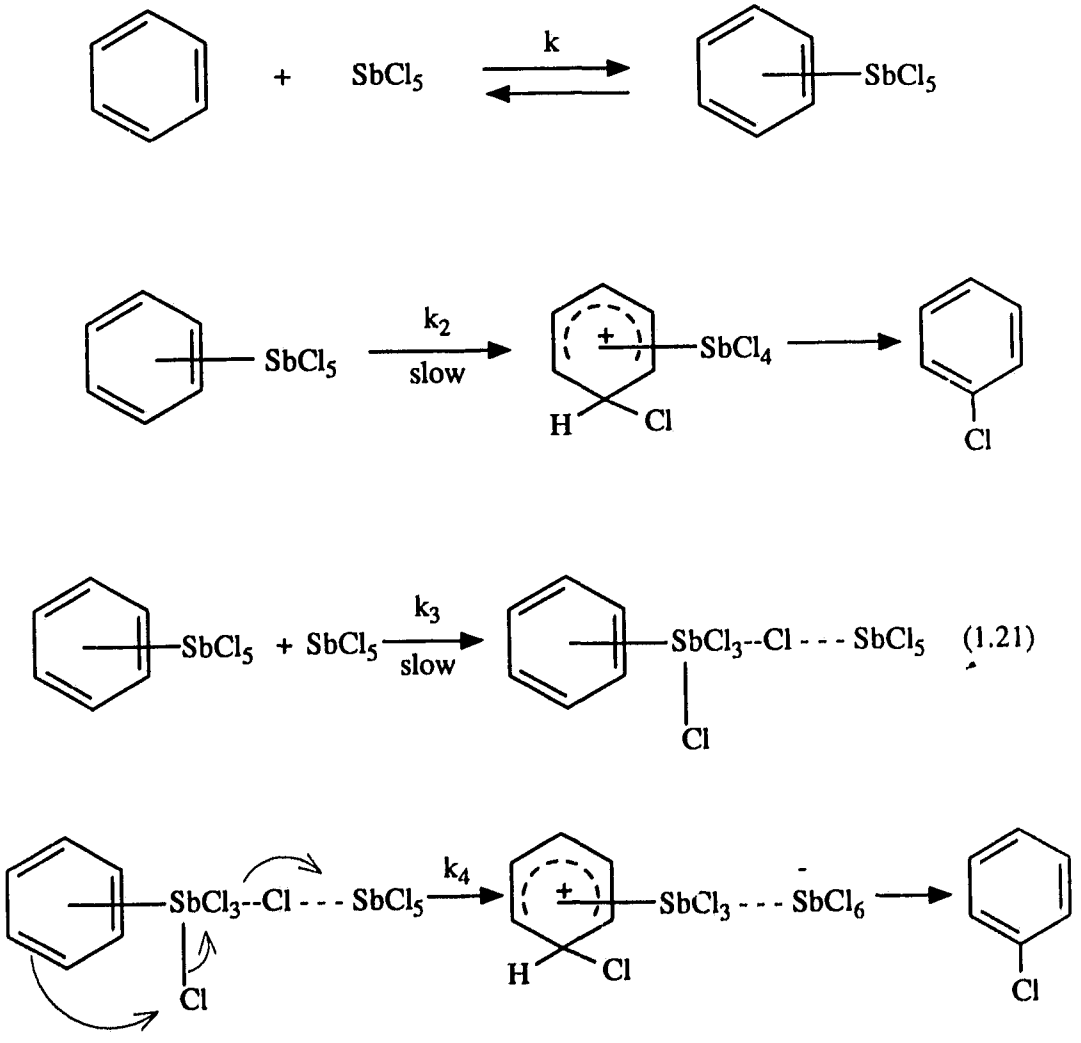
$$\text{rate} = k_1[ArH][SbCl_5] + k_2[ArH][SbCl_5]^2 \qquad (1.20)$$

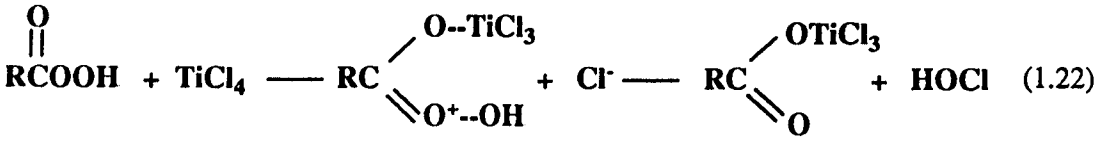
the equation implies a slow decomposition of the intermediate $ArH\text{-}SbCl_5$, which is promoted by a second molecule of $SbCl_5$ (eq. 1.21). The proposed mechanism is depicted in Scheme 1.5.

Chlorination of phenol by copper(II) chloride has been used in industry to achieve high *para/ortho* ratio of the products.[63] In contrast with the *para/ortho* ratio of 1.7:1 obtained with molecular chlorine as the chlorinating agent, chlorination with copper(II) chloride under anhydrous conditions with excess of phenol gave a 10 : 1 ratio. Recently a highly *para* selective chlorination of alkylbenzenes has been achieved by using alumina supported copper(II) chloride.[64] Very high yields of *para* chlorinated products (92-95%) have been obtained by this method.

Titanium(IV) chloride in the presence of an oxidizing reagent such as peroxytrifluoroacetic acid, reacts electrophilically with a variety of aromatic compounds. Some evidence[65] suggest that hypochlorous acid, formed by reaction of titanium(IV) chloride with a peroxide (eq. 1.22), is the attacking electrophile. The chlorination

Scheme 1.5



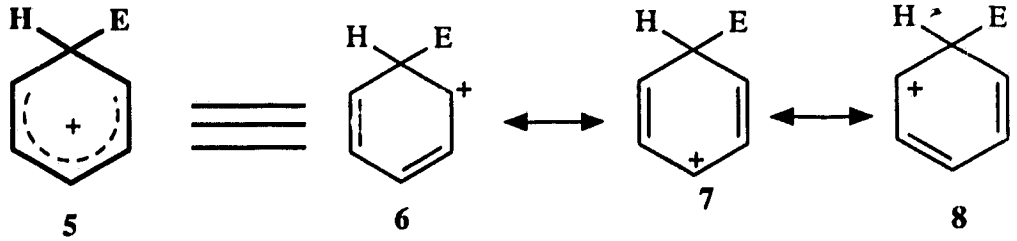


(1.22)

proceeds very cleanly and gives high yields of products with activated aromatics such as toluene, phenol, acetanilide etc, but fails to occur with aromatics bearing strongly deactivating substituents.

1.4 THE WHELAND INTERMEDIATE

The product forming intermediate involved in a electrophilic aromatic substitution is usually represented with a structure (**5**) called the Wheland intermediate. The intermediate is also referred to as a σ-complex (reflecting the nature of the bond by which the electrophile is attached to the ring), arenium, aronium, arenonium cation, cyclohexadienyl cation, and pfitzer complex. There are three possible resonance structures for **5**, i.e., **6-8**. The existence of the Wheland intermediate is supported by the



5 **6** **7** **8**

the following evidence:

1) The absence of a primary kinetic isotope effect in several cases such as chlorination and nitration of

deuteriated and tritiated aromatic compounds;[38, 39, 66]

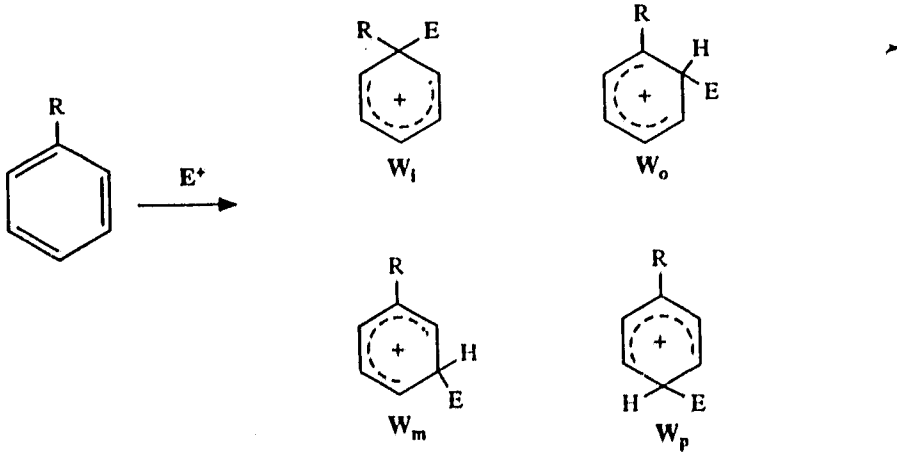
2) an excellent correlation between the relative rates of halogenation and other electrophilic substitutions, and the stabilities of the corresponding σ-complexes has been reported by Brown and Stock;[67]

3) the stable Wheland intermediates formed in nitration of hexamethylbenzene, trifluoromesitylene, and halopentamethylbenzenes in super acids have been observed at low temperature by NMR studies;[68]

4) capture of an *ipso* Wheland intermediate with a nucleophile leading to the formation of an *ipso* adduct (section 1.5).

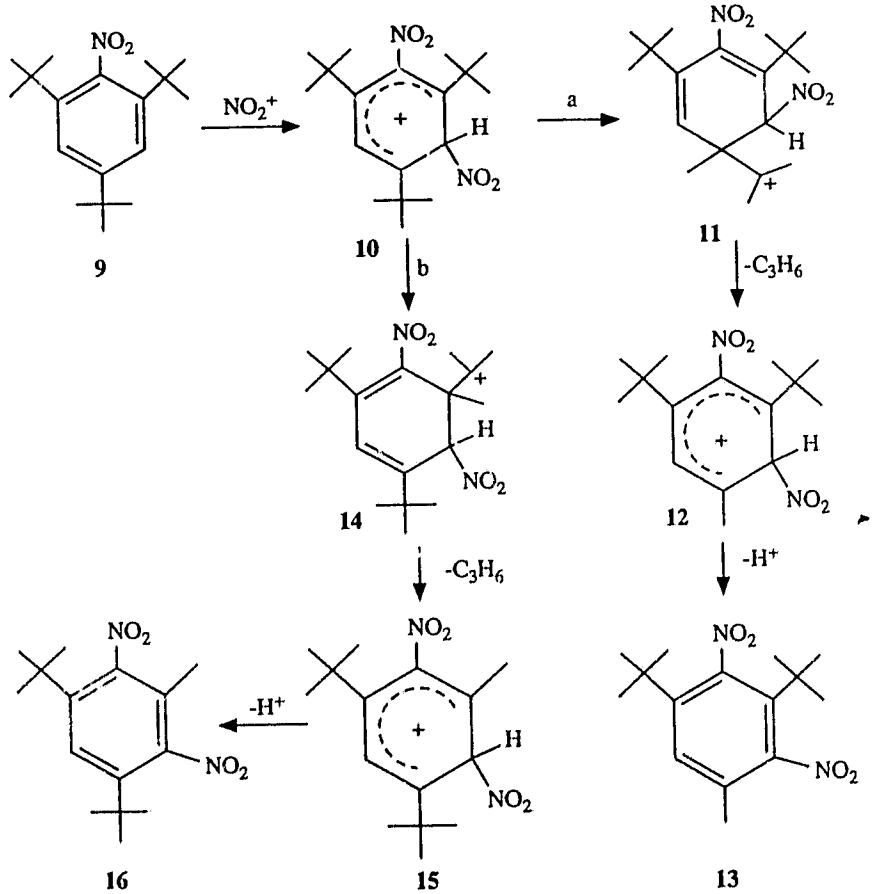
For a monosubstituted benzene the attack by an electrophile E^+ can lead to the following four possible Wheland intermediates: W_i, W_o, W_m, and W_p, as there are four non-equivalent nuclear positions in the substrate (Scheme 1.6). Among the four intermediates, the *ipso*

Scheme 1.6



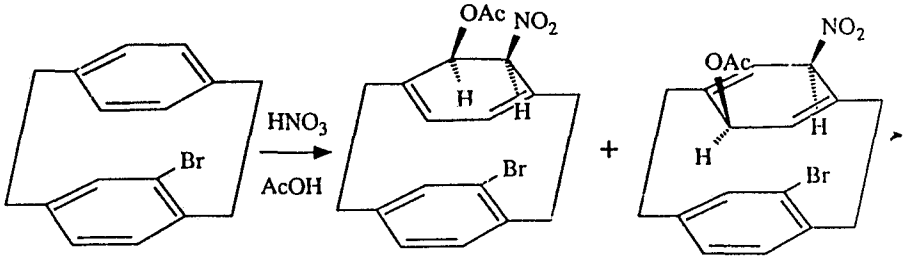
Wheland intermediate, W_i, is normally the most long-lived one, since the other three, W_o, W_m, and W_p, in which the electrophilic group is attached to an unsubstituted nuclear carbon, can readily undergo deprotonation to give the corresponding disubstituted benzenes. However, in some cases where the proton loss process is efficiently

Scheme 1.7



inhibited by factors such as a steric effect, it is even possible to trap these intermediates with suitable nucleophiles. A representative example is given by Myhre and coworkers who have observed molecular rearrangements in the long lived Wheland intermediate formed in nitration of 2,4,6-tri-t-butylnitrobenzene (**9**) (Scheme 1.7).[69] Reich and Cram[70] have isolated the acetyl nitrate adducts with a secondary nitro group from nitration of 4-bromo-[2,2]paracyclophane (**17**) (Scheme 1.8). Recently, a few adducts formed by intermolecular capture of the non-*ipso* Wheland intermediates have been observed and isolated in our laboratory.[71] In these cases, deprotonation of the proton at the tetrahedral center is sterically hindered , so that the nucleophilic capture becomes a competitive pathway with the deprotonation.

Scheme 1.8



17 **18** **19**

1.5 *IPSO* ATTACK IN AROMATIC SUBSTITUTION

In aromatic substitution reactions, some consequences of *ipso* attack, such as *ipso* substitution and reactions involving side chain modification, were often described as

anomalous or non-conventional.[72] In 1971 Perrin and Skinner[73] introduced the prefix, *ipso* (Latin: itself), to denote the attack of an electrophile on a substituted nuclear carbon in an aromatic ring. As the *ipso* Wheland intermediate is relatively more stable than the other intermediates, it usually exhibits quite interesting chemistry. Hartshorn[74] has summarized all of the reactions of the *ipso* Wheland intermediate into six categories:

1) Capture by nucleophiles.
2) Migration of the electrophile.
3) Migration of the original substituent.
4) Modification of the substituents in the *ortho* and *para* positions.
5) *Ipso* substitution (loss of the original substituent).
6) Return to the reactants by loss of the electrophile.

1.5.1 *Ipso* Positional Reactivities

The directing power of a substituent can be attributed to the following three factors: 1) an electronic effect (inductive or field effcts); 2) a resonance effect; and 3) a steric effect. Each factor influences differently the four distinct nuclear positions (*ipso, ortho, meta, and*

para) related to the position of the substituent. Generally, inductive effects affect all four positions, but become less important with distance. Resonance effects are only significant at the *ortho* or *para* positions, and steric effects are strongly associated with distance. Thus, at the *ipso* position, the substituent influences are mainly attributed to the inductive and steric effects. A substituent activates or deactivates electronically the *ipso* position in the same way as it does the *ortho/para* and *meta* positions, i.e., an inductive electron donating substituent activates the *ipso* position while an inductive electron withdrawing group deactivates it.

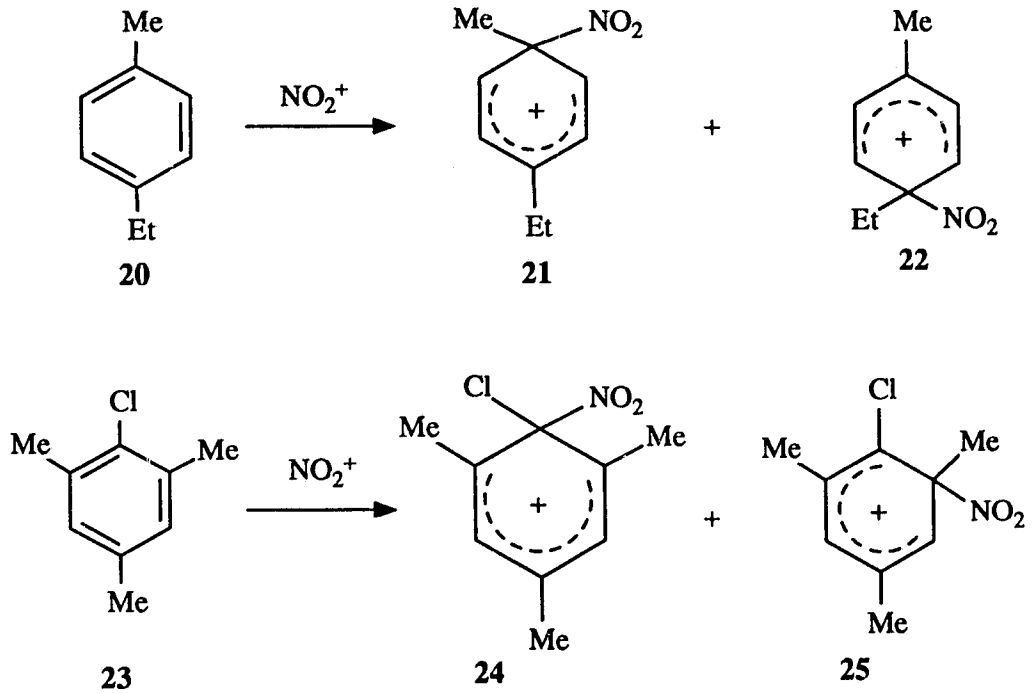
Substituent effects on the positional reactivities are quantitatively expressed in terms of partial rate factors[75], o_f^R, m_f^R, and p_f^R, which reflect the reactivities of each nuclear position, *ortho, meta* or *para* to the substituent R, relative to a single position in benzene. Similarly, an *ipso* partial rate factor (*ipso* factor), i_f^R, has been defined to measure the relative reactivity of the *ipso* position:[73]

$$i_f^R = \frac{k_{ArR}^{total} \times \%\ \text{attack at ipso position in ArR}}{k_{ArH}^{total} \times \%\ \text{attack at corresponding position in ArH}}$$

Like other partial rate factors, the *ipso* factor is

not only influenced by the substituent, but also by the the electrophile and the reaction conditions. Fischer and his coworkers[76] have obtained the partial rate factors for the nitration of toluene, i.e., o_f = 44, m_f = 2.1, p_f = 54, and i_f = 4.7. The *ipso* factors for other alkyl groups[77] have been determined relative to the methyl group in toluene i.e., i_f^{Me}: i_f^{Et}: $i_f^{i\text{-}Pr}$: $i_f^{t\text{-}Bu}$ = 1 : 0.3 : 0.2 : 0. Perrin[73] has measured the *ipso* partial rate factors for halogen substituents from the nitration of haloanisoles, i.e., i_f^{I} = 0.18, i_f^{Br} = 0.079, i_f^{Cl} = 0.061. All the values above indicate that although a methyl substituent activates the *ipso* position the most compared to other substituents, the position *ipso* to methyl is still about ten to twelve times less reactive than the *ortho* and *para* positions. However, the reactivity of an *ipso* position can be significantly enhanced by introducing a second activating substituent at the *ortho* or at the *para* position. For instance, *ipso* attack in nitration of toluene is only 4%,[78] but it becomes 60% in nitration of o-xylene,[79] 75% for p-xylene,[80] and 100% for p-tolyl acetate.[81] Competitive *ipso* attack may be observed at the site of the second substituent, as in the cases of p-ethyltoluene (**20**)[82a] and chloromesitylene (**23**)[82b] (Scheme 1.9).

Scheme 1.9



1.5.2 Capture of The *Ipso* Wheland Intermediate by Nucleophiles

Ipso Wheland intermediates can be captured by either external nucleophiles or internal nucleophiles to give the corresponding *ipso* adducts. This reaction has provided the most direct and convincing evidence for the formation of the *ipso* Wheland intermediates. Furthermore, the reaction is also crucial in terms of investigating the reactions of *ipso* Wheland intermediates, since the *ipso* Wheland intermediates can be regenerated the *ipso* adducts, without the presence of other isomeric Wheland intermediates. The

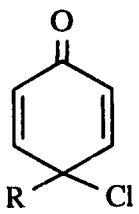
first isolated *ipso* adducts were obtained by Blackstock et al[83] as a pair of diastereomers, from nitration of o-xylene.

a) **Capture by internal nucleophiles**

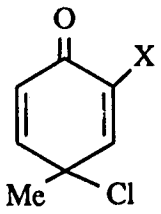
In *ipso* Wheland intermediates substituents bearing lone pair electrons such as OH, OMe, NMe_2 etc. located at the *ortho* or *para* position with respect to the *ipso* position can capture the intermediates, resulting in the formation of dienones or iminium salts as the *ipso* adducts. A large number of such products has been observed and isolated in nitration of phenols, aryl ethers, and anilines (Tables 1.1 and 1.2).

Recently, Fischer and Henderson[94] have isolated a series of 4-alkyl-4-chloro-1,4-cyclohexa-2,5-dienones from chlorination of phenols, as is shown in Scheme 1.10.

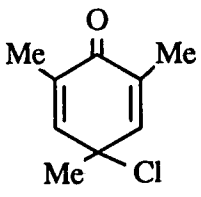
Scheme 1.10



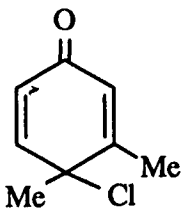
42 R = Me
43 R = Et
44 R = i-Pr
45 R = t-Bu



46 X = Cl
47 X = Me
48 X = t-Bu
49 X = Br



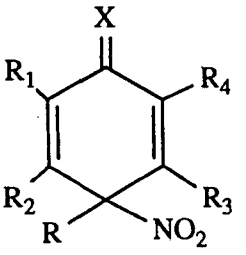
50



51

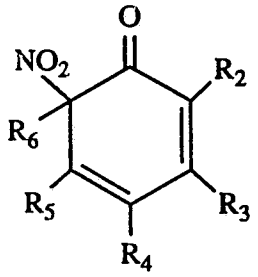
Capture of an *ipso* Wheland intermediate by a lone pair of electrons on a side chain, of suitable length from the

Table 1.1 *ipso* 1,4 adducts formed from intramolecular capture

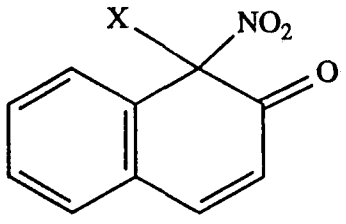


Compound	X	R	R_1	R_2	R_3	R_4	Ref.
26	O	Me	H	H	H	H	84
27	O	Et	H	H	H	H	84
28	O	i-Pr	H	H	H	H	84
29	O	t-Bu	H	H	H	H	84
30	O	OMe	H	OMe	OMe	H	85
31	O	Me	NO_2	Me	H	Me	86
32	O	CH_2OMe	t-Bu	H	H	t-Bu	87
33	O	CH_2CN	H	t-Bu	t-Bu	H	87
34	NMe^+_2	Me	H	Me	H	Me	88

Table 1.2 Conjugated *ipso* nitro adducts



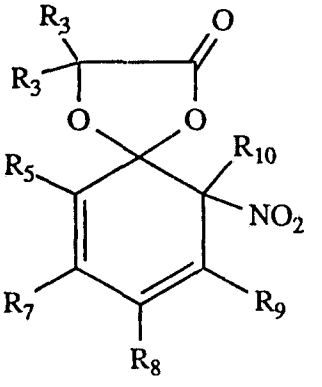
Compound	R_6	R_2	R_3	R_4	R_5	Ref.
35	Me	H	H	H	H	71
36	Me	H	Me	H	H	71
37	Me	Me	Me	Me	Me	89
38	Me	Br	Br	Br	Br	90
39	i-Pr	H	Me	H	H	91
40	t-Bu	t-Bu	H	H	H	71
41	t-Bu	t-Bu	H	NO_2	H	71

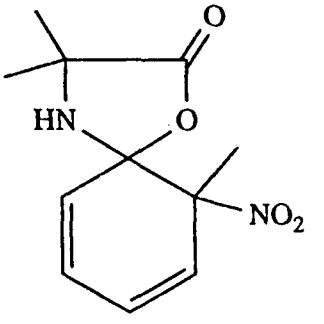


42[92] X = Cl

43[93] X = Br

Table 1.3 Conjugated *ipso* adducts by internal capture

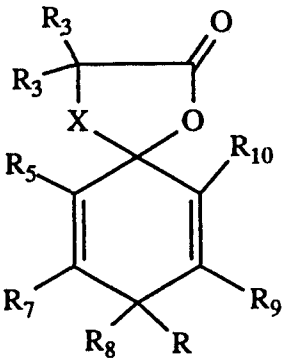




60[98]

Compound	R_3	R_{10}	R_9	R_8	R_7	R_6	Ref
52	H	Me	H	H	H	H	95
53	Me	Me	H	H	H	H	95
54	Me	Me	H	NO_2	H	H	95
55	Me	Me	Me	H	H	H	96
56	Me	Me	H	Me	H	H	96
57	Me	Me	H	H	Me	H	96
58	Me	Me	H	H	H	Me	96
59	H	Me	H	H	Cl	H	97

Table 1.4 Non-conjugated *ipso* adducts by internal capture



Compound	R	X	R_3	R_6	R_7	R_8	R_9	Ref.
61	Br	O	Me	H	H	Me	H	99
62	Br	O	cyclohexyl	H	H	Me	H	100
63	Br	O	Me	H	Me	Me	H	100
64	Br	O	Me	Me	H	Me	H	100
65	NO_2	O	H	H	H	H	Me	101
66	NO_2	O	Me	Me	H	Me	H	96
67	NO_2	O	Me	H	Me	Me	H	96
68	NO_2	$(CH_2)_2$	H	H	H	Me	H	102
69	NO_2	$(CH_2)_3$	H	H	H	Me	H	102

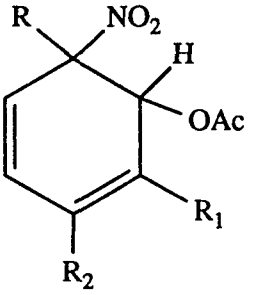
positively charged center, however, will lead to the formation of bicyclic spiro adducts. A number of the spiro adducts have been isolated (Tables 1.3 and 1.4).

b) **Capture by external nucleophiles**

Capture of an *ipso* Wheland intermediate by an external nucleophile usually leads to formation of two types of adducts: 1,2- and 1,4-adducts. The 1,4 adducts are formed as the result of attack of the nucleophile at the *para* position with respect to the *ipso* position, normally as a pair of diasteromers. On the other hand, nucleophilic attack at the *ortho* position results in the formation of 1,2 adducts, mostly as a single isomer.

Nitration of aromatics with acetyl nitrate is the most extensively studied reaction for formation of *ipso* adducts by external nucleophilic capture. In these cases, the

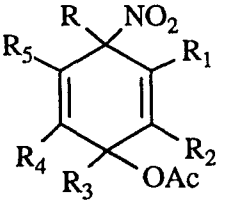
Table 1.5 Conjugated *ipso* adducts by external capture



Compound	R	R_1	R_2	Ref.
70	Me	H	F	101
71	Me	H	Cl	101
72	Me	H	Br	101
73	Me	H	OMe	101
74	Me	NO_2	OMe	103
75	Me	H	t-Bu	104
76	cyclopropyl	NO_2	OMe	105

acetate ion acts as the nucleophile to form the nitrocyclohexa-dienyl acetates. Some selected examples are summarized in Table 1.5 and 1.6. In some cases both 1,2 and 1,4 adducts are formed.

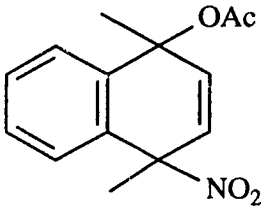
Table 1.6 Selected examples of 1, 4 -adducts by external capture



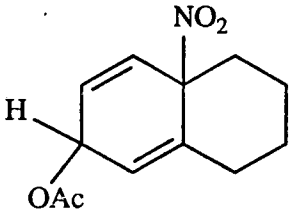
Compounds	R	R_1	R_2	R_3	R_4	R_5	Ref
77	Me	H	H	H	H	H	78
78	Me	H	H	Me	H	H	80
79	Me	H	H	Et	H	H	82a
80	Me	H	H	i-Pr	H	H	106
81	Me	H	H	t-Bu	H	H	104
82	Me	Me	H	OMe	H	H	107
83	Me	Me	CN	H	H	H	108
84	Me	H	COMe	H	H	Me	109
85	Me	Cl	Me	H	Me	H	82b
86	Me	Me	Me	Me	H	H	110
87	Me	Me	Me	H	H	Me	110
88	Et	H	H	Me	H	H	81
89	i-Pr	Me	H	H	H	H	111
90	Cl	Me	H	Me	H	Me	82

Other representative examples include the 1,4 adducts formed in nitration of polycyclic compounds (Scheme 1.11),

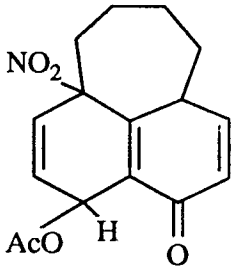
Scheme 1.11



91[112]



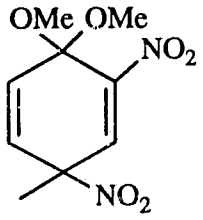
92[113]



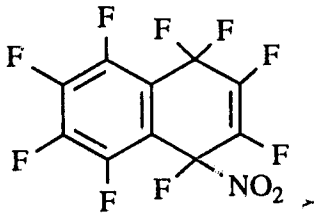
93[113]

and adducts obtained from the nucleophlic capture by nucleophiles other than acetate ion, e.g., F^-, NO_3^-, and OMe^- (Scheme 1.12).

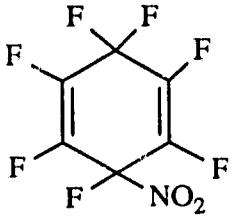
Scheme 1.12



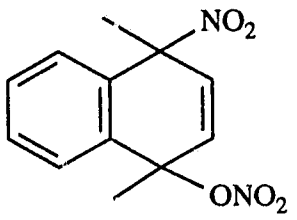
94[114]



95[115]



96[116]

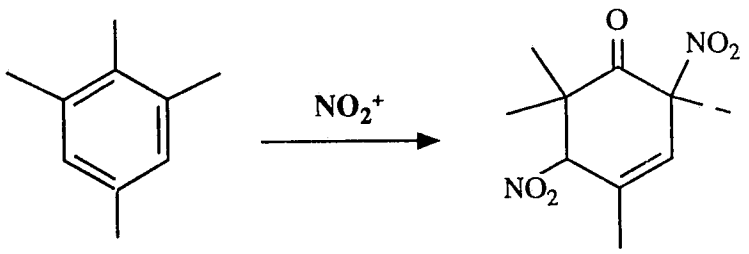


96a[112]

1.5.3 Migration of the Original Substituent

Migration of the original substituent, often a methyl, from an *ipso* position has been observed in nitration of polyalkylbenzenes. Suzuki and his coworkers[117] have reported that nitration of isodurene (97) yields a small amount of the cyclohexenone (98), as is shown in Scheme 1.13. A mechanism for the formation of 98 has been proposed

Scheme 1.13

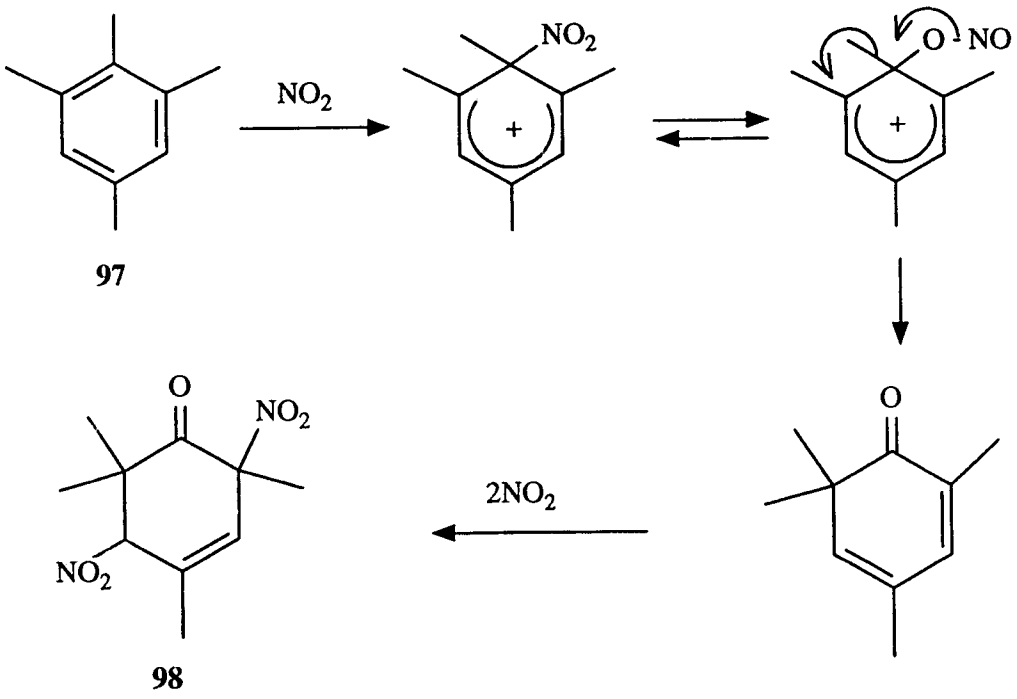


97 **98**

by Hartshorn and coworkers,[118] in which a 1,2 methyl migration, followed by the addition of nitrogen dioxide, is involved, as illustrated in Scheme 1.14.

It has been noted that the alkyl group migration is not very common, and that whenever it occurs, it always is the trivial pathway.

Scheme 1.14

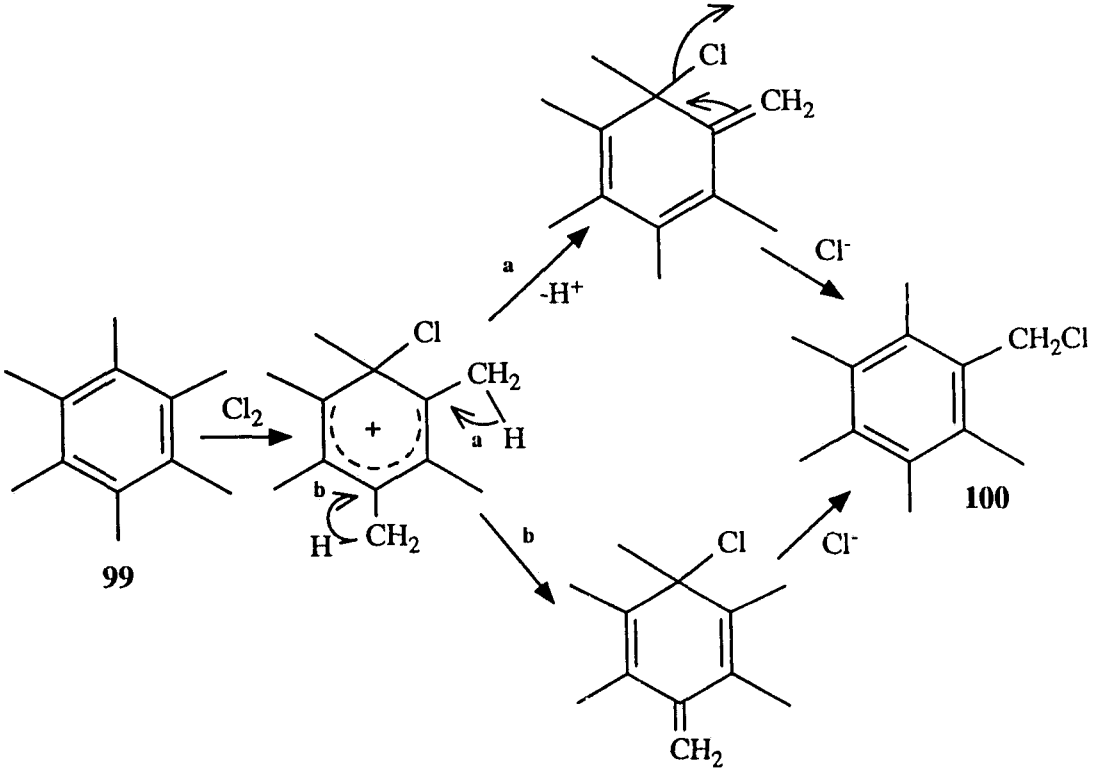


1.5.4 Modification of Substituents in The *Ortho* And *Para* Positions

Side chain modification reactions usually occur in the following cases: a) When there is a hydroxy group or an amino group at the *ortho* or *para* position with respect to the *ipso* position in the *ipso* Wheland intermediate; b) When there is an alkyl group with an α-hydrogen at the *ortho* or *para* position. The first case is ac ally the formation of a dienone or an iminium salt by internal nucleophilic capture, which has been discussed in section 1.5.1. In the latter case, the *ipso* Wheland intermediate is stabilized by

loss of an α-proton from the side chain to yield a methylenecyclohexadiene intermediate. Consequently, the process results in the substitution of the side chain. This type of reaction has been observed in a number of halogenations of polymethylbenzenes, in which side chain chlorinated products are formed.[119] Baciocchi and

Scheme 1.15

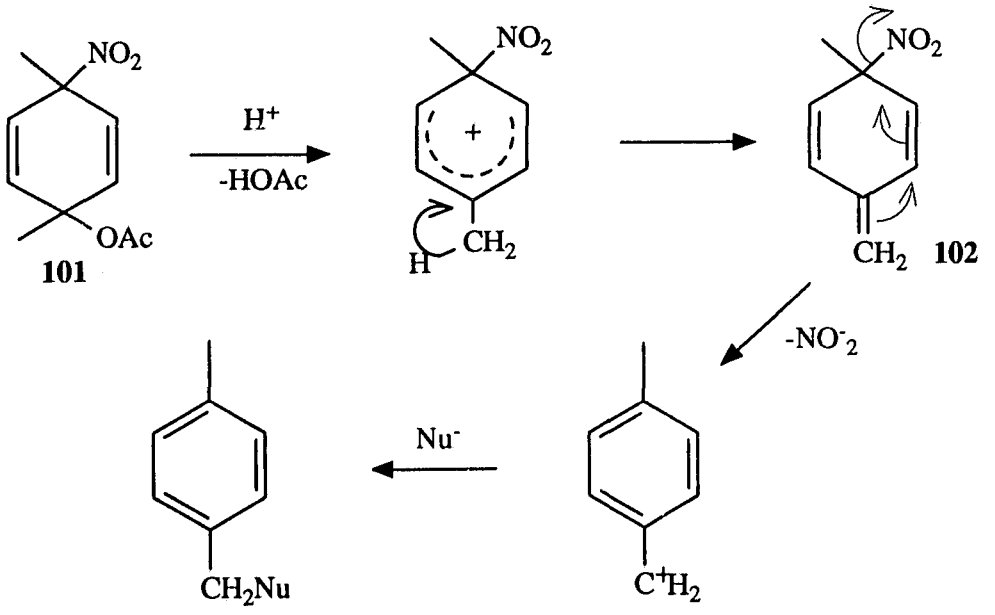


Illuminati[120] have investigated the reaction of hexamethylbenzene with molecular chlorine in acetic acid in the absence of catalysts and light, which affords chloromethyl pentamethylbenzene as the major product. From

the kinetic study of the reaction, a free radical mechanism has been ruled out, and an electrophilic process has been suggested as is shown in Scheme 1.15.

Side chain modification reactions are also frequently observed in the nitration of polymethyl substituted benzenes. Very recently, the formation of a methylene-cyclohexadiene intermediate (**102**), from the acid catalysed reaction of 1,4-dimethyl-4-nitrocyclohexa-2,5-dienone acetate (**101**) has been directly observed in our laboratory by a NMR spectroscopic study (Scheme 1.16).[121]

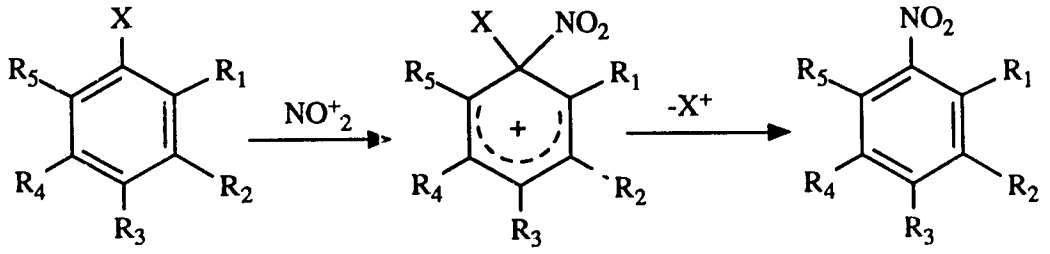
Scheme 1.16



1.5.5 *Ipso* Substitution

Ipso substitution usually takes place when the original substituent at the *ipso* position is a better electrofuge than the attacking electrophile. Hartshorn[74] has suggested the following order for increasing leaving ability of substituents: $Cl^+ \approx NO_2^+ \approx R^+ < Br^+ < D^+ \approx ArN_2^+ \approx SO_3 \approx RCO \approx H^+ < Hg^{2+} < Me_3Si^+$, which is consistent with the relative stabilities of the cations. Consequently, *ipso* substitutions are often observed in substrates with substituents such as acyl, i-Pr, t-Bu, Br, I, $SiMe_3$, SO_3H etc (Scheme 1.17).[122]

Scheme 1.17

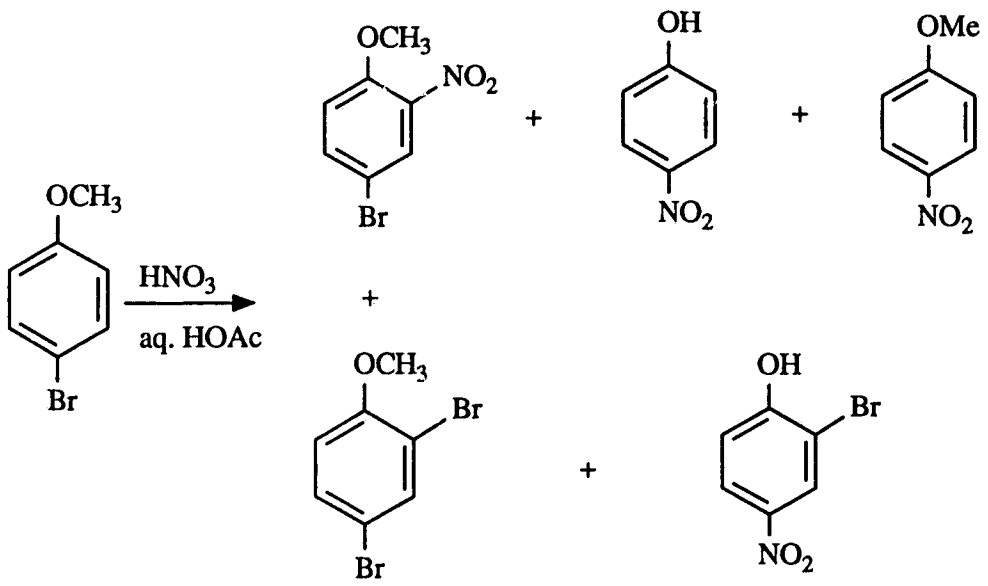


$X = COCH_3,\ SO_3H,\ i\text{-}Pr,\ t\text{-}Bu,\ Si(CH_3)_3,\ I,\ Br,\ CO_2H,\ ArCH_2$

As the leaving group is a positively charged species, the *ipso* substitution reaction is often accompanied by the attack of the cationic leaving group on another molecule of the substrate. It has been observed that 2,5-dibromoanisole (**103**) and 2-bromo-4-nitrophenol (**104**) are formed in the nitration of 4-bromoanisole in aqueous acetic acid, as a consequence of bromination by bromonium ion generated in

the *ipso* substitution (Scheme 1.18)[92].

Scheme 1.18

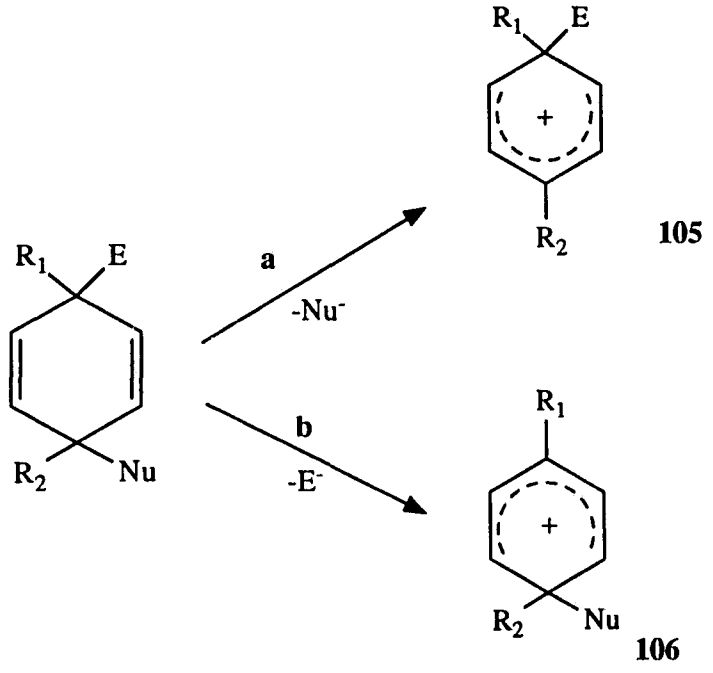


103 **104**

1.6 REACTIONS OF *IPSO* ADDUCTS

An *ipso* adduct can essentially undergo the following two pathways under appropriate conditions: a) loss of the nucleophilic anion, Nu^-, to give the cyclohexadienyl cation **105**; or b) loss of the electrophilic group as an anion, E^-, to afford cation **106**, as illustrated in Scheme 1.19. The

Scheme 1.19



intermediates **105** and **106**, being *ipso* Wheland intermediates, exhibit the reactions listed in sec. 1.5. Pathway a in Scheme 1.19 regenerates back the *ipso* Wheland intermediate formed previously in the initial *ipso* attack. Thus it is possible to investigate the reactions for *ipso*

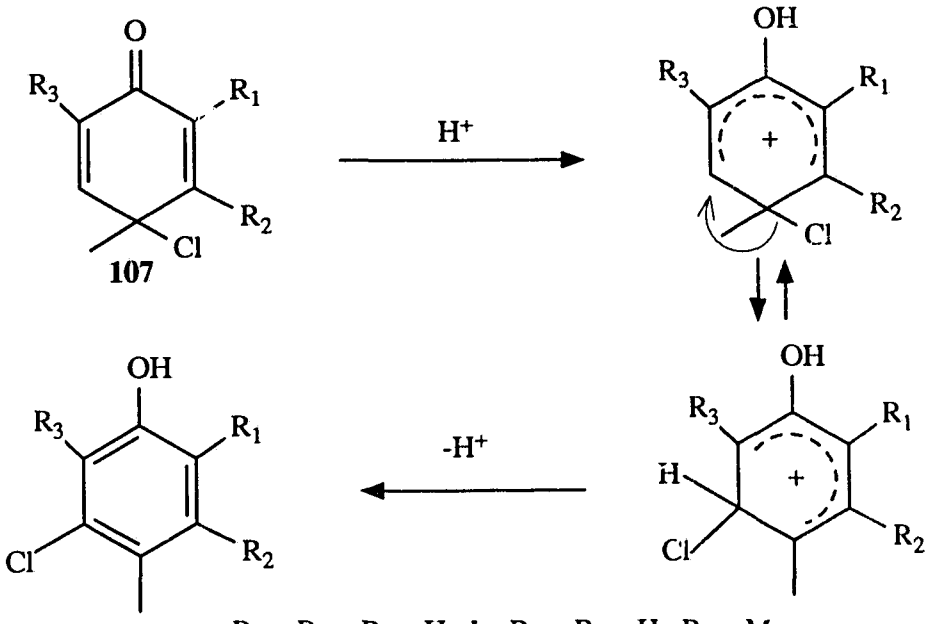
Wheland intermediates without complications arising from the reactions of other isomeric Wheland intermediates. Some of the reactions, such as *ipso* substitution, migration of the original substituent, and side chain modification have already been discussed in the previous section.

1.6.1 Acid Catalysed Reactions of *Ipso* Adducts

Under strongly acidic and non-nucleophilic conditions *ipso* adducts yield the intermediate, **105**, by protonation and cleavage of the nucleophilic group. In many cases the electrophilic group E in the intermediate undergoes 1,2 intramolecular migration under such reaction conditions, although a few examples of extra- and intermolecular migrations of E have been observed in some nitrocyclohexadienyl cation systems.[103]

Intramolecular 1,2 shift of E is often observed in chlorocyclohexadienyl and nitrocyclohexadienyl cations. Fischer and Henderson[123] have investigated the acid catalysed reaction for a series of 4-chloro-4-methyl-cyclohexa-2,5-dienones (**107**) and observed the 1,2-shift of chlorine in the reaction process (Scheme 1.20). This rearrangement has the result of introducing a chlorine at the position *meta* to the hydroxy group, a position not accessible by direct electrophilic substitution.

Scheme 1.20

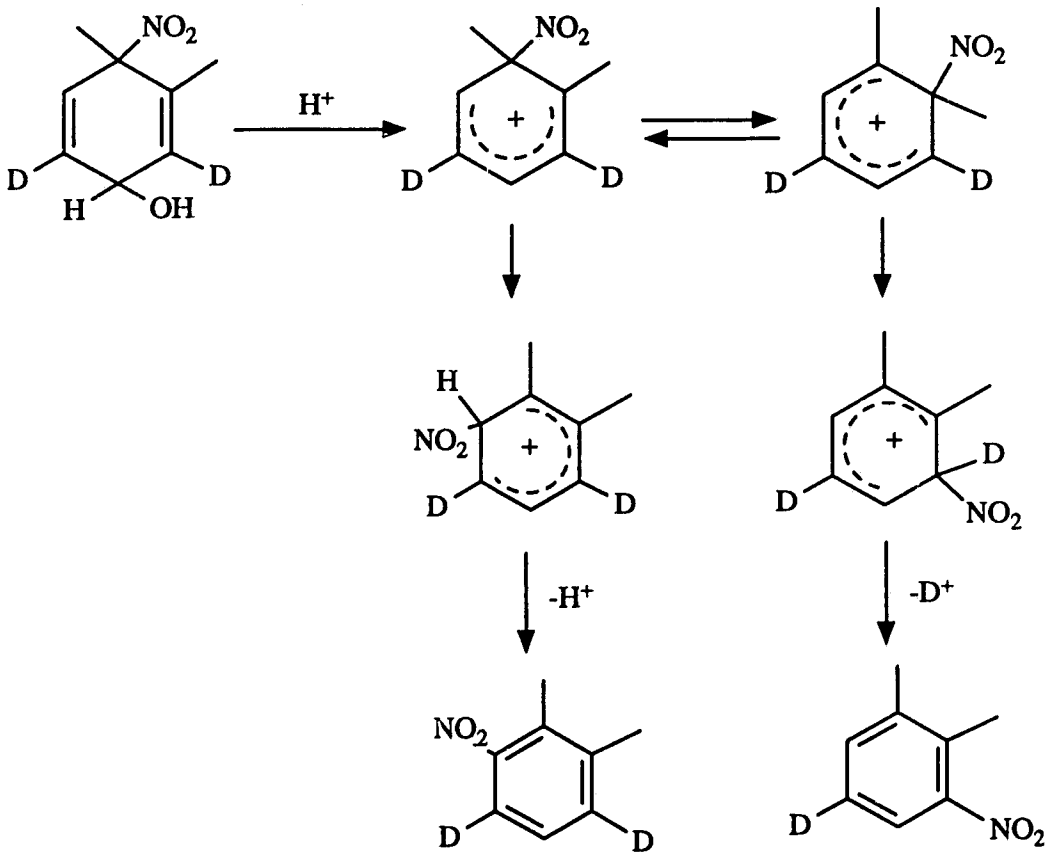


a. $R_1 = R_2 = R_3 = H$; **b.** $R_1 = R_3 = H$, $R_1 = Me$;

c. $R_2 = R_3 = H$, $R_1 = Me$; **d.** $R_1 = R_3 = Me$, $R_2 = H$.

Myhre and Barnes[124] have also reported the occurrence of the concerted 1,2 shift of a nitro group in adducts formed from the nitration of o-xylene in sulfuric acid. By labeling experiments, they have demonstrated that the 1,2 shift of a nitro group to a substituted nuclear carbon is 50 times faster than to an unsubstituted one (Scheme 1.21).

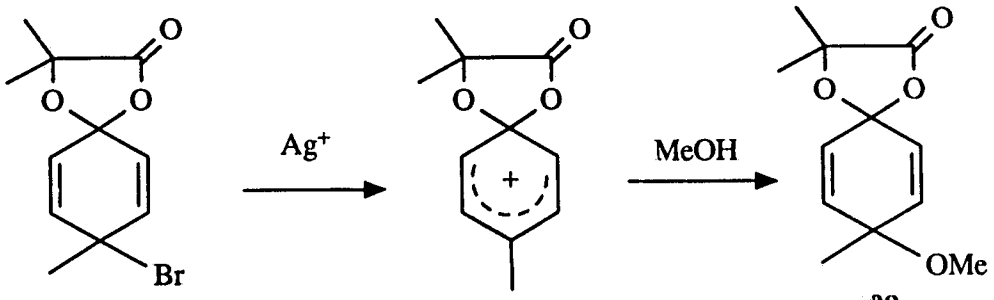
Scheme 1.21



1.6.2 Solvolysis reaction of *ipso* adducts

Under weakly acidic or neutral aqueous conditions, solvolysis of an *ipso* adduct leads to the formation of the intermediate **106**, via pathway b in Scheme 1.19. Corey and coworkers[99] have reported the solvolysis of the *ipso* bromo adduct **64** in methanol with the assistance of silver nitrate, which afforded the methoxy diene, **108**, as the sole product (Scheme 1.22)

Scheme 1.22

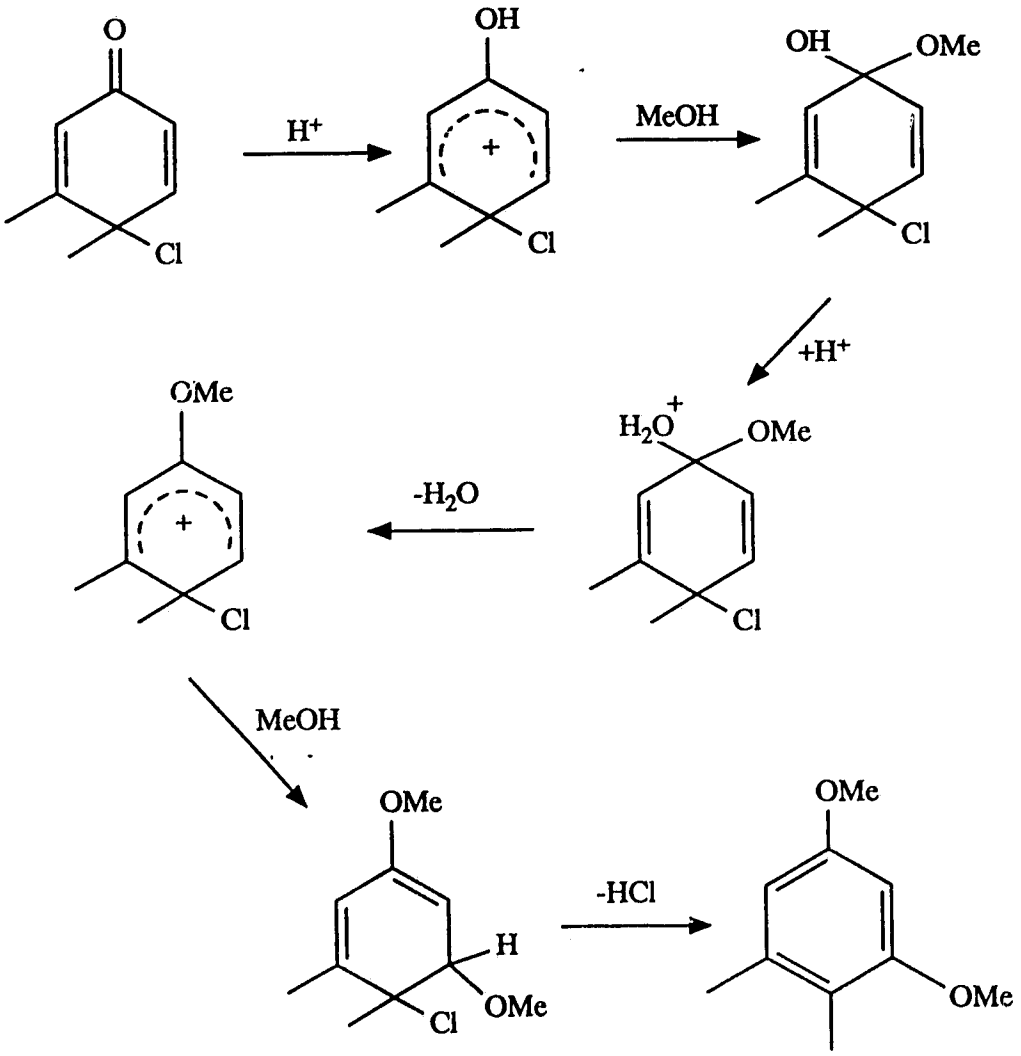


64 **108**

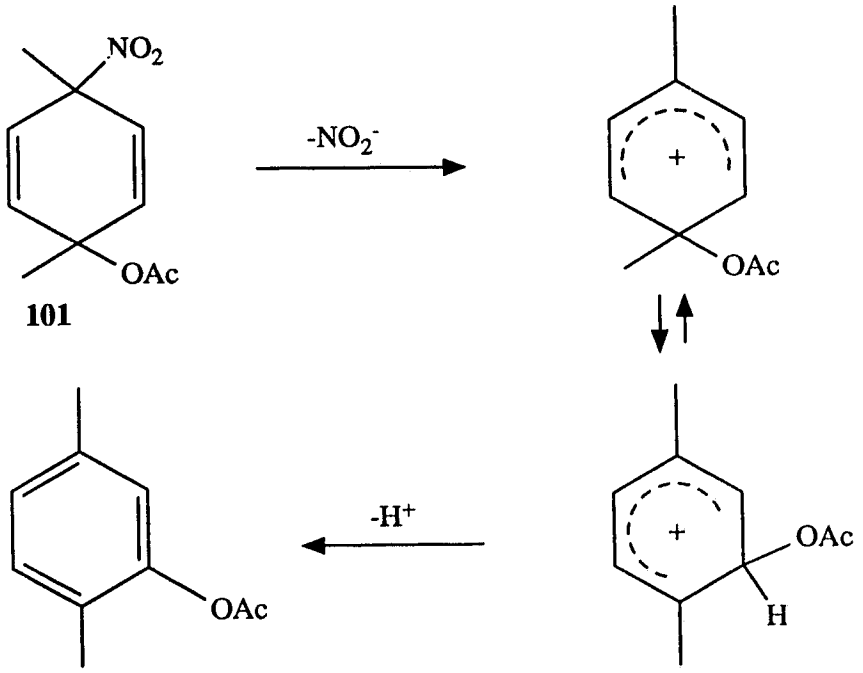
In the absence of a silver salt, the solvolysis has to compete with an acid-catalysed process, brought about by a catalytic amount of an acidic species in the reaction medium. For example, solvolysis of 4-chloro-3,4-dimethylcyclohexa-2,5-dienone (**109**) in methanol gives 4,5-dimethyl-1,3-dimethoxybenzene (**110**), via such a process (Scheme 1.23).[125]

Solvolysis of the nitro group in an *ipso* nitro adduct can be accompanied by 1,2-shift of the nucleophilic group, as the example demonstrated in Scheme 1.24.[79]

Scheme 1.23


O
Cl
H+
OH
+
Cl
MeOH
OH
OMe
Cl
+H+
H2O+
OMe
Cl
-H2O
OMe
+
Cl
MeOH
OMe
H
OMe
Cl
-HCl
OMe
OMe

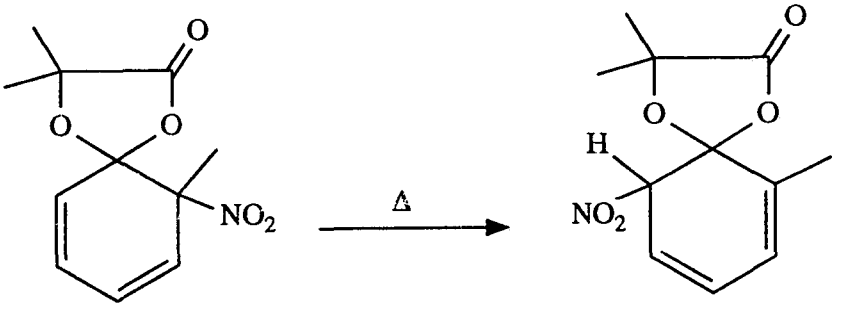
Scheme 1.24



1.6.3 Thermolysis Reactions of *Ipso* Adducts

Ipso adducts in inert solvents, under thermal conditions, often undergo a 1,5 shift of the electrophilic group to form new dienes. In some instances the rearranged diene intermediates have been isolated. Fischer and coworkers[126a] have recently observed that thermolysis of a series of conjugated nitro spiro dienes **111** gives the rearranged dienes **112**, by a 1,5 shift of the nitro group (Scheme 1.25). They have also demonstrated that the 1,5 nitro shift is concerted and is actually a sigmatropic rearrangement process.

Scheme 1.25



111 112

Additional support for the concerted reaction mechanism is provided by ^{15}N nuclear polarization experiments carried out by Ridd and coworkers.[126b]

1.7 OBJECTIVES OF THE PRESENT PROJECT

There has been a substantial amount of work related to the investigation of *ipso* attack in nitration over the past several years. Aromatic chlorination, which is not only important in a mechanistic study, but is also a crucial synthetic strategy for introducing other functional groups, has not received the same attention with respect to the possibility of *ipso* chlorination. Although a number of chlorocyclohexa-2,5-dienones are known,[127] e.g., 23 4-halocyclohexa-2,5-dienones are indexed in vol. 86 of Chemical Abstracts, most of them are derived from phenols which are fully substituted at the reactive *ortho* and *para* positions. Even with phenol substrates which are not 2,4,6-

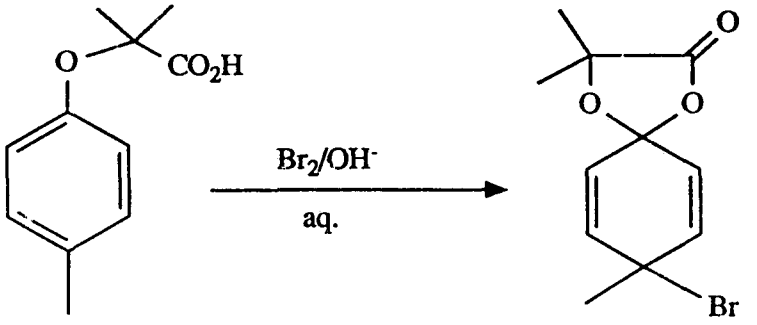
trisubstituted, polychlorocyclohexadienones are obtained by successive chlorination.[128] Apparently, the possibility of the formation of less substituted chlorodienones was not considered in the early work. Furthermore, little effort has been made to isolate the *ipso* adducts and little is known about their chemistry.

Recently, Fischer and Henderson[94] have synthesized a number of simple 4-chloro-cyclohexa-2,5-dienones from chlorination of simple phenols. These compounds are of interest as substrates for investigating the reactions of *ipso* chloro adducts,[123] and also are valuable for studying the "abnormal" or "non-conventional" pathways in reactions of aromatic compounds with electrophiles.[74, 124]

A preliminary investigation of the chlorination of p-xylene and isodurene, carried out in our laboratory, was unsuccessful in that no evidence was found for the formation of *ipso* adducts, nor of side chain product, although the same substrates gave high yields of *ipso* adducts in nitration.[110,130] Consequently, chlorocyclo-hexadienones were chosen as being more accessible systems for studying *ipso* chlorination.

Since most of the chloro-cyclohexadienones are unstable, which makes the investigation of their reactions difficult, it is desirable to obtain a related series of stable compounds. It will be recalled that the reaction of 2-methyl-2-(4-methylphenoxy)propanoic acid with bromine

under basic conditions, carried out by Corey and coworkers[99], afforded a stable spiro bromo adduct, 64. This is is in fact a protected 4-bromo-4-methylcyclohexa-2,5-



116 64

dienone. Thus such a spiro adduct would be an ideal model for our purpose. The nitration of a series of 2-methyl-2-aryloxypropanoic acids, which gives high yields of the analogous spiro nitro adducts, provided evidence for our expectation that it should be possible to prepare a similar series of spiro chloro adducts.

The objectives of the present work are:

1) to study the chlorination of a series of 2-methyl-2-aryloxypropanoic acids, to isolate and characterize the *ipso* adducts, and to evaluate the substituent effects on the chlorination;
2) to investigate the reactions of these adducts, including acid catalysed reactions, solvolysis, and thermolysis;
3) to measure the substituent effects on a quantitative basis by studying the kinetics of the reactions.

CHAPTER II

EXPERIMENTAL PROCEDURE

2.1 INSTRUMENTATION

Melting points are uncorrected and were determined on a Reichert 7905 melting point apparatus. Infrared spectra, of dispersions in KBr or chloroform solutions for solids and thin films between sodium chloride plates for liquids, were recorded on a Perkin-Elmer 283 spectrometer. Ultraviolet spectra were recorded on a Perkin-Elmer Lambda-4B spectrophotometer using hexane as solvent. Proton nuclear magnetic resonance spectra of solutions in chloroform-d, and acetone-d_6 were recorded on a Perkin-Elmer R-32 (90 MHz) or a Bruker WM 250 (250 MHz) spectrometer. Tetramethylsilane (90 MHz) or the solvent deuterium signal (250 MHz) was used as the lock signal. ^{13}C NMR spectra of solutions in chloroform-d or in acetone-d_6 were recorded on the Bruker WM-250 (62.9 MHz) using the solvent peaks at 77.0 ppm or 29.8 ppm, respectively, for calibration. Mass spectra were recorded on a Perkin-Elmer Hitachi RMU-7 spectrometer with 70 ev electron impact ionization using perfluorokerosene as the mass standard, or on a Finnigan 3300 gas chromatography mass spectrometry system using methane as the carrier gas for chemical ionization. Elemental analysis were performed by Canadian Microanalytical Ltd., Vancouver, British Columbia. Gas

chromatography was performed on a Varian-3700 chromatograph using either a SE-30 or a SE-55 glass capillary column. For high performance liquid chromatography a Waters Prep. LC/system 500A was used. Usually a flow rate of 100 cm^3/min and a chart speed of 2 min/cm were used and the relative response (sensitivity) was varied depending on the sample size. Both the column and the solvent reservoir were cooled by circulating ice-water. The X-ray diffraction study (crystallography) was performed by Kathy Beveridge on Picker 4 circle diffractometer automated with a PDP-11/10 computer and on a Nonius CAD4 diffractometer.

2.2 REAGENTS

The following chemicals were used without further purification:

calcium hypochlorite, *o*-cresol, *p*-cresol, 4-ethylphenol, 4-isopropylphenol, 4-*t*-butylphenol, 2,3-dimethylphenol, 2,4-dimethylphenol, 2,5-dimethylphenol, 3,4-dimethylphenol, 3,5-di-*t*-butylphenol, 2-chloro-4,5-dimethylphenol, 2,3,5-trimethylphenol, 3,4,5-trimethylphenol, 1,1,1-trichloro-2-methylpropan-2-ol (chloretone) (all from Aldrich), 2,4,5-trimethylphenol (Baker), and 2,4,5-trimethylphenol (Custom Chem. Lab.).

Solvents for chromatography including petroleum ether (bp. 30-60 ^{o}C, reagent grade, Fisher), ether (BDH, dried over sodium), and dichloromethane (van Walters and Rogers

Ltd., dried over calcium hydride) were distilled before use. Deuterated solvents used for NMR spectroscopy were chloroform-d (Aldrich Gold Label), and acetone-d_6 (Merck Sharp and Dohme). Methanol used for solvolytic reactions was HPLC grade from Aldrich.

Silica gel (60-200 mesh, Davidson Commercial grade H) and basic alumina (Camag, Brockmann/activity I) were used for chromatography. Anhydrous magnesium sulphate was used to dry solutions in organic solvents.

2.3 PREPARATION OF THE STARTING MATERIALS

2.3.1 Preparation of 2-Methyl-2-(2-methylphenoxy)-propanoic Acid (116)

A solution of *o*-cresol (31.2 g, 0.3 mol) and chloretone (106.5 g, 0.6 mol) in reagent grade acetone (1000 cm^3) was placed in 2000 cm^3 round bottom two-necked flask immersed in an ice bath and continuously stirred with a mechanical stirrer. Powdered sodium hydroxide (96 g, 2.4 mol) was added to the solution in three equal amounts at 2 h intervals. The temperature of the reaction mixture was maintained at 0-10 ^oC during the period of addition. After the addition, the ice bath was replaced with a water bath at ambient temperature, and the reaction mixture was stirred for a further 16 h. The solvent was removed on a rotavapor at 45 ^oC, the residue dissolved in water,

acidified with 1:1 (v/v) aqueous hydrochloric acid, extracted with ether (3 x 300 cm^3) and the ether extract re-extracted with saturated sodium bicarbonate solution (3 x 300 cm^3). The bicarbonate extract was acidified with 1:1 aqueous hydrochloric acid and extracted with ether (3 x 300 cm^3). The ether extract was dried and the solvent removed to gave the acid **116** (45.2 g, 78%). A trace amount of methacrylic acid, present in the crude product, was pumped off under reduced pressure. Crystallization from ether-petroleum ether gave the pure acid **116** (38.2 g); mp 74-75 ^oC (lit.[131] 75-76 ^oC); ^1H **NMR** ($CDCl_3$, 90 MHz) δ: 1.6 (s, 6H, $C(CH_3)_2$), 2.2 (s, 3H, 2-CH_3), and 6.7-7.2 (m, 4H, Ar-H) ppm.

2.3.2 Preparation of 2-Methyl-2-(4-methylphenoxy)-propanoic Acid (**117**)

p-Cresol (48.8 g, 0.4 mol) yielded acid **117** (68.8 g, 88%) as a pale yellow solid, following the same procedure described in 2.3.1. Recrystallization of the crude product from ether-petroleum ether gave the pure acid **117** as white crystals; m.p. 78 ^oC (lit.[132] 77-78 ^oC); ^1H **NMR** ($CDCl_3$, 250 MHz) δ: 1.55 (s, 6H, $C(CH_3)_2$), 2.27 (s, 3H, CH_3-4), 6.84 (d, 2H, H-2 and H-6, J= 10 Hz), 7.06 (d, 2H, H-3 and H-5, J = 10 Hz) ppm.

2.3.3 Preparation of 2-Methyl-2-(3,4-dimethylphenoxy)-

propanoic Acid (118)

3,4-Dimethylphenol (48.8 g, 0.4 mol) yielded acid **118** (72.1, 87%) as a light brown solid, following the same procedure described in 2.3.1. Recrystallization from ether-petroleum ether gave the pure acid **118** as white crystals; m.p. : 86-87 ^{o}C (lit.[131] 82-88 ^{o}C); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.56 (s, 6H, $C(CH_3)_2$), 2.20 (bs, 6H, CH_3-3 and CH_3-4), 6.68 (dd, 1H, H-6, J = 10 and 2 Hz), 6.75 (d, 1H, H-2, J = 2 Hz), 7.04 (d, 1H, H-5, J = 10 Hz) ppm.

2.3.4 Preparation of 2-Methyl-2-(2,4-dimethylphenoxy)-propanoic Acid (119)[133]

2,4-Dimethylphenol (48.8 g, 0.4 mol) yielded acid **119** (70.5 g, 85%) as a red oil (2.3.1). Acid **119** had ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.59 (s, 6H, $C(CH_3)_2$), 2.21 and 2.26 (s, 3H each, CH_3-2 and CH_3-4), 6.73 (d, 1H, H-6, J = 8.5 Hz), 6.89 (d, 1H, H-5, J = 8.5 Hz), 6.98 (s, 1H, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_c: 16.8 ($\underline{C}H_3$-2), 20.6 ($\underline{C}H_3$-4), 25.1 ($C(\underline{C}H_3)_2$), 79.9 ($\underline{C}(CH_3)_2$), 118.7 (C-6), 127.0 (C-5), 130.1 (C-2), 132.0 (C-3), 132.5 (C-4), 150.7 (C-1), 178.2 (C=O) ppm.

2.3.5 Preparation of 2-Methyl-2-(2,3-dimethylphenoxy)-propanoic Acid (120)[133]

2,3-Dimethylphenol (48.8 g, 0.4 mol) yielded acid **120** (70.4 g, 85%) (2.3.1). Crystallization from ether-petroleum

ether gave pure acid **120** as a white crystalline solid; m.p. 67-69 °C (lit.[96] 67-68°); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.62 (s, 6H, $C(CH_3)_2$), 2.17 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 6.71 (d, 1H, H-6, J = 8.0 Hz), 6.85 (d, 1H, H-4, J = 7.5 Hz), 6.99 (t, 1H, H-5, J = 7.9 Hz) ppm.

2.3.6 Preparation of 2-Methyl-2-(2,5-dimethylphenoxy-propanoic Acid (**121**)

2,5-Dimethylphenol (48.8 g, 0.4 mol) afforded acid **121** (69.1 g, 83%) as a pale brown solid (2.3.1). Recrystallization from ether-petroleum ether gave pure acid **121** as white crystals; m.p. 112 °C (lit.[96] 111-112 °C); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.61 (s, 6H, $C(CH_3)_2$), 2.20 (s, 3H, CH_3-2), 2.27 (s, 3H, CH_3-5), 6.65 (s, 1H, H-6), 6.77 (d, 1H, H-4, J = 7.4 Hz), 7.01 (d, 1H, H-3, J = 7.4 Hz) ppm.

2.3.7 Preparation of 2-Methyl-2-(2-chloro-4,5-dimethyl-phenoxy)propanoic Acid (**122**)

2-Chloro-4,5-dimethylphenol (46.84 g, 0.3 mol) was dissolved in a methanol solution (300 cm^3) of sodium methoxide (18.9 g, 0.35 mol). The mixture was stirred at ambient temperature for 2 h and the solvent evaporated at 45 °C on a rotatory evaporator. The phenoxide was reacted with chloretone (106.5 g, 0.6 mol) in acetone (1000 cm^3) and afforded the acid **122** (49.5 g, 68%) as white crystals (2.3.1); m.p. 99-100 °C; IR (KBr): 1180 (C-O), 1715 (C=O),

2700-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.59 (s, 6H, $C(CH_3)_2$), 2.17 (bs, 6H, CH_3-4 and CH_3-5), 6.86 (s, 1H, H-6), 7.13 (s, 1H, H-3) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 19.1 (CH_3-4), 19.7 (CH_3-5), 24.8 ($C(\underline{C}H_3)_2$), 82.0 ($\underline{C}(CH_3)_2$), 123.7 (C-6), 124.6 (C-2), 131.0 (C-3), 133.7 (C-4), 136.3 (C-5), 148.1 (C-1), 178.0 (C=O) ppm; analysis calculated for $C_{12}H_{15}ClO_3$: C 59.38%, H 6.23%, Cl 14.61%; found: C 59.39%, H 6.33%, Cl 15.07%.

2.3.8 Preparation of 2-Methyl-2-(2,4,5-trimethylphenoxy)-propanoic Acid (123)

2,4,5-Trimethylphenol (13.6 g, 0.1 mol) afforded acid **123** (10.6 g, 68%) as white crystals, following the same procedure described in 2.3.7. It had m.p. 78-80°C (lit[134]. 79-80 °C); IR (KBr): 1160 (C-O), 1695 (C=O), 2700-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.60 (s, 6H, $C(CH_3)_2$), 2.18 (bs, 9H, CH_3-2, CH_3-4, and CH_3-5), 6.64 (s, 1H, H-6), 6.92 (s, 1H, H-3) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.4 (CH_3-2), 19.0 (CH_3-4), 19.8 (CH_3-5), 25.2 ($C(\underline{C}H_3)_2$), 79.7 ($\underline{C}(CH_3)_2$), 120.3 (C-6), 127.5 (C-2), 131.1 (C-4), 132.5 (C-3), 134.5 (C-5), 150.9 (C-1), 179.5 (C=O) ppm; analysis calculated for $C_{13}H_{18}O_3$: C 70.24%, H 8.16%; found: C 70.15%, H 8.16%.

2.3.9 Preparation of 2-Methyl-2-(2,3,5-trimethylphenoxy)-propanoic Acid (124)

2,3,5-Trimethylphenol (40.8 g, 0.3 mol) gave acid **124** (35 g, 53%) as white crystals (2.3.7). It had m.p. 92-93 ^{o}C (lit.[96] 93 ^{o}C); **^{1}H NMR** ($CDCl_3$, 90 MHz) δ: 1.55 (s, 6H, $C(CH_3)_2$), 2.08 (s, 3H, CH_3)-2), 2.18 (s, 6H, CH_3-3, CH_3-5), 6.51 (s, 1H, H-6), 6.67 (s, 1H, H-4) ppm.

2.3.10 Preparation of 2-Methyl-2-(3,4,5-trimethylphenoxy)-propanoic Acid (**125**)

3,4,5-Trimethylphenol (20.4 g, 0.15 mol) yielded acid **125** (24.3 g, 73%) as a white solid (2.3.7). Acid **125** had m.p. 107-108 ^{o}C (lit.[100] 107-109 ^{o}C); IR (KBr): 1160 (C-O), 1700 (C=O), 2700-3200 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.58 (s, 6H, $C(CH_3)_2$), 2.09 (s, 3H, CH_3-4), 2.22 (s, 6H, CH_3-3, CH_3-5), 6.60 (s, 2H, H-2, H-6) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 14.7 (CH_3-4), 20.7 (CH_3-3, CH_3-5), 25.0 ($C(\underline{C}H_3)_2$), 79.3 ($\underline{C}(CH_3)_2$), 119.7 (C-2, C-6), 130.4 (C-4), 137.3 (C-3, C-5), 151.5 (C-1), 179.1 (C=O) ppm; analysis calculated for $C_{13}H_{18}O_3$: C 70.24%, H 8.16%; found: C 69.97%, H 8.26%.

2.3.11 Preparation of 2-Methyl-2-(4-ethylphenoxy)-propanoic Acid (**126**)

The preparation followed the same procedure as described in 2.3.1. 4-Ethylphenol (36.6 g, 0.3 mol) gave acid **126** as a white solid (37.8 g, 61%). It had m.p. 76-77 ^{o}C; IR (KBr): 1160 (C-O), 1710 (C=O), 2700-3200 (COOH) cm^{-}

^{1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.20 (t, 3H, $CH_2C\underline{H}_3$, J = 7.6 Hz), 1.58 (s, 6H, $C(CH_3)_2$), 2.59 (q, 2H, $C\underline{H}_2CH_3$, J = 7.6 Hz), 6.86 (d, 2H, C-2, C-6, J = 8.6 Hz), 7.08 (d, 2H, C-3, C-5, J = 8.6 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.5 ($CH_2\underline{C}H_3$), 25.5 ($C(\underline{C}H_3)_2$), 28.0 ($\underline{C}H_2CH_3$), 79.5 ($\underline{C}(CH_3)_2$), 120.6 (C-2, C-6), 128.5 (C-3, C-5), 139.1 (C-4), 152.3 (C-1), 179.2 (C=O) ppm; analysis calculated for $C_{12}H_{16}O_3$: C 69.21%, H 7.74%; found: C 69.18%, H 7.85%.

2.3.12 Preparation of 2-Methyl-2-(4-isopropylphenoxy)-propanoic Acid (**127**)

p-Isopropylphenol (34.1 g, 0.25 mol) afforded acid **127** (25 g, 45%) as white crystals (2.3.1); m.p. 96-98 °C; IR (KBr): 1160 (C-O), 1705 (C=O), 2700-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.22 (d, 6H, $CH(C\underline{H}_3)_2$, J = 6.9 Hz), 1.58 (s, 6H, $C(CH_3)_2$), 2.85 (sep, 1H, $C\underline{H}(CH_3)_2$, J = 6.9 Hz), 6.86 (d, 2H, H-2, H-6, J = 8.5 Hz), 7.11 (d, 2H, H-3, H-5, J = 8.6 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 24.5 ($CH(\underline{C}H_3)_2$), 25.1 ($C(\underline{C}H_3)_2$), 33.3 ($\underline{C}H(CH_3)_2$), 79.4 ($\underline{C}(CH_3)_2$), 120.5 (C-2, C-6), 127.1 (C-3, C-5), 143.7 (C-4), 152.3 (C-1), 179.2 (C=O) ppm; analysis calculated for $C_{13}H_{18}O_3$: C 70.24%, H 8.16; found: C 70.38%, H 8.27%.

2.3.13 Preparation of 2-Methyl-2-(4-t-butylphenoxy)-propanoic Acid (**128**)

p-t-Butylphenol (37.6 g, 0.25 mol) yielded acid **128**

(23.5 g, 33%) as white crystals (2.3.7). It had m.p. 97 ^{o}C; IR (KBr): 1160 (C-O), 1705 (C=O), 2700-3200 (COOH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.29 (s, 9H, $C(CH_3)_3$), 1.60 (s, 6H, $C(CH_3)_2$), 6.86 (d, 2H, H-2, H-6, J = 8.0 Hz), 7.28 (d, 2H, H-3, H-5, J = 7.9 Hz) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_c: 25.1 ($C(\underline{C}H_3)_2$), 31.4 ($C(\underline{C}H_3)_3$), 34.2 ($\underline{C}(CH_3)_3$), 79.3 ($\underline{C}(CH_3)_2$), 120.0 (C-2, C-6), 126.1 (C-3, C-5), 145.9 (C-4), 152.0 (C-1), 179.2 (C=O) ppm; analysis for calculated $C_{14}H_{20}O_3$: C 71.16%, H 8.53; found: C 71.31%, H 8.37%.

2.3.14 Preparation of 2-Methyl-2-(3,5-di-t-butylphenoxy)-propanoic Acid (129)

3,5-di-t-butylphenol (20.6, 0.1 mol) yielded acid **129** (18 g, 62%) as white crystals (2.3.7). Acid **129** had m.p. 115 ^{o}C (lit.[71a]: 115-116 ^{o}C); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.27 (s, 18H, $C(CH_3)_3$-3, $C(CH_3)_3$-5), 1.59 (s, 6H, $C(CH_3)_2$), 6.75 (d, 2H, H-2, H-6), 7.09 (s, 1H, H-4) ppm.

2.4 CHLORINATION REACTIONS

2.4.1 General Procedure for Preparation of The Chlorinating Reagent

Calcium hypochlorite (43% available chlorine, as determined by the iodometric method[135]) was triturated in a mortar with successive portions of water until it had disintegrated and no lumps remained. The mixture was

diluted with ice water and shaken until a homogeneous suspension was obtained. A precooled aqueous solution of sodium bicarbonate (1.2 equivalent amount) was added to the suspension. The white precipitate of calcium carbonate was filtered off to give a clear solution of sodium hypochlorite which was used as the chlorination agent.

2.4.2 Chlorination of 2-Methyl-2-(4-methylphenoxy)-propanoic Acid (117)

Acid **117** (7.76 g, 0.04 mol) was dissolved in aqueous saturated sodium bicarbonate (250 cm^3) and the solution was cooled to 0 ^oC. Sodium hypochlorite solution (250 cm^3, containing 0.06 mol hypochlorous acid), prepared from calcium hypochlorite (10 g, 0.07 mol) and sodium bicarbonate (7 g, 0.08 mol) following the general procedure described in 2.4.1, was added to the above solution together with ether (100 cm^3). The reaction mixture was stirred at 0 ^oC for 30 min and then extracted with ether (3 x 100 cm^3). The ether layer was washed with saturated aqueous sodium bicarbonate (2 x 100 cm^3) and dried over magnesium sulphate. The solvent was removed by evaporation in a rotatory evaporator at 10 ^oC, and gave 8-chloro-3,3,8-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**130**) as a pale yellow solid (3.1 g, 34%). Recrystallization of a sample from ether-petroleum ether gave colorless crystals of pure diene **130**. It had m.p. 95 ^oC; IR (KBr): 1185 (C-O),

1780 (C=O) cm^{-1}; UV (hexane): 212 nm (ϵ = 214 m^2 mol^{-1}); ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.52 (s, 6H, $C(CH_3)_2$), 1.71 (s, 3H, CH_3-8), 5.75 (d, 2H, H-6, H-10, J = 10 Hz), 6.27 (d, 2H, H-7, H-9, J = 10 Hz) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_c: 26.4 (CH_3-3, CH_3-3), 30.9 (CH_3-8), 58.7 (C-8), 77.4 (C-3), 98.2 (C-5), 124.9 (C-6, C-10), 138.4 (C-7, C-9), 175.2 (C-2) ppm; analysis calculated for $C_{11}H_{13}ClO_3$: C 57.77%, H 5.73%, Cl 15.50%; found: C 57.61%, H 5.57%, Cl 15.62%.

The bicarbonate extract obtained above was acidified with (1:1) aqueous hydrochloric acid and re-extracted with ether (3 x 50 cm^3). The dried ether extract on solvent evaporation gave 2-methyl-2-(2-chloro-4-methylphenoxy)-propanoic acid (131) (5.3 g, 59%) as a pale yellow oil; IR (neat film): 1705 (C=O), 2700-3200 (COOH) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.59 (s, 6H, $C(CH_3)_2$), 2.26 (s, 3H, CH_3-4), 6.95 (s, 2H, H-5, H-6), 7.18 (s, 1H, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_c: 20.5 (CH_3-4), 24.7 ($C(\underline{C}H_3)_2$), 81.6 ($\underline{C}(CH_3)_2$), 121.8 (C-6), 127.2 (C-2), 128.1 (C-5), 130.8 (C-3), 134.6 (C-4), 148.1 (C-1), 178.0 (C=O) ppm; MS (70 ev) M/Z (relative intensity): 230, 228 (M^+, 2.5, 9), 144, 142 (C_7H_7ClO, 29, 100); exact mass calculated for $C_{11}H_{13}ClO_3$: 228.055; found: 228.058.

2.4.3 Chlorination of 2-Methyl-2-(3,4-dimethylphenoxy)-propanoic Acid (118)

The chlorination followed the same procedure as

described in 2.4.2. Acid **118** (8.32 g, 0.04 mol) in saturated aqueous sodium bicarbonate (250 cm^3) was treated with aqueous sodium hypochlorite solution (250 cm^3, *ca.* 0.06 mol hypochlorous acid available) prepared from calcium hypochlorite (10 g) and sodium bicarbonate (7 g). The reaction mixture was stirred at 0 ^oC for 30 min. Work-up following the general procedure gave a diastereomeric mixture of 8-chloro-3,3,7,8-tetramethyl-1,4-dioxaspiro-[4,5]deca-6,9-dien-2-one (**132**) (4.5 g, 46%) as a pale yellow oil. Crystallization of the oil from ether-petroleum ether afforded one of the diastereomers (**132a**) as a white solid; **m.p.** 45 ^oC; **IR** (KBr): 1170 (C-O), 1790 (C=O) cm^{-1}; **UV** (hexane): 212 nm (ϵ = 370 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.47 (s, 3H, CH_3-3), 1.48 (s, 3H, CH_3-3), 1.64 (s, 3H, CH_3-8), 1.97 (s, 3H, CH_3-7), 5.52 (d, 1H, H-6, J = 2.5 Hz), 5.70 (dd, 1H, H-10, J = 9.9, 2.5 Hz), 6.23 (d, 1H, H-9, J = 9.9 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 18.4 (CH_3-7), 26.2 (CH_3-3, CH_3-3), 29.2 (CH_3-8), 61.8 (C-8), 77.1 (C-3), 99.7 (C-5), 122.7 (C-6), 123.6 (C-10), 139.0 (C-9), 144.0 (C-7), 175.0 (C-2) ppm; exact mass calculated for $C_{12}H_{15}ClO_3$: 242.071; found: 242.068. Concentration of the mother liquor gave an oil which contained the partially separated other diastereomer (**132b**). **132b** had identical ^{1}H NMR with **132a**; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 18.4 (CH_3-7), 26.2 (CH_3-3, CH_3-3), 29.0 (CH_3-8), 62.0 (C-8), 77.2 (C-3), 99.4 (C-5), 122.7 (C-6), 123.6 (C-10), 138.9 (C-9), 143.9

(C-7), 175.3 (C-2) ppm.

The aqueous bicarbonate extract, after work-up, afforded 2-methyl-2-(2-chloro-4,5-dimethylphenoxy)propanoic acid (**122**) (4.8 g, 49.6%) as a white crystalline solid.

2.4.4 Chlorination of 2-Methyl-2-(2,4-dimethylphenoxy)-propanoic Acid (119)

Acid **119** (8.32 g, 0.04 mol) was treated with aqueous sodium hypochlorite solution (containing 0.06 mol HOCl). The reaction mixture was stirred at 0 ^{o}C for 30 min. Workup following the general procedure gave a mixture (6.3 g) of 8-chloro-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**133**) and 8-hydroxy-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]-6,9-dien-2-one (**134**) (1 : 1) from the ether layer, and unreacted starting material (3.0 g) from the aqueous layer.

Separation of diene **133** and **134** was carried out by filtration of a pentane solution of the diene mixture through basic alumina (150 g), using a mixture of ether-petroleum ether (1:1) as the eluent. Diene **133** (2.6 g, 27%), a white solid, was obtained from the first fraction. It had m.p. 72 ^{o}C; **IR** (KBr): 1180 (C-O), 1790 (C=O) cm^{-1}; **UV** (hexane): 216 nm (ϵ = 324 m^{2} mol^{-1}); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.49 (s, 3H, CH_3-3), 1.51 (s, 3H, CH_3-3), 1.66 (s, 3H, CH_3-8), 1.77 (s, 3H, CH_3-10), 5.75 (d, 1H, H-6, J = 9.7 Hz), 6.02 (bs, 1H, H-9), 6.18 (dd, 1H, H-7, J = 9.8, 2.2

Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.5 (CH_3-10), 25.3, 26.7 (CH_3-3, CH_3-3), 31.2 (CH_3-8), 60.3 (C-8), 77.3 (C-3), 99.8 (C-5), 125.0 (C-6), 130.9 (C-10), 135.7 (C-7), 137.2 (C-9), 175.3 (C-2) ppm; analysis calculated for $C_{12}H_{15}ClO_3$: C 59.38%, H 6.23%; found: C 59.47%, H 6.23%. The hydroxy diene **134** (2.0 g) was obtained on elution with ether. It had m.p. 90-91 °C, **IR** (KBr): 1175 (C-O), 1765 (C=O), 3300 (OH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.30 (s, 3H, CH_3-8), 1.50, 1.53 (s, 3H, each CH_3-3), 1.76 (s, 3H, CH_3-10), 5.73 (d, 1H, H-6, J = 10 Hz), 5.92 (bs, 1H, H-9), 6.10 (dd, 1H, H-7, J = 10, 2.5 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.7 (CH_3-10), 25.4, 26.7 (CH_3-3, CH_3-3), 27.5 (CH_3-8), 65.8 (C-8), 77.2 (C-3), 100.6 (C-5), 125.4 (C-6), 130.8 (C-10), 137.6 (C-7), 139.2 (C-9), 175.6 (C-2) ppm; analysis calculated for $C_{12}H_{16}O_4$: C 64.27%, H 7.19%; found: C 64.10%, H 6.97%.

2.4.5 Chlorination of 2-Methyl-2-(2-methylphenoxy)-propanoic Acid (116)

Acid **116** (7.76 g, 0.04 mol) was treated with aqueous sodium hypochlorite (0.06 mol HOCl). The reaction mixture was stirred at 0 °C for 1 h. On work-up, 10-chloro-3,3,10-trimethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**135**) (1.6 g, 18%) was obtained from the ether layer as a light brown solid, and 2-methyl-2-(4-chloro-2-methylphenoxy)propanoic acid (**136**) (6.5 g, 71%) from the aqueous layer as a white

solid. Recrystallization of **135** gave a white crystalline solid, m.p. 79 ^{o}C; **IR** (KBr): 1180 (C-O), 1795 (C=O) cm^{-1}; **UV** (hexane): 265 nm (ϵ = 279 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.53 (s, 3H, CH_3-3), 1.57 (s, 3H, CH_3-3), 1.72 (s, 3H, CH_3-10), 5.93 (ddd, 1H, H-8, J = 9.5, 5.0, 1.0 Hz), 5.97 (dd, 1H, H-6, J = 9.5, 1.0 Hz), 6.02 (dd, 1H, H-9, J = 9.6, 1.0 Hz), 6.14 (ddd, 1H, H-7, J = 9.8, 5.0, 1.0 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 23.7 (CH_3-10), 24.5, 26.8 (CH_3-3, CH_3-3), 69.2 (C-10), 77.7 (C-3), 107.0 (C-5), 122.3 (C-6), 127.4 (C-8), 129.2 (C-7), 135.4 (C-9), 174.7 (C-2) ppm; analysis calculated for $C_{11}H_{13}ClO_3$: C 57.77%, H 5.73%; found: C 57.46%, H 5.77%.

Chloro acid **136** had m.p. 79-81 ^{o}C, **IR** (KBr): 1130 (C-O), 1700 (C=O) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.61 (s, 6H, $C(CH_3)_2$), 2.20 (s, 3H, CH_3-2), 6.73 (d, 1H, H-6, J = 8.7 Hz), 7.03 (dd, 1H, H-5, J = 8.8, 2.5 Hz), 7.13 (d, 1H, H-3, J = 2.7 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.8 (CH_3-2), 25.3 ($C(\underline{C}H_3)_2$), 79.6 ($\underline{C}(CH_3)_2$), 118.8 (C-6), 126.3 (C-5), 127.4(C-2), 131.0 (C-3), 132.3 (C-4), 152.0 (C-1), 179.7 (C=O) ppm; analysis calculated for $C_{11}H_{13}ClO_3$: C 57.77%, H 5.73%; found: C 57.65%, 5.84%.

2.4 6 Chlorination of 2-Methyl-2-(2,3-dimethylphenoxy)-propanoic Acid (**120**)

Acid **120** (8.32 g, 0.04 mol) was treated with aqueous sodium hypochlorite (0.06 mol HOCl). The reaction mixture

was stirred at 0 °C for 20 min. On ether-bicarbonate workup, 10-chloro-3,3,9,10-tetramethyl-1,4-dioxaspiro-[4,5]deca-6,8-dien-2-one (**137**) (4.0 g, 41%) was obtained from the ether layer as a white solid, and 2-methyl-2-(4-chloro-2,3-dimethylphenoxy)propanoic acid (**138**) (4.8 g, 50%) was obtained from the aqueous layer as a brown oil. Diene **137** had m.p. 65 °C; **IR** (KBr): 1180 (C-O), 1800 (C=O) cm^{-1}; **UV** (hexane): 271 nm (ϵ = 466 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.48 (s, 3H, CH_3-3), 1.53 (s, 3H, CH_3-3), 1.65 (s, 3H, CH_3-10), 1.92 (s, 3H, CH_3-9), 5.71 (d, 1H, H-8, J = 5.5 Hz), 5.86 (d, 1H, H-6, J = 9.8 Hz), 6.05 (dd, 1H, H-7, J = 9.7, 5.5 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 19.2 (CH_3-9), 22.5 (CH_3-10), 24.1, 26.8 (CH_3-3, CH_3-3), 73.8 (C-10), 77.9 (C-3), 107.9 (C-5), 119.3 (C-6), 126.5 (C-8), 128.0 (C-7), 142.2 (C-9), 174.8 (C-2) ppm; analysis calculated for $C_{12}H_{15}ClO_4$: C 59.38%, H 6.23%; found: C 59.20%, H 6.27%.

Acid **138** had **IR** (CCl_4): 1150 (C-O), 1710 (C=O), 2700-3300 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.59 (s, 6H, $C(CH_3)_2$), 2.20 (s, 3H, CH_3-2), 2.31 (s, 3H, CH_3-3), 6.66 (d, 1H, H-6, J = 8.8 Hz), 7.08 (s, 1H, H-5, J = 8.8 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 13.6 (CH_3-2), 16.9 (CH_3-3), 25.1 ($C(\underline{C}H_3)_2$), 79.7 ($\underline{C}(CH_3)_2$), 116.8 (C-6), 126.2 (C-5), 128.6 (C-2), 130.8 (C-4), 135.9 (C-3), 151.6 (C-1), 179.7 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 244, 242 (M^+, 6, 25), 158, 156 (C_8H_9ClO, 31, 100).

2.4.7 Chlorination of 2-Methyl-2-(2,5-dimethylphenoxy)-propanoic Acid (**121**)

Acid **121** (8.32 g, 0.04 mol) was treated with aqueous sodium hypochlorite (0.06 mol HOCl). The reaction was stirred at 0 °C for 20 min. Ether-bicarbonate work-up gave 10-chloro-3,3,7,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**139**) (1.0 g, 10%), a pale yellow oil, from the ether layer, and 2-methyl-2-(4-chloro-2,5-dimethylphenoxy)-propanoic acid (**140**) (7.2 g, 74%), a white solid, from the aqueous layer. Crystallization of diene **139** from ether-petroleum ether afforded a white crystalline solid. Pure diene **139** underwent partial melting at 58 °C; **IR** (KBr): 1180 (C-O), 1795 (C=O) cm^{-1}; **UV** (hexane): 272 nm (ϵ = 312 m^2 mol^{-1}); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.54 (s, 3H, CH_3-3), 1.55 (s, 3H, CH_3-3), 1.68 (s, 3H, CH_3-10), 1.84 (s, 3H, CH_3-7), 5.66 (bs, 1H, H-6), 5.80 (d, 1H, H-8, J = 9.6 Hz), 5.98 (d, 1H, H-9, J = 9.6 Hz) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 20.9 (CH_3-7), 23.7 (CH_3-10), 24.5, 26.7 (CH_3-3, CH_3-3), 68.8 (C-10), 77.8 (C-3), 107.8 (C-5), 123.5 (C-6), 126.6 (C-8), 134.4 (C-9), 136.8 (C-7), 174.9 (C-2) ppm; analysis calculated for $C_{12}H_{15}ClO_3$: C 59.88%, H 6.23%, Cl 14.61%; found: C 60.00%, H 6.03 %, Cl 14.55%.

Chloro acid **140** had m.p. 80-82 °C; **IR** (KBr): 1145 (C-O), 1705 (C=O), 2700-3300 (COOH) cm^{-1}; ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.59 (s, 6H, $C(CH_3)_2$), 2.16 (s, 3H, CH_3-2), 2.26

(s, 3H, CH_3-5), 6.67 (s, 1H, H-6), 7.11 (s, 1H, H-3) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 16.2 (CH_3-2), 19.9 (CH_3-5), 25.1 ($C(\underline{C}H_3)_2$), 79.6 ($\underline{C}(CH_3)_2$), 120.5 (C-6), 127.6 (C-2), 129.4 (C-4), 131.3 (C-3), 133.6 (C-5), 151.6 (C-1), 179.6 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 244, 242 (M^+, 3, 10), 158, 156 (C_8H_9ClO, 32, 100); exact mass calculated for $C_{12}H_{15}ClO_3$: 242.071; found: 242.064.

2.4.8 Chlorination of 2-Methyl-2-(2-chloro-4-methyl-phenoxy)propanoic Acid (**131**)

Acid **131** (9.12 g, 0.04 mol) was treated with aqueous sodium hypochlorite (0.06 mol HOCl). The reaction mixture was stirred overnight at 0 °C. Ether-bicarbonate work-up afforded 6,8-dichloro-3,3,8-trimethyl-1,4-dioxaspiro[4,5]-deca-6,9-dien-2-one (**141**) (1.8 g, 17%) from the ether layer as a pale yellow oil, and the unreacted starting acid **131** (6.5 g) from the aqueous layer.

Crystallization from ether-petroleum ether gave pure diene **141** as a white crystalline solid. It had m.p. 67-68 °C; **IR** (KBr): 1160 (C-O), 1800 (C=O) cm^{-1}; **UV** (hexane): 212 nm (ϵ = 433 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.54 (s, 3H, CH_3-3), 1.61 (s, 3H, CH_3-3), 1.75 (s, 3H, CH_3-8), 5.79 (d, 1H, H-10, J = 9.9 Hz), 6.22 (dd, 1H, H-9, J = 9.9, 2.3 Hz), 6.42 (d, 1H, H-7, J = 2.3 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 24.7, 27.1 (CH_3-3, CH_3-3), 30.9 (CH_3-8), 60.5 (C-8), 78.0 (C-3), 97.6 (C-5), 124.5 (C-10), 130.7 (C-6),

136.5 (C-9), 137.0 (C-7), 174.6 (C-2) ppm; analysis calculated for $C_{11}H_{12}Cl_2O_3$: C 50.20%, H 4.60%; found: C 49.90%, H 4.68%.

2.4.9 Chlorination of 2-Methyl-2-(2-chloro-4,5-dimethyl-phenoxy)propanoic Acid (**122**)

Acid **122** (4.82 g, 0.02 mol) was treated with aqueous sodium hypochlorite (ca. 0.03 mol HOCl). The reaction mixture was stirred at 0 ^{o}C for 12 h. On ether-bicarbonate work-up the diastereomers of 6-chloro-3,3-8,9-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**142**) (4.4 g, 74%) were obtained as the sole product. Recrystallization of the diastereomeric mixture afforded the Z-isomer (**142a**) from the solid phase. Diene **142a** had m.p. 66 ^{o}C, **IR** (CCl_4): 1170 (C-O), 1785 (C=O) cm^{-1}; **UV** (hexane): 218 nm (ϵ = 498 m^2 mol^{-1}); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.53 (s, 3H, CH_3-3), 1.59 (s, 3H, CH_3-3), 1.70 (s, 3H, CH_3-8), 2.00 (s, 3H, CH_3-9), 5.57 (s, 1H, H-10), 6.41 (s, 1H, H-7) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 18.9 (CH_3-9), 24.9, 27.3 (CH_3-3, CH_3-3), 29.8 (CH_3-8), 63.6 (C-8), 78.0 (C-3), 99.0 (C-5), 122.7 (C-10), 130.0 (C-6), 137.2 (C-7), 142.9 (C-9), 174.7 (C-2) ppm; analysis calculated for $C_{12}H_{14}Cl_2O_3$: C 52.03%, H 5.03%, Cl 25.59%; found: C 52.35%, H 5.03%, Cl 25.20%. Concentration of the mother liquor gave a mixture enriched with the E-isomer (**142b**). Partially separated diene **142b** had the identical ^{1}H NMR with **142a**; ^{13}**C NMR** ($CDCl_3$, 62.9

MHz) δ_C (obtained by subtracting the signals of **142a** from the spectrum of the mixture: 18.1 (CH_3-9), 24.9, 27.3 (CH_3-3, CH_3-3), 29.8 (CH_3-8), 63.9 (C-8), 78.0 (C-3), 99.0 (C-5), 122.9 (C-10), 130.1 (C-6), 137.3 (C-7), 143.0 (C-9), 174.6 (C-2) ppm.

2.4.10 Chlorination of 2-Methyl-2-(4-chloro-2-methyl-phenoxy)propanoic Acid (136)

Acid (**136**) (4.9 g, 0.0[illegible] mol) was treated with aqueous sodium hypochlorite (0.03 mol HOCl) and the reaction mixture was stirred at 0 °C for 4h. On bicarbonate work-up, a pale yellow oil (1.5 g) was obtained from the ether layer, which was identified as the mixture of 8,10-dichloro-3,3,10-trimethyl-1,4-dioxaspiro-[4,5]deca-6,8-dien-2-one (**143**) and 8,10-dichloro-3,3,6-trimethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**144**) in a ratio of 2:1. Work-up on the above aqueous layer gave unreacted acid **136** (3.2 g).

Attempted separation of diene **143** and diene **144** failed with various methods, e.g., recrystallization and column chromatography at low temperature, because the isomerization of diene **143** to diene **144** was so rapid that only the rearranged diene **144** was isolated. Diene **144** was a white crystalline solid; m.p. 112 °C, **IR** (KBr): 1175 (C-O), 1785 (C=O) cm^{-1}; **UV** (hexane): 275 nm (ϵ = 395 m^2 mol^{-1}); ^1H **NMR** ($CDCl_3$, 250 MHz) δ: 1.56 (s, 3H, CH_3-3), 1.59 (s, 3H,

CH_3-3), 1.91 (s, 3H, CH_3-6), 4.59 (d, 1H, H-10, J = 4.8 Hz), 5.99 (bs, 2H, H-7, H-9) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.6 (CH_3-6), 25.3, 25.7 (CH_3-3, CH_3-3), 59.1 (C-10), 77.8 (C-3), 104.9 (C-5), 121.3 (C-7), 127.8 (C-9), 131.1 (C-8), 174.2 (C-2) ppm; analysis calculated for $C_{11}H_{12}Cl_2O_3$: C 50.20%, H 4.60%; found: C 49.90%, H 4.48%.

Partially separated diene **143** had **^{1}H NMR** ($CDCl_3$, 250 MHz) δ (obtained by subtraction of the signals of diene **144** from the spectrum of the mixture): 1.54 (s, 3H, CH_3-3), 1.55 (s, 3H, CH_3-3), 1.72 (s, 3H, CH_3-10), 5.98 (d, 1H, H-6, J = 7.9 Hz), 6.05 (bs, 1H, H-9), 6.06 (d, 1H, H-7, J = 8.0 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.2 (CH_3-10), 24.6, 26.6 (CH_3-3, CH_3-3), 69.4 (C-10), 78.0 (C-3), 105.5 (C-5), 130.0 (C-8), 130.2 (C-6), 130.3 (C-7), 130.8 (C-9), 174.2 (C-2) ppm.

2.4.11 Chlorination of 2-Methyl-2-(4-chloro-2,3-dimethylphenoxy)propanoic Acid (138)

Acid **138** (4.84 g, [illegible] mol) was treated with aqueous sodium hypochlorite ([illegible] mol HOCl). The reaction mixture was stirred at 0°C for 8 h. On work-up, 8,10-dichloro-3,3,9,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**145**) (3.8 g, 69%) was obtained as the sole product. Diene **145** was a white crystalline solid. It had m.p. 86-87 °C, IR (KBr): 1160 (C-O), 1795 (C=O) cm^{-1}; **UV** (hexane): 277 nm (ε = 547 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.53 (s, 3H

CH_3-3), 1.57 (s, 3H, CH_3-3), 1.71 (s, 3H, CH_3-10), 2.06 (s, 3H, CH_3-9), 5.96 (d, 1H, H-6, J = 10 Hz), 6.11 (d, 1H, H-7, J = 10 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.9 (CH_3-9), 22.8 (CH_3-10), 24.2, 26.8 (CH_3-3, CH_3-3), 74.3 (C-10), 77.9 (C-3), 106.6 (C-5), 124.7 (C-8), 127.4 (C-6), 131.4 (C-7), 135.4 (C-9), 174.4 (C=O) ppm; analysis calculated for $C_{12}H_{14}Cl_2O_3$: C 52.00%, H 5.09%; found: C 51.90%, H 5.08%.

2.4.12 Chlorination of 2-Methyl-2-(4-chloro-2,5-dimethyl-phenoxy)propanoic Acid (**140**)

Acid **140** (4.84 g, 0.02 mol) was treated with aqueous sodium hypochlorite (0.03 mol HOCl). The reaction mixture was stirred at 0 ^{o}C for overnight. Ether bicarbonate work-up gave a mixture (5 g) of 8,10-dichloro-3,3,7,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**146**), and 8,10-dichloro-3,3,6,9-tetramethyl-1,4-dioxaspiro-[4,5]deca-6,8-dien-2-one (**147**) in a ratio of 3:1.

The products were separated by HPLC (Waters) by using with 10% (v/v) ether-petroleum ether as eluent. The first fraction on evaporation gave diene **146** as a white solid. It had m.p. 158-161 ^{o}C; **IR** (Nujol): 1180 (C-O), 1800 (C=O) cm^{-1}; **UV** (hexane): 270 nm (ϵ = 450 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.55 (s, 6H, CH_3-3, CH_3-3), 1.68 (s, 3H, CH_3-10), 1.93 (s, 3H, CH_3-7), 5.84 (s, 1H, H-6), 6.10 (s, 1H, H-9) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 19.7 (CH_3-7), 23.3 (CH_3-10), 24.6, 26.4 (CH_3-3, CH_3-3), 69.1 (C-10),

78.1 (C-3), 106.1 (C-5), 126.0 (C-6), 130.0 (C-9), 132.6 (C-8), 136.6 (C-7), 174.6 (C-2) ppm; analysis calculated for $C_{12}H_{14}Cl_2O_3$: C 52.00%, H 5.09%, Cl 25.59%; found: C 52.01%, H 5.01%, Cl 25.46%.

Diene **147** was obtained from the second fraction. It had m.p 160 ^{o}C; **IR** (KBr): 1180 (C-O), 1780 (C=O) cm^{-1}; **UV** (hexane): 282 nm (ϵ = 360 m^2 mol^{-1}); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.56 (s, 3H, CH_3-3), 1.57 (s, 3H, CH_3-3), 1.87 (s, 3H, CH_3-6), 2.00 (s, 3H, CH_3-9), 4.24 (s, 1H, H-10), 6.02 (s, 1H, H-7) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.3 (CH_3-6), 17.8 (CH_3-9), 25.7 (CH_3-3, CH_3-3), 64.0 (C-10), 77.8 (C-3), 105.8 (C-5), 127.4 (C-7), 128.0 (C-8), 128.8 (C-6), 133.0 (C-7), 174.5 (C-2) ppm; analysis calculated for $C_{12}H_{14}Cl_2O_3$: C 52.00%, H 5.09; found: C: 51.93%, H 5.09%.

2.4.13 Chlorination of 2-Methyl-2-(2,4,5-trimethyl-phenoxy)propanoic Acid (**123**)

Acid **123** (4.44 g, 0.02 mol) was treated with aqueous sodium hypochlorite (0.03 mol HOCl). The reaction mixture was stirred at 0 ^{o}C for 20 min. On ether-bicarbonate work-up, a mixture (4.8 g) of 8-chloro-3,3,7,8,10-pentamethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**148**) (41%) and 8-hydroxy-3,3,7,8,10-pentamethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**149**) (59%) was obtained as a yellow oil.

Filtration of a pentane solution of the diene mixture through basic alumina (100 g) and eluting with a mixture of

ether-petroleum ether (1:1) at - 60 °C gave, in the first fraction, pure diene **148** (1.8 g, 35%), as a white solid. Diene 32 had m.p. 75-76 °C; **IR** (KBr): 1190 (C-O), 1785 (C=O) cm^{-1}; **UV** (hexane): 216 nm (ϵ = 277 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.51 (s, 3H, CH_3-3), 1.57 (s, 3H, CH_3-3), 1.66 (s, 3H, CH_3-8), 1.80 (s, 3H, CH_3-10), 1.99 (s, 3H, CH_3-7), 5.57 (s, 1H, H-6), 6.04 (s, 1H, H-9) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.3 (CH_3-10), 18.4 (CH_3-7), 25.5, 27.1 (CH_3-3, CH_3-3), 30.0 (CH_3-8), 63.9 (C-8), 77.4 (C-3), 101.4 (C-5), 123.5 (C-6), 130.0 (C-10), 136.9 (-9), 143.1 (C-7), 175.8 (C-2) ppm; analysis calculated for $C_{13}H_{17}ClO_3$: C 60.82%, H 6.68%, Cl 13.81%; found: C 61.05%, H 6.70%, Cl: 14.02%.

Diene **149** (2 g) was obtained as a pale yellow oil, when the basic alumina was eluted with ether. It had **IR** (CCl_4): 1180 (C-O), 1760 (C=O), 3300 (OH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, ^{90} MHz) δ: 1.30 (s, 3H, CH_3-8), 1.49 (s, 3H, CH_3-3), 1.57 (s, 3H, CH_3-3), 1.62 (s, 3H, CH_3-10), 1.71 (s, 3H, CH_3-7), 5.58 (bs, 2H, H-6, H-9) ppm. **MS** (CI): 238 (molecular ion).

2.4.14 Chlorination of 2-Methyl-2-(2,3,5-trimethyl-phenoxy)propanoic Acid (124)

Acid **124** (6.66 g, 0.03 mol) was treated with aqueous sodium hypochlorite (0.05 mol HOCl), and the reaction

mixture was stirred for 30 min. Ether-bicarbonate work-up afforded 10-chloro-3,3,7,9,10-pentamethyl-1,4-dioxaspiro-[4,5]deca-6,8-dien-2-one (**150**) (0.8 g, 10%) from the ether layer, and 2-methyl-2-(4-chloro-2,3,5-trimethylphenoxy)-propanoic acid (**151**) (5.2 g, 68%) from the aqueous layer. Diene **150** was a white solid; m.p. 58 °C; **IR** (CCl_4): 1170 (C-O), 1795 (C=O) cm^{-1}; **UV** (hexane): 273 nm (ϵ = 369 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.53 (s, 3H, CH_3-3), 1.56 (s, 3H, CH_3-3), 1.67 (s, 3H, CH_3-10), 1.81 (s, 3H, CH_3-7), 1.85 (s, 3H, CH_3-9), 5.61 (s, 1H, H-6), 5.62 (s, 1H, H-8) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 19.1 (CH_3-7), 21.0 (CH_3-9), 22.6 (CH_3-10), 24.3, 26.9 (CH_3-3, CH_3-3), 73.3 (C-10), 77.7 (C-3), 108.9 (C-5), 121.4 (C-6), 123.8 (C-8), 137.3 (C-7), 140.8 (C-9), 175.2 (C-2) ppm; exact mass calculated for $C_{13}H_{17}ClO_3$: 256.087; found: 256.085.

Chloro-acid **151** was also a white crystalline solid; m.p. 112 °C; **IR** (KBr): 1150 (C-O), 1700 (C=O), 2700-3200 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.59 (s, 6H, $C(CH_3)_2$), 2.18 (s, 3H, CH_3-2), 2.29 (s, 3H, CH_3-5), 2.32 (s, 3H, CH_3-3), 6.63 (s, 1H, H-6) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 13.8 (CH_3-2), 17.5 (CH_3-5), 21.2 (CH_3-3), 25.2 ($C(\underline{C}H_3)_2$), 79.9 ($\underline{C}(CH_3)_2$), 118.7 (C-6), 128.3 (C-2), 129.3 (C-4), 133.5 (C-5), 136.1 (C-3), 151.0 (C-1), 179.9 (C=O)ppm; analysis calculated for $C_{13}H_{17}ClO_3$: C 60.82%, H 6.68%; found: C 60.91%, H 6.77%.

2.4.15 Chlorination of 2-Methyl-2-(3,4,5-trimethyl-phenoxy)propanoic Acid (**125**)

Acid **125** (4.44 g, 0.02 mol) was treated with aqueous sodium hypochlorite (0.03 mol HOCl). Ether-bicarbonate work-up gave diastereomeric 8-chloro-3,3,7,8,9-pentamethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**152**) (2.8 g, 55%), as a white solid, from the ether layer, and 2-methyl-2-(2-chloro-3,4,5-trimethylphenoxy)propanoic acid (**153**) (2.0 g, 39%) also as a white solid. Diene **152** had m.p. 78 ^{o}C; **IR** (KBr): 1190 (C-O), 1790 (C=O) cm^{-1}; **UV** (hexane): 219 nm (ϵ = 246 m^2 mol^{-1}); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.51 (s, 6H, CH_3-3, CH_3-3), 1.64 (s, 3H, CH_3-8), 2.05 (s, 6H, CH_3-7, CH_3-9), 5.55 (s, 2H, H-6, H-10) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 18.9 (CH_3-7, CH_3-9), 26.5 (CH_3-3, CH_3-3), 27.5 (CH_3-8), 65.7 (C-8), 77.4 (C-3), 100.0 (C-5), 122.7 (C-6, C-10), 144.8 (C-7, C-9), 175.5 (C-2) ppm; analysis calculated for $C_{13}H_{17}ClO_3$: C 60.82%, H 6.68%; found C 60.47%, H 6.57%.

Chloro-acid **153** had m.p. 136-138 ^{o}C; **IR** (KBr): 1160 (C-O), 1700 (C=O) cm^{-1}; ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.59 (s, 6H, $C(CH_3)_2$), 2.14 (s, 3H, CH_3-4), 2.21 (s, 3H, CH_3-5), 2.33 (s, 3H, CH_3-3), 6.76 (s, 1H, H-6) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 16.1 (CH_3-4), 17.3 (CH_3-5), 20.8 (CH_3-3), 24.6 ($C(\underline{C}H_3)_2$), 81.7 ($\underline{C}(CH_3)_2$), 120.8 (C-6), 125.4 (C-2), 132.1 (C-4), 135.1 (C-5), 135.7 (C-3), 147.5 (C-1), 177.7 (C=O) ppm; analysis calculated for $C_{13}H_{17}ClO_3$: C 60.82%, H

6.68%; found: 60.51%, H 6.70%.

2.4.16 Chlorination of 2-Methyl-2-(-2-chloro-3,4,5-trimethylphenoxy)propanoic Acid (**153**)

Acid **153** (1.3 g, 4.5 mmol) was treated with aqueous sodium hypochlorite (9 mmol HOCl). The reaction mixture was stirred at 0 ^{o}C for 30 min. On ether-bicarbonate work-up, 8,10-dichloro-3,3,7,8,9-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**154**) (1.3 g, 89%) was obtained as the sole product. Diene **154** was colorless crystals; m.p. 62 ^{o}C; **IR** (KBr): 1180 (C-O), 1795 (C=O) cm^{-1}; **UV** (hexane): 213 nm (ϵ = 665 m^2 mol^{-1}); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.54 (s, 3H, CH_3-3), 1.61 (s, 3H, CH_3-3), 1.70 (s, 3H, CH_3-8), 2,05 (s, 3H, CH_3-7), 2.14 (s, 3H, CH_3-9), 5.60 (s, 1H, H-6) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 17.1 (CH_3-7), 18.8 (CH_3-9), 24.6, 27.3 (CH_3-3, CH_3-3), 27.8 (CH_3-8), 67.6 (C-8), 78.0 (C-3), 99.3 (C-5), 122.2 (C-6), 127.8 (C-10), 141.6 (C-7), 143.1 (C-9), 174.9 (C-2) ppm; analysis calculated for $C_{13}H_{16}Cl_2O_3$: C 53.62%, H 5.54%; found: C 53.59%, H 5.67%.

2.4.17 Chlorination of 2-Methyl-2-(5-chloro-2,4-dimethyl-phenoxy)propanoic Acid (**155**)

a). Preparation of acid **155**

Diene **133** (3.2 g, 0.15 mol) was dissolved in chloroform (2 cm^3) and the solution was cooled to 0 ^{o}C.

Trifluoroacetic acid (TFA) (2 cm^3) was added to the above solution and the reaction mixture was stirred at ambient temperature for 10 min. Ether was added to the mixture and the solution was washed with aqueous sodium bicarbonate solution. The dried ether layer on evaporation under reduced pressure gave acid **155** (3 g, 94%) as a colorless oil. It had **IR** (CCl_4): 1150 (C-O), 1720 (C=O), 2700-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.60 (s, 6H, $C(CH_3)_2$), 2.16 (s, 3H, CH_3-2), 2.24 (s, 3H, CH_3-4), 5.83 (s, 1H, H-6), 6.99 (s, 1H, H-3) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.2 (CH_3-2), 19.0 (CH_3-4), 25.1 ($C(\underline{C}H_3)_2$), 79.8 ($\underline{C}(CH_3)_2$), 119.0 (C-6), 128.8 (C-2), 129.9 (C-4), 131.0 (C-5), 132.9 (C-3), 151.6 (C-1), 179.1 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 244, 242 (M^+, 3, 8); exact mass calculated for $C_{12}H_{15}ClO_3$: 242.071; found: 242.068.

b). Chlorination of acid **155**

Acid **155** (3 g, 0.012 mol) was treated with aqueous sodium hypochlorite (0.02 mol HOCl). The reaction mixture was stirred at 0 °C for 1 h. On the general ether-bicarbonate work-up, a mixture (3.2 g, 89%) of 7,8-dichloro-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**156**) and 7,10-dichloro-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**157**) was obtained in a ratio of 1 : 1.1.

The two diene mixture was separated by HPLC using 10% ether-petroleum ether mixture as the eluent. The first

fraction on evaporation gave diene **157** as white crystals. It had m.p. 72-73 °C; **IR** (KBr): 1180 (C-O), 1790 (C=O) cm^{-1}; **UV** (hexane): 275 nm (ϵ = 247 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.50 (s, 3H, CH_3-3), 1.51 (s, 3H, CH_3-3), 1.64 (s, 3H, CH_3-10), 1.86 (d, 3H, CH_3-8, J = 1.7 Hz), 5.83 (d, 1H, H-9, J = 1.7 Hz), 6.06 (s, 1H, H-6) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 19.0 (CH_3-8), 23.5 (CH_3-10), 24.5, 26.3 (CH_3-3, CH_3-3), 68.5 (C-10), 77.8 (C-3), 106.8 (C-5), 125.6 (C-6), 131.1 (C-8), 131.8 (C-9), 136.2 (C-7), 169.0 (C-2) ppm; analysis calculated for $C_{12}H_{14}Cl_2O_3$: C 52.00%, H 5.09%; found: C 51.70%, H 5.25%.

Diene **156** was obtained from the second fraction. It had m.p. 44-45 °C; **IR** (CCl_4): 1180 (C-O), 1800 (C=O) cm^{-1}; **UV** (hexane): 213 nm (ϵ = 677 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.53 (s, 3H, CH_3-3), 1.56 (s, 3H, CH_3-3), 1.77 (s, 3H, CH_3-8), 1.82 (d, 3H, CH_3-10, J = 1.4 Hz), 5.96 (s, 1H, H-6), 6.05 (d, 1H, H-9, J = 1.3 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.1 (CH_3-10), 25.4, 26.5 (CH_3-3, CH_3-3), 29.8 (CH_3-8), 62.6 (C-8), 77.6 (C-3), 101.6 (C-5), 125.2 (C-6), 130.0 (C-10), 134.9 (C-9), 142.0 (C-7), 174.9 (C-2) ppm; analysis calculated for $C_{12}H_{14}Cl_2O_3$: C 52.00%, H 5.09%; found: C 51.60%, H 5.16%.

2.4.18 Chlorination of 2-Methyl-2-(3,5-di-t-butylphenoxy)-propanoic Acid (**129**)

Acid **129** (5.84, 0.02 mol) was treated with aqueous sodium hypochlorite (0.03 mol HOCl). On ether-bicarbonate work-up, a diastereomeric mixture (E:Z = 5:1) of 8-chloro-7,9-di-t-butyl-3,3-dimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**158**) (5.6 g, 86%), was obtained from the ether layer, and a mixture (0.6 g, 9%) of 2-methyl-2-(2-chloro-3,5-di-t-butylphenoxy)propanoic acid (**159a**) and 2-methyl-2-(4-chloro-3,5-di-t-butylphenoxy)propanoic acid (**159b**) in a ratio of 4:1 from the aqueous layer. Crystallization of diene **158** from ether-petroleum ether gave colorless needles of the E-isomer (**158a**); m.p. 99-101 ^{o}C; **IR** (KBr): 1180 (C-O), 1785 (C=O) cm^{-1}; **UV** (hexane): 219 nm (ϵ = 559 m^2 mol^{-1}); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.20 (s, 18H, $C(CH_3)_3$-7, $C(CH_3)_3$-5), 1.53 (s, 6H, CH_3-3, CH_3-3), 4.86 (s, 1H, H-8), 5.81 (s, 2H, H-6, H-10) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 26.2 (CH_3-3, CH_3-3), 29.6 ($C(\underline{C}H_3)_3$-7, $C(\underline{C}H_3)_3$-9), 35.7 ($\underline{C}(CH_3)_3$-7, $\underline{C}(CH_3)_3$-9), 46.7 (C-8), 77.0 (C-3), 102.5 (C-5), 124.9 (C-6, C-10), 153.8 (C-7, C-9), 175.9 (C-2) ppm; analysis calculated for $C_{18}H_{27}ClO_3$: C 66.14%, H 8.33%, Cl 10.85%; found: C 66.59%, H 8.33%, Cl 10.90%. Concentration of the mother liquor gave partially separated the Z-isomer (**158b**) as a colorless oil. Compound **158b** had the identical ^{1}H NMR **158a**; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 26.5 (CH_3-3, CH_3-3), 29.5 ($C(\underline{C}H_3)_3$-7, $C(\underline{C}H_3)_3$-9), 35.7 ($\underline{C}(CH_3)_3$-7, $\underline{C}(CH_3)_3$-9),

46.4 (C-8), 77.4 (C-3), 102.5 (C-5), 125.3 (C-6, C-10), 155.3 (C-7, C-9), 175.9 (C-2) ppm.

Partially separated **159a** had **^{1}H NMR (250 MHz, $CDCl_3$)** δ: 1.26 (s, 9H, $C(CH_3)_3$-5), 1.46 (s, 9H, $C(CH_3)_3$-3), 1.60 (s, 6H, $C(CH_3)_2$), 6.96 (d, 1H, H-6, J = 2.1 Hz), 7.20 (d, 1H, H-4, J = 2.1 Hz) ppm; **^{13}C NMR (62.9 MHz, $CDCl_3$)** δ: 24.8 ($C(\underline{C}H_3)_2$), 29.9 , 31.3 ($C(\underline{C}H_3)_3$-3, & -5), 32.9, 36.9 ($\underline{C}(CH_3)_3$-3, & -5), 81.8 ($\underline{C}(CH_3)_2$), 116.8 (C-6), 120.0 (C-4), 124.4 (C-2), 147.6 (C-5), 149.1 (C-3), 150.9 (C-1), 177.8 (C=O) ppm.

Pure chloro-acid **159b**, obtained from acid-catalysed reaction of diene **158** (sec. 2.6.19), had m.p. 135-136 °C; **IR** (KBr): 1160 (C-O), 1695 (C=OO, 2700-3200 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.45 (s, 18H, $C(CH_3)_3$-3, $C(CH_3)_3$-5), 1.59 (s, 6H, $C(CH_3)_2$), 6.89 (s, 2H, H-2, H-6) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 25.1 ($C(\underline{C}H_3)_2$), 30.3 ($C(\underline{C}H_3)_3$-3, $C(\underline{C}H_3)_3$-5), 37.1 ($\underline{C}(CH_3)_3$-3, $\underline{C}(CH_3)_3$-5), 76.5 ($\underline{C}(CH_3)_2$), 117.7 (C-2, C-6), 128.4 (C-4), 149.6 (C-3, C-5), 152.0 (C-1), 178.6 (C=O) ppm; analysis calculated for $C_{18}H_{27}ClO_3$: C 66.14%, H 8.33%; found: C 66.52%; H 8.12%.

2.4.19 Chlorination of 2-Methyl-2-(4-ethylphenoxy)-propanoic Acid (126)

Acid **126** (8.32 g, 0.04 mol) was treated with aqueous sodium hypochlorite (0.06 mol HOCl) and the reaction mixture was stirred at ambient temperature for 1 h. Work-up

gave 8-chloro-8-ethyl-3,3-dimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**160**) (2.72 g, 28%) from the ether layer, and 2-methyl-2-(2-chloro-4-ethylphenoxy)propanoic acid (**161**) (6.2 g, 64%) from the bicarbonate layer. Crystallization of the crude diene from ether-petroleum ether gave pure diene **160** as a white crystalline solid. It had m.p. 74-75 ^{o}C; **IR** (KBr): 1195 (C-O), 1790 (C=O) cm^{-1}; **UV** (hexane): 212 nm (ϵ = 290 m^2 mol^{-1}); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 0.89 (t, 3H, $CH_2C\underline{H}_3$, J = 7.1 Hz), 1.51 (s, 3H, CH_3-3), 1.52 (s, 3H, CH_3-3), 1.97 (m, 2H, $C\underline{H}_2CH_3$, J = 7.0 Hz), 5.80 (d, 2H, H-6, H-10, J = 9.3 Hz), 6.17 (d, 2H, H-7, H-9, J = 9.3 Hz) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 9.20 ($CH_2\underline{C}H_3$), 26.4 (CH_3-3, CH_3-3), 36.0 ($\underline{C}H_2CH_3$), 62.8 (C-8), 77.2 (C-3), 98.4 (C-5), 126.2 (C-6, C-10), 137.1 (C-7, C-9), 175.3 (C-2) ppm; analysis calculated for $C_{12}H_{15}ClO_3$: C 59.38%, H 6.27%, Cl 14.61%; found C 59.30%, H 6.07%, Cl 14.92%.

Chloro-acid **161** was obtained as a brown oil; **IR** (CCl_4): 1145 (C-O), 1715 (C=O), 2700-3200 (COOH); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.19 (t, 3H, $CH_2C\underline{H}_3$, J = 7.5 Hz), 1.60 (s, 6H, $C(CH_3)_2$), 2.57 (m, 2H, $C\underline{H}_2CH_3$, J + 7.5 Hz)), 6.98 (bs, 2H, H-5, H-6), 7.20 (s, 1H, H-3) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.2 ($CH_2\underline{C}H_3$), 24.7 ($C(\underline{C}H_3)_2$), 27.9 ($\underline{C}H_2CH_3$), 81.7 ($\underline{C}(CH_3)_2$), 120.7 (C-2),121.8 (C-6), 126.9 (C-5), 128.6 (C-4), 129.7 (C-3), 148.3 (C-1), 178.0 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity) 244, 242 (M^+ 3.5, 12), 158,

156 (C_8H_9ClO, 19, 62), 143, 141 (C_7H_6ClO, 30, 100).

2.4.20 Chlorination of 2-Methyl-2-(4-isopropylphenoxy)-propanoic Acid (127)

Acid **127** (8.88 g, 0.04 mol) was treated with aqueous sodium hypochlorite (0.06 mol HOCl). The reaction mixture was stirred at ambient temperature for 1 h. Work-up gave 8-chloro-3,3-dimethyl-8-isopropyl-1,4-dioxaspiro-[4,5]deca-6,9-dien-2-one (**162**) (2.2 g, 22%) from the ether layer, and 2-methyl-2-(2-chloro-4-isopropylphenoxy)-propanoic acid (**163**) (7.2 g, 72%) from the aqueous layer. Crystallization of diene **162** from ether-petroleum ether gave pure diene **162** as a white solid; m.p. 85 °C; IR (KBr): 1100 (C-O), 1785 (C=O) cm^{-1}; UV (hexane): 212 nm (ϵ = 250 m^2 mol^{-1}); ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.99 (d, 6H, $CH(C\underline{H}_3)_2$, J = 6.9 Hz), 1.50 (s, 3H, CH_3-3), 1.52 (s, 3H, CH_3-3), 2.08 (m, 1H, $C\underline{H}(CH_3)_2$, J = 6.9 Hz), 5.82 (d, 2H, H-6, H-10, J = 10 Hz), 6.20 (d, 2H, H-7, H-9, J = 10 Hz) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_C: 17.8 ($CH(\underline{C}H_3)_2$), 26.4 (CH_3-3, CH_3-3), 38.6 ($\underline{C}H(CH_3)_2$), 66.6 (C-8), 77.1 (C-3), 98.6 (C-5), 126.7 (C-6, C-10), 136.1 (C-7, C-9), 175.4 (C-2) ppm; analysis calculated for $C_{13}H_{17}ClO_3$: C 60.82%, H 6.67%; found: C 60.74%, H 6.66%.

Chloro-acid **163** had m.p. 75-77 °C, IR (KBr): 1160 (C-O), 1710 (C=O), 2700-3300 (COOH) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.21 (d, 6H, $CH(C\underline{H}_3)_2$, J = 7.0 Hz), 1.60 (s, 6H,

$C(CH_3)_2$), 2.86 (sep, 1H, $C\underline{H}(CH_3)_2$, J =7.0 Hz), 6.99 (s, 2H, H-5, H-6), 7.23 (s, 1H, H-3) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 23.8 ($CH(\underline{C}H_3)_2$), 24.7 ($C(\underline{C}H_3)_2$), 33.3 ($\underline{C}H(CH_3)_2$), 81.7 ($\underline{C}(CH_3)_2$), 120.6 (C-2), 121.8 (C-6), 125.5 (C-5), 127.1 (C-4), 128.3 (C-3), 148.2 (C-1), 177.8 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 258, 256 (M^+, 1, 3), 216, 214 ($C_{11}H_{12}ClO_3$, 2, 5), 171, 169 ($C_9H_{10}ClO$, 6, 18), 128 (100).

2.4.21 <u>Chlorination of 2-Methyl-2-(4-t-butylphenoxy)-propanoic Acid (128)</u>

Acid **128** (9.44 g, 0.04 mol) was treated with aqueous sodium hypochlorite (0.06 mol HOCl). The reaction mixture was stirred at 0 °C for 1 h. Ether-bicarbonate work-up yielded 8-t-butyl-8-chloro-3,3-dimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**164**) (2.3 g, 21%) from the ether layer, and 2-methyl-2-(2-chloro-4-t-butyl-phenoxy)propanoic acid (**165**) (7.1 g, 66%) from the aqueous layer. Colorless crystals of pure diene **164** was obtained on recrystallization; m.p. 93-94 °C; **IR** (KBr): 1190 (C-O), 1780 (C=O) cm^{-1}; **UV** (hexane): 212 nm (ϵ = 402 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.06 (s, 9H, $C(CH_3)_3$), 1.50 (s, 3H, CH_3-3), 1.52 (s, 3H, CH_3-3), 5.81 (d, 2H, H-6, H-10, J = 9.5 Hz), 6.35 (d, 2H, H-7, H-9, J = 9.5 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 25.7 ($C(\underline{C}H_3)_3$), 26.4 (CH_3-3, CH_3-3), 38.9 ($\underline{C}(CH_3)_3$), 69.9 (C-8), 78.5 (C-3), 98.2 (C-5), 125.9 (C-6, C-10), 136.1 (C-7, C-9), 175.5 (C-2) ppm; analysis

calculated for $C_{14}H_{19}ClO_3$: C 62.10%, H 7.07%; found: C 61.98%, H 6.94%.

Chloro-acid **165** had m.p. 69-71 ^{o}C; **IR** (KBr): 1160 (C-O), 1705 (C=O), 2700-3500 (COOH) cm^{-1}; ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.27 (s, 9H, $C(CH_3)_3$), 1.60 (s, 6H, $C(CH_3)_2$), 6.98 (d, 1H, H-6, J = 8.5 Hz), 7.17 (dd, 1H, H-5, J = 8.6, 2.2 Hz), 7.37 (d, 1H, H-3, J = 2.1 Hz) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 24.7 ($C(\underline{C}H_3)_2$, 31.2 ($C(\underline{C}H_3)_3$), 34.4 ($\underline{C}(CH_3)_3$), 81.7 ($\underline{C}(CH_3)_2$), 121.3 (C-6), 121.7 (C-2), 124.5 (C-5), 127.5 (C-3), 147.9 (C-4), 148.0 (C-1), 177.8 (C=O) ppm; **MS** M/Z (relative intensity): 272, 270 (M^+, 4, 13), 186, 184 ($C_{10}H_{13}ClO$, 7, 22), 171, 169 ($C_9H_{10}ClO$, 33, 100). Analysis calculated for $C_{14}H_{19}ClO_3$: C 62.10%, H 7.07; found: C 61.91%, H 7.03%.

2.5 SHIFT REAGENT STUDIES

Tris (1,1,1,2,2,3,3-heptafluoro-7,7-[$^{2}H_6$]-dimethyl-4,6-[$^{2}H_3$]-octanedionato)europium (III) ($Eu(fod)_3$) was used to determine the relative stereochemistry of the diastereomeric dienes obtained from the chlorination of acids **122** (dienes **142a** and **142b**) and **129** (dienes **158a** and **158b**). In a typical experiment, a solution of the shift reagent (0.45 g) in chloroform-d (0.3 cm^3) was added in 0.01 mL increments to a solution of the diene (30 mg) in $CDCl_3$ (0.3 cm^3). After each addition the ^{1}H NMR spectrum (90 MHz) was recorded at 0 ^{o}C, using tetramethylsilane

(TMS) as the internal standard. The chemical shifts for each type of proton were plotted against the shift of the 3-$C(CH_3)_2$ group. The results are tabulated in Table 2.1.

The relative stereochemistry was assigned on the basis that the greater relative gradient of the proton shifts of 8-methyl or 8-H would be exhibited by the (E) isomer (Although the use of E and Z as description of cis and trans stereoisomers is normally restricted to structures involving isomers about carbon double bond, for the convenience of the reader we have used them to designate the stereochemistry with respect to the six membered cyclohexadiene ring. The use of cis and trans requires the relevant substituents be described as prefixes or suffixes in the name. In the present case the cis and trans groups at the spiro junction are not described in the form of prefixes or suffixes to which the cis and trans designation can be applied).

Table 2.1

Relative gradient of ^1H shifts upon addition of $Eu(fod)_3$ -

Diene	H-9	H-6	7-CH_3	8-CH_3	3-CH_3
142a (Z)	0.20	0.53	0.05	0.075	1.00
142b (E)	0.23	0.52	0.065	0.25	1.00

Diene	H-6,	H-10	H-8	3-CH_3
158a (E)		0.55	0.13	1.00
158b (Z)		0.81	0.04	1.00

2.6 REACTIONS OF *IPSO* ADDUCTS WITH ACIDS

2.6.1 Reactions of 8-Chloro-3,3,8-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (130)

a) Reaction with trifluoroacetic acid (TFA)

Diene **130** (20 mg, 0.09 mmol) was dissolved in a 1:1 (v/v) mixture of TFA and $CDCl_3$ (0.4 cm^3) at ambient temperature and the reaction was monitored by ^1H NMR (90 MHz). After 3 h, diene **130** had completely reacted. The reaction mixture was poured into ether (30 cm^3) and washed with aqueous sodium bicarbonate solution (10 cm^3). The ether layer was separated, dried over anhydrous magnesium sulfate, and evaporated on a rotavapor. The pale yellow oil (18 mg) obtained was 2-methyl-2-(3-chloro-4-methylphenoxy)-propanoic acid (**166**). Acid **166** had **MS** (70 ev) M/Z (relative intensity): 230, 228 (M^+, 3, 10), 144, 142 (C_7H_7ClO, 33, 100); **IR** (CCl_4): 1160 (C-O), 1710 (C=O), 2700-3200 (COOH) cm^{-1}; ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.58 (s, 6H, $C(CH_3)_2$), 2.29 (s, 3H, CH_3-4), 6.74 (dd, 1H, H-6, J = 8.4, 2.6 Hz), 6.96 (bs, 1H, H-2), 7.08 (d, 1H, H-5, J = 8.4 Hz) ppm; ^{13}C

NMR ($CDCl_3$, 62.9 MHz) δ_C: 19.2 (CH_3-4), 25.1 ($C(\underline{C}H_3)_2$), 79.8 ($\underline{C}(CH_3)_2$), 118.8 (C-6), 121.5 (C-2), 129.7 (C-4), 130.5 (C-5), 134.3 (C-3), 153.1 (C-1), 178.0 (C=O) ppm.

b) Reaction with trifluoromethane sulfonic acid (triflic acid)

Triflic acid (0.02 cm^3) was added to a solution of diene **130** (20 mg, 0.09 mmol) in chloroform-d (0.3 cm^3) in a ^1H NMR tube cooled to -40 ^oC. After 10 min at -20 ^oC, ^1Hnmr indicated that half of the starting diene had been converted to chloro-acid **166**. After 10 min at 0 ^oC, the reaction was complete and acid **166** was the sole product. The reaction mixture was dissolved in ether and washed with distilled water. The ether layer on evaporation gave acid **166** (15 mg).

c) Reaction with boron trifluoride-diethyl etherate

To a solution of boron trifluoride-diethyl etherate (0.4 cm^3) at 0 ^oC diene **130** (25 mg, 0.1 mmol) was added and the mixture was stirred for 20 min at ambient temperature. Work-up with ether-aqueous bicarbonate gave acid **166** (16 mg) as the sole product.

2.6.2 Reaction of 8-chloro-3,3,7,8-tetramethyl-1,4-dioxa-spiro[4,5]deca-6,9-dien-2-one (132)

a) Reaction with trifluoroacetic acid

Diene **132** (40 mg, 0.17 mmol) was dissolved in a 1:1

(v/v) mixture of TFA and chloroform-d (0.4 cm^3), plus a drop of trifluoroacetic anhydride, at 0 °C. After 20 min ^1H NMR of the mixture showed that the reaction was completed. Work-up with aqueous bicarbonate gave 2-methyl-2-(3-chloro-4,5-dimethylphenoxy)propanoic acid **167** (32 mg, 80%), a pale yellow oil, as the sole product. Acid **167** had **IR** (CCl_4): 1160 (C-O), 1710 (C=O), 2700-3300 (COOH) cm^{-1}; **^1H NMR** ($CDCl_3$, 250 MHz) δ: 1.74 (s, 6H, $C(CH_3)_2$), 2.23 (s, 3H, CH_3-4), 2.24 (s, 3H, CH_3-5), 6.66 (d, 1H, H-6, J = 2.4 Hz), 6.83 (d, 1H, H-2, J = 2.4 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 15.6 (CH_3-4), 21.1 (CH_3-5), 25.0 ($C(\underline{C}H_3)_2$), 80.0 ($\underline{C}(CH_3)_2$), 119.2 (C-6), 121.0 (C-2), 129.6 (C-4), 134.4 (C-3), 139.1 (C-5), 152 0 (C-1), 177.6 (C=O) pp; **MS** (70 ev) M/Z (relative intensity): 244, 242 (M^+, 8.9, 24.2), 158, 156 (C_8H_9ClO, 32, 100); exact mass calculated for $C_{12}H_{15}ClO_3$: 242.071; found: 242.070.

b) Reaction with triflic acid

Diene **132** (40 mg, 0.17 mmol) was dissolved in chloroform-d (0.4 cm^3) and the solution was cooled to -60 °C. Triflic acid (0.01 cm^3) was added to the above solution and the reaction was followed by ^1H NMR. When the mixture was warmed up to 0 °C in 10 min reaction was complete. Work-up with aqueous bicarbonate gave a mixture (30 mg) of chloro-acid **167** (57%) and 4-chloro-3,4-dimethylcyclohexa-2,5-dienone (**168**) (43%) as a light brown oil.

Partially separated dienone **168**[94] had **^1H NMR** ($CDCl_3$,

90 MHz) δ: 1.77 (s, 3H, CH_3-4), 2.16 (s, 3H, CH_3-3), 6.08 (bs, 1H, H-2), 6.15 (bd, 1H, H-6, J = 9 Hz), 6.94 (d, 1H, H-5, J = 9 Hz) ppm.

c) With boron trifluoride-diethyl etherate

To a solution of boron trifluoride-diethyl etherate (0.4 cm^3) at 0 °C diene **132** (40 mg, 0.17 mol) was added and the reaction mixture was stirred at ambient temperature for 30 min. After aqueous bicarbonate work-up dienone **168** was obtained as the sole product.

2.6.3 Reactions of 8-Chloro-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (133)

a) With trifluoroacetic acid

Diene **133** (20 mg, 0.08 mmol) was dissolved in a 1:3 (v/v) mixture (0.4 cm^3) of TFA and chloroform-d at -20 °C. After 10 min at ambient temperature the reaction was complete. Work-up gave 2-methyl-2-(5-chloro-2,4-dimethylphenoxy)propanoic acid (**155**) (17 mg, 80%) as the sole product.

b) With triflic acid

Diene **133** (20 mg, 0.08 mmol) was dissolved in chloroform-d (0.3 cm^3) and the solution cooled to -60 °C. Triflic acid was added to the above solution and the reaction mixture was warmed up to 0 °C over 10 min, after which time the reaction was complete. Work-up gave acid **155**

(18 mg, 80%) as the sole product.

c) With boron trifluoride-diethyl etherate

Diene **133** (30 mg, 0.12 mmol) was dissolved in boron trifluoride-diethyl etherate (0.4 cm^3) at ambient temperature. The reaction was complete after 30 min. On aqueous bicarbonate work-up, acid **155** (25 mg, 83%) was obtained.

2.6.4 Reactions of 10-Chloro-3,3,10-trimethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (135)

a) With trifluoroacetic acid

Diene **135** (20 mg, 0.08 mmol) was dissolved in a 3:1 (v/v) mixture (0.4 cm^3) of TFA and chloroform-d at 0 ^oC. The reaction mixture was warmed to ambient temperature over 10 min and the ^1H NMR showed that the reaction was complete. Aqueous bicarbonate work-up afforded 2-methyl-2-(5-chloro-2-methylphenoxy)propanoic acid (**169**) (17 mg, 85%), a white solid, as the sole product. Acid **169** had m.p. 73-74 ^oC; **IR** (KBr): 1160 (C-O), 1705 (C=O), 2700-3200 (COOH) cm^{-1}; **^1H NMR** ($CDCl_3$, 250 MHz) δ: 1.63 (s, 6H, $C(CH_3)_2$), 2.18 (s, 3H, CH_3-2), 6.80 (d, 1H, H-6, J = 2.0 Hz), 6.90 (dd, 1H, H-4, J = 8.0, 2.0 Hz), 7.06 (d, 1H, H-3, J = 8.0 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.3 (CH_3-2), 25.2 ($C(\underline{C}H_3)_2$), 79.7 ($\underline{C}(CH_3)_2$), 118.2 (C-6), 122.6 (C-4), 128.6 (C-2), 131.3 (C-5), 131.7 (C-3), 153.8 (C-1),

178.9 (C=O) ppm. **MS** (70 ev) M/Z (relative intensity): 230, 228 (M^+, < 1), 144, 142 (C_7H_7ClO, 32, 100); exact mass calculated for $C_{11}H_{13}Cl$: 228.055; found: 228.058.

b) <u>With triflic acid</u>

Diene **135** (20 mg, 0.09 mmol) was dissolved in chloroform-d (0.4 cm^3) at -60 ^oC. Triflic acid (0.02 cm^3) was added to the solution and the reaction mixture was warmed up to ambient temperature in 15 min. Work-up of the reaction mixture gave an oil (18 mg), which was identified by GC/Mass as a mixture of 2-methyl-2-(6-chloro-2-methyl-phenoxy)propanoic acid (**170**) (>95%) and 3,3,5-trimethylbenzo-1,4-dioxin-2-one (**170a**) (<5%). Dioxin **170a** had **MS** (70 ev) M/Z (relative intensity): 152 (M^+, 100).

The crude product mixture was dissolved in ether (50 cm^3) and the solution was extracted with saturated aqueous sodium bicarbonate (3 x 50 cm^3). The aqueous layer was acidified with aqueous hydrochloric acid and extracted with ether. Solvent evaporation of the ether layer gave acid **170** as a yellow oil; **IR** (CCl_4): 1140 (C-O), 1710 (C=O), 2700-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.57 ($C(CH_3)_2$), 2.28 (CH_3-2), 6.96 (t, 1H, H-4, J = 8 Hz), 6.96 (d, 1H, H-3, J = 8 Hz), 7.08 (d, 1H, H-5, J = 8 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 18.1 (CH_3-2), 25.1 ($C(\underline{C}H_3)_2$), 82.7 ($\underline{C}(CH_3)_2$), 125.3 (C-4), 128.0 (C-3), 129.4 (C-6), 129.7 (C-5), 135.0 (C-2), 149.5 (C-1), 176.9 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 230, 228 (M^+, 1, 3), 144,

142 (C_7H_7ClO, 30, 100); exact mass caculated for $C_{11}H_{13}ClO_3$: 228.055; found: 228.061.

2.6.5 Reactions of 10-Chloro-3,3,9,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (137)

a) With trifluoroacetic acid

Diene **137** (20 mg, 0.08 mmol) was dissolved in a 3:1 (v/v) mixture (0.4 cm^3) of TFA and chloroform-d at 0 ^oC, and the reaction mixture was warmed up to ambient temperature. After 10 min the NMR of the mixture showed that the reaction was complete. On aqueous bicarbonate work-up, 2-methyl-2-(5-chloro-2,3-dimethylphenoxy)propanoic acid (**171**) (15 mg, 75%), a pale yellow solid, was obtained as the sole product. Recrystallization from ether-petroleum ether gave colorless crystals of the pure acid **171**. m.p. 128-129 ^oC; **IR** (KBr): 1160 (C-O), 1705 (C=O), 2700-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.61 (s, 6H, $C(CH_3)_2$), 2.10 (s, 3H, CH_3-2), 2.21 (s, 3H, CH_3-3), 6.71 (bs, 1H, H-6), 6.84 (bs, 1H, H-4) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 12.3 (CH_3-2), 20.1 (CH_3-3), 25.1 ($C(\underline{C}H_3)_2$), 79.8 ($\underline{C}(CH_3)_2$), 116.3 (C-6), 124.2 (C-4), 127.3 (C-2), 130.3 (C-5), 139.5 (C-3), 153.5 (C-1), 179.7 (C=O); analysis calculated for $C_{12}H_{15}ClO_3$: C 59.38%, H 6.23%; found: C 59.08%, H 6.28%.

b) With TFA in the presence of sodium acetate

Diene **137** (40 mg, 0.16 mmol) and sodium acetate (0.16 mmol) was dissolved in the mixture of TFA (0.1 cm^3) and acetic acid (5 cm^3). The reaction mixture was refluxed for 10 h. Work-up gave a mixture of the 6-chloro acid **197** (sec. 2.7, part b), the 5-chloro acid **171**, and 2-methyl-2-(5-acetoxy-2,3-dimethylphenoxy)propanoic acid (**171a**) in a ratio of 6 : 1 : 3. Partially separated **171a** had **^{1}H NMR (90 MHz, $CDCl_3$)** δ: 1.60 (s, 6H, $C(CH_3)_2$), 2.00 (s, 6H, CH_3-2, CH_3-3), 2.10 (s, 3H, $OCOCH_3$), 6.50 (bs, 1H, H-6), 6.60 (s, 1H, H-4) ppm; GCMS: 266 (molecular ion).

c) <u>With triflic acid</u>

Triflic acid (0.02 cm^3) was added to a solution of diene **137** (40 mg, 0.17 mmol) in chloroform-d (0.4 cm^3) in a ^{1}H NMR tube at -40 ^oC. When reaction mixture was warmed up to ambient temperature over 20 min the reaction was complete. Work-up gave 3,3,5,6-tetramethylbenzo-1,4-dioxin-2-one (**172**) (32 mg), a pale yellow oil, as the sole product. It had **IR** (CCl_4): 1160 (C-O), 1785 (C=O) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.55 (s, 6H, CH_3-3, CH_3-3), 2.13 (s, 3H, CH_3-5), 2.22 (s, 3H, CH_3-6), 6.77 (s, 2H, H-7, H-8) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 11.5 (CH_3-5), 19.5 (CH_3-6), 23.8 (CH_3-3, CH_3-3), 75.9 (C-3), 113.0 (C-8), 123.3 (C-7), 126.0 (C-5), 133.9 (C-6), 139.0 (C-8a), 139.6 (C-4a), 167.8 (C-2) ppm; **MS** (70 ev) M/Z (relative intensity): 206 (M^+, 21), 178 ($C_{11}H_{14}O_2$, 16), 163 ($C_{10}H_{11}O_2$, 100); exact mass calculated for $C_{12}H_{14}O_3$: 206.094; found: 206.091.

2.6.6 Reactions of 10-Chloro-3,3,7,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (139)

a) With trifluoroacetic acid

Diene **139** (20 mg, 0.08 mmol) was dissolved in a 1:1 (v/v) mixture of TFA and chloroform-d (0.4 cm^3) at 0 ^oC. The reaction mixture was warmed to ambient temperature over 20 min after which time the ^1H NMR of the mixture showed the reaction was complete. Aqueous bicarbonate work-up gave 2-methyl-2-(5-chloromethyl-2-methylphenoxy)propanoic acid (**173**) (18 mg, 90%), a white solid, as the sole product. Acid **173** had m.p. 109-110 ^oC; **IR** (KBr): 1160 (C-O), 1710 (C=O), 2700-3200 (COOH) cm^{-1}; **^1H NMR** ($CDCl_3$, 250 MHz) δ: 1.62 (s, 6H, $C(CH_3)_2$), 2.22 (s, 3H, CH_3-2), 4.49 (s, 2H, CH_2-Cl), 6.82 (bs, 1H, H-6), 6.94 (bd, 1H, H-4, J = 7.6 Hz), 7.13 (d, 1H, H-3, J = 7.6 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.6 (CH_3-2), 25.2 ($C(\underline{C}H_3)_2$), 46.2 (CH_2Cl), 79.6 ($\underline{C}(CH_3)_2$), 118.1 (C-6), 122.7 (C-4), 130.4 (C-2), 131.3 (C-3), 135.9 (C-5), 153.2 (C-1), 178.4 (C=O) ppm; analysis calculated for $C_{12}H_{15}ClO_3$: C 59.38%, H 6.23%; found: C 59.39%, H 6.30%.

b) With triflic acid

To a solution of diene **139** (20 mg, 0.08 mmol) in chloroform-d (0.4 cm^3) at -40 ^oC triflic acid (0.02 cm^3) was added and the reaction mixture was warmed to 20 ^oC over

20 min. The ^{1}H NMR showed that the reaction was completed. Work-up gave a mixture of acid **173** and 2-methyl-2-(6-chloro-2,5-dimethylphenoxy)propanoic acid (**174**) in a ratio of 1:4. Acid **174** was obtained as a pale yellow oil; **IR** (CCl_4): 1140 (C-O), 1710 (C=O), 2700-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.56 (s, 6H, $C(CH_3)_2$), 2.25 (s, 3H, CH_3-2), 2.32 (s, 3H, CH_3-5), 6.93 (d, 1H, H-4, J = 10 Hz), 6.95 (d, 1H, H-3, J = 10 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 18.1 (CH_3-2), 20.3 (CH_3-5), 25.1 ($C(\underline{C}H_3)_2$), 82.9 ($\underline{C}(CH_3)_2$), 126.7 (C-4), 128.7 (C-3), 129.7 (C-2), 131.7 (C-6), 135.3 (C-5), 149.5 (C-1), 176.2 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 242 (M^+, 1), 156, 158 (C_8H_9ClO, 29, 100).

c) With boron trifluoride-diethyl etherate

Diene **139** (40 mg, 0.17 mmol) was dissolved in boron trifluoride-diethyl etherate (0.4 cm^3) at ambient temperature. The reaction mixture was stirred for 1 h. On aqueous bicarbonate work-up, a mixture (32 mg) which contained mainly acid **173** and trace of acid **174** was obtained.

2.6.7 Reactions of 8,10-Dichloro-3,3,8-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (141)

a) With trifluoroacetic acid

Diene **141** (25 mg, 0.1 mmol) was dissolved in a 1:3 mixture (0.4 cm^3) of TFA and chloroform-d at 0 ^{o}C. After

5 h at ambient temperature the ^1H NMR of the mixture showed that the reaction was complete. Aqueous bicarbonate work-up gave 2-methyl-2-(2,5-dichloro-4-methylphenoxy)propanoic acid (**175**) (18 mg, 72%), a pale yellow solid, as the sole product. Acid **175** had m.p. 78-80 ^oC; **IR** (CCl_4): 1160 (C-O), 1720 (C=O), 2800-3200 (COOH) cm^3; **^1H NMR** ($CDCl_3$, 250 MHz) δ: 1.61 (s, 6H, $C(CH_3)_2$), 2.28 (s, 3H, CH_3-4), 7.10 (s, 1H, H-6), 7.24 (s, 1H, H-3) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 19.3 (CH_3-4), 24.7 ($C(\underline{C}H_3)_2$), 82.4 ($\underline{C}(CH_3)_2$), 122.7 (C-6), 125.9 (C-2), 131.7 (C-3), 132.6 (C-4), 132.9 (C-5), 148.8 (C-1), 176.6 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 264, 262 (M^+, 1, 2), 178, 176 ($C_7H_6Cl_2O$, 12, 16), 28 (100).

b) <u>With triflic acid</u>

Diene **141** (30 mg, 0.12 mmol) was dissolved in chloroform-d (0.4 cm^3) in a ^1H NMR tube and the solution was cooled to -40 ^oC. Triflic acid was added to the above solution and the reaction mixture was warmed up to 0 ^oC. after 5 min at ^oC, the reaction was complete. On work-up following the general procedure acid **175** (27 mg, 90%) was obtained as the sole product.

2.6.8 <u>Reactions of 8,10-Dichloro-3,3,7,8-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (142)</u>

a) <u>With trifluoroacetic acid</u>

Diene **142** (50 mg, 0.18 mmol) was dissolved in a 1:3

mixture (0.4 cm^3) of TFA and chloroform-d. After 4 h at ambient temperature the reaction was complete. Aqueous bicarbonate work-up gave a mixture (42 mg) of 2-methyl-2-(2-chloro-5-chloromethyl-4-methylphenoxy)propanoic acid (**176**) and 2-methyl-2-(2,6-dichloro-3,4-dimethylphenoxy)-propanoic acid (**177**) in a ratio of 1:1.4.

Acid **176** and **177** were separated by TLC (silica) using 25% ether-petroleum ether as the eluent. The first fraction on evaporation gave acid **177** as a pale yellow oil; **IR** (CCl_4): 1160 (C-O), 1705 (C=O), 2700-3200 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.60 (s, 6H, $C(CH_3)_2$), 2.24 (s, 3H, CH_3-4), 2.27 (s, 3H, CH_3-3), 7.09 (s, 1H, H-5) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.9 (CH_3-4), 20.4 (CH_3-3), 24.9 ($C(\underline{C}H_3)_2$), 84.3 ($\underline{C}(CH_3)_2$), 123.3 (C-2), 123.6 (C-6), 129.1 (C-5), 131.5 (C-4), 135.3 (C-3), 150.4 (C-1), 175.5 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 278, 276 (M^+, 4, 7), 192, 190 ($C_8H_8Cl_2O$, 62, 100). Acid **176** was obtained from the second band as a white solid; m.p. 158-160 °C; **IR** (CCl_4): 1710 (C-O), 1715 (C=O), 2700-3200 (COOH) cm^{-1}; **^{1}H NMR** (Acetone-d_6, 250 MHz) δ: 1.57 (s, 6H, $C(CH_3)_2$), 2.20 (s, 3H, CH_3-4), 4.55 (s, 2H, CH_2-Cl), 6.87 (s, 1H, H-6), 7.40 (s, 1H, H-3) ppm; **^{13}C NMR** (Acetone-d_6, 62.9 MHz) δ_C: 18.4 (CH_3-4), 25.4 ($C(\underline{C}H_3)_2$), 61.8 (CH_2Cl), 81.1 ($\underline{C}(CH_3)_2$), 122.5 (C-6), 123.7 (C-2), 129.3 (C-3), 135.9 (C-4), 136.6 (C-5), 150.9 (C-1), 175.2 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 276 (M^+, < 1), 243, 241 ($C_{12}H_{14}ClO_3$,

3, 10), 192, 190 ($C_8H_8Cl_2O$, 10, 20), 157, 155 (C_8H_8ClO, 32, 100).

b) With boron trifluoride-diethyl etherate

Diene **142** (30 mg, 0.11 mmol) was dissolved in boron trifluoride-diethyl etherate (0.4 cm^3) at ambient temperature. The reaction was stirred for 1 h. On aqueous bicarbonate work-up a mixture (24 mg) of acid **176** and **177** was obtained in a ratio of 3.3 : 1.

2.6.9 Reaction of 8,10-dichloro-3,3,10-trimethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (143)

With trifluoroacetic acid

The mixture of dienes **143** and **144** (2:1) (30 mg, 0.11 mmol) was dissolved in a 1:3 mixture of TFA and chloroform-d (0.4 cm^3) at 0 ^oC. After 5 h at ambient temperature the reaction was complete. On aqueous bicarbonate work-up, 2-methyl-2-(2,4-dichloro-6-methylphenoxy)propanoic acid (**178**) (25 mg), a pale yellow oil, was obtained as the sole product. Acid **178** had **IR** (CCl_4): 1150 (C-O), 1710 (C=O), 2700-3200 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.55 (s,6H, $C(CH_3)_2$), 2.24 (s, 3H, CH_3-6), 7.06 (d, 1H, H-5, J = 2.5 Hz), 7.20 (d, 1H, H-3, J = 2.5 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 18.1 (CH_3-6), 25.0 ($C(\underline{C}H_3)_2$), 82.6 ($\underline{C}(CH_3)_2$), 127.6 (C-6), 129.6 (C-3), 129.8 (C-2), 130.2 (C-4), 136.3 (C-5), 148.6 (C-1), 177.4 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 262 (M^+, < 1), 178 176 ($C_7H_6Cl_2$,

20, 32), 28 (100); exact mass calculated for $C_{11}H_{12}Cl_2O_3$: 262.017; found: 262.016.

2.6.10 Reactions of 8,10-Dichloro-3,3,9,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (145)

a) With trifluoroacetic acid

Diene **145** (20 mg, 0.07 mmol) was dissolved in a 1:1 mixture (0.4 cm^3) of TFA and chloroform-d at 0 ^oC. After 20 min at ambient temperature the ^1H NMR of the mixture showed the completion of the reaction. On aqueous bicarbonate work-up, 2-methyl-2-(4,6-dichloro-2,3-dimethylphenoxy)-propanoic acid (**179**) (18 mg 90%) was obtained as the sole product. Recrystallization gave colorless crystals of **179**; m.p. 111 ^oC; **IR** (KBr): 1140 (C-O), 1710 (C=O), 2700-3300 (COOH) cm^{-1}; **^1H NMR** ($CDCl_3$, 250 MHz) δ: 1.54 (s 6H, $C(CH_3)_2$), 2.24 (s, 3H, CH_3-2), 2.28 (s, 3H, CH_3-3), 7.25 (s, 1H, H-5) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.5 (CH_3-2), 17.0 (CH_3-3), 25.0 ($C(\underline{C}H_3)_2$), 82.8 ($\underline{C}(CH_3)_2$), 127.0 (C-6), 127.3 (C-5), 130.5 (C-2), 134.7 (C-4), 135.1 (C-3), 148.2 (C-1), 175.0 (C=O) ppm; analysis calculated for $C_{12}H_{14}Cl_2O_3$: C 52.00%, 5.09%; found: C 52.09%, H 5.08%.

b) With triflic acid

To a solution of diene **145** (60 mg, 0.22 mmol) in chloroform-d (0.4 cm^3) at -20 ^oC triflic acid was added. After 10 min at ambient temperature the diene was converted

completely to a mixture of acid **179** (67%) and 7-chloro-3,3,5,6-tetramethylbenzo-1,4-dioxin-2-one (**180**) (33%).

The reaction mixture was poured on to a saturated aqueous bicarbonate solution (50 cm^3) and extracted with ether (3 x 20 cm^3). solvent evaporation of the ether extract gave dioxin **180** (18 mg) as white crystals. Dioxin **180** had m.p. 94-96 ^oC; **IR** (CCl_4): 1170 (C-O), 1785 (C=O) cm^{-1}; **^1H NMR** ($CDCl_3$, 250 MHz) δ: 1.55 (s, 6H, CH_3-3, CH_3-3), 2.17 (s, 3H, CH_3-5), 2.26 (s, 3H, CH_3-6), 6.94 (s, 1H, H-8) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 12.5 (CH_3-5), 16.2 (CH_3-6), 27.8 (CH_3-3, CH_3-3), 76.2 (C-3), 114.1 (C-8), 127.3 (C-5), 127.5 (C-7), 131.6 (C-6), 137.8 (C-8a), 139.4 (C-4a), 167.1 (C-2) ppm; exact mass calculated for $C_{12}H_{13}ClO_3$: 240.055; found: 240.052.

c) With boron trifluoride-diethyl etherate

Diene **145** (30 mg, 0.11 mmol) was dissolved in $BF_3.OEt_2$ (0.4 cm^3) at ambient temperature. The reaction was completed after 30 min. Aqueous bicarbonate work-up gave a mixture of **179** (75%) and **180** (25%) (26 mg).

2.6.11 Reactions of 8,10-Dichloro-3,3,7,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (146)

a) With TFA

Diene **146** (20 mg, 0.07 mmol) was dissolved in a 1:2 mixture of TFA and chloroform-d (0.3 cm^3) at -40 ^oC. After

10 min at 0 ^{o}C, the ^{1}H NMR of the mixture showed the the presence of 8,10-dichloro-3,3,6,9-tetramethyl-1,4-dioxa-spiro[4,5]deca-6,8-dien-2-one (**147**) (50%). When the reaction mixture was warmed to ambient temperature over 20 min, diene **146** was converted completely to the rearranged diene 147. After another 40 min at ambient temperature, diene 147 had aromatized completely to 2-methyl-2-(4,6-dichloro-2,5-dimethylphenoxy)propanoic acid (**181**). Work-up gave colorless crystals of acid **181**. It had m.p. 92-93 ^{o}C; **IR** (KBr): 1145 (C-O), 1705 (C=O), 2700-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.55 (s, 6H, $C(CH_3)_2$), 2.23 (s, 3H, CH_3-2), 2.41 (s, 3H, CH_3-5), 7.11 (s, 1H, H-3) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 17.8 (CH_3-2), 17.9 (CH_3-5), 25.0 ($C(\underline{C}H_3)_2$), 82.5 ($\underline{C}(CH_3)_2$), 129.3 (C-3), 130.4 (C-6), 131.0 (C-2), 132.6 (C-4), 132.9 (C-5), 148.7 (C-1), 177.5 (C=O) ppm; analysis calculated for $C_{12}H_{14}Cl_2O_3$: C 52.00%, H 5.09%; found: C 51.78%, H 5.20%.

b) <u>With triflic acid</u>

To a solution of diene **146** (36 mg, 0.13 mmol) in chloroform-d (0.3 cm^{3}) at -40 ^{o}C, triflic acid (0.03 cm^{3}) was added. The reaction mixture was warmed up to 0 ^{o}C in 10 min and the ^{1}H NMR showed the formation of 2-methyl-2-(4-chloro-5-chloromethyl-2-methylphenoxy)propanoic acid (**182**) (33%). After 15 min at 20 ^{o}C, the reaction was complete. Work-up gave acid **182** (30 mg), a white solid, as the sole product. Acid **182** had **IR** (KBr): 1150 (C-O), 1700 (C=O),

2500-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.62 (s,6H, $C(CH_3)_2$), 2.20 (s, 3H, CH_3-2), 4.60 (s, 2H, CH_2Cl), 6.90 (s, 1H, H-6), 7.18 (s, 1H, H-3) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.4 (CH_3-2), 25.2 ($C(\underline{C}H_3)_2$), 43.6 (CH_2-Cl), 79.8 ($\underline{C}(CH_3)_2$), 119.6 (C-6), 126.8 (C-2), 131.8 (C-3), 132.5 (C-4), 132.7 (C-5), 152.1 (C-1), 178.7 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 278, 276 (M^+, 1, 2), 192, 190 ($C_8H_8Cl_2O$, 40, 69), 157, 155 (C_8H_8ClO, 32, 100); exact mass calculated for $C_{12}H_{14}Cl_2O_3$: 276.032; found: 276.032.

c) With boron trifluoride-diethyl etherate

Diene **146** (100 mg, 0.36 mmol) was dissolved in BF_3OEt_2 (0.5 cm^3) at ambient temperature and the reaction was stirred for 2 h. Aqueous bicarbonate work-up gave a mixture (92 mg) of acids **181** (33%) and **182** (67%) as a yellow oil.

2.6.12 Reactions of 8-Chloro-3,3,7,8,10-pentamethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (148)

a) With TFA

Diene **148** (50 mg, 0.20 mmol) was dissolved in a 2:1 mixture of TFA and chloroform-d (0.3 cm^3) at 0 ^oC and the mixture was left to stand at ambient temperature for 20 min. On aqueous bicarbonate work-up, a mixture (42 mg) of 2-methyl-2-(5-chloromethyl-2,4-dimethylphenoxy)propanoic acid (**183**) (40%) and 2-methyl-2-(6-chloro-2,4,5-trimethylphenoxy)propanoic acid (**184**) was obtained as a yellow solid. Recrystallization of the crude products from

ether-petroleum ether gave colorless crystals of **184**; m.p. 115-116 °C; **IR** (KBr): 1150 (C-O), 1705 (C=O), 2700-3200 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.54 (s, 6H, $C(CH_3)_2$), 2.22 (s, 6H, CH_3-2, CH_3-4), 2.25 (s, 3H, CH_3-5), 6.89 (s, 1H, H-3) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.8 (CH_3-2), 18.0 (CH_3-4), 20.4 (CH_3-5), 25.2 ($C(\underline{C}H_3)_2$), 82.8 ($\underline{C}(CH_3)_2$), 130.0 (C-6), 130.5 (C-3), 130.9 (C-2), 133.4 (C-4), 134.1 (C-5), 147.5 (C-1), 176.5 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 258, 256 (M^+, 1, 5), 172, 170 ($C_9H_{11}ClO$, 33, 100).

b) <u>With boron trifluoride-diethyl etherate</u>

Diene **148** (50 mg, 0.20 mmol) was dissolved in BF_3OEt_2 (0.4 cm^3) at ambient temperature and the reaction mixture was stirred for 1 h. Bicarbonate work-up gave acid **183** (40 mg) as the sole product. Acid **183** had m.p. 148-150 °C; **IR** (KBr): 1150 (C-O), 1705 (C=O), 2700-3300 (COOH) cm^{-1}; **^{1}H NMR** (Acetone-d_6, 250 MHz) δ: 1.55 (s, 6H, $C(\underline{C}H_3)_2$), 2.14 (s, 3H, CH_3-2), 2.20 (s, 3H, CH_3-4), 4.50 (s, 2H, CH_2Cl), 6.62 (s, 1H, H-6), 7.11 (s, 1H, H-3) ppm; **^{13}C NMR** (Acetone-d_6, 62.9 MHz) δ_C: 16.4 (CH_3-2), 18.6 (s, 3H, CH_3-4), 25.6 ($C(\underline{C}H_3)_2$), 62.6 (CH_2-Cl), 79.4 ($\underline{C}(CH_3)_2$), 119.4 (C-6), 126.7 (C-2), 131.2 (C-3), 134.0 (C-4), 140.5 (C-5), 153.7 (C-1), 175.8 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 256 (M^+, < 1), 172, 170 ($C_9H_{11}ClO$, 64, 20), 135 ($C_9H_{11}O$, 100).

2.6.13 Reaction of 10-chloro-3,3,7,9,10-pentamethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**150**) With TFA

Diene **150** (50 mg, 0.2 mmol) was dissolved in a 1:1 mixture (0.4 cm^3) of TFA and chloroform-d at 0 ^oC. After 10 min at 40 ^oC, the reaction was complete. Aqueous bicarbonate work-up gave 2-methyl-2-(5-chloromethyl-2,3-dimethylphenoxy)propanoic acid (**185**) (46 mg), a pale yellow oil, as the sole product. Acid **185** had **IR** (CCl_4): 1150 (C-O), 1710 (C=O), 2700-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.61 (s, 6H, $C(CH_3)_2$), 2.14 (s, 3H, CH_3-2), 2.25 (s, 3H, CH_3-3), 4.47 (s, 2H, CH_2Cl), 6.72 (s, 1H, H-6), 6.88 (s, 1H, H-4) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 12.7 (CH_3-2), 20.4 (CH_3-3), 25.3 ($C(\underline{C}H_3)_2$), 46.4 (CH_2Cl), 79.9 ($\underline{C}(CH_3)_2$), 116.3 (C-6), 124.7 (C-4), 129.3 (C-2), 134.9 (C-5), 139.0 (C-3), 153.1 (C-1), 178.9 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 258, 256 (M^+, 4, 12), 221 ($C_{13}H_{17}O_3$, 3), 172, 170 ($C_9H_{11}ClO$, 17, 57), 135 ($C_9H_{11}ClO$, 100).

2.6.14 Reactions of 8-Chloro-3,3,7,8,9-pentamethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**152**)

a) With TFA

Diene **152** (30 mg, 0.12 mmol) was dissolved in a 1:3 mixture (0.4 cm^3) of TFA and chloroform-d at 0 ^oC and no

reaction was observed in 10 min. When the reaction mixture was warmed to ambient temperature, the reaction was complete after 2 h. On aqueous bicarbonate work-up 2-methyl-2-(5-chloromethyl-3,4-dimethylphenoxy)propanoic acid (**186**) (25 mg, 83%), a pale yellow viscous oil, was obtained as the sole product. It had **IR** (CCl_4): 1160 (C-O), 1715 (C=O), 2700-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.57 (s, 6H, $C(CH_3)_2$), 2.22 (s, 3H, CH_3-4), 2.23 (s, 3H, CH_3-3), 4.53 (s, 2H, CH_2Cl), 6.73 (d, 1H, H-6, J = 2.7 Hz), 6.76 (d, 1H, H-2, J = 2.7 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 14.2 (CH_3-4), 20.6 (CH_3-3), 25.1 ($C(\underline{C}H_3)_2$), 45.2 (CH_2Cl), 79.7 ($\underline{C}(CH_3)_2$), 119.9 (C-6), 121.9 (C-2), 126.3 (C-4), 136.4 (C-5), 138.8 (C-3), 151.8 (C-1), 177.8 (C=O) ppm. **MS** (70 ev) M/Z (relative intensity): 258, 256 (M^+, 3, 13), 221 ($C_{13}H_{11}ClO$, 4), 172, 170 ($C_9H_{11}ClO$, 25, 78), 135 ($C_9H_{11}O$, 100).

b) <u>With triflic acid</u>

Diene **152** (30 mg, 0.12 mmol) was dissolved in chloroform-d (0.3 cm^3) at 0 ^oC and triflic acid (0.1 cm^3) was then added to the solution. After 10 min at ambient temperature the reaction was complete. Workup of the mixture gave 4-chloro-3,4,5-trimethylcyclohexa-2,5-dienone (**187**) as the sole product. Dienone **187** was a white solid; m.p. 58-60 ^oC; **IR** (CCl_4): 1670 (C=O) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.76 (s, 3H, CH_3-4), 2.20 (s, 6H, CH_3-3, CH_3-5), 6.05 (s, 2H, H-2, H-6) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz)

δ_C: 19.5 (CH_3-3, CH_3-5), 27.2 (CH_3-4), 66.4 (C-4), 126.4 (C-2, C-6), 158.2 (C-3, C-5), 184.7 (C-1) ppm; MS (CI): 171 (M+1, 100), 199 (M+29, 6), 211 (M+41, 1); **MS (EI)** (70 ev) M/Z (relative intensity): 172, 170 (M^+, 4, 14), 135 (M^+-Cl, 55), 91 (100).

c). With boron trifluoride-diethyl etherate

Diene **152** (30 mg, 0.12 mmol) was dissolved in BF_3OEt_2 (0.4 cm^3) at ambient temperature. After 4 h the reaction was complete. On aqueous bicarbonate workup a mixture (25 mg) of acid **186** (29%) and dienone **187** (71%) was obtained.

2.6.15 Reactions of 8,10-Dichloro-3,3,7,8,9-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (154)

a) With TFA

Diene **154** (30 mg, 0.10 mmol) was dissolved in a 1:3 mixture (0.4 cm^3) of TFA and chloroform-d at 0 ^oC. No reaction was observed over 10 min. When the reaction mixture was warmed up to ambient temperature the reaction was complete after 4 h. Aqueous bicarbonate workup gave a mixture (27 mg) of 2-methyl-2-(2-chloro-5-chloromethyl-3,4-dimethylphenoxy)propanoic acid (**188**) (45%) and 2-methyl-2-(2,6-dichloro-3,4,5-trimethylphenoxy)propanoic acid (**189**) (55%) as a viscous oil. Crystallization of the crude products from ether-petroleum ether gave pure acid **189** as a white solid. It had m.p. 158-160 ^oC; **IR** (CCl_4): 1150 (C-O),

1720 (C=O), 2700-3200 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.60 (s, 6H, $C(CH_3)_2$), 2.24 (s, 3H, CH_3-4), 2.25 (s, 6H, CH_3-3, CH_3-5) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 17.6 (CH_3-4, CH_3-3, CH_3-5), 25.0 ($C(\underline{C}H_3)_2$), 78.4 ($\underline{C}(CH_3)_2$), 128.3 (C-2, C-6), 133.9 (C-3, C-5), 134.2 (C-4), 145.1 (C-1), 175.0 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 292, 290 (M^+, 2, 1), 206, 204 ($C_9H_{10}Cl_2O$, 100, 62). Concentration of the mother liquor gave acid **188** as a pale yellow oil; **IR** (CCl_4): 1160 (C-O), 1710 (C=O), 2700-3300 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.62 (s, 6H, $C(CH_3)_2$), 2.36 (s, 3H, CH_3-4), 2.47 (s, 3H, CH_3-3), 4.61 (s, 2H, CH_2-Cl), 6.75 (s, 1H, H-6) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.5 (CH_3-4), 19.6 (CH_3-3), 24.7 ($C(\underline{C}H_3)_2$), 41.2 (CH_2-Cl), 82.3 ($\underline{C}(CH_3)_2$), 120.8 (C-6), 131.1 (C-2), 133.9 (C-4), 136.6 (C-5), 137.6 (C-3), 150.0 (C-1), 175.4 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 290 (M^+, < 1), 206,204 ($C_9H_{10}Cl_2O$, 7, 13)), 171, 169 ($C_9H_{10}ClO$, 30, 100).

b) <u>With triflic acid</u>

To a solution of diene **154** (30 mg, 0.1 mmol) in chloroform-d (0.3 cm^3) cooled to 0 °C triflic acid (0.1 cm^3) was added. The reaction was complete after 1 h at ambient temperature. Workup gave 2,4-dichloro-3,4,5-trimethylcyclohexa-2,5-dienone (**190**) (18 mg) as the sole product. Dienone **190** was a viscous oil; **IR** (KBr): 1665 (C=O) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.79 (s, 3H, CH_3-4), 2.21 (s, 3H, CH_3-5), 2.32 (s, 3H, CH_3-3), 6.17 (s, 1H, H-6) ppm;

^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_C: 18.3 (CH_3-5), 19.6 (CH_3-3), 27.6 (CH_3-4), 67.9 (C-4), 125.1 (C-6), 131.2 (C-2), 153.0 (C-5), 158.1 (C-3), 177.2 (C-1) ppm; **MS (CI):** 205 (M+1, 100), 233 (M+29, 4), 245 (M+41, 2); **MS** (70 ev) M/Z (relative intensity): 204 (M^+, 33), 169 (M^+-Cl, 94), 106 (100).

c) With boron trifluoride-diethyl etherate

Diene 154 (30 mg, 0.1 mmol) was dissolved in BF_3OEt_2 (0.4 cm^3) at ambient temperature and the reaction mixture was stirred for 3 h. On aqueous bicarbonate workup a mixture of acid **188** (31%) and dienone **190** (69%) was obtained.

2.6.16 Reaction of 7,10-Dichloro-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (157)

With TFA

Diene **157** (30 mg, 0.11 mmol) was dissolved in a 1:3 mixture (0.4 cm^3) of TFA and chloroform-d at 0 ^oC. After 30 min at ambient temperature the ^1H NMR of the reaction mixture showed the formation of 9,10-dichloro-3,3,6,8-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**157a**)(10%). After 5 h at ambient temperature diene **157** reacted completely. Bicarbonate workup gave 2-methyl-2-(5,6-dichloro-2,4-dimethylphenoxy)propanoic acid (**192**) (28 mg) as the sole product. Acid **192** was a white solid; m.p. 83-85 ^oC; **IR** (CCl_4): 1140 (C-O), 1710 (C=O), 2700-3200 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.54 (s, 6H,

$C(CH_3)_2$), 2.22 (s, 3H, CH_3-2), 2.32 (s, 3H, CH_3-4), 6.95 (s, 1H, H-3) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_C: 17.9 (CH_3-2), 20.6 (CH_3-4), 25.0 ($C(\underline{C}H_3)_2$), 82.8 ($\underline{C}(CH_3)_2$), 117.7 (C-6), 128.7 (C-2), 130.6 (C-3), 132.3 (C-4), 133.9 (C-5), 148.7 (C-1), 176.9 (C=O) ppm; analysis calculated for $C_{12}H_{15}ClO_3$: C 52.00%; H 5.09%; found: C 51.52%, H 4.98%.

2.6.17 Reaction of 7,8-Dichloro-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (156)

With TFA

Diene **156** (30 mg, 0.11 mmol) was dissolved in a 1:3 mixture (0.4 cm^3) of TFA and chloroform-d at 0 ^oC. The reaction was complete after 2 h at ambient temperature. On bicarbonate workup acid **192** was obtained as the sole product.

2.6.18 Reaction of 8-Chloro-3,5-di-t-butyl-3,3-dimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (158)

With TFA

Diene **158** (30 mg, 0.09 mmol) was dissolved in a 1:3 mixture of TFA and chloroform-d (0.4 cm^3) at -60 ^oC. After 5 min at ambient temperature ^1H NMR of the solution showed that the diene was completely aromatized. Aqueous bicarbonate workup gave 2-methyl-2-(4-chloro-3,5-di-t-

butylphenoxy)propanoic acid (**159a**) (28 mg) as the sole product.

2.6.19 Reaction of 8-Chloro-8-ethyl-3,3-dimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**160**)

With TFA

Diene **160** (50 mg, 0.21 mmol) was dissolved in a 1:1 mixture of TFA and chloroform-d (0.4 cm^3) at 0 ^oC. The reaction was observed complete after 2 h at ambient temperature. On bicarbonate workup, a mixture (43 mg) of 2-methyl-2-(3-chloro-4-ethylphenoxy)propanoic acid (**193**) (71%) and 2-methyl-2-(2-chloro-4-ethylphenoxy)propanoic acid (**161**) (29%) was obtained as a pale yellow oil. Partially separated acid **193** had **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.18 (t, 3H, $CH_2C\underline{H}_3$, J = 7.5 Hz), 1.58 (s, 6H, $C(CH_3)_2$), 2.67 (q, 2H, $C\underline{H}_2CH_3$, J = 7.6 Hz), 6.77 (dd, 1H, H-6, J = 8.4, 2.4 Hz), 6.95 (d, 1H, H-2, J = 2.4 Hz), 7.10 (d, 1H, H-5, J = 8.4 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 14.0 ($CH_2\underline{C}H_3$), 25.1 ($C(\underline{C}H_3)_2$), 26.0 ($\underline{C}H_2CH_3$), 79.9 ($\underline{C}(CH_3)_2$), 119.1 (C-6), 121.8 (C-2), 129.6 (C-5), 133.8 (C-4), 136.5 (C-3), 153.0 (C-1), 178.2 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity) (from GC/MASS): 244, 242 (M^+, 5, 15), 158, 156 (C_8H_9ClO, 4, 15), 143, 141 (C_7H_6ClO, 32, 100).

2.6.20 Reaction of 8-Chloro-3,3-dimethyl-8-isopropyl-1,4-

dioxaspiro[4,5]deca-6,9-dien-2-one (162)

With TFA

Diene **162** (30 mg, 0.12 mmol) was dissolved in a 1:3 mixture of TFA and chloroform-d (0.4 cm^3) at 0 ^oC. After 2 h at ambient temperature the reaction was complete. Workup following the general procedure gave 2-methyl-2-(4-chlorophenoxy)propanoic acid (**194**) (20 mg) as the sole product. Crystallization of the crude product from ether-petroleum ether gave acid **194** as white crystals; m.p. 120-122 ^oC; **IR** (KBr): 1130 (C-O), 1700 (C=O), 2700-3200 (COOH) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.58 (s, 6H, $C(CH_3)_2$), 6.85 (d, 2H, H-2, H-6, J = 9.0 Hz), 7.21 (d, 2H, H-3, H-5, J = 9.0 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 25.1 ($C(\underline{C}H_3)_2$), 79.9 ($\underline{C}(CH_3)_2$), 121.9 (C-2, C-6), 128.4 (C-4), 129.3 (C-3, C-5), 153.2 (C-1), 178.2 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 216, 214 (M^+, 2, 6), 130, 128 (C_6H_5ClO, 30, 100); analysis calculated for $C_{10}H_{11}ClO_3$: C 55.95%, H5.17%; found: C 55.81%, H 5.09% .

2.6.21 Reaction of 8-Chloro-8-t-butyl-3,3-dimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (164)

With TFA

Diene **164** (30 mg, 0.11 mmol) was dissolved in a 1:3 (v/v) mixture (0.4 cm^3) of TFA and chloroform-d. After 4 h

at ambient temperature the reaction was complete. Workup gave acid **194** (18 mg) as the sole product.

2.7 THERMAL ISOMERIZATION REACTIONS OF 1,2-ADDUCTS

The general experimental procedure was as follows: the diene (*ca.* 0.1 mmol) was dissolved in chloroform-d (0.3-0.4 cm^3) in a ^1H NMR tube and the tube was placed in a thermostated water-bath at the desired temperature. The reaction was followed by observing the ^1H NMR (90 MHz) of the reaction mixture at suitable time intervals.

a) 10-Chloro-3,3,10-trimethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**135**) (25 mg, 0.11 mmol) in chloroform-d at 60 °C, gave after 8 h its rearranged isomer, 10-chloro-3,3,6-trimethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**195**) (90%). After 12 h at 60 °C, the reaction was complete. Evaporation of the solvent by bubbling nitrogen gas through the solvent gave diene **195** as a pale yellow oil. It had **IR** (CCl_4): 1170 (C-O), 1780 (C=O) cm^{-1}; **UV** (hexane): 267 nm (ϵ = 288 m^2 mol^{-1}; **^1H NMR** ($CDCl_3$, 250 MHz) δ: 1.54 (s, 3H, CH_3-3), 1.60 (s, 3H, CH_3-3), 1.87 (s, 3H, CH_3-6), 4.62 (d, 1H, H-10, J = 3.7 Hz), 5.94 (m, 2H, H-7, H-8), 6.02 (d, 1H, H-9, J = 7.2 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.7 (CH_3-6), 25.3, 26.1 (CH_3-3, CH_3-3), 59.2 (C-10), 77.8 (C-3), 106.6 (C-5), 125.1 (C-8), 125.4 (C-7), 126.1 (C-9), 134.5 (C-6), 174.8 (C-2) ppm; exact mass calculated for $C_{11}H_{13}ClO_3$: 228.055; found: 228.054.

b) 10-Chloro-3,3,9,10-tetramethyl-1,4-dioxaspiro-[4,5]deca-6,8-dien-2-one (137) (50 mg) in chloroform-d gave, after 18 h at 60 °C, the mixture of the rearranged diene, 10-chloro-3,3,6,7-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**196**) (60%) and 2-methyl-2-(6-chloro-2,3-dimethylphenoxy)propanoic acid **197** (30%). Separation of diene **196** and acid **197** was carried out by extracting the ether solution of the reaction mixture with aqueous sodium bicarbonate. The organic layer on evaporation gave a mixture of rearranged diene **196** (90%) and trace amount of unreacted diene **137** (10%). Partially separated diene **196** had **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.57 (s, 3H, CH_3-3), 1.62 (s, 3H, CH_3-3), 1.71 (s, 3H, CH_3-6), 1.86 (s, 3H, CH_3-7), 4.61 (s, 1H, H-10), 5.94 (bs, 2H, H-8, H-9) ppm; **MS** (70 ev) M/Z (relative intensity): 244, 242 (M^+, 4, 13), 207 ($C_{12}H15O_3$, 7), 158, 156 (C_8H_9ClO, 24, 72), 121 (C_8H_9O, 100).

The bicarbonate extract was acidified with conc. HCl, and extracted with ether. Solvent evaporation of the ether layer gave pure acid **197** as a viscous oil. It had **^{1}H NMR** ($CDCl_3$, 90 MHz) δ: 1.64 (s, 6H, $C(CH_3)_2$), 2.20 (s, 3H, CH_3-2), 2.22 (s, 3H, CH_3-3), 6.86 (d, 1H, H-4, J = 9 Hz), 7.12 (d, 1H, H-5, J = 9 Hz) ppm. **MS** (70 ev) M/Z (relative intensity): 244, 242 (M^+, 11, 3), 158, 156 (C_8H_9ClO, 28, 100).

c) 10-Chloro-3,3,7,10-tetramethyl-1,4-dioxaspiro-[4,5]deca-6,8-dien-2-one (139) (25 mg) in chloroform-d at 60

^{o}C was converted, after 1 h, to 10-chloro-3,3,6,9-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**198**) (23%). After 12 h at 60 ^{o}C the reaction gave a mixture of rearranged diene **198** (33%) and acid **174** (33%). After 18 h at 60 ^{o}C, the reaction was complete (55% of diene **198** and 45% of acid **174**). Separation of diene **198** from acid **174** was carried out by extracting the ether solution of the reaction mixture with saturated aqueous sodium bicarbonate solution. The ether extract on evaporation gave pure diene **198** (10 mg) as white crystals; m.p. 160 ^{o}C; **IR** (KBr): 1180 (C-O), 1790 (C=O) cm^{-1}; **UV** (hexane): 270 (ϵ = 350 m^2 mol^{-1}); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.59 (s, 3H, CH_3-3), 1.61 (s, 3H, CH_3-3), 1.87 (s, 3H, CH_3-6), 1.96 (s, 3H, CH_3-9), 4.19 (s, 1H, H-10), 5.81 (d, 1H, H-8, J = 5.7 Hz); 6.03 (d, 1H, H-7, J = 5.7 Hz) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 16.6 (CH_3-6), 20.5 (CH_3-9), 25.7, 25.8 (CH_3-3, CH_3-3), 63.1 (C-10), 77.8 (C-3), 107.2 (C-5), 121.6 (C-8), 126.2 (C-7), 130.5 (C-6), 134.0 (C-9), 175.0 (C-2) ppm; analysis calculated for $C_{12}H_{15}ClO_3$: C 59.38%, H 6.23%; found: C 59.08%, H 6.28%.

d) <u>8,10-dichloro-3,3,10-trimethyl-1,4-dioxaspiro-[4,5]-deca-6,8-dien-2-one (143)</u> (with a small amount of diene **144**) (25 mg) in chloroform-d at 60 ^{o}C gave, after 2 h, quantitatively the rearranged diene 8,10-dichloro-3,3,6-trimethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**144**).

e) <u>8,10-dichloro-3,3,9,10-tetramethyl-1,4-dioxaspiro-</u>

[4,5]deca-6,8-dien-2-one (**145**) (30 mg) in chloroform-d at 60 °C converted , after 9 h, to the rearranged diene, 8,10-dichloro-3,3,6,7-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**199**) (62%). After 18 h, 70% of diene **199** was formed. Evaporation of the solvent by bubbling nitrogen gas through the reaction mixture gave partially separated diene **199**. It had **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.54 (s, 3H, CH_3-3), 1.58 (s, 3H, CH_3-3), 1.88 (s, 3H, CH_3-6), 1,96 (s, 3H, CH_3-7), 4.56 (d, 1H, H-10, J = 5.0 Hz), 6.07 (d, 1H, H-9, J = 5.0 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 13.5 (CH_3-6), 16.4 (CH_3-7), 25.4, 26.0 (CH_3-3, CH_3-3), 58.7 (C-10), 77.9 (C-3), 106.0 (C-5), 121.5 (C-9), 130.7 (C-8), 131.7 (C-6), 135.2 (C-7), 174.6 (C-2) ppm; **MS** (70 ev) M/Z (relative intensity): 278, 276 (M^+, 7, 11), 199, 197 ($C_{11}H_{14}ClO$, 9, 28), 162, 164 ($C_6H_4Cl_2O$, 62, 100); exact mass calculated for $C_{12}H_{14}Cl_2O_3$: 276.032; found: 276.032.

f) 8,10-Dichloro-3,3,7,10-tetramethyl-1,4-dioxaspiro-[4,5]deca-6,8-dien-2-one (**146**) (25 mg) in chloroform-d at 60 °C converted, after 3 h, to 8,10-dichloro-3,3,6,9-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**147**) (100%).

g). 10-chloro-3,3,7,9,10-pentamethyl-1,4-dioxaspiro-[4,5]deca-6,8-dien-2-one (**150**) (30 mg) in chloroform-d was heated at 60 °C for 48 h. No reaction was observed.

h) 7,10-Dichloro-3,3,8,10-tetramethyl-1,4-dioxaspiro-[4,5]deca-6,8-dien-2-one (**157**) (30 mg) in chloroform-d at

60 °C gave, after 3 h, quantitatively 9,10-dichloro-3,3,6,8-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**191**). Solvent evaporation of the reaction mixture gave diene **191** as a white solid; m.p; 137-138 °C; **UV** (hexane): 280 (ϵ = 320 m^2 mol); **IR** (KBr): 1180 (C-O), 1790 (C=O) cm^{-1}; ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.57 (s, 6H, CH_3-3, CH_3-3), 1.86 (s, 3H, CH_3-6), 1.90 (s, 3H, CH_3-8), 4.31 (s, 1H, H-10), 5.96 (s, 1H, H-7) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.9 (CH_3-6), 18.0 (CH_3-8), 25.0 (CH_3-3, CH_3-3), 64.1 (C-10), 76.0 (C-3), 105.9 (C-5), 118.8 (C-6), 124.6 (C-8), 128.6 (C-7), 130.6 (C-9), 173.8 (C-2) ppm; analysis calculated for $C_{12}H_{14}Cl_2O_3$: 52.00%, H 5.09%; found: C 51.60%, H 5.14%.

2.8 SOLVOLYSES OF 1,4-ADDUCTS IN METHANOL

a) Reaction of diene 130

Diene **130** (50 mg, 0.22 mmol) was dissolved in methanol (2 cm^3) and the solution was stood at ambient temperature for 2 h. The reaction mixture was poured of ether (50 cm^3). The ether solution was washed with distilled water (2 x 50 cm^3) and dried over magnesium sulfate. Solvent evaporation of the ether solution under reduced pressure gave 2,4-dimethoxytoluene (**200**)[136] (32 mg, 92%) as a colorless oil. It had ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 2.14 (s, 3H, CH_3), 3.79, 3.80 (s, 3H, each 2-, 4-OCH_3), 6.39 (dd, 1H, H-5, J = 8.0,

2.4 Hz), 6.42 (d, 1H, H-3, J = 2.4 Hz), 7.02 (d, 1H, H-6, J = 8.0 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.4 (CH_3), 55.4, 55.5 (2-, 4-OCH_3), 98.4 (C-3), 103.7 (C-5), 104.1 (C-1), 130.6 (C-6), 158.2, 158.5 (C-2, C-4) ppm.

b) Reaction of diene **132**

Diene **132** (40 mg, 0.17 mmol) was dissolved in methanol (2 cm^3) and the reaction solution was stood at ambient temperature for 2 h. Workup following the general procedure gave 3,4-dimethyl-1,5-dimethoxybenzene (**201**) (25 mg, 87%) as the sole product. **201** was a colorless oil; **IR** (CCl_4): 1150 (C-O), 1600 (C=C) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 2.07 (s, 3H, CH_3-4), 2.25 (s, 3H, CH_3-3), 3.78, 3.79 (s, 3H, each 1-, 5-OCH_3), 6.34 (s, 2H, H-2, H-6) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 10.9 (CH_3-4), 20.4 (CH_3-3), 55.2, 55.5 (1-, 5-OCH_3), 96.0 (C-6), 106.3 (C-2), 117.2 (C-4), 138.1 (C-3), 158.0, 158.3 (C-1, C-5) ppm; **MS** (70 ev) M/Z (relative intensity): 166 (M^+, 100), 135 (M^+-OCH_3, 22).

c) Reaction of diene **133**

Diene **133** (40 mg, 0.17 mmol) was dissolved in methanol and the reaction mixture was stood at ambient temperature for 2 h. Workup following the usual procedure gave 2,4-dimethyl-1,5-dimethoxybenzene (**202**) (27 mg, 95%) as a pale yellow oil; **IR** (CCl_4): 1205 (C-O), 1610 (C=C) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 2.11 (s, 6H, CH_3-2, CH_3-4), 3.81 (s,

6H, 1-OCH_3, 5-OCH_3), 6.40 (s, 1H, H-6), 6.86 (s, 1H, H-3) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 15.1 (CH_3-2, CH_3-4), 55.7 (1-, 5-OCH_3), 95.5 (C-6), 117.8 (C-2, C-4), 132.4 (C-3), 156.4 (C-1, C-5) ppm; **MS** (70 ev) M/Z (relative intensity): 166 (M^+, 100), 151 (M^+-CH_3, 56), 135 (M^+-OCH_3, 25).

d) Reaction of diene **133** in the presence of tris(hydroxymethyl)aminomethane (trizma base)

Diene **133** (40 mg, 0.17 mmol) was dissolved in a methanol solution (2 cm^3) of trizma base (24 mg, 0.2 mmol) and the reaction mixture was stood at ambient temperature for 2 h. Workup gave 8-methoxy-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**203**) (36 mg, 89%) as a pale yellow oil. Methoxy diene **203** had **IR** (CCl_4): 1165 (C-O), 1790 (C=O) cm^{-1}; **UV** (hexane): 219 nm (ϵ = 100 m^2 mol^{-1}); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.28 (s, 3H, CH_3-8), 1.51, 1.54 (s, 3H, each CH_3-3), 1.80 (s, 3H, CH_3-10), 3.05 (s, 3H, OCH_3), 5.73 (s, 1H, H-9), 5.91 (s, 2H, H-6, H-7) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 15.7 (CH_3-10), 25.1, 26.8 (CH_3-3, CH_3-3), 27.3 (CH_3-8), 52.1 (OCH_3), 71.1 (C-8), 77.4 (C-3), 100.8 (C-5), 128.5 (C-6), 134.0 (C-10), 135.9 (C-9), 137.5 (C-7), 175.6 (C-2) ppm; **MS** (70 ev) M/Z (relative intensity): 238 (M^+, 1), 223 ($C_{12}H_{15}O_4$, 30), 121 (C_8H_9O, 100); exact mass calculated for $C_{12}H_{15}O_4$ (M^+-CH_3): 223.097; found: 223.092.

2.9 SOLVOLYSES OF 1,2-ADDUCTS IN METHANOL

a) Reaction of diene 135

Diene **135** (50 mg, 0.13 mmol) was dissolved in methanol (1 cm^3) and the reaction mixture was stood at ambient temperature for 4 h. Workup gave a mixture (40 mg) of 2-methyl-2-(2-methyl-5-methoxyphenoxy)propanoic acid (**208**) (30%) and methyl 2-methyl-2-(2-methyl-5-methoxyphenoxy)-propanoate (**209**) (70%) as a pale yellow oil. Separation of **208** and **209** was carried out by extracting the ether solution (50 cm^3) of the reaction mixture by saturated aqueous sodium bicarbonate solution (3 x 20 cm^3). Solvent evaporation of the ether layer gave pure **209** as a pale yellow oil; **IR** (CCl_4): 1160, 1185 (C-O), 1730 (C=O) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.57 (s, 6H, $C(CH_3)_2$), 2.13 (s, 3H, CH_3-2), 3.70 (s, 3H, 5-OCH_3), 3.77 (s, 3H, $COOCH_3$), 6.24 (d, 1H, H-6, J = 2.4 Hz), 6.43 (dd, 1H, H-4, J = 8.8, 2.4 Hz), 7.01 (d, 1H, H-3, J = 8.8 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.9 (CH_3), 25.4 ($C(\underline{C}H_3)_2$, 52.5 (5-OCH_3), 53.5 ($COO\underline{C}H_3$), 79.1 ($\underline{C}(CH_3)_2$), 104.1 (C-6), 106.4 (C-4), 121.7 (C-2), 130.9 (C-3), 154.3 (C-5), 158.3 (C-1), 175.0 (C=O) ppm. Mass (CI): 239 (M+1, 16), 259 (M+21, 1), 279 (M+41, weak); **MS** (70 ev) M/Z (relative intensity): 238 (M^+, 9), 179 ($C_{11}H_{15}O_2$, 9), 138 ($C_8H_{10}O_2$, 100).

The bicarbonate extract was acidified and extracted with ether. Pure acid **208** was obtained by the evaporation of

the ether layer. It had **^{1}H NMR** ($CDCl_3$, 90 MHz) δ: 1.60 (s, 6H, $C(CH_3)_2$), 2.16 (s, 3H, CH_3-2), 3.70 (s, 3H, OCH_3), 6.48 (s, 1H, H-6), 6.50 (d, 1H, H-4, J = 8 Hz), 7.05 (d, 1H, H-3, J = 8 Hz) ppm; **MS** (70 ev) M/Z (relative intensity): 224 (M^+, 11), 138 ($C_8H_{10}O_2$, 100).

b) Reaction of diene (137)

Diene **137** (50 mg, 0.21 mmol) was dissolved in methanol (1 cm^3) and the reaction mixture was stood at ambient temperature for 1 h. Workup gave a mixture (42 mg) of 2-methyl-2-(2,3-dimethyl-5-methoxyphenoxy)propanoic acid (**210**) (67%) and methyl 2-methyl-2-(2,3-dimethyl-5-methoxyphenoxy)propanoate (**211**) (33%). After separation acid **210** had **^{1}H NMR** ($CDCl_3$, 90 MHz) δ: 1.60 (s, 6H, $C(CH_3)_2$), 2.08 (s, 3H, CH_3-2), 2.22 (s, 3H, CH_3-3), 3.69 (s, 3H, 5-OCH_3), 6.35 (bs, 1H, H-6), 6.45 (bs, 1H, H-4) ppm; **MS** (70 ev) M/Z (relative intensity): 238 (M^+, 20), 152 ($C_9H_{12}O_2$).

Ester **211** had **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.55 (s, 6H, $C(CH_3)_2$), 2.05 (s, 3H, CH_3-2), 2.21 (s, 3H, CH_3-3), 3.68 (s, 3H, 5-OCH_3), 3.77 (s, 3H, $COOCH_3$), 6.12 (s, 1H, H-6), 6.37 (s, 1H, H-4) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 11.8 (CH_3-2), 20.6 (CH_3-3), 25.3 ($C(\underline{C}H_3)_2$), 52.4 (5-OCH_3), 55.2 ($COO\underline{C}H_3$), 79.3 ($\underline{C}(CH_3)_2$), 101.9 (C-6), 108.9 (C-4), 120.5 (C-2), 138.5 (C-3), 154.0 (C-5), 157.3 (C-1), 175.2 (C=O) ppm. MS (EI): 253 (M+1, 63), 281 (M+29, 6), 293 (M+41, 1); **MS** (70 ev) M/Z (relative intensity): 252 (M^+, 20), 193 ($C_{12}H_{17}O_2$, 17), 152 ($C_9H_{12}O_2$, 100).

c) Reaction of diene **139**

Diene **139** (50 mg, 0.21 mmol) was dissolved in methanol (1 cm^3) and the reaction mixture was stood at ambient temperature for 8 h. Workup following the general procedure gave methyl 2-methyl-2-(2-methyl-5-methoxymethylphenoxy)-propanoate (**212**) (48 mg) as a colorless oil. **212** had **IR** (CCl_4): 1140, 1165 (C-O), 1735 (C=O) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.58 (s, 6H, $C(CH_3)_2$), 2.20 (s, 3H, CH_3-2), 3.31 (s, 3H, $CH_2OC\underline{H}_3$), 3.76 (s, 3H, $COOCH_3$), 4.33 (s, 2H, $C\underline{H}_2OCH_3$), 6.59 (bs, 1H, H-6), 6.84 (bd, 1H, H-4, J = 7.5 Hz), 7.10 (d, 1H, H-3, J = 7.6 Hz) ppm; **MS** (70 ev) M/Z (relative intensity): 252 (M^+, 38), 221 ($C_{13}H_{17}O_3$, 4), 193 ($C_{12}H_{17}O_2$, 20), 152 ($C_9H_{12}O_2$, 100).

d) Reaction of diene **146**

Diene **146** (100 mg, 0.36 mmol) was dissolved in methanol (2 cm^3) and the reaction mixture was stood for overnight. Workup following the general procedure gave a mixture (89 mg) of methyl 2-methyl-2-(4-chloro-2-methyl-5-methoxy-methylphenoxy)propanoate (**213**) and 4-chloro-2-methyl-5-methoxymethylanisole (**214**) in a ratio of 1.2 : 1. Separation of the mixture was carried out by silica gel column chromatography, using 20% ether-petroleum ether as the eluent. The first fraction on evaporation gave ester **213** as a yellow viscous oil. It had **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.57 (s, 6H, $C(CH_3)_2$), 2.18 (s, 3H, CH_3-2), 3.38 (s, 3H, $CH_2OC\underline{H}_3$), 3.77 (s, 3H, $COOCH_3$), 4.42 (s, 2H, $C\underline{H}_2OCH_3$), 6.72

(s, 1H, H-6), 7.11 (s, 1H, H-3) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 16.2 (CH_3-2), 25.4 ($C(\underline{C}H_3)_2$), 52.5 ($CH_2O\underline{C}H_3$), 58.3 ($COO\underline{C}H_3$), 71.4 ($\underline{C}H_2OCH_3$), 79.4 ($\underline{C}(CH_3)_2$), 116.9 (C-6), 125.0 (C-2), 130.4 (C-4), 131.2 (C-3), 133.6 (C-5), 152.5 (C-1), 174.7 (C=O) ppm; **MS** (70 ev) M/Z (relative intensity): 288, 286 (M^+, 1, 5), 188, 86 ($C_9H_{11}ClO_2$, 11,38), 151 ($C_9H_{11}O_2$, 100).

Compound **214** was obtained from the second fraction as a colorless oil. It had **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 2.16 (s, 3H, CH_3-2), 3.44 (s, 3H, $CH_2O\underline{C}H_3$), 3.82 (s, 3H, $COOCH_3$), 4.50 (s, 2H, $C\underline{H}_2OCH_3$), 6.91 (s, 1H, H-6), 7.08 (s, 1H, H-3) ppm; **MS** (70 ev) M/Z (relative intensity): 200 (M^+, 100), 169 (M^+-OMe, 32).

2.10 KINETIC STUDIES OF SOLVOLYSES OF 1,4-ADDUCTS IN AQUEOUS METHANOL

The solvolysis generates hydrochloric acid which was titrated with base to follow the reaction.

Apparatus and materials

The titrating base (NaOH in aqueous methanol (80%), 4.88×10^{-2} M) was standardized with potassium acid phthalate. A constant ionic strength (0.1 M) was maintained by the addition of sodium chloride to the standard base and the solvolysis reaction medium.

Titrant was delivered from a Metrohm 655 Dosimat in

aliquots of 2-4 uL to a 20 ml sealed, temperature controlled (25 ± 0.1 ^{o}C) cell. The titration was performed in a nitrogen atmosphere. The electrodes included a glass electrode and a double junction (a KNO_3 external reservoir and an internal reservoir of Ag/AgCl in sat. KCl) reference electrode. The electrode system was calibrated using two standard aqueous methanol buffers at pH 2.80 and pH 5.89. The pH was measured by using a Metrohm 632 pH meter. The operation was directed through a Hewlett-Packed HP-85 micro computer. This allowed the titration to be monitored automatically and provided for the printing and plotting of the data points (volume of the base used *versus* reaction time) and the calculation of data points (ln C^{o}/C vs. t) for the first-order rate constant.

Preparation of Aqueous Methanol (80%) Buffers for The Solvolyses

a) Standard methanol buffers

The pH of the primary buffer standards (oxalic acid-ammonium hydrogen oxalate and succinic acid-lithium hydrogen succinate) in 80% v/v methanol/water was interpolated from tables of the pH of the same buffers in methanol/water solutions of known Wt%.[137]

pH 2.80: 0.01 m oxalic acid and 0.01 m ammonium hydrogen oxalate from 0.7635 g of oxalic acid dihydrate plus 0.2870 g of diammonium oxalate monohydrate dissolved

in 100 cm^3 water and made up to 500 cm^3 with methanol.

pH 5.89: 0.01 m succinic acid and 0.01 m lithium hydrogen succinate from 0.9540 g of succinic acid plus lithium hydroxide monohydrate dissolved in 100 cm^3 water and made up to 500 ml with methanol.

b) Buffers with various ranges of pH for the solvolyses

pH 2-3: The standard methanol buffer of pH 2.8 (10 ml) was delivered into a volumetric flask (100 ml) and made to 100 ml with a 4:1 (v/v) mixture of methanol and water.

pH 4-6: The standard methanol buffer of pH 5.89 (10 ml) was delivered in a volumetric flask and made to 100 ml with a 4:1 (v/v) mixture of methanol and water.

pH 7-9: Tris(hydroxymethyl)aminomethane (36 mg, 0.3 mmol) was dissolved in 20 ml water in a volumetric flask (100 ml) and made up to 100 ml with methanol.

To maintain a constant ionic strength throughout the solvolysis process, sodium chloride (58 mg, 10 mmol) was added to each of the above buffer solutions.

General procedure for the solvolysis

The 80% methanol solution (20 ml) of the buffer was delivered to the temperature controlled cell (25 ^oC) for auto titration. The pH of the solution was precisely adjusted to the chosen value by adding a small amount of an aqueous methanol solution (80%) of either sodium hydroxide (0.5 M) or hydrochloric acid (0.5 M) as appropriate. The

diene (ca. 30 mg) dissolved in dichloromethane (1 cm^3) was added to the buffer. The reaction was followed by successively titrating the HCl produced during the solvolysis, with the titrating base.

The reaction was completed when there was no additional consumption of the titrating base over the chosen time interval. Workup was then carried out by pouring the reaction mixture into ether. The ether solution was washed with water, dried over magnesium sulphate, and evaporated in a rotatory evaporator under reduced pressure. The product was identified by ^1H NMR. For each compound solvolysed at each different pH, the product from at least one kinetic run was worked up.

Calculation for the first order rate constants

The first order rate constant for the solvolysis was obtained from the relationship:

$\ln(C^o/C) = k \cdot t$ where:

C^o = initial concentration of the diene;

C = the concentration of the diene at time t (the data was corrected for the increasing volume of the reaction mixture as the reaction proceeded);

t = relative reaction time;

k = first order rate constant.

A standard linear regression program was used to obtain the best fit straight line using the method of least

squares. The rate constants were derived from the slope of the best-fit line. Correlation coefficients were generally 0.999 or better. The estimated standard deviation for k is about 7%.

2.10.1 Solvolyses of Diene 133 at pH 5, 6, 7, and 8

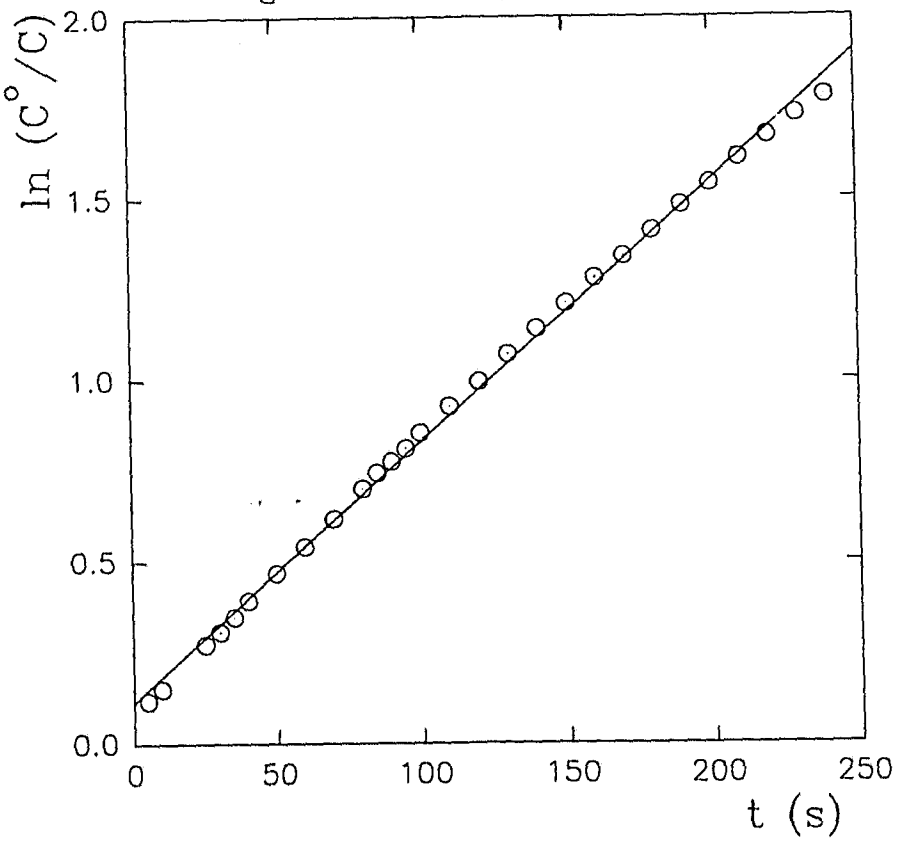
Diene **133** (30 mg) in dichloromethane (1 ml) was transferred to the aqueous methanol buffer of pH 5. Workup gave 8-methoxy-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**203**) as the sole product.

The first order kinetic data points (ln C^{o}/C vs. t) obtained from the micro computer are tabulated as follows:

t (s)	ln (C^{o}/C)	t (s)	ln (C^{o}/C)
5	0.117	110	0.927
10	0.150	120	0.994
25	0.272	130	1.07
30	0.307	140	1.14
35	0.347	150	1.21
40	0.392	160	1.28
50	0.468	170	1.34
60	0.541	180	1.41
70	0.618	190	1.48
80	0.701	200	1.54
85	0.744	210	1.61
90	0.775	220	1.67
95	0.811	230	1.73
100	0.854	240	1.78

A plot of ln (C^{o}/C) vs. t gave a straight line with a slope of 7.17×10^{-3} s (Fig. 1).

Fig. 1 Plot of $\ln(C^{\circ}/C)$ vs t (s)



$$\ln (C^{\circ}/C) = 0.1123 + 0.00717pH$$

correlation coefficient = 0.9991

The solvolyses at pH 6, 7, and 8 also gave diene **203** as the sole product in each of the cases.

The rate constants for the reaction at pH 5, 6, 7, and 8 are tabulated in the following table:

pH	$kx10^3$ (s^{-1})
5	7.17, 7.23
6	7.47, 8.07
7	9.23
8	8.45, 8.21

2.10.2 Solvolyses of Diene **141** at pH 5, 6, 7, and 8

Diene **141** (29.6 mg) was treated with the aqueous methanol buffer of pH 5 following the general procedure of the solvolysis. Workup following the general procedure gave 10-chloro-8-methoxy-3,3,8-trimethyl-1,4-dioxaspiro-[4,5]deca-6,9-dien-one (**215**) (26 mg), a colorless viscous oil, as the sole product. It had **IR** (CCl_4): 1165 (C-O), 1810 (C=O) cm^{-1}; **UV** (hexane): 211 nm (ϵ = 281 cm^2/mol); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.34 (s, 3H, CH_3-8), 1.53, 1.61 (s, 3H, each CH_3-3), 3.09 (s, 3H, OCH_3), 5.93 (s, 2H, H-6, H-7), 6.14 (s, 1H, H-9) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 24.7, 27.1 (each CH_3-3), 27.2 (CH_3-8), 52.6 (OCH_3), 73.2 (C-8), 78.0 (C-3), 98.2 (C-5), 125.0 (C-6), 128.0 (C-10),

137.2 (C-7, C-9), 174.8 (C-2) ppm; **MS** (70 ev) M/Z (relative intensity): 258 (M^+, < 1), 245, 243 ($C_{11}H_{12}ClO_4$, 14, 42), 229, 227 ($C_{11}H_{12}ClO_3$, 4, 11), 159, 157 ($C_7H_6ClO_2$, 21, 59), 141 (C_7H_6ClO, 100); exact mass calculated for $C_{11}H_{12}Cl^{37}O_4$ (M^+-CH_3): 245.040; found: 245.030.

The solvolyses at pH 6, 7, and 8 also gave diene **215** as the sole product in each of the cases.

The first order rate constants for the reaction at pH 5, 6, 7, and 8 are tabulated as follows:

pH	$kx10^5$
5	2.47, 2.58
6	2.26, 2.40
7	3.29
8	3.27

2.10.3 Solvolyses of Diene **142** at pH 5, 6, 7, and 8

Diene **142** (31.3 mg) was treated with the aqueous methanol buffer of pH 5. Workup of the reaction mixture following the general procedure gave 10-chloro-8-methoxy-3,3,7,8-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**216**) (30.5 mg), a white solid, as the sole product. It had m.p. 73-75 ^oC; **IR** (CCl_4): 1165 (C-O), 1800 (C=O) cm^{-1}; **UV** (hexane): 212 nm (ϵ = 220 m^2/mol); ^{1}**H NMR** ($CDCl_3$, 250 MHz)

δ: 1.33 (s, 3H, CH_3-8), 1.55, 1.61 (s, 3H, each CH_3-3), 1.79 (s, 3H, CH_3-7), 3.01 (s, 3H, OCH_3), 5.70 (s, 1H, H-6), 6.14 (s, 1H, H-9) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 16.7 (CH_3-7), 24.9, 25.9 (CH_3-3, CH_3-3), 27.5 (CH_3-8), 52.2 (OCH_3), 75.0 (C-8), 78.1 (C-3), 99.6 (C-5), 121.9 (C-10), 125.0 (C-6), 137.8 (C-9), 143.7 (C-7), 175.0 (C-2) ppm; exact mass calculated for M^+-CH_3: 257.058; found: 257.059.

The solvolyses at pH 6, 7, and 8 also gave diene **216** as the sole product in each of the cases.

The first order rate constants for the reaction at pH 5, 6, 7, and 8 are tabulated as follows:

pH	kx10^5 (s^{-1})
5	6.26
6	5.78
7	5.92
8	6.78

2.10.4 Solvolyses of Diene **148** at pH 5, 6, 7, and 8

Diene **148** (29.5 mg) was treated with the aqueous methanol buffer of pH 6. Workup of the reaction mixture 8-methoxy-3,3,7,8,10-pentamethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**217**) (25 mg) as the sole product. Methoxy diene **217** was a white solid; m.p. 62-64 °C; **IR** (CCl_4): 1170

(C-O), 1790 (C=O) cm^{-1}; **UV** (hexane): 219 nm (ϵ = 130 m^2/mol); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.23 (s, 3H, CH_3-8), 1.49, 1.53 (s, 3H, each CH_3-3), 1.73 (d, 3H, CH_3-10, J = 1.3 Hz), 1.78 (d, 3H, CH_3-7, J = 1.4 Hz), 2.92 (s, 3H, OCH_3), 5.66 (d, 1H, H-6, J = 1.4 Hz), 5.70 (d, 1H, H-9, J = 1.4 Hz) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 15.7 (CH_3-10), 16.9 (CH_3-7), 25.5, 26.0 (CH_3-3, CH_3-3), 27.0 (CH_3-8), 51.7 (OCH_3), 73.1 (C-8), 77.4 (C-3), 102.2 (C-5), 125.7 (C-6), 133.7 (C-10), 136.9 (C-9), 143.6 (C-7), 176.0 (C-2) ppm; analysis calculated for $C_{14}H_{20}O_4$: C 66.64%, H 7.99%; found: 66.64%, H 7.75%.

The solvolyses at pH 5, 7, and 8 also gave diene **217** as the sole product in each of the cases.

The first order rate constants for the reactions at pH 5, 6, 7, and 8 are tabulated as follows:

pH	$kx10^3$ (s^{-1})
5	8.99, 8.49
6	8.99, 8.30
7	9.03
8	9.05, 9.28

2.10.5 Solvolyses of Diene **154** at pH 5, 6, 7, and 8

Diene **154** (29.1 mg) was treated with the aqueous

methanol buffer of pH 5. Workup of the reaction mixture gave 10-chloro-8-methoxy-3,3,7,8,9-pentamethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**218**) (25 mg) as the sole product. Methoxy diene **218** was a white crystalline solid; m.p. 99-100 ^{o}C; **IR** (CCl_4): 1160 (C-O), 1805 (C=O) cm^{-1}; **UV** (hexane): 212 (ϵ = 330 m^2/mol); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.30 (s, 3H, CH_3-8), 1.53, 1.61 (s, 3H, each CH_3-3), 1.82 (d, 3H, CH_3-7, J = 1.3 Hz), 1.94 (s, 3H, CH_3-9), 2.87 (s, 3H, OCH_3), 5.73 (d, 1H, H-6, J = 1.3 Hz) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 14.5 (CH_3-7), 16.8 (CH_3-9), 24.7, 24.8 (CH_3-3, CH_3-3), 27.4 (CH_3-8), 51.7 (OCH_3), 77.2 (C-8), 78.0 (C-3), 100.0 (C-5), 121.5 (C-10), 124.6 (C-6), 142.9 (C-7), 143.7 (C-9), 175.1 (C-2) ppm; exact mass calculated for $C_{14}H_{19}ClO_4$: 286.097; found: 286.091.

The solvolyses at pH 6, 7, and 8 also gave diene **218** as the sole product in each of the cases.

The rate constants for the reaction at pH 5, 6, 7, and 8 are shown as follows:

pH	kx10^5 (s^{-1})
5	6.28
6	6.61
7	7.08
8	7.04, 7.33

2.10.6 Solvolyses of Diene **130** at pH 5, 6, 7, and 8

Diene **130** (30.3 mg) was treated with the aqueous methanol buffer of pH 5. Workup of the reaction mixture following the general procedure gave a mixture (24 mg) of 8-methoxy-3,3,8-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**219**) (75%) and 4a,8a-dihydro-4a-methoxy-3,3,7-trimethylbenzo-1,4-dioxin-2-one (**220**) (25%). Separation of methoxy diene **219** and dioxin **220** was carried out by TLC (silica gel) using 5% of ether and petroleum ether as the eluent. Diene **219** was obtained from the last band as a colorless oil.It had **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.31 (s, 3H, CH_3-8), 1.52 (s, 6H, CH_3-3, CH_3-3), 3.09 (s, 3H, OCH_3), 5.90 (s, 2H, H-6, H-10, J = 10.4 Hz), 6.00 (d, 2H, H-7, H-9, J = 10.3 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 26.4 (CH_3-3, CH_3-3), 27.1 (CH_3-8), 52.4 (OCH_3), 70.4 (C-8), 77.3 (C-3), 98.8 (C-5), 128.4 (C-6, C-10), 138.9 (C-7, C-9), 175.4 (C-2) ppm; **MS** (70 ev) M/Z (relative intensity): 224 (M^+, < 1), 209 ($C_{11}H_{13}O_4$, 46), 149 ($C_{10}H_{13}O$, 49), 107 (C_7H_7O, 100); exact mass calculated for $C_{11}H_{13}O_4$ (M^+-CH_3): 209.081; found: 209.079.

Diene **130** (30.0 mg) was treated with the aqueous methanol solution of pH 6. Workup of the reaction mixture gave a mixture of **219** (55%) and **220** (45%).

Diene **130** (mg), when treated with the aqueous methanol buffer of pH 7, gave a mixture of **219** (44%) and **220** (56%).

pure diene **220** was obtained from the first band of TLC (silica gel) of the product mixture, using 5% (v/v) ether-petroleum ether mixture as the eluent. It was a colorless oil; **IR** (CCl_4): 1160 (C-O), 1740 (C=O) cm^{-1}; **UV** (hexane): 258 nm (ϵ = 306 m^2/mol); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.49, 1.60 (s, 3H, each CH_3-3), 1.86 (dd, 3H, CH_3-7, J = 1.6, 1.5 Hz), 3.38 (s, 3H, OCH_3), 4.93 (dd, 1H, H-8a, J = 4.5, 1.6 Hz), 5.64 (dd, 1H, H-8, J = 4.5, 1.5 Hz), 5.91 (d, 1H, H-5, J = 9.1 Hz), 5.92 (d, 1H, H-6, J = 9.1 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 21.1 (CH_3-7), 24.7, 27.6 (CH_3-3, CH_3-3), 49.1 (OCH_3), 76.4 (C-8a), 76.5 (C-3), 93.8 (C-4a), 118.2 (C-5), 125.7 (C-8), 128.6 (C-6), 134.4 (C-7), 172.6 (C-2) ppm; exact mass calculated for $C_{12}H_{16}O_4$: 224.105; found: 224.107.

The rate constants for the solvolyses at pH 5, 6, 7, and 8 are shown as follows:

pH	kx10^5 (s^{-1})
5	4.55
6	5.37
7	6.48
8	7.86

2.10.7 <u>Solvolyses of Diene **132** at pH 5, 6, 7, and 8</u>

When diene **132** (29.6 mg) was solvolysed in the aqueous methanol solution of pH 8, a mixture of 8-methoxy-3,3,7,8-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**221**) (28%), 4a,8a-dihydro-4a-methoxy-3,3,7,8-tetramethylbenzo-1,4-dioxin-2-one (**222**) (36%), and 4a,8a-dihydro-4a-methoxy-3,3,6,7-tetramethylbenzo-1,4-dioxin-2-one (**223**) (36%).

The product mixture was prepared on a larger scale as follows: diene **132** (100 mg, 0.4 mmol) was dissolved in an aqueous methanol (80%) solution prepared from trizma base (121 mg, 1 mmol), hydrochloric acid (0.2 M, 3 ml), water (2 ml), and methanol (20ml), and the reaction mixture was stood at ambient temperature for overnight. Workup following the general procedure gave 90 mg of the reaction mixture as a viscous oil. Separation of the mixture was carried out by TLC (silica gel) at 0 ^{o}C, using 10% ether-petroleum ether mixture as the eluent. The first band on evaporation gave pure **223** (28 mg) as a colorless oil; **IR** (CCl_4): 1160 (C-O), 1745 (C=O) cm^{-1}; **UV** (hexane): 260 nm (ϵ = 253 m^2/mol); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.48, 1.57 (s, 3H, each CH_3-3), 1.84 (d, 3H, CH_3-7, J = 1.5 Hz), 1.85 (s, 3H, CH_3-6), 3.36 (s, 3H, OCH_3), 4.90 (dd, 1H, H-8a, J = 4.2, 1.8 Hz), 5.67, 5.68 (m, 2H, H-5, H-8) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 19.2 (CH_3-7), 19.5 (CH_3-6), 25.2, 27.7 (each CH_3-3), 49.1 (OCH_3), 75.1 (C-3), 77.0 (C-8a), 94.3 (C-4a), 119.9 (C-5), 121.2 (C-8), 125.2 (C-7), 135.7 (C-6), 172.6 (C-2) ppm; exact mass calculated for $C_{13}H_{18}O_4$:

238.121; found: 238.124.

Diene **222** (32 mg) was obtained from the second band as a white crystalline solid; m.p. 90-92 ^{o}C; **IR** (CCl_4): 1150 (C-O), 1750 (C=O) cm^{-1}; **UV** (hexane): 264 nm (ϵ = 320 m^2/mol); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.48, 1.61 (s, 3H, each CH_3-3), 1.80 (d, 3H, CH_3-8, J = 0.8 Hz), 1.89 (s, 3H, CH_3-7), 3.36 (s, 3H, OCH_3), 4.69 (d, 1H, H-8a, J = 0.7 Hz), 5.75 (d, 1H, H-5, J = 9.8 Hz), 5.89 (s, 1H, H-6, J = 9.8 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 16.2 (CH_3-7), 17.9 (CH_3-8), 24.6, 27.2 (each CH_3-3), 49.0 (OCH_3), 75.1 (C-3), 80.1 (C-8a), 94.7 (C-4a), 122.8 (C-5), 125.0 (C-7), 127.8 (C-8), 130.3 (C-6), 173.0 (C-2) ppm; analysis calculated for $C_{13}H_{18}O_4$: C 65.53%, H 7.61%; found: C 65.51, H 7.47%.

Diene **221** (18 mg) was obtained from the last band. It had **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.29 (s, 3H, CH_3-8), 1.52, 1.53 (s, 3H, each CH_3-3), 2.01 (d, 3H, CH_3-7, J = 1.4 Hz), 2.98 (s, 3H, OCH_3), 5.54 (dd, 1H, H-6, J = 2.5, 1.4 Hz), 5.88 (dd, 1H, H-10, J = 10, 2.4 Hz), 5.99 (d, 1H, H-9, J = 10 Hz) ppm; **MS** (70 ev) M/Z (relative intensity): 238 (M^+, 1), 223 ($C_{12}H_{15}O_4$, 44), 207 ($C_{12}H_{15}O_3$, 11), 152 ($C_9H_{12}O_2$, 21), 121 (C_8H_9O, 100); exact mass calculated for $C_{12}H_{15}O_4$ (M^+-CH_3): 223.097; found: 223.093.

Diene **132** (29.3 mg) was treated with the aqueous methanol buffer of pH 7. Workup of the reaction mixture gave a mixture (23 mg) of dienes **221** (32%), **222** (34%), and **223** (34%).

Diene **132** (30.5 mg) was treated with an aqueous buffer of pH 6. Workup of the reaction gave a mixture of 4-methoxy-3,4-dimethylcyclohexa-2,5-dienone (**224**) (13%), diene **221** (33), **222** (27%) and **223** (27%). The presence of dienone **224** was conformed by GC/MS; molecular ion (M^+): 152.

Diene **132** (29.6 mg) was treated with an aqueous methanol buffer of pH 5. Workup following the general procedure gave a mixture of dienone **224** (16%), diene **221** (63%), **222** (10%), and **223** (10%).

The first order rate constants for the solvolyses at pH 5, 6, 7, and 8 are tabulated as follows:

pH	$kx10^4$ (s^{-1})
5	0.768
6	1.30
7	1.67
8	1.77

2.10.8 Solvolyses of Diene **152** at pH 5, 6, 7, and 8

Diene **152** (30.6 mg) was treated with the aqueous methanol buffer of pH 8. Workup of the reaction yielded a mixture (26 mg) of 4-methoxy-3,4,5-trimethylcyclohexa-2,5-dienone (**225**) (25%) and 4a,8a-dihydro-4a-methoxy-3,3,6,7,8-pentamethylbenzo-1,4-dioxin-2-one (**226**) (75%).

Separation of dienes **225** and **226** was carried out by TLC (silica gel) at 0 ^{o}C, using 10% ether-petroleum ether mixture as the eluent. The first band gave pure diene **226** as a white crystalline solid; m.p. 95-97 ^{o}C; **IR** (CCl_4): 1145 (C-O), 1760 (C=O) cm^{-1}; **UV** (hexane): 266 nm (ϵ = 285 m^2/mol); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.46, 1.58 (s, 3H, each CH_3-3), 1.79 (s, 3H, CH_3-7), 1.85 (s, 3H, CH_3-8), 1.90 (s, 3H, CH_3-6), 3.35 (s, 3H, OCH_3), 4.68 (s, 1H, H-8a), 5.57 (s, 1H, H-5) ppm; ^{13}**C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 14.5 (CH_3-7), 16.4 (CH_3-8), 20.5 (CH_3-6), 25.0, 27.8 (each CH_3-3), 49.0 (OCH_3), 74.8 (C-3), 80.4 (C-8a), 94.4 (C-4a), 118.9 (C-5), 125.8 (C-7), 129.8 (C-8), 136.5 (C-6), 172.9 (C-2) ppm; analysis calculated for $C_{14}H_{20}O_4$: C 66.64%, H 7.99%; found: 66.60%; H 7.98%.

Dienone **225** was obtained from the last band. It had ^{1}**H NMR** ($CDCl_3$, 90 MHz) δ: 1.40 (s, 3H, CH_3-4), 2.01 (s, 6H, CH_3-3, CH_3-5), 2.98 (s, 3H, OCH_3), 6.20 (s, 2H, H-2, H-6) ppm; **MS** (70 ev) M/Z (relative intensity): 166 (M^+, 20).

Diene **152** (30.0 mg) was treated with the aqueous methanol solution of pH 7. Workup of the reaction gave a

mixture of dienone **225** (35%) and rearranged diene **226** (65%).

Diene **152** (29.4 mg) was treated with the aqueous methanol buffer of pH 6. Workup of the reaction gave a mixture of 4-chloro-3,4,5-trimethylcyclohexa-2,5-dienone (**187**) (13%), dienone **225** (50%) and diene **226** (37%).

Diene **152** (30.6 mg) was treated with the aqueous buffer of methanol. Workup of the reaction gave a mixture of dienone **187** (30%), **225** (63%), and diene **226** (7%).

The rate constants for the solvolyses at pH 5, 6, 7, and 8 are shown as follows:

pH	$kx10^4$ (s^{-1})
5	0.851, 0.843
6	2.08
7	3.18
8	4.26, 4.34

2.10.9 Solvolyses of Diene **160** at pH 5, 6, 7, and 8

Diene **160** (30 mg) was treated with the aqueous methanol buffer of pH 8. Workup of the reaction afforded a mixture (24 mg) of 8-ethyl-8-methoxy-3,3-dimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**227**) (24%) and 7-ethyl-4a,8a-dihydro-4a-methoxy-3,3-dimethylbenzo-1,4-dioxin-2-one (**228**) (76%). Separation of dienes **227** and **228** was carried

out by TLC at 0 ^{o}C, using 10% ether-petroleum ether as the eluent. Diene **228** was obtained from the first band as a colorless oil; **UV** (hexane): 254 nm (ϵ = 392 m^2/mol); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.05 (t, 3H, $CH_2\underline{CH}_3$, J = 7.5 Hz), 1.49, 1.60 (s, 3H, each CH_3-3), 2.16 (q, 2H, $C\underline{H}_2CH_3$, J = 7.5 Hz), 3.38 (OCH_3), 4.96 (d, 1H, H-8a, J = 4.4 Hz), 5.62 (d, 1H, H-8, J= 4.4 Hz), 5.92 (s, 1H, H-5, J = 10 Hz), 5.97 (s, 1H, H-6, J = 10 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_C: 11.9 ($CH_2\underline{C}H_3$), 24.9, 27.7 (each CH_3-3), 27.9 ($\underline{C}H_2CH_3$), 49.1 (OCH_3), 75.4 (C-3), 76.7 (C-8a), 94.1 (C-4a), 116.8 (C-5), 125.7 (C-8), 128.0 (C-6), 139.8 (C-7), 172.6 (C-2) ppm; exact mass calculated for $C_{13}H_{18}O_4$: 224.105; found: 224.107.

The second band gave a mixture of **227** and **228** with enriched **227**. Partially separated diene **227** had **^{1}H NMR** ($CDCl_3$, 90 MHz) δ: 0.8 (t, 3H, $CH_2\underline{CH}_3$, J = 8 Hz), 1.60 (s, 6H, CH_3-3, CH_3-3), 2.18 (m, 2H, $C\underline{H}_2CH_3$), 3.12 (s, 3H, OCH_3), 5.96 (m, 4H, H-6, H-7, H-9, H-10) ppm.

Diene **160** (30.4 mg) was treated with the aqueous methanol buffer of pH 7. Workup gave a mixture of dienes **227** (28%) and **228** (72%).

Diene **160** (29.7 mg) afforded a mixture of **227** (40 %) and **228** (60%), after solvolysed in the aqueous methanol buffer of pH 6.

Diene **160** (30.5 mg) yielded a mixture of dienes **227** (75%) and **228** (25%) after solvolysed in the aqueous

methanol buffer of pH 5.

The first order rate constants for the solvolyses at pH 5, 6, 7, and 8 are tabulated as follows:

pH	$kx10^5$ (s^{-1})
5	1.89
6	3.26
7	5.01
8	5.10

2.10.10 Solvolyses of Diene **162** at pH 6, 7, and 8

Diene **162** (29.7), when treated with an aqueous methanol buffer of pH 8, gave the rearranged diene, 4a,8a-dihydro-3,3-dimethyl-4a-methoxy-7-isopropylbenzo-1,4-dioxin-2-one (**229**) as the sole product. Diene **229** was a viscous oil; **UV** (hexane): 254 nm (ϵ = 440 m^2/mol); **^{1}H NMR** ($CDCl_3$, 250 MHz) δ: 1.05 (d, 6H, $CH(C\underline{H}_3)_2$, J = 6.9 Hz), 1.49, 1.60 (s, 3H, each CH_3-3), 2.37 (sep, 1H, $C\underline{H}(CH_3)_2$, J = 6.8 Hz), 3.39 (s, 3H, OCH_3), 4.99 (d, 1H, H-8a, J = 4.5 Hz), 5.61 (d, 1H, H-8, J = 4.5 Hz), 5.95 (d, 1H, H-5, J = 10 Hz), 6.03 (d, 1H, H-6, J = 10 Hz) ppm; **^{13}C NMR** ($CDCl_3$, 62.9 MHz) δ_c: 20.8 ($CH(\underline{C}H_3)_2$), 25.1, 27.7 (CH_3-3, CH_3-3), 32.8 ($\underline{C}H(CH_3)_2$), 49.1 (OCH_3), 75.3 (C-3), 77.2 (C-8a), 94.1 (C-4a), 116.0 (C-5), 125.6 (C-8), 127.2 (C-6), 143.8 (C-7),

172.6 (C-2) ppm; exact mass calculated for $C_{14}H_{20}O_4$: 252.136; found: 252.130.

Diene **162** (30 mg), when treated with an aqueous methanol of pH 6, gave a mixture (22mg) of 4-chloro-4-isopropylcyclohexa-2,5-dienone (**230**) (20%) and diene **229** (80%). Partially separated **230** had ^{1}**H NMR** ($CDCl_3$, 90 MHz) δ: 1.05 (m, 6H, $CH(C\underline{H}_3)_2$), 2.20 (m, 1H, $C\underline{H}(CH_3)_2$), 6.30 (d, 2H, H-2, H-6, J = 10 Hz), 6.95 (d, 2H, H-3, H-5) ppm.

The rate constants for the solvolyses at pH 6, 7, and 8 are shown as follows:

pH	$kx10^5$ (s^{-1})
6	1.42
7	3.27
8	2.78

2.10.11 Solvolyses of Diene **164** at pH 5, 7, and 8

Diene **164** (28.5 mg), when treated with an aqueous methanol buffer of pH 8, gave the rearranged diene, 7-t-butyl-4a,8a-dihydro-3,3-dimethyl4a-methoxybenzo-1,4-dioxin-2-one (**231**) (23 mg), as the sole product. Diene **231** was a colorless oil; **UV** (hexane): 254 nm (ε = 346 m^2/mol); ^{1}**H NMR** ($CDCl_3$, 250 MHz) δ: 1.07 (s, 9H, $C(CH_3)_3$), 1.47, 1.59 (s, 3H, each CH_3-3), 3.38 (s, 3H, OCH_3), 5.01 (d, 1H, H-8a, J= 4 Hz), 5.66 (dd, 1H, H-8, J = 4.0, 1.8 Hz), 5.97 (d, 1H, H-

5, J = 10.2 Hz), 6.22 (dd, 1H, H-6, J = 10.2, 1.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ_C: 25.4, 27.7 (CH_3-3, CH_3-3), 28.3 ($C(\underline{C}H_3)_3$), 34.0 ($\underline{C}(CH_3)_3$), 49.1 (OCH_3), 75.2 (C-3), 77.7 (C-8a), 93.7 (C-4a), 115.7 (C-5), 125.2 (C-8), 126.1 (C-6), 145.8 (C-7), 172.6 (C-2) ppm; exact mass calculated for $C_{15}H_{22}O_4$: 266.152; found: 266.154.

Diene **164** (29.8 mg), when treated with an aqueous methanol buffer of pH 5, gave, after 20 h, a mixture of diene **231** (50%) and unreacted diene **164** (50%).

The rate constants for the solvolyses at pH 5, 7, and 8 are tabulated as follows:

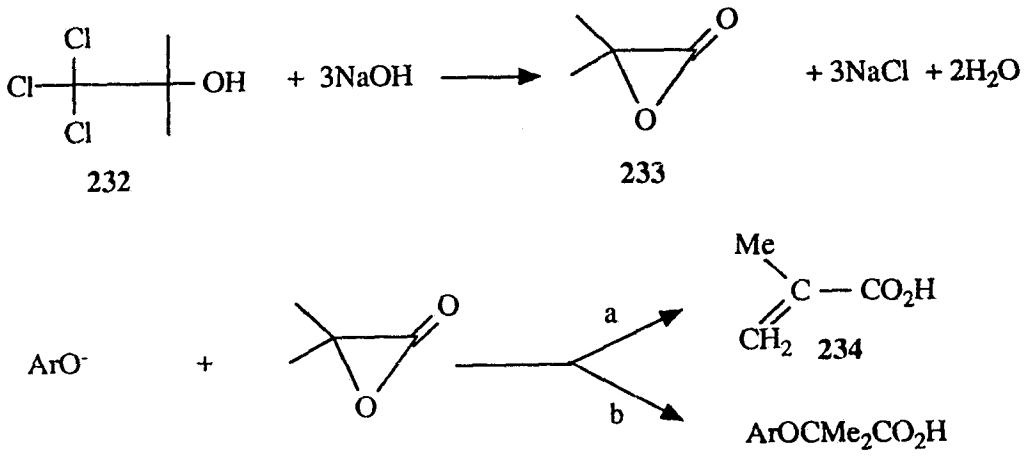
pH	$kx10^5$ (s^{-1})
5	0.549
7	2.81
8	1.81

CHAPTER III RESULTS AND DISCUSSION

3.1 FORMATION OF 2-METHYL-2-ARYLOXYPROPANOIC ACIDS

2-Methyl-2-aryloxypropanoic acids and their derivatives have long been known to be useful for the preparation of pharmaceuticals, and their pharmacological properties are well documented.[132,138] It was Corey et al. who first demonstrated their use in trapping *ipso* Wheland intermediates with the carboxyl group as an internal nucleophile.[99] In their work, bromination of 2-methyl-2-(4-methylphenoxy)propanoic acid (**117**) was carried out with bromine in aqueous potassium bicarbonate and 8-bromo-3,3,8-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**64**) was formed as the *ipso* adduct. Latter, Fischer and coworkers[95,96,103,110] carried out nitration for a series of 2-methyl-2-aryloxypropanoic acids. High yields of the *ipso* nitro spiro adducts, including 1,2- and 1,4-adducts, were obtained. In the present work a number of such acids have been prepared following a well established procedure developed by Weizmann and coworkers,[139] by the reaction of the corresponding phenols with 1,1,1-trichloro-2-methylpropan-2-ol (**232**). Weizmann et al proposed a mechanism for the reaction in which a dialkyl oxirinanone intermediate (**233**) was involved, as demonstrated in Scheme 3.1. A few dialkyl oxirinanones have been isolated by Adams and coworkers[140], providing support for the mechanism.

Scheme 3.1



As can be seen from Scheme 3.1, there are two modes of reaction of lactone **233**. Pathway b describes attack of phenoxide ion on **233**, which leads to the formation of the desired phenoxy acid. The striking feature of this path is that the attack occurs on the alkyl carbon instead of the carbonyl carbon. This is in accordance with the site of attack by a soft base on small ring lactones.[138] Furthermore, this is also in accordance with the direction of polarization of the carbon-oxygen single bond in the α-lactone. Alternatively, lactone **233** can also undergo the competing pathway a, i.e., deprotonation at methyl competes with ring opening of the lactone, resulting in the formation of methacrylic acid. In the present work, methacrylic acid was pumped off under reduced pressure from the crude reaction product. The yield of 2-methyl-2-

aryloxypropanoic acids varies from 33-89% (Table 3.1) and is lower for phenols substituted at one of the *ortho* positions. This may be attributed to steric hindrance in the *ortho* substituted phenoxide ion, which disfavors the attack of the phenoxide at the hindered tertiary carbon of the highly sterically strained lactone **233** (pathway b). As the size of the substituent at the *para* position is increased, e.g., from Me to t-Bu, the yield of the *para* substitued acid declines. The 62% yield of acid **129** appears surprisingly high. This may reflect the fact that **129**, with two electron donating t-butyl groups, is more nucleophilic than **128**

Table 3.1
Yields of 2-Methyl-2-aryloxypropanoic Acids

ArOH	$ArOCMe_2COOH$	Yield (%)
o-Cresol	**116**	78
p-Cresol	**117**	89
3,4-Dimethylphenol	**118**	87
2,4-Dimethylphenol	**119**	85
2,3-Dimethylphenol	**120**	85
2,5-Dimethylphenol	**121**	83
2-Chloro-4,5-dimethylphenol	**122**	68
2,4,5-Trimethylphenol	**123**	68
2,3,5-Trimethylphenol	**124**	53
3,4,5-Trimethylphenol	**125**	73
4-Ethylphenol	**126**	61
4-Isopropylphenol	**127**	45
4-t-Butylphenol	**128**	33
3,5-Di-t-butylphenol	**129**	62

3.2 CHLORINATION OF 2-METHYL-2-ARYLOXYPROPANOIC ACIDS

3.2.1 Chlorination of Acids 116, 120, 121, and 124

Chlorination of 2-methyl-2-(2-methylphenoxy)propanoic acid (**116**) with aqueous sodium hypochlorite afforded 18% of a non-aromatic compound and 71% of an aromatic acid. The acid was separated from the neutral component by extraction into base during workup, and was recovered after acidification of the base extract. It was identified as 2-methyl-2-(4-chloro-2-methylphenoxy)propanoic acid (**136**). None of its isomer, 2-methyl-2-(6-chloro-2-methylphenoxy)-propanoic acid, was detected in the product.

The purified neutral component was a white solid. Its ^{1}H NMR showed that there were four vinylic protons in the region of δ 5.9 - 6.2, a methyl group at δ 1.72, and *gem*-dimethyl protons which resonated at δ 1.53 and 1.57. ^{13}C NMR showed that there were four proton-bearing sp^2 carbon atoms and three fully substituted sp^3 carbons in addition to the carbonyl carbon and the three methyl carbons. The UV spectrum of the compound indicated that it was a conjugated diene (= 256 nm). All of these data are consistent with the 1,2 adduct structure of 10-chloro-3,3,10-trimethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**135**). Since only one diastereomer was present, the stereochemistry could not be determined by comparative shift reagent studies.

Chlorination of 2-methyl-2-(2,3-dimethylphenoxy)-propanoic acid (**120**) gave 50% of an aromatic compound and 41% of a non-aromatic compound. The aromatic acid was identified as 2-methyl-2-(4-chloro-2,3-dimethylphenoxy)-

propanoic acid (**138**). None of the 6-chloro isomer was detected in the product. The analytical data for the non-aromatic component suggested that it was an isomer of acid **138**. The IR spectrum indicated a chloroketone structure. The UV spectrum showed the presence of a conjugated diene system (λ_{max}= 271 nm). The coupling pattern observed in the ^{1}H NMR enabled the assignment of chemical shifts to the vinylic protons of the diene. The ^{13}C NMR showed that there were three proton-bearing sp^2 carbons and three fully-substituted sp^3 carbon atoms in addition to the carbonyl carbon and the methyl carbons. All above facts are consistent with the 1,2 adduct structure of 10-chloro-3,3,9,10-tetramethyl-1,4-dioxaspiro-[4,5]deca-6,8-dien-2-one (**137**).

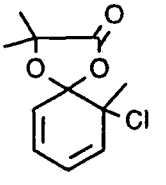
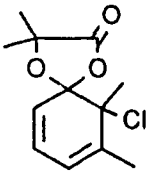
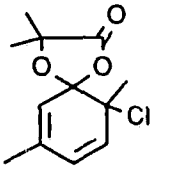
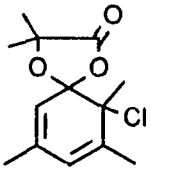
Chlorination of 2-methyl-2-(2,5-dimethylphenoxy)-propanoic acid (**121**) yielded 10% of an non-aromatic compound and 68% of an aromatic acid. The acid, separated from the product mixture by base extraction, was identified as 2-methyl-2-(4-chloro-2,5-dimethylphenoxy)propanoic acid (**140**). The UV spectrum of the non-aromatic component showed the presence of a conjugated diene system (λ_{max}= 272 nm). Other information including the elemental analysis, ^{1}H and ^{13}C NMR , and IR data are all consistent with the 1,2 adduct structure of 10-chloro-3,3,7,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**139**) for the neutral component.

When 2-methyl-2-(2,3,5-trimethylphenoxy)propanoic acid (**124**) was chlorinated with aqueous sodium hypochlorite, 10% of a single non-aromatic compound and 68% of an aromatic acid were obtained. The acid was identified as 2-methyl-2-(4-chloro-2,3,5-trimethylphenoxy)propanoic acid (**151**) by the IR and NMR spectral data. The UV spectrum of the non-aromatic component exhibited a strong absorption at λ_{max}= 273 nm, indicating that the compound contained a conjugated diene system. The mass, IR, ^{1}H and ^{13}C NMR spectral data are all consistent with the 1,2 adduct structure of 10-chloro-3,3,7,9,10-pentamethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**150**) for the non-aromatic component.

The notable features of the above chlorinations are that: i) *ipso* chloro attack occurs and the resultant Wheland intermediate is efficiently captured by the internal carboxylate nucleophile; ii) the 4-chloro acids are formed but no detectable amount of the isomeric 6-chloro-acids is obtained. The *ipso* attack, which occurs at the 2-methyl substituted position, is affected by other substituents in the substrates. The extent of the attack varies from 10 to 41%, depending on the location of the second and/or third methyl(s) in the phenoxyacids. Chlorination of acid **116** only affords 18% of the *ipso* adduct. However, introduction of a second methyl at the *ortho* position with respect to original methyl group, such as in the case of acid **120**, increases the extent of the

ipso attack to 41%. In contrast, introduction of a second methyl at the *para* position, e.g., in the cases of acids **121** and **124**, reduces the *ipso* attack to 10% (Table 3.2). The latter result appears surprising, since the presence of a second methyl group at either the *ortho* or *para* position relative to the *ipso* position should increase the reactivity of the *ipso* position.

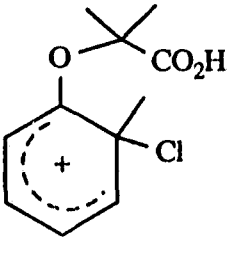
Table 3.2 Yields of 1,2 adducts

Structure				
	135	**137**	**139**	**150**
Yield (%)	18	41	10	10

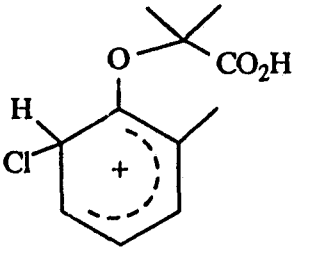
Nitration of the same series of substrates has been carried out by Bapat[95] and Mathivanan.[96] Much higher yields (> 80-100%) of the *ipso* nitro adducts were observed, indicating that compared with *ipso* nitration, *ipso* chlorination occurs less readily. One reason for this may be that the attacking electrophile for the chlorination, HOCl, is sterically more bulky than NO^+_2. The requirement that the OH group of the hypochlorous acid be replaced only as the bond between the aromatic ring and the chlorine is formed (an S_N2 reaction at the chlorine) imposes a larger

formed (an S_N2 reaction at the chlorine) imposes a larger steric constraint than the simple bond formation between the ring and the nitrogen of nitronium ion. The lower than expected reactivity of the *ipso* position toward chlorination is consistent with the behavior of hydrocarbon substrates in chlorination. p-Xylene, isodurene, and 5-t-butyl-1,2,3-trimethylbenzene all gave good yields of diene adducts in nitration. However, no adducts could be detected on chlorination.

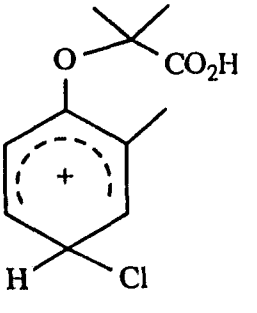
The absence of the 6-chloro acids in the chlorination products is surprising. The alkoxy group is *ortho/para* directing and should promote the formation of all three products arising from attack of chlorine at the *para* and the two *ortho* positions. Only the *ortho* position which is also *ipso* to methyl has the expected reactivity. Similar results were noted for the nitration of these compounds[96]. To account for the these observations, we consider the relative stabilities of the Wheland intermediates involved in the chlorination. The three stable Wheland intermediates are W_1, W_2, and W_3 (below), since these are stabilized by



W_1



W_2



W_3

the conjugative effect of the alkoxy group. W_1 can be captured by the internal nucleophile to give the *ipso* adduct, W_2 and W_3 can undergo deprotonation, leading to the formation of the 6-chloro- and 4-chloro-acid, respectively. In the formation of W_1 and W_2, the alkoxy side chain must adopt a confirmation in which it twists toward the *ortho* position which is not attacked, in order to avoid steric interaction with the incoming electrophile. This twist becomes difficult for W_2, since there is an o-methyl group on the non-attacked side. The non-bonding interaction between the alkoxy group and the o-methyl substituent leads to a high transition state energy for the formation of W_2, which seems to be high enough to prevent the formation of W_2.

3.2.2 Chlorination of 2-Methyl-2-(4-methylphenoxy)-propanoic Acids **117**, **118**, **119**, **123** and **125**

Chlorination of 2-methyl-2-(4-methylphenoxy)propanoic acid (**117**) gave 34% of a non-aromatic compound and 51% of an aromatic acid. The aromatic component was identified as 2-methyl-2-(2-chloro-4-methylphenoxy)propanoic acid (**131**). The neutral component had ^{1}H and ^{13}C NMR, IR, and UV (λ_{max}= 212 nm) spectral data that was consistent with the 1,4 adduct structure of 8-chloro-3,3,8-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**130**).

Chlorination of 2-methyl-2-(3,4-dimethylphenoxy)-propanoic acid (**118**) gave 46% of non-aromatic compounds and 50% of an aromatic acid. The acid was identified as 2-methyl-2-(2-chloro-3,4-dimethylphenoxy)propanoic acid (**122**). The neutral component was made up of two compounds. The major compound **132a** was isolated by crystallization. Its ^{1}H and ^{13}C NMR, IR, and UV (λ_{max}= 212 nm) indicated that it had the 1,4 adduct structure of 8-chloro-3,3,7,8-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**132a**). The other neutral compound **132b** was identified as the epimer of **132a** by its ^{1}H and ^{13}C spectral data. Since **132b** was not isolated from the product mixture, the relative stereochemistry of **132a** and **132b** could not be assigned by a shift reagent study.

Chlorination of 2-methyl-2-(2,4-dimethylphenoxy)-propanoic acid (**119**) afforded a mixture of two non-aromatic compounds, made up of 27% of **133** and 27% of **134**, and 36% of unreacted **119**. Acid **119** was recovered from the base extract during the workup. None of the 6-chloro acid was detected in the product mixture. The neutral compounds **133** and **134** were separated by column chromatography (alumina). Compound **133** had ^{1}H NMR, ^{13}C NMR, IR, and UV (λ_{max}= 216 nm) spectral data that were consistent with the 1,4 adduct structure of 8-chloro-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**133**). The IR spectrum of compound **134** showed the presence of an OH group in the structure (strong

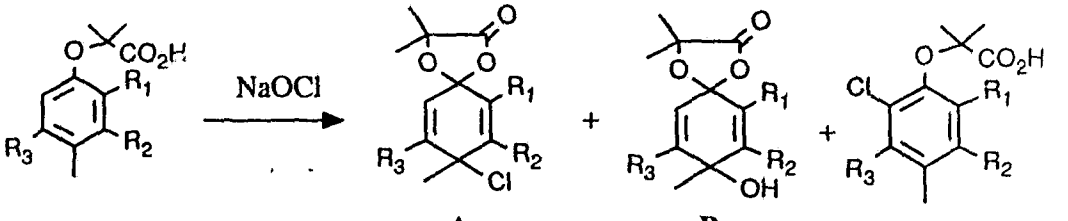
absorption at 3300 cm^{-1}). The ^{1}H NMR showed that there was a methyl group which resonated at very high field (δ 1.30). The corresponding methyl group in **133** absorbed at δ 1.66. This indicated that the methyl group in **134** was attached to the same carbon as the OH group. Other information from the ^{1}H and ^{13}C NMR, UV, and analytical data were all in agreement with the 1,4 adduct structure of 8-hydroxy-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**134**) for this compound.

Similarly, chlorination of 2-methyl-(2,4,5-trimethylphenoxy)propanoic acid (**123**) also afforded 90% of neutral compounds, which were made up of two 1,4 adducts, 8-chloro-3,3,7,8,10-pentamethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**148**), and 8-hydroxy-3,3,7,8,10-pentamethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**149**) in a ratio of 1 : 1.4.

Chlorination of 2-methyl-2-(3,4,5-trimethylphenoxy)-propanoic acid (**125**) gave 55% of 8-chloro-3,3,7,8,9-pentamethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**152**) and 39% of 2-methyl-2-(2-chloro-3,4,5-trimethyl)propanoic acid (**153**).

Results for the above chlorinations are summarized in Table 3.3.

Table 3.3 Product distribution of the chlorination of acids **117, 118, 119, 123,** and **125**



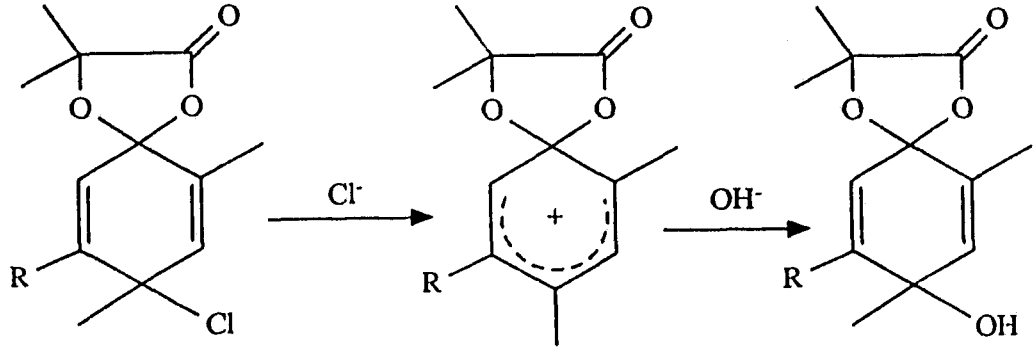
Substrate	R_1	R_2	R_3	%A *	%B *	%C*
117	H	H	H	34 (**130**)	0	51 (**131**)
118	H	Me	H	46 (**132a, b**)	0	50 (**122**)
119	Me	H	H	27 (**133**)	27 (**134**)	0
123	Me	H	Me	35 (**148**)	45 (**149**)	0
125	H	Me	Me	55 (**152**)	0	39 (**153**)

*** Isolated yields**

Chlorination of acids **117**, **118**, and **125** offers two types of products: the *ipso* chloro adduct and the 2-chloro acid. In these cases both *ortho* positions in the substrates are unsubstituted, so that the 2-chloro acids can easily be formed. In contrast, in the case of acids **119** and **123**, in which one of the *ortho* positions is substituted by a methyl group, the chlorination only gives the products of *ipso* attack at the 4 position. The formation of the 6-chloro acids does not occur. It is also to be noted that formation of the *ipso* product from chlorination at the 2 position also does not occur in these cases.

The formation of the hydroxy adducts, **134** and **149**, in the cases of the chlorination of **119** and **123**, respectively, is quite interesting. It is likely that these adducts are derived from the further hydrolysis of the corresponding chloro dienes in the aqueous reaction media (Scheme 3.2).

Scheme 3.2



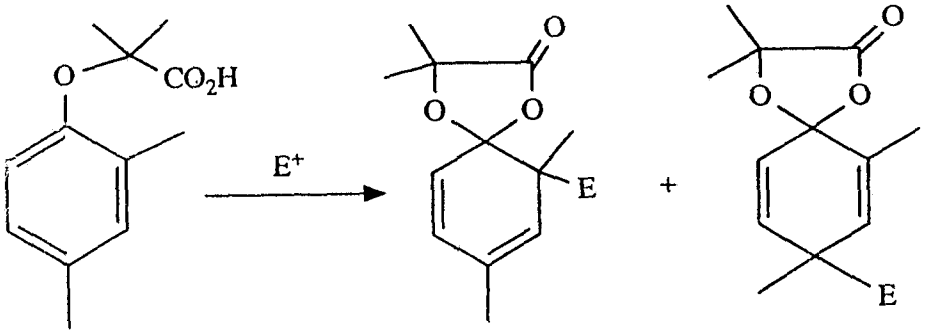
W_h

The hydrolysis process is facilitated in these systems more than in the others, possibly because the Wheland intermediate, W_h, formed from the ionization of the chloro diene, is stabilized by the electron donating inductive effect of the additional methyl *ortho* to the acetal center, which lowers the transition state energy for the formation of W_h.

Another striking feature of the chlorination of acids **119** and **123** is the absence of the 1,2 chloro adducts, as there are two potential *ipso* positions in the substrates, i.e., 2- and 4-methyl substituted carbons. In contrast, the

nitration of acid **119** yields both 1,2 and 1,4 nitro adducts[96] (Scheme 3.3). This result demonstrates again that an *ipso* position exhibits a lower reactivity towards chlorination than towards nitration.

Scheme 3.3



1,2- 1,4-adduct

E^+	Ratio (%)	
Cl^+	0	100
NO^+_2	29	71

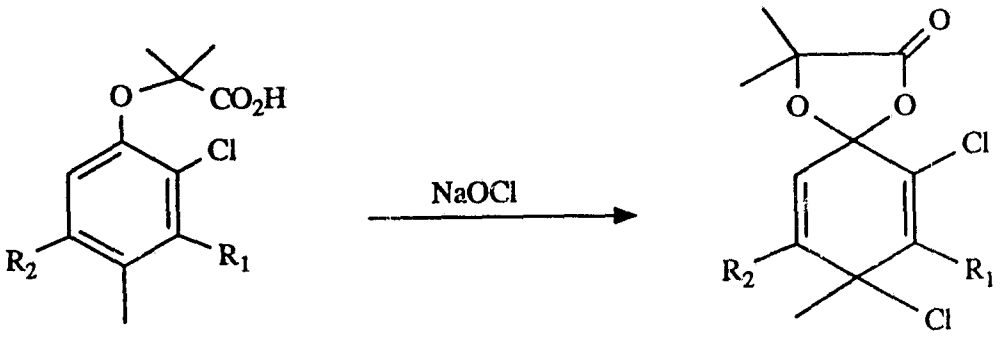
3.2.3 Chlorination of 2-Methyl-2-(chlorophenoxy)propanoic Acids **122**, **131**, **136**, **138**, **140**, **153**, and **155**

In contrast with the chlorinations discussed previously, the reactions of chlorophenoxy acids were very slow and generally required 10 to 15 h to achieve reasonable yields of the diene adducts. In all cases only the products of *ipso* attack were obtained. None of the dichloro acids was detected in the products.

Chlorination of 2-chloro-4-methylphenoxy acids **122**,

131 and **153** gave the 1,4 chloro adducts, **142**, **141**, and **154**, respectively. The results are summarized in Scheme 3.4. The extent of *ipso* attack for acid **131** is only 17% in 16 h, while for **122** and **153**, even in a shorter time interval, it is 74% and 89%, respectively. Obviously, the higher yield of the *ipso* adducts in the latter two cases is due to the presence of the methyl(s) ortho to the 4-methyl substituted carbon, the potential *ipso* position, in the substrates, which enhances the reactivity of the *ipso* position.

Scheme 3.4



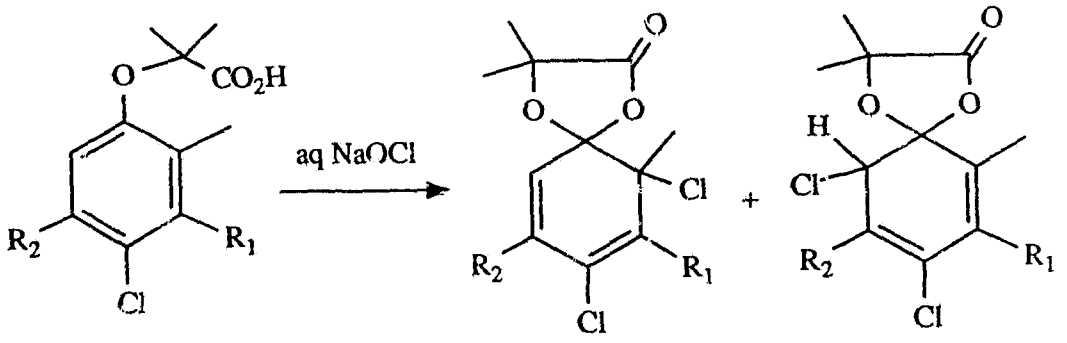
Compound	R_1	R_2	t (h)	Product	% yield
131	H	H	16	**141**	17
122	H	Me	12	**142** (E+Z)	74
153	Me	Me	0.5	**154**	89

Chlorination of 4-chloro-2-methylphenoxy acids **136**, **138**, and **140** gave the corresponding 1,2 chloro adducts, **143**, **145**, and **146**, respectively. In addition, chlorination of acids **136** and **140** also afforded the secondary chloro

adducts, **144** and **147**, respectively. The results are summarized in Scheme 3.5.

The secondary chloro adducts **144** and **147** can be formed via two possible pathways: a) direct electrophilic chloro attack at the 6-position followed by internal nucleophilic capture; b) 1,5 shift of the chlorine in

Scheme 3.5



Compound	R_1	R_2	t (h)	% yield	
136	H	H	4	40 (**143**)	10 (**144**)
138	Me	H	8	69 (**145**)	0
140	H	Me	16	66 (**146**)	23 (**147**)

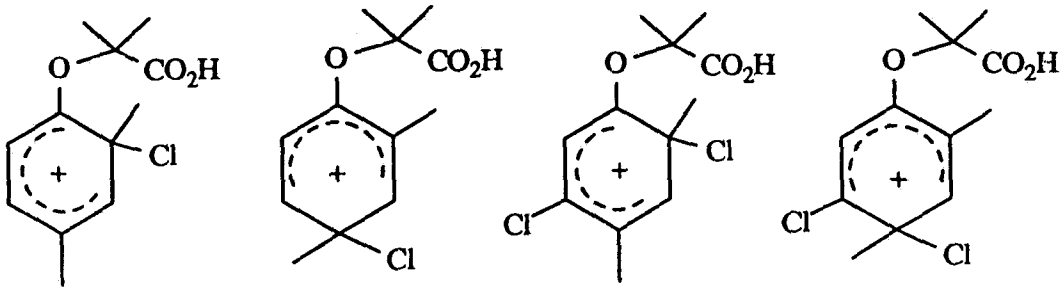
the corresponding *ipso* adducts. The study of thermal isomerization reactions of the 1,2 chloro adducts has suggested that the latter pathway is more likely to be the case (Sec. 3.3). Further support for the mechanism comes from the chlorination of acid **119**, in which none of the 6-chloro acid is formed, indicating that the direct attack of chlorine at the 6 position of a 2-methyl substituted

phenoxy acid is difficult.

Chlorination of 2-methyl-2-(5-chloro-2,4-dimethyl-phenoxy)propanoic acid (**155**) gave a mixture of two chloro dienes (89%) in a ratio of 1.1 : 1. The two products were separated by HPLC, and their analytical, ^{1}H, and ^{13}C NMR, and IR spectral data suggested that they were positional isomers. The UV data enabled the identification of the 1,4 adduct structure of 7,8-dichloro-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**156**) for the major isomer (λ_{max}= 213 nm), and the 1,2 adduct of 7,10-dichloro-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]-6,8-dien-2-one (**157**) for the minor isomer (λ_{max} = 275 nm).

The formation of both 1,2 and 1,4 adducts in this case is quite interesting, considering that in the case of 2-methyl-2-(2,4-dimethylphenoxy)propanoic acid (**119**) only the 1,4 adduct **133** is formed. The absence of the 1,2 adduct in the latter case may be attributed to the higher steric hindrance at the 2-methyl position relative to the 4-methyl position, which results in the transition state energy for the formation of the *ipso* Wheland intermediate **I** (below), the precursor of the 1,2 adduct, being so high that only the intermediate **II**, the precursor of the 1,4 adduct, is formed. However, in the case of chlorination of **155**, although the transition state of intermediate **III** for the 1,2 adduct is still destabilized by the non-bonding interaction between the 2-*ipso* chloro and the bulky alkoxy

side chain, the high energy of the transition state is compensated to a certain degree by the electron donating resonance effect of the 5-chloro group in **III**. The 5-chloro group in the 1,4 adduct intermediate **IV** on the one hand stabilizes the transition state by its resonance effect



I **II** **III** **IV**

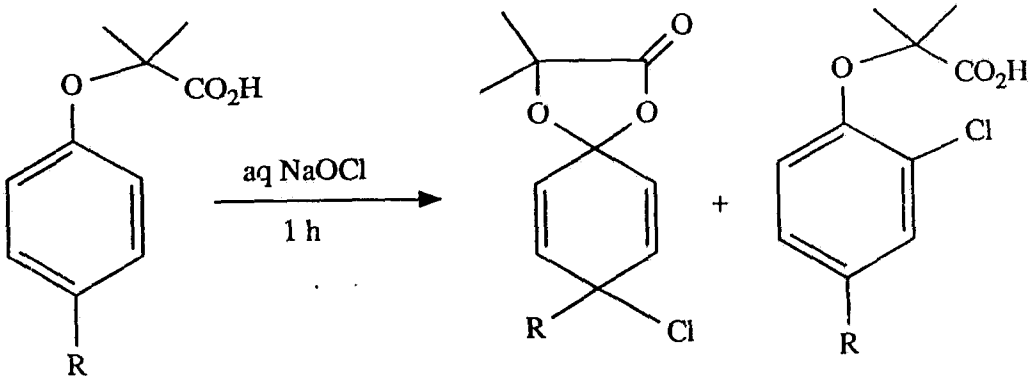
but, on the other hand, also destabilizes the transition state by introducing a steric interaction between the 5-chloro substituent and the 4-*ipso* chlorine in **IV**. As a result of this, the energies of the transition state for **III** and **IV** are comparable. In addition, the *ortho:para* ratio for chlorination of chlorobenzene,[142] 1/2o:p = 0.29 suggests that a chloro group activates its *para* position much more than it does the *ortho* position. The presence of the 5-chlorine in **155** therefore should enhance the reactivity of the 2-methyl *ipso* position more than that of the 4-methyl *ipso* position, and offset the disfavour for formation of the 1,2 adduct introduced by the steric effect. Thus *both 1,2* and 1,4 adducts are formed in this case.

3.2.4 Chlorination of 2-Methyl-2-(4-alkylphenoxy)propanoic Acids 126, 127, and 128

Chlorination of acids **126**, **127**, and **128** gave similar results to that for **117**, i.e., an *ipso* 1,4 adduct and a 2-chlorophenoxy acid were formed, as summarized in Scheme 3.6.

Although the extent of *ipso* attack declines from 34% to 21% as the alkyl group at the *ipso* position is increased in size from methyl to t-butyl, the reduction is too small

Scheme 3.6



Compound	R	% yield	
117	Me	34 (**130**)	51(**131**)
126	Et	28 (**160**)	64 (**161**)
127	i-Pr	22 (**162**)	72 (**163**)
128	t-Bu	21 (**164**)	66 (**165**)

to be reflective of the size change of the alkyl group alone. Substitution of a hydrogen of the alkyl group by a methyl should not only introduce steric hindrance at the *ipso* position, but also electronically enhance the

reactivity of the position. It is possible that primary, secondary, and tertiary alkyl groups are progressively even more activating at the *ipso* position than methyl and that this factor partially offsets the increase in steric hindrance through the series.

3.2.5 Chlorination of 2-Methyl-2-(3,5-di-t-butylphenoxy)propanoic Acid (129)

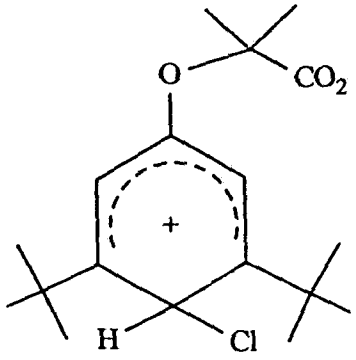
Chlorination of acid **129** gave 86% of non-aromatic compounds and 9% of aromatic acids. The aromatic component was made up of two positional isomers in a ratio of 4:1. The major isomer was identified as 2-methyl-2-(2-chloro-3,5-di-t-butylphenoxy)propanoic acid (**159a**) and the minor one as 2-methyl-2-(4-chloro-3,5,di-t-butylphenoxy)propanoic acid (**159b**) based on their ^{1}H and ^{13}C NMR spectral data.

The non-acidic component was made up of two diastereomers in the proportion of 5 : 1. The major isomer **158a** was isolated by recrystallization. The characteristic peak at δ 4.86 in the ^{1}H NMR indicated the presence of a secondary chlorine in the structure. Other information from the ^{13}C NMR, IR, and UV (λ_{max}= 219 nm) all pointed to **158a** having the 1,4 adduct structure of 8-chloro-7,9-di-t-butyl-3,3-dimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one. The stereochemistry of **158a** was assigned as that of the E-isomer, based on a shift reagent study. Similarly, the partially separated minor isomer was identified as Z-8-

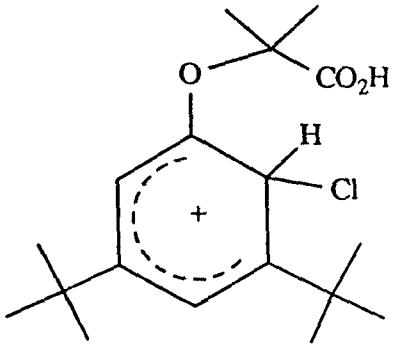
chloro-7,9-di-t-butyl-3,3-dimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**158b**).

The formation of the secondary diene **158** is of interest in that it is a genuine example of intramolecular capture of a non-*ipso* chloro Wheland intermediate. It is likely that in this case the presence of the two bulky t-butyl groups in the system results in the deprotonation of the Wheland intermediate for the 1,4 adduct, W_{14} (below), being slower than the internal nucleophilic capture.

The striking feature of the chlorination is the absence of the 1,2 adduct in the products. The formation of the 2-chloroacid **159a** in less than 9% yield shows that eletrophilic attack *ortho* to the alkoxy group occurs to a small extent and formation of a similar amount of the 1,2 adduct might not have been detected. The product distribution indicates that addition of chlorine at the 4-position is preferred over that at the 2-position. It is unlikely that steric hindrance in **129** dominates the product distribution. The Wheland intermediate for 1,2 adduct formation, W_{12}, should be no more strained than that for 1,4 adduct formation, W_{14}.



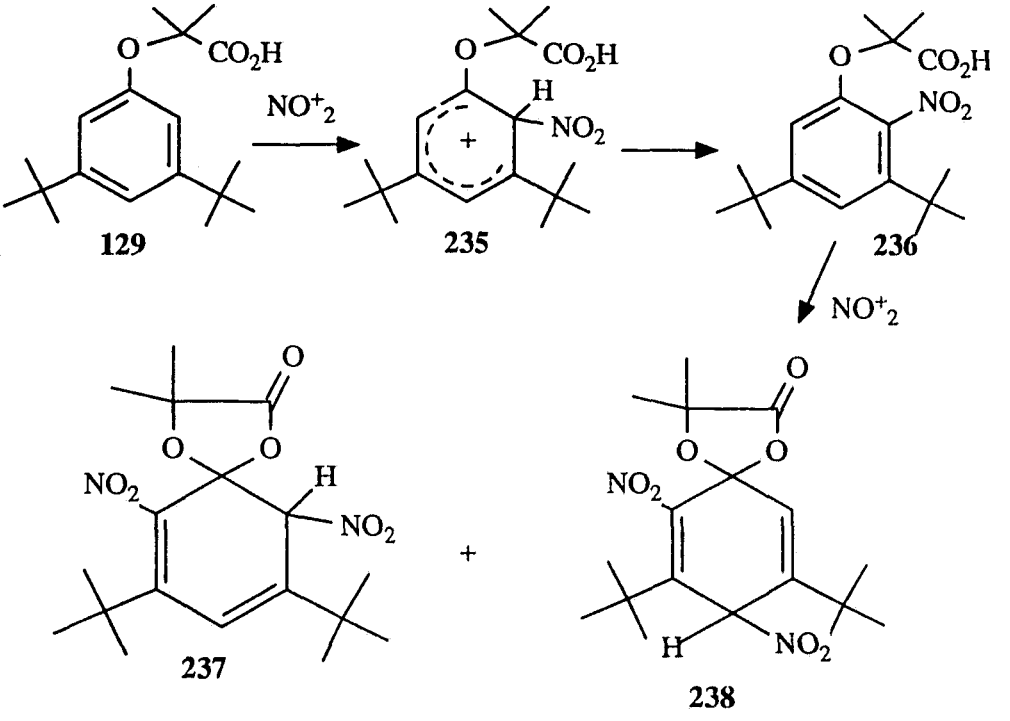
W_{14}



W_{12}

In contrast to chlorination, nitration of the same substrate with nitric acid in acetic anhydride[71a] gives exclusively the 2-nitroacid **236**, a product resulting from the addition of nitronium ion at the 2-position of the substrate. Further nitration of acid **236** yields 85% of the non-*ipso* 1,2 dinitro adduct **237** and 15% of the 1,4 adduct **238**, as illustrated in Scheme 3.7. The initial nitration fails to give a secondary nitro adduct, which is stable enough to be observed. Only the dinitro adducts 237 and 238 could be detected and isolated. The low stability of the mononitro adduct relative to the corresponding monochloro adduct may be attributed to the very strong electron withdrawing effect of the nitro group, which makes deprotonation of the Wheland intermediate **235** faster than lactone ring closure. Finally, the higher stability of dienes **237** and **238** may be attributed to the increasing

Scheme 3.7



steric crowding around the secondary nitro group in these structures.[71a]

3.3 THERMAL ISOMERIZATION OF CHLORO DIENES

3.3.1 Reactions of the 1,2 Adducts

a) Diene **135** in chloroform-d after 8 h at 60 °C gave 90% of a neutral compound. The ^{1}H and ^{13}C NMR of the product revealed the presence of three adjacent vinylic CH groups plus a CH group which appeared at δ 4.62 in the ^{1}H NMR spectrum and at 59.2 in the ^{13}C NMR spectrum. The UV spectral data (λ_{max} = 267 nm) indicated that the compound

contained a conjugated diene system. Other information from the IR and mass spectra all supported the 1,2 adduct structure of 10-chloro-3,3,6-trimethyl-1,4-dioxaspiro-[4,5]deca-6,8-dien-2-one (**195**) for the product.

The isomerization of diene **135** to its positional isomer **195** can be accounted for by a 1,5 sigmatropic migration of the chloro group. It is also possible to imagine a nucleophilic rearrangement by ionization of the chlorine as chloride and its reattachment at the other end of the pentadienyl cation system. This seems an unlikely process in a poorly ionizing solvent such as chloroform.

b) Diene **137** in chloroform-d at 60 ^{o}C gave, after 18 h, 60% of a non-aromatic compound and 30% of an aromatic acid. The acid was separated from the reaction mixture by base extraction. It was identified as 2-methyl-2-(6-chloro-2,3-dimethylphenoxy)propanoic acid (**197**). The nonaromatic component was identified as the positional isomer of **137** and had the 1,2 adduct structure of 10-chloro-3,3,6,7-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**196**). The assigned structure was also consistent with the formation of acid **197**. Deprotonation of **196** at the secondary center, coupled with opening of the lactone ring and protonation of the lactone carbonyl, likely all concerted would lead to **197**. The driving force in this process is of course the recapture of the resonance stabilization of the aromatic system in acid **197**.

c) Diene **139** in chloroform-d at 60 °C gave, after 18 h, 55% of a non-acidic compound and 45% of 2-methyl-2-(6-chloro-2,5-dimethylphenoxy)propanoic acid (**174**). The neutral compound was separated from the acid by base extraction. The ^{1}H and ^{13}C NMR, IR, and UV spectral data of the compound was consistent with the 1,2 adduct structure of 10-chloro-3,3,6,9-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**198**). Formation of acid **174** can be explained as in b.

d) The mixture of dienes **143** and **144** (2:1) in chloroform-d at 60 °C gave, after 2 h, only one non-aromatic compound, which was identified as 8,10-dichloro-3,3,6-trimethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**144**). This observation supports the proposition that the formation of diene **144** in the original chlorination of acid **136** occurs via the isomerization of diene **143**.

e) Diene **145** in chloroform-d at 60 °C gave after 18 h, 70% of a non-aromatic compound and 30% of unreacted diene **145**. The structure of the partially separated product **199** was assigned as 8,10-dichloro-3,3,6,7-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one, based on its ^{1}H and ^{13}C NMR spectral data.

f) Diene **146** in chloroform-d at 60 °C after 3 h isomerized completely to its positional isomer, 8,10-dichloro-3,3,6,9-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**147**), which was previously obtained in

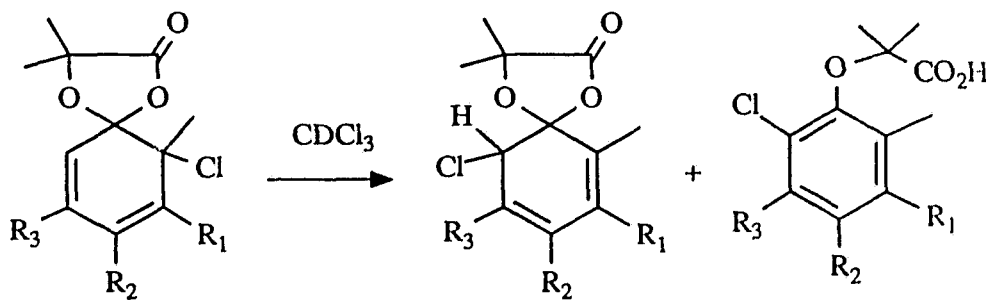
chlorination of acid **140** presumably via the isomerization of diene **146**.

g) Diene **150** in chloroform-d at 60 ^{o}C was not observed to undergo any reaction in 48 h. The starting material **150** was recovered after Workup.

h) Diene **157** in chloroform-d at 60 ^{o}C after 3 h, isomerized completely to a new isomer. The ^{1}H and ^{13}C NMR, IR, and UV spectral data of the compound showed that it had the 1,2 adduct structure of 9,10-dichloro-3,3,6,8-tetramethyl-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**191**).

Data relating to isomerization of the 1,2 adducts discussed above is summarized in Scheme 3.8. A similar thermal isomerization for a series of nitro spiro adduct analogues has been observed by Bapat[95] and Mathivanan[96], and rationalized as a [1,5] sigmatropic rearrangement process based on the following experimental evidence: i) a trapping experiment showed that the 1,5 shift of nitro group was intramolecular; ii) a stereochemical study demonstrated that the isomerization was stereospecific. The 1,5 shift of a nitro group has also been observed in related systems. Nitro group migrations in N-nitropyrazoles[143] and N-nitro-1,2,4-triazoles[144] have been reported. The migration of other groups in a series of 1-methyl-1-X-cyclohexa-2,4-diene systems has been studied by Schiess et al.[145] They have shown that the nature of the

Scheme 3.8



Diene	R_1	R_2	R_3	t(h)	% yield	
135	H	H	H	8	90 (**195**)	0
137	Me	H	H	18	60 (**196**)	30
139	H	H	Me	18	55 (**198**)	45
143	H	Cl	H	2	100 (**144**)	0
145	Me	Cl	H	18	70 (**199**)	0
146	H	Cl	Me	3	100 (**147**)	0
150	Me	H	Me	48	0	0
157	H	Me	Cl	3	100 (**191**)	0

migrating group X is very important to the rearrangement mechanism. For less polar substituents such as X = Me or Ph, the reaction occurs by successive ring opening, hydrogen shift, and ring closure. For more polar substituents such as CHO, $COCH_3$, or COPh, the rearrangement is exclusively a [1,5] sigmatropic process. Simple Hückel calculations[146] have also shown that the [1,5] sigmatropic rearrangement is favored by a polar migrating group. In

addition to the electronic effects of the migrating group, steric factors also play an important role in the rearrangement. If the migration terminus is extensively substituted, the steric interaction between the migrating group and and the substituents will raise the transition state energy and inhibit the rearrangement.

In the present study, the [1,5] sigmatropic rearrangement of chlorine has been observed in seven systems (Scheme 3.8). In some cases, in addition to the rearranged diene products, 6-chlorophenoxy acids are also formed. As explained above, these are derived from the subsequent aromatization of the corresponding rearranged dienes. From the summarized results (Scheme 3.8), one can see that the rearrangement rate is strongly influenced by the nature of the substituents in the diene system, R_1, R_2, and R_3. If R_1, R_2, and R_3 are all hydrogen, as in the case of diene **135**, it only takes 8 h for the reaction to proceed to substantial completion. However, when either R_1 or R_3 is substituted with a methyl group, as in the cases of dienes **137** and **139**, the reaction time is extended by a factor of two. In the case that both R_1 and R_3 are substituted with methyls (diene **150**), the rearrangement does not occur at all. On the other hand, if either R_2 or R_3 is substituted with a chloro group, as in the cases of dienes **143**, **146**, and **157**, the reaction only takes 2 to 3 h to complete. It appears that the electronic effect of the substituents

dominates in the rearrangement. Methyl, an electron donating group, reduces the reactivity of the substrates, whereas chlorine, an electron withdrawing group, does the opposite. These are certainly not the effects which would be expected for a carbonium ion type rearrangement.

General [1,5] sigmatropic rearrangements have been theoretically rationalized in terms of molecular orbital theory by Woodward and Hoffmann[147]. For a 1,3 pentadiene system, the orbital participating in the rearrangement is the frontier orbital $_3$. Since a electron withdrawing group lowers the energy of the orbital, it may be speculated that the presence of an electron withdrawing group lowers the transition state energy of the reaction, while an electron withdrawing substituent does the opposite.

3.3.2 Attempted Thermal Isomerization of 1,4 Adducts

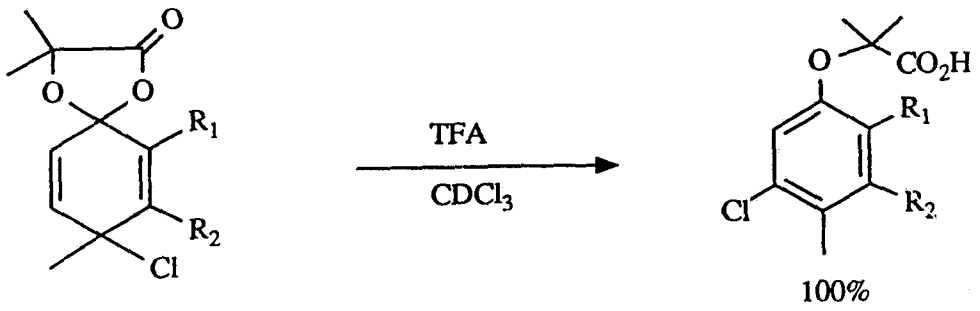
Some examples of [1,3] sigmatropic rearrangement have been observed in a few nitro diene systems[79b] and N-nitroenamines.[148] In the present work, the thermal isomerization of chloro 1,4 adducts was therefore investigated. However, these dienes were not observed to undergo rearrangement under thermal conditions. A similar observation has been made for a series of the nitro diene analogues.[95,96]

3.4 ACID CATALYSED REACTIONS OF *IPSO* CHLORO ADDUCTS

3.4.1 Reactions of 1,4 Adducts

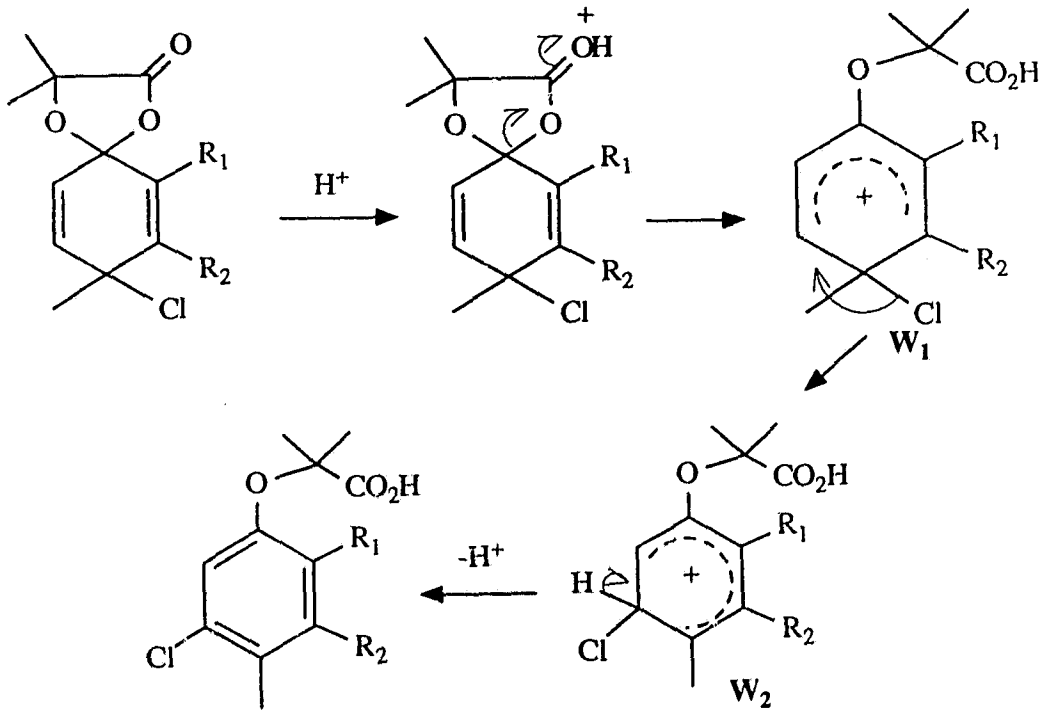
Reaction of diene **130** in chloroform-d with TFA gave exclusively the 3-chloroacid **166**, presumably via a concerted 1,2 chloro shift process. Similar reactions were observed for dienes **132** , **133** and **141**, as summarized in Scheme 3.9. The proposed mechanism for the reaction is shown in Scheme 3.10. In this mechanism, protonation of the substrate followed by lactone ring opening gives the *ipso* Wheland intermediate, W_1. The chlorine then undergoes a 1,2 shift to give the isomeric intermediate W_2. The cationic intermediate W_1 is stabilized by the alkoxy side chain, which should generally make intermediate W_1 more stable than W_2. However, provided that W_2 is formed at a finite rate it will be irreversibly removed by deprotonation, thus driving the rearrangement in the favored direction. Although the rearrangement from W_1 to W_2 is thermodynamically disfavorable the overall rearrangement process is favored by the gain in aromatic stabilization.

Scheme 3.9



Diene	R_1	R_2	Product
130	H	H	**166**
132	H	Me	**167**
133	Me	H	**155**
141	Cl	H	**175**

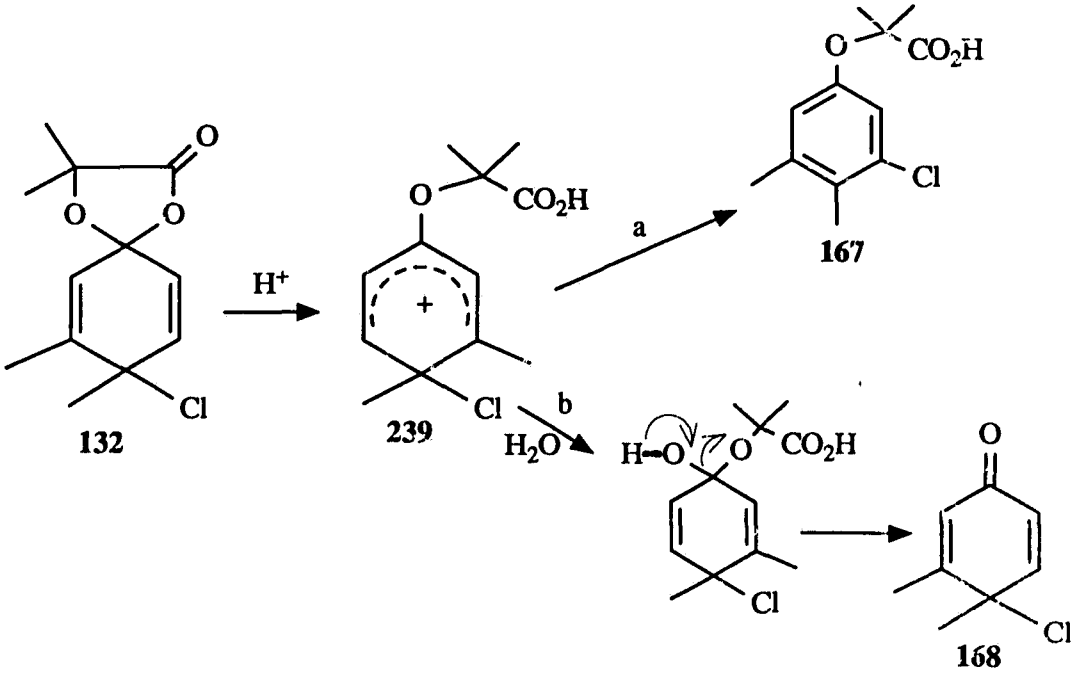
Scheme 3.10



A similar 1,2 chloro shift has been observed by Fischer and Henderson[123b] in the study of the acid catalysed reactions of a series of 4-chloro-4-methyl-cyclohexadienones. A notable feature of these reactions is the migration of chlorine in preference to that of the methyl group. A systematic study of a series of 4-X-4-methylcyclohexa-2,5-dienones has shown that the substituents X = CO_2Et,[149,150] OCOMe,[151] Ph,[150] and Cl[123b] have higher migration tendency than Me, whereas Me is better than OH[152] and OMe.[153] The competitive migratory aptitude of two substituents depends on both the intrinsic migration tendency of the substituents, and the stabilizing ability of the non-migrating group on the transition state. Since OH and OMe groups are particularly effective in stabilizing the transition state, they do not migrate in competition with Me. The CO_2Et group, an electron withdrawing group, destabilizes the transition state and thus migrates. The OCOMe and Ph groups can each form a new bridge bond during the migration, which stabilizes the transition states and thus these groups migrate. Chlorine on one hand has a destabilizing (electron-withdrawing) inductive effect, and on the other hand it has a stabilizing resonance effect. The inductive effect outweighs the resonance effect and chlorine migrates in preference to the stabilizing (electron-donating) methyl group.

The reactions of dienes **130** and **133** with other acids such as triflic acid or BF_3 were similar to the reactions with TFA. However, reaction of diene **132** with triflic acid yielded, in addition to the expected 3-chloro-acid **167**, 4-chloro-3,4-dimethylcyclohexa-2,5-dienone (**168**). The formation of dienone **168** indicates that in addition to the 1,2 chloro shift process (path a in Scheme 3.11), the *ipso*

Scheme 3.11



Wheland intermediate **239** undergoes another competitive reaction pathway, i.e., it reacts with the trace amount of water in the reaction media to give the dienone product (path b in Scheme 3.11). In this case, since the intermediate **239** is stabilized by the additional methyl group and it has a longer life time than the others, the

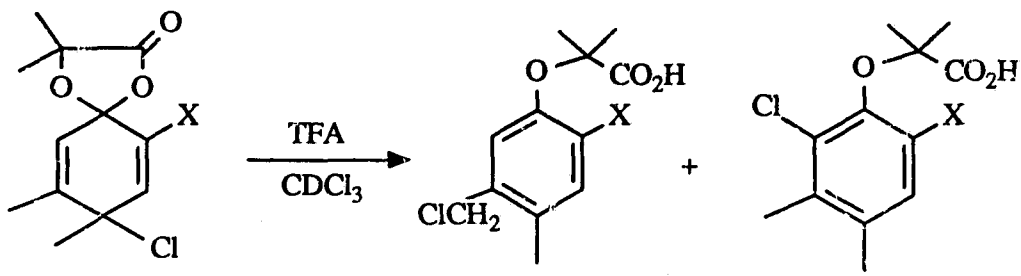
1,2 chloro shift is not the only favorable reaction pathway. The methyl group should inhibit the chlorine migration. In contrast, the methyl group in **133** is located so as to favor the rearrangement. Thus we can understand why dienone is obtained from **132** but not from **130** nor from **133**.

An interesting aspect of the 1,2 chloro shift reaction is that it exhibits high regioselectivity. The chlorine always migrates to the one adjacent position which is sterically less hindered than another one, e.g., in the case of diene **133**, only the 5-chloroacid **155** is formed and no 3-chloroacid is observed.

When diene **142** was treated with TFA in chloroform-d, a mixture of a side chain modified product, **176**, and the 6-chloro acid, **177**, was obtained. The reaction of **148** with TFA afforded similar types of products, i.e., the side chain product **183** and the 6-chloroacid **184**, as shown in Scheme 3.12.

The formation of the side chain products in these cases suggests that the reaction involves a pathway in which a methylenecyclohexadiene is formed as the

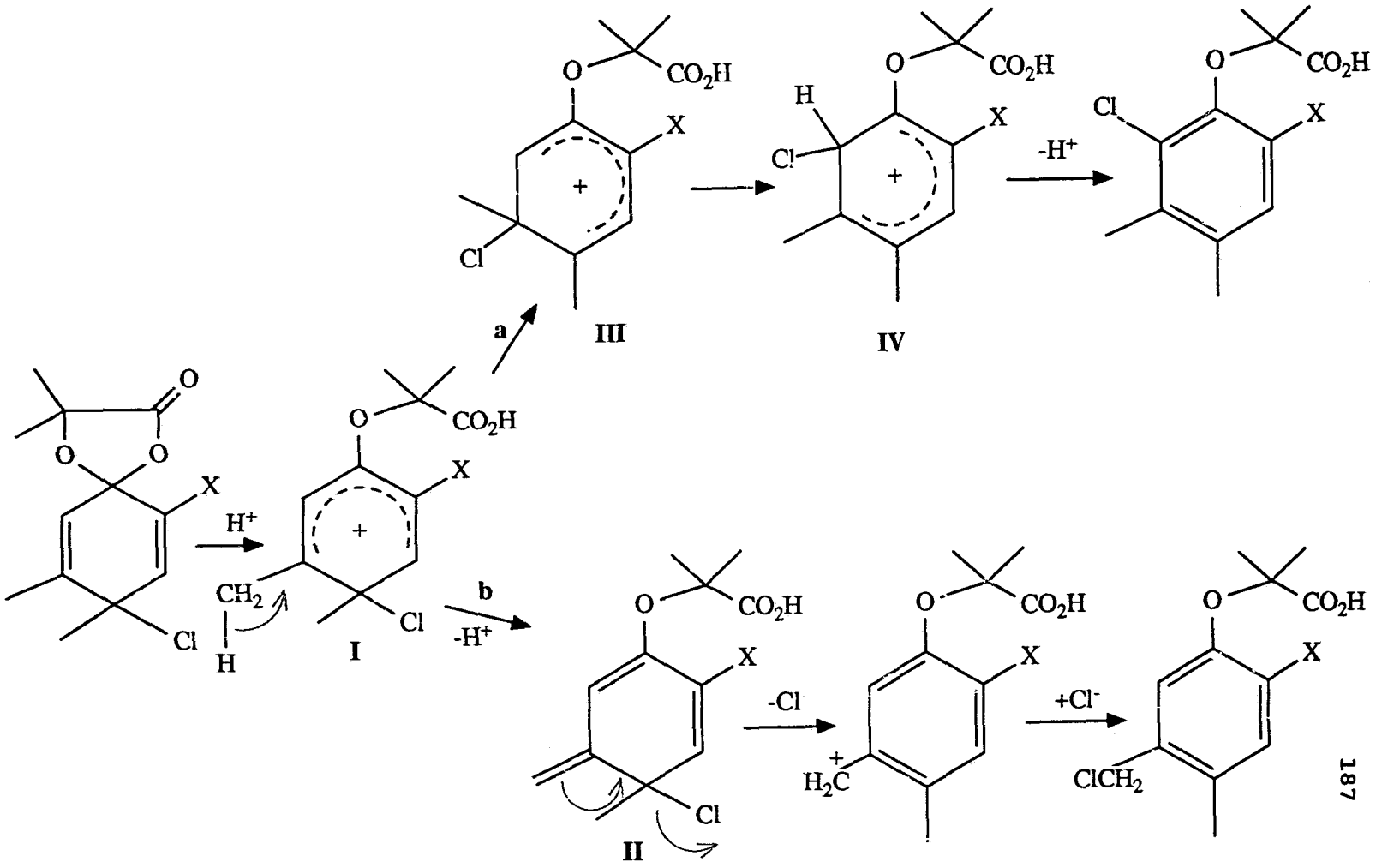
Scheme 3.12



Diene	X	Ratio	
142	Cl	1 (**176**)	1.4 (**177**)
148	Me	1 (**183**)	1.5 (**184**)

intermediate (path b in Scheme 3.13). In addition to this, the reaction also involves another competitive pathway in which the chloro group undergoes two successive 1,2 shifts to give the 6-chloroacid products (path a in Scheme 3.13). Because loss of the methyl group as a cation does not occur, intermediate **III** can only return to **I** (by a reverse 1,2 chlorine migration) or undergo a second 1,2 chlorine migration to **IV**. It is striking that even in this case the other 1,2 chlorine migration in **I** to give, after deprotonation, the 3-chloroacid does not occur. Instead, deprotonation of the 5-methyl group in **I** provides an alternative competitive pathway to the 1,? (**I** to **IV**) chlorine migration. Note that the presence of the 5-methyl group not only provides the opportunity for the formation of the methylenecyclohexadiene intermediate but also should inhibit the 1,2 chlorine migration as it stabilizes **I** more

Scheme 3.13

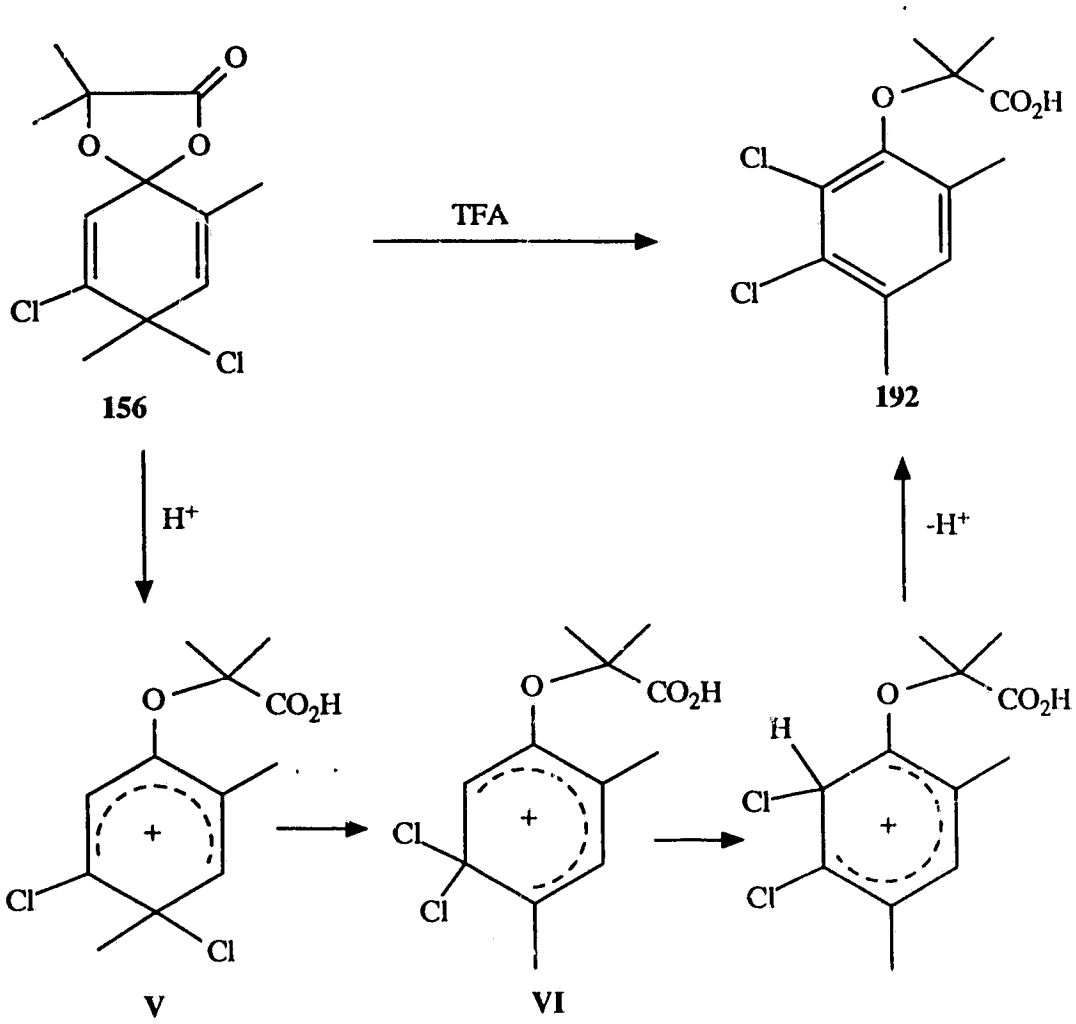


than **III**.

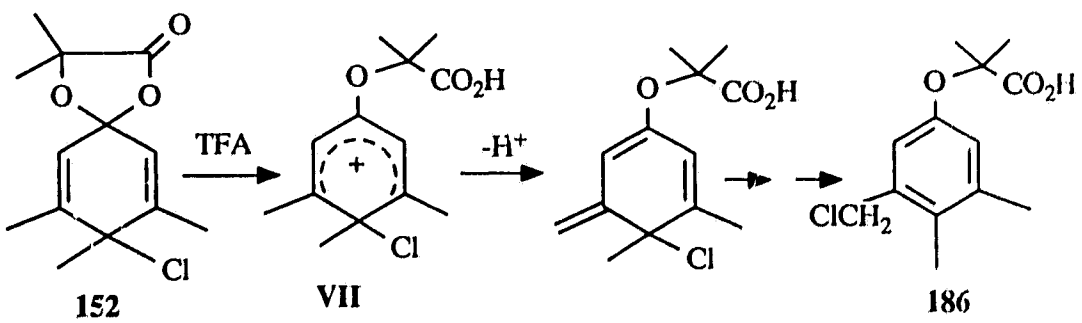
Diene **156** on reaction with TFA gave 2-methyl-2-(5,6-dichloro-2,4-dimethylphenoxy)propanoic acid (**192**) as the sole product, an apparent 1,3 chlorine migration. However, this likely occurs by successive 1,2 chlorine migrations, as shown in Scheme 3.14. In contrast to the reaction of diene **148** (Scheme 3.13), in which there is a competitive reaction pathway leading to side-chain substitution, the reaction of diene **156** is exclusive and occurs by pathway a of 3.13. Here again it is noteworthy that the chlorine 1,2 migration, to form ultimately the 3,5-dichloroacid, does not occur. It is surprising that the **V** to **VI** rearrangement occurs since the 5-chloro substituent in **V** should be much less destabilizing (chlorine can exhibit its stabilizing resonance effect) than in **VI**, where chlorine can only exhibit its destabilizing inductive effect. Once again the reaction is driven in the forward direction by the ultimate gain in aromatic resonance stabilization in **192**. The requirement for the **V** to **VI** rearrangement is not that it be rapid or favored, but that it occur at a rate not so slow that the overall reaction is prevented on the time scale used.

At the other extreme, the reaction of diene **152** with TFA yielded exclusively the side chain product **186** (Scheme 3.15). In this case the non-rearranged *ipso* Wheland

Scheme 3.14



Scheme 3.15



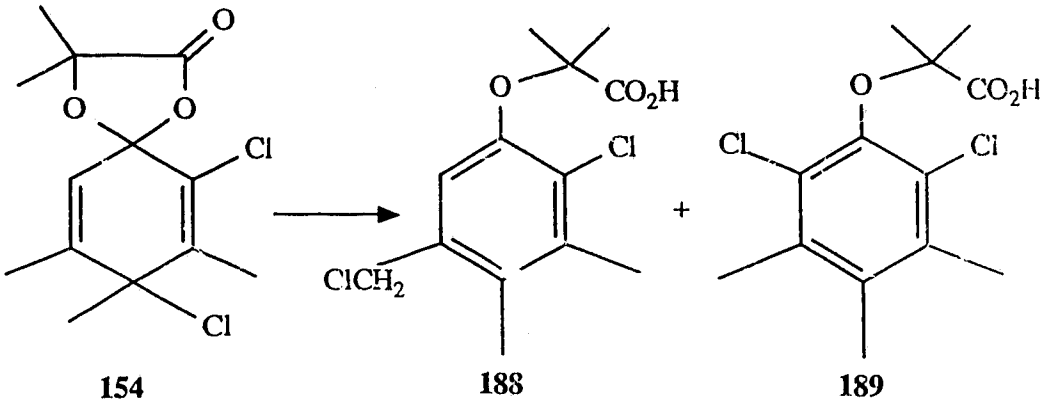
intermediate **VII** is stabilized by the two methyls at the positions *ortho* to the *ipso* center in addition to the alkoxy group. It is very obvious that the 1,2 chlorine shift would lead to a less stable intermediate. Thus loss of a proton from one of the methyls becomes the favored and only reaction pathway. On the other hand, as a highly stabilized intermediate, **VII** is also susceptible to attack by other nucleophiles, such as water in the reaction medium, at the position *ipso* to the alkoxy group to give, ultimately, the corresponding dienone. In fact, it has been observed that diene **152** on reaction with triflic acid gives dienone **187** as the single product.

Unlike diene **152**, diene **154** reacted with TFA to give both side chain product **188** and 6-chloroacid **189** in the ratio of 1 : 1.2 (Scheme 3.16). The presence of the chloro group at the position *ortho* to the acetal center facilitates the 1,2 chloro shift process as it destabilizes the rearranged cation in which the chlorine is *para* to the tetrahedral center less than in the initial cation, in which it is *meta* to the tetrahedral center.

The reaction of the secondary chlorodiene **158** with TFA appears very straightforward. It gives the 4-chloroacid **159b** as the sole product, presumably resulting from the deprotonation of the Wheland intermediate formed from

the lactone ring opening of the substrate (Scheme 3.17).

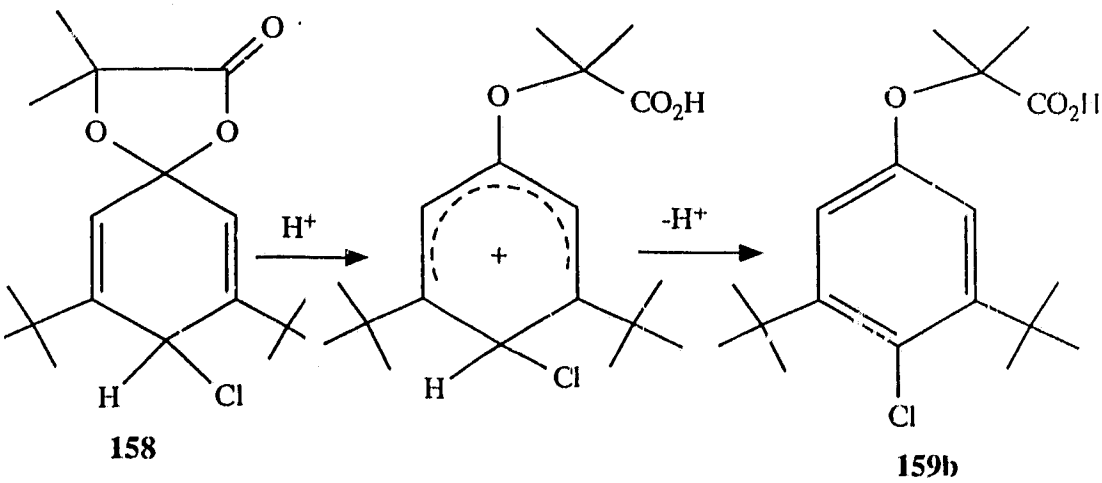
Scheme 3.16



154 **188** **189**

Ratio: 1 2

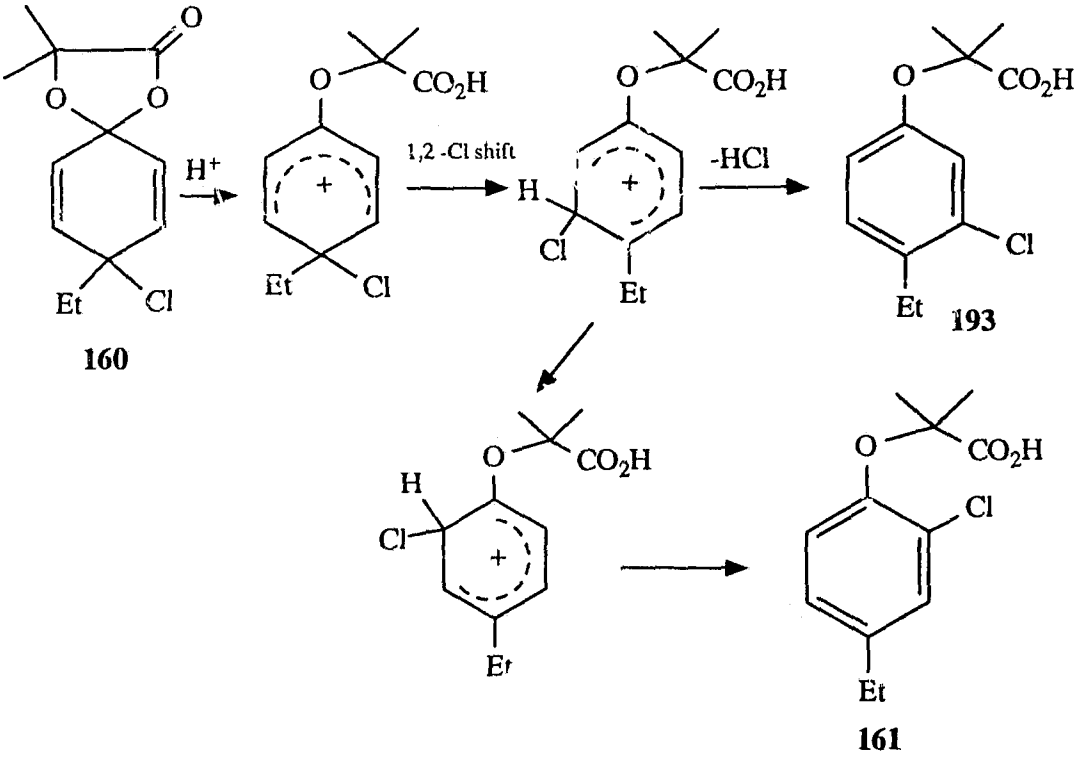
Scheme 3.17



158 **159b**

Diene **160** on reaction with TFA gave mixture of 2-chloroacid **161** and 3-chloroacid **193** in a ratio of 1 : 2.4. Presumably the former is resulted from two 1,2 chlorine shift processes and the latter is from a normal 1,2 chlorine shift. The mechanism is shown in Scheme 3.18. The

Scheme 3.18

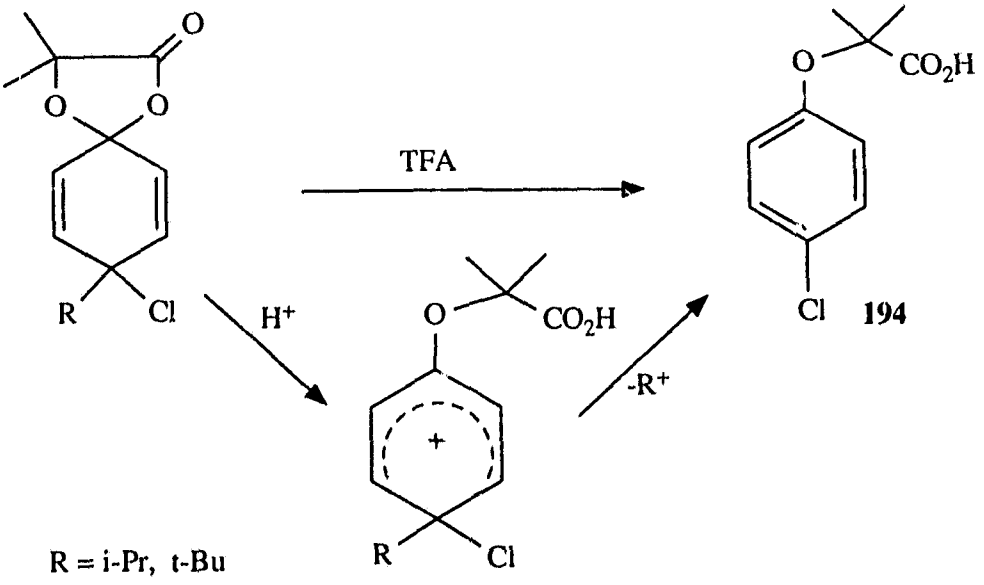


formation of the 2-chloroacid **161** in this case is interesting, comparing with the case of the reaction of diene **130**, in which only the corresponding 3-chloroacid **166** is formed. The formation of acid **161** indicates that the rearranged intermediate formed from the first 1,2 chlorine shift is slightly unstable due to the non-bonding

interaction between the chloro and the bulky ethyl group. To avoid the steric interaction in the intermediate, the chlorine group undergoes 1,2 shift again, which leads to the formation of **161**. This explanation also accounts for the absence of the corresponding 2-chloroacid in the case of diene **130**, since in that case the non-bonding interaction in the rearranged intermediate comes from a methyl and a chloro group, which is not severe enough to bring about a second 1,2 chlorine shift.

Diene **162** on reaction with TFA in chloroform-d gave 2-methyl-2-(4-chlorophenoxy)propanoic acid (**194**) as the sole product. The same product was obtained in the case of the reaction of diene **164**. In these cases, since both isopropyl and t-butyl cation are excellent leaving groups, loss of these groups takes place to give the 4-chloroacid **194**, as demonstrated in Scheme 3.19.

Scheme 3.19



Comparison of the acid catalysed reactions of the 1,4 chlorodienes with those of the nitrodiene or dienone analogues reveals a striking difference in the behavior of the two types of substrates. A nitrodiene/dienone can normally undergo the following two reaction pathways: a) a radical dissociation-recombination process under non-acidic or weakly acidic conditions;[154] b) dissociation of the nitrodiene to the phenol-nitronium ion encounter pair followed by recombination at the ortho position. In both of these cases, a 2-nitroacid or 2-nitrophenol is formed. However neither of the reaction pathways has been observed in the reactions of the chlorodienes/dienones. Fission of the C-N bond in nitromethane is 97 kJ/mol less endothermic than fission of the C-Cl bond in methyl chloride.[155] Obviously, this is the reason why a radical dissociation-recombination process is not accessible for the chlorodienes. On the other hand, loss of a chlorine cation from the conjugate acid of the chlorodienes requires a bimolecular attack by a good nucleophile,[156] which is not available under the present reaction conditions. Thus most of the chlorodienes are constrained to undergo either the side chain modification reaction or the intramolecular 1,2 chloro shift.

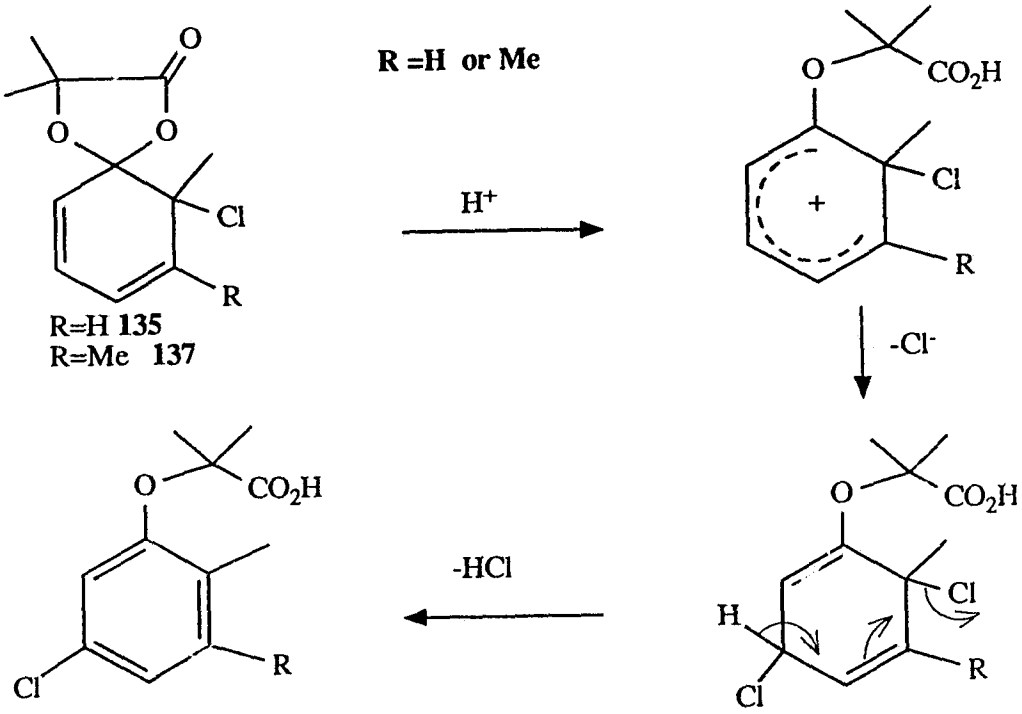
3.4.2 Reactions of 1,2 Adducts

a) With TFA

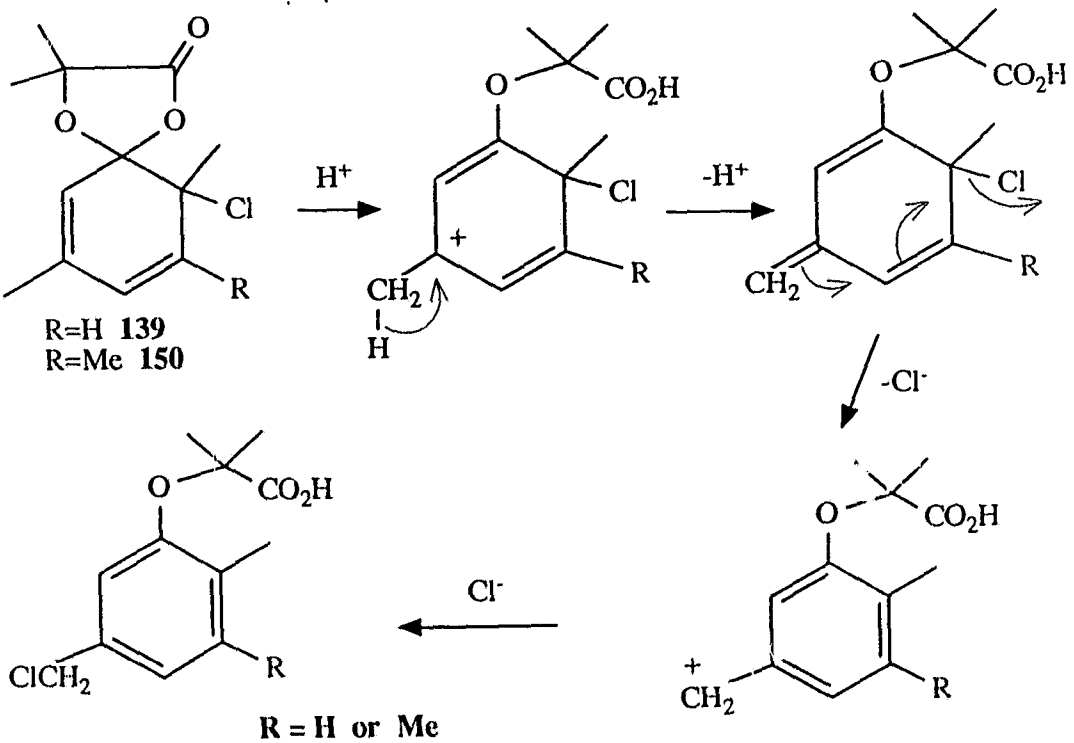
When diene **135** reacted with TFA in chloroform-d, the 5-chloroacid **169** was obtained exclusively. Similarly, the reaction of diene **137** gave the corresponding 5-chloroacid **171** as the sole product. These transformations represent a 1,4 chlorine migration. To find out whether the migration is intra- or intermolecular, a trapping experiment was carried out for diene **137** in acetic acid, using acetate ion as the external nucleophile. The formation of the 5-acetoxyphenoxy acid **171a** implies that the 1,4 chlorine migration is intermolecular. Based on this result, a mechanism for these acid catalysed reactions is proposed (Scheme 3.20). In this mechanism, the *ipso* Wheland intermediate, formed by an initial protonation of the substrate followed by the lactone ring opening, picks up a nucleophile such as a chloride or an acetate ion from the solvent at the 5-position, and gives a dichloro or chloroacetate 1,4 adduct, which then aromatizes to give the corresponding 5-chloro- /5-acetoxy-acid by loss of one molecule of HCl from the adduct.

When diene **139** reacted with TFA in chloroform-d, acid **173** was formed exclusively. In this case, loss of the proton from the 5-methyl is competitive with capture of a nucleophile at the 5-position, so much so that it becomes the only reaction pathway (Scheme 3.21).

Scheme 3.20



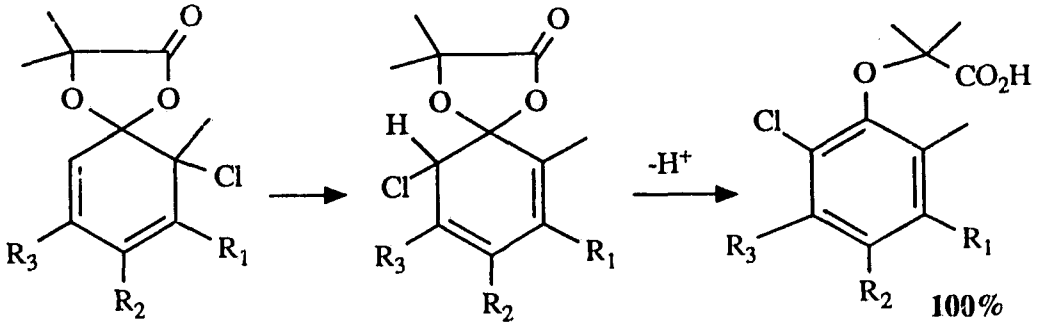
Scheme 3.21



Similarly, the reaction of diene **150** also gave the corresponding 5-chloroacid **185** as the sole product (Scheme 3.21).

Diene **146** on reaction with TFA was observed, at low temperature, to undergo a 1,5 chlorine shift to give the rearranged diene **147**, which then aromatized to the 6-chloroacid **181**. Similar results were obtained for the reactions of dienes **143**, **145**, and **157**. The corresponding 6-chloroacids **178**, **179**, and **192** were formed, respectively (Scheme 3.22).

Scheme 3.22



Diene	R_1	R_2	R_3	Product
143	H	Cl	H	**178**
145	Me	Cl	H	**179**
146	H	Cl	Me	**181**
157	H	Me	Cl	**192**

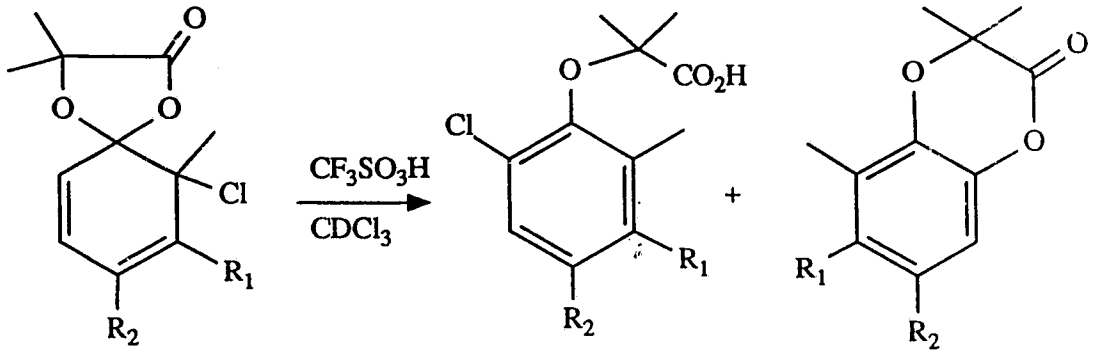
The common aspect of the above reactions is that the substrates all bear a second chlorine at either C-7 or C-8.

According to the discussion in sec. 3.3.1, the presence of a chlorine in these positions accelerates the rate of the 1,5 chlorine shift. Because of this, the 1,5 chlorine shift is much faster than the lactone ring opening, so that the rearranged dienes are formed (and actually observed) in the initial stage of the reactions. Acid-catalysed ring-opening followed by deprotonation at the tetrahedral center leads to the 6-chloroacid product.

b) With Triflic Acid

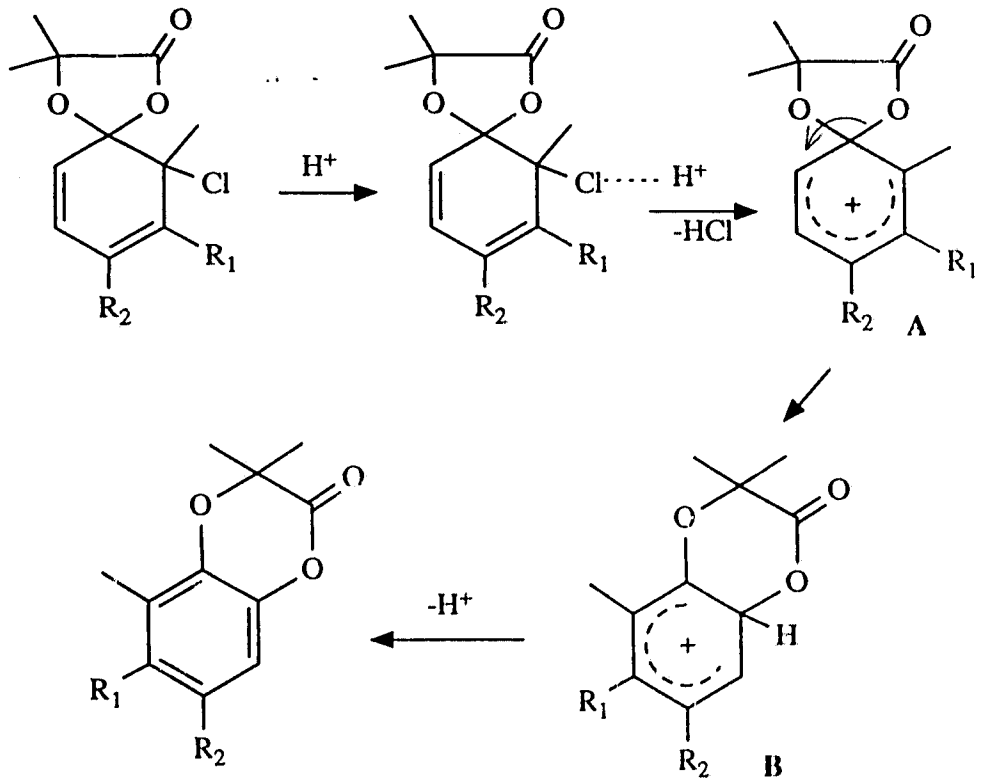
Diene **135** on reaction with triflic acid in chloroform-d gave, in addition to a substantial amount of the 6-chloroacid **170** formed via the 1,5 chlorine shift process described above, a detectable amount of the dioxin compound **170a** (< 5%). Similarly, the reactions of diene **137** and **145** afforded the corresponding dioxins **172** (100%) and **180** (33%), respectively (Scheme 3.23). The plausible route to the dioxin products involves the formation of cation **A** (Scheme 3.24) followed by a 1,2 migration of the lactone center function to form **B** and deprotonation. Support for the mechanism is provided by the solvolysis reactions discussed below. However, it is not obvious how cation **A** is formed under the strongly acidic conditions. Protonation of or hydrogen bonding to the chlorine might be possible for the extremely powerful triflic acid. However, protonation

Scheme 3.23



135	$R_1 = H$	$R_2 = H$	> 95% (**170**)	< 5% (**170a**)
137	$R_1 = Me$	$R_2 = H$	0	100% (**172**)
145	$R_1 = Me$	$R_2 = Cl$	67% (**179**)	33% (**180**)

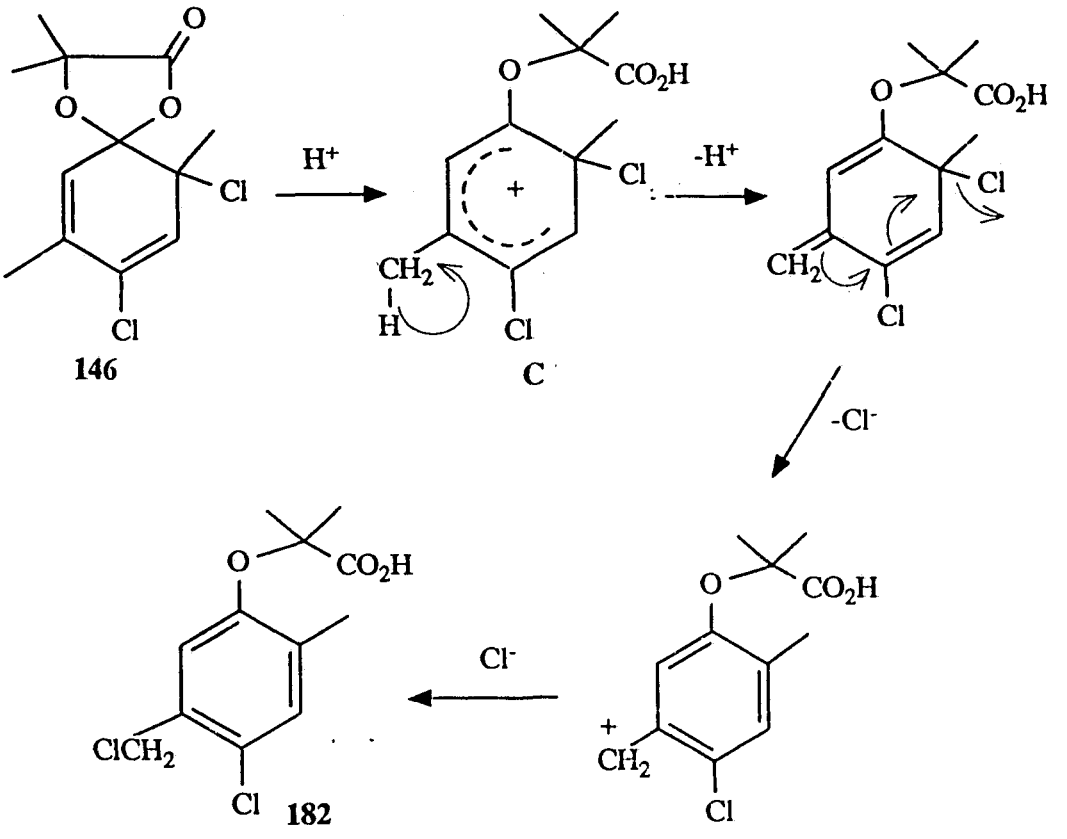
Scheme 3.24



of the lactone center function and ring opening of the lactone ring would be expected to be much more favored. The mechanism accounts for the product distribution of the reactions. In the case of diene **135**, in which the substituents R_1 and R_2 are hydrogen, the formation of intermediate **A** is not facilitated. Thus the formation of acid **170** is more accessible, and only a small amount of the dioxin product is formed. However, in the case of diene **137**, the R_1 is methyl, which stabilizes both **A** and **B** by its electron donating effect, and facilitates the rearrangement from **A** to **B**. Thus dioxin **172** is formed exclusively. The reaction of diene **145** is the intermediate case between the reaction of **135** and the reaction of **137**. In this case, R_2 = Cl, which destabilizes **A** and **B**, whereas, when R_1 = Me, formation of **B** is favored. The net result is that more dioxin **180** (33%) is formed than from **135** but less than from **137**.

Diene **146** on reaction with triflic acid neither underwent the 1,5 chloro shift reaction, nor the 1,2 carboxyl rearrangement process. It gave the side chain chlorinated acid **182** as the sole product. The formation of **182** indicates that in this case the lactone ring opening to give the *ipso* Wheland intermediate is the favored process, as illustrated in Scheme 3.25. The presence of

Scheme 3.25



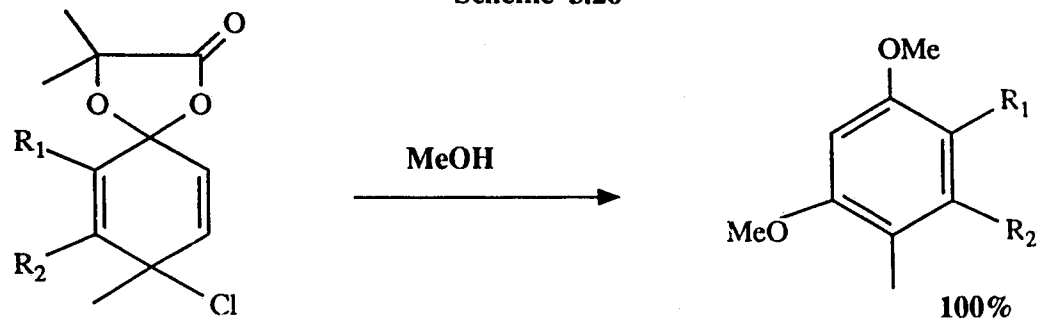
the 5-methyl group in the *ipso* Wheland intermediate stabilizes the transition state for formation of the intermediate **C**, so that the lactone ring opening process is much faster than other processes such as the 1,5 chloro shift and the 1,2 carboxyl shift.

3.5 SOLVOLYSES OF *IPSO* ADDUCTS

3.5.1 Solvolyses of 1,4 Adducts

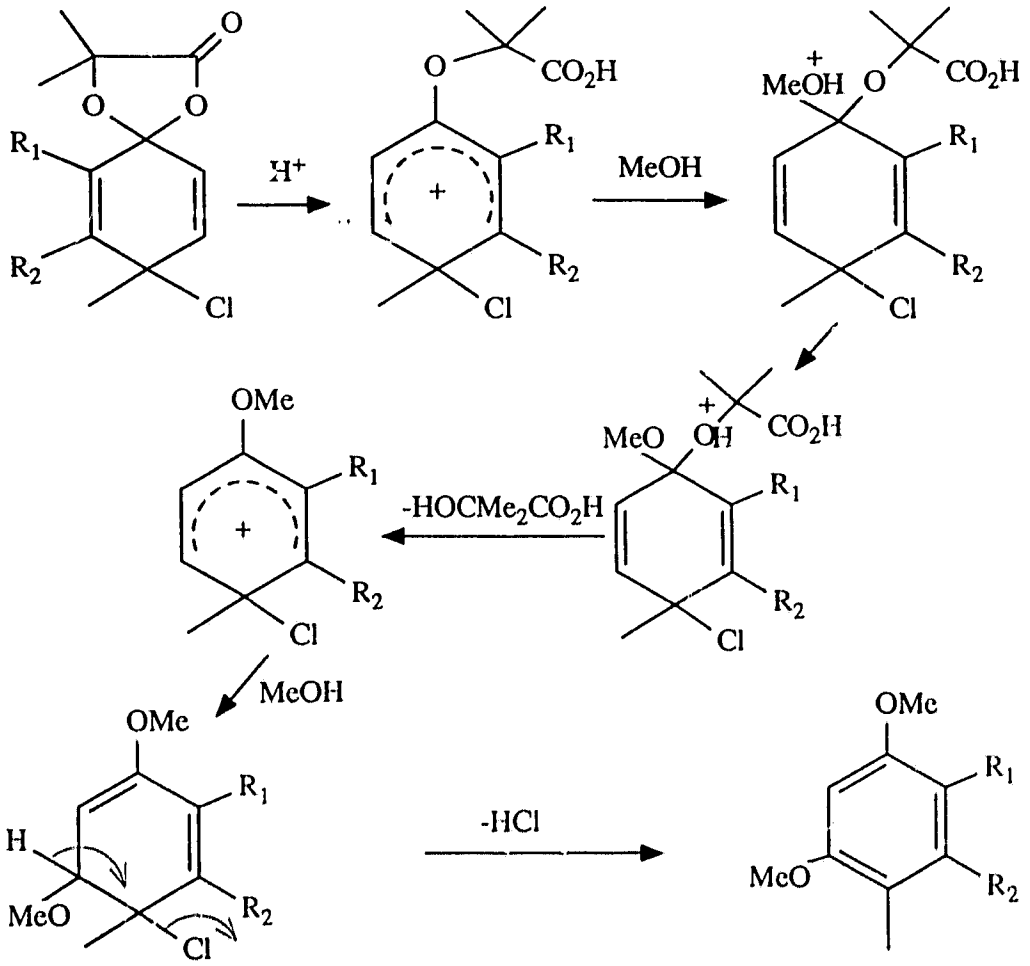
When a solution of diene **130** in methanol was let stand at ambient temperature for 2 h, 2,4-dimethoxytoluene (**200**) was formed as the sole product. Parallel results were observed in the reactions of dienes **132** and **133**, in which 3,4-dimethyl-1,5-dimethoxybenzene (**201**), and 2,4-dimethyl-1,5-dimethoxy-benzene (**202**) were formed, respectively (Scheme 3.26). Similar results were also observed by Bergquist et al[125] in the similar reactions of a series of 4-chloro-4-methyl-cyclohexa-2,5-dienones. Comparison of the structure of the substrates and the products shows that the lactone ring in the substrates is replaced by a methoxy group in the course of the reaction. Lactone ring opening assisted by protonation at the carbonyl group, followed by attack of a methanol on the position *ipso* to the alkoxy group is the apparent pathway of these reactions, as illustrated in Scheme 3.27. In further support of the proposed mechanism, the solvolysis of diene **133** was carried out in the presence of 1.2 equivalents of trizma base, which should inhibit the formation of the dimethoxy compound **202** if, as proposed, acid is required for the pathway leading to this product (Scheme 3.27). As was expected, in the presence of the base, the reaction gave only the methoxydiene **203**, from the direct (neutral) solvolysis of the chlorodiene (Scheme 3.28).

Scheme 3.26

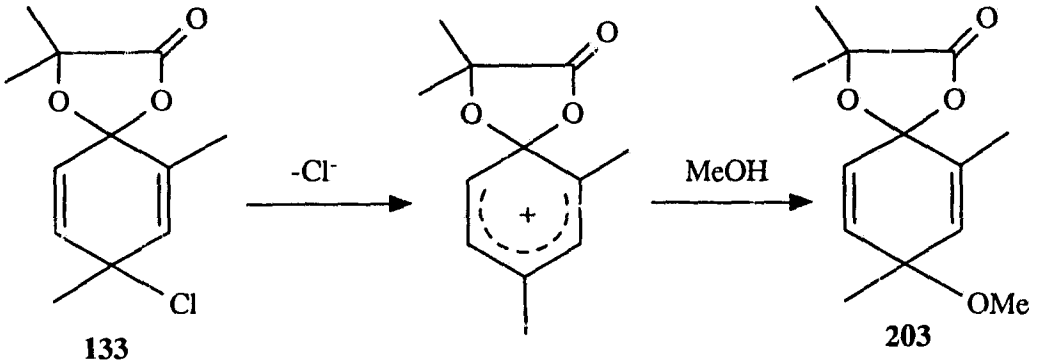


130	$R_1 = H$	$R_2 = H$	**200**
132	$R_1 = H$	$R_2 = Me$	**201**
133	$R_1 = Me$	$R_2 = H$	**202**

Scheme 3.27



Scheme 3.28

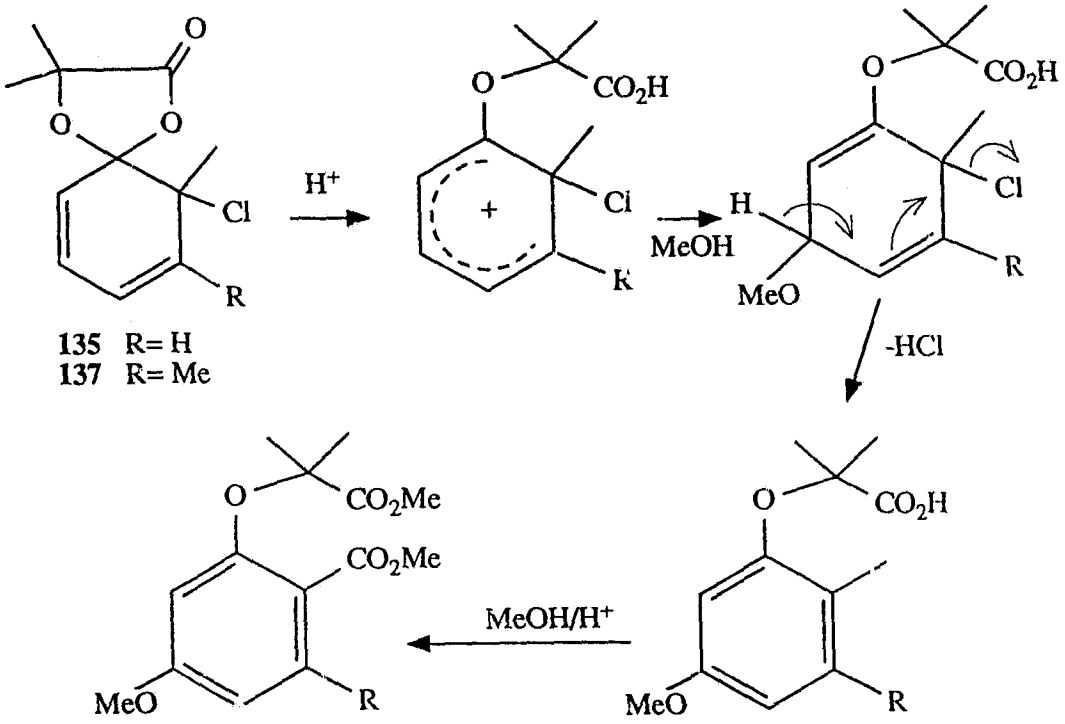


133 203

3.5.2 Reactions of 1,2 Adducts

When diene **135** in methanol was let stand at ambient temperature for 4 h, a mixture of the 5-methoxy acid **208** (30%) and its methyl ester **209** (70%) was obtained. A similar result was observed in the reaction of diene **137**. The latter reaction in 1 h gave the 5-methoxy acid **210** as the major product (67%) and its methyl ester **211** (33%) as the minor one (33%). It has been proposed that these reactions involve an acid-catalysed process, as illustrated in Scheme 3.29. We can compare these reactions with those acid-catalysed reactions in chloroform-d of the same substrates (Scheme 3.20). The reactions have similar mechanisms, except that in solvent methanol the methanol molecule competes as a nucleophile with chloride to yield, in each case, the 5-methoxy acid instead of the 5-

Scheme 3.29



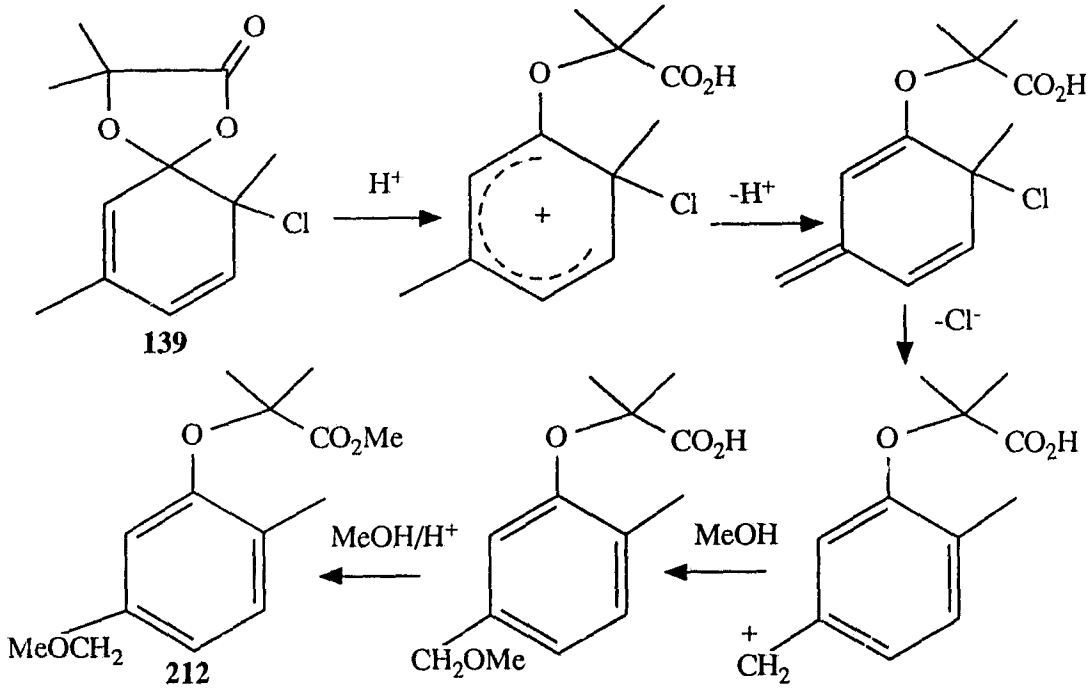
135 R= H
137 R= Me

chloroacid. Since the strong acid HCl is generated in the solvolysis, the 5-methoxyacid undergoes acid-catalysed esterification, leading to the corresponding methyl ester as a product with the acid. Since the esterification only can take place after the formation of the 5-chloroacid, it would afford more of the ester product in a longer reaction time interval. Thus, the reaction of diene **135**, for which the reaction time is four times longer than diene **137**, gives a higher ratio of the ester product than **137** does.

Diene **139** in methanol at ambient temperature gave,

after 8 h, methyl 2-methyl-2-(2-methyl-5-methoxymethyl-phenoxy)propanoate (**212**) as the sole product. Apparently, an acid-catalysed mechanism is involved in the reaction, as shown in Scheme 3.30. Here the acid-catalysed opening of

Scheme 3.30

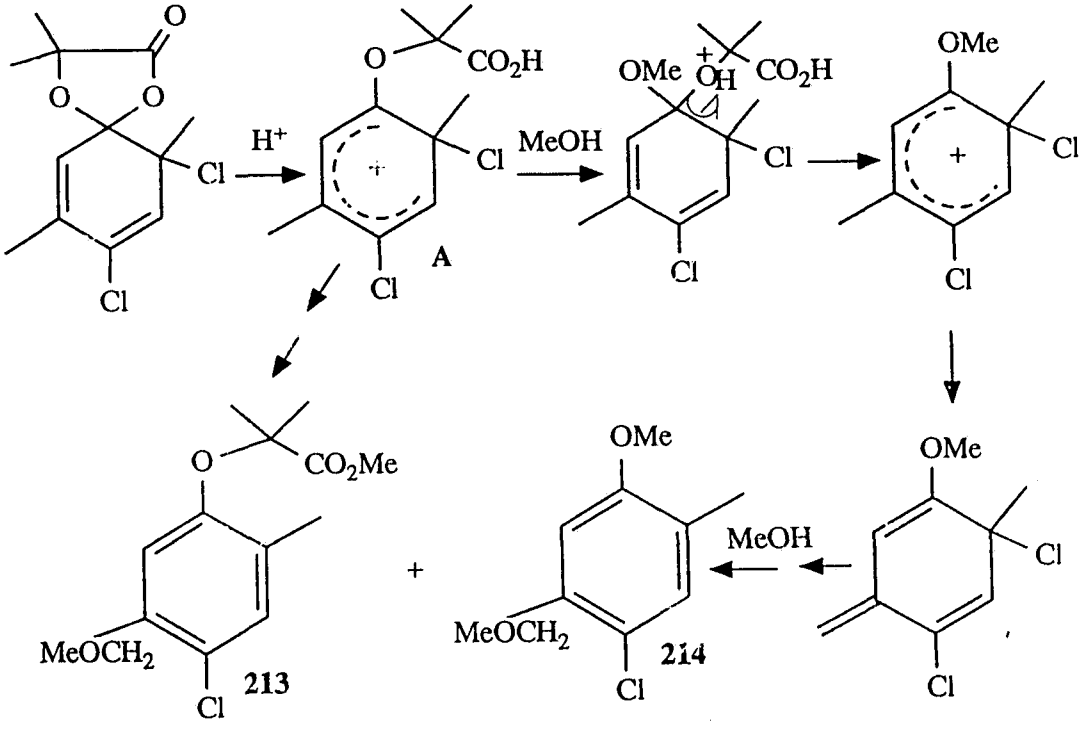


lactone ring is followed by deprotonation at the 5-methyl to give the methylenecyclohexadiene intermediate which in turn leads to the 5-methoxymethylphenoxy acid. As has been seen in many other examples this is a dominant sequence in the reactions of dienes containing a 5-methyl group.

However, the solvolysis of diene **146**, which also contains a 5-methyl substituent, is somewhat different from that of diene **139**. In addition to the expected 5-

methoxymethyl ester **213**, 4-chloro-2-methyl-5-methoxymethylanisole (**214**) was also formed. A plausible mechanism for the formation of anisole **214** is outlined in Scheme 3.31. In cation **A** addition of methanol at the carbon atom of the former spiro center competes with deprotonation of the 5-methyl.

Scheme 3.31



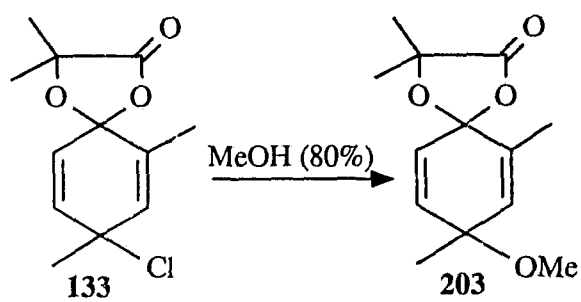
The proposed acid-catalysed mechanisms for the "solvolyses" are supported by the the fact that the reactions are inhibited by the presence of trizma base. In the absence of acid the only reaction observed for the 1,2 dienes is the 1,5 chloro shift. None of the products obtained from the acid-catalysed reactions is detected.

3.6 KINETIC STUDIES OF SOLVOLYSES OF 1,4 ADDUCTS

3.6.1 Solvolyses of Dienes 133, 141, 142, 148, And 154

Diene **133** was solvolysed in a series of aqueous methanol buffers (80% methanol) which had pH values of 5, 6, 7, and 8, respectively. In each of the cases, 8-methoxy-3,3,8,10-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**203**) was obtained as the only product. The first order rate constants of the reactions from plots of ln C^{o}/C vs. t were determined. The results for the solvolysis of diene **133** at pH values of 5, 6, 7, and 8 are summarized in Table 3.4.

Table 3.4 Rate Constants of Solvolysis of Diene **133** at Different pH



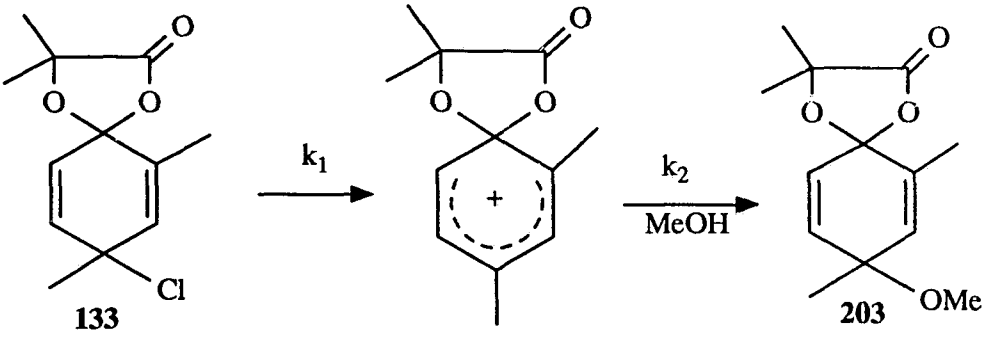
133 **203**

pH	5	6	7	8
k $x10^3$ (s^{-1})	9.8	8.1	9.2	8.5

The solvolysis involves two steps: a) departure of the chloride from the substrate to give a spiro Wheland intermediate; b) recapture of the intermediate by methanol,

as illustrated in Scheme 3.32.

Scheme 3.32



The results indicate that there is no systematic variation of rate with pH and this is confirmed by a plot of log k vs. pH which gives the order dependence n = 0 (Table 3.5 and Fig. 2).

Table 3.5

pH Dependence of Rate for Solvolysis of Diene 133[a,b]

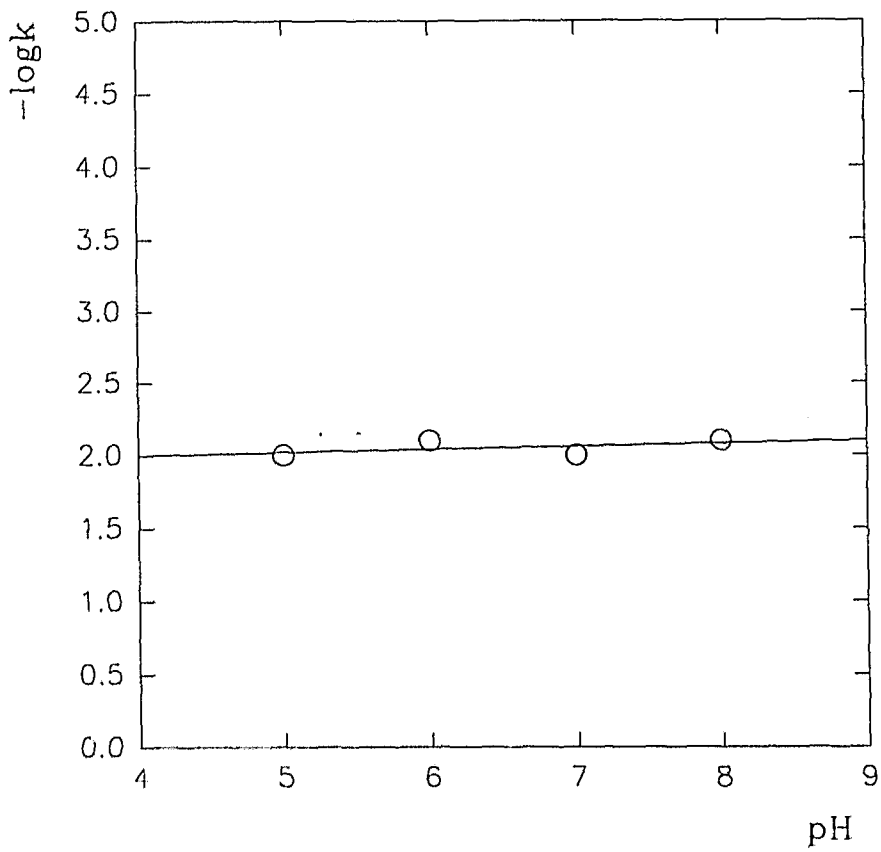
$-\log k = C + n.pH$

pH	5	6	7	8
-logk	2.0	2.1	2.0	2.1
n	0.0			

a. C is a constant;

b. n is the order dependence of k on $[H^+]$, i.e., $k = 10^{-C} [H^+]^n = \alpha[H^+]^n$.

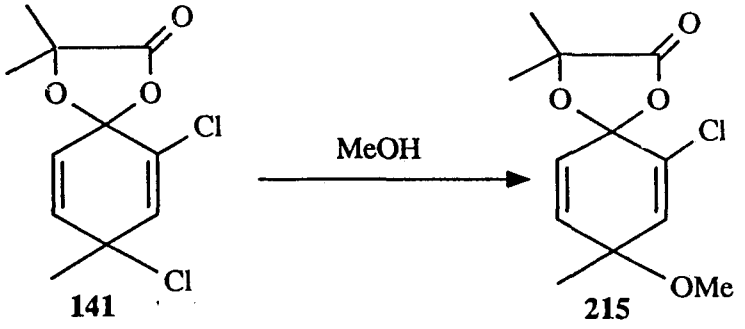
Fig.2 Plot of −logk vs. pH



$$-\log k = 1.92 + 0.02pH$$

When diene **141** was solvolysed in the methanol buffers of pH 5, 6, 7, and 8, respectively, 10-chloro-8-methoxy-3,3,8-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**215**) was obtained as the sole product in each case. The kinetic data and their pH dependence are summarized in Table 3.6.

Table 3.6 Rate Constants for Solvolysis of Diene **141** and Their pH Dependence



141 **215**

pH	5	6	7	8
k x10^5 (s^{-1})	2.5	2.3	3.3	3.3
-log k	4.6	4.6	4.5	4.5
n		~0		

The coefficient n = 0 again indicates that the solvolysis is pH independent.

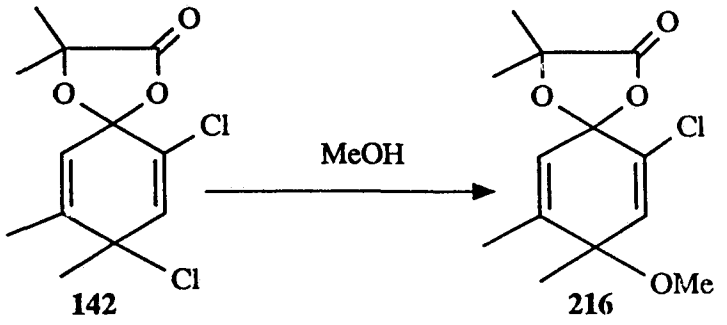
When diene **142** reacted with the methanol buffers of pH 5, 6, 7, and 8, respectively, 10-chloro-8-methoxy-3,3,7,8-tetramethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**216**) was obtained as the only product in each of the cases. The kinetic data under different pH conditions and their pH

dependence are summarized in Table 3.7. The constant value of the first order rate constant (k) under different pH conditions indicates that the solvolysis is pH independent.

Diene **148** reacted with the methanol buffers of pH 5, 6, 7, and 8, respectively, to give 8-methoxy-3,3,7,8,10-pentamethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**217**) as the single product in each of the cases. The kinetic data of the reaction and their pH dependence are summarized in Table 3.8.

When diene **154** was solvolysed in the methanol buffers of pH 5, 6, 7, and 8, respectively, 10-chloro-8-methoxy-3,3,7,8,9-pentamethyl-1,4-dioxaspiro[4,5]deca-dien-2-one (**218**) was formed as the sole product in each of the cases. The kinetic data of the reaction under different pH conditions are summarized in Table 3.9. Again the pH dependence coefficient n = 0 indicates the solvolysis is not pH dependent.

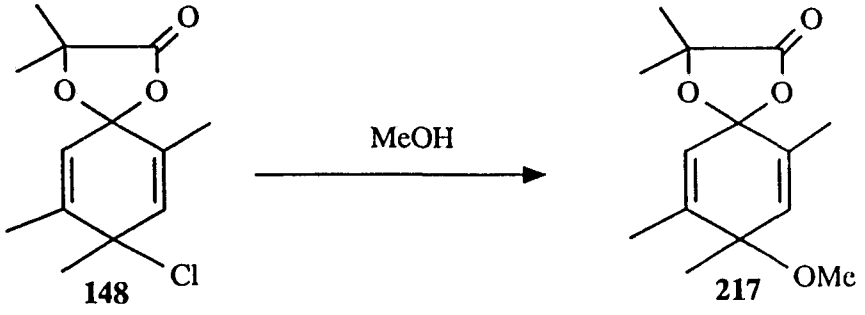
Table 3.7 Rate Constants for Solvolysis of Diene **142** at Different pH



142 **216**

pH	5	6	7	8
k x10^5 (s^{-1})	6.3	5.8	5.9	6.8
-log k	4.2	4.2	4.2	4.2
n		0.0		

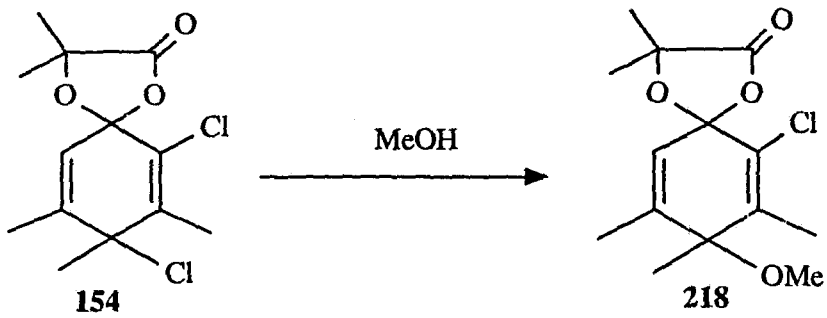
Table 3.8 Rate Constants for Solvolysis of Diene **148** at Different pH



148 **217**

pH	5	6	7	8
k x10^5 (s^{-1})	8.5	8.3	9.7	9.3
-log k	2.0	2.1	2.0	2.0
n		0.0		

Table 3.9 Rate Constants for Solvolysis of Diene **154** at Different pH



154 **218**

pH	5	6	7	8
k x10^5 (s^{-1})	6.3	6.6	7.1	7.3
-log k	4.2	4.2	4.2	4.1
n		0.0		

3.6.2 Solvolysis of Dienes 130, 132, and 152

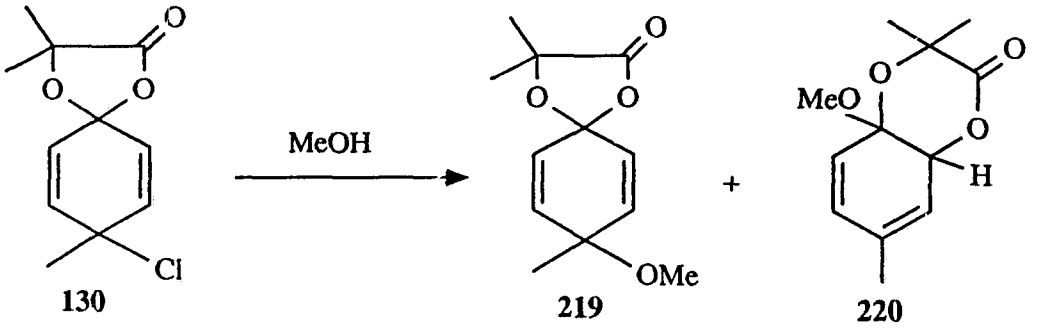
When diene **130** was solvolysed in the methanol buffers of pH 5, two non-aromatic compounds were obtained in a ratio of 3 : 1. The two compounds were separated by TLC (silica). The major product was identified as a 1,4 methoxy diene, 8-methoxy-3,3,8-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**219**). The ^{1}H NMR of the minor compound showed that there were three vinyl protons at δ 5.6 - 6.10, one methine proton at δ 4.93, and three methoxyl protons at δ 3.38. The UV spectra data (λ_{max}= 258 nm) indicated that there was a conjugated diene system in the compound. Other information from the ^{13}C NMR, UV and ms was all consistent with the 1,2 diene structure of 4a,8a-dihydro-4a-methoxy-

3,3,7-trimethylbenzo-1,4-dioxin-2-one (**220**) for the compound. The stereochemistry of **220** was uncertain since only one isomer was obtained. However, an X-ray crystallographic structure determination on an analogous compound, **226**, which was obtained under the same reaction conditions showed that this compound was the E-isomer and by analogy, **220** is assigned the same configuration.

The solvolysis of diene **130** at pH 6, 7, and 8, respectively, also gave a mixture of diene **219** and **220** in each case. However, the product ratio of **219** and **220** was different under the different pH conditions. The first order rate constant and the product distribution under different pH conditions are shown in Table 3.10.

The formation of dienes **219** and **220** indicates that there are two reaction pathways in the solvolysis. The Wheland intermediate A formed from the first step of the solvolysis can either be captured by a methoxide (path a in Scheme 3.33) to give the methoxy diene **219**, or undergo 1,2 carboxyl shift to give rearranged cationic intermediate B (path b, Scheme 3.33). Attack of a methoxide on B would lead to the formation of diene **220**.

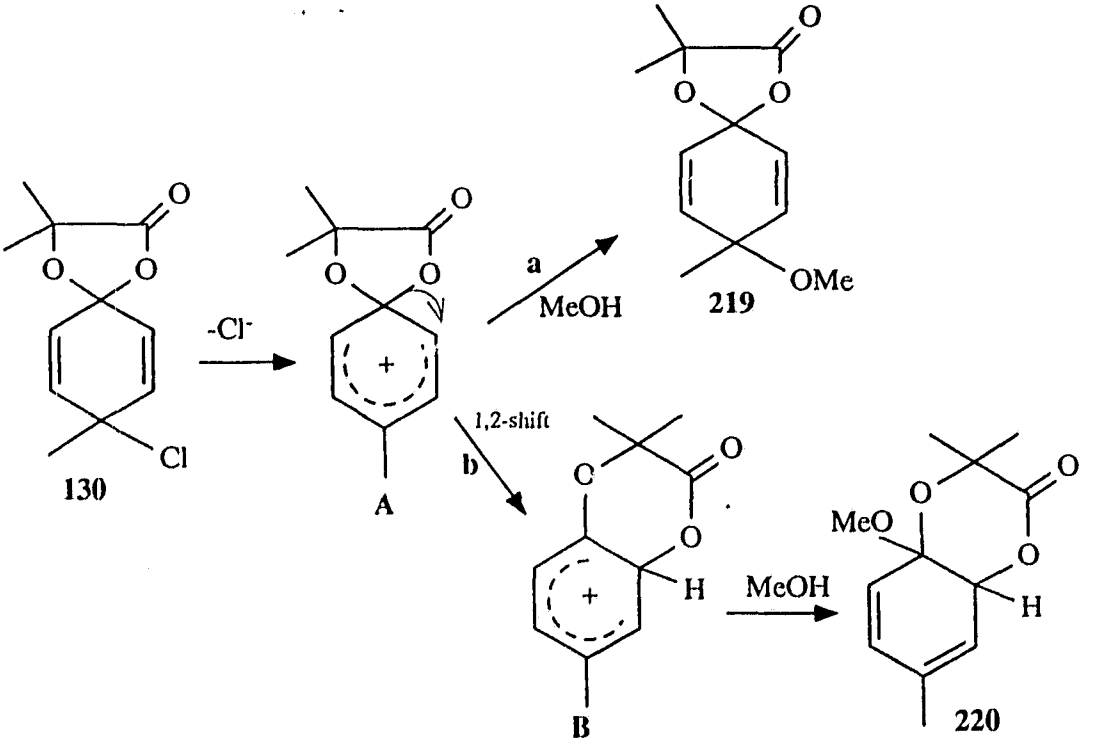
Table 3.10 Rate Constants and Product Distribution of Solvolysis of Diene **130** at Different pH



130 **219** **220**

pH	k x 10^{-5} (s^{-1})	219 (%)	220 (%)
5	4.5	75	25
6	5.4	55	45
7	6.5	44	56
8	7.9	--	--

Scheme 3.33



Apparently, which of the pathways is more favorable depends on the relative stability of the intermediates A and B. In the present case, A is stabilized by a methyl group at the position *para* to the acetal center and conjugated with the delocalized positive charge, and B is stabilized by the alkoxy group which is conjugated with the delocalized charge, and by the non-conjugated methyl group. Apparently A and B have comparable energies and both **219** and **220** are formed. If A has one more stabilizing substituent, such as a chloro or methyl group, at the position *ortho* to the acetal center, it would become much more stable than B, which would be highly destabilized by the non-conjugated halogen, and the formation of the non-rearranged diene would be dominant. In fact, many examples of this situation have been found in solvolyses of dienes **133**, **141**, **142**, **148**, and **154** (Sec. 3.6.1), in which the non-rearranged dienes are formed exclusively.

The first order rate constant for the solvolysis of diene **130** slightly increases with increase of pH. The amount of the rearranged product **220** increases with increase of pH, e.g., 25% at pH 5 and 56% at pH 7 (Table 3.10). Correspondingly, the amount of the non-rearranged diene **219** decreases with increase of pH. For the plot of the appearance rate of **219**, K_{219} (k x %219), vs. pH the order dependence for **219**, n_{219}, is zero (Table 3.11), indicating that the variation of pH does not affect the

rate of formation of **219**. However, the order dependence for **220**, n_{220} = -0.3, does show a small dependence of the rate of **220** on pH. It appears that the rearrangement process is subject to base-catalysis. However, the dependence of the rate on the base concentration, n, is rather less than first order.

Table 3.11

pH Dependence of Rates and Appearance rates for Solvolysis of Diene 130

pH	5	6	7	8
-logk	4.3	4.3	4.2	4.1
$-\log K_{219}$ [a]	4.5	4.5	4.5	-
$-\log K_{220}$ [a]	4.9	4.6	4.4	-
n [b]		-0.1		
n_{219} [c]		0.0		
n_{220} [c]		-0.3		

a. $K_{219/220}$ is the appearance rate for **219** or **220**;

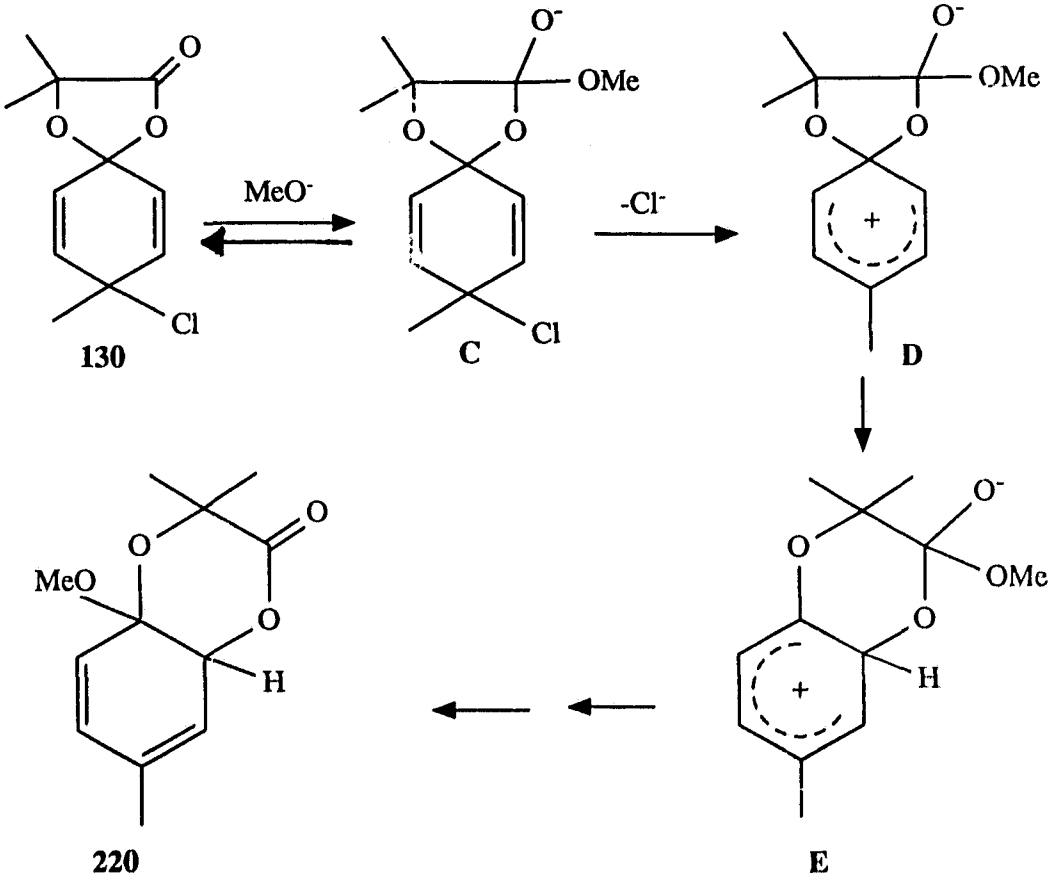
b. n is the order dependence of k on $[H^+]$;

c. $n_{219/220}$ is the dependence order of K on $[H^+]$ for **219** or **220**.

The mechanism outlined in Scheme 3.33 does not allow for the formation of a product to be base-catalysed, since

the rate-determining step in the pathway to either product is the initial ionization process. In order to account for the base-catalysis it is suggested that the rearranged product **220** is formed via a process in which the substrate reacts initially with OMe^-/OH^- to form **C** (Scheme 3.34). [C] then ionizes to form cation **D** which is the species which undergoes the rearrangement, involving the 1,2 migration of the oxygen. This process is facilitated by the negative charge in the migration group. The migration transition

Scheme 3.34

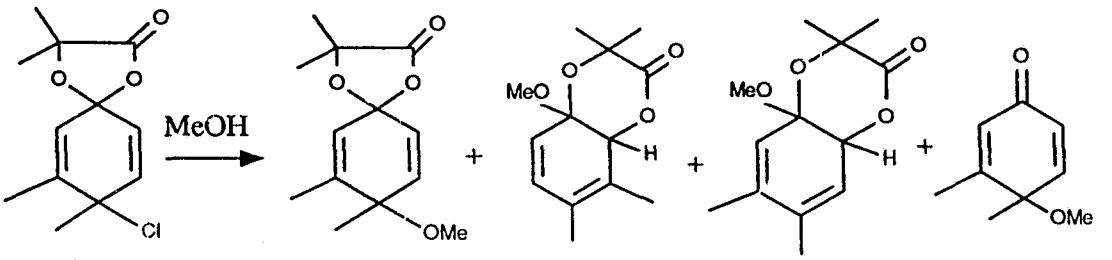


state would be more stabilized by the negatively charged group than it would be by the simple OCOR group. As a result of this, the rearrangement from **D** to **E** is much more efficient than from **A** to **B** (Scheme 3.33). This would account for the base-catalysis of the rearrangement reaction and thus the observation that at high pH the dominant product is **220** whereas at low pH the major product is **219**.

When diene **132** was solvolysed in methanol at pH = 7, and 8, respectively, a mixture of the methoxy diene **221**, and the rearranged dienes **222** and **223**, was obtained in each case. However, at pH 5 and 6, the solvolyses gave, in addition to **221**, **222**, and **223**, the methoxy dienone, **224**. The product distribution and the kinetic data under different pH conditions are shown in Table 3.12.

The formation of the positional isomers **222** and **223** occurs because of the two non-equivalent positions *ortho* to the acetal center in the substrate, to which the carboxyl group apparently has equal possibility to migrate. The stereochemistry of dienes **222** and **223** is assigned as that of the E-isomer in each case. The dienone **224** is only formed at low pH conditions (pH 5 and 6) as the minor product, indicating that the solvolysed product **221** undergoes acid-catalysed ring-opening, as shown in Scheme 3.35. The *ipso* Wheland intermediate formed from diene

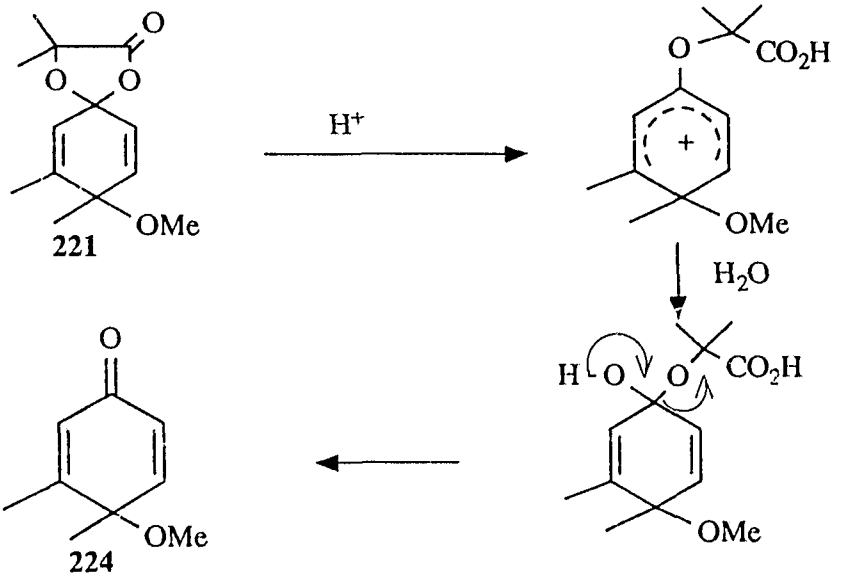
Table 3.12 Rate Constants and Product Distribution of Solvolysis of Diene **132** at Different pH



132 **221** **222** **223** **224**

pH	k x10^4 (s^{-1})	**221** (%)	**222** (%)	**223** (%)	**224** (%)
5	0.77	63	10	10	16
6	1.3	33	27	27	13
7	1.7	32	34	34	0
8	1.8	28	36	36	0
	n = 0.0	**n_{221} = 0.0**	**n_{222}=-0.30**	**n_{223}= -0.30**	

Scheme 3.35



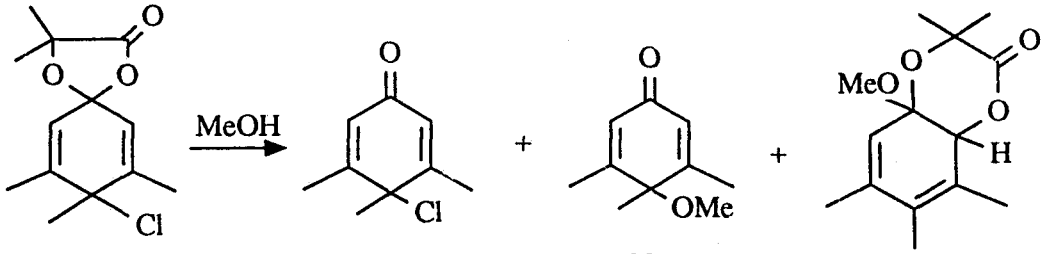
221 **224**

132 by the acid-catalysis process is relatively more stable and the acid catalysed reaction is relatively more favored than in the case of diene **130**. The additional methyl group in **132** is so located that it is conjugated with the positive charge in the ring-opened center. Thus the dienone product is observed in the present case but not in the case of diene **130** under the same reaction conditions.

The ratio of the rearranged products **222** and **223** increases with the increasing pH, indicating that the 1,2 carboxyl shift is subject to base-catalysis. The first order rate constant also increases with increase in pH. However, the coefficient n = 0 shows that this is an insignificant change. When the overall rate is dissected into the rates for the appearance of **221** and **222/223**, the rate of formation of the simple solvolysis product **221** is independent of pH but that of **222/223** has the order dependence n =-0.3, the same as that observed in the rearrangement reaction discussed above.

When diene **152** was solvolysed in the methanol buffers of pH 7 and 8, respectively, a mixture of the methoxy dienone **225** and the rearranged diene **226** was formed in each of the cases. However, under low pH conditions (pH 6 and 5), the reaction gave, in addition to **225** and **226**, the chloro dienone **187**. The rate constant for the reaction and product distribution under different pH conditions are summarized in Table 3.13.

Table 3.13 Rate Constants and Product Distribution of Solvolysis of Diene **152** at Different pH



152 **187** **225** **226**

pH	k x10^4 (s^{-1})	**187** (%)	**225** (%)	**226** (%)
5	0.85	30	63	7
6	2.1	13	50	37
7	3.2	0	35	65
8	4.3	0	25	75
	n =-0.3		**n_{225}= 0.0**	**n_{226}= -0.5**

The assigned structure of diene **226**, based on the NMR, IR, and UV spectral data, is further confirmed by its X-ray structure (Table 3.14 and 3.15, and Figure 3). The stereochemistry of **226** is therefore known to be that of E-isomer. The torsional angle data (Table 3.15) indicates that the OMe group in **226** is on the distorted equatorial position. So there is no apparent anormeric effect in this case. A mixture of diastereomers of **152** was used as the substrate. Thus formation of **226** is stereoselective. The exclusive formation of the E-isomer may be attributed to addition of methanol at the less sterically hindered side

of the positively charged center in the rearranged Wheland intermediate being preferred. Furthermore, the thermodynamic stability of the product also contributes to the exclusive formation of the E-isomer, since normally a *cis* fused ring is more stable than the *trans* one. The formation of dienone **187** under low pH conditions is consistent with the formation of the dienone **224** in the case of the solvolysis of diene **132**. Unlike the latter case, in which **224** is formed by the further reaction of the solvolysed diene **221**, dienone **187** is directly formed from the acid catalysed reaction of the substrate **152** without prior solvolysis. This may be attributed to the presence of the two methyls *ortho* to the *ipso* center in **152**, which lowers the transition state energy for the acid-catalysed process, since this involves the generation of a positive charge conjugation with the methyl groups, and makes this process faster than the solvolysis.

Table 3.14

Interatomic Distances of Diene **226** (A)

Atoms	Distance	Atoms	Distance
C(2) -O(1)	1.433(4)	C(9) -O(1)	1.422(4)
C(3) -O(4)	1.347(4)	C(10) -O(4)	1.464(4)
C(3) -O(13)	1.191(4)	C(9) -O(17)	1.420(4)
C(18) -O(17)	1.430(4)	C(3) -C(2)	1.527(5)
C(11) -C(2)	1.530(5)	C(12) -C(2)	1.513(5)
C(6) -C(5)	1.338(5)	C(10) -C(5)	1.505(5)
C(14) -C(5)	1.505(5)	C(7) -C(6)	1.477(5)
C(15) -C(6)	1.522(5)	C(9) -C(8)	1.495(5)
C(10) -C(9)	1.518(5)		

Estimated standard deviations are given in parentheses.

Table 3.15

Bond Angles and selected torsional angles of Diene **226** (d)

Atoms	Angle	Atoms	Angle
C(9)-O(1)-C(2)	118.0(2)	C(10)-O(4)-C(3)	117.1(2)
C(18)-O(17)-C(9)	116.0(3)	C(3)-C(2)-O(1)	108.8(3)
C(11)-C(2)-O(1)	112.3(3)	C(11)-C(2)-C(3)	110.8(3)
C(12)-C(2)-O(1)	104.4(3)	C(12)-C(2)-C(3)	109.2(3)
C(12)-C(2)-C(11)	111.1(4)	O(13)-C(3)-O(4)	119.6(3)
C(2)-C(3)-O(4)	116.5(3)	C(2)-C(3)-O(13)	123.8(3)
C(10)-C(5)-C(6)	120.3(3)	C(14)-C(5)-C(6)	124.9(3)
C(14)-C(5)-C(10)	114.8(3)	C(7)-C(6)-C(5)	121.1(3)
C(15)-C(6)-C(5)	120.8(4)	C(15)-C(6)-C(7)	118.1(4)
C(8)-C(7)-C(6)	120.9(3)	C(16)-C(7)-C(6)	119.8(4)
C(16)-C(7)-C(8)	119.4(4)	C(9)-C(8)-C(7)	121.7(3)
O(17)-C(9)-O(1)	111.3(2)	C(8)-C(9)-O(1)	104.2(3)
C(8)-C(9)-O(17)	112.1(3)	C(10)-C(9)-O(1)	112.3(3)
C(10)-C(9)-O(17)	102.9(2)	C(10)-C(9)-C(8)	114.3(3)
C(5)-C(10)-O(4)	105.8(3)	C(9)-C(10)-O(4)	111.9(3)
C(9)-C(10)-C(5)	116.1(3)		

Atoms	Torsional angle
H(101)-C(10)-C(9)-O(17)	24.2
C(5)-C(10)-C(9)-C(8)	26.8
C(5)-C(10)-C(9)-O(17)	95.0
C(8)-C(9)-C(10)-H(101)	146.0

Estimated standard deviations are given in parentheses.

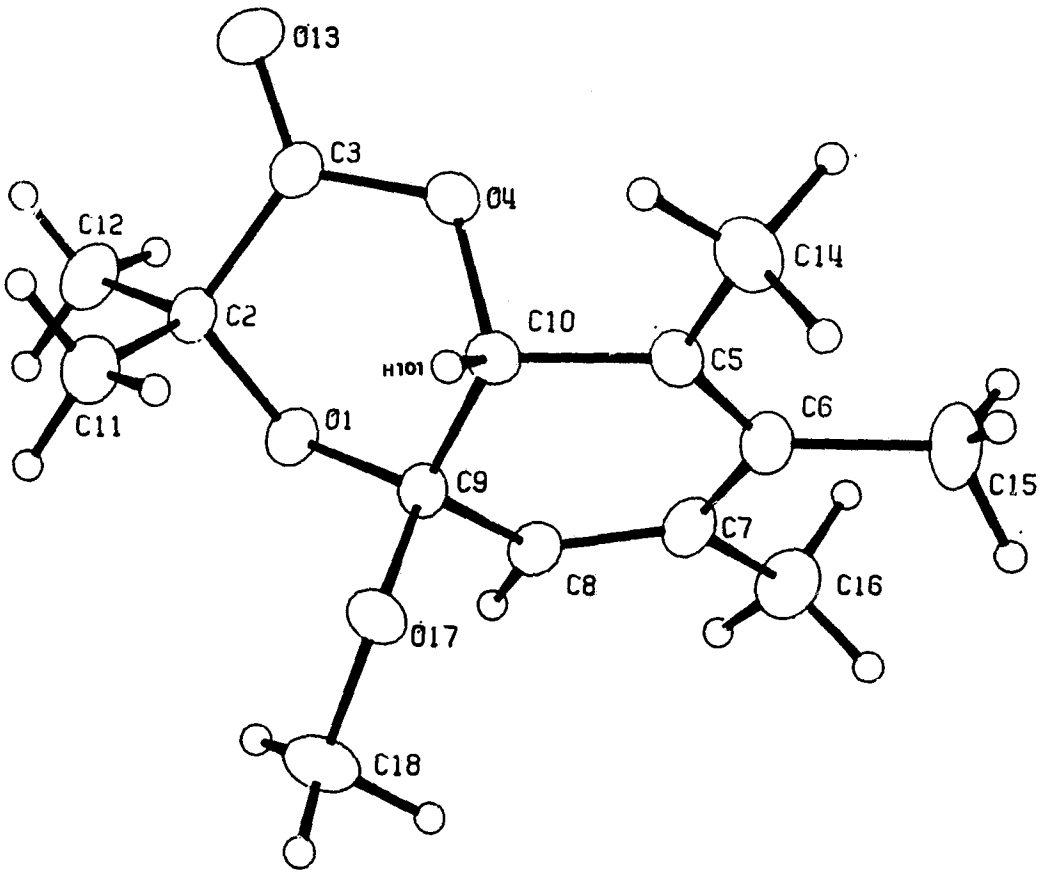


Fig. 3 An ORTEP Diagram of the Molecular structure of 4a,8a-Dihydro-4a-methyoxy-3,3,6,7,8-pentamethylbenzo-1,4-dioxin-2-one (226)

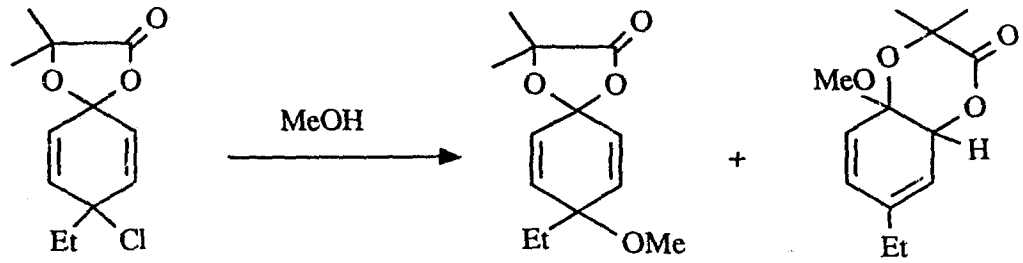
The ratio of the rearranged diene **226** changes with the variation of pH. This again demonstrates that the 1,2 carboxyl shift is base-catalysed. Dissection of the rate constants for the products shows again that the rate for the simple solvolysis product is pH independent ($n_{225} = 0$) whereas that for the rearranged product exhibits base-catalysis ($n_{226} = -0.5$).

3.6.3 Solvolyses of Dienes **160**, **162**, and **164**

When diene **160** was solvolysed in methanol buffers of pH 5, 6, 7, and 8 respectively, a mixture of the methoxy-diene **227** and the rearranged diene **228**, was obtained in each case. The first order rate constant of the solvolysis and the product distribution under each pH condition are summarized in Table 3.16. Here again formation of the simple solvolysis product is independent of pH whereas that of the rearranged product is pH dependent ($n_{228} = -0.3$).

When diene **162** was treated with methanol at pH 6, a mixture of the dienone **230** and the rearranged diene **229** was obtained. However, diene **162**, when treated with methanol at pH 8, gave **229** as the sole product. The rate constants and the product distribution of the solvolysis

Table 3.16 Rate Constants and Product Distribution of Solvolysis of Diene **160** at Different pH



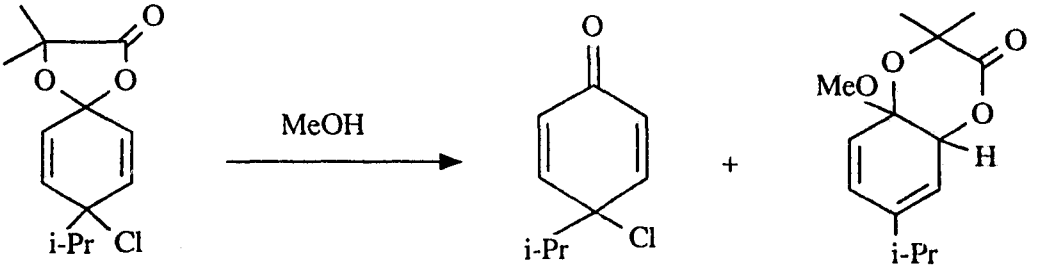
160 **227** **228**

pH	k x 10^{-5} (s^{-1})	-logk	227 (%)	228 (%)
5	1.9	4.7	75	25
6	3.3	4.5	40	60
7	5.0	4.3	28	72
8	5.1	4.3	24	76
n_k=-0.1			n_{227}=0.0	n_{228}=-0.3

under different pH conditions are shown in Table 3.17.

Unlike the solvolysis of diene **160** at low pH conditions, in which the methoxy diene **227** is obtained as the major product, the reaction of diene **162** gave the chloro dienone **230** as the minor product.This reveals that in the case of diene **162**, the solvolysis process of the chloride *from* the substrate competes with the acid-catalysed lactone ring opening mechanism. Since the iso-propyl *ipso* to the chloro group is a weaker stabilizing

Table 3.17 Rate Constants and Product Distribution of Solvolysis of Diene **162** at Different pH



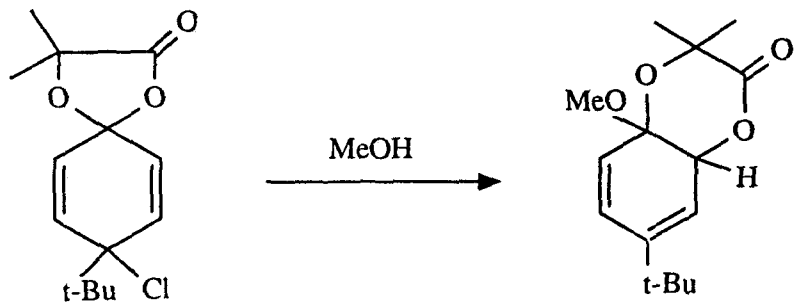
162 **230** **229**

pH	k x 10^{-5} (s^{-1})	-logk	**230** (%)	**229** (%)
6	1.4	4.8	20	80
7	3.3	4.5	--	--
8	2.8	4.6	0	100
	n ≈0			

substituent for the ionized intermediate than a methyl or ethyl group in terms of hypercojugation, the acid catalysed reaction pathway is relatively favored in this case.

Diene **164** reacted with the methanol at pH 8 to give the rearranged diene **231** as the only product. When the solvolysis was carried out at pH 5, the reaction was so slow that only 50% of the substrate was converted to diene **231** in 48 h. The rate constants and the product distribution at different pH are summarized in Table 3.18.

Table 3.18 Rate Constants and Product Yield of Solvolysis of Diene **164** at Different pH



164 **231**

pH	**k x 10^{-5} (s^{-1})**	**-logk**	**231** (%)
5	0.55	5.3	50
7	2.8	4.6	--
8	1.8	4.7	100
	n ≈0		

The reaction rate slightly increases with the increasing pH, reflecting that the formation of **231** is subject to base catalysis. The slow reaction rate relative to those for dienes **160** and **162** reflects the poor stabilization ability of the t-butyl group at the *ipso* position in the substrate of the ionized cationic intermediate.

3.6.4 Substituent Effects on The Solvolysis Reaction Mechanism and The Reaction Rate

The general pathways for solvolysis of an 1,4 adduct in aqueous methanol can be classified into the following types:

1) solvolysis of the chloride from the substrate,

followed by the addition of methanol and deprotonation to give a methoxy diene (Scheme 3.36, path a);

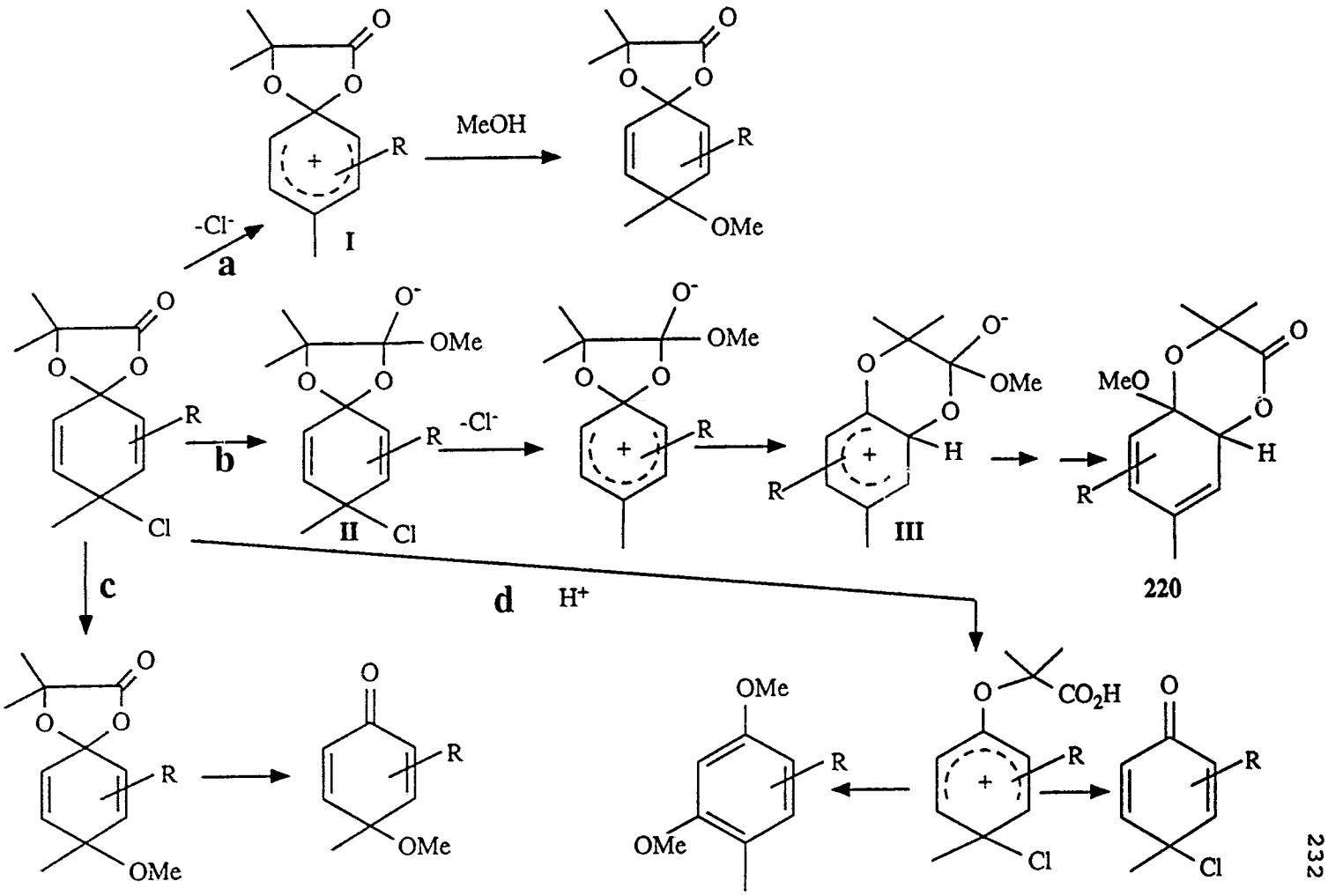
2) addition of methoxide/hydroxy to the carbonyl center followed by ionization and 1,2 carboxyl shift to give a rearranged intermediate **III** which leads to the formation of a rearranged diene (path b);

3) reaction type 1 followed by an acid-catalysed ring opening and loss of the spiro ring to give a methoxy dienone (path c);

4) a direct acid-catalysed opening and loss of the spiro ring to give a chlorodienone or dimethoxytoluene (path d).

The pathway involved in the solvolysis of a particular substrate depends upon the structure of the substrate and the reaction conditions. If the substrate contains a substituent which stabilizes the solvolysis intermediate **I** (Scheme 3.36) in preference to the rearranged cation **III**, then path a is important. Otherwise path b is favored. For example, dienes **133**, **141**, **142**, **148**, and **154** (Type I dienes) all contain such a stabilizing substituent at the position *ortho* to the acetal center and undergo path a exclusively. However, for those dienes which do not have a substituent at the *ortho* position, such as **130**, **132**, **152**, **160**, **162**, and **164** (Type II dienes), path b becomes competitive with path a (under neutral conditions). Path c and path d are often found in the case of solvolyses of dienes of

Scheme 3.36



Type II at low pH conditions, since high proton concentration facilitates the acid-catalysed processes and for these substrates the cation formed by ring opening is of comparable stability to that formed by the initial solvolysis.

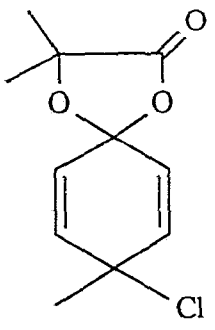
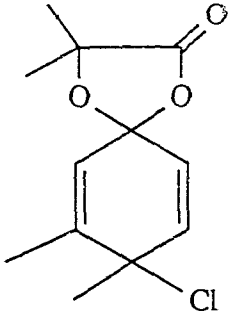
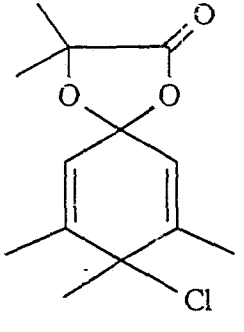
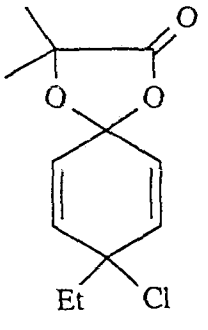
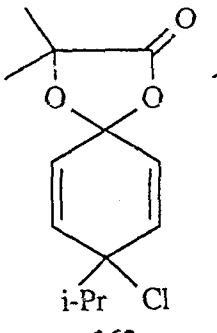
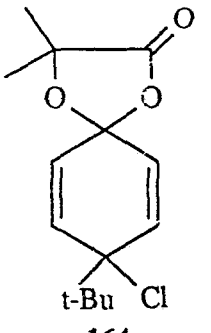
The solvolysis rates are also strongly influenced by both the location and the nature of the substituents. Since the rate-determining step for formation of the simple solvolysis products is the first step, i.e., formation of the cationic intermediate **I** (Scheme 3.36) by loss of the chloride, any factor that either promotes the leaving of the chloride or stabilizes the intermediate **I** accelerates the reaction rate. The first order rate constants for formation of the simple solvolysis products from solvolyses of eleven 1,4 dienes are summarized in Table 3.19.

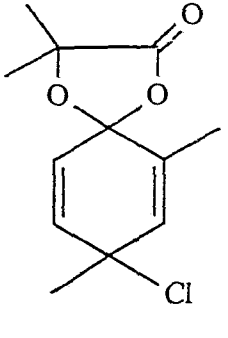
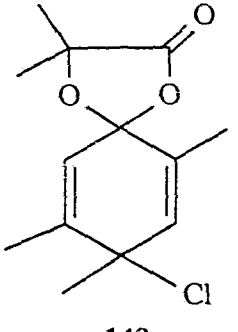
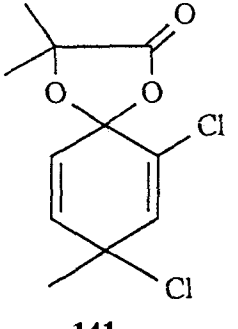
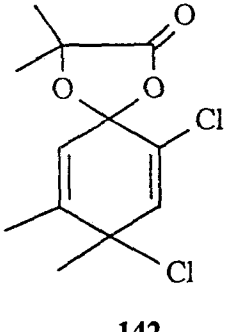
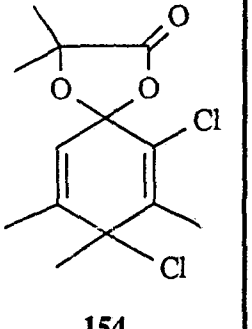
The following aspects emerge by examining the results in Table 3.19:

1) Comparison of the rate for diene **130** with that for **133** and the rate of **132** with that of **148** shows that a methyl group at the position *ortho* to the acetal center in the substrates accelerate the solvolysis rate about 150-300 times;

2) The presence of a chlorine group at the *ortho* position has almost no effect on the rate: compare **141** and **130**, **142** and **132**. Thus the electron-donating resonance effect for the chlorine at this position balances the

Table 3.19 Solvolysis Rate Constants of Dienes

Diene	 **130**	 **132**	 **152**	 **160**	 **162**	 **164**
k x10^5 (s^{-1})[a]	3.2	5.4	10.2	1.3	<2.8	<1.8

Diene	 **133**	 **148**	 **141**	 **142**	 **154**
k x10^5 (s^{-1})[b]	890	890	2.9	6.2	6.8

a: Average appearance rate constants for formation of simple solvolysis products.
b: Average rate constants.

electron-withdrawing inductive effect.

3) Introduction of a methyl group at the position *meta* to the acetal center accelerates the rate about 2 times, e.g., the rate for diene **132** is 2.3 times faster than for **130**, and the rate for **142** is 1.6 times faster than for **141**. In these cases, even though the introduced methyl is not conjugated with the positive charge in the solvolysis intermediate, the electron donating inductive effect still contributes to the stability of the intermediate.

4) In the series *ipso*- methyl, ethyl, isopropyl, and t-butyl (dienes **130**, **160**, **162**, and **164**) the rate decreases along the series. This is consistent with a decrease in the electron-donating effect of the *ipso* alkyl group resulting from a reduction in hyperconjugation along the series.

3.7 SUMMARY AND FUTURE WORK

The present work has described the formation of *ipso* chloro adducts from a number of 2-methyl-2-aryloxypropanoic acids, using the carboxylate group in the substrates as the internal nucleophile to capture the *ipso* Wheland intermediate formed in chlorination. The yields of the *ipso* adducts range from moderate to good. The phenoxyacids containing an *ortho* methyl group lead to the formation of 1,2 adducts, and those containing a *para* methyl result in the formation of 1,4 adducts. However, in a few cases in which the phenoxyacids contain both *ortho* and *para* methyl groups, only 1,4 adducts are formed. One exception is the chlorination of 2-methyl-2-(5-chloro-2,4-dimethylphenoxy)-propanoic acid, in which both the 1,2- and 1,4 adducts are formed. Generally, 1,4 adducts are formed in high yields while 1,2 adducts are formed in low yields. This has been attributed to the high steric sensitivity of chlorination towards an *ipso* position. In comparison with nitration, chlorination affords low yields of *ipso* adducts. This indicates that an *ipso* position shows a lower reactivity towards chlorination than towards nitration. Chlorination of a series of *para* alkyl substituted phenoxy acids has been carried out to determine the substituent effects on *ipso* chlorination. The ratio of *ipso* attack at ethyl, isopropyl, and t-butyl substituents as compared with that at a methyl is $i_{Me} : i_{Et} : i_{i\text{-}Pr} : i_{t\text{-}Bu} = 1 : 0.8 : 0.6 :$

0.6. In chlorination of 2-methyl-2-(3,5-di-t-butylphenoxy)propanoic acid, a secondary chloro-1,4-adduct has been isolated. This is the first example of capture of a non-*ipso* Wheland intermediate by an internal nucleophile in chlorination.

The *ipso* chloro adducts have revealed a rich variety of reactions. An 1,2-intramolecular chloro shift has been shown to be an important reaction pathway in the acid catalysed reactions of the 1,4 adducts. This type of reaction has provided a very useful route in the synthesis some *meta* chlorinated phenoxyacids, which cannot be obtained by conventional chlorination. Intermolecular 1,4 chloro migration and side chain modification reactions have been found in the acid-catalysed reactions of the 1,2 adducts. In addition, [1,5] chloro sigmatropic rearrangement reactions have also been found in the thermolyses of the 1,2 adducts. The [1,5] chloro shift rates are strongly affected by the nature of the substituents in the substrates. Generally, an electron donating substituent inhibits the rearrangement rates and an electron withdrawing group accelerates the rates.

Solvolysis of the *ipso* adducts in methanol in the absence of a base inhibitor results in acid-catalysed ring-opening reactions. If the solvolyses are carried out under neutral or basic conditions produced either by addition of an excess amount of a weak base or by titration with a base

to neutralize the acidic species formed in the reaction medium, then the acid-catalysed lactone ring opening process is inhibited and the solvolysis of the chloride from the substrate can be observed.

The kinetics of the solvolyses of the 1,4 adducts have been investigated by the base titration method. The results have revealed that the rates of the solvolyses highly depend on the structure of the substrates, or more precisely, depend on the nature and location of the substituents in the substrates. Substrates containing the substituents which are capable of stabilizing the Wheland intermediate involved in the solvolyses exhibit a high rate constant. Study of the solvolyses of the 1,4 adducts, under the base titration conditions, has shown that the solvolysis can undergo two reaction pathways: a) an initial ionization of the chloride followed by attack of methanol to give a methoxy spiro diene; b) a initial attack by a methoxide followed by ionization of the chloride and a 1,2 carboxyl shift to give a rearranged diene. The study has also shown that the 1,2 carboxyl shift process is subject to base catalysis.

Areas for future studies are as follows:

1) The 2-methyl-2-aryloxypropanoic acids are particularly suitable as substrates for *ipso* chloro adducts as the built-in carboxylate group can capture the *ipso* Wheland intermediate before it can undergo any of the other

reactions. However, it is important to ascertain if it is possible to obtain adducts under situations in which an external nucleophile must be involved. As mentioned before, chlorination of p-xylene did not give adducts. Anisole derivatives, starting with p-tolyl methyl ether, seem worthy of investigation as substrates. Even it does not prove possible to observe an adduct, it may be possible to obtain evidence that one had been formed. Thus a study of the chlorination of $Me_xMeO_yC_6H_{6-(x+y)}$ systems may prove to be rewarding.

2) In the present work, the mechanistic and kinetic studies of the solvolysis reactions have been investigated based on examination of the substituent effects. However, this work does not includ another important factor, the effect of the leaving groups on the solvolyses. It is known that nitrite NO_2^- is a poorer leaving group than Cl^-, while Br^- is better than Cl^-. Preparation of a number of analogous nitro and bromo dienes and the study of how the ability of the leaving group affects the kinetics and the mechanisms of the reactions would provide further insight into these reactions which have the unusual characteristic of involving Wheland type intermediates formed by solvolysis.

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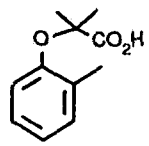
Structure Index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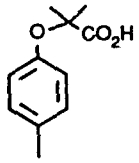
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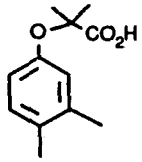
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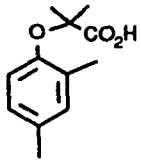
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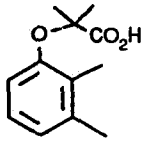
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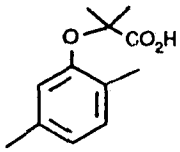
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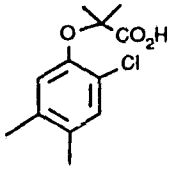
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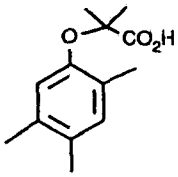
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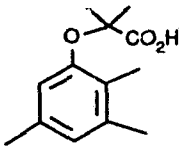
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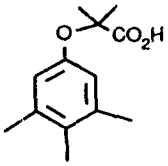
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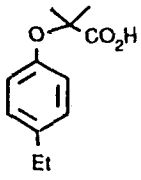
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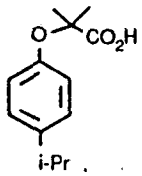
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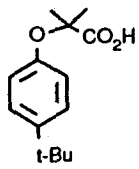
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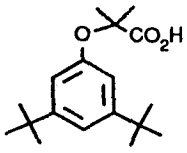
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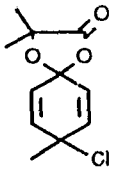
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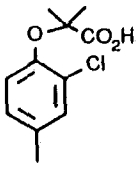
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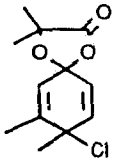
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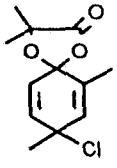
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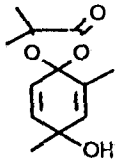
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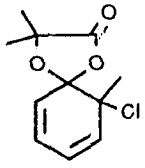
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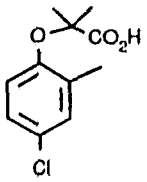
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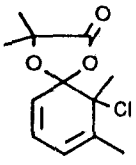
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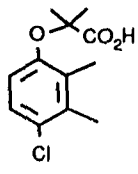
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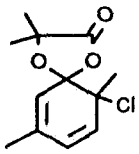
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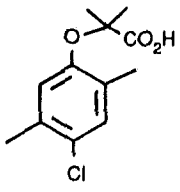
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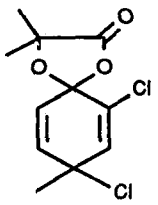

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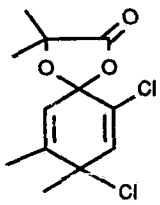

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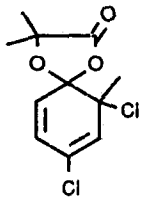

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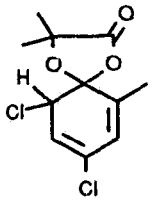

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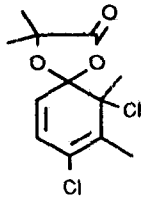

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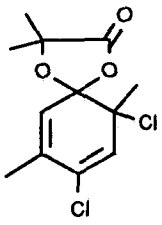

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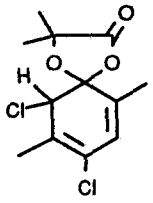

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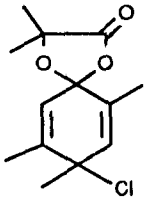

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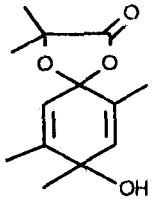

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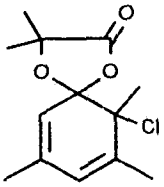

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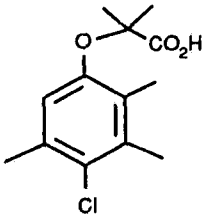

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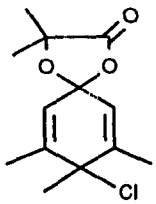

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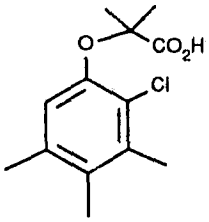

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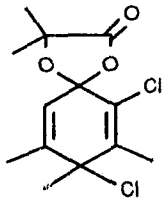

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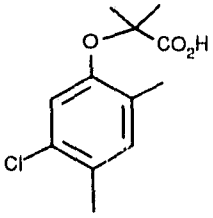

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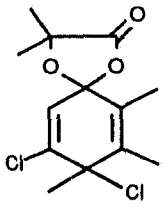

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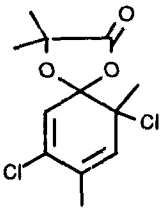

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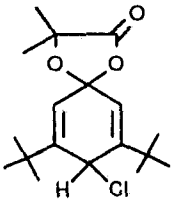

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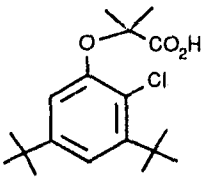

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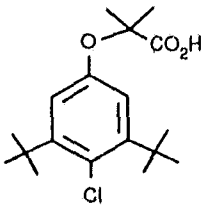

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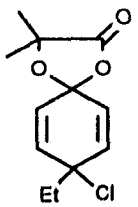

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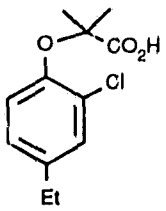

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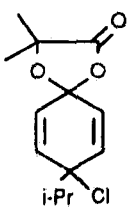

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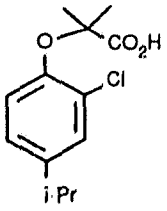

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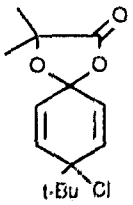

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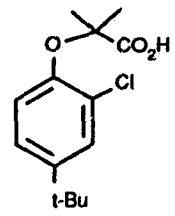

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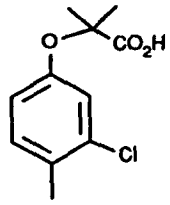

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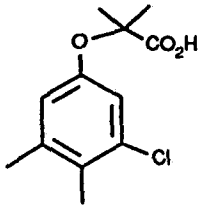

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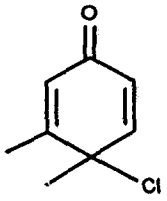

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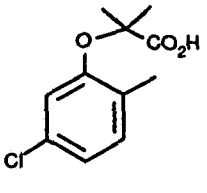

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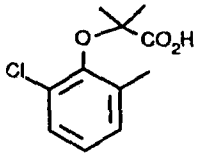

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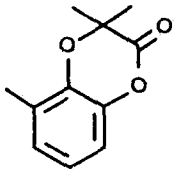

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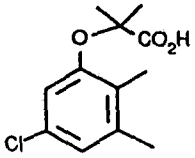

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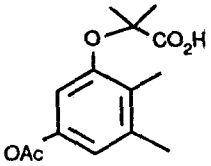

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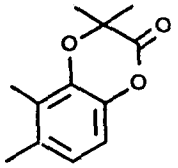

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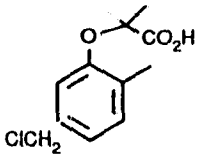

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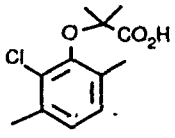

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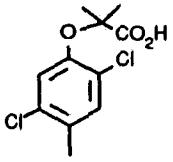

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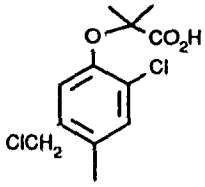

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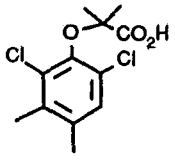

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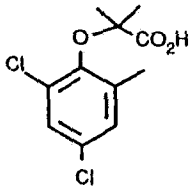

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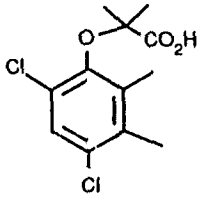

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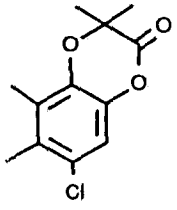

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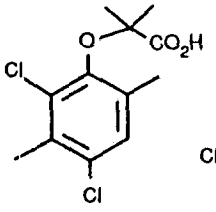

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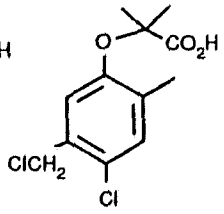

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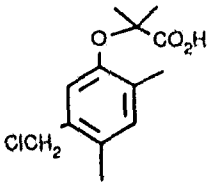

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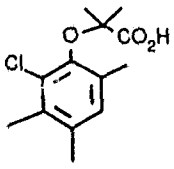

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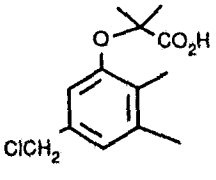

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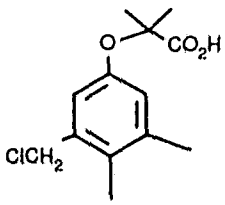

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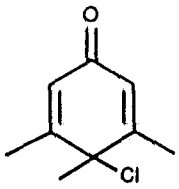

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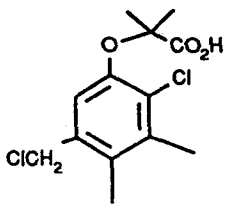

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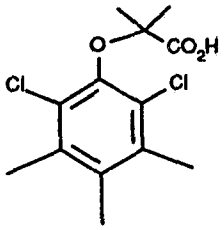

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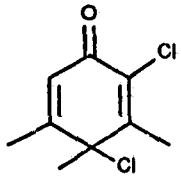

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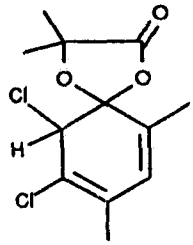

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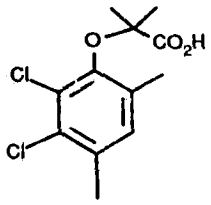

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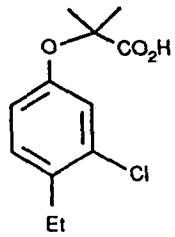

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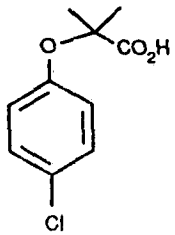

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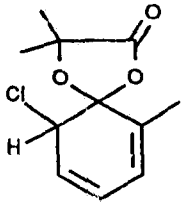

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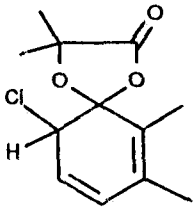

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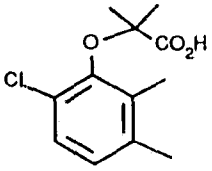

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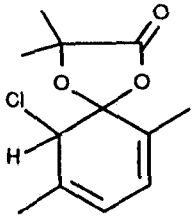

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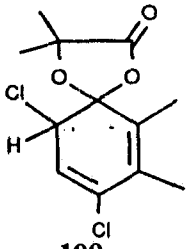

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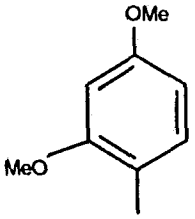

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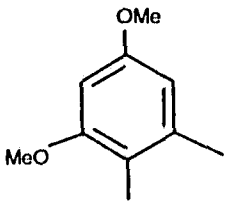

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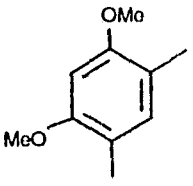

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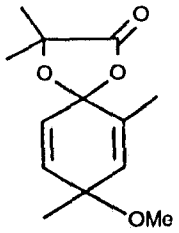

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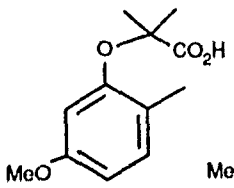

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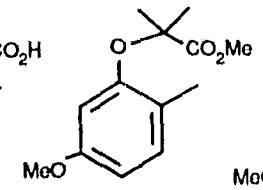

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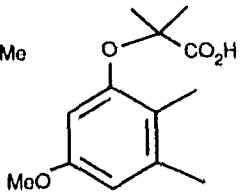

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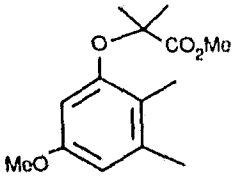

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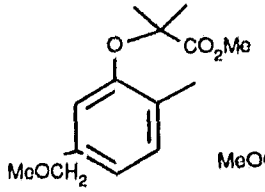

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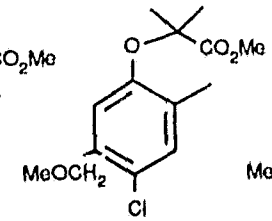

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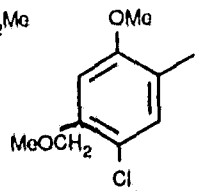

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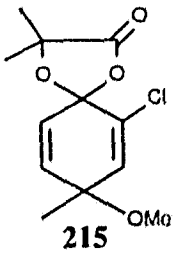

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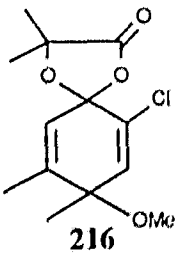

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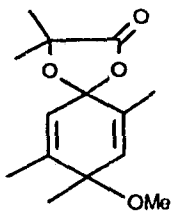

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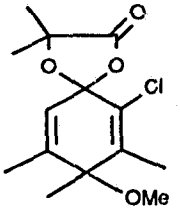

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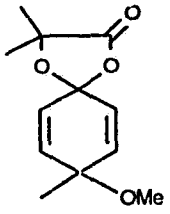

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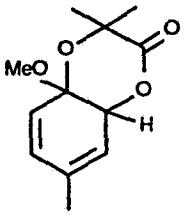

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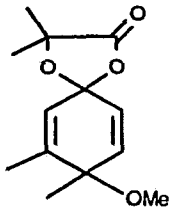

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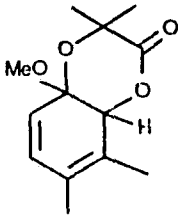

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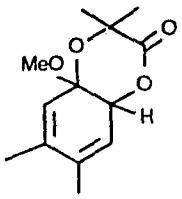

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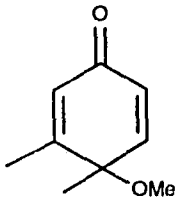

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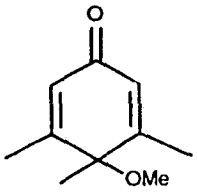

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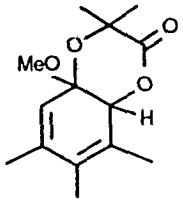

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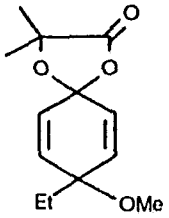

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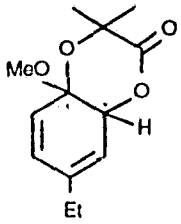

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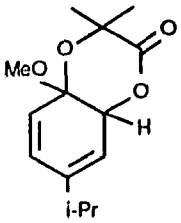

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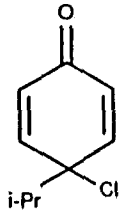

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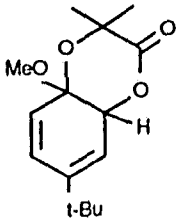

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